Progress Towards the Total Synthesis of 3α-Hydroxy-15-Rippertene

by

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The Rh(I)-catalyzed allenic cyclocarbonylation reaction is a formal [2 + 2 + 1] cyclocarbonylation process that has been used to gain access to 4-alkylidenecyclopentenones. Inclusion of a six-membered ring on the tether between the allene and the alkyne components allows access to a variety of [6-7-5] ring structures found in the core-skeletons of natural products such as rippertene. This thesis describes a synthetic approach to the carbocyclic skeleton of 3α-hydroxy-15-rippertene, utilizing the Rh(I)-catalyzed allenic cyclocarbonylation reaction. Starting from 2-butyn-1-ol the [6-7-5] carbocyclic core of rippertene was synthesized in 1.9% over 10 steps.

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ABBREVIATIONS

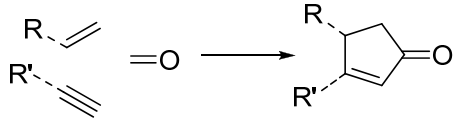
AcOH	Acetic Acid
BQ	1,4-Benzoquinone
COD	Cyclooctadiene
DIBAl-H	Diisobutylaluminum hydride
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
LAH	Lithium Aluminum Hydride
LDA	Lithium Diisopropylamide
LiHMDS	Lithium Hexamethyldisilazide
MsCl	Methanesulfonyl Chloride
NMO	*N*-Methylmorpholine-*N*-Oxide
NMR	Nuclear Magnetic Resonance
Rochelle's Salt	Sodium Potassium Tartrate
TBAF	Tetrabutylammonium fluoride
Tf_2O	Trifluoromethanesulfonic Anhydride
TfOH	Trifluoromethanesulfonic Acid
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Tol	Toluene
TsCl	*p*-Toluenesulfonyl Chloride
TsOH	*p*-Toluenesulfonic Acid

1.0 INTRODUCTION

1.1 TRANSITION-METAL CATALYZED CYCLOCARBONYLATION REACTIONS TO PREPARE CYCLOPENTENONES

The Pauson-Khand reaction, a [2+2+1] cyclocarbonylation, was first reported in 1971 by I.U. Khand.[1] The reaction between an alkyne, olefin, and carbon monoxide to form a cyclopentenone can be carried out in either an intra- or inter-molecular fashion. (Scheme 1.1) Subsequently the Pauson-Khand reaction, as well as closely related cyclocarbonylation reactions, have been widely used for the formation of cyclopentenones in total synthesis.[2-7] The originally discovered reaction is mediated by $Co_2(CO)_8$; however, the reaction is stoichiometric in dicobalt-octacarbonyl and is therefore problematic on larger scales as well as in waste-disposal due to the large amount of the reduced metal.

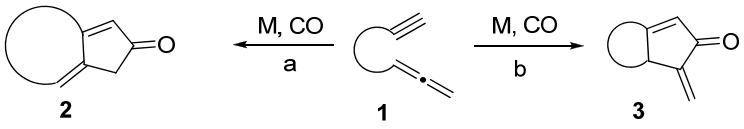


Scheme 1.1: The Pauson-Khand Reaction

There have been numerous modifications of the Pauson-Khand reaction over the intervening years.[8] The modification that has had the greatest impact, is the development of reaction conditions where the transition-metal is used catalytically.[9-12]

1.2 CYCLOCARBONYLATION OF ALLENE-YNES

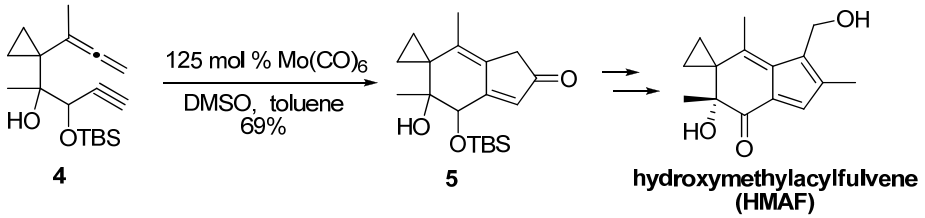
Replacement of the olefin present in the standard Pauson-Khand reaction with an allene provides for the construction of cyclopentenones that possess a higher degree of molecular complexity. This allene-yne starting material possesses two distinct modes of reactivity, either with the proximal or distal double bonds present in the allene. Reaction with the distal double bond of allene-yne **1** provides 4-alkylidene cyclopentenone **2** (Scheme 1.2, pathway a), while reaction with the proximal double bond provides α-methylene cyclopentenone **3** (Scheme 1.2, pathway b).



Scheme 1.2: Modes of Reactivity for the Cyclocarbonylation of Allene-ynes

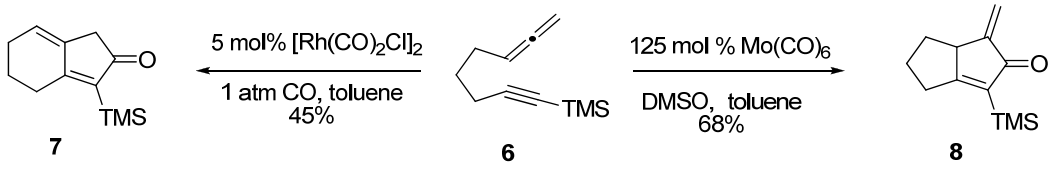
Brummond and co-workers were the first to report cyclocarbonylation of allene-ynes using $Mo(CO)_6$ to prepare α-methylene cyclopentenones.[13] This protocol can be applied to produce bicyclo[3.3.0] and bicyclo[4.3.0] ring systems, depending upon the length of the linker in the starting material. However, when the allene is additionally substituted on the proximal

double bond, the selectivity is reversed (b to a), yielding exclusively the 4-alkylidene cyclopentenone product. This methodology was utilized as a key step in the synthesis of the natural product hydroxymethylacylfulvene (HMAF). (Scheme 1.3).[2, 14]



Scheme 1.3: Cyclocarbonylation of Allene-yne 4 towards the formation of HMAF

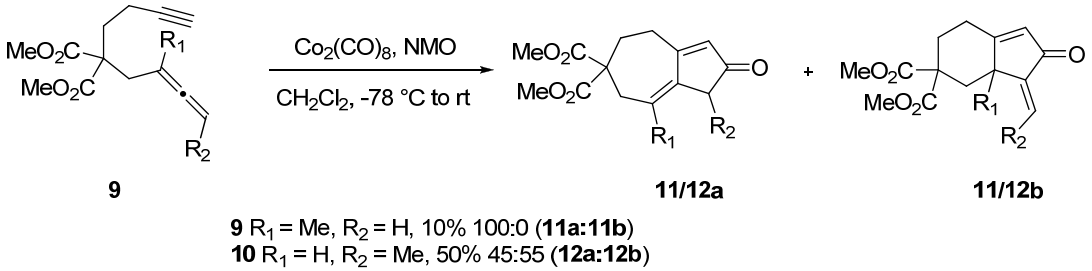
Subsequently, it was discovered that modification of the reaction conditions could produce a change in the selectivity that was not substrate, but reagent dependent.[15, 16] Using Rh(I)-catalyzed conditions developed by Narasaka,[17] Brummond and co-workers achieved selective reaction with the distal double bond present in allene-yne **6**, yielding exclusively the 4-alkylidene cyclopentenone **7**.[16] (Scheme 1.4)



Scheme 1.4: Regioselectivity via Reagent Control

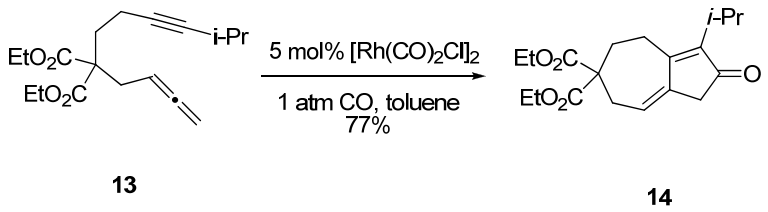
One of the greatest advantages of the incorporation of an allene in the [2+2+1] cyclocarbonylation reaction is that it allows the formation of seven-membered rings. This development vastly increases the utility of the reaction as seven-membered rings are present in a great deal of natural products that are of biological interest. In 1997 Cazes and co-workers

developed cobalt catalyzed conditions that produced a [7-5] bicycle; however, the reaction, while successful in producing the seven-membered ring, gave either a poor yield of **11a** or low selectivity of **12a** vs. **12b**.[18] (Scheme 1.5)



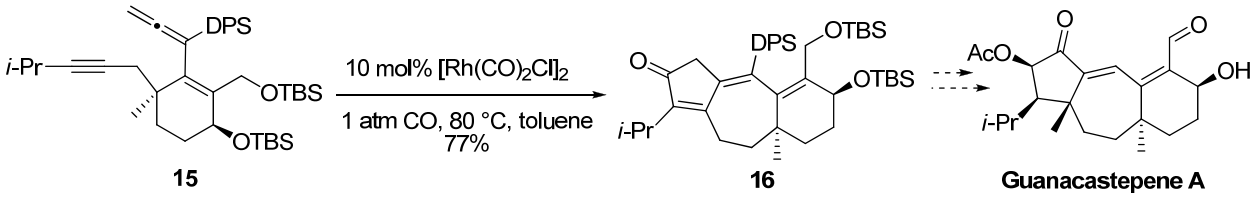
Scheme 1.5: Formation of [7-5] Bicycles using $Co_2(CO)_8$

In their development of the Rh(I)-catalyzed cyclocarbonylation reaction, Brummond and co-workers demonstrated that [7-5] ring systems could be accessed under Rh(I) conditions.[16] (Scheme 1.6) This method allows for the selective formation of the [7-5] ring system without any steric or other substrate control.



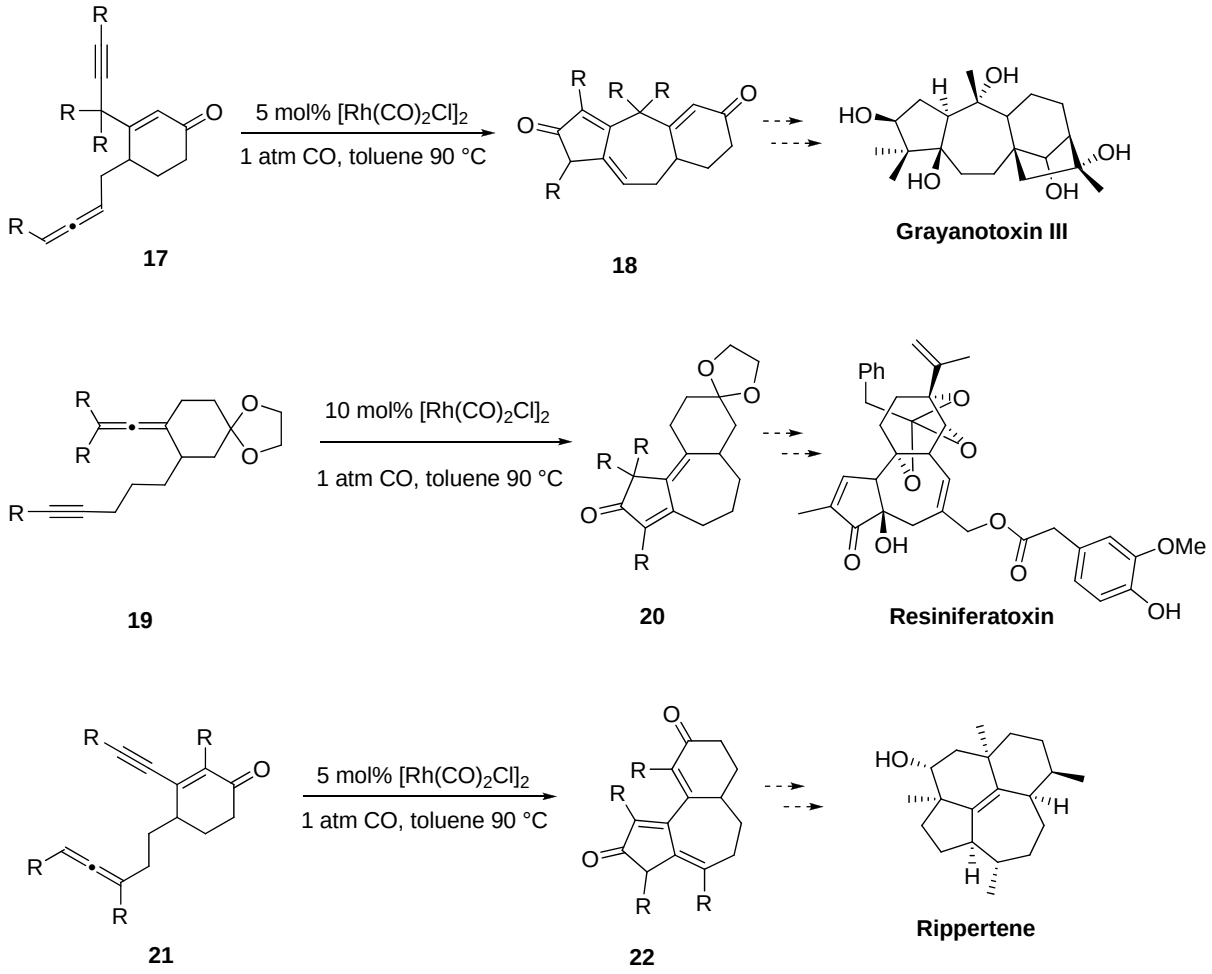
Scheme 1.6: Rh(I)-Catalyzed Cyclocarbonylation of Allene-ynes

This cyclocarbonylation reaction to form [7-5] ring systems was later utilized as a key step in the synthesis of the core of guanacastepene A.[19] (Scheme 1.7)



Scheme 1.7: Cyclocarbonylation in the Synthesis of Guanacastepene A

The Rh(I)-catalyzed cyclocarbonylation has also been applied to make allene-yne scaffolds in the pursuit of [6-7-5] tricyclic natural products. Modification of the placement of the allene and alkyne on the six-membered ring can yield a variety of [6-7-5] ring systems.[20] (Scheme 1.8) For example, reaction of allene-yne **17** affords the linear [6-7-5] tricyclic ring system **18**, which contains the basic skeleton of grayanotoxin III. Reaction of allene-yne **19** affords the angular tricycle **20**, which can be used to quickly generate the core of resiniferatoxin. Particularly inspiring, is the rapid access to the carbocyclic core of rippertene from reaction of allene-yne **21** to give angular [6-7-5] ring system **22**. This transformation establishes the [6-7-5] core as well as introduces synthetic handles for further functionalization.



Scheme 1.8: Formation of Alternate [6-7-5] Ring Systems

1.3 3A-HYDROXY-15-RIPPERTENE

1.3.1 Isolation, Characterization & Biological Activity of 3α-Hydroxy-15-Rippertene and Structurally Related Compounds

The defense secretions of termite soldiers contain terpene-derived natural products with interesting molecular architecture. In 1980 Prestwich and co-workers isolated several structurally

unique tri- and tetracyclic diterpenes from *Nasutitermes rippertii* and *N. ephratae*.[21] 3α-Hydroxy-15-rippertene, originally assigned as structure (**24**)[22, 23] was later identified as **23**, (Figure 1.1) determined from an x-ray crystal structure of functionalized derivative **25**.[21]

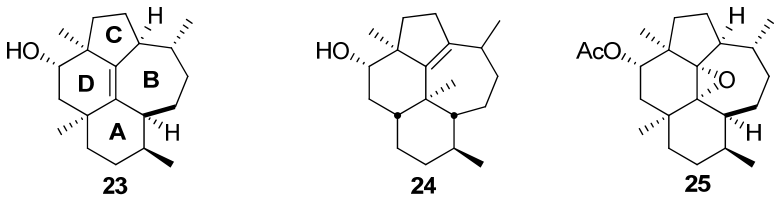
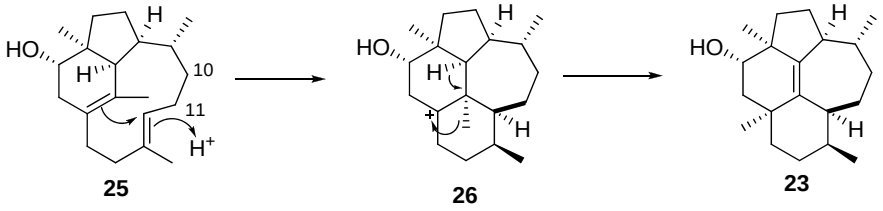


Figure 1.1 Rippertene Structures

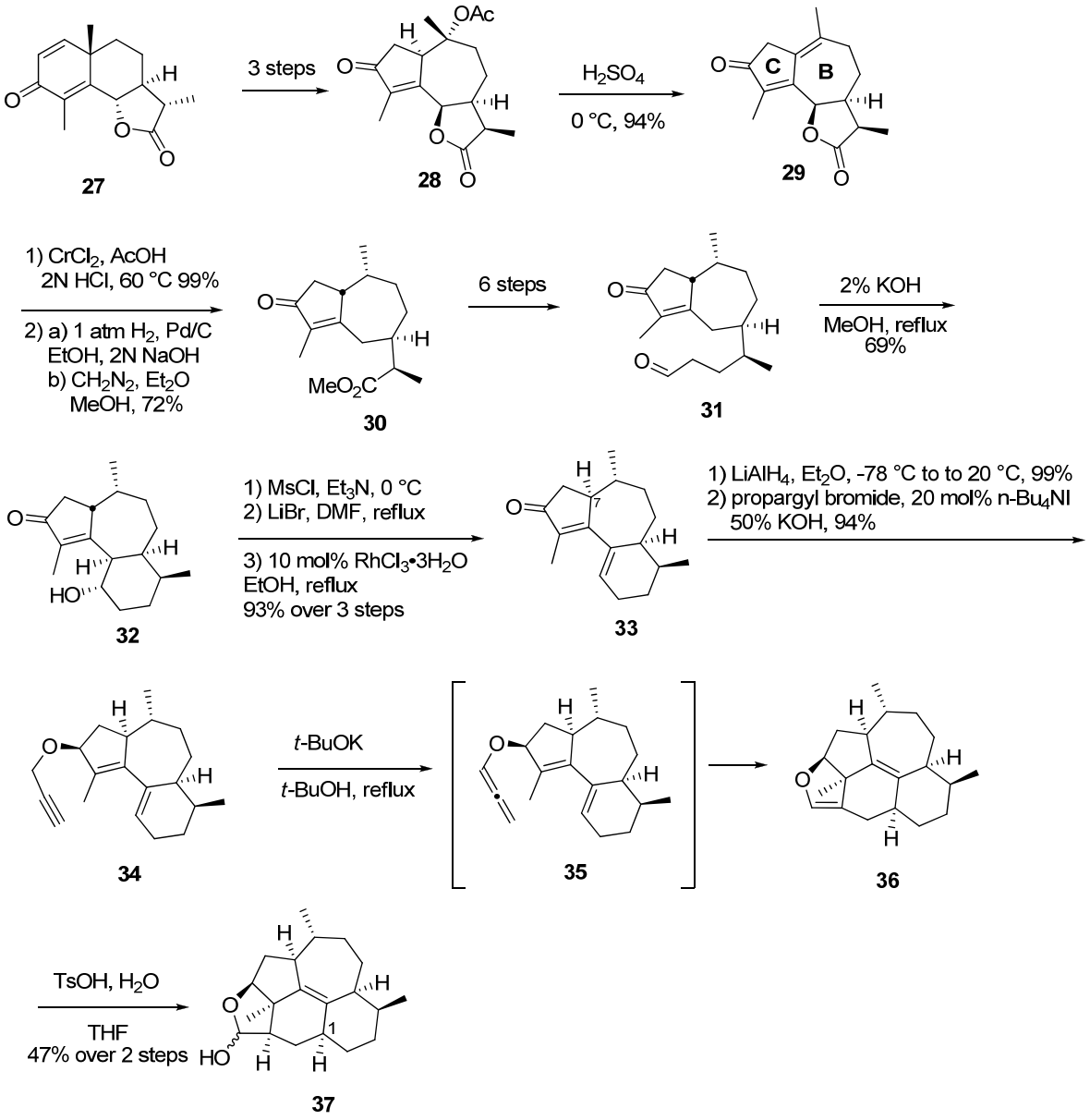
Biosynthetically the rippertene skeleton may arise via a 1,2-methyl migration from a tetracyclic intermediate such as **26**, in turn derived from proton-induced intramolecular cyclization of a tricycle such as **25**. (Scheme 1.9) Modeling studies show that unfavorable steric interactions resulting from the two boat-like fused six-membered rings and the axial C(10)-C(11) bond are alleviated by this migration and by the subsequent flattening of the convex dome cap by proton loss to the tetrasubstituted olefin.[21] Attempts to investigate the biosynthesis via feeding the termites ^{14}C-impregnated wood did not provide labeled rippertene.



