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Development of a Three Step Cascade Synthesis of 2,4-Dihydro-1H-benzo[f]isochromenes

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Development of a Three Step Cascade Synthesis of 2,4-dihydro-1*H*-benzo[*f*]isochromenes

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Bachelor of Science, Rensselaer Polytechnic Institute, 2007

A Thesis presented to the Graduate Faculty
of the College of William and Mary in Candidacy for the Degree of
Master of Science

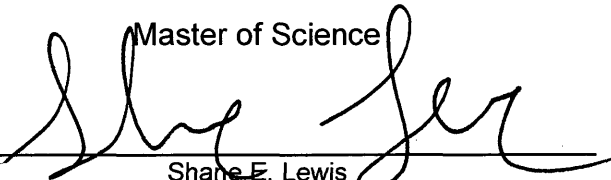Department of Chemistry

The College of William and Mary
January, 2015

APPROVAL PAGE

This Thesis is submitted in partial fulfillment of
the requirements for the degree of

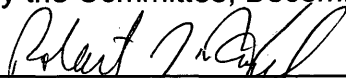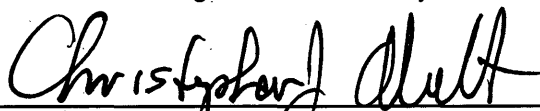Master of Science

Shane E. Lewis

Approved by the Committee, December 2014

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Professor Robert J. Hinkle, Chemistry
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The College of William & Mary

Professor Jonathan R. Scheerer, Chemistry
The College of William & Mary

ABSTRACT

A short linear synthesis providing a monocyclic substrate containing a propargylic and homopropargylic alcohol was developed. This diol was then reacted with a variety of aldehydes in the presence of a number of Lewis acids to provide tricyclic 2,4-dihydro-1*H*-benzo[*f*]isochromenes. This two component reaction provided the target molecules in moderate yields through a novel alkynyl-Prins/Friedel–Crafts/dehydration cascade.

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ACKNOWLEDGEMENTS

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For the enthusiasm she brought to lab every day we worked together and the friendship that developed from it, I would like to thank Ajara Rahman. I could not have asked for a better coworker and friend. I would also like to thank Jason Safko, who has become one of my closest friends. Finally, my deepest gratitude to Todd Hovey, who spent countless late nights working in lab with me and even more nights exchanging ideas and drawing molecules on napkins over drinks and basketball.

For my grandmother, Flossie Morgan, and my mother, Karen Forrest.

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I. Background

A. Introduction

The prevalence of cyclic ethers in natural products has led to a search for simple and adaptive methods of synthesis. The pyran ring, a simple 6 membered cyclic ether, and its derivatives are of particular importance, appearing in a multitude of biologically active compounds including kendomycin,[1] (-)-centrolobine,[2] and the aspergillides (Figure 1.1).[3] The high variety of substitution patterns has led to a wealth of research attempting to create stereoselective reactions and then incorporate these methods into total syntheses.

Kendomycin   (-)-Centrolobine   (+)-Aspergillide C
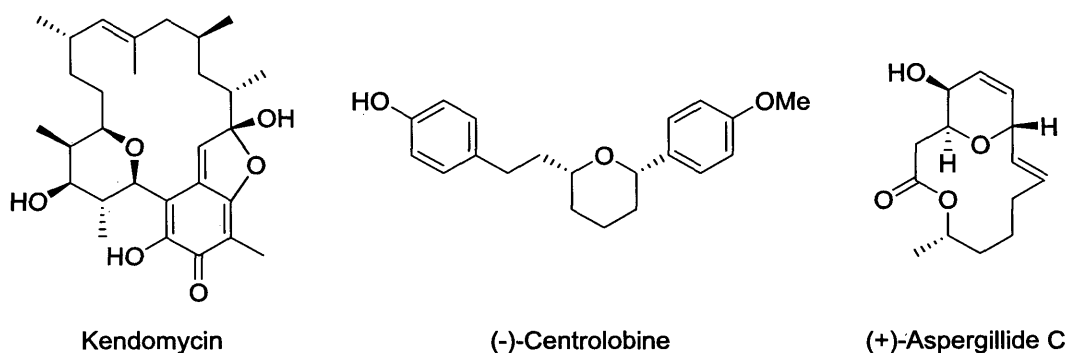
Figure 1.1: Examples of Pyran-containing Natural Products.

There have been a number of methods applied to creating these useful scaffolds. Prior work in the Hinkle lab has focused primarily on the Prins

[1] Tanaka, K.; Matsuyama, H.; Watanabe, M.; Fujimori, Y.; Ishibashi, K.; Ozawa, T.; Sato, T.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2014**, *79*, 9922-9947.
[2] Yang, Z.; Kim, H.-D. *Tetrahedron: Asymmetry* **2014**, *25*, 305-309.
[3] Nagasawa, T.; Kuwahara, S. *Heterocycles* **2012**, *85*, 587-613.

cyclization,[4] reductive etherification, and tandem cyclization-addition methods.[5]

Additional synthetic pathways leading to pyran derivatives include ring closing

metathesis[6] and Diels-Alder cyclizations, among others.[7]

B. The Prins Reaction and Cyclization

Originally reported in 1919, the Prins reaction is an acid-catalyzed reaction

involving an alkene and aldehyde.[8] In its simplest form, shown in Scheme 1.1, a

proton or Lewis acid coordinates with the aldehyde to create an oxonium ion, and

the π-electrons of the alkene act as a nucleophile and attack the carbonyl

carbon. This results in an alcohol intermediate with a β-cation. This intermediate

can then be further reacted with an aldehyde to afford a 1,3-dioxane, nucleophile

to afford a simple alcohol, or basic reagent to afford an allylic alcohol.
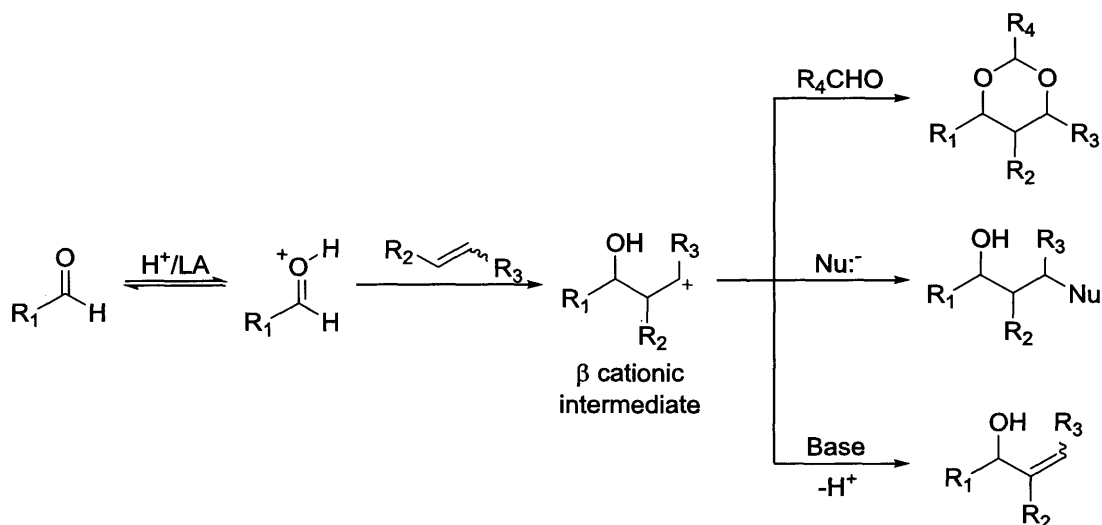
Scheme 1.1: Generalized Prins Reaction.

[4] Lian, Y.; Hinkle, R. J. *J. Org. Chem.* **2006**, *71*, 7071-7074.
[5] Hinkle, R. J.; Rahman, A. A.; *Unpublished Results.*
[6] Yadav, J. S.; Prakash, S. J.; Gangadhar, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2722-2728.
[7] Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095-3165.
[8] Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1072-1073.

The Prins cyclization has recently become a popular tool for creating a variety of pyran-containing compounds.[9] Studies on this intramolecular variant of the Prins reaction have shown it to be a highly versatile transformation. The portion of the Prins cyclization shown in Scheme 1.2 is directly analogous to the creation of the β-cationic alcohol in the Prins reaction and differs only by being an intramolecular process. Similarly to the addition in Scheme 1.1, the initial oxocarbenium ion is formed through an addition step in which an oxygen nucleophile, often a homoallylic alcohol, first attacks an activated carbonyl-containing compound. The hemiacetal formed then undergoes a proton transfer followed by the formation of a new carbon-oxygen double bond and the leaving of either water or the Lewis acid coordinated alcohol. The resulting oxocarbenium ion then undergoes cyclization, in which the alkene moiety attacks the oxocarbenium ion to create the heterocyclic cation. This cation, analogous to the β-cation from Scheme 1.1, can then be trapped in a number of ways. Often, halides from the Lewis acid activator are incorporated at the β position.

oxocarbenium
ion

β cationic
intermediate
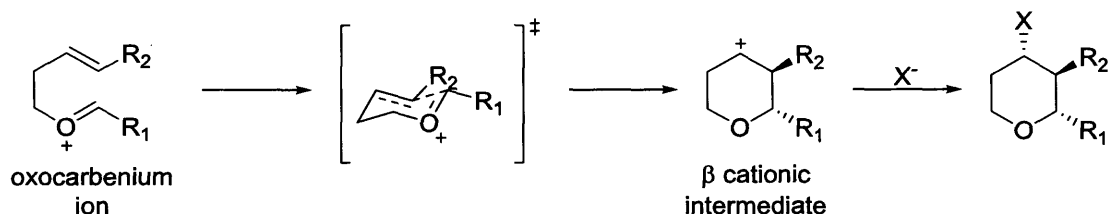
Scheme 1.2: Key Component of the Prins Cyclization.

[9] For a comprehensive review on both the Prins reaction and Prins cyclization, see Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2012**, *16*, 1277-1312.

3

The alkynyl-Prins cyclization is a similar reaction differing only in use of a triple bond in place of the double bond.[10] As depicted in Scheme 1.3, addition of a homopropargylic alcohol to an activated carbonyl-containing compound followed by rearrangement gives the oxocarbenium ion analogous to that shown in Scheme 1.2. Attack of the carbonyl carbon by a pair of π electrons from the triple bond creates a vinyl cation, which can then be trapped in similar fashion to the alkenyl-Prins cyclization.
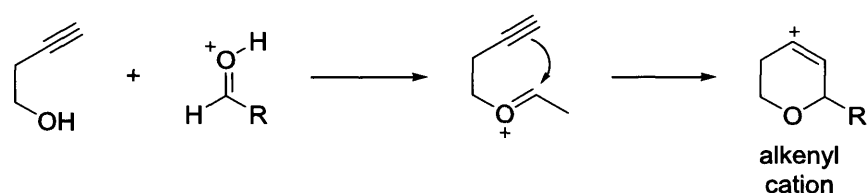
Scheme 1.3: Alkynyl-Prins Cyclization to Alkenyl Cation.

One of the most significant aspects of the Prins cyclization is the generation and control of multiple stereocenters. Arguably the most important control is the prevalence for *cis* diastereoselectivity of the substituents in the 2- and 6- positions detailed in Scheme 1.4.
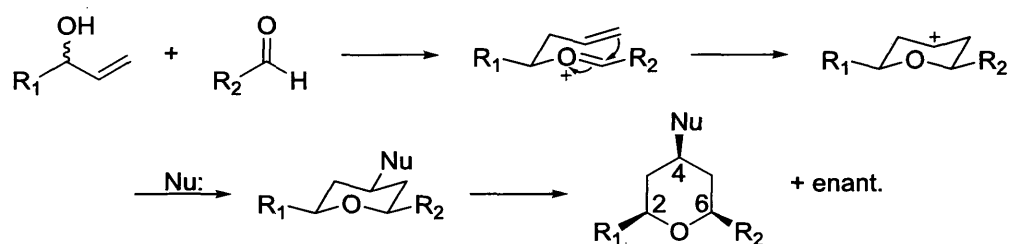
Scheme 1.4: Diastereoselectivity of the Prins Cyclization.

---

[10] Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979-1982.

The preferred orientation for R_1 is the energetically favorable pseudo-equatorial position as the alkene begins to attack the oxocarbenium ion. As the ring forms, R_2 favors the pseudo-equatorial position as well, creating the *cis* configuration with high selectivity. Literature reports often show diastereoselectivity of 99:1.[11] When the starting allylic alcohol is enantiomerically pure, this phenomenon allows for high enantioselectivity in products as well, and has been used to great effect in syntheses of natural products.[12,13]

More recently, a variation on the Prins cyclization has seen wide use (Scheme 1.5).[14,15] By incorporating a trimethylsilyl group on the terminal alkene, the double bond present in the starting material is effectively retained, providing a dihydropyran without the need for an added base. This reaction, called the silyl-Prins cyclization, also has the benefit of being quick, efficient, and highly diastereoselective. 6-, 2,6-, and 2,3,6- substituted dihydropyrans have been reported, showing that the modification was also highly versatile.
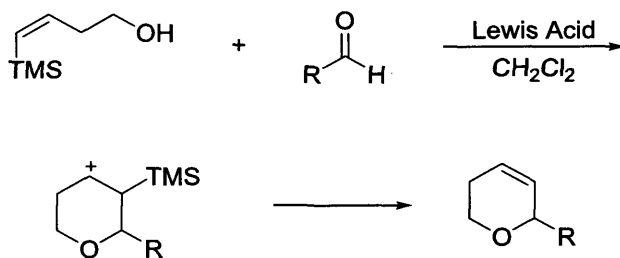
Scheme 1.5: Silyl-Prins Cyclization.

[11] Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480-16481.
[12] Pansare, S. V.; Jain, R. P. *Org. Lett.* **1999**, 2, 175-177.
[13] Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650-6652.
[14] Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426-3427.
[15] Dobbs, A. P.; Martinovic, S. *Tetrahedron Lett.* **2002**, *43*, 7055-7057.

In silyl-Prins, the intermediate cation is stabilized by the β-silicon effect.[16]

A counterion then attacks the silicon in the hyperconjugated TMS group,

affording the dihydropyran product. This pathway also allows for region-control

of the double bond, unlike the traditional Prins cyclization, where an added base

can remove either of two protons, creating two distinct dihydropyrans, as shown

in Scheme 1.6.
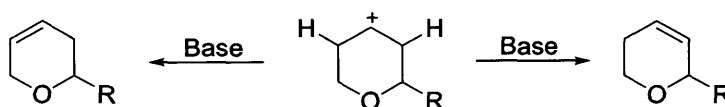
Scheme 1.6: Loss of Regiospecific Control in Traditional Prins
Cyclization

C. Polycyclic Pyran Derivatives

A fair number of benzoisochromenes and other fused polycyclic pyran

derivatives exist. Populene D is a recently discovered natural product with many

reported therapeutic properties.[17] While a total synthesis has not yet been

reported for this compound, a number of analogs were recently synthesized[18]

using the iodine catalyzed Prins cyclization originally reported by Silva and

Quintiliano (Scheme 1.7).[19] Many of these compounds showed biological activity

and this study also demonstrated some connection between substitution patterns

on the aromatic ring and relative usefulness in therapy.

[16] Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677-2689.

[17] Boonsri, S.; Karalai, C.; Ponglimanont, C.; Chantrapromma, S.; Kanjana-Opas, A. *J. Nat. Prod.* **2008**, *71*, 1173-1177.

[18] Reddy, K. R.; Longato, G. B.; de Carvalho, J. E.; Ruiz, A. L.; Silva, L. F., Jr. *Molecules* **2012**, *17*, 9621-9630.

[19] Silva Jr, L. F.; Quintiliano, S. A. *Tetrahedron Lett.* **2009**, *50*, 2256-2260.
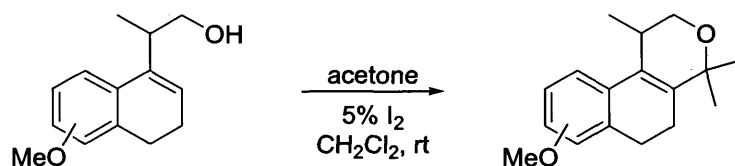
Scheme 1.7: Prins Cyclization Utilized Towards Populene D Analogs.
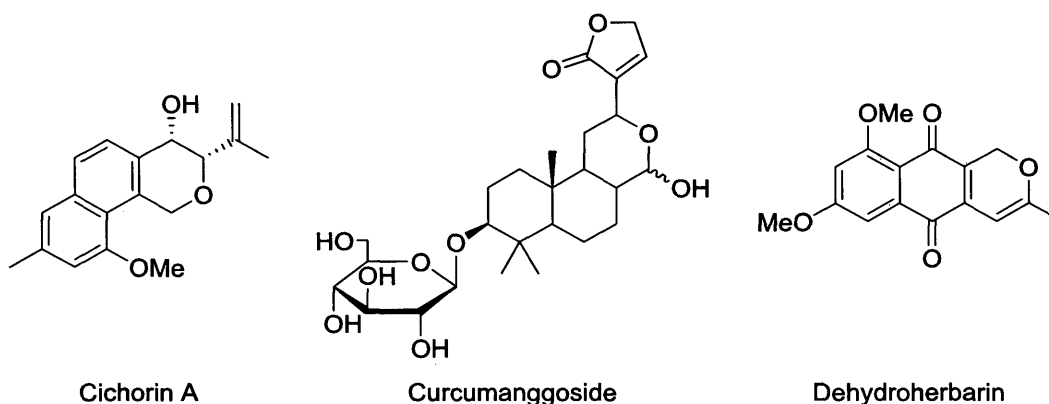
Other natural products containing fused oxygen heterotricycles include cichorin A,[20] curcumanggoside,[21] and dehydroherbarin[22] (Figure 1.2). The tricyclic cores for each of these molecules could easily be imagined to be formed through a Prins cyclization as well.

Cichorin A   Curcumanggoside   Dehydroherbarin

Figure 1.2: Natural Products Containing Fused Heterotricycles.

In addition to the previously mentioned iodine catalyzed Prins cyclization, other methods of ring closure to afford heterotricycles have been reported. The interesting approach of both creating a carbonyl and subsequent ring closure was reported by Pillay et al. by incorporating a Wacker oxidation to produce the

[20] Hussain, H.; Hussain, J.; Saleem, M.; Miana, G. A.; Riaz, M.; Krohn, K.; Anwar, S. *J. Asian Nat. Prod. Res.* **2011**, *13*, 566-569.

[21] Abas, F.; Lajis, N. H.; Shaari, K.; Israf, D. A.; Stanslas, J.; Yusuf, U. K.; Raof, S. M. *J. Nat. Prod.* **2005**, *68*, 1090-1093.

[22] Kadkol, M. V.; Gopalkrishnan, K. S.; Narasimhachari, N. *J. Antibiot.* **1971**, *24*, 245-248.

precursor of dehydroherbarin (eq 1.1).[23] The same molecule was also

synthesized utilizing a tandem base-promoted dehydrohalogenation and

electrocyclization (eq 1.2).[24] In 2001, Morley and Pincock reported a [2+2]

photocycloaddition of a naphthalene-tethered benzoate (eq 1.3).[25] Jana et al.

created a series of tri- and tetracycles using a Heck cyclization (eq 1.4).[26]
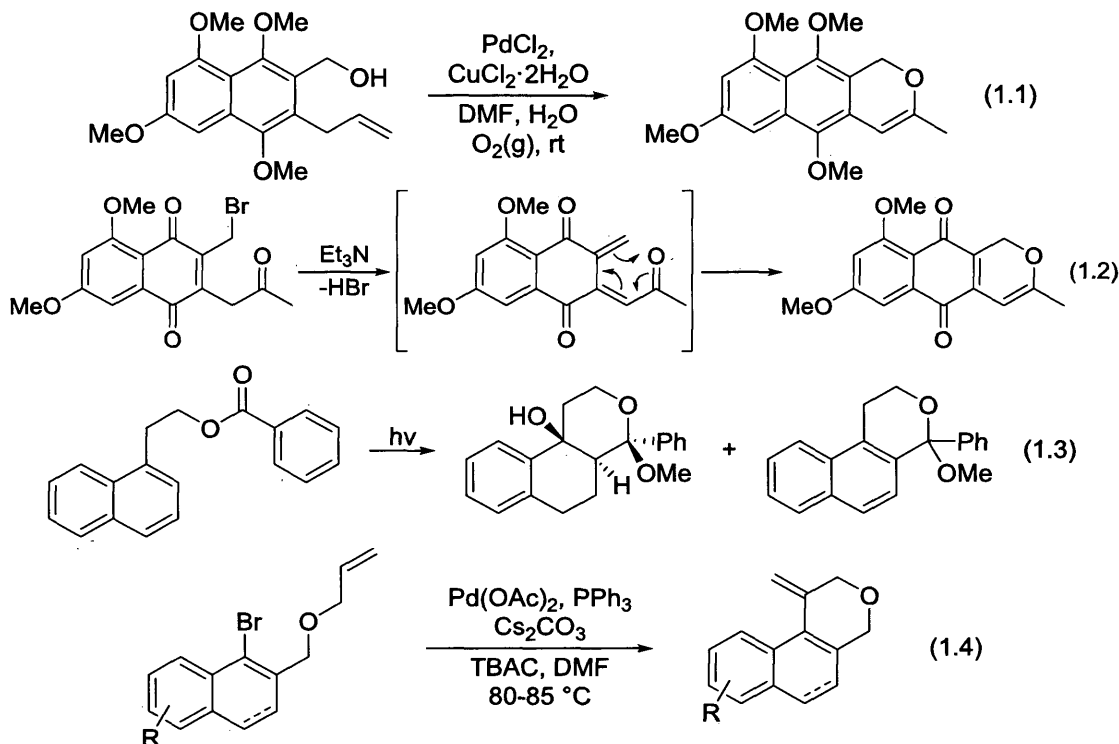
Syntheses of isochromenes and their related compounds are more

numerous than their benzo-fused relatives. Several metal-catalyzed cyclizations

have been reported. One, utilizing tungsten, incorporates an electrocyclization of

the vinylidene shown in eq 1.5 to afford an alkenyltungsten compound which can

[23] Pillay, A.; Rousseau, A. L.; Fernandes, M. A.; de Koning, C. B. *Org. Biomol. Chem.* **2012**, *10*, 7809-7819.
[24] Kesteleyn, B.; De Kimpe, N. *J. Org. Chem.* **2000**, *65*, 640-644.
[25] Morley, K.; Pincock, J. A. *J. Org. Chem.* **2001**, *66*, 2995-3003.
[26] Jana, R.; Samanta, S.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 851-854.

undergo further substitution.[27] A gold catalyzed annulation produced an

oxocarbenium ion from the interaction of a carbonyl lone pair and the gold-

coordinated triple bond (eq 1.6).[28] Leng et al. created two heterocycles and a

fused cyclopropane ring by reacting a diyne substrate with a copper catalyst

followed by addition of catalytic $PtCl_2$ (eq 1.7).[29] An S_N2' reaction between a

benzyllic alcohol and allyl bromide followed by a palladium catalyzed Heck

cyclization similar to eq 1.4 affords the compound shown in eq 1.8 where the

double bond formed in the cyclization can be inside or outside of the newly

formed pyran ring.[30]

$$(1.5)$$

$$(1.6)$$

$$(1.7)$$
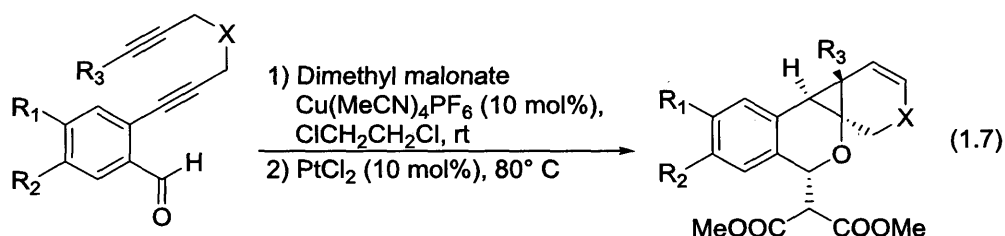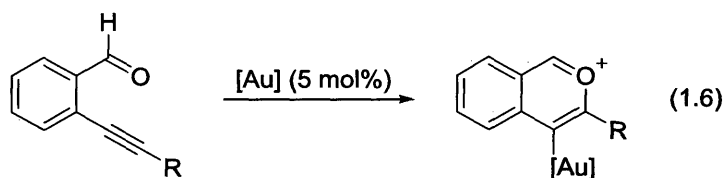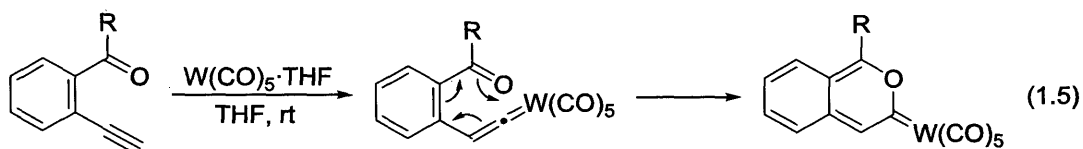
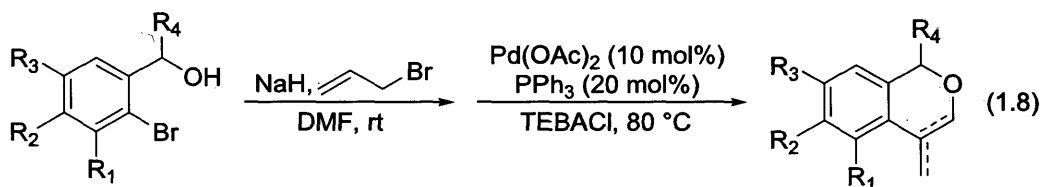[27] Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. J. Am. Chem. Soc. 2000, 122, 10226-10227.

[28] Malhotra, D.; Liu, L.-P.; Mashuta, M. S.; Hammond, G. B. Chem. - Eur. J. 2013, 19, 4043-4050.

[29] Leng, B.; Chichetti, S.; Su, S.; Beeler, A. B.; Porco, J. A., Jr. Beilstein J. Org. Chem. 2012, 8, 1338-1343.

[30] Reddy, A. G. K.; Krishna, J.; Satyanarayana, G. Tetrahedron Lett. 2012, 53, 5635-5640.

$$\text{(1.8)}$$

Guiso et al. have published examples of isochroman formation via an oxa-Pictet–Spengler reaction, which has a mechanism similar to that of the Prins cyclization.[31,32,33] Both reactions begin with the addition of an oxygen nucleophile to an activated aldehyde to form an oxocarbenium ion. At that point, the oxa-Pictet–Spengler reaction varies from the Prins cyclization by using a π bond from an aromatic system as the nucleophile that attacks the oxocarbenium ion. Deprotonation of the resultant cation then affords the final product and restores the aromaticity of the ring (Scheme 1.8). Similar compounds have shown to have antioxidant and antiplatelate activity.[34,35,36]
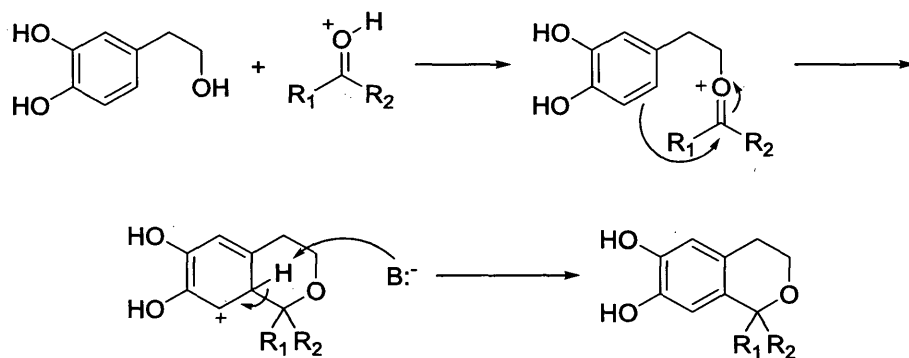
Scheme 1.8: Oxa-Pictet–Spengler Reaction to Isochromenes.

[31] Guiso, M.; Marra, C.; Cavarischia, C. *Tetrahedron Lett.* **2001**, *42*, 6531-6534.
[32] Guiso, M.; Bianco, A.; Marra, C.; Cavarischia, C. *Eur. J. Org. Chem.* **2003**, 3407-3411.
[33] Guiso, M.; Betrow, A.; Marra, C. *Eur. J. Org. Chem.* **2008**, 1967-1976.
[34] Togna, G. I.; Togna, A. R.; Franconi, M.; Marra, C.; Guiso, M. *J. Nutr.* **2003**, *133*, 2532-2536.
[35] Lorenz, P.; Zeh, M.; Martens-Lobenhoffer, J.; Schmidt, H.; Wolf, G.; Horn, T. F. *Free Radic Res* **2005**, *39*, 535-545.
[36] Djande, A.; Kiendrebeogo, M.; Compaore, M.; Kabore, L.; Nacoulma, G. O.; Aycard, J.-P.; Saba, A. *Res. J. Chem. Sci.* **2011**, *1*, 88-90.

One important consistency in nearly all of these syntheses is the extant

aromatic ring system in the substrate. Prior to the beginning of this work, no

syntheses of fused heterocycles where both rings in the isochromene core were

formed in one step could be found. Shortly after the start of our investigations,

Reddy et al. published a series of papers describing tandem Prins/Friedel–Crafts

reactions creating heterotricycles in a similar vein to our method, but did so using

alkenes instead of alkynes.[37,38,39] To the best of our knowledge, these were the

first examples of synthesizing both rings of an isochromene in one reaction. The

most comprehensive of the surveys, outlined in eq 1.9, was carried out with

oxygen, nitrogen, and sulfur as the heteroatoms.

$$\text{(1.9)}$$
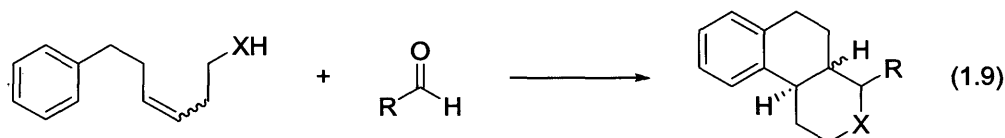
This synthesis, which uses the traditional alkenyl-Prins cyclization,

produced moderate to high yields for the majority of compounds. The group

focused on $Sc(OTf)_3$ as a catalyst and TsOH as a cocatalyst, finding the best

results when using 10 mol% and 30 mol%, respectively. Choice of cis or trans

alkenes in the starting material led in most cases to a high (9:1) selectivity with

regards to the hydrogens labeled in eq 1.9 and a single diastereomer in some

examples. The major component of reactions performed with cis alkenes was

the cis product and the major component of reactions performed with trans

[37]Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Sridhar, B.; Gree, R. *J. Org. Chem.* **2011**, *76*, 7677-7690.

[38] Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Reddy, P. P.; Kunwar, A. C.; Sridhar, B.; Gree, R. *Org Biomol Chem* **2012**, *10*, 1349-1358.

[39] Reddy, B. V. S.; Jalal, S.; Borkar, P.; Yadav, J. S.; Reddy, P. P.; Kunwar, A. C.; Sridhar, B. *Org. Biomol. Chem.* **2012**, *10*, 6562-6568.

alkenes was the trans product. In addition to a number of aldehydes, this methodology was successful with cyclohexanone, possibly creating inroads to a multitude of spiro compounds.

II. Results and Discussion

A. Introduction and Retrosynthetic Analysis

Methodology was recently reported by Yadav et al.[40] (eq 2.1) using

stoichiometric iodine to produce silylated 4-iododihydropyrans and Miranda et

al.[41] using catalytic $Fe(acac)_3$ and trimethylsilyl halides to produce 4-

halodihydropyrans (eq 2.2). These reactions follow the general method

described in Scheme 1.3. Upon production of the putative vinylic cation, these

important intermediates are trapped by iodine and TMS counterions, respectively.

$$(2.1)$$

$$(2.2)$$
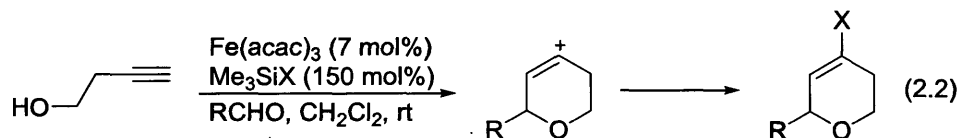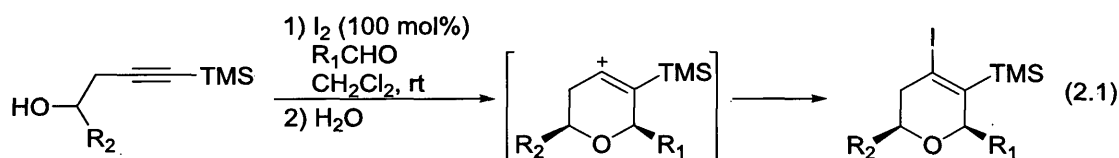
Ideally, our own bismuth salts could be used in catalytic quantities to

perform similar reactions. Initial investigations into these alkynyl-Prins

cyclizations were based on substrate produced for a previous project

investigated by the Hinkle lab.[42] A Barbier reaction with valeraldehyde and (3-

bromoprop-1-yn-1-yl)trimethylsilane afforded the homopropargylic alcohol 1

shown in eq 2.3.

[40] Yadav, J. S. T., N.; Lakshmi, K. A,; Prasad, A. R.; Reddy, B. V. S. *Tetrahedron Lett.* **2010**, *51*, 661-663.
[41] Miranda, P. O.; Carballo, R. M.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2009**, *11*, 357-360.
[42] Lambert, R. F.; Hinkle, R. J.; Ammann, S. E.; Lian, Y.; Liu, J.; Lewis, S. E.; Pike, R. D. *J. Org. Chem.* **2011**, *76*, 9269-9277.

$$\text{(2.3)}$$
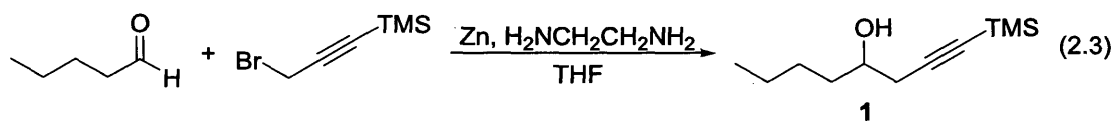
We envisioned that the homopropargylic alcohol would react with bismuth activated aldehydes to produce a cyclic dihydropyranyl cation intermediate that could then be trapped with various trimethylsilyl derivatives, yielding a wide array of 4-substituted dihydropyrans that would retain the TMS moiety at the 5- carbon (eq 2.4).

$$\text{(2.4)}$$
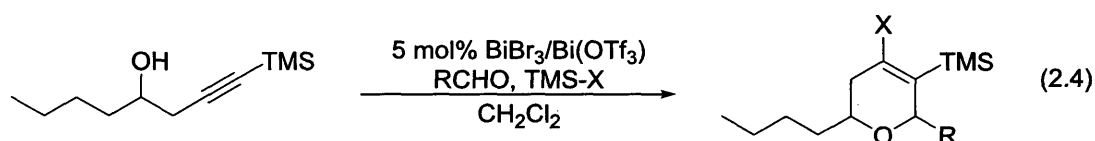
Results with trimethylsilyl halides, however, provided extremely complex mixtures of compounds. Furthermore, the desired product, was not apparent in crude mixtures, and the only compound isolated from the TMS-I analogue was the diiodotetrahydropyran **2** shown in Scheme 2.1. We believe this compound was formed from protodesilylation of the desired product followed by addition of HI produced *in situ* to the double bond. Unpurified mixtures from reactions using other TMS-X compounds, including TMS-CN, TMS-OTf, and TMS-H provided intractable mixtures.
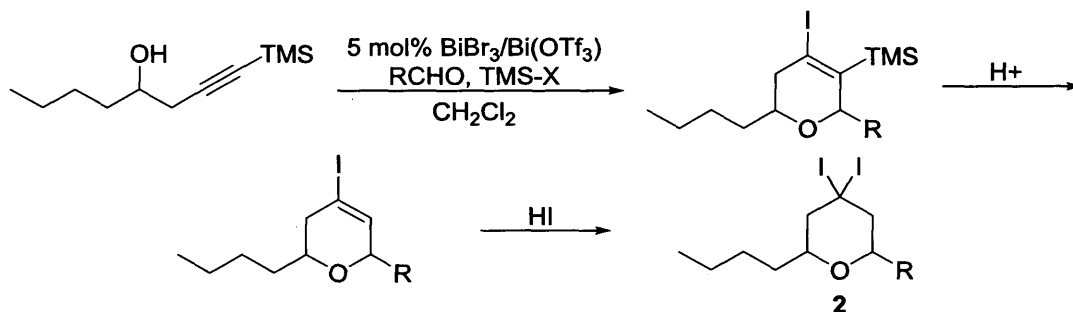
Scheme 2.1: Proposed Pathway for 4-Diiodotetrahydropyran Products.

Due to the difficulties in these intermolecular trapping experiments, we turned our attention to intramolecular reactions. Reddy et al. published two papers that formed the basis for the development of this new methodology.[43,44] Using homoallylic and homopropargylic alcohols and an aromatic solvent, the group was successfully able to manufacture a variety of 4-aryltetrahydropyrans and 4-aryldihydropyrans upon reaction with aldehydes and $BF_3 \cdot Et_2O$. These reactions follow the normal Prins cyclization mechanism until the aromatic solvent undergoes a Friedel–Crafts reaction with the key cationic intermediate to afford the final products (Scheme 2.2).
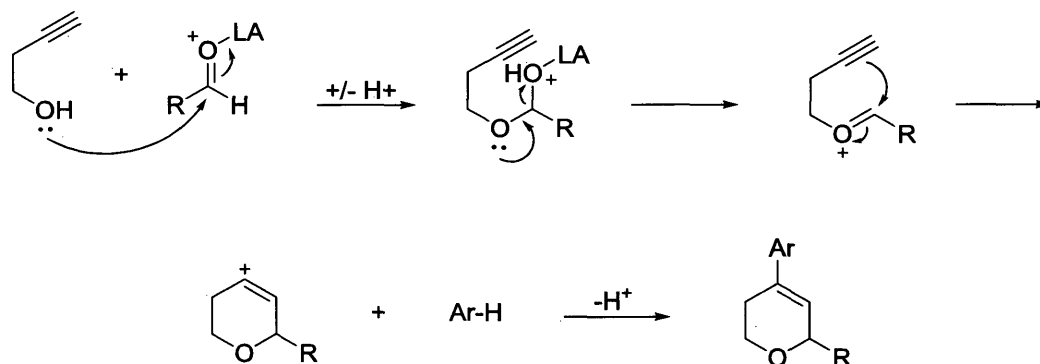
Scheme 2.2: Reddy's 4-Aryldihydropyran Synthesis.

Based on this approach, we hypothesized that tethering the aromatic ring to the alkyne substrate with an appropriate length chain would allow us to utilize this chemistry to create highly functionalized fused heterotricyclic compounds. Retrosynthetic analysis of the target compound suggested a simple sequence for the synthesis (Scheme 2.3). The desired product could be formed by a tandem

[43] Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605-2608.
[44] Reddy, U. C.; Saikia, A. K. *Synlett* **2010**, *2010*, 1027-1032.

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alkynyl-Prins/Friedel–Crafts reaction with a starting protected alkynediol and aldehyde. The protected alkynediol could be produced by a simple nucleophilic addition to phenylacetaldehyde followed by an epoxide opening. An alternative one-step synthesis using 3-butyn-1-ol and phenylacetaldehyde was also considered (Scheme 2.4), but this was ultimately rejected as the multistep synthesis provided for a wider variability of substituents at only a minor increase in time and materials.[45]
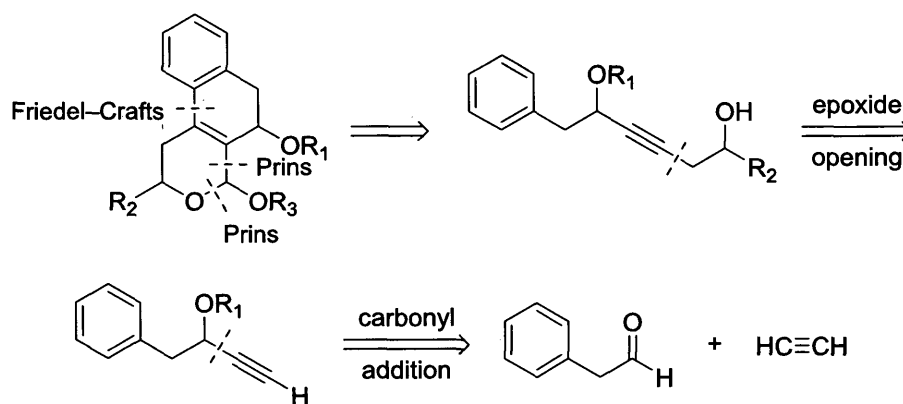
Scheme 2.3: Retrosynthetic Analysis of Target Benzo[f]isochromene-5-ols.
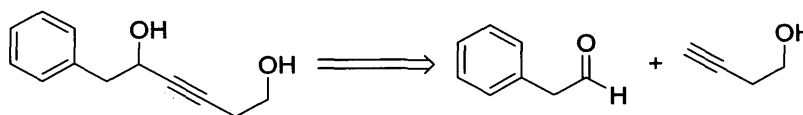
Scheme 2.4: Alternative Retrosynthetic Analysis of Alkynediol.

B. Initial Substrate Production and Preliminary Results

With a synthetic road map conceived, the initial specific synthetic strategy, shown in Scheme 2.5, was devised. Production of compound **3** proceeded

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[45] Waldo, J. P.; Zhang, X.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6679-6685.

unremarkably by a standard procedure in 66% yield.[46] Base promoted

desilylation of **3** led to **4** in 83% yield.[47,48] After introduction of the TES protecting

group (91% yield),[49] **5** was deprotonated and used to ring-open isobutylene oxide

in the presence of $BF_3 \cdot Et_2O$,[50] but this sequence did not afford compound **6**.

