SYNTHETIC EFFORTS TOWARDS INGENOL CROSS-CONJUGATED TRIENES AND THEIR APPLICATION TO RAPID INCREASES IN MOLECULAR COMPLEXITY

by

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Abstract

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Synthesis of the ingenol skeleton using a Pauson-Khand reaction as the key step was investigated. Although the Pauson-Khand reaction failed to provide the highly strained ingenol skeleton, several relatively complex Pauson-Khand precursors were prepared in about ten steps. The scope and limitation of the Pauson-Khand reaction in accessing highly strained molecules were studied.

A rhodium(I)-catalyzed allenic Alder-ene reaction was developed that provides cross-conjugated trienes in good yields. This method shows enticing functional group compatibility, and progress has been made to increase the stereoselectivity of the olefinic side chain via iridium(I) catalysis. A consecutive one-pot Alder-ene/[4+2]/[4+2] reaction has been developed to demonstrate the potential of the cross-conjugated triene for accessing polycyclic compounds. The reaction sequence is highly selective with the Alder-ene and the first Diels-Alder reaction only providing a single isomer and the intermolecular [4+2] cycloaddition giving two endo addition products resulting from addition of the dienophile to either face of the diene. The transformation is highly atom-efficient with all the atoms of the starting dialkynyl allenes and the dienophiles appearing in the products.

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List of Abbreviations

Ac.....acetyl
BDPP.....2,4-bis-(diphenylphosphino)pentane
Bn.....benzyl
Bu.....butyl
Bz.....benzoyl
COD.....1,5-cyclooctadiene
COE.....cyclooctene
Cp.....cyclopentadienyl
Cy.....cyclohexyl
DBU.....1,8-diazobicyclo[5.4.0]undec-7-ene
DCC.....dicyclohexylcarbodiimide
DEAD.....diethylazodicarboxylate
DIOP.....2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAP.....4-dimethylaminopyridine
DME.....1,2-dimethoxyethane
DMF.....*N*,*N*-dimethylformamide
DMS.....dimethyl sulfide
DMSO.....dimethyl sulfoxide
dppb.....bis(diphenylphosphino)butane
dppe.....bis(diphenylphosphino)ethane
dppm.....bis(diphenylphosphino)methane
dppp.....bis(diphenylphosphino)propane
DUPHOS.....1,2-bis-2,5-(dimethylphospholano)benzene
HMDS.....hexamethyldisilazane
HMPA.....hexamethylphosphoramide
Imid.....imidazole
m-CPBA.....3-chloroperoxybenzoic acid
Ms.....methanesulfonyl
PDC.....pyridinium dichromate
PG.....protective group
Ph.....phenyl
TBAF.....tetra-*n*-butylammonium fluoride
TBS.....*tert*-butyldimethylsilyl
TES.....triethylsilyl
Tf.....trifluoromethanesulfonyl
TFE.....trifluoroethanol
THF.....tetrahydrofuran
TIPS.....triisopropylsilyl
TMS.....trimethylsilyl
Tol.....*p*-tolyl
Ts.....*p*-toluenesulfonyl

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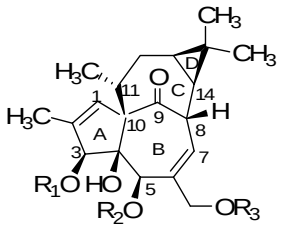
1. Synthetic Efforts Towards Ingenol

1.1 Introduction to Ingenol

1.1.1 Isolation and Structure Determination

Plants and plant materials of species in the family *Euphorbiaceae* (spurge family) have been known to be poisonous to human beings for centuries. *Euphorbia*, the largest genus (ca. 1600 species) of the family *Euphorbiaceae* (290 genera) live in most parts of the world. Although they are often held responsible for the poisoning of farm animals and are used as constituents of arrow poisons, many species are used in folk medicine as drugs to treat cancers, tumors and warts.[1,2] In 1968, Hecker isolated a new irritant and cocarcinogenic hexadecanoic acid monoester **1.1a** (Figure 1.1) with the molecular formula $C_{36}H_{58}O_6$ from the latex of *Euphorbia* ingens and from the seed oil of *Euphorbia lathyris*.[3] Mild base catalyzed transesterification of this ester yielded the biologically inactive parent diterpene alcohol **1.1b** with molecular formula $C_{20}H_{28}O_5$. When this diterpene alcohol was treated with acetic anhydride in pyridine, a crystalline triacetate **1.1c** was obtained. The constitution and conformation of this triacetate **1.1c** was determined by X-ray analysis.[4a,b] The absolute configuration was determined by measuring the intensity ratios of Bijvoet pairs, for which the calculated anomalous effects were strongest. Chrome radiation was used, the oxygen atoms being the only anomalous scatters.[4a,c]



1.1

1.1a $R_1=CO(CH_2)_{14}CH_3$; $R_2=R_3=H$
1.1b $R_1=R_2=R_3=H$
1.1c $R_1=R_2=R_3=COCH_3$

Figure 1.1 Ingenol and derivatives

Compound **1.1a** is a member of ingenanes, a group of highly oxygenated tetracyclic diterpene esters that share a common ingenol core. Central to the novel structure of ingenane skeleton is highly strained *trans*-intrabridgehead bicyclo[4.4.1]undecane BC ring system, also referred to as "inside-outside" ring system.[5]

Bridged bicyclic systems can exist as three different stereoisomers: an out-out isomer, an in-in isomer and an in-out isomer (Figure 1.2).[6] Usually the in-in isomer is most unstable because of the severe repulsive interaction between the inside atoms. However, the energy difference between in-out and out-out isomers varies depending on the system. In the ingenane system, the in-out isomer is generally more strained than the out-out isomer.

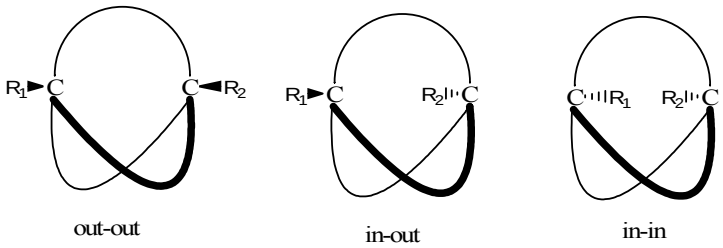


Figure 1.2 Inside-outside stereochemistry

Funk and coworkers performed MM2 calculations to compare the strain energy between in-out and out-out isomers of some bridge bicyclic compounds (Figure 1.3).[7] In-out bicyclo[4.4.1]undecan **1.2** is more strained than its out-out isomer **1.3** by 6.3 kcal/mol (Figure 1.3), whereas the corresponding in-out and out-out bicyclo[4.4.1]undecan-7-one conformers (**1.4** and **1.5**) differ in strain energy by 3.3 kcal/mol. Ingenol itself **1.1b** is more strained than its C-8 epimer (isoingenol) **1.6** by 5.9 kcal/mol. This energy difference underscores the synthetic challenge of correctly establishing the in-out configuration of ingenol.

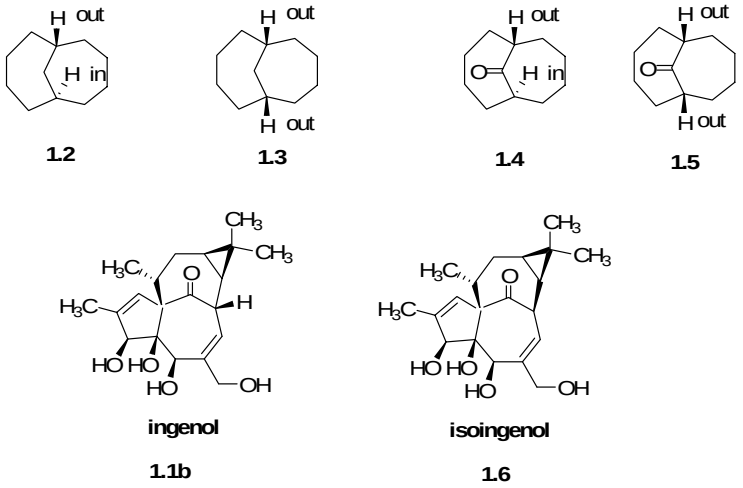


Figure 1.3 Energy difference between in-out and out-out ingenane isomers

1.1.2 Mechanism of Action

Biological studies show that ingenanes have a broad range of biological activities. Some derivatives have tumor-promoting[1] properties while others have powerful antileukemic[2] or anti-HIV[8] activities.

Studies have been carried out in efforts to explain the mechanism of action of the tumor promoting substances on a molecular basis. Although the mechanism of action of

ingenanes is not completely clear, studies have attributed the activity to their ability to activate protein kinase C (PKC).[9,10] Protein kinase C is a phosphorylation enzyme that is involved in many cellular functions including cell growth, differentiation and apoptosis.[11] The enzyme is normally quiescent and cytoplasmic, but upon activation it becomes associated with the inner leaflet of plasma membranes. Binding to the plasma membrane is transient, and is importantly regulated by the association of the hydrophobic intracellular secondary messenger (S)-diacylglycerides (DAGs) (Figure 1.4). The simultaneous binding of the hydrophobic DAGs to PKC and the lipid bilayer enhances the association of PKC to the membrane by hydrophobic interactions.[12] Some other natural products were found to be potent surrogates for DAGs even though they are structurally dissimilar to ingenol. These compounds include phorbol esters, debromoaplysiatoxin and teleocidin (Figure 1.4).

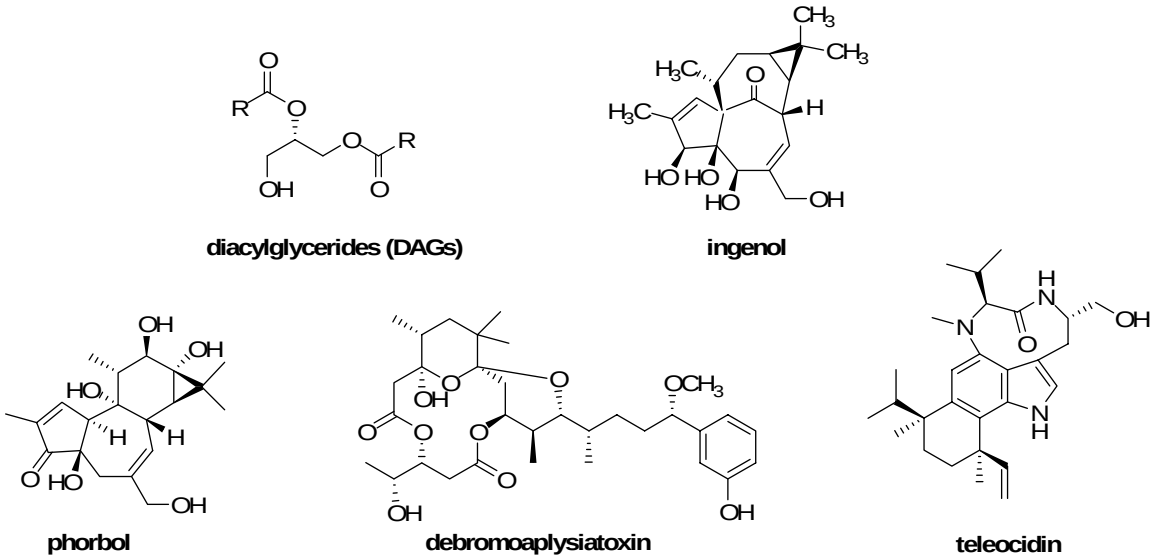


Figure 1.4 Protein kinase C activators

Kishi and Rando came up with a "Three-point Model" to explain the PKC activation by these structurally diverse compounds (Figure 1.5).[7] This model argues that molecules with three hydrophilic atoms separated by approximately 6 Å can activate PKCs. In addition, a hydrophobic moiety is also required for membrane docking. For example, the hydrophobic acyl chains of ingenol esters seem to play a very import role in PKC activation by translocating PKC to the plasma membrane from the cytoplasm via hydrophobic interactions. In an asssy to bind PKC-α, ingenol 3-monobenzoate has yielded a K_i of 0.15 nm. Without the acyl chain, ingenol itself is only a weak PKC activator with a K_i of 30 μM.[9]

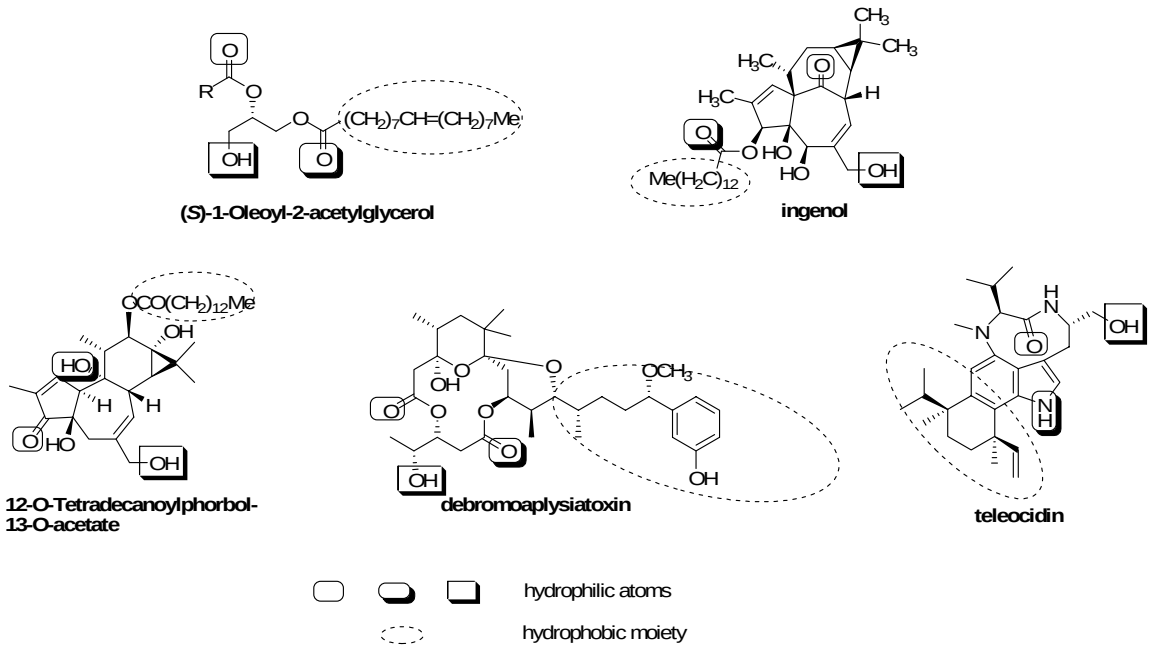
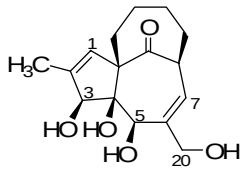


Figure 1.5 Kishi's three-point model to explain the PKC activation on molecular basis

1.1.3 Prior Synthetic Strategies to Ingenol

Ingenol's structure, which possesses four carbocyclic rings and eight stereogenic centers, is as intriguing as its biological activity. This unusual structure and biological activity make ingenol an interesting synthetic target.[13] The highly strained *trans* intrabridgehead is a major challenge causing some workers to initially synthesize the less strained isoingenol epimers.[14,15] Paquette and coworkers synthesized the highly functionalized *iso*-ingenoid **1.7** (Figure 1.6) with the *cis*-intrabridgehead (C-8/C-10) stereochemical relationship; however, esters of **1.7** showed no biological activity associated with the naturally occurring ingenane esters.[14] These results indicate the importance of the *trans*-intrabridgehead stereochemistry for the biological activity of the ingenanes.



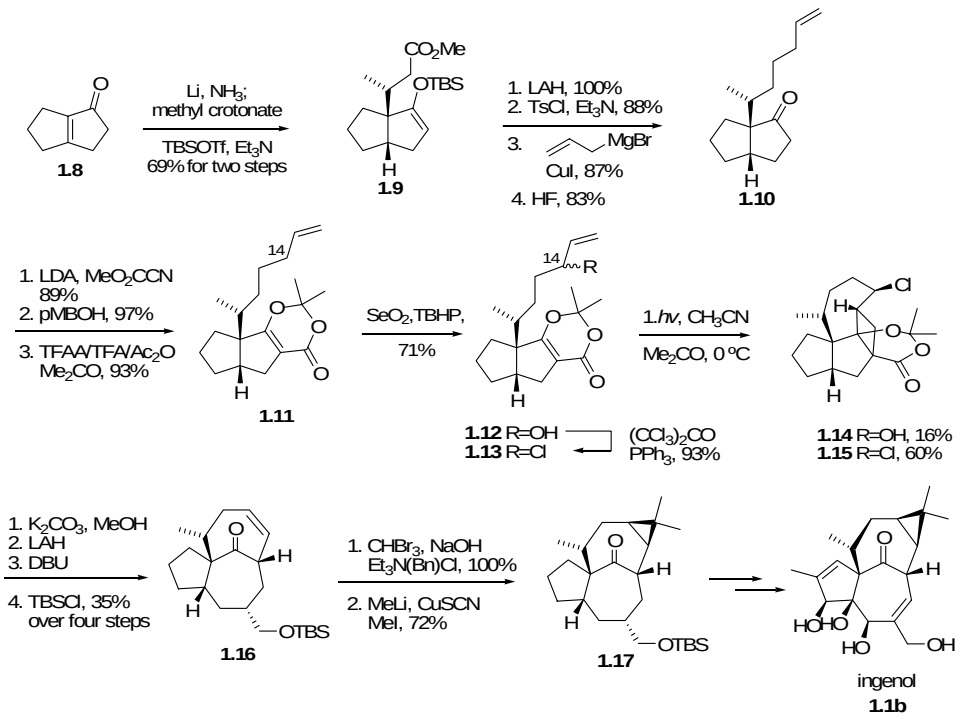
1.7

Figure 1.6 *Iso*-ingenoid synthesized by Paquette and coworkers

To date there are five different approaches giving the crucial *trans* 7,7- bicyclic ring system, among which three approaches have been used to finish the total synthesis.[16,17b, 18]

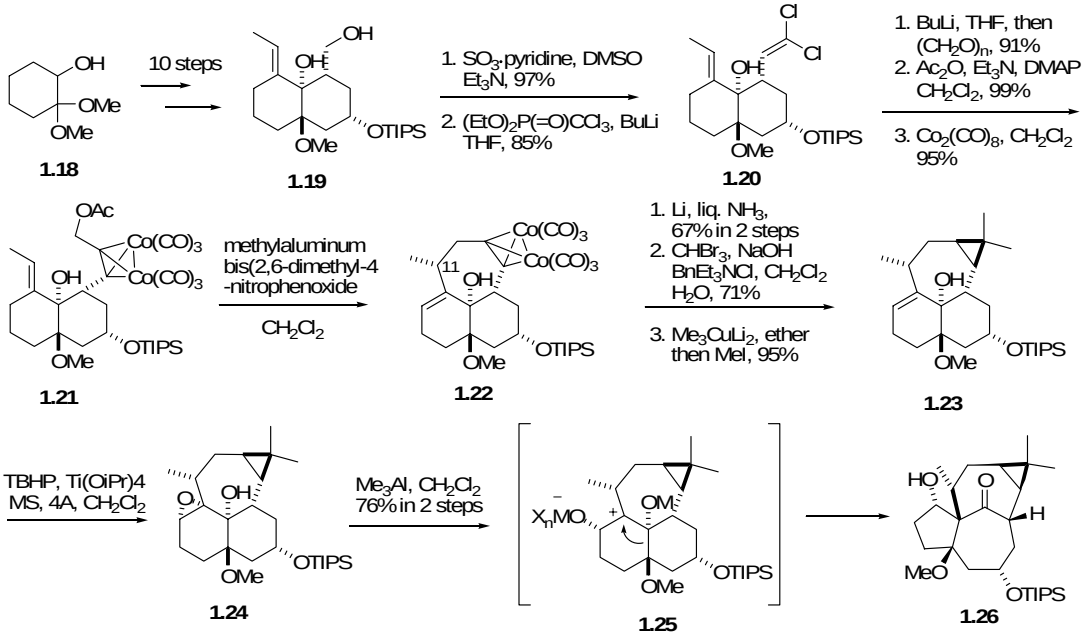
1.1.3.1 Winkler's Ring Expansion Strategy

After nearly two decades of pursuit,[19] Winkler accomplished the first total synthesis in 2002,[16] solving the *trans*-intrabridgehead problem with a remarkably short route from enone **1.8** *via* a novel intramolecular dioxolenone photocycloaddition (Scheme 1.1).[19] The conjugate reduction/Michael reaction led, after silylation of the intermediate ketone, to the formation of **1.9**. Reduction of the ester, elongation of the side chain and desilylation provided ketone **1.10**. Dioxenone chromophore **1.11** was obtained from **1.10** through carboxylation with Mander's reagent, ester exchange and dioxenone formation. A hydroxyl group was introduced on C-14 through allylic oxidation to give alcohol **1.12**, which was converted to chloride **1.13** in one step. **1.12** and **1.13** were subjected to photoaddition conditions to provide cyclobutane **1.14** and **1.15**. Fragmentation of **1.15**, followed by reduction of the resulting ester, elimination of the chloride with DBU, and silylation of the primary alcohol, gave ketone **1.16** with the key *trans*-intrabridgehead ring system. The olefin was strategically set in such a way that it was conveniently used to form gem-dimethylcyclopropane ring with facial selectivity via carbene addition and reductive methylation to give TBS ether **1.17**. Winkler and coworkers prepared the tetracycle **1.17** in 18 steps, on which the polyol functionality was installed in another 25 steps to complete the first total synthesis of ingenol in 43 steps from **1.8**.



Scheme 1.1 Winkler's ring expansion approach to ingenol

1.1.3.2 Kuwajima's Cyclization-Rearrangement Strategy

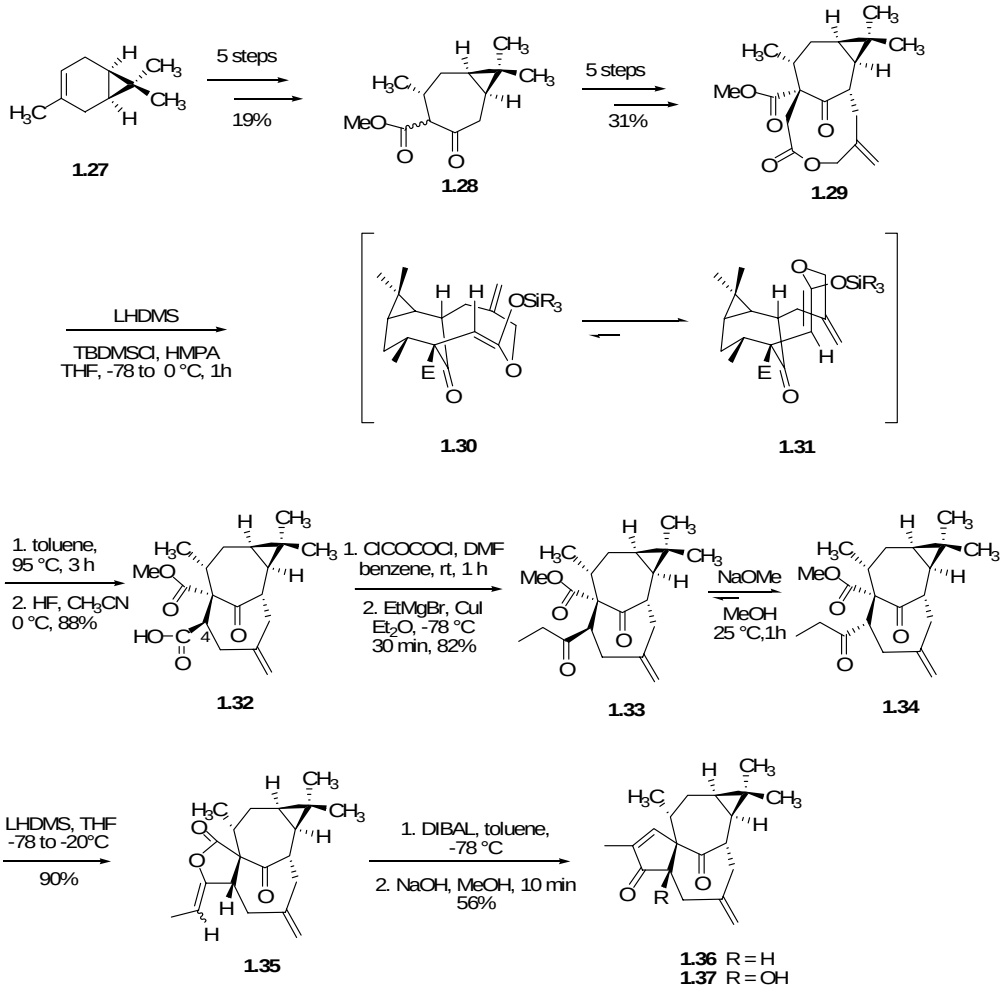


Scheme 1.2 Kuwajima's cyclization-rearrangement approach to ingenol

Kuwajima and coworkers prepared the in-out tetracycle through a Nicholas-pinacol strategy. Diol **1.19** was made from commercially available alcohol **1.18** in 10 steps. Dichloroolefin **1.20** was obtained from diol **1.19** *via* oxidation and Horner-Emmons reaction. Treatment with *n*-BuLi generated the acetylide anion, which reacted with formaldehyde to elongate the side chain. Acetylation of the resulting alcohol followed by complexation of the alkyne using $Co_2(CO)_8$ gave Nicholas precursor **1.21**. Under Lewis acidic conditions, removal of the acetate group resulted in a stabilized cation which was attacked by the neighbouring olefin followed by elimination to give alcohol **1.22** with the desired stereochemistry set on C11. Birch reduction removed the cobalt species to provide an olefin from which the *gem*-dimethylcyclopropane ring was

installed stereoselectively through dibromocyclopropanation and methylation. Stereoselective epoxidation of the olefin **1.23** followed by treatment with trimethylaluminum promoted a pinacol-type rearrangement to generate **1.26** with the ingenane skeleton. Kuwajima eventually finished the total synthesis in 45 steps and 0.1% overall yield. More recently, Cha also constructed the tetracyclic core of ingenol using a similar pinacol-type rearrangement of an epoxy alcohol as the key step.[20]

1.1.3.3 Funk's Ring Contraction Strategy

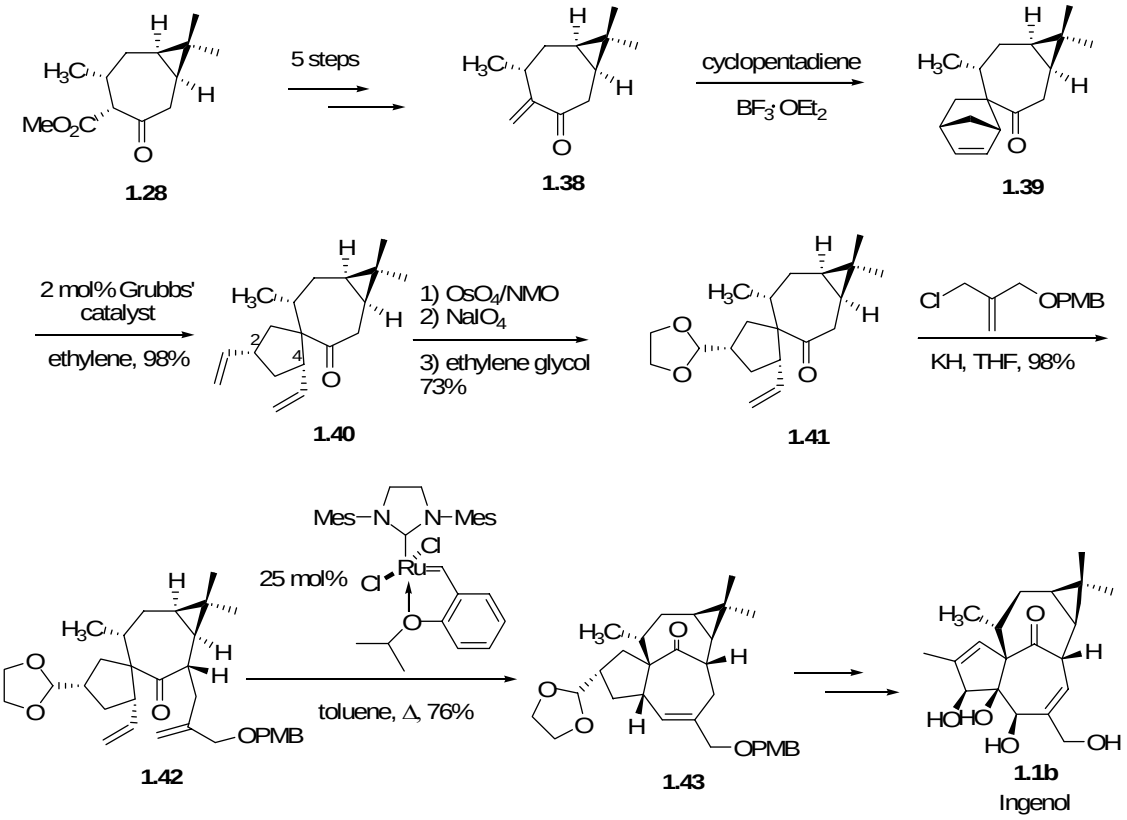


Scheme 1.3 Funk's ring contraction approach to ingenol

Funk reported the synthesis of compound **1.37** containing the tetracyclic skeleton of ingenol (Scheme 1.3).[21a] Initially, β-keto ester **1.28** was prepared from (+)-3-carene **1.27** in five steps and 19% overall yield,[21b] followed by formation of lactone **1.29** in 5 steps and 31% overall yield. The key transformation in this route is an Ireland-Claisen rearrangement of the silyl ketene acetal **1.31** to generate carboxylic acid **1.32** in 88% yield. It was predicted that a *chairlike* transition state arising from **1.31** was possible due to one sigmatropic atom being exocyclic to the macrocyclic ring. Obtaining compound **1.32** after desilylation as the major diastereomer confirmed the prediction and demonstrated that structure **1.31** was the preferred transition state conformation. It was rationalized that this may be a consequence of a through-space destabilizing interaction between the ketone and enol ether oxygen atoms in conformer **1.30**.[21a] The major diastereomer **1.32** possesses the BCD tricyclic ring system and the all-important *trans*-intrabridgehead stereochemistry; however, the stereochemistry at C(4) was β instead of the desired α. The problem was partially solved by converting the carboxylic acid **1.32** to ketone **1.33** and then subjection of this ketone to basic conditions gives a 1:1 mixture of **1.33** and **1.34**. The lithium enolate of ketone **1.34** (1.4 equiv of LHMDS, THF, -78 °C to –20 °C, 15 min) afforded only the product of *O*-acylation enol lactone **1.35**, which was converted to **1.36** *via* reduction and cyclization. Thus, the first tetracyclic ingenol skeleton was achieved in 13 steps from (+)-3-carene. Furthermore, alcohol **1.37** with the correct stereochemistry was made in two additional steps.[21a]

1.1.3.4 Wood's Ring-Closing Metathesis Strategy

Funk's strategy of attaching side chains on intermediate **1.28** is an inspiration for some of the following synthetic efforts, among which, is Wood's strategy to construct the tetracyclic skeleton of ingenol (Scheme 1.4).[22] Starting with Funk's intermediate **1.28**, Wood prepared the α-methylene ketone **1.38** in five steps. This ketone was subjected to a Diels-Alder reaction to provide intermediate **1.39**. Ring-opening metathesis of **1.39** generated diene **1.40**, followed by regioselective dihydroxylation of the C(2) olefin. This diol was subjected to the oxidative cleavage conditions providing the corresponding aldehyde, which was protected as the acetal **1.41**. Alkylation of **1.41** generated diene **1.42**, which underwent a ring-closing metathesis when treated with Hoveyda-Grubbs 2nd generation catalyst gave the tetracyclic compound **1.43** containing the desired "in-out" structure. The total synthesis was completed in 37 steps.[18]



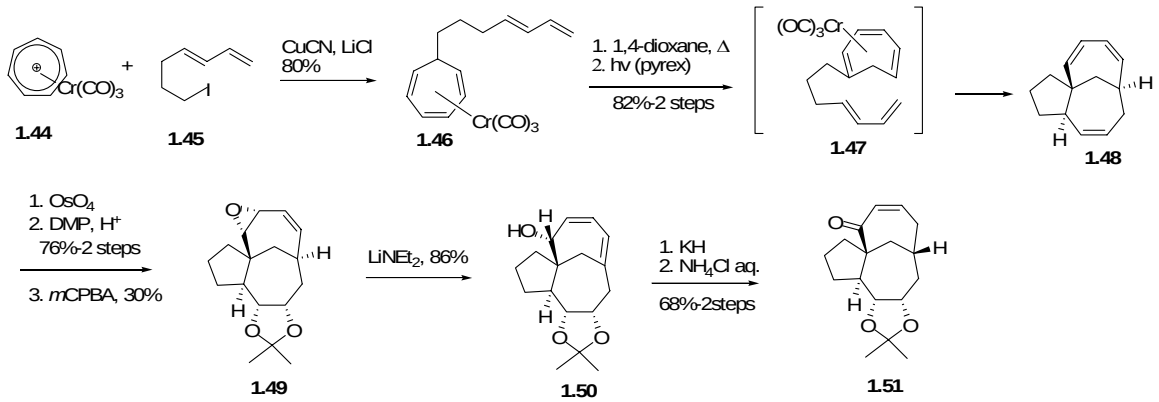
Scheme 1.4 Wood's ring-closing metathesis approach to ingenol

Similarly, Kigoshi has also used ring-closing metathesis to construct a tetracyclic compound with the ingenane skeleton[23] and reported a formal synthesis of ingenol in 2004.[24]

1.1.3.5 Rigby's 1,5-H Sigmatropic Approach

Rigby has successfully constructed the "in-out" ingenane ring system through an alkoxide accelerated 1,5-H shift.[25] Treatment of commercially available **1.44** with the organocopper complex of iodide **1.45** gave compound **1.46**.[24b] Thermolysis of iodide **1.45**

induced a series of 1,5-H shifts ultimately resulting in diene **1.47**, whereupon irradiation afforded the tricyclic compound **1.48**. Dihydroxylation with OsO_4 occurred at the isolated olefin and the resulting diol was protected as an acetonide, which upon epoxidation gave **1.49**. Under basic conditions, isomerization occurred to provide alcohol **1.50**, which was treated with potassium hydride to generate an alkoxide, promoting 1,5-H shift to give α,β–unsaturated ketone **1.51**. The 1,5-H shift occurred suprafacially and the hydrogen added to the β-face of the molecule to give the desired "in-out" stereochemistry. This is an interesting example of how the in-out isomer can be obtained from the out-out isomer.

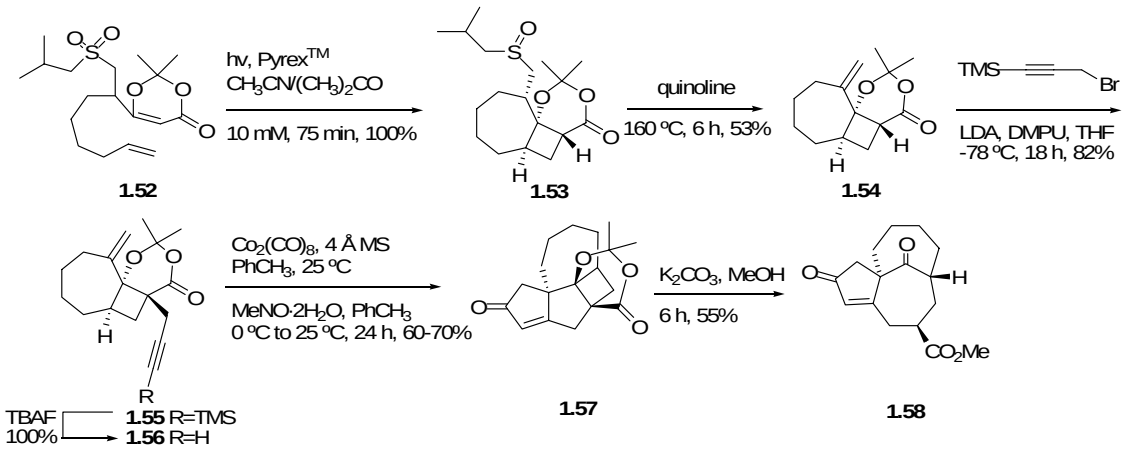


Scheme 1.5 Rigby's 1,5-H shift approach to ingenol

1.1.4 Retrosynthetic Analysis Utilizing Pauson-Khand Approach

1.1.4.1 Winkler's Pauson-Khand Approach to Ingenol

Recently, Winkler and coworkers reported preparation of tricycle **1.58** with *cis*-intrabridgehead stereochemistry using a Pauson-Khand reaction. Photoaddition of diene **1.52** yields cyclobutane sulfone **1.53** with a *cis*-fused bicyclo[5.2.0]nonane moiety. The exocyclic olefin **1.54** was obtained by heating **1.53** in quinoline. Alkylation of **1.54** followed by desilylation provided Pauson-Khand precursor **1.56** which underwent the Pauson-Khand reaction in the presence of $Co_2(CO)_8$ and NMO. Retro-aldol fragmentation gave the diketo methyl ester **1.58** with the undesired *cis*-intrabridgehead stereochemistry.



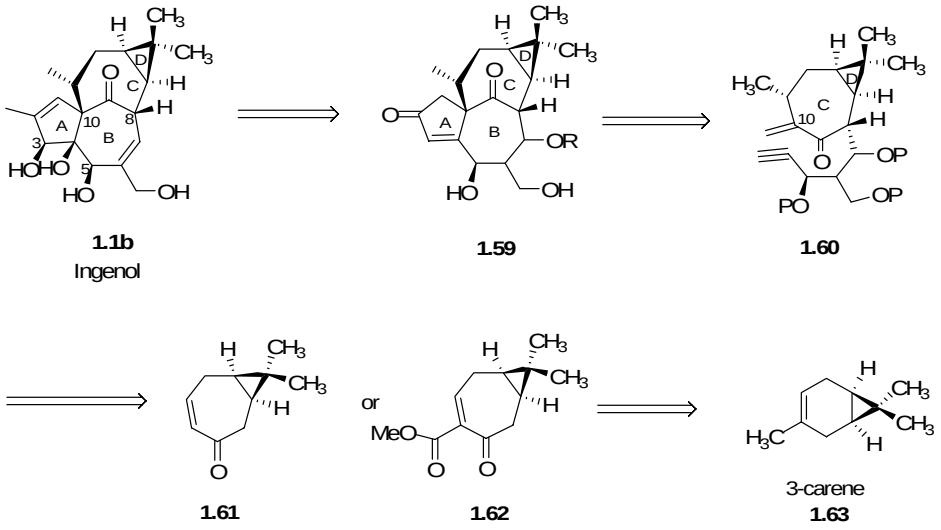
Scheme 1.6 Winkler's Pauson-Khand approach to ingenol

1.1.4.2 Our Synthetic Strategy Using a Pauson-Khand Reaction

Among ingenol's many challenges, the *trans* or in,out-7,7 bicyclic ring system is the most impressive. The strain imposed by the *trans*-fused bicyclic system has been a

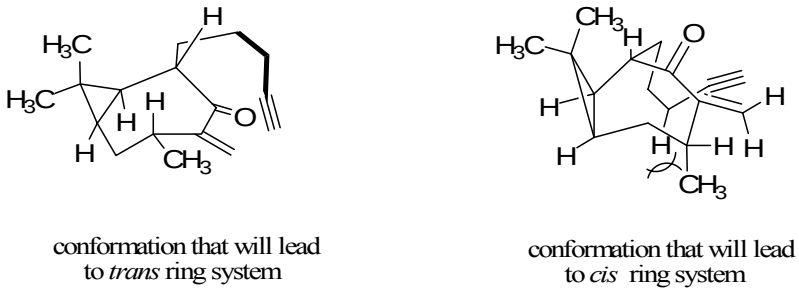
complicating factor to deal with in every synthetic approach reported to date. Concern existed about stability of the strained intermediate once formed, the in,out-7,7 bicyclic ring system was introduced late in the synthetic sequence, thus minimizing the reaction conditions to which this reactive intermediate is exposed.

The synthetic strategy is summarized in Scheme 1.7. First, retrosynthetic simplification of ingenol **1.1b** converts it to ketone **1.59**. In the synthetic direction, a hydroxyl directed dihydroxylation of the olefin in ketone **1.59**, followed by addition of methyl magnesium bromide to the carbonyl in the 5-memberd rings and subsequent elimination of the tertiary alcohols in the 5- and 7-membered rings was envisioned to give the desired ingenol **1.1b**. A judicious choice of protecting groups would allow the successful transformation of the corresponding ether **1.59** to the highly oxygenated ingenol **1.1b**. The key feature of intermediate **1.59** is the cyclopentenone moiety, which can be generated from the Pauson-Khand reaction.[26] It was thus envisioned that use of an intramolecular Pauson-Khand reaction with **1.60** would form the A and B ring of **1.59** in one step.



Scheme 1.7 Retrosynthetic analysis of ingenol utilizing Pauson-Khand approach

The formation of this strained structure using this approach may be possible since the metal could function as a template to bring the two reactive components together, possibly close enough to facilitate carbon-carbon bond formation. Furthermore, it was predicted based upon the examination of models that the alkyne would approach the alkene from the same face as the dimethylcyclopropane moiety to afford the desired *trans* bicyclic stereochemistry (Figure 1.3). The alternative approach, involving the alkyne coming in from the opposite face of the dimethylcyclopropane moiety to give the *cis* bicyclic stereochemistry, was predicted to be less likely due to severe steric interactions (Figure 1.4).



conformation that will lead to *trans* ring system

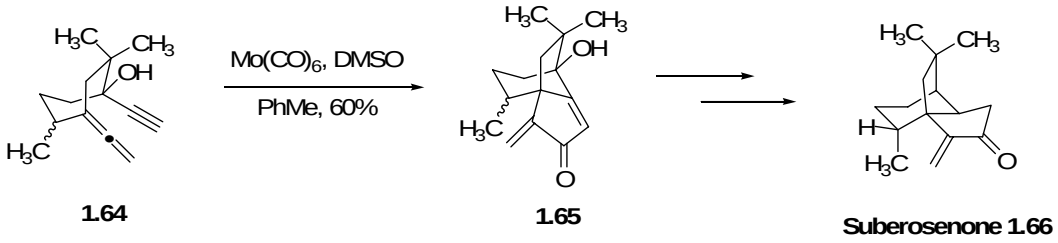
conformation that will lead to *cis* ring system

Figure 1.7 Conformations that will lead to *trans* and *cis* ring systems

Next, it was reasoned that the Pauson-Khand substrate **1.60** could be obtained from either **1.61** or **1.62,**[10b] each of which possesses the cyclopropane D ring and an α,β-unsaturated ketone. These intermediates could be used to stereoselectively introduce a methyl group on C-11 and an alkynyl side chain on C-14 via 1,4-addition and alkylation, respectively. Both compounds **1.61**[27] and **1.62**[21b] have been reported in previous work on ingenol and both can be made from commercially available (+)-3-carene **1.63**.

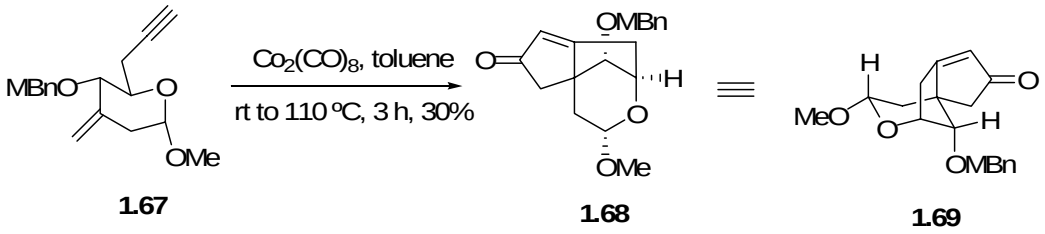
1.1.4.3 Pauson-Khand Reaction in Preparation of Bridged Compounds Synthesis

Precedent for synthesis of bridged compounds using the Pauson-Khand reaction is found in the Brummond laboratory. For example, the intramolecular Pauson-Khand reaction was used to construct the strained skeleton of the natural product suberosenone (Scheme 1.8).[28] Compound **1.65** was formed in 60% yield when allenyne **1.64** was treated with $Mo(CO)_6$ and DMSO and stirred in refluxing toluene.



Scheme 1.8 Construction of suberosenone skeleton utilizing Pauson-Khand reaction

Pauson-Khand reactions are not frequently used to build strained ring systems, nor are *exocyclic* olefins as prevalent, but they do exist.[29] Borodkin and coworkers prepared tricyclic compound **1.68** in 30% yield from 1,6-enyne **1.67** using a dicobalt octacarbonyl mediated Pauson-Khand reaction (Scheme 1.9).[29c] Simultaneous formation of the strained tricyclic ring system and installation of the quarternary center demonstrate the power of the Pauson-Khand reaction, but certainly are testing its limit based on the moderate yield.

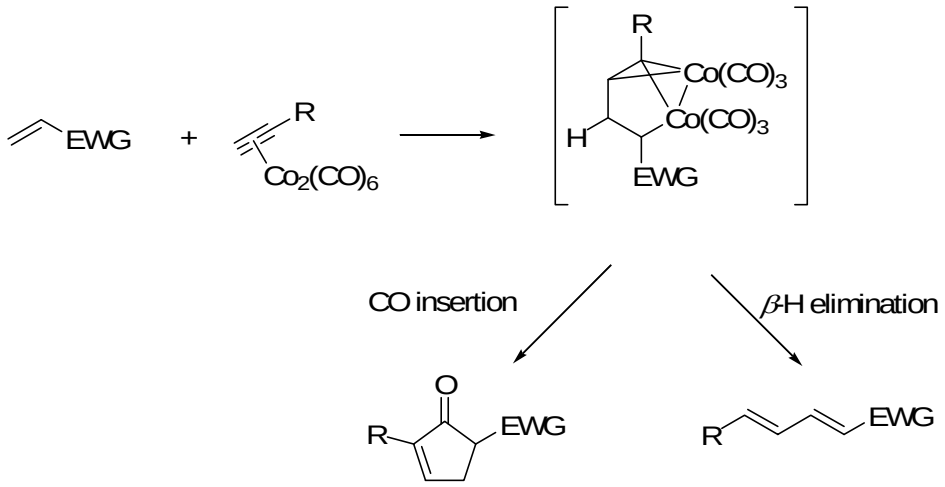


Scheme 1.9 Pauson-Khand reaction involving an exocyclic olefin

1.1.4.4 Pauson-Khand Reaction Involving Electron-Deficient Olefin

The Pauson-Khand reaction in our strategy (Scheme 1.10) also involves an electron-deficient olefin, namely an α, β–unsaturated enone. Regarding the current scope

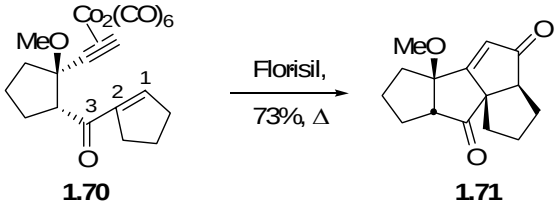
of the Pauson-Khand reaction, the functional group compatibility is very high for the substitution at the alkyne, in which both electron-donating and electron-withdrawing functional groups are well tolerated. On the other hand, it is widely accepted since the pioneering work of Pauson and Khand that electron-deficient alkenes such as α, β–unsaturated aldehydes, ketones, esters and nitriles undergo the Pauson-Khand reaction only with difficulty. [30] It was observed that the key cobaltacycle intermediate preferentially undergoes a β-hydride elimination process (Scheme 1.10), leading to the observed 1,3-diene rather that the carbonyl insertion step required for the formation of cyclopentenone product.[31]



Scheme 1.10 Competing pathway in Pauson-Khand reaction involving electron-deficient olefin

The absence of hydrogens at the β–position prevents the participation of the β–hydrogen elimination pathway, which can improve the likelihood of Pauson-Khand reaction. For example, Caple et al. showed the conformationally restricted 1-en-6-yn-3-

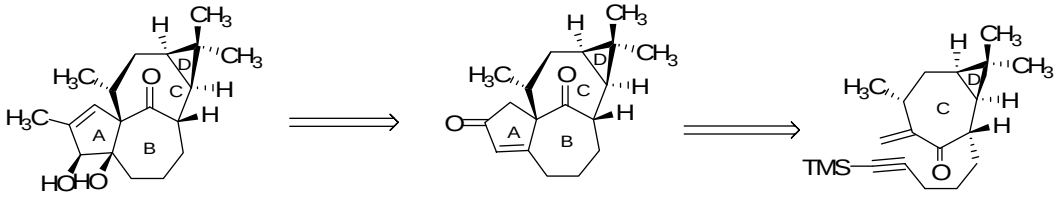
one **1.70** underwent intramolecular Pauson-Khand reaction in the presence of Florisil as promoter, affording the corresponding tetracyclic adducts **1.71** in 73% yield (Scheme 1.11).[32] It is worth noting that β–hydrogen elimination should not be a factor in the present synthetic strategy (Scheme 1.5) since there is no hydrogen on C-10.



1.70 **1.71**

Scheme 1.11 Caple's example of intramolecular Pauson-Khand reaction involving an alkyne and an enone

Therefore, this Pauson-Khand reaction was examined in a model study (Scheme 1.12).



1.72
Ingenol model

1.73 **1.74**

Scheme 1.12 Retrosynthetic analysis of ingenol model

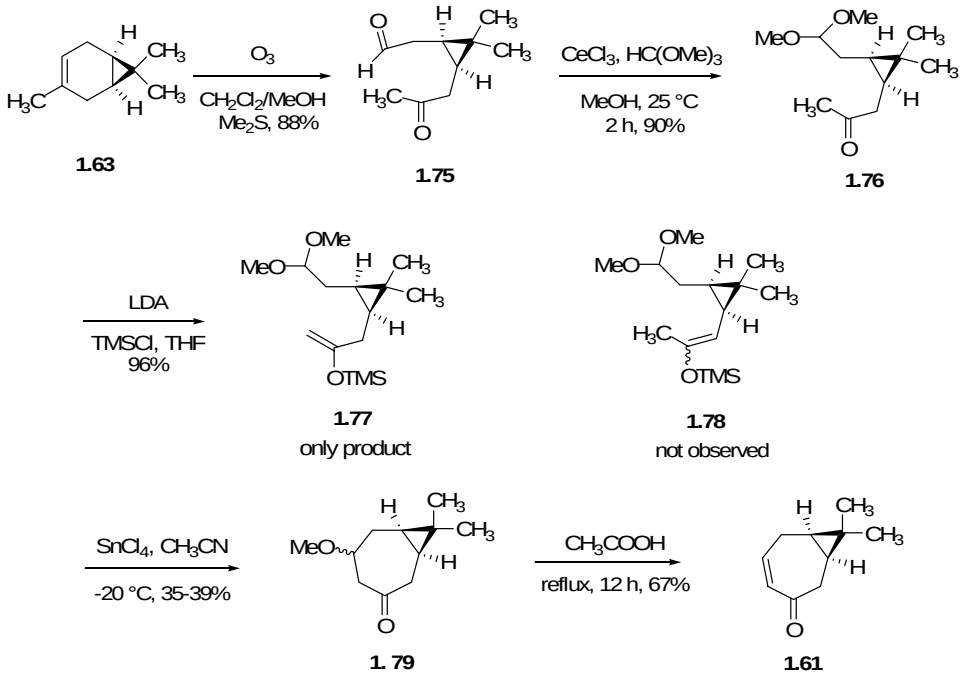
In order to quickly establish the viability of the somewhat risky Pauson-Khand reaction proposed within, compound **1.72** was considered to be an appropriate model to prepare since it possesses the tetracyclic skeleton of ingenol (Scheme 1.12). Thus, **1.74**

would be a suitable substrate to test the [2+2+1] cycloaddition reaction since it possesses the functionality necessary to effect the cycloaddition and to test the stereoselectivity. Compound **1.74** was therefore prepared (Scheme 1.13).

1.2 Results and Discussion

1.2.1 Preparation of Pauson-Khand Reaction Precursors

The synthesis of Pauson-Khand precursor **1.74** was approached in the following manner. Enone **1.61** was prepared by following the procedure reported by Yamakawa (Scheme 1.13).[27] Ozonolysis of racemic 3-carene **1.63** afforded the keto aldehyde **1.75** in 88% yield, which was purified by distillation. Next, aldehyde **1.75** was protected in the presence of the ketone to form acetal **1.76** by the Luche procedure.[33] Column chromatography followed by Kugelrohr distillation (147 °C/2mm Hg) gave keto acetal **1.76** in 90% yield. The ^{1}H NMR spectrum of this compound matched that reported by Yamakawa.[27] Slow addition of compound **1.76** to LDA (1.5 equiv) afforded the desired enolate, which was trapped with chlorotrimethylsilane. After Kugelrohr distillation (100-103 °C/ 2 mm Hg) of the crude product, enol ether **1.77** was obtained as the only product in 96% yield. Yamakawa reported formation of regioisomer **1.78**.



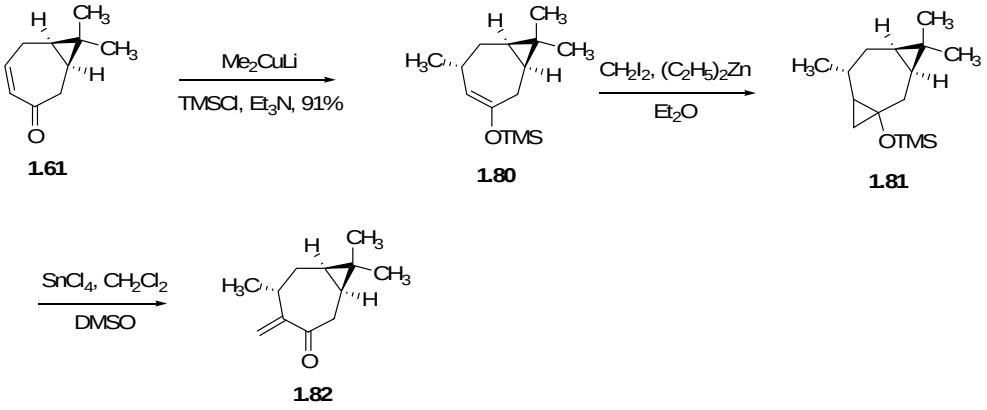
Scheme 1.13 Preparation of enone **1.61**

The purified ether **1.77** was then treated with tin tetrachloride in acetonitrile at –20 °C, wherein it underwent a Mukaiyama type aldol reaction to give the cycloheptanone **1.79** in 35-39% yield after column chromatography. Two singlets corresponding to the methyl ethers at δ = 3.33 and 3.35 ppm in ^{1}H NMR spectrum indicated it was a 2.5:1 mixture of diastereomers. Since these diastereomers will provide the same elimination product, they were not separated. Several attempts to improve the yield of the aldol condensation were not satisfying. Since only the feasibility of the synthetic route was under examination, the next step was performed without further optimization.

The methoxy group of **1.79** was eliminated by refluxing in acetic acid to provide the cycloheptenone **1.61** in 67% yield. The ^{1}H NMR spectrum of compound **1.61**

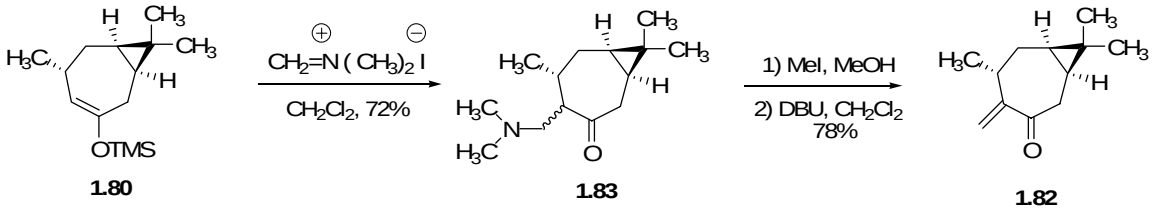
compared favorably to that reported by Yamakawa.[27] Overall, compound **1.61** was made with this five-step procedure in 15% overall yield on a two-gram scale.

Next, we need to insert the α-methylene moiety and the alkynyl side chain on enone **1.61** to prepare the Pauson-Khand reaction precursor **1.74**. The α-methylene moiety was added first, followed by the introduction of the alkynyl side chain (Scheme 1.14). Cycloheptenone **1.61** was treated with lithium dimethylcuprate to give a 1,4-addition product that was not isolated, but its enolate was trapped *in situ* with chlorotrimethylsilane to provide the silyl enol ether **1.80** as the only product in 96% yield. Based upon literature precedent performed on simpler substrates,[34,35] it was reasoned that the α-methylene moiety could be introduced in the following manner. Treatment of the silyl enol ether **1.80** with diiodomethane and diethylzinc should afford the corresponding cyclopropane **1.81**. Treatment of **1.81** with tin tetrachloride would then give the desired α-methylene cyclopentenone **1.82**. All attempts to effect this transformation as discussed in the literature (for much simpler substrates) led to successful formation of the compound **1.81** in 84% yield. However, treatment of compound **1.81** to tin tetrachloride led to low yields (38-46%) of the desired α-methylene cycloheptenone **1.82**. Two singlets at δ = 5.70 and 5.14 ppm in the ^{1}H NMR spectrum indicated the formation of the olefin. Based upon the low conversion of **1.81** to **1.82**, other methods to introduce the α-methylene moiety were tried.



Scheme 1.14 Preparation of α-methylene cycloheptenone **1.82**

Eschenmoser's salt[36] was used to introduce the *α*-methylene moiety. There are many reports showing that Eschenmoser's salt can be used to introduce an α-methylene moiety in complicated systems, and the reaction conditions are generally mild.[37]

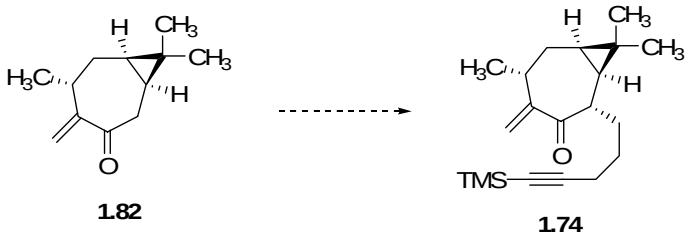


Scheme 1.15 Alternative approach to α-methylene cycloheptenone **1.82**

To this end, silyl enol ether **1.80** was treated with *N*,*N*-dimethylmethylene ammonium iodide at room temperature and stirred overnight to generate amine **1.83** in 72% yield (Scheme 1.15). A new polar spot on TLC strongly suggested that amine formation had occurred. After silica gel chromatography, this was shown to be the case

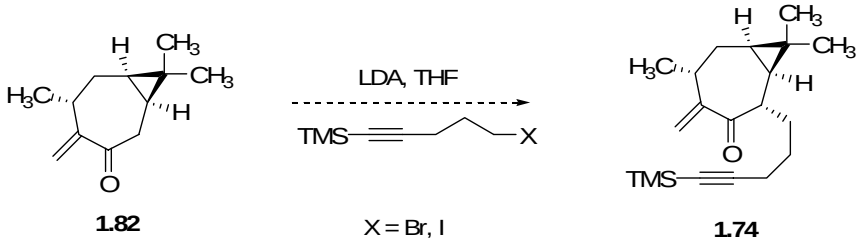
based upon disappearance of the olefinic proton resonance (δ = 4.70 ppm) and appearance of a singlet (6H, δ = 2.19 ppm) in the ^{1}H NMR spectrum. The purified amine **1.83** was then treated with iodomethane in methanol and the reaction was stirred overnight to give the quaternary ammonium salt. The salt was not purified, but simply concentrated to give a yellow solid. This solid was dissolved in methylene chloride and treated with diazabicycloundecene (DBU). Overnight stirring of the reaction provided the desired product **1.82** in 78% yield after purification by column chromatography. The overall yield from **1.80** to **1.82** was 56%.

The next step was to stereoselectively attach the alkynyl side chain to the methylene ketone **1.82** (Scheme 1.16). The difficulty encountered in obtaining the alkylation product **1.74** was not fully anticipated.



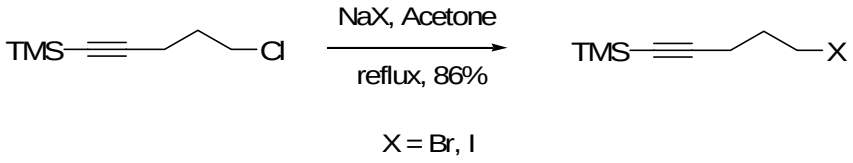
1.82 **1.74**

Scheme 1.16 Attachment of alkynyl side chain to methylene ketone **1.74**



1.82 **1.74**

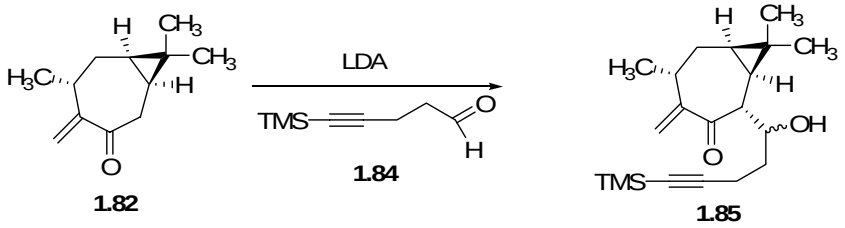
Scheme 1.17 Difficult alkylation of methylene ketone **1.82**



Scheme 1.18. Formation of alkyl iodide using Finkelstein reaction

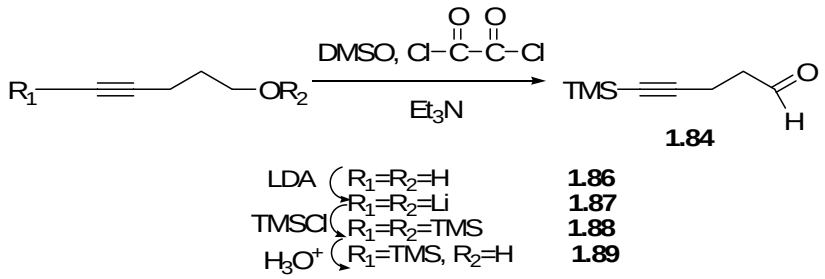
First, α-methylene cycloheptenone **1.82** was deprotonated with LDA at –78 °C, then the 5-bromotrimethylsilyl-1-pentyne was added (Scheme 1.17). The reaction mixture was stirred for twenty hours (–78 °C to room temperature) and by TLC there was no conversion. When using 5-iodotrimethylsilyl-1-pentyne as alkylating reagent, the reaction did not go as well, albeit these reactions were done in the absence of HMPA. 5-Iodotrimethylsilyl-1-pentyne was prepared using a Finkelstein reaction on the 5-chlorotrimethylsilyl-1-pentyne (Scheme 1.18). 5-Bromotrimethylsilyl-1-pentyne was prepared similarly.

An alternative way to attach the alkynyl side chain was considered. It seemed aldol condensation[38] could serve this purpose (Scheme 1.19).



Scheme 1.19 Alternative way to attach a side chain to **1.82** using an aldol reaction

Aldehyde **1.84** was prepared from commercially available 5-hexyn-1-ol **1.86** (Scheme 1.20). Formation of the dianion **1.87** was effected by adding 2 equiv of LDA. Next, chlorotrimethylsilane was added to give the bis-silyl-protected **1.88**. Subjection of this compound to a hydrolytic work-up gave the alcohol **1.89**.[23b] Oxidation of the alcohol **1.89** using Swern oxidation conditions gave the desired aldehyde **1.84**.[23c]

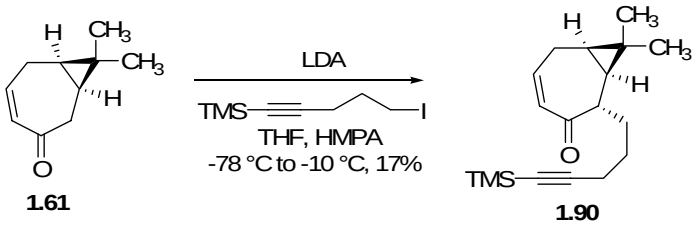


Scheme 1.20 Preparation of aldehyde **1.84**

α-Methylene ketone **1.82** was treated with LDA at −78 °C. The reaction was stirred for 30 min before aldehyde **1.84** was added. Attempted purification using column chromatography did not provide desired product **1.85** in pure form, only a mixture in 21% yield.

Based upon these results, it was concluded that *α*-methylene cycloheptenone **1.82** was not a suitable intermediate to attach an alkynyl side chain.

The next option was to attach the alkynyl side chain prior to the introduction of α-methylene moiety (Scheme 1.21). Naturally, it was thought that alkylation on cyclopentenone **1.61** was possible. The reaction conditions were verified, but the results were not satisfying (Table 1.1).



Scheme 1.21 Alkylation of enone **1.61**

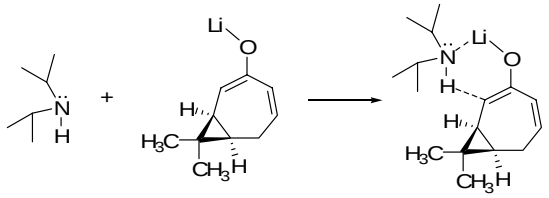
Table 1.1 Attempted alkylation of enone **1.61**

Entry	Conditions	Results
1	LDA, 5-bromotrimethylsilyl-1-pentyne THF, -78 °C to 0 °C	No reaction, recovered 77% of **1.61**
2	LDA, 5-iodotrimethylsilyl-1-pentyne HMPA, THF, -78 °C to -10 °C	10-17% of **1.90** recovered 50% of **1.61**
3	LDA, 5-mesyltrimethylsilyl-1-pentyne, HMPA	Decomposition of the mesylate, **1.61** was recovered
4	NaHMDS, 5-iodotrimethylsilyl-1-pentyne, HMPA, THF, -78 °C to -10 °C	Decomposition of **1.61** **1.90** was not observed

Treatment of compound **1.61** with LDA followed by the addition of 5-bromotrimethylsilyl-1-pentyne afforded only starting material in 77% yield (entry 1, Table 1.1). Next, the enolate of **1.61** was formed upon addition of LDA and this time 5-iodotrimethylsilyl-1-pentyne was added along with HMPA. This resulted in a 10% yield of the desired compound **1.90** (entry 2, Table 1.1), however, this reaction did not go to completion (recovered 50% of the starting material). The leaving group ability of the alkylating agent was increased by preparing the mesylate. Again, the formation of the enolate of **1.61** with LDA and this time trapping with 5-mesylate-1-trimethylsilyl-1-pentyne in the presence of HMPA only resulted in decomposition of the mesylate and compound **1.61** was recovered unchanged (entry 3, Table 1.1). Finally, an alternative base was used to effect the formation of the enolate of **1.61**. Treatment of compound

1.61 with sodium hexamethyldisilazide followed by 5-iodo-1-trimethyl-1-pentyne and HMPA resulted in decomposition of both starting materials.

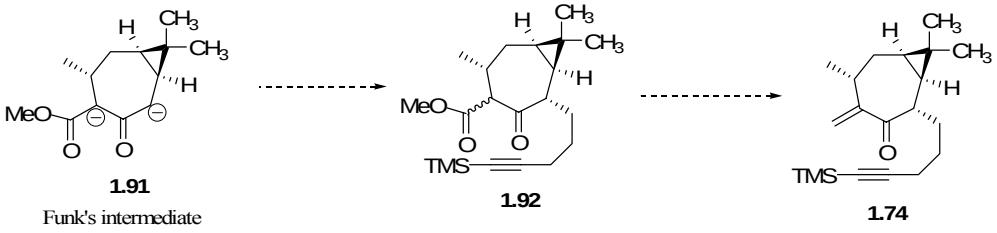
One possible explanation for the low yields of the alkylation reactions on different substrates is the internal proton return (ipr) phenomenon (Scheme 1.22).[39] It is rationalized that after enolate formation, the amine can coordinate the lithium cation and the resulting ammonium like N-H bond is close to the enolate carbon, perhaps within hydrogen bonding distance of the enolate π-system. The addition of an electrophile serves to increase electron demand in the complex, probably by interaction with amine nitrogen electron pairs. This increases the effective acidity of the N-H bond and results in rapid Cα protonation (internal return). This explains why enolate functionalization reactions with electrophiles may produce recovered starting enone compound even when the enolate formation probably is complete.



Scheme 1.22. A possible explanation of low yields of the alkylation-internal proton return

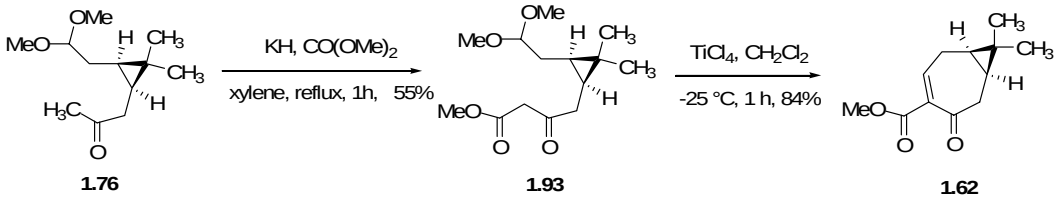
Other substrates that would potentially give better yield of alkylation product were next examined. Funk's intermediate seems to serve that purpose very well. In his approach,[21b] he successfully attached two different side chains on the α and α' position of the ketone moiety of the intermediate **1.91** (Scheme 1.23). It was reasoned that Funk's

intermediate **1.91** could be used to do a monoalkylation, followed by introduction of the α-methylene moiety.



Scheme 1.23 Alkylation using Funk's dianion intermediate

A two-step process of making substrate **1.62** from keto acetal **1.76** was reported by Funk[21b] et al. (Scheme 1.24). They first prepared β-keto ester **1.93** by treating **1.76** with 1.2 equiv of KH and 5 equiv of dimethyl carbonate in xylene at reflux for one hour. The resulting β-keto ester **1.93** was subjected to titanium tetrachloride in methylene chloride at –25 °C to afford cycloheptenone **1.62** *via* an internal aldol reaction. The yields for the two steps were 55% and 84%, respectively.

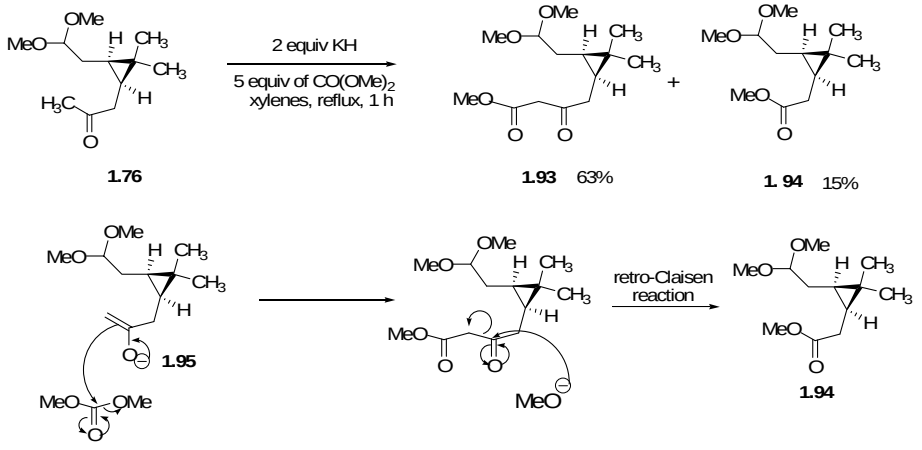


Scheme 1.24 Preparation of cycloheptenone **1.62**

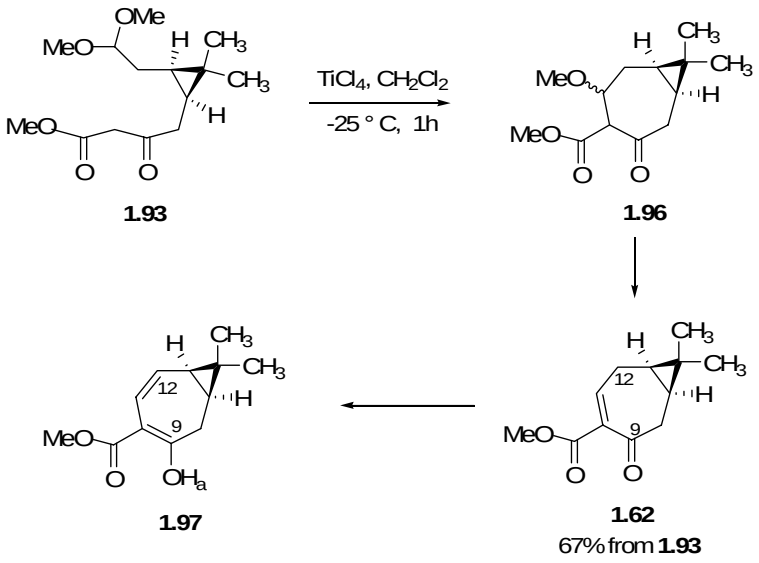
The process was repeated here yielded some observations worth acknowledging. For the preparation of **1.62**, 1.2 equiv. of KH did not completely convert **1.76** to **1.93** (Scheme 1.24). Due to the fact that β-keto ester **1.93** has very similar polarity on silica

gel to starting keto acetal **1.76**, separation of these two compounds was difficult whenever the reaction was incomplete. It was noticed that increasing the equivalents of KH seemed to drive the reaction closer to completion. When 2 equiv. of KH were used, the reaction went to completion and keto acetal **1.76** was not observed by TLC and the yield was increased to 63% as compared to the 55% reported by Funk.[21b]

An explanation for the observation is that β-keto ester **1.93** formed in the reaction possesses a more acidic proton than the one in keto acetal **1.76**. Thus, compound **1.93** reacted with KH and existed in its anionic form. The outcome was that two equiv of KH were needed to complete the reaction. The conditions did present one problem and that was the formation of a byproduct, which was characterized and assigned to the structure **1.62**. Its IR (1742 cm^{-1} peak) and ^{13}C NMR spectrum (δ 174.4) indicated the compound has an ester group. Its ^{1}H NMR spectrum shows three singlets (δ 3.69, 3.35 and 3.34), which are from the three methoxy groups. This byproduct was not reported in the procedure by Funk. A possible mechanism is shown in Scheme 1.25. Keto acetal **1.76** is deprotonated under basic conditions to form enolate **1.63,** which subsequently attacks dimethyl carbonate to generate β-keto ester **1.93**. The methoxy group then comes in and displaces the ester group. This step is known as the retro-Claisen reaction.[40] It was rationalized that retro-Claisen could happen given the reaction conditions used to generate β-keto ester **1.93**.



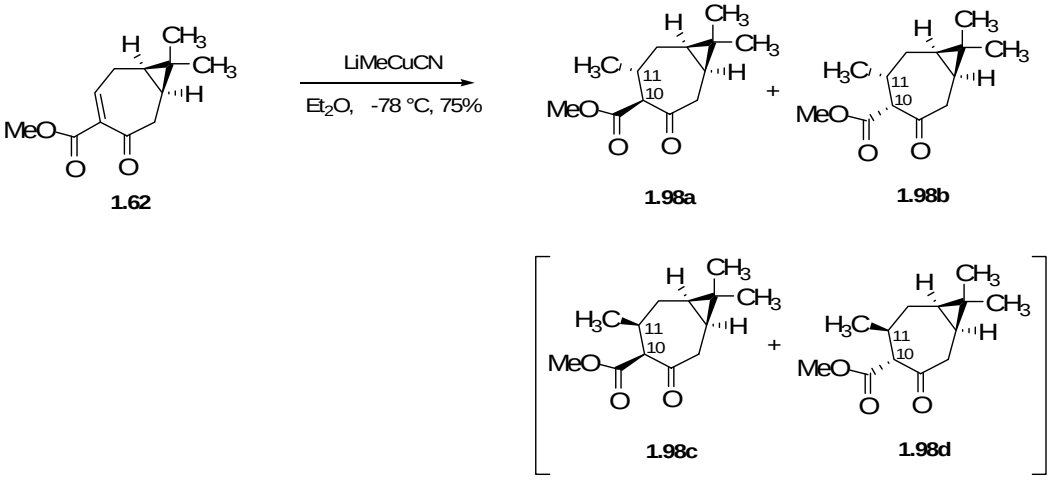
Scheme 1.25 Preparation of β-keto ester **1.93**



Scheme 1.26 Formation of byproduct dienol **1.97**

The cycloheptenone **1.62** was prepared by the method reported by Funk (Scheme 1.26).[21b] Compound **1.93** was treated with titanium tetrachloride in methylene chloride at –25 °C to afford **1.62** in one hour. This reaction goes in a stepwise fashion by first forming intermediate **1.96**, then **1.96** undergoes elimination to afford the product cycloheptenone **1.62**. TLC analysis showed the intermediate spot for **1.96** as a major

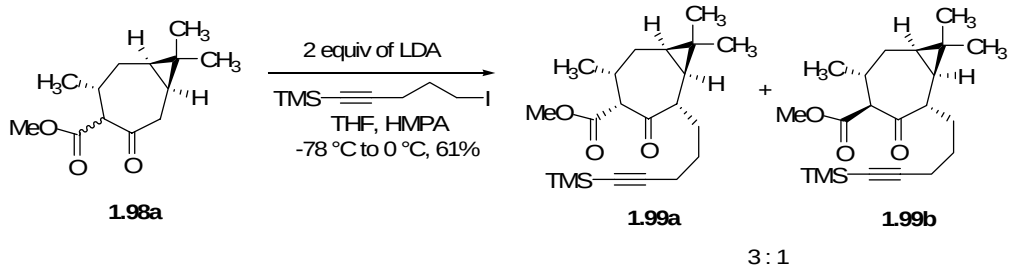
spot at the beginning, but as time progressed, the product spot for **1.62** became darker and the intermediate spot became lighter and eventually disappeared after one hour. Temperature control for this reaction was critical. If the reaction was left to warm to room temperature during this time, **1.62** tautomerized to dienol **1.97,** which could be isolated in yields as high as 79%. The ^{1}H NMR spectrum of **1.97** showed a distinctive singlet at δ = 12.95 ppm which was attributed to the hydrogen-bonded hydroxyl proton H_a. The reason this happens is that titanium tetrachloride is a strong Lewis acid, chelating to the two carbonyl oxygens of **1.62** and makes the γ protons on C(12) more acidic. Compound **1.97** is probably thermodynamically more stable than **1.62**, so upon warming, **1.97** is formed predominantly. Furthermore, it seems the tautomerization process is irreversible. Attempts to reverse this process by using basic conditions such as sodium methoxide or LDA were not successful. In both circumstances, dienol **1.97** was recovered.



Scheme 1.27 1,4-Addition to enone **1.62**

With substrate **1.62** in hand, the methyl group on C(11) was introduced using the procedure reported by Funk.[21a] Conjugate addition of LiMeCuCN to the enone **1.62** forms two new chiral centers and four possible diastereomers. Funk reported the separation of the four diastereomers by HPLC. In the present studies, three spots were observed by TLC, but only two of them were separated by silica gel chromatography. The combined yield of these two diastereomers was 75% and their relative ratio 1.5:1.

Sterically, the 1,4-addition more likely occurs from the face opposite to that of the cyclopropane ring. If that was the case, two diastereomers with the stereochemistry shown in **1.98a** and **1.98b** (Scheme 1.27) would be obtained, and they should be epimers with different stereochemistry at C(10). It was decided to move on to the next step alkylation to gain more information about the configuration of the diastereomers of **1.98**.

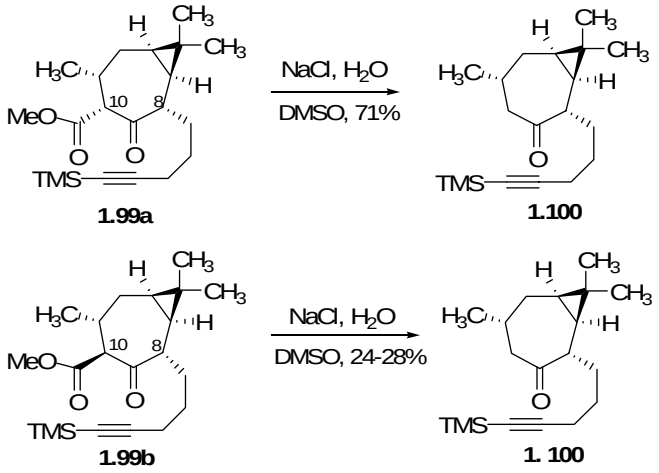


Scheme 1.28 Alkylation of keto-ester **1.98a**

The mixture of two diastereomers was treated with 2.1 equiv of LDA and converted to dianion (2.1 equiv of LDA, 1 equiv of HMPA, THF, -78 °C → 0 °C, 1 h) and then 5-iodo-1-trimethylsilyl-4-pentyne (1 equiv) was added (Scheme 1.28). Initially the alkylation was tried at -30 °C for 12 h; however, the reaction was sluggish at low temperature and resulted in recovery of some starting material, which was difficult to

separate from the products. Addition of 5-iodo-1-trimethylsilyl-1-pentyne to the dianion at 0 ºC was then attempted.[41] After the reaction was stirred for 2 h at 0 ºC, the reaction went to completion. Only two diastereomers were obtained in a 3:1 ratio and 61% combined yield.

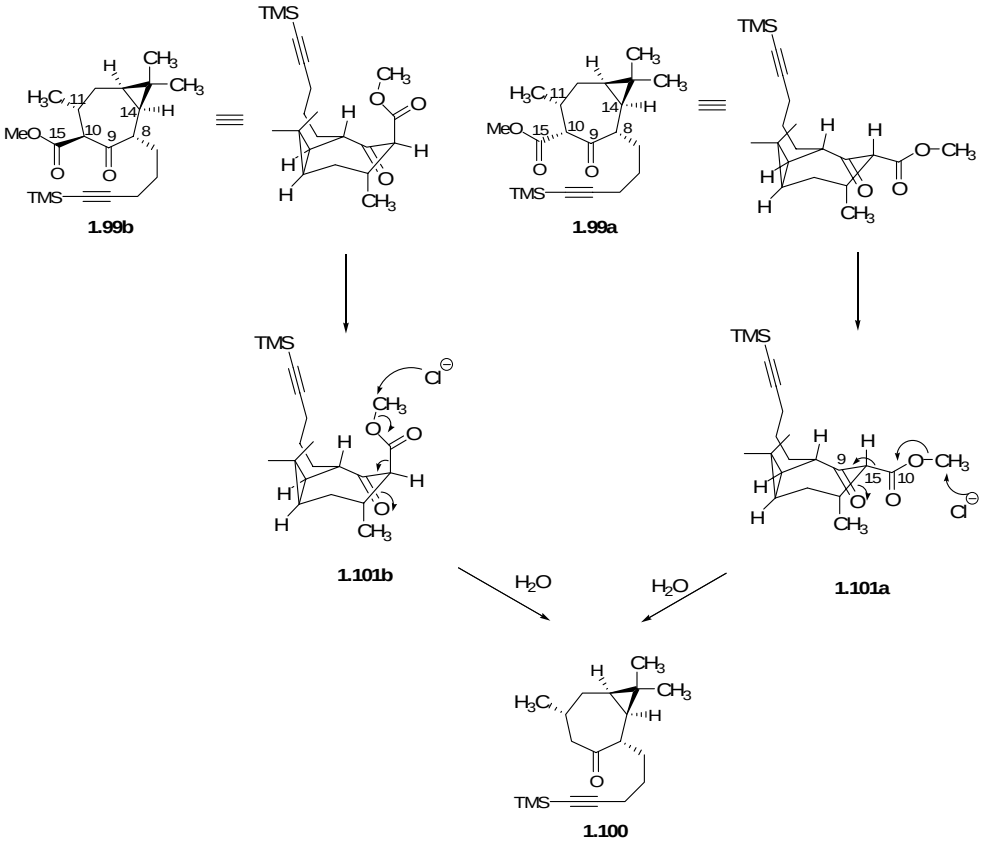
This result supported the assumption that mixture used for this alkylation is C10 epimer **1.98a** and **1.98b**. It also suggested the alkylation went with good selectivity. The two diastereomers were expected to be **1.99a** and **1.99b** based on steric preference. This was confirmed from the decarbalkoxylation results.



Scheme 1.29 Krapcho decarboxylation of keto-ester **1.99a** and **1.99b**

Initially, we attempts were made to remove the methyl ester moiety using the Krapcho decarboxylation protocol (Scheme 1.29).[42a] Heating a solution of faster moving isomer of **1.99** (DMSO, 20 equiv of H_2O, 1 equiv of NaCl) to reflux provided decarboxylated product **1.100** in 71% yield. However, heating a solution of slower moving isomer of **1.99** (DMSO, 20 equiv of H_2O, 1 equiv of NaCl) to reflux gave the product **1.100** in poor yield (24-28%). To this point, it was concluded that **1.99a** and

1.99b are epimeric at C(10) since they provided the same decarbalkoxylation product **1.100**. It was also noticed that unlike **1.99a**, decarboxylation of **1.99b** was slow and always led to recovery of **1.99b**. The tentative explanation is shown in Scheme 1.30.

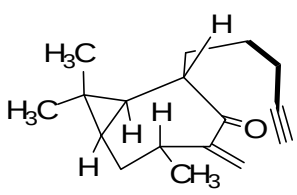


Scheme 1.30 Explanation of different decarbalkoxylation reaction rate for β–keto-ester **1.99a** and **1.99b**

Molecular modeling calculations using CaChe showed that due to the cyclopropane ring, the molecules **1.99a** and **1.99b** likely adopt the chair conformations shown in Scheme 1.30. In the reaction, chloride attacks the methyl carbon of esters **1.101a** and **1.101b** to form an enolate, which then reacts with water to give ketone **1.100**.

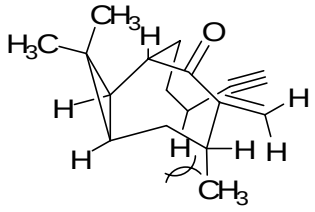
Diastereomer **1.99a** undergoes decarbalkoxylation faster than **1.99b** likely due to better orbital overlap of C10-C15 bond with π* of C9 carbonyl double bond. In addition, the methyl ester of **1.99a** is pseudo-equatorial and is more accessible for the chloride attack.

The stereochemical assignments for compounds **1.99a** and **1.99b** are predicted based upon the arguments above. ^{1}H COSY experiments were performed to locate the resonance for H_c, however the data was not definitive. An nOe was performed where H_a was irradiated and an enhancement of 2.32% and 1.51% was observed for H_b and H_c (the assignment of H_c is based upon a best guess analysis). An nOe performed on isomer **1.101b** where H_a was irradiated did not show any enhancements.



1.101a

conformation that will lead to *trans* ring system

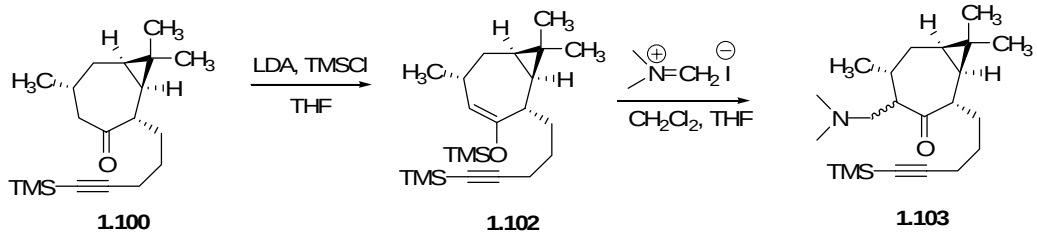


1.101b

conformation that will lead to *cis* ring system

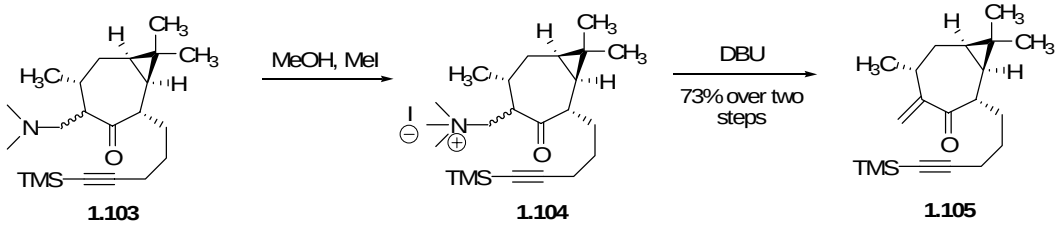
Figure 1.8 NOE analysis of **1.101a** and **1.101b**

Next, the same strategy of introducing an exocyclic olefin moiety as done before was applied. First, the ketone **1.100** was converted to silyl enol ether **1.102** (Scheme 1.31).



Scheme 1.31 Preparation of amine **1.103** using Eschenmoser's salt

Deprotonation of **1.100** (1.5 equiv of LDA, THF, -78 °C) followed by trapping of the resulting enolate with chlorotrimethylsilane (5 equiv) afforded silyl enol ether **1.102**. An attempt to purify the silyl enol ether via silica gel column led to largely hydrolysis back to ketone **1.100**. Purification at this stage was not necessary. So, the crude silyl enol ether was carried on and treated with Eschenmoser's salt in methylene chloride to provide amine **1.103** (67%) and some recovered ketone **1.100** (32%). It was reasoned that the hydrolysis of the enol ether back to the ketone was caused by the instability of silyl enol ether.



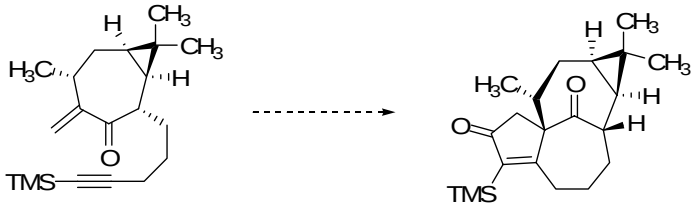
Scheme 1.32 Preparation of Pauson-Khand precursor **1.105**

Treatment of **1.103** with iodomethane in methanol at rt for 4 h afforded quarternary ammonium salt **1.104**. The ammonium salt **1.104** was obtained as a yellow solid after removal of the solvent. Without further purification, the yellow solid was

dissolved in methylene chloride and then treated with DBU to give the elimination product, α-methylene ketone **1.105**. The yield was 73% over two steps from **1.103** to **1.105**. Thus, the desired Pauson-Khand precursor **1.105** was made from (±)-3-carene in 11 steps.

1.2.2 Attempts to Construct Ingenol Skeleton Utilizing Pauson-Khand Reaction

Enone **1.105** was the first Pauson-Khand precursor made, and it was subsequently subjected to Pauson-Khand reaction conditions in hopes of obtaining the desired tetracyclic compound **1.106**.



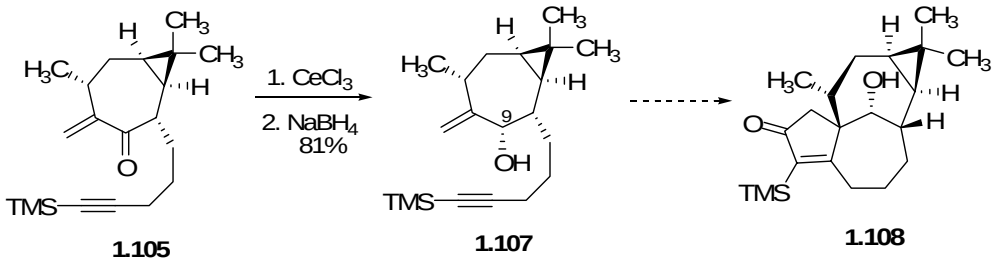
1.105 **1.106**

Table 1.2. Pauson-Khand conditions tested on enyne **1.105**

Entry	Substrate	Catalyst	Conditions	Results
1	**1.105**	$Co_2(CO)_8$	Benzene, reflux	Decomposition, Recovered s.m.
2	**1.105**	$Mo(CO)_6$	Toluene, reflux	Decomposition, Recovered s.m.
3	**1.105**	$[RhCl(CO)_2]_2$	Toluene, reflux	No reaction
4	**1.105**	$W(CO)_5 \cdot THF$	THF, reflux	Decomposition, Recovered s.m.

Treatment of α-methylene ketone **1.105** with dicobalt octacarbonyl[43] at room temperature in methylene chloride formed the alkyne-cobalt complex. The complex was then dissolved in degassed benzene and the solution heated to reflux for eight hours which led to decomposition and decomplexation of the alkyne-cobalt complex. **1.105** and the complex were partially recovered (entry 1, Table 1.2). Next, **1.105** was treated with molybdenum carbonyl[44] in toluene at reflux for eighteen hours, resulting only in partially recovery of starting material **1.105** and decomposition (entry 2, Table 1.2). Use of rhodium(I) biscarbonyl chloride dimer[45] as the catalyst and reaction was refluxed in refluxing toluene under CO atmosphere for fourteen hours gave no reaction occurred and only recovered **1.105** (83%) (entry 3, Table 1.2). Finally, tungsten pentacarbonyl THF complex[46] was tried. The reaction was refluxed in THF for sixteen hours under nitrogen, but decomposition still occurred and **1.105** (18%) was again recovered (entry 4, Table 1.2).

We reasoned that the carbonyl moiety may be problematic for two reasons, first the sp^2 hybridized carbon in the [7,7]-ring system will cause more strain than the same carbon possessing sp^3 hybridization. Also the electron withdrawing character of the carbonyl moiety will likely deactivate the olefin and slow the Pauson-Khand reaction. Thus we decided to reduce the carbonyl to the hydroxyl moiety in a effort to facilitate the Pauson-Khand reaction. Subsequent to the Pauson-Khand reaction, the hydroxyl group would be oxidized back to the ketone. We were somewhat concerned that the oxidation may be difficult to due to steric problems.

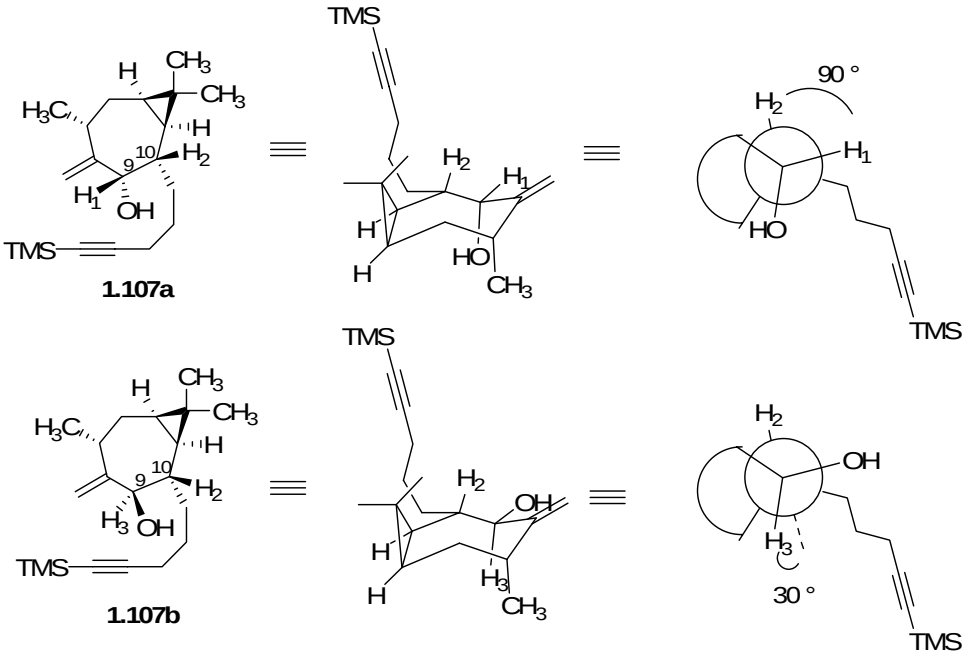


Scheme 1.33 Preparation of Pauson-Khand precursor **1.107** by reducing ketone **1.105**

α-Methylene ketone **1.105** was treated with cerium chloride and sodium borohydride at 0 °C (Scheme 1.28), and a new polar spot appeared instantly by TLC which indicted the formation of alcohol **1.107**. After column chromatography, a single diastereomer of **1.107** was isolated in 81% yield.

The stereochemistry at C(9) of **1.107** was decided by using Karplus plot. ^{1}H NMR of **1.107** showed a singlet at δ 4.28. This singlet is from the hydrogen on C(9). Clearly it has a very small coupling constant with neighbouring proton on C(10).

From the models we built (Scheme 1.34), we can tell the dihedral angle H1-C9-C10-H2 is 90° for diastereomer **1.107a** while that of **1.107b** is 150°. Karplus plot shows 90° dihedral angel protons' coupling constant is 0 Hz. Thus it was rationalized that the two protons should be *cis* to each other and **1.107a** should be the diastereomer we obtained from the reduction of **1.105**.



Scheme 1.34 Determination of the stereochemistry of **1.107a** and **1.107b** using Karplus plot

Alcohol **1.107** was then similarly subjected to the same Pauson-Khand conditions that we applied to substrate **1.105**.

