Understanding and developing PikC as a tool in organic synthesis. Part I: total synthesis of methymycin and neomethymycin featuring a catalytic nickel ynal cyclization and a biocatalytic PikC CH oxidation. Part II: regiodivergent nickel catalyzed macrocyclizations.

by

Abdur-Rafay Shareef

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Doctoral Committee:

Professor John Montgomery, Co-Chair
Professor David H. Sherman , Co-Chair
Professor Melanie Sanford
Assistant Professor Matthew Soellner
Assistant Professor Sylvie Garneau-Tsodikova

Acknowledgments:

"We are like dwarfs sitting on the shoulders of giants. We see more, and things that are more distant, than they did, not because our sight is superior or because we are taller than they, but because they raise us up, and by their great stature add to ours."

---Bernard of Chartres

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Chapter 1

INTRODUCTION TO PIKROMYCIN AND PIKC

The 2010 Nobel Prize in Chemistry was awarded to Heck, Suzuki, and Negishi, and prior to that, the last 'organic' chemist(s) to be awarded a Noble Prize were Robert Grubbs, Richard Schrock, and Yves Chauvin. The common theme amongst recent winners in the organic division is organometallic chemistry. Each developed or had a significant contribution towards bringing transition metal catalyzed reactions to widespread use. Mechanistic studies and/or studies towards developing a fundamental understanding of transition metals paved the way for current usage of transition metals by industrial and academic chemists alike.

During the course of millions of years of evolution, enzymes have become 'master' organic chemists. Enzymes are capable of transformations a traditional chemist can currently only dream about. Generations of students were trained that enzyme's exquisite selectivity was due to rigid substrate specificity. The 'Lock and Key' or 'Induced Fit' hypothesis suggested that enzymes change their active site to accommodate one, and only one substrate.[1] Indeed many enzymes conform to the notion of one substrate, one product; however contemporary studies have identified several enzymes countering the 'one substrate, one enzyme dogma.[2]

The pikromycin biosynthetic pathway is a unique polyketide biosynthetic pathway. The enzymes found within the pathway uniquely produce several substrates of

varying ring size and functionalty.[3] Polyketides share a common biosynthetic logic, whereby iterative chain elongation followed by reductive processing produces long linear chains that are often cyclized by dedicated enzymes into macrocyclic compounds;[4-6] although linear polyketides are known.[7] Seminal studies conducted on the erythromycin biosynthetic pathway established the modular nature of polyketide biosynthesis.[8-11] Based upon the erythromycin biosynthesis model studies the field of combinatorial biosynthesis blossomed. The genomes for polyketide biosynthetic enzymes are clustered together; with dedicated enzymes performing specific tasks in an assembly-line fashion. Unfortunately early applications of the 'plug and play' approach, whereby modules and domains from distinct biosynthetic pathways were traded, removed, and added, were only modestly successful. Efforts involving addition, elimination, or substitution of individual catalytic domains produced an impressive number of natural product analogs; however the analogs were often produced in poor yield and more frequently not at all.[12-14] The potential utility for using polyketide biosynthetic enzymes is astonishing; theoretical estimates hypothesize that polyketide biosynthetic pathways have the ability to generate hundreds of millions of compounds.[15] However, studies aimed at basic understanding must be conducted to fill in large knowledge gaps. The pikromycin biosynthetic pathway can serve as a model system to understand enzymes with substrate flexibility.

Pikromycin was first isolated in 1951, and has historical significance as the first ketolide antibiotic isolated.[16] Although itself not clinically useful, the enzymes found within the pathway hold tremendous promise. Several decades after initial isolation the Sherman laboratory reported the cloning and genetic sequence of the pikromycin

biosynthetic gene cluster from *S. venezuelae ATCC 15439*.[17] Subsequent analysis of the 60-kb of DNA sequence yielded the identification of 18 discrete genes, which were further subdivided into five separate loci: PKS (pikA), desosamine biosynthesis (des), cytochrome P450 hydrolase (PikC), a transcriptional activator (pikD), and a resistance locus (PikR).[17]

The PikA gene locus encodes for five polypeptide chains (PikAI-PikAV). These five polypeptide chains represent a type I modular polyketide synthase. The first four polypeptides, PikAI-PikAIV, are where the single loading modules and six PKS chain elongation modules that are responsible for synthesis of the linear chain elongation intermediates and subsequent macrolactone rings are found. The final two modules are monomodules and are therefore contained on separate polypeptide chains; whereas the first three modules are di-domains. The final polypeptide, PikAV is a type II thioesterase, the function of which remains controversial. Preliminary investigations suggest type II thioesterase serves an editing role during PKS biosynthesis.[18] On the basis of gene disruption studies, the Sherman lab demonstrated the unique ability of the pikromycin thioesterase to produce both a 12- and a 14-macrolactone.[19] For over a decade, the Sherman laboratory has studied the PKS portion of pikromycin biosynthesis and has made several noteworthy conclusions and hypotheses. Briefly the Sherman laboratory has demonstrated that understanding polyketide biosynthesis requires full length substrates, the pikromycin thioesterase is remarkably promiscuous, the alpha, beta-unsaturated moiety in the chain elongation intermediates plays a role in cyclization, and non-natural extender units have the potential for further increasing the diversity of

products generated by the pikromycin PKS.[2,20-23] Further discussion of the pikromycin PKS can be found in several reviews.[2,3,24]

A flexible glycosyl-transferase encoded by DesVII is responsible for appending a desosamine sugar on both 10-deoxymethynolide and narbonolide to produce the immature macrolide antibiotics YC-17 and narbonolide.[17] Finally a remarkable tailoring enzyme, PikC is responsible for the production of the mature macrolides. PikC is capable of both singly or doubly hydroxylating both immature macrolides YC-17 and narbonolide.[17,25] In the 12-membered macrolide series, methymycin and neomethymycin are the singly hydroxylated products with novamethymycin resulting from double hydroxylation.[26] In the 14-membered macrolide series, pikromycin and neopikromycin are the singly hydroxylated macrolides, and novapikromycin is the product of double hydroxylation as demonstrated by Figure 1. [27]

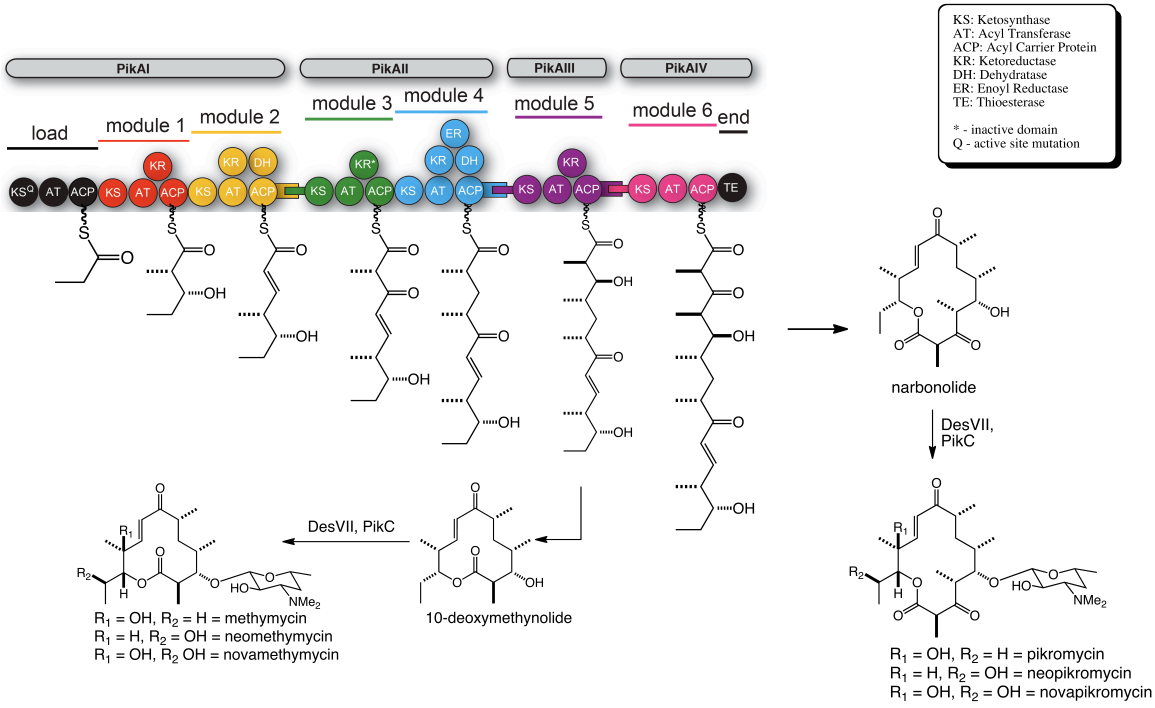


Figure 1. Pikromycin biosynthetic pathway

During xenobiotic metabolism, several promiscuous P450 enzymes are capable of a diverse set of transformations, including activation of C-H bonds with pK_a's above 50 and bond dissociation energies (BDEs) above 110 kcal mol^{-1}![28,29] Catabolic P450 enzymes often have rigid substrate specificity as demonstrated by the canonical erythromycin biosynthetic pathways;[30] albeit mutagenesis has expanded the native rigidity.[31] In contrast, the pikromycin biosynthetic pathway encodes for PikC, a cytochrome P450, possessing native substrate flexibility.[25] Promising preliminary efforts towards development of PikC as a general biocatalyst have been reported including preparation of a more active mutant,[32] use of an immobilized variant of PikC in microfluidic devices,[33] demonstration of activity against non-canonical substrates,[34] and engineering of a self-sufficient fusion protein.[35] Unfortunately, a detailed mechanistic understanding of the hydroxylation pattern has thus far not been developed. We endeavor to explicate a series of rules governing PikC catalyzed hydroxylations and a general understanding of the mechanism of this unique P450 enzyme.

