Cycloisomerization and Carbocyclization Reactions of Allenes for the Synthesis of Cross-Conjugated Trienes and Tryptophan-Derived Scaffolds

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Cycloisomerization and Carbocyclization Reactions of Allenes for the Synthesis of Cross-Conjugated Trienes and Tryptophan-Derived Scaffolds

Thomas O. Painter, Ph. D.

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A strategy for the preparation of 3-vinyl-2-alkylidene-3-cyclohexen-1-ones has been developed using an intramolecular rhodium(I)-catalyzed carbocyclization reaction of allene-ynones. Application of this strategy towards the preparation of analogs of the anticancer agent irofulven was realized, leading to highly functionalized spiro[2.5]octatrienes.

A novel approach to ε-lactams from allene-containing propargyl amides has been achieved, also using the rhodium(I)-catalyzed carbocyclization reaction. Further elaboration of this strategy has afforded triene-containing azepines and a pyrroloazepinone.

A diverging diversity-oriented synthesis (DOS) strategy using tryptophan as a key starting material was investigated. Constructon of allenic tetrahydro-β-carboline scaffolds via a Pictet-Spengler reaction and subsequent silver(I)-catalyzed cycloisomerization afforded tetrahydroindolizinoindoles. Conversion of the tetrahydro-β-carboline to an allenic propiolamide followed by a microwave-assisted allenic [2 + 2] cycloaddition reaction provided tetrahydrocyclobutaindoloquinolizinones. An allene-yne substituted derivative of tryptophan gave indolylmethylazabicyclooctadiene when subjected to a microwave-assisted allenic [2 + 2] cycloaddition reaction. This same tryptophan-derived precursor afforded an indolylmethyldihydrocyclopentapyridinone when subjected to a rhodium(I)-catalyzed cyclocarbonylation reaction.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

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It has been a long trip.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
aq.	aqueous
Ar	aryl
BBEDA	*N*,*N*-bisbenzylideneethylenediamine
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
Cat.	catalytic
Cbz	carbobenzyloxy
CN	cyano
CO	carbon monoxide
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylidene acetone
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
dppb	1,4-*bis*(diphenylphosphino)butane
dppe	1,2-*bis*(diphenylphosphino)ethane
dppm	*bis*(diphenylphosphino)methane
dppp	1,3- *bis*(diphenylphosphino)propane
dr	diastereomeric ratio
EDC•HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl
ee	enantiomeric excess

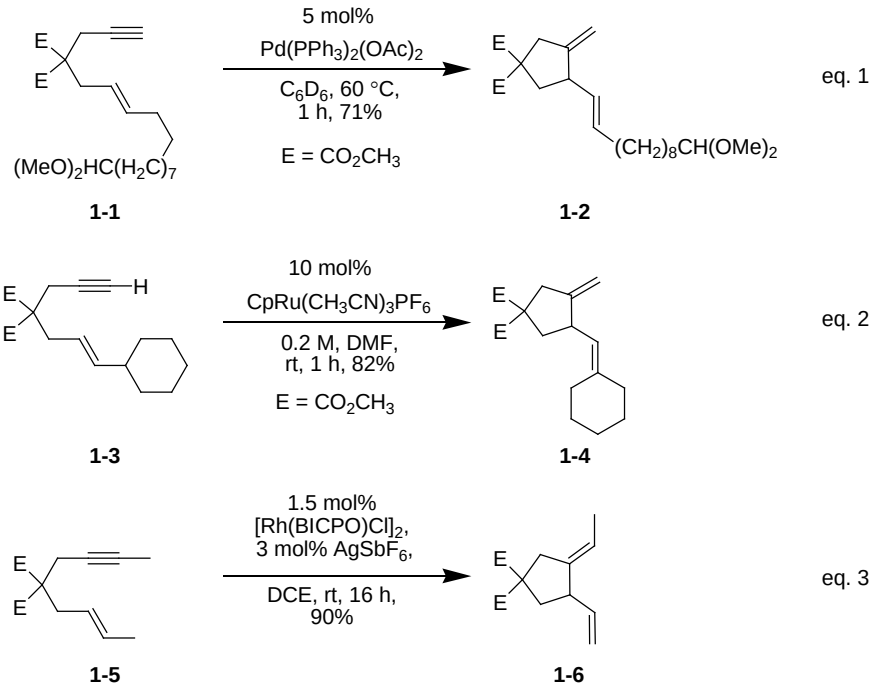
EI	electron impact (ionization)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
h	hours
HMAF	hydroxymethylacylfulvene
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
i-Bu	isobutyl
i-Pr	isopropyl
IR	infrared
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
min	minutes
MS	mass spectrometry
MWI	microwave irradiation
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NMO	*N*-methylmorpholine-*N*-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PPTS	pyridinum *p*-toluenesulfonate
PTAD	4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione
PTSA	*p*-toluenesulfonic acid
RI	refractive index
sat'd	saturated
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-Bu	tertiary butyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
TMS	trimethylsilyl
Tol	toluene
UPCMLD	University of Pittsburgh Center for Chemical Methodologies and Library Development
wt.	weight

1.0 RHODIUM(I)-CATALYZED CARBOCYCLIZATION REACTIONS OF ALLENE-YNONES: PREPARATION OF 3-VINYL-2-ALKYLIDENE-3-CYCLOHEXEN-1-ONES

1.1 INTRODUCTION

1.1.1 Transition Metal-Catalyzed Carbocyclization Reactions of Enynes

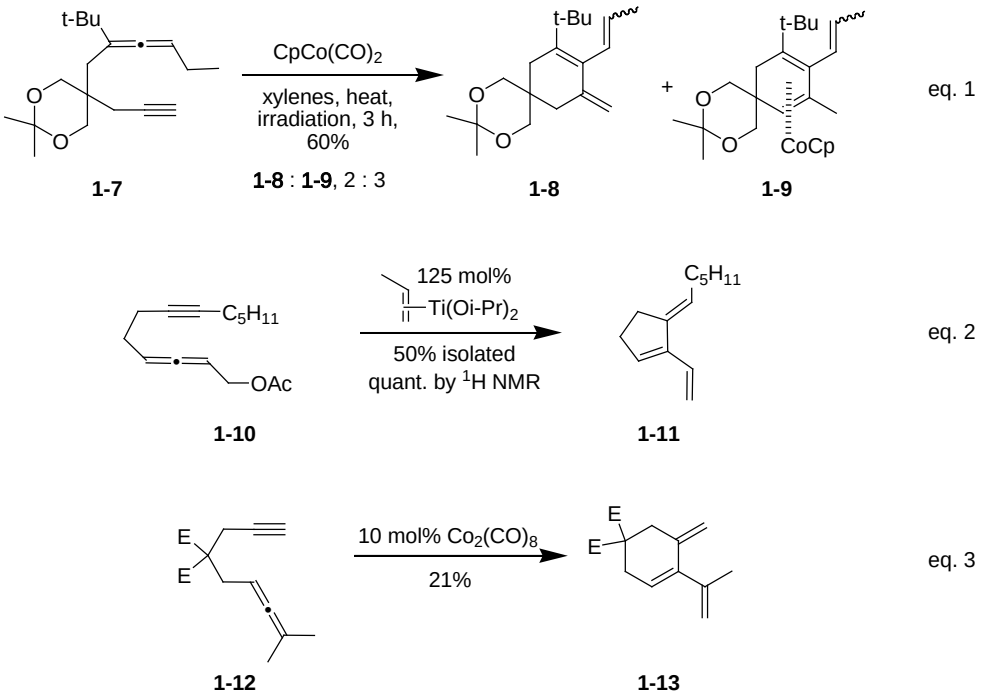
Transition metal-catalyzed carbocyclization reactions of enynes have been used extensively to prepare 1,4-dienes. A number of transition metals catalyze the carbocyclization process with palladium being the most popular metal.[1] For example, enyne **1-1** was reacted with 5 mol% palladium(II)triphenylphosphine acetate [$Pd(PPh_3)_2(OAc)_2$] to afford 1,4-diene **1-2** in 71% yield as only the *E* isomer (Scheme 1.1, eq. 1).[2a-c] Two other examples are shown below, highlighting metal complexes of ruthenium and rhodium, which are gaining in popularity. Enyne **1-3** was reacted with 10 mol% tris(acetonitrile)cyclopentadienyl ruthenium(II) hexafluorophosphate [$CpRu(CH_3CN)_3PF_6$] to obtain 1,4-diene **1-4** in 82% yield (Scheme 1.1, eq. 2).[2d] Zhang used rhodium(I)(BICPO) chloride dimer activated with silver hexafluoroantimonate ([$Rh(BICPO)Cl]_2$-$AgSF_6$) to produce 1,4-diene **1-6** in 84% yield (Scheme 1.1, eq. 3).[3]



Scheme 1.1 Transition Metal-Catalyzed Carbocyclization Reactions of Enynes Affording 1,4-Dienes

1.1.2 Transition Metal-Catalyzed Carbocyclization Reactions of Allene-ynes

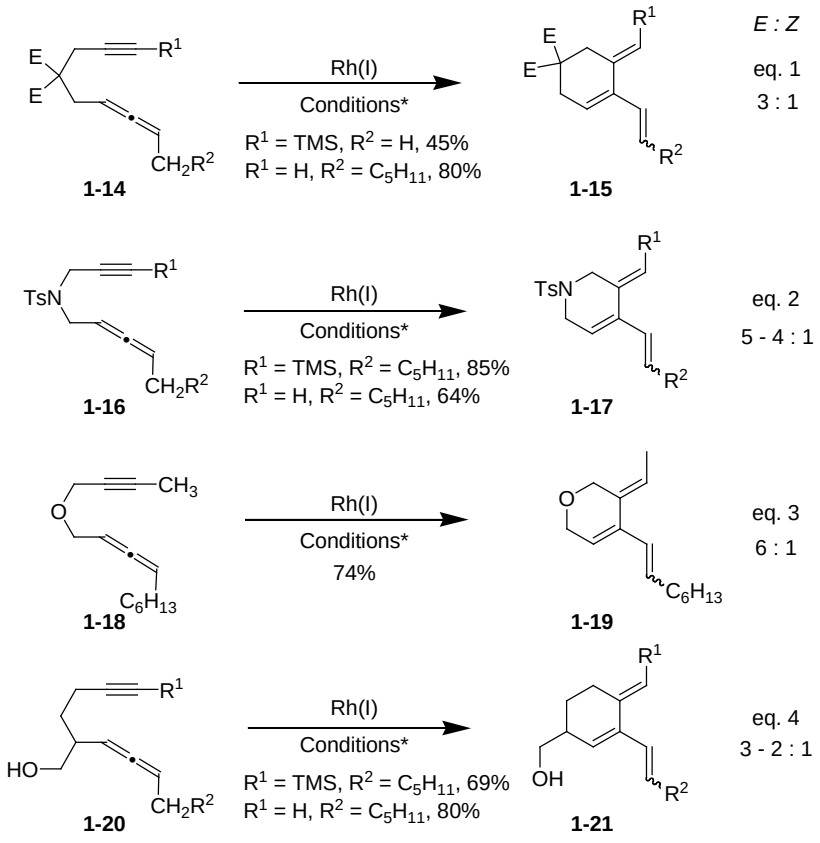
Until recently, transition metal catalyzed carbocyclization reactions of allene-ynes have been rare. The first transition metal-mediated allene-yne carbocyclization reaction was reported by Malacria; allene-yne **1-7** was reacted with stoichiometric cyclopentadienyl dicarbonyl cobalt(I) [$CpCo(CO)_2$] affording a 2 : 3 mixture of cross-conjugated trienes **1-8** and **1-9** (Scheme 1.2, eq. 1).[4] Sato reported the carbocyclization of allene-ynes **1-10** using 1.25 equivalents of propenyl titanium diisopropoxide to afford high yields of triene **1-11** when an alkoxide leaving group was present (Scheme 1.2, eq. 2).[5] Finally, Livinghouse reported triene **1-13** as a by-product in a cobalt-catalyzed cyclocarbonylation reaction of allene-yne **1-12** (Scheme 1.2, eq. 3).[6]



Scheme 1.2 Previous Transition Metal-Catalyzed Allenic Carbocyclization Reactions

In the first two examples, the substrate structure was used to control the double bond selectivity. For example, in Malacria's system, the bulky *t*-butyl group of **1-7** directed the reaction to the distal double bond, while in Sato's case, the metal was forced to react with the distal bond due to the decreased tether length of **1-10,** favoring formation of a five-membered ring over a four-membered ring.

In 2002, Brummond and coworkers showed that cross-conjugated trienes could be produced in high yields using rhodium or iridium containing catalysts, and for the first time, the catalyst, not the substrate, was responsible for a selective reaction with the distal double bond of the allene.[7,8] Similar carbocyclization reactions using Wilkinson's catalyst were subsequently reported by Shibata.[9] Examples demonstrating the scope and limitation of the initial study are shown in scheme 1.3.

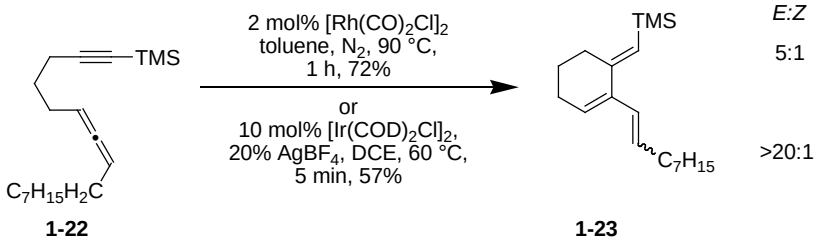


Scheme 1.3 Scope of the Rh(I)-Catalyzed Allenic Carbocyclization Reaction

Preliminary studies by Brummond on the Rh(I)-catalyzed carbocyclization reaction demonstrated a high tolerance for substrate functional groups. For example, all carbon containing tethers with a diester group at the homopropargylic position **1-14** cyclized to give trienes **1-15** in 45 – 80% yields (Scheme 1.3, eq. 1). Similarly, propargyl sulfonamides **1-16** and ethers **1-18** cyclized under the same conditions to afford trienes **1-17** and **1-19** in 64 – 85% yields (Scheme 1.3, eqs. 2 and 3). Finally, allene-ynes containing a hydroxymethyl group at the bis-homopropargylic position **1-20** reacted to provide trienes **1-21** in 69 – 80% yields (Scheme 1.3, eq. 4).

Another interesting observation by Brummond was that $[Ir(COD)Cl]_2$ activated with $AgBF_4$ produced much higher *E:Z* ratios than $[Rh(CO)_2Cl]_2$ (Scheme 1.4). This was presumably

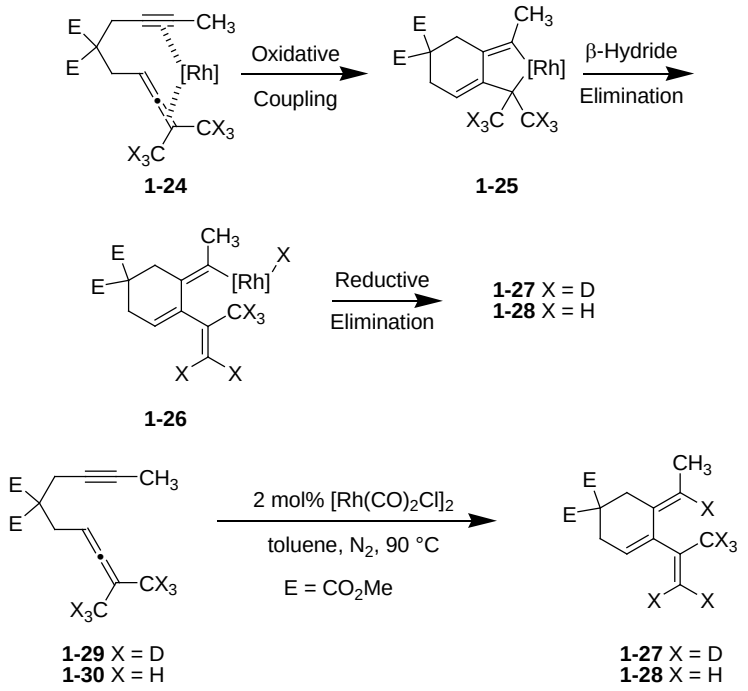
due to the fact that skeletal reorganization processes occur more slowly for transition metals lower on the periodic table.



1-22 **1-23**

Scheme 1.4 Selectivity Advantage of Ir(I)-Catalysis vs. Rh(I)-Catalysis

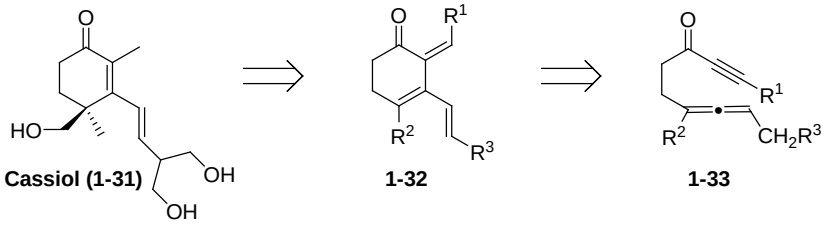
A mechanism for the rhodium(I)-catalyzed process is shown in Scheme 1.5 and is based upon the accepted carbocyclization mechanism of enynes. Chelation of the metal complex to the allene-yne provided complex **1-24**, then oxidative coupling afforded metallocycle **1-25**. β-Hydride elimination occurred to give rhodium hydride (deuteride) species **1-26** followed by reductive elimination to afford triene **1-27** or **1-28**. The proposed mechanism was supported by deuterium labeling experiments, where the carbocyclization of **1-29** afforded **1-27**.[7] A crossover experiment was performed using a 1 : 1 molar ratio of **1-29** and **1-30**, affording only **1-27** and **1-28**, respectively, with no signs of deuterium scrambling.



Scheme 1.5 Mechanism for the Rh(I)-Catalyzed Allenic Carbocyclization Reaction

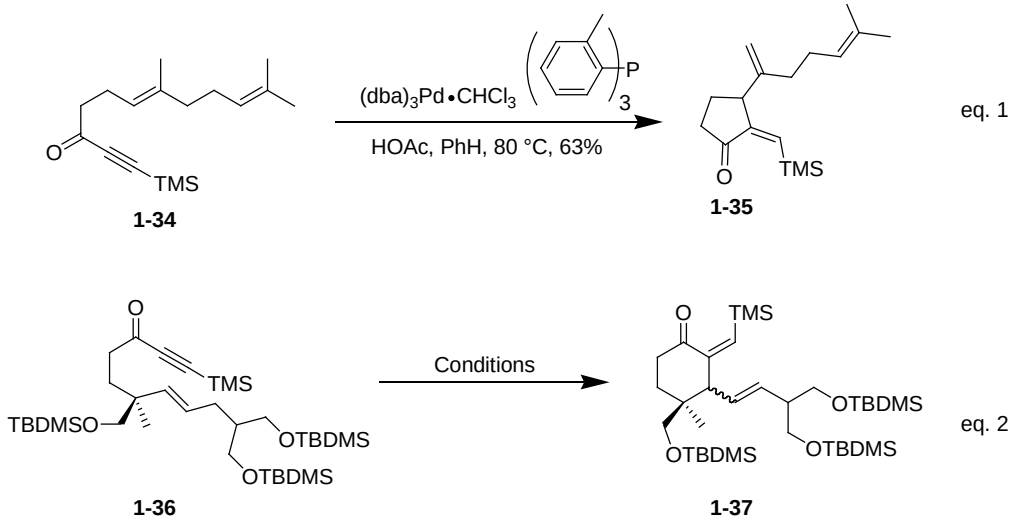
1.1.3 Transition Metal-Catalyzed Carbocyclization Reactions of Ynones and Allene-ynones

More recently, efforts to expand the scope of the allenic carbocyclization reaction were focused on substrates in which the resultant double bonds can be differentiated and chemoselectively manipulated. For example, 3-vinyl-2-alkylidene-3-cyclohexen-1-one **1-32** is a triene-containing ring system where each double bond is sterically and electronically different. It is anticipated that a suitably functionalized trienone such as **1-32** can be used in an expeditious synthesis of cassiol (**1-31**) (Scheme 1.6).



Scheme 1.6 Potnetial Use of an Allene-ynone in the Synthesis of Caassiol (1-31)

Interestingly, allene-ynones have not previously been employed in carbocyclization reactions; however, enynone carbocyclization reactions have been reported. For example, Trost reacted ynone **1-34** with tris(dibenzylideneacetone)dipalladium(0) chloroform adduct [$(dba)_3Pd_2 \bullet CHCl_3$] in the presence of tri-*o*-tolylphosphine to give cyclopentanone **1-35** in 63% yield (Scheme 1.7, eq. 1).[10] Extension of the reaction conditions to the preparation of alkylidene cyclohexenones was not as straightforward. For example, reaction of ynone **1-36** required "ligandless" conditions (4 mol% [$(dba)_3Pd_2 \bullet CHCl_3$] in the presence of formic acid in DCE) in order to access diene-one **1-37** (Scheme 1.7, eq. 2).[11]



Conditions: 4 mol% $(dba)_3Pd_2 \bullet CHCl_3$, BBEDA, HOAc, PhH, **no rxn**
4 mol% $(dba)_3Pd_2 \bullet CHCl_3$, HCO_2H, DCE, rt, **83%**

Scheme 1.7 Early Carbocyclization Reactions of Enynones

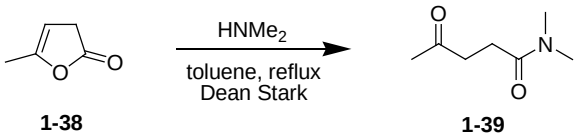
1.2 RESULTS AND DISCUSSION

1.2.1 Testing the Feasibility of a Rh(I)-Catalyzed Carbocyclization Reaction of Allene-ynones

We propose to test the feasibility of the carbocyclization reaction of allene-ynones using a triene like **1-32** as the initial target compound. This compound was chosen for three reasons: its structure resembled the natural product cassiol (**1-31**), the starting material could be rapidly synthesized, and *E/Z* isomers of the appending alkene are not possible, thus simplifying product analysis. The scope and limitations of this carbocyclization reaction will then be further tested by appending different groups to the alkyne terminus. Finally, the products will be reacted in with various dienophiles to gauge the chemoselectivity of the alkenes.

1.2.1.1 Preparation of Allene-ynones

Synthesis of amide **1-39** was accomplished by refluxing α-angelica lactone **1-38** and 40% aqueous dimethylamine in toluene with simultaneous removal of water, affording the γ-ketoamide **1-39** in 84 - 97% yields.[12] This reaction protocol was used to prepare 12 g of **1-39** (Scheme 1.8).



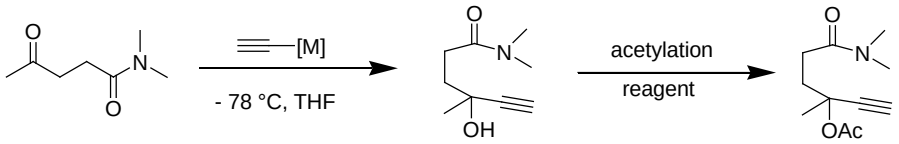
1-38 **1-39**

Scheme 1.8 Synthesis of γ-Ketoamide 1-39 from α-Angelica Lactone

Conversion of ketone **1-39** to allene **1-44** (Scheme 1.10) by way of the corresponding propargyl acetate **1-41** was challenging. Addition of ethynyl magnesium bromide or lithium acetylide to **1-39**, followed by acylation of the crude alcohol afforded acetate **1-41** in low yield

(Table 1.1, entries 1 and 2). Competing enolate formation of the ketone was deemed responsible for the low yields of **1-41**.

Table 1.1 Formation of Acetate 1-41

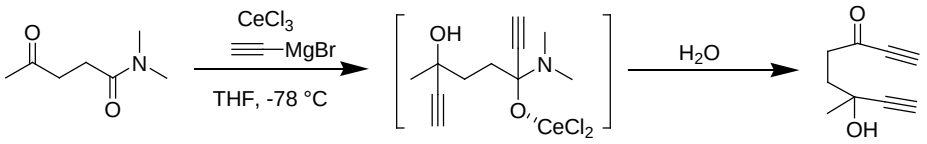


1-39 **1-40** **1-41**

Entry	Type	[M] (eq)	Acetyl Reagent (eq)	Yield of **1-41**
1	2 pot	MgBr (3)	Ac_2O (7)	26%
2	2 pot	Li (5)	Ac_2O (7)	24%
3	2 pot	$CeCl_2$ (3)	Ac_2O (7)	46 - 49%
4[1]	2 pot	$CeCl_2$ (1.5)	Ac_2O (7)	54%
5[1,2]	2 pot	$CeCl_2$ (2)	Ac_2O (7)	49%
6	1 pot	$CeCl_2$ (3)	Ac_2O (7)	80%
7	**1 pot**	**$CeCl_2$ (3)**	**AcCl (5)**	**92 - 97%**

Average yields shown. [1] Reaction incomplete. [2] Side product also isolated in small amount

Organocerium reagents were next explored.[13] In all cases use of organocerium reagents improved yields of acetate **1-41** by 20 – 30% (Table 1.1, entries 3 – 5); however, a three fold excess of the organocerium reagent was required for full conversion to alcohol product **1-40** (Table 1.1, compare entries 3 and 4). Attempts to add more ethynyl magnesium bromide (the organocerium reagent precursor) to the reaction after it had started gave a side product (Table 1.1, entry 5). This product was characterized as diyne **1-43** as evidenced by the loss of the resonances at 3.03 and 2.93 ppm in the ^{1}H NMR spectrum corresponding to the dimethylamide and the presence of a much less polar compound by TLC analysis (Scheme 1.9). It was reasoned that cerium activated the amide carbonyl to nucleophilic addition.



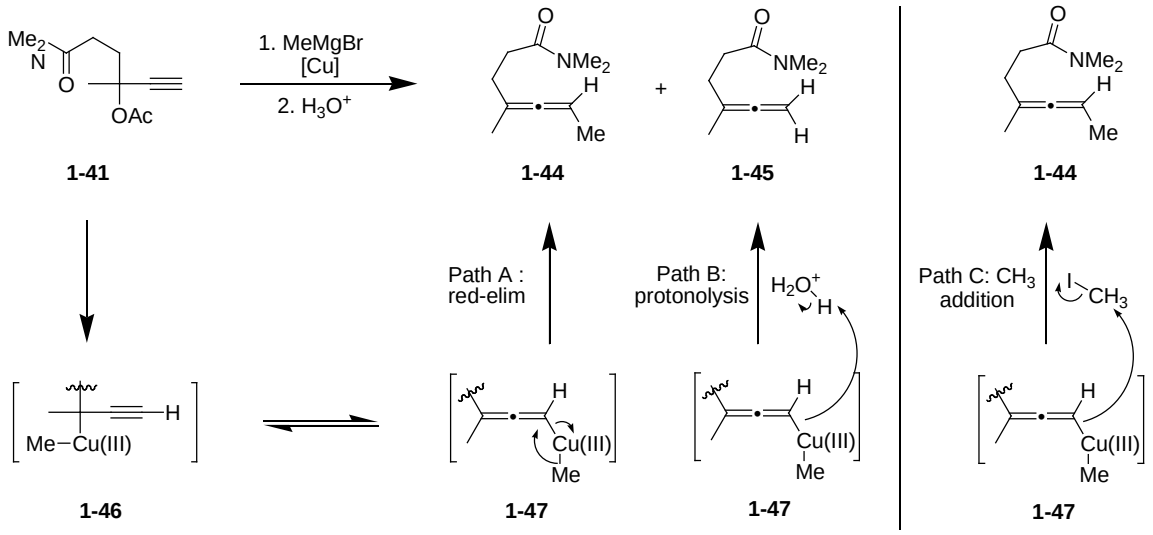
1-39 **1-42** **1-43**

Scheme 1.9 Proposed Mechanism for Formation of Diyne 1-43

Because of the water solubility of alcohol **1-40**, a one-pot procedure for acetylide addition/acetylation was investigated. Addition of acetic anhydride following alkyne formation afforded an 80% yield of acetate **1-41** (Table 1.1, entry 6). Addition of acetyl chloride, a more oxophilic acetylating reagent, provided optimal yields of **1-41**, averaging 95% (Table 1.1, entry 7).

With propargyl acetate **1-41** in hand, its conversion to allene-amide **1-44** was explored (Table 1.2). Stoichiometric CuBr·DMS was reacted with **1-41**, leading to the formation of allenes **1-44** and **1-45** in a 1 : 3 ratio. Use of copper bromide and lithium bromide resulted in a 1 : 2 ratio of **1-44** : **1-45** in 55% yield (Table 1.2, entry 2). Reducing the equivalents of methyl magnesium bromide reversed the selectivity in favor of the addition product, giving a 2 : 1 ratio of **1-44** : **1-45** (Table 1.2, entry 3). Because the products were inseparable by column chromatography and normal phase HPLC, investigations to lessen the amount of formal reduction product **1-45** began.

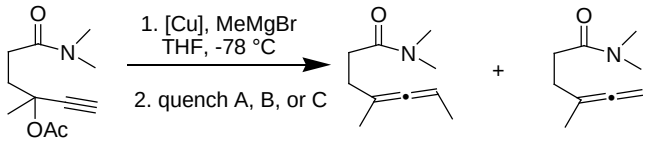
As proposed by Claesson, copper added across the acetate bond of **1-41** to form adduct **1-46** followed by reversible rearrangement to allenic copper adduct **1-47**. Copper intermediate isomers **1-46** and **1-47** were stable enough to survive until reaction workup (Scheme 1.10).[14] Two paths were possible; in path A, reductive elimination occured to afford the desired addition product **1-44**; in path B, upon workup, protonolysis occured to give the formal reduction product **1-45**.



Scheme 1.10 Formation of Allenes 1-44 and 1-45. Reductive Elimination vs. Protonolysis vs. CH_3 Addition

Marshall has reported a means to circumvent the reduction product by adding MeI to the reaction mixture before the acidic workup.[15] Under these conditions, the methyl group can be added to copper intermediate **1-47** via path C, to obtain the desired product **1-44** (Scheme 1.10). Indeed, using Marshall's protocol in the reaction of **1-41** with methyl cuprate afforded only **1-44** (Table 1.2, entry 4). A 1 : 1 mixture of aqueous 3% NH_4OH : sat'd NH_4Cl was also found to be the best quenching agent (Table 1.2, entry 4). Although successful, this reaction used copper bromide salt that required drying prior to use, making the conditions less convenient. These conditions were also less consistent, causing incomplete reactions.

Table 1.2 Conversion of Propargyl Acetate 1-41 to Allene 1-44



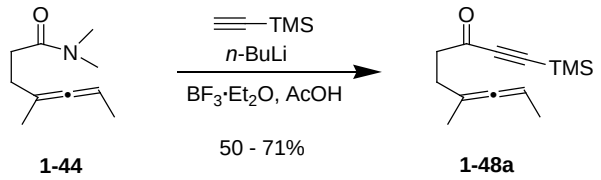
1-41 **1-44** **1-45**

Entry	[Cu] (eq)	MeMgBr (eq)	Quench Conditions	Yield	Product Ratio[1] (**1-44 :1-45**)
1	CuBr • DMS (2)	4	A	55%[2]	1 : 3
2	CuBr / LiBr (2)	4	A	55%[2]	1 : 2
3	CuBr / LiBr (2)	2	A	Not determined	2 : 1
4[3]	CuBr / LiBr (2)	2	B	Not determined	100 : 0
5	CuBr • DMS (2)	2	B	62%	1 : 3
6	CuCN / PBu_3 (1.2)	2	A	Not determined	10 : 1
7	CuCN / PBu_3 (1.2)	2	C	49%	10 : 1
8[4]	CuBr / LiBr (2)	2	B	85 - 100%	100 : 0

Quench Conditions A: sat'd NH_4Cl; B: 4 to 6 eq. MeI then 1 : 1 3% aq. NH_4OH : NH_4Cl;
C: 4 to 6 eq. MeI then sat'd NH_4Cl
[1] Determined by integration of allene resonances in the ^1H NMR spectrum
[2] Average Yield
[3] Reaction performed using improperly purified CuBr
[4] Reaction performed using properly purified CuBr

Formation of the cuprate using the more convenient CuBr·DMS complex followed by addition of MeI to the reaction mixture still resulted in a 1 : 3 ratio of **1-44** : **1-45** (Table 1.2, entry 5). Next, a procedure employing CuCN and PBu_3 was attempted. Mixed results were reported in the literature where addition of phosphine ligand has served to suppress the formation of the reduction product, and in other cases it increased the yield of the reduction product. This effect appeared to be complex and dependent upon conditions and substrates.[16] Using these conditions afforded the products **1-44** : **1-45** in a 10 : 1 ratio (Table 1.2, entry 6). Addition of MeI under the CuCN/PBu_3 conditions in the manner described in Table 1.2, entry 4 did not improve this ratio (Table 1.2, entry 7). During these experiments, an error in the published purification procedure for CuBr was corrected.[17] After which, scale-up of the original CuBr conditions afforded reproducibly high yields of only the desired allene **1-44** (Table 1.2, entry 8).

With sufficient quanties of allene **1-44** secured, the alkyne moiety was installed by addition of lithium trimethylsilyl acetylide to **1-44** in the presence of $BF_3{\cdot}Et_2O$ using Trost's procedure,[13] to afford allene-yne **1-48a** in 50 - 71% yield. The structure of **1-48a** is evidenced by the resonance at 0.21 ppm (s, 9H) in the ^1H NMR spectrum, corresponding to the TMS moiety, and the absorbance at 2151 cm^{-1} in the IR spectrum, corresponding to the alkyne (Scheme 1.11).

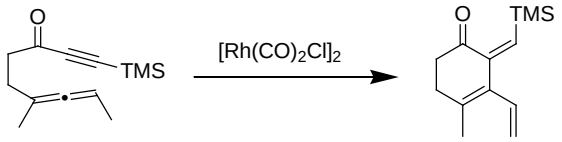


Scheme 1.11 Synthesis of Allene-Ynone 1-48a from Allene-Amide 1-44

1.2.1.2 Feasibility and Optimization of the Carbocyclization Reaction of Allene-ynones

To test the feasibility of the allenic carbocyclization reaction of allene-ynones, we reacted **1-48a** with 10 mol% rhodium biscarbonyl chloride dimer at room temperature in DCE. Complete consumption of the starting material occurred in less than five min based upon TLC analysis, affording trace amounts of the desired product **1-49a** (< 10%), and another product that decomposed before it could be characterized (Table 1.3, entry 1). Decreasing the reaction temperature to 0 °C gave 55% yield of triene **1-49a**, but an undesired product could still be seen by TLC analysis (Table 1.3, entry 2).

Table 1.3 Optimization of the Carbocyclization Reaction Conditions to form Trienone 1-49a



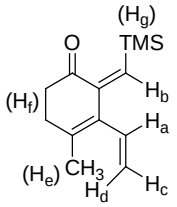
1-48a **1-49a**

Entry	mol% $[Rh(CO)_2Cl]_2$	Temp. (°C)	Solvent	Yield
1	10	rt	DCE	< 10%
2	10	0	DCE	55%
3	3	0	DCE	92%
4	3	0	Toluene	95%
5	1	0	Toluene	62%

All reactions were complete in 5 min or less.

Lowering the catalyst loading to 3 mol% had a much larger effect, and the product was obtained in 92% yield (Table 1.3, entry 3). Changing the solvent from DCE to toluene resulted in a marginal increase in the yield (Table 1.3, compare entries 3 and 4). Finally, reacting **1-48a** with 1 mol% catalyst in toluene gave 62% yield of **1-49a** (Table 1.3, entry 5). Characterization of triene **1-49a** was supported by the ^{1}H NMR spectrum; resonances at 6.27 (dd, 1H), 6.01 (s, 1H), 5.45 (dd, 1H), and 5.15 ppm (dd, 1H), corresponding to H_a, H_b, H_c, and H_d (Table 1.4).

Table 1.4 ^{1}H NMR Characterization of Trienone 1-49a



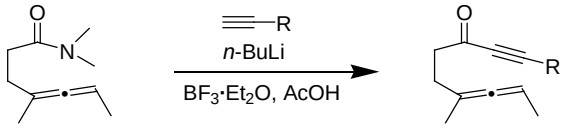
1-49a

Proton	Chemical Shift (ppm)	Multiplicity	Integration	*J*-value (Hz)
H_a	6.27	dd	1	17.7, 11.3
H_b	6.01	s	1	-
H_c	5.45	dd	1	11.3, 2.1
H_d	5.15	dd	1	17.7, 2.1
H_e	1.95	s	3	-
H_f	2.61 – 2.51	m	4	-
H_g	0.13	s	9	-

1.2.2 Exploration of the Scope and Limitations of Carbocyclization Reactions of Allenic-ynones by Varying Substitution at the Alkyne Terminus

Allene-ynones possessing alkyl **1-48b**,[18] alkyl ether **1-48c-e**, alkenyl **1-48f**, alkoxy **1-48g**, and aryl groups **1-48i-k**, were prepared in a manner entirely analogous to that discussed for **1-48a** (Table 1.5). Allene-ynone **1-48h** was prepared in 90% yield by removing the TMS-moiety from **1-48a** using dilute (0.05 M) aqueous sodium tetraborate.[19]

Table 1.5 Allene-ynones with Varied Substitution at the Alkyne Terminus



1-44 **1-48**

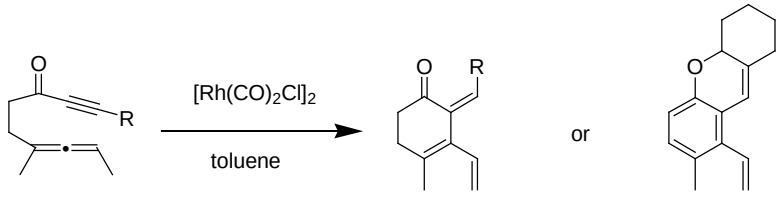
Cmpd.	R	Yield (%)	Cmpd.	R	Yield (%)
1-48a	TMS	63	**1-48g**	OCH_2CH_3	83
1-48b	Me	89	**1-48h***	H	90
1-48c	$(CH_2)_3OTBS$	41	**1-48i**	Ph	92
1-48d	CH_2CH_2OTBS	98	**1-48j**	*p*-C_6H_4OMe	88
1-48e	CH_2CH_2OTHP	98	**1-48k**	*p*-$C_6H_4CF_3$	89
1-48f	1-cyclohexenyl	94			

*Prepared from **1-48a**

When allene-ynone **1-48b** (R = Me) was subjected to the optimized Rh(I)-catalyzed carbocyclization conditions, the reaction proceeded much more slowly than the reaction of **1-48a** (R = TMS), requiring a higher temperature (room temperature vs. 0 °C) and a longer reaction time (1.5 h vs. 5 min) (Table 1.6, entry 1). Similarly, the alkyne substituted with a TBS-protected propanol (**1-48c** (R = $(CH_2)_3OTBS$), Table 1.6 entry 2), afforded trienone **1-49c** in 80% yield after 1.5 h at rt. However, the reaction of allene-ynone **1-48d** (R = $(CH_2)_2OTBS$) proceeded in 20 min at rt to give trienone **1-49d** proceeded in 20 min (Table 1.6, compare entries

2 and 3). Similarly, reaction of **1-48e** (R = $(CH_2)_2OTHP$, Table 1.6, entry 4) afforded **1-49e** in 15 min at rt.

Table 1.6 Formation of Substituted Trienones

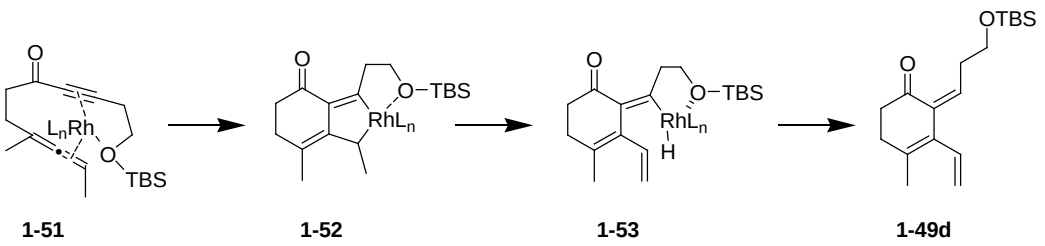


1-48 **1-49** **1-50**

Entry	Starting Material	R	T (°C)	Time	Product	Average Yield
1	**1-48b**	Me	rt	1.5 h	**1-49b**	73%
2	**1-48c**	$(CH_2)_3OTBS$	rt	1.5 h	**1-49c**	80%
3	**1-48d**	$(CH_2)_2OTBS$	rt	20 min	**1-49d**	88%
4	**1-48e**	$(CH_2)_2OTHP$	rt	15 min	**1-49e**	88%
5*	**1-48f**	1-cyclohexenyl	45 - 50	3 h	**1-50**	26%
6	**1-48g**	OEt	45	3 h	**1-49g**	Decomp.
7	**1-48h**	H	rt	-	**1-49h**	Decomp.
8†	**1-48i**	phenyl	50	5 min	**1-49i**	76%
9†	**1-48j**	*p*-C_6H_4OMe	50	5 min	**1-49j**	76%
10†	**1-48k**	*p*- $C_6H_4CF_3$	50	5 min	**1-49k**	76%

All reactions carried out at 0.3 M in toluene with 3 mol% catalyst except where noted.
* 5 mol% catalyst
† 8 mol% catalyst

Rate differences for allenic carbocyclization reactions of **1-48d** and **1-48e**, as compared to **1-48b** and **1-48c**, can be explained by chelation of the protected alcohol to the rhodium (Scheme 1.12).[20] It is proposed that the appending oxygen coordinated to the rhodium complex **1-51** facilitated the oxidative coupling to give **1-52** by stabilizing the rhodium metallocycle. Formation of a six-membered chelate did not occur (Table 1.6, compare entries 1 and 2).

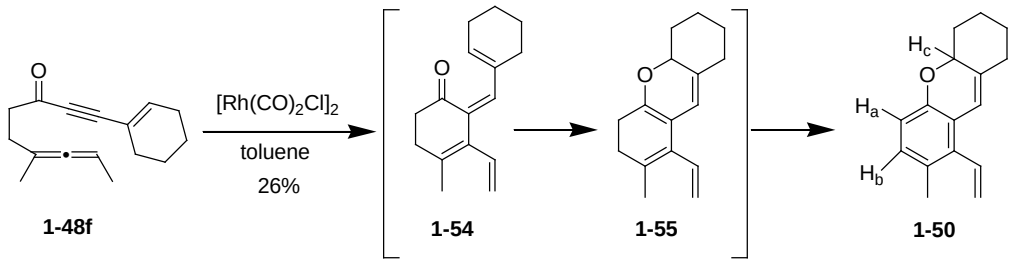


1-51 **1-52** **1-53** **1-49d**

Scheme 1.12 Effects of Ether Chelation in the Carbocyclization Reactions

Computational work on the mechanistically similar rhodium(I)-catalyzed cyclocarbonylation[8] and the ruthenium-catalyzed carbocyclization reactions[21] have found oxidative coupling to be the rate determining step for these similar reactions. There is also precedent for rate enhancements due to heteroatom chelation in cobalt mediated Pauson-Khand reactions reported by Krafft.[22,23]

Interestingly, reaction of **1-48f** (R = 1-cyclohexenyl, Table 1.6, entry 5) produced aromatic compound **1-50** as the only isolated product in 26% yield. The structure of **1-50** was supported by ^{1}H NMR analysis. For example, new resonances appeared at 6.85 ppm (d, 1H) and 6.56 ppm (d, 1H), corresponding to H_a and H_b, and at 4.86 ppm (dd, 1H), corresponding to H_c. Formation of this product can be explained through a carbocyclization/electrocyclization/ aromatization cascade mechanism in which tetraene **1-54** was first formed via the allenic carbocyclization reaction. Next, an electrocyclization reaction provided cyclic tetraene **1-55**. Finally, aromatization occurred, via an oxidative process, to afford styrene-derivative **1-50** (Scheme 1.13).



1-48f **1-54** **1-55** **1-50**

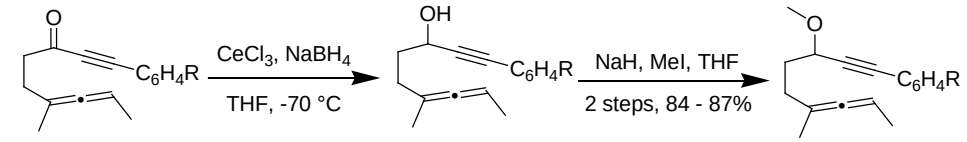
Scheme 1.13 A Carbocyclization/Electrocyclization/Aromatization Cascade Reaction

Performing the carbocyclization reaction on **1-48g** (R = OEt), produced a product that rapidly decomposed afterward (Table 1.6, entry 6). Terminal allene-ynone **1-48h** also decomposed with no sign of product (Table 1.6, entry 7).

Reaction of **1-48i** was carried out using 8 mol% $[Rh(CO)_2Cl]_2$ at 50 °C in 5 min to afford **1-49i** in 76% yield (Table 1.6, entry 8). A higher catalyst loading and elevated temperature were necessary to overcome the developing $A^{1,3}$ strain between the ketone and bulky phenyl group in the trienone. Allene-ynones with aryl groups possessing *para* electron-donating **1-48j** or electron-withdrawing groups **1-48k** gave similar results (Table 1.6, entries 9 and 10).

1.2.3 Carbocyclization Reactions of Allenes and Propargyl Ethers

It was hypothesized that the rate of cyclization would be slowed for propargyl ethers relative to the ynones. In order to test this possibility, ynones **1-48i** and **1-48j** were reduced under Luche conditions and then the alcohols protected to give **1-57i-j** (Scheme 1.14).



1-48i, R = H
1-48j, R = OMe

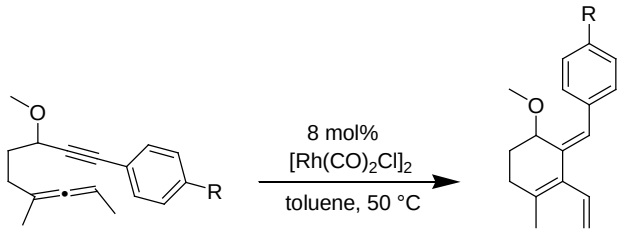
1-56i, R = H
1-56j, R = OMe

1-57i, R = H
1-57j, R = OMe

Scheme 1.14 Synthesis of Allenic Propargyl Ethers

Reaction of propargyl ethers **1-57i** and **1-57j** to 8 mol% rhodium(I) catalyst at 50 ºC afforded **1-58i** and **1-58j** in 5 – 10 min (Table 1.7). The yield increased significantly for **1-58i**, but the reaction rate was nearly identical for both for both ethers when compared to the allene-ynones (Table 1.6 enties 8 and 9 compare to Table 1.7 enties 1 and 2).

Table 1.7 Allenic Carbocyclization Reactions of Propargyl Ethers

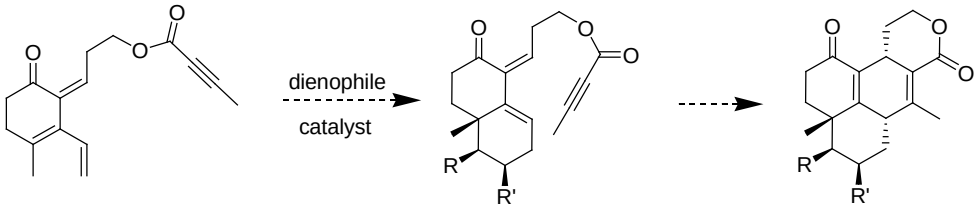


1-57 **1-58**

Entry	Starting Material	R	Time (min)	Product	Yield
1	**1-57i**	H	5	**1-58i**	95%
2	**1-57j**	OMe	< 10	**1-58j**	80%

1.2.4 Examining the Synthetic Utility of 3-Vinyl-2-Alkylidene-3-Cyclohexen-1-ones: Participation in Diels-Alder Reactions

Inspired by the work of Frank You in the Brummond group, it was hypothesized that triene **1-49l** would undergo an intermolecular Diels-Alder reaction with a dienophile.[24] In turn, this Diel-Alder adduct **1-59** would then react with the appended alkynoate in an intramolecular Diels-Alder reaction to give **1-60** (Scheme 1.15).

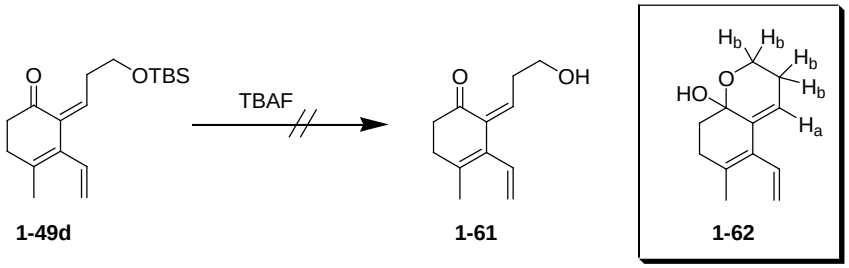


1-49l **1-59** **1-60**

Scheme 1.15 Potential Tandem Intra- and Intermolecular Diels-Alder Reactions of Trienones

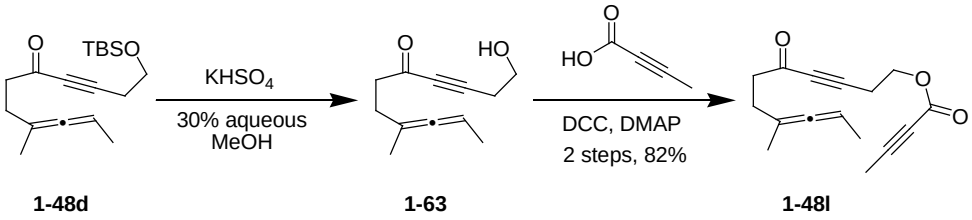
The most appealing approach to the synthesis of **1-49l** involved the removal of the TBS group from **1-48d** and coupling of the resultant alcohol with 2-butynoic acid. However, reaction of **1-48d** with TBAF did not produce the desired alcohol **1-61** (Scheme 1.16). Analysis of the crude ^{1}H NMR spectrum suggested formation hemiketal **1-62** as evidenced by changes in the

proton-proton splitting pattern. For example, the resonances at 6.20 ppm (dd, 1H) corresponding to H_a and 4.16 (m, 1H) and 3.83 (dd, 1H) corresponding to H_b (Scheme 1.16).



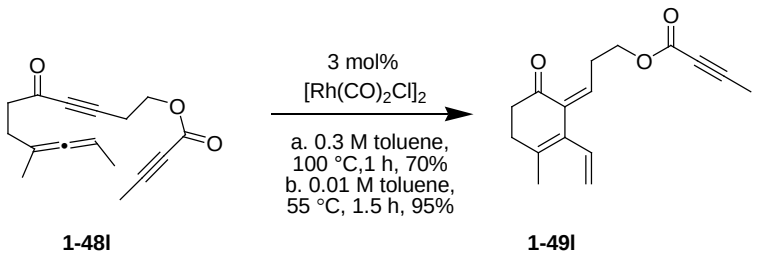
Scheme 1.16 Formation of Hemiketal 1-62 from Silyl Ether 1-49d Under TBAF Conditions

The next approach to **1-49l** involved coupling 2-butynoic acid to the allene-ynone prior to the allenic carbocyclization reaction (Scheme 1.17). Removal of the silyl group under $KHSO_4$ conditions provided alcohol **1-63** which was used without purification in a DCC coupling reaction to give **1-48l** in 82% yield over two steps (Scheme 1.17).[25]



Scheme 1.17 Formation of Butynoic Ester 1-48l

Reaction of allene-ynone **1-48l** under the optimized Rh(I)-catalyzed carbocyclization conditions afforded **1-49l** in 70% yield; however, this reaction required heating to 100 °C for 1 h (Scheme 1.18 conditions a). Diluting the reaction concentration from 0.3 M to 0.01 M (conditions b) afforded the product in 95% yield after 1.5 h at 55 °C. Interestingly, the reaction was slow in comparision with **1-48d** and **1-48e** (Table 1.6)



1-48l **1-49l**

Scheme 1.18 Rh(I)-Catalyzed Allenic Carbocyclization Reaction of 1-48l to Afford 1-49l

With the precursor **1-49l** in hand, efforts were made to effect Diels-Alder reactions of **1-49l** using a variety of dienophiles such as dimethyl acetylenedicarboxylate (DMAD), maleic anhydride, nitrosobenzene, and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). These reactions gave only complex mixtures over long reaction times or decomposed. Reaction of **1-49l** with sulfur dioxide gave decomposition and transition metal catalyzed formal Diels-Alder reactions using Wender's catalyst and 3-hexyne resulted in no reaction.[26] Thus, tandem Diels-Alder reactions of **1-49l** are not feasible. We attribute this to the propensity of the trienone **1-49l** to aromatize under forcing conditions.

1.3 CONCLUSIONS

In conclusion, 3-vinyl-2-alkylidene-3-cyclohexen-1-ones can be prepared from allene-ynones using a rhodium(I)-catalyzed carbocyclization reaction.[27] This reaction was tolerant of substitution at the alkyne terminus with observable rate effects caused by the groups appended at this position. Reactions of propargyl ethers showed similar results, indicating that the ketone played only a small role in the outcome of the reaction. These conditions are more general than the ligandless conditions reported by Trost to effect formation of six-membered rings, and provide rapid access trienones that possess electronically differentiated double bonds. However,

this method is not without its shortcomings since the stability of the 3-vinyl-2-alkylidene-3-cyclohexen-1-ones limits its utility, specifically in Tandem Diels-Alder reactions.

2.0 PROGRESS TOWARDS THE SYNTHESIS OF BICYCLIC IROFULVEN (HMAF) ANALOGS VIA RHODIUM(I)-CATALYZED ALLENIC CARBOCYCLIZATION REACTIONS

2.1 INTRODUCTION

Motivated by the success of the Rh(I)-catalyzed carbocyclization reaction of allene-ynones, we surmised that functionally dense trienes could be afforded using a Rh(I)-catalyzed carbocyclization reaction. The resultant spiro[2.5]octatrienes would serve as excellent targets due to their similarity to the illudins. A single step following the carbocyclization reaction would provide potentially biologically active compounds that exploit the placement of the double bonds found in the triene product via the known mode of action within cells.

2.1.1 Third Generation Illudin-type Compounds

In 1996, McMorris discovered a third generation analog of illudins M and S (**2-1**) with excellent therapeutic value against cancer (IC_{50} in HL-60 cells = 73 ± 8) - hydroxymethylacylfulvene (HMAF), also known as irofulven **2-3** (Fig 2.1).[28,29] This compound also promoted complete tumor regression in MV 522 lung carcinoma xenographs, a property that earlier illudin analogs did not possess.

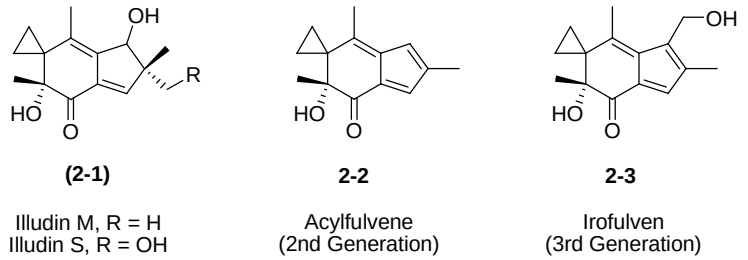
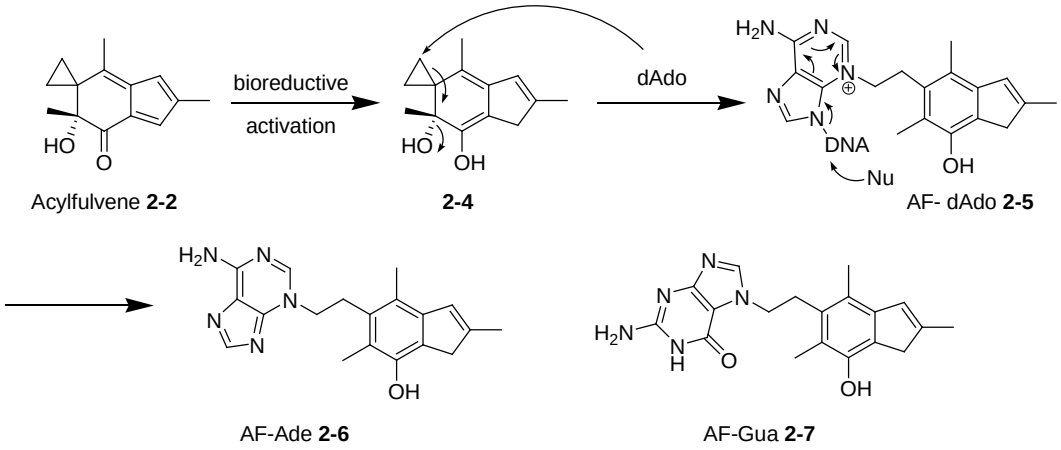


Figure 2.1 The Illudins (2-1), Acyclfulvene 2-2, and Irofulven 2-3

Several investigations into the mode of action for the illudins and their analogs have been performed.[30] Recently, Sturla investigated the mechanism of DNA alkylation by synthesizing acylfulvene-DNA.[31] In Sturla's report, acylfulvene **2-2** (Fig 2.1) was reacted with deoxyadenosine or deoxyguanosine in the presence of AOR/NADPH, affording acylfulvene metabolites of both nucleosides respectively (AF-dAdo **2-5** and AF-dGuo). The mechanism of DNA depurination involving acylfulvene **2-2** affording AF-Ade **2-6** or AF-Gua **2-7** is shown in Scheme 2.1.

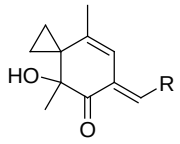


Scheme 2.1 Recently Proposed Biological Mode of Action of Acylfulvene 2-2

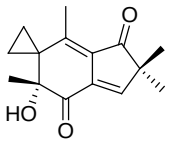
2.1.2 Kinder's Bicyclic Illudin Analogs

In 1996 Kinder synthesized and tested the activity of several bicyclic illudin analogs.[32] Biological activity of the analogs varied, but the general trend showed that as the inserted R group became bulkier, activity decreased. Table 2.1 shows IC_{50} values for various analogs as compared to dehydroilludin M **2-9** (Table 2.1, entry 8), another second generation illudin analog. The data showed a good correlation between the known mechanism and the functional groups present. When small groups were present as in **2-8a** and **2-8b** (R = Cl, Me, respectively), the α,β-unsaturated ketone was still very accessible to reduction, and the compounds showed high activity. As R became larger such as in **2-8e** and **2-8f** (R = Ph, thienyl), the activity diminished as the point of reductive activation became more sterically crowded. Although in the case of **2-8c** (R = *i*Pr) the activity is actually improved, other bulky groups, such as aromatic rings, decrease the activity. Interestingly, substituting another double bond, such as in **2-8d** (R = vinyl), onto the end of the analog resulted in an increased activity.

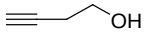
Table 2.1 Biological Activity of Kinder's Bicyclic Analogs 2-8 as Compared to Dehydroilludin M 2-9



2-8



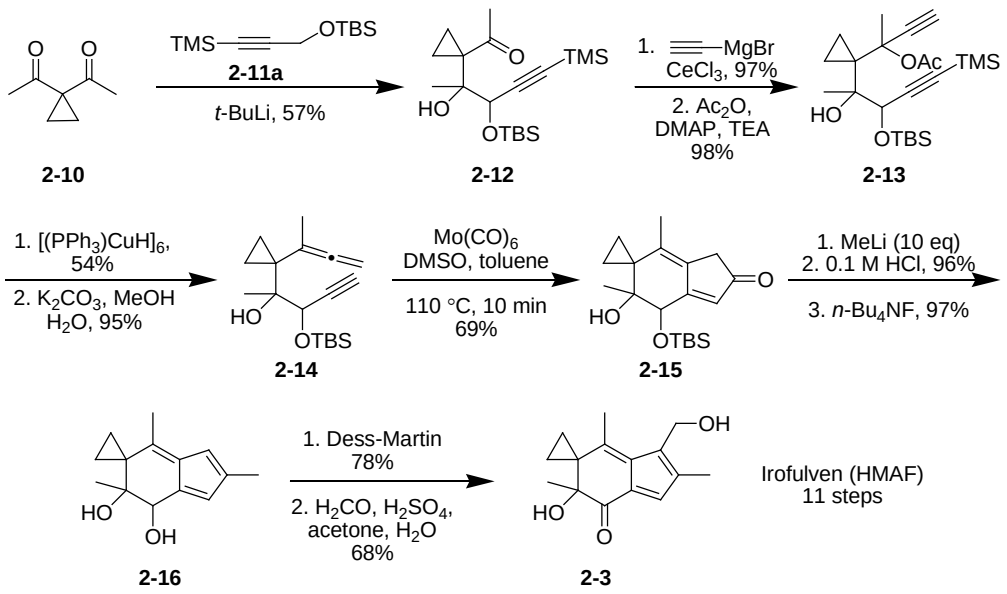
2-9
Dehydroilludin M

Entry	Compound	R	IC_{50} (nM)
1	**2-8a**	Cl	200
2	**2-8b**	Me	150
3	**2-8c**	*i*-Pr	110
4	**2-8d**	Vinyl	2
5	**2-8e**	Ph	1,500
6	**2-8f**	thienyl	> 10,000
7	**2-8g**		3,000
8	**2-9**	N/A	200

Kinder's experiments have shown that it is possible to construct bicyclic illudin analogs that have biological function. This observation provided support for the biological mode of action at the time, and also created precedent for possible future bicyclic analogs of the illudins.

2.1.3 Brummond Irofulven Synthesis.

In 1998, Brummond and Lu reported a synthesis of irofulven **2-3**, using a molybdenum-mediated allenic Pauson-Khand-type cyclocarbonylation reaction as the key step (Scheme 2.2).[33] The synthesis began with addition of alkyne **2-11a** to known cyclopropyl diketone **2-10** to afford ketone **2-12** as a mixture of diastereomers. Addition of ethynyl magnesium bromide to ketone **2-12a** followed by selective acylation of the resultant alcohol gave propargyl acetate **2-13**. The propargyl acetate **2-13** was reduced using Stryker's reagent to afford allene-yne **2-14**. A molybdenum-mediated cyclocarbonylation reaction produced the tricyclic core of irofulven **2-3**, ketone **2-15**, in 69% yield. Addition of methyl lithium to ketone **2-15** resulted in formation of an unstable alcohol that eliminated upon acidic workup, to give the fulvene skeleton. The TBS protecting group was then removed using tetrabutylammonium fluoride (TBAF) conditions to give fulvene **2-16**. The secondary alcohol was oxidized using Martin's reagent to give acylfulvene **2-2** and the hydroxymethyl group installed via an electrophilic aromatic substitution reaction to afford irofulven (**2-3**) in 11 linear steps.

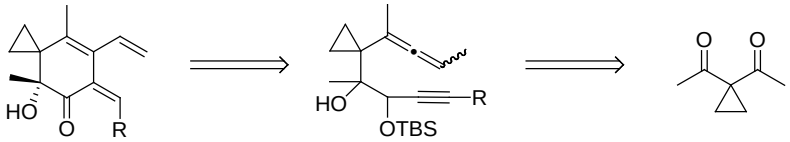


Scheme 2.2 Brummond Synthesis of Irofulven 2-3

2.1.4 Synthetic Route Towards Bicyclic Trienyl Acylfulvene Analogs

Inspired by the previously reported biological activity of the bicyclic analogs of the illudins and a potentially facile route approach to these using a Rh(I)-catalyzed allenic carbocyclization reaction, we initiated a program to prepare bicyclic illudin analogs. Challenges presented by this endeavor include the reactivity of functionally dense substrates.

We envisioned that trienone **2-17** could be synthesized via oxidation of the product of a Rh(I)-catalyzed carbocyclization reaction of allene-yne **2-18**. This allene-yne **2-18** could be formed in three steps from diketone **2-10** (Scheme 2.2 and 2.3). The synthesis of five spiro[2.5]octatrienes has been accomplished using the Rh(I)-catalyzed allenic carbocyclization reaction and the results described below.



2-17 **2-18** **2-10**

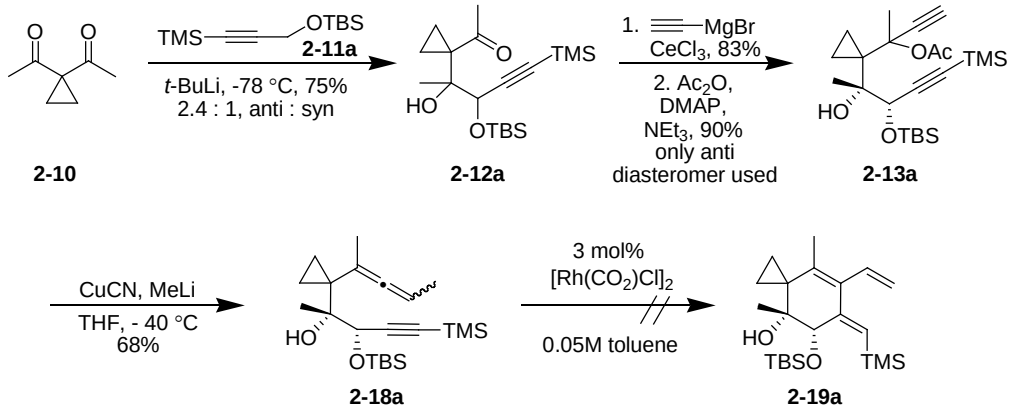
Scheme 2.3 Retrosynthetic Analysis for Bicyclic Acylfulvene Analog 2-17

2.2 RESULTS AND DISCUSSION

2.2.1 Testing the Feasibility of the Rh(I)-Catalyzed Carbocyclization Reaction for the Synthesis of Bicyclic Illudin Analogs

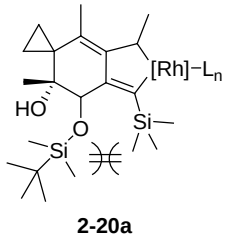
We began synthesis of analogs **2-17** by first reacting the propargyl anion of alkyne **2-11a** (1.25 eq. of the propargyl anion) with diketone **2-10**. Alkyne **2-12** was obtained in 75% yield as a 2.4 : 1 ratio of *anti* to *syn* hydroxyl isomers, as determined previously in the Brummond synthesis of irofulven **2-10**, that were separated by column chromatography on silica gel. The *anti* diastereomer **2-12a** was then subjected to ethynyl magnesium bromide in the presence of cerium trichloride to afford the respective alcohol in 83% yield. The alcohol was then reacted with acetic anhydride and 4-(dimethylamino)pyridine in triethylamine to provide propargyl acetate **2-13a** in 90% yield. Propargyl acetate **2-13a** was subjected to a number of different methyl cuprate addition conditions. Optimal conditions were copper cyanide and methyl lithium in THF at -40 °C. These conditions were reported by Krause to work well with substrates containing heteroatoms that could potentially coordinate to the copper and cause side reactions or loss of reactivity.[34] Allene-yne **2-18a** was obtained in 68% yield after S_N2' addition of the methyl cuprate. The structure of **2-18a** was evidenced in the ^1H NMR spectrum by the

resonance at 4.97 – 4.93 ppm (m, 1H) corresponding to the allene proton and in the IR spectrum by absorbances at 1961 cm^{-1} and 2177 cm^{-1} corresponding to the allene and alkyne respectively. With allene-yne **2-18a** in hand, the Rh(I)-catalyzed allenic carbocyclization reaction was next attempted using 3 mol% $[Rh(CO)_2Cl]_2$ in toluene at 0.05M; however, this reaction was not successful (Scheme 2.4). Two compounds were isolated from this reaction, one contained trace product, and the other contained some starting material as determined by ^1H NMR. Both ^1H NMR spectra for these products contained large resonances at 1.15 (m, 45H) and 0.83 ppm (m, 48H) that indicated that side reactions may have occured.



Scheme 2.4 Synthesis of Allene-yne 2-18a and Initial Attempt at the Allenic Carbocyclization Reaction

We hypothesized that developing $A^{1,3}$ strain in the transition state between the trimethylsilyl and TBS-ether groups was hindering formation of rhodacycle **2-20a**, and leading to side reactions (Fig. 2.2). Efforts were next undertaken to remove these silicon groups.

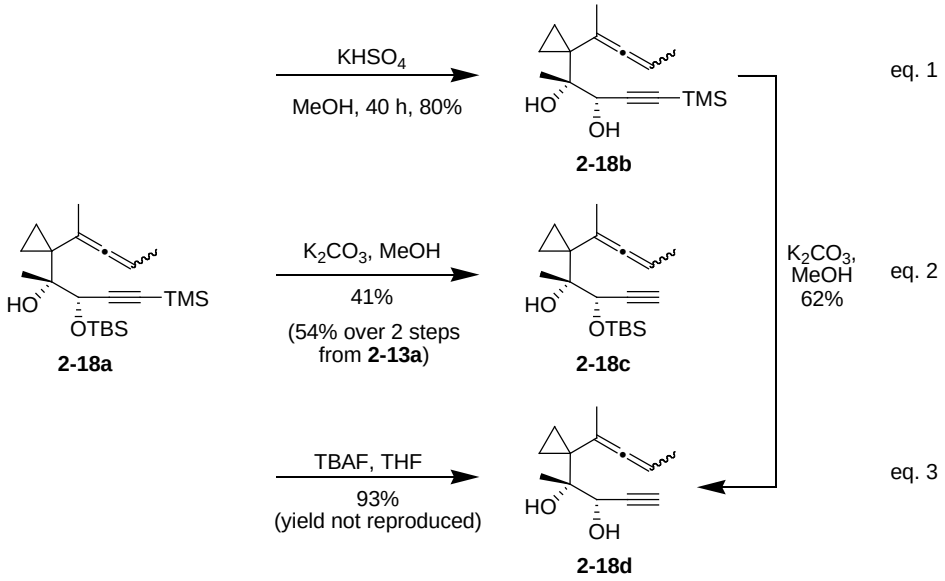


2-20a

Figure 2.2 Developing $A^{1,3}$ Strain in Rhodacycle 2-20a

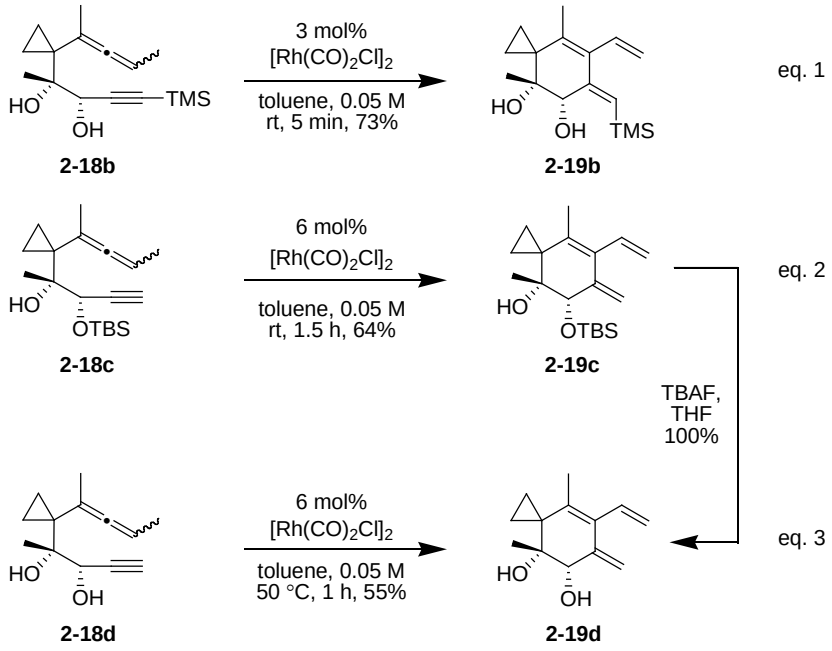
2.2.2 Selective Removal of the Silyl Protecting Groups of Allene-yne 2-18a and the First Successful Allenic Carbocyclization Reactions Affording Spiro[2.5]octatrienes

A strategy to selectively remove each or both silyl protecting groups was developed. First, **2-18a** was subjected to $KHSO_4$ in methanol, removing the TBS group to afford allene-yne diol **2-18b** in 80% yield (Scheme 2.5, eq. 1). The TMS group of **2-18a** was selectively cleaved from the alkyne terminus using K_2CO_3 in methanol to give **2-18c** in 41% yield. This deprotection reaction could also be performed on crude **2-18a** immediately following formation of the allene in 54% yield over two steps (Scheme 2.5, eq. 2). Finally, both silyl groups were removed simultaneously under TBAF conditions, affording **2-18d** in 93% yield (Scheme 2.5, eq 3). Unfortunately, the yield of the reaction of **2-18a** under TBAF conditions was not reproducible, as subsequent attempts gave only trace amounts of product. Removal of the TMS group from **2-18b** using K_2CO_3 in methanol afforded **2-18d** reproducibly in 62% yield (Scheme 2.5).



Scheme 2.5 Selective Removal of One or Both Silyl Protecting Groups of Allene-yne 2-18a

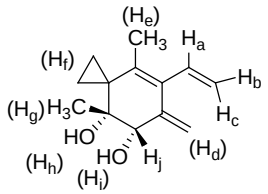
Allene-ynes **2-18b-d** were next subjected to the Rh(I)-catalyzed allenic carbocyclization reaction. Reaction of allenic TMS-protected alkyne **2-18b** afforded triene **2-19b** in 73% yield after 5 min, using 3 mol% of $[Rh(CO)_2Cl]_2$ (Scheme 2.6, eq. 1). Allene-yne **2-18c** also reacted under mild conditions, providing a 64% yield of triene **2-19c** in 1.5 h, using 6 mol% catalyst (Scheme 2.6, eq. 2). Finally, reaction of desilylated allene-yne **2-18d** required 6 mol% $[Rh(CO)_2Cl]_2$ and a temperature of 50 °C to give triene **2-19d** in 55% yield after 1 h (Scheme 2.6, eq. 3). Triene **2-19d** could also be obtained from triene **2-19c** in quantitative yield using TBAF in THF. The trienes were characterized similarly to the trienones discussed in chapter 1. For example, triene **2-19d** was identified by the presence of resonances at 6.29 (dd, 1H), 5.41 (dd, 1H), 5.21 (s, 1H), 5.17 (s, 1H) and 5.14 ppm (dd, 1H) in the ^{1}H NMR spectrum, corresponding to H_a, H_b, H_d, and H_c respectively (Table 2.2).



2-18b **2-19b** **2-18c** **2-19c** **2-18d** **2-19d**

Scheme 2.6 Initial Allenic Carbocyclization Reactions to form Spiro[2.5]octatrienes 2-19

Table 2.2 ^{1}H NMR Characterization of 2-19d



2-19d

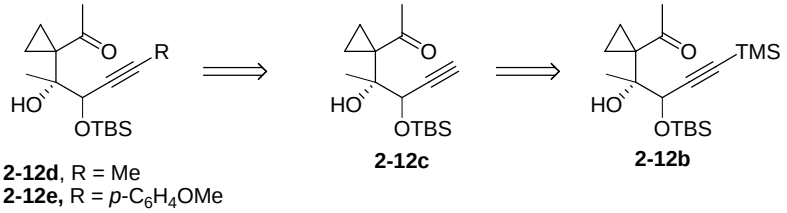
Proton	Chemical Shift (ppm)	Multiplicity	Integration	J-Value (Hz)
H_a	6.29	dd	1	17.7, 11.1
H_b	5.41	dd	1	11.1, 2.1
H_c	5.14	dd	1	17.7, 2.1
H_d	5.21, 5.17	s, s	1, 1	-
H_e	1.54	s	3	-
	1.19 – 1.11	m	1	-
H_f	0.91 – 0.84	m	1	-
	0.80 – 0.71	m	2	-
H_g	1.10	s	3	-
H_h	2.39	s	1	-
H_i	1.96	d	1	7.2
H_j	3.96	d	1	4.8

2.2.3 Synthesis of a *p*-Methoxybenzene Substituted Allene-yne

Following the initial allenic carbocyclization studies towards bicyclic illudin analogs, we became interested in the scope of this carbocyclization reaction with regards to substitution at the alkyne terminus. A route to both alkyl and aryl substituents was derived from alkynyl ketone **2-12**.

The minor diastereomer, alkynyl ketone **2-12b**, was chosen as the starting material for this synthetic endeavor because a large amount was left over from the synthesis of alkynyl ketone **2-12a**. It was envisioned that a methyl group could be appended via an alkylation reaction of terminal alkynyl ketone **2-12c**, which would afford alkynyl ketone **2-12d**. An aryl group would be added to the terminus of alkynyl ketone **2-12c** via a Sonogashira coupling reaction to obtain alkynyl ketone **2-12e** (Scheme 2.7). Alkynyl ketone **2-12c** could be synthesized from alkynyl ketone **2-12b** via removal of the TMS group from the alkyne terminus.

Alkynyl ketones **2-12d** and **2-12e** would then be carried through the previous synthetic steps to their respective allenic carbocyclization products.

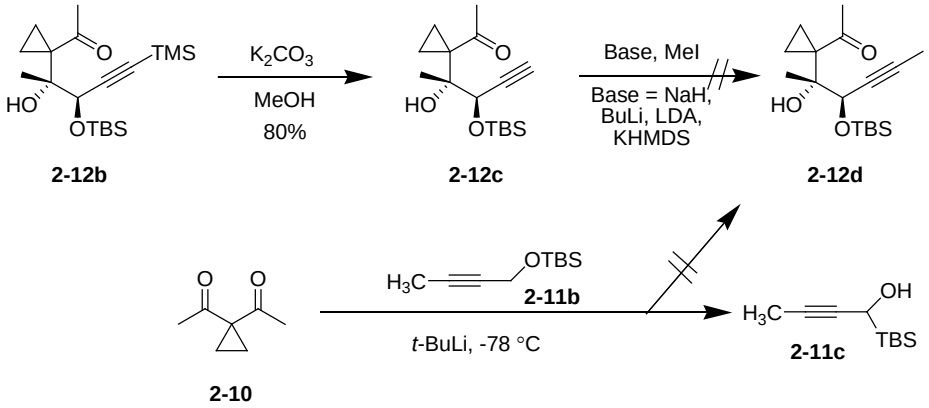


2-12d, R = Me
2-12e, R = *p*-C_6H_4OMe

2-12c **2-12b**

Scheme 2.7 Route to Terminal Alkyne Substituted Acylfulvene Analog Precursors

Alkynyl ketone **2-12b** was reacted with K_2CO_3 in methanol to give alkynyl ketone **2-12c** in 80% yield. Alkylation of the alkyne terminus was attempted using a variety of bases (NaH, *n*-BuLi, LDA, KHMDS) and methyl iodide; however, alkynyl ketone **2-12d** was never observed, likely due to the number of acidic protons within the molecule that could cause side reactions (Scheme 2.8). Synthesis of alkynyl ketone **2-12d** was also attempted from diketone **2-10** via addition of alkyne **2-11b** under the same conditions used to obtain **2-12a** and **2-12b**. This reaction also did not provide ketone **2-12d** because alkyne **2-11b** underwent a retro-Brook rearrangement to afford alkynol **2-11c**.



2-12b **2-12c** **2-12d**

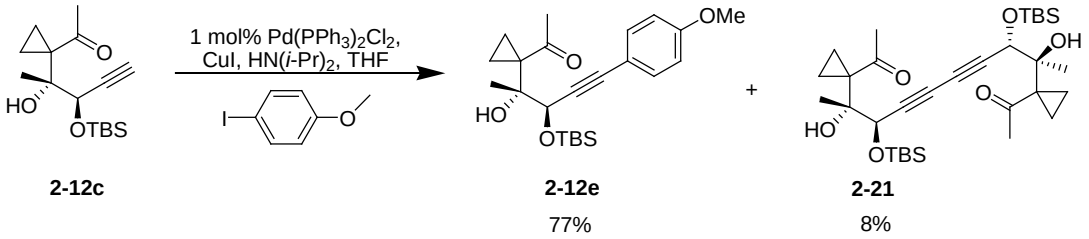
2-11b

2-10 **2-11c**

Scheme 2.8 Attempted Syntheses of Methyl Alkyne 2-12d

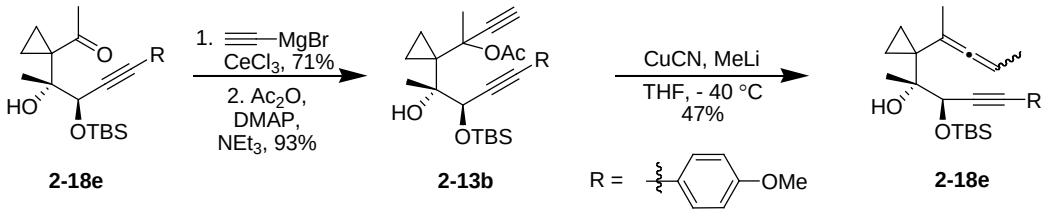
Coupling of *p*-iodoanisole to alkyne **2-12c** was accomplished via a Sonogashira reaction using 1 mol% $Pd(PPh_3)_2Cl_2$ in the presence of copper iodide and diisopropylamine in THF to

afford alkyne **2-12e** in 77% yield. An 8% yield of the Glaser alkyne dimerization product **2-21** was also obtained from this reaction (Scheme 2.9). Structural characterization of the dimer **2-21** was confirmed by ESI-HRMS (exact mass found = 613.3338) and by the absence of a resonance near 2.77 ppm (s, 1H), corresponding to the terminal alkyne proton, in the ^{1}H NMR spectrum.



Scheme 2.9 Sonogashira Coupling Reaction of Alkyne 2-12c with p-Iodoanisole to Afford Alkyne 2-12e

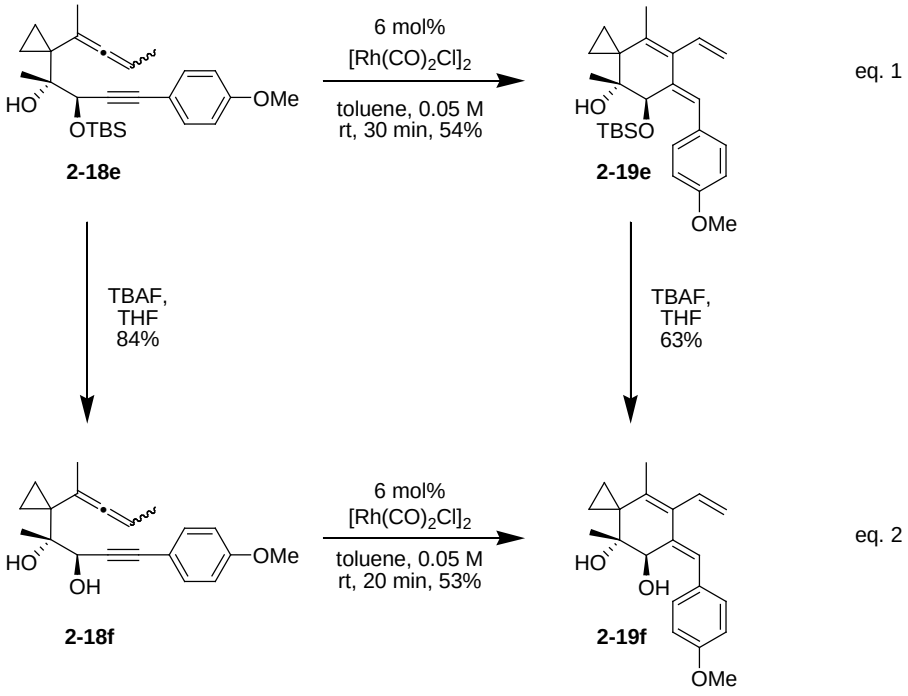
Alkynyl ketone **2-12e** was next subjected to the same synthetic sequence as alkynyl ketone **2-12a**. Reaction of **2-12e** with ethynyl magnesium bromide in the presence of cerium trichloride afforded the desired propargyl alcohol in 71% yield. Although, the alcohol contained minor impurities after column chromatography on silica gel, it was used without further purification. This propargyl alcohol was then reacted with acetic anhydride in triethylamine to give propargyl acetate **2-13b** in 84% yield. Finally, propargyl acetate **2-13b** was subjected to the optimized cuprate conditions to afford allene-yne **2-18e** in 47% yield as a 1.5 : 1 mixture of diastereomers as determined by the relative integrations of the resonances at 4.87 and 4.82 ppm in the ^{1}H NMR spectrum, corresponding to the propargylic protons (Scheme 2.10).



Scheme 2.10 Synthesis of Terminal Aryl Allene-yne 2-18e

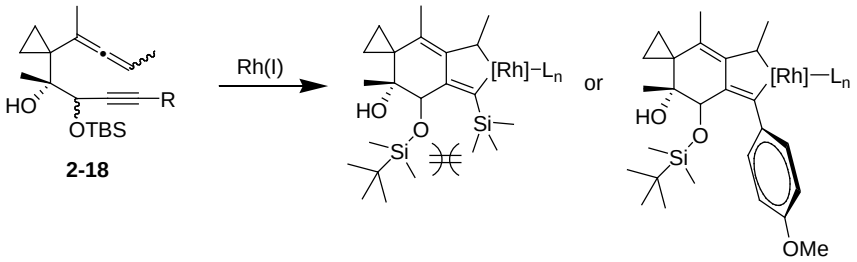
The TBS group of **2-18e** was removed using TBAF to give allene-yne **2-18f** in 84% yield. The allenic carbocyclization reaction was next performed on the protected and

unprotected allene-ynes **2-18e** and **2-18f**. Reaction of allene-yne **2-18e** with 6 mol% $[Rh(CO)_2Cl]_2$ afforded triene **2-19e** in 54% yield (Scheme 2.11, eq. 1). The desilylated allene-yne **2-18f** also reacted under the same conditions to afford triene **2-19f** in a similar 53% yield (Scheme 2.11, eq. 2). Triene **2-19f** could also be obtained in 63% yield from **2-19e** using TBAF in THF.



Scheme 2.11 Allenic Carbocyclization Reactions of 2-18e-f to Form Spiro[2.5]octatrienes 2-19e and 2-19f

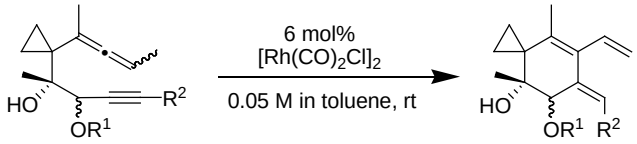
The results obtained for the carbocyclization reactions of allene-yne **2-18e** and allene-yne **2-18a** supported the hypothesis of developing $A^{1,3}$ strain in the rhodacycle transition state. This effect was observed in intermediate **2-20a**, where the TMS group caused a poor $A^{1,3}$ interaction with the OTBS group, whereas in **2-20e** the aromatic ring could position itself in an orthogonal conformation to avoid this interaction (Scheme 2.12).



Scheme 2.12 Conformational Considerations for Reactions of 2-18a vs. 2-18e

The results for all allenic carbocyclization reactions affording spiro[2.5]octatrienes discussed in this chapter are summarized in table 2.3. The stereochemistry is denoted by the configuration of the diol.

Table 2.3 Summary of Allenic Carbocyclization Reactions Affording Spiro[2.5]octatrienes



2-18 **2-19**

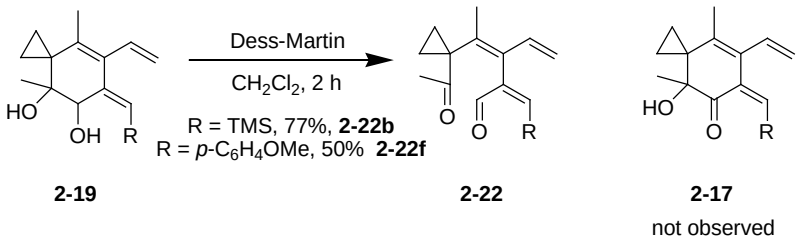
Entry	R^1	R^2	Product	Diol	Time (min)	Yield (%)
1	TBS	TMS	**2-19a**	Anti	N/A	Complex mixture
2[a]	H	TMS	**2-19b**	Anti	< 5	73
3	TBS	H	**2-19c**	Anti	90	64
4[b]	H	H	**2-19d**	Anti	60	55
5	TBS	*p*-C_6H_4OMe	**2-19e**	Syn	30	54
6	H	*p*-C_6H_4OMe	**2-19f**	Syn	20	53

a. 3 mol% $[Rh(CO)_2Cl]_2$ b. 50 °C

2.2.4 Progress Towards Bicyclic Acylfulvene Analog Synthesis Endgame

With the spiro[2.5]octatrienes **2-19** in hand, illudin analog synthesis was investigated. Oxidation of triene **2-19b** with DMP gave **2-22b** in 77% yield. The structural characterization of **2-22b** was supported by a resonance in the aldehyde region and resonances indicative of the triene in ^{1}H NMR spectrum. Reaction of **2-19f** with DMP afforded **2-22f** in 50% yield (Scheme 2.13).

This product was confirmed by the resonances in the ^{1}H NMR spectrum at 9.39 ppm (s, 1H), corresponding to the aldehyde and at 6.83 (dd, 1H), 5.14 (d, 1H), 4.97 ppm (d, 1H) corresponding to the triene was isolated from. Characteristic absorbances at 1673 cm^{-1} and 1602 cm^{-1} corresponding to the carbonyl groups are also observed in the IR spectrum.



2-19 **2-22** **2-17**

not observed

Scheme 2.13 Oxidative Cleavage of Spiro[2.5]octatrienes 2-19b and 2-19f

Several other oxidation conditions were attempted affording three typical results: cleavage, no reaction, or small amounts of uncharacterized products that did not resemble the desired analog as observed by ^{1}H NMR analysis. Cleavage products were obtained when using pyridinium dichromate (PDC), manganese dioxide (MnO_2), or Dess-Martin periodinane (DMP). No reaction occurred when using Swern conditions, sulfur trioxide pyridine complex (SO_3·pyr), or catalytic tetrapropylammonium perruthenate with stoichiometric *N*-methylmorpholine-*N*-oxide (TPAP/NMO). Uncharacterized products were found in small amounts when using 2-iodoxybenzoic acid (IBX) or Kinder's oxidation conditions (50 mol% $Ru(PPh_3)_2Cl_2$ and NMO). Although there is no mention, it seemed likely that Kinder used such uncommon oxidation conditions because he encountered similar problems with this step in his synthesis.

2.3 CONCLUSIONS

A route to spiro[2.5]octatrienes has been developed using the Rh(I)-catalyzed allenic carbocyclization reaction, affording five trienes in 53 – 73% yields under mild conditions. The carbocyclization reaction was tolerant of TBS-protected or deprotected alcohols, aryl and silyl substituted alkynes, and anti or syn diols and performed well in these structurally compact, yet highly functionalized systems.

Developing $A^{1,3}$ strain between the TBS ether and the TMS group at the alkyne terminus of **2-18a** prevented the desired carbocyclization reaction, resulting in complex mixtures. Removal of the TBS group or substituting a less bulky group at the alkyne terminus alleviated this limitation.