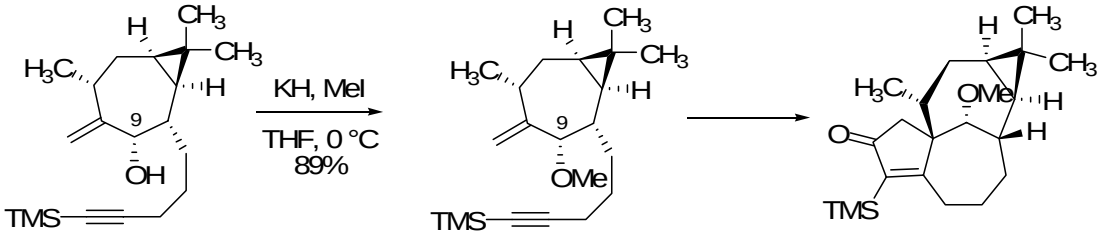
Table 1.3. Pauson-Khand conditions tried on enyne **1.107**

Entry	Substrate	Catalyst	Conditions	Results
1	**1.107**	$Co_2(CO)_8$	Benzene, reflux	Decomposition, Recovered s.m.
2	**1.107**	$Mo(CO)_6$	Toluene, reflux	Decomposition, Recovered s.m.
3	**1.107**	$[RhCl(CO)_2]_2$	Toluene, reflux	Decomposition, Recovered s.m.
4	**1.107**	$W(CO)_5 \cdot THF$	THF, reflux	Decomposition

First, alcohol **1.107** was treated with dicobalt octacarbonyl[28] to form the alkyne-cobalt complex. This was dissolved in benzene and the solution heated at reflux for eighteen hours. This only led to decomposition and decomplexation of the complex

(entry 1, Table 1.3). Using molybdenum hexacarbonyl[29] as the catalyst also led to decomposition of the starting material (entry 2, Table 1.3). When we used rhodium(I) biscarbonyl chloride dimer,[30] decomposition of **1.107** also occurred and **1.107** was partially recovered (entry 3, Table 1.3). Complete decomposition occurred when **1.107** was treated with tungsten pentacarbonyl THF complex[31] and heated to reflux in THF for twenty hours (entry 4, Table 1.3).

When subjected to the same Pauson-Khand conditions, alcohol **1.107** usually decomposed more than ketone **1.105**. We reasoned that free hydroxyl group could be a problem, so we decided to protect it with a methyl group to form precursor **1.110** (Scheme 1.35). We used a methyl group so the steric factors would be minimized during the Pauson-Khand reaction.



1.107 **1.109** **1.110**

Scheme 1.35 Synthesis of Pauson-Khand precursor ether **1.109**

Table 1.4. Pauson-Khand conditions attempted on enyne **1.109**

Entry	Substrate	Catalyst	Conditions	Results
9	**1.109**	$Co_2(CO)_8$	Benzene, reflux	Decomposition, Recovered s.m.
10	**1.109**	$Mo(CO)_6$	Toluene, reflux	Decomposition

1.109 was first treated with dicobalt carbonyl[28] in methylene chloride to generate the alkyne-cobalt complex. The complex was then dissolved in benzene and the solution heated to reflux for fifteen hours, resulting in decomposition of the starting material (entry 1, Table 1.4). The final attempt was using molybdenum hexacarbonyl[29] as catalyst. The reaction was refluxed in toluene for twelve hours and the starting material completely decomposed (entry 2, Table 4).

At this point, we depleted all of our starting material and decided that the Pauson-Khand reaction was too risky to continue.

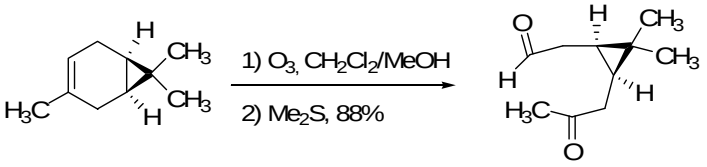
1.3 Conclusions

This project showed that Pauson-Khand precursors **1.105**, **1.107** and **1.109** can be easily synthesized in good yields and on large scale (0.1 g). However, the Pauson-Khand reactions attempted failed to produce the desired products and often resulted in decomposition. The metals used in these Pauson-Khand reactions are $Co_2(CO)_8$, $Mo(CO)_6$, $[Rh(CO)Cl_2]_2$ and $W(CO)_5{\cdot}THF$. Our observations suggest future studies should focus on milder conditions using a catalyst promoter to accelerate the Pauson-Khand reaction.[26a]

1.4 Experimental Section

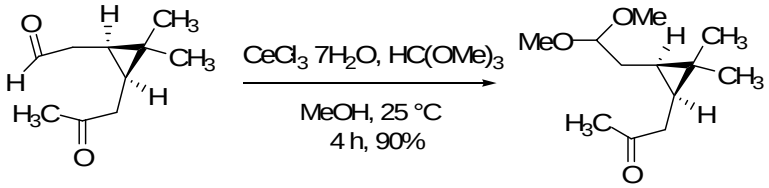
General Methods. Unless otherwise noted, all reactions were carried out under N_2 in oven- and/or flame-dried glassware using standard syringe, cannula, and septum techniques. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium benzophenone ketyl. Dichloromethane, benzene, toluene, and diisopropylamine were freshly distilled from calcium hydride. (±)-3-Carene was purchased from Aldrich and used without further purification. Dimethyl sulfoxide (DMSO) and *o*-xylene were distilled from calcium hydride and stored over activated 3Å molecular sieves. Molybdenum hexacarbonyl was purchased from Strem Chemicals, used as purchased, and stored and handled in a glove box under N_2 atmosphere. Rhodium(I) biscarbonyl chloride dimer and dicobalt octacarbonyl were stored in a desiccator in the freezer and warmed to room temperature prior to opening. Pentacarbonyltungsten tetrahydrofuran complex was freshly prepared. All other chemicals were purchased from Aldrich, Farchan (GFS Chemicals) and Lancaster.

Thin-layer chromatography was performed using precoated Kieselgel 60 F-254 plates. Flash chromatography was performed using Baker flash silica gel 60 (40 μm). NMR spectra were obtained on a JEOL GSX-270 (270 MHz spectrometer) and a Bruker UltraShield^{TM} (300 MHz spectrometer). IR spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR shifts were obtained in $CDCl_3$ and reported in ppm relative to the solvent shift of residual chloroform of δ 7.27. ^{13}C NMR shifts were obtained in $CDCl_3$ and reported in ppm relative to $CDCl_3$ 77.0. Mass spectra were obtained on a Micromass Autospec focusing instrument.



1.63 **1.75**

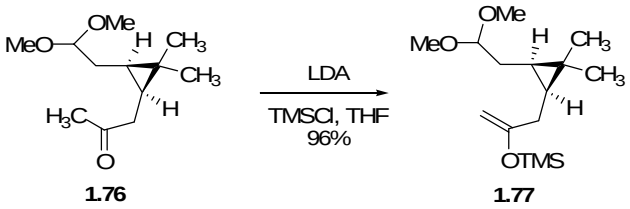
[2,2-Dimethyl-3-(2-oxopropyl)cyclopropyl]acetaldehyde (1.75). (±)-3-Carene **1.63** (25.0 g, 184 mmol) was dissolved in CH_2Cl_2: MeOH (5:1, 300 mL) and cooled to –78 °C. The solution was degassed with a steady stream of N_2 for 10 min then treated with ozone until the solution turned blue (ca. 5 h). N_2 was bubbled through the solution until the color turned from blue to pale yellow then dimethyl sulfide (38.7 mL, 423 mmol) was added and the solution was allowed to warm to room temperature over 12 h. Sodium bicarbonate (0.25 g, 2.98 mmol) was added and the solution was heated at 45 °C for 12 h. The reaction mixture was condensed, taken up in ether, washed with brine (2×), dried ($MgSO_4$) and concentrated to provide a light green oil. Distillation through a 10 cm Vigreux column gave **1.75** (27.2g, 162 mmol) as a yellow oil in 88% yield. bp 0.1 mm Hg 99-103 °C; R_f 0.61 (25% EtOAc/hexanes); ^{1}H NMR (270 MHz, $CDCl_3$) 9.75 (t, J = 1.7 Hz, 1H), 2.36-2.28 (m, 3H), 2.14 (s, 3H), 1.12 (s, 3H), 1.08-0.85 (m, 6H). The protocol reported by Funk was followed[21c] and the ^{1}H NMR spectrum matches with that reported by Funk.



1.75 **1.76**

1-[3-(2,2-Dimethoxyethyl)-2,2-dimethylcyclopropyl]propan-2-one (1.76). Keto aldehyde **1.75** (15.1 g, 89.9 mmol) was dissolved in MeOH (150 mL) and trimethyl

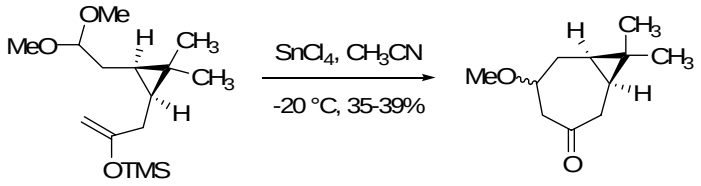
orthoformate (46.0 g, 451 mmol) and $CeCl_3 \cdot 7H_2O$ (33.5 g, 89.9 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h, then ether (150 mL) and a saturated solution of $NaHCO_3$ (120 mL) was added slowly. The layers were separated, the aqueous phase was extracted with ether (2×75 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Distillation of the crude product through a 10 cm Vigreux column provided **1.76** as a light yellow oil (16.1 g, 75.3 mmol) in 84% yield : R_f = 0.40 (20% EtOAc/hexanes); ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.31 (t, *J* = 5.2 Hz, 1H), 3.33 (s, 6H), 2.37-2.18 (m, 2H), 2.12 (s, 3H), 1.55-1.37 (m, 2H), 1.07 (s, 3H), 0.89 (s, 3H), 0.90-0.79 (m, 1H), 0.69-0.56 (m, 1H); ^{13}C NMR δ 208.9, 105.1, 53.3, 39.4, 29.6, 28.7, 28.2, 21.4, 21.1, 16.8, 15.1. The ^{1}H NMR matches that reported by Funk. The procedure reported by Funk[21c] for the preparation of optically enriched **1.76** was used for the preparation of racemic **1.76**.



1.76 **1.77**

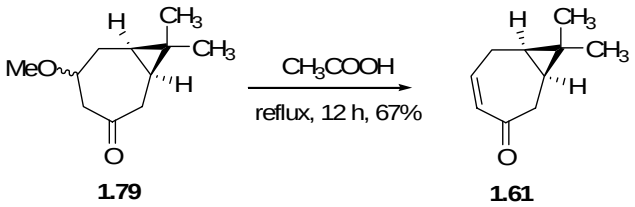
{1-[3-(2,2-Dimethoxyethyl)-2,2-dimethylcyclopropylmethyl]vinyloxy}trimethylsilane (1.77). A solution of **1.76** (6.51 g, 30.4 mmol) in 13 mL of THF was added slowly through a syringe to a freshly prepared LDA solution (91 mL, 45.5 mmol, 0.5 M in THF) at –78 °C under N_2. The reaction mixture was stirred at –78 °C for 30 min and then chlorotrimethylsilane (28.4 mL, 45.5 mmol) was added. The mixture was gradually allowed to warm to rt over a period of 3 h, then it was diluted with hexane. The hexane extract was washed with cold aq. $NaHCO_3$, dried and concentrated. The residue was purified *via* Kugelrohr distillation to provide **1.77** (8.34 g, 29.1 mmol) as a colorless oil

in 96% yield : ^{1}H NMR (270 MHz, C_6D_6) δ 4.53-4.40 (m, 1H), 4.29 (s, 1H), 4.21 (s, 1H), 3.20 (s, 6H), 2.21-1.88 (m, 2H), 1.85-1.60 (m, 2H), 1.05 (s, 3H), 0.93 (s, 3H), 0.82-0.66 (m, 1H), 0.53-0.37 (m, 1H), 0.20 (s, 9H). The Yamakawa procedure was followed.[27]



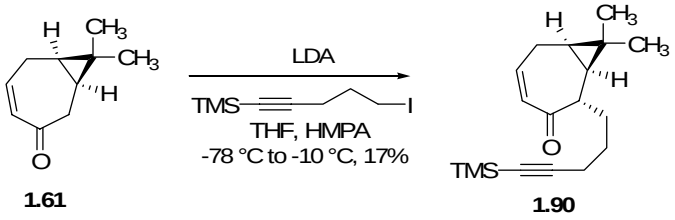
1.77 **1.79**

5-Methoxy-8,8-dimethylbicyclo[5.1.0]octan-3-one (1.79). A solution of **1.77** (500 mg, 1.75 mmol) in 4.5 mL dry acetonitrile was added dropwise to a solution of tin(IV) chloride (205 μL, 1.75 mmol) in 13 mL of dry acetonitrile at – 20 °C under N_2 with stirring. After 5 min, the reaction mixture was diluted with 20 mL of ether and saturated $NaHCO_3$ (15 mL) was added. The layers were separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The products were separated by silica gel column chromatography and then repurified by Kugelrohr distillation to afford a mixture of diastereomers **1.79** (112 mg, 0.615 mmol) as a colorless oil in 35% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.75-3.53 (m, 1H), 3.33 (s, 3H), 3.05 (dd, *J* = 11.4, 6.9 Hz, 1H), 2.66 (dd, *J* = 17.0, 8.6 Hz, 1H), 2.53 (dd, *J* = 11.1, 5.5 Hz, 1H), 2.39 (m, 2H), 2.37-2.21 (m, 1H), 2.20-2.07 (m, 2H), 1.09 (s, 3H), 1.18-1.01 (m, 1H), 1.00 (s, 3H), 0.95-0.73 (m, 2H). Yamakawa's procedure[27] was followed and the ^{1}H NMR spectrum matched theirs.



1.79 **1.61**

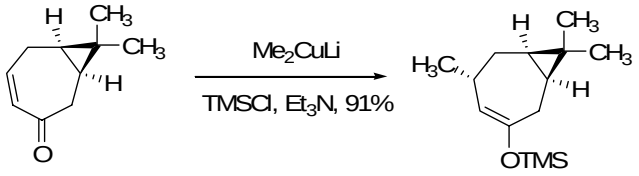
8,8-Dimethylbicyclo[5.1.0]oct-4-en-3-one (1.61). A solution of **1.79** (491 mg, 2.69 mmol) in 15 ml of acetic acid was refluxed for 12 h. The acetic acid was evaporated off and the residue was dissolved with 20 mL of ether. The solution was washed with sat. Na_2CO_3, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (25% EtOAc/hexanes) to give enone **1.61** (271 mg, 1.80 mmol) in 67% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.79 (ddd, *J* = 11.6, 8.6, 3.9 Hz, 1H), 5.95 (ddd, *J* = 11.8, 2.5, 2.2 Hz, 1H), 2.73 (ddd, *J* = 13.6, 4.9, 2.2 Hz, 1H), 2.55 (ddd, *J* = 14.8, 8.6, 6.2 Hz, 1H), 2.30 (dd, *J* = 14.8, 13.6 Hz, 1H), 2.18-2.00 (m, 1H), 1.17 (s, 3H), 1.07 (s, 3H), 0.91-0.79 (m, 1H), 0.71 (ddd, *J* = 13.6, 10.1, 4.9 Hz, 1H). The ^{1}H NMR matches that of Yamakawa's.[27]



1.61 **1.90**

8,8-Dimethyl-2-(5-trimethylsilanylpent-4-ynyl)bicyclo[5.1.0]oct-4-en-3-one (1.90). To a solution of freshly prepared LDA (0.8 mL, 0.5 M in THF, 0.4 mmol) at –78 °C was slowly added a solution of **1.61** (60 mg, 0.40 mmol) in 1 mL of THF. Then HMPA (70 μL, 0.40 mmol) was added. The resulting solution was warmed to 0 °C and stirred for 1.5 h. The reaction was cooled to –78 °C, and a solution of (5-iodo-pent-1-ynyl)-trimethyl-silane in 1mL of THF was added. The reaction was warmed to – 10 °C over a period of 4

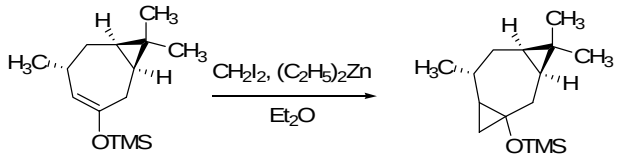
h and stirred at – 10 °C for 18 h. The reaction was quenched with 5 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography to provide **1.90** (19 mg, 0.066 mmol) as a colorless oil in 17% yield. **1.90**: R_f 0.39 (10% EtOAc/hexanes); IR (neat) 2946, 2350, 2178, 1671, 1460, 1246, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.72 (ddd, *J* = 11.9, 8.7, 3.2 Hz, 1H), 5.98 (dd, *J* = 11.9, 3.2 Hz, 1H), 2.57 (ddd, *J* = 16.6, 8.6, 6.4 Hz, 1H), 2.36-2.18 (m, 3H), 2.07 (ddt, *J* = 16.6, 10.6, 3.5 Hz, 1H), 1.97-1.82 (m, 1H), 1.65-1.40 (m, 3H), 1.26-1.10 (m, 1H), 1.18 (s, 3H), 1.07 (s, 3H), 0.39 (dd, *J* = 11.1, 10.1 Hz, 1H), 0.1 (s, 9H); ^{13}C NMR δ 201.8, 146.7, 133.5, 107.5, 84.1, 49.8, 30.7, 29.8, 29.1, 28.8, 26.6, 26.1, 24.5, 19.7, 15.8, 0.2.



1.61 **1.80**

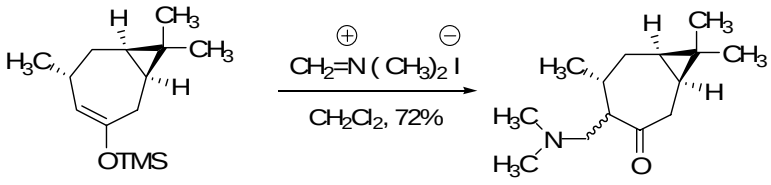
Trimethyl-(5,8,8-trimethylbicyclo[5.1.0]en-3-yloxy)silane (1.80). MeLi (1.4 M in ether, 5.0 mL, 7.0 mmol) was added dropwise to a suspension of copper(I) bromide-dimethyl sulfide (CuBr·DMS, 719 mg, 3.5 mmol) in 6 mL of dry ether with stirring under N_2 at – 55 °C. The mixture was stirred and cooled at – 65 °C for 10 min and then a solution of **1.61**(260 mg, 1.73 mmol) in 3.5 mL of dry ether was added dropwise via cannula at – 65 °C. After 5 min, chlorotrimethylsilane (1.32 mL, 10.4 mmol) followed by triethylamine (1.45 mL, 10.3 mmol) were added to the reaction mixture. The cooling bath was removed. After 40 min the reaction was quenched by adding saturated NH_4Cl solution. The aqueous layer was separated from the organic layer and was extracted with

hexane (3 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified *via* Kugelrohr distillation to give 1.48 (375 mg, 1.58 mmol) in 91% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.68 (bs, 1H), 2.42-2.28 (m, 2H), 2.10-1.98 (m, 1H), 1.75-1.60 (m, 2H), 1.09 (d, J = 7.7 Hz, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.98-0.80 (m, 1H), 0.74-0.62 (m, 1H), 0.2 (s, 9H). We followed the reference procedure and our ^{1}H NMR matches with the reported data.[27]



1.80 **1.81**

Trimethyl-(4,4,7-trimethyltricyclo[6.1.0.0^{3,5}]non-1-yloxy)silane (1.81). To a solution of **1.80** (293 mg, 1.23 mmol) in 5 mL ether was added diethylzinc (1.85 mL, 1 M in ether, 1.85 mmol). The resulting solution was stirred for 5 min before diiodomethane (150 μL, 1.86 mmol) was added. The reaction was refluxed for 18 h then cooled to rt and saturated NH_4Cl was added slowly. The layers were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated. The resulting residue was purified by column chromatography (100% hexanes) to afford **1.81** (261 mg, 1.03 mmol) as a colorless oil in 84% yield. R_f 0.75 (100% hexanes); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.37-2.23 (m, 2H), 1.84-1.65 (m, 2H), 1.63-1.47 (m, 1H), 1.11-0.98 (m, 4H), 0.97-0.71 (m, 9H), 0.70-0.55 (m, 1H), 0.1 (s, 9H).



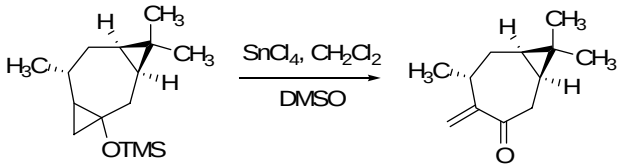
1.80 **1.83**

4-Dimethylaminomethyl-5,8,8-trimethylbicyclo[5.1.0]octan-3-one (1.83). To a solution of **1.80** (350 mg, 1.47 mmol) in 5 mL methylene chloride was added *N*,*N*-dimethylmethylene ammonium iodide (500 mg, 2.75 mmol) at rt. The resulting mixture was stirred for 12 h. 10% HCl (5 mL) was added, and then the aqueous layer was separated from the organic layer. The aqueous layer was neutralized with saturated Na_2CO_3 solution, then extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford **1.83** (237 mg, 1.06 mmol) in 72% yield as a white solid. **1.83**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.94-2.82 (m, 2H), 2.62 (dd, *J* = 16.3, 8.9 Hz, 1H), 2.28-2.04 (m, 9H), 1.71-1.56 (m, 2H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.08 (s, 3H), 0.97 (s, 3H), 0.97-0.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 59.9, 55.1, 45.9, 38.8, 34.1, 28.8, 26.9, 22.5, 20.4, 19.4, 19.3, 15.2.

1.83 **1.82**

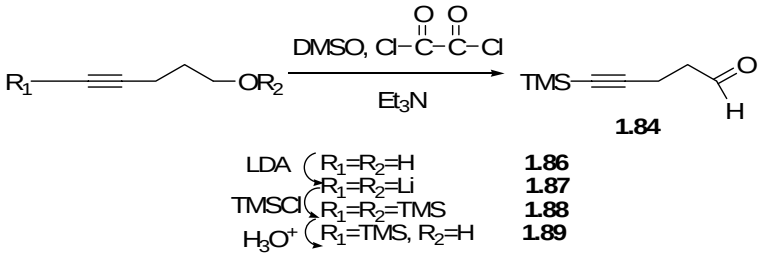
5,8,8-Trimethyl-4-methylenebicyclo[5.1.0]octan-3-one (1.82). MeI (500 μL, 8.1 mmol) was added to a solution of amine **1.83** (60 mg, 0.26 mmol) in 1 mL MeOH. The resulting solution was stirred at rt under N_2 for 12 h. The resulting solution was evaporated under reduced pressure to afford a yellow residue which was dissolved in CH_2Cl_2, then DBU (500 μL, 3.43 mmol) was added. The reaction was stirred for 4 h and then brine was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil which was purified by column chromatography (10% EtOAc/hexanes) to afford **1.82** (36 mg, 0.20 mmol) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.70 (s, 1H),

5.14 (s, 1H), 2.66-2.45 (m, 2H), 2.42-2.25 (m, 1H), 1.82-1.66 (m, 2H), 1.13 (d, J = 7.4 Hz, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.90-0.78 (m, 1H), 0.76-0.67 (m, 1H). The same compound was made by Wood from a different intermediate.[22] Their ^{1}H NMR was taken in C_6D_6.



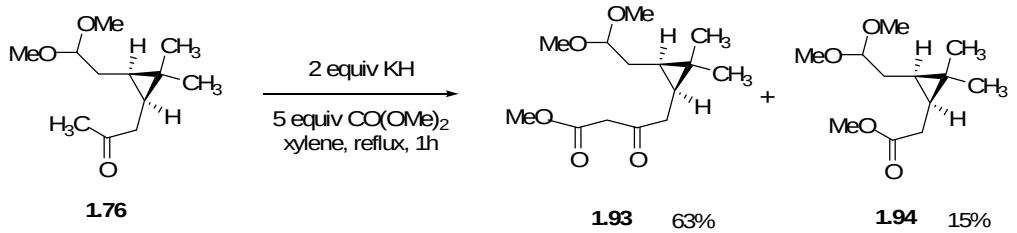
1.81 **1.82**

5,8,8-Trimethyl-4-methylenebicyclo[5.1.0]octan-3-one (1.82). To a solution of $SnCl_4$ (125 μL, 1.07 mmol) in 2 mL of CH_2Cl_2 was added a solution of **1.81** (256 mg, 1.01 mmol) in 1 mL of CH_2Cl_2 at 15 °C and the resulting solution was stirred for 1 h. The CH_2Cl_2 was evaporated off under reduced pressure and the resulting dark brown residue was dissolved in 2 mL of $CHCl_3$. To this solution was added DMSO (0.2 mL, 2.82 mmol). The reaction was refluxed at 60 °C for 15 h and then cooled to rt before saturated NH_4Cl was added. The aqueous layer was extracted with pentane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (10% EtOAc/hexanes) to afford **1.82** (111 mg, 0.62 mmol) as a colorless oil in 57% yield. We followed the procedure of the reference[31] and the ^{1}H NMR is identical to what we obtained from the last reaction.



5-Trimethylsilanylpent-4-ynal (1.84). *n*-BuLi (15 mL, 1.6 M in hexanes, 24 mmol) was added dropwise to a solution of alcohol **1.86** (1.01 g, 12.0 mmol) in 50 mL THF at -78 °C under N_2. After 10 min, chlorotrimethylsilane (4.6 mL, 36.2 mmol) was added. The reaction was stirred for 1 h at -78 °C, then warmed to rt. An aqueous 2N HCl solution (20 mL) was added, then the mixture was stirred for 12 h at rt. The aqueous layer was separated and extracted with ether (3 × 20 mL), the combined organic layers were dried ($MgSO_4$) and concentrated to give a colorless oil **1.89** (1.71 g, 10.9 mmol) in 91% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.77 (t, *J* = 6.9 Hz, 1H), 2.67 (t, *J* = 7.7 Hz, 2H), 1.85-1.70 (m, 2H), 1.59 (bs, 1H), 0.13 (s, 9H).

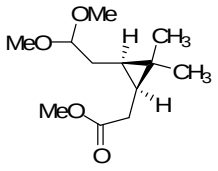
To a solution of oxalyl chloride (0.75 mL, 8.6 mmol) in 16 mL of CH_2Cl_2 at -78 °C was added a solution of DMSO (1.15 mL, 16.2 mmol) in 4 mL of CH_2Cl_2. After 5 min, **1.89** (1.20 g, 7.69 mmol) in 7.5 mL of CH_2Cl_2 was added dropwise. The reaction was stirred at -78 °C for 15 min before Et_3N (4.9 mL, 35.0 mmol). The reaction was then warmed to rt and diluted with ether (120 mL). The organic phase was washed with saturated NH_4Cl (50 mL), saturated $CuSO_4$ (2 × 50 mL), and brine (3 × 50 mL). Then the organic layer was dried (Na_2SO_4) and concentrated to provide **1.84** (0.98 g, 6.39 mmol) in 83% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.79 (s, 1H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.54 (t, *J* = 6.4 Hz, 2H), 0.13 (s, 9H).



1.76 **1.93** 63% **1.94** 15%

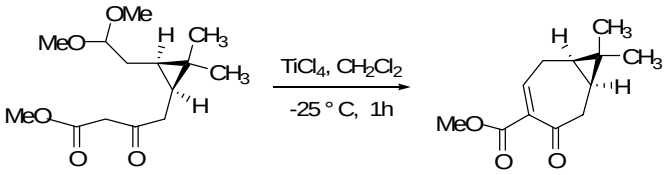
4-[3-(2,2-Dimethoxyethyl)-2,2-dimethylcyclopropyl]-3-oxobutyric acid methyl ester (1.93). Distilled o-xylene (18 mL) was added to dry potassium hydride (404 mg, 10.1

mmol), then distilled dimethyl carbonate (1.4 mL, 16.6 mmol) was added. The mixture was brought to reflux and keto acetal **1.76** (1.06 g, 4.95 mmol) in o-xylene (2 mL) was added dropwise over 20 min. After 30 min at reflux, the reaction mixture was allowed to cool to room temperature then poured into water (25 mL). The aqueous layer was acidified (3N HCl) to pH 2. The layers were separated and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The xylene was removed by distillation and the brown residue was purified by column chromatography (20% EtOAc/hexanes) to give **1.93** (0.849 g, 3.12 mmol) as a yellow oil in 63% yield and **1.94** (170 mg, 0.74 mmol) in 15% yield. **1.93**: R_f 0.24 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (t, *J* = 6.7 Hz, 1H), 3.74 (s, 3H), 3.50 (s, 2H), 3.36 (s, 3H), 3.34 (s, 3H), 2.54 (dd, *J* = 18.1, 6.9 Hz, 1H), 2.45 (dd, *J* = 18.1, 7.2 Hz, 1H), 1.60-1.41 (m, 2H), 1.10 (s, 3H), 0.95-0.83 (m, 4H), 0.74-0.63 (m, 1H). We followed Funk's procedure[21c] and our ^{1}H NMR matches with his data.



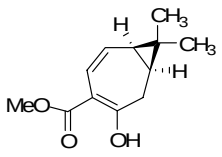
1.94

[3-(2,2-Dimethoxyethyl)-2,2-dimethylcyclopropyl]acetic acid methyl ester (1.94). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, *J* = 5.8 Hz , 1H), 3.69 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.28 (d, *J* = 7.35 Hz, 2H), 1.55 (dd, *J* = 5.7, 2.0 Hz, 1H), 1.53 (dd, *J* = 6.2, 2.0 Hz, 1H), 1.08 (s, 3H), 0.92 (s, 3H), 0.92-0.86 (m ,1H), 0.66 (dt, *J* = 9.0, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 105.4, 53.55,53.46, 51.9, 30.2, 29.0, 28.4, 22.0, 21.8, 17.2, 15.3; IR (neat) 2951, 1742, 1437, 1126 cm^{-1}.



1.93 **1.62**

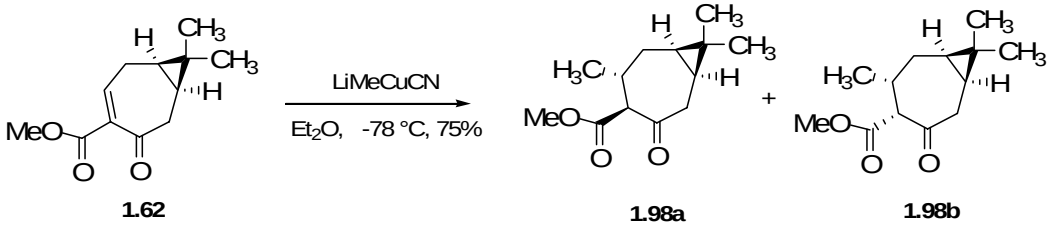
8,8-Dimethyl-5-oxobicyclo[5.1.0]oct-3-ene-4-carboxylic acid methyl ester (1.62). To 0.5 g of activated 4 Å molecular sieves was added a solution of *β*-keto ester **1.93** (0.51 g, 1.88 mmol) in 5 mL of CH_2Cl_2, the mixture was cooled to -25 °C and stirred for 10 min. Freshly distilled $TiCl_4$ (0.21 mL, 1.91 mmol) was added rapidly via a gastight syringe and the resulting purple solution was stirred for 1.5 h at -25 °C. The reaction mixture was poured into ether (10 mL) and a saturated solution of $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to provide a yellow solid which was purified by column chromatography (20% EtOAc/hexanes) to provide **1.62** (261 mg, 1.25 mmol) as a white solid in 67% yield: R_f 0.24 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.9, 3.7 Hz, 1H), 3.79 (s, 3H), 2.86 (dd, *J* = 13.5, 5.2, 1H), 2.75 (ddd, *J* = 17.0, 8.9, 6.2, 1H), 2.36 (dd, *J* = 13.5, 11.9, 1H), 2.18 (ddd, *J* = 17.0, 10.4, 3.7 Hz, 1H), 1.30-1.01 (m, 4H), 1.10 (s, 3H), 0.80 (ddd, *J* = 11.9, 9.1, 5.2 Hz, 1H). We followed Funk's procedure and ^{1}H NMR matches that of his.[21c]



1.97

(1R,2Z,4Z,7S)-Methyl 5-hydroxy-8,8-dimethylbicyclo[5.1.0]octa-2,4-diene-4-carboxylate (1.97). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.96 (s, 1H), 6.09 (dd, *J* = 11.1, 2.3

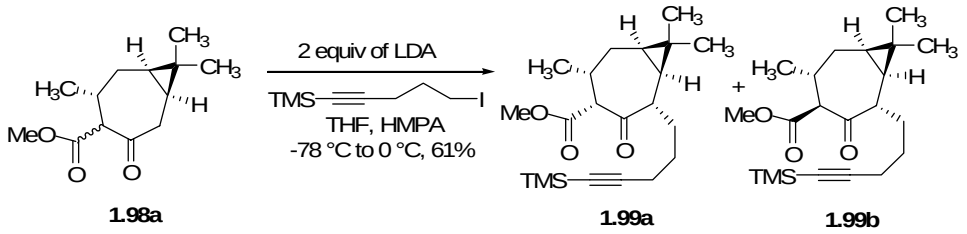
Hz, 1H), 5.85 (dd, *J* = 11.1, 1.8 Hz, 1H), 3.79 (s, 3H), 2.47 (dd, *J* = 14.1, 10.2 Hz, 1H), 2.40 (dd, *J* = 14.1, 6.8 Hz, 1H), 1.35-1.25 (m, 1H), 1.10 (s, 3H), 1.15-1.06 (m, 1H), 1.05 (s, 3H).



1.62 **1.98a** **1.98b**

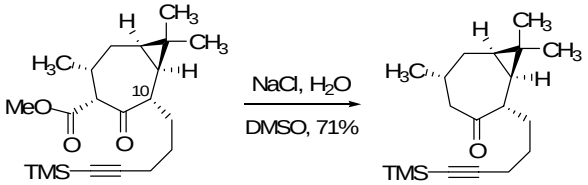
3,8,8-Trimethyl-5-oxobicyclo[5.1.0]octane-4-carboxylic acid methyl ester (1.98). Methyllithium (0.88 mL, 1.4 M, 1.23 mmol) was added dropwise to a slurry of CuCN (113 mg, 1.26 mmol) in 2 mL of ether. After 15 min, the resulting solution was cooled to –78 °C and cycloheptenone **1.62** (175 mg, 0.841 mmol) in 1 mL of ether was added over 2 min. The reaction mixture turned bright yellow and was stirred for 20 min. The reaction was diluted with 5 mL of ether then a saturated solution of NH_4Cl was added, the layers were separated and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The resulting oil was purified by column chromatography to give **1.98a** and **1.98b** as colorless oils. **1.98a** (49 mg, 26%): R_f 0.35 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (d, *J* = 8.2 Hz, 1H), 3.73 (s, 3H), 2.76 (dd, *J* = 17.4, 8.6 Hz, 1H), 2.59-2.46 (m, 1H), 2.25 (dd, *J* = 17.4, 8.2 Hz, 1H), 1.77 (ddd, *J* = 15.0, 4.6, 2.7 Hz, 1H), 1.26 (ddd, *J* = 15.0, 12.2, 4.6 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.11 (s, 3H), 0.99 (s, 3H), 0.96-0.86 (m, 1H), 0.79 (dd, *J* = 16.9, 8.5 Hz, 1H). **1.98b** (93 mg, 49%): R_f 0.42 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (d, *J* = 5.0 Hz, 1H), 3.69 (s, 3H), 2.58-2.45 (m, 2H), 2.32-2.18 (m, 1H), 1.84-1.74 (m, 1H), 1.64-1.50 (m, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 1.02

(d, J = 7.0 Hz, 3H), 0.93-0.80 (m, 1H), 0.79-0.70 (m, 1H). We followed Funk's procedure and the ^{1}H NMR looks favorable with the reported data.[21c]



5,8,8-Trimethyl-3-oxo(5-trimethylsilanylpentynyl)bicyclo[5.1.0]octan-4-carboxylic acid methyl ester (1.99a, 1.99b). A solution of β-keto ester **1.98a** (410 mg, 1.83 mmol) in 1.5 mL THF was added dropwise to a solution of LDA (7.7 mL, 3.9 mmol, 0.5 M in THF) at –78 °C. Then HMPA (318 μL, 1.83 mmol) was added. The reaction was warmed to 0 °C and stirred for 1 h, and then a solution of 1-(trimethylsilyl)-5-iodo-1-pentyne (487 mg, 1.83 mmol) in 1.5 mL of THF was added. After stirring for 1 h at 0 °C, the reaction solution was poured into saturated aqueous NH_4Cl (10 mL) and extracted with hexanes (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated by evaporation. Purification of the residue on silica gel (5% to 10% EtOAc/hexanes) afforded the products **1.99a** (305 mg, 46%) and **1.99b** (101 mg, 15%) as colorless oils. **1.99a**: R_f 0.60 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.46 (d, J = 3.6 Hz, 1H), 2.58-2.47 (m, 1H), 2.24 (t, J = 7.1 Hz, 2H), 2.23–2.07 (m, 2H), 1.94–1.81 (m, 1H), 1.68–1.43 (m, 2H), 1.38–1.25 (m, 2H), 1.11 (d, J = 6.8 Hz, 3H), 1.11 (s, 3H), 1.07 (s, 3H), 0.82–0.71 (m, 1H), 0.19 (t, J = 14.5 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 170.0, 107.1, 84.8, 65.5, 51.7, 49.6, 32.6, 30.3, 30.2, 28.8, 27.2, 26.3, 23.8, 20.8, 20.0, 15.4, 13.9, 0.1; IR (neat) 2953, 2173, 1748, 1711, 1249, 1201, 842, 760 cm^{-1}; MS(GC/EI-MS) m/z 362 ($M^{\cdot+}$), 347, 331, 145, 109, 96. **1.99b**: R_f

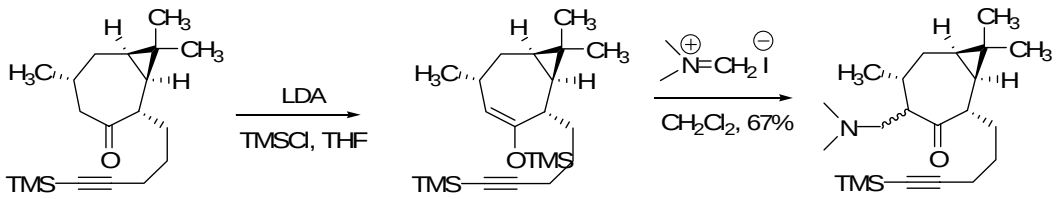
0.63 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.47 (d, J = 4.6 Hz, 1H), 2.66-2.54 (m, 1H), 2.28-2.14 (m, 4H), 1.95-1.80 (m, 3H), 1.64-1.37 (m, 6H), 1.10 (s, 3H), 1.07 (d, J = 7.2 Hz, 3H), 1.02 (s, 3H), 0.76 (ddd, J = 11.8, 9.0, 5.7 Hz, 1H), 0.24 (t, J = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 205.7, 170.6, 107.1, 84.7, 64.7, 52.0, 47.2, 32.8, 31.0, 28.8, 27.0, 26.4, 26.3, 22.8, 21.3, 19.9, 18.4, 15.2, 0.2; IR (neat) 2952, 2173, 1747, 1711, 1250, 843 cm^{-1}; MS(GC/EI-MS) m/z 362 ($M^{\cdot+}$), 347, 319, 173, 96, 73.



1.99a **1.100**

5,8,8-Trimethyl-2-(**5-trimethylsilanylpent-4-ynyl)bicyclo[5.1.0]octan-3-one (1.100).** To a stirred solution of *β*-keto ester **1.99a** (90 mg, 0.25 mmol) in 9 mL DMSO at rt were added NaCl (15 mg, 0.25 mmol) and H_2O (90 μl, 5.0 mmol). The resultant solution was heated at reflux (heating bath 170 °C) for 7 h. The solution was cooled and brine (5 mL) was added to the brown-colored reaction solution, then the aqueous layer was separated from organic layer and extracted with EtOAc (3×10 mL). The combined organic phases were dried (anhydrous $MgSO_4$), and concentrated under reduced pressure. The residual oil was purified *via* column chromatography using silica gel (eluting with 5% EtOAc/hexanes) affording **1.100** (54 mg, 0.18 mmol) as a yellow oil in 71% yield: R_f 0.65 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46–2.34 (m, 2H), 2.25 (m, 4H), 1.97-1.78 (m, 2H), 1.58-1.33 (m, 5H), 1.09 (s, 3H), 1.06 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.79-0.70 (ddd, J = 11.0, 9.2, 6.2 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2, 107.3, 84.6, 52.2, 48.1, 30.6, 30.5, 29.2, 28.9, 27.2, 26.4, 23.1, 20.6, 20.1, 18.5,

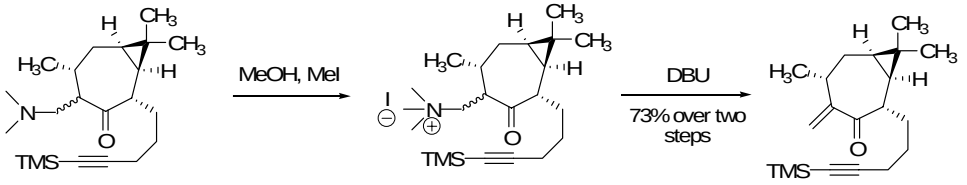
15.3, 0.2; IR (neat) 2956, 2174, 1704, 1249, 843, 760, 640 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 304 ($[M]^+$, 17), 289 (50), 261 (33), 208 (54), 96 (100), 73 (87): HRMS calcd for $C_{19}H_{32}OSi$ 304.2222, found 304.2229.



1.100 **1.102** **1.103**

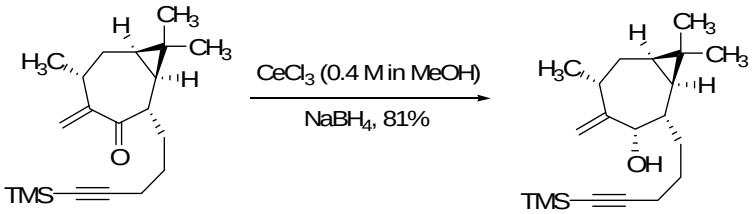
4-Dimethylaminomethyl-5,8,8-trimethyl-4-methylene-2-(5-trimethylsilanylpent-4-ynyl)bicyclo[5.1.0]octan-3-one (1.103). A flame dried 10-mL, round-bottomed flask was charged with 2 mL of THF and freshly prepared LDA (0.50mL, 0.25 mmol, 0.5 M in THF) and then cooled to –78 °C. Ketone **1.100** (50 mg, 0.17 mmol) in 1 mL of THF was added over 1 min to this cooled solution. The reaction was stirred for 20 min at –78 °C, then chlorotrimethylsilane (105 μL, 0.83 mmol) was added. The reaction solution was stirred for 10 min at –78 °C and then 1 mL of Et_3N was added. The reaction solution was stirred for another 10 min at –78 °C then warmed to rt and 4 mL of brine was added. The aqueous layer was separated and extracted with hexanes (3 × 10 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to give a colorless oil. The oil was dissolved in 2 mL of CH_2Cl_2, and *N*, *N*-dimethylmethylene ammonium iodide (92 mg, 0.50 mmol) was added then the resulting mixture was stirred for 3 h at rt. The CH_2Cl_2 solvent was evaporated under reduced pressure to give a yellow residue. Column chromatography (eluting with 4% methanol/methylene chloride) provided 16 mg (32%) of recovered ketone **1.100** and 40 mg (67%) of amine **1.103** as a white solid: IR ($CHCl_3$) 2955, 2820, 2172, 1691, 1249,

840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.78-2.63 (m, 2H), 2.26-2.08 (m, 8H), 1.77-1.68 (m, 3H), 1.65-1.41 (m, 5H), 1.41-1.23 (m, 2H), 1.13-1.02 (m, 9H), 0.76-0.65 (m, 1H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.1, 107.7, 84.3, 60.6, 57.1, 45.3, 44.5, 33.3, 30.9, 28.8, 27.0, 26.4, 25.6, 22.7, 21.0, 20.0, 18.9, 15.5, 0.1; IR ($CHCl_3$) 2955, 2820, 2172, 1691, 1249, 840 cm^{-1}; MS(GC/EI-MS) m/z 361 ($M^{\cdot+}$), 95, 81, 69, 58.



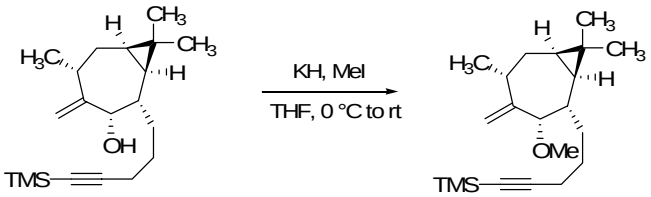
1.103 1.104 1.105

5,8,8-Trimethyl-4-methylene-2-(5-trimethylsilanylpent-4-ynyl)bicyclo[5.1.0]octan-3-one (1.105). Iodomethane (0.5 mL, 8.03 mmol) was added to a solution of amine **1.103** (39 mg, 0.11 mmol) in MeOH (1 mL), the reaction was stirred for 3 h at rt. The solvent was evaporated under reduced pressure to give a yellow solid. The resulting solid was dissolved in CH_2Cl_2 (2 mL) and DBU (33 μL, 0.22 mmol) was added. The reaction was stirred at rt for 15 h. The reaction solution was concentrated in vacuo. Purification by silica gel chromatography (eluting with CH_2Cl_2) afforded α-methylene ketone **1.105** (25 mg, 0.079 mmol) as a yellow oil in 73% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (s, 1H), 5.13 (s, 1H), 2.67-2.54 (hext, J = 6.7 Hz, 1H), 2.47-2.39 (m, 1H), 2.24 (t, J = 7.1 Hz, 2H), 1.96-1.83 (m, 1H), 1.80 (t, J = 6.7 Hz, 2H), 1.64-1.45 (m, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.09 (s, 3H), 1.07 (s, 3H), 0.78-0.69 (m, 1H), 0.30 (dd, J =10.1, 9.3 Hz, 1H), 0.2 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 154.7, 117.7, 107.6, 84.9, 45.5, 36.2, 32.2, 30.0, 29.4, 29.0, 26.8, 22.4, 20.4, 20.1, 19.3, 15.5, 0.5; IR (neat) 2958, 2174, 1696, 1249, 842 cm^{-1}; MS MS(GC/EI-MS) m/z 316 ($M^{\cdot+}$), 301, 105, 73.



1.105 **1.107**

5,8,8-Trimethyl-4-methylene-2-(5-trimethylsilanylpent-4-ynyl)-bicyclo[5.1.0]octan-3-ol (1.107). A solution of $CeCl_3$ (170 μL, 0.068 mmol, 0.4 M in MeOH) was added to a solution of α-methylene ketone **1.105** (20 mg, 0.062 mmol) in 1 mL of MeOH. The resulting solution was cooled to 0 °C and stirred for 10 min before sodium tetrahydroborate (3 mg, 0.07 mmol) was added. The reaction was stirred for 5 min at 0 °C then quenched with 1 mL of H_2O. The aqueous layer was separated from organic layer and extracted with chloroform (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Purification of the residue *via* silica gel column (10% EtOAc/hexanes) provided 16 mg of alcohol **1.107** in 81% yield: R_f 0.57 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (d, *J* = 2.3 Hz, 1H), 4.77 (d, *J* = 2.3 Hz, 1H), 4.28 (s, 1H), 2.72-2.59 (m, 1H), 2.28-2.19 (m, 1H), 1.87 (ddd, *J* = 14.5, 6.4, 6.0 Hz, 1H); 1.65-1.56 (m, 4H), 1.39-1.29 (m, 5H), 1.09 (s, 3H), 0.99 (s, 3H), 0.79 (ddd, *J* = 15.7, 9.2, 6.6 Hz, 1H), 0.46 (dd, *J* = 10.2, 9.2 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 113.3, 107.6, 84.5, 82.7, 40.4, 39.9, 34.1, 30.3, 29.2, 27.2, 26.7, 22.2, 20.5, 20.3, 18.4, 15.7, 0.2; IR (neat) 3481, 2934, 2174, 1249, 841 cm^{-1}; MS MS(GC/EI-MS) m/z 318 ($M^{\cdot+}$), 300, 285, 257, 73.



1.107 **1.109**

[5-(3-Methoxy-5,8,8-trimethyl-4-methylenebicyclo[5.1.0]oct-2-yl)-pent-1-ynyl]-trimethylsilane (1.109). KH (15 mg, 0.38 mmol) was added to a solution of alcohol **1.107** (30 mg, 0.094 mmol) in 8 ml THF at 0 °C. The resulting slurry was stirred for 10 min before iodomethane (200 μL, 3.22 mmol) was added. The reaction was warmed to rt and stirred for 4h at rt. 4 mL of saturated NH_4Cl solution was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was purified *via* column chromatography using silica gel (eluting with 10% EtOAc/hexanes) affording **1.109** (27 mg, 0.081 mmol) as a pale yellow oil in 87% yield: R_f 0.82 (20% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (d, *J* = 2.7 Hz, 1H), 4.72 (d, *J* = 2.7 Hz, 1H), 3.64 (s, 1H), 3.25 (s, 3H), 2.73-2.62 (m, 1H), 2.28-2.19 (m, 2H), 1.88 (ddd, *J* = 14.3, 6.0, 5.1 Hz, 1H), 1.63-1.45 (m, 4H), 1.30 (d, *J* = 7.4 Hz, 3H), 1.30-1.22 (m, 2H), 1.07 (s, 3H), 0.97 (s, 3H), 0.77 (ddd, *J* = 11.5, 9.3, 6.2 Hz, 1H), 0.51 (dd, *J* = 10.2, 9.3 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 115.4, 107.7, 92.4, 84.4, 56.5, 41.7, 40.2, 34.4, 30.4, 29.0, 27.8, 26.8, 22.2, 20.3, 18.6, 18.4, 15.6, 0.2; IR (neat) 2932, 2862, 2175, 1455, 1249, 1100, 842 cm^{-1}.

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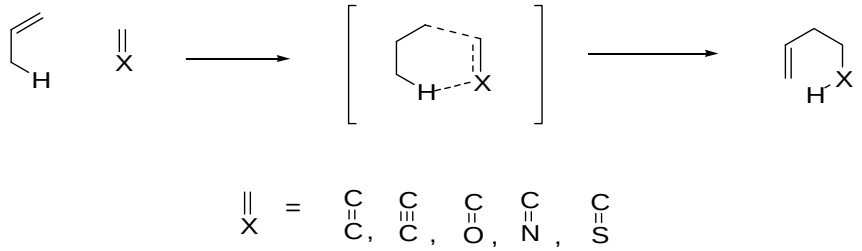
2. Rhodium(I)-Catalyzed Allenic Alder-ene Reaction

2.1 Introduction to Transition Metal Catalyzed Alder-ene Reaction

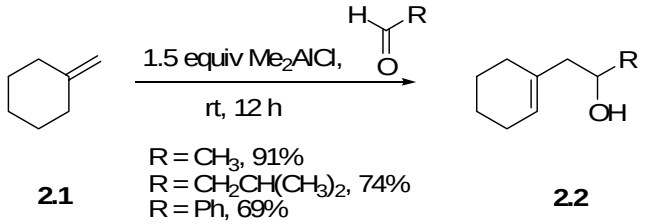


Scheme 2.1. Introduction to the Alder-ene reaction

The Alder-ene reaction (Scheme 2.1) is a [4+2] pericyclic reaction between an olefin containing an allylic hydrogen ("ene") and a compound containing a multiple bond ("enophile").[1] Since the discovery of this reaction, many variants have been developed using different enophiles, including alkenes, alkynes, ketones, aldehydes and imines. The Alder-ene reaction is a six-electron reaction and mechanistic studies[2] show that it is a concerted process like a Diels-Alder reaction.[3] The activation energy for an Alder-ene reaction is higher than that of a Diels-Alder reaction since one σ-bond and two π-bonds are broken in an Alder-ene reaction while three π-bonds are cleaved in a Diels-Alder reaction. For that reason thermal Alder-ene reactions require high temperatures to take place and their utilization is limited.

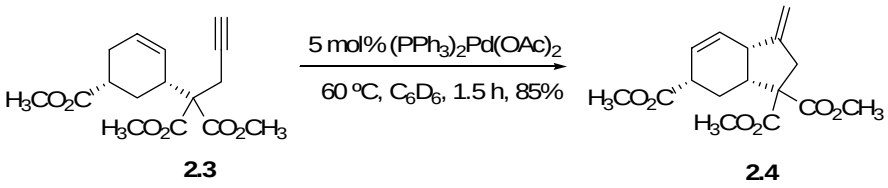
To make Alder-ene reactions more synthetically useful, Lewis acids, main group metals, and transition metal catalysts have been used to lower the activation energy. Lewis acids are mostly used in systems involving electronically different enophiles like aldehydes,[4] ketones[5] or double bonds in an α,β unsaturated systems.[6] For example,

Snider and coworkers showed dimethyl aluminum chloride can be used to catalyze an Alder-ene reaction between alkenes and aldehydes to give homoallylic alcohols.[4]



Scheme 2.2 Lewis acid-catalyzed Alder-ene reaction

On the other hand, transition metal catalysts are used mostly in systems involving enophiles such as alkenes and alkynes.[7] For example, **2.4** was obtained in 85% yield from 1,6-eneyne **2.3** in the presence of Pd(II) catalyst. It is worth noting that thermal ene reaction of **2.3** gave no reaction or decomposition.

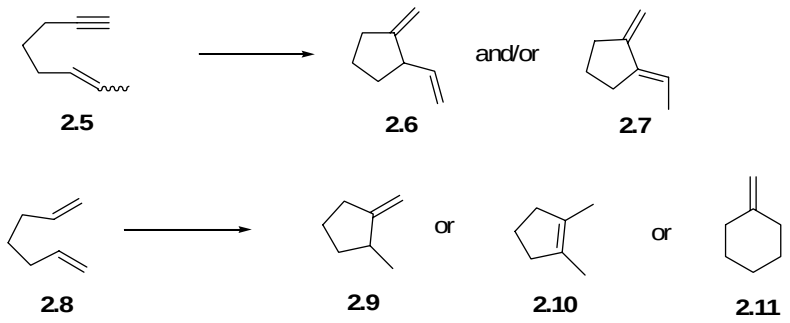


Scheme 2.3 Pd-catalyzed Alder-ene reaction

Most work on transition metal catalyzed formal Alder-ene reactions have been done in the last two decades. The Alder-ene reactions effected by transition metals typically take place at low temperatures thereby allowing some transformations which would be difficult under thermal conditions. Higher regioselectivity selectivity can also be achieved with transition metal catalysis.[8]

Extensive studies have been carried out on the Alder-ene reactions of enynes and dienes. For the enyne systems,[9] the 1,6-enyne is a well studied example. 1,4-Dienes **2.6**

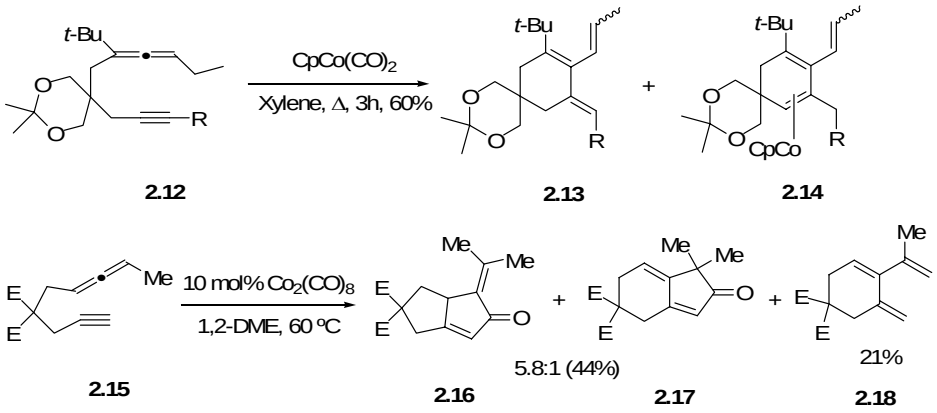
and/or 1,3-dienes **2.7** can be obtained from intramolecular Alder-ene reactions (Scheme 2.4). Various transition metals have been used in this cycloisomerization reaction, which include Pd,[10] Ni,[11] Ru,[12] Co,[13] Ti,[14] Rh,[15] Zr[16]and Pt.[17] Similarly, 1,6-dienes can undergo cycloisomerization in the presence of transition metal catalysts, and several products can be formed depending on the catalytic conditions. Rh,[18] Ru,[19] and Ni[20] have been used to form cyclopentene **2.9**. On the other hand, 1,2-dimethyl-1-cyclopentene **2.10** was observed when palladium catalysts[21] were used. In addition, cyclopentadienyl-based scandium complexes[22] and zirconocene[23] prefer to form endo cyclization products **2.11**.



Scheme 2.4 Alder-ene reactions of enynes and dienes

There are only a few examples of Alder-ene reactions with allenyne substrates compared to extensive studies utilizing enynes and dienes. Malacria and Livinghouse both used cobalt catalysts to effect an allenic Alder-ene reaction. Malacria subjected allenyne **2.12** to a stoichiometric amount of $CpCo(CO)_2$ to give formal allenic Alder-ene products **2.13** and **2.14** (Scheme 2.5).[24] The *tert*-butyl group on allene directs the cobalt complex to coordinate with the distal double bond of the allene, a regiochemical requirement for this reaction. However, isomerization of the exocyclic double bond of **2.13** leads to formation of byproduct **2.14**. In addition, both **2.13** and **2.14** are mixtures

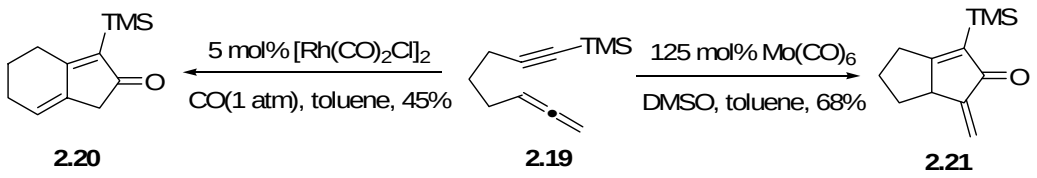
of *E* and *Z* isomers of the appending double bond. Livinghouse reported 21% yield of triene **2.18** which was isolated as a byproduct from a $Co_2(CO)_8$ catalyzed allenic Pauson-Khand reaction.[25] In summary, transition metal catalyzed allenic Alder-ene reactions have been reported but their synthetic usefulness is limited.



Scheme 2.5 Examples of transition metal catalyzed allenic Alder-ene reactions

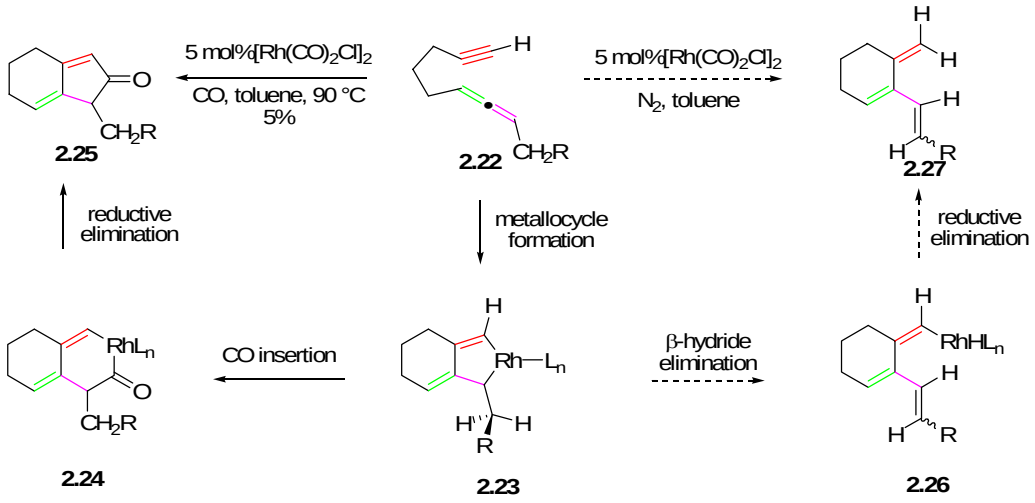
Studies performed in our group by Hongfeng Chen and Brenden Richards et al. in the area of the allenic Pauson-Khand reaction revealed an interesting double bond selectivity of the allene depending on the transition metal catalyst. For example, subjecting compound **2.19** to molybdenum hexacarbonyl and DMSO typically afforded a selective reaction with the proximal double bond of the allene to give methylene cyclopentenone **2.21** (Scheme 2.6). Interestingly, the same substrate **2.19**, when exposed to a catalytic amount of rhodium biscarbonyl chloride dimer, gave only the 4-alkylidene cyclopentenone **2.20**. Numerous substrates were examined and the selectivity is controlled by the catalyst and not the substrate structure.[26] Typically strategies used to control allene constitutional group selectivity involve 1) differential substitution of the

allene termini, 2) intramolecular reaction, and 3) incorporation of directing functional groups on the carbon adjacent to the allene. This result constitutes a rare example of transition metal-directed constitutional group selectivity of an allene.[27]



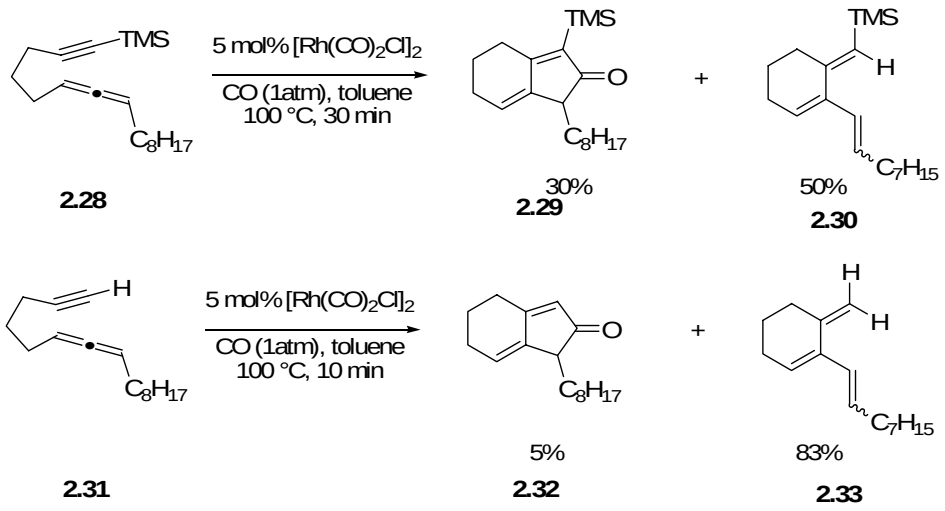
Scheme 2.6 Transition metal catalyzed Allenic Pauson-Khand reactions

A plausible mechanism for rhodium catalyzed allenic Pauson-Khand is shown in Scheme 2.7. First the rhodium complex coordinates with the alkyne and the external double of allenyne **2.22**, then rhodium oxidatively adds to form metallocycle **2.23**. Under a carbon monoxide atmosphere, CO insertion takes place to give metallocycle **2.24** which undergoes reductive elimination to give Pauson-Khand product **2.25**. It was reasoned that this regiocontrol element could be used in alternative cycloisomerization reactions. For example, a competing β-hydride elimination of the rhodium metallocycle **2.23** could take place resulting in the formation of **2.26** which then could reductively eliminate the rhodium complex to give the Alder-ene product **2.27**.



Scheme 2.7 Proposed mechanism of rhodium catalyzed allenic Pauson-Khand pathway and Alder-ene pathway

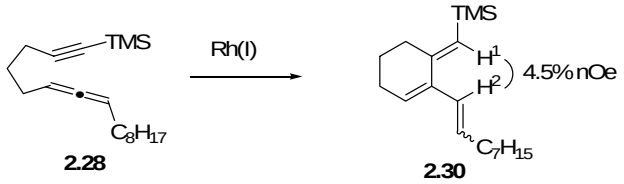
In fact, Alder-ene products had been observed as byproducts in some of the rhodium(I)-catalyzed allenic Pauson-Khand reactions. When allenynes **2.28** and **2.31** were subjected to the Pauson-Khand reaction conditions (5 mol% $[Rh(CO)_2Cl]_2$, CO (1atm), toluene, 100 ºC), Pauson-Khand products **2.29** and **2.32** were isolated as minor products, and the Alder-ene products **2.30** and **2.33** were the major products (Scheme 2.8). It was postulated then that the selective formation of trienes **2.30** and **2.33** would be possible by the absence of carbon monoxide in the reaction media.



Scheme 2.8 Examples showing cross-conjugated trienes as byproducts in Rhodium(I)-catalyzed Pauson-Khand reactions

A logical thing to do to shut down the Pauson-Khand reaction pathway is to replace the carbon monoxide atmosphere with a nitrogen or argon atmosphere. To test this hypothesis, we subjected **2.28** to $[Rh(CO)_2Cl]_2$ under a nitrogen atmosphere, which gave only Alder-ene product **2.30** in 72% yield (entry 1, Table 1). Several other commercially available rhodium catalysts were screened by Peter Sill in our group (Table 1).[28] Subjecting allenyne **2.28** to 5 mol% $[Rh(COD)Cl]_2$ and 10 mol% $AgSbF_6$ provided desilylated **2.30** in 67% yield and 13 : 1 *E*/*Z* ratio of the appending olefin (entry 2, Table 2.1). Treatment of **2.28** with 5 mol% $[Rh(CH_2CH_2)Cl]_2$ and 10 mol% $AgSbF_6$ gave desilylated **2.30** in 46% yield (entry 3, Table 2.1). When $Rh(PPh_3)_2(CO)Cl$ was used, only trace amounts of **2.30** formation was observed (entry 4, Table 2.1). Using 5 mol% $Rh(PPh_3)_3Cl$ and 10 mol% $AgSbF_6$, gave no reaction (entry 5, Table 2.1). Based upon these results, $[Rh(CO)_2Cl]_2$ is the catalyst of choice. It is worth noting that the geometry

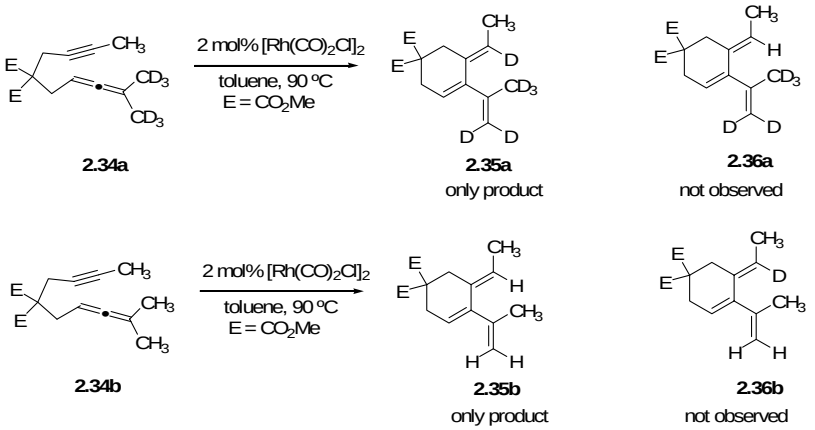
of the exocyclic double bond of **2.30** was obtained as the *E*-isomer exclusively. The geometry was determined by an nOe between the vinyl proton H_1 and H_2.



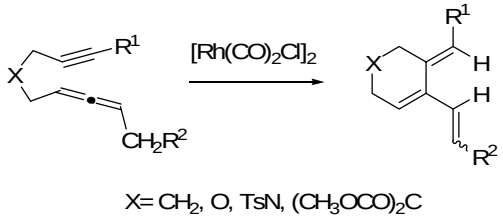
entry	Conditions	Additive	E/Z	yield (%)
1	$Rh[(CO)_2Cl]_2$	none	5 : 1	72
2	$Rh[(COD)Cl]_2$	$AgSbF_6$	13 : 1	67
3	$Rh[(C_2H_4)Cl]_2$	$AgSbF_6$	4 : 1	46
4	$Rh(PPh_3)_2(CO)Cl$	none		trace
5	$Rh(PPh_3)_3Cl$	$AgSbF_6$		no reaction

Table 2.1 Screen for optimum rhodium catalysts to form cross-conjugated trienes

The formation of only the *E*-isomer of exocyclic double supports our proposed mechanism (Scheme 2.9). Another piece of evidence for this mechanism comes from a deuterium labeling study performed by Hongfeng Chen in our group. Compound **2.24a** and **2.24b** were mixed in a 1 : 1 ratio and subjected to the rhodium condition to afford only compound **2.25a** and **2.25b** and none of **2.26a** or **2.26b**, which indicates that this process occurs intramolecularly and not intermolecularly.



Scheme 2.9 Deuterium labeling study of Rhodium(I)-catalyzed formal Alder-ene reaction



Scheme 2.10 Scope study of Alder-ene reaction

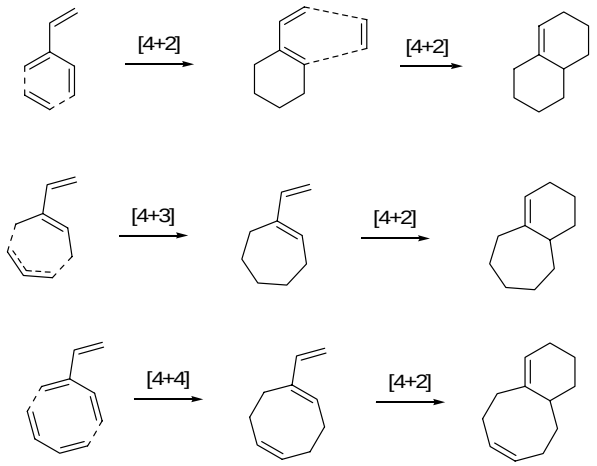
The scope of this allenic Alder-ene reaction was first examined on some simple substrates (Scheme 2.10). Different linkers were used to connect alkyne and allene moieties. All carbon tethered, gem-diester, ether and sulfonamide substrates were subjected to the Rh(I) conditions and all gave trienes in good yields. Among them, sulfonamides gave the best yields at room temperature (85-93%).

2.2 Results and Discussion of Rhodium(I)-Catalyzed Alder-ene Reaction

2.2.1 Synthesis of Allenyne Substrates

The formal allenic Alder-ene reaction affords good yields of cross-conjugated trienes from readily available alkynyl allenes. The scope and limitations of this new reaction are currently being explored in our group and others. My research contributions to this area are exploring the synthetic potential of the allenic Alder-ene reaction by combining this reaction with subsequent carbon-carbon bond forming procedures for rapid increases in molecular complexity. For example, cross-conjugated trienes can participate in tandem Diels-Alder reactions (*vide infra*). As shown in eq. 6, the triene reacts with a dienophile to give the vinylcyclohexene that can then react with another dienophile to give the decalin ring system. In addition to the Diels-Alder reaction, there

are other cycloaddition reactions that dienes can participate in. For example, a [4+3] and [4+4] cycloaddition[29] can also take place followed by [4+2] cycloadditions to give fused [5.4.0] and [6.4.0] ring system respectively (Scheme 2.11). While there are many more cycloaddition reaction sequences possible, these reactions are meant to show the enormous potential of the cross-conjugated triene moiety for synthetic access to diverse ring systems.



Scheme 2.11 Synthetic potentials of the cross-conjugated trienes

The bicyclic ring structures shown in scheme 2.11 are common subunits of natural products (Figure 2.1). For example, steroids contain decalin system and guanacastepene has fused 5,7,6 ring stystem. The 8, 6 ring system is part of the taxol skeleton.

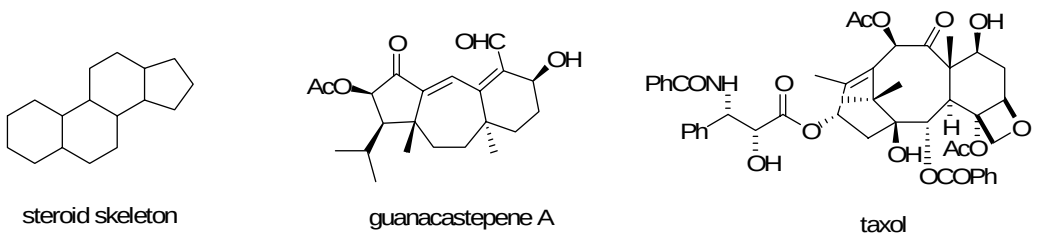
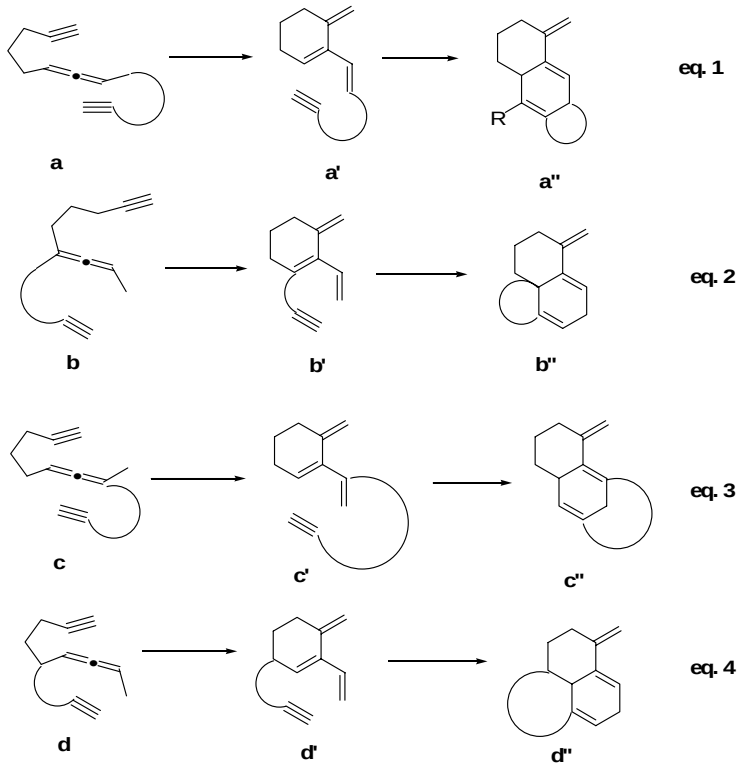


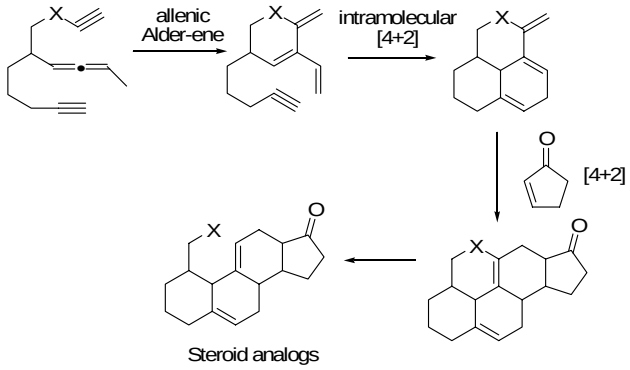
Figure 2.1 Natural products containing [4.4.0], [5.4.0] and [6.4.0] ring systems

Since transition metal catalyzed [4+2] cycloaddition reactions have been thoroughly investigated, we decided to begin our investigation by assembling alkynyl allenes in which dienophiles could be easily tethered on. Shown below are a variety of alternatives for tethering the dienophile (Scheme 2.12). For example in eq. 1, the dienophile is tethered to the terminus of the allene **a** and subsequent to the Alder-ene reaction should afford a triene **a'**, which gives the linear tricyclic compound **a"**. Eq. 2 has the dienophile tethered on the proximal double bond of the allene. The Alder-ene reaction of **b** produces **b'** which upon 4+2 cycloaddition should give **b"**. Access to bridging bicycle systems may also be possible as shown in eq. 3. Finally, attachment of the dienophile to the tethering carbons will give triene **d'** after the Alder-ene reaction and **d"** subsequent to the 4+2 cycloaddition (eq. 4).



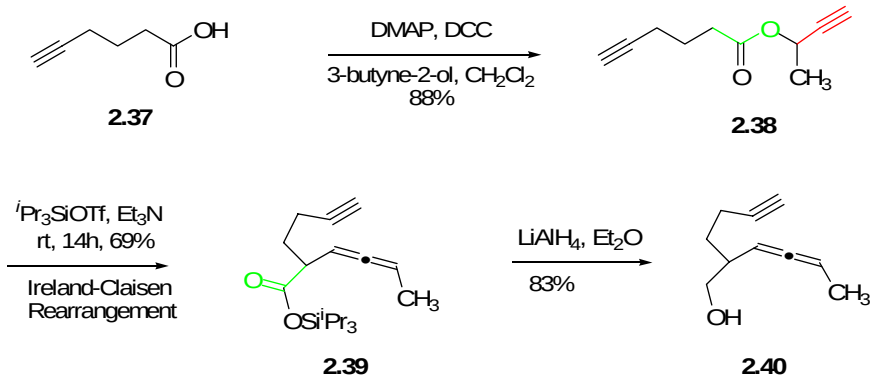
Scheme 2.12 Substrates can undergo serial Alder-ene/[4+2] reaction

It is this option (eq. 4) that we decided to investigate first with the premise that this process could be used to prepare steroid-like ring systems (Scheme 2.13).[30]



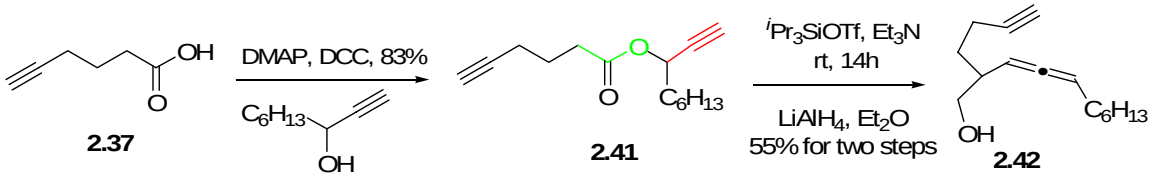
Scheme 2.13 Steroid-like ring systems can be formed from cross-conjugated trienes

Our substrate synthesis begins with Jones oxidation of 5-hexyn-1-ol to give 5-hexynoic acid **2.37** (Scheme 2.14).[31] The acid was then coupled with 3-butyne-2-ol using Steglich's method[32] to give ester **2.38**. Ester **2.38** was then dissolved in benzene and treated with TIPSOTf and triethylamine to form the silyl ketene acetal, which was not isolated but taken on immediately. Ireland-Claisen rearrangement[33] of the silyl ketene acetal occurred at rt in 16 h to afford allenyne **2.39** which was reduced to give allenyne **2.40**. This pathway has been used to generate alcohol **2.40** in three-gram scale.



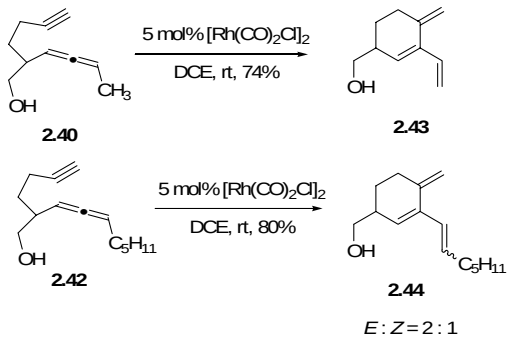
Scheme 2.14 Synthesis of allenyne alcohol **2.40**

Using the same sequence but changing the 3-butyn-2-ol to 1-nonyn-3-ol we can make allenyne alcohol **2.42** (Scheme 2.15).



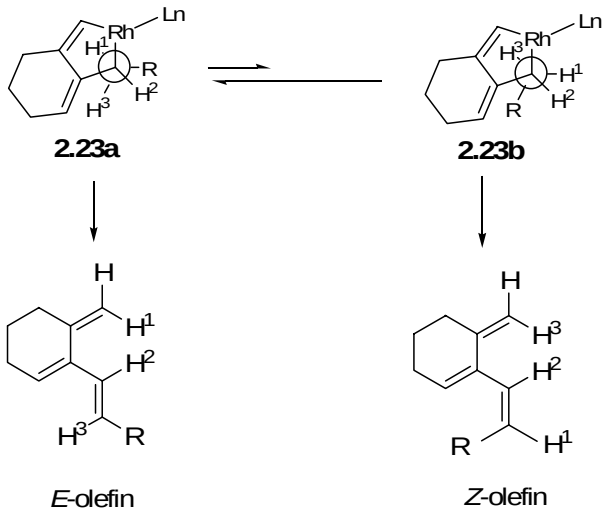
Scheme 2.15 Synthesis of allenyne alcohol **2.42**

2.2.2 The Alder-ene Reaction of 2.40 & 2.42 and *E*/*Z* Selectivity of 2.42



Scheme 2.16 Alder-ene reactions of allenyne alcohol **2.40** and **2.42**

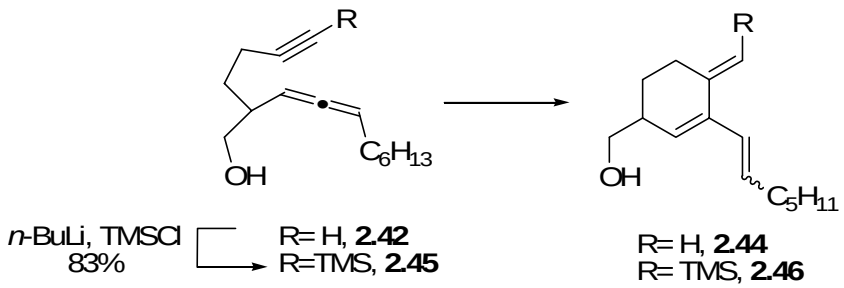
Allenyne **2.40** was then diluted in DCE and treated with 5 mol% of $[Rh(CO)_2Cl]_2$, the reaction went in 3 h at rt to give the corresponding triene **2.43** in 74% yield (Scheme 2.16). Subjecting **2.42** to the same conditions afforded two triene isomers in a combined yield of 80%. The *E*/*Z* ratio of **2.44** is 2/1 favoring the *E* isomer. The high functional group compatibility of the rhodium catalyst is evidenced by the reaction taking place in the presence of a free hydroxyl group. However, the poor *E*, *Z* selectivity could be a problem since separation of the isomers are difficult. Thus a study was carried out to improve the selectivity of the two isomers.



Scheme 2.17 Cross-conjugated triene *E*/*Z* selectivity

Our proposed mechanism in Scheme 2.17 can be used to explain the observed selectivity. Newman projections of the metallocycle **2.23** are shown in Scheme 2.17. It is postulated that the two rotamers **2.23a** and **2.23b** are in equilibrium and each one has a C-H in a synperiplanar orientation with the C-Rh bond which is requisite for β-hydride elimination. In rotamer **2.23a**, R is *syn* to H^2, β-hydride elimination takes place in this conformation the *E* isomer. Alternatively, rotamer **2.23b** has H^1 *syn* to H^2 which gives the *Z* isomer. It is reasoned that, when the cyclohexene ring is more sterically encumbering than the ligands on rhodium, **2.23a** is the preferred rotamer and the *E* isomer is the major product. On the other hand, if the ligands on rhodium are large and pose more steric hindrance than the cyclohexene ring, then rotamer **2.23b** is preferred and the *Z* isomer becomes the major isomer. In order to improve the *E*/*Z* selectivity, we have two options: 1) Changing the ligands or 2) changing the transition metal. From the previous study to screen for the optimum rhodium catalyst (Table 2.1), only small changes of *E/Z* ratios were observed by changing ligands on the rhodium catalysts. Thus

we turned to other transition metals. An iridium catalyst was chosen to test first since iridium is in the same group as rhodium. Indeed, Dr. Hongfeng Chen was able to demonstrate that $[Ir(COD)Cl]_2$ and a silver additive gave excellent *E/Z* selectivities of the appending double bond geometry.[34]



entry	allenyne	triene	catalysts	additives	E/Z	yield (%)
1	**2.42**	**2.44**	$[Ir(COD)Cl]_2$	AgOTf		decompostion
2	**2.42**	**2.44**	$[Ir(COD)Cl]_2$	$AgClO_4$		decompostion
3	**2.42**	**2.44**	$[Ir(COD)Cl]_2$	$AgBF_4$		decompostion
4	**2.45**	**2.46**	$[Ir(COD)Cl]_2$	$AgBF_4$	120 : 1	74
5	**2.45**	**2.46**	$[Rh(CO)_2Cl]_2$		5 : 1	69

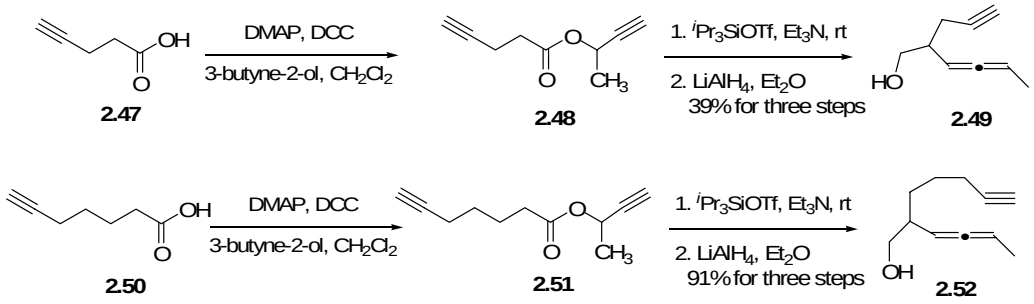
The reactions were done in DCE at 60 ºC using 10 mol% $[Ir(COD)Cl]_2$ and 20 mol% silver additive; for entry 1-4; for entry 5, the reaction was done in DCE at rt using 5 mol% $[Rh(CO)_2Cl]_2$

Table 2.2 Studies to improve the *E*/*Z* selectivity of cross-conjugated trienes

Allenyne **2.42** was diluted in DCE and treated with $[Ir(COD)Cl]_2$ and AgOTf (Table 2.2, entry 1), the reaction progressed slowly at rt, and decomposed when heated to 60 ºC. Similar results were seen with $AgClO_4$ or $AgBF_4$ (Table 2.2, entries 2 and 3). Since it is known that iridium catalysts react with the acidic proton of the alkyne,[35] thus it was replaced with a TMS group. Allenyne **2.45** afforded triene **2.46** in 74% yield at in 5 min 60 ºC. The reaction conditions also showed excellent *E* : *Z* selectivity of 120 : 1 (ratio measured by GC) for the conversion of **2.45** to **2.46**. We also subjected **2.45** to the $[Rh(CO)_2Cl]_2$ conditions and the *E* : *Z* selectivity was only 5 : 1. An interesting

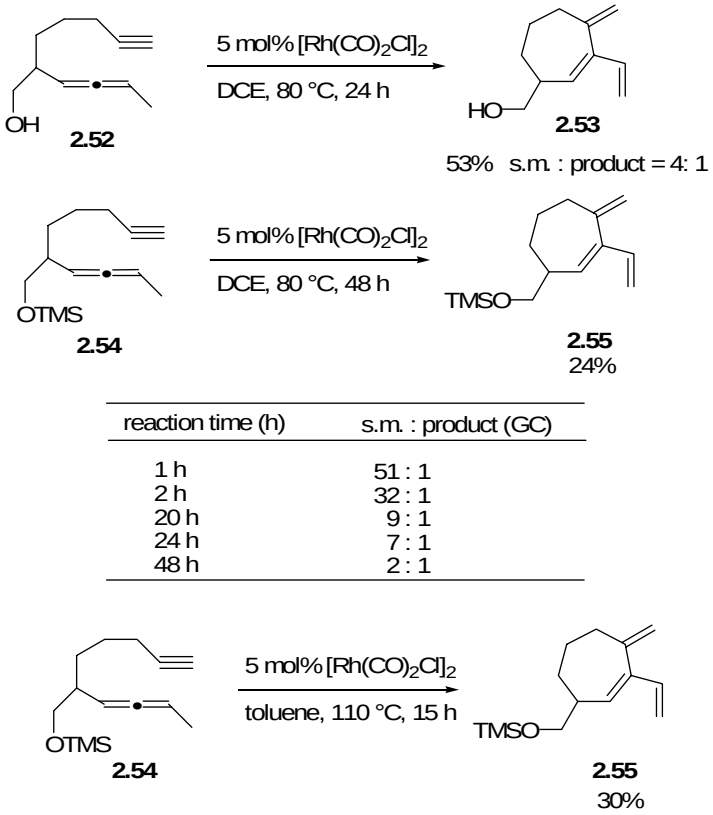
observation is that a TMS acetylene substrate gave better *E* : *Z* ratio than a methyl acetylene substrate. Although it is not clear how a TMS group helps to improve the *E* : *Z* selectivity, other silyl-facilitated reactions have been reported. For example, Carreira and coworkers observed only silylacetylenes participate in an addition to aldamines catalyzed by iridium(I) complex.[36] In summary, iridium(I)-catalyst gave better *E* : *Z* selectivity of cross-conjugated trienes than rhodium(I) catalyst.

2.2.3 Study of Five- and Seven-Membered Cross-Conjugated Triene Formation Through Rhodium(I)-Catalyzed Alder-ene Reactions



Scheme 2.18 Preparation of allenyne alcohols **2.49** and **2.52**

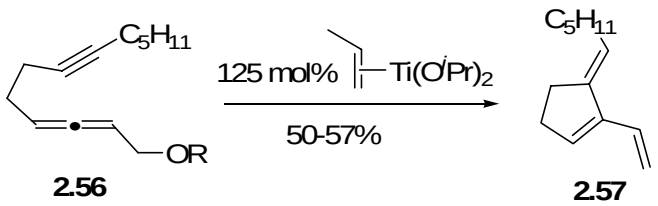
Allenyne alcohols **2.49** and **2.52** were synthesized (Scheme 2.18) in a manner entirely analogous to the synthesis of **2.40**. For **2.49**, the DCC coupling and Ireland-Claisen steps were not high yielding making the overall yield of this compound 39% for three steps. For synthesis of **2.52**, an excellent 91% overall yield was obtained.



Scheme 2.19 Seven-membered cross-conjugated triene formation

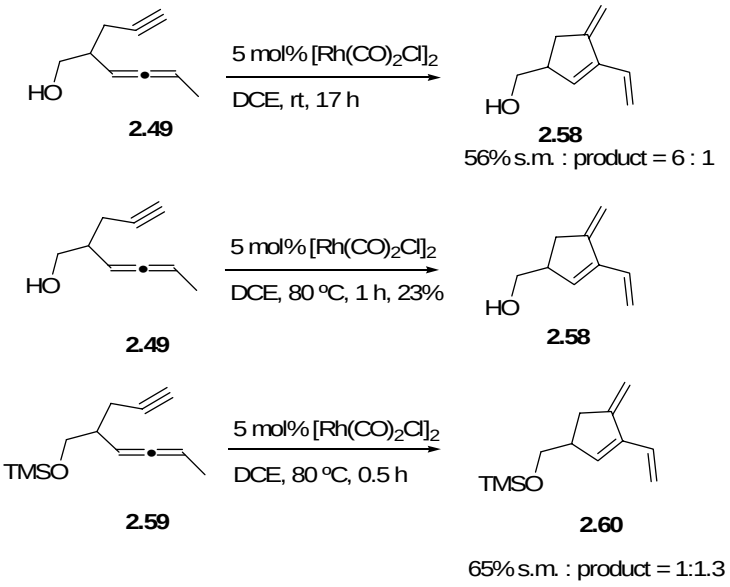
There are only limited examples of transition metal-catalyzed reactions to generate seven-membered rings.[37] Formation of seven-membered rings using the Alder-ene reaction turned out to be quite difficult too (Scheme 2.19). For example, allenynol **2.52** was diluted in DCE and treated with 5 mol% $[Rh(CO)_2Cl]_2$, and only after refluxing for 24 h was a mixture of starting material **2.52** and product **2.53** isolated in 53% yield and in 4:1 ratio. TMS ether **2.54** gave a 24% yield of a 2:1 mixture of **2.54** and **2.55** after refluxing in DCE for 48 h. The reaction was monitored by GC since **2.54** and **2.55** moved together on TLC plate. Refluxing **2.54** in toluene for 15 h gave **2.55** in 30% yield with some impurities but no starting material **2.54**. These preliminary results are

encouraging since Alder-ene reactions to form seven-membered rings are difficult, however, this substrate was very limiting so we decided not to pursue this any further.



Scheme 2.20 Sato's example of five-membered cross-conjugated triene formation

On the other hand, five-membered conjugated trienes synthesis has been reported by Sato[38] using stoichiometric amount of titanium complex to react with allenynol derivatives that contain a leaving group (Scheme 2.20). However, the isolated yields for these trienes were not high since they decomposed upon column chromatography.



Scheme 2.21 Rhodium(I)-catalyzed five-membered cross-conjugated triene formation

Alder-ene reactions to form five-membered rings occurred slowly at room temperature (Scheme 2.21). Only a small amount of triene **2.58** was formed after **2.49** was stirred for 17 h at room temperature with rhodium biscarbonyl chloride dimer. When heated to 80 ºC in DCE, **2.49** was converted to **2.58** completely in one hour. The yield is only 23% which is likely because of the unstable nature of five-membered cross-conjugated trienes. The NMR sample of **2.58** (in $CDCl_3$) turned milky white after being left at room temperature overnight, indicating that it probably polymerized under mildly acidic condition. To improve the stability, a silyloxy substrate **2.59** was used. A mixture of starting material and product was isolated after the reaction was heated for 30 min in refluxing DCE. The combined yield is 65% and the ratio is 1 : 1.3 determined by ^{1}H NMR.

Due to the limited success of the reaction to produce five- and seven-membered rings, we decided to focus on Alder-ene reaction that produce six-membered rings and their subsequent [4+2] cycloaddition reactions. Our interest is to study the selectivity of the Diels-Alder reactions of conjugated trienes and try to perform the Alder-ene/[4+2]/[4+2] reaction in a tandem fashion.

2.3 Conclusions

We have demonstrated rhodium(I)-catalyzed allenic formal Alder-ene reaction is an effective way to form six-membered rings with a synthetic useful cross-conjugated triene moiety. The reaction conditions are very mild and yields are good. Various functionalities are tolerated in the reaction conditions. Five and seven-membered rings

can also be formed, although in less satisfactory yields. The *E*/*Z* selectivity of cross-conjugated trienes can be drastically improved by using iridium catalyst. We have proposed that these trienes can be used in tandem Diels-Alder reactions, and these results will be discussed in the following chapter.

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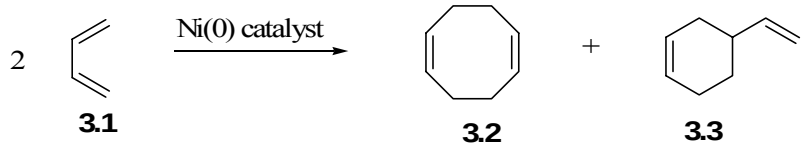
3. Cross-Conjugated Trienes and Their Application to Rapid Increases in Molecular Complexity

3.1 Introduction to Transition Metal Catalyzed [4+2] Cycloaddition

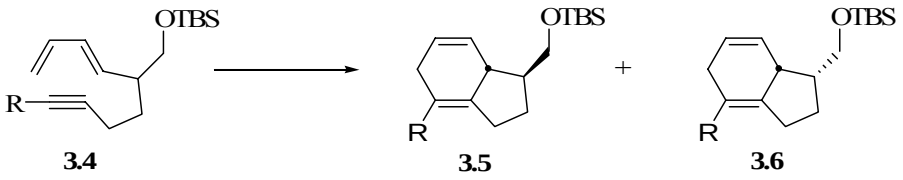
The Diels-Alder reaction is one of the most versatile synthetic transformations in organic chemistry.[1] This cycloaddition process can form a cyclohexene ring with as many as four contiguous stereogenic centers while intramolecular[2] and transannular[3] variants can form as many as three carbocyclic rings. The reaction can facilitate a rapid increase of molecular complexity and has been widely used in natural product synthesis.[4] The standard Diels-Alder [4+2] cycloaddition has long been studied and is a useful tool for synthetic chemists. However, this process normally is most efficient for reactions between electronically dissimilar dienes and dienophiles. Normally-difficult [4+2] cycloaddition reaction between electronically similar dienes and dienophiles can be efficiently catalyzed by a variety of low-valent metals.

One of the first metal-catalyzed [4+2] cycloaddition examples dated back to 1950s. In 1954, Reed observed the formation of 4-vinylcyclohexene as a byproduct in nickel(0)-catalyzed [4+4] cycloaddition (Scheme 3.1).[5] At that time, the [4+2] cycloaddition was only an undesired side reaction which seemed to give the same products as standard Diels-Alder reaction. It is clear now that this metal-catalyzed formal [4+2] cycloaddition is not only an alternative but also a complement to the concerted Diels-Alder reaction.