CYTOCHROME P450 BACKGROUND

Cytochrome P450 enzymes are found in nearly all organisms; several thousands are known and many more are reported annually. An arbitrary cutoff has been established to denote an enzyme as a cytochrome P450. When aligned correctly, approximately > 40 % identity is required to define an enzyme as a member of the family, and a high identity (>55 %) is required to be a member of a subfamily.[36] Bacterial variants have served as the model system because bacterial P450s are typically soluble, monomeric proteins as opposed to the membrane bound mammalian, plant, and fungal proteins.[37] Seminal studies were conducted with CYP101 ($P450_{cam}$) from *Pseudomonas*

putida.[38,39] The diversity of reactions catalyzed by P450 has resulted in the moniker "Nature's most versatile biological catalyst."[40]

The name cytochrome P450 is derived from the presence of a heme (iron protoporphyrin IX) group within the protein prosthetic group coordinated on the proximal side by a thiolate ion.[41,42] Due to this feature, cytochrome P450 enzymes have a characteristic spectroscopic signature; a Soret absorption maximum at ~450 nm.[42] Although all member of the cytochrome P450 family contain a thiolate-coordinated heme, not all proteins with a thiolate-coordinated heme are in the P450 family, e.g. chloroperoxidase.[42,43]

The defining reaction for cytochrome P450 enzymes is the reductive activation of molecular oxygen; P450 enzymes are able to insert one of the oxygen atoms of molecular oxygen into a substrate, and the other oxygen atom is converted into a water molecule. Typically, the electrons are supplied by reduced pyridine nucleotides (NADH or NADPH). Whereby the overall equation for the reaction is $RH + NAD(P)H + O_2 + H^+ \rightarrow ROH + NAD(P)^+ + H_2O$. Typically P450 enzymes belong to the monooxygenase class of enzymes because they only insert one oxygen atom into the substrate;[37] however P450 enzymes are capable of desaturation, carbon-carbon bond scission, and carbon-carbon bond formation![44-46]

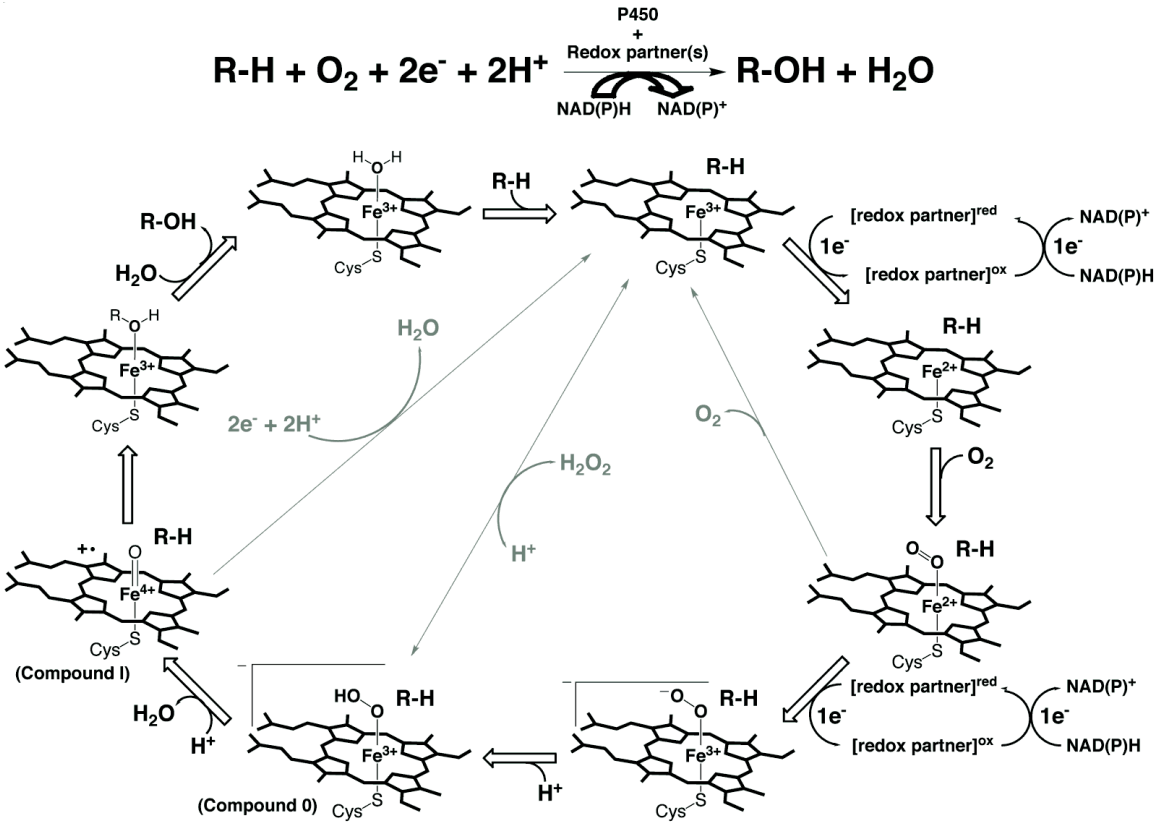


Figure 2. Overall catalytic cycle of cytochrome P450 enzymes[37]

The overall catalytic cycle is summarized in Figure 2; albeit controversy exists in the mechanism.[37] In the resting state, the enzyme is in the ferric state and has a thiolate proximal ligand. The distal ligand is typically a water molecule. [47] Upon substrate binding, a displacement of the water ligand occurs; at this point a shift in redox potential of the heme iron atom occurs. The resulting ferrous, substrate-bound protein then binds oxygen to yield the ferrous dioxy complex. The complex is represented as a ferric superoxide complex. A second electron transfer is usually the rate-limiting step of the catalytic cycle; exceptions are known.[48] The ferric hydroperoxo intermediate is unstable, and is protonated, and fragments to give a ferryl intermediate that can be shown as a protein radical cation Fe(IV) species or as a Fe(V) species. This intermediate is known as compound I. Compound I reacts with substrate to produce the hydroxylated species, and

after release of product and water binding, the resting state of the enzyme is obtained; alternative species are occasionally suggested as responsible for hydroxylating substrates.[37]

The Sherman laboratory is interested in developing unique cytochrome P450 enzymes as biocatalysts. PikC is a distinctive P450 enzyme not only for its native substrate promiscuity, but also for its specificity towards C-H bonds. A large body of literature has been assembled describing the preference for C-H oxidation with P450 enzymes. Seminal studies were conducted on oxidation of heptanes by microsomal P450 enzymes.[49] Subjecting 2-methylpropane to P450 C-H oxidation, the observed product is almost exclusive hydroxylation at the lone tertiary site, despite the presence of nine primary C-H bonds. The same trend is observed with secondary C-H bonds when products are examined from oxidation of *n*-heptane. Over four decades of research has supported the hypothesis that site of hydroxylation from a cytochrome P450 reaction is the C-H bond with the weakest bond strength. A generally accepted model predicts hydroxylation to occur: benzylic or allylic > tertiary > secondary > primary, although sterics can occasionally play a role.[37,49-52]

Intriguingly, PikC is able to deftly hydroxylate both an allylic and secondary alkane in the native pikromycin biosynthetic pathway. In addition when non-canonical substrates are presented to PikC, C-H oxidation is achieved at unactivated methylene positions.[34] Understanding and exploiting this unique reactivity pattern into a general biocatalyst could enable the rapid generation of un-natural macrolide compounds.

Currently, our understanding of PikC has evolved largely due to biochemical and

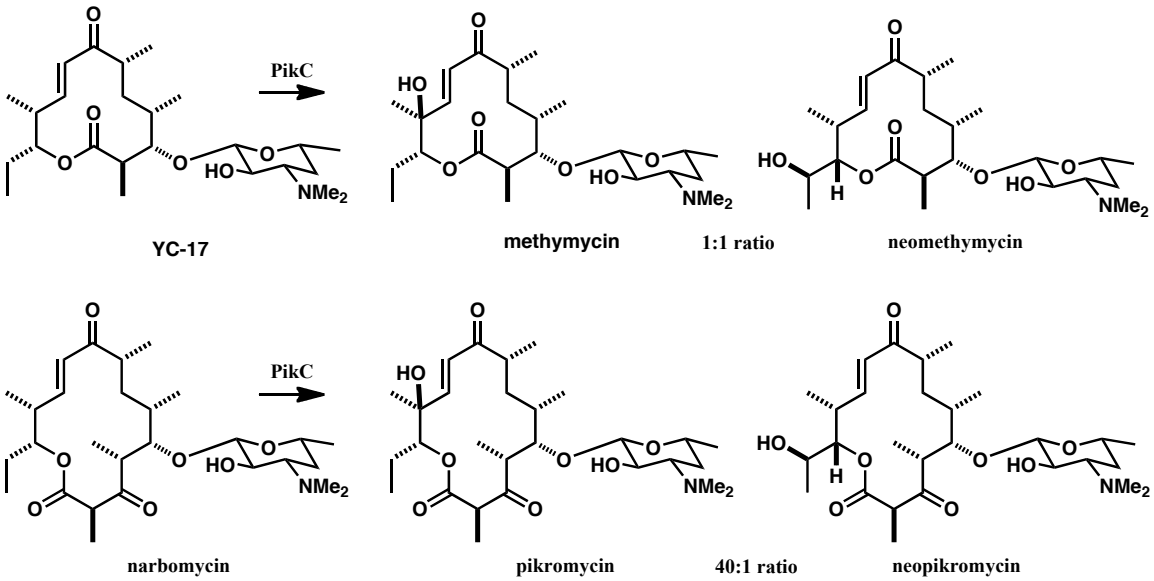


Figure 3. PikC hydroxylation products

crystallographic characterizations.[32] Based upon co-crystal structures of YC-17 and narbomycin bound to PikC we hypothesized that one enzyme could hydroxylate so many substrates due to a desosamine-anchoring mechanism. Whereby the tertiary amine on desosamine is responsible for the critical direct contact between the macrolide and the enzyme; other contacts seem to be non-specific. The macrolactone ring in narbomycin is bound almost entirely via hydrophobic interactions with amino acid side chains Leu-93, Phe-178, Val-179, Ile-239, Met-394, and Ile-395, and three hydrophilic amino acids, Glue-246, His-238, and Asn-392.[32] In the co-crystal structures no direct hydrogen bonding is observed with these residues. As demonstrated by Figure 3, the allylic position is preferentially hydroxylated in narbomycin in approximately a 40:1 ratio over the methylene oxidation product. Despite this product preference, in the co-crystal structure, the allylic C12 carbon is positioned 7.1 Å away from the heme iron, whereas the methylene position is only 5.3 Å away from the heme iron center. This difference in product preference is in line with expected products considering bond dissociation