Instead, deprotected alkynediol **8** was isolated in 77% yield (eq 2.5). Removal of

silyl-protecting groups with $BF_3 \cdot Et_2O$ is well documented,[51] but we had hoped

that conducting the ring-opening at low temperature would prevent this side

reaction. Isobutylene oxide was chosen to avoid the introduction of a new

stereocenter into the resultant alkynediol as well as to take advantage of its ease

of handling as a non-volatile liquid in comparison to the simpler oxirane, a gas.

Compound **8** was then subjected to reaction with various simple aldehydes and

catalytic $Bi(OTf)_3$. TLC and NMR spectroscopic analysis of the resultant products

showed large amounts of starting material.

[46] López, F.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 4218-4219.

[47] It was discovered that this deprotection was time sensitive and thus required quenching as soon as all starting material was consumed as evidenced by TLC. Allowing the reaction mixture to stir for longer led to significant loss of product.

[48] Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 732-757.

[49] Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002-2021.

[50] Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391-394.

[51] Pettersson, L.; Frejd, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1823-1825.
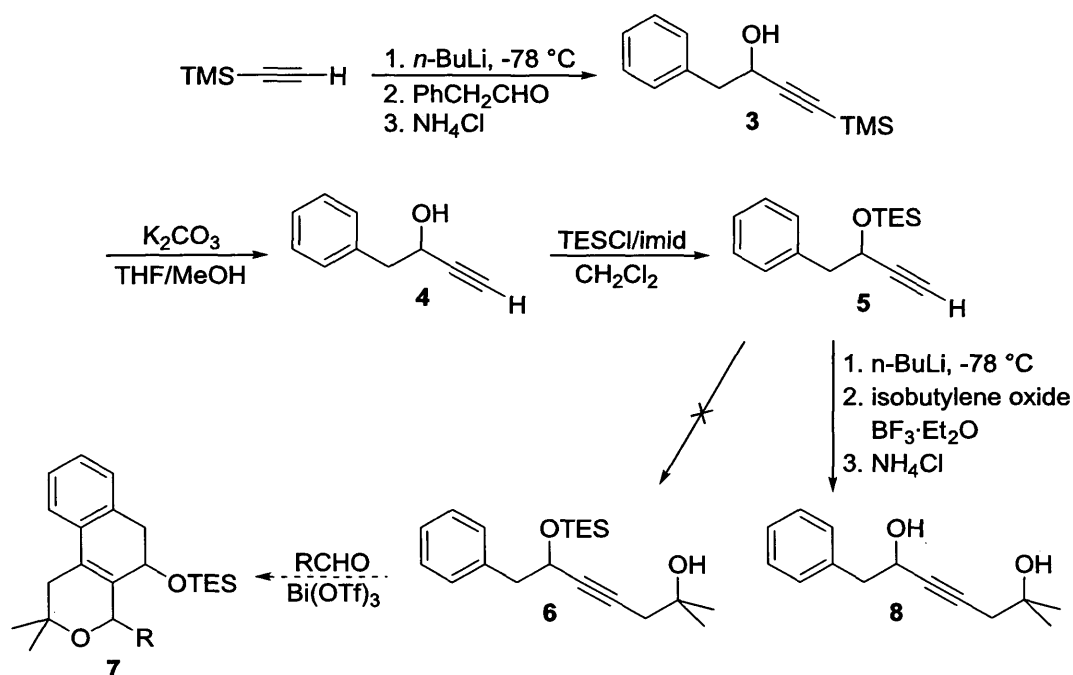
**Scheme 2.5:** Synthetic Pathway for Benzo[*f*]isochromene-5-ols.

Our first instinct was to replace the protecting group on the propargyl alcohol with something more robust. To that end, we chose the *tert*-butyldiphenylsilyl group primarily because of its resistance to BF$_3$·Et$_2$O mediated cleavage.[52] After introduction of the TBDPS group onto **4** using TBDPSCl and imidazole in DMF (78% yield), compound **9** was subjected to the epoxide opening conditions mentioned earlier to afford **10** in 87% yield (Scheme 2.6).[53]

This compound was subjected to a variety of simple aldehydes and catalytic Bi(OTf)$_3$ in an attempt to cyclize to the desired heterotricycles, but again, TLC and NMR spectroscopic analysis showed large amounts of starting material.

[52] Mabic, S.; Lepoittevin, J. P. *Synlett* **1994**, 851-852.
[53] Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975-2977.

Additionally, a number of other common Lewis acids were tried in catalytic quantities, including $BF_3 \cdot Et_2O$, $TiCl_4$, and $BiBr_3$, as well as the Brønsted acid HOTf. NMR spectroscopic analysis pointed to no reactions in these cases either.
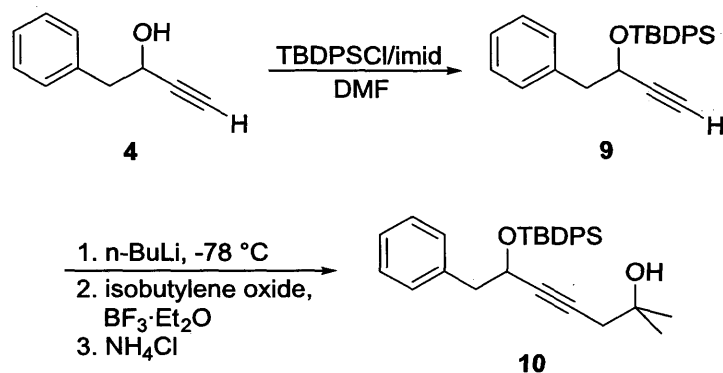

Scheme 2.6: Modified Pathway to TBDPS-Protected Propargylic Alcohol.

When this approach failed, we switched to a stoichiometric amount of $BF_3 \cdot Et_2O$, the approach originally used by Reddy's group in the intermolecular reactions. Again, this failed, as did stoichiometric amounts of $BiBr_3$ and $Bi(OTf)_3$.

Upon closer review of the NMR spectra, it was found that there were specific aromatic peaks in the reactions performed with **8** that did not appear in any reactions performed with **10**. We then hypothesized that these peaks were the result of stoichiometric conversion based on the amount of Lewis acid added. This was confirmed when 1.2 equivalents of $BF_3 \cdot Et_2O$ were used and NMR spectra of crude reaction mixtures showed no remaining starting material and strong signals indicative of a naphthalene system. Due to reactions with **10** not producing desired product, we concluded that the steric bulk of the TBDPS protecting group inhibited addition to the Lewis acid activated aldehydes.

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C. Synthesis of 2,4-Dihydro-1*H*-benzo[*f*]isochromenes

The realization that reactions of the unprotected alkynediol **8** with

aldehydes and stoichiometric quantities of Lewis acid produced a naphthalenic

product led us to investigate this transformation further. This reaction was shown

to produce a relatively novel class of tricyclic compounds called 2,4-dihydro-1*H*-

benzo[*f*]isochromenes (eq 2.5). This represented an additional dehydration

reaction in addition to the Prins cyclization and Friedel–Crafts reaction. While

unexpected, the subsequent dehydration was not surprising given the energy

gained due to the aromatization of the central ring of the heterotricycle and the

acidic conditions required to promote cyclization.[54]
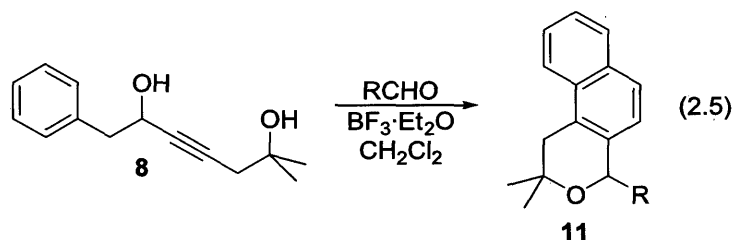
The proposed mechanism, shown in Scheme 2.7, proceeds quickly at

room temperature through a series of several steps. First, the homopropargylic

alcohol of **8** adds to the Lewis acid activated aldehyde, producing acetal **12**.

Proton transfer between the two oxygens of the acetal creates compound **13**,

making a good leaving group for oxocarbenium ion formation. Collapse of an

oxygen lone pair to create a new π bond facilitates removal of the

aforementioned leaving group and produces the key oxocarbenium ion **14**.

Attack of the carbonyl carbon by one of the π bonds of the alkyne completes the

Prins cyclization and produces the high-energy vinyl cation **15**. At this point, a π

[54] Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. *J. Org. Chem.* **2011**, *76*, 7005-7009.
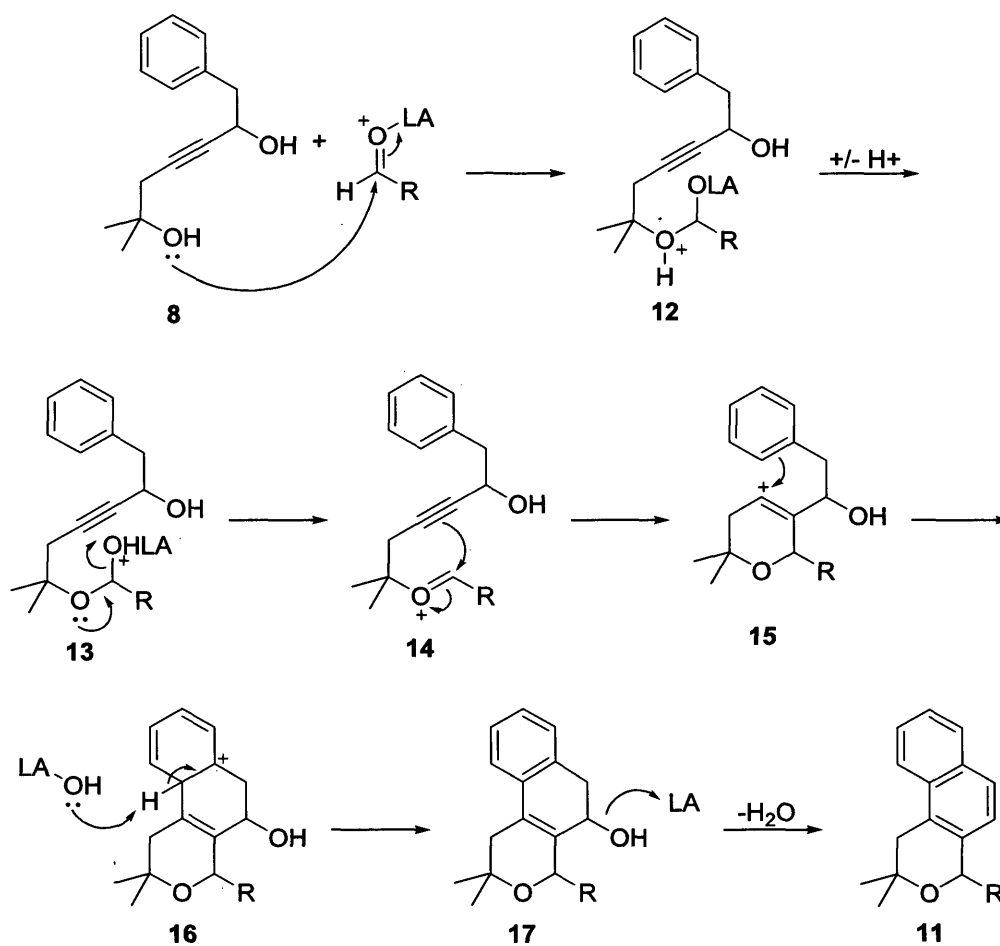
Scheme 2.7: Proposed Mechanism for Tandem Prins/Friedel–Crafts/dehydration Reaction Affording 2,4-Dihydro-1*H*-benzo[*f*]isochromenes.

bond from the pendant phenyl ring breaks and attacks the vinyl cation to form the Friedel–Crafts intermediate **16**. Then a base, likely the hydroxy-BF₃ complex created previously, removes the proton adjacent to the carbocation, restoring aromaticity of the upper ring in compound **17** and liberating one molecule of water. The remaining hydroxyl then coordinates with BF₃ and dehydrates to afford final product **11**.

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Initial efforts to isolate the final compound proved highly difficult. When the crude reaction mixture was viewed on TLC plates in common solvent systems, large streaks of material extending from the baseline to the solvent front were visible under UV light and using $KMnO_4$ stain. This apparently polymeric byproduct only proved separable when the polar phase was changed from an oxygenated solvent (EtOAc, Et_2O, MeOH) to methylene chloride. Solvent systems of methylene chloride in hexanes left the polymer at the baseline on TLC plates and thus allowed the purifications to proceed with relative ease. NMR spectroscopic analysis of the baseline byproduct, however, showed nothing that could be attributed to any specific functional groups.

A brief screening of potential Lewis acids was performed and the results are shown in Table 2.1. While the reaction did proceed with all Lewis acids used, the superiority of $BF_3 \cdot Et_2O$ quickly became apparent. The high molecular weight of bismuth compounds meant that for each 50 mg of **8** used, the reaction required 113 mg of $BiBr_3$ or 165 mg of $Bi(OTf)_3$ compared to 36 mg (32 μL) of $BF_3 \cdot Et_2O$. In addition, the considerably higher cost of bismuth salts compounded their inability to be practical reagents in stoichiometric quantities. $TiCl_4$ and $AlCl_3$ were also tested, but crude reaction mixtures appeared much more complex than reactions performed with $BF_3 \cdot Et_2O$ and bismuth salts, so these were eliminated from further consideration. Reactions shown in entries 1-5 were conducted at approximately 0.25 M in alkynediol whereas entry 6 was conducted at approximately 0.125 M. Entry 2 was also conducted with *bis*-TES protected .

alkynediol **18**, which was produced by reacting **8** with two equivalents of TESCl and imidazole. (eq 2.6).

**Table 2.1:** Screen of Potential Lewis Acid Mediators.
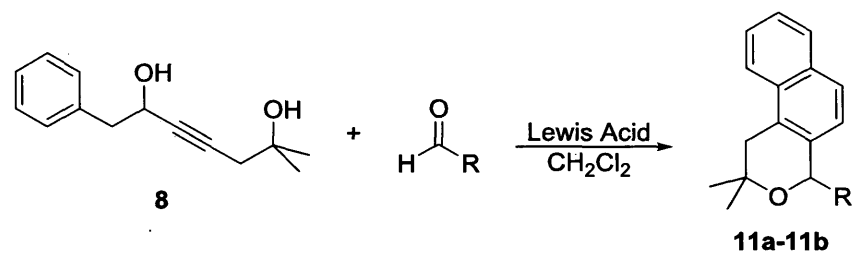
entry	aldehyde	product	Lewis acid	yield (%)^{a,b}
1			BF$_3$·Et$_2$O	38
2		**11a**	Bi(OTf)$_3$	19^c
3			BF$_3$·Et$_2$O	47
4			Bi(OTf)$_3$	42
5			BiBr$_3$	36
6		**11b**	BF$_3$·Et$_2$O	47^d

^{a} Reactions run under argon at ~0.25 M in **8** using 1.2 equiv of aldehyde and 1.1 equiv of corresponding Lewis acid. ^{b} Isolated yields of compounds after silica gel chromatography. ^{c} The *bis*-TES protected analog **18** was used. ^{d} Reaction conducted at ~0.125 M.

23
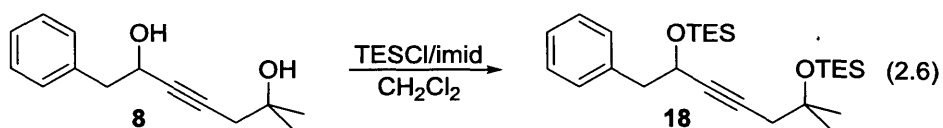
Target compounds **11a-11j** were then synthesized using alkynediol **8**,

various alkyl and aromatic aldehydes, and 10 mol% excess of $BF_3 \cdot Et_2O$. These

highly viscous, foaming oils were isolated by column chromatography and their

structures confirmed by IR, ^1H, ^{13}C APT, and ^{13}C DEPT NMR spectroscopy and

either combustion or HRMS analysis. Yields, shown in Table 2.2, were moderate

and showed only minor variability. Reactions with pivaldehyde and methyl ethyl

ketone showed no reaction, salicylaldehyde and acrolein provided very small

amounts of product, and phthalaldehyde provided what appeared to be an

amount of product comparable to **11a-11j**, but could not be separated from

unidentified byproducts.

Table 2.2: Yield Data for Synthesis of Benzo[f]isochromenes.

11a-11j
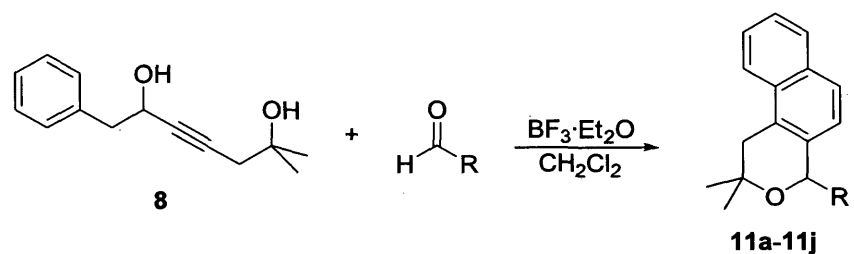
entry	product	aldehyde (R)	yield (%)[a]
1	**11a**	Et-	38
2	**11b**	i-Pr-	47
3	**11c**	sec-Bu-	52[b]
4	**11d**	pentan-3-yl-	44
5	**11e**	$PhCH_2CH_2$-	43
6	**11f**	Ph-	58
7	**11g**	p-Br-Ph-	58
8	**11h**	p-CF_3-Ph-	43
9	**11i**	p-NO_2-Ph-	46
10	**11j**	p-MeO-Ph-	58

[a] Isolated yields of compounds after silica gel column chromatography.
[b] **11c** isolated as a 7:3 mixture of diastereomers.

Compounds **11f-11j**, produced from aryl aldehydes, are highly stable with refrigeration for periods of time exceeding 1 year. In contrast, compounds **11a-11e**, produced from alkyl aldehydes, are highly unstable and oxidize to lactone **19** even with refrigeration as confirmed by X-ray diffraction experiments (eq 2.7).[55] The mechanism of oxidation is not entirely clear, but previous experiments with similar substrates show that oxidation occurs under relatively mild conditions.[56] GC-MS analysis of the ten products showed that the molecular ion peaks of **11f-11j** were much more prevalent than the molecular ion peaks of **11a-11e**, a pattern that is further evidence of the increased instability of **11a-11e**.

(2.7)

11a-11e   **19**
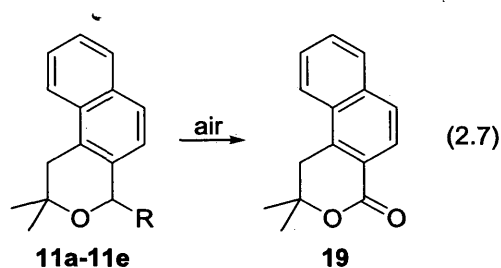
In comparison to work with homoallylic alcohols performed by Reddy et al. (eq 1.9), the cascade we developed with alkyne substrates affords products in lower overall yields. We believe there are three side-reactions possibly responsible for this difference.

The first potential pathway to byproducts is likely due to the propargylic alcohol present in our substrate. In contrast, Reddy's substrate did not contain an allylic alcohol in the analogous position. We believe that this secondary alcohol has the potential to undergo similar addition/oxocarbenium ion formation as shown in Scheme 2.8. At this point, however, formation of the vinyl cation

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[55] See Appendix B for X-ray crystallographic data.
[56] Guiso, M.; Marra, C.; Piccioni, F. *Nat. Prod. Res.* **2010**, *24*, 331-340.

through the expected Prins mechanism is highly unlikely given the significantly

high energy barrier associated with this strained species.[57] Thus, we believe that

decomposition through this undesired pathway would occur through the

oxocarbenium ion intermediate instead of the vinyl cation, but due to the

uncertainty in structure of the byproducts, we cannot discount some formation of

the cyclopentenyl cation.
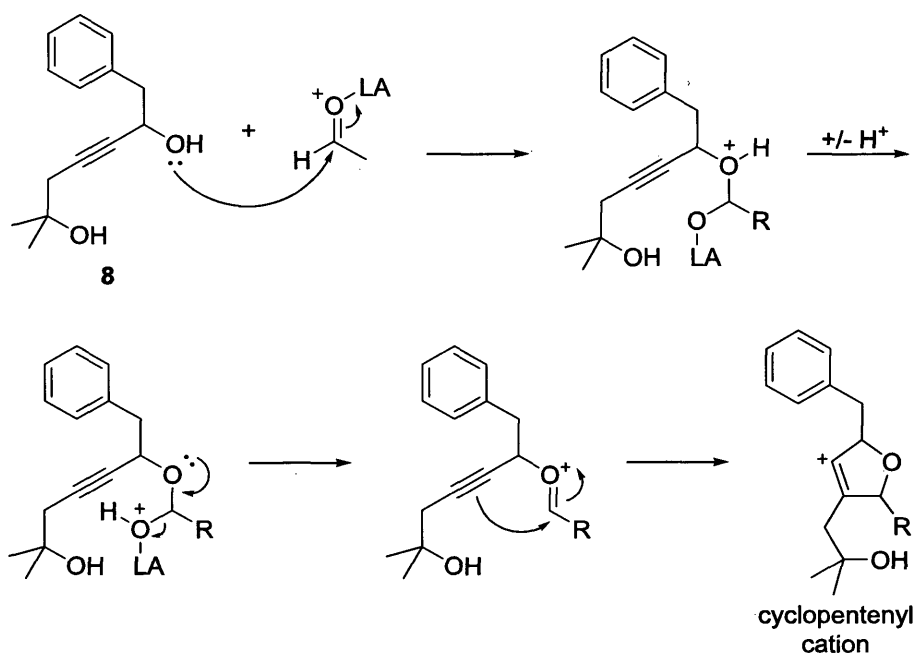
Scheme 2.8: Possible Side Reaction Involving Oxocarbenium Ion Formation
Through Propargylic Alcohol.

The second pathway involves 5-*exo-dig* cyclization instead of the

observed 6-*endo-dig* cyclization in the primary mechanism (Scheme 2.9). After

formation of the oxocarbenium ion **14**, attack of the carbonyl carbon by the triple

bond might afford vinyl cation **20**. An intramolecular Friedel–Crafts reaction

would then provide inden-2-ol **21**. This vinyl cation, again being very high

[57] Mayr, H.; Schneider, R.; Wilhelm, D.; Schleyer, P. V. R. *J. Org. Chem.* **1981**, *46*, 5336-5340.

energy, would be very reactive, and could lead to potential degradation of the reaction. This pathway could be another possible contributor to the polymeric byproduct.
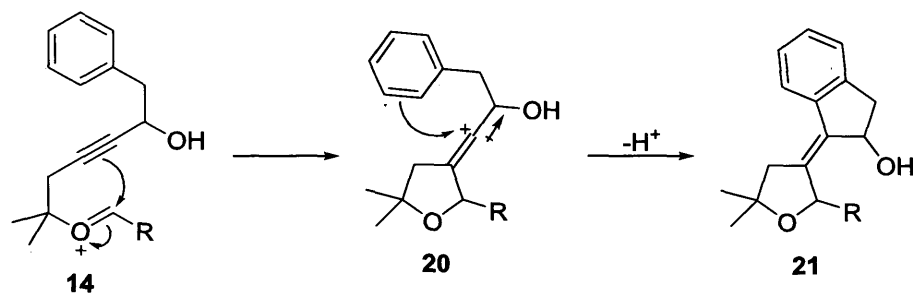
Scheme 2.9: Possible Side Reaction Involving 5-*exo-dig* Cyclization.

These two options, both favored by Baldwin's rules, seem to vary based on substituents adjacent to the triple bond. Chavre et al. reported exocyclic tetrahydrofuran products using an internal alkyne (Scheme 2.10).[58] In this work, the group investigated products formed when the group attached to the triple bond, R_1, is a terminal methyl or phenyl group and returned yields solely consisting of 5-*exo-dig* compounds.

[58] Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S. *Org. Lett.* **2006**, *8*, 3617-3619.
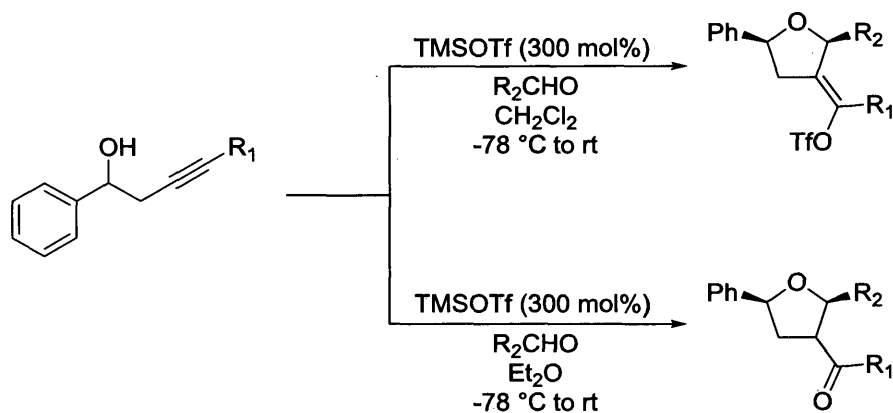
Scheme 2.10: Chavre's Approach to Exocyclic Prins Reactions.

Additionally, Xu et al. reported the use of an alkynyl diethyl acetal which, when combined with $FeCl_3$ or $FeBr_3$, produced exocyclic 5 membered rings (eq 2.8).[59] Again, these compounds have an internal alkyne with a methyl, phenyl, or substituted phenyl ring on the carbon bonded to the intermediate alkenyl cation. These cyclizations are in direct contrast to the Yadav, Miranda, and Reddy papers, referenced in eqs 2.2, 2.3, and Scheme 2.2 respectively. In the latter three reports, the alkyne was either terminal or bonded to a trimethylsilane group.
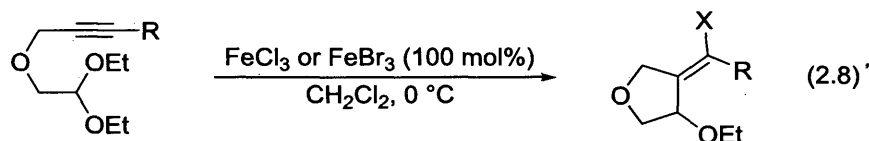
We believe this research, as well as our own, indicates a preference to have an electron-donating group bonded to the alkyne in order for it to stabilize the vinyl cation formed through 5-*exo-dig* cyclization (Scheme 2.11). In our case, the cation formed, **20**, would have an alcohol moiety on the neighboring carbon, causing a further reduction of electron density, creating additional instability.

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[59] Xu, T.; Yu, Z.; Wang, L. *Org. Lett.* **2009**, *11*, 2113-2116.

This leads to the conclusion that the 6-*endo-dig* reaction requires the propargylic alcohol present in **8**. This has been supported by other work performed in the Hinkle lab where no desired products are formed from reactions with the analog of **8** that is missing the propargylic alcohol (eq 2.9).[60]
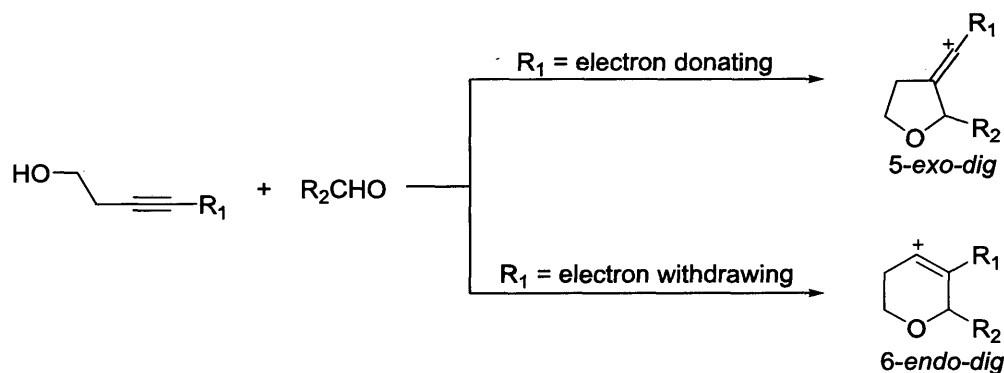
**Scheme 2.11:** Intermediate Cations Formed from 5-*exo-dig* and 6-*endo-dig* Cyclizations.

(2.9)
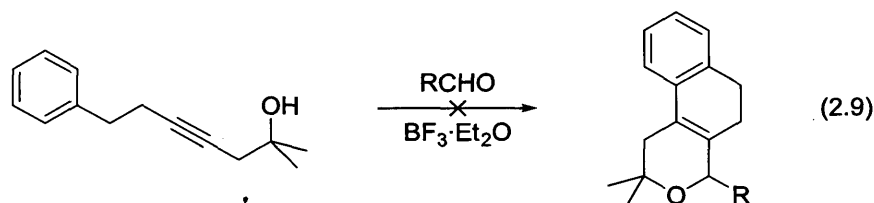
The final degradation pathway is based on the possibility of oxonia-Cope rearrangement (eq 2.10). [3,3] rearrangements are well known in Prins cyclizations.[61] In the alkenyl Prins cyclization, this often leads only to replacement of side chains and racemization of products. In the alkynyl-Prins cyclization, however, these transformations produce allene intermediates that isomerize to acyclic byproducts.[62]

[60] Chen, Y.; Lewis, S. E.; Hinkle, R. J. *Unpublished Results.*
[61] Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640-13648.
[62] Miranda, P. O.; Ramirez, M. A.; Martin, V. S.; Padron, J. I. *Chem. - Eur. J.* **2008**, *14*, 6260-6268.

$$(2.10)$$

14
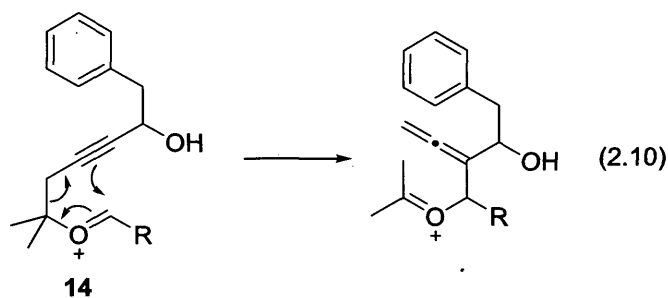
D. Future Work

As previously mentioned, in devising the original synthetic scheme, we desired a pathway that would allow us to easily create starting materials with various substitution patterns. The first of these varied materials is the methoxyphenyl based substrate **28**, originally developed in tandem with **8**, as shown in Scheme 2.12.
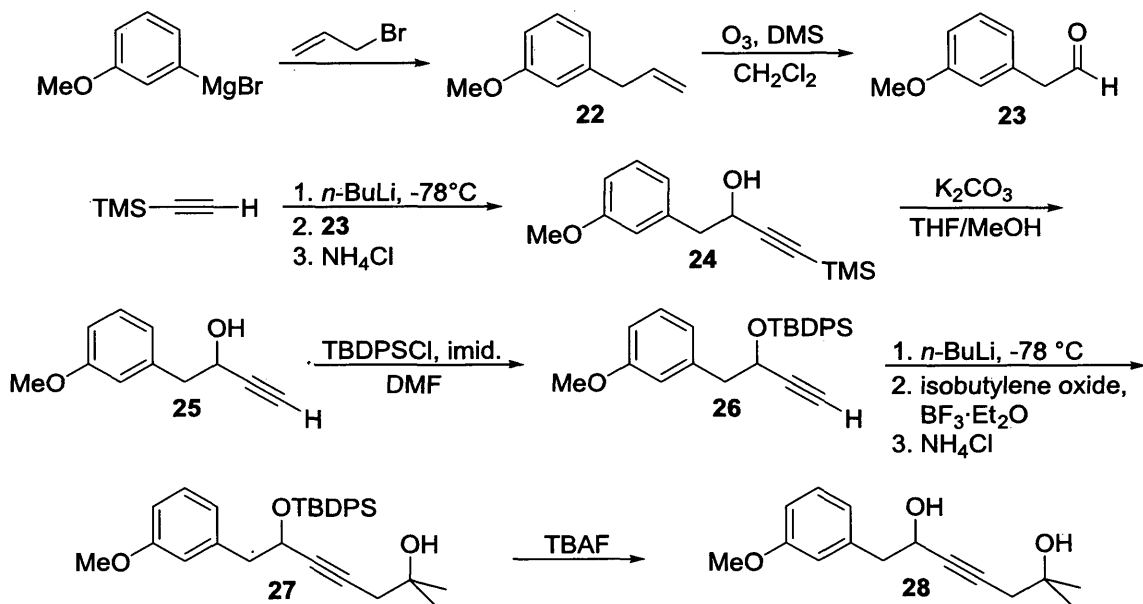
**Scheme 2.12:** Synthetic Pathway for Methoxyphenyl Based Starting Material

An S$_N$2' reaction between 3-methoxyphenylmagnesium bromide and allyl bromide afforded **22** in 79% yield.[63] Ozonolysis of **22** led to unstable aldehyde **23** which was utilized as a crude material.[64] Deprotonation of trimethylsilylacetylene followed by addition of **23** afforded **24** in 50% yield over two steps. K$_2$CO$_3$ deprotection of the alkyne led to **25** (71% yield), and introduction of the TBDPS protecting group proceeded to give **26** in 78% yield. Deprotonation and BF$_3$·Et$_2$O promoted opening of isobutylene oxide afforded **27** in 76% yield. After attempts at cyclizing **27** failed, **28** was produced by TBAF promoted deprotection of the TBDPS group (87% yield). At this time, production of **28** directly from **25**, analogous to the production of **8** from **4**, has not been attempted, but is likely to proceed smoothly (eq 2.11).

1. *n*-BuLi, -78 °C
2. isobutylene oxide, BF$_3$·Et$_2$O
3. NH$_4$Cl

(2.11)
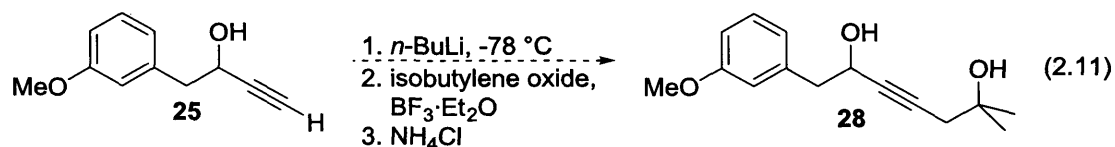
This substitution pattern was chosen due to the electron donating properties of methoxy groups in Friedel–Crafts reactions. As shown in Scheme 2.13, carbons *ortho* and *para* to the methoxy group can participate in attack of the dihydropyranyl cation. This creates a pair of regioisomeric compounds which are likely to have very different chemical properties. In addition to the activating character of the methoxy group, the aliphatic chain also attached to the aromatic ring donates electron density through induction, as both reactive sites are *ortho* to the chain.

[63] Yan, B.; Spilling, C. D. *J. Org. Chem.* **2004**, *69*, 2859-2862.
[64] Herb, C.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 8129-8135.
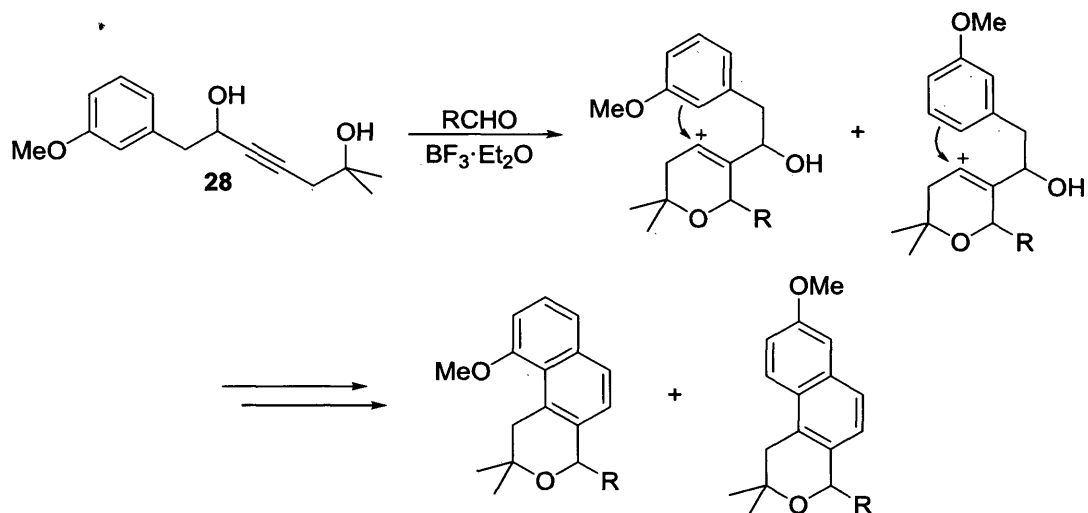
Scheme 2.13: Regiochemistry of Alternative Cyclization

Based on GC-MS NMR spectroscopic analysis of crude reaction mixtures, reactions of **28** with aldehydes and stoichiometric $BF_3 \cdot Et_2O$ afford mixtures of the corresponding 8- and 10-methoxybenzo[*f*]isochromenes. At this time, however, the regioisomers are inseparable from both each other and byproducts of the reactions. Further experiments with these and similar compounds will be conducted in the future.

In addition to this work, modifications to the starting material to produce heterotricycles with inner rings of differing sizes have begun. By modifying Scheme 2.5 to use benzaldehyde and phenylpropionaldehyde, potential products shown in Scheme 2.14 might be made.
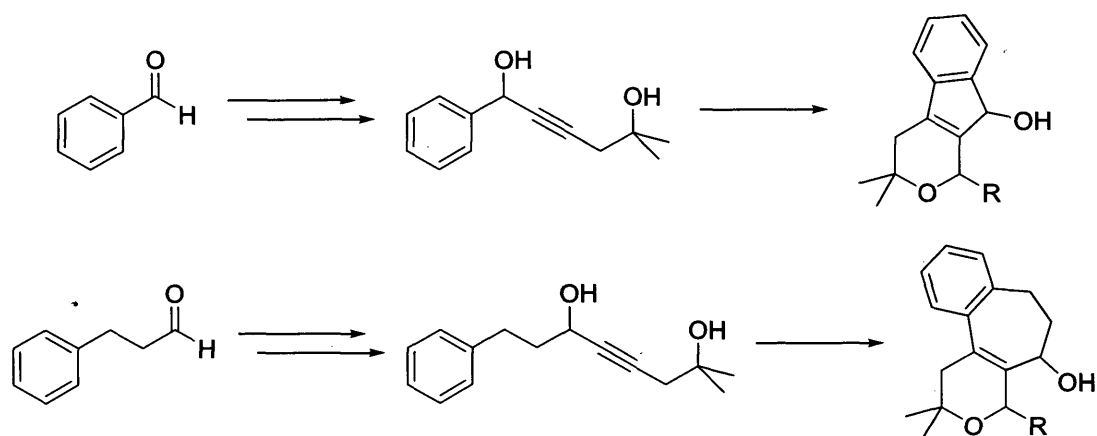
Scheme 2.14: Synthetic Pathways to Alternative Heterotricycles.

Currently, the alkynediols necessary for both of these pathways have been produced using non-optimized procedures. Investigations into both cyclizations have begun, but preliminary results do not look promising.

III. Conclusion

Research providing a short linear sequence to an alkynediol substrate which can be cyclized to a tricyclic product has been conducted. The ultimate mechanism consists of a three reaction cascade that proceeds in rapid fashion to produce novel 2,4-dihydro-1*H*-benzo[*f*]isochromenes. Initial investigations into effective catalysts have shown that $BF_3 \cdot Et_2O$ has significant benefits over others used. Aldehydes incorporated include both aliphatic and aromatic compounds and show only slight variability in yield (38%-58%), and only a few of the aldehydes tested were not compatible with this methodology.

Additionally, ground work for more highly-substituted benzo[*f*]isochromene compounds has begun, as well as research potentially leading to heterotricycles with central rings of varying sizes. These syntheses follow the general pathway of the original substrate preparation, demonstrating the adaptability of the procedure in creating new substrates for testing. Research is underway to investigate and improve these new opportunities.

IV. Experimental

A. General Information

All reagents and substrates were purchased from commercial sources and used as received unless otherwise noted. Dichloromethane was distilled from CaH_2 and THF was purified using a Solv-Tek® alumina drying column. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury FTNMR spectrometer (400, and 125 MHz, respectively) using $CDCl_3$ as solvent and referenced to internal standard (tetramethylsilane) or residual protonated chloroform at 7.27 ppm (^1H) or 77.23 ppm (^{13}C). ^{13}C NMR spectra were obtained with the aid of a DEPT experiment in which quaternary carbons are absent, methine (CH) carbons are listed as (t), methylene carbons (CH_2) are listed as (s), and methyl carbons (CH_3) are listed as (p). Additional carbon data, including quaternary carbons (q) were gleaned from an APT experiment in which quaternary (0 H) and methylene (2 H) carbons are even (e) and methine (1 H) as well as methyl (3 H) carbons are odd (o). Coupling constants were determined by the method outlined by Hoye, et al.[65] Thin layer chromatography was performed on Sorbent Technologies general-purpose silica gel on glass. Flash column chromatography was performed using Sorbent Technologies chromatographic silica gel (200-475 MESH) or through the use of Biotage – Isolera One™ chromatographic purification system. Unless otherwise noted, all experiments were conducted under argon atmosphere. All HRMS analyses were completed by the COSMIC laboratory of Old Dominion University through positive electrospray ionization on a Bruker 12 Tesla APEX –Qe FTICR-MS with and Apollo II ion source. GC-MS

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[65] Hoye, T. R.; Zhao, H. Y. *J. Org. Chem.* **2002**, *67*, 4014-4016.

analyses were conducted on an Agilent 6890 GC equipped with a 5973 mass-selective detector, and using a Rxi®-1ms capillary column. Combustion analyses were performed by Atlantic Microlabs, of Norcross, GA. All compounds were judged to be >95% homogeneous by ^{1}H NMR spectroscopy and GC MS.