Scheme 3.1 Ni(0)-catalyzed [4+4] cycloaddition with [4+2] side product

Wender has carried out some early mechanistic and synthetic investigations on Ni(0)-catalyzed [4+2] cycloaddition.[6] For example, Wender and Jenkins showed the first synthetically useful Ni(0) catalyzed intramolecular [4+2] cycloaddition.[6a] Treating compound **3.4** with 10 mol% of $Ni(COD)_2$ and 30 mol% of tri-*o*-biphenyl phosphine gave diastereomers **3.5** and **3.6** in almost quantitative yield (Scheme 3.2). Internal alkynes were a requisite for this cycloaddition reaction since terminal alkynes were susceptible to homo-oligomerization under the reaction conditions.[7]



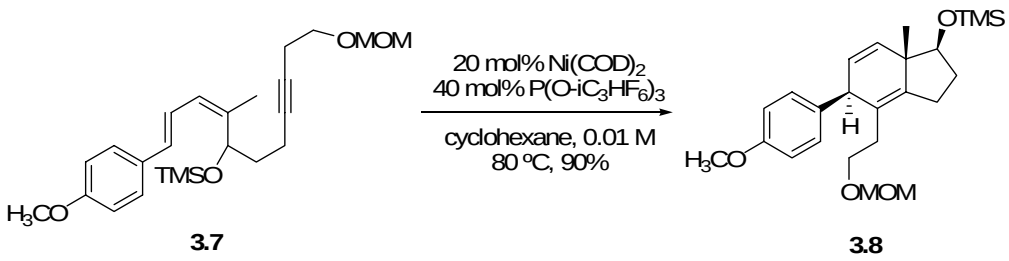
Substrate	Yield	dr
R=Me	>99%	2 : 1
R=TMS	98%	1.2 : 1

Conditions: Dienyne 0.01 M in THF; 10 mol% $Ni(COD)_2$; 30 mol% tri-*o*-biphenyl phosphite; 25 ºC

Scheme 3.2 Wender's example of Ni(0)-catalyzed [4+2] cycloaddition

Wender and Smith demonstrated that the stereochemistry of the diene component in nickel(0)-catalyzed dienyne cycloaddition is retained during the course of the reaction, even though the process involves multiple steps (Scheme 3.3).[6b] In addition, this

example also showed *Z*-alkenes can be used to produce products containing angular methyl groups.

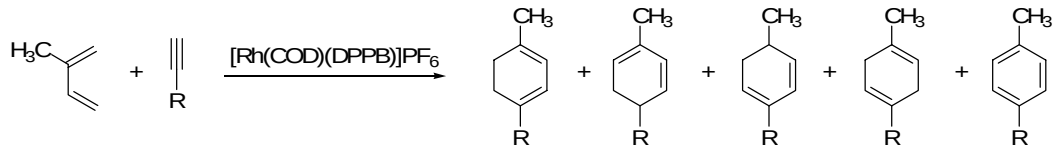


3.7 **3.8**

Scheme 3.3 Wender's example of Ni(0)-catalyzed stereoselective [4+2] cycloaddition

In addition to nickel, other transition metals like Fe,[8] Co,[9] Pt,[10] Ir,[11] Ti,[12] and Rh[13] have been used to catalyze the formal [4+2] cycloaddition reaction. Among them, Rh(I) is efficient at catalyzing [4+2] reaction under mild conditions.

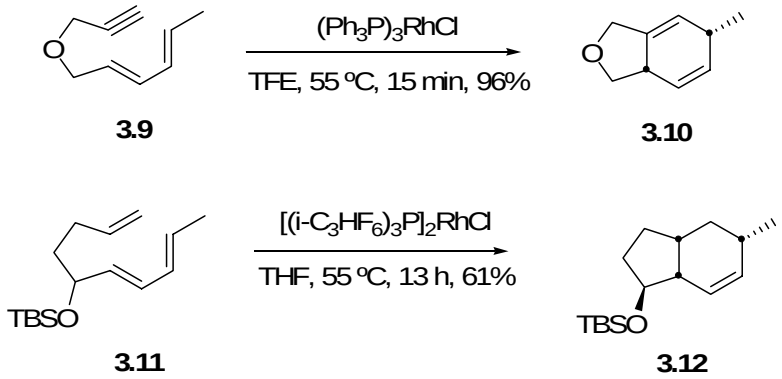
Matsuda showed one of the first examples of Rh(I) catalyzed [4+2] cycloaddition.[13a] He demonstrated that 1-5 mol% of $[Rh(COD)(DPPB)]PF_6$ can catalyze an intermolecular [4+2] addition under mild conditions (Scheme 3.4) to give cyclohexadienes in excellent yields although the major products are isomerized 1,3-cyclohexadienes.



Entry	R	(ºC)	yield (%)	Ratio of products				
1	C_6H_5	41	85	93	0	2	3	2
2	n-C_3H_7	43	65	94	1	1	3	1
3	n-C_5H_{11}	25	74	88	2	1	4	4

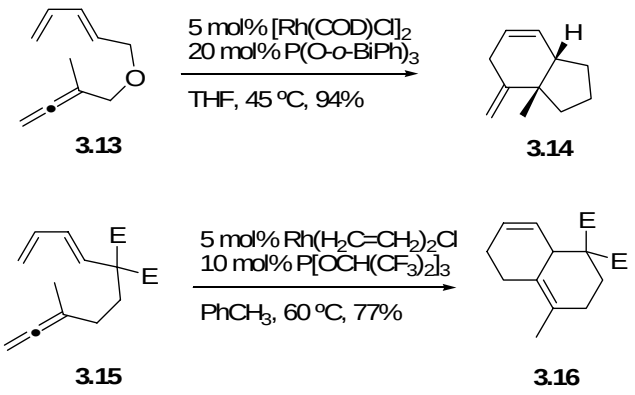
Scheme 3.4 Matsuda's example of Rh(I)-catalyzed intermolecular [4+2] cycloaddition

Livinghouse and coworkers briefly studied the influence of solvent effect on the formal Diels-Alder reaction of dieneyne **3.9** using commercial $(Ph_3P)_3RhCl$ as catalyst (Scheme 3.5).[13b] Several solvents were tested and trifluoroethanol was found to be a superior solvent over THF and ethanol in terms of reaction rate and efficiency. In addition, a rare example of transition metal catalyzed cycloaddition between alkene and diene was also shown. When triene **3.11** was treated with $[Rh(COD)Cl]_2$ modified with $P[OCH(CF_3)_2]_3$ at 55 ºC, bicyclic compound **3.12** was formed in 61% yield with good stereoselectivity although the reaction rate was slow.



Scheme 3.5 Livinghouse's example of Rh(I)-catalyzed intramolecular [4+2] cycloaddition

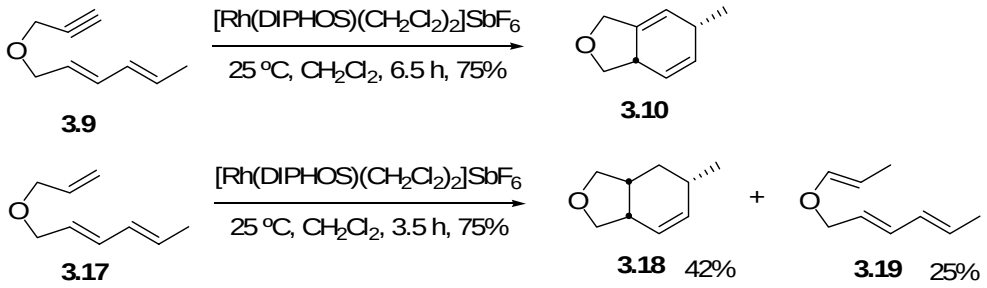
Wender and coworkers showed that allenes could be used as dienophiles and also that modifications in the rhodium catalyst can control the chemoselectivity and stereoselectivity of the cycloaddition (Scheme 3.6).[13c] Treatment of **3.13** in THF at 45 ºC with $[Rh(COD)Cl]_2$ modified with tri-*o*-biphenyl phosphine resulted in the chemospecific addition of the diene to the terminal π-system of the allene moiety, affording exclusively the angularly substituted cycloadduct **3.14** in 94% yield. When diene-allene **3.15** was treated with $[Rh(H_2C{=}CH_2)_2Cl]_2$ modified with $P[OCH(CF_3)_2]_3$, the cycloaddition proceeded with internal π-system of the allene moiety, providing compound **3.16** as a single diastereomer in 77% yield.



Scheme 3.6 Wender's example of Rh(I)-catalyzed intramolecular [4+2] cycloaddition of allene diene substrates

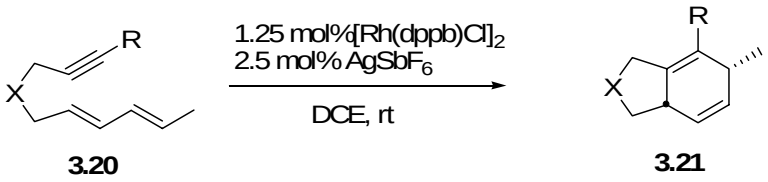
Gilbertson and Hoge reported a new catalyst $[Rh(DIPHOS)(CH_2Cl_2)_2]SbF_6$ that catalyzes the cycloisomerization of dieneynes and trienes (Scheme 3.7).[13e] The cycloaddition of dieneyne **3.9** proceeds at rt to give **3.10** in 75% yield. When triene **3.17**

was subjected to the same conditions, in addition to cycloaddition product **3.18**, an isomerization compound **3.19** was also formed.



Scheme 3.7 Gilbertson's example of Rh(I)-catalyzed intramolecular [4+2] cycloaddition

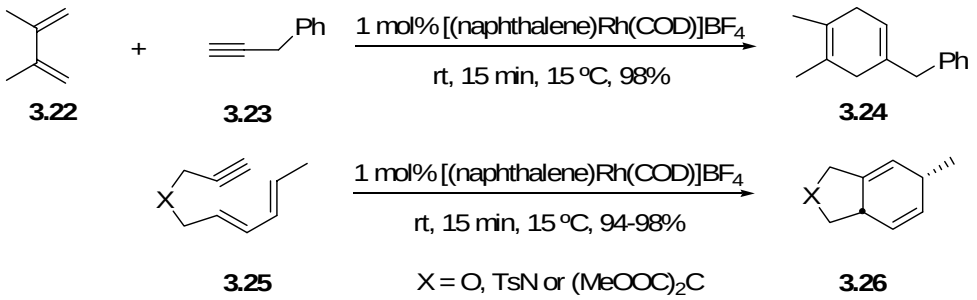
Zhang and coworkers also developed a new Rh-catalyst system for intramolecular [4+2] cycloaddition reactions (Scheme 3.8).[13h] They used $[Rh(bisphosphine)Cl]_2$ and $AgSbF_6$ to generate coordinatively unsaturated Rh catalysts. Different bisphosphine ligands can be used which allows for fine-tuning of the Rh-catalyst to meet steric and electronic requirements of the substrate. These conditions also showed high conversion for [4+2] cycloaddition at rt and excellent yields were obtained.



Substrate	Time	Yield (%)
X = $PhSO_2N$, R = H	1 hr	95
X = $PhSO_2N$, R = CH_3	1 hr	95
X = $(MeOOC)_2C$, R = H	3 hr	98
X = $(MeOOC)_2C$, R = CH_3	3 hr	99
X = O, R = H	10 min	75
X = O, R = CH_3	10 min	90

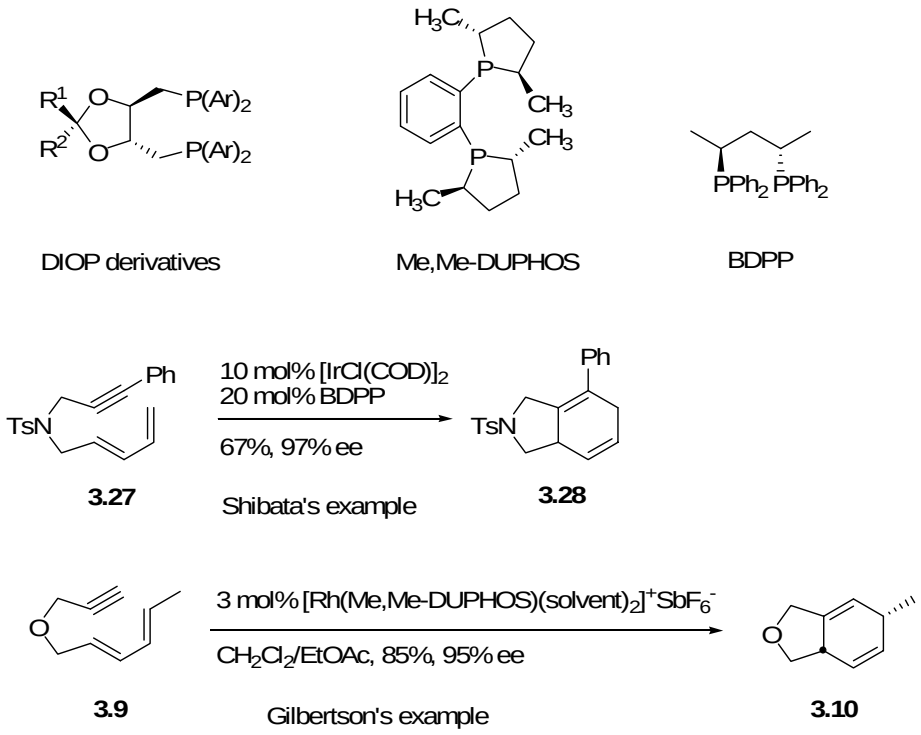
Scheme 3.8 Zhang's example of Rh(I)-catalyzed intramolecular [4+2] cycloaddition

Chung and coworkers found the cationic Rh(I) complex, $[(\eta^6\text{–}C_{10}H_8)Rh(COD)]BF_4$ to be a very effective catalytic system for both intermolecular and intramolecular [4+2] cycloadditions under very mild reaction conditions (CH_2Cl_2, 15 ºC, 15 min) (Scheme 3.9).[13h] Chung's catalyst is stable and can be stored under nitrogen for a long period of time. Wender and Williams developed a catalyst similar to that of Chung's catalyst except for the counter anion (BF_4^- vs SbF_6^-).[14] Wender's catalyst is just as efficient and can be stored on bench top for several months.



Scheme 3.9 Chung's example of Rh(I)-catalyzed intramolecular [4+2] cycloaddition

Transition-metal-catalyzed asymmetric [4+2] reaction can be achieved by using chiral ligands along with transition metals. The most common chiral ligands used include bisphosphine ligands related to DIOP,[15] Me, Me-DUPHOS,[16] and BDPP.[17] The enantiomeric purities are generally good and in some cases are higher than 95% *ee* (Scheme 3.10).[17,18]



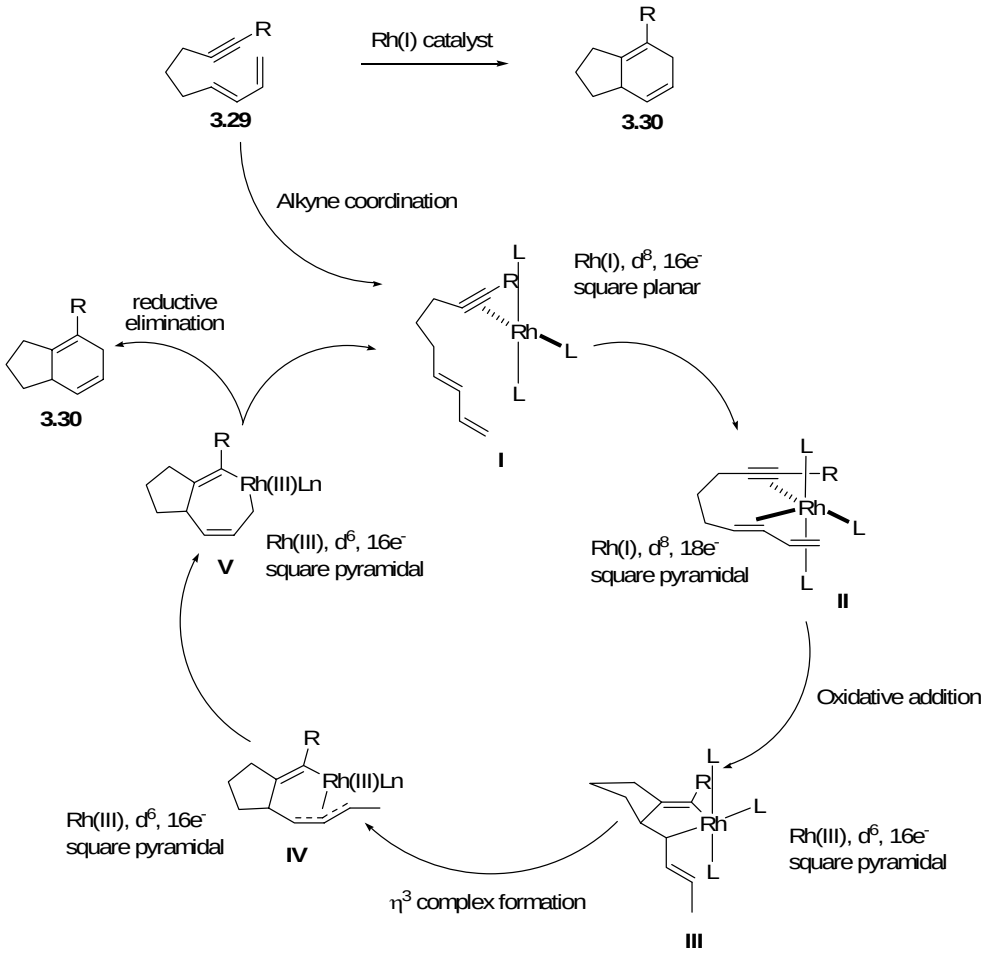
Scheme 3.10 Asymmetric [4+2] cycloadditions

In summary, transition metal catalyzed formal [4+2] cycloadditions are a useful complement to the concerted Diels-Alder reaction because they can catalyze cyclization reactions between electronically similar diene and dienophiles. It is also an effective tool in synthesizing complex molecule because of the generally mild condition.

3.2 Mechanism of Rhodium(I)-Catalyzed [4+2] Cycloaddition

Unlike concerted Diels-Alder reactions, transition metal-catalyzed [4+2] cycloadditions go through a multistep sequence.[13b,18] The mechanism of rhodium(I) catalyzed [4+2] cycloaddition is shown in Scheme 3.11. Initially, Rh(I) catalyst coordinates to the alkyne in substrate **3.29** give intermediate **I** which can coordinate with

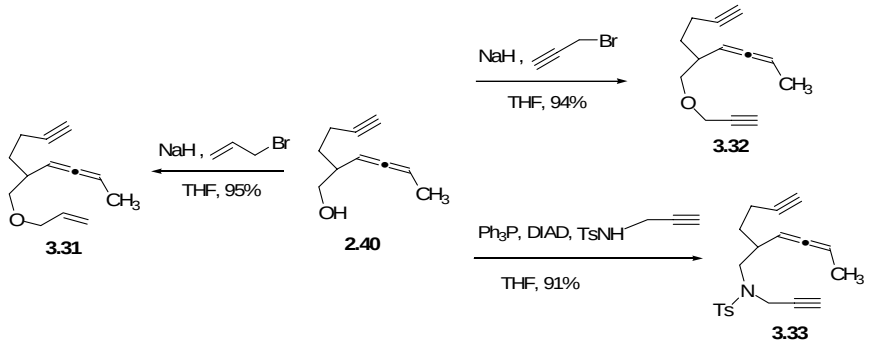
another double bond to give intermediate **II**. During this process, geometry of rhodium complex changes from square planar to square pyramidal. Oxidative addition occurs to afford five-membered metallocycle **III** which then is converted to seven-membered metallocycle **V** via a η^3 complex **IV**. Reductive elimination gives product **3.30** and rhodium(I) catalyst which goes to the next catalytic cycle. While the initial steps in this process are reversible, the exothermic reductive elimination step makes the whole process irreversible.



Scheme 3.11 Mechanism of Rh(I)-catalyzed [4+2] cycloaddition

3.3 Synthesis of Allenediyne and Allene Enyne Substrates for the Tandem Alder-ene/Diels-Alder Reactions

Allenynol **2.40** was considered an ideal starting material to make substrates suitable for study the tandem Alder-ene/Diels-Alder reactions for several reasons: the pending primary alcohol of **2.40** can easily be converted to a variety of functionalities such as propargyl ether or allyl ether to test the feasibility and scope of the transition metal catalyzed intramolecular Diels-Alder reaction; the Alder-ene reactions of allenyne substrates generated from **2.40** should go smoothly to generate six-membered cross-conjugated trienes; no *E*, *Z* selectivity issue in the Alder-ene reaction when a methyl group instead of a longer alkyl chain is on the allene moiety. In addition, these substrates could be potentially useful as biologically relevant compounds. Those substrates tethered a side chain like alkyne or alkene to the allenyne back bone. We were interested to see how these substrates react in the rhodium conditions, particularly the possible Diels-Alder reaction between the tethered alkyne/alkene and the cross-conjugated trienes from the Alder-ene reaction.



Scheme 3.12 Synthesis of allenyne substrates **3.31**, **3.32** and **3.33**

Alcohol **2.40** was converted to allene enyne **3.31** and allenediyne **3.32** *via* a Williamson etherification reaction (Scheme 3.12). Alcohol **2.40** was deprotonated using sodium hydride followed by addition of propargyl bromide or allyl bromide.[19] Compound **3.31** and **3.32** were obtained in almost quantitative yields. Sulfonamide **3.33** was formed in 91% yield under Mitsunobu reaction conditions.[20]

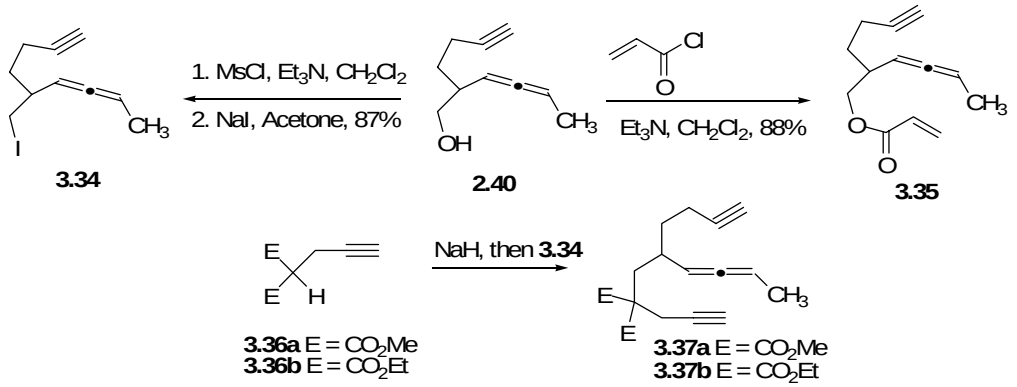


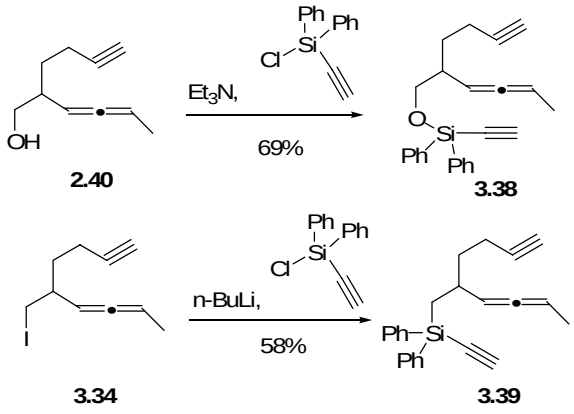
Table 3.1. Alkylation conditions to form allenediyne **3.37**

entry	conditions	yields
1	**3.36b**, 1.2 equiv.NaH, THF, rt	0%
2	**3.36b**, 2 equiv. NaH, THF/HMPA, rt to 50 ºC	0%
3	**3.36b**, 2.5 equiv. NaH, DMF, rt to 50 ºC	15%
4	**3.36a**, 1.2 equiv.NaH, DMF, rt	43%

Scheme 3.13 Synthesis of allenyne substrates **3.35**, **3.37**

Allenyne ester **3.35** was prepared by adding acryloyl chloride to alcohol **2.40** (Scheme 3.13). Attempts to prepare **3.37** using acrylic acid and DCC were not as successful, leading to a 54% yield of **3.35** and an unidentifiable byproduct. Alcohol **2.40** was converted to iodide **3.34** through mesylation and a Finkelstein reaction. Iodide **3.34** in turn was used in an alkylation of **3.36a** and **3.36b** to give substrates **3.37a** and **3.37b**. This reaction was problematic. Initially, we used 1.2 equivalents of sodium hydride in

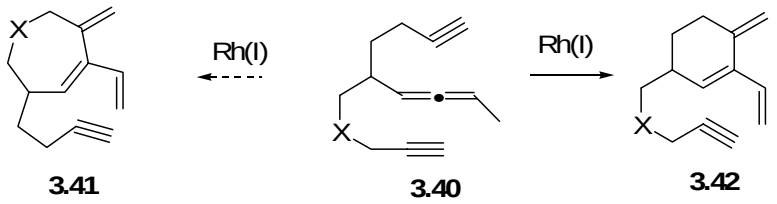
THF to deprotonate, but there was no reaction (entry 1, Table 3.1). Then, the amount of sodium hydride was increased to 2.0 equivalents and the solvent polarity was increased by adding HMPA. This also gave no product formation (entry 2, Table 3.1). Next, 2.5 equivalents of sodium hydride and DMF as solvent provided a 15% yield of alkylation product **3.37b** (entry 3, Table 3.1). Finally, changing from the diethyl propargylmalonate **3.36b** to dimethyl propargylmalonate **3.36a** gave a 43% yield of product **3.37** (entry 4, Table 3.1). It appears the size of the ester group makes a big difference in terms of yields. Harvey also reported similar observation on alkylation of propargylmalonate salts.[21]



Scheme 3.14 Synthesis of silicon-tethered substrates **3.38**, **3.39**

Silicon has been used in intramolecular reactions to tether two reactive moieties together.[22] The silicon serves as a temporary connection and can be removed after the reaction. Two silicon containing substrates **3.38** and **3.39** were synthesized (Scheme 3.14). Alcohol **2.40** reacted with diphenylchlorosilyl acetylene to give **3.38** in 69% yield. Compound **3.39** was prepared by treating iodide **3.34** with *n*-butyl lithium followed by adding a solution of diphenylchlorosilyl acetylene.

3.4 Rhodium(I)-Catalyzed Alder-ene Reaction of Allenediyne and Allene Enyne Substrates

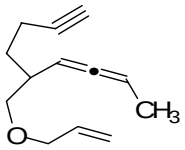
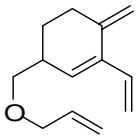
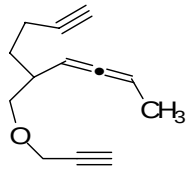
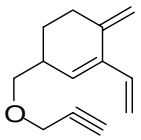
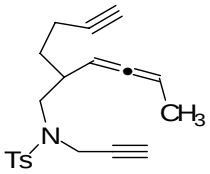
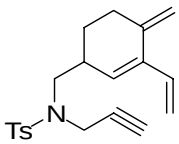
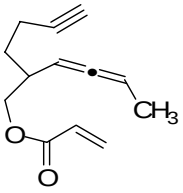
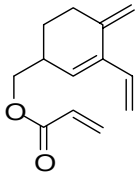
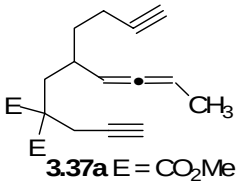
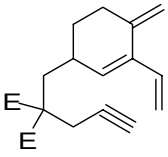
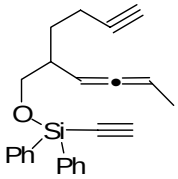
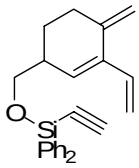
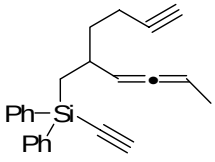
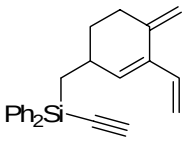


3.41 **3.40** **3.42**

Scheme 3.15 Two possible Alder-ene products from allenediyne **3.40**

The allenediyne substrates can form two possible Alder-ene products, six-membered **3.42** and seven-membered product **3.41** (Scheme 3.15). **3.42** should be formed predominantly. The allene enyne and allenediyne substrates were then subjected to 5 mol% $[Rh(CO)_2Cl]_2$. The results are summarized in Table 3.2. For ether substrates **3.32** and **3.33**, conjugated-trienes were formed after the reactions were stirred at rt for 2 h (Table 3.2, entries 1 and 2). The yields are 83% and 86% respectively and there is no sign of seven-membered Alder-ene products. The Alder-ene reaction of the sulfonamide **3.31** was much faster and gave product **3.45** in higher yield (Table 3.2, entry 3). After 10 minutes of stirring at rt, **3.45** was isolated in 93% yield. Acrylate ester **3.35** and gem-diester substrate **3.37a** also underwent Alder-ene reactions smoothly to give **3.46** and **3.47** in good yields. Silicon-tethered substrates **3.38** and **3.39** also worked well to give trienes **3.48** and **3.49** in high yields. Interestingly, **3.39** reacted a lot faster than **3.38** which has one more oxygen atom in the tether. A problem associated with silicon-containing compounds **3.38**, **3.39**, **3.48** and **3.49** is the impurities those compounds contain. The impurities contain diphenylsilyl group and are difficult to remove *via*

column chromatography. The aromatic region of these compounds is integrated for more for this reason. The cross-conjugated trienes formed from these formal allenic Alder-ene reaction did not proceed the following [4+2] cycloaddition as we hoped, which set us to look for catalysts that are effective for serial formal Alder-ene/[4+2] cycloaddition. The results will be discussed in chapter 3.5.

entry	allenyne	triene	time	yield
1	 **3.31**	 **3.43**	2h	83%
2	 **3.32**	 **3.44**	2h	86%
3	 **3.33**	 **3.45**	10 min	93%
4	 **3.35**	 **3.46**	2h	78%
5	 **3.37a** E = CO_2Me	 **3.47**	4h	74%
6	 **3.38**	 **3.48**	2h	83%
7	 **3.39**	 **3.49**	20 min	88%

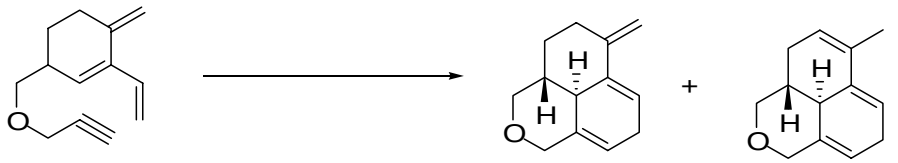
Conditions: 5 mol% $[Rh(CO)_2Cl]_2$, DCE, N_2, room temperature

Table 3.2 Alder-ene reaction of allene enyne and allenediyne substrates

3.5 Rhodium(I)-Catalyzed [4+2] Cycloadditions of Cross-Conjugated Trienes

Substrate **3.44** was chosen to study rhodium-catalyzed [4+2] cycloaddition of cross-conjugated trienes because transition-metal-catalyzed [4+2] cycloaddition between electronically similar diene and dienophile are the most common. Substrate **3.44** was first subjected to the $[Rh(CO)_2Cl]_2$ in DCE (Table 3.3, entry 1), the catalytic conditions that proved to be very efficient in catalyzing the allenic Alder-ene reaction. No [4+2] cycloaddition was observed under these conditions. We then tested two conditions reported by Livinghouse.[13] Using Wilkinson's catalyst in TFE (Table 3.3, entry 2), we only observed decomposition of the starting material and a 20% yield of a mixture of several unidentifiable compounds. When $[Rh(COE)Cl]_2$ was used along with a strong electron withdrawing ligand $(i\text{-}C_3HF_6)_3P$, we saw only decomposition (Table 3.3, entry 3). Using $[Rh(CO)_2Cl]_2$ and dppb along with $AgSbF_6$ as additive also gave decomposition (Table 3.3, entry 4). We then turned to the conditions reported by Zhang.[13h] Using $[Rh(dppe)Cl]_2$ in DCE along with $AgSbF_6$ as additive, we isolated **3.51** as the major product (Table 3.3, entry 5). Triene **3.51** presumably comes from isomerization of **3.50**. The trans relationship of the two hydrogens in **3.50** was characterized later through X-ray analysis of two Diels-Alder products of **3.50**. Solvent effects proved to be significant in this reaction. When DCE is replaced by acetone as solvent, **3.50** was isolated as the major product even though the reaction went slower (Table 3.3, entry 6). A similar catalyst $[Rh(dppb)Cl]_2$ with the additive $AgSbF_6$ also gave **3.51** as the major product (Table 3.3, entry 7). Catalysts $[Rh(dppe)Cl]_2$ and $[Rh(dppb)Cl]_2$ were prepared *in situ* following Zhang's procedure by treating $[Rh(COD)Cl]_2$ with ligands dppe or dppb.[23] For

entries 5, 6 and 7, small amounts of uncharacterizable byproducts (≤ 5%) were also observed. Wender's catalyst $[Rh(COD)(C_{10}H_8)]^+SbF_6^-$, afforded the cycloaddition in 15 min at rt to give **3.50** as the only product in 92% yield (Table 3.3, entry 8). Wender's catalyst was prepared following their procedure of treating $[Rh(COD)Cl]_2$ with naphthalene and the additive $AgSbF_6$.[15] More recently, we discovered commercially available $[Rh(COD)]_2OTf$ can also be used to catalyze [4+2] cycloaddition (Table 3.3, entry 9). When **3.44** was treated with $[Rh(COD)_2]OTf$, **3.50** was formed in 95% yield at rt. To the best of our knowledge, this is the first time $[Rh(COD)_2]OTf$ has been used to catalyze a [4+2] cycloaddition.



3.44 **3.50** **3.51**

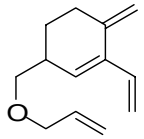
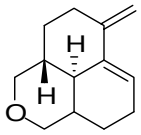
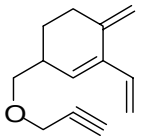
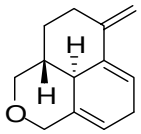
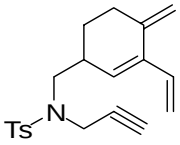
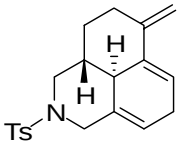
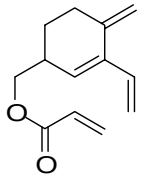
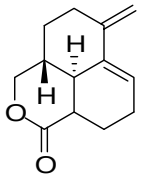
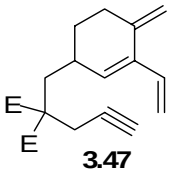
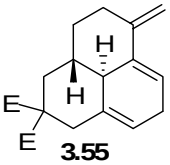
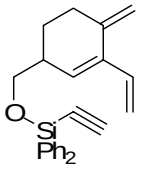
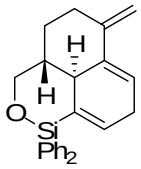
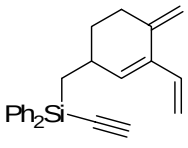
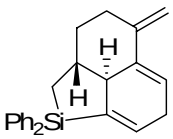
entry	Conditions	Additive	yield (%)
1	$[Rh(CO)_2Cl]_2$, DCE, rt	none	no reaction
2	$Rh(Ph_3P)_3Cl$, TFE, 65 ºC	none	20% of mixture
3	$[Rh(COE)_2Cl]_2$, THF, 55 ºC	$(i\text{-}C_3HF_6)_3P$	decompostion
4	$[Rh(CO)_2Cl]_2$	dppb, $AgSbF_6$	decompostion
5	$[Rh(dppe)_2Cl]_2$, DCE	$AgSbF_6$	78% of **3.51**
6	$[Rh(dppe)_2Cl]_2$, Acetone	$AgSbF_6$	73% of **3.50**
7	$[Rh(dppb)_2Cl]_2$, DCE	$AgSbF_6$	70% of **3.51**
8	$[Rh(C_{10}H_8)(COD)]^+SbF_6^-$	none	92% of **3.50**
9	$[Rh(COD)_2]OTf$, DCE	none	95% of **3.50**

Table 3.3 Rhodium(I)-catalyzed [4+2] cycloaddition of trienyne **3.44**

Based upon these studies, Wender's catalyst system was used to promote the [4+2] cycloaddition of the other trienes and the results are listed in Table 3.4.[24] When a double bond is tethered on as dienophile, the [4+2] cycloaddition did not occur (Table 3.4, entry 1). Oxygen tethered propargyl substrate **3.44**, nitrogen tethered **3.45** and gem diester

substrate **3.47** all reacted smoothly when treated with $[Rh(C_{10}H_8)(COD)]SbF_6$ in DCE (Table 3.4, entries 2, 3 and 5). Each of these reactions completed within 15 minutes at room temperature. An ester tethered substrate **3.46** was also tested and not surprisingly no reaction was observed (Table 3.4, entry 4). Silicon tethered acetylene substrates **3.48** and **3.49** did not provide the desired cyclic products under this catalytic condition presumably because the steric hindrance posed by the two phenyl groups on the silicon (Table 3.4, entry 6 and 7).

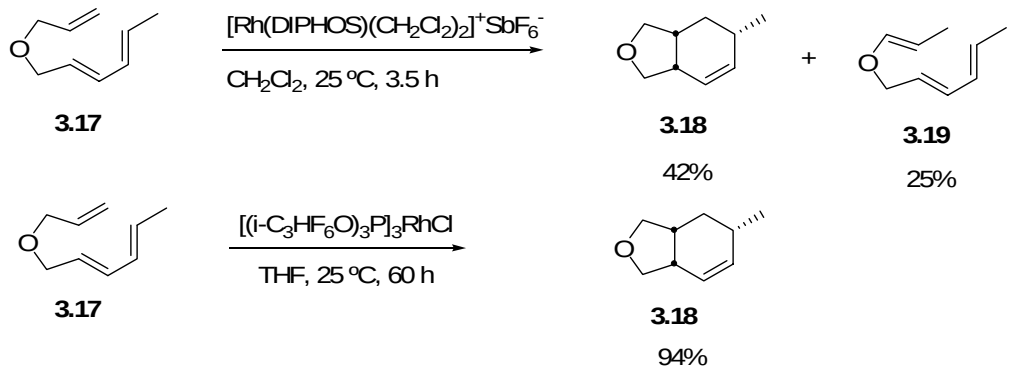
Zhang's conditions $[Rh(dppe)Cl]_2/AgSbF_6$ were also tested and still no cyclization was observed for substrates **3.43**, **3.46**, **3.48** and **3.49**.

entry	triene	Tricyclic product	time	yield
1	 **3.43**	 **3.52**	4h	No Reaction
2	 **3.44**	 **3.50**	10 min	92%
3	 **3.45**	 **3.53**	10 min	93%
4	 **3.46**	 **3.54**	4h	No Reaction
5	 **3.47**	 **3.55**	15 min	94%
6	 **3.48**	 **3.56**	4 h	No Reaction
7	 **3.49**	 **3.57**	4 h	No Reaction

Conditions: 5 mol% $[Rh(C_{10}H_8)(COD)]^+SbF_6^-$, DCE, N_2, room temperature

Table 3.4 [4+2] cyclizations of trienes **3.43-3.49** catalyzed by Wender's catalyst

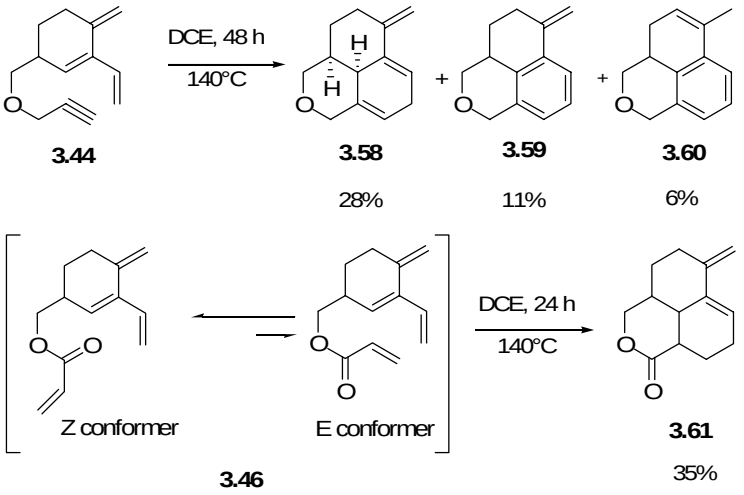
Rhodium-catalyzed [4+2] cycloadditions between a diene and a double bond have been reported (Scheme 3.16). Gilbertson used $[Rh(DIPHOS)(CH_2Cl_2)_2]^+SbF_6^-$ to effect [4+2] cyclization of triene **3.17** to give bicyclic product **3.18** in 42% yield and a double bond isomerization byproduct **3.19** was also isolated.[13e] Other conditions were reported by Livinghouse which gave 94% yield of the desired product **3.18** from the same substrate using $[(i\text{-}C_3HF_6O)_3P]_3RhCl$ as the catalyst. However, neither catalyst affected cyclization of our substrate **3.43**. Besides the fact that cross-conjugated trienes are more electron deficient than a diene, the corresponding cycloadduct posses a more strained fused tricyclic product **3.52**. In addition, there are no reports of decalin ring systems made from rhodium-catalyzed intramolecular [4+2] cycloaddition.



Scheme 3.16 Rhodium-catalyzed [4+2] cycloadditions between a diene and a double bond

Upon heating, cross-conjugated trienes can also react with dienophiles to give Diels-Alder products (Scheme 3.17). Triene **3.44** in DCE was heated to 140 ºC for 48 hours in a sealed tube to give Diels-Alder product **3.58** along with two aromatized products **3.59** and **3.60**. The requisite of prolonged heating is attributed to two factors.

First, the inner-outer ring diene[25] is less reactive than an open-chain diene. In addition to that, ester **3.46** needs to adopt less stable *E*-conformer to undergo an intramolecular Diels-Alder reaction. The energy barrier between *Z*-conformer and the *E*-conformer is around 10 kcal/mol. As a result, it takes 48 h at 140 ºC to complete the intramolecular Diels-Alder reaction to give **3.61** in 35% yield along with some uncharacterized byproducts.



Scheme 3.17 Thermal Diels-Alder reaction of cross-conjugated triene **3.44** and **3.46**

It would also be interesting to know how ester **3.46** reacts in the presence of Lewis acid. We did a brief study and the results are listed in Table 3.5. When trifluoroborane etherate was used, only decomposition of the ester was observed (Table 3.5, entry 1). Using aluminum trichloride or ethyl aluminum dichloride also resulted in decomposition of **3.46** (Table 3.5, entry 2 and 3). Milder Lewis acid such as ytterbium triflate and scandium triflate gave no reaction (Table 3.5, entry 4 and 5). Next, conditions

reported by Roush were tried.[26] When **3.46** was subjected to ethyl aluminum dichloride or tin tetrachloride, rapid decomposition was observed (Table 3.5, entry 6). Finally, methyl aluminum dichloride give isomerized cycloaddition product **3.33** in 80%, no **3.62** was isolated (Table 3.5, entry 7).

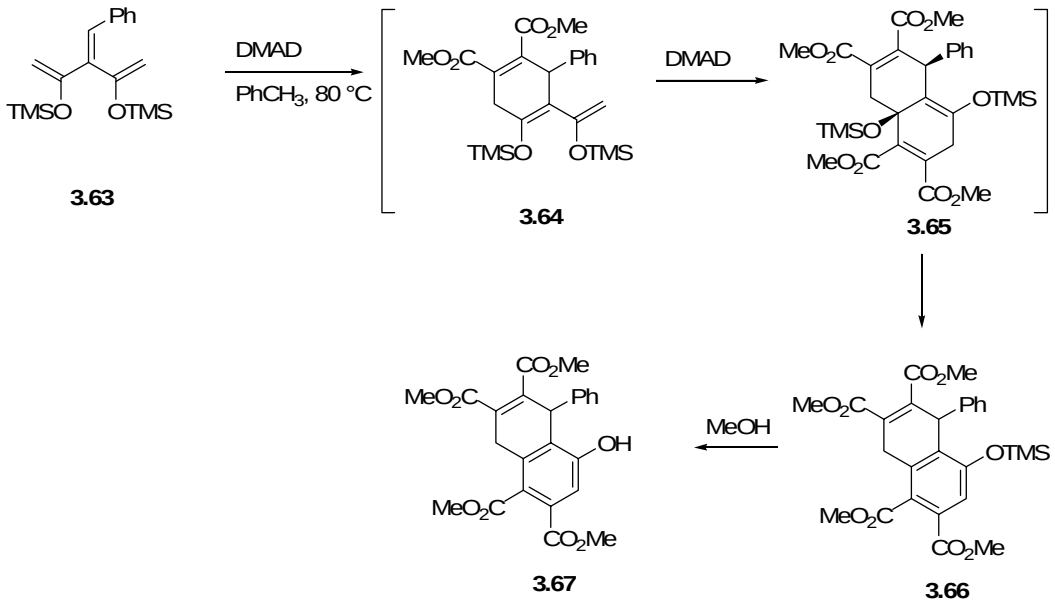
Entry	L. A.	temp (°C)	solvent	yield
1	$BF_3{\cdot}Et_2O$	0	CH_2Cl_2	decomposition
2	$AlCl_3$	rt	CH_2Cl_2	decomposition
3	$EtAlCl_2$	-78	CH_2Cl_2	decomposition
4	$Yb(OTf)_3$	rt	CH_2Cl_2	no reaction
5	$Sc(OTf)_3$	rt	Et_2O	no reaction
6	$SnCl_4$	-78	toluene/CH_2Cl_2	decomposition
7	$MeAlCl_2$	-78	toluene	80% of **3.62**

Table 3.5 Lewis acid catalyzed Diels-Alder reaction of triene ester **3.46**

3.6 Serial Alder-ene/[4+2]/[4+2] Reactions

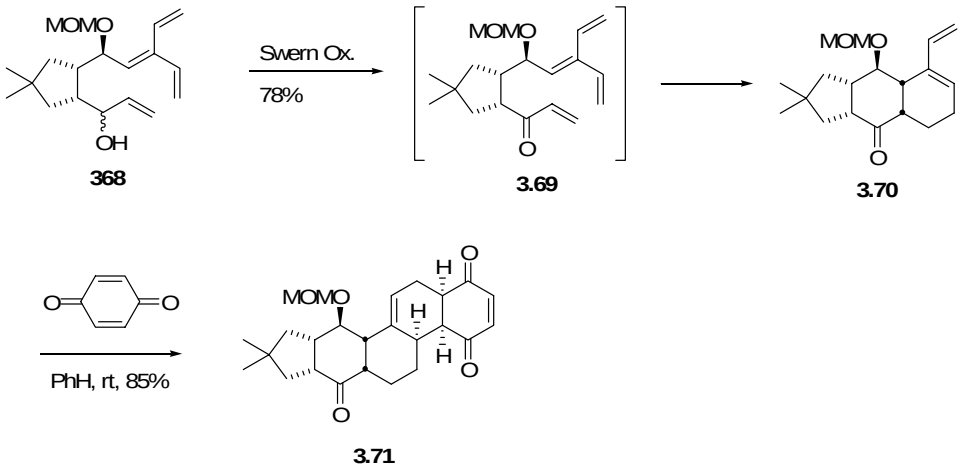
One goal of organic synthesis is to achieve molecular complexity in a rapid and efficient way. An ideal synthesis can quickly assemble complex targets through a simple operation based on readily available starting materials. A cross-conjugated triene is a suitable starting material to serve this purpose. Tsuge showed that cross-conjugated triene **3.63** functions as a bis-diene and undergoes two serial [4+2] cycloadditions (Scheme 3.18).[27] Both dienes of **3.63** are electronically activated by siloxyl groups to react with a dienophile. The initial [4+2] cycloaddition is sterically influenced to react with only one of the conjugated dienes forming a six-membered ring and a new

conjugated diene. The second [4+2] cycloaddition can now occur with the new diene to yield **3.65**. 1,4-Elimination of trimethylsilanol from **3.65** yields **3.66**, which is hydrolyzed to afford the isolated product **3.67**.



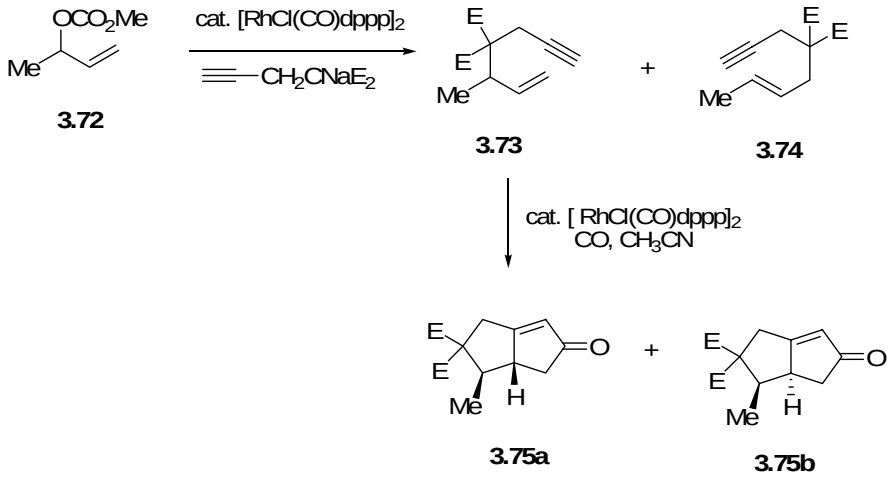
Scheme 3.18 Cross-conjugated triene in serial intermolecular/intermolecular Diels-Alder reactions

Fallis recently employed a sequential intramolecular/intermolecular Diels-Alder strategy for the synthesis of oxygenated nor-steroid and triterpenoid skeletons (Scheme 3.19).[28] Swern oxidation of **3.68** affords ketone **3.69**, activating the dienophile, which allowing the intramolecular Diels-Alder reaction to occur in 1 h at 0 ºC to afford **3.70**. Diene **3.70** undergoes a second, stereoselective [4+2] cycloaddition with a variety of dienophiles with high stereoselectivity. Thus two new rings, four carbon-carbon bonds, and five new stereocenters are set. The authors note that the cycloadditions can be conducted in the same reaction vessel, but purity is improved with a discrete workup of **3.70**.



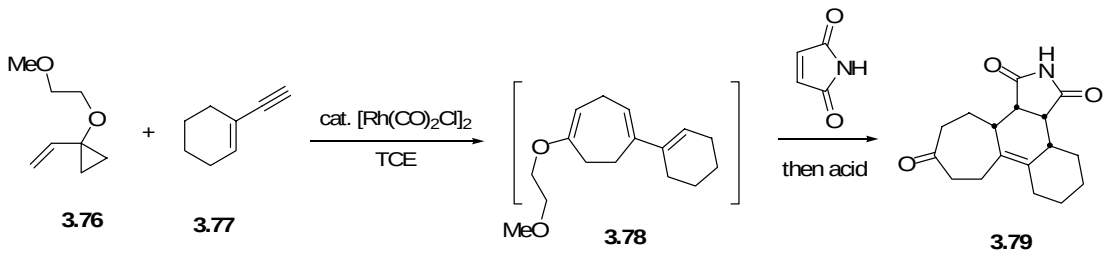
Scheme 3.19 Cross-conjugated trienes in serial intramolecular/intermolecular Diels-Alder reactions

Rhodium catalysts have been used in tandem or serial reactions.[29] For example, Evans used a rhodium(I) catalyst to catalyze a tandem allylic alkylation/Pauson-Khand annulation reaction in a regio- and diastereoselective fashion (Scheme 3.20).[30] When the allylic carbonate **3.72** was treated with the sodium salt of the α-branched dimethyl malonate derivative and $[RhCl(CO)dppp]_2$ in acetonitrile at 30 ºC, under an atmosphere of carbon monoxide, furnished the enynes **3.73**/**3.74** in a ratio of 37:1 favoring the secondary product **3.73**. The reaction mixture was then heated at reflux for 24 h, resulting in the formation of the bicyclic cyclopentenones **3.75a**/**3.75b** as a 7:1 mixture of diastereoisomers favoring **3.75a**.



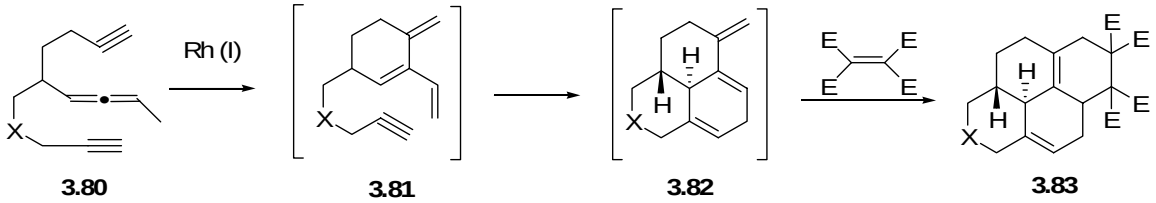
Scheme 3.20 Evans's example of Rh(I)-catalyzed tandem allylic alkylation/Pauson-Khand annulation reaction

Wender and coworkers reported a rhodium(I)-catalyzed serial [5+2]/[4+2] reaction (Scheme 3.21).[31] When a mixture of vinylcyclopropane **3.76**, enyne **3.77** and a dienophile in TCE solvent were treated with a catalytic amount of $[Rh(CO)_2Cl]_2$, a [5+2] cycloaddition occurred between **3.76** and **3.77** to give a diene **3.78**, which then reacted with the dienophile and upon acidic workup to give a polycyclic compound **3.79** as a single diastereomer. Two rings and four steric centers were formed in a predictable and specific manner in this one-pot process.



Scheme 3.21 Wender's example of rhodium(I)-catalyzed serial [5+2]/[4+2] reaction

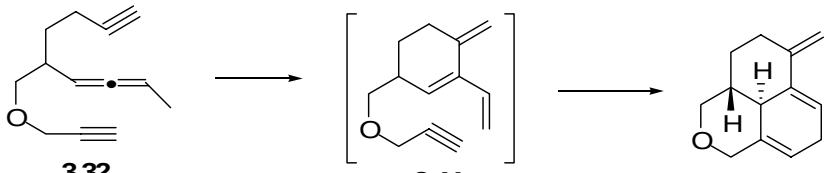
To efficiently increase molecular complexity using cross-conjugated trienes, we were interested in finding conditions that can convert allenyne substrate **3.80** to polycyclic compound **3.83** (Scheme 3.22). As we showed previously, Alder-ene reaction **3.80** to **3.81** can be catalyzed by $[Rh(CO)_2Cl]_2$ and [4+2] cyclization **3.81** to **3.82** reaction can be catalyzed using Wender's catalyst $[Rh(C_{10}H_8)(COD)]SbF_6$ or Zhang's condition $[Rh(dppe)Cl]_2/AgSbF_6$. Naturally, investigations were initiated to yield one rhodium catalyst to accomplish the transformation from **3.80** to **3.82**.



Scheme 3.22 Serial Alder-ene/[4+2]/[4+2] reaction

A variety of conditions were screened to look for a single rhodium catalyst that would effect a tandem Alder-ene/[4+2] reaction. $[Rh(CO)_2Cl]_2$ can only catalyze Alder-ene reaction to give triene **3.44** in 86% yield, no [4+2] cycloaddition product **3.50** was observed (entry 1, Table 3.6). The [4+2] cycloaddition catalysts were tested next. Wender's catalyst $[Rh(COD)(C_{10}H_{8})]SbF_6$ gave **3.50** in 23% (entry 2, Table 3.6). Zhang's conditions $[Rh(dppe)Cl]_2/AgSbF_6$ resulted in decomposition of the starting material. The newly discovered [4+2] catalyst $[Rh(COD)_2]OTf$ gave only 6% triene **3.44** and 54% of recovered allenediyne **3.32**. Oddly, **3.50** was not formed even though triene **3.44** was observed. $Rh(PPh_3)_3Cl$ in TFE at 65 ºC only caused decomposition of

3.32 (entry 5, Table 3.6). $Rh(PPh_3)_3Cl$ in DCE at 80 ºC gave a mixture of **3.44** and **3.50** in a combined yield of 24% (entry 6, Table 3.6). $[Rh(COD)Cl]_2$ with $AgSbF_6$ gave 45% of triene **3.44** (entry 7, Table 3.6). A different catalyst $[Rh(NBD)Cl]_2$ with $AgSbF_6$ gave only decomposition (entry 8, Table 3.6). $[Rh(COD)Cl]_2$ with ligand dppe and additive $AgSbF_6$ resulted in polymerization (entry 9, Table 3.6). Commercially available $[RhCl(CO)dppp]_2$ provided **3.44** in 70% and $[RhCl(CO)dppp]_2$ along with $AgSbF_6$ gave 25% of **3.50** (entry 10 and 11, Table 3.6). $[RhCl(CO)dppe]_2$ and $AgSbF_6$ afforded **3.50** in only 17% yield (entry 12, Table 3.6). We were concerned the oxidant character of $AgSbF_6$ would cause problems, so two different additives $In(OTf)_3$ and $NaBPh_4$ were tested with $[Rh(dppe)Cl]_2$ and no reaction was observed in each case.

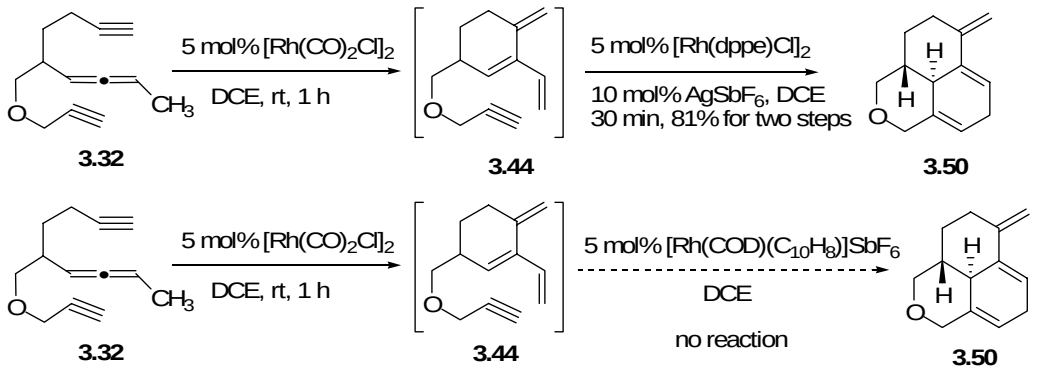


3.32 **3.44** **3.50**

entry	Conditions	Additive	Results
1	$[Rh(CO)_2Cl]_2$, DCE, rt	none	only forms **3.44**
2	$[Rh(C_{10}H_8)(COD)]^+SbF_6^-$	none	23% of **3.50**
3	$[Rh(dppe)_2Cl]_2$, DCE	$AgSbF_6$	decomposition
4	$[Rh(COD)_2OTf$	none	6% of **3.44** and 54% recovered S.M.
5	$Rh(Ph_3P)_3Cl$, TFE, 65 ºC	none	decomposition
6	$Rh(Ph_3P)_3Cl$, DCE, 80 ºC	none	18% of **3.44** and 6% of **3.50**
7	$[Rh(COD)Cl]_2$	$AgSbF_6$	45% of **3.44**
8	$[Rh(NBD)Cl]_2$	$AgSbF_6$	decomposition
9	$[Rh(COD)Cl]_2$, dppe	$AgSbF_6$	polymerization
10	$[RhCl(CO)dppp]_2$, DCE	none	70%of **3.44**
11	$[RhCl(CO)dppp]_2$, DCE	$AgSbF_6$	25% of **3.50**
12	$[RhCl(CO)dppe]_2$, DCE	$AgSbF_6$	17% of **3.50**
13	$[Rh(dppe)_2Cl]_2$, DCE	$In(OTf)_3$	No reaction
14	$[Rh(dppe)_2Cl]_2$, DCE	$NaBPh_4$	No reaction

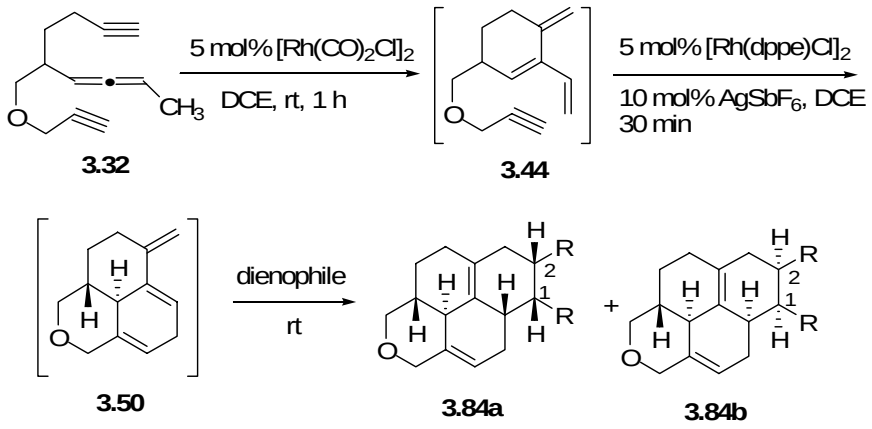
Table 3.6 Studies of tandem Alder-ene/[4+2] cycloaddition catalyzed by one Rhodium(I) catalyst

With limited success in our hasty attempt to find one rhodium catalyst to catalyze the tandem Alder-ene/[4+2] cycloaddition, we decided to settle with using two sets of rhodium catalysts in a sequential way to catalyze the serial Alder-ene/[4+2] cycloaddition in one pot (Scheme 3.23). Allenediyne **3.32** was treated with 5 mol% $[Rh(CO)_2Cl]_2$ to afford triene **3.44**. The reaction was monitored by TLC and 5 mol% $[Rh(dppe)Cl]_2$ and 10 mol% of $AgSbF_6$ were added upon completion of the Alder-ene reaction to give **3.50** as the only product in 81% yield. When Wender's catalyst $[Rh(C_{10}H_8)(COD)]SbF_6$ was used for second step, the [4+2] cyclization did not proceed. It was reasoned that catalysts $[Rh(COD)(C_{10}H_8)]SbF_6$ could react with the other rhodium catalyst $[Rh(CO)_2Cl]_2$ in the solution and form a new rhodium species that can not catalyze [4+2] cyclization.



Scheme 3.23 One-pot, two-step Alder-ene/[4+2] reaction

To further increase molecular complexity, we can add a dienophile to triene **3.50** after the first two steps are complete and an intermolecular Diels-Alder reaction can occur to give complex polycyclic compounds **3.84** (Scheme 3.24). This one-pot, three-step reaction can be used to generate a collection of polycyclic compounds by using a variety of dienophiles.



Scheme 3.24 One-pot, three-step Alder-ene/[4+2]/[4+2] reaction

Tetracyanoethylene (entry 1, Table 3.7) reacted within 0.5 h to give **3.85**. Less reactive maleic anhydride (entry 2, Table 3.7) and benzoquinone (entry 3, Table 3.7) were added as dienophiles. Both reactions gave high yields of the cycloadduct but with low diastereoselectivity. The reaction times for these two dienophiles were considerably longer than that of tetracyanoethylene. Next, investigation into the intermolecular Diels-Alder reaction with functionalized maleimides ensued. The R group on the maleimide moiety played almost no role in the rate of the cycloaddition, but did appear to have an effect on the diastereoselectivity (entry 5-9, Table 3.7). The fluorous containing maleimides were also examined and appeared to behave similar to nonfluorous dienophiles in terms of reactivity towards dienes. An unsymmetrical dienophile methyl vinyl ketone reacted with complete regioselectivity to give the cycloadducts with methyl ketone moiety on C1 (entry 4, Table 3.7). In all cases, only two diastereomers were isolated in each reaction.

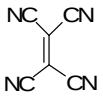
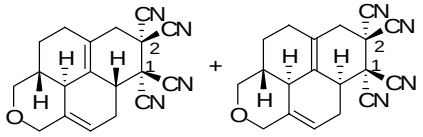
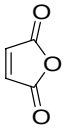
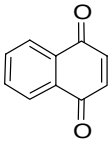
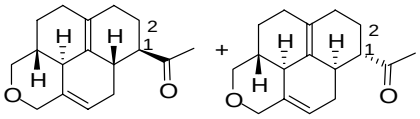
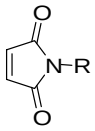
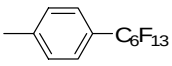
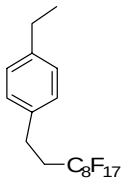
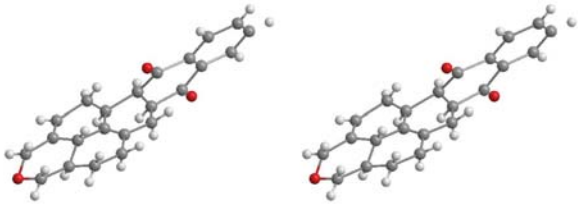
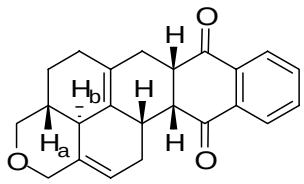
entry	dienophile	time	yield	dr
1		30 min	80%	 **3.85a** + **3.85b**
2		7 h	74%	**3.86a** : **3.86b** 1 : 1
3		24 h	87%	**3.87a** : **3.87b** 2 : 1
4		12 h	75%	 **3.88 a** + **3.88b** 1 : 1
				
5	R = Ph	24 h	66%	**3.89a** : **3.89 b** 2 : 1
6	R = Me	24 h	82%	**3.90 a** : **3.90b** 5 : 1
7	R = H	20 h	68%	**3.91a** : **3.91 b** 1 : 2
8	R = 	48 h	69%	**3.92a** : **3.92b** 1 : 2
9	R = 	36 h	61%	**3.93a** : **3.93b** 1 : 2

Table 3.7 Results of serial Alder-ene/[4+2]/[4+2] reaction

The two diastereomers are endo addition products of the intermolecular Diels-Alder reaction. The dienophile can add from both faces of compound **3.50**. The

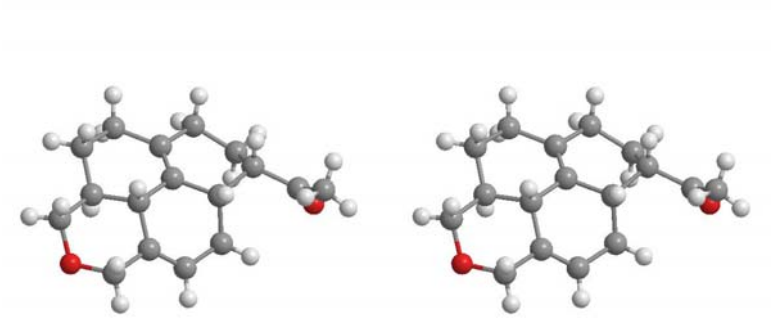
stereochemistry shown in **3.84a** and **3.84b** are based on X-ray analysis of two compounds that crystallized. For illustrative purposes, the X-ray structures of two polycyclic compounds are given in Figure 3.1. The two compounds crystallize in needle-like structure. The X-ray structures show that both compounds are endo addition product (Figure 3.1).

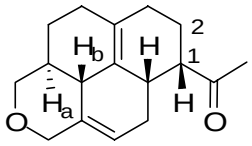




3.87a

Figure 3.1 Stereoview of the Chem3D representation of the x-ray crystal structure of **3.87a**

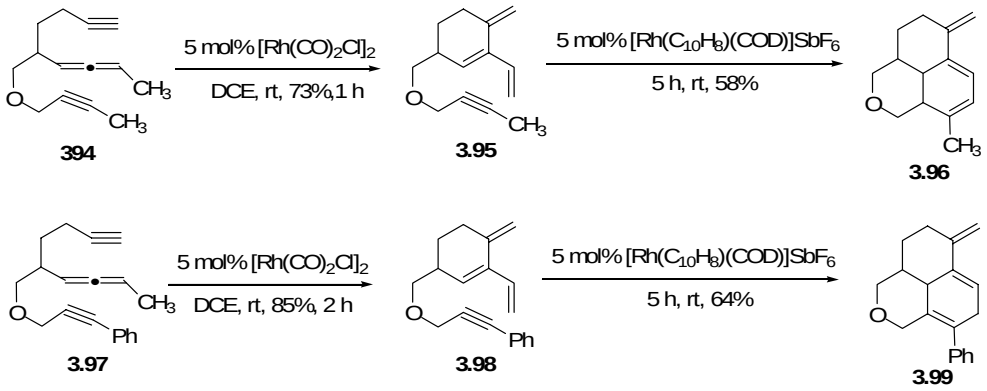




3.88b

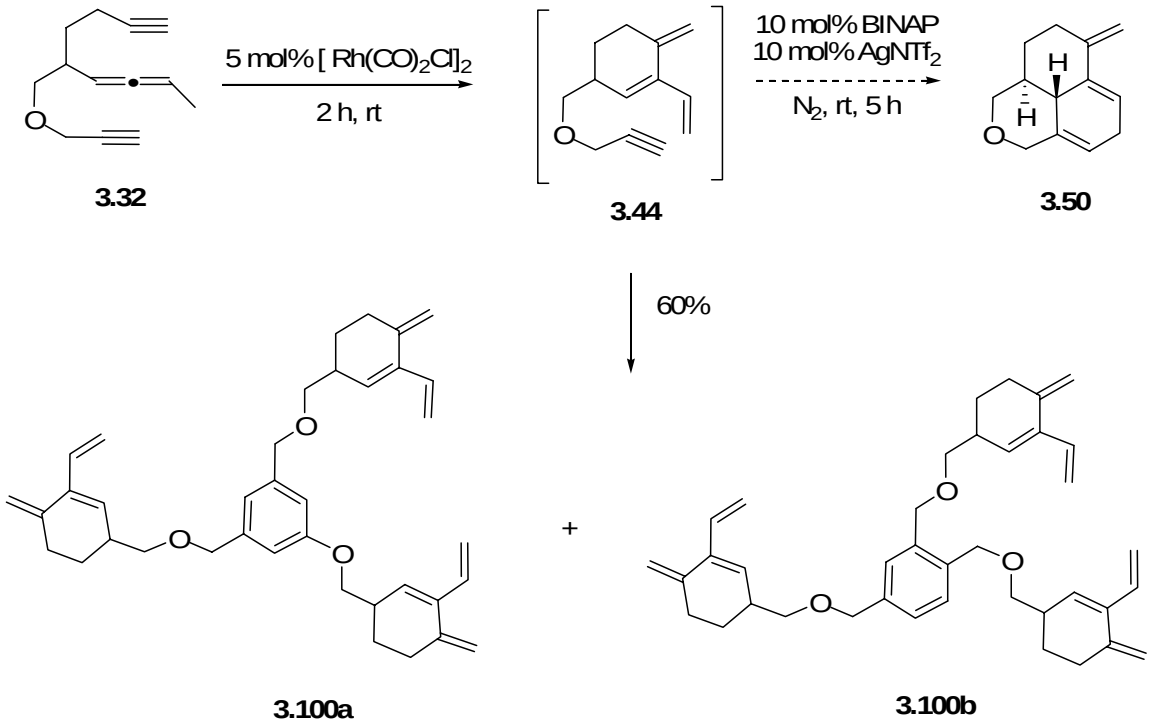
Figure 3.2 Stereoview of the Chem3D representation of the x-ray crystal structure of **3.88b**

Substrates **3.94** and **3.97** were synthesized to study substituent effects on the rate of [4+2] cycloaddition. Allenediynes **3.94** and **3.97** were treated with rhodium biscarbonyl chloride dimer to give cross-conjugated trienes **3.95** and **3.98** which were isolated and resubjected to Wender's conditions (Scheme 3.25). Both [4+2] cycloaddition were sluggish due to the steric hindrance caused by the substituents. Isomerized product **3.96** was isolated in modest yield and **3.99** gave a mixture of several isomers in a combined yield of 64%



Scheme 3.25 Alder-ene/[4+2] reaction of **3.94** and **3.97**

In our study of serial Alder-ene/[4+2] reaction, we discovered a mild condition for [2+2+2] cycloaddition (Scheme 3.26). First allenediyne **3.32** was converted to triene **3.44** in the presence of 5 mol% of $[Rh(CO)_2Cl]_2$, then 10 mol% of ligand BINAP and 10 mol% of additive $AgNTf_2$ were added to the reaction solution upon completion of the Alder-ene reaction. Instead of forming [4+2] cycloaddition product **3.50**, [2+2+2] products **3.100a** and **3.100b** were formed at room temperature. **3.100a** and **3.100b** were not separable via column chromatography. The ^{1}H NMR of the mixture has similar spectrum to that of **3.44** except that it does not have an acetylene resonance but instead an aromatic resonance. In the aromatic region of the ^{1}H NMR spectrum, a singlet at δ = 7.25 ppm presumably arising from compound **3.100a** and mutiplets from **3.100b** were observed. Although rhodium catalyzed [2+2+2] reactions have been reported previously,[32] our condition still can serve as a complementary option for substrates that require mild conditions.



Scheme 3.26 Rh(I)-catalyzed [2+2+2] reaction

3.7 Conclusions

A serial Alder-ene/[4+2]/[4+2] reaction has been developed to demonstrate the potential of a cross-conjugated triene for accessing polycyclic compounds. The reaction sequence is highly chemoselective with first two steps only providing a single isomer **3.50** and last step intramolecular Diels-Alder reaction gave two endo addition products resulting from addition occurred from either face of **3.50**. Four new bonds, four six-membered rings and five stereocenters can be formed in this one-pot, three-step operation. The reaction is also highly atom-efficient with all the atoms in the starting allenediynes and dienophiles in the final products.

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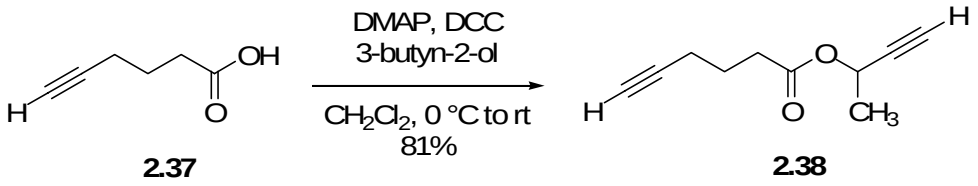
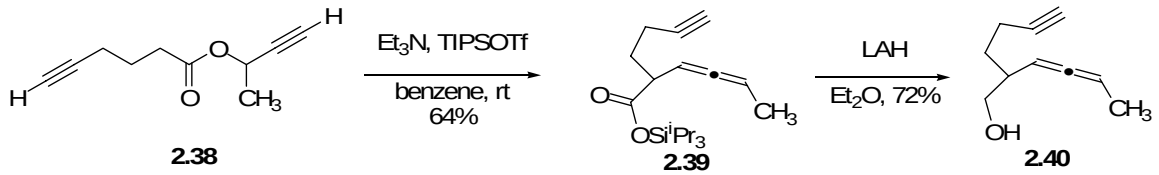
4. Experimental for Compounds from Chapter 2 and Chapter 3



2.37 **2.38**

But-3-yn-2-ylhex-5-ynoate (2.38). 4-Dimethylaminopyridine (163 mg, 1.33 mmol) and 3-butyn-2-ol (1.12 g, 16.0 mmol) were added to a stirred solution of 5-hexyn-1-carboxylic acid **2.37**[1] (1.49 g, 13.3 mmol) in dichloromethane (13 mL). The solution was cooled to 0 °C and 1,3-dicyclohexylcarbodiimide (3.30 g, 16.0 mmol) was added. The reaction was stirred at 0 °C for 5 min then warmed to rt and stirred for an additional 1 h. The precipitate was filtered off and the resulting filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel column using 5% ethyl acetate/hexanes as the eluant to afford hex-5-ynoic acid 1-methylprop-2-ynyl ester as a yellow oil (1.77 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (qd, *J* = 2.0, 6.7 Hz, 1H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.44 (d, *J* = 2.2 Hz, 1H), 2.25 (td, *J* = 2.6, 6.9 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.84 (p, *J* = 7.1 Hz, 2H), 1.48 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 83.0, 82.0, 72.8, 69.2, 59.9, 32.7, 23.4, 21.1, 17.7; IR (film) 3293, 2935, 2116, 1731, 1158 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 164 ($[M]^{\cdot+}$, 3), 124 (12), 95 (21), 83 (68), 67 (35): HRMS calcd for $C_{10}H_{12}O_2$: 164.0832; found: 164.0837.

[1] 5-hexynoic acid was prepared from 5-hexyn-1-ol using Jones oxidation: Delorme, D.; Girard, Y.; Rokach, J. *J. Org. Chem.* **1989**, *54*, 3635.

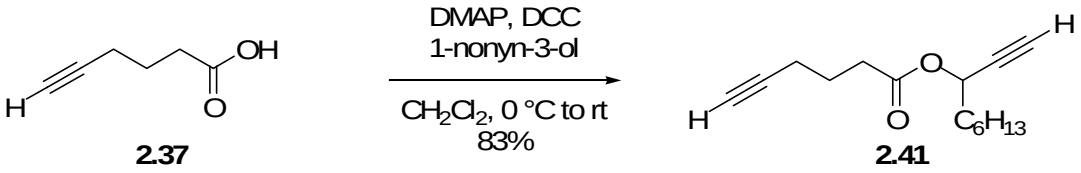


2.38 **2.39** **2.40**

2-(3-Butynyl)-3,4-hexadien-1-ol (2.40). Triethylamine (1.20 mL, 8.54 mmol) and triisopropylsilyl trifluoromethanesulfonate (1.72 mL, 6.41 mmol) were added to a stirred solution of 5-hexynoic acid 1-methyprop-2-ynyl ester **2.38** (700 mg, 4.27 mmol) in benzene (4 mL) respectively. The solution was stirred at rt for 9 h. The two layers were separated and the bottom layer was extracted with benzene. The benzene layers were combined and concentrated. The crude material was purified by flash column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to afford 2-(3-butynyl)-3,4-hexadienoic acid triisopropylsilyl ester **2.39** (874 mg, 2.73 mmol) in 64% yield as a colorless oil.

2-(3-Butynyl)-3,4-hexadienoic acid triisopropylsilyl ester **2.39** (874 mg, 2.73 mmol) was dissolved in ether (6 mL) and the solution was cooled to 0 °C. To this solution was added lithium aluminum hydride (75 mg, 1.98 mmol) portionwise. The reaction was stirred at 0 °C for 2 h. Water (75 μL), 15% NaOH (75 μL) and water (225 μL) were added successively. The resulting white precipitate was filtered off and the filtrate was concentrated. The crude material was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluant to afford title compound **2.40** as a colorless oil (295 mg, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18-5.08 (m, 1 H), 4.98-4.87 (m, 1 H), 3.59-3.48 (m, 2 H), 2.41-2.14 (m, 3 H), 1.99 (bs, 1 H), 1.93 (t, *J* = 2.7 Hz, 1 H), 1.75-1.68 (m, 1 H), 1.65 (dd, *J* = 3.2, 7.0 Hz, 3 H), 1.56-1.44 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$)

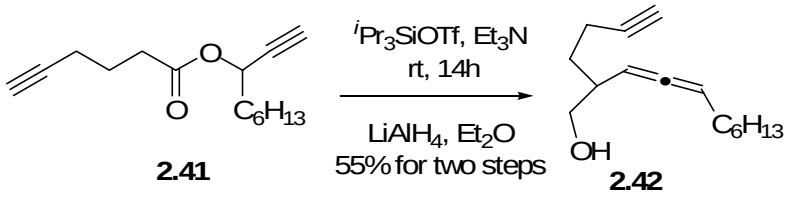
δ 205.1, 90.4, 86.7, 84.1, 68.4, 65.6, 41.0, 29.8, 16.0, 14.4; IR (film) 3356, 3300, 2922, 2860, 2110, 1961, 1726 cm^{-1}; EI-HRMS calcd for $C_{10}H_{14}O$ $[M]^{\cdot+}$ *m/z* 150.1045, found 150.1039.



2.37 **2.41**

Non-1-yn-3-ylhex-5-ynoate (2.41). 4-Dimethylaminopyridine (70 mg, 0.57 mmol) and 1-nonyn-3-ol (1.90 g, 13.6 mmol) were added to a stirred solution of 5-hexynoic acid **2.37**[2] (1.52 g, 13.6 mmol) in dichloromethane (13 mL). The solution was cooled to 0 °C and 1,3-dicyclohexylcarbodiimide (2.81 g, 13.6 mmol) was added. The reaction was stirred at 0 °C for 5 min then warmed to rt and stirred for an additional 1 h. The precipitate was filtered off and the resulting filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel column using 5% ethyl acetate/hexanes as the eluant to afford hex-5-ynoic acid 1-hexyl-prop-2-ynyl ester **2.41** as a yellow oil (2.62 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (td, *J* = 2.1, 6.7 Hz, 1H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.43 (d, *J* = 2.3 Hz, 1H), 2.25 (td, *J* = 2.6, 7.0 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.85 (p, *J* = 7.1 Hz, 2H), 1.80-1.72 (m, 2H), 1.47-1.23 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 83.1, 81.3, 73.3, 69.1, 63.7, 34.5, 32.8, 31.5, 28.7, 24.8, 23.5, 22.4, 17.7, 13.9; IR (film) 3293, 2925, 2853, 2116, 1737 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 234 ($[M]^{\cdot+}$, 5), 177 (44), 121 (27), 67 (45): HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1619.

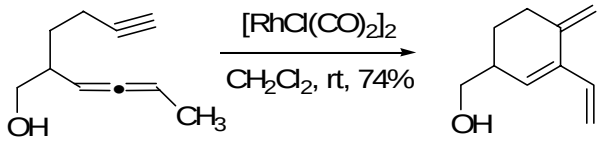
[2] 5-Hexynoic acid was prepared from 5-hexyn-1-ol using Jones oxidation: Delorme, D.; Girard, Y.; Rokach, J. *J. Org. Chem.* **1989**, *54*, 3635.



2.41 **2.42**

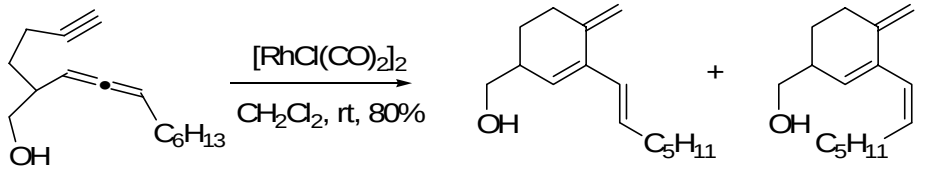
2-(3-Butynyl)-3,4-undecadien-1-ol (2.42). Triethylamine (1.44 mL, 10.26 mmol) and then triisopropylsilyl trifluoromethanesulfonate (2.1 mL, 7.7 mmol) were added to a stirred solution of 5-hexynoic acid 1-hexylprop-2-ynyl ester **2.41** (1.20 g, 5.13 mmol) in benzene (4 mL). The solution was stirred at rt for 9 h. The two layers were separated and the bottom layer was extracted with benzene. The benzene layers were combined and concentrated. The crude material was purified by flash column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to give 2-but-3-ynylundeca-3,4-dienoic acid methyl ester (1.38 g, 3.54 mmol) as a colorless oil.

This ester (1.38 g, 3.54 mmol) was dissolved in ether (7 mL) and the solution was cooled to 0 °C. To this solution was added lithium aluminum hydride (115 mg, 3.03 mmol) portionwise. The reaction was stirred at 0 °C for 2 h. Water (115 μL), 15% NaOH (115 μL) and water (345 μL) were added successively. The resulting white precipitate was filtered off and the filtrate was concentrated. The crude material was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluant to afford title compound **2.42** as a colorless oil (631 mg, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (dq, *J* = 2.0, 6.7 Hz, 1 H), 5.01-4.95 (m, 1 H), 3.64-3.51 (m, 2 H), 2.42-2.19 (m, 3 H), 2.05-1.95 (m, 3 H), 1.79-1.67 (m, 1 H), 1.61-1.51 (m, 2 H), 1.44-1.29 (m, 8 H), 0.89 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 92.4, 91.0, 84.1, 68.5, 65.7, 41.2, 31.6, 29.8, 29.1, 28.9, 28.8, 22.6, 16.2, 14.0; IR (film) 3365, 3309, 2930, 2858, 2121, 1958, 1460, 1035 cm^{-1}.



2.40 **2.43**

(4-Methylene-3-vinylcyclohex-2-enyl)methanol (2.43). To a stirred solution of 2-(3-Butynyl)-3,4-hexadien-1-ol (**2.40**, 50 mg, 0.33 mmol) in 2 mL of CH_2Cl_2 was added chlorodicarbonylrhodium(I) dimer (6 mg, 0.015 mmol). The reaction was stirred at rt for 3 h. After removal of CH_2Cl_2, the resulting crude material was purified by flash chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to afford 37 mg (74%) of **2.43** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (ddt, *J* = 1.0, 10.8, 17.2 Hz, 1 H), 5.89 (s, 1 H), 5.41 (dd, *J* = 1.9, 17.3 Hz, 1 H), 5.10 (dd, *J* = 1.9, 10.8 Hz, 1 H), 5.03 (s, 1 H), 4.89 (s, 1 H), 3.61 (d, *J* = 5.8 Hz, 2 H), 2.53-2.44 (m, 2 H), 2.40-2.30 (m, 1 H), 1.95-1.86 (m, 1 H), 1.55-1.43 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.2, 135.8, 128.1, 115.2, 109.8, 66.6, 39.6, 30.9, 26.0; IR (film) 3329, 2935, 2863, 1629, 1440, 1046 cm^{-1}; EI-HRMS calcd for $C_{10}H_{14}O$ $[M]^{\cdot+}$ *m/z* 150.1045, found 150.1045.



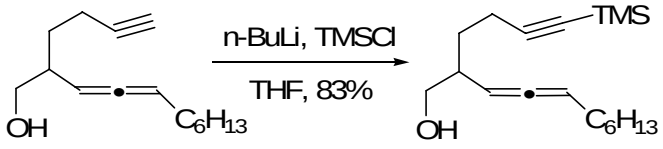
2.42 **2.44-E** **2.44-Z**

3-(1-Heptenyl)-4-methylene-2-cyclohexenylmethanol (2.44). Chlorodicarbonylrhodium (I) dimer (4 mg, 0.0103 mmol) was added to a stirred solution of 2-(3-butynyl)-3,4-undecadien-1-ol (**2.42**, 50 mg, 0.23 mmol) in 2 mL of CH_2Cl_2. The reaction was stirred at rt for 6 h. After removal of CH_2Cl_2 under reduced pressure, the resulting crude material

was purified by flash chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to afford **2.44-*E*** (27 mg, 54%) and **2.44-*Z*** (13 mg, 26%) as colorless oil.

2.44-*E*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (dt, *J* = 1.2, 15.4 Hz, 1 H), 5.86 (dt, *J* = 6.8, 15.4 Hz, 1 H), 5.80 (s, 1 H), 5.03 (s, 1 H), 4.86 (s, 1 H), 3.60 (t, *J* = 5.7 Hz, 1 H), 2.58-2.43 (m, 2 H), 2.38-2.29 (m, 1 H), 2.10 (q, *J* = 6.8 Hz, 2 H), 1.94-1.85 (m, 1 H), 1.55-1.40 (m, 4 H), 1.37-1.26 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.0, 132.2, 128.2, 126.9, 109.6, 66.8, 39.7, 32.9, 31.4, 31.0, 29.0, 26.2, 22.5, 14.0; IR (film) 3329, 2925, 2853, 1629, 1465, 1045 cm^{-1}; EI-HRMS calcd for $C_{15}H_{24}O$ $[M]^{\cdot+}$ *m/z* 220.1827, found 220.1832).

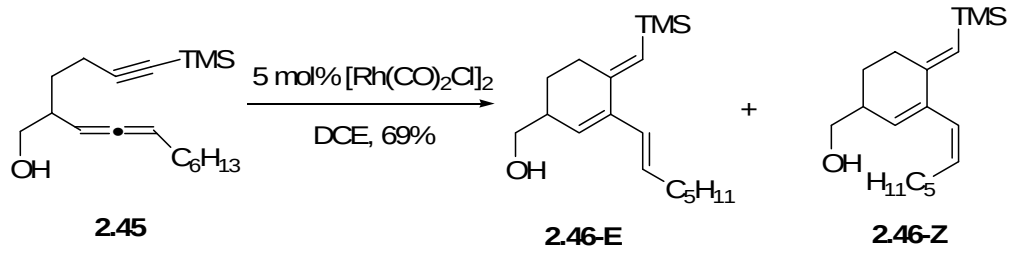
2.44-*Z*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, *J* = 11.4 Hz, 1 H), 5.63-5.54 (m, 2 H), 4.92 (s, 1 H), 4.81 (s, 1 H), 3.62 (t, *J* = 4.8 Hz, 2 H), 2.60-2.46 (m, 2 H), 2.41-2.30 (m, 1 H), 2.10 (qd, *J* = 1.3, 6.9 Hz, 2 H), 1.97-1.87 (m, 1 H), 1.58-1.48 (m, 1 H), 1.41-1.27 (m, 7 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 136.0, 133.1, 129.5, 127.5, 110.1, 69.7, 66.8, 39.5, 31.5, 30.4, 29.6, 28.4, 26.0, 22.5, 14.1; IR (film) 3329, 2925, 2853, 1465, 1045 cm^{-1}; EI-HRMS calcd for $C_{15}H_{24}O$ $[M]^{\cdot+}$ *m/z* 220.1827, found 220.1832.



2.42 **2.45**

2-(4-Trimethylsilanylbutynyl)undeca-3,4-dien-1-ol (2.45). n-BuLi (2.5 M, 0.80 mL) was added to a stirred solution of 2-(3-butynyl)-3,4-undecadien-1-ol **2.42** (210 mg, 0.955 mmol) in 3 mL of THF at –78 °C. The reaction was stirred for 10 min. Then chlorotrimethylsilane (0.37 mL, 2.92 mmol) was added. The reaction was stirred at –78

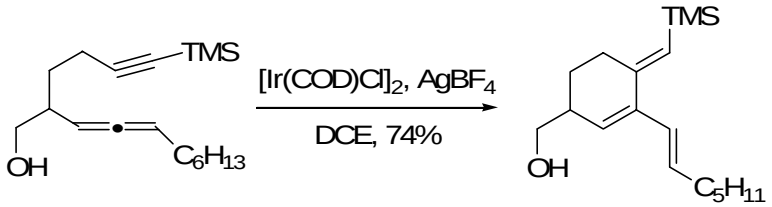
°C for 50 min, then the reaction was warmed up to rt and stirred for another 30 min. 10% aqueous HCl (3 mL) was added to the reaction solution and the mixture was stirred for 2 h at rt. The two layers were separated and the aqueous layer was extracted with ether (5 mL × 3). The organic layers were combined, dried (Na_2SO_4) and concentrated under vacuo. The resulting residue was purified by column chromatography to afford of 2-(4-trimethylsilanylbutynyl)undeca-3,4-dien-1-ol (**2.45**) as a colorless oil (230 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.192 (dq, *J* = 2.0, 6.6 Hz, 1 H), 5.03-4.93 (m, 1 H), 3.66-3.50 (m, 2 H), 2.40-2.23 (m, 3 H), 2.03-1.96 (m, 2 H), 1.72-1.52 (m, 3 H), 1.43-1.29 (m, 8 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.14 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 107.1, 92.4, 91.2, 84.8, 65.8, 41.4, 31.7, 30.2, 29.1, 29.0, 28.8, 22.6, 17.6, 14.0, 0.1; IR (film) 3338, 2960, 2923, 2167, 1956 cm^{-1}; EI-HRMS calcd for $C_{18}H_{32}OSi$ $[M]^{\cdot+}$ *m/z* 292.2222, found 292.2209.



2.45 **2.46-E** **2.46-Z**

(3-Hept-1-enyl-4-trimethylsilanylmethylenecyclohex-2-enyl)methanol (2.46). Chlorodicarbonylrhodium (I) dimer (5 mg, 0.012 mmol) was added to a stirred solution of 2-(4-trimethylsilanyl-but-3-ynyl)-undeca-3,4-dien-1-ol (**2.45**, 70 mg, 0.24 mmol) in 2 mL of 1,2-dichloroethane. The reaction was stirred at rt for 6 h. After removal of 1,2-dichloroethane, the resulting crude material was purified by flash chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to afford **2.46** (48 mg, 69%) as a

3:1 (determined by GC) mixture of *E* and *Z* isomers. The mixture was then subjected to HPLC to obtain **2.46-*E*** and **2.46-*Z*** in pure form.



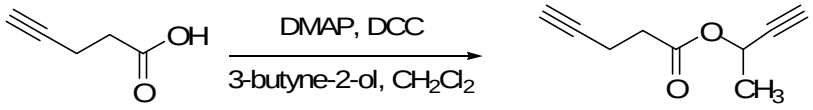
2.45 **2.46-E**

A stirred solution of 2-(4-trimethylsilanylbut-3-ynyl)undeca-3,4-dien-1-ol (**2.45**, 55 mg, 0.19 mmol) in 2 mL of 1,2-dichloroethane was treated with chloro-1,5-cyclooctadiene iridium(I) dimer (12 mg, 0.018 mmol). Then a solution of silver tetrafluoroborate (0.05 M in 1,2-dichloroethane, 0.72 mL, 0.036 mmol) was added dropwise. The reaction was monitored by GC and was complete after 2 h at rt. The reaction was filtered through a plug of silica gel and the resulting filtrate was concentrated to give **2.46-*E*** as a pale yellow oil (41 mg, 74%). The *E* to *Z* ratio was determined by GC to be larger than 99 : 1.

(**2.46-*E***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (d, *J* = 15.5 Hz, 1 H), 5.82 (s, 1 H); 5.81 (dt, *J* = 6.8, 15.5 Hz, 1 H), 5.56 (s, 1 H), 2.61 (ddd, *J* = 3.8, 5.8, 14.5 Hz, 1 H), 2.55-2.47 (m, 1 H), 2.38-2.28 (m, 1 H), 2.11 (q, *J* = 7.0 Hz, 1 H), 1.96-1.87 (m, 1 H), 1.53-1.26 (m, 8 H), 0.90 (t, *J* = 3.8 Hz, 3 H), 0.1 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 141.2, 132.3, 129.0, 127.1, 124.1, 66.8, 39.6, 32.9, 31.4, 30.1, 29.1, 26.3, 22.5, 14.0, 0.1; IR (film) 3389, 2916, 1665, 1244 cm^{-1}.

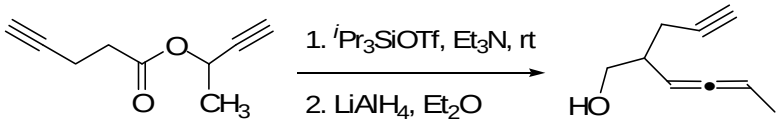
2.46-*Z*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, *J* = 11.4 Hz, 1 H); 5.61 (s, 1 H); 5.58 (dt, *J* = 7.3, 11.4 Hz, 1 H); 5.48 (s, 1 H); 3.61 (d, *J* = 4.5 Hz, 2 H); 2.63 (ddd, *J* = 3.8, 6.0, 14.5 Hz, 1 H); 2.57-2.50 (m, 1 H); 2.40-2.29 (m, 1 H); 2.08 (qd, *J* = 1.5, 7.3 Hz,

1 H); 1.99-1.90 (m, 1 H); 1.57-1.45 (m, 1 H), 0.1 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 137.9, 133.0, 129.5, 128.2, 124.6, 66.8, 39.3, 31.5, 29.7, 29.5, 28.4, 26.1, 22.5, 14.1, 0.1; IR (film) 3353, 2953, 2924, 1571 cm^{-1}.



2.47 **2.48**

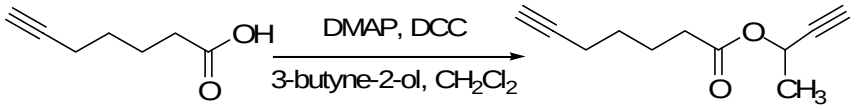
But-3-yn-2-ylpent-4-ynoate (2.48). 3-Butyn-2-ol (4.1 g, 58.9 mmol) and 4-dimethylaminopyridine (800 mg, 6.54 mmol) were added to a stirred solution of 4-hexyn-1-carboxylic acid **2.47** (6.4 g, 65.4 mmol) in dichloromethane (150 mL). The solution was cooled to 0 °C and 1,3-dicyclohexylcarbodiimide (13.5 g, 65.4 mmol) was added. The reaction was stirred at 0 °C for 5 min then warmed to rt and stirred for an additional 2 h. The precipitate was filtered off and the resulting filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel column using 5% ethyl acetate/hexanes as the eluant to afford **2.48** as a yellow oil (5.40 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (ddt, *J* = 1.9, 6.7, 13.4 Hz, 1H), 2.58-2.44 (m, 5H), 1.97-1.94 (m, 1H), 1.48 (dd, *J* = 1.5, 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 82.1, 81.9, 72.9, 69.1, 60.3, 33.3, 21.1, 14.2; IR (neat) 3293, 2991, 2934, 2121, 1742 cm^{-1}.