energies. The allylic C-H bond is weaker than the methylene C-H bond by approximately 16 kcal/mol;[53] in addition the position is conjugated to the alpha, beta-unsaturated carbonyl group, thus decreasing the activation barrier. However, when considering the 12-membered macrolactone ring YC-17, a different ratio of products is observed; approximately a 1:1 ratio is observed between hydroxylation at the allylic position to generate methymycin and at the unactivated methylene to generate neomethymycin. Once again, in the co-crystal structure, the macrolactone ring of YC-17 is almost entirely bound via hydrophobic interactions projecting the more hydrophilic surface of the lactone towards the *I*-helix and is devoid of hydrogen bonding. The binding site for the 12-membered ring lactone overlaps the binding site for the 14-membered ring, in addition YC-17 has one more amino acid contact, Val-290. For YC-17 the C3' dimethylamino group of the desosamine sugar is sandwiched between two carboxyl groups, Glu-85 and Glu-94; in a discrete binding pocket as compared to narbomycin. YC-17 is positioned deeper in the protein interior. Amino acids Trp-74, Asn-91, and Glu-94 participate in a network of hydrogen bond contacts with the tertiary amine on desosamine. Hydrophobic contacts are observed via Trp-74, Leu-81, Leu-88. In addition, contacts are observed between desosamine and Met-191 and His-238. Both macrolide antibiotics partially mimic the interaction between desosamine and bacterial ribosomes.[32]

From the co-crystal structure, insights into the hydroxylation pattern can be obtained. The allylic C10 site is 7.5 Å away from the iron oxo-center; however the unactivated methylene is 5.3 Å away. It is postulated that the closer distance to the heme iron center leads to the 1:1 ratio of methymycin to neomethymycin.

Sherman and Li demonstrated the critical role of a salt bridge between PikC and the dimethylamino group on desosamine. A series of mutants were prepared using site-directed mutagenesis where the Asp-50, Glu-85, and Glu-94 were replaced with alanine or glutamine/asparagines followed by functional analysis *in vitro*. Briefly, the data showed that replacement of the proximal carboxyl group (Glu-94 for YC-17 and Glu-85 for narbomycin) with an alanine almost completely abolished conversion. Substitution of the distal carboxyl group generated PikC mutants that were similar to wild type PikC. A surprising result was that preparation of the D50N mutant produced a more active variant of PikC.[32]

Shortly thereafter the utility of PikC was further advanced by the generation of a self-sufficient variant. In order to active molecular dioxygen, cytochrome P450 enzymes utilized redox partners to sequentially transfer two reducing equivalents from NAD(P)H to the heme center.[37] *In vitro* reactions on scale are challenging due to this requirement of heterologous redox partners. However self-sufficient P450 enzymes are known. The first identified was $P450_{BM3}$, which is naturally fused to a eukaryotic-like reductase.[54,55] $P450_{BM3}$ is a noteworthy enzyme, and is the most efficient P450 enzyme characterized.[56] Elegant studies have been conducted to generate membrane-bound P450 enzymes that have been used *in vitro*;[57,58] unfortunately class I biosynthetic P450 enzymes lack a universal reductase partner that can be used to engineer self-sufficient P450 enzymes.

A potential solution manifested with a new class of self-sufficient P450 enzymes from *Rhodococcus* sp. NCIMB 9784, $P450_{RhF}$ was discovered to be naturally fused to a novel FMN/Fe_2S_2 containing reductase partner.[59,60] Li and Sherman prepared the first *in vitro* characterization of a single component bacterial biosynthetic cytochrome P450 enzyme

fused to RhFRED and demonstrated its catalytic efficiency. Preparing a fusion protein of the $PikC_{D50N}$ resulted in a self sufficient P450 enzyme that was more active than wild type PikC *in vitro*.[35] The binding kinetics and analysis of the catalytic binding pocket was also reported.[61]

In addition, the desosamine-anchoring hypothesis was evaluated using completely unnatural macrocycles covalently bound to a desosamine sugar, termed carbolides. Surprisingly, PikC was able to hydroxylate these carbolides in good to modest yield. Although in select cases, the overall yield and conversion was suboptimal, these substrates could not be hydroxylated using any other traditional means given the sensitivity of the tertiary amine. Peculiarly, PikC hydroxylated the carbolides in a regio- and stereo-unselective manner as confirmed by authentic standard synthesis.[34] Understanding PikC is a goal of our current studies. During the course of this dissertation, the groundwork for synthesizing substrates for understanding this enzyme, PikC will be presented. A modular and flexible synthetic strategy was developed to synthesize analogs of YC-17 that will be utilized to interrogate PikC hydroxylations; with the ultimate goal of developing an empirical model to explain hydroxylation catalyzed by PikC.

Chapter 2

TOTAL SYNTHESIS OF METHYMYCIN AND NEOMETHYMYCIN FEATURING CATALYTIC NICKEL MACROCYCLIZATION AND BIOCATALYTIC C-H ACTIVATION

Traditional strategies for the preparation of complex molecules have often relied on assembly of appropriately oxidized linear substructures, and in cases of macrolides, macrolactonization or ring closing metathesis reactions are typically used to synthesize the target molecule.[62-64] In contrast, macrocylization of less functionalized structures, followed by late stage C-H oxidation, provides a potential strategy to increase efficiency in synthesis, in addition to allowing more rapid access to novel analogs.[65-67] Nature utilizes cytochrome P450 enzymes to produce mature macrolide antibiotics through site selective C-H oxidation of simpler intermediates.[37,40,46] Remarkable advancements have been achieved in chemical C-H functionalization reactions.[68] However site selective chemical C-H activation of complex structures remains a "holy grail" and subject of active research.[69-74] In contrast, Nature has had the advantage of millions of years of evolution to develop cytochrome P450 enzymes with remarkable selectivity; these enzymes have considerable promise in organic synthesis.[28,34,75-80] Moreover, developing selective chemical catalysts for remote functionalization may be guided by understanding biological mechanisms and strategies employed by natural product 450 enzymes.[81-86] The Sherman and Montgomery laboratories have independently developed programs aimed at utilizing and understanding natural product biosynthesis and developing nickel catalyzed reductive couplings. Studies described in this chapter merge these two

strategies in a synergistic fashion to synthesize methymycin and neomethymycin. Ultimately the strategy utilized in this total synthesis will allow the synthesis of analogs of YC-17 to interrogate PikC catalyzed hydroxylations.

Considerable prior art exists in total syntheses of natural products found within the pikromycin biosynthetic pathway. The first total synthesis methynolide was achieved by Masamune in 1975.[87-89] In the decades to follow eight syntheses of methynolide or the *seco*-acid have been reported. Grieco (formal) ,[90] Yamaguchi,[91,92] White (formal),[93] Yonemitsu,[94-97] and Ditrich[98] synthesized the fully oxidized and protected linear fragments and utilized acid activation esterification approaches to the lactone; Yonemitsu used a Wittig type esterification. Unconventional approaches to polypropionate frameworks were reported by Ireland,[99,100] Vedejs,[101-103] and Bartlett (formal).[104] Ireland approaches the framework through elaboration of homo-diels alder derived spiroketals.[99,100] Vedejs reported elegant sulfur ylide ring expansions to generate mercaptan-methynolide precursor which are converted to methynolide via a photochemical oxidation.[101-103] Bartlett communicated a conceptually similar approach as Ireland whereby cyclic ethers are generated via electrophilic cyclization of unsaturated alcohols. Using this methodology he prepares an intermediated in racemic form that Ireland prepared in enantioenriched form.[104] Most recently, Cossy has disclosed a formal synthesis of methynolide.[105,106] The more accessible aglycone 10-deoxymethynolide has been prepared by total synthesis by Pilli utilizing a Nozaki-Hiyama-Kisha macrocyclization[107] and Kang utilized ring closing metathesis.[108] Methymycin,

neomethymycin and novamethymycin were prepared by total synthesis by Kang and disclosed in 2009 and 2010.[109,110] O'Doherty and Liu reported analogs of YC-17 where the sugar was modified and the aglycone was presumably fermentation derived.[111]

The classic synthesis by Masamune set the stage for most total syntheses by other investigators. He utilized acid activation macrolactonization to prepare the target aglycone of methymycin. The most notable contribution was added by Yamaguchi where he introduced his 2,4,6-trichlorobenzoic acid 'Yamaguchi reagent' as the reagent for acid activation. Using the Yamaguchi reagent he was able to improve the yield of macrolactonization to a best case of 41 %. Ditrich utilized the same bond construction and Yamaguchi reagent acid activation to prepare the aglycone of methymycin. Yonemitsu was the first to recognize and achieve an alternative bond construction to produce the aglycone of methymycin. He utilized an intermolecular esterification followed by a Wittig-type cyclization, allowing a much more efficient ring closing reaction. Most recently, Kang has utilized an approach similar to Yonemitsu, whereby ring-closing metathesis was utilized to synthesize the aglycone of methymycin.