Scheme 1.9 Proposed Biosynthetic Pathway

1.3.2 Previous Synthetic Explorations of Rippertene and Analogs.

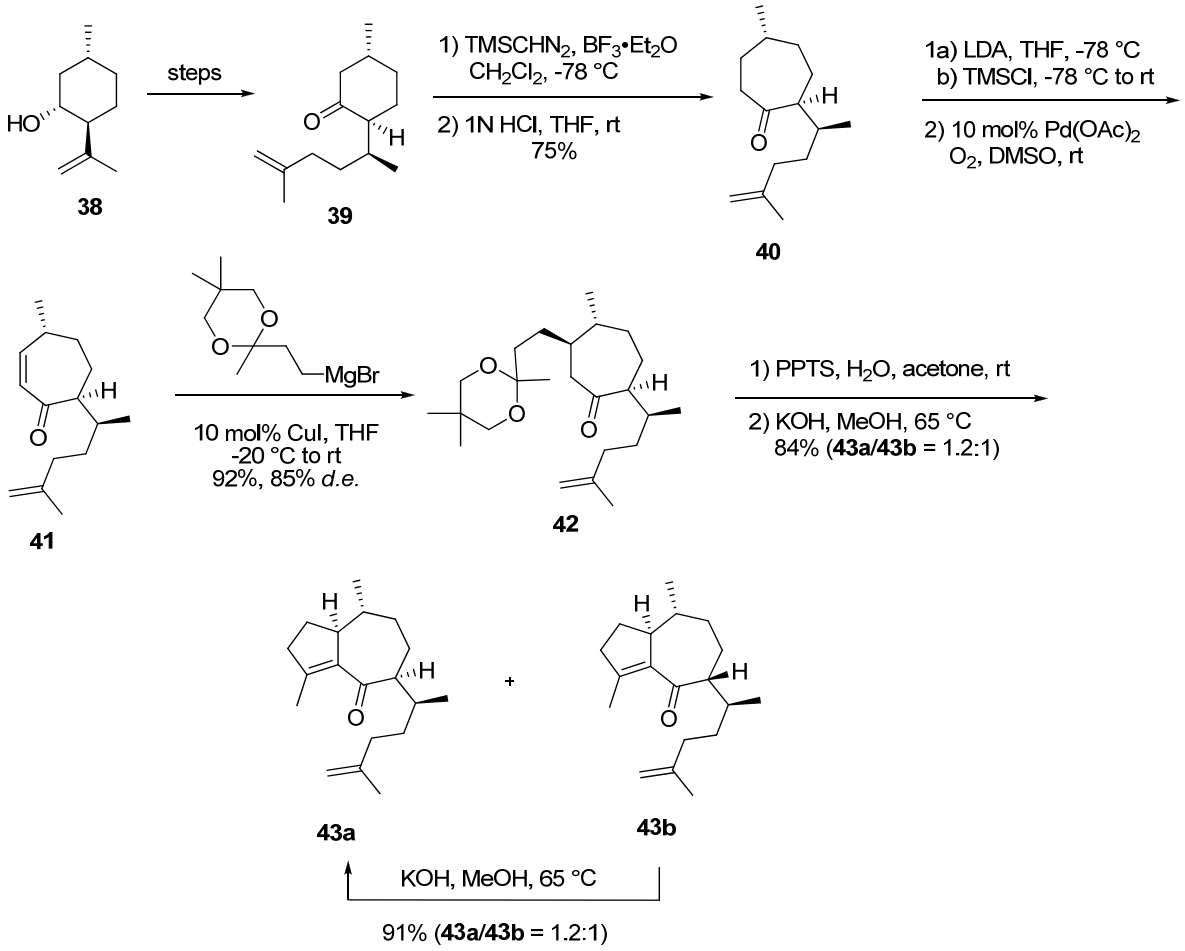
To date, there has not been a successful total synthesis of 3α-hydroxy-15-rippertene; however, Metz and coworkers have published three explorative syntheses.[24-26] The first generation approach was published in 1993, and demonstrated the synthesis of the rippertene core.[24] (Scheme 1.10) Starting with commercially available (-)-α-santonin **27** as the chiral source, he quickly established the B and C rings though a photolytic transformation of **27** to give **28**. Elimination of the acetate and reductive ring opening of lactone **29** provided unsaturated acid **30**. The acid was then elaborated to ring-closure precursor aldehyde **31**. The A ring was closed through a stereoselective vinylogous aldol under basic conditions to provided tricyclic alcohol **32**. To set the key C7 stereocenter as well as form the second olefin required for the upcoming [4+2] cycloaddition, alcohol **32** was mesylated and then subjected to heating with lithium bromide in DMF to provide an isomeric mixture of dienones. Rhodium-catalyzed isomerization of the crude mixture enhanced the desired ratio from 82:18 to 93:7. Concomitant with the elimination of the mesylate, the hydrogen present at C7 epimerized to the desired (*S*) configuration. Stereoselective reduction of the ketone and subsequent O-alkylation with propargyl bromide provided alkyne **34**, setting the stage for the key intramolecular [4+2] cycloaddition. Following the methodology of Kanematsu[27, 28] the alkyne was isomerized in situ to allene **35** and under the reaction conditions then cyclized to generate tetracyclic enol ether **36**. This product contains the entire core ring structure of **23**; however, it lacks the methyl substitution at C1.



Scheme 1.10: Metz's First Generation Approach[24]

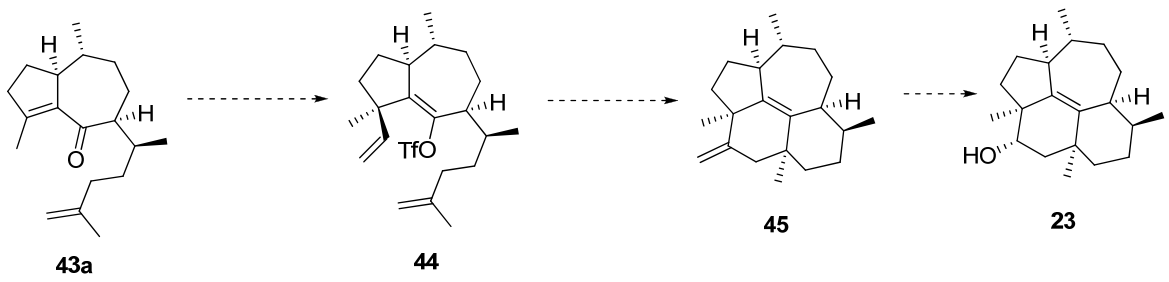
The second generation approach of **23** proceeded through an alternate disconnection strategy. Metz proposed a domino Heck cyclization of enol-triflate **44** to generate the A and D rings. To generate Heck-precursor **44**, the synthesis proceeded from (-)-isopulegol **38**. The B ring

was generated through a regioselective ring-expansion of ketone **39** using TMS-diazomethane to provide substituted-cycloheptanone **40**. (Scheme 1.11) Further elaboration through a Saegusa-Ito oxidation, conjugate addition, deprotection, and an aldol condensation provided **43a**. Following these transformations, the synthetic plan calls for a diastereoselective conjugate addition and enol-triflate formation to obtain the precursor for the domino-Heck cyclization, triflate **44**. (Scheme 1.12) Studies toward completion of the synthesis according to this strategy are reported to be in progress.



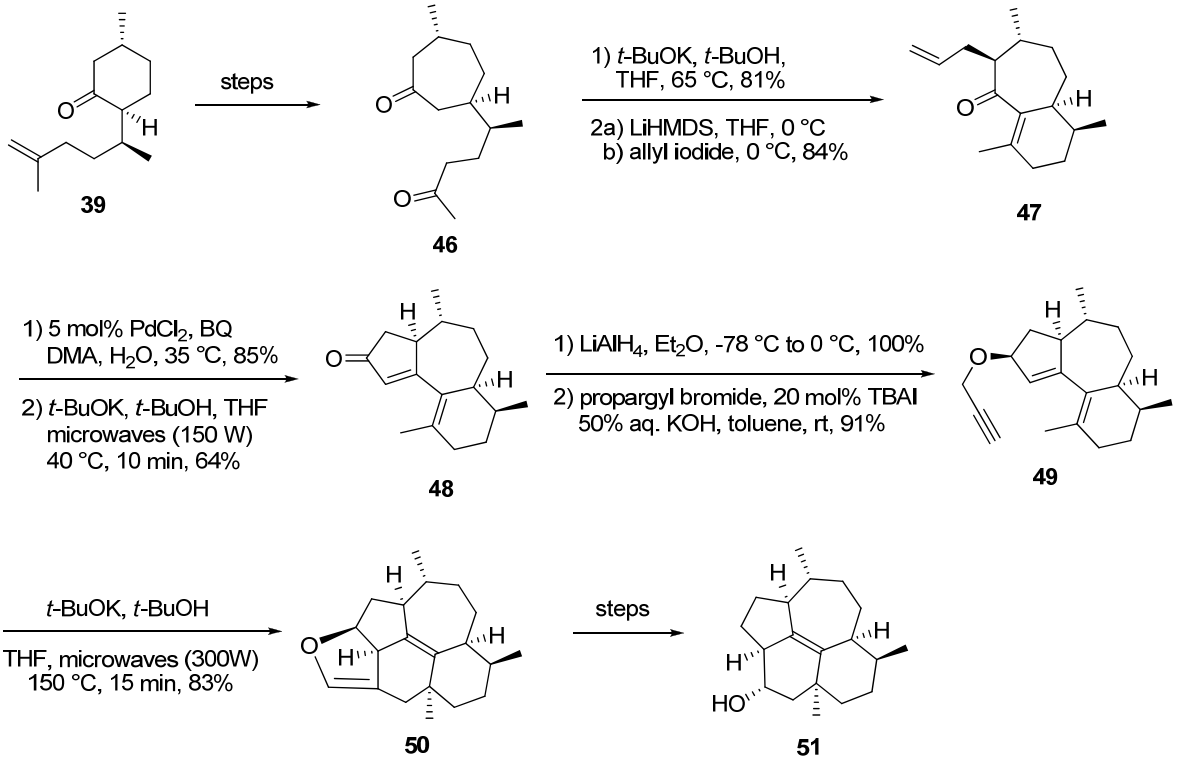
38 39 40 41 42 43a 43b

Scheme 1.11: Second Generation Approach [26]



Scheme 1.12: Proposed Completion

The most recent synthetic approach was pressed to completion as a close analog of 3α-hydroxy-15-rippertene (**23**), 4-desmethyl-3α-hydroxy-15-rippertene (**51**).[25] (Scheme 1.13) The synthetic strategy had a similar end-game as the previous attempts, but the core synthesis was based upon an aldol strategy. Cyclohexanone **39** was elaborated to diketone **46**, condensed and alkylated to provide bicycle **47**. Wacker oxidation followed by a second aldol reaction to close the C ring provided the core [6-7-5] ring structure present in **48**. Diastereoselective reduction and O-alkylation provided the cycloaddition precursor **49**. In situ isomerization followed by a [4+2] cycloaddition under basic microwave conditions formed the D ring in 83% yield. This was then elaborated to the desmethyl natural product **51** through a series of oxidation/reduction steps. The synthesis was 19 steps with an overall yield of 1.6% along the shortest linear sequence starting from cyclohexanone **39**. However, this is not a commercially available compound and is synthesized from (-)-isopulegol in 77% over a four-step sequence.

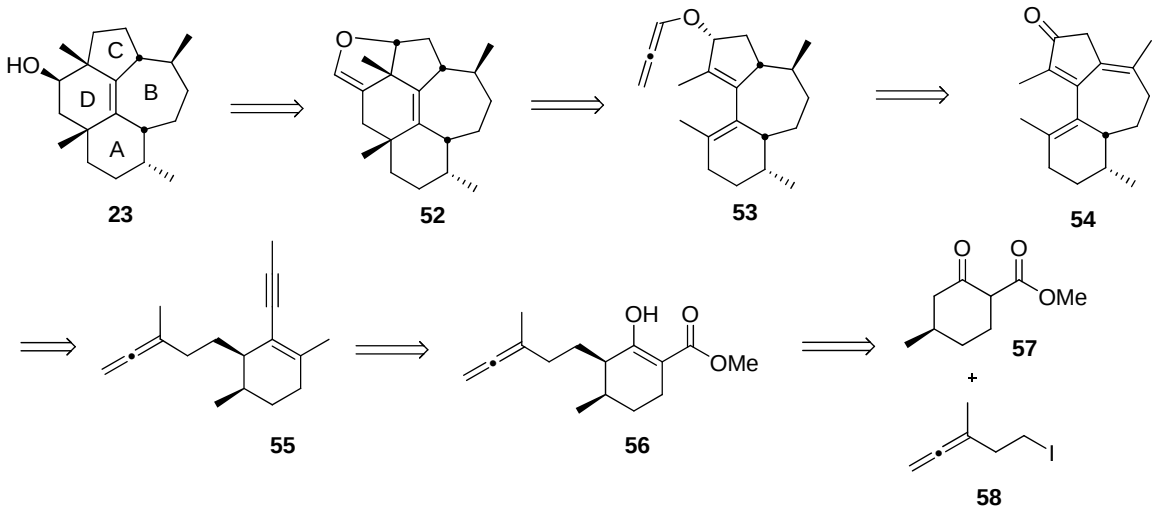


Scheme 1.13: Synthesis of 4-desmethyl-3α-hydroxy-15-rippertene[25]

2.0 RESULTS AND DISCUSSION

2.1 AN ALLENIC CYCLOCARBONYLATION APPROACH TO RIPPERTENE: A RETROSYNTHETIC ANALYSIS

We envision a total synthesis of 3α-hydroxy-15-rippertene (**23**) using a Rh(I)-catalyzed allenic cyclocarbonylation reaction of allene-yne **55** to give [6-7-5] tricycle **54**. (Scheme 2.1) Cyclocarbonylation affords the B and C rings of the rippertene core and places the ketone and olefins in strategic locations for the further introduction of functionality and stereochemistry. Ketone **54** can be elaborated to the desired natural product **23** through a [4+2] intramolecular cycloaddition of the distal double bond of an allene tethered to the core structure with a diene component. The resulting enol-ether can be transformed to the natural product through a series of oxidation/reduction functional group manipulations, as has been demonstrated by Metz on a closely related compound.[24, 25] We envision generating the allene-yne cyclocarbonylation precursor **55** from β-ketoester **56**, which in turn can be constructed through a diastereoselective dianion alkylation from methyl 4-methyl-2-oxocyclohexanecarboxylate (**57**) and 5-iodo-3-methylpenta-1,2-diene (**58**). This strategy would provide tricycle **54** in a rapid and concise manner, and allow for straightforward derivatization. While it uses a similar end-game strategy to Metz,[25] it reaches the convergent point with fewer chemical transformations.



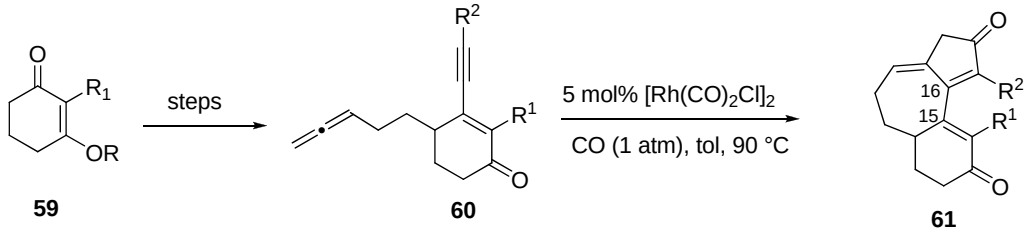
23 **52** **53** **54** **55** **56** **57** **58**

Scheme 2.1: Retrosynthetic Analysis of Rippertene

2.2 PRELIMINARY RESULTS AND FEASIBILITY STUDIES REPORTED BY CHEN/BRUMMOND

Studies directed at exploring the scope of the Rh(I)-catalyzed cyclocarbonylation of allene-ynes, have shown that the angular structure present in rippertene can be generated in a model system.[20] Preliminary results show that the cyclocarbonylation of **60a** (R^1=R^2=H) gives **61a** in 85% yield in 100 min. (Table 2.1) Cyclocarbonylation of **60b** (R^1=H, R^2=Me) and **60c** (R^1=Me, R^2=H) afford the more substituted dienones **61b** and **61c** in lower yields of 67% and 56%, respectively. Finally, reaction of **60d** (R^1=R^2=Me) with $[Rh(CO)_2Cl]_2$ affords **61d** in 58% yield in 20 h. The extended reaction time for this reaction is attributed to the developing A(1,3) strain between R^1 and R^2. This ring strain also hinders rotation along the C15-C16 bond leading to potential atropisomers (not observed), further increasing the stereo-complexity of the

molecule. Although this stereo-complexity was not explored, it may prove an interesting point for further explorations of this molecular architecture.



59 **60** **61**

Entry	Substrate	R^1	R^2	Time	Yield (%)	Product
1	**60a**	H	H	100 min	85	**61a**
2	**60b**	H	Me	130 min	67	**61b**
3	**60c**	Me	H	70 min	56	**61c**
4	**60d**	Me	Me	20 h	58	**61d**

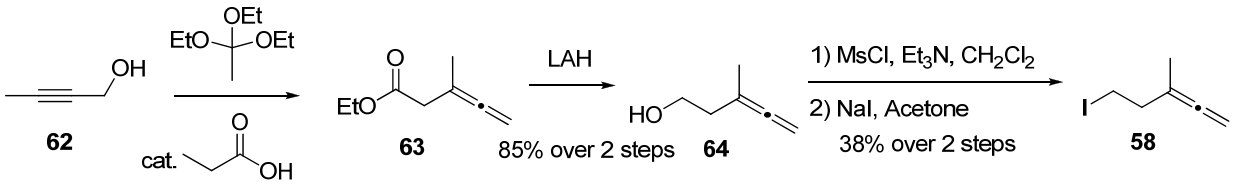
Table 2.1: Preliminary Results

These preliminary results demonstrate that the rhodium(I)-catalyzed cyclocarbonylation reaction is amenable to generating the A, B, and C rings of rippertene.

2.3 GENERATION OF ALLENYL IODIDE 58

Allenyl Iodide **58** was prepared using a 4-step reaction sequence following a procedure analogous to that reported previously.[20] (Scheme 2.2) 2-Butyne-1-ol was subjected to an acid

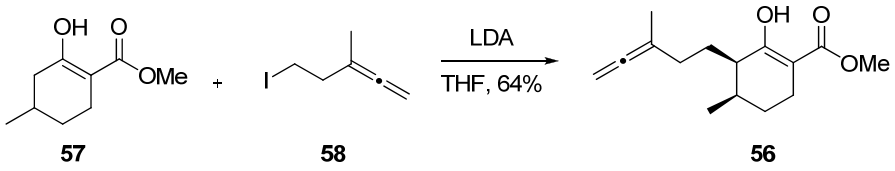
catalyzed Johnson-Claisen rearrangement to give ester **63**, which was immediately reduced to alcohol **64** with $LiAlH_4$ in 85% yield.[29] Alcohol **64** was then converted to the mesylate and subjected to Finkelstein reaction conditions to give allenyl iodide **58** in 38% yield over two steps. Attempts were made to effect a more direct conversion of alcohol **64** to iodide **58** using PPh_3 / I_2 conditions;[30] however, removal of the triphenylphosphine oxide proved problematic.