2.48 **2.49**

2-(Prop-2-ynyl)hexa-3,4-dien-1-ol (2.49). Triethylamine (8.0 mL, 57.4 mmol) and triisopropylsilyl trifluoromethanesulfonate (10.8 mL, 40.2 mmol) were added to a stirred solution of ester **2.48** (4.30 g, 28.7 mmol) in benzene (30 mL) were added. The solution

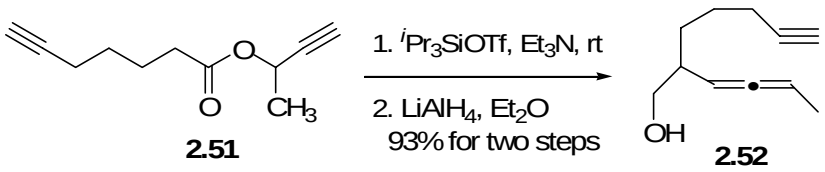
was stirred at rt for 16 h. The resulting two layers were separated and the bottom layer was extracted with benzene. The benzene layers were combined and concentrated. The crude material was purified by flash column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to afford a colorless oil which was dissolved in ether (60 mL) and the solution was cooled to 0 °C. To this solution was added lithium aluminum hydride (1.20 mg, 31.6 mmol). The reaction was stirred at 0 °C for 3 h. Water (1.20 mL), 15% NaOH (1.20 mL) and water (3.60 mL) were added successively. The resulting white precipitate was filtered off and the filtrate was concentrated. The crude material was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluant to afford title compound **2.67** as a colorless oil (1.82 g, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21–5.05 (m, 2H), 3.67 (d, *J* = 5.6 Hz, 2H), 2.50-2.37 (m, 1H), 2.36-2.29 (m, 2H), 2.09-1.95 (m, 2H), 1.66 (dd, *J* = 3.3, 6.9 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 204.7, 90.1, 87.5, 82.2, 69.7, 64.8, 40.3, 20.6, 14.4; IR(neat) 3355, 3298, 2925, 2116, 1962 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 136 ($[M]^{\cdot+}$, 2), 98 (26), 84 (58), 53 (100).



2.50 **2.51**

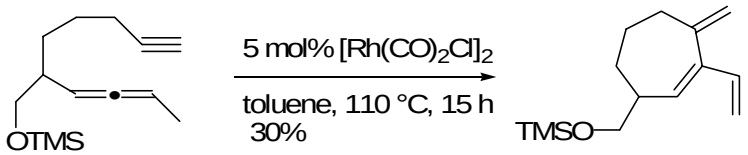
But-3-yn-2-ylhept-6-ynoate (2.51). 3-Butyn-2-ol (4.1 g, 58.9 mmol) and 4-dimethylaminopyridine (800 mg, 6.54 mmol) were added to a stirred solution of 6-heptynoic acid **2.50** (6.4 g, 65.4 mmol) in dichloromethane (150 mL). The solution was cooled to 0 °C and 1,3-dicyclohexylcarbodiimide (13.5 g, 65.4 mmol) was added. The reaction was stirred at 0 °C for 5 min then warmed to rt and stirred for an additional 2 h.

The precipitate was filtered off and the resulting filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel column using 5% ethyl acetate/hexanes as the eluant to afford **2.51** as a yellow oil (5.40 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.4082 (ddt, *J* = 1.2, 2.0, 6.7 Hz, 1H), 2.43 (d, *J* = 2.1 Hz, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.18 (ddt, *J* = 0.8, 2.5, 7.0 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.78-1.67 (m, 2H), 1.58-1.52 (m, 2H), 1.47 (dd, *J* = 1.0, 3.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 172.3, 84.1, 82.5, 73.1, 68.9, 60.1, 33.9, 28.0, 24.1, 21.5, 18.4; IR(neat) 3293, 2986, 2940, 2868, 2116, 1737, 1455 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 178 ([M]$^{\cdot+}$, 3), 163 (20), 135 (31), 121 (48), 109 (35), 81 (74), 79 (47): HRMS calcd for $C_{11}H_{13}O_2$ 177.0916, found 177.0917.



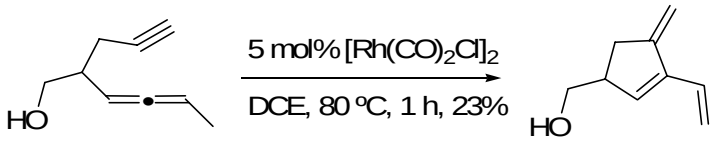
2-(Buta-1,2-dienyl)hept-6-yn-1-ol (2.52). Triethylamine (2.21 mL, 15.7 mmol) and triisopropylsilyl trifluoromethanesulfonate (3.0 mL, 11.0 mmol) were added to a stirred solution of ester **2.51** (1.40 g, 7.87 mmol) in benzene (8 mL). The solution was stirred at rt for 24 h. The resulting two layers were separated and the bottom layer was extracted with benzene. The benzene layers were combined and concentrated. The crude material was purified by flash column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to afford a colorless oil which was dissolved in ether (16 mL) and the solution was cooled to 0 °C. To this solution was added lithium aluminum hydride (360 mg, 9.49 mmol). The reaction was stirred at 0 °C for 3 h. Water (360 μL), 15% NaOH (360 μL) and water (360 μL) were added successively. The resulting white

precipitate was filtered off and the filtrate was concentrated. The crude material was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluant to afford title compound **2.52** as a colorless oil (1.20 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17–5.05 (m, 1H), 4.94-4.85 (m, 1H), 3.58-3.43 (m, 2H), 2.23-2.14 (m, 3H), 1.94-1.90 (m, 2H), 1.64 (ddd, *J* = 1.8, 3.2, 7.0 Hz, 3H), 1.61-1.49 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 205.0, 91.1, 86.4, 84.2, 68.3, 66.0, 41.8, 30.1, 25.9, 18.3, 14.4; IR(neat) 3355, 3298, 2940, 2863, 2116, 1957, 1025 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 164 ([M]$^{\cdot}$+, 7), 149 (12), 105 (74), 91 (100), 79 (85): HRMS calcd for $C_{11}H_{16}O$ 164.1201, found 164.1193.



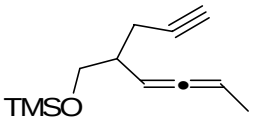
2.54 **2.55**

(((Z)-4-Methylene-3-vinylcyclohept-2-enyl)methoxy)trimethylsilane (2.55). The allenyne **2.54** (30 mg, 0.127 mmol) was dissolved in 1 mL of toluene. $[Rh(CO)_2Cl]_2$ (2.5 mg, 0.0064 mmol) was added to this solution. The reaction was stirred at 110 ºC under N_2 for 15 h. The solvent was removed under vacuo and the residue was purified via column chromatography using 5% ethyl acetate/hexanes as the eluant to afford 9 mg (30%) of **2.55** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 10.6, 17.1 Hz, 1H), 5.60 (d, *J* = 4.4 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 5.19 (s, 1H), 4.99 (d, *J* = 10.6 Hz, 1H), 4.83 (d, *J* = 2.2 Hz, 1H), 3.51-3.44 (m, 2H), 2.45-1.20 (m, 7H), 0.1 (s, 9H). (Region 2.45-1.20 is not clear due to an inseparable byproduct).



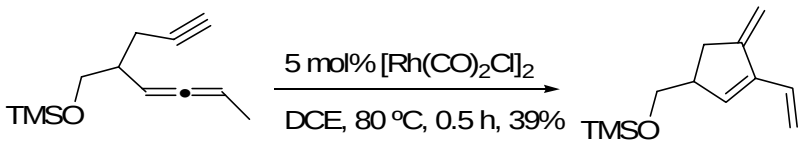
2.49 **2.58**

(4-Methylene-3-vinylcyclopent-2-enyl)methanol (2.58). $[Rh(CO)_2Cl]_2$ (4 mg, 0.011 mmol) was added to a stirred solution of 2-(3-butynyl)-3,4-hexadien-1-ol (**2.49**, 30 mg, 0.22 mmol) in 2 mL of DCE. The reaction was stirred at rt for 1 h in refluxing DCE. After removal of DCE, the resulting crude material was purified by flash chromatography on silica gel using 5% ethyl acetate/hexanes as the eluant to afford 7 mg (23%) of **2.58** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 11.1, 17.7 Hz, 1H), 6.19 (s, 1H), 5.60 (dd, *J* = 1.6, 17.7 Hz, 1H), 5.24 (dd, *J* = 1.6, 11.1 Hz, 1H), 5.04 (t, *J* = 2.3 Hz, 1H), 4.92-4.88 (m, 1H), 3.61 (d, *J* = 6.0 Hz, 2H), 3.03-2.93 (m, 1H), 2.81 (ddt, *J* = 2.2, 7.8, 16.6 Hz, 1H), 2.50-2.42 (m, 1H), 1.34 (bs, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 151.6, 143.8, 136.0, 129.5, 116.7, 102.4, 66.1, 45.4, 34.6; IR(neat) 3350, 2919, 2868, 1629, 1434, 1337, 1030 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 105 ($[M-31]^{\cdot+}$, 10), 88 (32), 74 (58), 61 (100), 59 (93): HRMS calcd for C_8H_9 105.0704, found 105.0706.



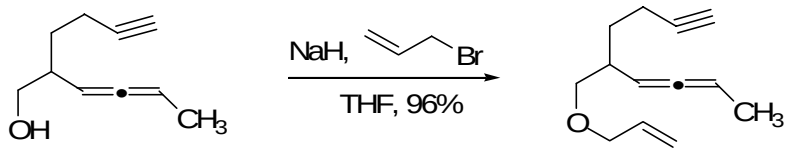
2.59

(2-(Prop-2-ynyl)hexa-3,4-dienyloxy)trimethylsilane (2.59). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19–5.05 (m, 2 H), 3.64-3.53 (m, 2H), 2.42-2.23 (m, 3H), 1.96 (t, *J* = 2.4 Hz, 1H), 1.66 (dd, *J* = 3.4, 6.8, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 204.7, 90.2, 86.9, 82.6, 69.3, 64.6, 40.3, 20.4, 14.4, –0.5.



2.59 **2.60**

((4-Methylene-3-vinylcyclopent-2-enyl)methoxy)trimethylsilane (2.60). Allenyne **2.59** (30 mg, 0.144 mmol) was dissolved in 1 mL of DCE. $[Rh(CO)_2Cl]_2$ (2.8 mg, 0.0072 mmol) was added to this solution. The reaction was heated to 80 ºC and stirred for 0.5 h. The solution was removed and the residue was purified via column chromatography using 5% ethyl acetate/hexanes as the eluant to afford 12 mg (40%) of **2.60** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (dd, *J* = 11.2, 17.7 Hz, 1H), 6.21 (s, 1H), 6.58 (dd, *J* = 1.7, 17.7 Hz, 1H), 5.22 (dd, *J* = 1.7, 11.2 Hz, 1H), 5.01 (t, *J* = 2.2 Hz, 1H), 4.88-4.84 (m, 1H), 3.48 (dd, *J* = 2.6, 7.2 Hz, 1H), 3.00-2.89 (m, 1H), 2.77 (ddt, *J* = 2.2, 7.7, 14.5 Hz, 1H), 2.39-2.31 (m, 1H), 0.1 (s, 9H).



2.40 **3.31**

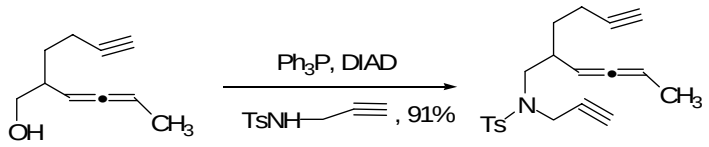
5-Allyloxymethylnona-6,7-dien-1-yne (3.31). A solution of alcohol **2.40** (210 mg, 1.40 mmol) in 2.5 mL of THF was cooled to 0 °C and sodium hydride (112 mg of a 60% dispersion in mineral oil, 2.80 mmol) was added portionwise. The reaction was stirred for 30 min at rt under N_2. Allyl bromide (182 μL, 2.10 mmol) was added and the reaction was stirred at rt for 20 h. The reaction was quenched by careful dropwise addition of H_2O (3 mL) to the reaction over 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). Then the organic layers were combined, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified *via* silica gel column

eluting with 5% EtOAc / hexanes to afford 254 mg of ether **3.31** in 96% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99–5.87 (m, 1H), 5.28 (dd, *J* = 1.4, 17.1 Hz, 1H), 5.18 (dd, *J* = 1.4, 11.6 Hz, 1H), 5.16-5.10 (m, 1H), 5.03-4.95 (m, 1H), 3.98 (d, *J* = 5.5 Hz, 2H), 3.45 (dd, *J* = 6.4, 13.7 Hz, 1H), 3.35 (dd, *J* = 6.6, 9.1 Hz, 1H), 2.50-2.42 (m, 1H), 2.35-2.18 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.86-1.76 (m, 1H), 1.67 (dd, *J* = 3.2, 6.9 Hz, 3H), 1.58-1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 134.9, 116.8, 90.7, 86.6, 84.4, 73.6, 72.0, 68.2, 38.6, 30.5, 16.2, 14.5; IR (neat) 3304, 2919, 2853, 2116, 1962, 1107 cm^{-1}; MS (GC/EI-MS) *m/z* 190 ([M]$^{\cdot}$+, 5), 175 (29), 137 (22), 119 (58), 91 (100), 79 (97): HRMS calcd for $C_{13}H_{16}O$: 190.1358; found: 190.1351.

2.40 **3.32**

5-(Prop-2-ynyloxy)methylnono-6,7-dien-1-yne (3.32). A solution of alcohol **2.40** (220 mg, 1.47 mmol) in 3 mL of THF was cooled to 0 °C and sodium hydride (117 mg of a 60% dispersion in mineral oil, 2.93 mmol) was added portionwise. The reaction was stirred for 30 min at rt under N_2. Propargyl bromide (244 μL of a 80% solution in toluene, 2.19 mmol) was added and the reaction was maintained at rt for 12 h. The reaction was quenched by careful dropwise addition of H_2O (3 mL) to the reaction over 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified via silica gel chromatography eluting with 5% EtOAc / hexanes to afford 262 mg of ether **3.32** in 96% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.15 (m, 5.19-5.09, 1H), 5.15-4.94 (m, 1H), 4.16 (d, *J* = 2.4 Hz, 2H), 3.51 (dd, *J* = 6.1,

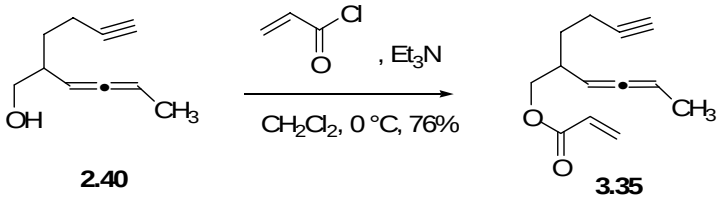
9.1 Hz, 1H), 3.44 (dd, *J* = 6.6, 9.1 Hz, 1H), 2.51-2.41 (m, 1H), 2.43 (t, *J* = 2.4 Hz, 1H), 2.37-2.18 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.87-1.74 (m, 1H), 1.67 (dd, *J* = 3.2, 7.0 Hz, 3H), 1.61-1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.9, 90.6, 86.7, 84.3, 79.8, 74.2, 73.3, 68.8, 58.2, 38.4, 30.5, 16.1, 14.5; IR (neat) 3293, 2920, 2853, 2116, 1962 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 188 ($[M]^{\cdot}+$, 6), 149 (25), 135 (64), 91 (100): HRMS calcd for $C_{13}H_{16}O$: 188.1201; found: 188.1204.



2.40 **3.33**

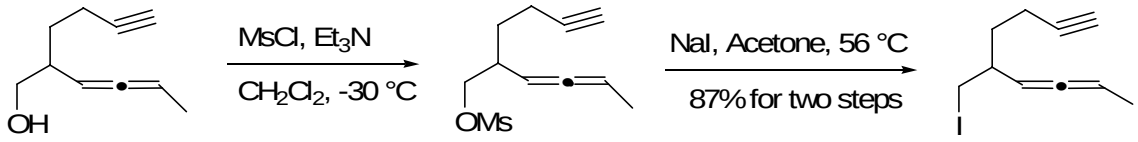
N-(2-But-3-ynylhexa-3,4-dienyl)-4-methyl-*N*-prop-2-ynylbenzenesulfonamide (3.33). Propargylic sulfonamide (147 mg, 0.70 mmol) was dissolved in 1.5 mL of THF. The solution was cooled to 0 °C, then triphenylphosphine (210 mg, 0.80 mmol), alcohol **2.40** (100 mg, 0.67 mmol) and DIAD (158 μL, 0.80 mmol) were added sequentially. The reaction was stirred for 24 h at rt. The solvent was removed in *vacuo* and the resulting sticky residue was dissolved in minimum amount of CH_2Cl_2 and loaded onto the column. The column was eluted with 10% EtOAc / hexanes to afford 207 mg of sulfonamide **3.33** in 91% yield as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.18-5.08 (m, 1H), 4.93-4.83 (m, 1H), 4.22-4.08 (m, 2H), 3.21-3.07 (m, 2H), 2.53-2.40 (m, 1H), 2.42 (s, 3H), 2.40-2.15 (m, 2H), 2.00 (t, *J* = 2.4 Hz, 1H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.83-1.70 (m, 1H), 1.66 (dd, *J* = 3.2, 7.0 Hz, 3H), 1.51-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 205.1, 143.4, 135.9, 129.4, 127.7, 90.5, 87.0, 83.9, 76.3, 73.9, 68.6, 50.3, 36.7, 36.6, 30.9, 21.5, 16.1, 14.3; IR (neat) 3288, 2919, 2858, 2116, 1962, 1598, 1342, 1163 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 340 ($[M-1]^+$, 9),

326 (18), 288 (35), 222 (76), 155 (84), 91 (100): HRMS calcd for $C_{20}H_{23}NO_2S$: 341.1450; found: 341.1438.



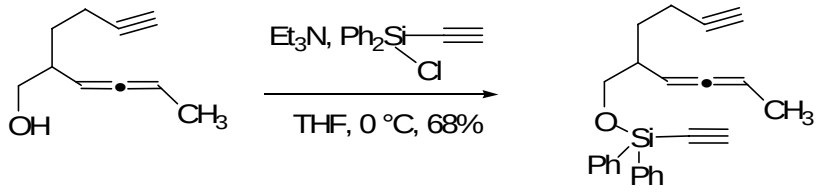
2.40 **3.35**

Acrylic acid 2-but-3-ynylhexa-3,4-dienyl ester (3.35). The alcohol **2.40** (200 mg, 1.33 mmol) was dissolved in 4 mL of CH_2Cl_2. The reaction solution was cooled to 0 °C, then acryloyl chloride (130 μL, 1.60 mmol) and triethylamine (407 μL, 2.92 mmol) were added sequentially. The reaction was stirred for 10 min at 0 °C, then H_2O (5 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated. The resulting material was purified *via* column chromatography eluting with 5% EtOAc / hexanes to afford 205 mg of ester **3.35** in 76% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.40 (dd, *J* = 1.5, 17.3 Hz, 1H), 6.12 (dd, *J* = 10.4, 17.3 Hz, 1H), 5.83 (dd, *J* = 1.5, 10.4 Hz, 1H), 5.19-5.08 (m, 1H), 5.00-4.91 (m, 1H), 4.15 (dd, *J* = 6.3, 10.9 Hz, 1H), 4.07 (dd, *J* = 6.3, 10.9 Hz, 1H), 2.61-2.48 (m, 1H), 2.38-2.16 (m, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.80-1.68 (m, 1H), 1.64 (dd, *J* = 3.2, 7.0 Hz, 3H), 1.63-1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 166.0, 130.6, 128.4, 89.9, 87.1, 83.8, 68.6, 67.0, 37.6, 30.2, 16.0, 14.3; IR (neat) 3298, 2945, 2116, 1962, 1721, 1629, 1409, 1184 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 204 ([M]$^{\cdot}$+, 9), 189 (27), 175 (68), 132 (16), 117 (45), 55 (100) : HRMS calcd for $C_{13}H_{16}O_2$: 204.1142; found: 204.1150.



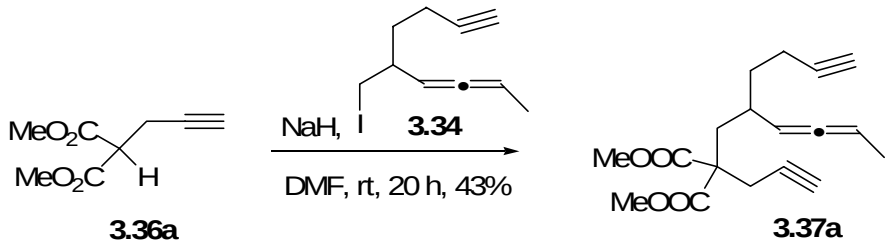
2.40 **3.34**

5-(Iodomethyl)nona-6,7-dien-1-yne (3.34). MsCl (310 μL, 4.0 mmol) was added to a -30 °C solution of allenyne alcohol **2.40** (500 mg, 3.33 mmol) and Et_3N (650 μL, 4.66 mmol) in 15 mL of CH_2Cl_2. The reaction was stirred at -30 °C for 1 h before it was quenched by addition of H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to dryness. Purification of the crude product by flash chromatography (20% EtOAc/hexanes) gave 760 mg (100% yield) of mesylate as a clear oil. To a solution of the mesylate (760 mg, 3.33 mmol) in acetone (10 mL) was added sodium iodide (1.02 g, 6.79 mmol) and the reaction was stirred at reflux for 14 h. The reaction was quenched with H_2O (10 mL) and the mixture was extracted with Et_2O (3 × 10 mL). The combined ethereal extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.23-5.12 (m, 1H), 5.00-4.91 (m, 1H), 3.29-3.18 (m, 2H), 2.35-2.16 (m, 3H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.82-1.70 (m, 1H), 1.69 (dd, *J* = 2.4, 7.0 Hz, 1H), 1.66-1.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.82, 92.2, 87.7, 83.5, 68.8, 39.3, 33.4, 16.0, 14.3, 13.1; (neat) 3298, 2945, 2919, 2116, 1957 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 260 ([M]$^{\cdot}$+, 2), 219 (31), 167 (37), 119 (45), 105 (78), 91 (100): HRMS calcd for $C_{10}H_{13}I$ 260.0062, found 260.0060.



2.40 **3.38**

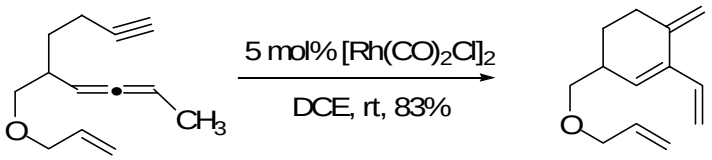
(2-(But-3-ynyl)hexa-3,4-dienyloxy)(ethynyl)diphenylsilane (3.38). A solution of chloroethynyldiphenylsilane (0.2 M in THF, 3.4 mL, 0.68 mmol) was added to a 0 °C solution of **2.40** (250 mg, 0.987 mmol) and triethylamine (188 μL, 1.35 mmol) in 2.5 mL of THF. The reaction was stirred for 1 h at 0 °C and was quenched with H_2O (5 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to dryness. The residue was purified via flash chromatography to give 163 mg (68% yield) **3.38** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82-7.68 (m, 4H), 7.52-7.37 (m, 6H), 5.18-5.09 (m, 1H), 5.08-4.99 (m, 1H), 3.86-3.69 (m, 2H), 2.78 (s, 1H), 2.50-2.40 (m, 1H), 2.38-2.18 (m, 2H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.96-1.84 (m, 1H), 1.71-1.65 (m, 3H), 1.64-1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.1, 135.0, 134.8, 134.6, 130.6, 130.5, 130.3, 128.2, 127.9, 127.8, 97.3, 90.7, 86.4, 68.3, 67.2, 66.4, 40.9, 30.0, 16.2, 14.4; IR (neat) 3273, 2919, 2116, 2034, 1962, 1423, 1117 cm^{-1};MS (GC/EI-MS) *m/z* (relative intensity) 331 ([M]$^{\cdot}$+, 48), 231 (67), 207 (89), 199 (100), 91 (58) : HRMS calcd for $C_{22}H_{23}SiO$: 331.1518; found: 331.1514.



3.36a **3.37a**

2-(2-But-3-ynylhexa-3,4-dienyl)-2-prop-2-ynylmalonic acid dimethyl ester. NaH (15 mg of 60% dispersion in mineral oil, 0.375 mmol) was added to a solution of dimethylpropargyl malonate **3.36a** (53 mg, 0.31 mmol) in 1 mL of DMF. The reaction was stirred at rt for 20 min before a solution of **3.34** (81 mg, 0.31 mmol) in 1 mL of DMF

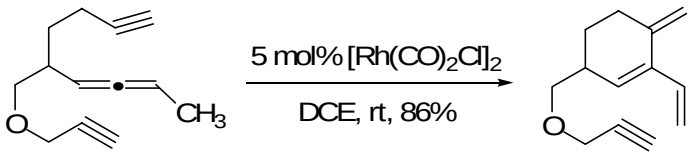
was added. Then the reaction was stirred at rt for 20 h. The reaction was quenched by careful addition of H_2O (3 mL) over 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (4 × 5 mL). The organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* silica gel chromatography to give 40 mg of **3.37** in 43% as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12–5.00 (m, 1H), 4.65-4.57 (m, 1H), 2.98 (dd, *J* = 2.6, 17.3 Hz, 1H), 2.83 (dd, *J* = 2.7, 17.3 Hz, 1H), 2.35-2.10 (m, 5H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.72-1.67 (m, 1H), 1.63 (dd, *J* = 3.1, 7.0 Hz, 3H), 1.57-1.47 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 204.9, 170.8, 92.7, 87.0, 86.5, 84.2, 79.3, 71.7, 68.6, 56.6, 53.0, 52.7, 37.8, 36.0, 35.8, 23.2, 16.5, 16.4; IR (neat) 3293, 2950, 2919, 2116, 1962, 1439, 1203 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 271 ([M-31]$^+$, 9), 245 (17), 231 (52), 183 (33), 132 (100), 117 (72), 91 (79): HRMS calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1516.



3.31 **3.43**

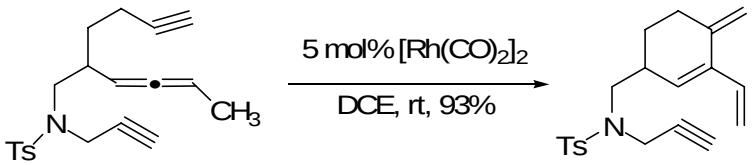
3-Allyloxymethyl-6-methylene-1-vinylcyclohexene (3.43). $[Rh(CO)_2Cl]_2$ (3.6 mg, 9.2 μmol) was added to a solution of allenyne (**3.31**, 35 mg, 0.18 mmol) in 1 mL of DCE. The reaction was stirred for 2 h at rt under N_2. The solvent was removed in *vacuo* and the residue was purified via column chromatography eluting with 10% EtOAc / hexanes to afford 29 mg of cross-conjugated triene **3.43** in 83% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.47 (dd, *J* = 10.8, 17.2 Hz, 1H), 6.00-5.87 (m, 2H), 5.40 (dd, *J* = 1.9, 17.2 Hz, 1H), 5.29 (dd, *J* = 1.5, 17.2 Hz, 1H), 5.19 (d, *J* = 10.9 Hz, 1H), 5.08 (dd, *J* = 1.9, 10.9 Hz, 1H), 5.01 (s, 1H), 4.86 (s, 1H), 4.01 (dt, *J* = 1.3, 5.6 Hz, 2H), 3.43-3.33 (m,

2H), 2.68-2.52 (m, 1H), 2.46 (ddd, J = 4.2, 10.2, 14.3 Hz, 1H), 2.37-2.26 (m, 1H), 1.96-1.84 (m, 1H), 1.50-1.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.0, 137.4, 135.9, 134.8, 128.8, 116.9, 115.0, 109.5, 73.9, 72.0, 37.2, 30.9, 26.5; IR (neat) 2919, 2848, 1629, 1102 cm^{-1}.



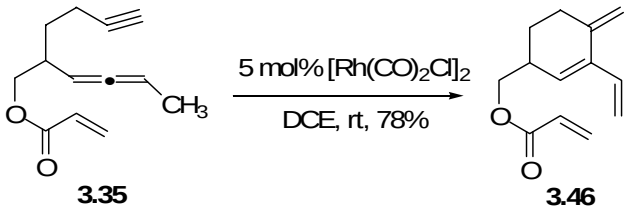
3.32 **3.44**

6-Methylene-3-prop-2-ynyloxymethyl-1-vinylcyclohexene (3.44). Allenediyne **3.32** (200 mg, 1.06 mmol) was dissolved in 2 mL of 1,2-dichloroethane. To this solution was added $[RhCl(CO)_2]_2$ (20 mg, 0.05 mmol). The reaction was stirred for 4 h at rt under N_2. The solvent was removed and the residue was purified *via* silica gel chromatography eluting with 5% EtOAc / hexanes to afford 172 mg of triene **3.44** in 86% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.47 (dd, J = 10.8, 17.2 Hz, 1H), 5.90 (s, 1H), 5.40 (dd, J = 1.9, 17.2 Hz, 1H), 5.09 (dd, J = 1.9, 10.8 Hz, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 4.18 (d, J = 2.4 Hz, 2H), 3.47 (d, J = 6.9 Hz, 2H), 2.70-2.54 (m, 1H), 2.51-2.33 (m, 2H), 2.44 (t, J = 2.4 Hz, 1H), 1.95-1.86 (m, 1H), 1.52-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 137.6, 135.8, 128.4, 115.1, 109.6, 79.8, 74.3, 73.6, 58.3, 37.0, 30.9, 26.4; IR (neat) 3298, 3078, 2940, 2858, 2116, 1634, 1440, 1358, 1096 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 188 ([M]$^{\cdot}$+, 26), 173 (52), 133 (12), 119 (79), 91 (100) : HRMS calcd for $C_{13}H_{16}O$: 188.1201; found: 188.1205.



3.33 **3.45**

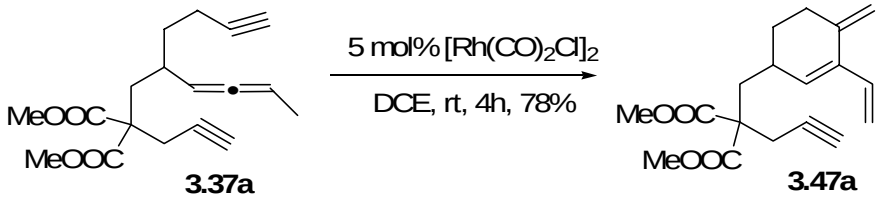
4-Methyl-*N*-(4-methylene-3-vinylcyclohex-2-enylmethyl)-*N*-prop-2-ynyl-benzenesulfonamide (3.45). $[Rh(CO)Cl_2]_2$ (2 mg, 4 μmol) was added to a solution of allenediyne **3.33** (30 mg, 0.088 mmol) in 1.5 mL of 1,2-dichloroethane. The reaction was stirred at rt for 10 min. The solvent was removed and the residue was purified *via* column chromatography eluting with 15% EtOAc / hexanes to give the triene **3.45** (28 mg, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.71 (m, 2H), 7.34-7.24 (m, 2H), 6.46 (ddt, *J* = 1.2, 10.7, 17.2 Hz, 1H), 5.83 (bs, 1H), 5.39 (dd, *J* = 1.9, 17.2 Hz, 1H), 5.10 (dd, *J* = 1.9, 10.7 Hz, 1H), 5.03 (bs, 1H), 4.89 (bs, 1H), 4.25-4.12 (m, 2H), 3.17 (d, *J* = 1.1 Hz, 1H), 3.15 (s, 1H), 2.70-2.58 (m, 1H), 2.52-2.42 (m, 1H), 2.43 (s, 3H), 2.37-2.23 (m, 1H), 2.04 (t, *J* = 2.5 Hz, 1H), 1.92-1.83 (m, 1H), 1.55-1.42 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 143.5, 142.6, 138.1, 135.9, 135.7, 129.5, 127.8, 127.7, 115.4, 110.1, 76.4, 74.0, 50.5, 37.0, 34.7, 30.6, 26.8, 21.5; IR (neat) 3288, 2925, 2116, 1347, 1153 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 341 ($[M]^{\cdot}$+, 10), 317 (21), 275 (49), 222 (99), 155 (98), 91 (100) : HRMS calcd for $C_{20}H_{23}NO_2S$: 341.1450; found: 341.1456.



3.35 **3.46**

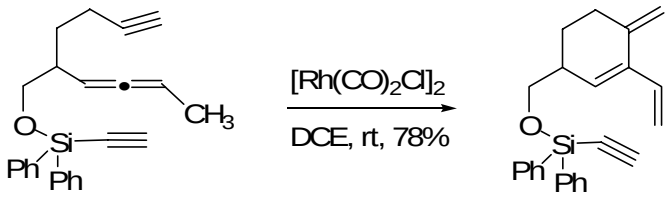
Acrylic acid 4-methylene-3-vinylcyclohex-2-enylmethyl ester (3.46). Allenyne **3.35** (58 mg, 0.28 mmol) was dissolved in 1 mL of DCE. To this solution was added $[Rh(CO)_2Cl_2]$ (6 mg, 15 μmol) and the reaction was stirred at rt for 2 h under N_2. The solvent was removed and the residue was purified via column chromatography eluting with 5% EtOAc / hexanes to afford 45 mg of triene **3.46** in 78% yield as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.50-6.40 (m, 1H), 6.43 (dd, *J* = 1.4, 17.3 Hz, 1H), 6.15 (dd, *J* = 10.4, 17.3 Hz, 1H), 5.85 (dd, *J* = 1.5, 10.3 Hz, 1H), 5.85 (s, 1H), 5.40 (dd, *J* = 1.9, 17.2 Hz, 1H), 5.11 (dd, *J* = 1.9, 10.8 Hz, 1H), 5.04 (s, 1H), 4.90 (s, 1H), 4.16-4.06 (m, 2H), 2.76-2.63 (m, 1H), 2.49 (ddd, *J* = 4.2, 10.1, 14.4 Hz, 1H), 2.40-2.27 (m, 1H), 1.97-1.85 (m, 1H), 1.55-1.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 142.4, 138.4, 135.8, 130.7, 128.4, 127.1, 115.4, 110.2, 67.5, 36.3, 30.7, 26.3; IR (neat) 2935, 1726, 1629, 1409, 1184 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 204 ([M]$^{\cdot}$+, 18), 132 (100), 117 (92), 55 (82) : HRMS calcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1150.



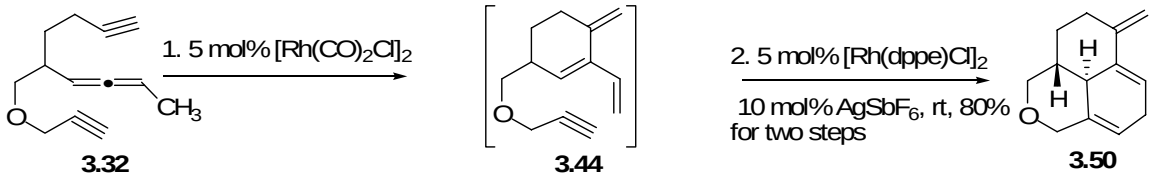
3.37a **3.47a**

2-(4-Methylene-3-vinylcyclohex-2-enylmethyl)-2-prop-2-ynylmalonic acid dimethyl ester (3.47a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (ddt, *J* = 1.0, 10.7, 17.2 Hz, 1H), 5.73 (s, 1H), 4.98 (s, 1H), 4.84 (s, 1H), 3.75 (s, 6H), 5.36 (dd, *J* = 2.0, 17.2 Hz, 1H), 5.07 (dd, *J* = 2.0, 11.3 Hz, 1H), ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.1, 171.0, 142.7, 137.0, 136.1, 131.8, 115.2, 109.8, 79.1, 72.0, 56.6, 53.0, 52.9, 38.1, 32.7, 31.2, 30.5, 23.7; IR (neat) 3287, 2953, 1731, 1433, 1193 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 302 ([M]$^{\cdot}$+, 11), 242 (16), 211 (13), 132 (100), 117 (70), 91 (69): HRMS (ESI) calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1516.



3.38 **3.48**

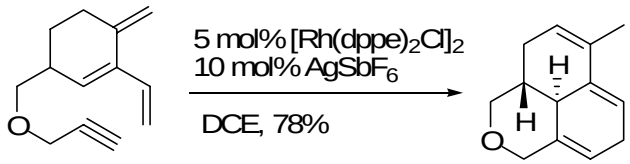
((4-Methylene-3-vinylcyclohex-2-enyl)methoxy)(ethynyl)diphenylsilane (**3.48**). Allediyne **3.38** (20 mg, 0.0561 mmol) was dissolved in 1 mL of DCE. To this solution was added $[Rh(CO)_2Cl_2]$ (6 mg, 0.014 mmol) and the reaction was stirred at rt for 20 min under N_2. The solvent was removed and the residue was purified via column chromatography eluting with 5% EtOAc / hexanes to afford 17 mg of triene **3.48** in 85% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82-7.67 (m, 4H), 7.53-7.38 (m, 6H), 6.48 (dd, *J* = 10.8, 17.2 Hz, 1H), 5.95 (s, 1H), 5.42-5.33 (m, 1H), 5.08 (dd, *J* = 2.0, 10.8 Hz, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 3.82-3.68 (m, 2H), 2.77 (s, 1H), 2.70-2.56 (m, 1H), 2.48-2.40 (m, 1H), 2.39-2.28 (m, 1H), 1.97-1.88 (m, 1H), 1.57-1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.0, 137.6, 135.9, 134.9, 132.6, 130.3, 128.6, 127.9, 115.0, 109.5, 66.5, 39.4, 30.8, 26.1, 22.6, 14.1 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 356 ([M]$^{\cdot}$+, 5), 331 (3), 278 (8), 237 (12), 207 (100), 117 (33), 97 (38): HRMS calcd for $C_{24}H_{24}OSi$ 356.1596, found 356.1594.



3.32 **3.44** **3.50**

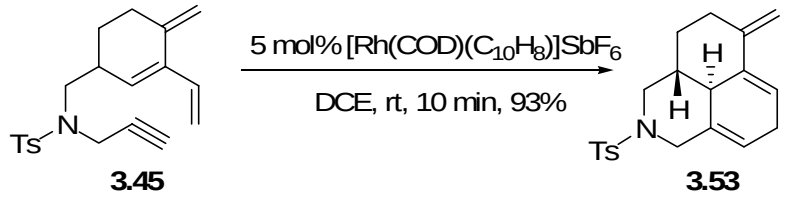
6-Methylene-3a,4,5,6,8,9b-hexahydro-*1H,3H*-benzo[*de*]isochromene (3.50). Allenediyne **3.32** (30 mg, 0.16 mmol) was dissolved in 1.6 mL of DCE. To this solution was added $[Rh(CO)_2Cl]_2$ (3 mg, 0.008 mmol). The reaction was stirred for 30 min at rt under N_2. TLC showed complete conversion of allenyne **3.32** to cross-conjugated triene **3.44**. Then $[Rh(dppe)Cl]_2$ (8 mg, 0.0075 mmol) and $AgSbF_6$ (0.05 M in DCE, 300 μL, 0.094 mmol) were added sequentially. The reaction was stirred at rt for 45 min. The

reaction solution was filtered through a plug of silica gel and filtrate was concentrated and purified via column chromatography to give 24 mg (80% yield) of **3.50** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.72-5.67 (m, 1H), 5.54-5.50 (m, 1H), 4.90 (t, *J* = 2.3 Hz, 1H), 4.68 (t, *J* = 2.3 Hz, 1H), 4.16 (d, *J* = 12.1 Hz, 1H), 3.96-3.88 (m, 2H), 3.28 (t, *J* = 11.0 Hz, 1H), 2.90-2.65 (m, 2H), 2.50-2.42 (m, 2H), 2.31-2.17 (m, 1H), 1.79-1.62 (m, 2H), 1.29-1.14 (qd, *J* = 4.3, 12.4 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 148.4, 137.3, 133.2, 117.5, 117.0, 108.2, 73.3, 72.2, 43.5, 33.8, 28.2, 26.7: IR (neat) 2815, 1622, 1084 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 188 ([M]$^{\cdot}$+, 34), 186 (46), 156 (100), 143 (55) :HRMS calcd for $C_{13}H_{16}O$ 188.1201, found 188.1207.



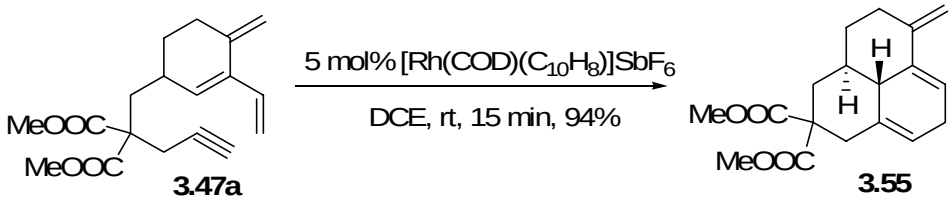
3.34 **3.51**

6-Methyl-3a,4,8,9b-tetrahydro-1*H*,3*H*-benzo[de]isochromene (3.51). $[Rh(dppe)Cl]_2$ (7 mg, 0.0065 mmol) and $AgSbF_6$ (260 μL, 0.05 M in DCE) were added to a stirred solution of triene **3.34** (25 mg, 0.133 mmol) in 1.5 mL of DCE. The reaction was stirred at rt for 10 min. The reaction solution was filtered through a plug of silica gel and filtrate was concentrated and purified via column chromatography to give 19.5 mg (78% yield) of **3.51** as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.65 (s, 1H), 5.56-5.51 (m, 2H), 4.21 (d, *J* = 12.4 Hz, 1H), 4.01 (d, *J* = 2.5 Hz, 1H), 3.97 (d, *J* = 3.0 Hz, 1H), 3.29 (t, *J* = 10.7 Hz, 1H), 2.86-2.83 (m, 2H), 2.64-2.55 (m, 1H), 2.05-1.85 (m, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 134.2, 133.2, 132.6, 123.5, 118.0, 117.4, 73.3, 72.4, 39.6, 39.1, 28.1, 26.9, 19.2.



3.45 **3.53**

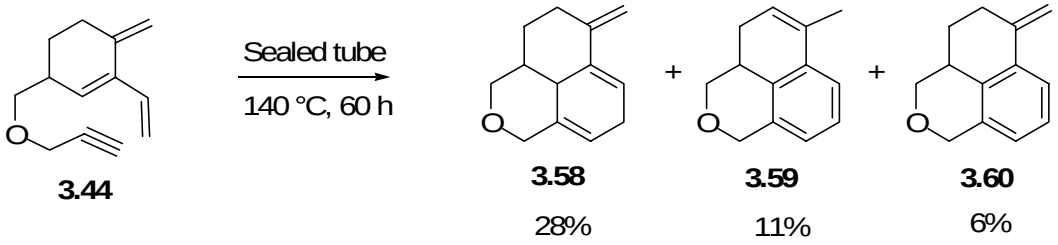
6-Methylene-2-(toluene-4-sulfonyl)-2,3,3a,4,5,6,8,9b-octahydro-*1H*-benzo[*de*]isoquinoline (3.53). $[Rh(COD)(C_{10}H_8)]SbF_6$ (2.3 mg, 0.004 mmol) was added to a stirred triene **3.45** (27 mg, 0.079 mmol) in 1.0 mL of DCE. The reaction was stirred at rt for 10 min. After removal of DCE, the resulting crude material was purified by flash chromatography on silica gel using 10% ethyl acetate/hexanes as the eluant to afford 25 mg (93% yield) of **3.53** as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.66-5.63 (m, 2H), 4.84 (t, *J* = 2.1 Hz, 1H), 4.64 (t, *J* = 2.1 Hz, 1H), 4.16 (dd, *J* = 1.5, 12.0 Hz, 1H), 3,78 (ddd, *J* = 1.7 Hz, 3.3, 11.3 Hz, 1H), 2.89-2.62 (m, 3H), 2.44 (s, 3H), 2.44-2.36 (m, 1H), 2.25-2.04 (m, 3H), 1.77-1.66 (m, 2H), 1.30-1.16 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 148.2, 143.5, 136.7, 133.0, 129.60, 129.55, 127.8, 120.2, 117.4, 108.4, 52.2, 52.0, 43.3, 41.3, 33.7, 30.0, 26.8, 21.5; IR (neat) 2924, 1455, 1347, 1164 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{23}NO_2S$ 341.1450, found 341.1450.



3.47a **3.55**

6-Methylene-3a,4,5,6,8,9b-hexahydro-1*H*,3*H*-phenalene-2,2-dicarboxylic acid dimethyl ester (3.55). $[Rh(COD)(C_{10}H_8)]SbF_6$ (1.7 mg, 0.003 mmol) was added to a stirred triene **3.47a** (18 mg, 0.06 mmol) in 1.0 mL of DCE. The reaction was stirred at rt for 15 min. After removal of DCE, the resulting crude material was purified by flash

chromatography on silica gel using 10% ethyl acetate/hexanes as the eluant to afford 17 mg (94% yield) of **3.55** as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64-5.60 (m, 1H), 5.50-5.48 (m, 1H), 4.83 (t, *J* = 2.3 Hz, 1H), 4.63 (t, *J* = 2.3 Hz, 1H), 2.92 (dd, *J* = 2.5, 13.7 Hz, 1H), 2.85-2.61 (m, 2H), 2.45-2.34 (m, 3H), 2.28-2.15 (m, 2H), 1.81 (dp, *J* = 2.1, 12.7 Hz, 1H), 1.62-1.52(m, 1H), 1.38-1.26(m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 172.2, 171.0, 149.4, 138.1, 131.8, 119.4, 117.2, 107.6, 59.2, 52.6, 56.2, 52.3, 44.9, 40.0, 39.5, 38.1, 34.3, 33.7, 27.1; IR(neat) 2953, 2916, 1731, 1433, 1244 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 302 ([M]$^{\cdot}$+, 78), 242 (100), 183 (97), 143 (92), 128 (76), 115 (58), 91 (42), 59 (73): HRMS (ESI) calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1516.

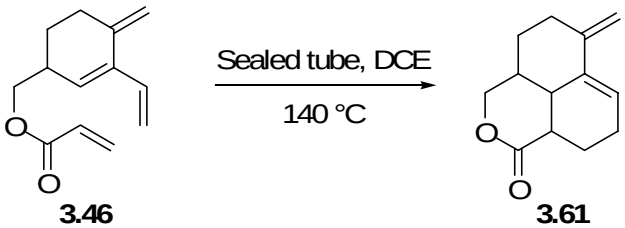


6-Methylene-3a,4,5,6,8,9b-hexahydro-1*H*,3*H*-benzo[*de*]isochromene (3.58), **6-Methyl-3a,4-dihydro-1*H*,3*H*-benzo[*de*]isochromene (3.59)**, **6-Methylene-3a,4,5,6-tetrahydro-1*H*,3*H*-benzo[*de*]isochromene (3.60)**: Cross-conjugated triene **3.44** (25 mg, 0.133 mmol) was dissolved in 2 mL of DCE and the reaction was heated to 140 °C in a sealed tube for 60 h. The solvent was removed to give 23 mg of a yellow oil. The oil was subjected to HPLC and colorless oils **3.58** (7 mg, 28%), **3.59** (1.5 mg, 6%) and a white solid **3.60** (2.8 mg, 11%) were separated. **3.58**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89–5.83 (m, 1H), 5.67 (bs, 1H), 5.06-5.03 (m, 1H), 4.74-4.70 (m, 1H), 4.25 (d, *J* = 12.1 Hz, 1H), 4.23-4.14 (m, 1H), 3.65 (d, *J* = 5.1 Hz, 2H), 3.15-3.04 (m, 1H), 2.93-2.80 (m, 1H), 2.72-2.55 (m, 1H), 2.50-2.27 (m, 2H), 2.14-2.03 (m, 1H), 1.47-1.38 (m, 2H);

^{13}C NMR (75 MHz; $CDCl_3$) δ 148.1, 137.9, 132.9, 121.1 (d), 108.1, 70.8, 69.8, 36.6, 35.4, 30.5, 27.1, 24.5; IR (neat) 2919, 2843, 1619, 1445, 805 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 186 ([M]$^{\cdot}$+, 60), 156 (100), 141 (76), 128 (61), 115 (58), 91 (40), 77 (38).

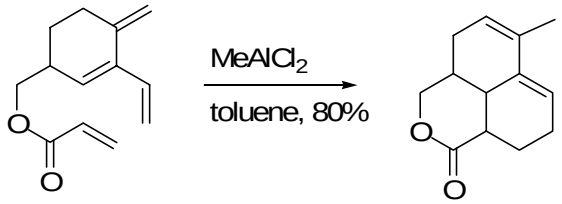
3.59: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (q, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 6.6 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 5.91-5.85 (m, 1H), 4.84 (s, 2H), 4.24 (dd, *J* = 5.6, 11.0 Hz, 1H), 3.51 (t, *J* = 10.8 Hz, 1H), 3.12-2.97 (m, 1H), 2.19-2.05 (m, 1H), 2.08 (s, 3H), 1.86-1.73 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) 134.9, 133.0, 132.4, 131.5, 126.2, 124.2, 122.7, 121.0, 70.2, 68.0, 31.7, 24.9, 19.3; IR (neat) 2919, 2848, 1460 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 186 ([M]$^{\cdot}$+, 43), 156 (100), 141 (89) : HRMS calcd for $C_{13}H_{14}O$: 186.1045; found: 186.1041.

3.60: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 5.58 (d, *J* = 2.1 Hz, 1H), 5.02-4.98 (m, 1H), 4.91 (d, *J* = 15.1 Hz, 1H), 4.81 (d, *J* = 15.1 Hz, 1 H), 4.12 (dd, *J* = 5.2, 10.7 Hz, 1H), 3.37 (t, *J* = 10.8 Hz, 1H), 3.04-2.92 (m, 1H), 2.77 (dt, *J* = 4.0, 15.3 Hz, 1H), 2.69-2.55 (m, 1H), 1.91-1.82 (m, 1H), 1.37-1.20 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) 142.3, 134.3, 134.0, 126.5, 123.7, 122.3, 109.5, 70.3, 68.4, 36.1, 32.0, 25.4; IR (neat) 2919, 2843, 1619, 1445 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 186 ([M]$^{\cdot}$+, 43), 156 (100), 141 (69) : HRMS calcd for $C_{13}H_{14}O$: 186.1045; found: 186.1040.



3.46 **3.61**

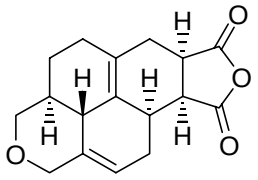
6-Methylene-3a,4,5,6,8,9,9a,9b-octahydro-3H-benzo[de]isochromen-1-one (3.61). A sealed tube was charged with triene (**3.46**, 15 mg, 0.073 mmol) and 2 mL of DCE. The the reaction was heated to 140 °C for 24 h. The solvent was removed *in vacuo* and the crude material was first purified via silica gel chromatography eluting with 20% EtOAc / hexanes to afford 14 mg of yellow oil. The oil was further purified *via* HPLC to afford 7 mg of lactone **3.61** in 47% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.04-5.99 (m, 1H), 4.98 (bs, 1H), 4.71-4.67 (m, 1H), 4.32 (dd, *J* = 11.3, 11.6 Hz, 1H), 4.19 (ddd, *J* = 1.6, 4.9, 11.1 Hz, 1H), 2.88-2.83 (m, 1H), 2.81-2.74 (m, 1H), 2.47-2.37 (m, 2H), 2.32-2.24 (m, 2H), 2.24-2.11 (m, 1H), 2.07-1.96 (m, 1H), 1.88-1.66 (m, 2H), 1.62-1.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.1, 146.5, 135.9, 125.0, 109.7, 69.2, 39.1, 37.4, 32.7, 29.2, 26.0, 23.5, 22.0; IR (neat) 2919, 2853, 1726, 1158 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 204 ($[M]^{\cdot}$+, 54), 159 (75), 117 (94), 91 (100) : HRMScalcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1149.



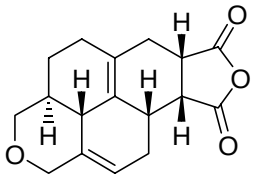
3.46 **3.62**

6-Methyl-3a,4,8,9,9a,9b-hexahydro-3H-benzo[de]isochromen-1-one (3.62). A 1.0 M solution of $MeAlCl_2$ in hexanes (0.13 mL, 0.13 mmol) was added to a -78 °C solution of ester **3.46** (15 mg, 0.073 mmol) in 1 mL of toluene. The reaction was stirred for 3 h and the temperature was slowly warmed to rt during this period. The reaction was quenched with addition of $NaHCO_3$ (1 mL). The mixture was diluted with ether and 1 N HCl. The aqueous layer was extracted with ether (3 × 1 mL). The combined ethereal extracts were dried (Na_2SO_4), filtered and concentrated to dryness. Purification of the crude product by

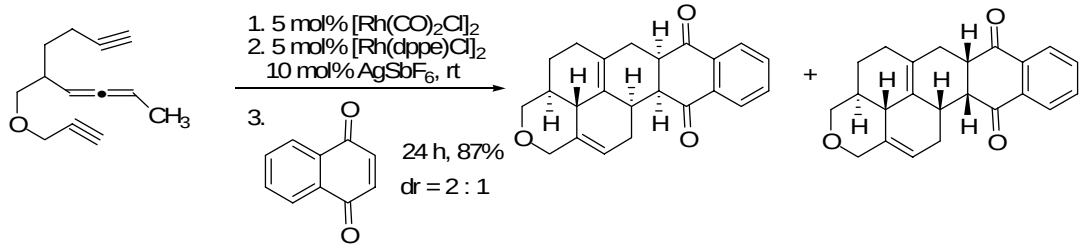
flash chromatography (20% EtOAc/hexanes) gave 12 mg (80% yield) of **3.62** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.89 (bs, 1H), 5.40 (d, *J* = 4.2 Hz, 1H), 4.22-4.08 (m, 2H), 2.88-2.82 (m, 2H), 2.60-2.45 (m, 3H), 2.36-2.12 (m, 2H), 1.88 (dd, *J* = 5.0, 17.8 Hz, 1H), 1.84 (s, 3H), 1.70-1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.8, 132.2, 131.6, 125.0, 121.4, 69.9, 40.0, 35.3, 31.8, 26.6, 23.7, 22.5, 19.4; IR (neat) 2930, 1716, 1178 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 204 ($[M]^{\cdot}$+, 34), 159 (74), 117 (100), 91 (94) : HRMS calcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1160.



3,3a,4,5,6,6a,9a,9b,10,11b-Decahydro-1*H*-2,8-dioxa-cyclopenta[a]pyrene-7,9-dione (3.52). 3.52a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (m, 1H), 4.26 (d, *J* = 13.6 Hz, 1H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.90 (dd, *J* = 3.5, 11.0 Hz, 1H), 3.44 (ddd, *J* = 1.8, 6.7, 9.6 Hz, 1H), 3.33 (dd, *J* = 6.7, 9.6 Hz, 1H), 3.25 (t, *J* = 10.9 Hz, 1H), 2.84-2.73 (m, 1H), 2.61-2.53 (m, 1H), 2.55 (dd, *J* = 1.8, 14.5 Hz, 1H), 2.44-2.34 (m, 2 H), 2.33-2.20 (m, 3H), 1.70-1.63 (m, 1H), 1.55-1.32 (m,2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 174.1, 172.2, 134.2, 131.7, 130.6, 117.7, 72.1, 70.4, 44.5, 40.8, 39.4, 38.9, 33.1, 29.9, 29.4, 24.6, 23.6; IR (neat) 2924, 1840, 1767 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1202.



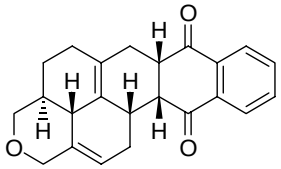
3.52b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (m, 1H), 4.14 (d, *J* = 12.4 Hz, 1H), 3.93 (d, *J* = 13.3 Hz, 1H), 3.88 (d, *J* = 3.9, 11.0 Hz, 1H), 3.45 (t, *J* = 8.9 Hz, 1H), 3.37 (td, *J* = 2.1, 8.4 Hz, 1 H), 3.29 (t, *J* = 10.9 Hz, 1H), 2.74-2.64 (m, 1H), 2.57 (d, *J* = 17.8 Hz, 1H), 2.35-1.95 (m, 5H), 1.69-1.62 (m, 2H), 1.60-1.46 (m, 1H), 1.36-1.24 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 173.2, 171.4, 135.8, 128.1, 125.4, 118.7, 72.3, 71.3, 43.5, 42.2, 41.3, 38.7, 30.5, 30.1, 29.1, 25.0, 24.0; IR (neat) 2916, 2829, 1862, 1782 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1210.



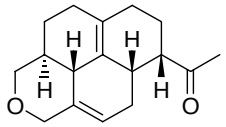
3.32 **3.87a** **3.87b**

3,3a,4,5,6,6a,12a,12b,13,14b-Decahydro-1*H*-2-oxanaphtho[2,1,8-*qra*]naphthacene-7,12-dione (3.87). Allenediyne **3.32** (30 mg, 0.16 mmol) was dissolved in 1.6 mL of DCE. To this solution was added $[Rh(CO)_2Cl]_2$ (3 mg, 0.008 mmol). The reaction was stirred for 30 min at rt under N_2. TLC showed complete conversion of allenyne **3.32** to cross-conjugated triene. Then $[Rh(dppe)Cl]_2$ (8 mg, 0.0075 mmol) and $AgSbF_6$ (0.05 M in DCE, 300 μL, 0.094 mmol) were added sequentially. The reaction was stirred at rt for 45 min. TLC showed the second step was complete. 1,4- benzoquinone (38 mg, 0.24 mmol) was added and the reaction was stirred at rt for 24 h. The solvent was removed under reduced pressure and the resulting residue was purified *via* flash chromatography to give 48 mg (87% yield) of yellow solid. The product consisted of 2 : 1 mixture of two cycloadducts according to ^{1}H NMR analysis. (**3.87a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (dd, *J* = 3.4, 5.7 Hz, 1H), 7.94 (dd, *J* = 3.1, 5.9 Hz, 1H), 7.75 (d, *J* = 3.4 Hz, 1H),

7.73 (d, *J* = 3.3 Hz, 1H), 5.69 (d, *J* = 4.5 Hz, 1H), 4.32 (d, *J* =13.6 Hz, 1H), 3.96 (dd, *J* = 4.1 Hz, 11.2 Hz, 1H), 3.54-3.44 (m, 2H), 3.21 (t, *J* = 11.0 Hz, 1H), 2.90 (t, *J* = 13.5, 1H), 2.59-2.49 (m, 2H), 2.27-1.91 (m, 6H), 1.74-1.51 (m, 1H), 1.39-1.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 197.8, 135.9, 134.4, 134.0, 132.6, 131.1, 127.2, 126.3, 123.5, 119.6, 72.7, 70.8, 50.8, 50.6, 39.1, 38.3, 36.2, 31.4, 28.0, 26.2, 24.6; IR (neat) 2919, 2853, 1685, 1588, 1250 cm^{-1}.

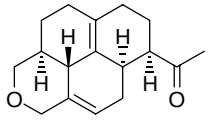


(**3.87b**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (dd, *J* = 3.5, 5.7 Hz, 1H), 8.04-7.98 (m, 1H), 7.76 (d, *J* = 3.3 Hz, 1H), 7.74 (d, *J* = 3.3 Hz, 1H), 5.25 (s, 1H), 4.01 (d, *J* = 12.2 Hz, 1H), 3.89-3.84 (m, 2H), 3.60 (dd, *J* = 6.3, 7.0 Hz, 1H), 3.27 (t, *J* = 10.9 Hz, 1H), 2.86 (d, *J* = 17.4 Hz, 1H), 2.70-2.65 (m, 2H), 2.47 (d, *J* = 8.9 Hz, 1H), 2.31-2.23 (m, 1H), 2.18-2.07 (m, 2H), 1.68-1.61 (m, 2H), 1.54-1.49 (m, 2H), 1.37-1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 197.1, 136.4, 136.0, 135.5, 134.4, 133.9, 127.8, 126.7, 126.2, 125.9, 119.0, 72.5, 71.6, 50.1, 44.8, 44.2, 41.3, 34.6, 30.6, 30.0, 26.4, 24.2; IR (neat) 2916, 2822, 1695, 1593, 1251, 735 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 346 ([M-2]$^+$, 17), 173 (14), 160 (100), 76 (30) :HRMS calcd for [M-2] $C_{23}H_{20}O_3$ 344.1412, found 344.1411.

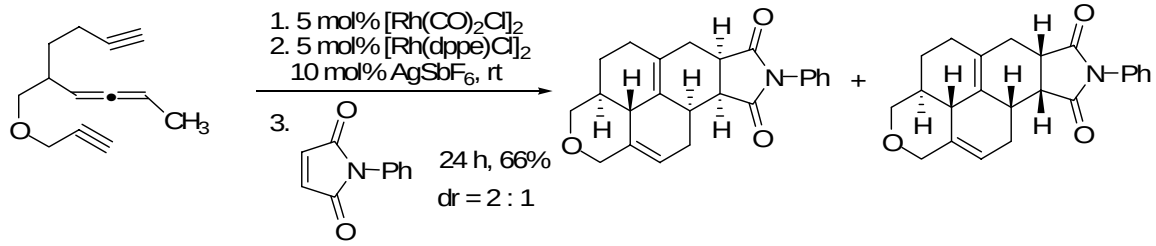


1-(3,5,5a,6,7,8,9,10a,10b-Decahydro-1*H*-2-oxapyren-6-yl)ethanone (3.88a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53–5.51 (m, 1H), 4.13 (d, *J* = 12.1 Hz, 1H), 3.96 (d, *J* = 12.1 Hz,

1H), 3.87 (dd, *J* = 3.6, 10.9 Hz, 1H), 3.32 (t, *J* = 10.9 Hz, 1H), 2.80 (ddd, *J* = 2.7, 6.1, 12.6 Hz, 1H), 2.63-2.53 (m, 2H), 2.07-1.99 (m, 2H), 1.99-1.89 (m, 2H), 1.77-1.68 (m, 2H), 1.65-1.43 (m, 3H), 1.34-1.22 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 210.9, 136.7, 129.6, 128.9, 119.8, 72.8, 71.9, 51.6, 44.8, 42.2, 34.7, 30.5, 29.8, 29.1, 28.6, 24.6, 19.8; IR (neat) 2893, 1696 cm^{-1}; HRMS (ESI) cacld for $C_{17}H_{22}O_2$ 258.1620, found 258.1623.



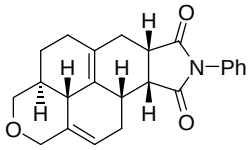
3.88b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64–5.61 (m, 1H), 4.26 (d, *J* = 13.5 Hz, 1H), 4.06-3.99 (m, 1H), 3.95 (dd, *J* = 4.1, 11.3 Hz, 1H), 3.18 (t, *J* = 11.0 Hz, 1H), 2.88 (dd, *J* = 4.2, 7.3 Hz, 1H), 2.51-2.37 (m, 2H), 2.17-1.85 (m, 11H), 1.70-1.51 (m, 2H), 1.38-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 135.1, 130.0, 125.8, 119.8, 73.2, 71.1, 50.9, 39.5, 38.6, 36.7, 29.7, 28.4, 27.6, 26.9, 26.6, 24.8; IR (CH_2Cl_2) 2919, 1706 cm^{-1}.



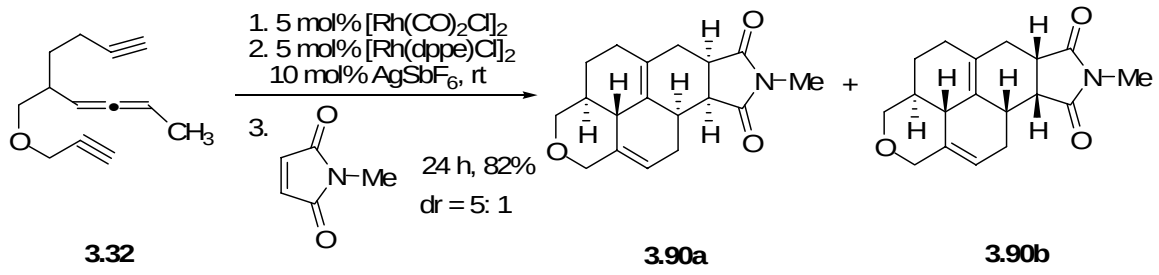
3.32 **3.89a** **3.89b**

8-Phenyl-1,3,3a,4,5,6,6a,7,8,9,9a,9b,10,11b-tetradecahydro-2-oxa-8-aza-cyclopenta[*a*]pyrene (3.55). Allenediyne **3.32** (30 mg, 0.16 mmol) was dissolved in 1.6 mL of DCE. To this solution was added $[Rh(CO)_2Cl]_2$ (3 mg, 0.008 mmol). The reaction was stirred for 30 min at rt under N_2. TLC showed complete conversion of allenyne **3.32** to cross-conjugated triene. Then $[Rh(dppe)Cl]_2$ (8 mg, 0.0075 mmol) and $AgSbF_6$ (0.05 M in DCE, 300 μL, 0.094 mmol) were added sequentially. The reaction was stirred at rt for 45 min. TLC showed the second step was complete. N-phenylmaleimide (33 mg,

0.192 mmol) was added and the reaction was stirred at rt for 24 h. The solvent was removed under reduced pressure and the resulting residue was purified *via* flash chromatography to give 38 mg (66% yield) of white solid. The product consisted of 2 : 1 mixture of two cycloadducts according to ^{1}H NMR analysis. (**3.89a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48-7.38 (m, 3H), 7.19-7.15 (m, 2H), 5.62 (s, 1H), 4.27 (d, *J* = 13.6 Hz, 1H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.90 (dd, *J* = 3.9, 11.0 Hz, 1H), 3.34-3.20 (m, 3H), 3.07-2.99 (m, 1H), 2.68-2.60 (m, 2H), 2.48-2.22 (m, 5H), 1.73-1.65 (m, 1H), 1.55-1.46 (m, 1H), 1.37-1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 177.7, 133.6, 132.0, 131.0, 129.8, 129.1, 126.5, 118.4, 78.3, 72.2, 70.5, 43.7, 40.8, 39.5, 39.0, 33.7, 29.9, 25.0, 23.6; IR (neat) 2925, 2863, 1706, 1383, 1194, 1660 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 361 ($[M]^{\cdot}$+, 48), 331 (19), 187 (23), 175 (100), 128 (37): HRMS calcd for $C_{23}H_{23}NO_3$ 361.1678, found 361.1673.



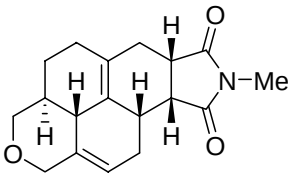
(**3.89b**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50-7.44 (m, 2H), 7.41-7.36 (m, 1H), 7.27-7.24 (m, 2H), 5.58 (s, 1H), 4.18 (d, *J* = 12.6 Hz, 1H), 3.97 (d, *J* = 12.6 Hz, 1H), 3.88 (dd, *J* = 3.6, 10.9 Hz, 1H), 3.40-3.26 (m, 2H), 2.60-2.15 (m, 6H), 1.68-1.61 (m, 1H), 1.54-1.41 (m, 1H), 1.38-1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 177.5, 135.2, 131.9, 129.2, 128.6, 128.4, 126.9, 126.3, 119.3, 72.4, 71.2, 42.6, 41.2, 39.1, 32.3, 30.3, 27.8, 25.9, 24.3; IR (neat) 2919, 2832, 1711, 1501, 1373, 1153 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 361 ($[M]^{\cdot}$+, 65), 213 (7), 187 (22), 175 (100), 157 (31), 129 (31): HRMS calcd for $C_{23}H_{23}NO_3$ 361.1678, found 361.1675.



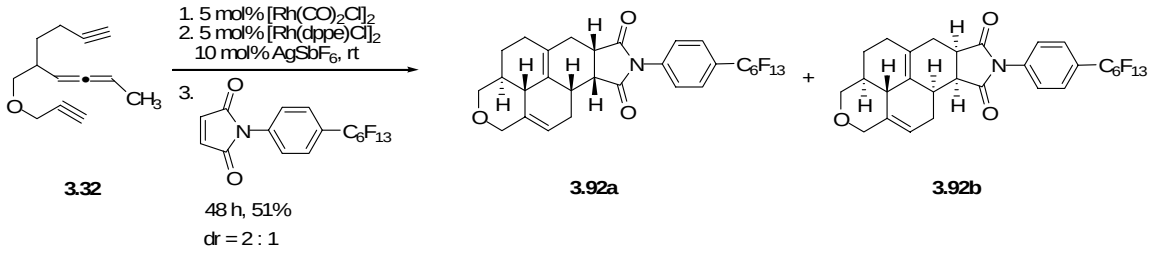
3.32 **3.90a** **3.90b**

8-Methyl-1,3,3a,4,5,6,6a,7,8,9,9a,9b,10,11b-tetradecahydro-2-oxa-8-aza-cylcopenta[*a*]pyrene (3.90a), (3.90b). Allenediyne **3.32** (30 mg, 0.16 mmol) was dissolved in 1.6 mL of DCE. To this solution was added $[Rh(CO)_2Cl]_2$ (3 mg, 0.008 mmol). The reaction was stirred for 30 min at rt under N_2. TLC showed complete conversion of allenyne **3.32** to cross-conjugated triene. Then $[Rh(dppe)Cl]_2$ (8 mg, 0.0075 mmol) and $AgSbF_6$ (0.05 M in DCE, 300 μL, 0.094 mmol) were added sequentially. The reaction was stirred at rt for 45 min. TLC showed the second step was complete. N-methylmaleimide (21 mg, 0.192 mmol) was added and the reaction was stirred at rt for 24 h. The solvent was removed under reduced pressure and the resulting residue was purified *via* flash chromatography to give 39 (82%) mg of white solid. The product consisted of 5 : 1mixture of two cycloadducts according to ^{1}H NMR analysis. (**3.90a**) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.61 (dd, *J* = 2.3, 5.9 Hz, 1H), 4.25 (d, *J* = 13.5 Hz, 1H), 4.04-3.96 (m, 1H), 3.88 (dd, *J* = 3.8, 11.0 Hz, 1H), 3.22 (t, *J* = 11.0 Hz, 1H), 3.13-3.02 (m, 3H), 2.93 (s, 3H), 2.60-2.50 (m, 1H), 2.53 (d, *J* = 14.4 Hz, 1H); 2.43-2.28 (m, 2H), 2.28-2.14 (m, 3H), 1.67-1.62 (m, 1H), 1.53-1.40 (m, 1H), 1.36-1.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179,8, 178.7, 133.8, 130.8, 129.6, 118.4, 72.3, 70.6, 43.6, 40.1, 39.5, 38.9, 33.5, 29.8, 29.7, 29.4, 24.8, 23.7; IR (neat) 2930, 1682, 1438, 1285,

1037 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 299 ([M]$^{\cdot}$+, 100), 187 (25), 157 (44), 113 (90), 69 (77): HRMS calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1519.

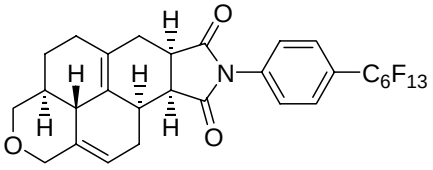


(**3.90b**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.53 (s, 1H), 4.14 (d, *J* = 12.6 Hz, 1H), 3.94 (d, *J* = 12.6 Hz, 1H); 3.86 (dd, *J* = 3.3, 10.9 Hz, 1H), 3.28 (t, *J* = 10.9 Hz, 1H), 3.18 (t, *J* = 8.5 Hz, 1H), 3.07 (td, *J* = 2.5, 8.4 Hz, 1H), 2.95 (s, 3H), 2.75-2.65 (m, 1H), 2.57 (d, *J* = 17.0 Hz, 1H), 2.46-2.43 (m, 1H), 2.38-2.27 (m, 1H), 2.23-2.10 (m, 3H), 2.05-1.92 (m, 1H), 1.66-1.61 (m, 2H), 1.44-1.24 (m, 4 H); ^{13} NMR (75 MHz, $CDCl_3$) δ 179.5, 178.5, 135.0, 128.6, 126.5, 119.2, 72.4, 71.2, 42.7, 42.1, 41.3, 38.8, 31.9, 30.2, 27.7, 26.0, 24.4, 24.3; IR (neat) 2922, 1700, 1435, 1382, 1279, 1042 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 299 ([M]$^{\cdot}$+, 75), 187 (19), 165 (34), 157 (40), 113 (100): HRMS calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1520.

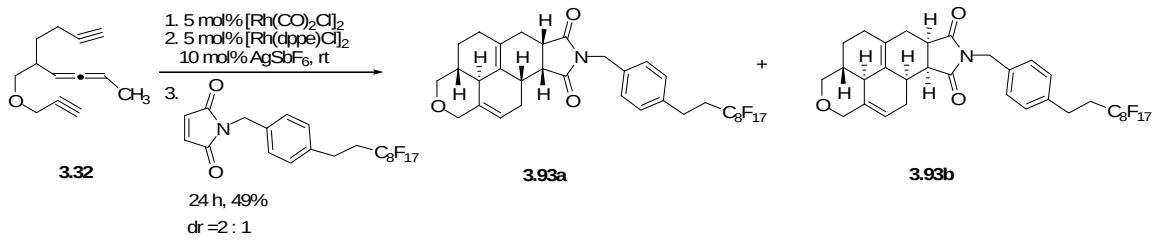


Allenediyne **3.32** (30 mg, 0.16 mmol) was dissolved in 1.6 mL of DCE. To this solution was added $[Rh(CO)_2Cl]_2$ (3 mg, 0.008 mmol). The reaction was stirred for 30 min at rt under N_2. TLC showed complete conversion of allenyne **3.32** to cross-conjugated triene. Then $[Rh(dppe)Cl]_2$ (8 mg, 0.0075 mmol) and $AgSbF_6$ (0.05 M in DCE, 300 μL, 0.094 mmol) were added sequentially. The reaction was stirred at rt for 45 min. TLC showed

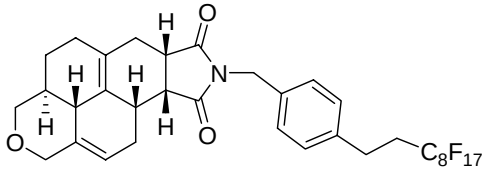
the second step was complete. Fluoromaleimide (71 mg, 112 mmol) was added and the reaction was stirred at rt for 48 h. The solvent was removed under reduced pressure and the resulting residue was purified *via* flash chromatography to give 96 mg (51% yield) of white solid. The product consisted of 2 : 1 mixture of two cycloadducts according to ^{1}H NMR analysis. (**3.92a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 5.58 (s, 1H), 4.19 (d, *J* = 12.7 Hz, 1H), 3.98 (d, *J* = 12.5 Hz, 1H), 3.87 (dd, *J* = 3.4, 10.9 Hz, 1H), 3.39-3.26 (m, 3H), 2.85-2.78 (m, 1H), 2.71 (d, *J* = 17.0 Hz, 1H), 2.53-2.45 (m, 1H), 2.45-2.33 (m, 1H), 2.32-2.13 (m, 4H), 1.48-1.25 (m, 6H), 0.93-0.85 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 177.6, 176.8, 135.2, 128.9, 127.8 (t, *J* = 25.8 Hz), 127.3, 126.4, 126.2, 119.1, 72.4, 71.1, 43.4, 42.8, 42.4, 41.2, 39.5, 32.6, 30.3, 29.7, 27.5, 26.2, 24.4; IR (CH_2Cl_2) 3155, 2254, 1711, 1378, 912, 728 cm^{-1}.



(**3.92b**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 5.63 (d, *J* = 4.1 Hz, 1H), 4.27 (d, *J* = 13.6 Hz, 1H), 4.01 (d, *J* = 13.5 Hz, 1H), 3.91 (dd, *J* = 4.0, 11.1 Hz, 1H), 3.36-3.21 (m, 3H), 3.04-2.94 (m, 1H), 2.71-2.63 (m, 1H), 2.66 (dd, *J* = 1.3, 14.5, 1H), 2.50-2.23 (m, 5H), 1.73-1.66 (m, 1H), 1.51-1.41 (m, 1H), 1.39-1.25 (m, 2H), 0.99-0.87 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 178.4, 177.3, 133.7, 131.1, 129.9, 127.8, 126.5, 118.3, 72.1, 70.5, 43.8, 40.4, 39.5, 39.0, 33.7, 29.9, 29.8, 29.7, 24.9, 23.6;

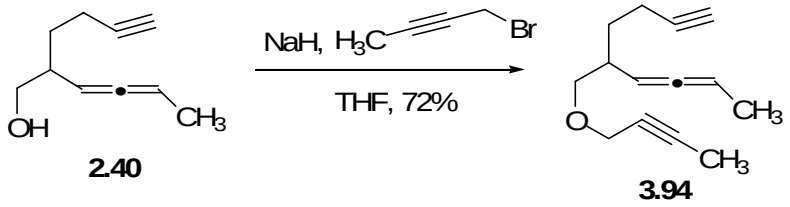


Allenediyne **3.32** (30 mg, 0.160 mmol) was dissolved in 1.6 mL of DCE. To this solution was added $[Rh(CO)_2Cl]_2$ (3 mg, 0.008 mmol). The reaction was stirred for 30 min at rt under N_2. TLC showed complete conversion of allenyne **3.32** to cross-conjugated triene. Then $[Rh(dppe)Cl]_2$ (8 mg, 0.0075 mmol) and $AgSbF_6$ (0.05 M in DCE, 300 μL, 0.015 mmol) were added sequentially. The reaction was stirred at rt for 45 min. TLC showed the second step was complete. Fluoromaleimide (101 mg, 0.16 mmol) was added and the reaction was stirred at rt for 24 h. The solvent was removed under reduced pressure and the resulting residue was purified *via* flash chromatography to give 64 mg (49% yield) of yellow solid. The product consisted of 2 : 1 mixture of two cycloadducts according to ^{1}H NMR analysis. (**3.93a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 5.58 (bs, 1H), 4.24 (d, *J* = 13.6, 1H), 3.95 (d, *J* = 13.5, 1H), 3.85 (dd, *J* = 4.0, 11.0, 1H), 3.15-3.00 (m, 4H), 2.91-2.85 (m, 2H), 2.55-2.50 (m, 1H), 2.49 (dd, *J* = 1.3, 14.8 Hz, 1H), 2.42-2.29 (m, 2H), 2.24-2.10 (m, 2H), 1.99-1.90 (m, 2H), 1.55 (ddd, *J* = 2.5, 7.7, 12.8 Hz, 1H), 1.48-1.34 (m, 1H), 1.05-0.93 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 179.3, 178.3, 138.6, 134.8, 133.6, 131.1, 129.3, 128.7, 128.4, 118.3, 118.3, 72.2, 70.5, 43.6, 41.8, 40.2, 39.2, 38.7, 33.6, 33.0 (t, *J* = 89.4 Hz), 29.8, 29.6, 26.1, 24.7, 24.7, 23.5; IR (neat) 2919, 1696, 1204 cm^{-1}; HRMS (ESI) cacld for $C_{34}H_{28}F_{17}NO_3$ 860.1464, found 860.1464.



3.93b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 5.43 (s, 1H), 4.09 (d, *J* = 12.6 Hz, 1H), 3.90 (d, *J* = 12.6 Hz, 1H), 3.77 (dd, *J* = 3.4, 11.0

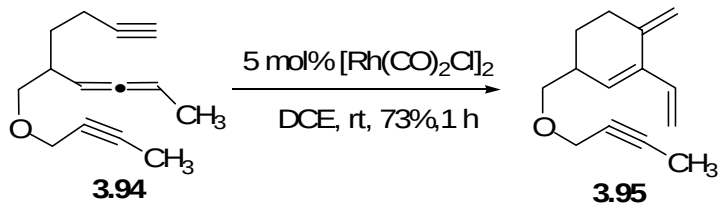
Hz, 1H), 3.23 (t, *J* = 10.7 Hz, 1H), 3.15 (t, *J* = 8.5 Hz, 1H), 3.06 (td, *J* = 2.3, 8.5 Hz, 1H), 2.91-2.85 (m, 1H), 2.69-2.62 (m, 1H), 2.53 (d, *J* = 17.0, 1H), 2.41-2.24 (m, 3H), 2.21-2.02 (m, 4H), 1.95-1.85 (m, 1H), 1.56-1.49 (m, 1H), 1.23-1.14 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 179.2, 178.1, 138.8, 134.6, 134.3, 129.6, 128.7, 128.5, 126.5, 119.1, 72.3, 71.0, 42.3, 42.2, 41.8, 38.8, 31.9, 30.1, 27.4, 26.2, 24.3 (sample is not concentrated enough, can not see all the carbons).



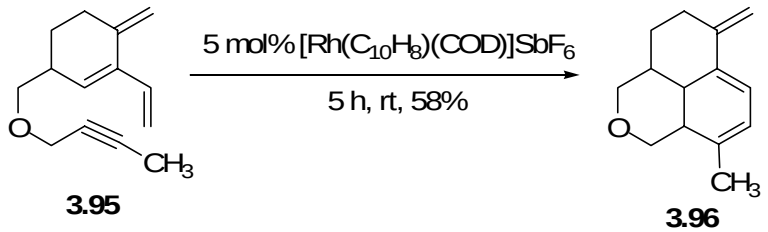
2.40 **3.94**

5-But-2-ynyloxymethyl-nona-6,7-dien-1-yne (3.60). A solution of alcohol **2.40** (200 mg, 1.33 mmol) in 3 mL of THF was cooled to 0 °C and sodium hydride (67 mg of a 95% dispersion in mineral oil, 2.67 mmol) was added portionwise. The reaction was stirred for 30 min at rt under N_2. 1-Bromo-2-butyne (175 μL, 2.00 mmol) was added and the reaction was stirred at rt for 20 h. The reaction was quenched by careful dropwise addition of H_2O (3 mL) to the reaction over 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). Then the organic layers were combined, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified *via* column chromatography eluting with 5% EtOAc / hexanes to afford 193 mg of ether **3.94** in 72% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17–5.08 (m, 1H), 5.02-4.94 (m, 1H), 4.10 (q, *J* = 2.3 Hz, 2H), 3.47 (dd, J = 6.1, 9.2 Hz, 1H), 3.39 (dd, J = 6.6, 9.1 Hz, 1H), 2.50-2.38 (m, 1H), 2.37-2.16 (m, 2H), 1.93 (t, J = 2.6 Hz, 1H), 1.86 (t, J = 2.3 Hz, 3H), 1.85-1.73 (m, 1H), 1.66 (dd, J = 3.2, 7.0 Hz, 3H), 1.60-1.47 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 204.8, 90.6, 86.6, 84.2, 82.2, 75.1, 73.1, 68.2, 58.7, 52.1,

38.4, 30.4, 17.8, 16.0, 14.4, 11.9, 3.5; IR(neat) 3298, 2919, 2858, 2116, 1962, 1445, 1358, 1132, 1081 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 202 ($[M]^{\cdot}+$, 4), 187 (31), 131 (21), 119 (44), 109 (48), 91 (71), 79 (72), 53 (100): HRMS calcd for $C_{14}H_{17}O$ 201.1279, found 201.1280.

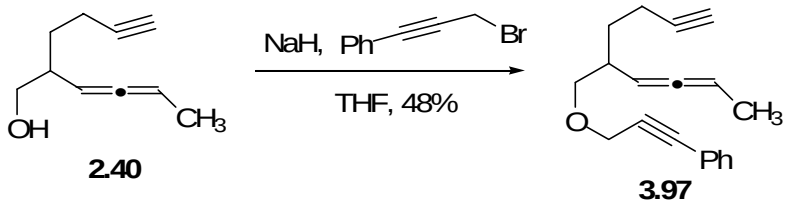


3-((But-2-ynyloxy)methyl)-6-methylene-1-vinylcyclohex-1-ene (3.95). Allenediyne **3.94** (122 mg, 0.604 mmol) was dissolved in 3 mL of 1,2-dichloroethane. To this solution was added $[RhCl(CO)_2]_2$ (12 mg, 0.03 mmol). The reaction was stirred for 1 h at rt under N_2. The solvent was removed and the residue was purified *via* silica gel chromatography eluting with 5% EtOAc / hexanes to afford 89 mg of triene **3.61** in 73% yield as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (dd, J = 10.8, 17.2 Hz, 1H), 5.90 (s, 1H), 5.39 (dd, J = 2.0, 17.2 Hz, 1H), 5.07 (dd, J = 2.0, 10.8 Hz, 1H), 4.11 (q, J = 2.3 Hz, 2H), 3.42 (dd, J = 1.1, 7.1 Hz, 2H), 2.67-2.54 (m, 1H), 2.49-2.39 (m, 1H), 2.38-2.26 (m, 1H), 1.87-1.84 (m, 4H), 1.49-1.37 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 142.8, 137.4, 135.8, 128.6, 115.0, 109.5, 82.3, 75.1, 73.4, 58.8, 37.0, 30.8, 26.4, 3.5; IR(neat) 2935, 2848, 1440, 1352, 1137, 1091 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 202 ($[M]^{\cdot}+$, 7), 187 (24), 119 (21), 91 (49), 74 (76), 59 (100): HRMS calcd for $C_{14}H_{18}O$ 202.1358, found 202.1360.



3.95 **3.96**

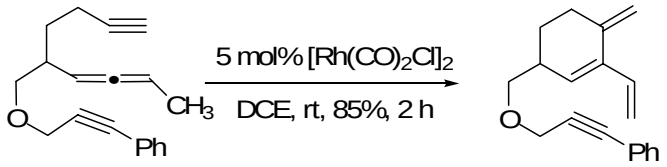
9-Methyl-6-methylene-3a,4,5,6,9b-hexahydro-1*H*,3*H*-benzo[de]isochromene (3.96). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70–5.65 (m, 1H), 4.88 (t, *J* = 2.3 Hz, 1H), 4.71 (d, *J* = 12.5 Hz, 1H), 4.66 (t, *J* = 2.3 Hz, 1H), 3.92 (dd, *J* = 4.0, 11.1 Hz, 1H), 3.69 (d, *J* = 12.5 Hz, 1H), 3.27 (t, *J* = 10.9, 1H), 2.79-2.57 (m, 2H), 2.47-2.35 (m, 2H), 2.28-2.15 (m, 1H), 1.76-1.58 (m, 5H), 1.20 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 148.7, 137.3, 125.4, 123.7, 117.1, 108.0, 73.3, 67.5, 44.4, 43.2, 33.8, 33.2, 28.3, 17.5; IR(neat) 2914, 2812, 1624, 1455, 1091 cm^{-1}.



2.40 **3.97**

[3-(2-But-3-ynyl-hexa-3,4-dienyloxy)-prop-1-ynyl]-benzene (3.97). A solution of alcohol **2.40** (200 mg, 1.33 mmol) in 3 mL of THF was cooled to 0 °C and sodium hydride (67 mg of a 95% dispersion in mineral oil, 2.67 mmol) was added portionwise. The reaction was stirred for 30 min at rt under N_2. Alkynyl bromide (390 mg, 2.00 mmol) was added and the reaction was stirred at rt for 18 h. The reaction was quenched by careful dropwise addition of H_2O (3 mL) to the reaction over 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). Then the organic layers were combined, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified *via* Biotage column eluting with 5% EtOAc / hexanes to afford 170 mg of ether

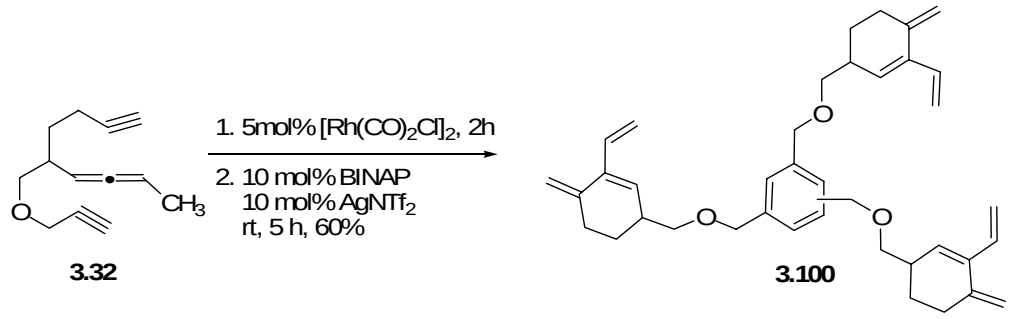
3.97 in 48% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.42 (m, 2H), 7.34-7.28 (m, 3H), 5.20-5.10 (m, 1H), 5.05-4.97 (m, 1H), 3.59 (dd, *J* = 6.1, 9.2 Hz, 1H), 3.51 (dd, *J* = 6.5, 9.2 Hz, 1H), 2.56-2.44 (m, 1H), 2.38-2.20 (m, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.90-1.77 (m, 1H), 1.68 (dd, *J* = 3.2, 7.0 Hz, 3H), 1.62-1.51 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 204.9, 131.7, 128.3, 128.2, 122.7, 90.7, 86.7, 86.1, 85.3, 84.3, 77.4, 77.0, 73.3, 68.3, 59.0, 38.5, 30.5, 16.1, 14.5; IR(neat) 3298, 2925, 2853, 2116, 1962, 1358, 1102 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 264 ([M]$^{\cdot}$+, 8), 249 (15), 219 (60), 205 (44), 179 (60), 169 (76), 115 (100), 77 (36): HRMS calcd for $C_{19}H_{19}O$ 263.1436, found 264.1442.



3.97 **3.98**

1-(3-((4-Methylene-3-vinylcyclohex-2-enyl)methoxy)prop-1-ynyl)benzene (3.98). Allenediyne **3.97** (105 mg, 0.398 mmol) was dissolved in 4 mL of 1,2-dichloroethane. To this solution was added $[RhCl(CO)_2]_2$ (7.7 mg, 0.020 mmol). The reaction was stirred for 2 h at rt under N_2. The solvent was removed and the residue was purified *via* silica gel chromatography eluting with 5% EtOAc/hexanes to afford 85 mg of triene **3.98** in 85% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2H), 7.37-7.30 (m, 3H), 6.50 (ddt, *J* = 1.1, 10.8, 17.2 Hz, 1H), 5.95 (bs, 1H), 5.43 (dd, *J* = 1.9, 17.2 Hz, 1H), 5.10 (dd, *J* = 1.9, 10.8 Hz, 1H), 5.04 (bs, 1H), 4.91-4.88 (m, 1H), 4.41 (s, 2H), 3.55 (d, *J* = 6.9 Hz, 1H), 2.74-2.62 (m, 1H), 2.50 (ddd, *J* = 4.2, 8.8, 14.4 Hz, 1H), 2.42-2.31 (m, 1H), 2.00-1.89 (m, 1H), 1.58-1.45 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 142.8, 137.6, 135.9, 131.7, 128.5, 128.4, 128.2, 122.7, 115.0, 109.6, 86.1, 85.2, 73.6,

59.2, 37.1, 30.9, 26.5; IR(neat) 2940, 2863, 1491, 1358, 1096 cm^{-1}; MS (GC/EI-MS) *m/z* (relative intensity) 264 ($[M]^{\cdot}+$, 12), 245 (40), 215 (51), 203 (61), 115 (67), 91 (100): HRMS calcd for $C_{19}H_{20}O$ 264.1514, found 264.1515.



1,2,4-tris(((4-methylene-3-vinylcyclohex-2-enyl)methoxy)methyl)benzene & 1,3,5-tris(((4-methylene-3-vinylcyclohex-2-enyl)methoxy)methyl)benzene (3.100). To a solution of allenediyne **3.32** (30 mg, 0.16 mmol, 0.10 M) in DCE was added $[Rh(CO)_2Cl]_2$ (3 mg, 0.008 mmol). The reaction was stirred for 2 h at 25 ºC. To this solution was added BINAP (9.9 mg, 0.016 mmol) and the reaction was stirred for 5 min before $AgNTf_2$ (6.2 mg, 0.016 mmol) was added. The reaction was stirred for another 5 h at 25 ºC. The solvent was removed and the resulting residue was purified via column chromatography to give 18 mg of **3.100** as a yellow oil in 60% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.25 (m, 3H), 6.47 (dd, J = 10.8, 17.2 Hz, 3H), 5.90 (bs, 3H), 5.38 (d, J = 17.2 Hz, 3H), 5.08 (dd, J = 1.8, 10.8 Hz, 3H), 4.86 (bs, 3H), 4.63-4.53 (m, 6H), 3.47-3.35 (m, 6H), 2.70-2.59 (m, 3H), 2.49-2.25 (m, 6H), 1.96-1.85 (m, 3H), 1.52-1.38 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 143.0, 138.9, 138.1, 137.6, 136.7, 136.0, 135.9, 128.81, 128.78, 127.9, 126.8, 126.0, 74.3, 74.2, 74.1, 74.0, 73.0, 72.9, 70.8, 70.6, 26.6, 26 .6; IR(neat) 2930, 2853, 1358, 1102 cm^{-1}.

Appendix A

X-ray crystal data for 3.87a

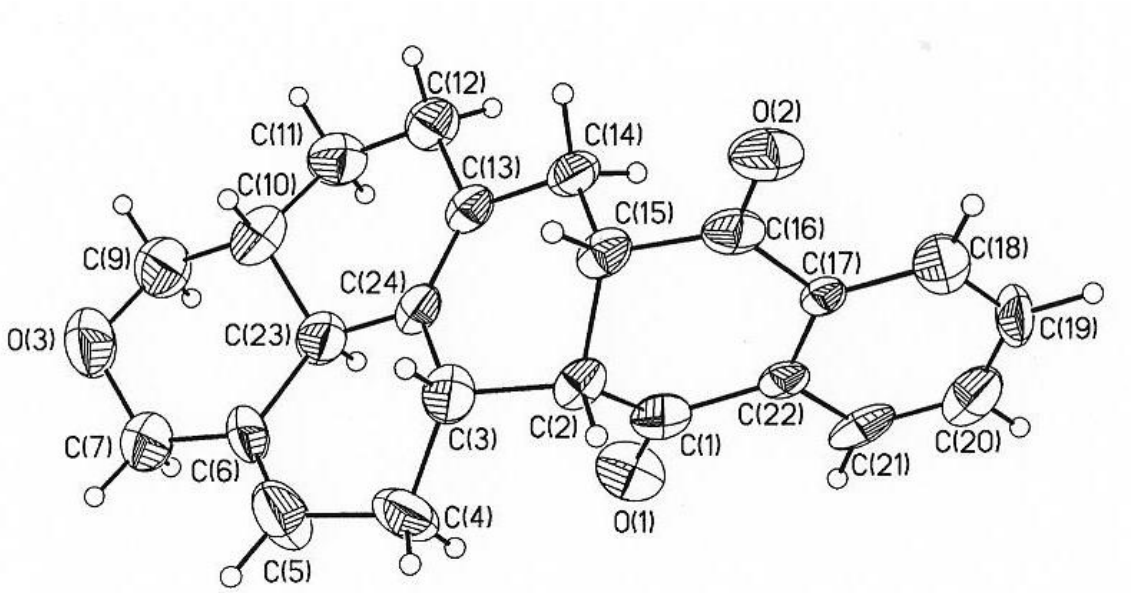


Table A1. Crystal data and structure refinement for **3.87a**.

