The Development of Iterative and Cascade Methods for the Rapid Synthesis of Ladder Polyether Natural Products

by

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Professor Timothy F. Jamison______________________________
Thesis Supervisor

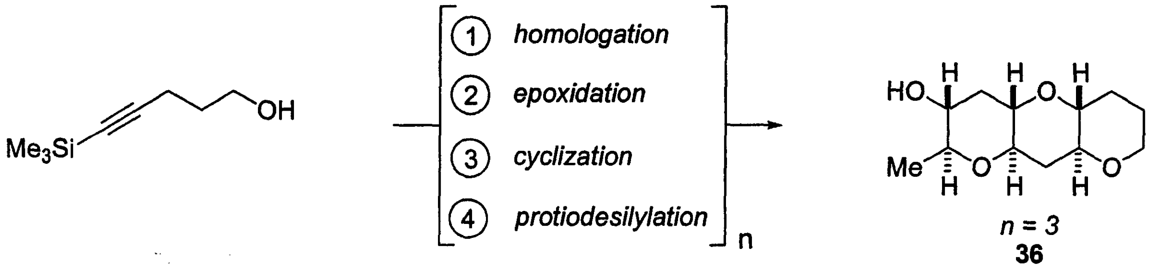
Professor Stephen L. Buchwald______________________________

To Jessica and my family

ABSTRACT

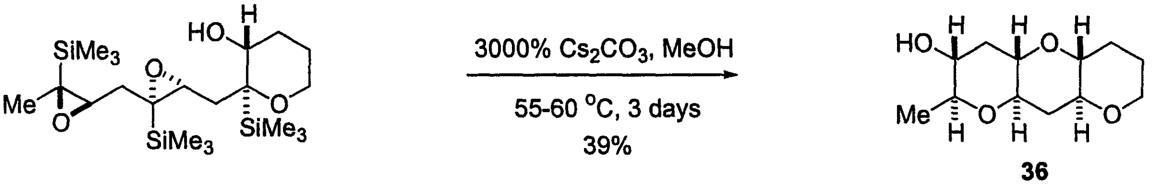
I. The Development of Methods for the Iterative Synthesis of Polytetrahydropyrans

An iterative method comprising chain homologation, epoxidation, 6-endo cyclization, and protiodesilylation was developed. Notable achievements include the development of a novel propargyl organocopper coupling method, and the complete control of stereoselectivity and regioselectivity during the iterative synthesis of a tristetrahydropyran. The synthesis of the tristetrahydropyran was achieved in 18 total operations.



II. The Development of a Cascade Synthesis of Polytetrahydropyrans with No Directing Groups at Ring Junctions

Cascade approaches to *trans*-fused tetrahydropyrans were studied. After exploring acid-promoted cascade cyclizations of polyepoxysilanes and polyepoxides without directing groups, the base-promoted cascade cyclization of polyepoxysilanes was realized. In this method, as many as five operations take place in a single step to provide a tristetrahydropyran with no directing groups at any ring junctions. The synthesis of the tristetrahydropyran was accomplished in 11 steps.



Thesis Supervisor: Timothy F. Jamison

Title: Paul M. Cook Development Associate Professor of Chemistry

Preface

Portions of this thesis have appeared in the following articles that were co-written by the author:

$SiMe_3$-Based Homologation-Epoxidation-Cyclization Strategy for Ladder THP Synthesis
Org. Lett. **2003**, *5*, 2339-2342.
Heffron, T. P.; Jamison, T. F.

Synthesis of skipped enynes via phosphine-promoted couplings of propargylcopper reagents
Tetrahedron **2003**, *Symposium-In-Print, New Synthetic Methods VII, 59,* 8913-8917.
Heffron, T. P.; Trenkle, J. D.; Jamison, T. F.

Acknowledgments

The past five years as a graduate student impacted me more profoundly than I would have predicted at the onset. At times it was thrilling. At other times it was a struggle. In each of those times it was the people who surrounded me that made my time as a graduate student the best that they could be.

Over the years I was lucky to have several coworkers that I proudly call my friends. From the first day in 2-304 I admired the way Johann Chan conducted his work and the diligence he showed. His commitment to finishing terpestacin was inspiring and surely contributed to the culture of our lab from the early days. Chudi Ndubaku showed me the way a person is supposed to be. His humility, respect, and determination are only overshadowed by his intellect. It was nice to have my desk and hood next to Sejal Patel, if only for a short while. It was so comforting to be able to turn to Sejal with whatever was on my mind and know that she would be supportive and not judgmental. The sketched flowers and discussions of Patels still make me smile.

I was fortunate to collaborate with Jim Trenkle and Dr. Graham Simpson during my time at MIT. I gained significantly in each of these collaborations and hope that I may have given something to them in return. My departure from MIT is made much easier knowing that the polyether project is in such capable hands.

I would like to thank my advisor for producing scientists. My graduate experience was very different from what I anticipated but I recognize the wisdom in Tim's approach. The graduates of this lab are unquestionably capable independent scientists. I am also grateful for his fairness with me and for giving me the freedom to explore my ideas. I would also like to thank Tim for not concluding my project prematurely and seeing the value in thorough exploration. The Jamison group has certainly evolved since my first days here and I see the success of the group only growing, owing significantly to the way Tim has managed.

I was inspired to attend graduate school during my time with Professor John Wood at Yale. I still am thankful for the time that he spent discussing my personal decisions with me. His genuine interest in his students both professionally and personally makes his group have more of a team atmosphere than any other I have encountered. His group is certainly a model for any professor.

My parents have provided me with unwavering support and love throughout my life. During my time at MIT, their understanding of my schedule, visits to Boston, and conversations while I was walking over the bridge always picked me up and reminded me that there are more important matters; something that is often hard to remember at MIT. My brother and sister have also helped to keep me grounded in similar ways, as I'm sure they will continue to do.

Without saying a word, Jessica reminded me to keep things in their proper perspective. She provided the balance in my life over the past five years. Jessica has shown more patience and tolerance than could be expected of anyone. She allowed the release of any frustration I met with on a day-to-day basis and was the one I turned to when making plans for the future...even if those plans changed on a weekly basis. Although very little seemed certain during my time here, I was always able to rely on Jessica to be there for me, and to know just what I needed. A simple thank you is terribly inadequate for all that Jessica has given to me. I hope that my love is forever felt in return and that I may be as supportive in all that she does as she has been for me. I look forward to the rest of my life with her!

Cambridge, Massachusetts
May, 2005

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Abbreviations

Ac	acetyl
Bn	benzyl
BOC	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
Cp	cyclopentadiene
CSA	D-(+)-camphorsulfonic acid
Cy	cyclohexyl
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMM	dimethoxymethane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diasteromeric ratio
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron ionization
er	enantiomeric ratio
ESI	electron spray ionization
Et	ethyl
g	gram(s)
h	hour(s)
Hal	halogen
hfc	3-heptafluoropropylhydroxymethylene-(+)-camphorate
HMBC	heteronuclear multiple bond correlation
i-Pr	isopropyl

LA	Lewis acid
LAH	lithium aluminum hydride
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethylene
mg	milligram(s)
min	minute(s)
n-Bu	*n*-butyl
n-Hex	*n*-hexyl
nm	nanometer
nOe	nuclear Overhauser effect
Nu	nucleophile
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridine *p*-toluenesulfonate
Pr	propyl
s-Bu	*sec*-butyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
THF	tetrahydrofuran
THP	tetrahydropyran
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

Chapter 1

The Development of Methods for the Iterative Synthesis of Polytetrahydropyrans

Introduction

The members of the ever-growing class of marine natural products containing *trans*-fused (ladder) polyethers including gymnocin A (**1**),[1] brevetoxin B (**2**),[2] yessotoxin (**3**),[3] brevetoxin A,[4] hemibrevetoxin B,[5] ciguatoxin CTX3C,[6] and gambierol,[7] among others,[8] impart varied and potent biological activities (Figure 1). This class of natural products is associated with massive fish killings and toxicity in humans related to the consumption of fish that have ingested these molecules. Of these natural products, the brevetoxins and ciguatoxins are implicated as neurotoxins present in the red tide phenomenon. More is known of these molecules' biological mode of action than other ladder polyethers. These polyethers are known to impart their toxic effects through binding to voltage sensitive Na^+ channels.[9] The neurological disruption caused by these compounds leads to several symptoms, including joint pain and the reversal of thermal sensation. Human ingestion of these compounds results in many other ailments including nauseau, vomiting, diarrhea, low blood pressure, and bradycardia.[10]

Gambierol has demonstrated similar toxicity to ciguatoxin and the brevetoxins and may contribute to the varied symptoms expressed after the consumption of toxic fish.[7] Meanwhile, yessotoxin was isolated from shellfish present during an episode of diarrhetic shellfish poisoning.[3]

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[1] Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett.* **2002**, *43*, 5829-5832.

[2] (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775. (b) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855-7856.

[3] (a) Murata, M.; Kumagai, M; Lee, J. S.; Yasumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5869-5872. (b) Takahashi, H.; Kusumi, T.; Kan, Y.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1996**, *37*, 7087-7090.

[4] (a) Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G. D.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514-515. (b) Pawlak, J.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144-1150.

[5] (a) Lin, Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775. (b) Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476-6477.

[6] Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975-1978.

[7] (a) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361-362. (b) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *40*, 97-100.

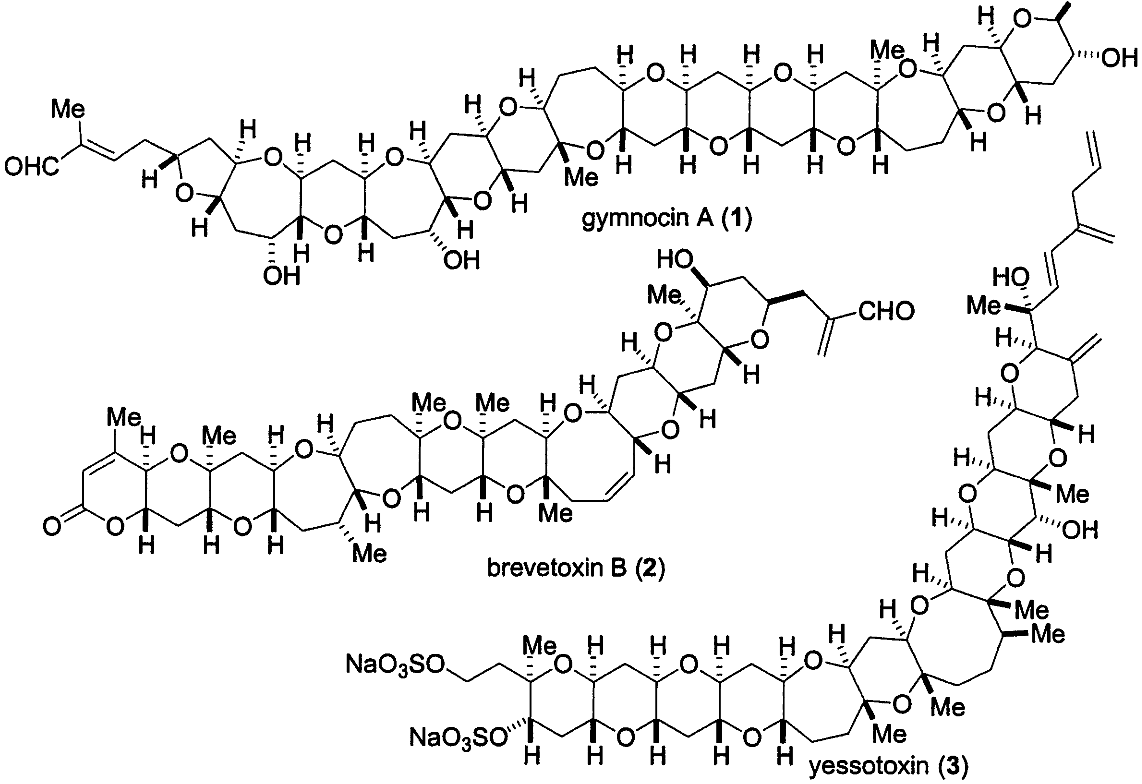
[8] For reviews: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897-1909. (b) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293-314. (c) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685-1698.

[9] Trainer, V. L.; Thomsen, W. J.; Catterall, W. A.; Baden, D. G. *Mol. Pharmacol.* **1991**, *40*, 988-994.

[10] (a) Sims, J. K. *Ann. Emerg. Med.* **1987**, *16*, 1006. (b) Johnson, G. L.; Spikes, J. J.; Ellis, S. *Toxicon* **1985**, *23*, 505-515. (c) Borison, H. L.; McCarthy, L. E.; Ellis, S. *Toxicon* **1985**, *23*, 517-524.

The ladder polyethers demonstrate potent bioactivity that is a threat to marine life and humans through consumption of seafood. In each case, the natural toxins are available in very limited quantities, making thorough biological studies and the development of assays for their detection difficult. This natural call to the synthetic organic chemist presents a formidable challenge because of their uniquely challenging architecture. In most cases, these molecules are very large natural products, on the order of three nm long. Each of these natural products contains a repeating motif of two oxygen atoms separated by two carbon atoms that form a *trans*-fused ring junction, and rarely are atoms other than carbon, hydrogen, and oxygen present. Nevertheless, the dense array of heteroatoms and stereocenters present in each of these natural products complicates their assembly by known organic methodology.

Figure 1. Representative ladder polyether natural products.



Known for more than twenty years, and with much attention from the synthetic community, relatively few reports of the chemical synthesis of these molecules have appeared.[11] To that end, many groups have contributed methods for the synthesis of portions of these compounds.[12] The landmark achievement of the total synthesis of brevetoxin B (**2**) was reported by the Nicolaou group.[11b-c] Within their work on the brevetoxins, and accompanying reports, methods for the assembly of the pyrans,[13] oxepanes,[14] oxocenes,[15] and didehydrononocanes[16] within these molecules were reported. Nicolaou's general strategy for pyran units utilizes the added stability of an allylic cation to control the regioselectivity in the cyclization of an alcohol upon a vinyl epoxide (Figure 2).[13]

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[11] For gymnocin A: (a) Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294-14295. For brevetoxin B: (b) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171-1172. (c) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1173-1174. (d) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374-14376. For brevetoxin A: (e) Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264-260. For total or formal syntheses of hemibrevetoxin B: (f) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935-7936. (g) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558-3575. (h) Kadota, I.; Park, J.-Y.; Koumura, N.; Pollaud, G.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5777-5780. (i) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365-6368. (j) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557-4558. (k) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6597-6606. (l) Rainer, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380-1386. (m) Holland, J. M.; Lewis, M.; Nelson, A. *J. Org. Chem.* **2003**, *68*, 747-753. (n) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822-7824. (o) Fujiwara, K.; Sato, D.; Watanabe, M.; Morishita, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 5243-5246. For ciguatoxin CTX3C: (p) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904-1907. For gambierol: (q) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *Org. Lett.* **2002**, *4*, 2981-2984. (r) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983-14992. (s) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46-47. (t) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848-849.

[12] For reviews on ladder ether synthesis: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953-1980. (b) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631-12670. (c) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4347-4353. (d) Hirama, M.; Rainier, J. D. Eds. *Tetrahedron Symposium-in-Print 90* **2002**, *58*, 1779-2040. (e) Evans, P. A.; Delouvrie, B. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 986-999.

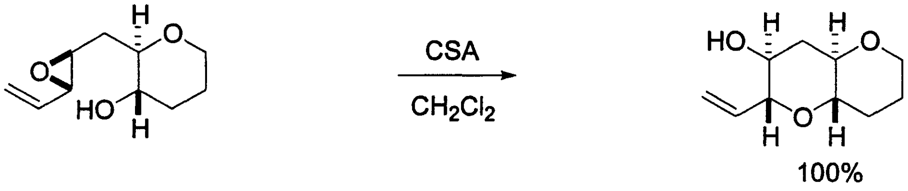
[13] (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359-1362. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330-5334.

[14] Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136-4137.

[15] Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468-2469.

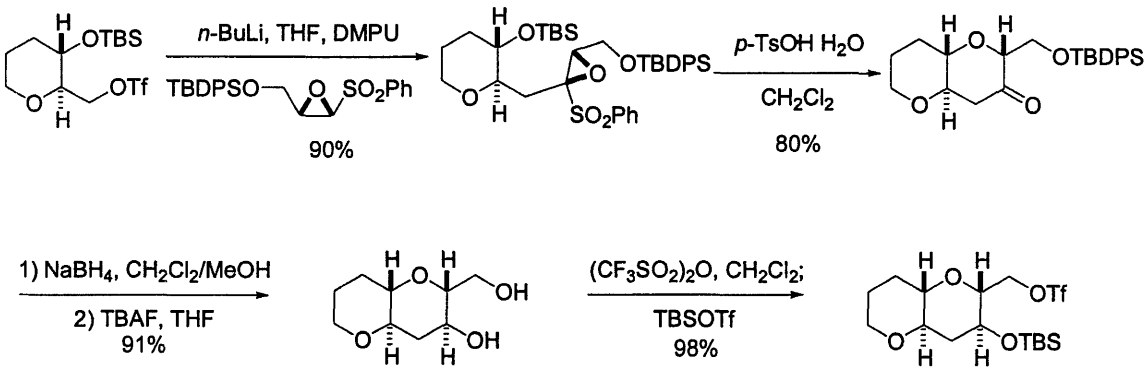
[16] Nicolaou, K. C.; Yang, Z.; Ouellette, M.; Shi, G.-Q.; Gärtner, P.; Gunzner, J. L.; Agrios, K. A.; Huber, R.; Chadha, R.; Huang, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 8105-8106.

Figure 2. Nicolaou's method for the 6-endo selective opening of epoxides.



One consistent portion of each of the ladder polyethers is the presence of *trans*-fused tetrahydropyrans (Figure 1). Aside from Nicolaou's method for the synthesis of this motif *via* vinyl epoxides, many other methods have been reported for the iterative synthesis of polytetrahydropyrans.[12c, 17, 18] Of particular interest is that of the Mori group, which utilizes a three carbon epoxysulfone unit to introduce each ring by way of an epoxy-alcohol cyclization to reveal a tetrahydropyran (Figure 3).[17] The sulfone serves a dual purpose in that it deactivates the site of undesired cyclization (5-exo) and is eliminated during the course of the reaction. This elimination allows for a proton to be introduced at what becomes the ring junction in a subsequent iteration, by reduction of the ketone that results during the cyclization event.

Figure 3. Mori's method for the iterative synthesis of *trans*-fused polytetrahydropyrans.



Despite the many examples of iterative syntheses of polytetrahydropyrans that were present, further work in this area was warranted as this motif is present in most

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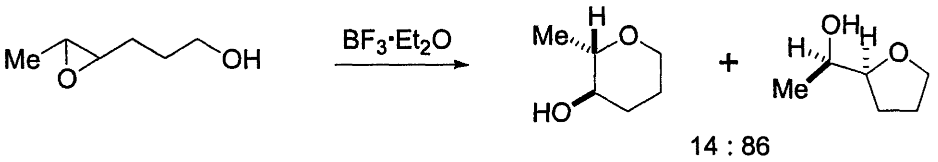
[17] (a) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158-8159. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 7239-7242. For a review: (c) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849-852.

[18] Trost, B. M.; Rhee, Y. H. *Org. Lett.* **2004**, *6*, 4311-4313.

ladder polyether natural products. Furthermore, the available methods required many steps, the multi-step synthesis of building blocks that are used in the iterative assembly, resulted in mixtures of stereoisomers, and/or produced racemic compounds.[17c, 18] Moreover, the use of epoxides in the generation of ladder polyethers is a particularly attractive approach as the biosynthesis of these natural products might comprise (1) polyene synthesis, (2) asymmetric epoxidation, and (3) a series of endo-selective epoxide-opening events (Chapter 2).[2b, 19]

Inspired by the proposed biosynthesis of ladder polyethers, we desired to achieve a cascade cyclization of a polyepoxide substrate leading to a *trans*-fused polyether framework. Recognizing the need to override the inherent 5-exo selectivity in a given alcohol-epoxide cyclization (Figure 4),[20] it was determined that a directing group would be used to control the regioselectivity in each cyclization.

Figure 4. Coxon's study demonstrates the preference for 5-exo cyclization.



Trimethylsilyl emerged as the directing group of choice primarily because of its demonstrated control of regioselectivity in the intermolecular opening of epoxysilanes.[21] While this is the case with numerous nucleophiles, the most compelling argument to study epoxysilanes was the regioselective opening of epoxysilanes with oxygen-centered

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[19] (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473-479. (b) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234-6241. (c) Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184-2185.

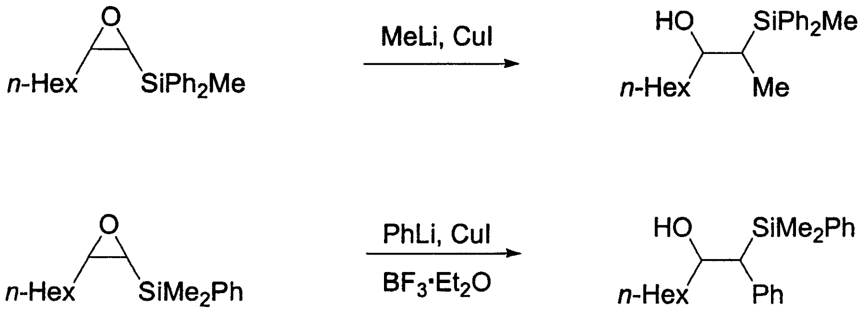
[20] Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521-2526.

[21] For examples of the regioselective opening of epoxysilanes: (a) Fristad, W. E.; Bailey, T. R.; Paquette, L. A. *J. Org. Chem.* **1980**, *45*, 3028-3037. (b) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004-5011. (c) Davis, A. P.; Hughes, G. J.; Lowndes, P. R.; Robbins, C. M.; Thomas, E. J.; Whitman, G. H. *J. Chem. Soc., Perkin Trans 1* **1981**, 1934-1941. (d) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 4412-4414. (e) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1989**, *30*, 967-970. (f) Yoshida, J. –I.; Maekawa, T.; Morita, Y.; Isoe, S. *J. Org. Chem.* **1992**, *57*, 1321-1322. (g) Jankowski, P.; Raubo, P.; Wicha, J. *Synlett* **1994**, 985-992. (h) Raubo, P.; Wicha, J. *Tetrahedron: Asymmetry* **1996**, *7*, 763-770. (i) Hodgson, D. M.; Comina, P. J. *J. Chem. Soc., Chem. Commun.* **1996**, 755-756. For a review: (j) Hudrlik, P. F.; Hudrlik, A. M. α, β-Epoxysilanes. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 1-89.

nucleophiles under acidic conditions,[22] the manner in which we envisioned conducting a polyepoxide cascade.

The origin of the directing ability demonstrated by $SiMe_3$ in regioselective epoxide openings has been the subject of much speculation and study. One suggestion, that the nucleophile in the epoxide opening first adds to the $SiMe_3$, generating a pentavalent intermediate, then migrates to open the epoxide, has been largely discounted by studies performed by the Hudrlik group (Figure 5). In these studies of the opening of epoxysilanes, in which the silyl group was $SiPh_2Me$, the addition of MeLi/CuI provides the product (regioselectively) in which the apparent nucleophile was Me. If a pentavalent intermediate were responsible for the regioselectivity observed in the opening, the nucleophile would be predicted to be Ph because of its greater migratory aptitude. The corresponding study in which the silyl group was $SiPhMe_2$ and the nucleophile was PhLi/CuI, provided the product of opening by Ph, again in high regioselectivity.[23]

Figure 5. Hudrlik's experiments suggest that a pentavalent intermediate is not involved in the opening of epoxysilanes.



Two other postulates have appeared in the literature that suggest the origin of the selectivity in the opening of epoxysilanes at the α position. The first suggests a stabilization of the transition state between the developing alcohol and silicon (**A**, Figure

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[22] (a) Robbins, C. M.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1976**, 697-698. (b) Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993-1996.

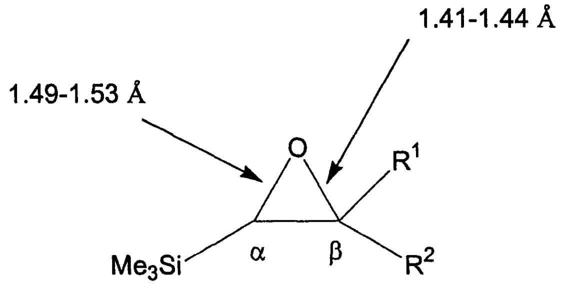
[23] Hudrlik, P. F.; Ma, D.; Bhamidipati, R. S.; Hudrlik, A. M. *J. Org. Chem.* **1996**, *61*, 8655-8658.

6).[24] Another suggestion is that the nucleophile coordinates simultaneously to the carbon and silicon atoms (**B**, Figure 6).[25]

Figure 6. Suggested transition states explaining the directing ability of $SiMe_3$.

Interestingly, the reported X-ray crystal structures of molecules containing epoxysilanes all show a longer, and therefore weaker, C-O bond at the α position relative to that between the oxygen and β-carbon (Figure 7).[26]

Figure 7. X-ray structures of epoxysilanes show longer C-O bonds α to silicon.



This lengthened bond in epoxysilanes has been predicted in a molecular orbital analysis and discussed by Paquette.[27] In an epoxide, the HOMO is C-O antibonding and by replacing an alkyl substituent about the epoxide with a silyl group leads to greater antibonding character.[27] Furthermore, $SiMe_3$ should be more inductively electron-

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[24] (a) Berti, G.; Canedoli, S.; Crotti, P.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1183-1188. (b) Hudrlik, P. F.; Wan, C.-H.; Withers, G. P. *Tetrahedron Lett.* **1976**, *19*, 1453-1456

[25] Eisch, J. J.; Trainor, J. T. *J. Org. Chem.* **1963**, *28*, 2870-2876.

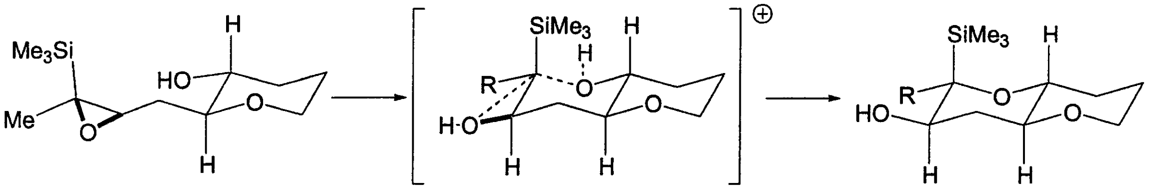
[26] (a) Hodgson, D. M.; Comina, P. J.; Drew, M. G. B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2279-2289. (b) Kabat, M. M. *J. Org. Chem.* **1995**, *60*, 1823-1827. (c) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042-4050. (d) Illa, O.; Gornitzka, H.; Baceiredo, A.; Bertrand, G.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2003**, *68*, 7707-7710. (e) Siriwardane, U.; Chu, S. S. C.; Buynak, J. D. *Acta Crystallogr. Sect. C.* **1989**, *45*, 531-533. (f) Yamamoto, K.; Kawanami, Y.; Miyazawa, M. *J. Chem. Soc., Chem. Commun.* **1993**, 436-437. (g) Kawai, T.; Isobe, M.; Peters, S. C. *Aust. J. Chem.* **1995**, *48*, 115-131.

[27] Fristad, W. F.; Bailey, T. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1979**, *101*, 4420-4423.

donating than an alkyl group.[28] The lengthened C-O bond and inductive nature of silicon may contribute to the high regioselectivity observed in the opening of epoxysilanes by encouraging an S_N2-borderline reaction mechanism.

Despite the precedented regioselectivity in the opening of epoxysilanes, the $SiMe_3$ group's effect on cyclization was still an issue. In order to achieve the desired relative stereochemistry at the ring junction in a synthesis of *trans*-fused ladder polyether subunits, the $SiMe_3$ would be axial in the predicted transition state (Figure 8).

Figure 8. The $SiMe_3$ group is placed in the axial position in the transition state in the cyclization of an epoxysilane.



No such cyclization with an axial $SiMe_3$ group had been reported and, in fact, Schaumann had reported that epoxy-alcohol cyclizations with $SiMe_3$ in an equivalent equatorial position led to unspecified ratios of 5-exo and 6-endo products (Figure 9). In this case, however, it can be inferred that the diasteromeric mixture of epoxides used as starting material was the source of low regioselectivity (eq 1, Figure 9). Nonetheless, when a single diastereomer was used, the formation of 6-endo products could be ascribed to a significant conformational predisposition such as avoidance of forming a strained *trans*-5,5 system (eq 2, Figure 9).[29]

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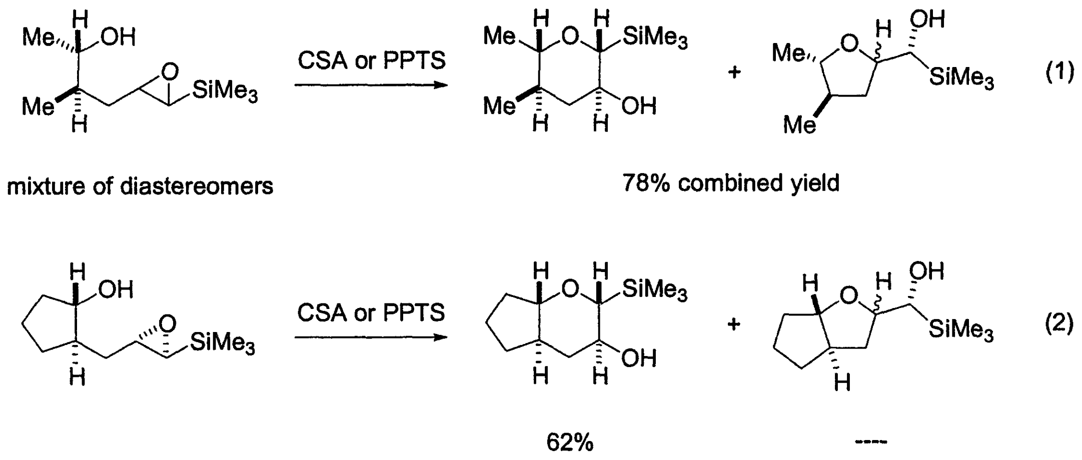
[28] Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975.

[29] Aidwidjaja, G.; Flörke, H.; Kirschning, A.; Schaumann, E. *Tetrahedron Lett.* **1995**, *36*, 8771-8774.

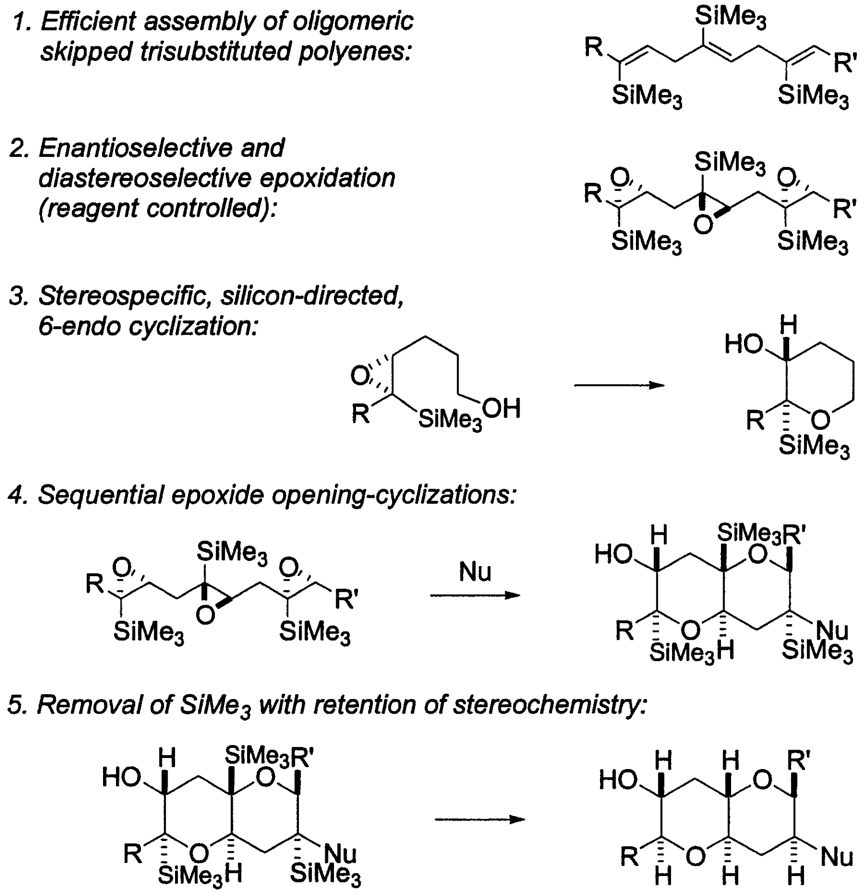
Figure 9. Demonstrated cyclizations of epoxysilanes in which $SiMe_3$ would occupy the equatorial position.



Another aspect was the need to remove the trimethylsilyl group after cyclizations. Initially, we envisioned a cascade of cyclizations that placed a $SiMe_3$ group at each ring junction. Those $SiMe_3$ groups would need to be protiodesilylated as a final step but there was no precedent for the protiodesilylation of a $SiMe_3$ group in such a system.

With these concerns, our approach to polyethers presented five challenges (Scheme 1): (1) Efficient synthesis of skipped polyenes incorporating a trimethylsilyl group; (2) Reagent-controlled, highly enantio- and diastereoselective epoxidation of these polyenes; (3) Stereospecific, silicon-directed, 6-endo cyclization; (4) Sequential cyclizations resulting in a series of *trans*-fused tetrahydropyrans; (5) Protiodesilylation of the directing trimethylsilyl group, with retention of stereochemistry, giving the *trans*-fused products with only hydrogen atoms at the ring junction.

Scheme 1



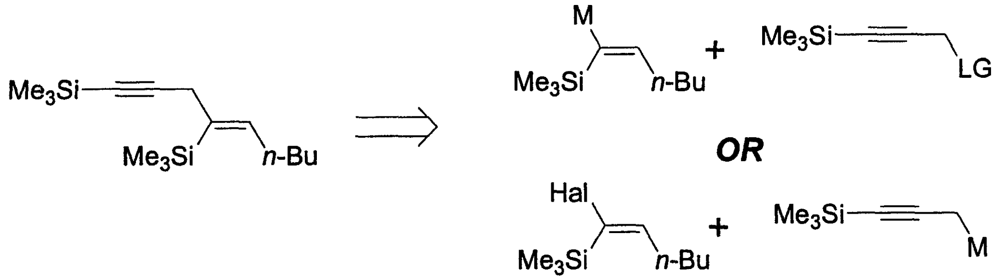
This chapter discusses solutions to four of these challenges: (1) The development of a novel propargylation method for the synthesis of methylene interrupted polyolefins, (2) Demonstration of the feasibility of the asymmetric epoxidation of the alkenylsilanes, (3) Demonstration of the directing ability of $SiMe_3$ when placed in an axial position in the proposed transition state, and (4) Protiodesilylation of the resulting $SiMe_3$ after a single cyclization event. Finally, an iterative synthesis of a tristetrahydropyran, reminiscent of that observed in several ladder polyether natural products, is discussed.

Results and Discussion

Synthesis of Requisite Alkenylsilanes

The first obstacle in our route to polytetrahydropyrans was a suitable assembly of skipped trisubstituted alkenylsilanes. Two disconnections that would lead to the precursory skipped enyne were studied (Figure 10). In the first of these a propargylic electrophile was used and in the other the propargyl group was a metalated nucleophilic coupling partner.

Figure 10. Two potential disconnections that would lead to the desired skipped enyne.



Both approaches studied initially utilized alkenyl halides that were derived from 1-trimethylsilyl-1-hexyne. These alkenyl halides, as well as all of those synthesized from $SiMe_3$ protected alkynes reported herein, were formed in very high regio- (>95:5) and stereoselectivity (>95% *E*) by hydroalumination (DIBAL) followed by conversion to the alkenyl iodide.[30] In our first approach we attempted to generate an alkenyllithium species that would then displace a propargylic leaving group (Scheme 2). As this disconnection did not lead to any desired skipped enyne, we sought a method for the propargylation *via* a propargyl cross-coupling method.

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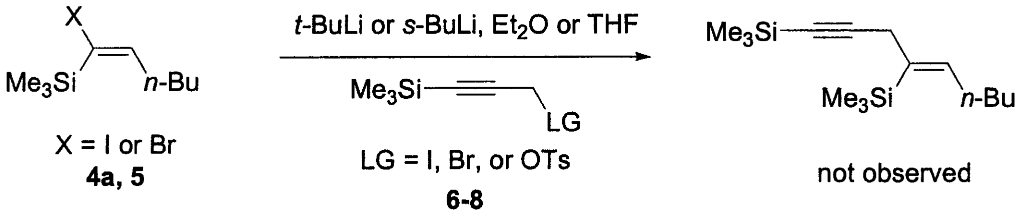
[30] Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978,** *43*, 2739-2744.

Scheme 2



The development of carbon-carbon bond forming reactions that favor propargyl-coupled products where allenyl-derived adducts are also possible has received much attention. Danheiser demonstrated that high propargyl selectivity is obtained in additions of allenylsilane reagents to carbonyl groups and oxocarbenium ions,[31] and Marshall found that chiral, enantiomerically enriched allenylstannanes also undergo propargyl-selective carbonyl addition. In related work, chiral allenylzinc species can be prepared in high enantiomeric excess from chiral propargyl mesylates, and subsequent 1,2-addition to achiral and chiral aldehydes can be effected with high diastereoselectivity.[32]

Prior to these carbonyl addition processes, Corey pioneered propargyl-selective alkylation and allylation of propargylcopper reagents,[33] and Ganem later reported the first propargyl-selective conjugate additions of these species.[34] Danheiser's allenylsilane reagents generally favor (trimethylsilyl)cyclopentene annulation in analogous reactions,[35] whereas Haruta showed that certain allenylstannanes were selective for 1,4-S_E2' addition, affording 4-alkynylcarbonyl compounds.[36]

The development of propargyl-selective cross-coupling methods, however, is much less developed. In a series of investigations, Ma observed that Pd-catalyzed cross-

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[31] (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925-3927. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870-3878.

[32] (a) Marshall, J. A.; *Chem. Rev.* **1996**, *96*, 31-47. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163-3185. See also: (c) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 878-880.

[33] Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, *9*, 5041-5043.

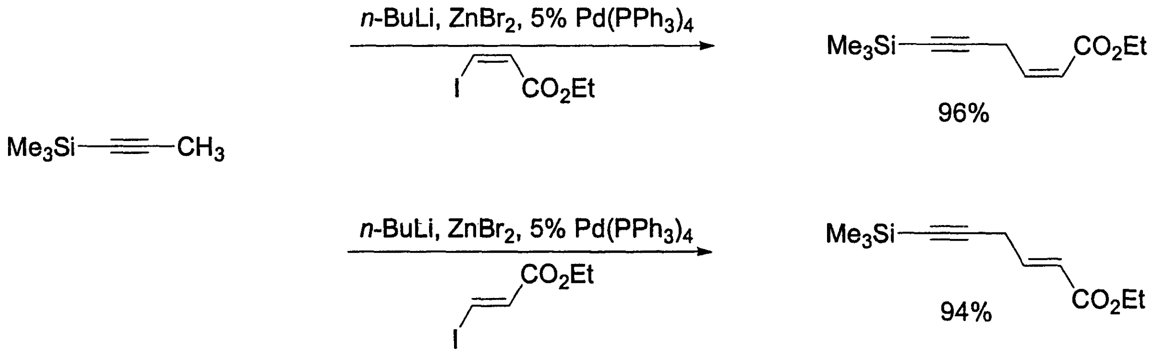
[34] Ganem, B. *Tetrahedron Lett.* **1974**, *15*, 4467-4470.

[35] (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604-1606. (b) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron*, **1983**, *39*, 935-947. See also: (c) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094-6097.

[36] (a) Haruta, J.; Nishi, K.; Matsuda, S.; Tamura, Y.; Kita, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1065-1066. (b) Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853-4859.

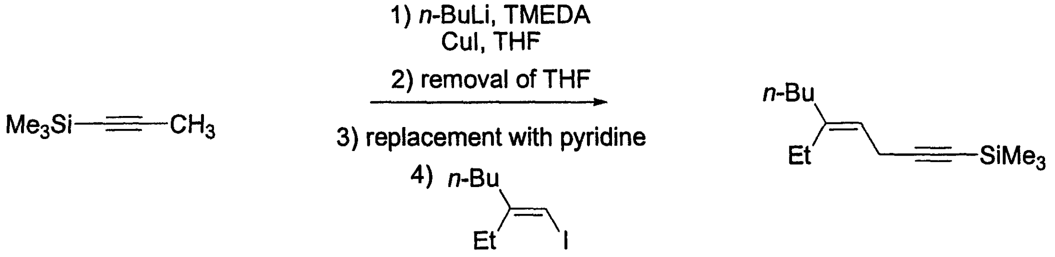
coupling of allenylzinc reagents and alkenyl iodides favored the propargyl regioisomer when the electrophile contained an electron-withdrawing group (Figure 11).[37]

Figure 11. Examples of Pd-catalyzed cross-coupling of allenylzinc reagents with electron deficient alkenyl iodides (ref 37).



Since propargyl coupling was not efficacious in cases closest to those for which we required reactivity, the starting point for our investigations was a singular example of selective propargyl–*sp*^{2} coupling described by Normant in 1975 (Figure 12).[38]

Figure 12. Normant's report of the coupling of an alkenyl iodide with a propargyl organocopper reagent.



Preparation of the organocopper reagent involved deprotonation of 1-(trimethylsilyl)-1-propyne with *n*-BuLi in TMEDA/THF, addition of CuI, removal of the THF *in vacuo*, and addition of pyridine. An explanation for the solvent switch was not provided, but we reasoned that modification of the organocopper species by interaction with pyridine

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[37] (a) Ma, S.; Zhang, A. *J. Org. Chem.* **1998**, *63*, 9601-9604. (b) Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* **2000**, *65*, 2287-2291. (c) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287-2294.

[38] Commercon, A.; Normant, J.; Villieras, J. *J. Organomet. Chem.* **1975**, *93*, 415-421.

might be necessary for maximum yield of the propargyl-coupled product. Anticipating an iterative process using such a propargylation for the synthesis of skipped polyolefins, and performing the coupling on both very large and very small scale, we sought a method that would obviate the need for the solvent exchange. In this vein, we examined a variety of additives with the aim of duplicating this high propargyl selectivity while simultaneously eliminating the solvent exchange.

As summarized in Scheme 3 and Table 1, we found that several additives had dramatically different effects upon both yield and propargyl/allenyl selectivity in our initial investigations with alkenyl iodide **4a**.[39] Although propargyl selectivity was high in reactions conducted in THF, they were not of preparative utility (entry 2). Nitrogen and sulfur containing additives were either efficacious or selective, but not both (entries 3-6). Organophosphines on the other hand (entries 7-9) displayed very high levels of propargyl selectivity, and of these, tributylphosphine (Bu_3P) also gave the desired product in good yield.

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[39] Mr. James D. Trenkle contributed to the completion of the studies of the additives for and to examination of the scope of this propargylation reaction.

Scheme 3

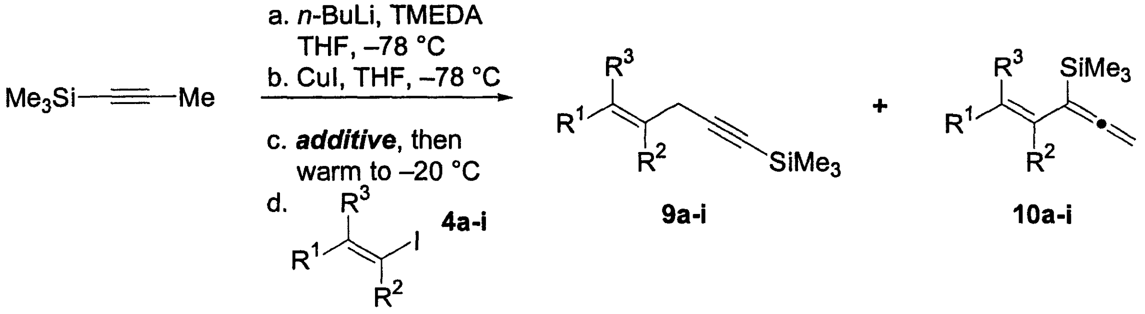

Table 1. Effects of additives upon yield and selectivity in coupling reactions of alkenyl iodide.[a]

Entry	Solvent	Additive	**9a** : **10a**[b]	Isolated Yield of **9a** (%)
1	ether	none	n.d.	< 5
2	THF	none	>20:1	37
3	THF	pyridine	10:1	47
4	THF	DMAP	7:1	69
5	THF	Et_3N	10:1	39
6	THF	Me_2S	20:1	33
7	THF	Ph_3P	>20:1	41
8	THF	Bu_3P	>20:1	81
9	THF	Cy_3P	>20:1	41

[a] Perfomed on 2.0-gram scale (7.1 mmol of iodide **4a**). See Scheme 3 and Experimental Section for details.

[b] Determined by ^1H NMR analysis of unpurified product mixture.

Several explanations for the higher yield and selectivity imparted by Bu_3P are possible, including increased solubility and/or thermal stability of the organocopper species, or a change in its aggregation state.[40, 41] Since higher yields are observed with the more electron-rich Bu_3P than with Ph_3P (entries 7 and 8), it is possible that oxidative addition into the carbon-iodine bond is accelerated by the former. Nevertheless, the

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[40] Whitesides, G. W.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379-1389.

[41] Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210-7211.

results with Cy_3P (entry 9) might suggest otherwise, unless the increased steric demand of this phosphine is responsible for the reduction in yield.

The scope of this transformation with respect to the substitution pattern and nature of the alkenyl iodide was also evaluated (Table 2). In all cases, the desired propargyl-coupled product is formed exclusively (>20:1, ^1H NMR). Protected (entry 2) and free hydroxyl groups (entries 3 and 4) are tolerated, and significantly, no π-bond isomerization is observed in entry 4 with skipped diene **4d**. A trimethylsilyl group geminal to the iodine atom is not required for efficacy or selectivity, as shown by entries 6-9. In one case, substitution *cis* to the iodide significantly reduces the efficiency of coupling (entry 5). Nevertheless, conjugated alkenyl iodides couple smoothly, as demonstrated by *(E)*-1-iodo-2-phenylpropene (entry 7). Finally, the coupling is stereospecific with respect to olefin geometry (entries 8 and 9).

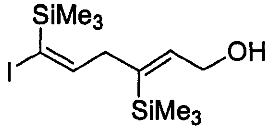
Table 2. Propargyl-selective coupling of alkenyl iodides **4a-i.**[a]

Entry	Iodide	R^1	R^2	R^3	**9 : 10**[b]	Yield (%)
1	**4a**	*n*–Bu	Me_3Si	H	>20:1	81
2	**4b**	$TBSOCH_2$	Me_3Si	H	>20:1	45
3	**4c**	$HO(CH_2)_3$	Me_3Si	H	>20:1	67
4	**4d**	(see below)	Me_3Si	H	>20:1	67
5	**4e**	H	*n*–Pr	*n*–Pr	n.d.	< 5
6	**4f**	*n*–Pr	*n*–Pr	H	>20:1	33[c]
7	**4g**	Ph	H	Me	>20:1	80
8	**4h**	*n*-Bu	H	H	>20:1	38
9	**4i**	H	H	*n*-Bu	>20:1	52

[a] See Scheme 3 and Experimental Section for details.

[b] Determined by ^1H NMR analysis of unpurified product mixture.

[c] NMR analysis of the unpurified product mixture indicated a 2:1 mixture of iodide **4f** and product **9f**., i.e. conversion was approximately 33%. The yield reported (33%) is the isolated yield based on a theoretical 100% and therefore is nearly quantitative based on conversion.



4d

In summary, an electron-rich phosphine additive is critical and sufficient for propargyl-selective couplings of propargylcopper reagents and alkenyl halides. This method is complementary to that reported by Ma, who observed efficient propargyl coupling with electron-deficient alkenyl halides. Despite the emergence of Bu_3P as the optimal additive in terms of propargyl selectivity, DMAP was used in the synthesis of all compounds used in our studies on the synthesis of ladder polyethers primarily because of the ease by which it is separated from the coupling product.

Asymmetric Epoxidation

The next requirement in our strategy for assembling polytetrahydropyrans was obtaining epoxysilanes in high enantioselectivity from the synthesized alkenylsilanes. Moreover, with an eye toward the synthesis of polytetrahydropyrans from polyepoxysilanes, a highly enantio- and diastereoselective epoxidation method was also required. Shi's catalytic asymmetric epoxidation of *trans* and trisubstituted olefins using a fructose-derived ketone catalyst seemed promising.[42] That Shi had also reported asymmetric epoxidation of alkenylsilanes was also encouraging, although the products reported were in a different stereochemical arrangement from the alkenylsilanes to be epoxidized in these studies.[43] As with all dioxirane epoxidations, the Shi epoxidation is believed to proceed through a spiro transition state (Figure 13), preferred over the competing planar transition state because of more effective overlap of the oxygen lone pair with the π^* of the olefin.[42, 44] In the Shi epoxidation, the olefin face that is exposed to the dioxirane is dictated by the demanding steric environment of the fructose derived catalyst. With *trans-* and trisubstituted olefins, one olefin face can approach the dioxirane and avoid much of the steric interaction that the other face would experience. It has been suggested also that the competing planar transition state, in which the lowest energy approach of the olefin leads to the opposite enantiomer of the epoxide as the spiro transition state, leads to decreased enantiomeric enrichment (Figure 13).

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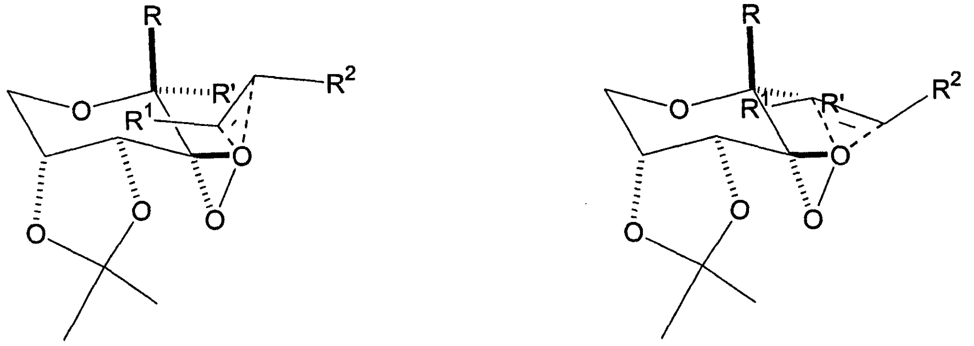
[42] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807. For support of the prediction of the absolute stereochemistry of epoxides produced using this method: (b) Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904-2911. For reviews: (c) Frohn, M.; Shi, Y. *Synthesis* **2000**, *14*, 1979-2000. (d) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488-496.

[43] Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675-7677.

[44] Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311-3314.

Figure 13. Competing transition states in the Shi asymmetric epoxidation (ref. 42).

Spiro (favored) Planar



Spiro (favored) Planar

As this model has been successful in predicting the absolute stereochemistry of the epoxide products, and steric difference seems to be the greatest factor governing enantioselectivity, [42a-b, 45] we were encouraged that the alkenylsilanes we were to study were suitable substrates for the Shi epoxidation. Significantly, this model for asymmetric induction in the Shi epoxidation predicts that polyepoxides of the required relative stereochemistry for polycyclizations would be produced from polyalkenylsilanes (e.g. Scheme 2, eq 2).

In our studies, the first substrate used in experimentation was alkenylsilane **9a** (Scheme 4), and the Shi epoxidation provided epoxide **11** in 51% yield. In this case, the induction achieved during the asymmetric epoxidation was determined using a chiral shift reagent (Eu(hfc)$_3$) and ^{1}H NMR.[43] When compared to the racemic material,[46] the epoxide produced by Shi epoxidation appeared as a single enantiomer to the limit of detection of ^{1}H NMR (>95% ee).

An epoxide with a pendant hydroxyl group was required for our epoxide cyclization studies. The known propensity of the dioxirane used in Shi epoxidation to

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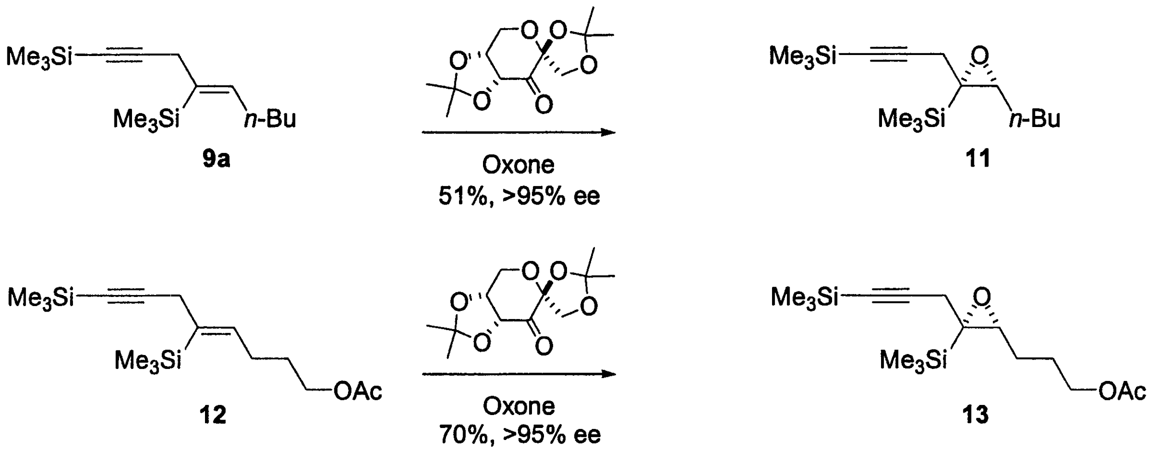
[45] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

[46] Synthesized using *m*-CPBA (See Experimental Section).

oxidize alcohols to aldehydes and ketones,[47] and of dioxiranes in general to oxidize aldehydes even more rapidly to carboxylic acids,[48] led to the decision to protect the alcohol prior to epoxidation. With the analog of olefin **9a** in which the terminal Me group had been replaced by a primary alcohol, the epoxidation was best performed on the acetate protected alcohol (**12**), which exhibited exceptional asymmetric induction (>95% ee, Scheme 4).[49]

Scheme 4



Regioselective Opening of Epoxysilanes

With access to epoxysilanes, we began exploring the directing ability of the trimethylsilyl appendage in the Lewis or Brønsted acid-promoted intramolecular ring opening of epoxysilanes. Cyclization of epoxide **14e** occured quite readily under several conditions in good yield (Scheme 5, Table 3). More importantly, in each case only a single regioisomer (6-endo) and stereoisomer (inversion of configuration) was observed, demonstrating that the trimethylsilyl group exhibits exceptional directing ability in epoxide opening cyclizations.

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[47] Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *J. Org. Chem.* **1999**, *64*, 7492-7497.

[48] For reviews discussing the reactivity of dioxiranes: (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.

[49] The ee of this compound was determined by chiral GC. See Experimental Section for details.

Scheme 5

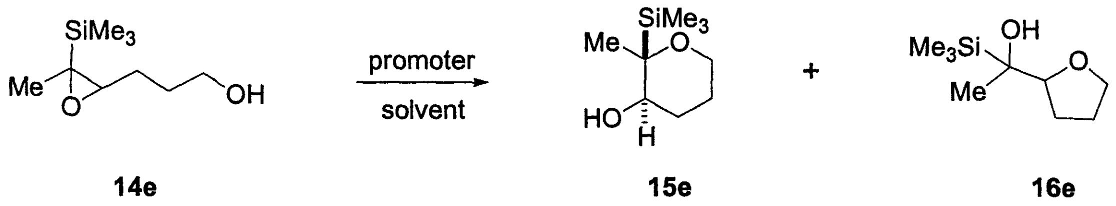


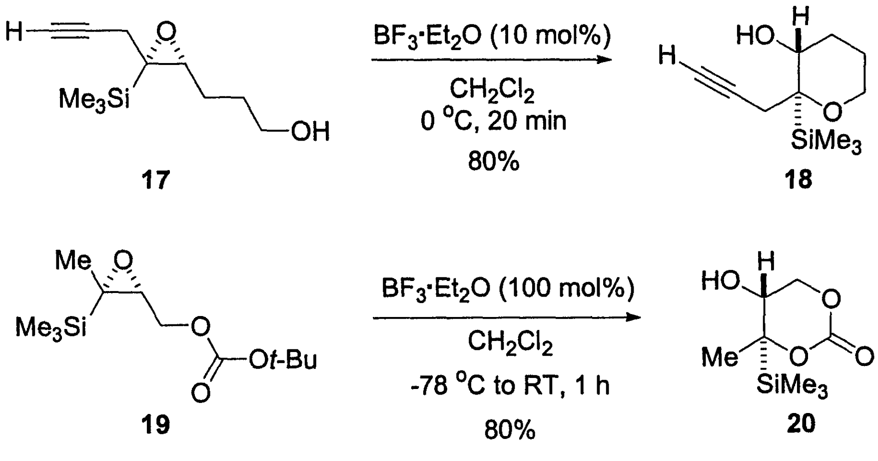
Table 3. Acid-Promoted Cyclization of Epoxysilane **14e**.

Entry	Promoter[a]	Solvent	Temperature	Time	**15e** : **16e**	Yield
1	BF_3·Et_2O	CH_2Cl_2	0 °C	20 min	>20:1	67 %
2	HCO_2H	CH_2Cl_2	23 °C	8 h	>20:1	60 %
3	$LiClO_4$	CH_3CN	80 °C	24 h	>20:1	72 %
4[b]	*m*-CPBA	CH_2Cl_2	23 °C	4 h	>20:1	63 %
5	CF_3CO_2H	CH_2Cl_2	23 °C	2 h	>20:1	61 %

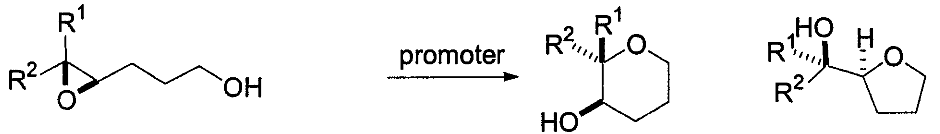
[a] 100 mol% was used in each case.
[b] Olefin **38** (see Experimental Section) was converted directly to the pyran in this experiment.

In addition, we showed that epoxy-alcohol **17** as well as *t*-butyl carbonate **19** also cyclize rapidly and with complete stereospecificity (Scheme 6).

Scheme 6



Interestingly, however, the epoxysilane of opposite stereochemistry (**14f**) provided 1-hydroxy-5-hexanone as the major product (entry 6, Table 4).[50] This is especially curious in light of the results of experiments in the Nicolaou and Mori labs involving endo hydroxy-epoxide cyclizations with pendant directing groups, as well as of the hydroxy-epoxide cyclization of *cis* and *trans* 3-(3-methyl-oxiranyl)-propan-1-ol reported by Coxon.[13a-b, 17, 20] In each of those cases when a substituent (vinyl, methyl) was placed in the axial position in the transition state (**14b, 14d**, Table 4, entries 2, 4) during cyclization, the product of the exo mode of cyclization was produced more so than with the equatorial analog.



14a-f **15a-f** **16a-f**

Table 1. Directing Group Effects in Hydroxy-Epoxide Cyclizations.

Entry	Epoxide	R^1	R^2	Promoter (mol%)	**15**:**16**
1[a]	**14a**	H	Me	$BF_3{\cdot}Et_2O$ (300)	14:86
2[a]	**14b**	Me	H	$BF_3{\cdot}Et_2O$ (300)	≤3:97
3[b]	**14c**	H	$CH=CH_2$	(+)-CSA (10)	>98:2
4[b]	**14d**	$CH=CH_2$	H	(+)-CSA (10)	44:56
5	**14e**	$SiMe_3$	Me	$BF_3{\cdot}Et_2O$ (100)	>95:5
6[c]	**14f**	Me	$SiMe_3$	$BF_3{\cdot}Et_2O$ (100)	-----

[a] See Coxon, ref 20.
[b] See Nicolaou, ref 13.
[c] Major product: $HO(CH_2)_4C(O)CH_3$.[51]

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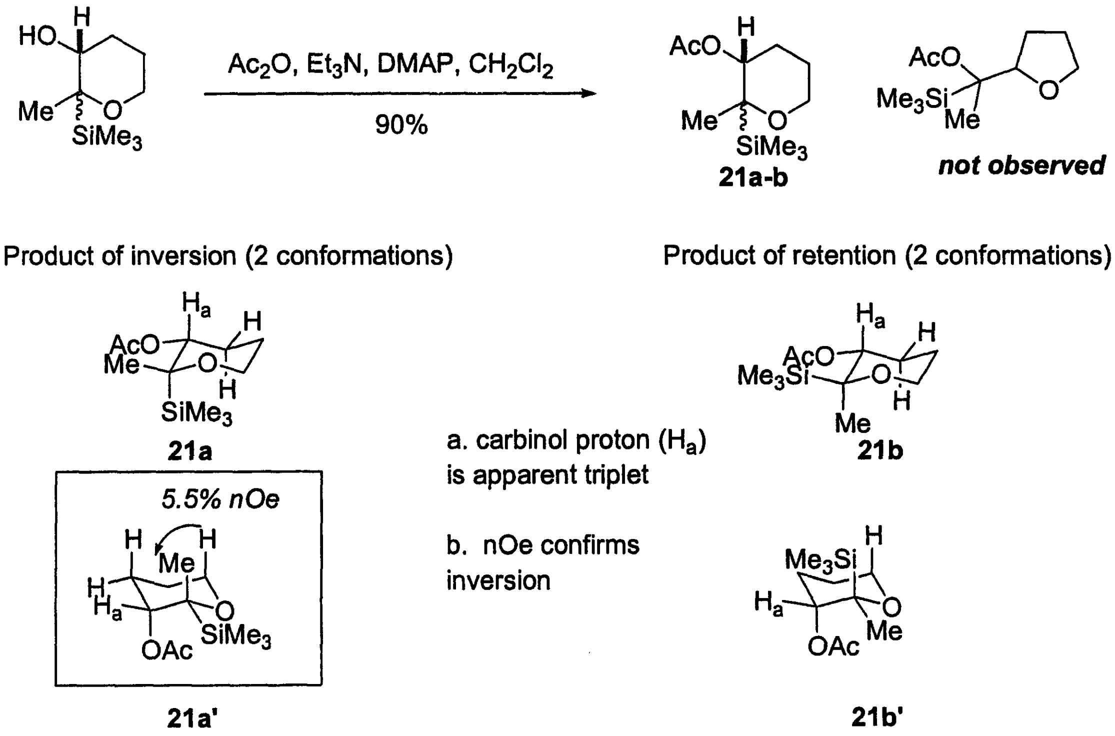
[50] The rearrangement of epoxysilanes to carbonyls is a known reaction. For examples: (a) Stork, G.; Colvin, E. *J. Am. Chem. Soc.* **1971**, *93*, 2080-2081. (b) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682-3684. (c) Flörke, H.; Schaumann, E. *Synthesis* **1996**, 647-651. (d) Gröbel, B.-T.; Seebach, D. *Angew. Chem. Int. Ed.* **1974**, *13*, 83-84. (e) Boeckman, R. K.; Bruza, K. J. *Tetrahedron Lett.* **1974**, *16*, 3365-3368. (f) Hudrlik, P. F.; Hudrlik, A. M.; Misra, R. N.; Peterson, D.; Withers, G. P.; Kulkarni, A. K. *J. Org. Chem.* **1980**, *45*, 4444-4448.

[51] Kabalka, G. W.; Yu, S.; Li, N.-S. *Can. J. Chem.* **1998**, *76*, 800-805.

In order to establish which regioisomer was actually formed, the cyclized product was acetylated (Figure 14). This confirmed that a pyran product was in hand because of the resulting downfield shift of the carbinol proton in the ^{1}H NMR spectrum. The furan product would be a tertiary alcohol and no carbinol shift would be observed.

Figure 14. Establishment of inversion of configuration in the silicon-directed epoxide opening.



a. carbinol proton (H$_a$) is apparent triplet

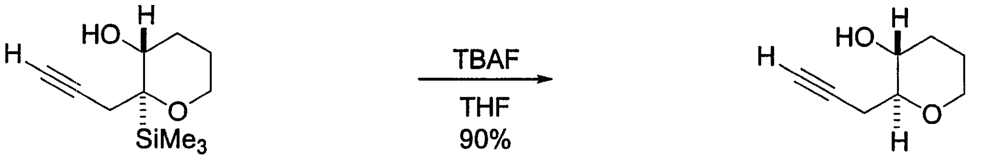
b. nOe confirms inversion

The next task was determining whether the tetrahydropyran formed was the product of inversion or retention of configuration at the center where the epoxide was opened. There are two possible chair conformations for each of these products. By noting that the carbinol proton was an apparent triplet it was possible to rule out two (**21a**, **21b**) because in those cases that proton would likely appear as a doublet of doublets. Next, nOe studies revealed a 5.5% enhancement between the axial methylene proton adjacent to the ring oxygen and the methyl group on the other side of the ring. This observation rules out the other possibility (**21b'**) and allows for the determination of the structure (**21a'**).

Stereospecific Protiodesilylation

With cyclized substrates in hand protiodesilylation was attempted. To this end, *n*-$Bu_4N^+F^-$ (TBAF) was shown to be very effective for the protiodesilylation of substrate **18**. The desilylation shown in Scheme 7 was affected in high yield and afforded a single diastereomer (retention of configuration) detectable by ^1H NMR. Furthermore, despite the *cis* relationship of the Me_3Si and OH groups, and the basic nature of TBAF solutions, byproducts corresponding to the formal elimination of Me_3SiOH were not observed.[52]

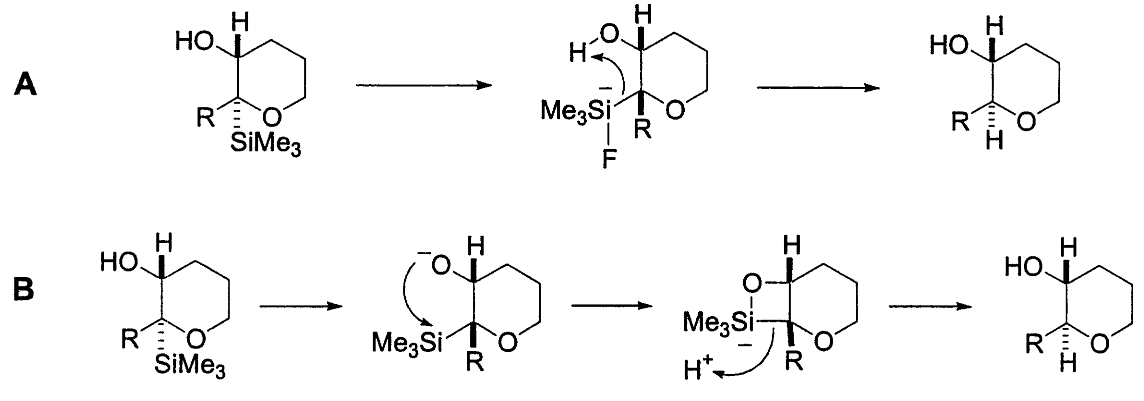
Scheme 7



18 **22**

Multiple reaction mechanisms are possible for this protiodesilylation. One suggestion is that the proton that replaces the $SiMe_3$ group is delivered from the neighboring hydroxyl group (**A**, Figure 15).

Figure 15. Potential reaction mechanisms in the protiodesilylation of β-hydroxysilanes.



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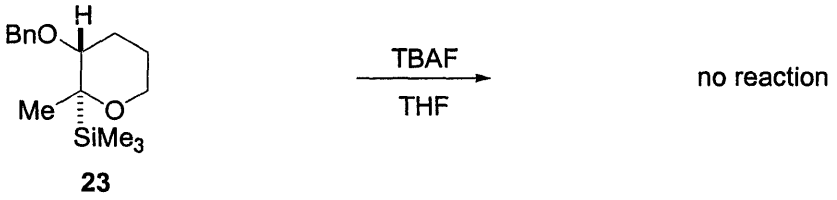
[52] (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780-784. (b) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822-823. (c) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809-6811. (d) Hudrlik, P. F.; Holmes, P. E.; Hudrlik, A. M. *Tetrahedron Lett.* **1988**, *29*, 6395-6398.

To explore the possibility of protiodesilylation in the absence of the hydroxyl group, the alcohol was protected as the benzyl ether. With this substrate, no reaction took place after 24 h at room temperature (Scheme 8). Very recently, McDonald has reported the synthesis of a polyoxepane that contains a $SiMe_3$ group at a ring junction. In that case the $SiMe_3$ could not be protiodesilylated.[53]

Scheme 8



The observation that the neighboring hydroxyl group is required for the protiodesilylation to take place under these conditions still leaves at least two possible reaction mechanisms. In the first case, a pentavalent silicon intermediate is generated by TBAF which then abstracts the hydroxyl proton (**A**, Figure 15). Alternatively, the hydroxyl group could be deprotonated to generate a putative intermediate in Peterson olefination (**B**, Figure 15).[52a, c-d] In this case, the presence of a proton source would lead to the hydrolyzed product rather than the olefin. Afterward, the silyl ether would be protiodesilylated to leave the free alcohol.

A series of experiments by the Hudrlik group on the protiodesilylation of β-hydroxytrimethylsilanes suggests that the latter is the likely reaction mechanism.[52c,d] In their studies, a cyclic β-hydroxysilane was protiodesilylated in a stereospecific manner under basic conditions in the presence of a proton source but in the absence of fluoride anion (Figure 16).

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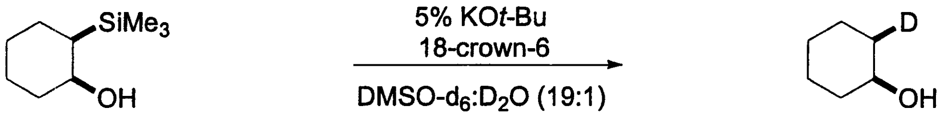
[53] Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586-4587.

Figure 16. Stereospecific protiodesilylation of β-hydroxysilanes under basic conditions (ref 52c).

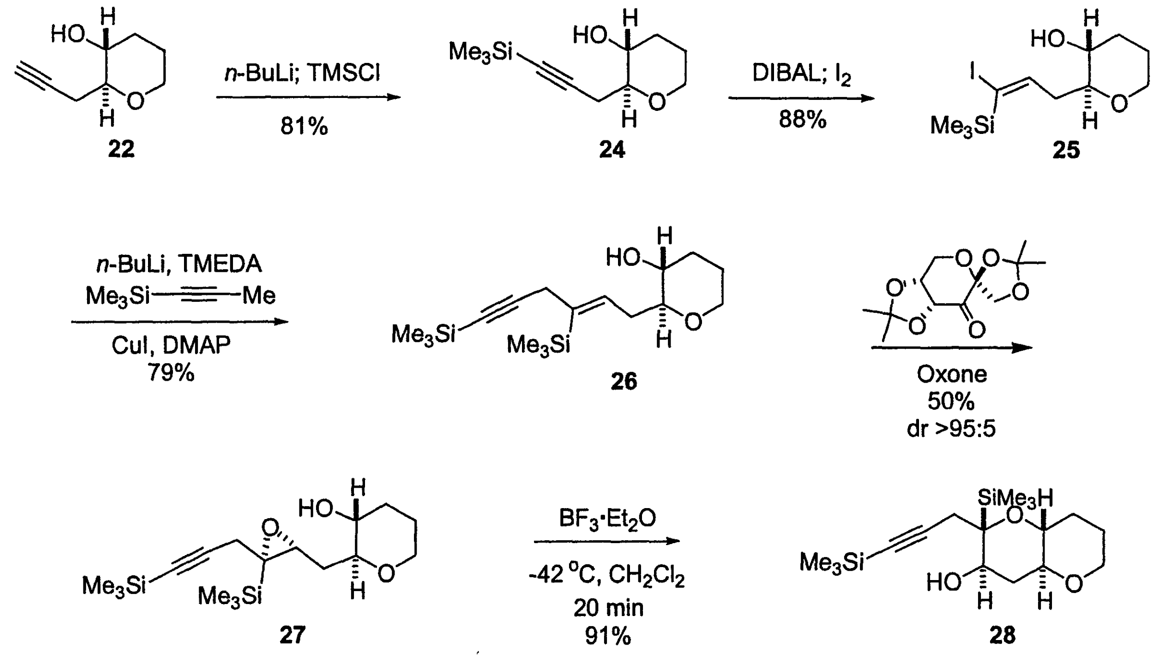


Having demonstrated that we could produce epoxysilanes of a given stereoarrangement in high enantioselectivity, that the $SiMe_3$ group is an effective directing group that provides the desired 6-endo product exclusively, and that the directing group can be replaced by a proton after the cyclization event, a viable iterative synthesis of polytetrahydropyrans appeared established. We, therefore, turned our attention to the synthesis of polytetrahydropyran units using our methodology.

Iterative Approach to Polytetrahydropyrans Using a Propargylation-Epoxidation-Cyclization-Desilylation Strategy

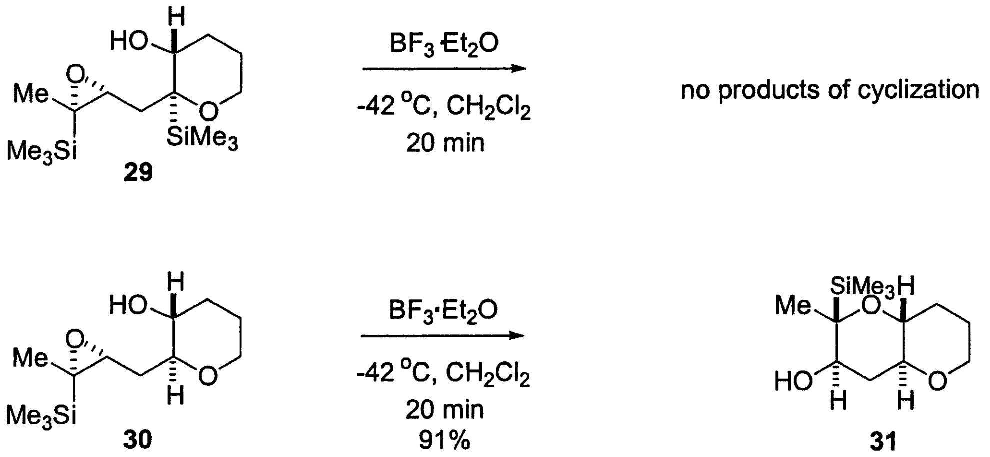
In order to establish that our methodology consitituted a viable iterative synthesis of polytetrahydropyrans we chose to target a tristetrahydropyran unit. The elaboration of pyran **22** to **28** demonstrated that a bispyran could be synthesized (Scheme 9). Significantly, in this sequence epoxide **27** was isolated in high diastereoselectivity (dr >95:5), demonstrating the utility of the Shi epoxidation method in diastereoselective epoxidations required for the synthesis of polytetrahydropyrans.

Scheme 9



During the development of an iterative synthesis of a tristetrahydropyran system, it became attractive to eliminate the need to remove the alkynyl trimethylsilyl group after cyclization (e.g. after conversion of **27** to **28**), because it would need to be reintroduced later. With respect to the requisite protiodesilylation there appeared to be three options. The first was to delay protiodesilylation until the end of the synthesis of the trispyran. Such a global desilylation approach would also require the development of a method for the protiodesilylation of $SiMe_3$ groups not adjacent to hydroxyl groups. This possibility proved not to be a legitimate option because, if protiodesilylation was not carried out after the first cyclization, attempted cyclization onto the next epoxysilane led to a complex mixture of compounds that did not contain any cyclized products (Scheme 10). This result appeared to justify our fear that the developing interactions faced when forcing a second $SiMe_3$ group into the axial position may be prohibitively high in energy. Furthermore, the corresponding cyclization with the substrate in which the $SiMe_3$ group at what becomes the ring junction had been previously removed (**30**) proceeded in high yield to afford bispyran **31** (Scheme 10).

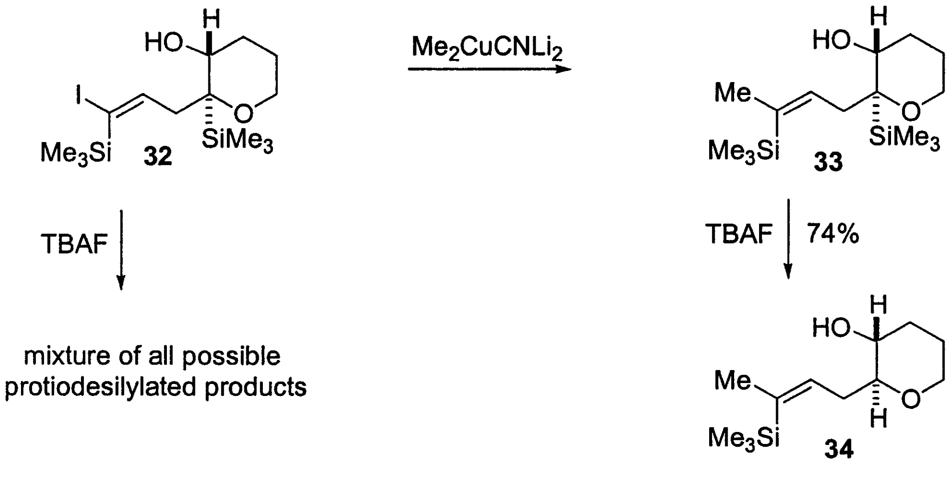
Scheme 10



A second approach would be to chemoselectively protiodesilylate the $SiMe_3$ group on the newly formed ring after elaborating the propargyl group to the alkenyl iodide. This approach would save one step per iteration, but also proved ineffective, as a selective protiodesilylation could not be achieved (Scheme 11).

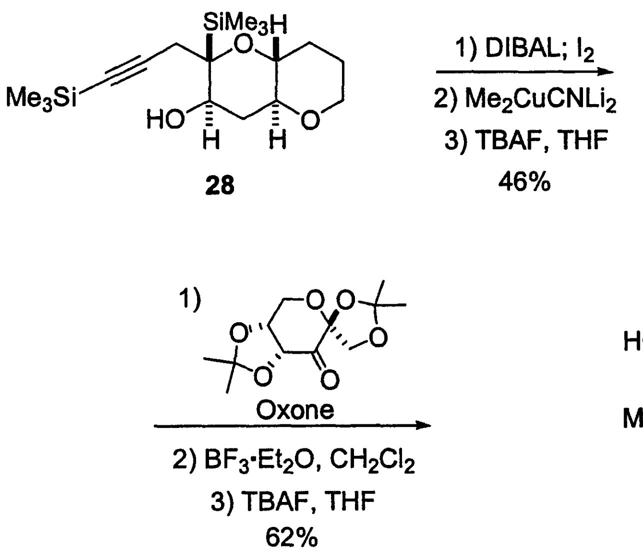
The final option, which would still save one step in every other iteration, was to generate the alkenyl iodide and then couple with an alkyl (or propargyl) group before chemoselective protiodesilylation. In this case, chemoselective protiodesilylation of the β-hydroxy $SiMe_3$ group proved to be possible after the addition of methyl cuprate to the alkenyl iodide (Scheme 11).

Scheme 11



These strategies were implemented in the successful iterative synthesis of a completely desilylated tristetrahydropyran (Scheme 12). From **28**, hydrometallation/iodination and coupling with methyl cuprate followed by the chemoselective protiodesilylation provided **35** in 46% yield over 3 steps. Next, diastereoselective epoxidation, cyclization, and protiodesilylation completed the sequence in 62% yield over 3 steps.

Scheme 12



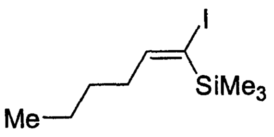
Conclusion

After the development of a novel propargylation method for the synthesis of skipped enynes, asymmetric epoxidation of trisubstituted alkenylsilanes, exploitation of the directing ability of $SiMe_3$ in epoxy-alcohol cyclizations, and demonstration of the removal of the directing group after cyclization, an iterative synthesis of *trans*-fused tetrahydropyrans with all-proton ring junctions was developed.

The Nicolaou,[13] Mori,[17] and $SiMe_3$-based approaches to iterative ladder polyether synthesis each mirror all three proposed biogenetic operations. Nicolaou's strategy uses an alkenyl group for π-stabilization of positive charge at the adjacent (α) epoxide carbon in the hydroxy-epoxide cyclization and is part of the carbon framework, whereas Mori uses the inductive effect of an electron-withdrawing $PhSO_2$ group to favor epoxide opening at the β carbon. In contrast, a $SiMe_3$ group appears to direct α opening in a different stereoelectronic manner and can occupy an axial position in the course of stereospecific and endo-selective cyclization. These features, in conjunction with the complete stereo- and regiocontrol in each step, make possible the assembly of THP triad **36** in 18 *total* operations, whereas the Nicolaou and Mori approaches average 10-13 operations *for each* THP including preparation of necessary building blocks.

Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) and Et_2O were distilled from a blue solution of benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh).[54] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova 500 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), C_6D_6 (128.4 ppm), or CD_2Cl_2 (54.0 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm.



(*E*)-1-Iodo-hex-1-enyl-trimethyl-silane (4a): To a solution of 1-trimethylsilyl-1-hexyne (10 g, 65 mmol) in Et_2O (32 mL) in a water bath was added a 1.0 M solution of DIBAL in hexane (71 mL, 71 mmol). The reaction mixture was brought to reflux and maintained

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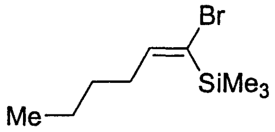
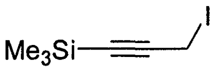
[54] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

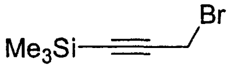
for 1 h. The solution was cooled to –78 °C and was diluted with Et_2O (38 mL). A solution of I_2 (21 g, 84 mmol) in Et_2O (140 mL) was added over 2 h. The resulting mixture stirred 1 h at –78 °C. The reaction mixture was warmed to 0 °C and stirred 30 min before pouring into 1 M HCl (250 mL) and ice (65 g). This stirred until the precipitate dissolved and then was extracted with hexane (3 × 200 mL). The combined organic layers were washed with 1 N NaOH, saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to provide **4a** (16 g, 89%). NMR spectral data were consistent with that reported.[30, 55]



(*E*)-1-Bromo-hex-1-enyl-trimethyl-silane (5): Synthesized according to a reported procedure.[30]



(3-Iodo-prop-1-ynyl)-trimethyl-silane (6): Synthesized according to a reported procedure.[56]



(3-Bromo-prop-1-ynyl)-trimethyl-silane (7): Synthesized according to a reported procedure.[57]

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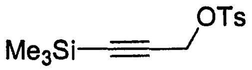
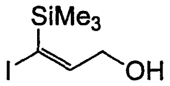
[55] Zweifel, G.; Murray, R. E. *J. Org. Chem.* **1981**, *46*, 1292-1295.
[56] Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286-6293.
[57] Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601-11624.



Toluene-4-sulfonic acid 3-trimethylsilanyl-prop-2-ynyl ester (8): Synthesized according to a reported procedure.[58]



(*E*)-3-Iodo-3-trimethylsilanyl-prop-2-en-1-ol (37): To a solution of 3-trimethylsilanyl-prop-2-yn-1-ol[59] (8.0 g, 63 mmol) in Et_2O (160 mL) was added a 1 M solution of DIBAL in hexane (156 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to –78 °C, diluted with Et_2O (60 mL), and a solution of I_2 (63.5 g, 250 mmol) in Et_2O (200 mL) was added. After stirring 2 h at –78 °C the reaction was quenched by pouring into 1 M HCl (100 mL) and ice (50 g). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **37** (10.7 g, 67%, >95% *E*): $R_f = 0.35$ (20% EtOAc in hexane); IR (thin film, NaCl) 3312, 2955, 1250, 1018, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, $J = 7.0$ Hz, 1H), 4.09 (dd, $J = 7.0, 6.1$ Hz, 2H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 111.6, 63.6, 1.2; HR-MS (ESI) Calcd for $C_6H_{13}NaIOSi$ $(M + Na)^+$ 278.9673, found 278.9673.

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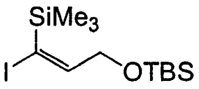
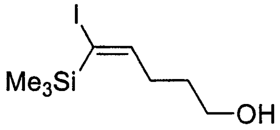
[58] Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N. *Bull Chem. Soc. Jpn.* **1995**, *68*, 297-300.

[59] Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935-948.



(*E*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-iodo-1-trimethylsilanyl-propene (4b): To a solution of alkenyl iodide **37** (5.1 g, 20 mmol) in DMF (20 mL) was added imidazole (1.9 g, 28 mmol), and TBSCl (4.2 g, 28 mmol). The reaction mixture stirred overnight at room temperature then was quenched with water. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield protected alcohol **4b** without the need for further purification (6.8 g, 92%): R_f = 0.45 (5% EtOAc in hexane); IR (thin film, NaCl) 3853, 2955, 2929, 2857, 1251, 1098, 838, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 6.0 Hz, 1H), 4.11 (d, J = 6.5 Hz, 2H), 0.90 (s, 9H), 0.27 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 109.0, 64.6, 26.6, 19.0, 1.6, –4.4; HR-MS (ESI) Calcd for $C_{12}H_{27}NaIOSi_2$ $(M + Na)^+$ 393.0537, found 393.0534.



(*E*)-5-Iodo-5-trimethylsilanyl-pent-4-en-1-ol (4c): To a solution of 5-trimethylsilanyl-pent-4-yn-1-ol[60] (12.2 g, 77.8 mmol) in Et_2O (190 mL) at 0 °C was added a 1 M solution of DIBAL in hexane (190 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to –78 °C, diluted with Et_2O (60 mL), and a solution of I_2 (79.0 g, 310 mmol) in Et_2O (175 mL) was added. After stirring 2 h at –78 °C, the reaction was warmed to 0 °C and stirred 1 h before the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (40 g). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl

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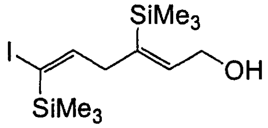
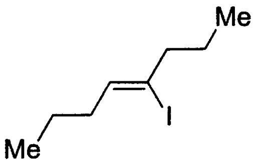
[60] Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699-2708.

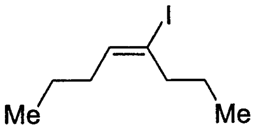
iodide **4c** (20.1 g, 91%, >95% *E*): R_f = 0.20 (20% EtOAc in hexane); IR (thin film, NaCl) 3335, 2952, 1588, 1407, 1249, 1059, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.9 Hz, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.18 (dt, *J* = 7.7, 7.6 Hz, 2H), 1.67 (m, 2H), 0.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 107.6, 62.2, 32.2, 31.7, 1.4; HR-MS (ESI) Calcd for $C_8H_{17}IOSi$ $(M)^+$ 284.0088, found 284.0091.



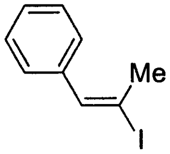
(2*Z*,5*E*)-6-Iodo-3,6-bis-trimethylsilanyl-hexa-2,5-dien-1-ol (4d): To a solution of **9b** (see below; 9.6 g, 25 mmol) in Et_2O (60 mL) was added a 1 M solution of DIBAL in hexane (60 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to –78 °C, diluted with Et_2O (50 mL), and a solution of I_2 (25 g, 98 mmol) in Et_2O (150 mL) was added. After stirring 2 h at –78 °C, the reaction mixture was warmed to 0 °C and stirred 1 h, then warmed to room temperature and stirred 40 min before the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (70 g). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **4d** (5.6 g, 55%, >95% *E*): R_f = 0.28 (20% EtOAc in hexane); IR (thin film, NaCl) 3324, 2954, 1250, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.6 Hz, 1H), 6.14 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.23 (dd, *J* = 6.7, 5.8 Hz, 2H), 2.87 (dd, *J* = 7.6, 1.5 Hz, 2H), 0.27 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 141.5, 141.4, 108.0, 62.3, 41.9, 1.2, 0.3; HR-MS (ESI) Calcd for $C_{12}H_{29}INaOSi_2$ $(M + Na)^+$ 391.0381, found 391.0394.



(*Z*)-4-Iodo-oct-4-ene (4e): Synthesized according to a reported procedure.[61] NMR spectral data were consistent with that reported.[62]



(*E*)-4-Iodo-oct-4-ene (4f): To a solution of Cp_2ZrHCl (22.0 g, 87.1 mmol) in CH_2Cl_2 (360 mL) was added 4-octyne (8.0 g, 73 mmol) and the reaction mixture stirred overnight. The mixture was cooled to 0 °C, I_2 (20 g, 80 mmol) was added and the reaction was warmed to room temperature, stirred 1 h, then was quenched by pouring into 1 M HCl (200 mL) and ice (50 g). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane) to yield **4f** (9.3 g, 54%, >95% *E*). NMR spectral data were consistent with that reported.[62]



[(*E*)-2-Iodo-1-methyl-vinyl]-benzene (4g): Synthesized according to a reported procedure.[63]

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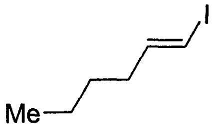
[61] Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709-713.

[62] Kropp, P. J.; Crawford, S. D. *J. Org. Chem.* **1994**, *59*, 3102-3112.

[63] Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639-6647.

(*Z*)-1-Iodo-hex-1-ene (4h): Synthesized according to a reported procedure.[64] NMR spectral data were consistent with that reported.[65]



(*E*)-1-Iodo-hex-1-ene (4i): Synthesized according to a reported procedure.[66]

Representative Procedure for the Propargyl/Allenyl Coupling of Alkenyl Iodides 4a-b, 4e-i. To a solution of 1-trimethylsilyl-1-propyne (1.5 mL, 10 mmol) in THF (21 mL) at −78 °C was added a 2.5 M solution of *n*-BuLi in hexane (4.6 mL) and TMEDA (1.7 mL, 11 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a −78 °C slurry of CuI (2.3 g, 12 mmol) and the additive (10 mmol) in THF (29 mL). The solution was warmed to −20 °C. The alkenyl iodide (7.1 mmol) was added and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The allenyl/propargyl ratio of the coupled products was determined by ^1H NMR analysis of the unpurified reaction mixture. The crude product was then purified by column chromatography.

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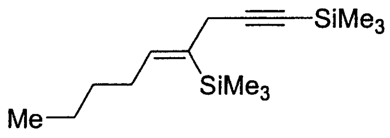
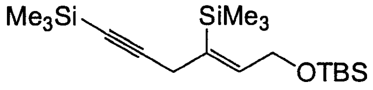
[64] (a) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274-5284. (b) Brown, H. C.; Blue, C. D.; Nelson, D. J.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6064-6067.

[65] Dieck, H. A.; Heck, F. R. *J. Org. Chem.* **1975**, *40*, 1083-1090.

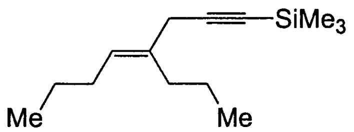
[66] Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138-2152.



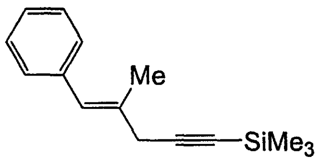
(*Z*)-1,4-Bis-trimethylsilanyl-non-4-en-1-yne (9a): $R_f = 0.31$ (hexane); IR (thin film, NaCl) 2958, 2859, 2174, 1618, 1466, 1420, 1250, 1054, 1010, 841, 759, 695, 642 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.24 (t, *J* = 7.6 Hz, 1H), 2.98 (s, 2H), 2.14 (app q, *J* = 13.7, 6.4 Hz, 2H), 1.36 (m, 4H), 0.92 (t, *J* = 6.7 Hz, 3H), 0.18 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.4, 132.7, 106.3, 87.6, 32.3, 31.8, 28.9, 22.7, 14.3, 0.4, 0.3; HR-MS (ESI) Calcd for $C_{15}H_{30}NaSi_2$ (M + Na)$^+$ 289.1778, found 289.1773.



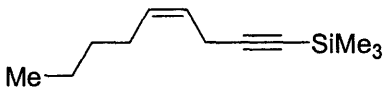
(*Z*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-1,4-bis-trimethylsilanyl-hex-4-en-1-yne (9b): $R_f = 0.41$ (5% EtOAc in hexane); IR (thin film, NaCl) 2957, 2857, 1645, 1472, 1250, 839, 759 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.36 (tt, *J* = 6.4, 1.5 Hz, 1H), 4.27 (tt, *J* = 6.2, 1.2 Hz, 2H), 3.02 (br d, *J* = 1.5 Hz, 2H), 0.91 (s, 9H), 0.17 (s, 9H), 0.16 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.8, 135.2, 105.7, 88.7, 63.3, 29.1, 26.7, 19.1, 0.8, 0.6, -4.3; HR-MS (ESI) Calcd for $C_{18}H_{38}NaOSi_3$ (M + Na)$^+$ 377.2123, found 377.2124.



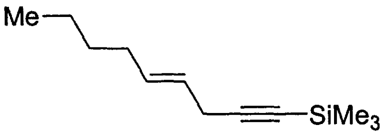
Trimethyl-[(*E*)-4-propyl-oct-4-en-1-ynyl]-silane (9f): $R_f = 0.39$ (hexane); IR (thin film, NaCl) 2960, 2932, 2873, 2176, 1250, 843, 760 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.46 (br t, *J* = 7.3 Hz, 1H), 2.94 (d, *J* = 1.2 Hz, 2H), 2.07 (t, *J* = 7.6 Hz, 2H), 2.01 (app q, *J* = 7.3 Hz, 2H), 1.45-1.34 (m, 4H), 0.91 (app q, *J* = 7.6 Hz, 6H), 0.17 (s, 9H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 133.7, 126.9, 105.3, 87.0, 32.6, 30.1, 27.9, 23.2, 21.6, 14.3, 14.1, 0.3; HR-MS (EI) Calcd for $C_{14}H_{26}Si$ (M)$^+$ 222.1798, found 222.1801.



Trimethyl-[(*E*)-5-phenyl-hex-4-en-1-ynyl]-silane (9g): R_f = 0.41 (5% EtOAc in hexane); IR (thin film, NaCl) 2960, 2931, 2873, 2176, 1249, 842, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.24 (m, 5H), 5.80 (tq, *J* = 6.1, 1.2 Hz, 1H), 3.17 (d, *J* = 6.7 Hz, 2H), 2.05 (br s, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 136.9, 128.5, 127.2, 126.0, 122.5, 105.3, 84.7, 26.6, 20.1, 0.4; HR-MS (ESI) Calcd for $C_{15}H_{21}Si$ $(M + H)^+$ 229.1407, found 229.1407.



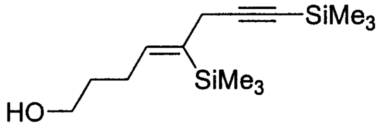
(*Z*)-Trimethyl-non-4-en-1-ynyl-silane (9h): R_f = 0.32 (hexane); IR (thin film, NaCl) 2959, 2929, 2177, 1250, 842, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51-5.38 (m, 2H), 2.99 (d, *J* = 6.4 Hz, 2H), 2.05 (app q, *J* = 6.4 Hz, 2H), 1.38-1.28 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2, 124.0, 105.7, 84.2, 31.7, 27.1, 22.6, 18.6, 14.2, 0.3; HR-MS (EI) Calcd for $C_{11}H_{19}Si$ $(M - CH_3)^+$ 179.1251, found 179.1252.



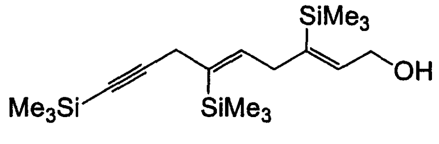
(*E*)-Trimethyl-non-4-en-1-ynyl-silane (9i): R_f = 0.24 (hexane); IR (thin film, NaCl) 2959, 2927, 1250, 842, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.39 (dt, *J* = 15.0, 5.5 Hz, 1H), 2.95 (d, *J* = 5.5 Hz, 2H), 2.03 (app q, *J* = 6.1 Hz, 2H), 1.39-1.29 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 132.2, 124.0, 105.7, 84.2, 31.7, 27.1, 22.6, 18.6, 14.2, 0.3; HR-MS (EI) Calcd for $C_{12}H_{22}Si$ $(M)^+$ 194.1485, found 194.1491.

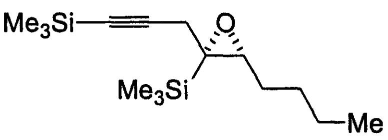
Representative Procedure for the Propargyl/Allenyl Coupling of Alkenyl Iodides 4c-d. To a solution of 1-trimethylsilyl-1-propyne (1.0 mL, 6.5 mmol) in THF (4.3 mL) at –78 °C was added a 2.5 M solution of *n*-BuLi in hexane (2.7 mL) and TMEDA (1.0 mL, 6.7 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a slurry of CuI (1.4 g, 7.2 mmol) and Bu_3P (1.6 mL, 6.5 mmol) in THF (5.7 mL) at –78 °C. The solution was warmed to –20 °C and the alkenyl iodide (1.4 mmol) was added. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography.

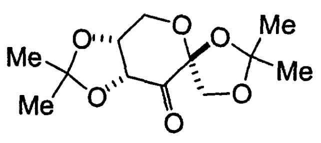


(*Z*)-5,8-Bis-trimethylsilanyl-oct-4-en-7-yn-1-ol (9c): R_f = 0.41 (20% EtOAc in hexane); IR (thin film, NaCl) 3314, 2956, 2898, 2173, 1618, 1420, 1249, 1053, 841, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (t, *J* = 7.6 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.99 (s, 2H), 2.24 (dt, *J* = 7.6, 7.3 Hz, 2H), 1.68 (m, 2H), 0.19 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 134.5, 106.5, 88.3, 63.3, 33.5, 29.4, 28.9, 0.8, 0.7; HR-MS (ESI) Calcd for $C_{14}H_{28}NaOSi_2$ $(M + Na)^+$ 291.1571, found 291.1577.



(2*Z*,5*Z*)-3,6,9-Tris-trimethylsilanyl-nona-2,5-dien-8-yn-ol (9d): R_f = 0.42 (20% EtOAc in hexane); IR (thin film, NaCl) 3313, 2956, 2898, 2173, 1249, 839 758 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.23 (tt, *J* = 7.3, 1.5 Hz, 1H), 6.13 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.22 (d, *J* = 7.0 Hz, 2H), 3.02 (d, *J* = 1.2 Hz, 2H), 2.96 (dd, *J* = 7.3, 1.2 Hz, 2H), 0.19 (s, 9H), 0.17 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.1, 141.9, 140.9, 134.5, 105.8, 87.9, 62.4, 39.1, 28.8, 0.49, 0.43, 0.20; HR-MS (ESI) Calcd for $C_{18}H_{36}NaOSi_3$ $(M + Na)^+$ 375.1966, found 375.1964.



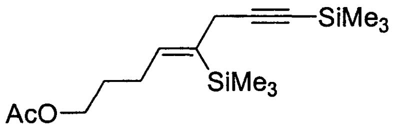


chiral ketone **A**

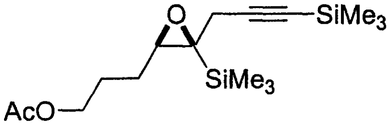
(2*S*,3*R*)-3-Butyl-2-trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-oxirane (11): Olefin **9a** (0.15 g, 0.56 mmol) was dissolved in CH_3CN/DMM (8.5 mL, 1:2 v:v) and a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_2O$ in 4.0 × 10^{-4} M Na_2-(EDTA) (5.6 mL), *n*-Bu_4NHSO_4 (0.12 g, 0.03 mmol), and chiral ketone **A** (90 mg, 0.36 mmol) were added. To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (0.57 g, 0.92 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (4.3 mL) and a 0.89 M solution of K_2CO_3 (4.3 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture stirred 20 min then was diluted with water (10 mL) and extracted with hexane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (1-3% EtOAc in hexane) to yield enantiomerically enriched epoxide **11** (80 mg, 51%): R_f = 0.17 (2.5% EtOAc in hexane); IR (thin film, NaCl) 2959, 2930, 2176, 1458, 1421, 1250, 1019, 841, 758 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.85 (dd, *J* = 6.4, 5.5 Hz, 1H), 2.78 (d, *J* = 16.8 Hz, 1H), 1.93 (d, *J* = 16.8 Hz, 1H), 1.65-1.59 (m, 1.54-1.36 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.19 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.9, 87.9, 64.4, 55.3, 30.4, 29.4, 28.9, 22.8, 14.3, 0.2, -1.0; HR-MS (ESI) Calcd for $C_{15}H_{30}NaOSi_2$ $(M + Na)^+$ 305.1727, found 305.1723.

The racemic epoxide was prepared using *m*-CPBA epoxidation: To a solution of **9a** (64 mg, 0.23 mmol) in CH_2Cl_2 (0.75 mL) at 0 °C was added *m*-CPBA (62 mg, 0.25 mmol). The resulting solution was warmed to room temperature and stirred 3.5 h. The reaction was quenched with a solution of 5% NaOH and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (1-3% EtOAc in hexane) to afford racemic epoxide **11** (53 mg, 81%).

The enantiomeric excess of epoxide **11** generated by the Shi asymmetric epoxidation was determined using $Eu(hfc)_3$ as a chiral shift reagent. Samples of the racemic epoxide and the enriched epoxide were prepared as 0.03 M solutions in $CDCl_3$ and to each sample was added 90 mol% $Eu(hfc)_3$ (er >95:5).



(*Z*)-Acetic acid 5,8-bis-trimethylsilanyl-oct-4-en-7-ynyl ester (12): To a solution of **9c** (16 g, 60 mmol) in CH_2Cl_2 (500 mL) at 0 °C was added Et_3N (12 g, 120 mmol), Ac_2O (11 mL, 120 mmol), and DMAP (0.7 g, 6.0 mmol). The resulting solution was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to afford acetate **12** (16.6 g, 90%): R_f = 0.55 (20% EtOAc in hexane); IR (thin film, NaCl) 2958, 2898, 2173, 1744, 1249, 1043, 841, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (t, *J* = 6.7 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.99 (s, 2H), 2.23 (dt, *J* = 7.6, 6.7 Hz, 2H), 2.06 (s, 3H), 1.76-1.70 (m, 2H), 0.18 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 142.9, 135.0, 106.3, 88.3, 64.7, 29.5, 29.4, 29.0, 21.7, 0.8, 0.6; HR-MS (ESI) Calcd for $C_{16}H_{30}NaO_2Si_2$ $(M + Na)^+$ 333.1677, found 333.1662.

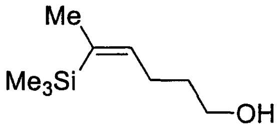


Acetic acid 3-[(2*R*,3*S*)-3-trimethylsilanyl-3-(3-trimethylsilanyl-prop-2-ynyl)-oxiranyl]-propyl ester (13): To acetate **12** (2.8 g, 8.9 mmol) was added CH_3CN/DMM (280 mL, 1:2 v:v), a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_2O$ in 4.0×10^{-4} M Na_2-(EDTA) (190 mL), *n*-Bu_4NHSO_4 (0.61 g, 1.8 mmol), and chiral ketone **A** (4.6 g, 17.8 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (22 g, 36 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (150 mL) and a 0.89 M solution of K_2CO_3 (150 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture stirred 20 min, then diluted with water (200 mL) and extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was then separated from the ketone catalyst (recovered for reuse) by column chromatography (20% EtOAc in hexane) to yield enantiomerically enriched epoxide **13** (2.0 g, 70%): $R_f = 0.46$ (20% EtOAc in hexane); $[\alpha]^{25}_D = -33.0$ (c = 0.91, in $CHCl_3$); IR (thin film, NaCl) 2960, 2176, 1743, 1367, 1250, 1025, 842, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.15 (m, 2H), 2.88 (dd, J = 7.9, 5.2 Hz, 1H), 2.79 (d, J = 17.1 Hz, 1H), 2.06 (s, 3H), 1.96 (d, J = 16.8 Hz, 1H), 1.90-1.73 (m, 3H), 1.58-1.51 (m, 1H), 0.20 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 103.1, 88.6, 64.6, 64.0, 55.9, 29.3, 27.8, 26.9, 21.7, 0.7, -0.5; HR-MS (ESI) Calcd for $C_{16}H_{31}O_3Si_2$ $(M + H)^+$ 327.1806, found 327.1805.

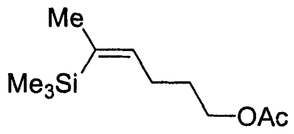
The racemic epoxide was prepared using *m*-CPBA epoxidation: To a solution of **12** (20 mg, 0.06 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added *m*-CPBA (30 mg, 0.09 mmol). The resulting solution was warmed to room temperature and stirred 3.5 h. The reaction was quenched with a solution of 5% NaOH and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$

and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford the racemic epoxide **13** (15 mg, 73%).

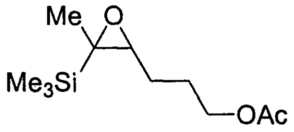
The enantiomeric ratio was determined by GC (Chiraldex-G-TA, 115 °C, 20 m × 0.25 mm, 25 psi) T_r(minor) 79 min, T_r(major) 82 min (er >95:5).



(*Z*)-5-Trimethylsilanyl-hex-4-en-1-ol (38): To a slurry of CuCN (3.2 g, 35 mmol) in Et_2O (45 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (50 mL) and the mixture stirred 15 min. A solution of alkenyl iodide **4c** (5.1 g, 18 mmol) in Et_2O (14 mL) was slowly added. The solution stirred 20 h at 0 °C then was carefully quenched with saturated NH_4Cl and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford olefin **38** (3.1 g, 99%): $R_f = 0.31$ (20% EtOAc in hexane); IR (thin film, NaCl) 3332, 2951, 1619, 1442, 1248, 1054, 838, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (dt, $J = 7.6$, 1.2 Hz, 1H), 3.65 (t, $J = 6.7$ Hz, 2H), 2.16 (q, $J = 14.9$, 7.6 Hz, 2H), 1.75 (d, $J = 1.2$ Hz, 3H), 1.63 (m, 2H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 135.6, 62.9, 33.3, 28.5, 24.9, 0.1; HR-MS (ESI) Calcd for $C_9H_{20}NaSiO$ $(M + Na)^+$ 195.1176, found 195.1188.

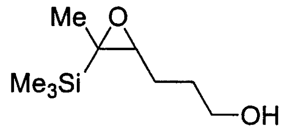


(*Z*)-Acetic acid 5-trimethylsilanyl-hex-4-enyl ester (39): To a solution of alcohol **38** (2.8 g, 14 mmol) in CH_2Cl_2 (130 mL) at 0 °C was added Et_3N (1.8 g, 18 mmol), Ac_2O (1.8 g, 18 mmol), and DMAP (0.2 g, 1.4 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford acetate **39** (2.8 g, 94%): $R_f = 0.65$ (20% EtOAc in hexane); IR (thin film, NaCl) 2954, 1744, 1620, 1441, 1366, 1248, 1042, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (tq, J = 12.5, 5.4, 2.7 Hz, 1H), 4.96 (t, J = 10.9 Hz, 2H), 2.19-2.11 (m, 2H), 2.04 (s, 3H), 1.74 (s, 3H), 1.72-1.63 (m, 2H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 141.0, 136.1, 64.3, 29.4, 28.6, 25.1, 21.4, 0.2; HR-MR (ESI) Calcd for $C_{11}H_{22}NaO_2Si$ $(M + Na)^+$ 237.1281, found 237.1271.



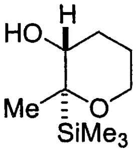
Acetic acid 3-(3-methyl-3-trimethylsilanyl-oxiranyl)-propyl ester (40): To a solution of **39** (1.0 g, 4.7 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added *m*-CPBA (0.8 g, 5.1 mmol). The resulting solution was warmed to room temperature and stirred 3.5 h. The reaction was quenched with a solution of 5% NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford epoxide **40** (0.8 g, 74%): $R_f = 0.39$ (20% EtOAc in hexane); IR (thin film, NaCl) 2958, 1742, 1448, 1368, 1251, 1039, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (m, 2H), 2.70 (dd, J = 7.6, 4.7 Hz, 1H), 2.04 (s, 3H), 1.87-1.66

(overlapping m, 3H), 1.54-1.45 (m, 1H), 1.21 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 65.8, 64.7, 55.6, 28.0, 27.0, 23.4, 21.7, -1.2; HR-MS (ESI) Calcd for $C_{11}H_{22}NaO_3Si$ $(M^+ + Na)^+$ 253.1230, found 253.1223.

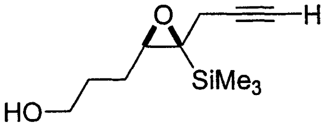


3-(3-Methyl-3-trimethylsilanyl-oxiranyl)-propan-1-ol (14e): To a solution of acetate **40** (0.8 g, 3.4 mmol) in THF (10 mL) and MeOH (10 mL) at 0 °C was added a 1.0 M solution of LiOH (10.2 mL) and the mixture stirred 20 min. The reaction was diluted with water and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford epoxide **14e** (0.6 g, 91%): R_f = 0.37 (50% EtOAc in hexane); IR (thin film, NaCl) 3419, 1957, 1446, 1251, 1062, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.1 Hz, 2H), 2.68 (dd, *J* = 8.2, 3.7 Hz; 1H), 1.77-1.65 (m, 3H), 1.42 (dt, *J* = 13.7, 7.9 Hz; 1H), 1.17 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.0, 62.3, 55.8, 30.3, 27.4, 22.9, -1.6; HR-MS (ESI) Calcd for $C_9H_{20}O_2Si$ $(M + Na)^+$ 211.1125, found 211.1119.

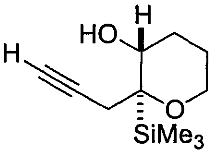
Representative Procedure for the Cyclization of 14e: To a solution of **14e** (100 mg, 0.5 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.5 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford pyran **15e** (67 mg, 67%).



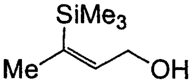
2-Methyl-2-trimethylsilanyl-tetrahydro-pyran-3-ol (15e): R$_f$ = 0.33 (20% EtOAc in hexane); IR (thin film, NaCl) 3444, 2952, 2866, 1246, 1076, 1033, 838 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.74 (td, *J* = 11.6, 3.1 Hz, 1H), 3.59-3.49 (m, 2H), 2.10 (d, *J* = 9 Hz, 1H), 2.03-1.96 (m, 1H), 1.92-1.83 (m, 1H), 1.68-1.62 (m, 1H), 1.47-1.41 (m, 1H), 1.24 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 72.9, 71.8, 60.1, 25.9, 21.5, 18.7, -2.2; HR-MS (ESI) Calcd for $C_9H_{20}NaO_2Si$ (M + Na)$^+$ 211.1125, found 211.1136.



3-[(2*R*,3*S*)-3-Prop-2-ynyl-3-trimethylsilanyl-oxiranyl]-propan-1-ol (17): To a solution of **13** (1.0 g, 3.1 mmol) in THF (10 mL) and MeOH (10 mL) at 0 °C was added a 1.0 M solution of LiOH (10 mL) and the mixture stirred 25 min. The reaction was diluted with water and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford 17 without the need for purification (0.6 g, 95%): R$_f$ = 0.16 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -21.6 (*c* = 1.67, in CHCl$_3$); IR (thin film, NaCl) 3419, 3310, 2957, 2119, 1438, 1422, 1251, 1062, 843, 759 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.72 (m, 2H), 2.94 (dd, *J* = 8.2, 4.0 Hz, 1H), 2.72 (dd, *J* = 16.8, 2.7 Hz, 2H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.86 (m, 2H), 1.78 (m, 2H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 80.6, 71.9, 64.1, 63.0, 56.0, 30.8, 27.8, 27.6, -0.6; HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_2Si$ (M + Na)$^+$ 235.1125, found 235.1117.

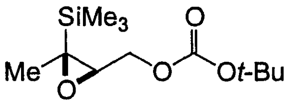


(2*R*,3*R*)-2-Prop-2-ynyl-2-trimethylsilanyl-tetrahydro-pyran-3-ol (18). To a solution of **17** (760 mg, 4.0 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.4 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford **18** as a colorless oil (0.61 g, 80%): R_f = 0.32 (20% EtOAc in hexane); $[\alpha]^{25}{}_D$ = -16.0 (*c* = 1.0, in $CHCl_3$); IR (thin film, NaCl) 3457, 3308, 2953, 2862, 2117, 1452, 1410, 1246, 1089, 1011, 986, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.88 (dd, *J* = 10.7, 6.7, 3.7 Hz, 1H), 3.66 (ddd, *J* = 11.9, 8.2, 3.4 Hz, 1H), 3.48 (dt, *J* = 11.9, 5.2 Hz, 1H), 2.76 (dd, *J* = 16.8, 2.7 Hz, 1H), 2.46 (d, *J* = 7.6 Hz, 1H), 2.39 (dd, *J* = 16.8, 2.7 Hz, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.93-1.87 (m, 1H), 1.82-1.74 (m, 1H), 1.69-1.63 (m, 1H), 1.49-1.42 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.2, 74.4, 71.6, 70.0, 61.4, 26.6, 23.8, 21.9, -0.7; HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_2Si$ $(M + Na)^+$ 235.1125, found 235.1120.



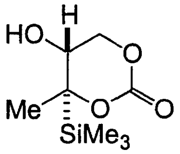
(*Z*)-3-Trimethylsilanyl-but-2-en-1-ol (41): To a slurry of CuCN (1.4 g, 16 mmol) in Et_2O (19 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (31 mL) and the mixture stirred 15 min. A solution of alkenyl iodide **37** (1.9 g, 7.0 mmol) in Et_2O (8.0 mL) was slowly added and the solution stirred 20 h at 0 °C. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford allylic alcohol **41** (0.7 g, 66%): R_f = 0.34 (20% EtOAc in hexane); IR (thin film, NaCl) 3329, 2954, 1440, 1249, 1051, 1001, 839, 757, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.16

(tq, $J = 7.0$, 1.7 Hz, 1H), 4.16 (app dt, $J = 5.8$, 1.1 Hz, 2 H), 1.82-1.81 (m, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 140.8, 62.8, 25.3, 0.6; HR-MS (ESI) Calcd for $C_7H_{16}NaOSi$ $(M + Na)^+$ 167.0863, found 167.0862.

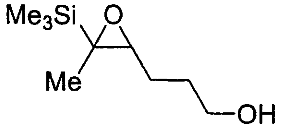


Carbonic acid *tert*-butyl ester (2*R*,3*S*)-3-methyl-3-trimethylsilanyl-oxiranylmethyl ester (19): To a solution of olefin **41** (0.7 g, 5.1 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (1.0 g, 10 mmol), BOC_2O (2.2 g, 10 mmol) and DMAP (60 mg, 0.5 mmol) and the solution stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were dissolved in water (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was carried to the next step without purification.

To the crude carbonate was added CH_3CN/DMM (60 mL, 1:2 v:v), a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_2O$ in 4.0×10^{-4} M Na_2-(EDTA) (40 mL), *n*-Bu_4NHSO_4 (0.13 g, 0.4 mmol), and chiral ketone **A** (1.0 g, 3.9 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (4.7 g, 7.6 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (32mL) and a 0.89 M solution of K_2CO_3 (32 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford epoxide **19** (0.34 g, 26% over two steps): $R_f = 0.43$ (10% EtOAc in hexane); IR (thin film, NaCl) 2960, 1745, 1370, 1279, 1254, 1163, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, $J = 11.6$, 2.7 Hz, 1H), 4.03 (dd, $J = 11.9$, 7.3 Hz, 1H), 3.05 (dd, $J = 7.3$, 4.0 Hz, 1H), 1.51 (s, 9H), 1.27 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 153.5, 82.7, 67.1, 62.3, 54.4, 27.9, 22.7, -1.8; HR-MS (ESI) Calcd for $C_{12}H_{24}NaO_4Si$ $(M + Na)^+$ 283.1336, found 283.1336.



(4*R*,5*R*)-5-Hydroxy-4-methyl-4-trimethylsilanyl-[1,3]dioxan-2-one (20): To a solution of epoxide **19** (20 mg, 0.08 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C was added $BF_3 \cdot Et_2O$ (0.20 g, 0.08 mmol). The reaction was warmed to room temperature and stirred 1 h. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The product of cyclization was not stable to silica gel but required no purification (13 mg, 80%): R_f = not stable to silica gel; $[\alpha]^{25}_D$ = -30.0 (*c* = 1.3, in $CHCl_3$); IR (thin film, NaCl) 3381, 2957, 1695, 1245, 1116, 1092, 844 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.65 (dd, *J* = 11.9, 1.8 Hz, 1H), 4.30 (dd, *J* = 11.9, 2.1 Hz, 1H), 3.94-3.91 (m, 1H), 2.18 (d, *J* = 6.1 Hz, 1H), 1.43 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 85.7, 70.3, 68.6, 29.5, 24.4, 22.9, -2.3; HR-MS Calcd for $C_8H_{20}NO_4$ $(M + NH_4)^+$ 222.1159, found 222.1142.



3-(3-Methyl-3-trimethylsilanyl-oxiranyl)-propan-1-ol (14f): To a slurry of CuCN (0.3 g, 3.4 mmol) in Et_2O (3.5 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (4.8 mL). After 15 min a solution of (*Z*)-5-iodo-5-trimethylsilanyl-pent-4-en-1-ol[67] (0.4 g, 1.5 mmol) in Et_2O (1.0 mL) was slowly added. The solution stirred 20 h at 0 °C then was carefully quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product

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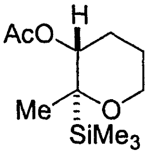
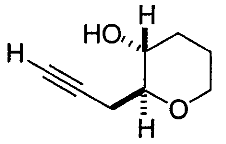
[67] Ma, S.; Liu, F.; Negishi, E. *Tetrahedron Lett.* **1997**, *38*, 3829-3832.

was passed through a plug of silica gel to remove the metal salts and was carried on to the next step without further purification (R_f = 0.31, 20% EtOAc in hexane).

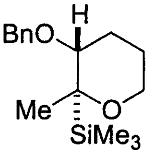
To a solution of the olefin (180 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was added *m*-CPBA (190 mg, 1.1 mmol) and the reaction mixture was warmed to room temperature and stirred 3.5 h. The reaction was quenched with 5% NaOH (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20-50% EtOAc in hexane) to afford **14f** (160 mg, 58% over two steps): R_f = 0.38 (50% EtOAc in hexane); IR (thin film, NaCl) 3423, 2956, 1449, 1249, 1055, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (m, 2H), 2.82 (dd, *J* = 7.0, 4.6 Hz, 1H), 1.78-1.73 (m, 3H), 1.68-1.62 (m, 1H), 1.24 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.7, 60.2, 55.1, 30.0, 24.9, 15.0, -3.9; HR-MS (ESI) Calcd for $C_9H_{24}NO_2Si$ $(M + NH_4)^+$ 206.1576, found 206.1578.



Acetic acid 2-methyl-2-trimethylsilanyl-tetrahydro-pyran-3-yl ester (21a): To a solution of pyran **15e** (0.3 g, 1.6 mmol) in CH_2Cl_2 (16 mL) at 0 °C was added Et_3N (0.3 g, 2.9 mmol), Ac_2O (0.3 g, 3.2 mmol), and DMAP (20 mg, 0.2 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to afford acetate **21a** (0.3 g, 90%): R_f = 0.48 (20% EtOAc in hexane); IR (thin film, NaCl) 2956, 2857, 1737, 1372, 1244, 1074, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (t, *J* = 4.0 Hz, 1H), 3.74 (dt, *J* = 11.3, 2.7 Hz, 1H), 3.59 (dt, *J* = 11.6, 3.7 Hz, 1H), 2.09 (s, 3H), 2.03-1.96 (m, 1H), 1.90-1.81 (m, 1H), 1.77-1.71 (m, 1H), 1.46-1.40 (m, 1H), 1.25 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.5, 74.6, 70.4, 60.4, 23.6, 22.0, 21.9, 18.9, -2.3; HR-MS (ESI) Calcd for $C_{11}H_{22}NaO_3Si$ $(M + Na)^+$ 253.1230, found 253.1240.



(2*S*,3*R*)-2-Prop-2-ynyl-tetrahydro-pyran-3-ol (22): To a solution of **18** (450 mg, 2.1 mmol) in THF (34 mL) was added a 1 M solution of TBAF in THF (8.3 mL). The reaction mixture stirred at room temperature overnight. The reaction was quenched with water and extracted with Et$_2$O (3 × 40 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (50% EtOAc in hexane) to afford desilylated product **22**[68] (270 mg, 90%): $[\alpha]^{25}_D = -24.8$ ($c = 0.44$, in CHCl$_3$).



(3-Benzyloxy-2-methyl-tetrahydro-pyran-2-yl)-trimethyl-silane (23): To a solution of pyran **15a** (0.1 g, 0.5 mmol) in THF (1.5 mL) at 0 °C was added NaH (50 mg, 2.1 mmol), benzyl bromide (0.1 g, 0.8 mmol) and TBAI (2 mg, 50 μmol). The solution was warmed to room temperature and stirred overnight. The reaction was quenched with water and extracted with Et$_2$O (3 × 5 mL). The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (5-10% EtOAc in hexane) to yield **23** (0.1 g, 68%): R_f = 0.51 (10% EtOAc in hexane); IR (thin film, NaCl) 2952, 2854, 1454, 1244, 1092, 1077, 1026, 837, 744, 697 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37-7.27 (m, 5H), 4.63 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 3.74 (ddd, J = 11.3, 7.6, 3.4 Hz, 1H), 3.56 (ddd, J = 10.4, 6.4, 3.7 Hz, 1H), 3.25 (dd, J = 6.4, 3.7 Hz, 1H), 1.99-1.79 (m, 3H), 1.49-1.42 (m, 1H), 1.25 (s, 3H), 0.08

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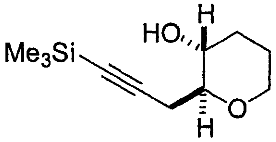
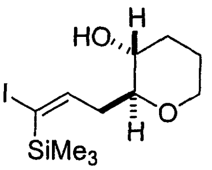
[68] Spectal data were identical to that reported for a racemic sample: Bowman, J. L.; McDonald, F. E. *J. Org. Chem.* **1998**, *63*, 3680-3682.

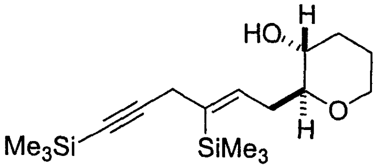
(s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 128.9, 128.4, 128.0, 81.5, 73.3, 71.3, 62.4, 23.5, 23.4, 21.7, -0.8; HR-MS (ESI) Calcd for $C_{16}H_{26}NaO_2Si$ $(M + Na)^+$ 301.1594, found 301.1601.



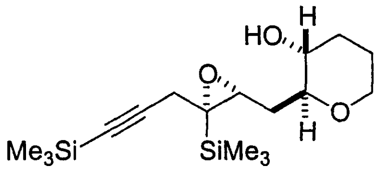
(2*S*,3*R*)-2-(3-Trimethylsilanyl-prop-2-ynyl)-tetrahydro-pyran-3-ol (24). To a solution of terminal alkyne **22** (170 mg, 1.2 mmol) in THF (8 mL) at −78 °C was added a 2.5 M solution of *n*-BuLi in hexane (1.1 mL). The solution was warmed to 0 °C, stirred 30 min, and was recooled to −78 °C. TMSCl (0.3 mL, 2.4 mmol) was added and the reaction was warmed to room temperature and stirred 20 h. The reaction was quenched with 1 M HCl and stirred 20 min. The aqueous layer was separated and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to yield **24** (210 mg, 81%): R_f = 0.13 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -18.0 (c = 1.67, in $CHCl_3$); IR (thin film, NaCl) 3424, 2958, 2857, 2177, 1250, 1096, 1068, 1038, 843, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (m, 1H), 3.57 (ddd, J = 13.7, 8.9, 4.9 Hz, 1H), 3.36 (m, 1H), 3.23 (m, 1H), 2.65 (dd, J = 17.1, 5.3 Hz, 1H), 2.59 (dd, J = 17.0, 5.3 Hz, 1H), 2.47 (br s, 1H), 2.15-2.09 (m, 1H), 1.74-1.66 (m, 2H), 1.47-1.39 (m, 1H), 0.165 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 103.4, 87.8, 79.9, 71.0, 68.0, 32.3, 25.5, 24.6, 0.2; HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_2Si$ $(M + Na)^+$ 235.1125, found 235.1133.



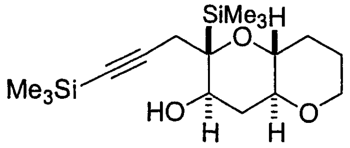
(2S,3*R*)-2-[(*E*)-3-Iodo-3-trimethylsilanyl-allyl]-tetrahydro-pyran-3-ol (25). To a solution of **24** (1.4 g, 6.4 mmol) in Et_2O (20 mL) was added a 1 M solution of DIBAL in hexane (16 mL). The resulting solution was heated 24 h at reflux, cooled to –78 °C, and diluted with Et_2O (5.0 mL). A solution of I_2 (6.5 g, 26 mmol) in Et_2O (10 mL) was added. After stirring 2 h at –78 °C the reaction was warmed to 0 °C and stirred 1 h. The mixture was carefully quenched by pouring into 1 M HCl (50 mL) and ice (15 g). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **25** (1.9 g, 88%, >95% *E*): $R_f = 0.37$ (20% EtOAc in hexane); $[\alpha]^{25}_D = -9.6$ (c = 0.83, in $CHCl_3$); IR (thin film, NaCl) 3402, 2939, 2853, 1249, 1096, 1036, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.6 Hz, 1H), 3.90 (m, 1H), 3.30 (m, 2H), 3.05 (dt, J = 8.2, 3.4 Hz, 1H), 2.64 (ddd, J = 15.3, 7.6, 3.4 Hz, 1H), 2.29 (m, 1H), 2.11 (m, 1H), 1.79-1.66 (m, 2H), 1.41 (m, 1H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.1, 109.4, 82.0, 70.8, 68.4, 38.1, 33.9, 26.2, 1.8; HR-MS (ESI) Calcd for $C_{11}H_{21}INaO_2Si$ $(M + Na)^+$ 363.0248, found 363.0256.



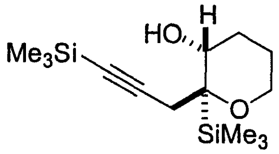
(2*S*,3*R*)-2-[(*Z*)-3,6-Bis-trimethylsilanyl-hex-2-en-5-ynyl]-tetrahydro-pyran-3-ol (26): To a solution of 1-trimethylsilyl-1-propyne (2.7 mL, 18 mmol) in THF (63 mL) at –78 °C was added a 2.5 M solution of *n*-BuLi in hexane (7.7 mL) and TMEDA (2.9 mL, 19 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred to a slurry of CuI (3.9 g, 20 mmol) and DMAP (2.3 g, 19 mmol) in THF (22 mL) at –78 °C. The solution was warmed to –20 °C. At that time alkenyl iodide **25** (1.4 g, 4.1 mmol) was added and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **26** (1.1 g, 79%): R_f = 0.24 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -6.0 (*c* = 0.33, in $CHCl_3$); IR (thin film, NaCl) 3441, 2957, 2948, 2173, 1620, 1250, 1098, 840.3, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 (tt, *J* = 6.4, 1.2 Hz, 1H), 3.91 (m, 1H), 3.40 (m, 1H), 3.36-3.31 (m, 1H), 3.10 (ddd, *J* = 11.9, 7.6, 4.3 Hz, 1H), 3.02 (d, *J* = 1.2 Hz, 2H), 2.70 (ddd, *J* = 14.9, 7.9, 4.3 Hz, 1H), 2.40-2.34 (m, 1H), 2.14-2.08 (m, 1H), 1.70-1.67 (m, 2H), 1.45-1.37 (m, 1H), 0.21 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 136.1, 106.5, 88.4, 82.9, 71.4, 68.4, 35.5, 33.6, 29.6, 26.3, 0.8, 0.7; HR-MS (ESI) Calcd for $C_{17}H_{32}NaO_2Si_2$ $(M + Na)^+$ 347.1883, found 347.1841.



(2*S*,3*R*)-2-[(2*R*,3*S*)-3-Trimethylsilanyl-3-(3-trimethylsilanyl-prop-2-ynyl)-oxiranylmethyl]-tetrahydro-pyran-3-ol (27): To olefin **26** (200 mg, 0.62 mmol) was added CH_3CN/DMM (20 mL, 1:2 v:v), a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_2O$ in 4.0 × 10^{-4} M Na_2-(EDTA) (13 mL), *n*-Bu_4NHSO_4 (40 mg, 0.1 mmol), and chiral ketone **A** (400 mg, 1.6 mmol). The solution was cooled to 0 °C, and to it was added, simultaneously over 1.5 h *via* syringe pump, a solution of Oxone® (1.9 g, 3.1 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (13 mL) and a 0.89 M solution of K_2CO_3 (13 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (30 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to yield epoxide **27** (100 mg, 50%, dr >95:5): R_f = 0.25 (20% EtOAc in hexane); $[\alpha]^{25}_{D}$ = -16.8 (*c* = 0.83, in $CHCl_3$); IR (thin film, NaCl) 3445, 2958, 2852, 2176, 1250, 1096, 842 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96-3.93 (m, 1H), 3.63 (ddd, *J* = 15.6, 9.5, 4.6 Hz, 1H), 3.38 (dt, *J* = 11.3, 4.0 Hz, 1H), 3.25 (ddd, *J* = 8.5, 5.2, 2.7 Hz, 1H), 3.19 (dd, *J* = 9.2, 2.4 Hz, 1H), 2.78 (d, *J* = 17.1 Hz, 1H), 2.26 (d, *J* = 4.9 Hz, 1H), 2.21 (dt, *J* = 15.0, 2.4 Hz, 1H), 2.12 (m, 1H), 2.00 (d, *J* = 16.8 Hz, 1H), 1.79-1.69 (m, 2H), 1.48-1.39 (m, 2H), 0.21 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.9, 86.6, 81.7, 70.1, 68.8, 61.1, 55.4, 33.7, 32.8, 29.3, 26.6, 0.7, -0.5; HR-MS (ESI) Calcd for $C_{17}H_{33}O_3Si_2$ $(M + H)^+$ 341.1963, found 341.1953.

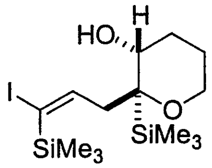


(2*R*,3*R*,4a*S*,8a*R*)-2-Trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-octahydropyrano[3,2-*b*]pyran-3-ol (28): To a solution of epoxysilane **27** (130 mg, 0.39 mmol) in CH_2Cl_2 (4.0 mL) at –42 °C was added $BF_3{\cdot}Et_2O$ (2 μL, 16 μmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford bispyran **28** (120 g, 91%): R_f = 0.24 (20%, EtOAc in hexane); $[\alpha]^{25}_{D}$ = -12.0 (*c* = 0.33, in $CHCl_3$); IR (thin film, NaCl) 3580, 2959, 2930, 2853, 2176, 1743, 1249, 1100, 842 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (ddd, *J* = 11.6, 5.5, 3.4 Hz, 1H), 3.92-3.89 (m, 1H), 3.41-3.35 (m, 1H), 3.13 (ddd, *J* = 13.4, 9.1, 4.6 Hz, 1H), 2.96 (ddd, *J* = 13.1, 8.9, 4.3 Hz, 1H), 2.74 (d, *J* = 3.4 Hz, 1H), 2.65 (d, *J* = 17.1 Hz, 1H), 2.44 (d, *J* = 17.1 Hz, 1H), 2.24 (dt, *J* = 11.9, 4.6 Hz, 1H), 2.01-1.96 (m, 1H), 1.81-1.68 (m, 3H), 1.38-1.30 (m, 1H), 0.25 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 106.2, 87.8, 77.9, 76.9, 75.0, 74.5, 68.0, 37.5, 30.6, 30.4, 26.3, 1.0, 0.5; HR-MS (ESI) Calcd for $C_{17}H_{32}NaO_3Si_2$ $(M + Na)^+$ 363.1782, found 363.1794.

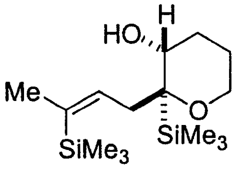


(2*R*,3*R*)-2-Trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-tetrahydro-pyran-3-ol (42): To olefin **9c** (6.4 g, 24 mmol) was added CH_3CN/DMM (760 mL, 1:2 v:v), a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_2O$ in 4.0×10^{-4} M Na_2-(EDTA) (500 mL), *n*-Bu_4NHSO_4 (1.6 g, 4.8 mmol), and chiral ketone **A** (12 g, 48 mmol). To this solution was added, simultaneously over 20 min *via* pressure equalizing addition funnels, a solution of Oxone® (59 g, 96 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (400 mL) and a 0.89 M solution of K_2CO_3 (400 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture stirred 10 min then diluted with water (800 mL) and extracted with hexane (3 × 400 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst by column chromatography and was carried on to the next step as a mixture.

To a solution of the crude epoxide in CH_2Cl_2 (150 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.3 mL, 1.2 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10-20% EtOAc in hexane) to afford **42** (0.9 g, 19% over two steps): R_f = 0.53 (20%, EtOAc in hexane); $[\alpha]^{25}_D = -20.0$ ($c = 2.0$, in $CHCl_3$); IR (thin film, NaCl) 3470, 2957, 2175, 1249, 1089, 1003, 842, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.68 (ddd, J = 12.2, 9.5, 3.4 Hz, 1H), 3.54 (app dt, J = 11.9, 4.6 Hz, 1H), 2.88 (d, J = 16.8 Hz, 1H), 2.45 (d, J = 17.1 Hz, 1H), 2.29 (d, J = 4.6 Hz, 1H), 2.02-1.95 (m, 1H), 1.89-1.80 (m, 1H), 1.74-1.68 (m, 1H), 1.52-1.45 (m, 1H), 0.20 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.4, 88.9, 75.2, 70.7, 61.6, 28.7, 25.7, 22.1, 0.6, -0.2; HR-MS (ESI) Calcd for $C_{14}H_{28}NaO_2Si_2$ $(M + Na)^+$ 307.1520, found 307.1517.

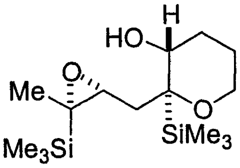


(2*R*,3*R*)-2-[(*E*)-3-Iodo-3-trimethylsilanyl-allyl]-2-trimethylsilanyl-tetrahydro-pyran-3-ol (32): To a solution of **42** (3.5 g, 12 mmol) in Et_2O (35 mL) was added a 1 M solution of DIBAL in hexane (30 mL). The resulting solution was heated 24 h at reflux then cooled to –78 °C and diluted with Et_2O (10 mL). A solution of I_2 (13 g, 49 mmol) in Et_2O (20 mL) was added. After stirring 2 h at –78 °C the reaction was warmed to 0 °C and stirred 1 h. The mixture was quenched by pouring into 1 M HCl (50 mL) and ice (15 g). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10-20% EtOAc in hexane) to yield alkenyl iodide **32** (3.2 g, 62%, >95% *E*): $R_f = 0.50$ (20%, EtOAc in hexane); $[\alpha]^{25}_{D} = -10.5$ ($c = 15.8$, in $CHCl_3$); IR (thin film, NaCl) 3476, 2955, 2866, 1394, 1251, 1070, 837 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, $J = 7.9, 6.1$ Hz, 1H), 3.71-3.62 (m, 2H), 3.49 (ddd, $J = 11.9$, 8.5, 3.4 Hz, 1H), 2.55 (15.9, 7.9 Hz, 1H), 2.44 (dd, $J = 15.9, 6.1$ Hz, 1H), 1.94-1.88 (m, 1H), 1.78-1.66 (m, 2H), 1.59-1.52 (m, 1H), 0.28 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 109.4, 75.9, 71.6, 63.3, 39.8, 29.2, 24.1, 1.8, 0.6; HR-MS (ESI) Calcd for $C_{14}H_{29}INaO_2Si_2$ $(M + Na)^+$ 435.0643, found 435.0636.



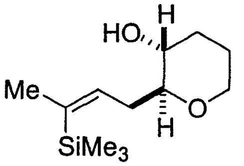
(2*R*,3*R*)-2-Trimethylsilanyl-2-((*Z*)-3-trimethylsilanyl-but-2-enyl)-tetrahydro-pyran-3-ol (33): To a slurry of CuCN (0.4 g, 3.2 mmol) in Et_2O (6.0 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (4.9 mL). After 15 min a solution of alkenyl iodide **32** (0.6 g, 1.4 mmol) in Et_2O (3.0 mL) was slowly added. The solution was maintained at 0

°C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10-20% EtOAc in hexane) to yield olefin **33** (0.4 g, 91%): R_f = 0.64 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -17.0 (*c* = 1.2, in $CHCl_3$); IR (thin film, NaCl) 3486, 2953, 2932, 2869, 1249, 1086, 1069, 1016, 835, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (app tq, *J* = 6.9, 1.9 Hz, 1H), 3.75-3.66 (m, 2H), 3.51 (ddd, *J* = 10.7, 6.3, 3.6 Hz, 1H), 2.56-2.51 (m, 2H), 1.99-1.88 (m, 1H), 1.85-1.62 (m, 3H) 1.77 (d, *J* = 1.7 Hz, 3H), 1.56-1.44 (m, 1H), 0.15 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 137.1, 76.4, 71.0, 62.5, 35.7, 28.1, 25.6, 23.3, 0.4, 0.3; HR-MS (ESI) Calcd for $C_{15}H_{32}NaO_2Si_2$ $(M + Na)^+$ 323.1833, found 323.1831.