Scheme 2.2: Preparation of Allenyl Iodide 58

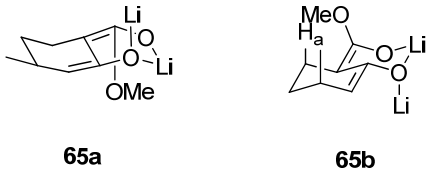
2.4 INSTALLATION OF THE ALLENE COMPONENT VIA AN ALKYLATION OF ALLENYL IODIDE 58 WITH BETA-KETOESTER 57

To install the allene side chain in a regio and stereo-selective manner we choose to utilize the methodology of Weiler and co-workers.[31] This methodology has been previously utilized by Corey in a stereoselective manner in his synthesis of Desogestrel.[32] Deprotonation of β-ketoester **57** with 2.1 equiv of LDA gives a dianion. Alkylation with iodide **58** gives allene **56** in 64% yield. (Scheme 2.3)



Scheme 2.3: Dianion Alkylation

Determining the diastereoselectivity for this reaction is difficult due to the keto/enol tautomerization. However, later in the synthetic sequence this problem is resolved due to the removal of all other stereogenic centers. While the cis-diastereomer is represented, it was not definitively confirmed. It is predicted that the cis-diastereomer will be obtained for stereo-electronic reasons. As seen in figure 2.1, there are two predominant configurations the dianion may adopt. Both configurations contain a six-membered ring through coordination between the lithium and oxyanions, thereby stabilizing the intermediate. It is known that enolate alkylations have an early transition state, and therefore the diastereoselectivity depends on the relative populations of the enolate configurations.[33] If the electrophile approaches from a pseudo-axial position, **65a** would generate the cis product, and **65b** would generate the trans product. Since an equatorial approach would necessitate a boat or twist-boat transition state, and thereby disrupt the coordination of the oxygens and lithium, it was theorized that the equatorial approach would have a minimal impact on the stereochemical result.



65a **65b**

Figure 2.1: Dianion Conformations

When comparing **65a** to **65b**, the most important difference is the conformation of the methyl group; in **65a** the methyl group is equatorial, while in **65b** it is axial. This difference would normally result in a 1.8 kcal/mol energy difference in a methyl-substituted cyclohexane in the ground state,[34] while in the case of **65** the energy difference will be modified. A 1.8 kcal/mol energy difference would result in a 21:1 ratio of diasteromeric products; however, the experimental ratio (determined in section 2.7) is 19:1 (an energy difference of 1.74 kcal/mol). This disparity can be explained by the fact that only one proton, H_a, is present to interfere with the ideal conformation as well as the constrained nature of the ring. Therefore, alkylation product **65** is conditionally assigned as cis.

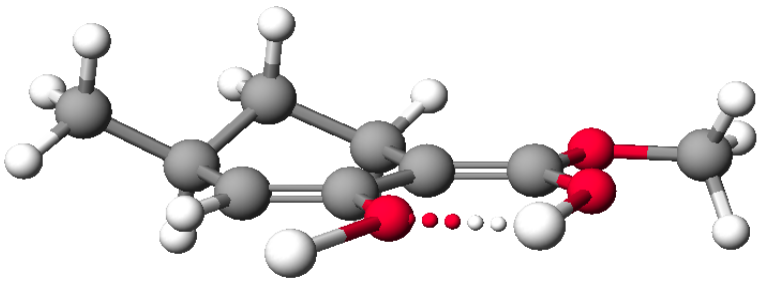


Figure 2.2: 65a (MM3 Modeling)

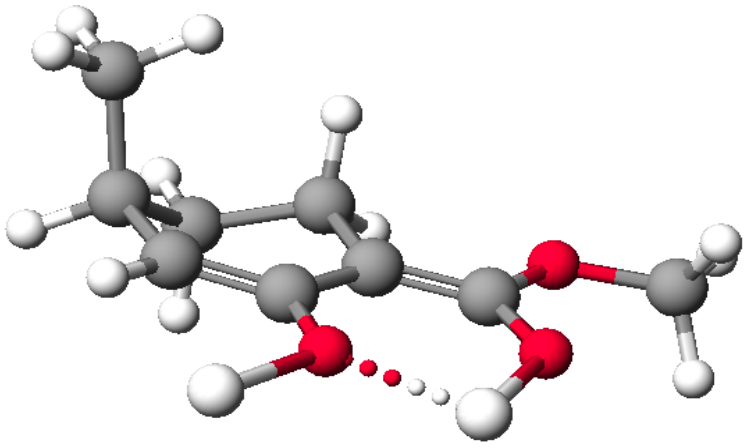


Figure 2.3: 65b (MM3 Modeling)

In the ^{1}H NMR spectrum of **56**, there are three methyl doublets present. (Figure 2.4) These doublets represent the keto-enol tautomerization of **56**. The major tautomer in solution is the enol tautomer, identified by the resonance at 12.27 ppm which is indicative of an enol proton. This corresponds to the resonance at 0.94 ppm with an integration of 2.26. The other two doublets can result from the two epimers of the methyl ester in the keto form, which would provide two diastereomers. The ratio of the enol tautomer to the keto tautomer was roughly 3:2 based upon the ratio of methyl resonances.

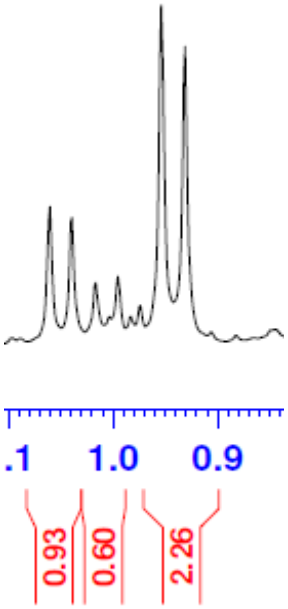
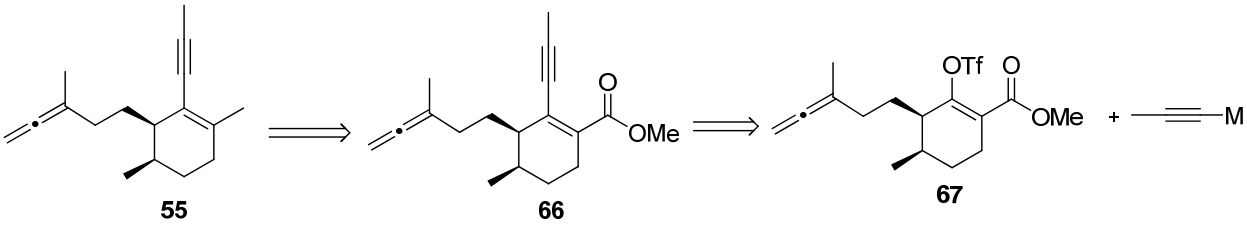


Figure 2.4: Expansion of ^{1}H NMR Showing the Methyl Doublets of 56

2.5 INSTALLATION OF THE ALKYNE COMPONENT: A CROSS-COUPLING STRATEGY



Scheme 2.4: Cross-Coupling Disconnection

Two different strategies were considered for the introduction of the alkyne component into the cyclocarbonylation precursor. The first involves the enol tautomer of **56**, its conversion into the corresponding enol triflate **67** and subsequent cross-coupling with an alkynyl component to give ene-yne **66**. (Scheme 2.4) The second strategy involves the direct addition of an acetylide anion to the ketone and then a dehydrative decarboxylation to afford **55**.

Because neither of these approaches is well-precedented, the feasibility of a cross-coupling route to allene-yne **55** was investigated through a model system. Vinyl triflate **70** was produced from β-keto ester **57** using triflic anhydride and sodium hydride and taken on crude to the cross-coupling. Formation of the triflate was confirmed through ^{13}C NMR analysis, where the quartet resulting from the CF_3 (δ=118.3 ppm) was clearly present with a J_{CF} = 320 Hz coupling constant. [35] (Figure 2.5)

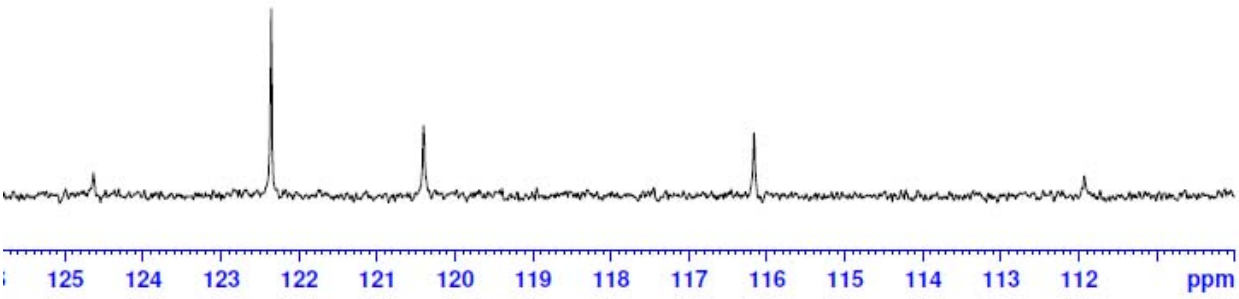
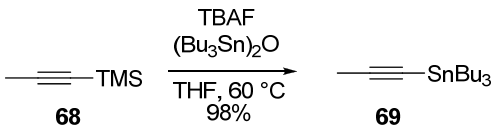


Figure 2.5: CF_3 Quartet in the ^{13}C NMR Spectrum of 70

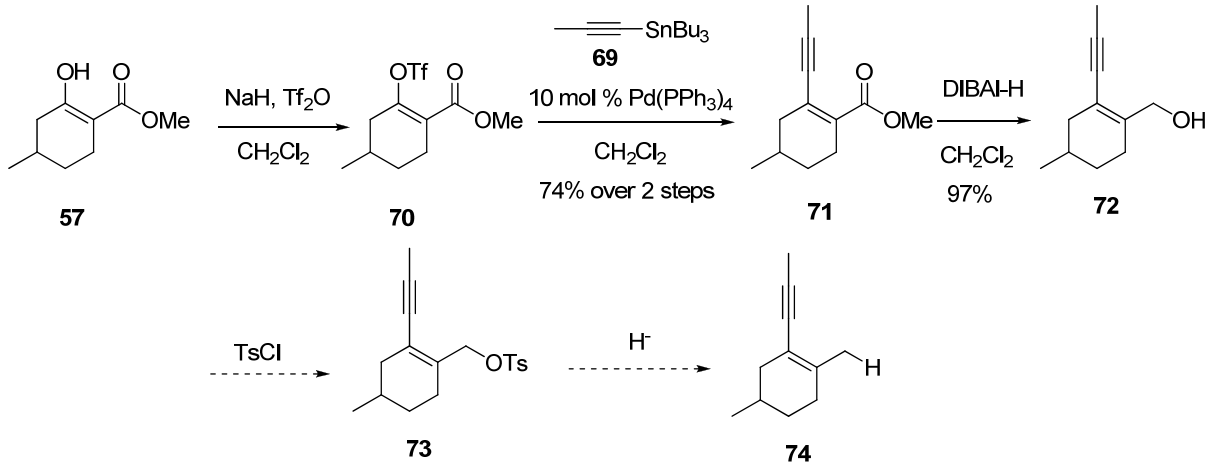
With triflate **70** in hand, a number of coupling protocols were tested including Kumada conditions and the silver-mediated direct coupling of TMS-protected alkynes.[36] The Stille coupling proved to be the optimal way to synthesize the ene-yne, giving **71** in 74% yield over 2

steps. (Scheme 2.6) However, the procurement of the required stannane proved interesting. In 1994 Buchwald and co-workers developed a catalytic method of converting silanes to stannanes, which allowed production of stannane **69** in a straightforward manner.[37] (Scheme 2.5)



Scheme 2.5: Buchwald's Silane to Stannane Conversion

Following cross-coupling, reduction of the ester was effected with DIBAl-H in 97% yield to give alcohol **72**. Deoxygenation was planned via tosylation of the alcohol, followed by S_N2 displacement with either DIBAl-H[38] or $NaBH_4$.[39, 40] (Scheme 2.6)

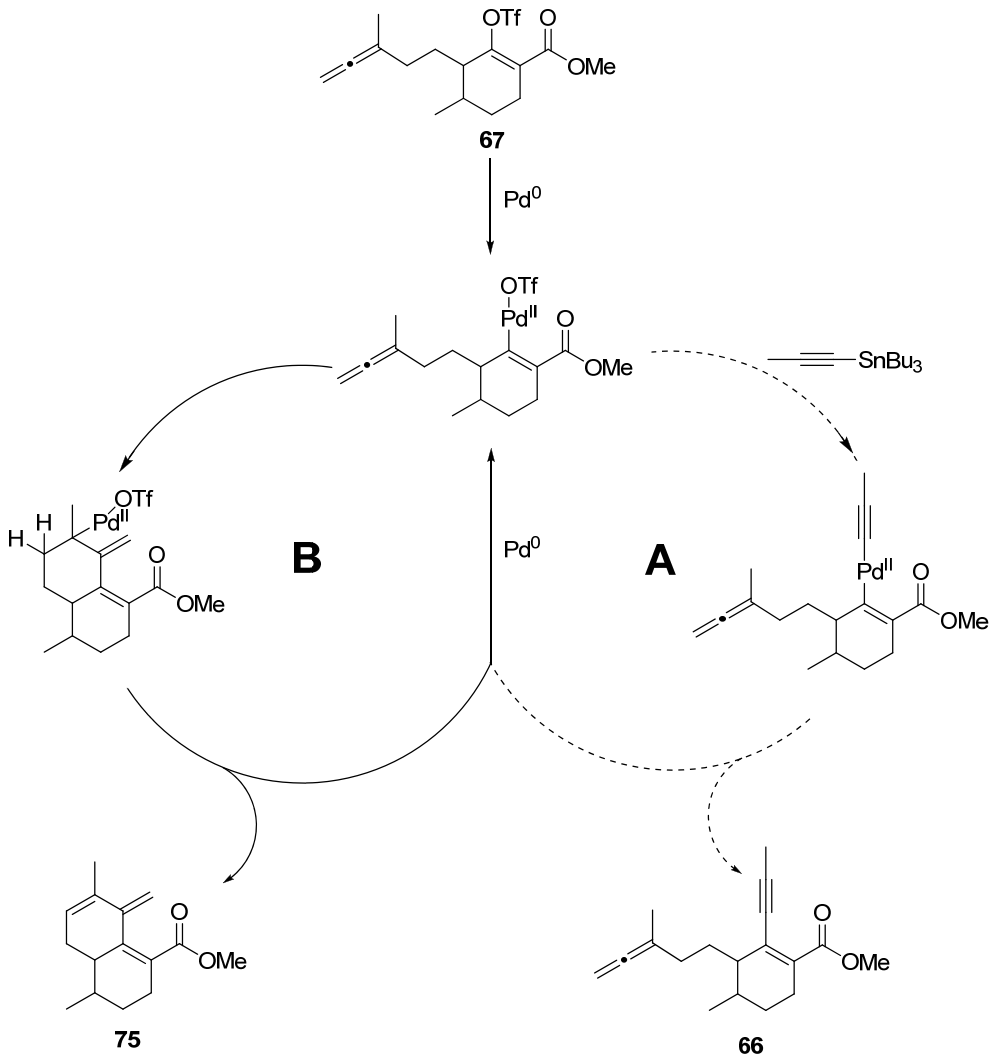


Scheme 2.6: Model System

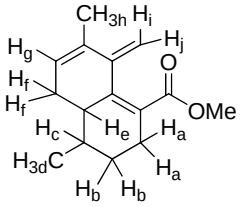
Once the cross-coupling was successfully carried out on the model system, work began on the system with the appendant allene. β-Ketoester **56** was converted to the corresponding vinyl triflate using *N*-phenyl-bis(trifluoromethanesulfonimide) and sodium hydride to give the

expected vinyl triflate.[41] The formation of the triflate was confirmed by ^{13}C NMR, which showed a quartet at 118.3 ppm with a coupling constant of J_{CF} = 320 Hz.

Enol triflate **67** was then subjected to the cross-coupling conditions developed for the model system. Unfortunately, instead of the cross-coupling to give the desired ene-yne (Scheme 2.7, Cycle A) an intramolecular carbopalladation of the allene occurred, giving bicycle **75** in 47% yield. (Scheme 2.7, Cycle B) The structure of **75** was tentatively assigned through the presence of vinyl protons (δ= 5.65, 4.96, 4.91) and supported by the appearance of new olefinic carbon resonances at the appropriate resonances. (Tables 2.2 & 2.3)



Scheme 2.7: Potential Mechanisms

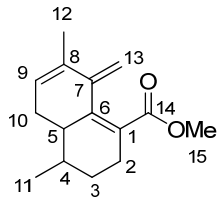


75

Proton	Chemical Shift (ppm)	Multiplicity, Coupling Constant (Hz)
H_a	2.25-1.88[a]	m
H_b	1.78-1.63[b]	m
H_c	1.78-1.63[b]	m
H_d	1.01	d, 6.3
H_e	2.25-1.88[a]	m
H_f	2.25-1.88[a]	m
H_g	5.66	d, 4.5
H_h	1.84-1.82	m
H_i	4.91	s
H_j	4.96	s
OMe	3.63	s

[a] These assignments may be interchangeable, [b] These assignments may be interchangeable

Table 2.2: Tentative ^{1}H NMR Assignments for Compound 75



75

Carbon	Chemical Shift (ppm)
1	126.8
2	27.8
3	29.8
4	35.9
5	43.9
6	145.5
7	143.6
8	133.0
9	127.1
10	34.3
11	19.8
12	20.5
13	110.7
14	173.0
15	52.3

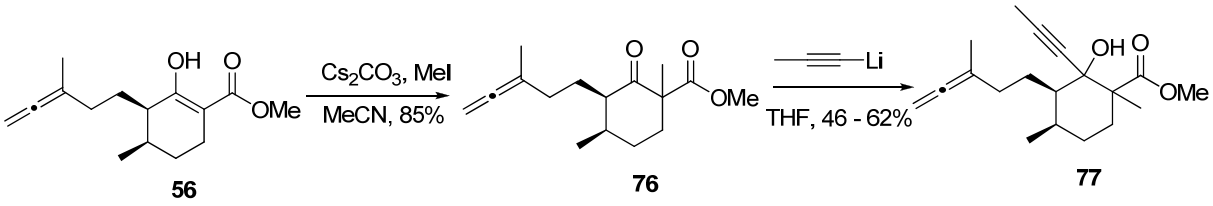
Table 2.3: Tentative ^{13}C Assignments for Compound 75

This type of allenic carbopalladation has been observed previously by Negishi and co-workers to form medium to large rings.[42, 43] In 1990 Negishi and co-workers encountered a similar problem with intra vs. intermolecular coupling.[44] In his attempts at performing a tandem carbopalladation and subsequent cross-coupling. They noted that when organozincs were used in the Pd-catalyzed reaction, they underwent the transmetallation step much faster than those containing Al, B, Cu, Sn and Zr. When they substituted the Zn for Sn, they were able to affect the carbopalladation step prior to the cross-coupling. We sought to take advantage of this effect in reverse, by substituting the Sn for Zn. However, when enol triflate **67** was subjected to Pd-catalyzed cross-coupling using the organozinc propyne, no cross-coupling product was detected via NMR.

2.6 INSTALLATION OF THE ALKYNE: AN ORGANOMETALLIC ADDITION TO THE KETONE

The secondary strategy explored to install the alkyne functionality, was a 1,2 addition of the acetylide to the ketone of β-ketoester **56**. Standard Grignard and organolithium additions of propyne failed to produce the desired reactivity, and more involved methods such as the organocerium were also unsuccessful.[45] This was most likely due to the poor electrophilicy of the desired ketone, due to its predominate enol tautomer, and the basicity of the organometallic reagents. β-Ketoester **56** was α-methylated using cesium carbonate and methyl iodide to give ketone **76** in 85% yield; thus eliminating the keto-enol equilibrium. (Scheme 2.9) Addition of 1-

propynyl lithium[46] gave alcohol **77** in yields ranging from 46 – 62%. The addition was confirmed by the loss of the ketone resonance (210.5 ppm) and appearance of the propynyl-methyl resonance (3.5 ppm) in the ^{13}C NMR.