Identification code	ling111n	
Empirical formula	C92 H88 O12	
Formula weight	1385.62	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 16.099(2) Å	α= 90°.
	b = 5.0944(7) Å	β= 126.290(6)°.
	c = 25.523(3) Å	γ = 90°.
Volume	1687.2(4) $Å^3$	
Z	1	

Density (calculated)	1.364 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	736
Crystal size	0.22 x 0.22 x 0.35 mm^3
Theta range for data collection	1.57 to 25.00°.
Index ranges	-19<=h<=19, -6<=k<=6, -30<=l<=30
Reflections collected	12560
Independent reflections	2956 [R(int) = 0.1802]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2956 / 0 / 235
Goodness-of-fit on F^2	0.837
Final R indices [I>2sigma(I)]	R1 = 0.0721, wR2 = 0.1226
R indices (all data)	R1 = 0.2055, wR2 = 0.1538
Largest diff. peak and hole	0.322 and -0.186 $e.Å^{-3}$

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.87a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1662(3)	-1173(7)	3824(2)	56(1)
C(1)	1109(4)	559(10)	3789(2)	39(1)
O(2)	-767(3)	5723(7)	3893(2)	50(1)
C(2)	1539(4)	3010(9)	4194(2)	34(1)
C(3)	2667(4)	2919(12)	4798(3)	53(2)
C(4)	3439(4)	2653(12)	4658(3)	66(2)
C(5)	4530(4)	2355(12)	5276(3)	74(2)
C(6)	4706(4)	1086(12)	5770(3)	50(2)
C(7)	5741(4)	182(12)	6327(3)	66(2)
O(3)	5918(3)	256(9)	6939(2)	77(1)
C(9)	5195(4)	-1407(13)	6930(3)	64(2)
C(10)	4100(4)	-351(11)	6446(2)	51(2)
C(11)	3283(4)	-2070(11)	6400(3)	56(2)
C(12)	2209(4)	-883(10)	5928(2)	47(2)
C(13)	2059(4)	640(9)	5377(2)	35(1)
C(14)	989(4)	1750(9)	4909(2)	40(1)
C(15)	884(4)	3771(9)	4431(2)	37(1)
C(16)	-229(4)	4076(11)	3880(2)	40(1)
C(17)	-679(4)	2156(9)	3334(2)	27(1)
C(18)	-1727(4)	1978(10)	2880(3)	46(2)
C(19)	-2133(4)	78(12)	2410(3)	53(2)
C(20)	-1510(5)	-1626(11)	2377(3)	55(2)
C(21)	-474(5)	-1457(9)	2820(2)	42(2)
C(22)	-34(4)	410(9)	3309(2)	30(1)
C(23)	3868(4)	-160(11)	5778(2)	51(2)
C(24)	2806(4)	1090(10)	5303(2)	36(1)

Table A3. Bond lengths [Å] and angles [°] for **3.87a.**

O(1)-C(1) 1.218(5)	O(1)-C(1)-C(22) 121.1(5)
C(1)-C(22) 1.491(6)	O(1)-C(1)-C(2) 122.1(5)
C(1)-C(2) 1.505(6)	C(22)-C(1)-C(2) 116.7(5)
O(2)-C(16) 1.220(5)	C(1)-C(2)-C(3) 117.0(4)
C(2)-C(3) 1.536(6)	C(1)-C(2)-C(15) 109.6(4)
C(2)-C(15) 1.544(6)	C(3)-C(2)-C(15) 107.0(4)
C(3)-C(4) 1.488(7)	C(4)-C(3)-C(24) 115.5(5)
C(3)-C(24) 1.496(7)	C(4)-C(3)-C(2) 115.0(5)
C(4)-C(5) 1.522(7)	C(24)-C(3)-C(2) 111.5(4)
C(5)-C(6) 1.292(7)	C(3)-C(4)-C(5) 112.1(5)
C(6)-C(7) 1.485(7)	C(6)-C(5)-C(4) 120.9(5)
C(6)-C(23) 1.500(7)	C(5)-C(6)-C(7) 124.2(5)
C(7)-O(3) 1.415(6)	C(5)-C(6)-C(23) 123.0(5)
O(3)-C(9) 1.428(6)	C(7)-C(6)-C(23) 111.5(5)
C(9)-C(10) 1.531(7)	O(3)-C(7)-C(6) 115.2(5)
C(10)-C(23) 1.517(6)	C(7)-O(3)-C(9) 109.7(4)
C(10)-C(11) 1.526(7)	O(3)-C(9)-C(10) 110.0(5)
C(11)-C(12) 1.530(6)	C(23)-C(10)-C(11) 108.8(4)
C(12)-C(13) 1.495(6)	C(23)-C(10)-C(9) 109.2(5)
C(13)-C(24) 1.344(6)	C(11)-C(10)-C(9) 112.9(5)
C(13)-C(14) 1.509(6)	C(10)-C(11)-C(12) 110.8(5)
C(14)-C(15) 1.525(6)	C(13)-C(12)-C(11) 115.1(4)
C(15)-C(16) 1.493(7)	C(24)-C(13)-C(12) 124.2(5)
C(16)-C(17) 1.494(6)	C(24)-C(13)-C(14) 121.4(5)
C(17)-C(18) 1.372(6)	C(12)-C(13)-C(14) 114.4(4)
C(17)-C(22) 1.397(6)	C(13)-C(14)-C(15) 114.9(4)
C(18)-C(19) 1.370(7)	C(16)-C(15)-C(14) 109.1(4)
C(19)-C(20) 1.366(7)	C(16)-C(15)-C(2) 112.0(4)
C(20)-C(21) 1.355(7)	C(14)-C(15)-C(2) 111.4(4)
C(21)-C(22) 1.384(6)	O(2)-C(16)-C(15) 121.4(5)
C(23)-C(24) 1.532(6)	O(2)-C(16)-C(17) 121.1(5)
	C(15)-C(16)-C(17) 117.4(5)
	C(18)-C(17)-C(22) 119.7(5)
	C(18)-C(17)-C(16) 120.3(5)
	C(22)-C(17)-C(16) 119.8(5)
	C(19)-C(18)-C(17) 119.8(5)
	C(20)-C(19)-C(18) 121.0(5)
	C(21)-C(20)-C(19) 119.7(5)
	C(20)-C(21)-C(22) 121.0(5)
	C(21)-C(22)-C(17) 118.8(5)
	C(21)-C(22)-C(1) 119.9(5)
	C(17)-C(22)-C(1) 121.3(5)
	C(6)-C(23)-C(10) 114.6(5)
	C(6)-C(23)-C(24) 113.9(5)
	C(10)-C(23)-C(24) 109.5(5)
	C(13)-C(24)-C(3) 122.6(5)
	C(13)-C(24)-C(23) 119.4(5)
	C(3)-C(24)-C(23) 117.9(5)

Symmetry transformations used to generate equivalent atoms:

Table A4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.87a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	64(3)	37(2)	77(3)	12(2)	48(3)	14(2)
C(1)	54(4)	30(3)	44(4)	15(3)	35(3)	4(3)
O(2)	63(3)	49(3)	56(3)	10(2)	45(2)	16(2)
C(2)	48(4)	24(3)	29(3)	1(2)	22(3)	-6(3)
C(3)	47(4)	67(4)	41(4)	-1(3)	24(4)	-9(3)
C(4)	46(4)	101(5)	63(5)	23(4)	38(4)	-1(4)
C(5)	41(4)	104(5)	60(5)	36(4)	20(4)	-7(4)
C(6)	22(3)	78(4)	38(4)	2(3)	10(3)	-4(3)
C(7)	50(4)	100(6)	39(4)	1(4)	22(4)	-8(4)
O(3)	42(3)	114(4)	51(3)	1(3)	15(2)	-11(2)
C(9)	50(4)	87(5)	47(4)	13(3)	24(4)	2(4)
C(10)	62(4)	43(4)	41(4)	-3(3)	27(4)	4(3)
C(11)	63(4)	62(4)	54(4)	0(3)	39(4)	-4(3)
C(12)	47(4)	55(4)	35(3)	10(3)	23(3)	6(3)
C(13)	44(4)	33(3)	28(3)	1(2)	21(3)	-2(3)
C(14)	48(4)	44(3)	33(3)	-3(3)	26(3)	-1(3)
C(15)	51(4)	29(3)	34(3)	-6(3)	27(3)	-9(3)
C(16)	51(4)	38(3)	45(4)	14(3)	36(4)	6(3)
C(17)	33(3)	30(3)	22(3)	1(2)	18(3)	-2(3)
C(18)	43(4)	45(4)	46(4)	6(3)	25(4)	-3(3)
C(19)	26(4)	80(5)	33(4)	-2(3)	7(3)	-18(3)
C(20)	70(5)	54(4)	37(4)	-7(3)	30(4)	-18(4)
C(21)	79(5)	28(3)	35(3)	3(3)	42(4)	-6(3)
C(22)	41(3)	28(3)	30(3)	3(3)	25(3)	-5(3)
C(23)	50(4)	61(4)	40(4)	-4(3)	26(3)	-12(3)
C(24)	43(4)	36(3)	26(3)	-2(3)	19(3)	-5(3)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **3.87a**.

	x	y	z	U(eq)
H(2A)	1477	4430	3914	41
H(3A)	2795	4666	4992	64
H(4A)	3407	4192	4422	80
H(4B)	3269	1133	4382	80
H(5A)	5077	3097	5298	89
H(7A)	5839	-1606	6242	79
H(7B)	6256	1264	6348	79
H(9A)	5356	-1483	7361	77
H(9B)	5241	-3171	6806	77
H(10A)	4062	1412	6584	61
H(11A)	3434	-2239	6827	68
H(11B)	3299	-3810	6252	68
H(12A)	1706	-2291	5750	56
H(12B)	2070	267	6171	56
H(14A)	778	2559	5157	48
H(14B)	519	313	4663	48
H(15A)	1135	5460	4657	44
H(18A)	-2160	3145	2892	55
H(19A)	-2845	-53	2108	63
H(20A)	-1796	-2895	2053	66
H(21A)	-51	-2615	2796	51
H(23A)	3808	-1970	5629	61

Appendix B

X-ray crystal data for 3.88b

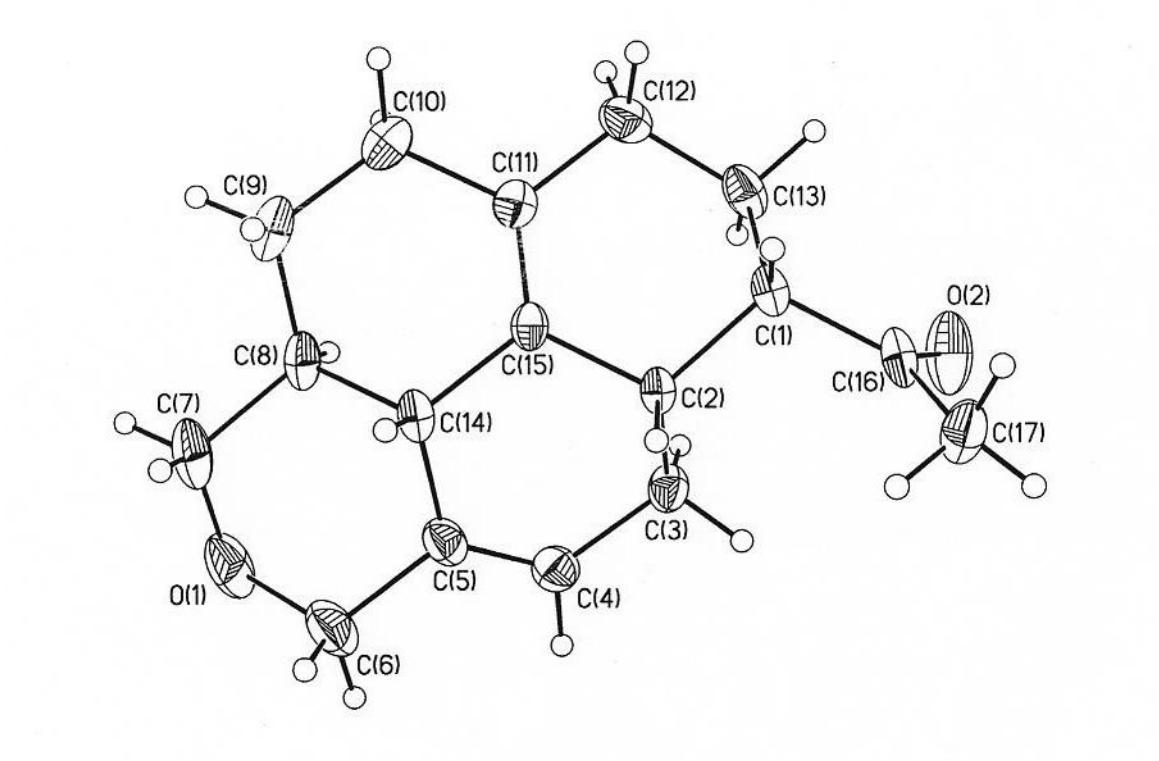


Table B1. Crystal data and structure refinement for **3.88b**.

Identification code	ly203	
Empirical formula	C17 H22 O2	
Formula weight	258.35	
Temperature	150.0(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.3148(4) Å	α= 90°.
	b = 13.1627(6) Å	β= 94.277 (1)°.
	c = 10.1497(4) Å	γ = 90°.
Volume	1374.19(10) $Å^3$	
Z	4	
Density (calculated)	1.249 Mg/m^3	

Absorption coefficient	0.080 mm^{-1}
F(000)	560
Crystal size	0.28 x 0.24 x 0.24 mm^3
Theta range for data collection	1.98 to 32.51°.
Index ranges	-15<=h<=15, -19<=k<=19, -15<=l<=15
Reflections collected	17668
Independent reflections	4865 [R(int) = 0.0320]
Completeness to theta = 32.51°	97.8 %
Absorption correction	Sadabs
Max. and min. transmission	0.9811 and 0.9780
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4865 / 0 / 260
Goodness-of-fit on F^2	1.178
Final R indices [I>2sigma(I)]	R1 = 0.0608, wR2 = 0.1473
R indices (all data)	R1 = 0.0791, wR2 = 0.1571
Largest diff. peak and hole	0.461 and -0.183 $e.Å^{-3}$

Table B2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.88b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	10695(1)	2183(1)	8362(1)	22(1)
O(1)	5253(1)	4645(1)	6761(1)	41(1)
C(2)	9698(1)	3020(1)	7931(1)	19(1)
O(2)	11998(1)	2533(1)	10356(1)	46(1)
C(3)	9398(1)	3785(1)	9017(1)	25(1)
C(4)	8340(1)	4506(1)	8524(1)	28(1)
C(5)	7530(1)	4329(1)	7470(1)	26(1)
C(6)	6530(1)	5075(1)	6920(2)	39(1)
C(7)	5217(1)	3744(1)	5981(1)	36(1)
C(8)	6102(1)	2933(1)	6621(1)	27(1)
C(9)	6077(1)	1918(1)	5920(1)	35(1)
C(10)	6893(1)	1149(1)	6748(1)	33(1)
C(11)	8130(1)	1582(1)	7408(1)	24(1)
C(12)	9007(1)	826(1)	8145(1)	31(1)
C(13)	10042(1)	1324(1)	9073(1)	29(1)
C(14)	7499(1)	3337(1)	6729(1)	22(1)
C(15)	8435(1)	2568(1)	7355(1)	19(1)
C(16)	11846(1)	2639(1)	9166(1)	27(1)
C(17)	12802(1)	3215(1)	8420(1)	34(1)

Table B3. Bond lengths [Å] and angles [°] for **3.88b**.

C(1)-C(16) 1.5142(15)	C(16)-C(1)-C(13) 113.30(9)
C(1)-C(13) 1.5240(16)	C(16)-C(1)-C(2) 110.37(9)
C(1)-C(2) 1.5487(14)	C(13)-C(1)-C(2) 110.73(8)
O(1)-C(7) 1.4247(19)	C(7)-O(1)-C(6) 112.16(11)
O(1)-C(6) 1.4314(17)	C(15)-C(2)-C(3) 108.76(8)
C(2)-C(15) 1.5095(14)	C(15)-C(2)-C(1) 111.38(9)
C(2)-C(3) 1.5415(15)	C(3)-C(2)-C(1) 115.28(8)
O(2)-C(16) 1.2137(14)	C(4)-C(3)-C(2) 110.66(9)
C(3)-C(4) 1.5039(16)	C(5)-C(4)-C(3) 123.73(11)
C(4)-C(5) 1.3274(17)	C(4)-C(5)-C(6) 123.95(12)
C(5)-C(6) 1.5008(16)	C(4)-C(5)-C(14) 122.88(10)
C(5)-C(14) 1.5065(17)	C(6)-C(5)-C(14) 113.14(10)
C(7)-C(8) 1.5180(17)	O(1)-C(6)-C(5) 112.61(11)
C(8)-C(9) 1.5133(19)	O(1)-C(7)-C(8) 110.95(10)
C(8)-C(14) 1.5321(15)	C(9)-C(8)-C(7) 115.53(10)
C(9)-C(10) 1.5276(19)	C(9)-C(8)-C(14) 108.79(10)
C(10)-C(11) 1.5082(17)	C(7)-C(8)-C(14) 108.65(10)
C(11)-C(15) 1.3370(16)	C(8)-C(9)-C(10) 109.68(10)
C(11)-C(12) 1.5059(16)	C(11)-C(10)-C(9) 114.02(10)
C(12)-C(13) 1.5185(18)	C(15)-C(11)-C(12) 121.83(10)
C(14)-C(15) 1.5054(14)	C(15)-C(11)-C(10) 122.84(10)
C(16)-C(17) 1.4940(18)	C(12)-C(11)-C(10) 115.33(10)
	C(11)-C(12)-C(13) 113.01(10)
	C(12)-C(13)-C(1) 109.98(10)
	C(15)-C(14)-C(5) 112.52(9)
	C(15)-C(14)-C(8) 111.57(9)
	C(5)-C(14)-C(8) 108.69(9)
	C(11)-C(15)-C(14) 121.59(9)
	C(11)-C(15)-C(2) 124.43(9)
	C(14)-C(15)-C(2) 113.95(9)
	O(2)-C(16)-C(17) 121.43(11)
	O(2)-C(16)-C(1) 121.90(11)
	C(17)-C(16)-C(1) 116.67(10)

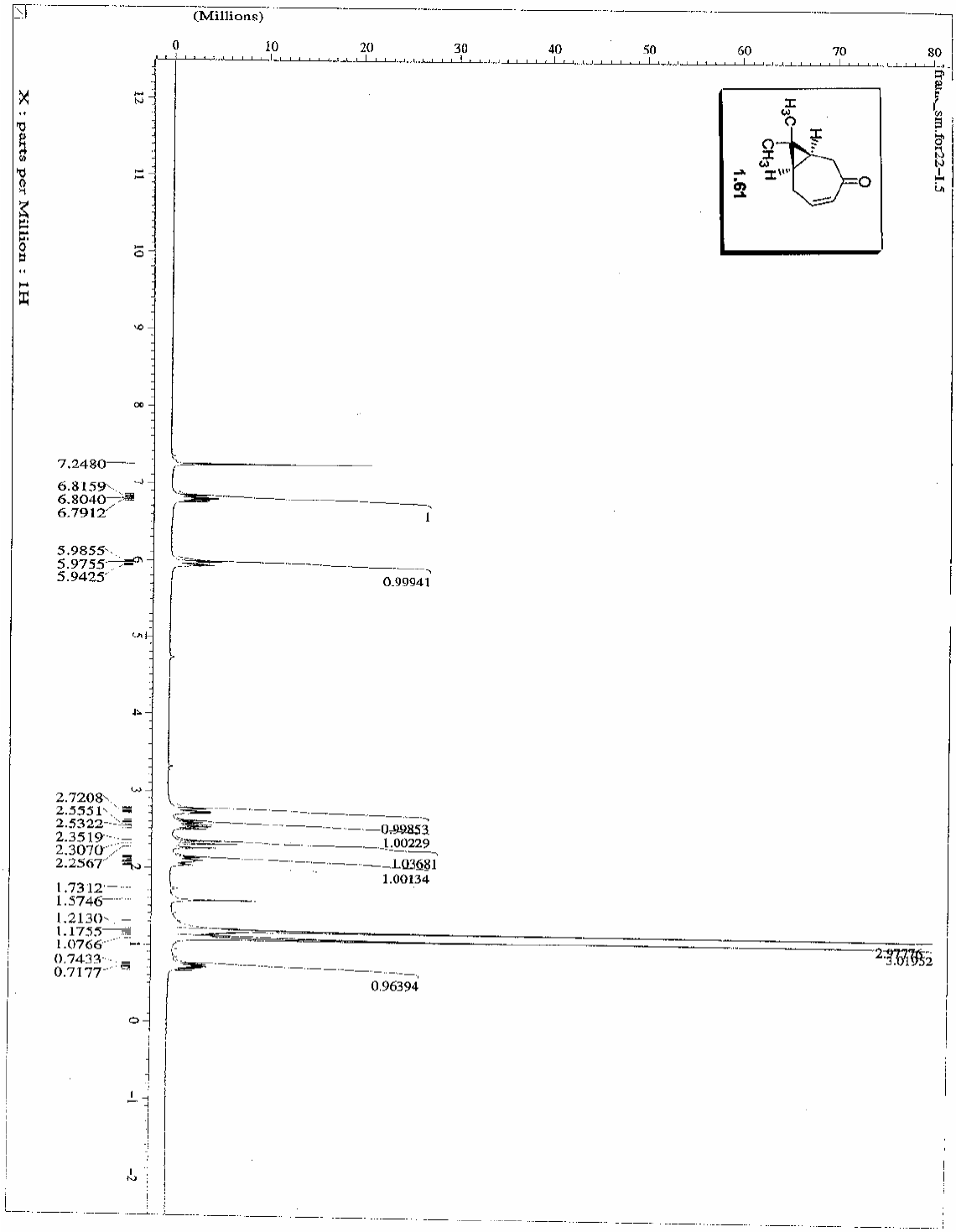
Symmetry transformations used to generate equivalent atoms:

Table B4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.88b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	17(1)	29(1)	19(1)	4(1)	0(1)	4(1)
O(1)	22(1)	50(1)	53(1)	12(1)	3(1)	14(1)
C(2)	15(1)	25(1)	17(1)	2(1)	-1(1)	1(1)
O(2)	31(1)	86(1)	22(1)	6(1)	-5(1)	3(1)
C(3)	23(1)	29(1)	23(1)	-3(1)	-2(1)	1(1)
C(4)	26(1)	25(1)	35(1)	-3(1)	3(1)	3(1)
C(5)	20(1)	26(1)	32(1)	5(1)	3(1)	4(1)
C(6)	28(1)	36(1)	54(1)	12(1)	1(1)	10(1)
C(7)	18(1)	58(1)	33(1)	13(1)	-1(1)	5(1)
C(8)	16(1)	42(1)	22(1)	6(1)	-1(1)	-1(1)
C(9)	25(1)	49(1)	30(1)	-2(1)	-6(1)	-9(1)
C(10)	29(1)	34(1)	36(1)	-4(1)	0(1)	-9(1)
C(11)	22(1)	28(1)	22(1)	-1(1)	3(1)	-1(1)
C(12)	30(1)	24(1)	38(1)	6(1)	6(1)	3(1)
C(13)	24(1)	33(1)	29(1)	12(1)	3(1)	6(1)
C(14)	16(1)	31(1)	19(1)	5(1)	0(1)	2(1)
C(15)	16(1)	27(1)	15(1)	0(1)	1(1)	1(1)
C(16)	18(1)	40(1)	22(1)	1(1)	-2(1)	9(1)
C(17)	24(1)	42(1)	34(1)	3(1)	-6(1)	-6(1)

Table B5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **3.88b**.

	x	y	z	U(eq)
H(1)	11020(12)	1925(9)	7547(12)	16(3)
H(2)	10057(13)	3421(10)	7192(13)	25(3)
H(3A)	9152(13)	3421(11)	9794(15)	32(4)
H(3B)	10186(13)	4175(10)	9280(13)	23(3)
H(4)	8261(14)	5148(11)	8962(14)	33(4)
H(6A)	6825(15)	5349(11)	6011(16)	39(4)
H(6B)	6506(15)	5659(13)	7509(16)	41(4)
H(7A)	4301(16)	3527(11)	5948(14)	34(4)
H(7B)	5500(15)	3885(12)	5080(16)	40(4)
H(8)	5817(13)	2820(10)	7541(14)	28(3)
H(9A)	6459(15)	2005(12)	5044(15)	38(4)
H(9B)	5190(15)	1676(12)	5758(15)	38(4)
H(10A)	7094(15)	560(13)	6151(16)	46(4)
H(10B)	6358(15)	870(12)	7445(16)	41(4)
H(12A)	9410(15)	393(11)	7473(15)	34(4)
H(12B)	8456(15)	346(12)	8688(15)	42(4)
H(13A)	9650(15)	1604(11)	9867(15)	35(4)
H(13B)	10680(14)	799(11)	9348(15)	33(4)
H(14)	7723(13)	3473(10)	5790(13)	26(3)
H(17A)	13390(20)	3586(15)	8940(20)	66(6)
H(17B)	12382(19)	3656(15)	7758(19)	65(6)
H(17C)	13280(20)	2732(18)	7950(20)	76(6)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20
30
40
50
60
70
80
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6.8040
6.7912
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5.9755
5.9425
0.99941
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2.5551
2.5322
2.3519
2.3070
2.2567
0.99853
1.00229
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1.1755
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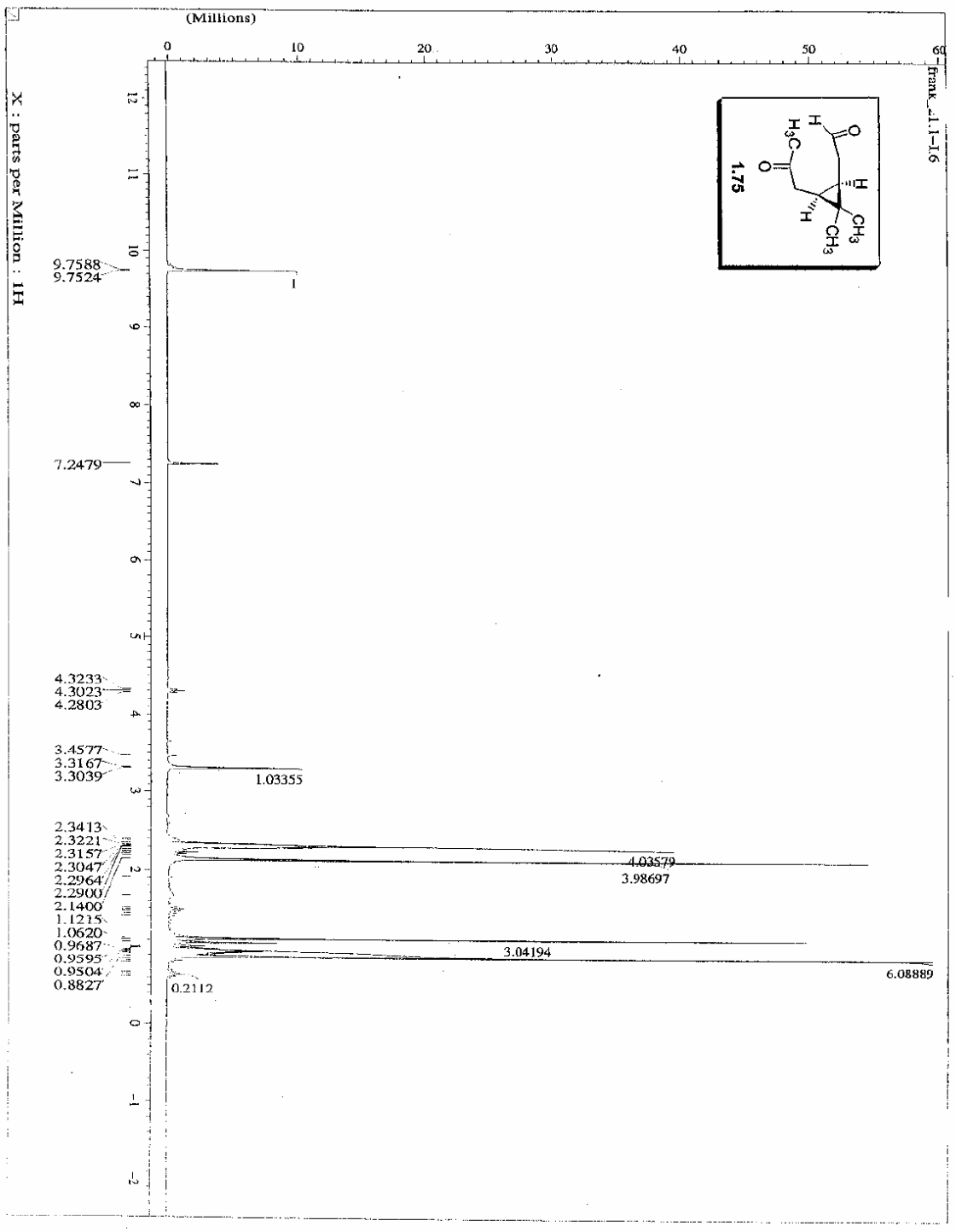
0.96394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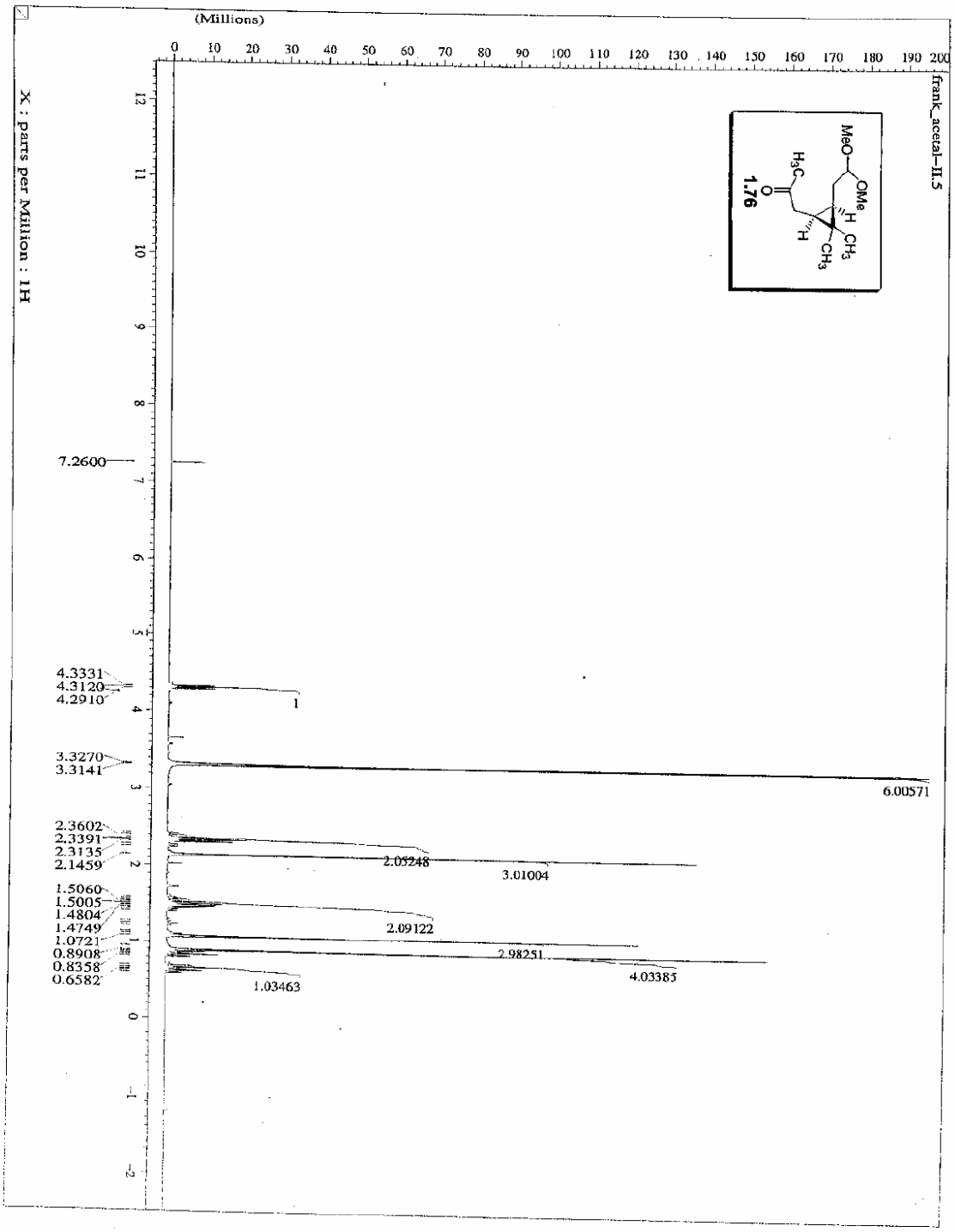
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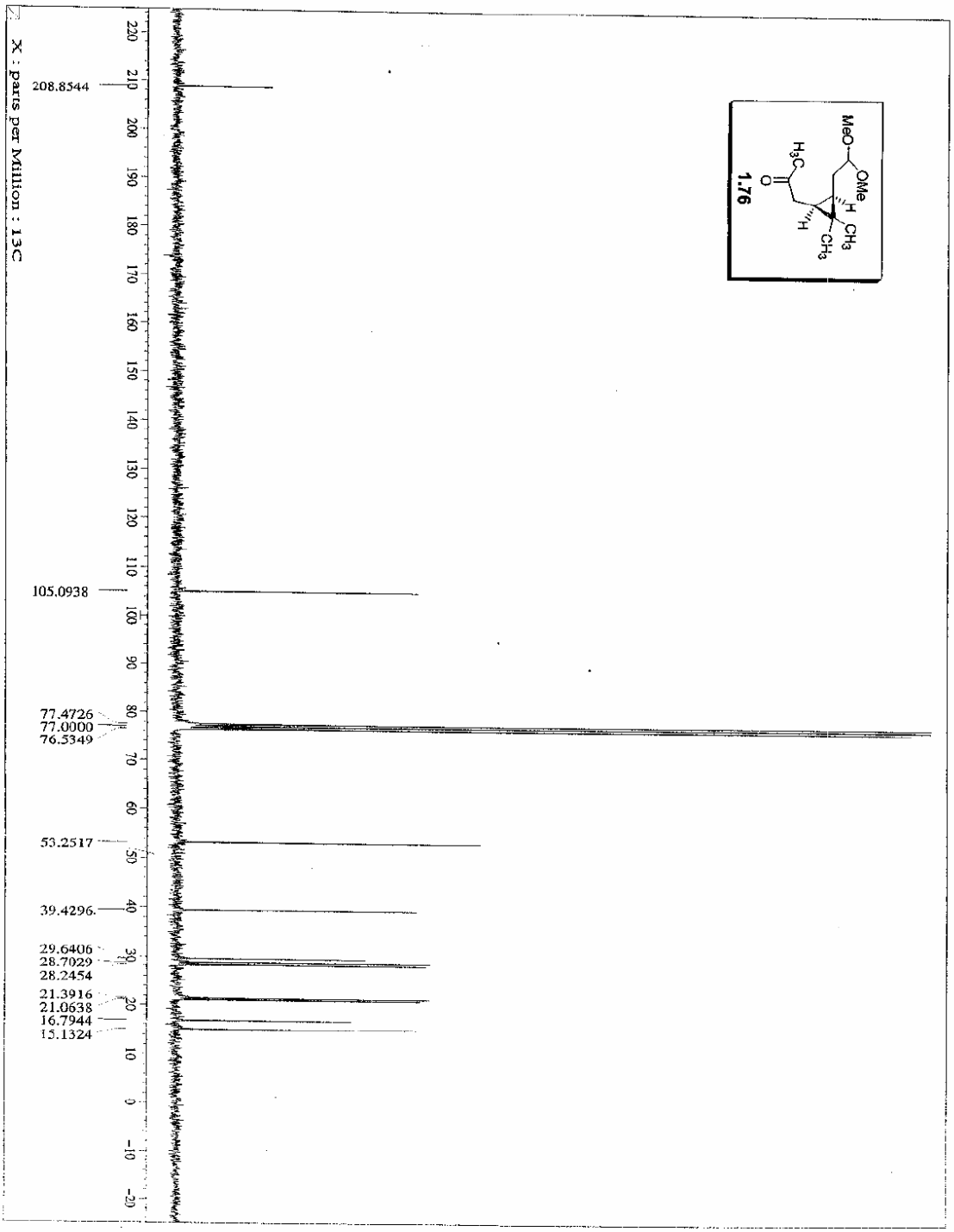
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77.0000
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21.0638
16.7944
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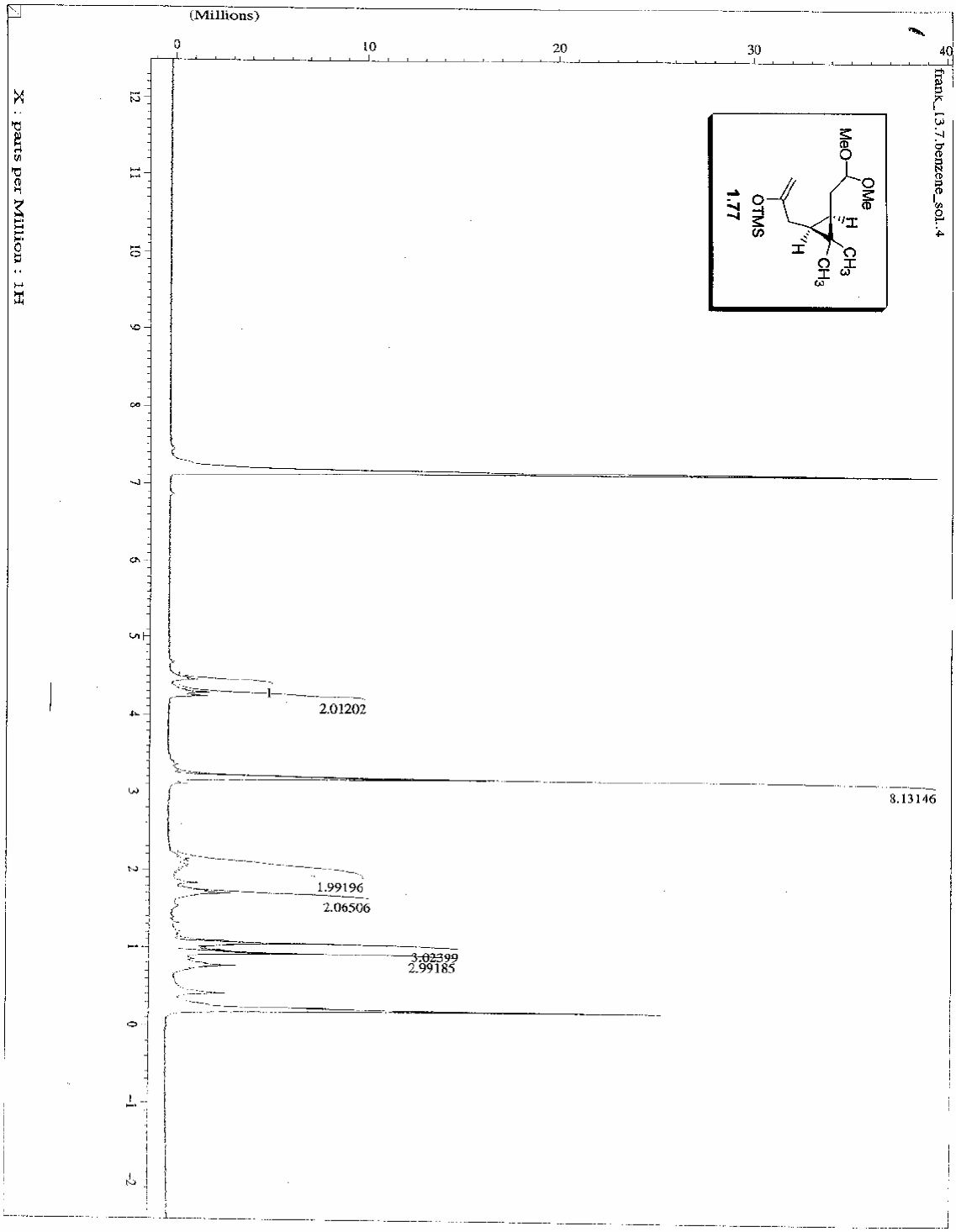
OMe
H3C
O
H
CH3
CH3
1.76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MeO
OMe
H
CH3
H
CH3
OTMS
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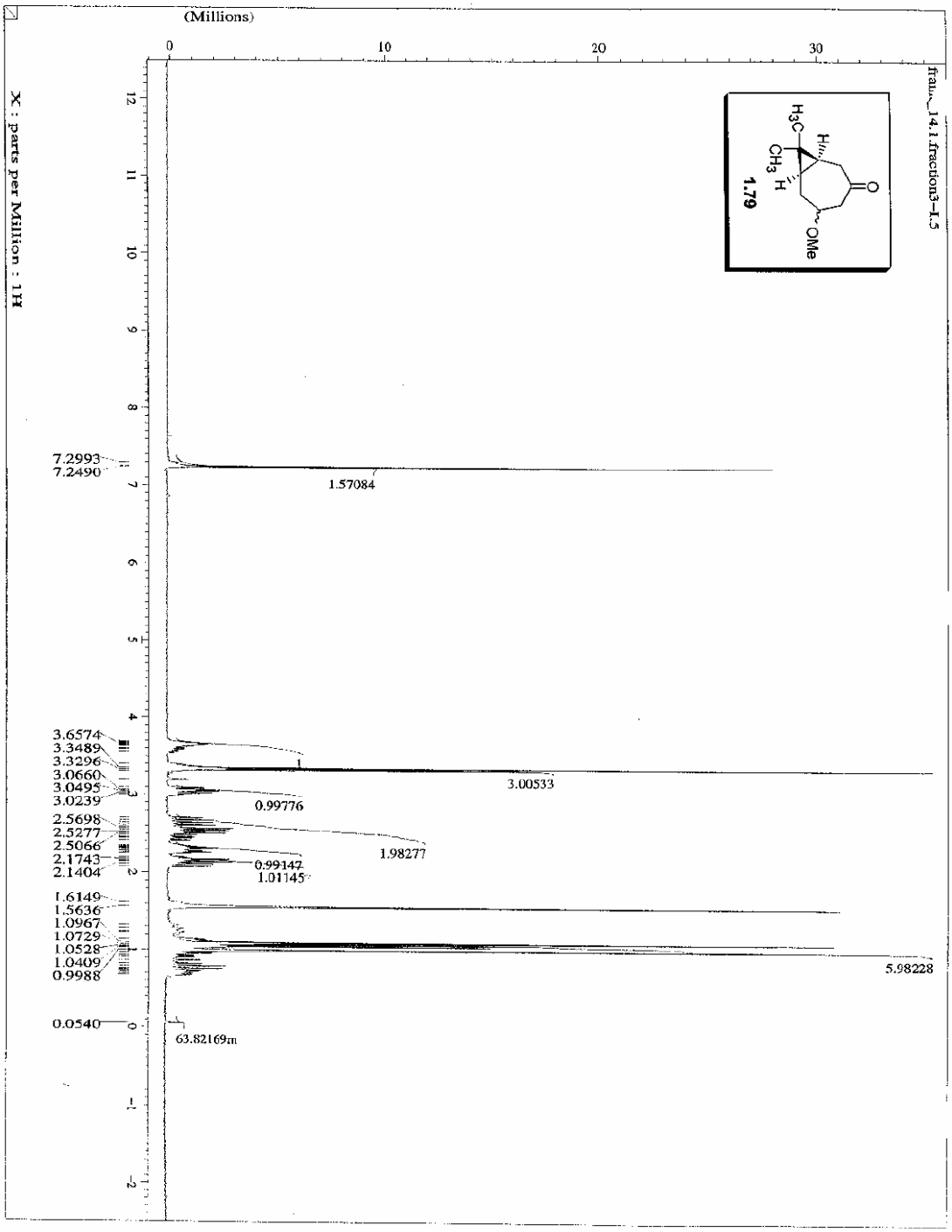
8.13146
1.99196
2.06506
3.02399
2.99185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20
30
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3.3296
3.0660
3.0495
3.0239
3.00533
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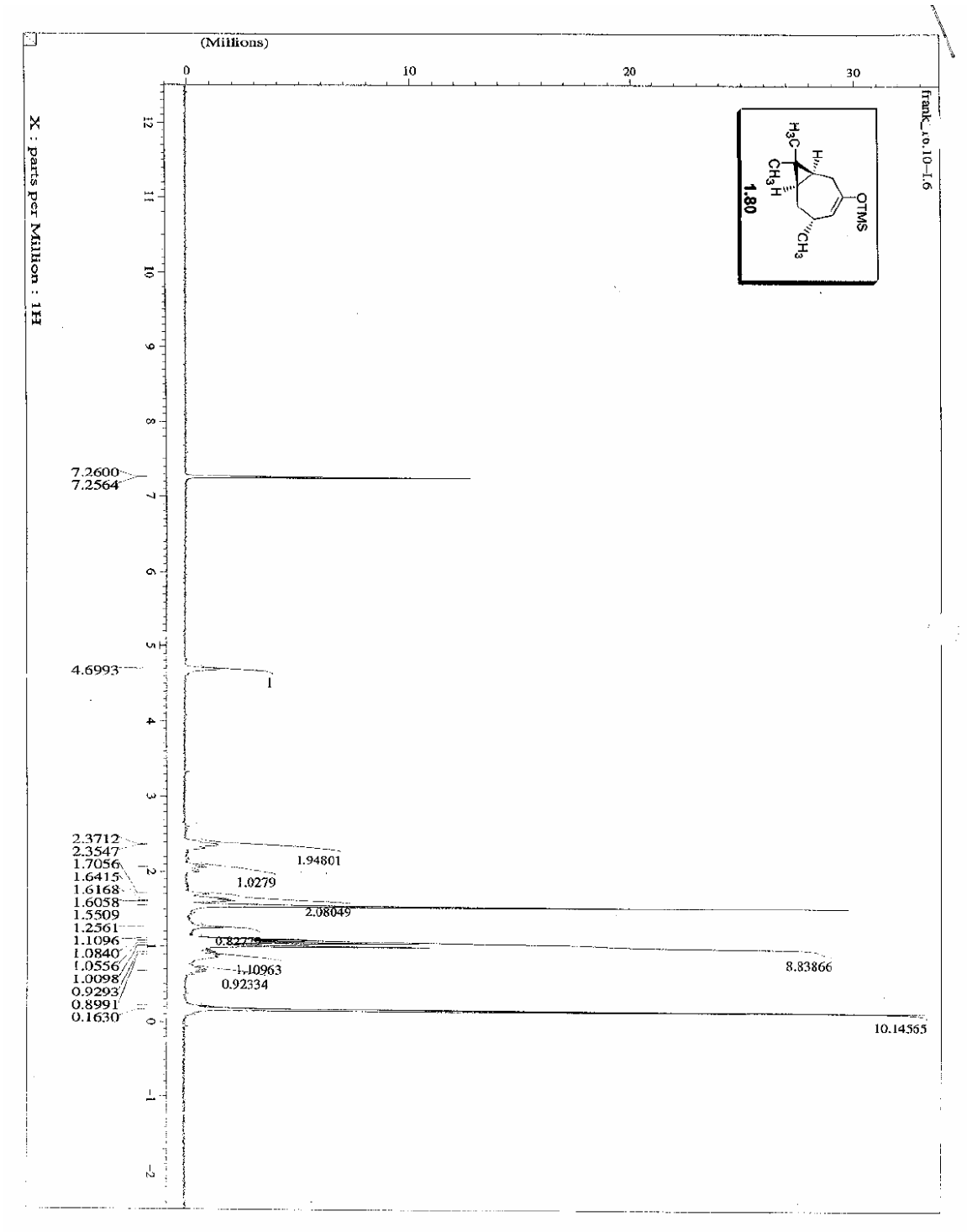
2.5698
2.5277
2.5066
2.1743
2.1404
1.98277
0.99147
1.01145
1.6149
1.5636
1.0967
1.0729
1.0528
1.0409
0.9988
5.98228
0.0540
63.82169m
1.79
OMe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20
30
frank_10-10-16
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OTMS
H3C
CH3
H
CH3
X : parts per Million : 1H
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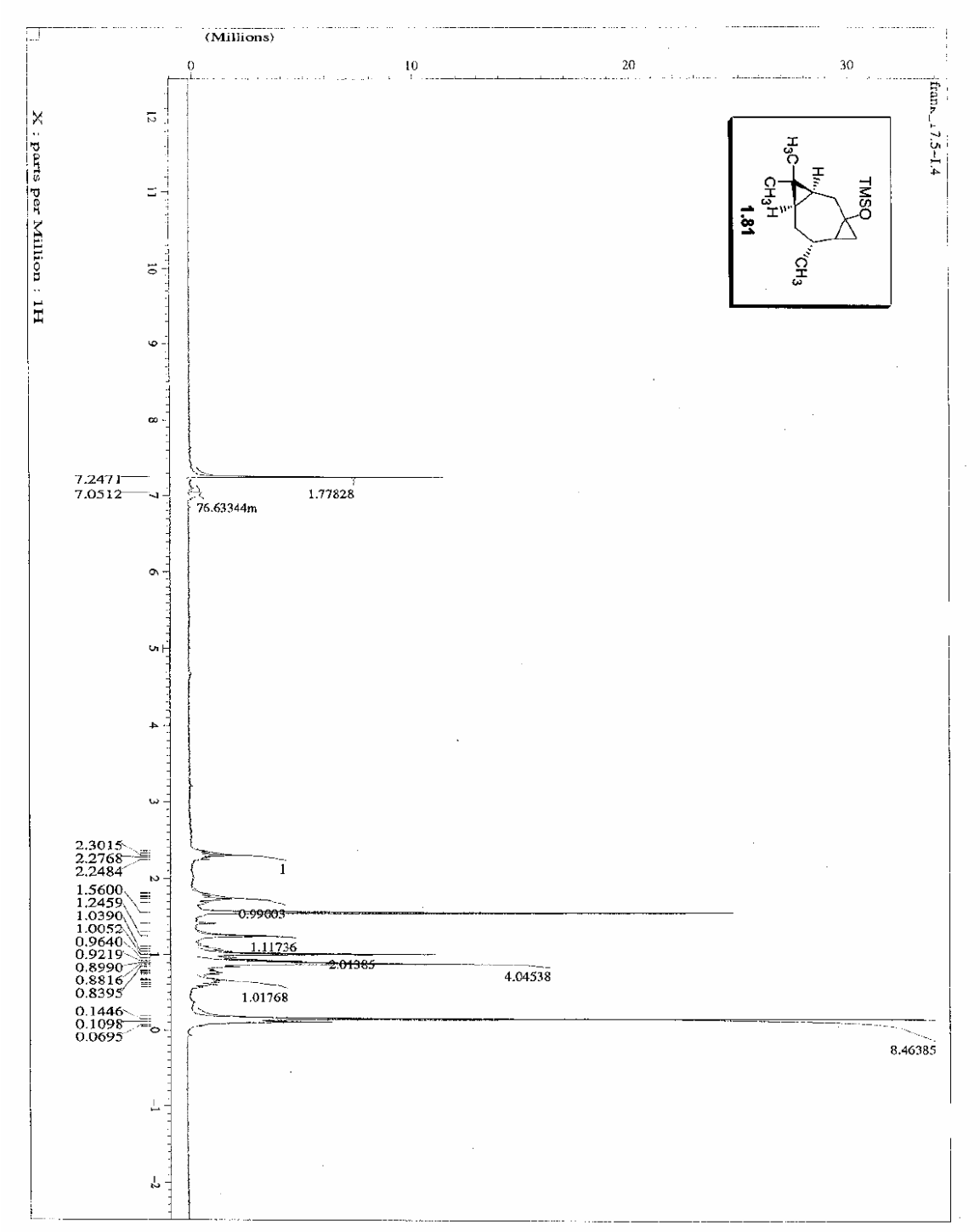
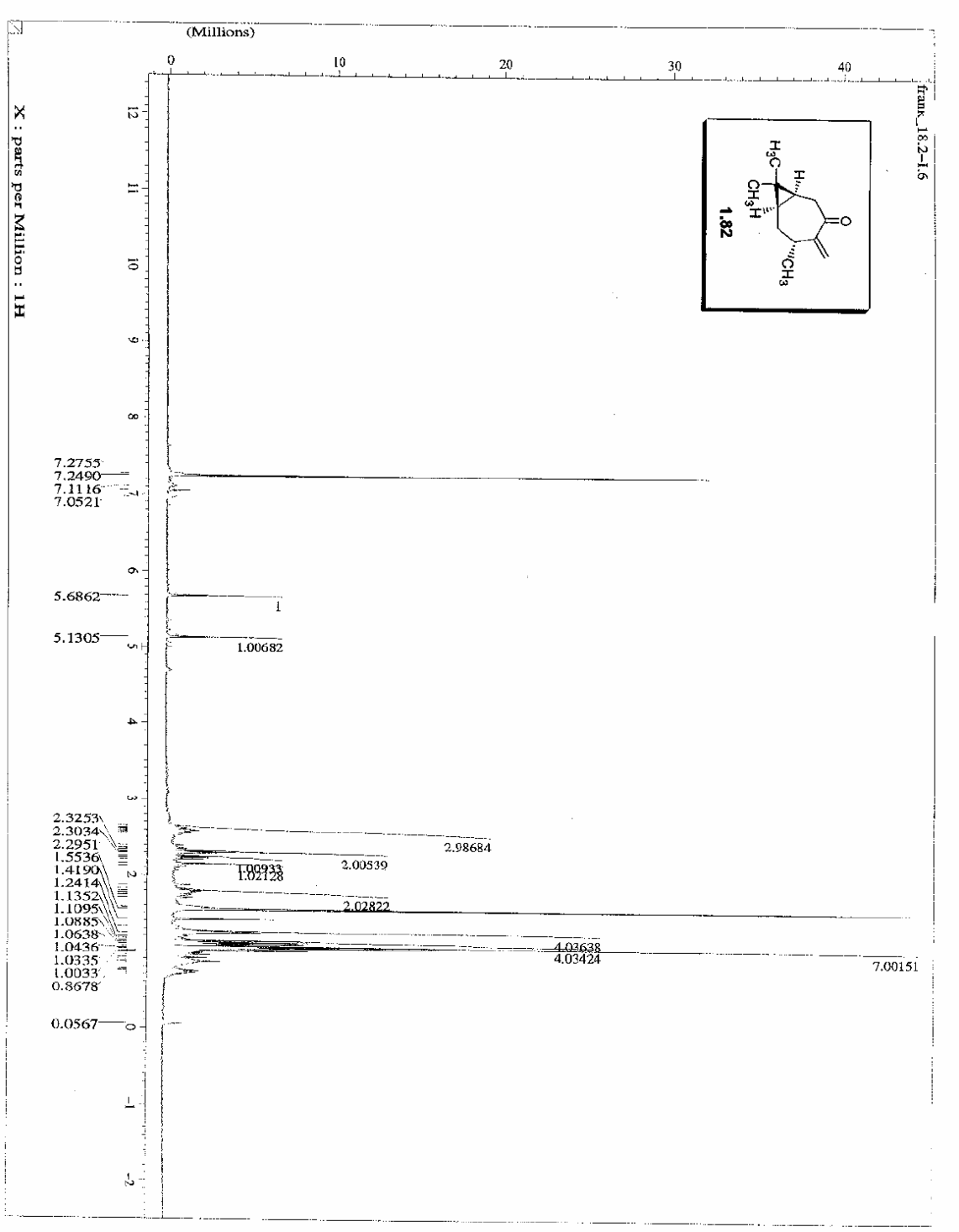
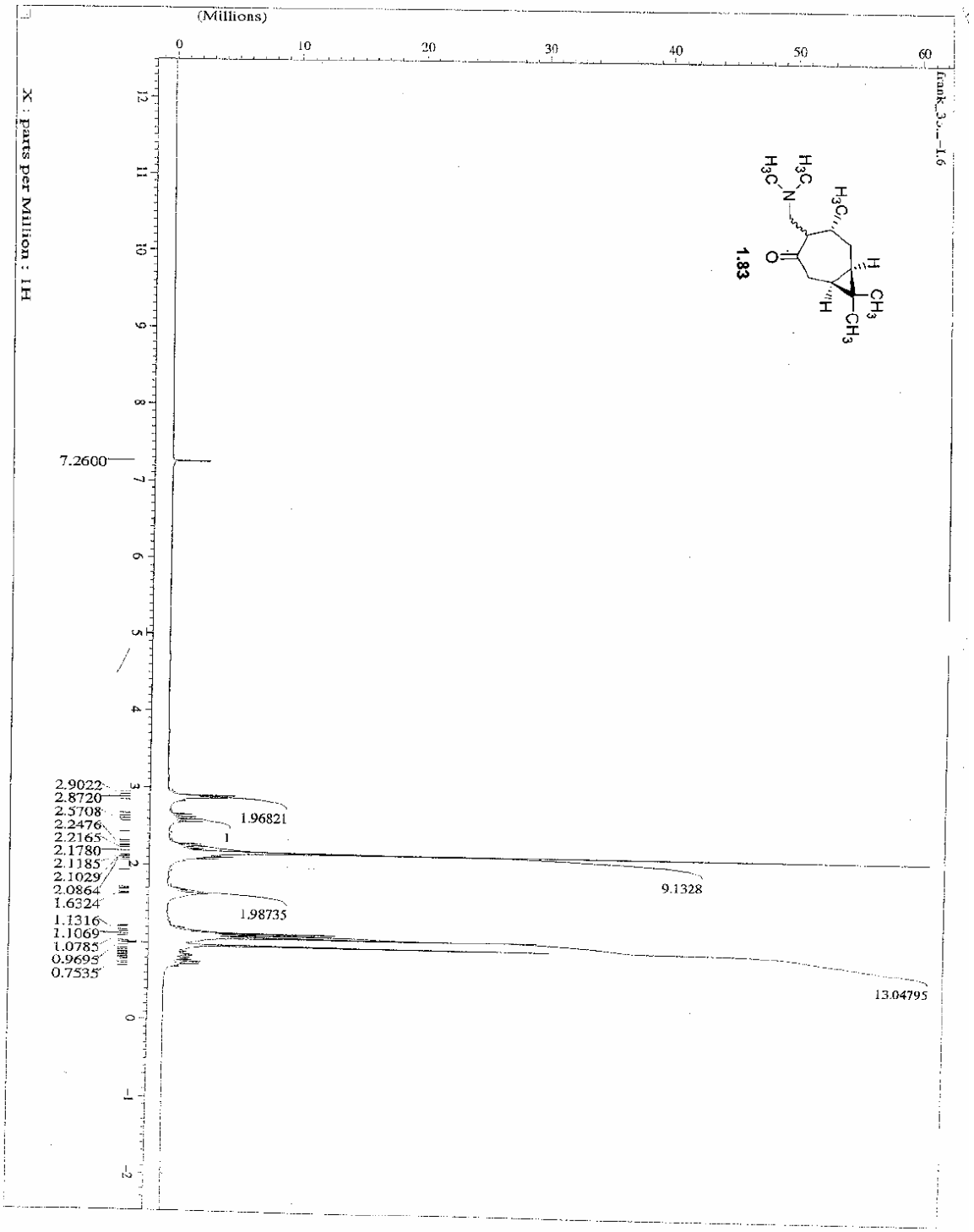
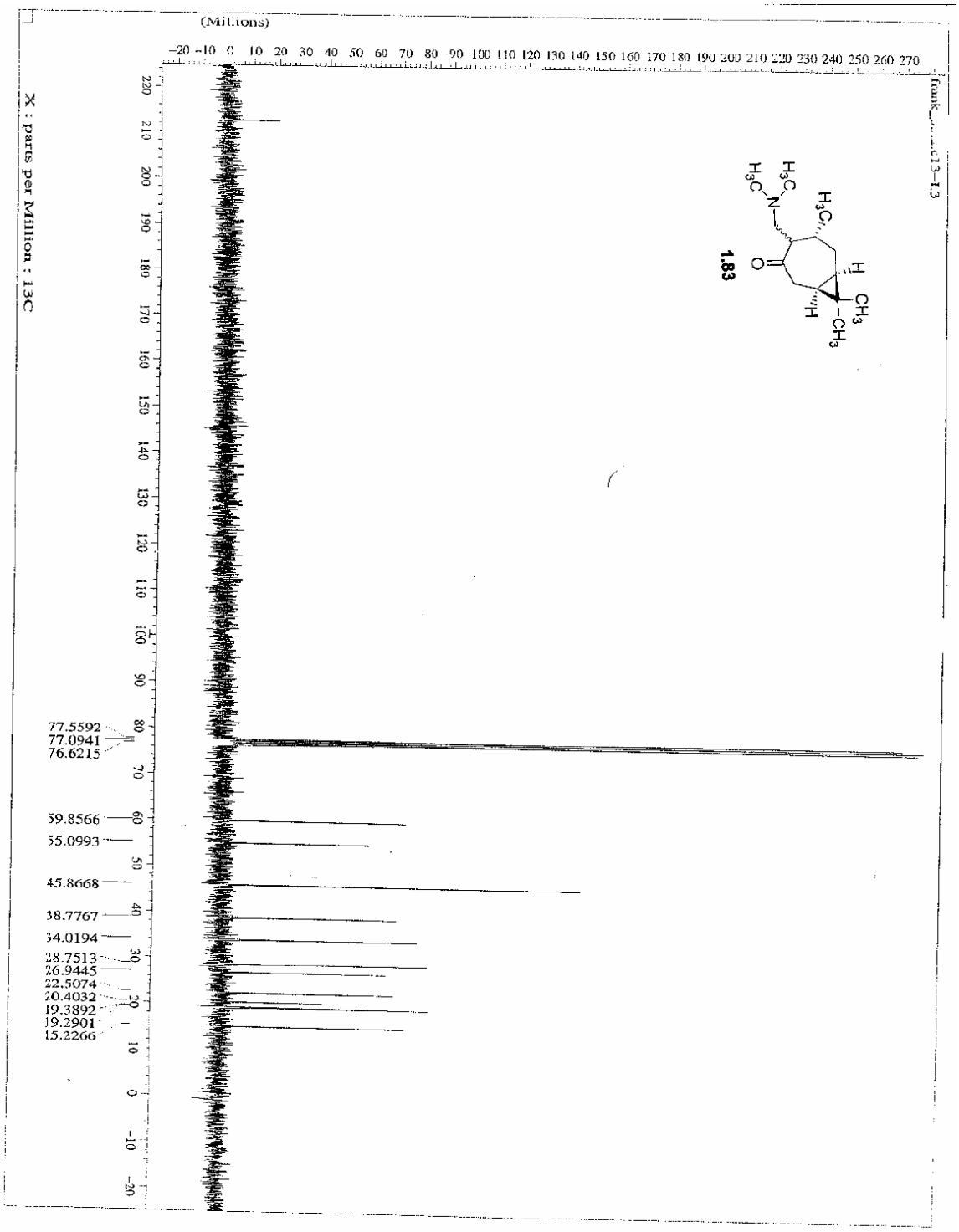
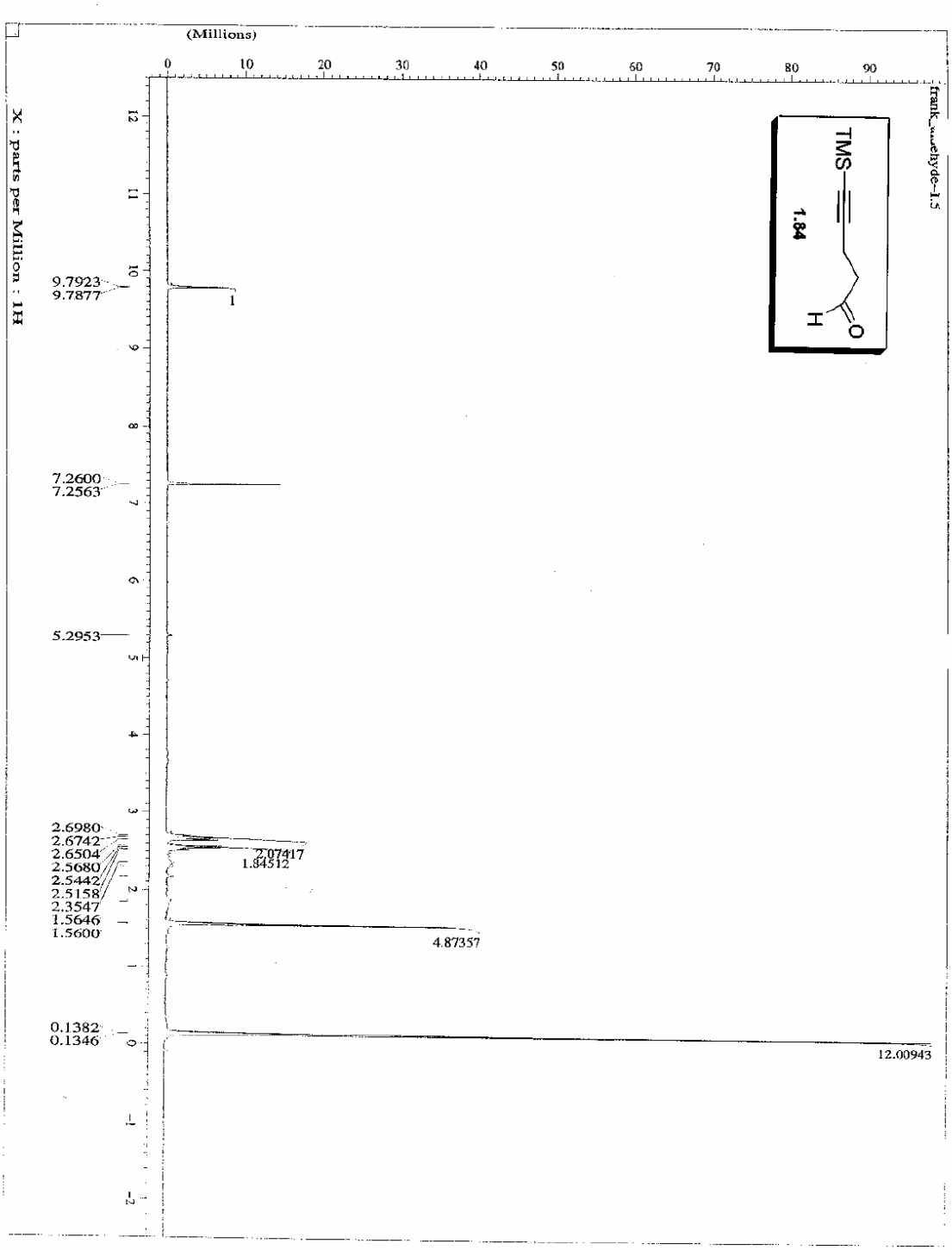
7.2564
4.6993
1
2.3712
2.3547
1.7056
1.6415
1.6168
1.6058
1.5509
1.2561
1.1096
1.0840
1.0556
1.0098
0.9293
0.8991
0.1630
1.94801
1.0279
2.08049
0.82779
1.10963
0.92334
8.83866
10.14565

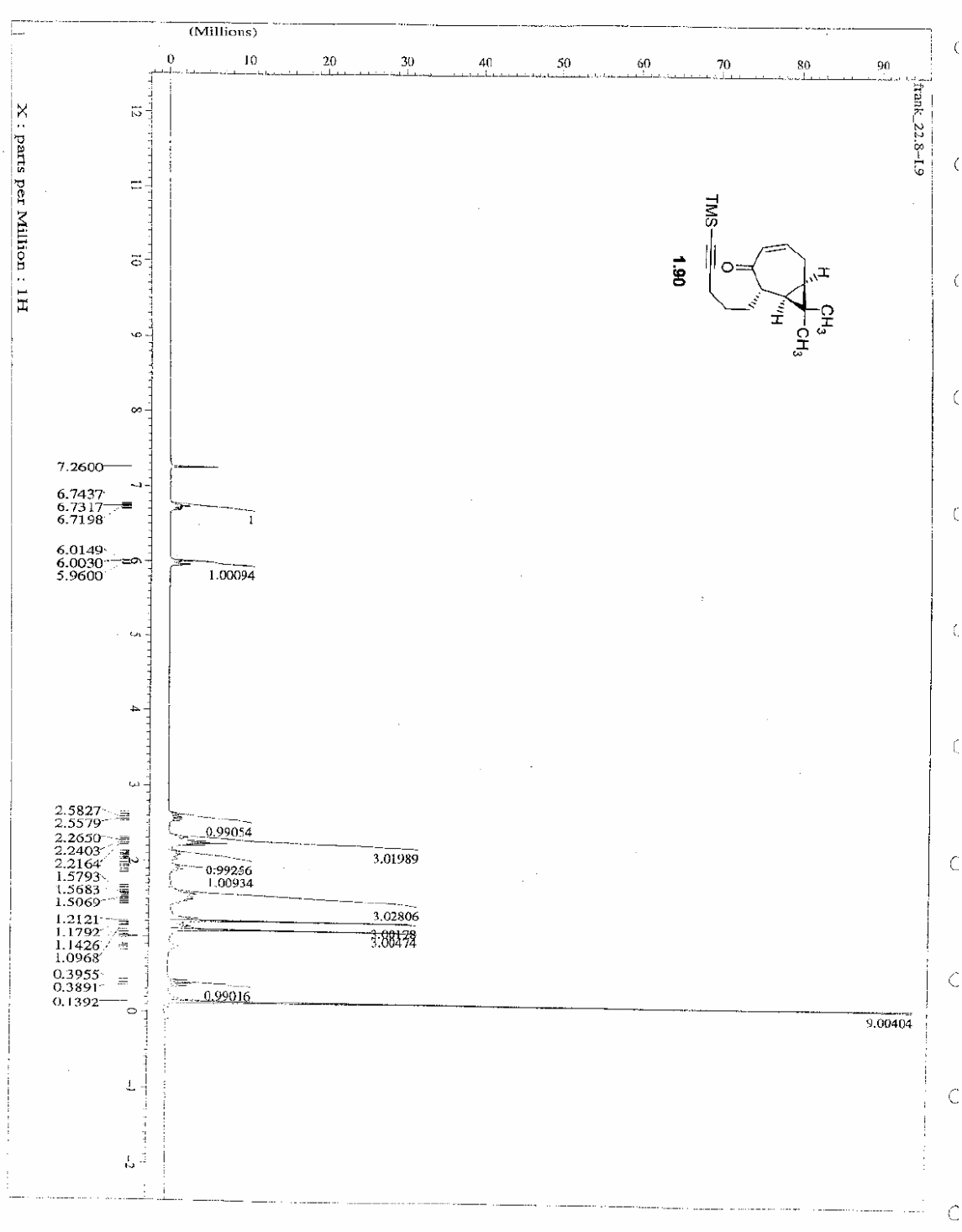

(Millions)
0
10
20
30
X : parts per Million : 1H
TMSO
H3C
CH3
H
1.81
CH3
7.2471
7.0512
76.63344m
1.77828
2.3015
2.2768
2.2484
1
1.5600
1.2459
1.0390
1.0052
0.9640
0.9219
0.8990
0.8816
0.8395
0.99603
1.11736
2.01385
4.04538
1.01768
0.1446
0.1098
0.0695
8.46385

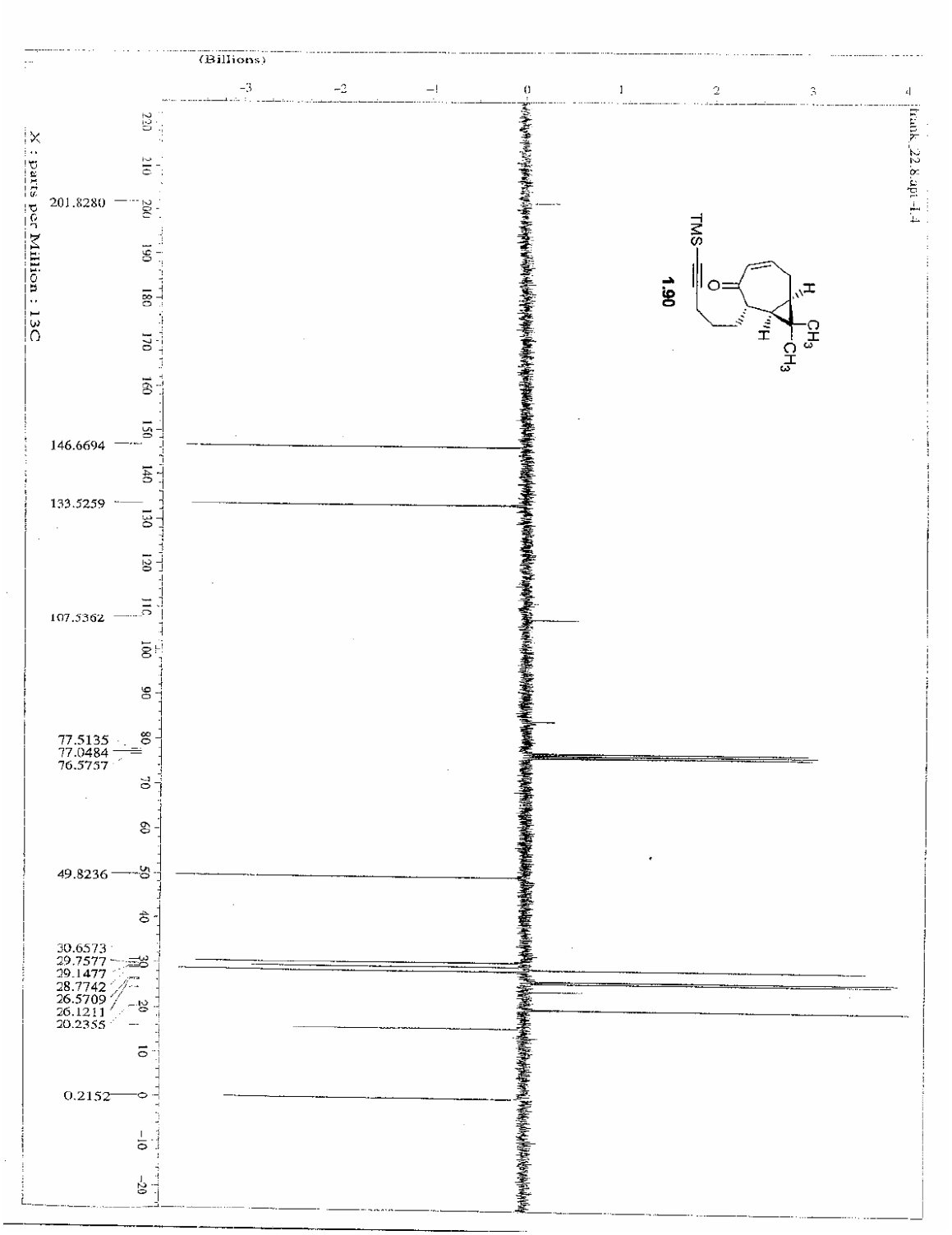

(Millions)
0
10
20
30
40
frank_18.2-1.6
X : parts per Million : 1H
1.82
7.2755
7.2490
7.1116
7.0521
5.6862
1
5.1305
1.00682
2.3253
2.3034
2.2951
1.5536
1.4190
1.2414
1.1352
1.1095
1.0885
1.0638
1.0436
1.0335
1.0033
0.8678
0.0567
2.98684
2.00539
1.00933
1.02128
2.02822
4.03638
4.03424
7.00151

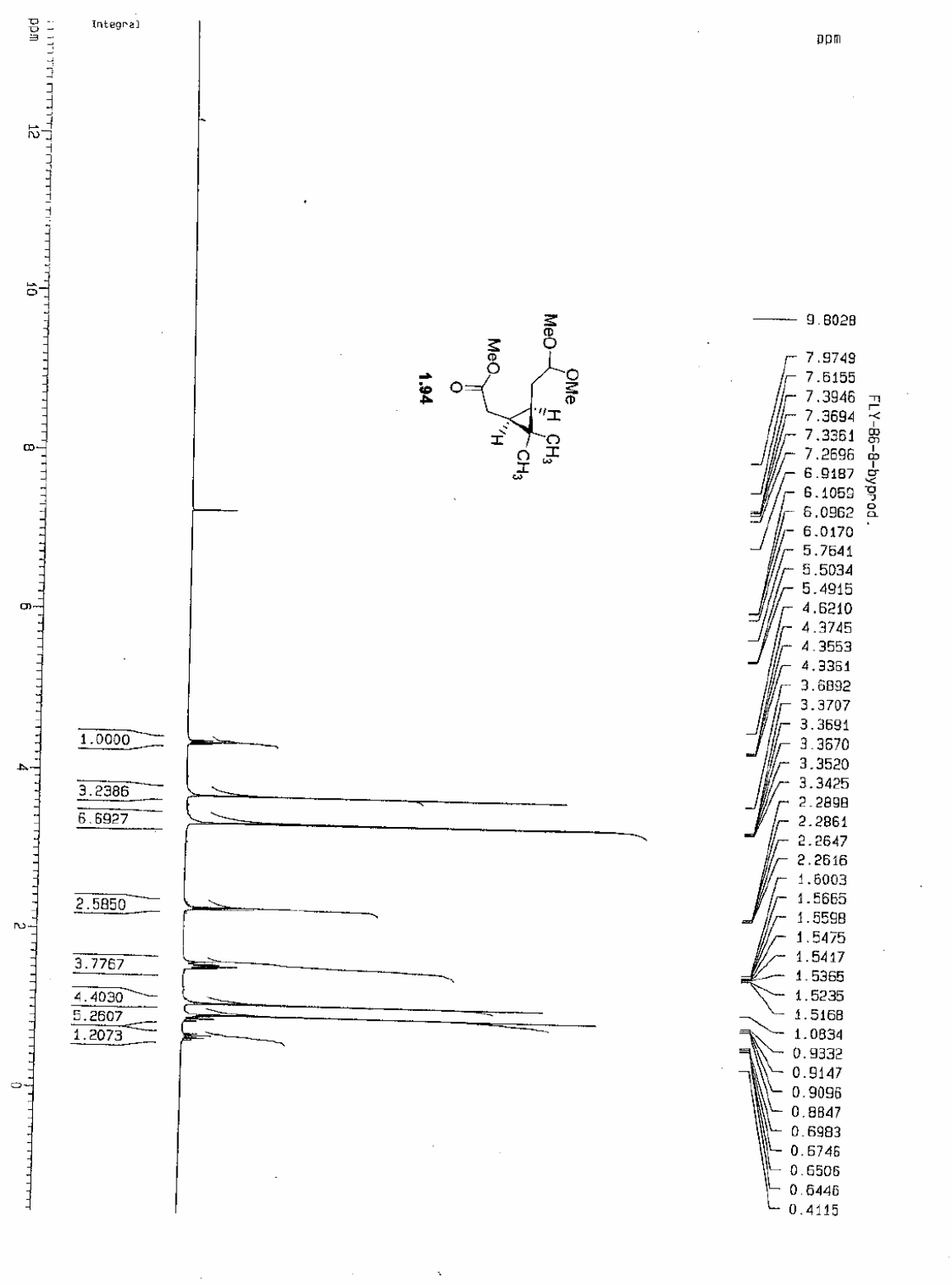

(Millions)
0
10
20
30
40
50
60
X : parts per Million : 1H
7.2600
2.9022
2.8720
2.5708
2.2476
2.2165
2.1780
2.1185
2.1029
2.0864
1.6324
1.1316
1.1069
1.0785
0.9695
0.7535
1.96821
1
9.1328
1.98735
13.04795
1.83
H3C
N
O
CH3
CH3
H
H

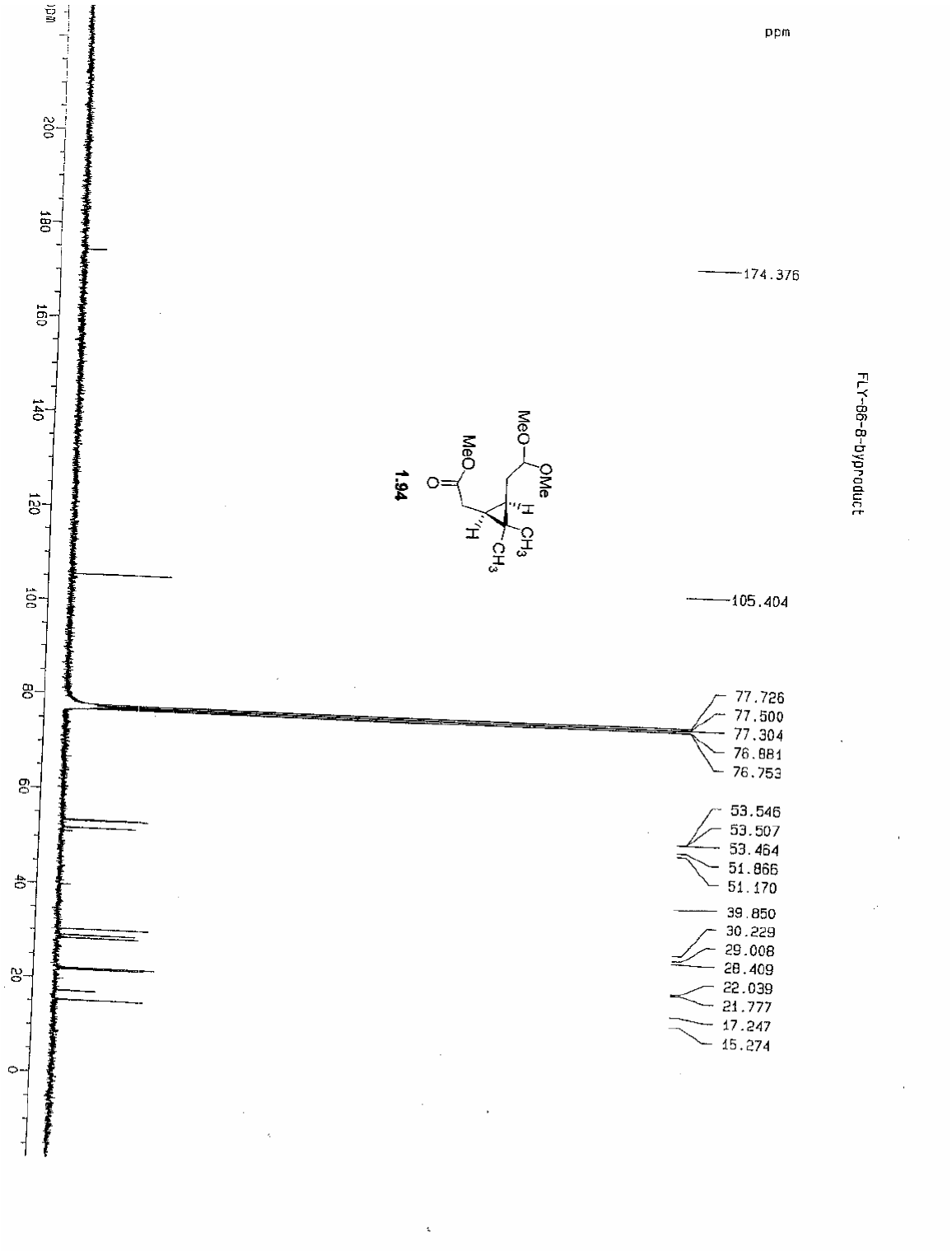

(Millions)
X : parts per Million : 13C
77.5592
77.0941
76.6215
59.8566
55.0993
45.8668
38.7767
34.0194
28.7513
26.9445
22.5074
20.4032
19.3892
19.2901
15.2266
1.83

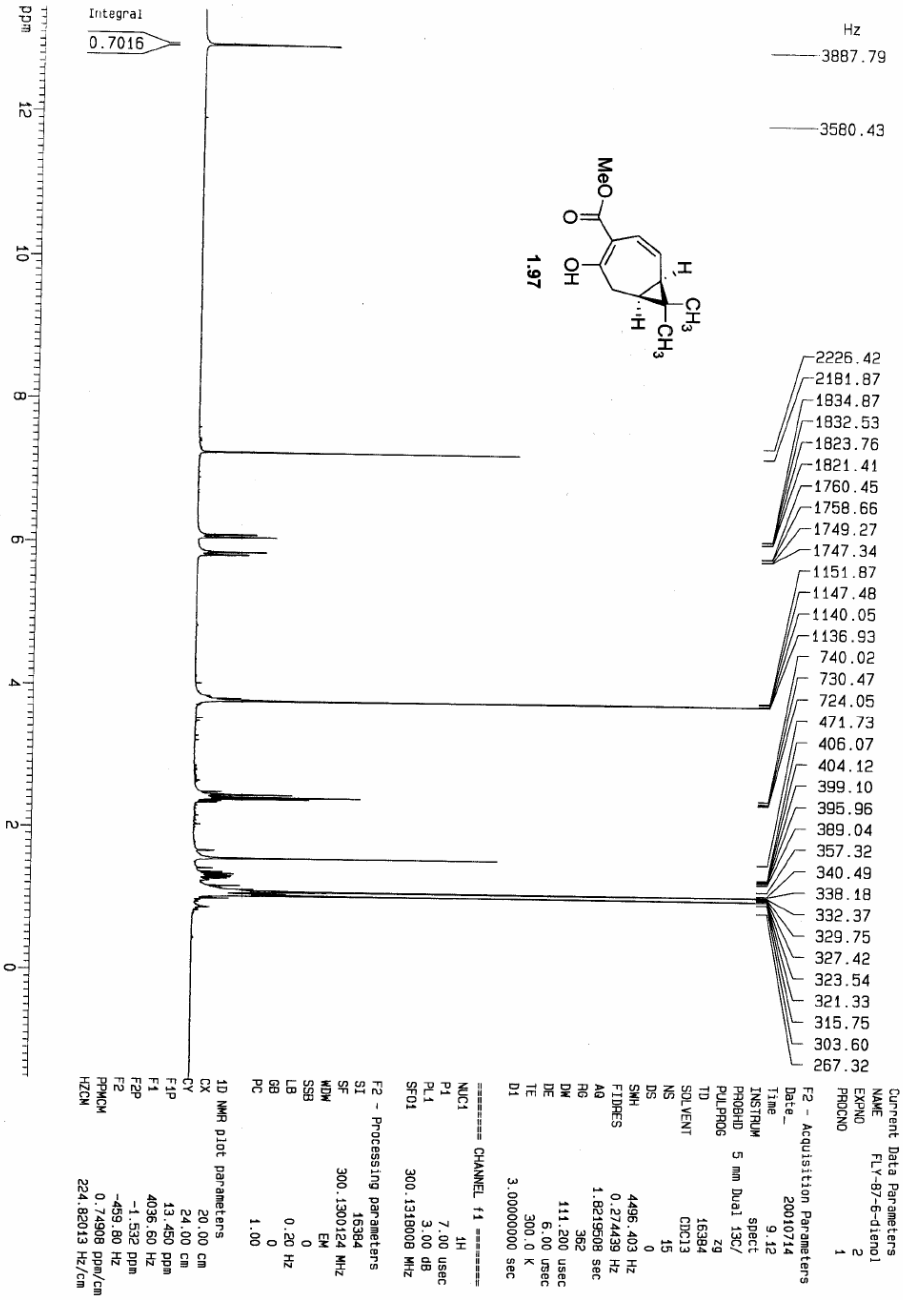

(Millions)
0
10
20
30
40
50
60
70
80
90
X : parts per Million : 1H
9.7923
9.7877
1
7.2600
7.2563
5.2953
2.6980
2.6742
2.6504
2.5680
2.5442
2.5158
2.3547
1.5646
1.5600
2.07417
1.84512
4.87357
0.1382
0.1346
12.00943
TMS
1.84
O
H

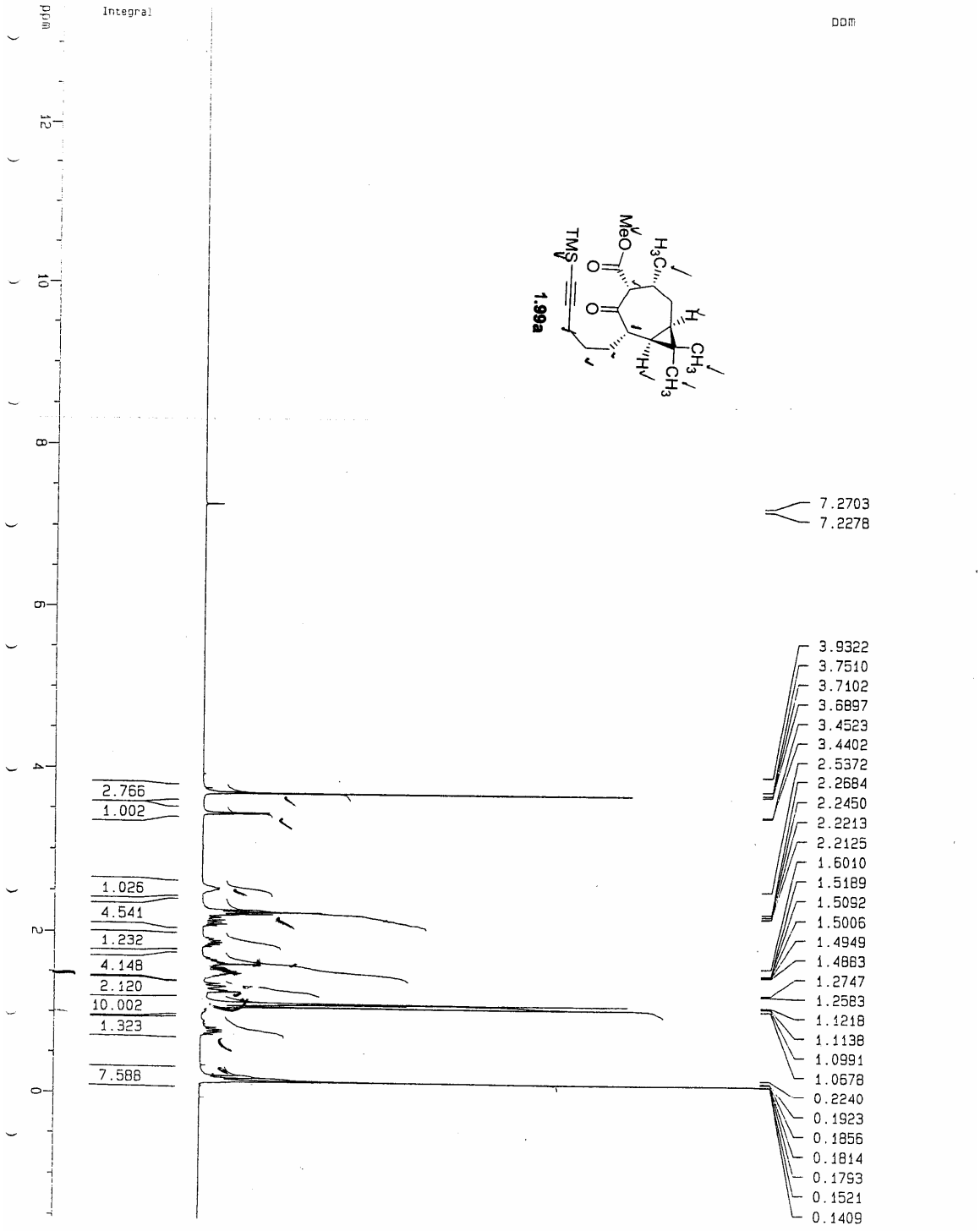

(Millions)
0
10
20
30
40
50
60
70
80
90
frank_22.8-1.9
X : parts per Million : 1H
TMS
O
H
CH3
H
CH3
1.90
7.2600
6.7437
6.7317
6.7198
6.0149
6.0030
5.9600
1
1.00094
2.5827
2.5579
2.2650
2.2403
2.2164
1.5793
1.5683
1.5069
1.2121
1.1792
1.1426
1.0968
0.3955
0.3891
0.1392
0.99054
3.01989
0.99256
1.00934
3.02806
3.00128
3.00474
0.99016
9.00404

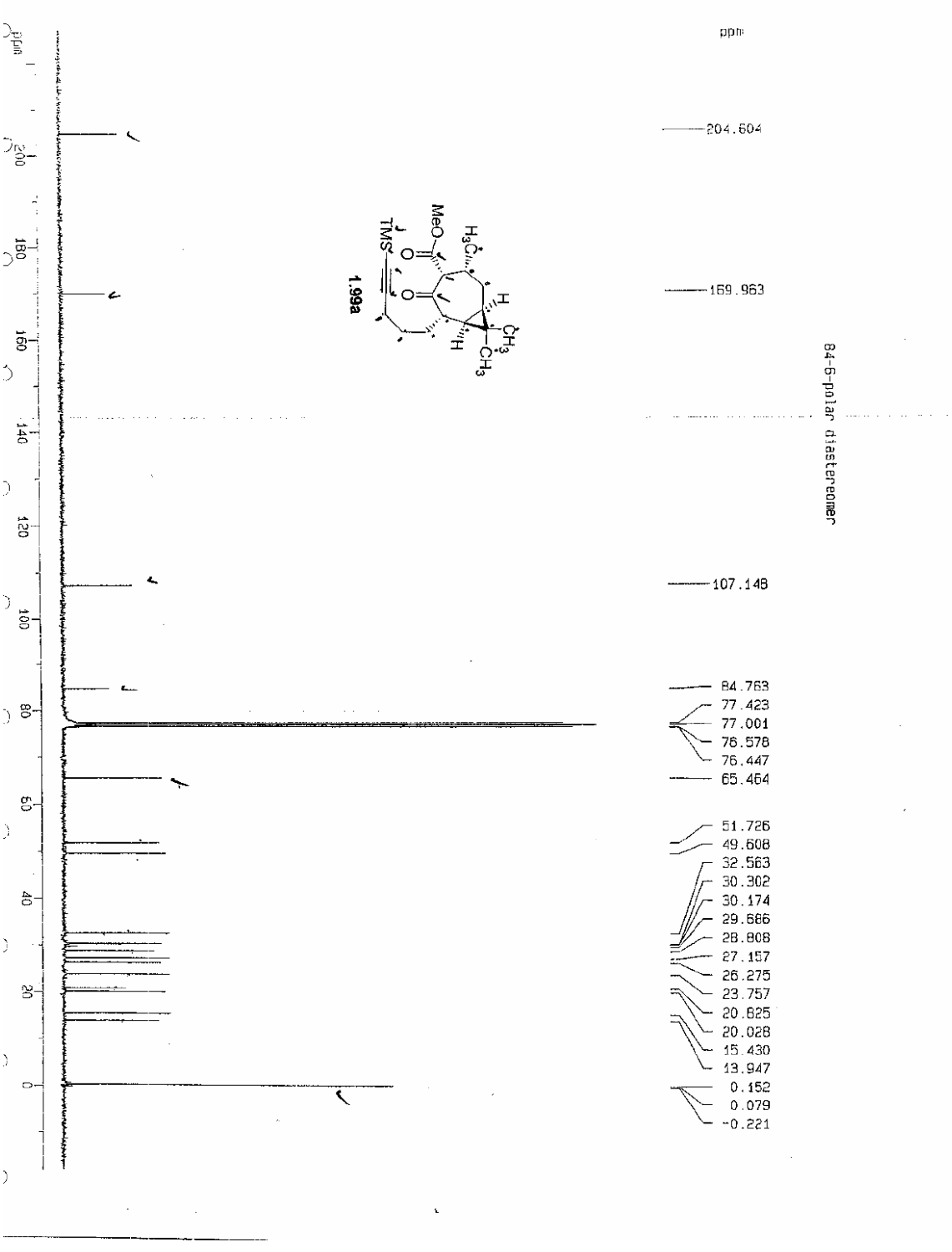

(Billions)
X : parts per Million : 13C
201.8280
146.6694
133.5259
107.5362
77.5135
77.0484
76.5757
49.8236
30.6573
29.7577
29.1477
28.7742
26.5709
26.1211
20.2355
0.2152
TMS
O
H
CH3
H
CH3
1.90

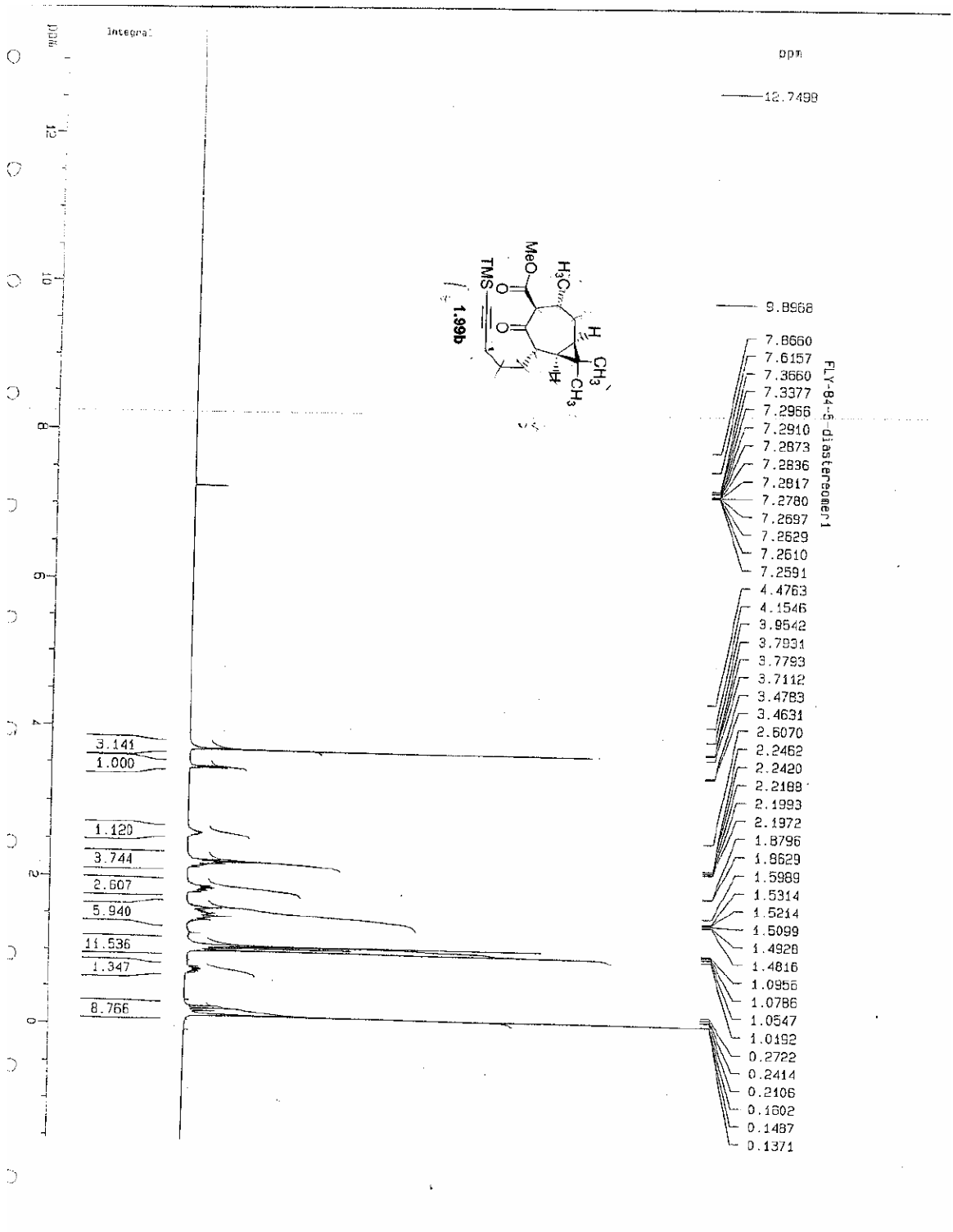

Integral
ppm
1.0000
3.2386
6.6927
2.5850
3.7767
4.4030
5.2607
1.2073
1.94
MeO
OMe
MeO
H
CH3
H
CH3
9.8028
7.9749
7.6155
7.3946
7.3694
7.3361
7.2696
6.9187
6.1059
6.0962
6.0170
5.7641
5.5034
5.4915
4.6210
4.3745
4.3553
4.3361
3.6892
3.3707
3.3691
3.3670
3.3520
3.3425
2.2898
2.2861
2.2647
2.2616
1.6003
1.5665
1.5598
1.5475
1.5417
1.5365
1.5235
1.5168
1.0834
0.9332
0.9147
0.9096
0.8847
0.6983
0.6746
0.6506
0.6446
0.4115
FLY-86-8-hydprod.