B. Synthesis of Starting Material

1-phenyl-4-(trimethylsilyl)but-3-yn-2-ol (3):

Chemical Formula: $C_{13}H_{18}OSi$
Exact Mass: 218.11
Molecular Weight: 218.37
m/z: 218.11 (100.0%), 219.12 (14.3%), 219.11 (5.1%), 220.11 (3.3%), 220.12 (1.9%)
Elemental Analysis: C, 71.50; H, 8.31; O, 7.33; Si, 12.86
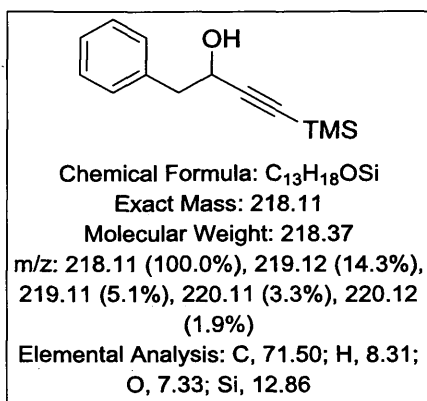
To a cooled (-78 °C) solution of TMS-acetylene (200 mmol) in 400 mL of THF was added n-butyl lithium (2.5 M in hexanes, 200 mmol) dropwise with stirring under Ar gas. The reaction was then stirred for 30 minutes, after which phenylacetaldehyde (220 mmol) was added dropwise. The reaction was stirred for 1 hour and quenched with NH_4Cl. The reaction mixture was then extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography (10%-30% EtOAc in hexanes) to afford 132 mmol (66%) of a yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.16-7.06 (m, 5H), 4.37 (q, J=6.3 Hz, 1H), 2.87-2.77 (overlapping dd, J=13.7, 6.6, 6.3 Hz, 2H), 2.00 (broad s, 1H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.6 (q), 130.1 (t), 128.5 (t), 127.1 (t), 106.1 (q), 90.7 (q), 63.7 (t), 44.1 (s), 0 (p); HRMS (CI): HRMS (CI): m/z [M + Na]$^+$ calcd for ($C_{13}H_{18}OSi$)Na (M+Na)$^+$ 241.1019, found 241.1021.

1-phenylbut-3-yn-2-ol (4):

Chemical Formula: $C_{10}H_{10}O$
Exact Mass: 146.07
Molecular Weight: 146.19
m/z: 146.07 (100.0%), 147.08 (11.0%)
Elemental Analysis: C, 82.16; H, 6.90; O, 10.94
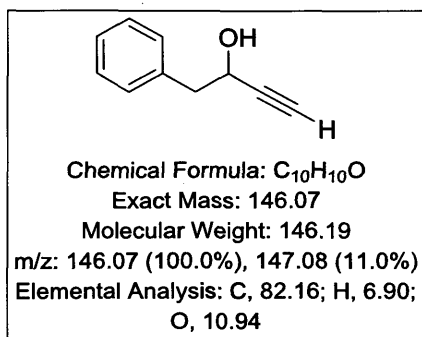
To a solution of **3** (130 mmol) in 260 mL of a 1:1 mixture of THF and methanol was added K_2CO_3 (260 mmol) with stirring. 13 mL of DI H_2O was added to the mixture and the reaction was stirred under Ar gas for 3-4 h until completion as indicated by TLC. The reaction mixture was diluted with water, extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography (10%-20% EtOAc in hexanes) to afford 95 mmol (73%) of a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33-7.23 (m, 5H), 5.05 (qd, J=6.3,2.0 Hz, 1H), 3.00 (overlapping dd, J=13.7, 6.6, 6.3 Hz, 2H), 2.46 (d, J=2.3 Hz, 1H), 2.19 (dd, J= 3.9 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.5 (q), 129.9 (t), 128.6 (t), 127.1 (t), 74.0 (t), 63.1 (t), 44.0 (s).

Triethyl((1-phenylbut-3-yn-2-yl)oxy)silane (5):

Chemical Formula: $C_{16}H_{24}OSi$
Exact Mass: 260.16
Molecular Weight: 260.45
m/z: 260.16 (100.0%), 261.16 (22.4%), 262.16 (4.4%), 262.17 (1.5%)
Elemental Analysis: C, 73.79; H, 9.29; O, 6.14; Si, 10.78
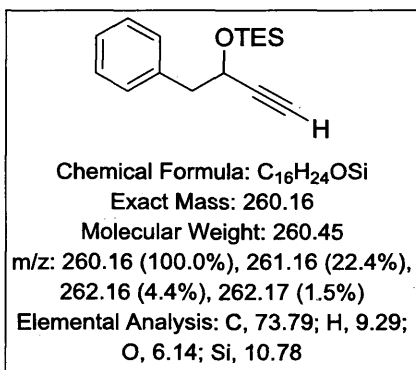
To a cooled (0°C) solution of **4** (5.8 mmol) in 25 mL of CH_2Cl_2 was added imidazole (9.9 mmol) under Ar gas. Upon dissolution of the imidazole, chlorotriethylsilane (8.7 mmol) was added dropwise and the reaction was monitored by TLC. Upon completion of the reaction, the mixture was quenched with $NaHCO_3$, extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by

column chromatography using 10% EtOAc in hexanes to afford 5.3 mmol (91%)

of a yellow liquid. R_f = 0.68 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz,

CDCl$_3$): δ = 7.30-7.20 (m, 5 H), 4.483 (dt, J = 6.6, 1.9 Hz, 1 H), 2.97 (d, J = 6.6

Hz, 2 H), 2.39 (d, J = 1.9 Hz, 1 H), 0.89 (t, J = 7.8 Hz, 9 H), 0.55 (dec, J = 7.8 Hz,

3 H). ^{13}C (100 MHz, CDCl$_3$): δ = 137.5 (q), 130.0 (t), 128.3 (t), 126.8 (t), 85.2

(q), 73.0 (t), 64.0 (t), 45.4 (s), 6.9 (p), 4.8 (s). HRMS (CI): m/z [M + Na]$^+$ calcd

for C$_{16}$H$_{24}$O$_2$SiNa: 283.1489; found: 283.1488.

6-methyl-1-phenylhept-3-yne-2,6-diol (8):

Chemical Formula: C$_{14}$H$_{18}$O$_2$
Exact Mass: 218.1307
Molecular Weight: 218.2915
m/z: 218.1307 (100.0%), 219.1340
(15.1%), 220.1374 (1.1%)
Elemental Analysis: C, 77.03; H,
8.31; O, 14.66
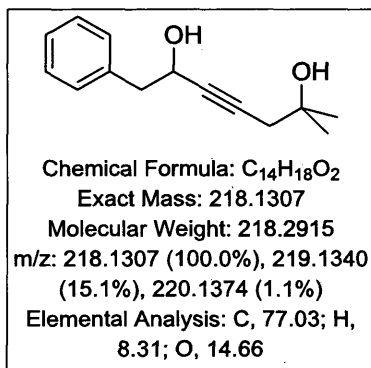
To a cooled (-78 °C) solution of 4 (5.0 mmol) in 10 mL of THF was added n-butyl lithium (1.8 M in hexanes, 10 mmol) dropwise under Ar gas. After stirring for 30 minutes, BF$_3$·Et$_2$O (7.5 mmol) was added. After stirring for 15 minutes, isobutylene oxide (5.5 mmol) was added dropwise and the

mixture was left to stir for 1h. The reaction was then quenched with NH$_4$Cl,

extracted with Et$_2$O, dried (MgSO$_4$), and concentrated in vacuo. The crude

product was then purified by column chromatography using 7%-60% EtOAc in

hexanes to afford 3.85 mmol (77%) of a viscous yellow oil. R_f = 0.07 (30%

CH$_2$Cl$_2$ in hexanes). IR (neat): 3427, 3030, 2977, 2932, 1496, 1456, 1375,

1152, 1035 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31-7.20 (m, 5 H), 4.55 (t, J =

6.6 Hz, 1 H), 3.56 (broad s, 1 H), 2.97 (overlapping dd, J = 13.7, 6.6, 6.3 Hz, 2

H), 2.70 (broad s, 1 H), 2.31 (s, 2 H), 1.22 (s, 6 H). ^{13}C (100 MHz, CDCl$_3$): δ =

137.2 (q), 129.8 (t), 128.3 (t), 126.7 (t), 83.6 (q), 82.8 (q), 70.1 (q), 63.3 (t), 44.4

(s), 34.2 (s), 28.62 (p), 28.56 (p). HRMS (CI): m/z [M + Na]$^+$ calcd for

$C_{14}H_{18}O_2Na$: 241.1199; found: 241.1198.

tert-Butyldiphenyl((1-phenylbut-3-yn-2-yl)oxy)silane (9):

Chemical Formula: $C_{26}H_{28}OSi$
Exact Mass: 384.19
Molecular Weight: 384.59
m/z: 384.19 (100.0%), 385.19 (33.2%),
386.19 (4.8%), 386.20 (4.1%)
Elemental Analysis: C, 81.20;
H, 7.34; O, 4.16; Si, 7.30
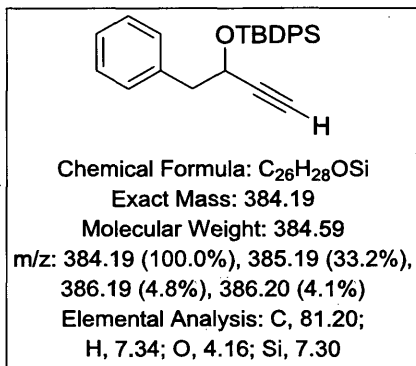
To a cooled (0 °C) solution of **4** (25 mmol) in 150 mL of DMF was added imidazole (27.5 mmol) under Ar gas. Upon dissolution of the imidazole, *tert*-butyldiphenylsilyl chloride was added slowly and the reaction was allowed to stir overnight and gradually warm to room temperature. Upon completion of the reaction, Et_2O and water were added and the organic layer was extracted. The organic layer was then washed with water, dried (MgSO4) and concentrated in vacuo. The crude product was then purified by column chromatography using 10% EtOAc in hexanes to afford 19.5 mmol (78%) of a viscous, light pink oil. R_f = 0.73 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (dd, J = 7.0, 1.2 Hz, 2 H), 7.64 (d, J = 7.8 Hz, 2 H), 7.49-7.38 (m, 6 H), 7.28-7.24 (m, 3 H), 7.14 (d, J = 7.4 Hz, 2 H), 4.55 (t, J = 6.3 Hz, 1 H), 3.01 (overlapping dd, J = 13.3, 7.0, 6.3 Hz, 2 H), 2.33-2.32 (m, 1 H), 1.11 (s, 9 H). ^{13}C (100 MHz, CDCl$_3$): δ = 137.0 (q), 136.3 (t), 136.1 (t), 133.5 (q), 133.4 (q), 130.1 (t), 130.0 (t), 129.9 (t), 128.2 (t), 127.8 (t), 127.6 (t), 126.8 (t), 84.6 (q), 73.8 (t), 65.1 (t), 45.0 (s), 27.0 (p), 19.4 (q).

6-(($tert$-butyldiphenylsilyl)oxy)-2-methyl-7-phenylhept-4-yn-2-ol (10):

Chemical Formula: $C_{30}H_{36}O_2Si$
Exact Mass: 456.25
Molecular Weight: 456.70
m/z: 456.25 (100.0%), 457.25 (38.0%)
458.25 (5.4%), 458.26 (5.2%), 459.25 (1.4%)
Elemental Analysis: C, 78.90; H, 7.95;
O, 7.01; Si, 6.15
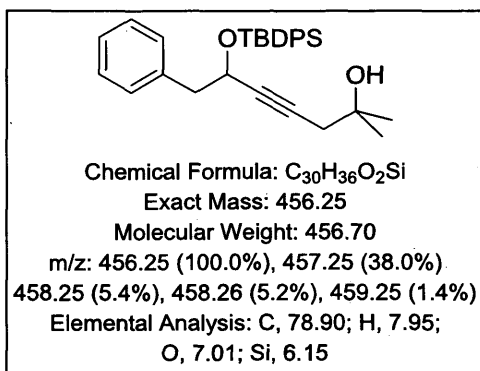
To a cooled (-78 °C) solution of **9** (2.6 mmol) in 10 mL of THF was added n-butyl lithium (2.5 M in hexanes, 2.7 mmol) dropwise under Ar gas. After stirring for 30 minutes, $BF_3 \cdot Et_2O$ (3.9 mmol) was added. After stirring for 15 minutes, isobutylene oxide

(2.9 mmol) was added dropwise and the mixture was left to stir for 1h. The reaction was then quenched with NH_4Cl, extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography using 2%-20% EtOAc in hexanes to afford 2.3 mmol (87%) of a viscous pink oil. R_f = 0.23 (10% EtOAc in hexanes). IR (neat): 3085, 2969, 2935, 2858, 1472, 1430, 1365, 1112, 1081, 860, 825, 742, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, J = 6.6, 1.2 Hz, 2 H), 7.59 (dd, J = 6.6, 1.2 Hz, 2 H), 7.40-7.31 (m, 6 H), 7.24-7.18 (m, 3 H), 7.10 (d, J = 7.0 Hz, 2 H), 4.56 (t, J = 6.3 Hz, 1 H), 2.94 (overlapping dd, J = 13.7, 6.6, 6.2 Hz, 2 H), 2.13 (s, 2 H), 1.4 (s, 1 H), 1.05 (s, 3 H), 1.04 (s, 3 H), 1.01 (s, 9 H). ^{13}C (100 MHz, $CDCl_3$): δ = 137.6 (q), 136.2 (t), 136.0 (t), 133.9 (q), 133.6 (q), 130.1 (t), 129.9 (t), 129.8 (t), 128.3 (t), 127.8 (t), 127.6 (t), 126.8 (t), 84.1 (q), 82.8 (q), 69.6 (q), 65.3 (t), 45.3 (s), 34.5 (s), 28.6 (p), 27.0 (p), 19.4 (q). HRMS (CI): m/z [M + Na]$^+$ calcd for $C_{30}H_{36}O_2SiNa$: 479.2377; found: 479.2370.

5-benzyl-3,3,11,11-tetraethyl-9,9-dimethyl-4,10-dioxa-3,11-disilatridec-6-yne (18):

Chemical Formula: $C_{26}H_{46}O_2Si_2$
Exact Mass: 446.30
Molecular Weight: 446.81
m/z: 446.30 (100.0%), 447.31 (28.7%), 447.30 (10.2%), 448.31 (7.3%), 448.30 (7.0%), 449.30 (2.2%), 449.31 (1.0%)
Elemental Analysis: C, 69.89; H, 10.38; O, 7.16; Si, 12.57
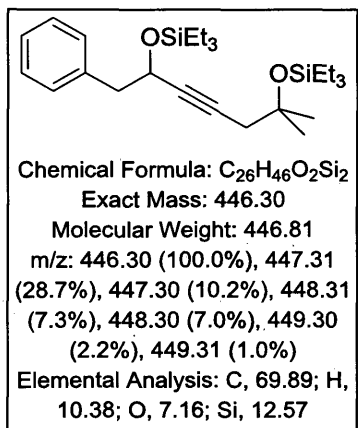
To a cooled (0°C) solution of **2a** (0.92 mmol) in 10 mL of CH_2Cl_2 was added imidazole (3.1 mmol) under Ar gas. Upon dissolution of the imidazole, chlorotriethylsilane (2.7 mmol) was added dropwise and the reaction was monitored by TLC. Upon completion of the reaction, the mixture was quenched with $NaHCO_3$, extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography using 5% EtOAc in hexanes to afford 0.52 mmol (57%) of a yellow oil. R_f = 0.64 (5% EtOAc in hexanes). IR (neat): 3032, 2959, 2879, 1496, 1459, 1417, 1365, 1238, 1075, 1015, 966, 737, 608 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.18 (m, 5 H), 4.45 (tt, J = 6.7, 1.8 Hz, 1 H), 2.94 (d, J = 6.7 Hz, 2 H), 2.33 (d, J = 1.8 Hz, 2 H), 1.26 (s, 3 H), 1.24 (s, 3 H), 0.94 (t, J = 7.9 Hz, 9 H), 0.89 (t, J = 7.9 Hz, 9 H), 0.61-0.46 (m, 12 H). ^{13}C (100 MHz, $CDCl_3$): δ = 138.1 (q), 130.1 (t), 128.2 (t), 126.6 (t), 83.2 (q), 83.0 (q), 73.4 (q), 64.4 (t), 45.9 (s), 35.7 (s), 29.55 (p), 29.50 (p), 7.3 (p), 6.92 (p), 6.86 (s), 4.9 (s). HRMS (CI): m/z [M + Na]$^+$ calcd for $C_{26}H_{46}O_2Si_2Na$: 469.2929; found: 469.2924.

C. Synthesis of Target Compounds

General Procedure for Synthesis of Benzo[f]isochromenes:

To a stirred solution of 6-methyl-1-phenylhept-3-yne-2,6-diol (**8**, ~0.25 mmol) and appropriate aldehyde (~0.30 mmol) in 1 mL dry CH_2Cl_2 was added $BF_3 \cdot Et_2O$ (~0.275 mmol) dropwise under Ar gas. The reaction was stirred at room temperature for 12 h. The reaction mixture was then quenched with aqueous $NaHCO_3$, extracted with Et_2O, and the organic layer washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford the crude product, which was purified by column chromatography to afford the product.

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4-ethyl-2,2-dimethyl-2,4-dihydro-1*H*-benzo[*f*]isochromene (11a):
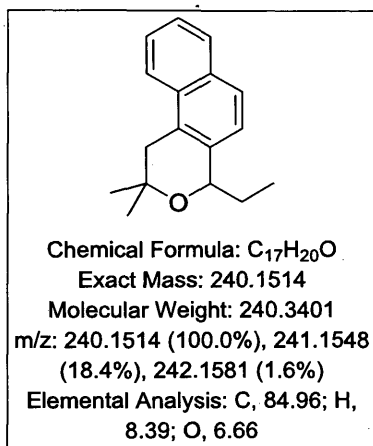
Chemical Formula: $C_{17}H_{20}O$
Exact Mass: 240.1514
Molecular Weight: 240.3401
m/z: 240.1514 (100.0%), 241.1548 (18.4%), 242.1581 (1.6%)
Elemental Analysis: C, 84.96; H, 8.39; O, 6.66

The title compound was prepared according to the general procedure and purified by column chromatography using 10%-40% CH_2Cl_2 in hexanes to afford 0.15 mmol (36%) of a viscous yellow oil. R_f = 0.37 (20% CH_2Cl_2 in hexanes). IR (neat): 3055, 2968, 2935, 2851, 1602, 1512, 1464, 1448, 1377, 1366, 1183, 1134, 1107, 1058, 1018, 1002 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.2 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 1 H), 7.54-7.44 (m, 2 H), 7.24 (d, *J* = 8.6 Hz, 1 H), 4.94 (br m, *J* = 1.56 Hz, 1 H), 3.05, (d, *J* = 16.0 Hz, 1 H), 2.97 (d, *J* = 16.0 Hz, 1 H), 2.12-2.02 (m, 1 H), 1.95-1.81 (m, 1 H), 1.50 (s, 3 H), 1.19 (s, 3 H), 0.83 (t, *J* = 7.03 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.3 (q), 132.3 (q), 132.2 (q), 129.2 (q), 128.7 (t), 126.2 (t), 125.4 (t), 123.0 (t), 122.9 (t), 72.4 (t), 70.5 (q), 36.7 (s), 31.1 (p), 29.1 (s), 23.5 (p), 8.7 (p). Anal. calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.10; H, 8.54.

4-isopropyl-2,2-dimethyl-2,4-dihydro-1*H*-benzo[*f*]isochromene (11b):
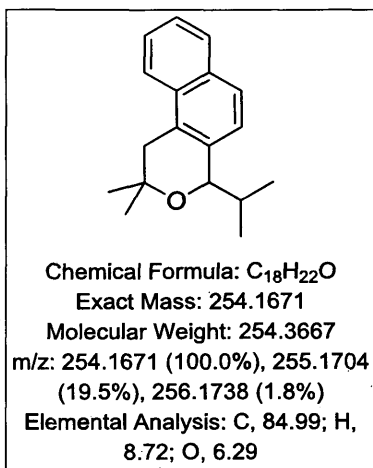
Chemical Formula: $C_{18}H_{22}O$
Exact Mass: 254.1671
Molecular Weight: 254.3667
m/z: 254.1671 (100.0%), 255.1704 (19.5%), 256.1738 (1.8%)
Elemental Analysis: C, 84.99; H, 8.72; O, 6.29

The title compound was prepared according to the general procedure and purified by column chromatography using 20% CH_2Cl_2 in hexanes to afford 0.12 mmol (47%) of a viscous yellow oil. R_f = 0.36 (20% CH_2Cl_2 in hexanes). IR (neat): 3059, 2932, 2822, 1602, 1512, 1469, 1379, 1367, 1303, 1263, 1227, 1205, 1177, 1049, 810, 763 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.67 (d, J = 8.6, 1 H), 7.53-7.44 (m, 2 H), 7.24 (d, J = 8.6 Hz, 1 H), 4.78 (s, 1 H), 3.03 (d, J = 15.6 Hz, 1 H), 2.89 (d, J = 16.0 Hz, 1 H), 2.30 (sept., J = 7.0, 2.3 Hz, 1 H), 1.47 (s, 3 H), 1.16 (d, J = 7.0, 3 H), 1.12 (s, 3 H), 0.60 (d, J = 6.6, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 134.6 (q), 132.3 (q), 132.2 (q), 129.5 (q), 128.7 (t), 126.1 (t), 125.3 (t), 123.1 (t), 122.9 (t), 76.0 (t), 70.2 (q), 36.7 (s), 34.0 (t), 31.0 (p), 23.5 (p), 20.2 (p), 15.1 (p). Anal. calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.87; H, 8.85.

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4-(sec-butyl)-2,2-dimethyl-2,4-dihydro-1H-benzo[f]isochromene (11c):
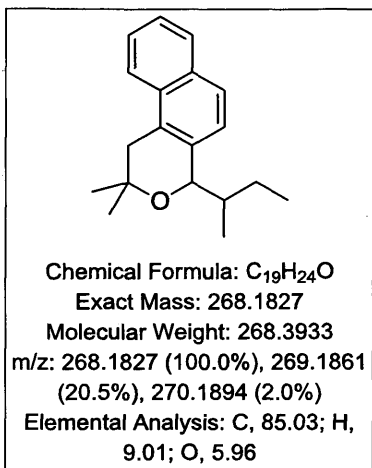
Chemical Formula: $C_{19}H_{24}O$
Exact Mass: 268.1827
Molecular Weight: 268.3933
m/z: 268.1827 (100.0%), 269.1861 (20.5%), 270.1894 (2.0%)
Elemental Analysis: C, 85.03; H, 9.01; O, 5.96

The title compound was prepared according to the general procedure and purified by column chromatography using 10% CH_2Cl_2 in hexanes to afford 0.13 mmol (52%) of a viscous yellow oil as a 7:3 mixture of diastereomers. R_f = 0.33 (10% CH_2Cl_2 in hexanes). IR (neat): 3060, 2978, 2930, 2875, 2832, 1602, 1512, 1457, 1396, 1378, 1366, 1188, 1132, 1053, 1027, 809, 760 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 8.2 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.54-7.44 (m, 2 H), 7.24 (d, J = 8.5 Hz, 1 H), 4.90 (s, 1 H), 3.03 (d, J = 16.1 Hz, 1 H), 2.90 (d, J = 15.8 Hz, 1 H), 2.03-1.96 (m, 1 H), 1.74-1.61 (m, 1 H), 1.55-1.45 (m, 1 H), 1.45 (s, 3 H), 1.13 (s, 3 H), 1.03 (t, J = 7.3 Hz, 3 H), 0.57 (d, J = 6.74, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 134.8 (q), 132.2 (q), 129.5 (q), 128.6 (t), 126.13 (t), 126.12 (t), 125.3 (t), 123.0 (t), 122.9 (t), 73.8 (t), 70.0 (q), 40.8 (t), 36.6 (s), 31.0 (p), 27.1 (s), 23.4 (p), 12.9 (p), 12.7 (p). Anal. Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.79; H, 9.15.

2,2-dimethyl-4-(pentan-3-yl)-2,4-dihydro-1*H*-benzo[*f*]isochromene (11d):
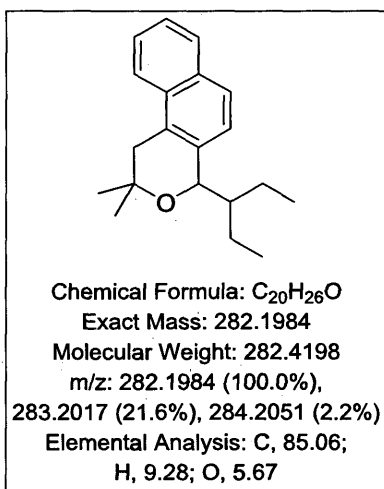
Chemical Formula: $C_{20}H_{26}O$
Exact Mass: 282.1984
Molecular Weight: 282.4198
m/z: 282.1984 (100.0%),
283.2017 (21.6%), 284.2051 (2.2%)
Elemental Analysis: C, 85.06;
H, 9.28; O, 5.67

The title compound was prepared according to the general procedure and purified by column chromatography using 10% CH_2Cl_2 in hexanes to afford 0.11 mmol (44%) of a viscous yellow oil. R_f = 0.34 (10% CH_2Cl_2 in hexanes). IR (neat): 3058, 2972, 2925, 2874, 2834, 1601, 1511, 1464, 1378, 1366, 1187, 1133, 1061, 818, 803, 756 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (d, *J* = 8.2 Hz, 1 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 8.6 Hz, 1 H), 7.53-7.43 (m, 2 H), 7.24 (d, *J* = 8.6 Hz, 1 H), 4.98 (d, *J* = 1.6 Hz), 3.03 (d, *J* = 15.2 Hz, 1 H), 2.90 (d, *J* = 16.02, 1 H), 1.80-1.73 (m, 1 H), 1.64-1.56 (m, 2 H), 1.44 (s, 3 H), 1.12 (s, 3 H), 1.07 (t, *J* = 7.4 Hz, 3 H), 1.18-1.00 (m, 2 H), 0.68 (t, *J* = 7.4 Hz, 3 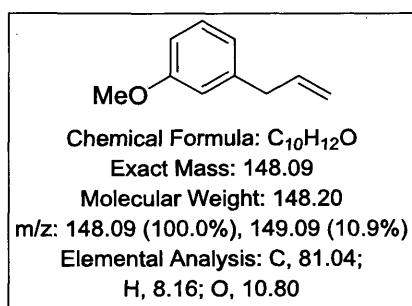H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 135.0 (q), 132.3 (q), 132.2 (q), 129.7 (q), 128.6 (t), 126.13 (t), 126.05 (t), 125.2 (t), 123.0 (t), 122.9 (t), 72.5 (t), 70.1 (q), 47.4 (t), 36.6 (s), 31.1 (p), 23.26 (s), 23.25 (p), 21.6 (s), 12.8 (p), 12.7 (p). Anal. Calcd for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found: C, 84.81; H, 9.26.

2,2-dimethyl-4-phenethyl-2,4-dihydro-1*H*-benzo[*f*]isochromene (11e):
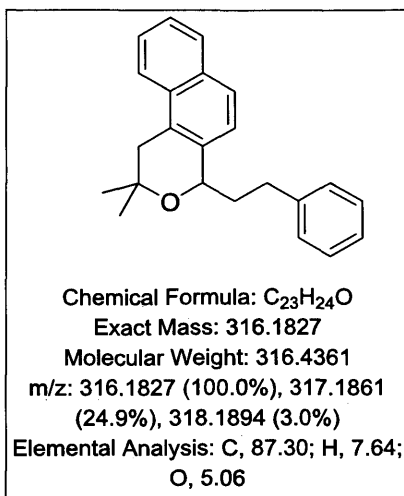
Chemical Formula: $C_{23}H_{24}O$
Exact Mass: 316.1827
Molecular Weight: 316.4361
m/z: 316.1827 (100.0%), 317.1861 (24.9%), 318.1894 (3.0%)
Elemental Analysis: C, 87.30; H, 7.64; O, 5.06

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH_2Cl_2 in hexanes to afford 0.16 mmol (43%) of a viscous yellow oil. R_f = 0.39 (40% CH_2Cl_2 in hexanes). IR (neat): 3068, 3030, 2989, 2870, 1604, 1512, 1496, 1457, 1380, 1274, 1185, 1132, 1100, 1068, 1029, 983, 816, 746 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.94 (d, *J* = 8.6 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.68 (d, *J* = 8.6 Hz, 1 H), 7.55-7.45 (m, 2 H), 7.31-7.13 (m, 6 H), 4.96 (br m , 1 H), 3.06 (d, *J* = 15.4 Hz, 1 H), 3.01 (d, *J* = 15.2 Hz, 1 H), 2.79 (ddd, *J* = 13.7, 10.6, 6.6 Hz, 1 H), 2.54 (ddd, *J* = 14.5, 10.6, 4.3 Hz, 1 H), 2.34 (dddd, *J* = 13.7, 10.6, 6.3, 3.1 Hz, 1 H), 2.13 (dddd, *J* = 13.7, 10.6, 6.6, 4.7 Hz, 1 H), 1.53 (s, 3 H), 1.19 (s, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 142.9 (q), 134.2 (q), 132.31 (q), 132.27 (q), 129.0 (q), 128.8 (t), 128.7 (t), 128.4 (t), 126.34 (t), 126.31 (t), 125.8 (t), 125.5 (t), 122.9 (t), 122.8 (t), 70.8 (t), 70.7 (q), 38.2 (s), 36.7 (s), 31.1 (p), 30.8 (s), 23.5 (p). GC-MS (EI 70 eV): [M$^+$–CH$_2$CH$_2$Ph] = 211 (100%); [M$^+$–HOCH$_2$CH$_2$Ph] = 193 *32%).

2,2-dimethyl-4-phenyl-2,4-dihydro-1*H*-benzo[*f*]isochromene (11f):
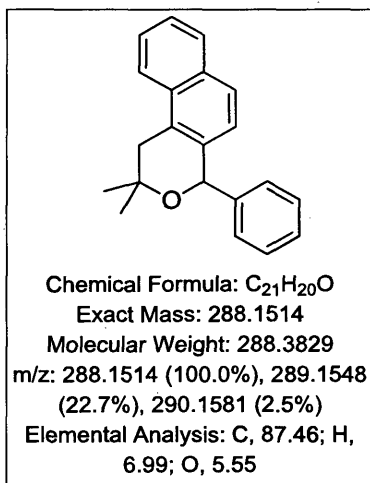
Chemical Formula: $C_{21}H_{20}O$
Exact Mass: 288.1514
Molecular Weight: 288.3829
m/z: 288.1514 (100.0%), 289.1548 (22.7%), 290.1581 (2.5%)
Elemental Analysis: C, 87.46; H, 6.99; O, 5.55

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH_2Cl_2 in hexanes to afford 0.14 mmol (58%) of a viscous yellow oil. R_f = 0.34 (40% CH_2Cl_2 in hexanes). IR (neat): 3073, 2991, 2839, 1601, 1512, 1495, 1454, 1366, 1301, 1273, 1180, 1057, 1027, 816, 759, 696 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.00 (d, *J* = 8.6 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.57-7.46 (m, 3 H), 7.34-7.27 (m, 5 H), 6.87 (d, *J* = 8.6 Hz, 1 H), 5.85 (s, 1 H), 3.22 (d, *J* = 16.4 Hz, 1 H), 3.16 (d, *J* = 16.4 Hz, 1 H), 1.55 (s, 3 H), 1.36 (s, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 143.0 (q), 134.1 (q), 132.4 (q), 132.1 (q), 129.2 (t), 128.7 (t), 128.3 (q), 128.2(t), 126.4 (t), 126.1 (t), 125.7 (t), 124.7 (t), 123.0 (t), 76.2 (t), 71.9 (q), 36.6 (s), 31.2 (p), 23.6 (p). HRMS (CI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{20}$ONa: 311.1406; found: 311.1405.

4-(4-bromophenyl)-2,2-dimethyl-2,4-dihydro-1H-benzo[f]isochromene (11g):
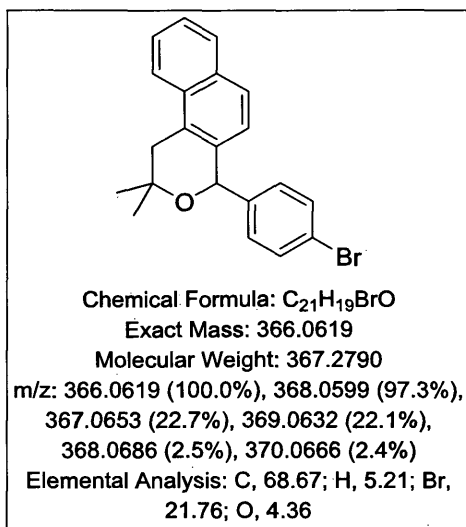
Chemical Formula: $C_{21}H_{19}BrO$
Exact Mass: 366.0619
Molecular Weight: 367.2790
m/z: 366.0619 (100.0%), 368.0599 (97.3%), 367.0653 (22.7%), 369.0632 (22.1%), 368.0686 (2.5%), 370.0666 (2.4%)
Elemental Analysis: C, 68.67; H, 5.21; Br, 21.76; O, 4.36

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH_2Cl_2 in hexanes to afford 0.16 mmol (58%) of a viscous yellow oil. R_f = 0.44 (40% CH_2Cl_2 in hexanes). IR (neat): 3058, 2978, 2935, 2849, 1720, 1588, 1486, 1397, 1275, 1180, 1071, 1011, 814, 752 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.01 (d, J = 8.6 Hz, 1 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.58-7.47 (m, 5 H), 7.23 (d, J = 8.2 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 1 H), 5.84 (s, 1 H), 3.20 (overlapping d, J = 19.5, 16.8 Hz, 2 H), 1.57 (s, 3 H), 1.38 (s, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 142.2 (q), 133.5 (q), 132.6 (q), 132.2 (q), 131.9 (t), 130.9 (t), 128.8 (t), 128.5 (q), 126.6 (t), 126.3 (t), 125.9 (t), 124.5 (t), 123.0 (t), 122.2 (q), 75.7 (t), 72.1 (q), 36.7 (s), 31.2 (p), 23.6 (p). HRMS (CI): m/z [M + Na]$^+$ calcd for $C_{21}H_{19}BrONa$: 389.0511; found: 389.0508.

2,2-dimethyl-4-(4-(trifluoromethyl)phenyl)-2,4-dihydro-1*H*-benzo[*f*]isochromene (11h):
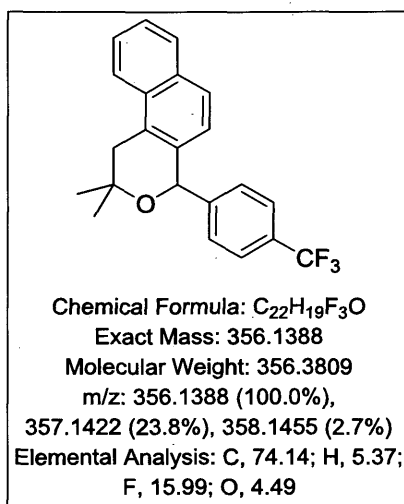
Chemical Formula: $C_{22}H_{19}F_3O$
Exact Mass: 356.1388
Molecular Weight: 356.3809
m/z: 356.1388 (100.0%),
357.1422 (23.8%), 358.1455 (2.7%)
Elemental Analysis: C, 74.14; H, 5.37;
F, 15.99; O, 4.49

The title compound was prepared according to the general procedure and purified by column chromatography using 20%-40% CH_2Cl_2 in hexanes to afford 0.11 mmol (43%) of a viscous yellow oil. R_f = 0.47 (40% CH_2Cl_2 in hexanes). IR (neat): 3055, 2975, 2925, 1620, 1512, 1419, 1369, 1326, 1160, 1133, 1067, 1019, 915, 841, 814, 766 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.00 (d, *J* = 8.5 Hz, 1 H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.60-7.45 (m, 7 H), 6.82 (d, *J* = 8.5 Hz, 1 H), 5.91 (s, 1 H), 3.23 (d, *J* = 16.7 Hz, 1 H), 3.18 (d, *J* = 16.1 Hz, 1 H), 1.55 (s, 3 H), 1.37 (s, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 146.9 (q), 133.0 (q), 132.6 (q), 132.1 (q), 130.6 (CF$_3$, *J* = 32.4 Hz), 129.6 (t), 128.8 (t), 128.5 (q), 126.6 (t), 126.4 (t), 126.0 (t), 125.8 (t), 125.7 (t), 124.3 (t), 123.0 (t), 75.7 (t), 72.2 (q), 36.5 (s), 31.1 (p), 23.6 (p). HRMS (CI): m/z [M + Na]$^+$ calcd for $C_{22}H_{19}F_3OH$: 379.1280; found: 379.1287.

2,2-dimethyl-4-(4-nitrophenyl)-2,4-dihydro-1*H*-benzo[*f*]isochromene (11i):
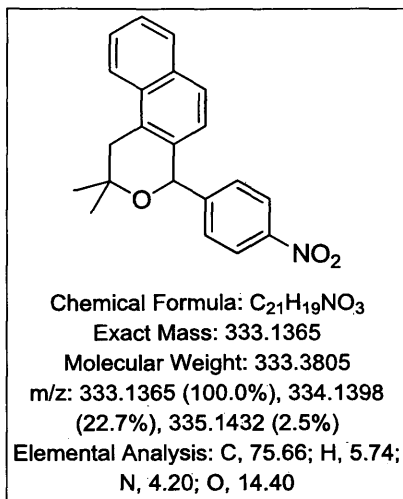
Chemical Formula: $C_{21}H_{19}NO_3$
Exact Mass: 333.1365
Molecular Weight: 333.3805
m/z: 333.1365 (100.0%), 334.1398 (22.7%), 335.1432 (2.5%)
Elemental Analysis: C, 75.66; H, 5.74; N, 4.20; O, 14.40

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH_2Cl_2 in hexanes to afford 0.11 mmol (46%) of a viscous yellow oil. R_f = 0.19 (40% CH_2Cl_2 in hexanes). IR (neat): 3060, 2980, 2930, 2854, 1603, 1521, 1353, 1275, 1183, 1079, 1064, 916, 854, 812, 765 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.18 (d, J = 8.6 Hz, 2 H), 8.00 (d, J = 8.6 Hz, 1 H), 7.80 (d, J = 8.2 Hz, 1 H), 7.60-7.49 (m, 5 H), 6.79 (d, J = 8.6 Hz, 1 H), 5.96 (s, 1 H), 3.21 (overlapping d, J = 18.0, 16.8 Hz, 2 H), 1.56 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 150.2 (q), 148.0 (q), 132.7 (q), 132.5 (q), 132.2 (q), 130.0 (t), 128.9 (t), 128.7 (q), 126.8 (t), 126.6 (t), 126.1 (t), 124.0 (t), 123.0 (t), 75.4 (t), 72.4 (q), 36.6 (s), 31.1 (p), 23.6 (p). HRMS (CI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{19}NO_3Na$: 356.1257; found: 356.1255.

4-(4-methoxyphenyl)-2,2-dimethyl-2,4-dihydro-1*H*-benzo[*f*]isochromene (11j):
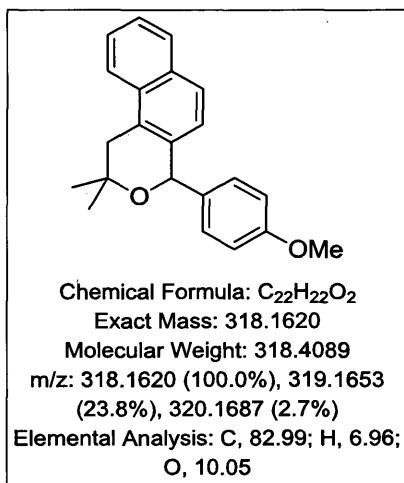
Chemical Formula: $C_{22}H_{22}O_2$
Exact Mass: 318.1620
Molecular Weight: 318.4089
m/z: 318.1620 (100.0%), 319.1653 (23.8%), 320.1687 (2.7%)
Elemental Analysis: C, 82.99; H, 6.96; O, 10.05

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH_2Cl_2 in hexanes to afford to afford 0.14 mmol (58%) of a viscous yellow oil. R_f = 0.16 (40% CH_2Cl_2 in hexanes). IR (neat): 3061, 3006, 2827, 1599, 1586, 1508, 1456, 1366, 1302, 1241, 1170, 1027, 963, 912, 816, 768, 733 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.99 (d, J = 8.6 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.56-7.52 (m, 2 H), 7.45 (dd, J = 7.8, 7.0 Hz, 1 H), 7.24 (d, J = 8.6 Hz, 2 H), 6.86 (overlapping d, J = 9.0, 8.2 Hz, 3 H), 5.82 (s, 1 H), 3.77 (s, 3 H), 3.20 (d, J = 16.4 Hz, 1 H), 3.14 (d, J = 16.0 Hz, 1 H), 1.54 (s, 3 H), 1.35 (s, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.7 (q), 134.5 (q), 132.6 (q), 132.2 (q), 130.4 (t), 128.8 (t), 128.4 (t), 126.4 (t), 126.1 (t), 125.6 (t), 124.9 (t), 123.0 (t), 114.2 (t), 75.7 (t), 71.8 (q), 55.5(p), 36.7 (s), 31.3 (p), 23.6 (p). HRMS (CI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{22}O_2Na$: 341.1512; found: 341.1510.