(2*S*,3*R*)-2-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-2-trimethylsilanyl-tetrahydro-pyran-3-ol (29): To olefin **33** (0.14 g, 0.46 mmol) was added CH_3CN/DMM (16 mL, 1:2 v:v), a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_2O$ in 4.0 × 10^{-4} M Na_2-(EDTA) (10.2 mL), *n*-Bu_4NHSO_4 (0.03 g, 0.09 mmol), and chiral ketone **A** (0.22 g, 0.87 mmol). To this solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (0.22 g, 0.87 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (7.5 mL) and a 0.89 M solution of K_2CO_3 (7.5 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture stirred 10 min then diluted with water (50 mL) and extracted with hexane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to yield **29** (0.09 g, 62%, dr >95:5): R_f = 0.49 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = +18.3 (*c* = 6.0, in $CHCl_3$); IR (thin film, NaCl) 3436, 2955, 2854, 1440, 1408, 1370, 1250, 1091, 1025, 837, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (app dt, *J* = 9.8, 4.6 Hz, 1H), 3.79-3.74 (m, 1H), 3.55 (app dt, *J* = 10.4, 3.0 Hz, 1H), 3.09 (dd,

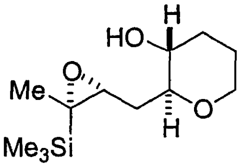
J = 8.5, 1.2 Hz, 1H), 2.10 (d, J = 5.5 Hz, 1H), 2.06 (dd, J = 15.0, 1.2 Hz, 1H), 1.97-1.93 (m, 1H), 1.78-1.70 (m, 4H), 1.24 (s, 3H), 0.18 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.1, 72.0, 64.6, 61.9, 54.2, 36.3, 29.4, 25.6, 23.3, 0.9, -1.1; HR-MS (ESI) Calcd for $C_{15}H_{32}NaO_3Si_2$ $(M + Na)^+$ 339.1782, found 339.1772.



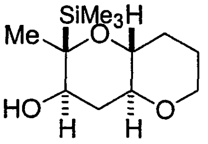
(2*S*,3*R*)-2-((*Z*)-3-Trimethylsilyanyl-but-2-enyl)-tetrahydro-pyran-3-ol (34): To a slurry of CuCN (0.6 g, 7.0 mmol) in Et_2O (9.0 mL) at 0 °C was added a 1.6 M solution of MeLi in Et_2O (8.7 mL). After 15 min a solution of alkenyl iodide **25** (1.0 g, 3.1 mmol) in Et_2O (3.0 mL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **34** (0.6 g, 89%).

Alternatively, to a solution of **33** (0.20 g, 0.67 mmol) in THF (6.5 mL) was added a 1 M solution of TBAF in THF (2.0 mL). The reaction mixture stirred at room temperature overnight then was quenched with water (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexane) to afford monodesilylated **34** (0.14 g, 95%): R_f = 0.27 (20%, EtOAc in hexane); $[\alpha]^{25}_D$ = -23.9 (*c* = 9.2, in $CHCl_3$); IR (thin film, NaCl) 3422, 2945, 2853, 1618, 1442, 1248, 1097, 1035, 838, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (app tq, J = 6.3, 1.7 Hz, 1H), 3.91-3.87 (m, 1H), 3.37 (ddd, J = 13.6, 8.8, 4.7 Hz, 1H), 3.31 (dt, J = 11.1, 3.5 Hz, 1H) 3.06 (ddd, J = 11.7, 7.2, 4.6 Hz, 1H), 2.66-1.60 (m, 1H), 2.34-2.27 (m, 1H), 2.11-2.05 (m, 1H), 1.78 (d, J = 1.5 Hz, 3H), 1.70-1.63 (m, 1H), 1.43-1.34 (m, 1H), 0.15 (s, 9H); ^{13}C

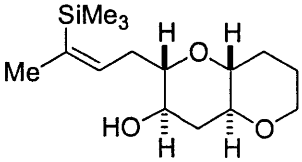
NMR (125 MHz, $CDCl_3$) δ 138.8, 138.0, 83.0, 78.0, 71.6, 68.4, 35.8, 33.4, 26.2, 25.6, 0.5; HR-MS (ESI) Calcd for $C_{12}H_{24}NaO_2Si$ $(M + Na)^+$ 251.1438, found 251.1433.



(2*S*,3*R*)-2-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-tetrahydro-pyran-3-ol (30): To olefin **34** (0.3 g, 1.3 mmol) was added CH_3CN/DMM (40 mL, 1:2 v:v), a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_2O$ in 4.0×10^{-4} M Na_2-(EDTA) (26 mL), *n*-Bu_4NHSO_4 (80 mg, 0.24 mmol), and chiral ketone **A** (0.6 g, 2.4 mmol). To this solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (2.9 g, 4.8 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (20 mL) and a 0.89 M solution of K_2CO_3 (20 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture stirred 10 min then diluted with water (10 mL) and extracted with hexane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (10-20% EtOAc in hexane) to yield **30** (0.24 g, 75%, dr 9:1): $R_f = 0.46$ (20% EtOAc in hexane); $[\alpha]^{25}_D = +8.6$ ($c = 4.7$, in $CHCl_3$); IR (thin film, NaCl) 3438, 2956, 2853, 1440, 1251, 1097, 1039, 841, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.92 (m, 1H), 3.64 (ddd, J = 15.4, 9.2, 4.4 Hz, 1H), 3.36 (app dt, J = 11.3, 3.7 Hz, 1H), 3.22 (ddd, J = 8.9, 5.3, 2.9 Hz, 1H), 3.01 (dd, J = 9.5, 2.4 Hz, 1H), 2.37 (d, J = 4.7 Hz, 1H), 2.16-2.09 (m, 2H), 1.77-1.66 (m, 2H), 1.47-1.38 (m, 1H), 1.24 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.9, 70.1, 68.8, 62.7, 55.3, 33.8, 32.7, 26.6, 23.3, -1.1; HR-MS (ESI) Calcd for $C_{12}H_{24}NaO_3Si$ $(M + Na)^+$ 267.1387, found 267.1385.



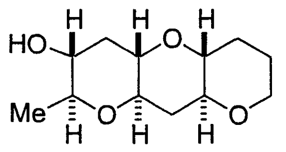
(2*R*,3*R*,4a*S*,8a*R*)-2-Methyl-2-trimethylsilanyl-octahydro-pyrano[3,2-*b*]pyran-3-ol (31): To a solution of epoxysilane **30** (0.22 g, 0.92 mmol) in CH_2Cl_2 (10 mL) at –42 °C was added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.09 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20-50% EtOAc in hexane) to afford **31** (0.20 g, 91%): $R_f = 0.48$ (50%, EtOAc in hexane); $[\alpha]^{25}_D = +20.9$ ($c = 4.3$, in $CHCl_3$); IR (thin film, NaCl) 3444, 2953, 2865, 1453, 1347, 1248, 1100, 1069, 1039, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93-3.89 (m, 1H), 3.58 (dd, $J = 11.6, 5.2$ Hz, 1H), 3.41-3.35 (m, 1H), 3.12 (ddd, $J = 13.1, 8.9, 4.3$ Hz, 1H), 2.98 (ddd, $J = 13.4, 9.2, 4.6$ Hz, 1H), 2.19 (app dt, $J = 11.6, 4.9$ Hz, 1H), 2.03-1.97 (m, 1H), 1.80-1.69 (m, 3H), 1.40-1.31 (m, 1H), 1.28 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.6, 77.0, 75.5, 74.3, 68.0, 37.3, 29.9, 25.9, 25.2, 0.3; HR-MS (ESI) Calcd for $C_{12}H_{24}NaO_3Si$ $(M + Na)^+$ 267.1387, found 267.1385.



(2*S*,3*R*,5*S*,10*R*)-2-[(*Z*)-3-Trimethylsilanyl-but-2-enyl]-octahydro-pyrano[3,2-*b*]pyran-3-ol (35): To a solution of **31** (16 mg, 47 μmol) in Et_2O (1.5 mL) was added a 1 M solution of DIBAL in hexane (0.3 mL). The resulting solution was heated for 24 h at reflux, cooled to –78 °C and diluted with Et_2O (0.5 mL). A solution of I_2 (47 mg, 0.2 mmol) in Et_2O (1.0 mL) was added. After stirring at –78 °C for 4 h, the reaction was warmed to 0 °C and stirred 4 h. The mixture was carefully quenched by pouring into 1 M HCl (5 mL) and ice (3 g). The aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane; R_f = 0.32, 20% EtOAc in hexane) and a portion was carried to the next step.

To a slurry of CuCN (6 mg, 70 μmol) in Et_2O (0.5 mL) at 0 °C was added a 1.2 M solution of MeLi in Et_2O (120 μL). After 15 min a solution of the alkenyl iodide (15 mg, 30 μmol) in Et_2O (300 μL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was passed through a plug of silica gel to remove the metal salts and carried on to the next step without further purification (R_f = 0.41, 20% EtOAc in hexane).

To the methylated olefin (7 mg, 21 μmol) in THF (0.5 mL) was added a 1 M solution of TBAF in THF (40 μL) and the reaction mixture stirred at room temperature overnight. The reaction was quenched with water and the aqueous layer was separated and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (50% EtOAc in hexane) to afford monodesilylated **35** (6 mg, 46% over 3 steps): R_f = 0.66 (50% EtOAc in hexane); $[\alpha]^{25}_{D} = +12.0$ (c = 0.17, in $CHCl_3$); IR (thin film, NaCl) 3435, 2926, 2853, 1721 (OH overtone), 1618, 1247, 1099, 1023, 837 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 6.13 (m, 1H), 3.86 (m, 1H), 3.45 (m, 1H), 3.35 (m, 1H), 3.12 (ddd, J = 11.6, 7.6, 4.0 Hz, 1H), 2.96 (m, 2H), 2.62 (m, 1H), 2.27 (m, 2H), 2.03 (m, 1H), 1.79 (d, J = 1.2 Hz, 3H), 1.70 (m, 2H), 1.46 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 138.8, 123.6, 82.7, 78.4, 77.5, 70.8, 68.3, 39.8, 35.2, 29.9, 26.2, 25.2, 0.1; HR-MS (ESI) Calcd for $C_{15}H_{28}NaO_3Si$ $(M + Na)^+$ 307.1700, found 307.1710.



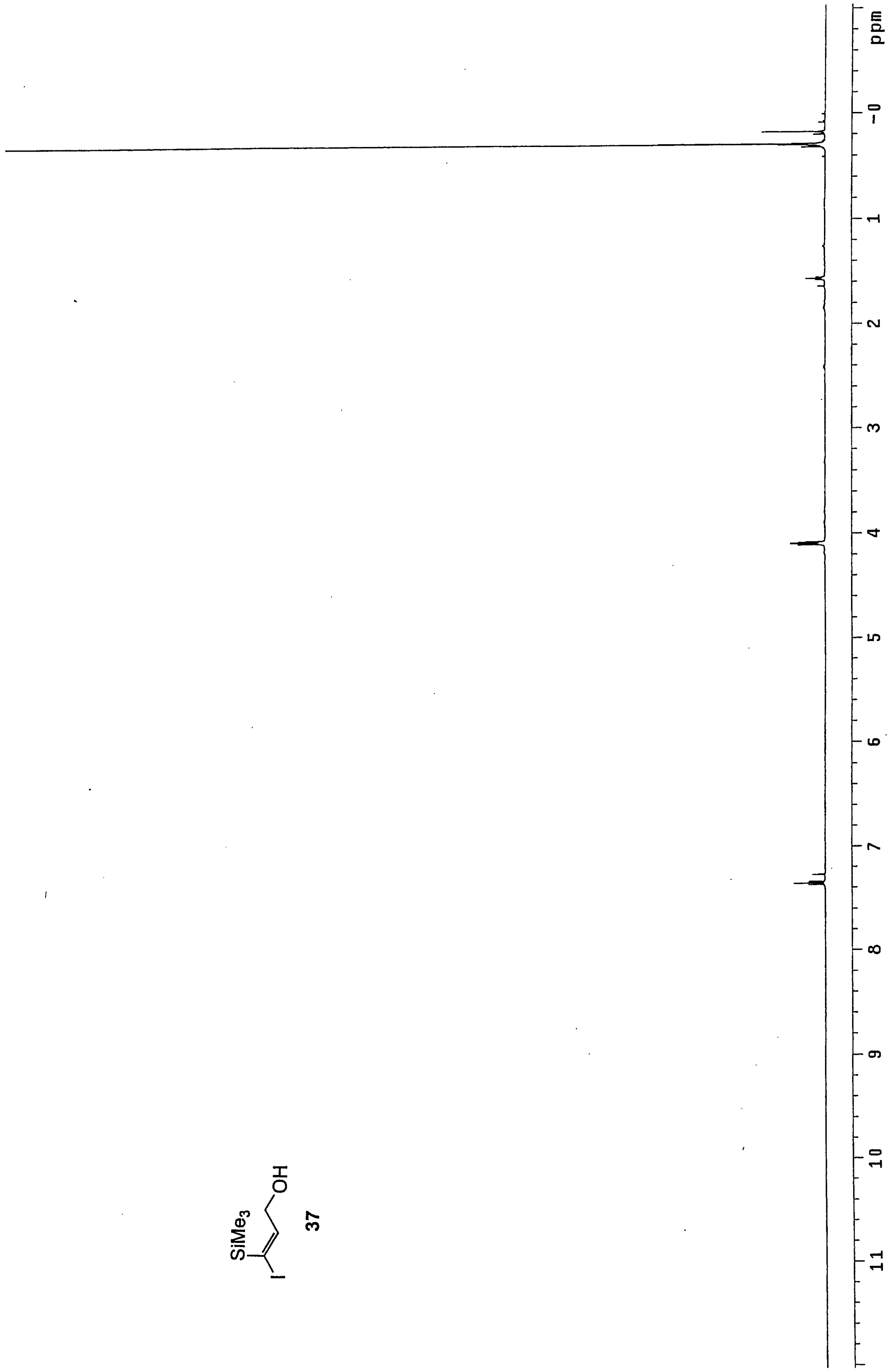
(2*S*,3*R*,4a*S*,8a*S*,9a*R*,10a*R*)-2-Methyl-decahydro-1,8,10-trioxa-anthracen-3-ol (36): To a solution of **35** (4 mg, 14 μmol) in CH_3CN/DMM (0.5 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_2O$ in 4.0×10^{-4} M Na_2-(EDTA) (0.3 mL), *n*-Bu_4NHSO_4 (0.1 mg, 3 μmol), and chiral ketone **A** (7 mg, 0.03 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (3.6 mg, 0.06 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (0.2 mL) and a 0.89 M solution of K_2CO_3 (0.20 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (0.5 mL) and extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The product was separated from the ketone catalyst by column chromatography (50% EtOAc in hexane) and carried on to the next step without further purification.

To a solution of the epoxide in CH_2Cl_2 (0.5 mL) at –42 °C was added $BF_3 \cdot Et_2O$ (2 μL, 16 μmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated $NaHCO_3$ and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The unpurified reaction mixture was carried on to the next step (R_f = 0.35, 50% EtOAc in hexane).

To a solution of the tristetrahydropyran in THF (0.5 mL) was added a 1 M solution of TBAF in THF (0.2 mL) and the reaction mixture stirred at room temperature overnight. At that time the solution was diluted with water (2 mL). The aqueous layer was separated and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude reaction mixture was purified by column chromatography (50-80% EtOAc in hexane) to afford **36** (2 mg, 62% over 3 steps): R_f = 0.26 (75% EtOAc in hexane); $[\alpha]^{25}_D = +4.5$ (c = 0.50, in $CHCl_3$); IR (thin film, NaCl) 3364, 2927, 2855, 1460, 1113, 1080, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93 (m, 1H), 3.39 (m, 2H), 3.24 (dq, J = 9.2, 6.1 Hz, 1H), 3.15-

3.02 (m, 4H), 2.39 (dt, *J* = 11.3, 4.3 Hz, 1H), 2.32 (dt, *J* = 11.6, 3.7 Hz, 1H), 2.09-2.06 (m, 1H), 1.77-1.72 (m, 2H), 1.54-1.44 (m, 4 H), 1.31 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 78.9, 78.8, 78.0, 77.3, 77.2, 72.1, 68.5, 39.3, 36.4, 30.0, 26.3, 18.3; HR-MS (ESI) Calcd for $C_{12}H_{21}O_4$ $(M + H)^+$ 229.1434, found 229.1441.

Chapter 1: Spectra



37

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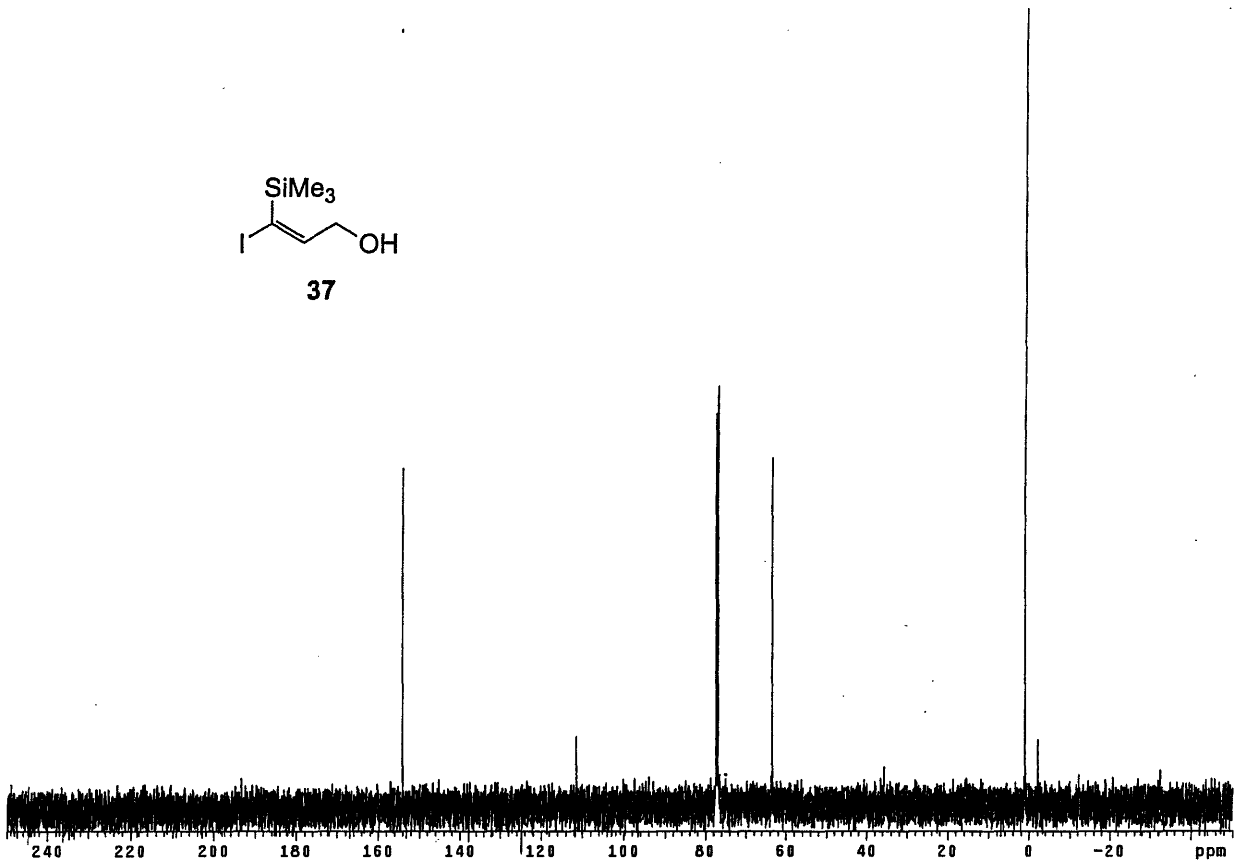
OH

37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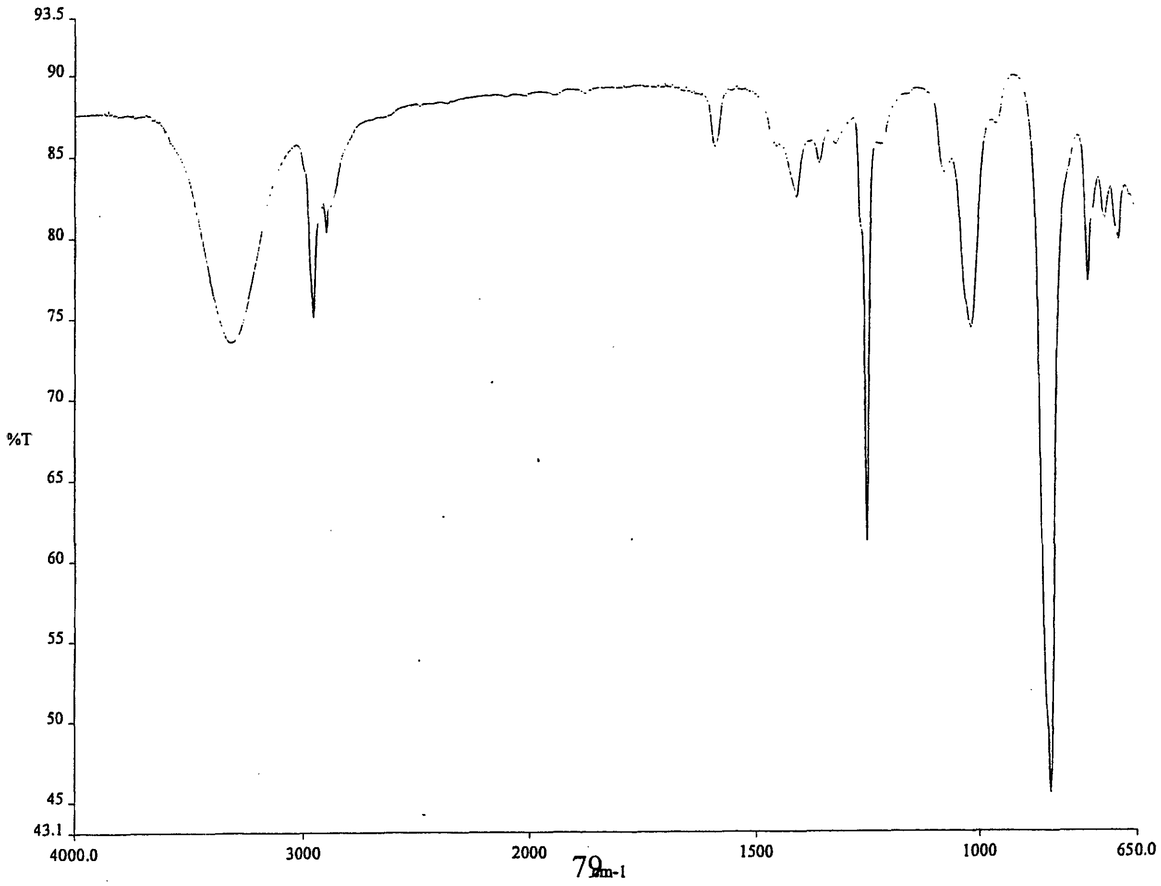
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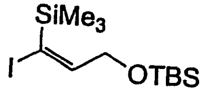

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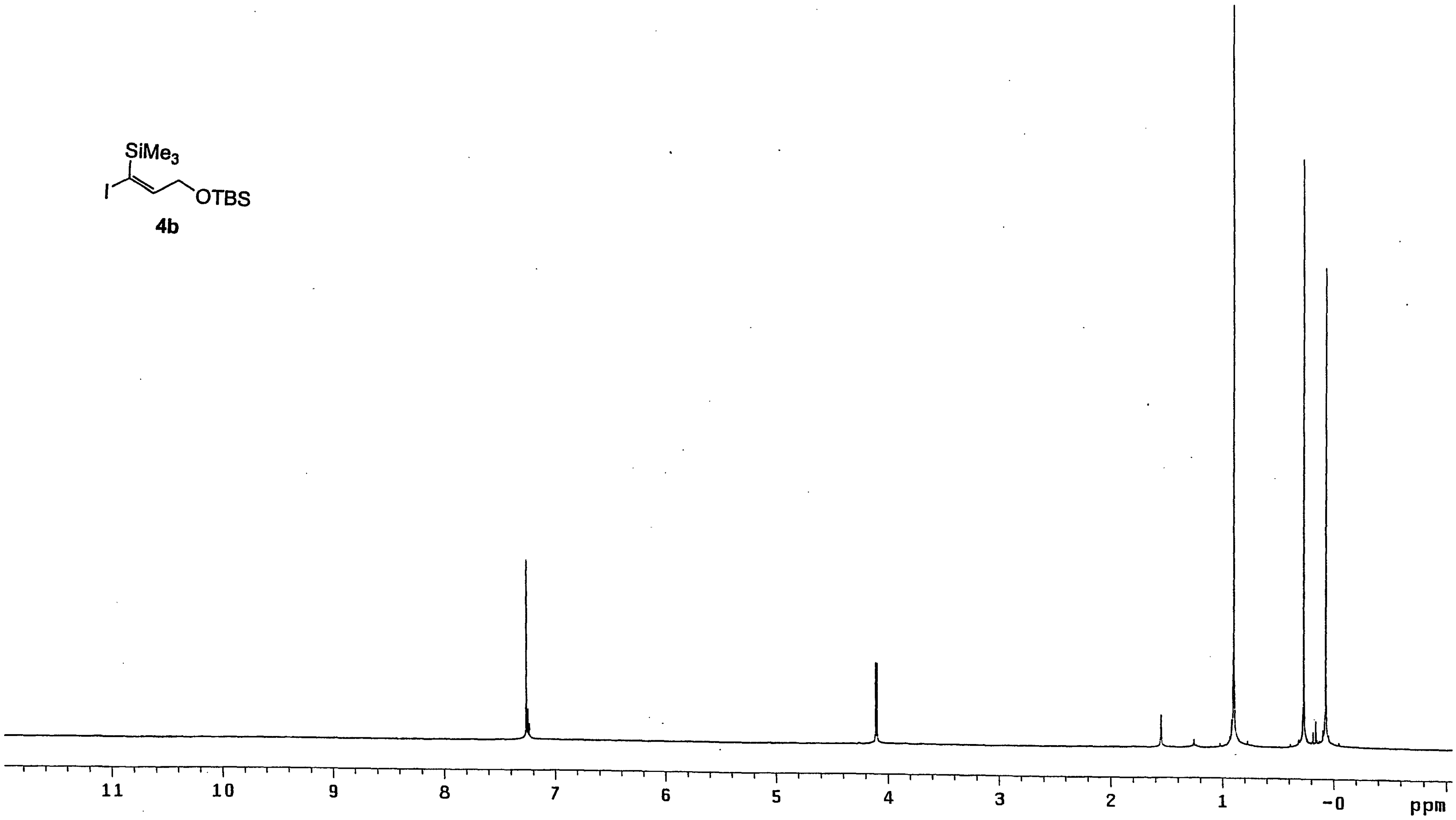

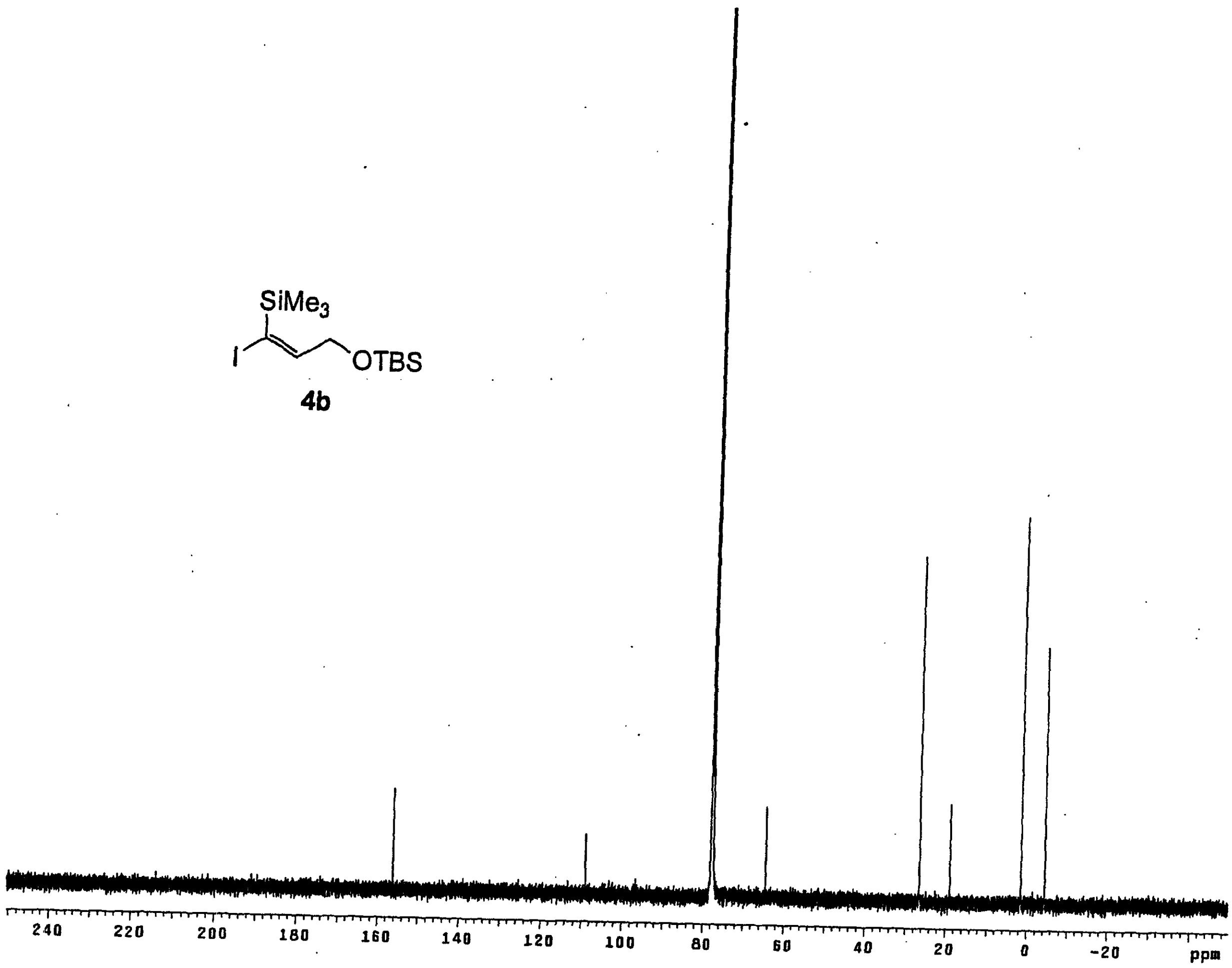
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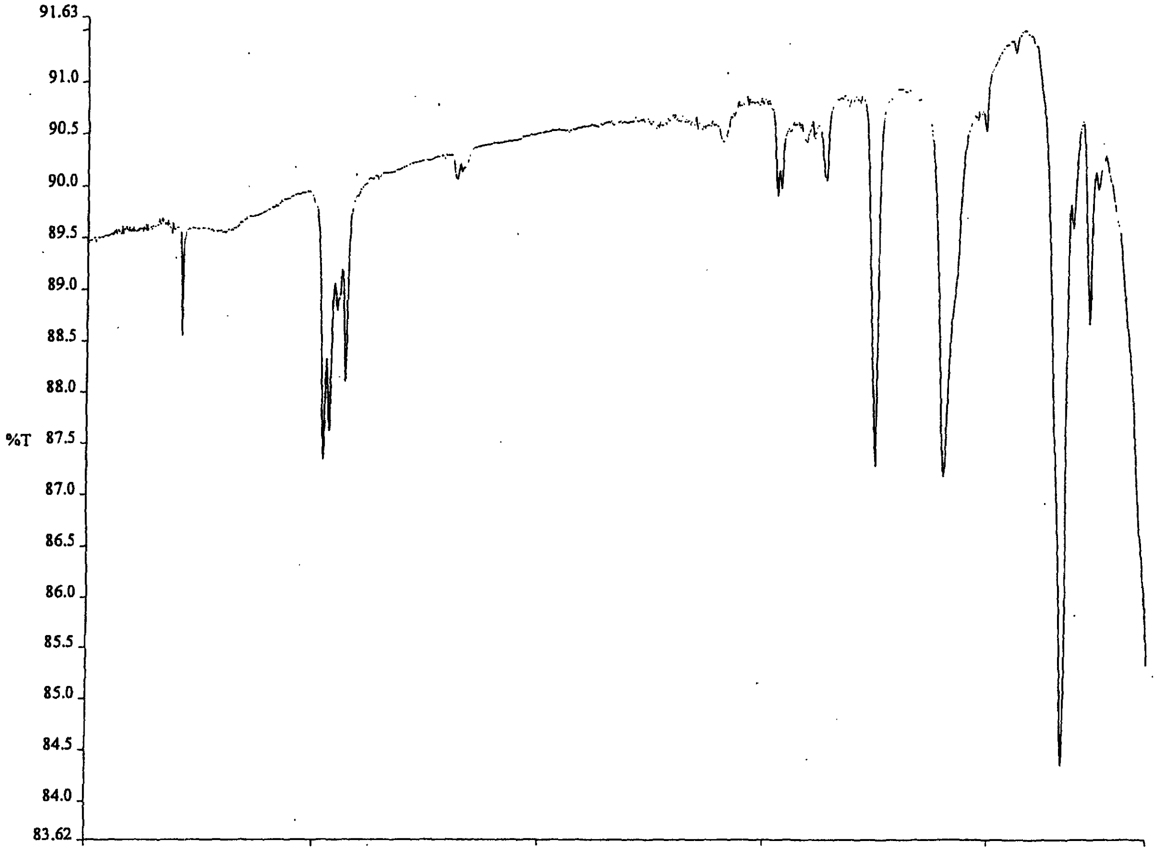
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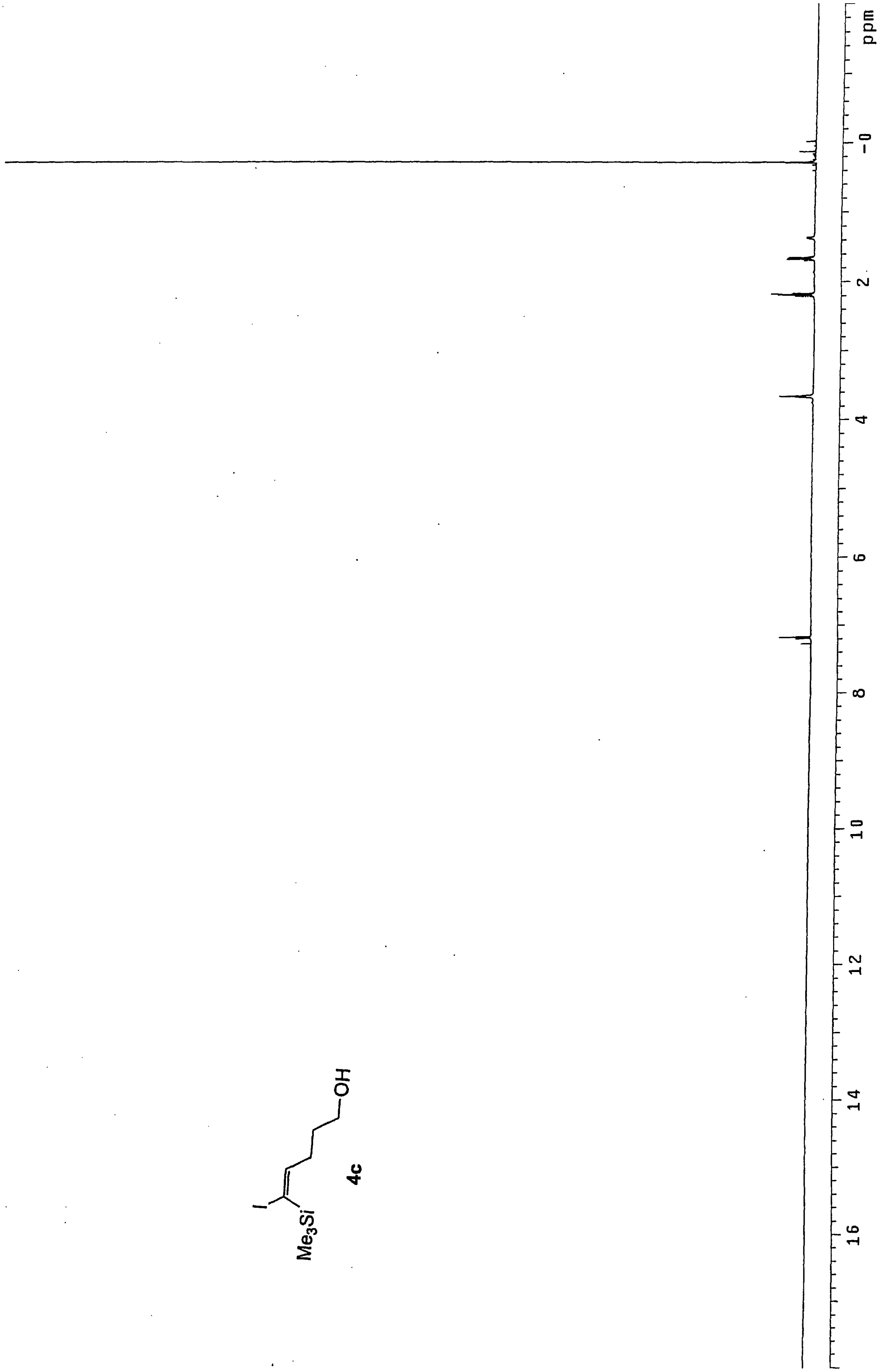

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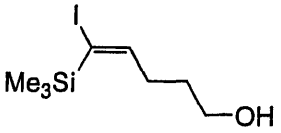
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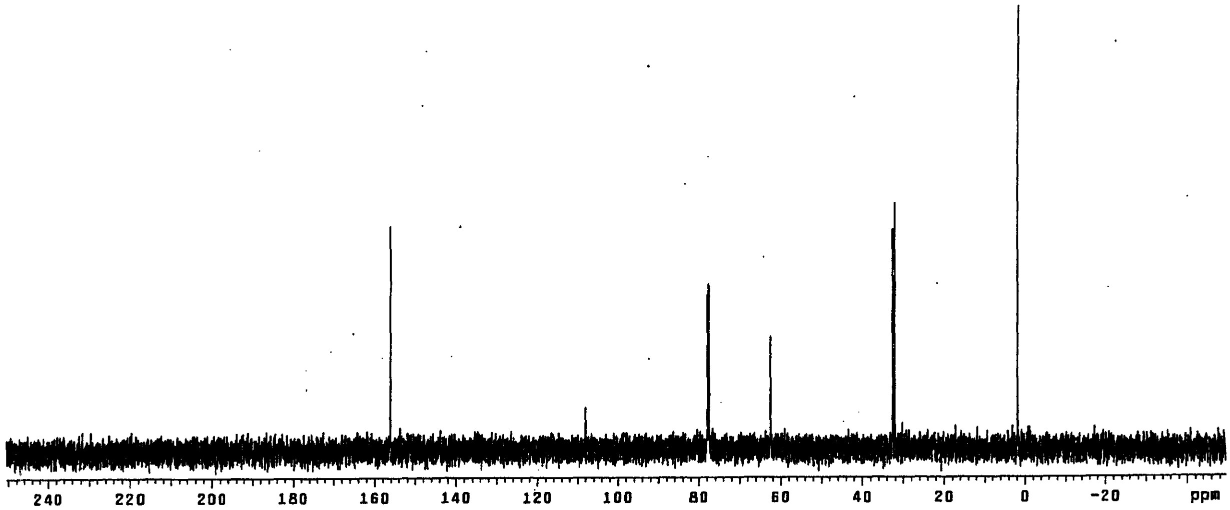
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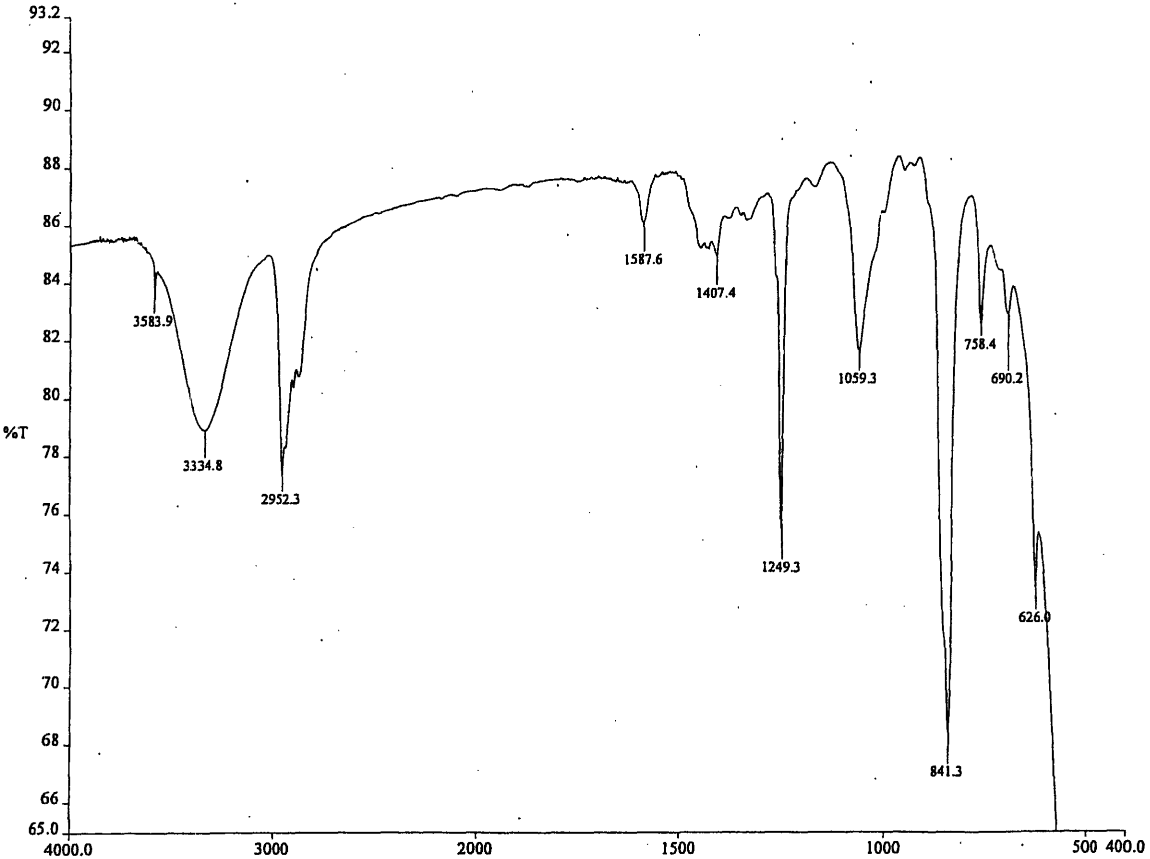
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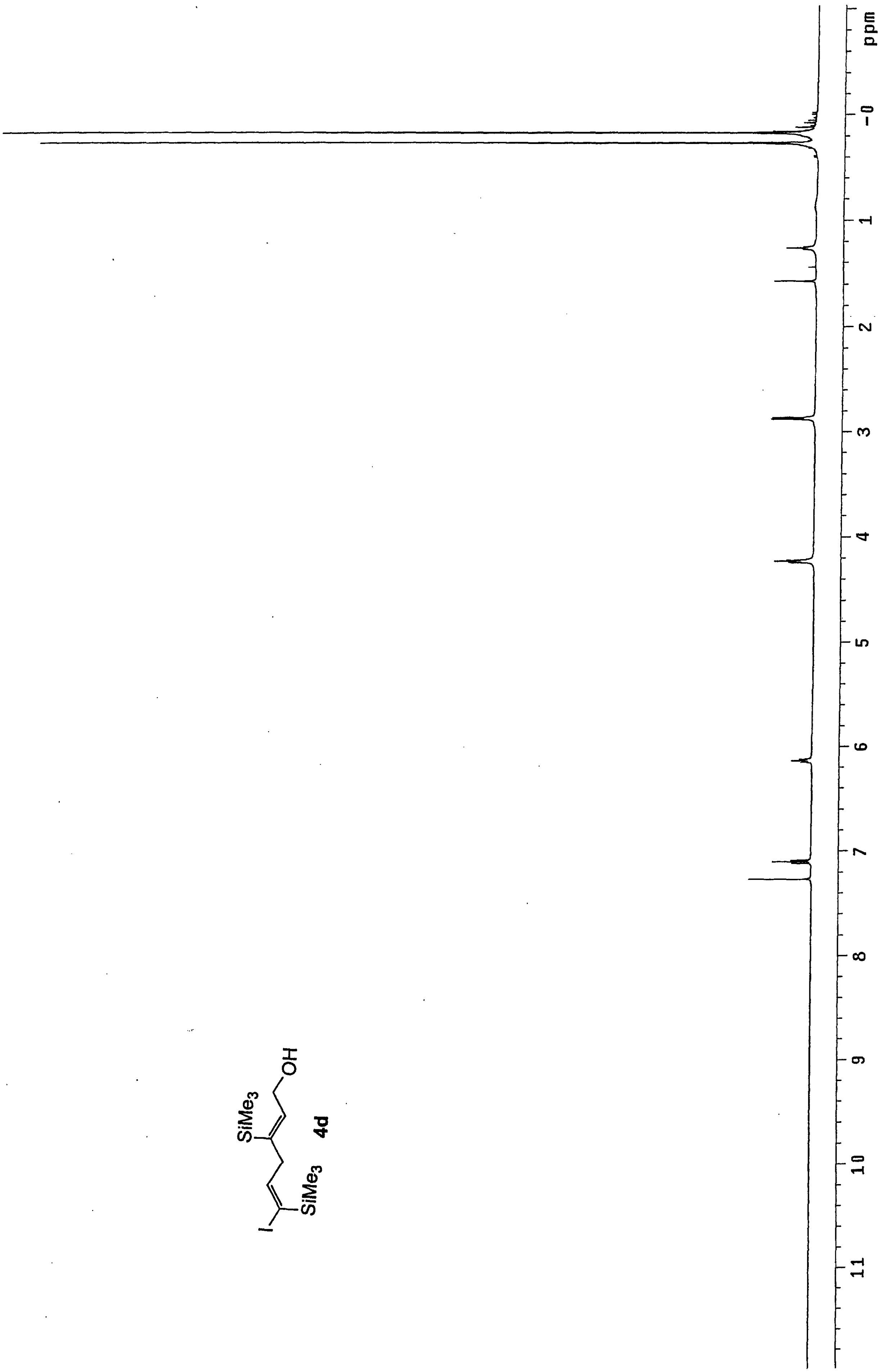

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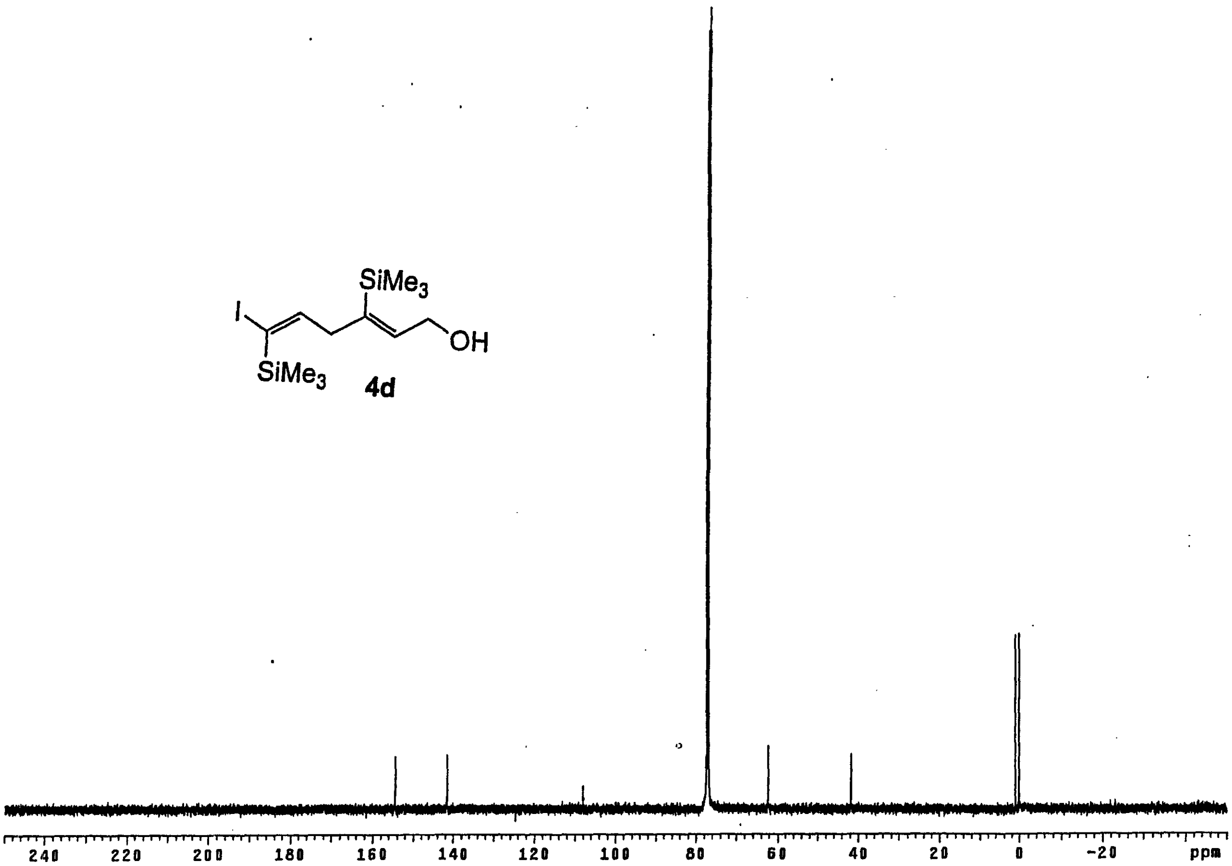
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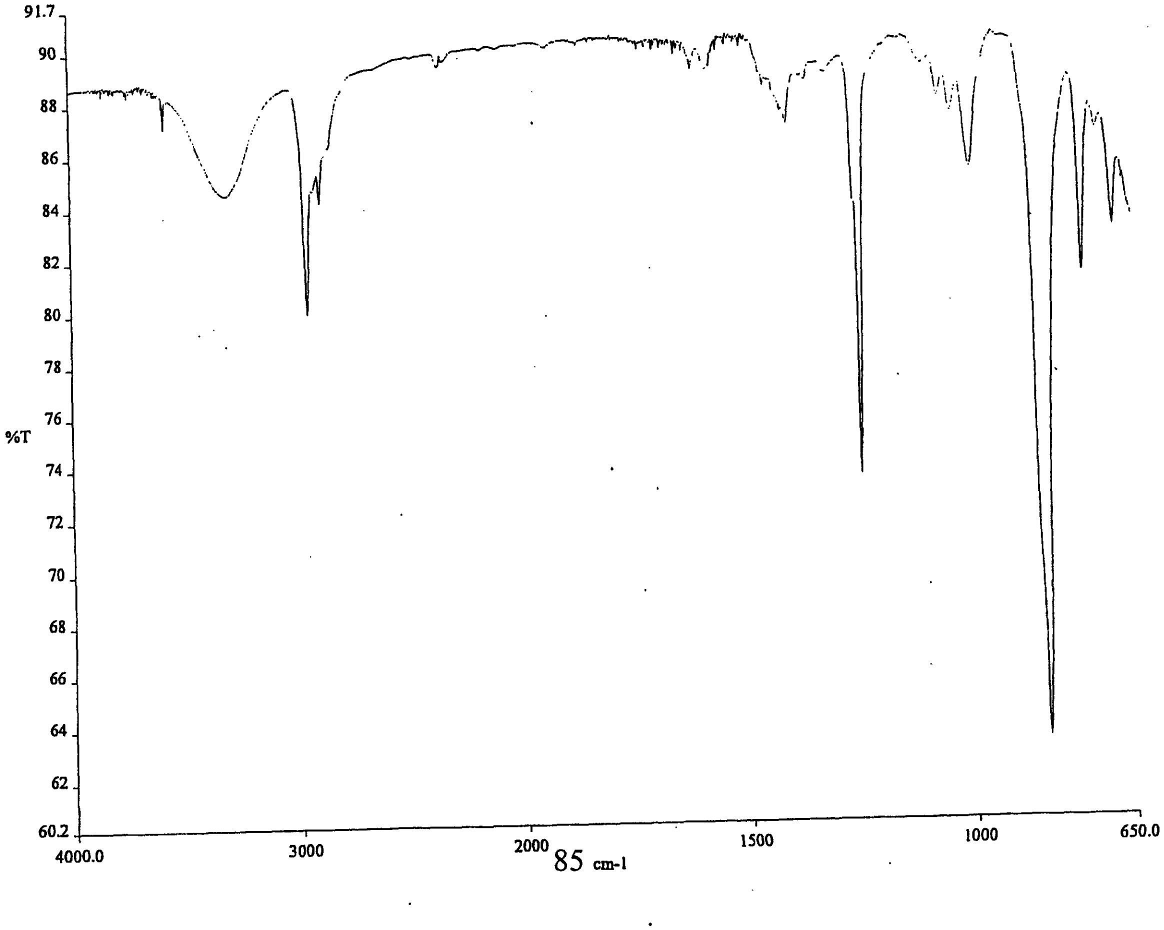
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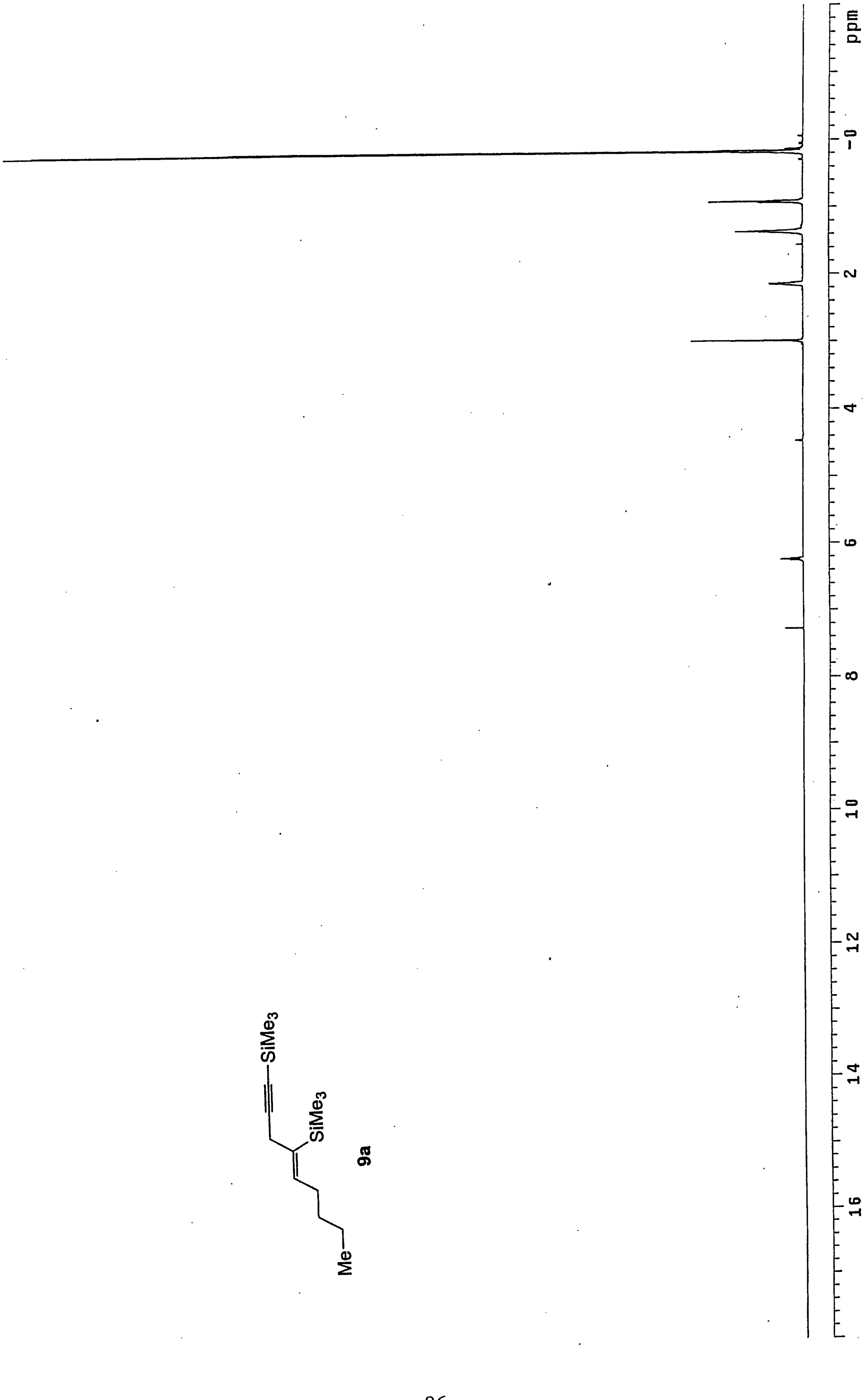

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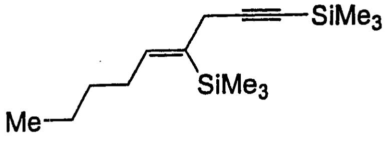
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SiMe3
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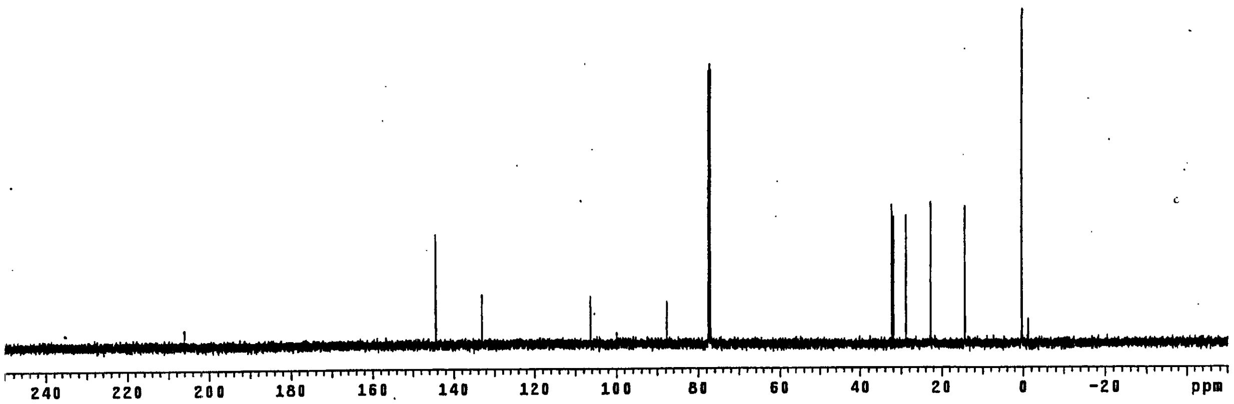
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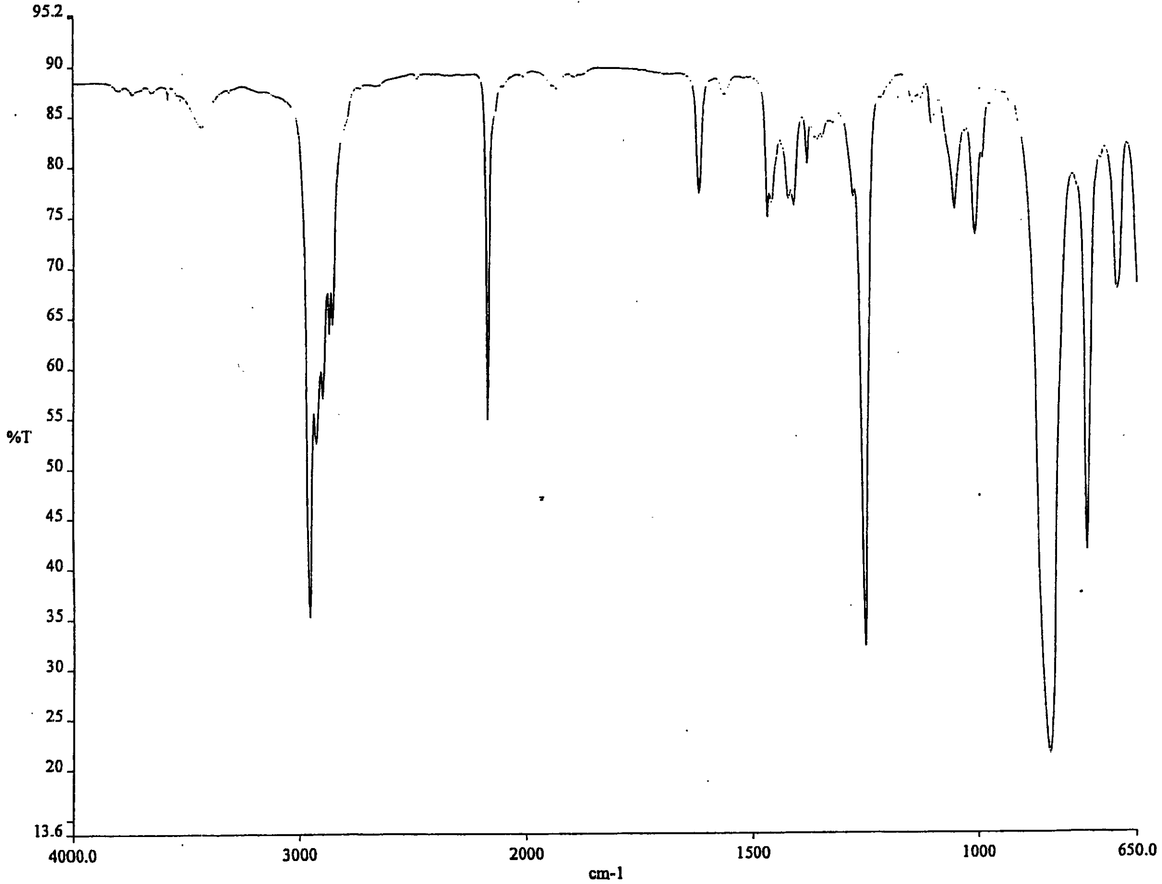
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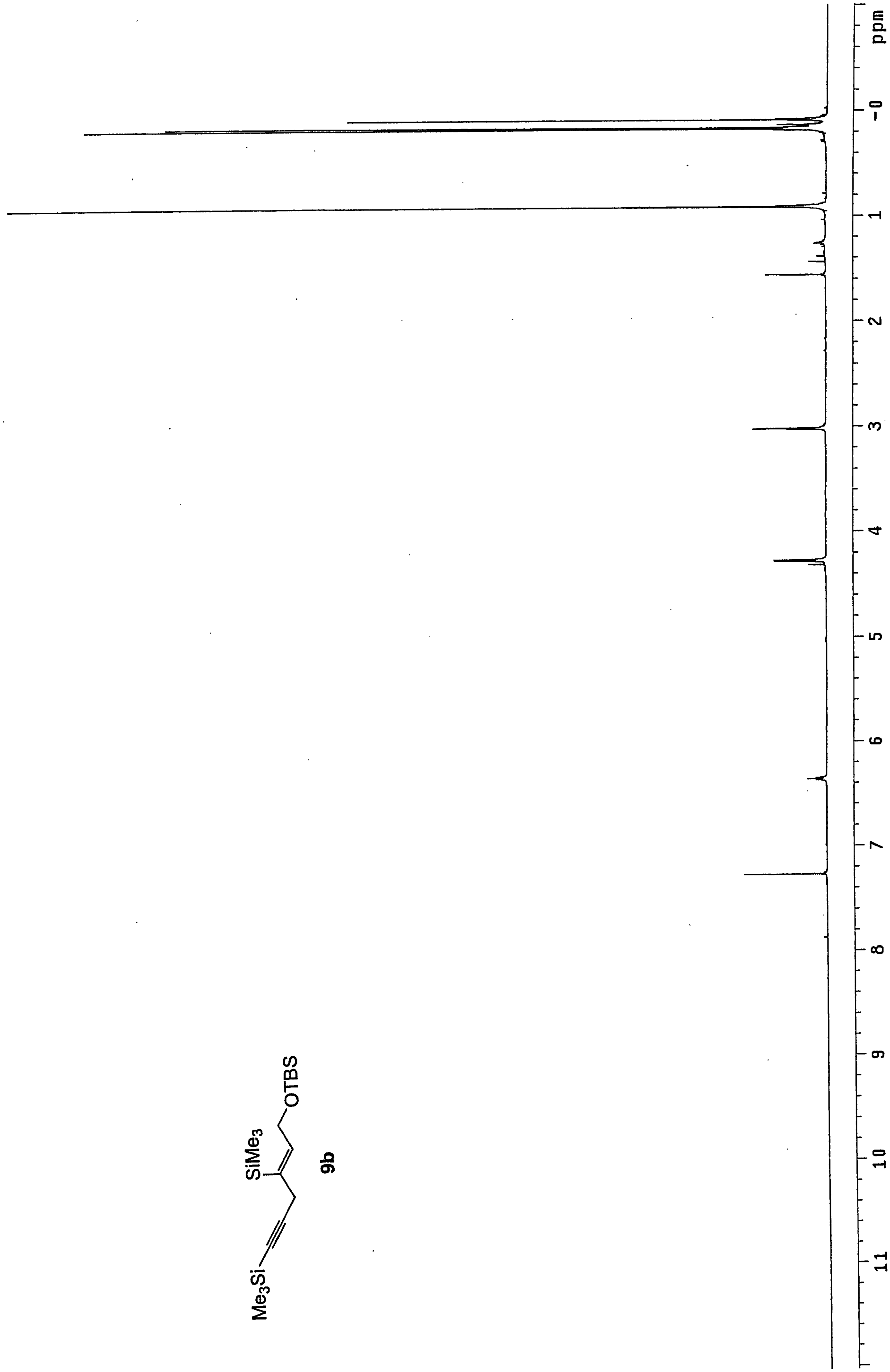

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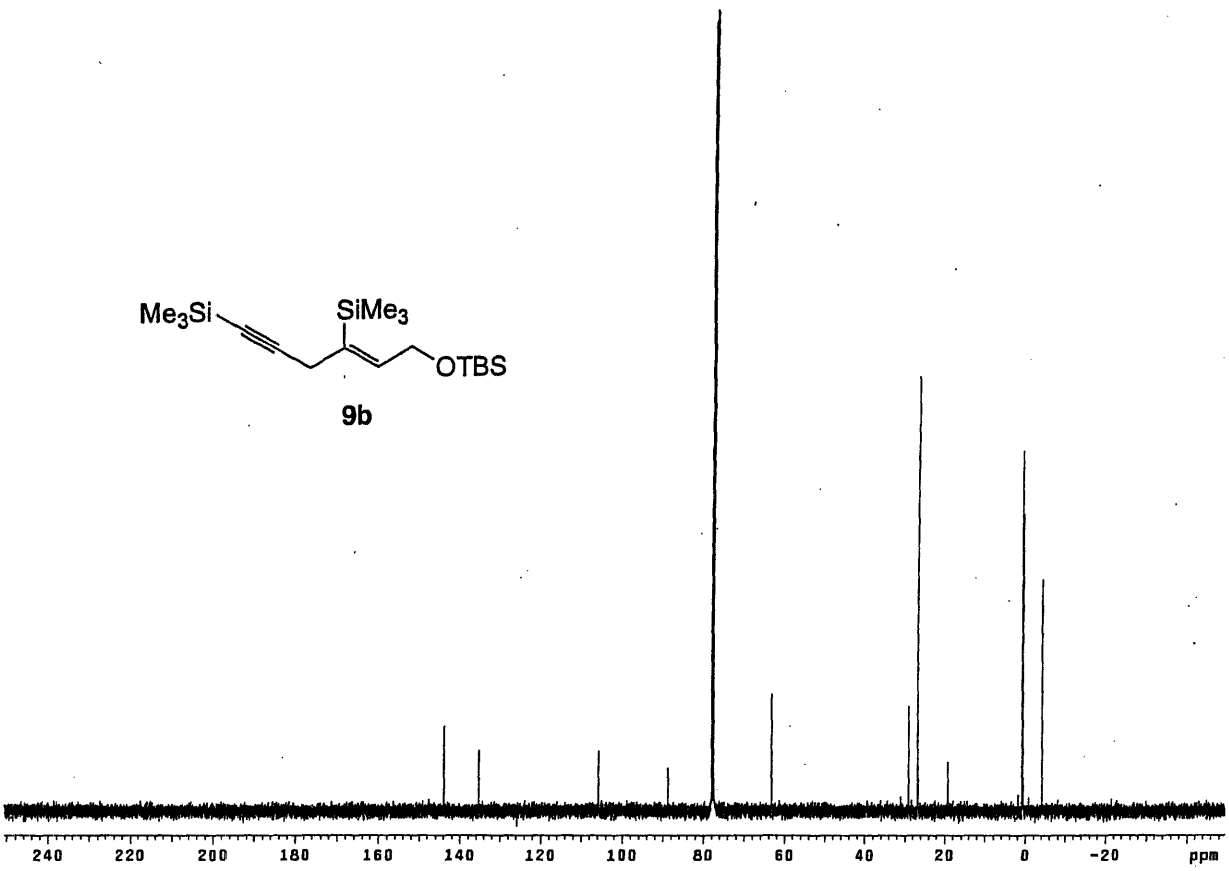
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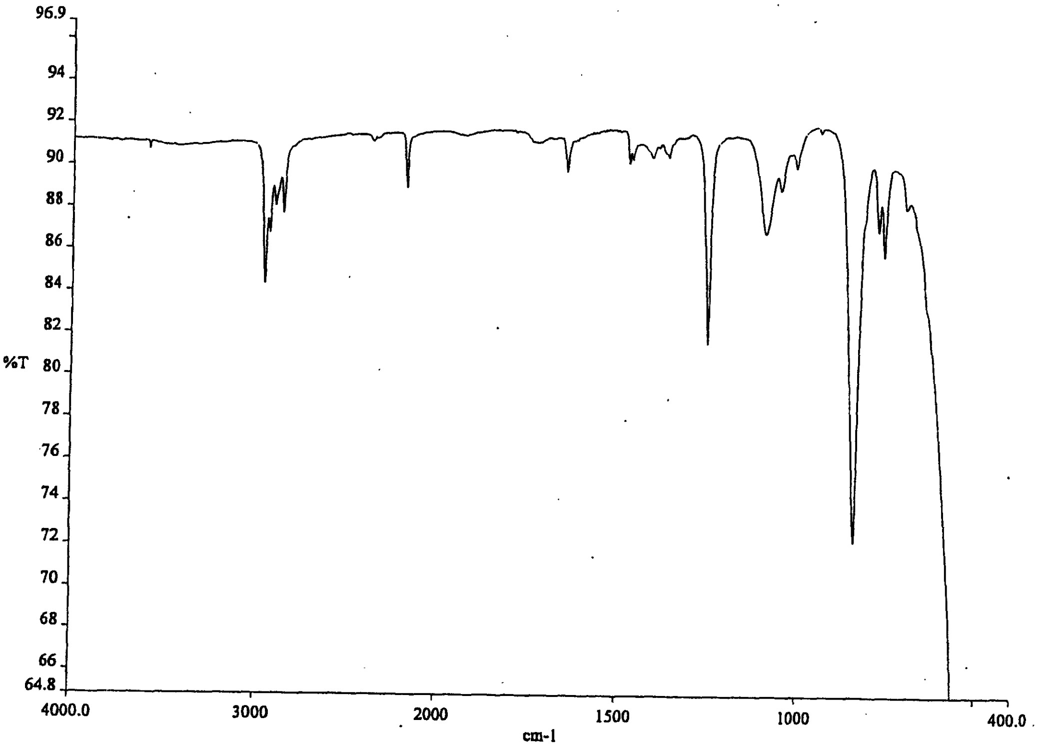
ppm

9b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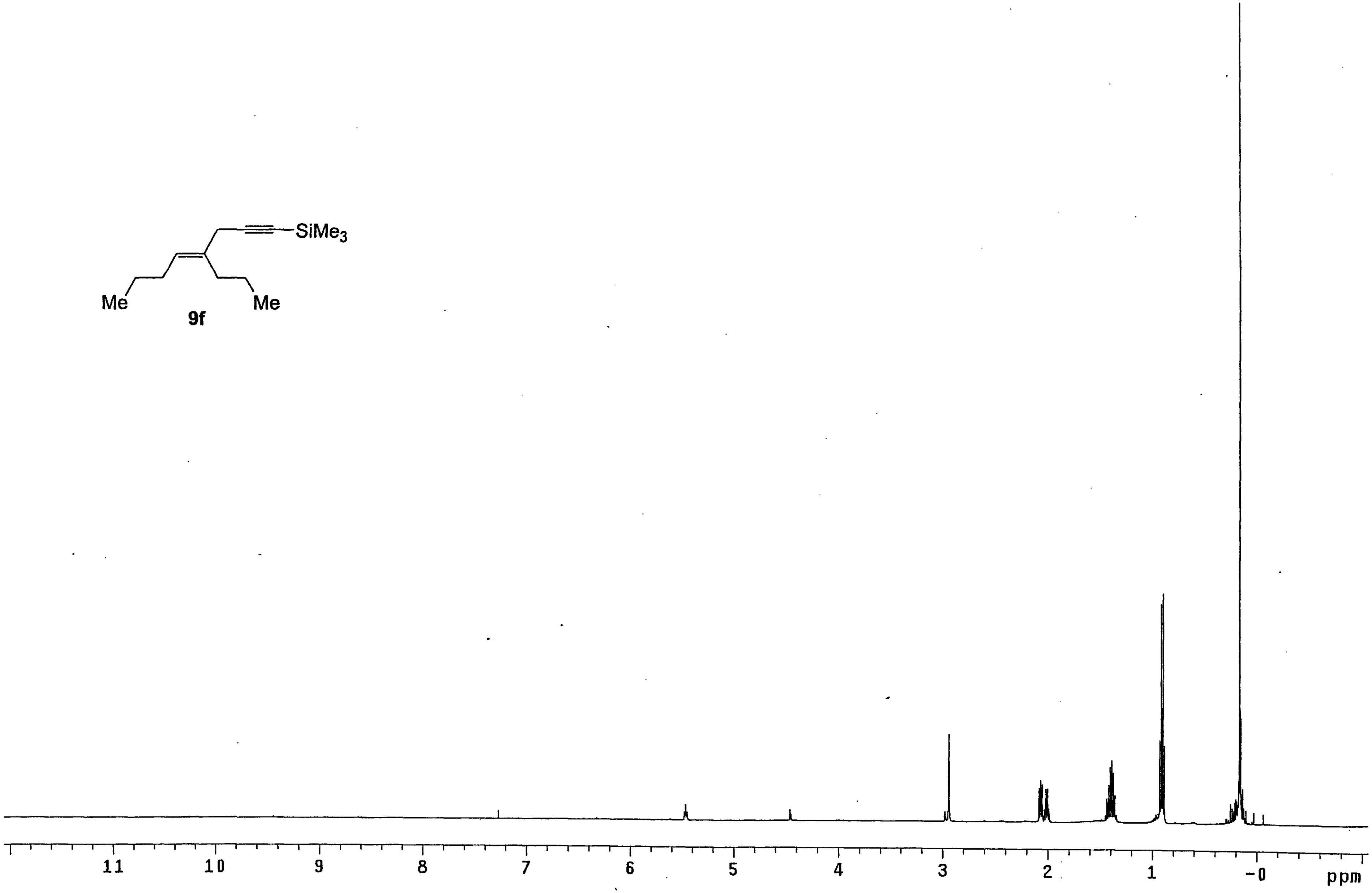

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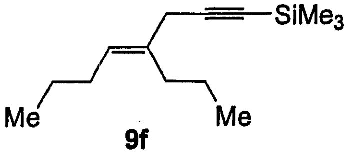
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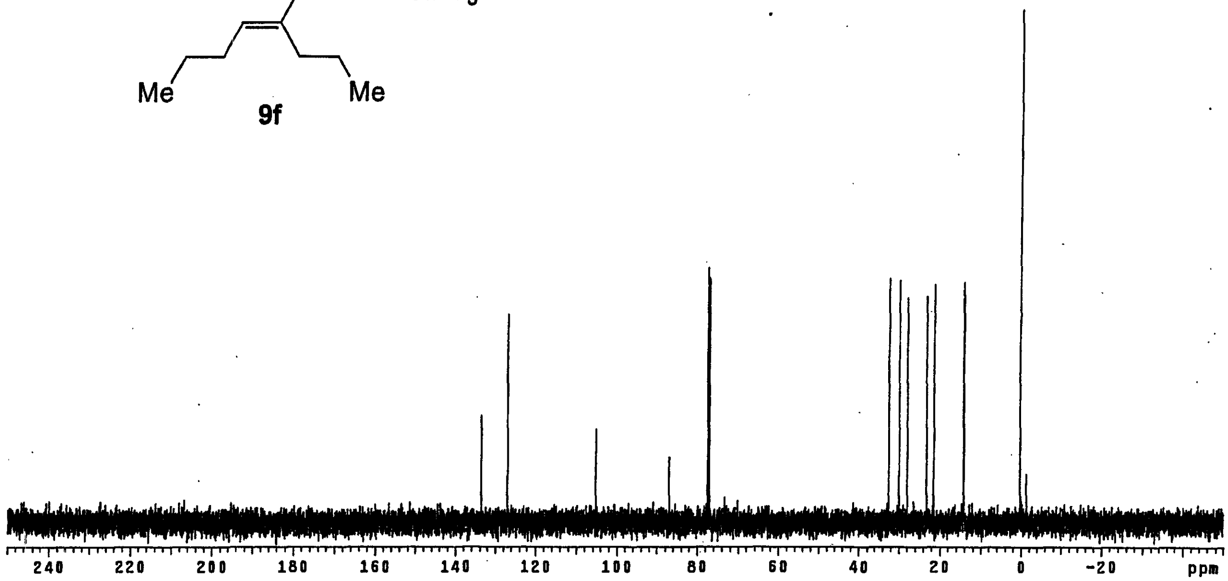
Me
Me

9f


240
220
200
180
160
140
120
100
80
60
40
20
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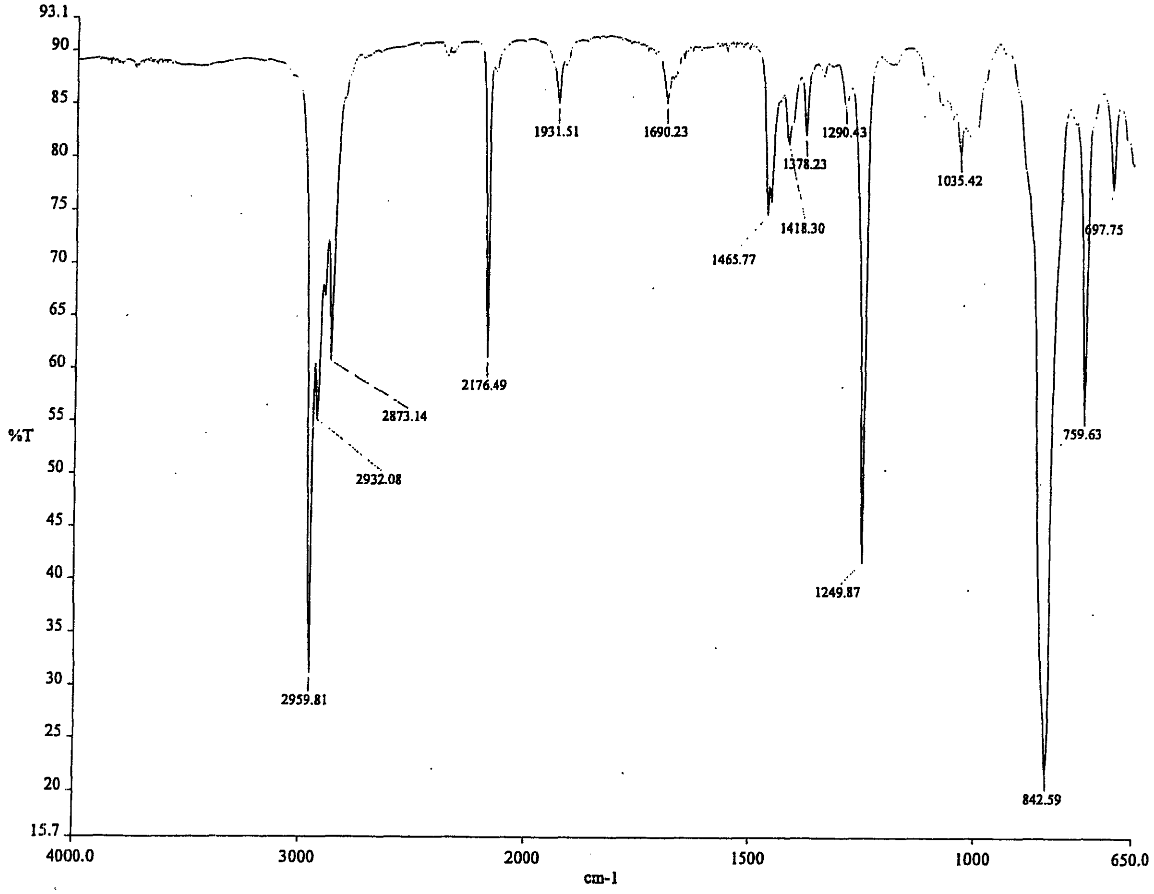
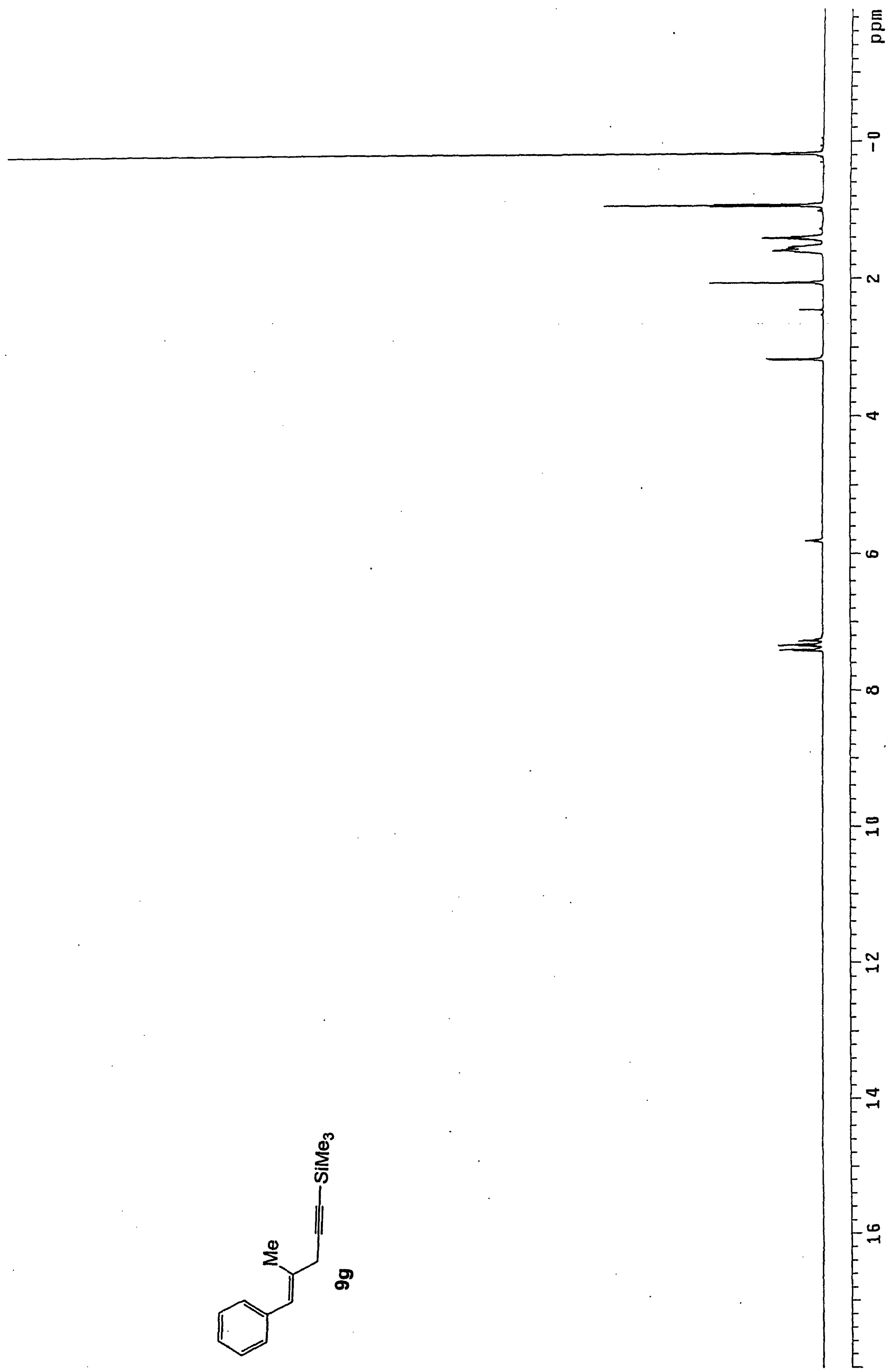
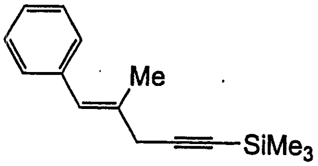
-20
ppm

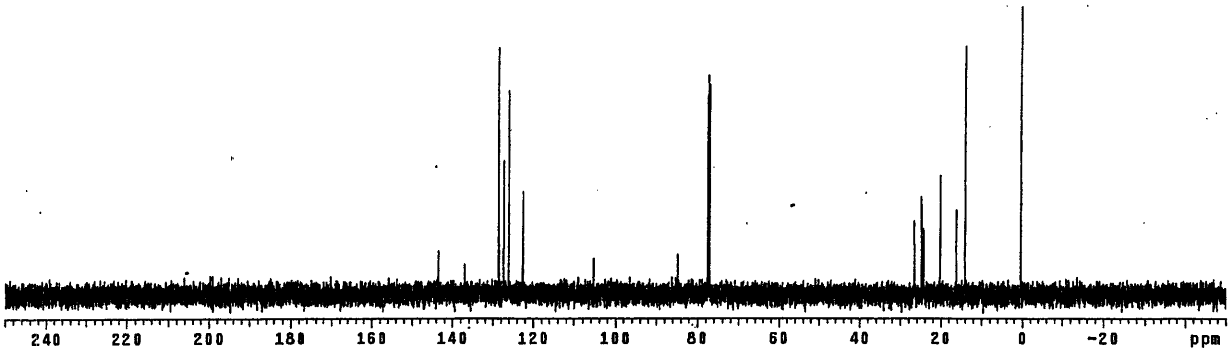

93.1
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15.7
%T
4000.0
3000
2000
1500
1000
650.0
cm-1
1931.51
1690.23
1290.43
1378.23
1035.42
1418.30
697.75
1465.77
2176.49
2873.14
759.63
2932.08
1249.87
2959.81
842.59

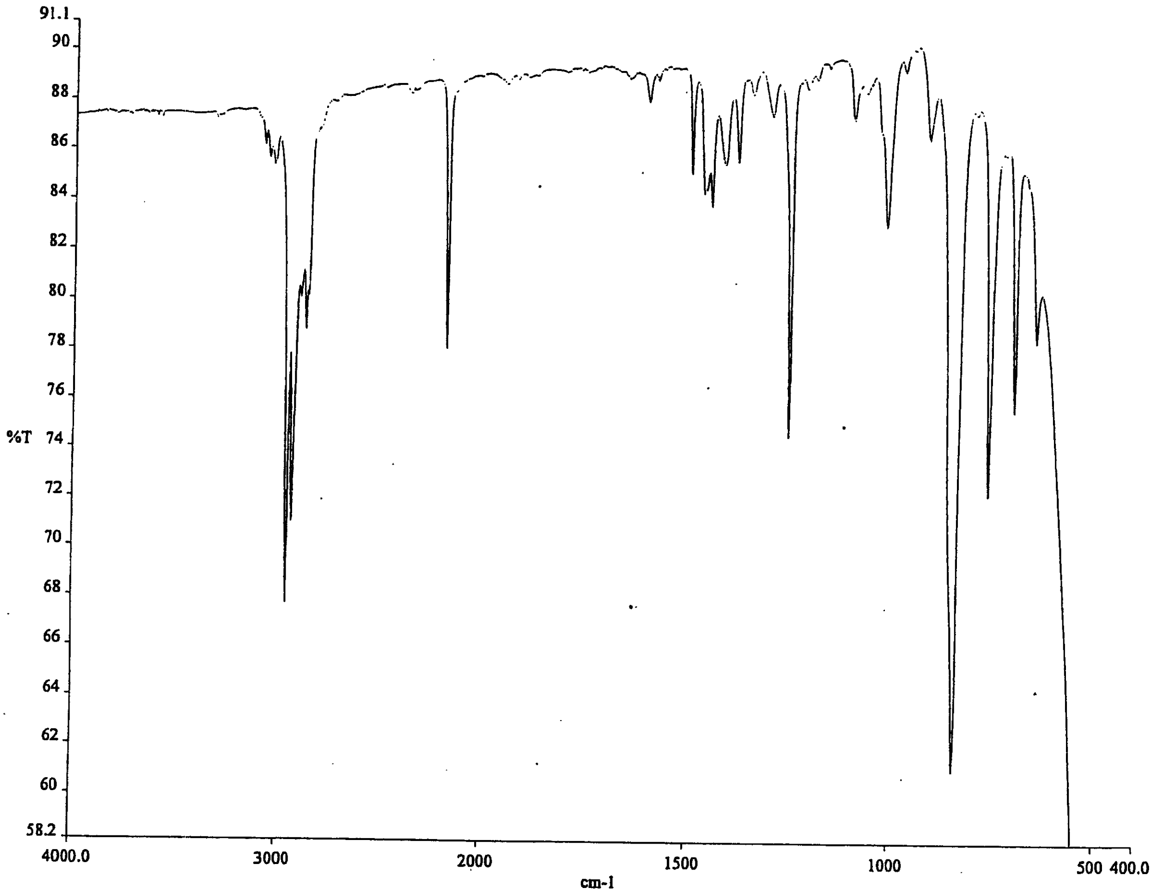


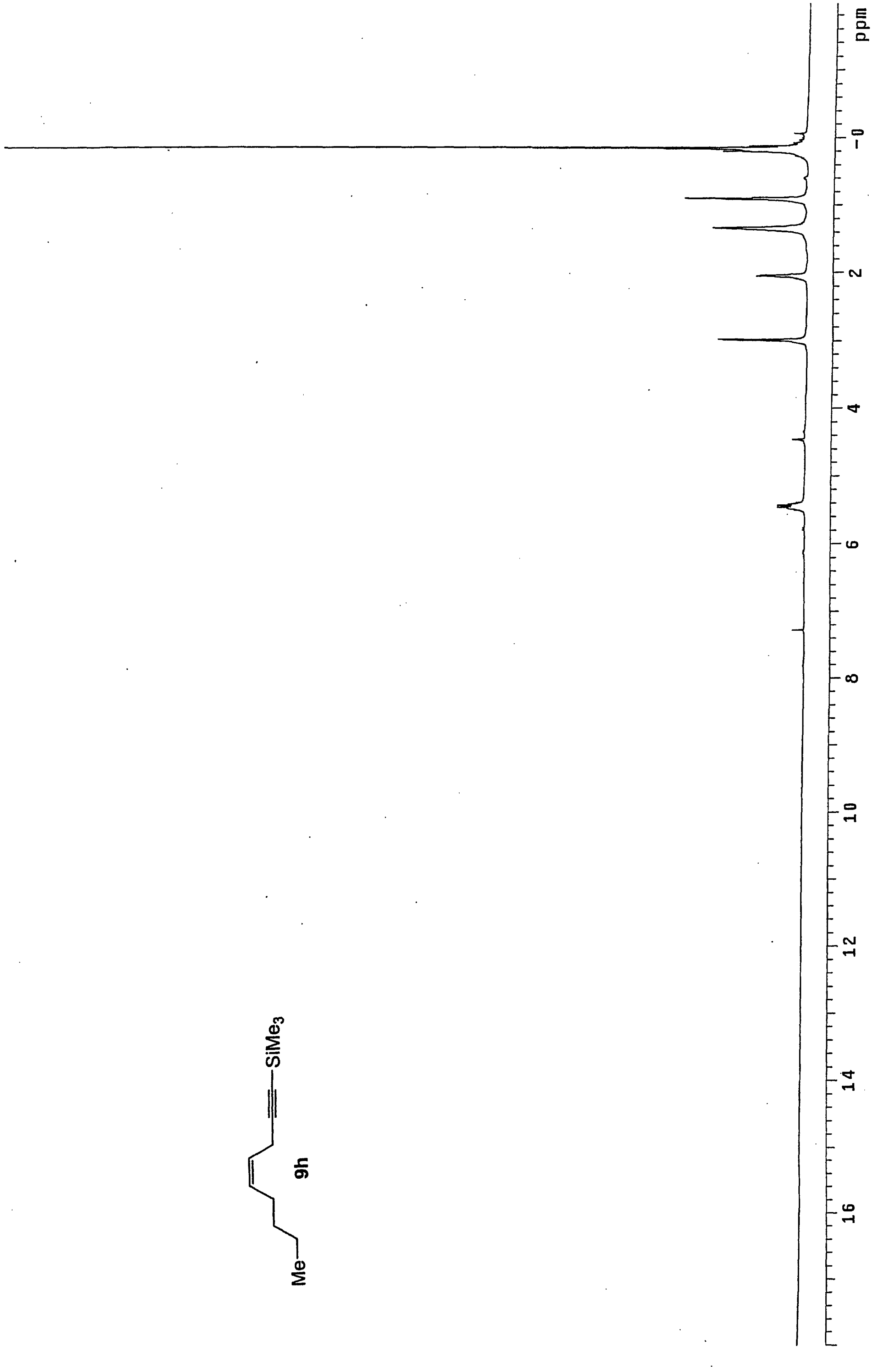
9g


Me
SiMe3

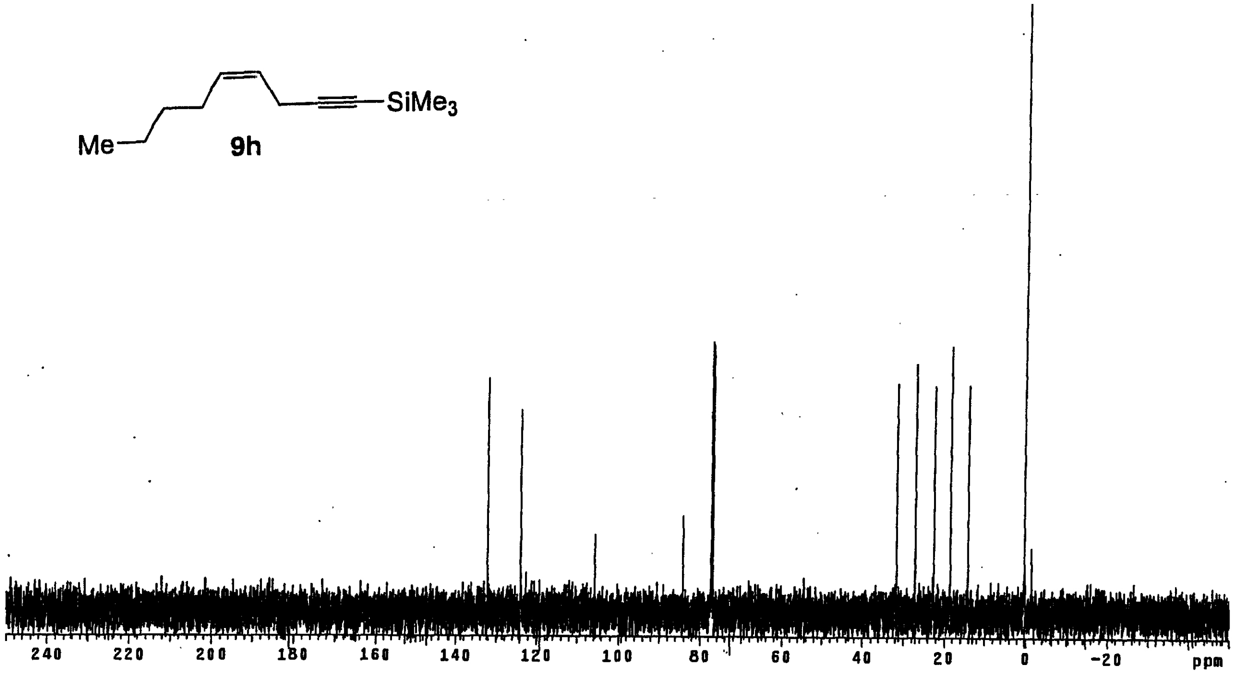
9g


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


91.1
90
88
86
84
82
80
78
76
%T 74
72
70
68
66
64
62
60
58.2
4000.0
3000
2000
1500
1000
500 400.0
cm-1

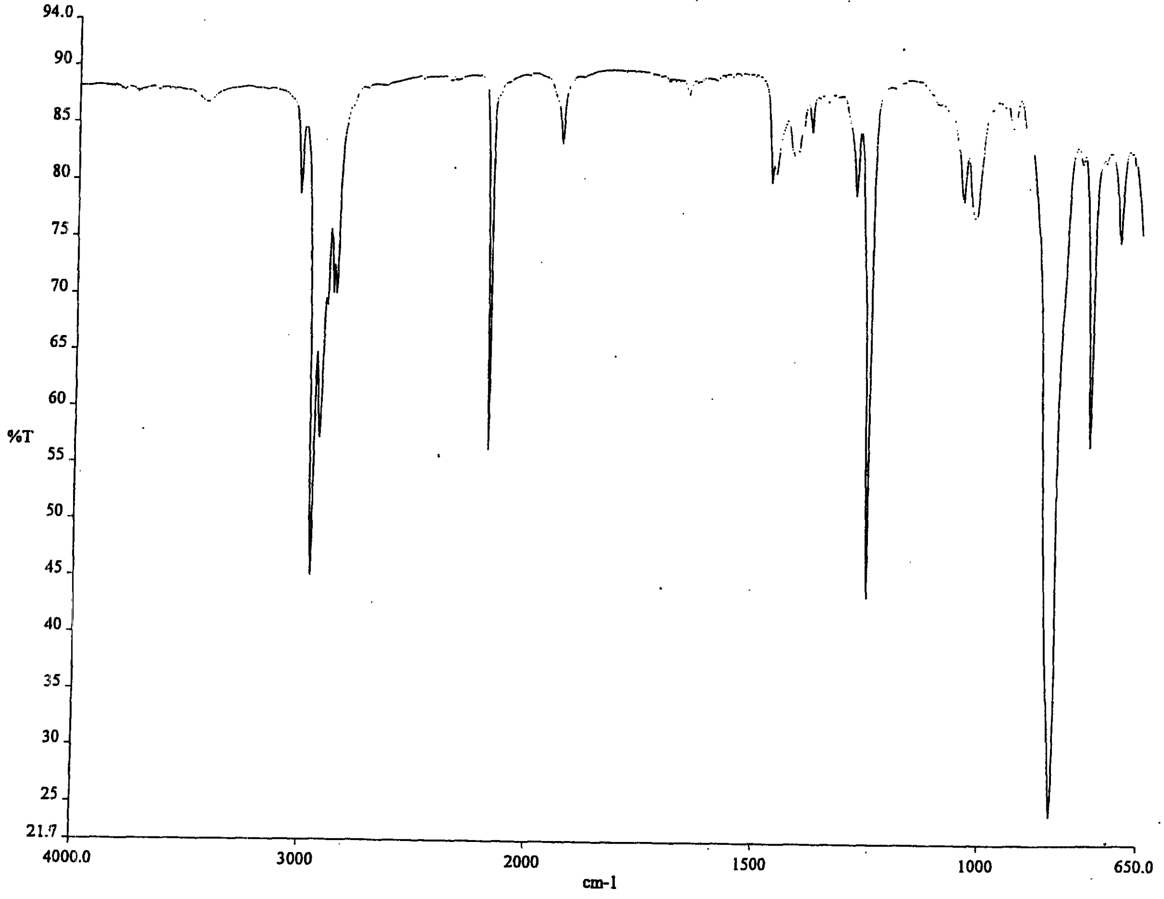


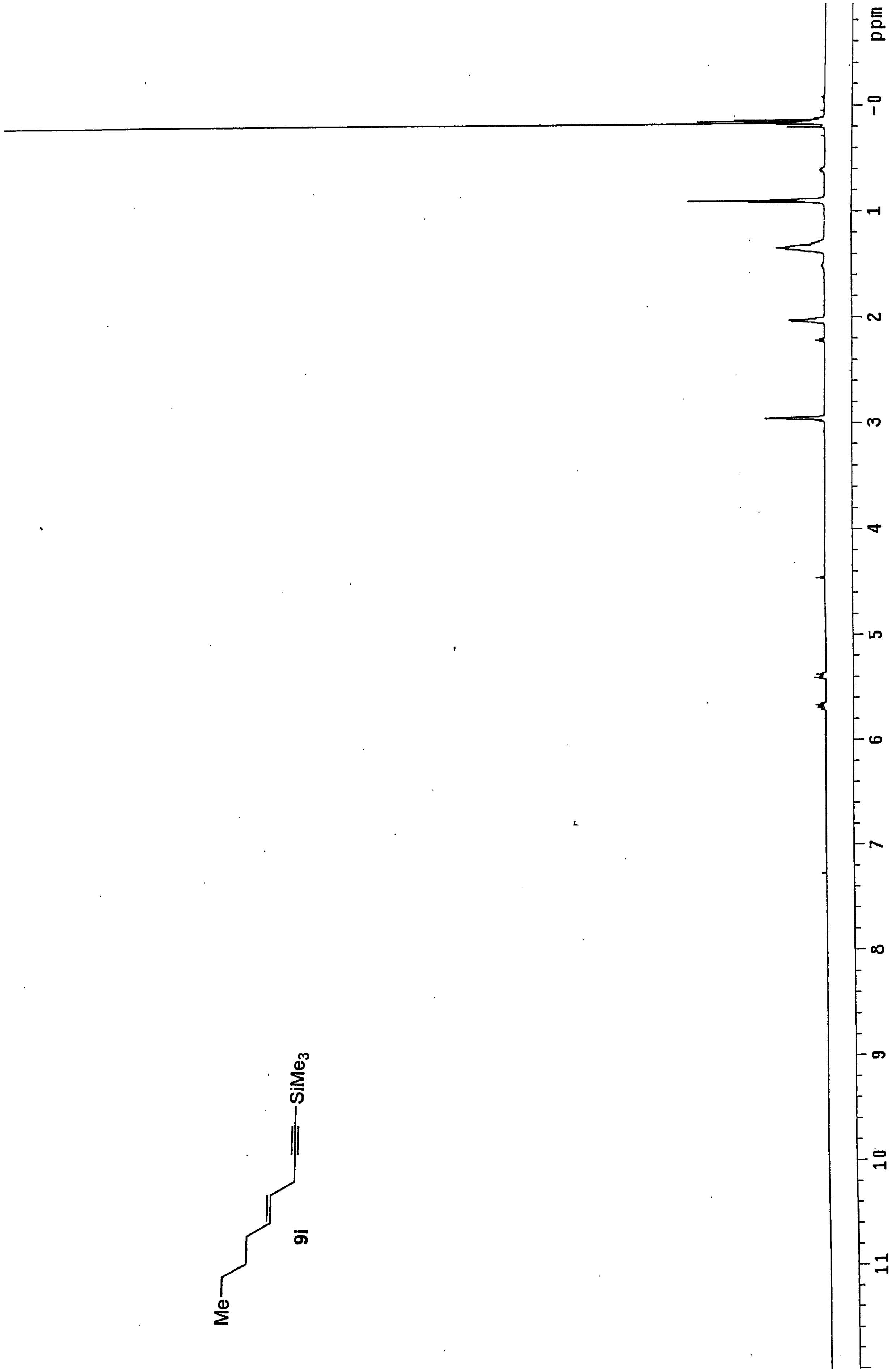
9h

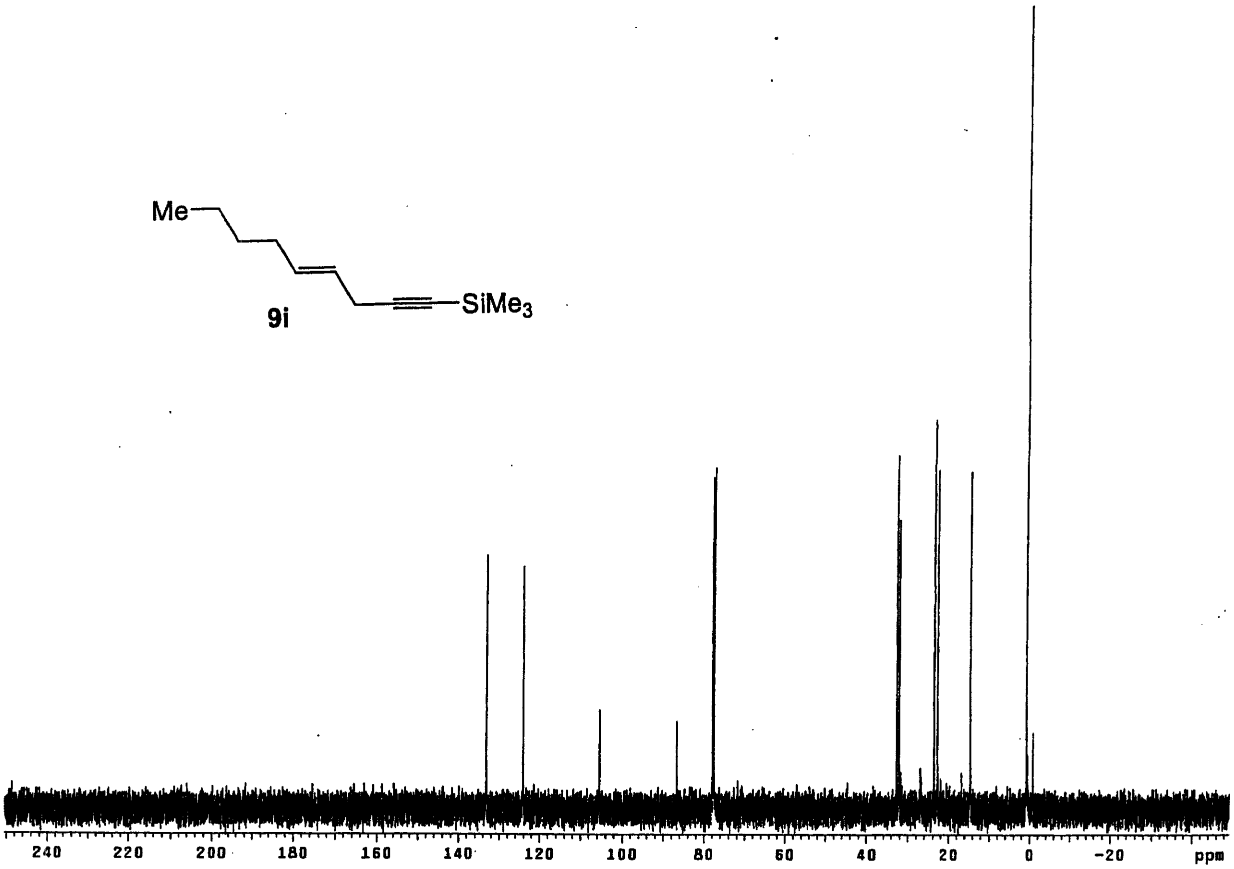

SiMe3
Me

9h

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

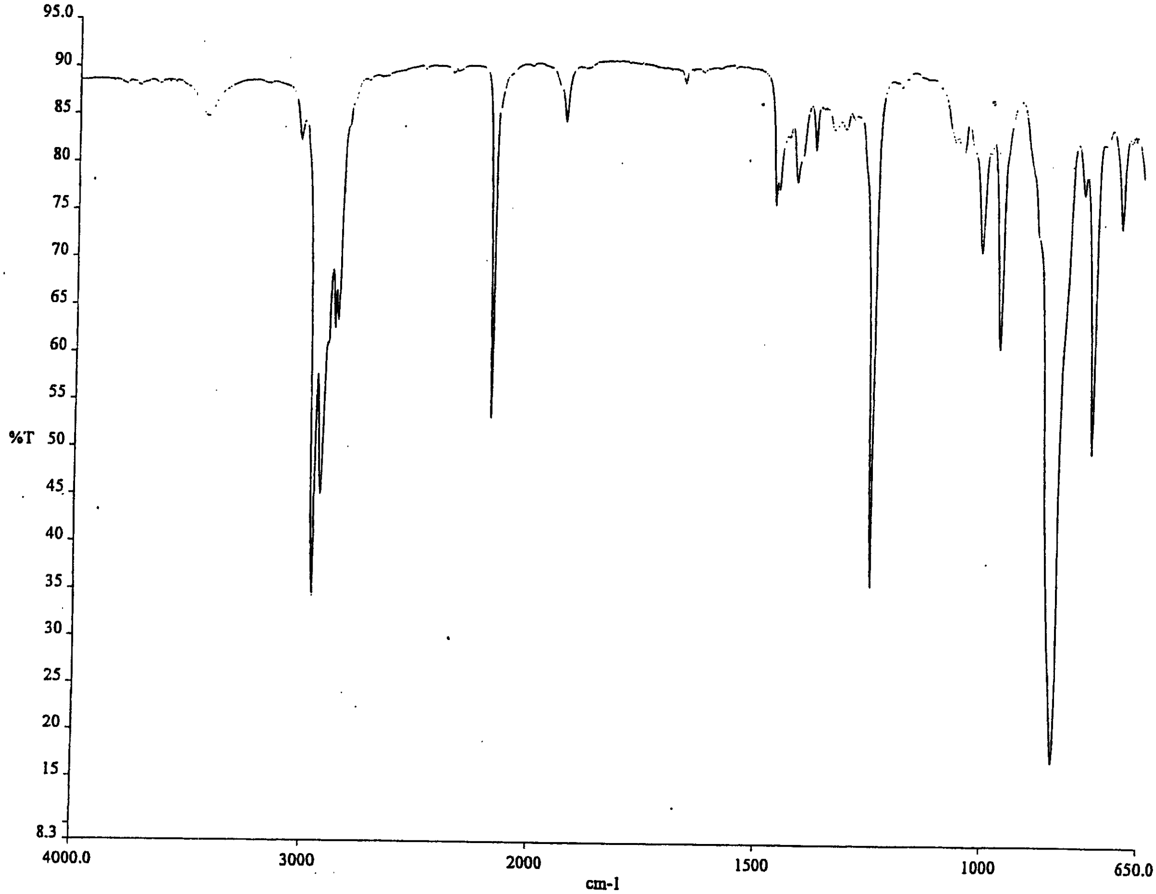

94.0
90
85
80
75
70
65
60
%T
55
50
45
40
35
30
25
21.7
4000.0
3000
2000
1500
1000
650.0
cm-1

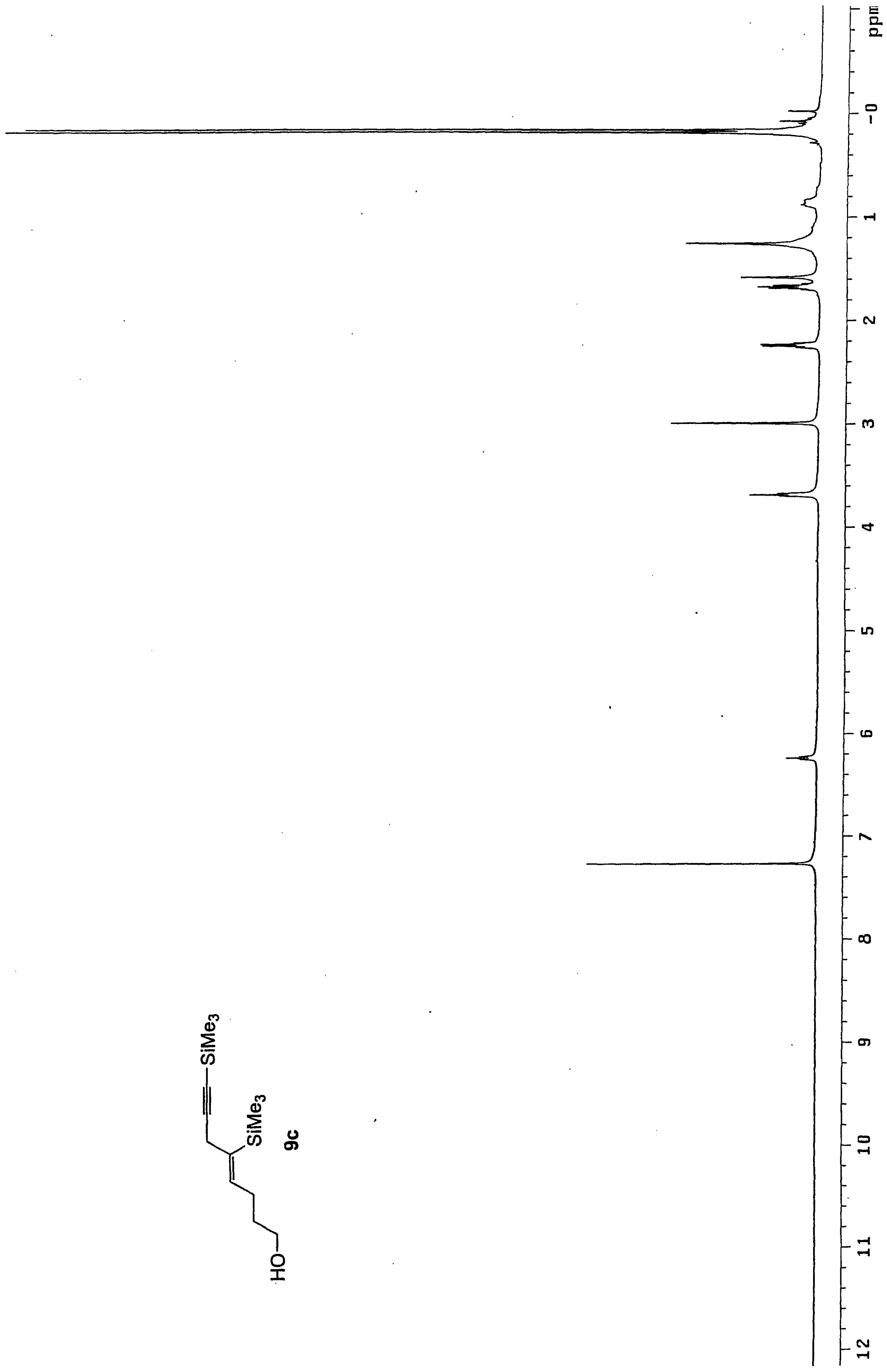

ppm
0
1
2
3
4
5
6
7
8
9
10
11
Me
SiMe3
9i

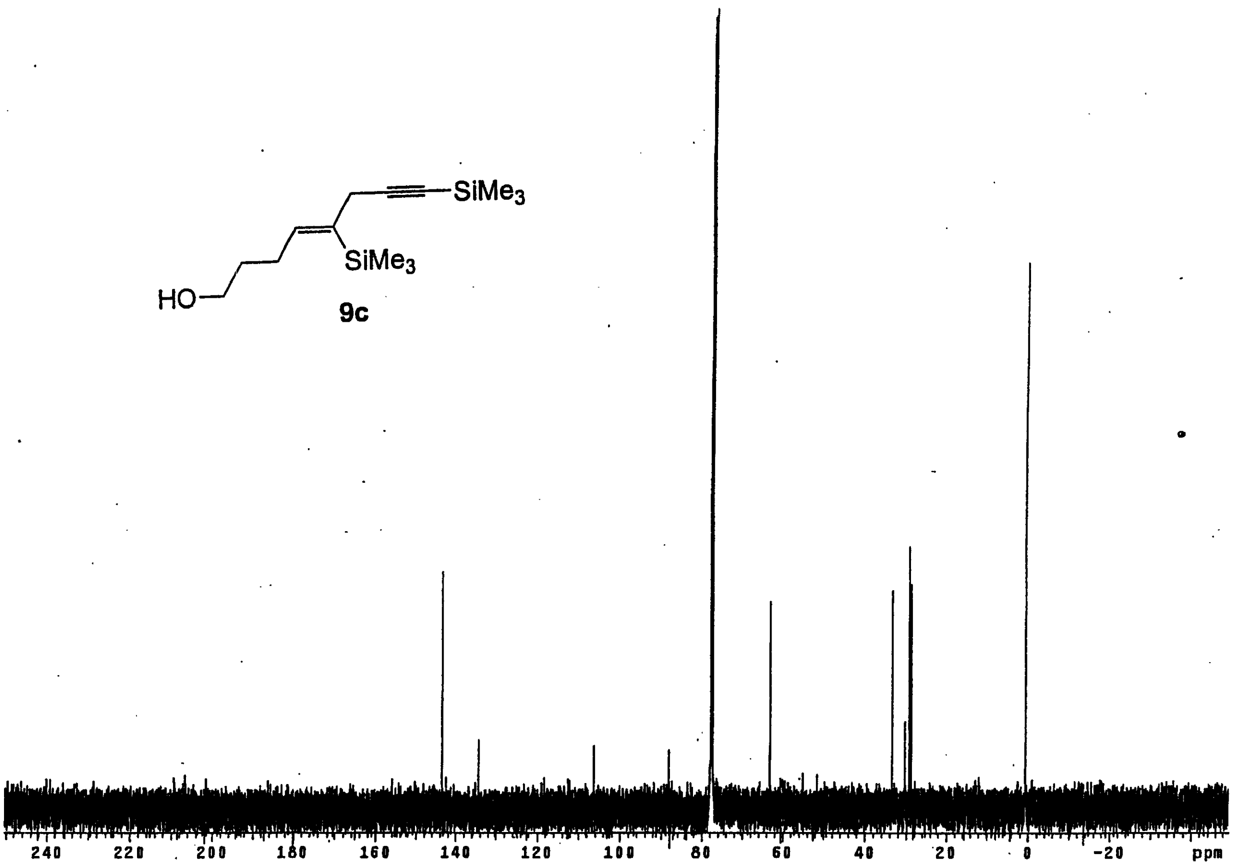

Me
SiMe3

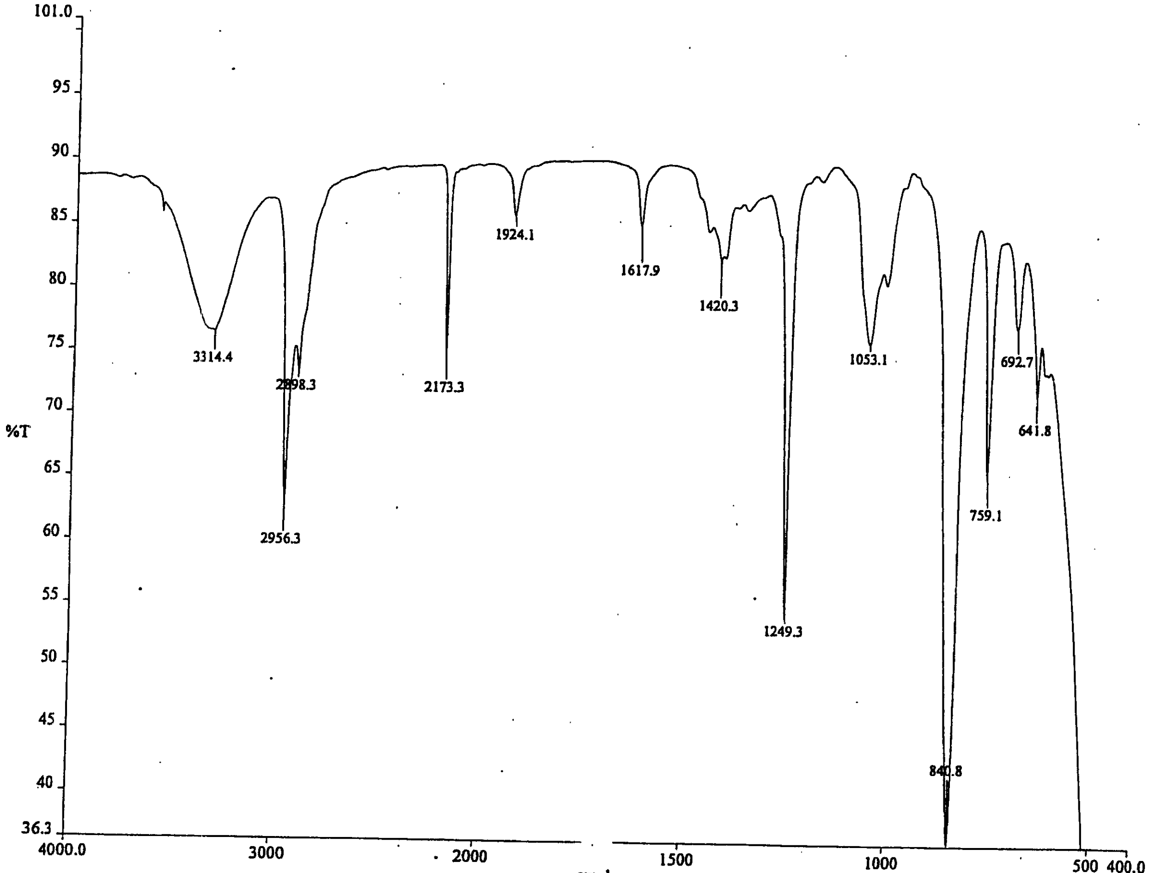
9i

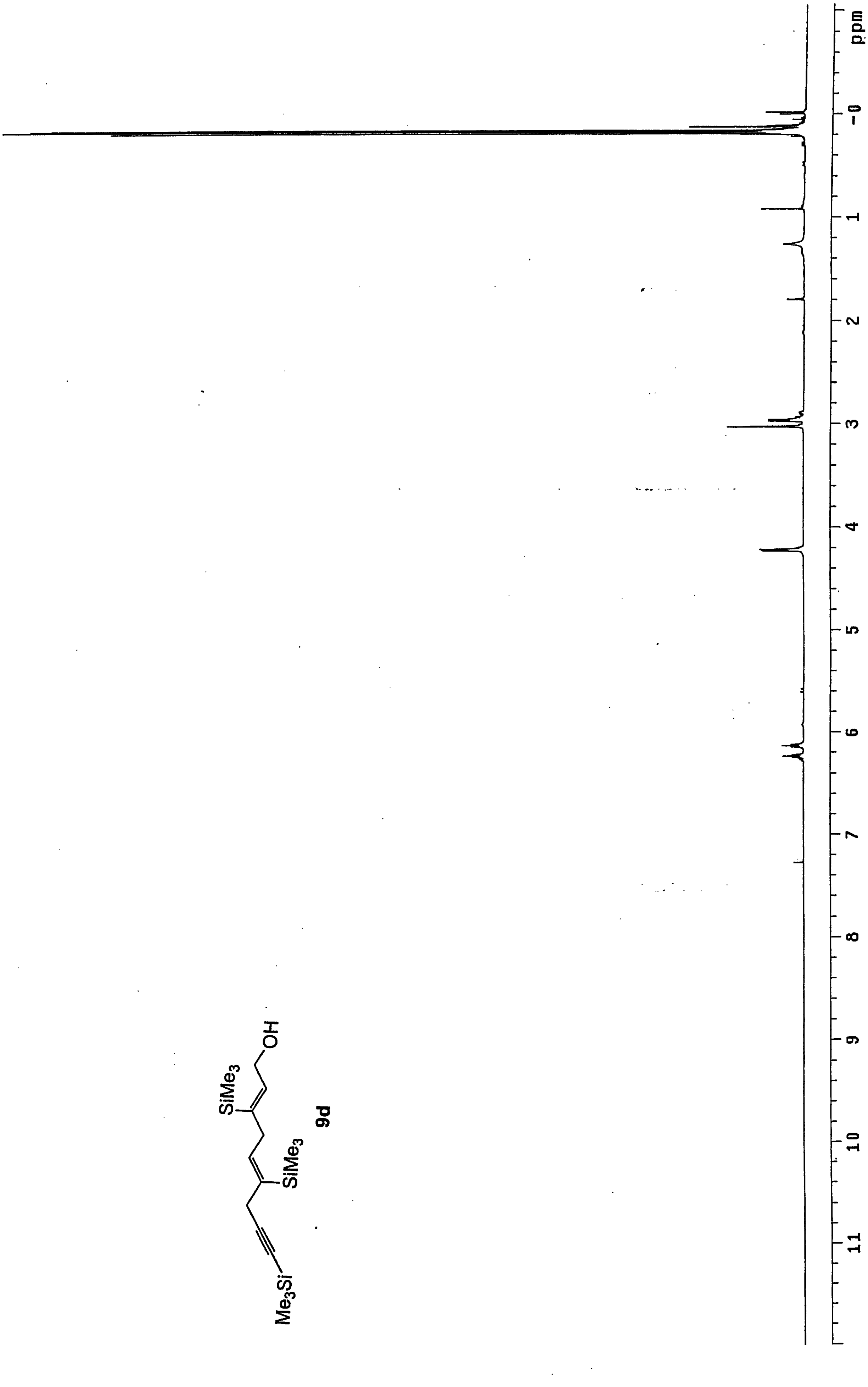
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


95.0
90
85
80
75
70
65
60
55
%T
50
45
40
35
30
25
20
15
8.3
4000.0
3000
2000
1500
1000
650.0
cm-1

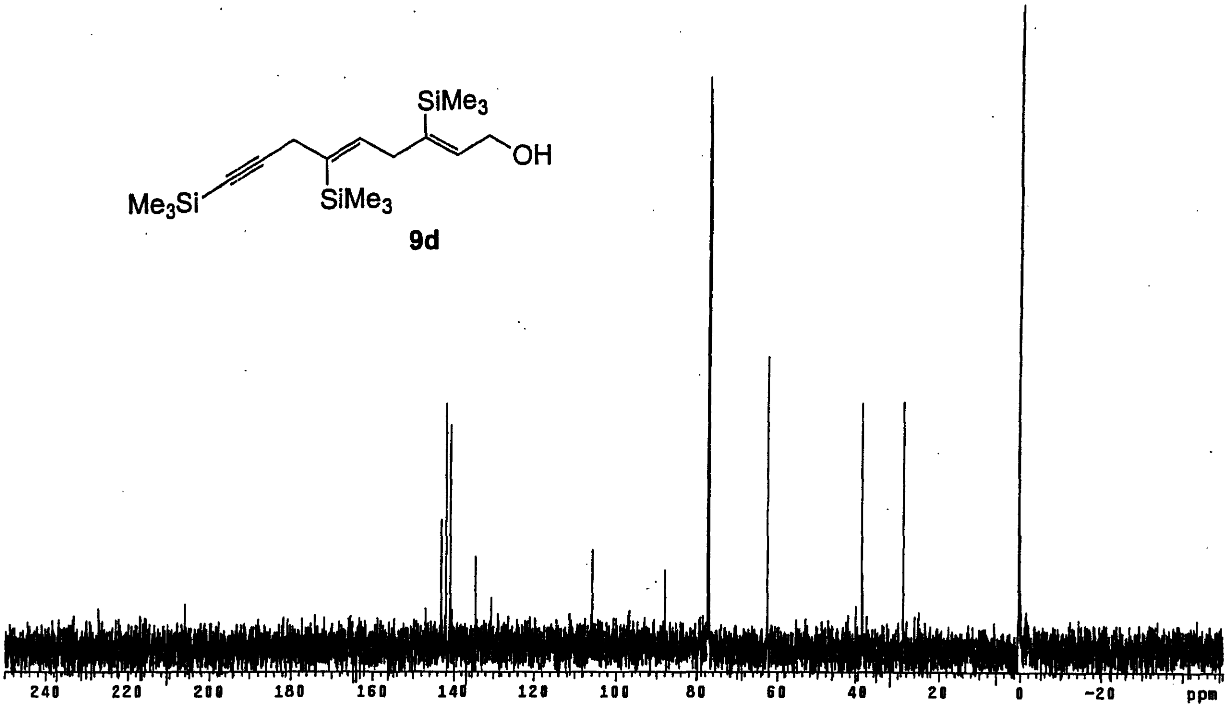

SiMe$_3$
SiMe$_3$
HO
9c
ppm
0
1
2
3
4
5
6
7
8
9
10
11
12


SiMe3
SiMe3
HO
9c
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

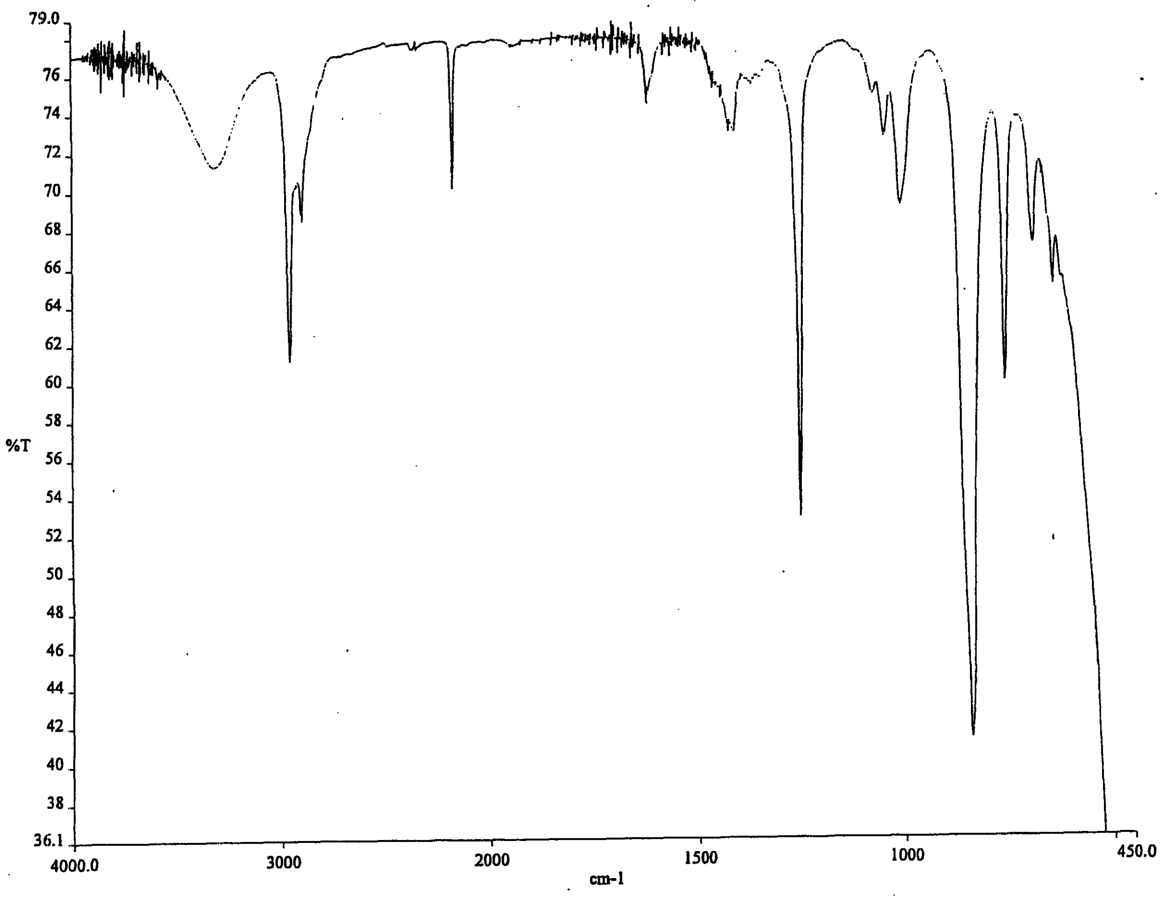

101.0
95
90
85
80
75
70
%T
65
60
55
50
45
40
36.3
3314.4
2898.3
2956.3
2173.3
1924.1
1617.9
1420.3
1249.3
1053.1
840.8
759.1
692.7
641.8
4000.0
3000
2000
1500
1000
500 400.0
cm-1