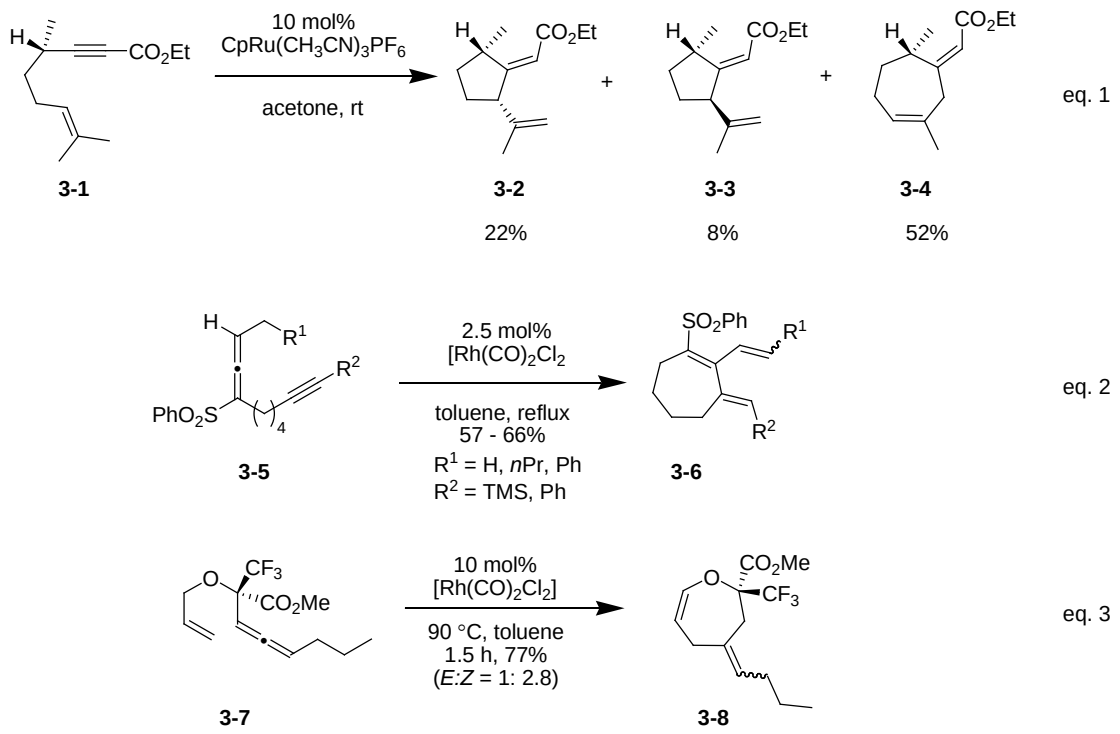
Synthesis of the final analogs through oxidation of the secondary alcohol was problematic, affording only ketoaldehyde **2-22**, an oxidative cleavage product. This final oxidation step was necessary to the biological function of these molecules, as tests performed by John Skoko in the laboratories of Dr. John Lazo have shown that spiro[2.5]octatriene **2-19d** has no activity against A549 lung carcinoma cells at concentrations up to 50 μM.

3.0 SYNTHESIS OF ε-LACTAMS USING RHODIUM(I)-CATALYZED ALLENIC CARBOCYCLIZATION REACTIONS

3.1 INTRODUCTION

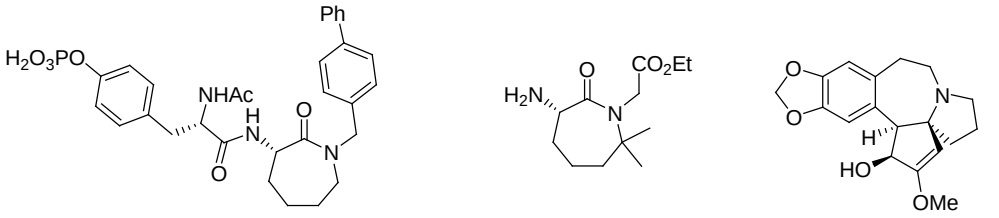
3.1.1 Transition Metal-Catalyzed Cycloisomerizations Affording Seven-Membered Rings

Transition metal-catalyzed cycloisomerization reactions to form seven-membered rings are rare. Trost has reported a ruthenium catalyzed enyne cycloisomerization reaction that produces both five- and seven-membered rings, and the ratio was dependent upon the substrate structure (Scheme 3.1, eq. 1).[35] Similarly, Mukai has synthesized cross-conjugated cycloheptenes **3-6** in 57-66% yield by reacting allene-yne **3-5** with 2.5 mol% $[Rh(CO)_2Cl]_2$ in refluxing toluene (Scheme 3.1, eq. 2).[36] Azepines and oxepines **3-8** have also been synthesized from ene-allenes in the Brummond group under Rh(I)-catalyzed carbocyclization conditions (Scheme 3.1, eq. 3).[37,38]



Scheme 3.1 Formation of Seven-Membered Rings via Transition Metal-Catalysis

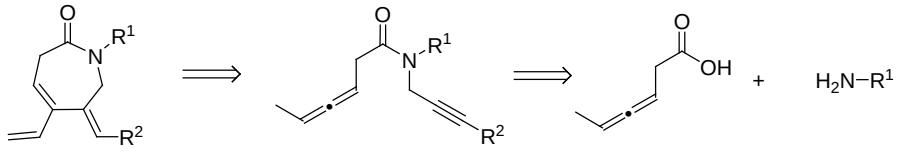
While formation of seven-membered rings using rhodium(I)-catalyzed cyclocarbonylation conditions has been demonstrated, all attempts to obtain seven-membered rings from allene-ynes using rhodium(I)-catalyzed carbocyclization conditions have met with failure.[39] Inspired by the successful conversion of allene-containing propiolamides to δ-lactams via a Rh(I)-catalyzed carbocyclization reaction, we turned our attention to the feasibility of forming ε-lactams.[40] The importance of ε-lactams can be put into perspective by a simple search showing 16,000 ε-lactams in over 8,000 references in the literature.[41] For example, caprolactam **3-9** showed binding activity to src protein, which is thought to be involved in the complications of osteoporosis (Fig 3.1).[42] Rolb has reported use of ε-lactams, such as **3-10**, as Leu-Phe replacements in vasopeptidase inhibitors (Fig 3.1).[43] Finally, cephalotaxine (**3-11**) has anticancer activity (Fig 3.1).[44]



3-9 **3-10** (-)-Cephalotaxine (**3-11**)

Figure 3.1 Biologically Active ε-Lactam Derivatives

We envisioned that ε-lactams like **3-12** could be accessed via the Rh(I)-catalyzed allenic carbocyclization reaction of **3-13**. The allene-yne precursor **3-13** could be readily synthesized via DCC coupling reaction between a secondary amine **3-15**, and allenic acid **3-14** followed by alkylation of the resultant amide (Scheme 3.2). The successful synthesis of ε-lactams and extensions of this methodology to form azepines and fused 7-5 lactams are discussed herein.



3-12 **3-13** **3-14** **3-15**

R^1, R^2 = Alkyl, aryl, H

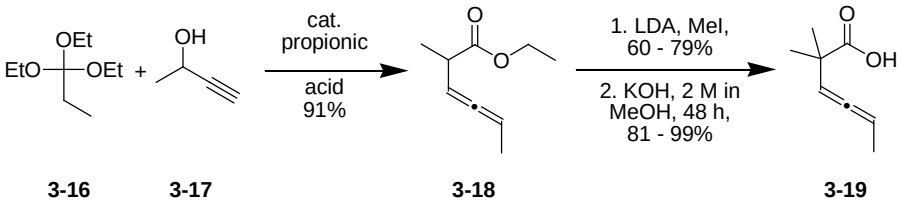
Scheme 3.2 Synthetic Route to ε-Lactams

3.2 RESULTS AND DISCUSSION

3.2.1 Testing the Feasibility of a Rh(I)-Catalyzed Carbocyclization Reaction to form ε-Lactams

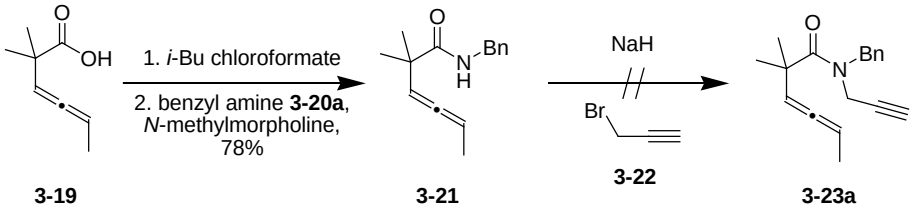
We thus set out to synthesize a suitable precursor to test the feasibility of the rhodium(I)-catalyzed carbocycliation reaction to form **3-12**. We first determined that disubstitution at the α-

position of the ester would be necessary to prevent isomerization of the allene to the conjugated diene under basic conditions. Formation of α-methyl allenic ester **3-18** was effected via Johnson-Claisen rearrangement of triethyl orthopropionate (**3-16**) and 3-butyn-2-ol (**3-17**) in 91% yield.[45] Chris Wach, in the Brummond group, has shown that ester **3-18** can be α-methylated using LDA and iodomethane in 60-79% yield.[46] The resultant α,α-dimethyl ester was then saponified using 2M KOH in methanol to afford the desired allenic acid **3-19** in 81-99% yield (Scheme 3.3).



Scheme 3.3 Synthesis of Allenic Acid 3-19

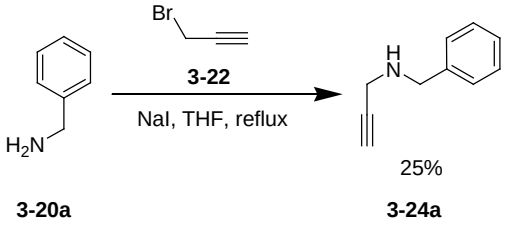
Next, the isobutyl chloroformate mixed anhydride of acid **3-19** was prepared and reacted with benzyl amine (**3-20a**), affording a 78% yield of amide **3-21**.[40] Attempts to effect this coupling with DCC gave a 28% yield of product along with an uncharacterized product that contained multiple resonances in the alkyl region of the ^{1}H NMR spectrum. Attempts to alkylate amide **3-21** using sodium hydride and propargyl bromide (**3-22**) resulted in no reaction or multiple product spots by TLC analysis over prolonged reaction times (Scheme 3.4).



Scheme 3.4 Formation of Amide 3-21 and Attempts at Alkylation to Afford 3-23a

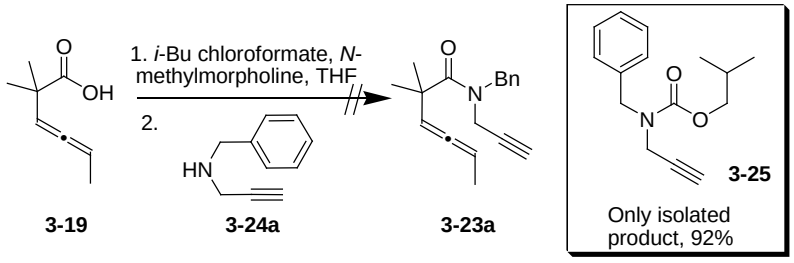
To circumvent the difficulties associated with amide alkylation of **3-21**, we considered coupling acid **3-19** with a 2° propargyl amine to obtain **3-23a** directly. Reaction of benzyl amine

(**3-20a**) with propargyl bromide (**3-22**) afforded benzyl propargyl amine (**3-24a**) in 25% yield as shown in Scheme 3.5.[47]



Scheme 3.5 Formation of Secondary Propargyl Amine 3-24a

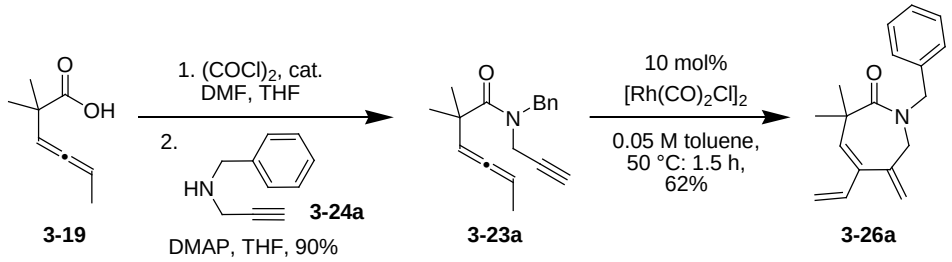
Reaction of **3-19** with isobutyl chloroformate, *N*-methylmorpholine, and amine **3-24a** did not afford the desired amide **3-23a**, but instead gave only isobutylcarbamate **3-25** in 92% yield (Scheme 3.6). The presence of a resonance at 0.88 ppm (d, 6H) corresponding to the methyl groups in the isobutyl unit of the carbamate supported the characterization of **3-25** by ^{1}H NMR spectroscopy. Carbamate **3-25** resulted from attack of the amine at the undesired carbonyl center of the mixed anhydride, due to the bulky gem dimethyl group next to the carbonyl.



Scheme 3.6 Attempted Coupling to Form Allenyl Propargyl Amide 3-23a

Alternatively, reaction of acid **3-19** with oxalyl chloride and catalytic DMF for 3 h resulted in formation of an acid chloride that was concentrated and redissolved in THF. The resultant solution was added via cannula to a solution of amine **3-24a** to provide allenic propargyl amide **3-23a** in 90% yield (Scheme 3.7). With the allene-containing propargyl amide **3-23a** in hand, reaction to the standard conditions for δ-lactam formation (10 mol%

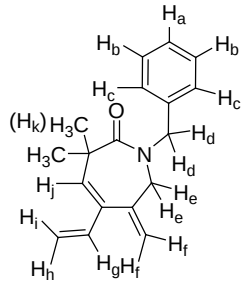
$[Rh(CO)_2Cl]_2$ in toluene at 0.05M immersion in an oil bath preheated to 50 °C) provided ε-lactam **3-26a** in 62% yield (average) after 1.5 h (Scheme 3.7).[40]



Scheme 3.7 Synthesis of e-Lactam 3-26a

Lactam **3-26a** was characterized by ^{1}H NMR as shown in Table 3.1. The ^{1}H NMR spectrum has also been reproduced below (Fig. 3.5, see chapter 3 experimental section for full characterization data). Evidence for the trienyl structure of **3-26a** was supported by the resonances at 6.36 (dd, 1H), 5.69 (s, 1H), 5.36 (d, 1H), 5.12 (d, 1H), 5.09 (s, 1H), 4.45 ppm (s, 1H), corresponding to H_g, H_j, H_i, H_h, and H_f respectively.

Table 3.1 ^{1}H NMR Characterization of ε-Lactam 3-26a



3-26a

Proton	Chemical Shift (ppm)	Multiplicity	Integration	*J*-Value (Hz)
H_a, H_b, H_c	7.35-7.24	m	5	-
H_d, H_e	4.68, 3.93	s, s	2, 2	-
H_f	5.09, 4.95	s, s	1, 1	-
H_g	6.36	dd	1	17.0, 10.6
H_h	5.12	d	1	10.6
H_i	5.36	d	1	17.0
H_j	5.69	s	1	-
H_k	1.52	s	6	-

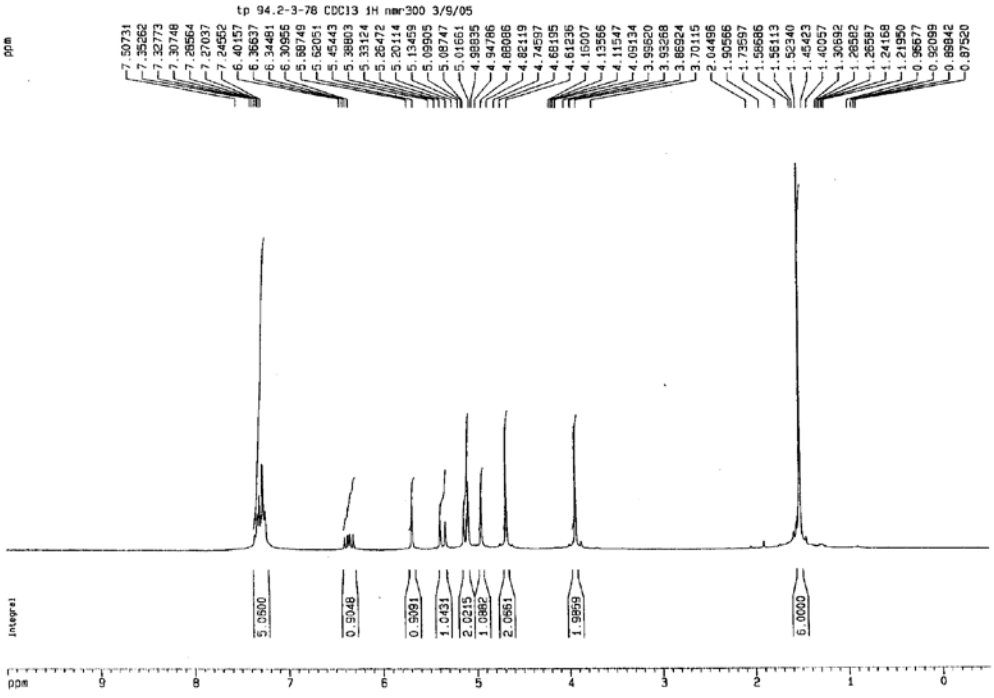
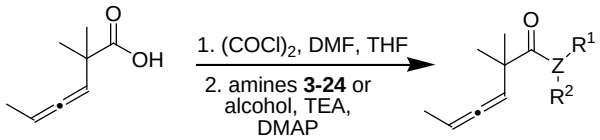


Figure 3.2 ^{1}H NMR Spectrum of 3-26a

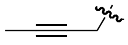
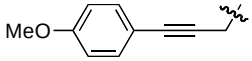
3.2.2 Exploration of the Scope of the Allenic Carbocyclization Reaction for the Formation of ε-Lactams via Substitution at the Propargyl Amide

Investigations into the scope and limitations of the Rh(I)-catalyzed allenic carbocyclization reaction for the formation of ε-lactams were undertaken through modifications at the amide nitrogen atom and the alkyne terminus. Using previously described conditions to generate the acid chloride *in situ*, eight amides (Table 3.2, entries 1-4 and 6-9) and one ester (Table 3.2, entry 5) were synthesized from allenic acid **3-19** and a variety of substituted secondary amines **3-24** or propargyl alcohol (Table 3.2). Yields from these coupling reactions ranged from 69% to 96%, with the volatile propargyl ester **3-23e** affording the lowest yield.

Table 3.2 Formation of Allenic Propargyl Amides 3-23



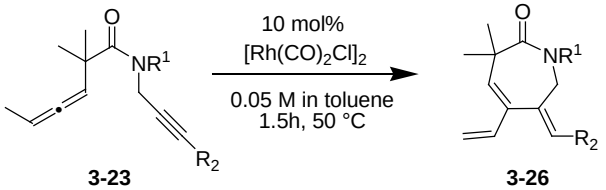
3-19 **3-23**

Entry	Z	R^1	R^2	Product	Yield (%)
1	N	Bn	propargyl	**3-23a**	90
2	N	H	propargyl	**3-23b**	81
3	N	H	allyl	**3-23c**	86
4	N	Bn	allyl	**3-23d**	81
5	O	-	propargyl	**3-23e**	69
6	N	$(CH_2)_2OTBS$	propargyl	**3-23f**	96
7	N	furfuryl	propargyl	**3-23g**	79
8	N	Bn		**3-23h**	83
9	N	Bn		**3-23i**	88

Reaction of amide **3-23f** to the optimized carbocyclization conditions afforded lactam **3-26f** in 61% yield (average). Furfuryl amide **3-23g** reacted to afford **3-26g** in 63% yield in 1.5 h (Table 3.3, entry 3). Both methyl substituted alkyne **3-23h** and *p*-methoxyphenyl substituted alkyne **3-23i** reacted under the optimized conditions to afford **3-26h** and **3-26i** in 49% and 65%

yields, respectively (Table 3.3, entries 4 and 5). The spectral data of crude products from the carbocyclization reactions contained impurities, typically in the 1.9 to 1.0 ppm region of the ^{1}H NMR spectrum (resonances were not integrated). A brown precipitate was also observed upon dilution of each reaction mixture with 30% ethyl acetate/hexanes during workup; however, no by-products could be isolated.

Table 3.3 Formation of Substituted ε-Lactams via Rh(I)-Catalyzed Allenic Carbocyclization Reactions

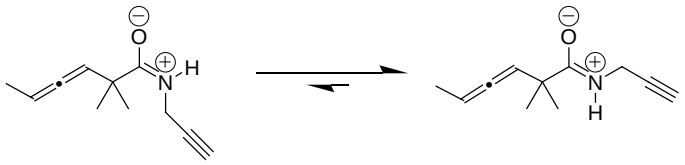


3-23 **3-26**

Entry	Starting Material	R^1	R^2	Time (h)	Product	Yield (%)
1	**3-23a**	Bn	H	1.5	**3-26a**	62[a]
2	**3-23f**	$(CH_2)_2OTBS$	H	2	**3-26f**	61[a]
3	**3-23g**	furfuryl	H	1.5	**3-26g**	63
4	**3-23h**	Bn	Me	1.5	**3-26h**	49
5	**3-23i**	Bn	*p*-C_6H_4OMe	1.5	**3-26i**	65

[a] Average of 4 yields

Secondary allenic propargyl amide **3-23b,** allyl amides **3-23c-d**, and propargyl ester **3-23e**, were unreactive under the optimized Rh(I) conditions and this can be attributed to their unfavorable rotamer populations (Scheme 3.8). These compounds favor the O(N)-Z conformation and, the alkyne is too distant to take part in the carbocyclization reaction. Attempts to overcome the unfavorable rotamer populations (~18 kcal/mol) in the secondary amides by heating to 90 – 100 °C only resulted in formation of insoluble solids that could not be characterized.

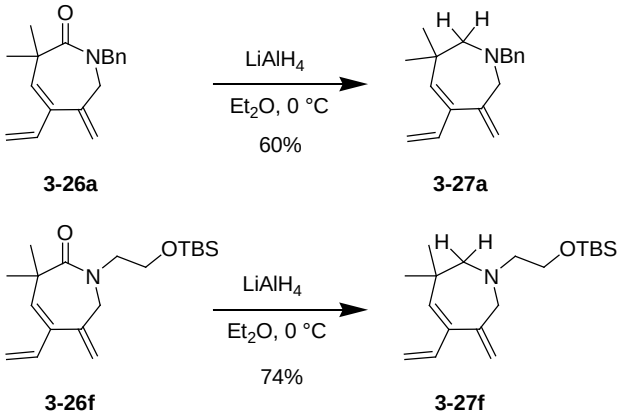


E-**3-23b** *Z*-**3-23b**

Scheme 3.8 Conformational Considerations of Secondary and Tertiary Propargyl Amides

3.2.3 Formation of Trienyl Azepines via Reductions of ε-Lactams

Extension of the ε-lactam forming reaction to the synthesis of additional alkaloids, was accomplished by reduction of the amide moiety. Trienyl azepines **3-27a** and **3-27f** were synthesized in 60% and 74% yields, respectively, by reacting **3-26a** and **3-26f** with four equivalents of lithium aluminum hydride (LAH) in ether at 0 °C (Scheme 3.9).

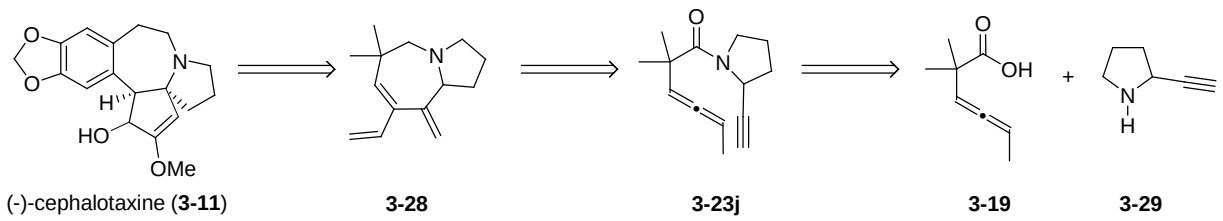


Scheme 3.9 Reduction of ε-Lactams 3-26 to form Trienyl Azepines 3-27

3.2.4 Synthesis of a 7-5 Fused ε-Lactam via a Rh(I)-Catalyzed Allenic Carbocyclization Reaction

With the successful reduction of the lactams to azepines in hand, efforts were made to synthesize a 7-5-fused ε-lactam scaffold. Synthesis of such a scaffold would open the door to a synthesis of the structurally similar natural product cephalotaxine (**3-11**) (Fig 3.1).

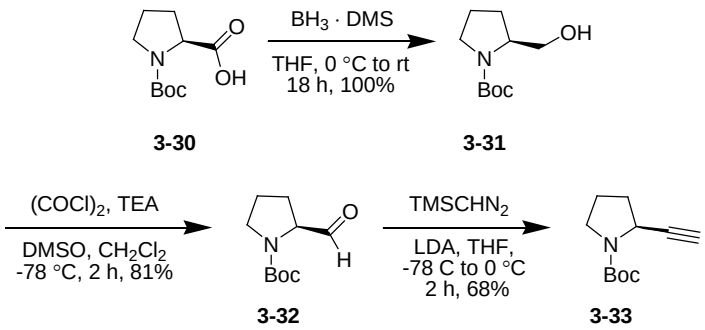
For example, it was envisioned that 7-5 fused azepine **3-28** could be accessed from allenic propargyl amide **3-23j** via a Rh(I)-catalyzed carbocyclization followed by a reduction of the lactam. An ideal synthetic route to allenic propargyl amide **3-23j** would start with the five-membered ring already intact. Coupling of allenic acid **3-19** and propargyl amine **3-29** would rapidly provide the desired compound **3-23j** (Scheme 3.10).



(-)-cephalotaxine (**3-11**) **3-28** **3-23j** **3-19** **3-29**

Scheme 3.10 Synthetic Route to 7-5 Fused Azepines

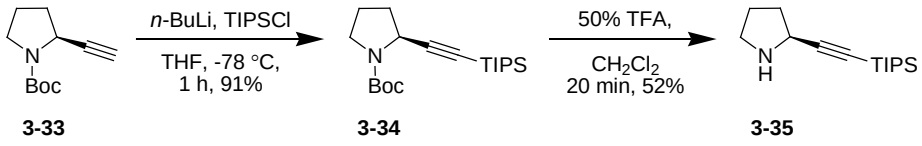
Commercially available Boc-L-proline **3-30** was first reduced using borane dimethylsulfide complex to afford Boc-L-prolinol **3-31** in quantitative yield. Boc-L-prolinol **3-31** is then oxidized under Swern conditions to give aldehyde **3-32** in 81% yield. This aldehyde **3-32** was then subjected to a Colvin rearrangement using Shioiri's conditions, producing the Boc-protected proline derivative **3-33** in 68% yield (Scheme 3.11).[48]



Scheme 3.11 Synthesis of Boc-Protected Propargyl Amine 3-33

Removal of the protecting group from Boc-amine **3-33** under standard trifluoroacetic acid conditions to give **3-29** (Scheme 3.10) appeared to proceed by TLC analysis; however, isolation of the volatile product proved difficult. The trifluoroacetate salt of propargyl amine **3-33** could be isolated as observed by loss of the resonance near 1.6 ppm (s, 9H) corresponding to the Boc group in the crude ^{1}H NMR spectrum, but attempts to couple it to acid **3-19** proved unsuccessful.

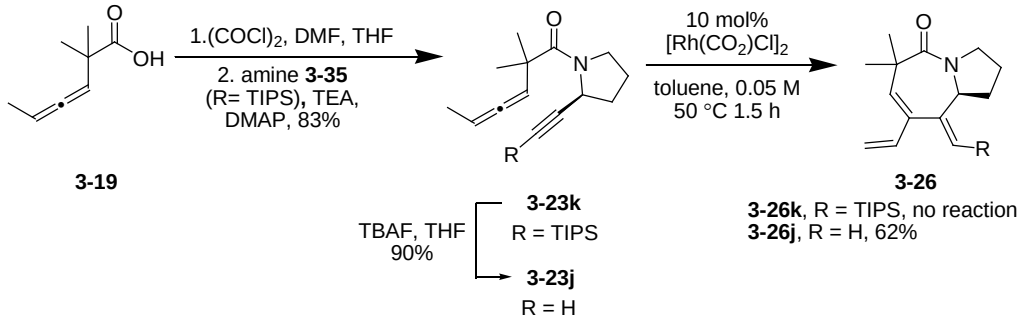
In an effort to decrease the volatility of amine **3-29**, a TIPS group was appended to the end of the alkyne of **3-33** under *n*-BuLi conditions, providing Boc-amine **3-34** in 91% yield. The Boc group was then removed under TFA conditions immediately following purification of **3-34** providing propargyl amine **3-35**, which was easily isolated by column chromatography in 52% yield (72% brsm, Scheme 3.12).



Scheme 3.12 Formation of TIPS Propargyl Amine 3-35

The TIPS-protected propargyl amine **3-35** was next coupled to allenic acid **3-19** via the acid chloride to afford allenic propargyl amide **3-23k** in 83% yield (Scheme 3.13). Allenic carbocyclization reaction of **3-23k** did not afford **3-26k** due to the steric bulk of the TIPS group at the alkyne terminus. Removal of the TIPS group under TBAF conditions gave allenic

propargyl amide **3-23j** as a 1 : 1 mixture of diastereomers in 90% yield. The structural characterization of **3-23j** was evidenced by the terminal alkyne singlet at 2.94 ppm by ^{1}H NMR analysis. Absorbances at 1962 cm^{-1}, 2110 cm^{-1}, and 1630 cm^{-1} in the IR spectrum, corresponding to the allene, alkyne, and amide respectively, also support the structure. Allenic carbocyclization of amide **3-23j** was successful under the optimized conditions for the formation of ε-lactams, providing 7-5 fused bicyclic ε-lactam **3-26j** in 62% yield. Support for the structure of **3-26j** was provided by the appearance of similar trienyl splitting patterns as described for **3-26a** in the ^{1}H NMR spectrum (Scheme 3.13).



Scheme 3.13 Final Synthesis of the 7-5 Fused Bicyclic ε-Lactam 3-26j

3.3 CONCLUSIONS

In conclusion, a Rh(I)-catalyzed allenic carbocyclization reaction, affording ε-lactams has been developed. Furthermore, the transition metal-catalyzed process proceeded readily in the presence of an amide, alkyl, and aryl functional groups under relatively mild conditions. ε-Lactams can be reduced to form trienyl azepines, a functionality that may be used in the synthesis of natural product-like compounds.

4.0 A DIVERGING DOS STRATEGY: APPLICATION OF ALLENIC RHODIUM(I)-CATALYZED CYCLOCARBONYLATION, MICROWAVE-ASSISTED [2 + 2] CYCLOADDITION, AND SILVER(I)-CATALYZED CYCLOISOMERIZATION REACTIONS TO THE SYNTHESIS OF FUSED TETRA- AND PENTACYCLIC INDOLE SCAFFOLDS

4.1 INTRODUCTION

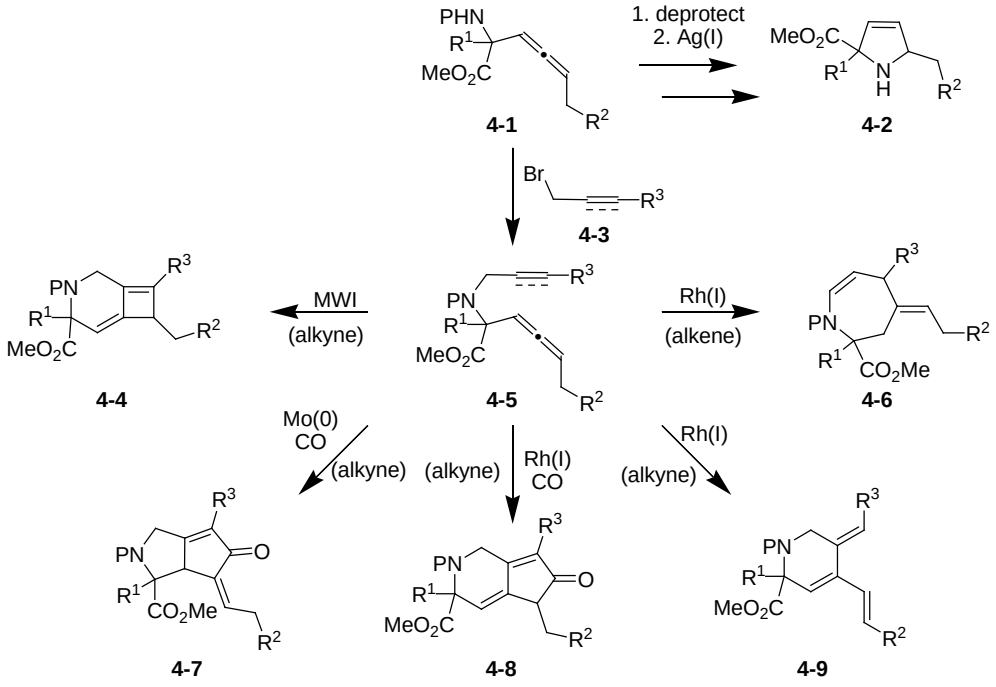
4.1.1 Diversity-Oriented Synthesis and Common Chemical Methods to Achieve Diversity

Chemical synthesis of complex organic molecules has branched into three directions over the years: target-oriented synthesis (TOS), medicinal (and combinatorial) chemistry, and diversity-oriented synthesis (DOS).[49] In DOS, forward synthetic analyses, are used to design routes to diverse targets and plans to achieve molecular complexity normally involve appendage diversity, stereochemical diversity, and skeletal diversity. Skeletal diversity provides sets of distinct compound scaffolds, and is often considered the most powerful technique of the three because each different scaffold is likely to occupy a separate region of chemical space.

4.1.2 Strategies to Achieve Skeletal Diversity

Skeletal diversity can be achieved by a substrate-based approach that employs a common set of reagents to elaborate several substrates, or a reagent-based approach that is less common.[50] In the reagent-based approach a common intermediate (sometimes referred to as the pluripotent substrate) is subjected to varied conditions to afford different scaffolds.[51] The common intermediate approach to skeletal diversity has also been expanded to a "functional group pairing" methodology, recently referred to as the "build/couple/pair" strategy by Schreiber.[52] Such examples have included work by Porco starting with β-nitrostyrenes,[53] and most recently by Hanson, who incorporated masked functionality that is selectively activated through functional group interconversions.[54]

The Brummond group was the first to demonstrate a DOS strategy in which multiple scaffolds were formed from a common intermediate through catalyst and condition control. For example, deprotection of α-allenic amino-ester **4-1** followed by reaction with silver(I)-nitrate under Dieter's conditions afforded 3,4-dehydroproline **4-2**.[55,56] Coupling of **4-1** to propargyl (or allyl) bromide (**4-3)** provided allene-yne or allene-ene **4-5** (Scheme 4.1). Subjecting allene-yne **4-5** to microwave irradiation afforded bicyclo[4.2.0]octa-1,6-diene **4-4**.[57] Reaction of **4-5** with Mo(0) under carbon monoxide atmosphere afforded α-alkylidene cyclopentenone **4-7**.[58] Reacting **4-5** with Rh(I) in the presence of CO provided 4-alkylidene cyclopentenone **4-8** via a cyclocarbonylation reaction,[58c,58f,59] whereas similar catalytic conditions in the absence of CO gave cross-conjugated triene **4-9** via a carbocyclization process.[20,27,38,40,60] Finally, reacting the allene-ene version of **4-5** with Rh(I) afforded azepine **4-6**.[37,38]



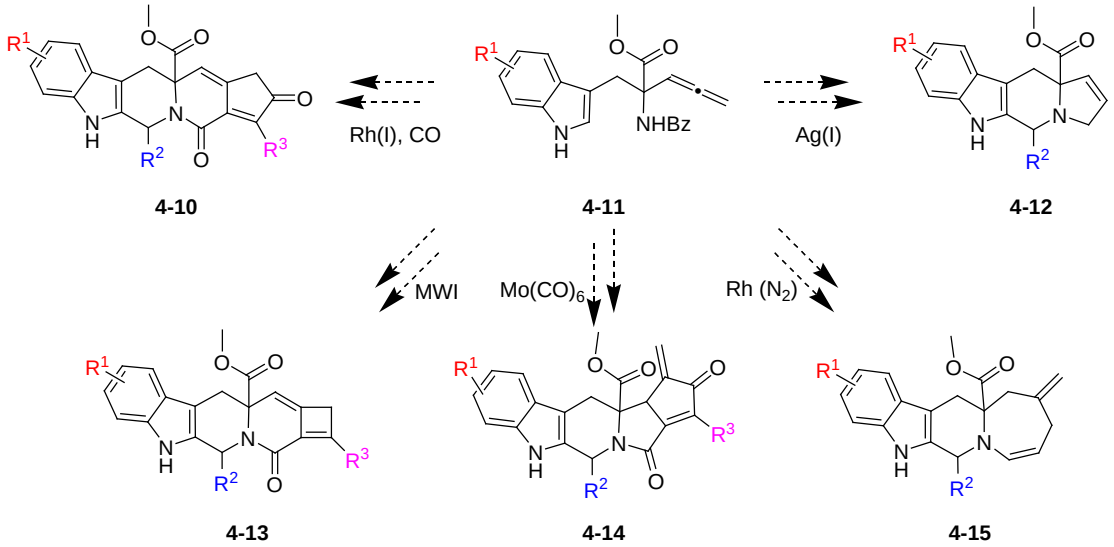
Scheme 4.1 Brummond Group Strategy for Diversification of α-Allenic Amino-esters

Several scaffolds shown in Scheme 4.1 have been further elaborated by subjecting each to complexity generating reactions.[61] These studies have produced libraries of 2-pyrrole carboxamides,[58b,62] 5-iminoozazolodin-2-ones, hydantoins, and acylureas,[63] 3,4-dehydroprolines,[64] and cyclic ethers.[38] All compound structures and biological assay data have been uploaded to the Pubchem database.[65]

4.1.3 New Scaffold Diversity: Tryptophan-Derived Amino-Esters

We propose to continue investigating the potential of the diverging DOS strategy of allene-ynes by attachment of an allene and alkyne directly to a heterocycle. It is hypothesized that this heterocycle template will serve as a starting point for rapid access to a number of compounds possessing interesting biological activity. Moreover, it is envisioned that minimal effort will be required to prepare a number of heterocycle-containing allene-ynes, thus lowering the barrier to

the preparation of more compound libraries with greater chemical diversity. Our general strategy is depicted in Scheme 4.2.

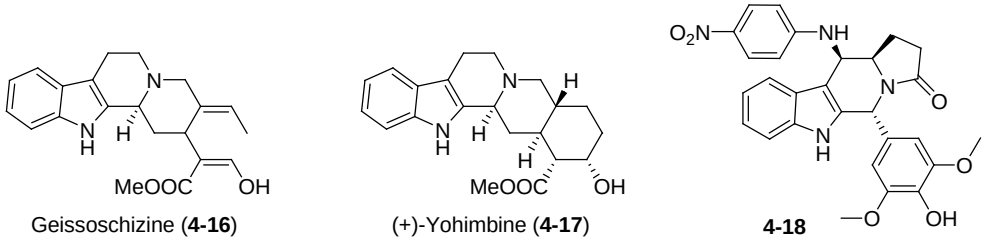


Scheme 4.2 Diverging DOS Strategy for the Synthesis of Tryptophan-Derived Scaffolds

Starting with an allene-substituted tryptophan **4-11**, it is reasoned that a Pictet-Spengler reaction could be employed at an early stage, providing access to a tetrahydro-β-carboline. Conversion of the tetrahydro-β-carboline amine group to a propiolamide followed by: 1. A Rh(I)-catalyzed cyclocarbonylation reaction should give **4-10**; 2. A microwave-assisted [2 + 2] cycloaddition reaction will afford **4-13**; and 3. Reaction with molybdenum hexacarbonyl in turn provides **4-14**. Alternatively, appending an allyl group to the nitrogen atom of the tetrahydro-β-carboline is postulated to give azepine **4-15** when reacted under Rh(I)-catalyzed carbocyclization conditions. Finally, reaction of the tetrahydro-β-carboline with Ag(I) should afford **4-12**.

The value of synthesizing a novel and diverse set of tetrahydro-β-carboline scaffolds is exemplified by the number of biologically important indole-alkaloids possessing this substrate. Examples include: geissoschizine (**4-16**), a known biosynthetic intermediate for a number of indole alkaloid natural products including strychnine;[66] yohimbine (**4-17**); and **4-18**, a compound

that has been reported in the National Cancer Institute's database as having topoisomerase II activity comparable to doxorubicin.[67]



Geissoschizine (**4-16**) (+)-Yohimbine (**4-17**) **4-18**

Figure 4.1 Biologically Important Tetrahydro-β-Carbolines

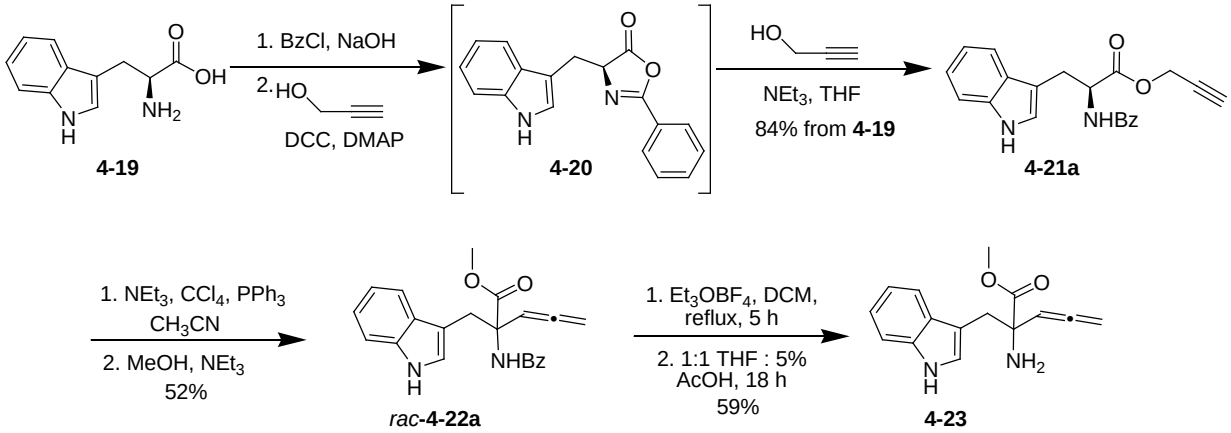
4.2 RESULTS AND DISCUSSION

4.2.1 Diverging DOS Strategy of Allenic Tetrahydro-β-Carbolines: Early Stage Pictet-Spengler Reaction

4.2.1.1 Synthesis of Allenic Tetrahydro-β-Carbolines

The first goal of the new diverging DOS strategy was to synthesize allenic amino-ester intermediate **4-23** for use in the Pictet-Spengler reaction. The amine moiety of commercially available L-tryptophan (**4-19**) was first protected as the benzamide, and the product then coupled to propargyl alcohol using DCC and DMAP to afford propargyl ester **4-21a** in 84% yield over 2 steps after purification via column chromatography. This esterification reaction proceeded through isoxazolone intermediate **4-20**, which was attacked by propargyl alcohol to afford propargyl ester **4-21a** (Scheme 4.3).[68] Ester **4-21a** was next subjected to carbon tetrachloride, triethylamine, and triphenylphosphine in acetonitrile to affect a dehydrative Claisen rearrangement that also racemized the product. Addition of methanol to the reaction mixture

provided racemic α-allenic amino-ester *rac*-**4-22a** in 52% yield.[69] The synthesis of *rac*-**4-22a** (Scheme 4.3) provided an intermediate of type **4-11** as shown in Scheme 4.2. Finally, the *N*-benzoyl group was removed using Meerwein's reagent (Et_3OBF_4) to give α-allenic tryptophan methyl ester **4-23** in 59% yield following flash chromatography.[40]

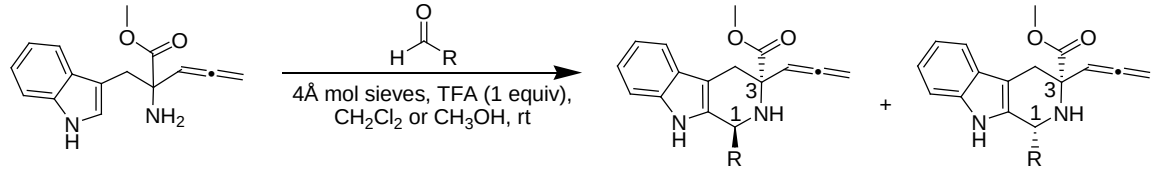


Scheme 4.3 Synthesis of the α-Allenic Amine Precursor to the Pictet-Spengler Reaction

No examples of a Pictet-Spengler reaction performed in the presence of an allene could be identified in the literature; this fact is likely because strong acids and elevated temperatures are typically required for the Pictet-Spengler reaction and could lead to allene hydrolysis.[70] We reasoned that hydrolysis of the allene of **4-23** during the Pictet-Spengler reaction could be avoided by performing the reaction at ambient temperature, and in the presence of an organic acid and molecular sieves.[69,71,72] We subjected allenic amine **4-23** to aqueous formaldehyde and trifluoroacetic acid in the presence of 4 Å molecular sieves in methanol at room temperature to afford allenic tetrahydro-β-carboline **4-24a** in 71% yield. Reaction of **4-23** with *p*-fluorobenzaldehyde under similar conditions in CH_2Cl_2 afforded **4-24b** in 70% yield as a 2 : 1 *trans* : *cis* isomeric mixture (Table 4.1, entry 2). Reacting **4-23** with *n*-butanal under the same conditions gave tetrahydro-β-carboline **4-24c** in 68% yield, also as a 2 : 1 *trans* : *cis* isomeric mixture (Table 4.1, entry 3).

The *trans*- and *cis*-isomers of **4-24b** were not separated, but characterized as a mixture. Loss of the primary amine resonance at 1.92 ppm and the appearance of secondary amine resonances at 2.80 and 2.65 ppm, and the C-1 methine proton resonances at 5.43 and 5.24 ppm were observed in the ^{1}H NMR spectrum of the 2 : 1 *trans* : *cis* mixture. The diastereomers of **4-24c** were separated by column chromatography, and then characterized independently. The *trans* : *cis* product ratios for **4-24b** and **4-24c** were determined using the relative integrations of the resonances corresponding to the C-1 methine protons in the pure and crude ^{1}H NMR spectra for each, respectively.

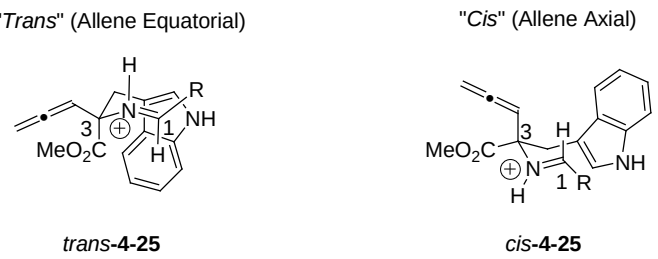
Table 4.1 Synthesis of Allenic Tetrahydro-β-Carboline Derivatives via a Pictet-Spengler Reaction



4-23 *trans*-**4-24** *cis*-**4-24**

Entry	R	Solvent	Time	Product	Yield (%)	dr
1	H	CH_3OH	5 h	**4-24a**	71	N/A
2	*p*-C_6H_4F	CH_2Cl_2	2.5 h	**4-24b**	70	2 : 1
3	*n*-Pr	CH_2Cl_2	50 min	**4-24c**	68	2 : 1

We determined that the *trans*-isomers were the major products of the Pictet-Spengler reactions for reasons provided in section 4.2.1.2. The product ratio can be explained through chair-like transition states *trans*-**4-25** (allene equatorial) and *cis*-**4-25** (allene axial).[72a,b,73,74] Thus, the allene moiety at C-3 more favorably occupied the pseudoequatorial position due to its larger A-value (1.53 kcal/mol vs. 1.2 – 1.3 kcal/mol for a methyl ester), resulting in the *trans*-tetrahydro-β-carbolines as the major products (Fig 4.2).[75]

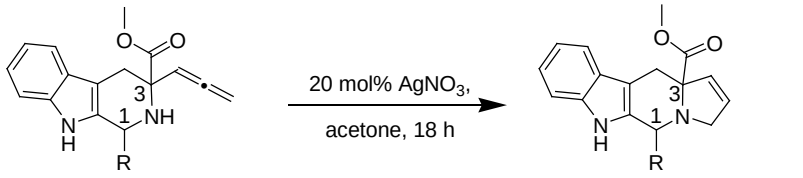


trans-**4-25** *cis*-**4-25**

Figure 4.2 Hypothesized Transition States for the Pictet-Spengler Reactions to Form 4-24

4.2.1.2 Synthesis and Characterization of New Scaffolds Using the Early Stage Pictet-Spengler Strategy

Allenic tetrahydro-β-carbolines **4-24** were next subjected to the Ag(I)-catalyzed allenic cycloisomerization reaction.[55,76] Reaction of tetrahydro-β-carboline derivative **4-24a** with 20 mol% silver nitrate in acetone in a vial wrapped in aluminum foil and kept in a dark hood for 18 h afforded **4-26a** in 56% yield. Treatment of a 2 : 1 *trans* : *cis* mixture of tetrahydro-β-carboline **4-24b** to the same conditions gave **4-26b** in 72% yield as a 2 : 1 *trans* : *cis* isomeric mixture (Scheme 4.4).



4-24a, R = H
4-24b, R = *p*-C_6H_4F, 2 : 1 dr

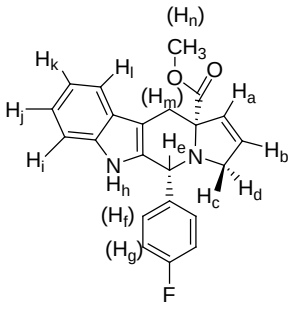
4-26a, R = H, 56%
4-26b, R = *p*-C_6H_4F, 72%, 2 : 1 dr

Scheme 4.4 Silver(I)-Catalyzed Allenic Cycloisomerization Reactions Affording Tetracyclic Indole Scaffolds

The diastereomeric ratio of **4-26b** was determined by the relative integrations of the resonances at 5.04 ppm and 5.51 ppm, which correspond to the protons at C-1 for the *trans*- and *cis*-isomers respectively (Scheme 4.5). The *trans*- and *cis*-isomers were separated by column chromatography and characterized. The alkenyl protons labeled H_a and H_b on structure *cis*-**4-26b** (Table 4.2) have identical vicinal and allylic coupling constants with H_c and H_d (Table

4.2). Both H_a and H_b were split into a ddd with coupling constants of 6.3, 2.1, and 1.4 Hz. For comparison, ^{1}H NMR spectral assignments for *cis*-**4-26b** and pyrroline **4-27** reported by Mitasev are shown below (Tables 4.2 and 4.3, compare entries for H_a and H_b for each compound).[55b] These data are also similar to data reported by Rüeger and Benn, who observed that both olefinic resonances of 3,4-dehydroproline had nearly identical coupling constants [δ = 6.05 (dddd, *J* = 6.5, 2, 2, 2 Hz, 1H), 5.92 (dddd, *J* = 6.5, 2.5, 2, 2 Hz, 1H)].[77] Also of note, H_m exhibited coupling with H_l in structure *cis*-**4-26b**, as evidenced by the 1.4 Hz and 2.8 Hz couplings observed in the ^{1}H NMR and COSY spectra.

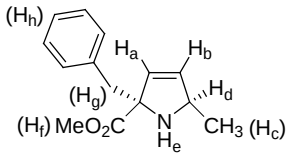
Table 4.2 ^{1}H NMR Spectral Assignment for *cis*-4-26b



***cis*-4-26b**

Entry	Chemical Shift (ppm)	Multiplicity	Integration	*J* Value (Hz)
H_a, H_b	6.11, 6.01	ddd, ddd	1, 1	6.3, 2.1, 1.4 and 6.3, 2.1, 1.4
H_c	3.73 – 3.71	m	1	-
H_d	3.38	dt	1	13.3, 1.4
H_e	5.51	s	1	-
H_f	7.37	dd	2	J_{HF} = 5.6, *J* = 8.4
H_g	7.03	dd	2	J_{HF} = 9.1, *J* = 8.4
H_h	7.37	bs	1	-
H_i	7.56	ddd	1	7.7, 1.4, 0.7
H_j, H_k	7.14 – 7.10	m	2	-
H_l	7.20	ddd	1	7.7, 1.4, 0.7
H_m	3.70, 2.99	dd, dd	1, 1	14.0, 1.4 and 14.0, 2.8
H_n	3.57	s	3	-

Table 4.3 ^{1}H NMR Spectral Assignment for 4-27 as Reported by Branko Mitasev



4-27

Entry	Chemical Shift (ppm)	Multiplicity	Integration	*J* Value (Hz)
H_a, H_b	5.92, 5.86	dd, dd	1, 1	5.8, 1.5 and 5.7, 1.4
H_c	1.11	d	3	6.6
H_d	4.08 – 4.01	m	1	-
H_e	Not reported	-	-	-
H_f	3.79	s	3	-
H_g	3.35, 3.09	d, d	1, 1	14.0 and 14.0
H_h	7.45 – 7.20	m	5	-

The silver(I)-catalyzed cycloisomerization reaction was successfully used to afford *trans*- and *cis*-**4-26b**, but obtaining a single isomer would make library synthesis and characterization more convenient. Cook has reported that subjecting tertiary amino Pictet-Spengler adducts to trifluoroacetic acid for prolonged periods of time yielded only the thermodynamically favored isomer.[72b] Thus, the 2 : 1 *trans* : *cis* mixture of **4-26b** was subjected to 2.4 equivalents of trifluoroacetic acid in deuterated chloroform for 2.5 h to afford a 1 : 4 *trans* : *cis* mixture of **4-26b**, as determined by ^{1}H NMR analysis, in 100% crude yield.[72b] Further exposure to trifluoroacetic acid over 48 h did not change the product ratio, so we concluded that the 1 : 4 ratio represented thermodynamic equilibrium. We were now able to select either the *trans*- or *cis*-isomer of **4-26b** as the desired major component of the product mixture.

Efforts to assign the relative configurations of each isomer of **4-26b** using various spectroscopic methods were unsuccessful.[78] Accordingly, we used calculations to identify which isomer was the most stable. Using the CAChe modeling package (Copyright © Fujitsu), *cis*- and *trans*-**4-26b** were independently optimized using conflex with MM3 geometry. Heats of

formation were then calculated using the PM5 level of theory. These calculations found that H_f *cis* = -38.8 kcal/mol, H_f *trans* = -37.8 kcal/mol, and ΔH_f = 1.0 kcal/mol. The product ratio was thus calculated to be about 1 : 6 in favor of *cis*-**4-26b** at room temperature (Fig. 4.4). Therefore the major product of the equilibration study, *cis*-**4-26b**, was the minor product of the Ag(I)-catalyzed cycloisomerization reaction. Because the Ag(I)-catalyzed cycloisomerization reaction did not effect the isomeric product ratio, we can conclude that *trans*-**4-24b** was the major product of the Pictet-Spengler reaction.

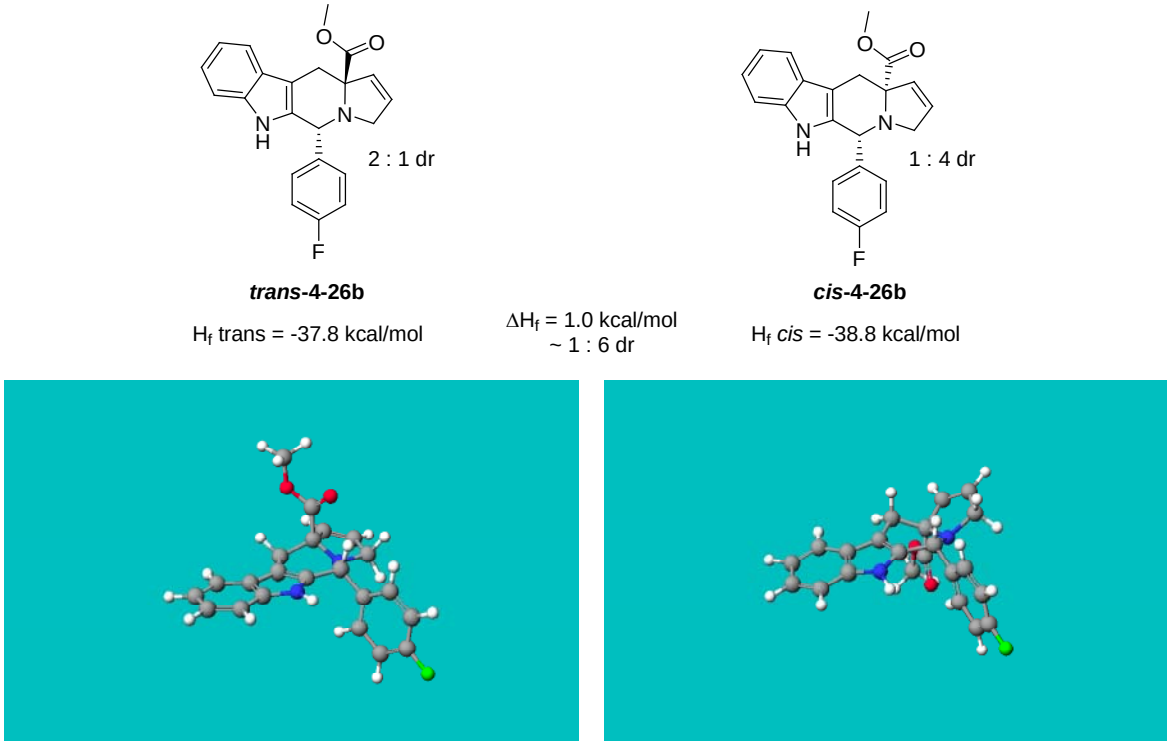
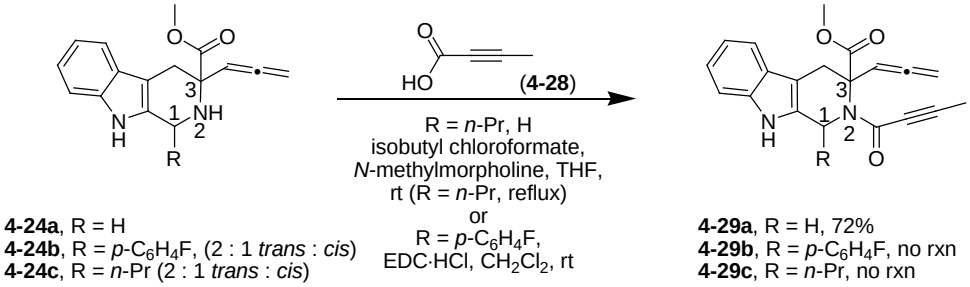


Figure 4.3 Cache Models of *trans*- and *cis*-4-26b

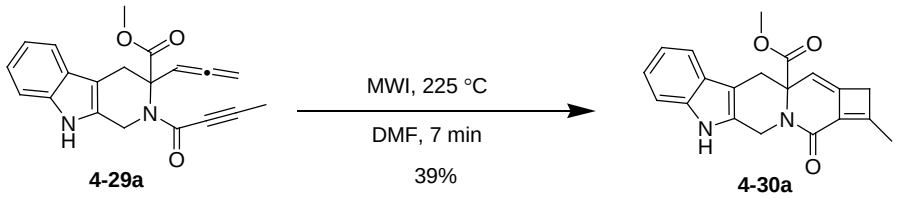
Reacting tetrahydro-β-carboline **4-24a** with 2-butynoic acid (**4-28**) and isobutyl chloroformate at room temperature for 18 h afforded allene-yne **4-29a** in 72% yield after flash chromatography (Scheme 4.5). Analysis of the ^{1}H NMR spectrum revealed a new methyl group resonance at 1.99 ppm (s, 3H), the IR spectrum showed a C-C alkyne stretch at 2236 cm^{-1}, and the molecular ion signal (*m/z* = 334) was present by mass spectroscopy. Reaction of a 2 : 1

trans : *cis* mixture **4-24b** with 2-butynoic acid (**4-28**) and EDC•HCl gave only unreacted starting material in 76% recovery (Scheme 4.5).[79] Similarly, no product was observed when a 2 : 1 *trans* : *cis* isomeric mixture of **4-24c** was reacted with 2-butynoic acid (**4-28)** and isobutyl chloroformate, even in refluxing THF. These results suggested that the steric bulk surrounding the N-2 position of tetrahydro-β-carbolines **4-24b** and **4-24c** was inhibiting the coupling reaction.



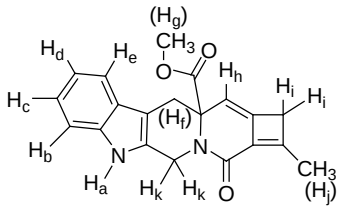
Scheme 4.5 Synthesis of Allene-yne 4-29a

With allene-yne **4-29a** in hand, we proceeded with the allenic [2 + 2] cycloaddition reaction. Recently Brummond, Painter, Davis, and Osbourn have eliminated the ionic liquid, used in Chen's earlier studies, from the reaction mixture. Instead, dimethyl formamide (DMF), an excellent microwave-absorbing solvent that is easily removed from the reaction mixture via an aqueous workup, was used.[80] Employing DMF also circumvented the potential for explosions that have been reported when using ionic liquids in the presence of unsaturation under microwave conditions.[81] Heating a DMF solution of **4-29a** in the microwave at 225 °C for 7 min afforded fused pentacyclic indole **4-30a** in 39% yield after flash chromatography (Scheme 4.6). The ^{1}H NMR spectrum of bicyclo[4.2.0]octa-1,6-diene **4-30a** showed resonances corresponding to H_h and H_i at 5.30 ppm (s, 1H) and at 3.22 and 3.17 ppm (AB pattern, 2H), respectively (Table 4.4).



Scheme 4.6 Synthesis of Fused Pentacycle 4-30a

Table 4.4 ^{1}H NMR Characterization of 4-30a

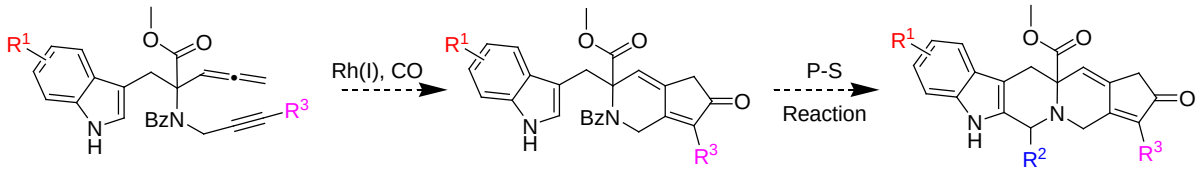


Proton	Chemical Shift (ppm)	Multiplicity	Integration	*J*-Value (Hz)
H_a	8.22	bs	1	-
H_b	7.50	d	1	7.5
H_c, H_d	7.17, 7.12	t, t	1, 1	7.5 and 7.5
H_e	7.34	d	1	7.5
H_f	3.79, 3.03	d, dt	1, 1	15.3 and 15.3, 2.0
H_g	3.59	s	3	-
H_h	5.30	s	1	-
H_i	A 3.22 B 3.17	A of ABq, B of ABq	1, 1	16.5 and 16.5
H_j	2.27	s	3	-
H_k	5.55, 4.47	d, d	1, 1	17.5 and 17.5

Unfortunately, the Rh(I)-catalyzed cyclocarbonylation reaction of **4-29a** afforded only a brown precipitate that could not be characterized. This result, combined with the low yielding [2 + 2] cycloaddition reaction limits the scope of the allene-yne-containing indoline as a precursor in the diverging DOS strategy.

4.2.2 Late-Stage Pictet-Spengler Route to Tryptophan-Derived Scaffolds

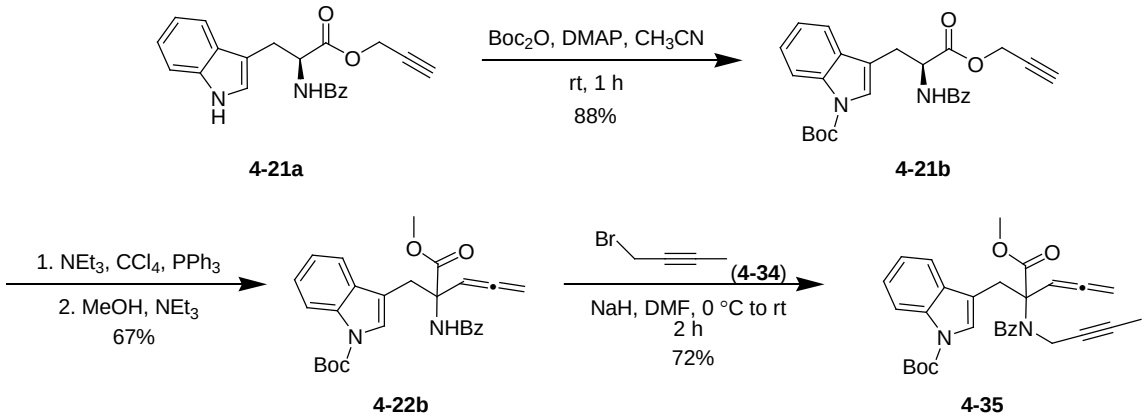
Scheme 4.7 outlines the next endeavor, a late stage Pictet-Spengler strategy where cyclocarbonylation and carbocyclization reactions of the tryptophan-containing allene-ynes are performed first, followed by a tetrahydro-β-carboline forming Pictet-Spengler reaction. The former has precedent in the Brummond group, the latter has precedent in the Grigg and Raghunathan laboratories.[82]



4-31 **4-32** **4-33**

Scheme 4.7 Late Stage Pictet-Spengler Strategy to Diverse Tetrahydro-β-Carboline Scaffolds

Starting with propargyl ester **4-21a**, Boc-protection of the indolyl nitrogen using di-*t*-butyldicarbonate (Boc_2O) and DMAP in acetonitrile afforded **4-21b** in 88% yield after flash chromatography.[83] Next, dehydrative Claisen rearrangement/methanol addition of **4-21b** afforded α-allenic amino-ester *rac*-**4-22b** in 67% yield.[69,68] Finally, allenic amino-ester *rac*-**4-22b** was *N*-alkylated with 1-bromo-2-butyne (**4-34**) to afford allene-yne **4-35** in 72% yield after flash chromatography.[69,68]

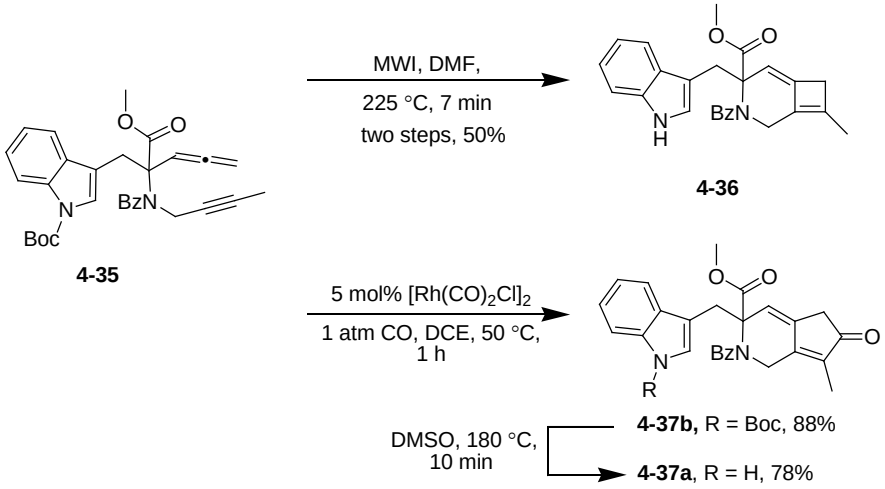


Scheme 4.8 Synthesis of Allene-yne 4-35

Cyclization of allene-yne **4-35** was now possible via the allenic [2 + 2] cycloaddition and Rh(I)-catalyzed cyclocarbonylation reactions. Reacting **4-35** in DMF under microwave-irradiation at 225 °C for 7 min gave bicyclo[4.2.0]octa-1,6-diene **4-36** in 50% yield after flash chromatography (Scheme 4.9). Resonances corresponding to the alkene proton of the doubly allylic methylene group were observed at 5.10 ppm (s, 1H) and 2.99 ppm (unresolved AB pattern), respectively, in the ^{1}H NMR spectrum. This microwave-assisted reaction has been scaled from < 60 mg up to 0.5 g affording the same 50% yield, thus demonstrating the reliability of these conditions.

Next, **4-35** was heated with 5 mol% $[Rh(CO)_2Cl]_2$ in dichloroethane at 50 °C under a carbon monoxide atmosphere for 1 h affording 4-alkylidene cyclopentenone **4-37b** in 88% yield following column chromatography (Scheme 4.9). The ^{1}H NMR spectrum of **4-37b** contained new resonances corresponding to the α-methylene unit at 3.04 and 2.95 ppm (AB pattern, 2H) and the IR spectrum contained no absorbances in the 2250 – 2050 cm^{-1} and 1960 cm^{-1} regions to indicate the presence of an alkyne or allene, respectively. Finally, the indolyl Boc group of **4-37b** was removed under thermal conditions in DMSO to provide **4-37a** in 78% yield (Scheme

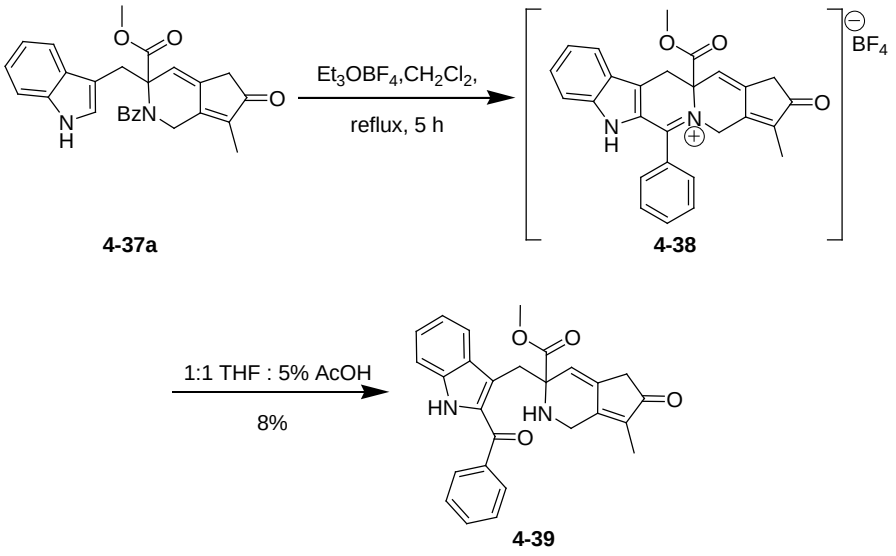
4.9). Other protocols to remove the Boc group (CH_3OH/HCl; TFA/CH_2Cl_2) lead to decomposition of the starting material as observed by TLC analysis.



Scheme 4.9 Synthesis of 4-36 and 4-37a via [2 + 2] Cycloaddition and Cyclocarbonylation Reactions

Removal of the benzoyl groups from **4-36** and **4-37a** proved challenging. A number of conditions were attempted including: Meerwein's reagent,[39] DIBAL-H,[84] super hydride,[85] and Schwartz's reagent,[86] none of which provided the desired secondary amine. Reacting DIBAL-H with **4-37a** produced only a complex mixture by TLC analysis. Reaction of **4-36** with super hydride appeared to selectively reduce the ester as observed by ^{1}H NMR analysis of the crude product.

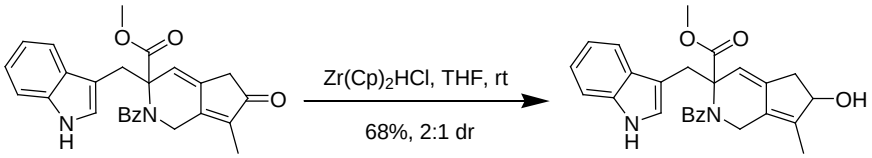
Reaction of **4-37a** with Meerwein's reagent provided only ring-opened amine adduct **4-39** in 8% yield. The benzoyl group had migrated to the 2-position of the indole ring, as observed by loss of the resonance at 6.95 ppm (d, 1H) and retention of the benzoyl resonances around 7.20 ppm in the ^{1}H NMR spectrum. Formation of **4-39** is thought to occur through Bischler-Napieralski-type intermediate **4-38**. Hydrolysis of **4-38** in the presence of acid afforded **4-39** (Scheme 4.10).



4-37a **4-38** **4-39**

Scheme 4.10 Reaction of 4-37a with Meerwein's Reagent

Georg has shown that aldehydes could be obtained from amides using Schwartz's reagent, and it was reasoned that this methodology could be adapted to amine deprotection.[86] When 4-alkylidene cyclopentenone **4-37a** was treated with Schwartz's reagent only alcohol **4-40** was isolated as a 2 : 1 mixture of diastereomers (Scheme 4.11). New resonances at 4.62 (d, J = 5.1 Hz, 1H) and 4.44 ppm (d, J = 6.9 Hz, 1H) in the ^{1}H NMR spectrum of **4-40**, and a change from the AB quartet at 2.96 ppm in the ^{1}H NMR spectrum of **4-37a** into two sets of double doublets in the 3.04 ppm to 2.30 ppm region of the ^{1}H NMR spectrum of **4-40** provided evidence for the product. The relative integrations of the two resonances at 5.38 ppm and 5.35 ppm indicated a 2 : 1 diastereomeric ratio by ^{1}H NMR analysis. Bicyclo[4.2.0]octa-1,6-diene **4-36** did not react with Schwartz's reagent; and other methods to remove the benzoyl group have not yet been explored.



4-37a **4-40**

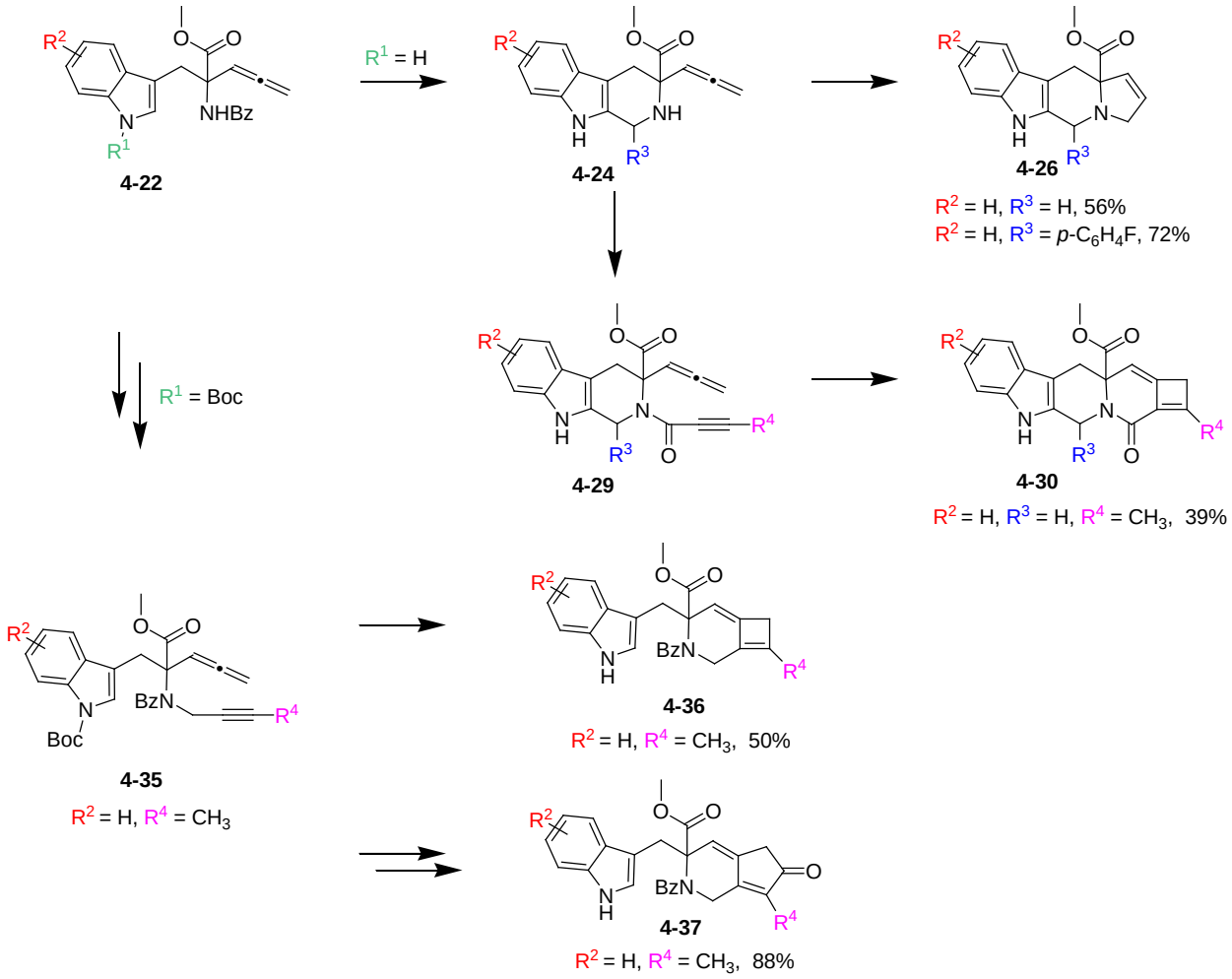
Scheme 4.11 Reaction of 4-37a with Schwartz's Reagent

4.3 CONCLUSIONS

We have developed two complementary strategies resulting in the synthesis of four novel indole-alkaloid scaffolds. The first strategy provided scaffolds **4-26** and **4-30**, and employed a Pictet-Spengler reaction early in the synthetic sequence to afford α-allenic tetrahydro-β-carbolines **4-24**. The carboline scaffolds were further elaborated through a silver(I)-catalyzed allenic cycloisomerization reaction, affording tetracyclic fused indole-alkaloid derivatives **4-26**. Alternatively, formation of a propiolamide from the tetrahydro-β-carboline provided an allene-yne substrate **4-29a** suitable for a microwave-assisted allenic [2 + 2] cycloaddition reaction, which gave a fused pentacyclic cyclobutane-containing indole-alkaloid **4-30a**. The second strategy provided two ring-opened indole-alkaloid scaffolds **4-36** and **4-37**,[68] via microwave-assisted allenic [2 + 2] cycloaddition and Rh(I)-catalyzed allenic cyclocarbonylation reactions, respectively. Removal of the benzoyl group remained a challenge in the late-stage strategy, but further development may lead to substrates that will result in better diastereoselectivity during the Pictet-Spengler reaction.

The results from both strategies are summarized in Scheme 4.12, which provides a roadmap for further development through library synthesis. The value of this methodology to

library synthesis is high as exemplified by the novelty and ease of construction of the scaffolds, and availability of starting materials.



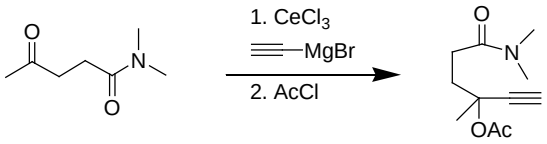
Scheme 4.12 Summary of Scaffolds Synthesized from Indolyl α-Allenic Amino-Esters

5.0 EXPERIMENTAL SECTION

5.1 GENERAL METHODS

Unless otherwise noted, all reactions were carried out under nitrogen atmosphere. All commercially available compounds were purchased and used as received, unless otherwise specified. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by passing through alumina. Dichloromethane (CH_2Cl_2) was passed through alumina and Q5. Toluene and dichloroethane were freshly distilled from CaH_2 prior to use. Purification of the compounds by flash chromatography was performed by using silica gel (32-63 μm particle size, 60 Å pore size). TLC analyses were performed on EM Science Silica Gel 60 F_{254} plates (250 μm thickness). All ^{1}H NMR and ^{13}C NMR spectra were obtained on 300, 500, or 700 MHz Bruker Biospin NMR spectrometers with Topspin NMR software. Chemical shifts (δ) are reported relative to residual solvent resonances as indicated. All NMR spectra were obtained at room temperature unless otherwise specified. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectrometry was performed on a Micromass Autospec high resolution mass spectrometer. The glassware was typically oven-dried or flame-dried.

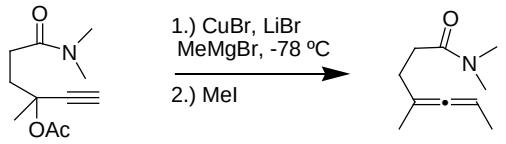
5.2 EXPERIMENTAL: CHAPTER 1



1-39 **1-41**

Acetic acid 1-(2-dimethylcarbamoyl-ethyl)-1-methyl-prop-2-ynyl ester 1-41. Cerium trichloride heptahydrate (23.6 g, 63.4 mmol) was dried at 140 ºC under vacuum (3 torr) in a 500 mL round bottomed flask for 14 h. The off-white solid was allowed to cool to rt, placed under a nitrogen atmosphere then suspended in THF (63 mL). The suspension was cooled to 0 ºC and stirred for 20 min. A THF solution of ethynyl magnesium bromide (127 mL of a 0.5 M solution, 63.5 mmol) was then added slowly via syringe at 0 ºC. The resultant orange-brown suspension was allowed to warm to rt over 1.5 h when it was cooled to 0º C and amide **1-39** (3.03 g, 21.1 mmol) in a solution of THF (7 mL) was added via cannula. The reaction was allowed to warm to rt. After 4.5 h, acetyl chloride (7.54 mL, 106 mmol) was added via syringe. After an additional 3.5 h at ambient temperature the reaction mixture was diluted with ethyl acetate (300 mL) and water (200 mL). The layers were separated the aqueous layer extracted with ethyl acetate (3x). The combined organic layers were dried over $MgSO_4$, decolorized with charcoal, and filtered through a pad of silica gel. The solvent was removed under vacuum and the residue chromatographed on silica gel (60% ethyl acetate/hexanes) to give a red-brown oil (4.33 g, 20.5 mmol, 97%, yield avg. of two = 95%). (R_f = 0.21, 60% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (bs, 3H), 2.97 (bs, 3H), 2.58 (s, 1H), 2.57 (t, *J* = 7.8 Hz, 2H), 2.36-2.26 (m, 1H), 2.17-2.11 (m, 1H), 2.04 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, benzene – d_6) δ 170.9, 168.4, 83.7, 74.3, 74.3, 37.6, 36.1, 34.9, 28.7, 26.6, 21.3; IR (thin film) υ 3262, 3211, 2940,

2110, 1737, 1639 cm $^{-1}$; MS *m/z* (%) 196 (14, M - 15), 183 (28), 168 (16), 152 (50), 125 (18), 72 (100); EI-HRMS calcd for $C_{10}H_{14}NO_3$ *m/z* [M - 15$^+$] 196.0974; found 196.0967.

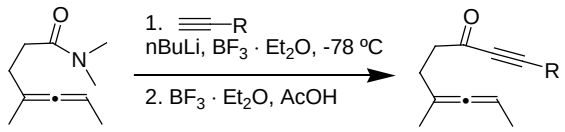


1-41 **1-44**

3-Methyl-hexa-3,4-dienoic acid dimethylamide 1-44. Copper bromide (2.82 g, 19.7 mmol) and lithium bromide (1.71 g, 19.7 mmol) were dried together at 140 ºC under vacuum (3 torr) in a 250 mL round bottomed flask for 14 h. The salts were allowed to cool and placed under a nitrogen atmosphere. THF (98 mL) was then added resulting in a pale light-green to yellow suspension that was cooled to -78 ºC. An ether solution of methyl magnesium bromide (6.56 mL of a 3 M solution, 19.7 mmol) was added slowly via syringe, producing a mustard yellow suspension. The reaction mixture was allowed to warm to -40 ºC over a period of 1.5 – 2 h, cooled to -78 ºC, and the alkynylamide **1-41** (2.08 g, 9.84 mmol) in a solution of THF (10 mL) was added via cannula. The reaction was allowed to warm to -30 ºC and methyl iodide (3.7 mL, 59 mmol) was added rapidly via syringe, and the suspension slowly changed to a green-brown color. After warming to -10 ºC over 35 min, the reaction mixture was poured into ether and a solution of sat'd aqueous NH_4Cl : 3% aqueous NH_4OH (1 : 1) in a 500 mL round bottomed flask. This was stirred vigorously until a dark blue color persisted in the aqueous phase. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic layers were dried over $MgSO_4$ and the solvent removed under vacuum. The crude residue was chromatographed on silica gel (50% ethyl acetate/hexanes) to give a pale yellow oil (1.64 g, 9.80 mmol, 100%, yield avg. of three = 94%). (R_f = 0.36, 60% ethyl acetate/hexanes) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 – 4.97 (m 1H), 3.00 (bs, 3H), 2.93 (bs, 3H), 2.39 (dd, *J* = 9.3, 6.7 Hz, 2H),

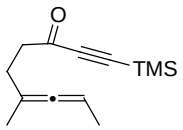
2.28 – 2.19 (m, 2H), 1.69 (d, J = 2.7 Hz, 3H), 1.59 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 172.5, 98.5, 85.9, 37.0, 35.2, 31.1, 28.7, 19.4, 14.7; IR (thin film) υ 2976, 2925, 1962, 1650 cm^{-1}; MS *m/z* (%) 167 (15), 95 (13), 72 (100); EI-HRMS calcd for $C_{10}H_{17}NO$ *m/z* [M^+] 167.1310; found 167.1308.

Substituted allene-ynones 1-48a – 1-48l



1-44 **1-48**

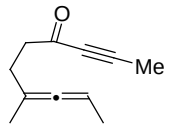
General Procedure B: Preparation of **1-48a**.



1-48a

6-Methyl-1-(trimethylsilyl)nona-6,7-dien-1-yn-3-one 1-48a. In a manner entirely analogous to Trost; A solution of alkyne (R = TMS) (1.813 mmol) in THF (4.0 mL) was cooled to -78 ºC and *n*-butyl lithium (1.0 mL, 1.6 M solution in hexanes, 1.6 mmol) was added rapidly via syringe. After 5 min, boron trifluoride diethyl etherate (215 mL, 1.71 mmol) was added. The resultant solution (or mixture) was stirred for 15 min then a solution of allenyl amide **1-44** (169 mg, 1.01 mmol) in THF (3 mL) was added via cannula. The reaction was allowed to stir for 1.5 h, after which time more boron trifluoride diethyl etherate (215 μL, 1.71 mmol) and acetic acid (98 μL, 1.71 mmol) were added. The reaction was allowed to warm to -20 ºC and quenched with sat'd aqueous NH_4Cl (3.5 mL). After warming to rt, the reaction mixture was diluted with ether and water. The layers were separated and the aqueous layer was extracted with ether (3x). The combined organic layers were washed with water (2x) and dried over $MgSO_4$. This mixture was

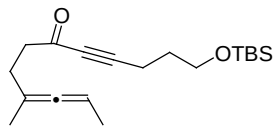
filtered through a pad of silica gel (30 mL fritted funnel, approximately half full), and concentrated under vacuum. The crude residue was chromatographed on silica gel (3% ethyl acetate/hexanes) to give **1-48a** (119 mg, 54%) as a faint yellow oil. Average of three yields: 63%. (R_f = 0.92, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.06 – 4.98 (m, 1H), 2.62 (dd, *J* = 7.5, 6.7 Hz, 2H), 2.28 – 2.21 (m, 2H), 1.66 (d, *J* = 2.7 Hz, 3H), 1.57 (d, *J* = 7.0 Hz, 3H) 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 187.1, 101.9, 97.5, 97.1, 87.0, 43.0, 27.8, 19.3, 14.6, -0.9; IR (thin film) ν 2962, 2900, 2151, 1967, 1679, 1252, 847 cm^{-1}; MS *m/z* (%) 220 (14), 205 (7), 178 (13), 163 (29), 73 (100), 61 (100); EI-HRMS calcd for $C_{13}H_{20}OSi$ *m/z* [M^+] 220.1283; found 220.1289.



1-48b

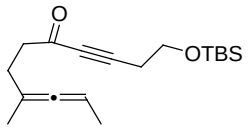
7-Methyldeca-7,8-dien-2-yn-4-one 1-48b. To a solution of 1-bromo-1-propene (100 μL, 1.17 mmol), in THF (0.80 mL) at -78 °C was added *n*-butyl lithium (1.3 mL, 1.6 M solution in hexanes, 2.1 mmol). The resultant white suspension was stirred for 2 h then diluted with THF (1.8 mL) to prepare the acetylide solution. According to General Procedure B, **1-44** (109 mg, 0.65 mmol) in THF (3.3 mL) was reacted with the acetylide (R = Me, 1.17 mmol as described above) in THF (2.6 mL as described above), borontrifluoride diethyl etherate (157 μL, 1.11 mmol, 1st addition), borontrifluoride diethyl etherate (157 μL, 1.11 mmol, 2nd addition) and acetic acid (63 μL, 1.11 mmol) to afford allene-ynone **1-48b** (98 mg, 93%) as a pale yellow oil (chromatographed on silica gel using 3% ethyl acetate/hexanes). Average of two yields: 89%. (R_f = 0.53, 10% ethyl acetate/hexanes eluted twice); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.08 – 4.98 (m, 1H), 2.61 (dd, *J* = 8.1, 6.7 Hz, 2H), 2.26 – 2.18 (m, 2H), 2.00 (s, 3H), 1.67 (d, *J* = 2.7 Hz,

3H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 187.4, 97.6, 89.5, 86.8, 80.2, 43.3, 27.8, 19.4, 14,7, 3.9; IR (thin film) ν 2980, 2922, 2853, 2217, 1962, 1675 cm^{-1}; MS *m/z* (%) 162 (12), 147 (23), 120 (72), 105 (69), 95 (33), 79 (61), 67 (100); EI-HRMS calcd for $C_{11}H_{14}O$ *m/z* [M^+] 162.1045; found 162.1042.



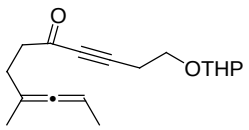
1-48c

1-*t*-butyldimethlysilyloxy-9-methyldodeca-9,10-dien-4-yn-6-one 1-48c. According to General Procedure B, **1-44** (88 mg, 0.53 mmol) in THF (2.6 mL) was reacted with the acetylide (R = $(CH_2)_3$OTBS, 188 mg, 0.95 mmol) in THF (2.1 mL), *n*-butyl lithium (0.53 mL, 1.6 M solution in hexanes, 0.84 mmol), borontrifluoride diethyl etherate (112 μL, 0.89 mmol, 1st addition), borontrifluoride diethyl etherate (112 μL, 0.89 mmol, 2nd addition), and acetic acid (51 μL, 0.89 mmol) to afford allene-ynone **1-48c** (54 mg, 32%) as a clear oil (chromatographed on silica gel using 3% ethyl acetate/hexanes). Average of two yields: 41%. (R_f = 0.66, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 – 5.01 (m, 1H), 3.70 (t, *J* = 5.9 Hz, 2H), 2.64 (dd, *J* = 8.3, 6.8 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.28 – 2.22 (m, 2H), 1.82 – 1.73 (m, 2H), 1.69 (d, *J* = 2.8 Hz, 3H), 1.61 (d, *J* = 6.9 Hz, 1H), 0.90 (s, 9H), 0.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 187.4, 97.6, 93.5, 86.8, 80.9, 61.1, 43.4, 30.8, 27.9, 25.8, 19.4, 18.2, 15.4, 14.7, -5.4; IR (thin film) ν 2954, 2929, 2898, 2857, 2212, 1967, 1676, 1256, 1106, 973, 835, 777 cm^{-1}; MS *m/z* (%) 320 (9), 263 (14), 189 (19), 145 (58), 75 (100); EI-HRMS calcd for $C_{19}H_{32}O_2Si$ *m/z* 320.2172 [M^+]; found 320.2170.