The Kang syntheses represent the state of the art in macrolide total synthesis as the current field stands. Fully oxidized and protected subunits are prepared followed by ring closing metathesis to prepare the macrolactone. While these syntheses are impressive for targeting and preparing a complex molecule, the fully oxidized fragments

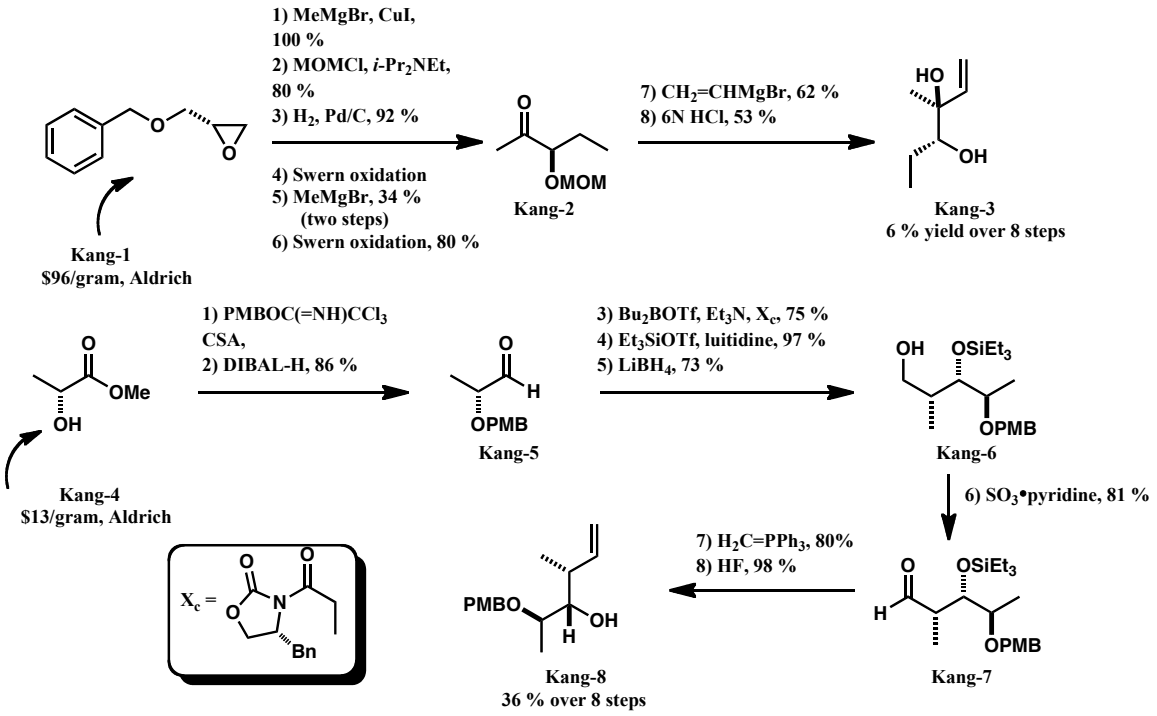


Figure 4. Fragment synthesis for Kang's synthesis of methymycin and neomethymycin[109,110]

required for the synthesis are difficult to synthesize and rely on the chiral pool to set key stereocenters. As described in Figure 4, for the key fragment for the synthesis of methymycin begins with commercially available (*S*)-(+)-glycidyl benzyl ether, available from Aldrich ($96/gram). **Kang-1** was subjected to a six-step sequence, initially treated with methyl magnesium bromide in the presence of copper iodide, followed by protection of the alcohol as a MOM-ether. The benzyl group is removed using using palladium on carbon in a hydrogen atmosphere (Pd/C, H_2) to unmask the primary alcohol which is oxidized to the aldehyde using Swern oxidation. The resulting aldehyde is treated with MeMgBr followed by direct oxidation of the resulting alcohol to yield **Kang-2**. A chelation-controlled addition of vinyl magnesium bromide to **Kang-2**, followed by removal of the MOM-ether using 6N HCl achieves the appropriately oxidized subunit for the synthesis of methymycin, **Kang-3**, in diastereomerically pure form in 6 % yield over

8 steps.[109]

Kang synthesizes the appropriately oxidized fragment for neomethymycin as described in Figure 4 beginning with, **Kang-4**, methyl (*R*)-(+)-lactate; more reasonably priced at $13/gram. The first step was a PMB protection, followed by a DIBAL-H reduction of the methyl ester to **Kang-5**, which is used in an Evans syn aldol. The resulting secondary alcohol is protected as a TES silyl-ether, followed by removal of the Evans chiral auxiliary to yield **Kang-6**, which is oxidized using Parikh-Doering conditions to **Kang-7**, a Wittig homologation, and removal of TES silyl-ether by HF allowed the synthesis of diasteromerically pure protected diol, **Kang-8** in 36 % yield over 8 steps.

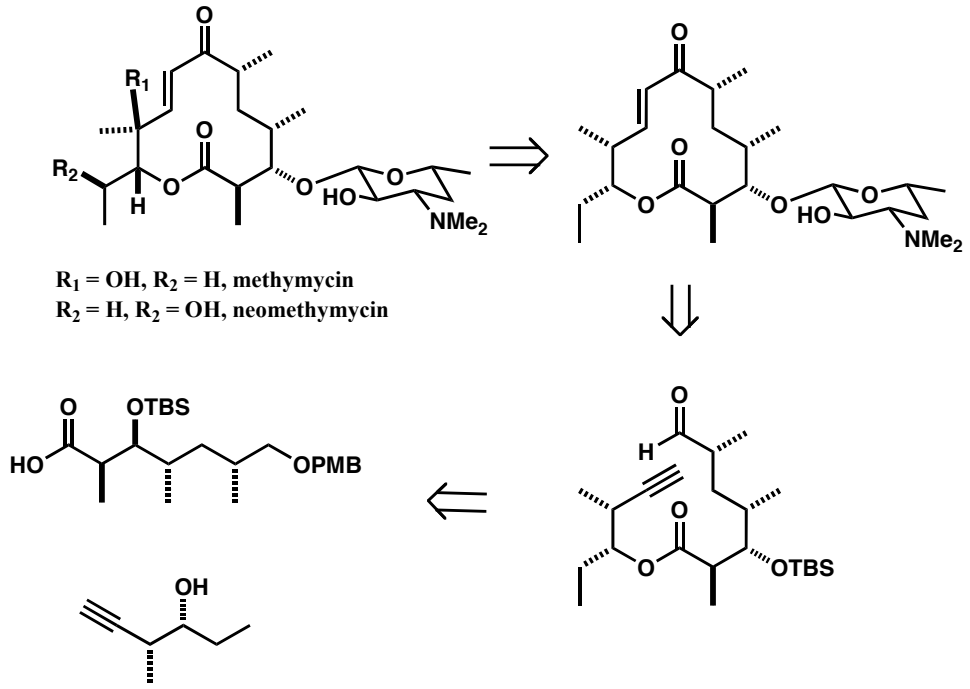


Figure 5. Retrosynthetic analysis for methymycin and neomethymycin

DISSERTATION STUDIES

Late state C-H oxidation may potentially speed up the synthesis of natural product analogs. Although major pharmaceutical companies have phased out natural product

programs over the last several years, select companies have been quite successful synthesizing and developing natural products as drugs.[112-114] A remarkable effort by Eisai pharmaceuticals entailing a 62 step total synthesis of a halichondrin analog was recently approved by the FDA in 2010 for breast cancer.[115] Increasing efficiency of natural product synthesis is a highly desirable goal. Our approach to methymycin and neomethymycin is presented in Figure 5. The final step is PikC catalyzed C-H oxidation. The macrolactone core of YC-17 is synthesized using a nickel-catalyzed ynal cyclization developed in the Montgomery laboratory.[116-119] The key ynal precursor can be disconnected to a carboxylic acid and alkyne fragment.

In the forward direction, as described in Figure 6, the synthesis of the carboxylic acid fragment commenced with methyl (S)-(+)-3-hydroxy-2-methylpropionate, known as the (S)-Roche-ester. Although this sequence begins with a chiral pool reagent, the cost of this reagent is only $5/gram. The Roche ester is protected as a PMB-ether using the PMB-trichloroacetimidate, the ester is reduced using $LiAlH_4$, followed by an Appel reaction to prepare alkyl iodide **4**, in 3 steps and 86 % yield from **1**. Alkyl iodide **4** is used in a Myers alkylation reaction using the pseudoephedrine-derived Myers auxiliary.[120] Followed by removal of the chiral auxiliary using $LiNH_2{\bullet}BH_3$, the resulting alcohol is oxidized using using Dess-Martin[121] reagent to prepare aldehyde **7**. An Evans syn aldol reaction was done using the phenylalanine derived *(R)*-Evans auxiliary.[122] The resulting secondary alcohol, **8**, is protected as a TBS-silyl ether, and the Evans auxiliary is removed using H_2O_2 and LiOH to prepare carboxylic acid **9** in 9 steps and 39 % overall yield from **1**. Our approach paralleled a reported by Kang and colleagues.[108]

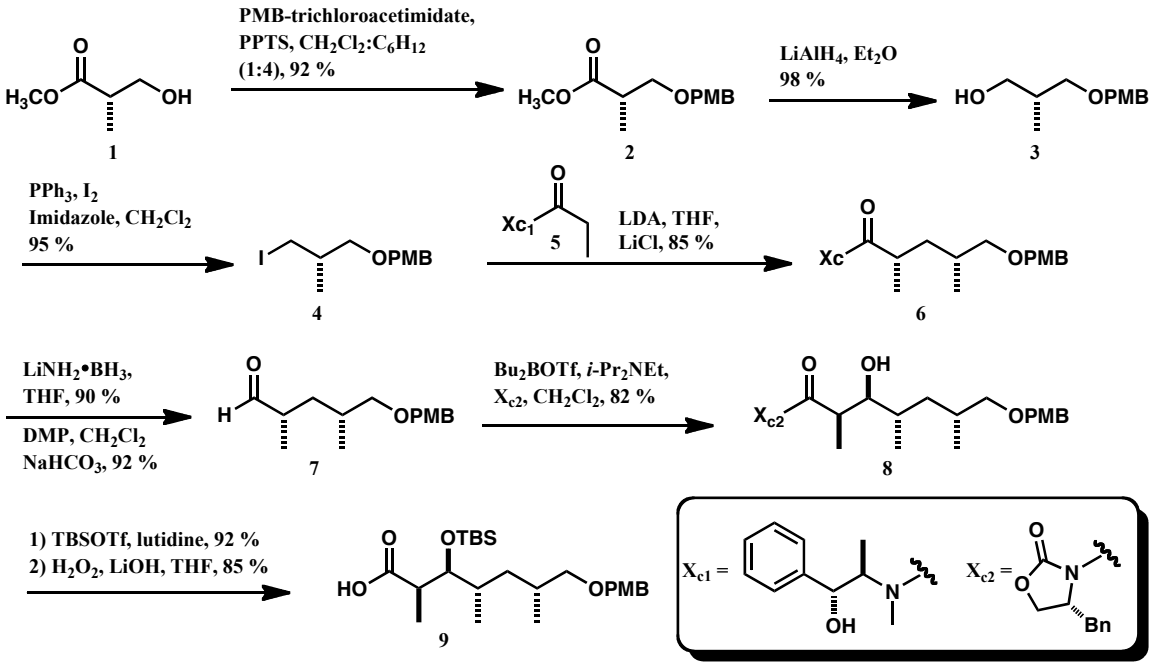


Figure 6. Synthesis of protected carboxylic acid fragment for methymycin synthesis

The requisite alkyne fragment was synthesized in an analogous fashion. An Evans syn aldol reaction,[122] followed by protection of the secondary hydroxyl as a TBS sily ether and removal of the (*S*)-Evans auxiliary was done using $LiBH_4$ to generate alcohol **13**. A Dess-Martin oxidation followed by two step Corey-Fuchs[123] dibromoolefination-elimination afforded alkyne **15** in six steps and 54 % overall yield from oxazolidinone **11**, as described in Figure 7.