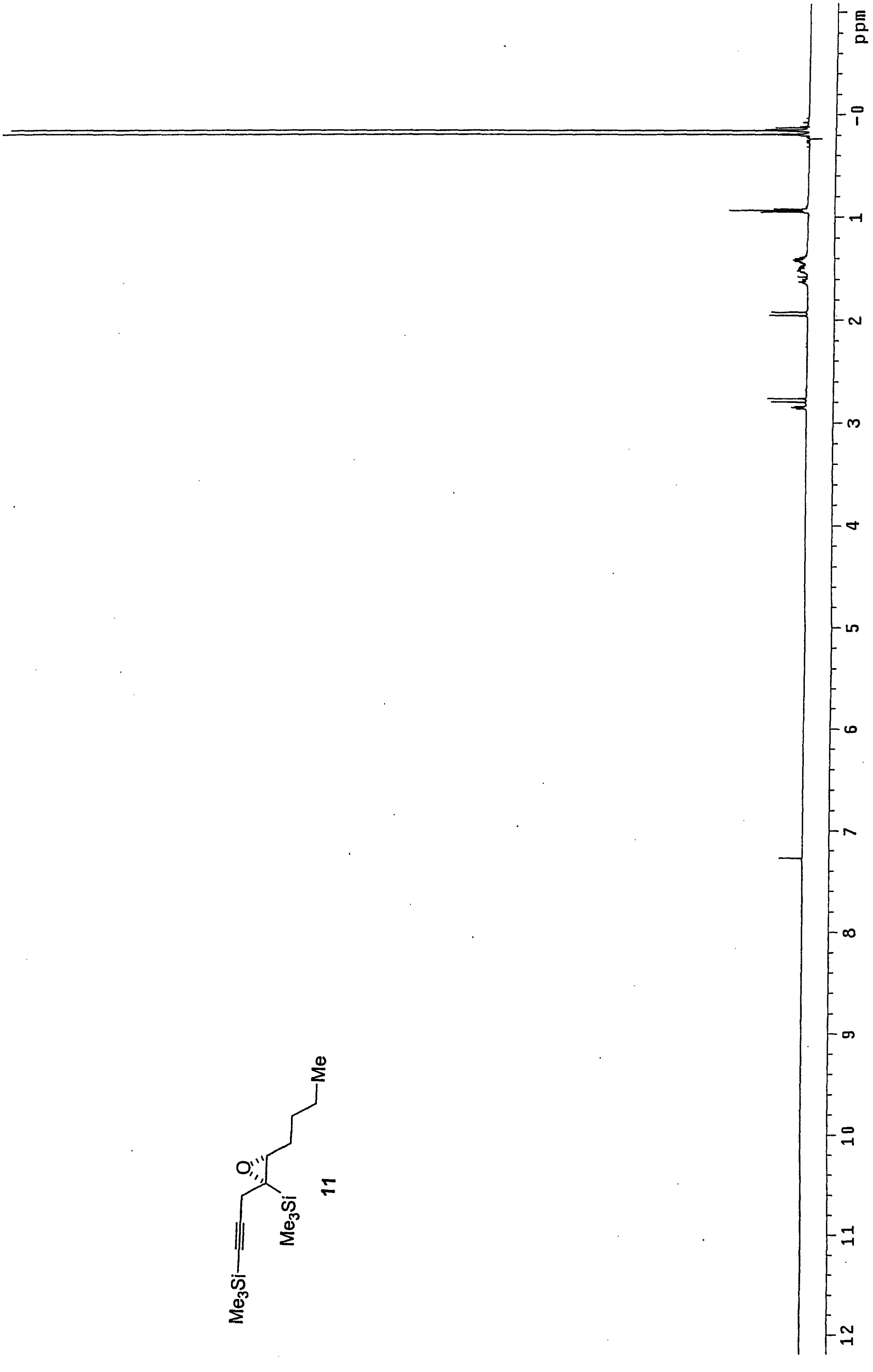


9d

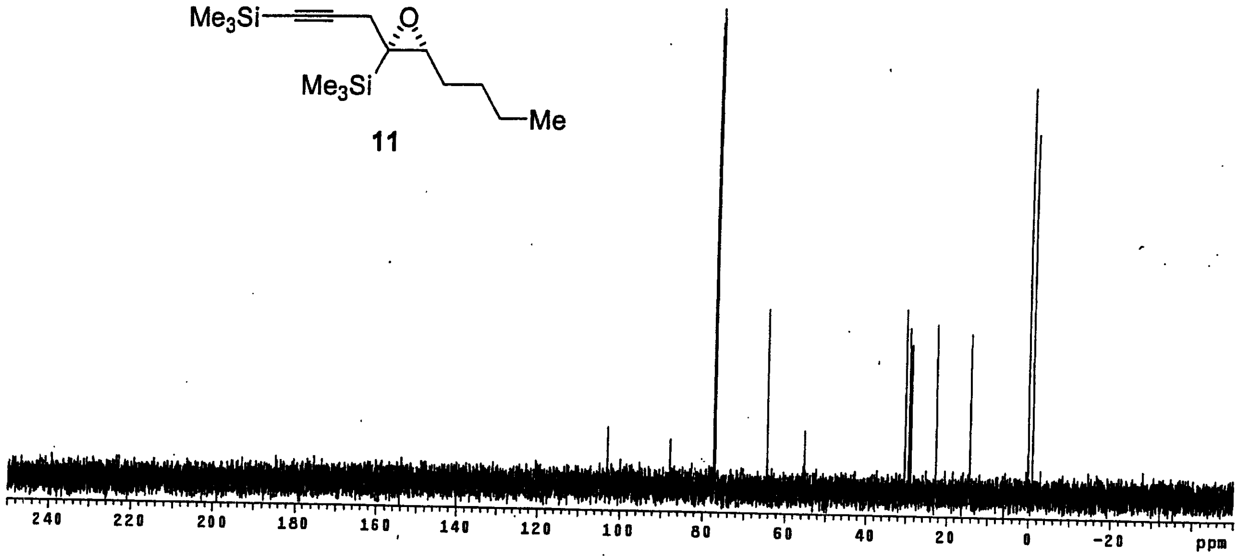

SiMe3
OH
Me3Si
SiMe3
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

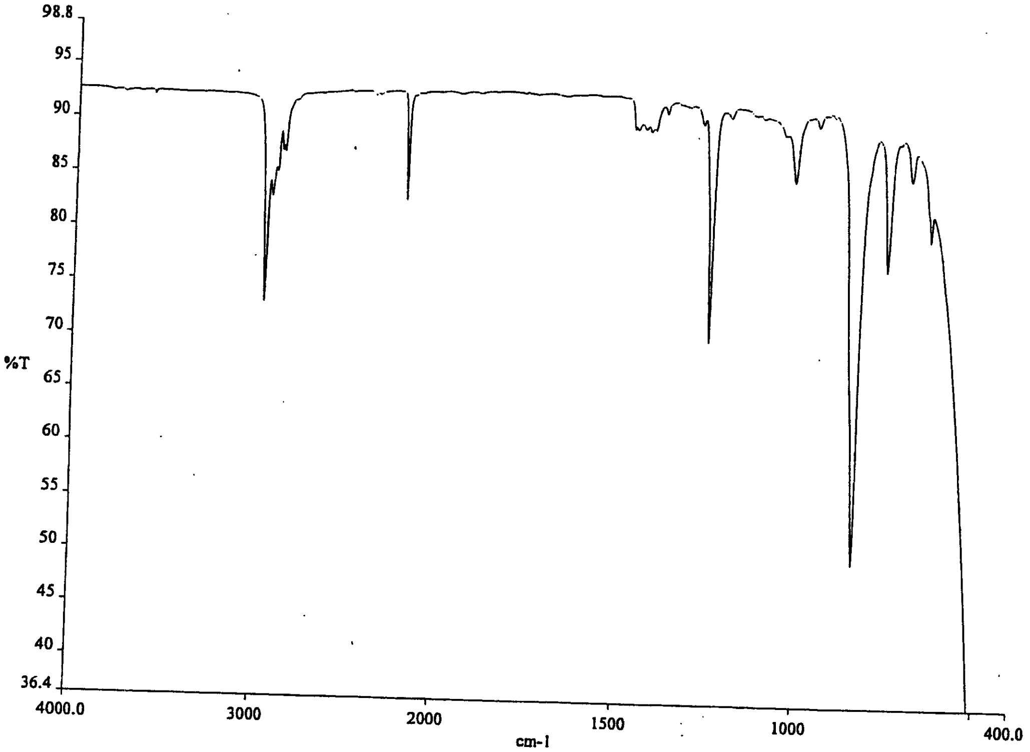
9d

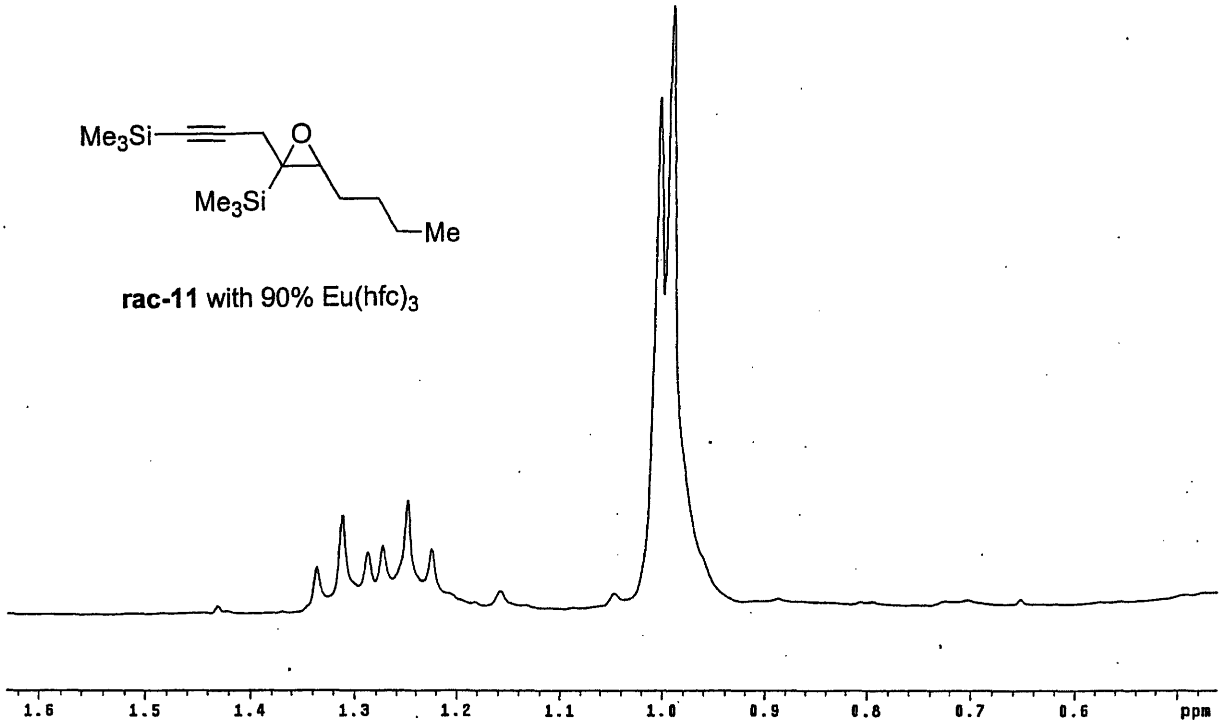

79.0
76
74
72
70
68
66
64
62
60
58
%T
56
54
52
50
48
46
44
42
40
38
36.1
4000.0
3000
2000
1500
1000
450.0
cm-1



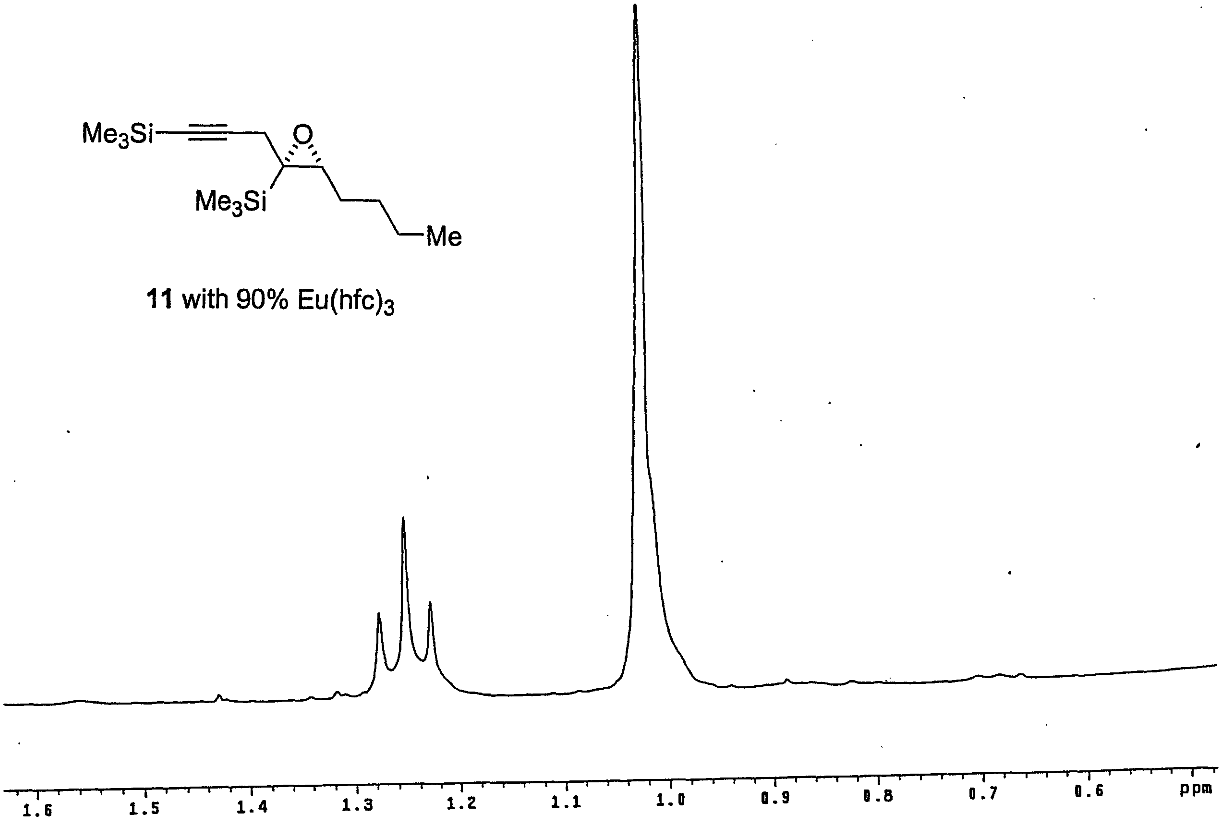
11


Me$_3$Si
Me$_3$Si
O
Me
11
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

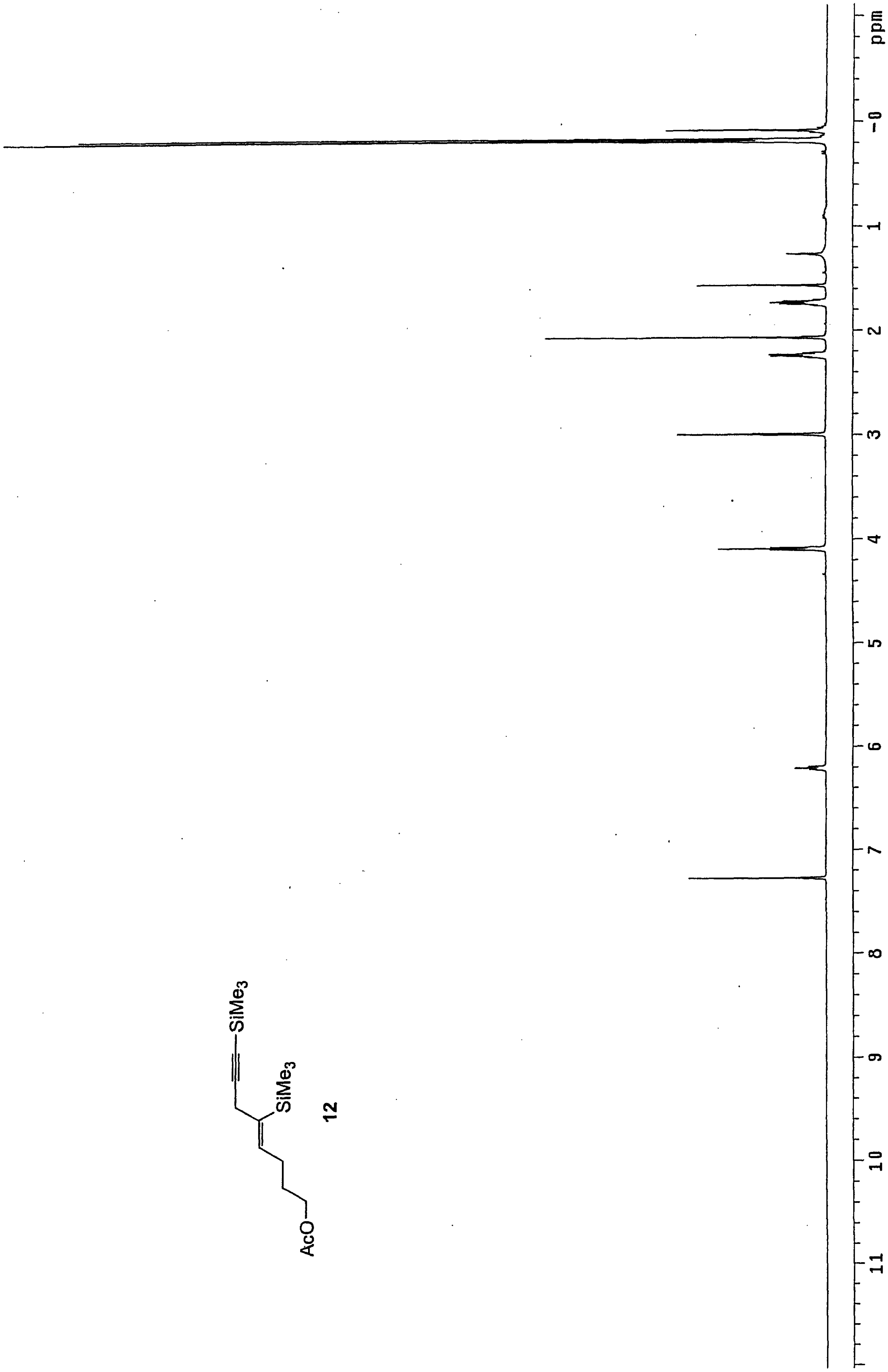

98.8
95
90
85
80
75
70
%T
65
60
55
50
45
40
36.4
4000.0
3000
2000
1500
1000
400.0
cm-1

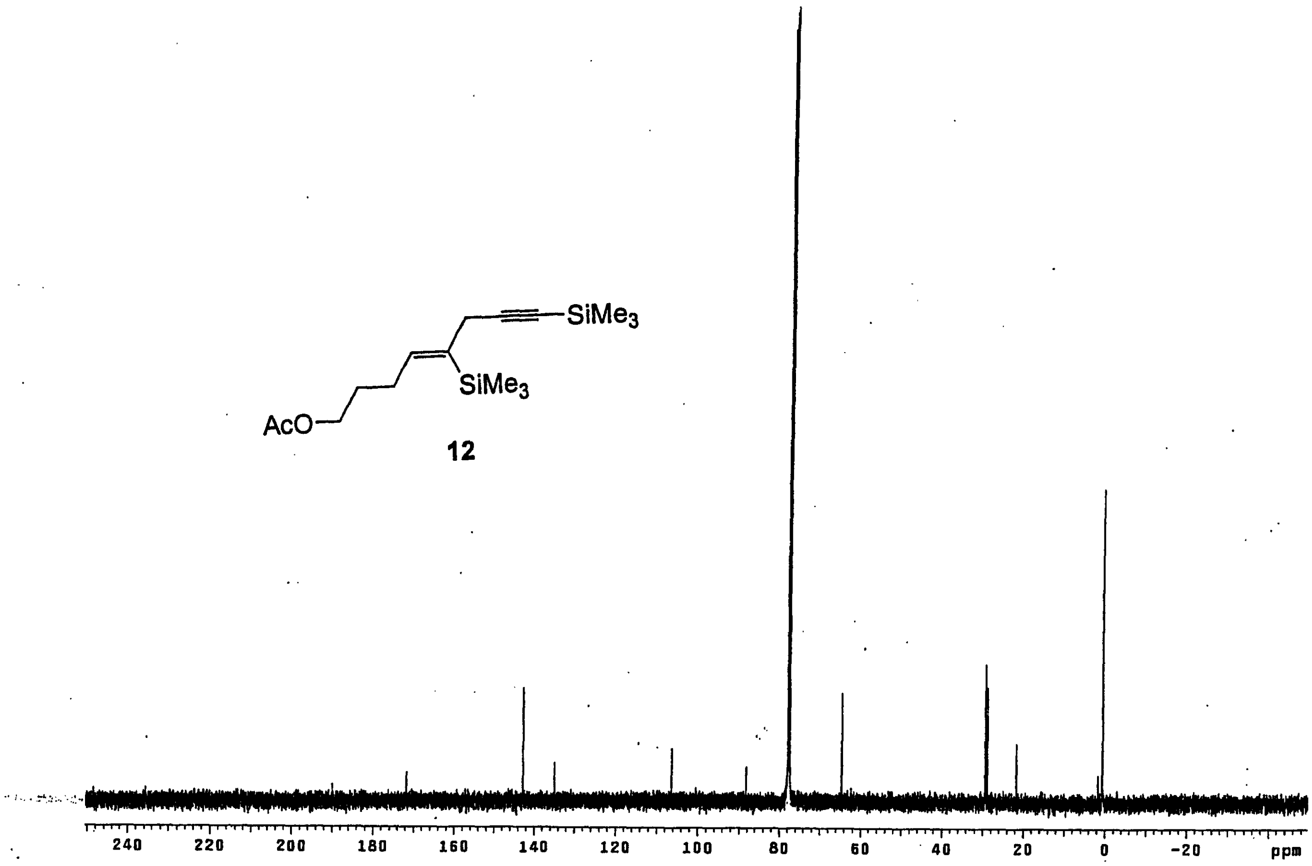


rac-11 with 90% Eu(hfc)$_3$

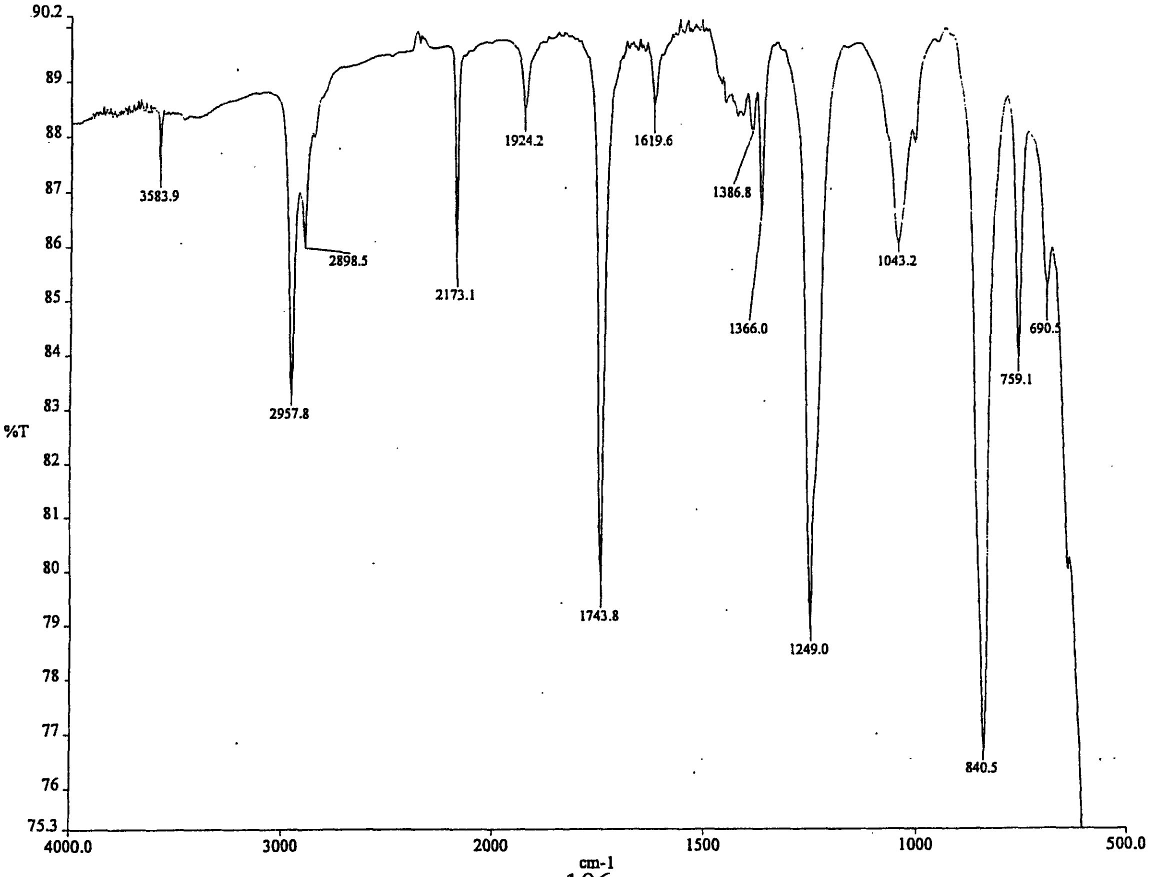


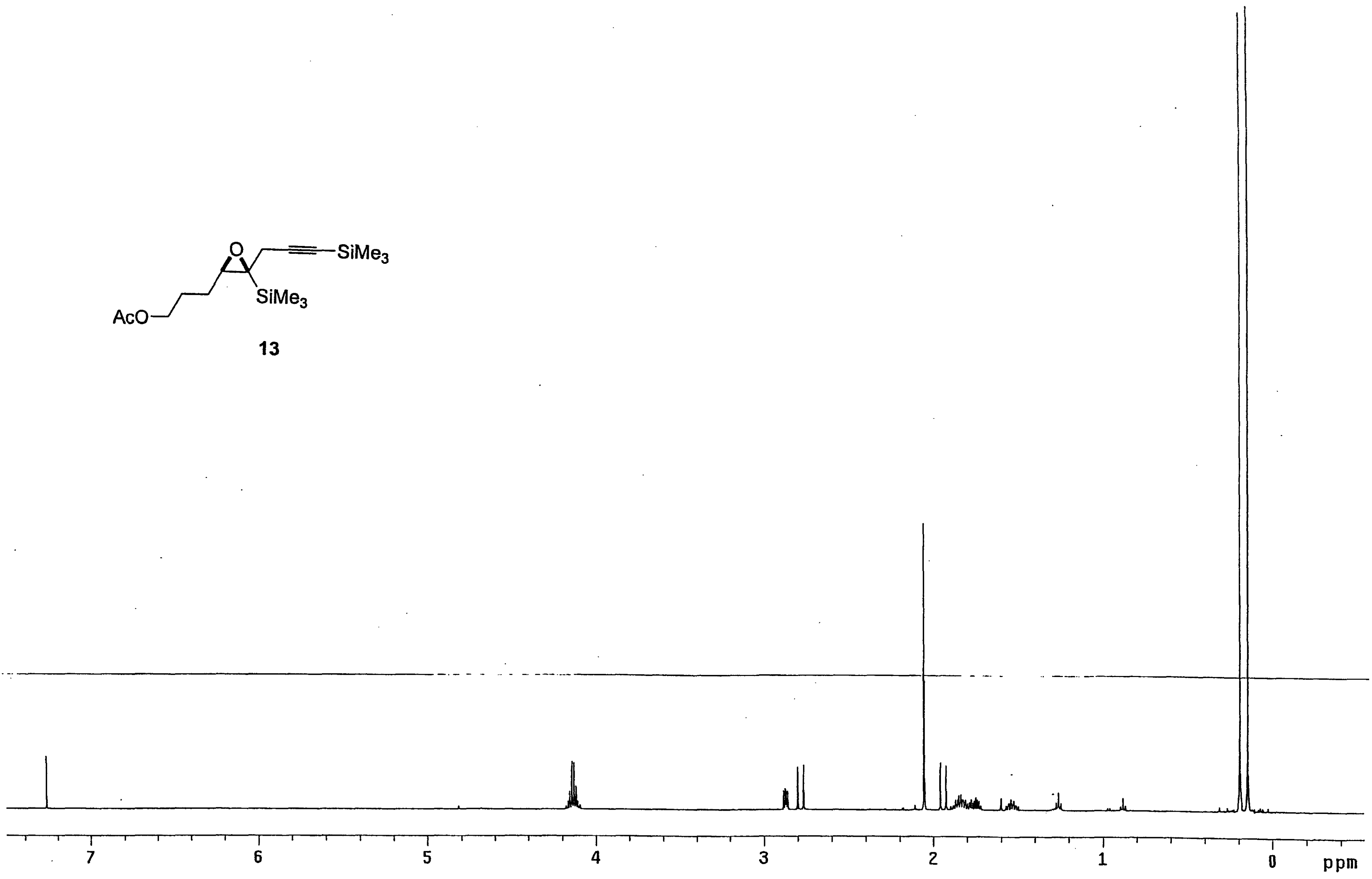
11 with 90% Eu(hfc)$_3$

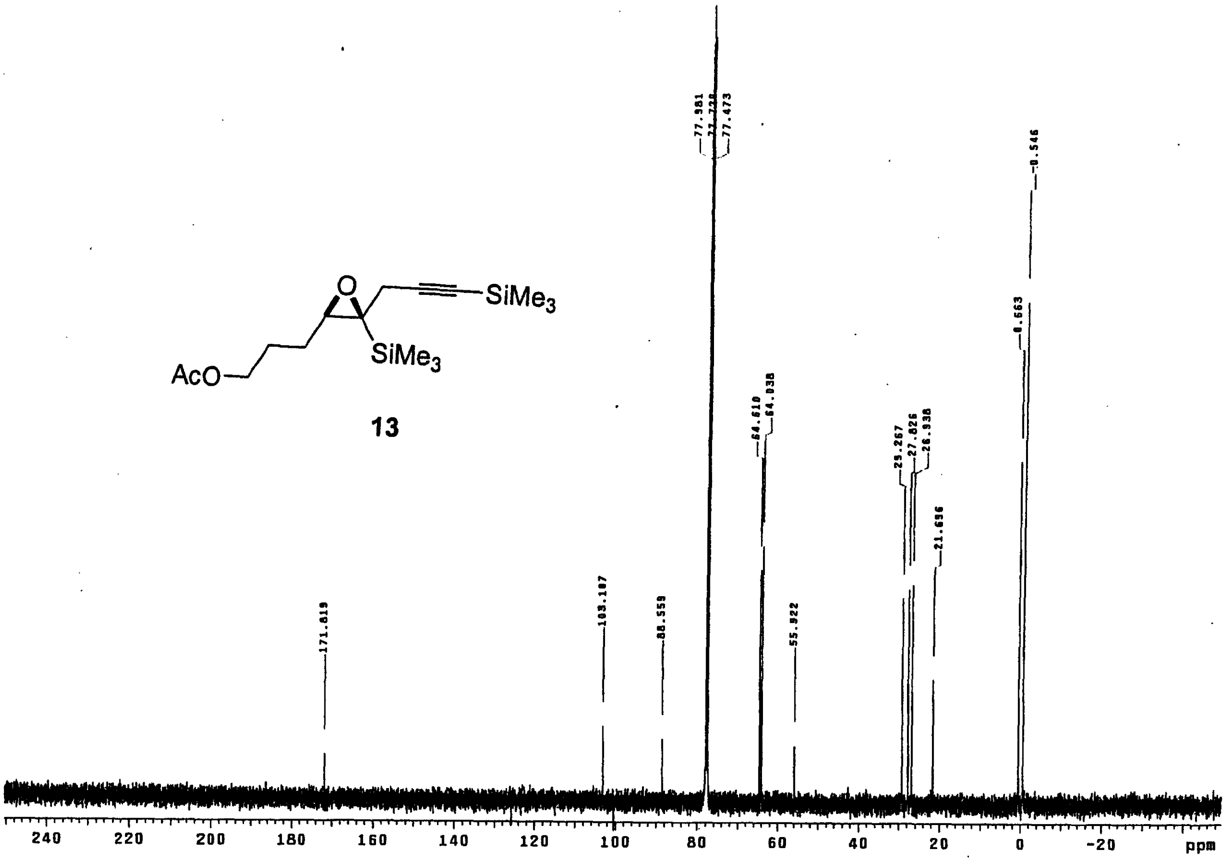

AcO
SiMe3
SiMe3
12
ppm
0
1
2
3
4
5
6
7
8
9
10
11

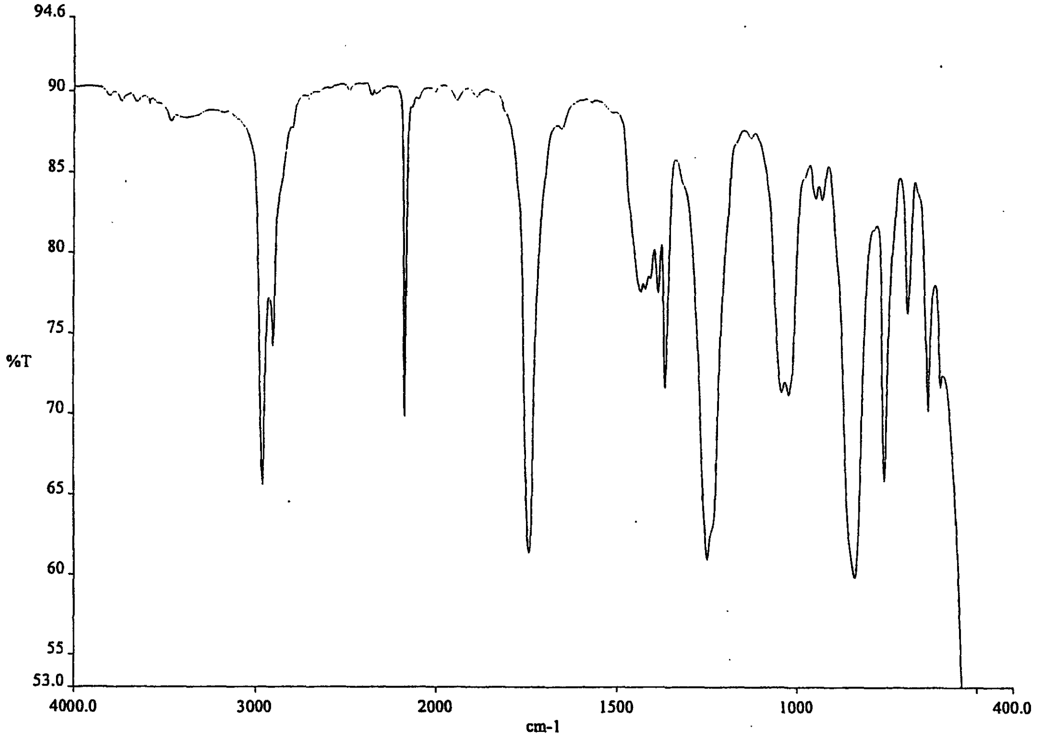

SiMe$_3$
SiMe$_3$
AcO
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

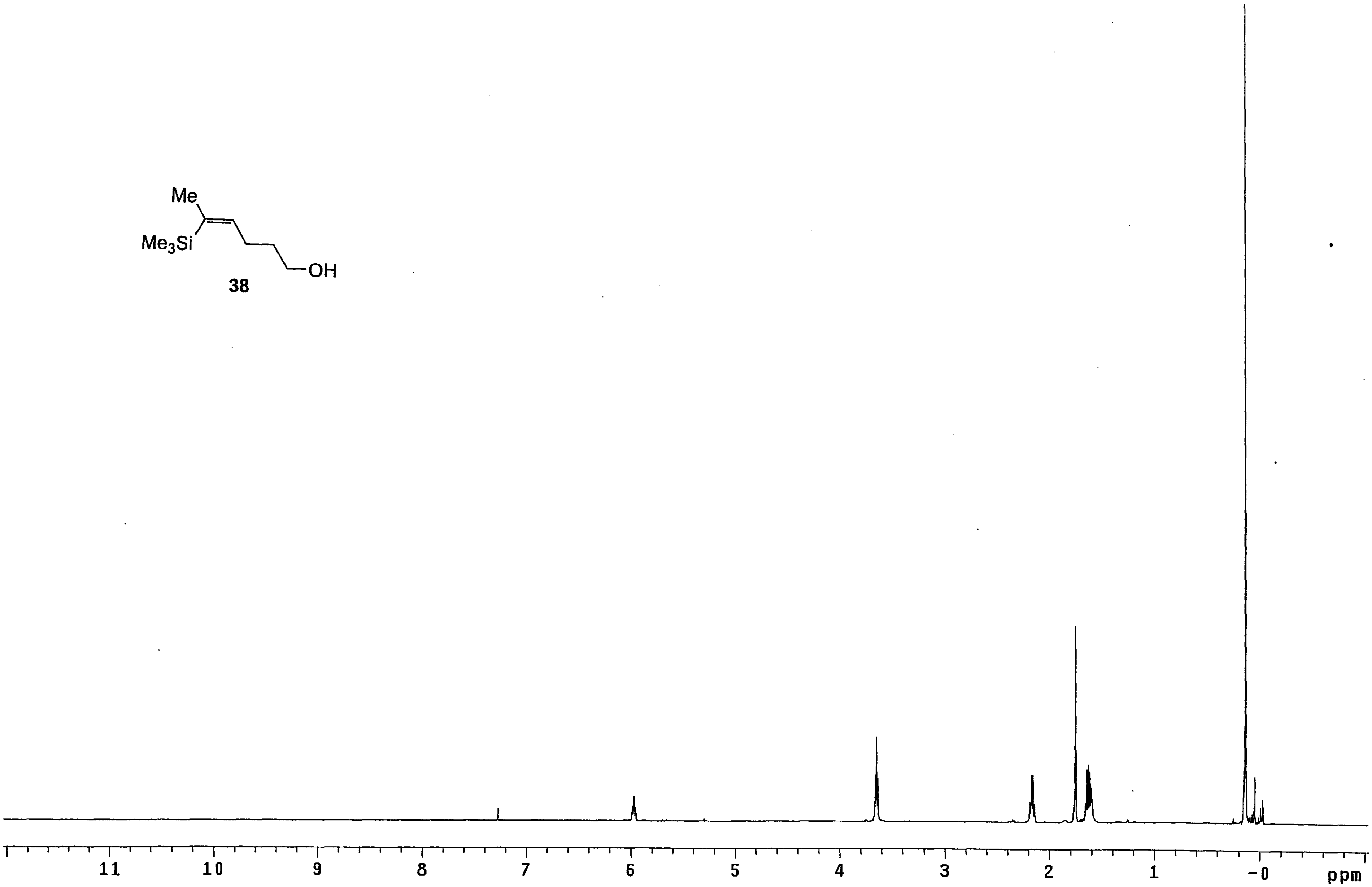
12


90.2
89
88
87
86
85
84
83
%T
82
81
80
79
78
77
76
75.3
4000.0
3000
2000
1500
1000
500.0
cm-1
3583.9
2957.8
2898.5
2173.1
1924.2
1743.8
1619.6
1386.8
1366.0
1249.0
1043.2
840.5
759.1
690.5

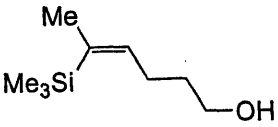

AcO
O
SiMe$_3$
SiMe$_3$
13
7
6
5
4
3
2
1
0
ppm


AcO
O
SiMe$_3$
SiMe$_3$
13
171.819
103.107
88.559
77.981
77.728
77.473
64.610
64.038
55.922
29.267
27.826
26.938
21.696
0.663
-0.546
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

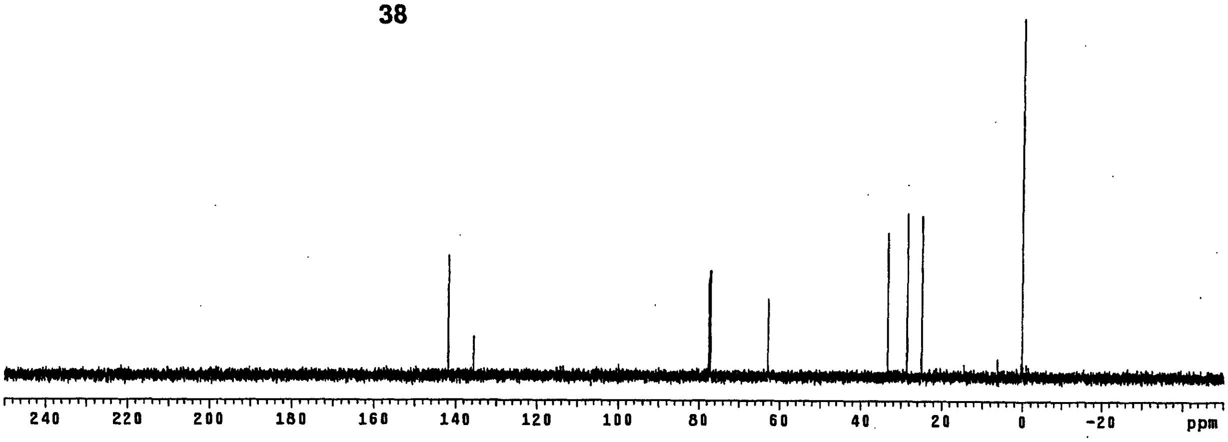

94.6
90
85
80
75
70
65
60
55
53.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1

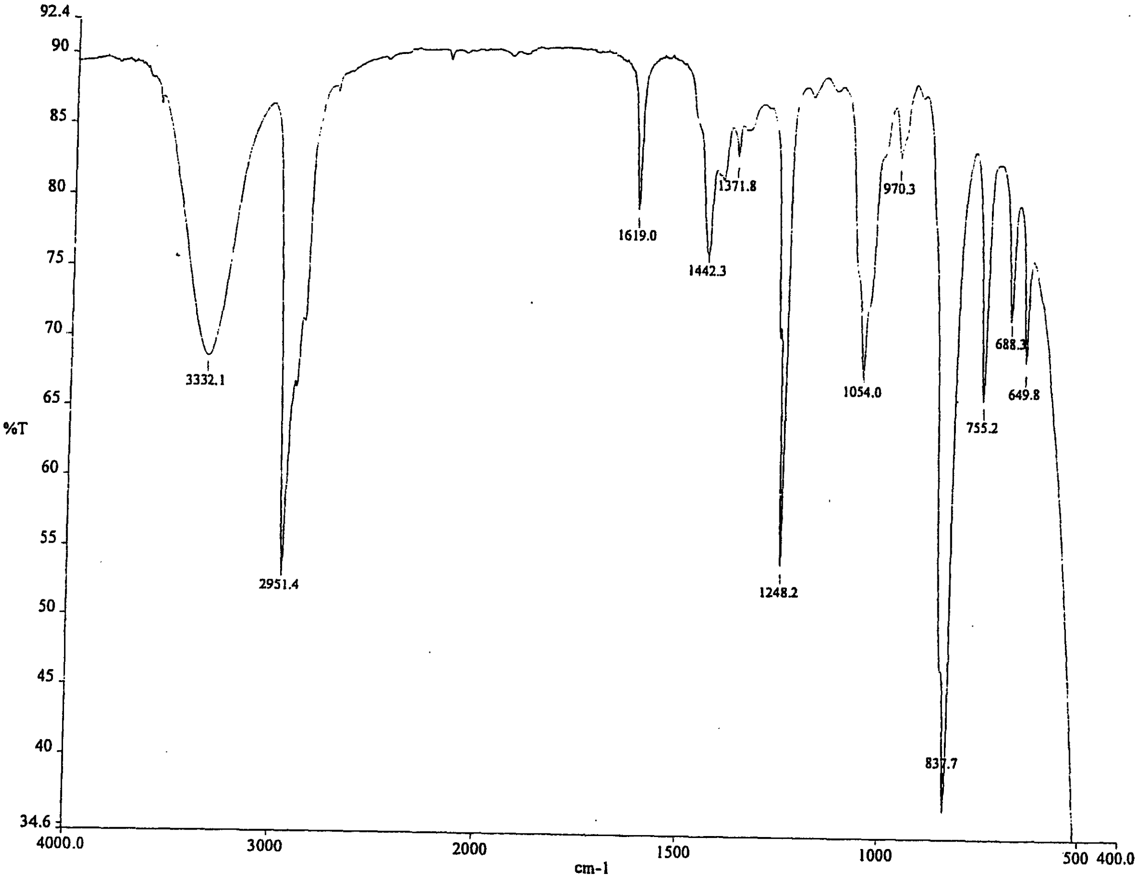


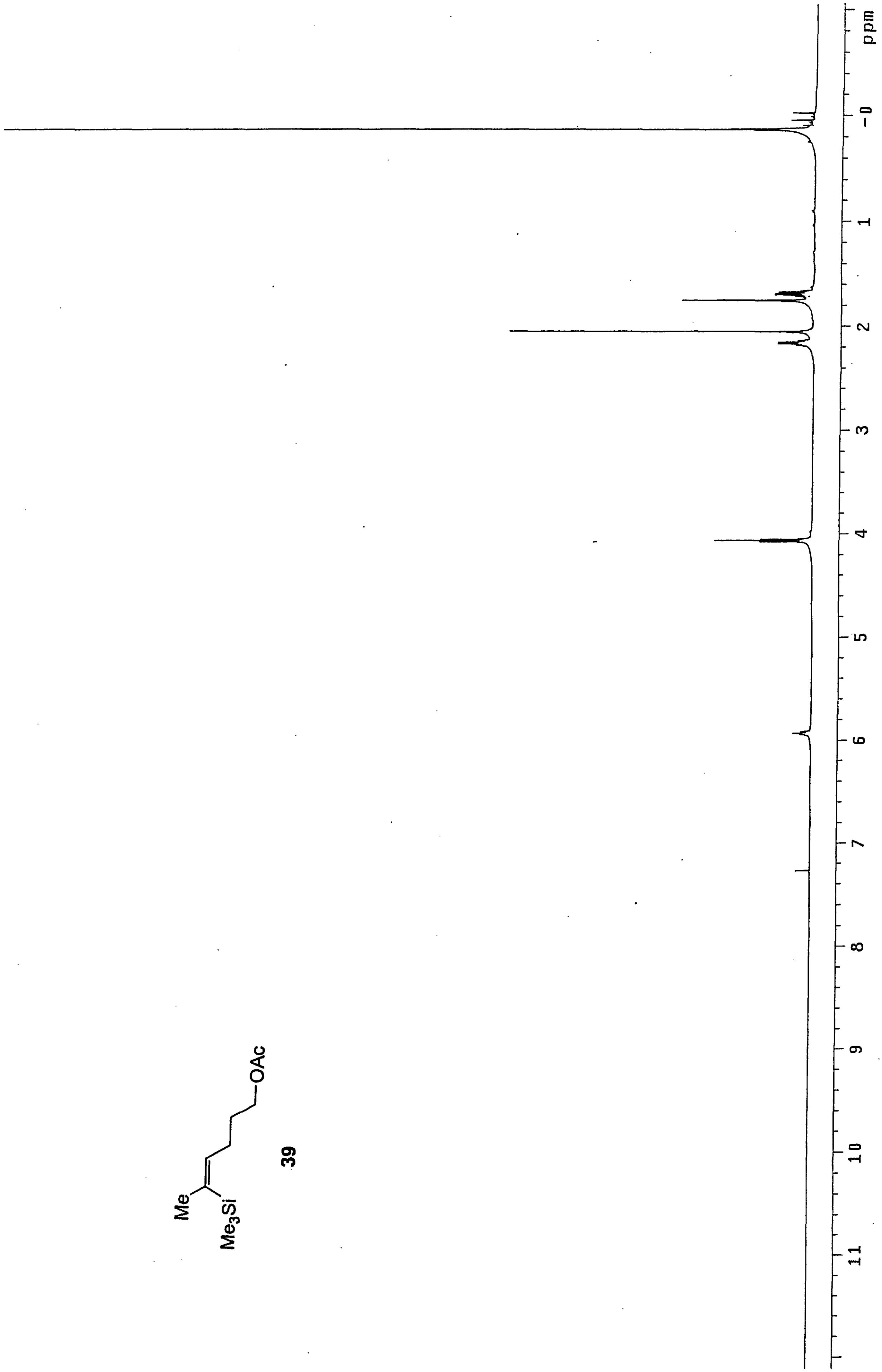
38


Me
Me3Si
OH

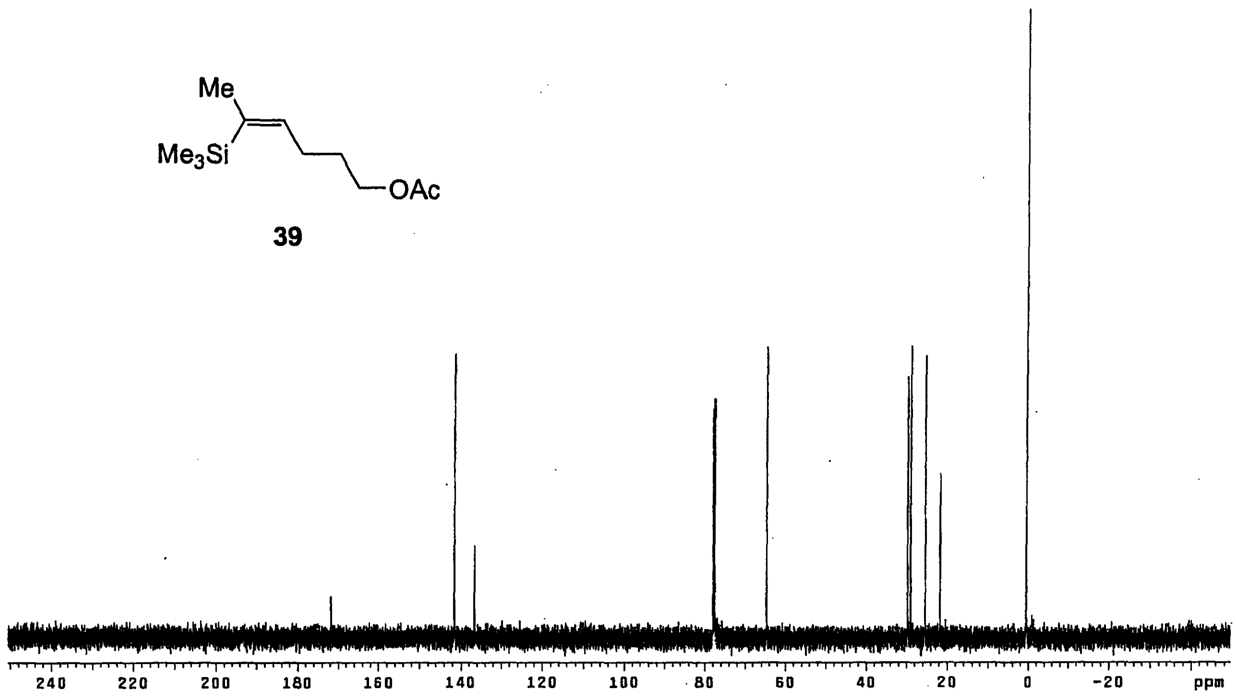
38


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


92.4
90
85
80
75
70
65
60
55
50
45
40
34.6
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3332.1
2951.4
1619.0
1442.3
1371.8
1248.2
1054.0
970.3
837.7
755.2
688.3
649.8

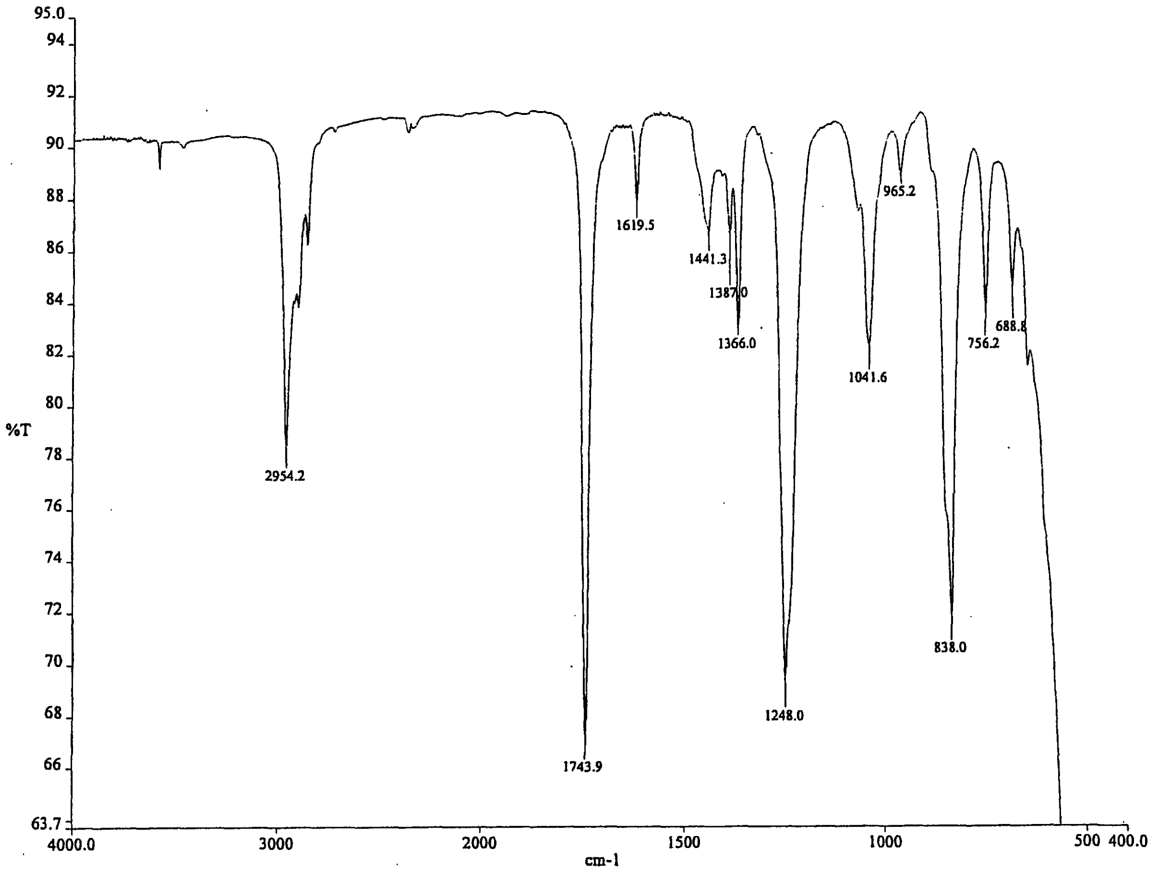


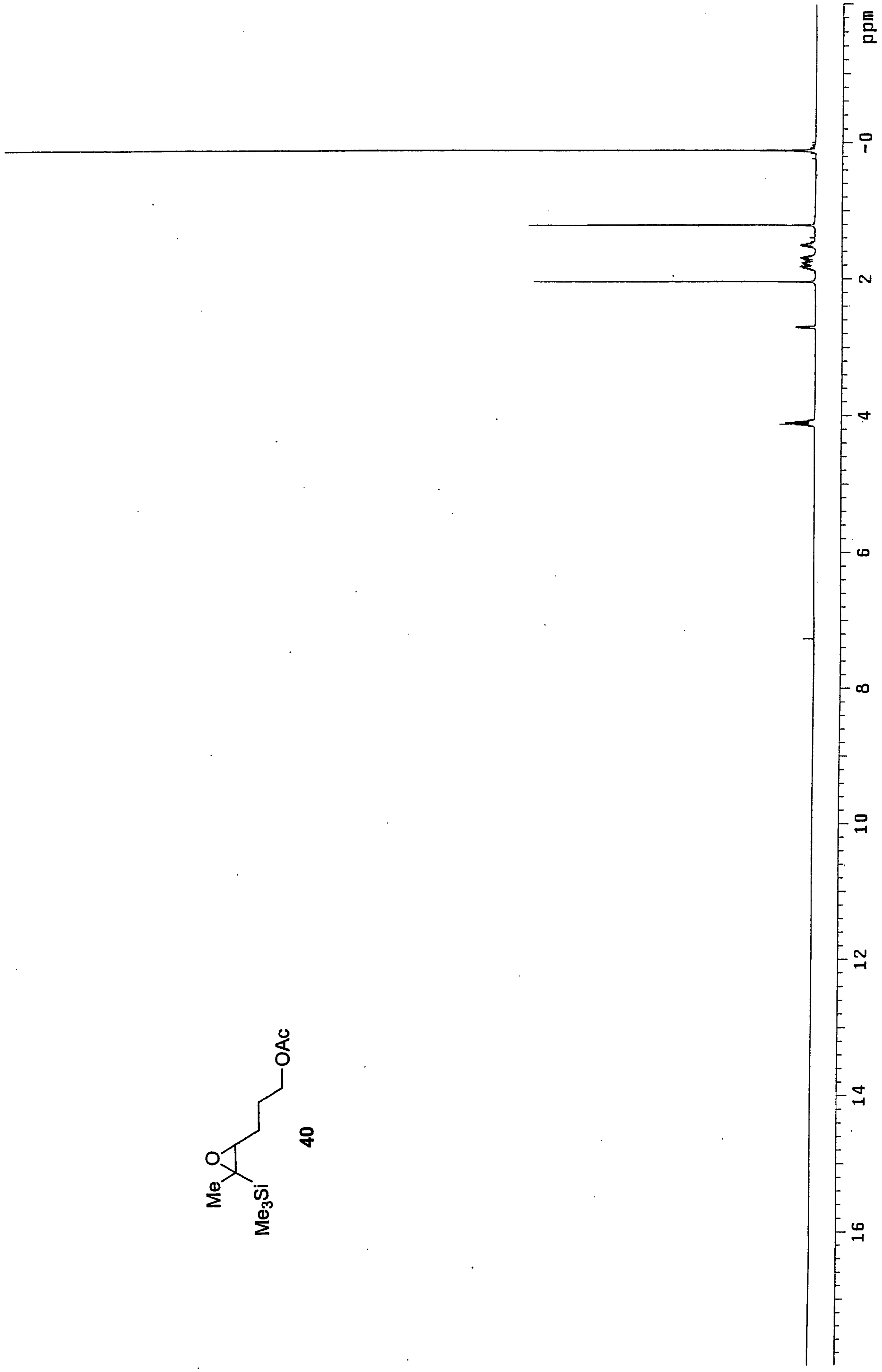
39


Me
Me3Si
OAc

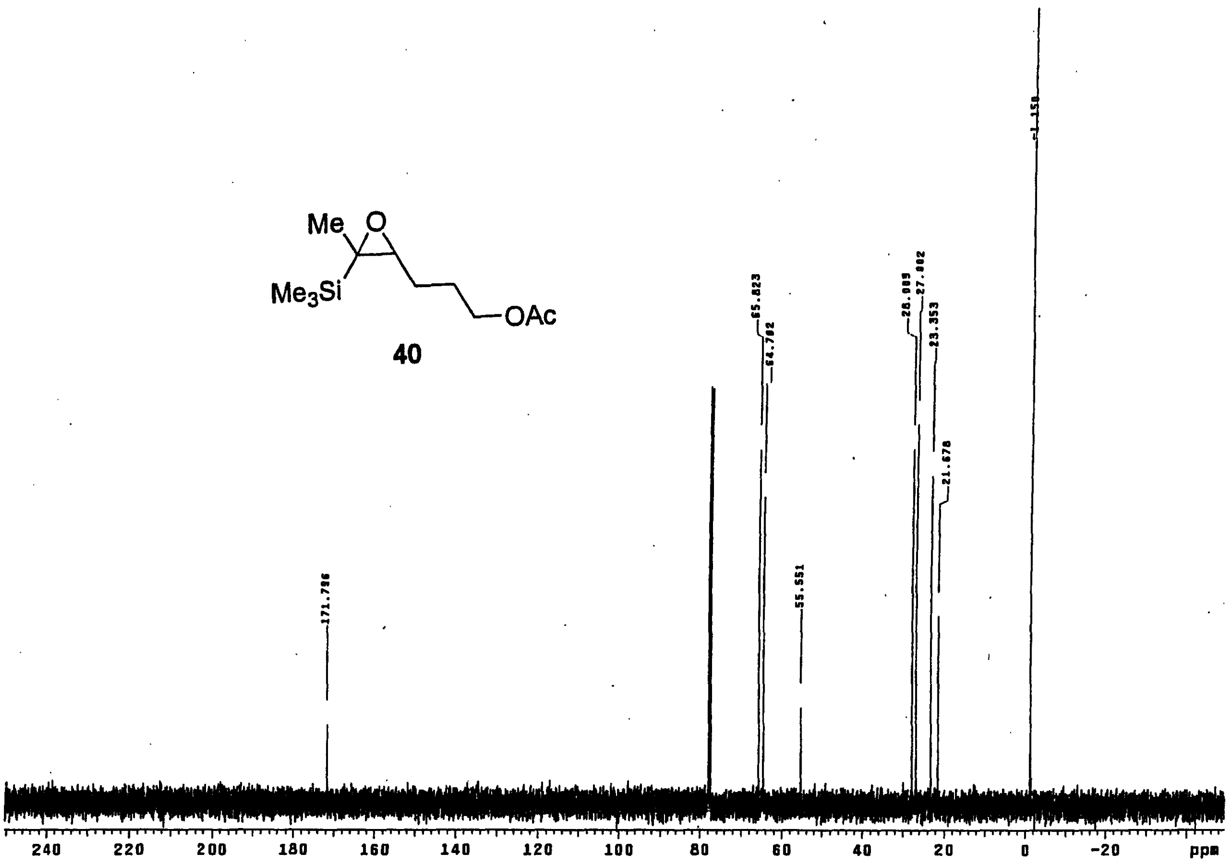
39

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

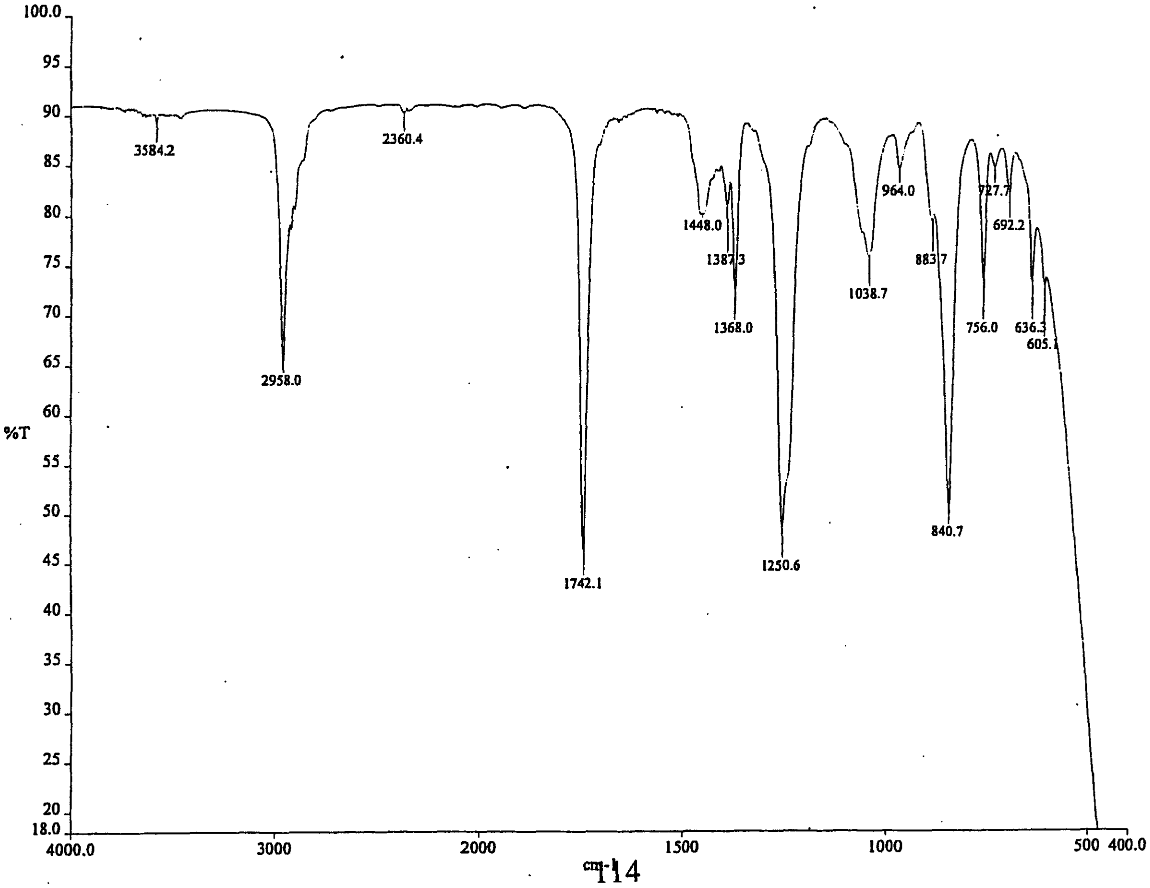

95.0
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
63.7
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2954.2
1743.9
1619.5
1441.3
1387.0
1366.0
1248.0
1041.6
965.2
838.0
756.2
688.8

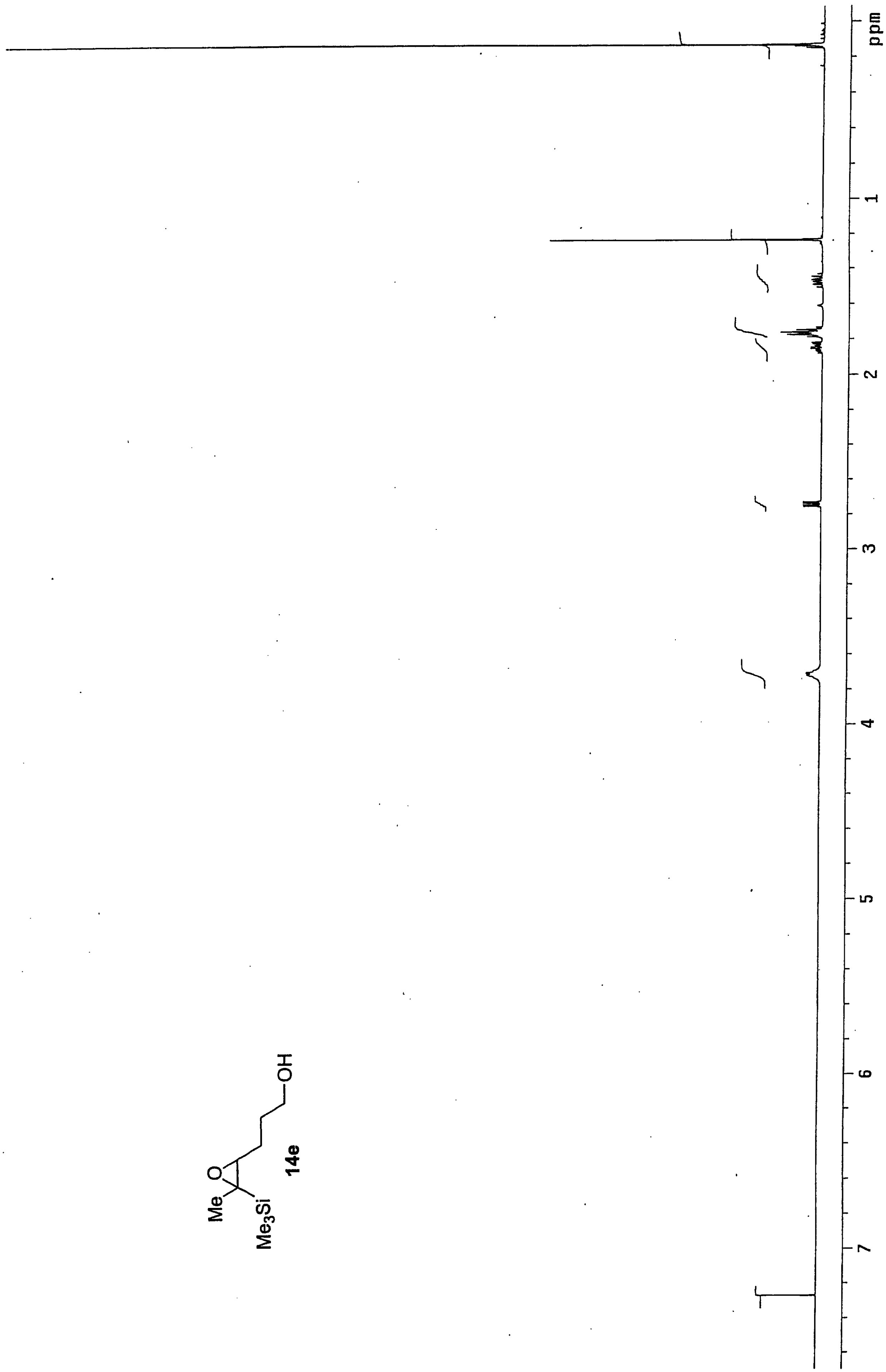


40

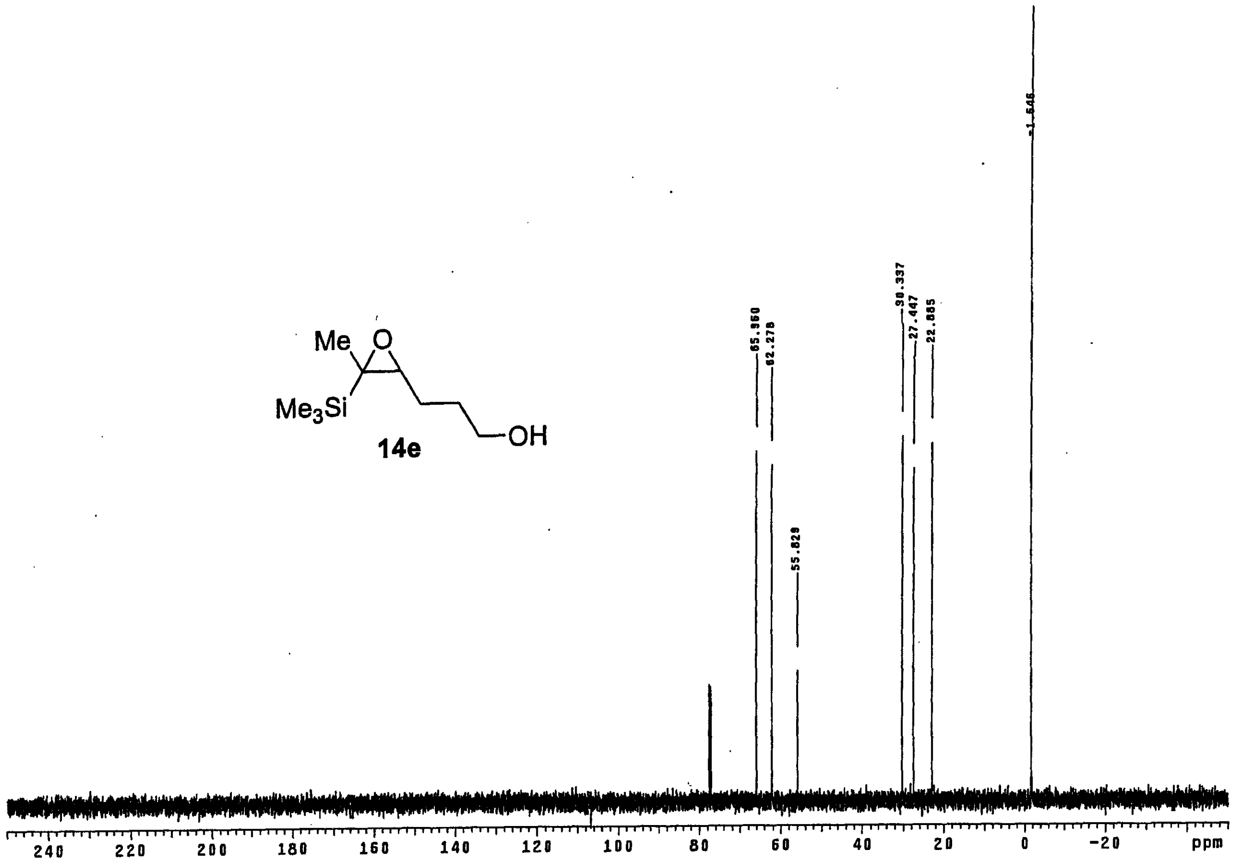

Me
O
Me3Si
OAc
171.786
65.823
64.782
55.551
28.009
27.002
23.353
21.678
-1.158
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

40


100.0
95
90
85
80
75
70
65
60
%T
55
50
45
40
35
30
25
20
18.0
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3584.2
2958.0
2360.4
1742.1
1448.0
1387.3
1368.0
1250.6
1038.7
964.0
883.7
840.7
756.0
727.7
692.2
636.3
605.1

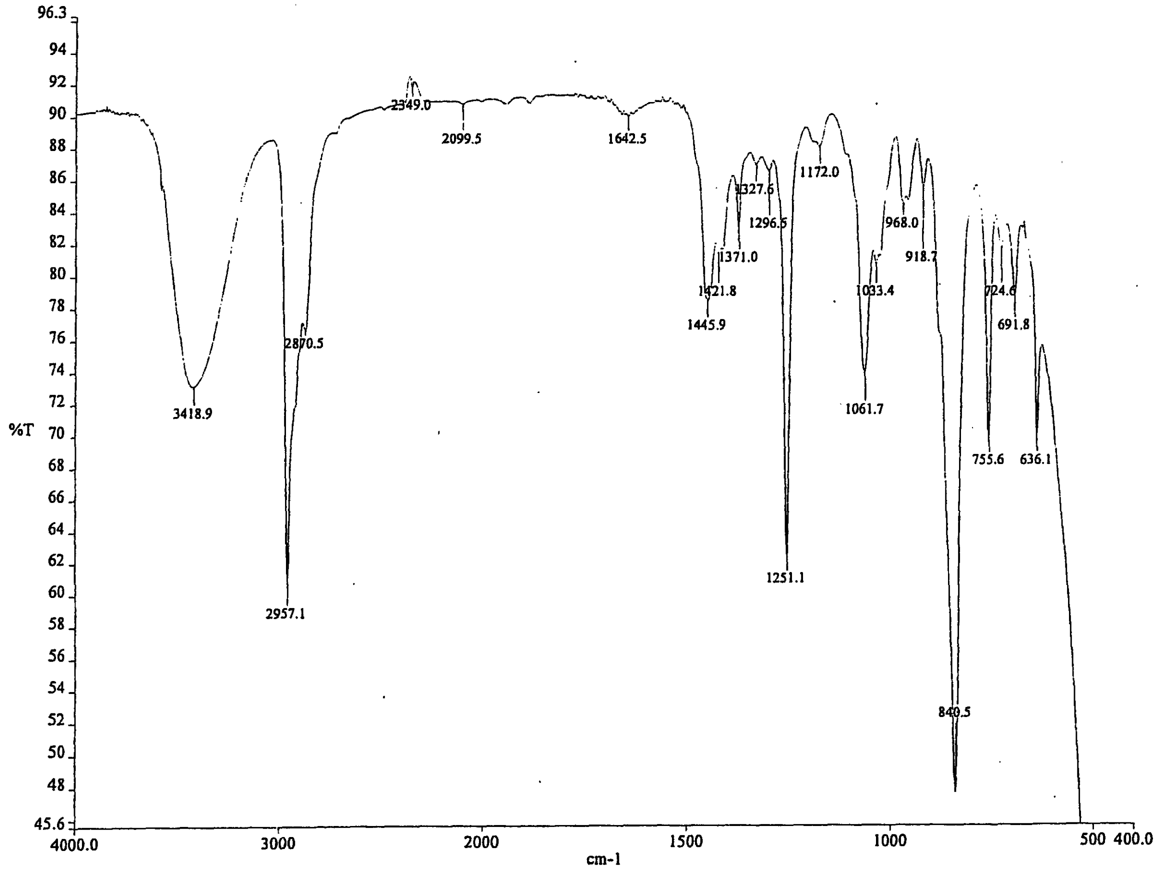


14e

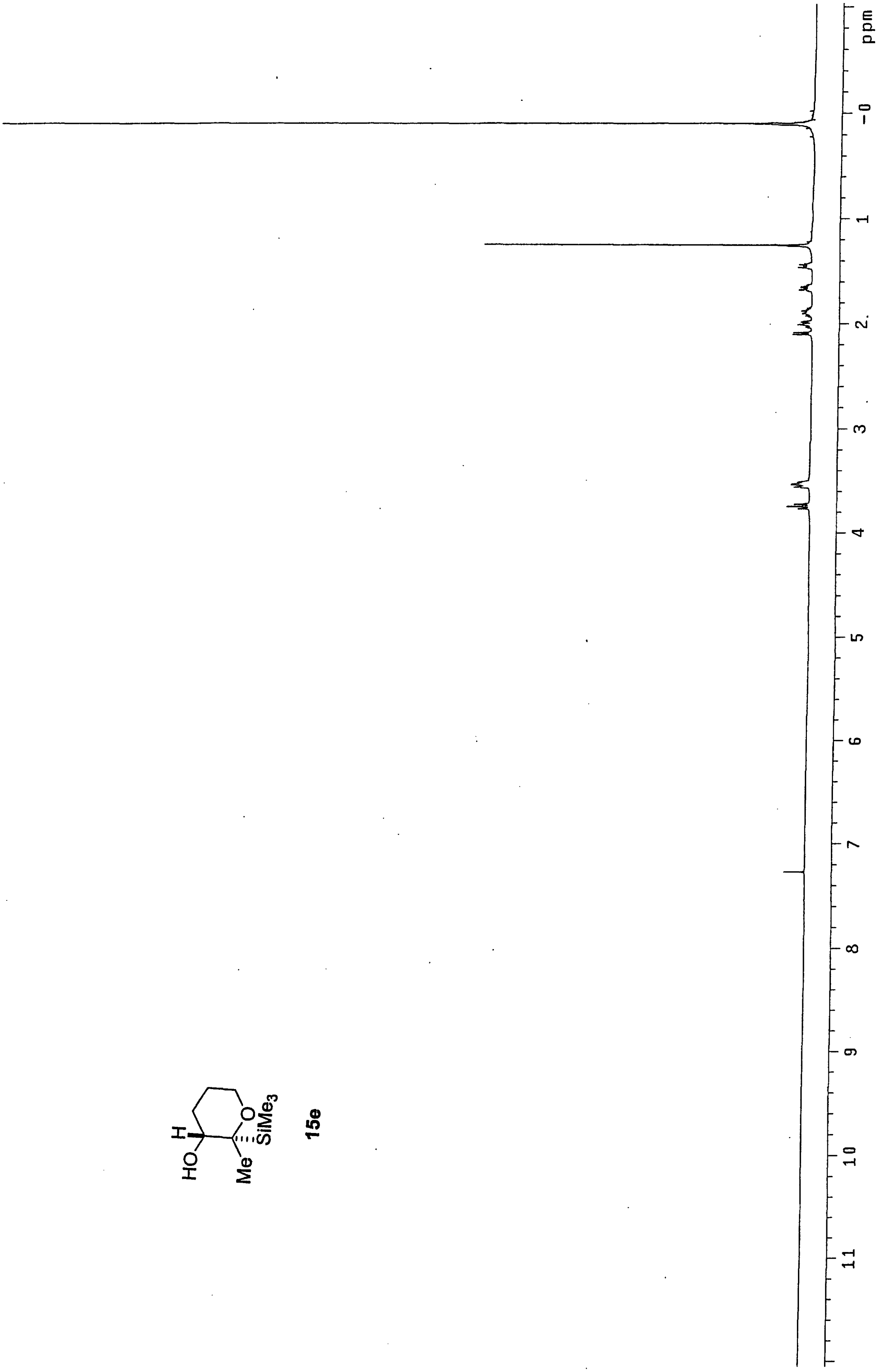


14e

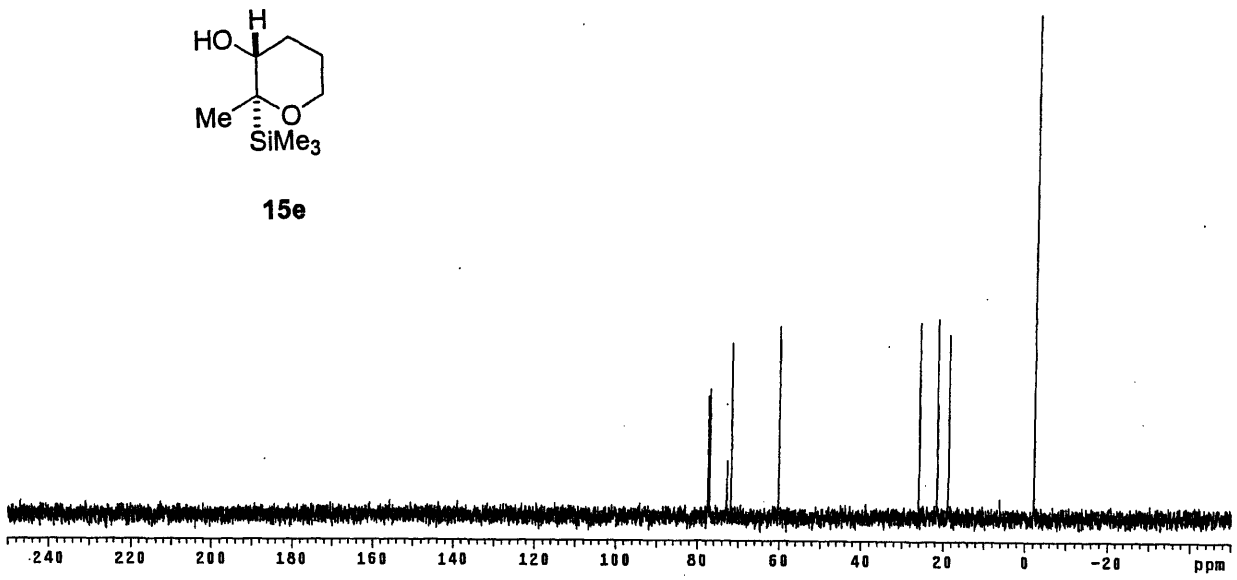
Me
O
Me3Si
OH
65.960
62.278
55.829
30.337
27.447
22.885
-1.646
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



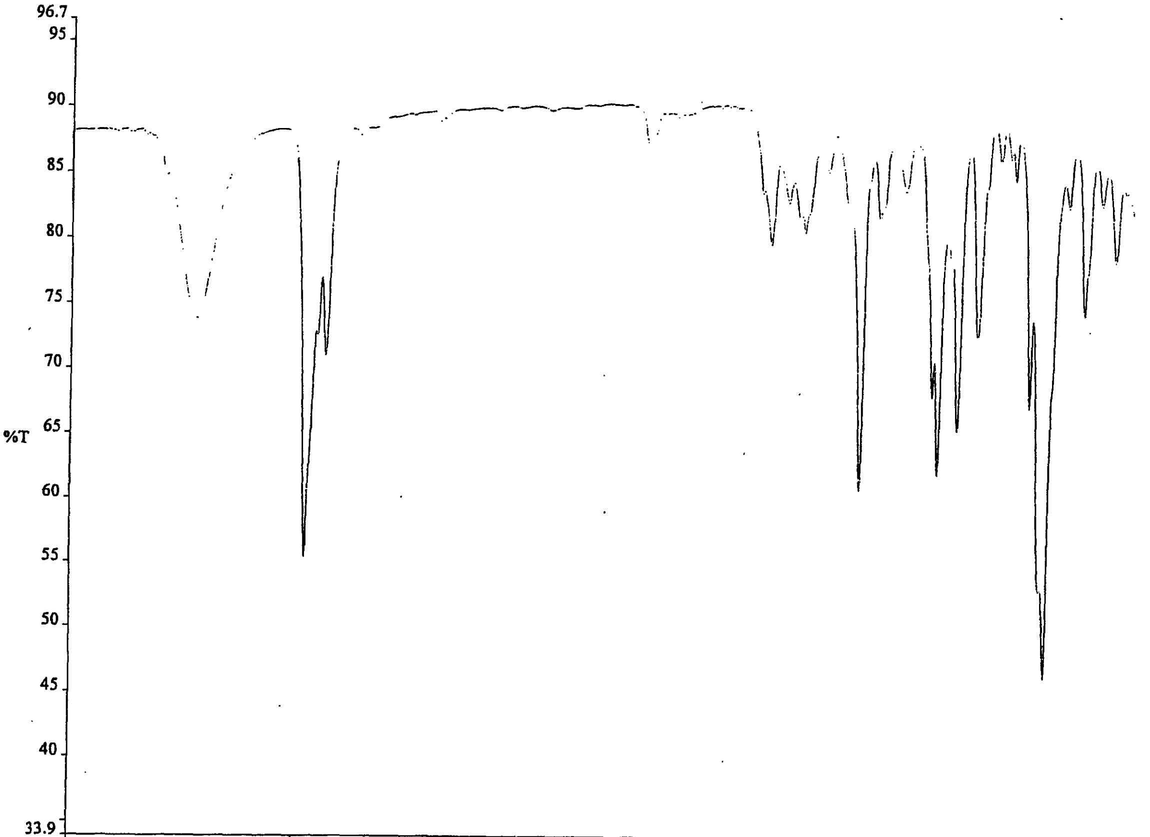
96.3
94
92
90
88
86
84
82
80
78
76
74
72
%T 70
68
66
64
62
60
58
56
54
52
50
48
45.6
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3418.9
2957.1
2870.5
2349.0
2099.5
1642.5
1445.9
1421.8
1371.0
1327.6
1296.5
1251.1
1172.0
1061.7
1033.4
968.0
918.7
840.5
755.6
724.6
691.8
636.1

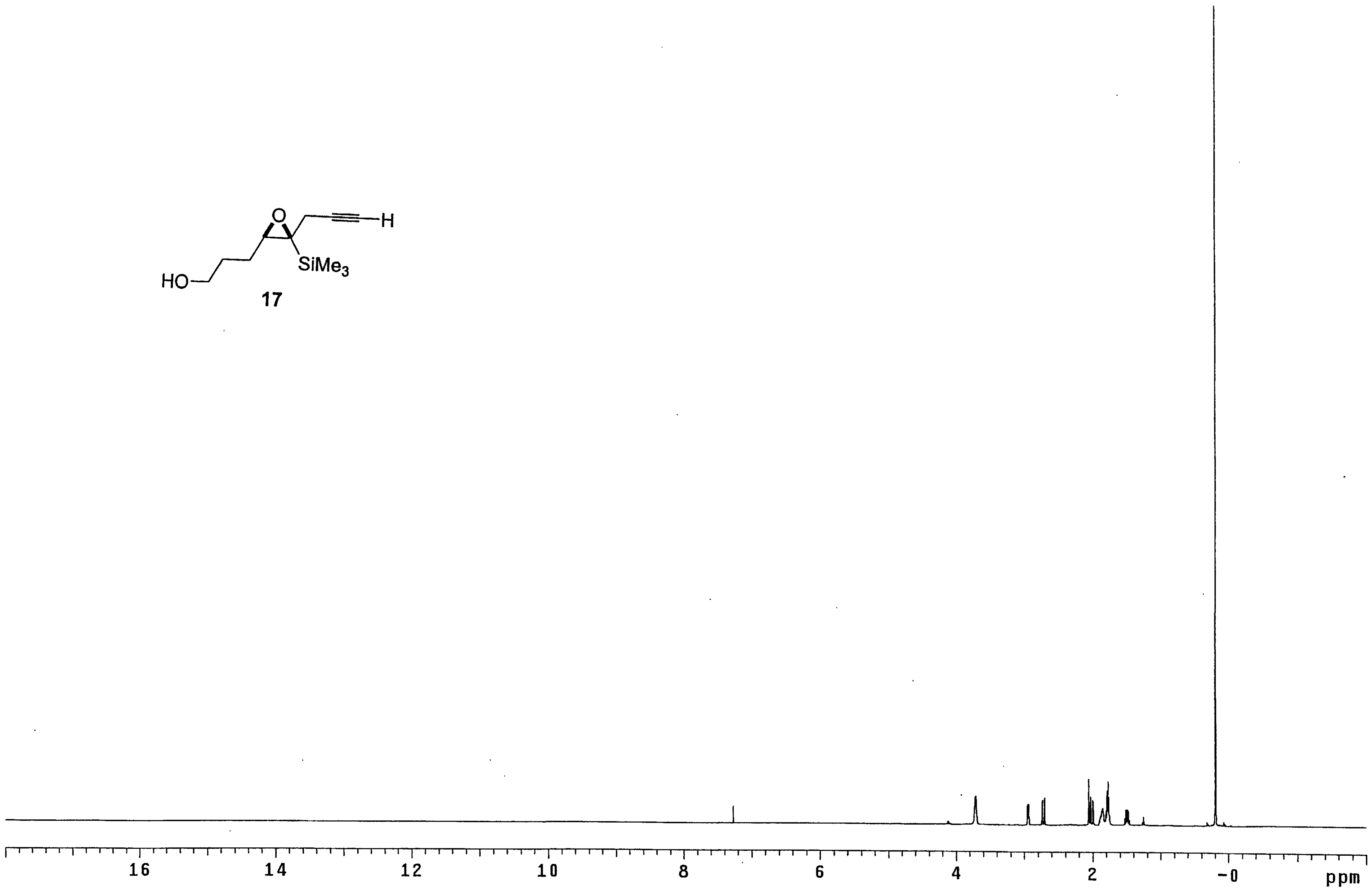


15e

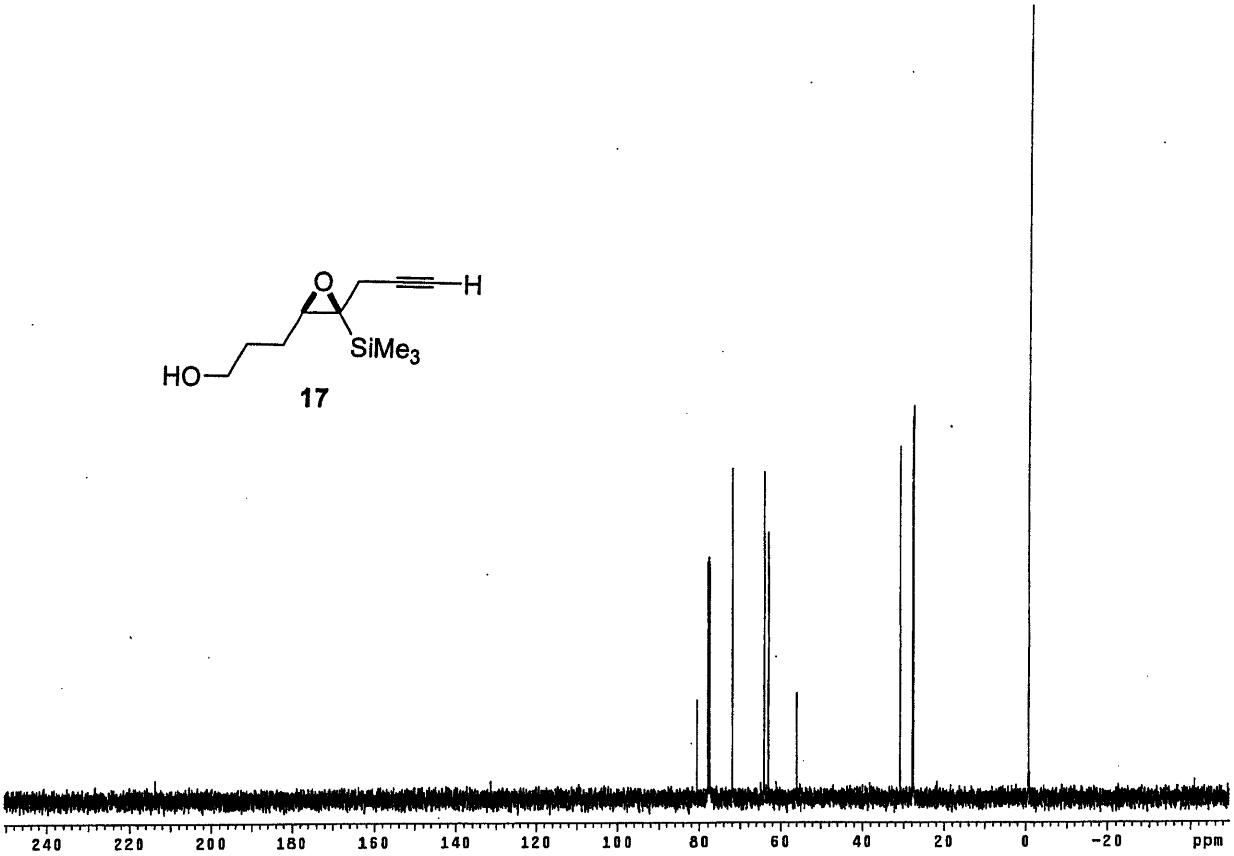

H
HO
Me
O
SiMe3
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

15e


96.7
95
90
85
80
75
70
65
60
55
50
45
40
33.9
%T
4000.0
3000
2000
1500
1000
650.0
cm-1

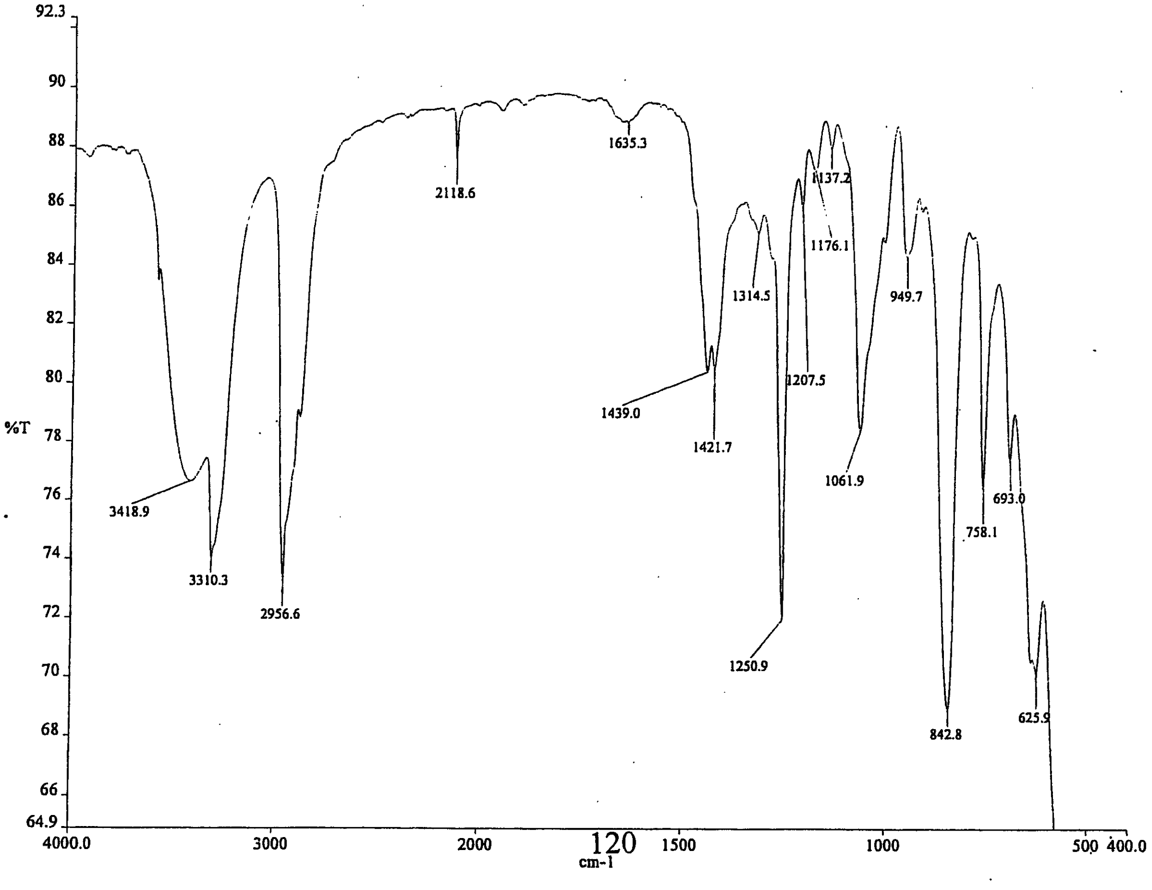


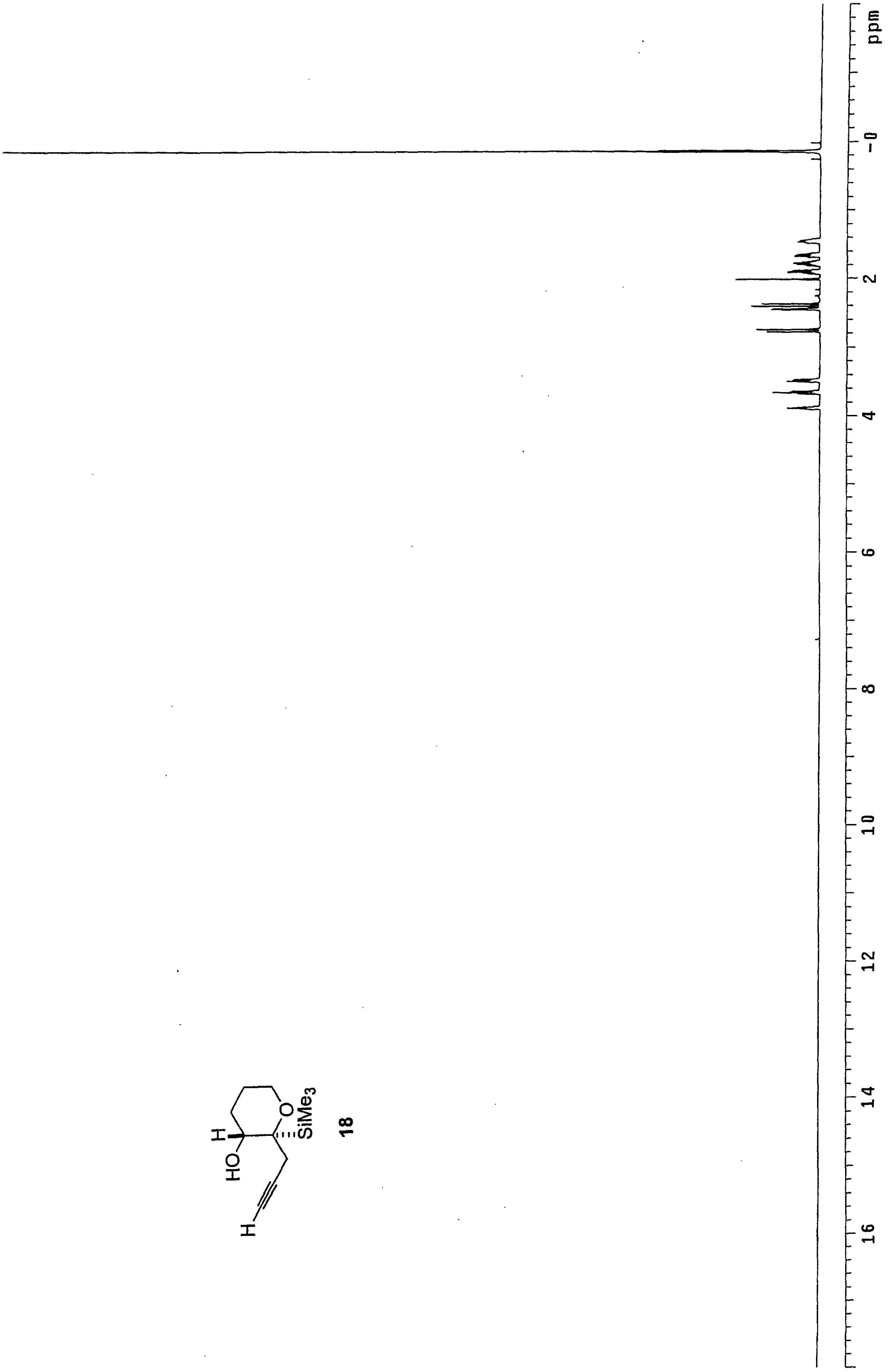
17

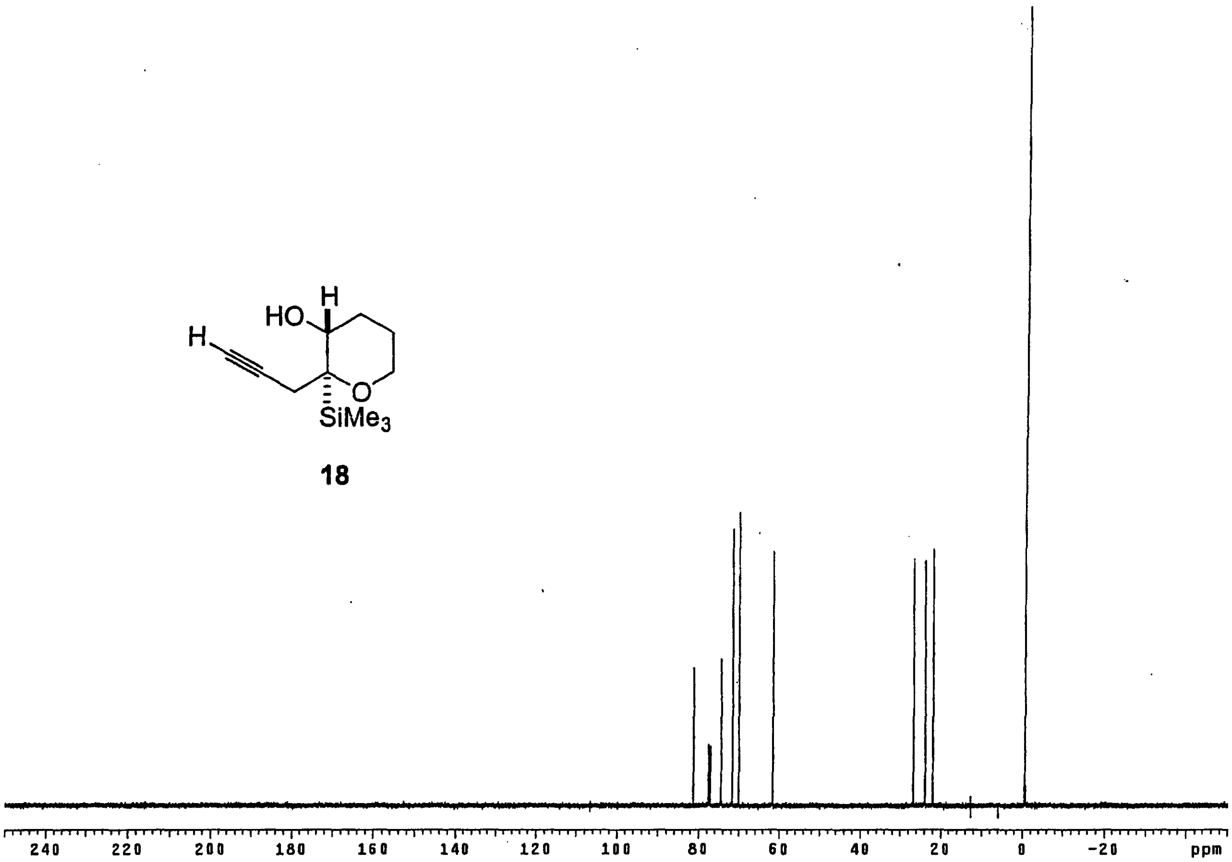

O
H
SiMe$_3$
HO

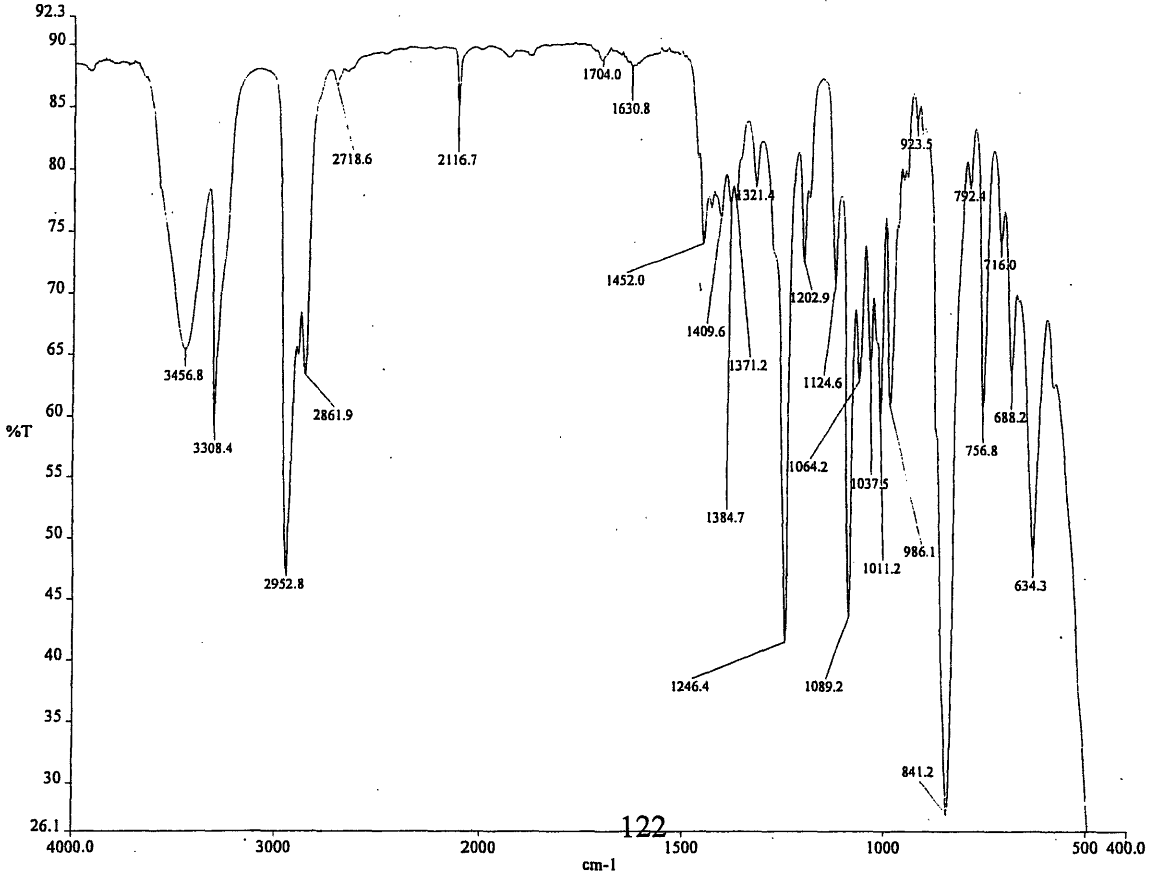
17

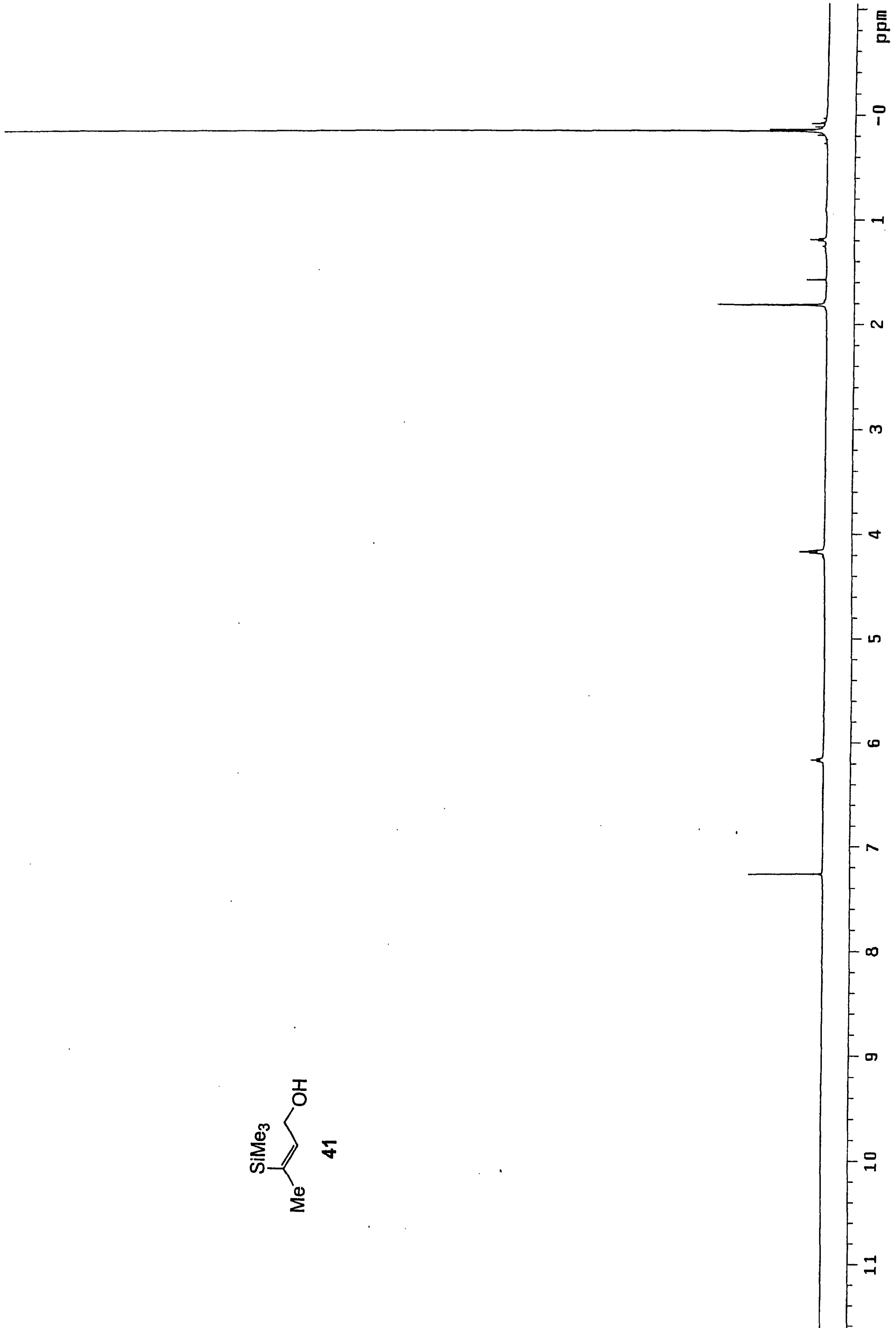
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


92.3
90
88
86
84
82
80
%T
78
76
74
72
70
68
66
64.9
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3418.9
3310.3
2956.6
2118.6
1635.3
1439.0
1421.7
1314.5
1250.9
1207.5
1137.2
1176.1
1061.9
949.7
842.8
758.1
693.0
625.9

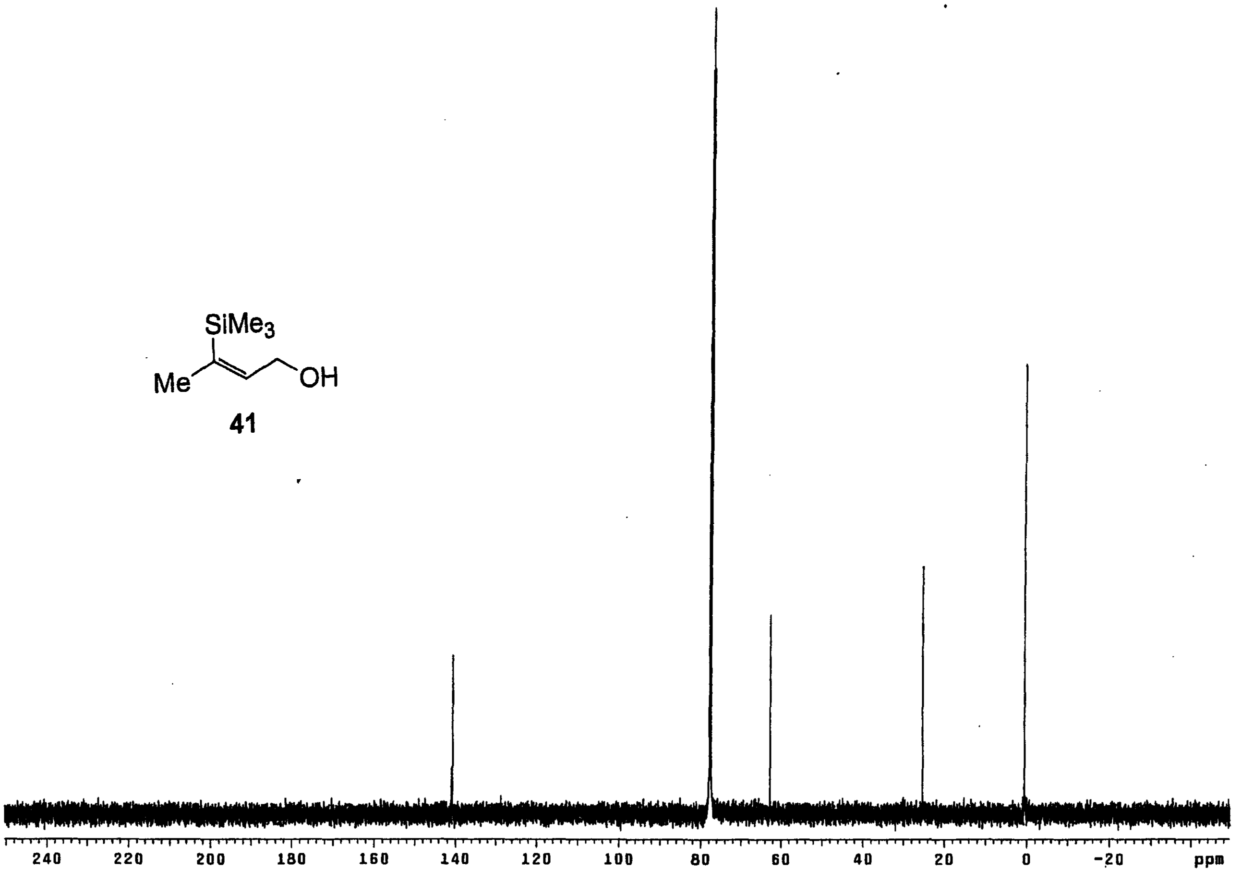

ppm
0
2
4
6
8
10
12
14
16
HO
H
O
SiMe3
H
18

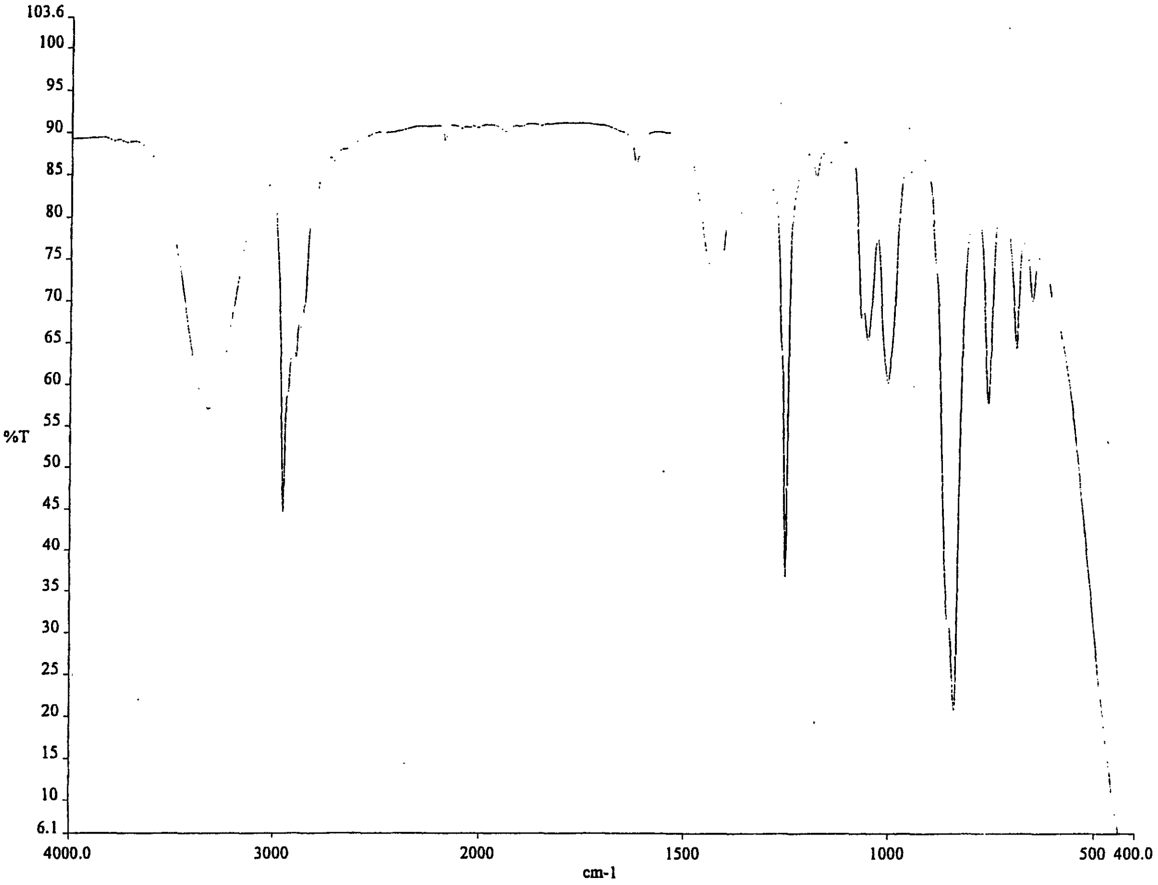

HO
H
H
O
SiMe3
18
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

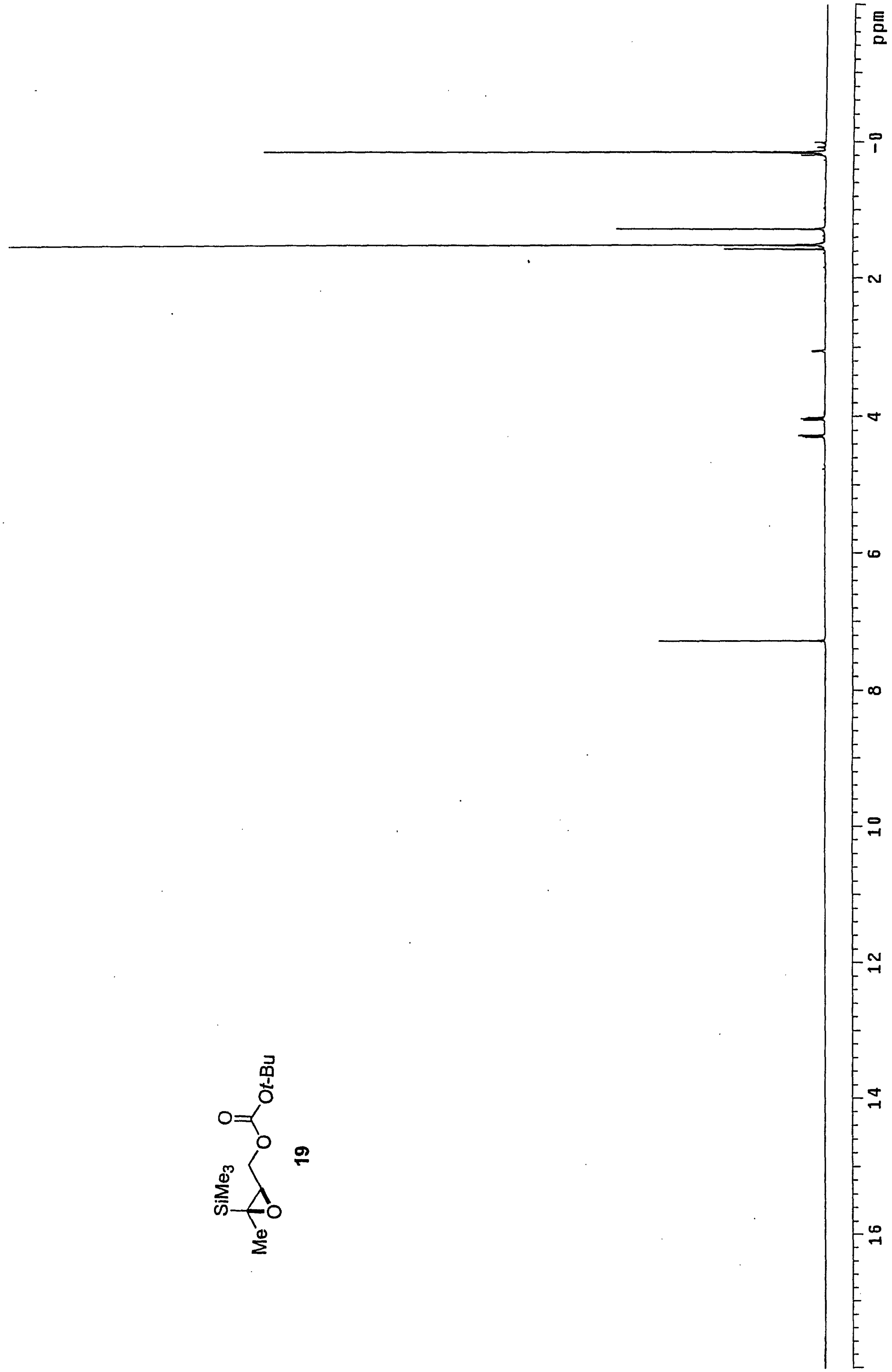

92.3
90
85
80
75
70
65
60
55
50
45
40
35
30
26.1
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3456.8
3308.4
2952.8
2861.9
2718.6
2116.7
1704.0
1630.8
1452.0
1409.6
1384.7
1371.2
1321.4
1246.4
1202.9
1124.6
1089.2
1064.2
1037.5
1011.2
986.1
923.5
841.2
792.4
756.8
716.0
688.2
634.3



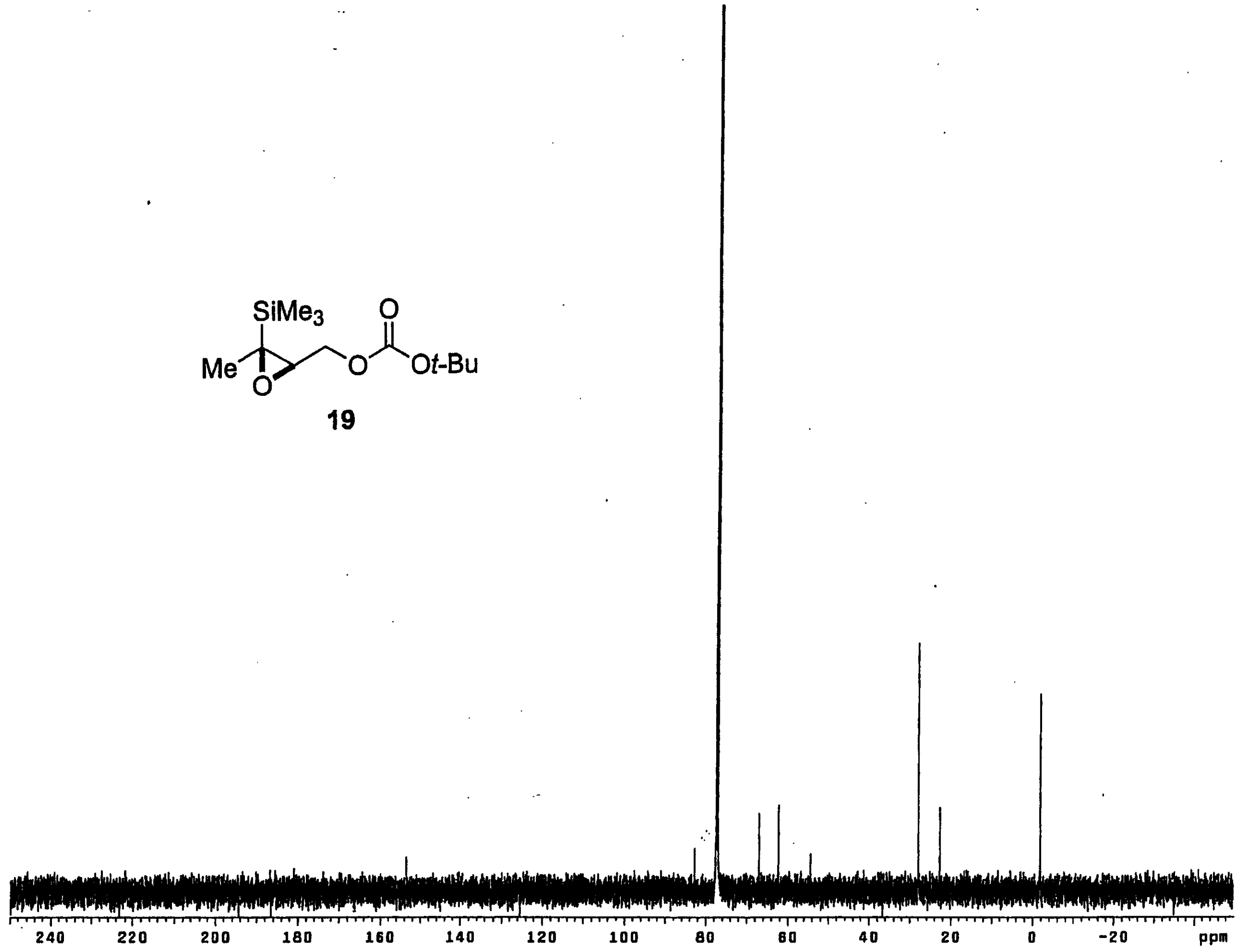
41


SiMe3
Me
OH
41
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

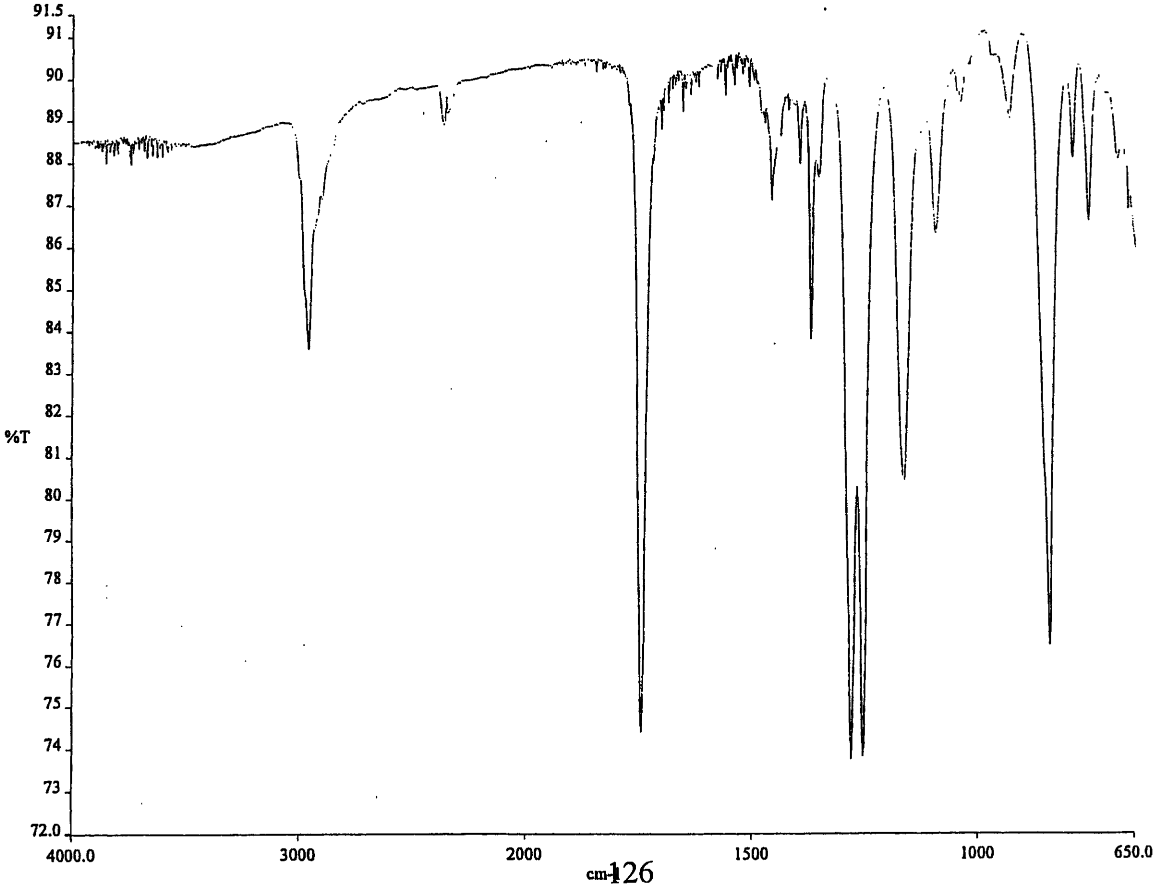

103.6
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
6.1
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1



19


SiMe3
Me
O
O
O
Ot-Bu
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

19


91.5
91
90
89
88
87
86
85
84
83
82
%T
81
80
79
78
77
76
75
74
73
72.0
4000.0
3000
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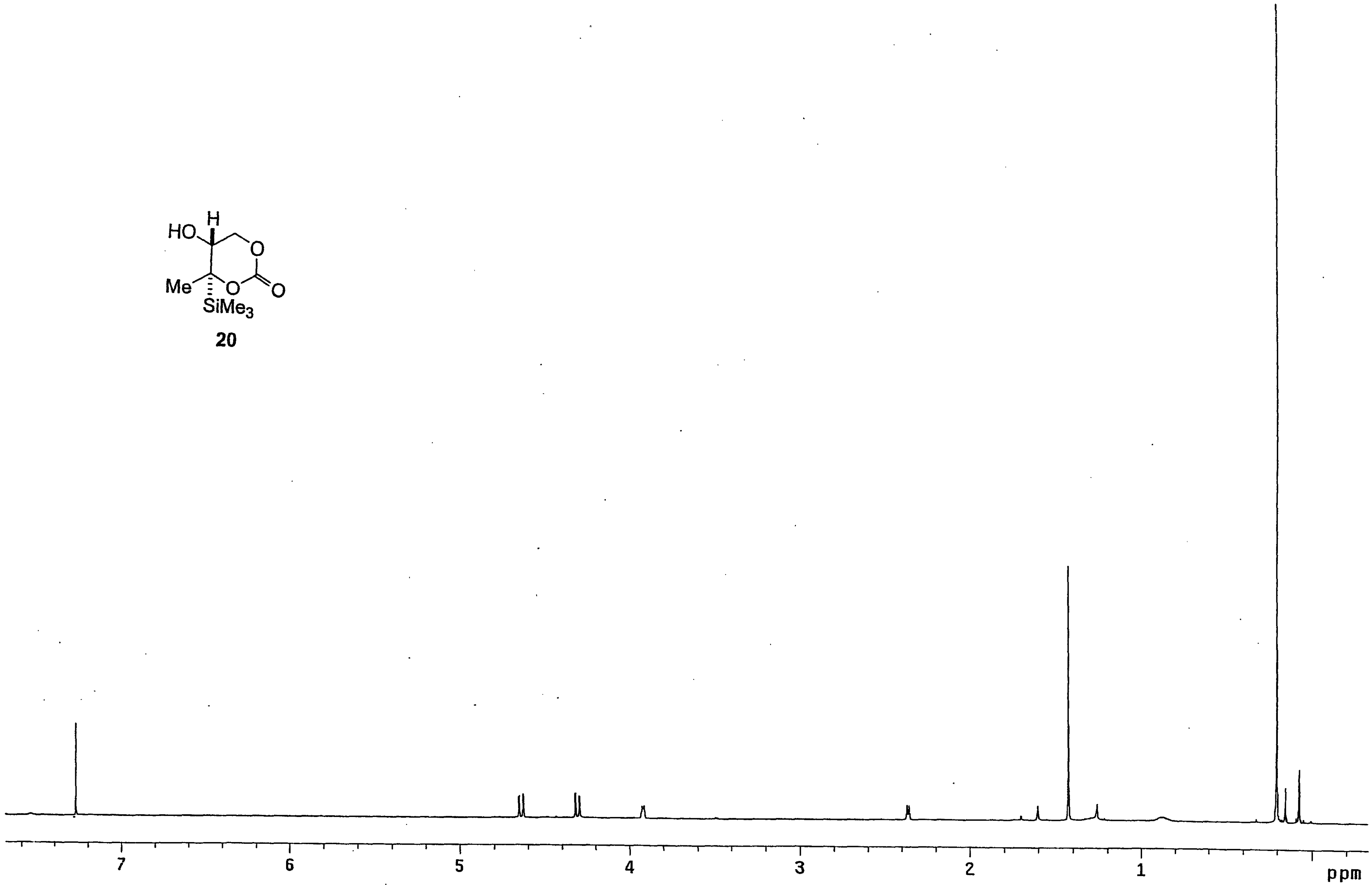
1500
1000
650.0
cm-1



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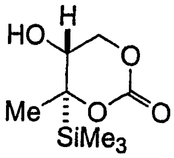
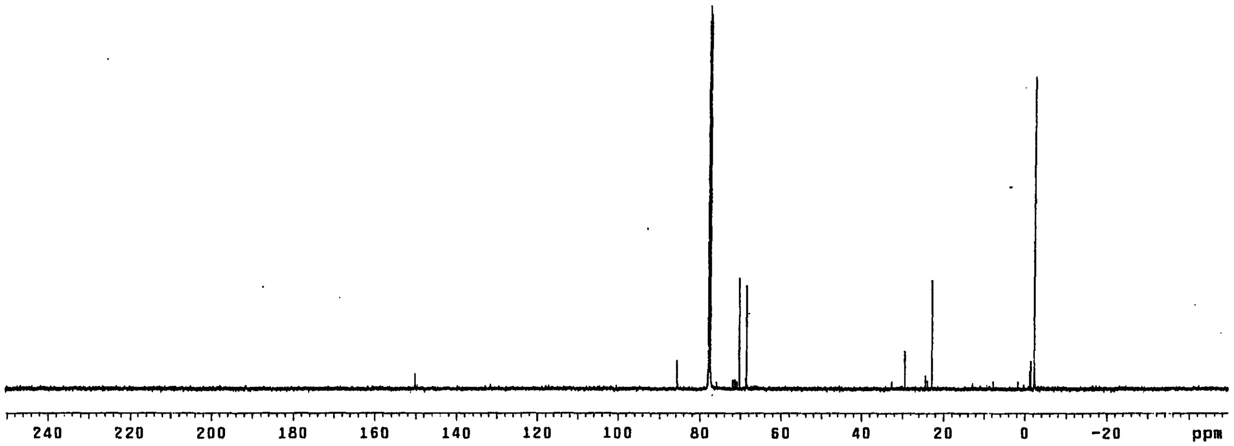
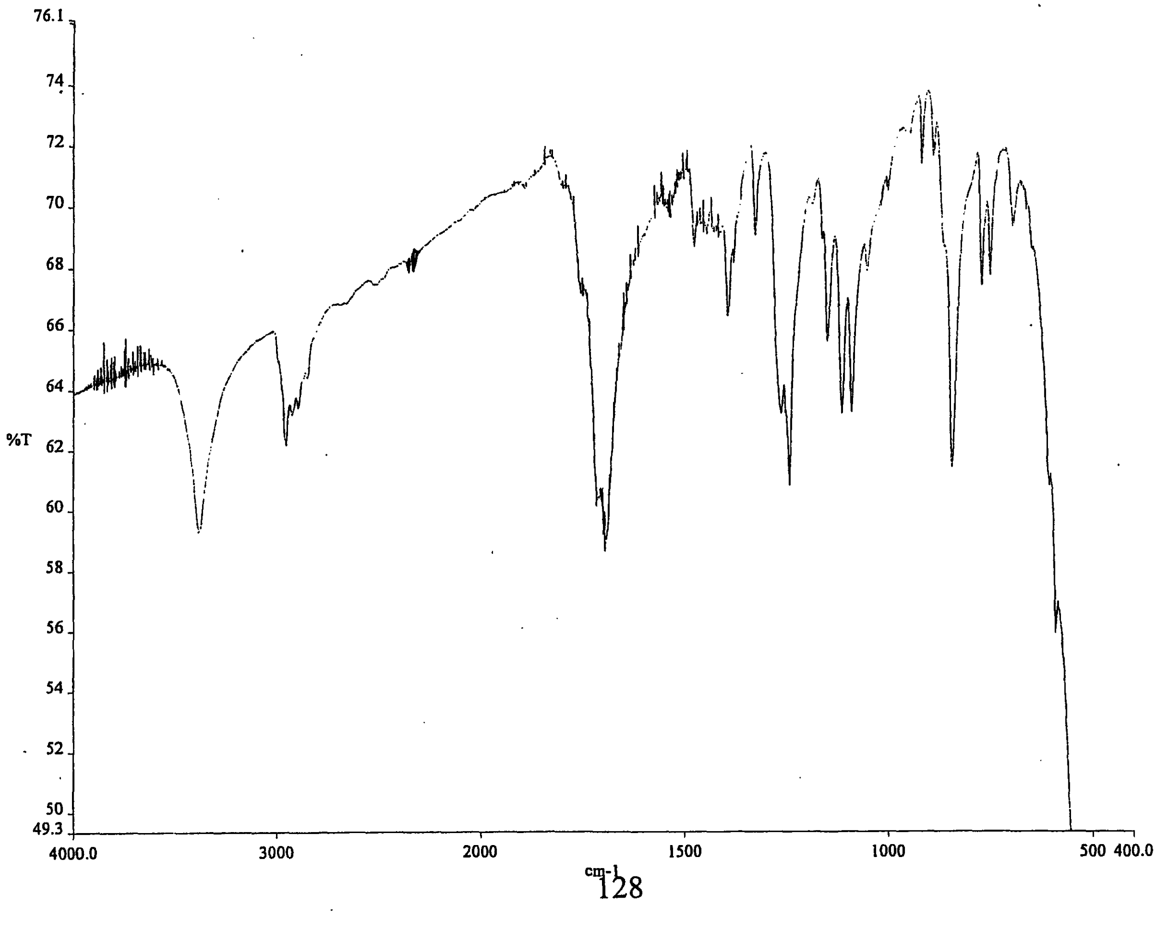


H
HO
O
O
Me
O
SiMe3

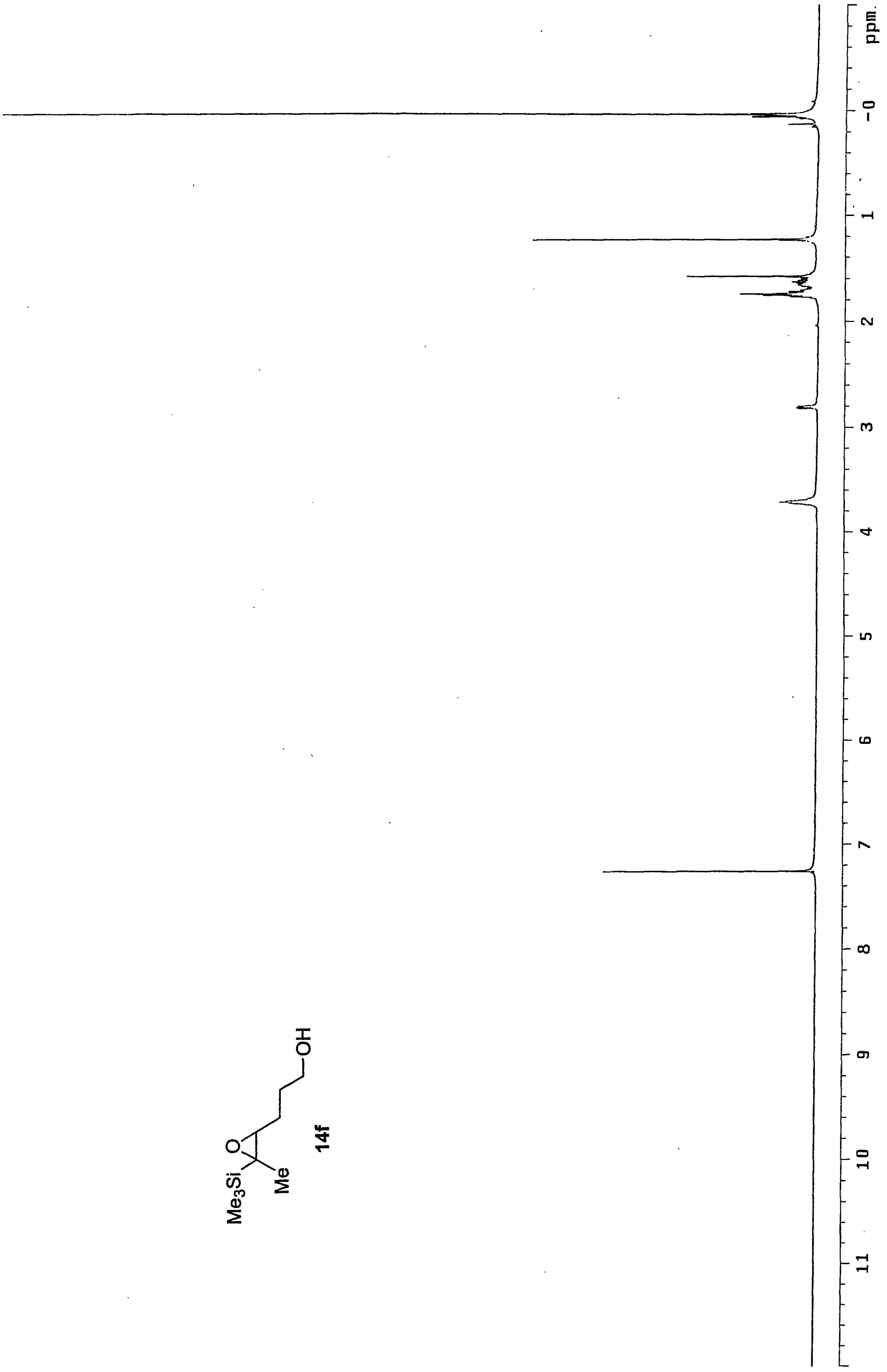
20



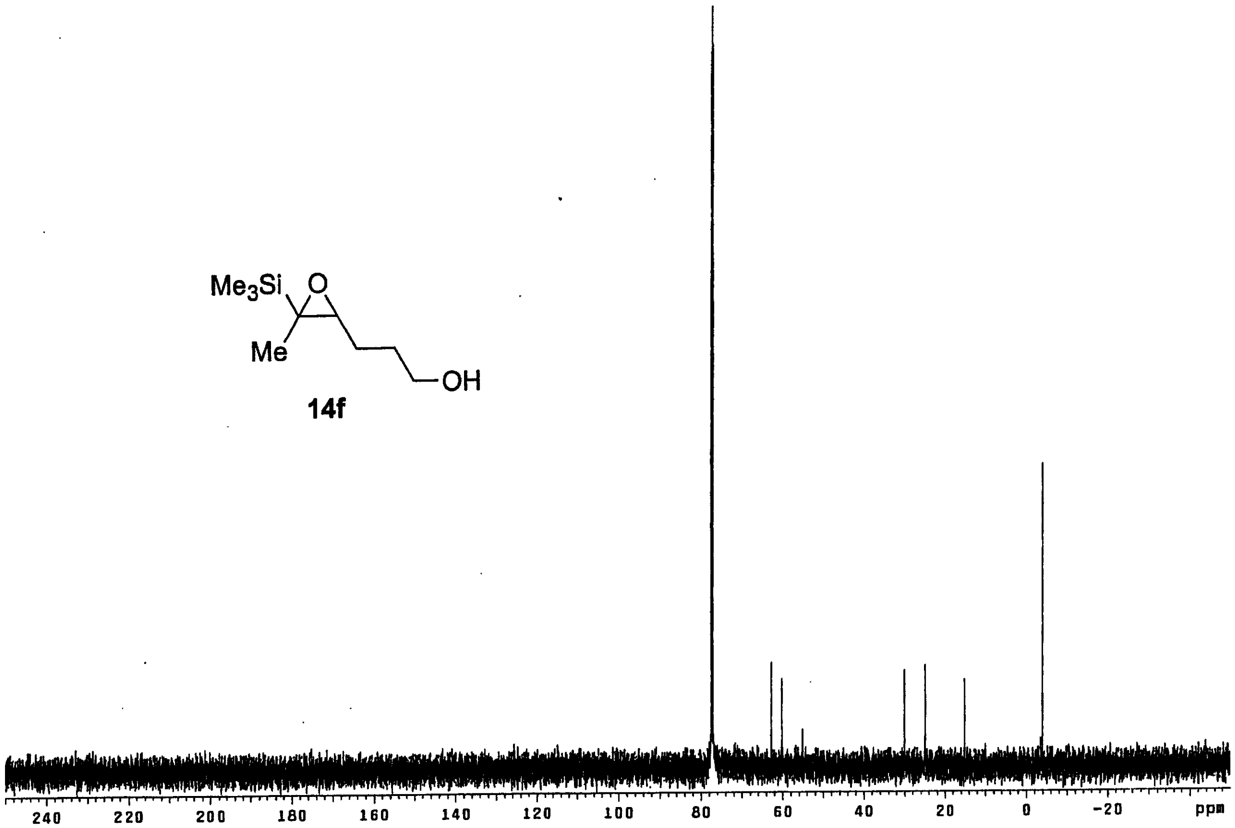
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