1-48d

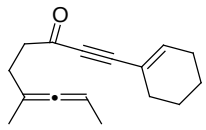
1-*t*-butyldimethylsilyloxy-8-methylundeca-8,9-dien-3-yn-5-one 1-48d. According to General Procedure B, **1-44** (144 mg, 0.86 mmol) in THF (4.3 mL) was reacted with the acetylide (R = $(CH_2)_2$OTBS, 286 mg, 1.55 mmol) in THF (3.4 mL), *n*-butyl lithium (0.86 mL, 1.6 M solution in hexanes, 1.38 mmol), borontrifluoride diethyl etherate (184 μL, 1.46 mmol, 1st addition), borontrifluoride diethyl etherate (184 μL, 1.46 mmol, 2nd addition), and acetic acid (83 μL, 1.46 mmol) to afford allene-ynone **1-48d** (262 mg, 99%) as a clear oil (chromatographed on silica gel using 3% ethyl acetate/hexanes). Average of two yields: 98%. (R_f = 0.68, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 – 5.02 (m, 1H). 3.79 (t, *J* = 6.8 Hz, 2H), 2.65 (dd, *J* = 8.2, 6.9 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.29 – 2.21 (m, 2H), 1.70 (d, *J* = 2.8 Hz, 3H), 1.61 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 187.2, 97.5, 90.7, 86.8, 81.4, 60.7, 43.2, 27.7, 25.8, 25.7, 23.3, 19.4, 18.1, 14.7, -5.5; IR (thin film) ν 2954, 2929, 2899, 2857, 2216, 1967, 1677, 1255, 1110, 837, 777 cm^{-1}; MS *m/z* (%) 330 (20, M + 23Na + H), 329 (100, M + 23Na); ESI-HRMS calcd for $C_{18}H_{30}O_2SiNa$ *m/z* [M + $23Na^+$] 329.1913; found 329.1922.



1-48e

8-Methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)undeca-8,9-dien-3-yn-5-one 1-48e. According to General Procedure B, **1-44** (97 mg, 0.58 mmol) in THF (2.9 mL) was reacted with the acetylide (R = $(CH_2)_2$OTHP, 160 mg, 1.04 mmol) in THF (2.3 mL), *n*-butyl lithium (0.58 mL, 1.6 M

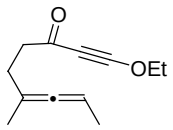
solution in hexanes, 0.93 mmol), borontrifluoride diethyl etherate (124 μL, 0.99 mmol, 1st addition), borontrifluoride diethyl etherate (124 μL, 0.99 mmol, 2nd addition), and acetic acid (57 μL, 0.99 mmol) to afford allene-ynone **1-48e** (157 mg, 98%) as a clear oil (chromatographed on silica gel using 15% ethyl acetate/hexanes). (R_f = 0.46, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 – 4.98 (m, 1H), 4.64 (t, *J* = 3.2 Hz, 1H), 3.90 – 3.83 (m, 2H), 3.63 – 3.48 (m, 2H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.63 (dd, *J* = 8.6, 6.9 Hz, 2H), 2.29 – 2.21 (m, 2H), 1.83 – 1.50 (m, 6H), 1.68 (d, *J* = 2.7 Hz, 3H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 187.3, 98.8, 97.6, 90.6, 86.8, 81.3, 64.6, 62.1, 43.4, 30.4, 27.9, 25.3, 20.5, 19.4, 19.2, 14.7; IR (thin film) ν 2941, 2894, 2868, 2217, 1967, 1675, 1034 cm^{-1}; MS *m/z* (%) 276 (5), 275 (9), 261 (6), 231 (11), 219 (25), 174 (24), 85 (100); EI-HRMS calcd for $C_{17}H_{24}O_3$ *m/z* 276.1725 [M^+]; found 276.1720.



1-48f

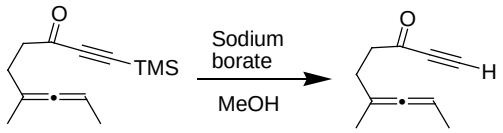
1-Cyclohexenyl-6-methylnona-6,7-dien-1-yn-3-one 1-48f. According to General Procedure B, **1-44** (99 mg, 0.59 mmol) in THF (3.0 mL) was reacted with the acetylide (R = 1-cyclohexenyl, 125 μL, 1.06 mmol) in THF (2.4 mL), *n*-butyl lithium (0.59 mL, 1.6 M solution in hexanes, 0.94 mmol), borontrifluoride diethyl etherate (126 μL, 1.00 mmol, 1st addition), borontrifluoride diethyl etherate (126 μL, 1.00 mmol, 2nd addition), and acetic acid (57 μL, 1.00 mmol) to afford allene-ynone **1-48f** (131 mg, 97%) (chromatographed on silica gel using 3% ethyl acetate/hexanes). Average of two yields: 94%. (R_f = 0.63, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 – 6.43 (m, 1H), 5.08 – 5.00 (m, 1H), 2.66 (dd, *J* = 7.9, 6.6 Hz, 2H), 2.31 – 2.24 (m, 2H), 2.18 – 2.15 (m, 4H), 1.69 (d, *J* = 2.7 Hz, 3H), 1.67 – 1.61 (m, 4H), 1.60 (d,

J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 187.7, 142.1, 118.9, 97.6, 93.0, 86.9, 86.0, 43.2, 28.3, 28.0, 26.0, 21.9, 21.0, 19.4, 14.8; IR (thin film) ν 3027, 2979, 2932, 2859, 2185, 1967, 1670, 1621, 1085 cm^{-1}; MS *m/z* (%) 229 (7), 228 (42), 213 (20), 185 (35), 143 (73), 133 (79), 91 (87), 77 (100); EI-HRMS calcd for $C_{16}H_{20}O$ *m/z* [M^+] 228.1514; found 228.1506.



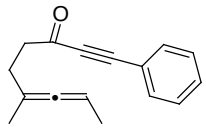
1-48g

1-Ethoxy-6-methylnona-6,7-dien-1-yn-3-one 1-48g. According to General Procedure B, **1-44** (88 mg, 0.52 mmol) in THF (2.6 mL) was reacted with ethoxy acetylene (225 μL, 40% wt. solution in hexanes, 0.94 mmol) in THF (2.0 mL), *n*-butyl lithium (0.52 mL, 1.6 M solution in hexanes, 0.83 mmol), borontrifluoride diethyl etherate (111 μL, 0.88 mmol, 1st addition), borontrifluoride diethyl etherate (111 μL, 0.88 mmol, 2nd addition), and acetic acid (51 μL, 0.88 mmol) to afford allene-ynone **1-48g** (83 mg, 83%) (chromatographed on silica gel using 10% ethyl acetate/hexanes). (R_f = 0.46, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 – 5.00 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.60 (dd, *J* = 8.0, 6.9 Hz, 2H), 2.31 – 2.20 (m, 2H), 1.69 (d, *J* = 2.8 Hz, 3H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 201.6, 187.4, 102.4, 97.7, 86.5, 77.2, 44.2, 43.3, 28.2, 19.4, 14.7, 14.3; IR (thin film) ν 2982, 2901, 2226, 1666, 1443, 1393, 1068, 1004 cm^{-1}; MS *m/z* (%) 192 (6), 164 (13), 149 (15), 97 (100); EI-HRMS calcd for $C_{12}H_{16}O_2$ *m/z* [M^+] 192.1150; found 192.1138.



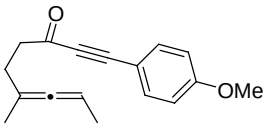
1-48a **1-48h**

6-Methylnona-6,7-dien-1-yn-3-one 1-48h. Using the method of Walton and Waugh; the TMS-protected alkyne, **1-48a** (60 mg, 0.27 mmol) was dissolved in methanol (3.4 mL) and sodium borate (0.4 mL, 0.01 M solution in H_2O) was added via syringe. After 10 min the reaction mixture was poured into HCl (10 mL, 1% by wt. in H_2O) over dichloromethane (10 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3x). The combined organic layers were dried over $MgSO_4$, filtered through a pad of silica gel (10 mL fritted funnel approximately half full) using 10% ether/dichloromethane to elute, and concentrated under vacuum to give **1-48h** as a pale yellow oil (36 mg, 0.24 mmol, 90%) that was pure enough for further use. Due to the volatility of this compound, it was not concentrated under vacuum for more than 2 min. A portion of the sample was purified by silica gel column chromatography (3% ethyl acetate/hexanes). (R_f = 0.69, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 – 5.04 (m, 1H), 3.21 (s, 1H), 2.69 (dt, *J* = 2.3, 7.3 Hz, 2H), 2.31 – 2.26 (m, 2H), 1.69 (d, *J* = 2.8 Hz, 3H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 186.6, 97.4, 87.4, 81.4, 78.0, 43.3, 27.6, 19.3, 14.6; IR (thin film) ν 3259, 2982, 2924, 2854, 2093, 1967, 1682 cm^{-1}; MS *m/z* (%) 148 (23), 147 (15), 133 (26), 106 (81), 91 (100), 79 (98); EI-HRMS calcd for $C_{10}H_{12}O$ *m/z* 148.0888 [M^+]; found 148.0886.



1-48i

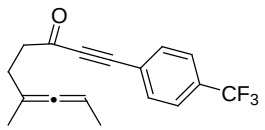
6-Methyl-1-phenylnona-6,7-dien-1-yn-3-one 1-48i. According to General Procedure B, **1-44** (83 mg, 0.50 mmol) in THF (2.5 mL) was reacted with phenyl acetylene (92 mg, 0.90 mmol) in THF (2.0 mL), *n*-butyl lithium (0.50 mL, 1.6 M solution in hexanes, 0.80 mmol), borontrifluoride diethyl etherate (107 μL, 0.85 mmol, 1st addition), borontrifluoride diethyl etherate (107 μL, 0.85 mmol, 2nd addition), and acetic acid (49 μL, 0.85 mmol) to afford allene-ynone **1-48i** (95 mg, 85%) (chromatographed on silica gel using 3% ethyl acetate/hexanes). Note that a white suspension will form after addition of the first portion of borontrifluoride diethyl etherate. Average of two yields: 92%. (R_f = 0.36, 10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 – 7.56 (m, 2H), 7.48 – 7.35 (m, 3H) 5.12 – 5.04 (m, 1H), 2.78 (dd, *J* = 7.5, 6.8 Hz, 2H), 2.39 – 2.32 (m, 2H), 1.73 (d, *J* = 2.8 Hz, 3H), 1.62 (dd, *J* = 6.9, 2.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 187.5, 132.9, 130.6, 128.5, 120.0, 97.6, 90.3, 87.8, 87.0, 43.3, 28.0, 19.4, 14.7; IR (thin film) ν 3058, 2976, 2914, 2894, 2853, 2203, 1962, 1670 cm^{-1}; MS *m/z* (%) 224 (100), 209 (24); EI-HRMS calcd for $C_{16}H_{16}O$ *m/z* [M^+] 224.1201; found 224.1194.



1-48j

1-(4-Methoxyphenyl)-6-methylnona-6,7-dien-1-yn-3-one 1-48j. According to General Procedure B, **1-44** (71 mg, 0.43 mmol) in THF (2.1 mL) was reacted with the *p*-methoxyphenyl acetylene (101 mg, 0.77 mmol) in THF (1.7 mL), *n*-butyl lithium (0.43 mL, 1.6 M solution in hexanes, 0.68 mmol), borontrifluoride diethyl etherate (91 μL, 0.72 mmol, 1st addition),

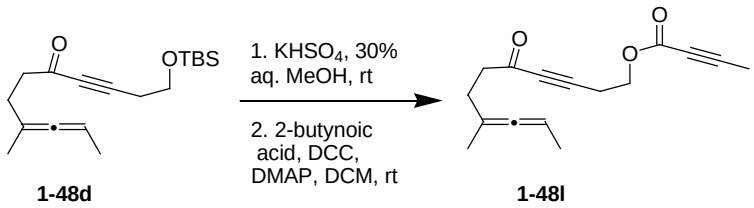
borontrifluoride diethyl etherate (91 μL, 0.72 mmol, 2nd addition), and acetic acid (41 μL, 0.72 mmol) to afford allene-ynone **1-48j** (91 mg, 84%) (chromatographed on silica gel using 3% ethyl acetate in hexanes). Note that a white suspension will form after addition of the first portion of borontrifluoride diethyl etherate. Average of two yields: 88%. (R_f = 0.26, 10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.11 – 5.04 (m, 1H), 3.85 (s, 3H), 2.76 (dd, *J* = 8.1, 6.8 Hz, 2H), 2.39 – 2.31 (m, 2H), 1.73 (d, *J* = 2.8 Hz, 3H), 1.62 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 187.2, 161.5, 134.9, 114.2, 111.8, 97.6, 91.4, 87.6, 86.8, 55.2, 43.2, 28.1, 19.3, 14.6; IR (thin film) ν 2979, 2899, 2849, 2553, 2197, 1965, 1665, 1254, 1092 cm^{-1}; MS *m/z* (%) 254 (26), 239 (41), 211 (42), 197 (42), 159 (100); EI-HRMS calcd for $C_{17}H_{18}O_2$ *m/z* [M^+] 254.1307; found 254.1282.



1-48k

1-(4-(Trifluoromethyl)phenyl)-6-methylnona-6,7-dien-1-yn-3-one 1-48k. According to General Procedure B, **1-44** (74 mg, 0.44 mmol) in THF (2.2 mL) was reacted with *p*-trifluoromethyl acetylene (0.13 mL, 0.80 mmol) in THF (1.8 mL), *n*-butyl lithium (0.44 mL, 1.6 M solution in hexanes, 0.71 mmol), borontrifluoride diethyl etherate (94 μL, 0.75 mmol, 1st addition), borontrifluoride diethyl etherate (94 μL, 0.75 mmol, 2nd addition), and acetic acid (43 μL, 0.75 mmol) to afford allene-ynone **1-48k** (111 mg, 86%) (chromatographed on silica gel using 3% ethyl acetate/hexanes). Average of two yields: 89%. (R_f = 0.38, 10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 5.13 – 5.04 (m, 1H), 2.80 (dd, *J* = 8.6, 7.0, 2H), 2.42 – 2.32 (m, 2H), 1.72 (d, *J* = 2.8 Hz, 3H), 1.61 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 186.9, 133.0, 132.5 (q, J_{C-F} =

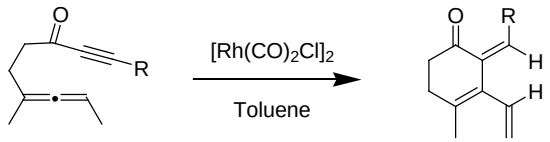
32.6 Hz), 125.5 (q, $J_{C\text{-}F}$ = 3.6 Hz), 123.9, 123.5 (q, $J_{C\text{-}F}$ = 271.0 Hz), 97.5, 89.0, 87.6, 87.1, 43.3, 27.9, 19.3, 14.7; IR (thin film) ν 2982, 2901, 2860, 2209, 1969, 1677, 1615, 1323, 843 cm^{-1}; MS *m/z* (%) 292 (21), 277 (11), 250 (41), 235 (24), 197 (100), 165 (23), 79 (25); EI-HRMS calcd for $C_{17}H_{15}OF_3$ *m/z* [M^+] 292.1075; found 292.1073.



8-Methyl-5-oxoundeca-8,9-dien-3-ynyl but-2-ynoate 1-48l. Using the method of Perumal; the TBS ether, **1-48d** (164 mg, 0.54 mmol) was suspended in MeOH : H_2O (1.6 mL, 7 : 3, v/v) and stirred vigorously, forming an emulsion. $KHSO_4$ (29 mg, 0.21 mmol) was added and the reaction stirred at rt for 1.5 h when there was an absence of starting material observed by TLC. The reaction mixture was diluted with ethyl acetate, dried over $MgSO_4$, and filtered through a pad of silica gel (30 mL fritted funnel, approximately half full). The solvent was removed under vacuum to afford a thick pale yellow residue (102 mg, 0.53 mmol, 99%). The crude product was redissolved in CH_2Cl_2 (1 mL), cooled to 0 °C, and 4-(dimethylamino)pyridine (7 mg, 0.06 mmol) and N,N′-dicyclohexylcarbodiimide (126 mg, 0.61 mmol) were added. A solution of 2-butynoic acid (48 mg, 0.57 mmol) in CH_2Cl_2 (0.50 mL) was then added via syringe. The reaction progress was monitored by TLC. After 1.5 – 2h, he reaction mixture was diluted in CH_2Cl_2 and filtered through a pad of silica gel (30 mL fritted funnel, approximately half full) eluting with CH_2Cl_2. The solvent was removed under vacuum and the residue chromatographed on silica gel (15% ethyl acetate/hexanes) to give the product as a pale yellow oil (113 mg, 0.44 mmol, 82% over two steps). (R_f = 0.60, 30% ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 – 5.01 (m, 1H), 4.30 (t, *J* = 6.7 Hz, 2H), 2.76 (t, *J* = 6.7 Hz, 2H), 2.65 (dd, *J* = 6.8,

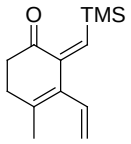
7.4 Hz, 2H), 2.30 – 2.23 (m, 2H), 2.01 (s, 3H), 1.70 (d, *J* = 2.8 Hz, 3H), 1.61 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 187.1, 153.1, 97.5, 87.9, 86.9, 86.5, 81.6, 71.8, 62.1, 43.2, 27.7, 19.3, 19.2, 14.7, 3.7; IR (thin film) ν 2980, 2900, 2243, 2223, 1967, 1715, 1675, 1252, 1083 cm^{-1}; MS *m/z* (%) 258 (8), 240 (5), 174 (100), 159 (27), 132 (62), 67 (97); EI-HRMS calcd for $C_{16}H_{18}O_3$ *m/z* 258.1256 [M^+]; found 258.1256.

3-Vinyl-2-alkylidene-3-cyclohexen-1-ones



1-48 **1-49**

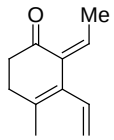
General Procedure A: Preparation of **1-49a**



1-49a

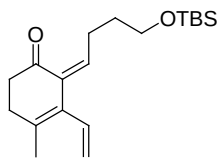
(2*Z*)-4-Methyl-2-((trimethylsilyl)methylene)-3-vinylcyclohex-3-enone 1-49a. A solution of allene-ynone **1-48a** (64.1 mg, 0.29 mmol) in toluene (0.97 mL) was degassed by bubbling argon through the stirred solution for 20 min. Rhodium biscarbonyl chloride dimer (3.4 mg, 0.009 mmol, 3 mol%) was added at 0 °C. The reaction was followed by TLC an after 5 min the reation was complete. The reaction mixture was diluted with a 10% ethyl acetate/hexanes solution and filtered through a pad of silica gel (10 mL fritted funnel, approximately half full), further eluting with 10% ethyl acetate/hexanes solution. The resultant yellow solution was concentrated under vacuum to give **1-49a** (60.9 mg, 95%) as a yellow oil without further purification. Average of two yields: 90%. (A 92% yield was obtained when the reaction was performed in DCE under the same conditions during optimization experiments). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, *J* =

17.7, 11.3 Hz, 1H), 6.01 (s, 1H), 5.45 (dd, *J* = 11.3, 2.1 Hz, 1H), 5.15 (dd, *J* = 17.7, 2.1 Hz, 1H), 2.61 – 2.51 (m, 4H), 1.95 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 200.6, 145.6, 139.1, 135.3, 134.0, 133.7, 119.8, 37.8, 30.8, 21.8, -0.2; IR (thin film) ν 2945, 1701, 1542, 1245, 856 cm^{-1}; MS *m/z* (%) 220 (6), 205 (100); EI-HRMS calcd for $C_{13}H_{20}OSi$ *m/z* [M^+] 220.1283; found 220.1281.



1-49b

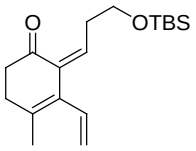
(2*Z*)-2-Ethylidene-4-methyl-3-vinylcyclohex-3-enone 1-49b. According to General Procedure A, allene-ynone **1-48b** (40.1 mg, 0.25 mmol) in toluene (0.82 mL) was reacted with rhodium biscarbonyl chloride dimer (2.9 mg, 0.007 mmol, 3 mol%) to afford **1-49b** (30.3 mg, 76%). The reaction was performed at room temperature and was complete after 1.5 h as observed by TLC. Average of two yields: 73%. (R_f = 0.22, 10% ethyl acetate/hexanes eluted twice); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (dd, *J* = 11.2, 17.7 Hz, 1H), 6.02 (q, *J* = 7.5 Hz, 1H), 5.37 (dd, *J* = 1.4, 11.2 Hz, 1H), 5.13 (dd, *J* = 1.4, 17.7) Hz, 1H), 2.55 – 2.40 (m, 4H), 2.06 (d, *J* = 7.5 Hz, 3H), 1.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 134.5, 133.8, 133.7, 132.5, 131.9, 119.1, 39.2, 31.0, 21.0, 15.8; IR (thin film) ν 3078, 2916, 2851, 1697, 1596 cm^{-1}; MS *m/z* (%) 163 (10), 162 (81), 147 (96), 119 (58), 105 (98), 91 (100); ESI-HRMS calcd for $C_{11}H_{14}O$ *m/z* 162.1045 [M^+]; found 162.1042.



1-49c

(2*Z*)-2-(4-*t*-Butyldimethylsilyloxybutylidene)-4-methyl-3-vinylcyclohex-3-enone 1-49c.

According to General Procedure A, allene-ynone **1-48c** (23.8 mg, 0.19 mmol) in toluene (0.25 mL) was reacted with rhodium biscarbonyl chloride dimer (1.0 mg, 0.002 mmol, 3 mol%) to afford **1-49c** (19.3 mg, 81%). The reaction was performed at roo temperature and was complete after 1.5 h as observed by TLC. Average of two yields: 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.93 (t, *J* = 7.4 Hz, 1H), 5.39 (dd, *J* = 2.0, 11.2 Hz, 1H), 5.15 (dd, *J* = 2.0, 17.7 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.60 (q, *J* = 7.5 Hz, 2H), 2.55 – 2.45 (m, 4H), 1.90 (s, 3H), 1.70 – 1.59 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 139.3, 133.8, 133.7, 132.6, 132.2, 119.2, 62.9, 61.1, 39.2, 33.0, 31.1, 25.9, 21.0, 18.3, -5.3; IR (thin film) ν 2954, 2928, 2856, 1693, 1588, 1255, 1098, 836 cm^{-1}; MS *m/z* (%) 320 (7), 291 (6), 263 (39), 160 (60), 75 (100); EI-HRMS calcd for $C_{19}H_{32}O_2Si$ *m/z* 320.2172 [M^+]; found 320.2171.

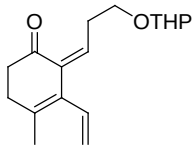


1-49d

(2*Z*)-2-(3-*t*-Butyldimethylsiyloxypropylidene)-4-methyl-3-vinylcyclohex-3-enone 1-49d.

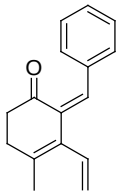
According to General Procedure A, allene-ynone **1-48d** (90.2 mg, 0.29 mmol) in toluene (1.0 mL) was reacted with rhodium biscarbonyl chloride dimer (3.4 mg, 0.009 mmol, 3 mol%) to afford **1-49d** (80.1 mg, 89%). The reaction was performed at room temperature and was complete after 20 min as observed by TLC. Average of four yields: 88%. (R_f = 0.63, 30% ethyl

acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25 (dd, *J* = 11.2, 17.7 Hz, 1H), 6.04 (t, *J* = 7.2 Hz, 1H), 5.40 (dd, *J* = 2.0, 11.2 Hz, 1H), 5.16 (dd, *J* = 2.0, 17.7 Hz, 1H), 3.70 (t, *J* = 6.3 Hz, 2H), 2.78 (q, *J* = 6.6 Hz, 2H), 2.57 – 2.46 (m, 4H), 1.91 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 136.2, 134.5, 133.6, 132.7, 132.7, 119.3, 62.7, 39.2, 33.0, 31.1, 25.8, 21.1, 18.3, -5.3; IR (thin film) ν 2950, 2925, 2853, 1696, 1255, 1091, 835 cm^{-1}; MS *m/z* (%) 330 (20, M + 23Na + H), 329 (100, M + 23Na); ESI-HRMS calcd for $C_{18}H_{30}O_2SiNa$ *m/z* [M + 23Na^{+}] 329.1913; found 329.1900.



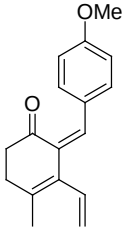
1-49e

(2*Z*)-4-Methyl-2-(3-(tetrahydro-2*H*-pyran-2-yloxy)propylidene)-3-vinylcyclohex-3-enone 1-49e. According to General Procedure A, allene-ynone **1-48e** (40.5 mg, 0.15 mmol) in toluene (0.49 mL) was reacted with rhodium biscarbonyl chloride dimer (1.7 mg, 0.004 mmol, 3 mol%) to afford **1-49e** (37.8 mg, 93%). The reaction was performed at room temperature and was complete after 15 min as observed by TLC. Average of two yields: 88%. (R_f = 0.46, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 11.2, 17.7 Hz, 1H), 6.00 (t, *J* = 7.2 Hz, 1H), 5.37 (dd, *J* = 2.1, 11.2 Hz, 1H), 5.15 (dd, *J* = 2.1, 17.7 Hz, 1H), 4.60 (dd, *J* = 2.7, 3.8 Hz, 1H), 3.87 – 3.74 (m, 2H), 3.51 – 3.44 (m, 2H), 2.85 (q, *J* = 6.7 Hz, 2H), 2.55 – 2.45 (m, 4H), 1.89 (s, 3H), 1.84 – 1.76 (m, 1H), 1.72 – 1.65 (m, 1H), 1.57 – 1.47 (m, 4H); ^{13}C NMR (75 MHz, CDCl3) δ 202.3, 136.1, 134.8, 133.9, 132.9, 132.8, 119.5, 98.8, 67.2, 62.3, 39.5, 31.4, 30.9, 30.4, 25.8, 21.4, 19.7; IR (thin film) ν 2940, 2870, 1697, 1032 cm^{-1}; MS *m/z* (%) 276 (9), 258 (30), 228 (37), 202 (69), 192 (86), 174 (100), 159 (77), 91 (59); EI-HRMS calcd for $C_{17}H_{24}O_3$ *m/z* [M^{+}] 276.1725; found 276.1723.



1-49i

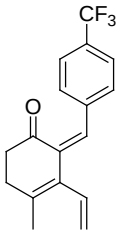
(2*Z*)-2-Benzylidene-4-methyl-3-vinylcyclohex-3-enone 1-49i. According to General Procedure A, allene-ynone **1-49i** (42.4 mg, 0.19 mmol) in toluene (0.63 mL) was reacted with rhodium biscarbonyl chloride dimer (5.9 mg, 0.015 mmol, 8 mol%) to afford **1-49i** (34.0 mg, 80%). The reaction mixture was placed into a preheated oil bath at 50 °C after addition of $[Rh(CO)_2Cl]_2$ and the reaction was complete after 5 min as observed by TLC. Average of three yields: 76%. (R_f = 0.326, 10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.32 – 7.25 (m, 3H), 6.67 (s, 1H), 6.35 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.52 (dd, *J* = 2.0, 11.2 Hz, 1H), 5.29 (dd, *J* = 2.0, 17.7 Hz, 1H), 2.74 – 2.60 (m, 4H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 136.1, 135.7, 134.6, 133.5, 133.4, 132.1, 129.3, 127.9, 127.8, 120.1, 39.6, 32.6, 21.2; IR (thin film) ν 2919, 2851, 1704, 1593, 1492, 928, 757 cm^{-1}; MS *m/z* (%) 224 (100), 209 (44), 181 (57), 167 (74); EI-HRMS calcd for $C_{16}H_{16}O$ *m/z* [M^+] 224.1201; found 224.1199.



1-49j

(2*Z*)-2-(4-Methoxybenzylidene)-4-methyl-3-vinylcyclohex-3-enone 1-49j. According to General Procedure A, allene-ynone **1-48j** (39.2 mg, 0.15 mmol) in toluene (0.51 mL) was reacted with rhodium biscarbonyl chloride dimer (4.8 mg, 0.012 mmol, 8 mol%) to afford **1-49j** (29.8 mg, 76%). The reaction mixture was placed into a preheated oil bath 50 °C after addition

of $[Rh(CO)_2Cl]_2$ and the reaction was complete after 5 min as observed by TLC. Average of three yields: 76%. (R_f = 0.17, 10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.8 Hz), 6.56 (s, 1H), 6.34 (dd, *J* = 17.7, 11.2, 1H), 5.49 (dd, *J* = 11.2, 2.1 Hz, 1H), 5.27 (dd, *J* = 17.8, 21. Hz, 1H), 3.81 (s, 3H), 2.71 – 2.59 (m, 4H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 159.5, 133.7, 133.6, 132.7, 132.5, 131.3, 128.4, 119.7, 113.3, 55.1, 39.6, 32.3, 21.1; IR (Thin film) ν 3081, 2908, 2836, 1698, 1603, 1509, 1254, 1032, 829 cm^{-1}; MS *m/z* (%) 277 (100, M + 23Na), 255 (55); ESI-HRMS calcd for $C_{17}H_{18}O_2Na$ *m/z* [M + 23Na$^+$] 277.1204; found 277.1215.

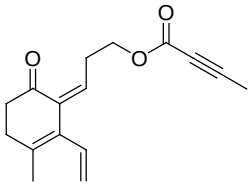


1-49k

(2*Z*)-2-(4-(Trifluoromethyl)benzylidene)-4-methyl-3-vinylcyclohex-3-enone 1-49k.

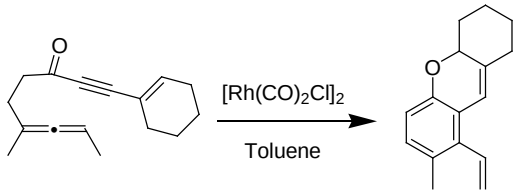
According to General Procedure A, allene-ynone **1-48k** (30.5 mg, 0.10 mmol) in toluene (0.35 mL) was reacted with rhodium biscarbonyl chloride dimer (3.0 mg, 0.008 mmol, 8 mol%) to afford **1-49k** (23.3 mg, 76%). The reaction mixture was placed into a preheated oil bath at 50 °C after addition of $[Rh(CO)_2Cl]_2$ and the reaction was complete after 5 min as observed by TLC. (R_f = 0.23, 10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 6.34 (dd, *J* = 17.8, 11.2, 1H), 5.54 (dd, *J* = 11.2, 2.0 Hz, 1H), 5.29 (dd, *J* = 17.8, 2.0 Hz), 2.74 – 2.63 (m, 4H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 140.2, 137.1, 136.2, 133.3, 133.2, 130.2, 129.3, 129.1 (q, J_{C-F} = 32.7 Hz), 124.7 (q, J_{C-F} = 3.2 Hz), 124.2 (q, J_{C-F} = 270.4 Hz), 120.5, 39.8, 32.5, 21.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -60.5; IR (Thin film) ν 3085, 2911, 2844, 1704, 1611, 1324, 835 cm^{-1}; MS *m/z* (%) 293 (20), 292

(100), 275 (43), 250 (60), 235 (49), 181 (54), 165 (49); EI-HRMS calcd for $C_{17}H_{15}OF_3$ *m/z* [M^+] 292.1075; found 292.1055.



1-49l

(3*Z*)-3-(3-Methyl-6-oxo-2-vinylcyclohex-2-enylidene)propyl but-2-ynoate 1-49l. According to General Procedure A, allene-ynone **1-48l** (32.4 mg, 0.13 mmol) in toluene (0.42 mL) was reacted with rhodium biscarbonyl chloride dimer (3.9 mg, 0.010 mmol, 8 mol%) to afford **1-49l** (22.6 mg, 70%). The reaction mixture was placed into a preheated oil bath at 100 °C after addition of $[Rh(CO)_2Cl]_2$ and the reaction was complete after 20 min as observed by TLC. Average of two yields: 76%. Alternatively, allene-ynone **1-48l** (74.5 mg, 0.29 mmol) in toluene (28.8 mL, 0.01 M) can be reacted with rhodium biscarbonyl chloride dimer (3.4 mg, 0.009 mmol, 3 mol%) to afford **1-49l** (70.6 mg, 95%). The reaction mixture was placed into a preheated oil bath at 50 °C after addition of $[Rh(CO)_2Cl]_2$ and the reaction was complete after 1 h as observed by TLC. (R_f = 0.60, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 11.2, 17.7 Hz, 1H), 5.87 (t, *J* = 7.3 Hz, 1H), 5.42 (dd, *J* = 2.1, 11.2 Hz, 1H), 5.16 (dd, *J* = 2.1, 17.7 Hz, 1H), 4.22 (t, *J* = 6.5 Hz, 2H), 2.92 (q, *J* = 6.8 Hz, 2H), 2.57 – 2.47 (m, 4H), 1.98 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 201.9, 153.7, 135.4, 133.5, 133.3, 132.7, 132.3, 119.6, 85.5, 72.4, 65.3, 39.1, 31.0, 28.8, 21.1, 3.7; IR (thin film) ν 2962, 2921, 2851, 2242, 1708, 1596, 1256, 1070 cm^{-1}; MS *m/z* (%) 282 (15, M + 23Na + H), 281 (100, M + 23Na); ESI-HRMS calcd for $C_{16}H_{18}O_3Na$ *m/z* 281.1154 [M + 23Na$^+$]; found 281.1149.

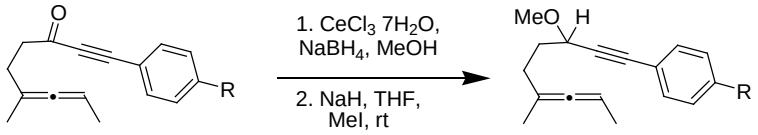


1-48f **1-50**

6,7,8,10a-Tetrahydro-2-methyl-1-vinyl-5H-xanthene 1-50.

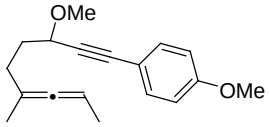
According to General Procedure A, allene-ynone **1-48f** (32.1 mg, 0.14 mmol) in toluene (2.8 mL, 0.05 M) was reacted with rhodium biscarbonyl chloride dimer (1.6 mg, 0.004 mmol, 3 mol%) to afford **1-50** (23.3 mg, 29%) as a green solid. The reaction mixture was placed into a preheated oil bath at 50 °C after addition of $[Rh(CO)_2Cl]_2$ and the reaction was complete after 3 h as observed by TLC. Purification was performed by silica gel column chromatography (2% ethyl acetate/hexanes, pretreated with 1% triethylamine/hexanes). (R_f = 0.70, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.1 Hz, 1H), 6.63 (dd, *J* = 11.4, 17.8 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 6.39 (s, 1H), 5.58 (dd, *J* = 2.0, 11.4 Hz, 1H), 5.23 (dd, *J* = 2.0, 17.8 Hz, 1H), 4.86 (dd, *J* = 5.7, 10.9 Hz, 1H), 2.60 – 1.19 (m, 8H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 151.3, 137.5, 134.4, 133.7, 128.8, 127.8, 120.4, 119.1, 114.9, 113.5, 76.1, 34.7, 33.2, 26.5, 24.2, 19.8; IR (thin film) ν 3078, 3058, 2932, 2857, 1582, 1468, 1235, 1041, 811 cm^{-1}; MS *m/z* (%) 226 (100), 225 (90), 209 (28), 198 (70), 115 (60); EI-HRMS calcd for $C_{16}H_{18}O$ *m/z* [M^+] 226.1358; found 226.1353.

Allenyl Methylpropargyl Ethers 1-57



1-48 **1-57**

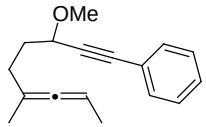
General Procedure C: Preparation of **1-57j**



1-57j

1-Methoxy-4-(3-methoxy-6-methylnona-6,7-dien-1-ynyl)benzene 1-57j. To a solution of the ketone, **1-48j** (R = OMe) (91 mg, 0.38 mmol) in methanol (14 mL) was added cerium trichloride heptahydrate (200 mg, 0.54 mmol). This suspension was allowed to stir for 10 min at rt then cooled to -70 °C. Sodium borohydride (27 mg, 0.71 mmol) was added in one portion and the reaction allowed to stir for another 10 min. Next, water (0.7 ml) was added and the reaction mixture was further diluted with water (5 mL) and CH_2Cl_2 (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered though a pad silica gel, and concentrated under vacuum to give a yellow residue. This was dissolved in THF (0.6 mL) and carried on directly to the next step. The THF solution was added via syringe to a suspension of sodium hydride (8 mg, 0.34 mmol) in THF (1.2 mL) at rt via syringe. After 10 min a solution of iodomethane (43 μL, 0.69 mmol) in THF (0.9 mL) was added via syringe. The reaction was stirred for an additional 10 min and quenched with water (0.75 mL). The reaction mixture was diluted with water and CH_2Cl_2, the organic layer separated, and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was

chromatographed on silica gel (3% ethyl acetate/hexanes) to give **1-57j** as a pale yellow oil (79 mg, 0.32 mmol, 84% over two steps). (R_f = 0.66, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.09 – 4.99 (m, 1H), 4.21 (t, 6.5 Hz, 1H), 3.80 (s, 3H), 3.47 (s, 3H), 2.14 (dt, *J* = 7.3, 2.9 Hz, 2H), 2.01 – 1.87 (m, 2H), 1.71 (d, *J* = 2.8 Hz, 3H), 1.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 159.6, 133.1, 114.9, 113.8, 98.0, 86.5, 85.8, 85.4, 71.2, 56.4, 55.2, 33.7, 29.5, 19.4, 14.8; IR (thin film) ν 2980, 2934, 2837, 2220, 1961, 1607, 1509, 1291, 1249, 1105, 1033, 832 cm^{-1}; MS *m/z* (%) 271 (9), 270 (47), 239 (100), 223 (51), 212 (83), 159 (95); EI-HRMS calcd for $C_{18}H_{22}O_2$ *m/z* 270.1620 [M^+]; found 270.1615.

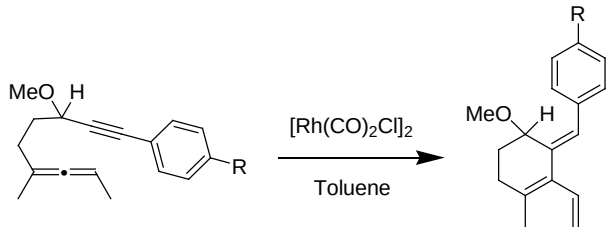


1-57i

1-(3-Methoxy-6-methylnona-6,7-dien-1-ynyl)benzene 1-57i. According to General Procedure C, allene-ynone **1-48i** was reacted with cerium trichloride heptahydrate (212 mg, 0.57 mmol) and sodium borohydride (29 mg, 0.76 mmol) to afford a crude alcohol. The crude residue was then reacted with sodium hydride (13 mg, 0.55 mmol) and iodomethane (35 μL, 0.55 mmol) to afford **1-57i** (80 mg, 87% over two steps) as a pale yellow oil. (R_f = 0.45, 10% ethyl acetate/hexanes) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.35 – 7.31 (m, 3H), 5.10 – 5.00 (m, 1H), 4.23 (t, *J* = 6.5 Hz, 1H), 3.49 (s, 3H), 2.16 (dd, *J* = 10.2, 7.3 Hz, 2H), 2.00 – 1.89 (m, 2H), 1.72 (d, *J* = 2.8 Hz, 3H), 1.65 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 131.7, 128.2, 122.8, 97.9, 88.0, 85.9, 85.5, 71.2, 56.4, 33.6, 29.5, 19.4, 14.8; IR (thin film) ν 3052, 2980, 2933, 2821, 2226, 1965, 1717, 1598, 1105, 917, 757, 691 cm^{-1}; MS *m/z* (%) 240 (11), 225 (20), 215

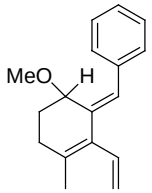
(46), 158 (53), 129 (69), 105 (100); EI-HRMS calcd for $C_{17}H_{20}O$ *m/z* 240.1514 [M^+]; found 240.1507.

Allylmethoxy trienes 1-58.



1-57 **1-58**

General Procedure A was followed.

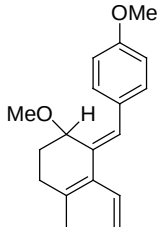


1-58i

1-((1*Z*)-(6-Methoxy-3-methyl-2-vinylcyclohex-2-enylidene)methyl)benzene 1-58i.

According to General Procedure A, allenic methylpropargyl ether **1-57i** (25.8 mg, 0.11 mmol) in toluene (0.36 mL) was reacted with rhodium biscarbonyl chloride dimer (3.3 mg, 0.009 mmol, 8 mol%) at 50 °C to afford **1-58i** (24.8 mg, 96%). The reaction mixture was placed into a preheated oil bath at 50 °C after addition of $[Rh(CO)_2Cl]_2$ and the reaction was complete after 5 min as observed by TLC. Average of two yields: 95%. (R_f = 0.34, 10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H), 6.65 (s, 1H), 6.35 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.46 (dd, *J* = 11.1, 2.3 Hz, 1H), 5.21 (dd, *J* = 17.7, 2.3 Hz, 1H), 4.34 (dd, *J* = 3.4, 2.0 Hz, 1H), 3.35 (s, 3H), 2.50 – 2.40 (m, 1H), 2.19 (dt, *J* = 10.4, 3.7 Hz, 1H), 2.08 (dd, *J* = 18.5, 5.8 Hz, 1H), 1.92 (s, 3H), 1.60 (tdd, *J* = 14.2, 5.9, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 137.1, 135.4, 134.9, 130.6, 128.9, 128.0, 127.8, 126.5, 119.3, 72.0, 54.5, 27.4, 25.0, 21.7; IR (thin film) ν 3078, 2923, 2817, 1626, 1192, 1084, 919, 760, 701 cm^{-1}; MS *m/z* (%) 241 (15),

240 (75), 225 (8), 208 (64), 193 (100), 182 (58), 165 (52), 115 (77); EI-HRMS calcd for $C_{17}H_{20}O$ *m/z* [M^+] 240.1514; found 240.1515.

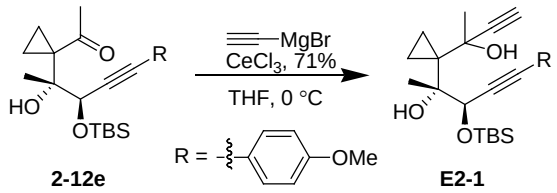


1-58j

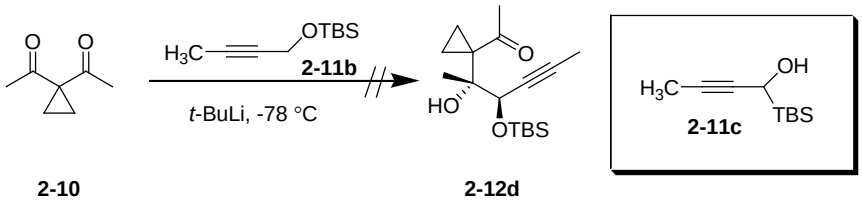
1-Methoxy-4-((1*Z*)-(6-methoxy-3-methyl-2-vinylcyclohex-2-enylidene)methyl)benzene

1-58j. According to General Procedure A, allenic methylpropargyl ether **1-57j** (26.3 mg, 0.10 mmol) in toluene (0.34 mL) was reacted with rhodium biscarbonyl chloride dimer (3.0 mg, 0.008 mmol, 8 mol%) at 50 °C to afford **1-58j** (22.3 mg, 80%). The reaction mixture was placed into a preheated oil bath at 50 °C after addition of $[Rh(CO)_2Cl]_2$ and the reaction was complete in < 10 min as observed by TLC. Average of two yields: 80%. (R_f = 0.63, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.57 (s, 1H), 6.32 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.44 (dd, *J* = 11.1, 2.4 Hz, 1H), 5.19 (dd, *J* = 17.7, 2.4, 1H), 4.32 (dd, *J* = 3.2, 2.0, 1H), 3.82 (s, 3H), 3.35 (s, 3H), 2.48 – 2.38 (m, 1H), 2.19 (dt, *J* = 14.1, 3.7, 1H), 2.05 (dd, *J* = 18.4, 5.7, 1H), 1.90 (s, 3H), 1.59 (tdd, *J* = 14.2, 5.8, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 158.4, 136.0, 135.0, 134.7, 130.8, 130.5, 130.1, 127.5, 119.2, 113.6, 72.1, 55.2, 54.5, 27.4, 24.9, 21.8; IR (thin film) ν 3077, 2927, 2834, 1606, 1509, 1248, 1035, 831 cm^{-1}; MS *m/z* (%) 271 (22), 270 (100), 238 (53), 223 (68), 212 (37), 121 (69); EI-HRMS calcd for $C_{16}H_{18}O$ *m/z* [M^+] 270.1620; found 270.1621.

5.3 EXPERIMENTAL: CHAPTER 2

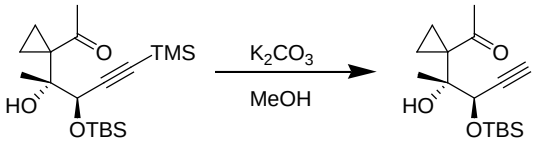


Propargyl Alcohol E2-1. Cerium trichloride heptahydrate (2.91 g, 7.8 mmol) was dried under vacuum (~4 torr) at 140 – 150 °C for approximately 5 h. The flask was cooled, filled with nitrogen, and the dried salt suspended in THF (52 mL) and stirred for 16 h overnight. The suspension was cooled to 0 °C and ethynyl magnesium bromide (15.6 mL of a 0.5 M solution in THF, 7.8 mmol) was added via syringe. The mixture was stirred for 1.5 h and then a solution of **2-12e** (523 mg, 1.3 mmol) in THF (8.7 mL) was added via cannula. The reaction mixture was stirred for 30 – 40 min until no starting material was evident by TLC (Starting material and product R_f values are both approximately 0.53, 30% ethyl acetate/hexanes. Using *p*-anisaldehyde TLC stain the starting material spot is black and the product spot is brown). The reaction mixture was quenched with water (8 mL) and diluted with ether. The mixture was poured into a separatory funnel and solid citric acid was added with swirling until the emulsion had dissipated. The layers were separated and the aqueous layer extracted into ether (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (15% ethyl acetate/hexanes) to afford **E2-1** (393 mg, 71%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, 8.7 Hz, 2H), 6.85 (d, 8.7 Hz, 2H), 5.02 (s, 1H), 4.49 (s, 1H), 3.82 (s, 3H), 3.29 (s, 1H), 2.43 (s, 1H), 1.62 – 1.56 (m, 4H), 1.45 – 1.29 (m, 4H), 1.02 – 0.89 (m, 11H), 0.26 (s, 3H), 0.22 (s, 3H). Impurities: 5.31 (s, 1H), 1.63 – 1.56 (m, 1H), 1.45 – 1.29 (m, 1H), 1.02 – 0.89 (m, 3H).



2-10 **2-12d**

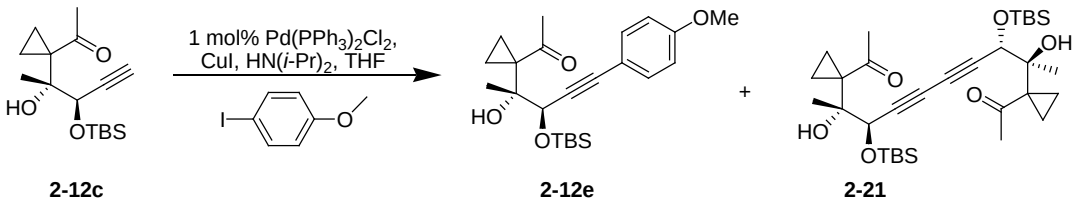
1-(*t*-Butyldimethylsilyl)but-2-yn-1-ol 2-11c. **(**Isolated as the only product from attempted addition reaction). To a solution of **2-11b** (214 mg, 1.16 mmol) in THF (2 mL) at -78 °C was added *t*-butyl lithium (0.61 mL of a 1.7 M solution in pentane, 1.04 mmol) dropwise via syringe over 2-3 min. The yellow reaction mixture was stirred for 1 h, at which point it was colorless, and then a solution of **2-10** (105 mg, 0.83 mmol) in THF (2 mL) was added via cannula. The reaction mixture was stirred for 2.5 h. Water (3 mL) was then added at -78 °C, the mixture was warmed to room temperature and then diluted with water (5 mL) and ether (5 mL). The layers were separated and the aqueous layer extracted into ether (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (2% to 6% ethyl acetate/hexanes) to afford **2-11c** (83 mg, 39%). No starting material was recovered. (R_f = 0.33, 10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.19 (q, *J* = 2.4 Hz, 1H), 1.89 (d, *J* = 2.4 Hz, 3H), 0.98 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.0, 80.2, 55.1, 26.9, 16.9, 3.81, -8.0, -8.6 (minor impurities at 25.6, 25.5, -3.6, -4.8); IR (thin film) ν 3445, 2929, 2954, 2884, 2857, 2245, 1696, 1463, 1249, 975, 838, 781 cm^{-1}.



2-12b **2-12c**

1-(1-((2*R*,3*R*)-2-hydroxy-3-*t*-Butyldimethylsilyloxypent-4-yn-2-yl)cyclopropyl)ethanone 2-12c. To a solution of TMS alkyne **2-12b** (3.75 g, 10.2 mmol) in MeOH (102 mL), was added

K_2CO_3 (1.83 g, 13.2 mmol). The reaction mixture was stirred for 2 h until no starting material was evident by TLC. The mixture was diluted with ether, vacuum filtered through a pad of silica gel (60 mL fritted funnel approximately half full), and concentrated under vacuum. The residue was chromatographed on silica gel (10% EtOAc/Hexanes) to give **2-12c** (2.41 g, 80%). (R_f = 0.45, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.24 (d, *J* = 2.1 Hz, 1H), 2.77 (s, 1H), 2.43 (d, *J* = 2.1 Hz, 1H), 1.84 (s, 3H), 1.38 (s, 3H), 1.29 – 1.12 (m, 3H), 1.10 – 1.01 (m, 1H), 0.92 (s, 9H), 0.15 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 83.1, 74.2, 73.4, 67.6, 37.3, 25.7, 24.7, 22.3, 18.0, 13.5, 10.7, -4.7, -5.1; IR (thin film) ν 3520, 3309, 2955, 2932, 2887, 2858, 2114, 1679, 1361, 1320, 1254, 1072, 838, 779 cm^{-1}; MS *m/z* (%) 240 (6), 239 (35), 221 (37), 197 (10), 147 (28), 127 (100), 113 (81); EI-HRMS calcd for $C_{12}H_{19}O_3Si$ *m/z* [M – (*t*-Bu)$^+$] 239.1103; found 239.1097.



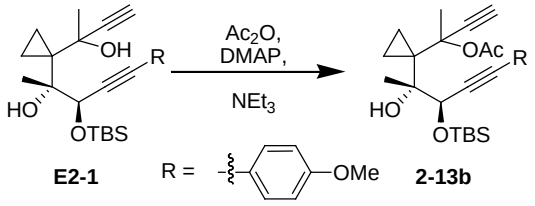
2-12c **2-12e** **2-21**

1-(1-((2*R*,3*R*)-2-Hydroxy-3-*t*-butyldimethylsilyloxy-5-(4-methoxyphenyl)pent-4-yn-2-yl)cyclopropyl)ethanone 2-12e and Dialkyne 2-21. In a 50 mL round bottomed flask was charged **2-12c** (505 mg, 1.70 mmol), $Pd(PPh_3)_2Cl_2$ (12 mg, 0.017 mmol), copper iodide (7 mg, 0.034 mmol), and 4-iodoanisole (286 mg, 5.10 mmol). The flask was evacuated and filled with nitrogen. The mixture was suspended in THF (8.5 mL) and to the resultant mixture was added freshly distilled diisopropyl amine (2.4 mL, 17.0 mmol) via syringe. The reaction mixture became a clear orange color that slowly changed to a cloudy yellow. After 2 h no starting material was evident by TLC. The reaction mixture was concentrated under vacuum and the

resultant brick red residue chromatographed on silica gel (5% ethyl acetate/hexanes to 30% ethyl acetate/hexanes) to give **2-12e** (524 mg, 77%) and **2-22** (48 mg, 8%).

2-12c: (R_f = 0.62, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.43 (s, 1H), 3.82 (s, 3H), 2.91 (s, 1H), 1.88 (s, 3H), 1.45 (s, 3H), 1.29 – 1.06 (m, 4H), 0.93 (s, 9H), 0.20 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 159.6, 132.9, 115.1, 113.9, 87.1, 86.1, 73.8, 68.4, 55.3, 37.4, 25.8, 24.9, 22.6, 18.1, 13.4, 10.8, -4.5, -5.0; IR (thin film) ν 3548, 3310, 2932, 2858, 2115, 1681, 1468, 1362, 1320, 1254, 1068, 838, 778 cm^{-1}; MS *m/z* (%) 425 (100, M + 23Na), 365 (10); ESI-HRMS calcd for $C_{23}H_{34}O_3Si$ Na *m/z* [M + 23Na$^+$] 425.2124; found 425.2104.

2-21: (R_f = 0.54, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.31 (s, 2H), 2.83 (s, 2H), 1.84 (s, 6H), 1.35 (s, 6H), 1.30 – 1.07 (m, 8H), 0.90 (s, 18H), 0.15 (s, 6H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 78.5, 73.9, 70.5, 68.4, 37.3, 25.7, 24.7, 22.1, 18.0, 13.4, 10.8, -4.7, -5.1; IR (thin film) ν 3521, 2932, 2857, 2148, 1679, 1469, 1360, 1320, 1254, 1067, 838, 778 cm^{-1}; MS *m/z* (%) 614 (32, M + 23Na + H), 613 (100, M + 23Na), 527 (30), 441 (26); ESI-HRMS calcd for $C_{32}H_{54}O_6Si_2Na$ *m/z* [M + H$^+$] 613.3357; found 613.3338.

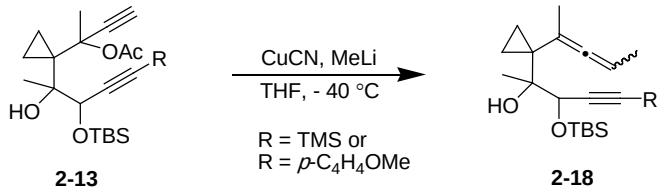


E2-1 **2-13b**

Propargyl Acetate 2-13b. To a solution of **E2-1** (305 mg, 0.71 mmol) and 4-(dimethylamino)pyridine (43 mg, 0.36 mmol) in triethylamine (1 mL, 7.1 mmol) was added acetic anhydride (0.33 mL, 3.6 mmol). The reaction mixture was stirred for 3 h until no starting material was evident by TLC. The mixture was diluted with ethyl acetate and vacuum filtered through a pad of florisil (30 mL fritted funnel approximately half full). The filtrate was

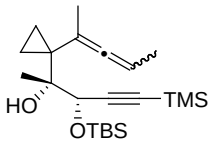
concentrated under vacuum and the residue chromatographed on florisil (10% ethyl acetate/hexanes) to give **2-13b** (312 mg, 93%).

Allene-ynes 2-18a and 2-18e



2-13 **2-18**

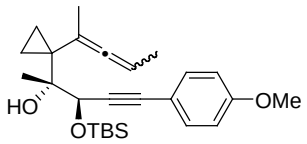
General Procedure G: Preparation of **2-18a**



2-18a

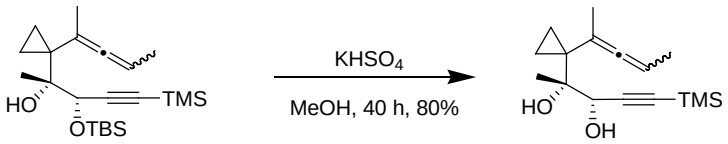
3-*t*-Butyldimethylsilyloxy-5-(Trimethylsilyl)-2-(1-(penta-2,3-dien-2-yl)cyclopropyl)pent-4-yn-2-ol 2-18a. Using the method of Krause; to a suspension of copper(I) cyanide (367 mg, 4.10 mmol) in diethyl ether (20 mL) at -40 ºC is added *n*-butyl lithium (2.55 mL of a 1.6 M solution in hexanes, 4.07 mmol). The resultant cloudy gray/white suspension was stirred for 20 min and then a solution of acetate **2-13a** (332 mg, 0.76 mmol) in diethyl ether (3 mL) was added slowly via syringe over 5 min. The resultant yellow mixture was stirred for 20 – 30 min until no starting material was evident by TLC. The mixture was poured into a suspension of diethyl ether over aqueous 3% NH_4OH : sat'd NH_4Cl (1 : 1) and stirred vigorously until a deep blue color persisted in the aqueous layer. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was chromatographed on silica gel (1% ethyl acetate/hexanes) to give **2-18a** as a pale yellow oil (204 mg, 68%). (R_f = 0.62, 10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 – 4.93 (m, 1H), 4.51 (s, 1H), 2.27 (s, 1H), 1.73 (d, *J* = 2.7 Hz, 3H), 1.62 (d, *J* =

6.9 Hz, 3H), 1.26 (s, 3H), 1.25 – 1.20 (m, 1H), 0.96 – 0.81 (m, 1H), 0.92 (s, 9H), 0.58 – 0.51 (m, 1H), 0.44 – 0.37 (m, 1H), 0.19 (s, 3H), 0.17 (s, 9H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 105.4, 100.2, 91.6, 83.9, 74.9, 69.9, 29.3, 25.8, 23.8, 19.2, 18.3, 14.1, 11.2, 9.2, -0.4, -4.4, -5.1; IR (thin film) υ 3575, 2957, 2930, 2897, 2858, 2177, 1961, 1251, 1065, 843, 778 cm^{-1}; MS *m/z* (%) 392 (15), 377 (20), 335 (11), 319 (25), 261 (43), 242 (51), 201 (36), 151 (64), 147 (100), 133 (68); EI-HRMS calcd for $C_{22}H_{40}O_2Si_2$ *m/z* [M^+] 392.2568; found 392.2567.



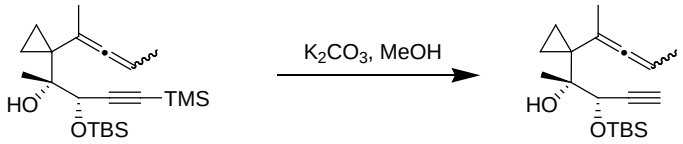
2-18e

(2*R*,3*R*)-3-*t*-butyldimethylsilyloxy-5-(4-methoxyphenyl)-2-(1-(penta-2,3-dien-2-yl)cyclopropyl)pent-4-yn-2-ol 2-18e. According to General Procedure G, **2-13b** (184 mg, 0.39 mmol) was reacted with copper(I) cyanide (350 mg, 3.91 mmol), and methyl lithium (2.44 mL of a 1.6 M solution in ether, 3.91). The crude product was chromatographed on silica gel (5% ethyl acetate/hexanes) to afford **2-18e** (79 mg, 47%). (R_f = 0.66, 30% ethyl acetate/hexanes); *Denotes minor diastereomer. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.34 (d, *J* = 9.1 Hz, 1.2H), *7.33 (d, *J* = 9.1 Hz, 0.8H), 6.84 (d, *J* = 9.1 Hz, 2H), 4.99 – 4.94 (m, 1H), *4.87 (s, 0.4H), 4.82 (s, 0.6H), 3.82 (s, 3H), 2.63 (s, 0.6H), *2.60 (s, 0.4H), *1.80 (d, *J* = 2.8 Hz, 1.2H), 1.79 (d, *J* = 2.8 Hz, 1.8H), 1.63 (d, *J* = 7.0 Hz, 1.8H), *1.61 (d, *J* = 7.0 Hz, 1.2H), 1.25 (s, 1.8H), *1.22 (s, 1.2H), 0.98 – 0.97 (m, 1H), *0.96 (s, 3.6H), 0.95 (s, 5.4H), 0.90 – 0.88 (m, 1H), 0.61 – 0.47 (m, 2H), 0.25 (s, 3H), *0.22 (s, 1.2H), 0.21 (s, 1.8H); IR (thin film) ν 3543, 2954, 2930, 2895, 2857, 2224, 1735, 1605, 1510, 1251, 1067, 835, 778 cm^{-1}; MS *m/z* (%) 426 (21), 411 (8), 369 (11), 318 (15), 276 (53), 275 (63), 151 (63); EI-HRMS calcd for $C_{26}H_{38}O_3Si$ *m/z* [M^+] 426.2590; found 426.2585.



2-18a **2-18b**

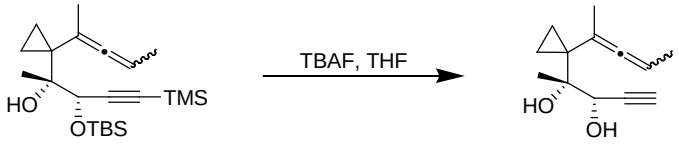
(2R,3R)-5-(Trimethylsilyl)-2-(1-(penta-2,3-dien-2-yl)cyclopropyl)pent-4-yne-2,3-diol 2-18b. To a solution of **2-18b** (55 mg, 0.14 mmol) in freshly distilled methanol (0.5 mL) was added $KHSO_4$ (19 mg, 0.14 mmol). The resultant brown mixture was stirred for 7 h and then diluted with ethyl acetate and filtered through a pad of silica gel (10 mL fritted funnel approximately 30% full). The filtrate was concentrated under vacuum and the crude residue was chromatographed on silica gel (10% ethyl acetate/hexanes) to give an off white solid (23 mg, 0.083 mmol, 59%) and remaining starting material (26% recovery, 85% yield brsm). (R_f = 0.30, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 – 4.97 (m, 1H), 4.52 (d, *J* = 7.8 Hz, 1H), 2.33 (d, *J* = 7.8 Hz, 1H), 1.81 (s, 1H), 1.77 (d, *J* = 3.0 Hz, 3H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 1.04 – 0.97 (m, 1H), 0.82 – 0.76 (m, 1H), 0.61 – 0.47 (m, 2H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 104.2, 100.6, 92.1, 84.6, 75.4, 69.8, 29.9, 21.9, 19.1, 14.0, 10.8, 9.9, -0.24; IR (thin film) υ 3447, 2960, 2926, 2177, 1960, 1250, 1042, 1005, 841, 761 cm^{-1}; MS *m/z* (%) 279 (8), 278 (23), 260 (49), 245 (17), 170 (22), 151 (75), 109 (49), 72 (100); EI-HRMS calcd for *m/z* $C_{16}H_{26}O_2Si$ [M^+] 278.1702; found 278.1709.



2-18a **2-18c**

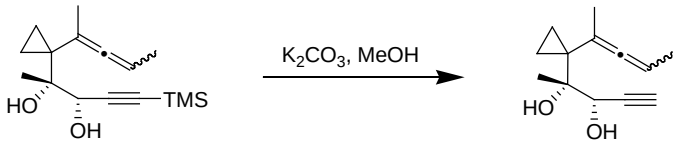
(2R,3R)-3-*t*-Butyldimethylsilyloxy-2-(1-(penta-2,3-dien-2-yl)cyclopropyl)pent-4-yn-2-ol 2-18c. To a solution of **2-18a** (90 mg, 0.23 mmol), in methanol (2.2 mL) and water (0.3 mL) at 0 ºC was added K_2CO_3 (63 mg, 0.46 mmol). After 10 min the reaction was warmed to rt and stirred for 2.5 h until no starting material was evident by TLC. The mixture was diluted with

ether (10 mL) and water (10 mL) and the layers separated. The aqueous layer was extracted into ether (3x) and the combined organic layers dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was chromatographed on silica gel (2% ethyl acetate/hexanes) to give a pale yellow oil (30 mg, 0.094 mmol, 41%). (R_f = 0.39, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 – 4.93 (m, 1H), 4.56 (d, *J* = 2.1 Hz, 1H), 2.45 (d, *J* = 2.1 Hz, 1H), 2.28 (s, 1H), 1.72 (d, *J* = 3.0 Hz, 3H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 3H), 1.26 – 1.22 (m, 1H), 0.93 (s, 9H), 0.91 – 0.83 (m, 1H), 0.60 – 0.54 (m,1H), 0.47 – 0.41 (m, 1H), 0.20 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 100.1, 84.2, 83.5, 75.1, 74.8, 69.3, 29.2, 25.8, 23.7, 19.1, 18.2, 14.2, 11.0, 9.2, -4.4, -5.1; IR (thin film) υ 3578, 3311, 2955, 2930, 2896, 2858, 2118, 1960, 1252, 1067, 837, 778 cm^{-1}; MS *m/z* (%) 344 (25, M + 23Na + H), 343 (100, M + 23Na); ESI-HRMS calcd for $C_{19}H_{32}O_2NaSi$ *m/z* [M + $23Na^+$] 343.2069; found 343.2069.



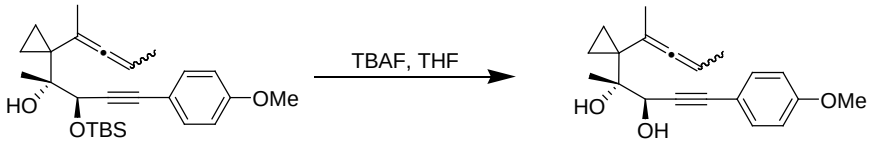
2-18a **2-18d**

(2R,3R)-2-(1-(Penta-2,3-dien-2-yl)cyclopropyl)pent-4-yne-2,3-diol 2-18d. To a solution of **2-18a** (95 mg, 0.24 mmol) in THF (1.2 mL) at 0 °C was added tetrabutylammonium fluoride (0.29 mL of a 1 M solution in THF, 0.29 mmol). The mixture was stirred for 30 min until no starting material was evident by TLC. The mixture was diluted with ether, vacuum filtered through a pad of silica gel (30 mL fritted filter approximately 30% full) and concentrated under vacuum. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **2-18d** (46 mg, 93%). Subsequent yields for this reaction did not exceed 19%. Characterization data is listed below. The ^{1}H NMR characterization data matched that *vide infra*.



2-18b **2-18d**

(2R,3R)-2-(1-(Penta-2,3-dien-2-yl)cyclopropyl)pent-4-yne-2,3-diol 2-18d. To a solution of **2-18b** (73 mg, 0.26 mmol) in methanol (2.6 mL) at 0 ºC was added K_2CO_3 (47 mg, 0.34 mmol). After 1h the ice bath was removed and the reaction mixture stirred for an additional 3 h until no starting material was evident by TLC. The reaction mixture was diluted with ether, filtered through a pad of silica gel (10 mL fritted funnel approximately 30% full) and concentrated under vacuum. The crude residue was chromatographed on silica gel (25% ethyl acetate/ hexanes) to give an off-white solid (32 mg, 0.16 mmol, 62%). (R_f = 0.34, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 – 4.98 (m, 1H), 4.57 (d, *J* = 5.1 Hz, 1H), 2.52 (d, *J* = 2.1 Hz, 1H), 2.47 (d, *J* = 7.2 Hz, 1H), 1.85 (s, 1H), 1.77 (d, *J* = 3.0 Hz, 3H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.27 (s, 3H), 1.04 – 1.00 (m, 1H), 0.82 – 0.77 (m, 1H), 0.60 – 0.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 100.5, 84.8, 82.6, 75.6, 75.1, 69.1, 29.8, 21.4, 19.1, 14.0, 10.3, 10.2; IR (thin film) υ 3420, 3287, 2982, 2924, 2115, 1959, 1372, 1082, 1031, 776 cm^{-1}; MS *m/z* (%) 206 (21), 205 (6), 187 (17), 173 (44), 159 (30), 151 (91), 131 (58), 109 (64), 105 (67), 93 (94), 91 (100); EI-HRMS calcd for *m/z* $C_{13}H_{18}O_2$ [M^+] 206.1307; found 206.1307.

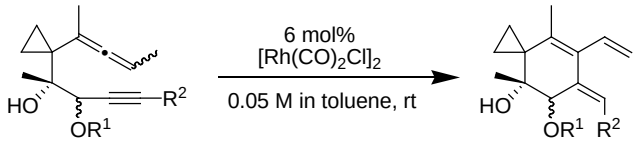


2-18e **2-18f**

(2*R*,3*S*)-5-(4-Methoxyphenyl)-2-(1-(penta-2,3-dien-2-yl)cyclopropyl)pent-4-yne-2,3-diol 2-18f. To a solution of **2-18e** (79 mg, 0.19 mmol) in THF (1.9 mL) at 0 °C was added tetrabutylammonium fluoride (0.56 mL of a 1 M solution in THF, 0.56 mmol). The mixture was stirred for 1 h, then the ice bath was removed and the mixture stirred for an additional 2 h until

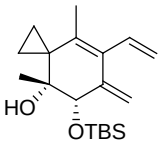
no starting material was evident by TLC. The reaction mixture was concentrated under vacuum and the residue chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **2-18f** (50 mg, 84%).

Spiro[2.5]octatrienes



2-18 **2-19**

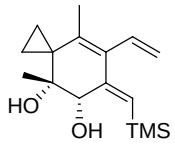
General Procedure H: Preparation of **2-19c**



2-19c

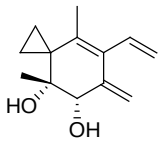
Spiro[2.5]octatriene 2-19c. A solution of allene-yne **2-18c** (41.4 mg, 0.129 mmol) in toluene (2.6 mL) was degassed by bubbling argon through the solution for 20 min. Rhodium biscarbonyl chloride dimer (3.0 mg, 0.008 mmol, 6 mol%) was then added. The reaction mixture was stirred for 1.5 h until no starting material was evident by TLC. The reaction mixture was diluted with 10% ethyl acetate/hexanes solution and vacuum filtered through a pad of silica gel (10 mL fritted funnel approximately half full), eluting with 10% ethyl acetate/hexanes solution. The filtrate was concentrated under vacuum and the residue chromatographed on silica gel (2% ethyl acetate in hexanes) to afford **2-19c** (26.3 mg, 64%). (R_f = 0.36, 10% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 17.7, 11.4 Hz, 1H), 5.39 (dd, *J* = 11.4, 2.4 Hz, 1H), 5.17 (d, *J* = 1.2 Hz, 1H), 5.13 (dd, *J* = 17.7, 2.4 Hz, 1H), 5.04 (d, *J* = 0.9 Hz, 1H), 4.00 (s, 1H), 2.45 (d, *J* = 0.6 Hz, 1H), 1.51 (s, 3H), 1.04 (s, 3H), 1.04 – 1.00 (m, 1H), 0.87 (s, 9H), 0.85 – 0.79 (m, 1H), 0.76 – 0.66 (m, 2H), 0.12 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 136.6, 135.2, 128.5, 118.7, 114.6, 80.6, 71.2, 28.9, 25.8, 22.3, 18.1, 15.0, 10.0, 4.8, -3.8, -4.8; IR (thin

film) υ 3564, 3088, 2954, 2930, 2885, 2857, 1617, 1378, 1250, 1074, 837, 777 cm^{-1}; MS *m/z* (%) 321 (9), 320 (36), 305 (51), 287 (26), 263 (78), 245 (26), 171 (64), 145 (60), 131 (56), 75 (100); EI-HRMS calcd for *m/z* [M^+] 320.2172; found 320.2167.



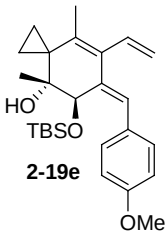
2-19b

Spiro[2.5]octatriene 2-19b. According to General Procedure H, **2-18b** (29.4 mg, 0.106 mmol) in toluene (2.0 mL) was reacted with rhodium biscarbonyl chloride dimer (123 μL, of a 1 mg/0.1 mL stock solution in toluene, 0.003 mmol, 3 mol%). Upon completion, the mixture was diluted with 30% ethyl acetate/hexanes solution and filtered through silica gel. The residue was chromatographed on silica gel using 15% ethyl acetate/hexanes solution to afford **2-19b** (21.6 mg, 73%). (R_f = 0.30, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.76 (s, 1H), 5.42 (dd, *J* = 11.2, 2.3 Hz, 1H), 5.05 (dd, *J* = 17.8, 2.3 Hz, 1H), 4.14 (d, *J* = 7.1 Hz, 1H), 2.48 (s, 1H), 1.82 (d, *J* = 7.6 Hz, 1H), 1.55 (s, 3H), 1.19 – 1.13 (m, 1H), 1.10 (s, 3H), 0.91 – 0.86 (m, 1H), 0.78 – 0.71 (m, 2H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 136.3, 135.6, 131.2, 130.6, 119.9, 70.9, 27.8, 22.9, 15.9, 9.6, 4.6, 0.7; IR (thin film) υ 3443, 3082, 2954, 1588, 1378, 1249, 854 cm^{-1}; MS *m/z* (%) 278 (14), 263 (4), 245 (28), 231 (23), 200 (22), 173 (100), 159 (44), 145 (42); EI-HRMS calcd for *m/z* [M^+] 278.1702; found 278.1692.



2-19d

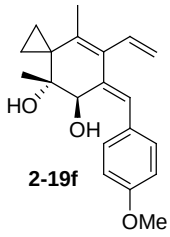
Spiro[2.5]octatriene 2-19d. According to General Procedure H, **2-18d** (45.0 mg, 0.218 mmol) in toluene (4.4 mL) was reacted with rhodium biscarbonyl chloride dimer (5 mg, 0.013 mmol, 6 mol%). After addition of the Rh(I) catalyst, the reaction mixture was placed into an oil bath, preheated to 50 °C. Upon completion, the mixture was diluted with 30% ethyl acetate/hexanes solution and filtered through silica gel. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **2-19d** (24.9 mg, 55%). (R_f = 0.17, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.41 (dd, *J* = 11.1, 2.1 Hz, 1H), 5.21 (s, 1H), 5.17 (s, 1H), 5.14 (dd, *J* = 17.7, 2.1 Hz, 1H), 3.96 (d, *J* = 4.8 Hz, 1H), 2.39 (s, 1H), 1.96 (d, *J* = 7.2 Hz, 1H), 1.54 (s, 3H), 1.19 – 1.11 (m, 1H), 1.10 (s, 3H), 0.91 – 0.84 (m, 1H), 0.80 – 0.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 135.9, 134.7, 128.9, 119.6, 114.9, 79.3, 71.0, 28.0, 22.8, 15.3, 9.1, 5.0; IR (thin film) υ 3420, 3081, 3014, 2975, 2931, 1616, 1378, 1104, 1031, 919, 899 cm^{-1}; MS *m/z* (%) 207 (5), 206 (37), 191 (26), 188 (46), 173 (74), 161 (75), 145 (100), 131 (68), 117 (73); EI-HRMS calcd for *m/z* [M^+] 206.1307; found 206.1303.



2-19e

Spiro[2.5]octatriene 2-19e. According to General Procedure H, **2-18e** (52.2 mg, 0.122 mmol) in toluene (2.4 mL) was reacted with rhodium biscarbonyl chloride dimer (2.8 mg, 0.007 mmol, 6 mol%). Upon completion, the mixture was diluted with 30% ethyl acetate/hexanes solution and filtered through silica gel. The residue was chromatographed on silica gel (10% ethyl

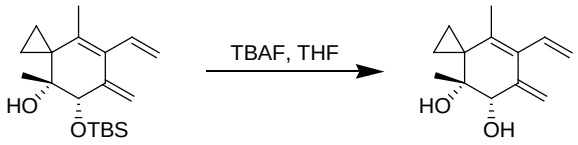
acetate/hexanes) to afford **2-19e** (28.2 mg, 54%). (R_f = 0.54, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.39 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.46 (dd, *J* = 11.1, 2.4 Hz, 1H), 5.23 (dd, *J* = 17.7, 2.4 Hz, 1H), 4.73 (s, 1H), 3.83 (s, 3H), 1.95 (s, 1H), 1.54 (s, 3H), 1.06 (s, 3H), 0.98 – 0.83 (m, 4H), 0.77 (s, 9H), -0.22 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 136.5, 135.6, 133.8, 130.7, 130.1, 129.9, 129.2, 119.2, 113.5, 74.0, 71.4, 55.2, 28.7, 25.6, 20.9, 18.0, 14.7, 12.7, 5.5, -4.4, -5.5; IR (thin film) ν 3442, 2953, 2930, 2855, 1607, 1509, 1463, 1250, 1177, 1083, 1042, 858, 776 cm^{-1}; MS *m/z* (%) 427 (14), 426 (42), 383 (21), 305 (26), 251 (37), 121 (100); EI-HRMS calcd for $C_{26}H_{38}O_3Si$ *m/z* [M^+] 426.2590; found 426.2579.



2-19f

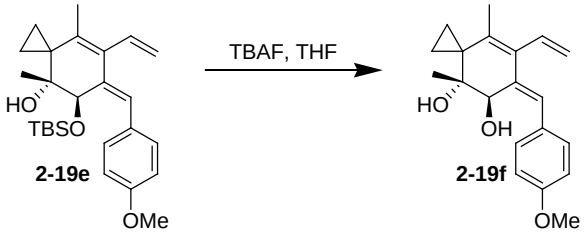
Spiro[2.5]octatriene 2-19f. According to General Procedure H, **2-18f** (17.8 mg, 0.057 mmol) in toluene (1.1 mL) was reacted with rhodium biscarbonyl chloride dimer (1.3 mg, 0.003 mmol, 6 mol%). Upon completion, the mixture was diluted with 30% ethyl acetate/hexanes solution and filtered through silica gel. The residue was chromatographed on silica gel (15% ethyl acetate/hexanes) to afford **2-19f** (9.5 mg, 53%). (R_f = 0.24, 30% ethyl acetate/hexanes)^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.80 (s 1H), 6.34 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.50 (dd, *J* = 11.1 Hz, 1H), 5.20 (dd, *J* = 17.7, 2.1 Hz, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 1H), 1.96 (d, *J* = 9.3 Hz, 1H), 1.90 (s, 1H), 1.59 (s, 1H), 1.08 (s, 1H), 1.04 – 0.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 135.4, 134.5, 133.7, 131.1, 130.8, 130.5, 129.6, 120.3, 113.8, 73.2, 72.3, 55.3, 27.2, 20.5, 15.6, 11.5, 5.5; IR (thin film) ν 3441, 3080,

2933, 2836, 1606, 1509, 1250, 1178, 1032 cm^{-1}; MS *m/z* (%) 313 (10), 312 (47), 279 (23), 265 (24), 251 (26), 121 (100); EI-HRMS calcd for $C_{20}H_{24}O_3$ *m/z* $[M]^+$ 312.1725; found 312.1718.



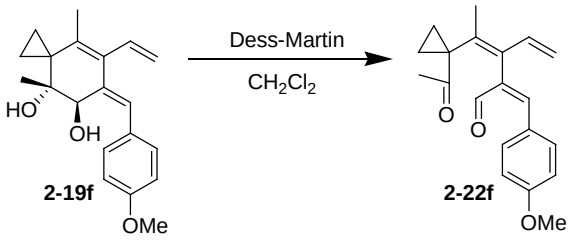
2-19c **2-19d**

Spiro[2.5]octatriene 2-19d. Preparation of **2-19d** from **2-19c**. To a solution of **2-19c** (61 mg, 0.19 mmol) in THF (4.8 mL) at 0 ºC was added tetrabutylammonium fluoride (0.42 mL of a 1 M solution in THF, 0.42 mmol). The orange/yellow solution was stirred of 1.5 h when no starting material was evident by TLC. The reaction mixture was concentrated under vacuum and chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **2-19d** (39 mg, 0.19 mmol, 100%). The ^{1}H NMR characterization data matched that *vide supra*.



2-19e **2-19f**

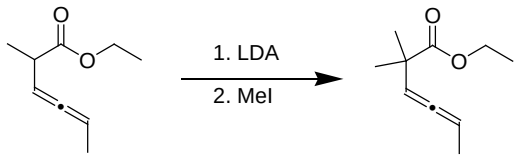
Spiro[2.5]octatriene 2-19d. Preparation of **2-19f** from **2-19e**. To a solution of **2-19e** (24 mg, 0.056 mmol) in THF (1.4 mL) was added tetrabutylammonium fluoride (0.12 mL of a 1 M solution in THF, 0.12 mmol). The reaction mixture was stirred for 2 h, then more tetrabutylammonium fluoride (0.12 mL of a 1 M solution in THF, 0.12 mmol) was added and the mixture was stirred for an additional 1 h at room temperature, then heated to reflux for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under vacuum and the residue chromatographed on silica gel (30% ethyl acetate in hexanes) to afford **2-19f** (11 mg, 63%). The ^{1}H NMR characterization data matched that *vide supra*.



(2*Z*,3*Z*)-2-(4-Methoxybenzylidene)-3-(1-(1-acetylcyclopropyl)ethylidene)pent-4-enal 2-22f.

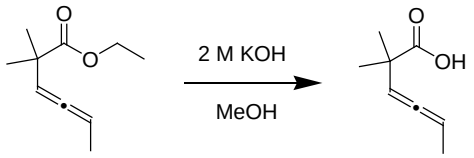
To a suspension of Dess-Martin periodinane (20 mg, 0.046 mmol) in CH_2Cl_2 (2 mL) was added a solution of **2-19f** (13.0 mg, 0.042 mmol) in CH_2Cl_2 (0.5 mL) via cannula. After 2 h the reaction mixture was diluted with ether and filtered through a pad of silica gel (10 mL fritted funnel approximately 30% full). The filtrate was concentrated under vacuum and the residue chromatographed on silica gel (20% ethyl acetate/hexanes) to afford **2-22f** (6.5 mg, 50%). (R_f = 0.18, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.89 (s, 1H), 7.39 (s, 1H), 7.29 (d, *J* = 6.9 Hz, 2H), 6.95 (d, *J* = 6.9 Hz, 2H), 6.83 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.97 (d, *J* = 17.1 Hz, 1H), 3.86 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 1.34 (dd, *J* = 7.2, 4.2 Hz, 2H), 1.03 (dd, *J* = 7.2, 4.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 192.1, 161.0, 148.7, 139.2, 136.9, 136.7, 134.0, 131.8, 126.5, 116.4, 114.1, 55.4, 39.3, 26.2, 19.5, 19.0; IR (thin film) ν 3009, 2933, 2839, 1673, 1602, 1509, 1256, 1177, 1030, 833 cm^{-1}; MS *m/z* (%) 333 (100), 321 (20), 281 (35), 272 (60), 191 (55); ESI-HRMS calcd for $C_{20}H_{22}O_3Na$ *m/z* $[M+23Na]^+$ 333.1467; found 333.1453.

5.4 EXPERIMENTAL: CHAPTER 3



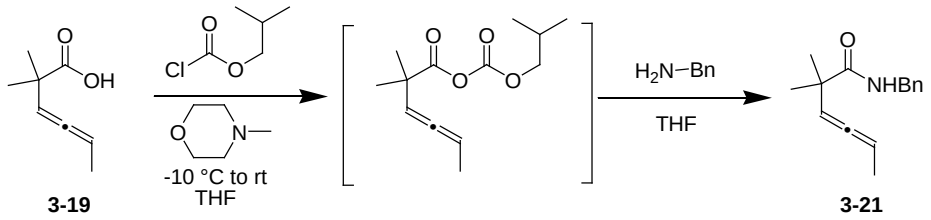
3-18 **E3-1**

Ethyl 2,2-dimethylhexa-3,4-dienoate E3-1. A solution of LDA was prepared by addition of *n*-butyl lithium (18 mL, 1.6 M solution in hexanes, 29 mmol) to a solution of diisopropylamine (4.1 mL, 29 mmol) in THF (45 mL) at 0 ºC. The solution was allowed to stir for 1 h then cooled to -78 °C and ethyl ester **3-18** (1.5 g, 9.8 mmol) in THF (33 mL) was added via cannula. After 1 h, iodomethane (1.8 mL, 29 mmol) was slowly added neat. After the addition was complete, a precipitate was observed and the reaction was slowly warmed to rt. After stirring for 18 h a solution of sat'd aqueous NH_4Cl (30 mL) was added followed by dilution with ether (50 mL). The layers were separated and the aqueous layer extracted with ether (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (5% ethyl acetate/hexanes) to give the product **E3-1** as a pale, brown oil (1.30 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (dq, *J* = 7.0, 3.2 Hz, 1H), 5.18 (p, *J* = 7.0 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.65 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.26 (s, 3H), 1.26 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 176.4, 97.0, 88.8, 60.6, 42.3, 25.4, 25.3, 14.3, 14.1; IR (thin film) ν 2980, 2933, 2872, 1965, 1731, 1254, 1138 cm^{-1}; MS *m/z* (%) 167 (6), 153 (56, M - 15), 125 (77), 95 (49), 73 (100); EI-HRMS calcd for $C_9H_{13}O_2$ *m/z* [M - 15^+] 153.0916; found 153.0916.



E3-1 **3-19**

2,2-Dimethylhexa-3,4-dienoic acid 3-19. Ester **E3-1** (847 mg, 5.03 mmol) was dissolved in a solution of KOH (6.3 mL, 2 M in CH_3OH). The reaction mixture was heated to 60 °C for 48 h until no starting material was observed by TLC. The reaction mixture was diluted with ether (20 mL) and water (20 mL) and the layers separated. The organic layer was washed with water (2x) and a solution of KOH (10 mL, 2 M in H_2O) (1x). The combined aqueous layers were acidified with a solution of HCl (10% by wt., H_2O) to a pH < 2. The acidified aqueous phase was extracted with ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford the product **3-19** as a brown oil (696 mg, 99%). This was taken on directly to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.39 (bs, 1H), 5.36–5.22 (m, 2H), 1.69 (ddd, *J* = 6.9, 3.2, 1.0 Hz), 1.32 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 183.3, 96.6, 89.1, 42.2, 25.2, 25.1, 14.1; IR (thin film) ν 3077, 2979, 2930, 1961, 1703, 1296, 1168 cm^{-1}; MS *m/z* (%) 140 (4), 139 (24), 125 (100), 107 (21); EI-HRMS calcd for $C_8H_{12}O_2$ *m/z* [M^+] 140.0837; found 140.0831.

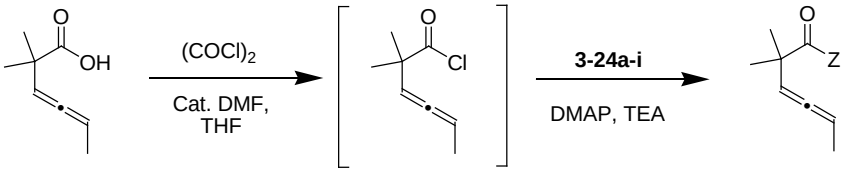


3-19 **3-21**

***N*-Benzyl-2,2-dimethylhexa-3,4-dienamide 3-21.** To a solution of allenic acid **3-19** (102.0 mg, 0.73 mmol) in THF (3.6 mL) at -10 °C was added *N*-methylmorpholine (89 μL, 0.80 mmol) and isobutyl chloroformate (0.11 mL, 0.80 mmol). The resultant cloudy brown suspension was stirred for 5 min and then benzyl amine (0.1 mL, 0.87 mmol) was added. The resultant white

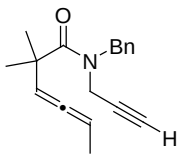
suspension was stirred for 2 h and then reaction was quenched with sat'd aqueous $NaHCO_3$ (0.8 mL). The reaction mixture was diluted with enough water to dissolve the salts and the layers were separated. The aqueous layer was extracted with ether (4 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was chromatographed on silica gel (15% ethyl acetate/hexanes) to afford **3-21** as a clear, colorless oil (130.1 mg, 0.57 mmol, 78%). (R_f = 0.38, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 5H), 6.29 (bs, 1H), 5.28 – 5.23 (m, 2H), 4.43 (d, *J* = 5.7 Hz, 2H), 1.66 (dd, *J* = 6.0, 4.2 Hz, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 176.3, 138.5, 128.6, 127.4, 127.3, 97.2, 88.9, 43.5, 42.8, 25.9, 25.7, 14.2; IR (thin film) ν 3348, 3031, 2968, 2928, 1960, 1647, 1525 cm $^{-1}$; MS *m/z* (%) 229 (10), 215 (26), 214 (87), 150 (26), 91 (100); EI-HRMS calcd for $C_{15}H_{19}NO$ *m/z* 229.1467 [M^+]; found 229.1469.

Allenic propargyl Amides and Ester 3-23



3-19 **3-23a-i**

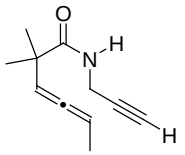
General Procedure E: Preparation of **3-23a**



3-23a

***N*-Benzyl-2,2-dimethyl-*N*-(prop-2-ynyl)hexa-3,4-dienamide 3-23a.** In a round bottomed flask sealed with a rubber septum, allenic acid **3-19** (302 mg, 2.16 mmol) was dissolved in THF (7 mL) under N_2, and one drop of DMF was added via syringe. Oxalyl chloride (0.24 mL, 2.8 mmol) was added dropwise via syringe to control the gas evolution. The reaction mixture was

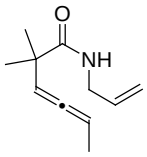
allowed to stir 3 h and was then concentrated under vacuum to remove the excess oxalyl chloride. To a solution of amine **3-24a** (470 mg, 3.24 mmol) in THF (32 mL) was added triethylamine (0.90 mL, 6.5 mmol) and 4-(dimethylamino)pyridine (26 mg, 0.22 mmol). The crude acid chloride was redissolved in THF (7 mL) and added to the solution of amine **3-24a** via cannula. The progress of the reaction was monitored by TLC and upon disappearance of the starting material (18 h), the solution was diluted with ether, filtered through celite (60 mL fritted funnel approximately half full), and concentrated under vacuum. The crude residue was chromatographed on silica gel (10% ethyl acetate/hexanes) to afford amide **3-23a** (519 mg, 90%) as a pale yellow oil. (R_f = 0.49, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6, 75 °C) δ 7.36–7.22 (m, 5H), 5.43 (dq, J = 6.9, 3.2 Hz, 1H), 5.28 (dq, J = 6.9, 6.9 Hz, 1H), 4.76 (A of an ABq, J = 15.6 Hz, 1H), 4.67 (B of an ABq, J = 15.6 Hz, 1H), 4.18 (A of an ABq, d, 17.8, 2.0 Hz, 1H), 4.09 (B of an ABq, d, J = 17.8, 2.0 Hz, 1H), 3.05–3.03 (m, 1H), 1.58 (dd, J = 6.9, 3.2 Hz, 3H), 1.31 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 75 °C) δ 201.9, 173.8, 136.6, 127.9, 126.8, 126.6, 97.3, 88.6, 79.0, 73.8, 48.9, 41.8, 36.0, 26.9, 26.7, 13.0; IR (thin film) ν 3292, 3240, 2977, 2117, 1962, 1643, 1409, 1360 cm^{-1}; MS *m/z* (%) 253 (4), 252 (29, M - 15), 95 (28), 91 (100); EI-HRMS calcd for $C_{17}H_{18}NO_2$ *m/z* [M - 15$^+$] 252.1388; found 252.1385.