D. Synthesis of Alternative Starting Material

1-allyl-3-methoxybenzene (22):

Chemical Formula: $C_{10}H_{12}O$
Exact Mass: 148.09
Molecular Weight: 148.20
m/z: 148.09 (100.0%), 149.09 (10.9%)
Elemental Analysis: C, 81.04; H, 8.16; O, 10.80

To a solution of 1-bromoprop-2-ene (12.4 mmol, 1.05 equiv.) in THF (25 mL), 3-methoxyphenylmagnesium bromide (1.0M in THF, 11.8 mmol, 1 equiv.) was added dropwise with stirring. The reaction was stirred for 4h at 0 °C. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl (25 mL) and extracted with Et_2O (2x25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes to afford 9.34 mmol (79.1%) of a yellow oil. Spectra agree with previously published spectral data.[66]

2-(3-methoxyphenyl)acetaldehyde (23):

Chemical Formula: $C_9H_{10}O_2$
Exact Mass: 150.07
Molecular Weight: 150.18
m/z: 150.07 (100.0%), 151.07 (9.9%)
Elemental Analysis: C, 71.98; H, 6.71; O, 21.31
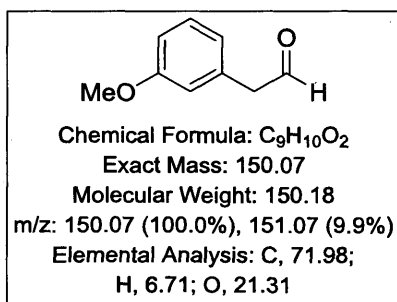
To a cooled (-78 °C) solution of **22** (17.6 mmol) in 100 ml of CH_2Cl_2 and 20 mL of MeOH was added a large excess of $NaHCO_3$. Ozone gas was bubbled through the reaction flask until the mixture turned blue. Oxygen gas was then bubbled through the reaction flask until the mixture was colorless. Dimethylsulfide (88.0 mmol) was added and the reaction was allowed to warm to room temperature

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[66] Taber, D. F.; Paquette, C. M.; Gu, P.; Tian, W. *J. Org. Chem.* **2013**, *78*, 9772-9780.

and stir overnight under Ar gas. The reaction mixture was diluted with water, extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude product was then used without further purification. Spectra agree with previously published spectral data.[67]

1-(3-methoxyphenyl)-4-(trimethylsilyl)but-3-yn-2-ol (24):

Chemical Formula: $C_{14}H_{20}O_2Si$
Exact Mass: 248.12
Molecular Weight: 248.40
m/z: 248.12 (100.0%), 249.13 (15.4%),
249.12 (5.1%), 250.12 (3.3%), 250.13 (2.3%)
Elemental Analysis: C, 67.70; H, 8.12;
O, 12.88; Si, 11.31
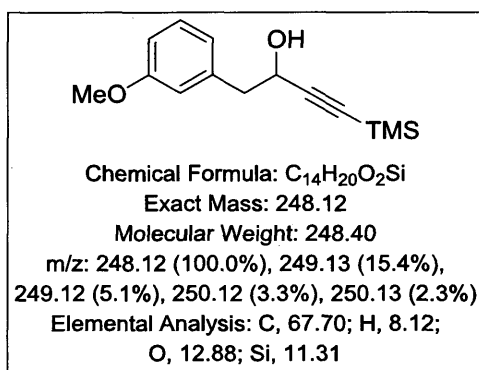
To a cooled (-78 °C) solution of TMS-acetylene (17.5 mmol) in 100 mL of THF was added n-butyl lithium (2.5 M in hexanes, 18.4 mmol) dropwise with stirring under Ar gas. The reaction was then stirred for 30 minutes, after which **23** (18.4 mmol) was added dropwise. The reaction was stirred for 1 hour and quenched with NH_4Cl. The reaction mixture was then extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography (10%-30% EtOAc in hexanes) to afford 8.8 mmol (50% over two steps) of a yellow liquid. R_f = 0.14 (10% EtOAc in hexanes). ^1H NMR (400 MHz, CDCl$_3$): δ = 7.24 (t, J = 7.8 Hz, 1 H), 6.89-6.81 (m, 3 H), 4.58 (t, J = 6.7 Hz, 1 H), 3.82 (s, 3 H), 3.00, (overlapping dd, J = 13.7, 7, 5.9 Hz, 2 H), 2.21 (s, 1 H), 0.18 (s, 9 H) ^{13}C (100 MHz, CDCl$_3$): δ = 159.6 (q), 138.2 (q), 129.3 (t), 122.3 (t),

[67] Inokuchi, T.; Matsumoto, S.; Fukushima, M.; Torii, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 796-800.

115.6 (t), 112.4 (t), 106.2 (q), 90.3 (q), 63.5 (t), 55.2 (p), 44.1 (s), 0 (p). HRMS

(CI): m/z [M + Na]$^+$ calcd for $C_{14}H_{20}O_2SiNa$: 271.1125; found: 271.1122.

1-(3-methoxyphenyl)but-3-yn-2-ol (25):

Chemical Formula: $C_{11}H_{12}O_2$
Exact Mass: 176.08
Molecular Weight: 176.21
m/z: 176.08 (100.0%),
177.09 (12.1%), 178.09 (1.1%)
Elemental Analysis: C, 74.98;
H, 6.86; O, 18.16
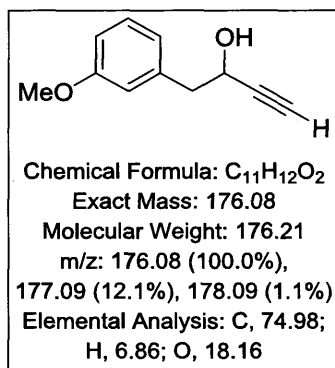
To a solution of **24** (8.8 mmol) in 50 mL of a 1:1 mixture of THF and methanol was added K_2CO_3 (17.5 mmol) with stirring. 2 mL of DI H_2O was added to the mixture and the reaction was stirred under Ar gas for 3-4 h until completion as indicated by TLC. The reaction mixture was diluted with water, extracted with Et_2O,

dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography (10% EtOAc in hexanes) to afford 6.2 mmol (71%) of pure product. Liquid; R_f = 0.19 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.22 (t, J = 7.8 Hz, 1 H), 6.87-6.78 (m, 3 H), 4.56 (d, J = 3.9 Hz, 1 H), 3.78 (s, 3 H), 2.97 (overlapping dd, J = 13.7, 6.6, 6.3 Hz, 2 H), 2.48 (d, J = 1.9 Hz, 1 H), 2.33 (s, 1 H). ^{13}C (100 MHz, CDCl$_3$): δ = 159.7 (q), 138.0 (q), 129.5 (t), 122.2 (t), 115.6 (t), 112.5 (t), 84.3 (q), 73.9 (t), 63.0 (t), 55.3 (p), 44.0 (s).

Tert-butyl((1-(3-methoxyphenyl)but-3-yn-2-yl)oxy)diphenylsilane (26):

Chemical Formula: $C_{27}H_{30}O_2Si$
Exact Mass: 414.20
Molecular Weight: 414.62
m/z: 414.20 (100.0%), 415.20 (34.3%), 416.20 (4.8%), 416.21 (4.7%)
Elemental Analysis: C, 78.22; H, 7.29; O, 7.72; Si, 6.77
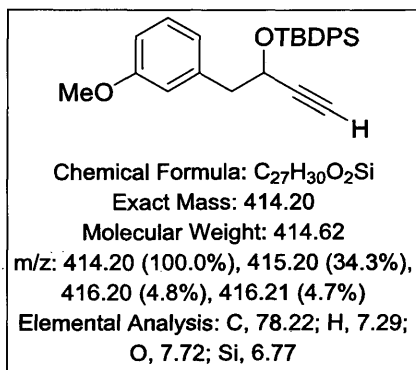
To a cooled (0 °C) solution of **25** (25 mmol) in 150 mL of DMF was added imidazole (27.5 mmol) under Ar gas. Upon dissolution of the imidazole, *tert*-butyldiphenylsilyl chloride was added slowly and the reaction was allowed to stir overnight and gradually warm to room temperature. Upon completion of the reaction, Et_2O and water were added and the organic layer was extracted. The organic layer was then washed with water, dried (MgSO4) and concentrated in vacuo. The crude product was then purified by column chromatography using 10% EtOAc in hexanes to afford 19.5 mmol (78%) of a viscous, light pink oil. R_f = 0.73 (10% EtOAc in hexanes). ^1H NMR (400 MHz, CDCl$_3$): δ = 7.69 (dd, *J* = 6.2, 1.6 Hz, 2 H), 7.59 (dd, *J* = 6.2 1.6 Hz, 2 H), 7.44-7.32 (m, 6 H), 7.12 (t, *J* = 7.8 Hz, 1 H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.67 (d, *J* = 7.4 Hz, 1 H), 6.61 (t, *J* = 2.0 Hz, 1 H), 4.48 (td, *J* = 6.3, 2.0 Hz, 1 H), 3.71 (s, 3 H), 2.92 (overlapping dd, *J* = 13.3, 6.3 Hz, 2 H), 2.3 (d, *J* = 2.0 Hz, 1 H), 1.05 (s, 9 H). ^{13}C (100 MHz, CDCl$_3$): δ = 159.5 (q), 138.5 (q), 136.3 (t), 136.1 (t), 133.5 (q), 133.4 (q), 130.0 (t), 129.9 (t), 129.2 (t), 127.8 (t), 127.6 (t), 122.5 (t), 115.4 (t), 112.5 (t), 84.6 (q), 73.8 (t), 65.1 (t), 55.3 (p), 45.2 (s), 27.1 (p), 19.4 (q).

6-((tert-butyldiphenylsilyl)oxy)-7-(3-methoxyphenyl)-2-methylhept-4-yn-2-ol (27):

Chemical Formula: $C_{31}H_{38}O_3Si$
Exact Mass: 486.26
Molecular Weight: 486.73
m/z: 486.26 (100.0%), 487.26 (38.7%), 488.26 (5.7%), 488.27 (5.6%), 489.26 (1.2%), 489.27 (1.1%)
Elemental Analysis: C, 76.50; H, 7.87; O, 9.86; Si, 5.77
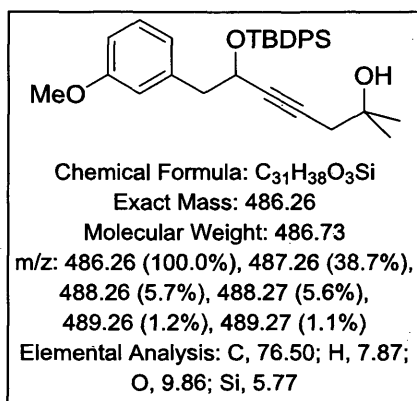
To a cooled (-78 °C) solution of **26** (5.2 mmol) in 20 mL of THF was added *n*-butyl lithium (2.5 M in hexanes, 5.5 mmol) dropwise under Ar gas. After stirring for 30 minutes, BF$_3$·Et$_2$O (7.8 mmol) was added. After stirring for 15 minutes, isobutylene oxide (5.7 mmol) was added

dropwise and the mixture was left to stir for 1h. The reaction was then quenched with NH$_4$Cl, extracted with Et$_2$O, dried (MgSO$_4$), and concentrated in vacuo. The crude product was then purified by column chromatography using 2%-20% EtOAc in hexanes to afford 4.0 mmol (76%) of a viscous pink oil. R_f = 0.19 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.71 (dd, J = 6.2, 1.6 Hz, 2 H), 7.61 (dd, J = 6.3, 1.5 Hz, 2 H), 7.44-7.33 (m, 6H), 7.15 (t, J = 7.8 Hz, 1 H), 6.76-6.71 (m, 2 H), 6.66 (t, J = 1.9 Hz, 1 H), 4.57 (tt, J = 6.7, 1.9 Hz, 1 H), 3.73 (s, 3 H), 2.94 (overlapping dd, J = 13.3, 6.2 Hz, 2 H), 2.17 (d, J = 2.0 Hz, 2 H), 1.47 (s, 1 H), 1.09 (s, 3 H), 1.08 (s, 3 H), 1.04 (s, 9 H). ^{13}C (100 MHz, CDCl$_3$): δ = 159.6 (q), 139.1 (q), 136.2 (t) ,136.1 (t), 133.9 (q), 133.6 (q), 130.0 (t), 129.8 (t), 129.2 (t), 127.8 (t), 127.6 (t), 122.4 (t), 115.5 (t), 112.4 (t), 84.2 (q), 82.7 (q), 69.8 (q), 55.3 (p), 45.4 (s), 34.5 (s), 28.6 (p), 27.0 (p), 19.4 (q). HRMS (CI): *m/z* [M + Na]$^+$ calcd for C$_{14}$H$_{20}$O$_2$SiNa: 271.1125; found: 271.1122.

1-(3-methoxyphenyl)-6-methylhept-3-yne-2,6-diol (28):

Chemical Formula: $C_{15}H_{20}O_3$
Exact Mass: 248.14
Molecular Weight: 248.32
m/z: 248.14 (100.0%), 249.14 (16.2%), 250.15 (1.9%)
Elemental Analysis: C, 72.55; H, 8.12; O, 19.33
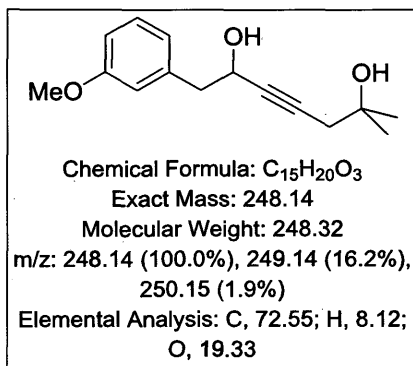
To a solution of **27** (3.5 mmol) in 60 mL of THF was added tetrabutylammonium fluoride (1 M in THF, 10.5 mmol) under Ar gas. The mixture was allowed to stir overnight at room temperature. The reaction was then quenched with potassium sodium tartrate (40 mL), extracted with EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography using 7%-70% EtOAc in hexanes to afford 3.0 mmol (87%) of a viscous yellow oil. R_f = 0.07 (30% EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (t, J = 7.8 Hz, 1 H), 6.86-6.77 (m, 3 H), 4.59 (s, 1 H), 3.79 (s, 3 H), 2.97-2.95 (m, 3 H), 2.34 (d, J = 1.6 Hz, 3 H), 1.24 (s, 6 H). ^{13}C (100 MHz, $CDCl_3$): δ = 159.7 (q), 138.7 (q), 129.5 (t), 122.2 (t), 115.7 (t), 112.3 (t), 83.6 (q), 82.9 (q), 70.1 (q), 63.4 (t), 55.3 (p), 44.5 (s), 34.4 (s), 28.8 (p) 28.7 (p). HRMS (CI): m/z [M + Na]$^+$ calcd for $C_{15}H_{20}O_3Na$: 271.1305; found: 271.1302.

Appendix A

NMR and GCMS Data
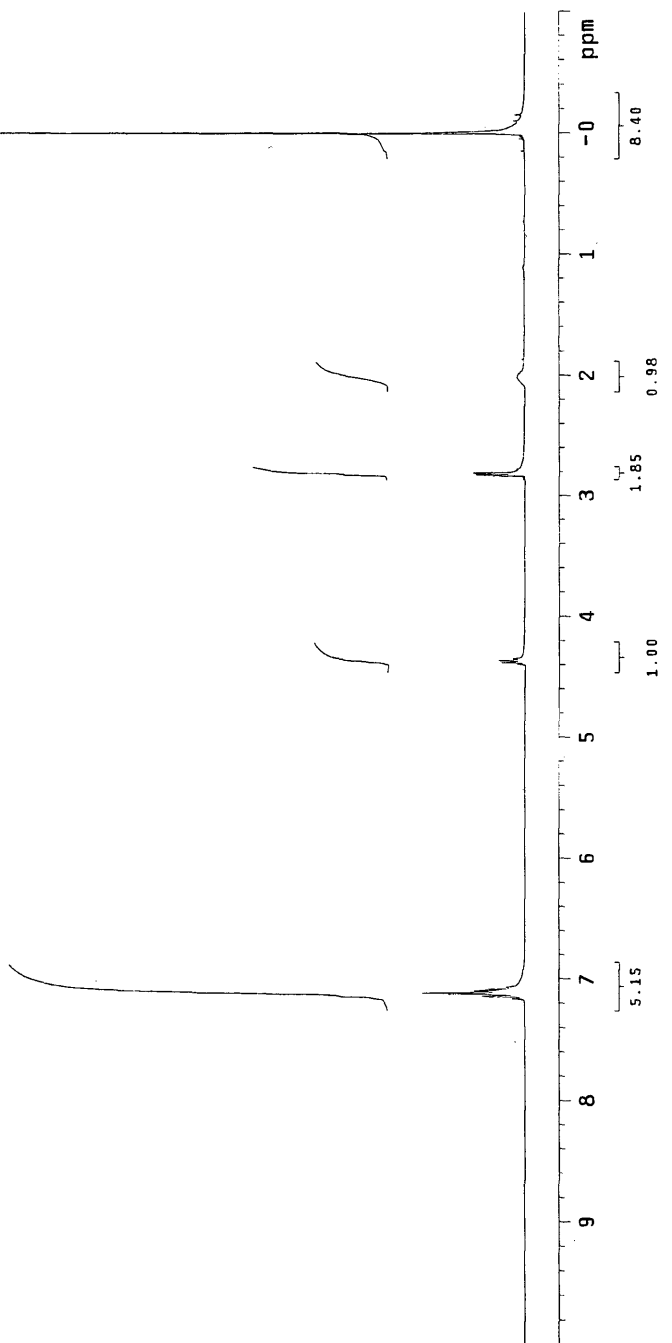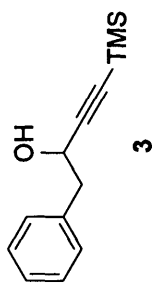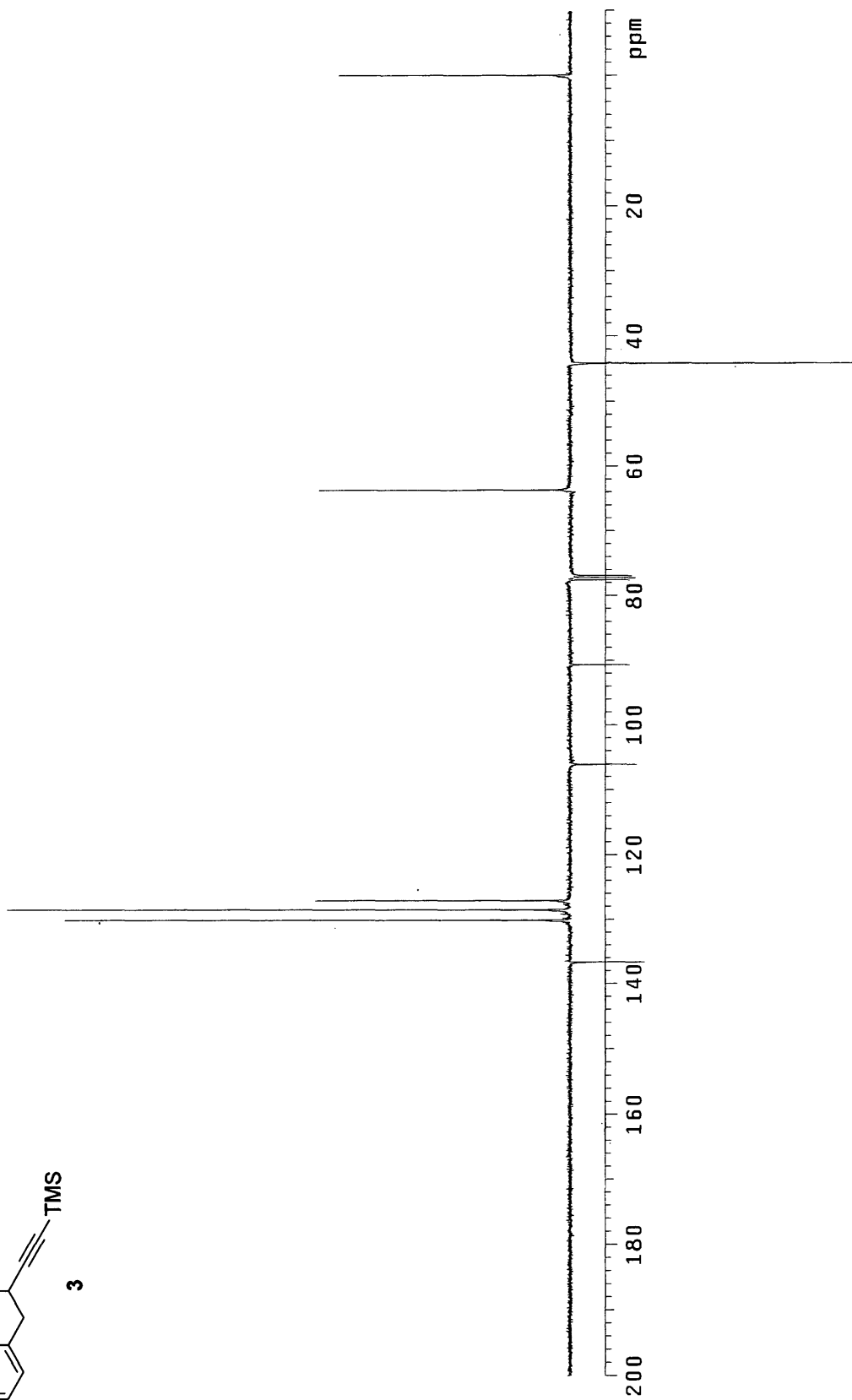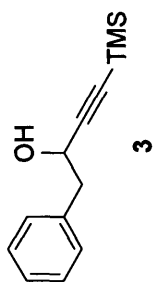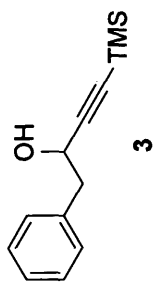
62

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

63

64

65

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm

66

67

68

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

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

69

71

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

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

72

OTBDPS

H

9

74

OTBDPS

9

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

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

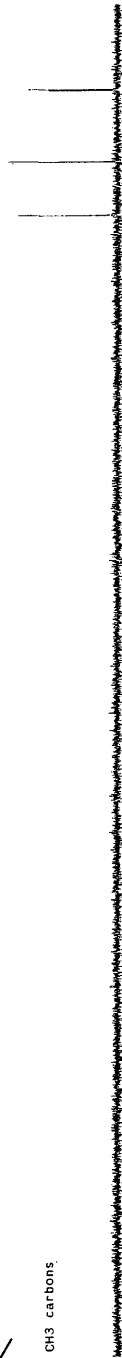75

OTBDPS

OH

10

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm
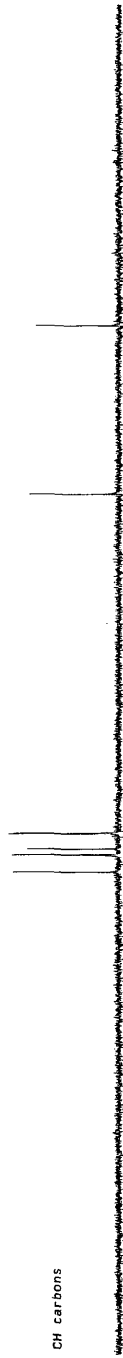
11a