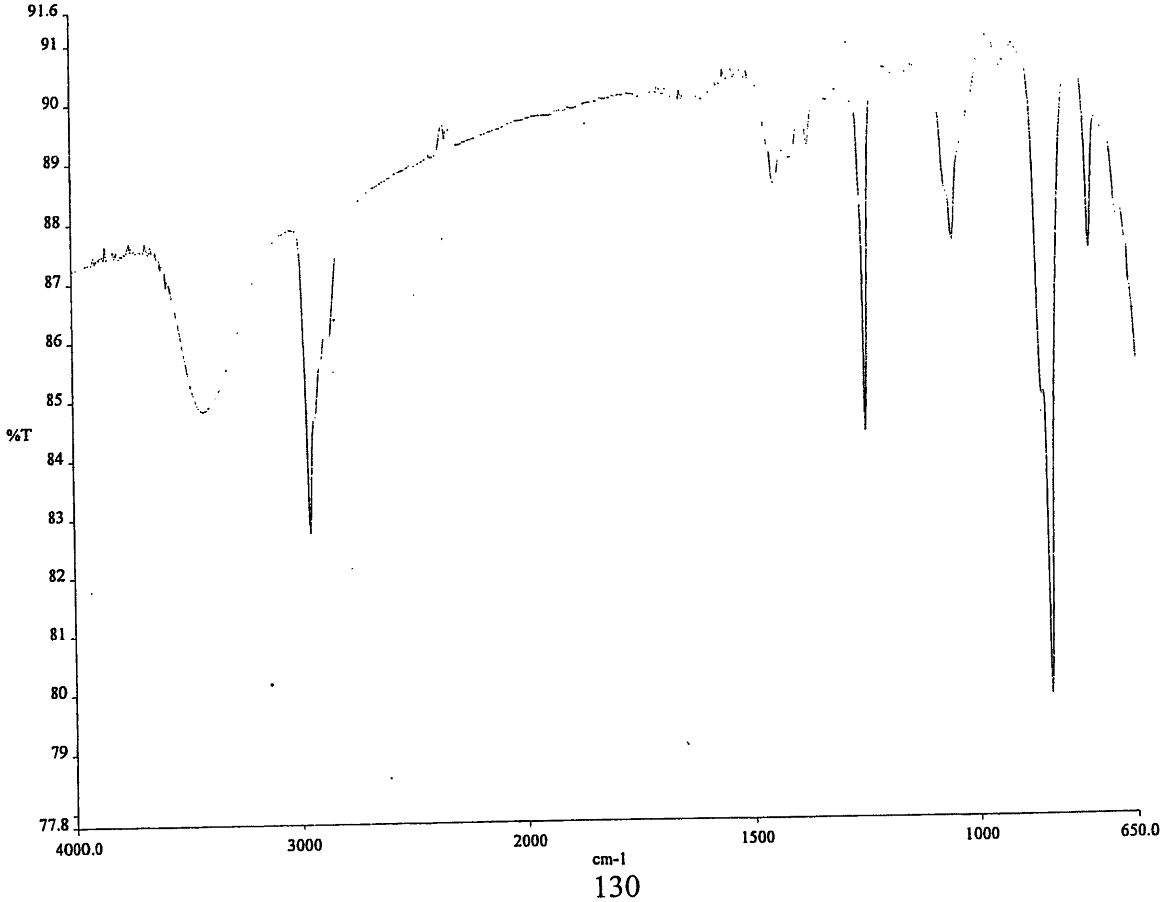


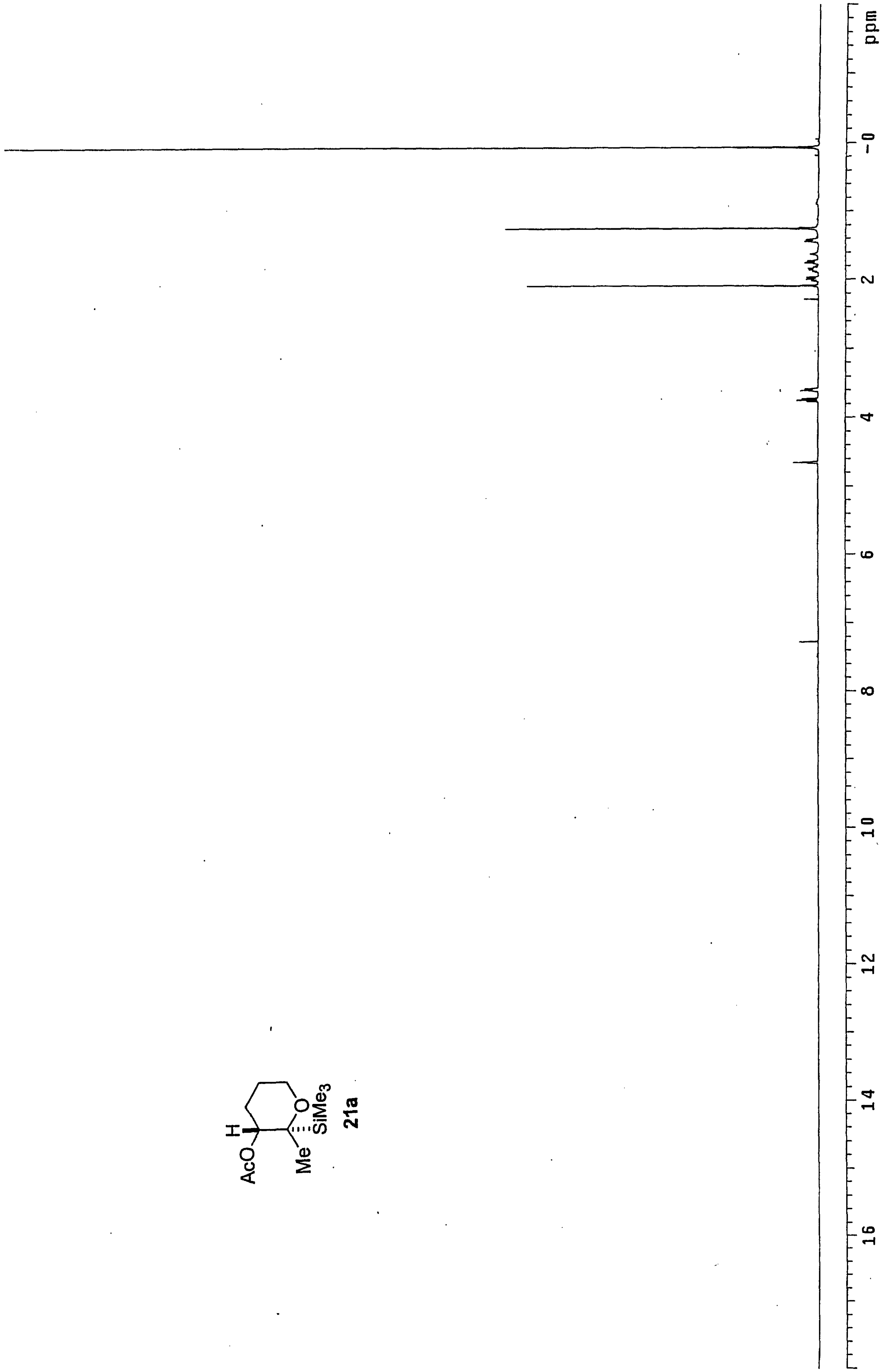
76.1
74
72
70
68
66
64
%T
62
60
58
56
54
52
50
49.3
4000.0
3000
2000
1500
1000
500 400.0
cm-1

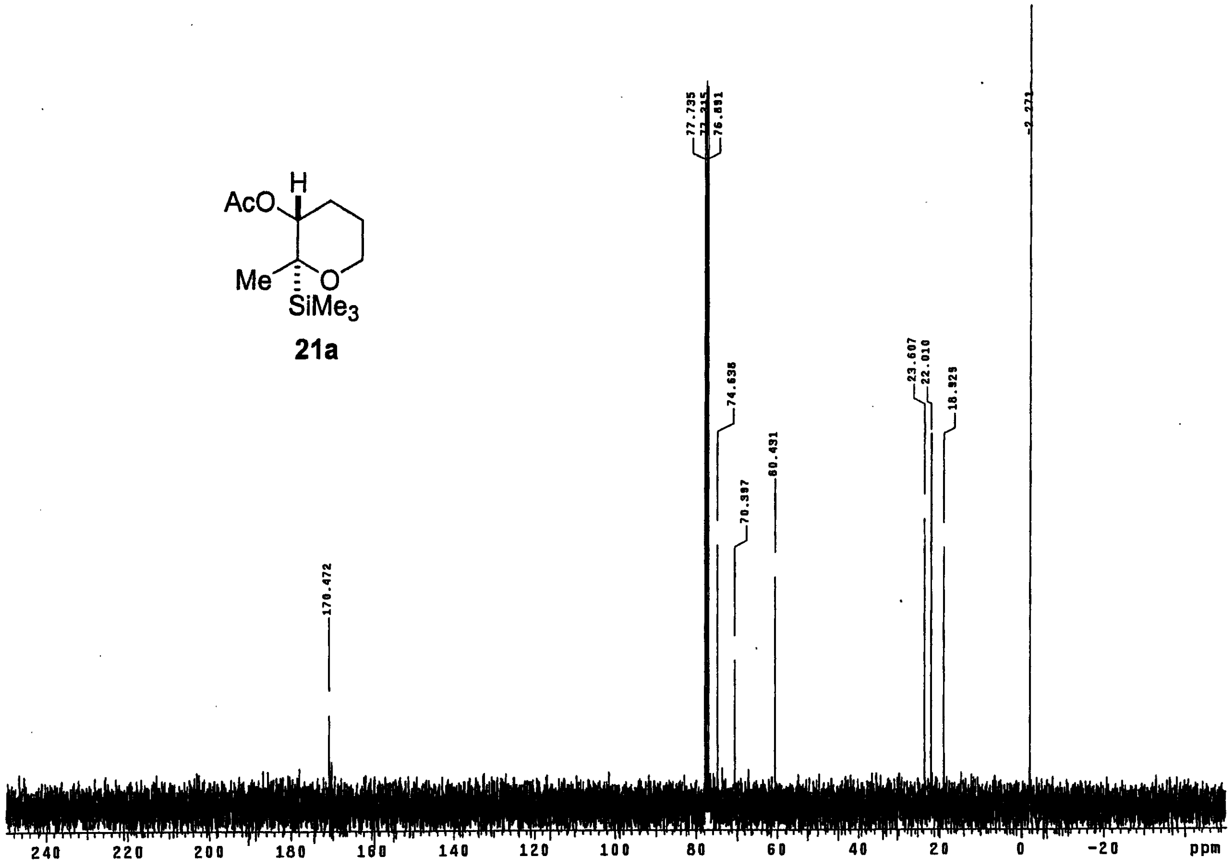


14f

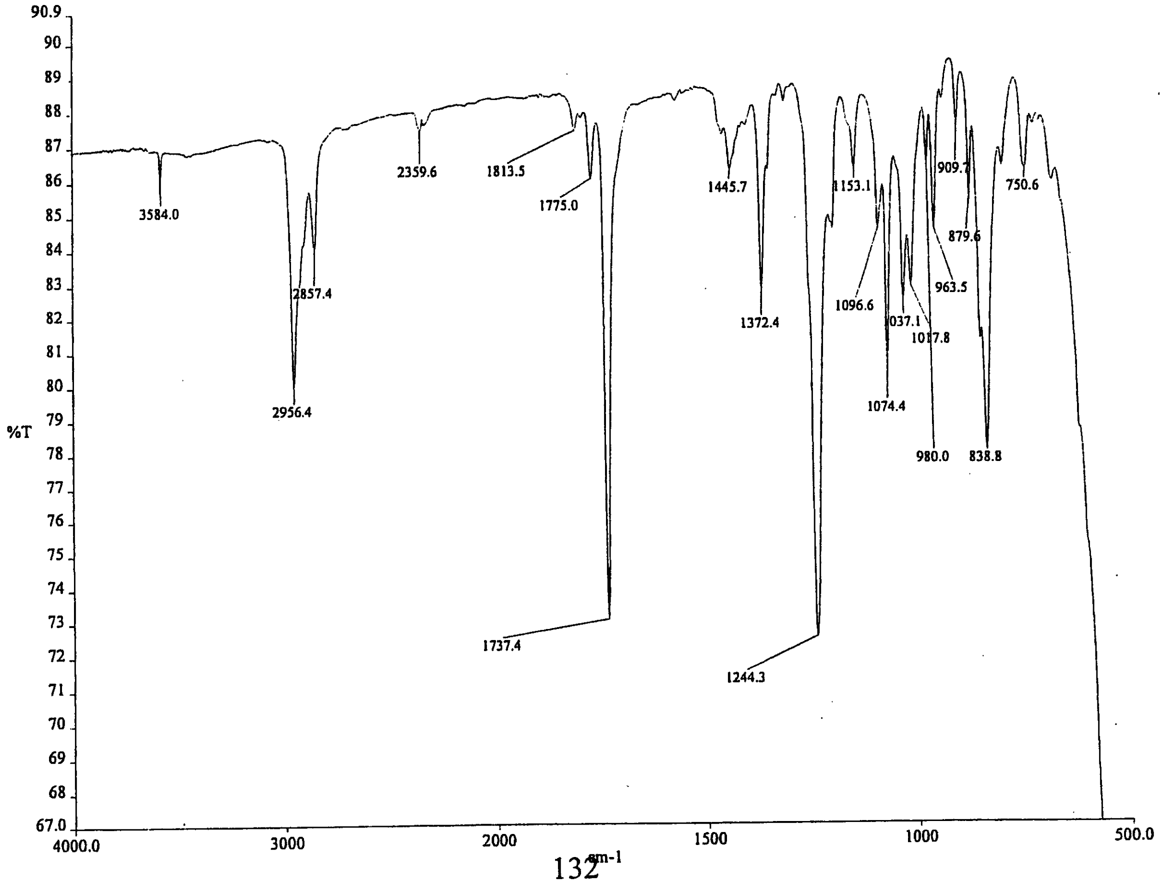

Me3Si
O
Me
OH
14f
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

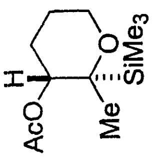

91.6
91
90
89
88
87
86
85
%T
84
83
82
81
80
79
77.8
4000.0
3000
2000
1500
1000
650.0
cm-1


ppm
0
2
4
6
8
10
12
14
16
AcO
H
O
Me
SiMe3
21a

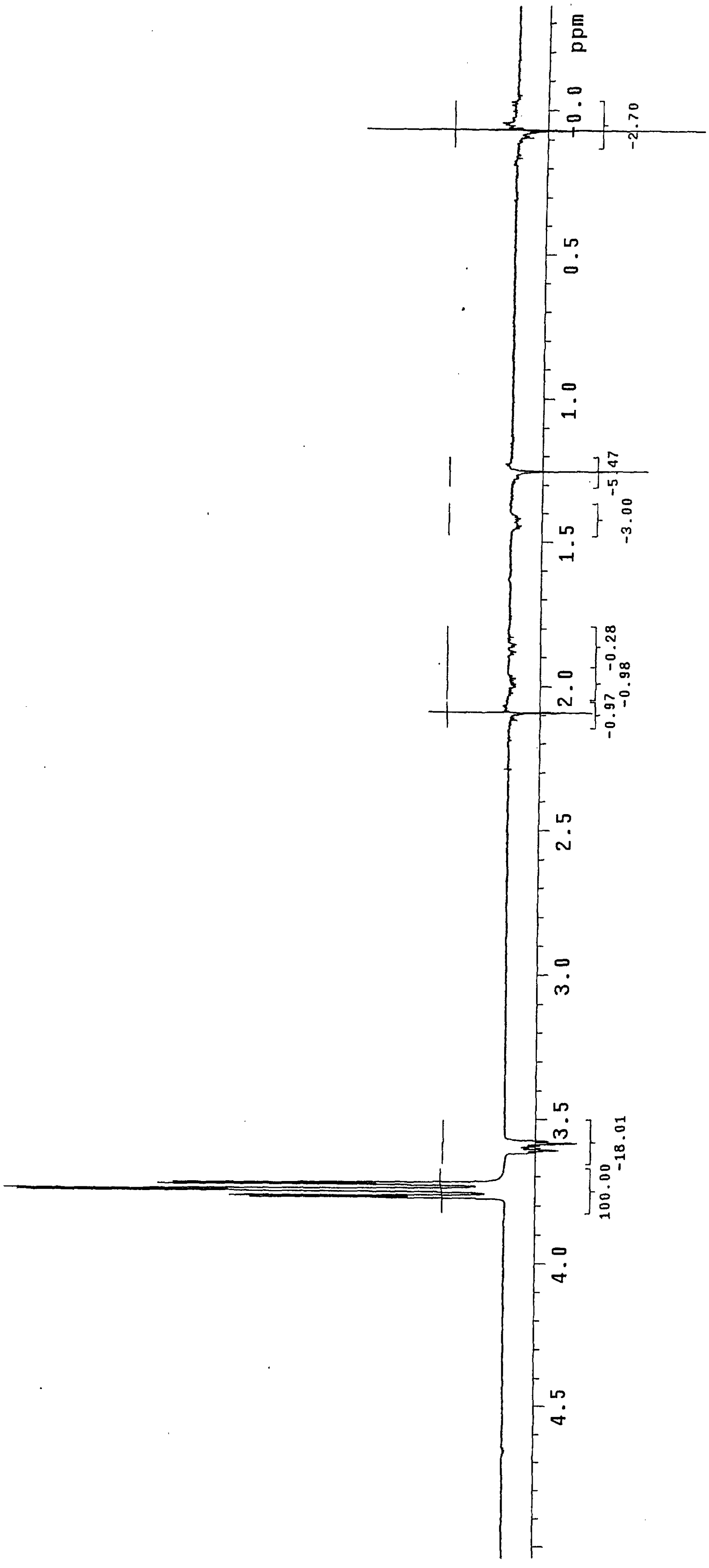

AcO
H
Me
O
SiMe3
170.472
77.735
77.315
76.891
74.638
70.397
60.431
23.607
22.010
18.929
-2.271
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

21a

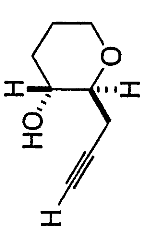

90.9
90
89
88
87
86
85
84
83
82
81
80
79
%T
78
77
76
75
74
73
72
71
70
69
68
67.0
4000.0
3000
2000
1500
1000
500.0
cm-1
3584.0
2956.4
2857.4
2359.6
1813.5
1775.0
1737.4
1445.7
1372.4
1244.3
1153.1
1096.6
1074.4
1037.1
1017.8
980.0
963.5
909.7
879.6
838.8
750.6



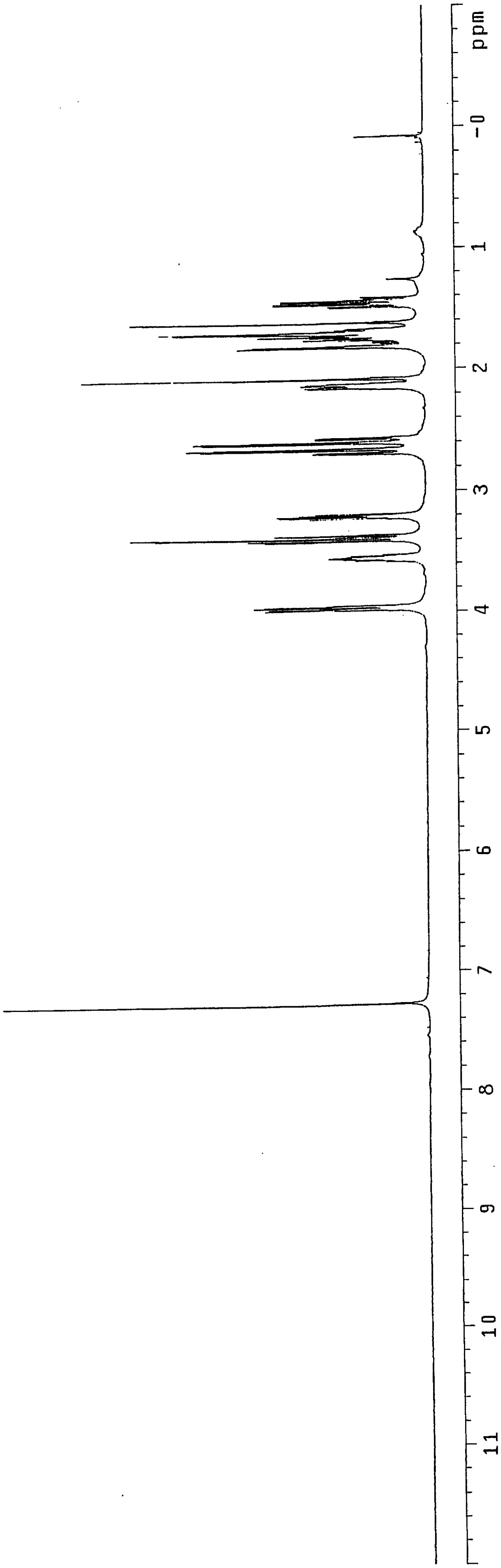
21a

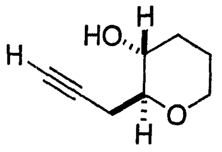


ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
-2.70
-5.47
-3.00
-0.28
-0.97
-0.98
100.00
-18.01

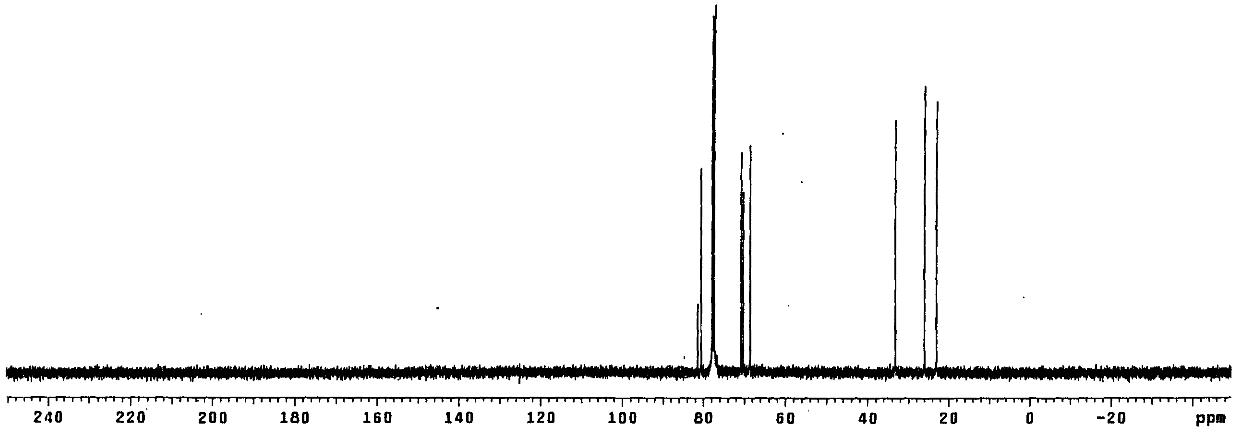


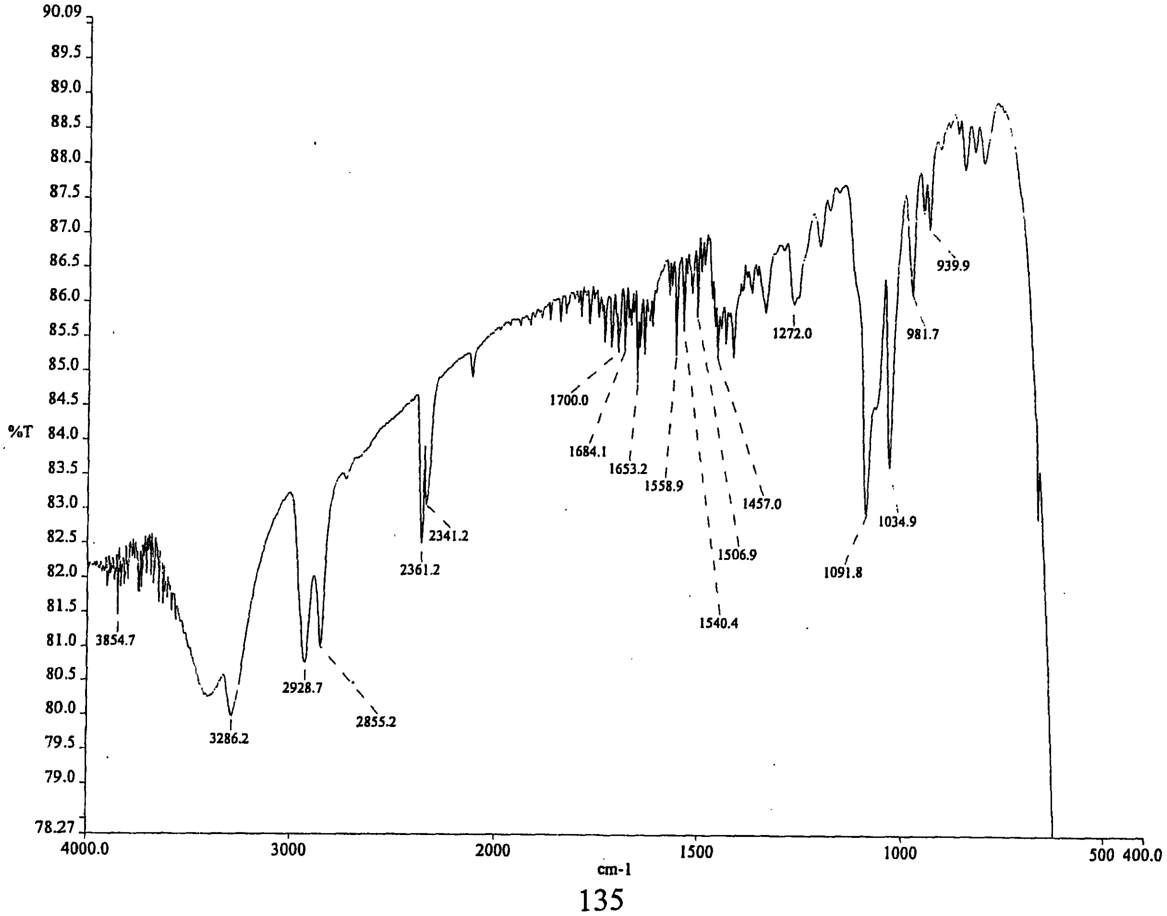
22

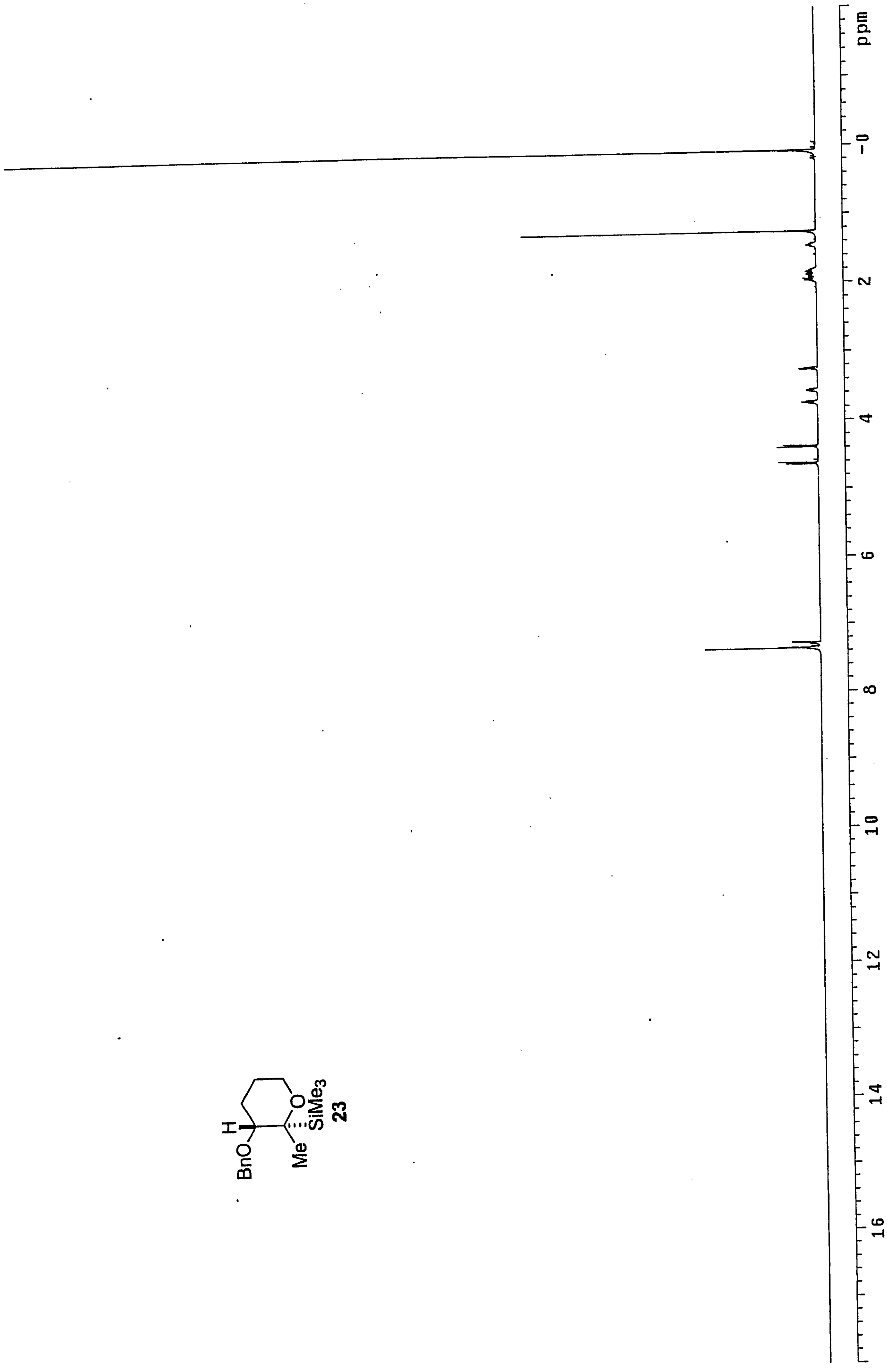



HO
H
H
O
H

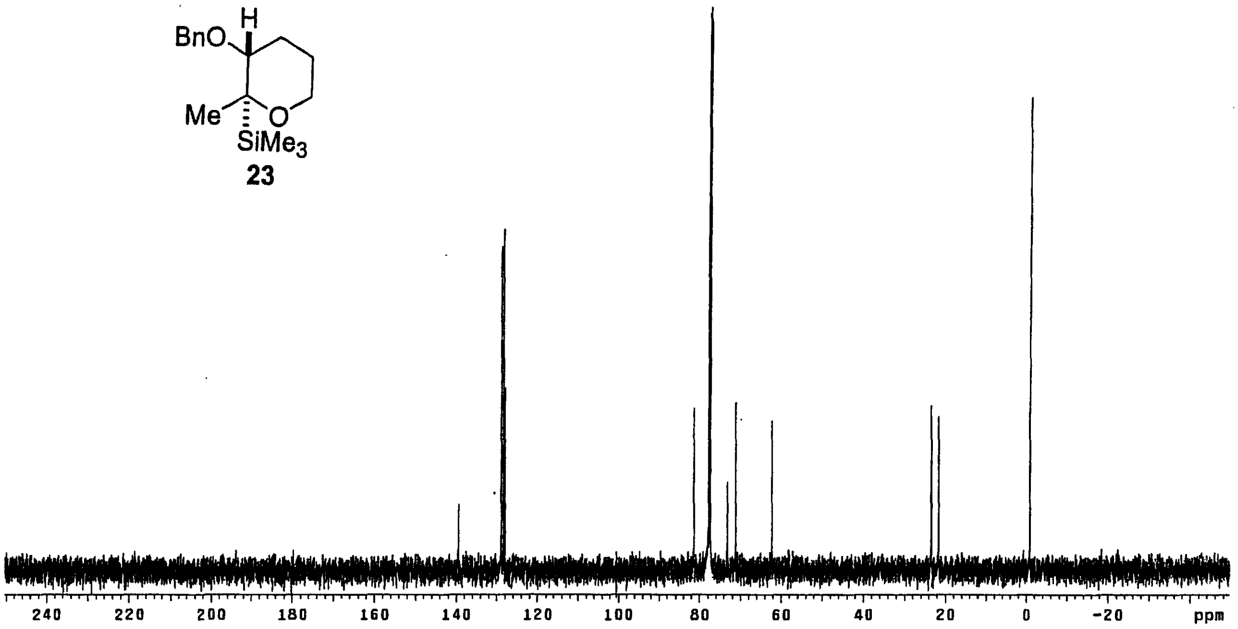
22


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

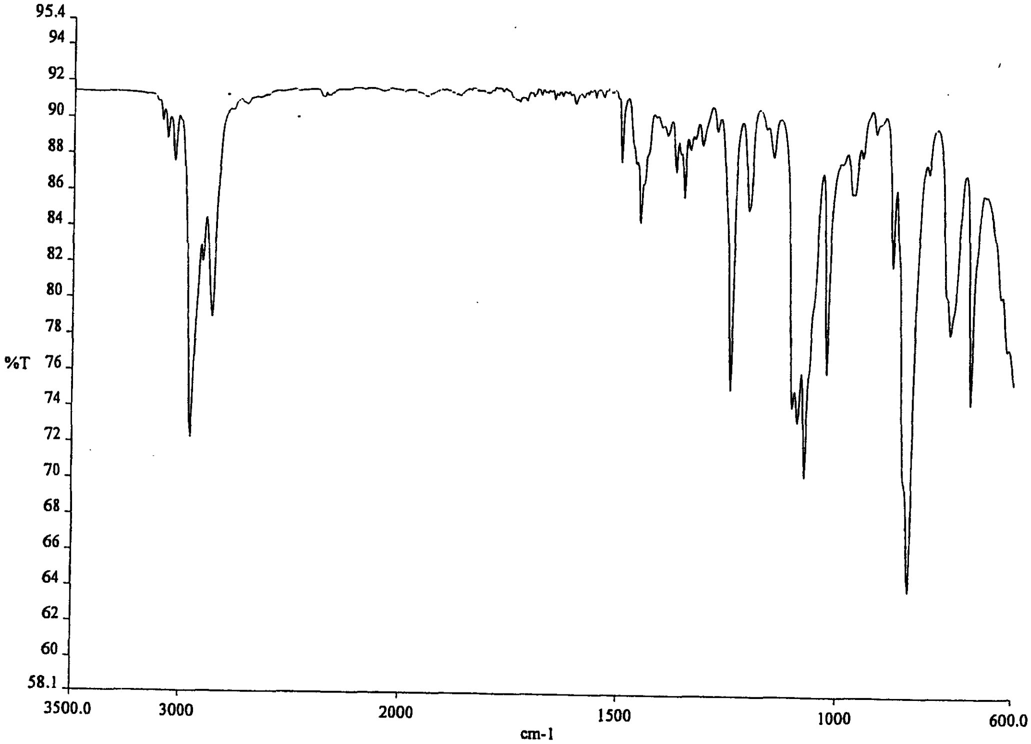

90.09
89.5
89.0
88.5
88.0
87.5
87.0
86.5
86.0
85.5
85.0
84.5
%T
84.0
83.5
83.0
82.5
82.0
81.5
81.0
80.5
80.0
79.5
79.0
78.27
3854.7
3286.2
2928.7
2855.2
2361.2
2341.2
1700.0
1684.1
1653.2
1558.9
1540.4
1506.9
1457.0
1272.0
1091.8
1034.9
981.7
939.9
4000.0
3000
2000
1500
1000
500
400.0
cm-1

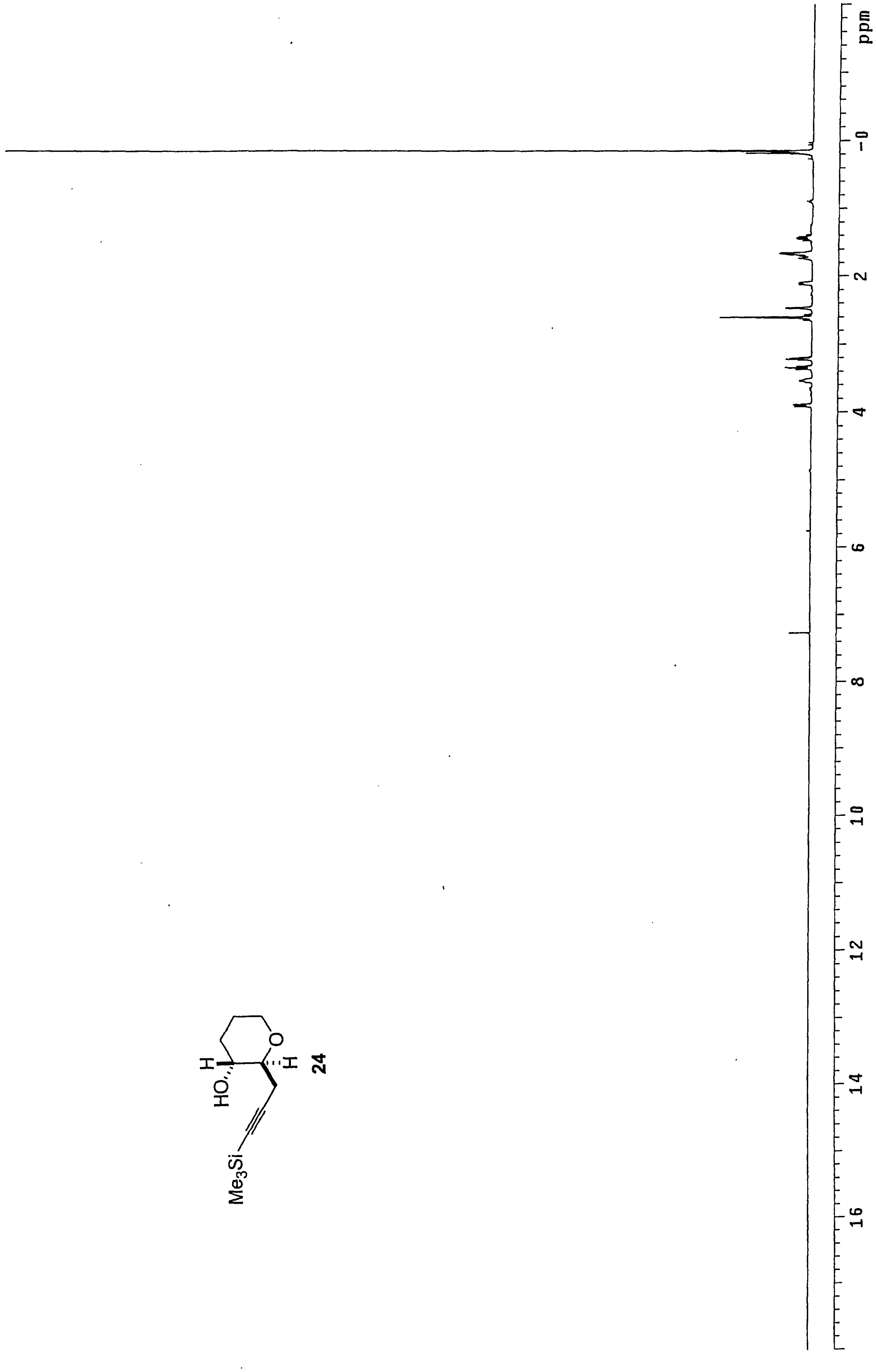


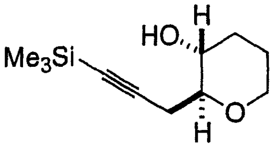
23


BnO
H
Me
O
SiMe$_3$
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

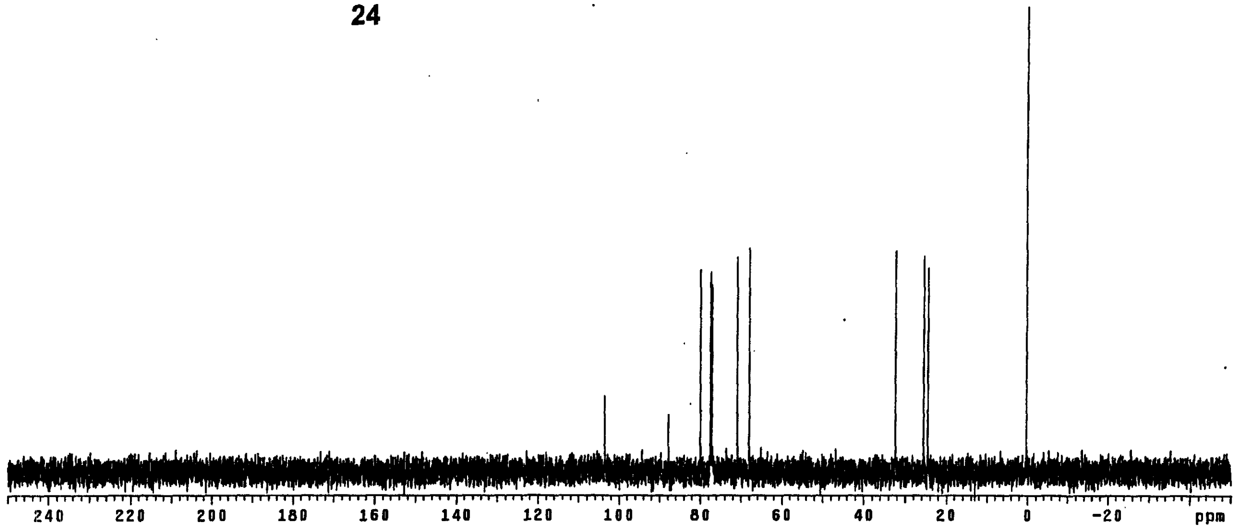
23

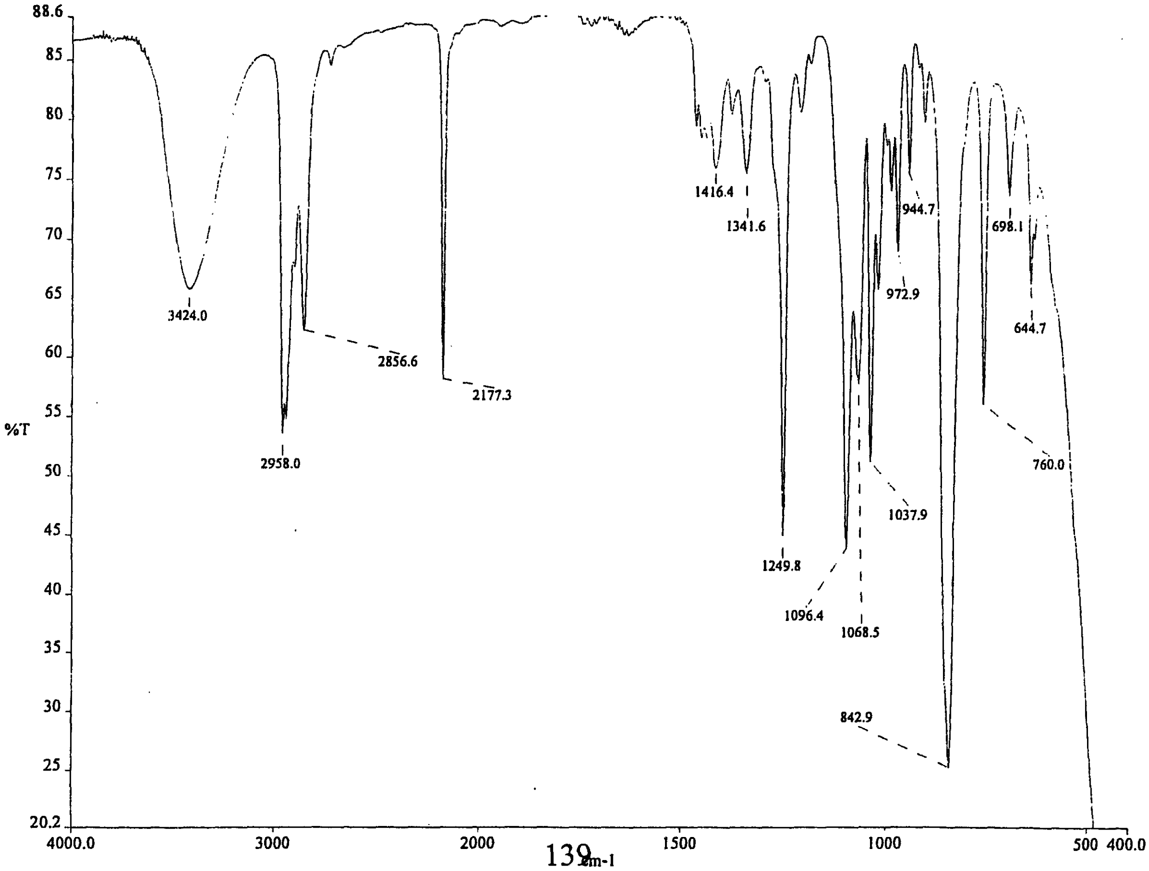

95.4
94
92
90
88
86
84
82
80
78
%T
76
74
72
70
68
66
64
62
60
58.1
3500.0
3000
2000
1500
1000
600.0
cm-1

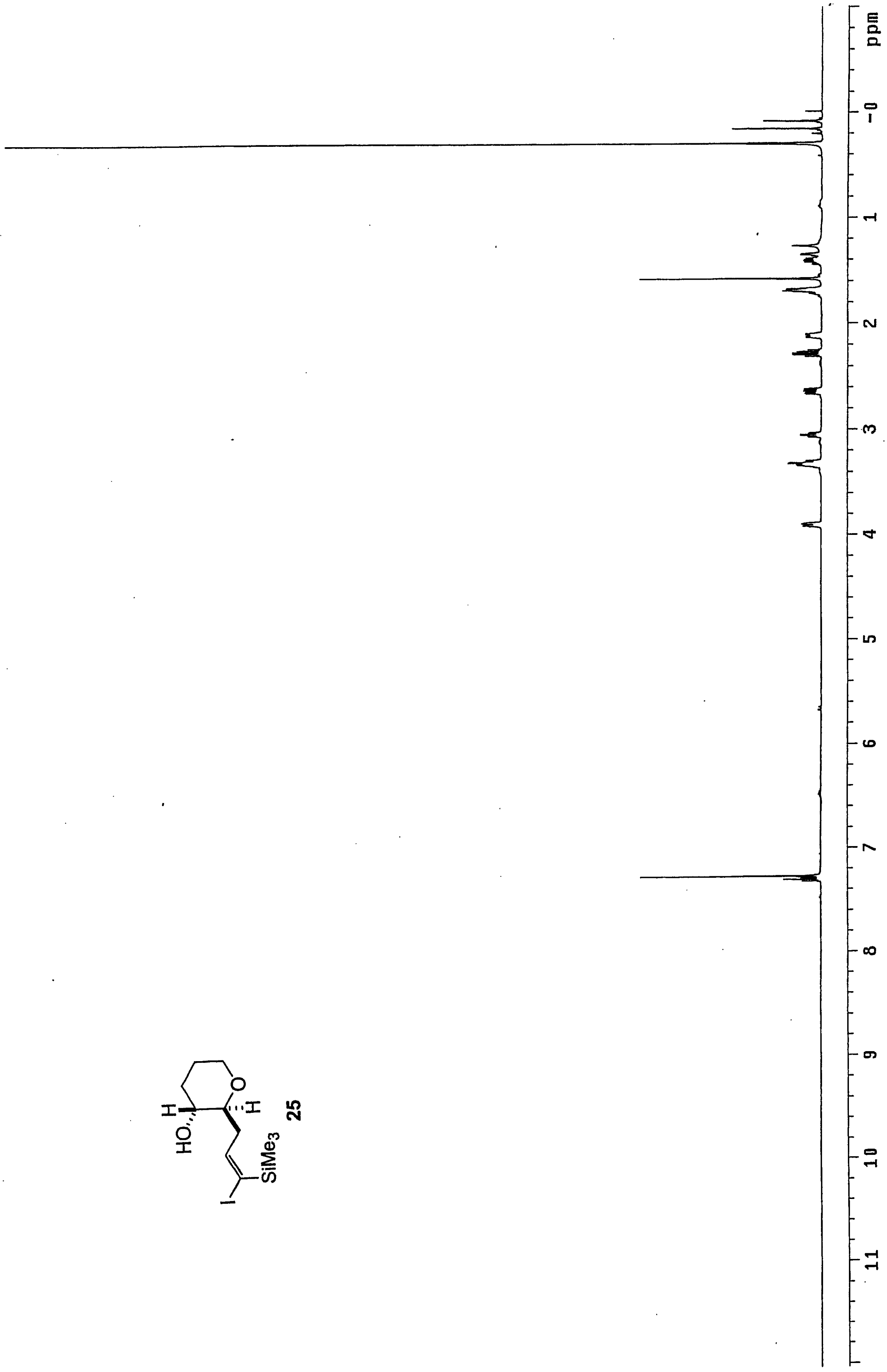

ppm
0
2
4
6
8
10
12
14
16
HO
H
O
H
Me3Si
24


Me3Si
HO
H
H
O

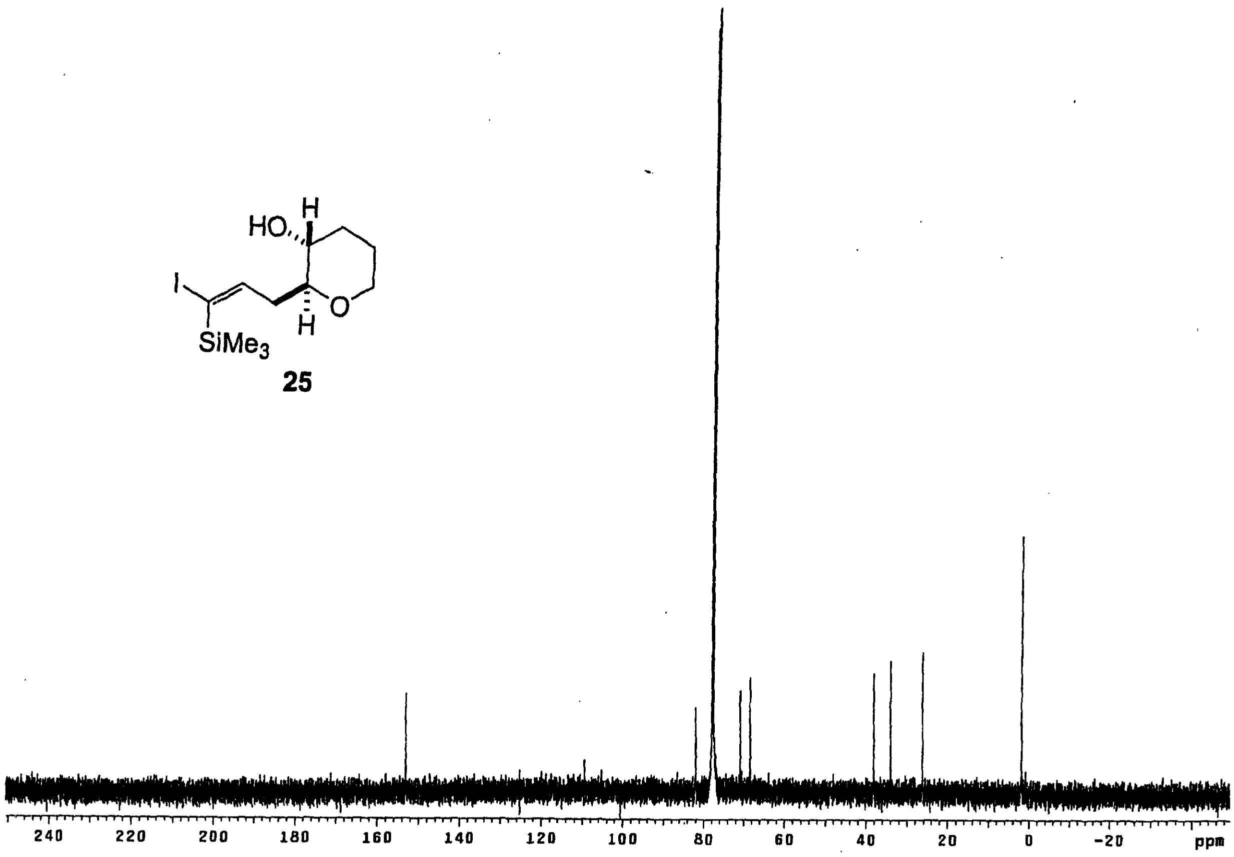
24


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


88.6
85
80
75
70
65
60
55
50
45
40
35
30
25
20.2
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3424.0
2958.0
2856.6
2177.3
1416.4
1341.6
1249.8
1096.4
1068.5
1037.9
972.9
944.7
842.9
760.0
698.1
644.7

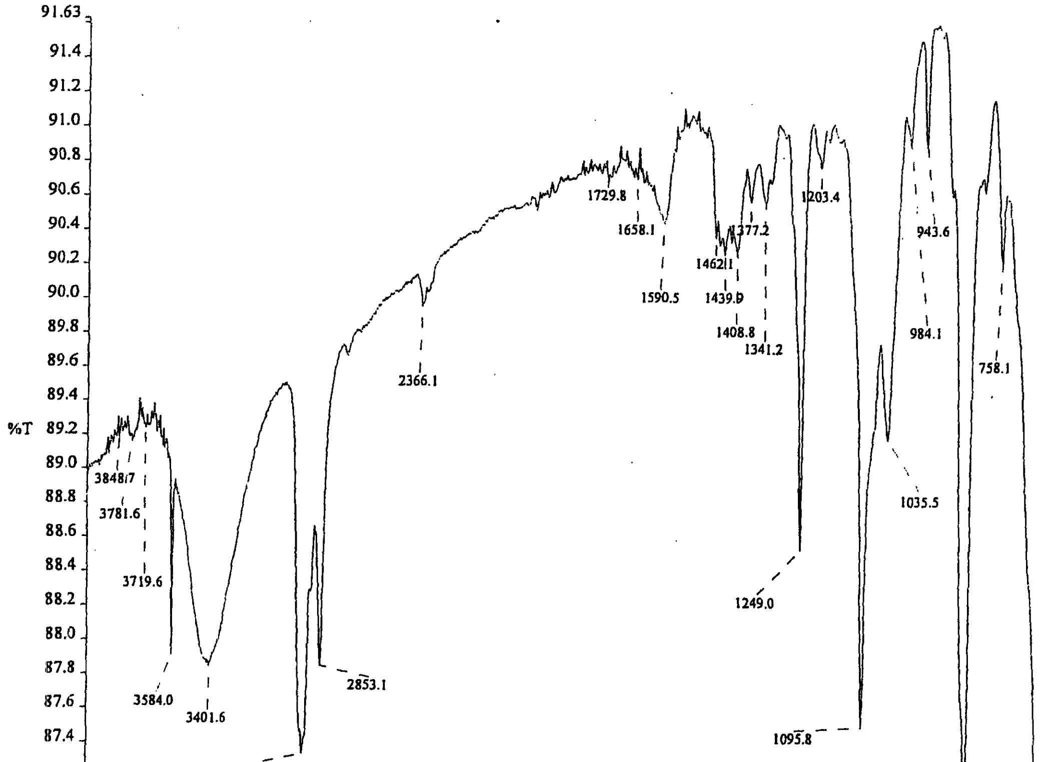


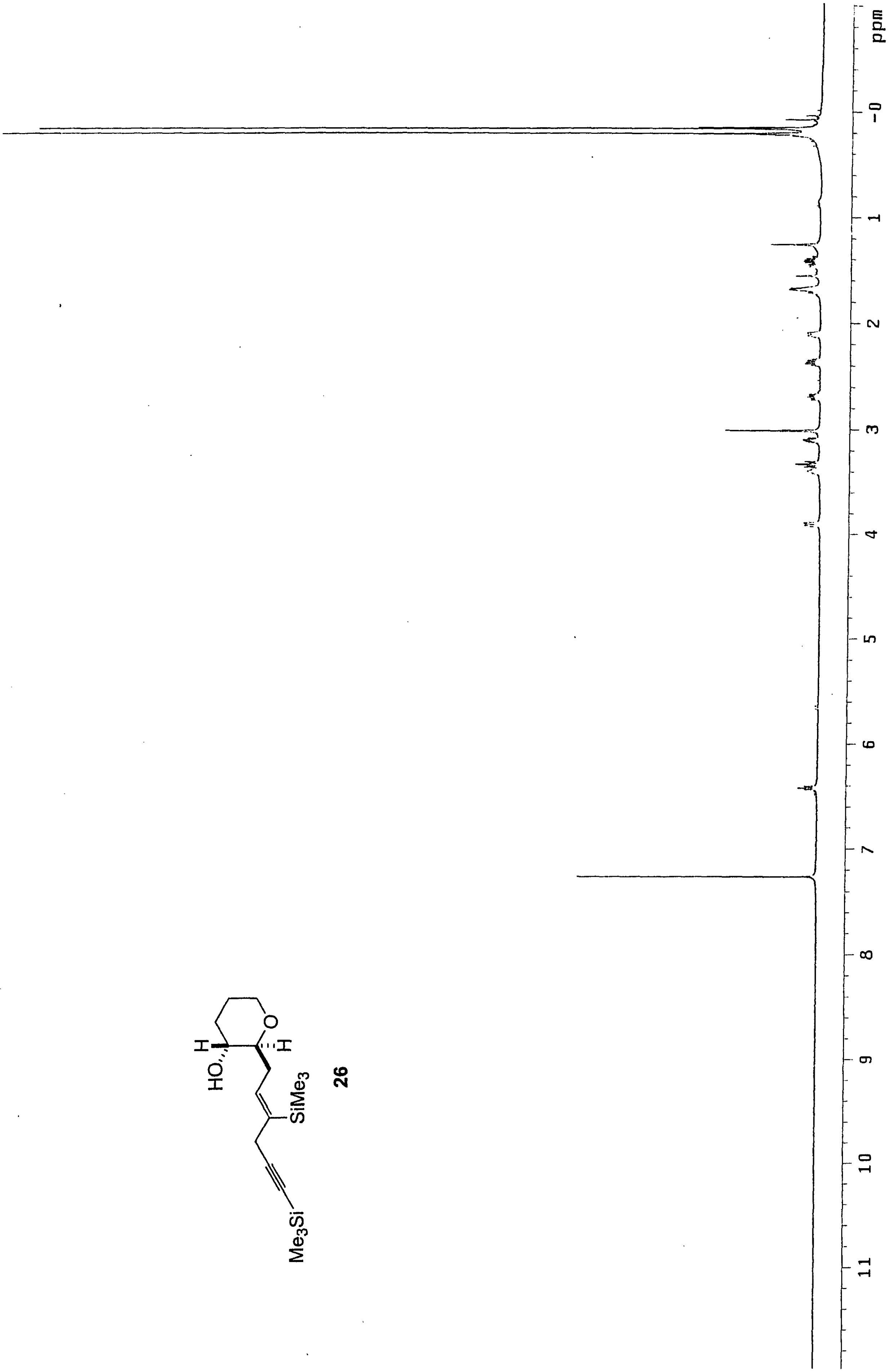
25


HO
H
I
O
H
SiMe3

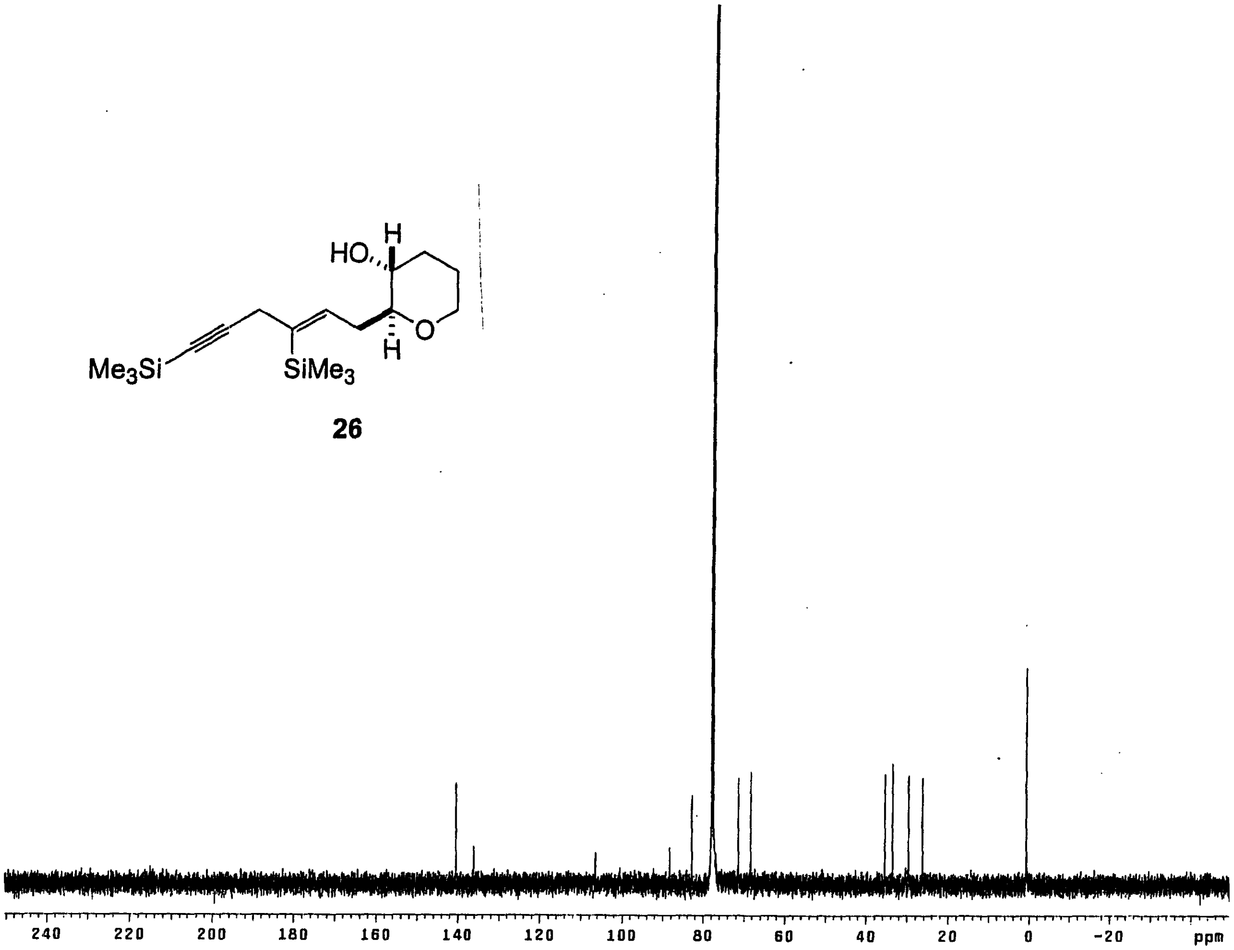
25

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

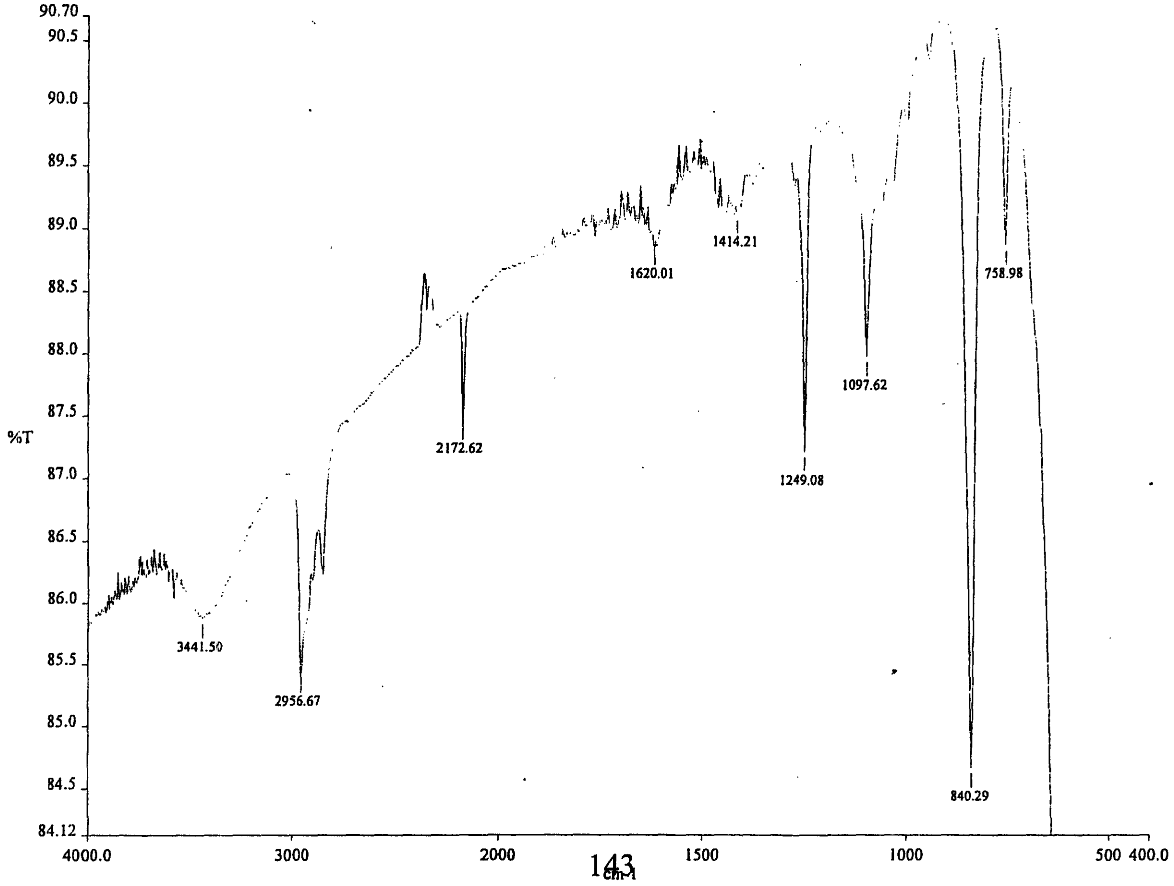

91.63
91.4
91.2
91.0
90.8
90.6
90.4
90.2
90.0
89.8
89.6
89.4
%T 89.2
89.0
88.8
88.6
88.4
88.2
88.0
87.8
87.6
87.4
87.2
87.0
86.89
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3848.7
3781.6
3719.6
3584.0
3401.6
2939.3
2853.1
2366.1
1729.8
1658.1
1590.5
1462.1
1439.0
1408.8
1377.2
1341.2
1249.0
1203.4
1095.8
1035.5
984.1
943.6
841.4
758.1

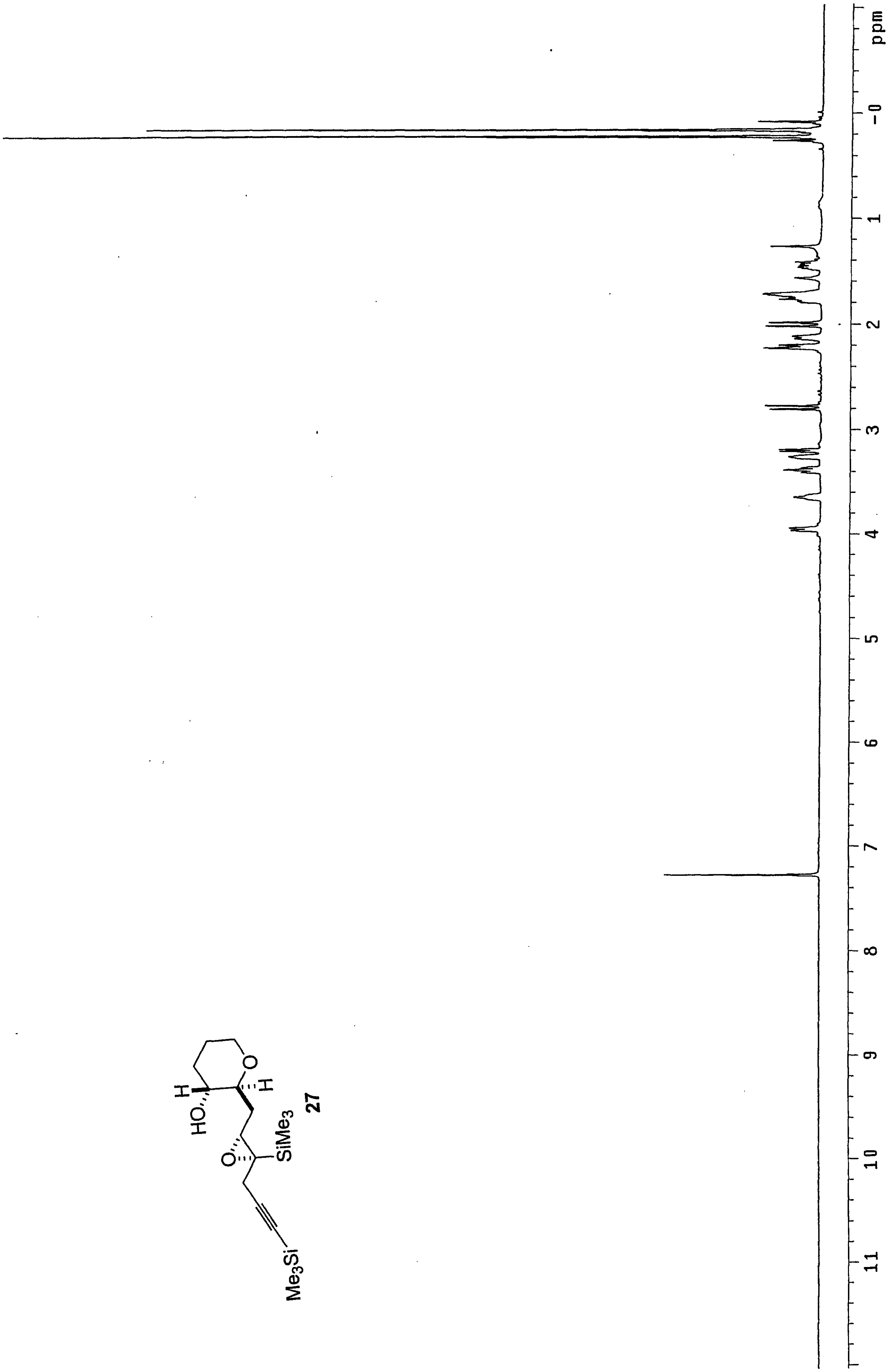


26

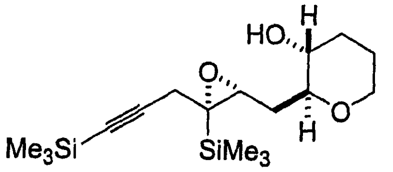

HO
H
H
O
Me3Si
SiMe3
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

26

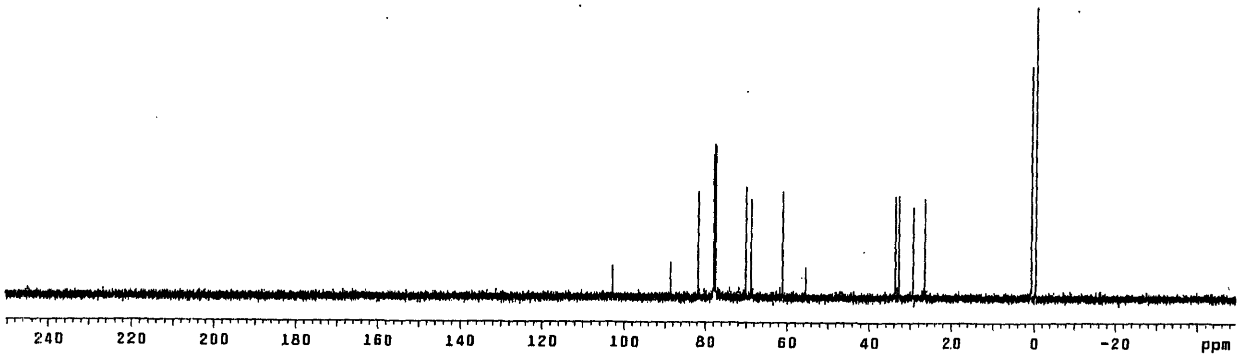

90.70
90.5
90.0
89.5
89.0
88.5
88.0
87.5
%T
87.0
86.5
86.0
85.5
85.0
84.5
84.12
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3441.50
2956.67
2172.62
1620.01
1414.21
1249.08
1097.62
840.29
758.98

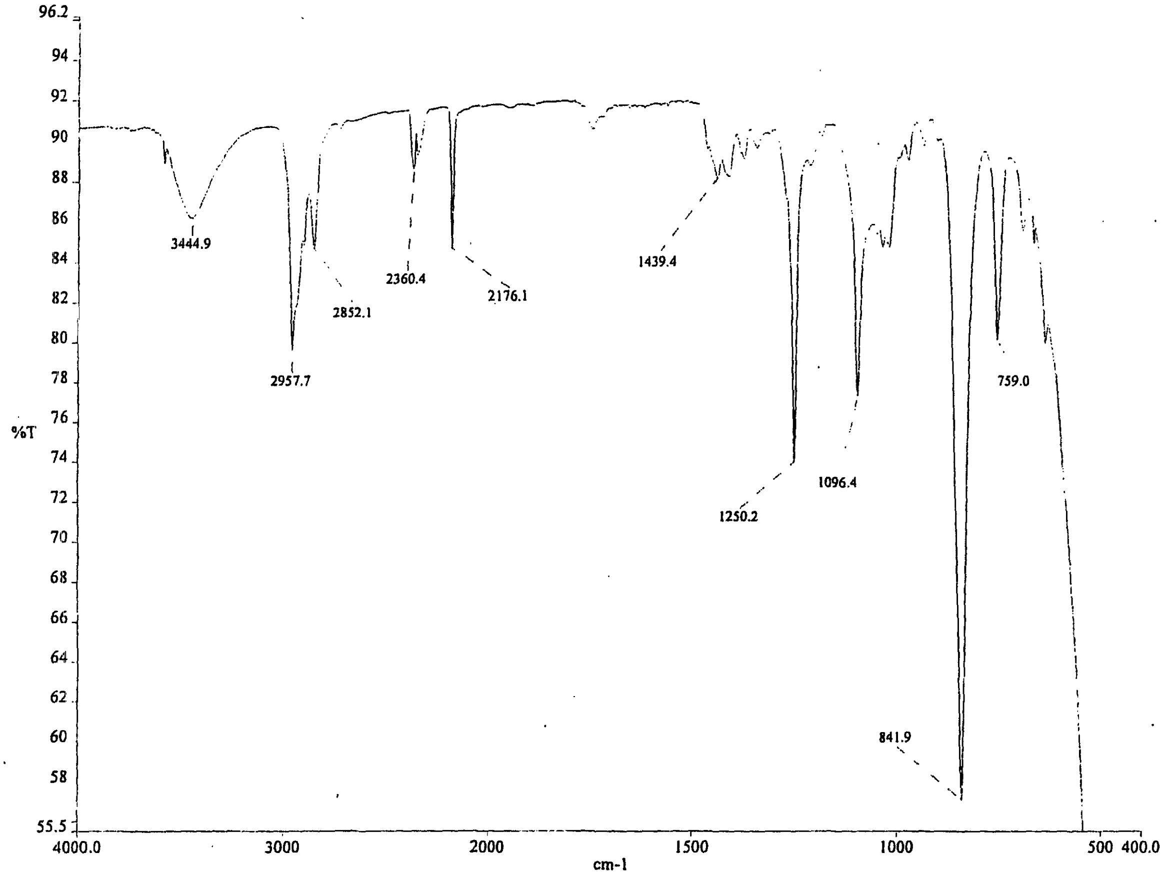


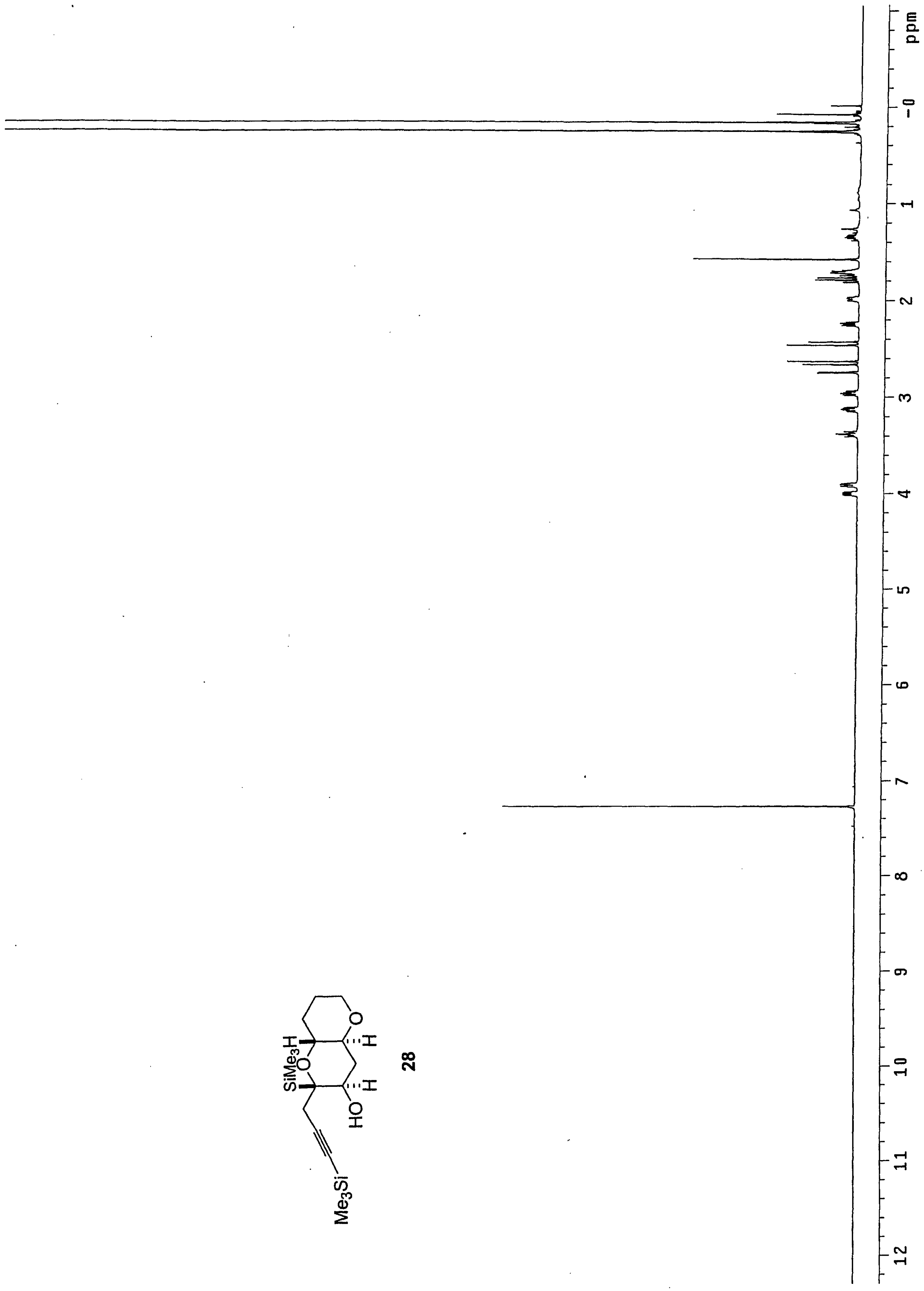
27


HO
H
O
O
H
Me3Si
SiMe3

27


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

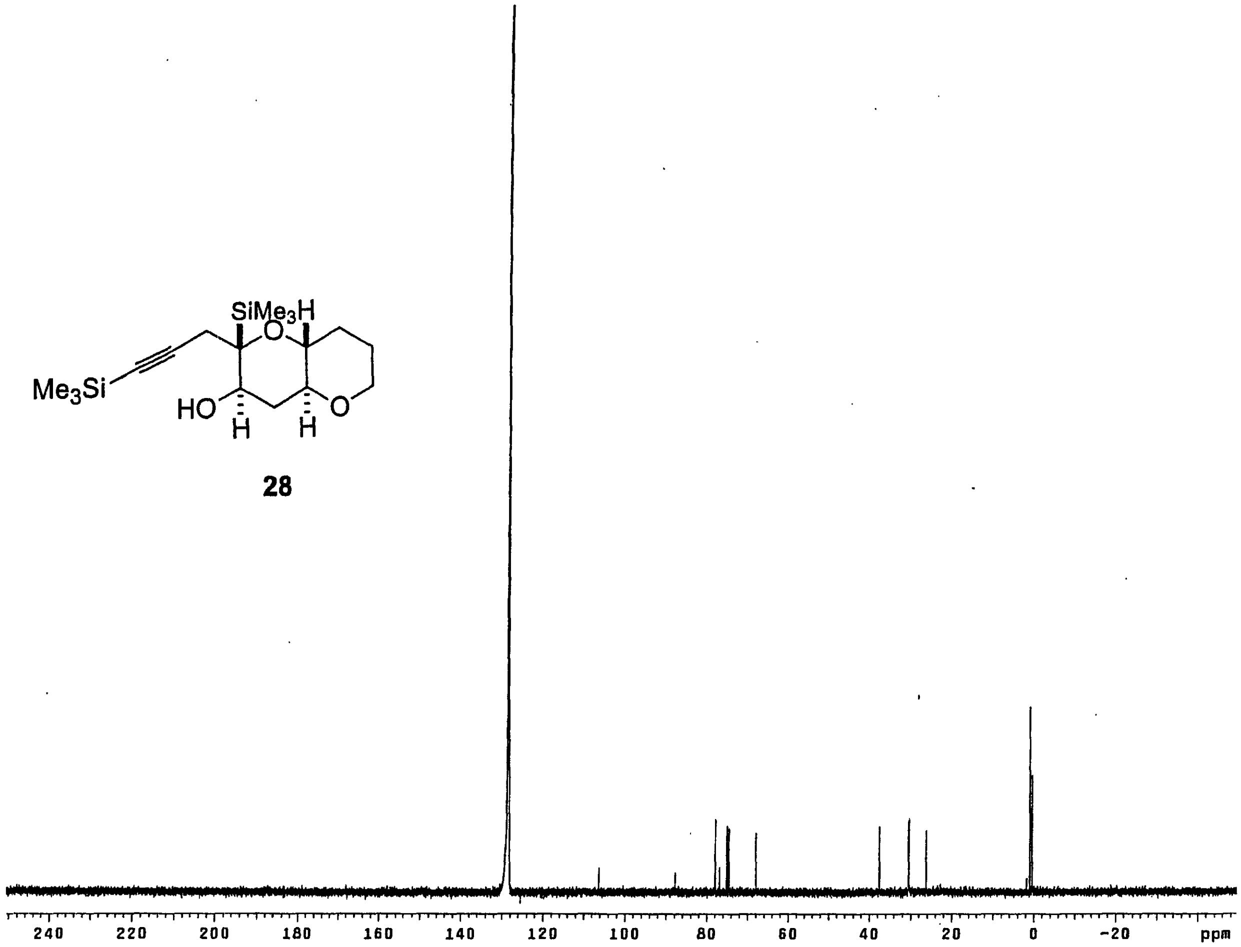

96.2
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
55.5
%T
3444.9
2957.7
2852.1
2360.4
2176.1
1439.4
1250.2
1096.4
841.9
759.0
4000.0
3000
2000
1500
1000
500
400.0
cm-1



28

SiMe3
H
O
Me3Si
HO
H
H
O

28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180
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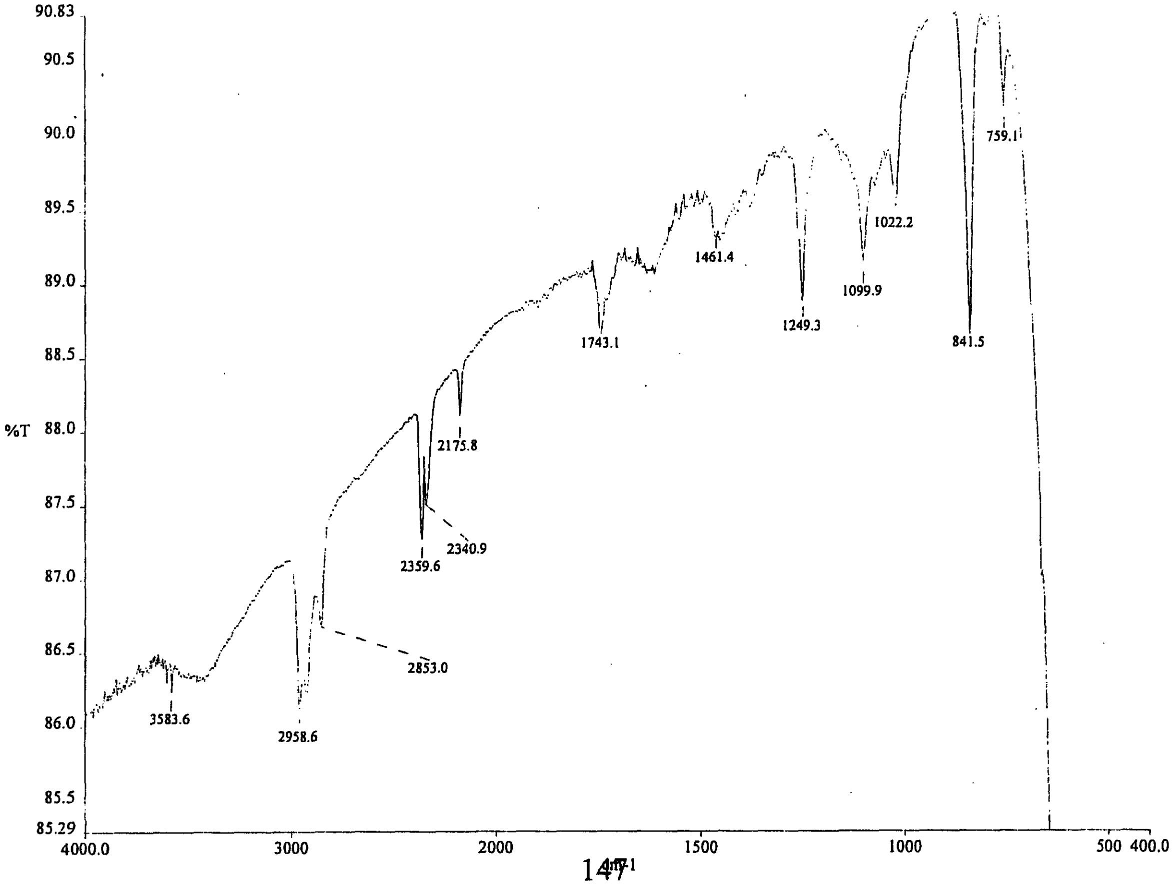
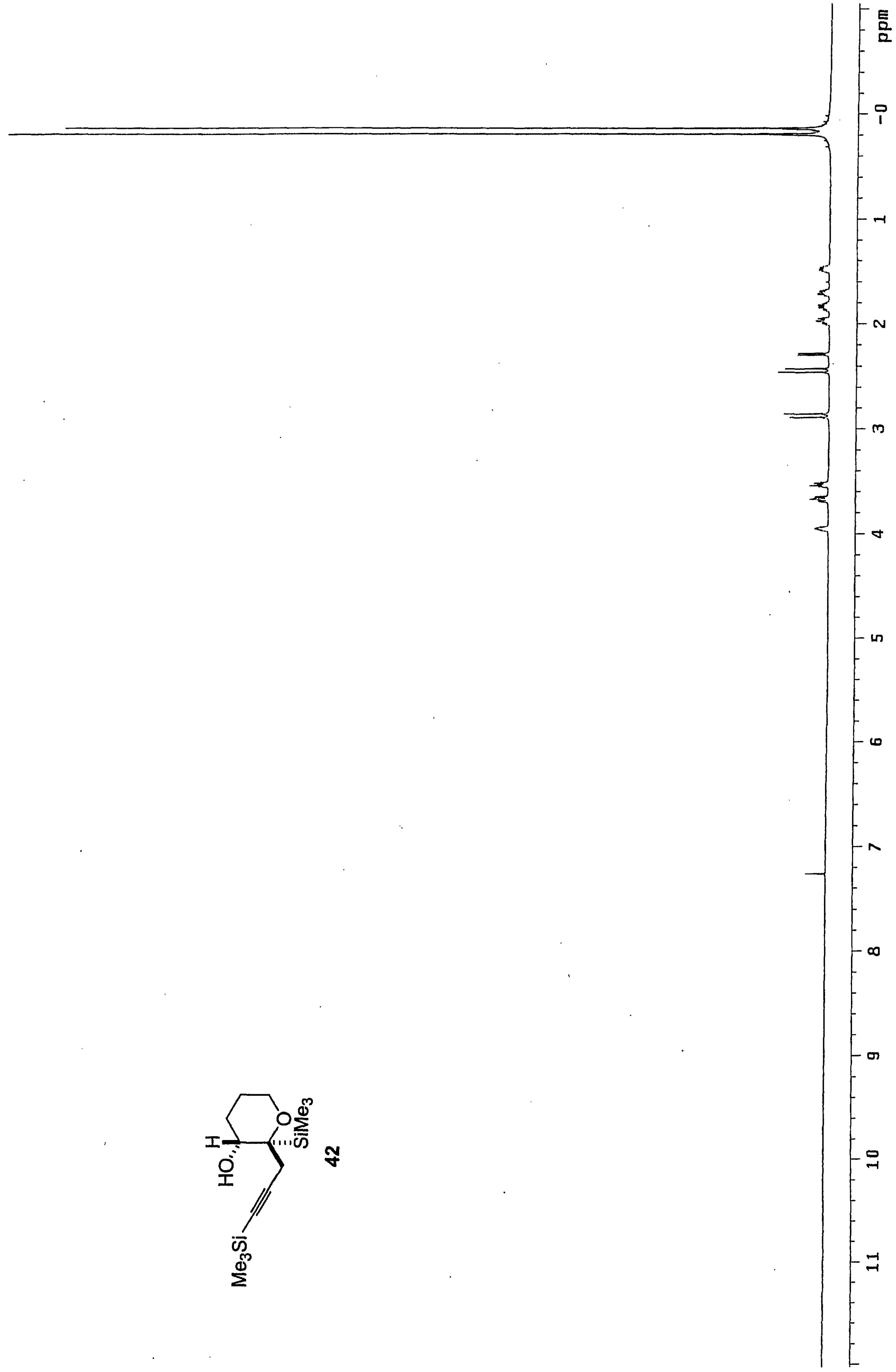
140
120
100
80
60
40
20
0
-20
ppm


90.83
90.5
90.0
89.5
89.0
88.5
%T
88.0
87.5
87.0
86.5
86.0
85.5
85.29
4000.0
3000
2000
1500
1000
500
400.0
cm-1
759.1
1022.2
1461.4
1099.9
1249.3
1743.1
841.5
2175.8
2340.9
2359.6
2853.0
3583.6
2958.6



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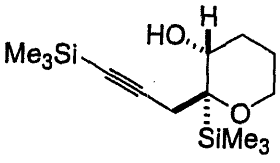
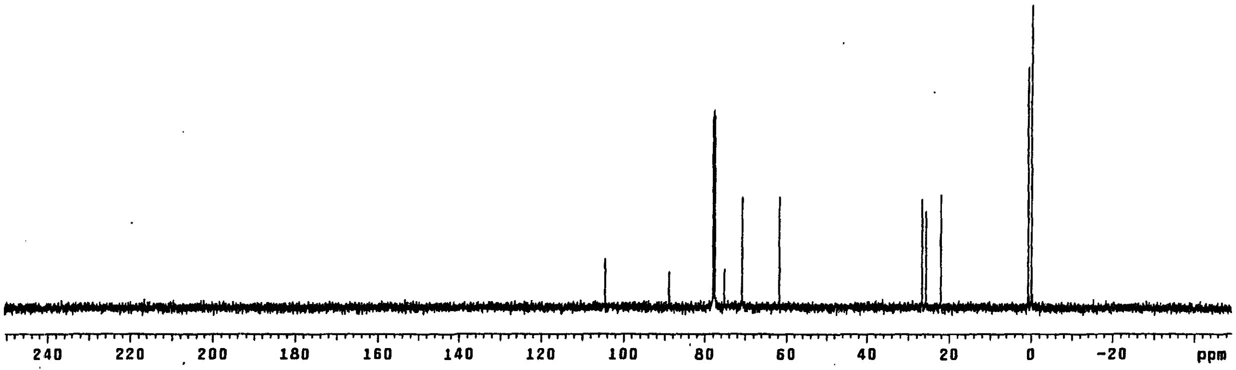

HO
H
Me3Si
O
SiMe3

42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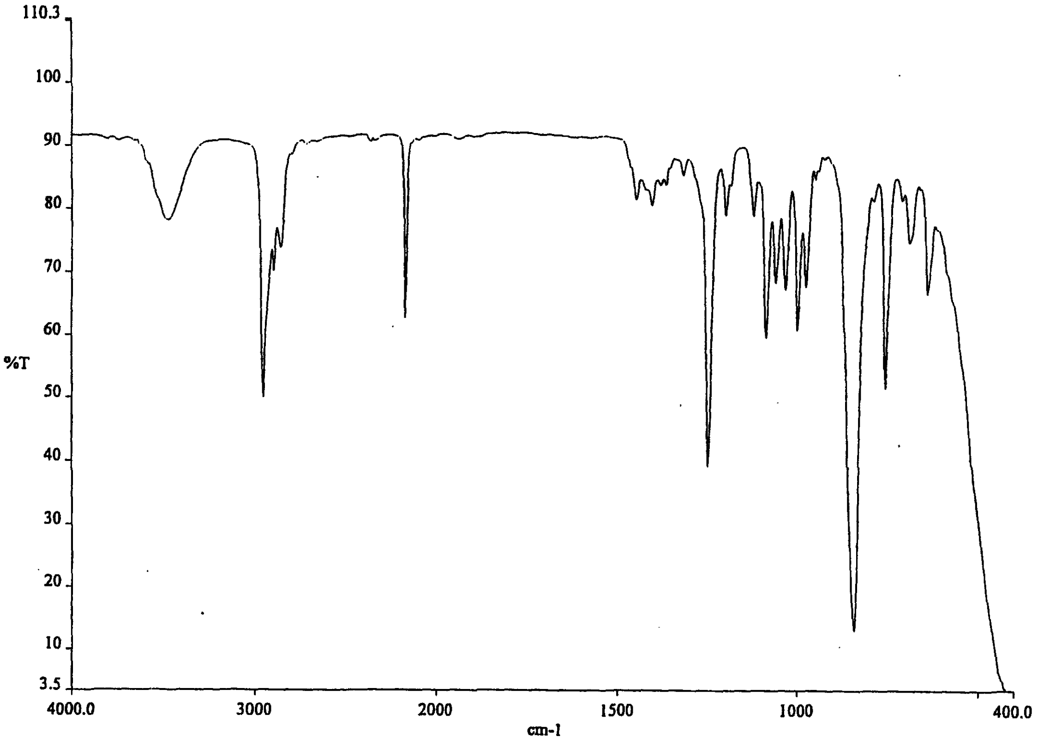
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90
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50
40
30
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10
3.5
%T
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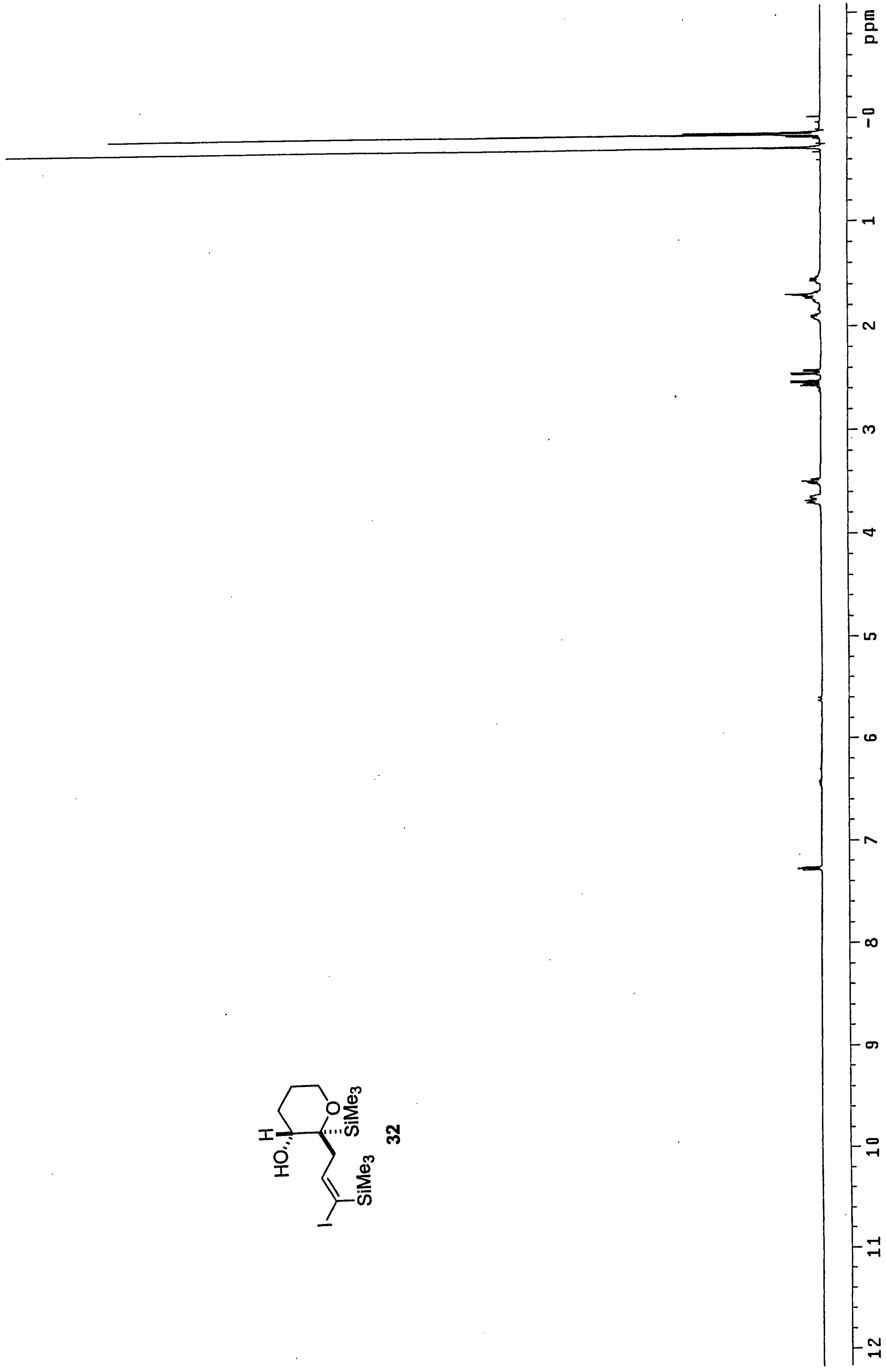
1500
1000
400.0
cm-1



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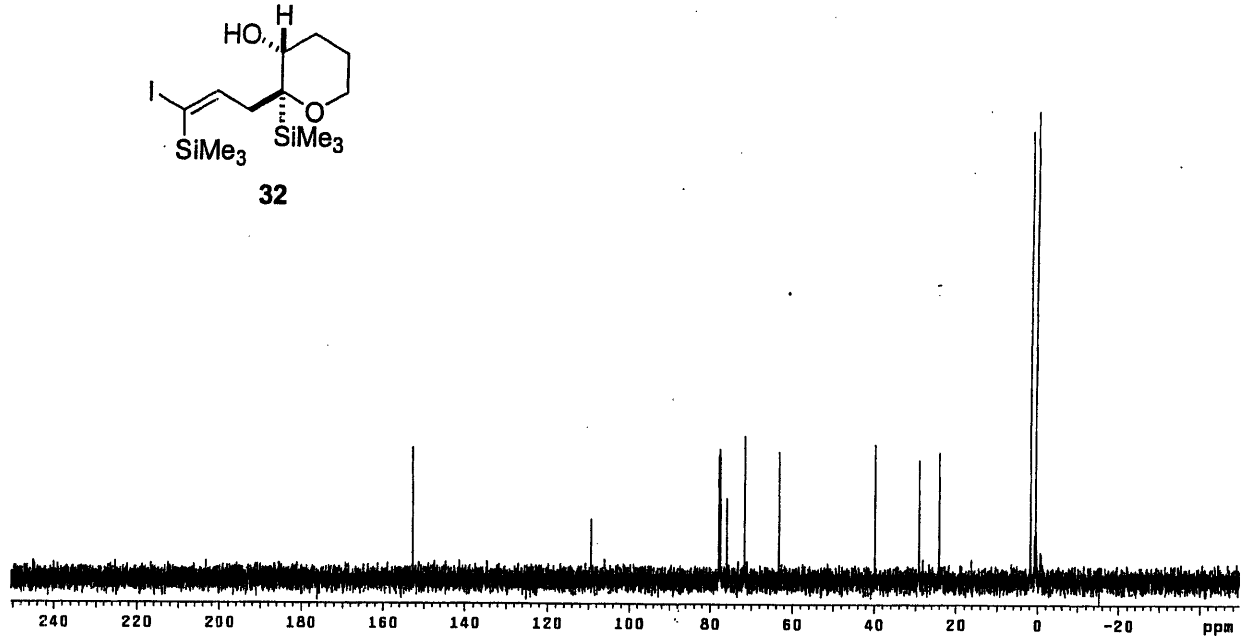
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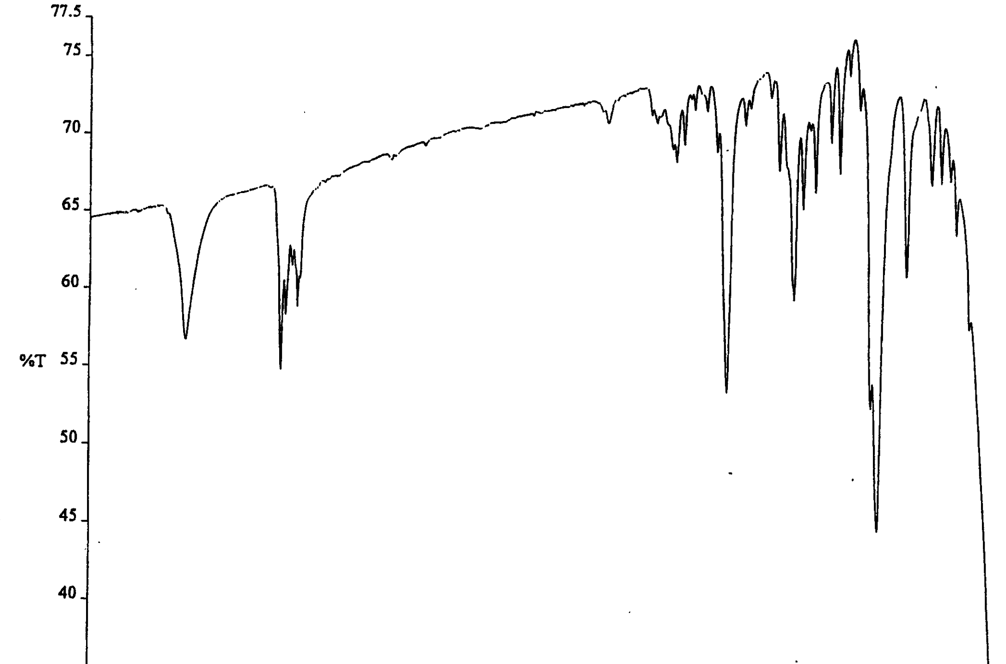
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


77.5
75
70
65
60
%T
55
50
45
40
34.1
4000.0
3000
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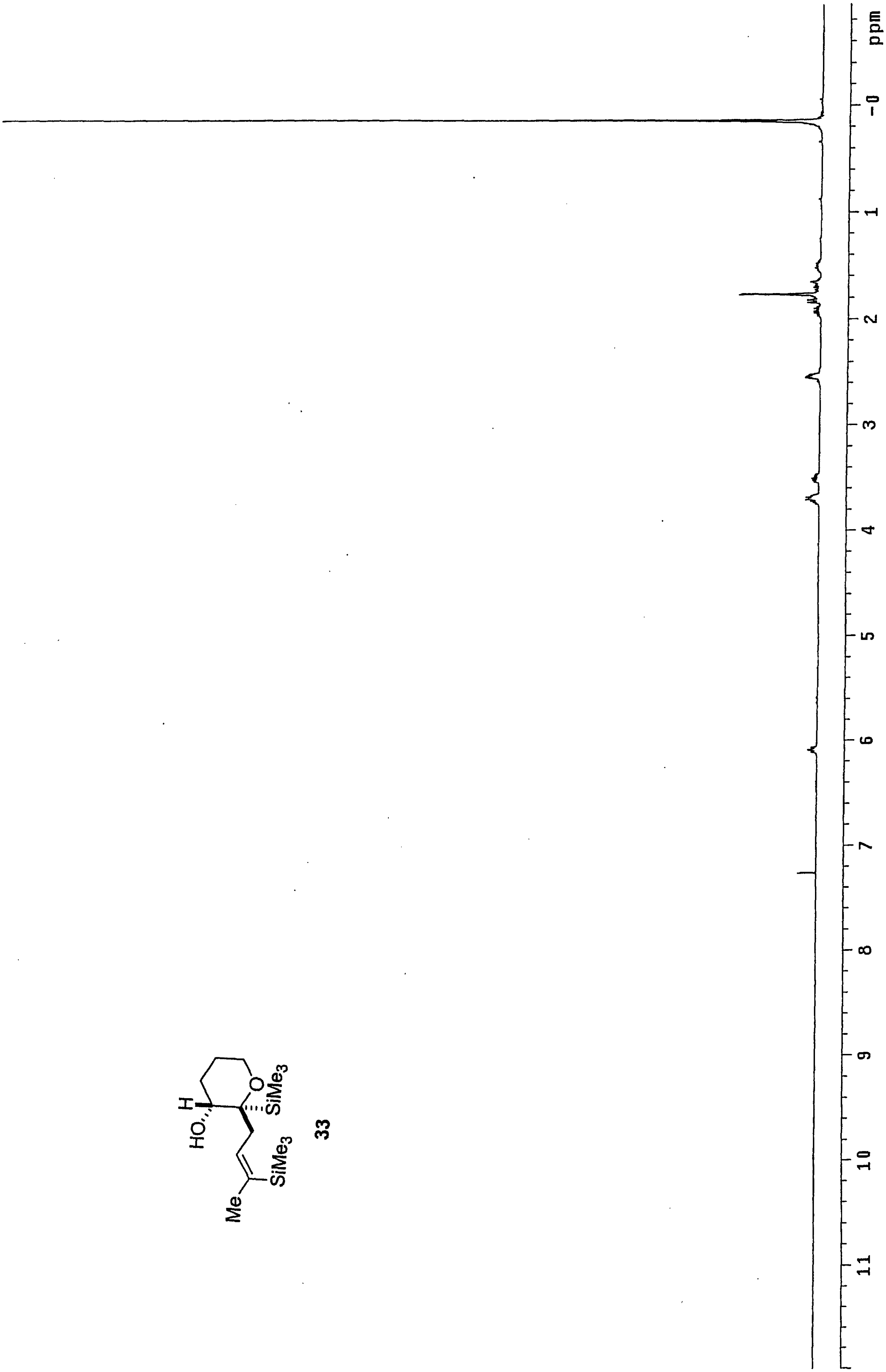
1500
1000
400.0
cm-1



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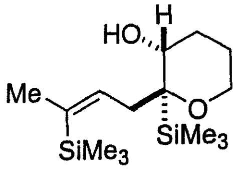
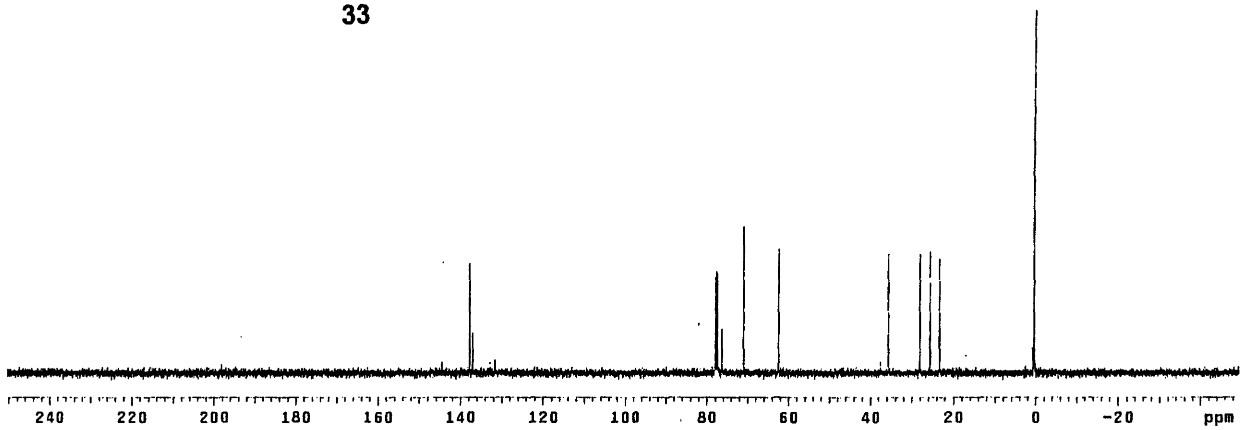

HO
H
Me
O
SiMe3
SiMe3

33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200
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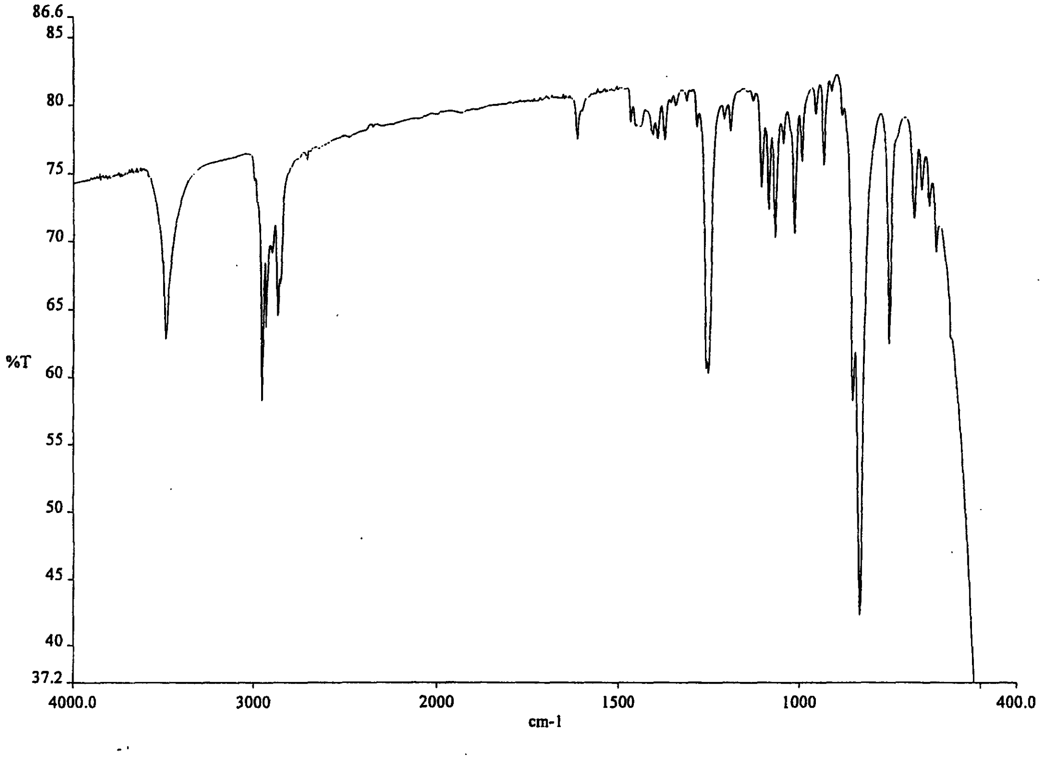
100
80
60
40
20
0
-20
ppm


86.6
85
80
75
70
65
%T
60
55
50
45
40
37.2
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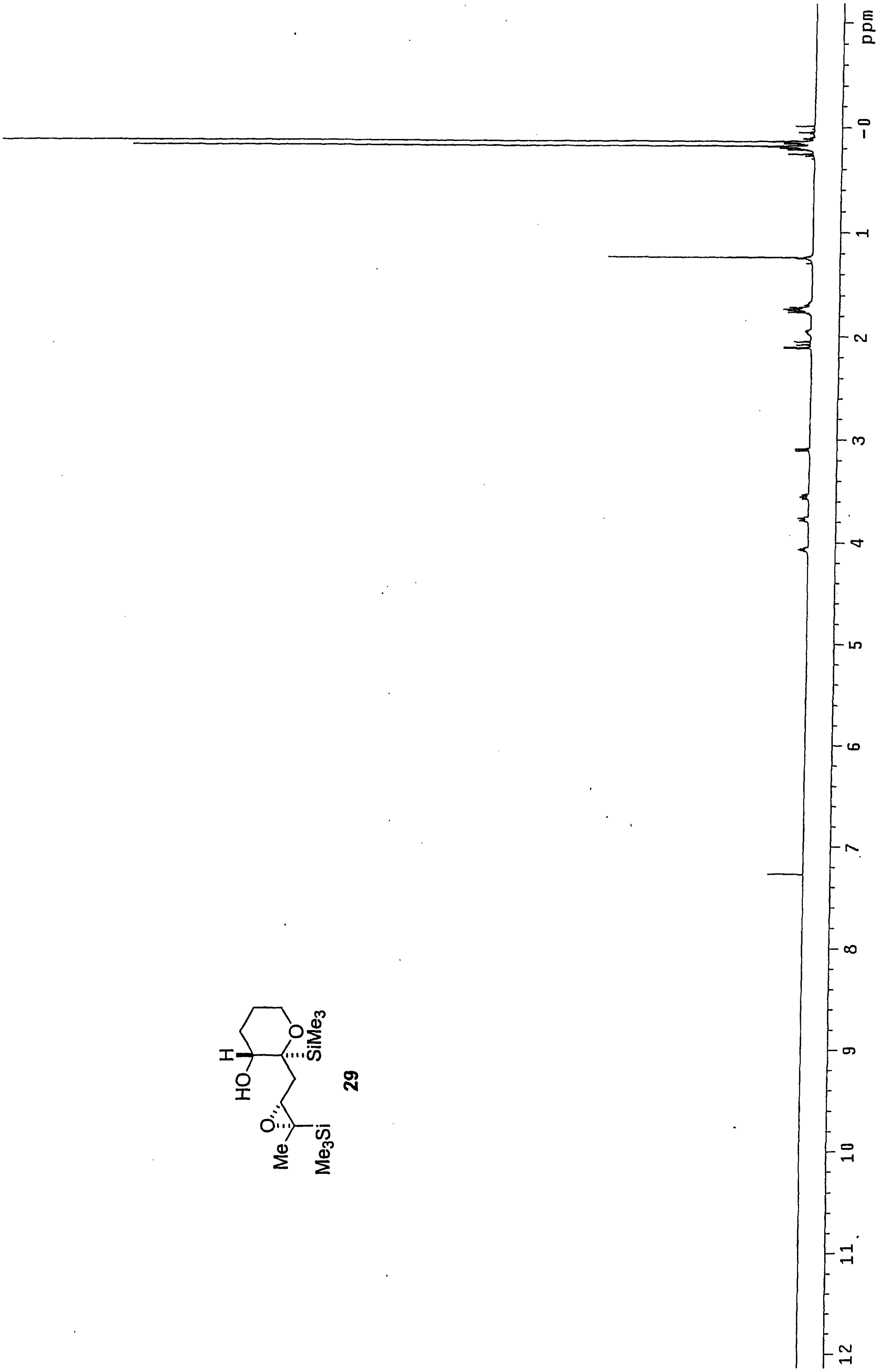
3000
2000
1500
1000
400.0
cm-1



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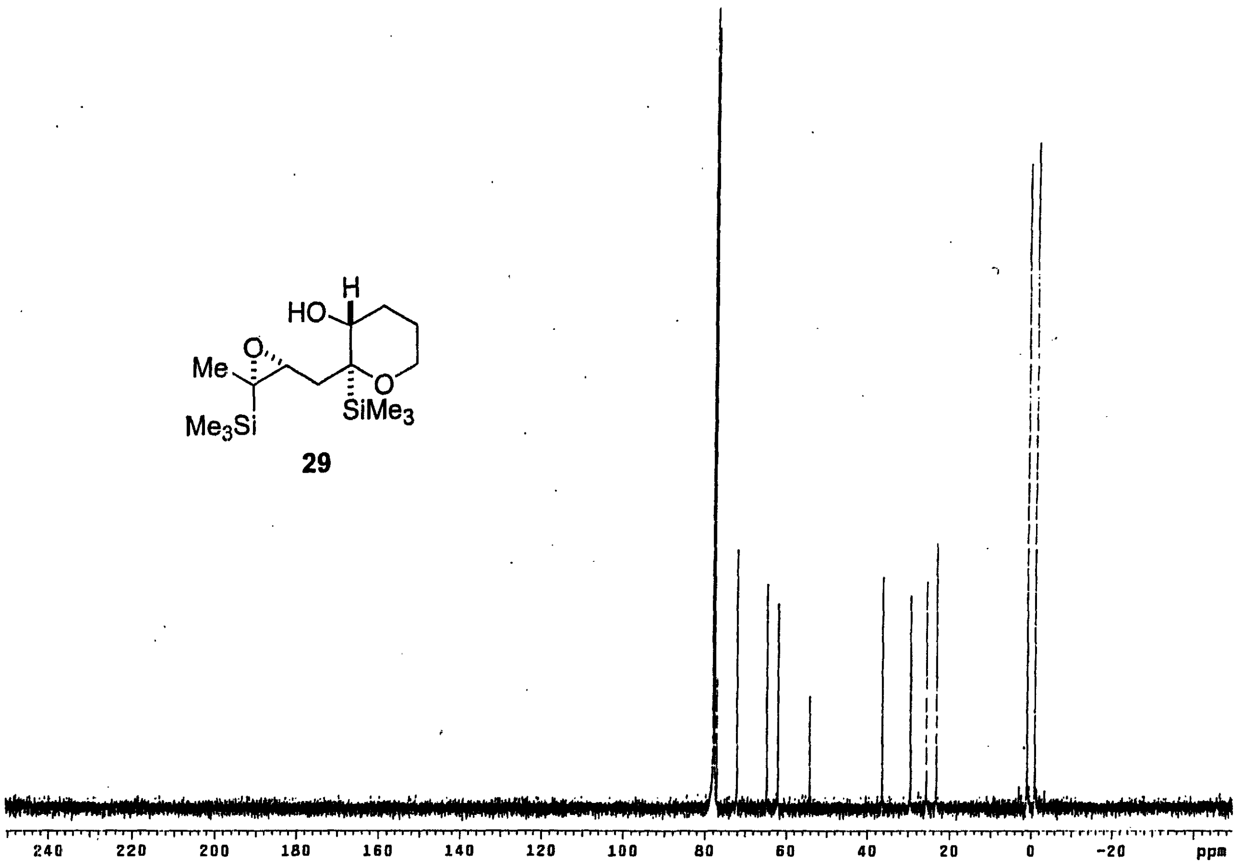
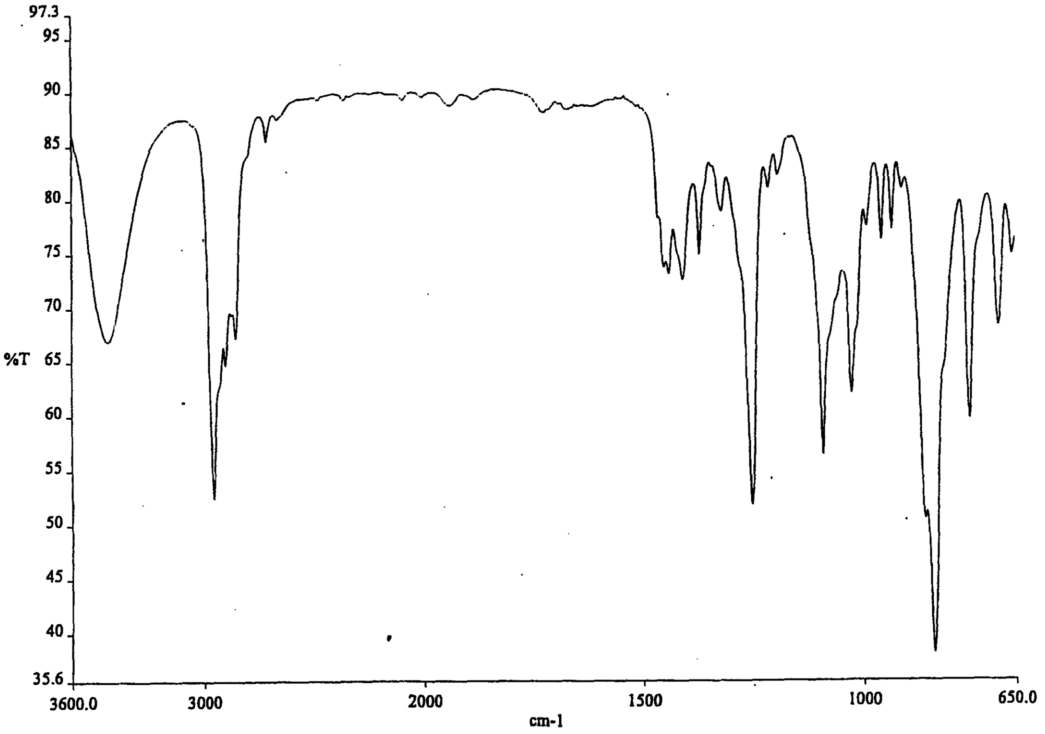
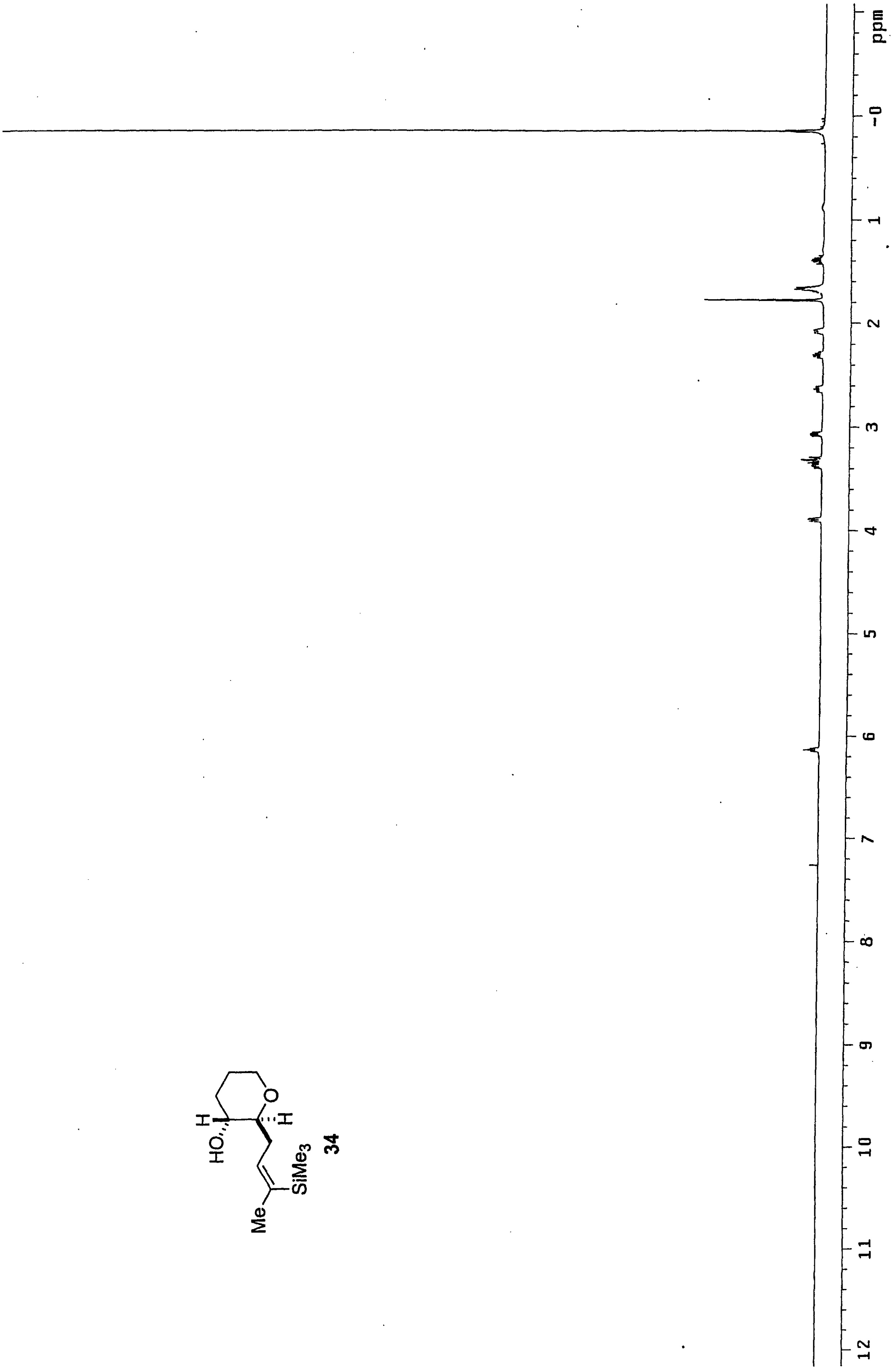

H
HO
O
Me
Me$_3$Si
O
SiMe$_3$
29
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


97.3
95
90
85
80
75
70
%T
65
60
55
50
45
40
35.6
3600.0
3000
2000
1500
1000
650.0
cm-1



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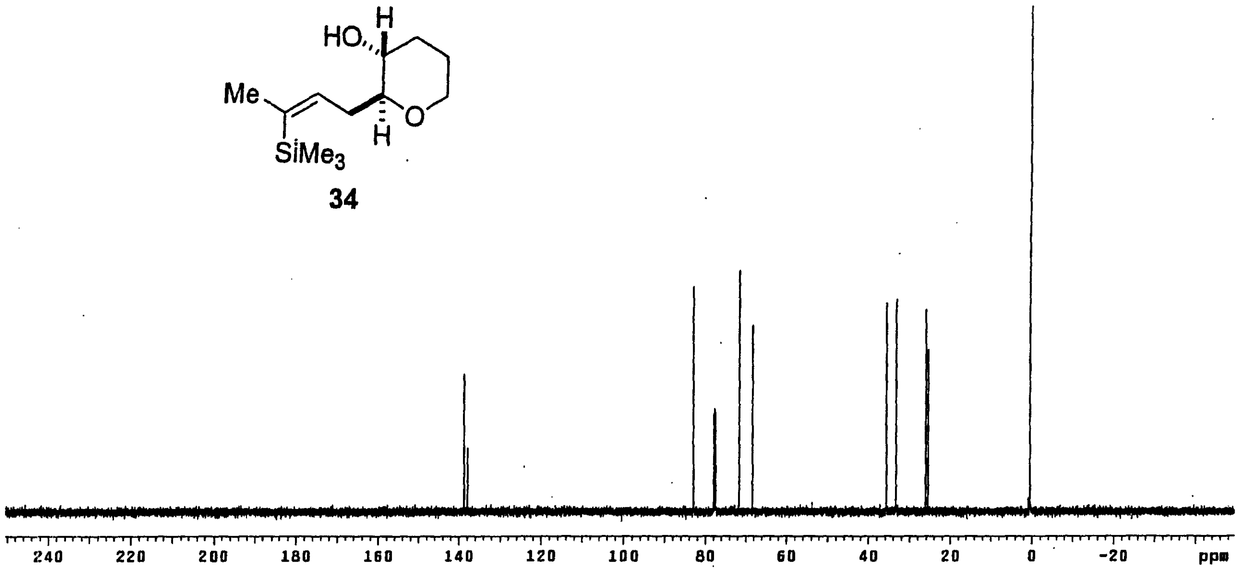
HO
H
Me
SiMe3
O
H
240
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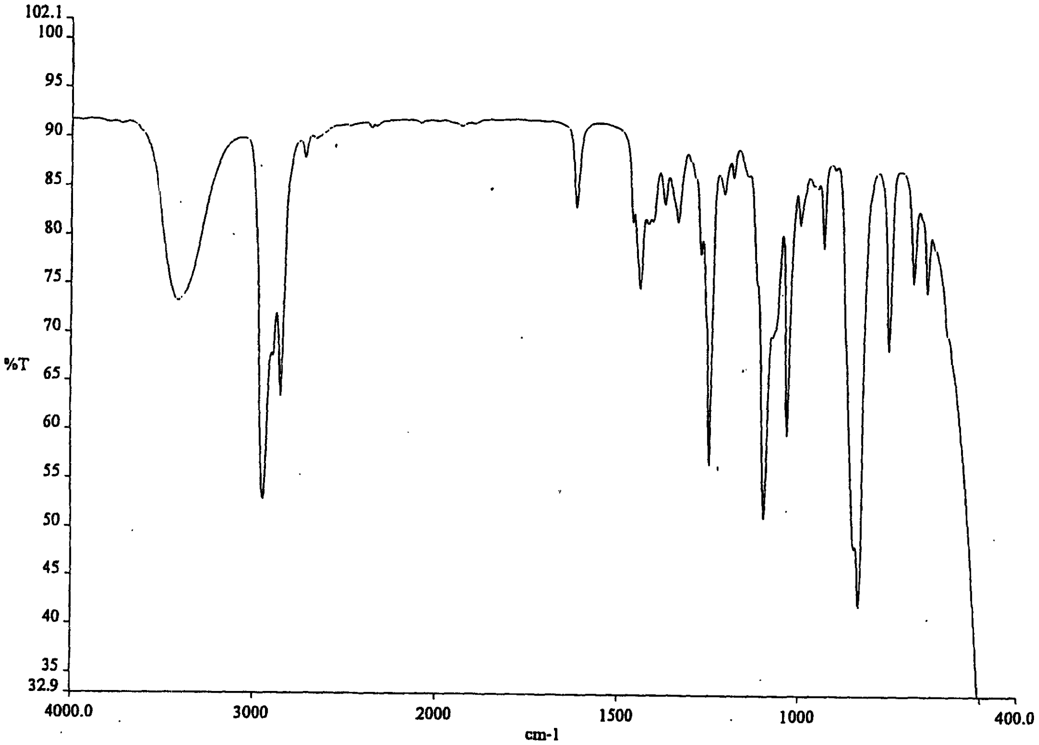
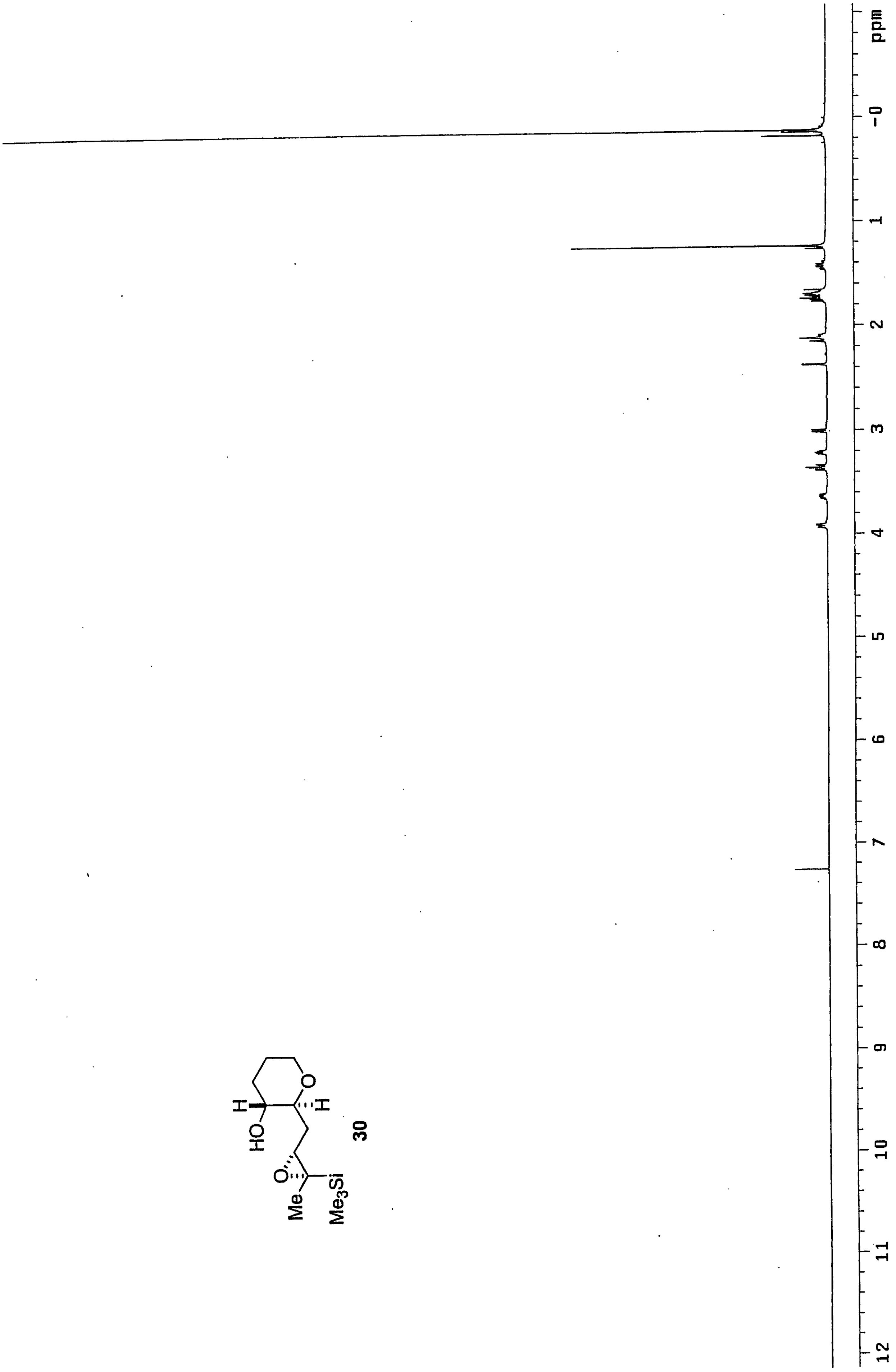
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

34


102.1
100
95
90
85
80
75
70
%T
65
60
55
50
45
40
35
32.9
4000.0
3000
2000
1500
1000
400.0
cm-1