3-23b

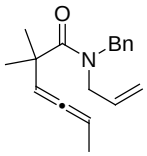
2,2-Dimethyl-*N*-(prop-2-ynyl)hexa-3,4-dienamide 3-23b. According to General Procedure E, **3-19** (97 mg, 0.69 mmol) in THF (2.3 mL) was reacted with oxalyl chloride (0.08 mL, 0.90 mmol) and DMF (1 drop via syringe). The resultant acid chloride was then reacted with amine **3-24b** (71 μL, 1.0 mmol), triethylamine (0.29 mL, 2.1 mmol), and 4-(dimethylamino)pyridine

(8.4 mg, 0.07 mmol) in THF (10 mL) to afford propargyl amide **3-23b** (99 mg, 81%). ^{1}H NMR (300 MHz, toluene-d_8) δ 6.22 (bs, 1H), 5.20 (dq, *J* = 7.0, 3.2 Hz, 1H), 5.06 (p, *J* = 7.0 Hz, 1H), 3.88 (dd, *J* = 5.3, 2.4 Hz, 2H), 1.91 (t, *J* = 2.4 Hz, 1H), 1.50 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.26 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, toluene-d_8) δ 204.2, 175.4, 97.8, 88.9, 80.8, 71.3, 42.9, 29.5, 26.1, 26.0, 14.4; IR (thin film) ν 3346, 3307, 2971, 2929, 2869, 2120, 1961, 1651, 1515, 1275, 1174 cm^{-1}; MS *m/z* (%) 176 (8), 163 (11), 162 (100), 95 (18), 73 (28); EI-HRMS calcd for $C_{11}H_{14}NO$ *m/z* [M - H$^+$] 176.1075; found 176.1078.



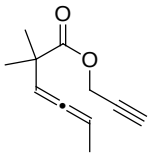
3-23c

***N*-Allyl-2,2-dimethylhexa-3,4-dienamide 3-23c**. According to General Procedure E, **3-19** (87 mg, 0.62 mmol) in THF (2.1 mL) was reacted with oxalyl chloride (0.07 mL, 0.81 mmol) and DMF (1 drop via syringe). The resultant acid chloride was then reacted with amine **3-24c** (70 μL, 0.93 mmol), triethylamine (0.26 mL, 1.9 mmol), and 4-(dimethylamino)pyridine (8.0 mg, 0.06 mmol) in THF (9 mL) to afford propargyl amide **3-23c** (96 mg, 86%) as a pale yellow oil. (R_f = 0.34, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (bs, 1H), 5.84 – 5.71 (m, 1H), 5.26 – 5.03 (m, 4H), 3.79 (t, *J* = 5.4 Hz, 2H), 1.65 – 1.61 (m, 3H), 1.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 176.1, 134.3, 115.6, 97.2, 88.7, 42.7, 41.8, 25.8, 25.6, 14.0; IR (thin film) ν 3348, 3082, 2970, 2928, 1961, 1643, 1525, 1275, 1176, 915 cm^{-1}; MS *m/z* (%) 165 (11), 164 (100), 95 (43), 81 (55); EI-HRMS calcd for $C_{11}H_{17}NO$ *m/z* [M$^+$] 179.1310; found 179.1295.



3-23d

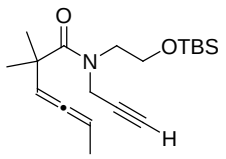
***N*-allyl-*N*-benzyl-2,2-dimethylhexa-3,4-dienamide 3-23d**. According to General Procedure E, **3-19** (84 mg, 0.60 mmol) in THF (2.0 mL) was reacted with oxalyl chloride (0.07 mL, 0.78 mmol) and DMF (1 drop via syringe). The resultant acid chloride was then reacted with amine **3-24d** (132 mg, 0.89 mmol), triethylamine (0.25 mL, 1.8 mmol), and 4-(dimethylamino)pyridine (8.0 mg, 0.06 mmol) in THF (9 mL) to afford propargyl amide **3-23d** (130 mg, 81%). (R_f = 0.53, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 60 °C) δ 7.34 – 7.17 (m, 5H), 5.80 – 5.71 (m, 1H), 5.43 (dq, *J* = 6.9, 3.2 Hz, 1H), 5.25 (p, *J* = 6.9 Hz, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 5.09 (d, *J* = 17.3 Hz, 1H), 4.62 (A of an ABq, *J* = 15.7, 1H), 4.54 (B of an ABq, *J* = 15.7 Hz, 1H), 4.02 – 3.90 (m, 2H), 1.56 (dd, *J* = 6.9, 3.2 Hz, 3H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 60 °C) δ 201.8, 174.0, 137.4, 133.5, 128.0, 126.8, 126.5, 116.8, 97.7, 88.5, 48.7, 48.*7*, 41.8, 27.2, 26.9, 13.1; IR (thin film) ν 3060, 2981, 2929, 2860, 1961, 1636, 1409, 925, 726, 699; MS *m/z* (%) 254 (26, M - 15), 95 (25), 91 (100); EI-HRMS calcd for $C_{17}H_{20}NO$ *m/z* [M - 15$^+$] 254.1545; found 254.1547.



3-23e

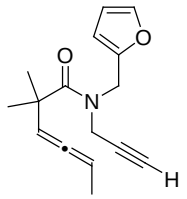
Prop-2-ynyl 2,2-dimethylhexa-3,4-dienoate 3-23e. According to General Procedure E, **3-19** (92 mg, 0.66 mmol) in THF (2.2 mL) was reacted with oxalyl chloride (0.08 mL, 0.86 mmol) and DMF (1 drop via syringe). The resultant acid chloride was then reacted with propargyl alcohol (58 μL, 0.99 mmol), triethylamine (0.28 mL, 2.0 mmol), and 4-(dimethylamino)pyridine

(8.0 mg, 0.07 mmol) in THF (10 mL) to afford propargyl ester **3-23e** (82 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (dq, *J* = 6.9, 3.3 Hz, 1H), 5.25 (p, *J* = 6.9 Hz, 1H), 4.68 (d, *J* = 2.4 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 1H), 1.68 (dd, *J* = 6.9, 3.3 Hz, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 175.5, 96.6, 89.1, 77.7, 74.6, 52.2, 42.4, 25.3, 25.2, 14.2; IR (thin film) ν 3297, 2979, 2934, 2868, 2130, 1963, 1738, 1469, 1248, 1127 cm $^{-1}$; MS *m/z* (%) 164 (13), 163 (100), 135 (26), 95 (78); EI-HRMS calcd for $C_{11}H_{14}O_2$ *m/z* [M^+] 178.0993; found 178.1005.



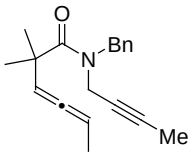
3-23f

***N*-(2-*t*-Butyldimethylsilyloxyethyl)-2,2-dimethyl-N-(prop-2-ynyl)hexa-3,4-dienamide 3-23f.** According to General Procedure E, **3-19** (250 mg, 1.78 mmol) in THF (6 mL) was reacted with oxalyl chloride (0.20 mL, 2.3 mmol) and DMF (1 drop via syringe). The resultant acid chloride was then reacted with amine **3-24f** (569 mg, 2.67 mmol), triethylamine (0.75 mL, 5.3 mmol), and 4-(dimethylamino)pyridine (22 mg, 0.18 mmol) in THF (27 mL) to afford propargyl amide **3-23f** (576 mg, 96%) as a pale yellow oil. ^{1}H NMR (500 MHz, toluene-d_8, 60 °C) δ 5.27 (dq, *J* = 7.0, 3.2 Hz, 1H), 5.09 (p, *J* = 7.0 Hz, 1H), 4.33 (d, *J* = 2.4 Hz, 2H), 3.73 (t, *J* = 5.8 Hz, 2H), 3.65 (t, *J* = 5.8 Hz, 2H), 1.85 (t, *J* =2.4 Hz, 1H), 1.51 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.35 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, toluene-d_8, 60 °C) δ 203.1, 174.2, 98.8, 89.3, 80.4, 72.1, 61.8, 49.4, 42.9, 38.7, 27.6, 26.1, 18.4, 13.9, -5.3; IR (thin film) ν 3311, 3240, 2930, 2120, 1961, 1642, 1470, 1407, 1256, 1106, 837, 778 cm^{-1}; MS *m/z* (%) 321 (8), 320 (34, M - 15), 278 (100), 240 (31), 95 (82), 73 (79); EI-HRMS calcd for $C_{18}H_{30}NO_2Si$ *m/z* [M - 15^+] 320.2046; found 320.2043.



3-23g

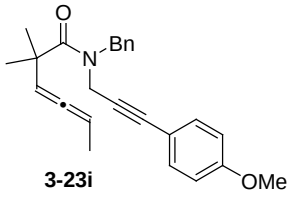
***N*-((Furan-2-yl)methyl)-2,2-dimethyl-*N*-(prop-2-ynyl)hexa-3,4-dienamide 3-23g.** According to General Procedure E, **3-19** (149 mg, 1.06 mmol) in THF (3.5 mL) was reacted with oxalyl chloride (0.12 mL, 1.4 mmol) and DMF (1 drop via syringe). The resultant acid chloride was then reacted with amine **3-24g** (215 mg, 1.59 mmol), triethylamine (0.44 mL, 3.2 mmol), and 4-(dimethylamino)pyridine (13 mg, 0.11 mmol) in THF (16 mL) to afford propargyl amide **3-23g** (216 mg, 79%) as a pale yellow oil. (R_f = 0.59, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, toluene-d_8, 60 °C) δ 7.05 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.08–6.05 (m, 2H), 5.22 (dq, *J* = 7.0, 3.2 Hz, 1H), 5.02 (p, *J* = 7.0 Hz, 1H), 4.76 (A of an ABq, *J* = 15.7 Hz, 1H), 4.69 (B of an ABq, *J* = 15.7 Hz, 1H), 4.18 (A of an ABq, d, *J* = 17.7, 2.4 Hz, 1H), 4.11 (B of an ABq, d, *J* = 17.7, 2.4 Hz, 1H), 1.94 (t, *J* = 2.4 Hz, 1H), 1.44 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.33 (s, 6H); ^{13}C NMR (75 MHz, toluene-d_8, 60 °C) δ 203.1, 174.1, 151.7, 142.2, 110.6, 108.8, 98.7, 89.4, 79.8, 72.2, 43.1, 43.0, 36.6, 27.6, 27.6, 13.8; IR (thin film) ν 3294, 3240, 2978, 2929, 2112, 1961, 1644, 1407, 1160, 734 cm^{-1}; MS *m/z* (%) 258 (14), 257 (60), 242 (48), 95 (40), 81 (100); EI-HRMS calcd for $C_{16}H_{19}NO_2$ *m/z* [M^+] 257.1416; found 257.1413.



3-23h

***N*-Benzyl-*N*-(but-2-ynyl)-2,2-dimethylhexa-3,4-dienamide 3-23h.** According to General Procedure E, **3-19** (105 mg, 0.751 mmol) in THF (2.5 mL) was reacted with oxalyl chloride (0.08 mL, 0.98 mmol) and DMF (1 drop). The resultant acid chloride was then reacted with

amine **3-24h** (180 mg, 1.13 mmol), triethylamine (0.31 mL, 2.3 mmol), and 4-(dimethylamino)pyridine (9 mg, 0.1 mmol) in THF (11 mL) to afford propargyl amide **3-23h** (175 mg, 83%) as a pale yellow oil. (R_f = 0.38, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C) δ 7.35–7.21 (m, 5H), 5.43 (dq, *J* = 7.0, 3.2 Hz, 1H), 5.27 (p, *J* = 7.0, 1H), 4.73 (A of an ABq, *J* = 15.5 Hz, 1H), 4.64 (B of an ABq, *J* = 15.5 Hz, 1H), 4.15 (A of an ABq, *J* = 17.3 Hz, 1H), 4.05 (B of an ABq, *J* = 17.3 Hz, 1H), 1.77 (s, 3H), 1.57 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.29 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 60 °C) δ 201.9, 173.7, 137.0, 128.0, 126.9, 126.6, 97.5, 88.7, 79.6, 74.3, 48.8, 41.9, 36.4, 27.0, 26.9, 13.2, 2.6; IR (thin film) ν 3027, 2976, 2923, 2214, 1961, 1703, 1640, 1410, 1237, 1163 cm^{-1}; MS *m/z* (%) 266 (22), 143 (5), 95 (17), 91 (100); EI-HRMS calcd for $C_{19}H_{23}NO$ *m/z* [M^+] 281.1780; found 281.1776.

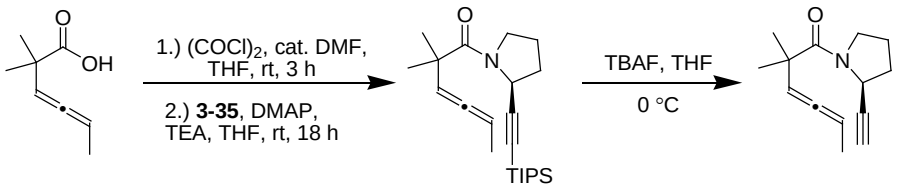


3-23i

***N*-Benzyl-*N*-(3-(4-methoxyphenyl)prop-2-ynyl)-2,2-dimethylhexa-3,4-dienamide 3-23e.**

According to General Procedure E, **3-19** (67 mg, 0.48 mmol) in THF (1.6 mL) was reacted with oxalyl chloride (0.05 mL, 0.62 mmol) and DMF (1 drop). The resultant acid chloride was then reacted with amine **3-24i** (180 mg, 0.72 mmol), triethylamine (0.20 mL, 1.4 mmol), and 4-(dimethylamino)pyridine (6.0 mg, 0.05 mmol) in THF (7.2 mL) to afford propargyl amide **3-23i** (156 mg, 88%) as a pale yellow oil. (R_f = 0.48, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C) δ 7.36 (m, 7H), 6.90 (d, *J* = 7.0 Hz, 2H), 5.48 (dq, *J* = 7.0, 3.2 Hz, 1H), 5.30 (p, *J* = 7.0 Hz, 1H), 4.80 (A of an ABq, *J* = 15.6 Hz, 1H), 4.71 (B of an ABq, *J* = 15.6 Hz, 1H), 4.42 (A of an ABq, *J* = 17.9 Hz, 1H), 4.31 (B of an ABq, *J* = 17.9 Hz, 1H), 3.76 (s, 3H), 1.58 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.32 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 60 °C) δ 202.0, 173.9,

159.2, 137.0, 132.6, 128.1, 127.0, 126.7, 114.0, 113.8, 97.5, 88.7, 83.4, 83.3, 55.0, 49.4, 42.0, 37.1, 27.1, 26.9, 13.2; IR (thin film) ν 2974, 2210, 1965, 1702, 1640, 1509, 1408, 1249, 1171, 1031 cm^{-1}; 374 (9), 373 (34), 358 (91), 282 (12), 145 (100); EI-HRMS calcd for $C_{25}H_{27}NO_2$ *m/z* [M^+] 373.2042; found 373.2039.



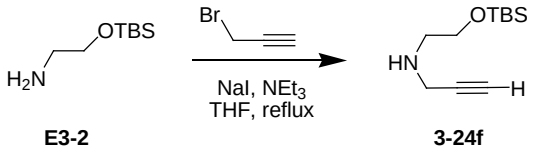
3-19 **3-23k** **3-23j**

1-((S)-2-Ethynylpyrrolidin-1-yl)-2,2-dimethylhexa-3,4-dien-1-one 3-23j. According to General Procedure E, **3-19** (43 mg, 0.31 mmol) in THF (1 mL) was reacted with oxalyl chloride (0.04 mL, 0.4 mmol) and DMF (1 drop via syringe). The resultant acid chloride was then reacted with amine **3-35** (52 mg, 0.21 mmol), triethylamine (0.09 mL, 0.62 mmol), and 4-(dimethylamino)pyridine (3.0 mg, 0.02 mmol) in THF (2 mL) to afford propargyl amide **3-23k** (64 mg, 83%) as a pale yellow oil. Amide **3-23k** (54 mg, 0.15 mmol) is then dissolved in THF (0.5 mL) and cooled to 0 ºC. A solution of TBAF (0.19 mL of a 1 M solution in THF) was then added and the reaction mixture was warmed to rt over 1.5 h. The reaction mixture was then diluted with 30% ethyl acetate/hexanes solution, filtered through a pad of silica gel (10 mL fritted funnel approximately half full), and concentrated under vacuum. The residue was chromatographed on silica gel (10% ethyl acetate/hexanes) to afford amide **3-23j** as a colorless oil as a 1 : 1 mixture of diastereomers (29 mg, 87%). (R_f = 0.35, 30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C) δ 5.32–5.28 (m, 2H), 4.71 (bs, 1H), 3.64–3.50 (m, 2H), 2.94 (s, 1H), 1.99–1.88 (m, 4H), 1.64 (d, *J* = 5.1 Hz, 1.5), 1.62 (d, *J* = 5.1 Hz, 1.5), 1.22 (dd, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 60 °C) δ 202.2, 172.1, 96.9, 88.2, 84.4, 71.6, 48.4, 46.4, 46.3, 42.0, 31.3, 26.1, 25.8, 13.3; IR (thin film) ν 3233, 2975, 2929, 2110, 1962, 1630, 1391 cm^{-1}; MS *m/z*

(%) 216 (12), 203 (11), 202 (77), 174 (29), 147 (36), 122 (84), 77 (100); EI-HRMS calcd for $C_{14}H_{19}NO$ *m/z* [M - 15^+] 202.1232; found 202.1233.

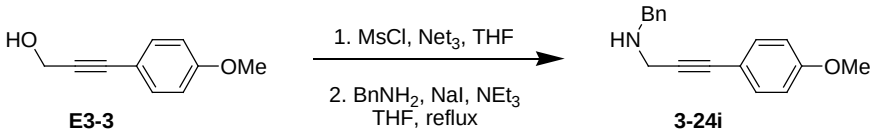
Secondary Propargyl Amines 3-24f and 3-24i.

All secondary amines were prepared using a known procedure.[87] Propargyl amines that were not commercially available were characterized.

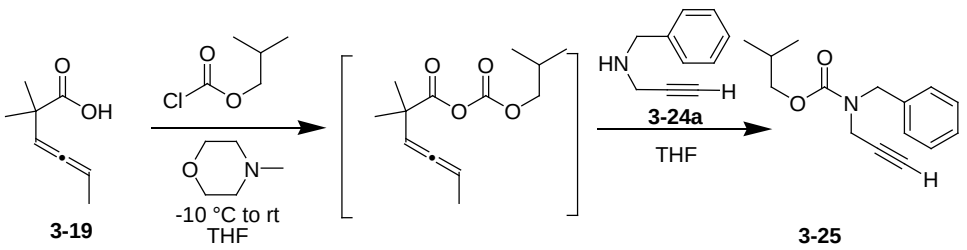


E3-2 **3-24f**

N-(2-t-butyldimethylsilyloxyethyl)prop-2-yn-1-amine 3-24f. In a manner analogous to Hsung;[h] to a solution of amine **E3-2** (2.05 g, 11.7 mmol), sodium iodide (176 mg, 1.17 mmol), and triethylamine (4.90 mL, 35.0 mmol) in THF (115 mL) was added propargyl bromide (1.24 mL, 80% wt. solution in toluene, 11.1 mmol). The mixture was heated to reflux for ~ 18 h when no starting material was observed by TLC. The mixture was diluted with ether (100 mL), filtered through celite (150 mL fritted filter approximately half full), and the filtrate concentrated under vaccum. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes to 100% ethyl acetate) to afford **3-24f** (570 mg, 24%) as a pale yellow oil. (R_f = 0.44, ethyl acetate); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (t, *J* = 5.2 Hz, 2H), 3.35 (d, *J* = 2.4 Hz, 2H), 2.69 (t, *J* = 5.2 Hz, 2H), 2.13 (t, *J* = 2.4 Hz, 1H), 1.56 (bs, 1H), 0.80 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.1, 71.2, 62.3, 50.5, 38.1, 25.9, 18.2, -5.4; IR (thin film) ν 3311, 2955, 2930, 2857, 2104, 1463, 1256, 1106, 836, 777 cm^{-1}; MS *m/z* (%) 157 (18, M – (*t*-Bu)), 156 (100), 130 (72), 68 (100); EI-HRMS calcd for $C_7H_{14}NOSi$ *m/z* 156.0845 [M - (*t* -Bu)$^+$]; found 156.0838.

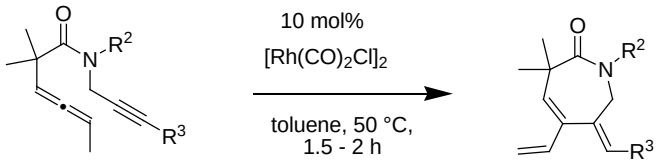


N-benzyl-3-(4-methoxyphenyl)prop-2-yn-1-amine 3-24i. To a solution of alcohol **E3-3**[88] (507 mg, 3.13 mmol) and triethylamine (0.61 mL, 4.4 mmol) in THF (16 mL) at 0 ºC was added methane sulfonylchloride (0.29 mL, 3.8 mmol). The reaction mixture warmed slowly to room temperature over 2 h and then diluted with EtOAc (30 mL). The layers were separated and the organic layer was washed with brine (2x). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to afford the mesylate (747 mg, 99%) as a yellow oil that was immediately used in the next step. The mesylate (747 mg, 3.11 mmol) was dissolved in THF (39 mL), and added via cannula to a 100 mL round bottomed flask containing sodium iodide (47.0 mg, 0.311 mmol). Benzyl amine (0.430 mL, 3.89 mmol) and triethylamine (1.30 mL, 9.33 mmol) were added and the solution heated to reflux for ~ 18 h when no starting material was observed by TLC. The mixture was diluted with ether (100 mL), filtered through celite (150 mL fritted filter approximately half full), and the filtrate concentrated under vaccum. The residue was chromatographed on silica gel (40% ethyl acetate/hexanes) to afford **3-24i** (200 mg, 26%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.27 (m, 7H), 6.87 (d, J = 8.8 Hz, 2H), 3.96 (s, 2H), 3.79 (s, 3H), 3.66 (s, 2H), 1.64 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 139.5, 132.8, 128.1, 126.8, 115.2, 113.7, 85.9, 83.3, 54.9, 52.3, 38.1; IR (thin film) ν 3306, 3031, 2837, 2230, 1606, 1509, 1246, 1031, cm^{-1}; MS *m/z* (%) 251 (61), 250 (69), 236 (7), 174 (31), 145 (81), 91 (100); EI-HRMS calcd for $C_{17}H_{16}NO$ *m/z* [M - H^+] 250.1232; found 250.1234.



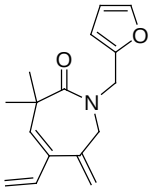
Isobutyl benzylprop-2-ynylcarbamate 3-25. To a solution of allenic acid **3-18** (92.0 mg, 0.66 mmol) in THF (2.6 mL) at -10 °C was added *N*-methylmorpholine (80 μL, 0.72 mmol) and isobutyl chloroformate (95 μL, 0.72 mmol). The resultant cloudy brown suspension was stirred for 5 min then amine **3-24a** (110 mg, 0.76 mmol) in a solution of THF (0.6 mL) was added via syringe. The resultant white suspension was allowed to stir for 1 h and then the reaction was quenched with sat'd aqueous $NaHCO_3$ (0.8 mL). The reaction mixture was diluted with enough water to dissolve the salts and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was chromatographed on silica gel (10% ethyl acetate/hexanes) to afford the product **3-25** as a clear, colorless oil (163 mg, 100%). ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C) δ 7.36–7.24 (m, 5H), 4.53 (s, 2H), 4.03 (d, J = 2.4 Hz, 2H), 3.88 (d, J = 6.4 Hz, 2H), 3.03 (t, J = 2.4 Hz, 1H), 1.91 – 1.86 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 60 °C) δ 155.0, 137.0, 128.0, 127.1, 126.8, 79.1, 73,7, 71.0, 49.2, 35.6, 27.2, 18.4; IR (thin film) ν 3293, 3250, 2962, 2874, 2116, 1701, 1237, 769, 699 cm^{-1}; MS *m/z* (%) 246 (16), 245 (56), 206 (14), 188 (37), 150 (88), 91 (100); EI-HRMS calcd for $C_{15}H_{19}NO_2$ *m/z* $[M]^+$ 245.1416; found 245.1412.

ε-Lactams 3-26.



3-23 **3-26**

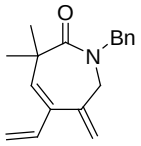
General Procedure D: Preparation of **3-26**



3-26g

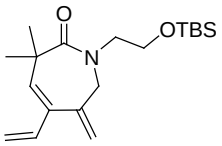
(Z)-1-((Furan-2-yl)methyl)-6,7-dihydro-3,3-dimethyl-6-methylene-5-vinyl-1H-azepin-2(3H)-one 3-26g. A solution of amide **3-23g** (96 mg, 0.37 mmol) in toluene (7.5 mL, 0.05 M) was degassed by bubbling argon through the solution for 20 min. Rhodium biscarbonylchloride dimer (15 mg, 0.04 mmol) was then added all at once and the reaction flask immediately immersed in an oil bath preheated to 50 °C. The reaction was stirred for 1.5 h. The reaction mixture was cooled to rt and diluted with a solution of 30% ethyl acetate/hexanes. This solution was filtered through a pad of silica gel (30 mL fritted funnel approximately half full), eluting with 30% ethyl acetate/hexanes solution. The solvent was removed under vacuum and the residue was chromatographed on silica gel (10% ethyl acetate/hexanes) to afford lactam **3-26g** (60 mg, 63%) as a clear oil that solidifies in the freezer. (R_f = 0.50, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 1H), 6.34 (dd, *J* = 17.0, 10.7 Hz, 1H), 6.31–6.23 (m, 2H), 5.63 (s, 1H), 5.32 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.08 (dd, *J* = 10.7, 1.7 Hz, 1H), 5.07 (s, 1H), 4.96 (s, 1H), 4.63 (s, 2H), 4.02 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 151.2, 141.9, 139.1, 137.8, 137.2, 135.1, 116.2, 115.9, 110.3, 108.4, 52.3, 44.6, 43.9, 28.9; IR

(thin film) ν 3115, 2981, 2959, 1632, 1477, 923 cm^{-1}; MS *m/z* (%) 258 (5), 257 (32), 187 (24), 81 (100); EI-HRMS calcd for $C_{16}H_{19}NO_2$ *m/z* [M^+] 257.1420; found 257.1416.



3-26a

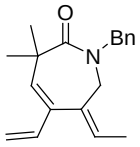
(Z)-1-Benzyl-6,7-dihydro-3,3-dimethyl-6-methylene-5-vinyl-1H-azepin-2(3H)-one 3-26a. According to General Procedure D, **3-23a** (108 mg, 0.403 mmol) in toluene (8 mL, 0.05 M) was reacted with $[Rh(CO)_2Cl]_2$ (16 mg, 0.04 mmol). Isolated yield (69 mg, 65%) as a clear oil that solidifies in the freezer. (R_f = 0.41, 30% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.24 (m, 5H), 6.36 (dd, *J* = 17.0, 10.6 Hz, 1H), 5.69 (s, 1H), 5.36 (d, *J* = 17.0 Hz, 1H), 5.12 (d, *J* = 10.6 Hz, 1H), 5.09 (s, 1H), 4.95 (s, 1H), 4.68 (s, 2H), 3.93 (s, 2H), 1.52 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 139.1, 137.7, 137.6, 137.2, 135.3, 128.4, 128.0, 127.2, 116.3, 115.9, 52.5, 50.8, 44.5, 29.0; IR (thin film) ν 3081, 3023, 2973, 2925, 2860, 1641 cm^{-1}; MS *m/z* (%) 268 (25), 267 (88), 252 (25), 240 (5), 197 (62), 176 (11), 119 (60), 91 (100); ESI-HRMS calcd for $C_{18}H_{21}NO$ *m/z* [M^+] 267.1623; found 267.1628.



3-26f

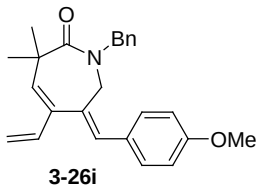
(Z)-6,7-Dihydro-1-(2-t-butyldimethylsilyloxyethyl)-3,3-dimethyl-6-methylene-5-vinyl-1H-azepin-2(3H)-one 3-26f. According to General procedure D, **3-23f** (101 mg, 0.302 mmol) in toluene (6 mL, 0.05 M) was reacted with $[Rh(CO)_2Cl]_2$ (12 mg, 0.03 mmol). Reaction time was 2 h. Isolated yield (67 mg, 67%) as a clear oil that solidifies in the freezer. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.35 (dd, *J* = 17.0, 10.6 Hz, 1H), 5.62 (s, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.14–5.07

(m, 3H), 4.13 (s, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.54 (t, *J* = 5.5 Hz, 2H), 1.44 (s, 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 139.7, 137.8, 137.1, 135.2, 116.2, 115.5, 61.6, 55.2, 51.4, 44.4, 29.0, 25.8, 18.1, -5.5; IR (thin film) ν 3085, 2955, 2929, 2857, 1644, 1473, 1252, 1104, 836 cm^{-1}; MS *m/z* (%) 336 (4), 335 (17), 320 (6), 279 (22), 278 (100), 204 (3), 73 (53); ESI-HRMS calcd for $C_{19}H_{33}NO_2Si$ *m/z* [M^+] 335.2281; found 335.2278.



3-26h

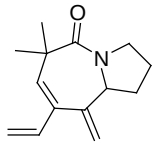
(4Z,6Z)-1-Benzyl-6-ethylidene-6,7-dihydro-3,3-dimethyl-5-vinyl-1H-azepin-2(3H)-one 3-26h. According to General procedure D, **3-23h** (42 mg, 0.15 mmol) in toluene (3 mL, 0.05 M) was reacted with $[Rh(CO)_2Cl]_2$ (5.9 mg, 0.015 mmol). Isolated yield (21 mg, 50%) as a clear oil that solidifies in the freezer. (R_f = 0.28, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.25 (m, 5H), 6.32 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.69 (q, *J* = 7.0 Hz, 1H), 5.55 (s, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 4.68 (s, 2H), 3.99 (s, 2H), 1.68 (d, *J* = 7.0 Hz, 3H), 1.51 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 139.1, 138.6, 137.9, 133.0, 132.4, 128.6, 127.7, 127.2, 126.1, 116.2, 51.3, 45.0, 44.6, 29.3, 22.6, 13.9; IR (thin film) ν 3081, 3023, 2972, 2928, 2856, 1641 cm^{-1}; MS *m/z* (%) 282 (5), 281 (35), 280 (3), 266 (5), 211 (25), 133 (39), 91 (100); ESI-HRMS calcd for $C_{19}H_{23}NO$ *m/z* [$M]^+$ 281.1780; found 281.1774.



3-26i

(4Z,6Z)-6-(4-Methoxybenzylidene)-1-benzyl-6,7-dihydro-3,3-dimethyl-5-vinyl-1H-azepin-2(3H)-one 3-26i. According to General Procedure D, **3-23i** (62 mg, 0.17 mmol) in toluene (3.3

mL, 0.05 M) was reacted with $[Rh(CO)_2Cl]_2$ (6.4 mg, 0.017 mmol). Isolated yield (40 mg, 65%) as a clear oil that solidifies in the freezer. (R_f = 0.40, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.18 (m, 3H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.78–6.76 (m, 2H), 6.71 (s, 1H), 6.45 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.72 (s, 1H), 5.41 (dd, *J* = 17.0, 1.6 Hz, 1H), 5.17 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.30 (s, 2H), 4.12 (s, 2H), 3.87 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 158.9, 139.2, 138.5, 137.6, 134.7, 132.8, 130.7, 129.9, 129.4, 128.5, 128.2, 128.1, 127.0, 116.7, 113.9, 55.3, 50.5, 44.9, 44.4, 29.0; IR (thin film) ν 3023, 2970, 2929, 1642, 1509, 1249, 1033 cm^{-1}; MS *m/z* (%) 374 (19), 373 (68), 372 (4), 304 (22), 303 (95), 225 (48), 121 (43), 91 (100); EI-HRMS calcd for $C_{25}H_{27}NO_2$ *m/z* [M^+] 373.2042; found 373.2040.

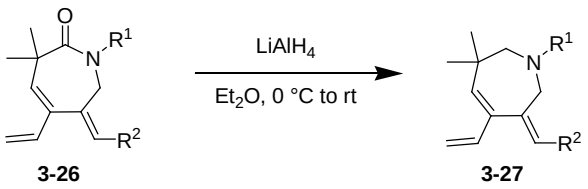


3-26j

(Z)-2,3,9,9a-Tetrahydro-6,6-dimethyl-9-methylene-8-vinyl-1H-pyrrolo[1,2-a]azepin-5(6H)-one 3-23j. According to General Procedure D, **3-23j** (28 mg, 0.13 mmol) in toluene (2.5 mL, 0.05 M) was reacted with $[Rh(CO)_2Cl]_2$ (5.0 mg, 0.013 mmol). Isolated yield (17 mg, 62%) as a clear oil that solidifies in the freezer. (R_f = 0.18, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.32 (dd, *J* = 17.1, 10.6 Hz, 1H), 5.60 (s, 1H), 5.31 (dd, *J* = 17.0, 1.6 Hz, 1H), 5.24 (s, 1H), 5.17 (s, 1H), 5.08 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.54 (dd, *J* = 7.3, 4.2 Hz, 1H), 3.71–3.63 (m, 1H), 3.58–3.49 (m, 1H), 2.31–2.08 (m, 2H), 1.97–1.80 (m, 2H), 1.43 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 142.2, 139.0, 137.9, 135.3, 115.8, 113.0, 58.6, 47.8, 44.0, 30.8, 29.6, 26.7, 22.5; IR (thin film) ν 3090, 2972, 2879, 1634, 1426 cm^{-1}; MS *m/z* (%) 217 (41),

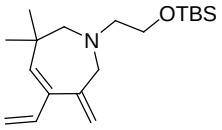
202 (24), 147 (66), 146 (56), 86 (87), 84 (100); EI-HRMS calcd for $C_{14}H_{19}NO$ *m/z* [M^+] 217.1467; found 217.1464.

Trienyl Azepines 3-27



3-26 **3-27**

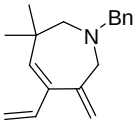
General Procedure F: Preparation of **3-27f**



3-27f

(*Z*)-2,3,6,7-Tetrahydro-1-(2-dimethyl-*t*-butoxysilylethyl)-3,3-dimethyl-6-methylene-5-vinyl-1*H*-azepine 3-26f. To a suspension of $LiAlH_4$ (29 mg, 0.76 mmol) in diethyl ether (3.8 mL) at 0 °C was added caprolactam **3-26f** (R^1 = $(CH_2)_2OTBS$, R^2 = H) (64 mg, 0.19 mmol) in a solution of diethyl ether (0.6 mL) via syringe. After 5 min the ice bath was removed and the reaction allowed to warm to rt. After 1.5 h, an absence of starting material was observed by TLC and the reaction was quenched slowly via syringe by sequential addition of H_2O (0.06 mL), 10% NaOH solution (0.12 mL), and sat'd aqueous KF solution (0.24 mL). This resulted in precipitation of a white, granular solid. The mixture was dried over $MgSO_4$, celite was added, and the whole mixture filtered through a pad of silica gel (10 mL fritted funnel, approximately 30% full). The solvent was removed under vacuum to give **3-27f** (45 mg, 74%) as a clear oil without further purification. The product solidified in the freezer. (R_f = 0.58, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.28 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.37 – 5.20 (m, 3H), 5.00 (s, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 3.73 (t, *J* = 6.6 Hz, 2H), 3.37 (s, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.52 (s, 2H), 1.04 (s, 6H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 140.5, 139.6,

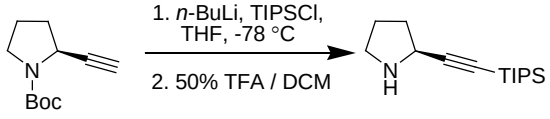
136.8, 117.6, 113.0, 63.9, 63.7, 61.7, 60.6, 38.7, 28.2, 25.9, 18.2, -5.3; IR (thin film) ν 3081, 2954, 2928, 2857, 1605, 1471, 1255, 1102, 836, 775 cm^{-1}; MS *m/z* (%) 323 (6), 322 (9), 321 (21), 265 (17), 176 (100); ESI-HRMS calcd for $C_{19}H_{36}NOSi$ *m/z* [M + H^+] 322.2566; found 322.2572.



3-27a

(*Z*)-1-Benzyl-2,3,6,7-tetrahydro-3,3-dimethyl-6-methylene-5-vinyl-1*H*-azepine 3-27a.

According to General Procedure F, **3-26a** (59 mg, 0.22 mmol) in diethyl ether (0.75 mL) was reacted with lithium aluminum hydride (34 mg, 0.88 mmol) to afford **3-27a** (34 mg, 60%). (R_f = 0.73, 30% ethyl acetate/hexanes) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 – 7.26 (m, 5H), 6.34 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.50 (s, 1H), 5.29 (d, *J* = 17.2, 1H), 5.28 (s,1H), 5.08 (s, 1H), 5.01 (d, *J* = 10.6 Hz, 1H), 3.73 (s, 2H), 3.26 (s, 2H), 2.50 (s, 2H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 140.7, 139.6, 137.4, 128.9, 128.1, 126.8, 117.9, 113.2, 64.1, 63.3, 62.9, 37.1, 28.3; IR (thin film) ν 3085, 3026, 2955, 2864, 2786, 1609, 1453, 904, 739, 698 cm^{-1}; MS *m/z* (%) 253 (44), 238 (42), 197 (53), 119 (52), 91 (100); ES-HRMS calcd for $C_{17}H_{20}NO$ *m/z* [M - 15^+] 238.1596; found 238.1599.

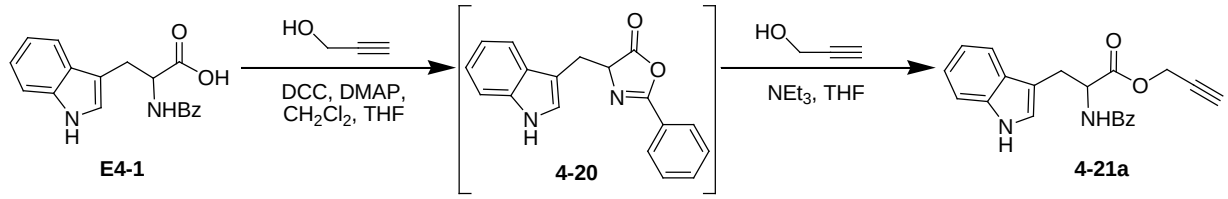


3-33 **3-35**

(S)-2-(2-(Triisopropylsilyl)ethynyl)pyrrolidine 3-35. To a solution of Boc-protected amine **3-33** (209 mg, 1.1 mmol) in THF (11 mL) at -78 ºC was added *n*-butyl lithium (0.77 mL of a 1.6 M solution in hexanes, 1.2 mmol). The resultant brown solution was stirred for 30 min then a solution of TIPSCl (350 μL, 1.6 mmol) in THF (8 mL) was added via syringe. After 1 h the

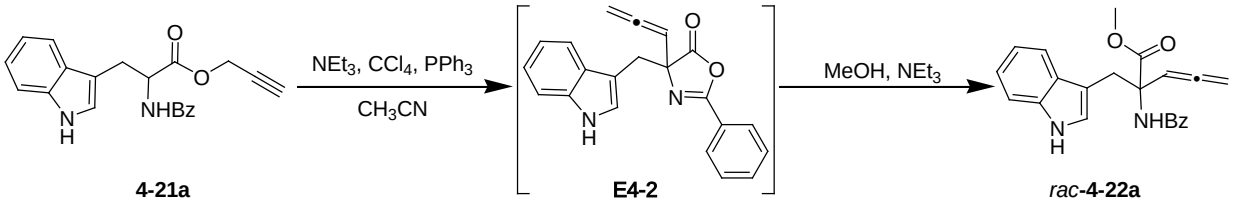
reaction mixture was allowed to warm to rt and a sat'd, aqueous solution of NH_4Cl (2 mL) was added. The reaction mixture was partitioned between ether and water and the layers separated. The aqueous phase was extracted with ether and the combined organic layers dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (5% ethyl acetate/hexanes) to afford the TIPS protected alkyne (342 mg, 91%). The alkyne (342 mg, 1.07 mmol) was then redissolved in CH_2Cl_2 (2.5 mL) and trifluoroacetic acid (2.5 mL) was added. After 20 min the reaction mixture was quenched with sat'd, aqueous Na_2CO_3 (10 mL) then diluted with ether and water and the layers separated. The organic layer was washed with sat'd aqueous Na_2CO_3 (10 mL) and the combined aqueous layers were extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was chromatographed on silica gel (40% ethyl acetate/hexanes) to give the product **3-35** (128 mg, 48% from **3-33**). (R_f = 0.12, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (dd, *J* = 7.2, 4.7 Hz, 1H), 3.15–3.09 (m, 1H), 2.95–2.89 (m, 1H), 2.17 (bs, 1 H), 2.10–1.71 (m, 4H), 1.06 (s, 3H) 1.05 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1110.5, 82.5, 49.5, 45.8, 33.4, 24.5, 18.6, 11.1; IR (thin film) ν 3266, 2943, 2866, 2160, 1463, 883 cm^{-1}; MS *m/z* (%) 252 (7), 251 (29), 209 (47), 208 (100), 180 (15), 83 (36); EI-HRMS calcd for $C_{15}H_{29}NSi$ *m/z* [M^+] 251.2069; found 251.2069.

5.5 EXPERIMENTAL: CHAPTER 4



Prop-2-ynyl 2-(benzamido)-3-(1*H*-indol-3-yl)propanoate 4-21a. To a solution of propargyl alcohol (1.73 mL, 29.7 mmol), dicyclohexylcarbodiimide (5.10 g, 24.7 mmol), and 4-dimethylaminopyridine (152 mg, 1.24 mmol) in CH_2Cl_2 (150 mL) was added a solution of **E4-1** (7.62 g, 24.7 mmol) in THF : CH_2Cl_2 (1 : 1) (82 mL) via cannula over 5-10 min. The resultant suspension was stirred for 16 h overnight until no starting material was evident by TLC (R_f **4-20** = 0.28, 30% ethyl acetate/hexanes). The mixture was filtered through a pad of silica gel (150 mL fritted funnel approximately half full) eluting with 250 mL of a 50% ethyl acetate/hexanes solution and the filtrate concentrated under vacuum. The residue (crude **4-20**, assumed 100% from **E4-1**) was dissolved in THF (40 mL) and to this solution was added propargyl alcohol (0.87 mL, 12.4 mmol) and triethylamine (7 mL, 50.4 mmol). The solution was stirred for 1 h, when full conversion to the product from the intermediate oxazolidinone was observed by TLC. The reaction mixture was filtered through celite (150 mL fritted funnel approximately half full), eluting with ethyl acetate, and the filtrate concentrated under vacuum. The crude residue was chromatographed on silica gel (30% to 50% ethyl acetate/hexanes) to afford **4-21a** (6.82 g, 84%) as an amorphous, brown solid. (R_f = 0.15, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (bs, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.39 – 7.34 (m, 3H), 7.20 (dt, *J* = 6.9, 0.9 Hz, 1H), 7.09 (dt, *J* = 6.9, 0.9 Hz, 1H), 7.05 (d, *J* = 2.9 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.21 (dt, *J* = 7.8, 5.1 Hz, 1H), 4.77 (A of an ABq, d, *J* = 15.6,

2.4 Hz, 1H), 4.67 (B of an ABq, d, J = 15.6, 2.4 Hz, 1H), 3.49 (d, J = 5.1 Hz, 2H), 2.54 (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 167.0, 136.1, 133.6, 131.7, 128.5, 127.6, 127.0, 123.1, 122.2, 119.7, 118.5, 111.4, 109.5, 77.1, 75.5, 53.5, 52.8, 27.4; IR (thin film) ν 3412, 3293, 3057, 2932, 2129, 1745, 1648, 1521, 1182, 743 cm^{-1}; MS *m/z* (%) 347 (15), 346 (64), 325 (13), 225 (29), 130 (100); EI-HRMS calcd for $C_{21}H_{18}N_2O_3$ *m/z* [M^+] 346.1317; found 346.1391.

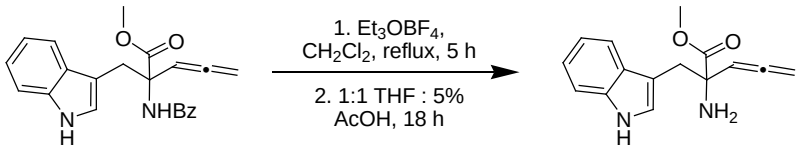


4-21a **E4-2** ***rac*-4-22a**

Methyl 2-((1*H*-indol-3-yl)methyl)-2-(benzamido)penta-3,4-dienoate *rac*-4-22a.[89]

To a solution of propargyl ester **4-21a** (6.33 g, 18.3 mmol) in freshly distilled CH_3CN (91 mL) was added triethylamine (10.7 mL, 76.7 mmol), carbon tetrachloride (6.2 mL, 64.0 mmol), and triphenylphosphine (14.7 g, 56.6 mmol). The reaction mixture was stirred for 20 h until no starting material was evident by TLC (R_f **E4-2** = 0.59, 30% ethyl acetate/hexanes). The mixture was poured into a solution of ether : hexanes (350 mL : 100 mL) and the yellow/white solid precipitate was removed by vacuum filtration through celite (150 mL fritted funnel approximately half full). The filtrate was concentrated under vacuum and the residue dissolved in a solution of methanol (150 mL) and triethylamine (15 mL). The reaction mixture was stirred for another 20 h when TLC showed full conversion from **E4-2** to the product and an impurity spot (R_f = 0.35, 30% ethyl acetate/hexanes). The solvent was removed under vacuum and the residue chromatographed on silica gel (25% ethyl acetate/ hexanes) to afford pure *rac*-**4-22a** (664 mg, ~10%), and *rac*-**4-22a** contaminated with triphenylphosphine oxide (> 8 g, mass ratio ~ 29% based upon isolated product. See below). The contaminated material was dissolved in

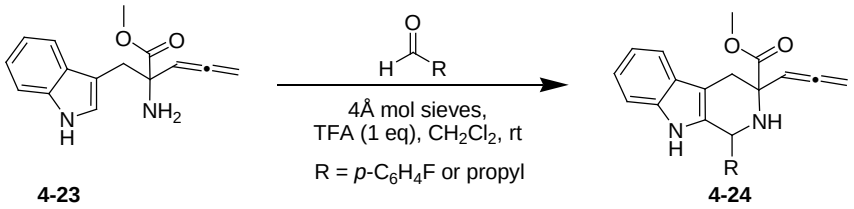
ether and stored in a freezer (-20 °C) overnight. The mixture was filtered through celite (150 mL fritted funnel approximately half full) to remove precipitated triphenylphosphine oxide and the filtrate concentrated under vacuum. The residue was chromatographed on silica gel (40% to 50% ether/pentane) to afford pure **4-22a** (2.35 g, 36%) as an amorphous, off-white solid. [Performing the reaction on 1.25 g of **4-21a** affords 673 mg (52%) of *rac*-**4-22a** and the second triphenylphosphine oxide precipitation step was not necessary.] (R_f = 0.31, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (bs, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.49 – 7.44 (m 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.96 (s, 1H), 5.79 (t, *J* = 6.6 Hz, 1H), 4.95 (dd, *J* = 11.1, 6.6 Hz, 1H), 4.85 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.90 (A of an ABq, *J* = 14.7 Hz, 1H), 3.76 (s, 3H), 3.70 (B of an ABq, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 172.5, 166.6, 135.8, 134.5, 131.5, 128.5, 127.9, 126.9, 124.0, 121.8, 119.5, 118.8, 111.2, 109.2, 93.2, 79.7, 62.9, 52.9, 31.0; IR (thin film) ν 3404, 3325, 3057, 2950, 1958, 1736, 1655, 1515, 1484, 1248, 1099, 739 cm^{-1}; MS *m/z* (%) 361 (12), 360 (35), 255 (25), 240 (62), 239 (98), 105 (100); EI-HRMS calcd for $C_{22}H_{20}N_2O_3$ *m/z* [M^+] 360.1474; found 360.1471.



rac-**4-22a** **4-23**

Methyl 2-((1*H*-indol-3-yl)methyl)-2-aminopenta-3,4-dienoate 4-23. To a solution of **4-22a** (1.00 g, 2.77 mmol) in CH_2Cl_2 (2.8 mL) was added Et_3OBF_4 (9.90 mL of a 1.4 M solution in CH_2Cl_2, 13.9 mmol).[90] The mixture was heated to reflux (cold finger) for 5 h when no starting material was evident by TLC (baseline iminium salt intermediate and impurity R_f = 0.78, 60% ethyl acetate/hexanes). The reaction mixture was cooled to room temperature then concentrated

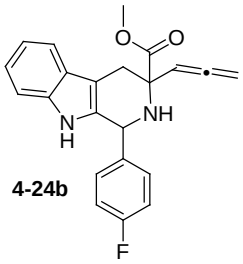
under vacuum. The residue was dissolved in THF (2.5 mL) and 5% aqueous acetic acid (2.5 mL) and stirred open to the atmosphere at room temperature for 16 h. The mixture was quenched with sat'd K_2CO_3 and stirred for 5 – 10 min then diluted with ethyl acetate and water. An emulsion forms that dissipates over ~ 5 min. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (20% to 40% to 80% ethyl acetate/hexanes) to afford **4-23** (421 mg, 59%) as a viscous, red/brown oil. Yields consistently ranged from 36% to 46% when using less than 1 g of starting benzamide *rac*-**4-22a**. (R_f = 0.08, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (bs, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.18 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.12 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 5.62 (t, *J* = 6.6 Hz, 1H), 4.96 (d, *J* = 6.6 Hz, 2H), 3.69 (s, 3H), 3.46 (A of an ABq, *J* = 14.1 Hz, 1H), 3.14 (B of an ABq, *J* = 14.1 Hz, 1H), 1.92 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 175.5, 135.9, 128.0, 123.6, 122.0, 119.5, 119.2, 111.1, 110.0, 96.4, 79.4, 61.1, 52.4, 35.7; IR (thin film) ν 3365, 3176, 3057, 2950, 2872, 1956, 1732, 1242, 1203, 859, 744 cm^{-1}; MS *m/z* (%) 256 (74), 239 (37), 196 (16), 130 (100); EI-HRMS calcd for $C_{15}H_{16}N_2O_2$ *m/z* [M^+] 256.1212; found 256.1215.



4-23 **4-24**

Allenic Tetrahydro-β-Carbolines 4-24.

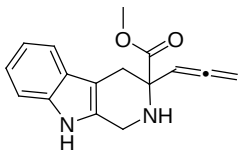
General Procedure I: Preparation of **4-24b**.



4-24b

Methyl 1-(4-fluorophenyl)-2,3,4,9-tetrahydro-3-(propa-1,2-dienyl)-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 4-24b. To a solution of **4-23** (204 mg, 0.79 mmol) in CH_2Cl_2 (7.9 mL, use MeOH for formation of **4-24a**, see below) was added and activated powdered 4 Å molecular sieves (373 mg, 470 mg/mmol), *p*-fluorobenzaldehyde (0.09 mL, 0.83 mmol), and trifluoroacetic acid (0.06 mL, 0.79 mmol). The reaction mixture was stirred for 3 h when an absence of starting material was observed by TLC. The mixture was quenched with sat'd $NaHCO_3$ (~ 2 – 3 mL) and stirred for 5 min. (Alternatively, the molecular sieves can be removed by gravity filtration through filter paper prior to $NaHCO_3$ workup with no change in yield). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (10% to 20% ethyl acetate hexanes; the residual *p*-fluorobenzaldehyde can be observed by UV on the TLC plate and removed) to afford **4-24b** (200 mg, 70%) in a 2 : 1 mixture of diastereomers as an amorphous white solid. *Denotes minor diastereomer. (R_f = 0.44, 30% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57

– 7.55 (m, 1H), 7.41 – 7.37 (m, 3H), 7.25 – 7.02 (m, 5H), *5.48 (t, *J* = 6.6 Hz, 0.3H), *5.43 (bs, 0.3H), 5.35 (t, *J* = 6.6 Hz, 0.7H), 5.24 (bs, 0.7H), *5.01 (d, *J* = 6.6 Hz, 0.7H), 4.92 (dd, *J* = 11.4, 6.6 Hz, 0.7H), 4.73 (dd, *J* = 11.1, 6.6 Hz, 0.7H), 3.83 (s, 2.1H), *3.66 (s, 0.9H), *3.64 (A of an ABq, d, *J* = 15.3, 2.7 Hz, 0.3H), 3.28 – 3.26 (m, 1.3H), *3.04 (B of an ABq, d, *J* = 15.3, 2.7 Hz, 0.3H), 2.80 (bs, 0.7H), *2.65 (bs, 0.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, *206.9, *174.2, 173.5, 162.8 (d, J_{CF} = 245.3 Hz), *137.7 (d, J_{CF} = 3.0 Hz), 136.8 (d, J_{CF} = 3.0 Hz), *133.6, 133.4, 130.5 (d, J_{CF} = 8.3 Hz), *130.3 (d, J_{CF} = 8.3 Hz), 127.4, *127.0, 121.9, 119.5, *118.4, 118.2, 115.7 (d, J_{CF} = 21.0 Hz), 110.8, *107.9, 107.8, *95.5, 92.6, *79.6, 78.7, 77.2, *76.8, *62.4, 60.9, *55.1, 54.0, 52.6, *52.4, *29.9, 29.1; IR (thin film) ν 3391, 3057, 2951, 2847, 1952, 1732, 1604, 1508, 1253, 1224, 1153, 842, 742 cm^{-1}; MS *m/z* (%) 363 (11), 362 (45), 323 (9), 303 (52), 239 (81), 236 (100); EI-HRMS calcd for $C_{22}H_{19}FN_2O_2$ *m/z* $[M]^+$ 362.1431; found 362.1427.

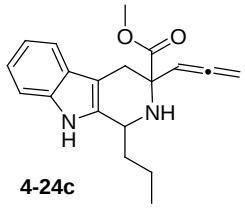


4-24a

Methyl 2,3,4,9-Tetrahydro-3-(propa-1,2-dienyl)-1*H*-pyrido[3,4-*b*]indole-3-carboxylate

4-24a. According to General Procedure I, **4-23** (57 mg, 0.22 mmol), activated powdered 4 Å molecular sieves (207 mg, 940 mg/mmol), formaldehyde (0.02 mL of a 37% aqueous solution, 0.26 mmol), and trifluoroacetic acid (16 μL, 0.22 mmol) were reacted in MeOH (5.5 mL) for 6 h to afford **4-24a** (42 mg, 71%) as an amorphous brown solid. (R_f = 0.08, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (bs, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.19 – 7.08 (m, 2H), 5.39 (t, *J* = 6.6 Hz, 1H), 4.98 (dd, *J* = 11.1, 6.6 Hz, 1H), 4.90 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.25 (A of an ABq, *J* = 15.6 Hz, 1H), 4.12 (B of an ABq, *J* = 15.6 Hz, 1H), 3.71 (s, 3H), 3.37 (A of ABq, t, *J* = 15.3, 1.5 Hz, 1H), 3.01 (B of ABq, t, *J* = 15.3,

1.5 Hz, 1H), 2.49 (bs, 1H), minor inseparable impurities: 7.4 (d, *J* = 8.1 Hz, 0.19H), 5.33 (s, 0.26H), 3.19 (s, 0.39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 173.9, 136.2, 131.0, 127.2, 121.4, 119.2, 117.8, 110.7, 106.7, 94.1, 79.2, 60.6, 52.4, 39.8, 29.7; IR (thin film) ν 3395, 3175, 3058, 2949, 2849, 1954, 1732, 1453, 1258, 857, 743 cm^{-1}; MS *m/z* (%) 268 (13), 267 (5), 239 (55), 143 (100); EI-HRMS calcd for $C_{16}H_{16}N_2O_2$ *m/z* [M^+] 268.1212; found 268.1210.

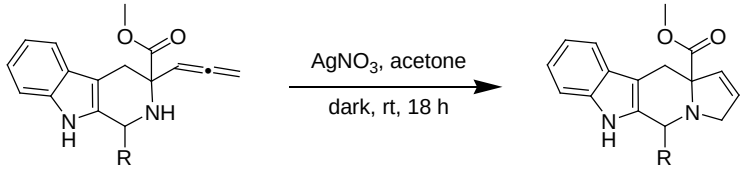


4-24c

Methyl 2,3,4,9-tetrahydro-3-(propa-1,2-dienyl)-1-propyl-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 4-24. According to General Procedure I, **4-23** (51 mg, 0.20 mmol), activated powdered 4 Å molecular sieves (93 mg, 470 mg/mmol), butyraldehyde (19 μL, 0.21 mmol), and trifluoroacetic acid (15 μL, 0.20 mmol) were reacted in CH_2Cl_2 (2 mL) for 50 min to afford **4-24c** (41 mg, 68%) as a 2 : 1 mixture of diastereomers. The diastereomers were separated by chromatography on silica gel (25% ethyl acetate/hexanes). *Trans*-isomer (off-white solid, contains ~ 10% *cis*-isomer by ^{1}H NMR): (R_f = 0.28, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (bs, 1), 7.51 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 5.25 (t, *J* = 6.5 Hz, 1H), 4.84 (dd, *J* = 11.0, 6.5 Hz, 1H), 4.69 (dd, *J* = 11.5, 6.5 Hz, 1H), 4.25 – 4.24 (m, 1H), 3.85 (s, 3H), 3.20 (A of an ABq, *J* = 15.5 Hz, 1H), 3.08 (B of an ABq, d, *J* = 15.5, 2.5 Hz, 1H), 2.57 (bs, 1H), 1.93 – 1.87 (m, 1H), 1.79 – 1.71 (m, 1H), 1.59 – 1.51 (m, 2H), 1.02 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 173.9, 136.2, 134.6, 127.6, 121.5, 119.4, 117.9, 110.7, 106.9, 92.8, 78.5, 60.4, 52.5, 48.4, 37.1, 29.5, 18.7, 14.1; IR (thin film) ν 3402, 3056, 2956, 2932, 2870, 1952, 1732, 1452, 1257, 1156, 852, 742 cm^{-1}; MS *m/z* (%) 311 (7), 310 (20), 267 (23), 239 (39), 207 (46), 180 (70), 119 (94);

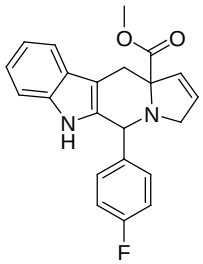
EI-HRMS calcd for $C_{19}H_{22}N_2O_2$ *m/z* [M^+] 310.1681; found 310.1691. *Cis*-isomer (yellow oil, contains ~ 4% major diastereomer by ^{1}H NMR): (R_f = 0.34, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (bs, 1), 7.52 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.17 – 7.09 (m, 2H), 5.48 (t, *J* = 6.5 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.40 – 4.38 (m, 1H), 3.60 (s, 3H), 3.55 (A of an ABq, d, *J* = 15.0, 2.0 Hz, 1H), 2.87 (B of an ABq, d, *J* = 15.0, 2.0 Hz, 1H), 2.47 (bs, 1H), 1.88 – 1.82 (m, 1H), 1.77 – 1.68 (m, 1H), 1.58 – 1.51 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 174.2, 136.2, 134.7, 127.2, 121.5, 119.43, 118.2, 110.6, 107.3, 95.7, 79.5, 61.8, 52.3, 49.7, 38.1, 29.9, 18.6, 14.1; IR (thin film) ν 3397, 3056, 2955, 2871, 1955, 1728, 1452, 1260, 1204, 857, 742 cm^{-1}. MS *m/z* (%) 311 (11), 310 (44), 267 (63), 239 (76), 207 (74), 180 (67); EI-HRMS calcd for $C_{19}H_{22}N_2O_2$ *m/z* [M^+] 310.1681; found 310.1684.

Tetracyclic Indolyl Pyrrolines 4-26



4-24 **4-26**

General Procedure J: Preparation of **4-26b**

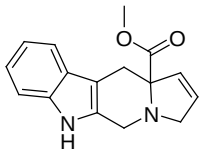


4-26b

Methyl 5-(4-Fluorophenyl)-5,6,11,11a-tetrahydro-3*H*-indolizino[6,7-*b*]indole-11a-carboxylate 4-26b. To a solution of allenic tetrahydro-β-carboline **4-24b** (51 mg, 0.141 mmol, as a 2 : 1 mixture of diastereomers) in acetone (2.8 mL) in a septum-sealed 10 mL reaction vial

wrapped in aluminum foil, was added silver nitrate (4.8 mg, 0.028 mmol, 20 mol%, weighed and transferred under low light). The reaction mixture was kept in a dark hood and stirred for 18 h until no starting material was evident by TLC (R_f = 0.51, 30% ethyl acetate/hexanes). The reaction mixture was diluted with CH_2Cl_2 and washed with sat'd $NaHCO_3$ (2x). The combined aqueous layers were extracted with CH_2Cl_2 (2x) and the combined organic layers dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (15% ethyl acetate/hexanes) to afford **4-26b** (37 mg, 72%) as a 2 : 1 mixture of diastereomers as an amorphous yellow solid. An 83% yield of **4-26b** was obtained when using 40 mol% silver nitrate under similar conditions. The diastereomers were separated via silica gel column chromatography (column diameter: 1.5 cm; silica gel height: 14.5 cm; 100% toluene; column progress followed by UV and $KMnO_4$ staining of the TLC plates). Major diastereomer (amorphous yellow solid, contains ~ 6% minor diastereomer by ^{1}H NMR): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (dd, J_{HF} = 5.4 Hz, J = 8.4 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.40 – 7.35 (m, 1H), 7.25 – 7.20 (m, 1H), 7.17 – 7.09 (m, 4H), 6.02 (dt, J = 6.3, 1.8 Hz, 1H), 5.97 (dt, J = 6.3, 1.8 Hz, 1H), 5.04 (d, J = 1.5 Hz, 1H), 4.12 (A of an ABq, t, J = 13.8, 1.8 Hz, 1H), 3.84 (A of an ABq, J = 14.7 Hz, 1H), 3.80 (B of an ABq, t, J = 13.8, 1.8 Hz, 1H), 3.47 (s, 3H), 2.79 (B of an ABq, d, J = 14.7, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 162.5 (d, J_{CF} = 245.0 Hz), 136.8 (d, J_{CF} = 2.5 Hz), 136.0, 134.3, 131.1, 130.1 (d, J_{CF} = 7.5 Hz), 128.4, 126.9, 121.6, 119.6, 118.2, 115.6 (d, J_{CF} = 21.3 Hz), 111.0, 107.7, 74.9, 61.3, 59.9, 52.1, 29.3. Minor diastereomer (amorphous white solid, spectroscopically pure by ^{1}H NMR): ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.56 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.37 (bs, 1H), 7.37 (dd, J_{HF} = 5.6 Hz, J = 8.4 Hz, 2H), 7.20 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.14 – 7.10 (m, 2H), 7.03 (dd, J_{HF} = 9.1 Hz, J = 8.4 Hz, 2H), 6.11 (ddd, J = 6.3, 2.1, 1.4 Hz, 1H), 6.01 (ddd, J = 6.3, 2.1, 1.4 Hz, 1H), 5.51 (s, 1H), 3.73 – 3.71 (m, 1H), 3.70 (A

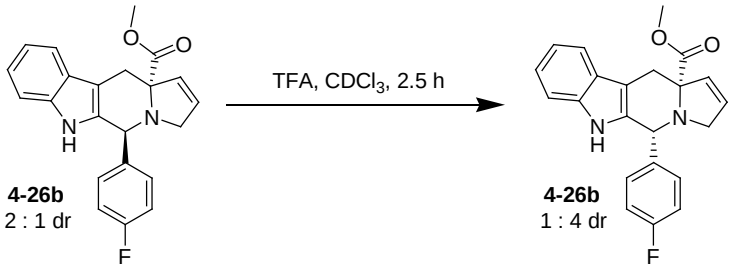
of an ABq, d, J = 14.0, 1.4 Hz, 1H), 3.57 (s, 3H), 3.38 (B of an ABq, t, J = 13.3, 1.4 Hz, 1H), 2.99 (B of an ABq, d, J = 14.0, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 162.6 (d, J_{CF} = 245 Hz), 136.8, 136.6, 136.1, 132.1, 131.5, 130.3 (d, J_{CF} = 8.8 Hz), 127.1, 121.7, 119.4, 118.4, 115.6 (d, J_{CF} = 21.3 Hz), 110.8, 108.0, 74.0, 58.6, 54.3, 51.7, 29.5. (IR, MS, and HRMS analyses performed on the original 2 : 1 diastereomeric mixture.) IR (thin film) ν 3386, 3059, 2950, 2845, 2800, 1724, 1603, 1506, 1463, 1221, 1054, 840, 742 cm^{-1}; MS *m/z* (%) 362 (20), 331 (19), 303 (100), 236 (80); EI-HRMS calcd for $C_{22}H_{19}FN_2O_2$ *m/z* [M^+] 362.1431; found 362.1416.



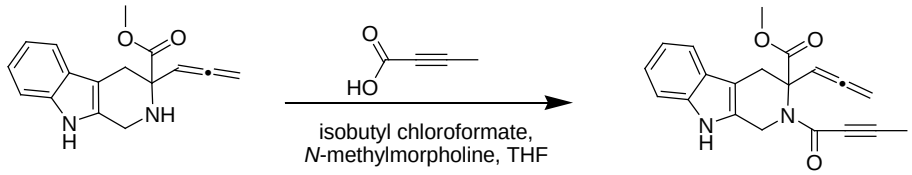
4-26a

Methyl 5,6,11,11a-tetrahydro-3*H*-indolizino[6,7-*b*]indole-11a-carboxylate 4-26a. According to General Procedure J, **4-24a** (33.7 mg, 0.126 mmol) in acetone (2.5 mL), was reacted with silver nitrate (4.3 mg, 0.025 mmol) for 18 h. The crude residue was chromatographed on silica gel (25% ethyl acetate/hexanes) to afford **4-26a** (18.9 mg, 56%) as an amorphous, white solid. (R_f = 0.46, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (bs, 1), 7.51 (d, J = 7.5 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.18 – 7.07 (m, 2H), 6.17 (dt, J = 6.0, 1.8 Hz, 1H), 6.02 (dt, J = 6.0, 1.8 Hz, 1H), 4.49 (A of an ABq, J = 14.4, 1.8 Hz, 1H), 4.10 (B of an ABq, J = 14.4 Hz, 1H), 3.99 (A of an ABq, t, J = 12.9, 1.8 Hz, 1H), 3.88 (B of an ABq, t, J = 12.9, 1.8 Hz, 1H), 3.61 (A of an ABq, d, J = 14.7, 2.1 Hz, 1H), 3.55 (s, 3H), 2.82 (B of an ABq, t, J = 14.7, 2.1 Hz, 1H), minor inseparable impurities: 5.40 (A of an ABq, J = 11.4 Hz, 0.15H), 5.35 (B of an ABq, J = 11.4 Hz, 0.15H), 3.21 (s, 0.18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 136.4, 132.5, 132.0, 131.4, 127.4, 121.4, 119.2, 118.0, 110.7, 107.5, 72.7, 56.9, 51.7, 43.7, 29.3; IR (thin film) ν 3392, 3144, 3060, 2947, 2878, 2845, 1726, 1448, 1170, 1027, 741 cm^{-1}; MS *m/z* (%) 268 (17),

253 (25), 209 (69), 143 (66), 117 (100); EI-HRMS calcd for $C_{16}H_{16}N_2O_2$ *m/z* [M^+] 268.1212; found 268.1210.



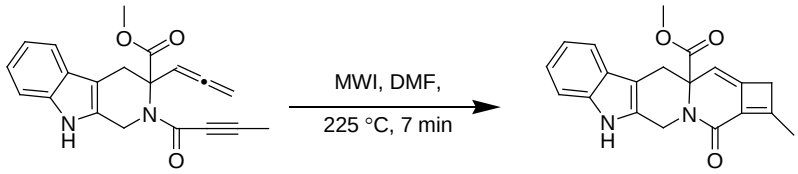
Thermodynamic Isomerization of 4-26b. To a solution of **4-26b** (5.0 mg, 0.014 mmol, 2 : 1 mixture of diastereomers) in $CDCl_3$ (0.5 mL) in an NMR tube was added trifluoroacetic acid (3 μL, 0.034 mmol). The reaction was followed by ^1H NMR (peaks are broadened in the mixture due to TFA-amine salts). Analysis after 2.5 h indicated a reversal in the diastereomer ratio from 2 : 1 to 1 : 4 in favor of the major product isomer (*cis*) shown above. Analysis after 24 h showed the same ratio. The reaction mixture was diluted with ether and washed with sat'd $NaHCO_3$ (2x). The combined aqueous layers were extracted into ether (2x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford crude **4-26b** (5.0 mg, 100%) as a 1 : 4 mixture of diastereomers. Subsequent reaction of the crude product with 6 μL trifluoroacetic acid in the same manner for an additional 24 h did not change the diastereomeric ratio. Spectral data for each isomer is provided above. The isomers shown are supported by modeling studies (see text).



4-26a **4-29a**

Methyl 2-(but-2-ynoyl)-2,3,4,9-tetrahydro-3-(propa-1,2-dienyl)-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 4-29a. To a solution of 2-butynoic acid (16 mg, 0.18 mmol) and *N*-methylmorpholine (51 μL, 0.46 mmol) in THF (1.8 mL) at 0 °C was added isobutyl chloroformate (24 μL, 0.18 mmol). The resultant white suspension was warmed to room temperature and stirred for 25 min. A solution of **4-24a** (41 mg, 0.15 mmol) in THF (1.5 mL) was added via cannula and the mixture stirred for 20 h until no starting material was evident by TLC. The reaction mixture was quenched with sat'd $NaHCO_3$ and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted into ethyl acetate (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **4-29a** (37 mg, 72%) as an amorphous white solid. (R_f = 0.49, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (bs, 1), 7.48 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 5.46 (t, *J* = 6.6 Hz, 1H), 5.35 (A of an ABq, *J* = 16.2 Hz, 1H), 4.76 (dd, *J* = 11.7, 6.6 Hz, 1H), 4.72 (B of an ABq, *J* = 16.2 Hz, 1H), 4.52 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.81 (s, 1H), 3.46 (A of an ABq, *J* = 15.9 Hz, 1H), 3.21 (B of an ABq, *J* = 15.9 Hz, 1H), 1.99 (s, 3H), minor inseparable impurities: 7.58 (dd, *J* = 7.5 Hz, 0.15H), 7.02 (s, 0.07H), 6.57 (s, 0.08H), 5.63 (t, 0.12H), 5.41 (s, 0.17H), 5.03 (m, 0.31H), 3.74 (s, 0.28H), 3.61 (s, 0.05H), 3.58 – 3.53 (m, 0.07H), 3.21 (m, 0.20H), 1.90 (s, 0.23H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 171.3, 155.9, 136.4, 128.8, 126.9, 121.9, 119.6, 118.0, 110.9, 107.6, 90.8, 90.7, 79.3, 73.4, 62.6, 52.6, 44.2, 26.9, 4.0; IR (thin film) ν 3057, 2949, 2855, 2236, 1958, 1739, 1628, 1395, 1257, 1044, 741 cm^{-}

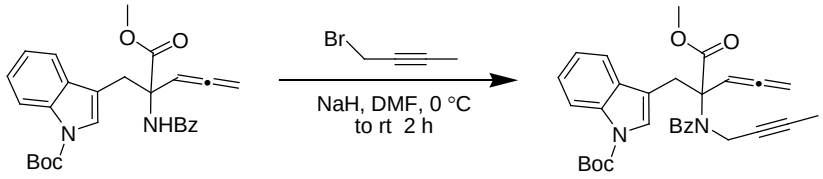
[1]; MS *m/z* (%) 335 (11), 334 (41), 275 (44), 192 (34), 174 (81), 143 (100); EI-HRMS calcd for $C_{20}H_{18}N_2O_3$ *m/z* [M^+] 334.1317; found 334.1323.



4-29a **4-30a**

Fused Pentacyclic Indolyl bicyclo[4.2.0]octa-1,6-diene 4-30a. A solution of **4-29a** (10.0 mg, 0.03 mmol) in freshly distilled DMF (0.3 mL) was heated under microwave irradiation in a Biotage Initiator microwave reactor at 225 °C for 7 min (Absorption level: very high; vial type: 0.2 – 0.5 mL; pre-stirring: 0; initial power: 0; dynamic deflector optimization: on; stir rate: 600; approximate ramp time: 4 min). An absence of starting material was observed by TLC after the described reaction time (R_f = 0.49 for both starting material and product, 60% ethyl acetate/hexanes; staining with PAA followed by a secondary water dip gives the product a green color and the starting material a brown/yellow color). The mixture was partitioned between ether and water and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic layers were washed with water (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **4-30a** (3.9 mg, 39%) as a white powder. (R_f = 0.49, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (bs, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 5.55 (A of an ABq, *J* = 17.5 Hz, 1H), 5.30 (s, 1H), 4.47 (B of an ABq, *J* = 17.5 Hz, 1H), 3.79 (A of an ABq, *J* = 15.3 Hz, 1H), 3.59 (s, 3H), 3.22 (A of an ABq, *J* = 16.5 Hz, 1H), 3.17 (B of an ABq, *J* = 16.5 Hz, 1H), 3.03 (B of an ABq, t, *J* = 15.3, 2.0 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.6, 153.3, 137.3, 136.6, 131.6, 129.5, 126.5, 121.9, 119.5, 118.1, 110.9, 106.4, 106.0, 70.7,

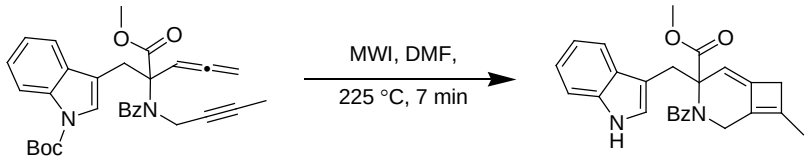
53.1, 40.4, 39.3, 32.9, 16.6; IR (thin film) ν 3310, 2951, 2913, 2858, 1732, 1663, 1623, 1432, 1333, 1199, 1043, 743 cm^{-1}; MS *m/z* (%) 357 (93, M + 23Na), 335 (40).



4-22b **4-35**

***Tert*-butyl 3-(2-(methoxycarbonyl)-2-(*N*-(but-2-ynyl)benzamido)penta-3,4-dienyl)-1*H*-indole-1-carboxylate) 4-35.** To a mixture of sodium hydride (108 mg of a 60% dispersion in mineral oil, 2.70 mmol) in DMF (6.8 mL), was added a solution of **4-22b** (623 mg, 1.35 mmol) in DMF (4.5 mL) via cannula and the mixture stirred for 5 min. 1-Bromo-2-butyne (0.24 mL, 2.70 mmol) was added via syringe. After 2.5 h, sodium hydride (54 mg of a 60% dispersion in mineral oil, 1.35 mmol) was added to the mixture, in one portion, followed by 1-bromo-2-butyne (0.12 mL, 1.35 mmol) via syringe. The reaction mixture was stirred for another 30 min, until no starting material was evident by TLC. The reaction mixture was poured into water and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted into ethyl acetate (4x). The combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (10% to 30% ethyl acetate/hexanes) to afford **4-35** (500 mg, 72%) as an amorphous, light brown solid. (R_f = 0.67, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, *J* = 7.2 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.50 (s, 1H), 7.45 – 7.35 (m, 3H), 7.32 – 7.19 (m, 2H), 5.97 (t, *J* = 6.6 Hz, 1H), 5.11 – 4.98 (m, 2H), 4.14 (A of an ABq, *J* = 14.4 Hz, 1H), 3.78 – 3.76 (m, 5H), 3.51 (B of an ABq, *J* = 14.4 Hz, 1H), 1.66 (s, 9H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 172.3, 171.3, 149.6, 135.8, 135.2, 131.7, 130.3, 128.2, 127.4, 125.8, 124.2, 122.6, 119.8, 115.1, 115.0, 91.2, 83.5, 80.4, 79.1, 75.8, 69.1, 52.3, 39.7, 29.1, 28.2, 3.1; IR (thin film) ν 3058,

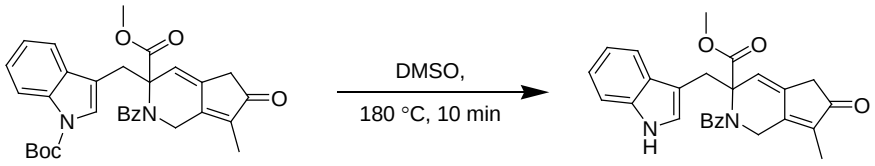
2980, 2949, 2228, 1958, 1735, 1640, 1453, 1369, 1259, 1157, 1085, 856, 742 cm^{-1}; MS *m/z* (%) 513 (11), 512 (36), 412 (49), 411 (25), 283 (67), 174 (78), 105 (100); EI-HRMS calcd for $C_{31}H_{32}N_2O_5$ *m/z* $[M]^+$ 512.2311; found 512.2307.



4-35 **4-36**

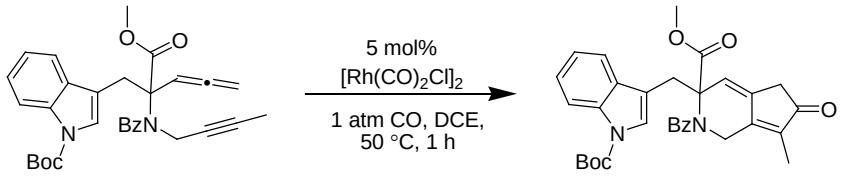
Heterocyclic bicyclo[4.2.0]octa-1,6-diene 4-36. A solution of **4-35** (503 mg, 0.98 mmol) in freshly distilled DMF (9.8 mL) was heated under microwave irradiation in a Biotage Initiator microwave reactor at 225 °C for 7 min (Absorption level: very high; vial type: 10 – 20 mL; pre-stirring: 0; initial power: 0; dynamic deflector optimization: on; stir rate: 600; approximate ramp time: 4 min). No starting material was evident by TLC after the described reaction time. The mixture was partitioned between ether and water and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic layers were washed with water (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to afford **4-36** (203 mg, 50%) as an amorphous brown solid (please note that the indolyl Boc group is also removed during this reaction). (R_f = 0.13, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (bs, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.34 – 7.26 (m, 4H), 7.20 – 7.07 (m, 4H), 7.01 (d, *J* = 1.2 Hz, 1H), 5.10 (s, 1H), 4.41 (A of an ABq, *J* = 14.7 Hz, 1H), 3.82 (s, 3H), 3.80 – 3.74 (m, 4H), 3.40 (B of an ABq, *J* = 14.7 Hz, 1H), 2.99 (m, 2H), 2.65 – 2.59 (m, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.1, 138.9, 137.0, 136.4, 135.8, 134.4, 129.0, 128.6, 128.3, 126.2, 123.5, 121.7, 119.7, 119.3, 110.9, 110.5, 105.9, 66.1, 52.5, 43.7, 39.1, 30.0, 15.1; IR (thin film) ν 3351,

3056, 2947, 2853, 1735, 1626, 1405, 1243, 1057, 740 cm^{-1}; MS *m/z* (%) 412 (32), 282 (42), 130 (74), 105 (100) ; EI-HRMS calcd for $C_{26}H_{24}N_2O_3$ *m/z* [M^+] 412.1787; found 412.1780.



4-37b **4-37a**

Heterocyclic bicyclo[4.3.0]nona-2,7-dien-1-one 4-37a. A solution of **4-37b** (239 mg, 0.44 mol) in DMSO (4.4 mL) in a 10 mL round bottomed flask was placed into a silicone oil bath preheated to 180 °C for 15 min until no starting material was evident by TLC. The reaction mixture was cooled to room temperature and partitioned between water and ether. The layers were separated and the aqueous layer extracted with ether (2x). The combined organic layers were washed with water (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (50% to 60% ethyl acetate/hexanes) to afford **4-37a** (152 mg, 78%) as an amorphous, brown solid. (R_f = 0.38, 60% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.23 – 7.15 (m, 3H), 7.10 (dt, *J* = 6.9, 1.2 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 5.83 (s, 1H), 4.42 (A of an ABq, *J* = 14.7 Hz, 1H), 4.30 (A of an ABq, *J* = 17.7 Hz, 1H), 3.81 (s, 3H), 3.49 (B of an ABq, *J* = 14.7 Hz, 1H), 3.04 (A of and ABq, *J* = 21.6 Hz, 1H), 2.95 (B of an ABq, *J* = 17.7 Hz, 1H), 2.95 (B of an ABq, *J* = 21.6 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 171.9, 171.7, 155.2, 135.9, 135.8, 135.6, 134.1, 129.9, 128.6, 128.0, 126.5, 123.6, 122.0, 121.5, 119.6, 119.2, 111.2, 109.8, 66.4, 52.8, 44.5, 37.4, 29.6, 7.7; IR (thin film) ν 3351, 3056, 2947, 2853, 1735, 1626, 1405, 1243, 1057, 740 cm^{-1}; MS *m/z* (%) 412 (32), 282 (42), 130 (74), 105 (100) ; EI-HRMS calcd for $C_{26}H_{24}N_2O_3$ *m/z* [M^+] 412.1787; found 412.1780.

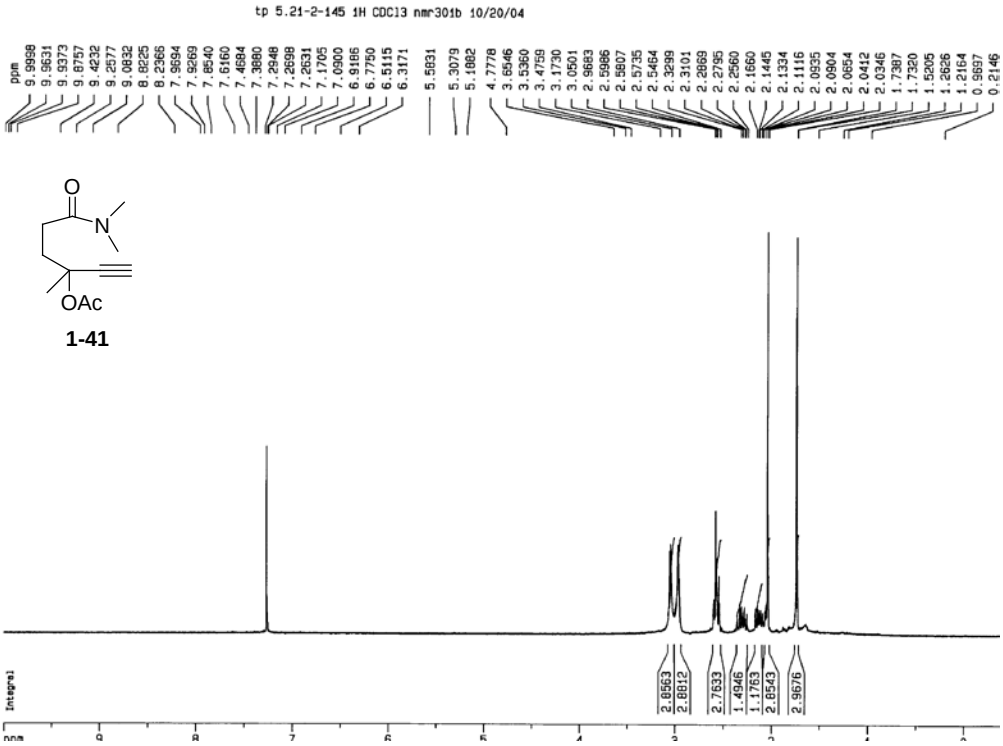


4-35 **4-37b**

Heterocyclic Bicyclo[4.3.0]nona-2,7-dien-1-one 4-37b. Allene-yne **4-35** (204 mg, 0.398 mmol) and rhodium biscarbonyl chloride dimer (7.8 mg, 0.02 mmol, 5 mol%) were dissolved in DCE (4 mL) in a septum-sealed 10 mL round bottomed flask. The headspace was evacuated under vacuum and filled with CO gas three times then the reaction mixture was placed into an oil bath preheated to 50 °C. The reaction mixture was stirred for 1 h until no starting material was evident by TLC. The mixture was concentrated to approximately 1 – 2 mL under vacuum and directly chromatographed on silica gel (40% ethyl acetate/hexanes) to afford **4-37b** (189 mg, 88%) as an amorphous, brown solid. (R_f = 0.09, 30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.27 (m, 5H), 7.24 – 7.19 (m, 3H), 5.81 (s, 1H), 4.35 (A of an ABq, *J* = 14.7 Hz, 1H), 4.33 (A of an ABq, *J* = 18.0 Hz, 1H), 3.82 (s, 3H), 3.43 (B of an ABq, *J* = 14.7 Hz, 1H), 3.21 (B of an ABq, *J* = 18.0 Hz, 1H), 3.02 (A of an ABq, *J* = 20.1 Hz, 1H), 2.91 (B of an ABq, *J* = 20.7 Hz, 1H), 1.62 (s, 9H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 171.9, 171.5, 154.7, 149.3, 136.2, 135.6, 135.1, 134.4, 130.8, 130.0, 128.6, 126.4, 124.8, 124.6, 122.7, 121.0, 119.6, 115.1, 115.1, 83.8, 65.8, 53.0, 44.7, 37.3, 29.4, 28.1, 7.9; IR (thin film) ν 3056, 2980, 2950, 1736, 1707, 1645, 1453, 1372, 1258, 1157, 1073, 736 cm^{-1}; MS *m/z* (%) 540 (69), 525 (30), 510 (19), 311 (46), 230 (35); EI-HRMS calcd for $C_{32}H_{32}N_2O_6$ *m/z* [M^+] 540.2260; found 540.2258.