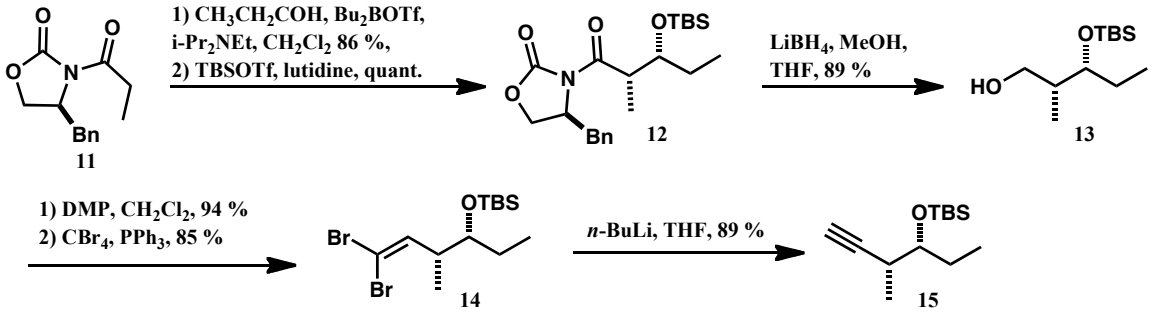


Figure 7. Synthesis of alkyne fragment

With fragments **15** and **9** synthesized, a model system was utilized to probe the ability of the nickel catalyzed ynal cyclization to produce the required macrolactone rings. Therefore, using commercially available alkyne, **16**, an EDCI mediated esterification was

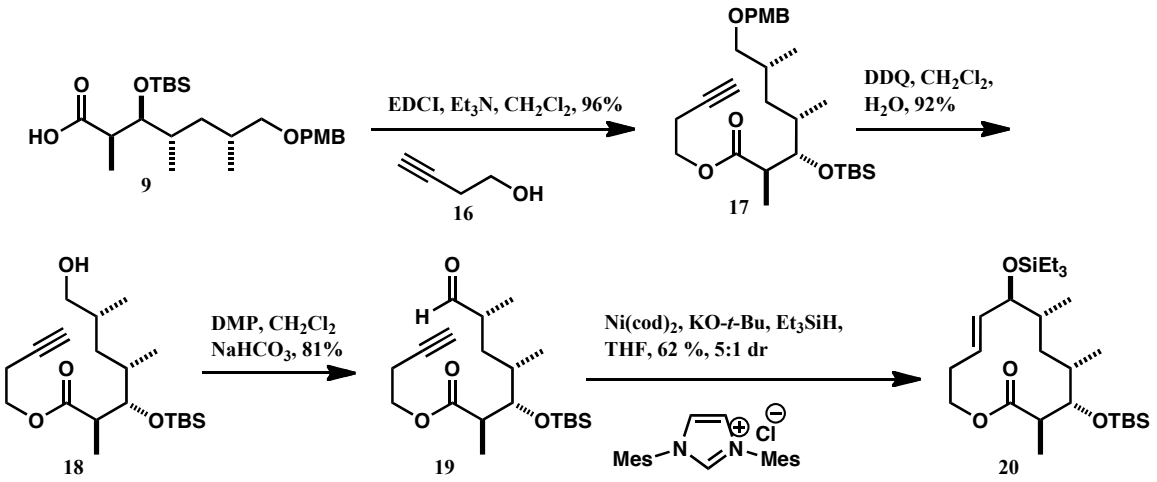


Figure 8. Nickel catalyzed ynal cyclization (model system)

used to prepare ester **17**. Removal of the protecting group with DDQ yielded **18** which was oxidized to ynal **19** using Dess-Martin reagent. Compound **19** was not isolated and characterized in pure form as chiral alpha branched aldehydes are often unstable. Gratifyingly using the previously developed $Ni(cod)_2$-IMes catalyst system,[116,118] macrolactone **20** was prepared in 62 % yield; notably a 5:1 dr was observed at the allylic alcohol as described in Figure 8. During reaction optimization, several different combinations were attempted; however after considerable optimization, optimal conditions were developed: 30 mol $Ni(cod)_2$, 29 mol % IMes-HCl, and 40 mol % KO-*t*-Bu, in 0.01 M THF.

Applying this procedure to the fully functionalized carbon framework of YC-17 was the next goal, as described in Figure **9**. Yamaguchi conditions were required to efficiently prepare ester **21**, followed by analogous PMB deprotection and oxidation

using Dess-Martin reagent to synthesize ynal **22**. Using the previously developed cyclization conditions, macrocyclization was achieved using 30 mol % $Ni(cod)_2$, 29 mol % IMes-HCl, and 40 mol % KO-*t*-Bu, in 0.01 M THF. Notably a 4:1 dr was observed at the allylic alcohol; however the distereoselectivity is inconsequential as the

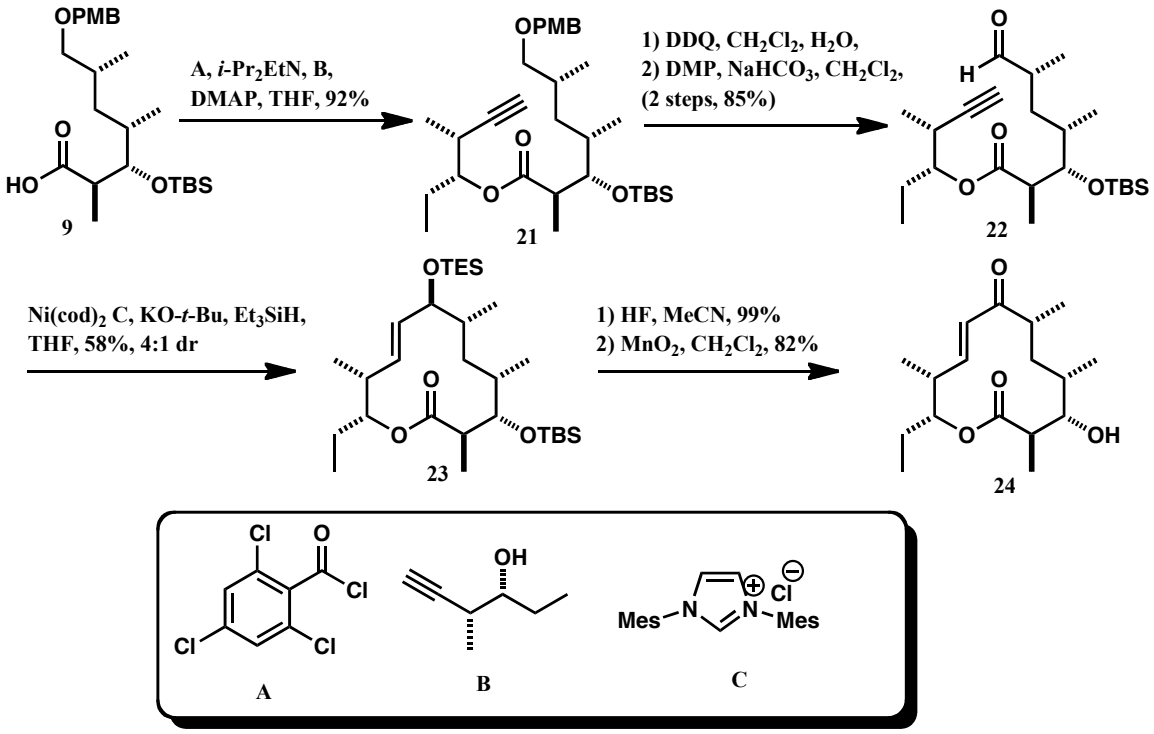


Figure 9. Synthesis of 10-deoxymethynolide featuring catalytic nickel cyclization

next steps involve global deprotection and chemoselective oxidation using MnO_2 to synthesize 10- deoxymethynolide, **24**, in six steps and in 37 % overall yield from **9**.