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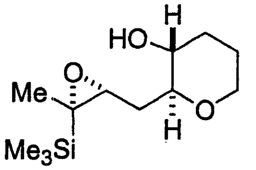
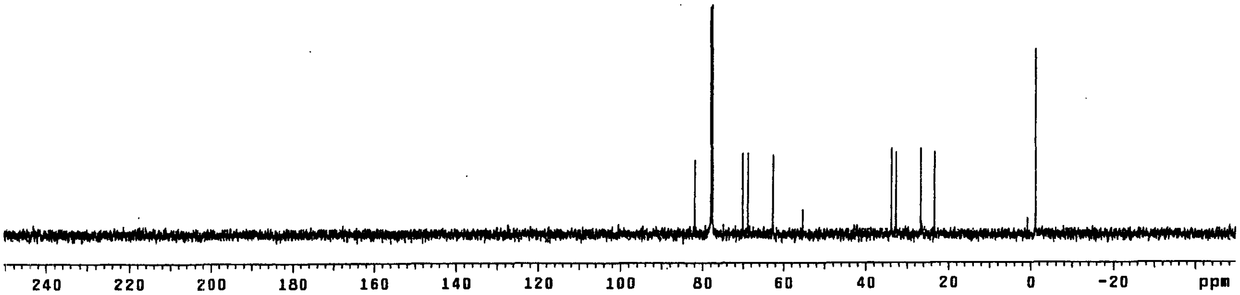
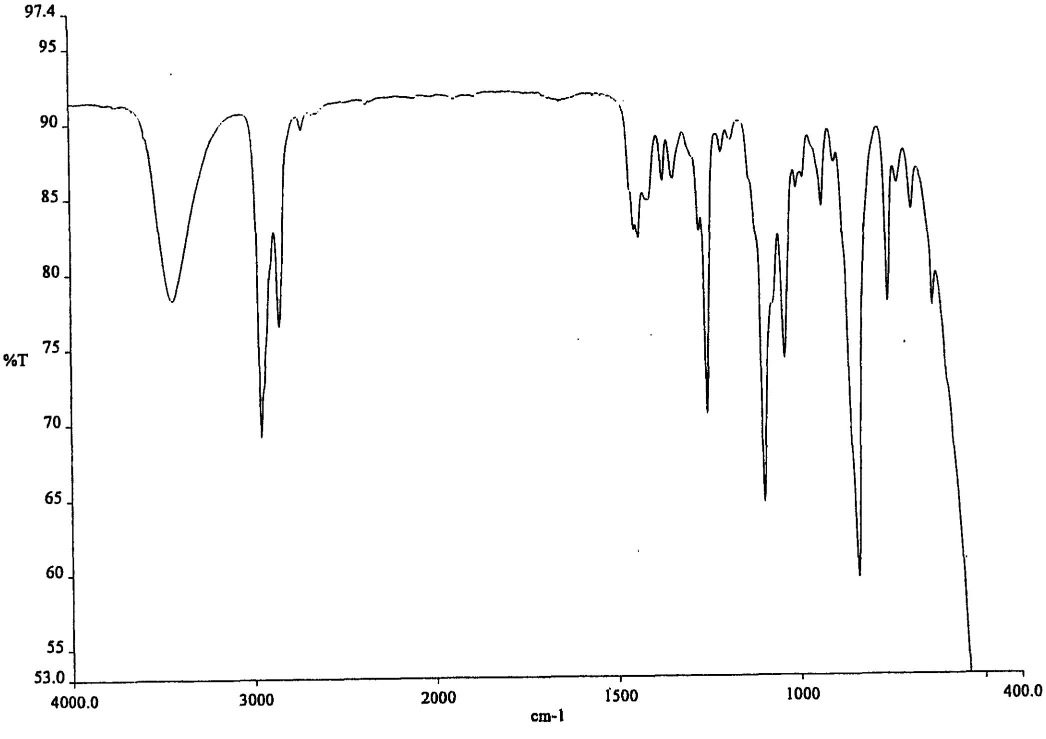
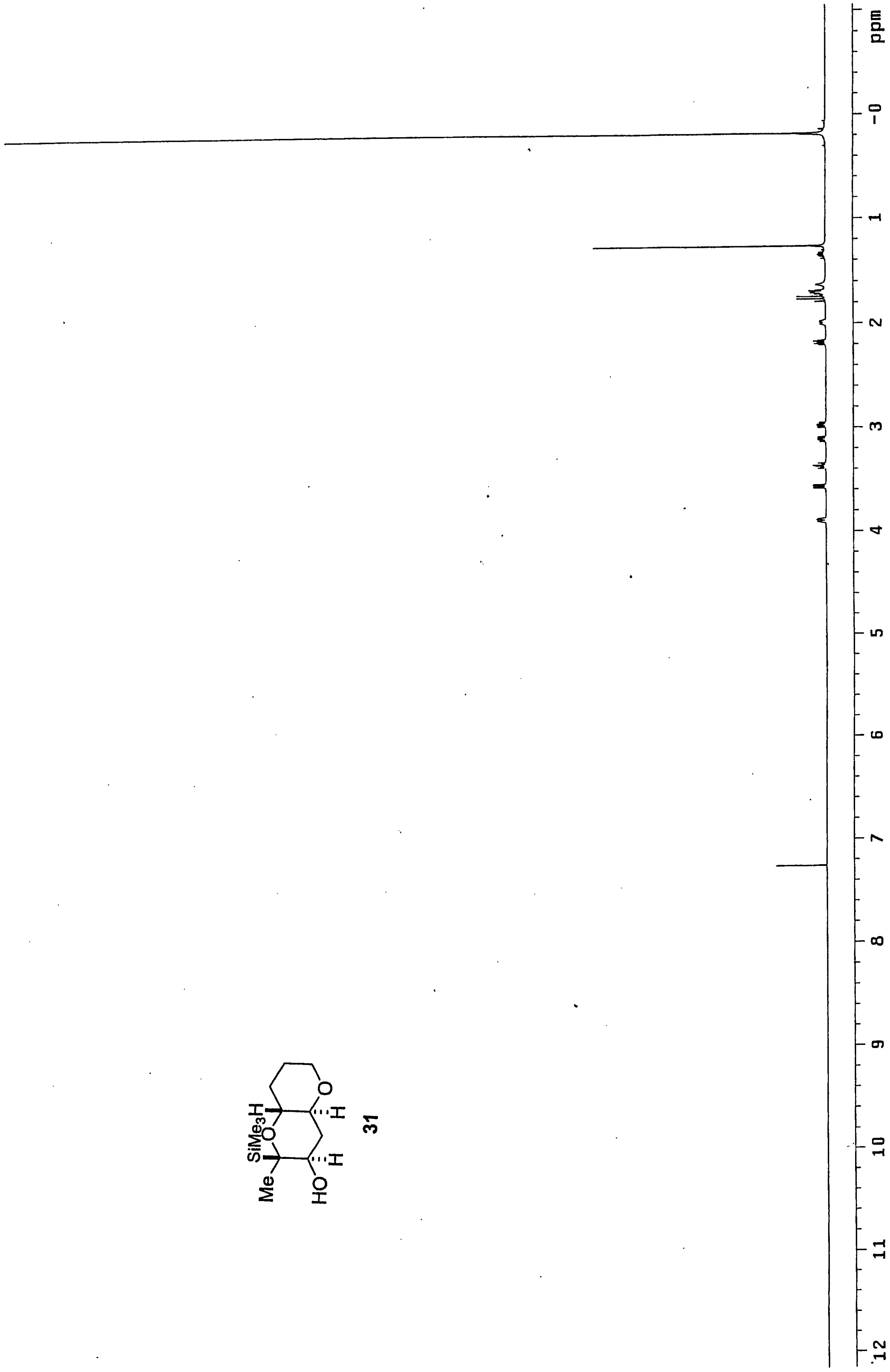

H
HO
Me
O
O
H
Me3Si

30


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


97.4
95
90
85
80
75
%T
70
65
60
55
53.0
4000.0
3000
2000
1500
1000
400.0
cm-1



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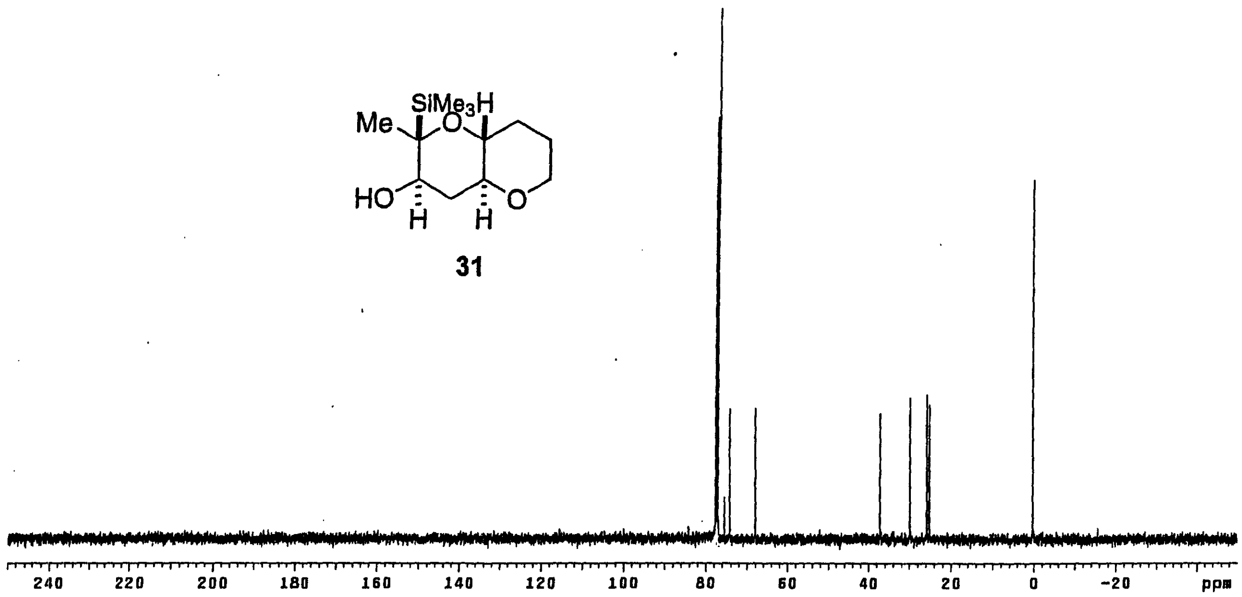
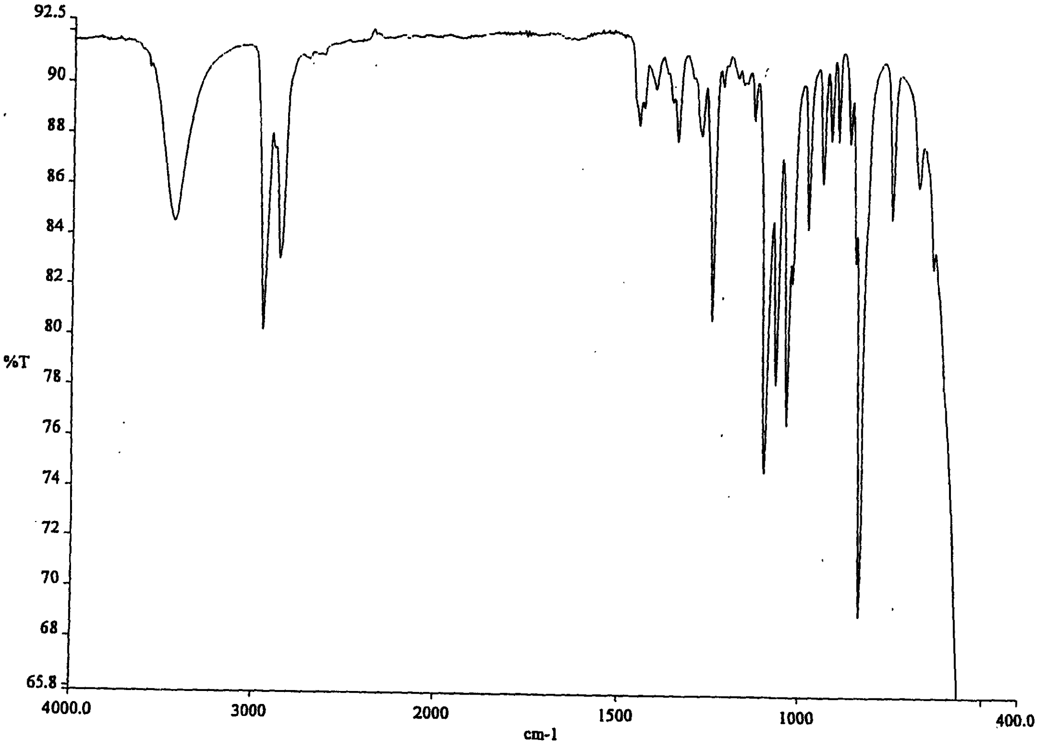
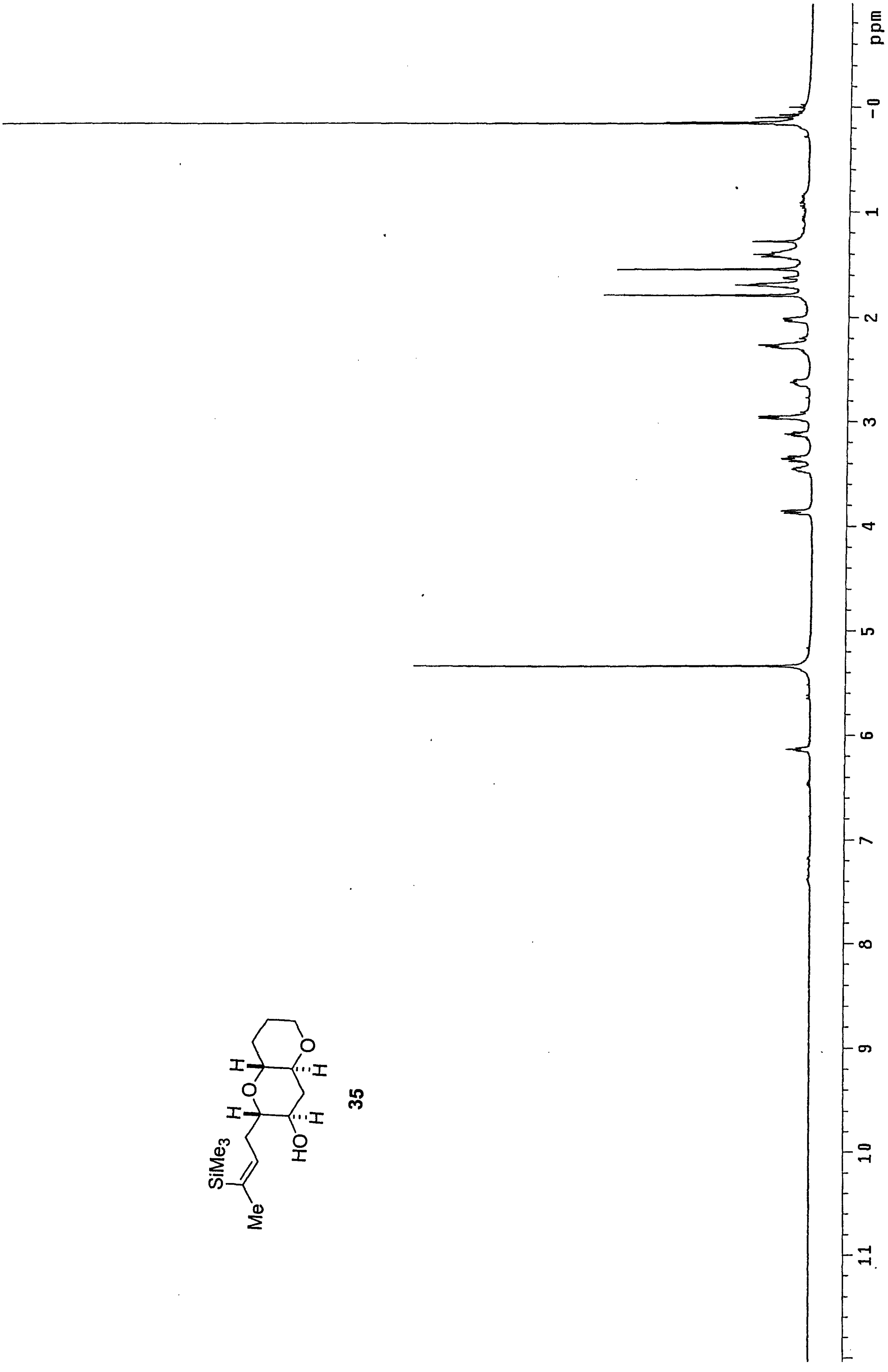

SiMe3H
Me
O
HO
H
H
O
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

31


92.5
90
88
86
84
82
80
%T
78
76
74
72
70
68
65.8
4000.0
3000
2000
1500
1000
400.0
cm-1



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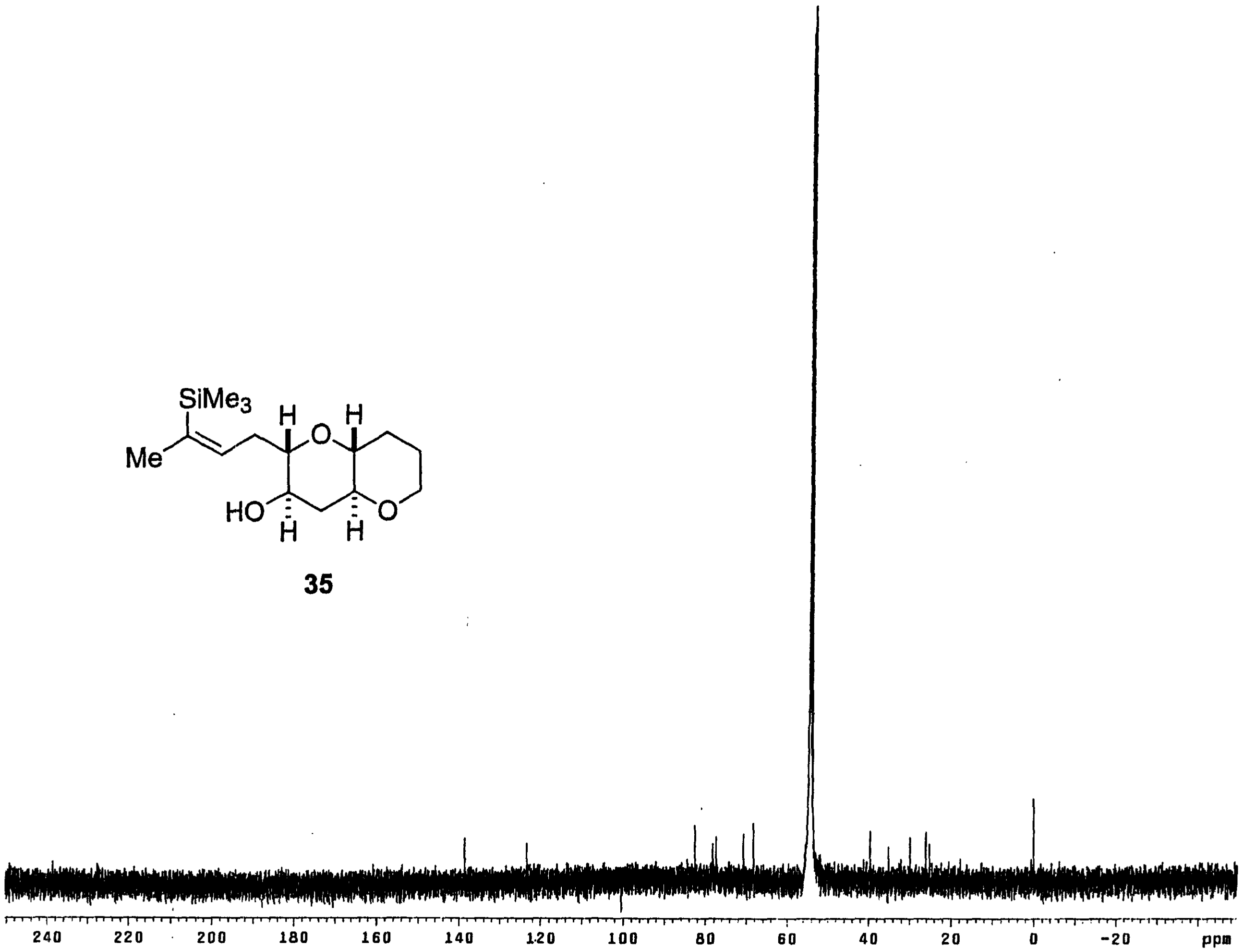
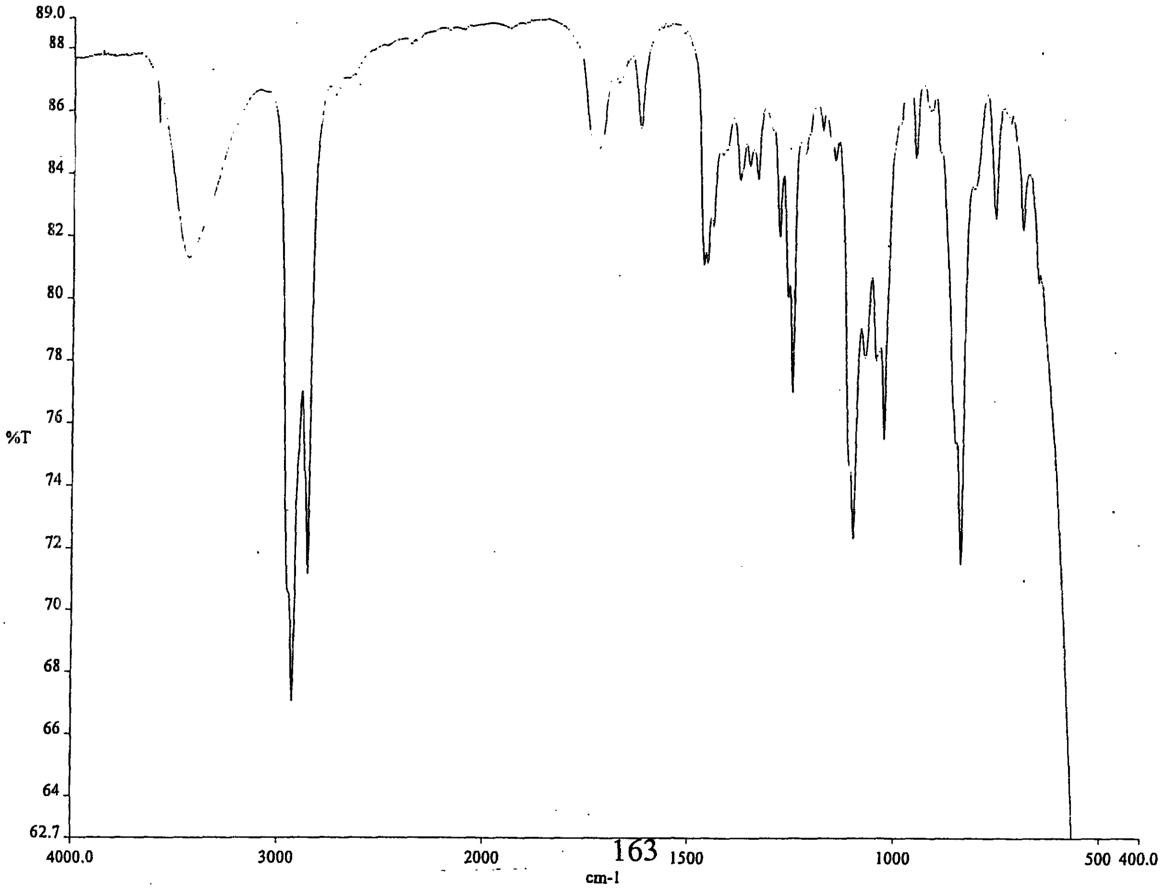
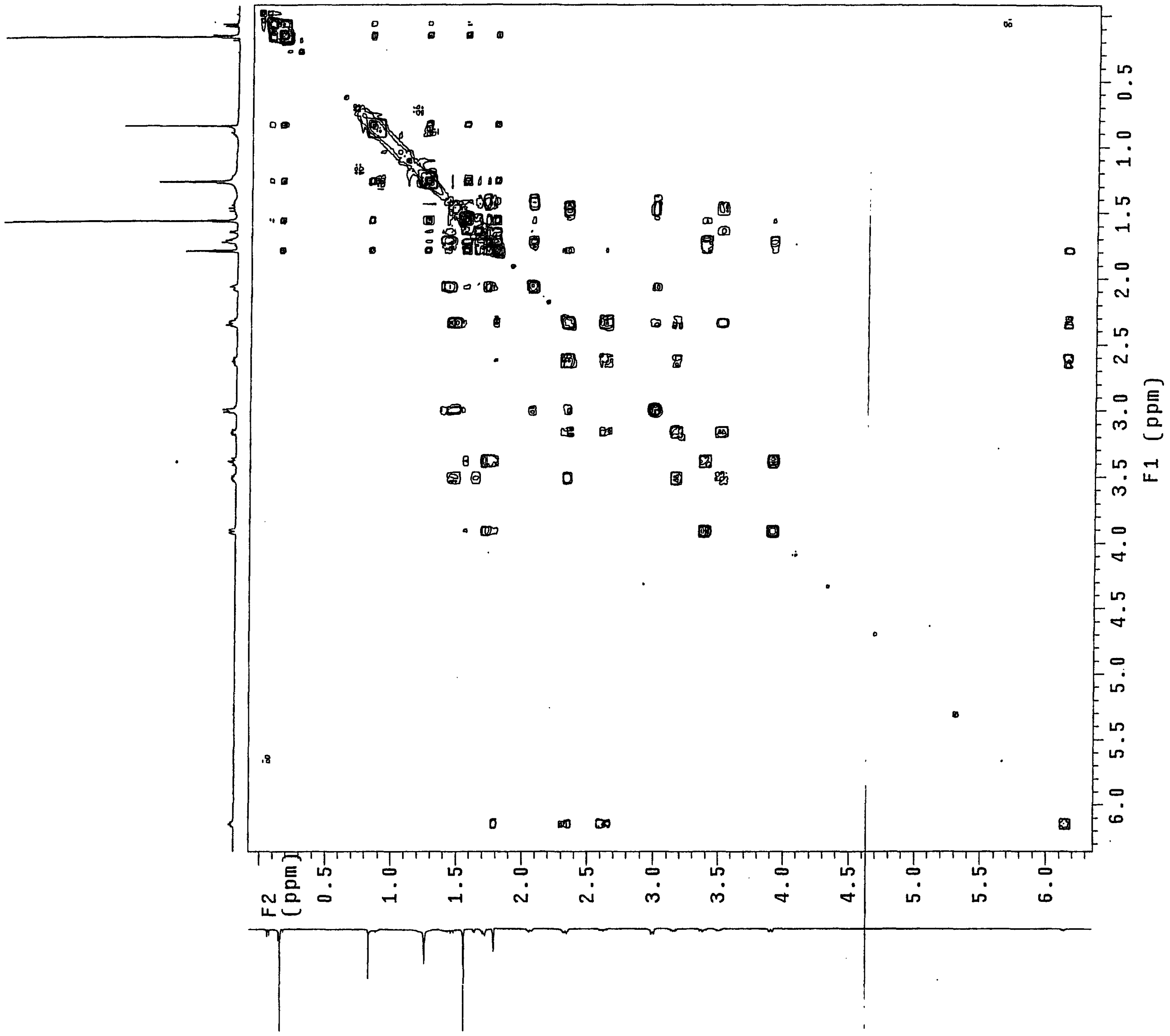
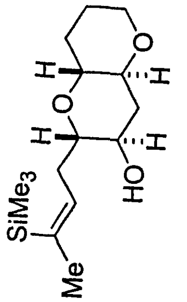

SiMe3
Me
H
O
H
HO
H
H
O
35
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

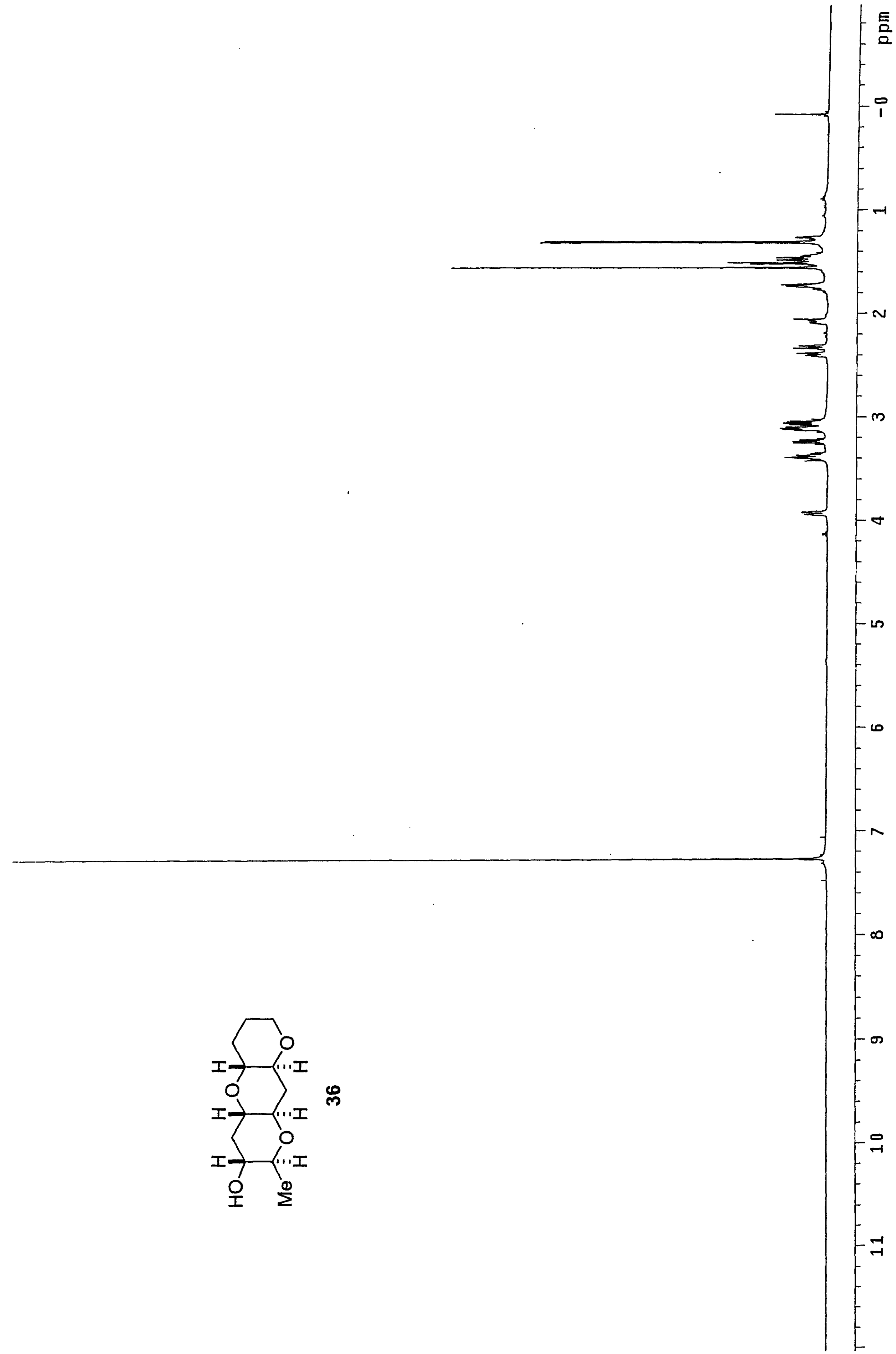

89.0
88
86
84
82
80
78
76
74
72
70
68
66
64
62.7
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1


F1 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0


SiMe3
Me
H
H
O
O
HO
H
H

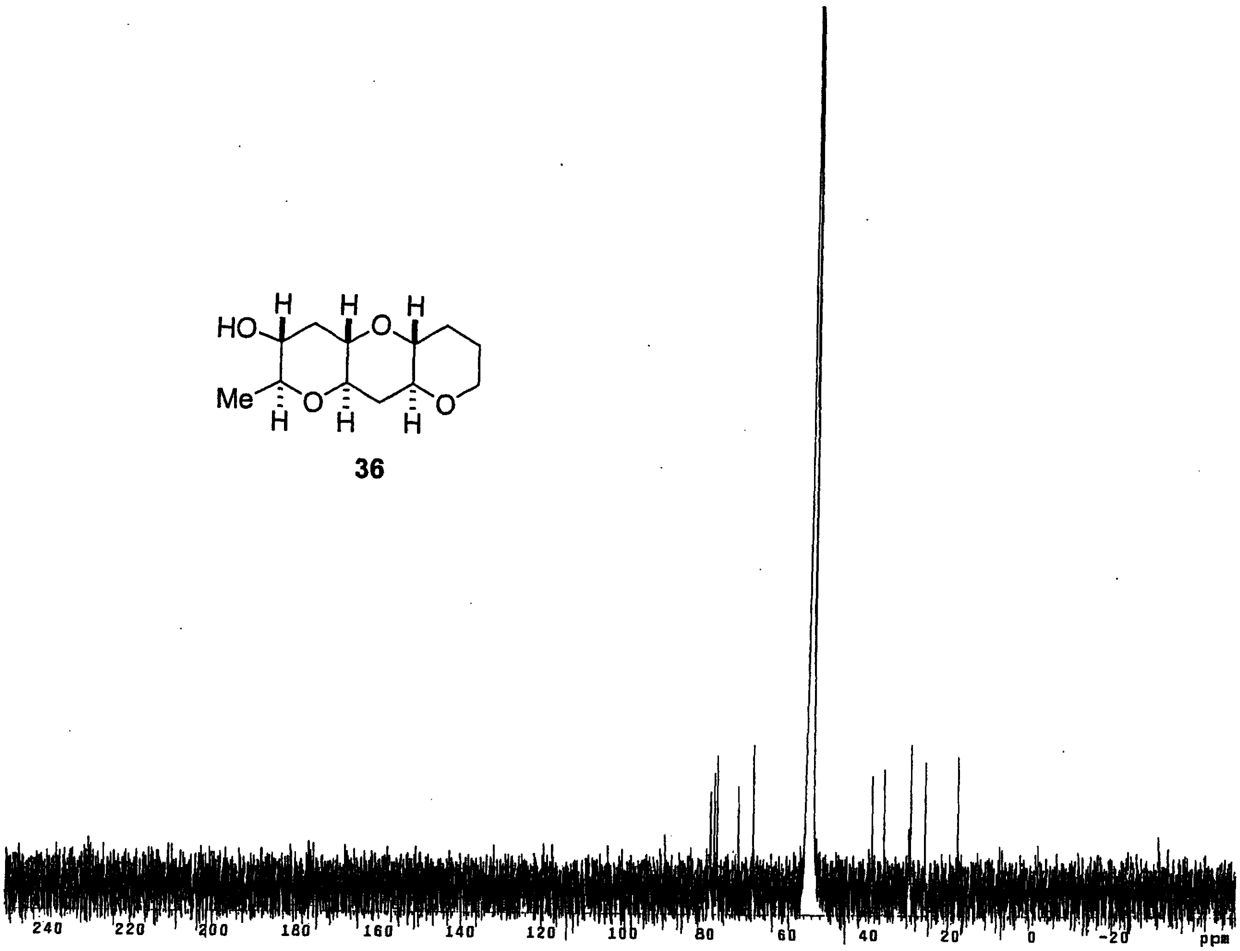
35

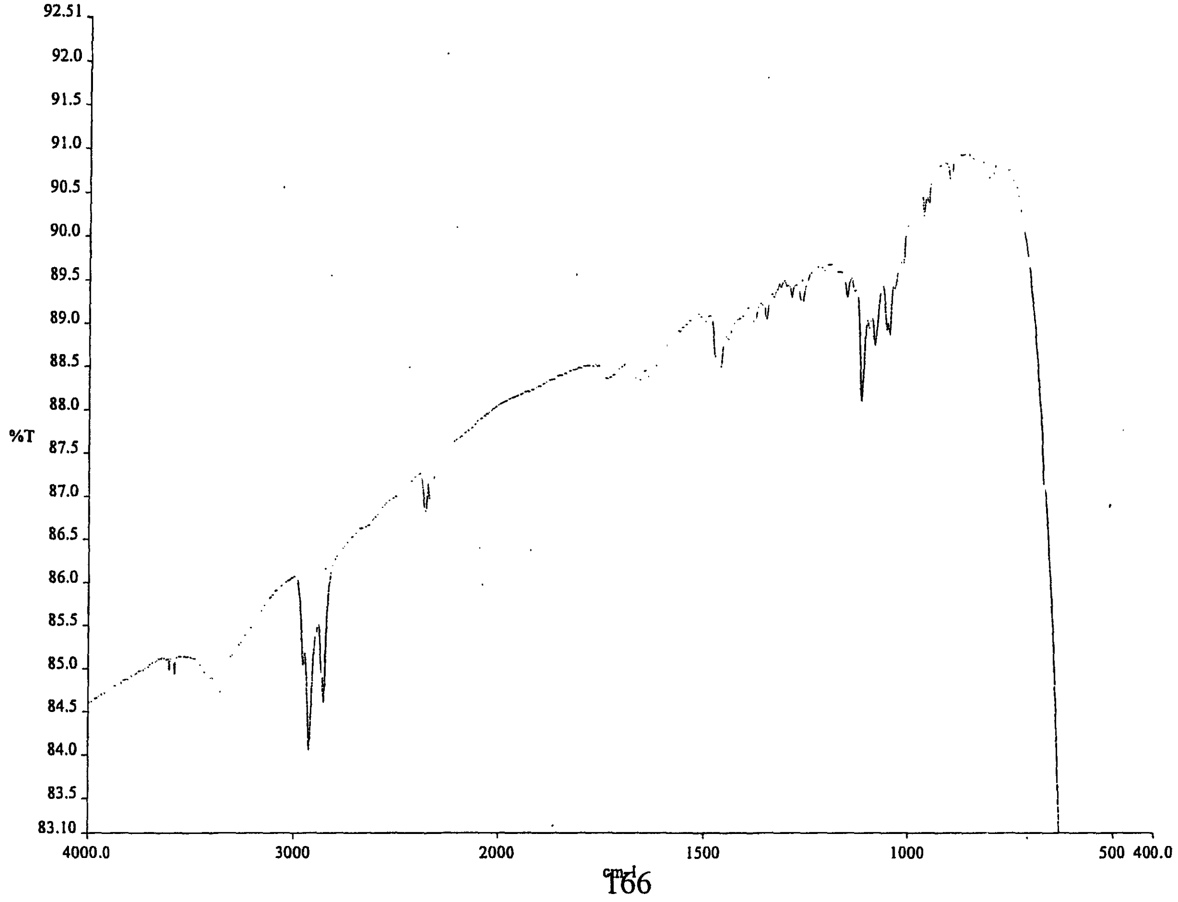
gCOSY

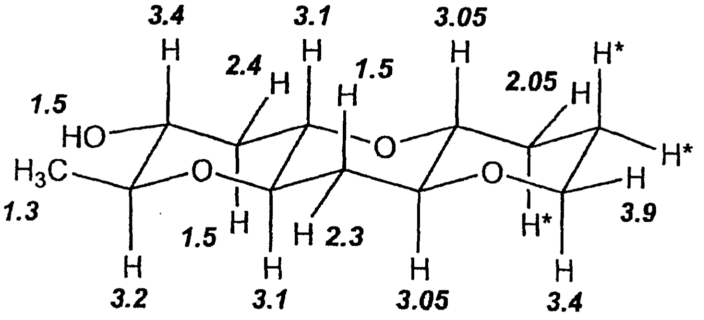

ppm
0
1
2
3
4
5
6
7
8
9
10
11
HO
Me
H
O
36

HO
H
H
O
H
Me
H
O
H
H
O

36


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

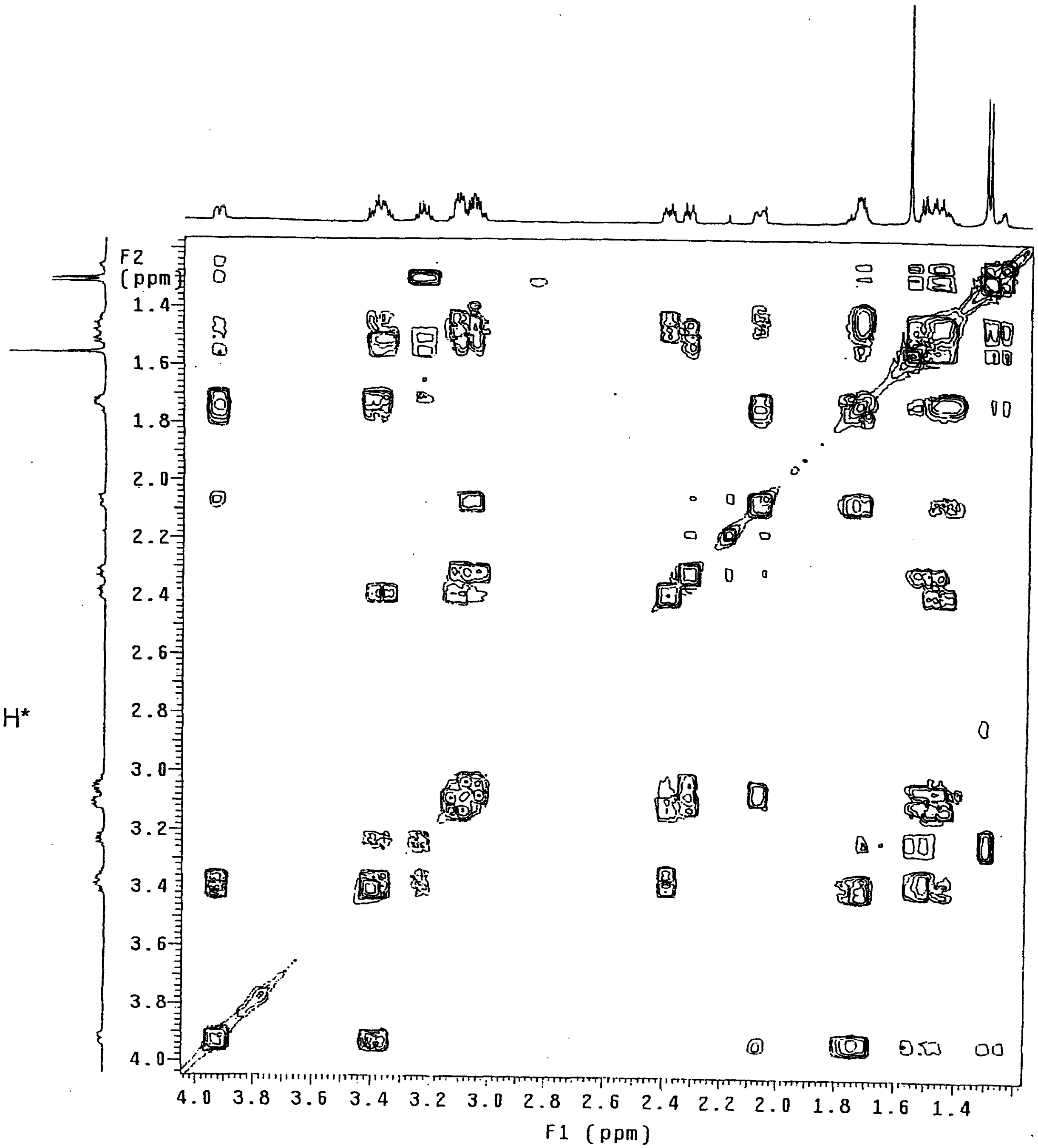

92.51
92.0
91.5
91.0
90.5
90.0
89.5
89.0
88.5
88.0
%T
87.5
87.0
86.5
86.0
85.5
85.0
84.5
84.0
83.5
83.10
4000.0
3000
2000
1500
1000
500 400.0
cm-1



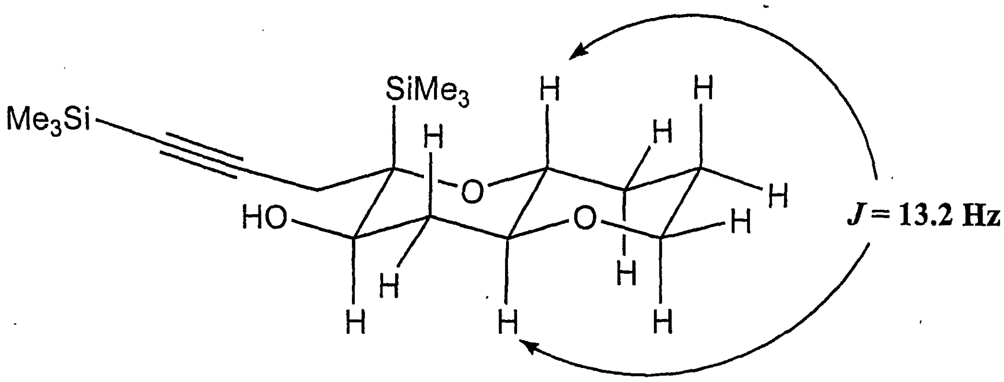
3 resonances could not be assigned explicitly
(H*): 1 at 1.5 ppm and 2 at 1.7 ppm.

36

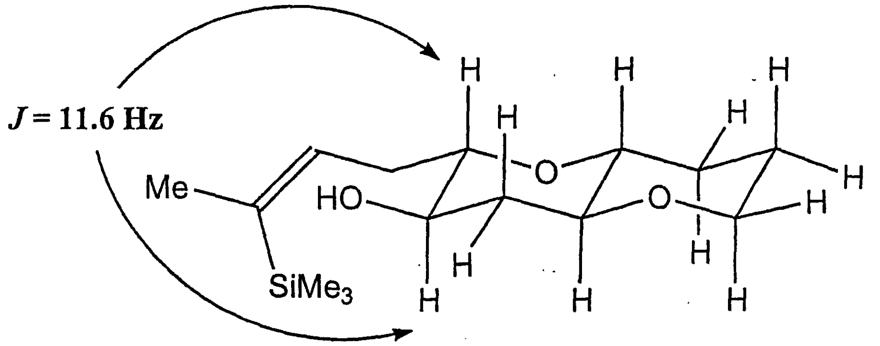
gCOSY



Stereochemical assignment based on selected J *values and nOe data*



28



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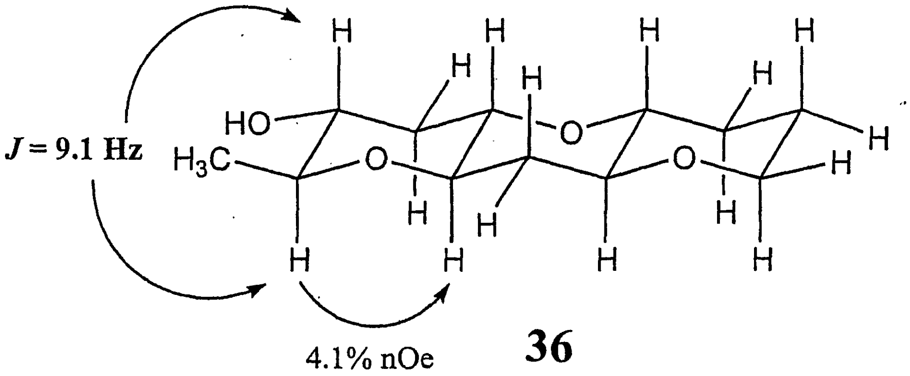


36

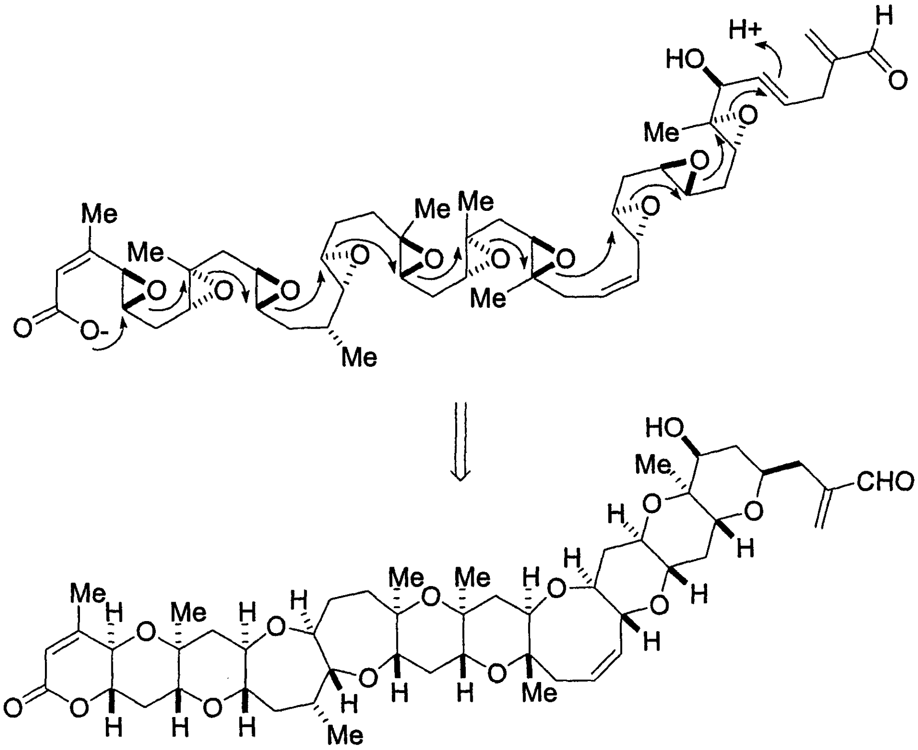
Chapter 2

The Development of a Cascade Synthesis of Polytetrahydropyrans with No Directing Groups at Ring Junctions

Introduction

When the unique structure of brevetoxin B was disclosed as the first member of the ladder polyether natural products,[2] speculation about its biosynthesis began. In a modification of the Cane, Celmer, and Westley hypothesis of the biosynthesis of monensin and related products,[69] Nakanishi proposed a polyepoxide-opening cascade as the biogenetic source of these molecules (e.g. **2**, Figure 1).[19] While this suggestion is routinely cited as an attractive biosynthetic hypothesis, neither verification nor duplication of this general cascade strategy for the synthesis of *trans*-fused ladder polyether natural products has been achieved to date.[70]

Figure 1. Nakanishi's proposed epoxide cyclization cascade for the biosynthesis of brevetoxin B.



brevetoxin B (**2**)

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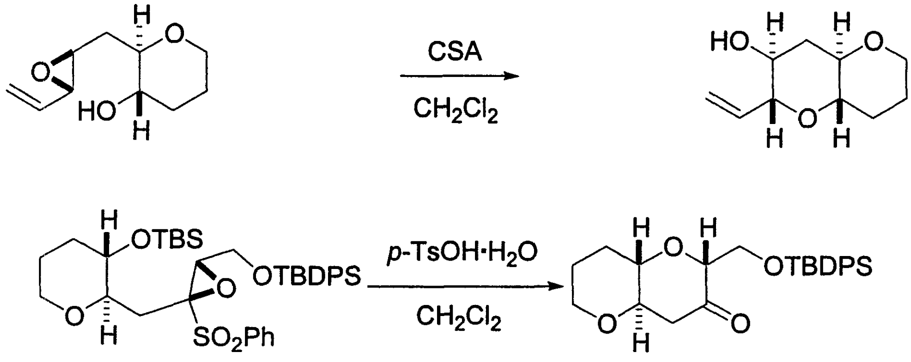
[69] Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.

[70] In the course of a synthesis of hemibrevetoxin B Holton reported the use of a cascade reaction wherein a hydroxy-epoxide cyclization takes place: ref 11m.

In the suggested biosynthesis, a series of epoxy-alcohol cyclizations leads to the formation of the *trans*-fused ether rings in the natural product. While the Nicolaou[14] and Mori[17] methods for the iterative synthesis of polytetrahydropyrans effectively override the inherent preference for the 5-exo mode of cyclization and afford 6-endo products, they are not suitable substrates for polyepoxide cyclization studies. In Nicolaou's case, the vinyl directing group requires elaboration, eventually becoming the next epoxide, before a second cyclization. In the case of Mori, reduction of the ketone functionality to an alcohol is necessary before subsequent cyclization. Thus, in both of these cases modification of the substrate is required before a second cyclization (Figure 2).

Figure 2. Nicolaou and Mori methods for the 6-endo selective opening of epoxides.



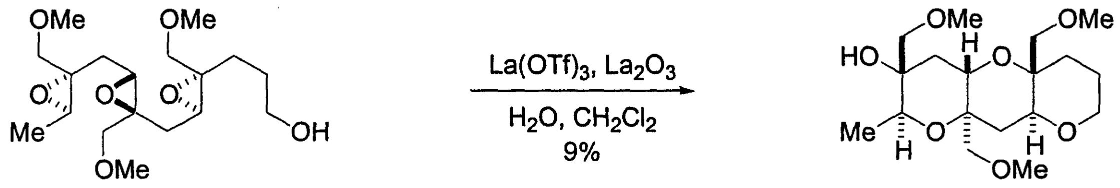
Multiple approaches to epoxide cascade cyclizations that lead to *trans*-fused polyethers have been reported (*vide infra*). More specifically, reports from two groups have described examples in which multiple epoxides are opened to afford *trans*-fused polyether systems.

The Murai group has achieved regioselective openings of epoxy-alcohols that they suggest are directed by a methoxymethylene through the bidentate binding of a lanthanide transition metal catalyst (Figure 3).[71]

---

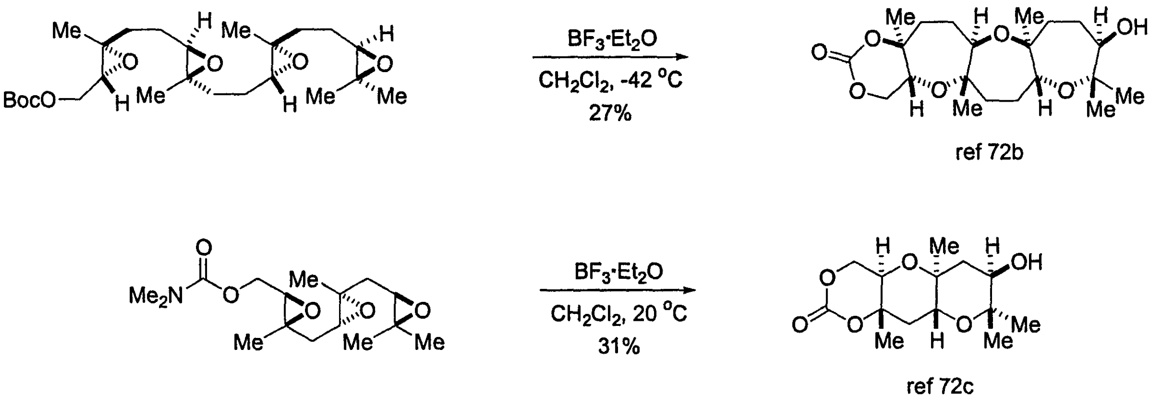
[71] Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335-338.

Figure 3. Murai cascade leading to a tristetrahydropyran.



McDonald has reported several examples of cascades leading to both *trans*-fused polyoxepanes and polytetrahydropyrans with methyl groups at each ring junction (Figure 4).[53, 72]

Figure 4. Examples of McDonald's cascade production of trans-fused ether ring systems.

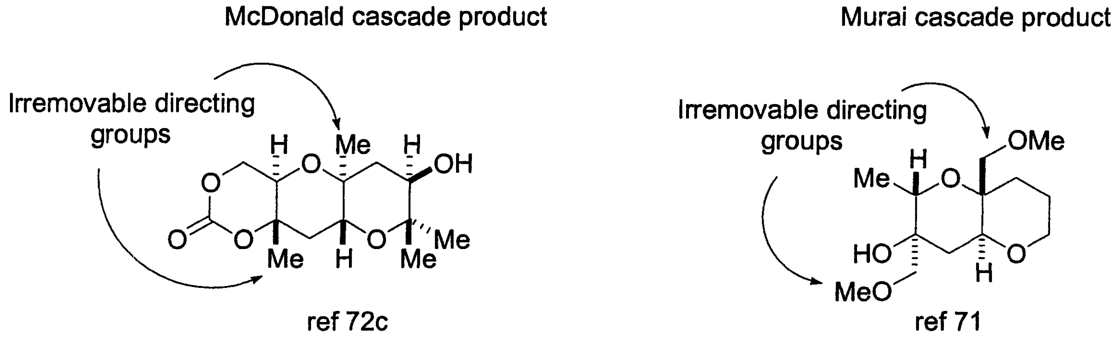


Utilized in each of these cases, however, are control elements (methoxymethylene and methyl groups, respectively) that are neither present in the natural products nor easily removed after cyclization. The inclusion of such groups limits the utility of these approaches in the synthesis of naturally occurring ladder polyethers as in these examples the series of rings formed do not occur in any natural product (Figure 5).

---

[72] (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917-2919. (b) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515-2523. (c) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123-2126. (d) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487-4489.

Figure 5. Reported examples of epoxide opening cascades.

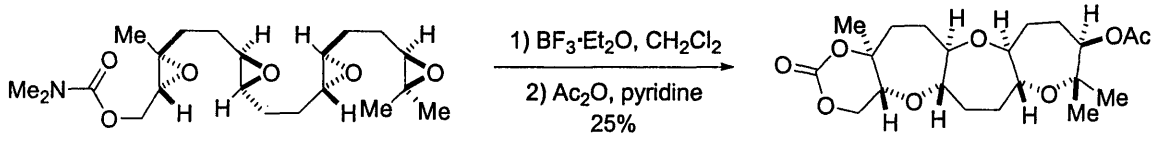


ref 72c

ref 71

The methyl groups in McDonald's substrates were believed to be required to control regioselectivity by stabilizing developing positive charge at the more substituted side of each epoxide. Very recently, in the cascade synthesis of polyoxepane products, McDonald reported the synthesis of a system with two ring junctions without directing groups (Figure 6).[53] While significant as the first report of a cascade synthesis of a *trans*-fused ring system that contains a ring junction without a directing group, the cascade production of the ubiquitous polytetrahydropyran motif with no directing groups at the ring junctions has yet to be reported.

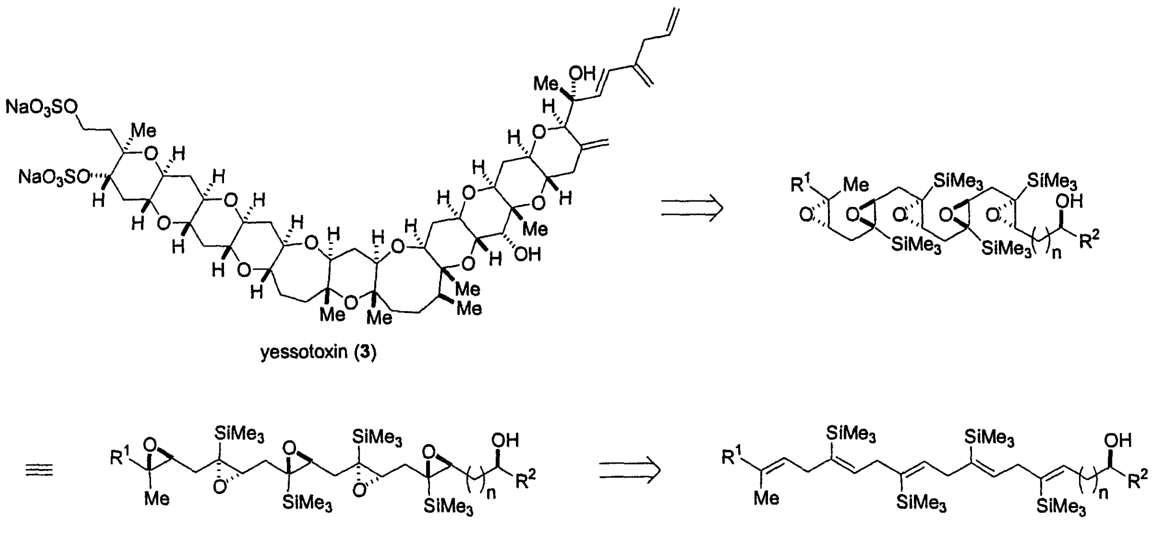
Figure 6. McDonald's cascade synthesis of a polyoxepane that contains two ring junctions without directing groups.



We initiated a program directed toward the realization of an epoxide cascade-based method for the rapid assembly of *trans*-fused polyether natural products based on the methods developed in Chapter 1. In particular we were interested in polytetrahydropyran units because they are present in most of the ladder polyether natural products. Like previous efforts in other laboratories, we envisioned utilizing a directing group to control regioselectivity in the epoxy-alcohol cyclizations. In contrast to previous efforts, however, we further required that the directing group be easily removed after cyclization to reveal the junction that appears in the natural products.

Having developed methods for the synthesis of polytetrahydropyrans in an iterative fashion using epoxysilanes (Chapter 1), we were positioned to extend those studies to the synthesis of polyepoxides and to study cascade cyclizations of them. We envisioned applying the methods developed for the iterative synthesis of polytetrahydropyrans to the synthesis of polyepoxide substrates that would then undergo sequential, regioselective epoxide openings to reveal polytetrahydropyran units as found in ladder polyether natural products (e.g. yessotoxin (**3**), Scheme 1).

Scheme 1


yessotoxin (**3**)

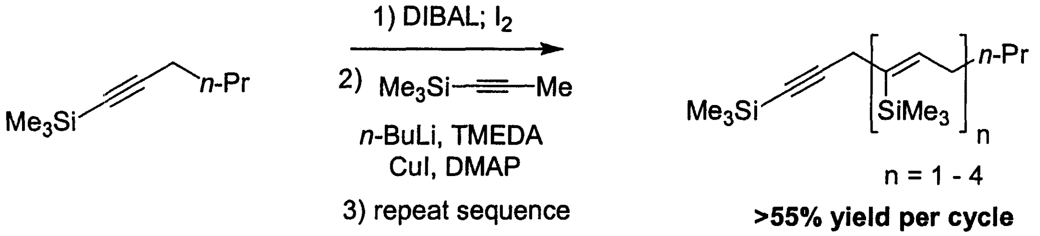
Our initial approach to polyethers *via* a cascade cyclization sought to utilize our previous efforts in the synthesis of skipped enynes and epoxysilanes. While the directing ability of $SiMe_3$ in the cyclization of a monoepoxide was successful, questions remained about the need to force the directing group into the axial position at each ring junction of a polytetrahydropyran and the protiodesilylation of the $SiMe_3$ groups at the completion of a cascade (see Chapter 1).

This chapter details our stereoselective synthesis of polyepoxides and attempted cascade cyclizations of polyepoxysilanes under acidic conditions. Also discussed are attempted cascade cyclizations of polyepoxides that contain no directing group. Finally, the development of a successful cascade cyclization of polyepoxysilanes, promoted by a Brønsted base, is presented.

Results and Discussion

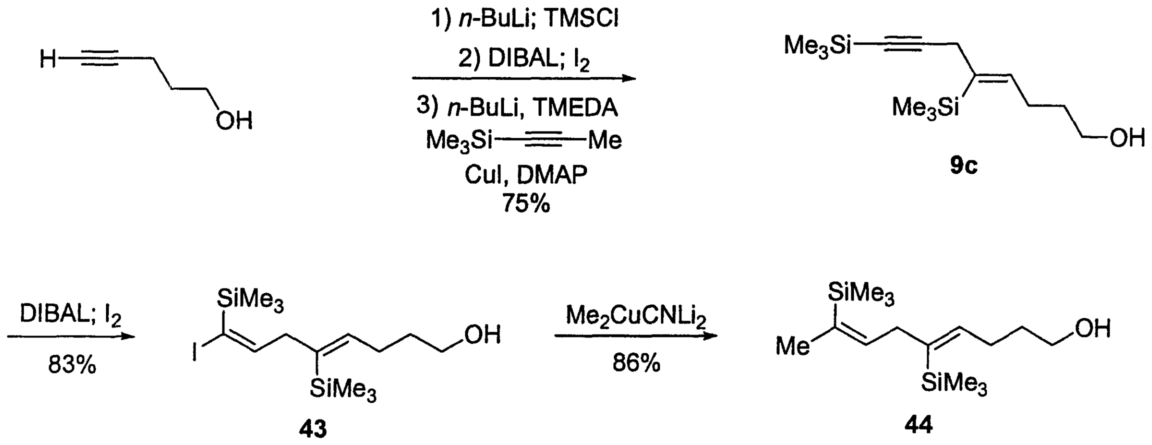
Using the novel organocopper propargyl coupling reaction (Chapter 1), ready access to stereodefined skipped trisubstituted polyalkenylsilanes appeared present. To demonstrate that a hydroalumination/iodination sequence followed by propargylation was, in fact, a viable approach to the desired polyolefins, 1-trimethylsilyl-1-hexyne was carried through four iterations to a tetraenyne.

Scheme 2



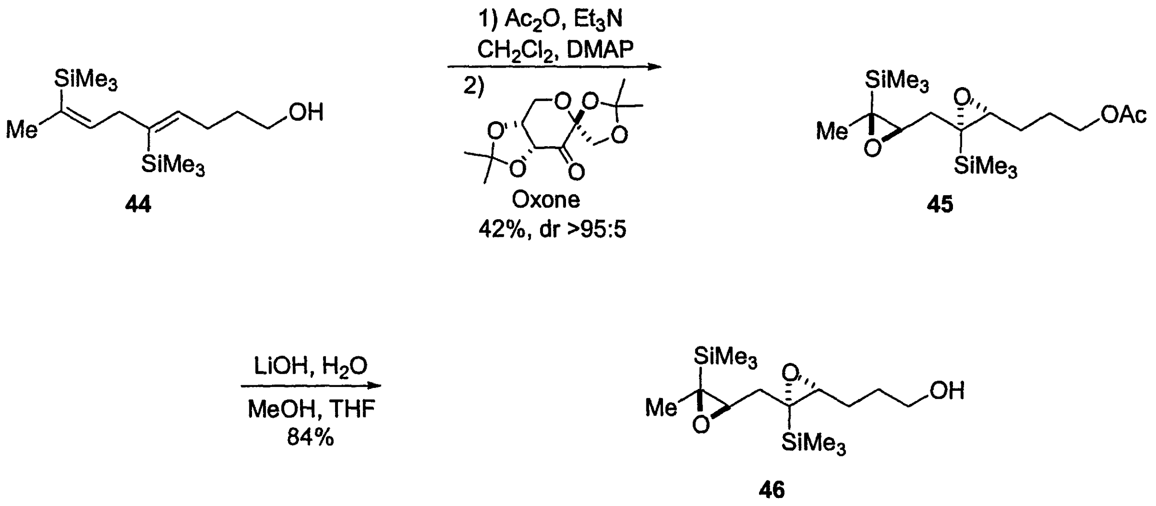
Having demonstrated that a synthesis of skipped polyolefins of requisite stereochemistry was available, we prepared several such compounds that would be subjected to conditions for epoxidation of all of the alkenes in a single operation. For cascade cyclizations we desired an internal nucleophile that would initiate an epoxide-opening cascade. Beginning with 4-pentyn-1-ol, we prepared skipped diene **44**, the precursor to the first polyepoxysilane for study as a cascade substrate (Scheme 3).

Scheme 3



In order to carry out the asymmetric epoxidation of diene **44**, the primary alcohol was first protected as an acetate in order to prevent the loss of material to oxidation of the alcohol (Scheme 4).[47, 48] After this protection, the asymmetric epoxidation proceeded smoothly to provide bisepoxide **45** in high diastereoselectivity (dr >95:5). The acetate was then removed to leave the free alcohol (**46**).

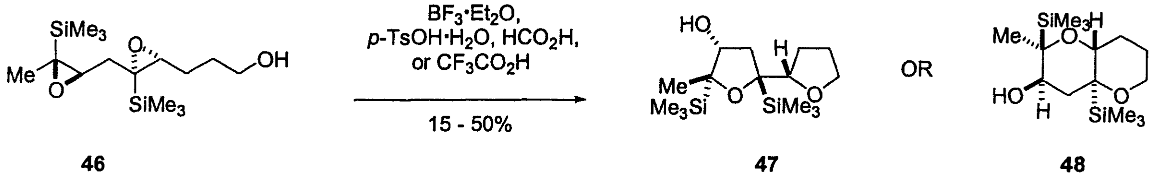
Scheme 4



Examination of Cascade Cyclizations of Polyepoxysilanes Promoted by Lewis and Brønsted Acids

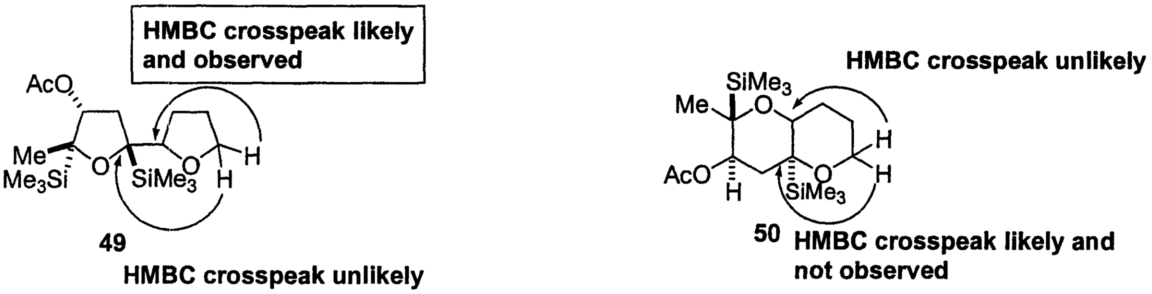
The first attempt at a cascade of cyclizations employed bisepoxide **46**, containing a primary alcohol as an internal nucleophile (Scheme 5). With either protic acids or $BF_3 \cdot Et_2O$, similar results were obtained. Although there was a significant amount of acid-promoted decomposition, a common bicyclic compound was generated in each of these attempts. After acetylation of the compound it became evident by ^1H NMR that a secondary alcohol was present. At this point it became necessary to distinguish between the bisfuran (**47**) and bispyran (**48**).

Scheme 5



A closer look at compounds **47** and **48** reveals that standard characterization protocol would not distinguish between these two compounds. Both of these molecules have the same molecular formula, contain a methylene adjacent to a ring oxygen, a methine proton next to a ring oxygen, and a secondary alcohol. Moreover, each of these molecules has the same number of carbons next to an oxygen atom. In fact, IR spectroscopy would not tell these two molecules apart due to similar stretching frequencies of their functional groups. In order to determine which of the two bicyclic compounds had been generated HMBC analysis was employed.

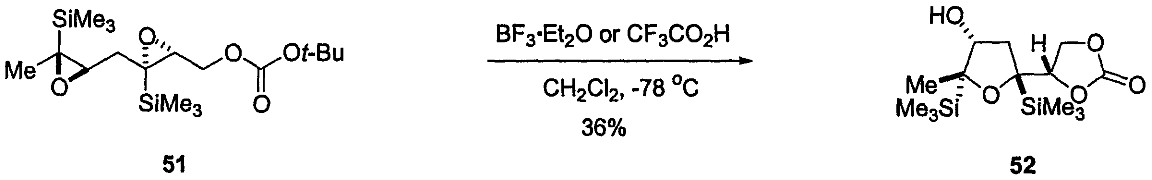
Figure 7. HMBC analysis used to distinguish between two potential products of cascade.



For bisfuran **49**, a crosspeak between both methylene protons adjacent to the oxygen in the less-substituted furan and the methine carbon on the other side of the same furan should be observed in the HMBC spectrum (Figure 7). For bispyran **50**, a crosspeak between the methylene protons adjacent to oxygen in the less-substituted pyran and the methine carbon at the ring junction would be unlikely, but that crosspeak was observed. Moreover, that methine proton appeared as a triplet. In a *trans*-fused bistetrahydropyran that proton would likely appear as a doublet of doublets. Also aiding in the structure determination was that no HMBC crosspeak was observed between the methylene adjacent to oxygen and a quaternary carbon with a $SiMe_3$ group attached. In the case of the bistetrahydropyran, this crosspeak would most likely be observed. The diagnostic crosspeaks in the HMBC spectrum allowed for the conclusion that the repeatedly observed product in the epoxide-opening cascade of **46** was actually the bistetrahydrofuran (**47**).[73]

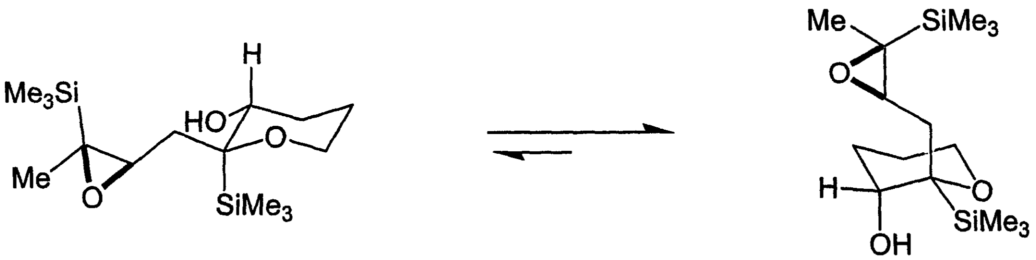
A bisepoxide containing a *tert*-butyl carbonate (**51**) as an internal nucleophile was also studied (Scheme 6). Under identical conditions, the product isolated was found to be **52**.

Scheme 6



Discouraged by the results of the cascades described above, we grew concerned that the steric bulk of the trimethylsilyl group might cause it to reside in the equatorial position after cyclization. If that were the case, after the first epoxide was opened by the internal nucleophile, the resulting alcohol and the remaining epoxide would be locked in a *trans*-diaxial relationship (Figure 8).

Figure 8. A possible conformational bias that may disfavor an epoxide opening cascade.



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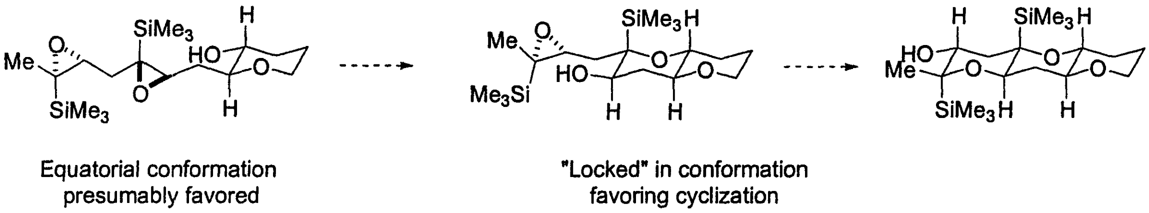
[73] Dr. Jeff Simpson aided in the acquisition and analysis of the HMBC data.

If such a conformational bias were present, the desired bispyran would not be able to form. It was also postulated that the significant amounts of decomposition observed during the course of the attempted cascades of **46** and **51** may have been due to the inability of the second ring to form. It was possible that formation of bisfuran **47** followed a minor reaction pathway and that the initial, desired, cyclization took place but subsequently decomposed without access to the requisite conformation for further cyclization.

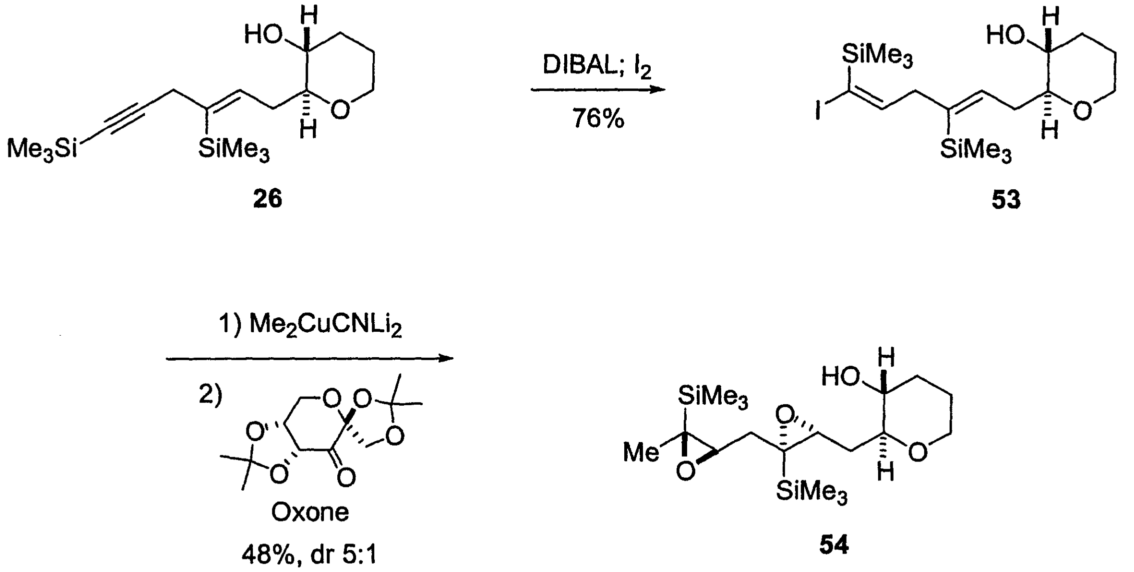
We reasoned that if the first epoxide was opened by an alcohol on an already formed tetrahydropyran, the bicyclic system would then be locked in a conformation in which the alcohol could approach the next epoxide (Figure 9). Perhaps more significantly, utilizing an internal nucleophile positioned on a preformed pyran scaffold also might encourage the desired cyclization by forcing the nucleophile in greater proximity to the proximal epoxide.

Figure 9. A conformational bias to promote cyclization.



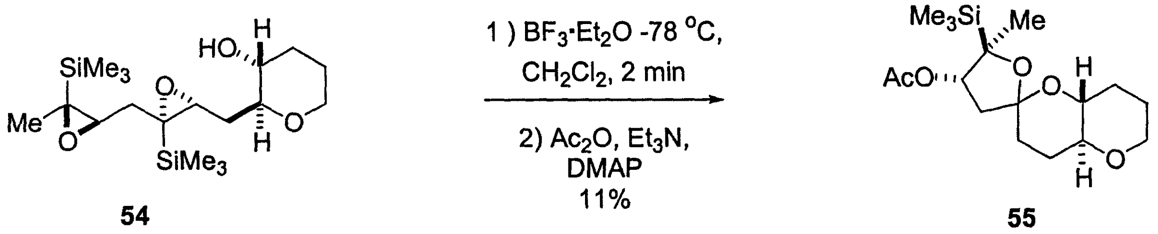
To test this, bisepoxide **54** was constructed (Scheme 7). In order to generate **54**, an intermediate (**26**) in the iterative synthesis of a tristetrahydropyran was converted to alkenyl iodide **53**. After this, the alkenyl iodide was methylated and then subjected to Shi asymmetric epoxidation.

Scheme 7



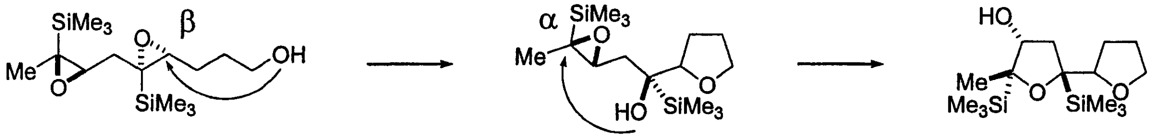
We found that this bisepoxide was an extraordinarily reactive compound under acidic conditions. In a very rapid reaction in the presence of $BF_3{\cdot}Et_2O$ at –78 °C, the majority of the material was lost to decomposition, but a new compound that retained the pyran ring present in the starting material was isolated. However, although there were two trimethylsilyl groups in the starting material, the major product of the reaction contained only one. This product, on the basis of ^1H NMR, HR-MS, and HMBC analysis that shows a ^{13}C signal at 106 ppm, has been assigned the structure of spiroketal **55** (Scheme 8).

Scheme 8



In each of the attempted cascades described above, unexpected products were isolated as the major compounds produced. Mechanistic insight into how these products could be produced proved instrumental in our understanding of the behavior of epoxysilanes. In the case of substrate **46** a bisfuran (**47**) was formed, a puzzling result in light of the regioselectivity observed in each of the cyclizations of monoepoxysilanes (Chapter 1). In order to arrive at a bistetrahydrofuran the two epoxysilanes must be opened, regioselectively, in contrary fashion (Figure 10). With an internal nucleophile present (an alcohol in **46**), the first epoxide must be opened selectively at the β position relative to $SiMe_3$, contrary to our earlier studies showing exceptionally high α selectivity. In the second cyclization, though, the epoxide must be opened selectively at the α position relative to $SiMe_3$. An analogous mechanism could be invoked for compound **51**, where the internal nucleophile was a *t*-butyl carbonate.

Figure 10. Unusual regioselective preference required for the formation of bisfuran **47** with an internal nucleophile initiating a cascade.



46

47

Alternatively, the observed formation of bisfuran **47** can be rationalized by proceeding through a mechanism whereby the first epoxide opened is distal to the internal nucleophile (Figure 11). If the distal epoxide is activated by the acid, the neighboring *epoxide* may serve as a nucleophile upon that activated epoxide.[53, 72, 74, 75] After formation of a furan, the internal nucleophile could then trap a cation to form the bisfuran.

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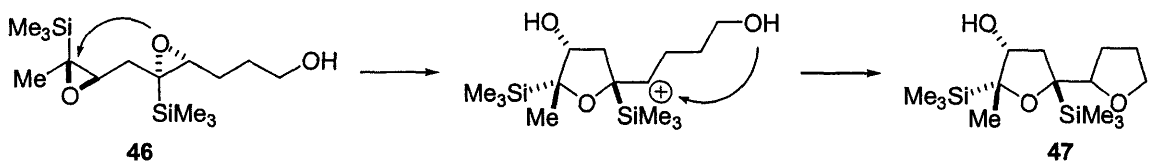
[74] For examples of epoxides as nucleophiles: (a) Crisóstomo, F. R. P.; Martín, T.; Martín, V. S. *Org. Lett.* **2004**, *6*, 565-568. (b) Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848-2876. (c) David, F. *J. Org. Chem.* **1981**, *46*, 3512-3519. (d) Tokumasu, M.; Sasaoka, A.; Takagi, R.; Hiraga, Y.; Ohkata, K. *J. Chem. Soc., Chem. Commun.* **1997**, 875-876.

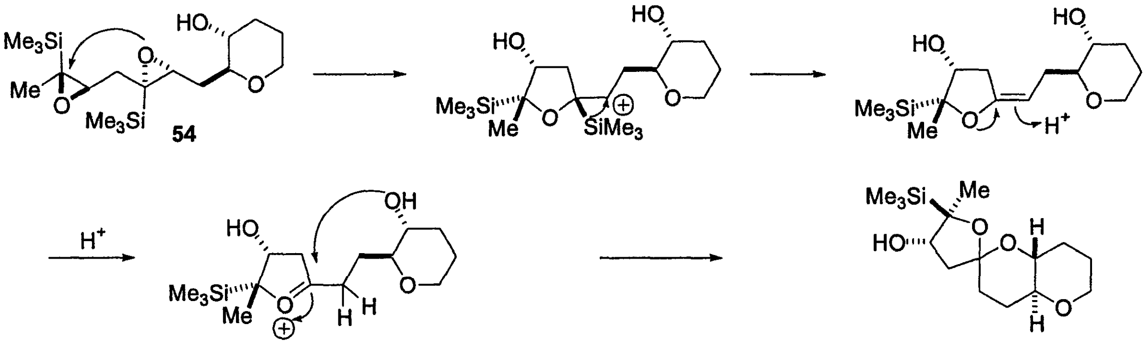
[75] (a) Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 6173-6176. (b) Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron* **1997**, *53*, 12425-12468. (c) Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561-593.

Figure 11. Proposed mechanism for the formation of bisfuran **47** in a cascade cyclization.



In the case of the cascade cyclization of bisepoxide **54**, the spiroketal product can also be rationalized by a mechanism in which the distal epoxide is activated first (Figure 12). In this case the neighboring epoxide again acts as a nucleophile. Next, the silyl group would eliminate and an acid catalyzed rearrangement may lead to the spiroketal product.

Figure 12. Proposed mechanism for the formation of a spiroketal.

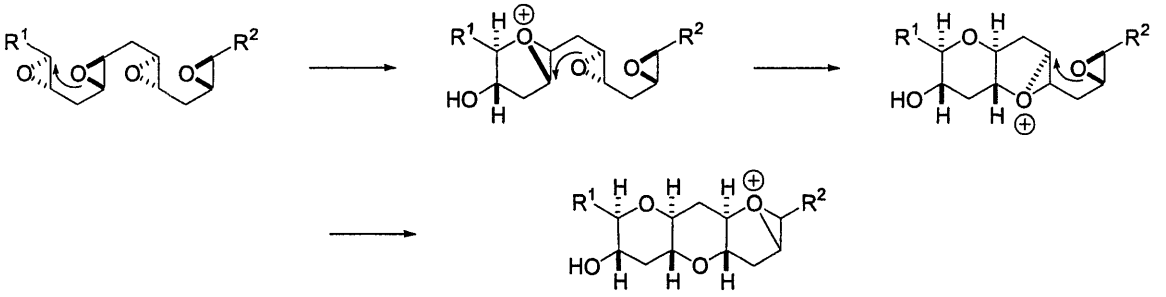


Based on the suggested mechanisms for the outcomes in the attempted cascades of polyepoxysilanes under acid promotion, it appeared that initiation of the cascade was by attack of the distal epoxide (relative to the internal nucleophile) *by the other epoxide* in the substrate, rather than by the internal nucleophile that we had anticipated would initiate the cascade. In this light it appeared that the most reactive nucleophile was actually an epoxide rather than the internal nucleophile that we had anticipated initiating a cascade.

Directing Group-Free Polyepoxide Cascades

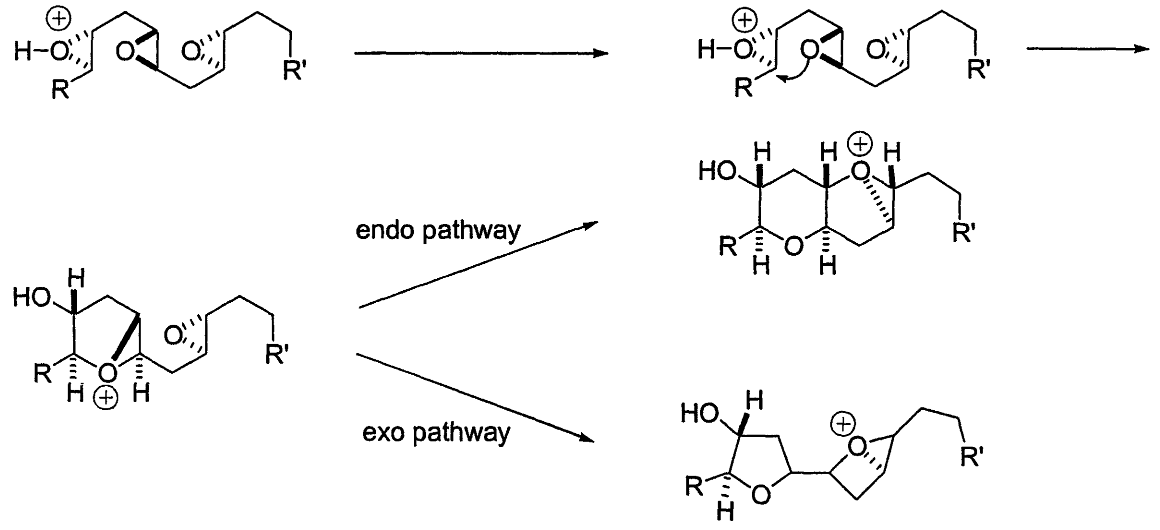
As epoxysilanes appeared to be the most active nucleophiles in our initial cascade attempts, we sought to achieve a cascade that took advantage of this reactivity. In the initially suggested epoxide cascade biosynthesis, epoxides are opened that lead to new alcohols that serve as nucleophiles in subsequent cyclizations. An alternative mechanism in the same cascade can be suggested in which epoxides act as nucleophiles upon other epoxides until an internal nucleophile terminates the cascade (Figure 13).[75]

Figure 13. A nucleophilic epoxide cascade model for the synthesis of ladder ethers.



In a simplified model of such a cascade where epoxides act as nucleophiles in stepwise fashion, the epoxide at the terminus, activated by an acid, is opened by the proximal epoxide in the substrate (Scheme 9). If the next epoxide in the substrate acts as a nucleophile, the resulting oxonium ion becomes fused to either a four- or five-membered ring in the case of exo or endo cyclization respectively. If five-membered ring formation (endo) is favored, considering the significant strain involved in a fused 3,4-ring system, then polytetrahydropyrans could be realized without the need for a directing group. This scenario requires a disubstituted epoxide to act as a nucleophile and also requires that at least three epoxides be part of the cascade cyclization (Scheme 9). If any fewer than three epoxides are used, even if cyclization is endo selective, the cascade may not lead to the formation of even one pyran (this depends upon at which site the cascade is terminated).

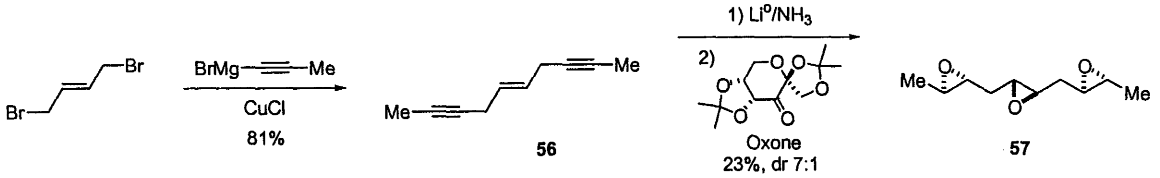
Scheme 9



The first substrate studied in the context of directing group-free cascades was trisepoxide **57** (Scheme 10), chosen based on its ease of synthesis and symmetry that would, ideally, allow for simpler structural determination of the products. Furthermore, this compound contained the requisite three epoxides that would lead to at least one pyran if the predicted mechanism were in operation.

The synthesis of trisepoxide **57** utilized a bidirectional approach in which a direct double displacement reaction of commercially available (*E*)-1,4-dibromo-2-butene with propynylmagnesium bromide provided diyne **56** in good yield (Scheme 10).[76] Diyne **56**, when reduced with Li°/NH_3 provided the (*E*,*E*,*E*)-triene which was subjected to Shi epoxidation conditions to afford trisepoxide **57**.

Scheme 10



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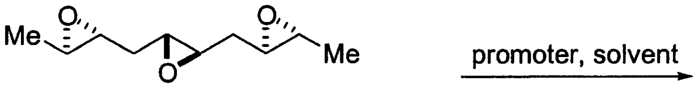
[76] Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.

The cascade cyclization of trisepoxide **57** was attempted under a variety of acidic conditions. Unfortunately, in each case polymerization or decomposition of the starting material was the only detectable reaction (Table 1). Moreover, harsher conditions, relative to those employed for epoxysilane cyclizations, were required to promote the reaction (entries 1-2).



57

Table 1. Attempted cascade cyclization of trisepoxide **57**.

Entry	Promoter	Solvent	Temperature	Result
1	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 °C	No reaction
2	$BF_3{\cdot}Et_2O$	CH_2Cl_2	23 °C	Decomposition
3	Formic Acid	CH_2Cl_2	23 °C	No reaction
4	CH_3SO_3H	Toluene	23 °C	Polymerization
5	CF_3CO_2H	THF/H_2O (6:1)	23 °C	Decomposition
6	*p*-$TsOH{\cdot}H_2O$	Toluene	23 °C	Polymerization
7	D-(+)-CSA	Toluene	23 °C	Polymerization

We recognized that several potential problems may have led to the disappointing results when using trisepoxide **57** for cascade cyclization. One issue that must be addressed in the nucleophilic epoxide model is controlling which epoxide is activated first. In the case of trisepoxide **57** all three epoxides are similarly substituted and therefore activation of one terminal epoxide relied upon a combination of statistical probability and a questionable difference in steric bulk.

The rate of the acid hydrolysis of epoxides is significantly influenced by the electronic nature of its substituents.[77] The more electron donating the substituents, the greater the rate of hydrolysis. Therefore, we anticipated that the epoxide in a

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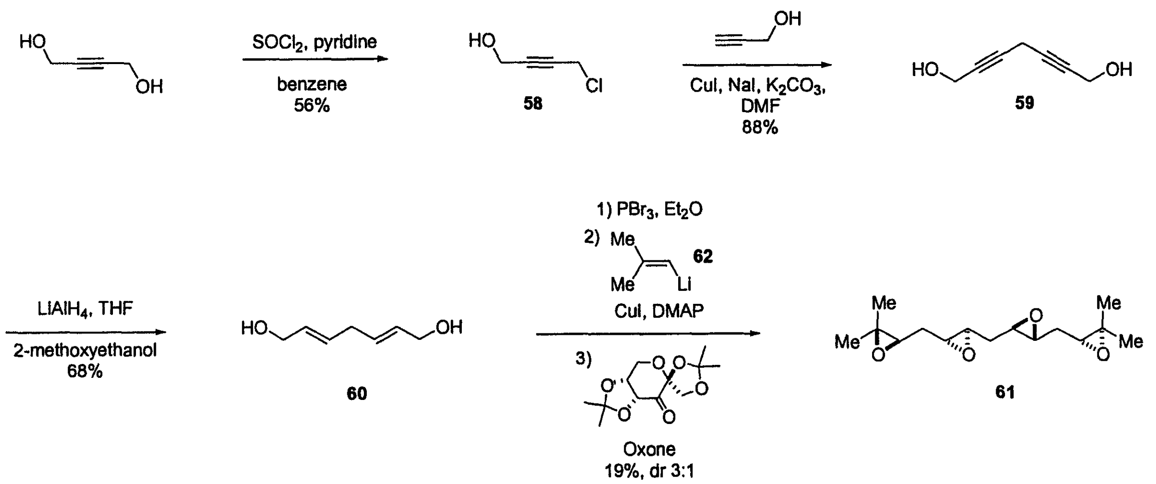
[77] Except for epoxides with aromatic substituents (e.g. styrene oxides), whose ring-opening reactions often display different mechanistic profiles. (a) Pritchard, J. G.; Long, F. A. *J. Am. Chem. Soc.* **1956**, *78*, 2667-2670. Reviews: (b) Winstein, S.; Henderson, R. B. Ethylene and Trimethylene Oxides. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; Wiley: New York, 1950; Vol. 1. (c) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737-799. (d) Wohl, R. A. *Chimia* **1974**, *28*, 1-5.

polyepoxide substrate that is activated first could be controlled by altering the electronic nature of a terminal epoxide. In this vein we selected a substrate to utilize this hypothesis in the attempted cascade cyclization of polyepoxides. The first substrate selected (**61**) was C_2-symmetric but contained trisubstituted epoxides at both ends.

The synthesis of tetraepoxide **61** again utilized bidirectional synthesis. After the conversion of 2-butyne-1,4-diol to the monochloride (**58**),[78] displacement by propargyl alcohol provided **59** (Scheme 11).[79] This diol was doubly reduced to bisallyl alcohol **60**, converted to the corresponding dibromide, and doubly displaced by alkenyllithium species **62** to afford a tetraene. The tetraene was then polyepoxidized using the Shi method to provide tetraepoxide **61** as an inseparable mixture of diastereomers.

Scheme 11



In an extensive screen of acidic conditions, we found that the starting material (**61**) either polymerized, decomposed, or was left unreacted. As we anticipated potential significant solvent effects, we screened a variety of Brønsted and Lewis acids in multiple solvents. A sample of our results in this study is summarized in Table 2.

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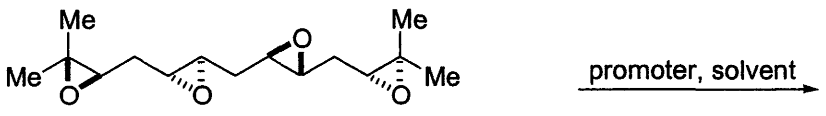
[78] Dasse, O.; Mahadevan, A.; Han, L.; Martin, B.; Marzo, V. D.; Razdan, R. K. *Tetrahedron* **2000**, *56*, 9195-9202.

[79] Hoffmann, R. W.; Kahrs, B. C.; Schiffer, J.; Fleischauer, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2407-2414.



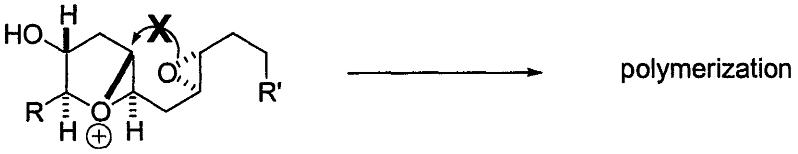
61

Table 2. Conditions studied in attempted cascade cyclization of tetraepoxide **61**.

Entry	Promoter	Solvent	Temperature	Result
1	*p*-TsOH·H_2O	Toluene	0 °C	No reaction
2	BF_3·Et_2O	CH_2Cl_2	-78 °C	Decomposition
3	D-(+)-CSA	Toluene	0 °C	No reaction
4	$ClH_2C_2O_2H$	CH_2Cl_2	23 °C	Decomposition
5	$ClH_2C_2O_2H$	THF	23 °C	Decomposition
6	$ClH_2C_2O_2H$	MeOH	23 °C	Decomposition
7	$MgBr_2$	Et_2O	23 °C	No reaction
8	$MgBr_2$	Toluene	23 °C	No reaction
9	$ZnBr_2$	Et_2O	23 °C	No reaction
10	$ZnBr_2$	Toluene	23 °C	Decomposition
11	$ZnBr_2$	CH_2Cl_2	0 °C	Decomposition
12	$ZnBr_2$	MeOH	23 °C	No reaction
13	Et_3Al	Et_2O	23 °C	No reaction
14	Et_3Al	Toluene	23 °C	No reaction
15	Et_3Al	CH_2Cl_2	23 °C	No reaction
16	$ClH_2C_2O_2H$	CD_3OD	23 °C	Decomposition
17	CF_3CO_2H	CD_3OD	23 °C	Decomposition
18	$ClEt_2Al$	CH_2Cl_2	0 °C	Decomposition
19	$ClEt_2Al$	Et_2O	0 °C	Decomposition
20	$ClEt_2Al$	Toluene	0 °C	Decomposition
21	$ClEt_2Al$	MeOH	0 °C	Decomposition
22	$Yb(OTf)_3$	CH_2Cl_2	23 °C	Decomposition
23	$Tl(OAc)_3$	CH_2Cl_2	23 °C	Decomposition
24	$FeCl_3$	CH_2Cl_2	0 °C	Decomposition

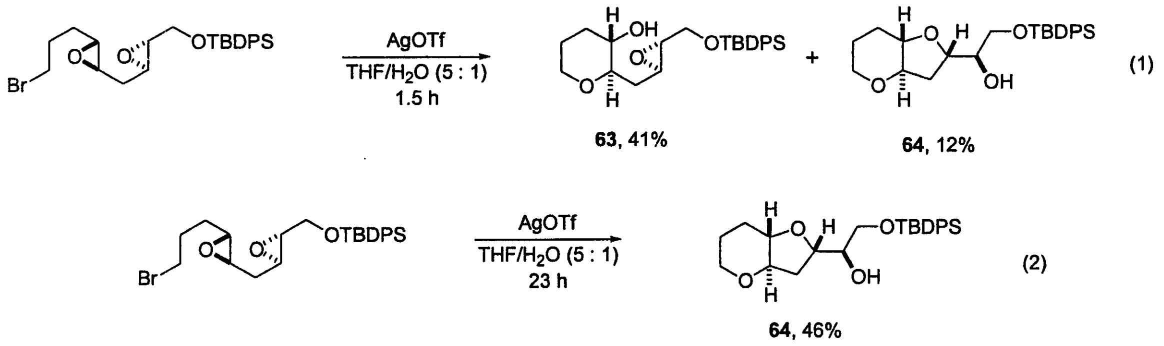
The disappointing results of this series of experiments led us to reconsider the use of C_2-symmetric polyepoxides in the study of polyepoxide cascade cyclizations. We sought, instead, a polyepoxide substrate in which one epoxide could be selectively activated over all others. Furthermore, a potentially fatal flaw in substrate design appeared possible. In spite of the conviction that epoxysilanes were nucleophiles in previous studies, there was a growing concern that perhaps disubstituted epoxides are not competent nucleophiles to open oxiranium intermediates as we proposed (Figure 14).

Figure 14. If a disubstituted epoxide does not act as a nucleophile polymerization may result.



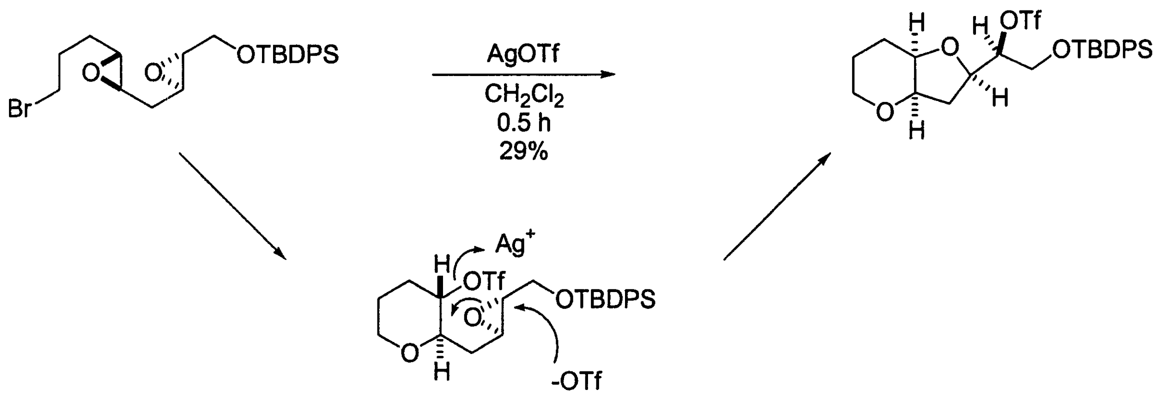
The Murai group has studied the cascade cyclization of disubstituted bisepoxides using silver promoters to activate primary alkyl bromides.[75] In these studies, an initial oxiranium intermediate is believed to be generated after activation of the primary alkyl bromide with the silver promoter (Figure 15). However, in these cases no *trans*-fused polytetrahydropyrans are observed. With a bisepoxide, using AgOTf as a promoter in a mixture of THF and water, the major product was determined to be epoxypyran **63**, produced alongside a small amount of furanylpyran **64** (eq 1, Figure 15). On extending the reaction time, however, the furanylpyran became the major product and it was suggested that the intermediate epoxypyran (**63**) was being converted directly to **64** (eq 2, Figure 15). However, in both experiments, there was no explanation for the fate of a significant amount of material.

Figure 15. Murai's cascades leading to furanylpyran **64**.



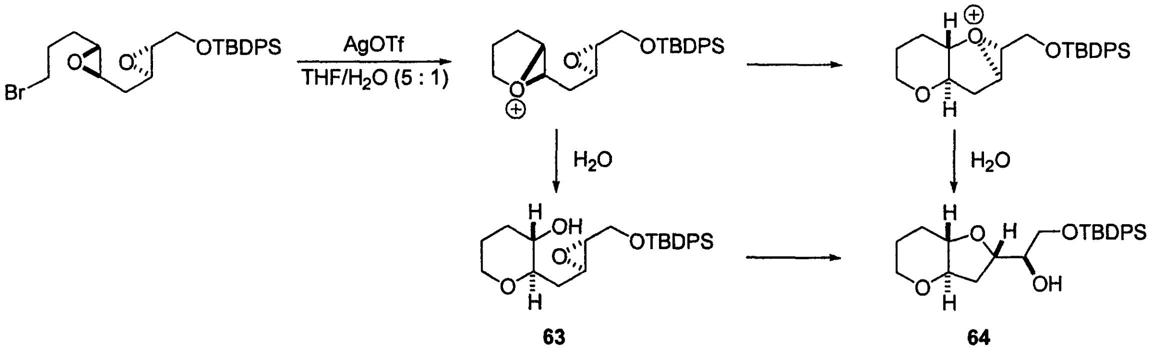
In another case, when anhydrous CH_2Cl_2 was used as solvent, a *cis*-fused furanylpyran was obtained. In this case, it was suggested that the intermediate oxiranium ion was opened by triflate anion that was then displaced by the next epoxide (Figure 16).[75] Interestingly, this suggestion requires that triflate anion behave as a nucleophile, intermolecularly, more readily than a disubstituted epoxide does intramolecularly.

Figure 16. Murai's cascade leading to a *cis*-fused furanylpyran and the mechanistic rationale.



Murai's proposition that oxiranium intermediates in his studies are opened by water or triflate anion suggests that disubstituted epoxides are not effective nucleophiles to open neighboring oxiranium ions. Therefore, after generation of the initial oxiranium ion, water or a triflate anion intermolecularly opens it before further reaction. In the case of the formation of furanylpyran **64** (Figure 15) water is suggested to open the first intermediate. On the contrary, it was also possible in these experiments that *an epoxide* *was opening the initial oxiranium intermediate* and water terminated the reaction (Figure 17). In this scenario the first oxiranium ion is opened by the next epoxide. At this point the final oxiranium ion is opened by water to reveal furanylpyran **64**.

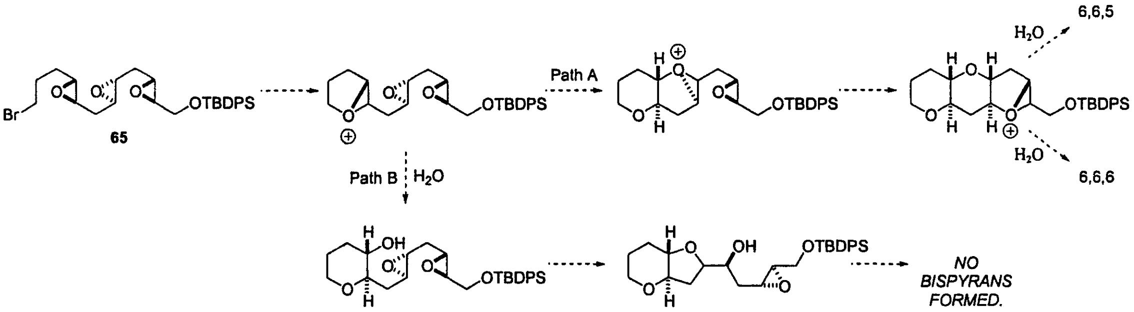
Figure 17. Two possible mechanistic pathways lead to the same product in Murai's cascade.



Since two potential mechanisms lead to the same product, we deemed that the Murai group's published studies did not conclusively establish that the second epoxide in their substrate was not an effective nucleophile. Although their suggestion was surely plausible, we envisioned a single set of experiments that would demonstrate whether an epoxide or water was opening the first oxiranium intermediate.

By extending Murai's study to a substrate that contains three epoxides, instead of just two, it could be determined if a disubstituted epoxide can function as an active nucleophile in an epoxide cascade cyclization (Scheme 12). A substrate with just two epoxides leads to an intermediate oxiranium ion where, if water acts as a nucleophile rather than the remaining epoxide, an alcohol is generated which then opens the neighboring epoxide *via* 5-exo cyclization (Figure 17). If a trisepoxide was employed for the studies, and the disubstituted epoxides acted as nucleophiles, an intermediate would be generated in which two pyrans are formed before opening of the last oxiranium ion by water terminates the reaction (Path A). If water acts as a nucleophile upon the first oxiranium intermediate and the resulting alcohol opens the next epoxide, a furan would be formed (Path B). In this case, regardless of what happened in the rest of the reaction, no *trans*-fused bispyran would be observed (Scheme 12). By this logic, it could be determined whether or not disubstituted epoxides are viable nucleophiles upon neighboring oxiranium intermediates.

Scheme 12



The synthesis of trisepoxide **65** began with protection of 4-pentyn-1-ol as the methoxymethyl ether (Scheme 13).[80] The terminal alkyne was then deprotonated and added to paraformaldehyde to afford propargylic alcohol **67**. The resulting propargylic alcohol was reduced to the allylic alcohol that was converted to the corresponding allylic bromide. This allylic bromide was displaced by lithiated alkyne **72**.[81] After deprotection of the THP ether, to afford **69**, the iteration was repeated and the resulting allylic alcohol was protected as the TBDPS ether (**71**) and the MOM ether was deprotected. Finally, the primary alcohol was converted to the bromide, and asymmetric epoxidation produced trisepoxide **65** in high diastereoselectivity (dr 9:1).

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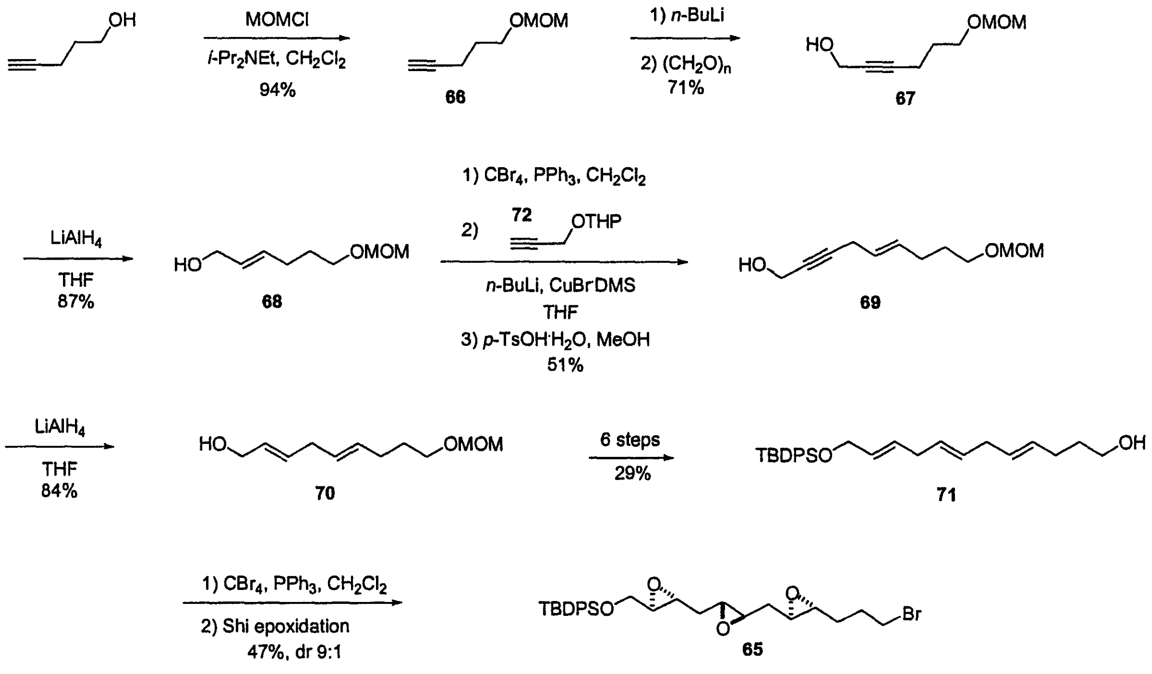
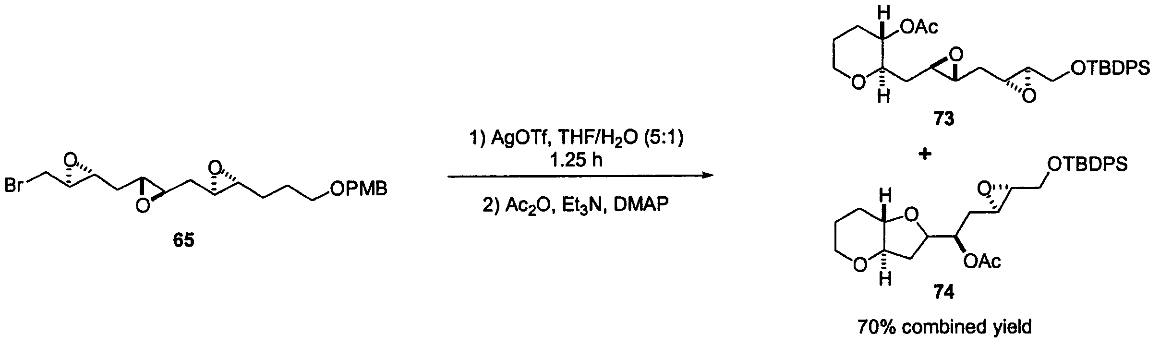
[80] Piers, E.; McEachern, E. J.; Romero, M. A. *J. Org. Chem.* **1997**, *62*, 6034-6040.
[81] Horino, Y.; Kimura, M.; Tanaka, S.; Okajima, T.; Tamaru, Y. *Chem. Eur. J.* **2003**, *9*, 2419-2438.

Scheme 13



The study of cascade cyclizations using trisepoxide **65** began using Murai's conditions that had produced *trans*-fused furanylpyran **64**. The use of AgOTf as a promoter in a mixture of THF and water gave, after 1.25 h, a mixture of two products (Scheme 14). Acetylation of the mixture allowed the two products to be separated and identified as bisepoxypyran **73** and furanylpyran **74** (70% yield, 3:1 **73**:**74**). When the reaction time was extended to 3 h the ratio of the two products shifted to favor the furanylpyran product (64% yield, 1:5 **73**:**74**). Since >60% of the starting material could be accounted for in both cases, it was concluded that, indeed, an intermediate oxonium ion is being opened by water and that the resulting alcohol subsequently opens the proximal epoxide in 5-exo fashion (i.e. Path B, Scheme 12).

Scheme 14



Although the results of the above experiments suggested that after the formation of an initial oxiranium intermediate the neighboring epoxide did not participate as a nucleophile,[82] cascade cyclization attempts of **65** remained the focus of our efforts. The possibility remained that the formation of **73** and **74** was the result of copious amounts of water and that the neighboring epoxide would act as a nucleophile upon the oxiranium intermediate in the absence of water. Under anhydrous conditions, Murai reported the formation of a *cis*-fused bispyran (presumably resulting from the opening of the oxiranium intermediate by triflate anion followed by displacement by the neighboring epoxide). We postulated that by extending those studies to the trisepoxide (**65**) in a variety of solvents under anhydrous conditions, and also by studying the reaction with silver promoters with less nucleophilic counterions such as $AgBF_4$ and $AgPF_6$, the desired course of reaction might be realized. Through these studies we anticipated elucidating the viability of using disubstituted epoxides in cascade cyclizations. The results of these studies are complied in Table 3.

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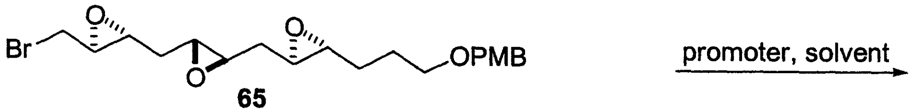
[82] See also: Capon, R. J.; Barrow, R. J. *J. Org. Chem.* **1998**, *63*, 75-83.



65

Table 3. Conditions studied in the attempted cascade cyclization of trisepoxide **65**.

Entry	Promoter	Solvent	Temperature	Result
1	$AgPF_6$	CH_2Cl_2	-78 °C	No reaction
2	AgOTf	CH_2Cl_2	-78 °C	No reaction
3	$AgSbF_6$	CH_2Cl_2	-78 °C	Decomposition
4	$AgPF_6$	CH_2Cl_2	0 °C	Decomposition
5	AgOTf	CH_2Cl_2	0 °C	Unidentifiable Products
6	$AgSbF_6$	CH_2Cl_2	0 °C	Decomposition
7	$AgPF_6$	HFIP	0 °C	Decomposition
8	AgOTf	HFIP	0 °C	Decomposition
9	$AgSbF_6$	HFIP	0 °C	Decomposition
10	$AgPF_6$	HFIP	-42 °C	Decomposition
11	AgOTf	HFIP	-42 °C	Decomposition
12	$AgSbF_6$	HFIP	-42 °C	Decomposition
13	$AgPF_6$	THF	-78 °C	No reaction
14	AgOTf	THF	-78 °C	No reaction
15	$AgSbF_6$	THF	-78 °C	Polymerization of solvent
16	$AgPF_6$	THF	0 °C	Polymerization of solvent
17	AgOTf	THF	0 °C	Polymerization of solvent
18	$AgSbF_6$	THF	0 °C	Polymerization of solvent
19	AgOTf	Et_2O	-42 °C	Decomposition
20	$AgPF_6$	Et_2O	-42 °C	Decomposition
21	$AgSbF_6$	Et_2O	-42 °C	Decomposition
22	AgOTf	THF : *t*-amyl alcohol (5:1)	0 °C	Decomposition
23	AgOTf	THF : MeOH (5:1)	0 °C	Decomposition

In nearly every case either no reaction took place or decomposition of the starting material was observed. In the absence of water, decomposition of the starting material proceeded readily. The exception was when AgOTf was used as a promoter in anhydrous

CH_2Cl_2 (entry 5). With a bisepoxide, Murai obtained a *cis*-fused bispyran under these conditions, but in the case of the trisepoxide we observed a multitude of products in low yield (entry 5). At lower temperature no reaction took place (entry 2). In anhydrous THF polymerization of the solvent occurred, which was the only reaction observed (entries 13-18) and as a result Et_2O was also studied as a solvent (entries 19-21). We postulated that when a mixture of THF and water was utilized as solvent the high isolated yield of compounds, as opposed to complete decomposition of the starting material, resulted from water moderating the Lewis acidic nature of the silver salt. In an effort to achieve this advantageous effect without water, *t*-amyl alcohol and MeOH were studied as additives in separate experiments (entries 22-23). In each of these experiments, however, no desired reaction took place.

The results summarized above led to the conclusion that disubstituted epoxides are not viable nucleophiles in the cascade production of polytetrahydropyrans. Only in the presence of water was the smooth production of any products observed. Unfortunately, the isolated products were not desired.

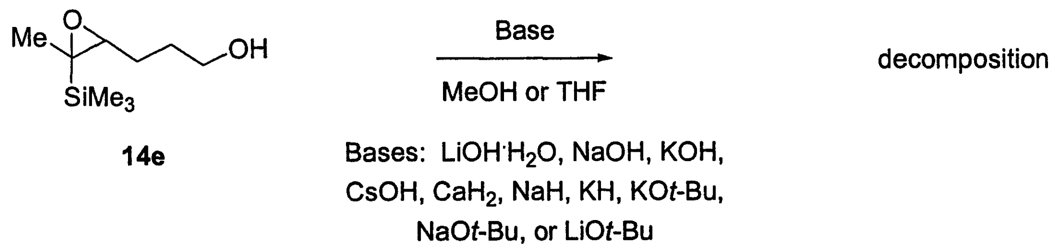
We had first studied disubstituted epoxides as cascade substrates because in our studies of the cascade cyclization of polyepoxysilanes under acidic conditions it was discovered that epoxides appeared to be more active nucleophiles than either the alcohols or *t*-butyl carbonate that were included as internal nucleophiles. Although our attempts to take advantage of this reactivity in directing group-free epoxide cascades did not lead to the synthesis of *trans*-fused polytetrahydropyrans, an alternate strategy remained. Rather than utilizing the more effective nucleophile, we sought, instead, to enhance the nucleophilicity of the desired internal nucleophile, particularly an alcohol, by attempting cascade cyclizations under basic conditions.

Cyclizations of Epoxysilanes Under Basic Conditions

In order to enhance the nucleophilicity of the internal nucleophile in epoxy-alcohol cyclizations we turned to study these reactions under basic conditions.[83] Before beginning cascade attempts, however, the cyclization of monoepoxysilane **14e** under basic conditions was first studied to understand the behavior of the simple system.

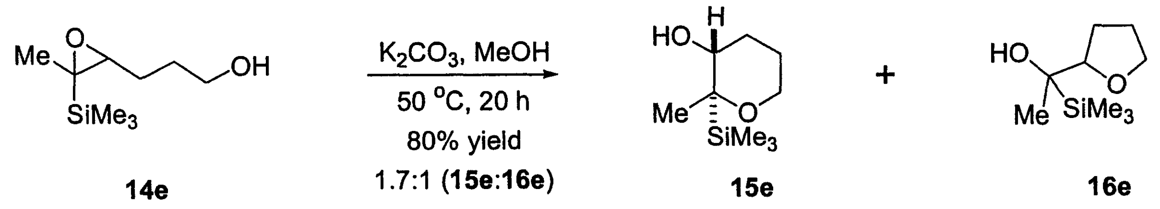
With bases that would readily deprotonate the alcohol (hydride, *t*-butoxide, and hydroxide bases), the starting material primarily decomposed and only trace amounts of cyclized products could be detected (Scheme 15).

Scheme 15



In a screen of conditions for the intramolecular cyclization of epoxysilane **14e** it was discovered that K_2CO_3 in MeOH at elevated temperature provided the desired product (Scheme 16).[83b]

Scheme 16



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[83] For examples of hydroxy-epoxide cyclizations under basic conditions: (a) Boons, G.-J.; Brown, D. S.; Clase, J. A.; Lennon, I. C.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 319-322. (b) Emery, F.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 5843-5854. (c) Masamune, T.; Ono, M.; Sato, S.; Murai, A. *Tetrahedron Lett.* **1978**, *4*, 371-374. (d) Murai, A.; Ono, M.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1976**, 864-865.

Only modest regioselectivity was obtained, with incomplete conversion of starting material, and so a screen of basic conditions was undertaken (Table 4).

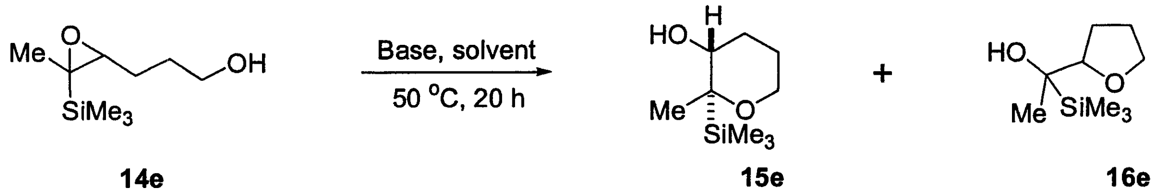


Table 4. Cyclization of epoxysilane **14e** under basic conditions.

Entry	Base[a]	Solvent	Conversion[b]	Yield[c]	**15e : 16e**[b]
1	Li_2CO_3	MeOH	20%	>99%	5:1
2	Na_2CO_3	MeOH	25%	>99%	2:1
3	K_2CO_3	MeOH	85%	>99%	2:1
4	Cs_2CO_3	MeOH	97%	>99%	1.7:1
5	Cs_2CO_3	EtOH	70%	>99%	1.7:1
6	Cs_2CO_3	*i*-PrOH	25%	>99%	2.5:1
7	Li_2CO_3	H_2O	45%	>99%	8.5:1
8	Na_2CO_3	H_2O	<10%	>99%	>95:5
9	K_2CO_3	H_2O	<5%	----------	----------
10	Li_2CO_3	$MeOH/H_2O$ (1:9)	30%	>99%	8.5:1
11	Li_2CO_3	$MeOH/H_2O$ (1:1)	20%	>99%	5:1
12	$KHCO_3$	MeOH	<5%	----------	----------

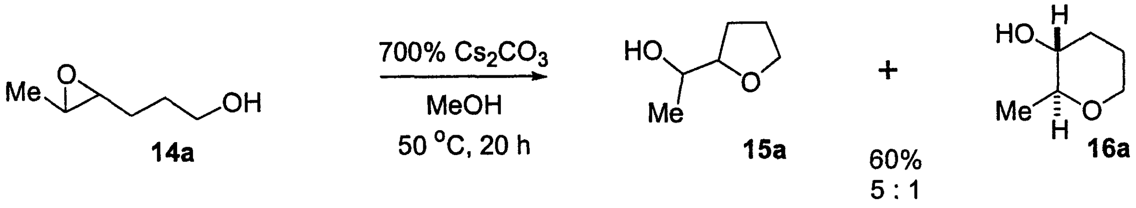
[a] 700 mol% used in each case.
[b] Determined by ^1H NMR analysis of the unpurified product mixture.
[c] All yields are based on conversion of starting material as determined by ^1H NMR of the unpurified product mixture.

This survey of conditions demonstrated that while the use of carbonate bases generally led to less than complete conversion of the starting material, little if any decomposition took place (entries 1-11). It was found that the counterion of the carbonate base affected the reactivity, with Li_2CO_3 providing the lowest conversion of starting material in MeOH (entry 1) and Cs_2CO_3 leading to near complete conversion (entry 4). This trend in reactivity may be the result of the greater solubility of the carbonate bases that lead to more complete conversion of the starting material. However, the added reactivity of Cs_2CO_3 relative to other carbonate bases has been described in other cases.[84]

After initially studying MeOH as solvent, it was found that the use of either EtOH or *i*-PrOH as the solvent retarded the reaction (entries 5 and 6). In water, the reactivity was again sluggish but showed the opposite reactivity trend when the counterion of the carbonate base is considered (entries 7-9). Interestingly, the regioselectivity observed when the reaction was carried out in water was significantly higher. It may be that, because of the low solubility of the substrate in water, any reaction that takes place does so on the surface and a limited amount of deprotonation actually occurs. If this is the case, more of the product may result from promotion of the cyclization by the carbonate counterion (a Lewis acid promoted cyclization) leading to the higher regioselectivity obtained. Again, the lower solubility of Li_2CO_3 relative to Cs_2CO_3 may contribute to this observed reactivity trend.

Although the regioselectivity in the cyclization of disubstituted epoxide **14a** under acidic conditions was reported by Coxon to favor the tetrahydrofuran, the corresponding cyclization under basic conditions had not been reported.[20] In order to demonstrate that the $SiMe_3$ group was still necessary to achieve even the modest 6-endo selectivity observed in the cyclizations discussed above, we performed the base promoted cyclization of epoxide **14a** under conditions we found for the corresponding epoxysilane (**14e**). Not surprisingly, in this reaction the furan was produced as the major regioisomer.

Scheme 17



The above studies demonstrated that it is possible to perform epoxy-alcohol cyclizations under basic conditions. Moreover, the $SiMe_3$ group was critical for the

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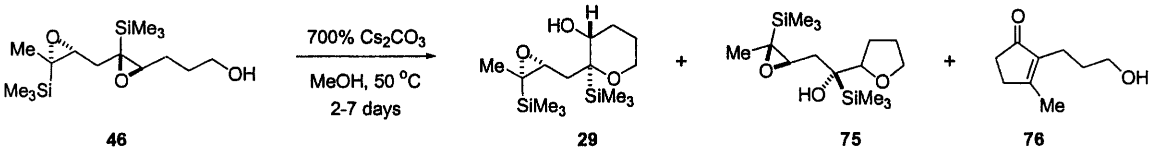
[84] Matsubara, S. Rubidium and Cesium in Organic Synthesis. In *Main Group Metals in Organic Synthesis*; Yamamoto, H.; Oshima, K., Eds.; Wiley: New York, 2003; Vol. 1, pp 35-50.

production of the pyran as the major regioisomer. Having demonstrated that the base-promoted cylcization of a monoepoxysilane was possible, we moved on to study polyepoxides and cascade cyclizations under basic conditions.

Cascade Cyclizations of Polyepoxysilanes Under Basic Conditions

To begin studying cascade cyclizations of polyepoxysilanes under basic conditions we returned to bisepoxide **46** (Scheme 18). The initially attempted cascade cyclization of bisepoxide **46**, under conditions that had been successfully applied to the monoepoxide (700 mol% Cs_2CO_3 in MeOH at 50 °C for 20 h), achieved less than 10% conversion of the starting material.[85] Among the factors that may contribute to the decrease in reactivity observed for bisepoxysilane (**46**), relative to the monoepoxysilane (**14e**), are the added steric encumbrance at the proximal epoxide and/or a conformational preference that is unfavorable for cyclization. Only by extending the reaction time was useful consumption of the starting material observed. Upon longer reaction time (2-7 days), the conversion of starting material remained sluggish and many products were produced as a complex mixture. Among those identified were monopyran **29** in which only one epoxide had been opened and enone **76**. Another, tentatively identified compound was the corresponding furan regioisomer (**75**) in which the first epoxide had been opened but the other epoxide remained intact.

Scheme 18



The isolation of monopyran **29**, although a predicted intermediate in a base promoted cascade that would lead to a bispyran, was the source of some concern. It was conceivable that the developing diaxial interactions that would need to be faced in the

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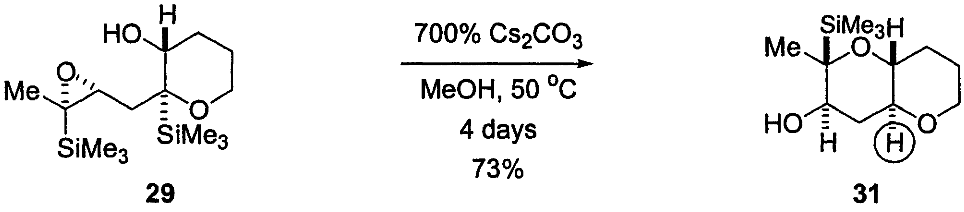
[85] The use of 700 mol% Li_2CO_3 in H_2O led to no conversion of starting material (**46**) after 3 days at 50 °C.

formation of the second ring posed too great an energetic barrier to overcome when a $SiMe_3$ group was placed at the ring junction. Under acidic conditions this intermediate could not be forced to the bispyran (Chapter 1). Indeed, under any conditions, the formation of a fused pyran system in which a $SiMe_3$ group is forced into the axial position at a ring junction has not been achieved.

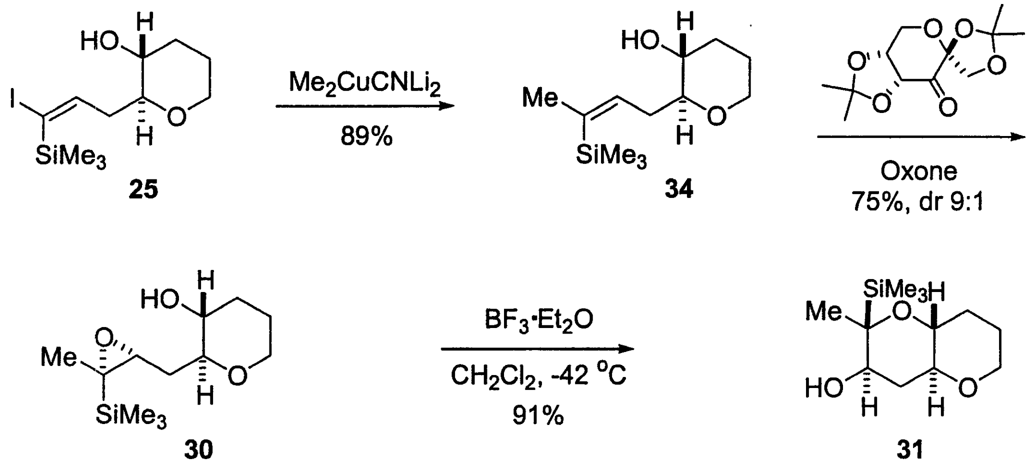
When monopyran **29** was resubjected to the basic conditions being used in this study, however, a lone product was isolated (Scheme 19).

Scheme 19



With every indication suggesting that this product was a bispyran, it was immediately apparent that this compound had only one $SiMe_3$ group remaining. In order to confirm that the silyl group that was removed was that at the ring junction, an iterative synthesis of a bispyran was performed (Scheme 20). To this end alkenyl iodide **25** was converted to the methyl analog and then subjected to Shi asymmetric epoxidation. This epoxide (**30**) then cyclized under acidic conditions to lead to bispyran **31**, which was identical to that obtained from the reaction of monopyran **29** with Cs_2CO_3 in MeOH (Scheme 19).

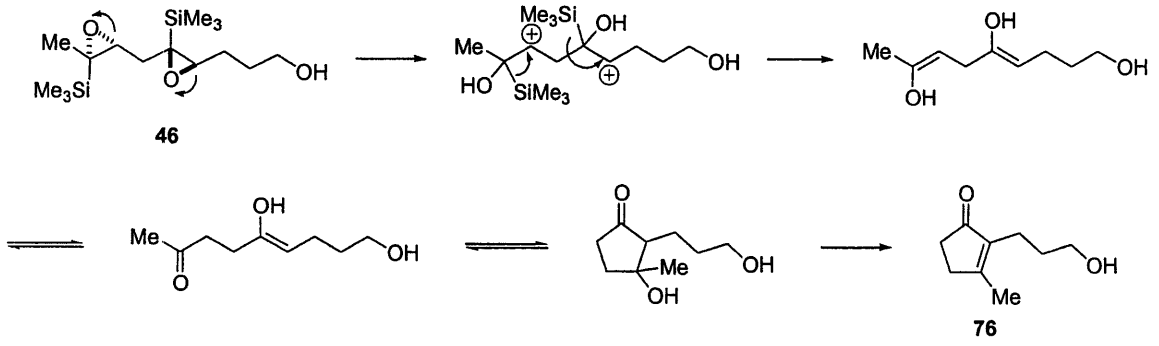
Scheme 20



Most significantly, was that this established that an intermediate isolated from the attempted cascade cyclization of bisepoxide **46** was directly converted to a bispyran under the same reaction conditions.

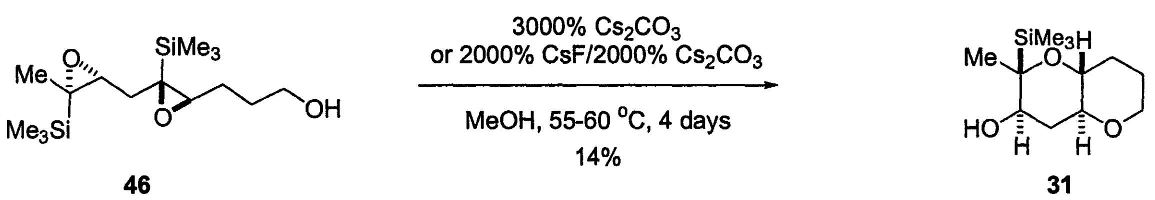
After 2-4 days at 50 °C less than 30% of the starting material (**46**) had been consumed, and the distribution of products was not consistent, prompting a careful screen of the reaction parameters. During the search for conditions that led to a cleaner and more rapid consumption of starting material, the presence of enone **76** proved to be constant. This compound may arise from the rearrangement of each of the epoxysilanes in the starting material to ketones that then undergo aldol condensation (Figure 18).[50]

Figure 18. An aldol condensation pathway that leads to enone **76**.



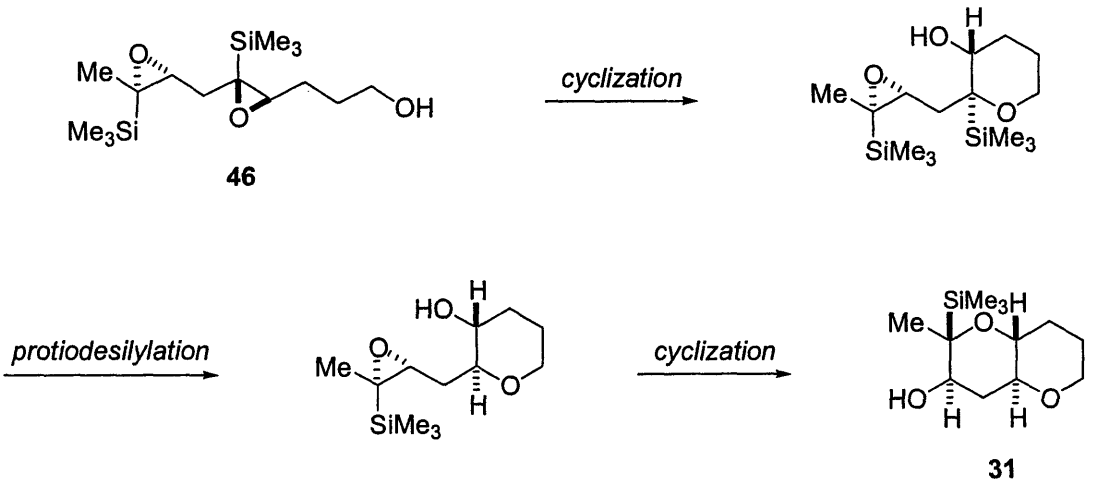
Simply by increasing the amount of Cs_2CO_3 (from 700 mol% to 3000 mol%), despite still observing slow conversion of starting material, the production of enone **76** was suppressed. Alternatively, the addition of an equivalent amount of CsF allowed for a reduction in the amount of Cs_2CO_3 (2000 mol%) used. It is possible that the rearrangement of the epoxysilanes to the enone is a competitive thermal process and the introduction of more base makes the cyclization faster relative to the rearrangement process. Of greatest interest in these studies was the *production of cascade product bispyran* **31** (Scheme 21).

Scheme 21



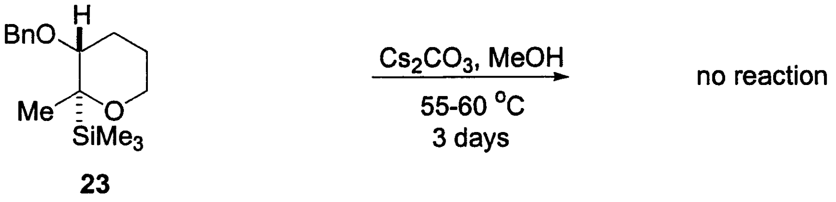
As no $SiMe_3$ group remained at the ring junction of the product, it was presumed that the silyl group was removed before cyclization upon the second epoxide. The protiodesilylation likely proceeds through a putative Peterson olefination intermediate that, because of the protic solvent in which the reaction takes place, is trapped by a proton (Chapter 1). The proposed overall mechanism is illustrated in Figure 19.

Figure 19. Suggested mechanism for the cascade formation of bispyran **31**.



Further support for the suggestion that the $SiMe_3$ group is protiodesilylated prior to cyclization was obtained in the attempted desilylation of **23**. When the β-hydroxyl had been previously protected as the benzyl ether, under the reaction conditions no conversion of the starting material could be detected (Scheme 22).

Scheme 22



It is interesting to note that in the base-promoted cyclization of **29** to **31** only a single regioisomer was isolated (Scheme 19). This was especially encouraging because in the cyclization of monoepoxysilane **14e** using Cs_2CO_3/MeOH a mixture of regioisomers was isolated. Moreover, a mixture of regioisomers appeared to be formed when the same conditions were applied to the incomplete conversion of bisepoxysilane **46** (Scheme 18). In the case where high regioselectivity was observed, a pyran scaffold was already in place. Recognizing a potential template effect on the regioselectivity in base-promoted cyclizations, bisepoxide **79** (Scheme 23) was selected for further study. This substrate maintained the attributes of **29** but included a second epoxide.

Bisepoxide **79** was synthesized using the methods developed for earlier substrates (Scheme 23).[86] Enyne **9c** was epoxidized using the Shi asymmetric epoxidation. In this epoxidation a significant amount of material was lost to C-H oxidation of the primary alcohol. Furthermore, the epoxide product could not be separated from the ketone catalyst and so cyclization was performed on the mixture. The resulting pyran was then elaborated into the bisepoxide using the previously discussed sequence.