APPENDIX

SPECTRAL DATA


tp 5.21-2-145 1H CDCl3 nmr301b 10/20/04
ppm
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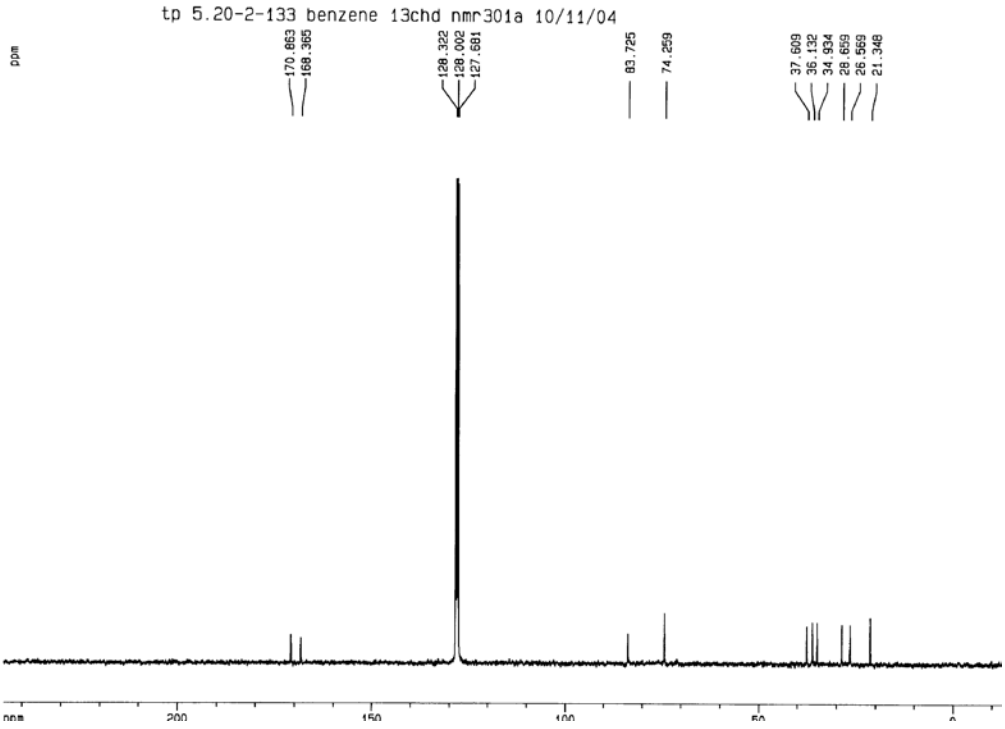
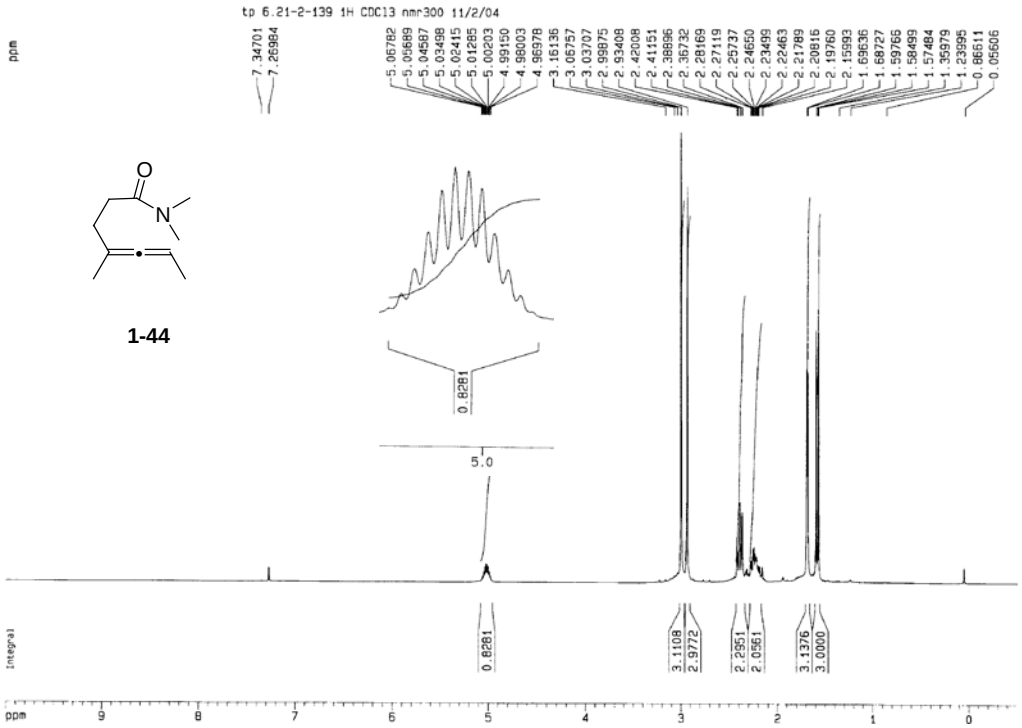
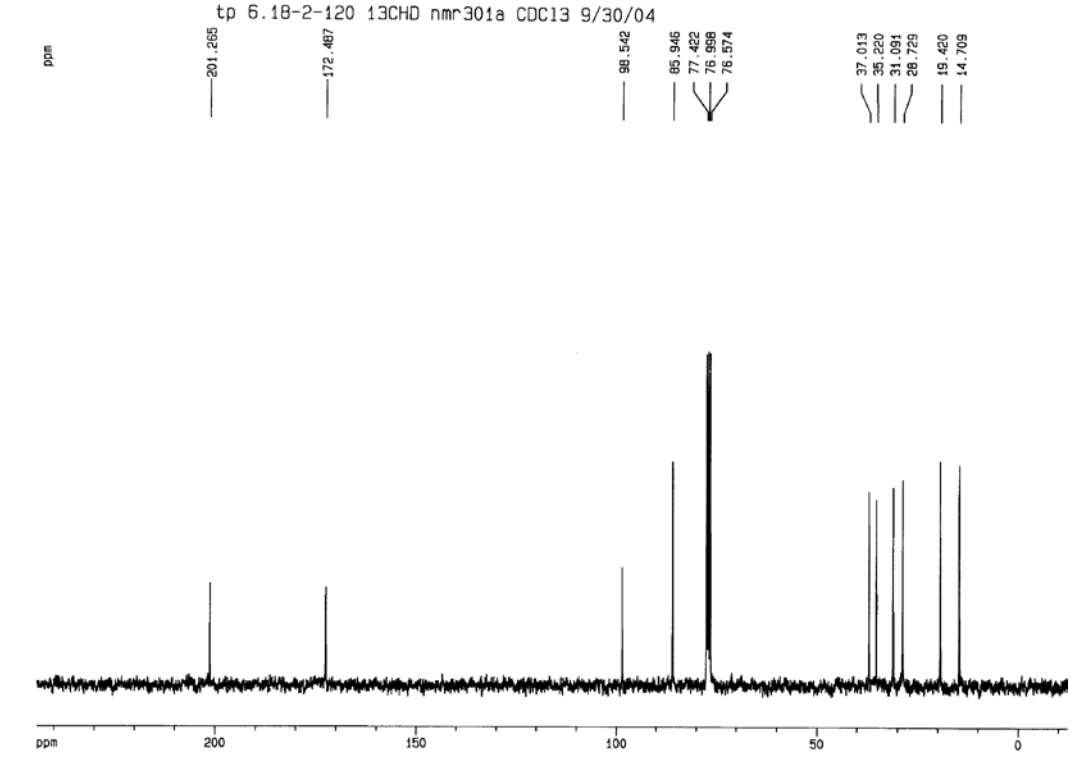
9.9631
9.9373
9.8757
9.4232
9.2577
9.0832
8.8825
8.2366
7.9894
7.9269
7.8540
7.6160
7.4684
7.3880
7.2948
7.2698
7.2631
7.1705
7.0900
6.9186
6.7780
6.5115
6.3171
5.5831
5.3079
5.1882
4.7778
3.6546
3.5360
3.4759
3.1730
3.0501
2.9683
2.5986
2.5807
2.5735
2.5464
2.3299
2.3101
2.2869
2.2795
2.2560
2.1660
2.1445
2.1334
2.1116
2.0935
2.0904
2.0654
2.0412
2.0346
1.7387
1.7320
1.5205
1.2626
1.2164
0.9697
0.2146
O
N
OAc
1-41
Integral
2.0563
2.0812
2.7633
1.4946
1.1763
2.8543
2.9676


tp 5.20-2-133 benzene 13chd nmr301a 10/11/04
ppm
170.863
168.365
128.322
128.002
127.681
83.725
74.259
37.609
36.132
34.934
28.659
26.569
21.348


tp 6.21-2-139 1H CDCl3 nmr300 11/2/04
ppm
7.34701
7.26984
5.06782
5.05689
5.04587
5.03498
5.02415
5.01285
5.00203
4.99150
4.98003
4.96978
3.16136
3.06757
3.03707
2.99875
2.93408
2.42008
2.41151
2.38896
2.36732
2.28169
2.27119
2.25737
2.24650
2.23499
2.22463
2.21789
2.20816
2.19760
2.15593
1.69636
1.68727
1.59766
1.58499
1.57484
1.35979
1.23995
0.86611
0.05606
O
N
1-44
0.8281
5.0
integral
0.8281
3.1108
2.9772
2.2951
2.0561
3.1376
3.0000
ppm
9
8
7
6
5
4
3
2
1
0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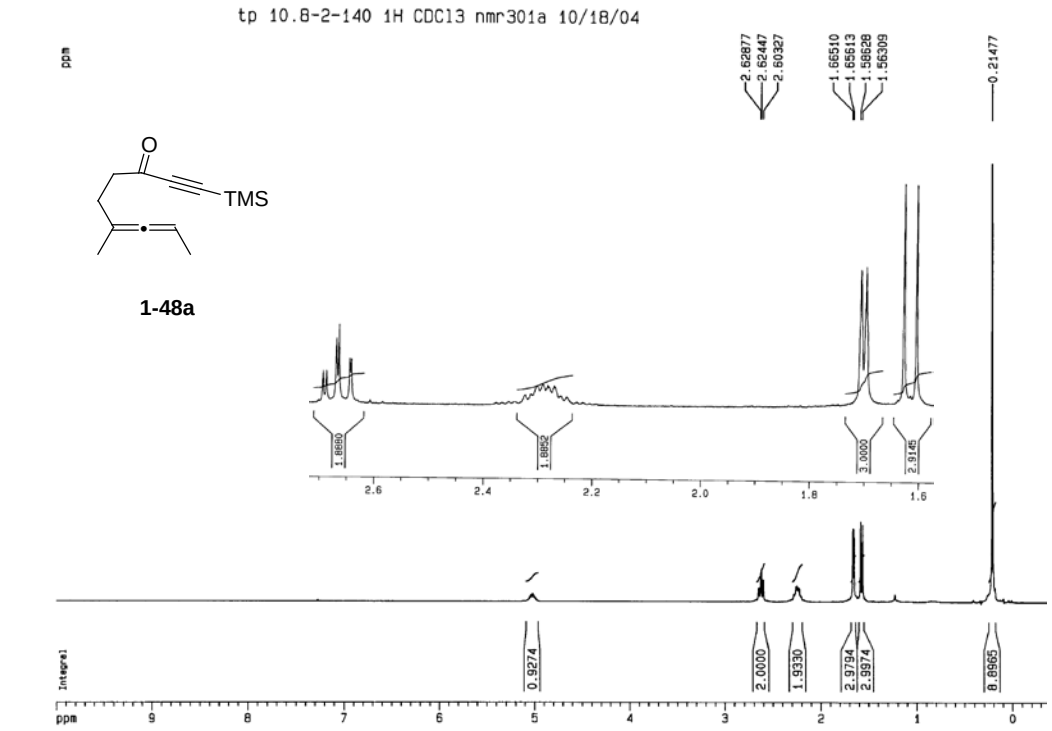
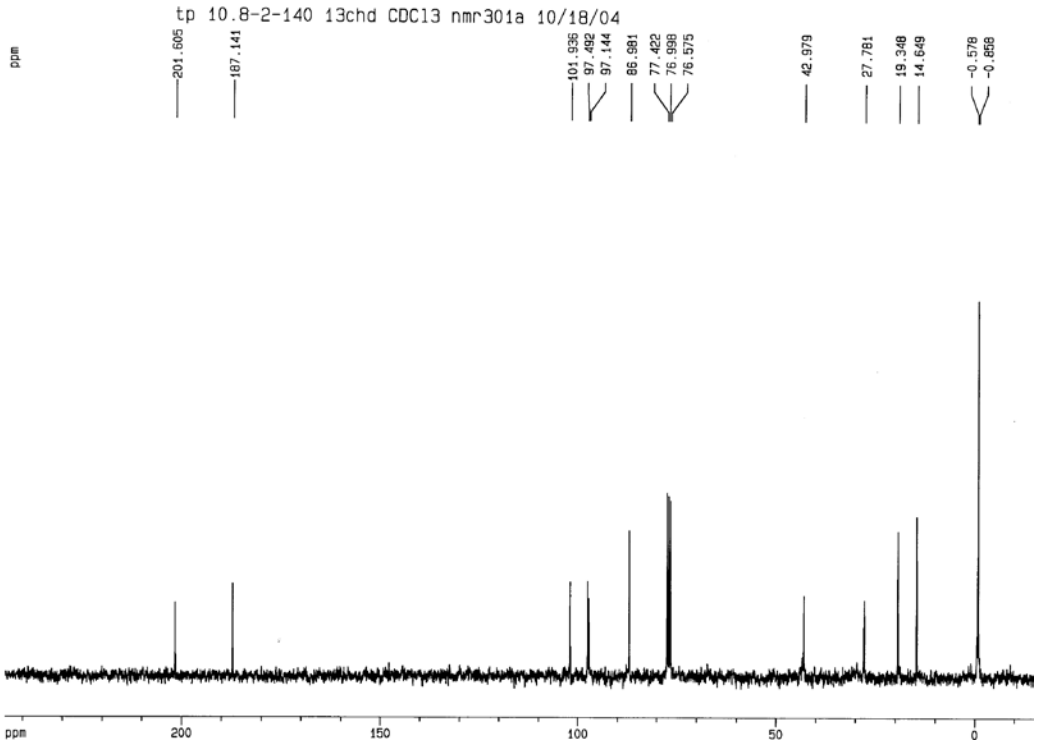
201.265
172.487
98.542
85.946
77.422
76.998
76.574
37.013
35.220
31.091
28.729
19.420
14.709
ppm
200
150
100
50
0


tp 10.8-2-140 1H CDCl3 nmr301a 10/18/04
ppm
2.62877
2.62447
2.60327
1.66510
1.65513
1.58628
1.56309
0.21477
O
TMS
1.8680
1.8852
3.0000
2.9145
Integral
0.9274
2.0000
1.9330
2.9794
2.9974
8.6965
ppm

1-48a


tp 10.8-2-140 13chd CDCl3 nmr301a 10/18/04
ppm
201.605
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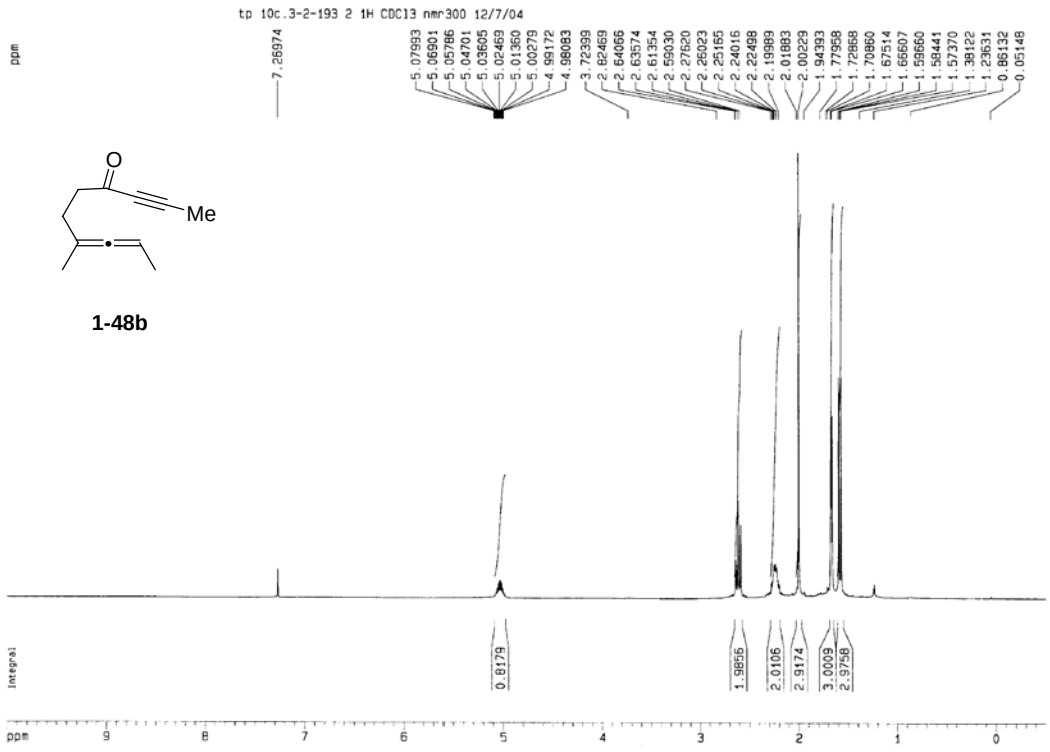
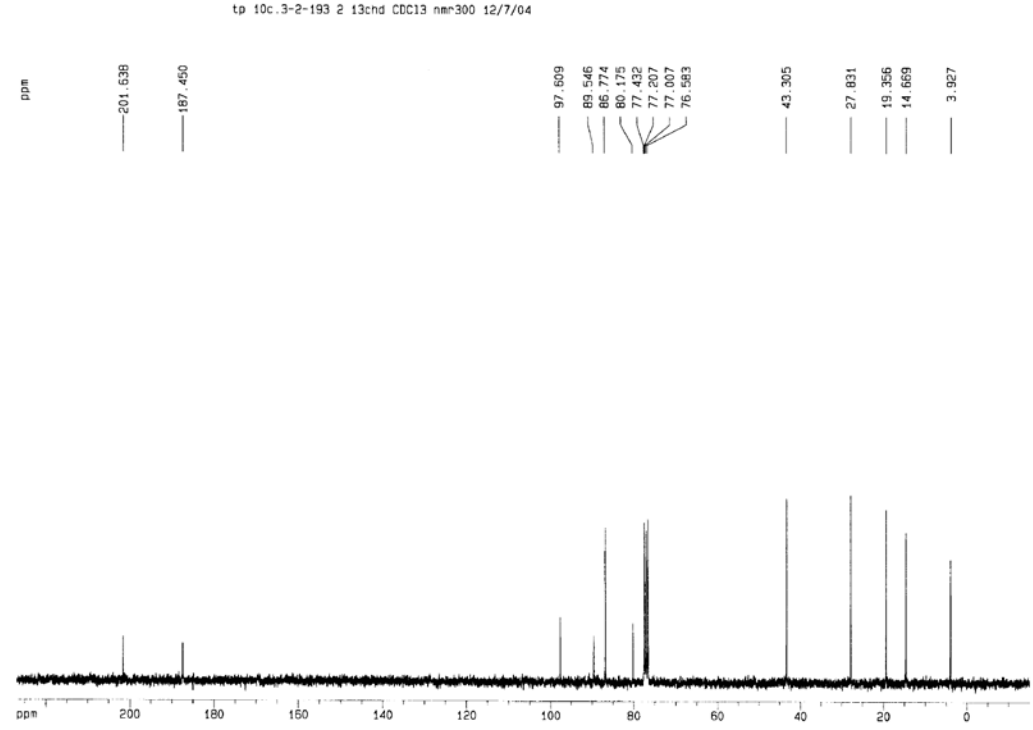
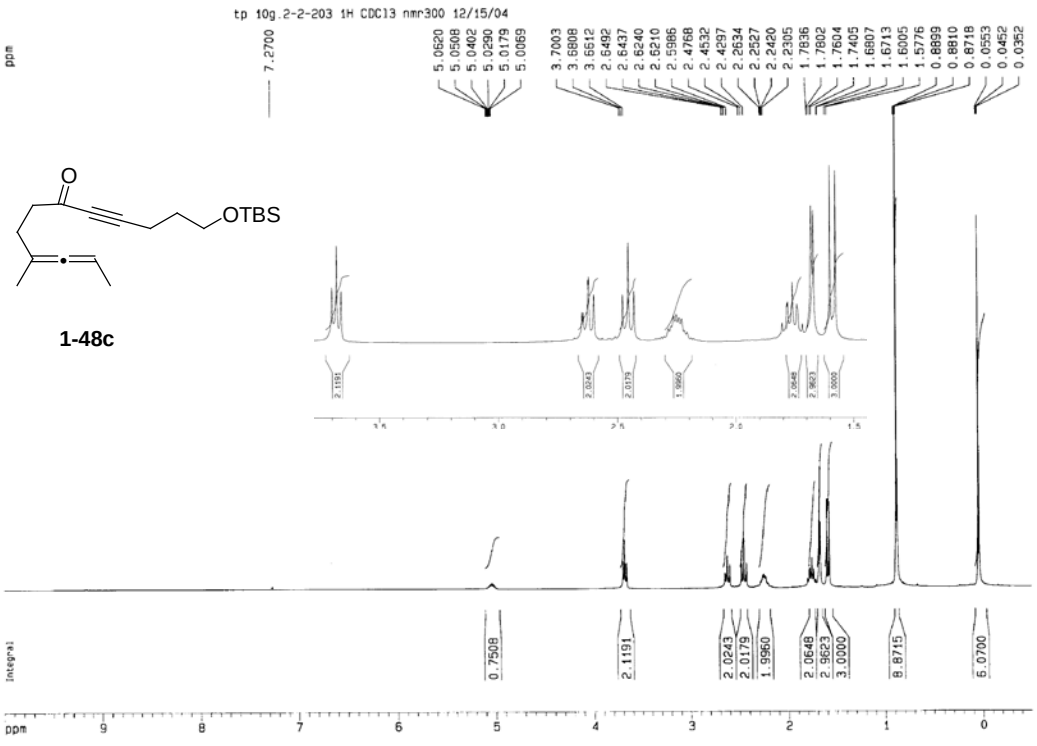
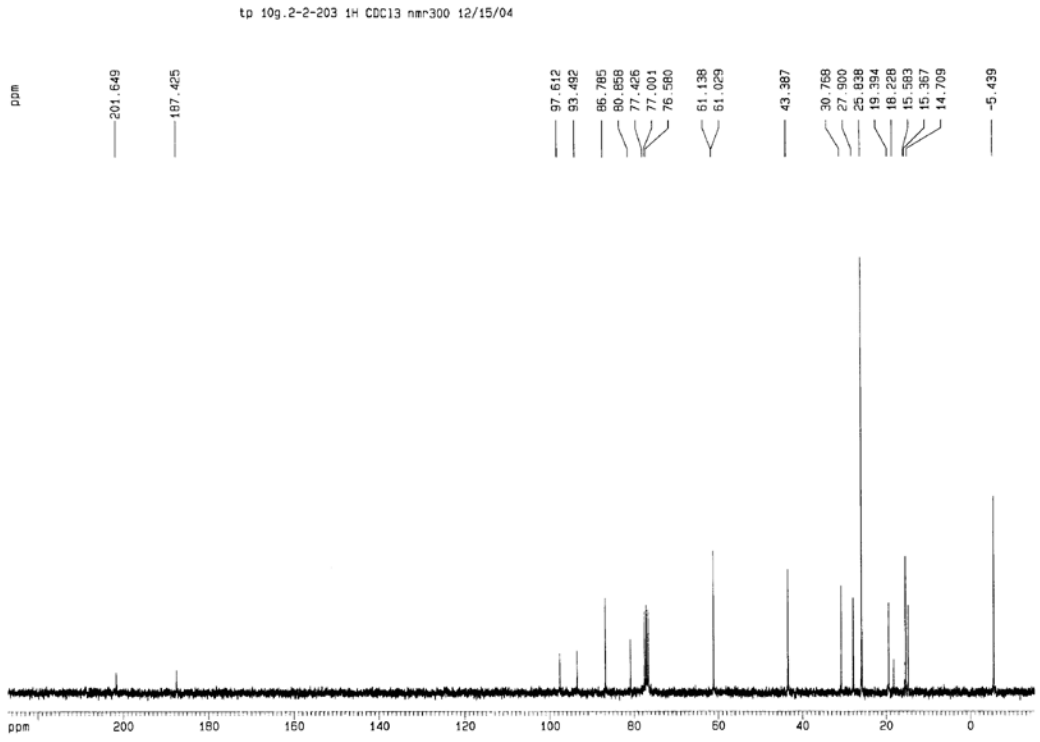
101.936
97.492
97.144
86.981
77.422
76.998
76.575
42.979
27.781
19.348
14.649
-0.578
-0.858
ppm

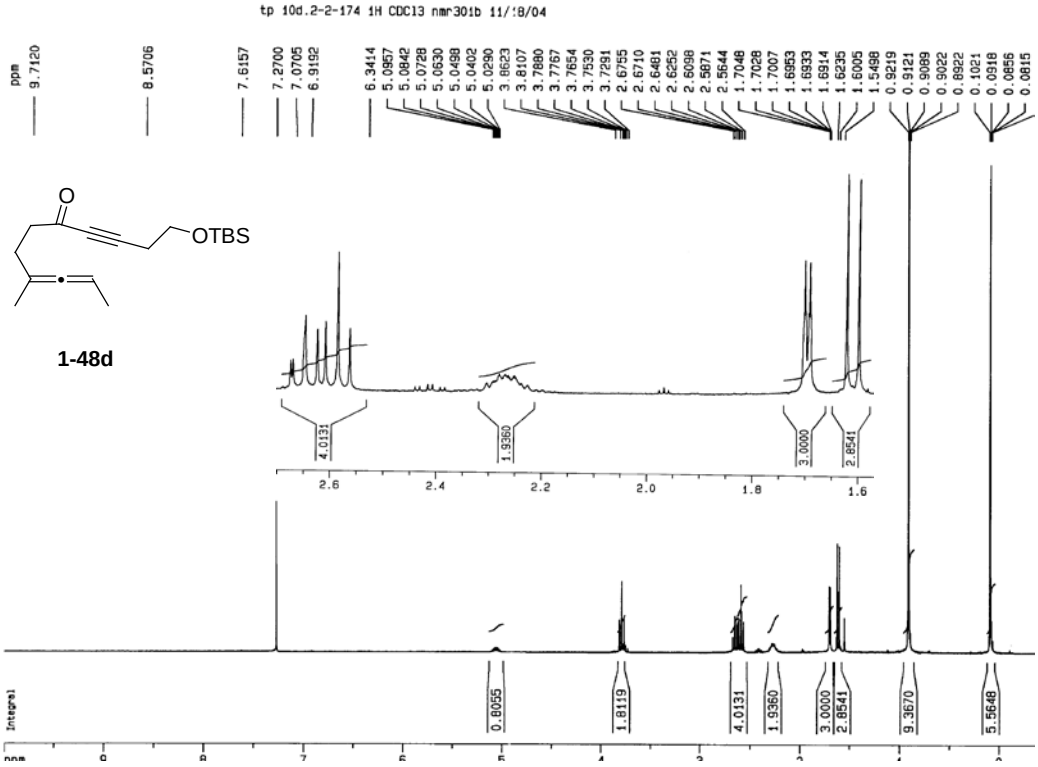

tp 10c.3-2-193 2 1H CDCl3 nmr300 12/7/04
ppm
7.26974
5.07993
5.06901
5.05786
5.04701
5.03605
5.02469
5.01360
5.00279
4.99172
4.98083
3.72399
2.82469
2.64066
2.63574
2.61354
2.59030
2.27620
2.26023
2.25165
2.24016
2.22498
2.19989
2.01883
2.00229
1.94393
1.77958
1.72868
1.70860
1.67514
1.66607
1.59660
1.58441
1.57370
1.38122
1.29631
0.86132
0.05148
O
Me
Integral
0.8179
1.9856
2.0106
2.9174
3.0009
2.9758
ppm
9
8
7
6
5
4
3
2
1
0

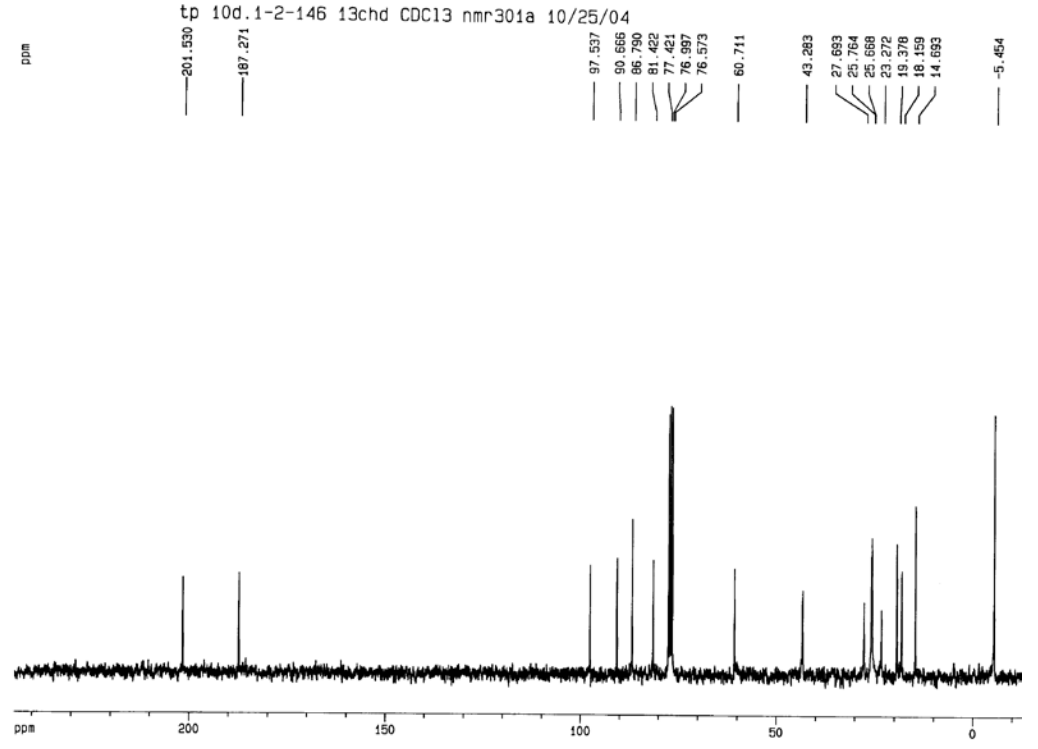
1-48b

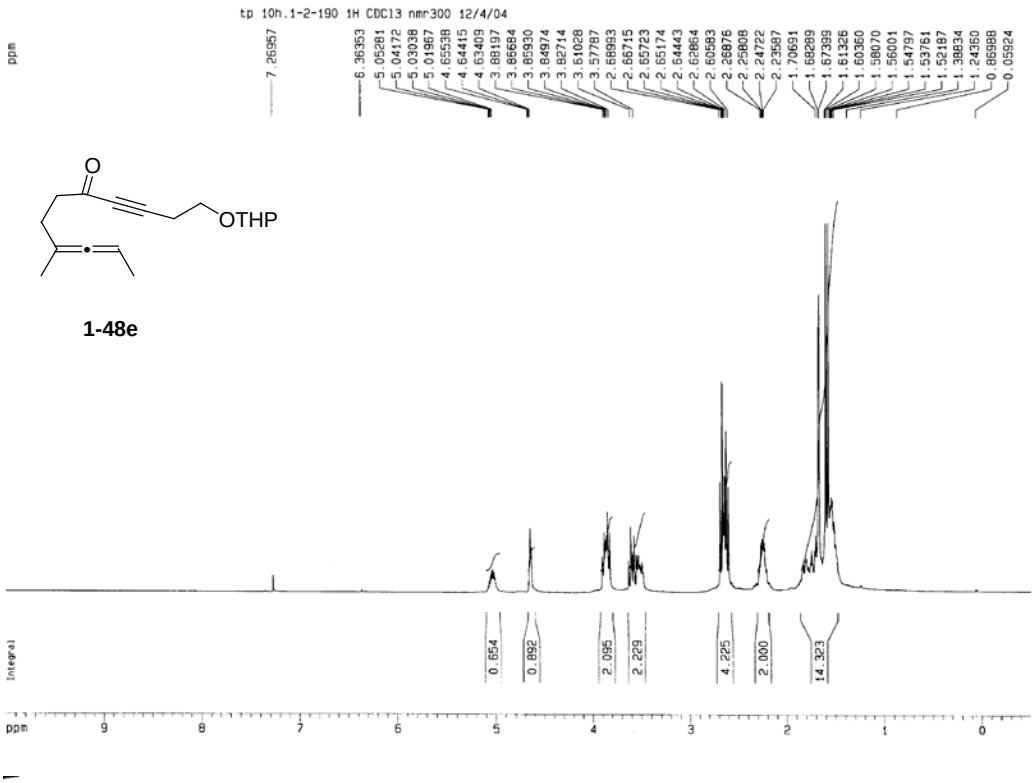

tp 10c.3-2-193 2 13cnd CDCl3 nmr300 12/7/04
ppm
201.638
187.450
97.609
89.546
86.774
80.175
77.432
77.207
77.007
76.583
43.305
27.831
19.356
14.669
3.927
ppm
200
180
160
140
120
100
80
60
40
20
0


tp 10g.2-2-203 1H CDCl3 nmr300 12/15/04
ppm
7.2700
5.0620
5.0508
5.0402
5.0290
5.0179
5.0069
3.7003
3.6808
3.6612
2.6492
2.6437
2.6240
2.6210
2.5986
2.4768
2.4532
2.4297
2.2634
2.2527
2.2420
2.2305
1.7836
1.7802
1.7604
1.7405
1.6807
1.6713
1.6005
1.5776
0.8899
0.8810
0.8718
0.0553
0.0452
0.0352
O
OTBS
1-48c
integral
0.7508
2.1191
2.0243
2.0179
1.9960
2.0648
2.9623
3.0000
8.8715
6.0700
ppm

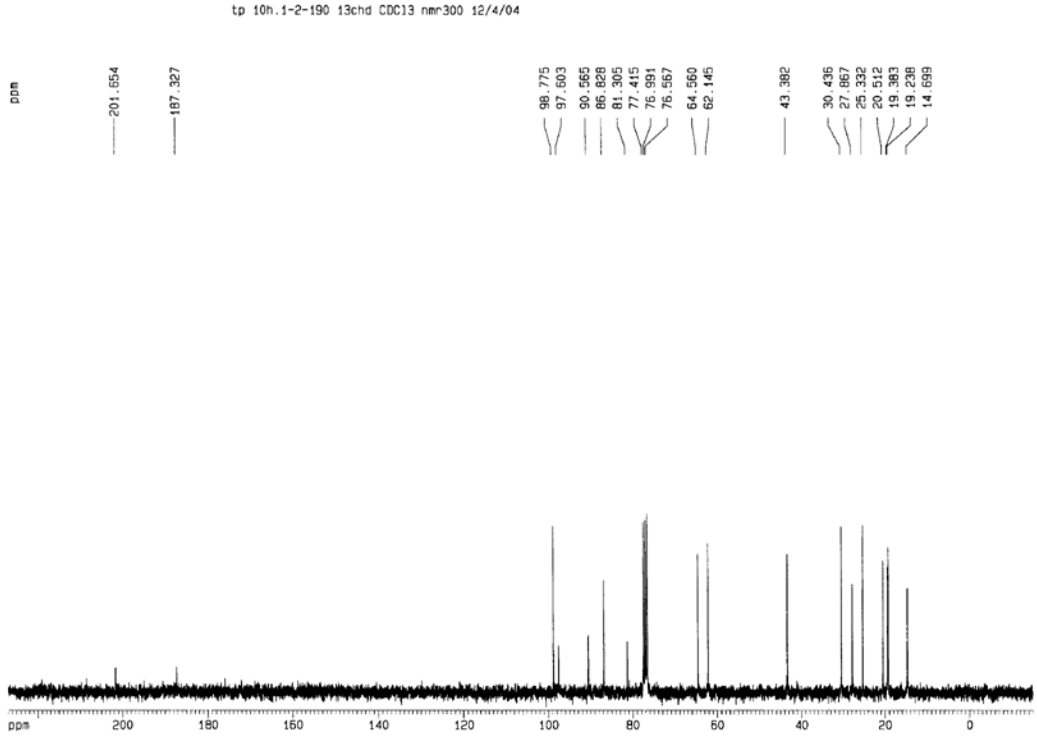

tp 10g.2-2-203 1H CDCl3 nmr300 12/15/04
ppm
201.649
187.425
97.612
93.492
86.785
80.858
77.426
77.001
76.580
61.138
61.029
43.387
30.768
27.900
25.838
19.394
18.228
15.583
15.367
14.709
-5.439
ppm


tp 10d.2-2-174 1H CDCl3 nmr301b 11/18/04
O
OTBS
1-48d


tp 10d.1-2-146 13chd CDCl3 nmr301a 10/25/04


tp 10h.1-2-190 1H CDCl3 nmr300 12/4/04
ppm
7.26957
6.36353
5.05281
5.04172
5.03038
5.01967
4.65538
4.64415
4.63409
3.88197
3.86684
3.85930
3.84974
3.82714
3.61028
3.57787
2.68993
2.66715
2.65723
2.65174
2.64443
2.62864
2.60583
2.26876
2.25808
2.24722
2.23587
1.70691
1.68289
1.67399
1.61326
1.60360
1.58070
1.56001
1.54797
1.53761
1.52187
1.38834
1.24360
0.86988
0.05924
O
OTHP
Integral
0.654
0.892
2.095
2.229
4.225
2.000
14.323
ppm
9
8
7
6
5
4
3
2
1
0

1-48e


tp 10h.1-2-190 13chd CDCl3 nmr300 12/4/04
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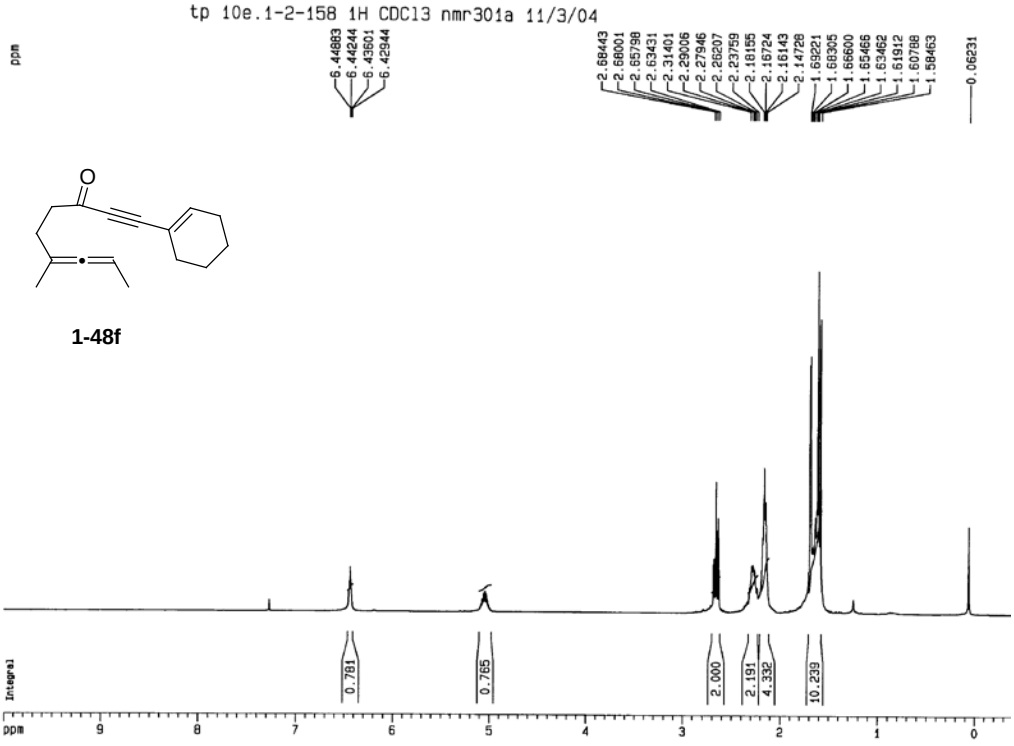
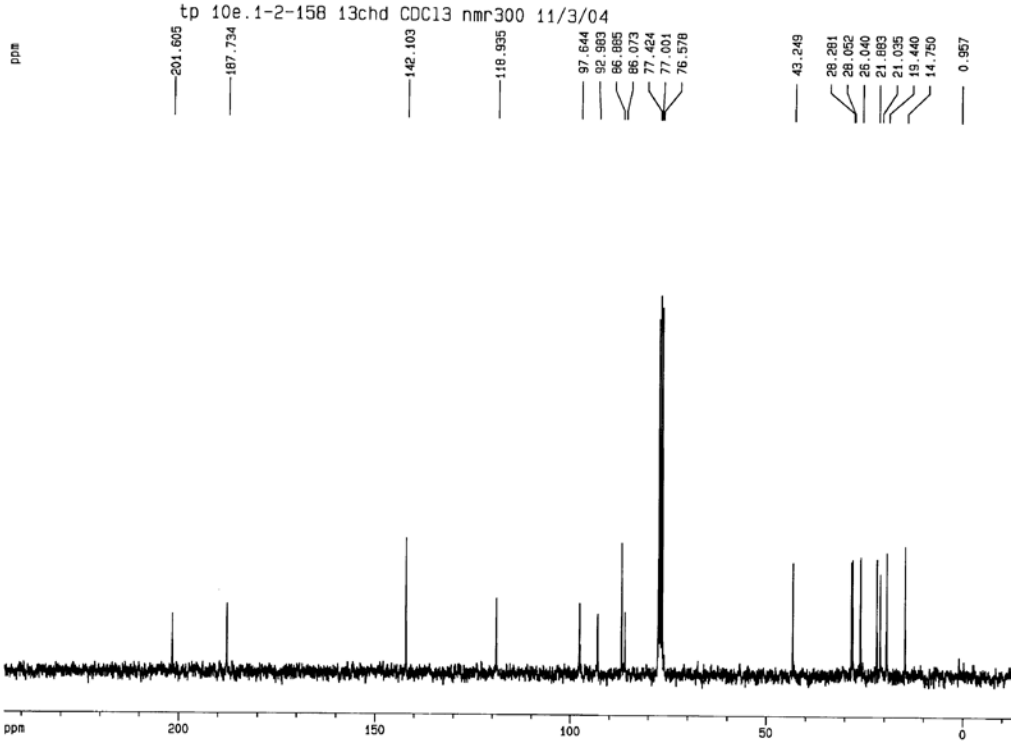
98.775
97.603
90.565
86.828
81.305
77.415
76.991
76.567
64.560
62.145
43.382
30.436
27.867
25.332
20.512
19.383
19.238
14.699
ppm
200
180
160
140
120
100
80
60
40
20
0


tp 10e.1-2-158 1H CDCl3 nmr301a 11/3/04
ppm
6.44863
6.44244
6.43601
6.42944
2.68443
2.68001
2.65798
2.63431
2.31401
2.29006
2.27946
2.26207
2.23759
2.18155
2.16724
2.16143
2.14728
1.69221
1.68305
1.66600
1.65466
1.63462
1.61912
1.60788
1.58463
0.06231
O
1-48f
Integral
0.781
0.765
2.000
2.191
4.332
10.239
ppm
9
8
7
6
5
4
3
2
1
0


tp 10e.1-2-158 13chd CDCl3 nmr300 11/3/04
ppm
201.605
187.734
142.103
118.935
97.644
92.983
86.885
86.073
77.424
77.001
76.578
43.249
28.281
28.052
26.040
21.883
21.035
19.440
14.750
0.957
ppm
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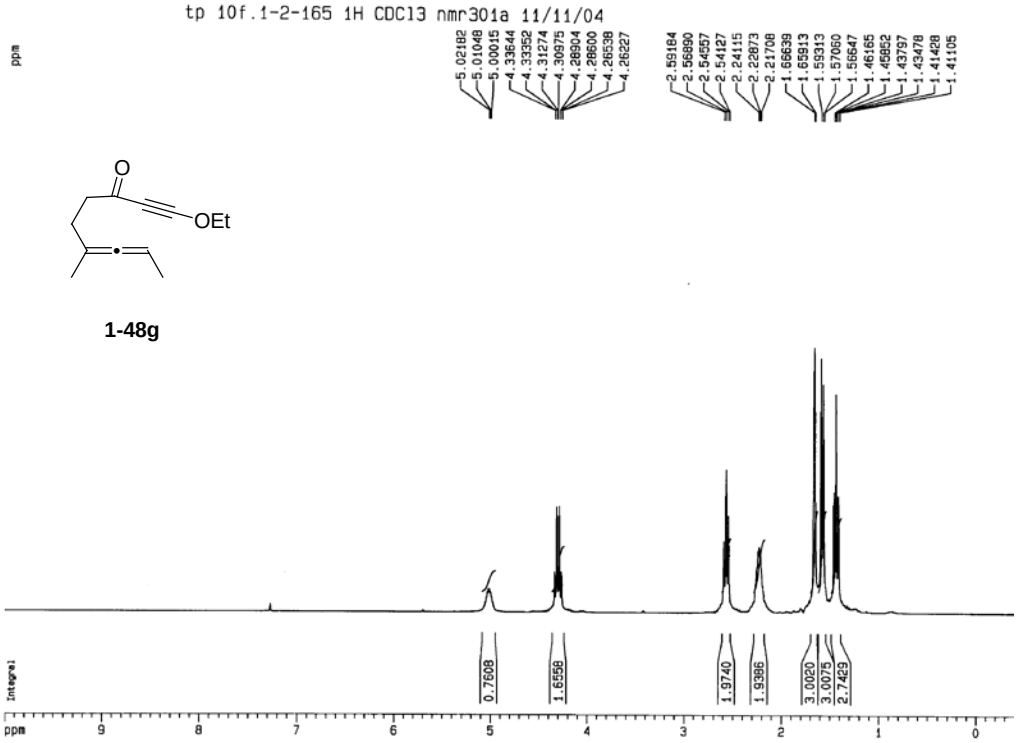
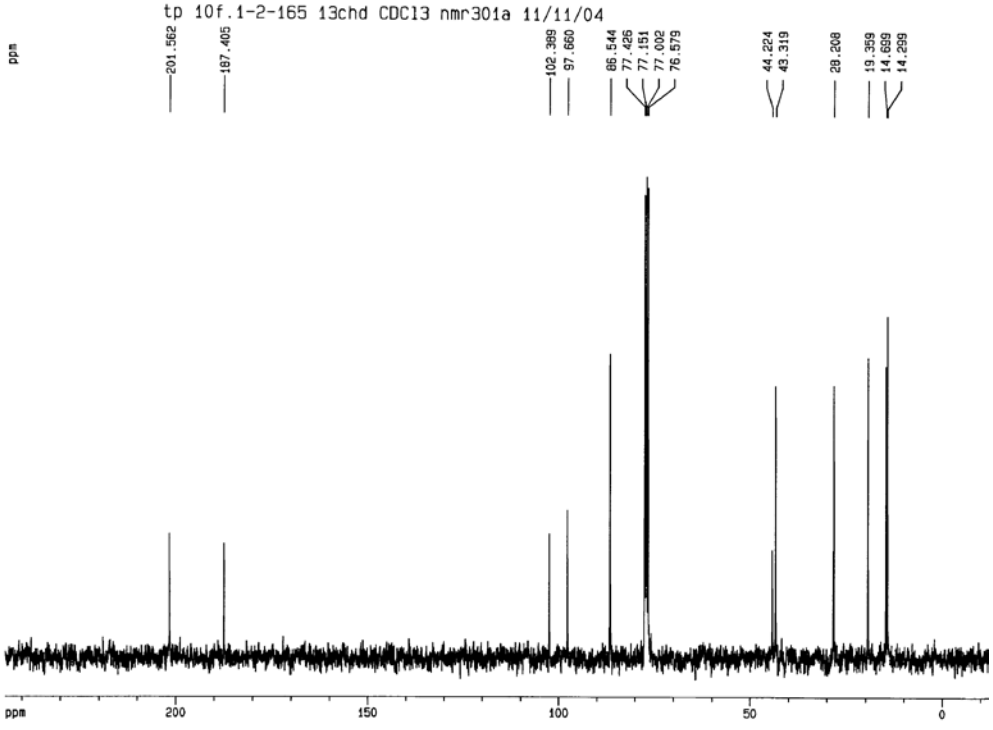
150
100
50
0


tp 10f.1-2-165 1H CDCl3 nmr301a 11/11/04
ppm
5.02182
5.01049
5.00015
4.33644
4.33352
4.31274
4.30975
4.28904
4.28600
4.26538
4.26227
2.59164
2.56890
2.54557
2.54127
2.24115
2.22873
2.21708
1.66639
1.65913
1.59313
1.57060
1.56647
1.46165
1.45852
1.43797
1.43478
1.41428
1.41105
O
OEt
1-48g
Integral
0.7608
1.6556
1.9740
1.9386
3.0020
3.0075
2.7429
ppm
9
8
7
6
5
4
3
2
1
0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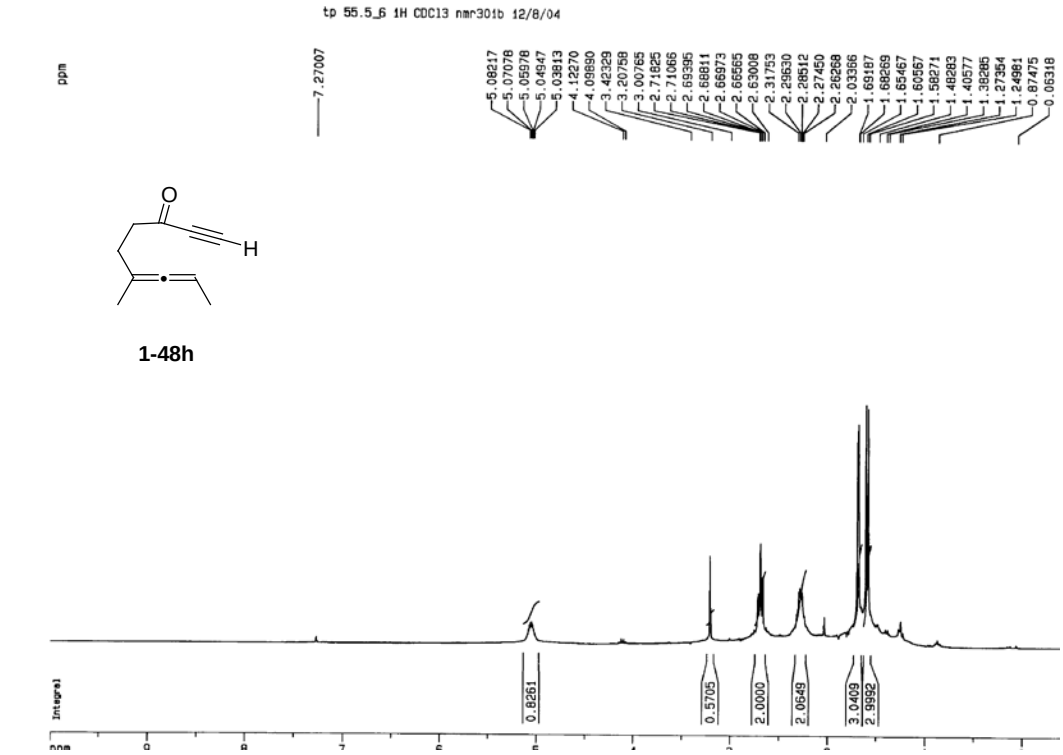
ppm
201.562
187.405
102.389
97.660
86.544
77.426
77.151
77.002
76.579
44.224
43.319
28.208
19.359
14.699
14.299
ppm
200
150
100
50
0


tp 55.5_6 1H CDCl3 nmr301b 12/8/04
ppm
7.27007
5.08217
5.07078
5.05978
5.04947
5.03813
4.12270
4.09890
3.42329
3.20758
3.00765
2.71825
2.71066
2.69395
2.68811
2.66973
2.66565
2.63008
2.31753
2.29530
2.28512
2.27450
2.26268
2.03366
1.69187
1.68269
1.65467
1.60557
1.58271
1.48283
1.40577
1.38285
1.27354
1.24981
0.87475
0.06318
O
H
Integral
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0.5705
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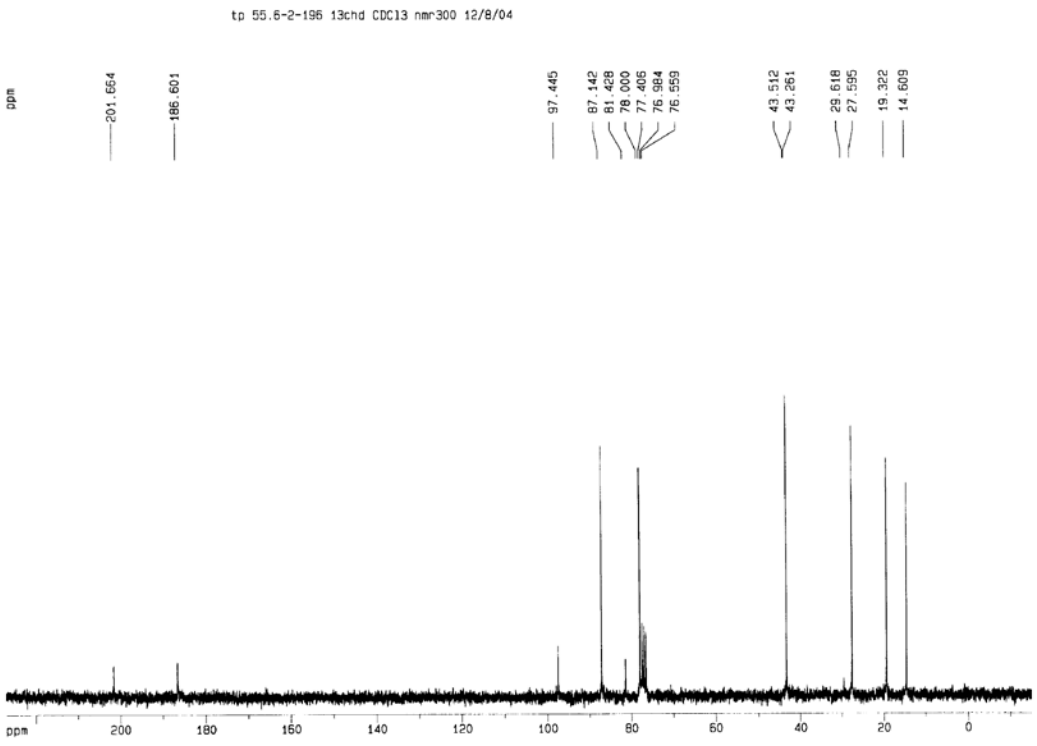
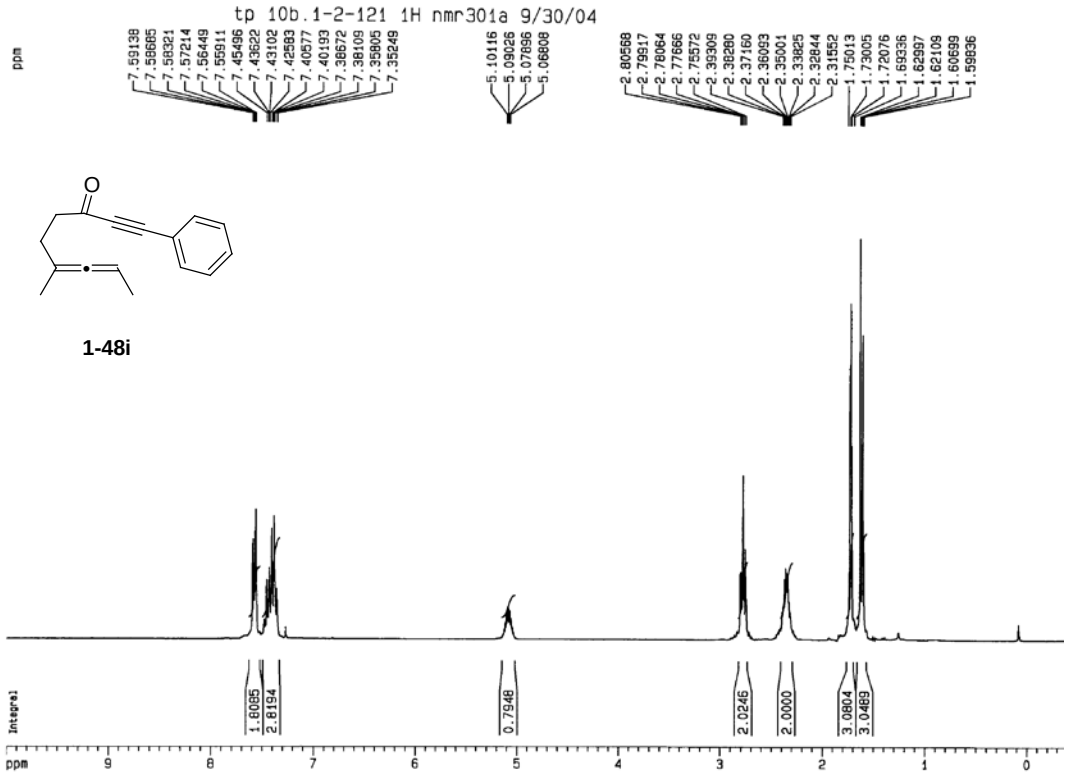
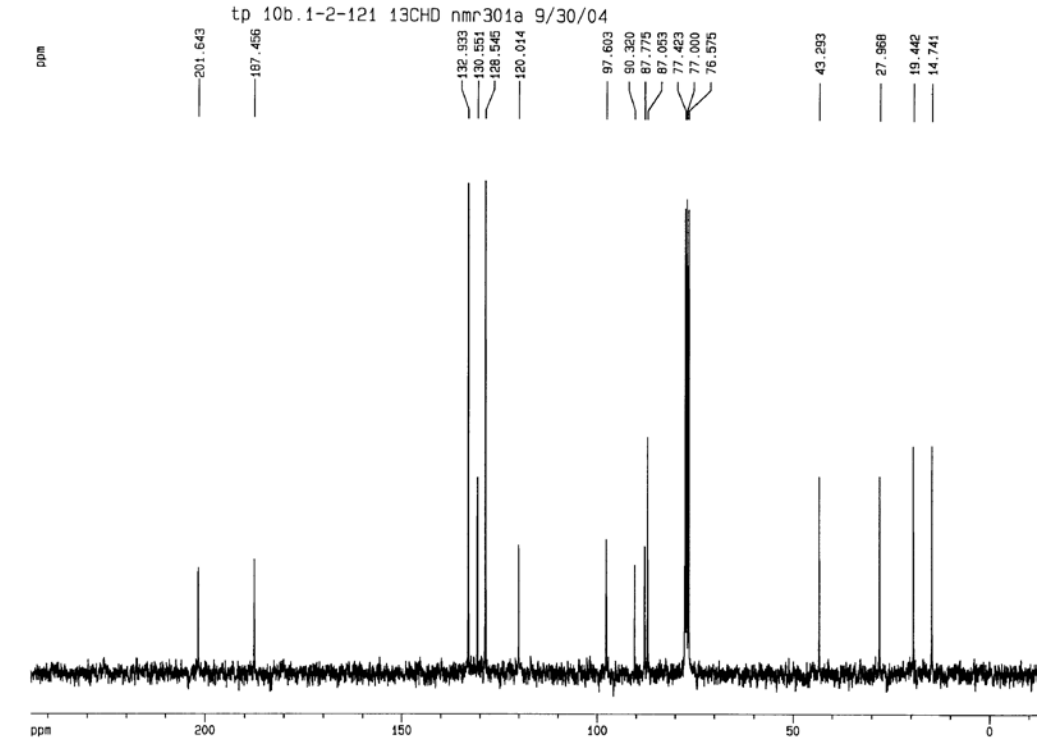
2.0549
3.0409
2.9992

1-48h


tp 55.6-2-196 13chd CDCl3 nmr300 12/8/04
ppm
201.664
186.601
97.445
87.142
81.428
78.000
77.406
76.984
76.559
43.512
43.261
29.618
27.595
19.322
14.609
200
180
160
140
120
100
80
60
40
20
0


tp 10b.1-2-121 1H nmr301a 9/30/04
ppm
7.59138
7.58685
7.58321
7.57214
7.56449
7.55911
7.45496
7.43622
7.43102
7.42583
7.40577
7.40193
7.38672
7.38109
7.35805
7.35249
5.10116
5.09026
5.07896
5.06808
2.80568
2.79917
2.78064
2.77666
2.75572
2.39309
2.38280
2.37160
2.36093
2.35001
2.33825
2.32644
2.31552
1.75013
1.73005
1.72076
1.69336
1.62997
1.62109
1.60699
1.59836
O
1-48i
Integral
1.8085
2.8194
0.7948
2.0246
2.0000
3.0804
3.0489
ppm
9
8
7
6
5
4
3
2
1
0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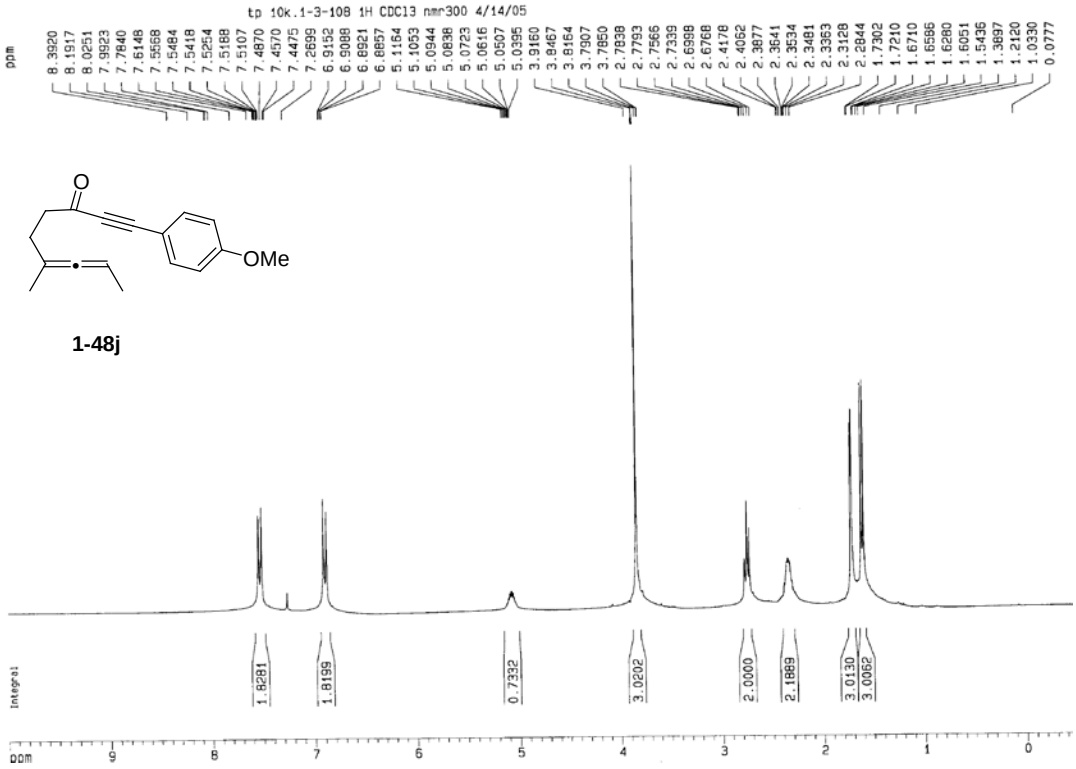
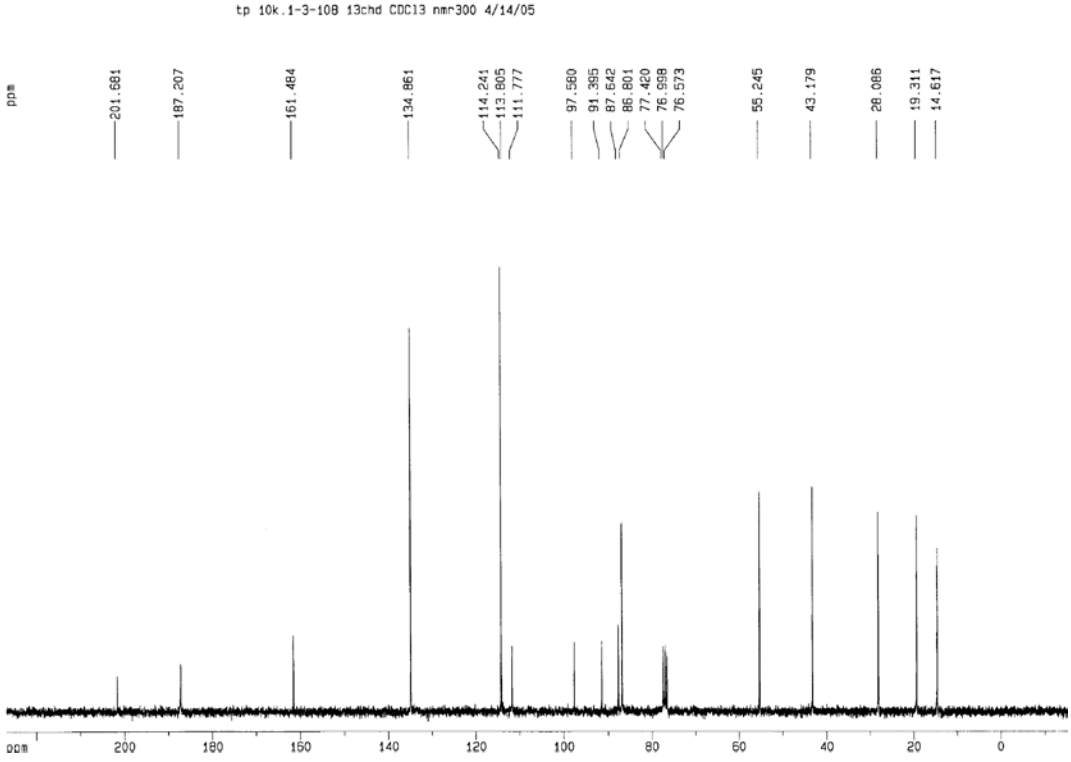
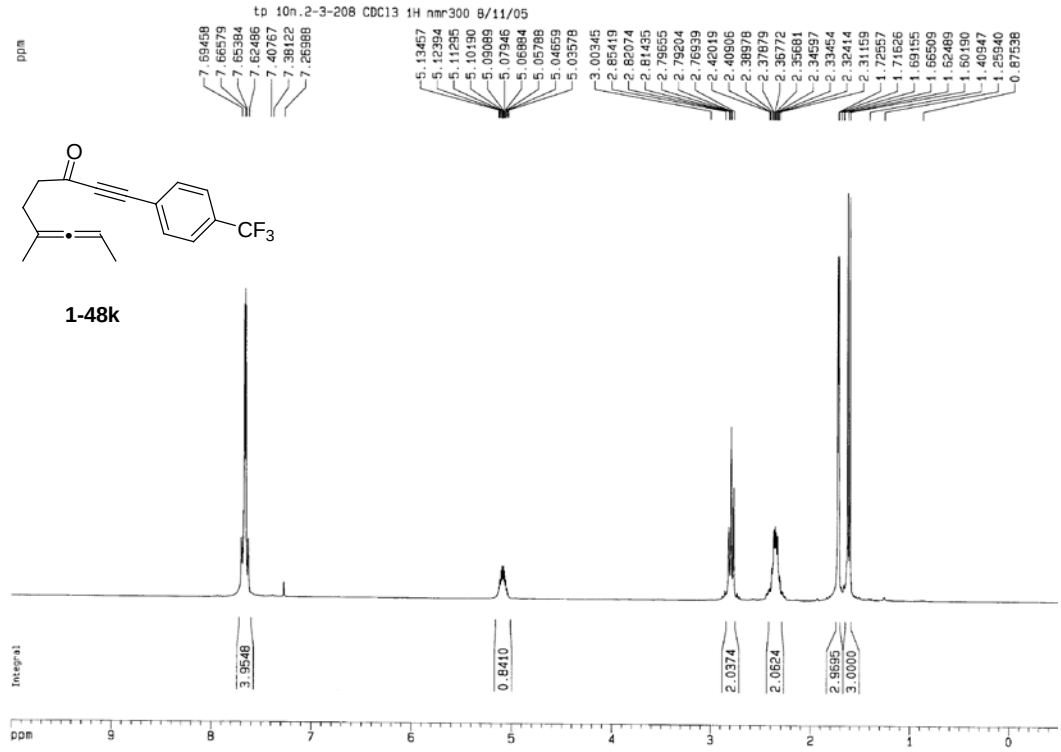
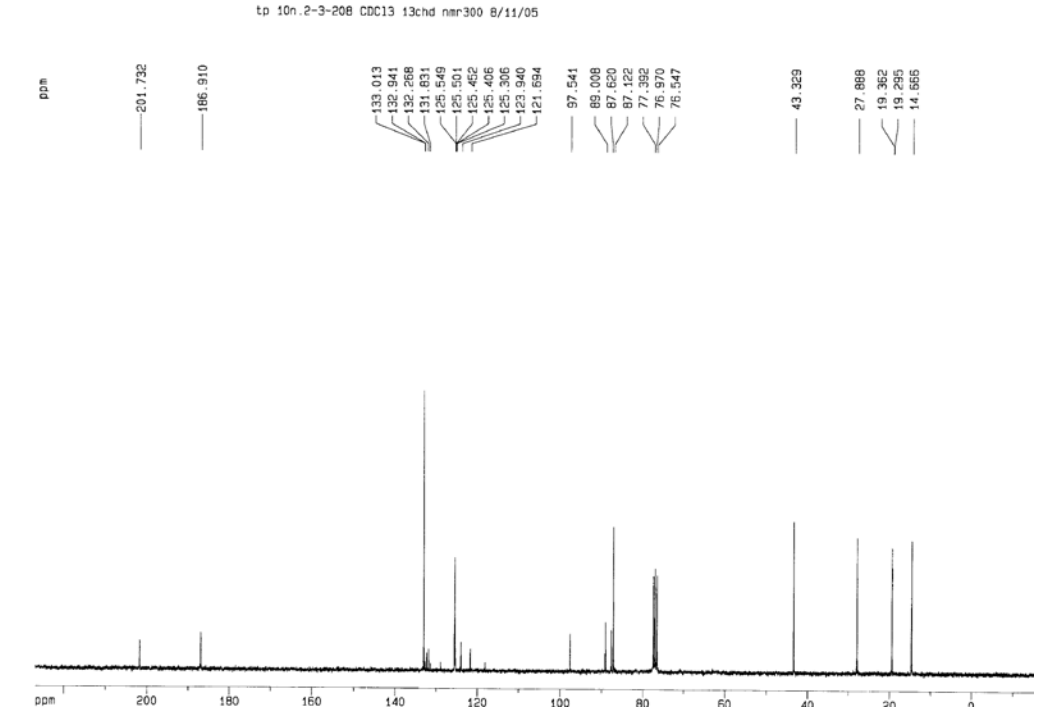
ppm
201.643
187.456
132.933
130.551
128.545
120.014
97.603
90.320
87.775
87.053
77.423
77.000
76.575
43.293
27.968
19.442
14.741
ppm
200
150
100
50
0

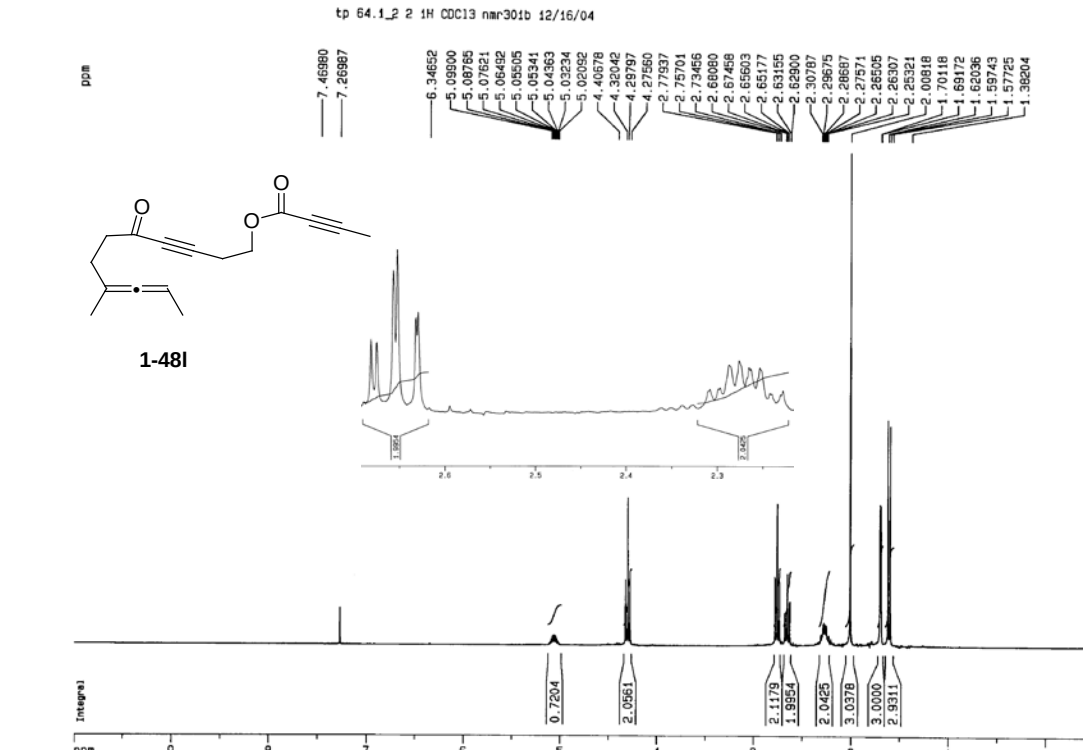

tp 10k.1-3-108 1H CDCl3 nmr300 4/14/05
ppm
8.3920
8.1917
8.0251
7.9923
7.7840
7.6148
7.5568
7.5484
7.5418
7.5254
7.5188
7.5107
7.4870
7.4570
7.4475
7.2699
6.9152
6.9088
6.8921
6.8857
5.1164
5.1053
5.0944
5.0838
5.0723
5.0616
5.0507
5.0395
3.9160
3.8467
3.8154
3.7907
3.7850
2.7938
2.7793
2.7565
2.7339
2.6998
2.6768
2.4178
2.4052
2.3877
2.3641
2.3534
2.3481
2.3353
2.3128
2.2844
1.7302
1.7210
1.6710
1.6586
1.6280
1.6051
1.5436
1.3697
1.2120
1.0330
0.0777
O
OMe
Integral
1.8281
1.8199
0.7332
3.0202
2.0000
2.1889
3.0130
3.0062
ppm

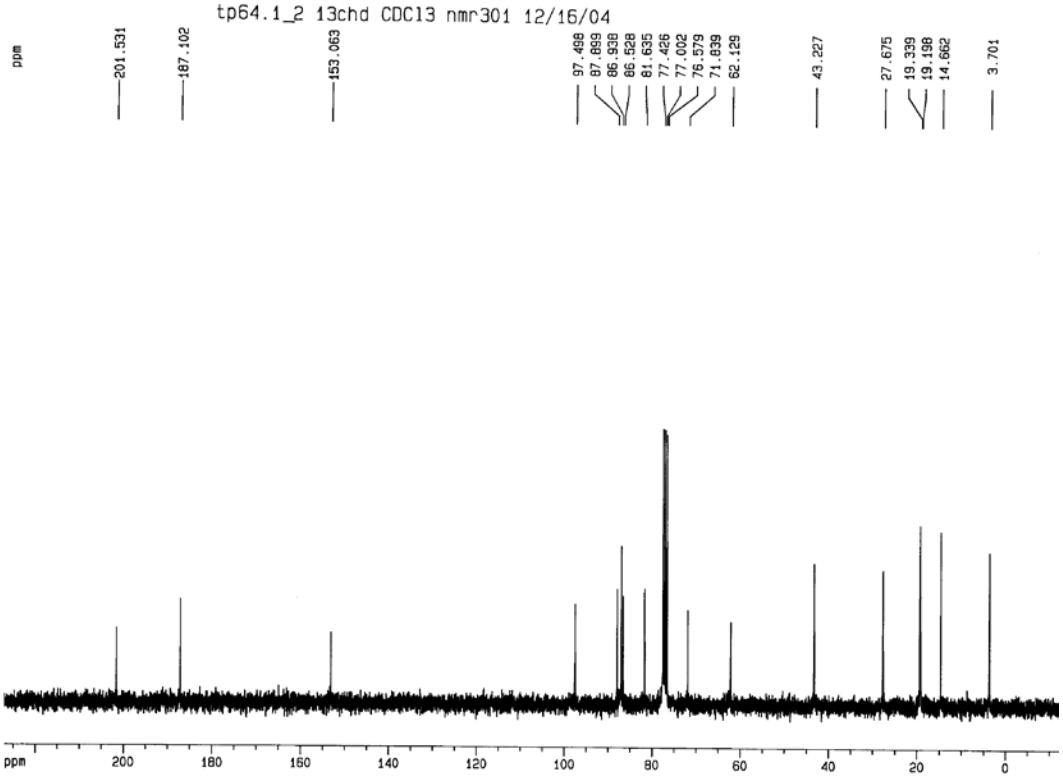
1-48j

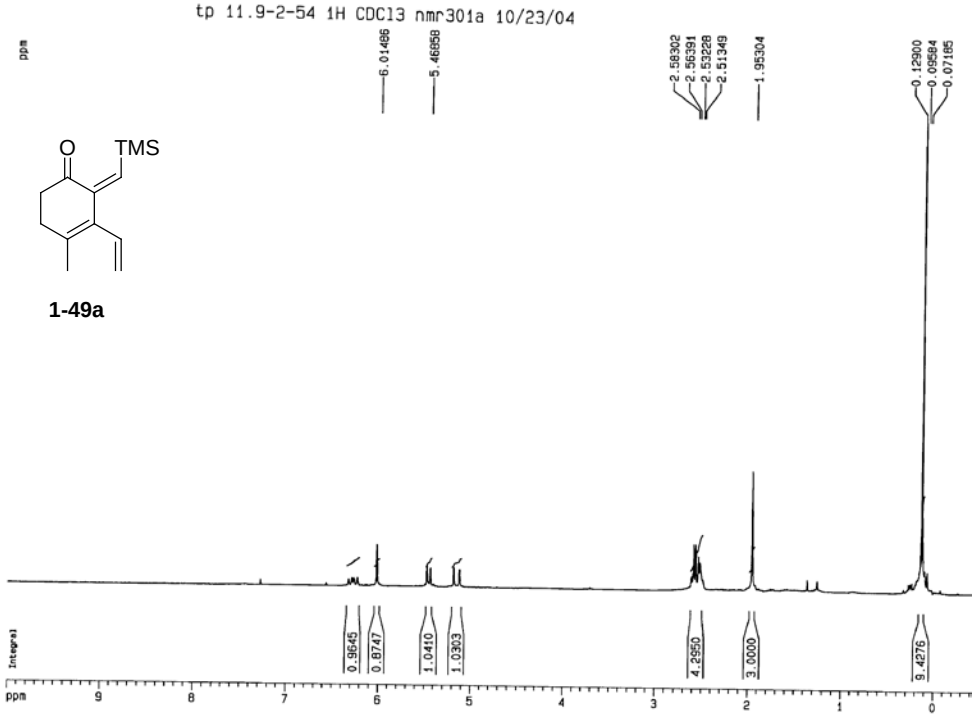

tp 10k.1-3-108 13chd CDCl3 nmr300 4/14/05
ppm
201.681
187.207
161.484
134.861
114.241
113.805
111.777
97.580
91.395
87.642
86.801
77.420
76.998
76.573
55.245
43.179
28.086
19.311
14.617
ppm


tp 10n.2-3-208 CDCl3 1H nmr300 8/11/05
ppm
7.69458
7.66579
7.65384
7.62486
7.40767
7.38122
7.26988
5.13457
5.12394
5.11295
5.10190
5.09089
5.07946
5.06884
5.05788
5.04659
5.03578
3.00345
2.85419
2.82074
2.81435
2.79655
2.79204
2.76939
2.42019
2.40906
2.38978
2.37879
2.35772
2.35681
2.34597
2.33454
2.32414
2.31159
1.72557
1.71626
1.69155
1.66509
1.62489
1.60190
1.40947
1.25940
0.87538
O
CF3
1-48k
Integral
3.9548
0.8410
2.0374
2.0624
2.9595
3.0000
ppm
9
8
7
6
5
4
3
2
1
0

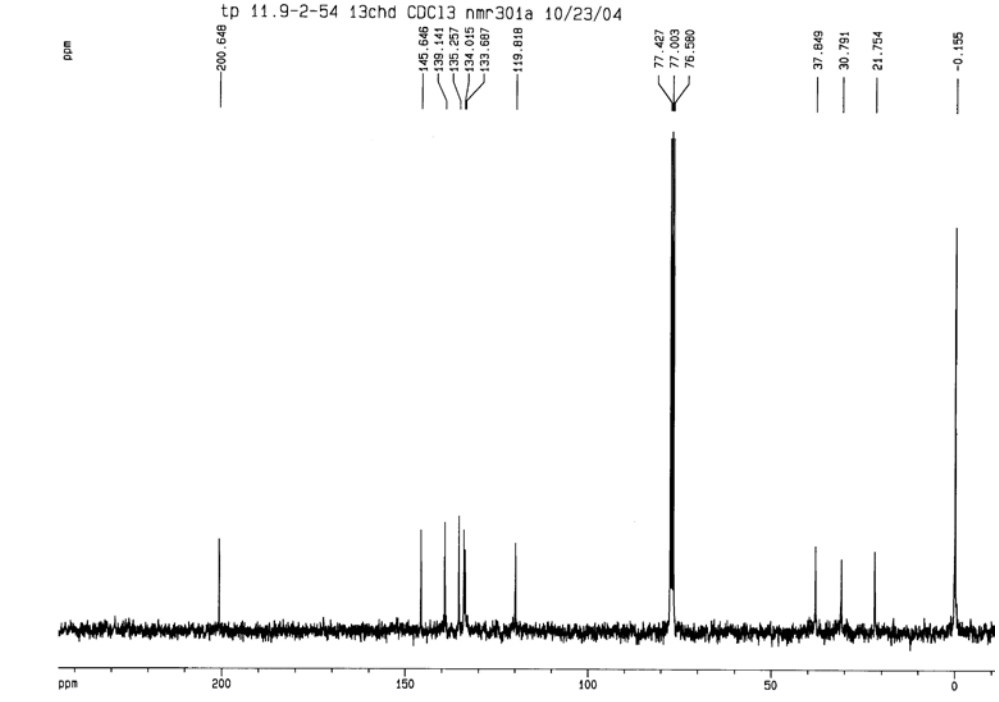

tp 10n.2-3-208 CDCl3 13chd nmr300 8/11/05
ppm
201.732
186.910
133.013
132.941
132.268
131.831
125.549
125.501
125.452
125.406
125.306
123.940
121.694
97.541
89.008
87.620
87.122
77.392
76.970
76.547
43.329
27.888
19.362
19.295
14.566
ppm
200
180
160
140
120
100
80
60
40
20
0

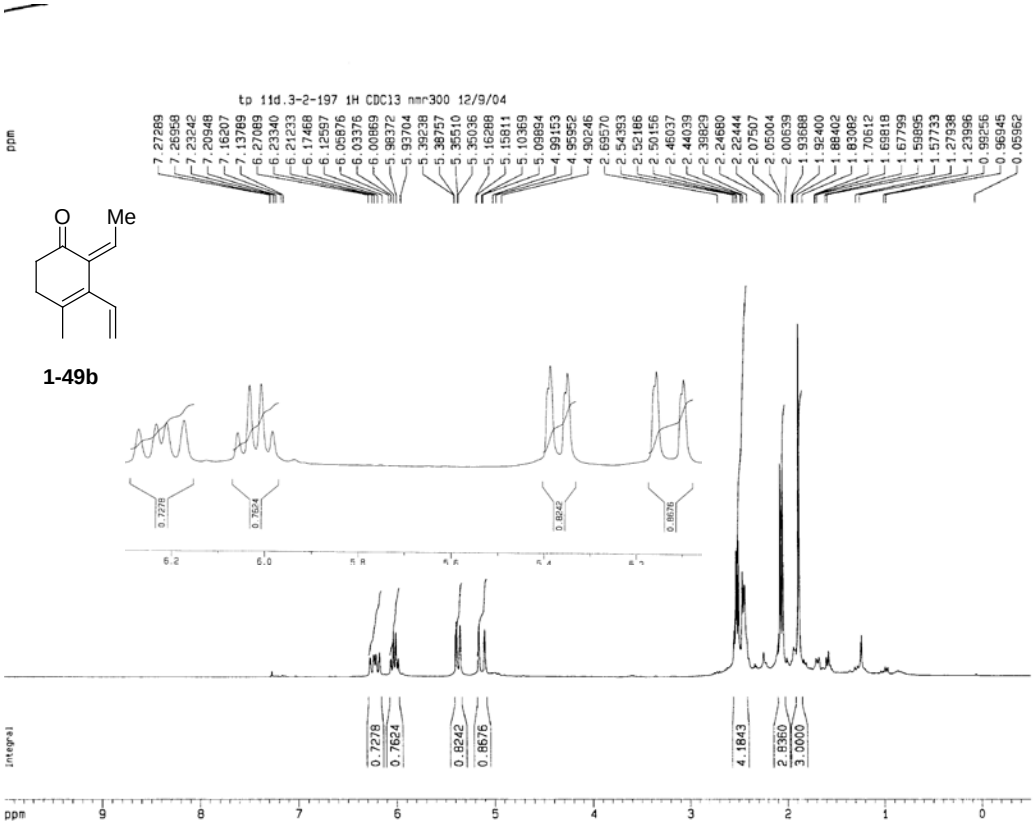

tp 64.1_2 2 1H CDCl3 nmr301b 12/16/04
ppm
7.46980
7.26987
6.34652
5.09900
5.08765
5.07621
5.06492
5.05505
5.05341
5.04363
5.03234
5.02092
4.40678
4.32042
4.28797
4.27560
2.77937
2.75701
2.73456
2.68080
2.67458
2.65603
2.65177
2.63155
2.62900
2.30787
2.29675
2.28687
2.27571
2.26505
2.26307
2.25321
2.00818
1.70118
1.69172
1.62036
1.59743
1.57725
1.38204
O
O
O
1-48l
Integral
0.7204
2.0561
2.1179
1.9954
2.0425
3.0378
3.0000
2.9311

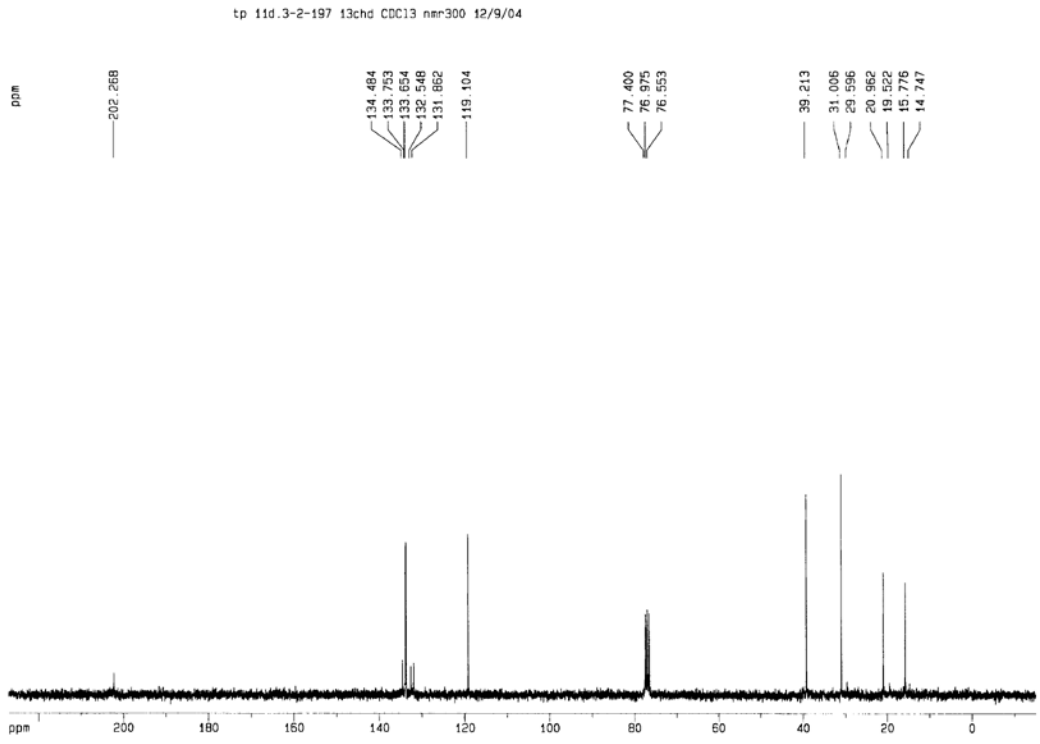

tp64.1_2 13chd CDCl3 nmr301 12/16/04
ppm
201.531
187.102
153.063
97.498
87.899
86.938
86.528
81.635
77.426
77.002
76.579
71.839
62.129
43.227
27.675
19.339
19.198
14.662
3.701
ppm
200
180
160
140
120
100
80
60
40
20
0

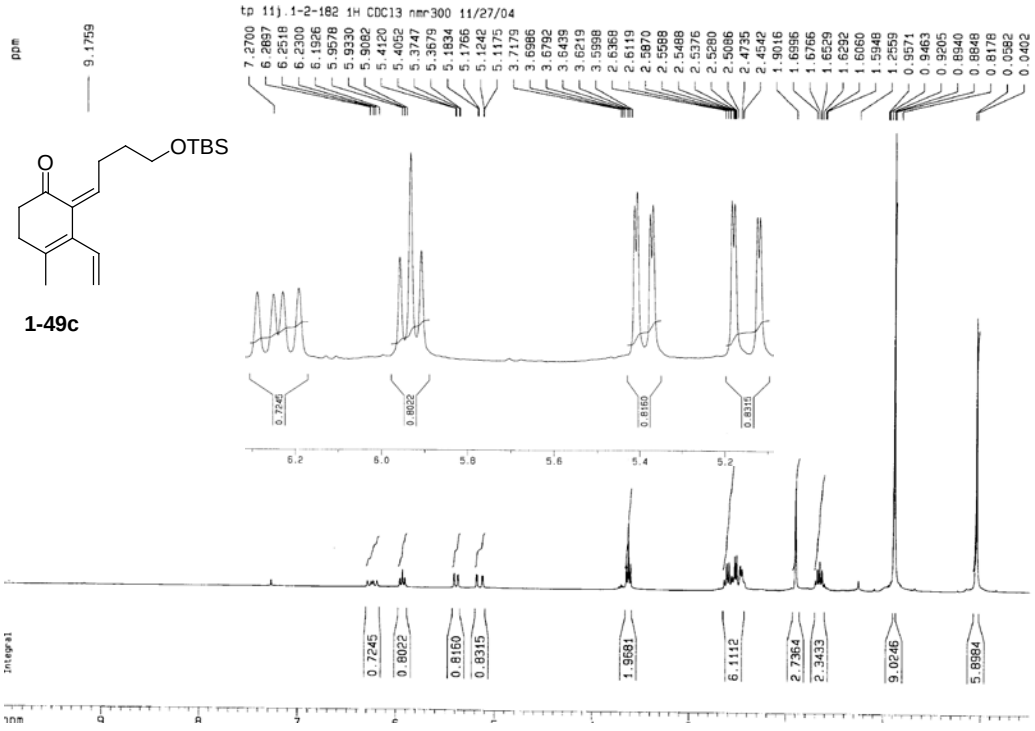

tp 11.9-2-54 1H CDCl3 nmr301a 10/23/04
ppm
6.01486
5.46858
2.58302
2.56391
2.53228
2.51349
1.95304
0.12900
0.09584
0.07185
O
TMS
Integral
0.9645
0.8747
1.0410
1.0303
4.2950
3.0000
9.4276
ppm

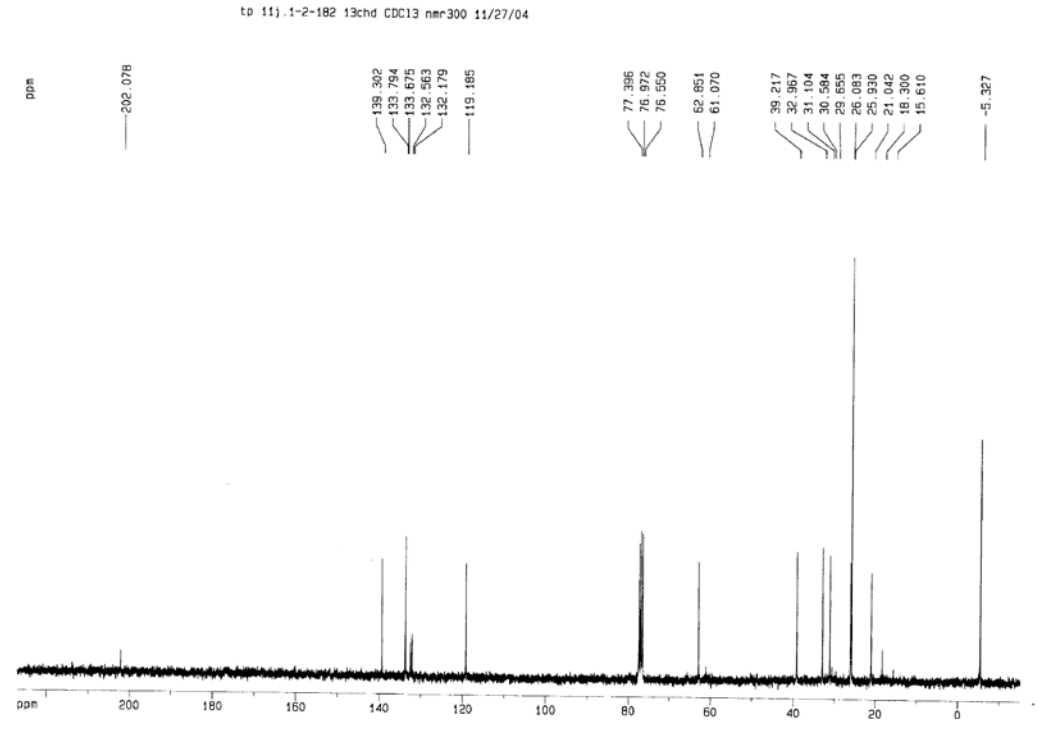
1-49a

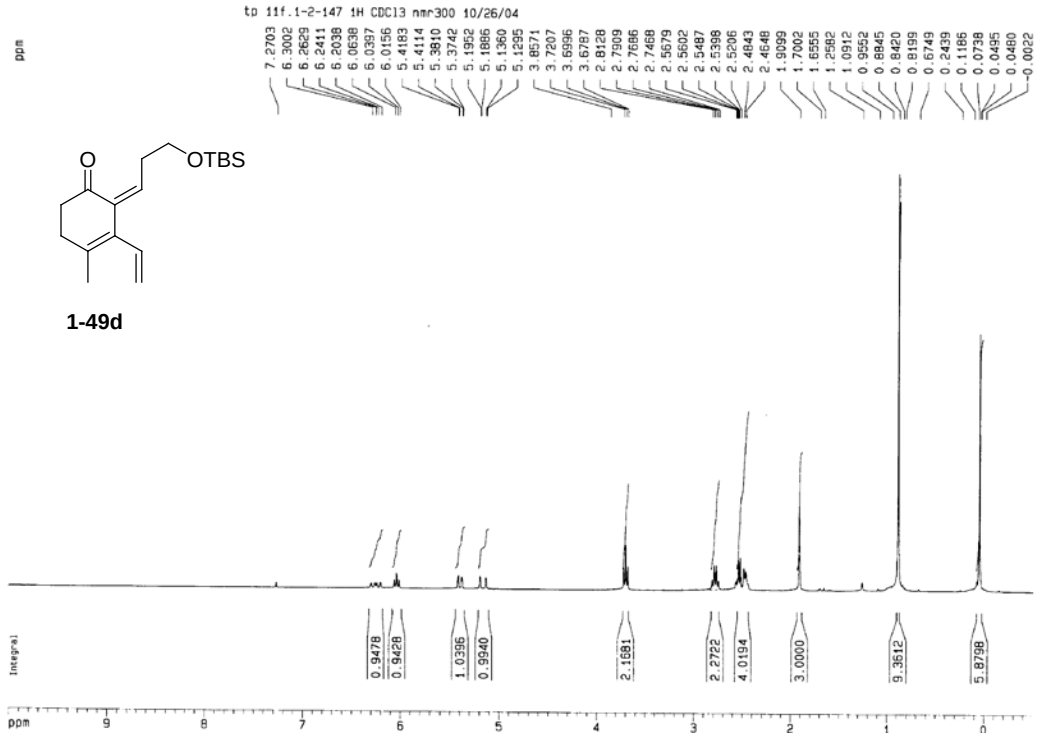

tp 11.9-2-54 13chd CDCl3 nmr301a 10/23/04
ppm
200.648
145.646
139.141
135.257
134.015
133.687
119.818
77.427
77.003
76.580
37.849
30.791
21.754
-0.155
ppm


tp 11d.3-2-197 1H CDCl3 nmr300 12/9/04
O
Me
1-49b
Integral
0.7278
0.7624
0.8242
0.8676
4.1843
2.8360
3.0000
ppm