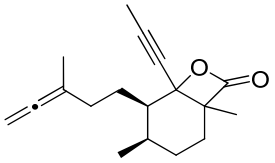


56 **76** **77**

Scheme 2.8: Formation of Alcohol 77

2.7 SYNTHESIS OF CYCLOCARBONYLATION PRECURSOR 55: SAPONIFICATION AND DEHYDRATIVE DECARBOXYLATION

In order to form the ene-yne present in the cyclocarbonylation precursor **55**, the ester and the β-hydroxyl group needed to be converted to an olefin. Our first plan for this transformation was to form the β-lactone **78** (Figure 2.6) and under thermal conditions it would undergo a retro [2+2] cycloreversion to form **55**.[47] However, the formation of the β-lactone was complicated by expected lack of stereo-control at the two pertinent carbons, and therefore difficulty in the lactonization.

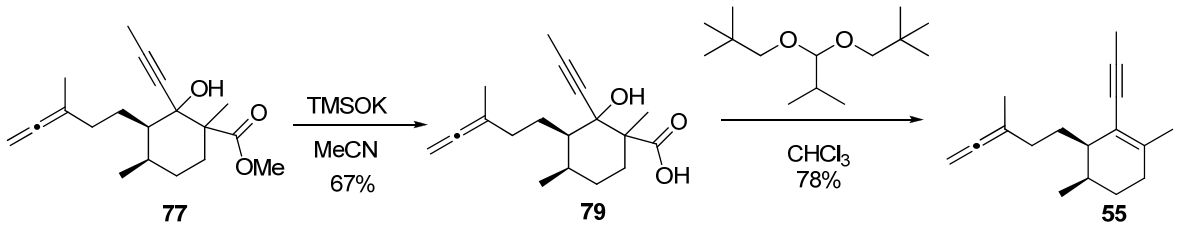


78

Figure 2.6: β-Lactone 78

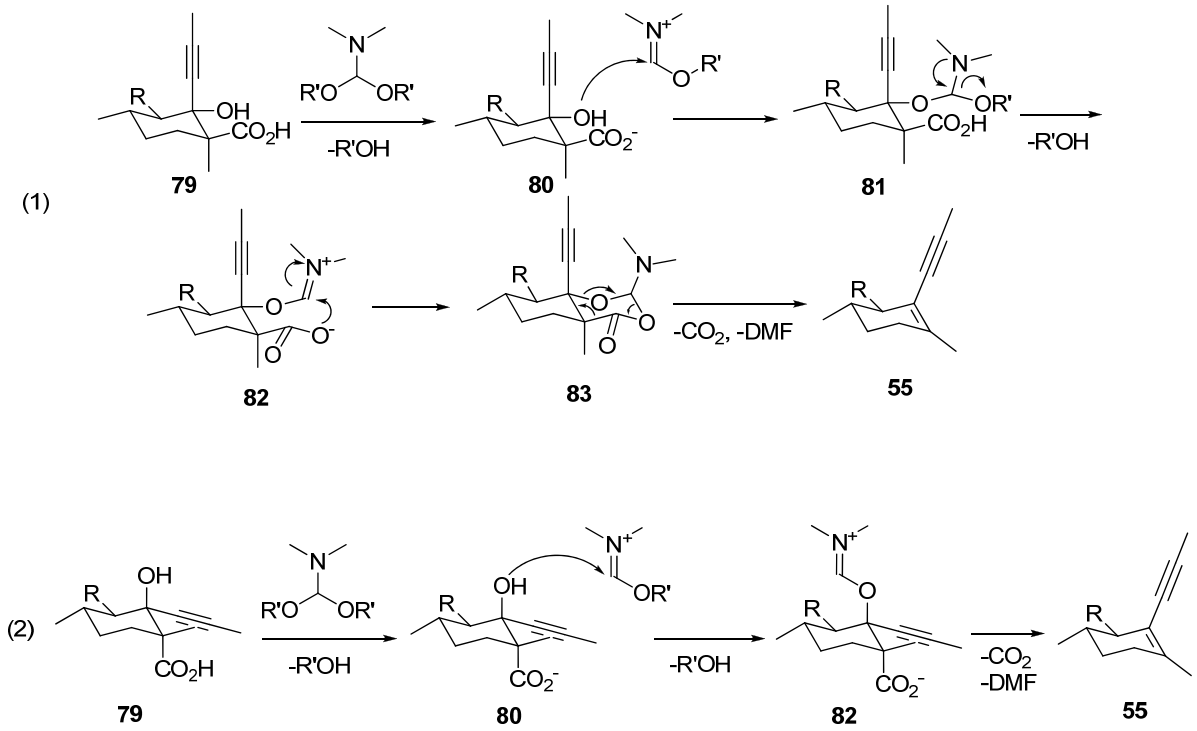
Alternatively, when β-hydroxy acid **79** is treated with an acetal of N,N-dimethylformamide a dehydrative decarboxylation can occur and yield the required olefin. This methodology, originally pioneered by Nozaki and co-workers[48] and later explored by Mulzer[49, 50] is not commonly used, but proved ideal for our purposes. Carbocyclic acid **79** was generated through anhydrous saponification conditions using potassium trimethylsilanolate.[51] (Scheme 2.10) Using these conditions, acid **79** was produced from ester **77** in 67% yield. Standard $LiOH•H_2O$ conditions were explored but proved unsuccessful, most likely due to the poor solubility of ester **77** in aqueous solutions.

Dehydrative decarboxylation with dimethylformamide dineopentyl acetal gave ene-yne **55** in 78% yield. The neopentyl acetal was necessary due to the methyl ester being reformed with the dimethyl acetal. This was due to methanol, produced in situ, reacting with the activated carbonyl group and producing methyl ester **77** as the primary product. Mulzer noted this effect as well and used the neopentyl acetal to avoid this, due to the decreased nucleophilicity of neopentanol with respect to methanol.



Scheme 2.9: Saponification and Elimination

The mechanism for this elimination is not fully understood, but it has been explored by Mulzer.[50] Two of the most promising mechanism are displayed in Scheme 2.10. In both mechanisms the first step is the loss of R'OH and formation of zwitterionic intermediate **80**, followed by attack of the alcohol onto the iminium carbon and loss of another equivalent of R'OH to give zwitterionic intermediate **82**. From here two possibilities emerge, either formation of six-membered lactone **83** and subsequent cycloreversion (Scheme 2.11, eq. 1.), or it could undergo an elimination reaction (either E1 or E2) (Scheme 2.11, eq. 2.). The results of Mulzer's experimentation show that the pathway shown in eq. 1 is unlikely as they obtain a mixture of E and Z isomers from the reaction. The alternate mechanism also has two possibilities for the elimination, E1 or E2 type elimination. Mulzer discovered that both modes of elimination appear to be operative; however, by controlling the steric interactions the E1 pathway can become the dominant or even the exclusive pathway.



Scheme 2.10: Decarboxylation Mechanism

With this elimination successfully carried out, the spectra were greatly simplified, due to the reduced number of stereogenic centers and it was possible to determine the diastereoselectivity the alkylation of the allenyl side chain. (Figure 2.7) From the ratio of methyl doublets of C-20 present in the ^{1}H NMR, a diasteromeric ratio of 19:1 was deduced. Unfortunately, it was not possible to determine the relative configuration of the two stereocenters as the relevant proton resonances for C-11 and C-12 were unresolved in the ^{1}H NMR spectrum.

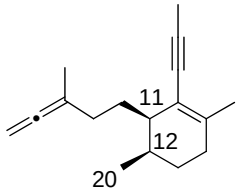
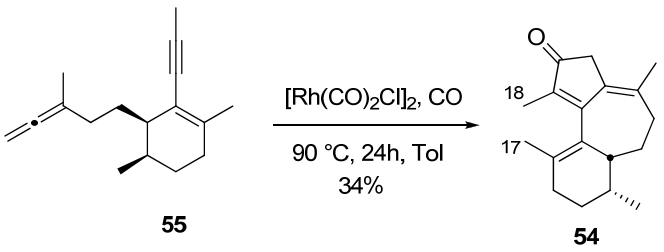


Figure 2.7: Carbocycle 55

2.8 RHODIUM CATALYZED CYCLOCARBONYLATION

The key step in the synthetic plan for rippertene is the Rh(I)-catalyzed cyclocarbonylation of allene-yne **55** to give tricycle **54**. The reaction occurred as expected under the conditions used by Brummond and co-workers to give cyclopentenone **54** in 34% yield.[20] (Scheme 2.12) Changing the catalyst to the one formed in situ from $[Rh(COD)Cl]_2$ and dppp[52] did not show improvement in reaction time or yield for this reaction. In our experience, longer reaction times result in decreased yields for the Rh(I)-catalyzed cyclocarbonylation reaction and therefore the extended reaction time causes a diminished yield, although in Brummond's previously reported example of **61d** (Table 2.1) the yield was not as greatly reduced. The long reaction time observed for this system is most likely caused by the developing A(1,3) steric strain between carbons 17 and 18. This strain can be seen in the model of cyclopentenone **54** in Figure 2.8.



Scheme 2.11: Cyclocarbonylation

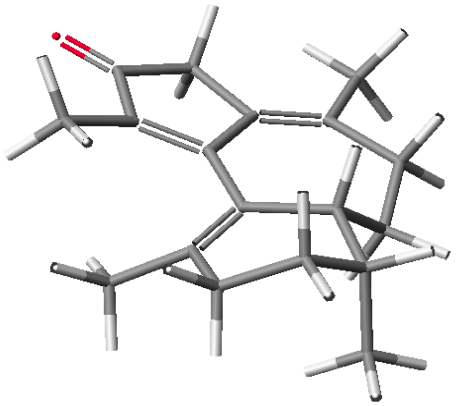
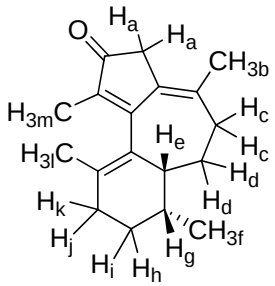
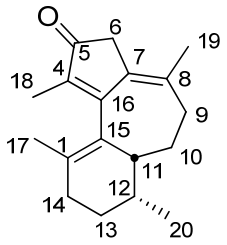


Figure 2.8: Cyclopentenone 54, Least Energy Conformer (MM3)



Proton	Chemical Shift (ppm)	Multiplicity, Coupling Constant (Hz)
H_a	2.88, 2.82	2 x 1/ 2 AB q, (21)
H_b	1.79	s
H_c	1.87-1.83, 1.66-1.58	2 x m
H_d	1.87-1.83, 1.66-1.58	2 x m
H_e	2.49-2.43	m
H_f	0.9	d, (6.5)
H_g	1.95-1.88	m
H_h	1.87-1.81	m
H_i	1.36	ddd, (6.5, 7, 7)
H_j	2.12-2.04	m
H_k	2.04-1.95	m
H_l	1.47	s
H_m	1.58	s

Table 2.4: ^{1}H NMR Assignments for Cyclocarbonylation Product 54



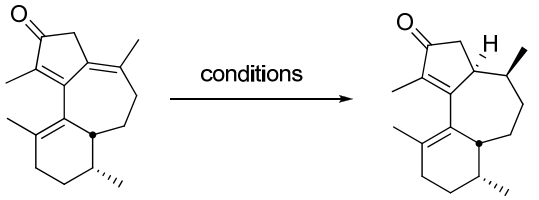
Carbon	Chemical Shift (ppm)
1	132.0
4	136.4
5	205.6
6	39.0
7	130.9
8	137.6
9	31.2[a]
10	33.7[a]
11	32.3
12	42.4
13	25.7
14	28.4
15	128.2
16	169.0
17	21.0
18	9.3
19	23.4
20	19.3

[a] These assignments may be interchangeable

Table 2.5: ^{13}C NMR Assignments for Cyclocarbonylation Product 54

2.9 ATTEMPTS AT HYDROGENATION

The goal for the next step in the synthesis was to regioselectively and stereoselectively hydrogenate the C7-C8 olefin. In Metz's 1993 partial synthesis, he was able to affect this type of transformation using $Pd/BaSO_4$ or Pd/C catalysis with substrate control. Although not perfectly selective, this reaction demonstrated the possibility of this transformation. Initially conditions that were demonstrated to be tolerant of α,β-unsaturated ketones were explored (Table 2.6, entries 1 & 3); however, these failed to provide **84**. More forcing conditions were also attempted (entry 5); however, while these proved to consume the starting material, it did not affect the desired transformation. We were unable to identify conditions for the regioselective hydrogenation of triene **54**.



54 84

Trial	Conditions	Reaction Time	Result
1	10 mol % $Pd/BaSO_4$ EtOAc	1.5 h	Partial reduction of unknown olefin (by ^1H NMR analysis)
2	10 mol% Pd/C EtOAc	1h	Partial Reduction, regioselectivity unclear (LC/MS monitoring)
3	10 mol% $Pd/BaSO_4$ EtOH	5 d	No Reaction
4	10 mol % Pd/C THF	2 h	No Reaction
5	10 mol % Pd/C THF, reflux	20 h	Messy, SM consumed by LC/MS 2 peaks by LC/MS, unidentifiable by NMR

Table 2.6: Hydrogenation Results

3.0 CONCLUSIONS

Our proposed synthetic plan required that we construct carbocyclic allene-yne **55**, and carry out the key Rh(I)-catalyzed cyclocarbonylation reaction. We synthesized the desired intermediate in a diastereoselective manner in six steps from 3-methylcyclohexanone. Since 3-methylcyclohexanone is commercially available in its enantiomerically enriched form it is possible to construct allene-yne **55** in its enantiomerically enriched form. The key cyclocarbonylation reaction was performed successfully and the product fully characterized, providing insights for future attempts at the synthesis. This carbocycle (**54**), represents the A, B, and C rings present in 3α-hydroxy-15-rippertene (**23**) and contains much of the necessary stereochemistry present in the natural product.

4.0 EXPERIMENTAL

General methods and Chromatography: Unless otherwise specified, all reactions were carried out in glassware that was flame-dried under vacuum, and allowed to cool under an atmosphere of dry nitrogen. Liquids and solutions were transferred via syringe or by stainless steel cannula. Stirring of reaction vessels was accomplished with Teflon™ coated magnetic stir bars. Elevated temperatures were maintained in variac-controlled oil baths. Thin layer chromatography plates (0.25 mm, silica gel 60, F254, glass-backed) were visualized by ultraviolet light or treatment with the appropriate stain followed by gentle heating. Chromatographic purification of products was accomplished by flash chromatography, as described by Still and co-workers[1]. Silica gel 60, 230-400 mesh was purchased from EM Science. Toluene and Acetonitrile were purchased from Mallinckrodt Chemicals and distilled from CaH_2 before use. Dichloromethane (DCM) and diethyl ether (Et_2O) were purchased from Mallinckrodt Chemicals and were purified through a Soltek column purification apparatus before use. Tetrahydrofuran (THF) was purchased from Aldrich and purified through a Soltek column purification apparatus before use. All other chemicals were used as received.

1H and 13C NMR spectra were obtained on Bruker 300 or 500 MHz instruments. All chemical shifts (δ) are reported in ppm. ^{1}H NMR spectra were calibrated to the residual $CHCl_3$

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

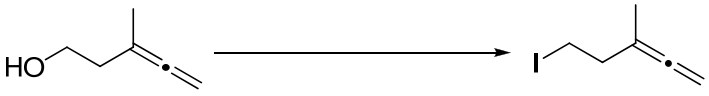
peak at δ 7.26; ^{13}C NMR spectra were referenced to the $CDCl_3$ resonance at δ 77.16. The following abbreviations are used to denote the indicated splitting pattern 1H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; abbreviations are used in combination to indicate more complex splitting (e.g., dtd = doublet of triplets of doublets). Infrared spectra were obtained on a Nicolet Avatar E. S. P. 360 FT-IR.

3-Methylpenta-3,4-dien-1-ol (64)

2-Butyn-1-ol (5.34 mL, 71.4 mmol), triethyl orthoacetate (17 mL, 93 mmol) and propionic acid (0.3 mL, 4 mmol) were combined in a 50 mL round-bottom flask equipped with a Dean-Stark trap and heated to 130 °C under an atmosphere of N_2 for 24 h. The reaction was then cooled to rt, diluted with Et_2O, quenched with 10% aq HCl, and stirred for 30 min. The layers were separated, and the aqueous layer was extracted with Et_2O (2X). The combined organic layers were washed with sat'd aq $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was applied to a silica gel plug, eluted with 10% EtOAc / hexanes, concentrated in vacuo, and taken on to the next step crude. $LiAlH_4$ (4.23 g, 95%, 106 mmol) was suspended in 180 mL Et_2O and cooled to 0 °C. The crude product was dissolved in 24 mL Et_2O and added to this suspension slowly via cannula. Upon completion of the addition, the mixture was warmed to rt and stirred for 4 h at which time TLC analysis showed consumption of the starting material. The mixture was cooled to 0 °C and quenched slowly with sat'd aq Rochelle's Salt solution. The precipitate was filtered off and the resulting solution was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude

product was passed through a silica gel plug, eluting with 30% EtOAc / hexanes, and concentrated in vacuo to give 3-methylpenta-3,4-dien-1-ol **(64)** (5.96 g, 85%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.74-4.69 (m, 2H), 3.80-3.74 (m, 2H), 2.28-2.20 (m, 2H), 1.76 (t, *J*= 3 Hz, 3H).

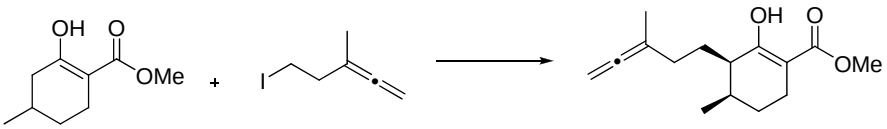


5-Iodo-3-methylpenta-1,2-diene (58)

To a solution of alcohol **64** (2.00 g, 20.4 mmol) in 68 mL CH_2Cl_2 at -78 °C was added triethylamine (3.97 mL, 28.5 mmol) and methanesulfonyl chloride (1.89 mL, 24.5 mmol). The mixture was stirred for 1 h before warming to 0 °C whereupon it was stirred for 3 h at which time the reaction was complete as shown by TLC analysis. The reaction mixture was diluted with CH_2Cl_2, and washed with 1M aq HCl, sat'd aq $NaHCO_3$, and brine. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and dissolved in 102 mL dry acetone. Sodium iodide (4.58 g, 30.6 mmol) was added and the reaction was heated to reflux overnight (16 h). The reaction was then cooled to rt, diluted with Et_2O and H_2O. The layers were separated, and the aqueous was extracted with Et_2O (2X). The combined organic layers were washed with sat'd aq sodium thiosulfate (2X), brine, dried over $MgSO_4$, and concentrated carefully in vacuo (keeping rotovap water bath below 10 °C). The crude product was purified on a silica gel column, eluted with pentane to give iodide **58** (1.63 g, 38% over 2 steps) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.72-4.66 (m, 2H), 3.19 (t, *J*= 7.5 Hz, 2H), 2.51-2.46 (m, 2H), 1.70-1.66 (m, 3H).