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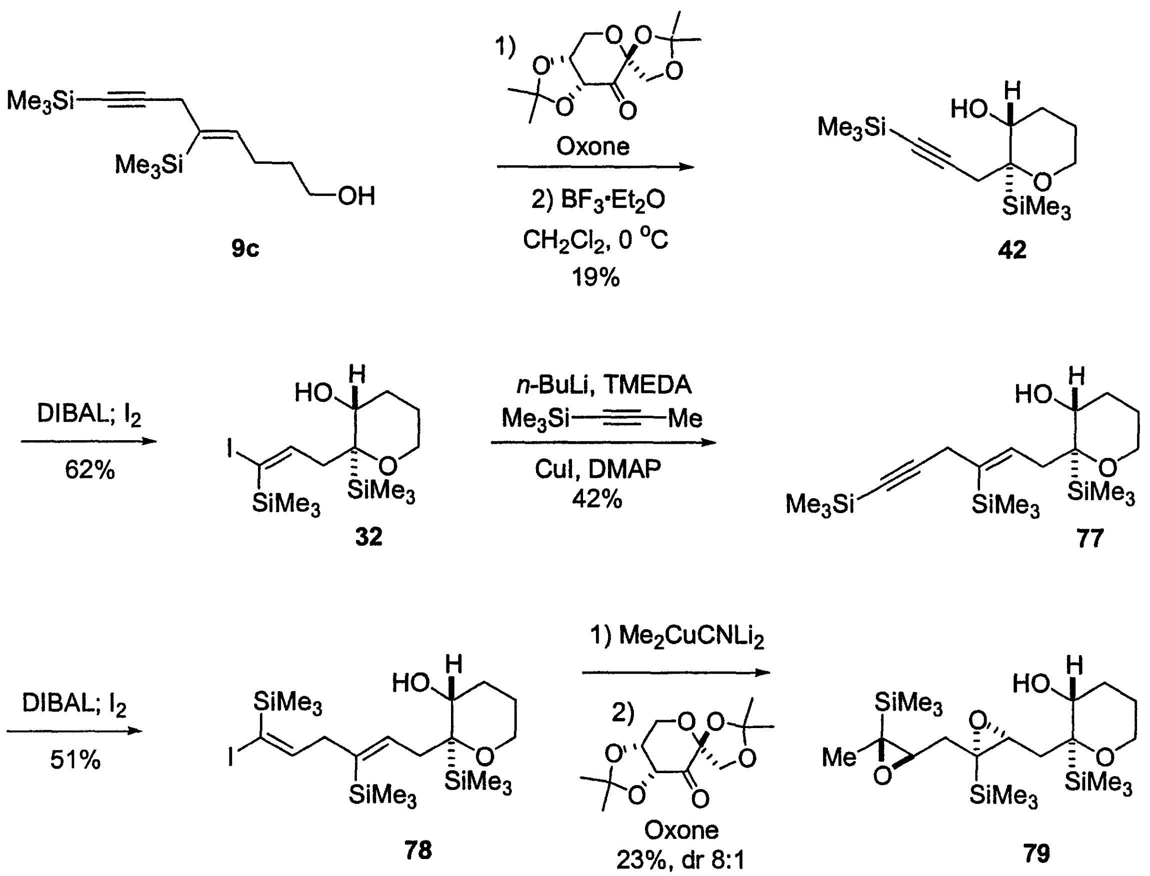
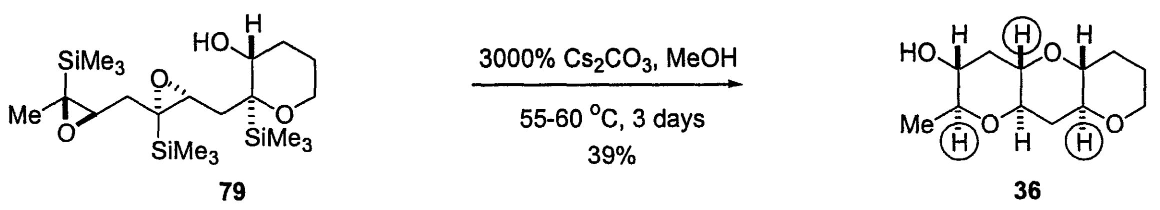
[86] The remaining experiments described were performed in collaboration with Dr. Graham L. Simpson.

Scheme 23



With bisepoxide **79**, we returned to the study of cascade cyclizations (Scheme 24). With much delight, we found that heating the substrate to 55-60 °C for 3 days provided the product of the cascade cyclization of both epoxides in the substrate. Moreover, all $SiMe_3$ directing groups had been protiodesilylated; leaving a tristetrahydropyran in which *no directing groups remained.*

Scheme 24



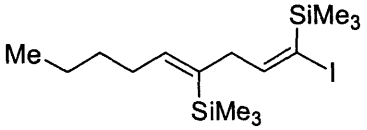
In the cascade reaction of **79**, all three $SiMe_3$ groups are replaced with protons and two new pyrans are formed. Remarkably, in this one reaction *five* operations take place. Also, despite the possibility of 5-exo cyclization in two different epoxide openings, only one product is isolated. The compound produced in this cascade was identical to that produced in iterative fashion (Chapter 1). While the iterative route to tristetrahydropyran **36** comprised 18 linear steps, the route to the same compound in which a bisepoxide is converted to **36** in cascade fashion comprised just 11 total steps.

Conclusion

The production of tristetrahydropyran **36** from bisepoxide **79** constitutes the first report of a cascade cyclization of a polyepoxide that produces the ubiquitous polytetrahydropyran motif without directing groups at the ring junctions. Such a polytetrahydropyran unit is found in several of the ladder polyethers. Moreover, these studies mimic the proposed biosynthesis of the ladder polyethers initially suggested more than 20 years ago. Furthermore, these studies demonstrate that the cascade production of polytetrahydropyrans *via* epoxides is a viable approach and one that may be applied to the synthesis of fragments found in those uniquely challenging natural products.

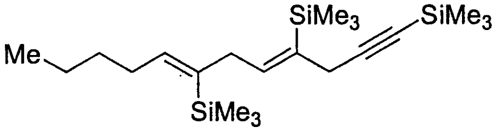
Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) and Et_2O were distilled from a blue solution of benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh).[54] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova 500 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), C_6D_6 (128.4 ppm), or CD_2Cl_2 (54.0 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm.



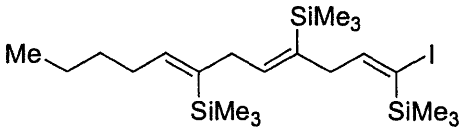
(1*E*,4*Z*)-1-Iodo-1,4-bis-trimethylsilanyl-nona-1,4-diene (80): To a solution of **9a** (2.5 g, 9.4 mmol) in Et_2O (7.4 mL) was added a 1 M solution of DIBAL in hexane (10.3 mL, 10.3 mmol). The reaction mixture stirred 48 h at room temperature. The reaction was cooled to –78 °C and a solution of I_2 (3.3 g, 13.2 mmol) in Et_2O (21.0 mL) was added.

The mixture was maintained at –78 °C for 2 h then was warmed to room temperature and stirred 45 min. The reaction mixture was poured into 10% HCl (100 mL) and ice (30 g). This stirred until the precipitate dissolved and was extracted with hexane (3 × 100 mL). The organic layer was washed with 1 N NaOH, saturated $Na_2S_2O_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to provide **80** (2.8 g, 74%, >95% *E*): R_f = 0.63 (hexane); IR (thin film, NaCl) 2956, 2858.6, 2361, 1615, 1457, 1406, 1249, 839, 756, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, *J* = 7.6 Hz, 1H), 5.94 (t, *J* = 7.6 Hz, 1H), 2.81 (dd, *J* = 7.6, 0.9 Hz, 2H), 2.11 (app q, *J* = 14.0, 7.0 Hz, 2H), 1.33 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.26 (s, 9 Hz), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 144.5, 136.1, 107.0, 42.4, 34.5, 32.1, 22.7, 14.3, 1.3, 0.4; HR-MS (EI) Calcd for $C_{15}H_{31}ISi_2$ $(M)^+$ 394.1003, found 394.1005

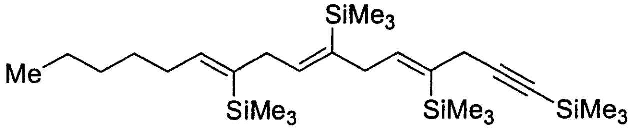


(4*Z*,7*Z*)-1,4,7-Tris-trimethylsilanyl-dodeca-4,7-dien-1-yne (81): A solution of 1-trimethylsilyl-1-propyne (2.8 g, 25 mmol) in THF (53 mL) at –78 °C was treated with a 2.5 M solution of *n*-BuLi in hexane (12 mL) and TMEDA (4.6 mL, 30 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a –78 °C slurry of CuI (8.2 g, 43 mmol) in THF (30 mL) and stirred 30 min. The reaction was warmed to 0 °C and DMAP (3.1 g, 25 mmol) was added. After 15 min alkenyl iodide **80** (5.0 g, 13 mmol) was added and the reaction was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to afford **81** that could not be separated from the allene regioisomer (3.1 g, 79%): R_f = 0.33 (hexane); IR (thin film, NaCl) 2957, 2360, 2341, 2173, 1615, 1419, 1249, 838, 758, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (t, *J* = 7.0 Hz, 1H) 5.94 (t, *J* = 7.6 Hz, 1H), 3.01 (d, *J* = 1.2 Hz, 2H), 2.90 (d, *J* = 7.0

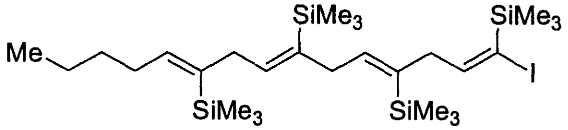
Hz, 2H), 2.11 (app q, *J* = 13.7, 6.7 Hz, 2H), 1.33 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.16 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 143.9, 138.1, 133.7, 106.5, 88.2, 39.9, 33.0, 32.6, 29.2, 23.2, 14.8, 1.0, 0.8, 0.7; HR-MS (ESI) Calcd for $C_{21}H_{42}NaSi_3$ $(M + Na)^+$ 401.2487, found 401.2500.



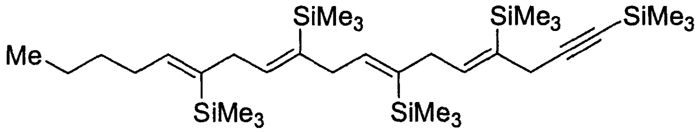
(1*E*,4*Z*,7*Z*)-1-Iodo-1,4,7-tris-trimethylsilanyl-dodeca-1,4,7-triene (82): To a solution of **81** (2.9 g, 7.7 mmol) in Et_2O (6.0 mL) was added a 1 M solution of DIBAL in hexane (8.5 mL). The reaction mixture stirred 48 h at room temperature. The reaction was cooled to –78 °C and a solution of I_2 (2.7 g, 10.8 mmol) in Et_2O (18.0 mL) was added. The mixture was maintained at –78 °C for 2 h then was warmed to room temperature and stirred 45 min. The reaction mixture was poured into 10% HCl (50 mL) and ice (10 g). This stirred until the precipitate dissolved and was extracted with hexane (3 × 50 mL). The organic layer was washed with 1 N NaOH, saturated $Na_2S_2O_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to provide **82** (2.7 g, 69%, >95% *E*): R_f = 0.69 (hexane); IR (thin film, NaCl) 2956, 2926, 2858, 2361, 1700, 1613, 1457, 1406, 1249, 839, 757, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, *J* = 7.9 Hz, 1H), 5.94-5.88 (m, 2H), 2.88 (dd, *J* = 7.0, 1.2 Hz, 2H), 2.84 (dd, *J* = 7.6, 1.2 Hz, 2H), 2.12 (app q, *J* = 13.9, 6.9 Hz, 2H), 1.33 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.27 (s, 9H), 0.15 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 143.6, 143.5, 137.6, 136.7, 107.0, 42.1, 39.4, 32.5, 32.1, 22.7, 14.4, 1.3, 0.5, 0.3; HR-MS (EI) Calcd for $C_{21}H_{43}ISi_3$ $(M)^+$ 506.1712, found 506.1703.



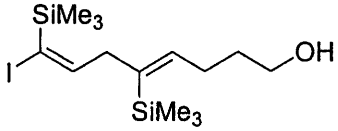
(4*Z*,7*Z*,10*Z*)-1,4,7,10-Tetrakis-trimethylsilanyl-hexadeca-4,7,10-trien-1-yne (83): A solution of 1-trimethylsilyl-1-propyne (0.9 g, 7.9 mmol) in THF (16 mL) at –78 °C was treated with a 2.5 M solution of *n*-BuLi in hexane (3.7 mL) and TMEDA (1.4 mL, 9.5 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a –78 °C slurry of CuI (2.6 g, 13.5 mmol) in THF (9.0 mL) and stirred 30 min. The reaction was warmed to 0 °C and DMAP (1.0 g, 7.9 mmol) was added. After 15 min alkenyl iodide **82** (2.0 g, 4.0 mmol) was added and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by silica gel chromatography (hexane) to afford **83** that could not be separated from the allene regioisomer (1.7 g, 83%): R_f = 0.32 (hexane); IR (thin film, NaCl) 2957, 2898, 2361, 2174, 1614, 1419, 1249, 838, 757, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (t, *J* = 6.7 Hz, 1H), 5.89 (m, 2H), 3.01 (s, 2H), 2.93 (d, *J* = 7.0 Hz, 2H), 2.87 (d, *J* = 7.0 Hz, 2H), 2.10 (app q, *J* = 13.4, 6.1 Hz, 2H), 1.32 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H), 0.17 (s, 9H), 0.15 (s, 9H), 0.15 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 143.7, 143.1, 138.8, 138.2, 133.8, 106.5, 88.1, 39.9, 39.8, 33.0, 32.5, 29.2, 23.2, 14.8, 1.0, 0.9, 0.8, 0.7; HR-MS (ESI) Calcd for $C_{27}H_{54}NaSi_4$ $(M + Na)^+$ 513.3195, found 513.3185.



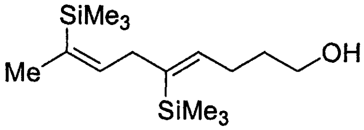
(1*E*,4*Z*,7*Z*,10*Z*)-1-Iodo-1,4,7,10-tetrakis-trimethylsilanyl-pentadeca-1,4,7,10-tetraene (84): To a solution of **83** (0.9 g, 1.8 mmol) in Et_2O (1.5 mL) was added a 1 M solution of DIBAL in hexane (2.0 mL). The reaction mixture stirred 48 h at room temperature. The reaction was cooled to –78 °C and a solution of I_2 (0.7 g, 2.6 mmol) in Et_2O (4.2 mL) was added. The mixture was maintained at –78 °C for 2 h then was warmed to room temperature and stirred 45 min. The reaction mixture was poured into 10% HCl (20 mL) and ice (2 g). This stirred until the precipitate dissolved and was extracted with hexane (3 × 20 mL). The organic layer was washed with 1 N NaOH, saturated $Na_2S_2O_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to provide **84** (0.8 g, 72%, >95% *E*): $R_f = 0.68$ (hexane); IR (thin film, NaCl) 2955, 2898, 2361, 1716, 1613, 1456, 1406, 1249, 1079, 838, 757, 688, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, $J = 7.6$ Hz, 1H), 5.94-5.84 (m, 3H), 2.90 (d, $J = 7.0$ Hz, 2H), 2.87 (d, $J = 6.7$ Hz, 2H), 2.84 (d, $J = 7.6$ Hz, 2H), 2.11 (m, 2H), 1.33 (m, 4H), 0.90 (t, $J = 7.0$ Hz, 3H), 0.26 (s, 9H), 0.14 (s, 27H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 143.4, 143.4, 142.5, 138.3, 137.7, 136.8, 106.9, 42.2, 39.5, 39.4, 32.6, 32.1, 22.7, 14.4, 1.3, 0.6, 0.5, 0.4; HR-MS (EI) Calcd for $C_{27}H_{55}Si_4$ $(M - I)^+$ 491.3351, found 491.3348.



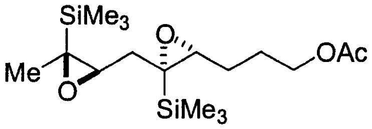
(4*Z*,7*Z*,10*Z*,13*Z*)-1,4,7,10,13-Pentakis-trimethylsilanyl-octadeca-4,7,10,13-tetraen-1-yne (85): A solution of 1-trimethylsilyl-1-propyne (0.2 g, 1.8 mmol) in THF (3.6 mL) at –78 °C was treated with a 2.5 M solution of *n*-BuLi in hexane (0.8 mL) and TMEDA (0.3 mL, 2.1 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a –78 °C slurry of CuI (0.6 g, 3.0 mmol) in THF (2.1 mL) and stirred 30 min. The reaction was warmed to 0 °C and DMAP (0.2 g, 1.8 mmol) was added. After 15 min alkenyl iodide **84** (0.5 g, 0.9 mmol) was added and the reaction mixture was allowed to warm gradually to room temperature and stirred overnight. The reaction was quenched with 1 M HCl and was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane) to afford **85** that could not be separated from the allene regioisomer (0.44 g, 85%): R_f = 0.39 (hexane); IR (thin film, NaCl) 2957, 2898, 2174, 1931, 1614, 1407, 1249, 839, 758, 689, 642 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (t, *J* = 7.0 Hz, 1H), 5.93-5.86 (m, 4H), 3.01 (s, 2H), 2.94 (d, *J* = 7.3 Hz, 2H), 2.91 (d, *J* = 7.0 Hz, 2H), 2.87 (d, *J* = 6.7 Hz, 2H), 2.11 (m, 2H), 1.32 (app q, *J* = 7.0, 3.7 Hz, 4H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.17 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H), 0.14 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 142.6, 142.3, 138.6, 138.2, 137.8, 133.4, 131.8, 106.1, 87.5, 39.5, 39.4, 32.6, 32.1, 28.9, 26.9, 22.7, 14.3, 0.5, 0.5, 0.4, 0.4, 0.3; HR-MS (ESI) Calcd for $C_{33}H_{66}NaSi_5$ $(M + Na)^+$ 625.3903, found 625.3926.



(4*Z*,7*E*)-8-Iodo-5,8-bis-trimethylsilanyl-octa-4,7-dien-1-ol (43): To a solution of alkyne **9c** (18.7 g, 69.8 mmol) in Et_2O (170 mL) at 0 °C was added a 1 M solution of DIBAL in hexane (170 mL). The resulting solution was heated 24 h at reflux. The solution was then cooled to –78 °C, diluted with Et_2O (50 mL), and a solution of I_2 (71.0 g, 279.1 mmol) in Et_2O (150 mL) was added. After stirring 2 h at –78 °C the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (40 g). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **43** (22.9 g, 83%, >95% *E*): R_f = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 3324, 2953, 2896, 1614, 1407, 1249, 1057, 839, 756 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.07 (t, *J* = 7.6 Hz, 1H), 5.93 (t, *J* = 7.6 Hz, 1H), 3.65 (t, *J* = 6.4, Hz, 2H), 2.81 (d, *J* = 7.6 Hz, 2H), 2.21 (q, *J* = 14.9, 7.3 Hz, 2H), 1.64 (t, *J* = 7.3 Hz, 3H), 1.42 (s, 1H-OH), 0.25 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.6, 143.3, 137.3, 107.2, 62.7, 42.3, 33.2, 28.6, 1.3, 0.4; HR-MS (ESI) Calcd for $C_{14}H_{29}NaIOSi_2$ (M + Na)$^+$ 419.0694, found 419.0674.

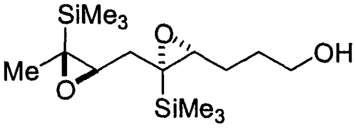


(4*Z*,7*Z*)-5,8-Bis-trimethylsilanyl-nona-4,7-dien-1-ol (44): To a slurry of CuCN (2.5 g, 28.4 mmol) in Et$_2$O (34.0 mL) at 0 °C was added a 1.4 M solution of MeLi in Et$_2$O (35.5 mL) and the mixture stirred 15 min. A solution of alkenyl iodide **43** (5.0 g, 12.6 mmol) in Et$_2$O (12.8 mL) was slowly added. The reaction stirred 20 h at 0 °C then was carefully quenched with saturated NH$_4$Cl and extracted with Et$_2$O (3 × 40 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford diene **44** (3.1 g, 86%): R$_f$ = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 3322, 2953, 1615, 1248, 1058, 836, 755 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.95-5.89 (m, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.85-2.82 (m, 2H), 2.21 (app q, *J* = 7.0 Hz, 2H), 1.78 (d, *J* = 2.7 Hz, 3H), 1.67-1.62 (m, 2H), 0.15 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.1, 141.5, 139.2, 135.6, 62.9, 39.3, 33.3, 28.7, 24.9, 0.5, 0.0; HR-MS (ESI) Calcd for $C_{15}H_{32}NaOSi_2$ (M + Na)$^+$ 307.1884, found 307.1889.



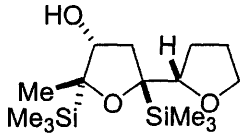
Acetic acid 3-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranyl]-propyl ester (45): To a solution of alcohol **44** (2.5 g, 8.7 mmol) in CH_2Cl_2 (87 mL) at 0 °C was added pyridine (0.8 g, 10.4 mmol), Ac_2O (1.1 g, 10.4 mmol), and DMAP (0.11 g, 0.9 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) and carried to the next step.

To a solution of the acetate (2.0 g, 6.2 mmol) in CH_3CN/DMM (192 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (129 mL), *n*-$BuNHSO_4$ (0.4 g, 1.2 mmol), and chiral ketone **A** (3.2 g, 12.3 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (12.5 g, 20.0 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (86.0 mL) and a 0.89 M solution of K_2CO_3 (86.0 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (4 × 400 mL). The combined organic layers where washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford **45** (1.3 g, 42% over 2 steps, dr >95:5): $R_f = 0.47$ (20% EtOAc in hexane); $[\alpha]^{25}_D = +3.7$ ($c = 2.7$, $CHCl_3$); IR (thin film, NaCl) 2958, 1742, 1367, 1250, 1045, 840, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.18-4.09 (m, 2H), 2.87 (dd, $J = 7.9$, 4.9 Hz, 1H), 2.73 (dd, $J = 8.2$, 3.7 Hz, 1H), 2.18 (dd, $J = 14.7$, 3.9 Hz, 1H), 2.05 (s, 3H), 1.92-1.72 (m, 3H), 1.58-1.50 (m, 1H), 1.34 (dd, $J = 14.6$, 8.5 Hz, 1H), 1.22 (s, 3H), 0.19 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 64.7, 63.7, 62.8, 56.6, 55.5, 38.9, 28.0, 27.0, 23.4, 21.7, -0.5, -1.1; HR-MS (ESI) Calcd for $C_{17}H_{34}O_4Si_2$ $(M + Na)^+$ 381.1888 found, 381.1997.

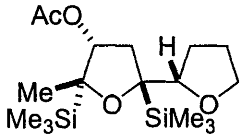


3-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranyl]-propan-1-ol (46): To a solution of acetate **45** (1.3 g, 3.7 mmol) in THF (8.0 mL) and MeOH (8.0 mL) at 0 °C was added a 1.0 M solution of LiOH (8.0 mL) and the mixture stirred 20 min. The mixture was diluted with water and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford bisepoxide **46** (1.0 g, 84%): $R_f = 0.47$ (50% EtOAc in hexane); $[\alpha]^{25}_D = +4.4$ (c = 18.3, $CHCl_3$); IR (thin film, NaCl) 3445, 2957, 2360, 2341, 1441, 1418, 1371, 1250, 1062, 840, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.68 (dt, J = 5.5, 4.0 Hz, 2H), 2.88 (dd, J = 7.9, 4.0 Hz, 1H), 2.71 (dd, 8.2, 3.7 Hz, 1H), 2.16 (dd, J = 14.3, 3.4 Hz, 1H), 1.85-1.71 (m, 4H), 1.55-1.28 (m, 2H), 1.19 (s, 3H), 0.17 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.7, 62.7, 62.4, 56.7, 55.1, 38.4, 30.5, 27.6, 22.9, -0.9, -1.5; HR-MS (ESI) Calcd for $C_{15}H_{33}OSi_2$ $(M + H)^+$ 317.1968 found, 317.1958.

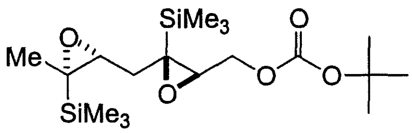
Representative procedure for the acid-promoted cyclization of 46: To a solution of bisepoxide **46** (10 mg, 32 μmol) in CH_2Cl_2 (0.3 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (7 mg, 32 μmol) and the mixture stirred 2 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford bisfuran **47** (5 mg, 50%).



(2*S*,4*R*,5*R*,2'*S*)-5-Methyl-2,5-bis-trimethylsilanyl-octahydro-[2,2']bifuranyl-4-ol (47): IR (thin film, NaCl) 3375, 2953, 1739, 1451, 1246, 1052, 1063, 839 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.80 (d, *J* = 11.6 Hz, 1H), 3.99-3.94 (m, 2H), 3.88-3.83 (m, 1H), 3.79-3.74 (m, 1H), 2.26 (dd, *J* = 14.0, 5.8 Hz, 1H), 1.95-1.91 (m, 3H), 1.82 (d, *J* = 14 Hz, 1H), 1.33-1.28 (m, 1H), 0.94 (s, 3H), 0.09 (s, 9H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 85.1, 83.3, 82.1, 81.1, 67.0, 35.7, 29.6, 26.1, 25.4, -1.5, -1.8; HR-MS (ESI) Calcd for $C_{15}H_{33}O_3Si_2$ $(M + H)^+$ 317.1963, found 317.1967.



Acetic acid (2*S*,4*R*,5*R*,2'*S*)-5-methyl-2,5-bis-trimethylsilanyl-octahydro-[2,2']bifuranyl-4-yl ester (49): To a solution of bisfuran **47** (6 mg, 19 μmol) in CH_2Cl_2 (0.4 mL) was added *i*-Pr_2EtN (80 mg, 0.6 mmol), Ac_2O (60 mg, 0.6 mmol), and DMAP (2 mg, 16 μmol). The mixture stirred overnight and was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexane) to afford acetate **49** (5 mg, 87%): R_f = 0.47 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -50.0 (*c* = 1.0, CHCl$_3$); IR (thin film, NaCl) 2959, 1743, 1450, 1368, 1246, 1109, 1072, 1045, 838, 754 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.16 (d, *J* = 5.6 Hz, 1H), 3.95-3.91 (m, 1H), 3.88-3.83 (m, 1H), 3.63-3.59 (m, 1H), 2.42 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.20 (d, *J* = 14.6 Hz, 1H), 2.02 (s, 3H), 1.96-1.82 (m, 4H), 1.03 (s, 3H), 0.07 (s, 18H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.3, 85.3, 84.8, 82.0, 80.0, 68.0, 39.6, 28.4, 26.0, 25.0, 21.7, -0.6, -1.8; HR-MS (ESI) Calcd for $C_{17}H_{34}NaO_4Si_2$ $(M + Na)^+$ 381.1888, 381.1893.

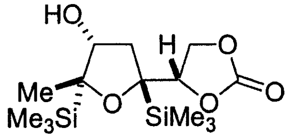


Carbonic acid *tert*-butyl ester (2*R*,3*S*)-3-((2*R*,3*S*)-3-methyl-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl ester (51): To a slurry of CuCN (0.7 g, 7.3 mmol) in Et_2O (8.8 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (10.5 mL). After 15 min a solution of alkenyl iodide **4d** (1.2 g, 3.3 mmol) in Et_2O (3.3 mL) was slowly added. The solution stirred 20 h at 0 °C then was carefully quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was passed through a plug of silica gel to remove the metal salts and was carried on to the next step without further purification ($R_f = 0.35$, 20% EtOAc in hexane).

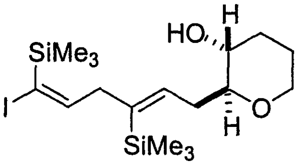
To a solution of the diene (0.7 g, 2.8 mmol) in CH_2Cl_2 (28 mL) was added Et_3N (0.8 mL, 5.6 mmol), BOC_2O (1.2 g, 5.6 mmol), and DMAP (30 mg, 0.3 mmol). The mixture stirred at room temperature overnight then was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The unpurified product mixture was carried on to the next step.

To a solution of the crude carbonate (1.0 g, 1.0 mmol) in CH_3CN/DMM (94 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (63 mL), *n*-Bu_4NHSO_4 (0.2 g, 0.6 mmol), and chiral ketone **A** (1.6 g, 6.0 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (6.1 g, 9.9 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (42 mL) and a 0.89 M solution of K_2CO_3 (42 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (150 mL) and extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated two times.

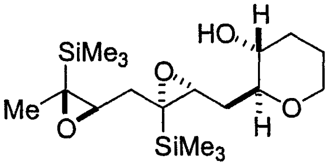
The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford **51** (0.5 g, 39% over 3 steps, dr 6:1): R*f* = 0.62 (20% EtOAc in hexane); $[\alpha]^{25}_{D}$ = +6.4 (*c* = 4.7, $CHCl_3$); IR (thin film, NaCl) 2958, 1744, 1456, 1370, 1280, 1253, 1164, 1095, 842, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 11.9, 2.4 Hz, 1H), 4.03 (dd, *J* = 11.9, 8.5 Hz, 1H), 3.23 (dd, *J* = 7.9, 3.1 Hz, 1H), 2.74 (dd, *J* = 7.6, 4.3 Hz, 1H), 2.07 (dd, *J* = 14.6, 3.7 Hz, 1H), 1.59 (dd, *J* = 14.6, 7.6 Hz, 1H), 1.51 (s, 9H), 1.22 (s, 3H), 0.21 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 83.2, 67.5, 62.4, 60.9, 55.8, 55.6, 38.1, 28.4, 23.3, -0.7, -1.1; HR-MS (ESI) Calcd for $C_{13}H_{36}NaO_5Si$ $(M + Na)^+$ 411.1993, found 411.2007.



(*S*)-4-((2*S*,4*R*,5*R*)-4-Hydroxy-5-methyl-2,5-bis-trimethylsilanyl-tetrahydro-furan-2-yl)-[1,3]dioxolan-2-one (52): To a solution of **51** (42 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C was added $BF_3 \cdot Et_2O$ (24 μL, 0.11 mmol). After 2 min the reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **52** (13 mg, 36%): R*f* = 0.31 (20% EtOAc in hexane); $[\alpha]^{25}_{D}$ = -20.0 (*c* = 1.0, $CHCl_3$); IR (thin film, NaCl) 3496, 2955, 1786, 1250, 1180, 1074, 838, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.52 (dd, *J* = 9.0, 6.6 Hz, 1H), 4.45 (app t, *J* = 9.0 Hz, 1H), 4.32 (app t, *J* = 4.6 Hz, 1H), 2.35 (dd, *J* = 14.3, 5.0 Hz, 1H), 2.13 (d, *J* = 14.3 Hz, 1H), 1.80 (d, *J* = 3.8 Hz, 1H-OH), 0.99 (s, 3H), 0.14 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 84.3, 82.6, 80.8, 80.7, 68.2, 41.7, 25.4, -1.1, -1.3; HR-MS (ESI) Calcd for $C_{14}H_{28}NaO_5Si$ $(M + Na)^+$ 355.1367, found 355.1375.



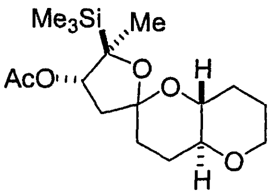
(2*S*,3*R*)-2-((2*Z*,5*E*)-6-Iodo-6-silanyl-3-trimethylsilanyl-hexa-2,5-dienyl)-tetrahydro-pyran-3-ol (53): To a solution of alkyne **26** (0.6 g, 2.0 mmol) in Et_2O (4.8 mL) at 0 °C was added a 1 M solution of DIBAL in hexane (4.8 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to –78 °C, diluted with Et_2O (5.0 mL), and a solution of I_2 (2.0 g, 8.0 mmol) in Et_2O (10.0 mL) was added. After stirring for 2 h at –78 °C, the reaction was quenched by pouring into 1 M HCl (20 mL) and ice (5 g). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10-20% EtOAc in hexane) to yield alkenyl iodide **53** (0.7 g, 76%, >95% *E*): R_f = 0.39 (20% EtOAc in hexane); IR (NaCl) 3399, 2952, 2852, 2361, 1249, 1097, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.6 Hz, 1H), 6.12 (t, *J* = 6.8 Hz, 1H), 3.89 (m, 1H), 3.40-3.28 (m, 2H), 3.07 (app dt, *J* = 7.9, 4.0 Hz, 1H), 2.85 (dd, *J* = 7.3, 1.2 Hz, 1H), 2.67 (ddd, *J* = 14.9, 7.9, 4.0 Hz, 1H), 2.33 (m, 1H), 2.08 (m, 1H), 1.67 (m, 2H), 1.47 (d, *J* = 4.6 Hz, 1H), 1.44-1.36 (m, 2H), 0.26 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 140.8, 139.1, 107.9, 89.0, 71.4, 68.3, 43.2, 35.6, 33.6, 26.3, 1.7, 0.8; HR-MS (ESI) Calcd for $C_{17}H_{33}NaIO_2Si_2$ $(M + Na)^+$ 475.0956, found 475.0962.



(2*S*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (54): To a slurry of CuCN (0.2 g, 2.0 mmol) in Et_2O (3.0 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (2.9 mL) and the mixture stirred 15 min. A solution of alkenyl iodide **53** (0.4 g, 0.9 mmol) in Et_2O (1.2

mL) was slowly added. The solution stirred 20 h at 0 °C then was carefully quenched with saturated NH_4Cl and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) before a portion was carried on to the next step ($R_f = 0.28$, 20% EtOAc in hexane).

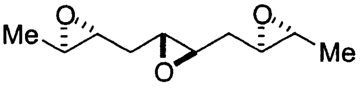
To a solution of the diene (0.1 g, 0.4 mmol) in CH_3CN/DMM (12.0 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (8.0 mL), *n*-Bu_4NHSO_4 (30 mg, 80 μmol), and chiral ketone **A** (0.2 g, 0.8 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (0.8 g, 1.3 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (5.3 mL) and a 0.89 M solution of K_2CO_3 (5.3 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (20 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to yield bisepoxide **54** (66 mg, 27% over 2 steps, dr 5:1): $R_f = 0.53$ (50% EtOAc in hexane); $[\alpha]^{25}_D = -2.62$ ($c = 26.7$, $CHCl_3$); IR (NaCl) 3444, 2955, 2854, 2361, 1750, 1440, 1412, 1373, 1251, 1096, 1048, 840, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93-3.88 (m, 1H), 3.60-3.54 (m, 1H), 3.34 (td, $J = 11.3$, 4.0 Hz, 1H), 3.22 (ddd, $J = 9.0$, 5.6, 3.2 Hz, 1H), 3.16 (dd, $J = 8.7$, 3.1 Hz, 1H), 2.74 (dd, $J = 7.5$, 4.3 Hz, 1H), 2.33 (br s, 1H-OH), 2.16 (dt, $J = 14.8$, 3.2 Hz, 1H), 2.11-2.07 (m, 1H), 2.01 (dd, $J = 14.6$, 4.1 Hz, 1H), 1.76 (ddd, $J = 14.8$, 8.9, 6.0 Hz, 1H), 1.73-1.63 (m, 2H), 1.56 (dd, $J = 14.8$, 7.5 Hz, 1H), 1.48-1.37 (m, 1H), 1.19 (s, 3H), 0.18 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.7, 70.3, 68.6, 62.7, 61.1, 56.5, 55.6, 38.4, 34.0, 33.0, 26.5, 23.3, -0.5, -1.1; HR-MS (ESI) Calcd for $C_{18}H_{36}NaO_4Si_2$ $(M + Na)^+$ 395.2044, found 395.2040.



Spiroketal (55): To a solution of bisepoxide **54** (10 mg, 27 μmol) in CH_2Cl_2 (0.3 mL) at −78 °C was added $BF_3{\cdot}Et_2O$ (5 μL, 40 μmol) and the mixture stirred 2 min. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo.*

To a solution of the crude mixture in CH_2Cl_2 (0.5 mL) was added Et_3N (6 μL, 40 μmol), Ac_2O (3 μL, 30 μmol), and DMAP (1 mg, 8 μmol). The mixture stirred overnight then was quenched with saturated NH_4Cl and concentrated *in vacuo.* The remaining contents were extracted with Et_2O (3 × 2 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography to yield what has been tentatively assigned the structure of spiroketal **55** (1 mg, 11% over 2 steps): IR (thin film, NaCl) 3584, 2939, 2862, 1743, 1247, 1096, 1048, 1025, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (dd, J = 5.5, 1.0 Hz, 1H), 3.94-3.89 (m, 1H), 3.62 (ddd, J = 13.6, 9.2, 4.4 Hz, 1H), 3.40 (app dt, J = 11.9, 2.8 Hz, 1H), 3.00-2.95 (m, 1H), 2.63-2.53 (m, 2H), 2.04 (s, 3H), 1.89-1.68 (m, 7 H), 1.43-1.35 (m, 1H), 1.33 (s, 3H), 0.08 (s, 9H); HR-MS (ESI) Calcd for $C_{17}H_{30}NaO_5Si$ $(M + Na)^+$ 365.1760, found 365.1758.

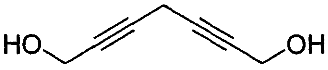
(*E*)-Dec-5-ene-2,8-diyne (56): To a 0.5 M solution of propynylmagnesium bromide in THF (47.0 mL) at 0 °C was added CuCl (20 mg, 0.2 mmol). After 15 min (*E*)-1,4-dibromo-2-butene (2.0 g, 9.3 mmol) in THF (10.0 mL) was added over 10 min. The reaction mixture was heated 20 h at reflux. After cooling to room temperature the reaction was quenched with saturated NH_4Cl, and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude material was purified by column chromatography (2-5% EtOAc in hexane) to yield diyne **56** (1.0 g, 81%): R$_f$ = 0.56 (5% EtOAc in hexane); IR (NaCl) 3038, 2894, 1680, 1422, 1333, 973 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.67 (dt, *J* = 5.5, 1.8 Hz, 2H), 2.88 (m, 4H), 1.81 (t, *J* = 2.4 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 126.5, 77.8, 76.4, 21.9, 3.7; HR-MS (ESI) Calcd for $C_{10}H_{12}$ (M)$^+$ 132.0934, found 132.0924.



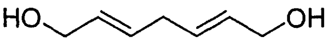
(2*R*,3*R*,5*R*,6*R*,8*R*,9*R*)-Trioxydecatriene (57): To a condensed solution of NH_3 (~30 mL) was added *t*-BuOH (12.0 g, 161.9 mmol), ammonium sulfate (10.0 g, 75.7 mmol), and lithium wire (0.7 g, 100.9 mmol). To this solution was added diyne **56** (1.0 g, 7.6 mmol) in Et_2O (13 mL). The reaction mixture was warmed to reflux and maintained for 30 min. The reaction was quenched with K_2CO_3 (20 g) and water (50 mL), extracted with Et_2O (3 × 20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude triene.

To a solution of the unpurified triene (0.5 g, 3.7 mmol) in CH_3CN/DMM (210 mL, 1:2 v:v) at 0 °C was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10\ H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (140 mL), *n*-Bu_4NHSO_4 (0.2 g, 0.6 mmol), and chiral ketone **A** (1.1 g, 4.3 mmol). To this rapidly stirring solution was added, simultaneously over 1.5 h *via* syringe pump, a solution of Oxone® (11.8 g, 19.1 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (90 mL) and a 0.89 M solution of K_2CO_3 (90 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water and extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated two more times. The epoxide product was separated from the ketone catalyst by column chromatography (50% EtOAc in hexane) to yield trisepoxide **57** (0.3 g, 23% over 2 steps, dr 7:1): R$_f$ = 0.45 (50% EtOAc in hexane); $[\alpha]^{25}_D$ = +63.6 (*c* = 14.3, in $CHCl_3$); IR (thin film, NaCl) 2997, 2974, 2959, 2923, 2251, 1737, 1483, 1412, 1248, 911, 856, 731 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.87-2.85 (m, 2H), 2.79-2.76 (m, 4H), 1.74-1.72 (m, 4H), 1.29 (d, J = 4.9 Hz, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 56.6, 55.6, 54.7, 35.2, 17.7; HR-MS (ESI) Calcd for $C_{10}H_{16}O_3Na$ $(M + Na)^+$ 207.0992, found 207.0998.

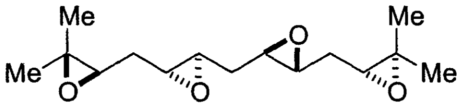
4-Chloro-but-2-yn-1-ol (58): Synthesized according to the reported procedure.[78]



Hepta-2,5-diyne-1,7-diol (59): Synthesized according to the reported procedure.[79]



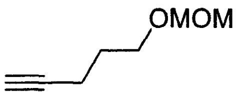
(2*E*,5*E*)-Hepta-2,5-diene-1,7-diol (60): Synthesized according to the reported procedure.[79]



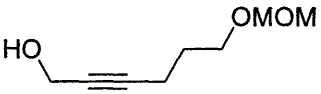
2,12-Dimethyl-(2*R*,3*R*,5*R*,6*R*,8*R*,9*R*,11*R*,12*R*)-tetraoxydodecatetraene (61): To a solution of PBr_3 (6.0 mL, 63.8 mmol) in Et_2O (240 mL) at –20 °C was added bisallyl alcohol **60** (6.0 g, 46.8 mmol) *via* syringe pump over 1 h. The reaction mixture stirred 1.5 h then was quenched with saturated $NaHCO_3$ and was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide the bisallyl bromide that was carried on to the next step without purification.

To a solution of 1-bromo-2-methyl-1-propene (4.8 mL, 47.0 mmol) in Et_2O (250 mL) at –78 °C was added a 1.7 M solution of *t*-BuLi in pentane (58.0 mL) and the solution stirred 2 h. This solution was transferred *via* canula to a slurry of CuI (9.0 g, 47.3 mmol) and DMAP (5.7 g, 46.6 mmol) in THF (120 mL) at –40 °C. The crude bisallyl bromide (3.7 g, 13.1 mmol) was added to the reaction mixture and the solution was warmed to 0 °C and stirred 7 min. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was partially purified by column chromatography (hexane) before a portion was carried on to the next step.

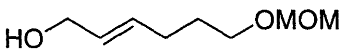
To a solution of the tetraene (0.3 g, 1.3 mmol) in CH_3CN/DMM (36.5 mL, 1:2 v:v) was added a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (24.4 mL), *n*-Bu_4NHSO_4 (0.2 g, 0.5 mmol), and chiral ketone **A** (1.3 g, 5.2 mmol). This solution was cooled to 0 °C and to this rapidly stirring solution was added, simultaneously over 1.5 h *via* syringe pump, a solution of of Oxone® (6.4 g, 10.4 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (17.5 mL) and a 0.89 M solution of K_2CO_3 (17.5 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (50 mL) and was extracted with EtOAc (4 × 100 mL). The combined organic layers where washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to yield tetraepoxide **61** (0.14 g, 19% over 3 steps, dr 3:1): $R_f = 0.35$ (50% EtOAc in hexane); $[\alpha]^{25}_D = +30.8$ ($c = 1.3$, $CHCl_3$); IR (solution in $CDCl_3$, NaCl) 2964, 2927, 1459, 1379, 1252, 1117 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.95-2.90 (m, 6H), 1.88-1.70 (m, 4H), 1.54-1.37 (m, 2H), 1.34 (s, 6 H), 1.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.6, 59.0, 56.5, 56.1, 35.6, 32.7, 25.4, 19.5; HR-MS (ESI) Calcd for $C_{15}H_{24}NaO_4$ $(M + Na)^+$ 291.1567, found 291.1557.



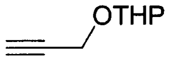
5-Methoxymethoxy-pent-1-yne (61): Synthesized according to the literature procedure.[80]



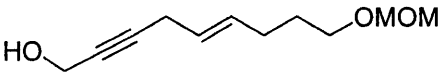
6-Methoxymethoxy-hex-2-yn-1-ol (67): To a solution of alkyne **61** (17.0 g, 133 mmol) in THF (125 mL) at -78° C was added a 2.5 M solution of *n*-BuLi in hexane (58.0 mL) and the resulting solution stirred 1 h. Paraformaldehyde (4.4 g, 146 mmol) was added and the solution was warmed to room temperature and stirred 2 h. The reaction was quenched by adding ice (5 g) and saturated $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to yield propargyl alcohol **67** (14.8 g, 71%): $R_f = 0.37$ (50% EtOAc in hexane); IR (thin film, NaCl) 3427, 2932, 1443, 1217, 1148, 1109, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.25 (dt, $J = 5.8$, 2.1 Hz, 2H), 3.62 (t, $J = 6.1$ Hz, 2H), 3.37 (s, 3H), 2.35 (tt, $J = 7.0$, 2.1 Hz, 2H), 1.83-1.77 (m, 2H), 1.65 (t, $J = 6.1$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.1, 86.3, 79.5, 66.8, 55.9, 52.1, 29.3, 16.3; HR-MS (ESI) Calcd for $C_8H_{13}NaO_3$ $(M + Na)^+$ 181.0835, found 181.0833.



(*E*)-6-Methoxymethoxy-hex-2-en-1-ol (68): To a solution of $LiAlH_4$ (5.4 g, 141 mmol) in THF (300 mL) at 0 °C was added a solution of propargyl alcohol **67** (14.8 g, 93.7 mmol) in THF (180 mL). The solution was warmed to room temperature and stirred 48 h. The solution was diluted with Et_2O (200 mL), cooled to 0 °C, and carefully quenched by the addition of 1 M HCl (100 mL). After the mixture stirred at room temperature 20 min, the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product required no purification to yield allylic alcohol **68** (13.1 g, 87%): $R_f = 0.27$ (50% EtOAc in hexane); IR (thin film, NaCl) 3406, 2938, 1442, 1150, 1111, 1041, 971, 920 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74-5.64 (m, 2H), 4.62 (s, 2H), 4.10 (t, $J = 5.2$ Hz, 2H), 3.54 (t, $J = 6.4$ Hz, 2H), 3.37 (s, 3H), 2.17-2.13 (m, 2H), 1.72-1.67 (m, 2H), 1.41 (t, $J = 5.5$ Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 133.0, 130.2, 97.1, 67.8, 64.4, 55.9, 29.9, 29.6; HR-MS (ESI) Calcd for $C_8H_{16}NaO_3$ $(M + Na)^+$ 183.0992, found 183.0990.



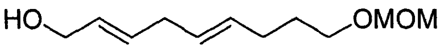
2-Prop-2-ynyloxy-tetrahydro-pyran (72): Synthesized according to a reported procedure.[81]



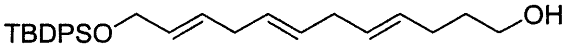
(*E*)-9-Methoxymethoxy-non-5-en-2-yn-1-ol (69): To a solution of allylic alcohol **68** (13 g, 81 mmol) in CH_2Cl_2 (800 mL) was added PPh_3 (26 g, 98 mmol) and CBr_4 (40 g, 122 mmol). The resulting solution stirred 5 min. The reaction was quenched with saturated $NaHCO_3$ (200 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with water (4 × 200 mL) and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) to yield the allylic bromide that was carried on to the next step ($R_f = 0.44$, 20% EtOAc in hexane).

To a solution of alkyne **72** (20 g, 142 mmol) in THF (600 mL) at −78 °C was added a 2.5 M solution of *n*-BuLi in hexane (57 mL, 2.5 M in hexane) dropwise over 30 min. After 30 min CuBr·DMS (29 g, 142 mmol) was added. After 10 min a solution of the allylic bromide (13 g, 64 mmol) in THF (150 mL) was added and the solution was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl (300 mL) and the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) to yield the protected propargyl alcohol that was carried on to the next step (R_f = 0.61, 20% EtOAc in hexane).

To a solution of the THP protected propargyl alcohol (12.6 g, 44.7 mmol) in MeOH (400 mL) was added *p*-TsOH·H_2O (0.5 g, 2.9 mmol). The reaction stirred at room temperature 30 min, was diluted with EtOAc (1.2 L), washed with saturated $NaHCO_3$ (200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to yield propargyl alcohol **69** (8.3 g, 51% over 3 steps): R_f = 0.46 (50% EtOAc in hexane); IR (thin film, NaCl) 3432, 2936, 1423, 1149, 1111, 1037, 971, 919 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71-5.65 (m, 1H), 5.47-5.41 (m, 1H), 4.63 (s, 2H), 4.29 (tt, *J* = 6.1, 2.1 Hz, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.37 (s, 3H), 2.96-2.93 (m, 2H), 2.13 (dt, *J* = 7.3, 7.0 Hz, 2H), 1.71-1.65 (m, 2H), 1.64 (t, *J* = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.3, 125.0, 97.1, 84.6, 80.7, 67.8, 55.9, 52.1, 29.9, 29.5, 22.7; HR-MS (ESI) Calcd for $C_{11}H_{18}NaO_3$ $(M + Na)^+$ 221.2486, found 221.2483.



(2*E*,5*E*)-9-Methoxymethoxy-nona-2,5-dien-1-ol (70): To a solution of $LiAlH_4$ (1.3 g, 34.1 mmol) in THF (100 mL) at 0 °C was added a solution of propargyl alcohol **69** (4.5 g, 22.7 mmol) in THF (25 mL). The solution was warmed to room temperature and stirred 48 h. The solution was diluted with Et_2O (200 mL), cooled to 0 °C, and carefully quenched by the addition of 1 M HCl (50 mL). After the mixture stirred 20 min at room temperature, the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product required no purification to yield allylic alcohol **70** (3.8 g, 84%): R_f = 0.37 (50% EtOAc in hexane); IR (thin film, NaCl) 3420, 2931, 1429, 1148, 1111, 1039, 970, 919 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74-5.62 (m, 2 H), 5.47-5.45 (m, 2H), 4.63 (s, 2H), 4.13-4.10 (m, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 3.37 (s, 3H), 2.77-2.74 (m, 2H), 2.13-2.08 (m, 2H), 1.70-1.64 (m, 2H), 1.31 (t, J = 5.80 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2, 131.6, 130.2, 128.9, 97.1, 67.9, 64.4, 55.8, 35.9, 30.1, 29.8; HR-MS (ESI) Calcd for $C_{11}H_{20}NaO_3$ $(M + Na)^+$ 223.1305, found 223.1313.



(4*E*,7*E*,10*E*)-12-(*tert*-Butyl-diphenyl-silanyloxy)-dodeca-4,7,10-trien-1-ol (71): To a solution of allylic alcohol **70** (3.5 g, 17.5 mmol) in CH_2Cl_2 (175 mL) was added PPh_3 (5.5 g, 21.0 mmol) and CBr_4 (8.7 g, 26.3 mmol). The resulting solution stirred 5 min. The reaction was quenched with saturated $NaHCO_3$ (100 mL) and the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water (4 × 100 mL), brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was partially purified by column chromatography (5-20% EtOAc in hexane) to yield the allylic bromide that was carried on to the next step (R_f = 0.64, 20% EtOAc in hexane).

To a solution of alkyne **72** (3.4 g, 24.4 mmol) in THF (150 mL) at –78 °C was added a 2.5 M solution of *n*-BuLi in hexane (9.7 mL) dropwise over 30 min. After 30 min CuBr·DMS (5.0 g, 24.4 mmol) was added. After 10 min, a solution of the allylic bromide (3.2 g, 12.2 mL) in THF (40 mL) was added and the solution was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) to yield the protected propargyl alcohol that was carried on to the next step (R_f = 0.42, 20% EtOAc in hexane).

To a solution of the THP protected propargyl alcohol (3.6 g, 11.2 mmol) in MeOH (290 mL) was added *p*-TsOH·H_2O (0.1 g, 0.6 mmol). The reaction stirred at room temperature 30 min, was diluted with EtOAc (600 mL), washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (50% EtOAc in hexane) to yield the propargyl alcohol that was carried on to the next step.

To a solution of $LiAlH_4$ (0.6 g, 15.1 mmol) in THF (40 mL) at 0 °C was added a solution of the propargyl alcohol (1.8 g, 7.6 mmol) in THF (20 mL). The reaction mixture was warmed to room temperature and stirred 48 h. The solution was diluted with Et_2O (50 mL), cooled to 0 °C, and carefully quenched by the addition of 1 M HCl (30 mL). After the mixture stirred 20 min at room temperature the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The unpurified allylic alcohol was carried to the next step ($R_f = 0.16$, 20% EtOAc in hexane).

To a solution of the allylic alcohol (1.8 g, 7.6 mmol) in DMF (35.0 mL) at 0 °C was added imidazole (1.1 g, 15.8 mmol) and TBDPSCl (2.2 mL, 8.7 mmol) and the solution stirred overnight. The reaction mixture was diluted with Et_2O (200 mL), washed with water (3 × 50 mL), brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was partially purified by column chromatography to afford the silyl ether that was carried on to the next step ($R_f = 0.63$, 20% EtOAc in hexane).

To a solution of $MgBr_2{\cdot}Et_2O$ (9.2 g, 35.6 mmol) in Et_2O (70 mL) was added the silyl ether (3.4 g, 7.1 mmol) and *n*-BuSH (1.9 mL, 17.8 mmol).[87] The reaction stirred at room temperature for 5.5 h and was quenched with water. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford alcohol **71** (2.2 g, 29% over 6 steps): $R_f = 0.16$ (20% EtOAc in hexane); IR (thin film, NaCl) 3347, 2931, 2858, 1428, 1112, 1059, 969, 823, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.68 (m, 4H), 7.29-7.36 (m, 6H); 5.72-5.65 (m, 1H), 5.61-5.54 (m, 1H), 5.47-5.45 (m, 2H), 5.44-5.42 (m, 2H), 4.17 (dd, $J = 5.2$, 1.5 Hz, 2H), 3.66 (t, $J = 6.1$ Hz, 2H), 2.74-2.71 (m, 4H), 2.13-2.07 (m, 2H), 1.68-1.61 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 134.5, 131.0, 130.3, 130.2, 130.1, 130.0, 129.9, 129.5, 128.3, 68.2, 63.3, 36.3, 35.8, 33.0, 29.6, 27.6, 19.9; HR-MS (ESI) Calcd for $C_{28}H_{38}NaO_2Si$ $(M + Na)^+$ 457.2533, found 457.2533.

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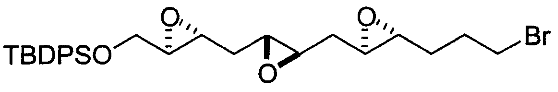
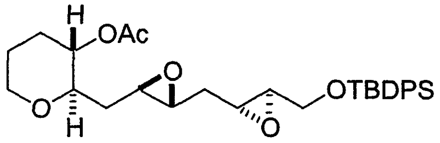
[87] Kim, S.; Kee, I. S.; Park, Y. H.; Park J. H. *Synlett* **1991**, 183.



((2*R*,3*R*)-3-{(2*R*,3*R*)-3-[(2*R*,3*R*)-3-(3-Bromo-propyl)-oxiranylmethyl]-oxiranylmethyl}-oxiranylmethoxy)-*tert*-butyl-diphenyl-silane (65): To a solution of allylic alcohol **71** (50 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (36 mg, 0.14 mmol) and CBr_4 (60 mg, 0.17 mmol). The resulting solution stirred 5 min. The reaction was quenched with saturated $NaHCO_3$ (1 mL) and the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (4 × 10 mL), brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (5% EtOAc in hexane) to yield the alkyl bromide that was carried on to the next step (R_f = 0.37, 5% EtOAc in hexane).

To a solution of the alkyl bromide (35 mg, 64 μmol) in CH_3CN/DMM (2.2 mL, 1:2, v:v) was added a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (1.4 mL), *n*-Bu_4NHSO_4 (7 mg, 0.02 mmol), and chiral ketone **A** (52 mg, 0.2 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (0.26 g, 0.2 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (1.1 mL) and a 0.89 M solution of K_2CO_3 (1.1 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (5 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (20 % EtOAc in hexane) to afford trisepoxide **65** (28 mg, 47 % over 2 steps, dr 9:1): R_f = 0.21 (20% EtOAc in hexane); $[\alpha]^{25}_D = +34.8$ (*c* = 2.3, in $CHCl_3$); IR (NaCl) 2930, 2857, 1427, 1113, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4H), 7.46-7.38 (m, 6H), 3.82 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.76 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.50-3.42 (m, 2H), 3.01-2.98 (m, 1H), 2.97-2.95 (m, 1H), 2.91-2.86 (m, 3H), 2.78-2.75 (m, 1H), 2.07-1.98 (m, 2H), 1.87-1.69 (m, 5H), 1.66-1.59 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 136.2, 133.9, 130.5, 128.5, 128.4, 64.4, 58.9, 58.3, 56.1, 56.0, 55.9, 53.6, 35.7, 35.3, 33.8, 31.1, 29.8, 27.5, 19.9; HR-MS (ESI) Calcd for $C_{28}H_{37}NaBrO_4Si$ $(M + Na)^+$ 567.1537, found 567.1553.

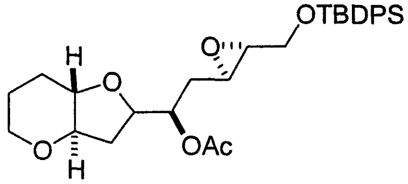


Acetic acid (2*R*,3*S*)-2-{(2*R*,3*R*)-3-[(2*R*,3*R*)-3-(*tert*-butyl-diphenyl-silanyloxymethyl)-oxiranylmethyl]-oxiranylmethyl}-tetrahydro-pyran-3-yl ester (73): To a solution of bromotrisepoxide **65** (6 mg, 11 μmol) in THF/H_2O (150 μL, 5:1) was added AgOTf (28 mg, 0.11 mmol) and the mixture stirred 1.25 h. The reaction was quenched with saturated $NaHCO_3$ (0.5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*.

The crude material was dissolved in CH_2Cl_2 (0.2 mL). To this solution was added Et_3N (2.3 μL, 0.017 mmol), Ac_2O (1.2 μL, 0.013 mmol), and DMAP (1 mg, 8 μmol). The reaction stirred overnight and the crude reaction mixture was directly purified by PTLC (50% EtOAc in hexane) to afford **73** (3 mg, 53%) and **74** (1 mg, 17%).

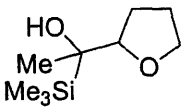
Alternatively, to a solution of bromotrisepoxide **65** (10 mg, 18 μmol) in THF/H_2O (0.3 mL, 5:1) was added AgOTf (50 mg, 0.18 mmol) and the mixture stirred 3 h. The reaction was quenched with saturated $NaHCO_3$ (1 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*.

The crude reaction mixture was dissolved in CH_2Cl_2 (0.2 mL). To this solution was added Et_3N (3.0 μL, 22 μmol), Ac_2O (2.0 μL, 21 μmol), and DMAP (1 mg, 8 μmol). The reaction stirred overnight and the crude reaction mixture was directly purified by PTLC (50% EtOAc in hexane) to afford **73** (1 mg, 11%) and **74** (5 mg, 53%): $R_f = 0.41$ (50% EtOAc in hexane); $[\alpha]^{25}_D = +12.9$ ($c = 2.3$, in $CHCl_3$); IR (thin film, NaCl) 2930, 2856, 1741, 1472, 1428, 1374, 1239, 1112, 1038, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 4.52 (dt, $J = 10.4$, 4.6 Hz, 1H), 3.94-3.90 (m, 1H), 3.84 (dd, $J = 11.9$, 3.4 Hz, 1H), 3.73 (dd, $J = 11.9$, 4.6 Hz, 1H), 3.44 (dt, $J = 9.2$, 3.4 Hz, 1H), 3.38 (dt, $J = 11.3$, 2.4 Hz, 1H), 3.02-2.93 (m, 3H), 2.86-2.83 (m, 1H), 2.21-2.15 (m, 1H), 2.04 (s, 3H), 1.80-1.63 (m, 6H), 1.50-1.42 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 136.3, 136.2, 133.9, 130.5, 128.4, 78.2, 72.6, 68.4, 64.4, 58.9, 56.7, 56.0, 53.6, 35.7, 35.4, 30.4, 27.4, 25.9, 21.9, 19.9; HR-MS (ESI) Calcd for $C_{30}H_{40}NaO_6Si$ $(M + Na)^+$ 547.2486, found 547.2495.

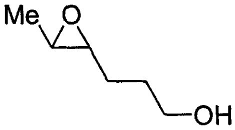


Acetic acid (*R*)-2-[(2*R*,3*R*)-3-(*tert*-butyl-diphenyl-silanyloxymethyl)-oxiranyl]-1-(3a*R*,7a*S*)-hexahydro-furo[3,2-*b*]pyran-2-yl-ethyl ester (74): $R_f = 0.43$ (50% EtOAc in hexane); $[\alpha]^{25}_D = + 17.4$ ($c = 2.3$, in $CHCl_3$); IR (NaCl): 2932, 2857, 1741, 1472, 1428, 1371, 1237, 1113, 1042, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.45-7.38 (m, 6H), 5.07 (dt, $J = 8.5$, 4.3 Hz, 1H), 4.24 (dt, $J = 5.5$ 4.0 Hz, 1H), 4.01-3.97 (m, 1H), 3.79 (dd, $J = 11.9$, 3.4 Hz, 1H), 3.68 (dd, $J = 11.6$, 4.6 Hz, 1H), 3.45 (dt, $J = 11.9$, 2.7 Hz, 1H), 3.20-3.15 (ddd, $J = 12.5$, 8.8, 4.0 Hz, 1H), 3.09-3.03 (m, 1H), 2.94-2.87 (m, 2H), 2.23-2.20 (m, 1H), 2.03 (s, 3H), 2.06-1.45 (m, 7H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 136.3, 136.2, 133.9, 133.8, 130.5, 128.5, 128.4, 80.9, 79.5, 77.8, 73.4, 69.6, 64.5, 59.3, 53.3, 33.4, 31.6, 30.0, 27.4, 25.1, 21.8, 19.9; HR-MS (ESI) Calcd for $C_{30}H_{40}NaO_6Si$ $(M + Na)^+$ 547.2486, found 547.2494.

Representative Procedure for the Base-Promoted Cyclization of 14e: To a solution of epoxide **14e** (30 mg, 0.1 mmol) in MeOH (1.5 mL) was added Cs_2CO_3 (33 mg, 1.0 mmol). The reaction mixture was heated to 50 °C for 20 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford a mixture of pyran **15e** and furan **16e** (29 mg, 97%, 1.7:1 **15e**:**16e**).



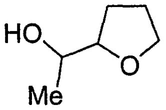
1-(Tetrahydro-furan-2-yl)-1-trimethylsilanyl ethanol (16e): R_f = 0.45 (20% EtOAc in hexane); IR (NaCl) 3469, 2957, 2863, 1461, 1290, 1247, 1060, 839, 752, 623 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (m, 2H), 3.74 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 1.90-1.70 (m, 4H), 1.09 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.3, 68.9, 67.6, 26.7, 25.2, 20.1, -2.6; HR-MS (ESI) Calcd for $C_9H_{20}NaO_2Si$ (M + Na)$^+$ 211.1125, found 211.1120.



3-(3-Methyl-oxiranyl)-propan-1-ol (14a): Synthesized according to a reported procedure.[88]

Representative Procedure for the Base-Promoted Cyclization of 14a.

To a solution of **14a** (10 mg, 0.1 mmol) in MeOH (0.5 mL) was added Cs_2CO_3 (20 mg, 0.6 mmol). The resulting solution was heated to 50 °C and stirred 20 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. ^{1}H NMR of the unpurified reaction mixture showed a mixture of furan **15a** and pyran **16a** (6 mg, 60%, 5:1 **15a**:**16a**).



1-(Tetrahydro-furan-2-yl)-ethanol (15a): Spectral data were identical to that reported.[20, 89]

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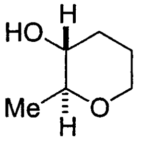
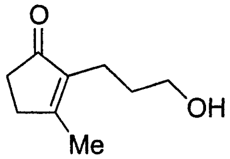
[88] Hansen, K. B. Ph.D. Thesis, Harvard University, Cambridge, MA, 1998.



2-Methyl-tetrahydro-pyran-3-ol (16a): Spectral data were identical to that reported.[20, 90]

Representative Procedure for the Base-Promoted Cyclization of 46:

To bisepoxide **46** (20 mg, 0.1 mmol) was added a 1.92 M solution of Cs_2CO_3 in MeOH (1.0 mL). The resulting solution was heated to 55-60 °C for 5 days. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (**31**: 2 mg, 14%).



2-(3-Hydroxy-propyl)-3-methyl-cyclopent-2-enone (76): R_f = 0.16 (80% EtOAc in hexane); IR (thin film, NaCl) 3421, 2920, 1694, 1639, 1441, 1386, 1176, 1061 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.51 (t, J = 6.1 Hz, 2H), 2.56-2.53 (m, 2H), 2.44-2.41 (m, 2H), 2.33 (t, J = 7.0 Hz, 2H), 2.09 (s, 3H), 1.66-1.60 (m, 2H); ^{13}C NMR (125 MHz) δ 196.3, 172.9, 140.7, 61.5, 34.9, 32.5, 31.9, 18.9, 17.9; HR-MS (ESI) Calcd for $C_9H_{14}NaO_2$ $(M + Na)^+$ 177.0886, found 177.0885.

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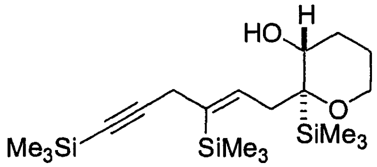
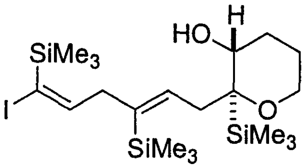
[89] Taillez, B.; Bertrand, M. P.; Surzur, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1983**, 547-554.

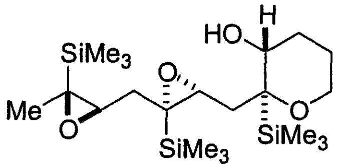
[90] Bartner, P.; Boxler, D. L.; Brambilla, R.; Mallams, A. K.; Morton, J. B.; Reichert, P.; Sancilio, F. D.; Surprenant, H.; Tomalesky, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1600-1624.



(2*R*,3*R*)-2-((*Z*)-3,6-Bis-trimethylsilanyl-hex-2-en-5-ynyl)-2-trimethylsilanyl-tetrahydro-pyran-3-ol (77): To a solution of 1-trimethylsilyl-1-propyne (0.9 mL, 6.2 mmol) in THF (10.5 mL) at –78 °C was added a 2.5 M solution of *n*-BuLi in hexane (2.6 mL) and TMEDA (1.0 mL, 6.5 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred to a slurry of CuI (1.3 g, 7.0 mmol) and DMAP (760 mg, 6.3 mmol) in THF (8.5 mL) at –78 °C. The solution was warmed to –20 °C, alkenyl iodide **32** (570 mg, 1.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **77** (220 mg, 42%): R_f = 0.49 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = -9.3 (*c* = 8.6, in $CHCl_3$); IR (thin film, NaCl) 3463, 2955, 2898, 2173, 1610, 1408, 1249, 1091, 839, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.49 (t, *J* = 6.4 Hz, 1H), 3.78-3.65 (m, 2H), 3.57-3.48 (m, 1H), 3.04 (s, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.01-1.91 (m, 1H), 1.85 (d, J = 7.0 Hz, 1H), 1.87-1.77 (m, 1H), 1.76-1.65 (m, 1H), 1.60-1.49 (m, 1H), 0.21 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 134.8, 106.0, 88.2, 76.0, 70.9, 62.2, 35.6, 29.0, 27.9, 23.1, 0.5, 0.3, 0.1; HR-MS (ESI) Calcd for $C_{20}H_{40}NaO_2Si_3$ $(M + Na)^+$ 419.2234, found 419.2241.

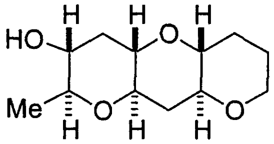


(2*R*,3*R*)-2-((2*Z*,5*E*)-6-Iodo-3,6-bis-trimethylsilanyl-hexa-2,5-dienyl)-2-trimethylsilanyl-tetrahydro-pyran-3-ol (78): To a solution of enyne **77** (0.5 g, 1.2 mmol) in Et_2O (5.0 mL) was added a 1 M solution of DIBAL in hexane (2.9 mL). The resulting solution was heated 24 h at reflux then cooled to –78 °C and diluted with Et_2O (0.5 mL). A solution of I_2 (1.2 g, 4.8 mmol) in Et_2O (1.0 mL) was added. After stirring 2 h at –78 °C the reaction was warmed to 0 °C and stirred 1 h. The reaction was quenched by pouring into 1 M HCl (5 mL) and ice (2 g). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to yield alkenyl iodide **78** (0.3 g, 51%, >95% *E*): $R_f = 0.33$ (10% EtOAc in hexane); $[\alpha]^{25}_{D} = -2.3$ ($c = 21.3$, in $CHCl_3$); IR (thin film, NaCl) 3463, 2953, 2898, 2855, 1725, 1407, 1249, 1092, 839, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, $J = 7.9$ Hz, 1H), 6.13 (t, $J = 6.4$ Hz, 1H), 3.72-3.63 (m, 2H), 3.50 (ddd, $J = 11.0, 6.7, 3.7$ Hz, 1H), 2.83 (d, $J = 7.6$ Hz, 2H), 2.62-2.50 (m, 2H), 1.95-1.88 (m, 2H), 1.82-1.74 (m, 1H), 1.72-1.64 (m, 1H), 1.54-1.46 (m, 1H), 0.25 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 139.4, 138.1, 107.1, 75.8, 70.6, 62.2, 42.4, 35.6, 27.9, 22.9, 1.3, 0.3, 0.0; HR-MS (ESI) Calcd for $C_{20}H_{41}INaO_2Si_3$ $(M + Na)^+$ 547.1351, found 547.1349.



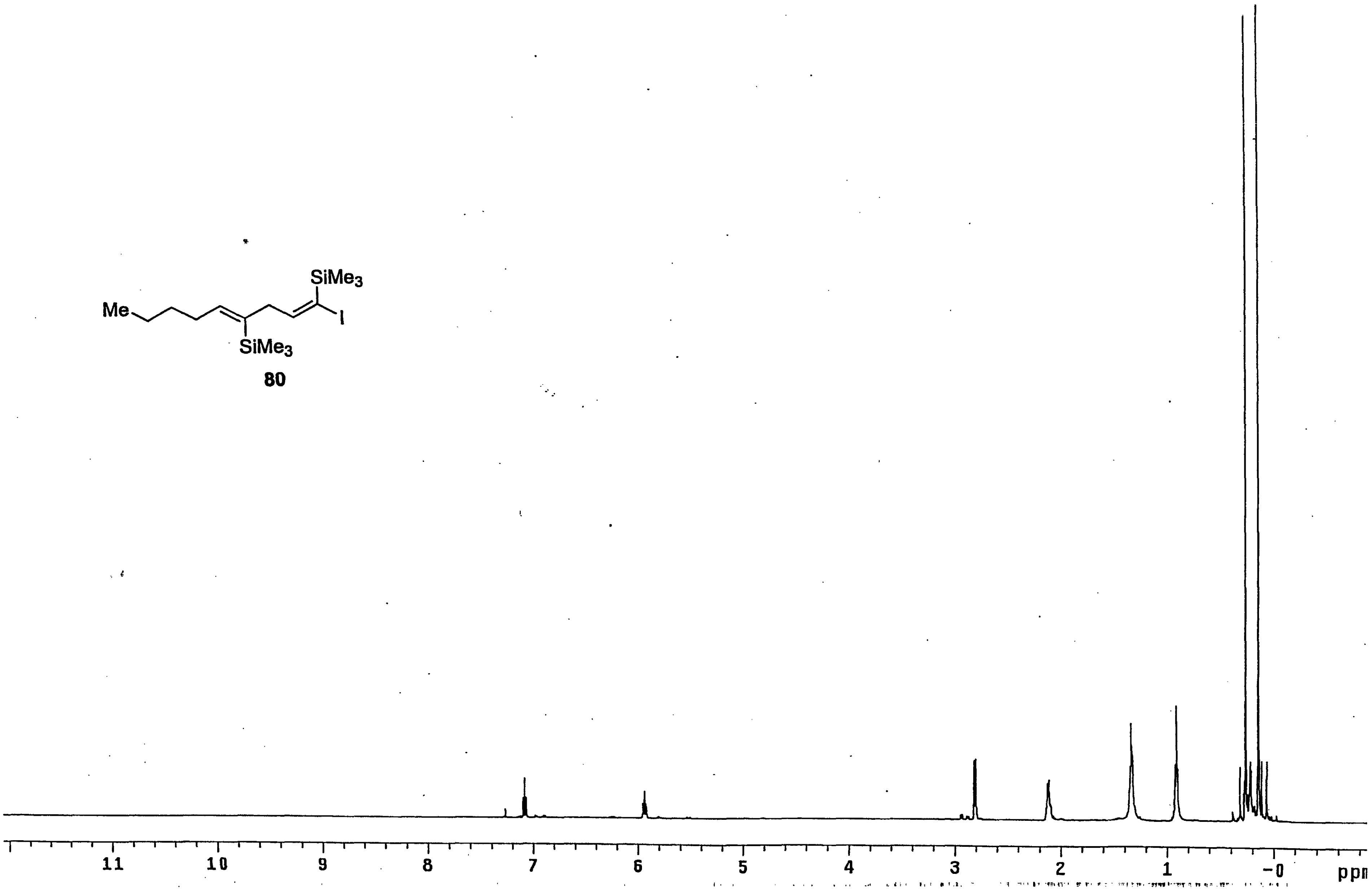
(2*R*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl]-2-trimethylsilanyl-tetrahydro-pyran-3-ol (79): To a slurry of CuCN (0.12 g, 1.4 mmol) in Et_2O (3.0 mL) at 0 °C was added a 1.6 M solution of MeLi in Et_2O (1.7 mL). After 15 min a solution of alkenyl iodide **78** (0.32 g, 0.6 mmol) in Et_2O (1.0 mL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (10% EtOAc in hexane) to yield the diene ($R_f = 0.26$, 10% EtOAc in hexane).

To a solution of the crude diene (40 mg, 97 μmol) was added CH_3CN/DMM (3.1 mL, 1:2 v:v), a 0.05 M solution of $Na_2B_4O_7{\cdot}10\ H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (2.1 mL), *n*-$BuNHSO_4$ (7 mg, 21 μmol), and chiral ketone **A** (50 mg, 2.0 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone® (0.20 g, 0.33 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (1.4 mL) and a 0.89 M solution of K_2CO_3 (1.4 mL). After the Oxone® and K_2CO_3 solutions had been added, the resulting mixture was diluted with water and extracted with EtOAc (4 × 10 mL). The combined organic layers where washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH_2Cl_2 (350 μL) and to this was added $NaHCO_3$ (29 mg, 340 μmol), and *m*-CPBA (12 mg, 68 μmol) and the reaction stirred 5 min. The reaction was quenched with 1 M NaOH and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to afford bisepoxide epoxide **79** (8 mg, 23% over 2 steps, dr 8:1): $R_f = 0.55$ (30% EtOAc in hexane); $[\alpha]^{25}_D =$ +17.4 ($c = 2.3$, in $CHCl_3$); IR (thin film, NaCl) 3442, 2955, 2853, 2360, 1250, 1091, 838, 755 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.08-4.02 (m, 1H); 3.66 (dt, *J* = 11.4, 3.5 Hz, 1H), 3.42 (td, *J* = 11.4, 2.8 Hz, 1H), 3.17 (dd, *J* = 8.7, 1.3 Hz, 1H), 2.66 (d, *J* = 7.1 Hz, 1H), 2.65 (d, *J* = 7.1 Hz, 1H), 2.18-2.06 (m, 2H), 1.98-1.90 (m, 2H), 1.79-1.69 (m, 2H), 1.68-1.60 (m, 2H), 1.11 (s, 3H), 0.10 (s, 9H), 0.08 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 76.8, 72.0, 64.4, 62.8, 60.6, 55.5, 38.5, 36.5, 29.6, 25.6, 23.3, 0.9, -0.4, -1.1; HR-MS (ESI) Calcd for $C_{21}H_{44}NaO_4Si_3$ (M + Na)$^+$ 467.2445, found 467.2443.



(2*S*,3*R*,4a*S*,8a*S*,9a*R*,10a*R*)-2-Methyl-decahydro-1,8,10-trioxa-anthracen-3-ol (36): To bisepoxide **79** (4 mg, 9 μmol) was added a 1.92 M solution of Cs_2CO_3 in MeOH (210 μL). The resulting solution was heated to 55-60 °C for 3 days. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (50-70% EtOAc in hexane) to afford tristetrahydropyran **36** (1 mg, 39%). Spectral data were identical to the previously prepared material (Experimental Section, Chapter1).

Chapter 2: Spectra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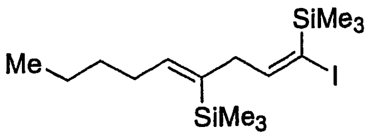
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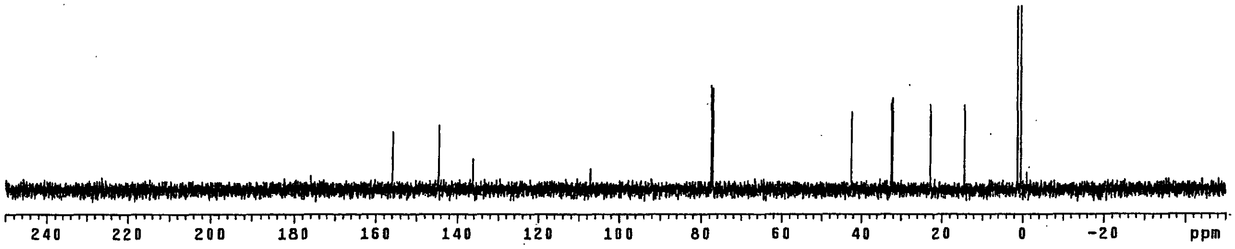
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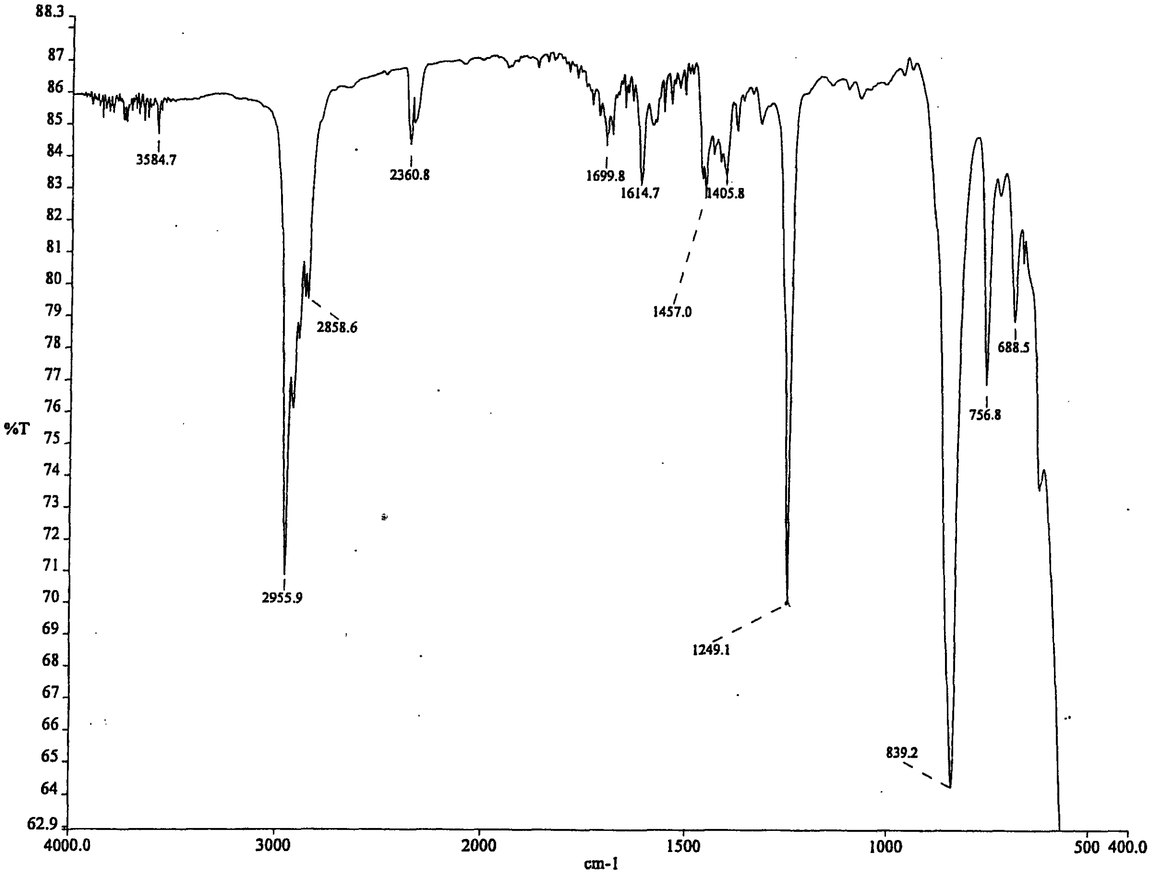
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1405.8
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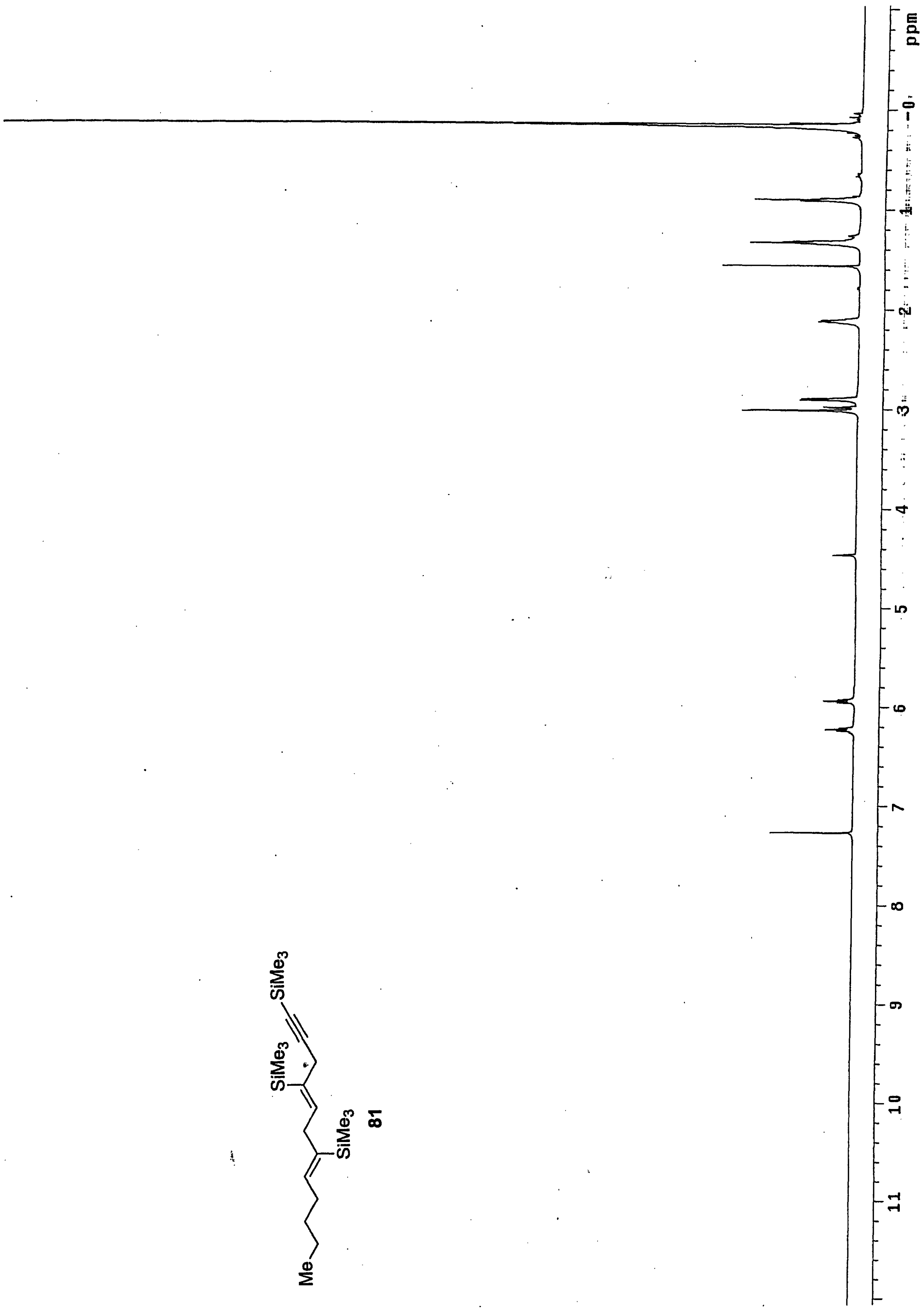

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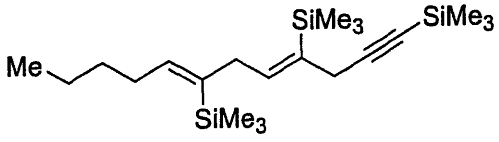
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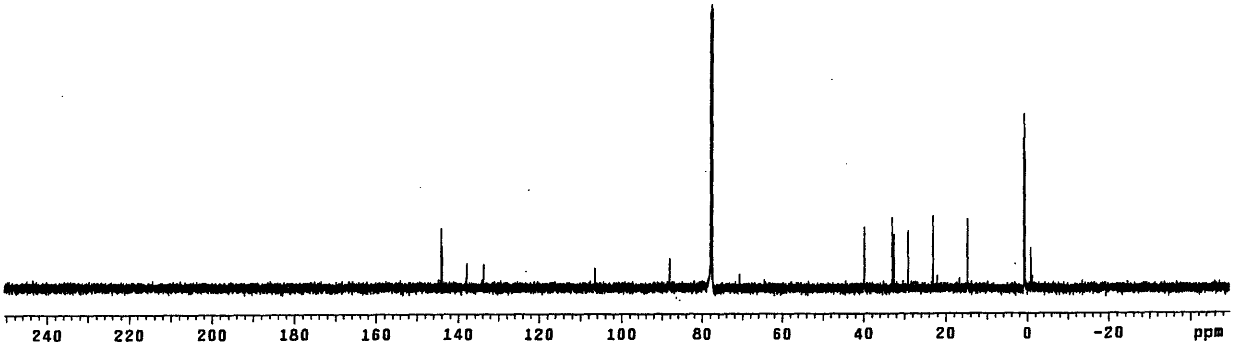
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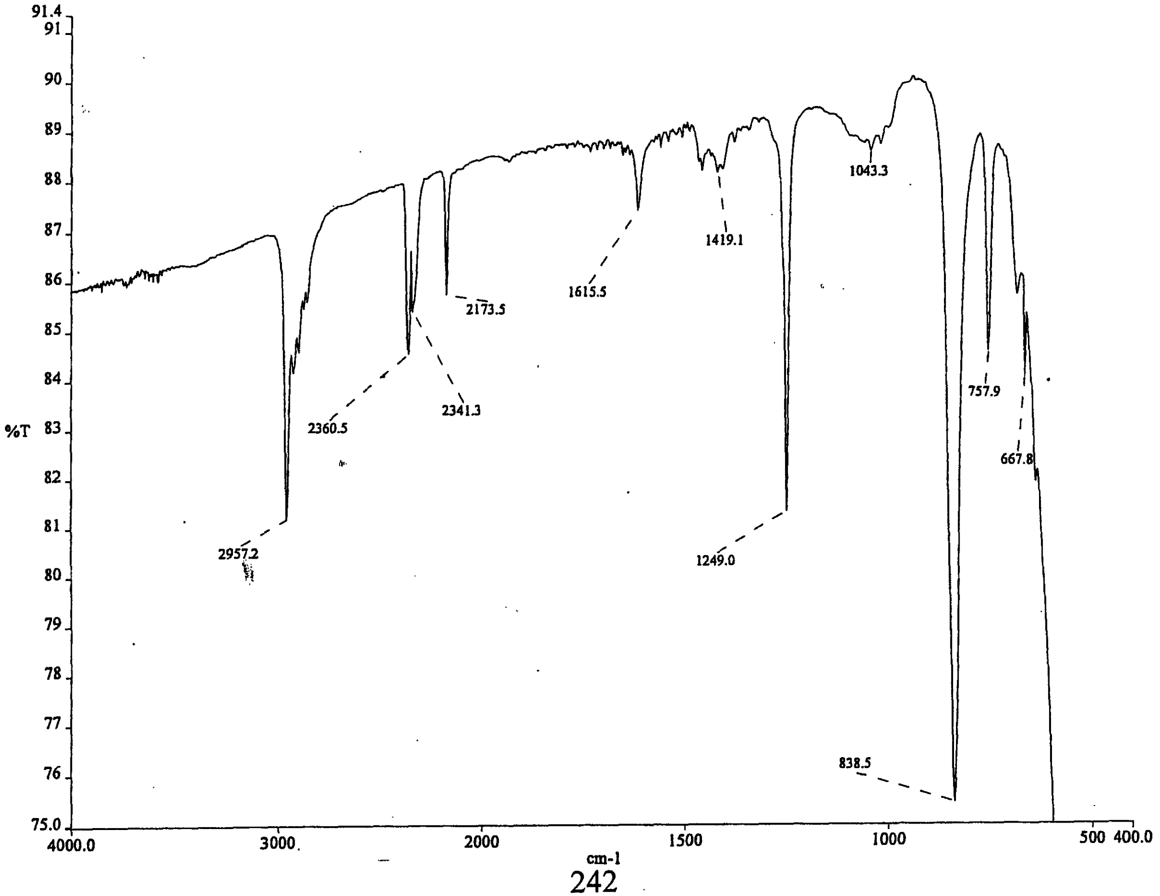
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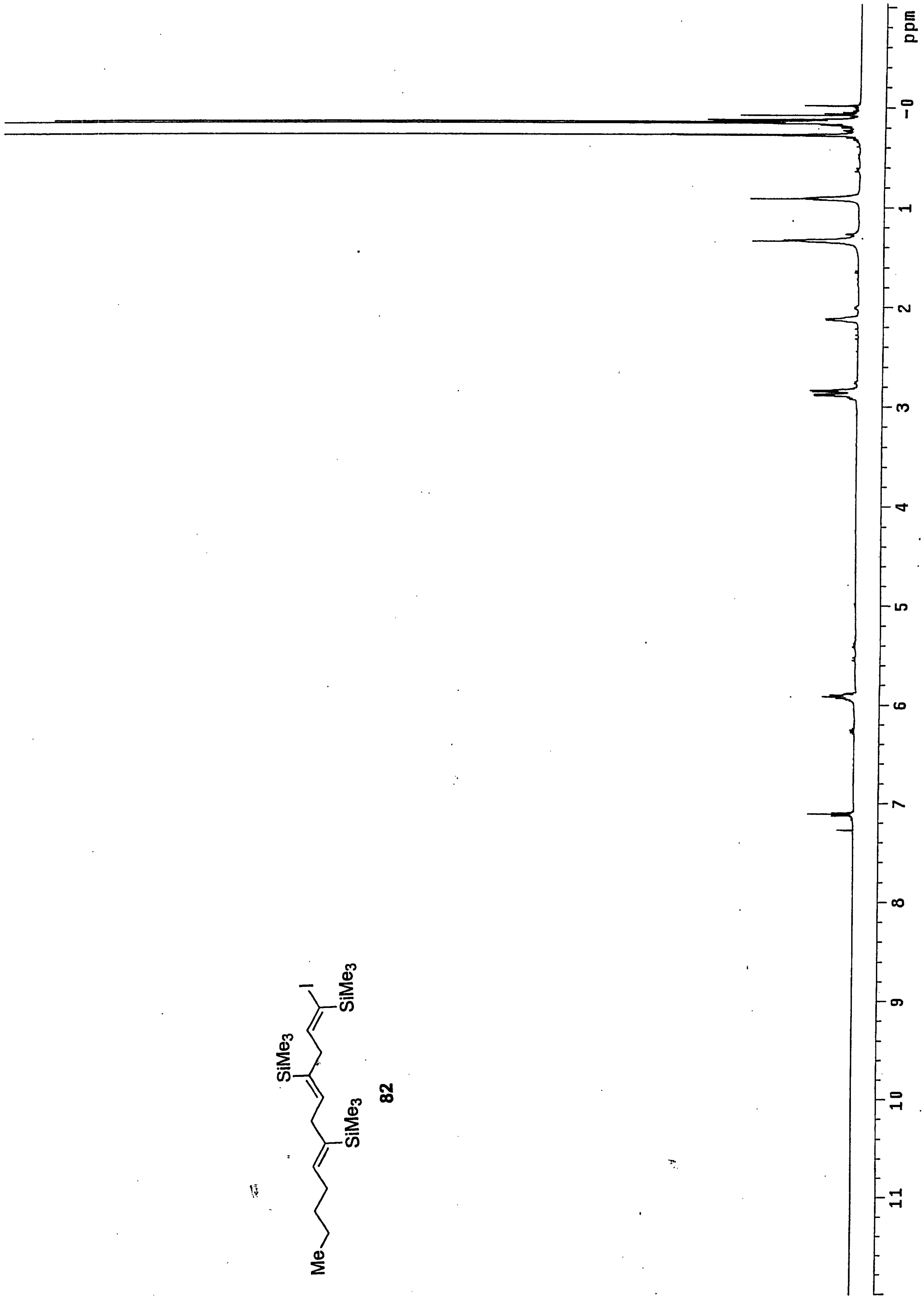

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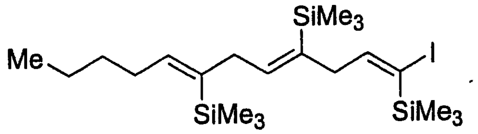
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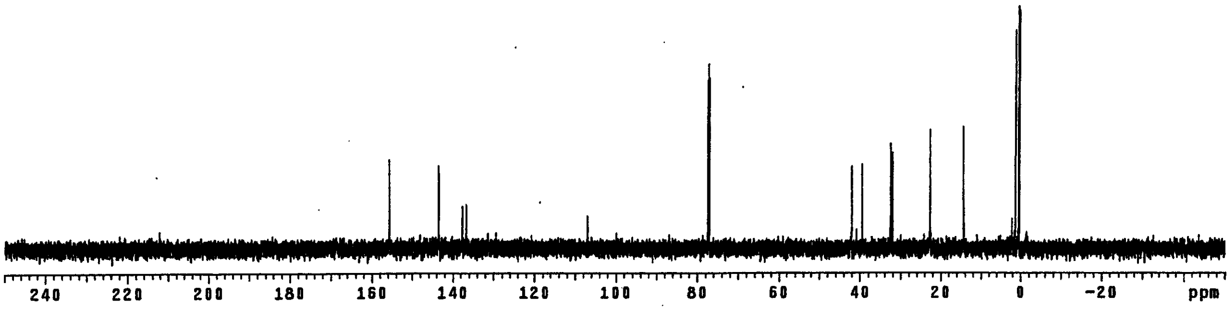
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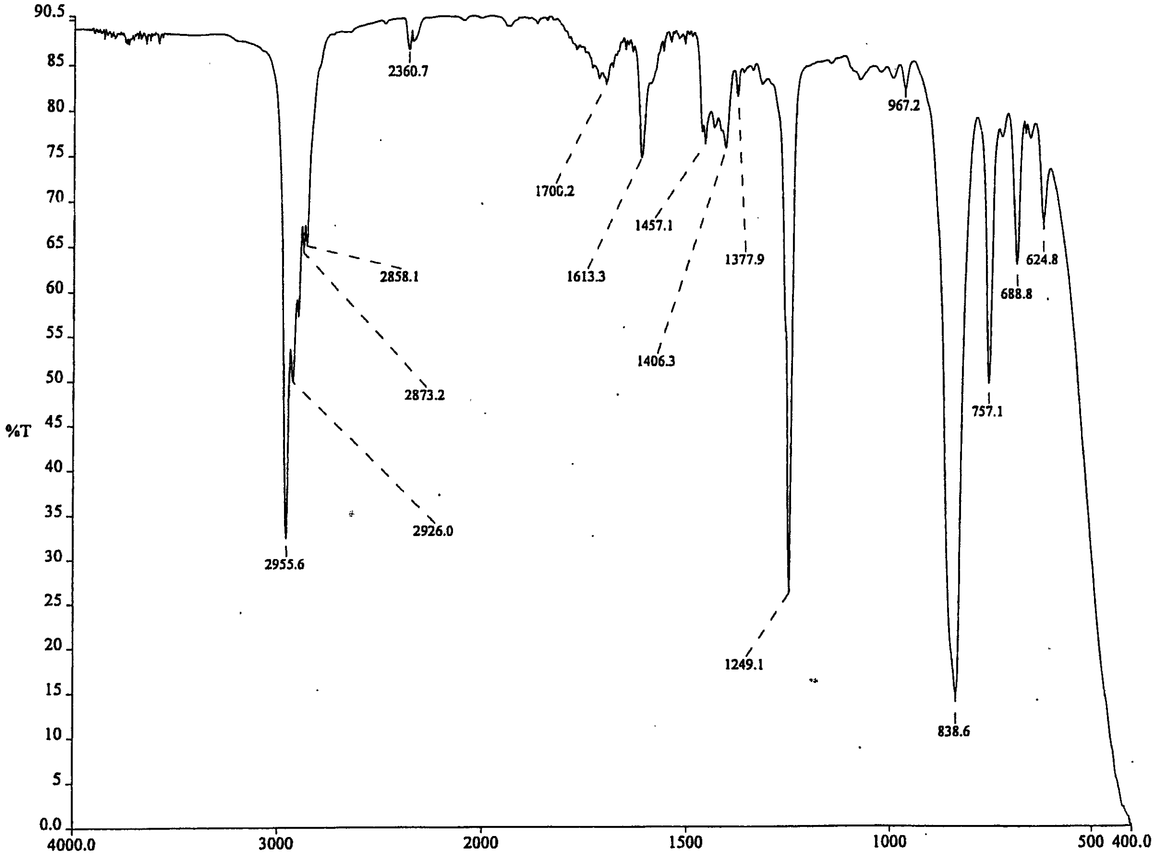
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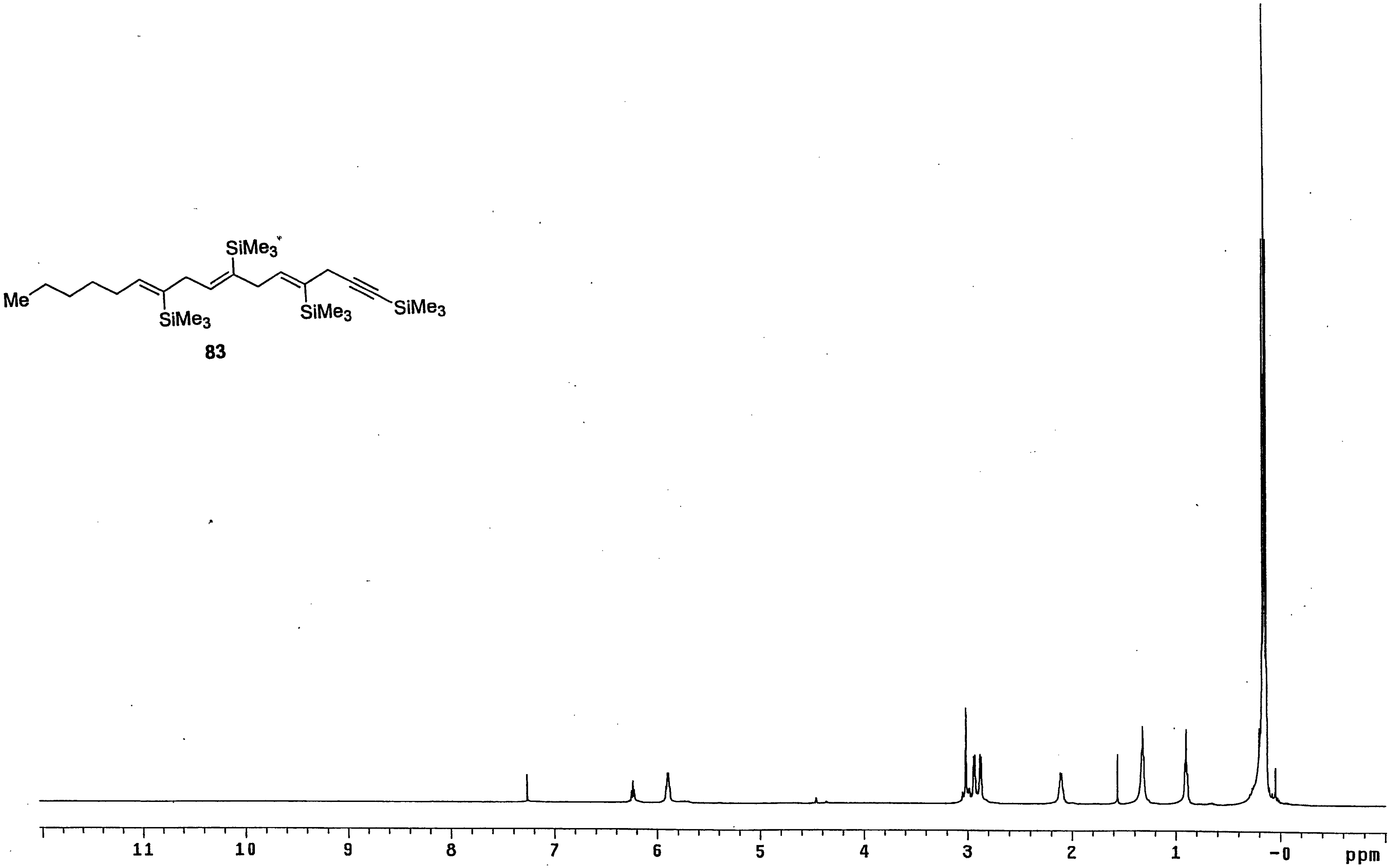
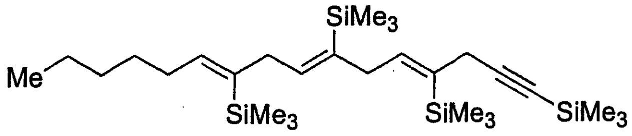
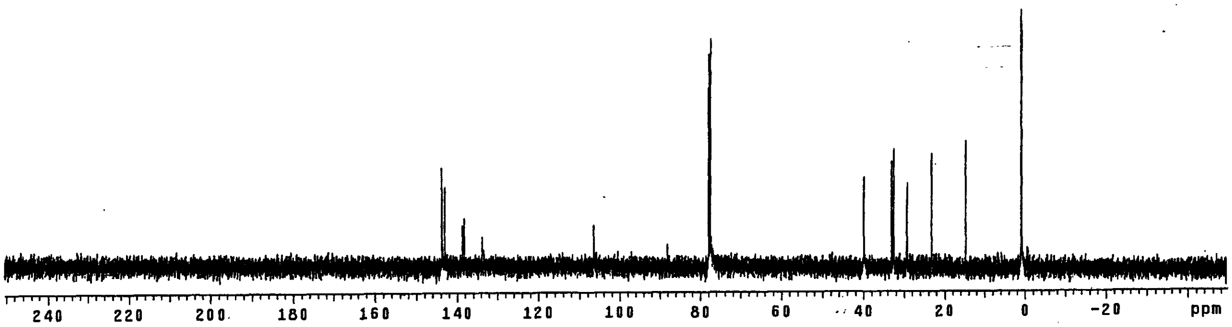
2873.2
2926.0
2955.6
1249.1
838.6
757.1
688.8
624.8

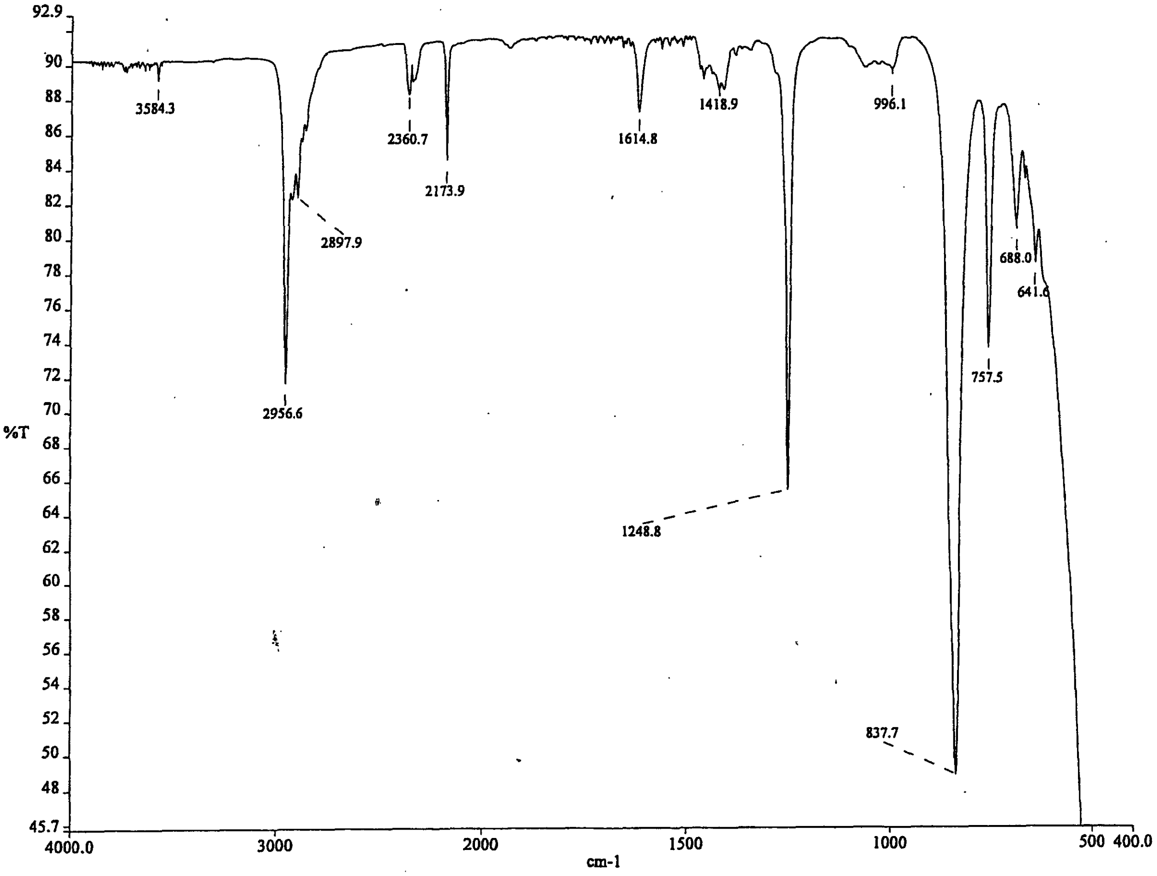


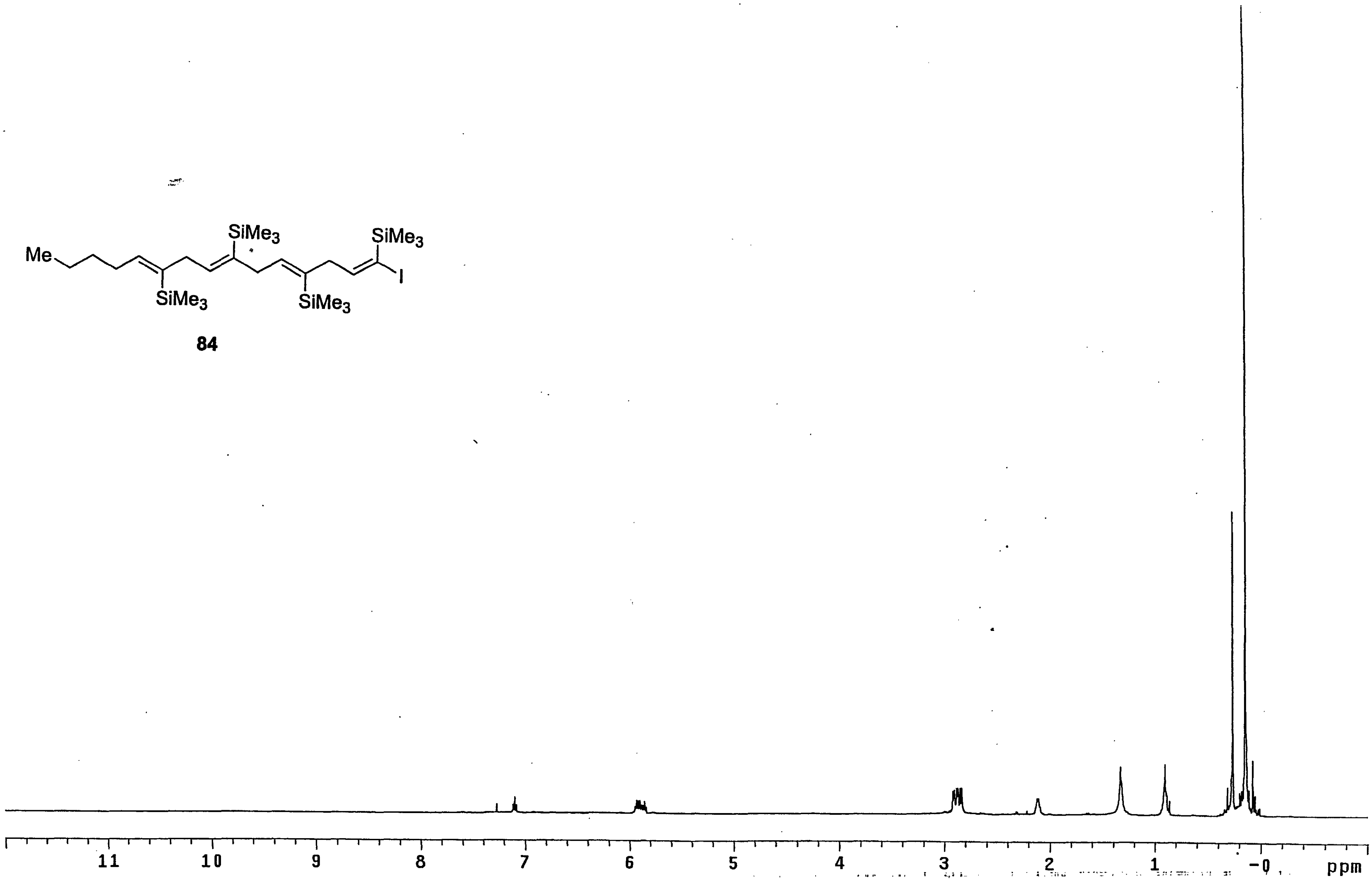
83


SiMe3
Me
SiMe3
SiMe3
SiMe3

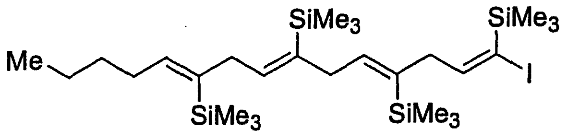
83


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

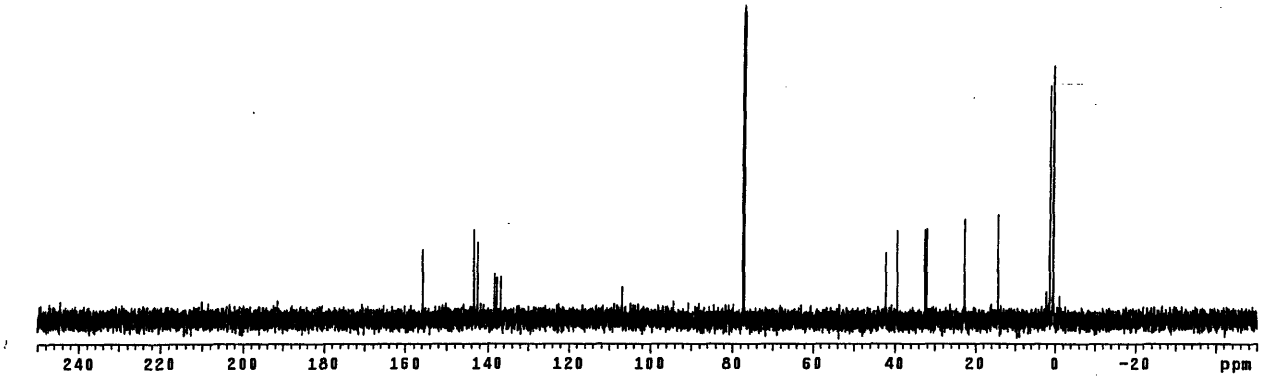

92.9
90
88
86
84
82
80
78
76
74
72
70
%T
68
66
64
62
60
58
56
54
52
50
48
45.7
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3584.3
2956.6
2897.9
2360.7
2173.9
1614.8
1418.9
1248.8
996.1
837.7
757.5
688.0
641.6

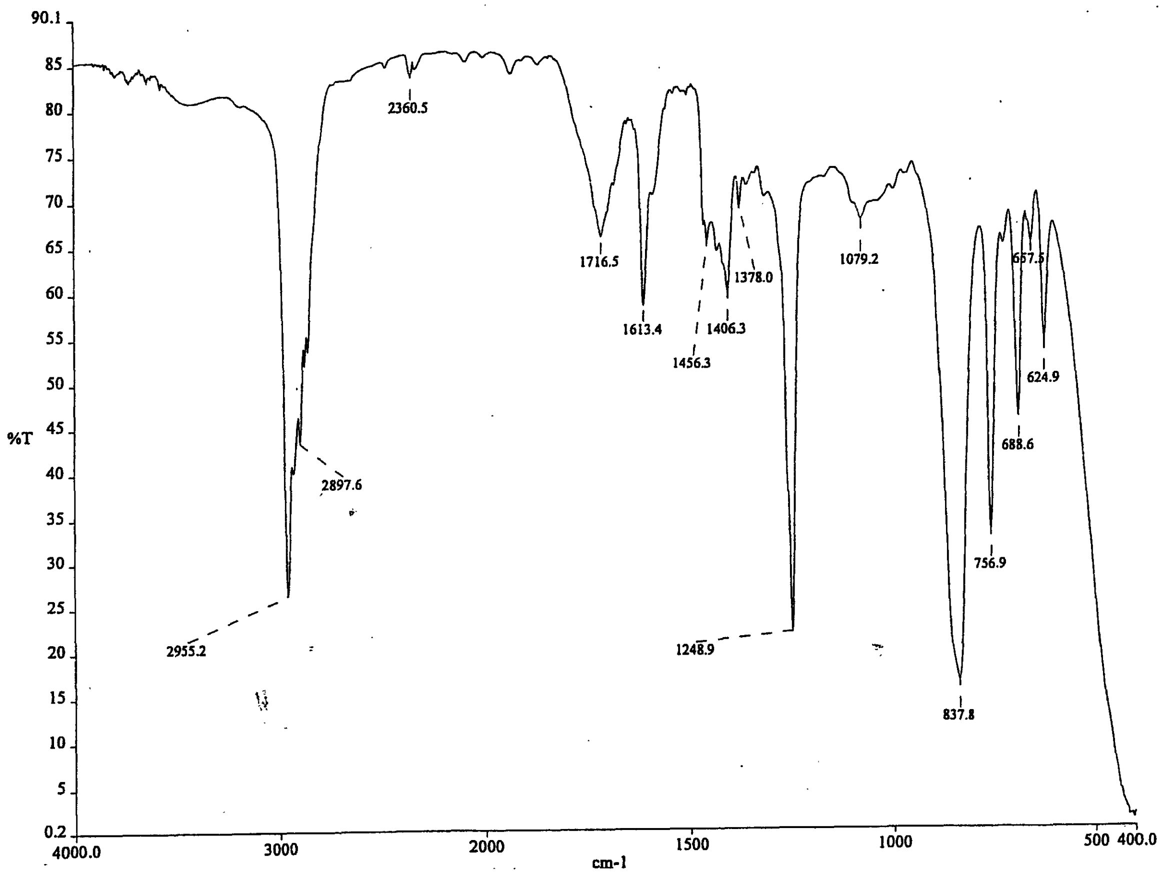


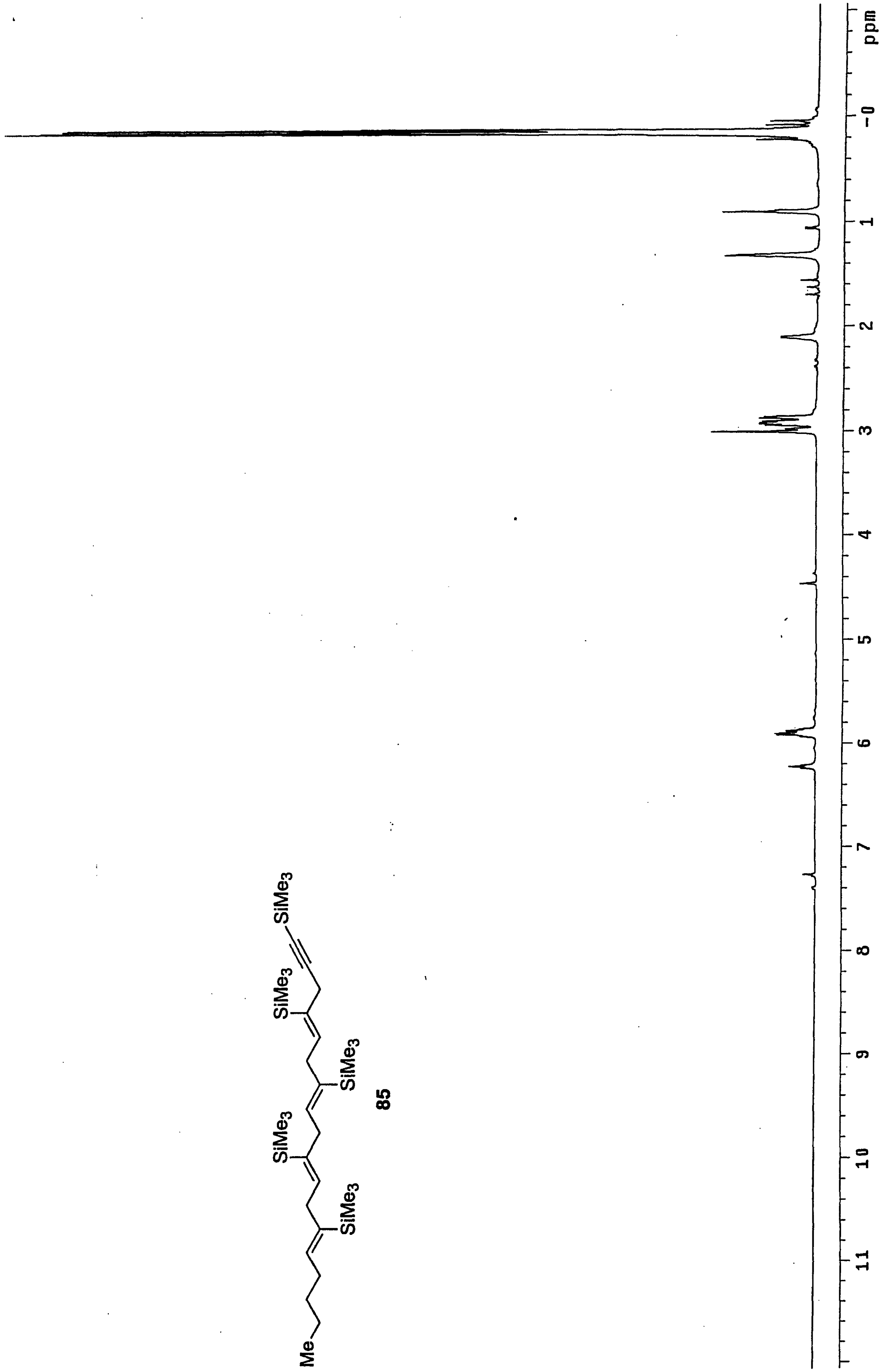
84


SiMe3
SiMe3
Me
I
SiMe3
SiMe3

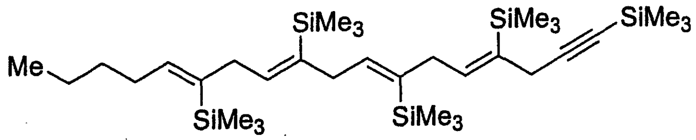
84


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

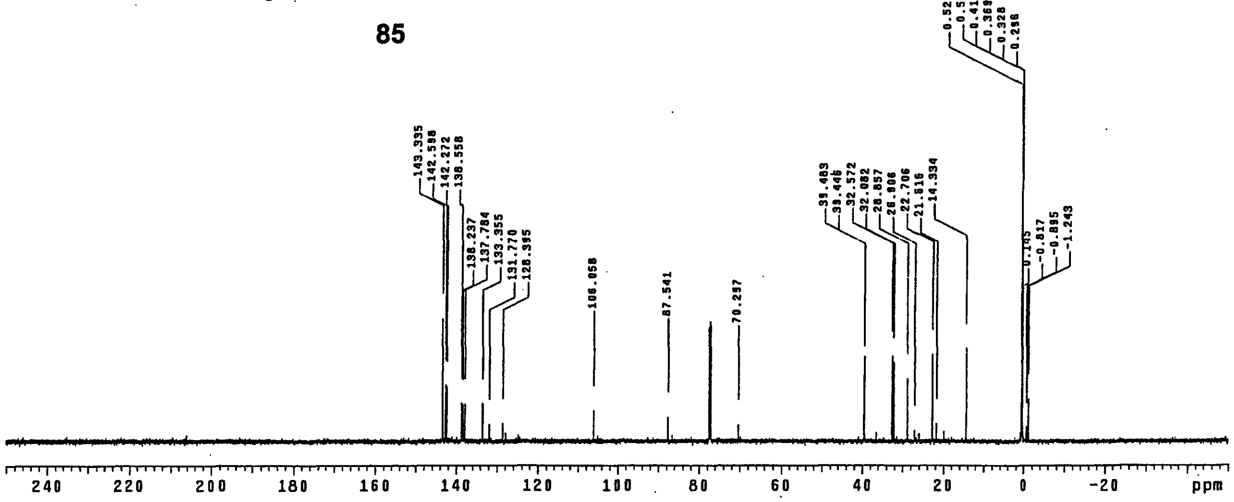

90.1
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.2
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2360.5
1716.5
1613.4
1456.3
1406.3
1378.0
1079.2
657.5
624.9
688.6
2897.6
756.9
2955.2
1248.9
837.8

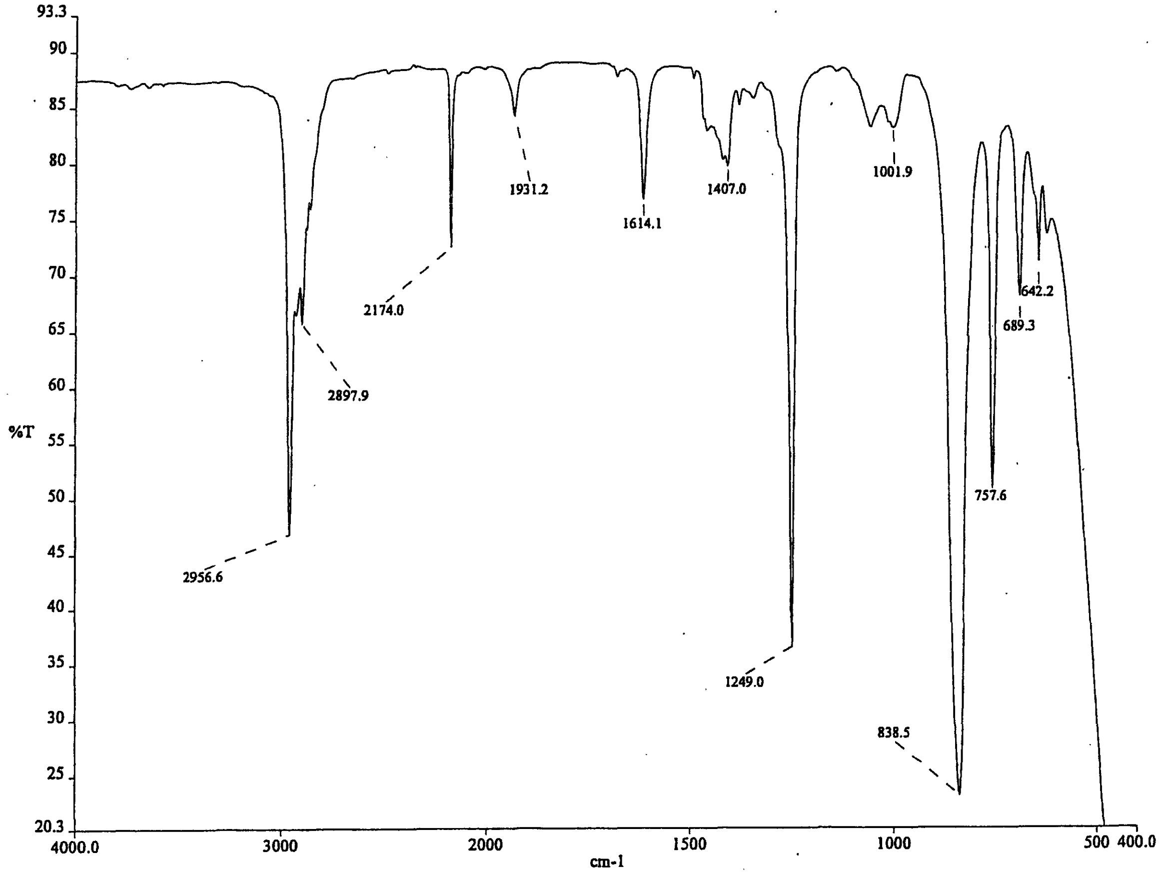


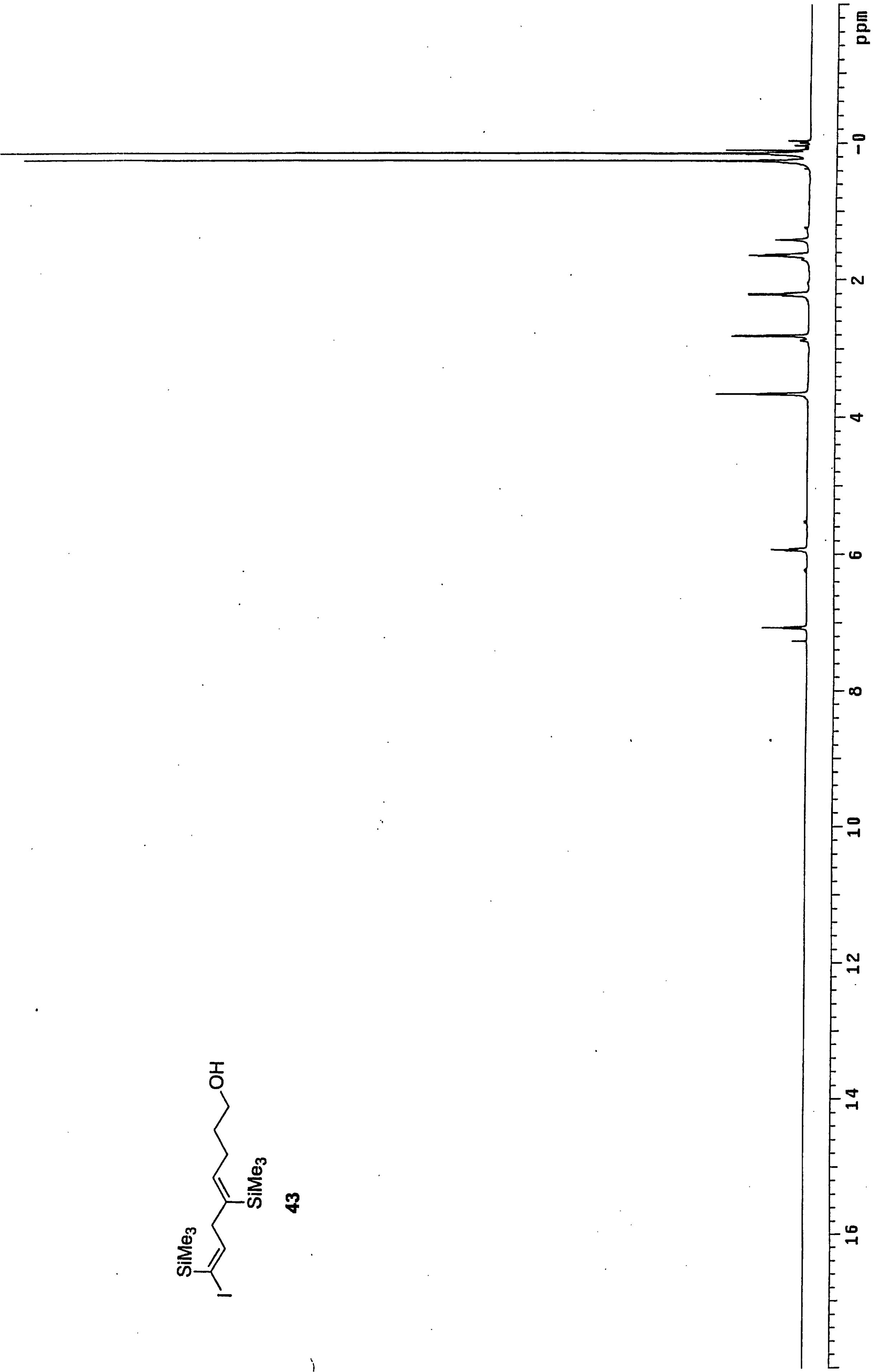
85


Me
SiMe3
SiMe3
SiMe3
SiMe3
SiMe3

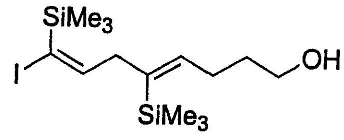
85


0.521
0.511
0.411
0.369
0.328
0.296
143.335
142.598
142.272
138.558
138.237
137.784
133.955
131.770
128.395
106.058
87.541
70.297
39.483
39.446
32.572
32.082
28.857
26.906
22.706
21.616
14.334
0.145
-0.817
-0.885
-1.243
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

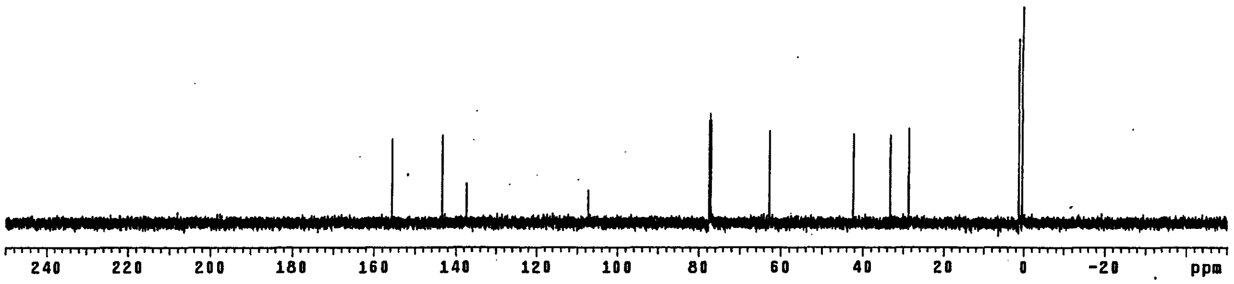

93.3
90
85
80
75
70
65
60
%T
55
50
45
40
35
30
25
20.3
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2956.6
2897.9
2174.0
1931.2
1614.1
1407.0
1249.0
1001.9
838.5
757.6
689.3
642.2

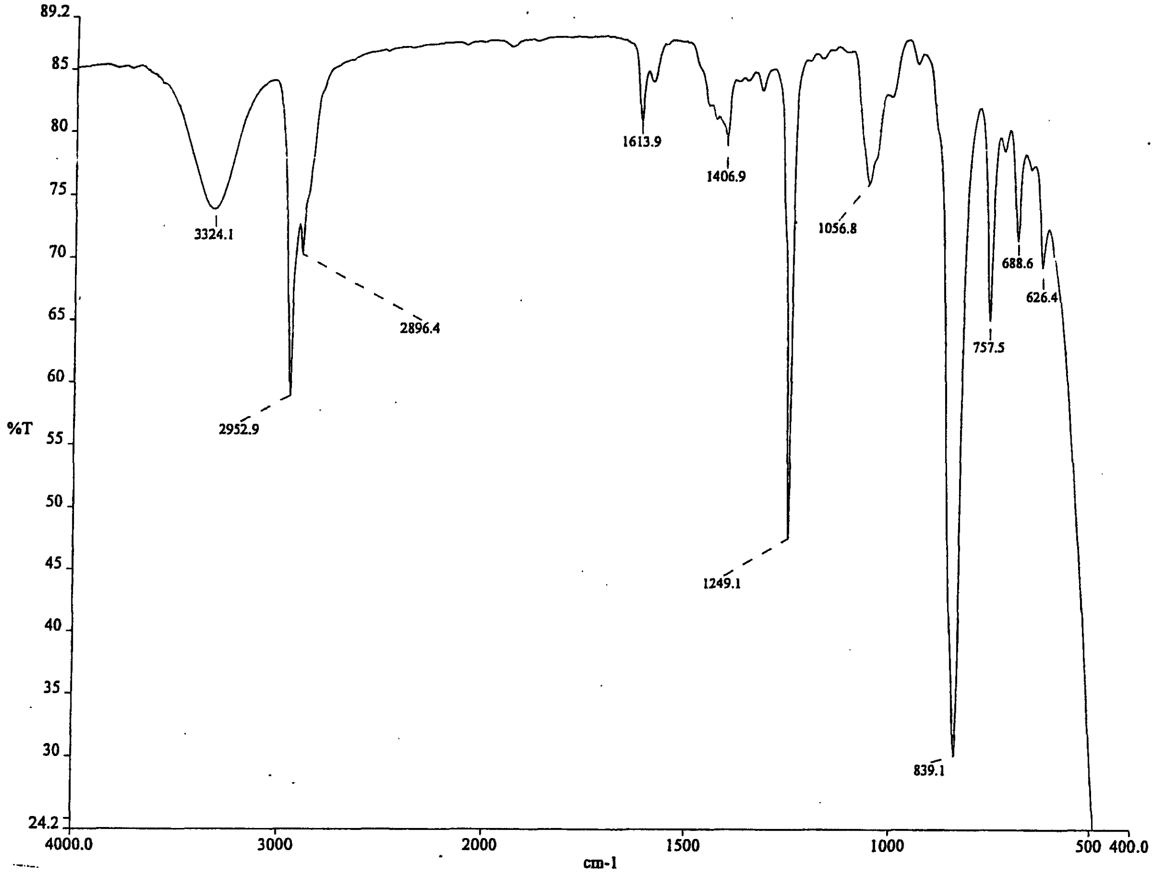


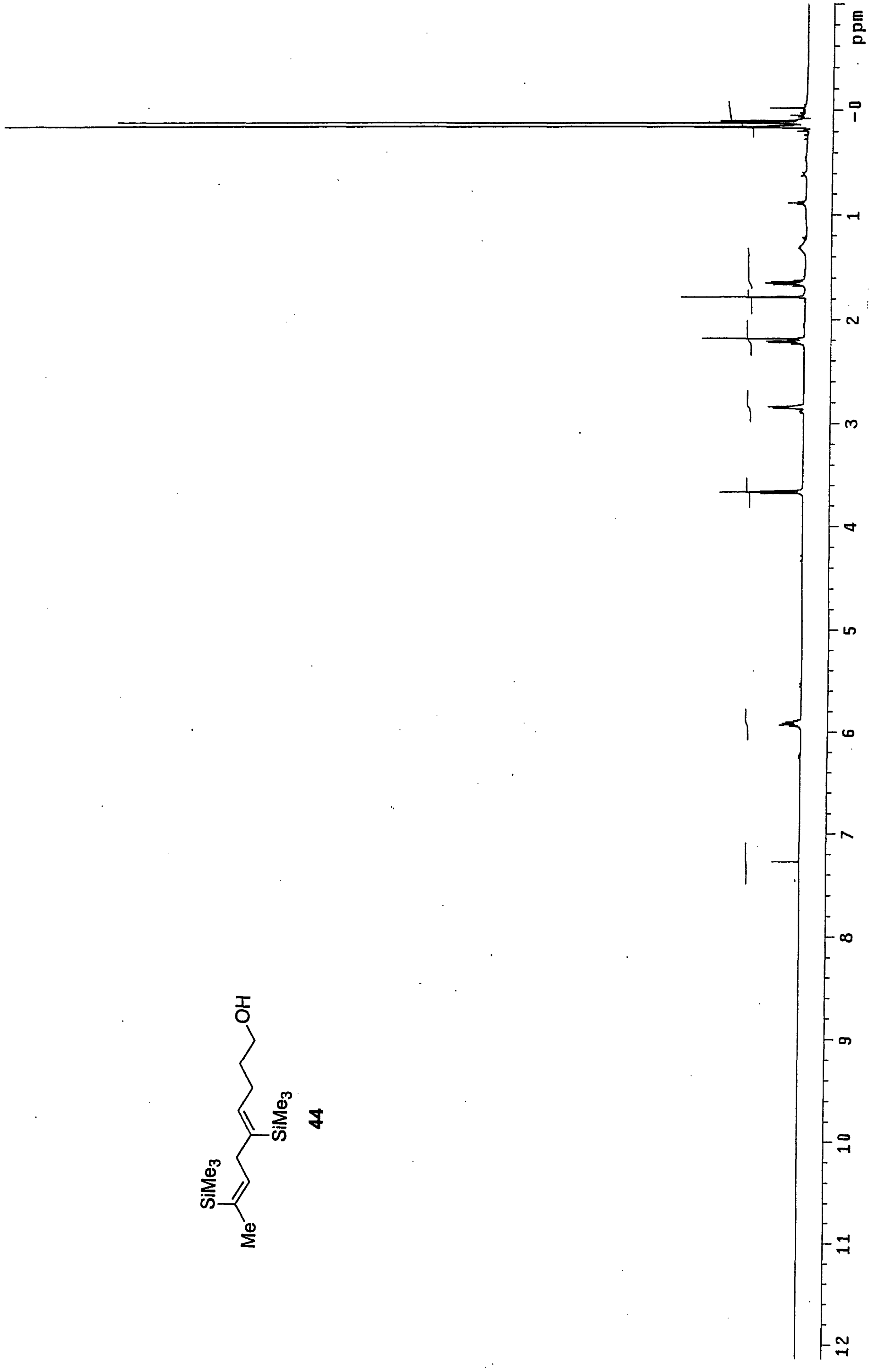
43


SiMe3
I
SiMe3
OH

43


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

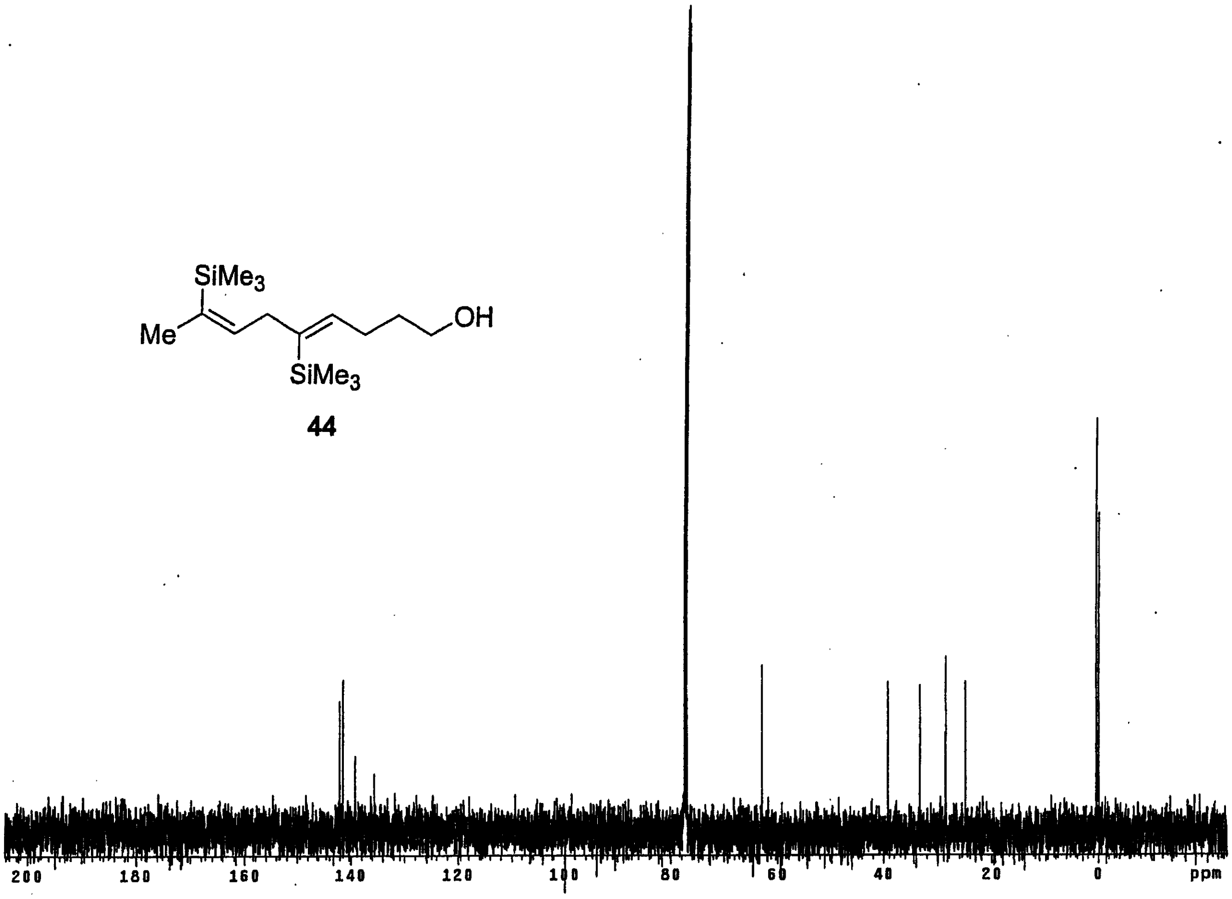

89.2
85
80
75
70
65
60
55
50
45
40
35
30
24.2
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3324.1
2952.9
2896.4
1613.9
1406.9
1249.1
1056.8
839.1
757.5
688.6
626.4