With **24** in hand, the end game involved a glycosylation and the penultimate PikC catalyzed C-H oxidation as described in Figure 11. Given the sensitivity of the tertiary

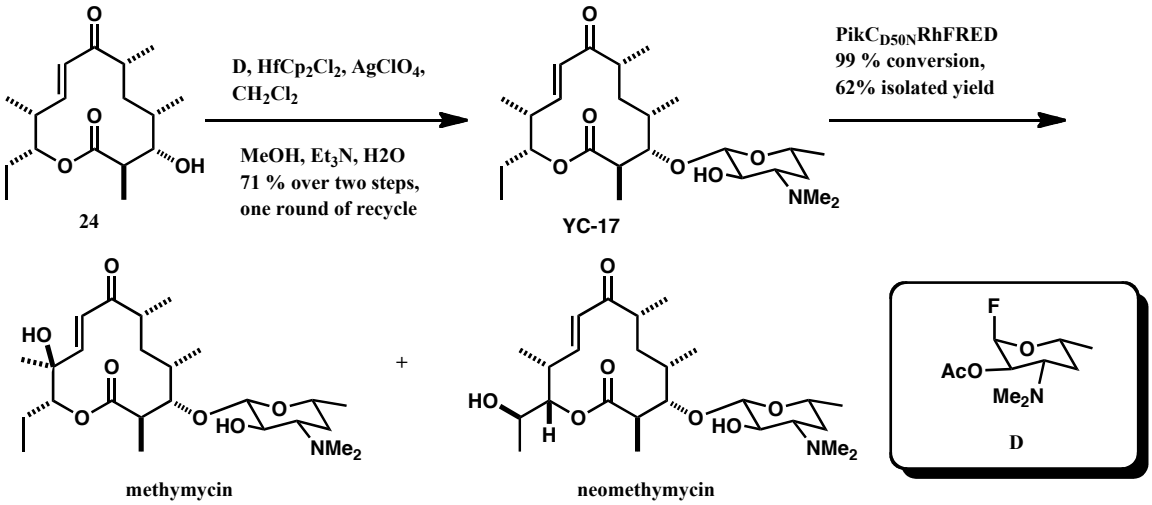


Figure 10. End game in total synthesis of methymycin and neomethymycin

amine of desosamine, very mild glycosylation conditions developed by Suzuki were employed.[124] Unfortunately, the reaction requires a large excess of both hafnium and silver salts along with a long reaction time, during which the C2' acetate on desosamine is partially deprotected along with starting material. Analysis of crude material presents **YC-17**, C2' acetylated **YC-17**, and **24.** Therefore **24** is subjected to one round of recycle and **YC-17** is isolated in 71 % yield over two steps. The final step involves PikC catalyzed C-H oxidation to prepare a mixture of methymycin and neomethymycin. The crude material is analyzed using LC-MS and shows over 99 % conversion, and a mixture of methymycin and neomethymycin is isolated in 62 % yield.

In summary a total synthesis of methymycin and neomethymycin has been developed featuring nickel-catalyzed ynal cyclization and biocatalytic PikC C-H oxidation. The synthesis required 18 linear steps (25 total), and was accomplished in 6.3 % overall yield from the commercial Roche-ester. The strategy developed during this synthesis will be utilized to synthesized analogs to study PikC catalyzed C-H oxidations.

Chapter 3

REGIO-DIVERGENT NICKEL MACROCYCLIZATION

Reductive couplings have evolved as powerful methods for the synthesis of complex molecules. Traditionally reductive couplings involved coupling two carbonyl-type species to form pinicol type products, e.g. McMurry coupling. The Nicolaou lab disclosed a beautiful example in a total synthesis of taxol as described in Figure 11.[125]

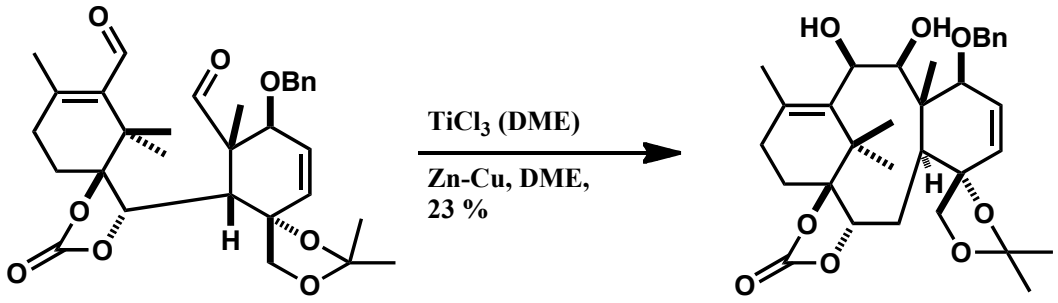


Figure 11. McMurry coupling in Nicolau's taxol total synthesis

A second, more recently developed variant involves a transition metal catalyzed C-C

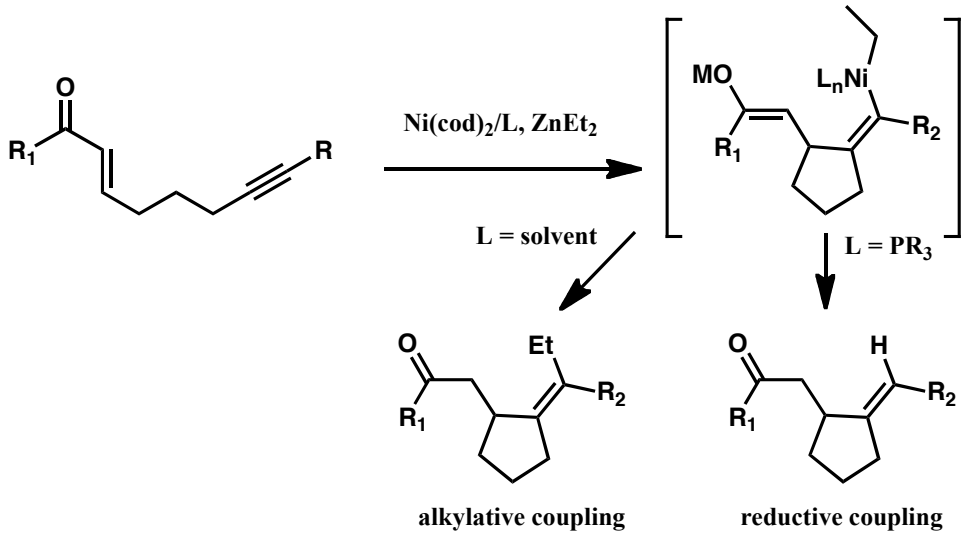


Figure 12. Reductive coupling versus alkylative coupling

bond forming event where a hydrogen atom (reductive coupling) is transferred instead of an alkyl group (alkylative coupling) in the reductive elimination step,[118] as depicted in Figure 12.

Several different classes and variants of transition metal catalyzed reductive couplings have been developed; alkyllithium promoted couplings are not discussed.[126-129] The major focus will be upon nickel catalyzed reductive couplings. Briefly, for selected examples utilizing titanium see Sato;[130-132] which were later extended and expanded by Cha,[133] and Micalizio.[134-137] For selected examples with rhodium, and hydrogen as a reductant, see work by Krische.[138-142] Select examples of cobalt couplings were developed by Cheng.[143-145] Nickel catalyzed variants have mostly been developed by Montgomery[118,119,146] and Jamison;[147] although Chang has also developed select variants, which were reviewed and are not discussed.[145] The methodology has been applied in both inter- and intramolecular couplings. Several variants exist where $Ni(cod)_2$ can be complexed with monodentate phosphines or *N*-heterocyclic carbene (NHC) ligands, and reducing agents such as silane, organozinc, organoborane, or vinylzirconium reagents have been utilized. Several complex molecules have been synthesized using methodology developed in the Montgomery and Jamison labs,[118,119,147] however the focus will be upon nickel complexed with *N*-heterocyclic carbene (NHC) ligands. Although phopshine variants are incredibly powerful and robust reactions, they suffer from one major limitation; terminal alkynes are generally not well tolerated, due to competing alkyne trimerization. In addition, recent computational studies have demonstrated that ligand structure has moderate impact on product regioselectivity in aldehyde-alkyne reductive couplings with Ni(0)-phosphine catalysts and organoborane reducing

agents.[148,149]

In 2004, the Montgomery laboratory developed the nickel-*N*-heterocyclic carbene variant with silane reducing agents. Using this procedure, synthetically useful terminal alkynes were tolerated, as demonstrated in macrocylization reactions with both simple hydrocarbon frameworks and in a total synthesis of aigialomycin D as depicted in Figure 13.[116,150] The Montgomery synthesis of aigialomycin D and the Jamison synthesis of amphidinolide T1, Figure 15, discussed below, represent the previous start of the art approach to complex molecules using catalytic transition metal catalyzed reductive couplings. Strongly electronically biased alkynes are used to set the regiochemistry.

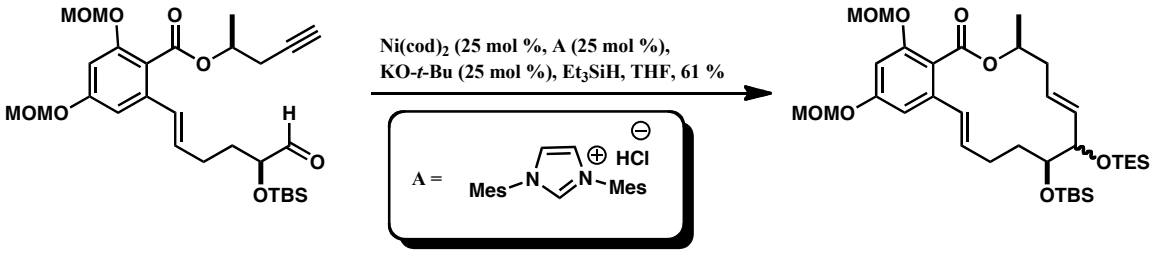


Figure 13. Total synthesis of aigialomycin D featuring a catalytic nickel cyclization cyclization using biased substrates

The mechanism of aldehyde-akyne couplings using an *N*-heterocyclic carbene ligand has been examined computationally[151] and experimentally[152] and is presented in Figure 14. The key step involves formation of the Ni^{II} metallacycle. The regio-selectivity observed in the reaction is determined during this step. The observed product is postulated to be favored due to its ability to better stabilize developing positive charge during metallacycle formation. The Jamison group disclosed an elegant total synthesis of amphidinolide T1 utilizing the previous state of the art solution; the inherent substrate bias of aromatic alkynes is used to synthesize the correct regioisomer resulting from reductive coupling as described in Figure 15.[153]