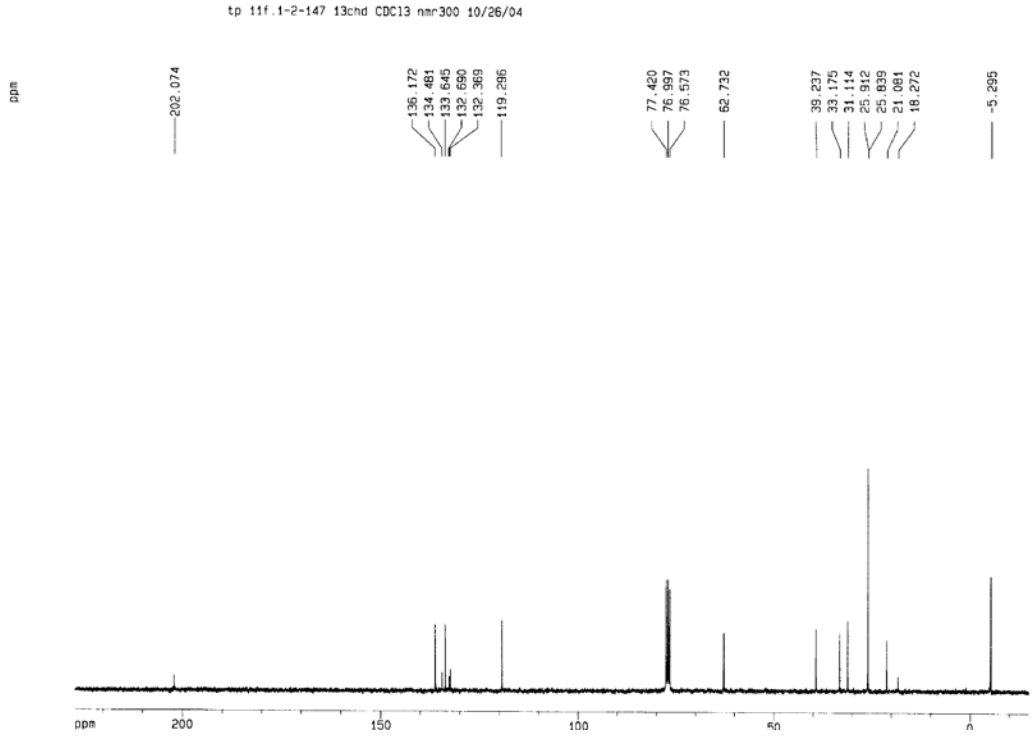

tp 11d.3-2-197 13chd CDCl3 nmr300 12/9/04
ppm
202.268
134.484
133.753
133.634
132.548
131.862
119.104
77.400
76.975
76.553
39.213
31.006
29.596
20.962
19.522
15.776
14.747

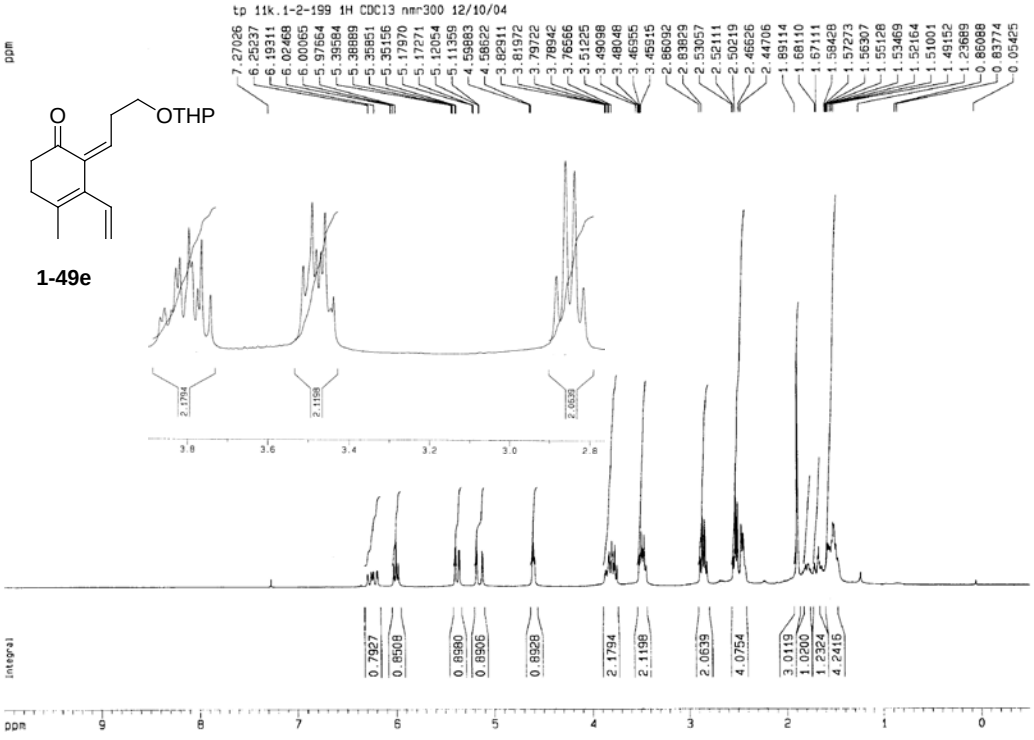

tp 11j.1-2-182 1H CDCl3 nmr300 11/27/04
ppm
9.1759
OTBS
O
1-49c
7.2700
6.2697
6.2518
6.2300
6.1926
5.9578
5.9330
5.9082
5.4120
5.4052
5.3747
5.3679
5.1834
5.1766
5.1242
5.1175
3.7179
3.6986
3.6792
3.6439
3.6219
3.5998
2.6368
2.6119
2.5870
2.5588
2.5488
2.5376
2.5280
2.5086
2.4735
2.4542
1.9016
1.6996
1.6766
1.6529
1.6292
1.6060
1.5948
1.2559
0.9571
0.9463
0.9205
0.8940
0.8848
0.8178
0.0582
0.0402
0.7245
0.8022
0.8160
0.8315
6.2
6.0
5.8
5.6
5.4
5.2
Integral
0.7245
0.8022
0.8160
0.8315
1.9681
6.1112
2.7364
2.3433
9.0246
5.8984

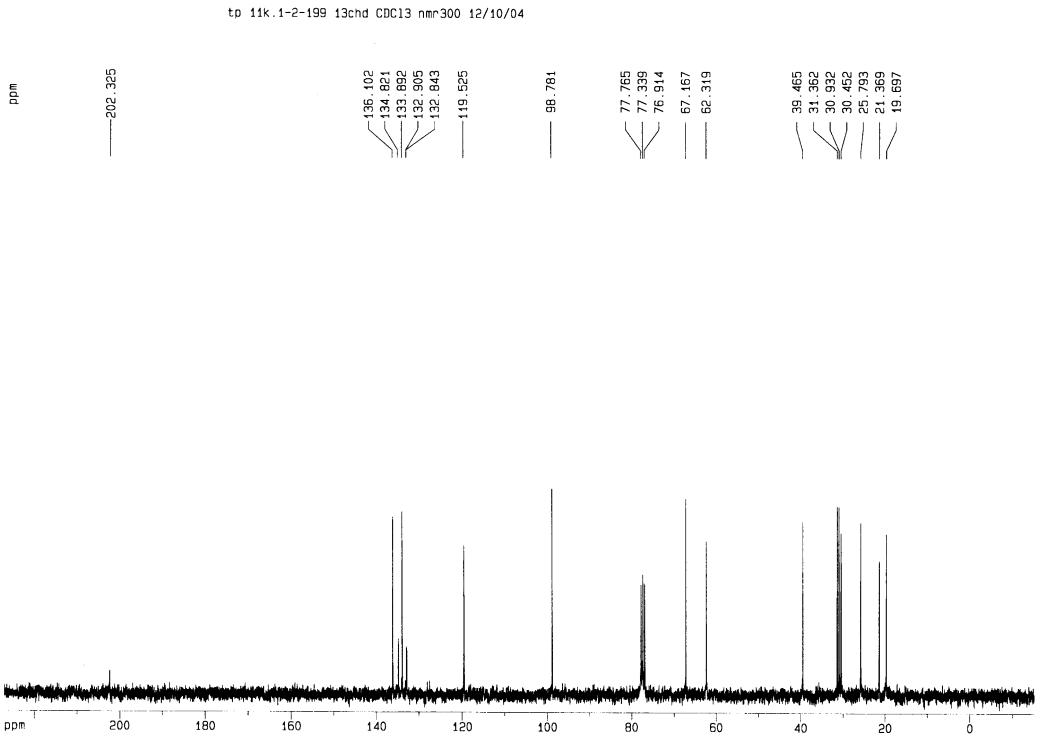

tp 11j.1-2-182 13chd CDCl3 nmr300 11/27/04
ppm
202.078
139.302
133.794
133.675
132.563
132.179
119.185
77.396
76.972
76.550
62.851
61.070
39.217
32.967
31.104
30.584
29.655
26.083
25.930
21.042
18.300
15.610
-5.327
ppm
200
180
160
140
120
100
80
60
40
20
0

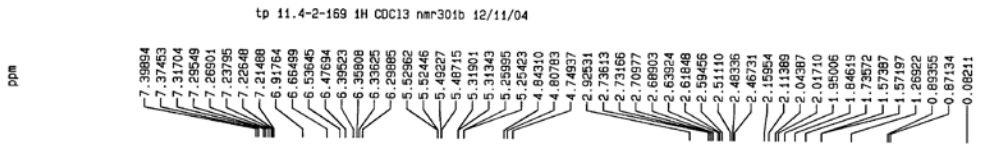

tp 11f.1-2-147 1H CDCl3 nmr300 10/26/04
ppm
7.2703
6.3002
6.2629
6.2411
6.2038
6.0638
6.0397
6.0156
5.4183
5.4114
5.3810
5.3742
5.1952
5.1886
5.1360
5.1295
3.8571
3.7207
3.6996
3.6787
2.8128
2.7909
2.7686
2.7468
2.5679
2.5602
2.5487
2.5398
2.5296
2.4843
2.4648
1.9099
1.7002
1.6555
1.2582
1.0912
0.9552
0.8845
0.8420
0.8199
0.6743
0.2439
0.1186
0.0738
0.0495
0.0480
-0.0022
O
OTBS
Integral
0.9478
0.9428
1.0396
0.9940
2.1681
2.2722
4.0194
3.0000
9.3612
5.8798
ppm
9
8
7
6
5
4
3
2
1
0

1-49d


tp 11f.1-2-147 13chd CDCl3 nmr300 10/26/04
ppm
202.074
136.172
134.481
133.645
132.690
132.369
119.296
77.420
76.997
76.573
62.732
39.237
33.175
31.114
25.912
25.839
21.081
18.272
-5.295
ppm
200
150
100
50
0


tp 11k.1-2-199 1H CDCl3 nmr300 12/10/04
O
OTHP
1-49e
ppm
Integral


tp 11k.1-2-199 13chd CDCl3 nmr300 12/10/04
ppm


tp 11.4-2-169 1H CDCl3 nmr301b 12/11/04
ppm
7.39894
7.37453
7.31704
7.29549
7.26901
7.23795
7.22648
7.21488
6.91764
6.66499
6.53645
6.47694
6.39523
6.35808
6.33625
6.29985
5.52962
5.52446
5.49227
5.48715
5.31901
5.31343
5.25995
5.25423
4.84310
4.80783
4.74937
2.92531
2.73613
2.73166
2.70977
2.68903
2.63924
2.61848
2.59456
2.51110
2.48336
2.46731
2.15954
2.11389
2.04387
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1.84619
1.73572
1.57387
1.57197
1.26922
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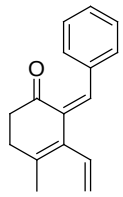
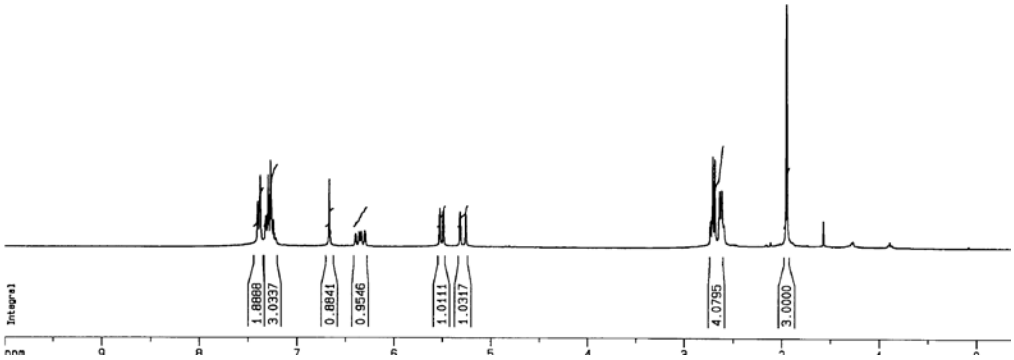
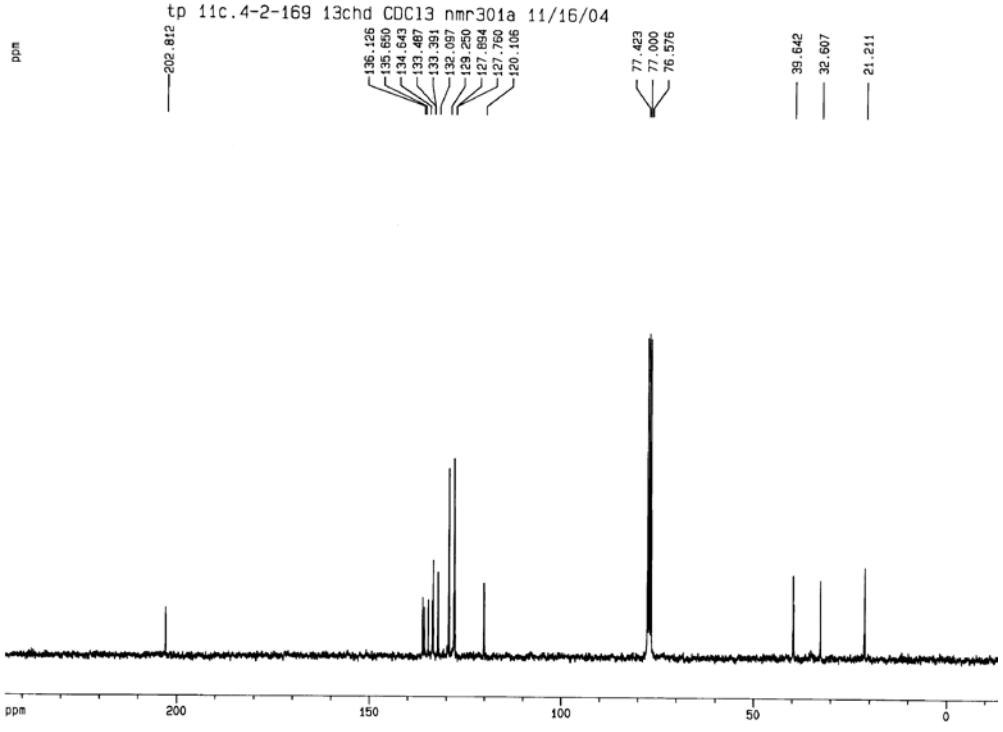
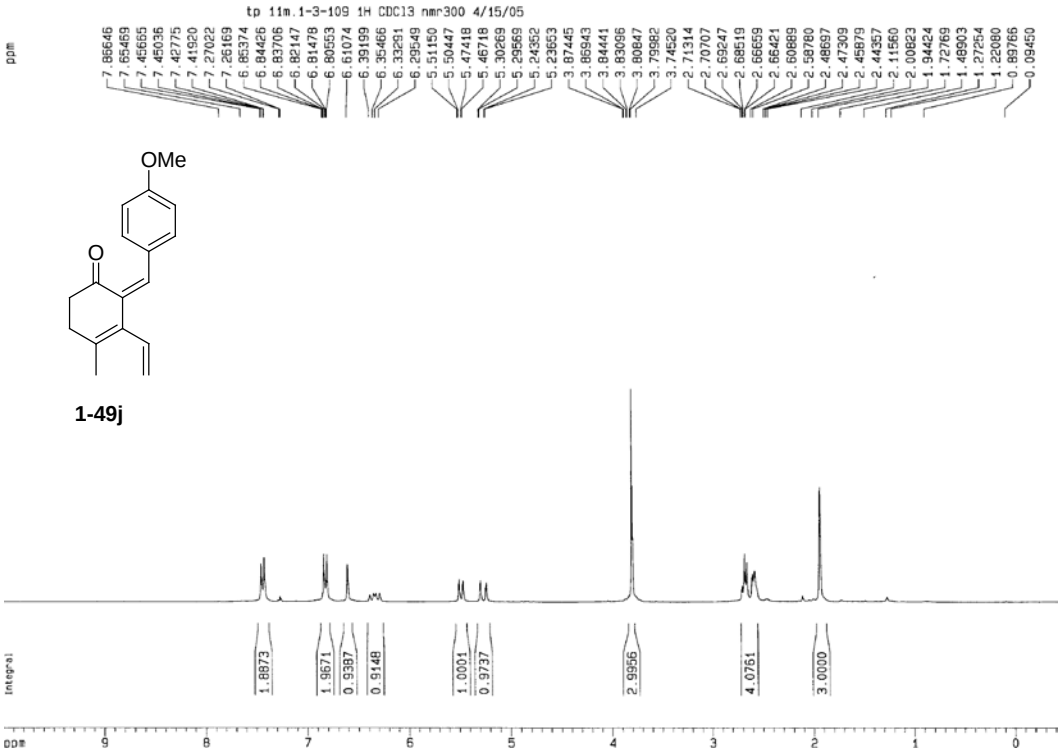
0.87134
0.08211

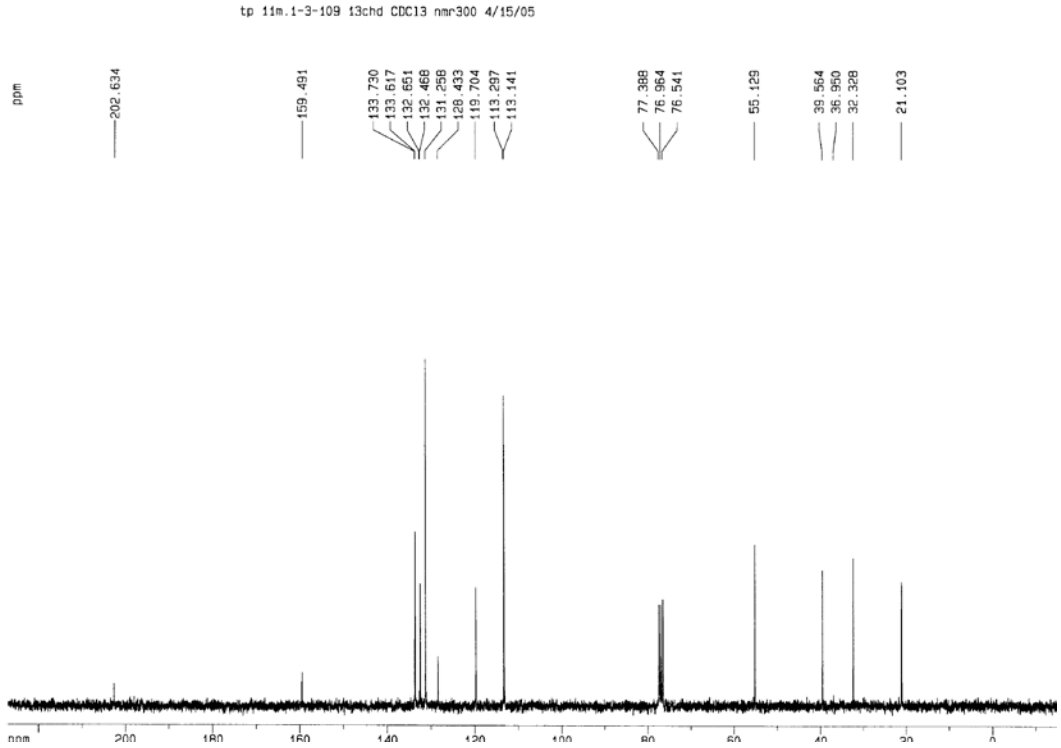

O

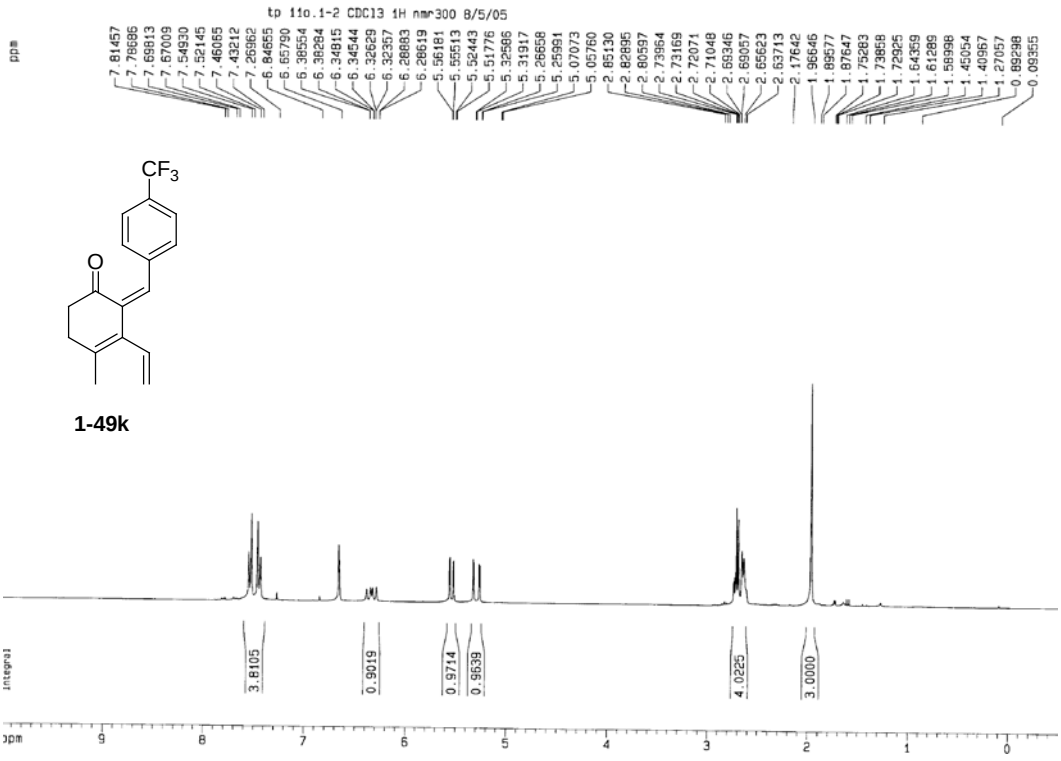
1-49i


Integral
1.8888
3.0337
0.8841
0.9546
1.0111
1.0317
4.0795
3.0000


tp 11c.4-2-169 13chd CDCl3 nmr301a 11/16/04
ppm
202.812
136.126
135.650
134.643
133.487
133.391
132.097
129.250
127.894
127.766
120.106
77.423
77.000
76.576
39.642
32.607
21.211
ppm
200
150
100
50
0


tp 11m.1-3-109 1H CDCl3 nmr300 4/15/05
ppm
7.86646
7.65469
7.45665
7.45036
7.42775
7.41920
7.27022
7.26169
6.86374
6.84426
6.83706
6.82147
6.81478
6.80553
6.61074
6.39199
6.35466
6.33291
6.29549
5.51150
5.50447
5.47418
5.46718
5.30269
5.29569
5.24352
5.23653
3.87445
3.86943
3.84441
3.83096
3.80847
3.79982
3.74520
2.71314
2.70707
2.69247
2.68519
2.66659
2.66421
2.60889
2.58760
2.48697
2.47309
2.45879
2.44357
2.11560
2.00823
1.94424
1.72769
1.48903
1.27254
1.22080
0.89766
0.09450
OMe
O
1-49j
Integral
1.6873
1.9671
0.9387
0.9148
1.0001
0.9737
2.9956
4.0761
3.0000
ppm
9
8
7
6
5
4
3
2
1
0


tp 11m.1-3-109 13chd CDCl3 nmr300 4/15/05
ppm
202.634
159.491
133.730
133.617
132.651
132.468
131.258
128.433
119.704
113.297
113.141
77.388
76.964
76.541
55.129
39.564
36.950
32.328
21.103
ppm
200
180
160
140
120
100
80
60
40
20
0


tp 11o.1-2 CDCl3 1H nmr300 8/5/05
ppm
7.81457
7.78686
7.69813
7.67009
7.54930
7.52145
7.46065
7.43212
7.25962
6.84655
6.65790
6.38554
6.38284
6.34815
6.34544
6.32629
6.32357
6.28883
6.28619
5.56181
5.55513
5.52443
5.51776
5.32586
5.31917
5.26658
5.25991
5.07073
5.05760
2.85130
2.82895
2.80597
2.73964
2.73169
2.72071
2.71048
2.69346
2.69057
2.65623
2.63713
2.17642
1.96646
1.89577
1.87647
1.75283
1.73868
1.72925
1.64359
1.61289
1.58998
1.45054
1.40967
1.27057
0.89298
0.09355
CF3
O
1-49k
Integral
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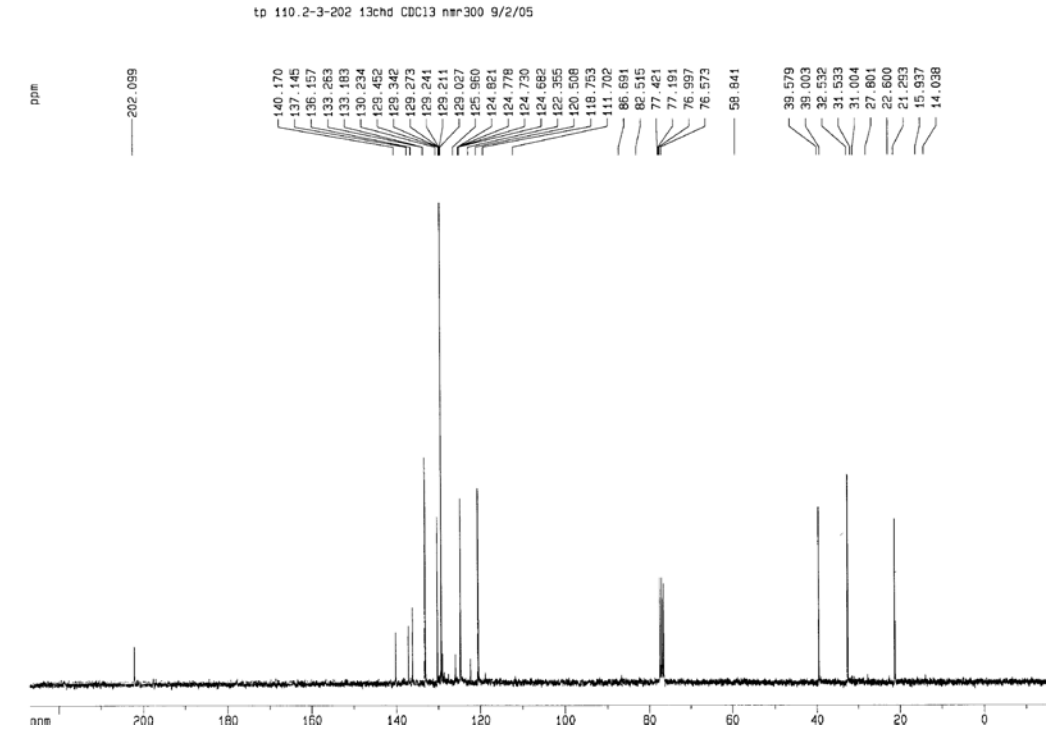
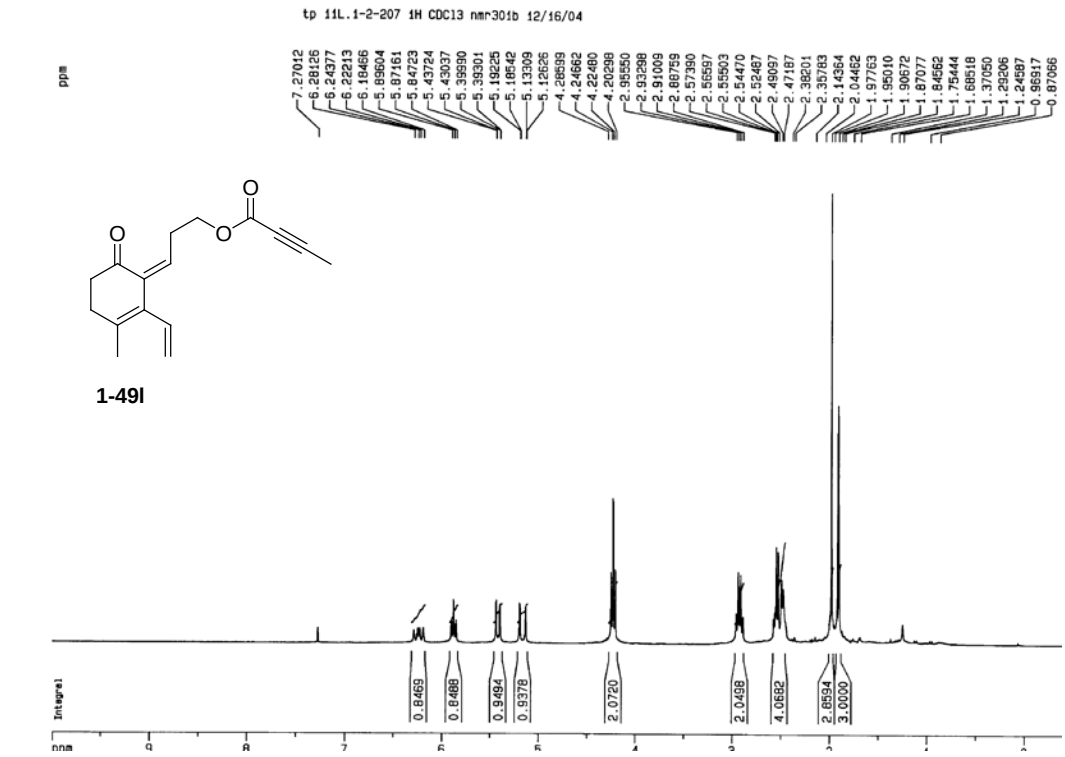
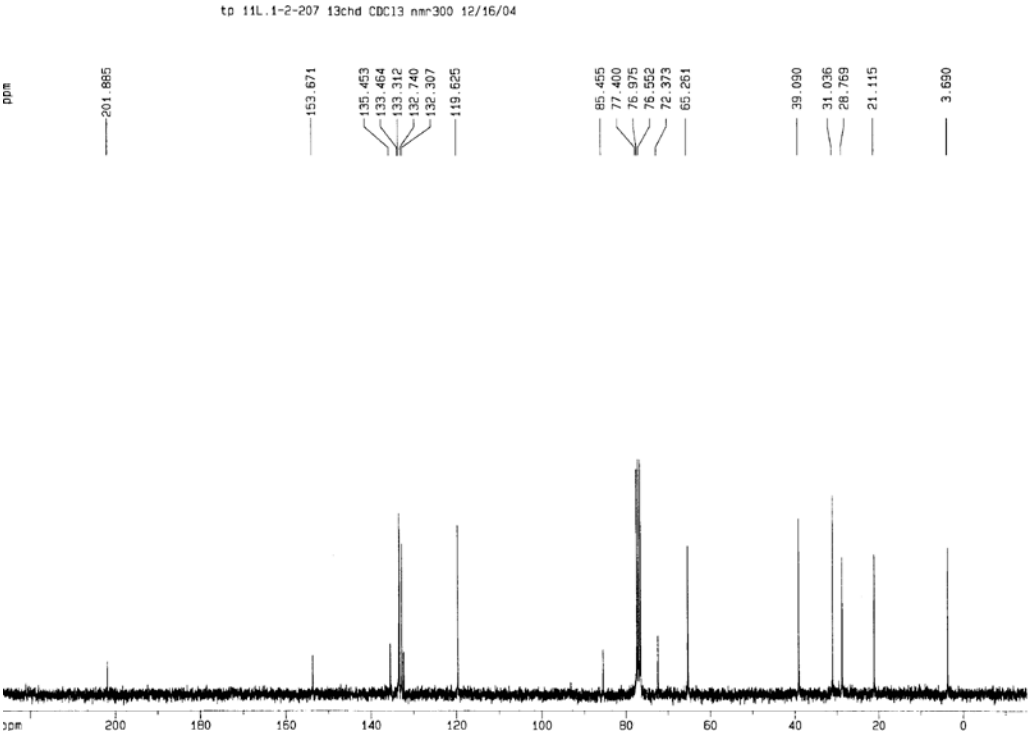
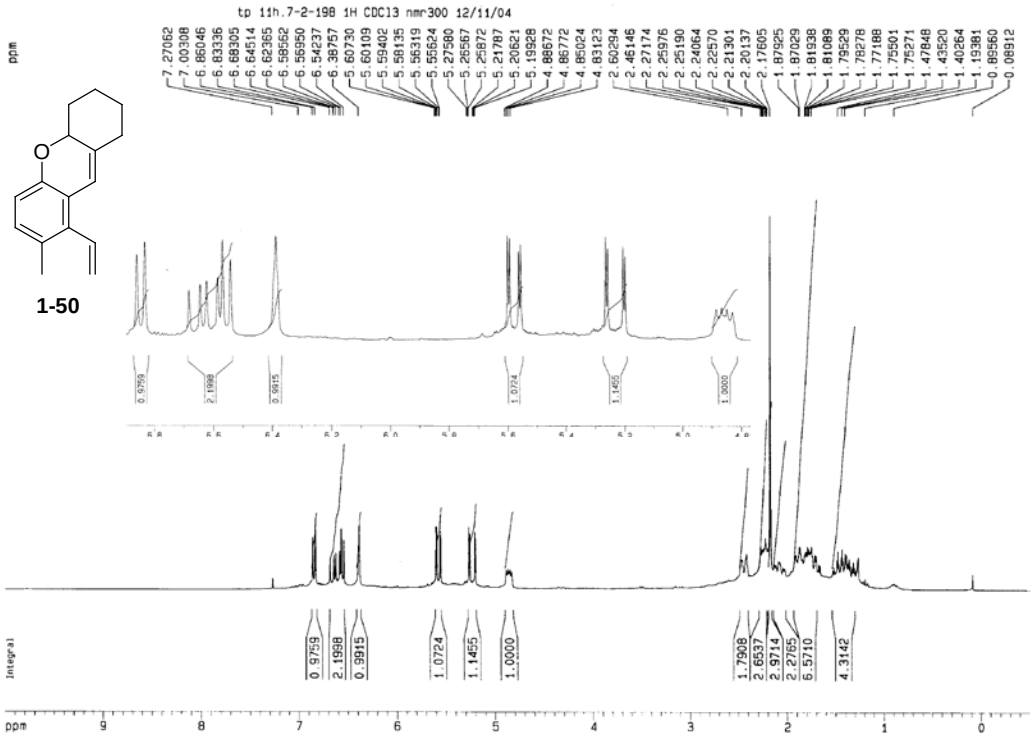
0.9019
0.9714
0.9639
4.0225
3.0000
ppm

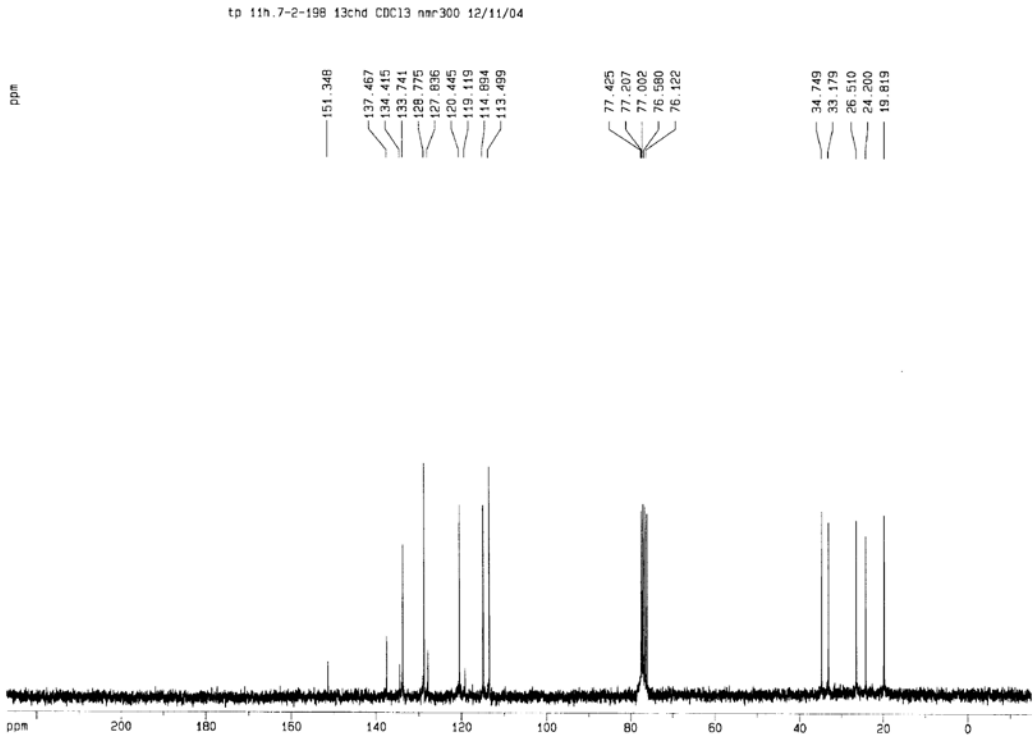

tp 110.2-3-202 13chd CDCl3 nmr300 9/2/05
ppm
202.099
140.170
137.145
136.157
133.263
133.183
130.234
129.452
129.342
129.273
129.241
129.211
129.027
125.960
124.821
124.778
124.730
124.682
122.355
120.508
118.753
111.702
86.691
82.515
77.421
77.191
76.997
76.573
58.841
39.579
39.003
32.532
31.533
31.004
27.801
22.600
21.293
15.937
14.038
nnm

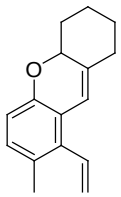

tp 11L.1-2-207 1H CDCl3 nmr301b 12/16/04
ppm
7.27012
6.28126
6.24377
6.22213
6.18466
5.89604
5.87161
5.84723
5.43724
5.43037
5.39990
5.39301
5.19225
5.18542
5.13309
5.12626
4.28699
4.24662
4.22480
4.20298
2.95550
2.93298
2.91009
2.88759
2.57390
2.56597
2.55503
2.54470
2.52487
2.49097
2.47187
2.38201
2.35783
2.14364
2.04462
1.97763
1.95010
1.90672
1.87077
1.84562
1.75444
1.68518
1.37050
1.29306
1.24587
0.96917
0.87066
O
O
O
Integral
0.8469
0.8488
0.9494
0.9378
2.0720
2.0498
4.0682
2.8694
3.0000
ppm

1-49l

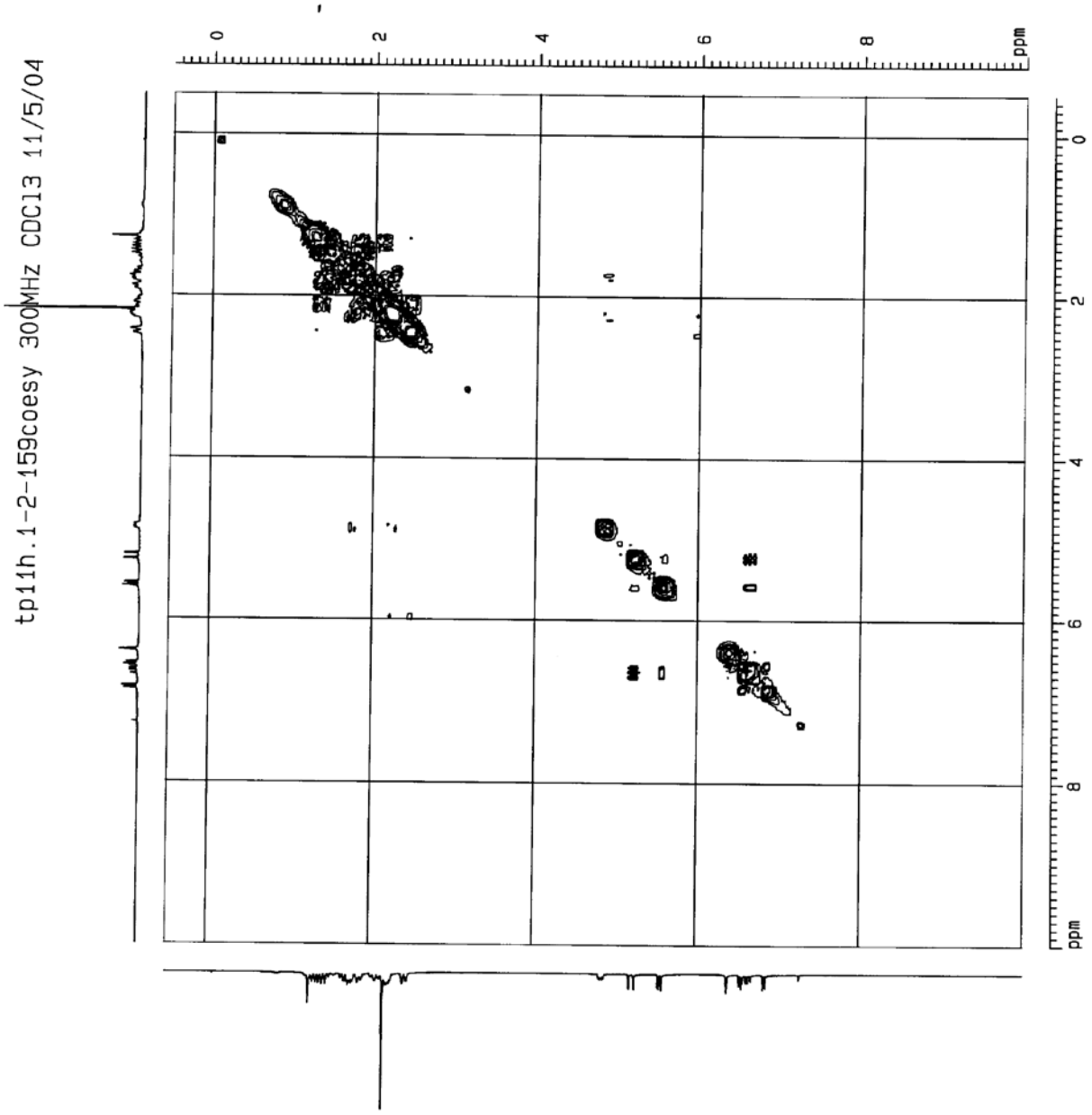

tp 11L.1-2-207 13chd CDCl3 nmr300 12/16/04
ppm
201.885
153.671
135.453
133.464
133.312
132.740
132.307
119.625
85.455
77.400
76.975
76.552
72.373
65.261
39.090
31.036
28.769
21.115
3.690
ppm
200
180
160
140
120
100
80
60
40
20
0

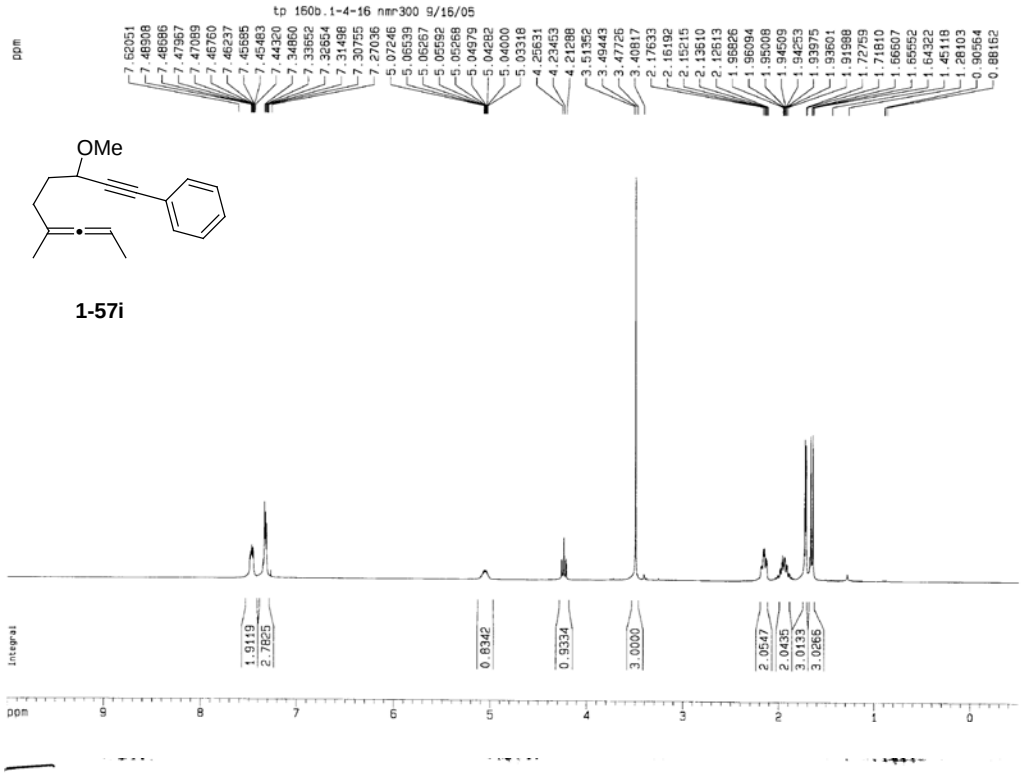

tp 11h.7-2-198 1H CDCl3 nmr300 12/11/04
ppm
1-50
Integral
0.9759
2.1998
0.9915
1.0724
1.1465
1.0000
1.7908
2.6537
2.9714
2.2765
6.5710
4.3142
ppm


tp 11h.7-2-198 13chd CDCl3 nmr300 12/11/04
ppm
151.348
137.467
134.415
133.741
128.775
127.836
120.445
119.119
114.884
113.499
77.425
77.207
77.002
76.580
76.122
34.749
33.179
26.510
24.200
19.819
ppm

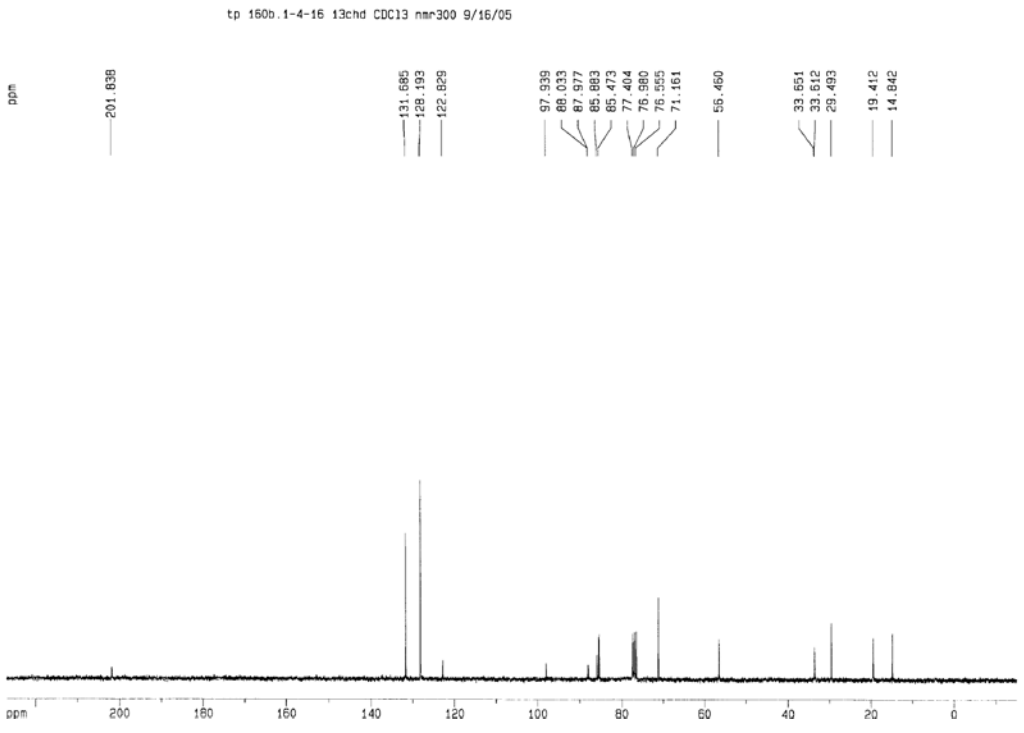


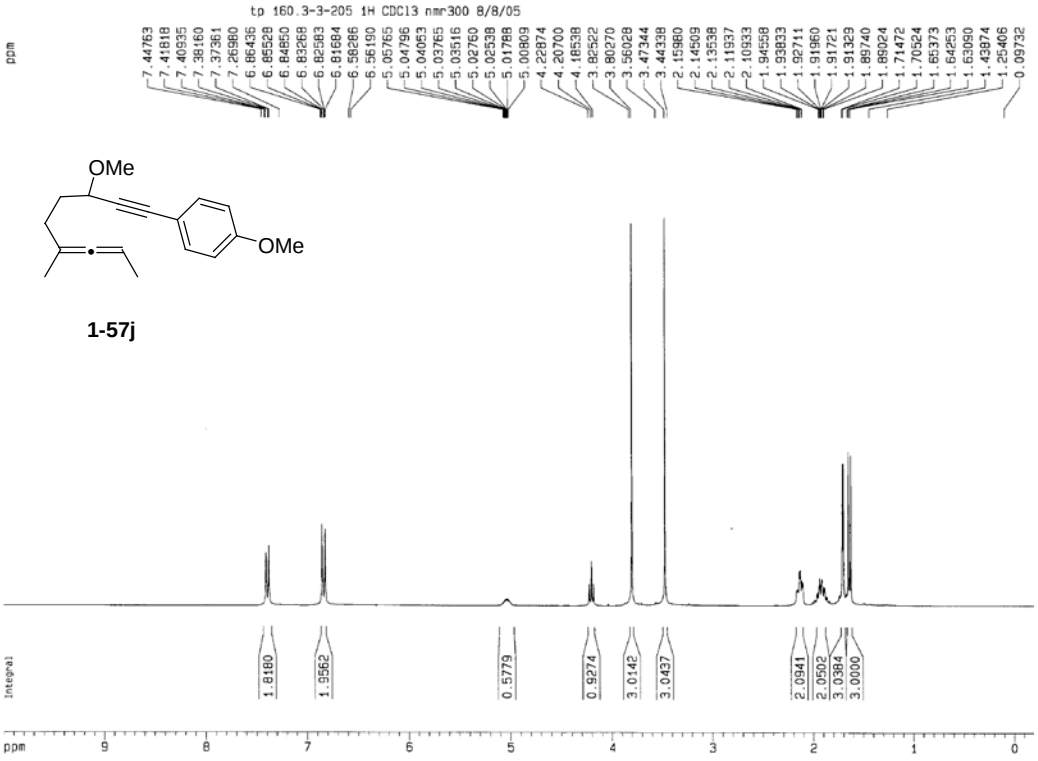
1-50



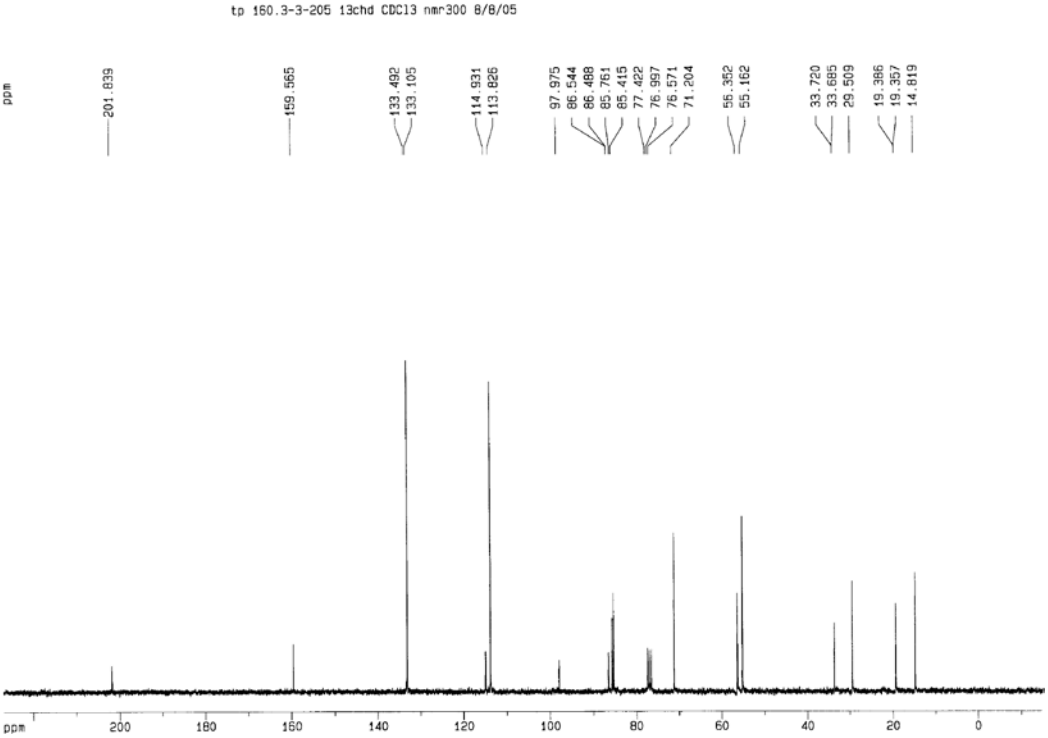

tp 160b.1-4-16 nmr300 9/16/05
ppm
OMe
Integral
1.9119
2.7825
0.8342
0.9334
3.0000
2.0547
2.0435
3.0133
3.0266
ppm

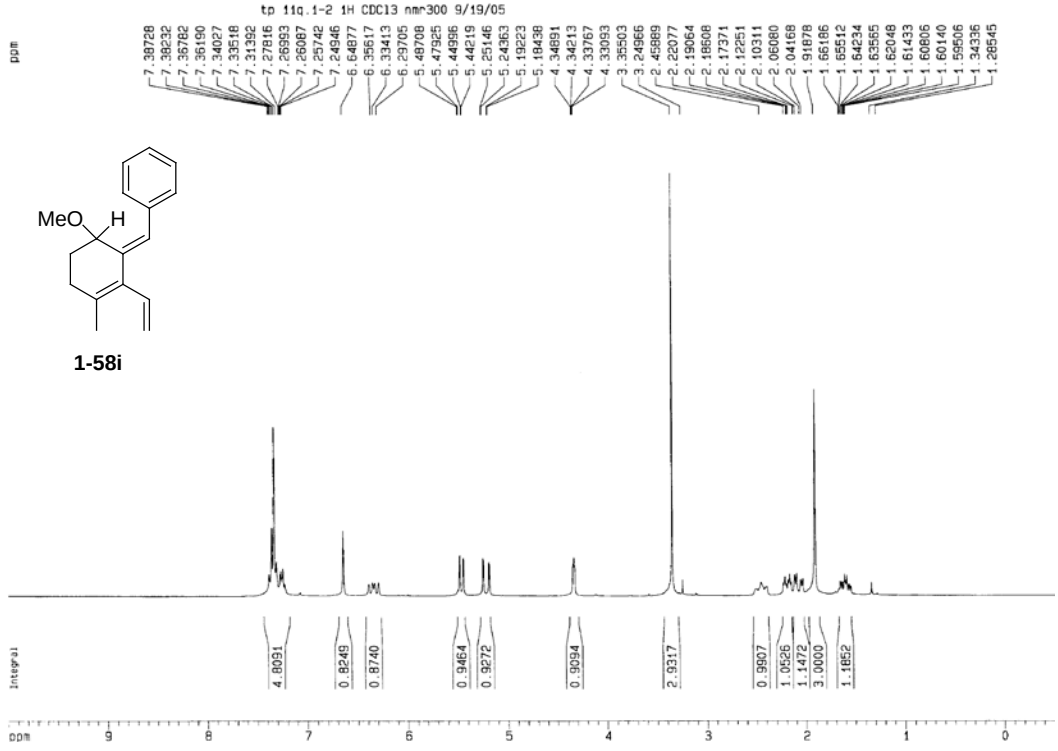
1-57i


tp 160b.1-4-16 13chd CDCl3 nmr300 9/16/05
ppm
201.838
131.685
128.193
122.829
97.939
88.033
87.977
85.883
85.473
77.404
76.980
76.555
71.161
55.460
33.651
33.612
29.493
19.412
14.842
ppm

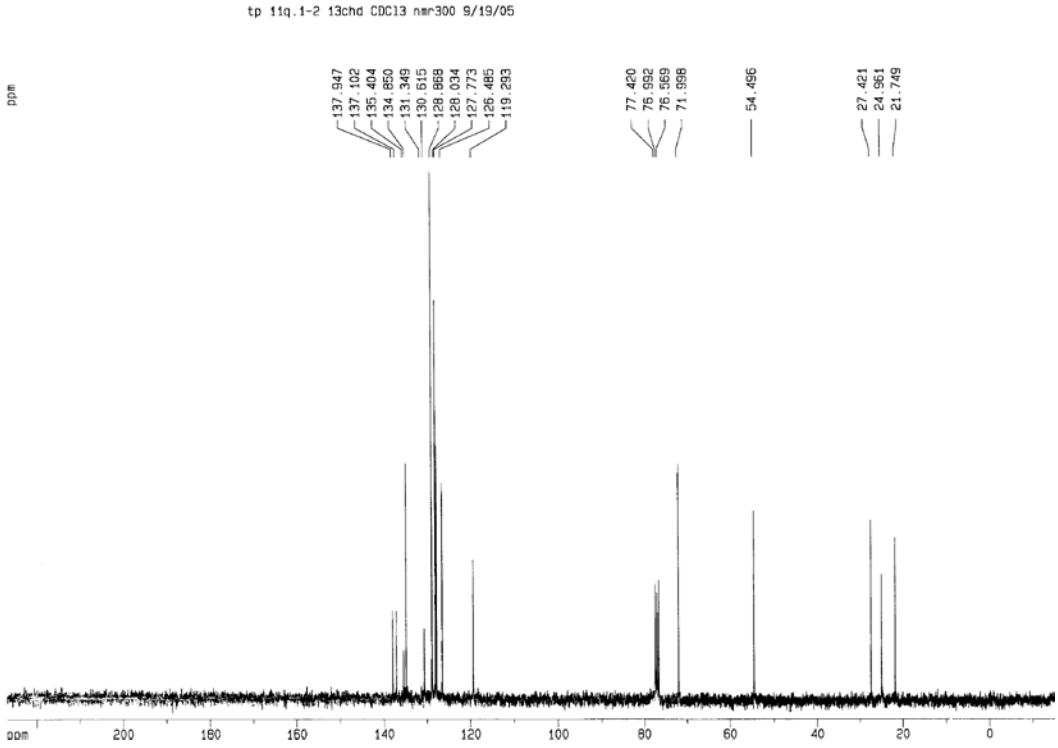

tp 160.3-3-205 1H CDCl3 nmr300 8/8/05
ppm
OMe
OMe
Integral
1.8180
1.9562
0.5779
0.9274
3.0142
3.0437
2.0941
2.0502
3.0384
3.0000
ppm

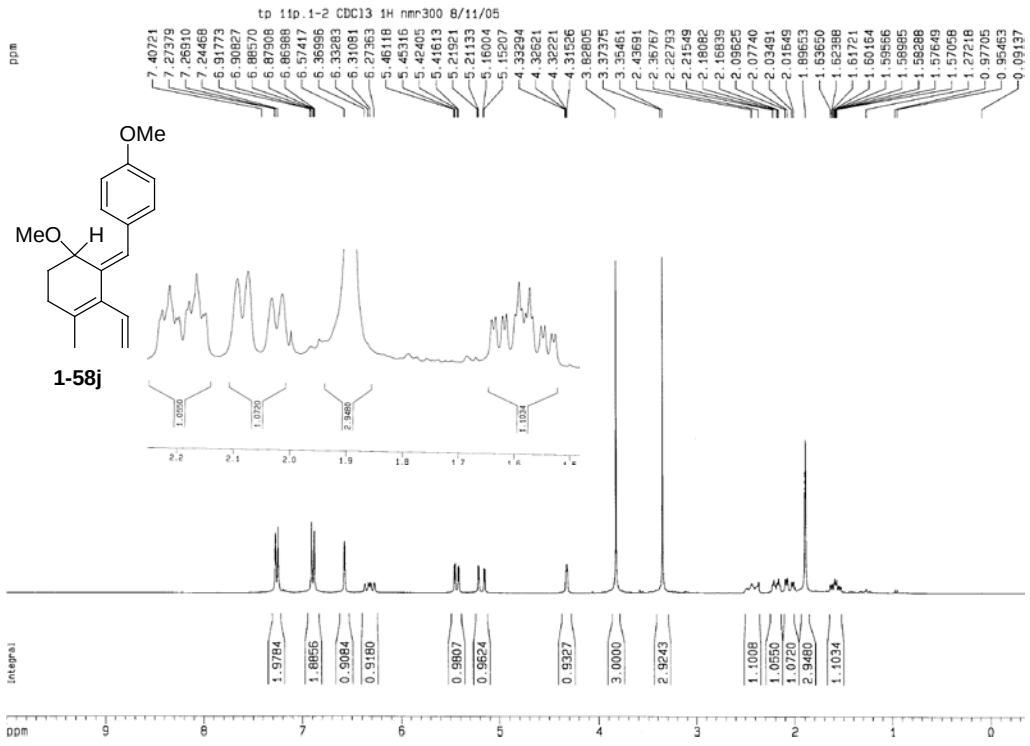
1-57j

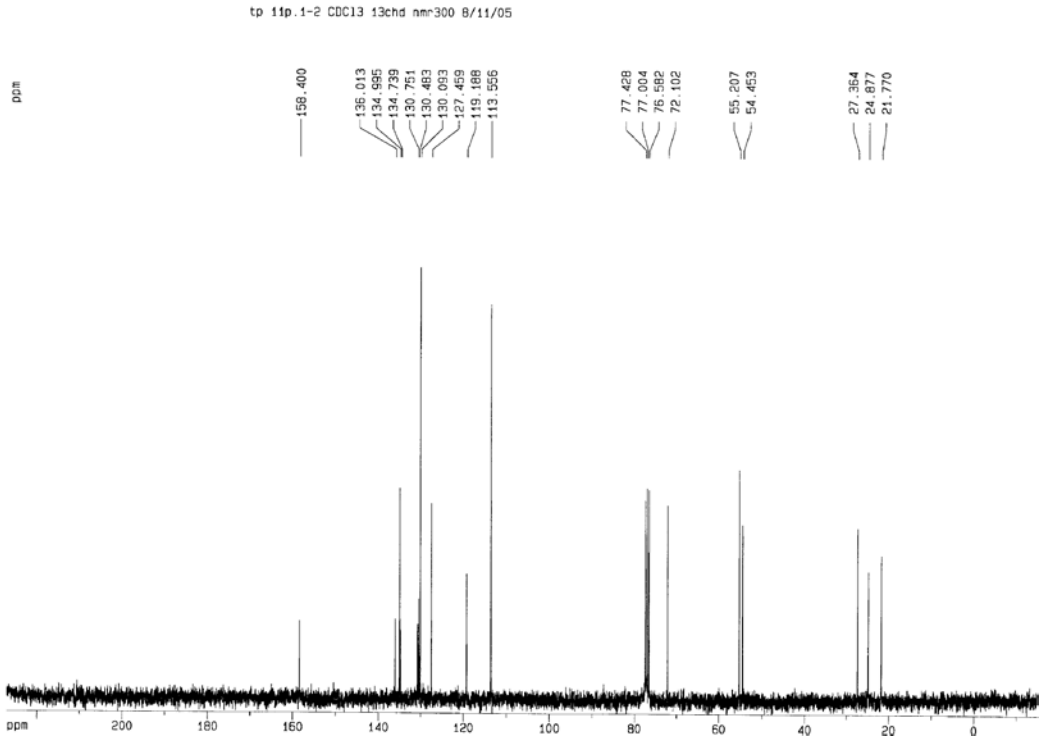

tp 160.3-3-205 13chd CDCl3 nmr300 8/8/05
ppm
201.839
159.565
133.492
133.105
114.931
113.826
97.975
86.544
86.488
85.761
85.415
77.422
76.997
76.571
71.204
56.352
55.162
33.720
33.685
29.509
19.386
19.357
14.819
ppm


tp 11q.1-2 1H CDCl3 nmr300 9/19/05
ppm
MeO
H
Integral
4.8091
0.8249
0.8740
0.9464
0.9272
0.9094
2.9317
0.9907
1.0526
1.1472
3.0000
1.1852
ppm

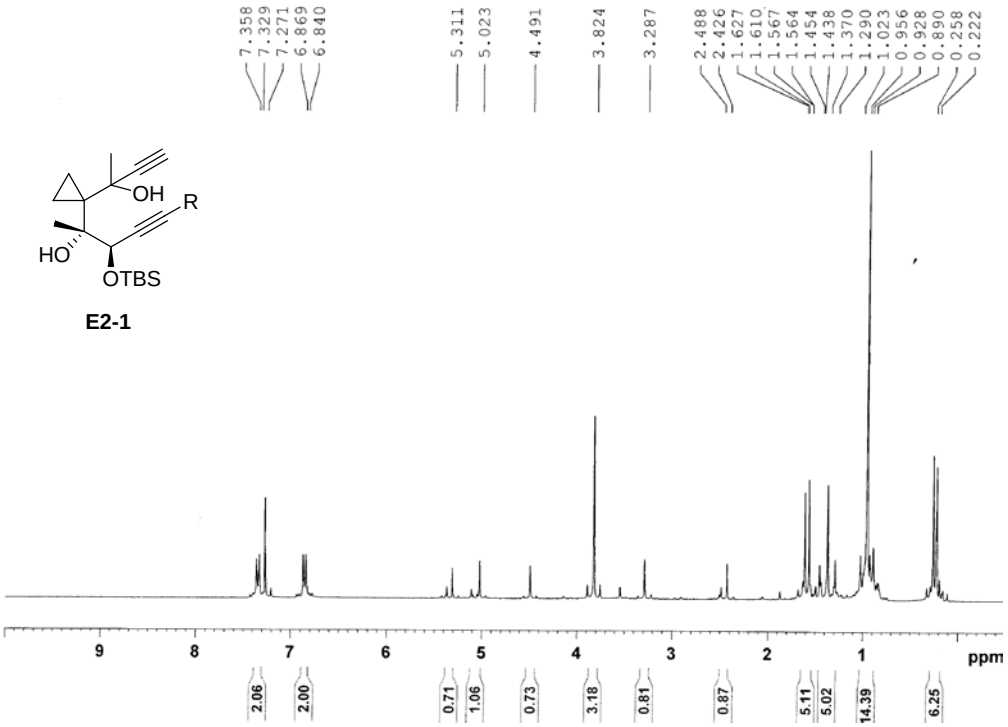
1-58i


tp 11q.1-2 13chd CDCl3 nmr300 9/19/05
ppm
137.947
137.102
135.404
134.850
131.349
130.615
128.868
128.034
127.773
126.485
119.293
77.420
76.992
76.569
71.998
54.496
27.421
24.961
21.749
ppm


tp 11p.1-2 CDCl3 1H nmr300 8/11/05
OMe
MeO
H
1-58j
Integral
ppm

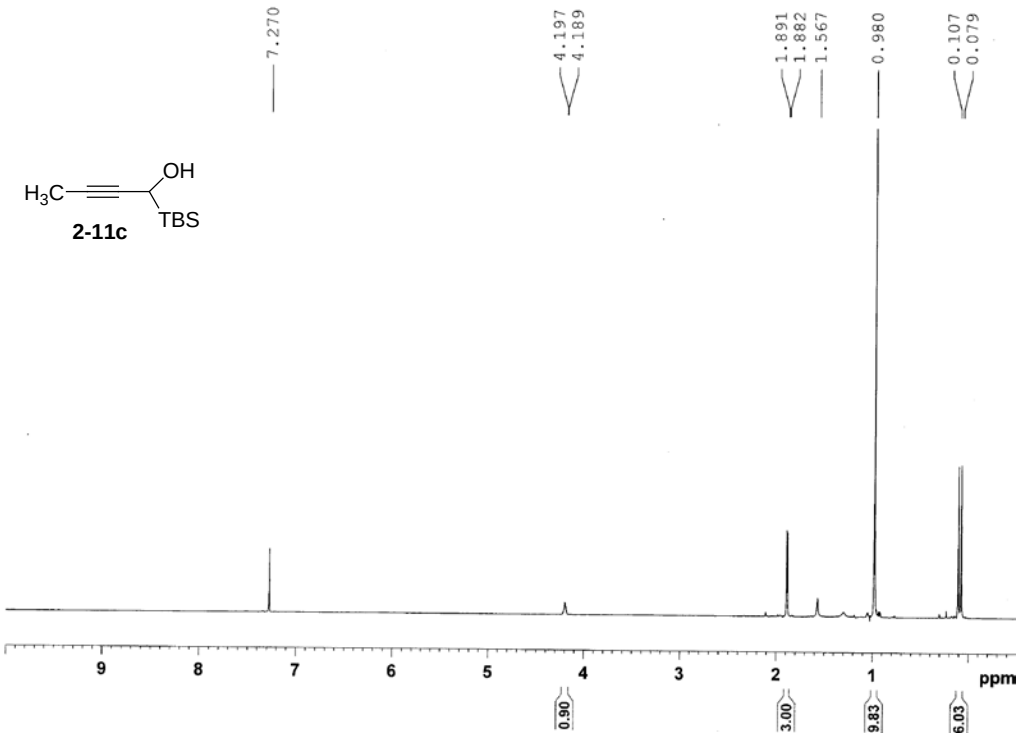

tp 11p.1-2 CDCl3 13chd nmr300 8/11/05
ppm

tp 193b.1-5-146 nmr301 1/10/07

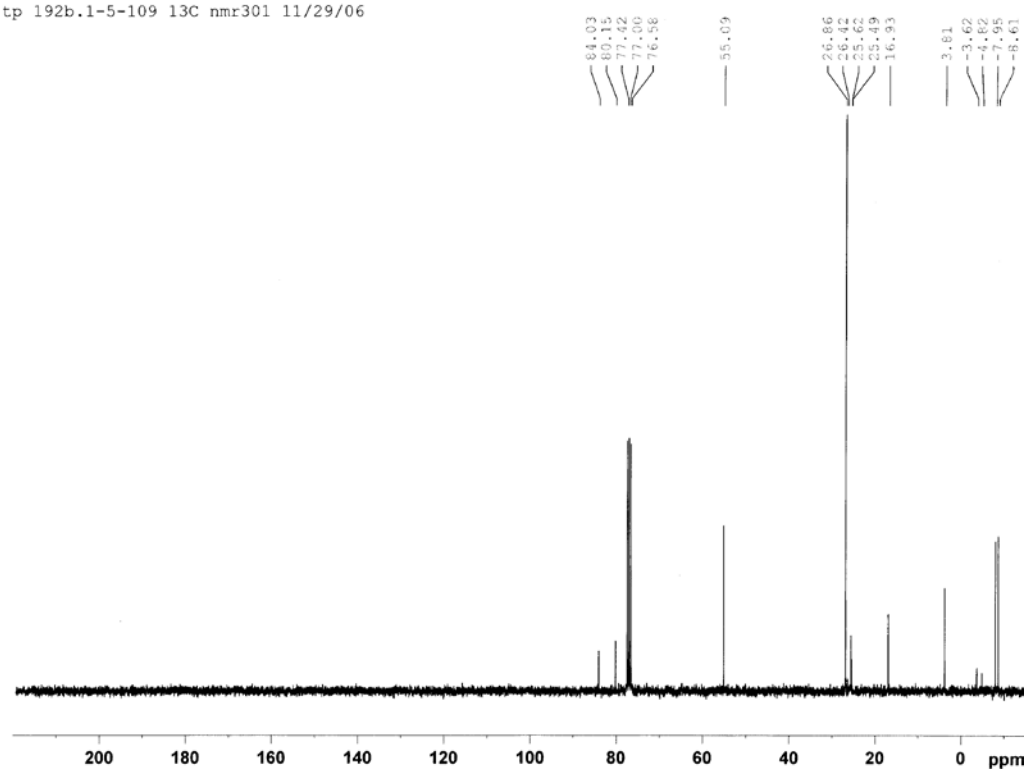


E2-1

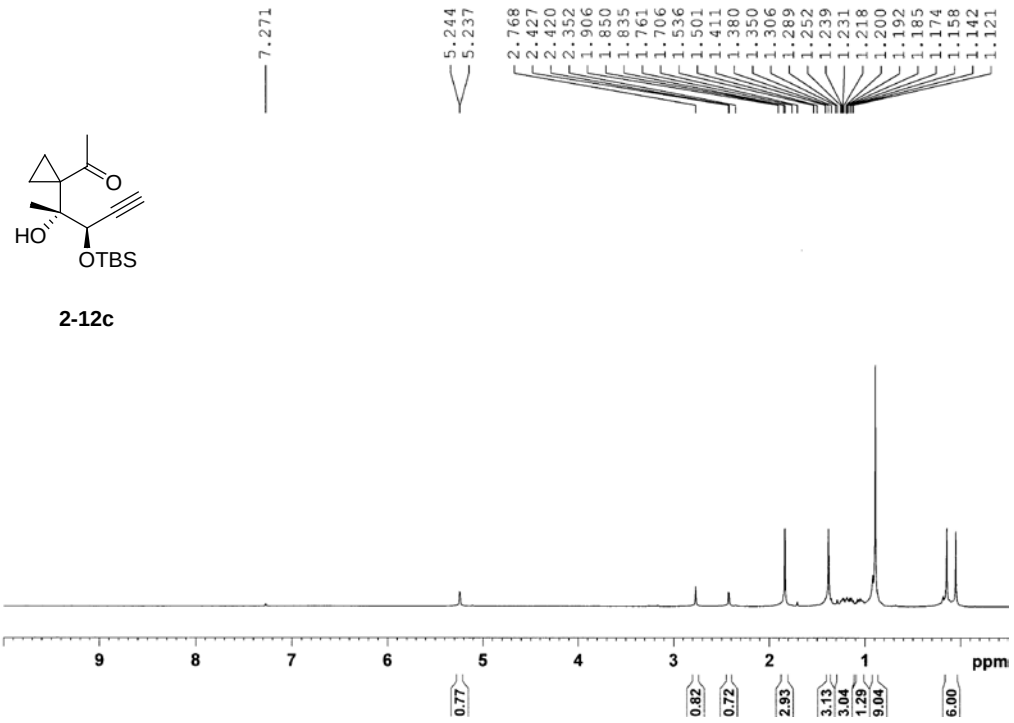
tp 192b.1-5-109 nmr301a 11/28/06



tp 192b.1-5-109 13C nmr301 11/29/06

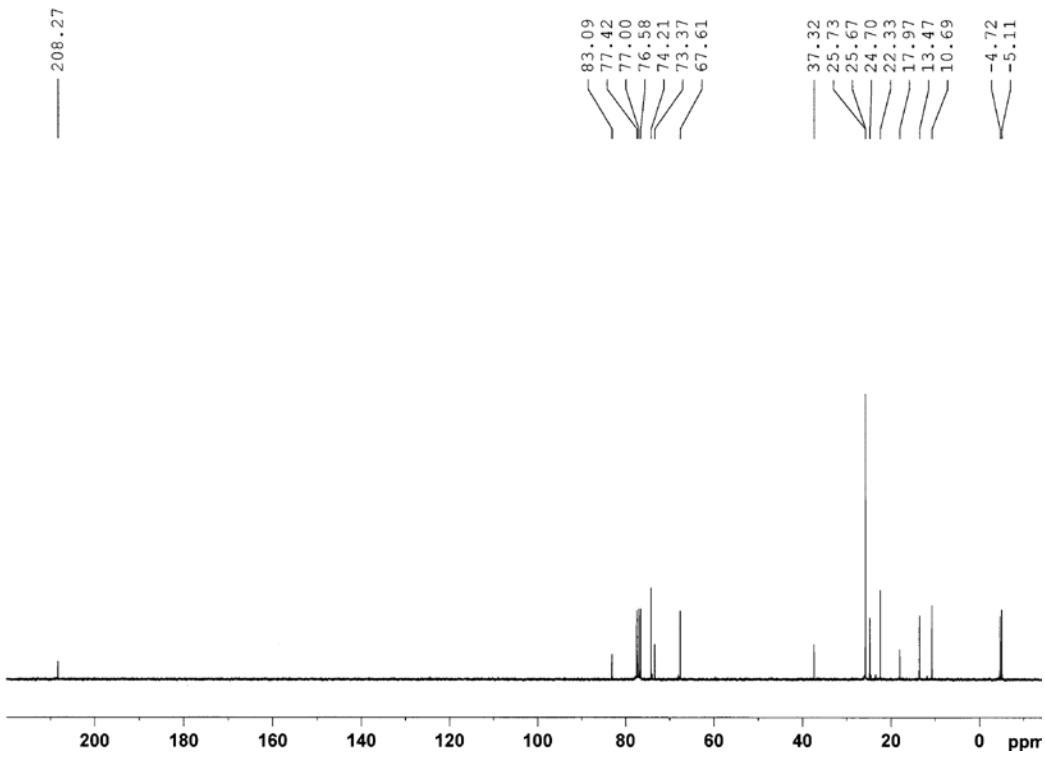


tp 247.1-5-114 nmr301a 2/22/07

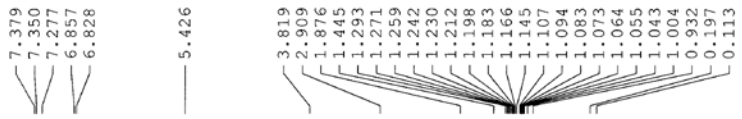


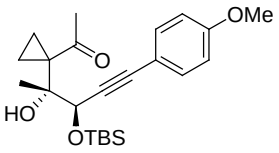
2-12c

tp 247.1-5-114 nmr301a 2/22/07

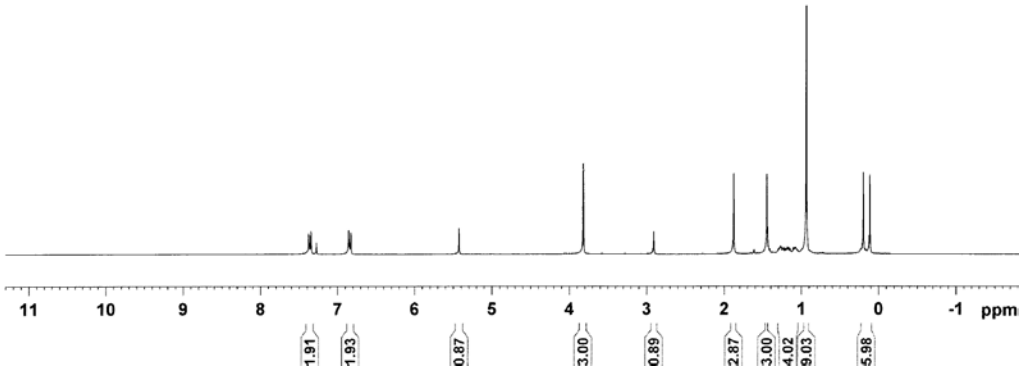


tp 248.1-5-116 1H CDCl3 nmr301 4/13/07

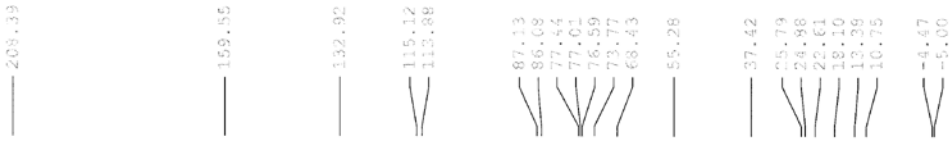


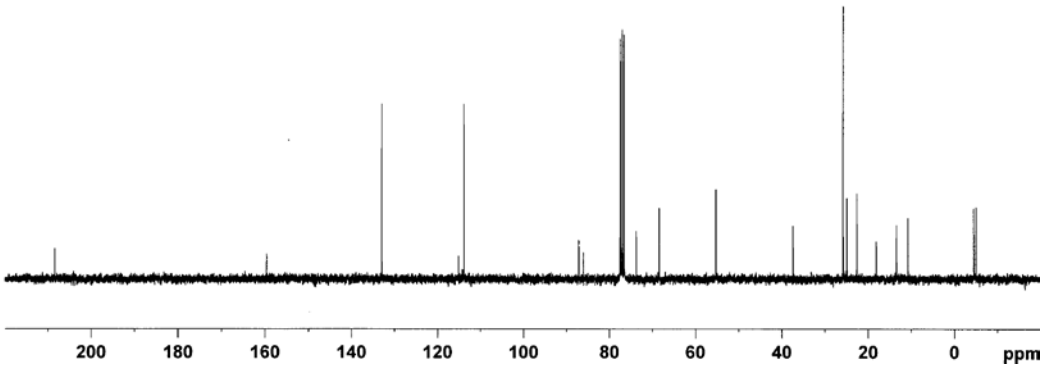


2-12e

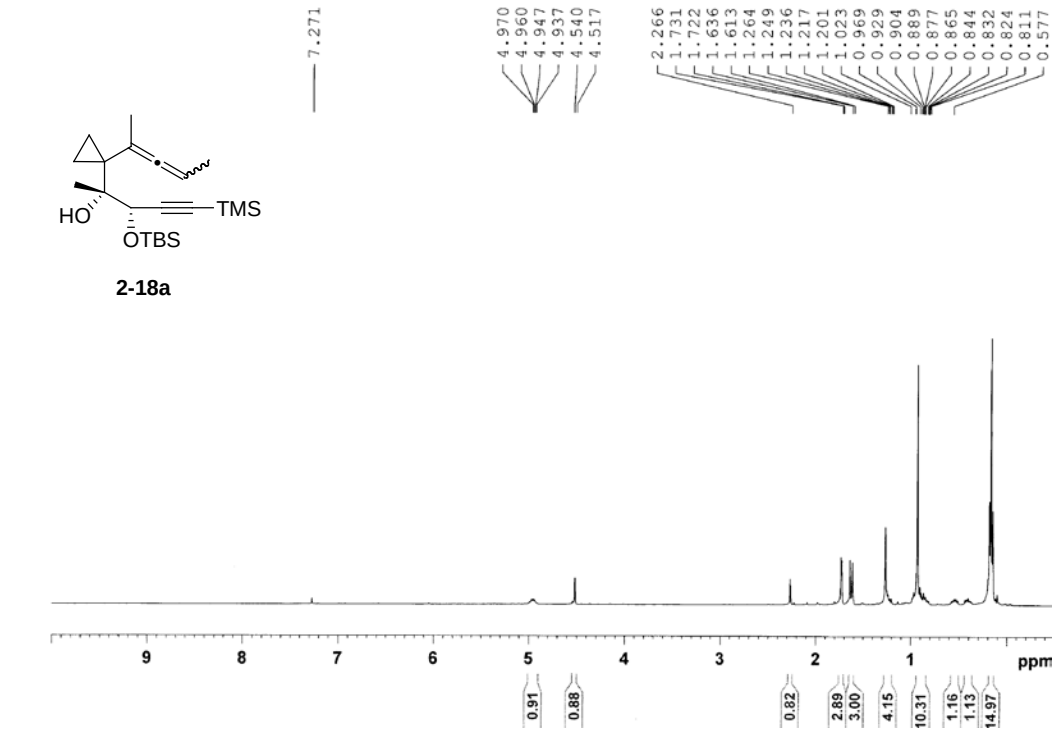


tp 248.1-5-116 13C CDCl3 nmr301a 4/13/07



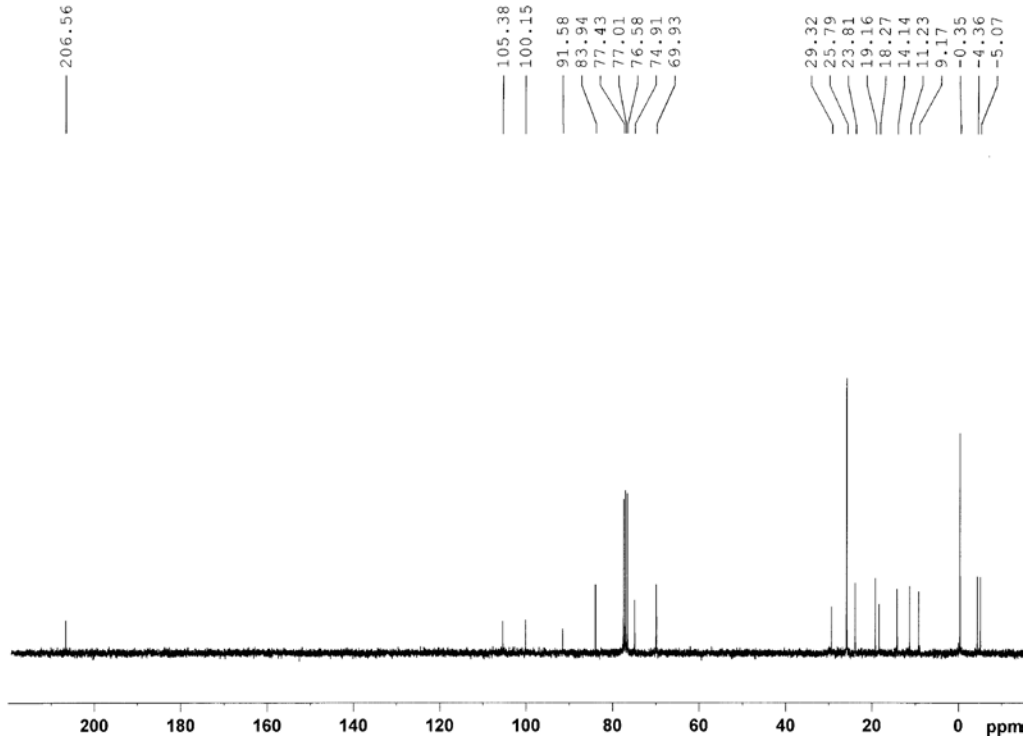


tp 195.20-5-175 13C CDCl3 nmr301 3/2/07

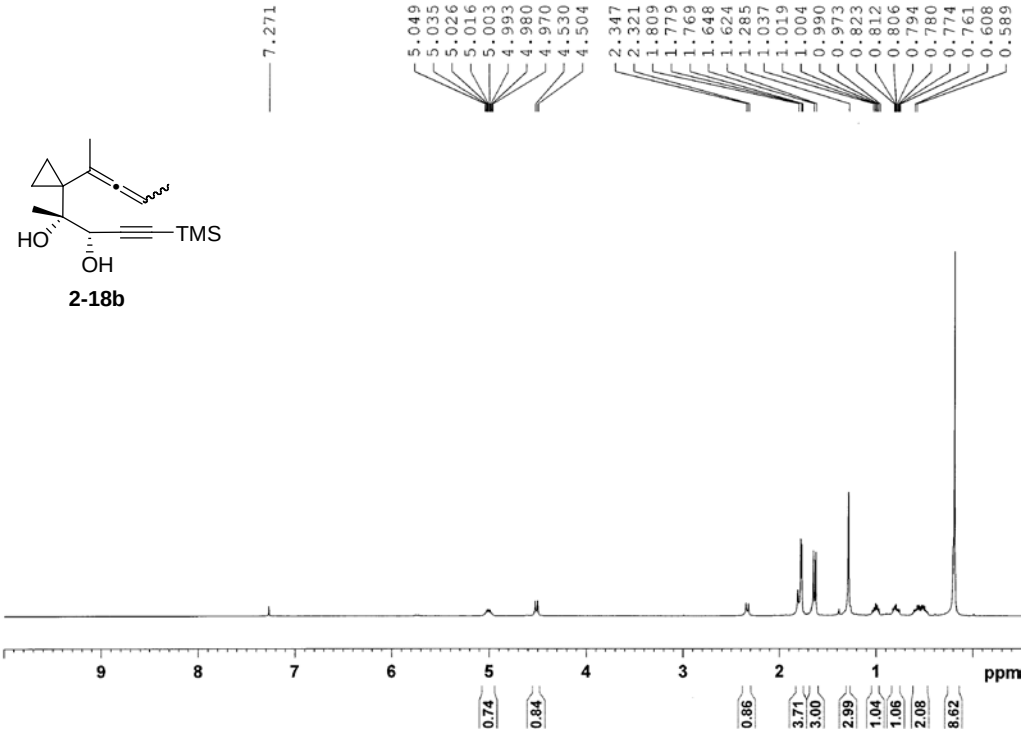


2-18a

tp 195.20-5-175 13C CDCl3 nmr301 3/2/07

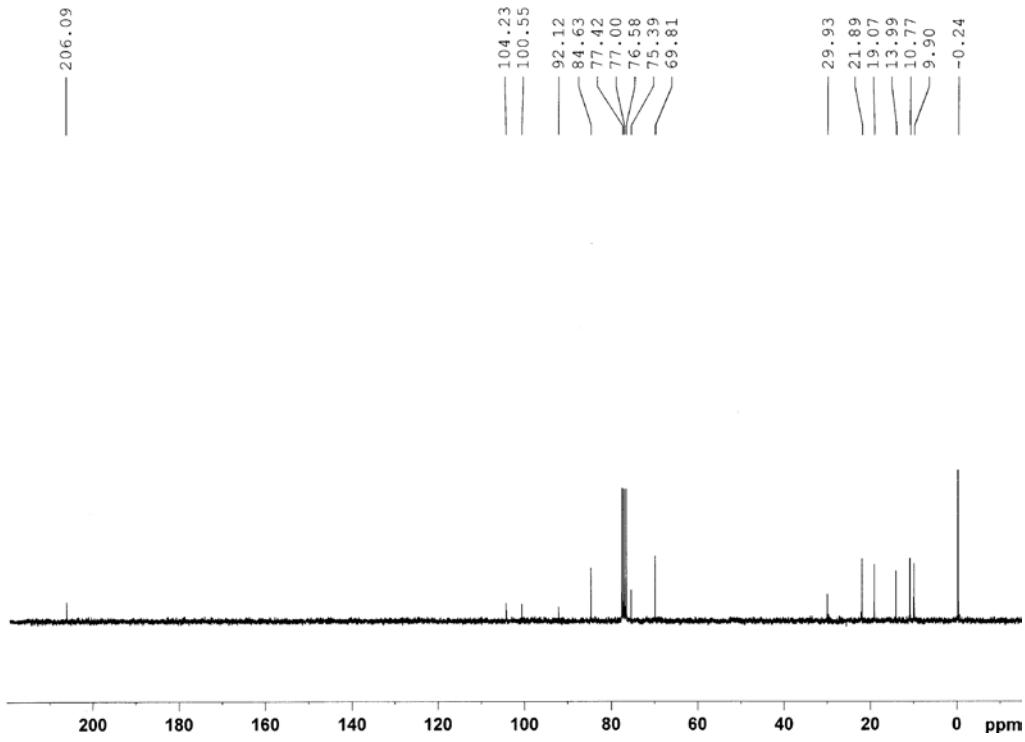


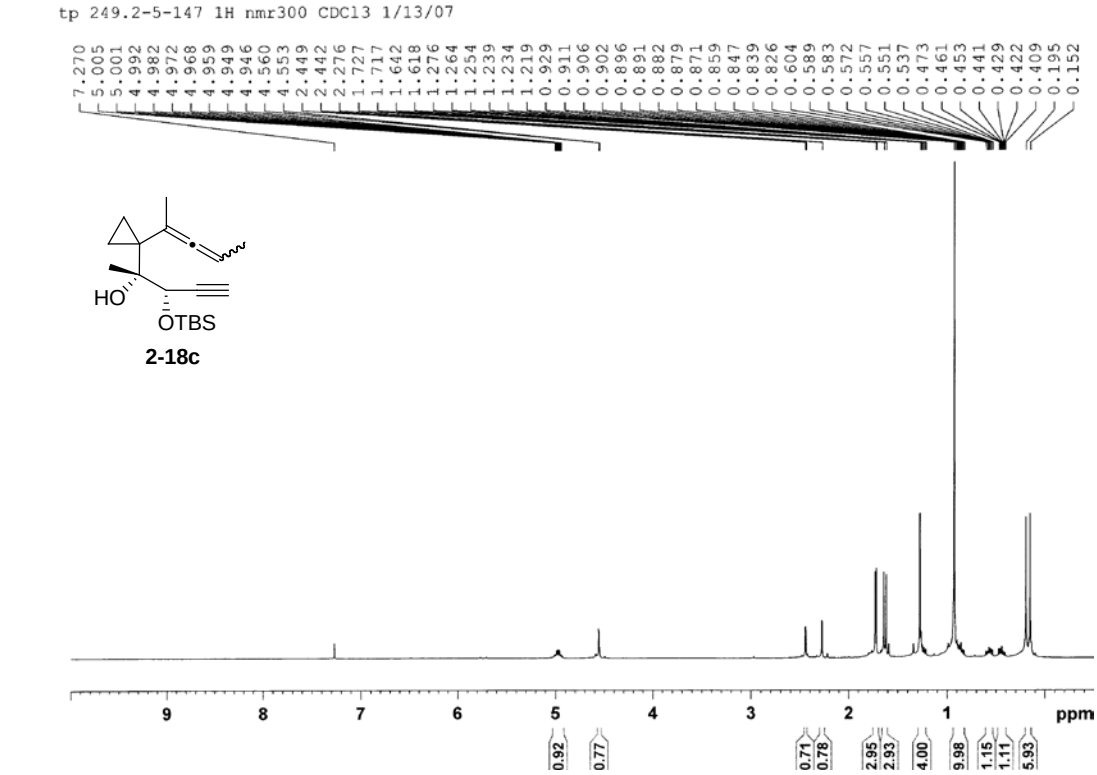
tp 210.8-5-142 nmr300 1H CDCl3 3/12/07



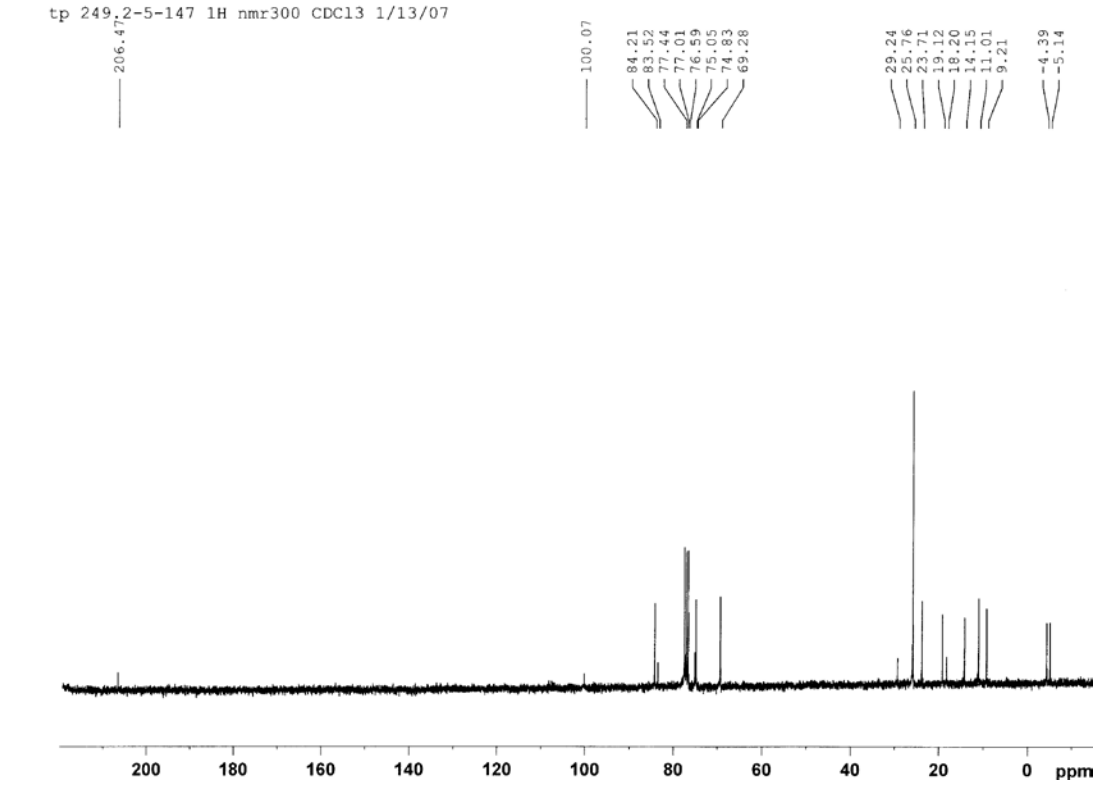
2-18b

tp 210.8-5-142 nmr301 13C CDCl3 3/12/07

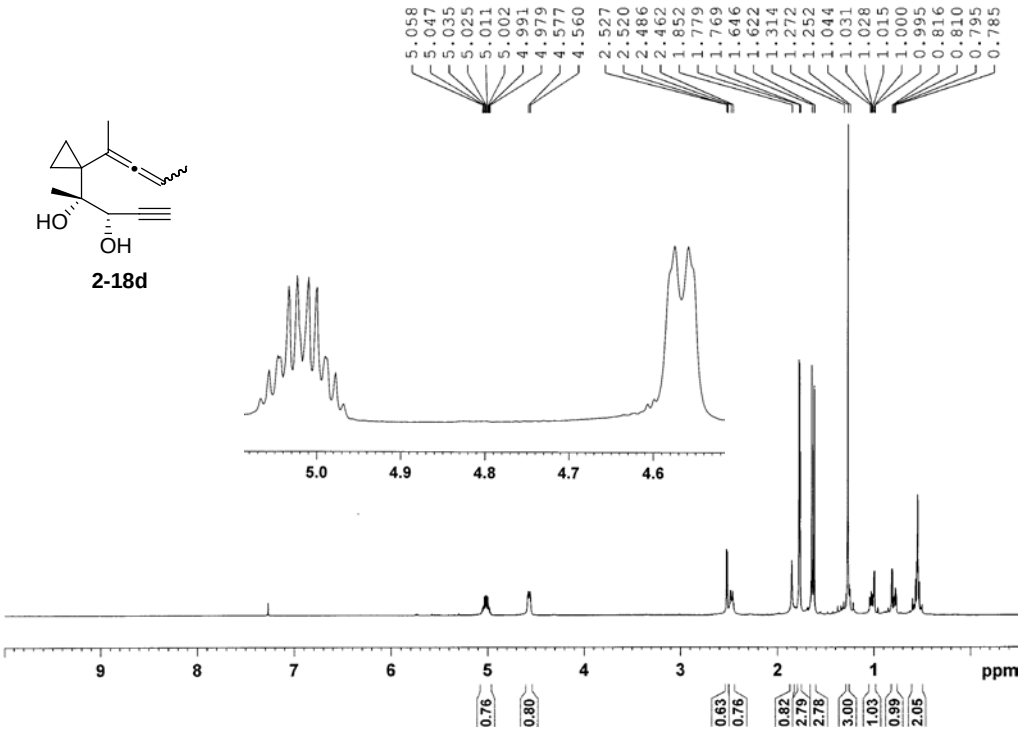



tp 249.2-5-147 1H nmr300 CDCl3 1/13/07
7.270
5.005
5.001
4.992
4.982
4.972
4.968
4.959
4.949
4.946
4.560
4.553
2.449
2.442
2.276
1.727
1.717
1.642
1.618
1.276
1.264
1.254
1.239
1.234
1.219
0.929
0.911
0.906
0.902
0.896
0.891
0.882
0.879
0.871
0.859
0.847
0.839
0.826
0.604
0.589
0.583
0.572
0.557
0.551
0.537
0.473
0.461
0.453
0.441
0.429
0.422
0.409
0.195
0.152
HO
OTBS
9
8
7
6
5
4
3
2
1
ppm
0.92
0.77
0.71
0.78
2.95
2.93
4.00
9.98
1.15
1.11
5.93