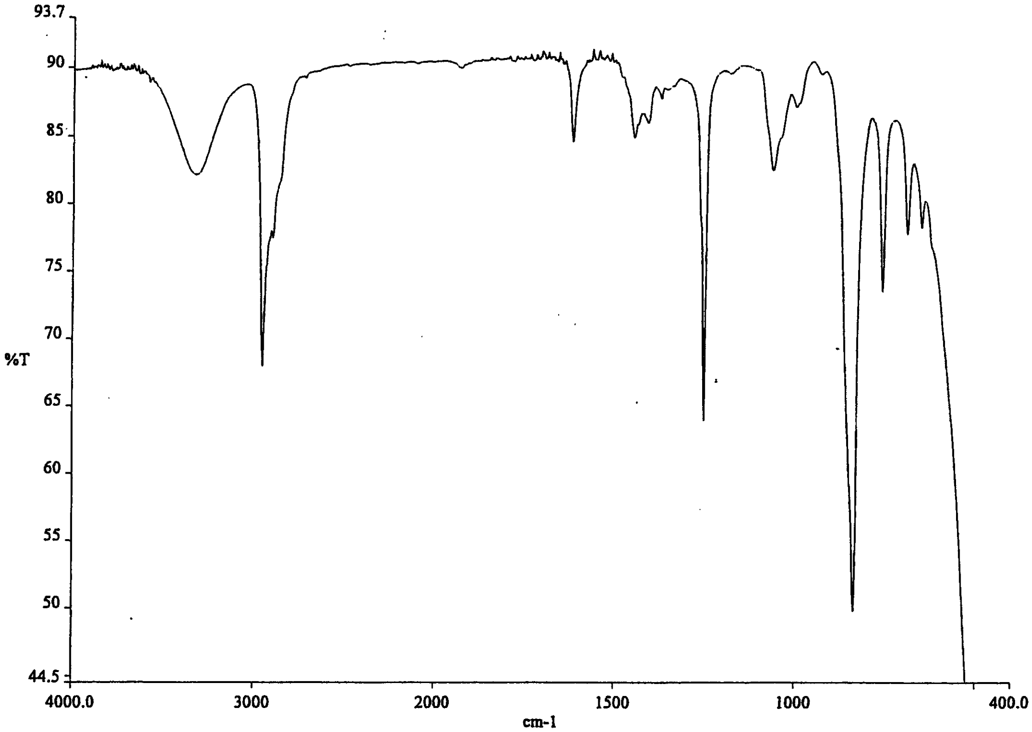


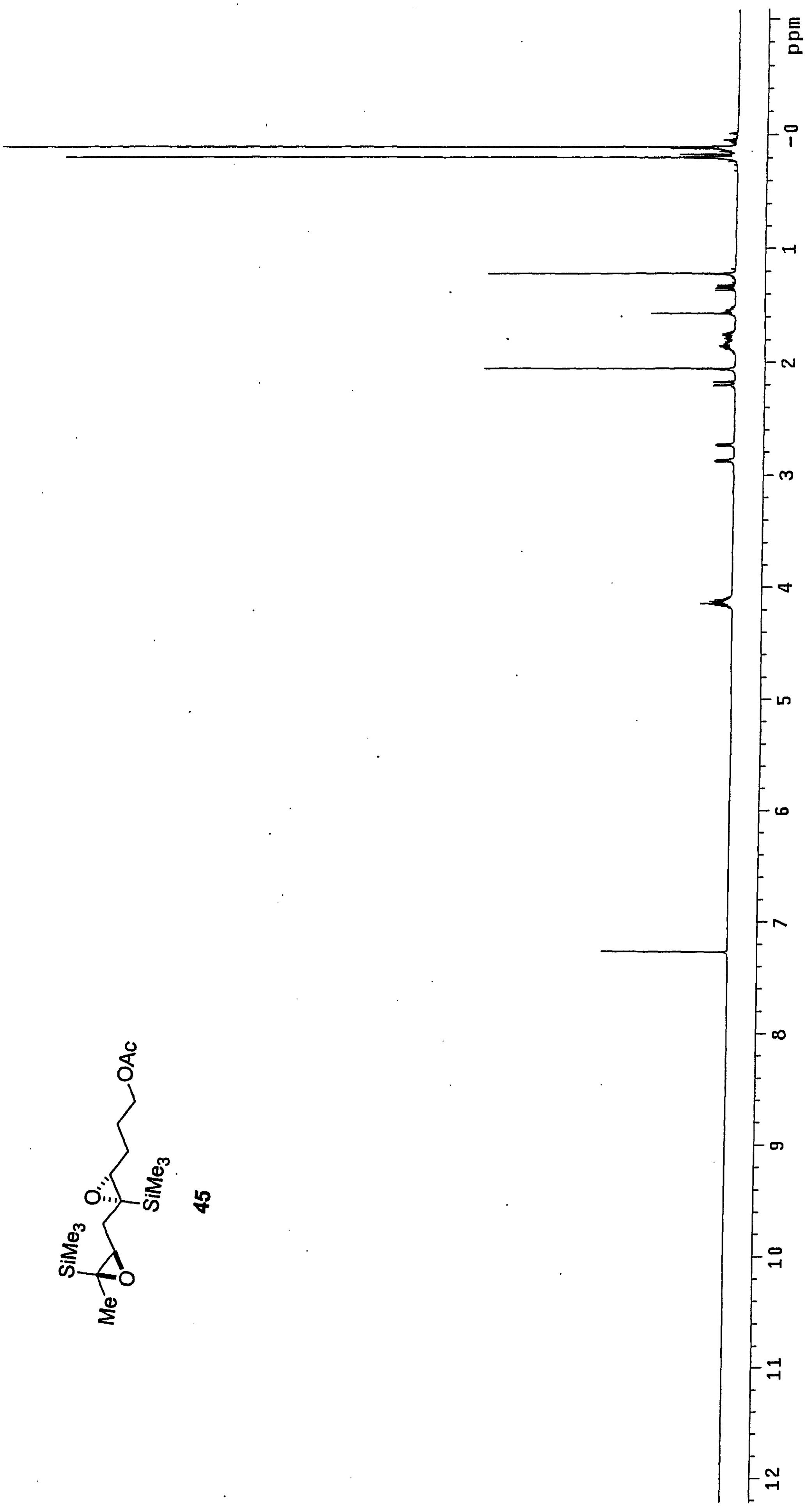
44

SiMe3
Me
OH
SiMe3

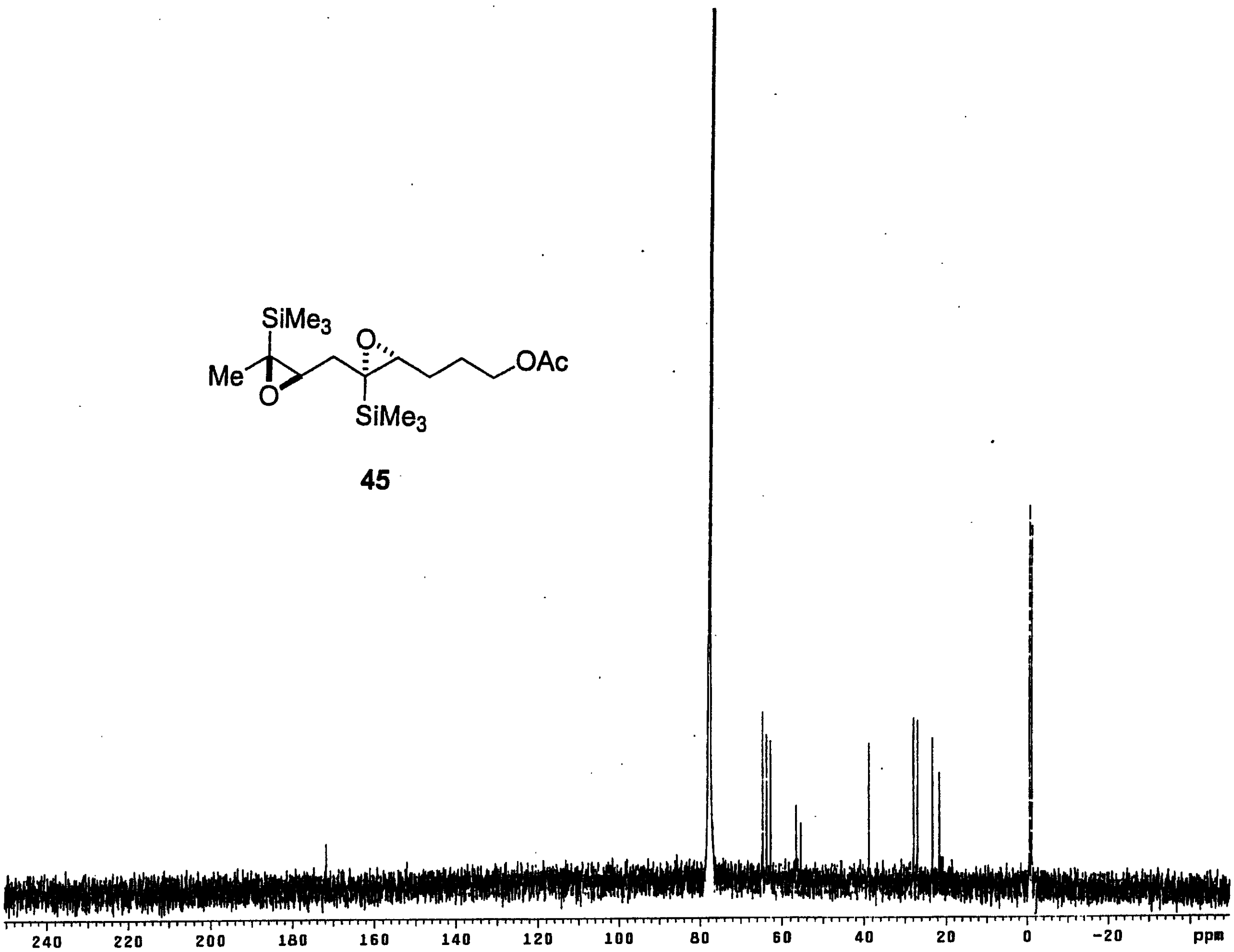
44


200
180
160
140
120
100
80
60
40
20
0
ppm


93.7
90
85
80
75
70
65
60
55
50
44.5
%T
4000.0
3000
2000
1500
1000
400.0
cm-1

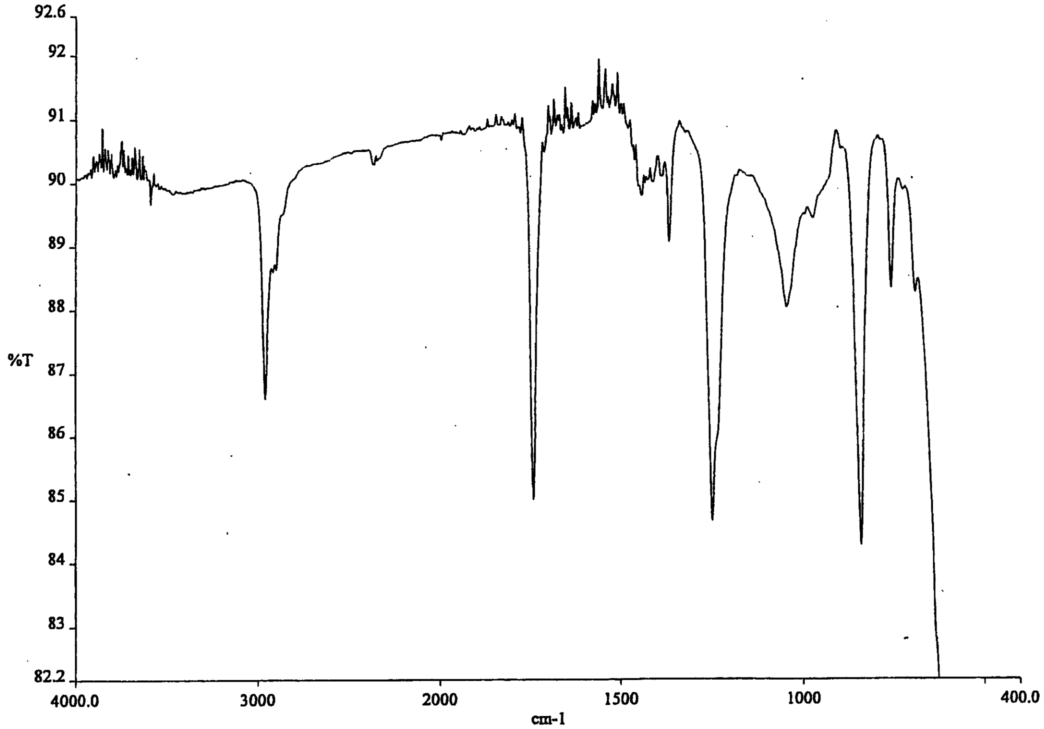


45

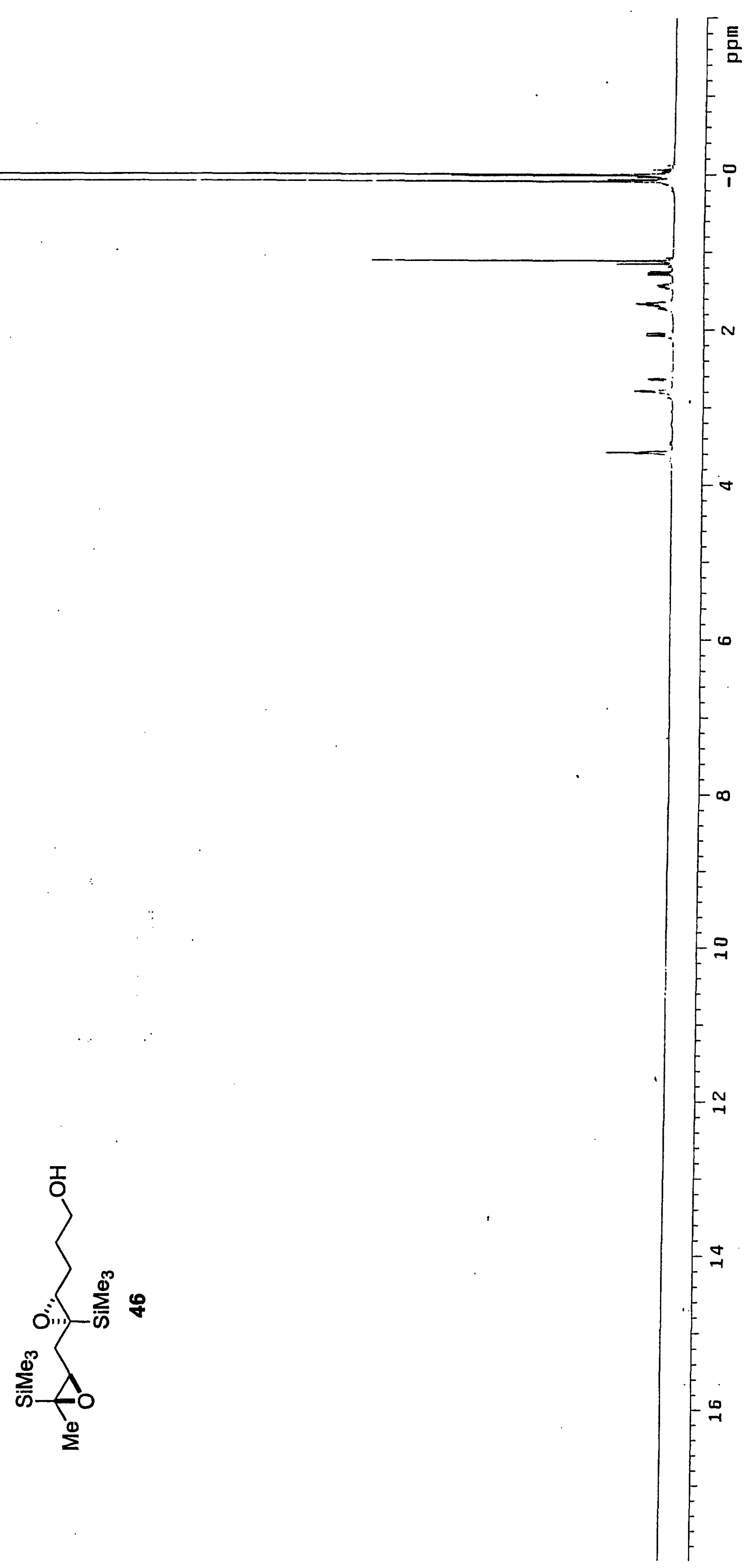


45

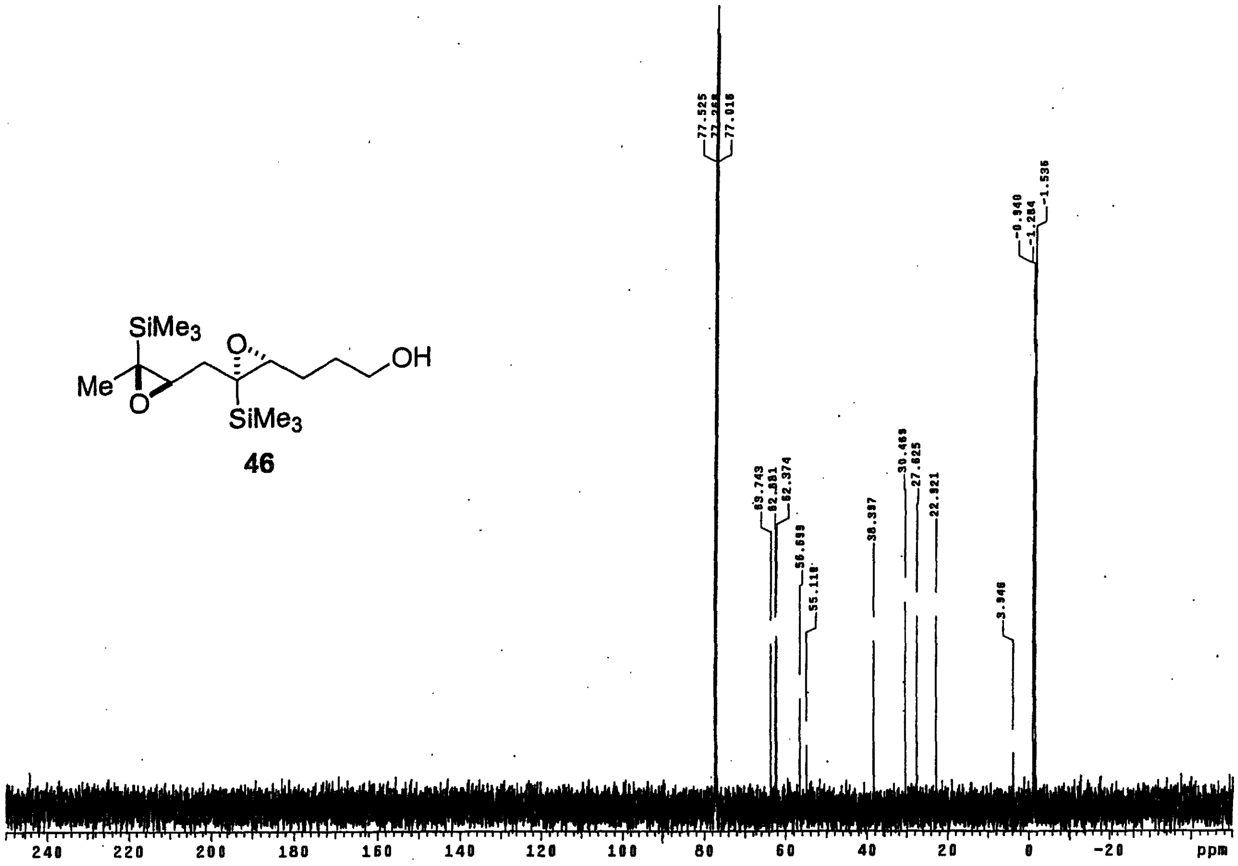
SiMe3
Me
O
O
SiMe3
OAc
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



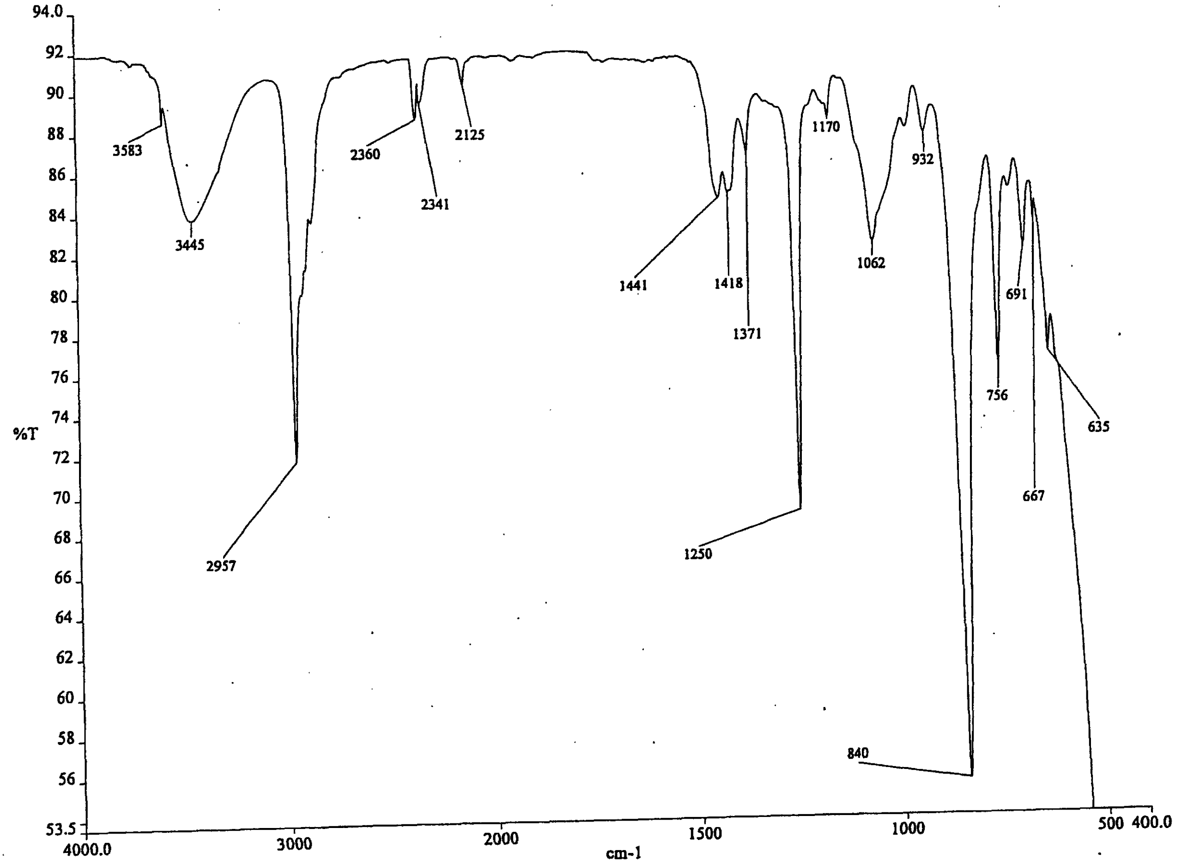
92.6
92
91
90
89
88
%T
87
86
85
84
83
82.2
4000.0
3000
2000
1500
1000
400.0
cm-1

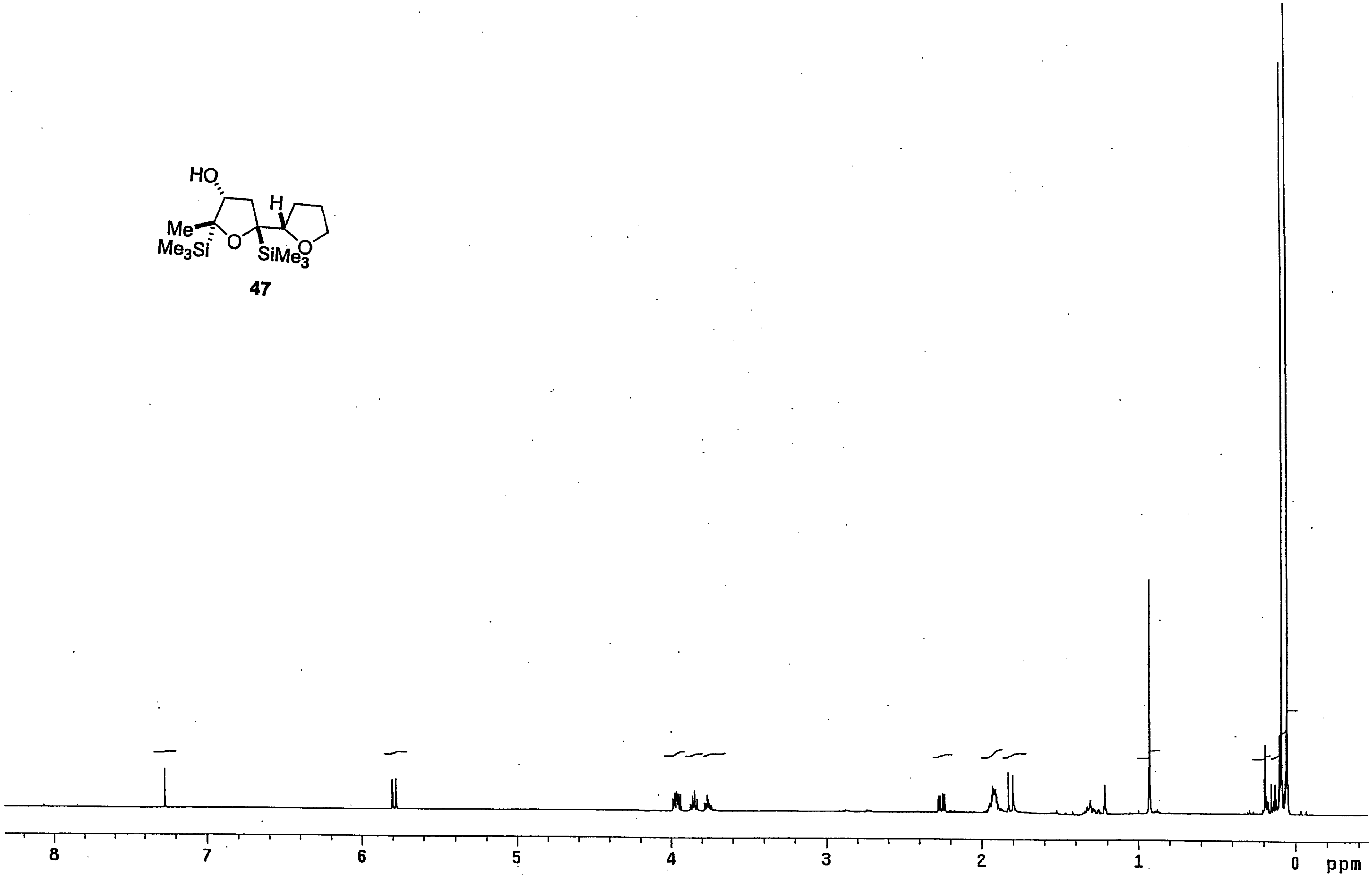


46

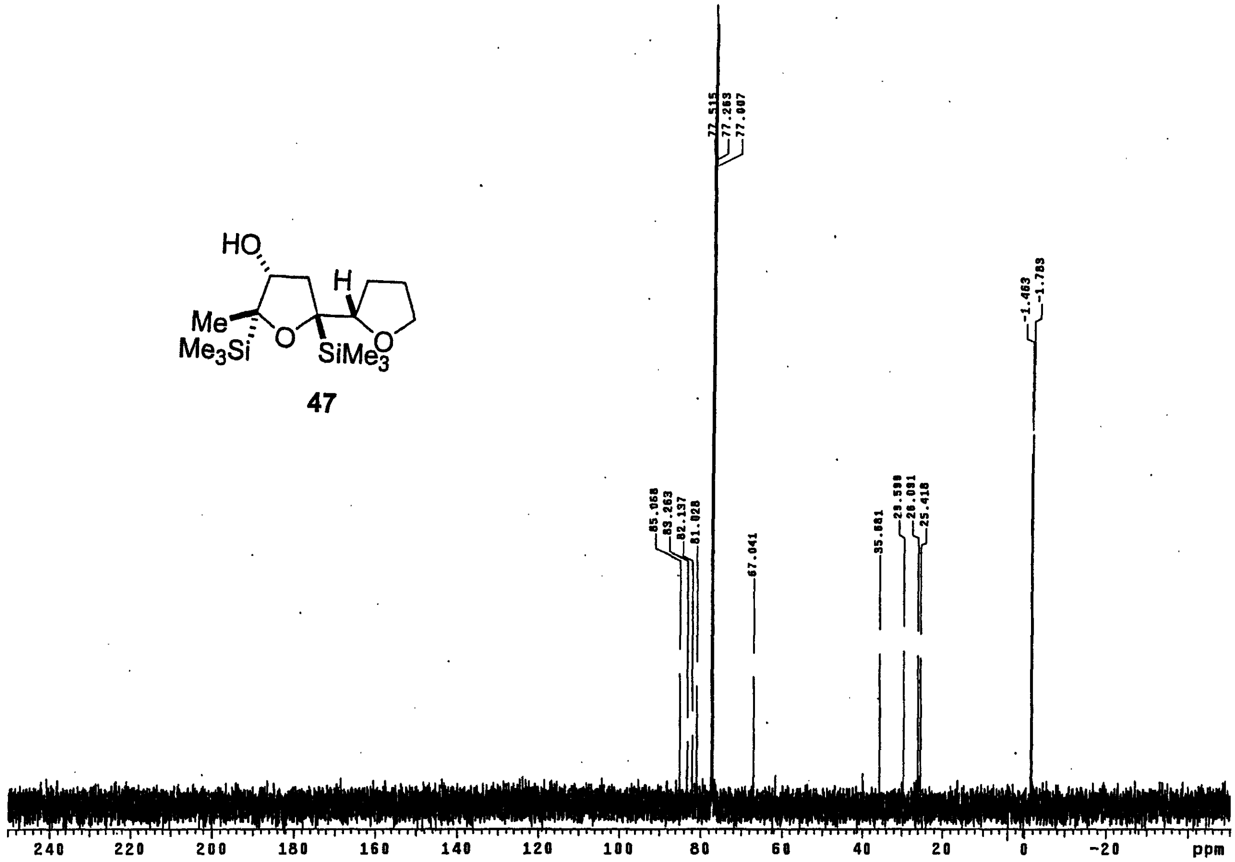

SiMe3
Me
O
O
OH
SiMe3
77.525
77.268
77.016
-0.940
-1.284
-1.536
63.743
62.881
62.374
56.699
55.118
38.397
30.469
27.625
22.921
3.946
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

46

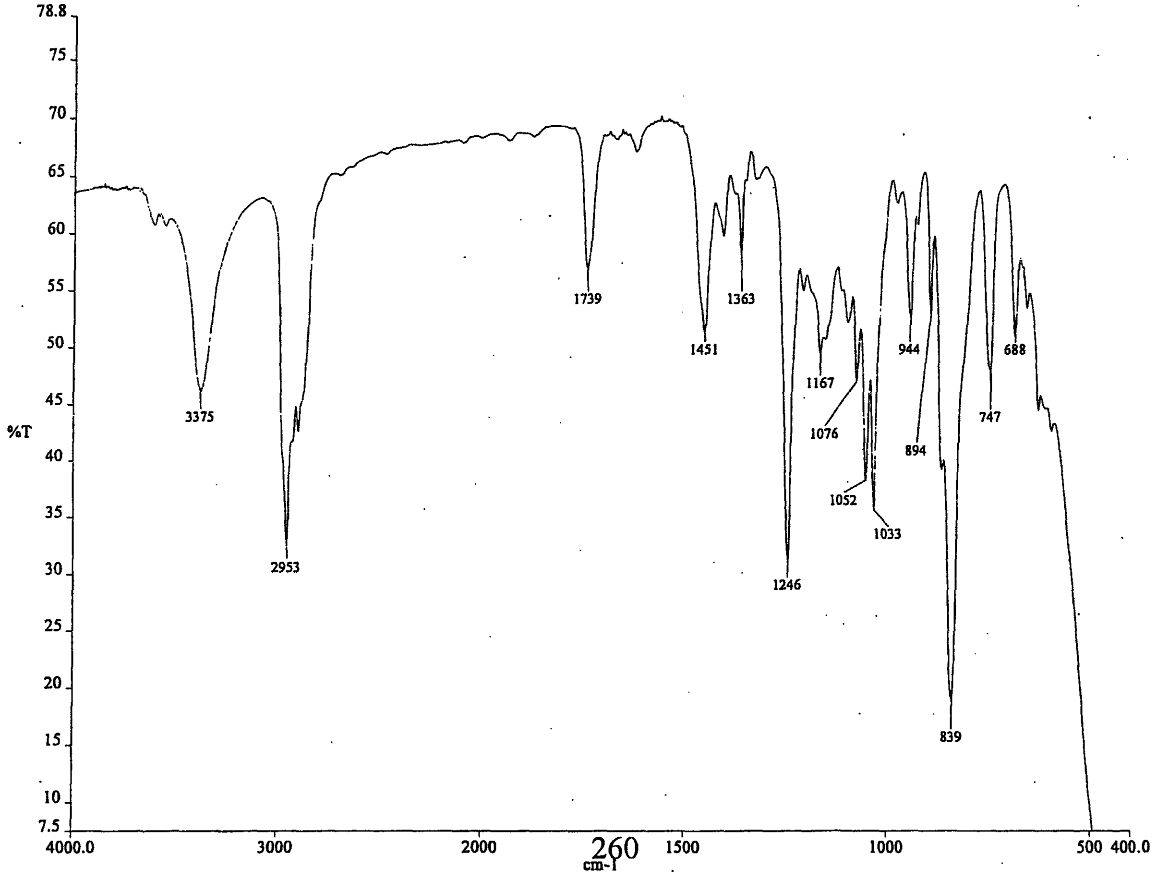

94.0
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
53.5
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583
3445
2957
2360
2341
2125
1441
1418
1371
1250
1170
1062
932
840
756
691
667
635

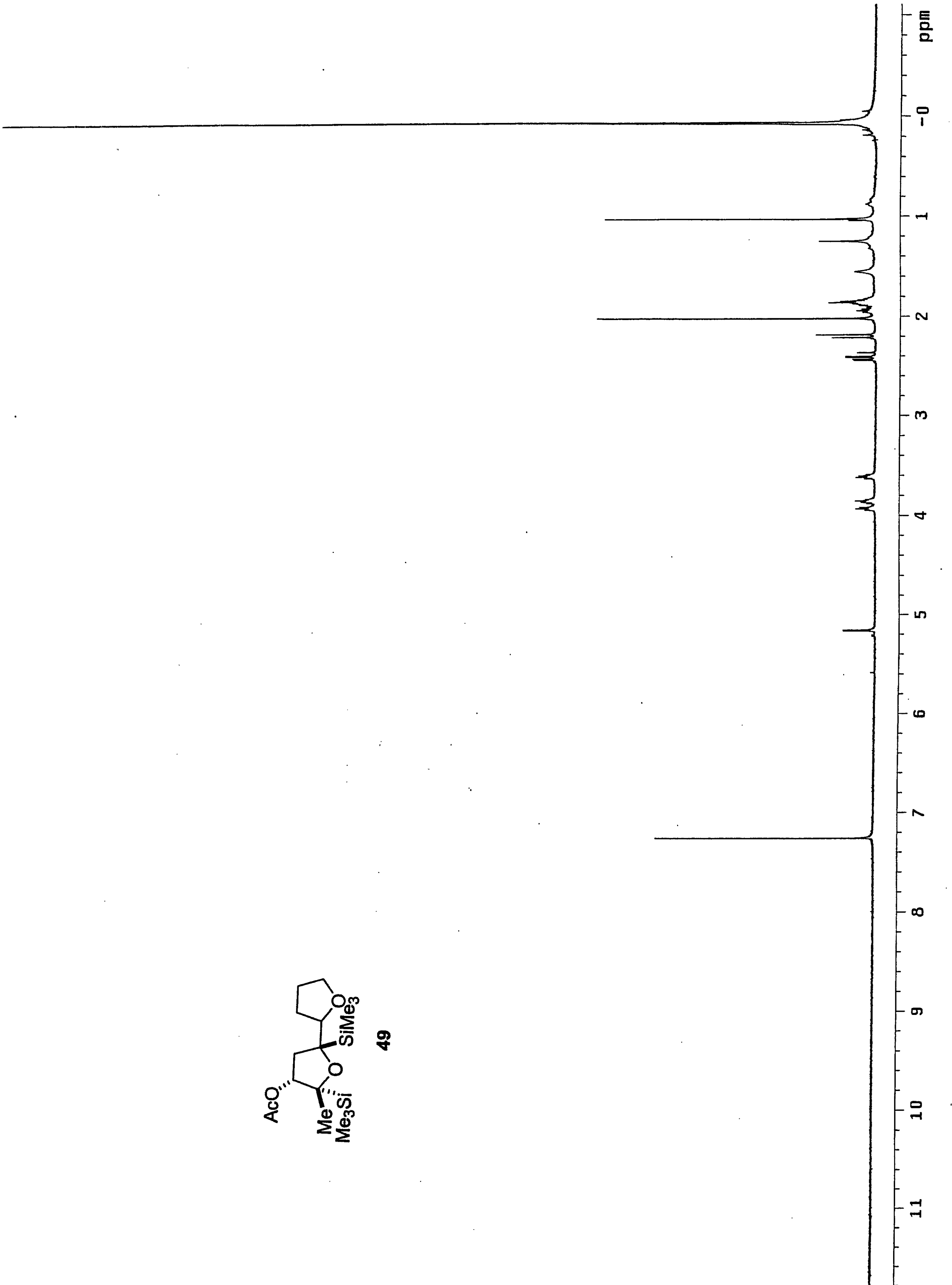


47

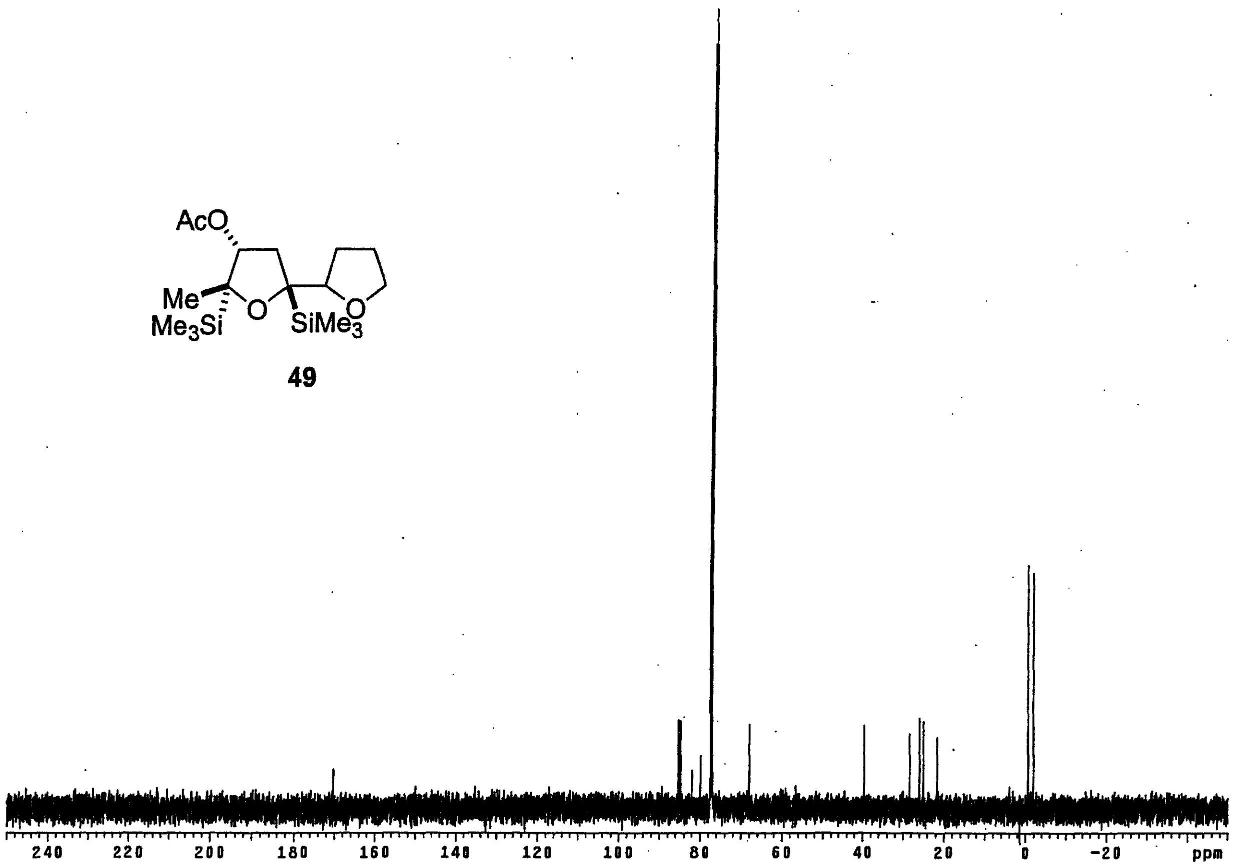

HO
H
Me
Me3Si
O
SiMe3
O
77.515
77.263
77.007
-1.463
-1.789
85.068
83.263
82.137
81.028
67.041
35.881
29.598
26.091
25.418
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

47

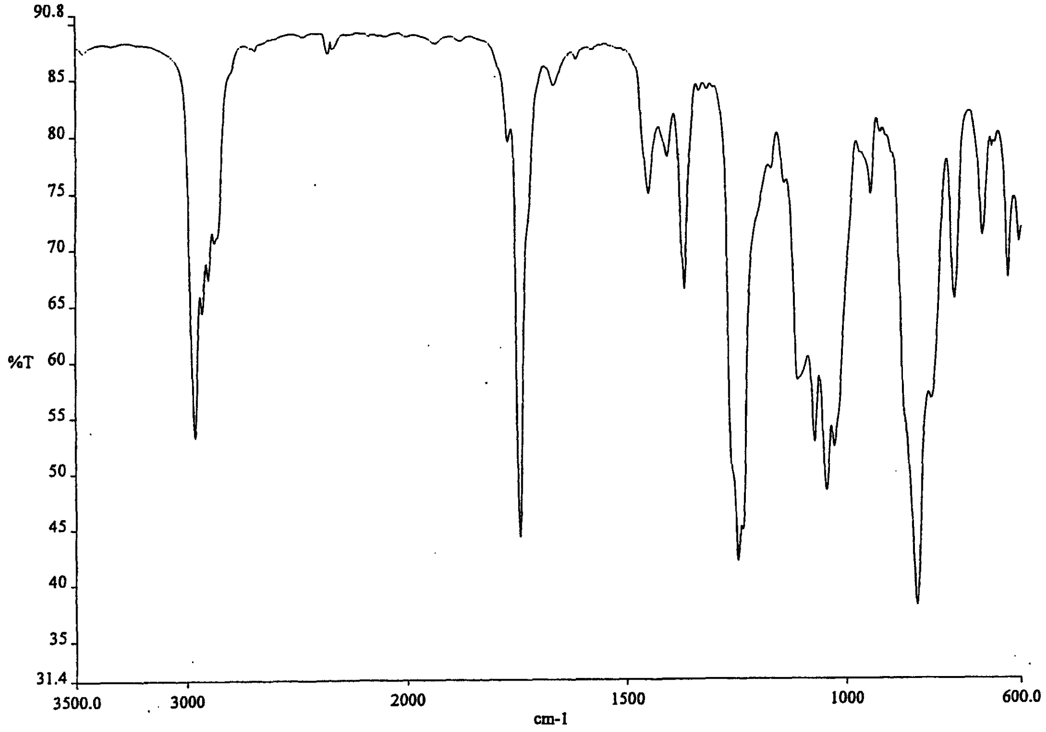

78.8
75
70
65
60
55
50
45
%T
40
35
30
25
20
15
10
7.5
3375
2953
1739
1451
1363
1246
1167
1076
1052
1033
944
894
839
747
688
4000.0
3000
2000
1500
1000
500 400.0
cm-1

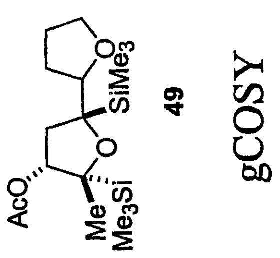


49


AcO
Me
Me3Si
O
SiMe3
O
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

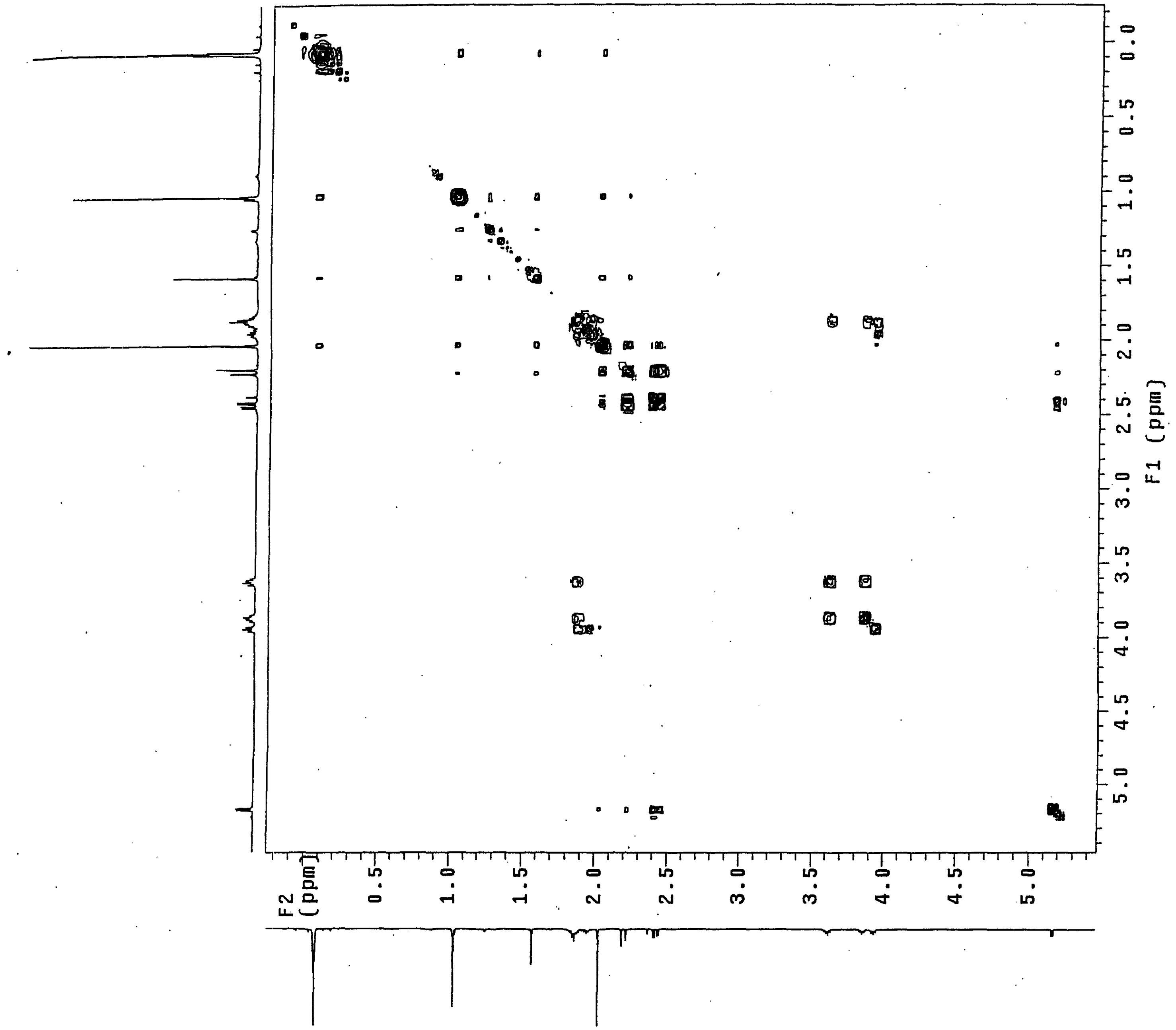
49

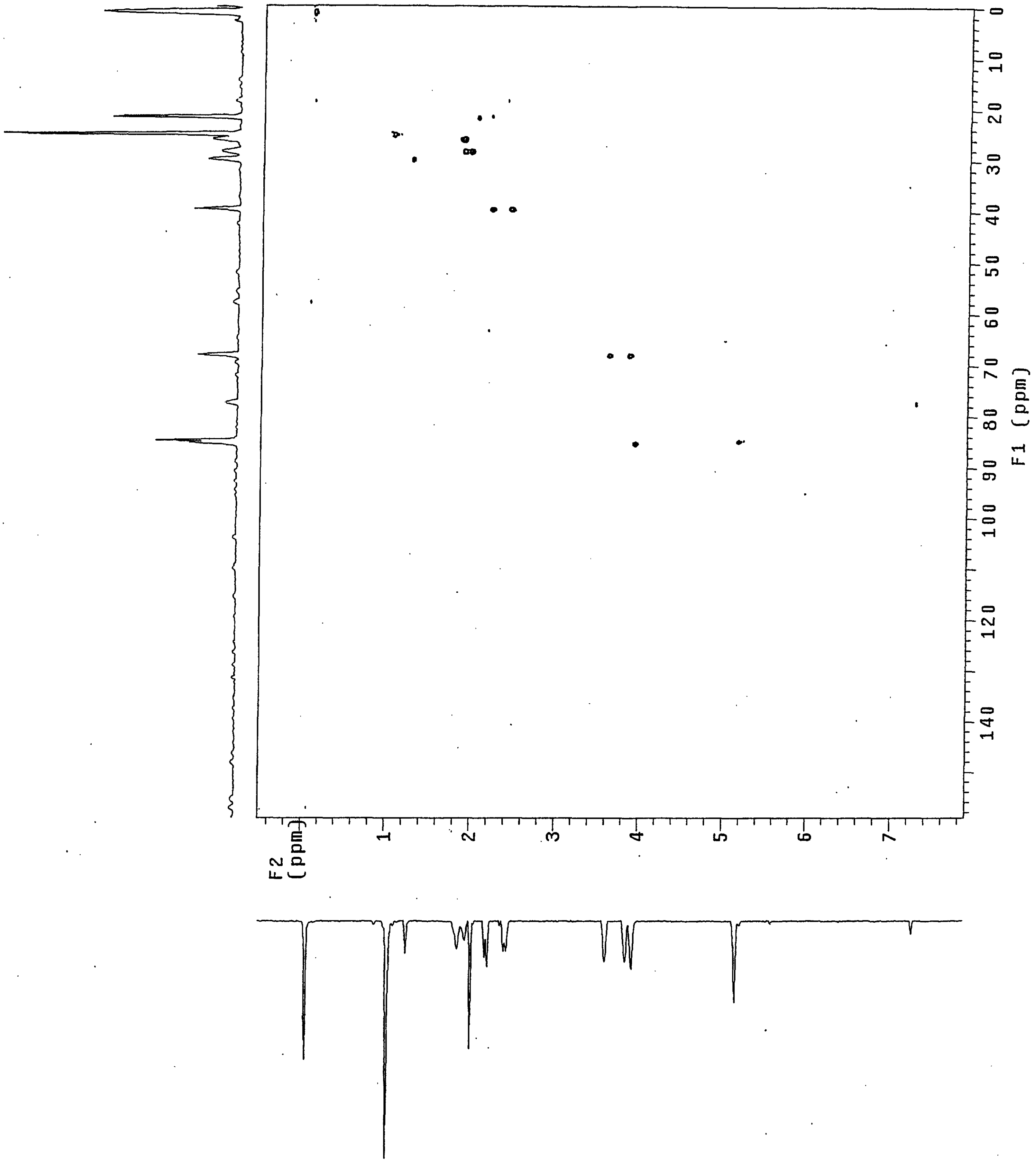

90.8
85
80
75
70
65
%T 60
55
50
45
40
35
31.4
3500.0
3000
2000
1500
1000
600.0
cm-1

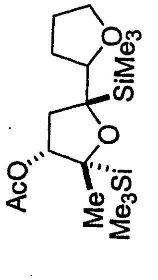


49

gCOSY

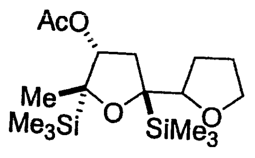



F1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
120
140
F2 (ppm)
1
2
3
4
5
6
7


AcO
O
O
SiMe$_3$
Me
Me$_3$Si

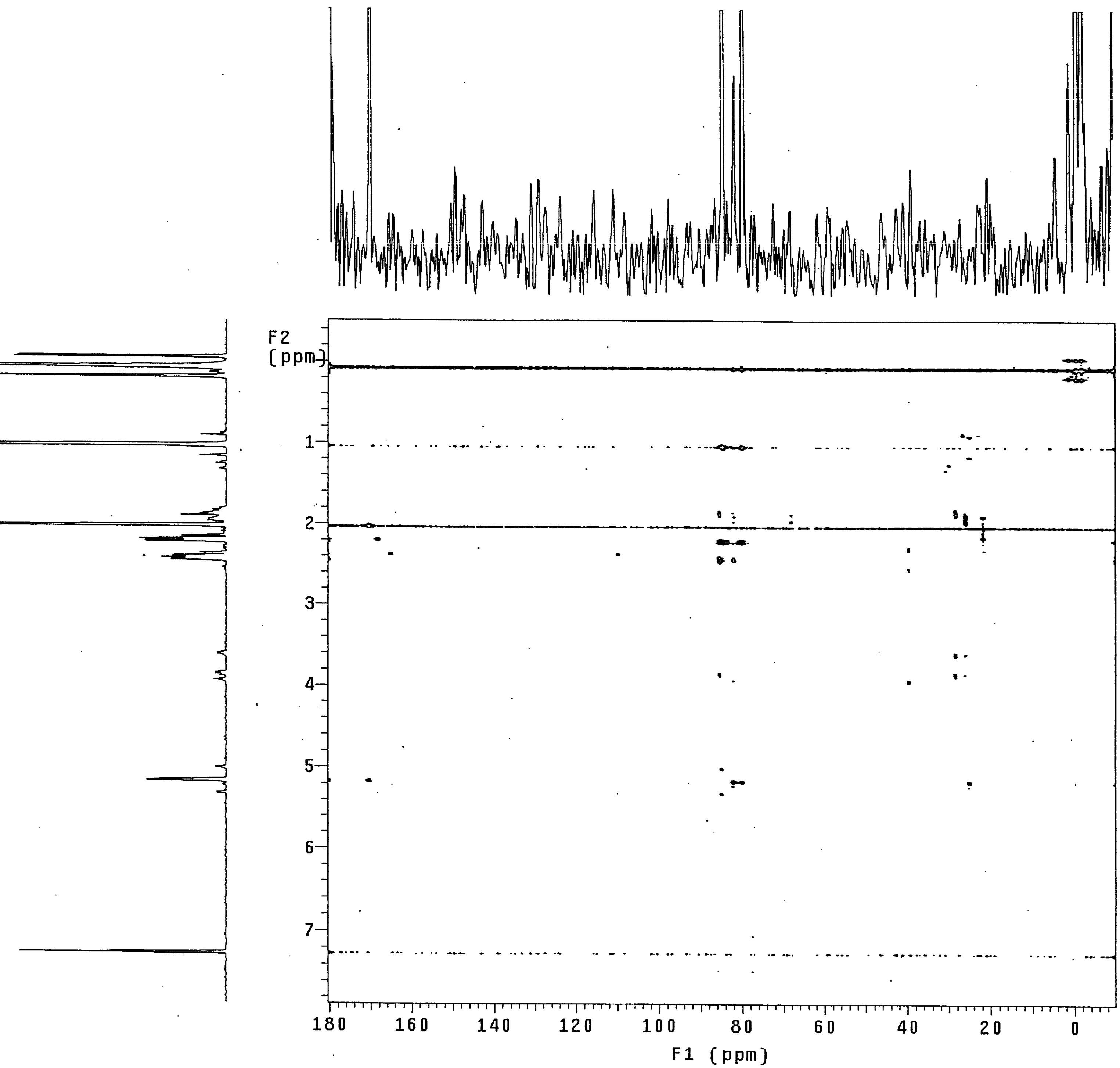
49

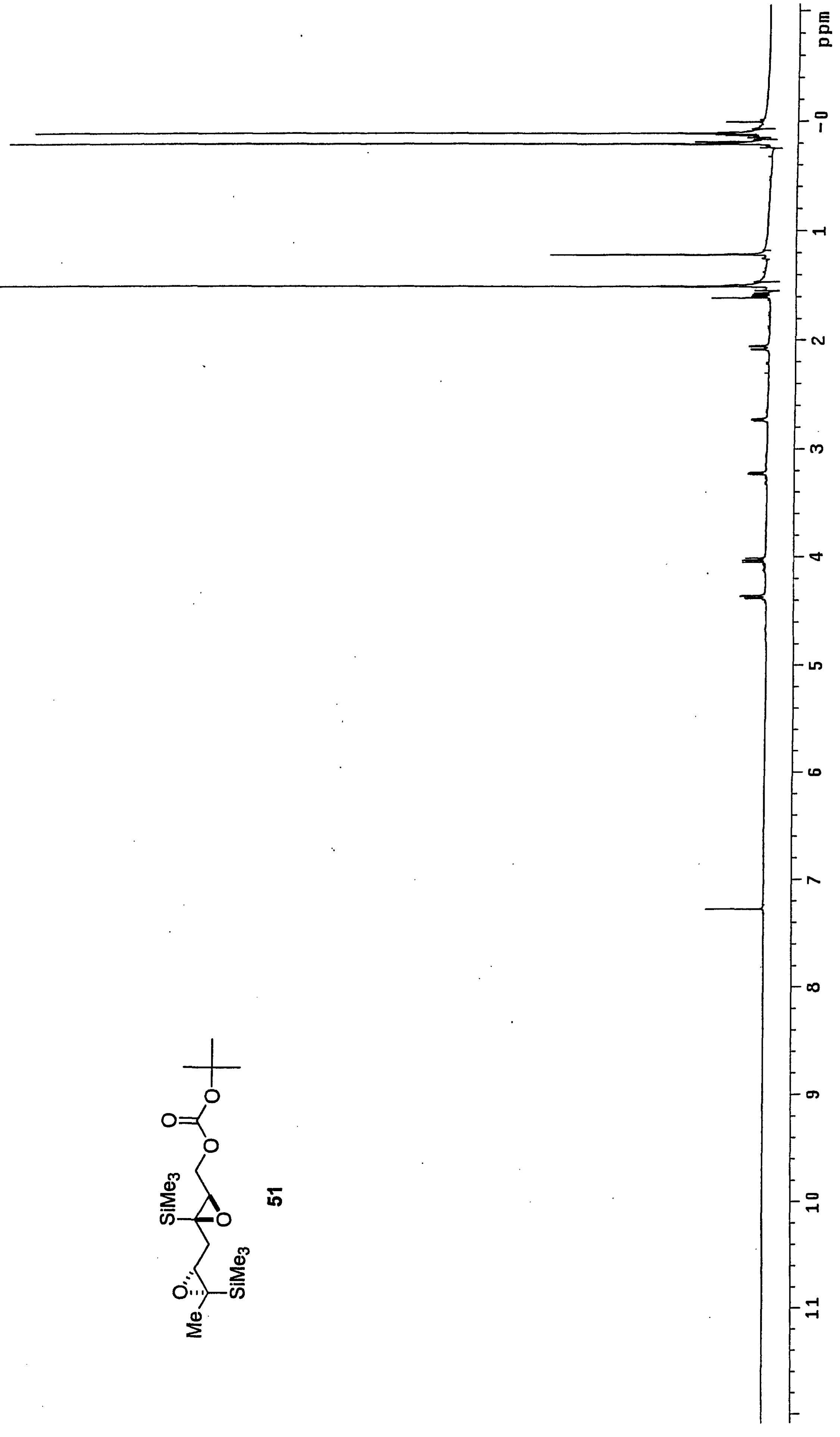
gHSQC


AcO
Me
Me3Si
O
SiMe3
O

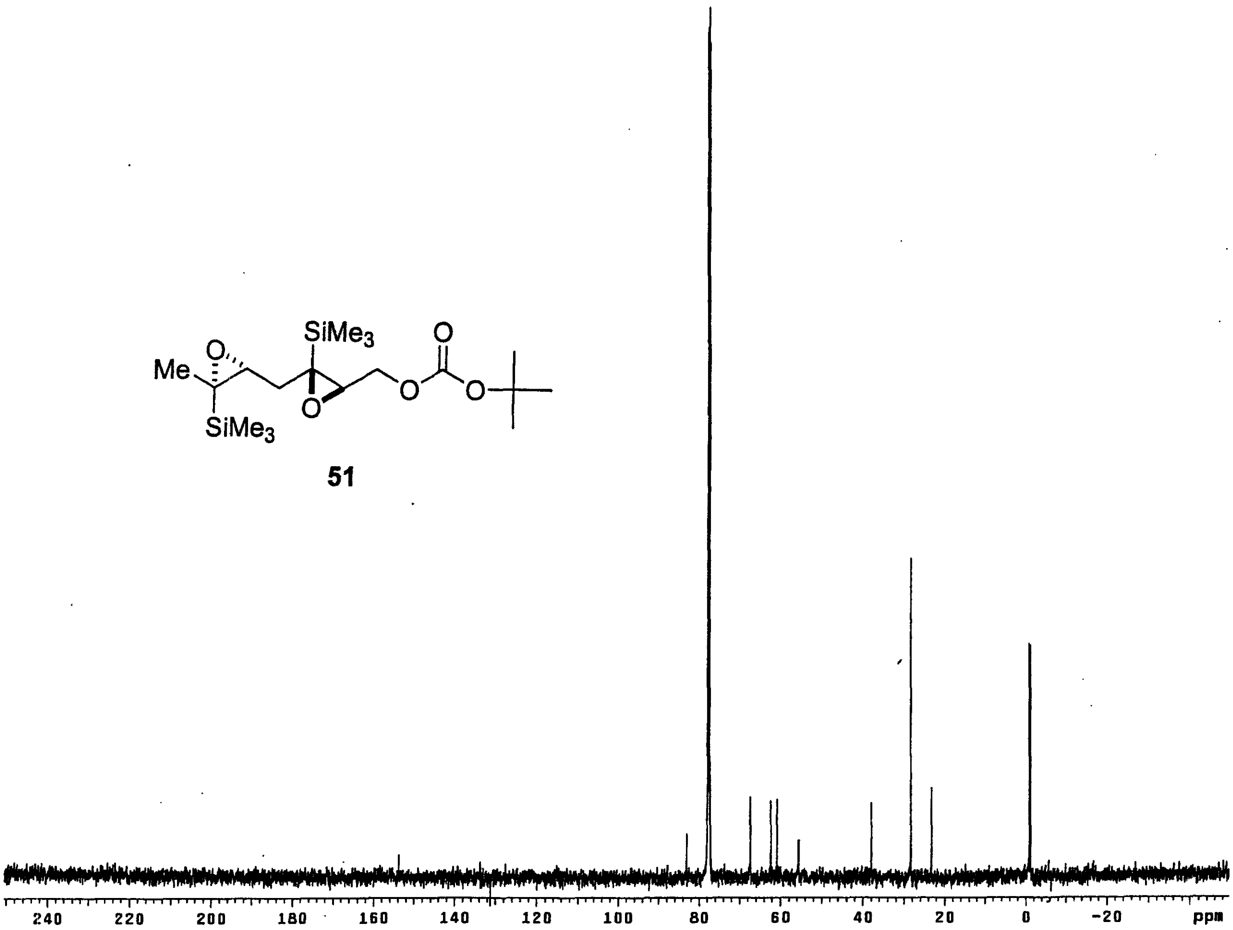
49

gHMBC

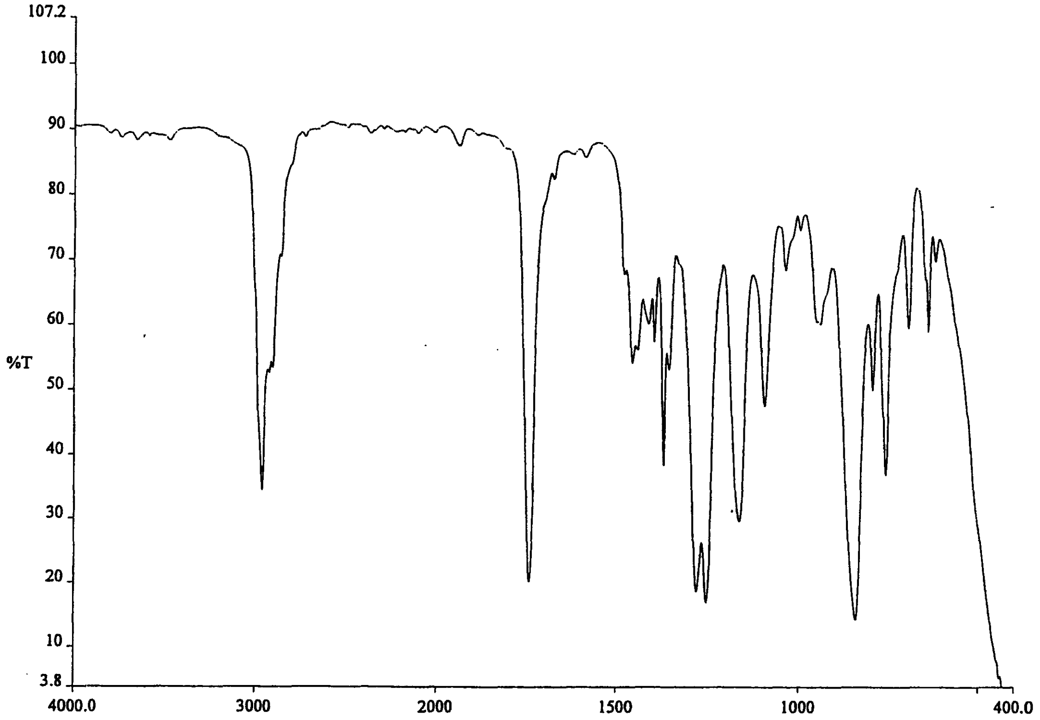

F2 (ppm)
1
2
3
4
5
6
7
180
160
140
120
100
80
60
40
20
0
F1 (ppm)



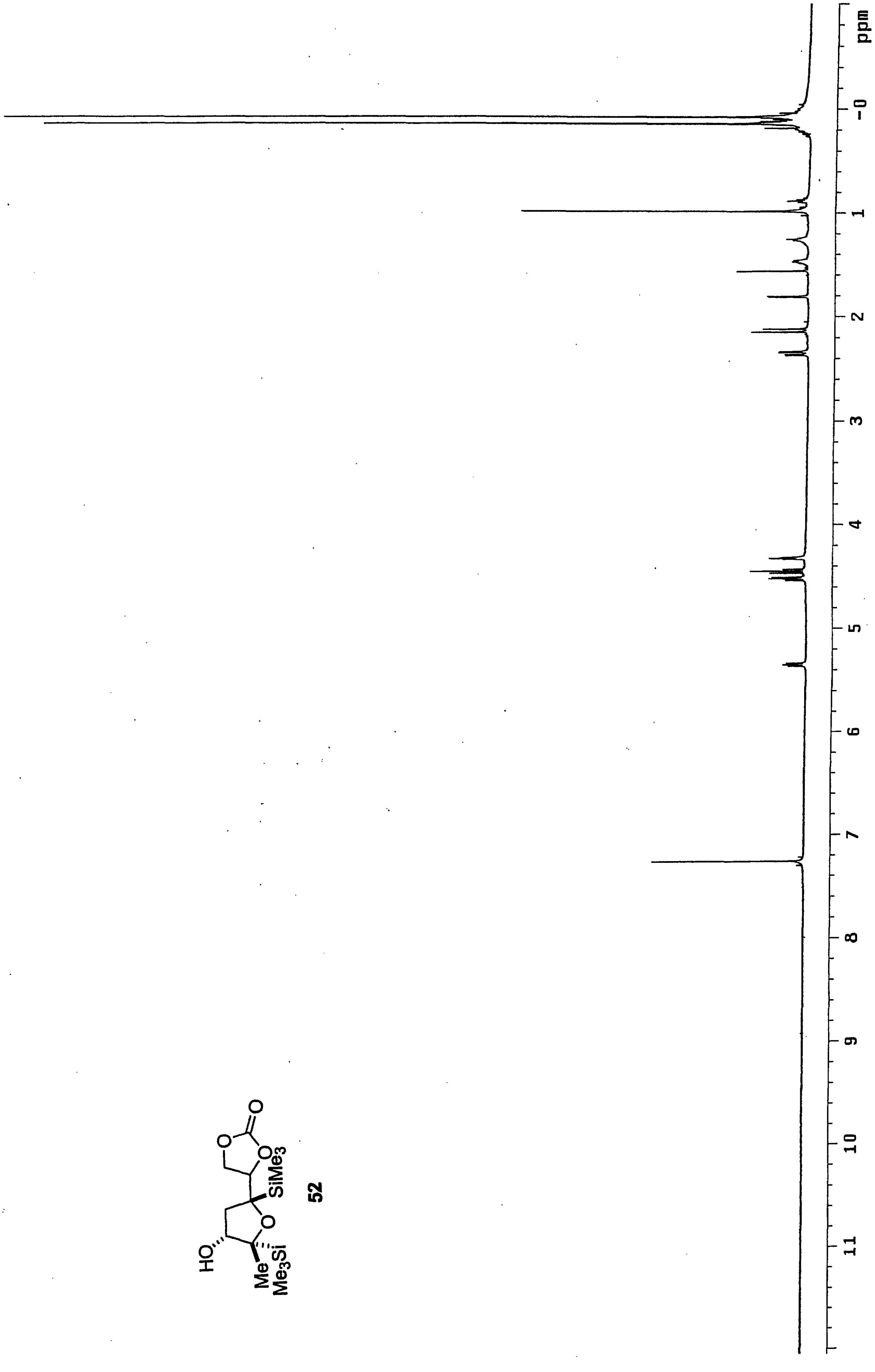
51


51

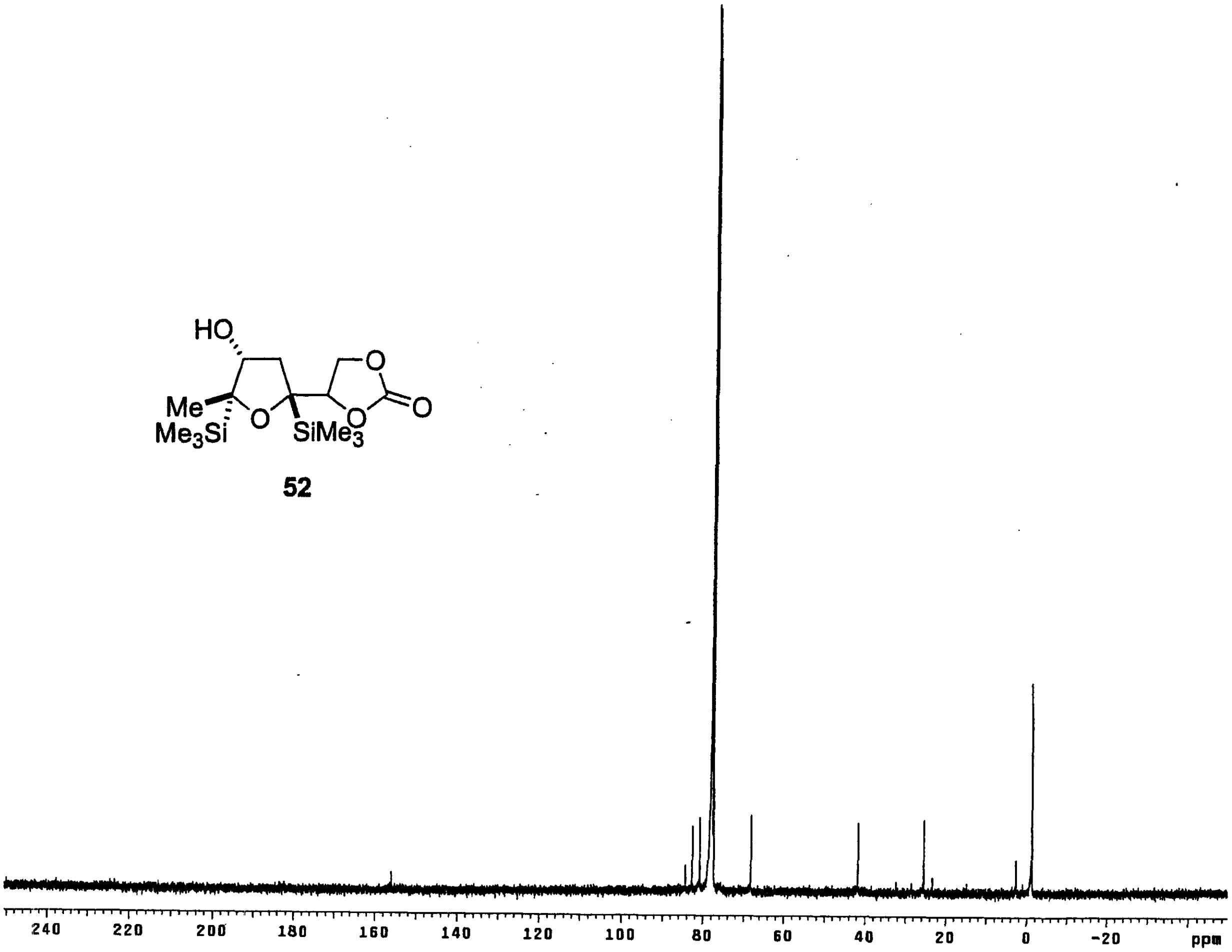
SiMe3
Me
SiMe3
O
O
O
O
O
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

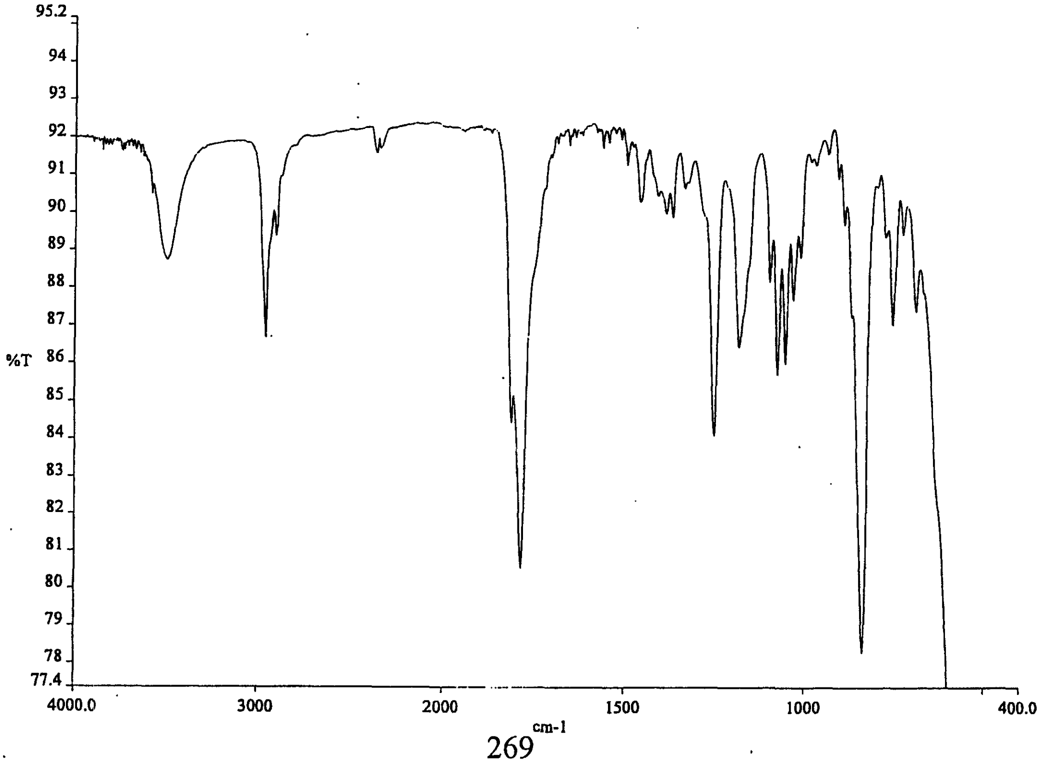


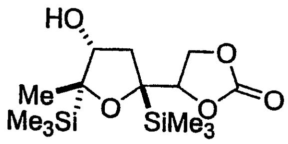
107.2
100
90
80
70
60
50
40
30
20
10
3.8
%T
4000.0
3000
2000
1500
1000
400.0
cm-1



52

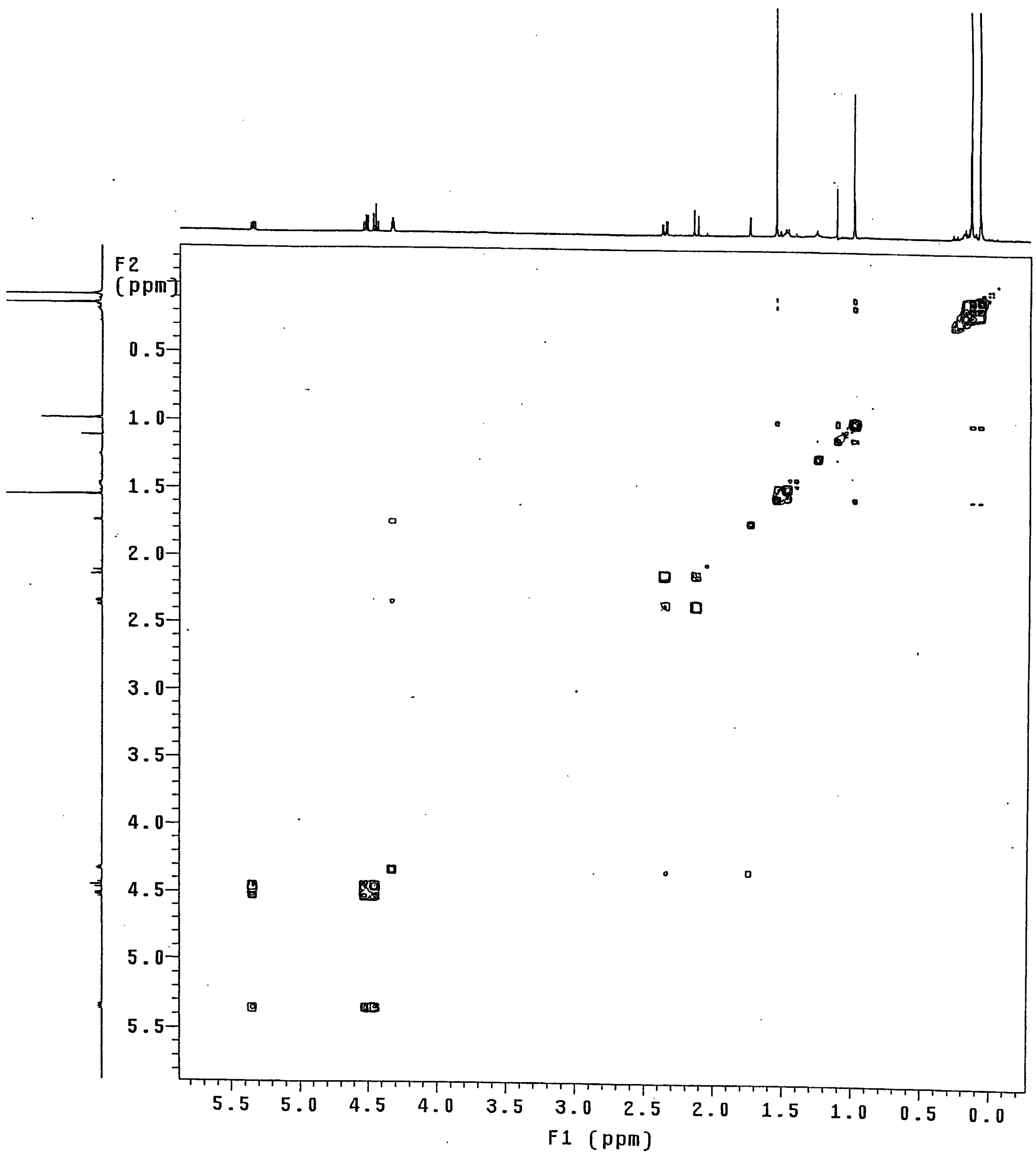

HO
Me
Me3Si
O
SiMe3
O
O
O
52
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

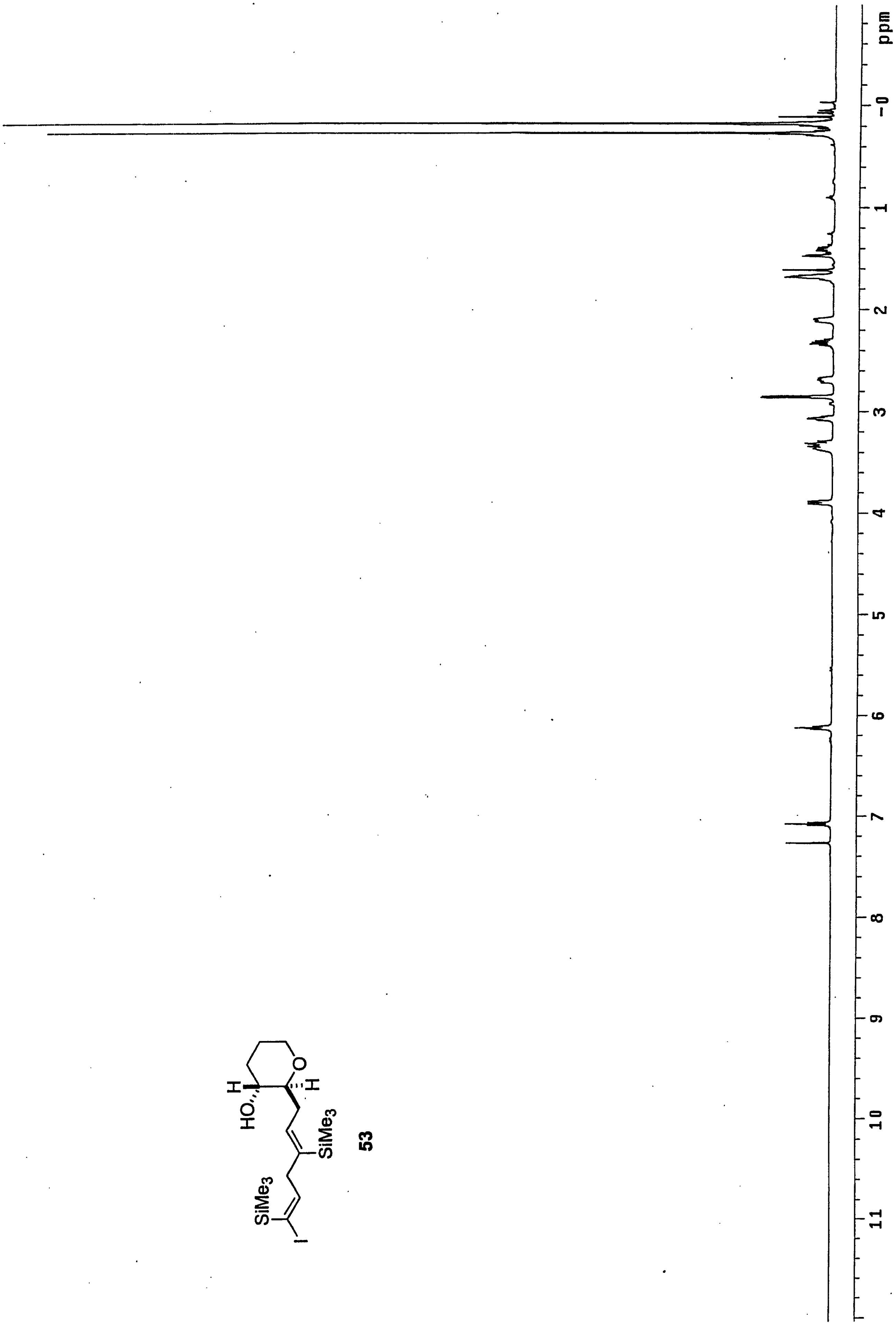

95.2
94
93
92
91
90
89
88
87
%T
86
85
84
83
82
81
80
79
78
77.4
4000.0
3000
2000
1500
1000
400.0
cm-1


HO
Me
Me3Si
O
SiMe3
O
O
O

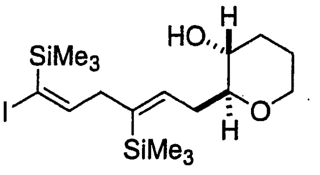
52

gCOSY

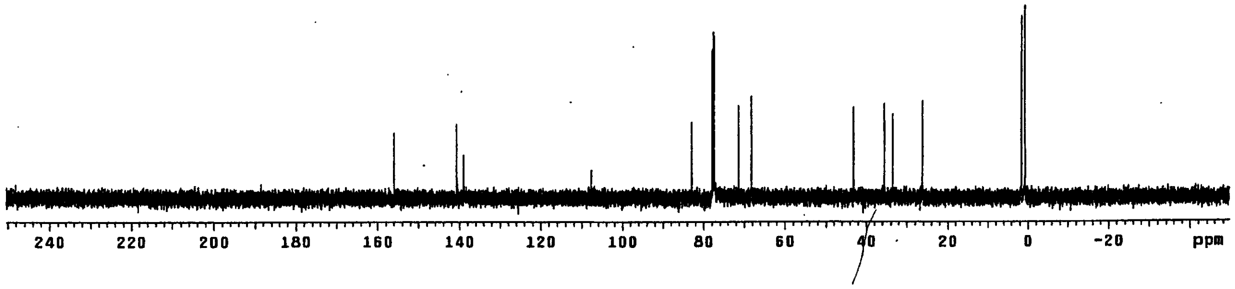

F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
F1 (ppm)

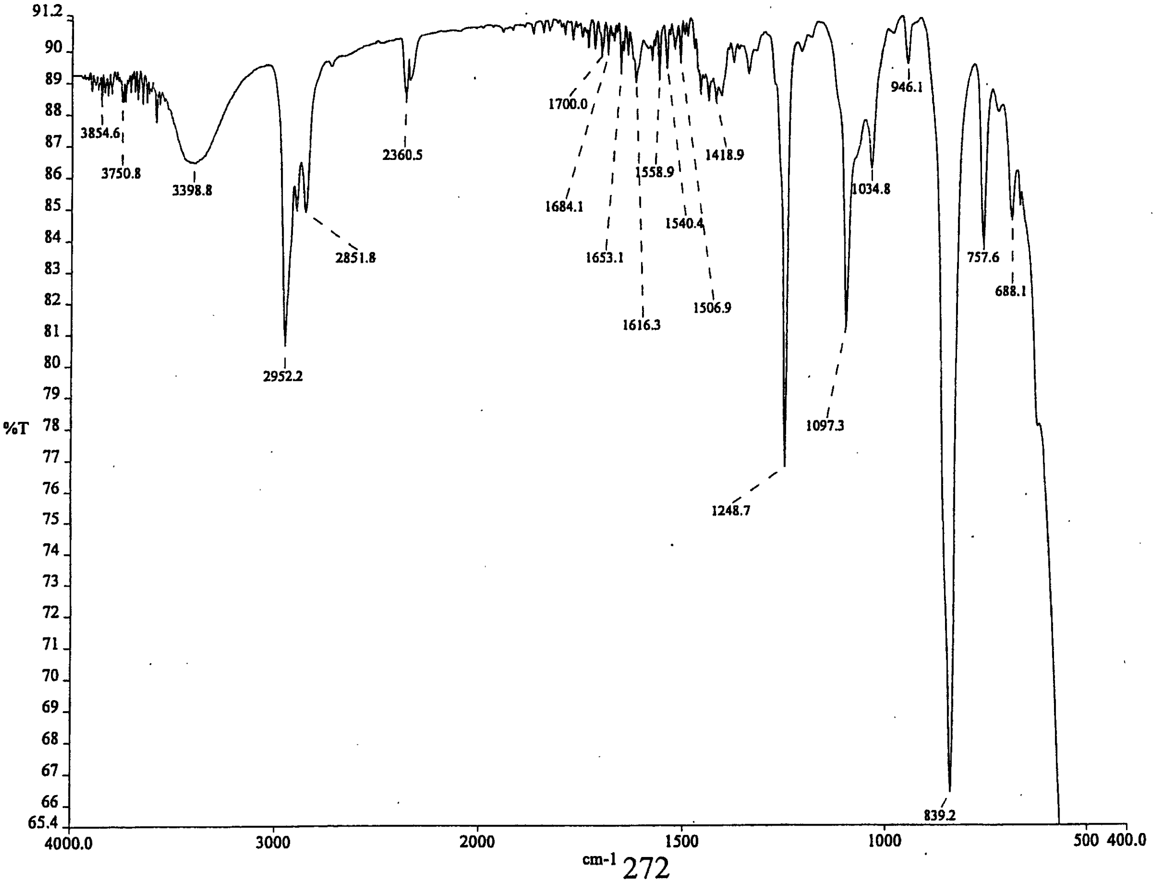


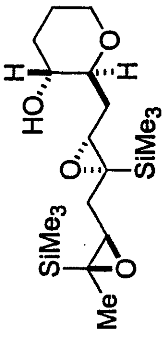
53


SiMe3
HO
H
I
O
H
SiMe3

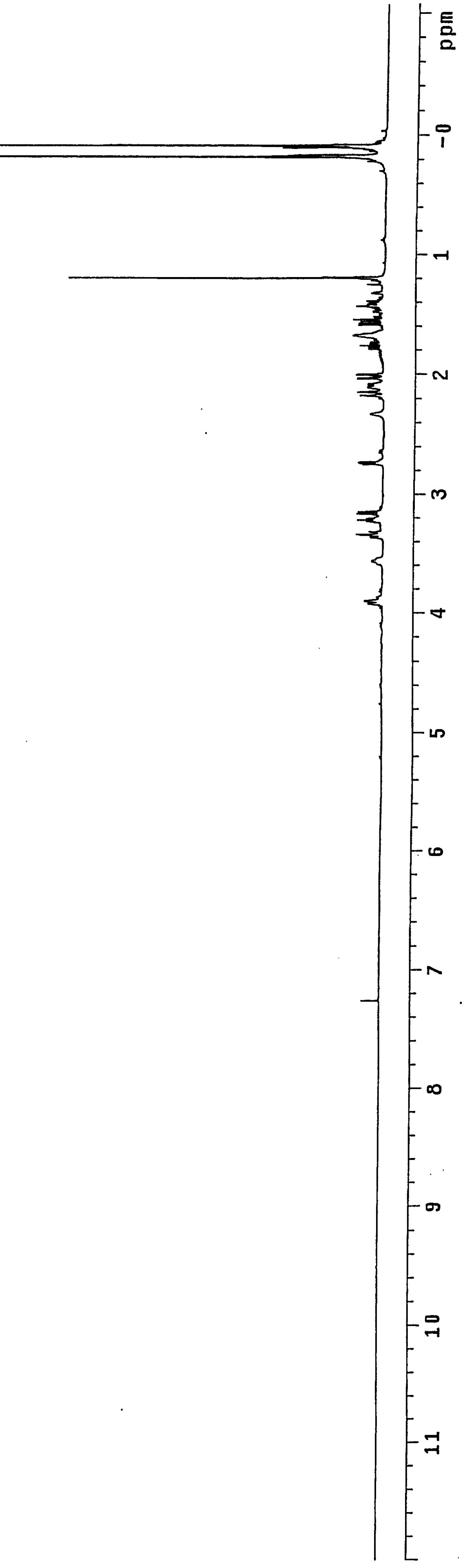
53

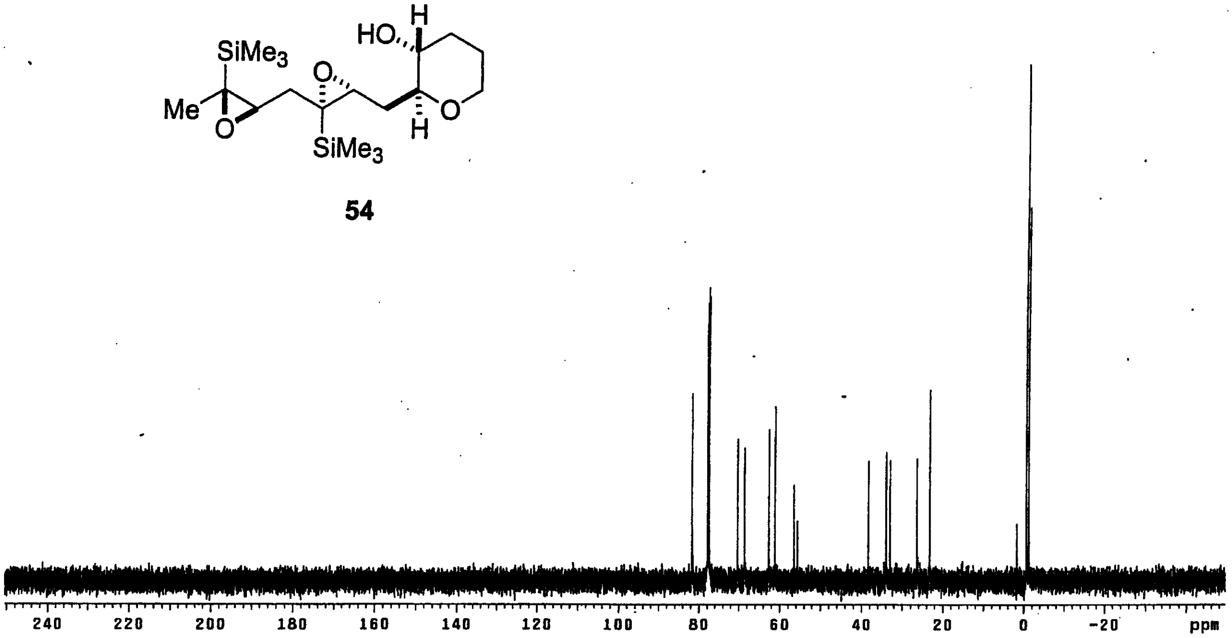

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


91.2
90
89
88
87
86
85
84
83
82
81
80
79
%T
78
77
76
75
74
73
72
71
70
69
68
67
66
65.4
3854.6
3750.8
3398.8
2952.2
2851.8
2360.5
1700.0
1684.1
1653.1
1616.3
1558.9
1540.4
1506.9
1418.9
1248.7
1097.3
1034.8
946.1
839.2
757.6
688.1
4000.0
3000
2000
1500
1000
500
400.0
cm-1



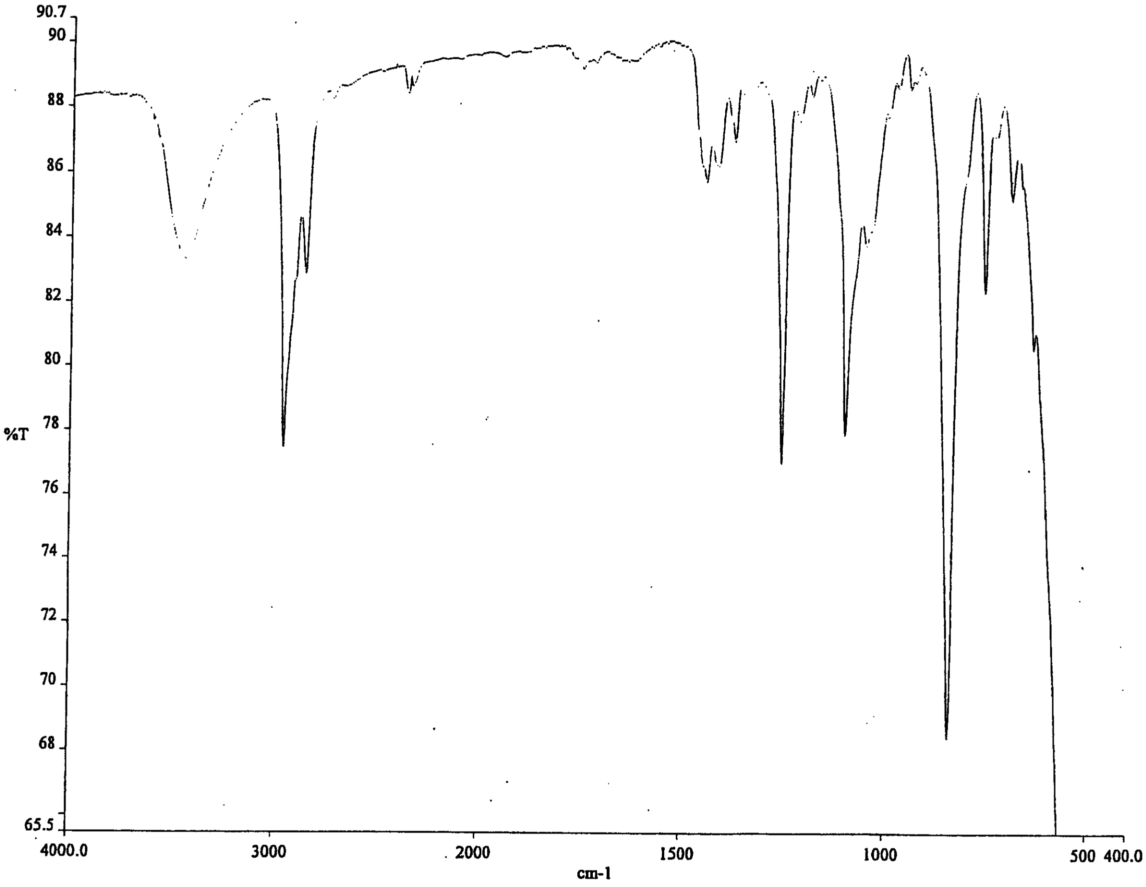
54

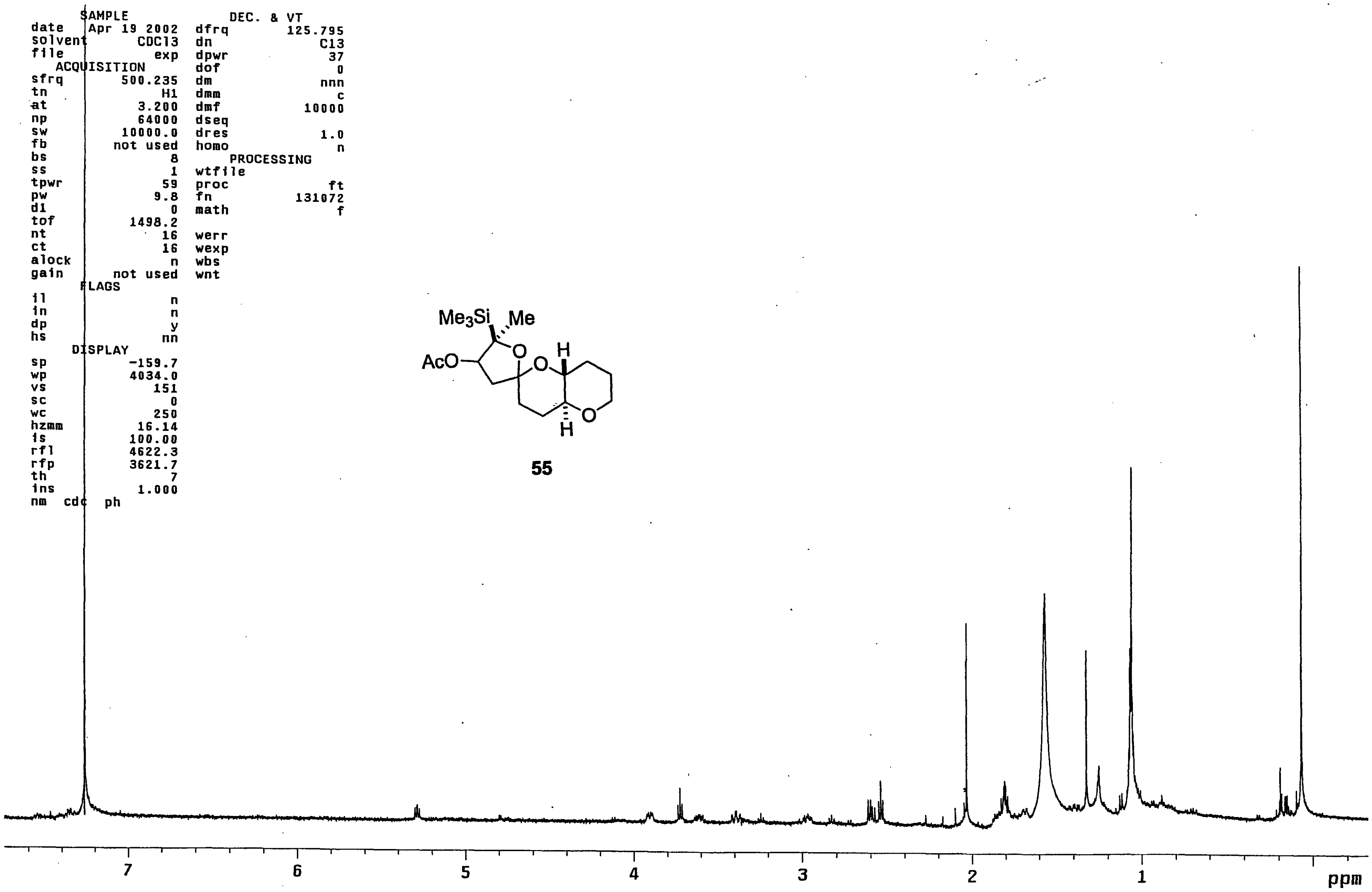



SiMe3
Me
O
O
SiMe3
HO
H
H
O

54

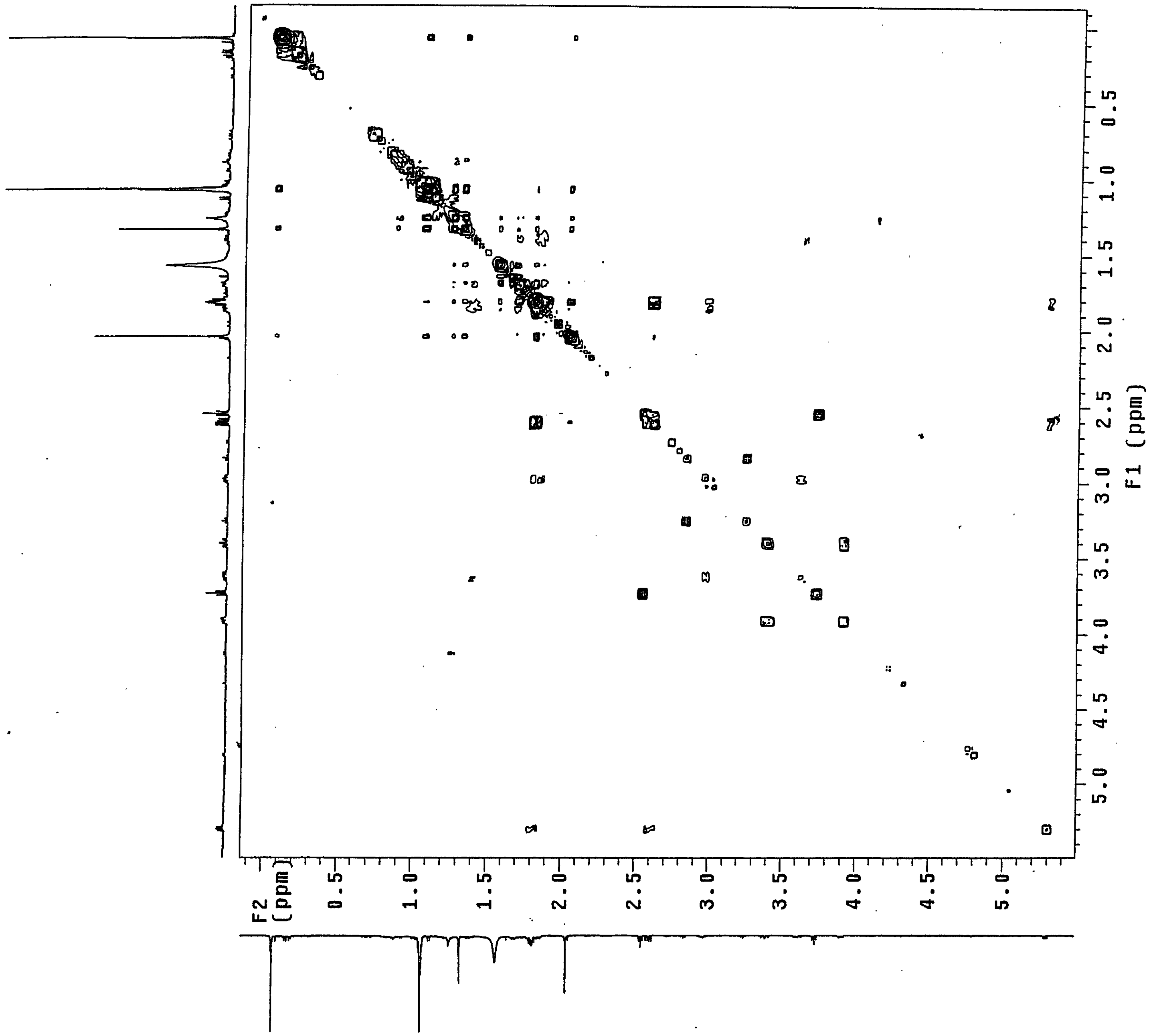
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

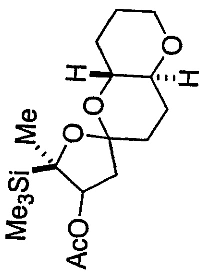

90.7
90
88
86
84
82
80
%T
78
76
74
72
70
68
65.5
4000.0
3000
2000
1500
1000
500
400.0
cm-1



55

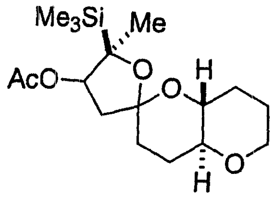
```
       SAMPLE                 DEC. & VT
date    Apr 19 2002   dfrq        125.795
solvent       CDCl3   dn              C13
file            exp   dpwr             37
   ACQUISITION        dof               0
sfrq        500.235   dm              nnn
tn               H1   dmm               c
at            3.200   dmf           10000
np            64000   dseq
sw          10000.0   dres            1.0
fb         not used   homo              n
bs                8        PROCESSING
ss                1   wtfile
tpwr             59   proc             ft
pw              9.8   fn           131072
d1                0   math              f
tof          1498.2
nt               16   werr
ct               16   wexp
alock             n   wbs
gain       not used   wnt
       FLAGS
il                n
in                n
dp                y
hs               nn
      DISPLAY
sp           -159.7
wp           4034.0
vs              151
sc                0
wc              250
hzmm          16.14
is           100.00
rfl          4622.3
rfp          3621.7
th                7
ins           1.000
nm  cdc   ph
```


F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
F1 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0


Me
Me3Si
O
AcO
O
H
O
H

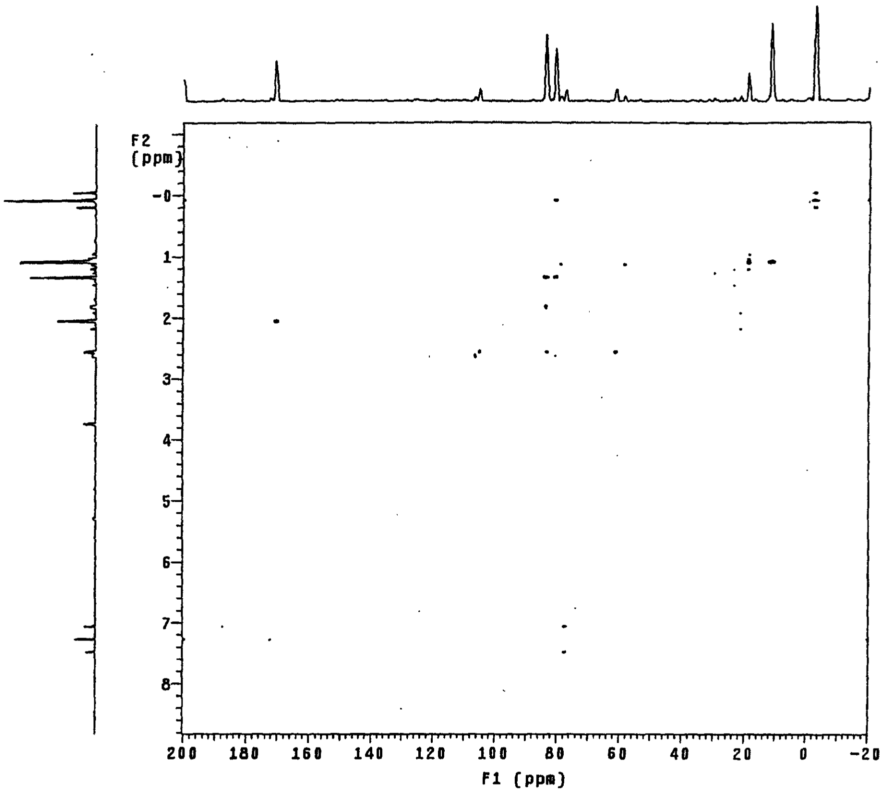
55

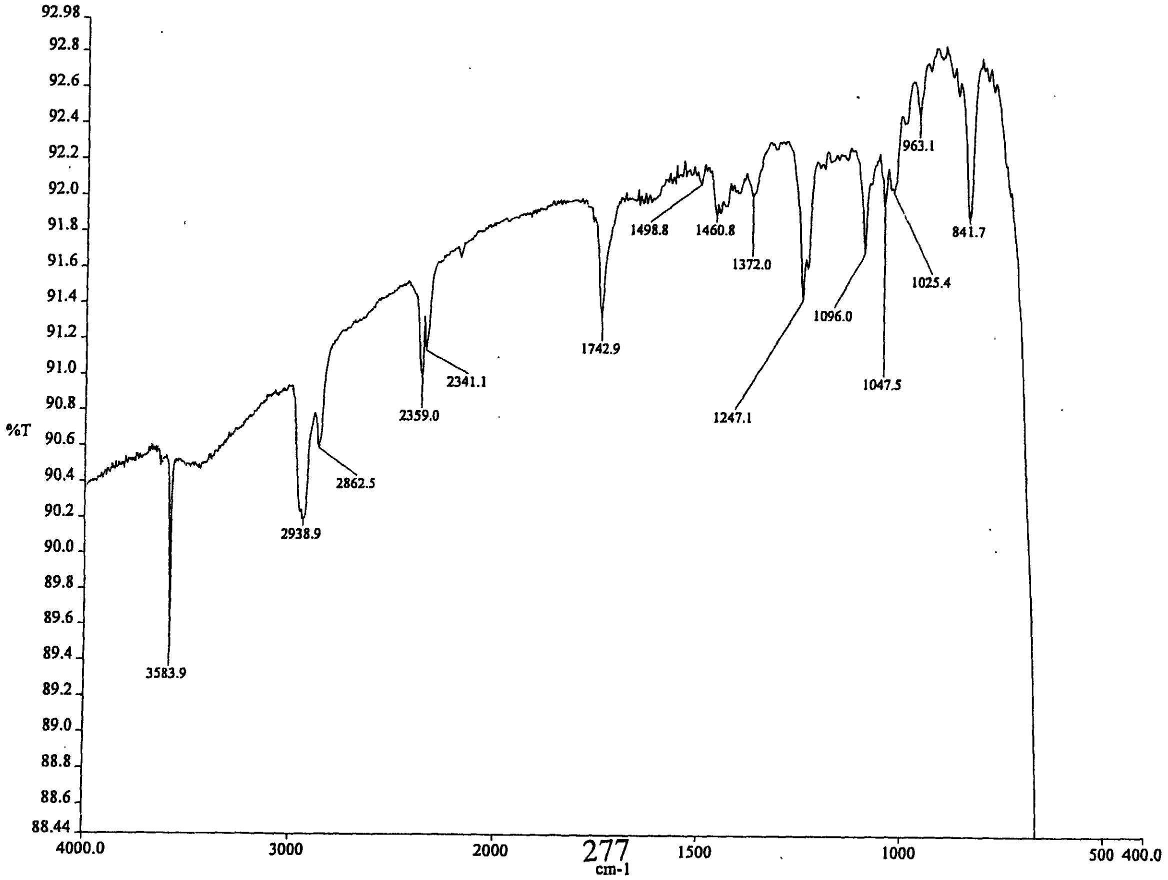
gCOSY

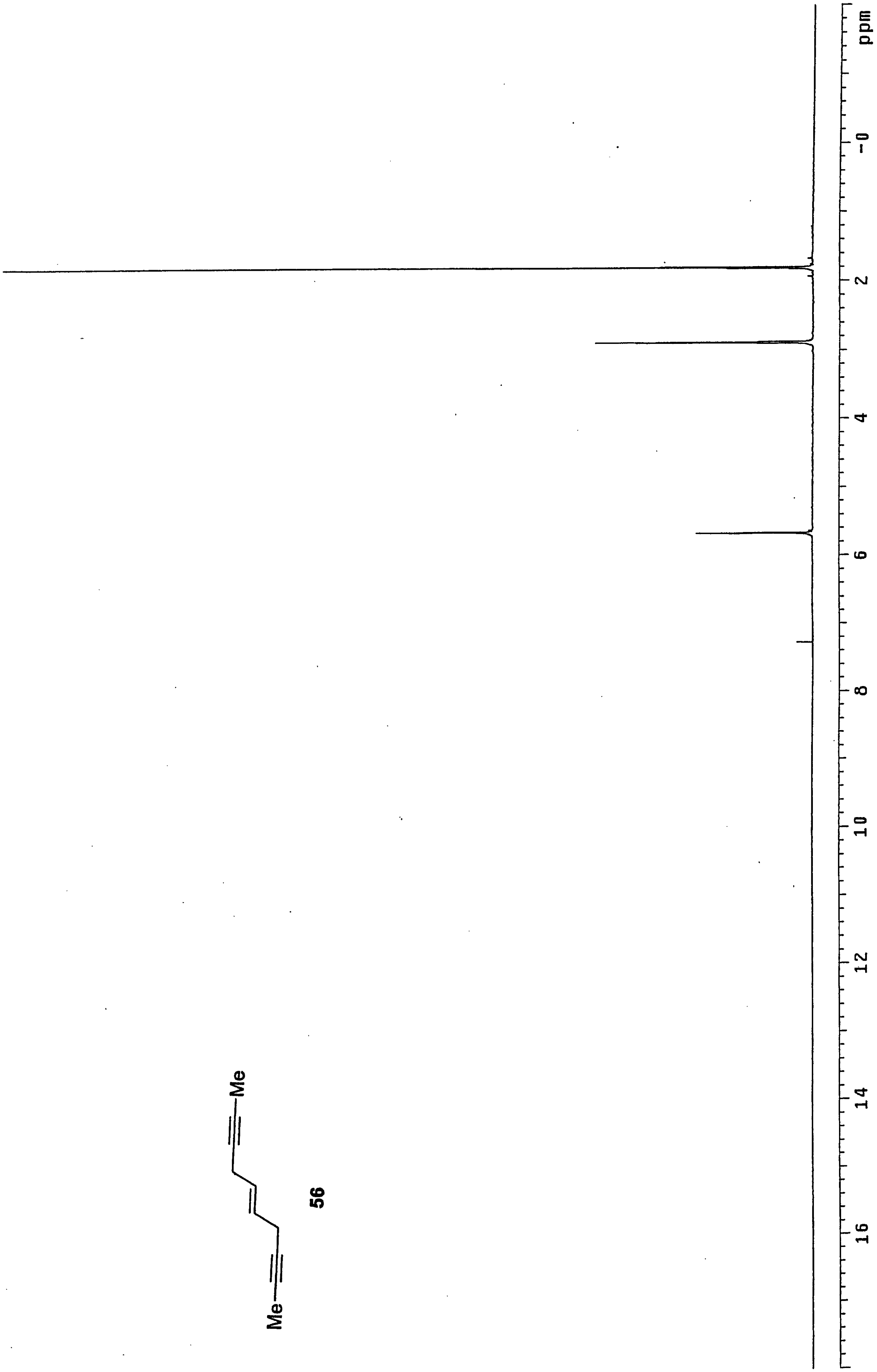

Me3Si
Me
AcO
O
O
H
H
O

55

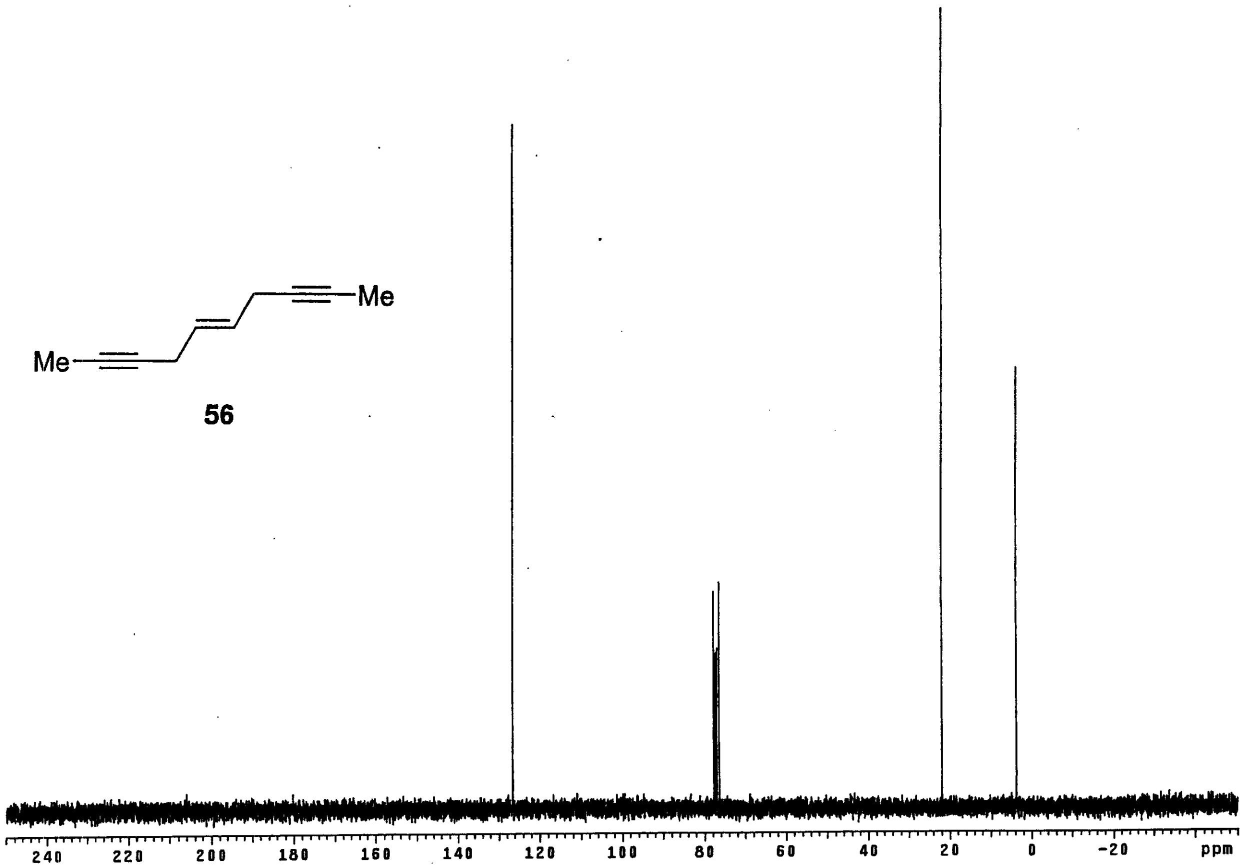
gHMBC


F2
(ppm)
-0
1
2
3
4
5
6
7
8
200
180
160
140
120
100
80
60
40
20
0
-20
F1 (ppm)

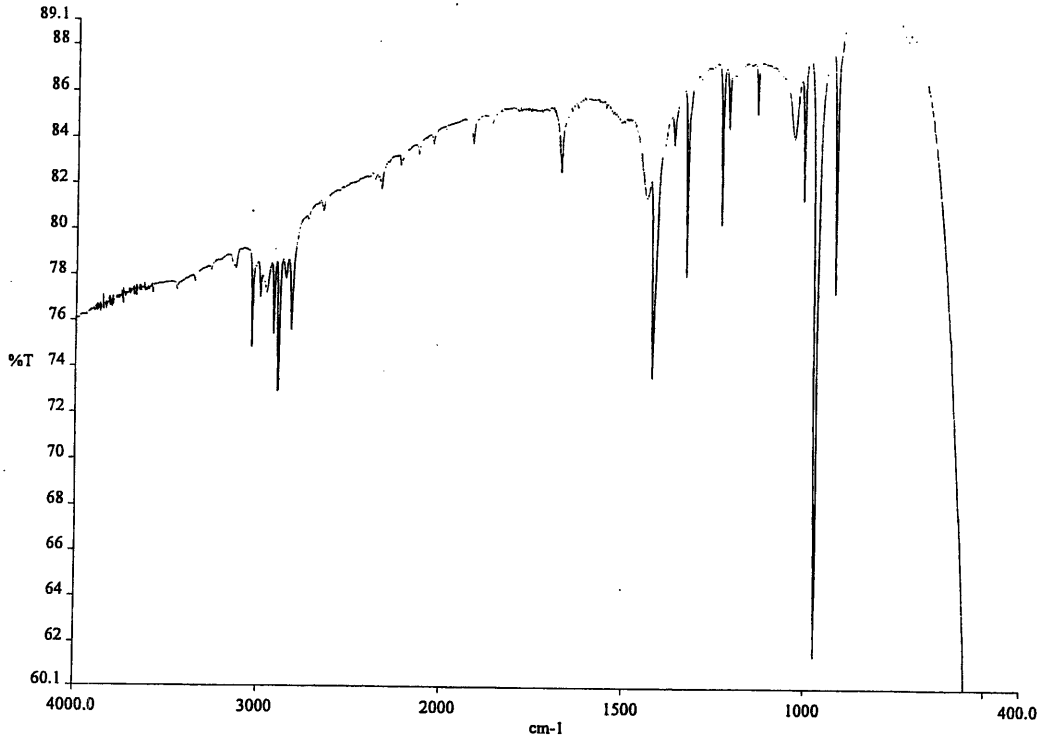

92.98
92.8
92.6
92.4
92.2
92.0
91.8
91.6
91.4
91.2
91.0
90.8
%T
90.6
90.4
90.2
90.0
89.8
89.6
89.4
89.2
89.0
88.8
88.6
88.44
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3583.9
2938.9
2862.5
2359.0
2341.1
1742.9
1498.8
1460.8
1372.0
1247.1
1096.0
1047.5
1025.4
963.1
841.7

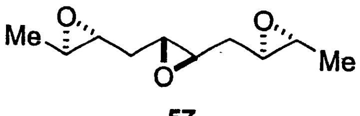


56

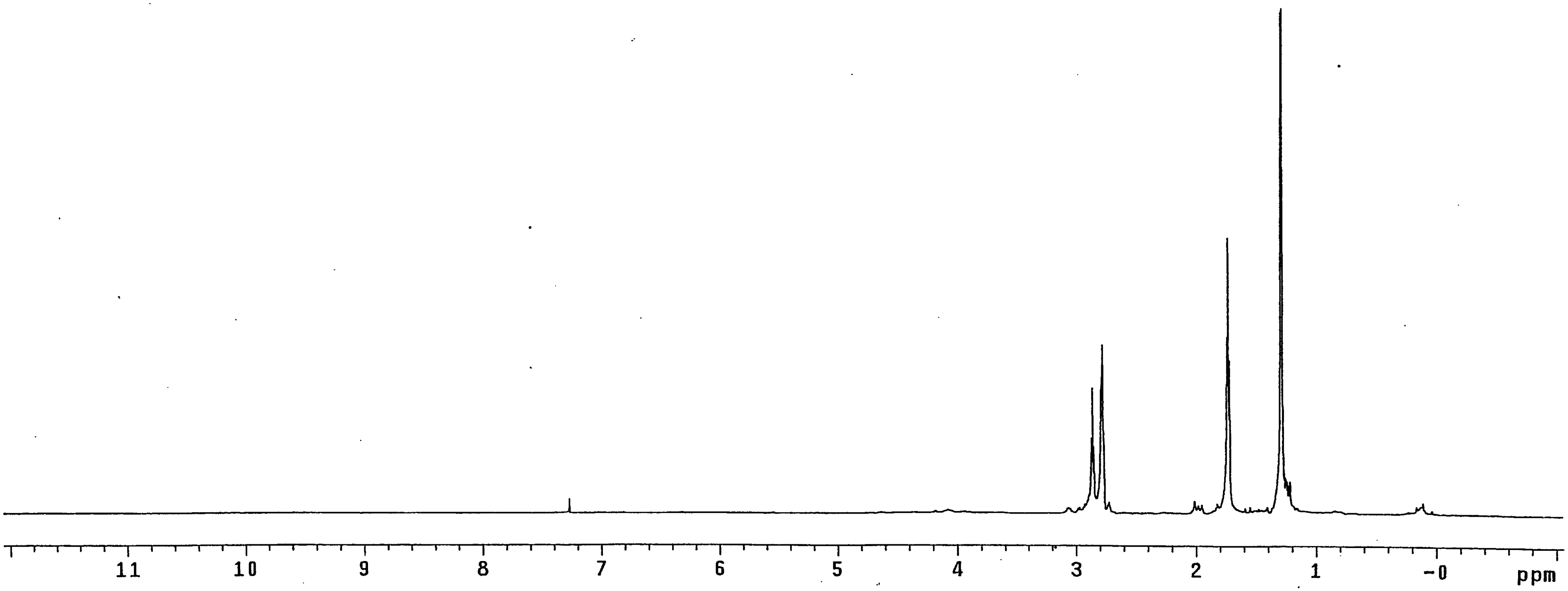

Me
Me
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

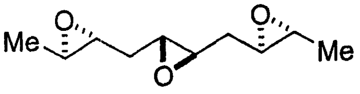
56


89.1
88
86
84
82
80
78
76
%T
74
72
70
68
66
64
62
60.1
4000.0
3000
2000
1500
1000
400.0
cm-1

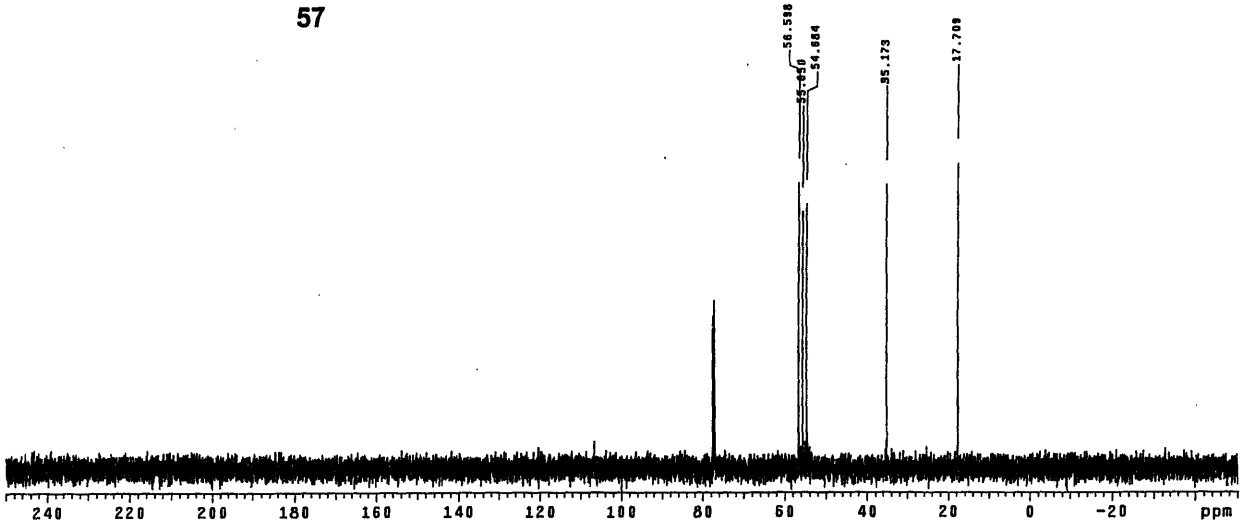


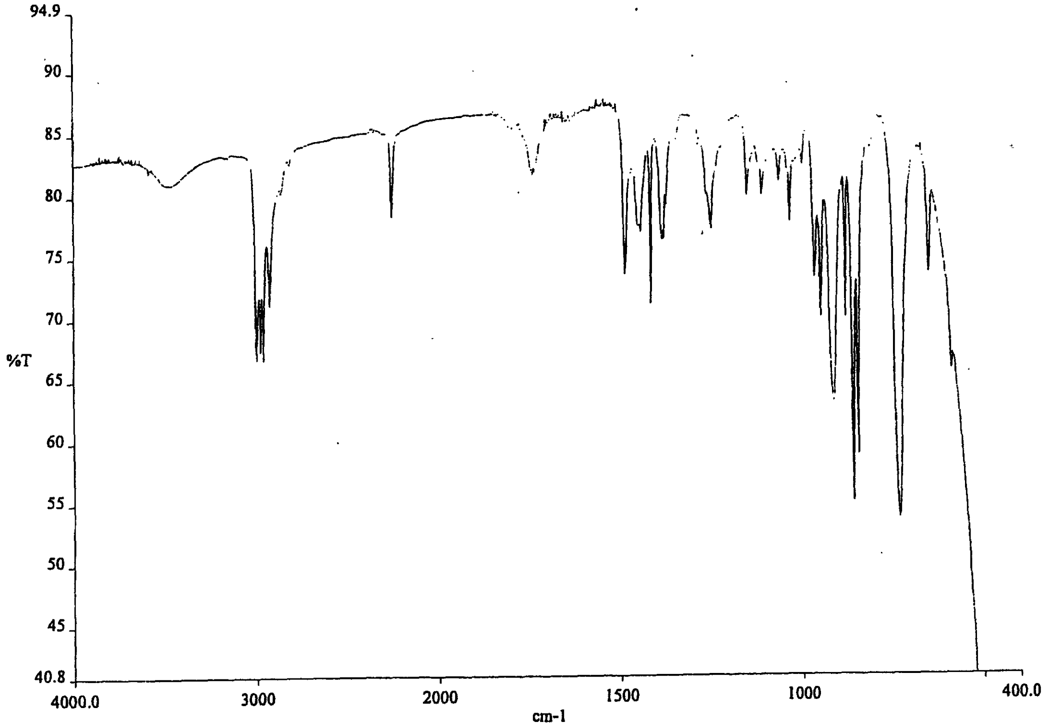
57

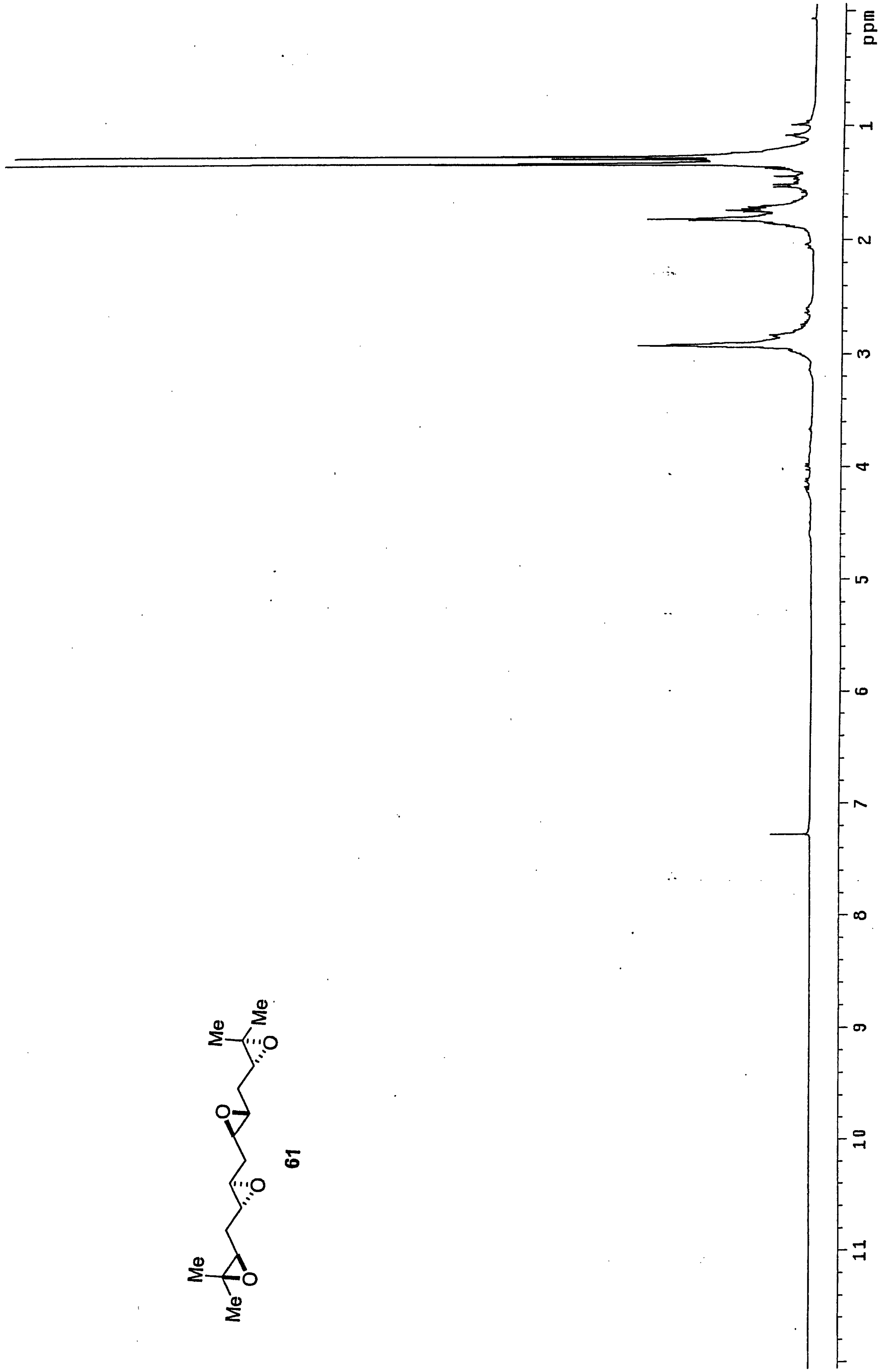



Me
O
O
O
Me

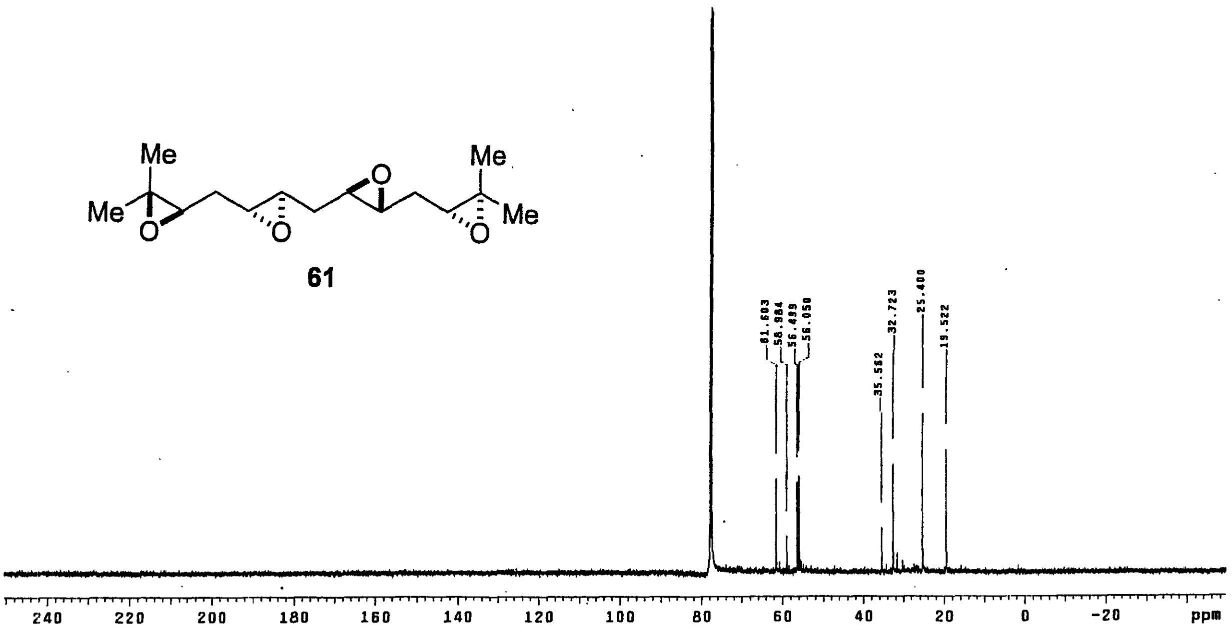
57


56.598
55.650
54.884
35.173
17.709
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