11a

11a

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm
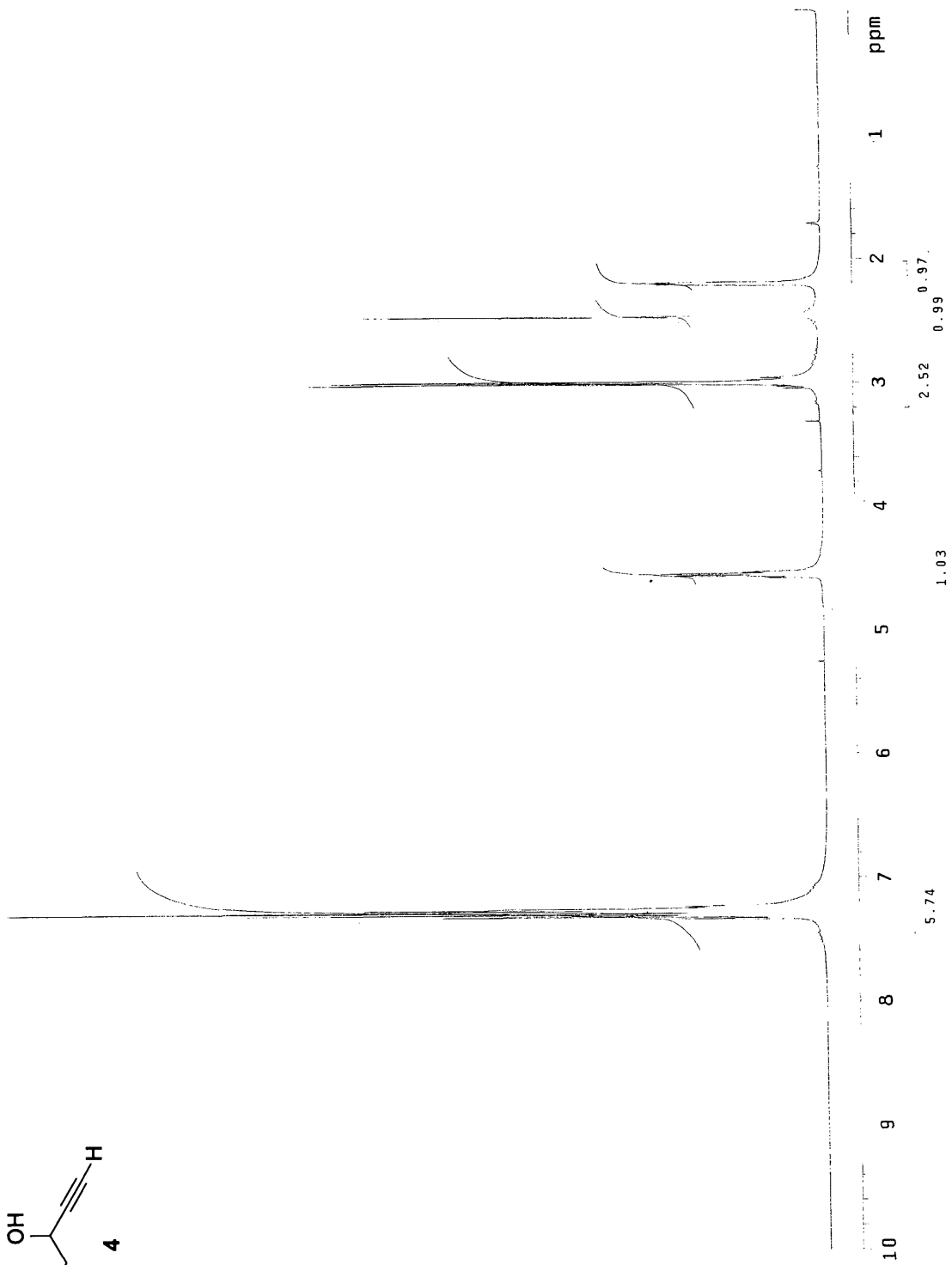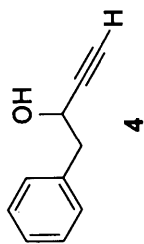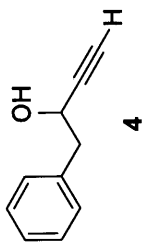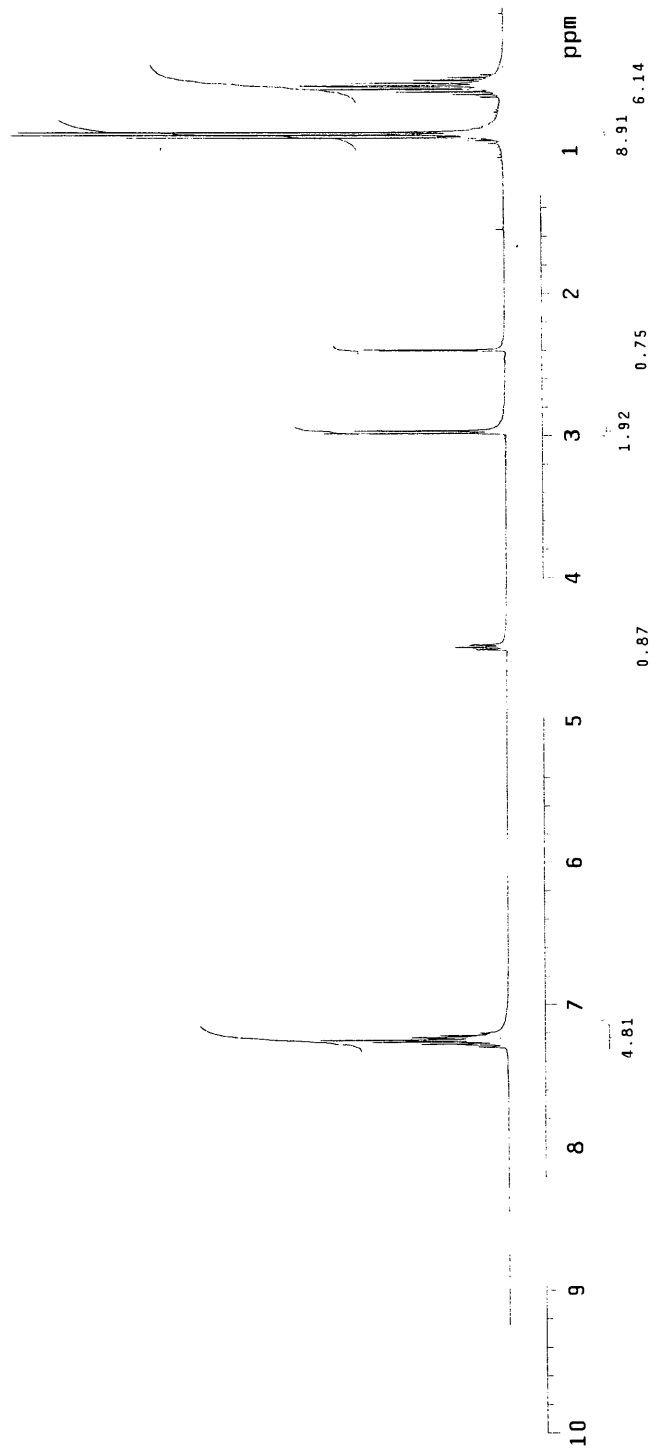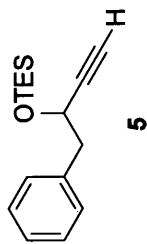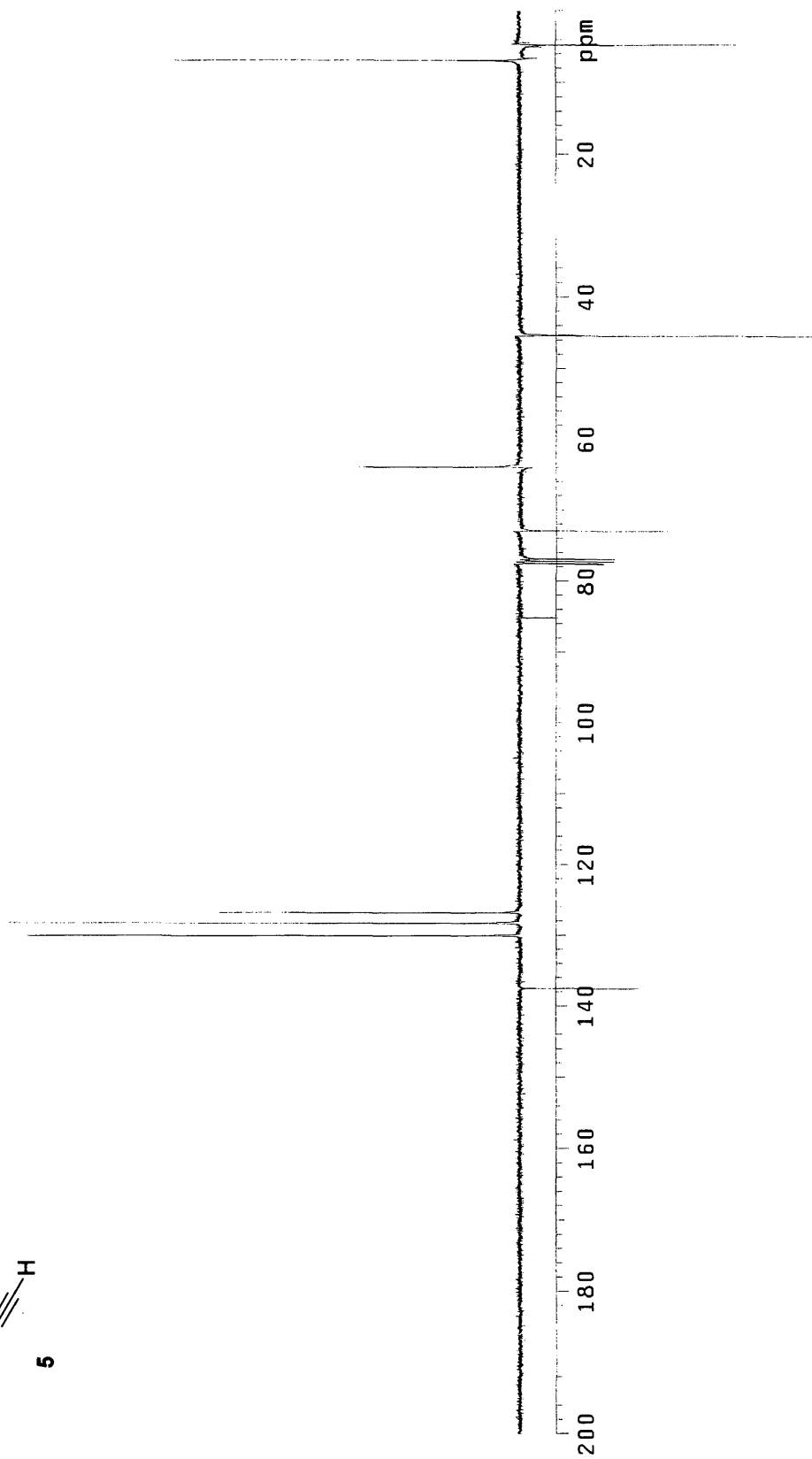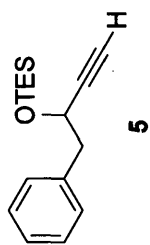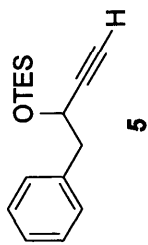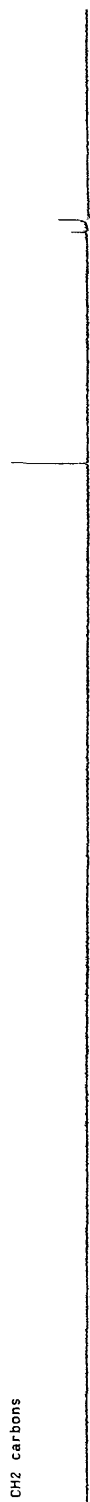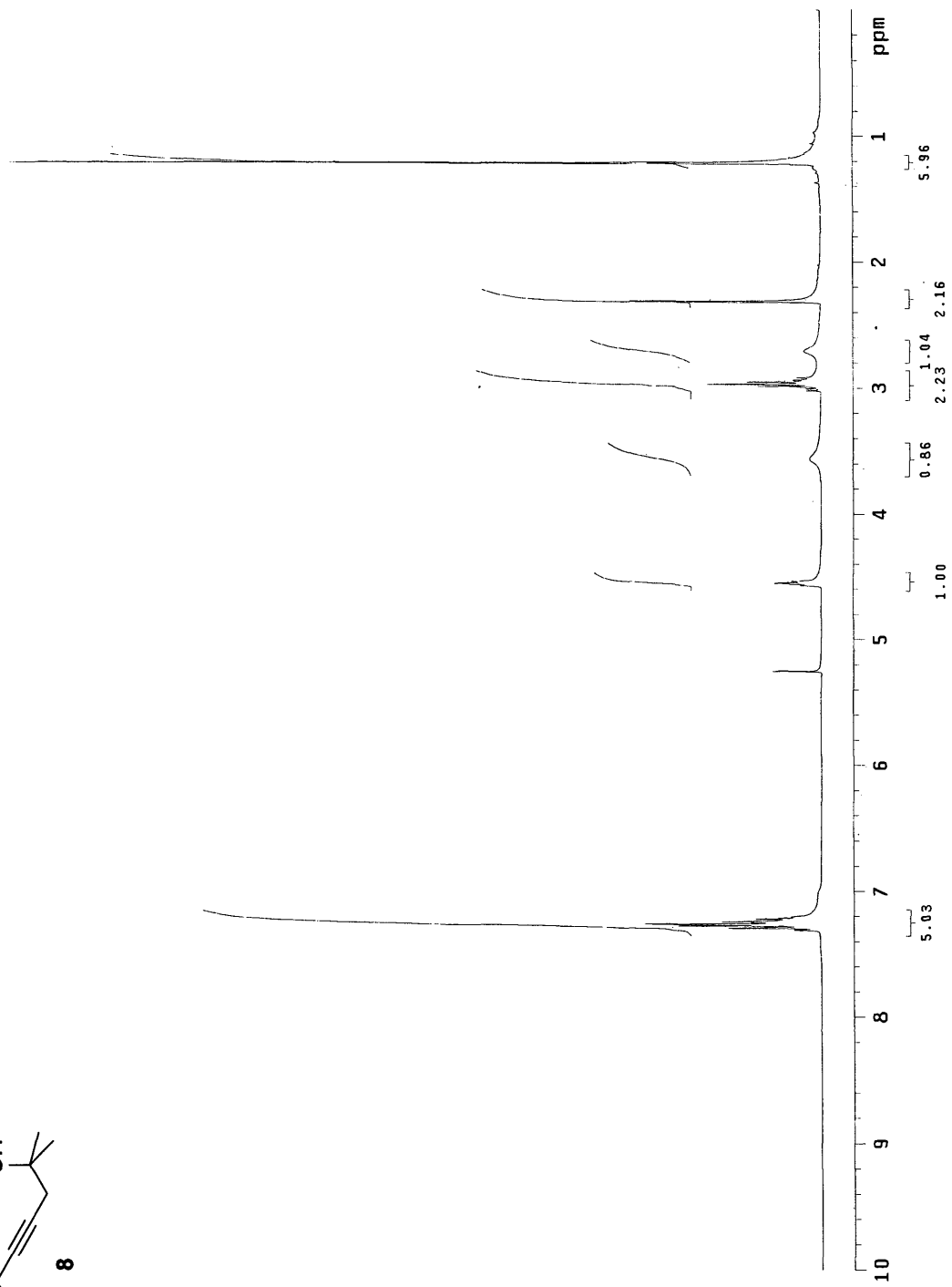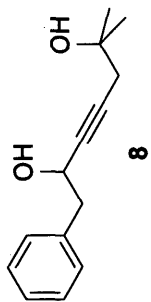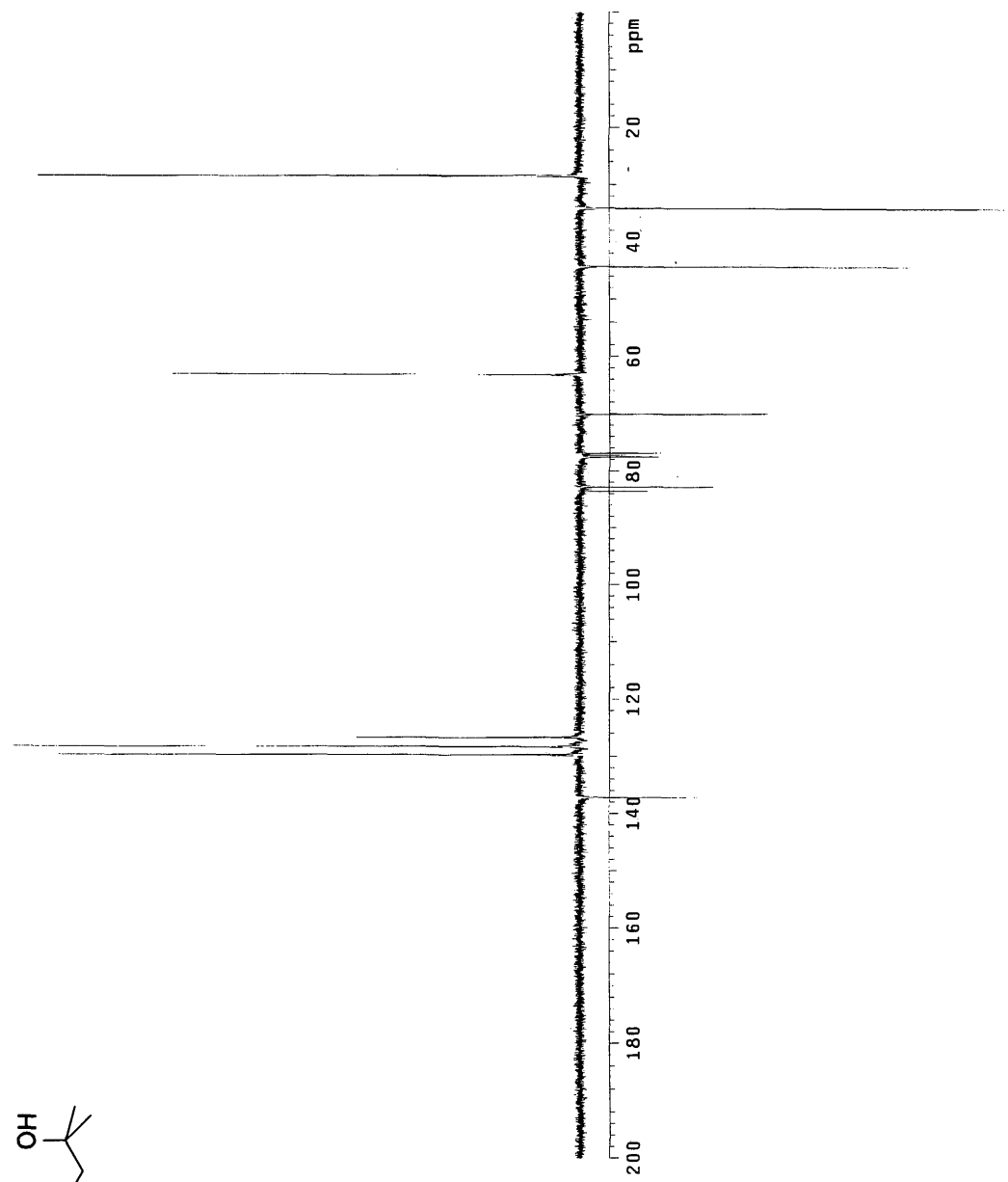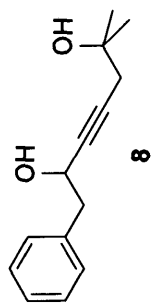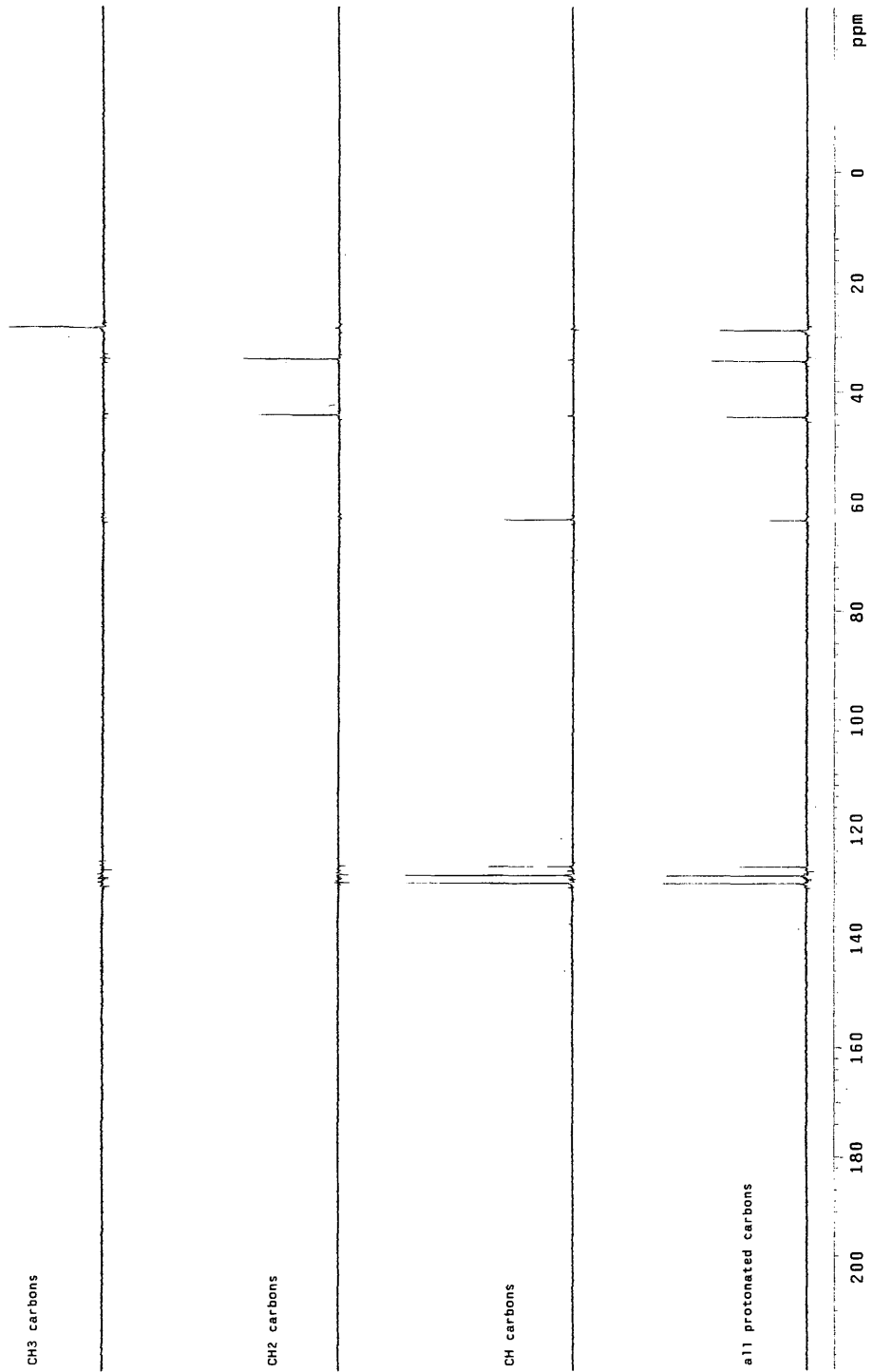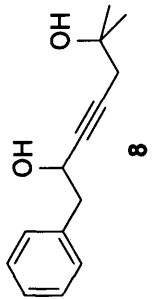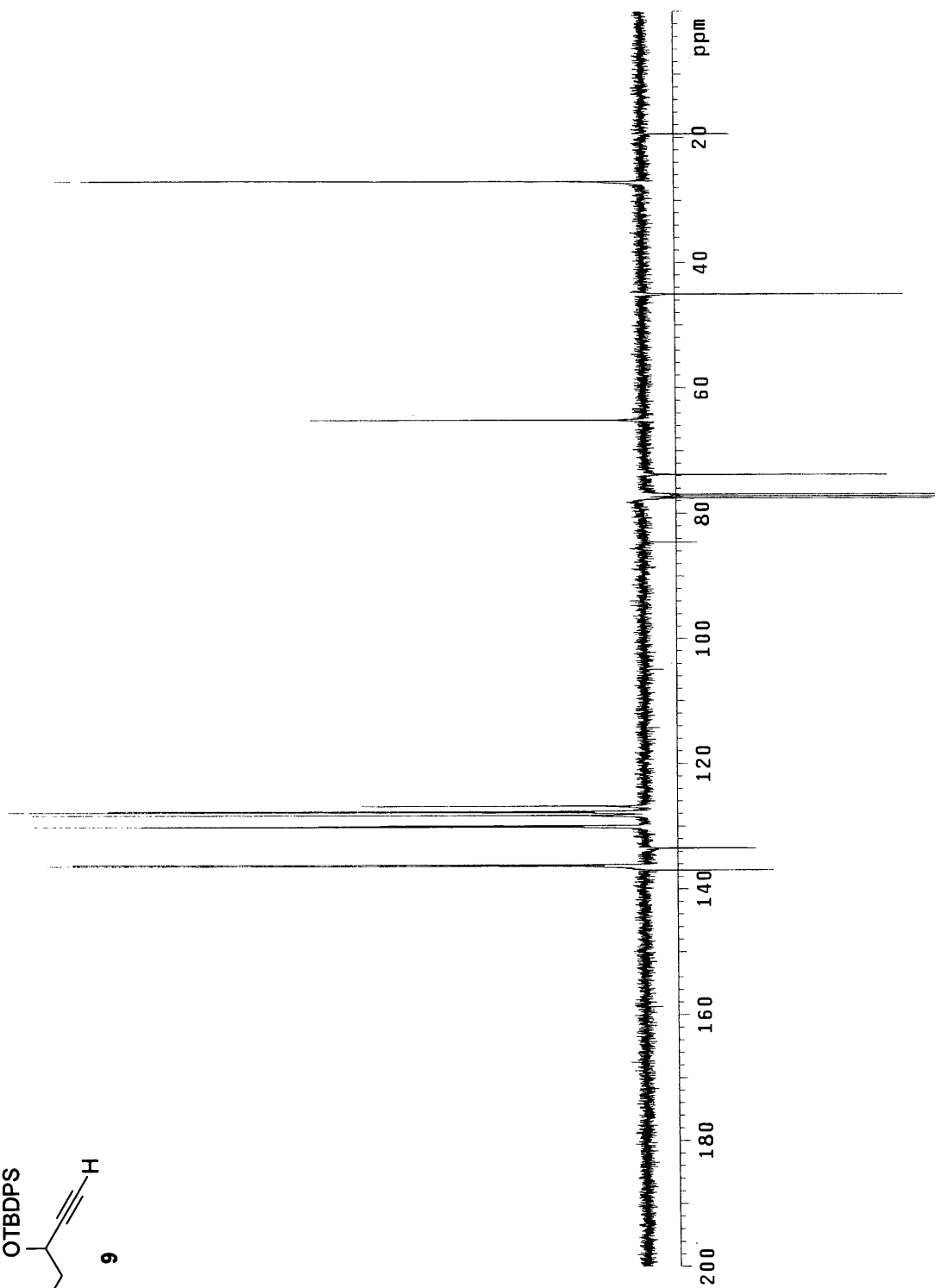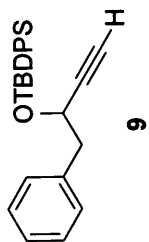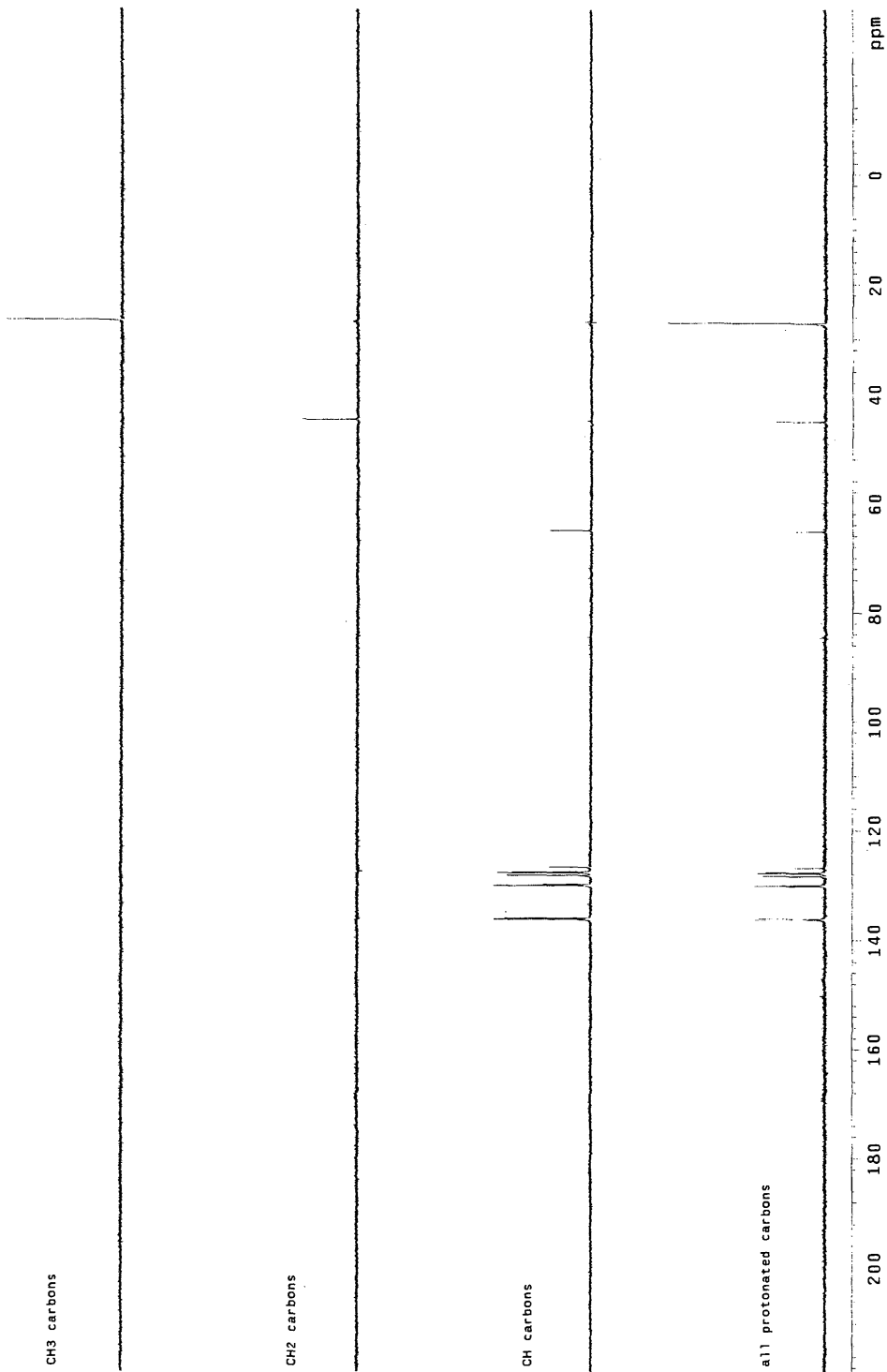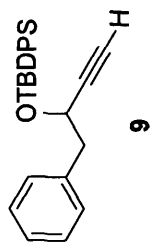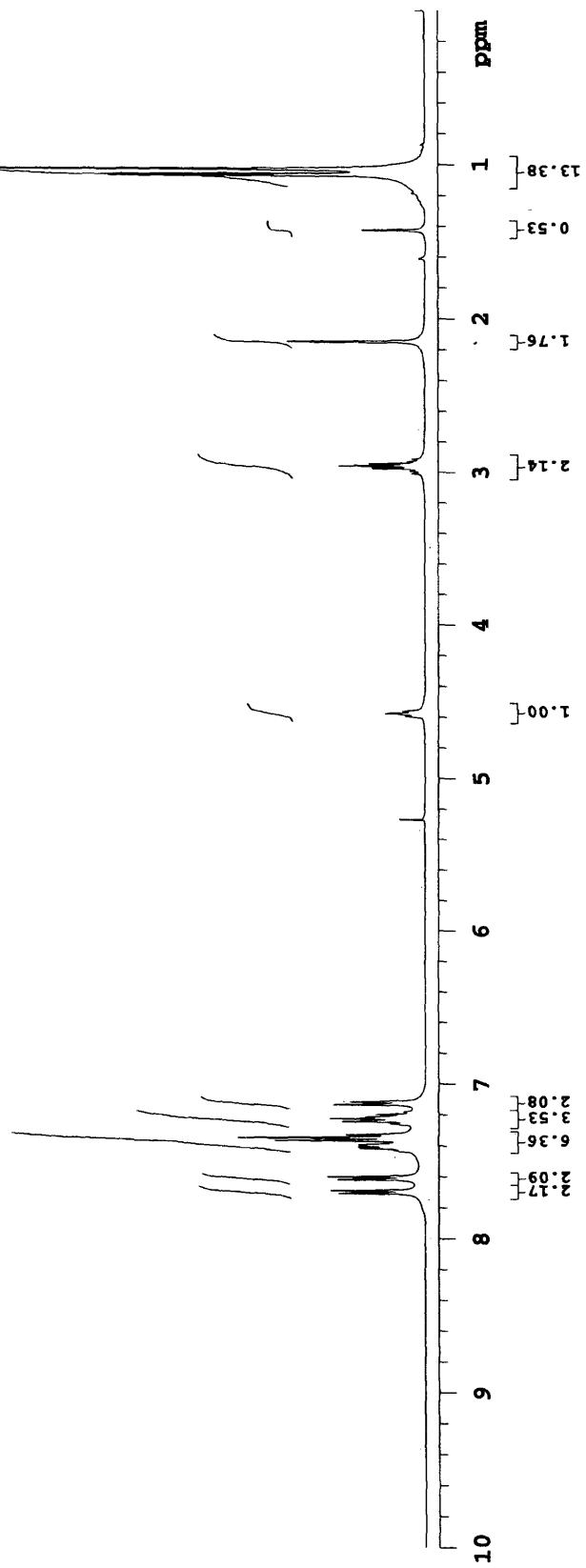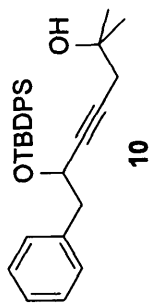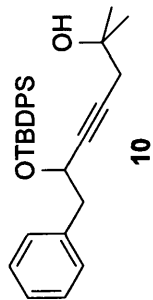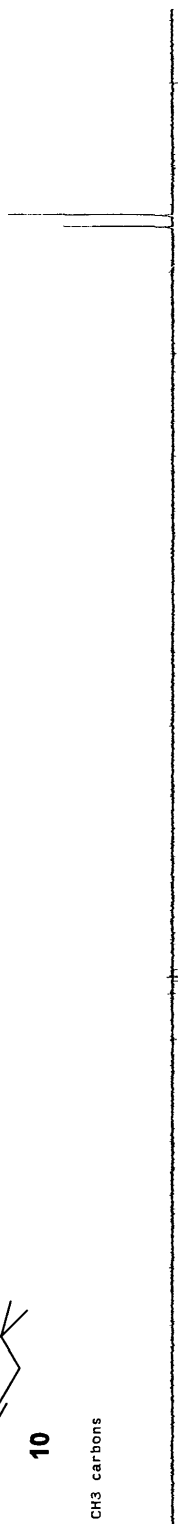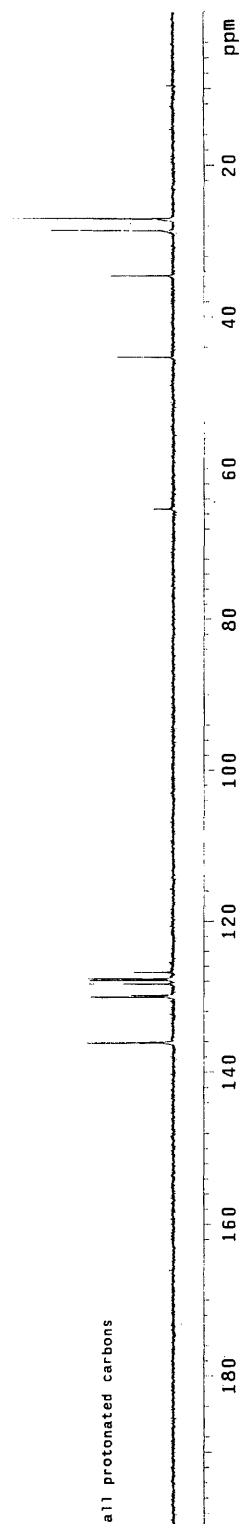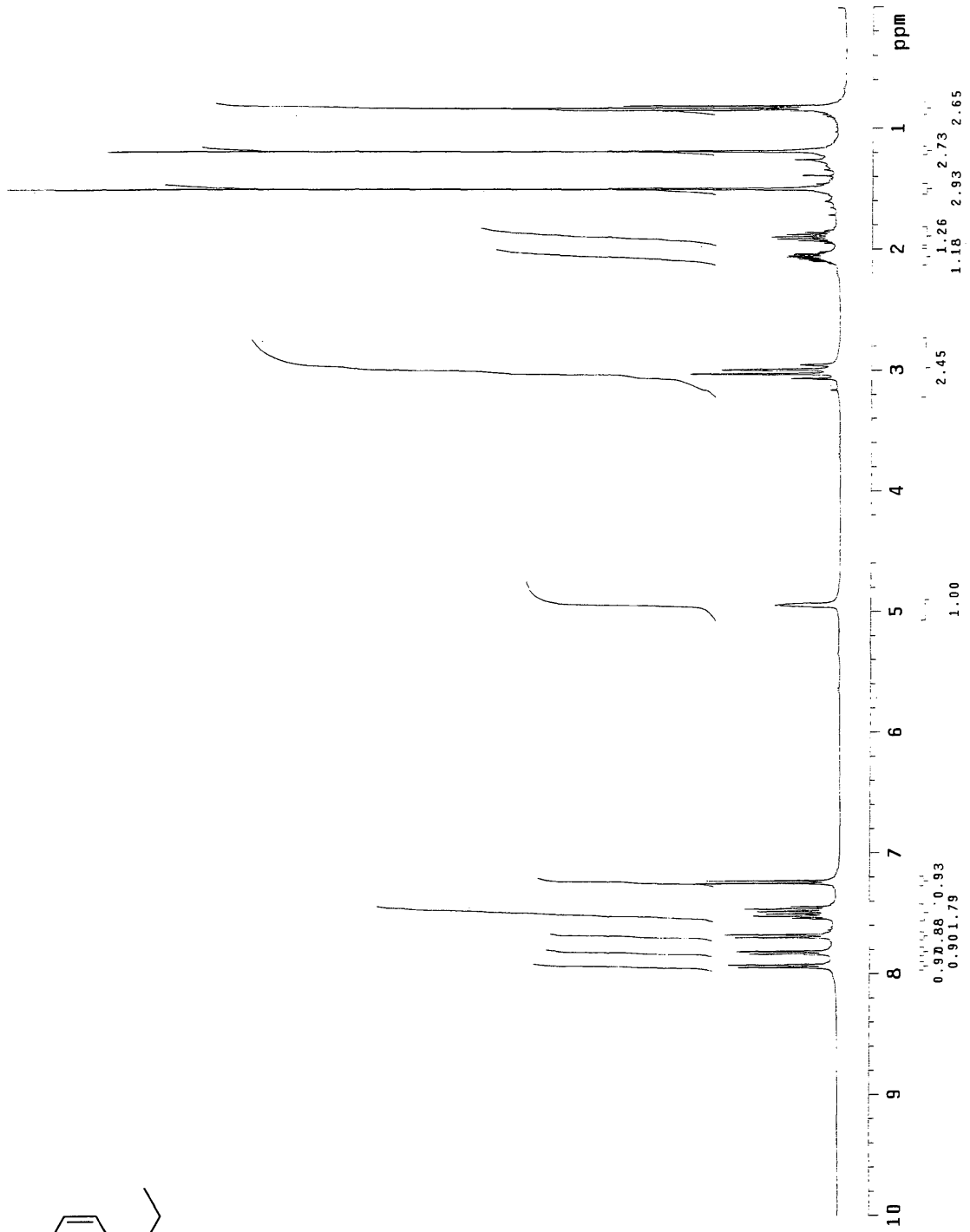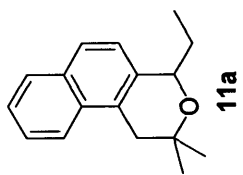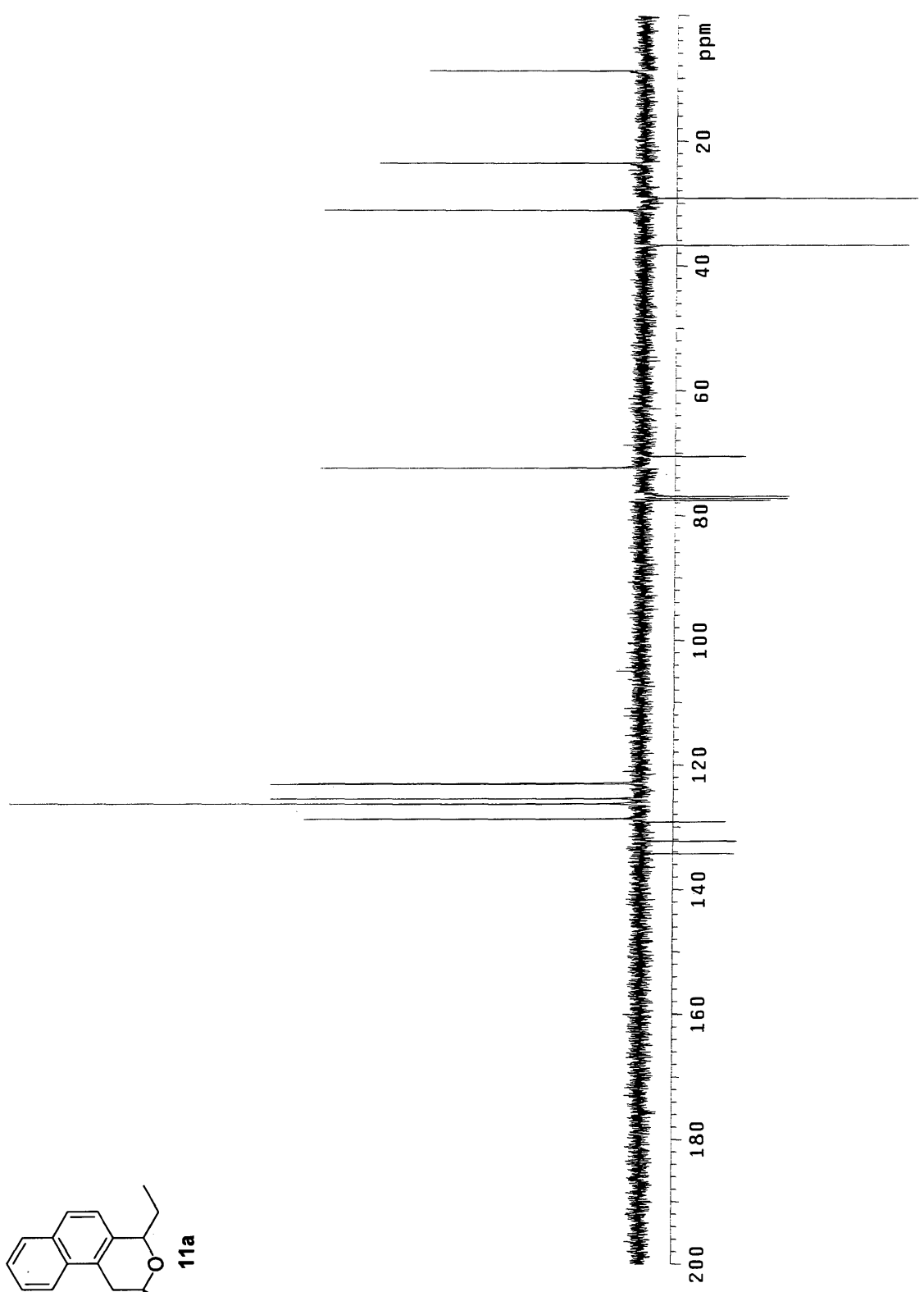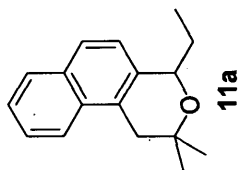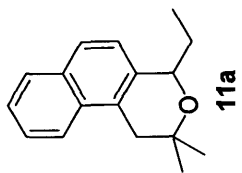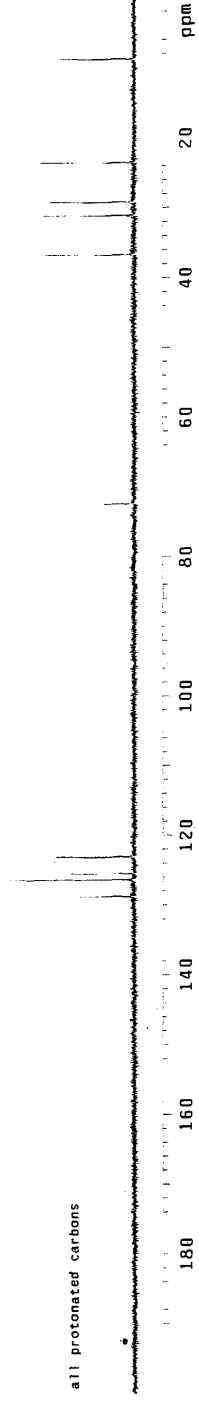
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Operator   :
Acquired   : 11 Apr 2013 00:05   using AcqMethod RJHSAM_LONG (260).M
Instrument :   Instrument #1
Sample Name: SEL-432
Misc Info   :
Vial Number: 1

11a

Abundance   TIC: SEL-432.D\data.ms

1.8e+07

1.6e+07

1.4e+07

1.2e+07

1e+07

8000000

6000000

4000000

2000000

0
Time-->   5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance   Scan 7419 (46.172 min): SEL-432.D\data.ms
                                                                                          211.2

4000000

3500000

3000000

2500000   193.2

2000000

1500000

1000000   165.1

500000   141.1 155.1   178.1   240.2
          43.1   115.1   127.1
                55.1 65.1 76.1 89.1 105.6   202.1   223.2
0
m/z-->   30   40   50   60   70   80   90   100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250

82

11b

83

11b

84

CH3 carbons

11b

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm
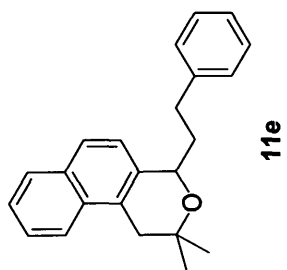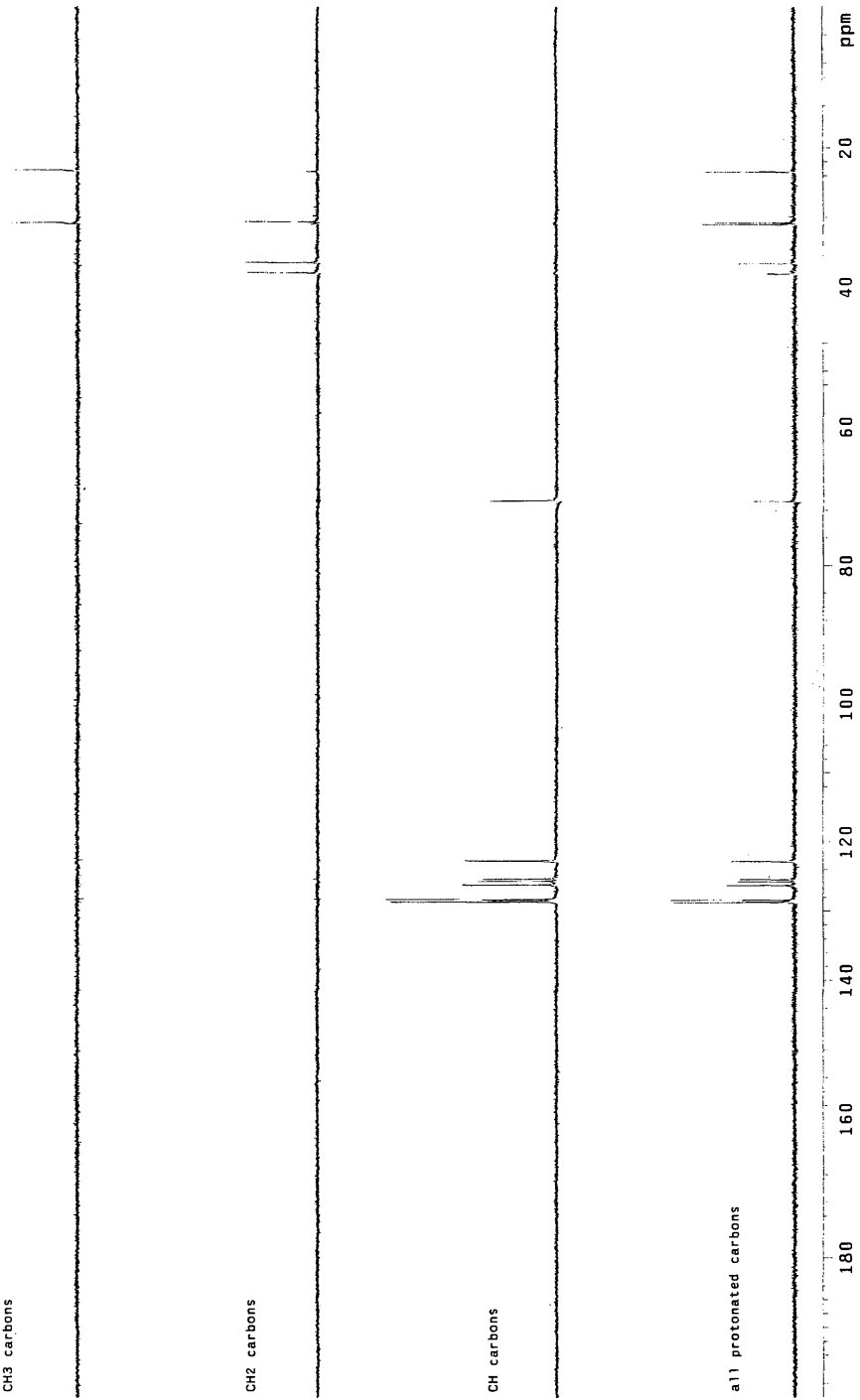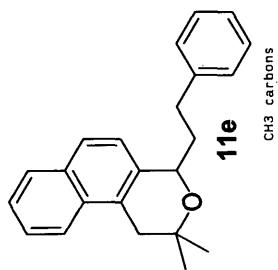
85

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Operator   :
Acquired   : 10 Apr 2013 21:46   using AcqMethod RJHSAM_LONG (260).M
Instrument :   Instrument #1
Sample Name: SEL-431
Misc Info   : FRAC 20
Vial Number: 1
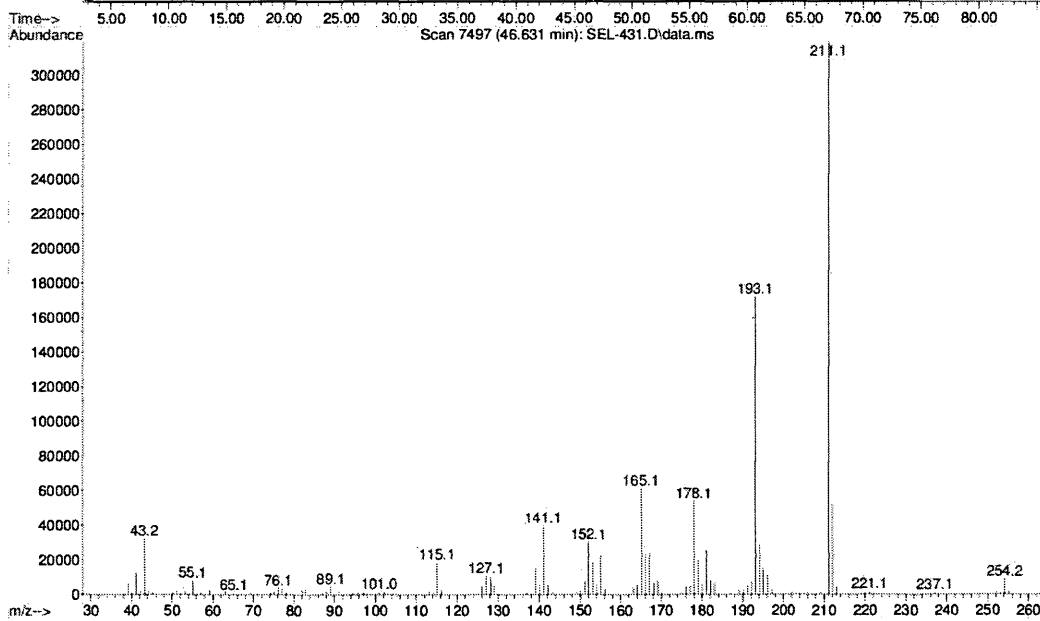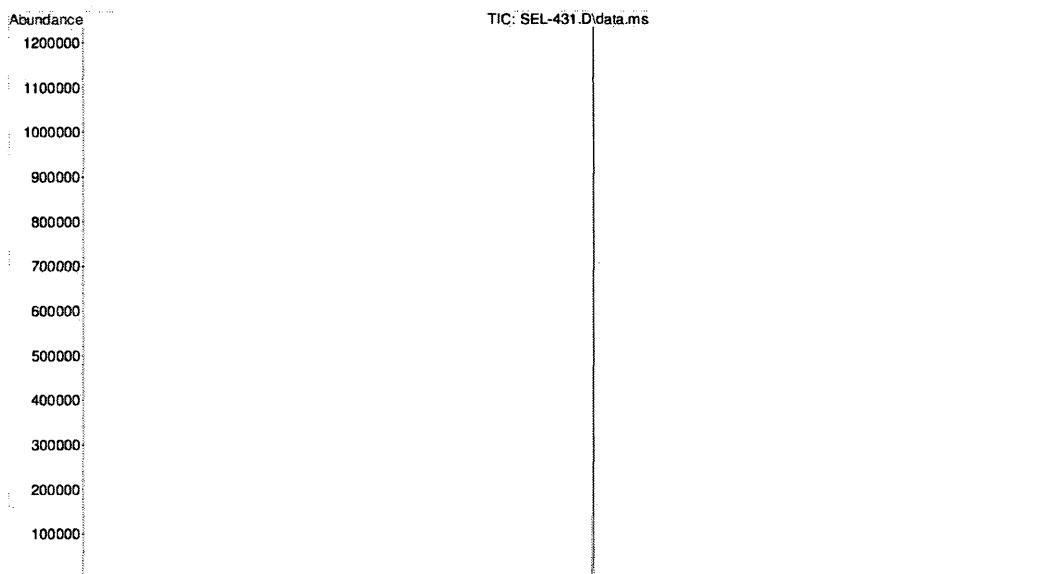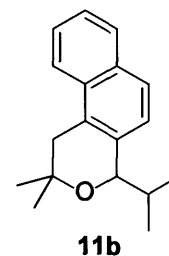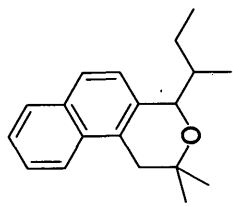
11b

TIC: SEL-431.D\data.ms

Scan 7497 (46.631 min): SEL-431.D\data.ms

211.1

193.1

165.1

178.1

141.1

152.1

43.2

55.1

65.1 76.1 89.1 101.0

115.1

127.1

221.1 237.1

254.2

86

11c
Mixture of Diastereomers

87

11c
Mixture of Diastereomers

88

11c
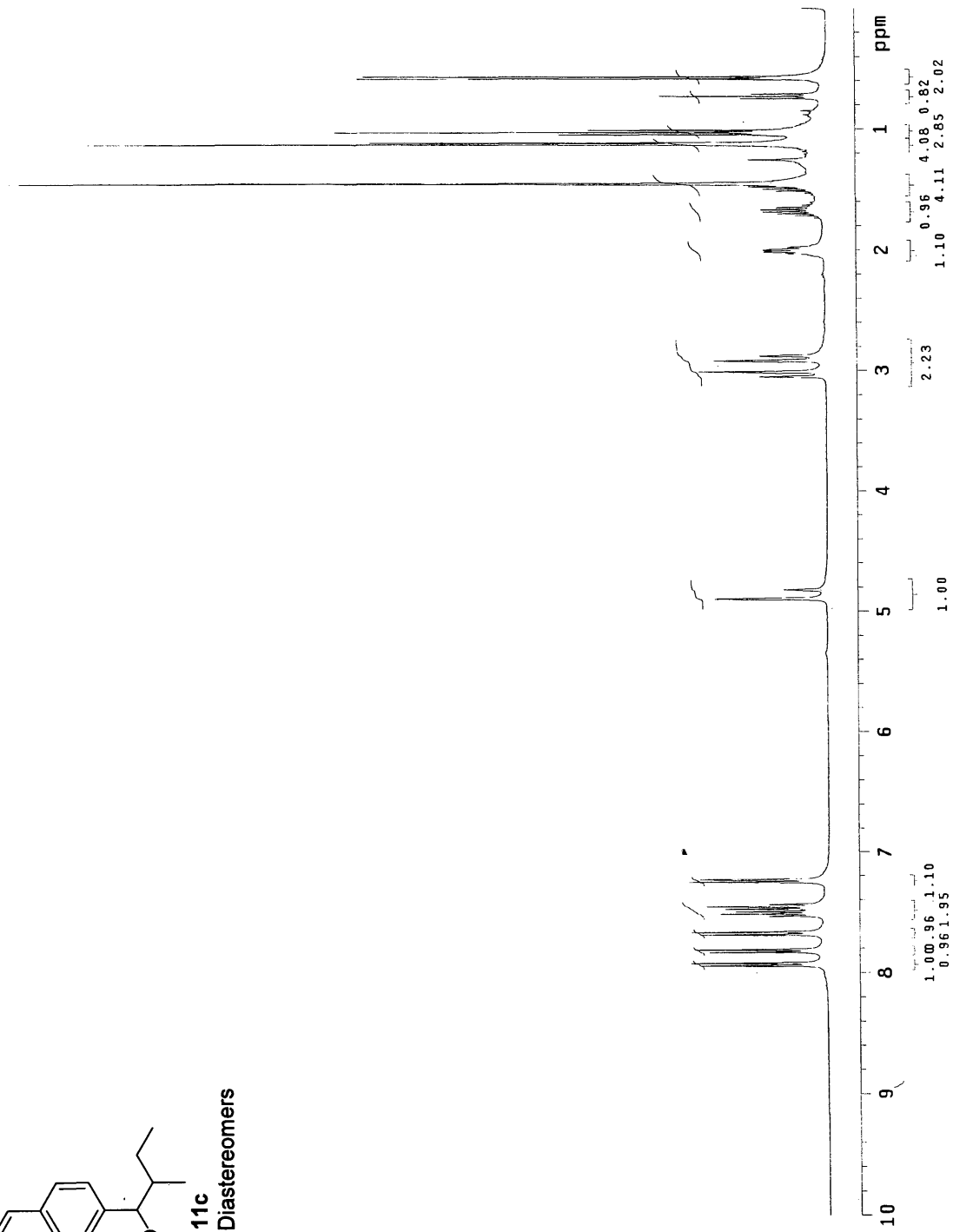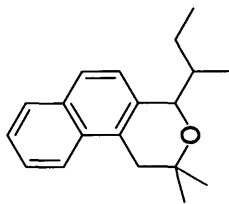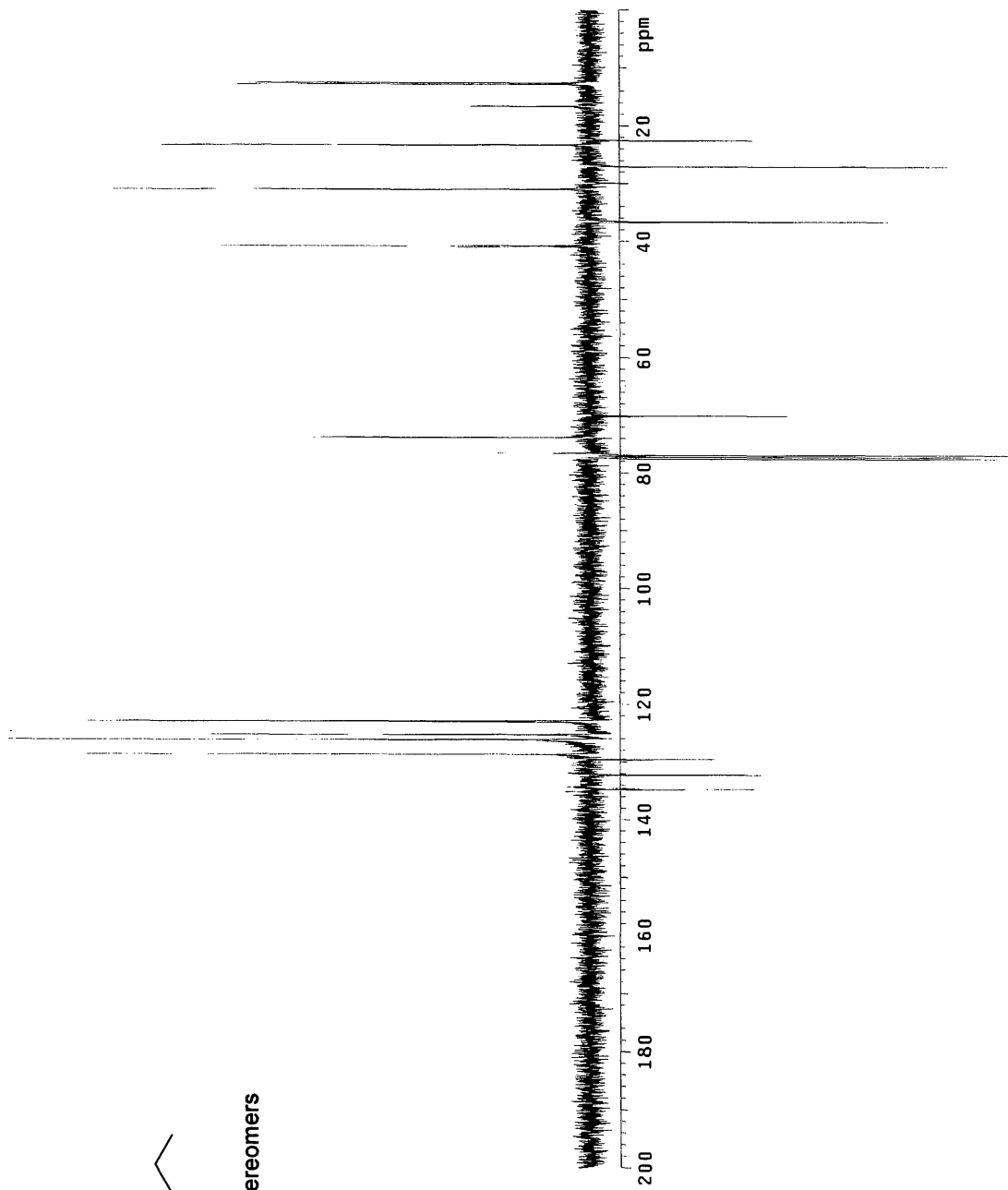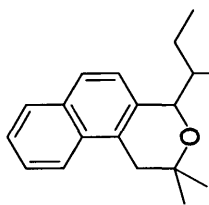
Mixture of Diastereomers