Methyl 2-hydroxy-4-methyl-3-(3-methylpenta-3,4-dienyl)cyclohex-1-enecarboxylate (56)



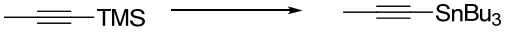
To a solution of diisopropylamine (0.37 mL, 2.64 mmol) in 6.5 mL THF at -78 °C was added 1.54 mL n-BuLi (1.6 M in hexanes, 2.46 mmol) slowly. The solution was allowed to warm to -20 °C and β-Ketoester **57**[53] (200 mg, 1.17 mmol) was added as a solution in 1.2 mL THF. The mixture was stirred for 30 min while warming to 0 °C. Allenyl iodide **58** (256 mg, 1.23 mmol) was added as a solution in 1.2 mL THF. The reaction mixture was allowed to stir for 4 h while warming to room temperature. When the starting material was consumed as shown by TLC analysis, the reaction was quenched by the addition of sat'd aq NH_4Cl, and further diluted with Et_2O and H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo giving crude **56** (261 mg). The crude product was purified on a silica gel column eluted with 10% EtOAc / hexanes to give **56** (186 mg, 64%) as a mixture of keto/enol tautomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 12.27 (br s, 0.5 H), 4.60 – 4.52 (m, 2H), 3.71 (s, 3H), 3.70 (s, 0.4 H), 2.50 – 1.70 (m, 8H), 1.70 – 1.63 (m, 3H), 1.35 – 1.15 (m, 2H), 1.05 (d, *J*= 6.3 Hz, 0.71H), 1.00 (d, *J*= 6.3 Hz, 0.46H), 0.94 (d, *J*= 6.6 Hz, 1.8H)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 207.0, 206.1, 174.1, 173.1, 170.5, 98.3, 97.2, 74.6, 74.4, 74.2, 57.5, 56.8, 55.7, 55.3, 52.2, 52.0, 51.4, 45.1, 39.5, 38.1, 33.2, 30.7, 30.6, 30.5, 29.1, 28.7, 27.1, 25.2, 23.6, 20.6, 20.2, 19.6, 18.8

FT-IR (NaCl, thin film) ν= 2952, 2930, 2857, 1960, 1748, 1713, 1655, 1614, 1441 cm^{-1}

R_f (10% EtOAc / hexanes) : 0.65



General Procedure for the Preperation of Tributyl(prop-1-ynyl)stannane (69)

To a solution of 1-trimethylsilyl propyne (0.66 mL, 96%, 4.5 mmol) in 11.1 mL THF was added bis(tributyltin) oxide (1.13 mL, 2.13 mmol) and TBAF (1M in THF, 0.089 mL, 0.089 mmol). The reaction was heated in a 60 °C oil-bath for 2.5 h, cooled to rt, concentrated in vacuo and and used without further purification.

Methyl 4-methyl-2-(prop-1-ynyl)cyclohex-1-enecarboxylate (71)

Sodium hydride (60% in mineral oil, 223 mg, 5.57 mmol) was washed with hexanes, suspended in 11 mL CH_2Cl_2 and cooled in an ice-water bath. Enol **57** (631 mg, 3.71 mmol) was added as a solution in 5 mL CH_2Cl_2. The reaction was stirred for 10 min, trifluoromethanesulfonic anhydride (1.25 ml, 7.42 mmol) was added and the reaction was stirred for a further 10 min when the starting material was consumed via TLC analysis. The reaction was quenched through the addition of sat'd aq NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was added to a solution of tributyl(prop-1-ynyl)stannane (4.5 mmol) in 5 mL THF. Palladium tetrakis-triphenylphosphine (427 mg, 0.37 mmol) was added to the reaction mixture and it was heated in a 60 °C oil-bath for 1.5 h at which time TLC analysis showed consumption of starting material. The reaction was cooled to rt,

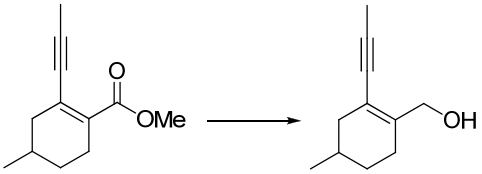
concentrated in vacuo, and purified on a silica gel column which was eluted with 7.5% EtOAc / hexanes to provide ene-yne **71** (527 mg, 74%)[2].

^{1}H NMR (300 MHz, $CDCl_3$) δ= 3.73 (s, 3H), 2.58-2.10 (m, 4H), 2.05 (s, 3H), 1.80-1.50 (m, 3H), 0.95 (d, *J*= 6.6 Hz, 3H)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 167.8, 132.2, 129.5, 93.7, 79.9, 51.5, 50.0, 30.0, 27.8, 26.1, 20.0, 4.8

FT-IR (NaCl, thin film) ν= 2950, 2221, 1723, 1613, 1434 cm^{-1}

HRMS (EI+) Calc ($C_{12}H_{16}O_2$): 192.1150, Found: 192.1144



(4-Methyl-2-(prop-1-ynyl)cyclohex-1-enyl)methanol (72)

To a solution of ester **71** (200 mg, 1.04 mmol) in 2.1 mL CH_2Cl_2 at - 78 °C was added DIBAL-H (1 M in hexanes, 2.3 mL, 2.3 mmol) slowly. The reaction was stirred for 15 min at which time TLC analysis showed consumption of the starting material. The reaction was warmed to 0 °C and quenched through the addition of sat'd aq Rochelle's salt and a few drops of 10% aq HCl. The mixture was stirred for 30 min, filtered through celite, and diluted with H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5X). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to provide crude alcohol **72** (165 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.21 (1/2 AB q, *J*= 5.7 Hz, 1H), 4.19 (1/2 AB q, *J*= 5.7 Hz, 1H), 2.45-2.00 (m, 4H), 1.91 (s, 3H), 1.80-1.40 (m, 3H), 0.89 (d, *J*= 6.3 Hz, 3H)

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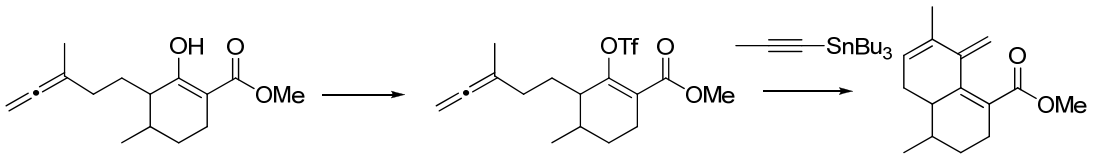
[2] Contaminated with Silicon or Tin based impurities

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 142.0, 117.0, 88.4, 78.9, 64.7, 38.7, 30.4, 28.3, 26.8, 21.3, 4.2

FT-IR (NaCl, thin film) ν= 3342, 2949, 2917, 2870, 1454 cm^{-1}

HRMS (EI+) Calc ($C_{11}H_{16}O$): 164.1201, Found: 164.1198



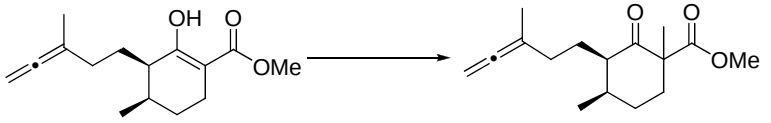
Methyl 4,7-dimethyl-8-methylene-2,3,4,4a,5,8-hexahydronaphthalene-1-carboxylate (75)

To a solution of enol **56** (50 mg, 0.20 mmol) in 2 mL THF at 0 °C was added NaH (60% in mineral oil, 12 mg, 0.30 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (79 mg, 0.22 mmol). The reaction was stirred for 3.5 h at which time TLC analysis showed consumption of starting material. The reaction was cooled to 0 °C, quenched with H_2O and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the intermediate vinyl triflate **67** (76 mg, 99%).

Separately, to a solution of 1-trimethylsilyl propyne (0.16 mL, 0.11 mmol) 0.3 mL THF was added bis(tributyltin) oxide (0.28 mL, 0.055 mmol) and TBAF (1M in THF, 0.002 mL, 0.002 mmol). The reaction was heated in a 60 °C oil-bath for 2.5 h, at which time it was cooled to 50 °C. Vinyl triflate **67** was added as a solution in 0.2 mL THF. Palladium tetrakis(triphenylphosphine) (10.4 mg, 0.009 mmol) was added and the reaction was stirred for 1.5 h and concentrated in vacuo. The mixture was applied to a silica gel column which was eluted with 10% EtOAc / hexanes to provide **75** (22 mg, 47%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.65 (d, *J*= 4.5 Hz, 1H), 4.96 (s, 1H), 4.91 (s, 1H), 3.63 (s, 3H), 2.64-2.50 (m, 2H), 2.20-1.90 (m, 4H), 1.84-1.80 (m, 3H), 1.78-1.62 (m, 2H), 1.01 (d, *J*= 6.3 Hz, 3H)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 173.0, 145.5, 143.6, 133.0, 127.1, 126.8, 110.7, 52.3, 43.9, 35.9, 34.3, 29.8, 27.8, 20.5, 19.8,



Methyl 1,4-dimethyl-3-(3-methylpenta-3,4-dienyl)-2-oxocyclohexanecarboxylate (76)

To a solution of enol **56** (787 mg, 3.15 mmol) in 31.5 mL MeCN was added cesium carbonate (5.13 g, 15.7 mmol) and methyl iodide (0.98 mL, 15.7 mmol). The resulting suspension was stirred for 6 h, quenched through the addition of H_2O and stirred until the precipitate was dissolved. The reaction mixture was diluted with Et_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to provide **76** (707 mg, 85%) as a complex mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.54-4.48 (m, 2H), 3.70-3.60 (m, 3H), 2.52-1.61 (m, 8H), 1.59 (t, *J*= 3 Hz, 3H), 1.58-1.48 (m, 2H), 1.37* (s, 2.2H), 1.20** (s, 0.8 H), 1.07* (d, *J*= 6.6 Hz, 0.3H), 0.99** (d, *J*= 6.3 Hz, 2H), 0.93*** (d, *J*= 6.3 Hz, 1.2H), 0.80**** (d, *J*= 6.9 Hz, 0.35H)

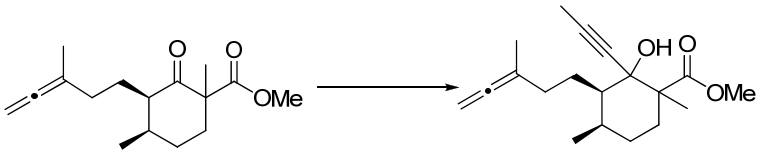
^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 210.5, 206.1, 173.5, 98.2, 74.3, 57.2, 53.0, 52.1, 49.0, 38.1, 37.2, 25.2, 33.9, 21.4, 30.8, 28.9, 24.7, 22.2, 21.1, 20.6, 18.7

FT-IR (NaCl, thin film) ν= 2951, 2870, 1959, 1741, 1710, 1455 cm^{-1}

HRMS (EI+) Calc: 264.1727, Found: 264.1729

* Diastereomer 1 ** Diastereomer 2 *** Diastereomer 3 **** Diastereomer 4

Methyl 2-hydroxy-1,4-dimethyl-3-(3-methylpenta-3,4-dienyl)-2-(prop-1-ynyl)cyclohexanecarboxylate (77)



To a solution of (E/Z)-1-bromo-1-propene (83 μL, 0.97 mmol) in 0.65 mL THF at -78 °C was added n-BuLi (1.6 M in hexanes, 0.89 mL, 1.4 mmol).[46] The mixture was stirred for 2 h at -78 °C at which time ketone **76** (145 mg, 0.55 mmol) was added in 0.55 mL THF. The mixture was allowed to warm to room temperature overnight at which time the no starting material was observed via TLC. The reaction was quenched through the addition of sat'd aq NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo giving crude **77** (131 mg). The crude product was purified in a silica gel column that was eluted with 10% EtOAc / hexanes to provide alcohol **77** (77 mg, 46%) as a mixture of diastereomers. No attempt was made to separate the diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.60-4.50 (m, 2H), 3.74* (s, 0.18H), 3.73** (s, 0.15H), 3.71*** (s, 1.17H), 3.71**** (s, 1.48H), 2.15-1.85 (m, 5H), 1.84* (s, 0.7H), 1.79-1.78**/*** (2 x s, 2.3H), 1.77-1.70 (m, 1H), 1.69-1.65 (m, 3H), 1.64-1.40 (m, 4H), 1.40* (s, 1.2H), 1.36** (s, .75H), 1.23*** (s, 1.1H), 0.95-0.88 (m, 3H)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 206.6, 206.3, 179.1, 178.7, 99.0*, 98.8**, 98.7***, 82.5, 81.7, 81.6, 80.5, 80.2, 78.6, 78.0, 75.3, 74.5, 73.7, 73.5, 52.2, 52.0, 51.5, 51.4, 47.5, 47.2, 36.4, 35.3,

34.8, 34.7, 34.3, 33.7, 32.8, 31.7, 31.6, 30.8, 30.3, 29.8, 29.4, 28.5, 27.7, 27.6, 22.7, 22.6, 20.2, 20.0, 18.7, 18.6, 16.8, 14.1, 3.6*, 3.5**/***

* Diastereomer 1 ** Diastereomer 2 *** Diastereomer 3 **** Diastereomer 4

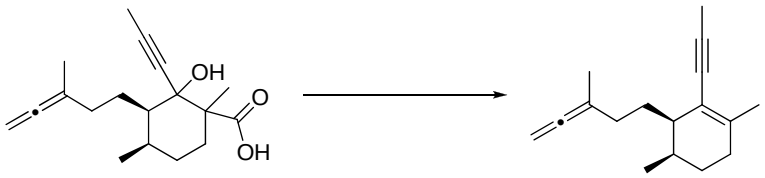
2-Hydroxy-1,4-dimethyl-3-(3-methylpenta-3,4-dienyl)-2-(prop-1-ynyl)cyclohexanecarboxylic acid (79)

To a solution of ester **77** (200 mg, 0.66 mmol) in 6.6 mL MeCN was added potassium trimethylsilanolate (281 mg, 90% purity, 2.0 mmol). The mixture was stirred for 2 d at which time TLC analysis showed consumption of the starting ester. The reaction was diluted with Et_2O and quenched by adding 10% aq HCl. The layers were separated and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give crude acid **79** (181 mg). The crude product was purified on a silica gel column that was eluted with EtOAc : hexanes : AcOH (70:30:1) to provide carboxylic acid **79** (128 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.60-4.50 (m, 2H), 2.07-2.00 (m, 2H), 2.00-1.85 (m, 1H), 1.84 (s, 0.6H), 1.79 (2 x s, 2.4H), 1.69-1.64 (m, 3H), 1.61-1.44 (m, 3H), 1.44 (s, 0.6H), 1.39 (s, 1.1 H), 1.29 (s, 1.3H), 1.27-1.13 (m, 2H), 0.95-0.85 (m, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ= 206.3, 183.8, 99.0, 98.7, 83.5, 82.5, 81.0, 80.9, 79.9, 75.3, 74.5, 73.8, 73.6, 36.3, 35.4, 34.7, 34.6, 34.2, 31.8, 30.6, 30.2, 29.7, 29.3, 28.5, 27.6, 20.2, 20.1, 20.0, 18.7, 18.6, 16.8, 4.6

HRMS: Pending



1,4-Dimethyl-3-(3-methylpenta-3,4-dienyl)-2-(prop-1-ynyl)cyclohex-1-ene (55)

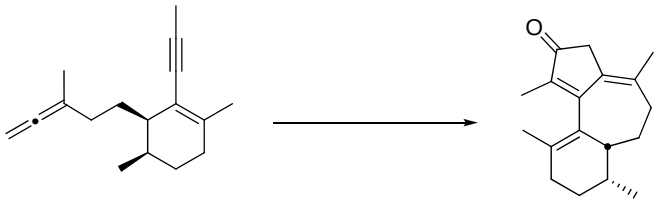
To a solution of β-hydroxy acid **79** (250 mg, 0.86 mmol) in 17 mL of freshly distilled $CHCl_3$ was added *N,N*-dimethyl formamide dineopentyl acetal (0.72 mL, 99%, 2.6 mmol). The reaction was stirred for 1 h at rt and then refluxed for 2 h, at which time TLC analysis of the reaction mixture indicated consumption of starting material. The reaction was cooled to rt, diluted with H_2O and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product (318 mg). Purification of the crude product on a silica gel column, eluted with 1% Et_2O / pentanes provided **55** (153 mg, 78%) as a pale oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.60-4.55 (m, 2H), 1.98 (s, 3H), 1.97-1.88 (m, 2H), 1.85 (s, 3H), 1.84-1.72 (m, 3H), 1.70 (t, *J*= 3.3 Hz, 3H), 1.68-1.58 (m, 3H), 1.35-1.22 (m, 2H), 0.92 (d, *J*= 6.6 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ= 206.4, 139.9, 118.0, 98.9, 87.4, 80.2, 73.8, 45.1, 30.7, 30.6, 29.6, 29.0, 26.7, 22.3, 19.7, 18.8, 4.5

HRMS (EI+): Calc ($C_{17}H_{24}$): 228.1878; Found: 228.1884

R_f: (10% Et_2O / pentanes) 0.6



1,4,7,10-Tetramethyl-5,6,6a,7,8,9-hexahydrobenzo[e]azulen-2(3H)-one (54)

To a 25mL round-bottom flask was added $[Rh(CO)_2Cl]_2$ (52 mg, 0.13 mmol). The flask was placed under vacuum and then filled with CO gas (1 ATM). The flask was then evacuated and refilled with CO gas twice more. A solution of allene-yne **55** (304 mg, 1.33 mmol) in 13.3 mL toluene was added to the flask which was then placed in an oil-bath pre-heated to 90 °C and the reaction mixture was allowed to stir for 11.5 h, at which time TLC analysis showed no detectable starting material. The reaction was cooled to room temperature, passed through a silica gel plug, eluting with 10% EtOAc / hexanes, and concentrated in vacuo to provide crude **54** (250 mg). The crude product was purified on a silica gel column, eluting with 10% EtOAc / hexanes to provide cyclopentenone **54** (114 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ= 2.90 (½ AB q, *J*= 20.5 Hz), 2.82 (½ AB q, *J*= 21 Hz), 2.50-2.40 (m, 1H), 2.15-1.80 (m, 5H), 1.80 (s, 3H), 1.79-1.74 (m, 1H), 1.67-1.60 (m, 1H), 1.59 (s, 3H), 1.57-1.48 (m, 1H), 1.47 (s, 3H), 1.40-1.32 (m, 1H), 0.90 (d, *J*= 6.5 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ= 205.6, 169.0, 137.6, 136.4, 132.0, 130.9, 128.2, 42.3, 39.0, 33.7, 32.2, 31.2, 28.4, 25.7, 23.4, 21.0, 19.3, 9.3