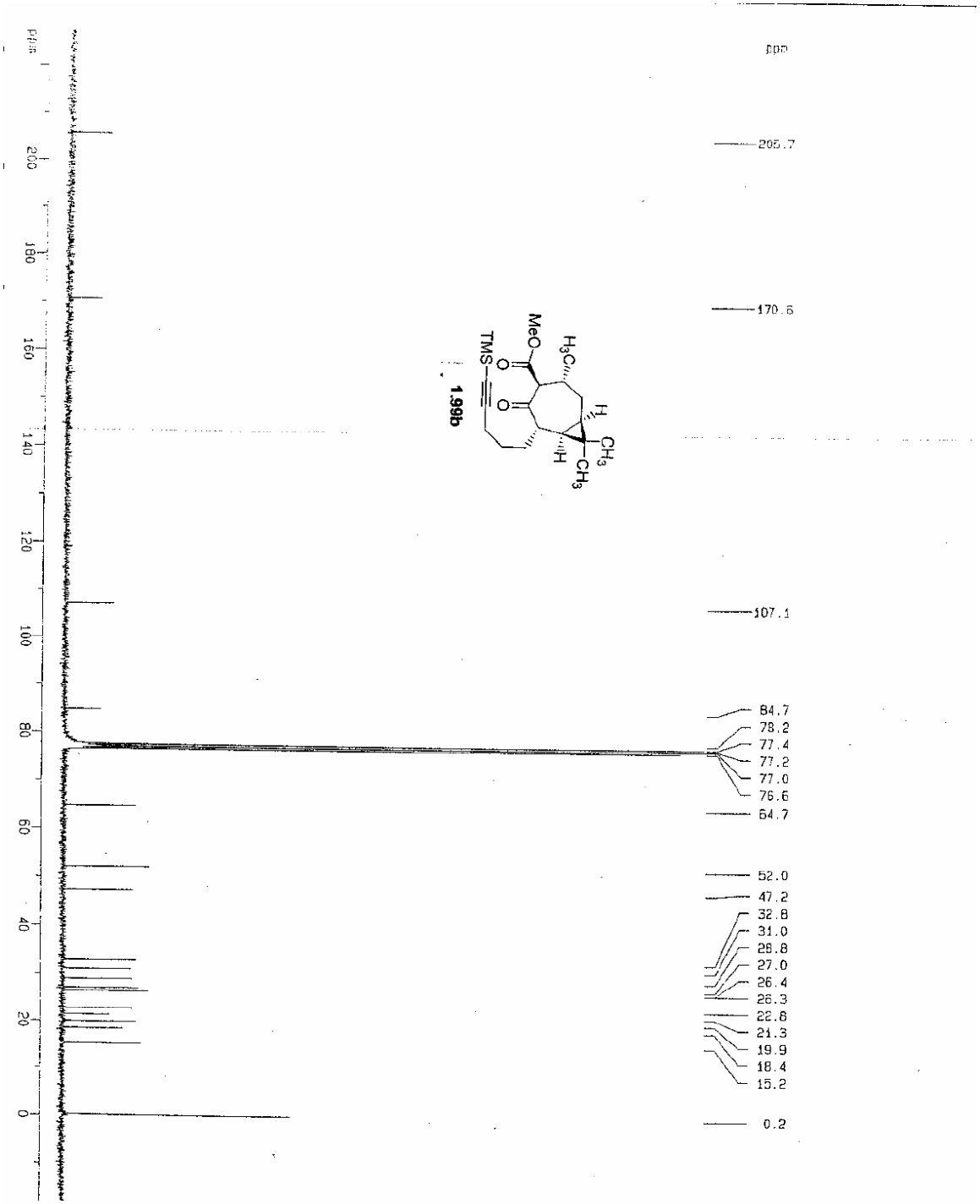

ppm
FLY-66-8-byproduct
174.376
105.404
77.726
77.500
77.304
76.881
76.753
53.546
53.507
53.464
51.866
51.170
39.850
30.229
29.008
28.409
22.039
21.777
17.247
15.274
1.94
MeO
O
MeO
OMe
H
CH3
CH3
H

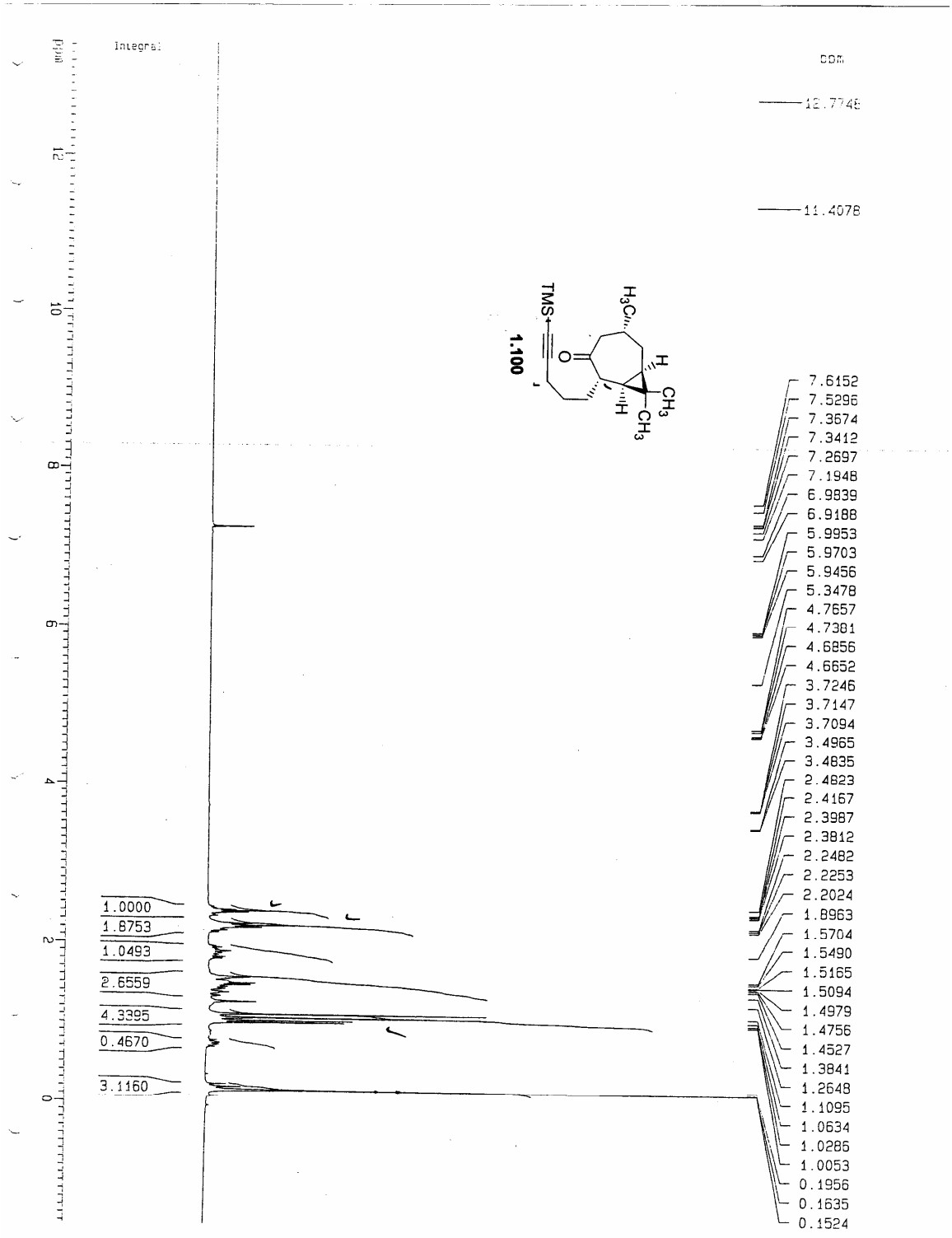

Integral
0.7016
ppm
12
10
8
6
4
2
0
Hz
3887.79
3580.43
MeO
O
OH
1.97
H
CH3
H
CH3
2226.42
2181.87
1834.87
1832.53
1823.76
1821.41
1760.45
1758.66
1749.27
1747.34
1151.87
1147.48
1140.05
1136.93
740.02
730.47
724.05
471.73
406.07
404.12
399.10
395.96
389.04
357.32
340.49
338.18
332.37
329.75
327.42
323.54
321.33
315.75
303.60
267.32
Current Data Parameters
NAME FLY-87-6-dienol
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20010714
Time 9.12
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 15
DS 0
SWH 4496.403 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 362
DW 111.200 usec
DE 6.00 usec
TE 300.0 K
D1 3.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.00 usec
PL1 3.00 dB
SFO1 300.1318008 MHz
F2 - Processing parameters
SI 16384
SF 300.1300124 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 24.00 cm
F1P 13.450 ppm
F1 4036.60 Hz
F2P -1.532 ppm
F2 -459.80 Hz
PPMCM 0.74908 ppm/cm
HZCM 224.82013 Hz/cm

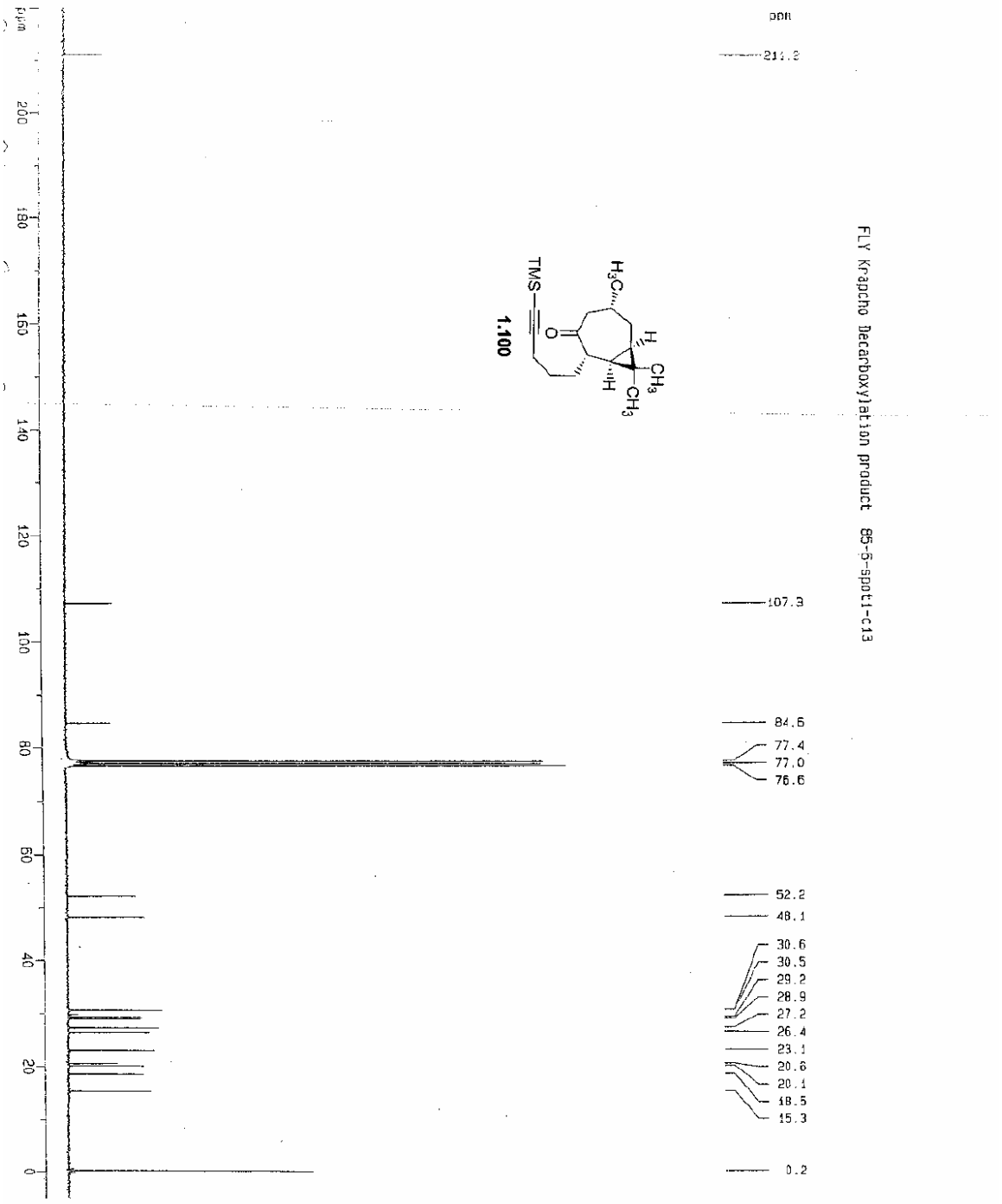

Integral
DDM
ppm
12
10
8
6
4
2
0
MeO
O
O
TMS
H3C
H
CH3
CH3
H
1.99a
7.2703
7.2278
3.9322
3.7510
3.7102
3.6897
3.4523
3.4402
2.5372
2.2684
2.2450
2.2213
2.2125
1.6010
1.5189
1.5092
1.5006
1.4949
1.4863
1.2747
1.2583
1.1218
1.1138
1.0991
1.0678
0.2240
0.1923
0.1856
0.1814
0.1793
0.1521
0.1409
2.766
1.002
1.026
4.541
1.232
4.148
2.120
10.002
1.323
7.588

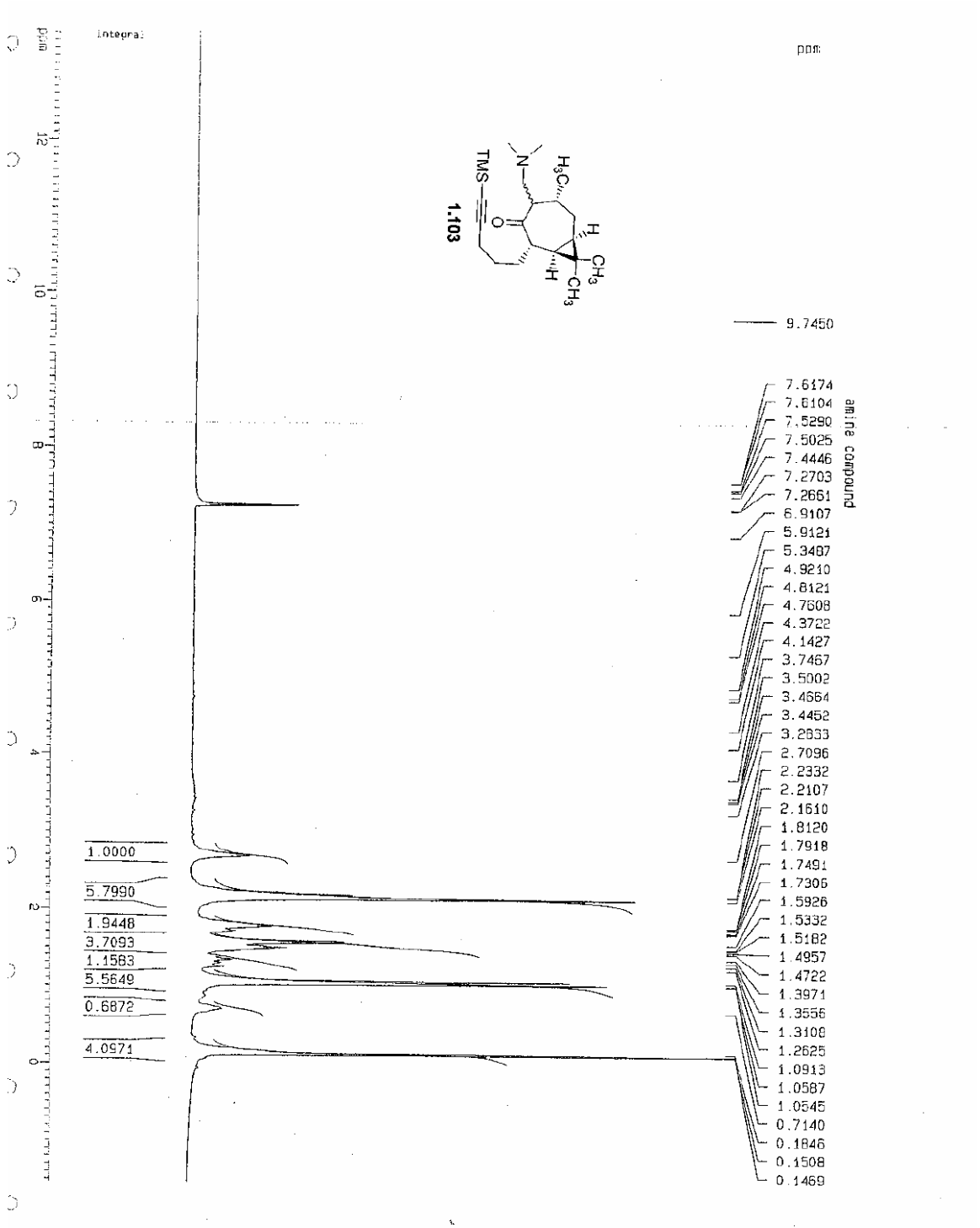

ppm
204.604
169.963
107.148
84.763
77.423
77.001
76.578
76.447
65.464
51.726
49.608
32.563
30.302
30.174
29.686
28.808
27.157
26.275
23.757
20.825
20.028
15.430
13.947
0.152
0.079
-0.221
84-6-polar diastereomer
MeO
TMS
H3C
CH3
CH3
H
H
O
O
1.99a

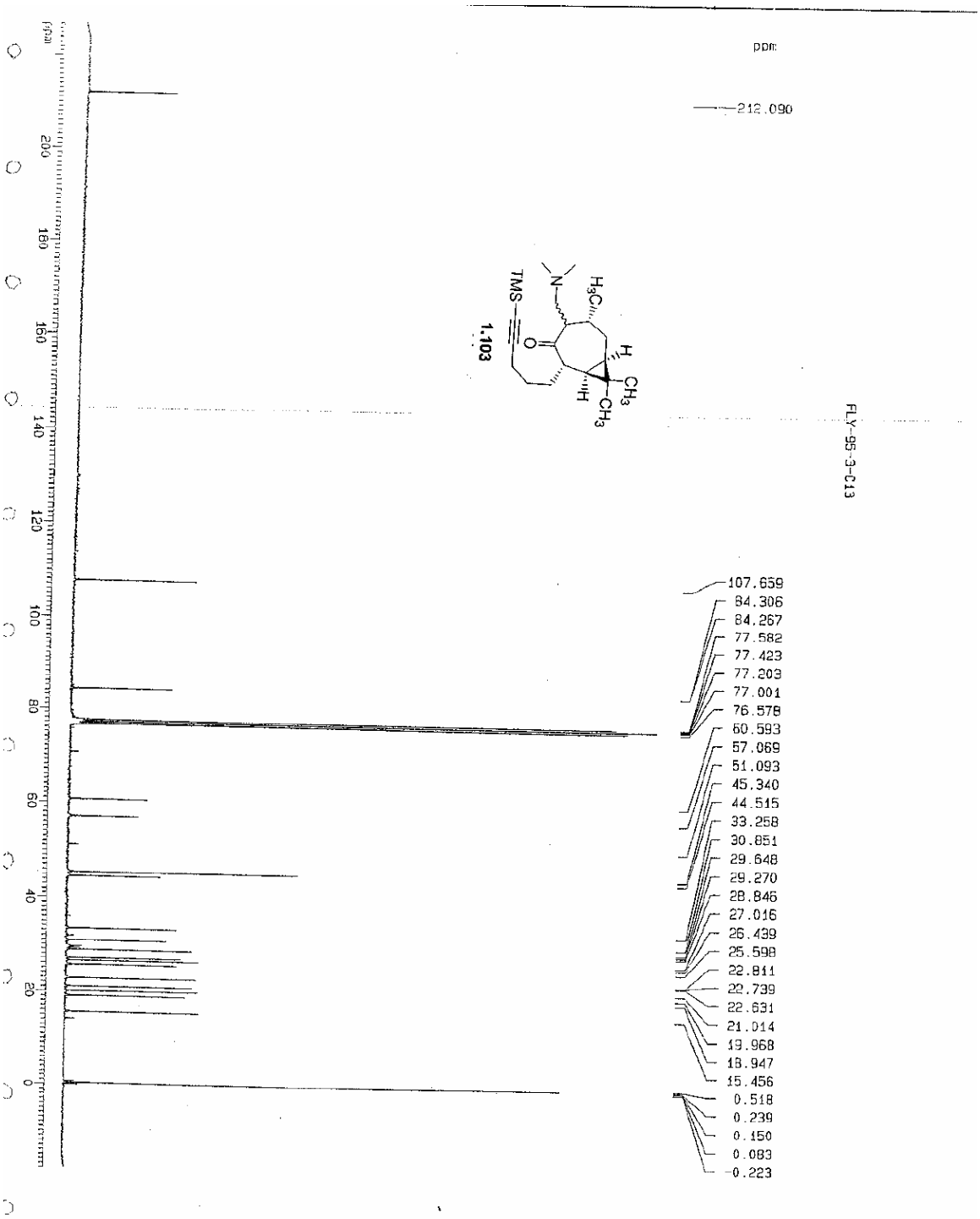

Integral
ppm
12.7498
9.8968
7.8660
7.6157
7.3660
7.3377
7.2966
7.2910
7.2873
7.2836
7.2817
7.2780
7.2697
7.2629
7.2610
7.2591
4.4763
4.1546
3.9542
3.7931
3.7793
3.7112
3.4783
3.4631
2.6070
2.2462
2.2420
2.2188
2.1993
2.1972
1.8796
1.8629
1.5989
1.5314
1.5214
1.5099
1.4928
1.4816
1.0956
1.0786
1.0547
1.0192
0.2722
0.2414
0.2106
0.1602
0.1487
0.1371
FLY-84-5-diastereomer1
3.141
1.000
1.120
3.744
2.607
5.940
11.536
1.347
8.766
1.99b
MeO
TMS
H3C
CH3
H
H

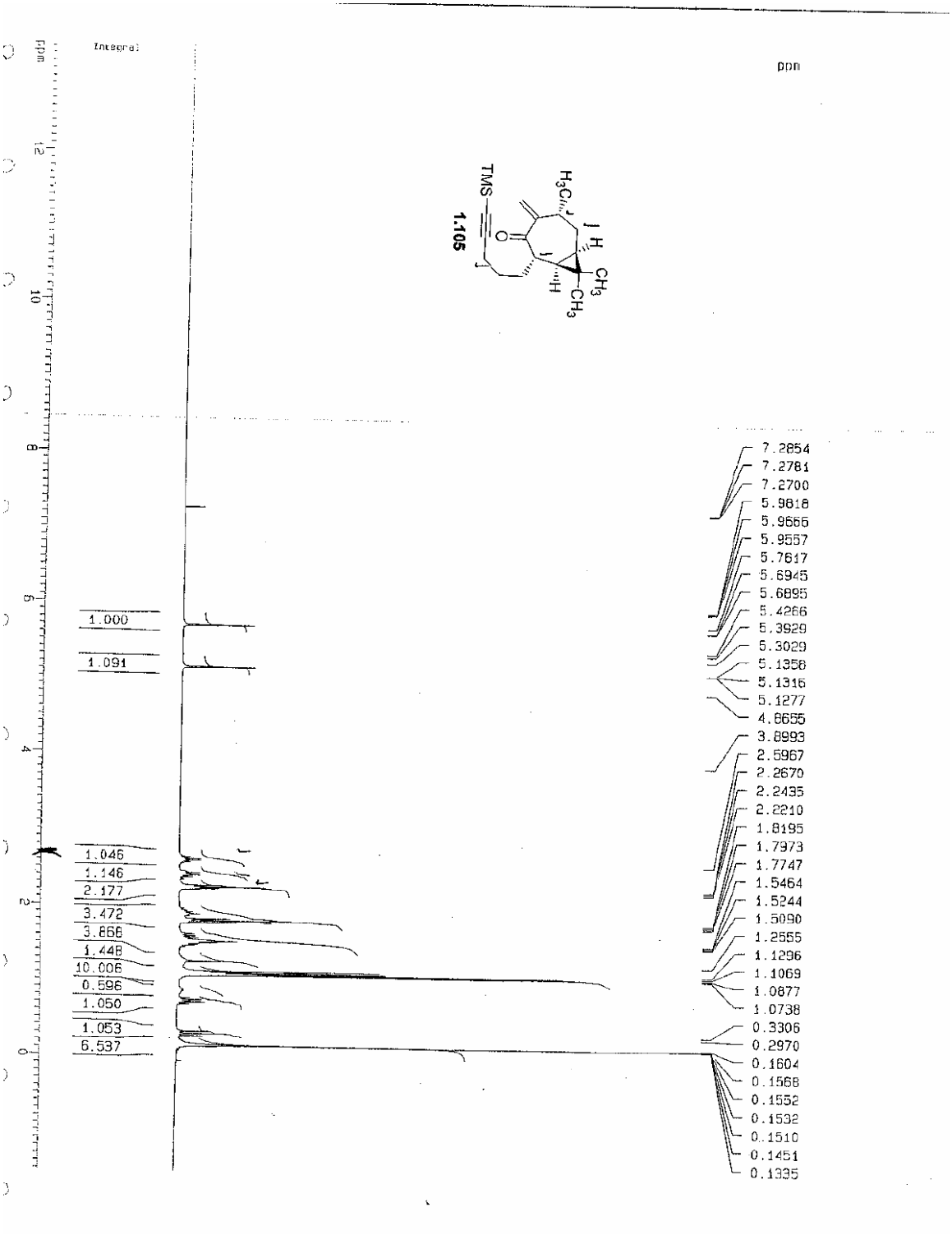

ppm
205.7
170.6
107.1
84.7
78.2
77.4
77.2
77.0
76.6
64.7
52.0
47.2
32.8
31.0
28.8
27.0
26.4
26.3
22.6
21.3
19.9
18.4
15.2
0.2
MeO
TMS
H3C
CH3
CH3
1.99b

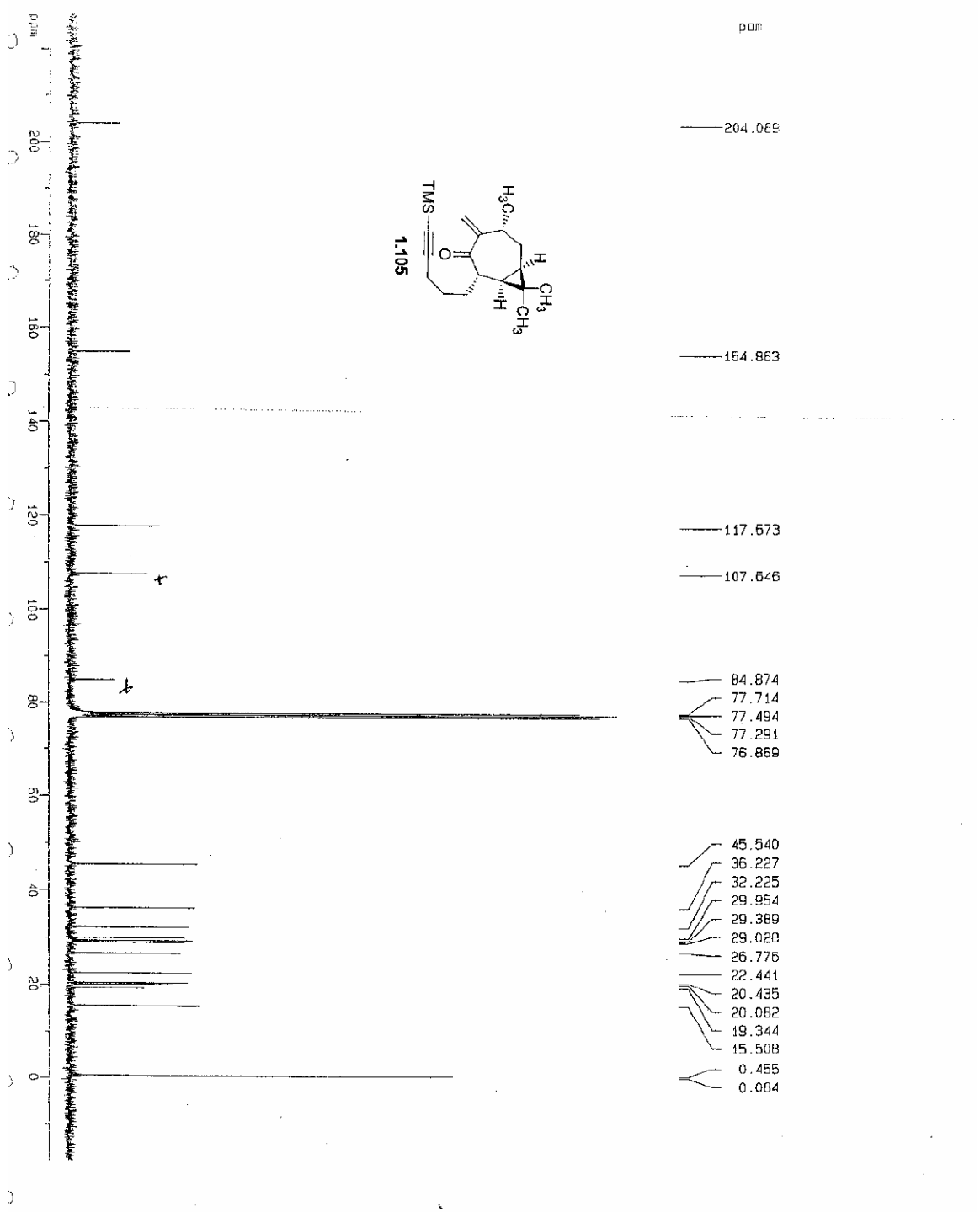

Integral
ppm
12.7748
11.4078
TMS
1.100
H3C
CH3
H
CH3
7.6152
7.5296
7.3674
7.3412
7.2697
7.1948
6.9839
6.9188
5.9953
5.9703
5.9456
5.3478
4.7657
4.7381
4.6856
4.6652
3.7246
3.7147
3.7094
3.4965
3.4835
2.4823
2.4167
2.3987
2.3812
2.2482
2.2253
2.2024
1.8963
1.5704
1.5490
1.5165
1.5094
1.4979
1.4756
1.4527
1.3841
1.2648
1.1095
1.0634
1.0286
1.0053
0.1956
0.1635
0.1524
1.0000
1.8753
1.0493
2.6559
4.3395
0.4670
3.1160

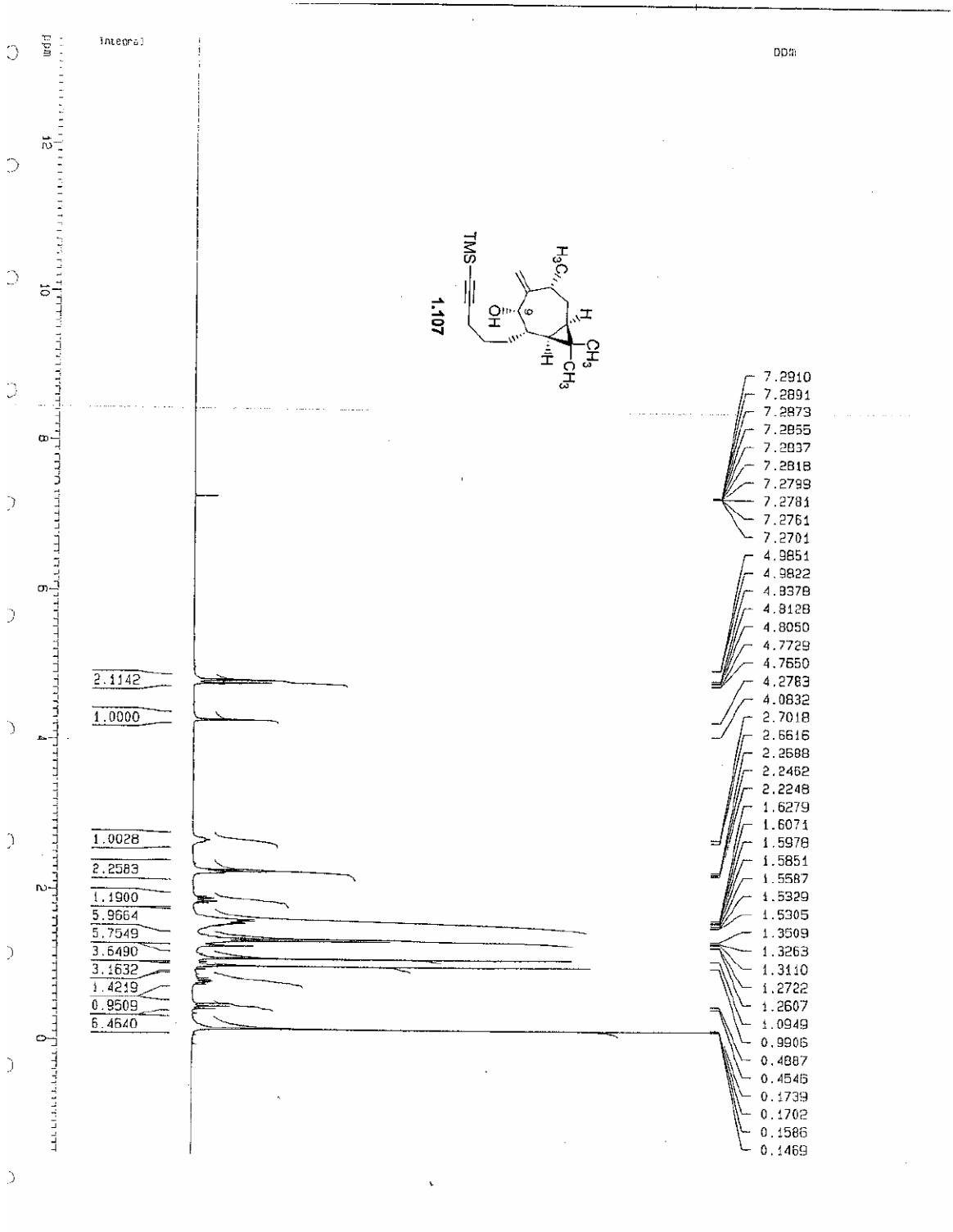

FLY Krapcho Decarboxylation product 85-5-spot1-c13
ppm
211.2
107.3
84.6
77.4
77.0
76.6
52.2
48.1
30.6
30.5
29.2
28.9
27.2
26.4
23.1
20.6
20.1
18.5
15.3
0.2
TMS
O
H3C
CH3
H
H
1.100

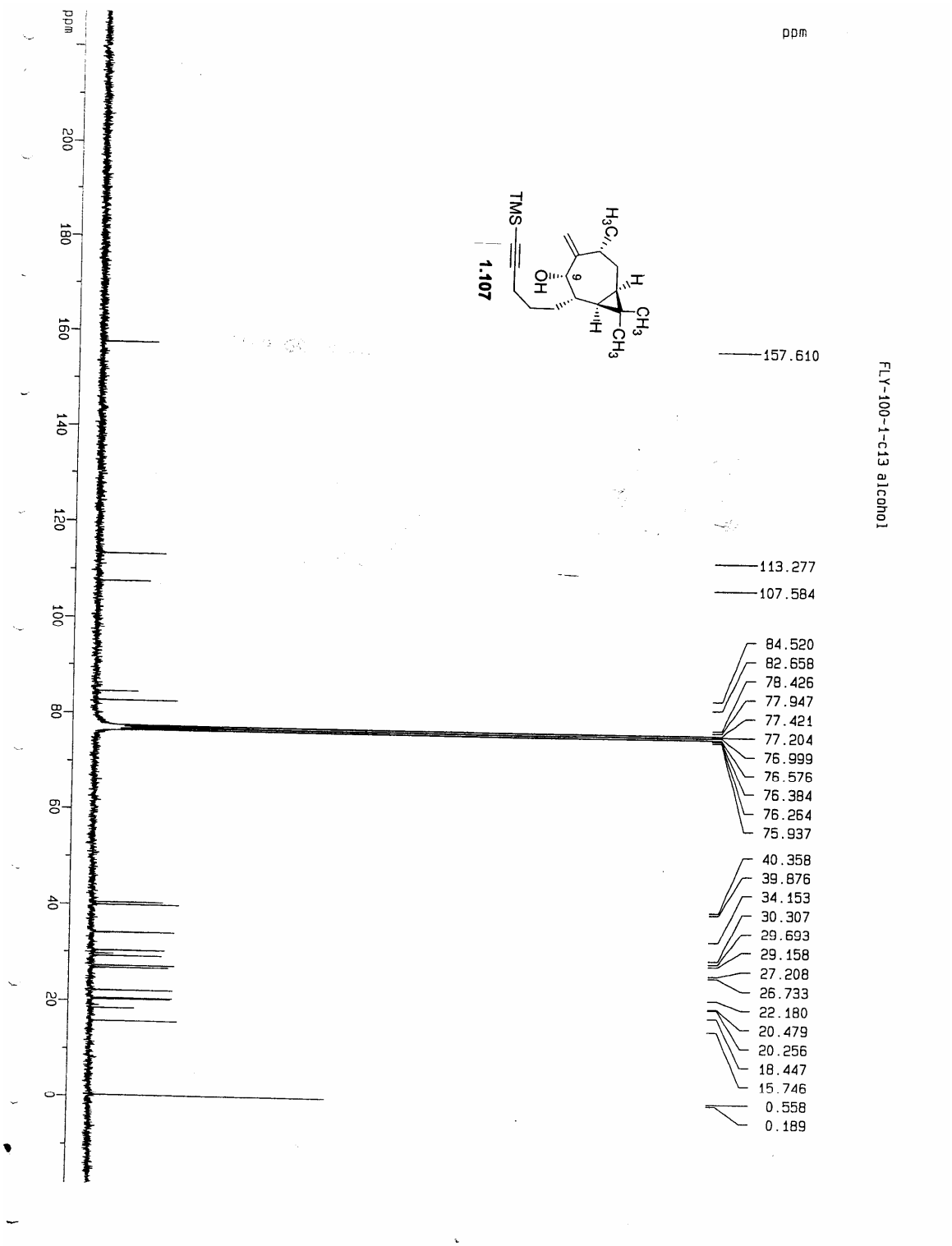

integral
ppm
1.103
TMS
9.7450
7.6174
7.6104
7.5290
7.5025
7.4446
7.2703
7.2661
6.9107
5.9121
5.3487
4.9210
4.8121
4.7608
4.3722
4.1427
3.7467
3.5002
3.4654
3.4452
3.2833
2.7096
2.2332
2.2107
2.1610
1.8120
1.7918
1.7491
1.7306
1.5926
1.5332
1.5182
1.4957
1.4722
1.3971
1.3556
1.3108
1.2625
1.0913
1.0587
1.0545
0.7140
0.1846
0.1508
0.1469
amine compound
1.0000
5.7990
1.9448
3.7093
1.1583
5.5649
0.6872
4.0971

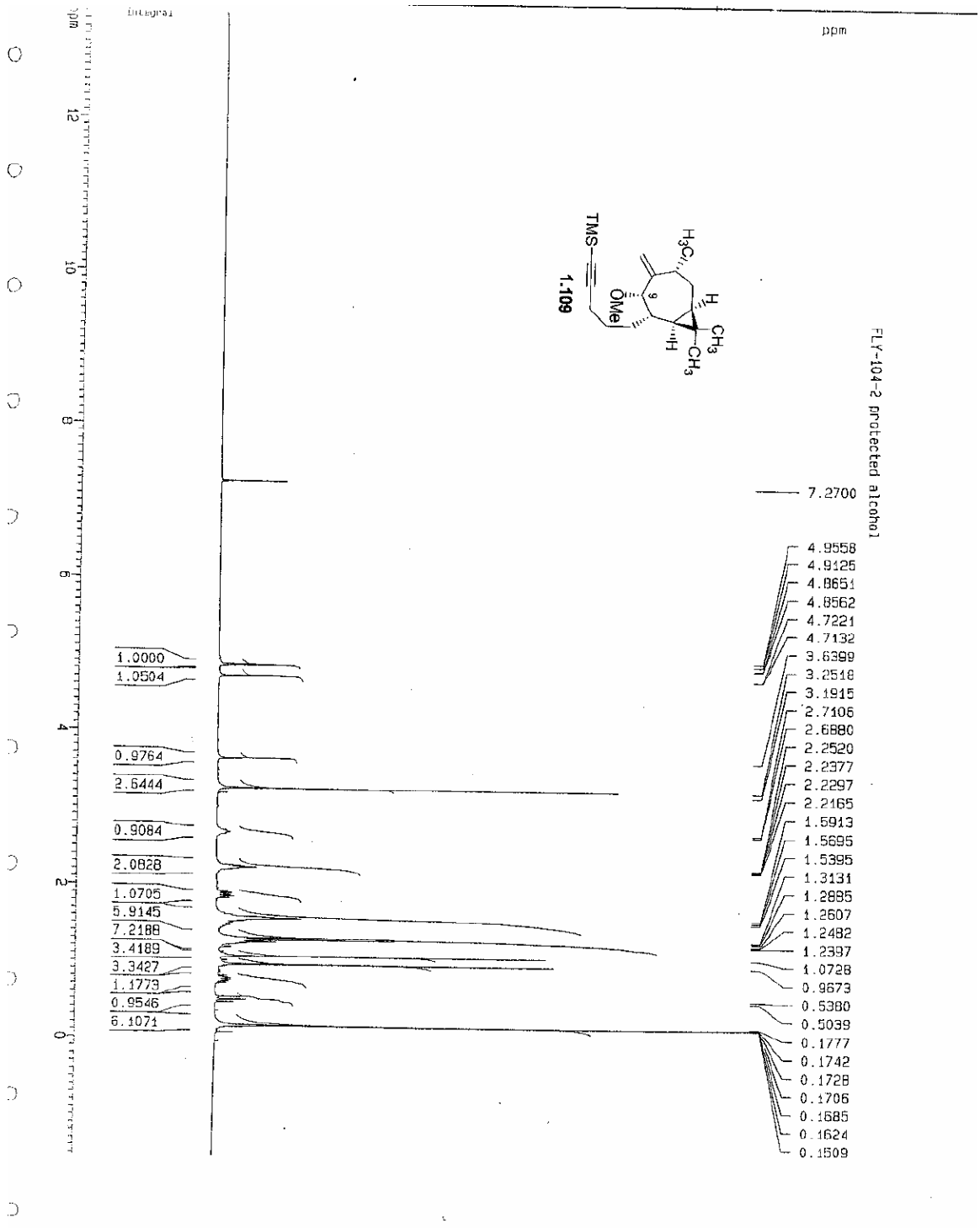

ppm
212.090
107.659
84.306
84.267
77.582
77.423
77.203
77.001
76.578
60.593
57.069
51.093
45.340
44.515
33.258
30.851
29.648
29.270
28.846
27.016
26.439
25.598
22.811
22.739
22.631
21.014
19.968
18.947
15.456
0.518
0.239
0.150
0.083
-0.223
TMS
1.103
FLY-95-3-C13

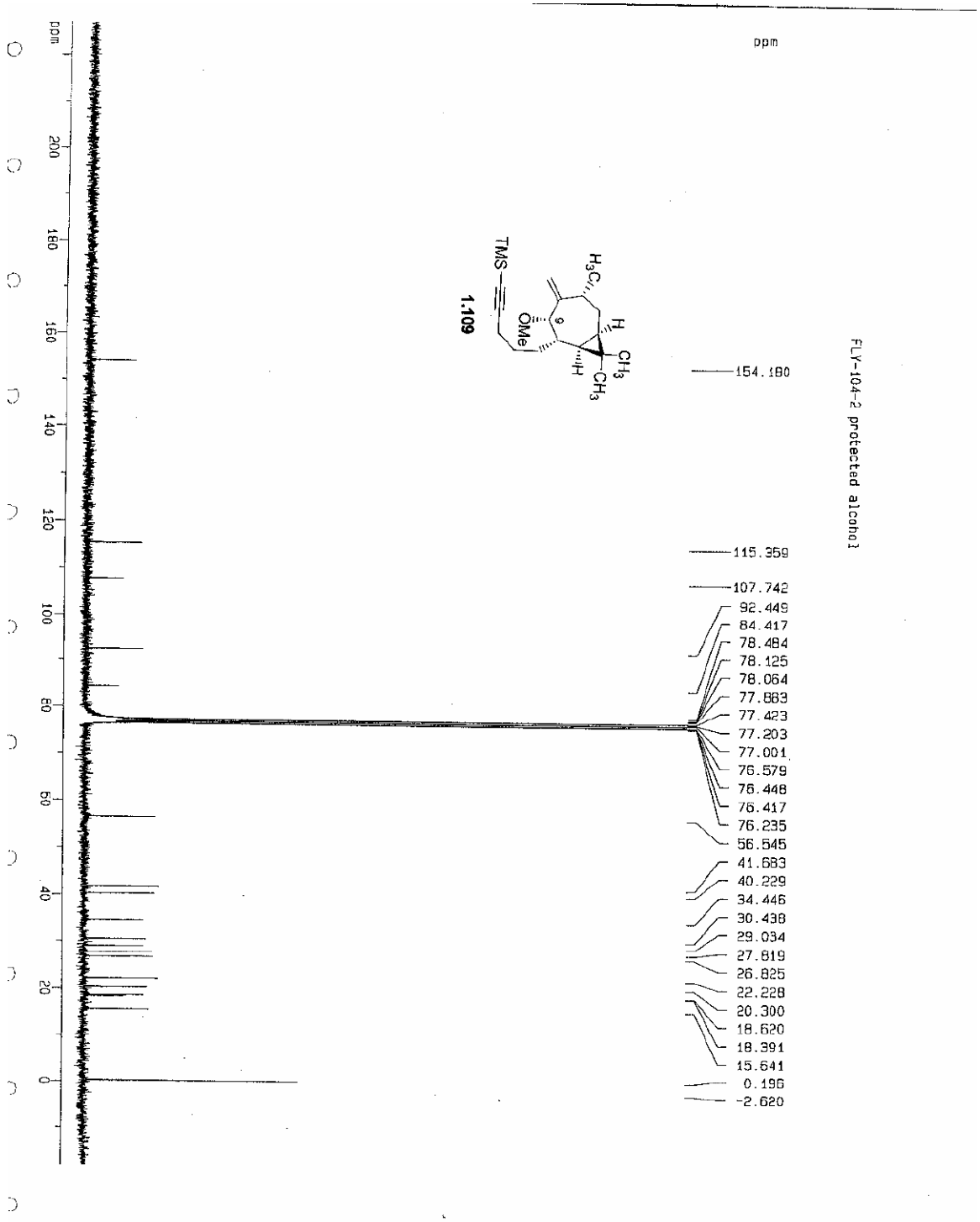

Integral
ppm
TMS
1.105
1.000
1.091
1.046
1.146
2.177
3.472
3.868
1.448
10.006
0.596
1.050
1.053
6.537
7.2854
7.2781
7.2700
5.9818
5.9666
5.9557
5.7617
5.6945
5.6895
5.4266
5.3929
5.3029
5.1358
5.1316
5.1277
4.8655
3.8993
2.5967
2.2670
2.2435
2.2210
1.8195
1.7973
1.7747
1.5464
1.5244
1.5090
1.2555
1.1296
1.1069
1.0877
1.0738
0.3306
0.2970
0.1604
0.1568
0.1552
0.1532
0.1510
0.1451
0.1335

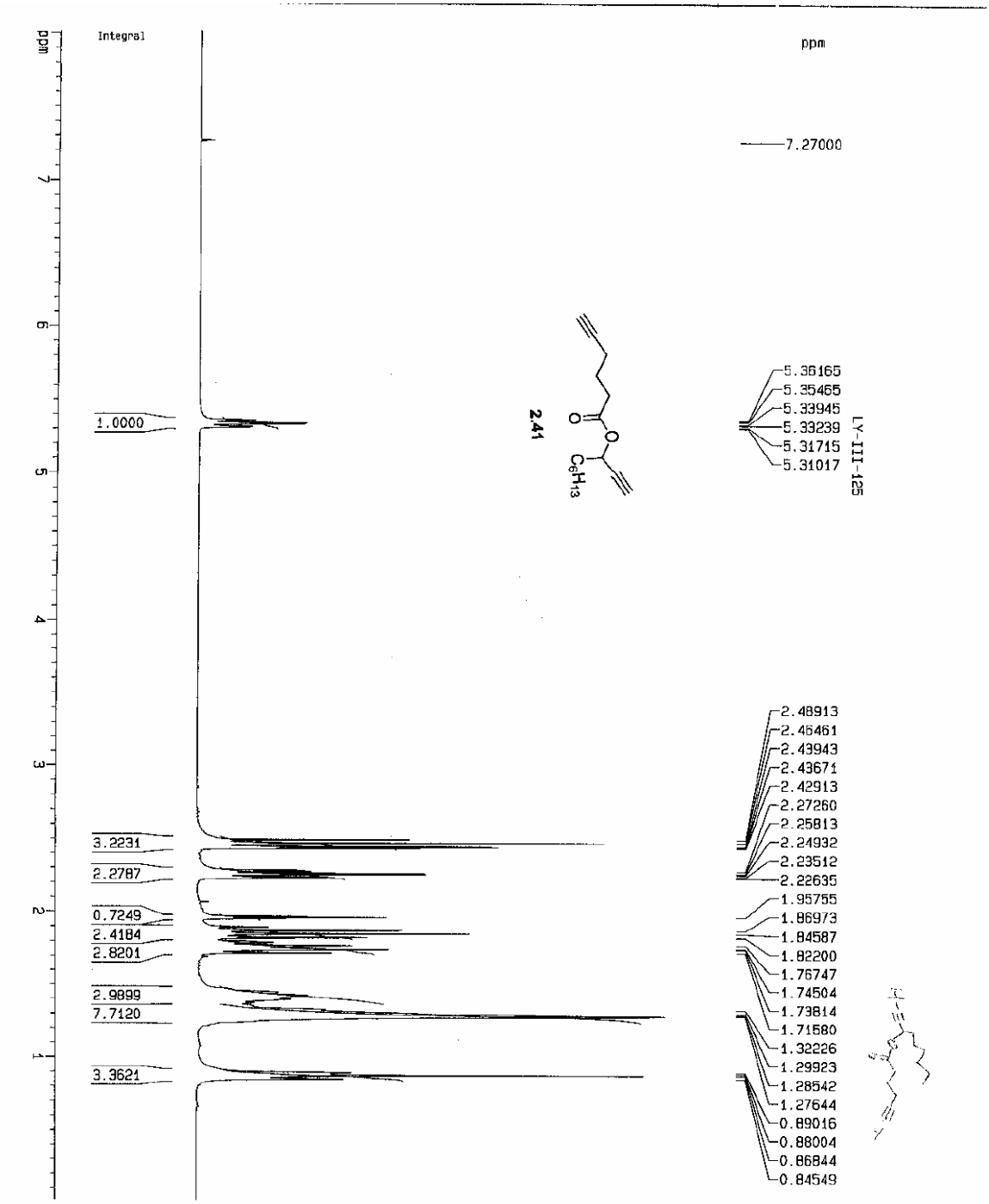

ppm
204.089
154.863
117.673
107.646
84.874
77.714
77.494
77.291
76.869
45.540
36.227
32.225
29.954
29.389
29.028
26.776
22.441
20.435
20.082
19.344
15.508
0.455
0.084
TMS
O
H3C
H
CH3
H
CH3
1.105

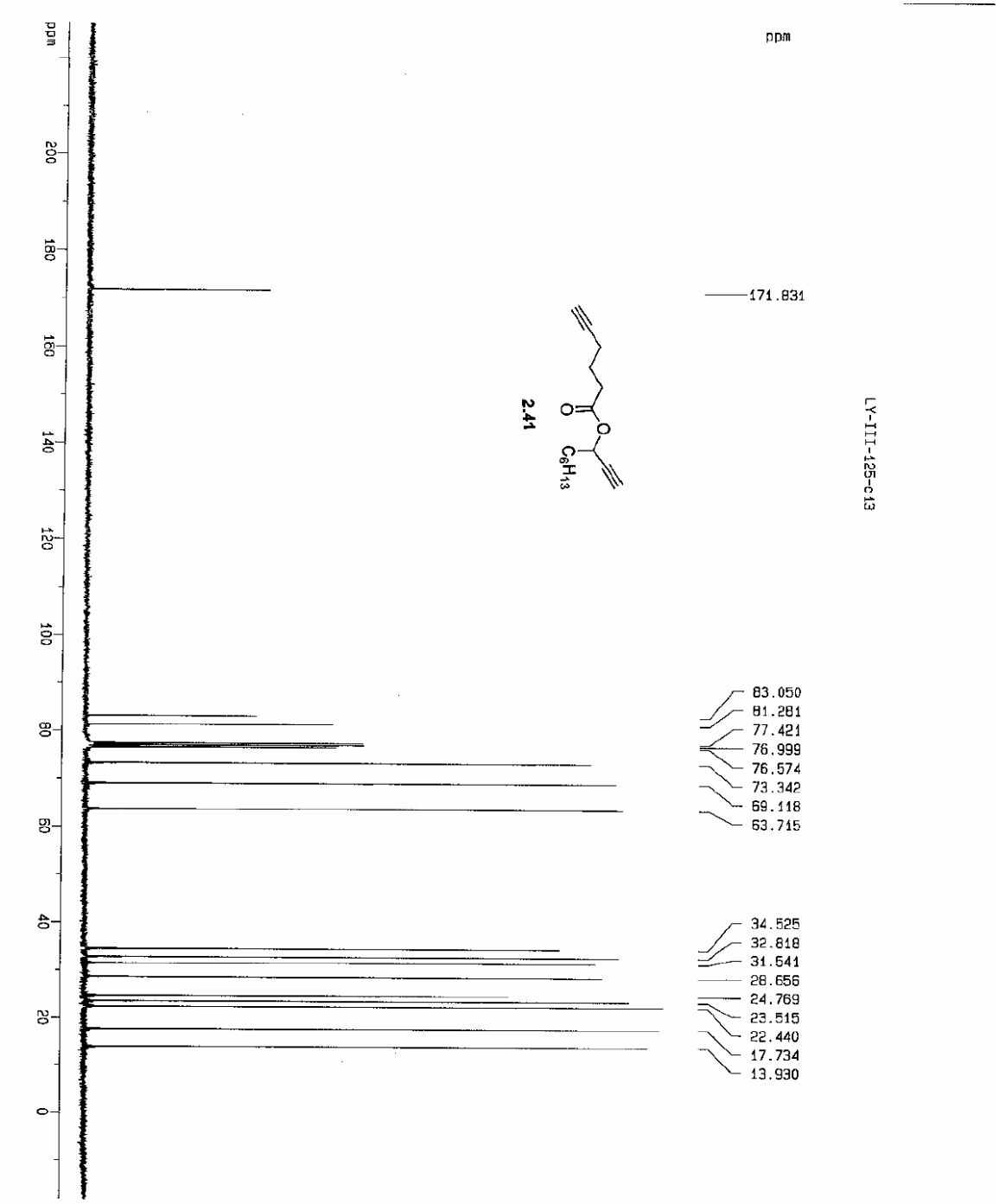

Integral
DD3
TMS
1.107
2.1142
1.0000
1.0028
2.2583
1.1900
5.9664
5.7549
3.6490
3.1632
1.4219
0.9509
6.4640
7.2910
7.2891
7.2873
7.2855
7.2837
7.2818
7.2799
7.2781
7.2761
7.2701
4.9851
4.9822
4.8378
4.8128
4.8050
4.7729
4.7650
4.2783
4.0832
2.7018
2.6616
2.2688
2.2462
2.2248
1.6279
1.6071
1.5978
1.5851
1.5587
1.5329
1.5305
1.3509
1.3263
1.3110
1.2722
1.2607
1.0949
0.9906
0.4887
0.4545
0.1739
0.1702
0.1586
0.1469

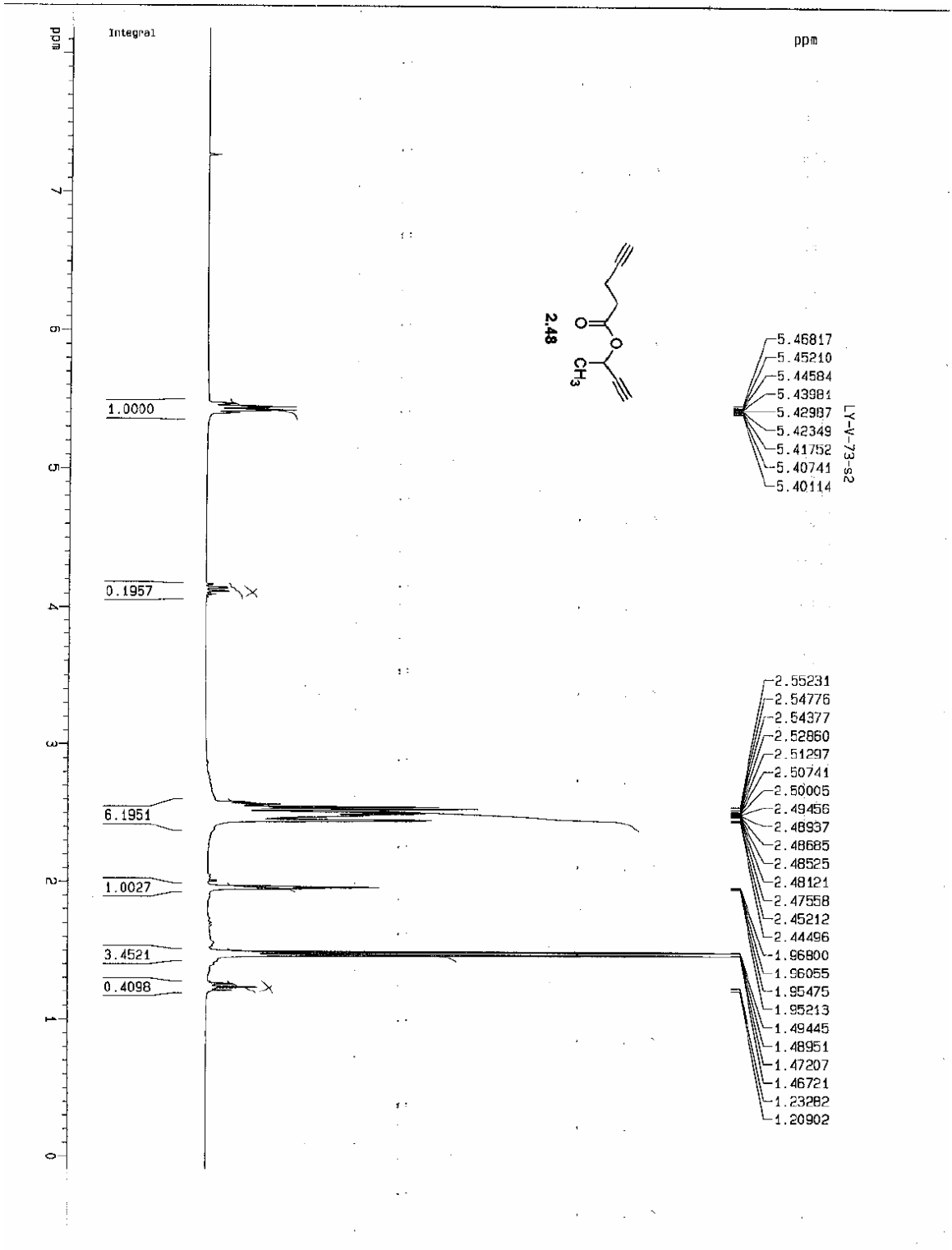

ppm
200
180
160
140
120
100
80
60
40
20
0
TMS
1.107
OH
H
CH3
CH3
H3C
H
157.610
113.277
107.584
84.520
82.658
78.426
77.947
77.421
77.204
76.999
76.576
76.384
76.264
75.937
40.358
39.876
34.153
30.307
29.693
29.158
27.208
26.733
22.180
20.479
20.256
18.447
15.746
0.558
0.189
FLY-100-1-c13 alcohol

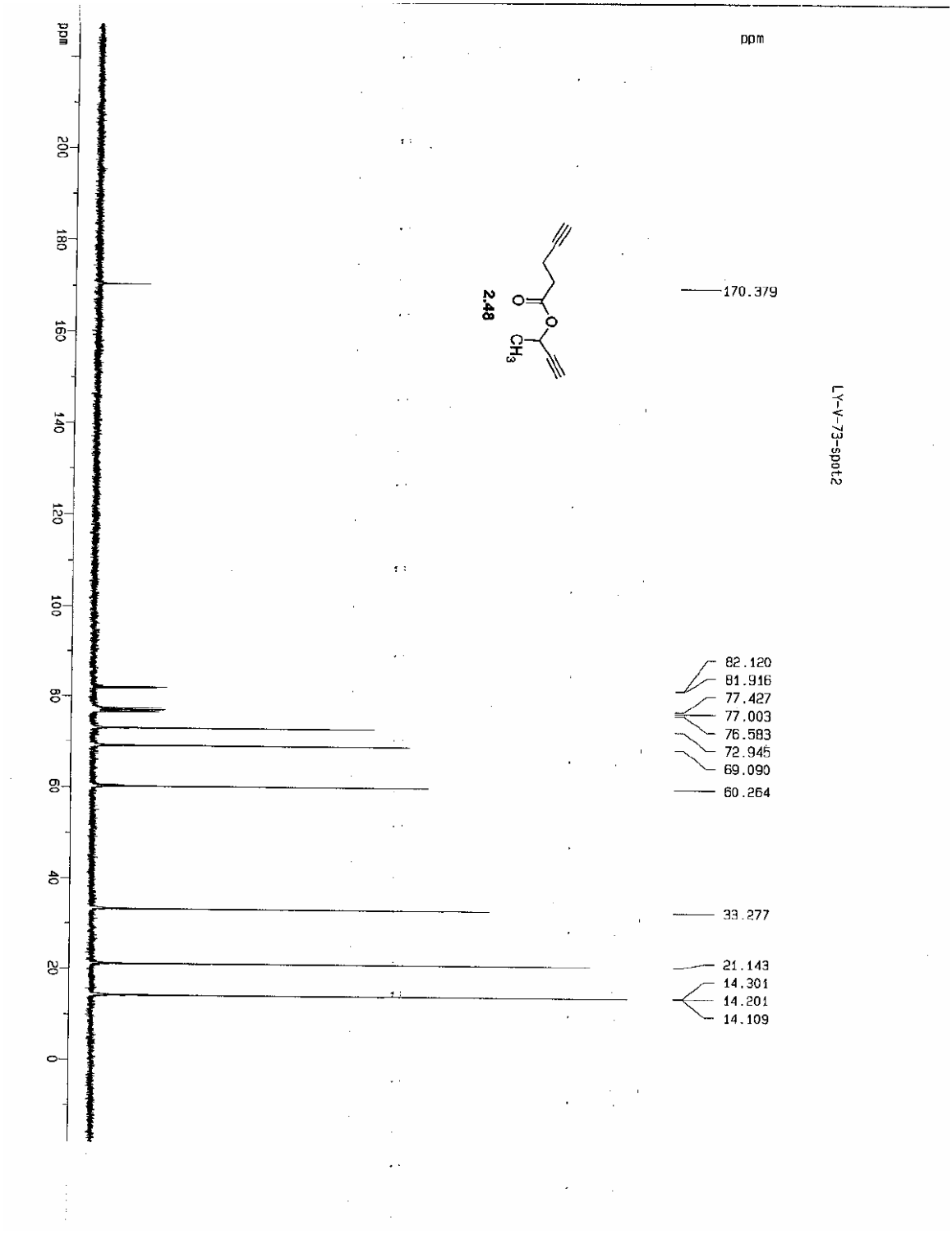

ppm
FLY-104-2 protected alcohol
TMS
1.109
OMe
H3C
CH3
H
H
9
7.2700
4.9558
4.9125
4.8651
4.8562
4.7221
4.7132
3.6399
3.2518
3.1915
2.7106
2.6880
2.2520
2.2377
2.2297
2.2165
1.5913
1.5695
1.5395
1.3131
1.2885
1.2607
1.2482
1.2397
1.0728
0.9673
0.5380
0.5039
0.1777
0.1742
0.1728
0.1706
0.1685
0.1624
0.1509
1.0000
1.0504
0.9764
2.6444
0.9084
2.0828
1.0705
5.9145
7.2188
3.4189
3.3427
1.1773
0.9546
6.1071

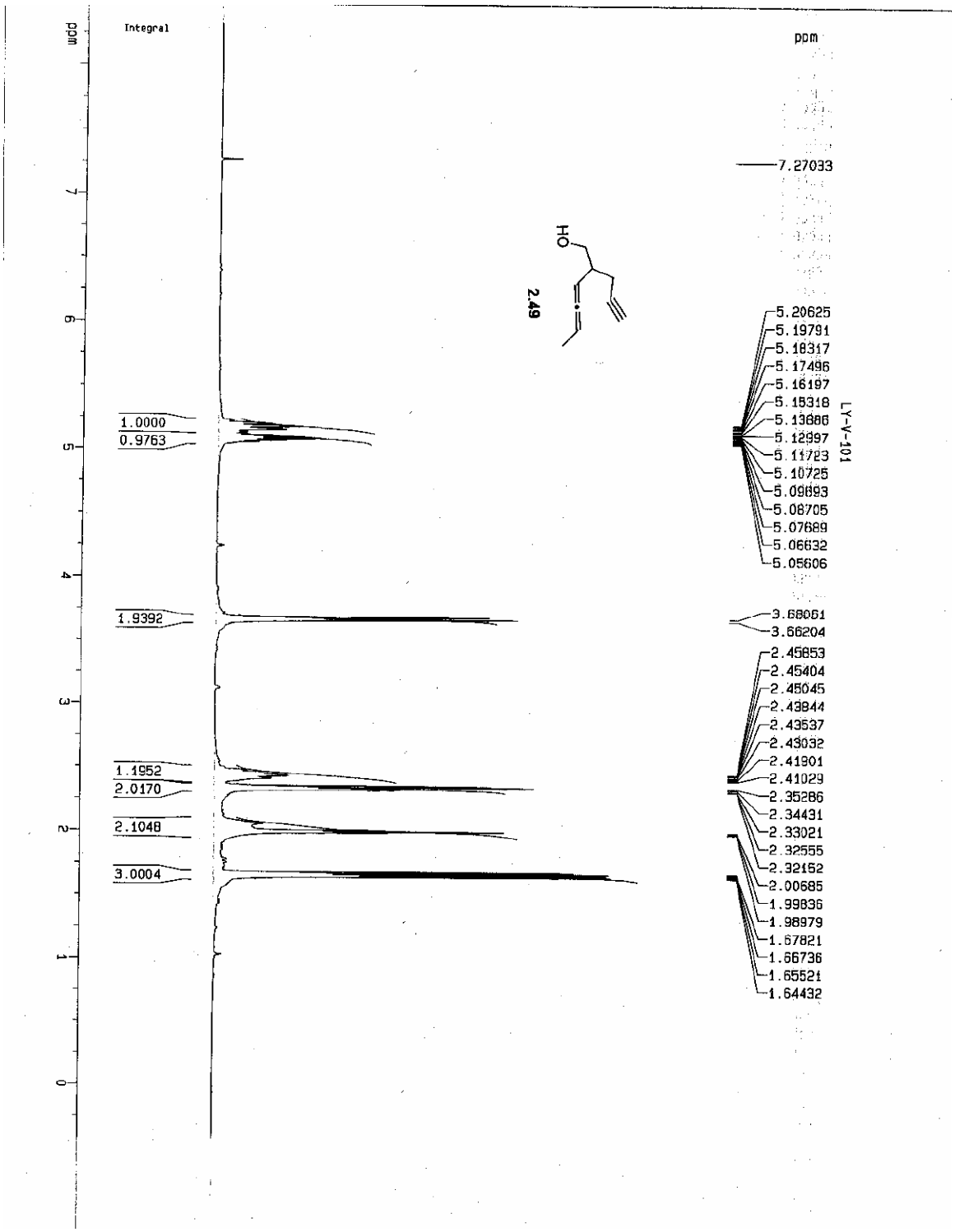

ppm
200
180
160
140
120
100
80
60
40
20
0
TMS
OMe
H3C
CH3
CH3
H
H
1.109
ppm
154.180
115.359
107.742
92.449
84.417
78.484
78.125
78.064
77.863
77.423
77.203
77.001
76.579
76.448
76.417
76.235
56.545
41.683
40.229
34.446
30.438
29.034
27.819
26.825
22.228
20.300
18.620
18.391
15.641
0.196
-2.620
FLY-104-2 protected alcohol


ppm
Integral
ppm
7.27000
5.36165
5.35465
5.33945
5.33239
5.31715
5.31017
LY-III-125
1.0000
2.41
3.2231
2.2787
0.7249
2.4184
2.8201
2.9899
7.7120
3.3621
2.48913
2.46461
2.43943
2.43671
2.42913
2.27260
2.25813
2.24932
2.23512
2.22635
1.95755
1.86973
1.84587
1.82200
1.76747
1.74504
1.73814
1.71580
1.32226
1.29923
1.28542
1.27644
0.89016
0.88004
0.86844
0.84549


ppm
200
180
160
140
120
100
80
60
40
20
0
171.831
83.050
81.281
77.421
76.999
76.574
73.342
69.118
63.715
34.525
32.818
31.541
28.656
24.769
23.515
22.440
17.734
13.930
2.41
LY-III-125-c13


Integral
ppm
1.0000
0.1957
6.1951
1.0027
3.4521
0.4098
2.48
5.46817
5.45210
5.44584
5.43981
5.42987
5.42349
5.41752
5.40741
5.40114
LY-Y-73-S2
2.55231
2.54776
2.54377
2.52860
2.51297
2.50741
2.50005
2.49456
2.48937
2.48685
2.48525
2.48121
2.47558
2.45212
2.44496
1.96800
1.96055
1.95475
1.95213
1.49445
1.48951
1.47207
1.46721
1.23282
1.20902


ppm
200
180
160
140
120
100
80
60
40
20
0
2.48
170.379
82.120
81.916
77.427
77.003
76.583
72.945
69.090
60.264
33.277
21.143
14.301
14.201
14.109
LY-V-73-spot2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Integral
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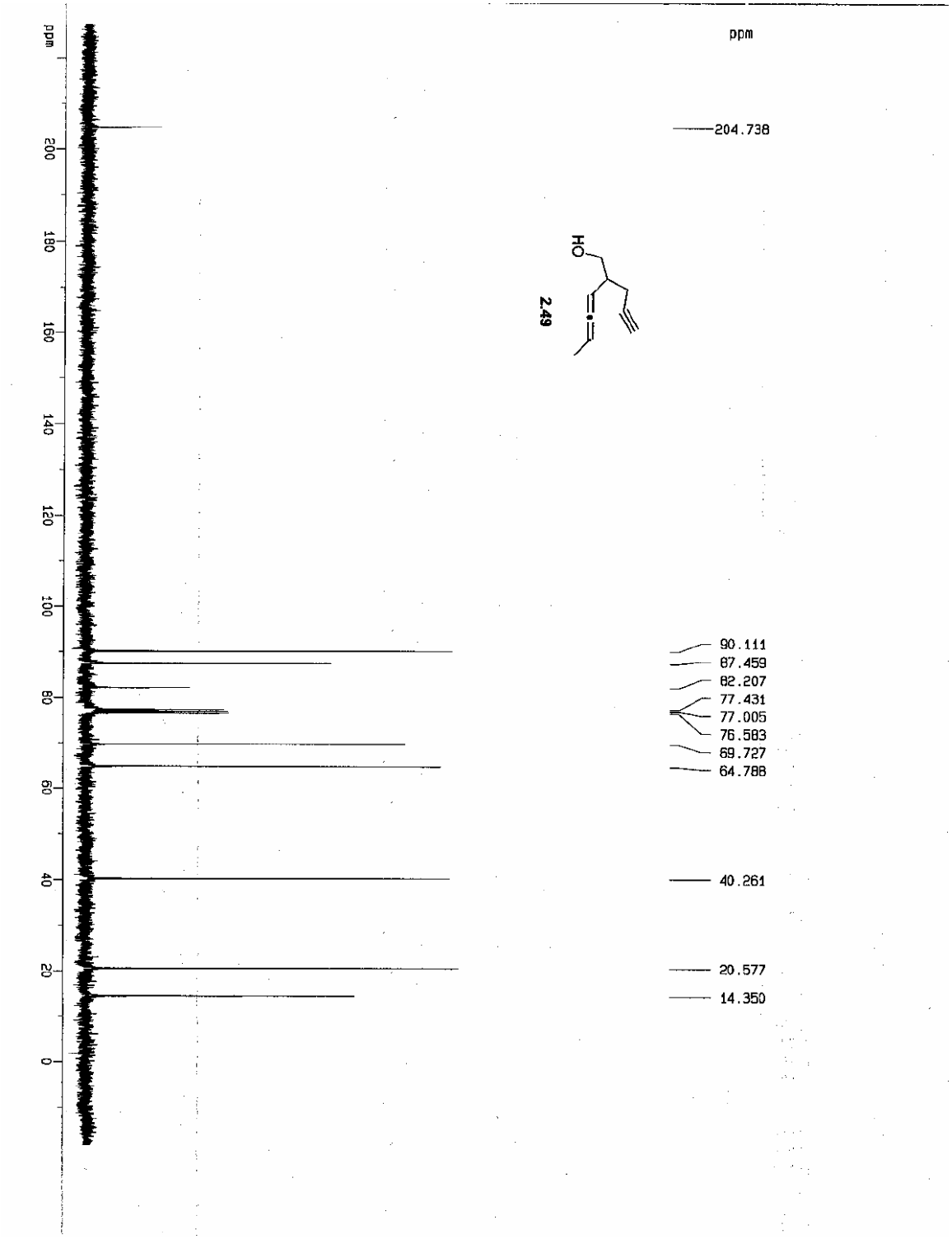
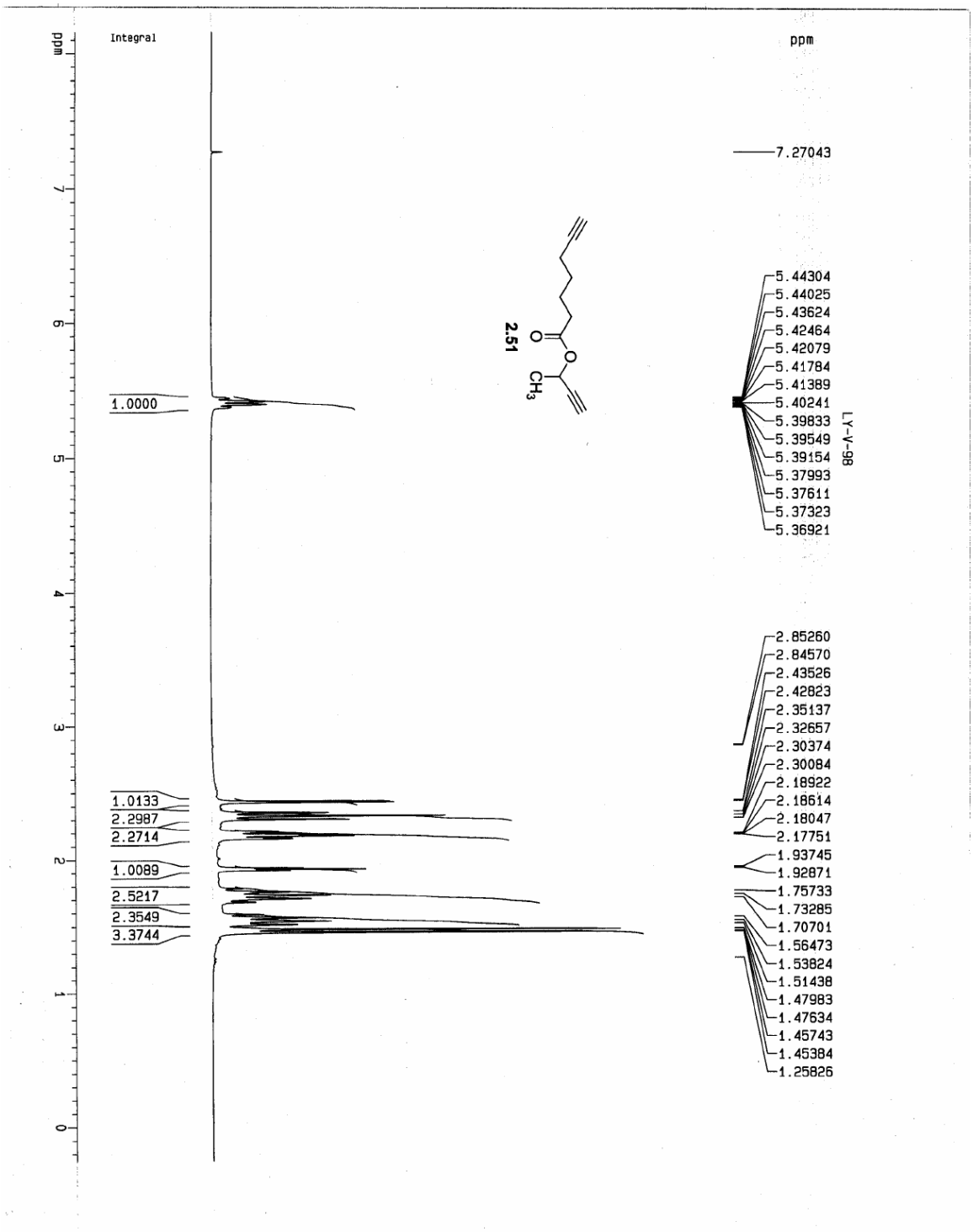
0.9763
1.9392
1.1952
2.0170
2.1048
3.0004
HO
2.49
ppm
7.27033
5.20625
5.19791
5.18317
5.17496
5.16197
5.15318
5.13686
5.12997
5.11723
5.10725
5.09893
5.08705
5.07689
5.06632
5.05606
3.68061
3.66204
2.45853
2.45404
2.45045
2.43844
2.43537
2.43032
2.41901
2.41029
2.35286
2.34431
2.33021
2.32555
2.32152
2.00685
1.99836
1.98979
1.67821
1.66736
1.65521
1.64432
LY-V-101


ppm
204.738
90.111
87.459
82.207
77.431
77.005
76.583
69.727
64.788
40.261
20.577
14.350
HO
2.49


ppm
Integral
ppm
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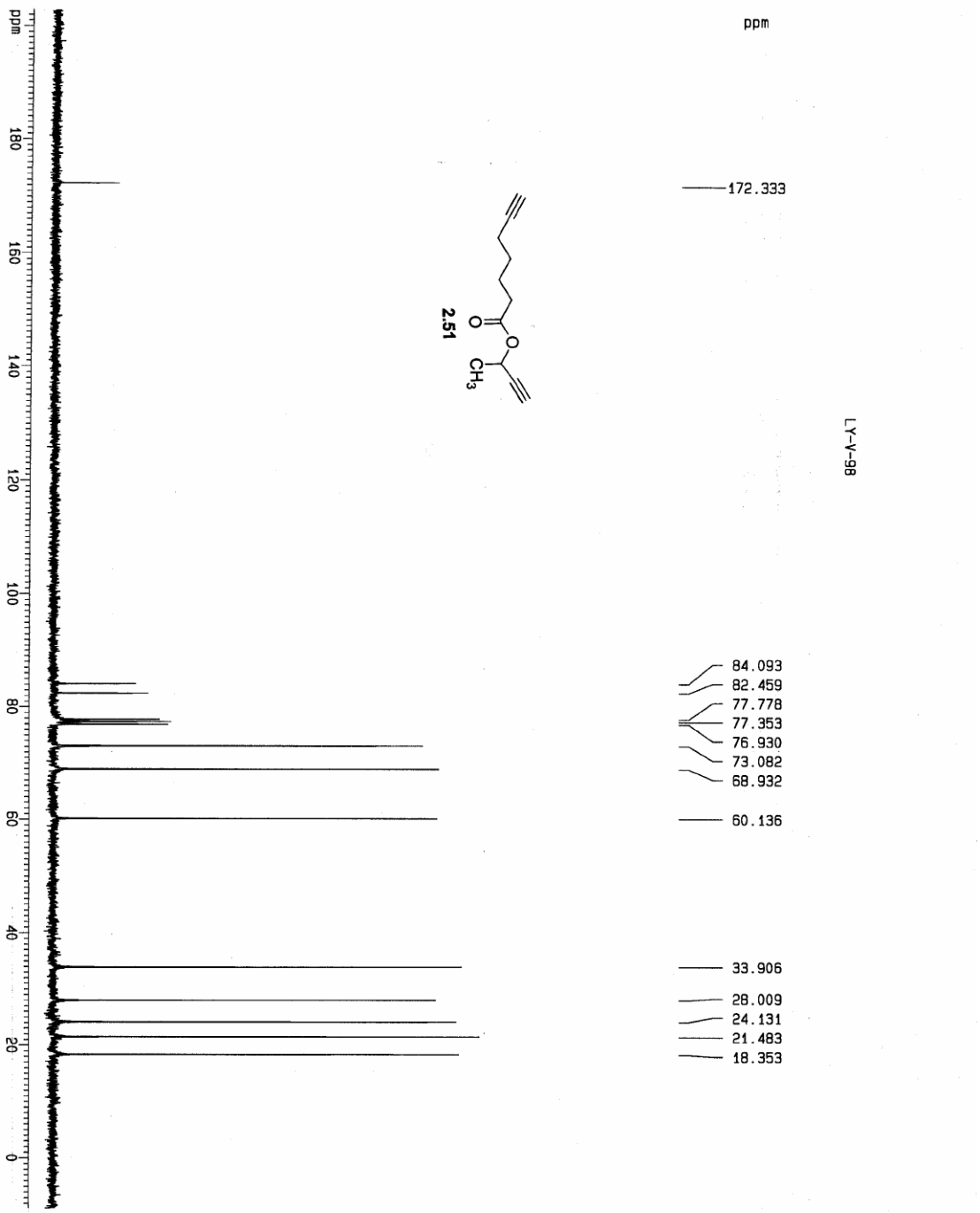
5.44304
5.44025
5.43624
5.42464
5.42079
5.41784
5.41389
5.40241
5.39833
5.39549
5.39154
5.37993
5.37611
5.37323
5.36921
LY-A-98
2.85260
2.84570
2.43526
2.42823
2.35137
2.32657
2.30374
2.30084
2.18922
2.18614
2.18047
2.17751
1.93745
1.92871
1.75733
1.73285
1.70701
1.56473
1.53824
1.51438
1.47983
1.47634
1.45743
1.45384
1.25826
1.0000
1.0133
2.2987
2.2714
1.0089
2.5217
2.3549
3.3744
2.51
O
O
CH3


ppm
172.333
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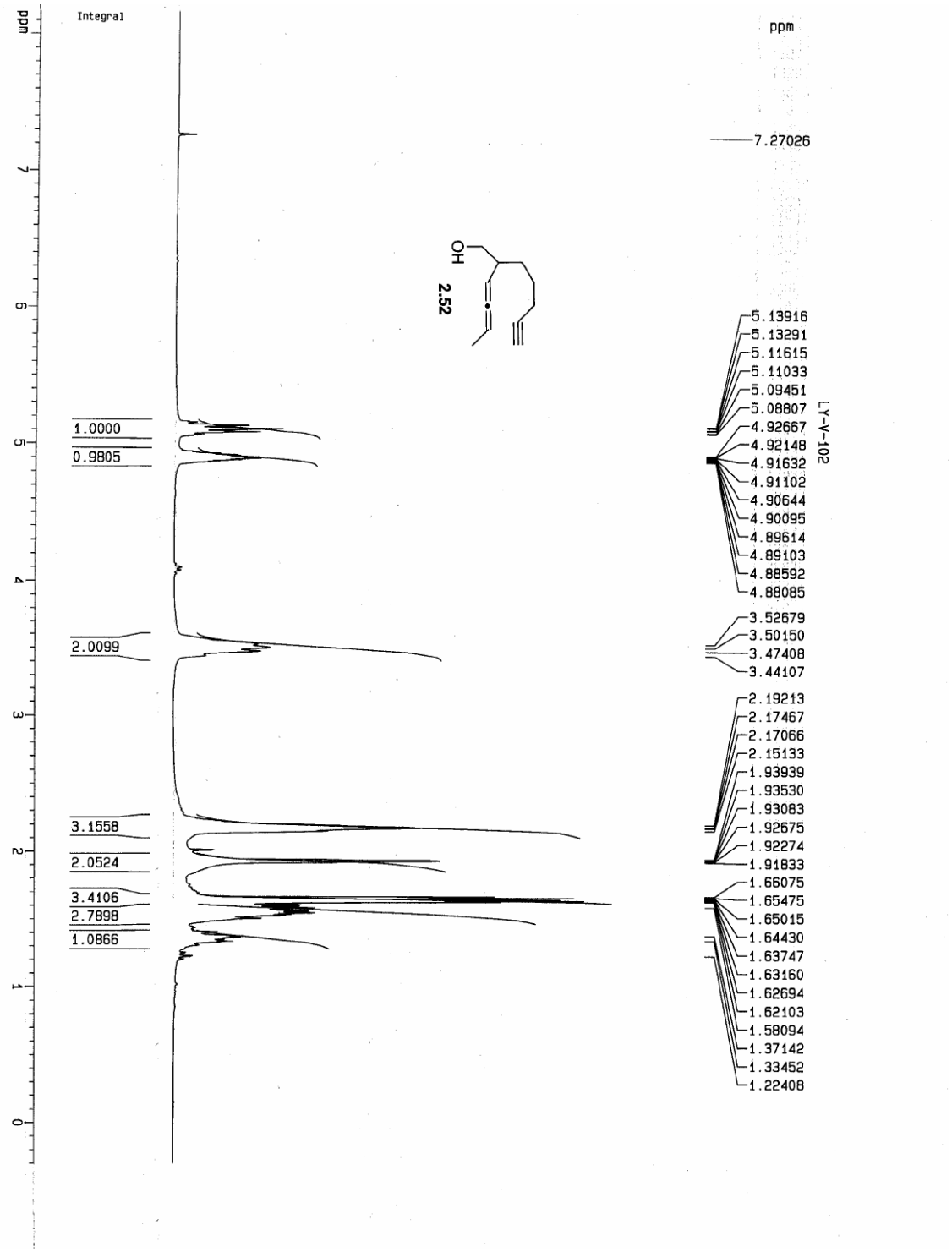
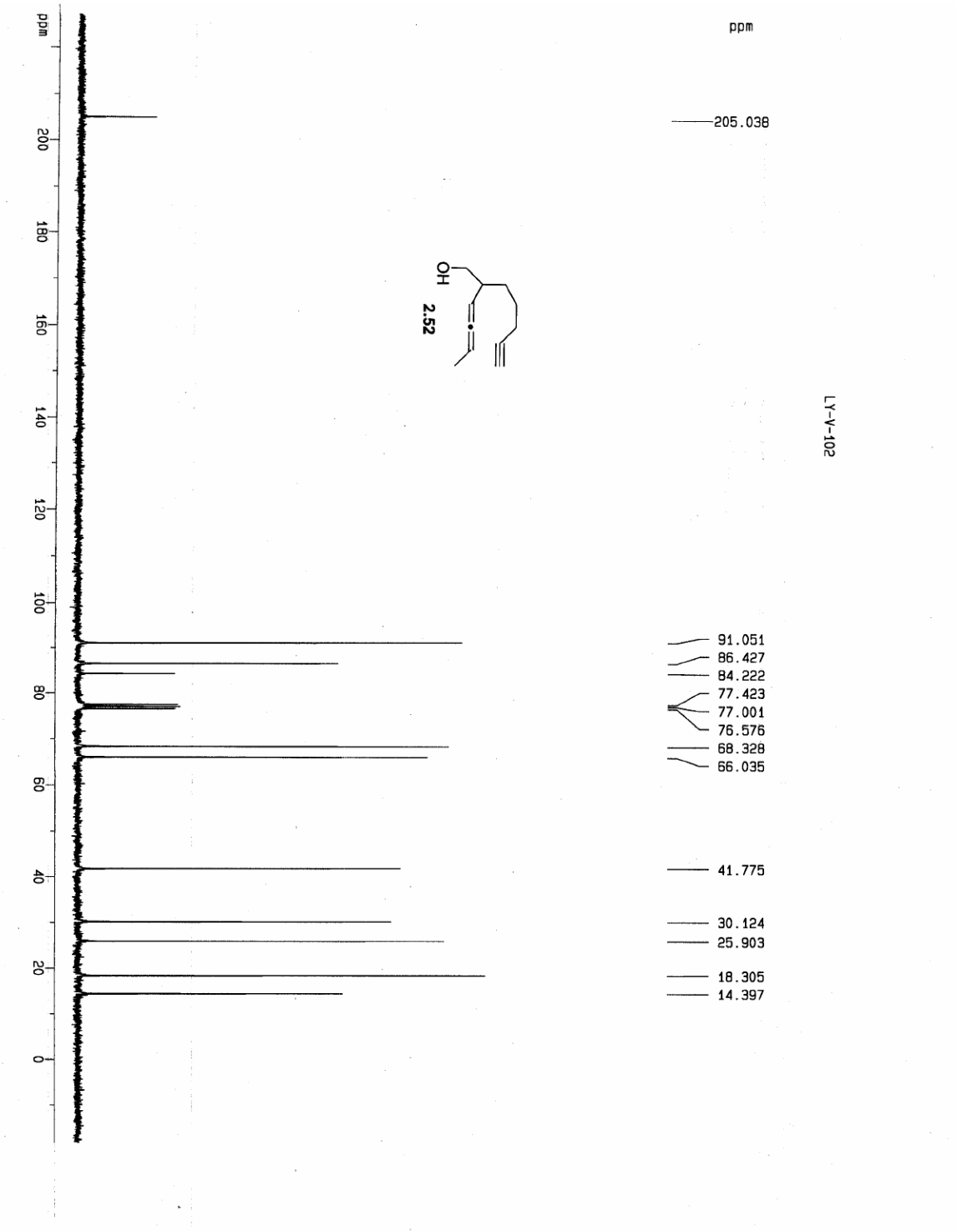
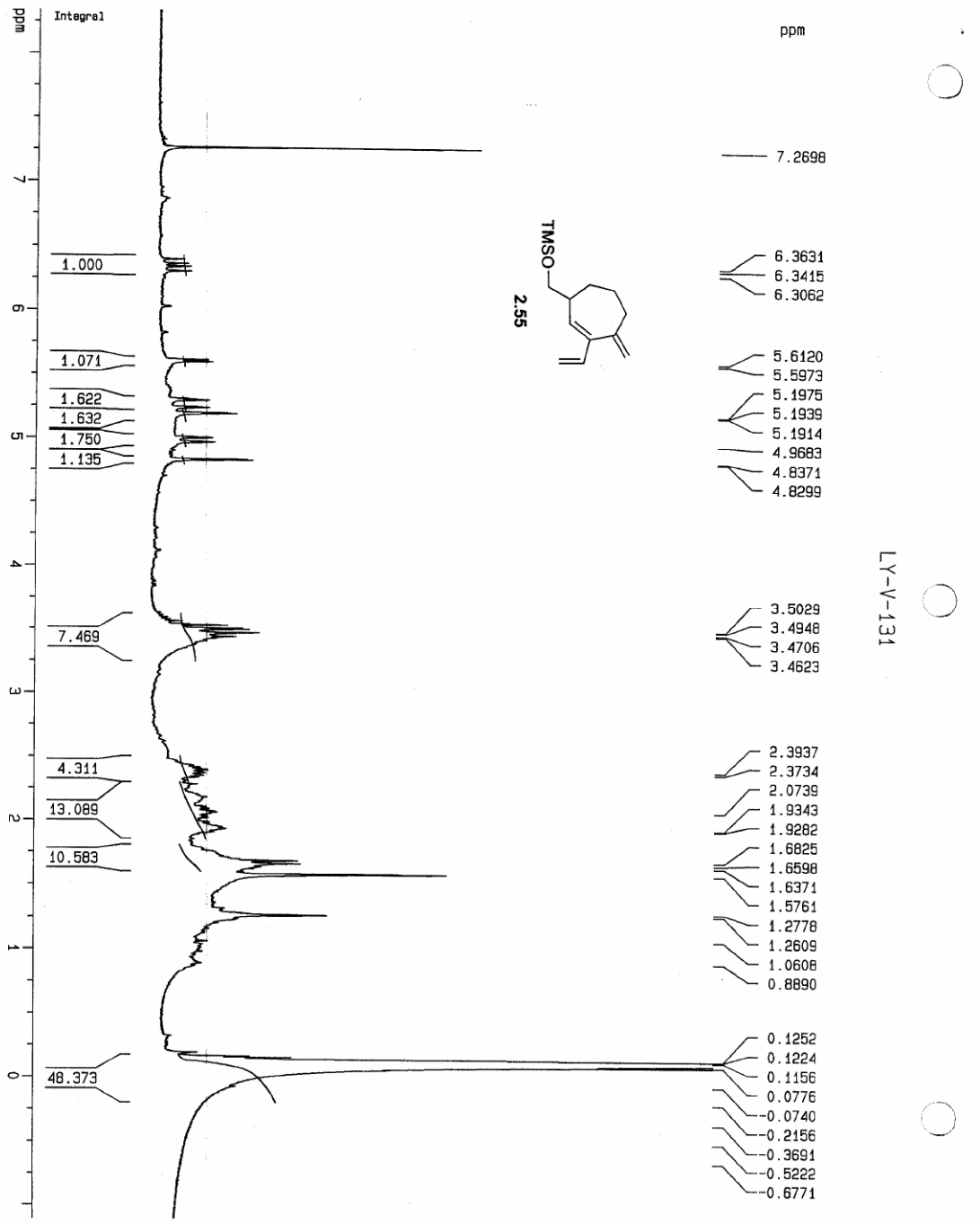
82.459
77.778
77.353
76.930
73.082
68.932
60.136
33.906
28.009
24.131
21.483
18.353
2.51
LY-X-98


ppm
Integral
OH
2.52
ppm
7.27026
5.13916
5.13291
5.11615
5.11033
5.09451
5.08807
4.92667
4.92148
4.91632
4.91102
4.90644
4.90095
4.89614
4.89103
4.88592
4.88085
3.52679
3.50150
3.47408
3.44107
2.19213
2.17467
2.17066
2.15133
1.93939
1.93530
1.93083
1.92675
1.92274
1.91833
1.66075
1.65475
1.65015
1.64430
1.63747
1.63160
1.62694
1.62103
1.58094
1.37142
1.33452
1.22408
LY-V-102
1.0000
0.9805
2.0099
3.1558
2.0524
3.4106
2.7898
1.0866


ppm
205.038
OH
2.52
91.051
86.427
84.222
77.423
77.001
76.576
68.328
66.035
41.775
30.124
25.903
18.305
14.397
LY-V-102


ppm
Integral
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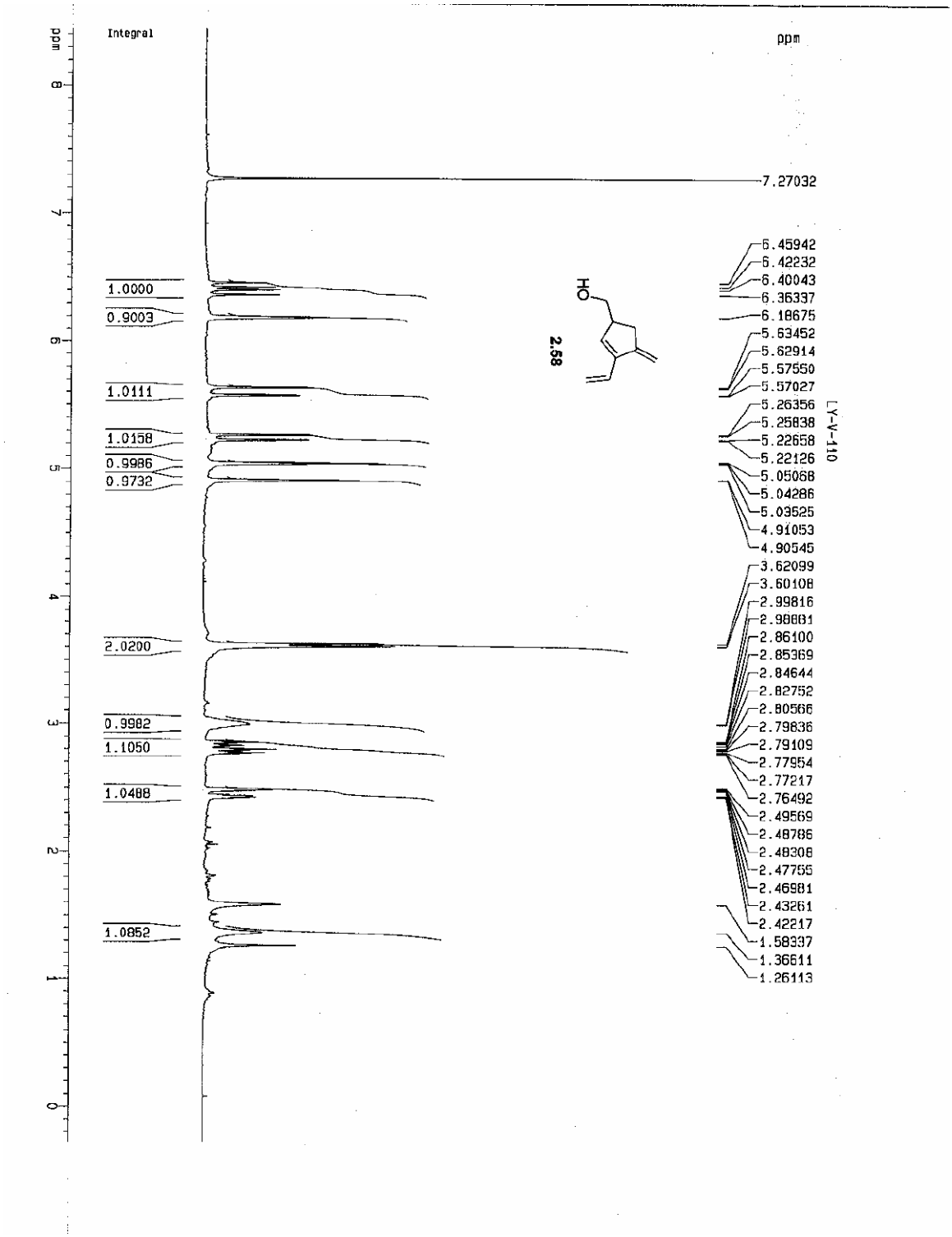
1.071
1.622
1.632
1.750
1.135
7.469
4.311
13.089
10.583
48.373
TMSO
2.55
ppm
7.2698
6.3631
6.3415
6.3062
5.6120
5.5973
5.1975
5.1939
5.1914
4.9683
4.8371
4.8299
3.5029
3.4948
3.4706
3.4623
2.3937
2.3734
2.0739
1.9343
1.9282
1.6825
1.6598
1.6371
1.5761
1.2778
1.2609
1.0608
0.8890
0.1252
0.1224
0.1156
0.0776
-0.0740
-0.2156
-0.3691
-0.5222
-0.6771
LY-V-131