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm

89

11c
Major Diastereomer

90

11c

Major Diastereomer

ppm

200 180 160 140 120 100 80 60 40 20

91

11c
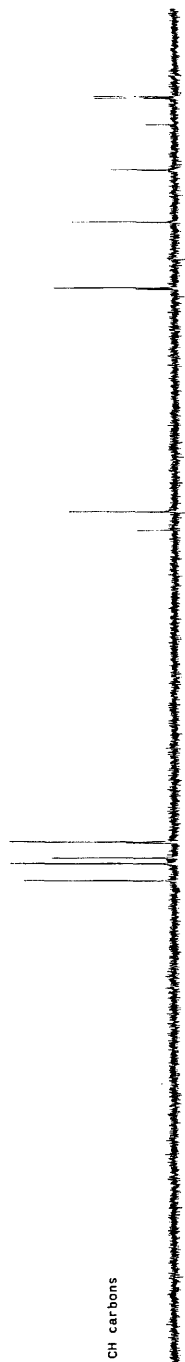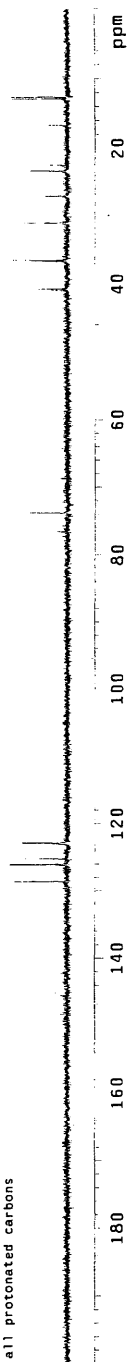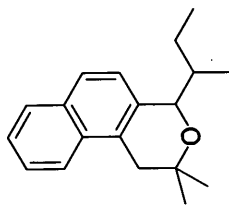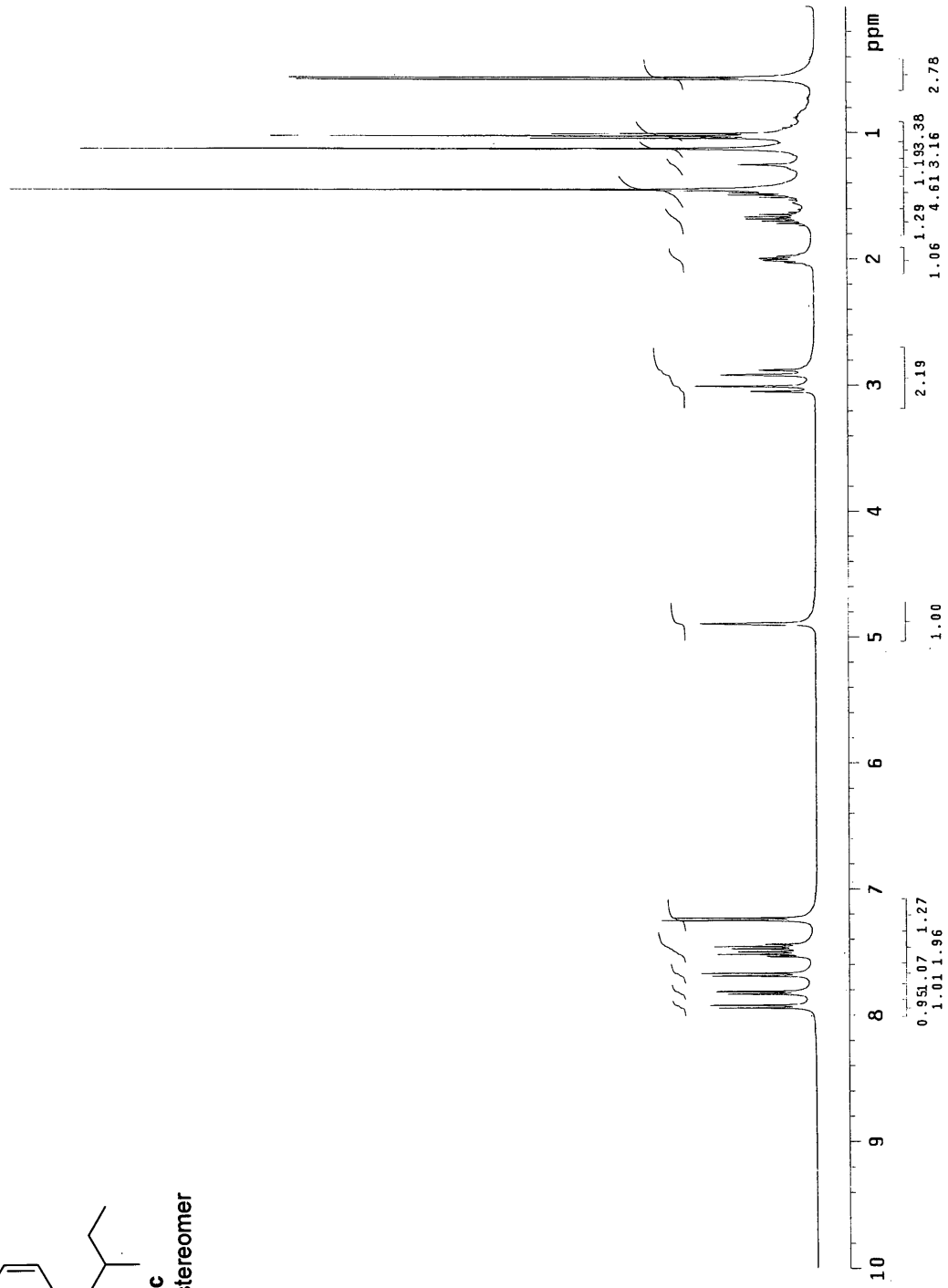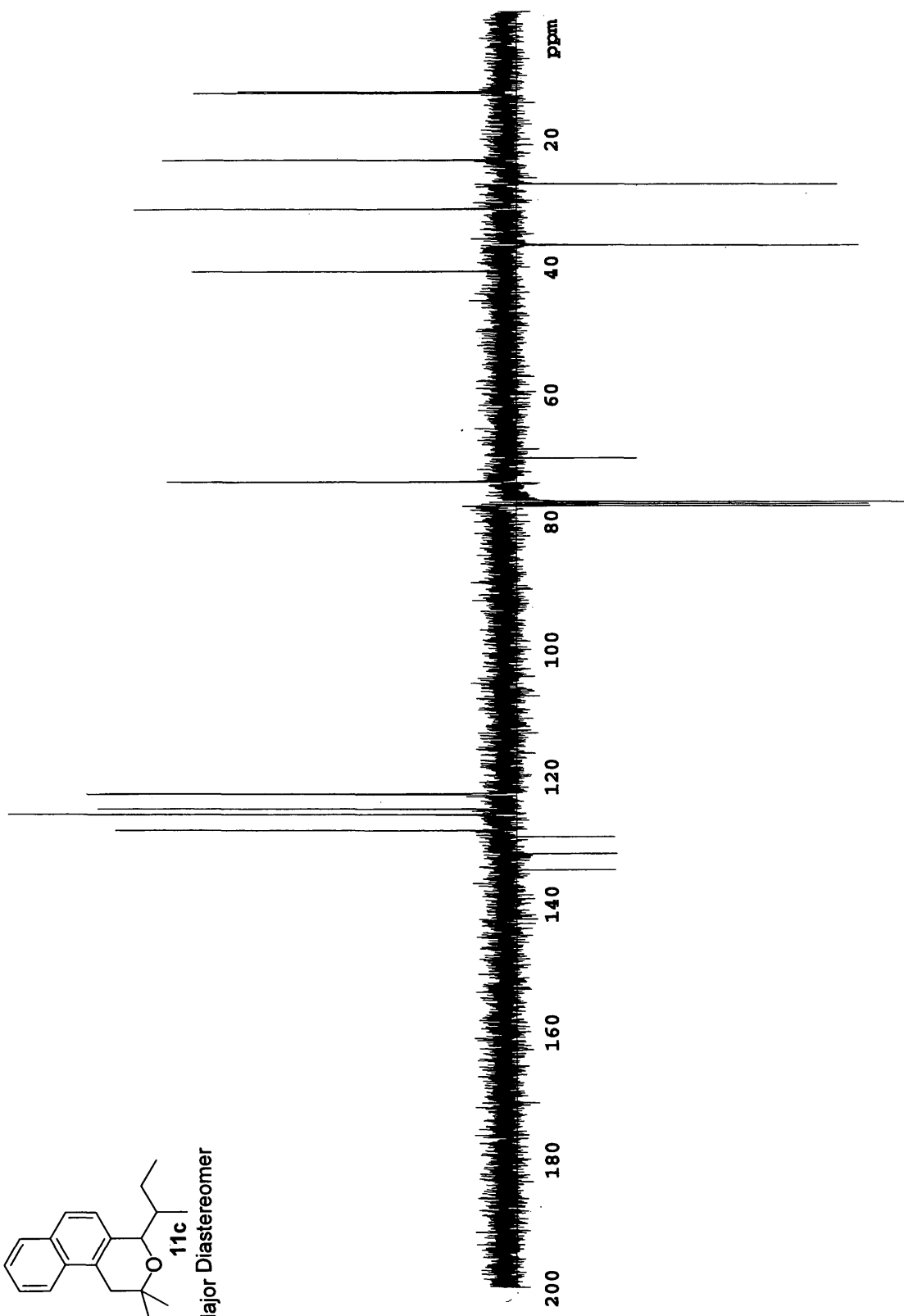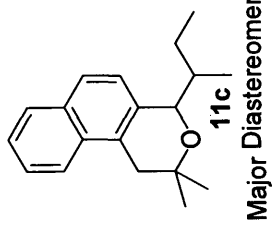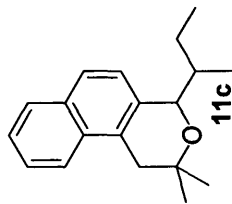
Major Diastereomer

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180　160　140　120　100　80　60　40　20　ppm

92
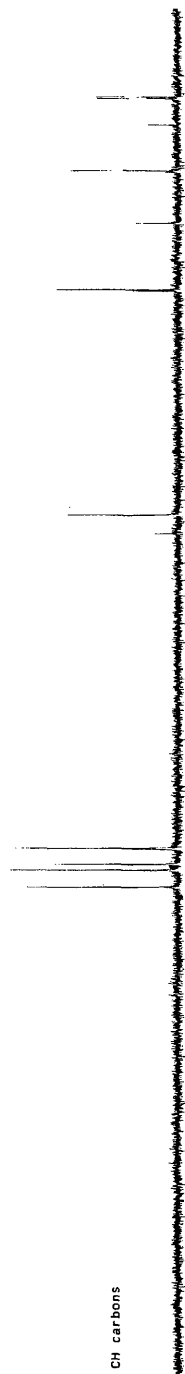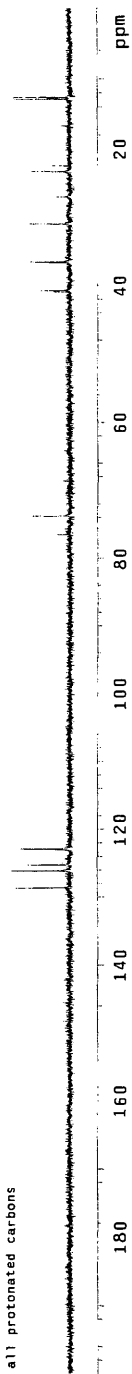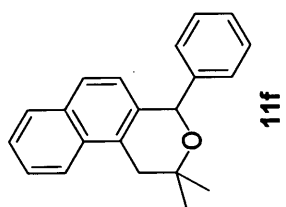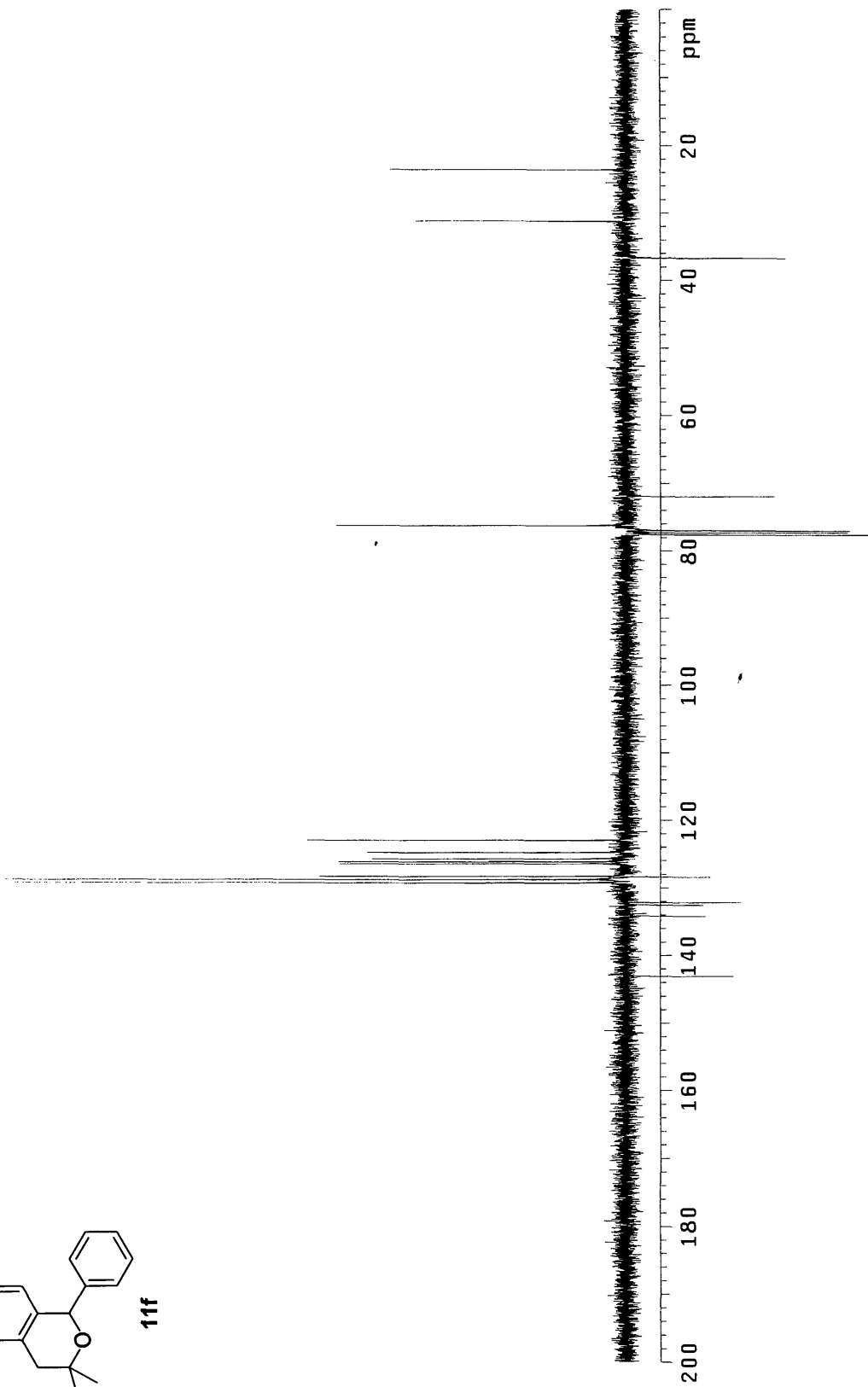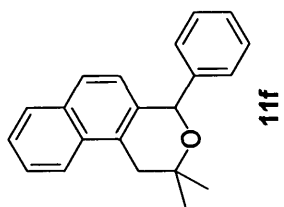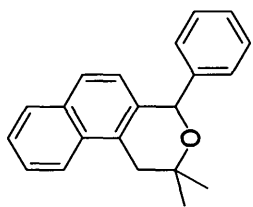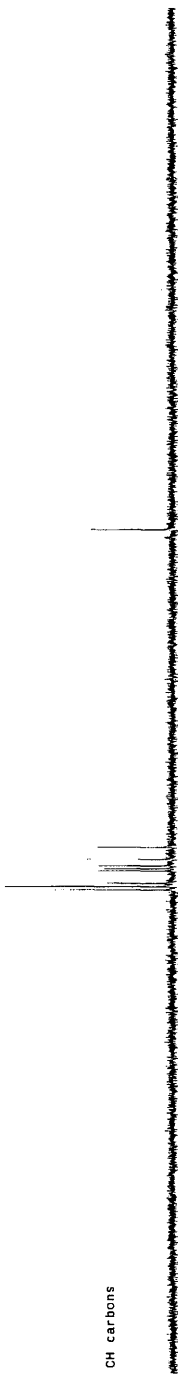
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Acquired   : 15 Apr 2013 16:22   using AcqMethod RJHSAM_LONG (260).M
Instrument :   Instrument #1
Sample Name: SEL-415
Misc Info : cyclization with methylbuteraldehyde
Vial Number: 1

11c

Major Diastereomer

Abundance   TIC: SEL-415.D\data.ms

5000000

4500000

4000000

3500000

3000000

2500000

2000000

1500000

1000000

500000

Time-->   5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance   Scan 8065 (49.968 min): SEL-415.D\data.ms

211.2

1600000

1400000

1200000

1000000

800000   193.2

600000

400000

200000   141.2 152.1 165.2 178.2

           43.2 55.2 65.1 76.1 89.1 101.1 115.2 127.1   221.2 235.2 251.2 268.1
0
m/z-->   30   40   50   60   70   80   90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270

93

11c
Minor Diastereomer

Abundance   TIC: SEL-415.D\data.ms

5000000

4500000

4000000

3500000

3000000

2500000

2000000

1500000

1000000

500000

Time-->   5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance   Scan 8016 (49.680 min): SEL-415.D\data.ms   211.2

550000

500000

450000

400000

350000

300000
                                                                      193.2
250000

200000

150000

100000   165.1 178.2
                                     141.2
50000   43.2   115.1   152.1
                  55.2 65.2 76.1 89.1 101.1   127.1   223.2 235.3   251.2   268.3
      0
m/z-->   30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270

94

11d

11d

96

11d

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm

97

11d

TIC: SEL-418.D\data.ms

Scan 8454 (52.254 min): SEL-418.D\data.ms

211.2

193.2

178.2

165.2

141.2

152.2

127.1

115.1

101.1

89.1

71.2

55.2

43.2

222.2 233.2   249.2   265.1   282.3

11e

99

11e

100

11e

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm

101

11e

Abundance   TIC: SEL-437B.D\data.ms

4500000

4000000

3500000

3000000

2500000

2000000

1500000

1000000

500000

Time-->   5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance   Scan 11033 (67.407 min): SEL-437B.D\data.ms
1400000   211.2

1300000

1200000

1100000

1000000

900000

800000

700000

600000

500000   193.2

400000

300000

200000   165.1

100000   91.2   152.1   178.1   316.2
        43.2   65.2 77.2   103.1 115.1 128.1 140.2   224.2 238.2   258.1 271.1 283.1 299.1
      0
m/z-->   30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320

102

11f

103

11f

104

11f

CH3 carbons

CH2 carbons

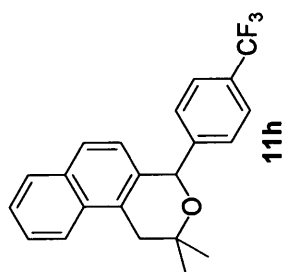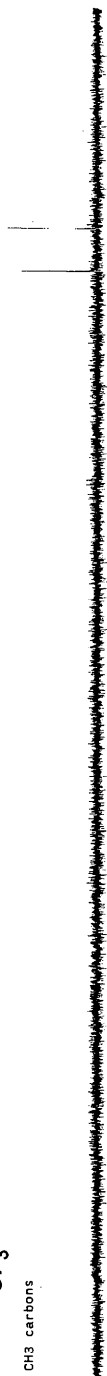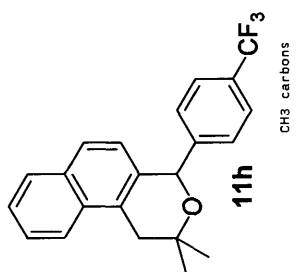CH carbons

all protonated carbons

ppm

105

File   :C:\GC-MS Data\rjhink\SEL-478.D
Operator :
Acquired : 17 Apr 2013 20:07   using AcqMethod RJHSAM_LONG (260).M
Instrument :   Instrument #1
Sample Name: SEL-478
Misc Info : cyclization with benzaldehyde
Vial Number: 1
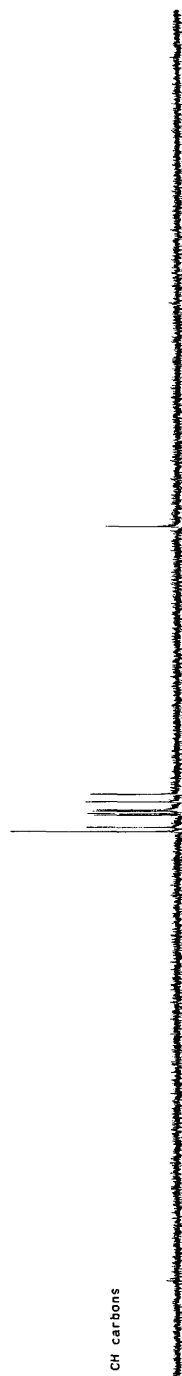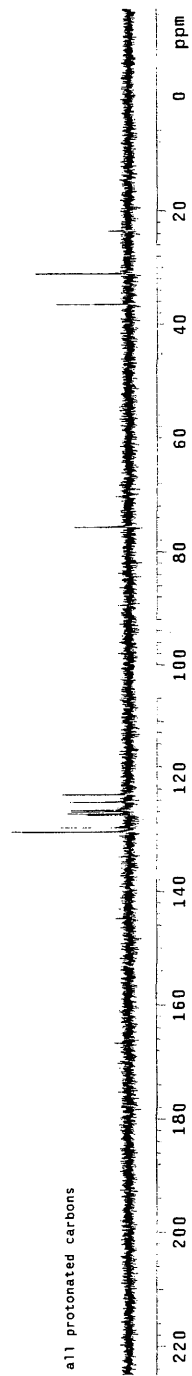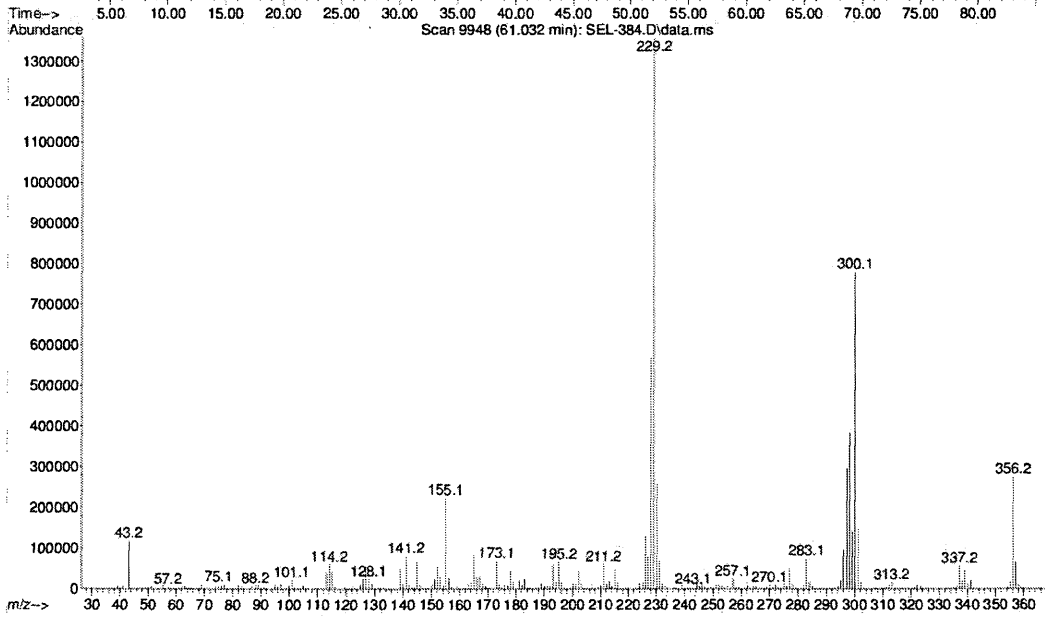
11f

Abundance   TIC: SEL-478.D\data.ms

9000000

8000000

7000000

6000000

5000000

4000000

3000000

2000000

1000000

Time-->   5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance   Scan 10053 (61.649 min): SEL-478.D\data.ms

1400000   229.2

1300000

1200000

1100000

1000000

900000

800000

700000

600000

500000

400000   215.2   288.1

300000   155.1

200000   105.1   195.2

100000   43.2   77.2   141.2   167.2 178.2   245.2   271.1
            55.2 66.2   91.2   116.1 127.1   257.1
          0

m/z-->   30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290

106

11g

107

11g

108

11g

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

200   180   160   140   120   100   80   60   40   20   ppm

File   :C:\GC-MS Data\rjhink\SEL-417.D
Operator   :
Acquired   : 17 Apr 2013 18:34   using AcqMethod RJHSAM_LONG (260).M
Instrument :   Instrument #1
Sample Name: SEL-417
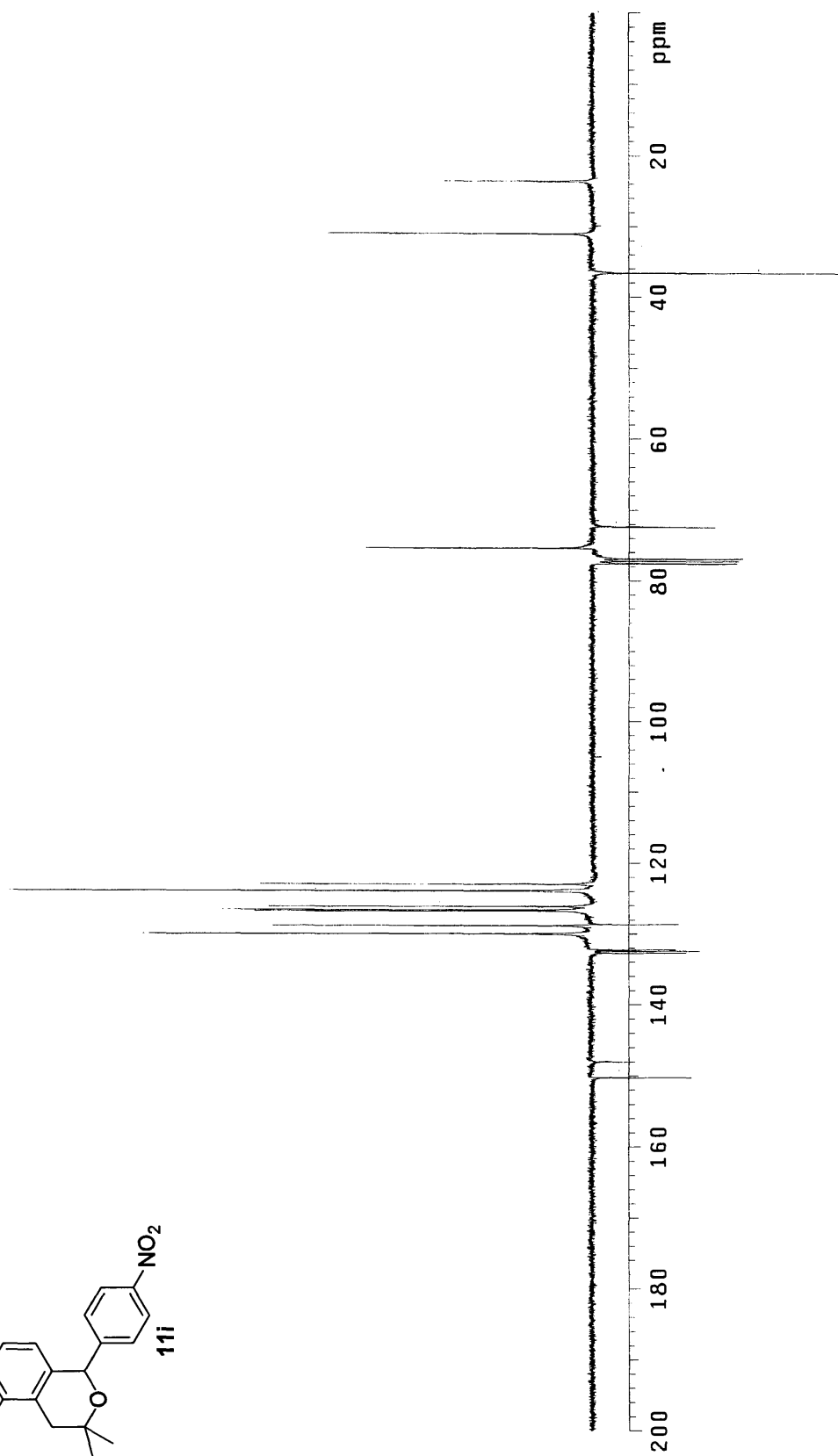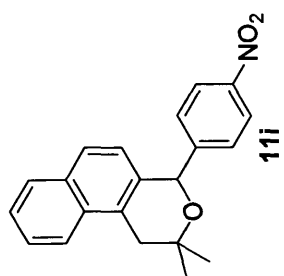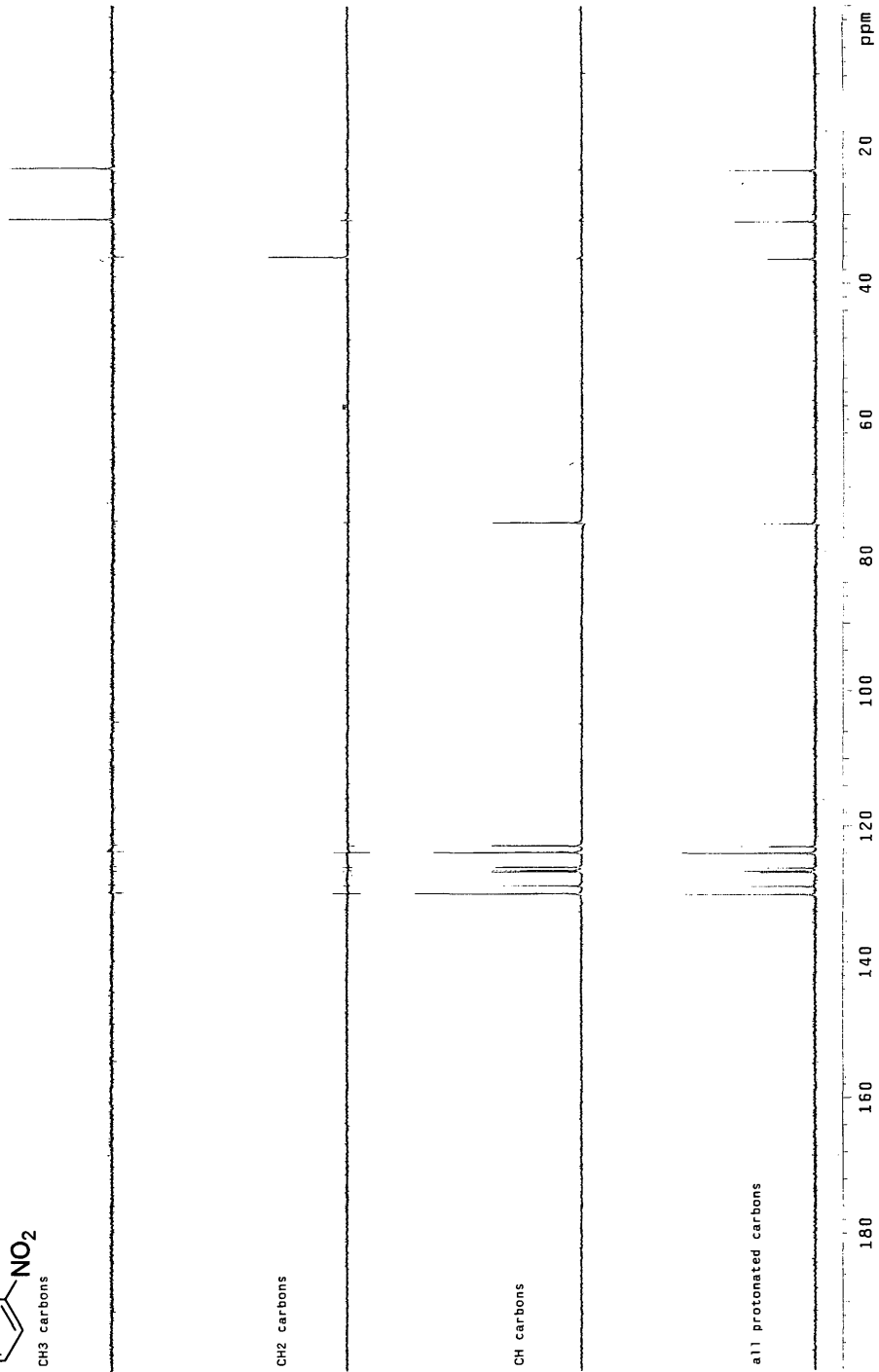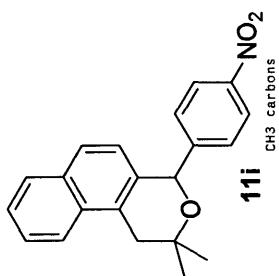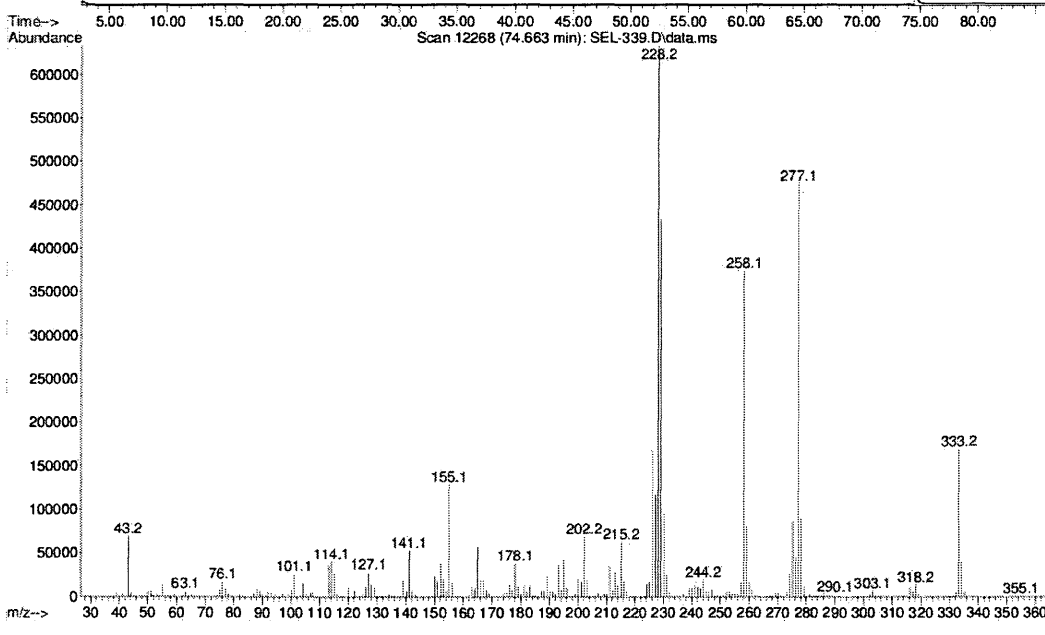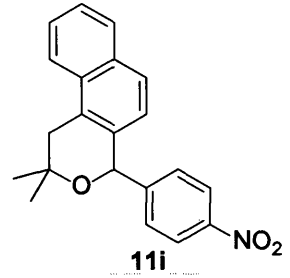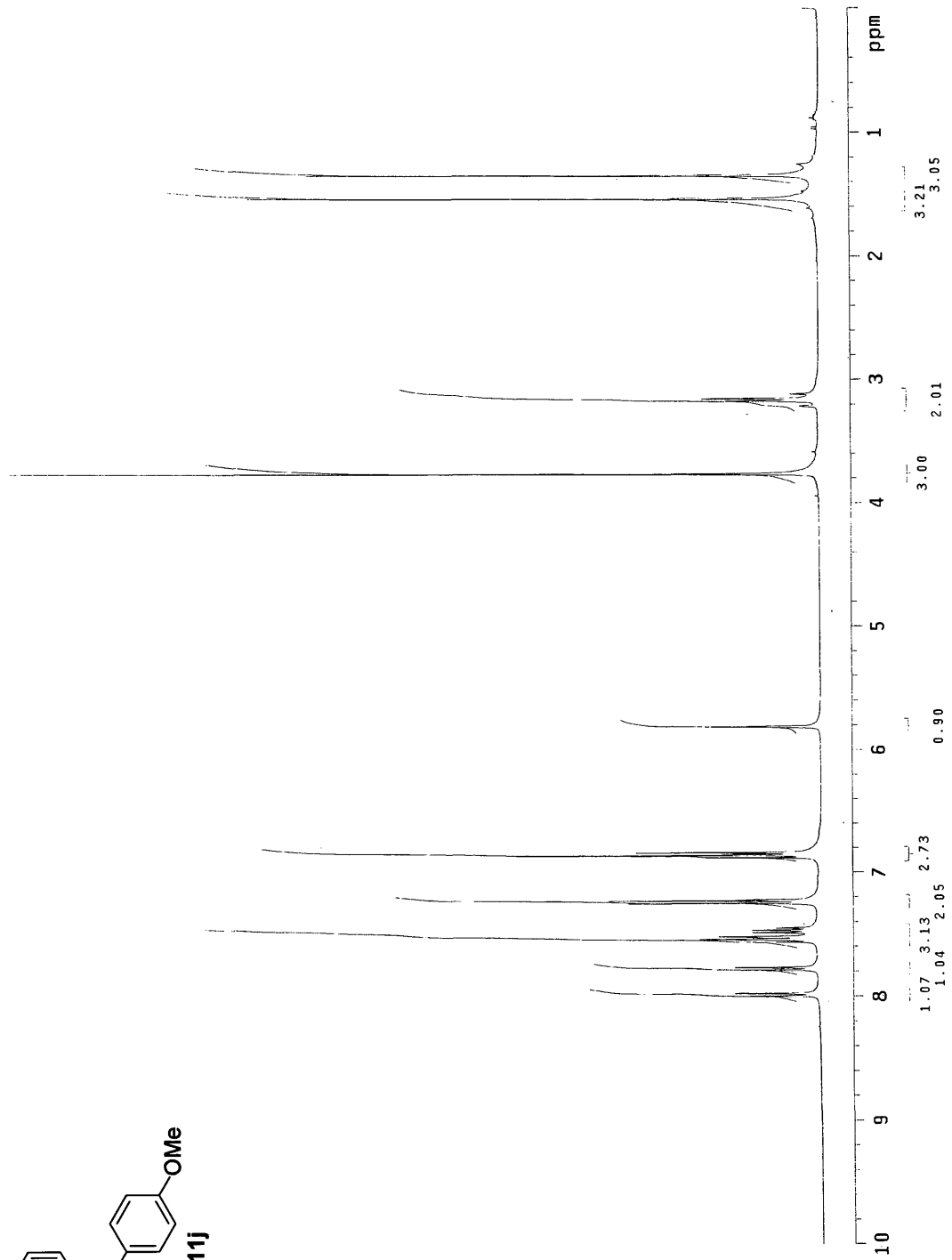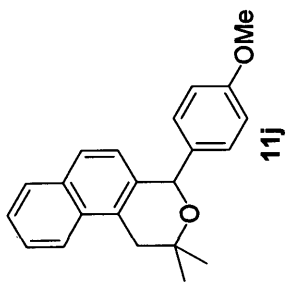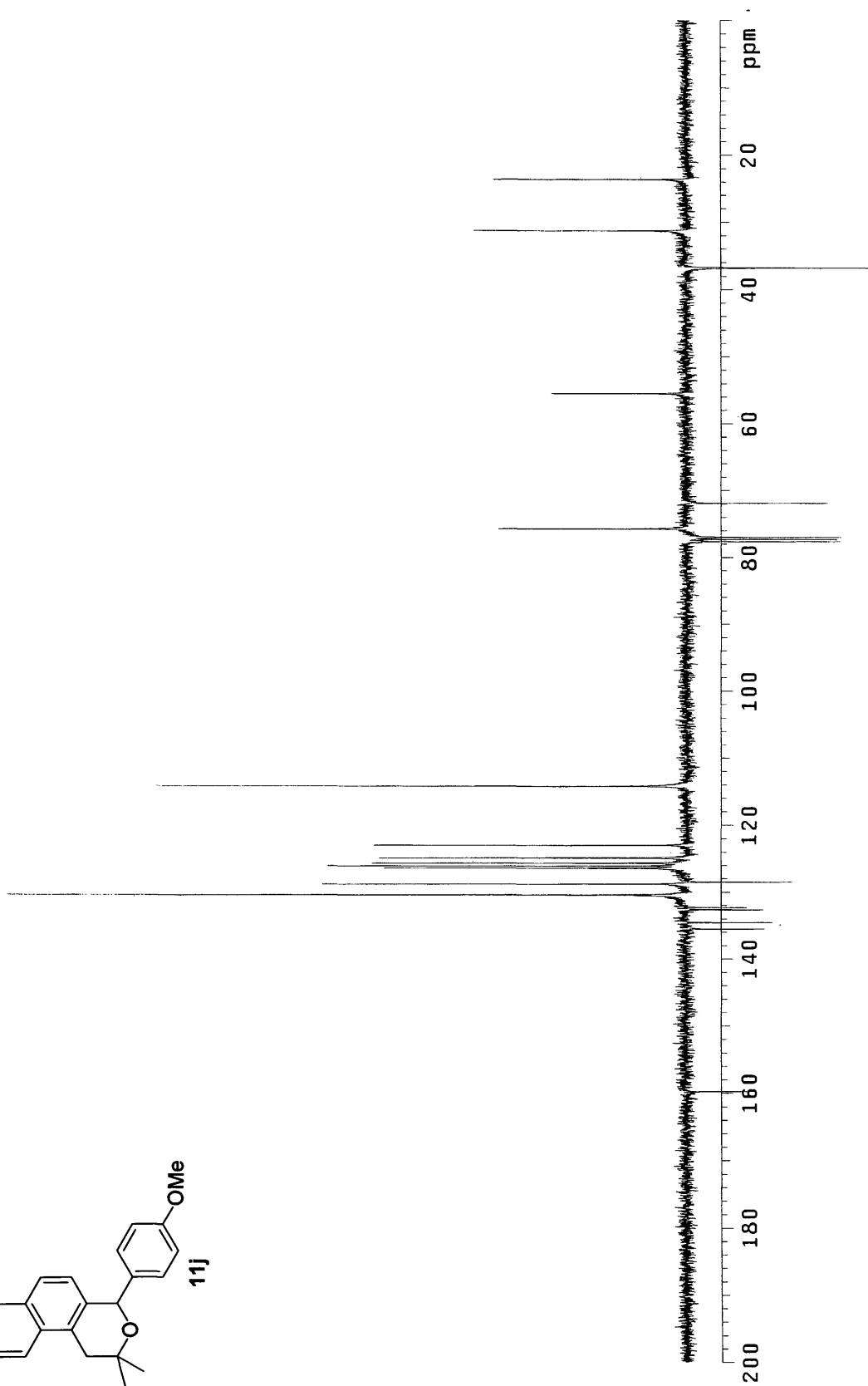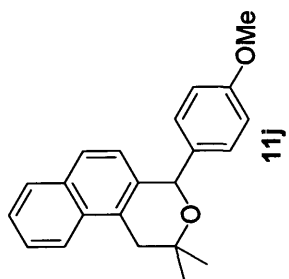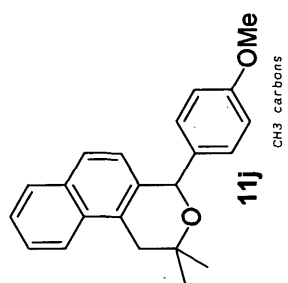Misc Info   : cyclization with bromobenzaldehyde
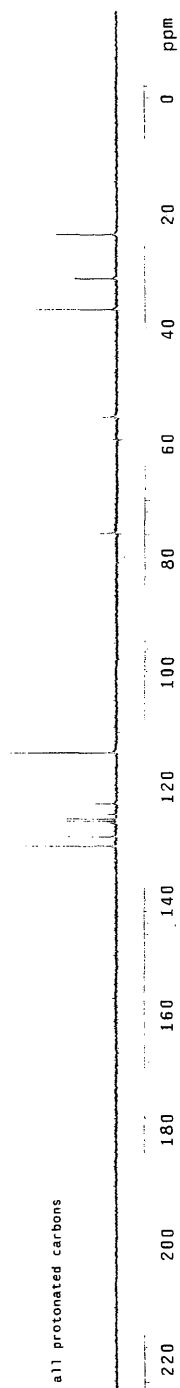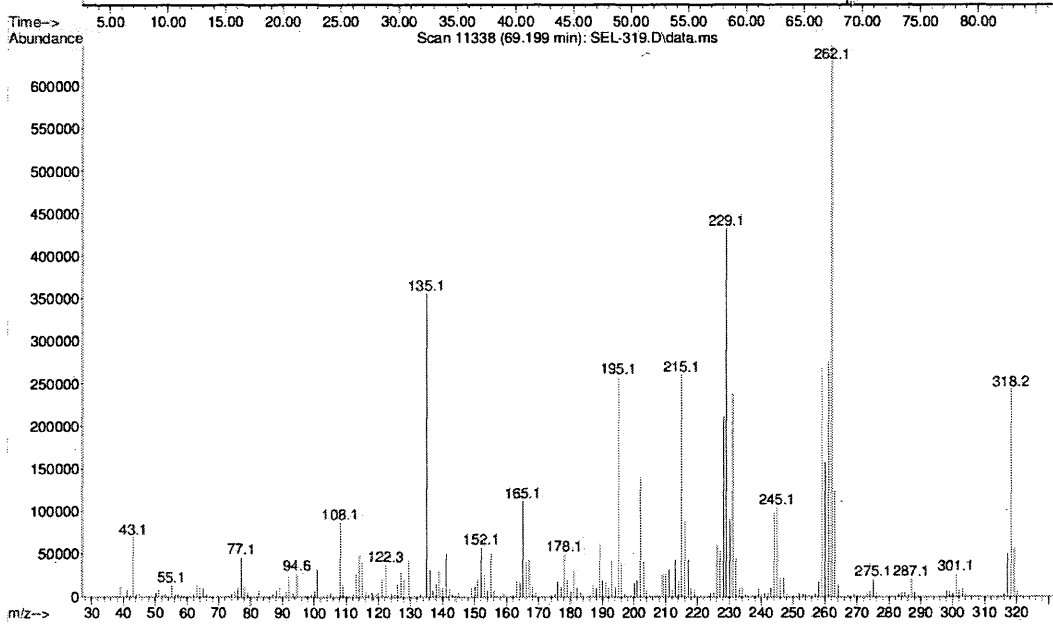Vial Number: 1