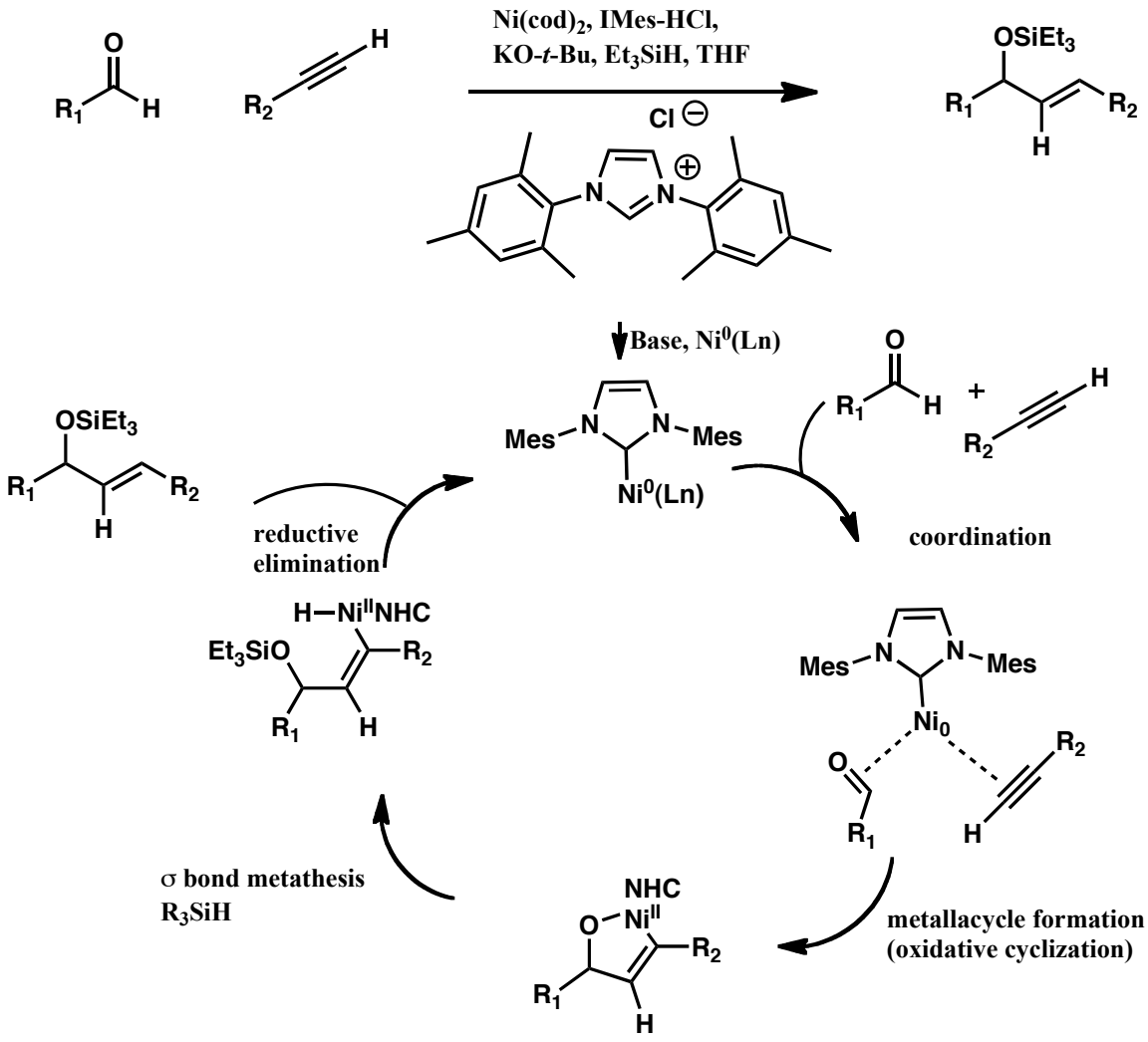


Figure 14. Mechanism of nickel-*N*-heterocyclic carbene aldehyde alkyne cyclization

The control of regiochemistry in unsymmetrical alkynes remained an unsolved problem until very recently in reductive couplings. The current state of the art prior to the 2010 disclosure by the Montgomery laboratory was reviewed,[154] and experimentally documented by Trost and colleagues.[155] Briefly, in most cases of successful addition reactions, the alkynes that are utilized either possesses a strong electronic or steric bias.

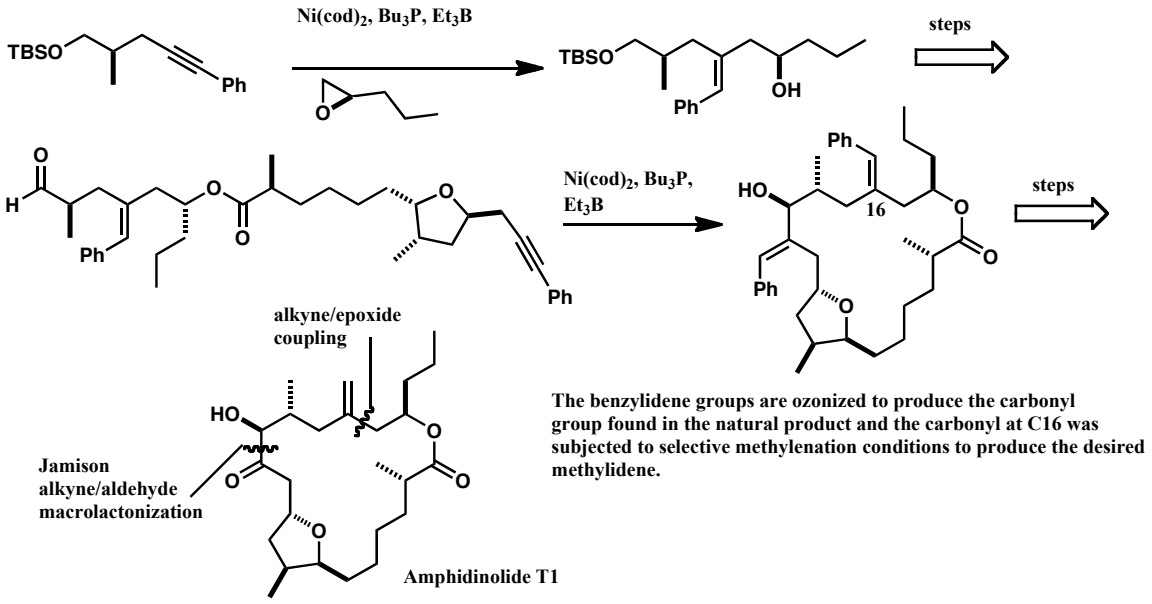


Figure 15. Jamison synthesis of amphidinolide T1 using electronically biased substrates[153]

This substrate control allows products to be prepared in good to excellent regiocontrol; unfortunately only a single reioisomeric product is possible. Alternatively when alkynes that do not possess a strong electronic or steric bias are used in alkyne addition reactions, poor regioselectivity is observed. Classes of alkynes that possess either a strong electronic or steric bias include aromatic alkynes,[118] terminal alkynes[118], silyl alkynes,[118] ynamides,[156] and conjugated diynes[141] and enynes.[140,157,158] In processes that utilize these classes of alkynes, products can be prepared with good to excellent regiocontrol. Another strategy for biasing substrates has involved the utilization of remote directing functionality such as alkenes and alcohols in Ni-catalyzed and Ti-promoted reactions.[154,159-161]

The Montgomery group envisioned a strategy that would provide a general strategy for regiocontrol, whereby the inherent substrate bias could be overridden by appropriate catalyst design. Preliminary studies demonstrated that product regiocontrol

could be modestly impacted by ligand structure; albeit regioselectivities were only modestly synthetically useful.[116,117,162,163]

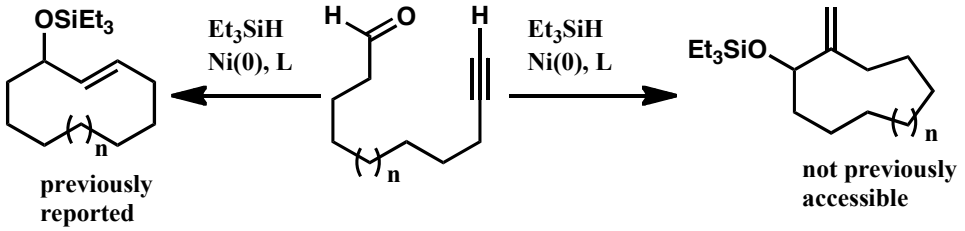


Figure 16. Reductive macrocyclizations of aldehydes with terminal alkynes

Studies disclosed in 2010 addressed and rectified the previous limitations; method development studies were conducted using heptaldehyde with 2-hexyne. Briefly the results demonstrated that selecting the appropriate ligand allows the desired product regiochemistry to be produced. For example, to generate product when C-C bond formation at the less hindered alkyne terminus is desired, the commercially available IMes-HCl ligand should be employed. To generate product when C-C bond formation at the more hindered alkyne terminus is desired, commercially available SIPr ligand is a good choice; however (±)-DP-IPr is the ideal choice of ligand, especially with terminal alkynes.[164] A simple steric model as depicted in Figure 18, whereby reorientation of the alkyne in π-complexes ultimately governs the regiochemistry of the product. The Malik, Sormunen, and Montgomery 2010 communication describes that with careful optimization of ligand structure, the impact of ligand size effect is quite substantial and

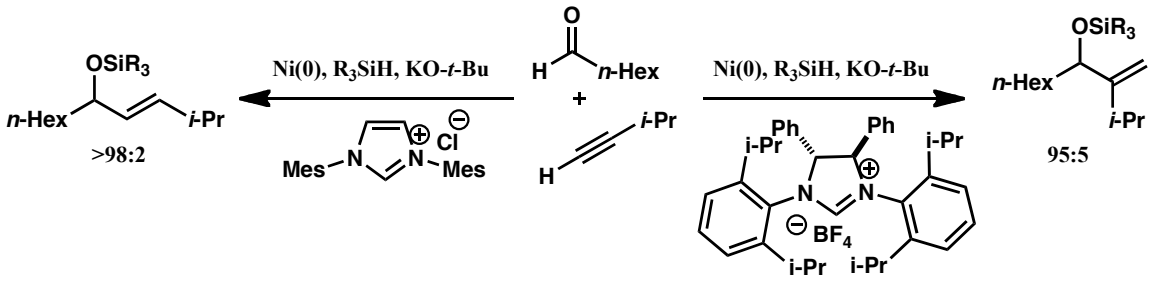


Figure 17. Reversal of regiochemistry based upon selection of ligand

allows the inherent substrate bias to be reversed across a broad range of biased and unbiased alkynes.