Integral
ppm
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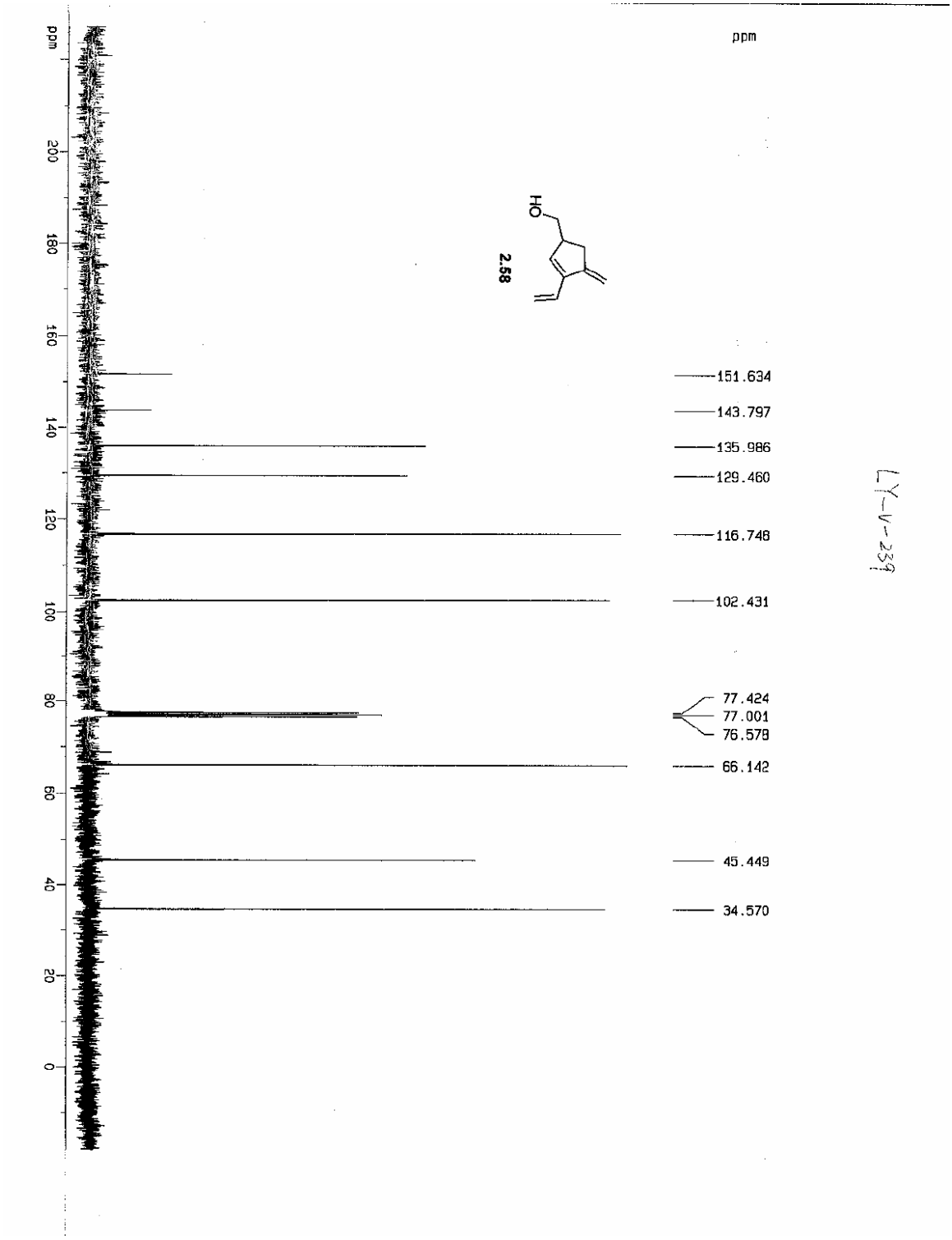
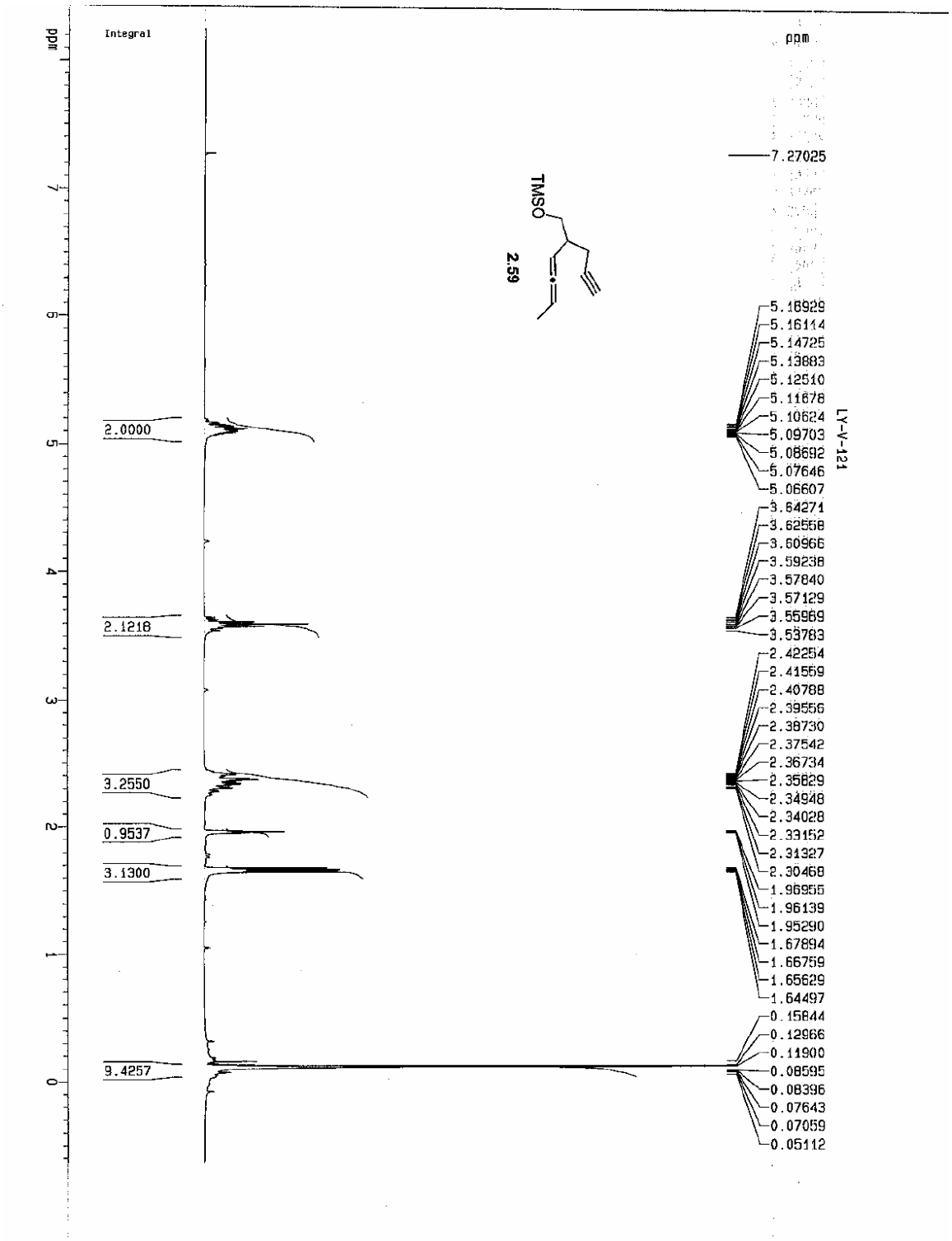
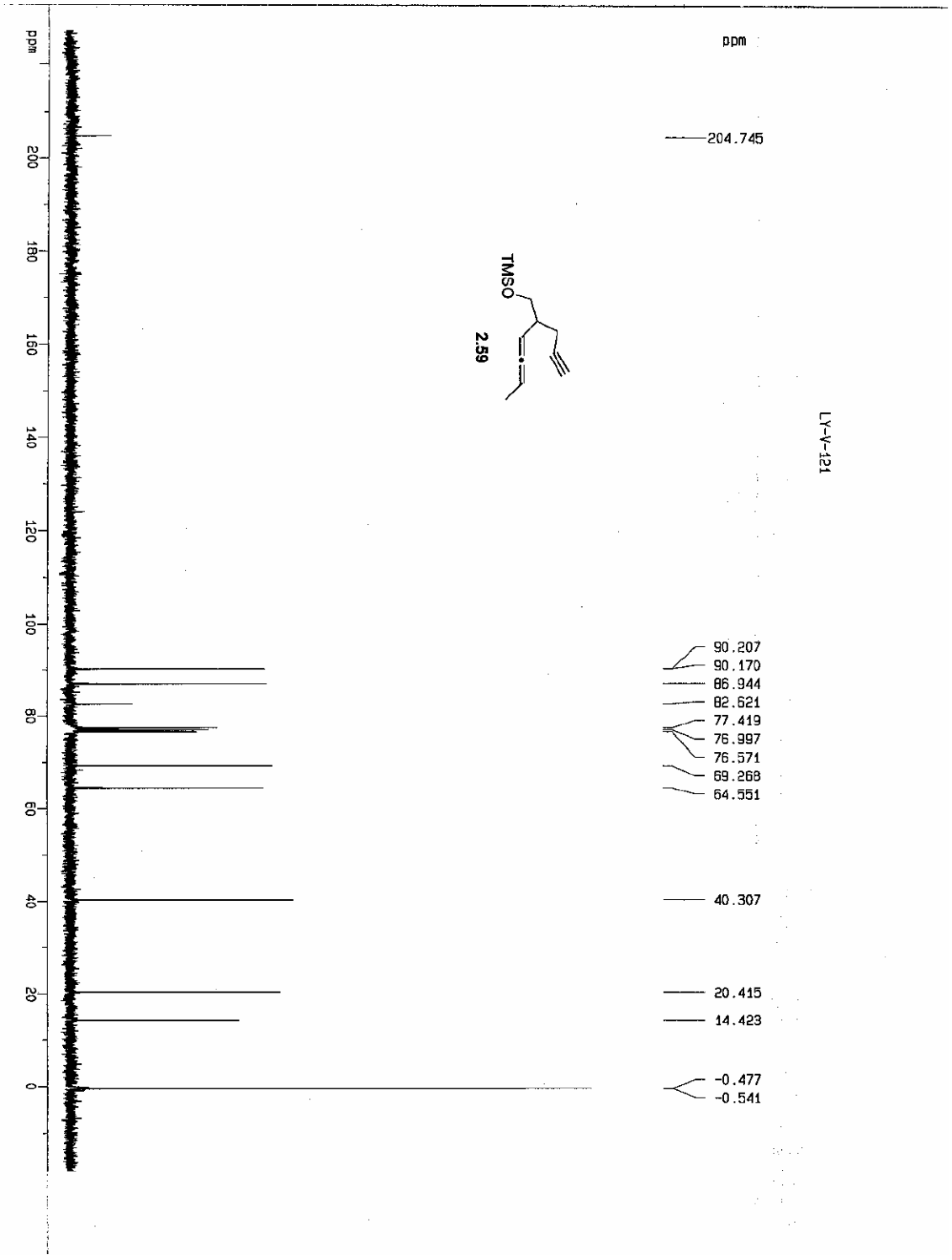
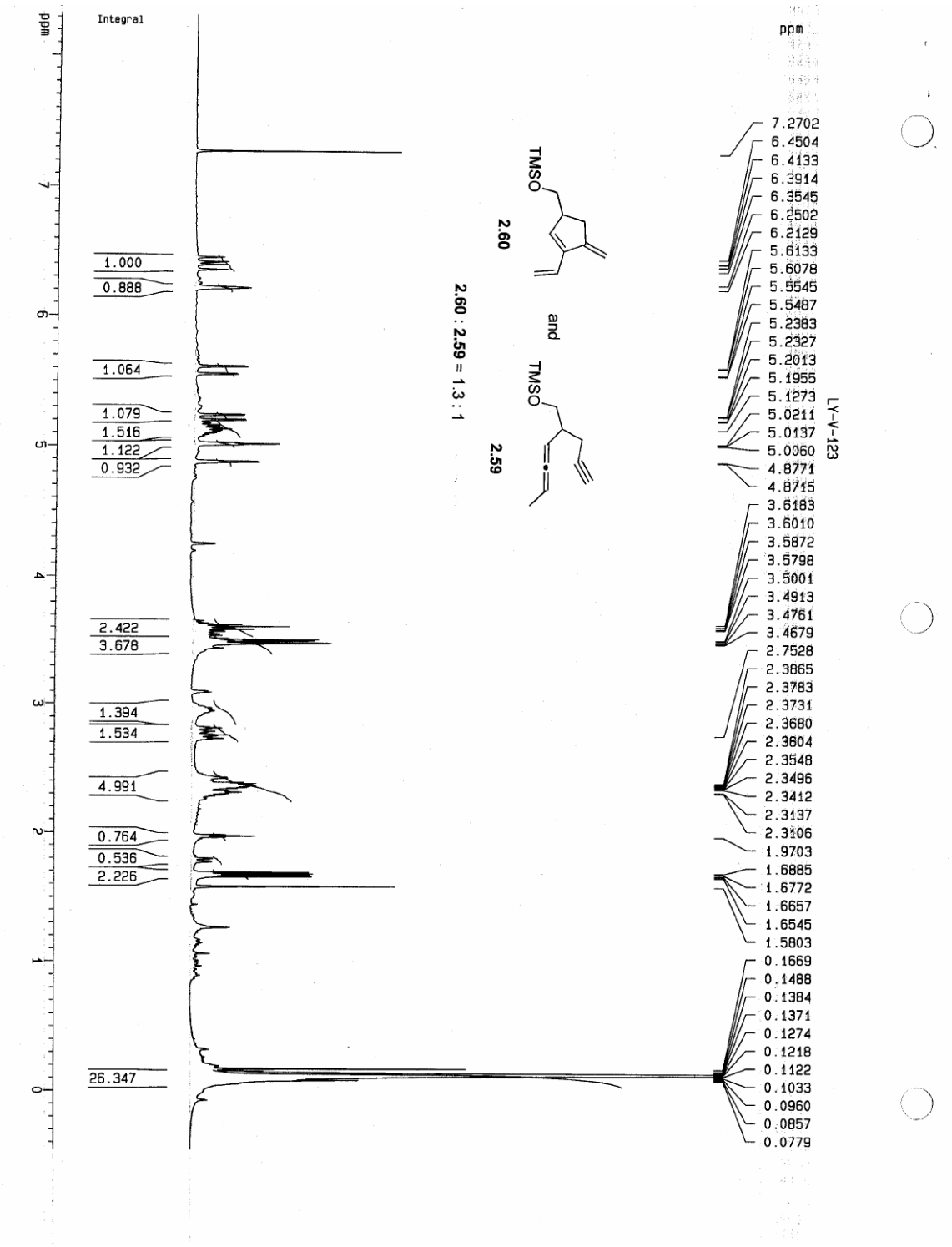
6.45942
6.42232
6.40043
6.36337
6.18675
5.63452
5.62914
5.57550
5.57027
5.26356
5.25838
5.22658
5.22126
5.05068
5.04286
5.03525
4.91053
4.90545
3.62099
3.60108
2.99816
2.98881
2.86100
2.85369
2.84644
2.82752
2.80566
2.79836
2.79109
2.77954
2.77217
2.76492
2.49569
2.48786
2.48308
2.47755
2.46981
2.43261
2.42217
1.58337
1.36611
1.26113
1.0000
0.9009
1.0111
1.0158
0.9986
0.9732
2.0200
0.9982
1.1050
1.0488
1.0852
2.58
HO
LY-V-110

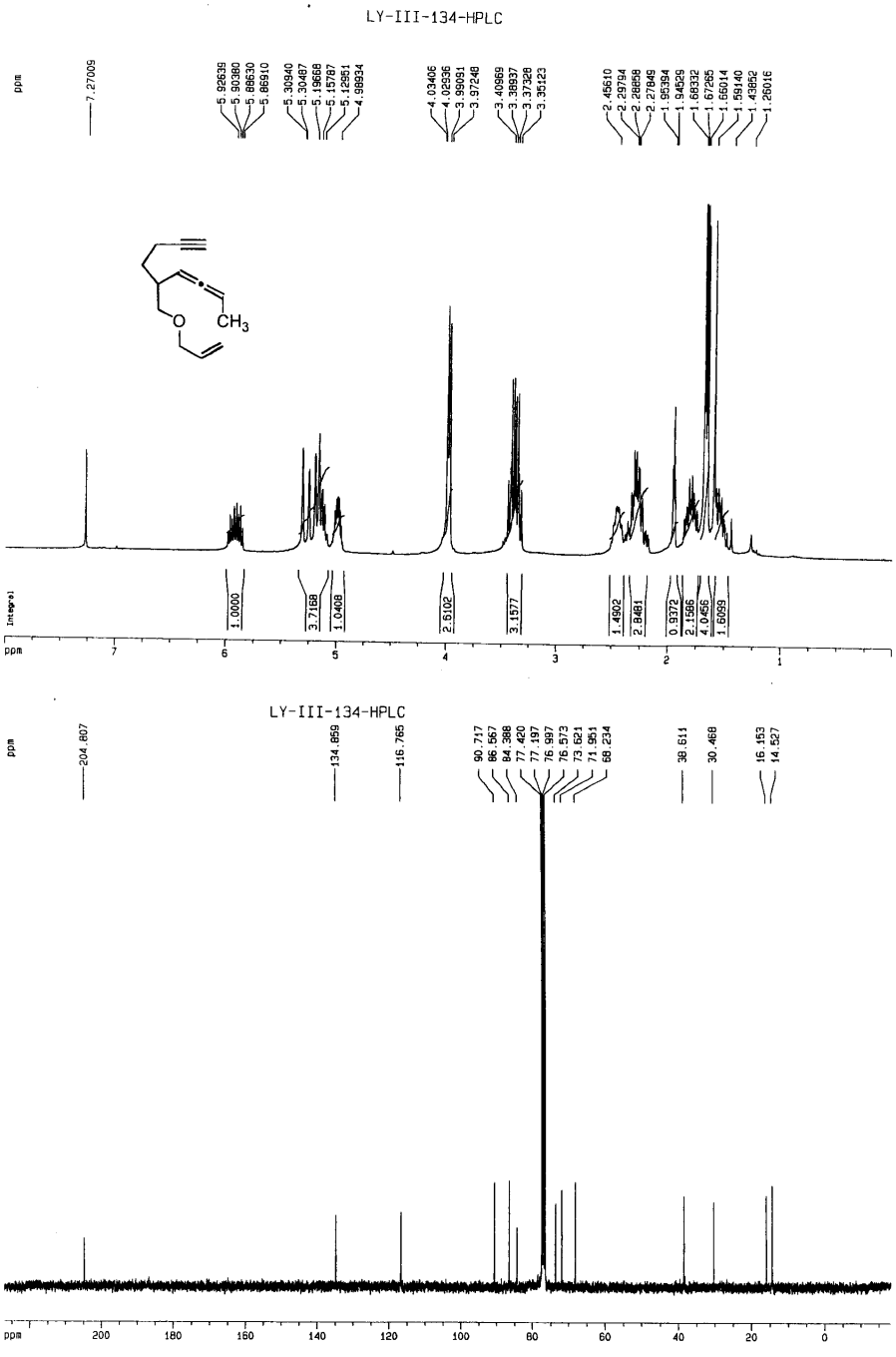

ppm
200
180
160
140
120
100
80
60
40
20
0
HO
2.58
151.634
143.797
135.986
129.460
116.748
102.431
77.424
77.001
76.578
66.142
45.449
34.570
LY-V-239


Integral
ppm
TMSO
2.59
7.27025
5.18929
5.16114
5.14725
5.13883
5.12510
5.11678
5.10624
5.09703
5.08692
5.07646
5.06607
3.64271
3.62558
3.60966
3.59238
3.57840
3.57129
3.55989
3.53783
2.42254
2.41559
2.40788
2.39556
2.38730
2.37542
2.36734
2.35829
2.34948
2.34028
2.33152
2.31327
2.30468
1.96955
1.96139
1.95290
1.67894
1.66759
1.65629
1.64497
0.15844
0.12966
0.11900
0.08595
0.08396
0.07643
0.07059
0.05112
2.0000
2.1218
3.2550
0.9537
3.1300
9.4257
LY-V-121

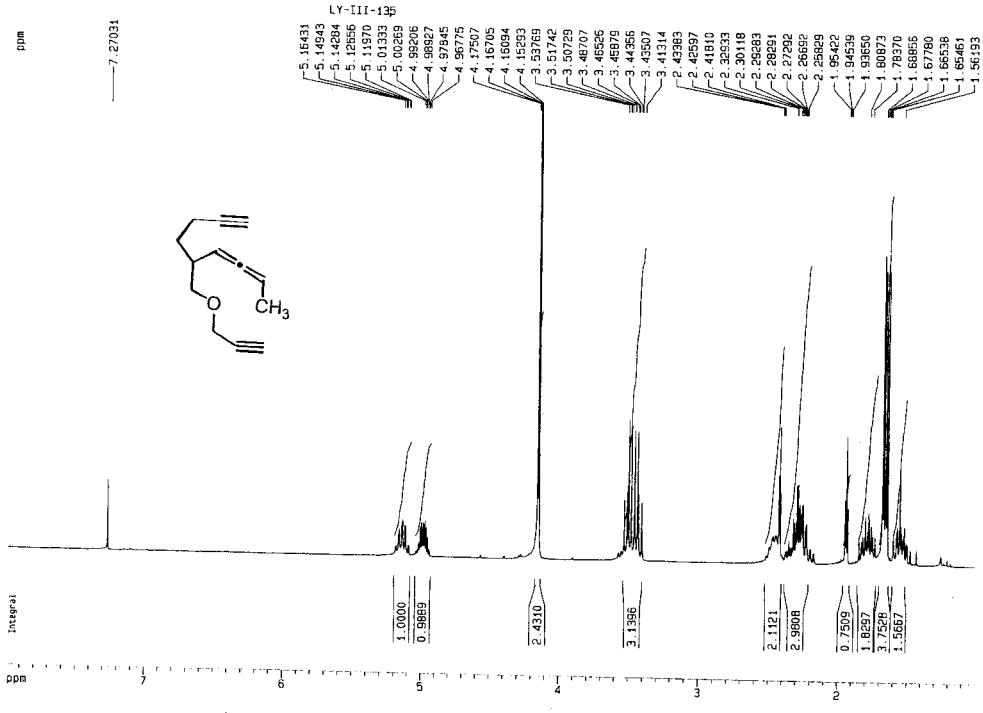

ppm
204.745
TMSO
2.59
LY-V-121
90.207
90.170
86.944
82.621
77.419
76.997
76.571
69.268
64.551
40.307
20.415
14.423
-0.477
-0.541

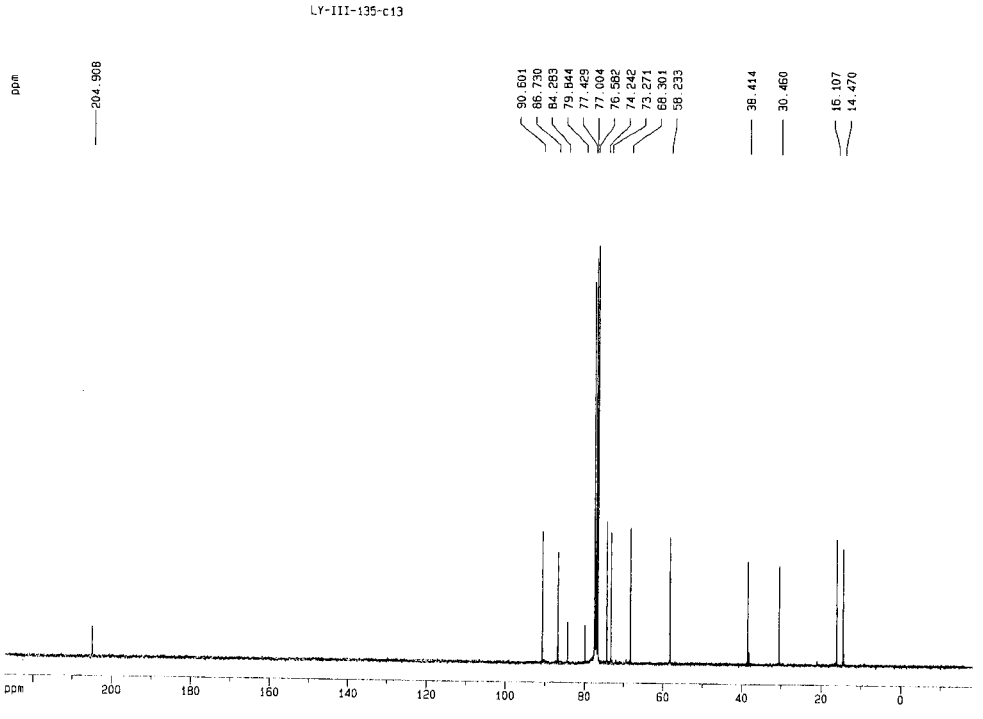

Integral
ppm
1.000
0.888
1.064
1.079
1.516
1.122
0.932
2.422
3.678
1.394
1.534
4.991
0.764
0.536
2.226
26.347
TMSO
2.60
and
TMSO
2.59
2.60 : 2.59 = 1.3 : 1
ppm
7.2702
6.4504
6.4133
6.3914
6.3545
6.2502
6.2129
5.6133
5.6078
5.5545
5.5487
5.2383
5.2327
5.2013
5.1955
5.1273
5.0211
5.0137
5.0060
4.8771
4.8715
3.6183
3.6010
3.5872
3.5798
3.5001
3.4913
3.4761
3.4679
2.7528
2.3865
2.3783
2.3731
2.3680
2.3604
2.3548
2.3496
2.3412
2.3137
2.3106
1.9703
1.6885
1.6772
1.6657
1.6545
1.5803
0.1669
0.1488
0.1384
0.1371
0.1274
0.1218
0.1122
0.1033
0.0960
0.0857
0.0779
LY-V-123

Compound 3.31

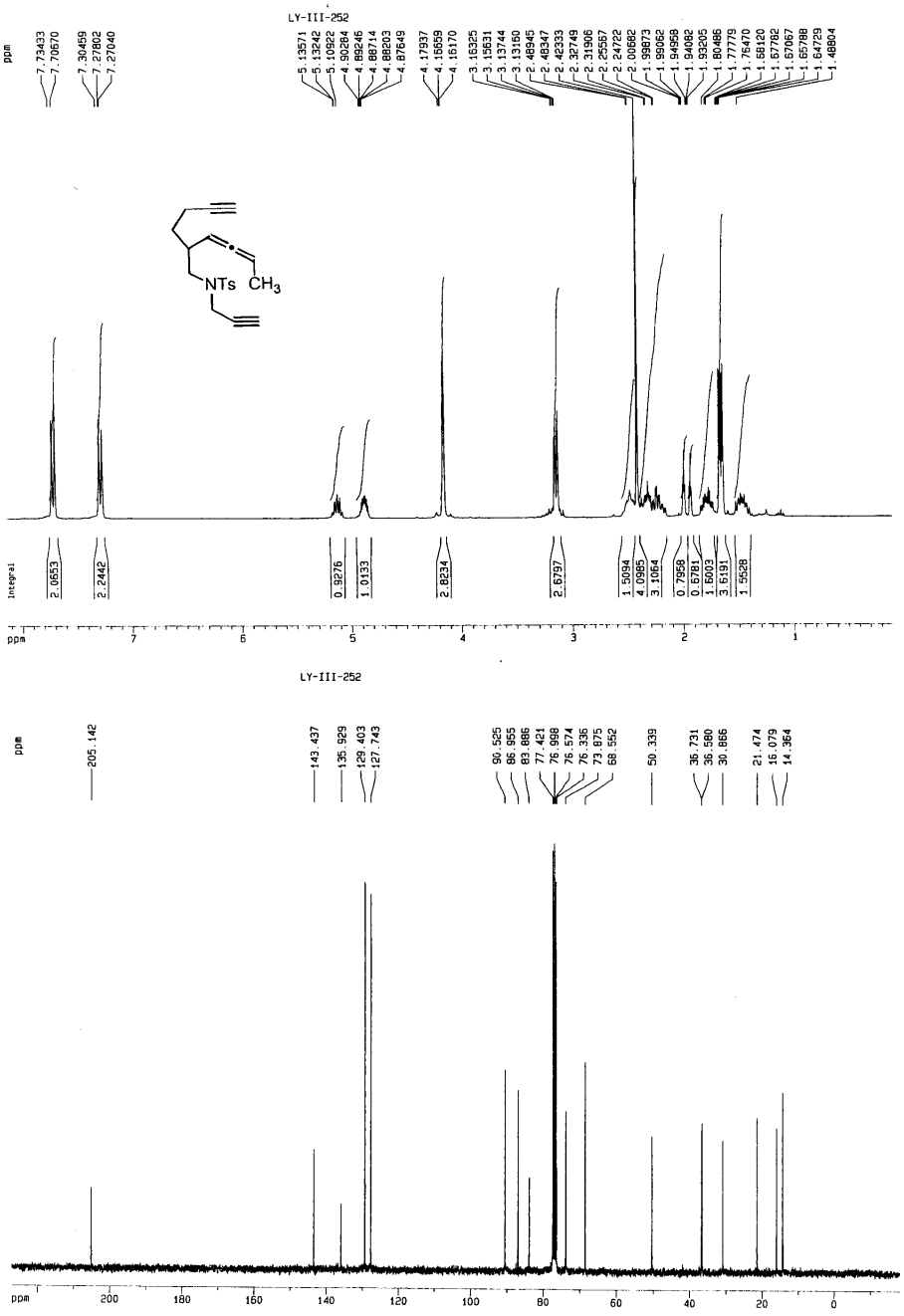


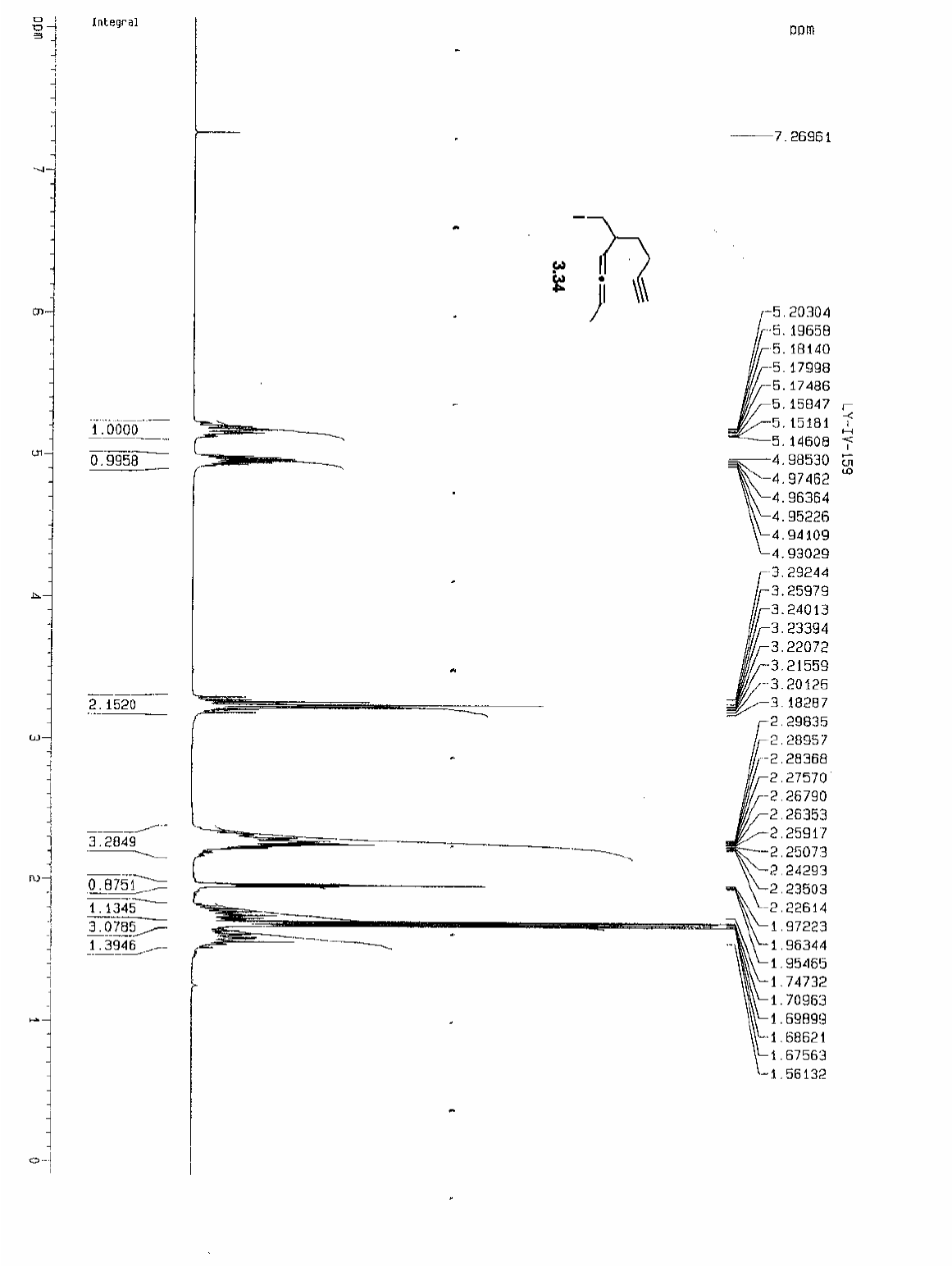
Compound 3.32





Compound 3.33




Integral
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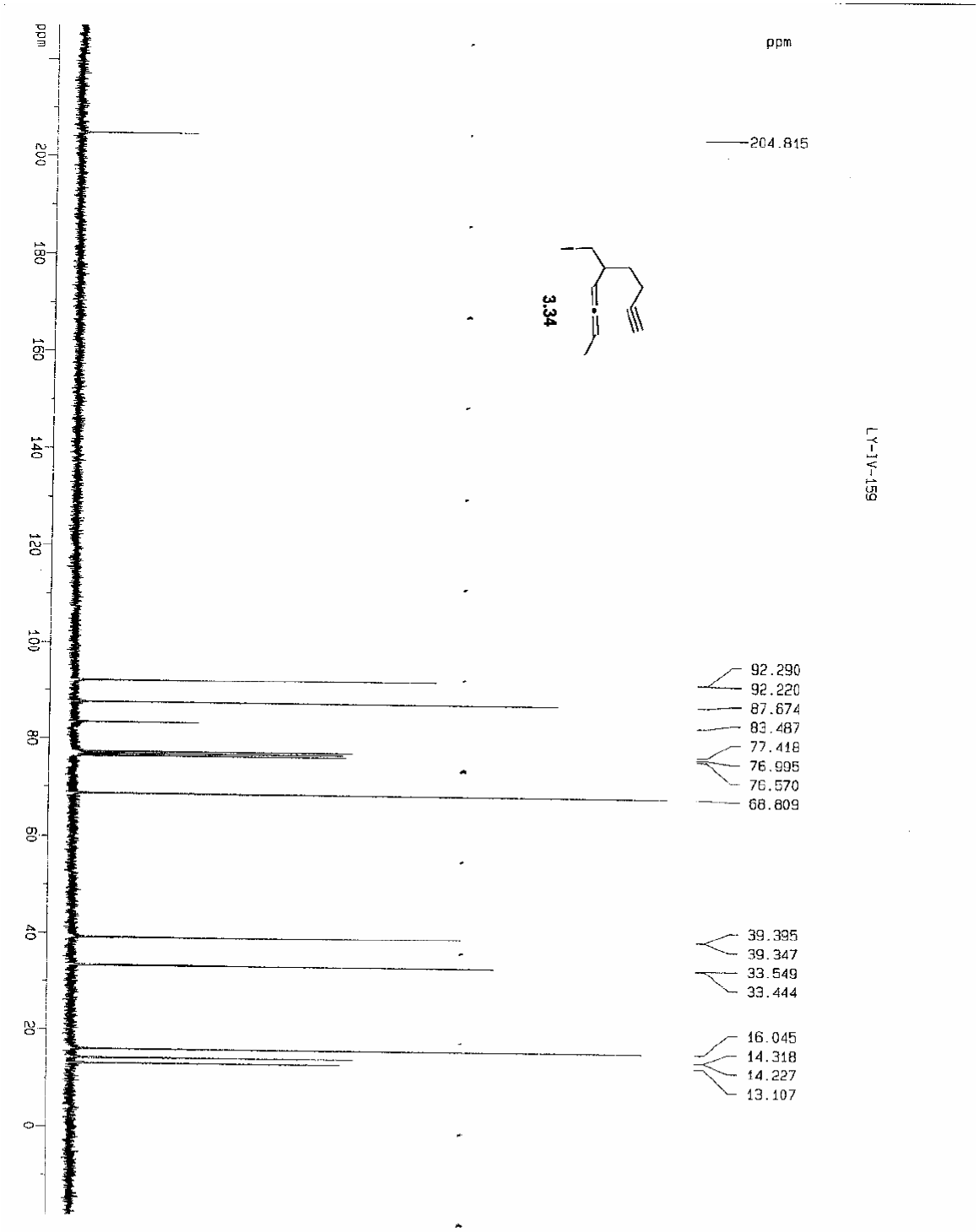
3.34
5.20304
5.19658
5.18140
5.17998
5.17486
5.15847
5.15181
5.14608
4.98530
4.97462
4.96364
4.95226
4.94109
4.93029
3.29244
3.25979
3.24013
3.23394
3.22072
3.21559
3.20126
3.18287
2.29835
2.28957
2.28368
2.27570
2.26790
2.26353
2.25917
2.25073
2.24293
2.23503
2.22614
1.97223
1.96344
1.95465
1.74732
1.70963
1.69899
1.68621
1.67563
1.56132
1.0000
0.9958
2.1520
3.2849
0.8751
1.1345
3.0785
1.3946
LY-IV-159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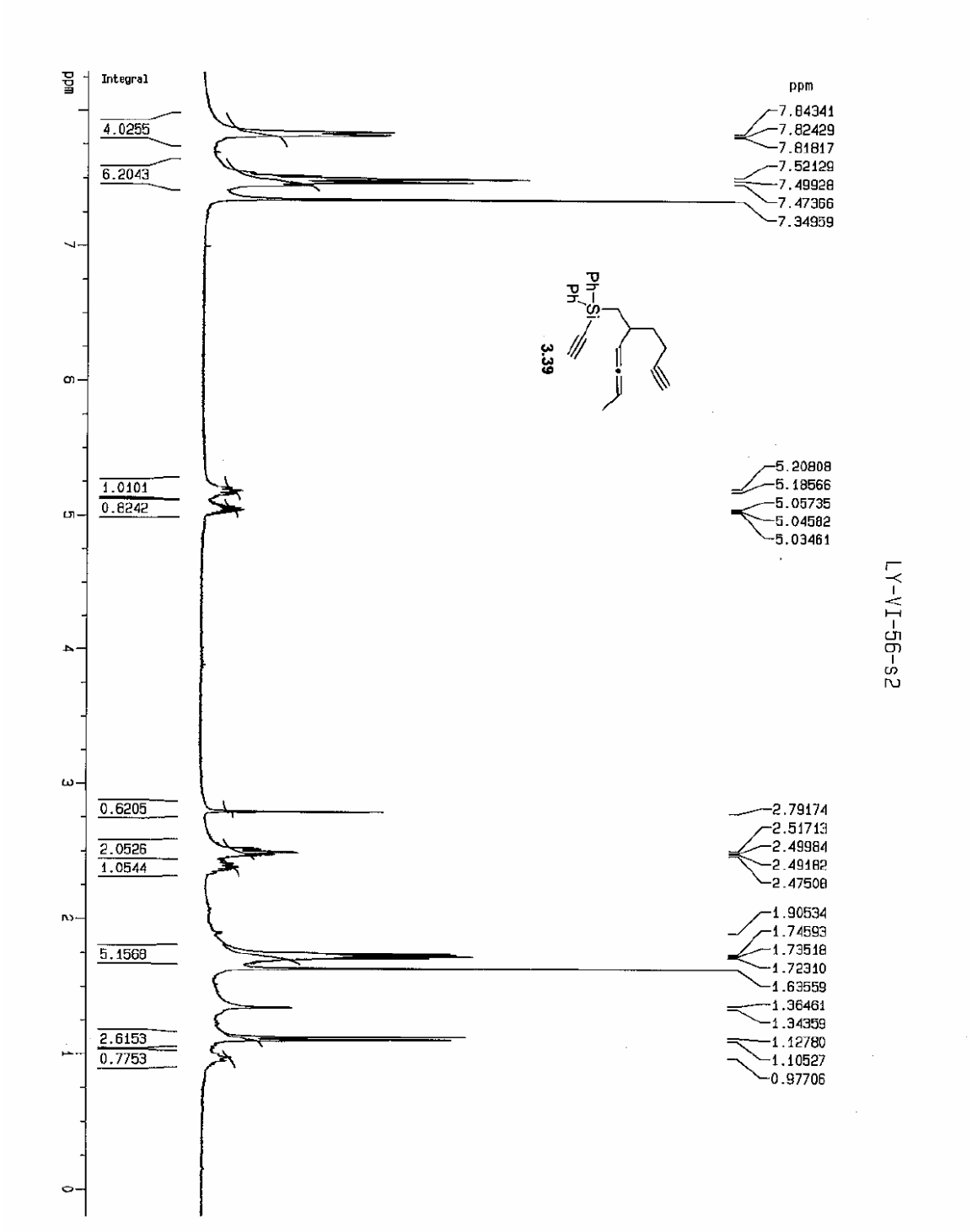
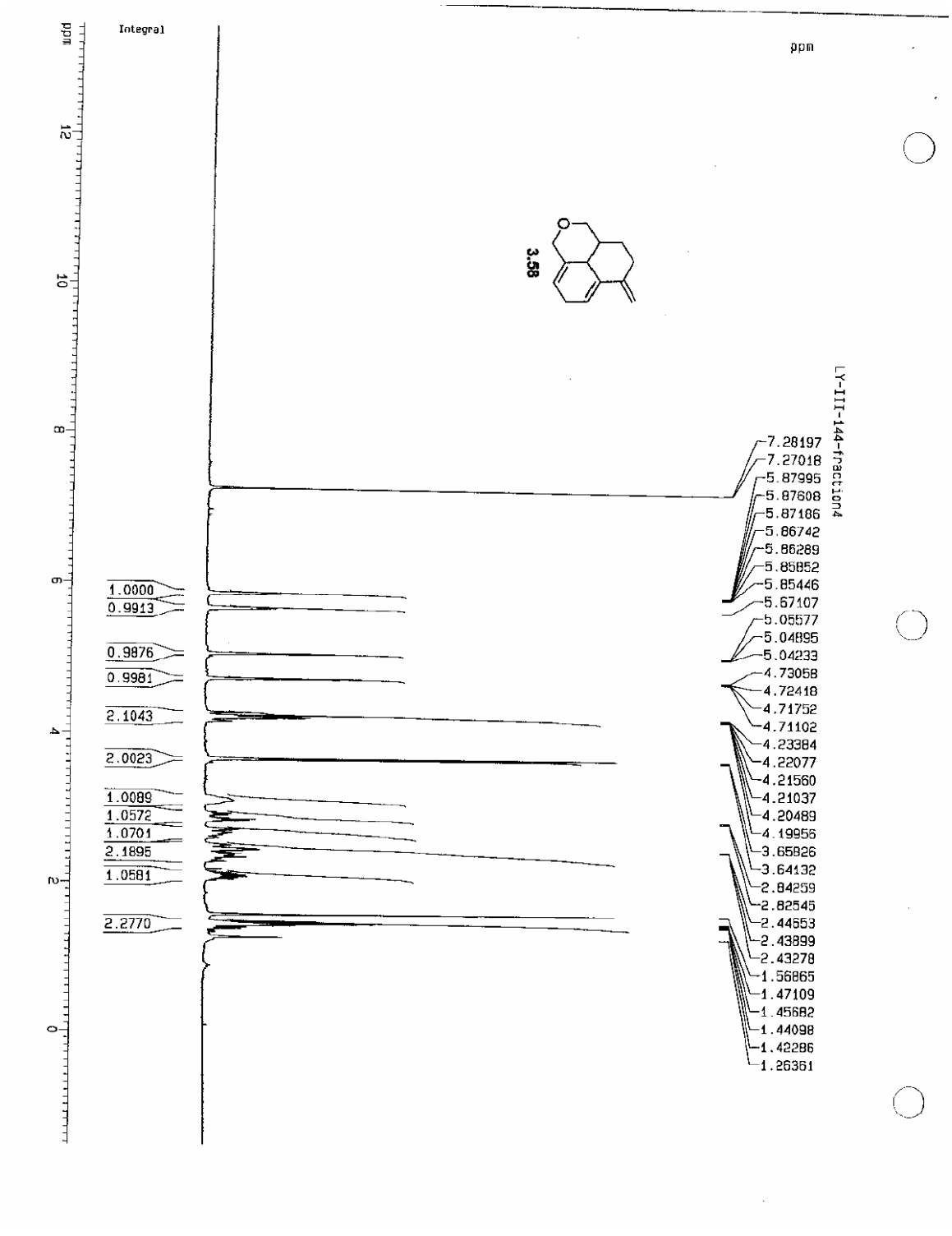
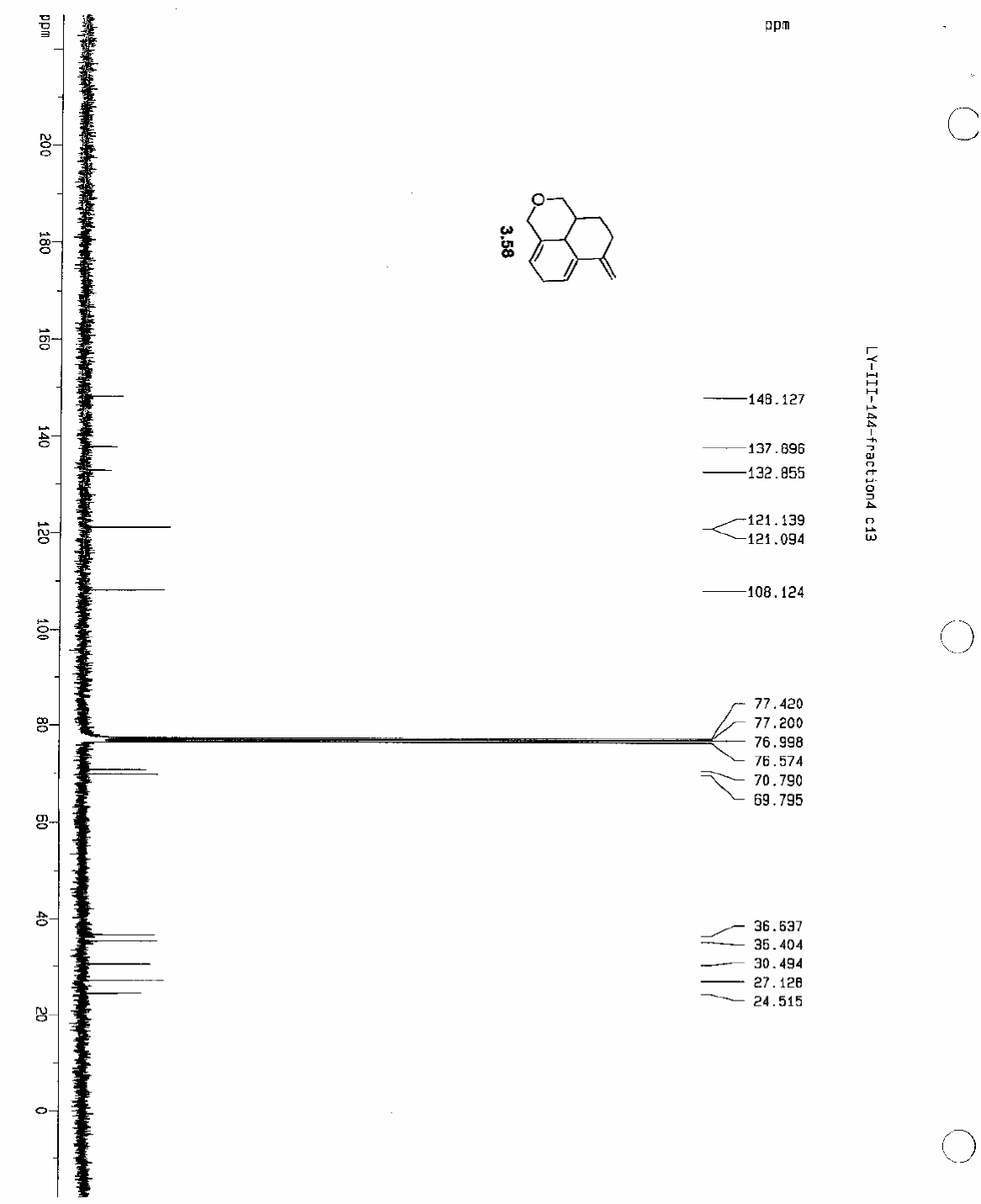
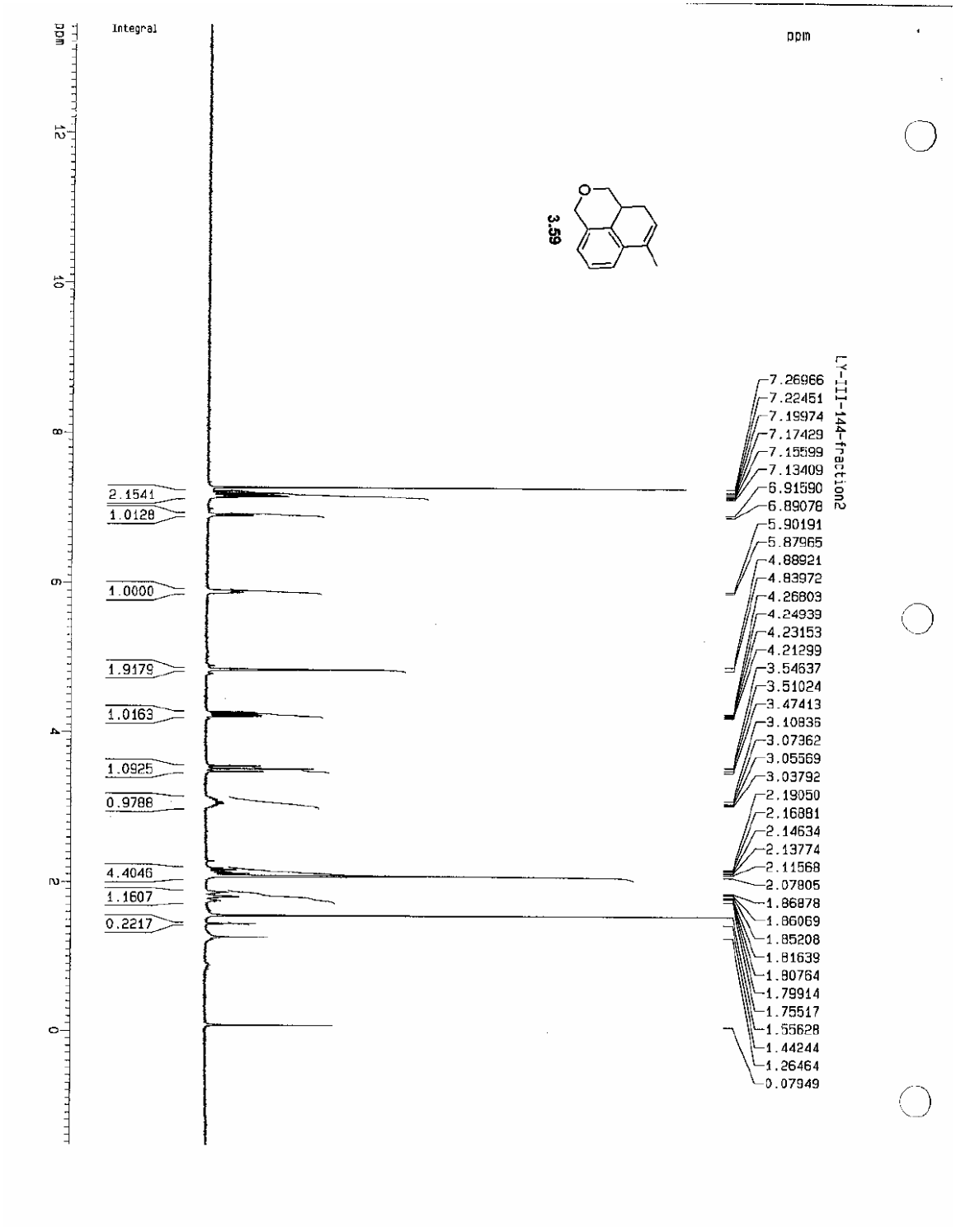
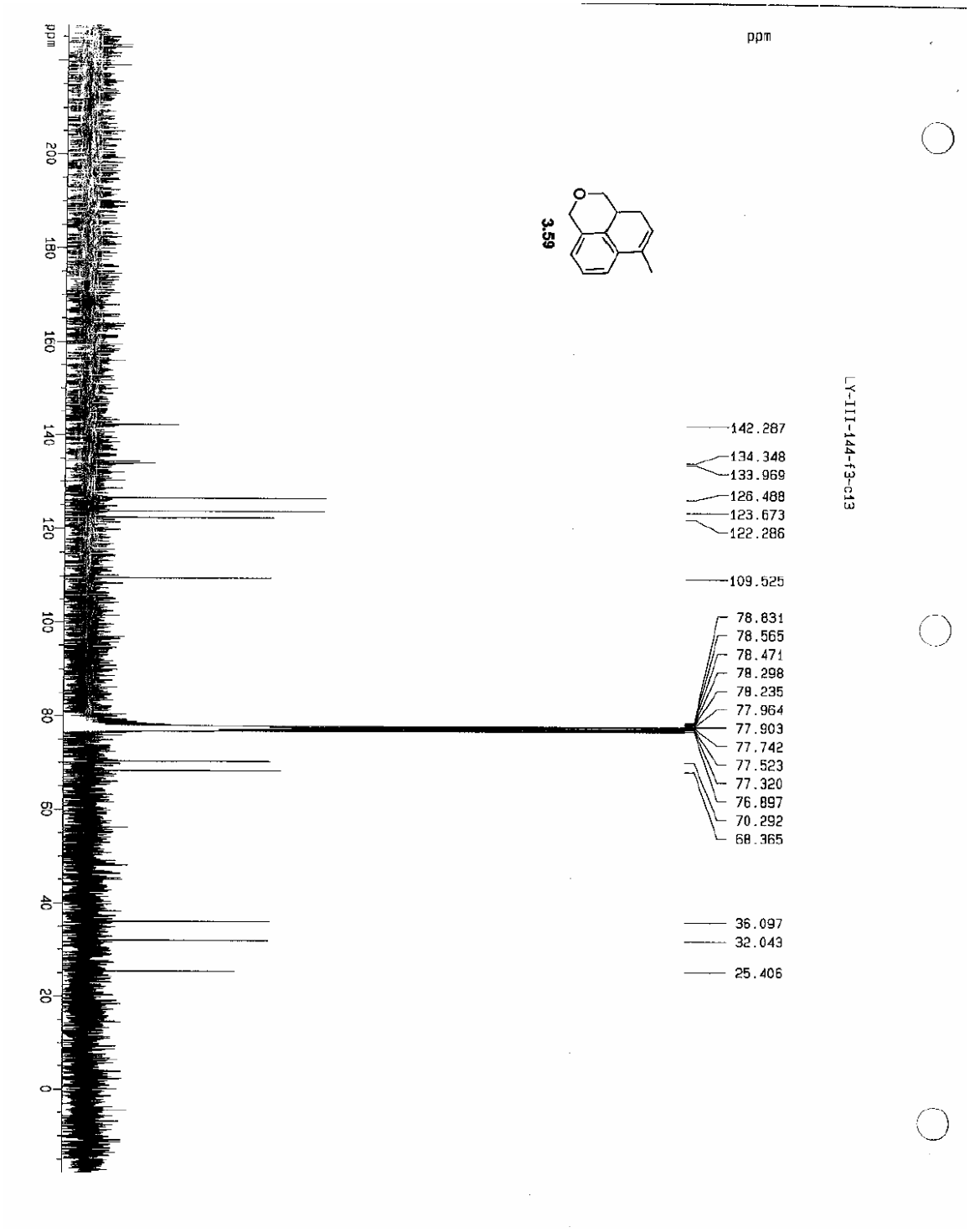
204.815
3.34
92.290
92.220
87.674
83.487
77.418
76.995
76.570
68.809
39.395
39.347
33.549
33.444
16.045
14.318
14.227
13.107
LY-IV-159

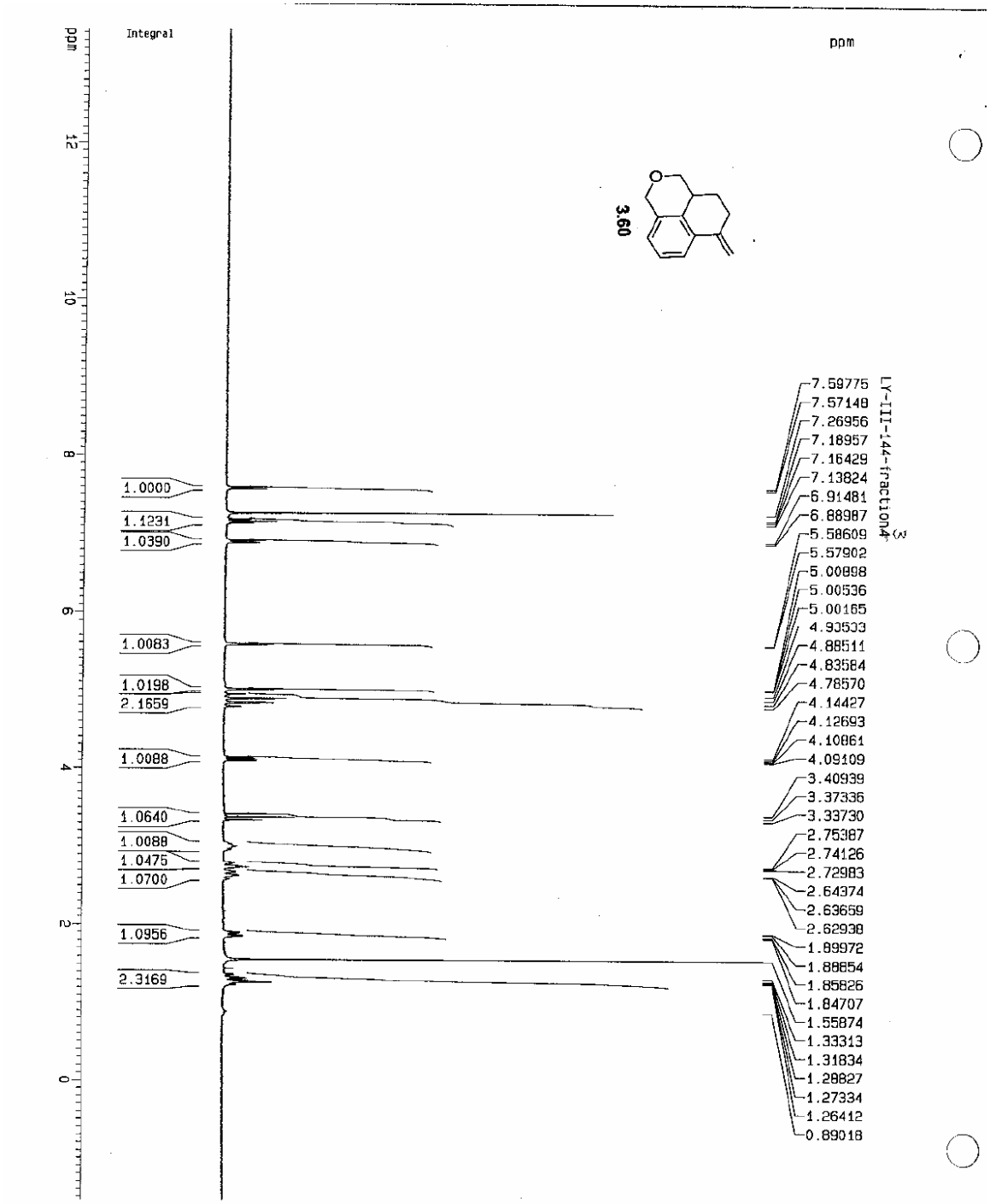

ppm
Integral
4.0255
6.2043
1.0101
0.8242
0.6205
2.0526
1.0544
5.1568
2.6153
0.7753
7.84341
7.82429
7.81817
7.52129
7.49928
7.47366
7.34959
5.20808
5.18566
5.05735
5.04582
5.03461
2.79174
2.51713
2.49984
2.49182
2.47508
1.90534
1.74593
1.73518
1.72310
1.63559
1.36461
1.34359
1.12780
1.10527
0.97706
Ph
Ph
Si
3.39
LY-VI-56-S2

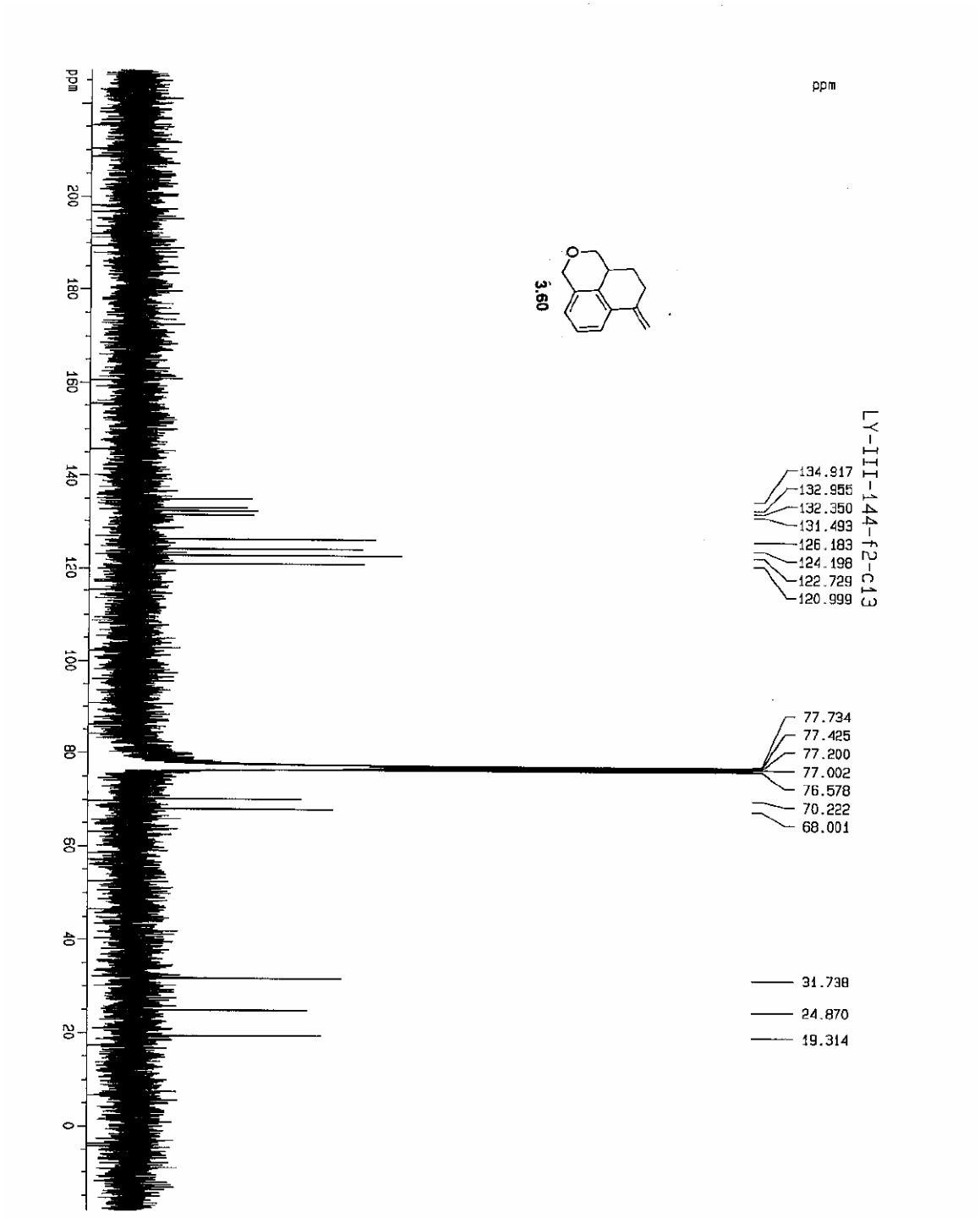

Integral
ppm
3.58
LY-III-144-fraction4
1.0000
0.9913
0.9876
0.9981
2.1043
2.0023
1.0089
1.0572
1.0701
2.1895
1.0581
2.2770
7.28197
7.27018
5.87995
5.87608
5.87186
5.86742
5.86289
5.85852
5.85446
5.67107
5.05577
5.04895
5.04233
4.73058
4.72418
4.71752
4.71102
4.23384
4.22077
4.21560
4.21037
4.20489
4.19956
3.65826
3.64132
2.84259
2.82545
2.44653
2.43899
2.43278
1.56865
1.47109
1.45682
1.44098
1.42286
1.26361


ppm
200
180
160
140
120
100
80
60
40
20
0
ppm
3.58
148.127
137.696
132.855
121.139
121.094
108.124
77.420
77.200
76.998
76.574
70.790
69.795
36.637
36.404
30.494
27.128
24.515
LY-III-144-fraction4 c13

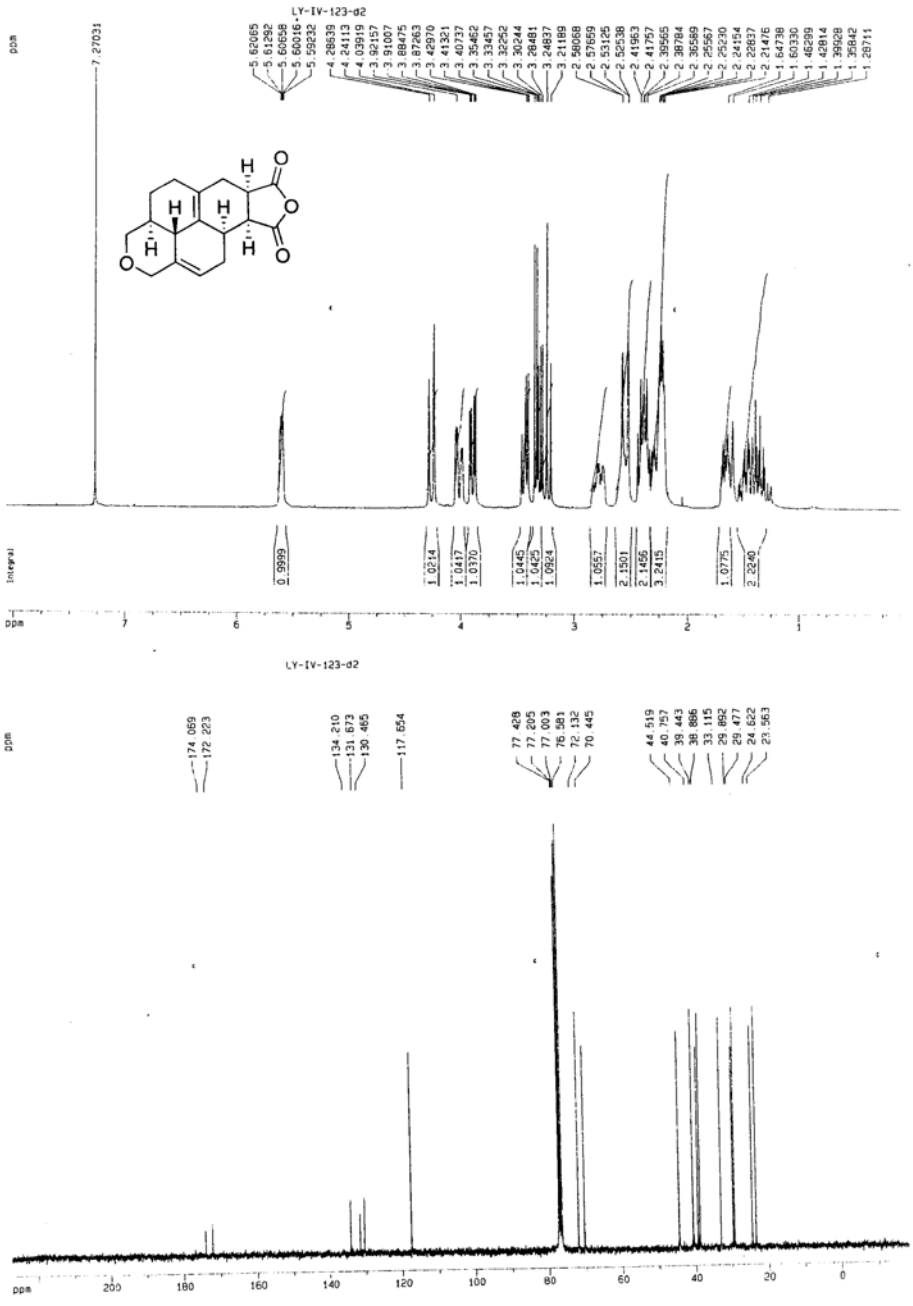

ppm
Integral
ppm
3.59
2.1541
1.0128
1.0000
1.9179
1.0163
1.0925
0.9788
4.4046
1.1607
0.2217
LY-III-144-fraction2
7.26966
7.22451
7.19974
7.17429
7.15599
7.13409
6.91590
6.89078
5.90191
5.87965
4.88921
4.83972
4.26803
4.24939
4.23153
4.21299
3.54637
3.51024
3.47413
3.10835
3.07362
3.05569
3.03792
2.19050
2.16881
2.14634
2.13774
2.11568
2.07805
1.86878
1.86069
1.85208
1.81639
1.80764
1.79914
1.75517
1.55628
1.44244
1.26464
0.07949


ppm
200
180
160
140
120
100
80
60
40
20
0
3.59
142.287
134.348
133.969
126.488
123.673
122.286
109.525
78.831
78.565
78.471
78.298
78.235
77.964
77.903
77.742
77.523
77.320
76.897
70.292
68.365
36.097
32.043
25.406
LY-III-144-f3-c13

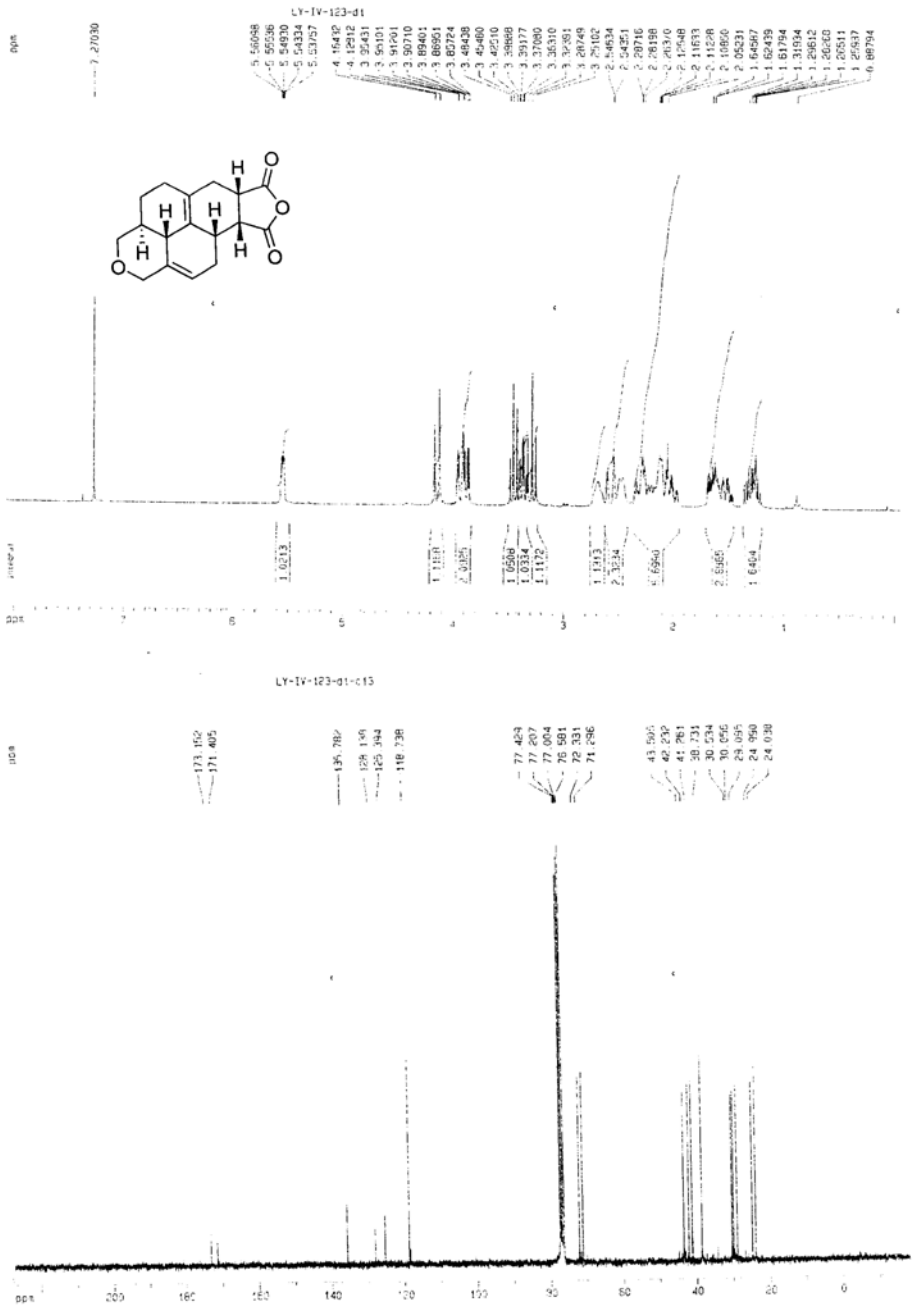

Integral
ppm
3.60
LY-III-144-fraction4
7.59775
7.57148
7.26956
7.18957
7.16429
7.13824
6.91481
6.88987
5.58609
5.57902
5.00898
5.00536
5.00165
4.90503
4.88511
4.83584
4.78570
4.14427
4.12693
4.10861
4.09109
3.40939
3.37336
3.33730
2.75387
2.74126
2.72983
2.64974
2.63659
2.62938
1.89972
1.88854
1.85826
1.84707
1.55874
1.33313
1.31834
1.28827
1.27334
1.26412
0.89018
1.0000
1.1231
1.0390
1.0083
1.0198
2.1659
1.0088
1.0640
1.0088
1.0475
1.0700
1.0956
2.3169


ppm
200
180
160
140
120
100
80
60
40
20
0
3.60
ppm
LY-III-144-f2-c13
134.917
132.955
132.350
131.493
126.183
124.198
122.729
120.999
77.734
77.425
77.200
77.002
76.578
70.222
68.001
31.738
24.870
19.314

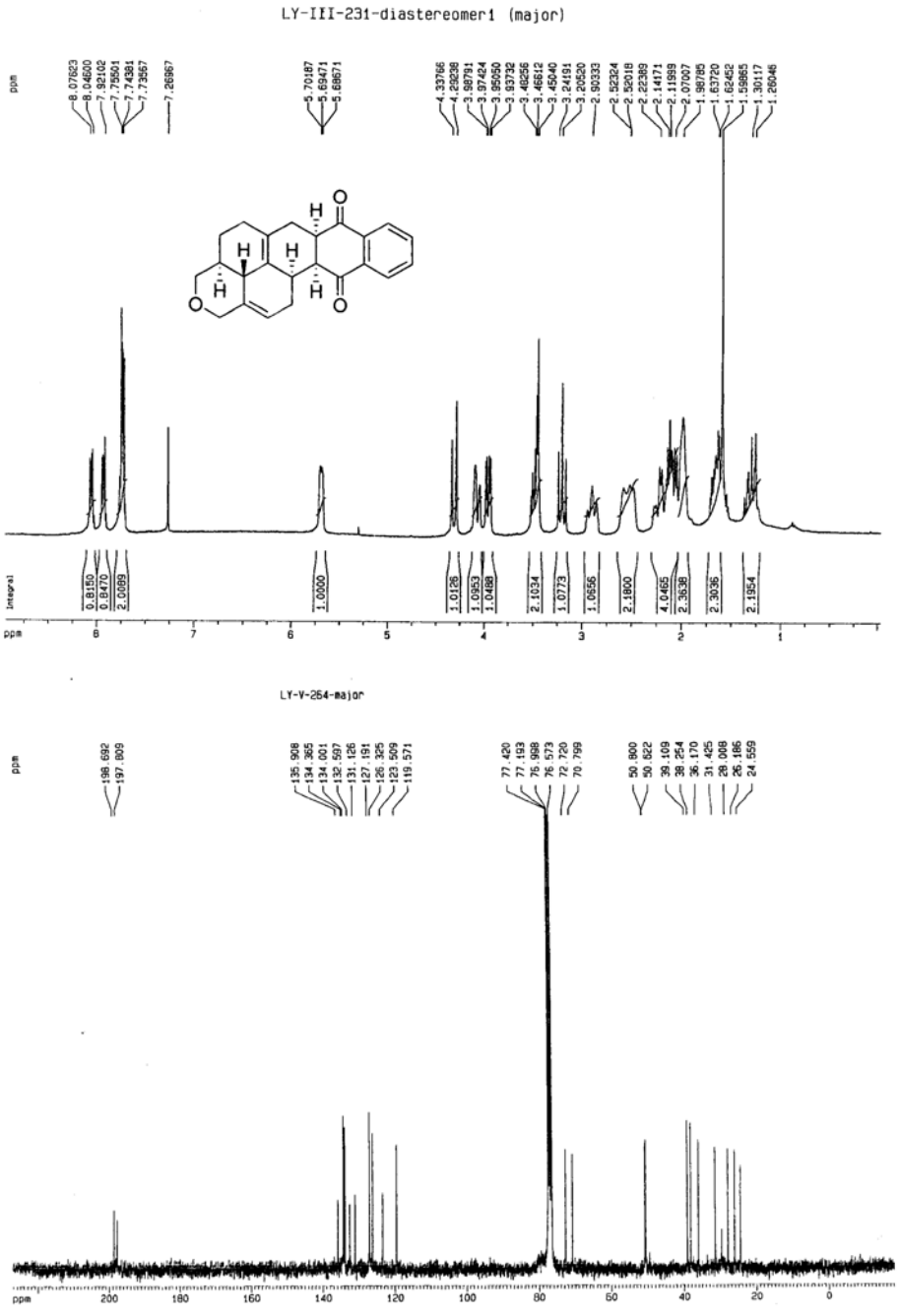
3.86a


LY-IV-123-d2
ppm
7.27031
5.62065
5.61292
5.60658
5.60016
5.59232
4.28639
4.24113
4.03919
3.92157
3.91007
3.88475
3.87263
3.42970
3.41321
3.40737
3.35462
3.33457
3.32252
3.30244
3.28481
3.24837
3.21189
2.58068
2.57659
2.53125
2.52538
2.41963
2.41757
2.39565
2.38784
2.36589
2.25567
2.25230
2.24154
2.22837
2.21476
1.64738
1.60330
1.46299
1.42814
1.39928
1.35842
1.28711
Integral
0.9999
1.0214
1.0417
1.0370
1.0445
1.0425
1.0924
1.0557
2.1501
2.1456
3.2415
1.0775
2.2240
ppm
LY-IV-123-d2
ppm
174.069
172.223
134.210
131.673
130.485
117.654
77.428
77.205
77.003
76.581
72.132
70.445
44.519
40.757
39.443
38.886
33.115
29.892
29.477
24.622
23.563
ppm

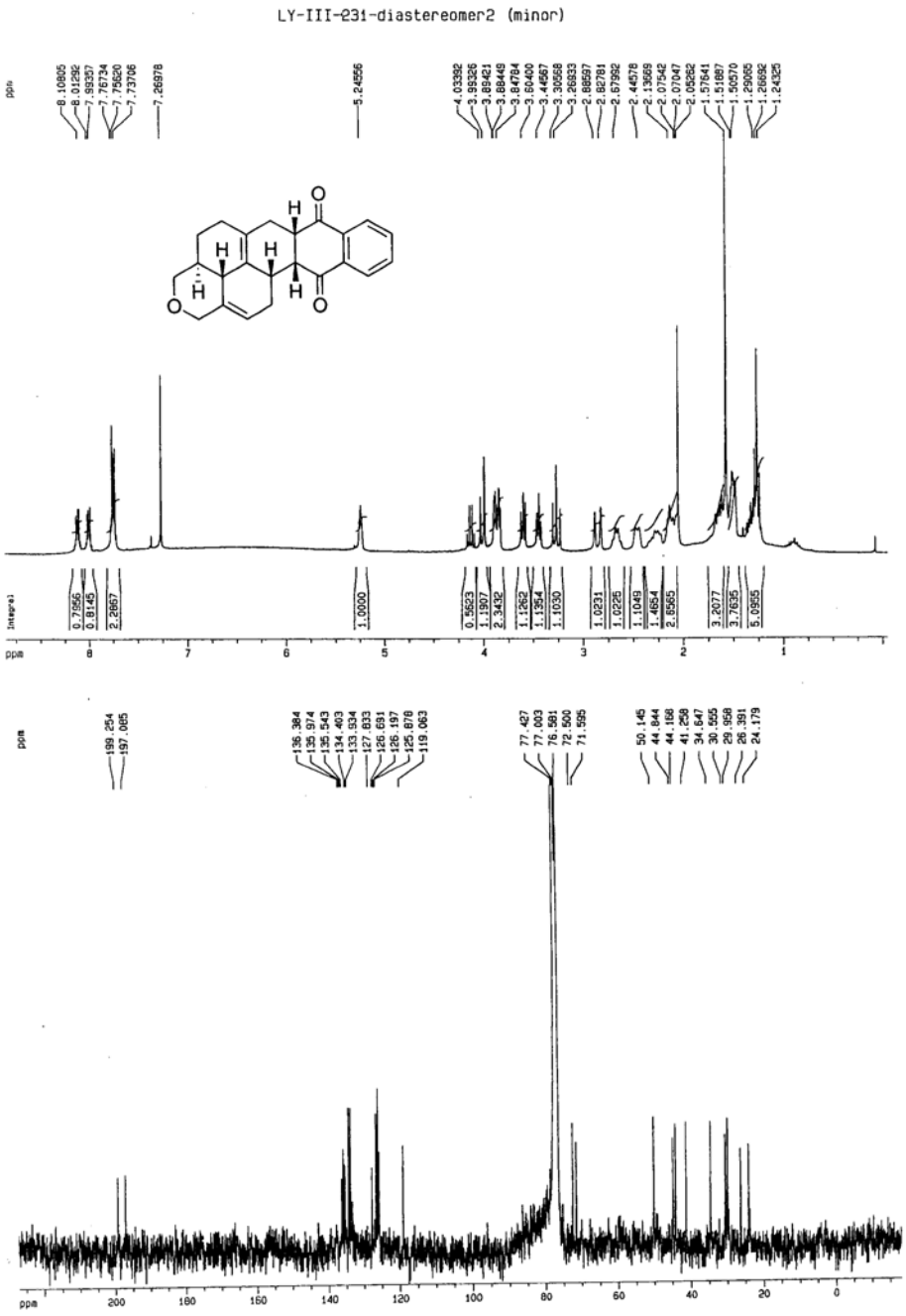
3.86b



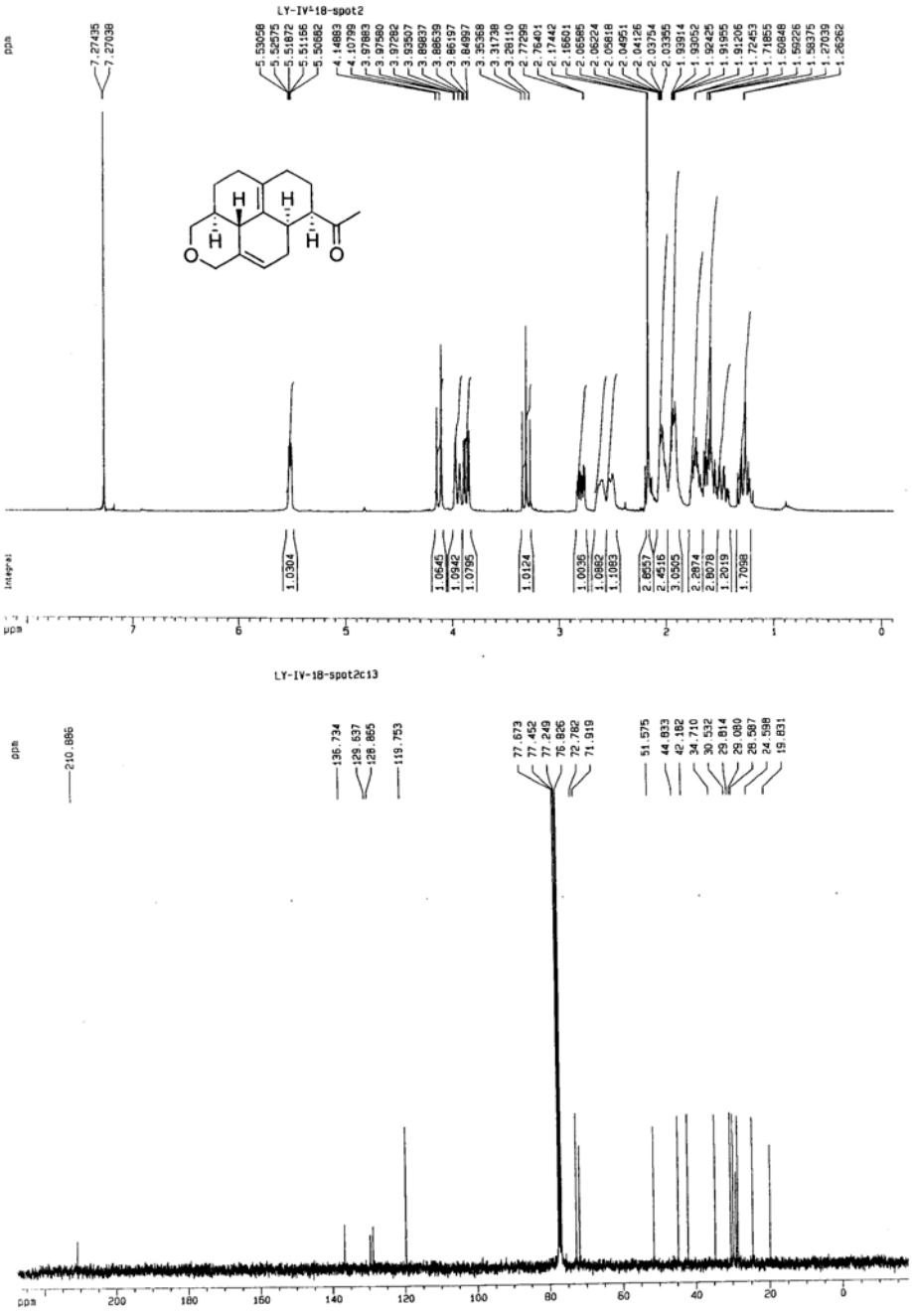
3.87a



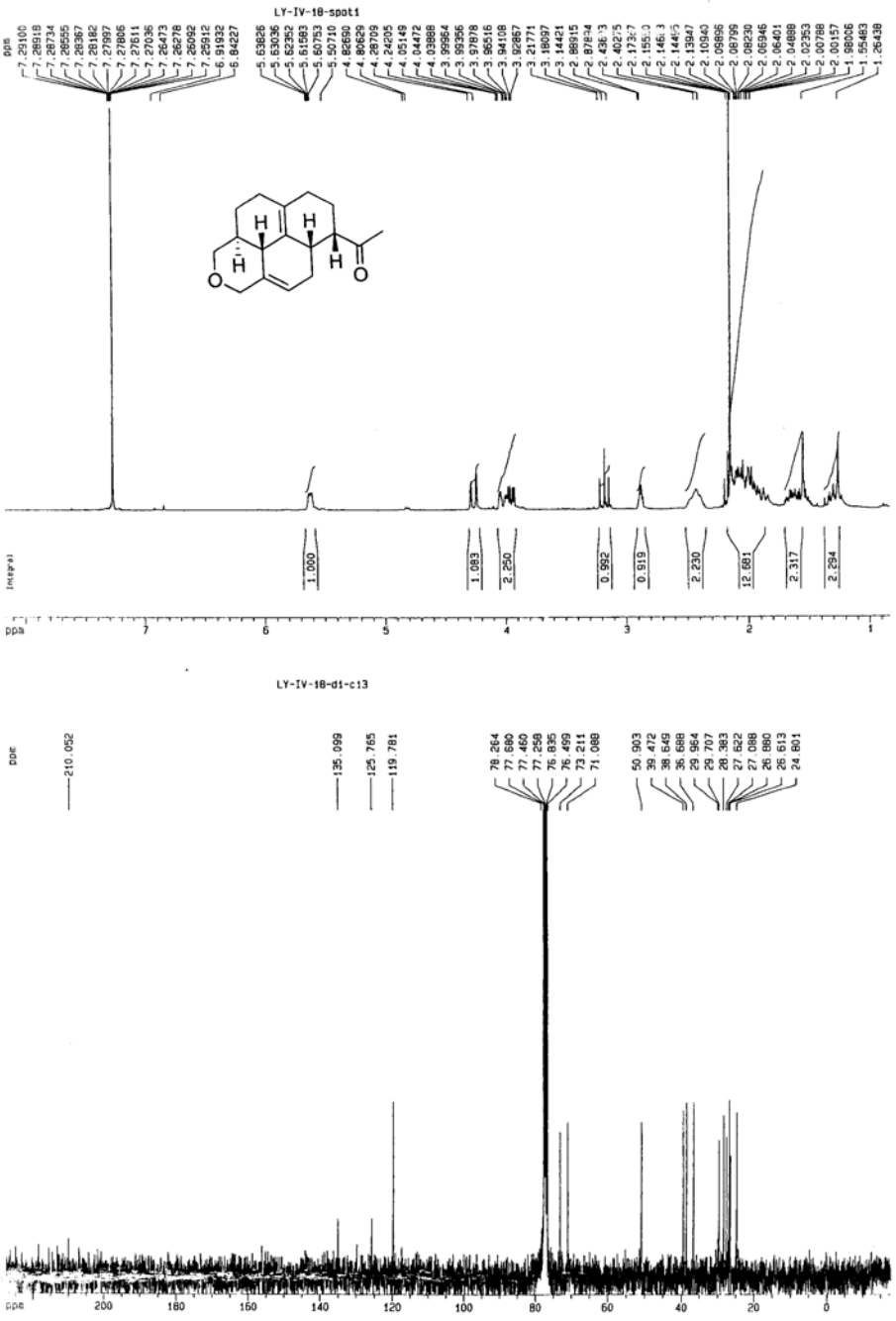
3.87b



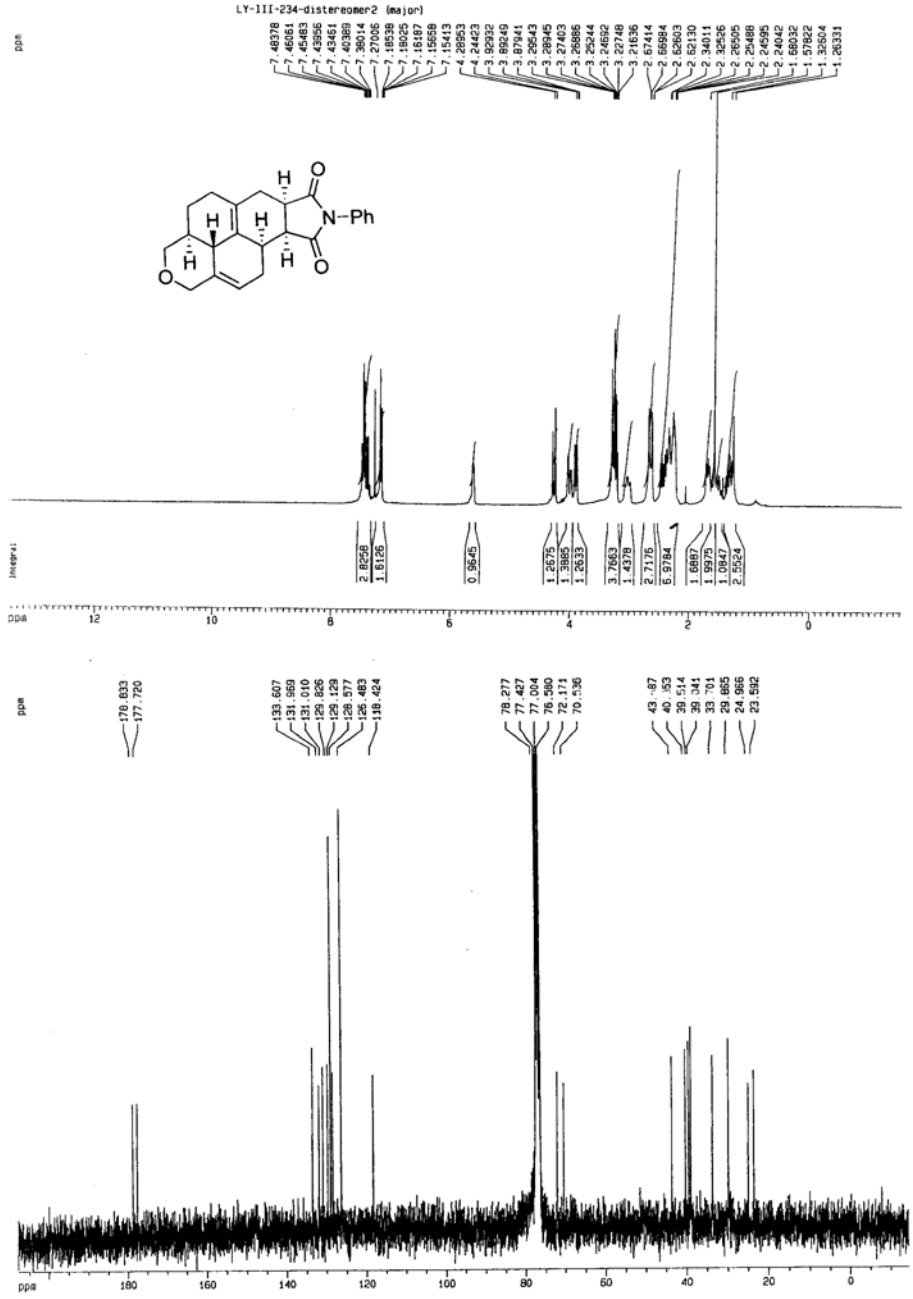
3.88a



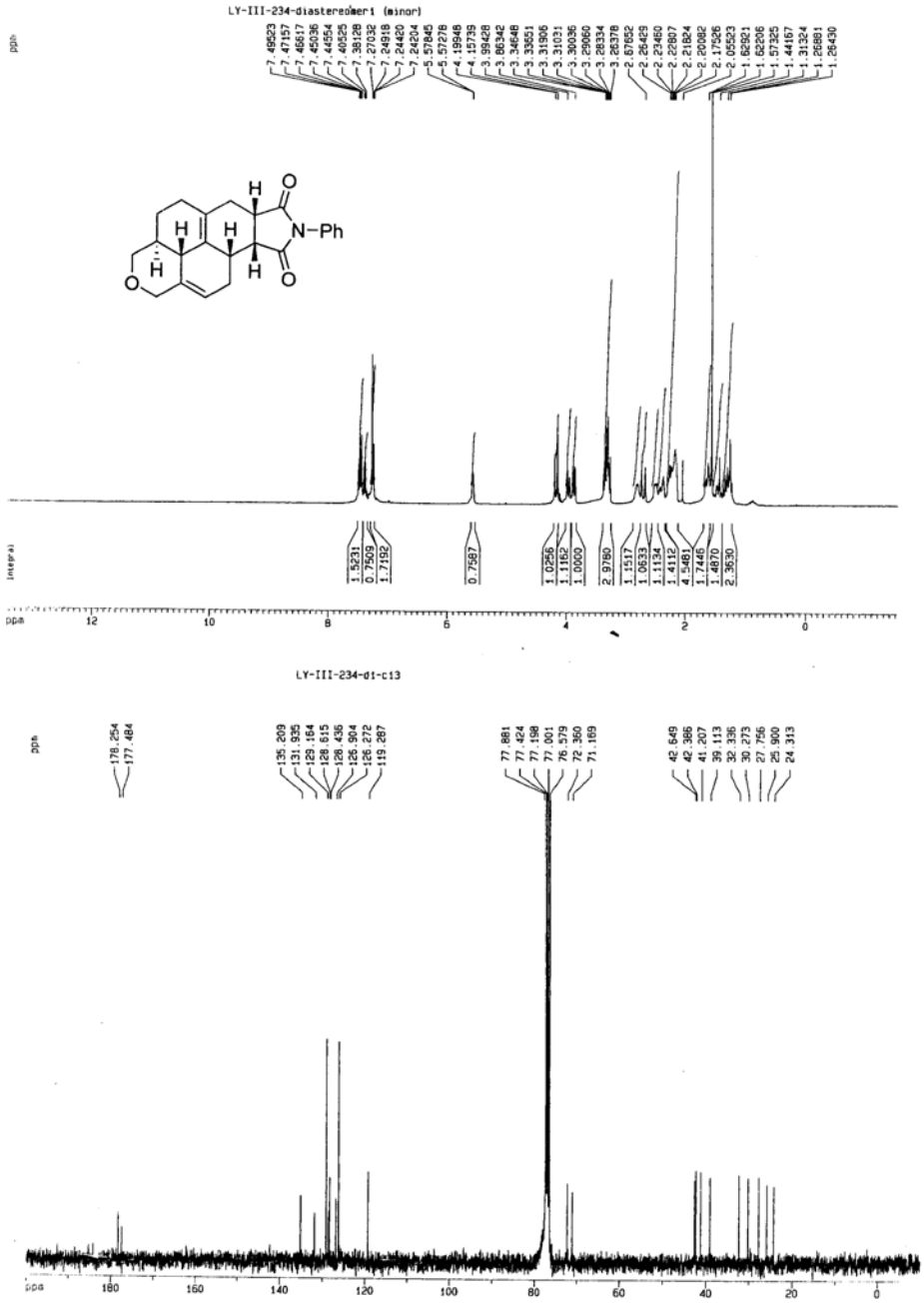
3.88b


LY-IV-18-spot1
integral
1.000
1.083
2.250
0.992
0.919
2.230
12.681
2.317
2.284
LY-IV-18-d1-c13
210.052
135.099
125.765
119.781
78.264
77.680
77.460
77.258
76.835
76.499
73.211
71.088
50.903
39.472
38.649
36.688
29.984
29.707
28.383
27.622
27.088
26.880
26.613
24.801