11g

Abundance   TIC: SEL-417.D\data.ms

1.4e+07

1.3e+07

1.2e+07

1.1e+07

1e+07

9000000

8000000

7000000

6000000

5000000

4000000

3000000

2000000

1000000

Time--> 5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance   Scan 11566 (70.538 min): SEL-417.D\data.ms
                                            229.2

2200000

2000000

1800000

1600000

1400000

1200000

1000000   310.1

800000

600000

400000
                                  155.1
                        114.2   195.2   366.1
200000   43.2   141.2   211.2
              63.1 77.1 100.2   178.1   244.2 268.1 293.1   324.0   351.1

m/z--> 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370
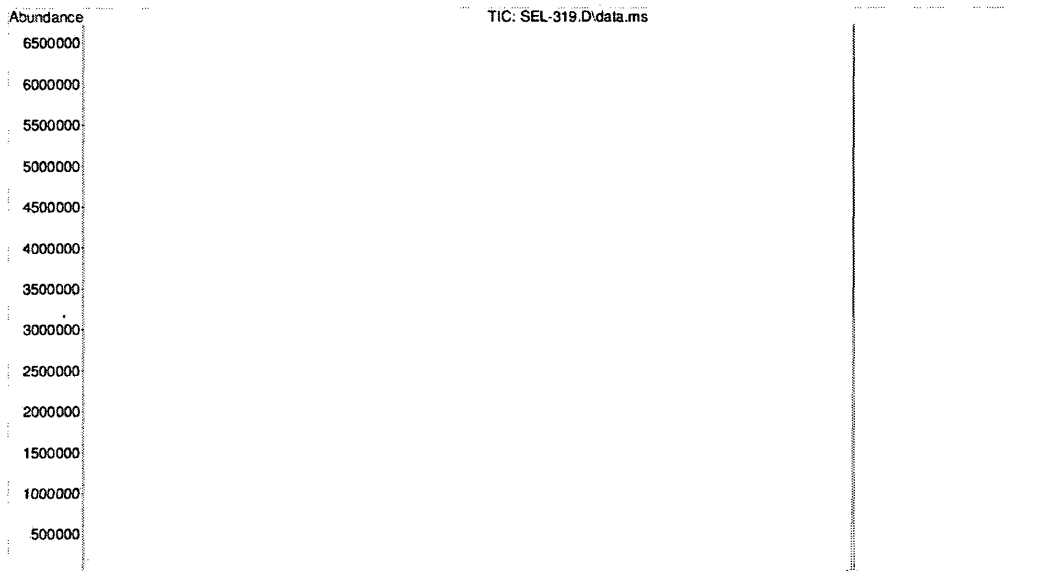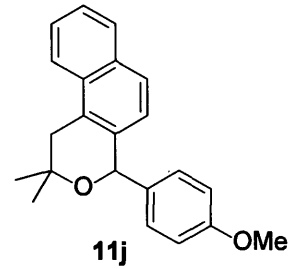
110

11h

111

11h

112

11h

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

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

113

11h

Abundance   TIC: SEL-384.D\data.ms
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000

Time-->   5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance   Scan 9948 (61.032 min): SEL-384.D\data.ms
                                                          229.2
1300000
1200000
1100000
1000000
900000
800000   300.1
700000
600000
500000
400000
300000   356.2
              155.1
200000
100000   43.2   283.1   337.2
         57.2 75.1 88.2 101.1 114.2 128.1 141.2 173.1 195.2 211.2 243.1 257.1 270.1   313.2
0
m/z-->   30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360

114

11i

11i

116

11i

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

117

11i

TIC: SEL-339.D\data.ms

Abundance

4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000

Time--> 5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance

Scan 12268 (74.663 min): SEL-339.D\data.ms

228.2

600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0

277.1
258.1
333.2
155.1
43.2
202.2 215.2
141.1
114.1 127.1
178.1
101.1
63.1 76.1
244.2
290.1 303.1 318.2
355.1

m/z--> 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360

118

11j

119

11j

120

11j

OMe

CH2 carbons

CH carbons

all protonated carbons

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

121

File   :C:\GC-MS Data\rjhink\SEL-319.D
Operator   :
Acquired   : 11 Apr 2013 19:54   using AcqMethod RJHSAM_LONG (260).M
Instrument :   Instrument #1
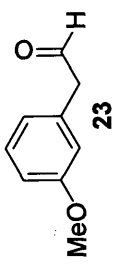Sample Name: SEL-319
Misc Info   : PhOMe isochromene
Vial Number: 1
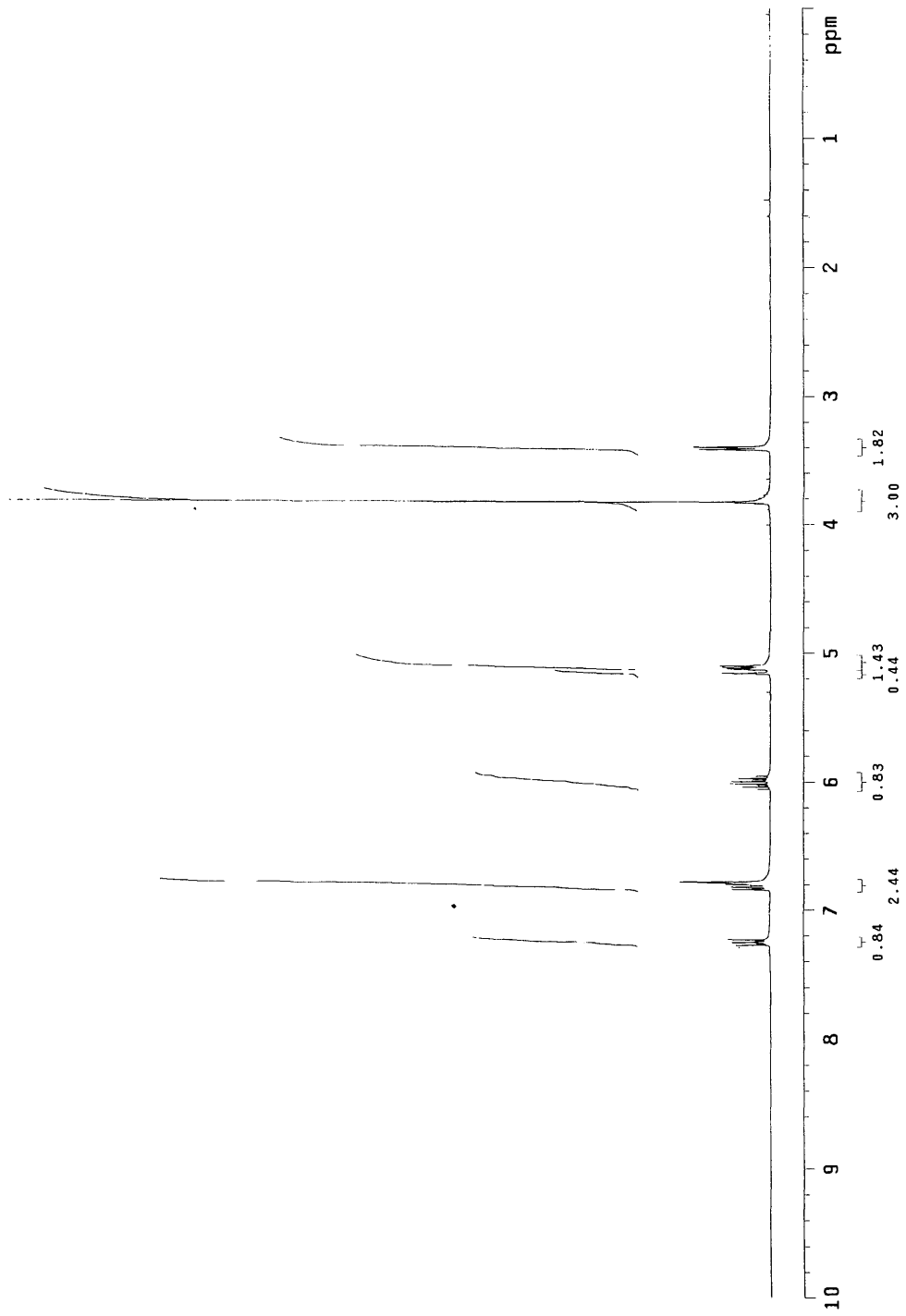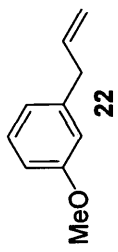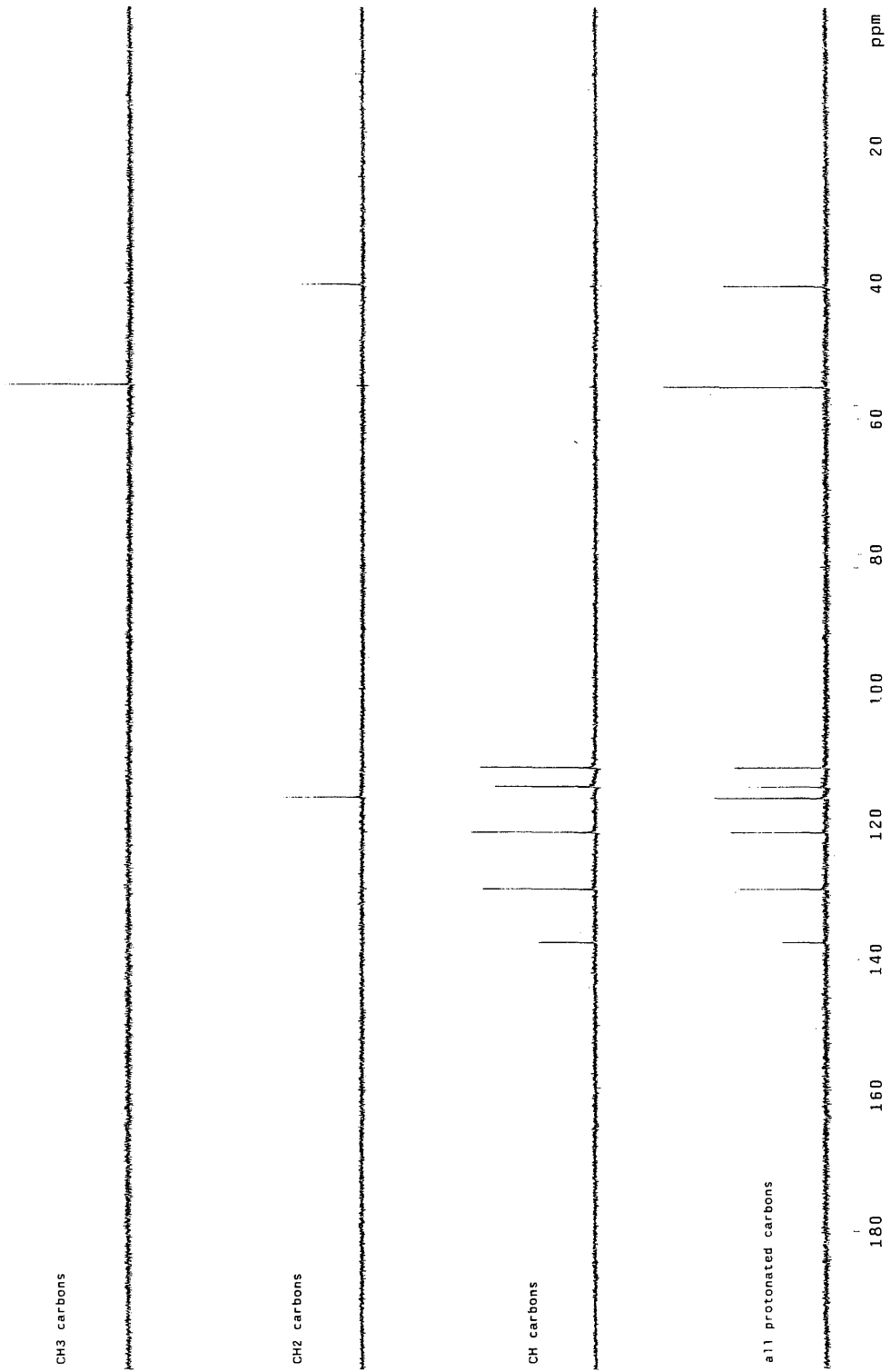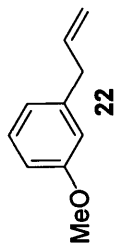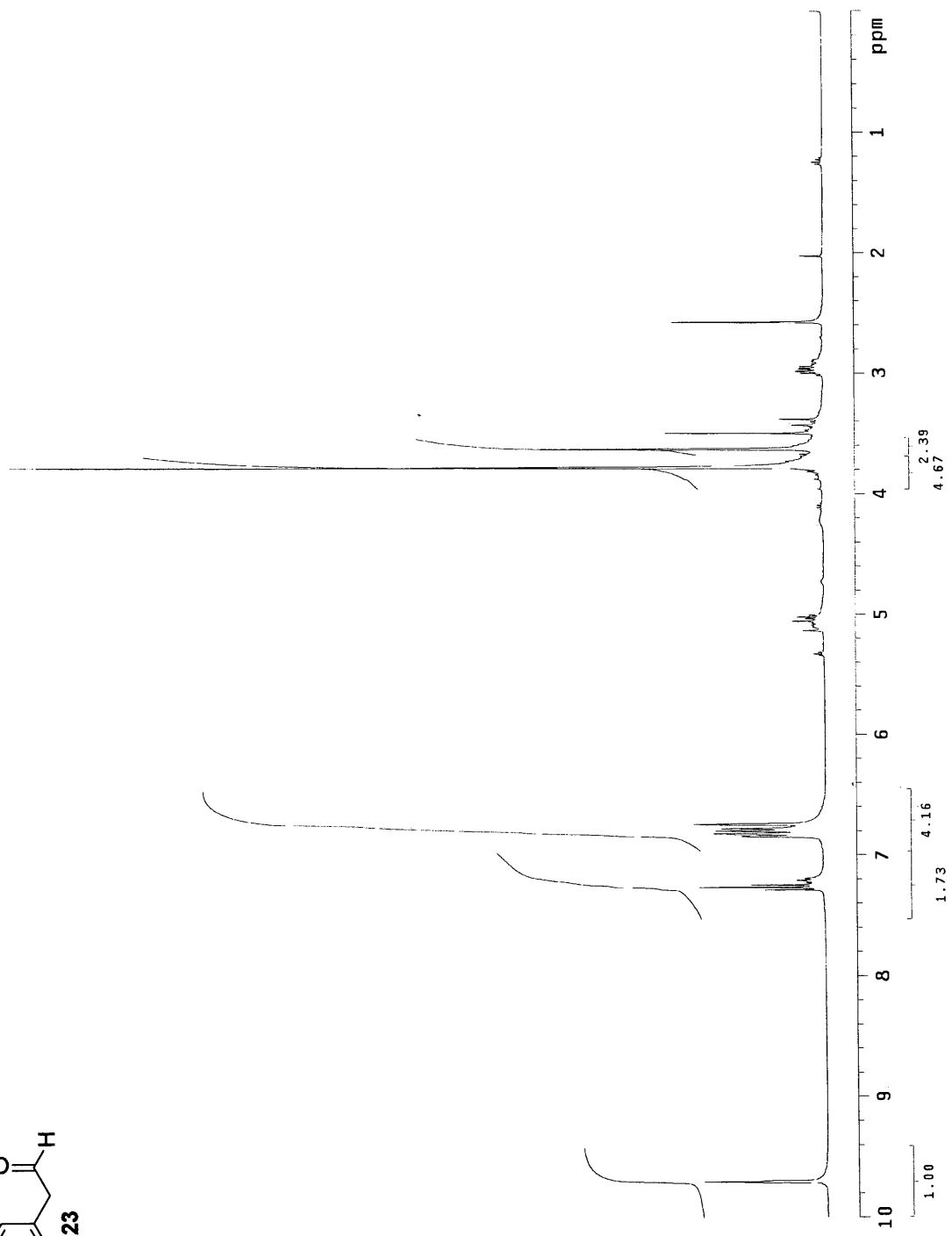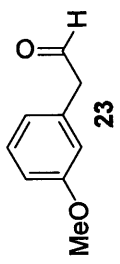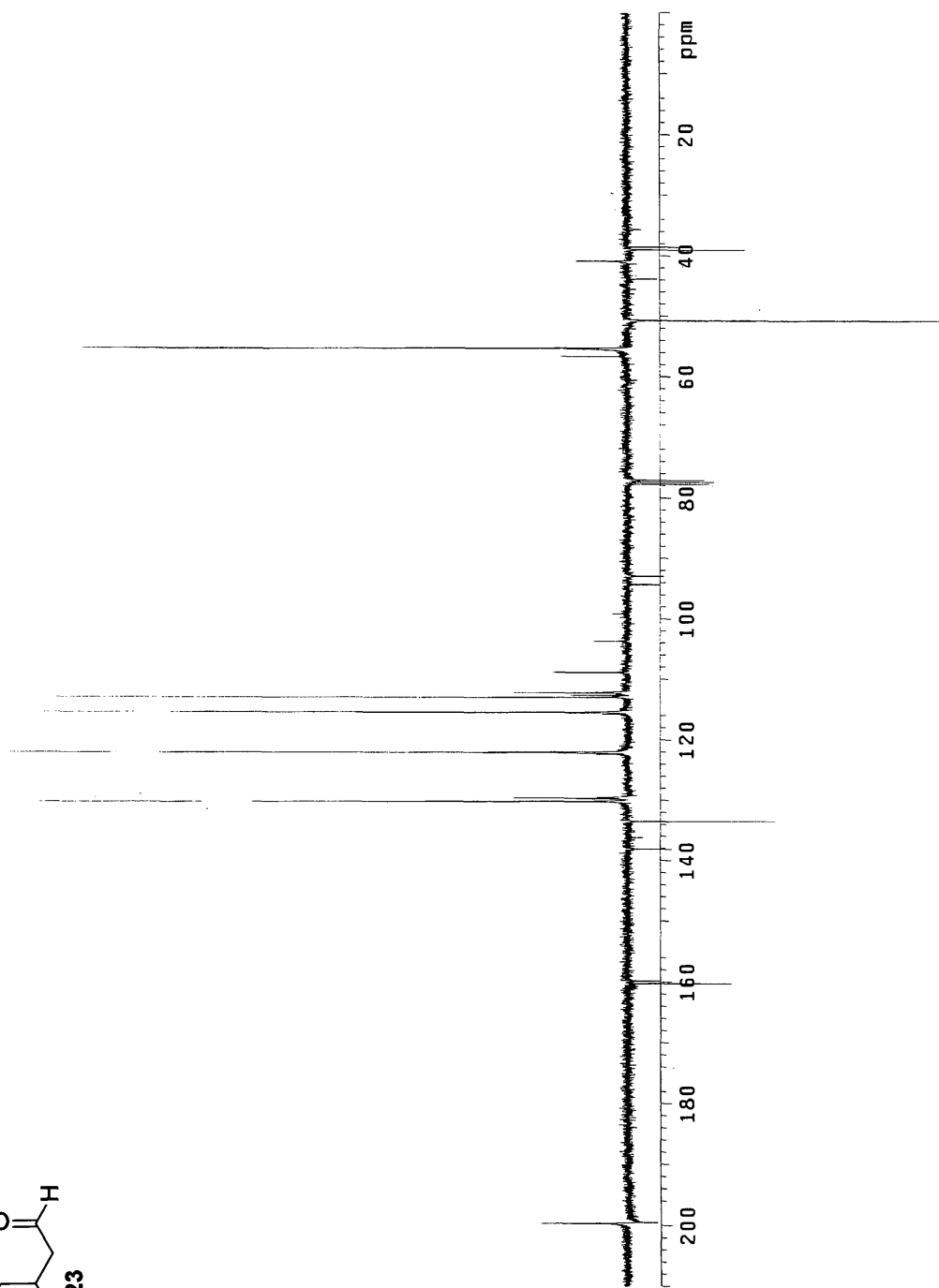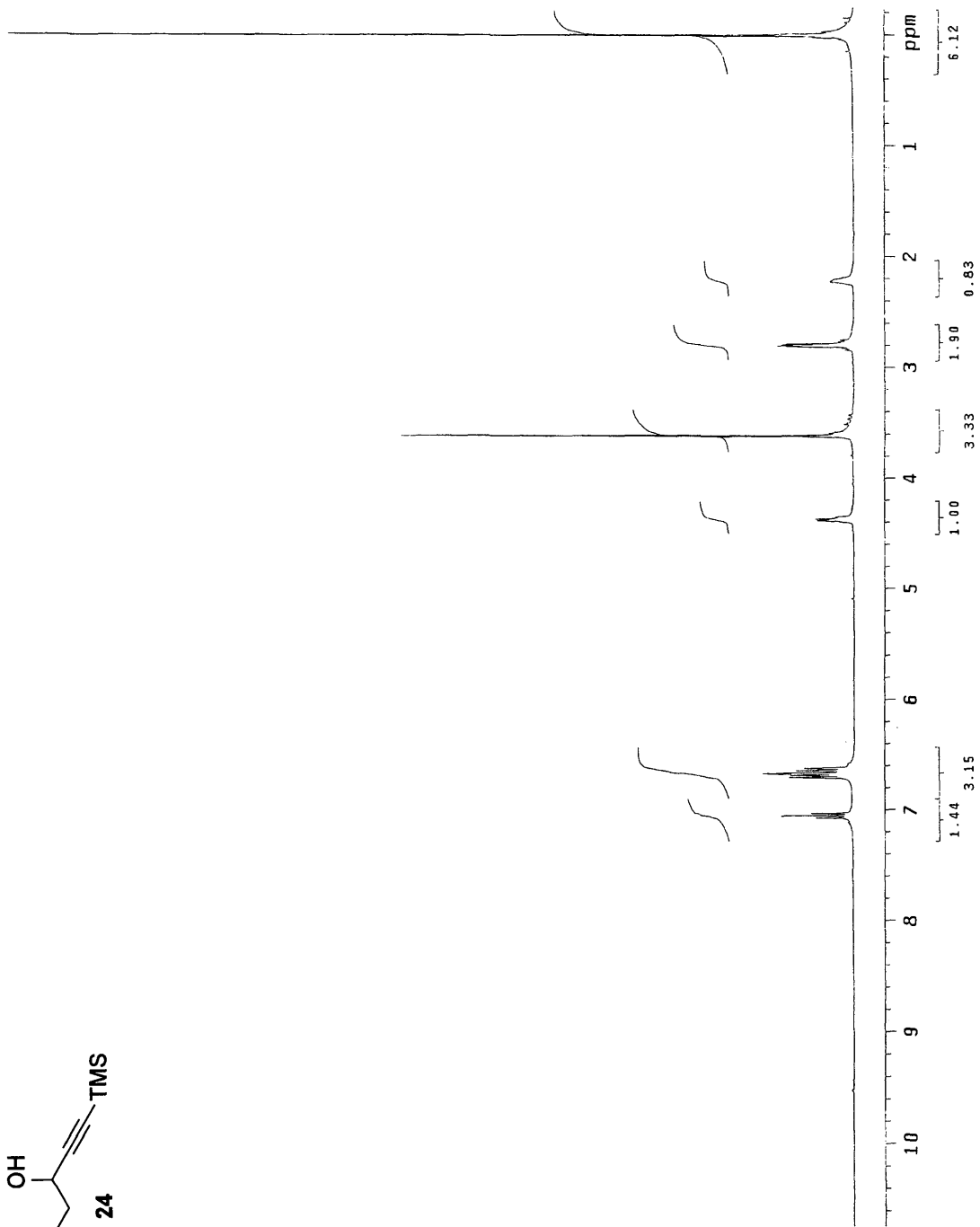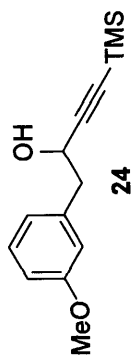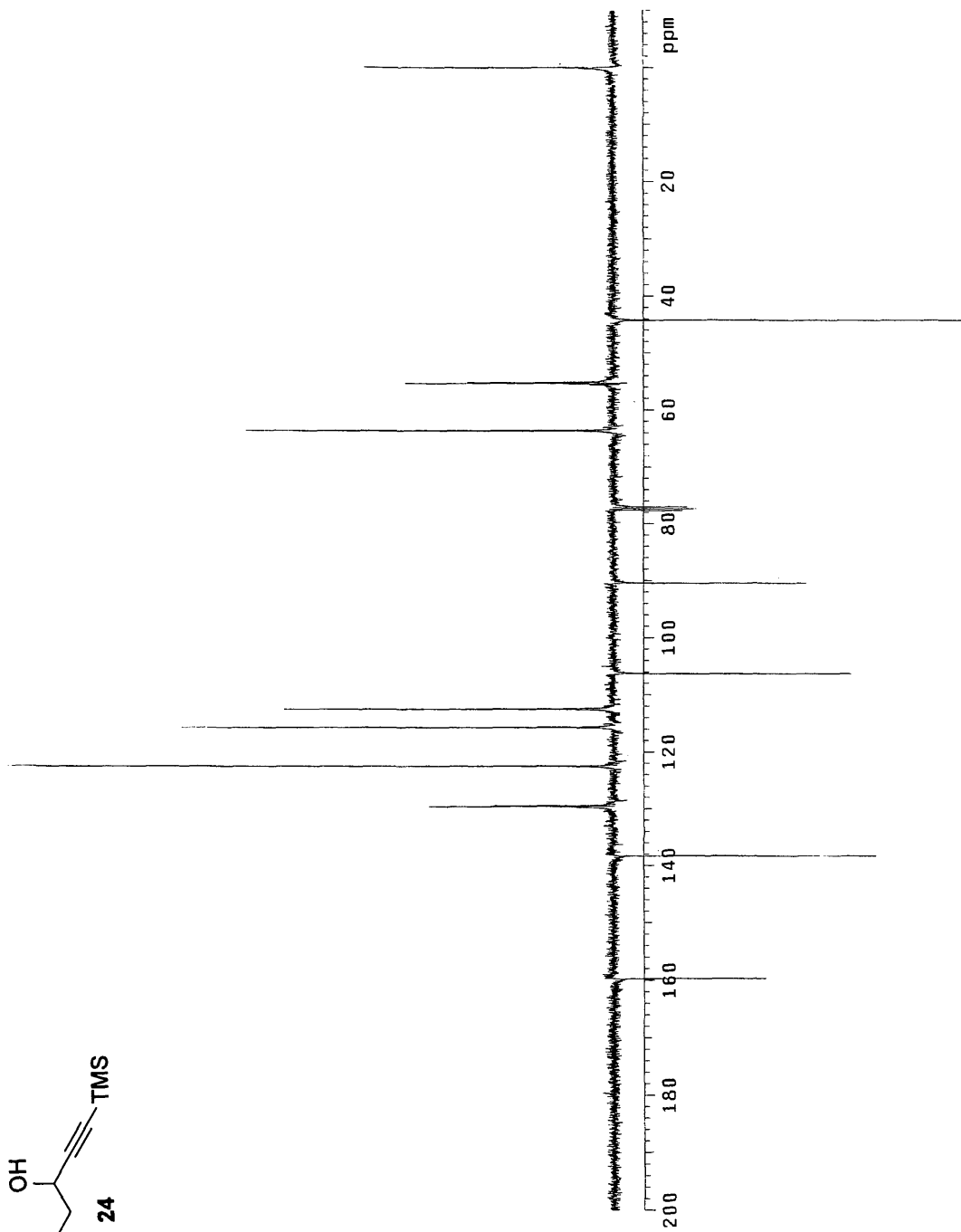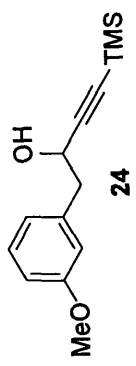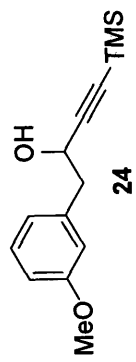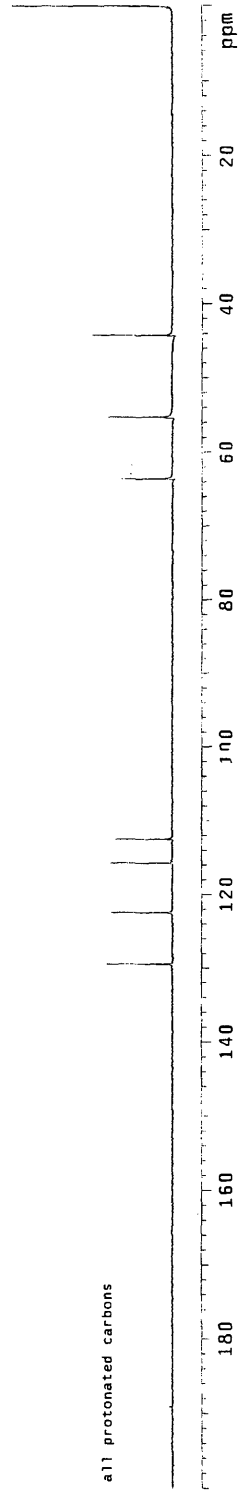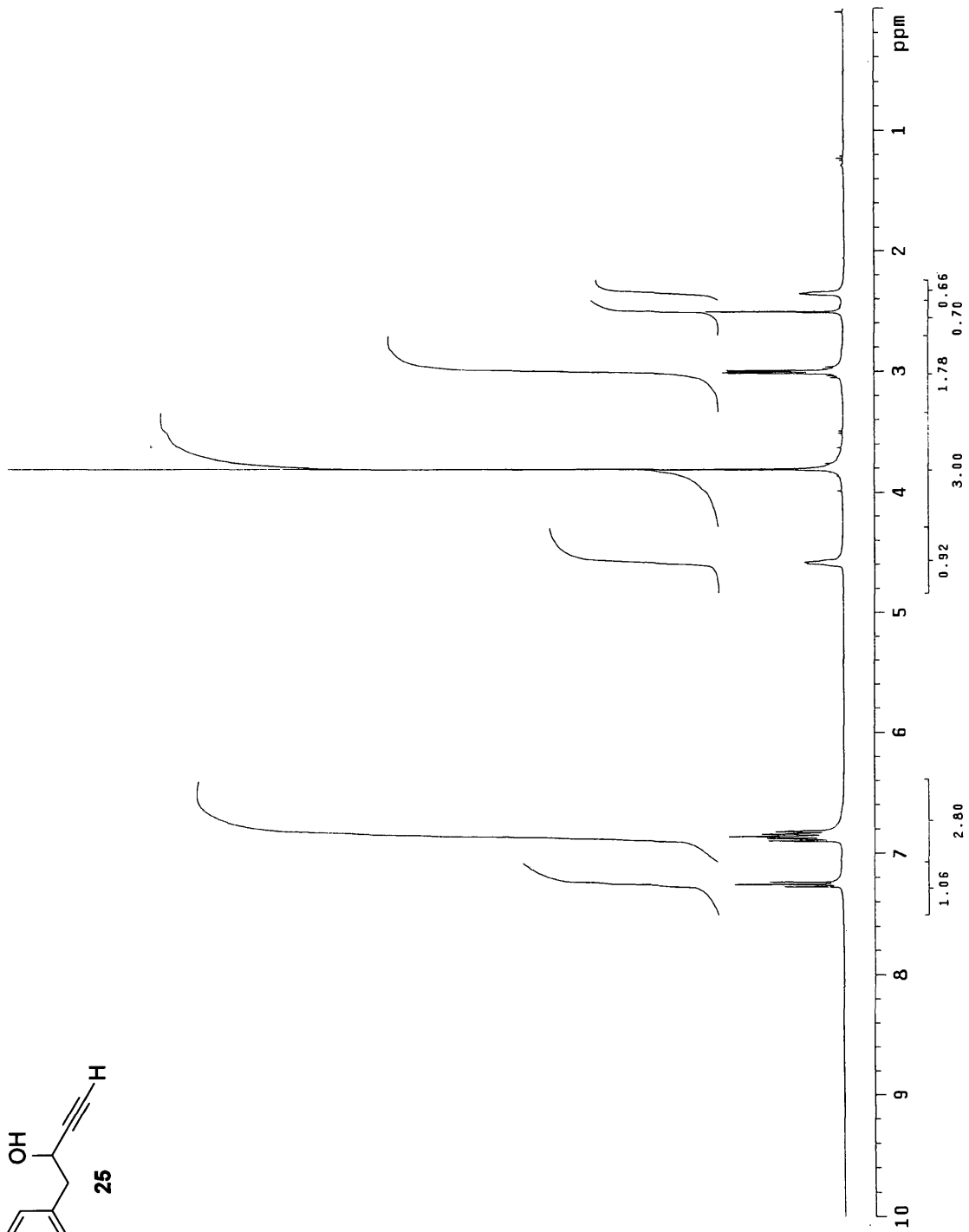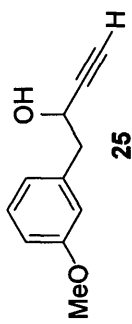
11j

TIC: SEL-319.D\data.ms

Scan 11338 (69.199 min): SEL-319.D\data.ms

124

22

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   100   80   60   40   20   ppm