2-18c

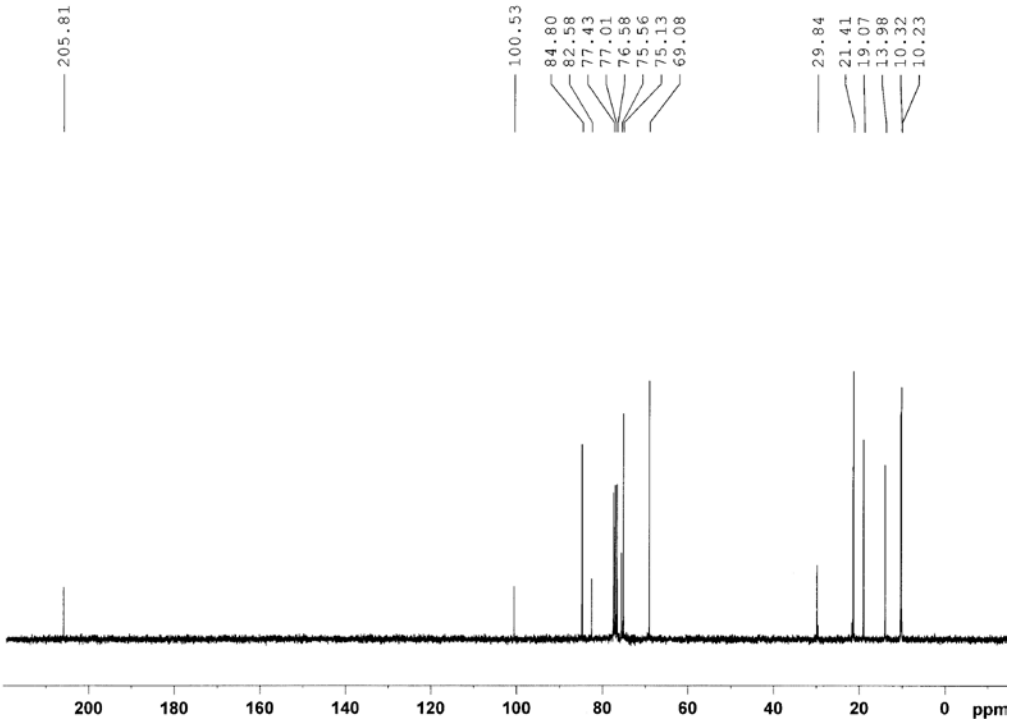

tp 249.2-5-147 1H nmr300 CDCl3 1/13/07
206.47
100.07
84.21
83.52
77.44
77.01
76.59
75.05
74.83
69.28
29.24
25.76
23.71
19.12
18.20
14.15
11.01
9.21
-4.39
-5.14
200
180
160
140
120
100
80
60
40
20
0
ppm

tp 216.3-5-133 1H CDCl3 nmr300 3/15/07

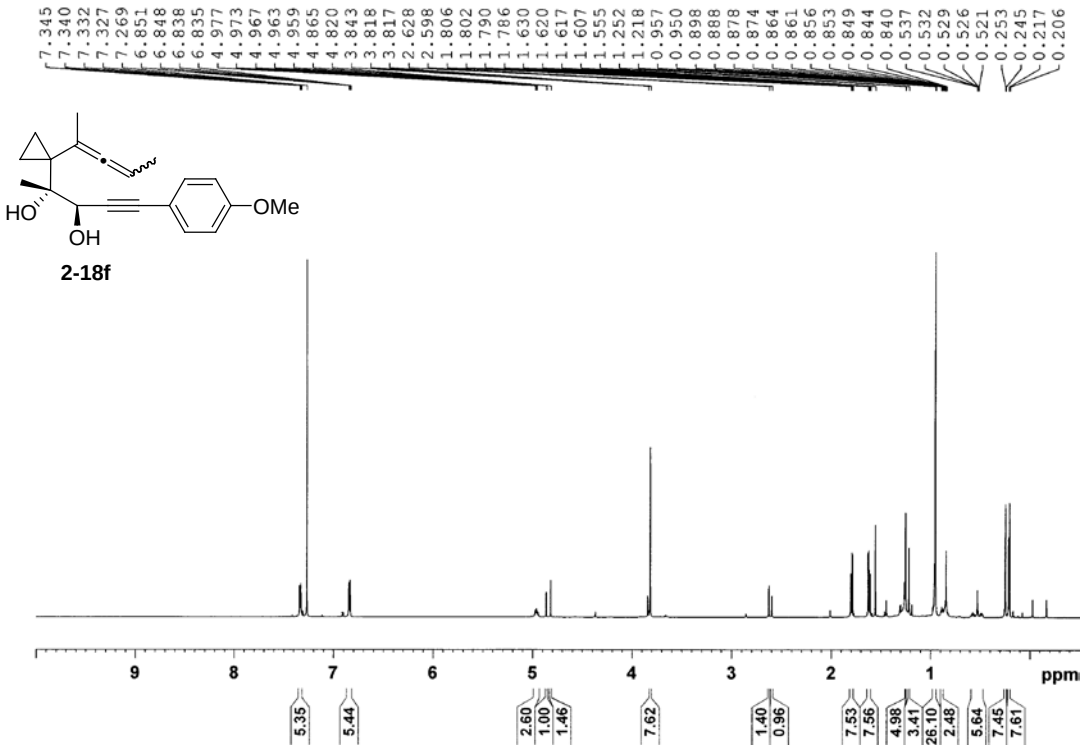


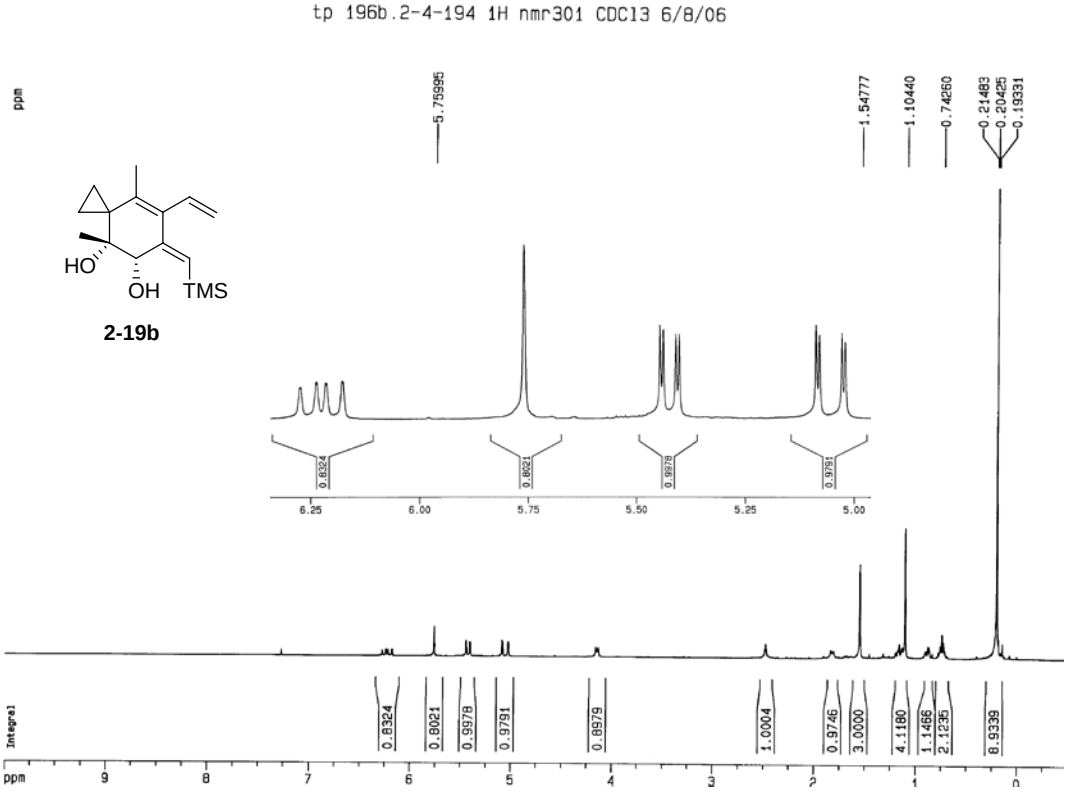
2-18d

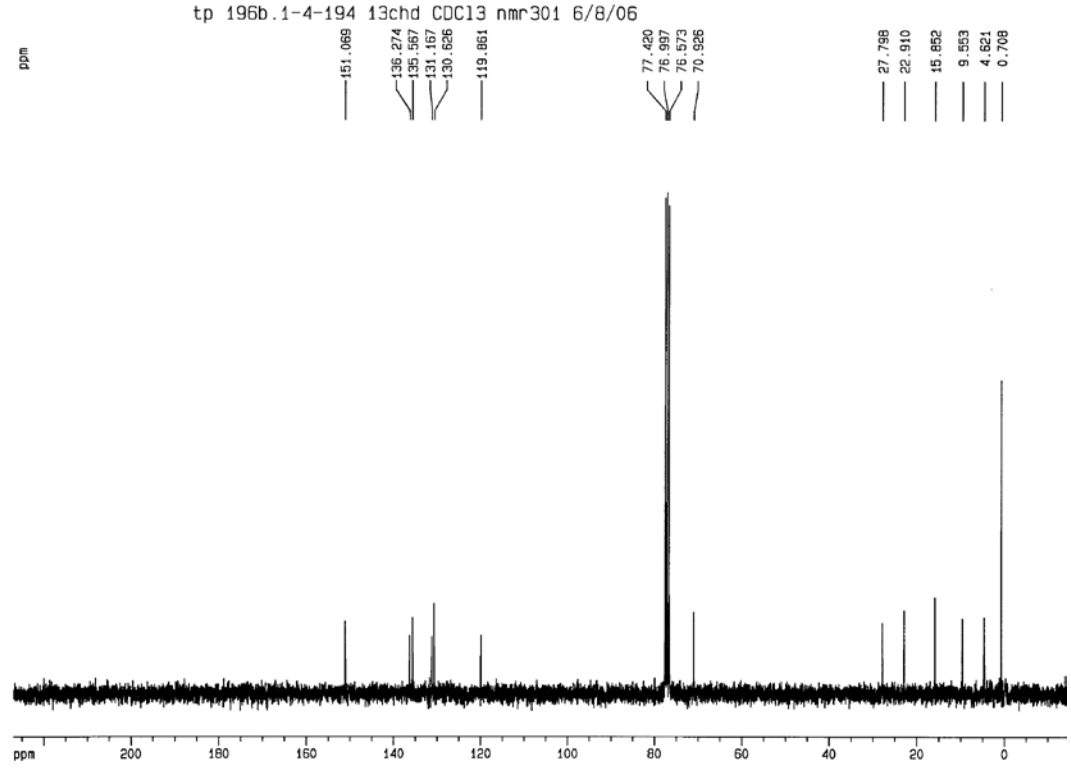
tp 216.3-5-133 13C CDCl3 nmr301 3/15/07



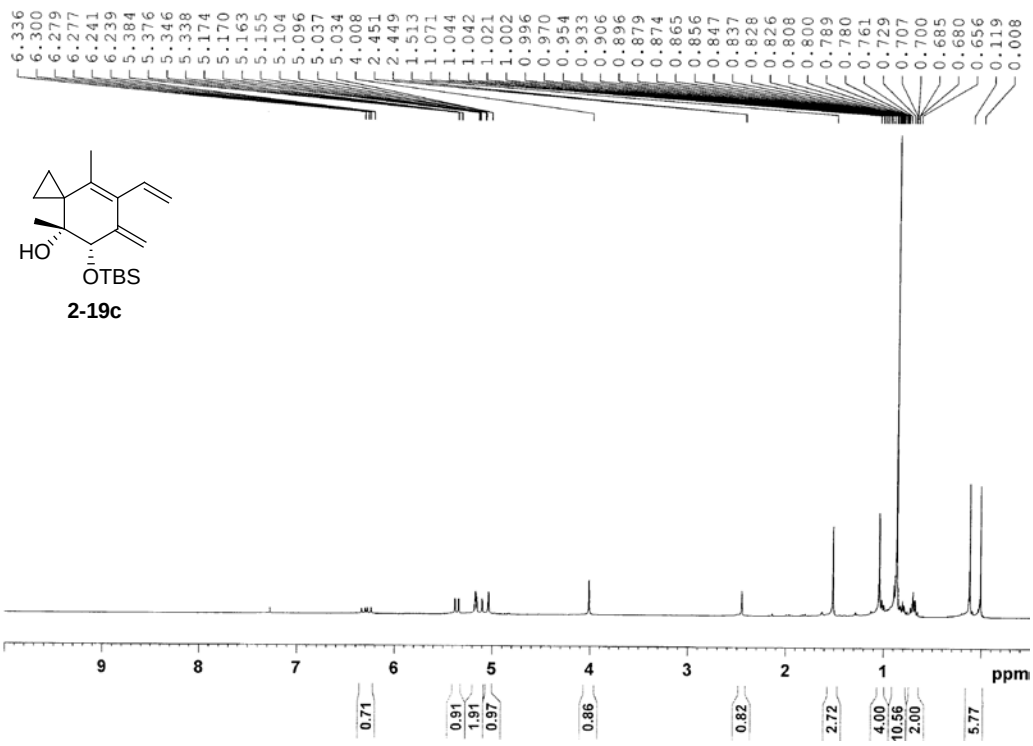
tp 195b.7-6-22 2nd HPLC frxn 1H CDCl3 nmr700 1/19/09




tp 196b.2-4-194 1H nmr301 CDCl3 6/8/06
HO
OH
TMS
2-19b

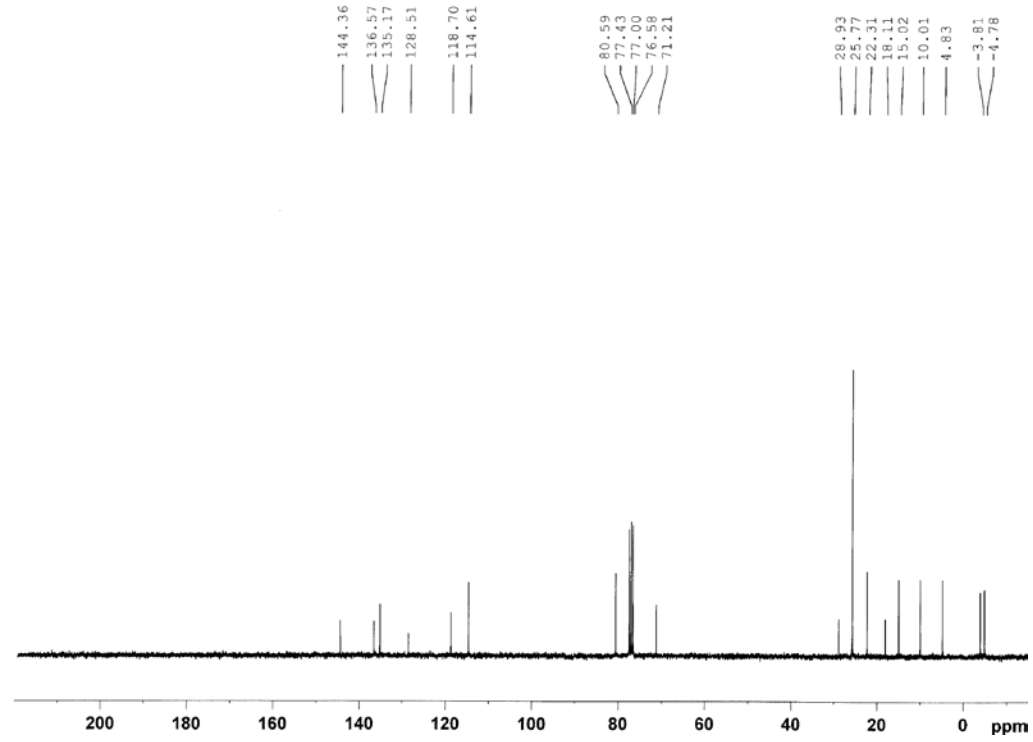

tp 196b.1-4-194 13chd CDCl3 nmr301 6/8/06

tp 196d.2-5-156 nmr300 1/18/07

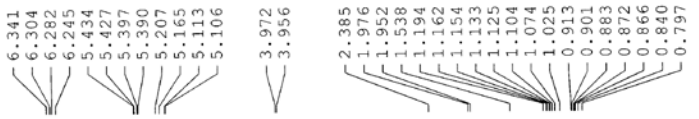


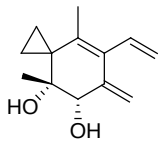
2-19c

tp 196d.2-5-156 nmr301 13C 1/18/07

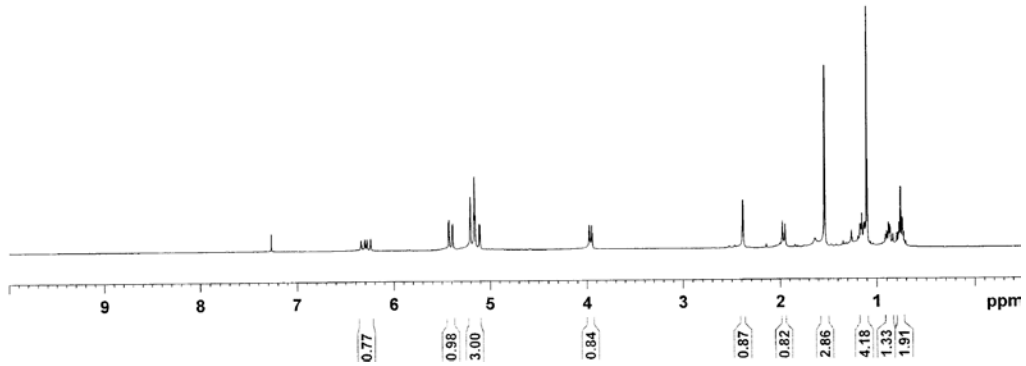


tp 250.2-5-159 1H CDCl3 nmr300 1/22/07

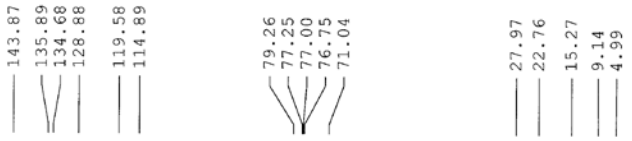


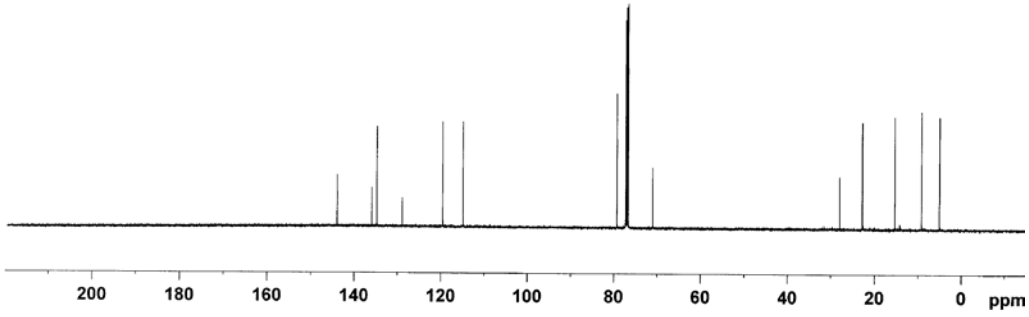


2-19d

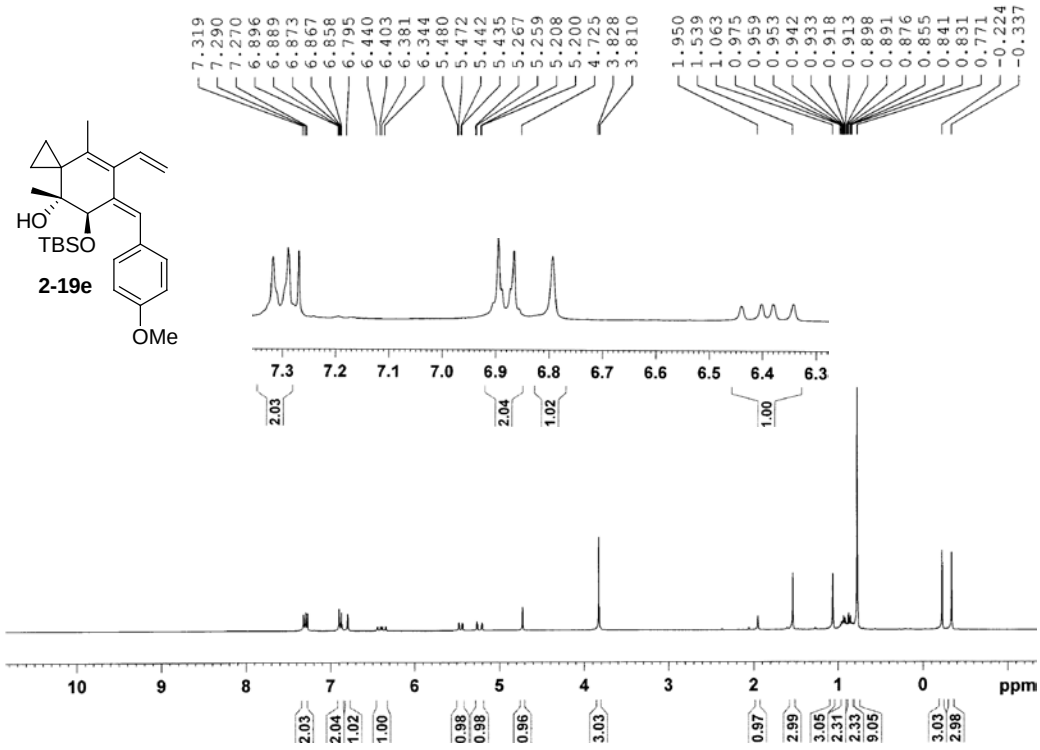


tp 250.3-5-163 13C CDCk3 nmr500 1/26/07

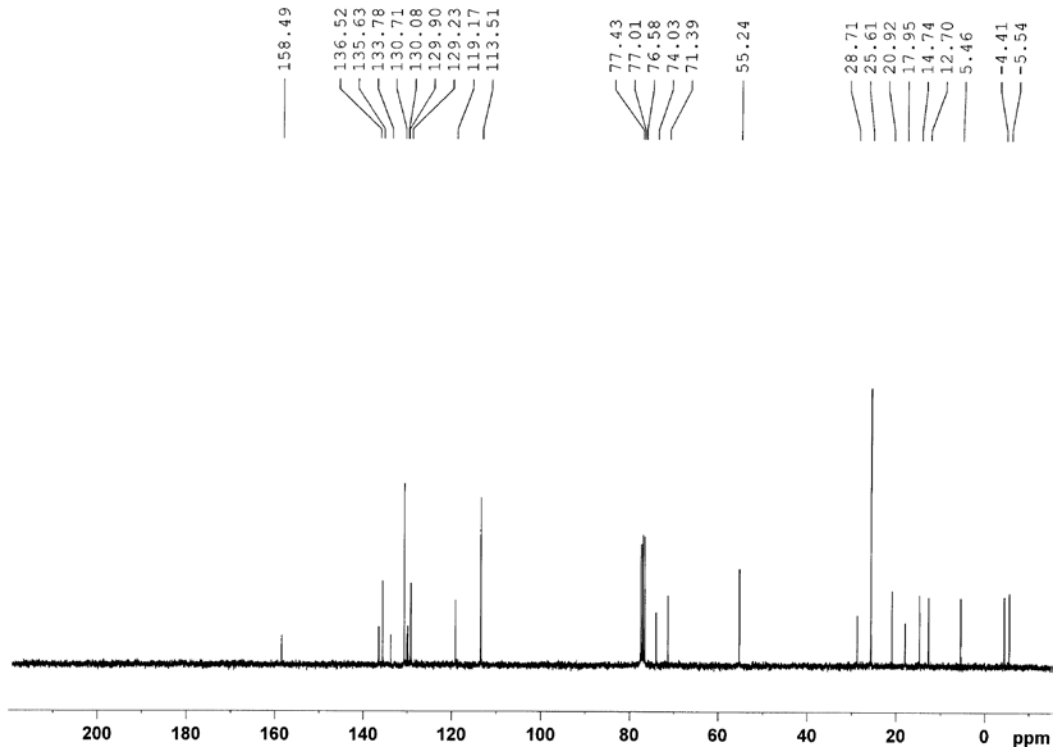




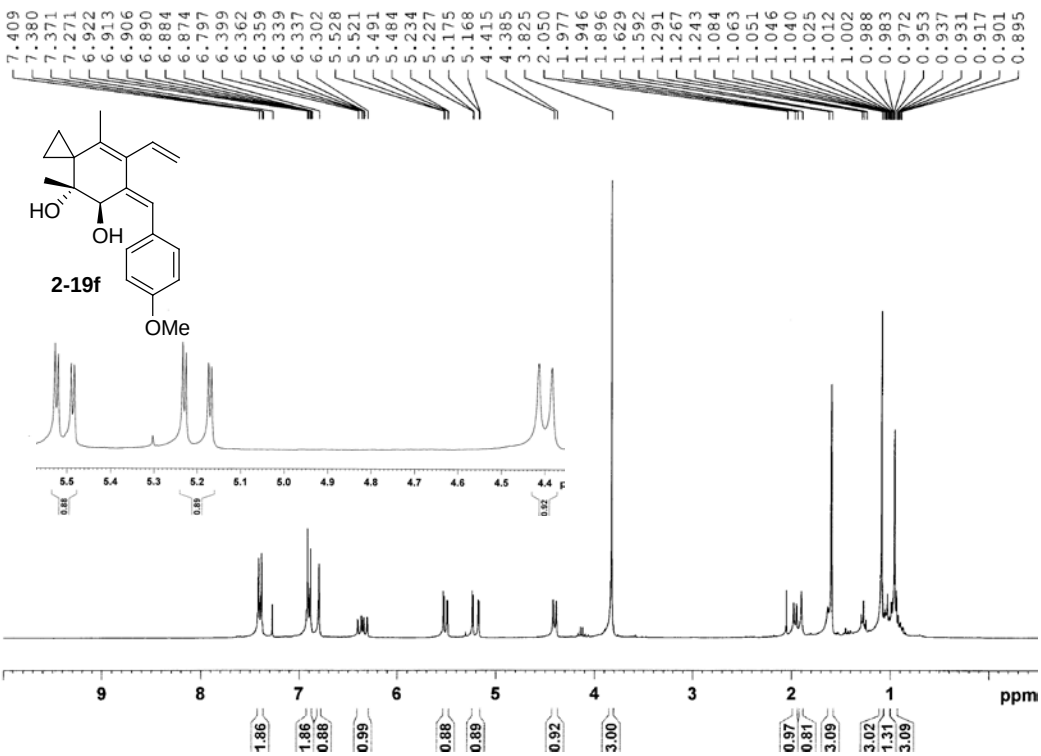
tp 196e.2-5-208 1H CDCl3 nmr301 4/26/07



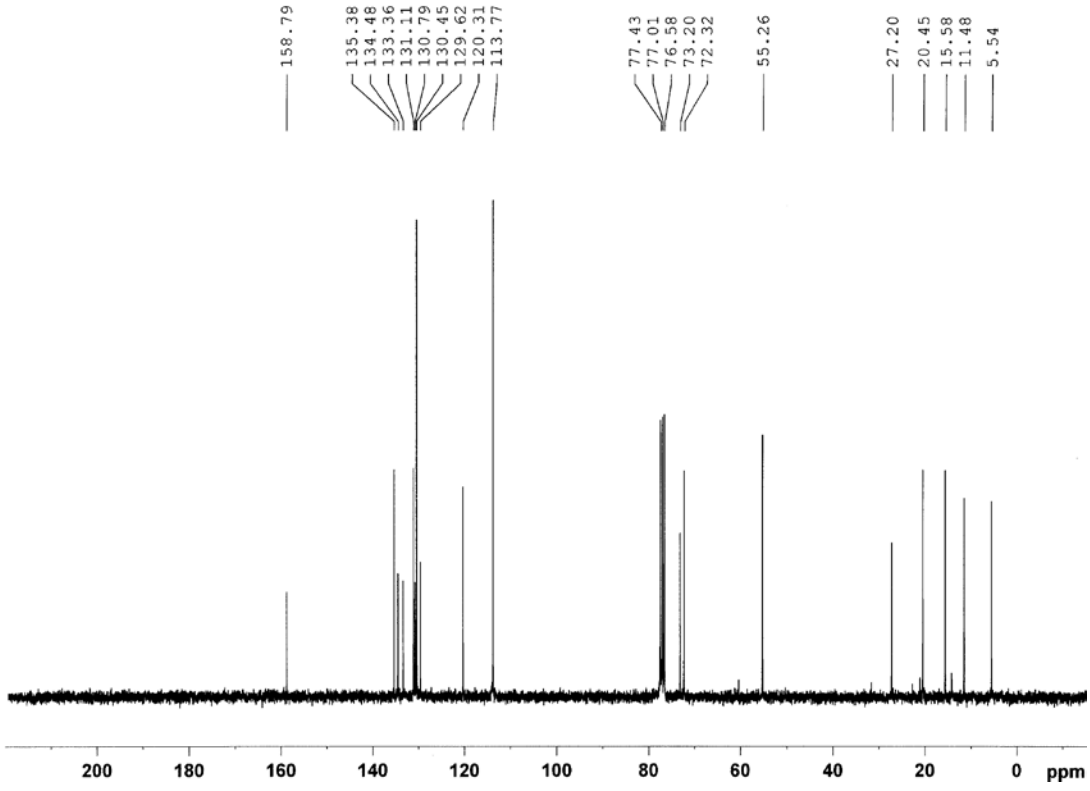
tp 196e.2-5-208 13C CDCl3 nmr301 4/26/07



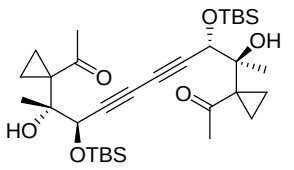
tp 250+196f nmr301 5/15/07 CDCl3 1H



tp 250+196f nmr301 5/15/07 CDCl3 13C

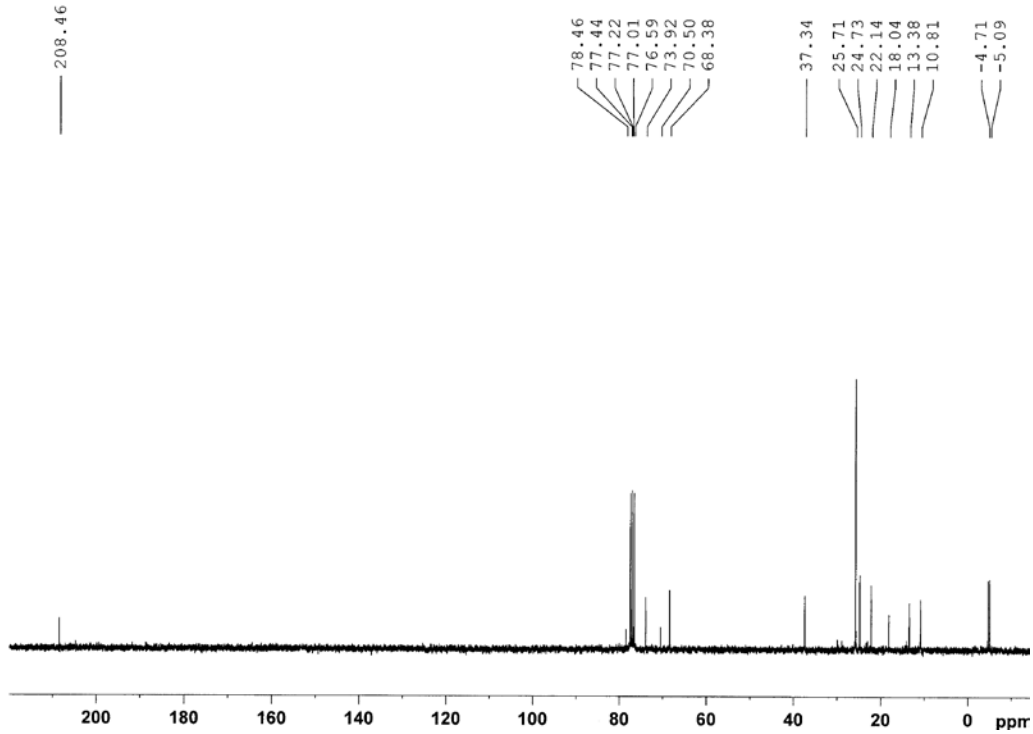


tp 248.1-5-116 1H 2nd spot CDCl3 nmr301a 4/13/07

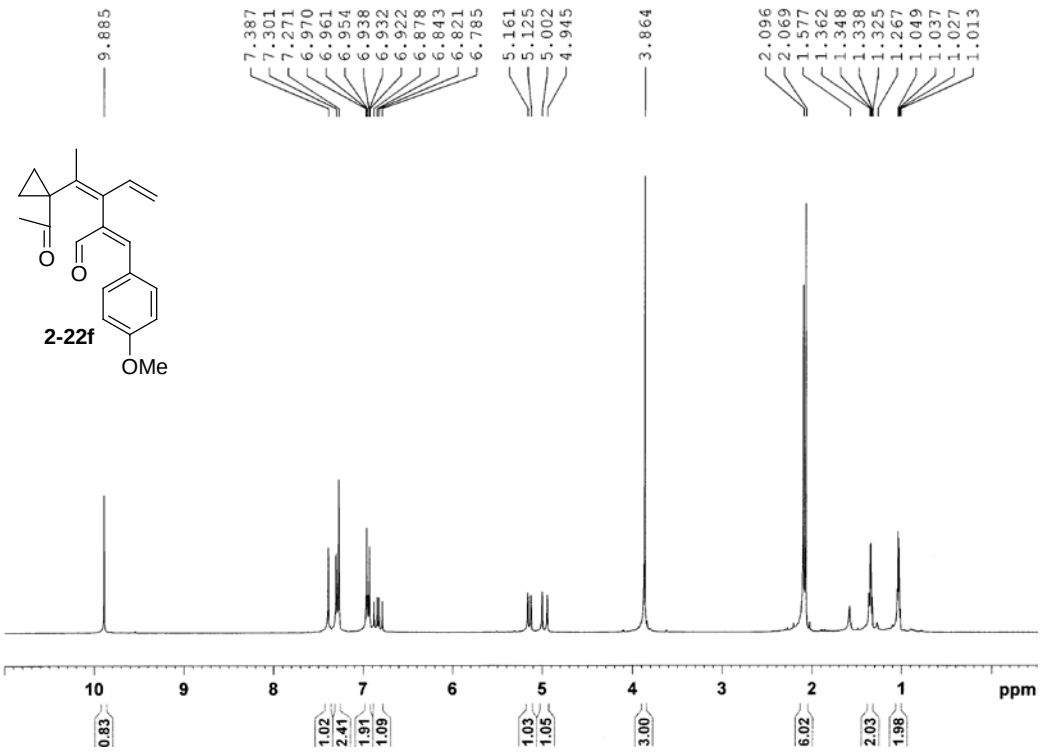


2-21

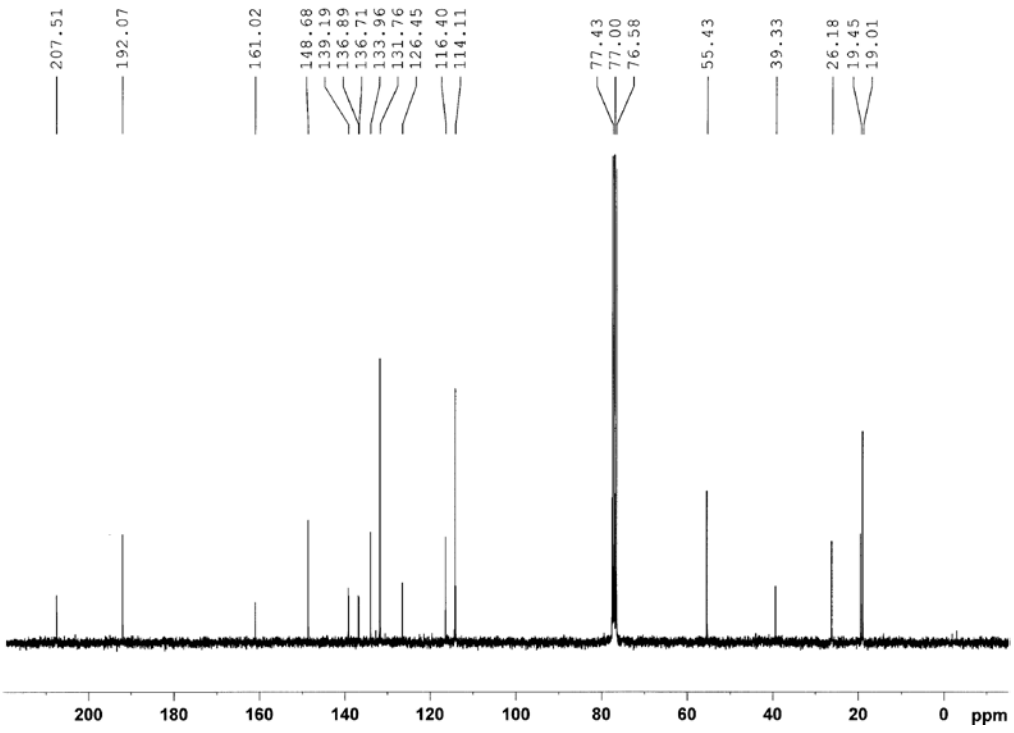
tp 248.1-5-116 13C 2nd spot CDCl3 nmr301a 4/13/07



tp 221b.1-6-25 2nd nmr301 5/18/07



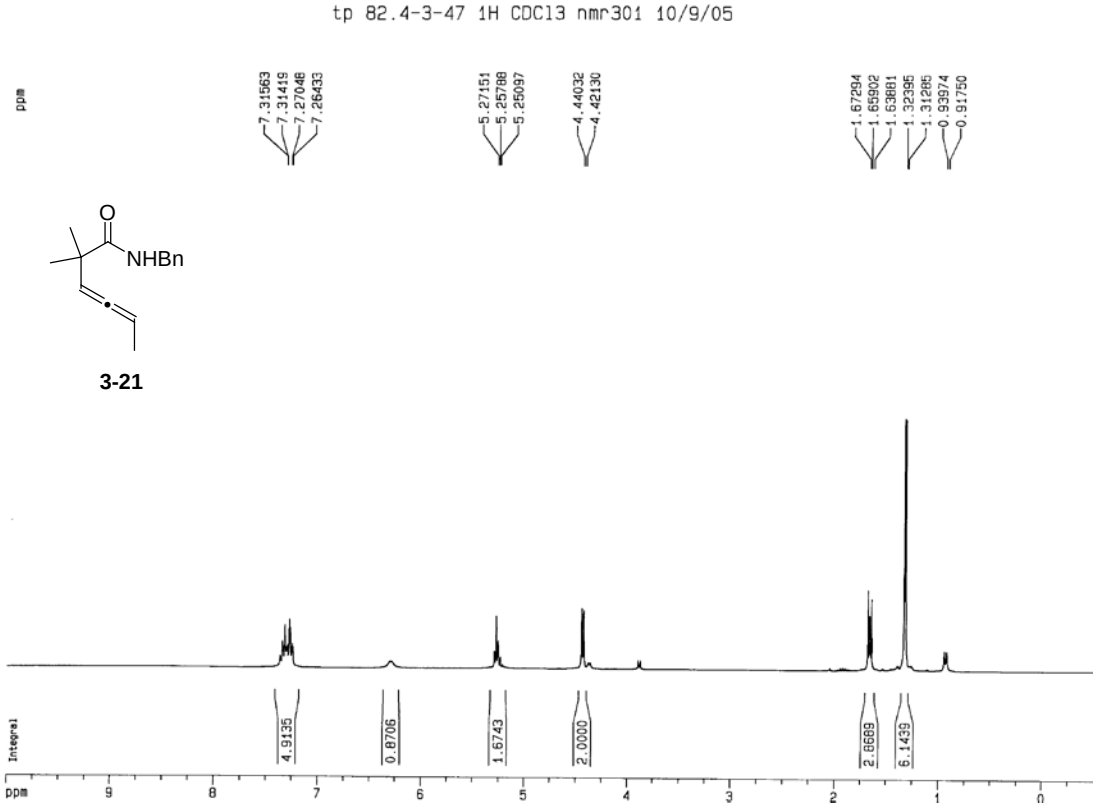
221b.1-6-25 2nd 13C nmr301 CDCl3 5/19/07



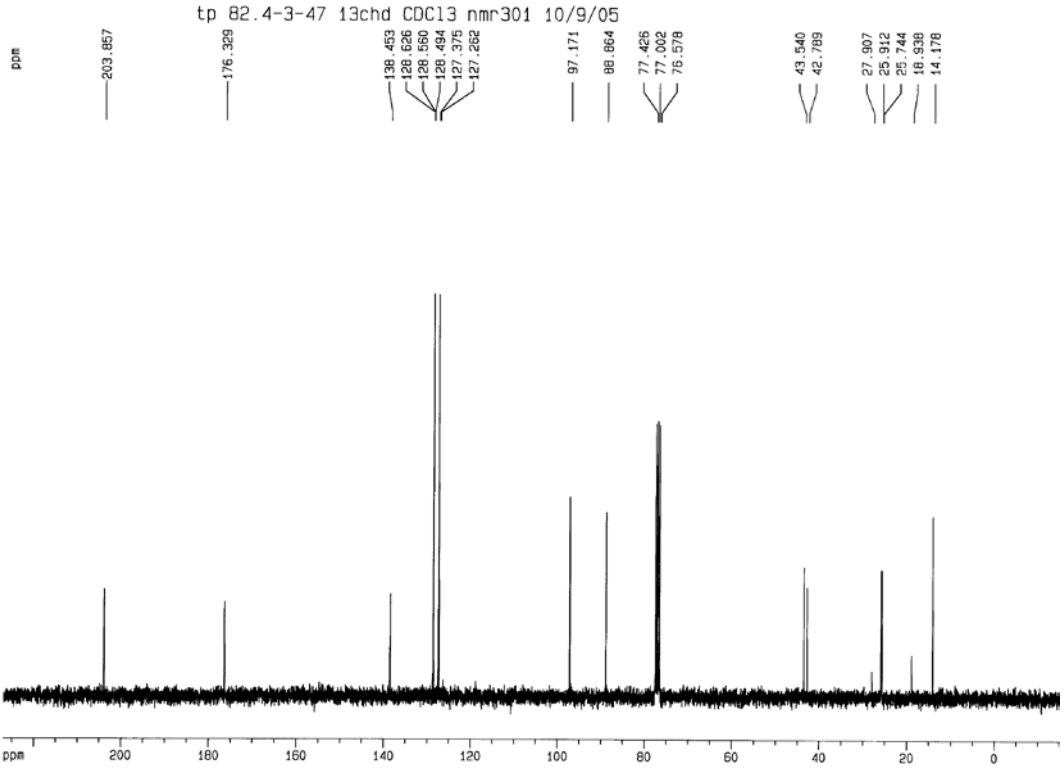
Most spectra for compounds from Chapter 3 have been uploaded with the supporting information for our δ- and ε-lactam publication in *Organic Letters*.[40] Those compounds not reported in that publication have spectra depicted below.

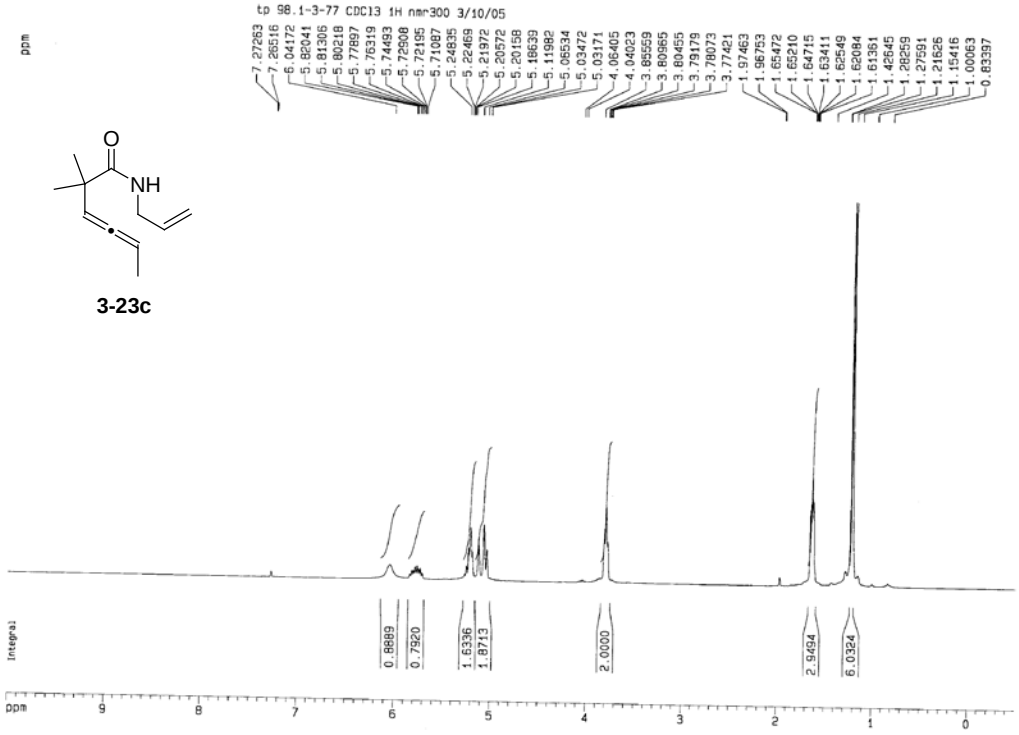
Compound Cross-Reference

Current Compound Number	Compound Number in Organic Letters
E3-1	**6b**
3-26a	**9a**
3-26f	**9b**
3-26g	**9c**
3-26h	**9d**
3-26i	**9e**
3-26j	**11**
3-23a	**8a**
3-23b	**8f**
3-23f	**8b**
3-23g	**8c**
3-23h	**8d**
3-23i	**8e**
3-23j	**10**
3-19	**6c**
3-24f	**7b**
3-24i	**7e**
3-25	**13**
3-35	**15**

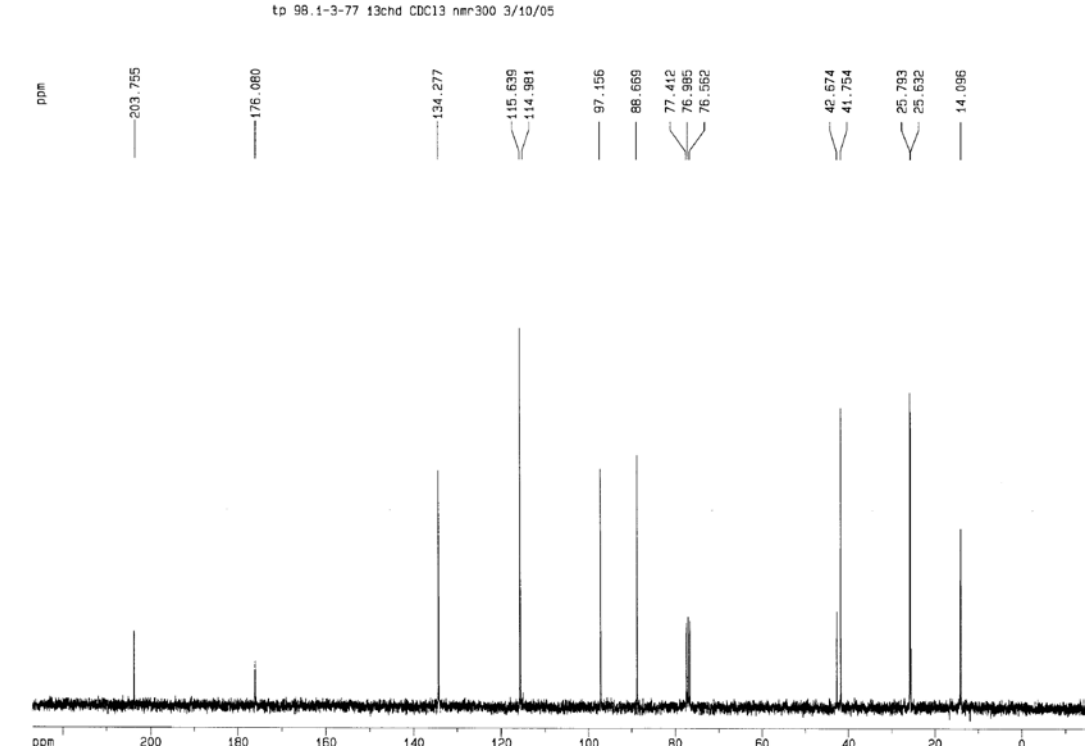

tp 82.4-3-47 1H CDCl3 nmr301 10/9/05
ppm
7.31563
7.31419
7.27048
7.26433
5.27151
5.25788
5.25097
4.44032
4.42130
1.67294
1.65902
1.63881
1.32395
1.31285
0.93974
0.91750
O
NHBn
Integral
4.9135
0.8706
1.6743
2.0000
2.6689
6.1439
ppm
9
8
7
6
5
4
3
2
1
0

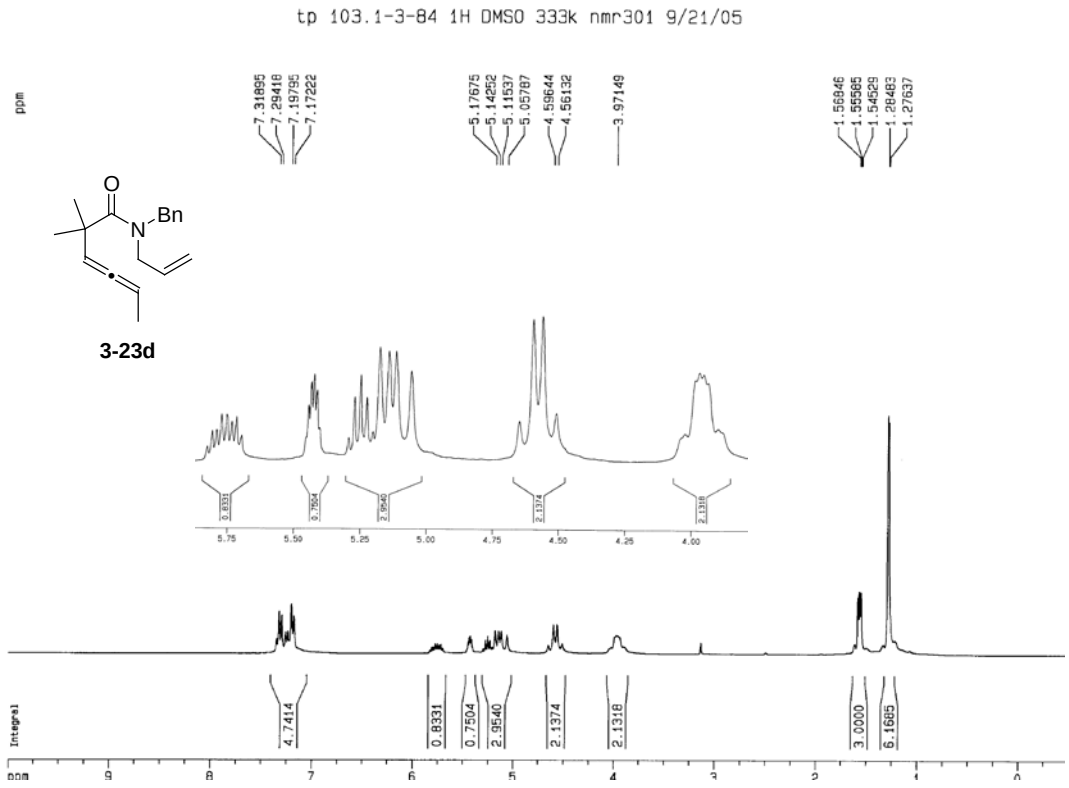
3-21

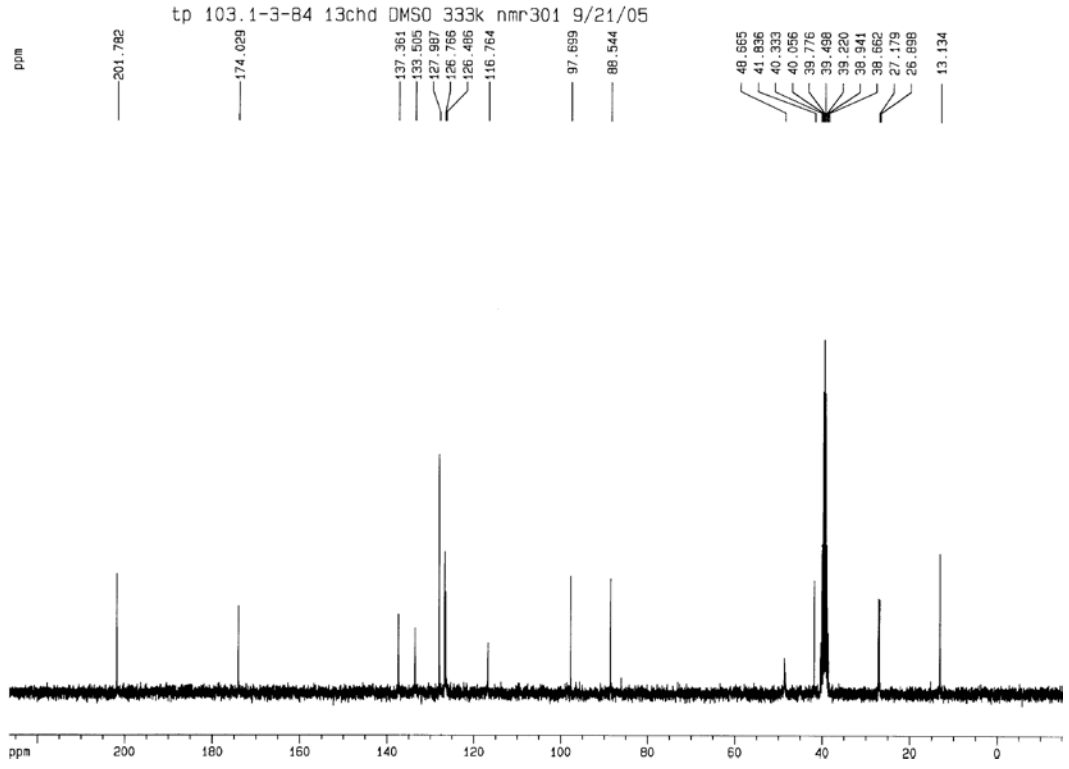

tp 82.4-3-47 13chd CDCl3 nmr301 10/9/05
ppm
203.857
176.329
138.453
128.626
128.560
128.494
127.375
127.262
97.171
88.864
77.426
77.002
76.578
43.540
42.789
27.907
25.912
25.744
18.938
14.178
ppm
200
180
160
140
120
100
80
60
40
20
0

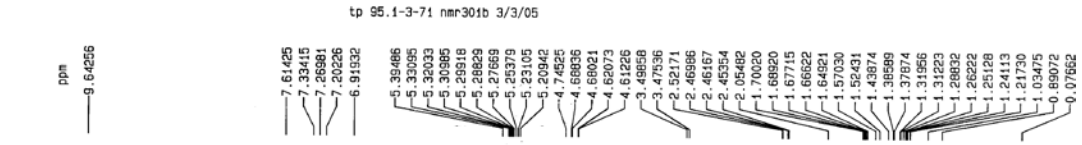

tp 98.1-3-77 CDCl3 1H nmr300 3/10/05
ppm
7.27263
7.26516
6.04172
5.82041
5.81306
5.80218
5.77897
5.76319
5.74493
5.72908
5.72195
5.71087
5.24835
5.22469
5.21972
5.20572
5.20158
5.18639
5.11982
5.06534
5.03472
5.03171
4.06405
4.04023
3.86559
3.80965
3.80455
3.79179
3.78073
3.77421
1.97463
1.96753
1.65472
1.65210
1.64715
1.63411
1.62549
1.62084
1.61361
1.42645
1.28259
1.27591
1.21626
1.15416
1.00063
0.83397
O
NH
Integral
0.8889
0.7920
1.6336
1.8713
2.0000
2.9494
6.0324
ppm
9
8
7
6
5
4
3
2
1
0

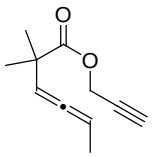
3-23c


tp 98.1-3-77 13chd CDCl3 nmr300 3/10/05
ppm
203.755
176.080
134.277
115.639
114.981
97.156
88.669
77.412
76.985
76.562
42.674
41.754
25.793
25.632
14.096
ppm
200
180
160
140
120
100
80
60
40
20
0

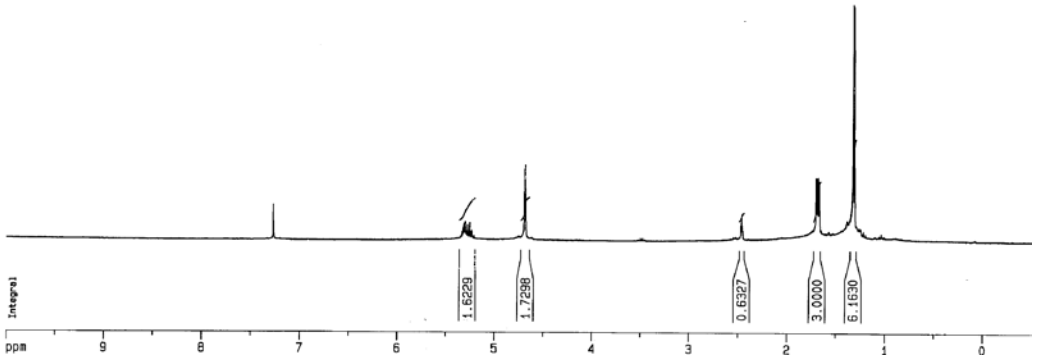

tp 103.1-3-84 1H DMSO 333k nmr301 9/21/05
ppm
7.31895
7.29418
7.19795
7.17222
5.17675
5.14252
5.11537
5.05787
4.59644
4.56132
3.97149
1.56846
1.55565
1.54529
1.28483
1.27637
O
N
Bn
3-23d
Integral
4.7414
0.8331
0.7504
2.9540
2.1374
2.1318
3.0000
6.1665

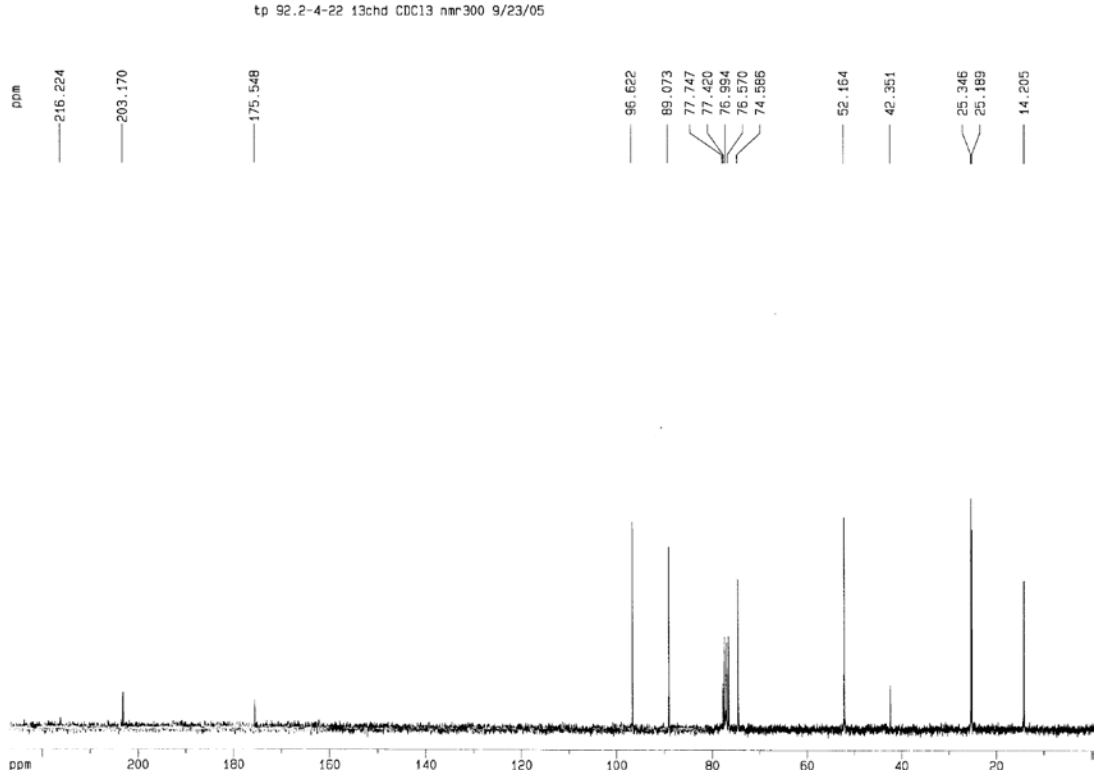

tp 103.1-3-84 13chd DMSO 333k nmr301 9/21/05
ppm
201.782
174.029
137.361
133.505
127.987
126.766
126.486
116.764
97.699
88.544
48.665
41.836
40.333
40.056
39.776
39.498
39.220
38.941
38.662
27.179
26.898
13.134

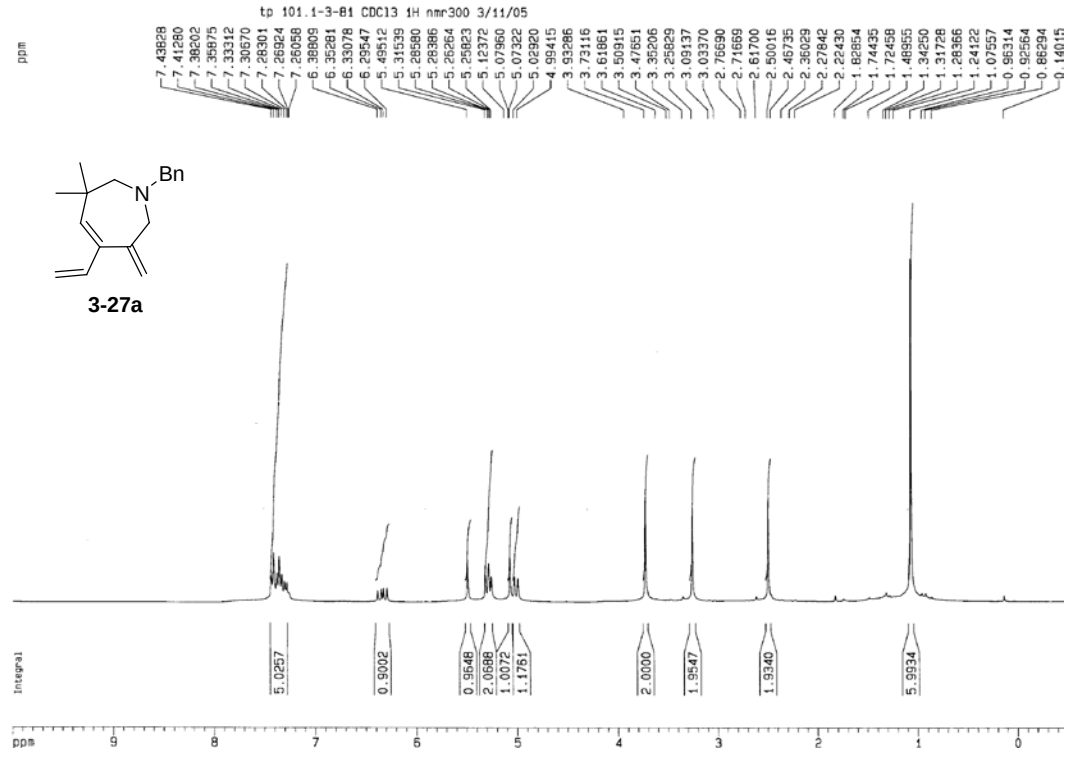

tp 95.1-3-71 nmr301b 3/3/05
ppm
9.64256
7.61425
7.33415
7.26981
7.20226
6.91932
5.39486
5.33095
5.32033
5.30985
5.29918
5.28829
5.27669
5.25379
5.23105
5.20942
4.74525
4.68836
4.68021
4.62073
4.61226
3.49858
3.47536
2.52171
2.46986
2.46167
2.45354
2.05482
1.70020
1.68920
1.67715
1.66622
1.64921
1.57030
1.52431
1.43874
1.38589
1.37874
1.31956
1.31223
1.28832
1.26222
1.25128
1.24113
1.21730
1.03475
0.89072
0.07662



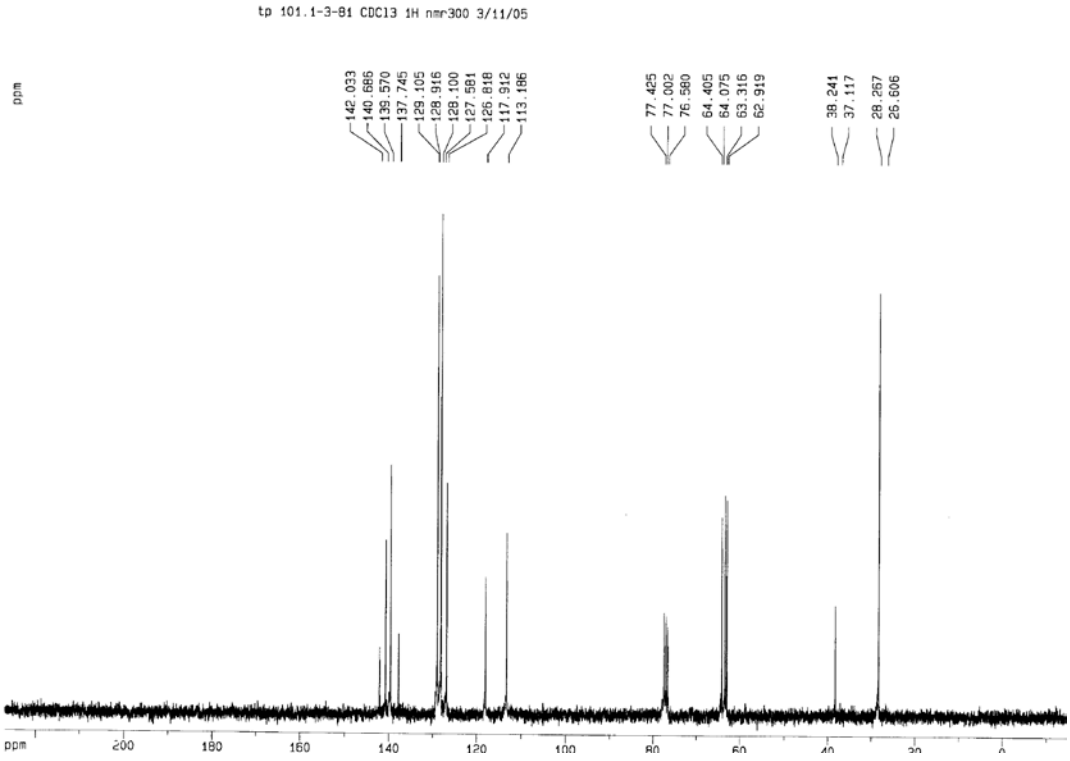
3-23e

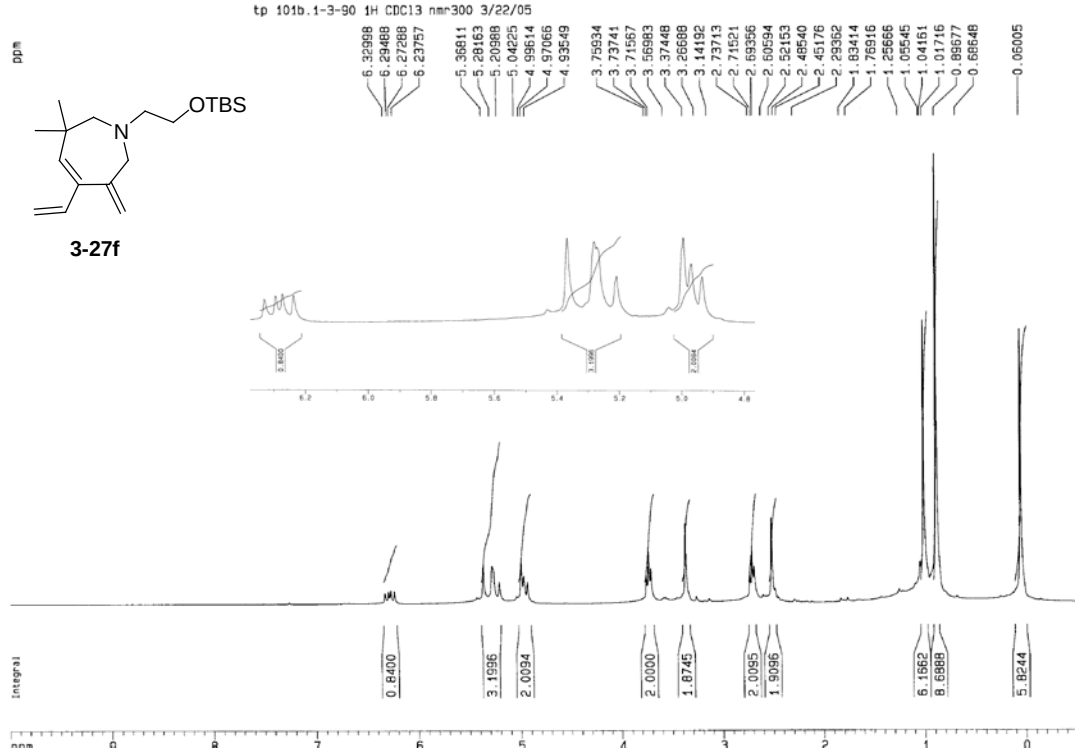

Integral
1.6229
1.7298
0.6327
3.0000
6.1630
ppm
9
8
7
6
5
4
3
2
1
0

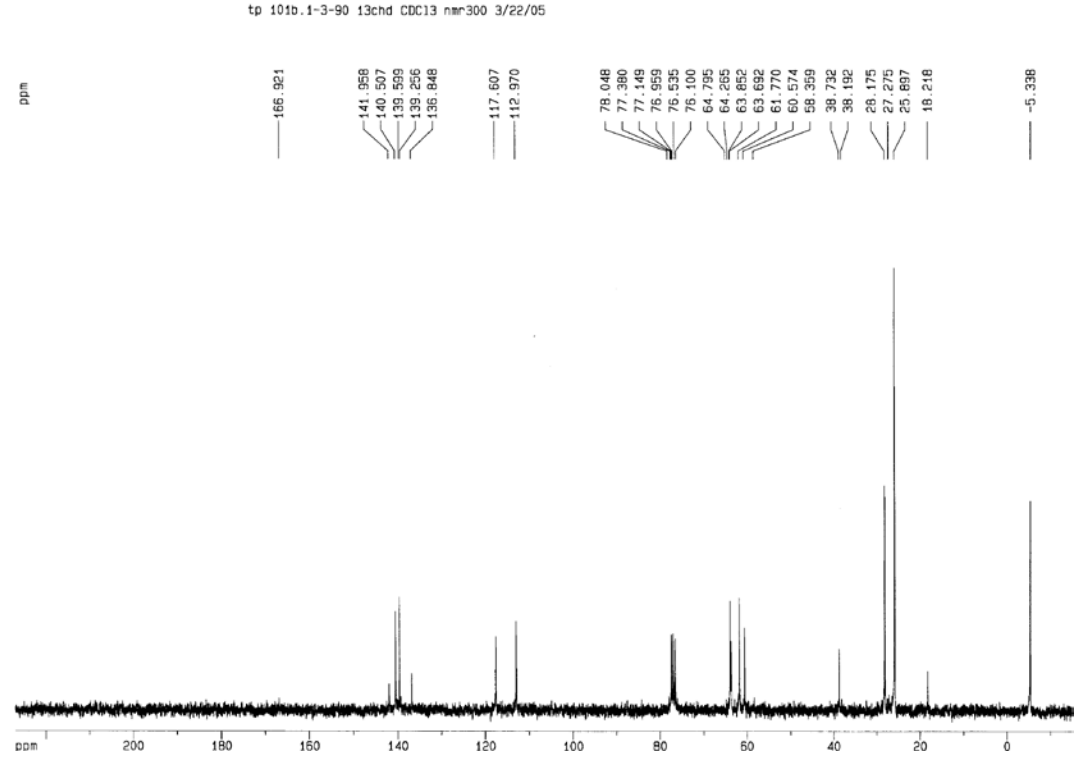

tp 92.2-4-22 13chd CDCl3 nmr300 9/23/05
ppm
216.224
203.170
175.548
96.622
89.073
77.747
77.420
76.994
76.570
74.566
52.164
42.351
25.346
25.189
14.205
200
180
160
140
120
100
80
60
40
20


tp 101.1-3-81 CDCl3 1H nmr300 3/11/05
ppm
Bn
N
Integral
5.0257
0.9002
0.9648
2.0688
1.0072
1.1761
2.0000
1.9547
1.9340
5.9934
ppm

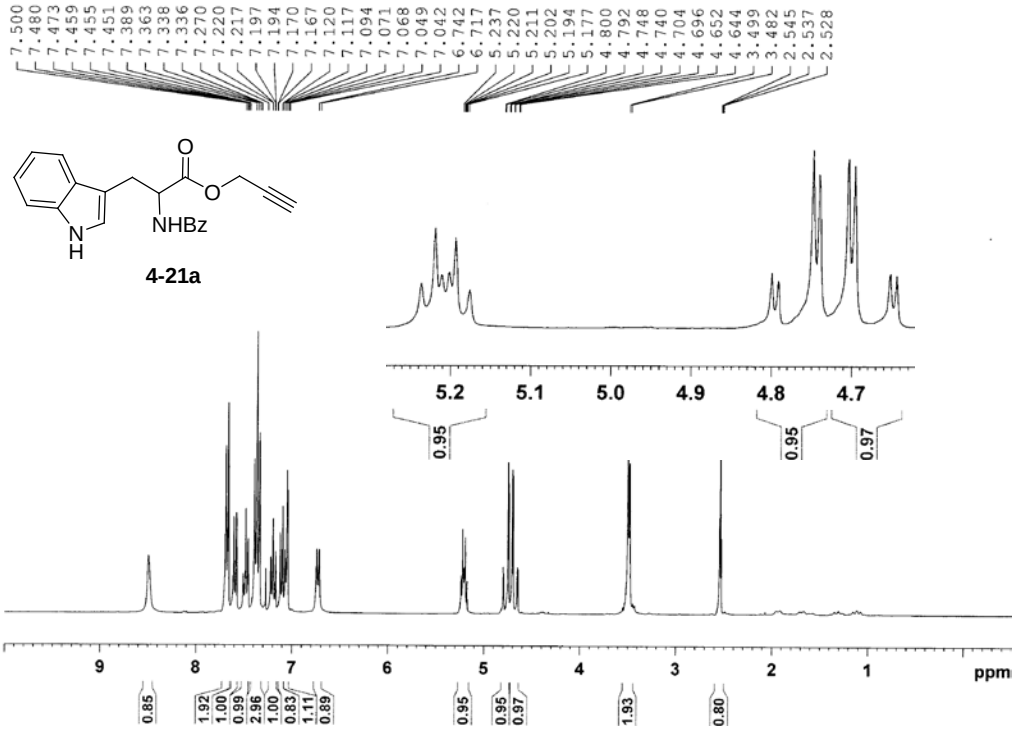
3-27a


tp 101.1-3-81 CDCl3 1H nmr300 3/11/05
ppm
142.033
140.686
139.570
137.745
129.105
128.916
128.100
127.581
126.818
117.912
113.186
77.425
77.002
76.580
64.405
64.075
63.316
62.919
38.241
37.117
28.267
25.606
ppm


tp 101b.1-3-90 1H CDCl3 nmr300 3/22/05
ppm
OTBS
N
3-27f
integral
0.8400
3.1996
2.0094
2.0000
1.8745
2.0095
1.9096
6.1662
8.6888
5.8244