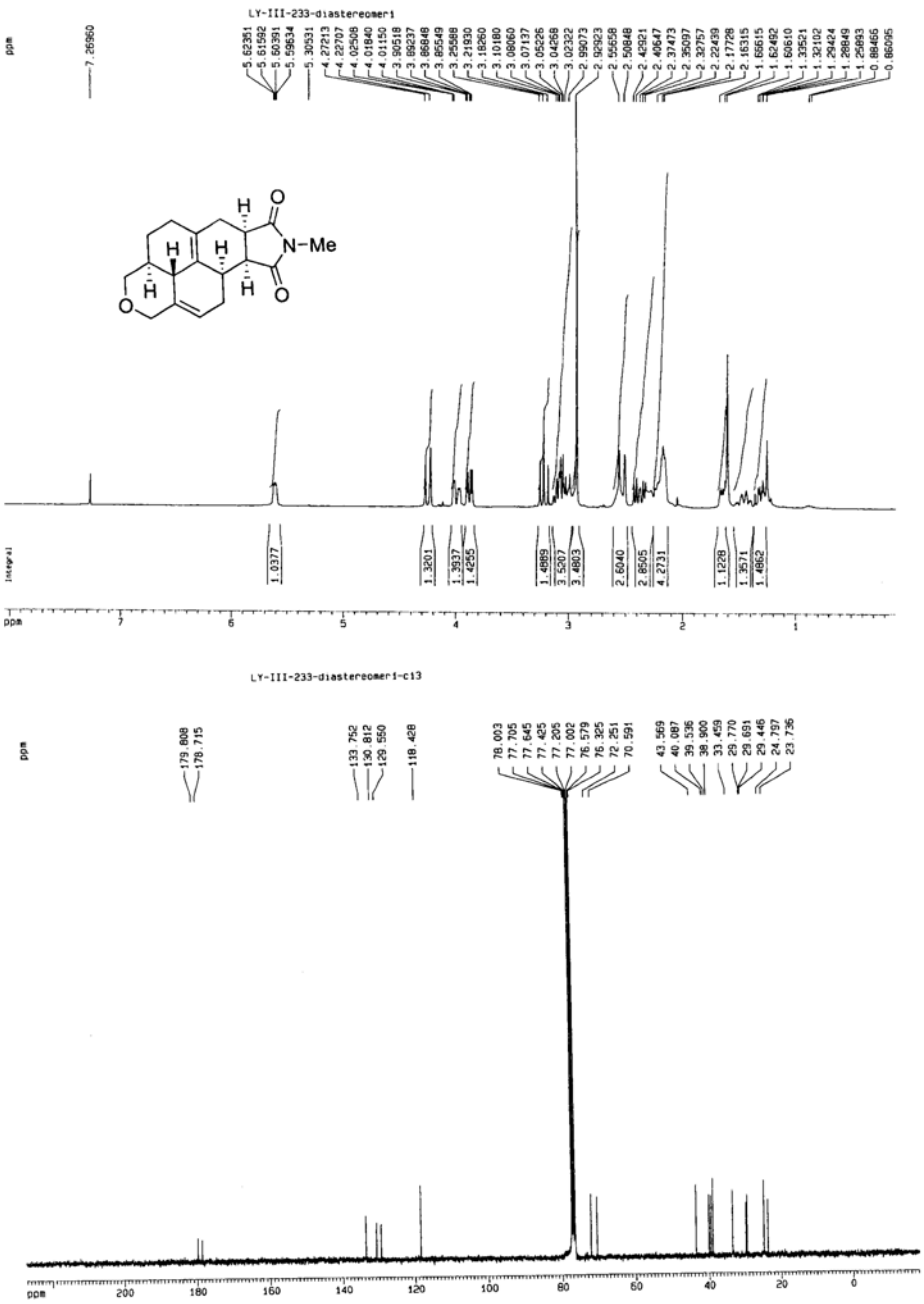
3.89a



3.89b

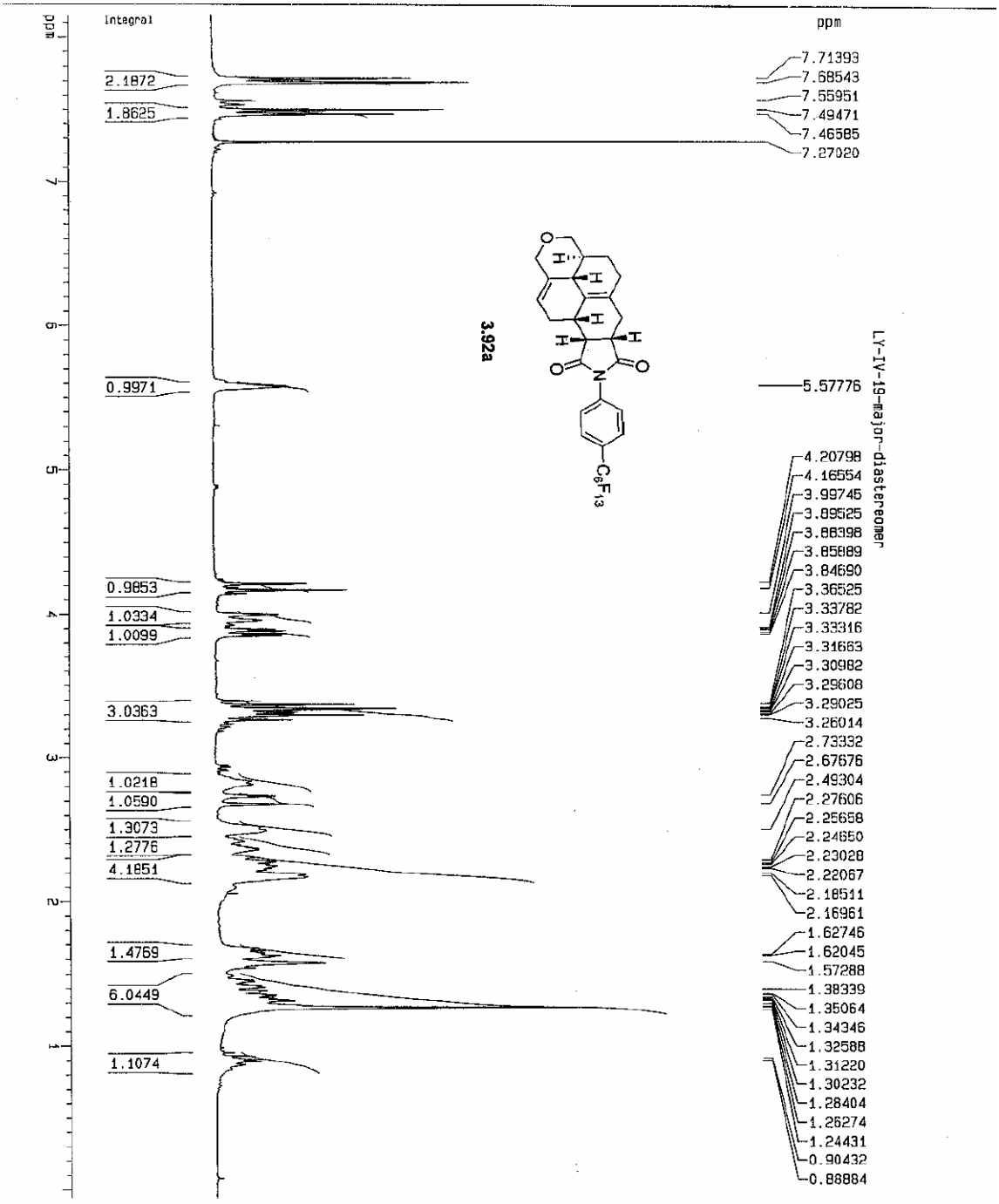


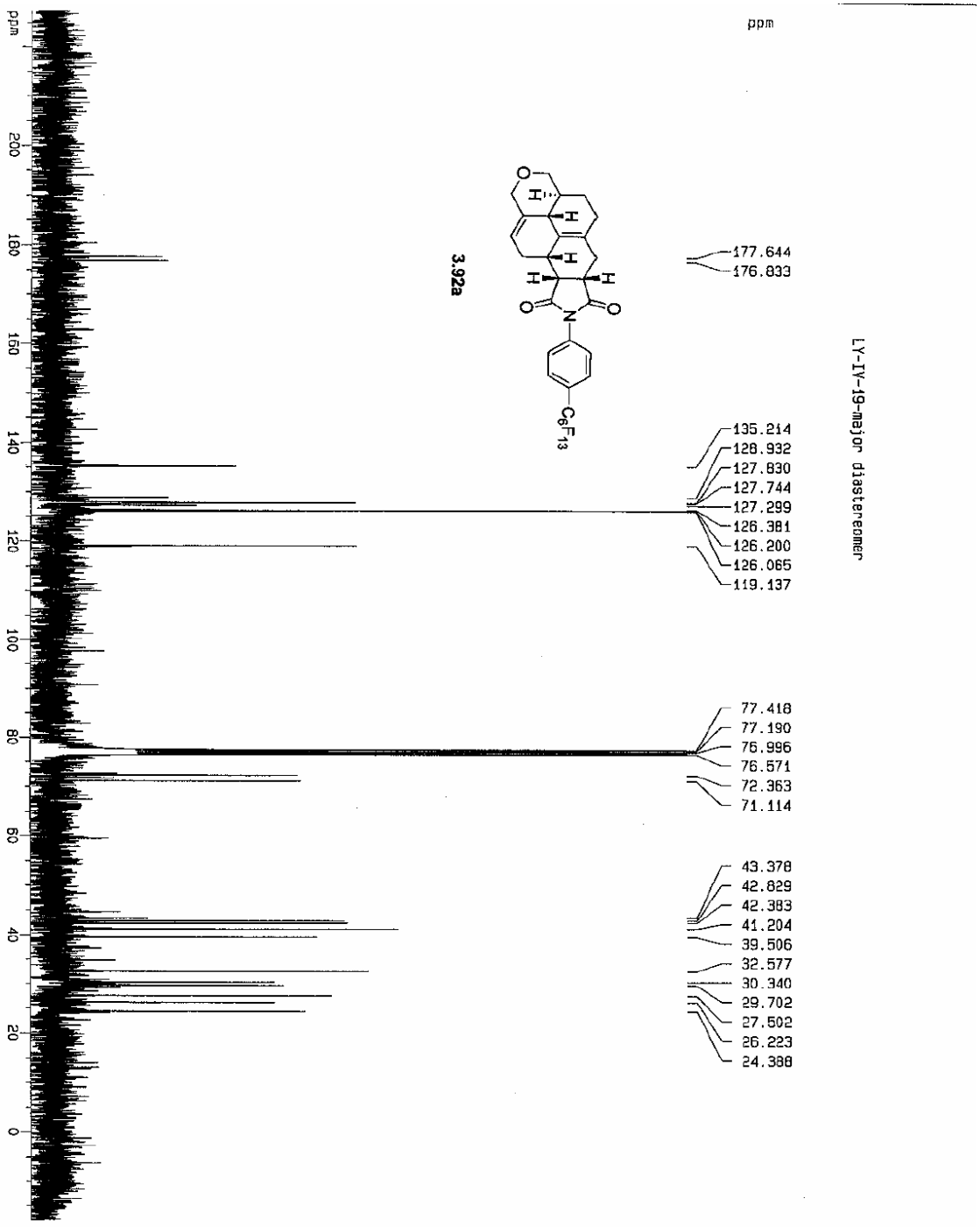
3.90a

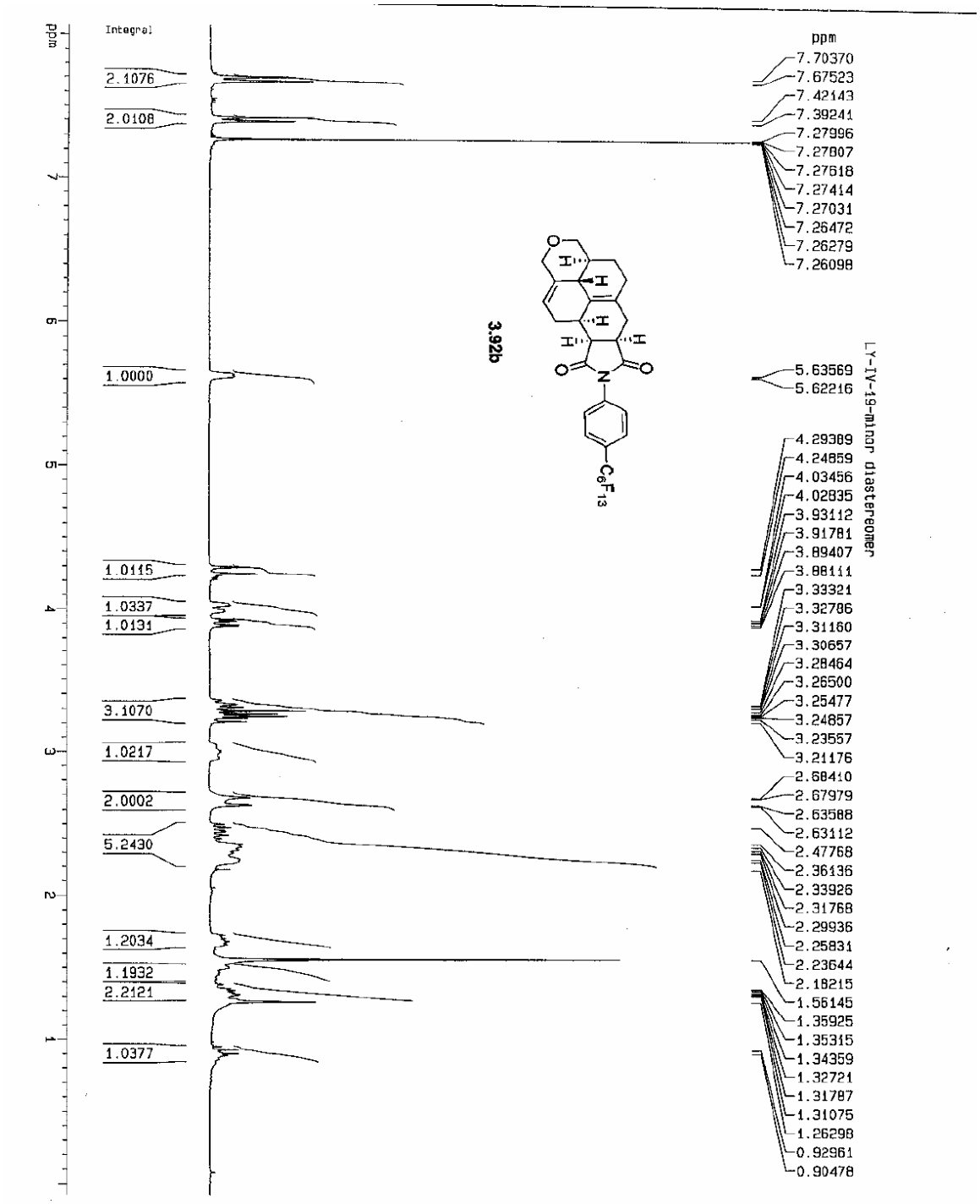

LY-III-233-diastereomer1
ppm
7.26960
5.62351
5.61592
5.60291
5.59634
5.30531
4.27213
4.22707
4.02508
4.01840
4.01150
3.90518
3.89237
3.86648
3.85549
3.25588
3.21930
3.18260
3.10180
3.08060
3.07137
3.05226
3.04258
3.02322
2.99073
2.92823
2.55558
2.50648
2.42521
2.40647
2.37473
2.35097
2.32757
2.22439
2.17728
2.16315
1.66615
1.62492
1.60610
1.39521
1.32102
1.29424
1.28849
1.25693
0.88465
0.86095
N-Me
Integral
1.0377
1.3201
1.3937
1.4255
1.4889
3.5207
3.4803
2.6040
2.8505
4.2731
1.1228
1.3571
1.4862
LY-III-233-diastereomer1-c13
179.808
178.715
133.752
130.812
129.550
118.428
78.003
77.705
77.645
77.425
77.205
77.002
76.579
76.325
72.251
70.591
43.569
40.087
39.536
38.900
33.459
29.770
29.691
29.446
24.797
23.736

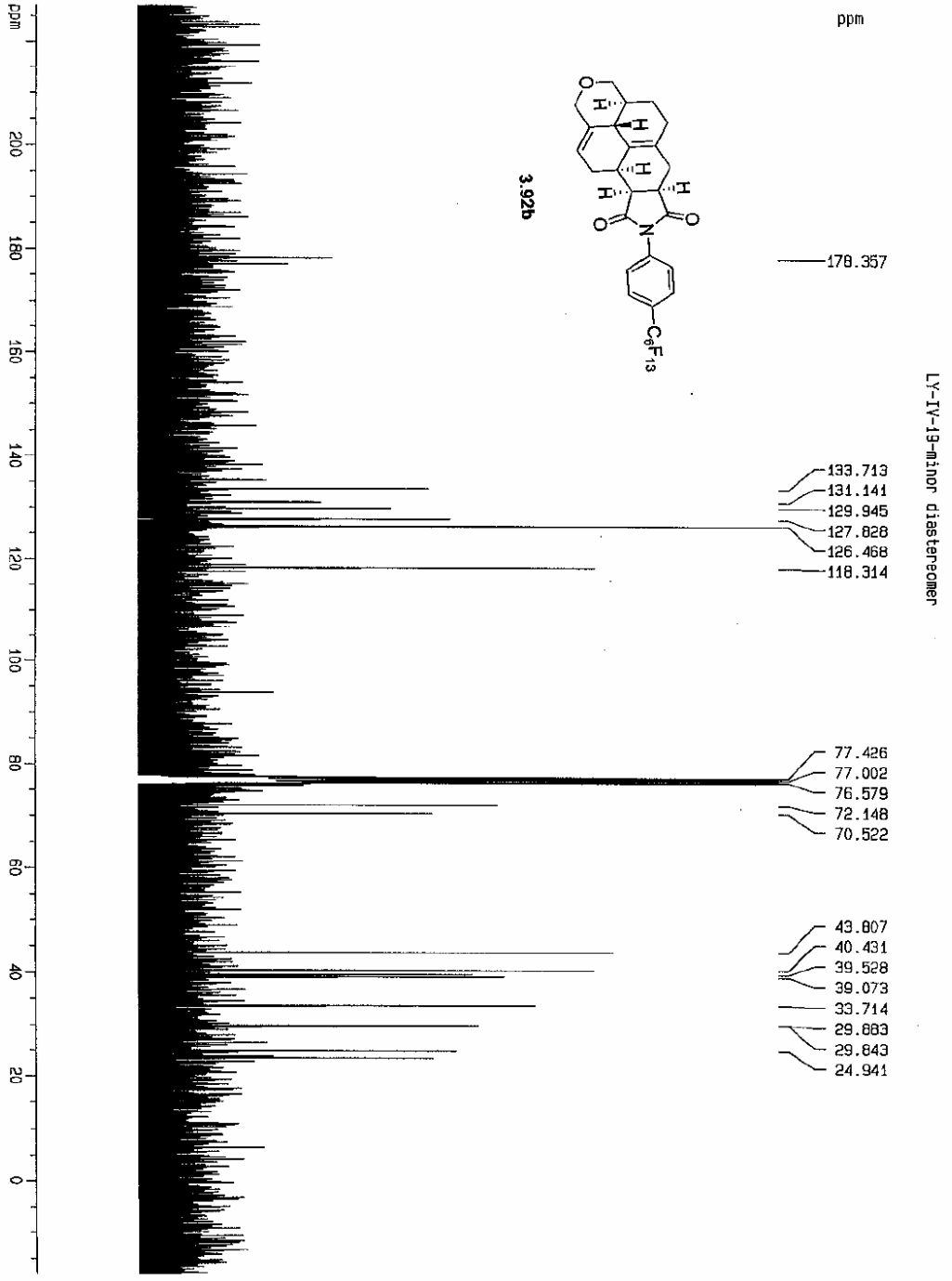
3.90b

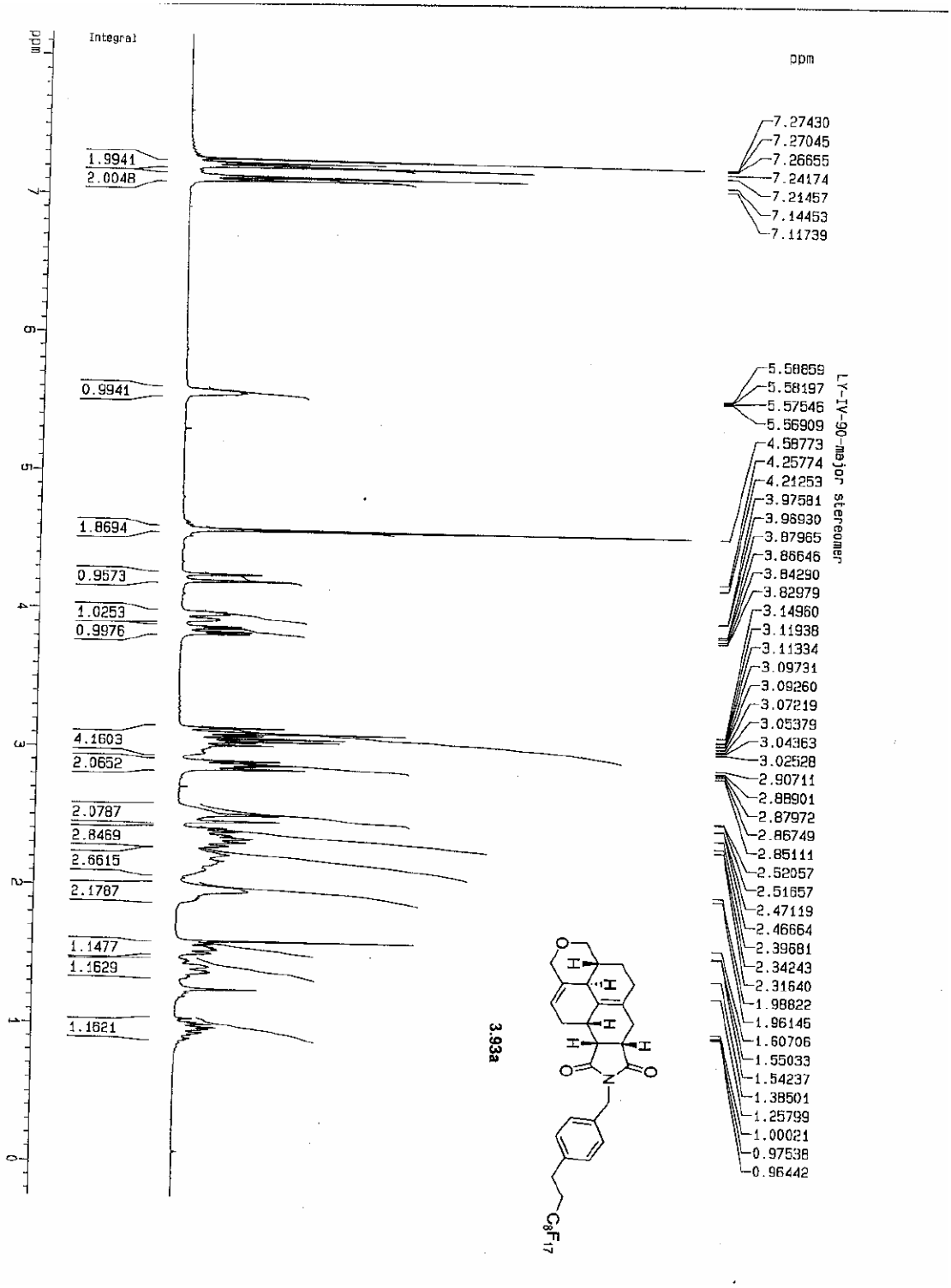

LY-III-233-diastereomer2
ppm
7.27023
5.53227
5.52623
4.16374
4.12188
3.96084
3.95875
3.84615
3.83442
3.31100
3.27525
3.18403
3.15548
3.00534
2.94727
2.59911
2.54256
2.27827
2.14646
2.13707
2.11906
2.02792
1.61008
1.60512
1.58203
1.32436
1.28504
1.26237
N-Me
Integral
1.0000
1.1173
1.2372
1.1156
1.3223
1.2704
1.3315
3.2724
1.4632
1.4794
1.4371
1.9477
4.6265
1.9845
2.3637
5.5007
LY-III-233-diastereomer2 (minor)
179.491
178.530
139.034
128.596
126.501
119.233
77.784
77.420
76.997
76.573
72.373
71.218
42.686
42.143
41.306
38.750
31.889
30.212
27.724
26.001
24.352
24.275

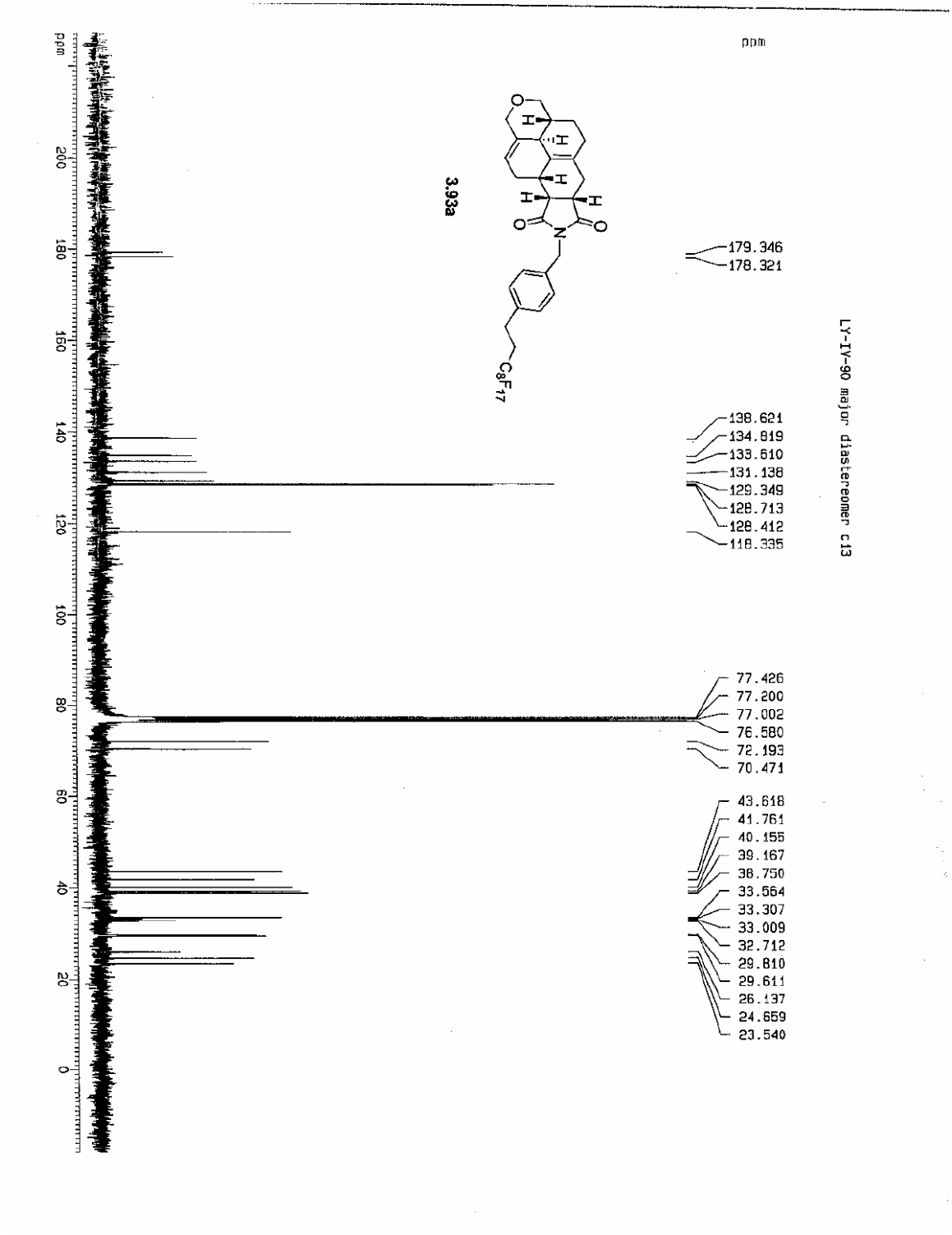

Integral
ppm
2.1872
1.8625
0.9971
0.9853
1.0334
1.0099
3.0363
1.0218
1.0590
1.3073
1.2776
4.1851
1.4769
6.0449
1.1074
7.71393
7.68543
7.55951
7.49471
7.46585
7.27020
5.57776
4.20798
4.16554
3.99745
3.89525
3.88398
3.85889
3.84690
3.36525
3.33782
3.33316
3.31663
3.30982
3.29608
3.29025
3.26014
2.73332
2.67676
2.49304
2.27606
2.25658
2.24650
2.23028
2.22067
2.18511
2.16961
1.62746
1.62045
1.57288
1.38339
1.35064
1.34346
1.32588
1.31220
1.30232
1.28404
1.26274
1.24431
0.90432
0.88884
3.92a
LY-IV-19-major-diastereomer

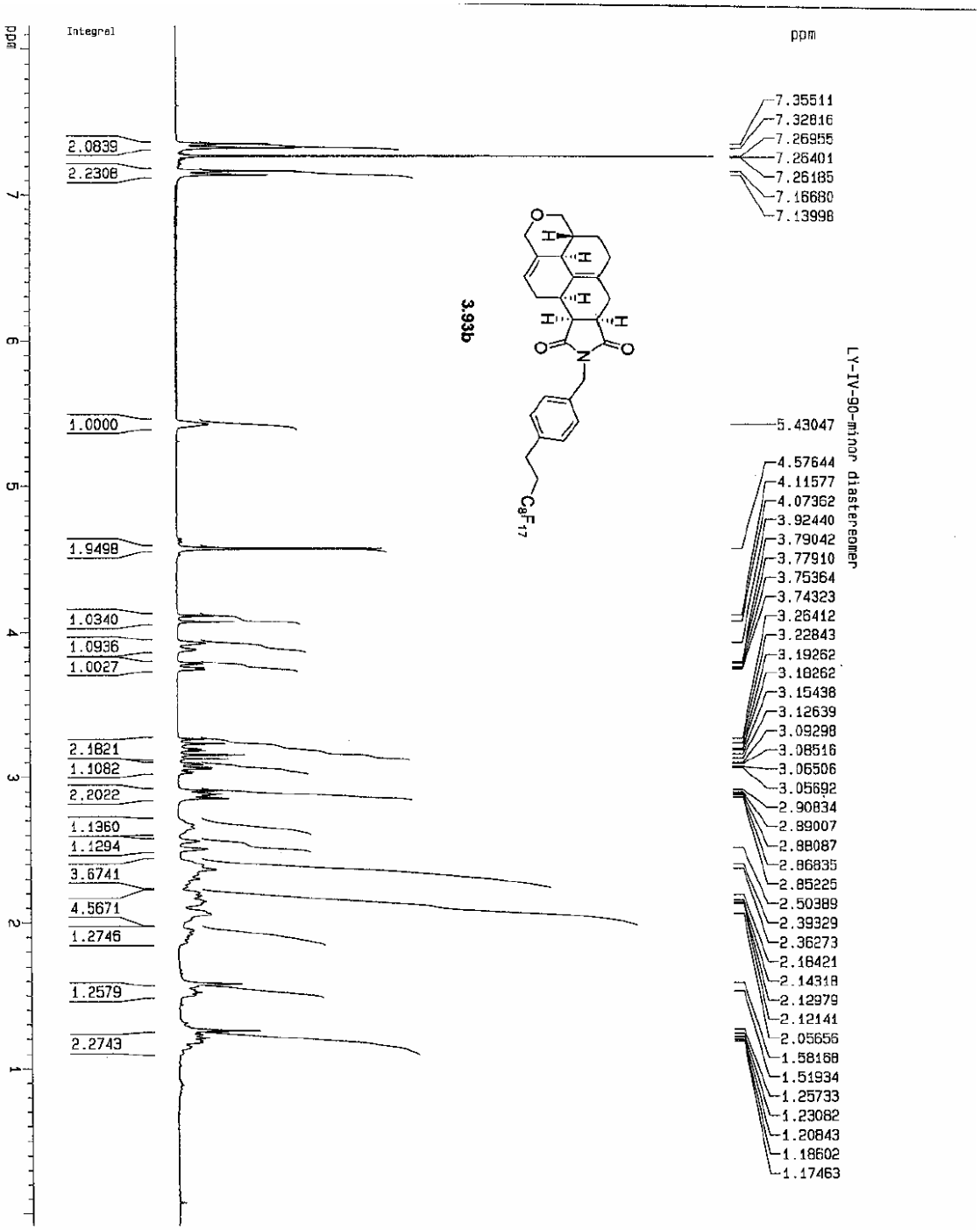

ppm
200
180
160
140
120
100
80
60
40
20
0
3.92a
177.644
176.833
135.214
128.932
127.830
127.744
127.299
126.381
126.200
126.065
119.137
77.418
77.190
76.996
76.571
72.363
71.114
43.378
42.829
42.383
41.204
39.506
32.577
30.340
29.702
27.502
26.223
24.388
LY-IV-49-major diastereomer

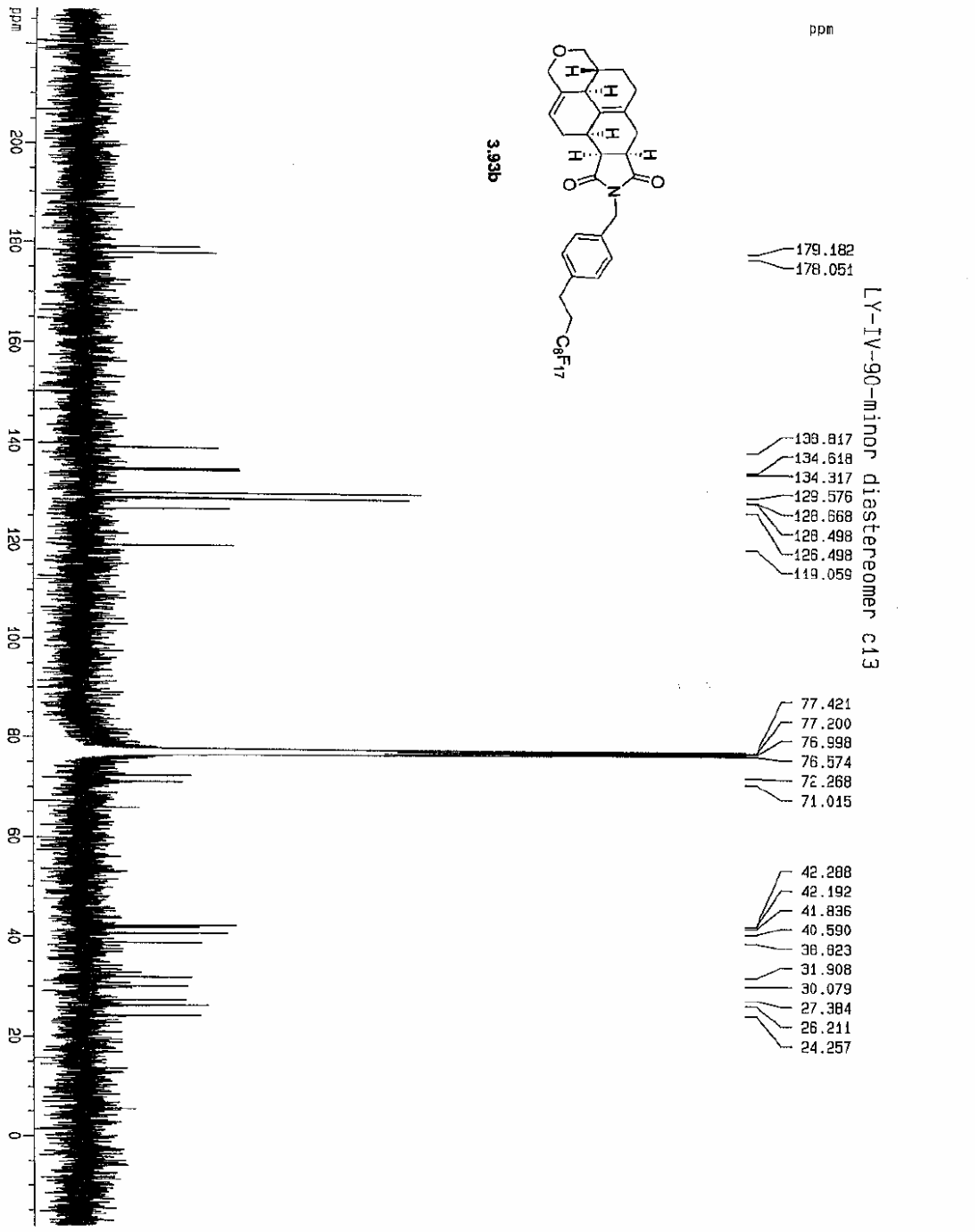

Integral
2.1076
2.0108
1.0000
1.0115
1.0337
1.0131
3.1070
1.0217
2.0002
5.2430
1.2034
1.1932
2.2121
1.0377
3.92b
ppm
7.70370
7.67523
7.42143
7.39241
7.27996
7.27807
7.27618
7.27414
7.27031
7.26472
7.26279
7.26098
5.63569
5.62216
4.29389
4.24859
4.03456
4.02835
3.93112
3.91781
3.89407
3.88111
3.33321
3.32786
3.31160
3.30657
3.28464
3.26500
3.25477
3.24857
3.23557
3.21176
2.68410
2.67979
2.63588
2.63112
2.47768
2.36136
2.33926
2.31768
2.29936
2.25831
2.23644
2.18215
1.56145
1.35925
1.35315
1.34359
1.32721
1.31787
1.31075
1.26298
0.92961
0.90478
LY-IV-19-minor diastereomer

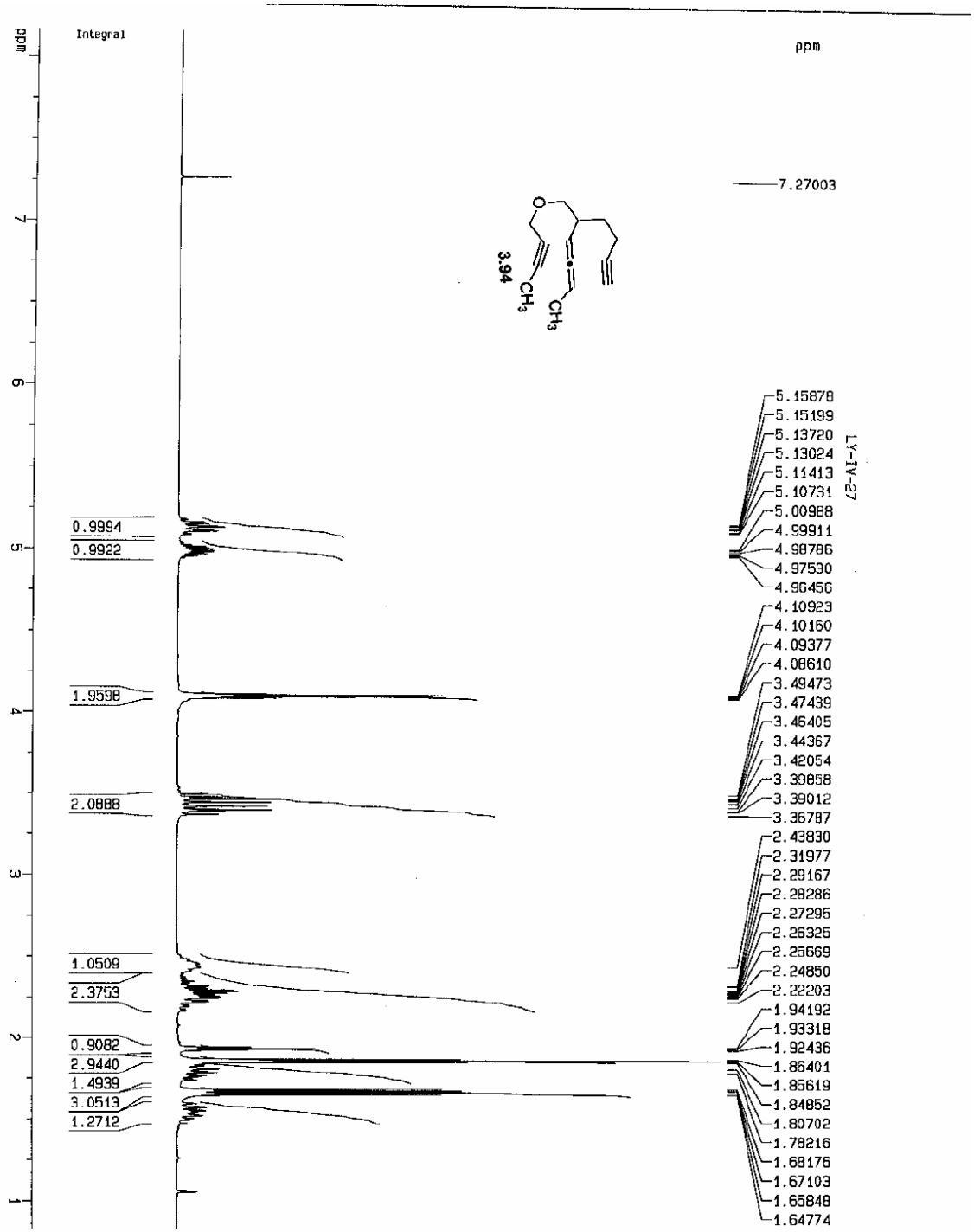

ppm
3.92b
178.357
133.713
131.141
129.945
127.828
126.468
118.314
77.426
77.002
76.579
72.148
70.522
43.807
40.431
39.528
39.073
33.714
29.883
29.843
24.941
LY-IV-19-minor diastereomer

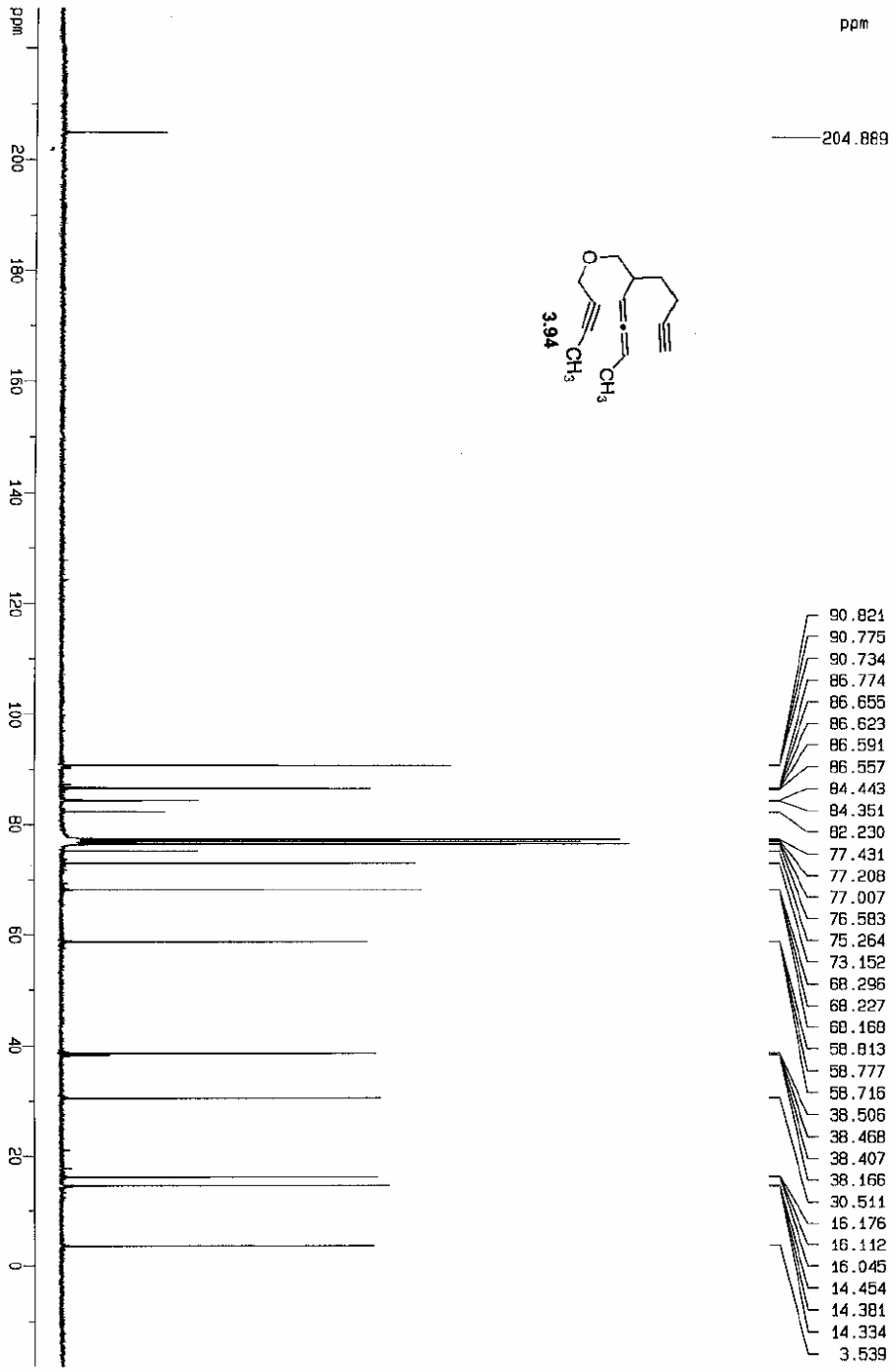

ppm
Integral
1.9941
2.0048
0.9941
1.8694
0.9573
1.0253
0.9976
4.1603
2.0652
2.0787
2.8469
2.6615
2.1787
1.1477
1.1629
1.1621
ppm
7.27430
7.27045
7.26655
7.24174
7.21457
7.14453
7.11739
5.58659
5.58197
5.57546
5.56909
4.58773
4.25774
4.21253
3.97581
3.96930
3.87965
3.86646
3.84290
3.82979
3.14960
3.11938
3.11334
3.09731
3.09260
3.07219
3.05379
3.04363
3.02528
2.90711
2.88901
2.87972
2.86749
2.85111
2.52057
2.51657
2.47119
2.46664
2.39681
2.34243
2.31640
1.98822
1.96146
1.60706
1.55033
1.54237
1.38501
1.25799
1.00021
0.97538
0.96442
LY-IV-90-major stereomer
3.93a
C8F17

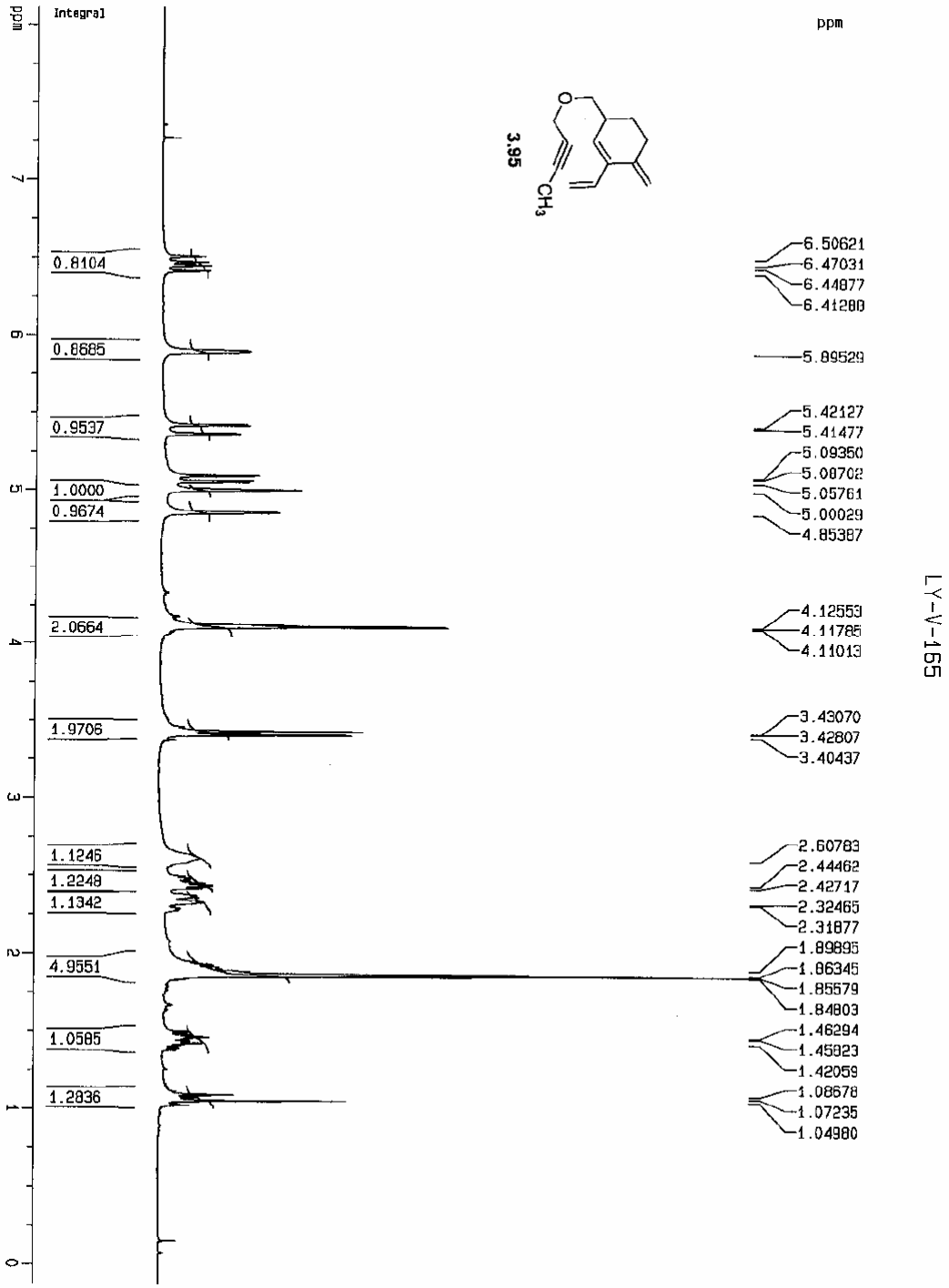

ppm
3.93a
179.346
178.321
138.621
134.819
133.610
131.138
129.349
128.713
128.412
118.335
77.426
77.200
77.002
76.580
72.193
70.471
43.618
41.761
40.155
39.167
38.750
33.564
33.307
33.009
32.712
29.810
29.611
26.197
24.659
23.540
LY-IV-90 major diastereomer c13


ppm
Integral
2.0839
2.2308
1.0000
1.9498
1.0340
1.0936
1.0027
2.1821
1.1082
2.2022
1.1360
1.1294
3.6741
4.5671
1.2746
1.2579
2.2743
3.93b
7.35511
7.32816
7.26955
7.26401
7.26185
7.16680
7.13998
5.43047
4.57644
4.11577
4.07362
3.92440
3.79042
3.77910
3.75364
3.74323
3.26412
3.22843
3.19262
3.18262
3.15438
3.12639
3.09298
3.08516
3.06506
3.05692
2.90834
2.89007
2.88087
2.86835
2.85225
2.50389
2.39329
2.36273
2.18421
2.14318
2.12979
2.12141
2.05656
1.58168
1.51934
1.25733
1.23082
1.20843
1.18602
1.17463
LY-IV-90-minor diastereomer


ppm
3.93b
LY-IV-90-minor diastereomer c13
179.182
178.051
138.817
134.618
134.317
129.576
128.668
128.498
126.498
119.059
77.421
77.200
76.998
76.574
72.268
71.015
42.288
42.192
41.836
40.590
38.823
31.908
30.079
27.384
26.211
24.257


Integral
ppm
7.27003
3.94
CH3
CH3
0.9994
0.9922
1.9598
2.0888
1.0509
2.3753
0.9082
2.9440
1.4939
3.0513
1.2712
5.15878
5.15199
5.13720
5.13024
5.11413
5.10731
5.00988
4.99911
4.98786
4.97530
4.96456
4.10923
4.10160
4.09377
4.08610
3.49473
3.47439
3.46405
3.44367
3.42054
3.39858
3.39012
3.36787
2.43830
2.31977
2.29167
2.28286
2.27295
2.26325
2.25669
2.24850
2.22203
1.94192
1.93318
1.92436
1.86401
1.85619
1.84852
1.80702
1.78216
1.68176
1.67103
1.65848
1.64774
LY-1-V-27


ppm
200
180
160
140
120
100
80
60
40
20
0
3.94
CH3
CH3
O
ppm
204.869
90.821
90.775
90.734
86.774
86.655
86.623
86.591
86.557
84.443
84.351
82.230
77.431
77.208
77.007
76.583
75.264
73.152
68.296
68.227
68.168
58.813
58.777
58.716
38.506
38.468
38.407
38.166
30.511
16.176
16.112
16.045
14.454
14.381
14.334
3.539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ppm
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CH3
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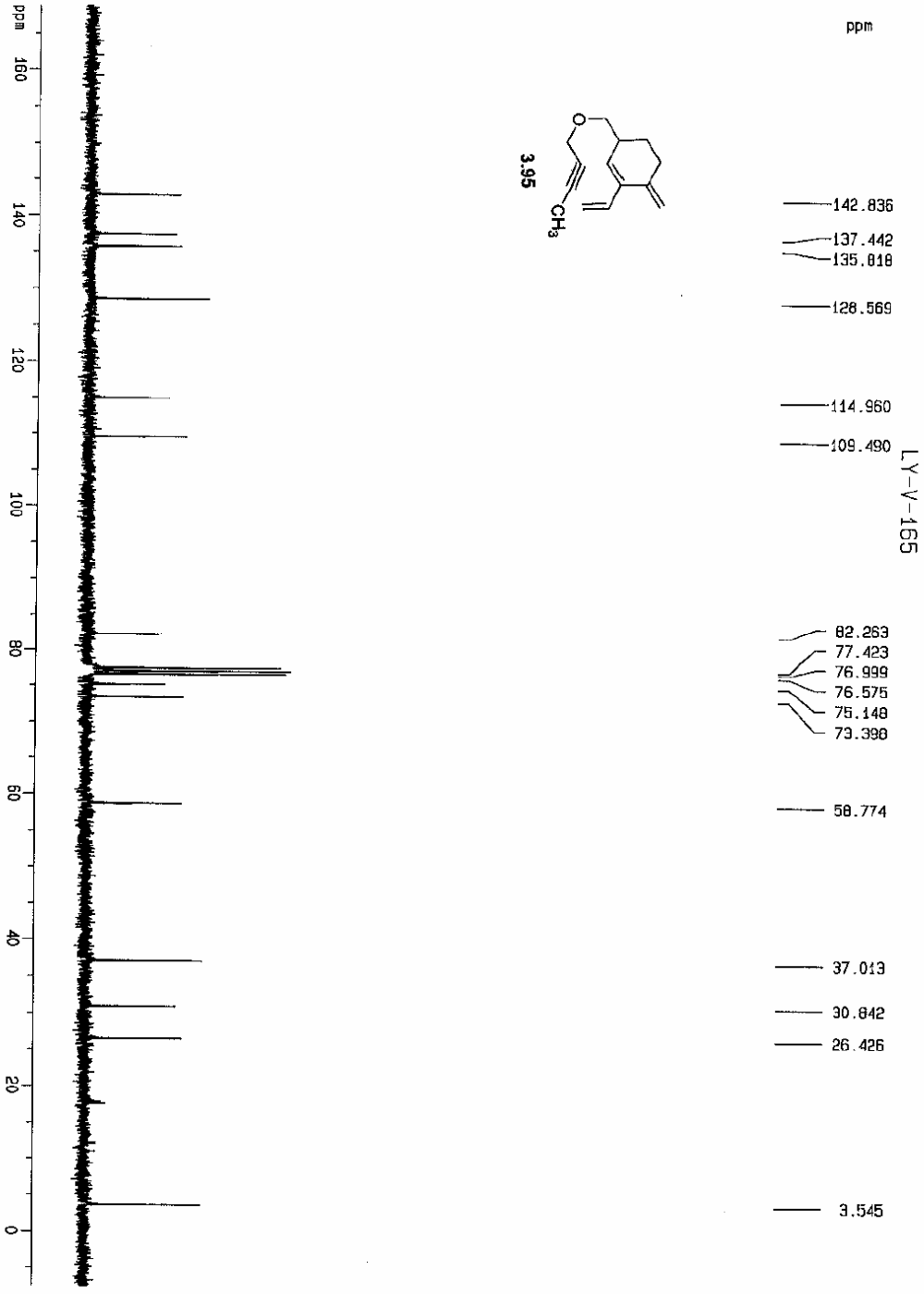
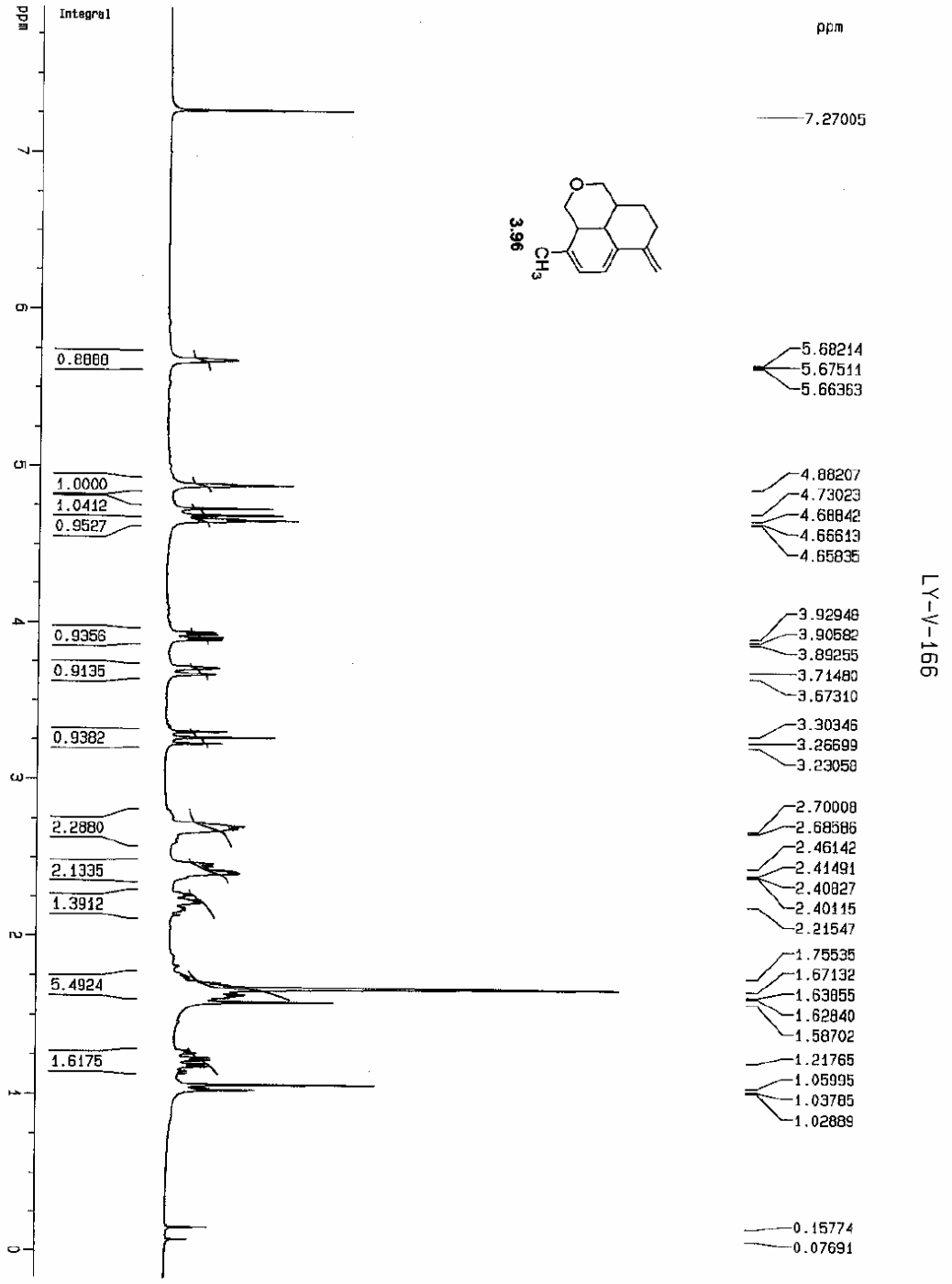
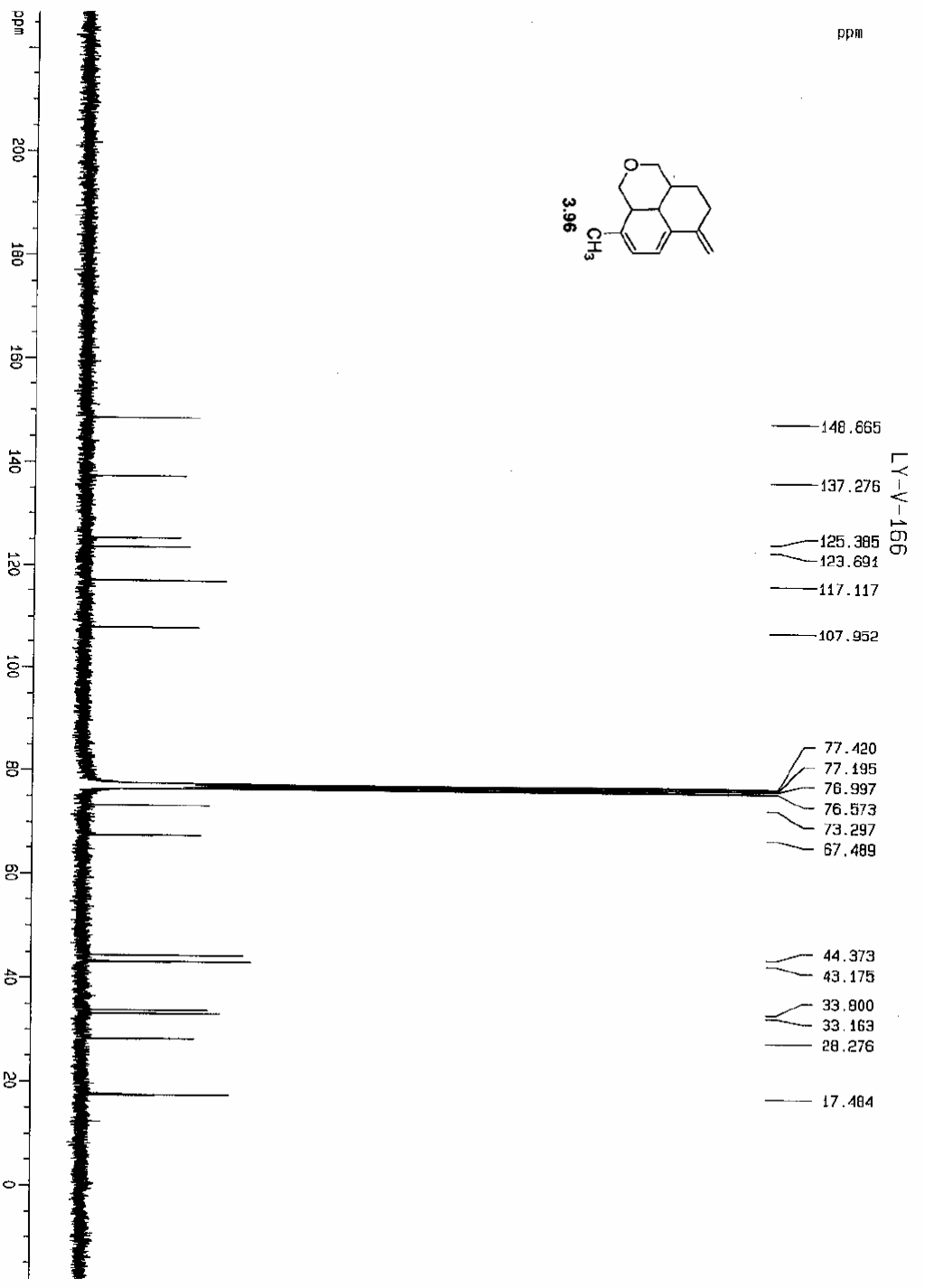
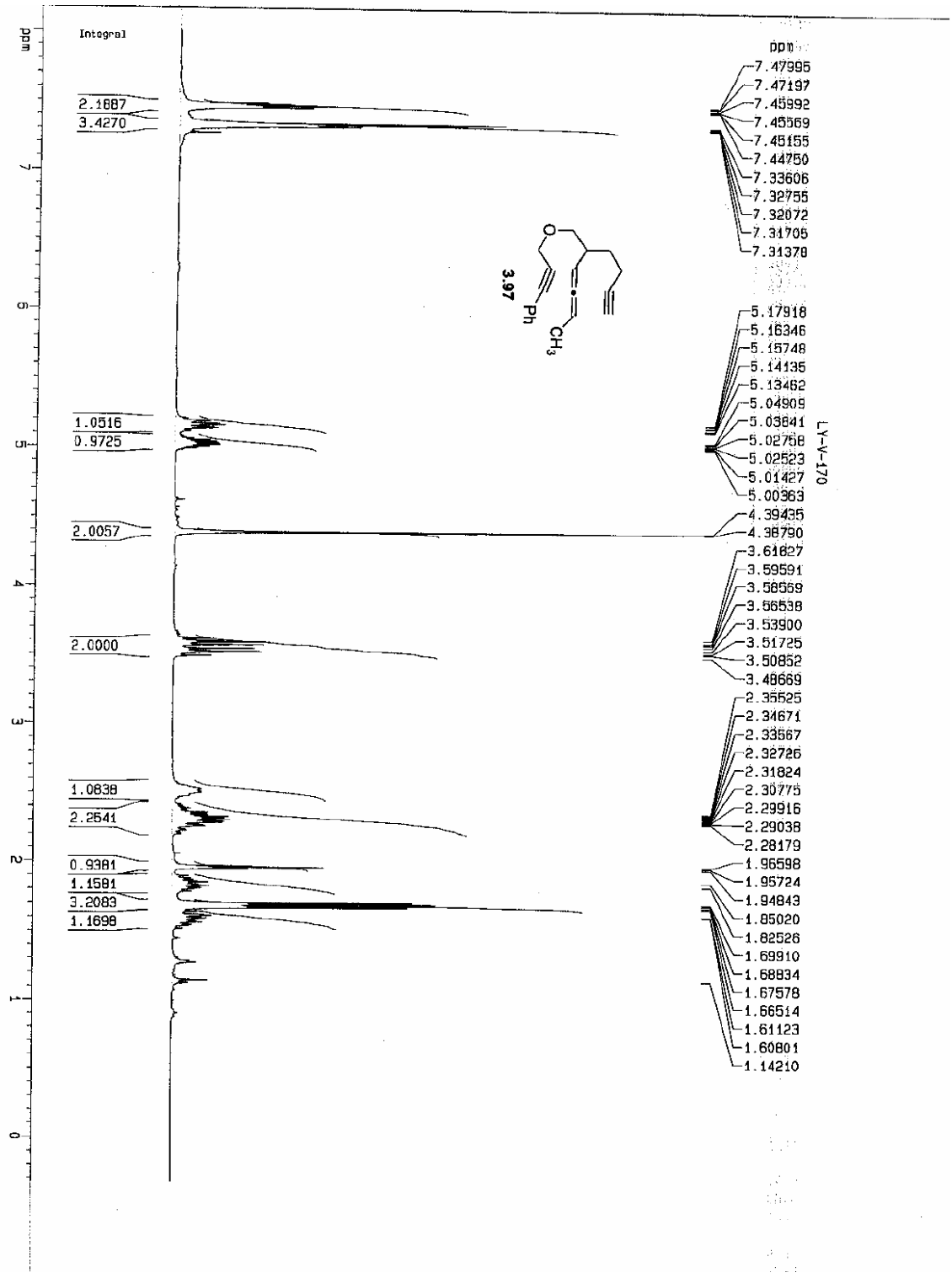
0.8685
0.9537
1.0000
0.9674
2.0664
1.9706
1.1245
1.2248
1.1342
4.9551
1.0585
1.2836
6.50621
6.47031
6.44877
6.41280
5.89529
5.42127
5.41477
5.09350
5.08702
5.05761
5.00029
4.85387
4.12553
4.11785
4.11013
3.43070
3.42807
3.40437
2.60783
2.44462
2.42717
2.32465
2.31877
1.89895
1.86345
1.85579
1.84803
1.46294
1.45923
1.42059
1.08678
1.07235
1.04980
LY-V-155


ppm
160
140
120
100
80
60
40
20
0
3.95
CH3
ppm
142.836
137.442
135.818
128.569
114.960
109.490
82.263
77.423
76.999
76.575
75.148
73.398
58.774
37.013
30.842
26.426
3.545
LY-V-165


ppm
Integral
ppm
7.27005
3.96
CH3
0.8880
1.0000
1.0412
0.9527
0.9356
0.9135
0.9382
2.2880
2.1335
1.3912
5.4924
1.6175
5.68214
5.67511
5.66363
4.88207
4.73023
4.68842
4.66613
4.65835
3.92948
3.90582
3.89255
3.71480
3.67310
3.30346
3.26699
3.23058
2.70008
2.68586
2.46142
2.41491
2.40827
2.40115
2.21547
1.75535
1.67132
1.63855
1.62840
1.58702
1.21765
1.05995
1.03785
1.02889
0.15774
0.07691
LY-V-166


ppm
ppm
3.96
CH3
O
148.665
137.276
125.385
123.691
117.117
107.952
77.420
77.195
76.997
76.573
73.297
67.489
44.373
43.175
33.800
33.163
28.276
17.484
LY-V-166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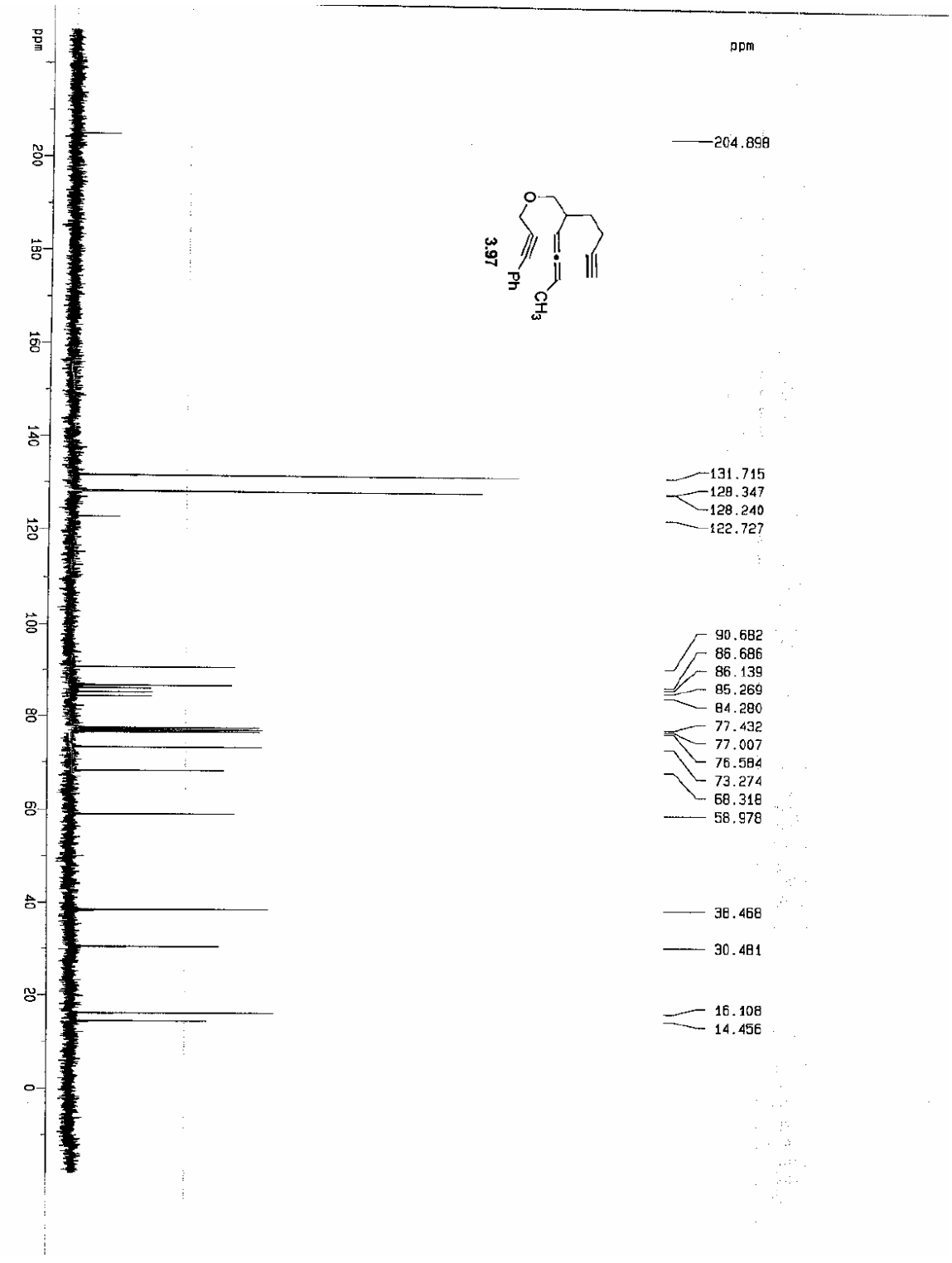
2.1687
3.4270
1.0516
0.9725
2.0057
2.0000
1.0838
2.2541
0.9381
1.1581
3.2083
1.1698
3.97
Ph
CH3
ppm
7.47995
7.47197
7.45992
7.45569
7.45155
7.44750
7.33606
7.32755
7.32072
7.31705
7.31378
5.17918
5.16346
5.15748
5.14135
5.13462
5.04909
5.03841
5.02758
5.02523
5.01427
5.00363
4.39435
4.38790
3.61627
3.59591
3.58569
3.56538
3.53900
3.51725
3.50852
3.48669
2.35525
2.34671
2.33567
2.32726
2.31824
2.30775
2.29916
2.29038
2.28179
1.96598
1.95724
1.94843
1.85020
1.82526
1.69910
1.68834
1.67578
1.66514
1.61123
1.60801
1.14210
LY-V-170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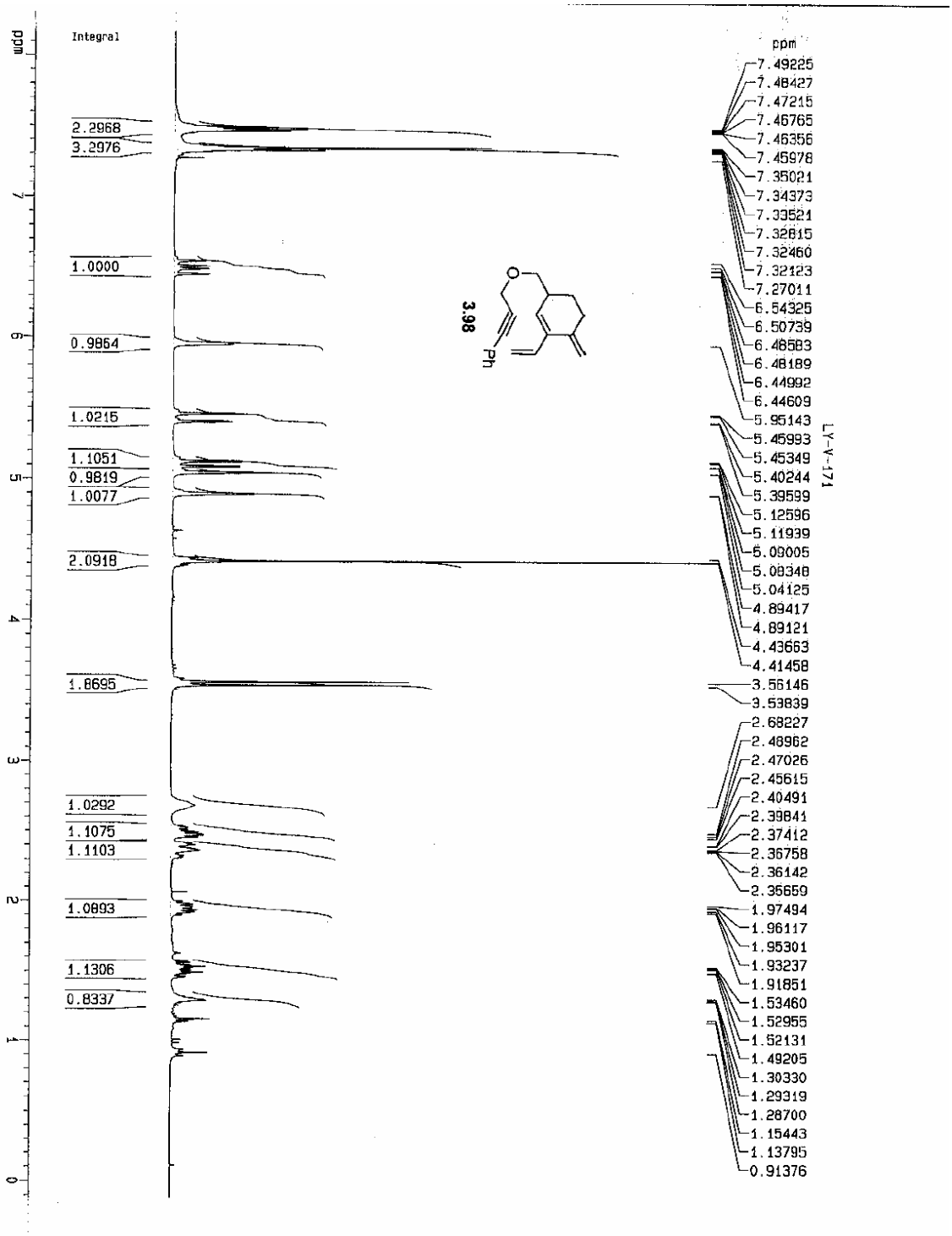
128.240
122.727
90.682
86.686
86.139
85.269
84.280
77.432
77.007
76.584
73.274
68.318
58.978
38.468
30.481
16.108
14.456
3.97
Ph
CH3
O


ppm
Integral
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3.2976
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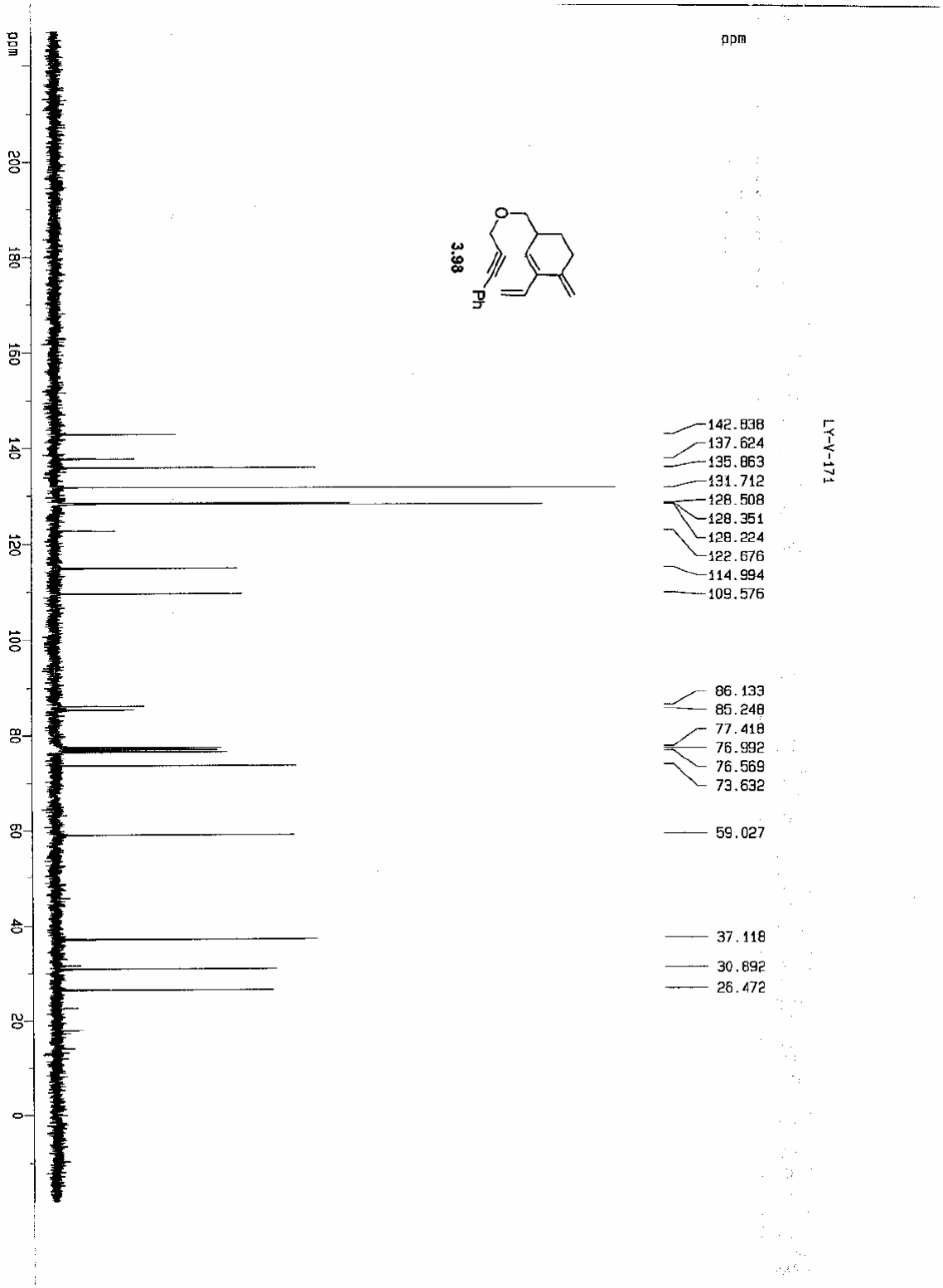
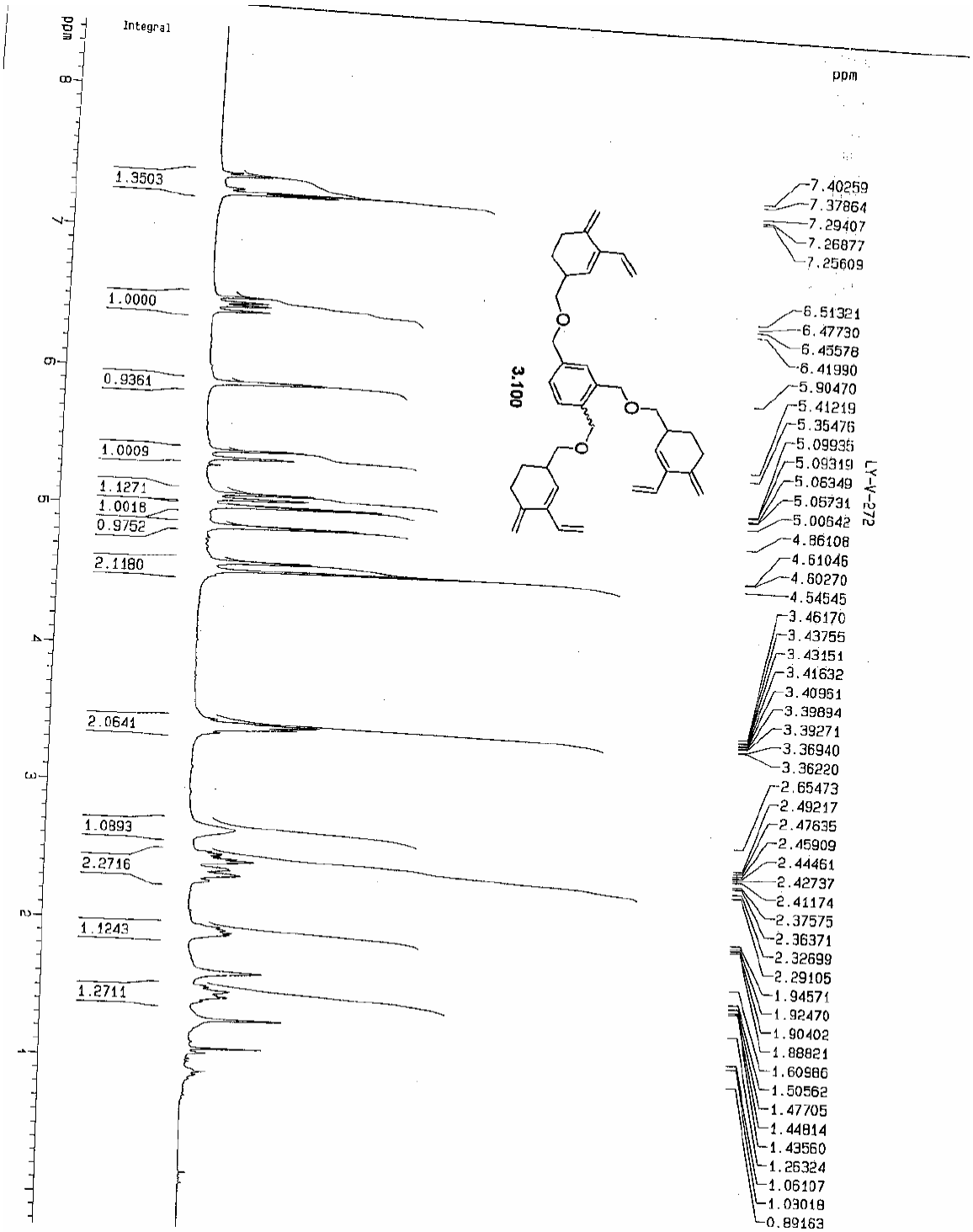
0.9864
1.0215
1.1051
0.9819
1.0077
2.0918
1.8695
1.0292
1.1075
1.1103
1.0893
1.1306
0.8337
3.98
Ph
ppm
7.49225
7.48427
7.47215
7.46765
7.46356
7.45978
7.35021
7.34373
7.33521
7.32815
7.32460
7.32123
7.27011
6.54325
6.50739
6.48583
6.48189
6.44992
6.44609
5.95143
5.45993
5.45349
5.40244
5.39599
5.12596
5.11939
5.09005
5.08348
5.04125
4.89417
4.89121
4.43663
4.41458
3.56146
3.53839
2.68227
2.48962
2.47026
2.45615
2.40491
2.39841
2.37412
2.36758
2.36142
2.35659
1.97494
1.96117
1.95301
1.93237
1.91851
1.53460
1.52955
1.52131
1.49205
1.30330
1.29319
1.28700
1.15443
1.13795
0.91376
LY-V-171


ppm
200
180
160
140
120
100
80
60
40
20
0
3.98
Ph
O
142.838
137.624
135.863
131.712
128.508
128.351
128.224
122.676
114.994
109.576
86.133
85.248
77.418
76.992
76.569
73.632
59.027
37.118
30.892
26.472
LY-V-171


ppm
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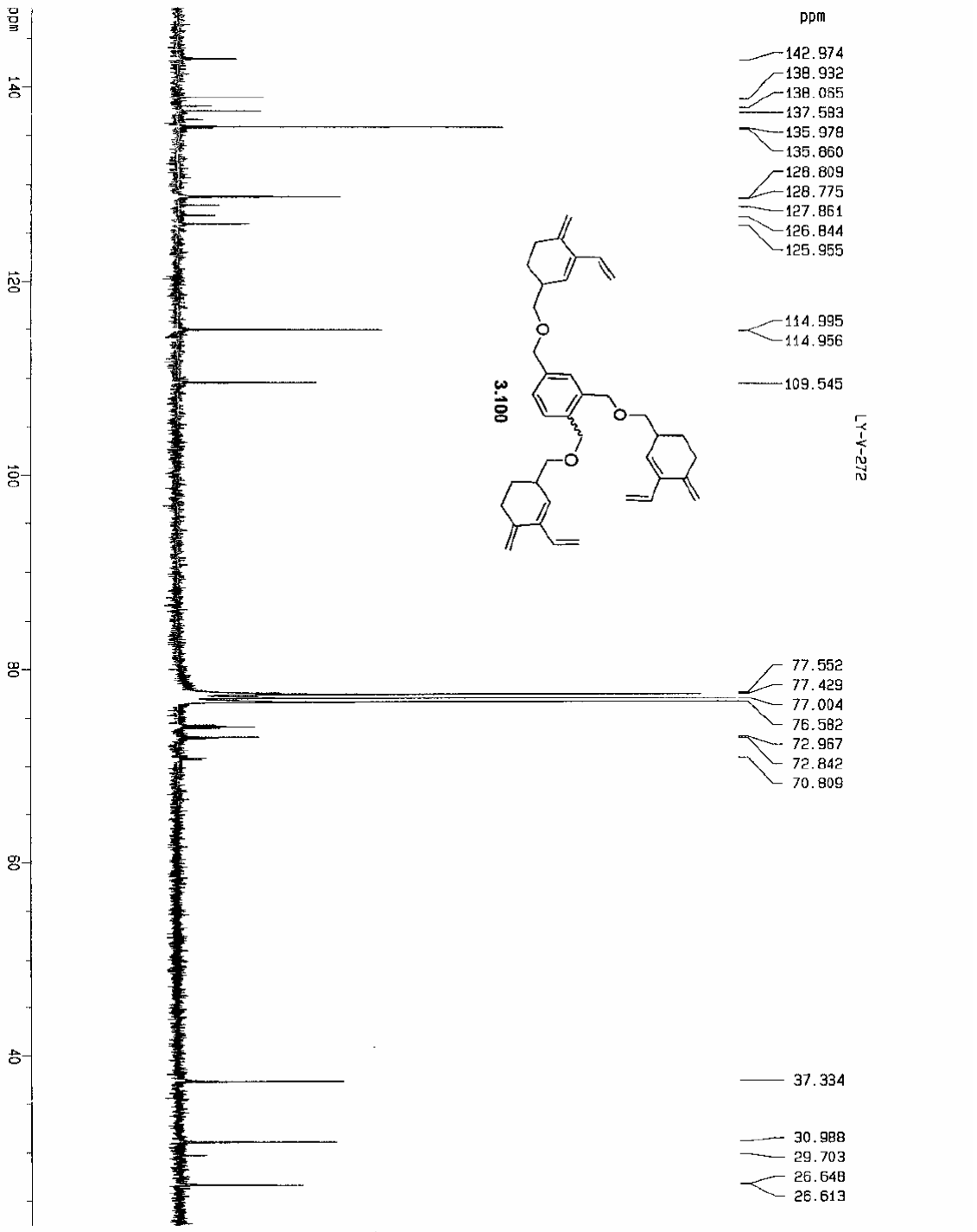
1.0009
1.1271
1.0018
0.9752
2.1180
2.0641
1.0893
2.2716
1.1243
1.2711
3.100
7.40259
7.37864
7.29407
7.26877
7.25609
6.51321
6.47730
6.45578
6.41990
5.90470
5.41219
5.35476
5.09935
5.09319
5.08349
5.05731
5.00642
4.86108
4.61046
4.60270
4.54545
3.46170
3.43755
3.43151
3.41632
3.40951
3.39894
3.39271
3.36940
3.36220
2.65473
2.49217
2.47635
2.45909
2.44461
2.42737
2.41174
2.37575
2.36371
2.32699
2.29105
1.94571
1.92470
1.90402
1.88821
1.60986
1.50562
1.47705
1.44814
1.43560
1.26324
1.06107
1.03018
0.89163
LY-V-272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137.583
135.978
135.860
128.809
128.775
127.861
126.844
125.955
114.995
114.956
109.545
77.552
77.429
77.004
76.582
72.967
72.842
70.809
37.334
30.988
29.703
26.648
26.613
3.100
LY-V-272
ppm
140
120
100
80
60
40