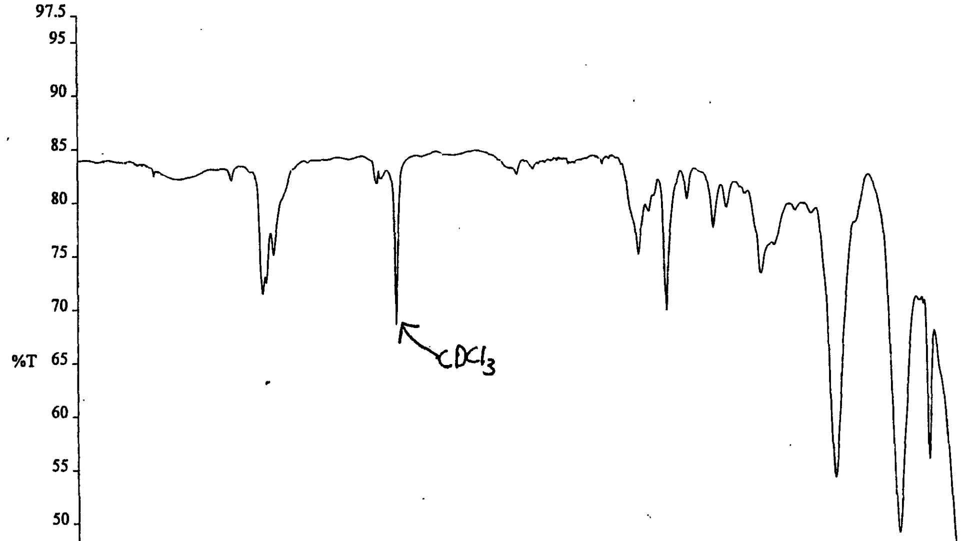

94.9
90
85
80
75
70
%T
65
60
55
50
45
40.8
4000.0
3000
2000
1500
1000
400.0
cm-1



61

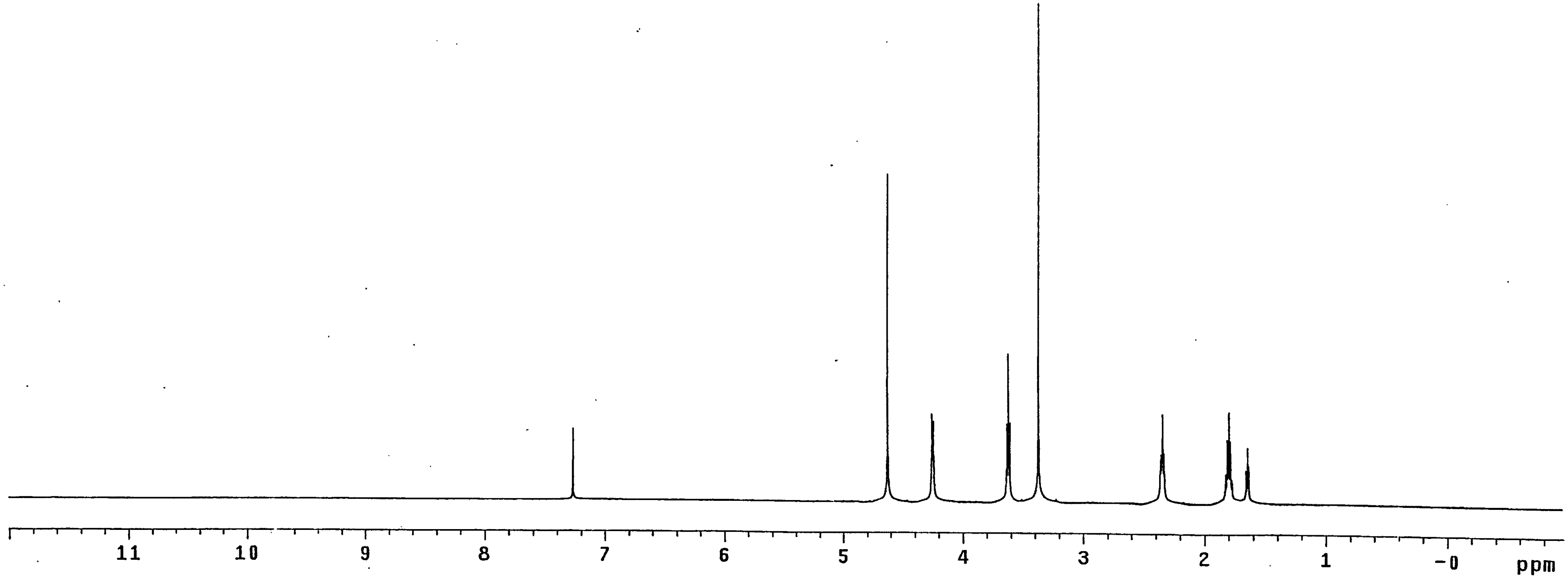

Me
Me
O
O
O
Me
O
Me
61.603
58.984
56.499
56.050
35.562
32.723
25.400
19.522
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

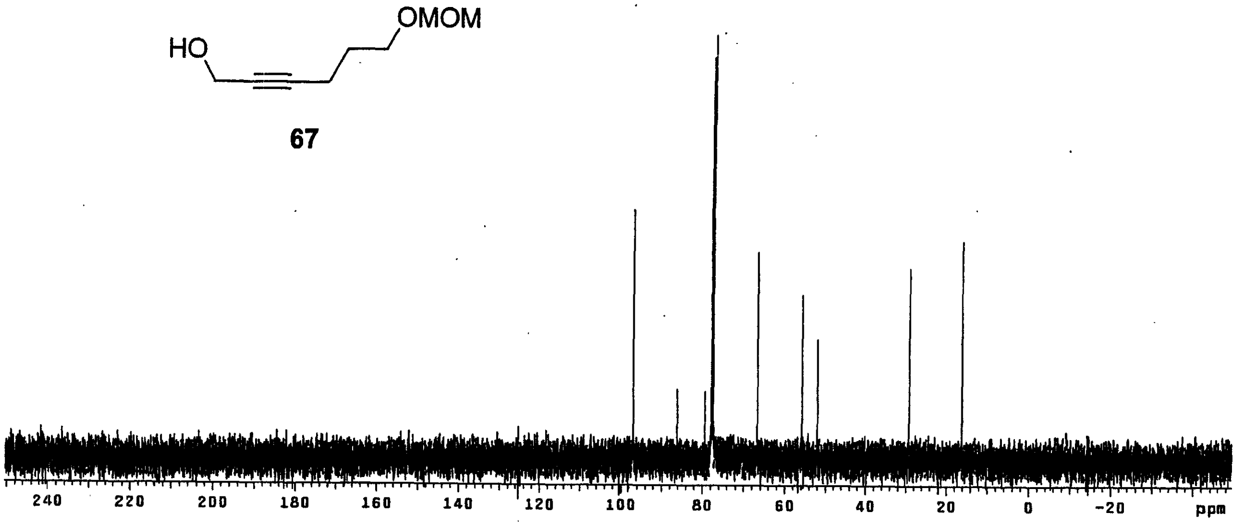
61


97.5
95
90
85
80
75
70
%T
65
60
55
50
45
40
34.9
4000.0
3000
2000
1500
1000
400.0
cm-1

$CDCl_3$

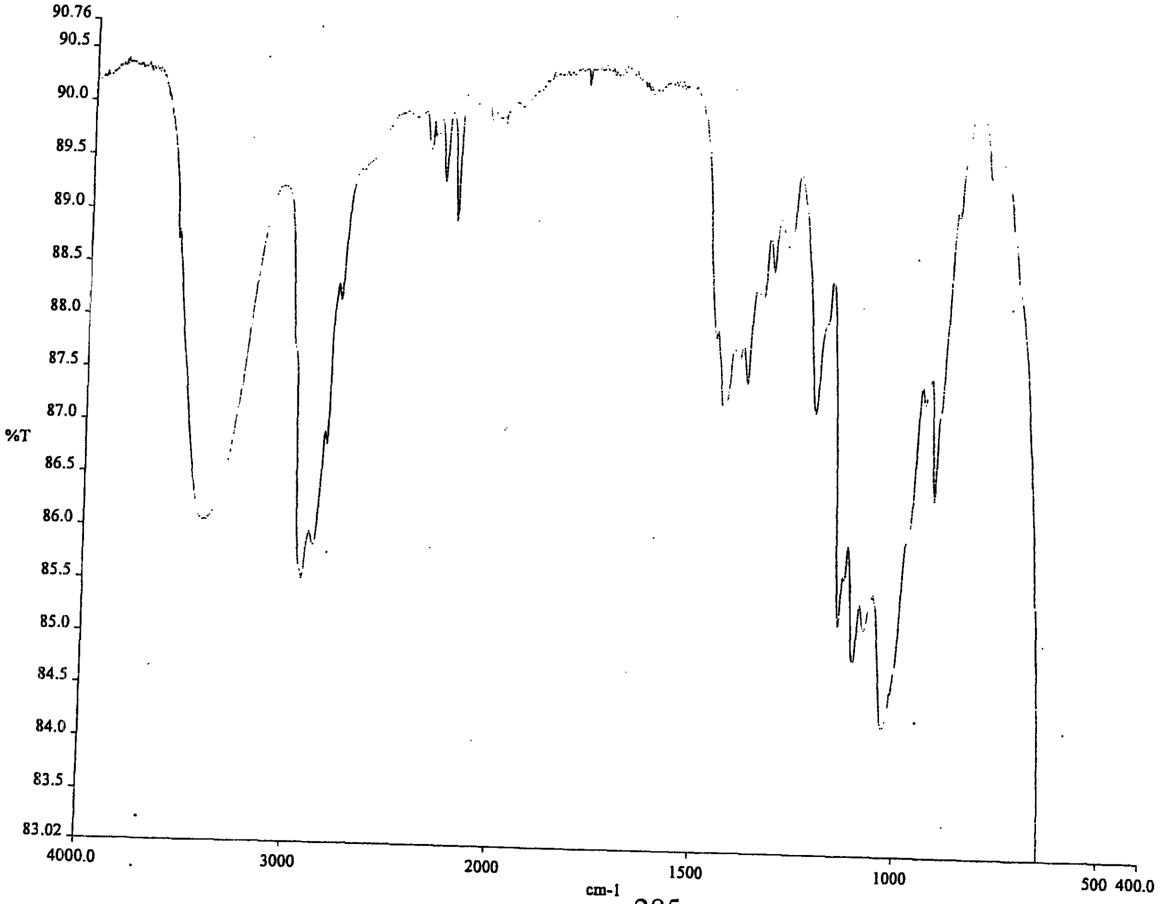
67

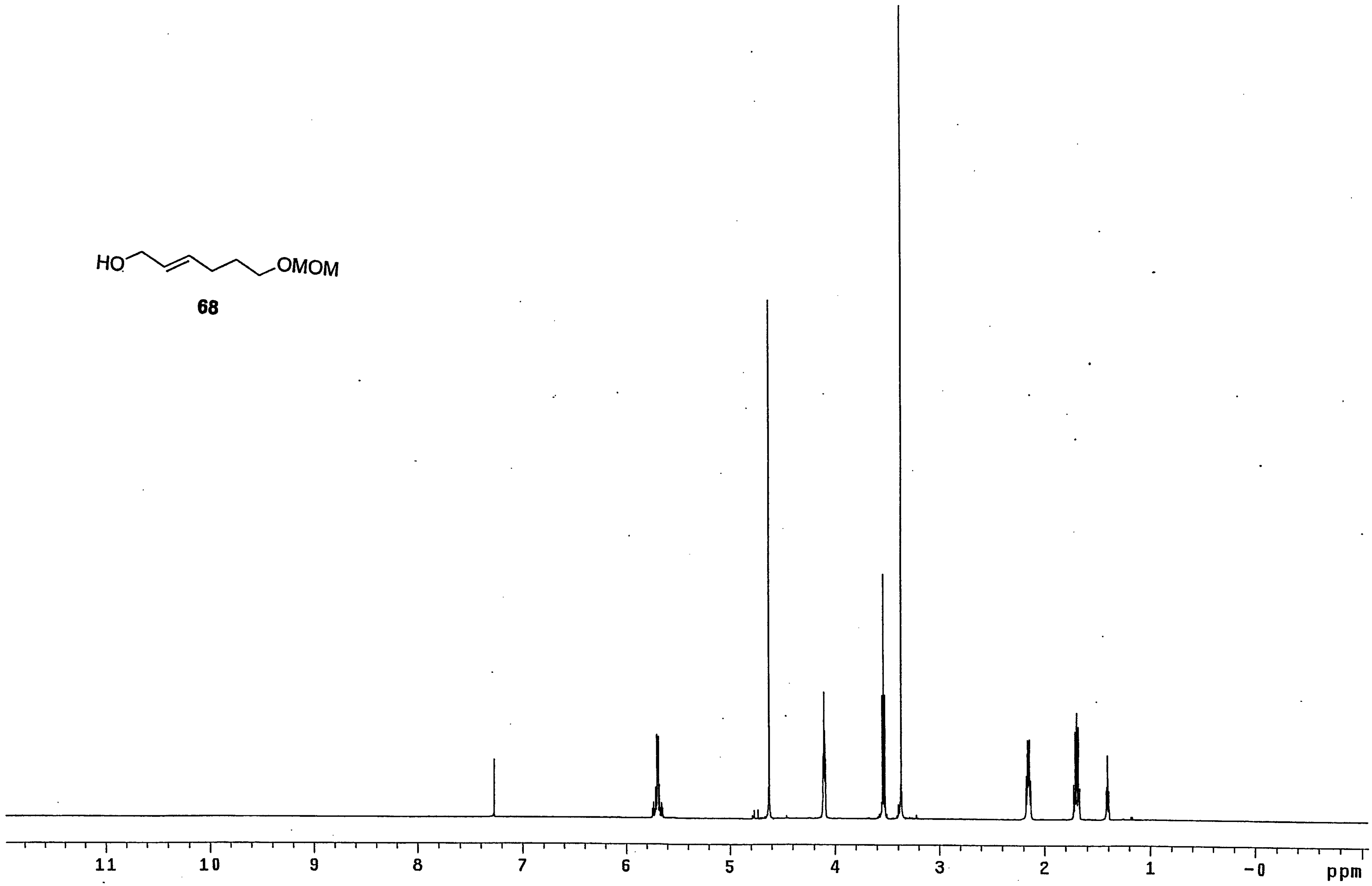



HO
OMOM

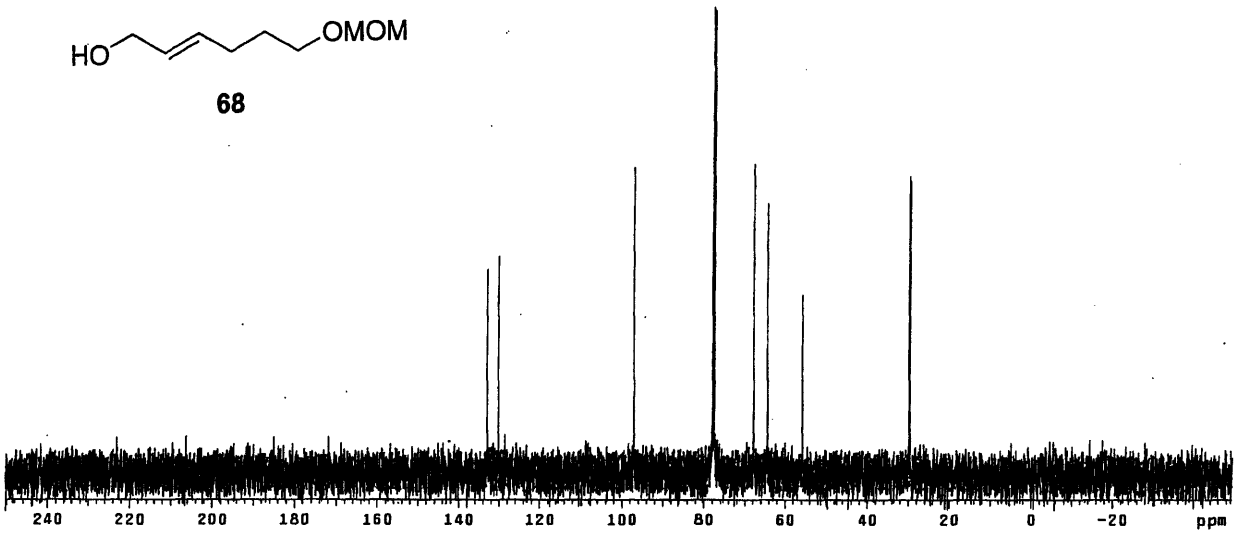
67

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

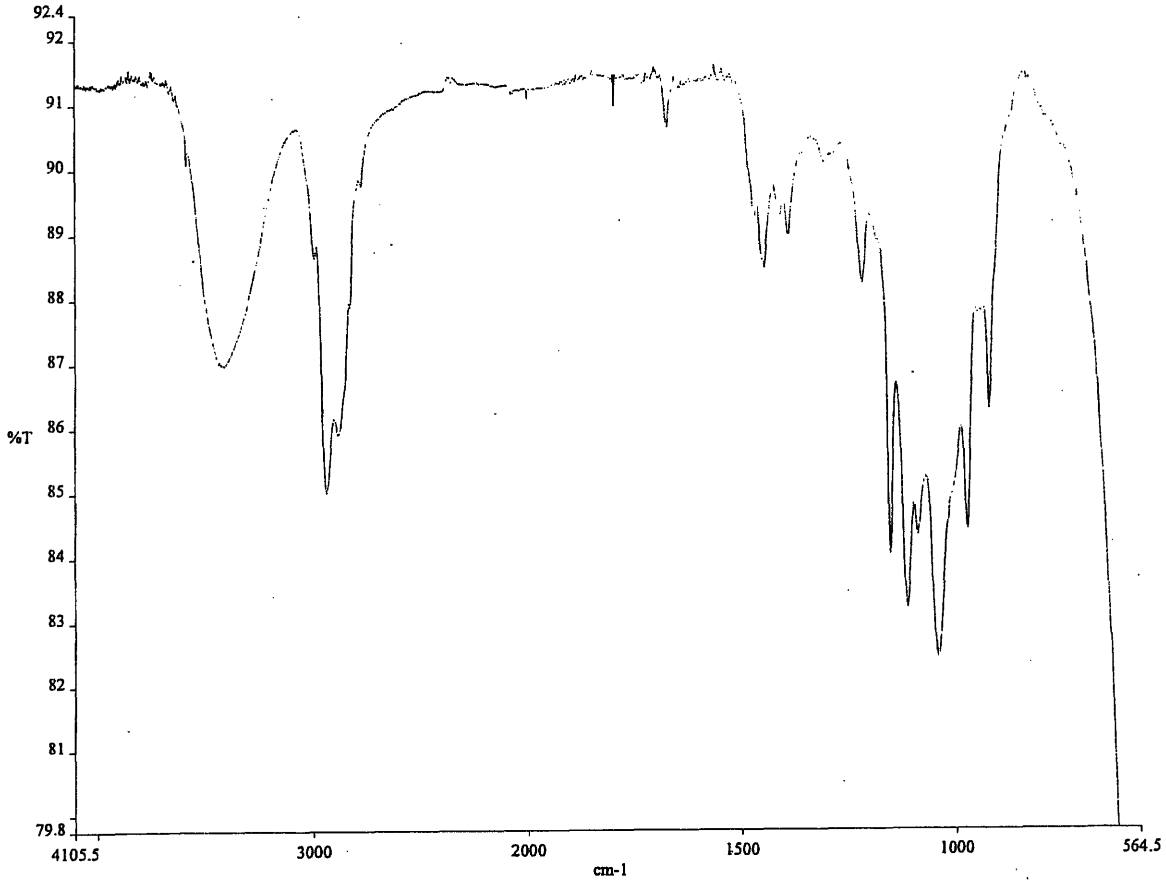

90.76
90.5
90.0
89.5
89.0
88.5
88.0
87.5
87.0
%T
86.5
86.0
85.5
85.0
84.5
84.0
83.5
83.02
4000.0
3000
2000
1500
1000
500 400.0
cm-1

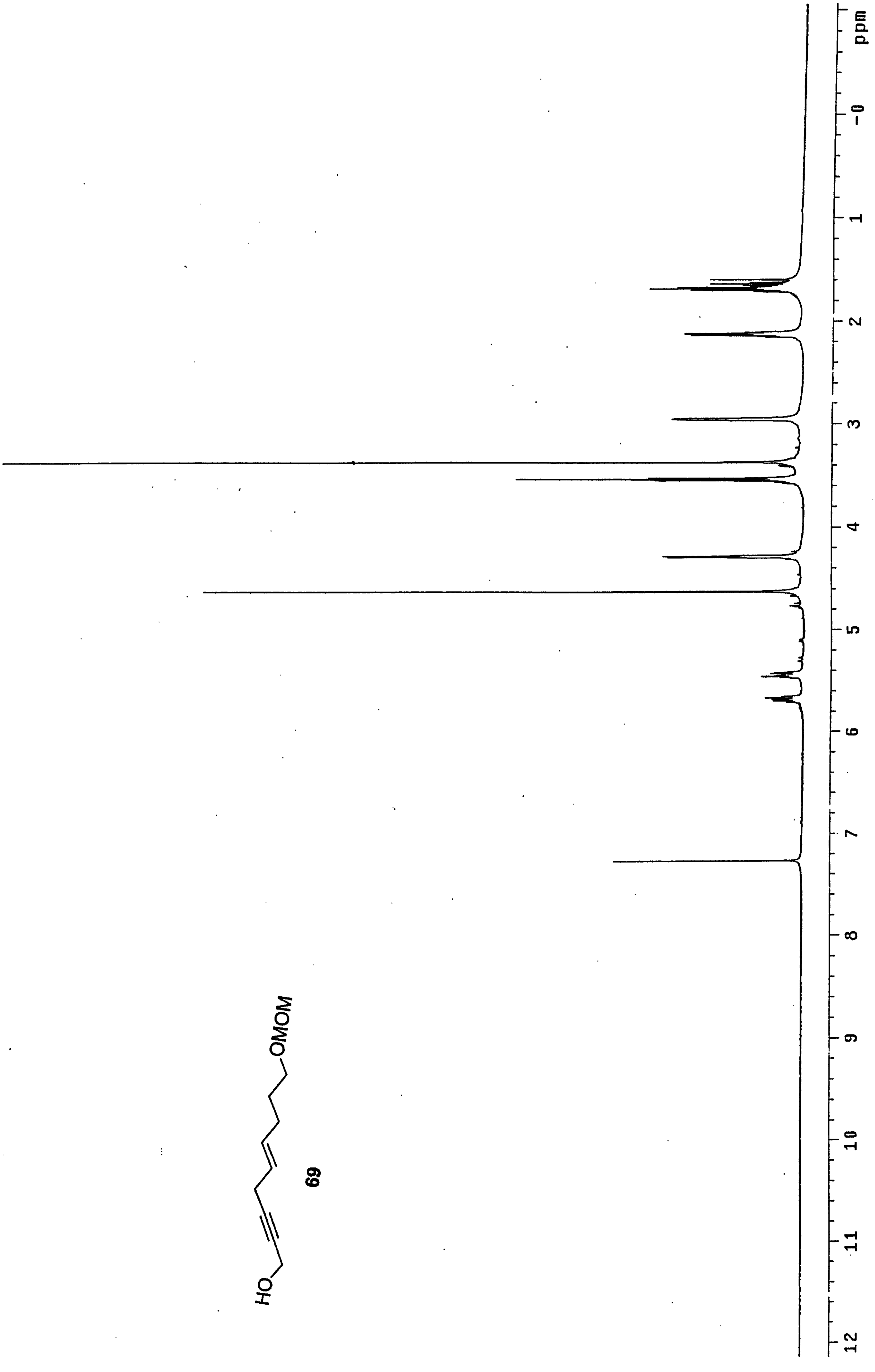


68

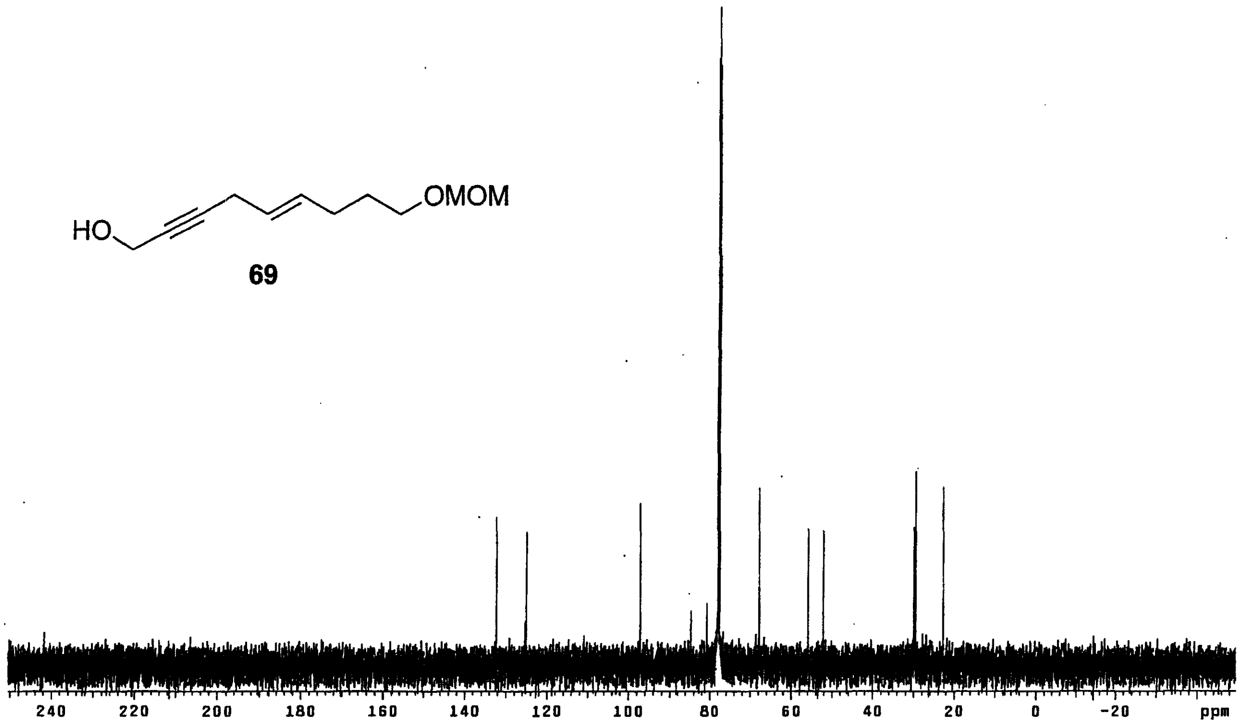

HO
OMOM
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

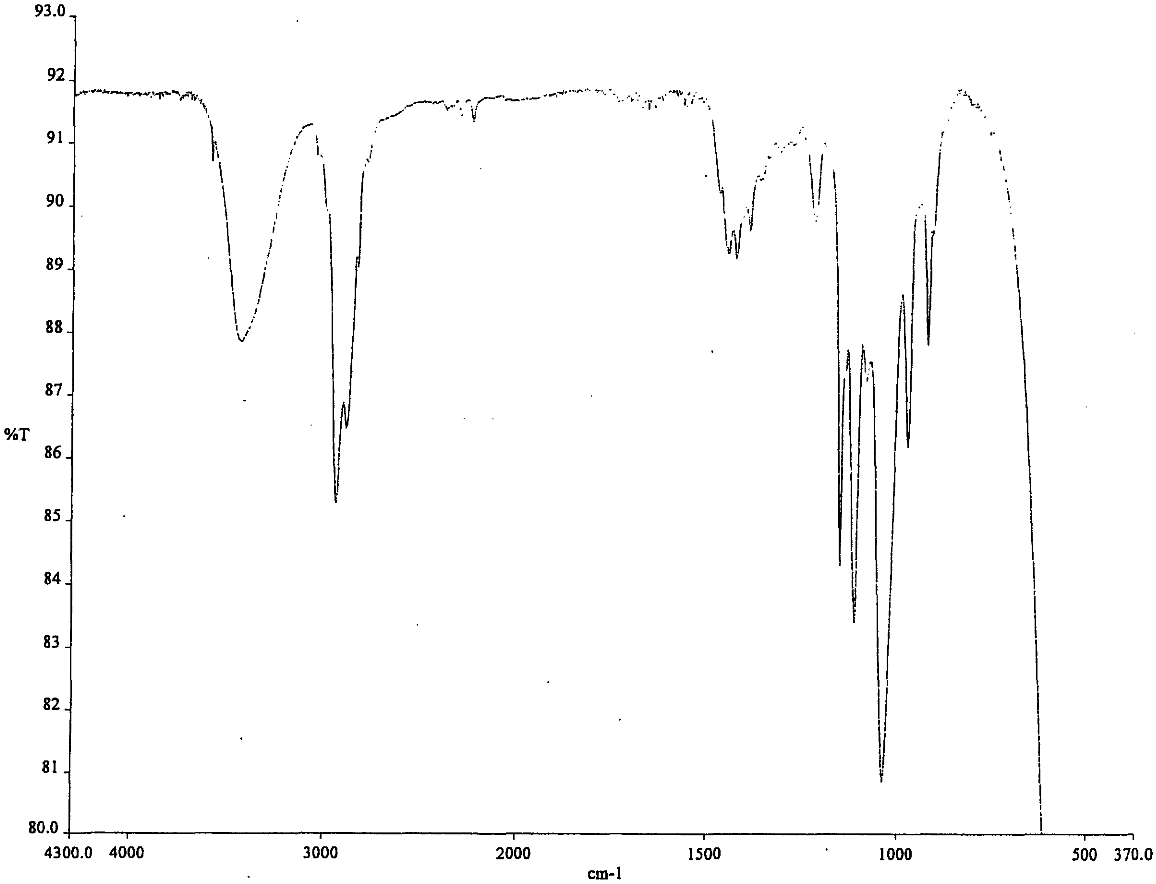
68

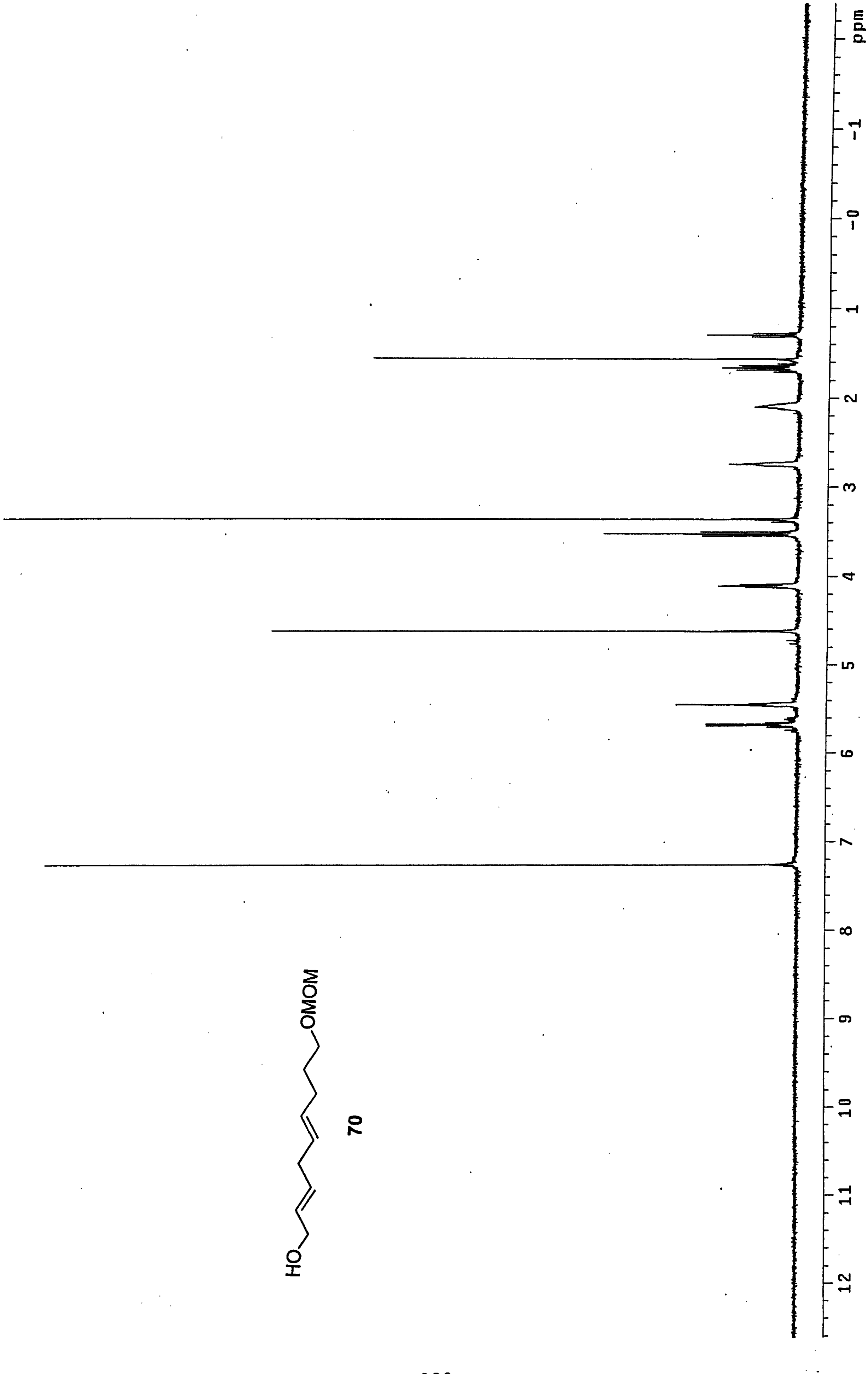

92.4
92
91
90
89
88
87
86
85
84
83
82
81
79.8
%T
4105.5
3000
2000
1500
1000
564.5
cm-1



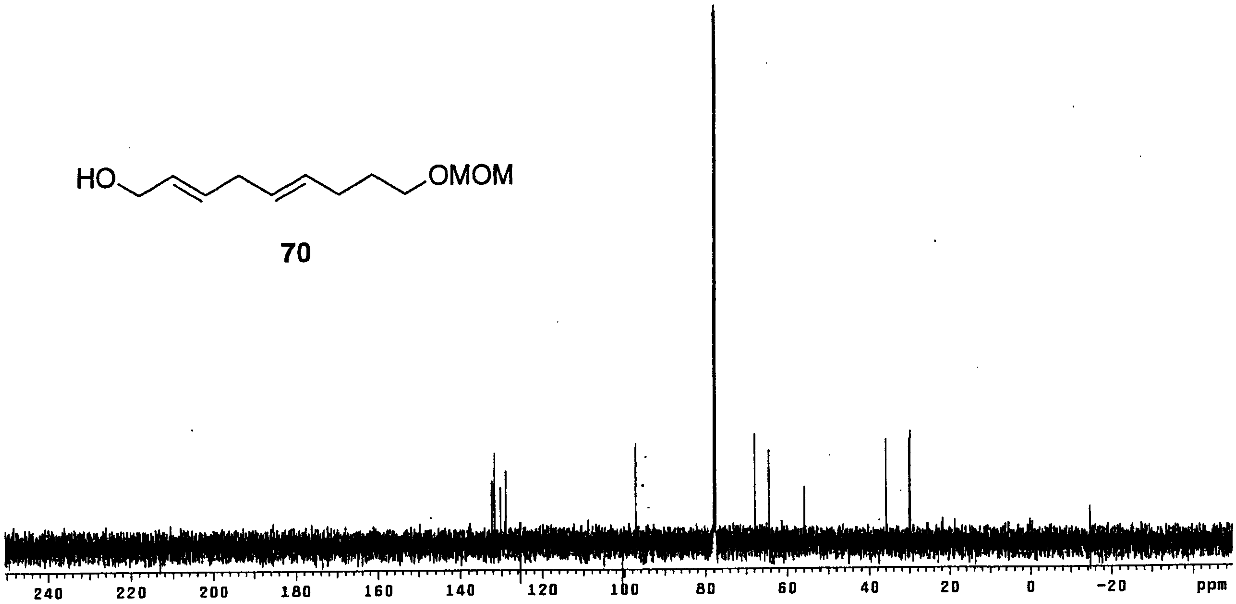
69


HO
OMOM
69
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


93.0
92
91
90
89
88
87
%T
86
85
84
83
82
81
80.0
4300.0
4000
3000
2000
1500
1000
500
370.0
cm-1

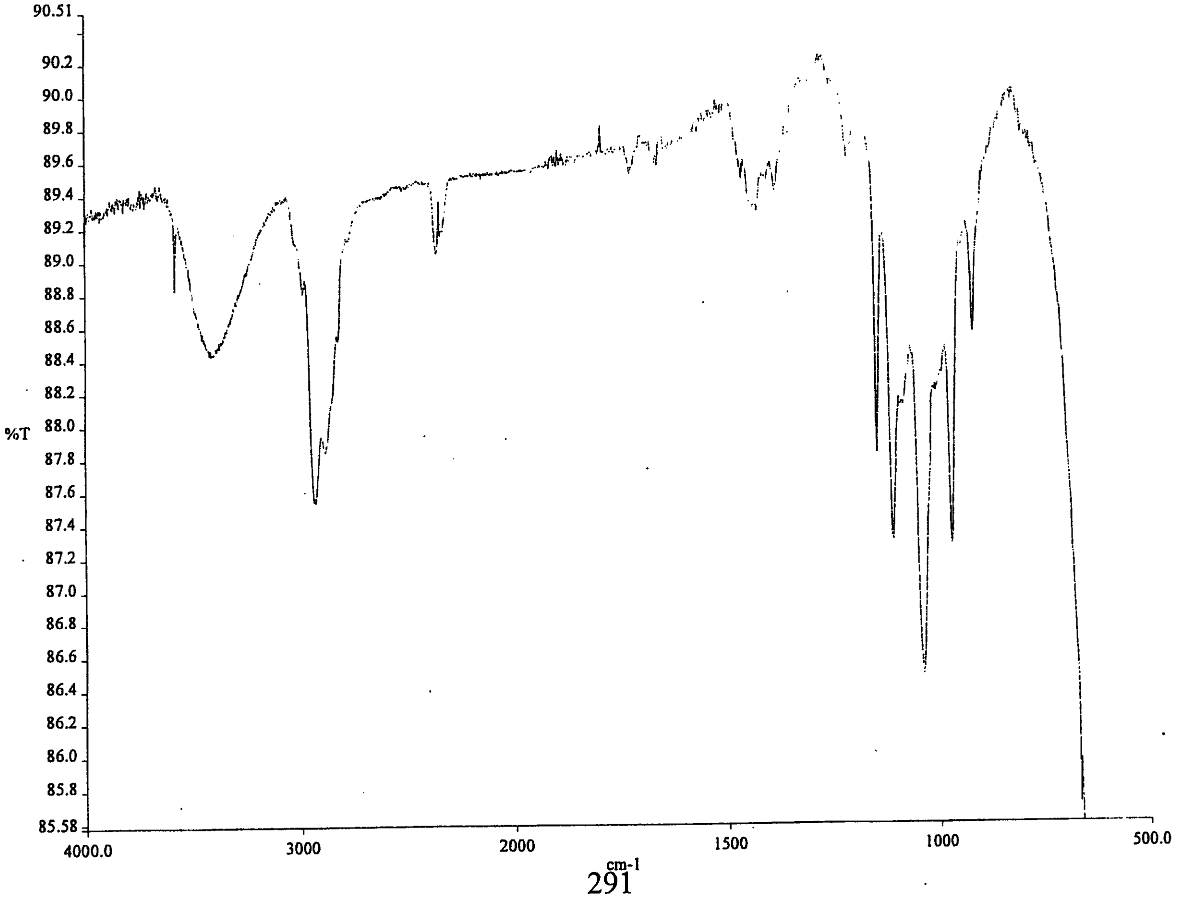


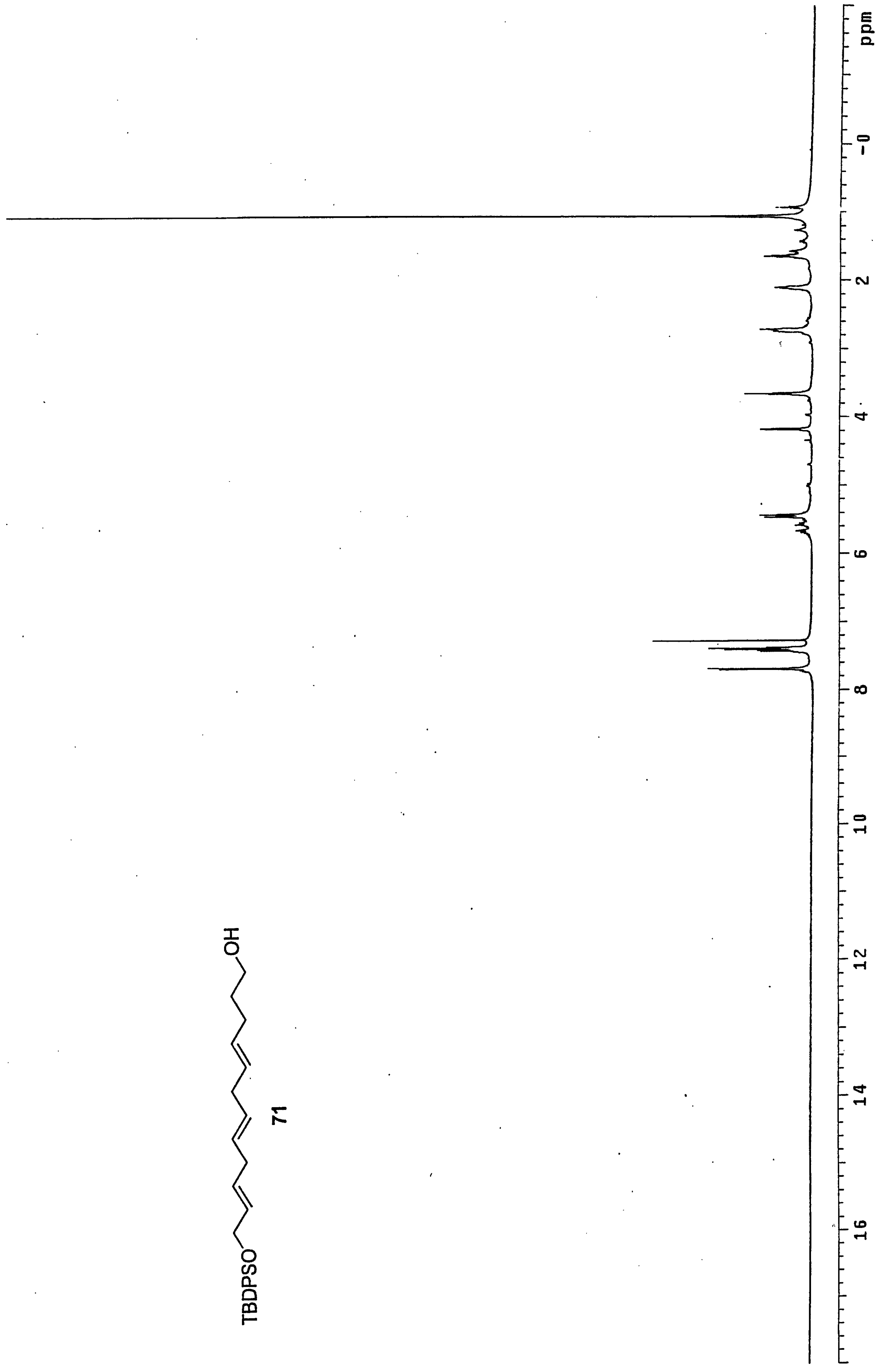
70

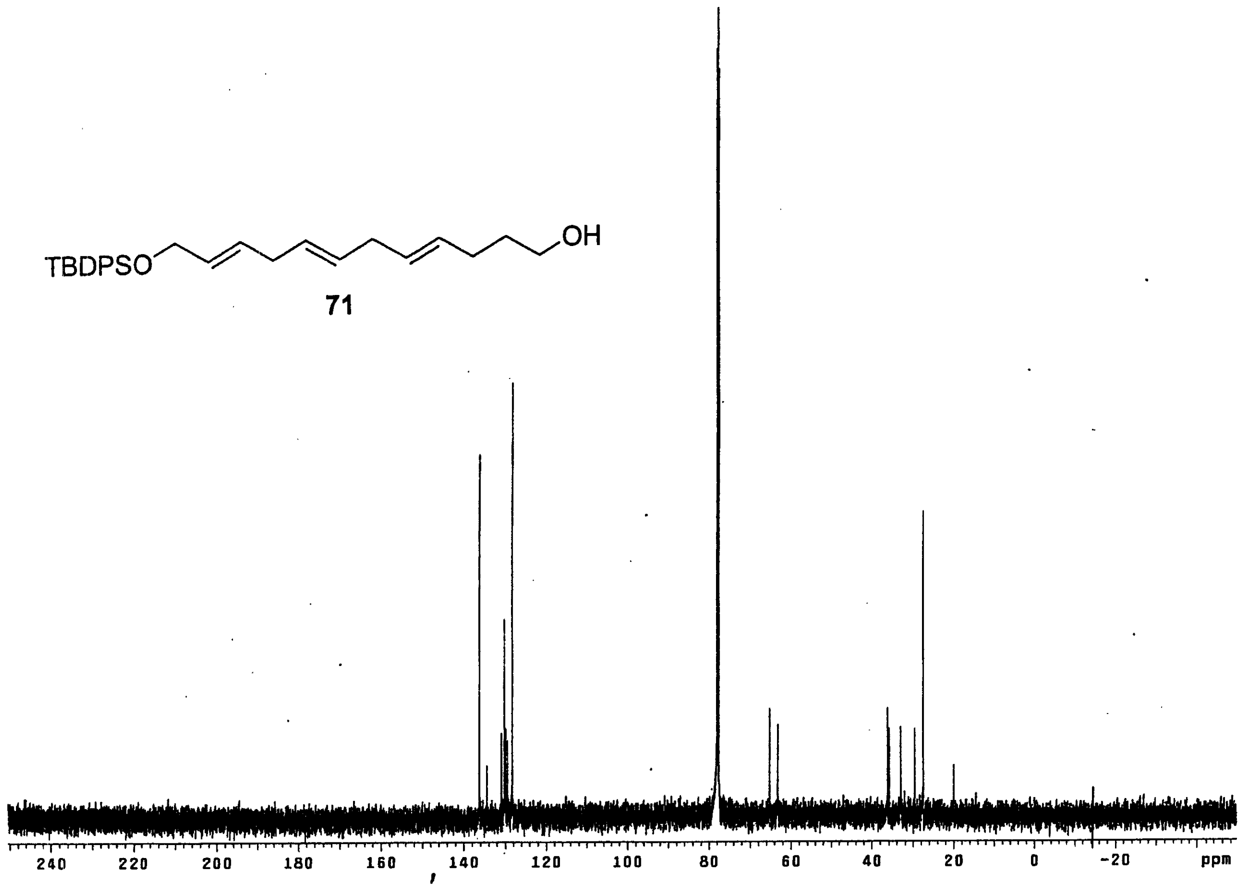

HO
OMOM

70

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

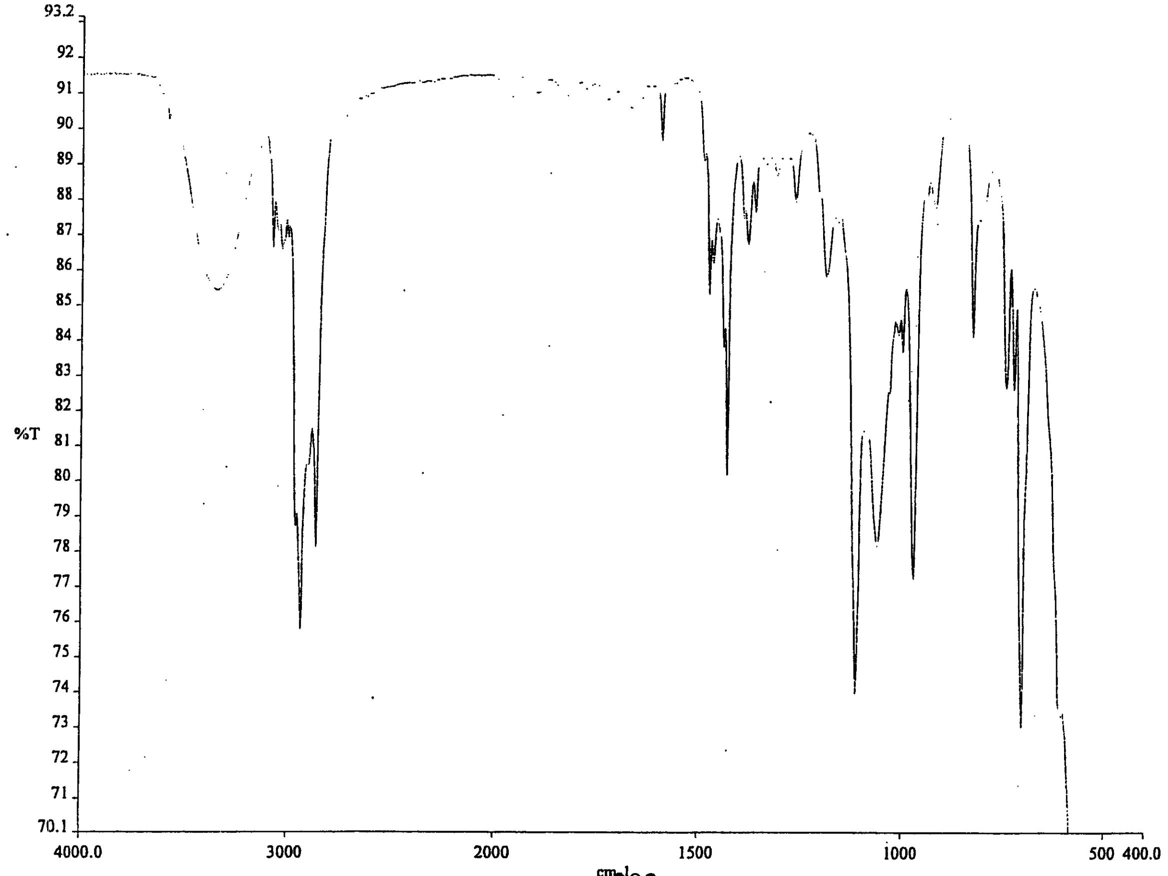

90.51
90.2
90.0
89.8
89.6
89.4
89.2
89.0
88.8
88.6
88.4
88.2
88.0
87.8
87.6
87.4
87.2
87.0
86.8
86.6
86.4
86.2
86.0
85.8
85.58
%T
4000.0
3000
2000
1500
1000
500.0
cm-1

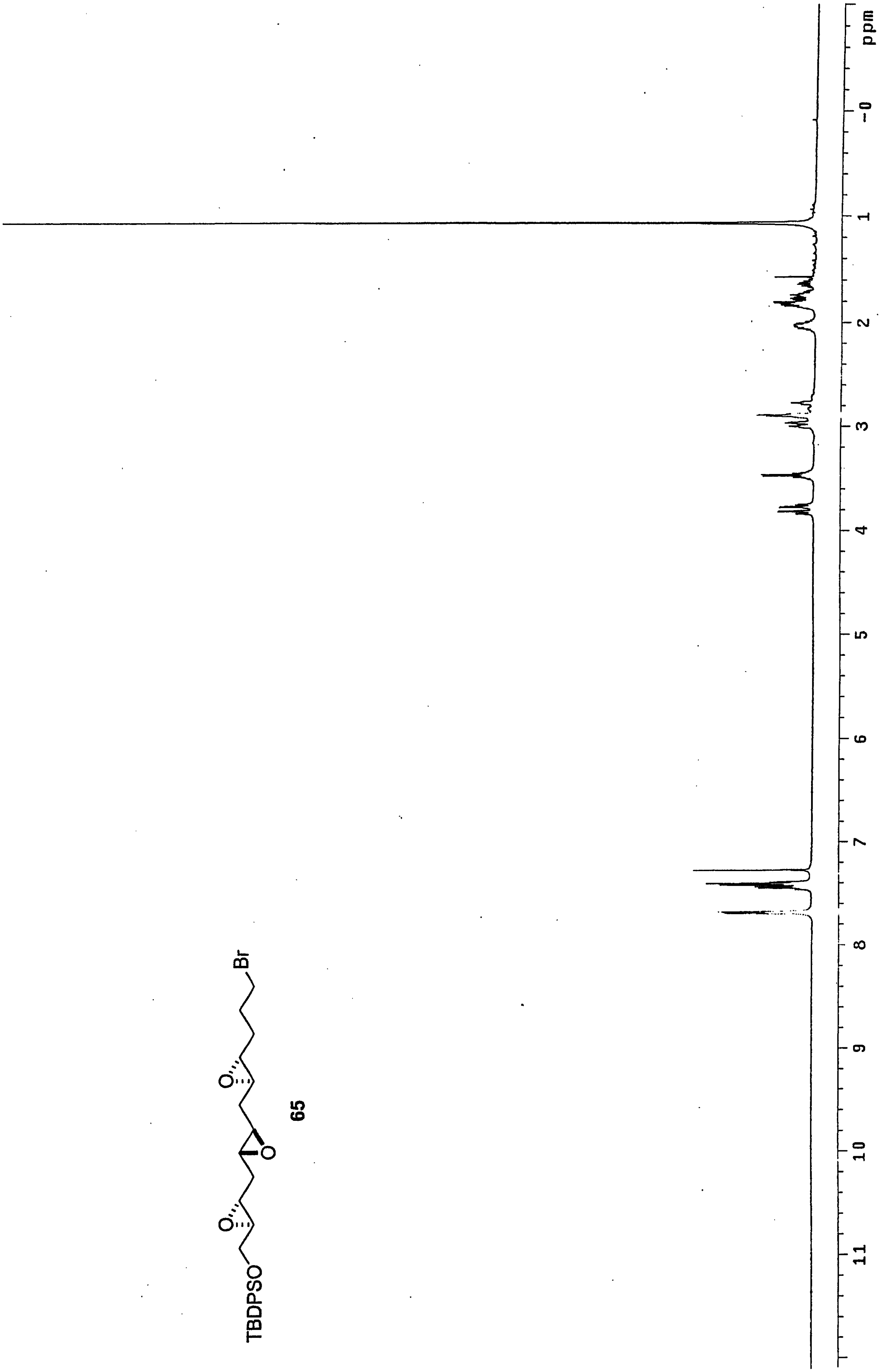

ppm
0
2
4
6
8
10
12
14
16
TBDPSO
OH
71


TBDPSO
OH

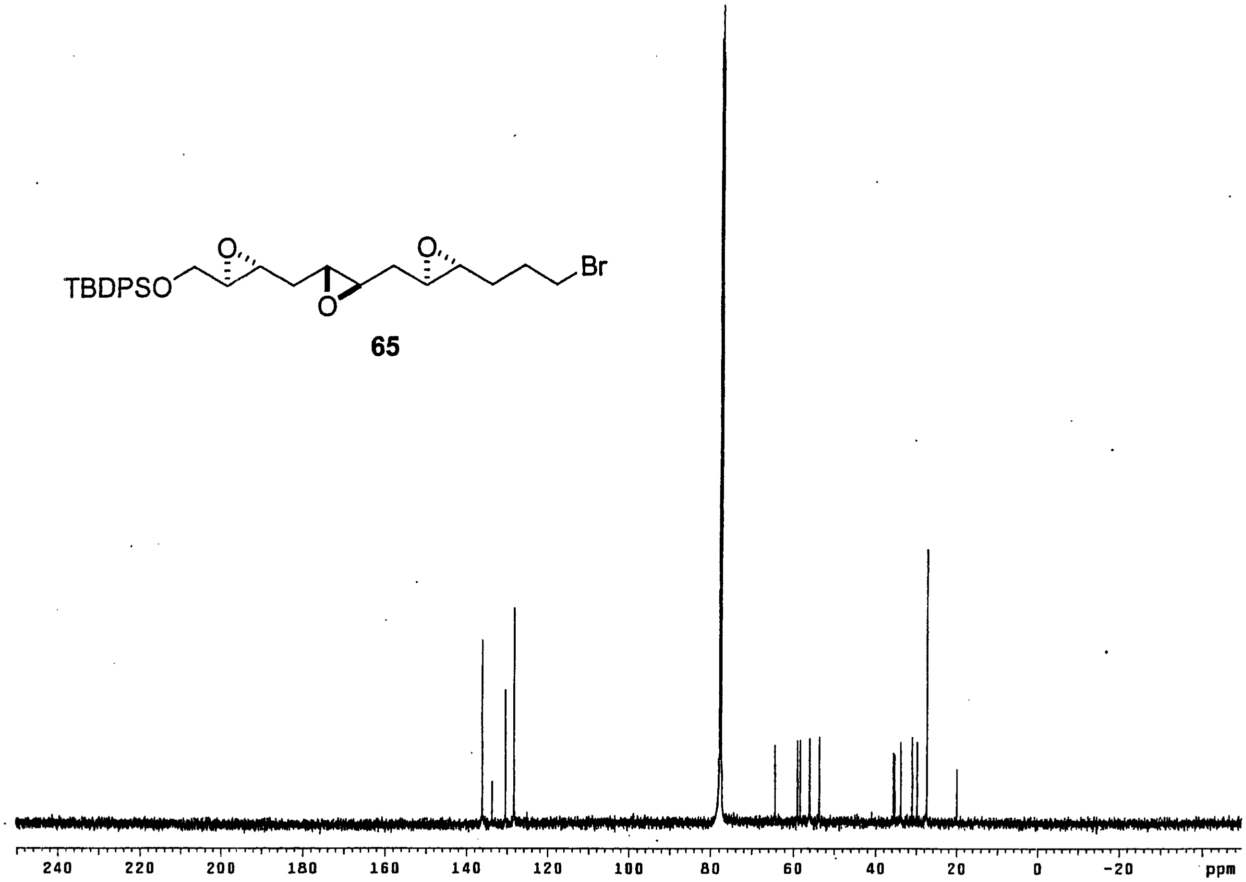
71

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


93.2
92
91
90
89
88
87
86
85
84
83
82
%T
81
80
79
78
77
76
75
74
73
72
71
70.1
4000.0
3000
2000
1500
1000
500 400.0
cm-1

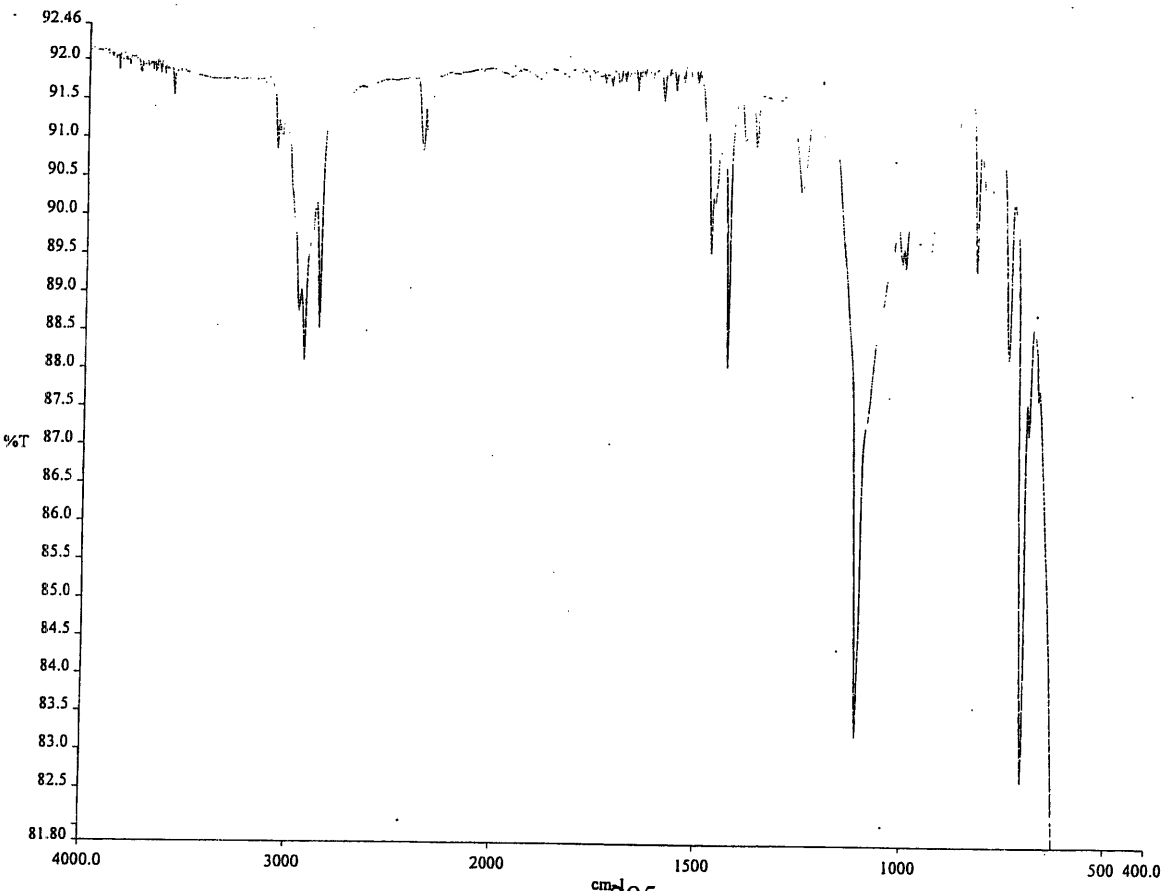


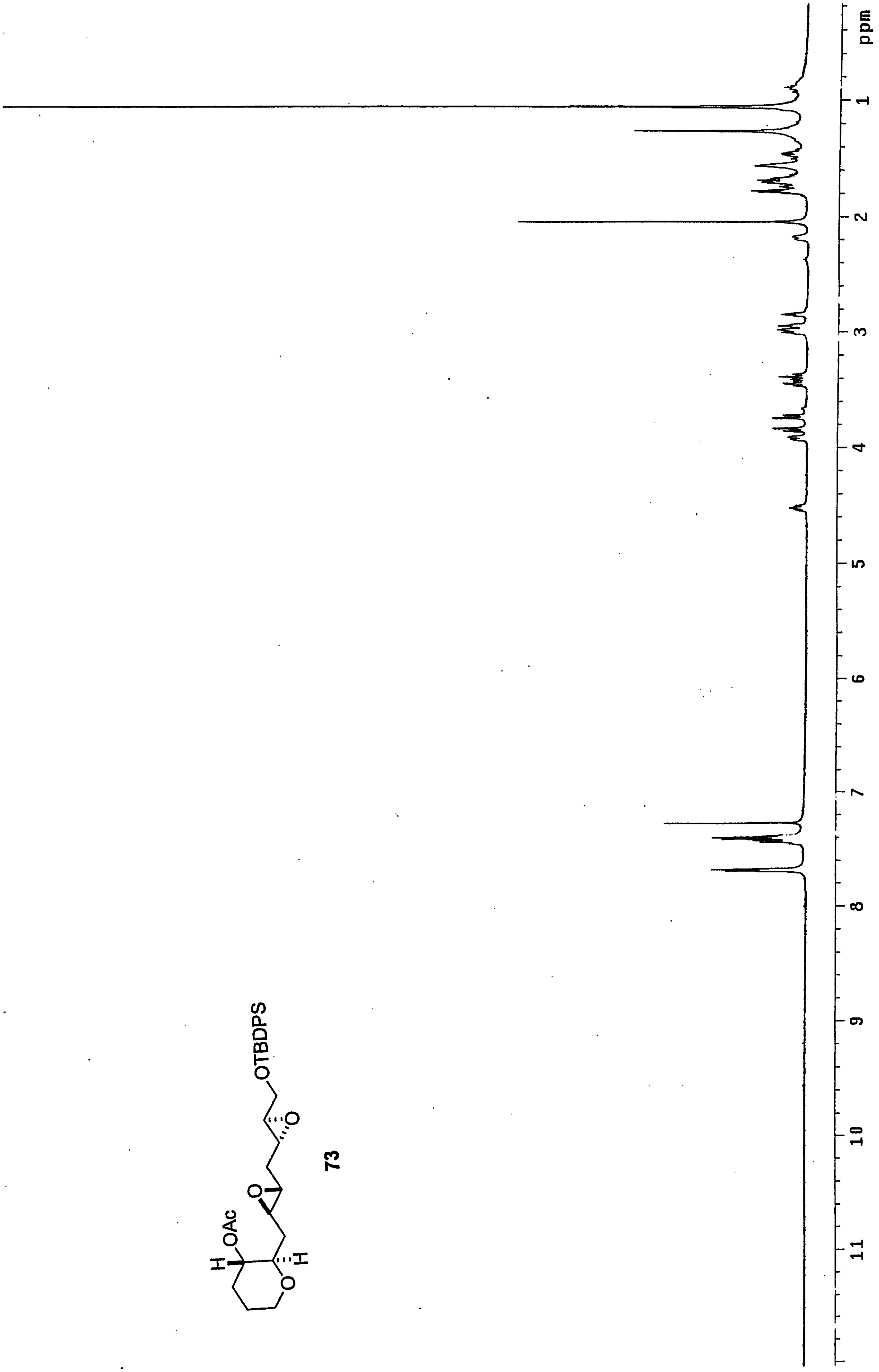
65


TBDPSO
O
O
O
Br

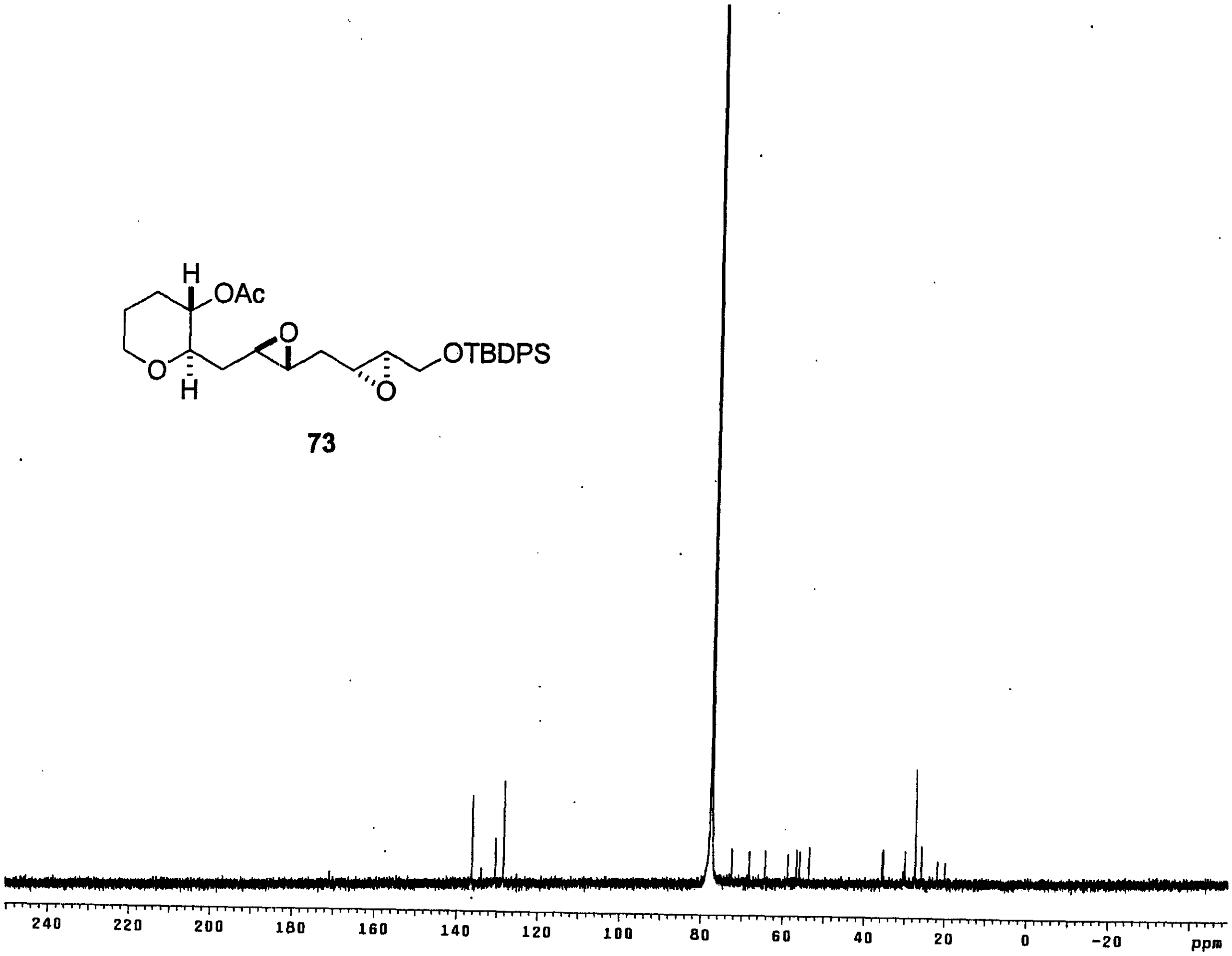
65

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


92.46
92.0
91.5
91.0
90.5
90.0
89.5
89.0
88.5
88.0
87.5
%T
87.0
86.5
86.0
85.5
85.0
84.5
84.0
83.5
83.0
82.5
81.80
4000.0
3000
2000
1500
1000
500
400.0
cm-1

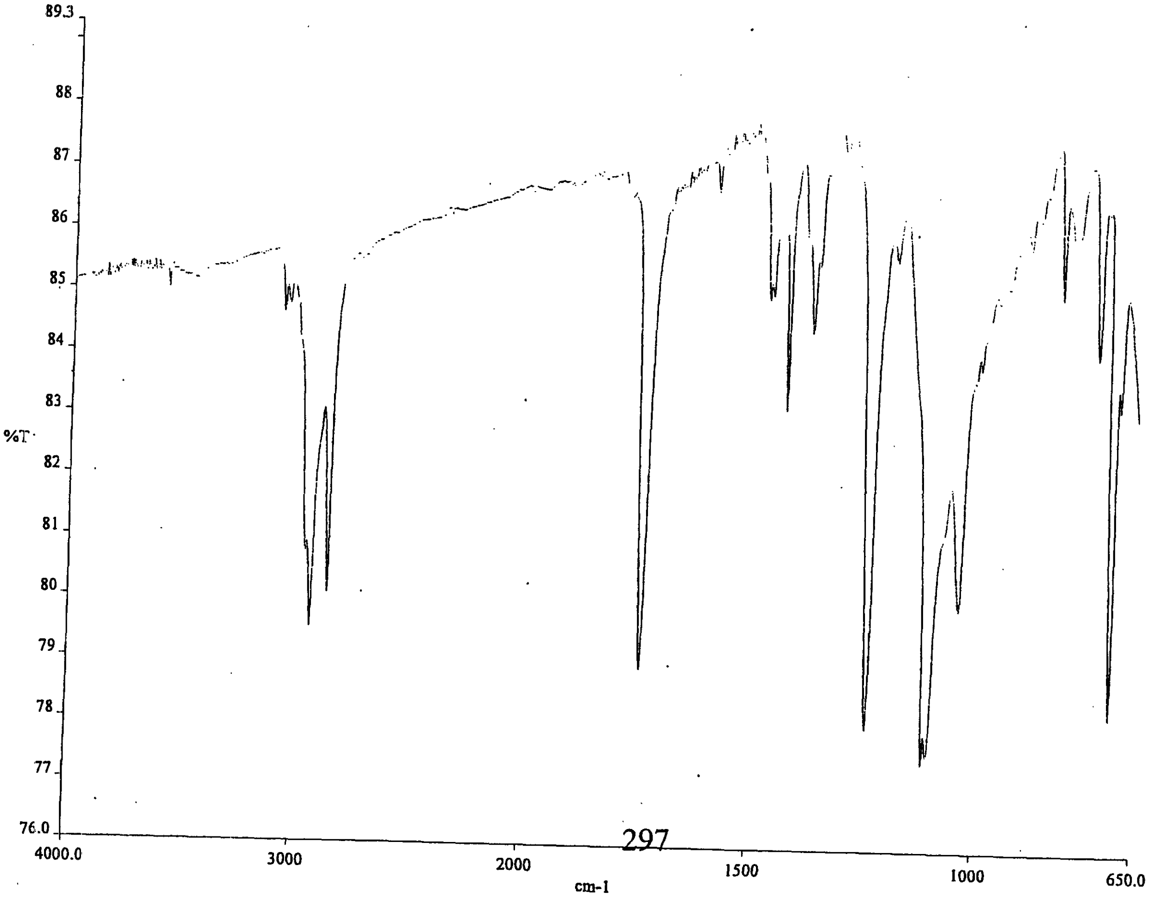


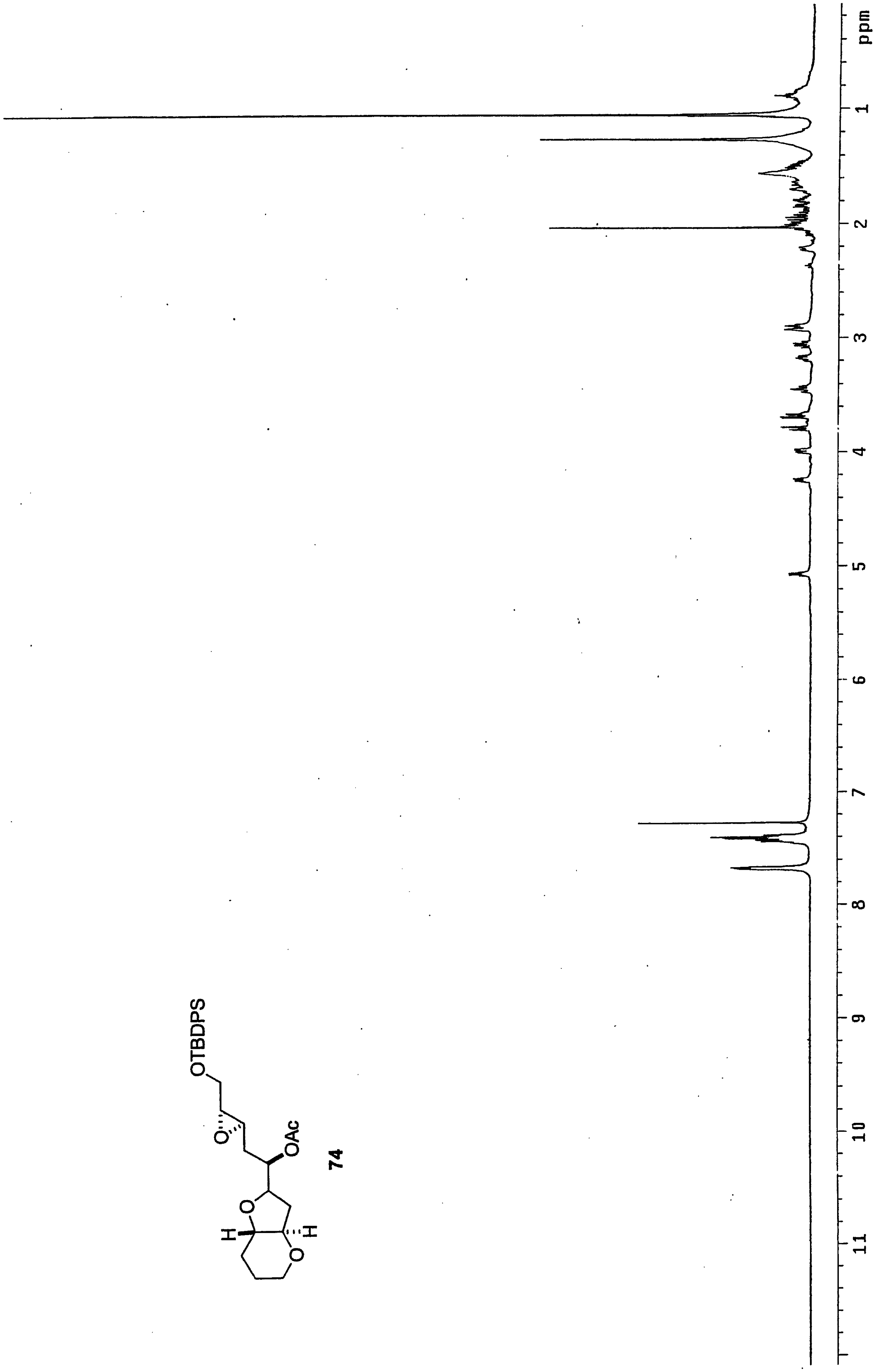
73


H
OAc
O
O
H
O
OTBDPS

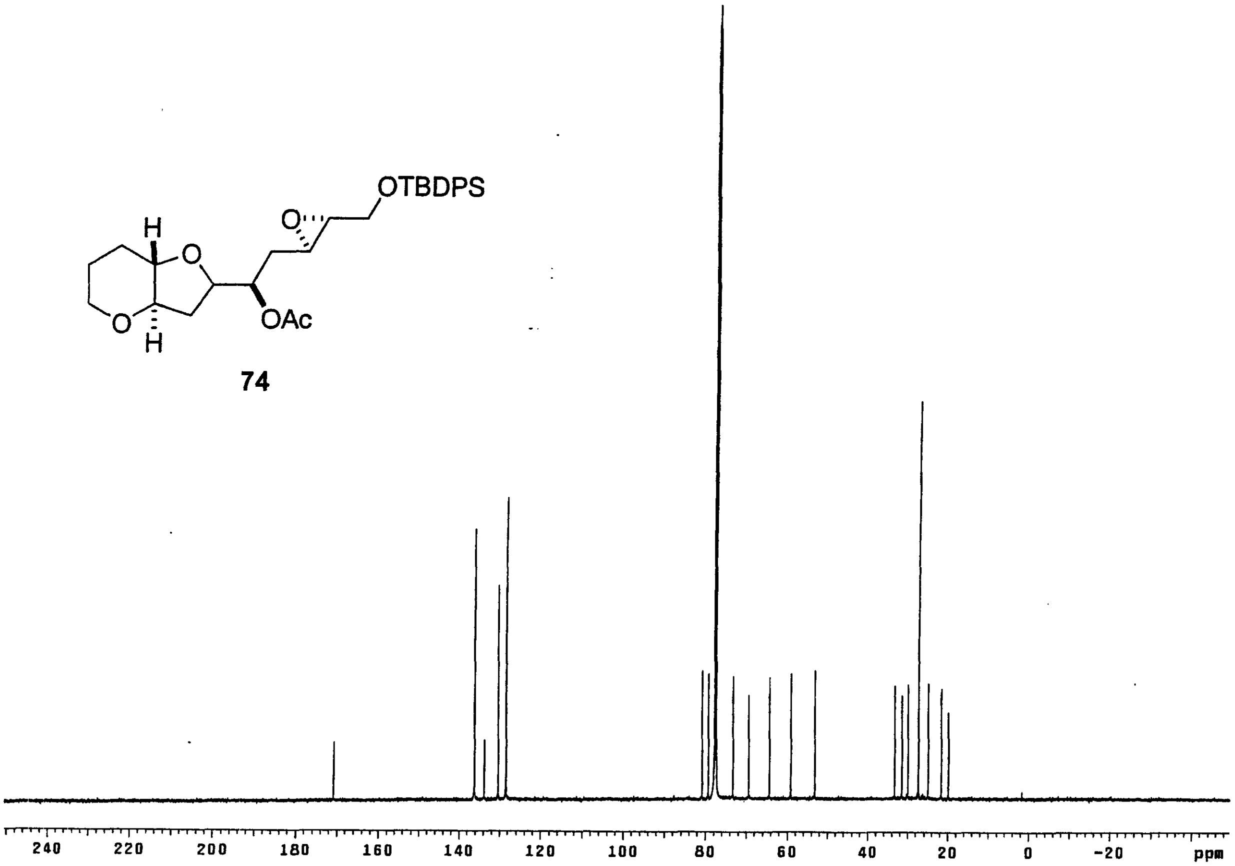
73

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

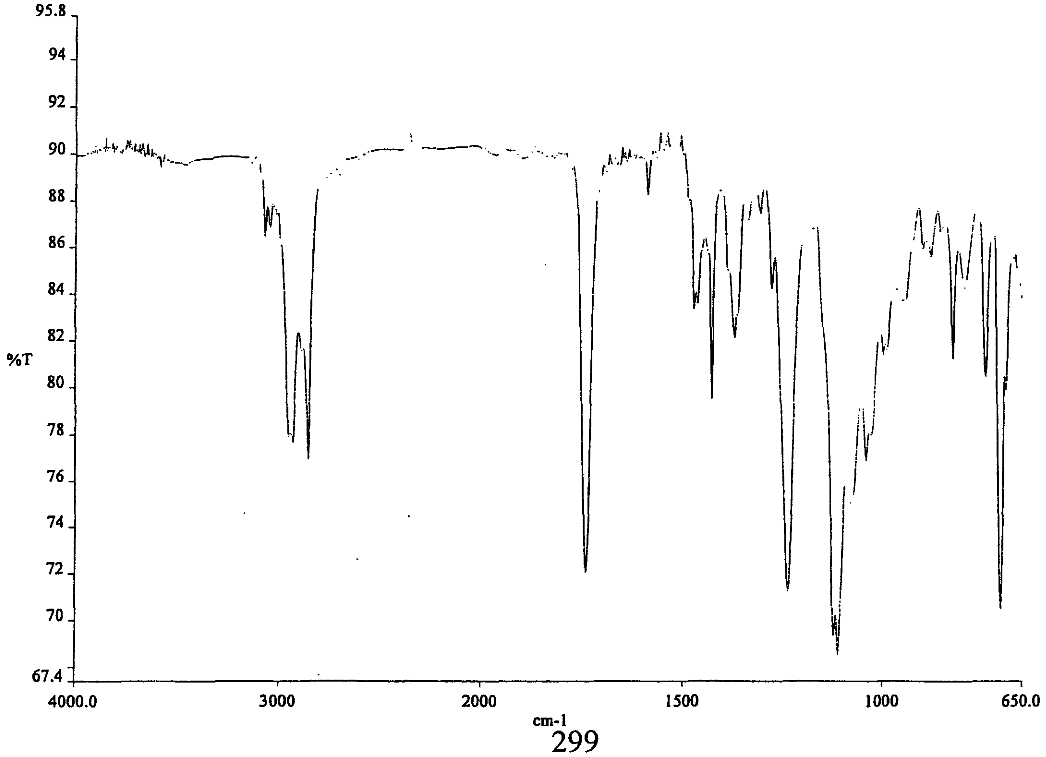

89.3
88
87
86
85
84
83
82
81
80
79
78
77
76.0
%T
4000.0
3000
2000
1500
1000
650.0
cm-1

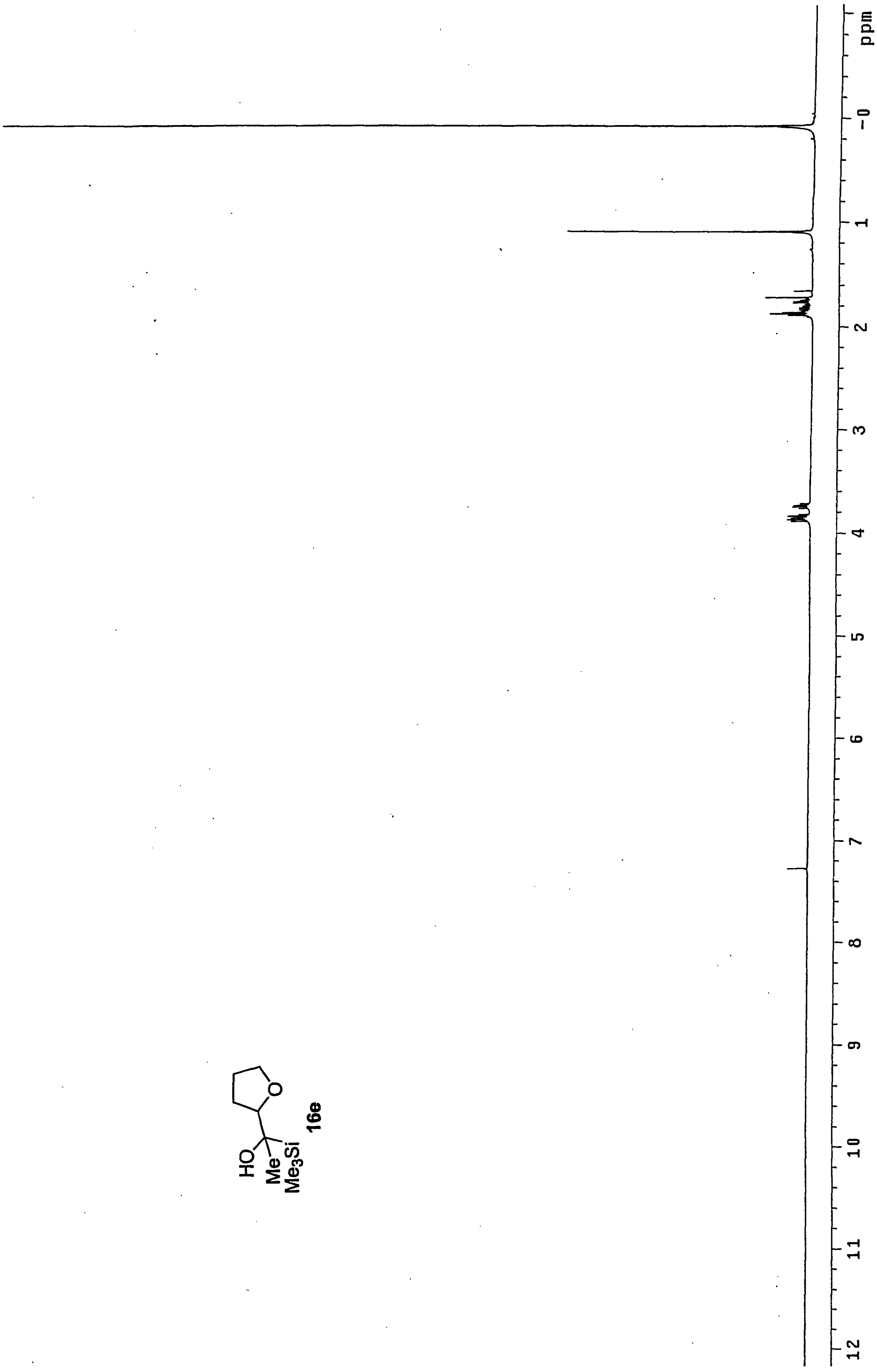


74

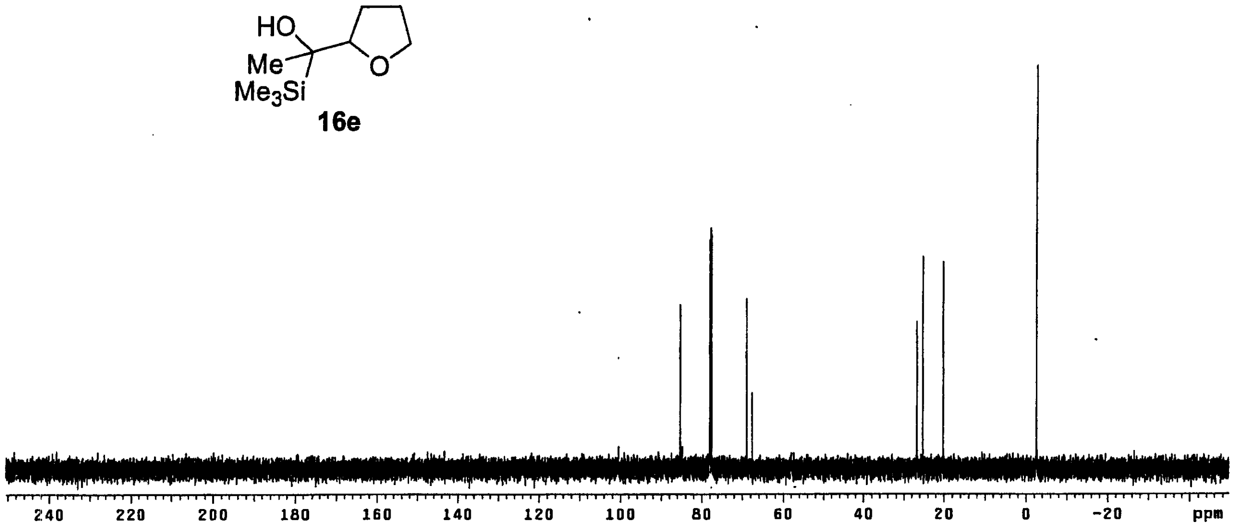

OTBDPS
H
O
O
H
OAc
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

74

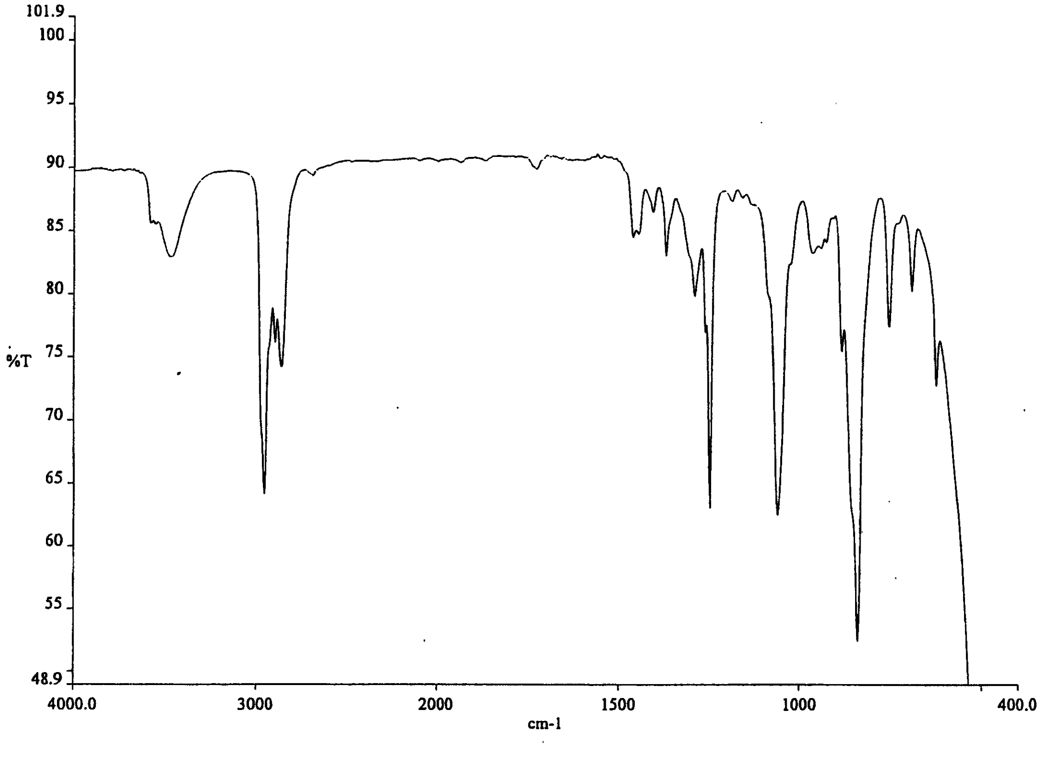

95.8
94
92
90
88
86
84
82
%T
80
78
76
74
72
70
67.4
4000.0
3000
2000
1500
1000
650.0
cm-1

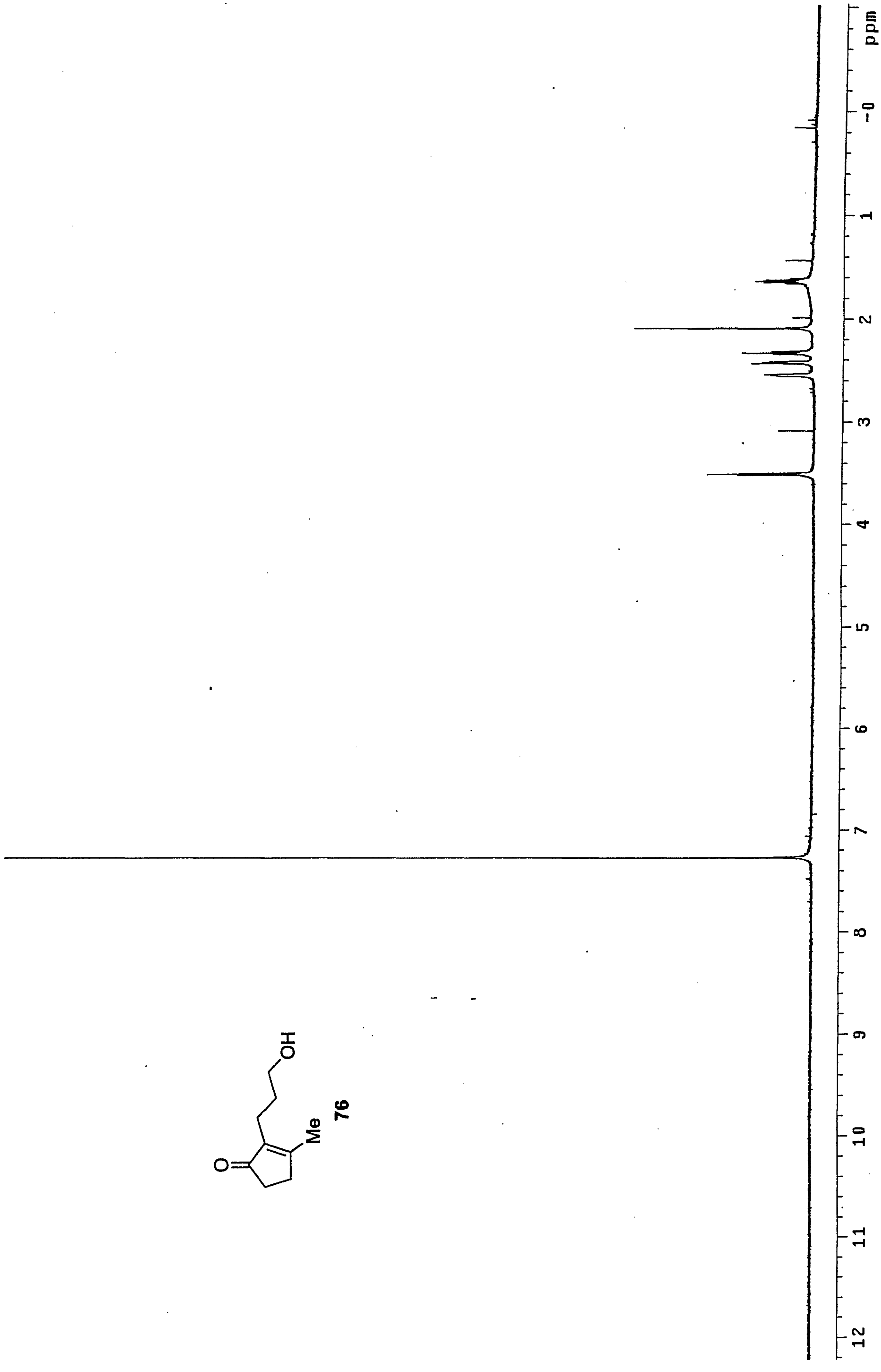


16e

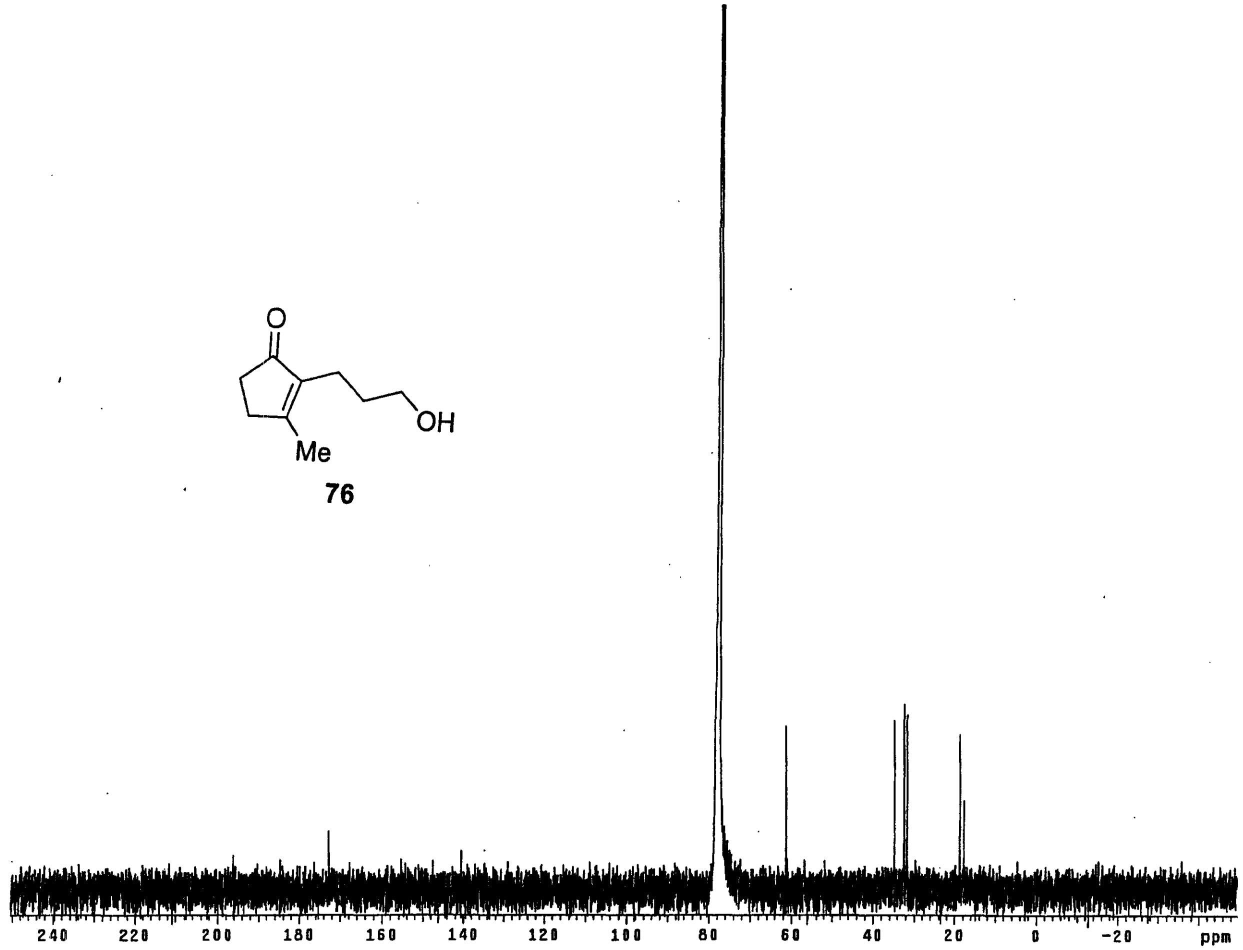

HO
Me
Me3Si
O
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

16e

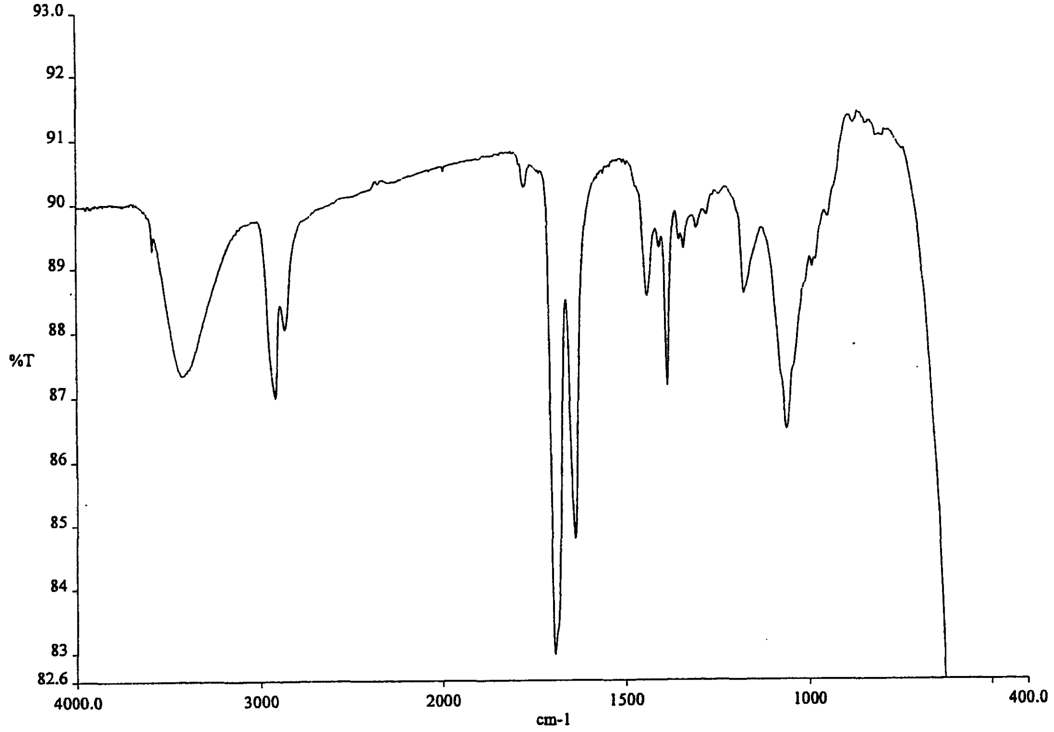

101.9
100
95
90
85
80
%T
75
70
65
60
55
48.9
4000.0
3000
2000
1500
1000
400.0
cm-1

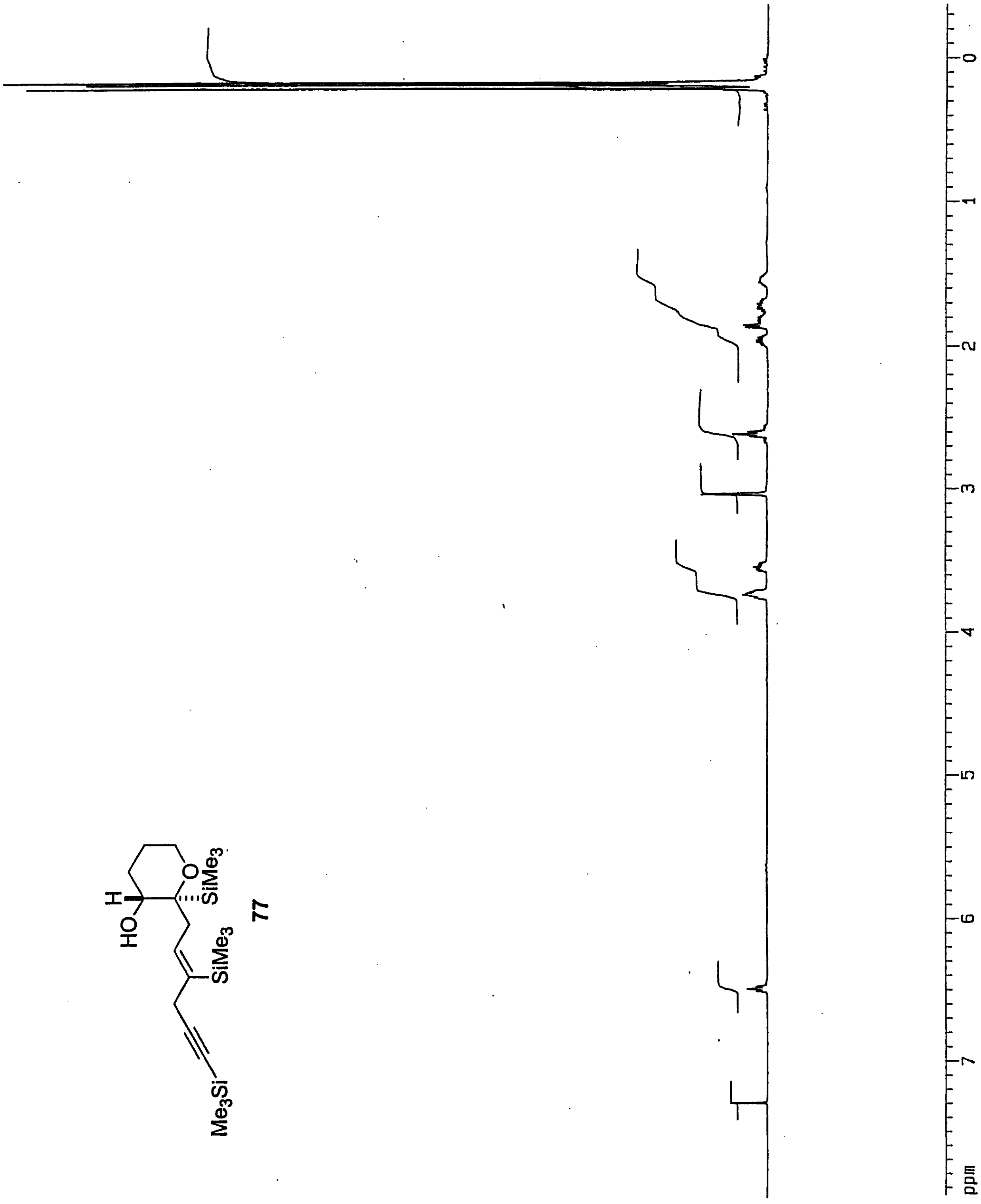


76

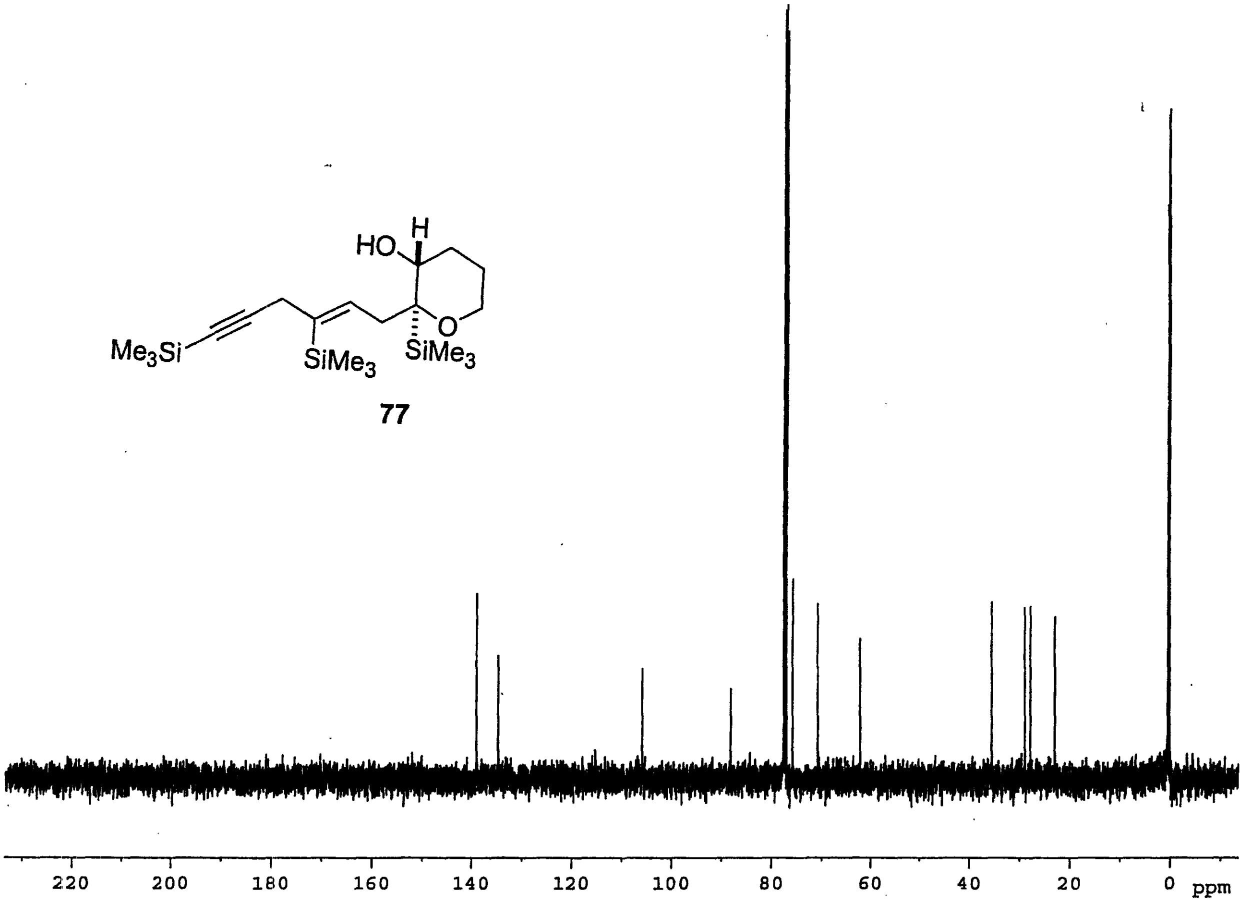

O
OH
Me
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

76

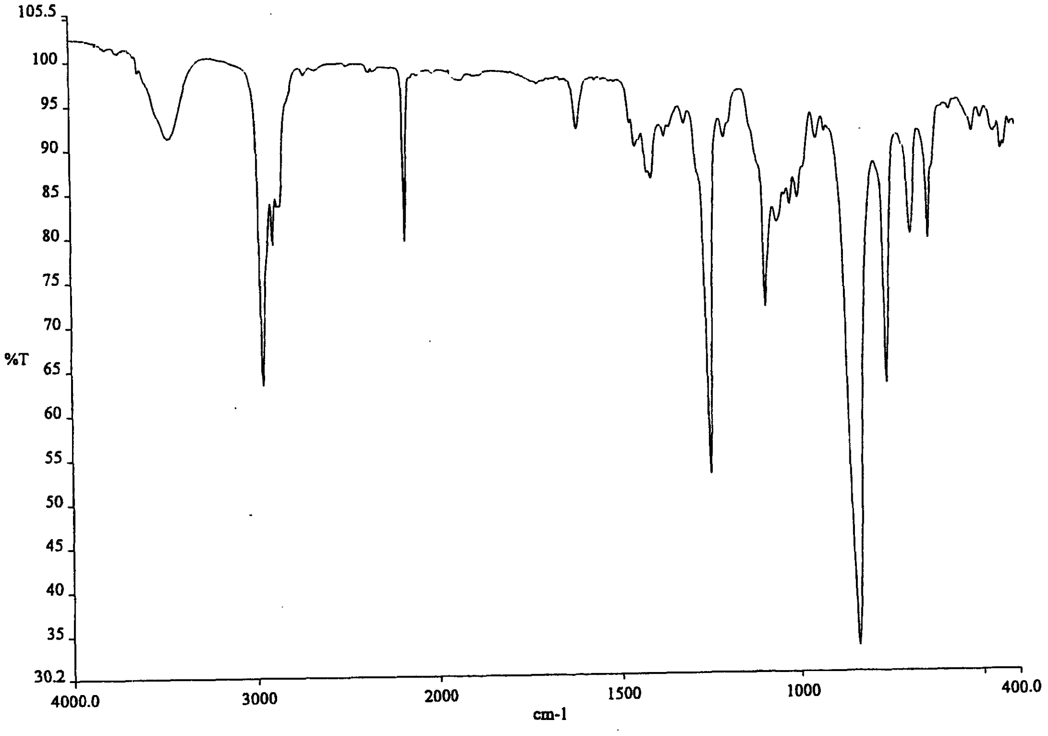

93.0
92
91
90
89
88
%T
87
86
85
84
83
82.6
4000.0
3000
2000
1500
1000
400.0
cm-1

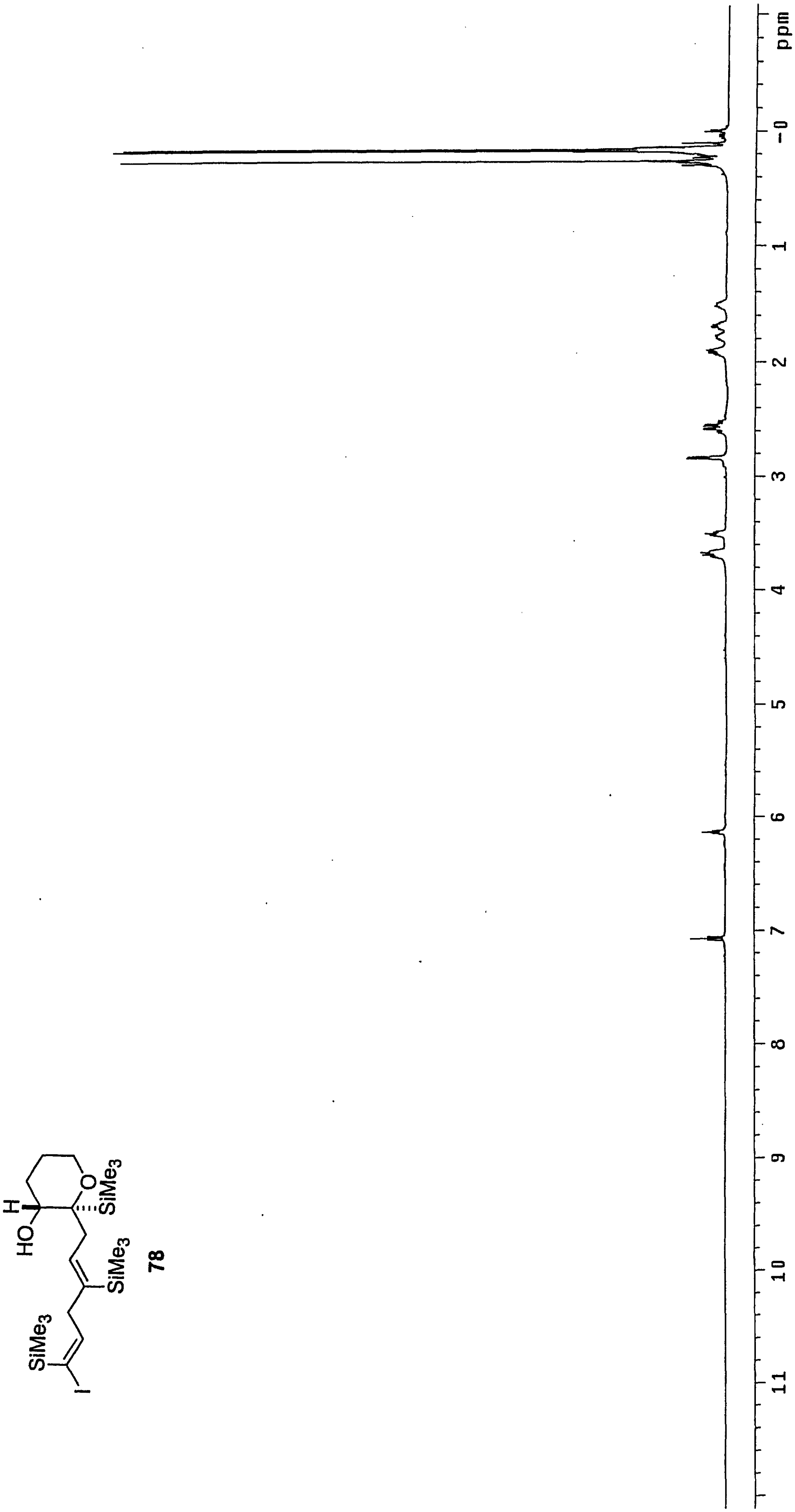


77

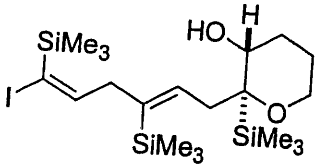

HO
H
O
Me3Si
SiMe3
SiMe3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

77

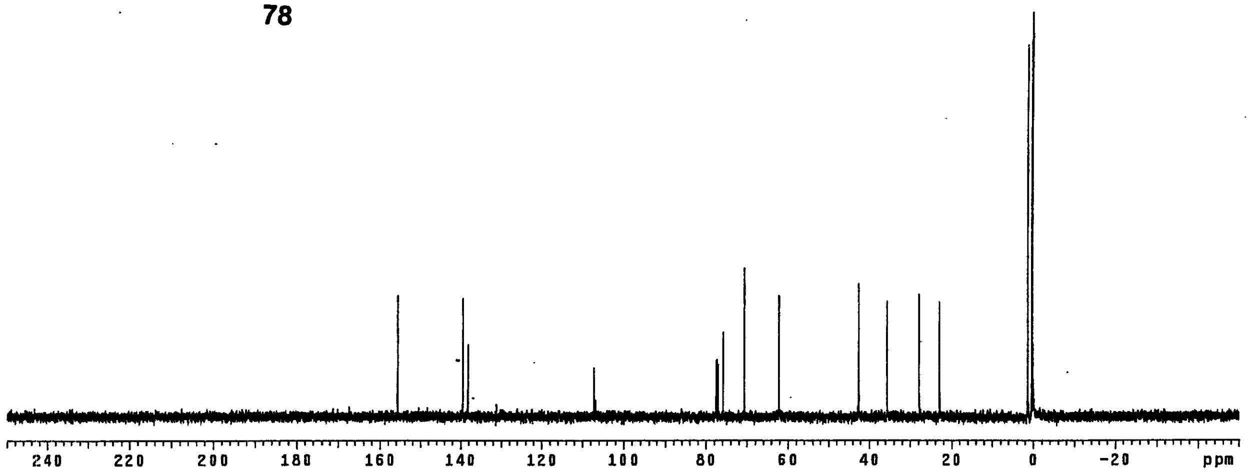

105.5
100
95
90
85
80
75
70
%T
65
60
55
50
45
40
35
30.2
4000.0
3000
2000
1500
1000
400.0
cm-1

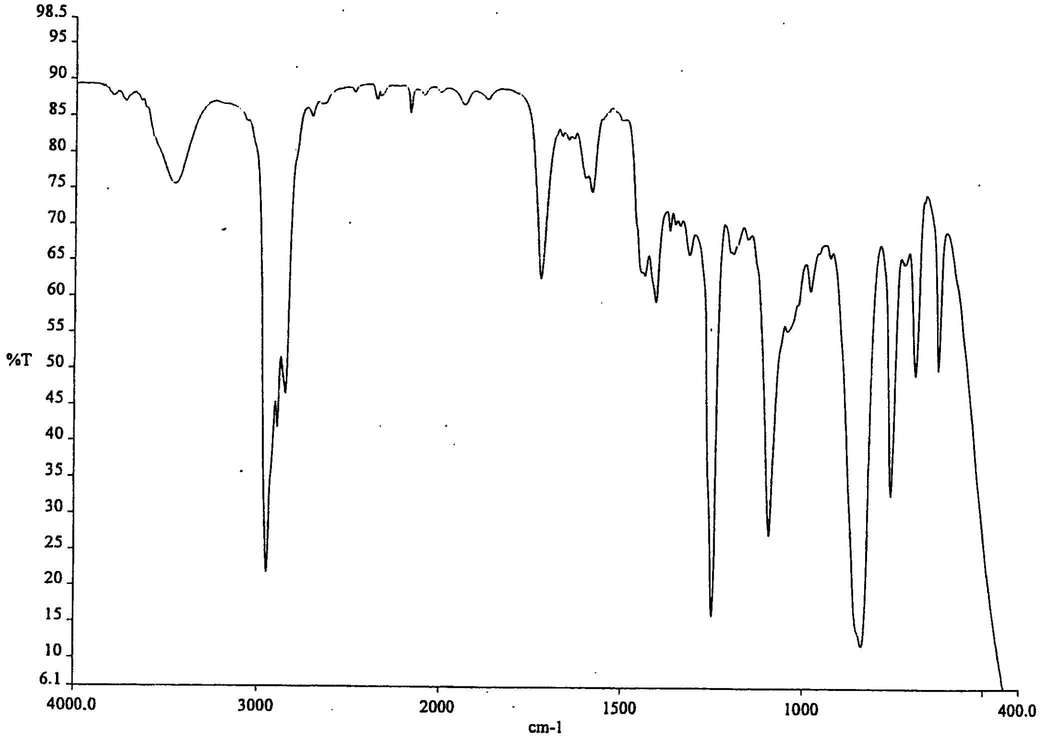


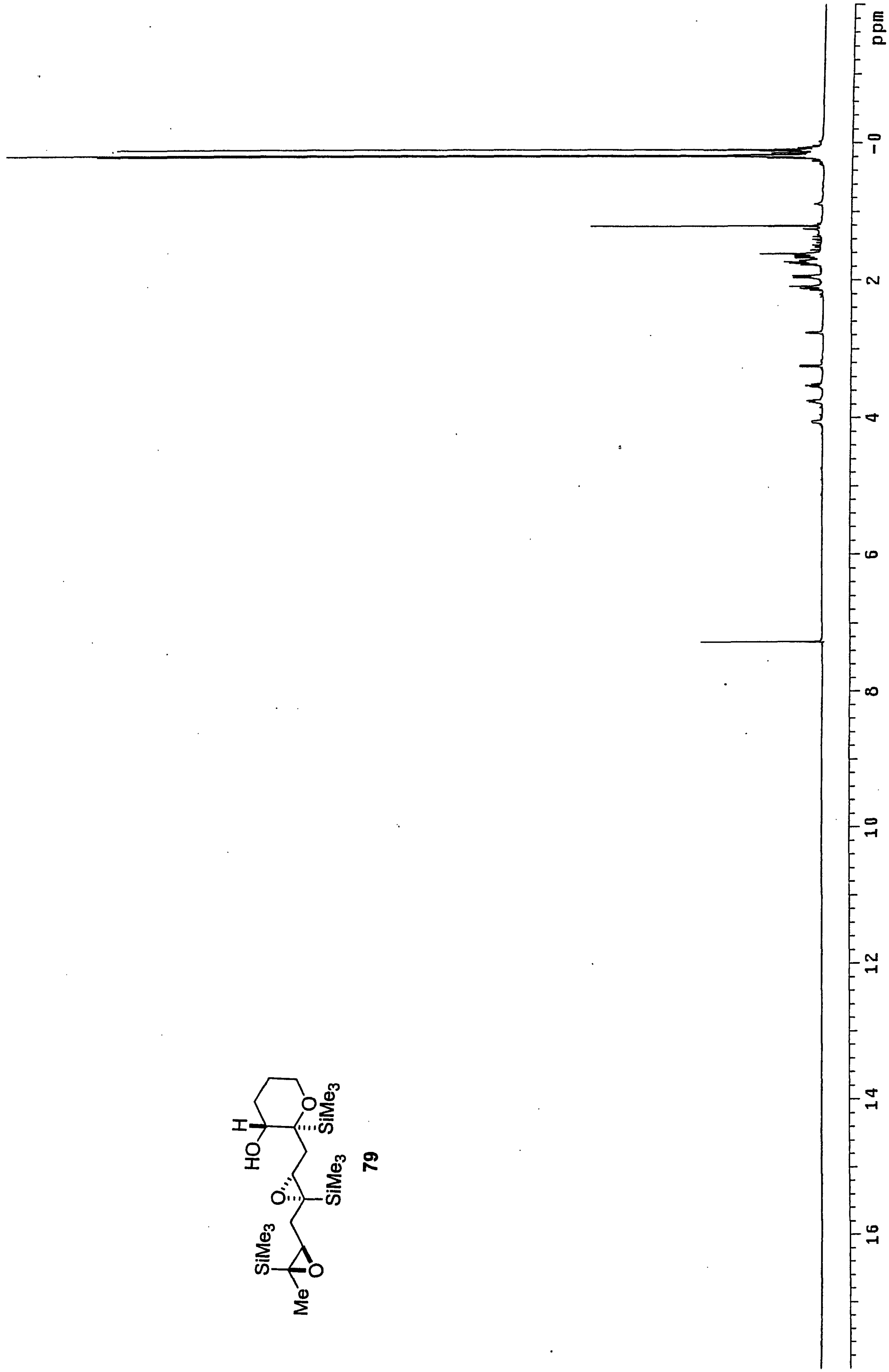
78


SiMe3
HO
H
I
O
SiMe3
SiMe3

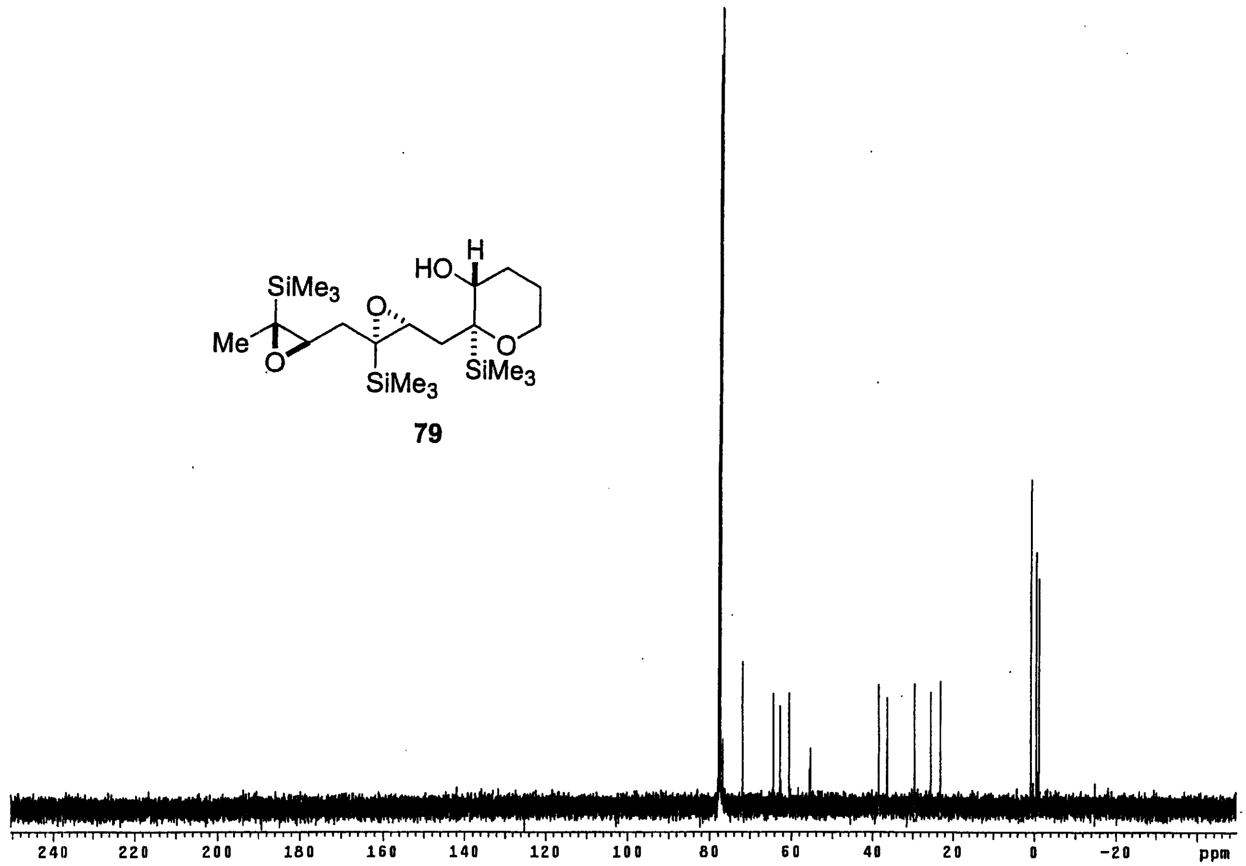
78

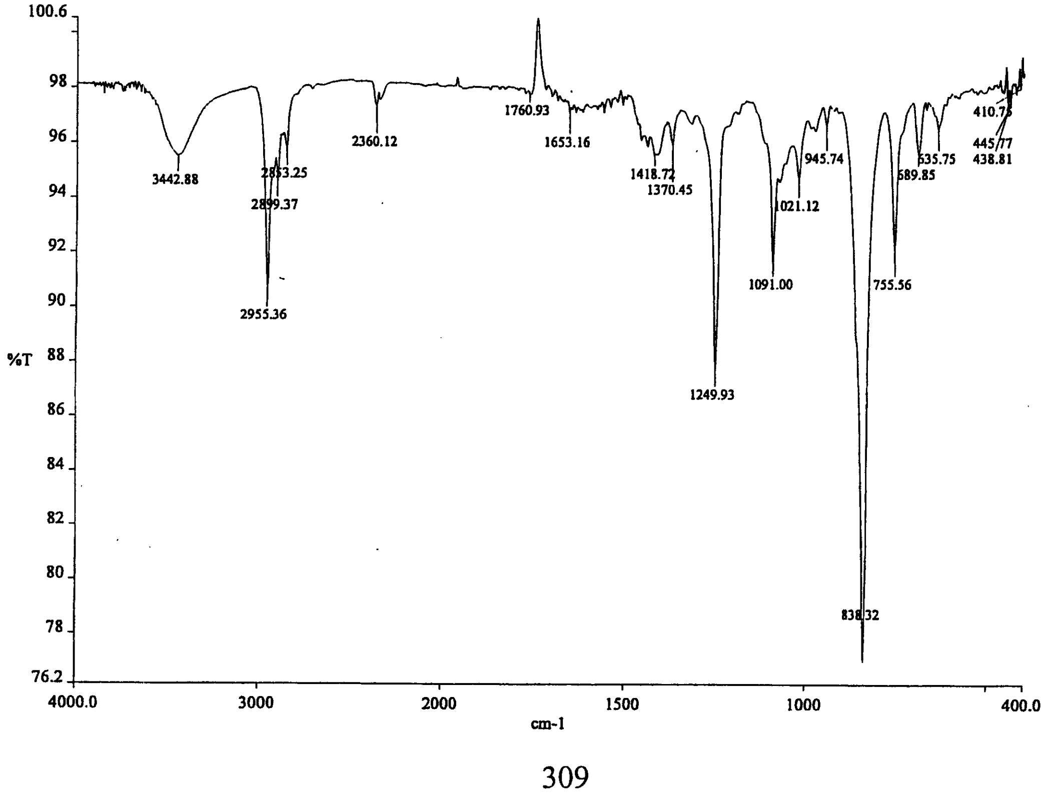

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


98.5
95
90
85
80
75
70
65
60
55
%T
50
45
40
35
30
25
20
15
10
6.1
4000.0
3000
2000
1500
1000
400.0
cm-1



79


HO
H
SiMe3
O
Me
O
O
SiMe3
SiMe3
79
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


100.6
98
96
94
92
90
%T
88
86
84
82
80
78
76.2
4000.0
3000
2000
1500
1000
400.0
cm-1
3442.88
2853.25
2899.37
2955.36
2360.12
1760.93
1653.16
1418.72
1370.45
1249.93
1091.00
1021.12
945.74
838.32
755.56
689.85
635.75
410.75
445.77
438.81

Curriculum Vitae

Education

Ph.D. Organic Chemistry Massachusetts Institute of Technology (June 2005)

Thesis Title: "The Development of Iterative and Cascade Methods for the Rapid Synthesis of Ladder Polyether Natural Products"

Thesis Advisor: Professor Timothy F. Jamison

B.S. Chemistry with Distinction Yale University (May 2000)

Thesis Title: "Progress Toward the Total Synthesis of *N*-Methylwelwitindolinone C Isothiocyanate"

Undergraduate Thesis Advisor: Professor John L. Wood

Research and Teaching Experience

Massachusetts Institute of Technology January 2001-May 2005
Graduate Reseach Assistant

Massachusetts Institute of Technology September 2000-May 2004
Recitation Instructor
Grader and Web Designer for Graduate Organic Structure Determination (Course 5.46), Spring 2004
Instructor for Organic Chemistry II (Course 5.13), Spring 2002
Head Instructor for Organic Chemistry II (Course 5.13), Spring 2001
Instructor for Introductory General Chemistry (Course 5.111), Fall 2000

Yale University May 1998-2000
Undergraduate Research Assistant

Bristol-Myers Squibb June 1999-August 1999
Summer Intern

Publications and Presentations

Heffron, T. P.; Jamison, T. F. "The Development of an Iterative Synthesis of Polypyrans and Cascade Approaches Toward Polyether Natural Products," Massachusetts Institute of Technology Graduate Symposium, Cambridge, MA, May 2004.

Heffron T. P.; Jamison, T. F. "$SiMe_3$-Based Homologation-Epoxidation-Cyclization Strategy for Ladder THP Synthesis," *Org. Lett.* **2003**, *5*, 2339-2342.

Heffron, T. P.; Trenkle, J. D.; Jamison, T. F. "Synthesis of Skipped Enynes via Phosphine-Promoted Couplings of Propargylcopper Reagents," *Tetrahedron, Symposium-in-Print, New Synthetic Methods*. **2003**, *59*, 8913-8917.

Heffron, T. P.; Jamison, T. F. "$SiMe_3$ as a Traceless Control Element in the Enantioselective Synthesis of Ladder Polyethers," Johnson & Johnson, Raritan, NJ, August 2003.

Heffron, T. P.; Jamison, T. F. "Toward the Development of Epoxidation/Cyclization Cascades for the Enantioselective Synthesis of *trans*-Fused Tetrahydropyrans," 224th American Chemical Society National Meeting, Boston, MA, oral presentation, August 2002.

Wood, J. L.; Holubec, A. H.; Stoltz, B. M.; Weiss, M. W.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; **Heffron, T. P.** "Application of Reactive Enols in Synthesis: A Versatile, Efficient, and Stereoselective Construction of the Welwitindolinone Carbon Skeleton," *J. Am. Chem. Soc.* **1999**, *121*, 6236-6327.

Academic Honors

Johnson & Johnson Fellowship in Synthetic Organic Chemistry, 2002
National Science Foundation Graduate Research Fellowship, Honorable Mention, 2001
Robert C. Byrd Scholarship (Nebraska Department of Education), 1996-2000
Knights of Columbus Academic Scholarship, 1996-1997