FT-IR (NaCl, thin film) ν= 2924, 1690, 1577, 1439 cm^{-1}

HRMS (TOF MS ES+): Calc ($C_{18}H_{24}ONa^+$): 279.1725; Found: 279.1702

R_f: (10% EtOAc / hexanes) 0.4

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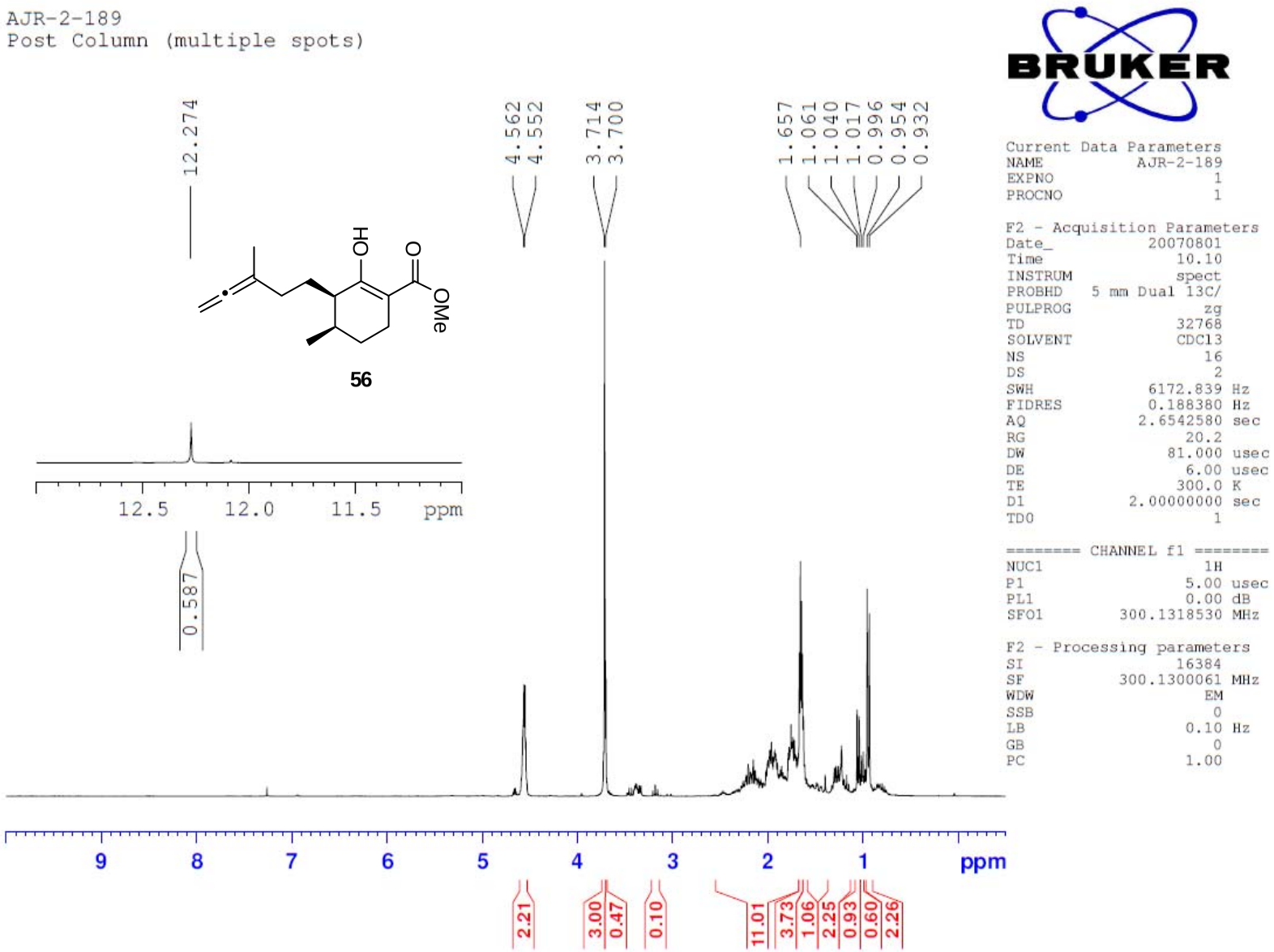
6.0 SPECTRA



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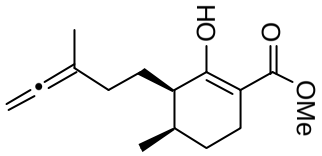

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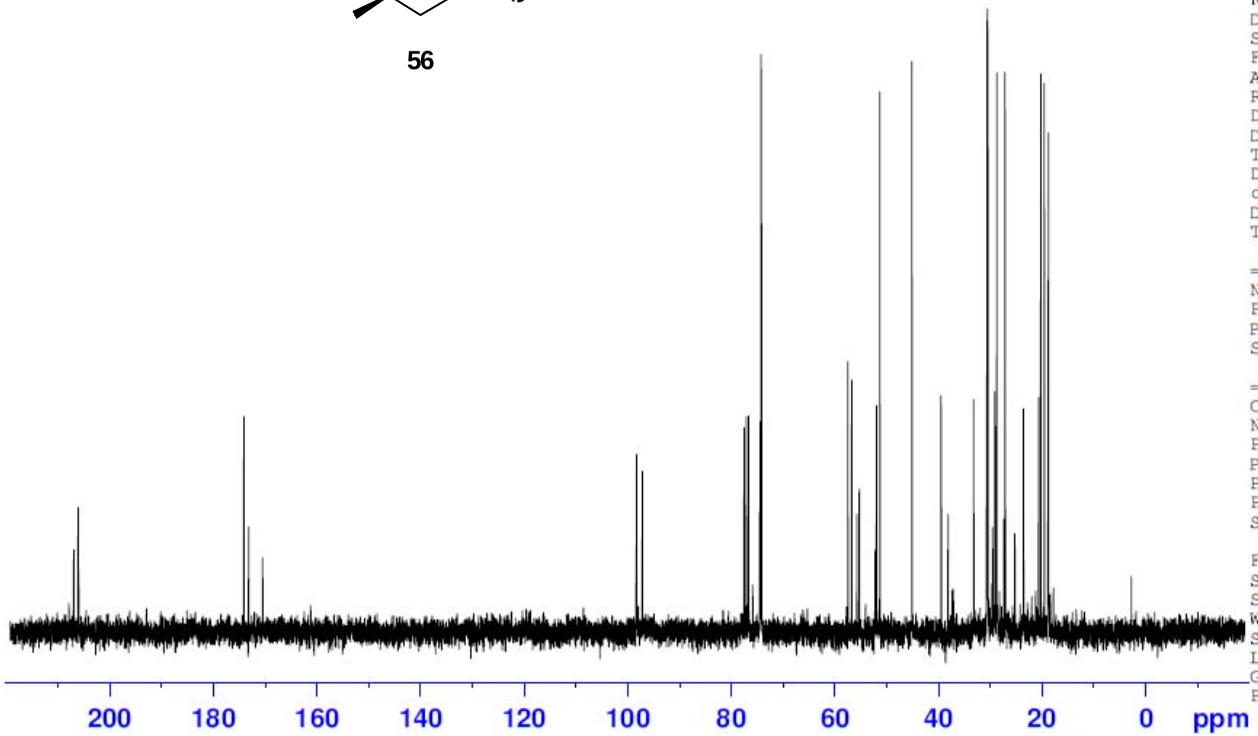

BRUKER

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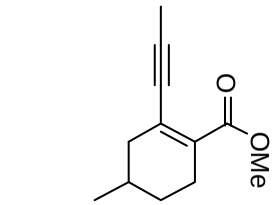
AJR-2-105



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BRUKER

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PL1                       1.00 dB
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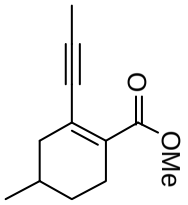

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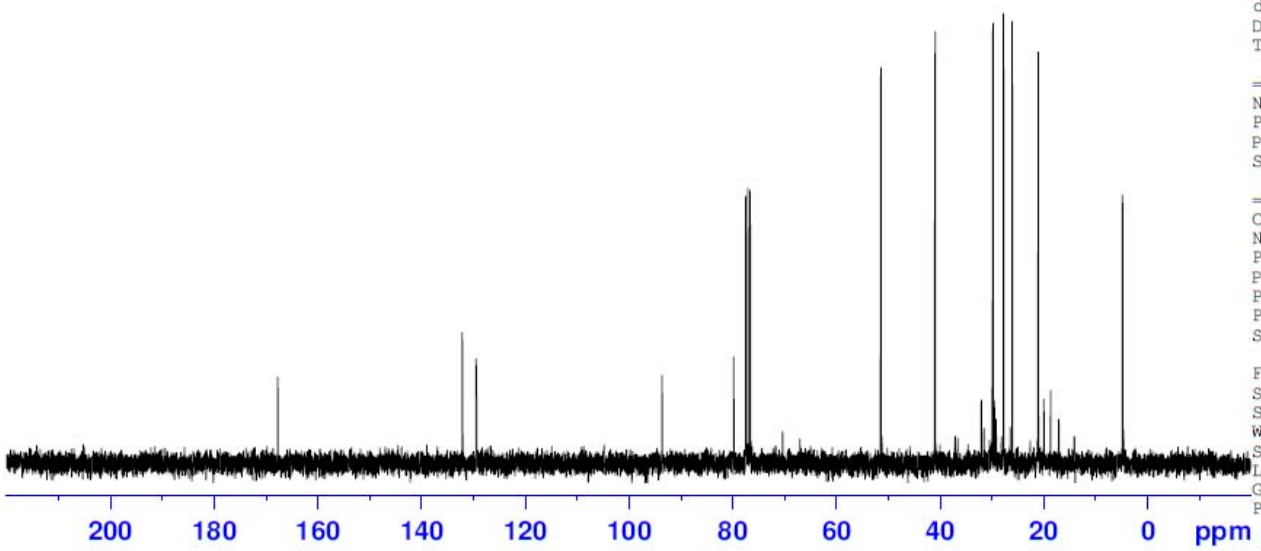


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PL1                        1.80 dB
SFO1                 75.5381641 MHz

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PCPD2                     92.00 usec
PL2                        0.00 dB
PL12                      20.00 dB
PL13                      20.00 dB
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F2 - Processing parameters
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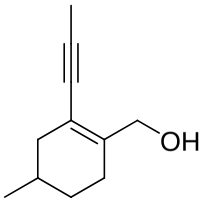
AJR-2-106



72

BRUKER

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TE 300.0 K
D1 2.00000000 sec
TD0 1

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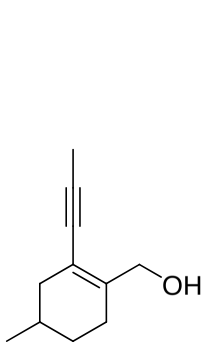
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72

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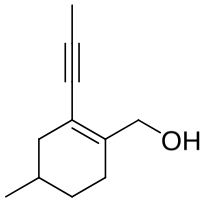

72

BRUKER

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d11                 0.03000000 sec
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======== CHANNEL f1 ========
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SFO1                75.5381641 MHz

======== CHANNEL f2 ========
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PCPD2                    92.00 usec
PL2                       0.00 dB
PL12                     20.00 dB
PL13                     20.00 dB
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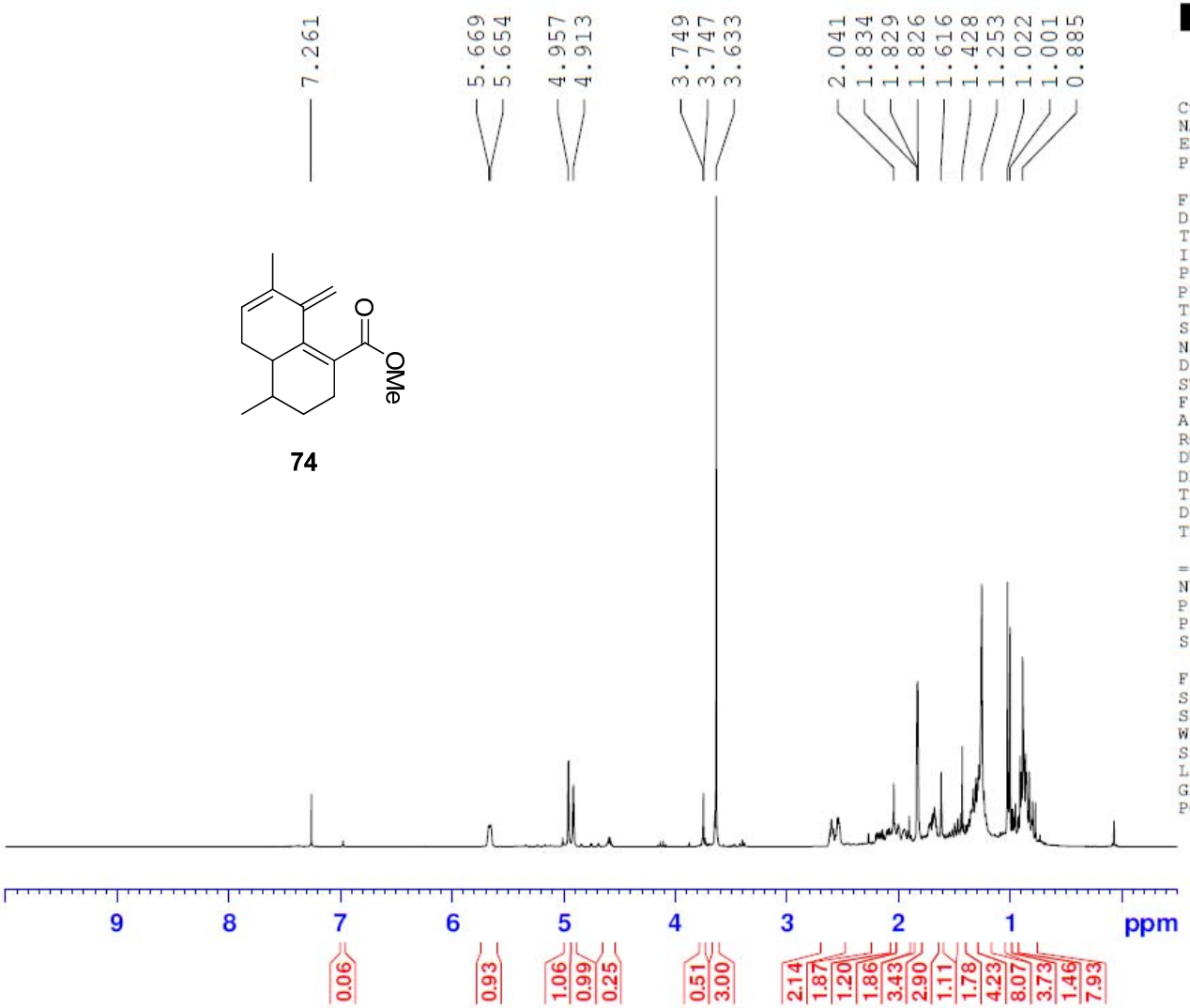