125

127

128

24

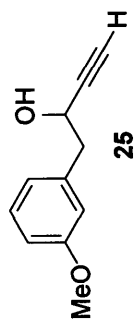CH3 carbons

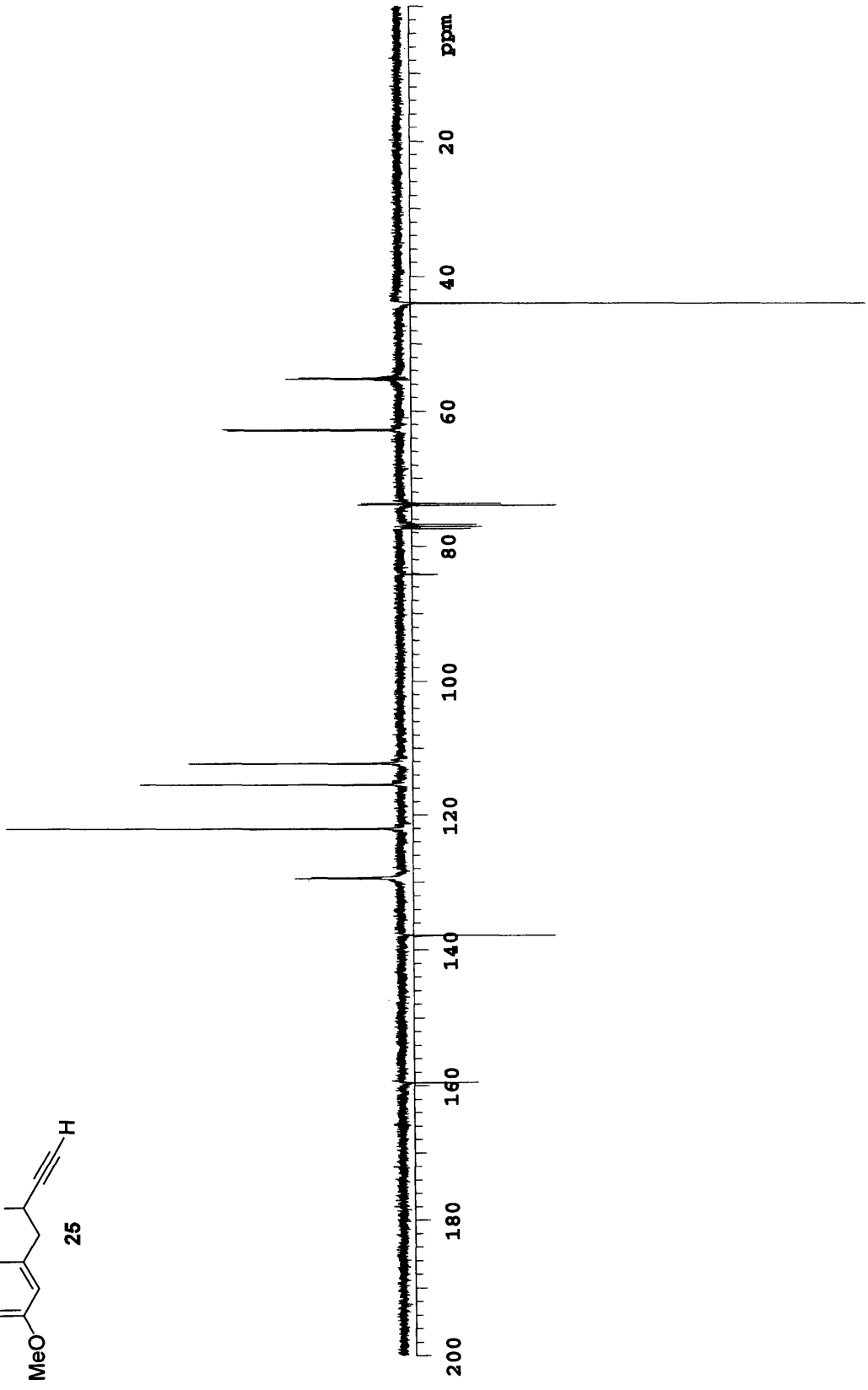CH2 carbons

CH carbons

all protonated carbons

180   160   140   120   110   100   80   60   40   20   ppm

130

131

132

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

133

135

OTBDPS

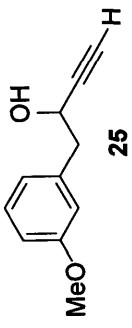MeO

26

H

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

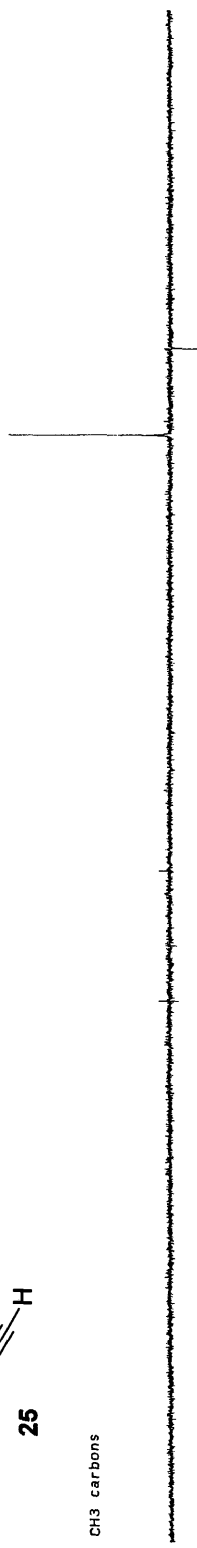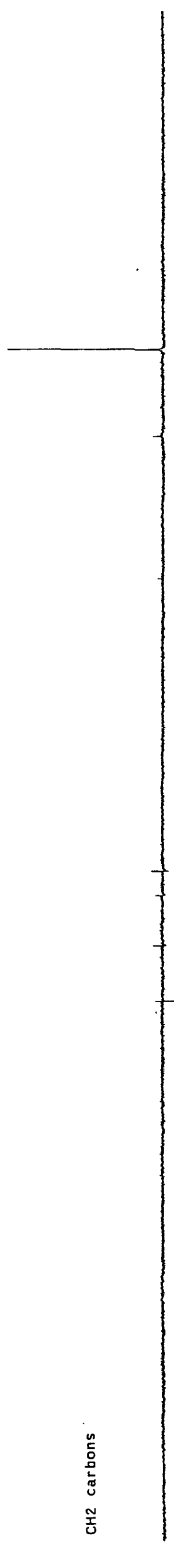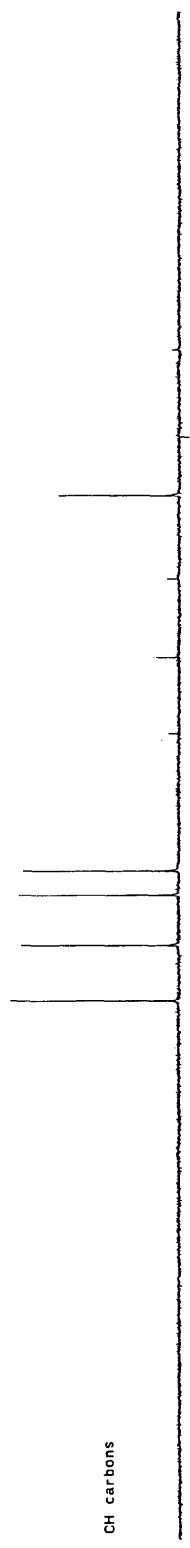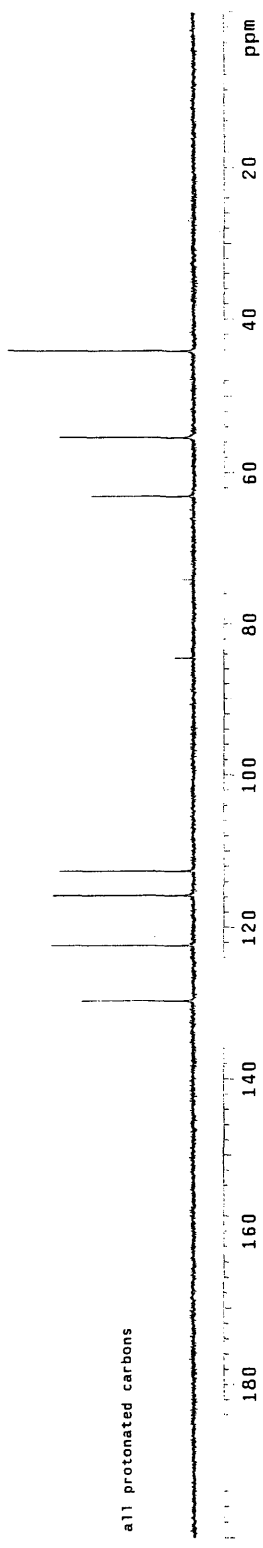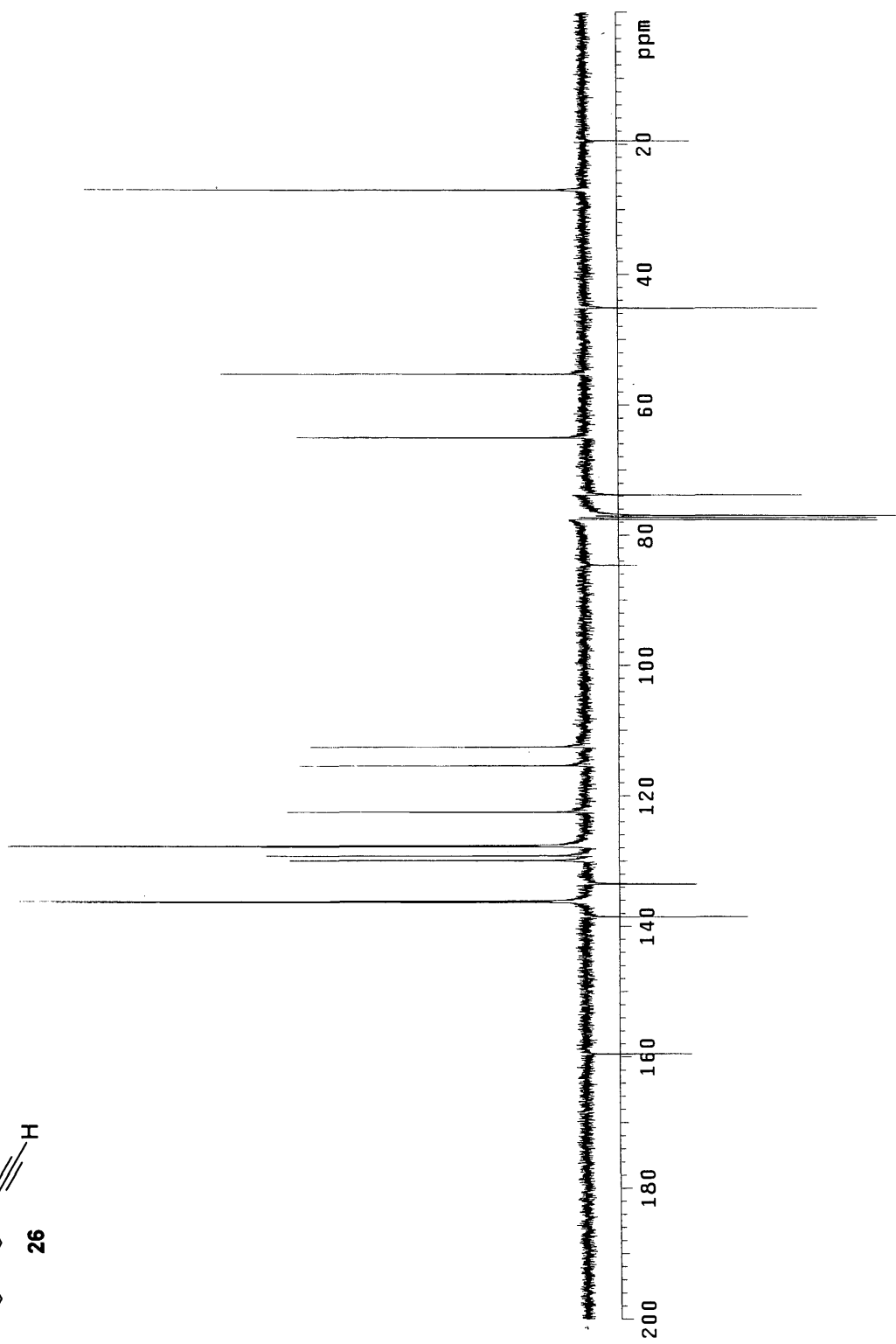180   160   140   120   100   80   60   40   20   ppm

136

137

138

139

140

141

CH3 carbons

CH2 carbons

CH carbons

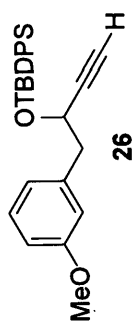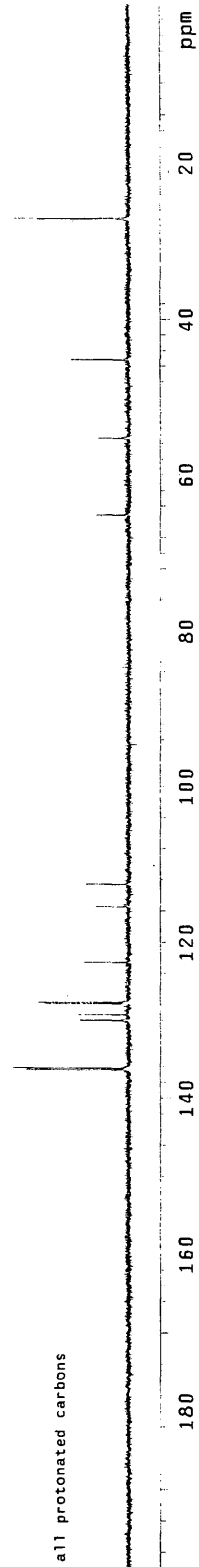all protonated carbons

142
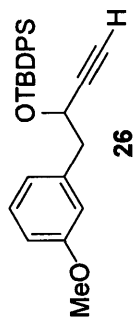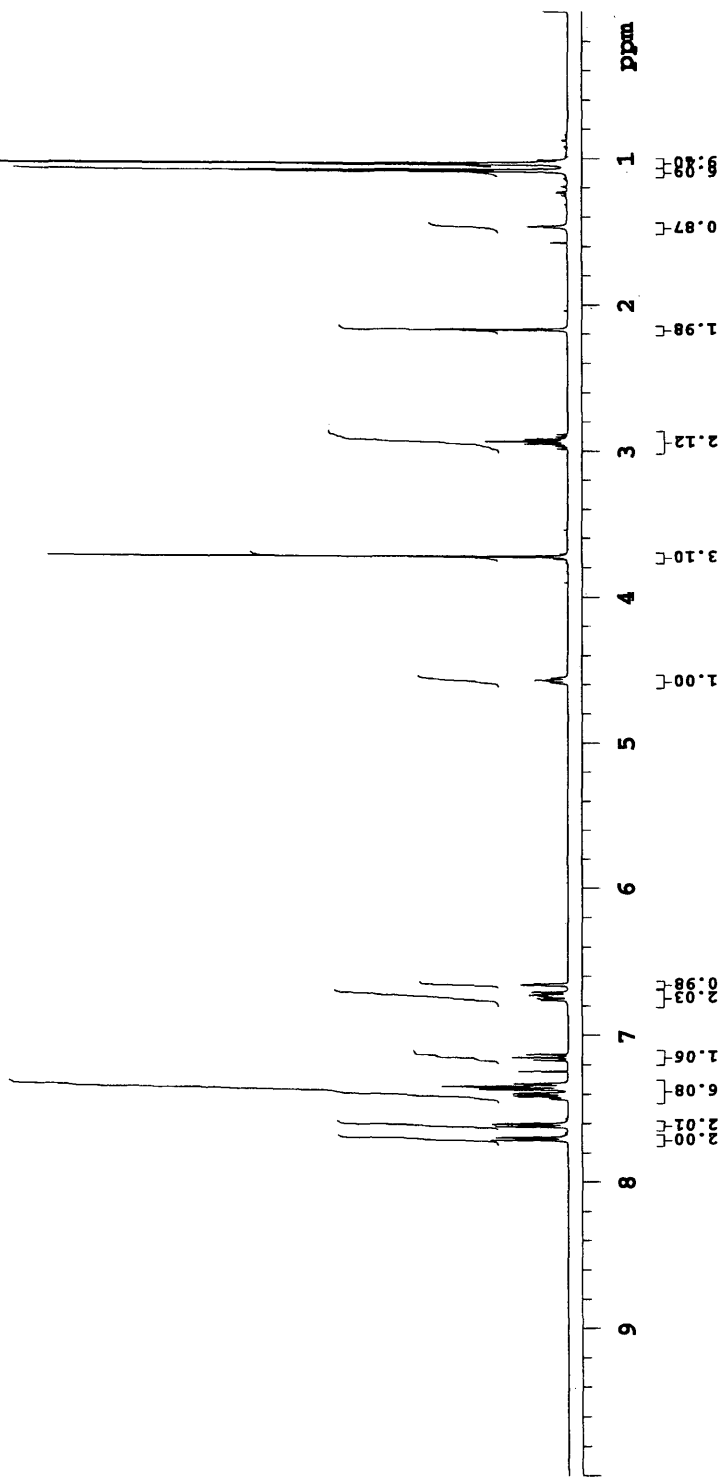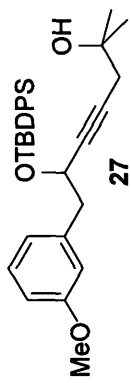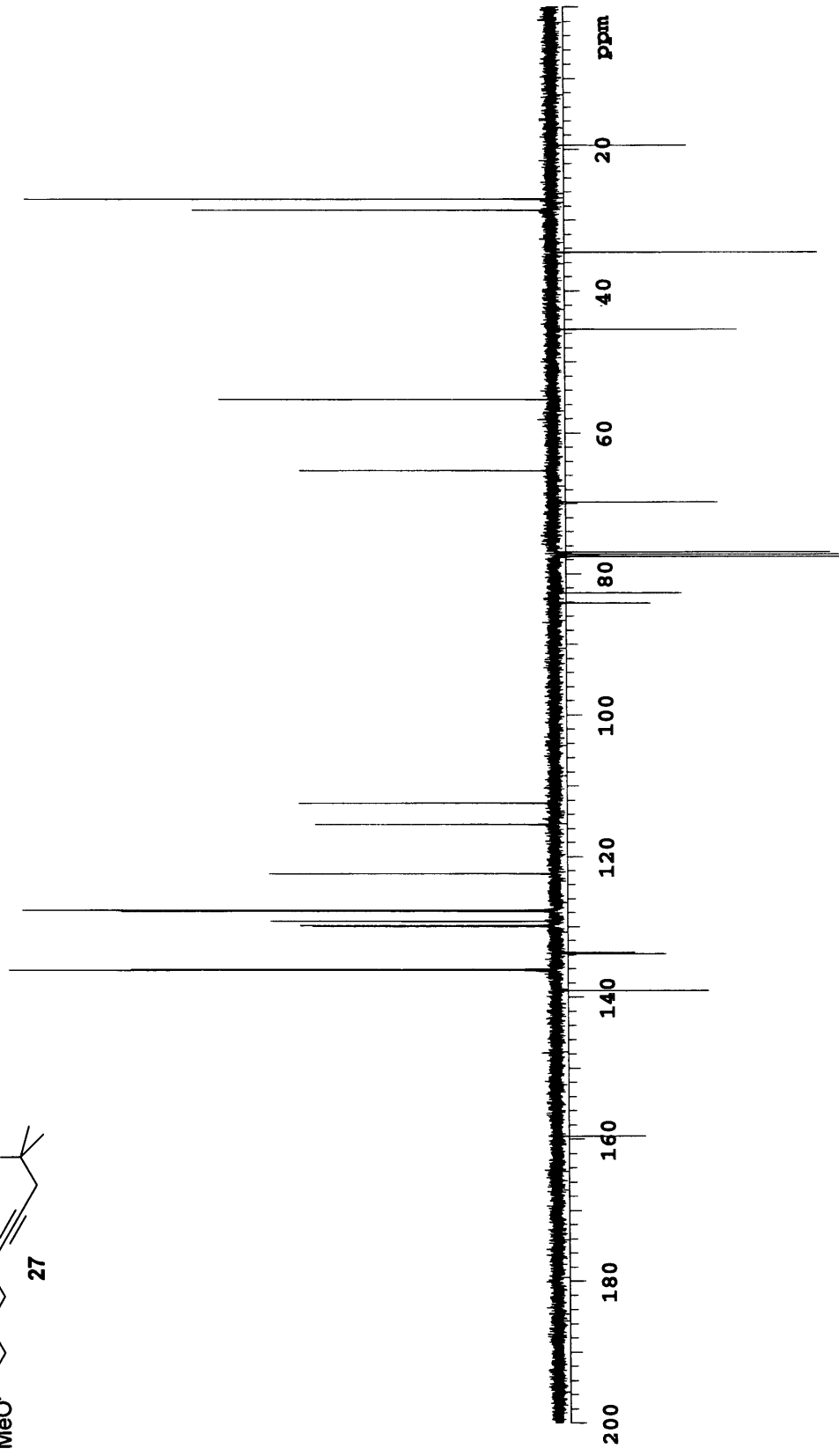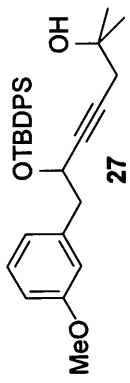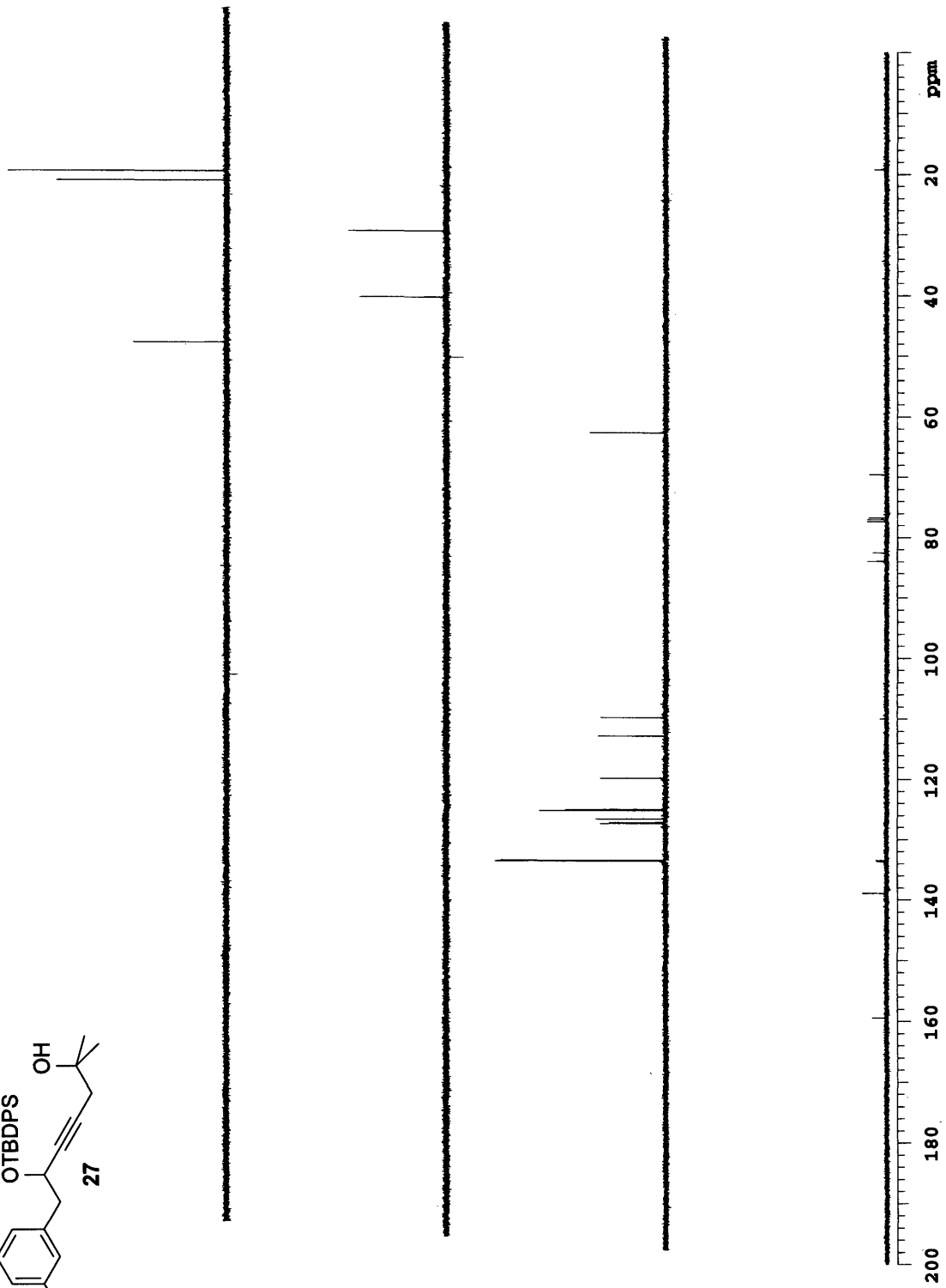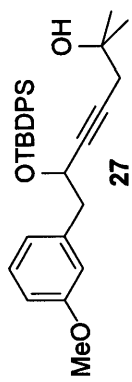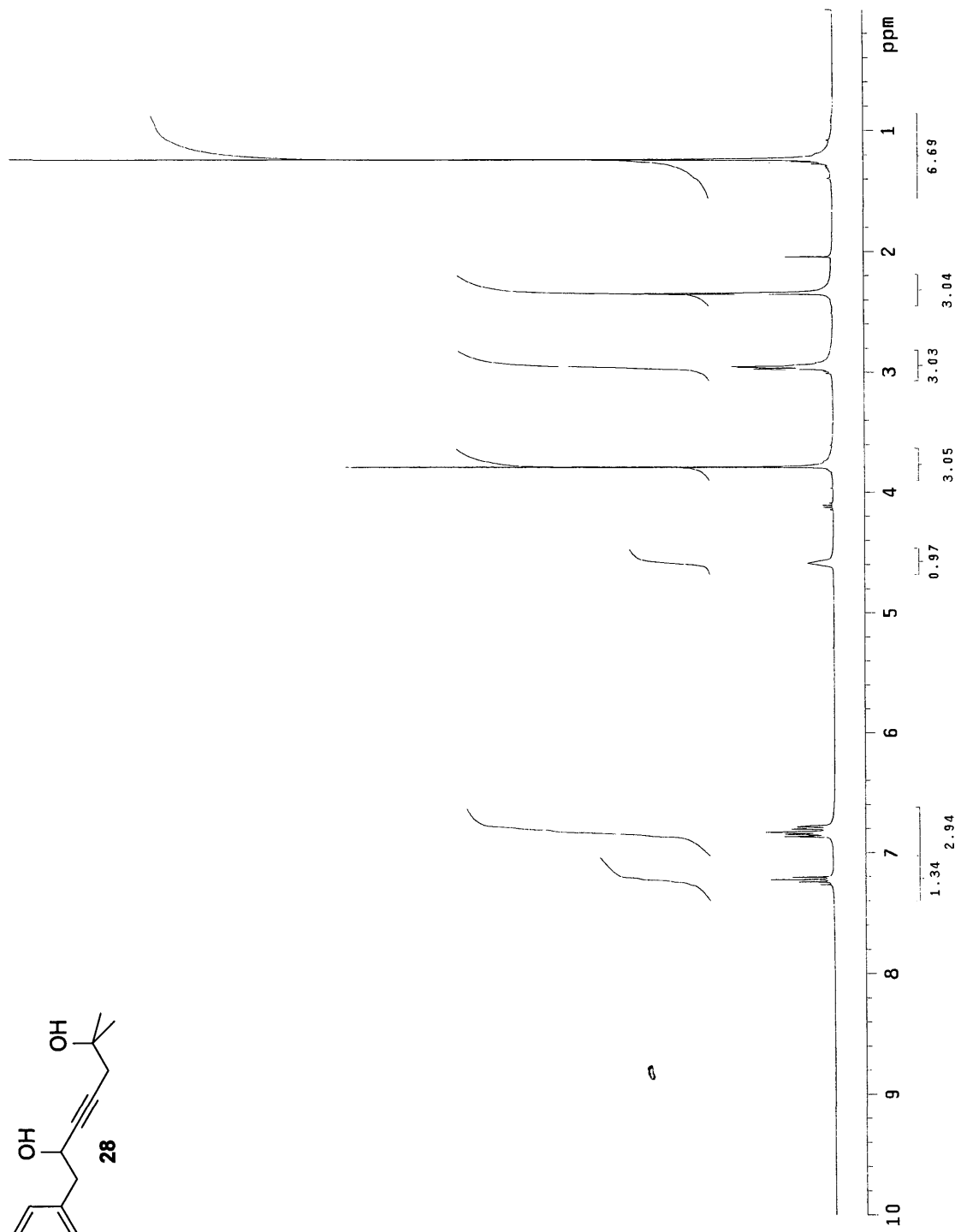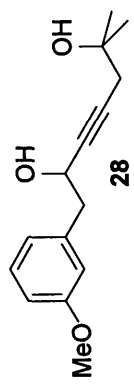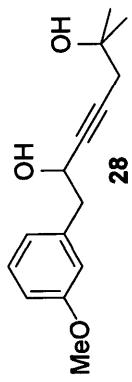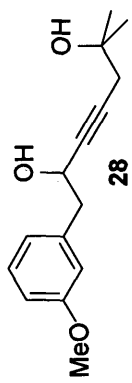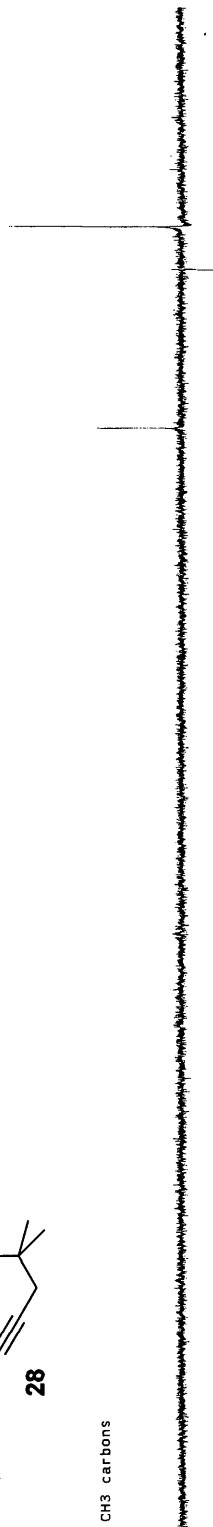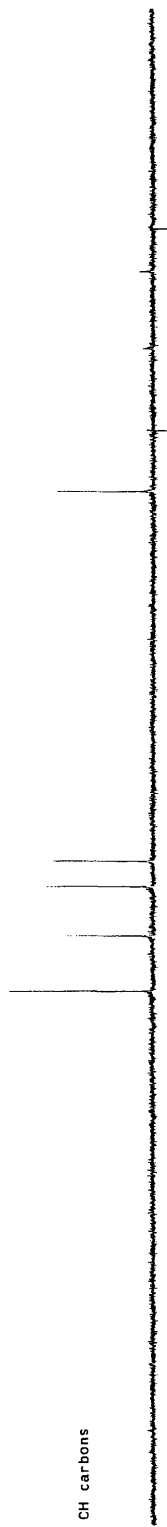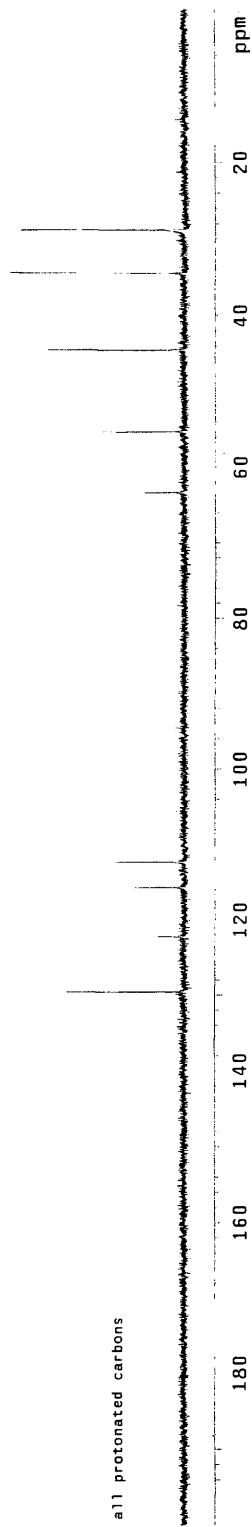
Appendix B

Crystallographic Data

Crystallographic Data for 2,2-dimethyl-1,2-dihydro-4*H*-benzo[*f*]isochromen-4-one:
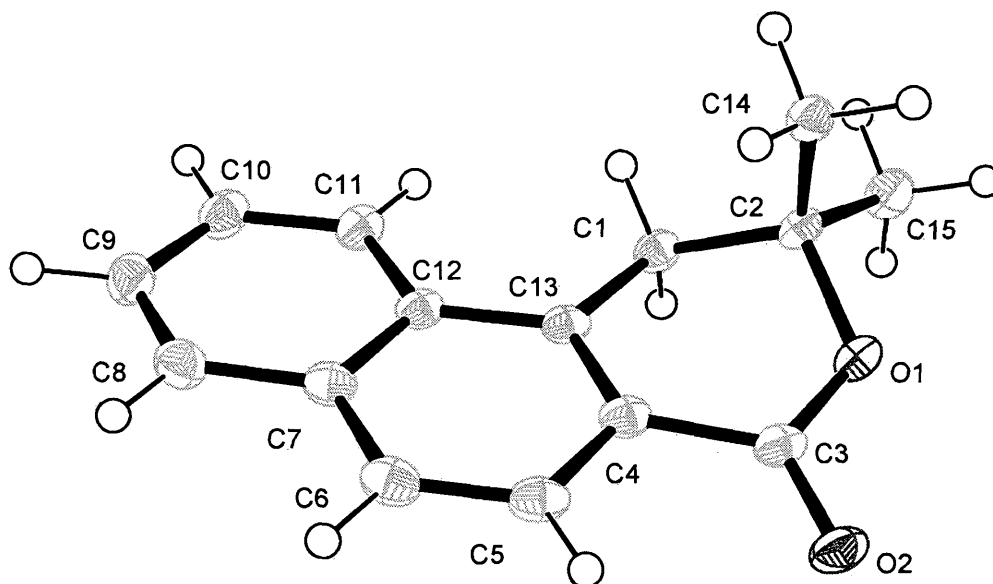
Figure B.1: ORTEP of Lactone **19**

19
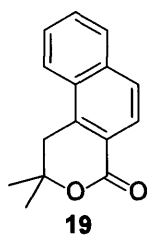
Table B.1. Crystal data and structure refinement for p21onc.

Identification code	p21onc
Empirical formula	C15 H14 O2
Formula weight	226.26
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 10.06000(10) Å $\alpha = 90°$.
	b = 16.5507(2) Å $\beta = 105.7830(10)°$.
	c = 7.08520(10) Å $\gamma = 90°$.
Volume	1135.21(2) Å³
Z	4
Density (calculated)	1.324 Mg/m³
Absorption coefficient	0.693 mm⁻¹
F(000)	480
Crystal size	0.33 x 0.25 x 0.11 mm³
Theta range for data collection	4.57 to 66.89°.
Index ranges	-11<=h<=11, -19<=k<=16, -7<=l<=8
Reflections collected	11695
Independent reflections	1959 [R(int) = 0.0341]
Completeness to theta = 66.89°	96.8 %
Absorption correction	Numerical
Max. and min. transmission	0.9290 and 0.8032
Refinement method	Full-matrix least-squares on F²
Data / restraints / parameters	1959 / 0 / 210
Goodness-of-fit on F²	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0330, wR2 = 0.0842
R indices (all data)	R1 = 0.0377, wR2 = 0.0877
Largest diff. peak and hole	0.163 and -0.202 e.Å⁻³

Table B.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\mathring{A}^2$x 10^3) for p21onc. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8350(1)	3649(1)	850(1)	23(1)
O(2)	9343(1)	3940(1)	-1471(1)	28(1)
C(1)	9739(1)	3245(1)	4120(2)	20(1)
C(2)	8407(1)	3647(1)	2958(2)	21(1)
C(3)	9476(1)	3847(1)	269(2)	21(1)
C(4)	10829(1)	3894(1)	1768(2)	20(1)
C(5)	11966(1)	4219(1)	1197(2)	24(1)
C(6)	13236(1)	4239(1)	2491(2)	25(1)
C(7)	13461(1)	3920(1)	4413(2)	22(1)
C(8)	14779(1)	3936(1)	5784(2)	26(1)
C(9)	14992(1)	3605(1)	7612(2)	27(1)
C(10)	13886(1)	3236(1)	8154(2)	26(1)
C(11)	12588(1)	3227(1)	6880(2)	22(1)
C(12)	12330(1)	3574(1)	4984(2)	19(1)
C(13)	10990(1)	3586(1)	3622(2)	19(1)
C(14)	8282(1)	4516(1)	3577(2)	23(1)
C(15)	7163(1)	3149(1)	3064(2)	27(1)

Table B.3. Bond lengths [Å] and angles [°] for p21onc.

O(1)-C(3)	1.3470(15)
O(1)-C(2)	1.4789(14)
O(2)-C(3)	1.2133(15)
C(1)-C(13)	1.5061(17)
C(1)-C(2)	1.5226(17)
C(1)-H(1A)	1.008(14)
C(1)-H(1B)	0.983(15)
C(2)-C(15)	1.5165(18)
C(2)-C(14)	1.5191(17)
C(3)-C(4)	1.4835(17)
C(4)-C(13)	1.3774(17)
C(4)-C(5)	1.4182(18)
C(5)-C(6)	1.3559(19)
C(5)-H(5)	0.953(15)
C(6)-C(7)	1.4202(18)
C(6)-H(6)	0.995(15)
C(7)-C(8)	1.4154(18)
C(7)-C(12)	1.4268(17)
C(8)-C(9)	1.368(2)
C(8)-H(8)	0.971(16)
C(9)-C(10)	1.4104(19)
C(9)-H(9)	0.989(16)
C(10)-C(11)	1.3705(19)
C(10)-H(10)	0.986(15)
C(11)-C(12)	1.4182(17)
C(11)-H(11)	0.959(15)
C(12)-C(13)	1.4287(18)
C(14)-H(14A)	0.999(15)
C(14)-H(14B)	0.994(15)
C(14)-H(14C)	1.012(15)
C(15)-H(15A)	0.996(17)
C(15)-H(15B)	0.984(16)
C(15)-H(15C)	1.010(17)

C(3)-O(1)-C(2)	120.30(9)
C(13)-C(1)-C(2)	112.23(10)
C(13)-C(1)-H(1A)	108.8(8)
C(2)-C(1)-H(1A)	109.8(8)
C(13)-C(1)-H(1B)	111.3(8)
C(2)-C(1)-H(1B)	107.4(8)
H(1A)-C(1)-H(1B)	107.2(11)
O(1)-C(2)-C(15)	104.18(10)
O(1)-C(2)-C(14)	107.85(10)
C(15)-C(2)-C(14)	111.49(11)
O(1)-C(2)-C(1)	109.48(10)
C(15)-C(2)-C(1)	110.63(10)
C(14)-C(2)-C(1)	112.81(10)
O(2)-C(3)-O(1)	118.21(11)
O(2)-C(3)-C(4)	123.12(12)
O(1)-C(3)-C(4)	118.58(10)
C(13)-C(4)-C(5)	121.19(12)
C(13)-C(4)-C(3)	120.66(11)
C(5)-C(4)-C(3)	118.03(11)
C(6)-C(5)-C(4)	120.06(12)
C(6)-C(5)-H(5)	121.7(9)
C(4)-C(5)-H(5)	118.2(9)
C(5)-C(6)-C(7)	120.95(12)
C(5)-C(6)-H(6)	120.2(9)
C(7)-C(6)-H(6)	118.9(9)
C(8)-C(7)-C(6)	121.74(12)
C(8)-C(7)-C(12)	118.91(12)
C(6)-C(7)-C(12)	119.35(11)
C(9)-C(8)-C(7)	121.22(12)
C(9)-C(8)-H(8)	120.5(9)
C(7)-C(8)-H(8)	118.3(9)
C(8)-C(9)-C(10)	119.91(12)
C(8)-C(9)-H(9)	119.0(9)
C(10)-C(9)-H(9)	121.1(9)
C(11)-C(10)-C(9)	120.42(12)
C(11)-C(10)-H(10)	120.1(9)

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C(9)-C(10)-H(10)	119.5(9)
C(10)-C(11)-C(12)	121.04(12)
C(10)-C(11)-H(11)	119.7(9)
C(12)-C(11)-H(11)	119.2(9)
C(11)-C(12)-C(7)	118.43(11)
C(11)-C(12)-C(13)	122.80(11)
C(7)-C(12)-C(13)	118.77(11)
C(4)-C(13)-C(12)	119.61(11)
C(4)-C(13)-C(1)	118.27(11)
C(12)-C(13)-C(1)	122.09(11)
C(2)-C(14)-H(14A)	112.1(8)
C(2)-C(14)-H(14B)	110.1(9)
H(14A)-C(14)-H(14B)	109.0(11)
C(2)-C(14)-H(14C)	110.3(8)
H(14A)-C(14)-H(14C)	107.6(11)
H(14B)-C(14)-H(14C)	107.6(12)
C(2)-C(15)-H(15A)	110.3(9)
C(2)-C(15)-H(15B)	108.0(9)
H(15A)-C(15)-H(15B)	108.6(12)
C(2)-C(15)-H(15C)	110.7(9)
H(15A)-C(15)-H(15C)	110.3(13)
H(15B)-C(15)-H(15C)	108.9(12)

Symmetry transformations used to generate equivalent atoms:

Table B.4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for p21onc. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2} U^{11} + \ldots + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	27(1)	15(1)	-1(1)	3(1)	-1(1)
O(2)	37(1)	31(1)	15(1)	3(1)	7(1)	7(1)
C(1)	24(1)	19(1)	16(1)	2(1)	5(1)	0(1)
C(2)	24(1)	24(1)	13(1)	-1(1)	4(1)	-1(1)
C(3)	29(1)	16(1)	17(1)	1(1)	7(1)	4(1)
C(4)	27(1)	16(1)	19(1)	-1(1)	7(1)	4(1)
C(5)	34(1)	20(1)	20(1)	3(1)	12(1)	4(1)
C(6)	28(1)	22(1)	29(1)	0(1)	14(1)	-1(1)
C(7)	25(1)	16(1)	24(1)	-3(1)	9(1)	2(1)
C(8)	23(1)	25(1)	32(1)	-5(1)	10(1)	1(1)
C(9)	23(1)	26(1)	29(1)	-6(1)	1(1)	4(1)
C(10)	30(1)	24(1)	21(1)	0(1)	2(1)	4(1)
C(11)	26(1)	19(1)	20(1)	0(1)	5(1)	1(1)
C(12)	24(1)	14(1)	19(1)	-2(1)	6(1)	3(1)
C(13)	25(1)	14(1)	18(1)	-2(1)	7(1)	3(1)
C(14)	25(1)	25(1)	19(1)	0(1)	4(1)	3(1)
C(15)	26(1)	31(1)	23(1)	0(1)	5(1)	-4(1)

Table B.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2x 10^3) for p21onc.

	x	y	z	U(eq)
H(1A)	9693(14)	2646(9)	3850(20)	20(3)
H(1B)	9801(14)	3315(8)	5520(20)	22(3)
H(5)	11806(14)	4423(9)	-100(20)	25(4)
H(6)	14030(16)	4479(9)	2100(20)	30(4)
H(8)	15533(16)	4194(9)	5400(20)	30(4)
H(9)	15926(16)	3632(9)	8540(20)	29(4)
H(10)	14050(15)	2994(9)	9470(20)	30(4)
H(11)	11841(15)	2982(9)	7270(20)	24(4)
H(14A)	9048(15)	4862(8)	3385(19)	23(3)
H(14B)	8284(15)	4537(9)	4980(20)	28(4)
H(14C)	7381(15)	4760(9)	2780(20)	26(4)
H(15A)	7248(16)	2587(11)	2610(20)	35(4)
H(15B)	7140(15)	3130(9)	4440(20)	28(4)
H(15C)	6281(17)	3405(10)	2250(20)	36(4)