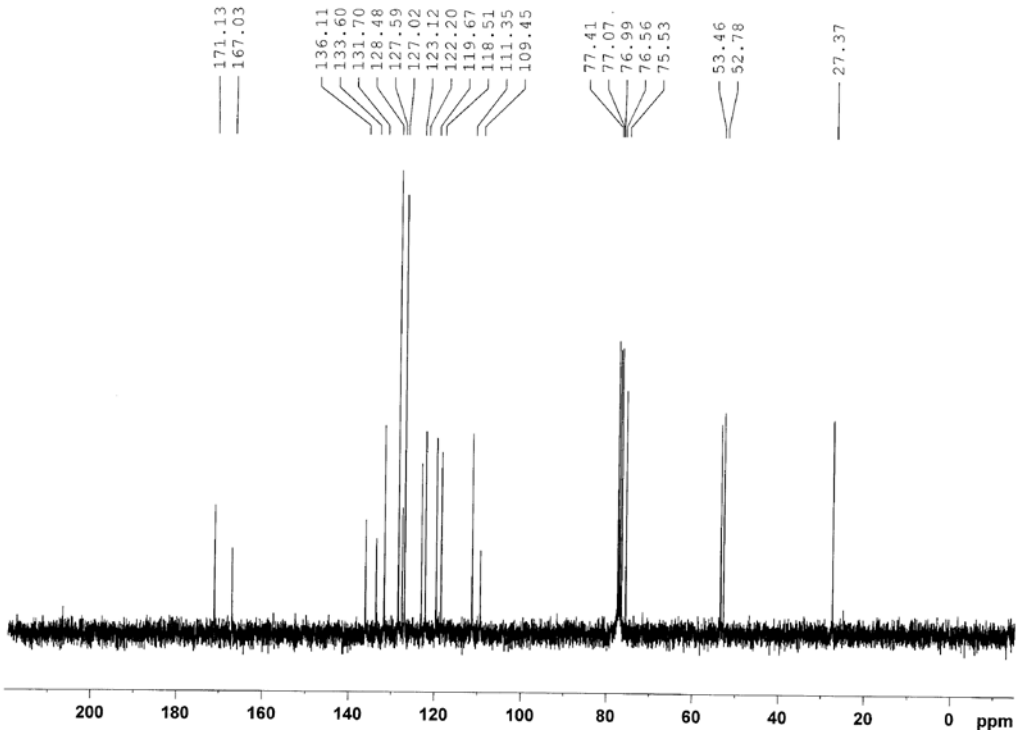

tp 101b.1-3-90 13chd CDCl3 nmr300 3/22/05
ppm
166.921
141.958
140.507
139.599
139.256
136.848
117.607
112.970
78.048
77.380
77.149
76.959
76.535
76.100
64.795
64.265
63.852
63.692
61.770
60.574
58.359
38.732
38.192
28.175
27.275
25.897
18.218
-5.338

tp 411.4-8-901H nmr301a 10/11/08

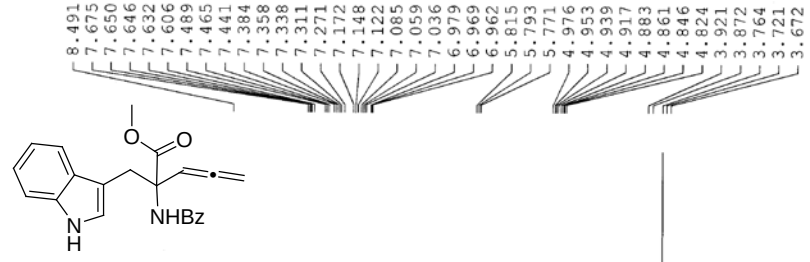


4-21a

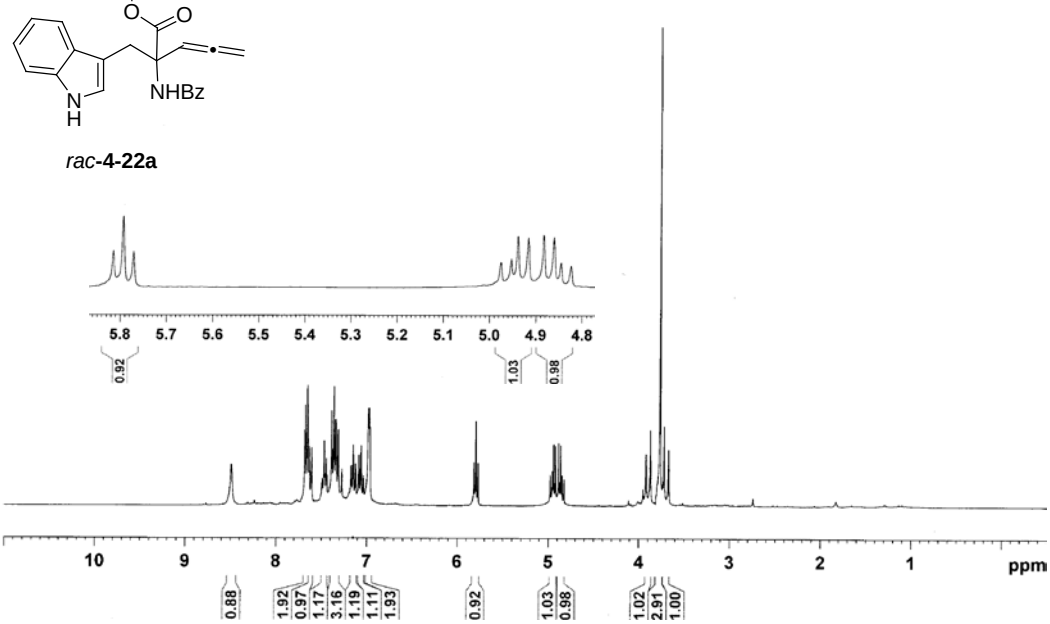
tp 411.4-8-90 13C nmr300 10/11/08



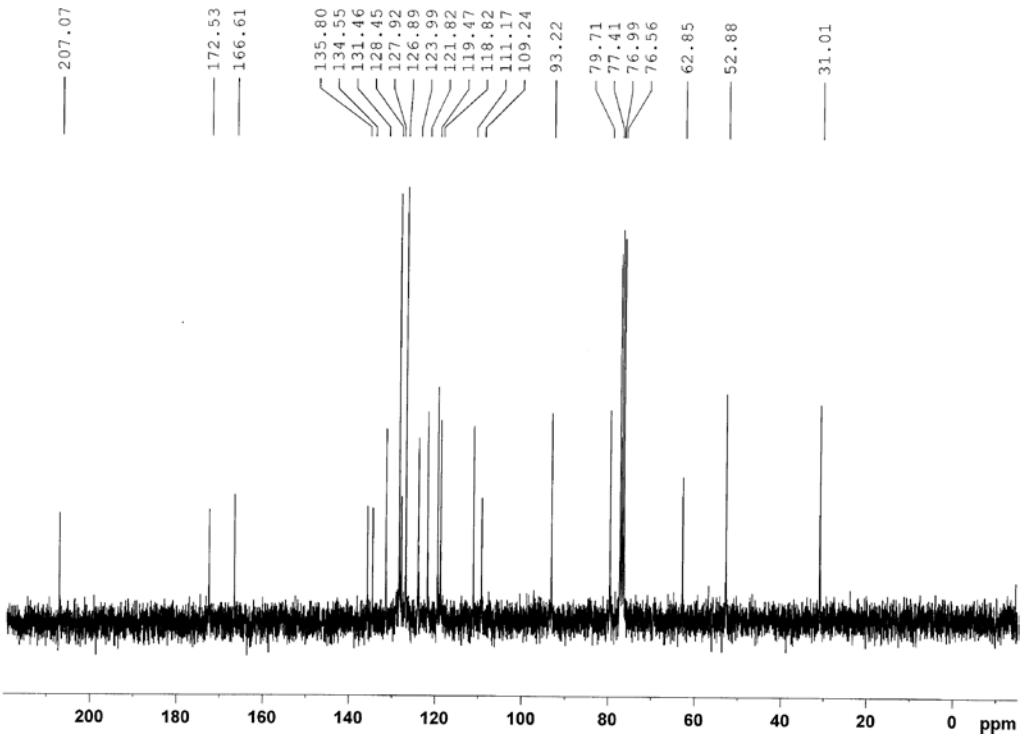
tp 420.3-8-92 nmr301a 10/11/08



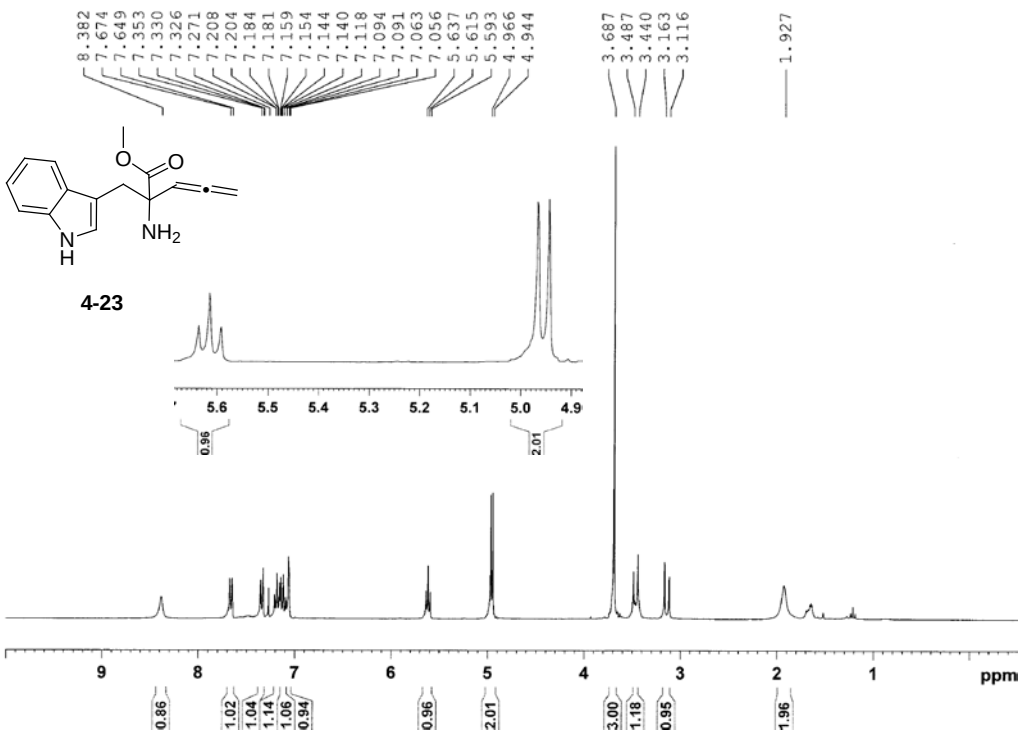
rac-**4-22a**



tp 420.3-8-92 13C nmr300 10/11/08

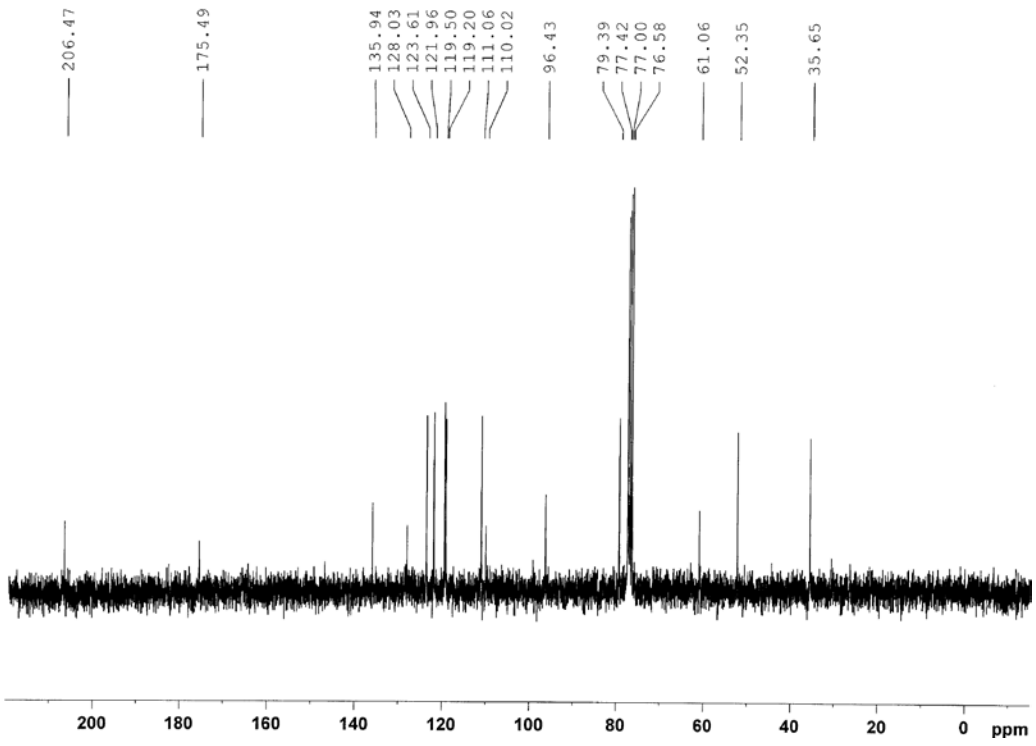


tp 419b.2-8-98 nmr301a 10/11/08

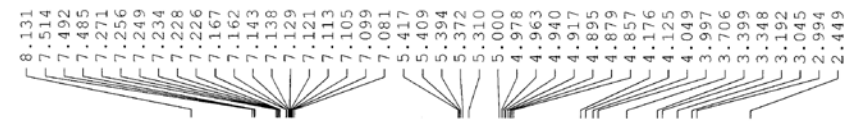


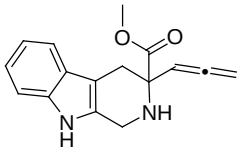
4-23

tp 419b.2-8-98 13C nmr300 10/11/08



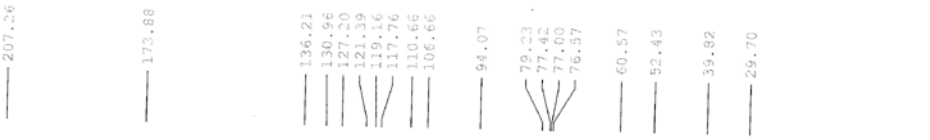
tp 429.3-4 1H CDCl3 nmr300 12/2/08

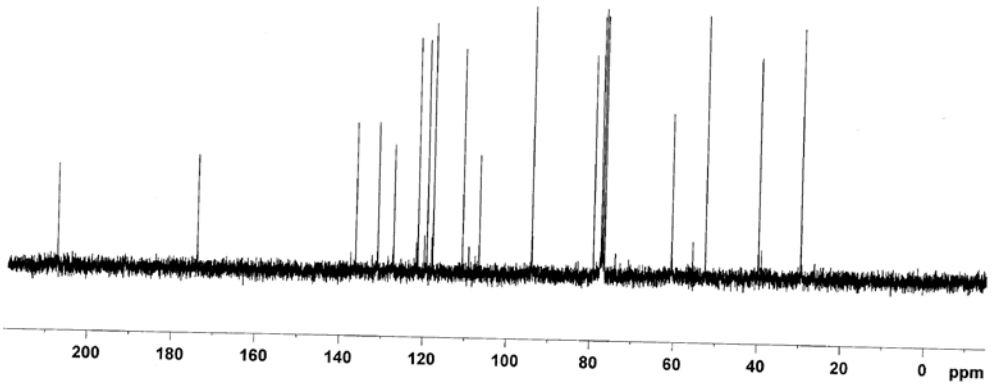




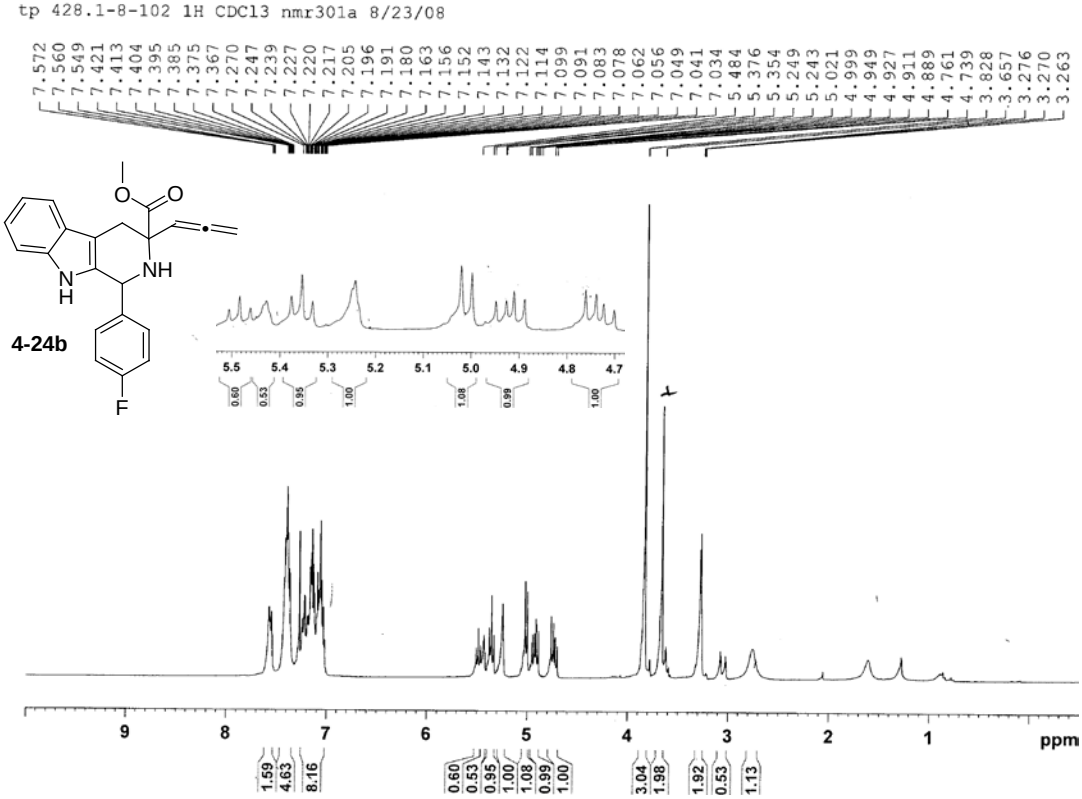
4-24a

tp 429.3-4 13C CDCl3 nmr300 12/2/08

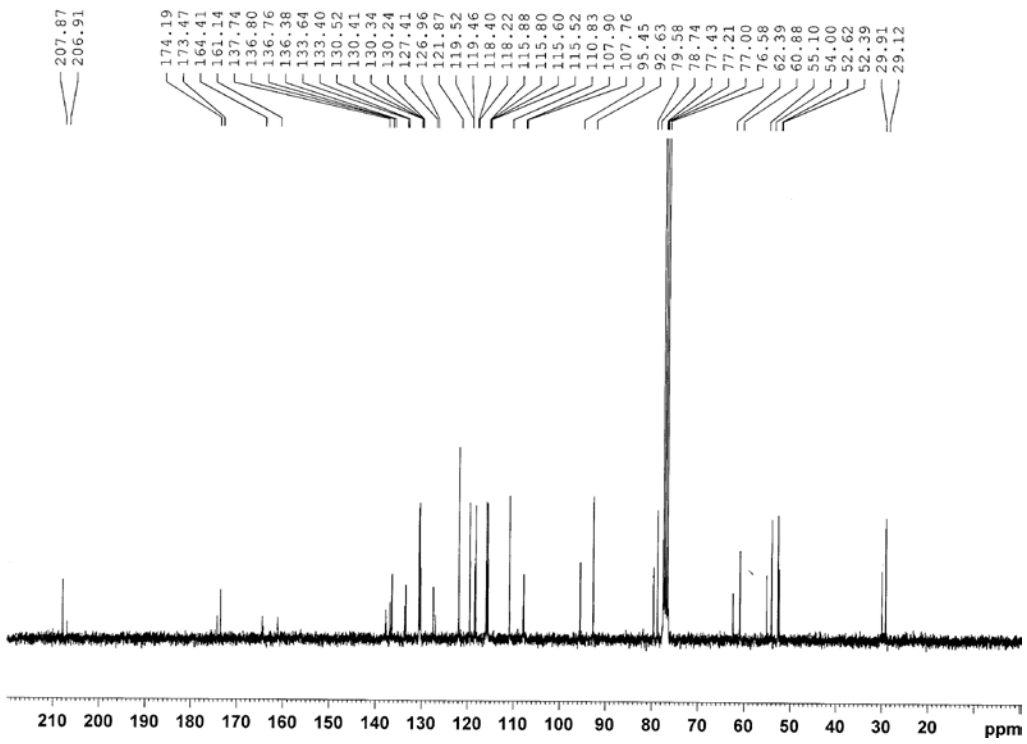




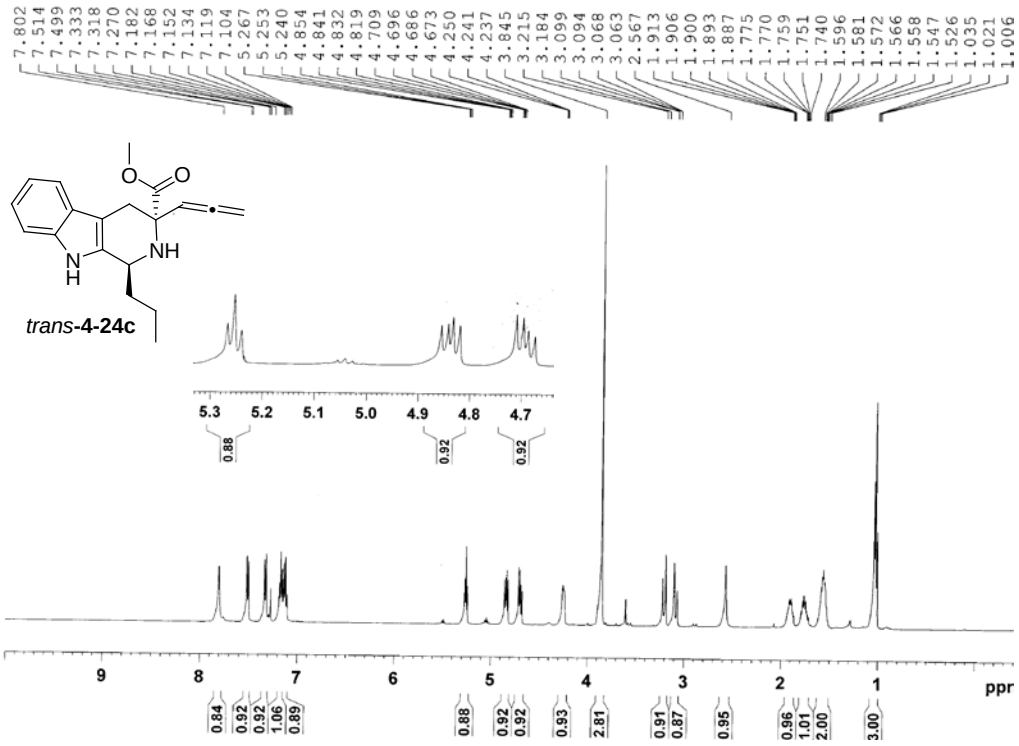
tp 428.1-8-102 1H CDCl3 nmr301a 8/23/08



tp 428.1-8-102 13C CDCl3 nmr301a 8/23/08

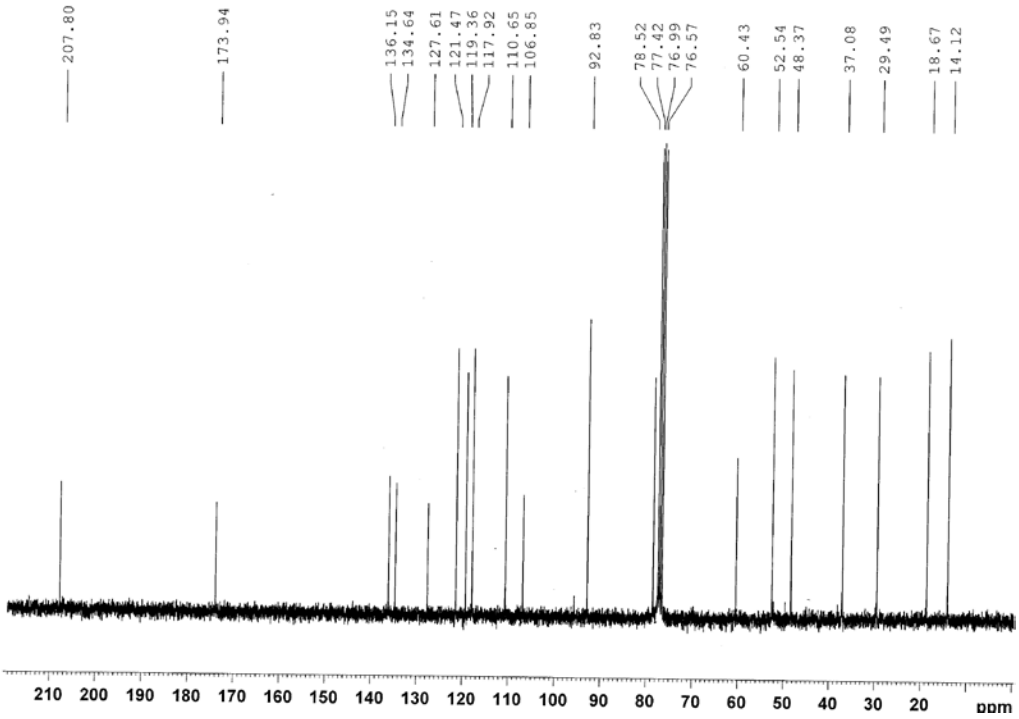


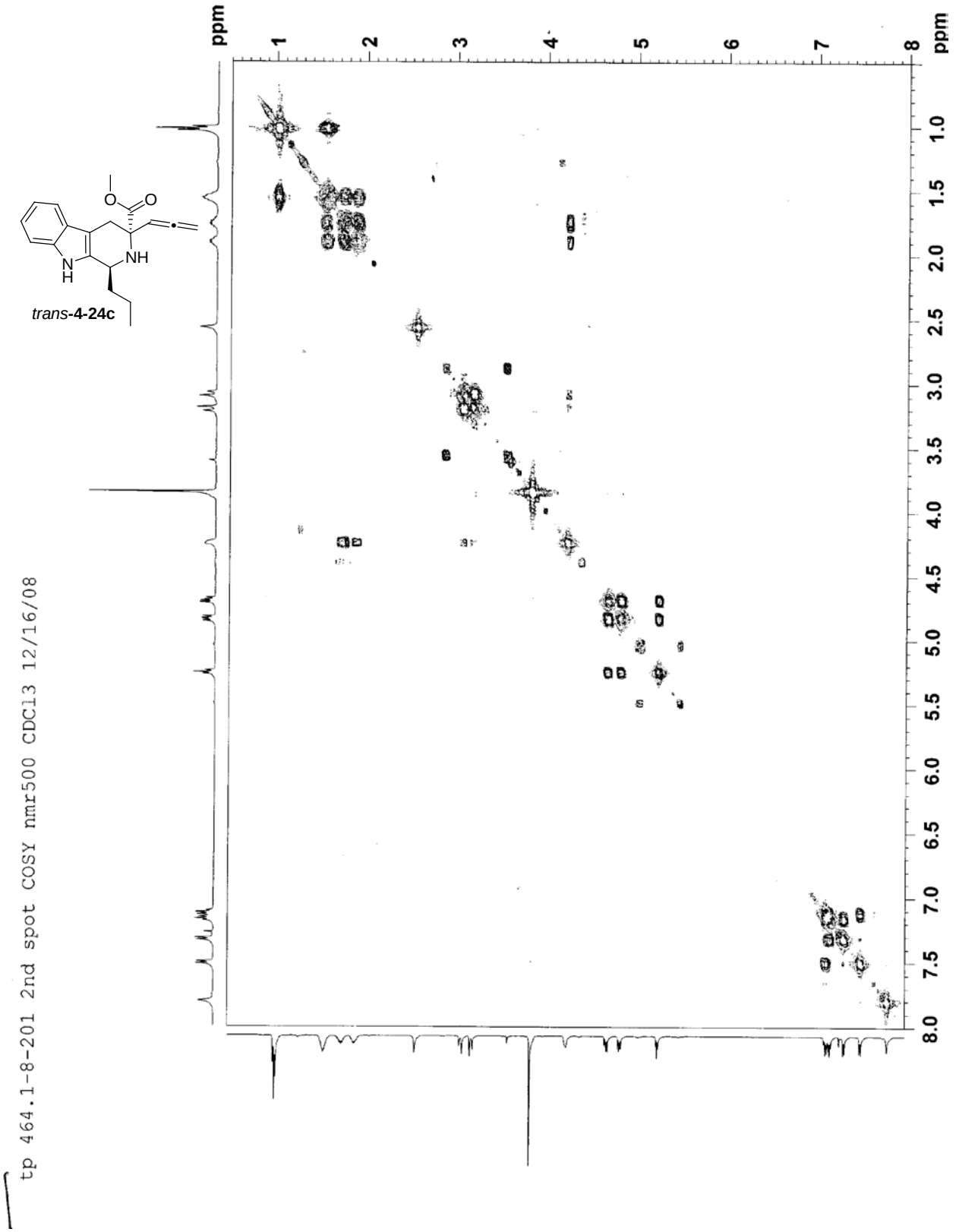
tp 464.1-8-201 2nd spot 1H nmr500 CDCl3 12/16/08



trans-**4-24c**

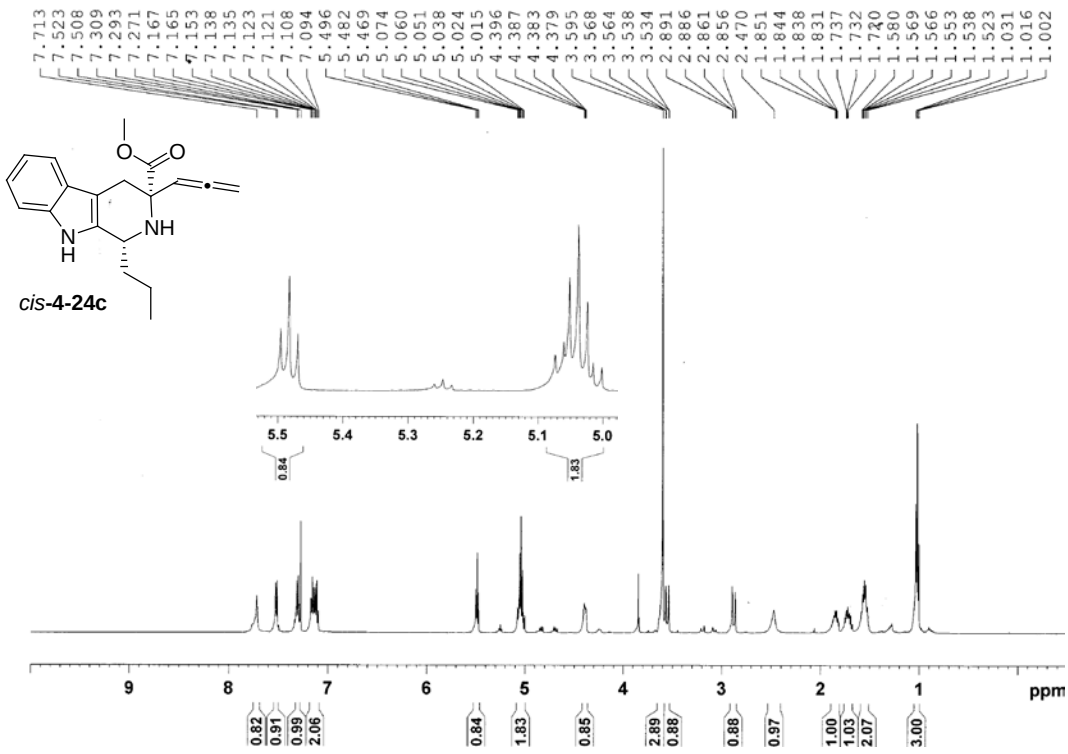
tp 464.1-8-201 2nd spot major diastereomer
13C CDCl3 nmr300 12/18/08




tp 464.1-8-201 2nd spot COSY nmr500 CDCl3 12/16/08
ppm
1
2
3
4
5
6
7
8
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
O
O
NH
N
H

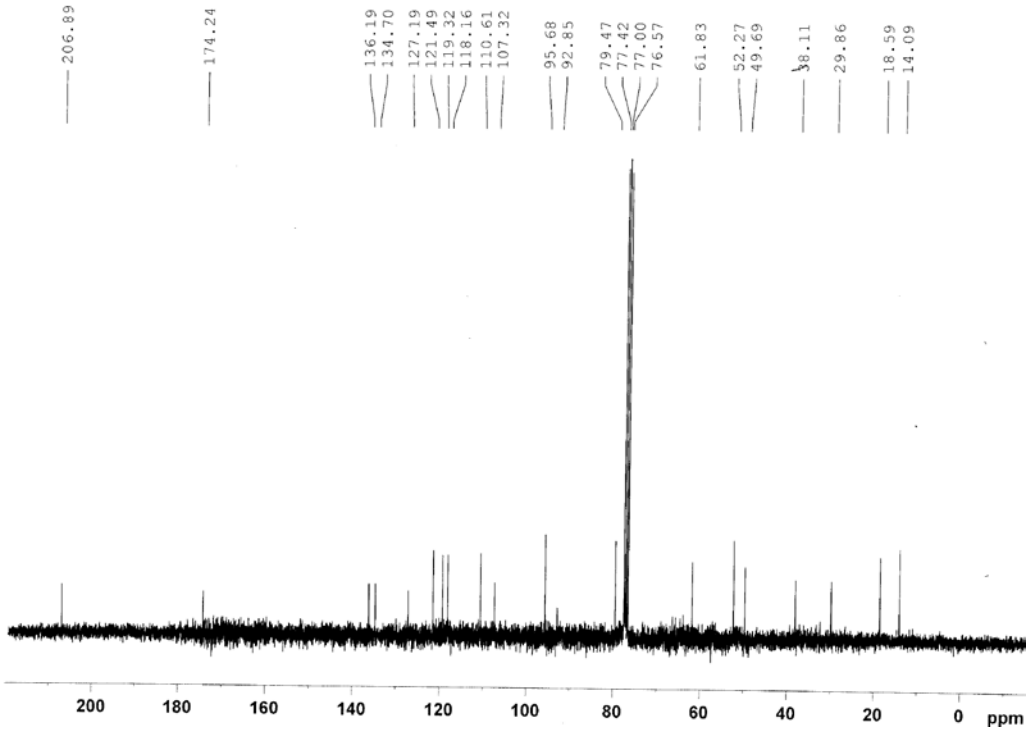
trans-**4-24c**

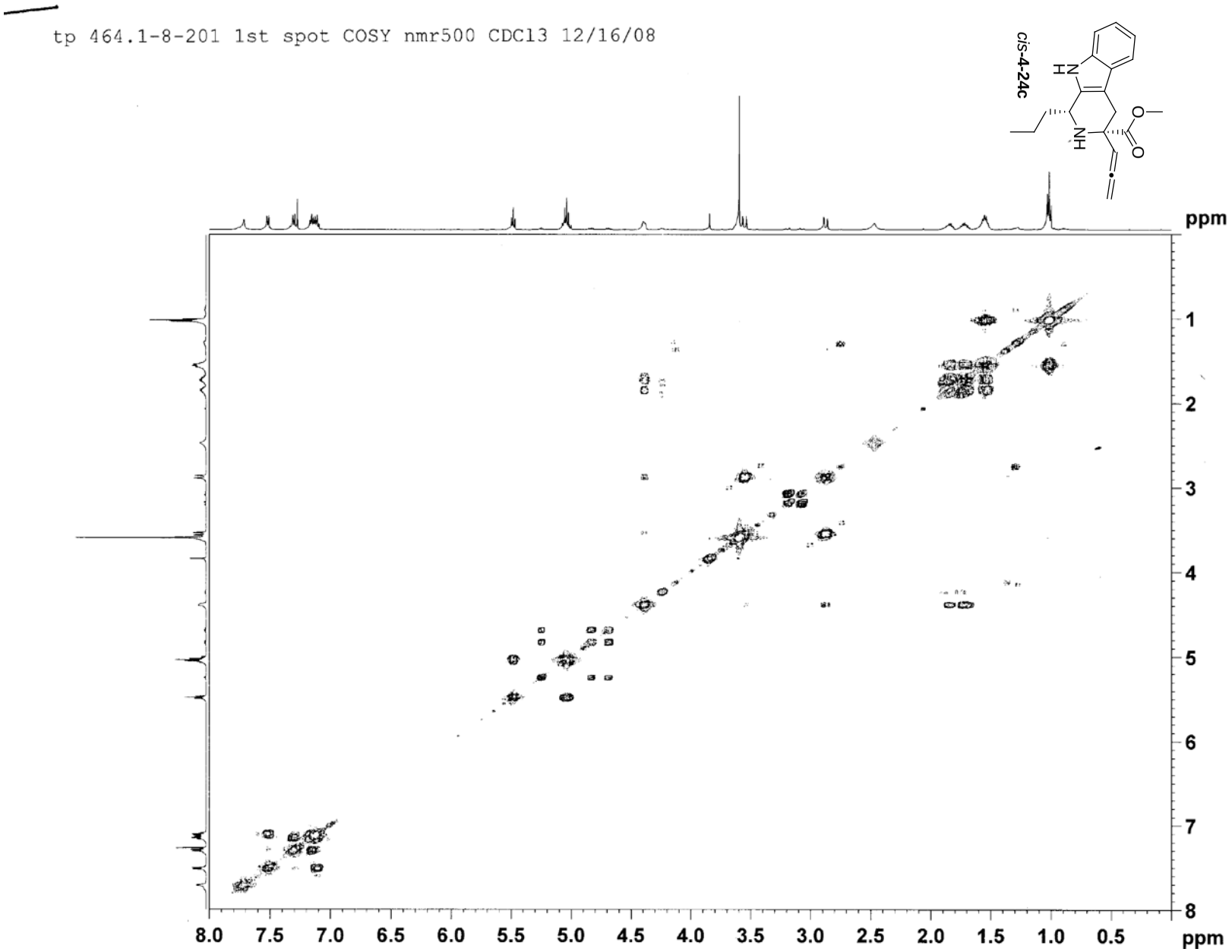
tp 464.1-8-201 1st spot nmr500 CDCl3 12/16/08

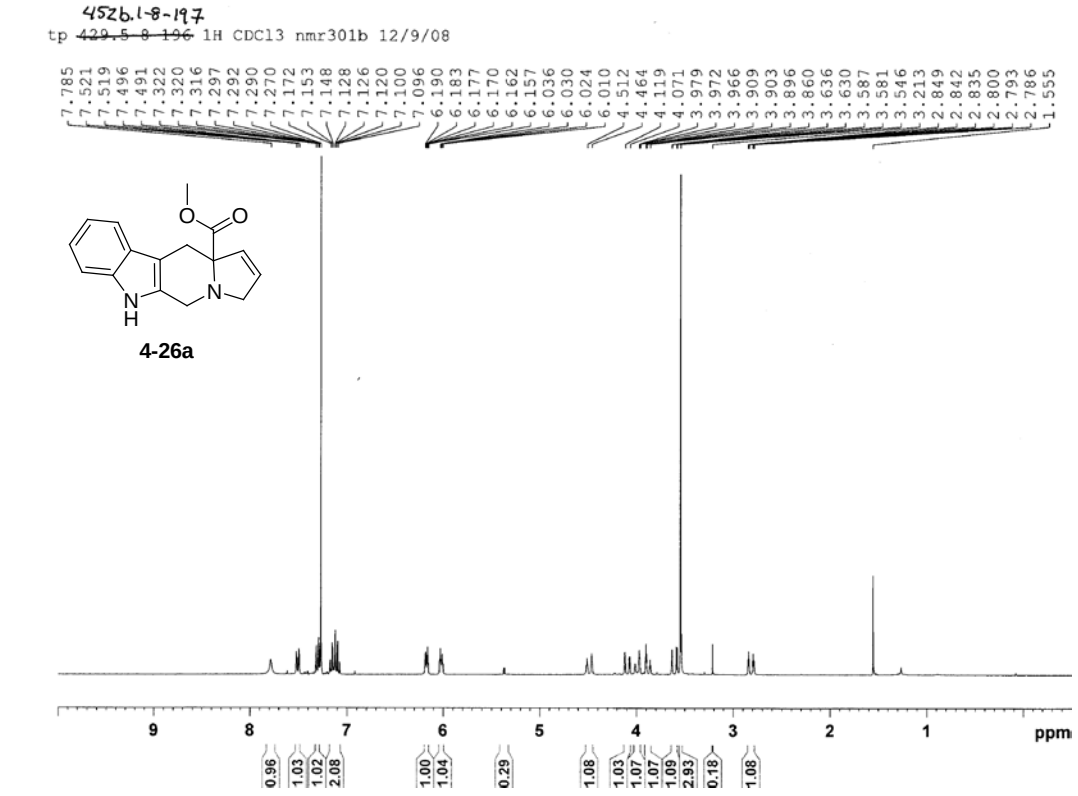


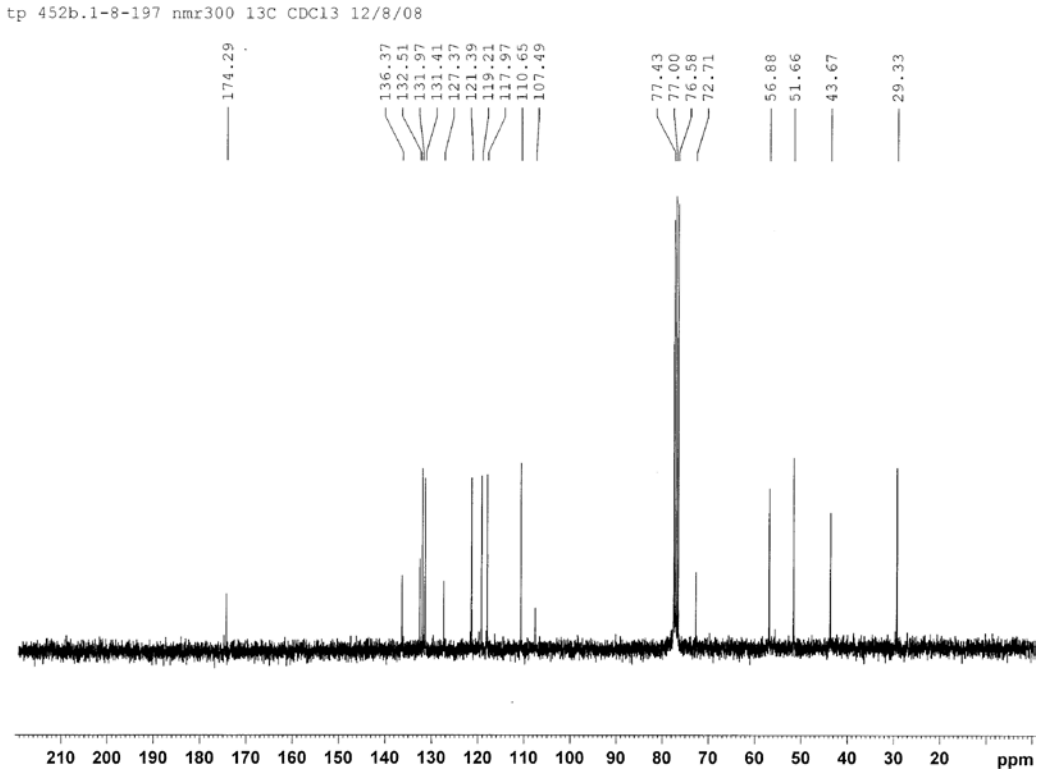
cis-**4-24c**

tp 464.1-8-201 1st spot (minor diastereomer)2
13C nmr301 12/18/08

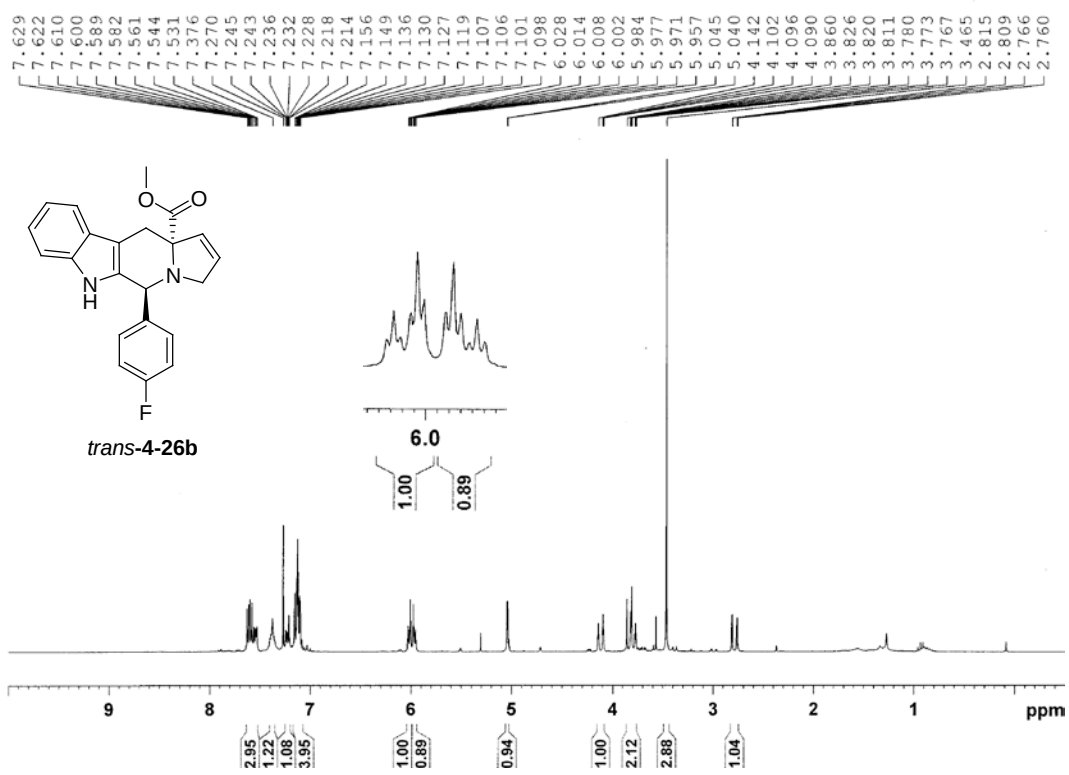



tp 464.1-8-201 1st spot COSY nmr500 CDCl3 12/16/08
cis-4-24c
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


452b.1-8-197
tp 429.5-8-196 1H CDCl3 nmr301b 12/9/08
7.785
7.521
7.519
7.496
7.491
7.322
7.320
7.316
7.297
7.292
7.290
7.270
7.172
7.153
7.148
7.128
7.126
7.120
7.100
7.096
6.190
6.183
6.177
6.170
6.162
6.157
6.036
6.030
6.024
6.010
4.512
4.464
4.119
4.071
3.979
3.972
3.966
3.909
3.903
3.896
3.860
3.636
3.630
3.587
3.581
3.546
3.213
2.849
2.842
2.835
2.800
2.793
2.786
1.555
O
O
N
H
N
4-26a
9
8
7
6
5
4
3
2
1
ppm
0.96
1.03
1.02
2.08
1.00
1.04
0.29
1.08
1.03
1.07
1.07
1.09
2.93
0.18
1.08

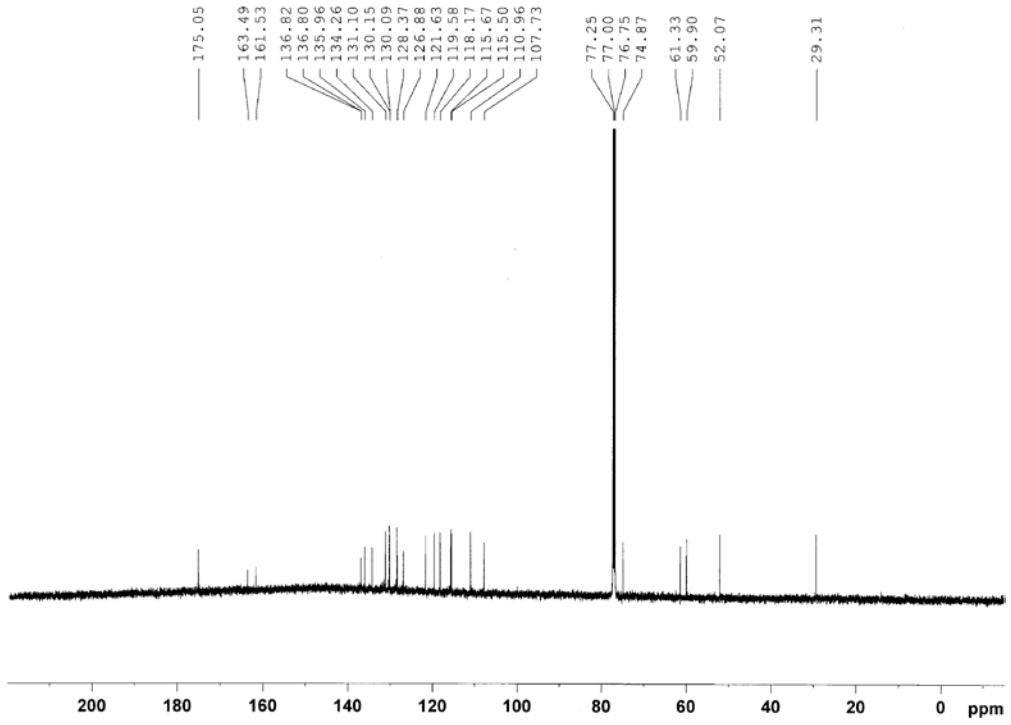

tp 452b.1-8-197 nmr300 13C CDCl3 12/8/08
174.29
136.37
132.51
131.97
131.41
127.37
121.39
119.21
117.97
110.65
107.49
77.43
77.00
76.58
72.71
56.88
51.66
43.67
29.33
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

tp 452.3-8-189 final frxns nmr300 12/26/08

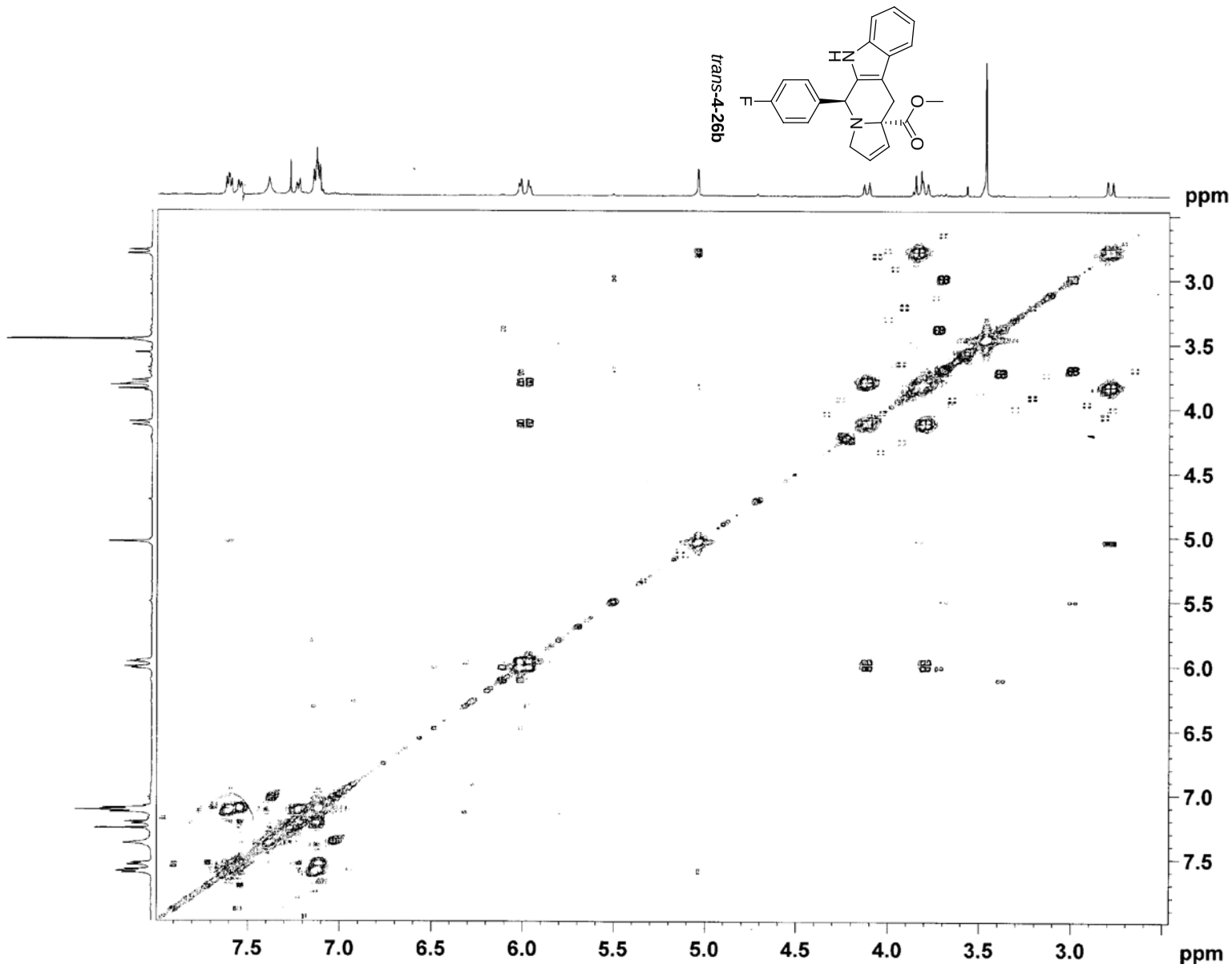


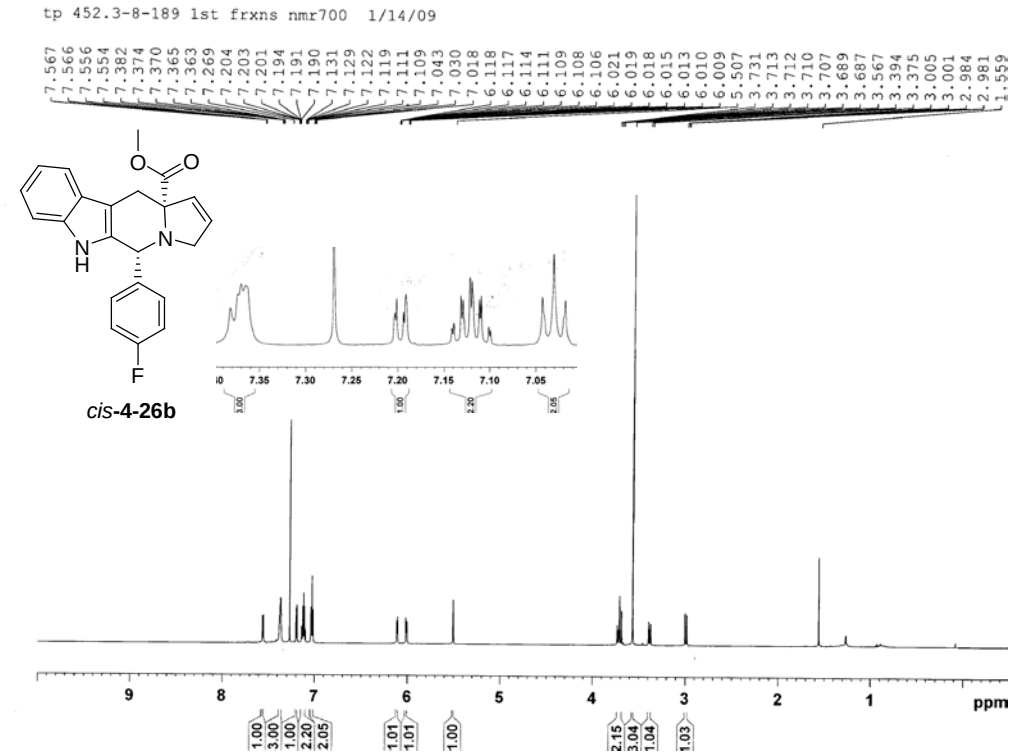
trans-**4-26b**

tp 452.3-8-189 2nd spot 13C CDCl3 nmr500 1/11/09

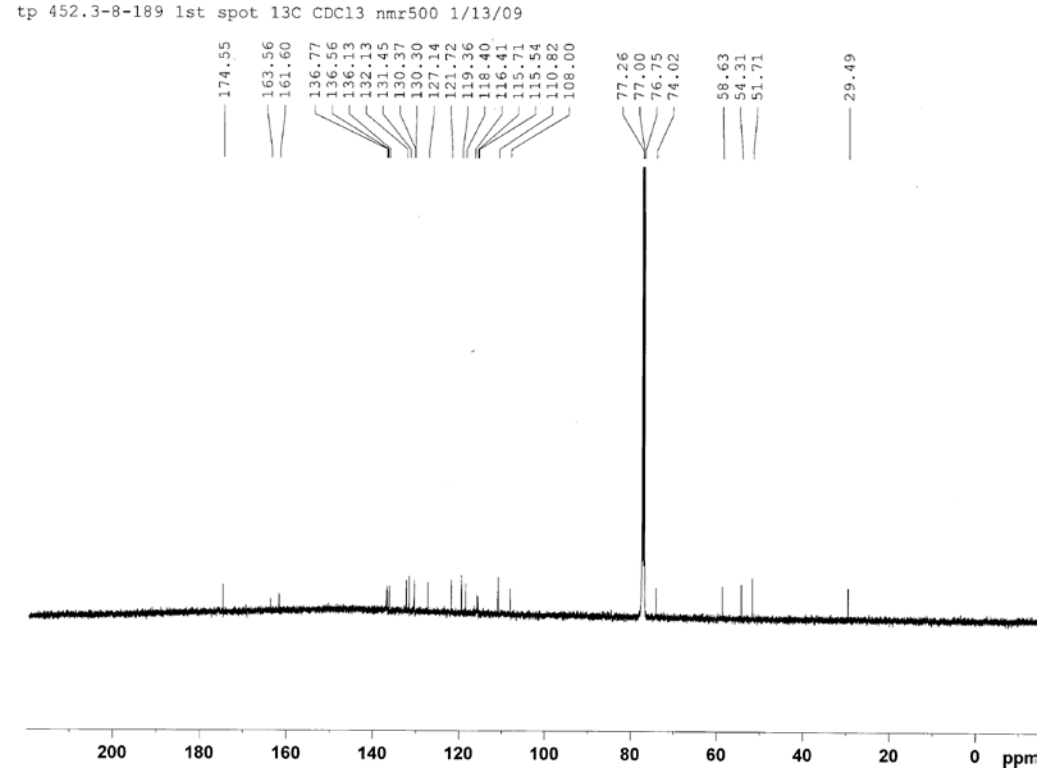


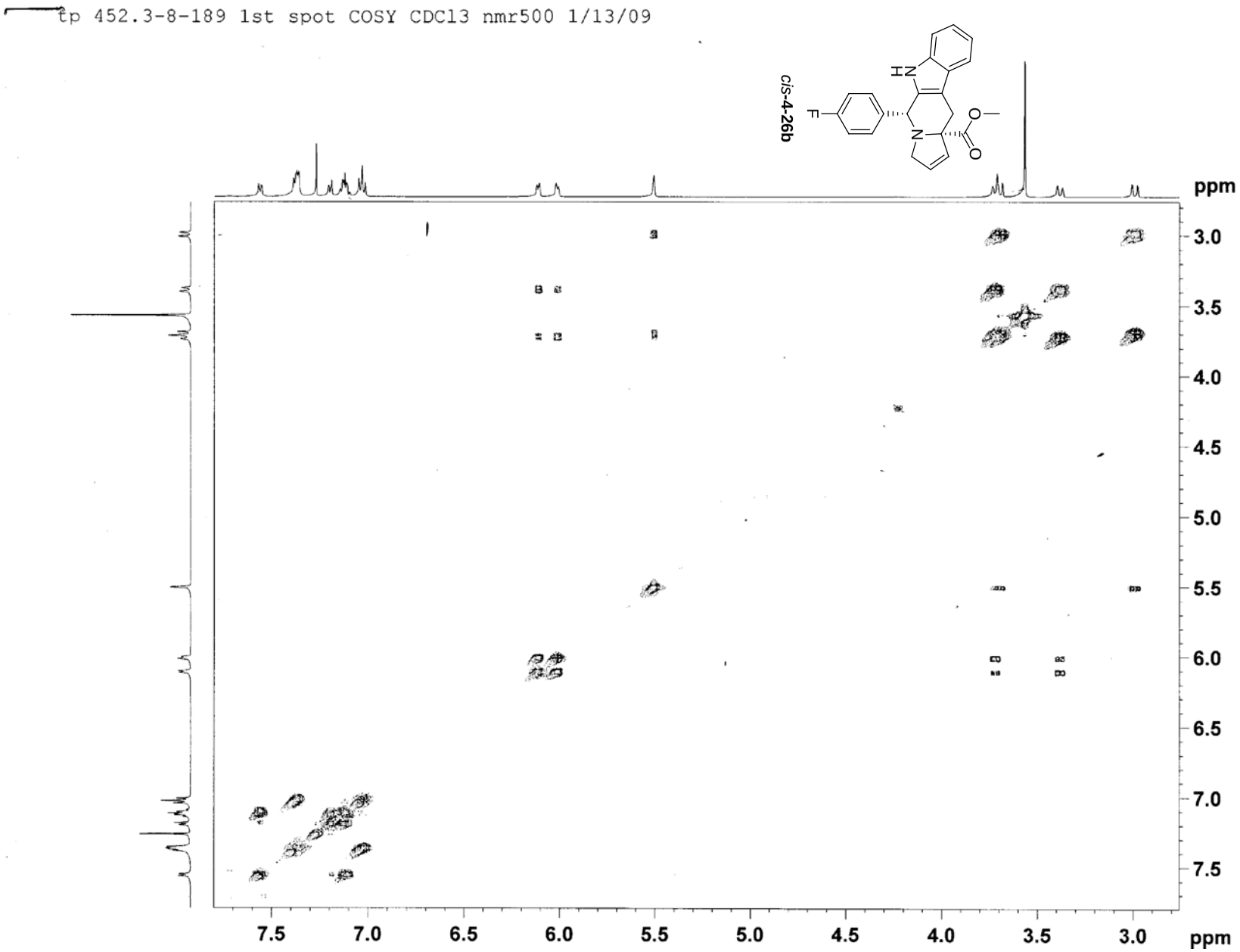
tp 452.3-8-189 2nd spot COSY CDCl3 nmr500 1/11/09



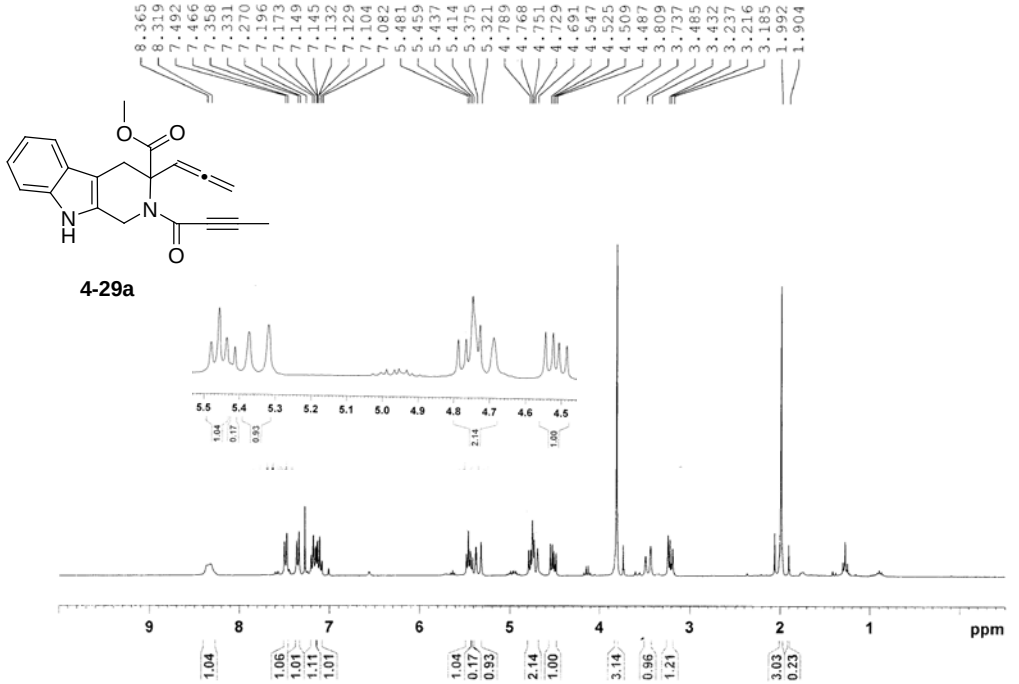

tp 452.3-8-189 1st frxns nmr700 1/14/09
7.567
7.566
7.556
7.554
7.382
7.374
7.370
7.365
7.363
7.269
7.204
7.203
7.201
7.194
7.191
7.190
7.131
7.129
7.122
7.119
7.111
7.109
7.043
7.030
7.018
6.118
6.117
6.114
6.111
6.109
6.108
6.106
6.021
6.019
6.018
6.015
6.013
6.010
6.009
5.507
3.731
3.713
3.712
3.710
3.707
3.689
3.687
3.567
3.394
3.375
3.005
3.001
2.984
2.981
1.559
O
O
N
H
N
F
7.35
7.30
7.25
7.20
7.15
7.10
7.05
9
8
7
6
5
4
3
2
1
ppm
1.00
3.00
1.00
2.20
2.05
1.01
1.01
1.00
2.15
3.04
1.04
1.03

cis-**4-26b**


tp 452.3-8-189 1st spot 13C CDCl3 nmr500 1/13/09
174.55
163.56
161.60
136.77
136.56
136.13
132.13
131.45
130.37
130.30
127.14
121.72
119.36
118.40
116.41
115.71
115.54
110.82
108.00
77.26
77.00
76.75
74.02
58.63
54.31
51.71
29.49
200
180
160
140
120
100
80
60
40
20
0
ppm

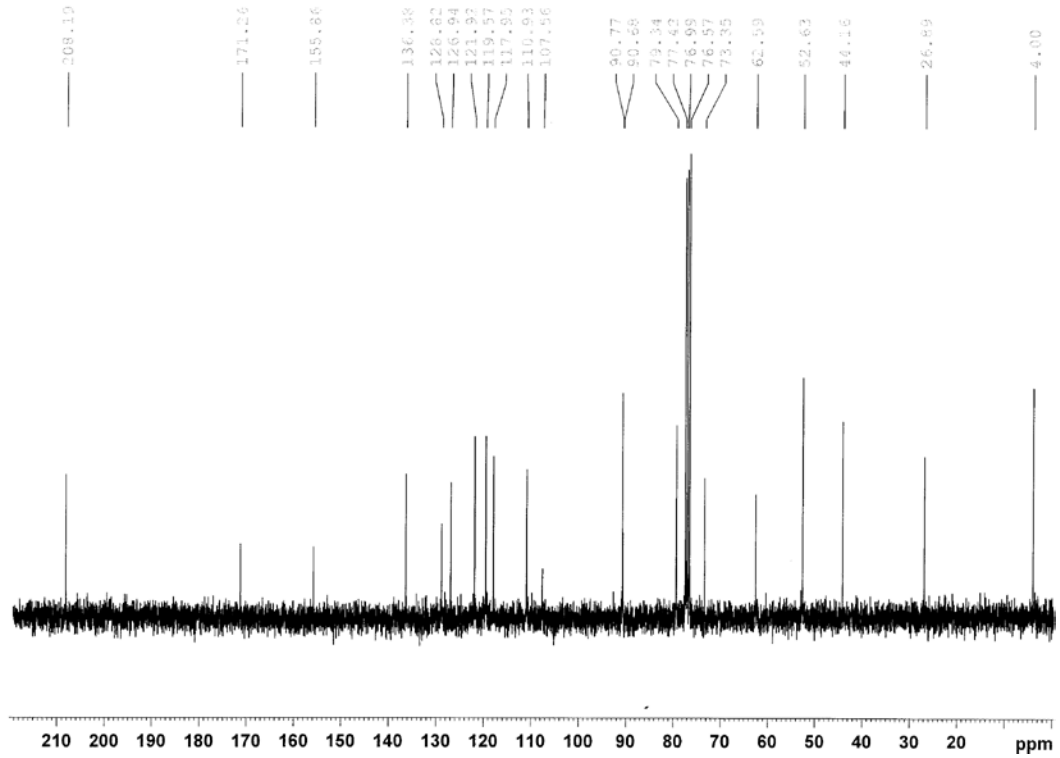

tp 452.3-8-189 1st spot COSY CDCl3 nmr500 1/13/09
cis-4-26b
F
H
N
N
O
O
ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

tp 442b.2-8-199 1H CDCl3 nmr301 12/12/08

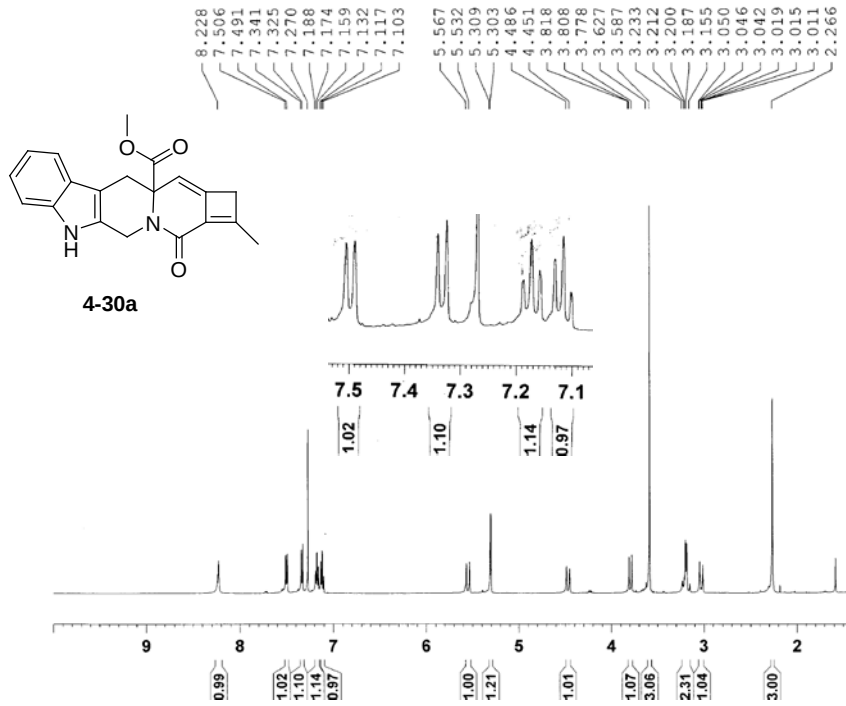


4-29a

tp 442b.2-8-199 C13C CDCl3 nmr300 12/12/08

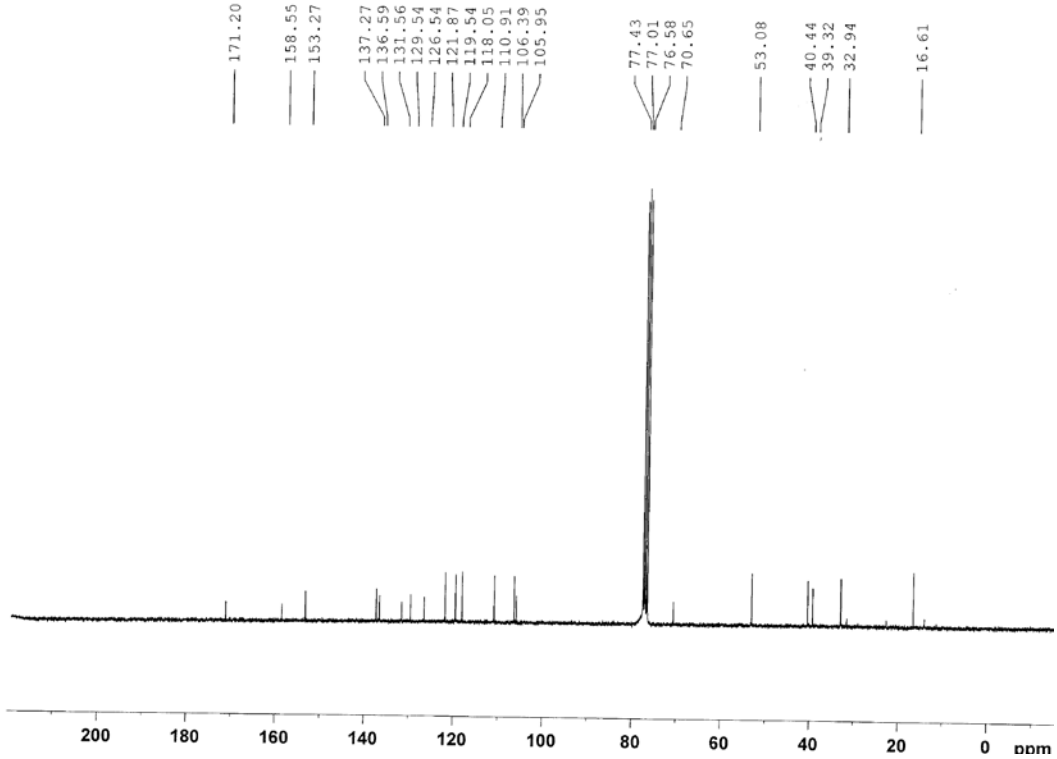


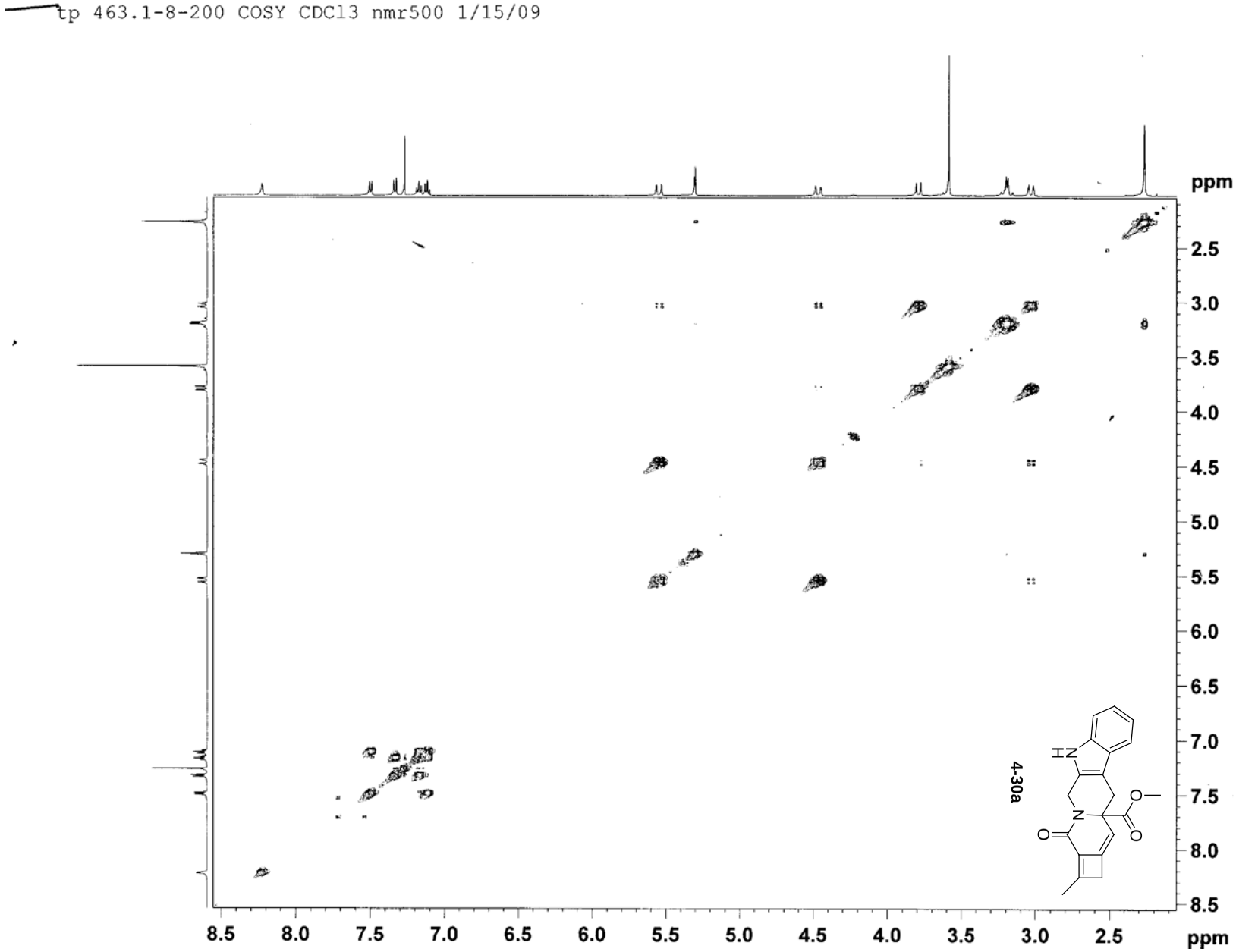
tp 463.1-8-200 1H CDCl3 nmr500 1/15/09



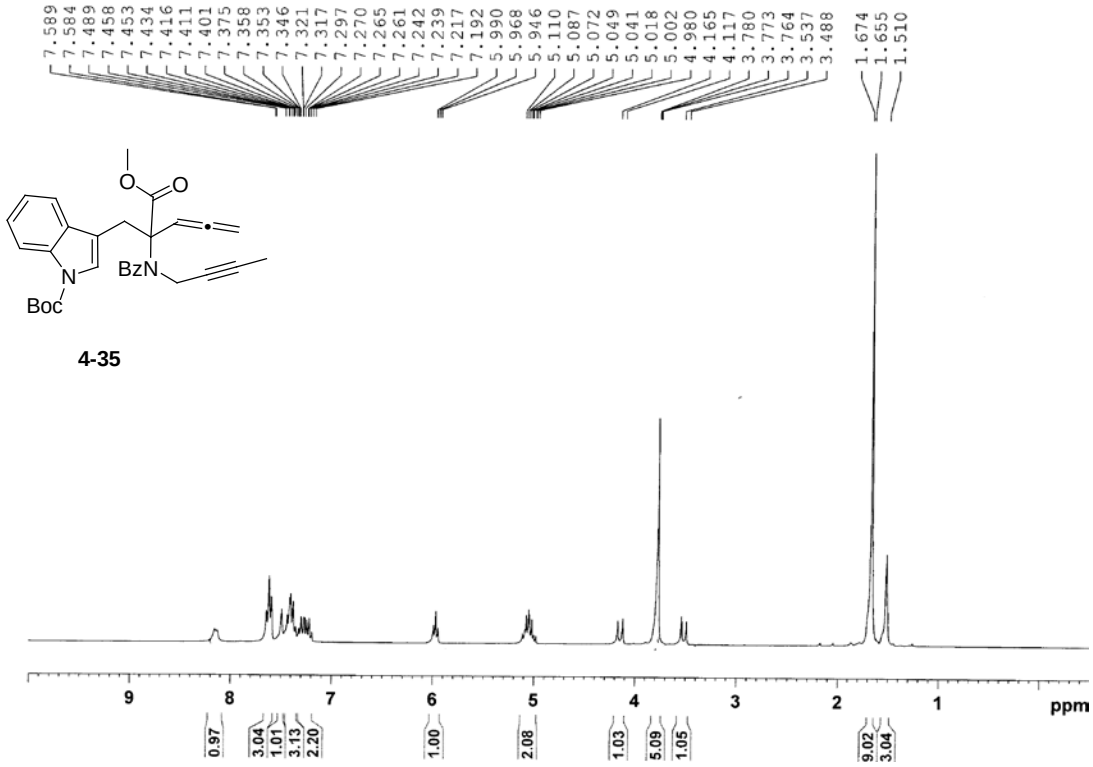
4-30a

tp 463.2-8-207 13C CDCl3 nmr300 1/18/09



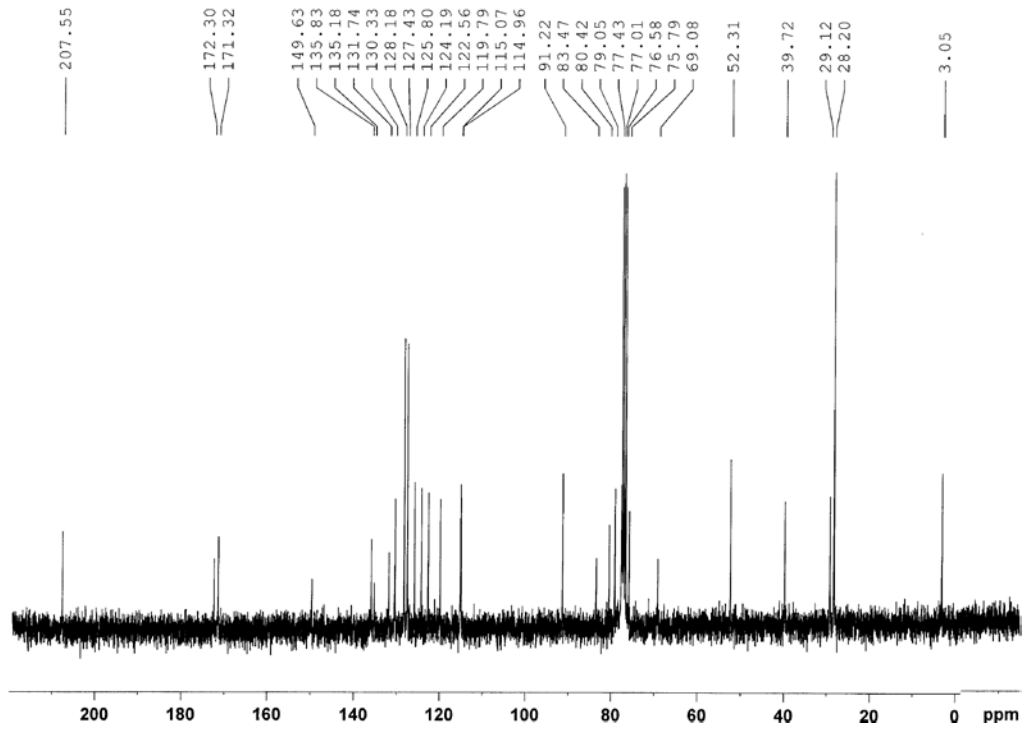

tp 463.1-8-200 COSY CDCl3 nmr500 1/15/09
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
4-30a
H
N
N
O
O
O

tp 432b.4-8-144 1H nmr301a 10/12/08

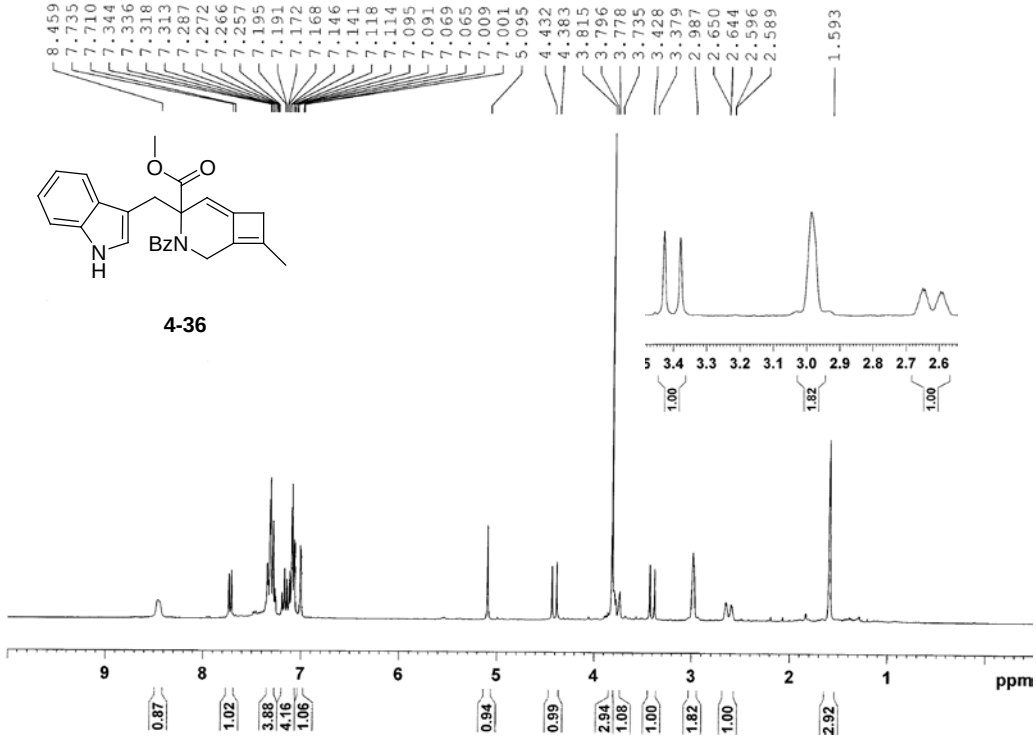


4-35

tp 432b.4-8-144 13C nmr300 10/12/08

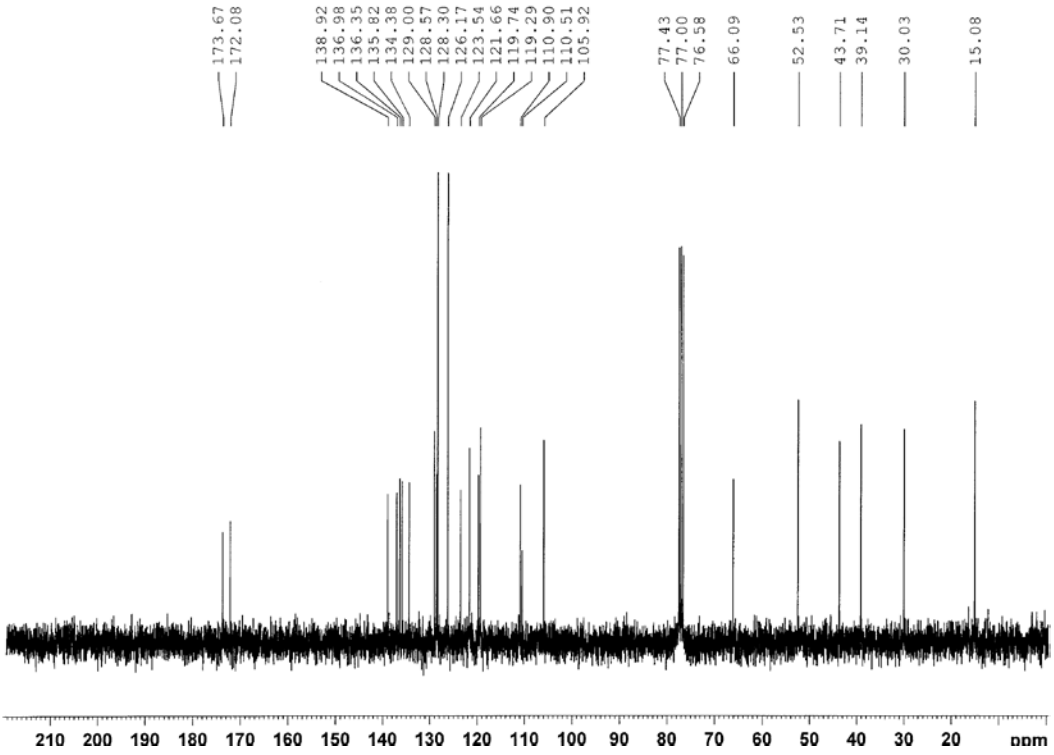


tp 436.4-8-158 1H CDCl3 nmr300 10/21/08

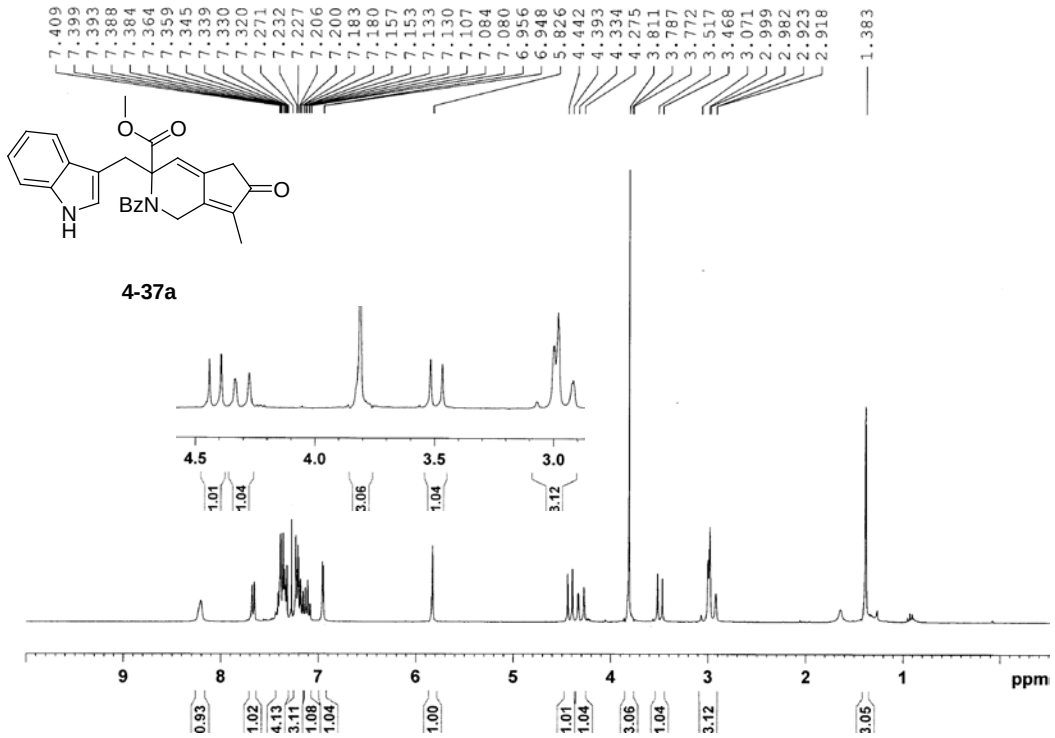


4-36

tp 436.4-8-158 13C CDCl3 nmr300 10/21/08

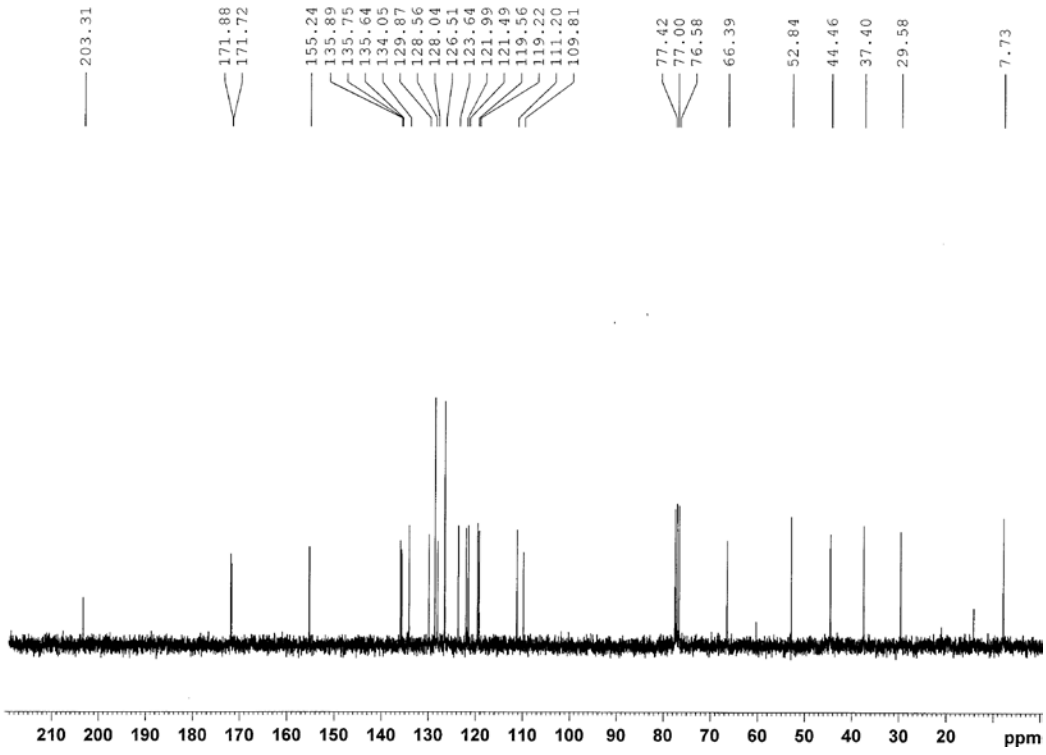


tp 441.5-8-145 1H nmr301a 10/11/08

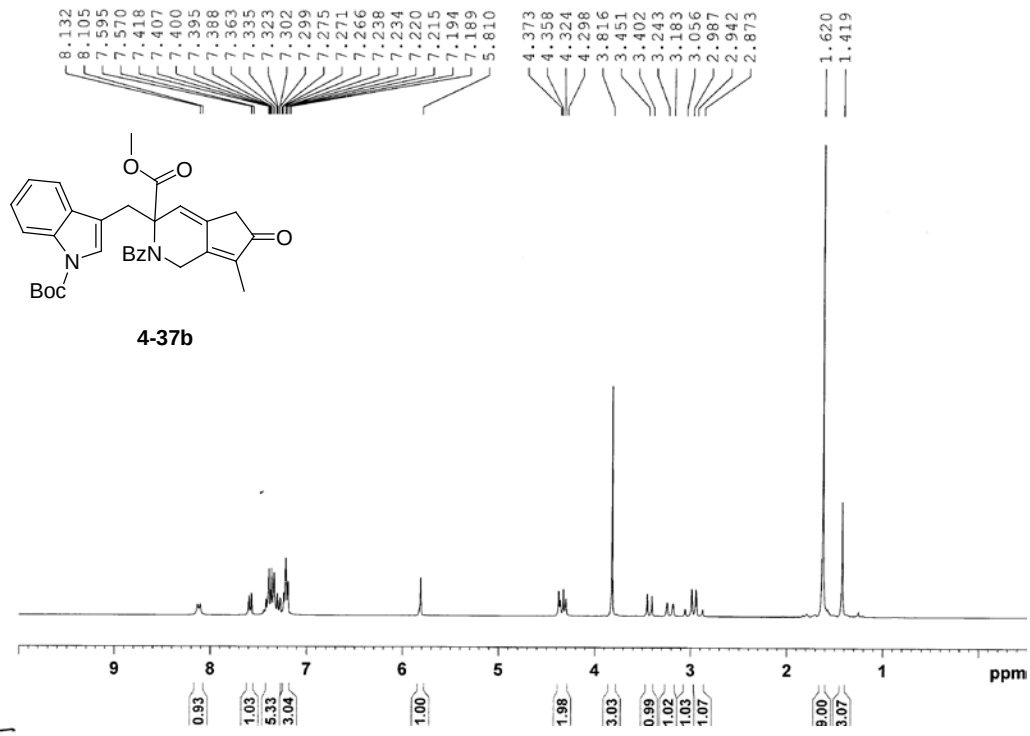


4-37a

tp 441.6-8-152 13C CDCl3 nmr300 11/11/08

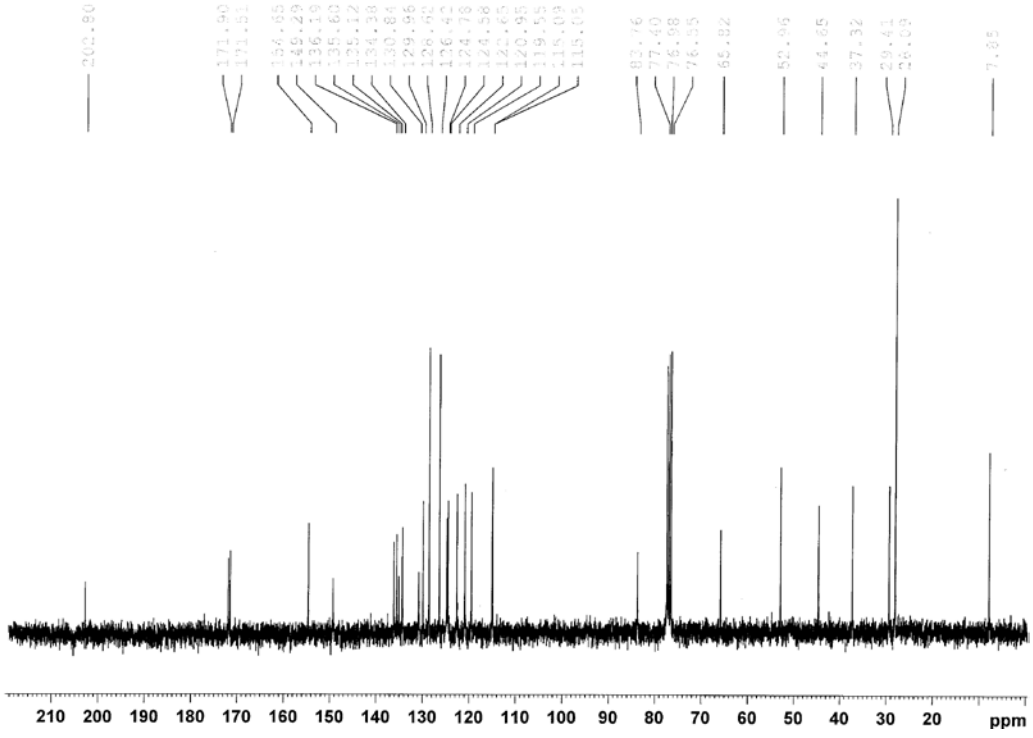


tp 440.2-8-125 1H nmr301a 10/11/08



4-37b

tp 440.2-8-125 13C nmr300 10/11/08



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