74

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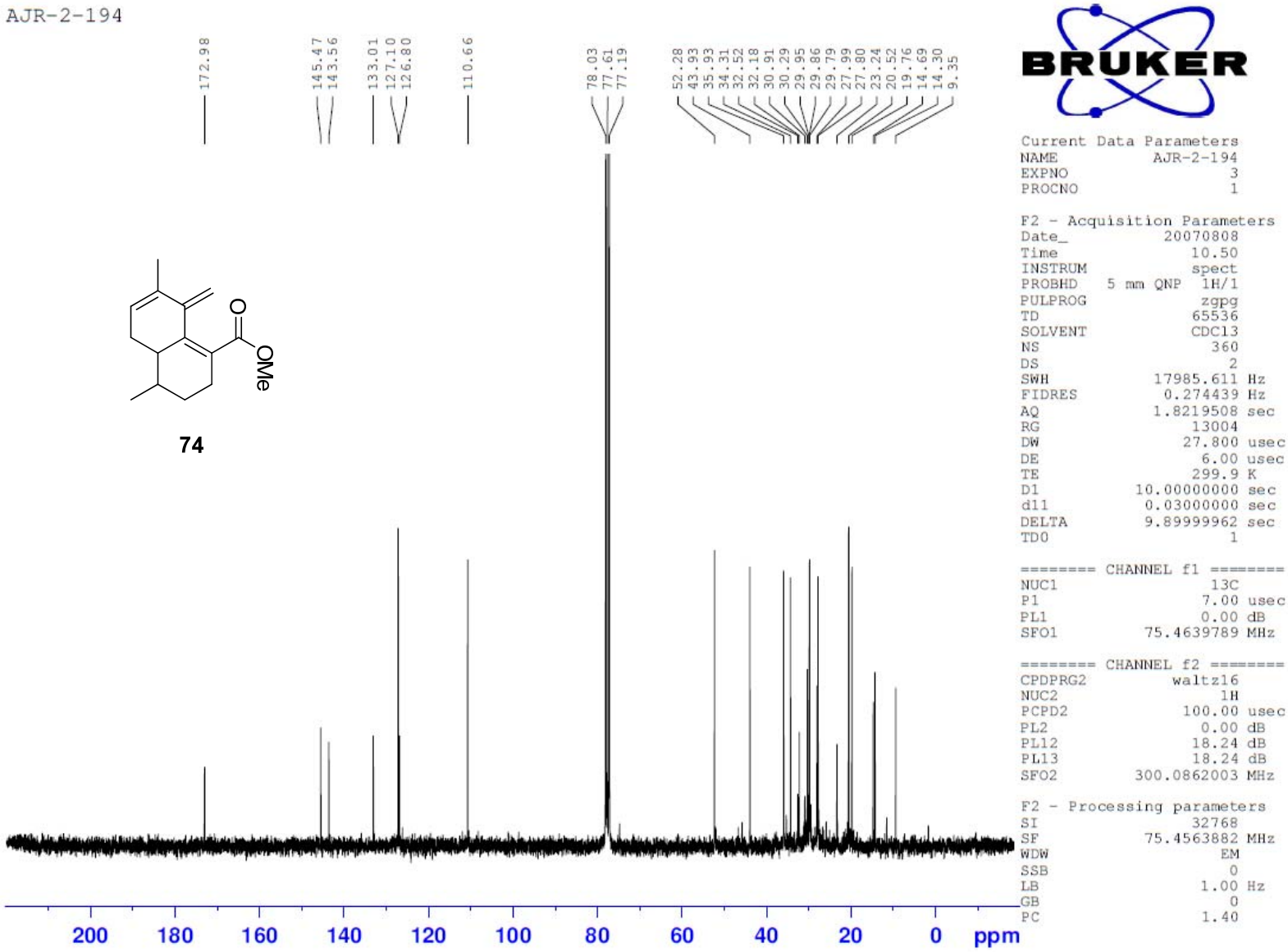
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DE 6.00 usec
TE 299.9 K
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d11 0.03000000 sec
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SFO1 75.4639789 MHz
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PCPD2 100.00 usec
PL2 0.00 dB
PL12 18.24 dB
PL13 18.24 dB
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F2 - Processing parameters
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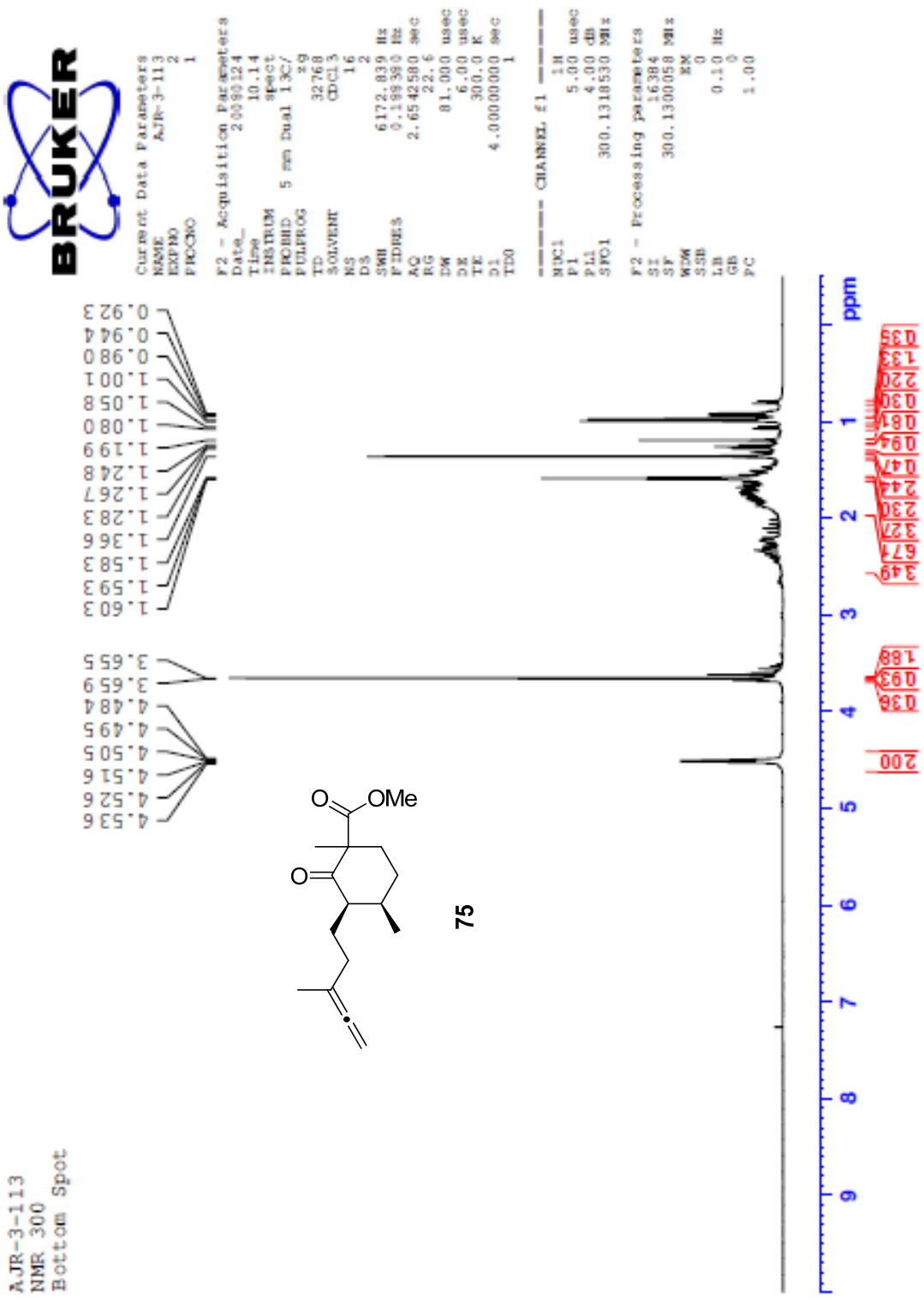
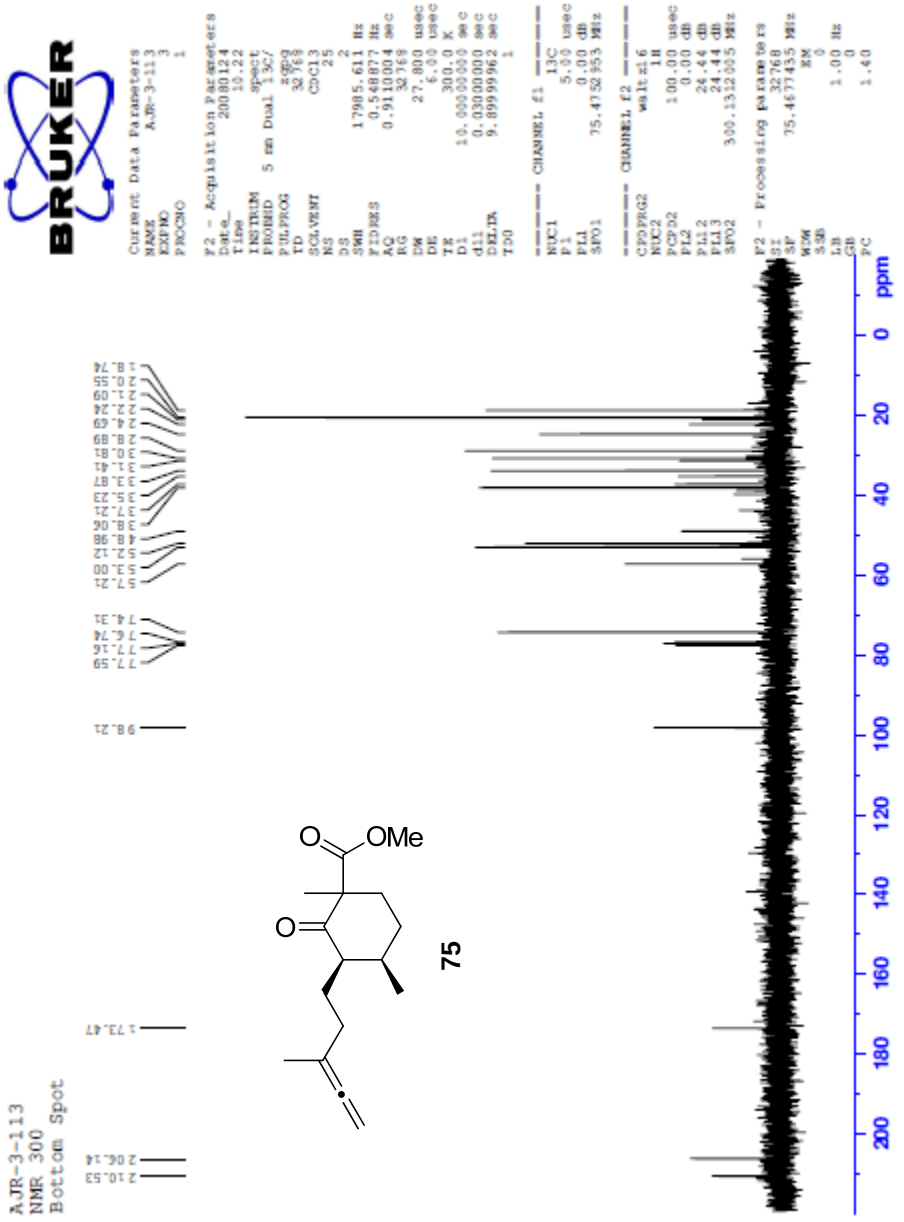
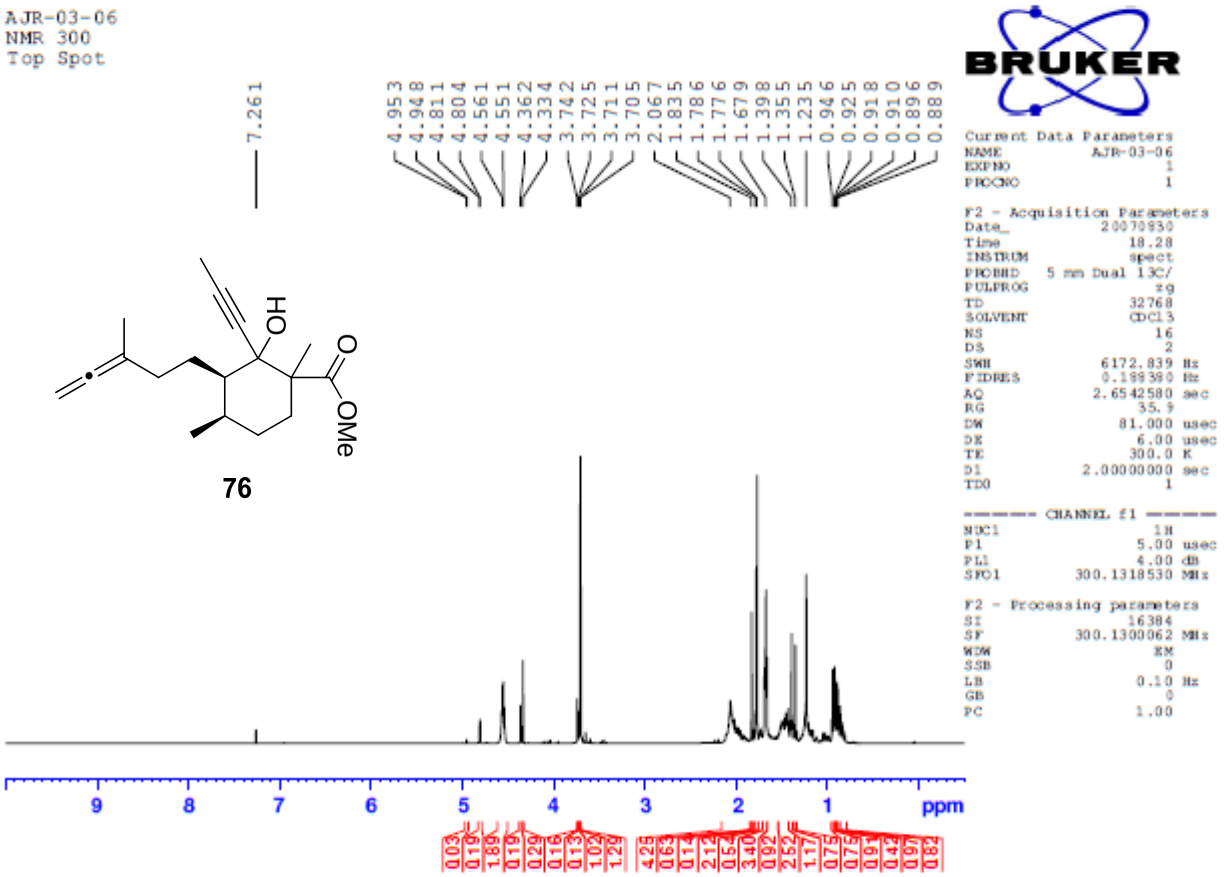
LB 1.00 Hz
GB 0
PC 1.40

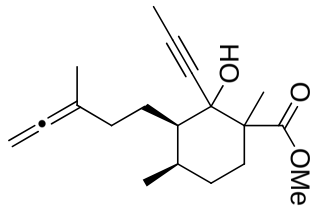

AJR-3-113
NMR 300
Bottom Spot
Current Data Parameters
NAME AJR-3-113
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090324
Time 10.14
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 22.6
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 4.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz
F2 - Processing parameters
SI 16384
SF 300.1300058 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1.603
1.593
1.583
1.566
1.283
1.267
1.248
1.199
1.080
1.058
1.001
0.980
0.944
0.923
3.659
3.655
4.536
4.526
4.516
4.505
4.495
4.484
O
OMe
O
75
ppm
1 2 3 4 5 6 7 8 9
200
036
093
188
349
671
321
230
244
047
094
081
220
130
133
039


AJR-3-113
NMR 300
Bottom Spot
Current Data Parameters
NAME AJR-3-113
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080124
Time 10.22
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 25
DS 2
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 10.00000000 sec
d11 0.03000000 sec
DELTA 9.89999962 sec
TD0 1
CHANNEL f1 13C
NUC1
P1 5.00 usec
PL1 0.00 dB
SFO1 75.4752953 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 24.44 dB
PL13 24.44 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677435 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
O
OMe
O
75
ppm


AJR-03-06
NMR 300
Top Spot
7.261
4.953
4.948
4.811
4.804
4.561
4.551
4.362
4.334
3.742
3.725
3.711
3.705
2.067
1.835
1.786
1.776
1.679
1.398
1.355
1.235
0.946
0.925
0.918
0.910
0.896
0.889
OH
O
OMe
76
9
8
7
6
5
4
3
2
1
ppm
BRUKER
Current Data Parameters
NAME AJR-03-06
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070930
Time 18.28
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 35.9
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1
====== CHANNEL f1 ======
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz
F2 - Processing parameters
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

AJR-03-06
NMR 300
Top Spot

206.56
206.30
179.12
179.08
178.68
99.04
98.78
98.67
82.47
81.66
81.56
80.51
80.16
78.60
78.00
77.48
77.05
76.63
75.25
74.45
73.68
73.51
73.45
52.17
52.04
51.49
51.44
50.80
47.45
47.23
36.37
35.26
34.82
34.65
34.32
33.67
32.79
31.74
31.58
30.76
30.33
29.81
29.36
28.53
27.69
27.63
22.65
22.56
20.24



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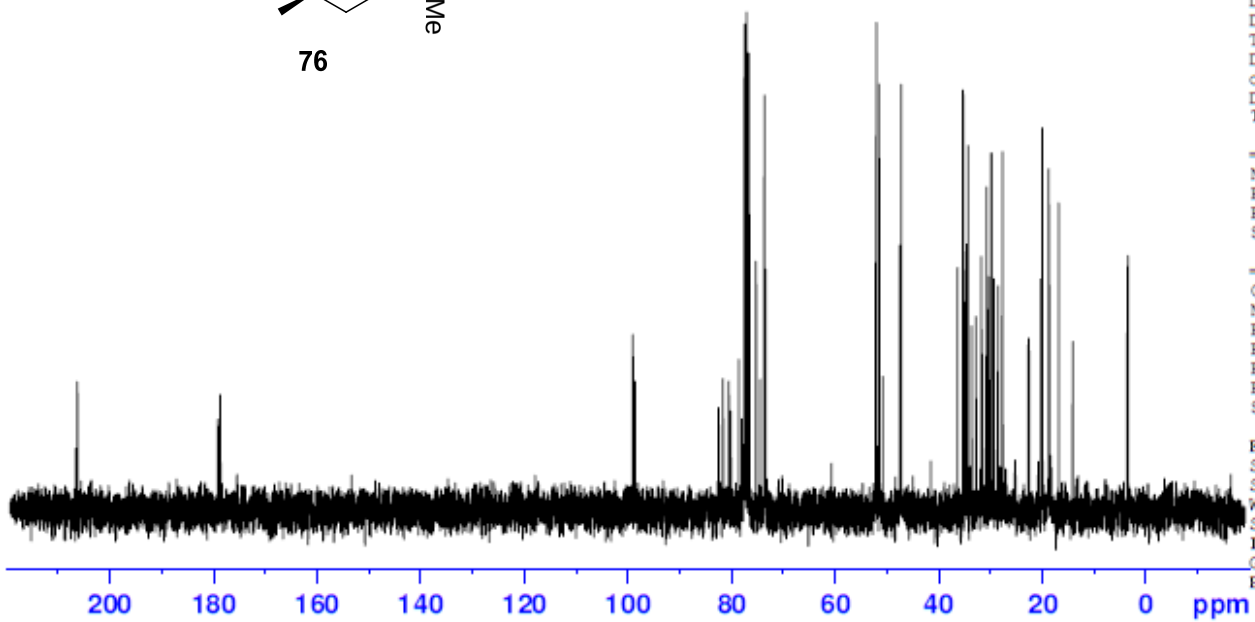
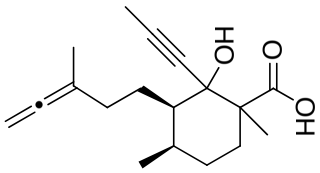


BRUKER

```
Current Data Parameters
NAME                  AJR-03-06
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20070830
Time                      18.37
INSTRUM                   spect
PROBHD    5 mm Dual 13C/
PULPROG                   zgpg
TD                       32768
SOLVENT                  CDCl3
NS                          32
DS                           2
SWH                  17985.611 Hz
FIDRES                0.548877 Hz
AQ                    0.9110004 sec
RG                         2048
DW                       27.800 usec
DE                        6.00 usec
TE                       300.0 K
D1                    8.00000000 sec
d11                   0.03000000 sec
DELTA                 7.90000010 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                        13C
P1                         5.00 usec
PL1                        0.00 dB
SFO1                 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                    100.00 usec
PL2                        0.00 dB
PL12                      24.44 dB
PL13                      24.44 dB
SFO2                300.1312005 MHz

F2 - Processing parameters
SI                         32768
SF                  75.4677480 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

AJR-3-34
NMR 300
Pure B-Hydroxyacid



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BRUKER

Current Data Parameters
NAME AJR-3-34
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20071004
Time 17.27
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 32
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1

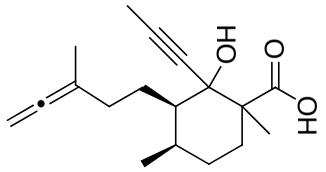
======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz

F2 - Processing parameters
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

AJR-3-34
NMR 300
Pure B-Hydroxyacid

206.27
183.84
177.85

98.97
98.68
83.52
82.46
81.01
80.90
79.92
77.49
77.07
76.65
75.25
74.46
73.82
73.60
51.38
51.27
47.52
47.31
36.31
35.38
34.68
34.57
34.22
31.80
30.59
30.25
29.68
29.28
28.50
27.63
20.84
20.21
20.06
19.98
18.74
18.59
16.81
3.50



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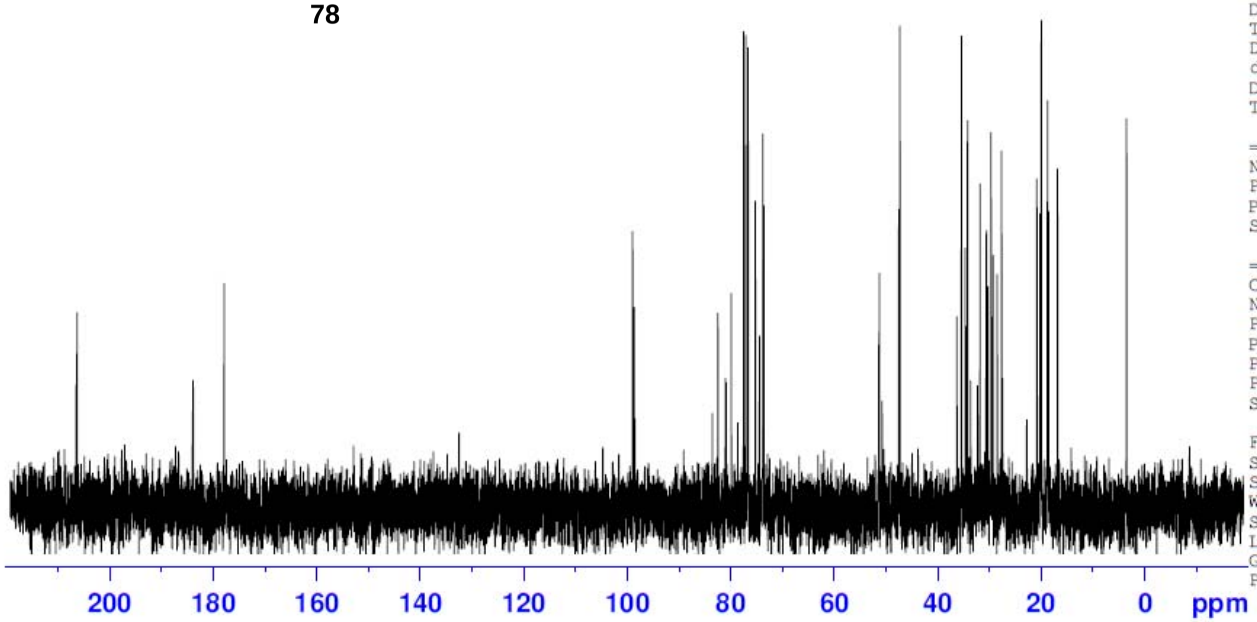


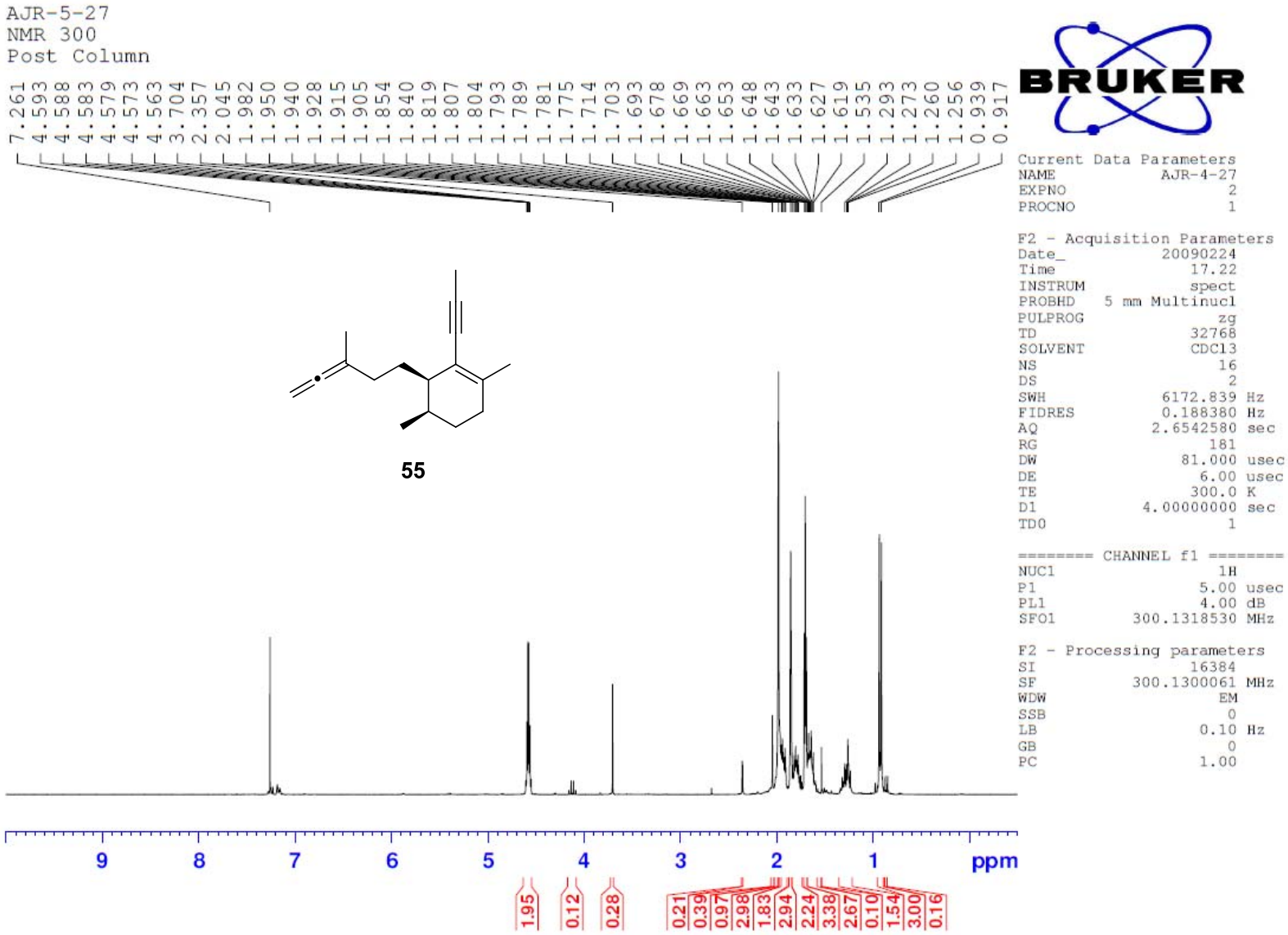

```
Current Data Parameters
NAME                 AJR-3-34
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_               20071004
Time                   17.31
INSTRUM                spect
PROBHD    5 mm Dual 13C/
PULPROG                 zgpg
TD                     32768
SOLVENT                CDC13
NS                         9
DS                         2
SWH               17985.611 Hz
FIDRES             0.548877 Hz
AQ                 0.9110004 sec
RG                    2896.3
DW                    27.800 usec
DE                     6.00 usec
TE                    300.0 K
D1                 6.00000000 sec
d11                0.03000000 sec
DELTA              5.90000010 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                      5.00 usec
PL1                     0.00 dB
SFO1              75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                     0.00 dB
PL12                   24.44 dB
PL13                   24.44 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF                75.4677480 MHz
WDW                         EM
SSB                          0
LB                      1.00 Hz
GB                           0
PC                        1.40
```



BRUKER

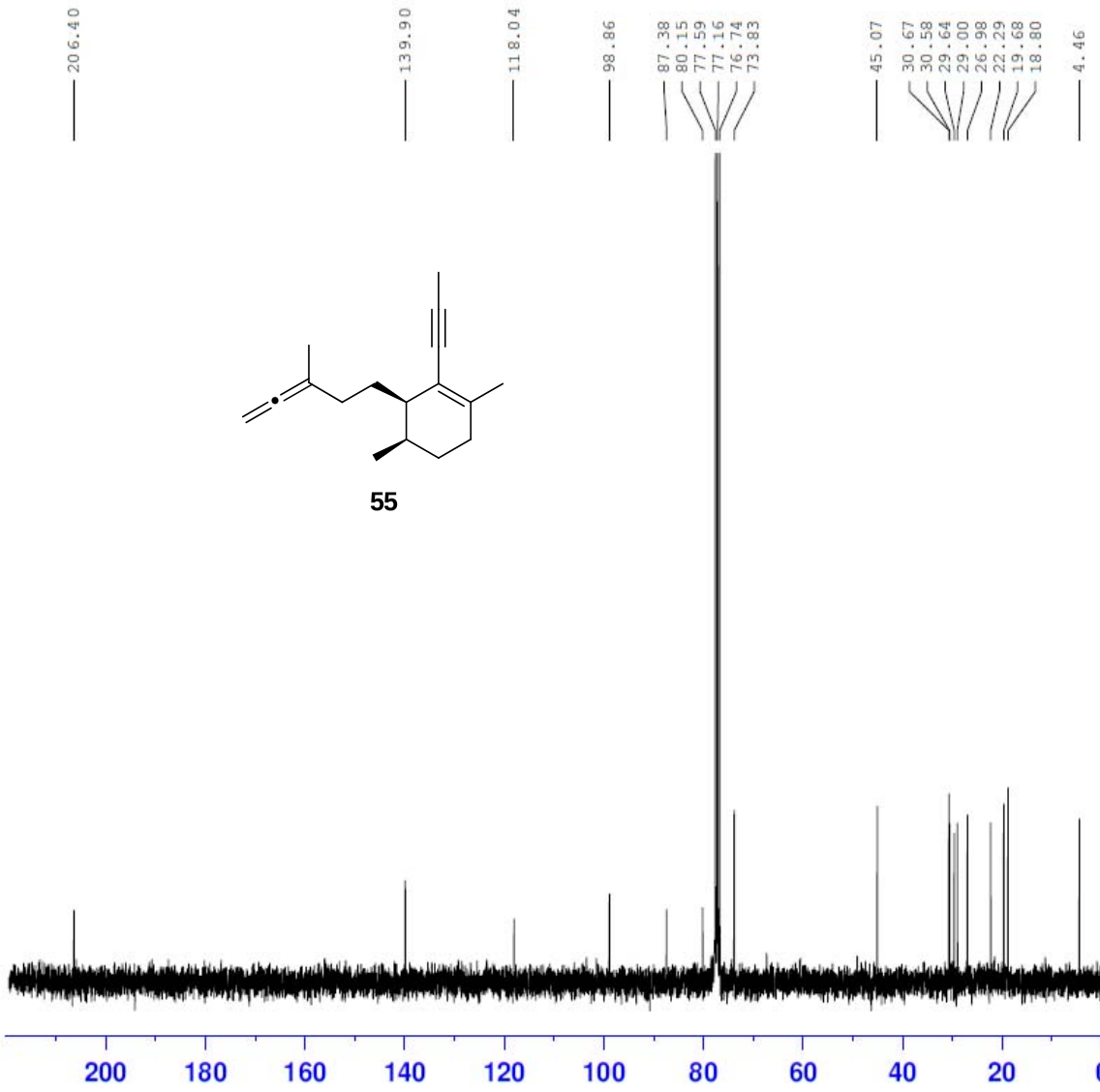
Current Data Parameters
NAME AJR-4-27
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090224
Time 17.22
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 181
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 4.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 4.00 dB
SFO1 300.1318530 MHz

F2 - Processing parameters
SI 16384
SF 300.1300061 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

AJR-5-27
NMR 300
Post Column



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Current Data Parameters

NAME	AJR-5-27
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20090224
Time	18.09
INSTRUM	spect
PROBHD	5 mm Multinucl
PULPROG	zgpg
TD	32768
SOLVENT	CDCl3
NS	224
DS	2
SWH	17985.611 Hz
FIDRES	0.548877 Hz
AQ	0.9110004 sec
RG	32768
DW	27.800 usec
DE	6.00 usec
TE	300.0 K
D1	10.00000000 sec
d11	0.03000000 sec
DELTA	9.89999962 sec
TD0	1

======== CHANNEL f1 ========

NUC1	13C
P1	5.00 usec
PL1	0.00 dB
SFO1	75.4752953 MHz

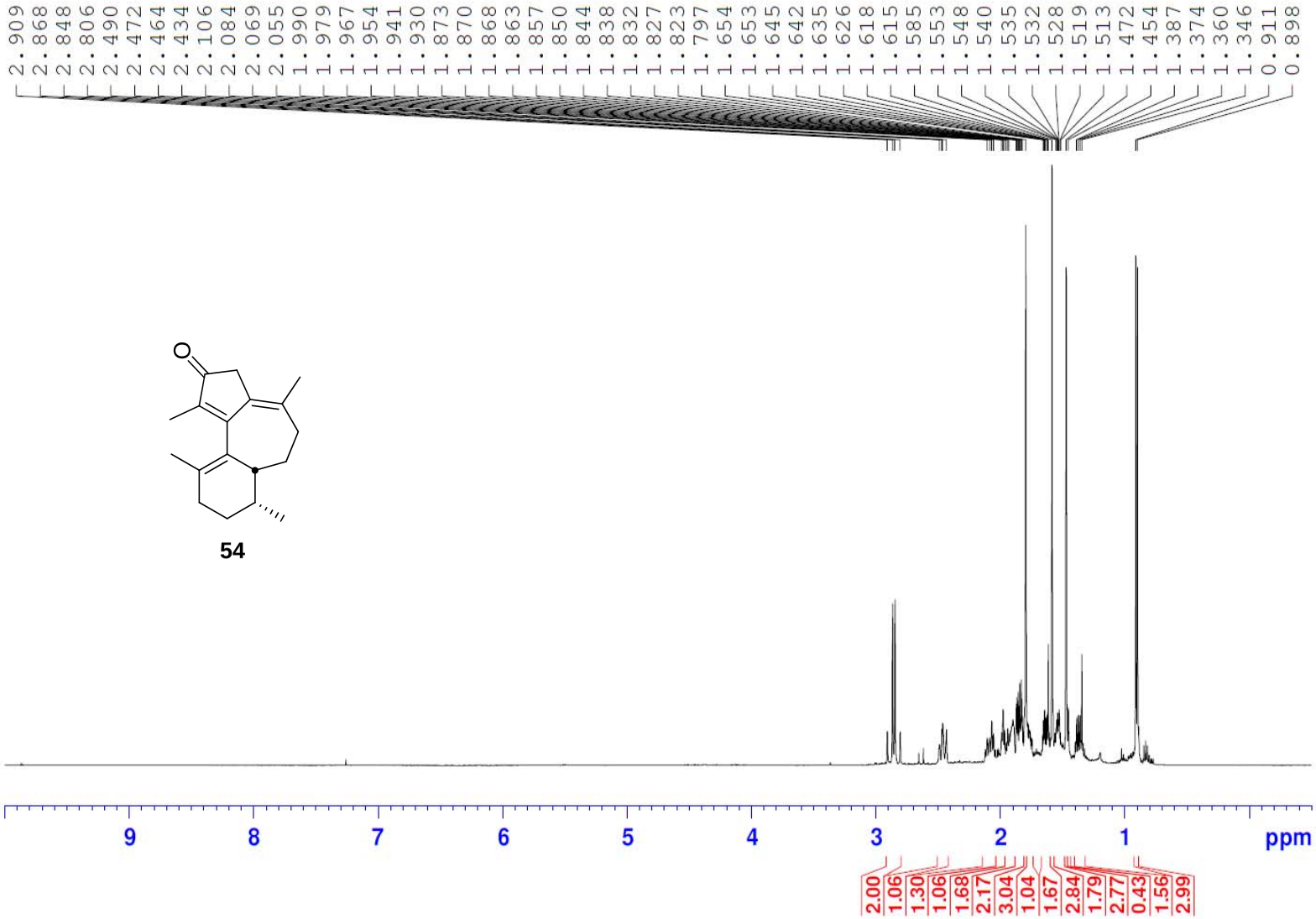
======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	60.00 usec
PL2	4.00 dB
PL12	22.98 dB
PL13	120.00 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677370 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

AJR-3-75
NMR 500
Post Column



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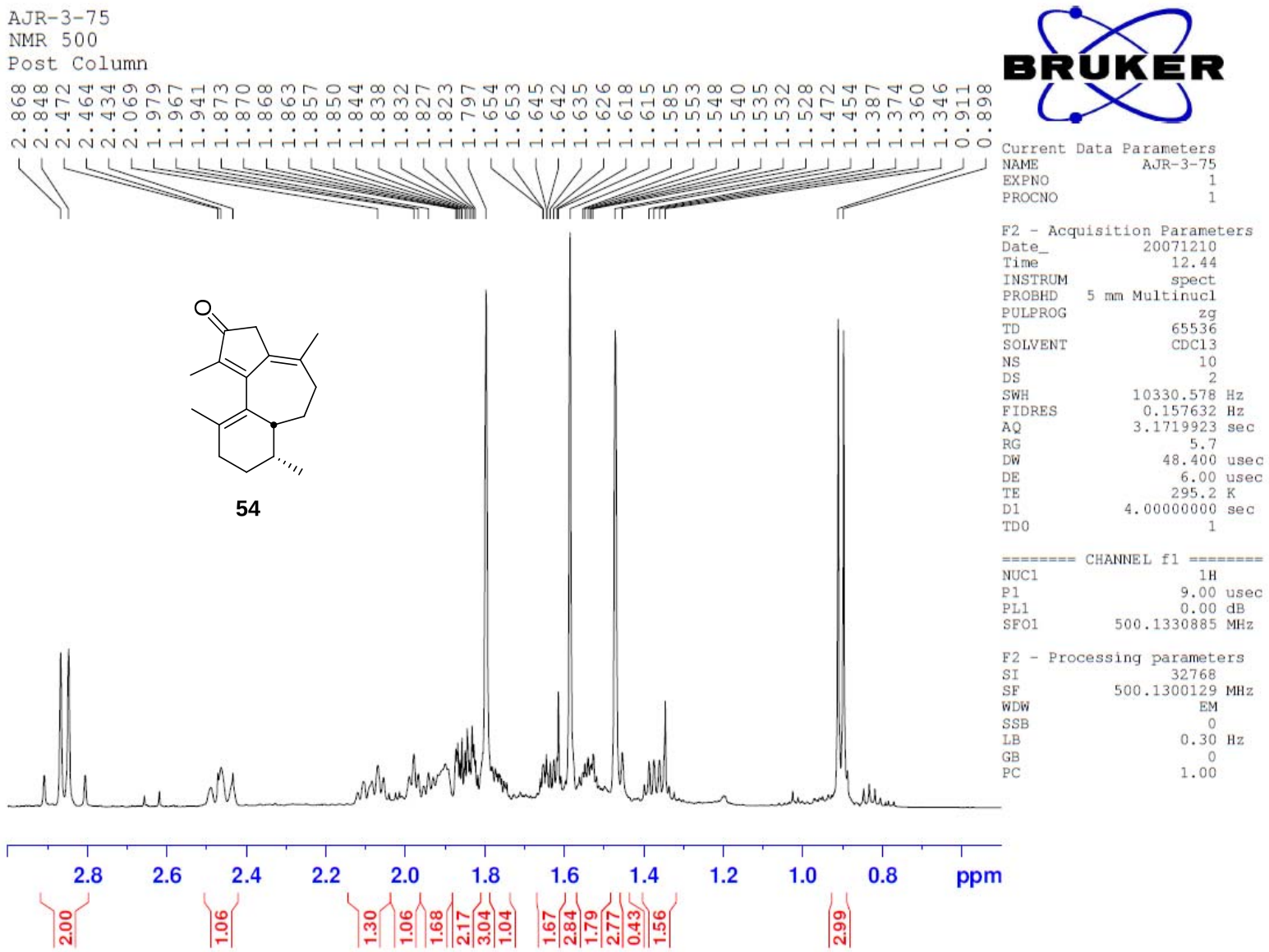
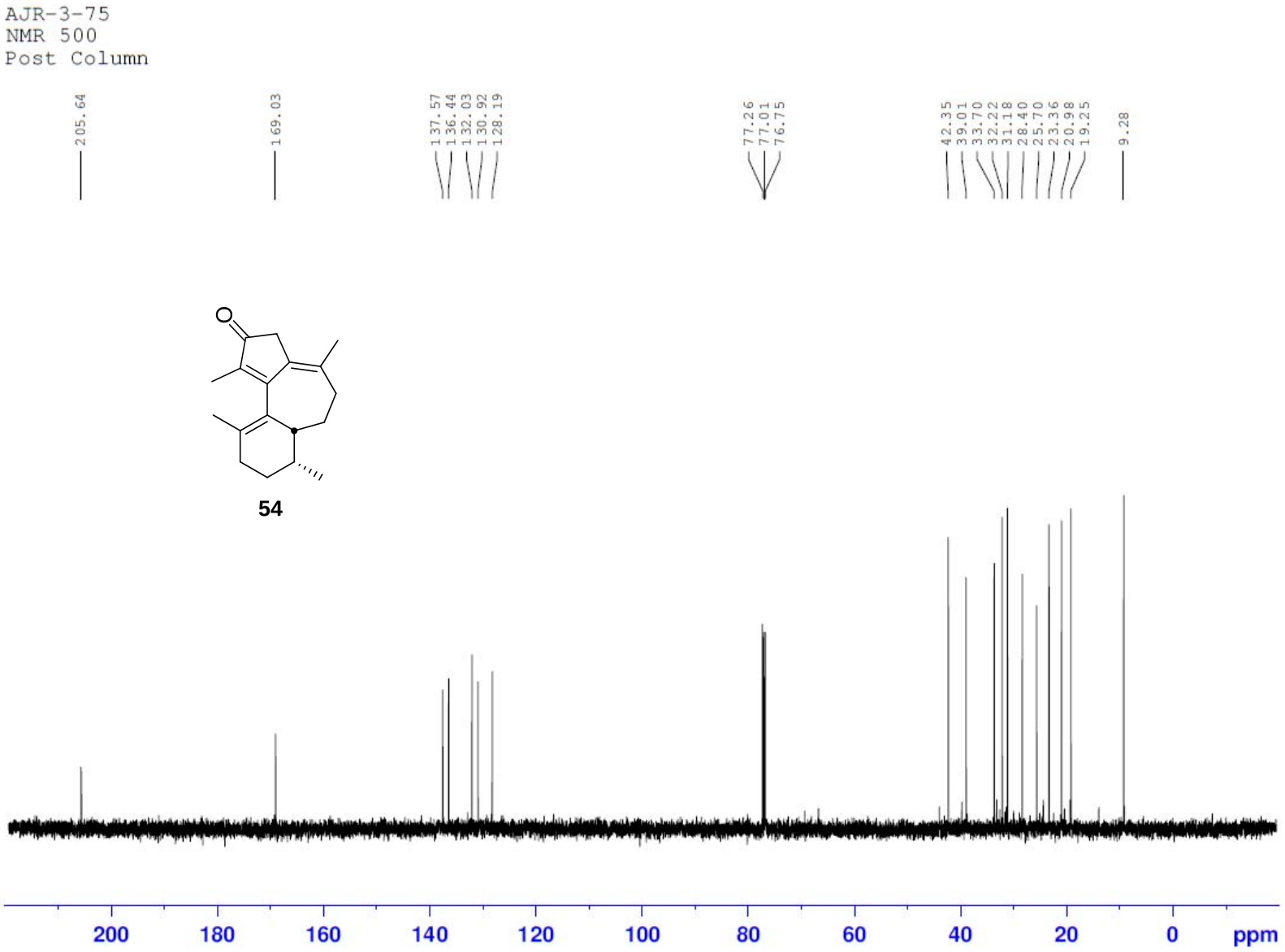

AJR-3-75
NMR 500
Post Column
2.868 2.848 2.472 2.464 2.434 2.069 1.979 1.967 1.941 1.873 1.870 1.868 1.863 1.857 1.850 1.844 1.838 1.832 1.827 1.823 1.797 1.654 1.653 1.645 1.642 1.635 1.626 1.618 1.615 1.585 1.553 1.548 1.540 1.535 1.532 1.528 1.472 1.454 1.387 1.374 1.360 1.346 0.911 0.898
54
2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 ppm
2.00 1.06 1.30 1.06 1.68 2.17 3.04 1.04 1.67 2.84 1.79 2.77 0.43 1.56 2.99
Current Data Parameters
NAME AJR-3-75
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071210
Time 12.44
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT CDC13
NS 10
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 5.7
DW 48.400 usec
DE 6.00 usec
TE 295.2 K
D1 4.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300129 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


AJR-3-75
NMR 500
Post Column
205.64
169.03
137.57
136.44
132.03
130.92
128.19
77.26
77.01
76.75
42.35
39.01
33.70
32.22
31.18
28.40
25.70
23.36
20.98
19.25
9.28
200
180
160
140
120
100
80
60
40
20
0
ppm

54