Figure 18. Ligand steric model for control of regiochemistry

Studies described in this dissertation involve applying the reversal of regiochemistry with a complex substrate in a macrocyclization reaction. Our ultimate goal is to understand PikC catalyzed hydroxylations, and a substrate where we have altered the role of the position of the olefin, i.e. the allylic position for PikC hydroxylations could serve as a useful tool for studying PikC. In addition, developing a macrocyclization reaction allowing the synthesis of substrates with a 1,1- disubstituted allylic alcohol would be a highly desirable outcome. Current state of the art techniques involve addition of a prefunctionalized olefins such as in Nozaki-Hiyama-Kishi type coupling. Although NHK couplings are incredibly powerful and are often used in complex molecule synthesis, they require the prefunctionalization of the desired olefin, followed by macrolactonization. An example of a Nozaki-Hiyama-Kishi macrocyclization to produce an exo-methylene was described in a natural product synthesis by Kishi.[165] A more contemporary approach to an exo-methylene-allylic alcohol within a natural products was disclosed by the Vanderwal group combining the power of ring closing metathesis in conjunction with an electrophilic desilylation.[166] His group has applied this strategy to a wide range of natural products containing this motif,[167] as described in Figure 19.

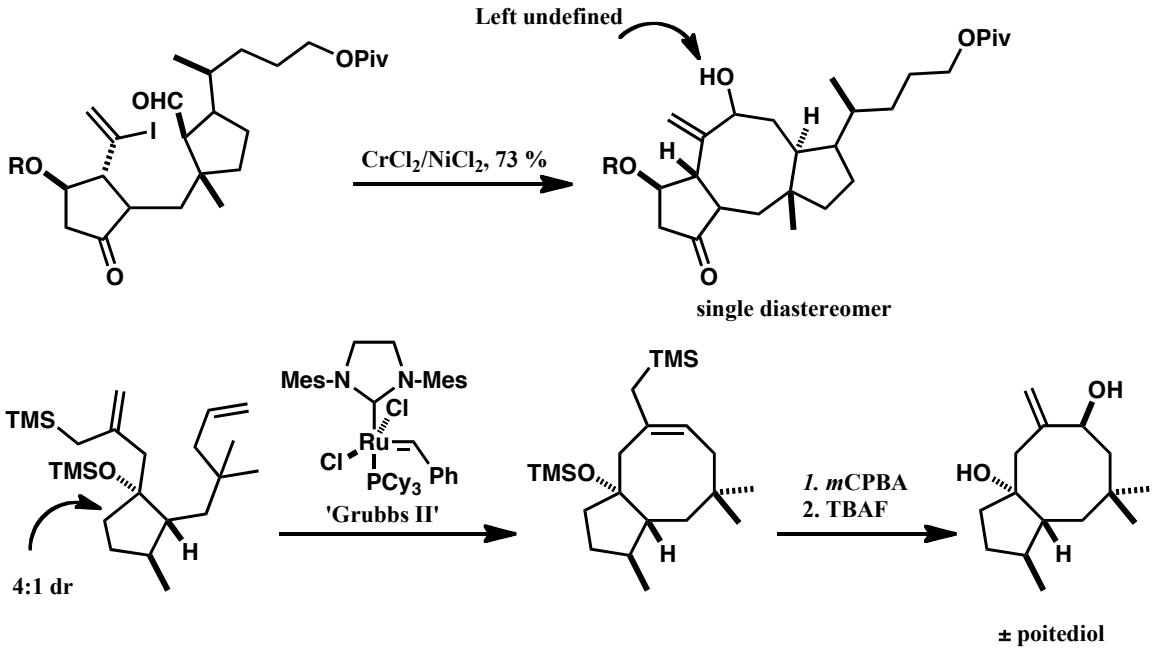


Figure 19. Vanderwal and Kishi synthesis of natural products containing an 1,1-disubstituted allylic alcohol moiety

Although both of these approaches are beautiful and comprise very robust chemistry, we envisioned a direct approach whereby one can disconnect to non-stereodefined starting materials. Our initial goal was to apply this reversal of regiochemistry to our fully functionalized carbon skeleton of the 10-deoxymethynolide ynal precursor. Using the Ni(0)-IMes catalyst system, the endo cyclic allylic alcohol was cleanly obtained. The effect to utilizing the (±)-DP-IPr ligand was initially examined with the same model system used during the 10-deoxymethynolide synthesis. Gratifyingly we were able to cleanly synthesize the 11-membered exo methylene-containing lactone in 52 % yield as a single diastereomer. Applying these conditions towards the fully functionalized carbon skeleton efficiently allowed the synthesis of an 11-membered lactone containing a 1,1-disubstituted allylic alcohol in 59 % yield. Optimized conditions were developed using 30 mol $Ni(cod)_2$, 29 mol % (±)-DP-IPr, and 40 mol % KO-*t*-Bu in 0.01 M THF, as

described in Figure 20.

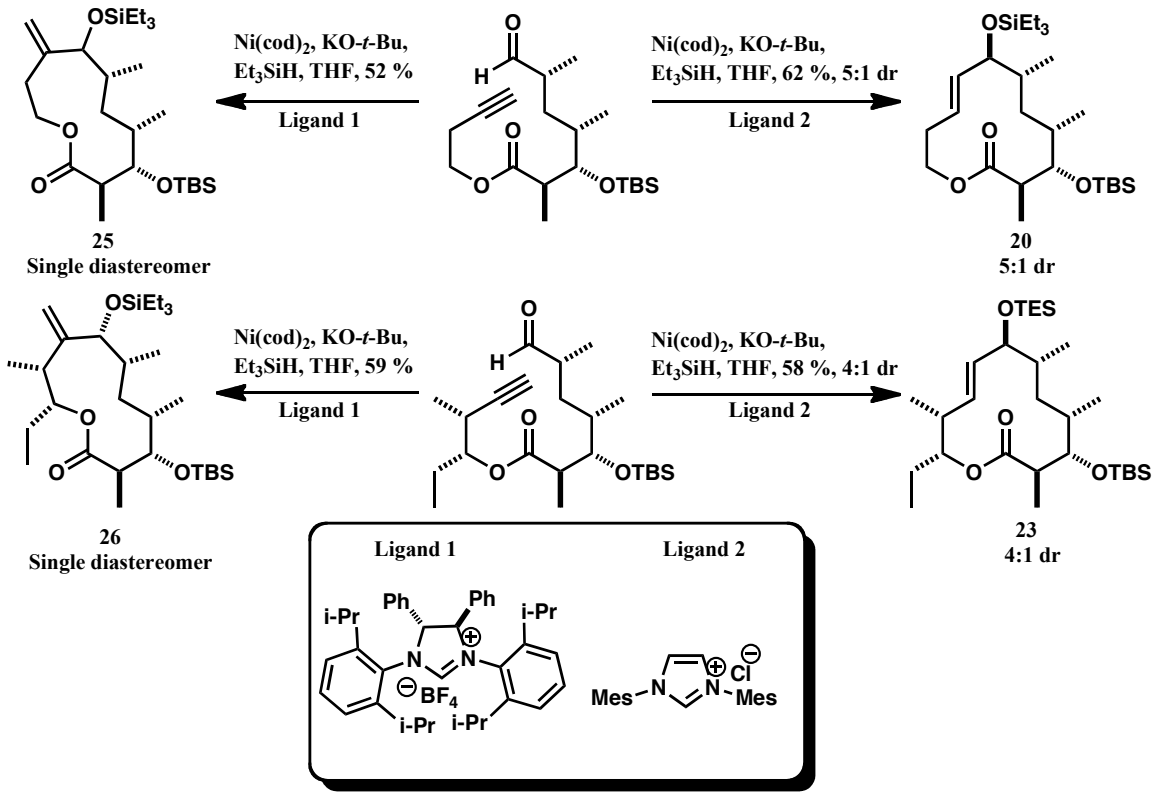


Figure 20. Reversal of regiochemistry in Ni-catalyzed macrocylizations

Understanding the impact of the ligand requires careful analysis of the mechanism of reductive couplings. During the metallacycle formation, having the alkyne substituent positioned next to nickel helps stabilize developing positive charge, and therefore terminal alkynes are strongly electronically biased. The strategy used to reverse this strong electronic bias involved positioning large groups on the *N*-heterocyclic carbene and creating a large steric clash between the alkyl group and the carbene ligand. Therefore only the small group, an acetylenic hydrogen, can be accommodated as depicted in Figure 21.

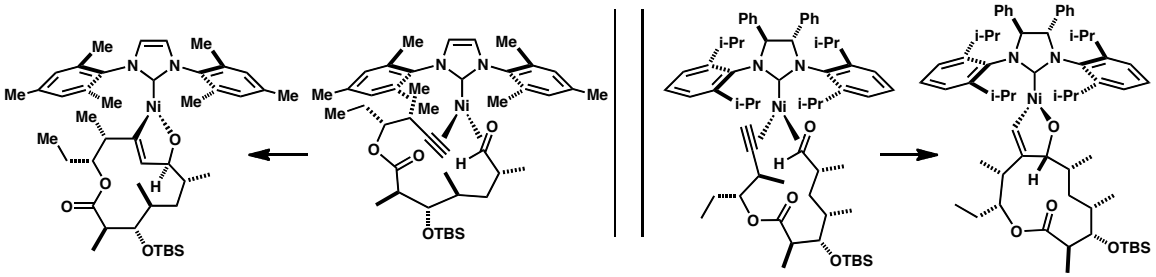


Figure 21. Rationale for regiochemistry reversal

CONCLUSIONS

The collaboration between the Montgomery and Sherman laboratories uniquely allows two laboratories at the cutting edge of two traditionally disparate fields: transition metal catalyzed method development/complex molecule synthesis, in addition, biosynthesis and biocatalytic chemistry, to work synergistically towards the goal of developing more efficient routes to unnatural macrolide analogs. Studies described during this dissertation represent a first step towards this long-term goal.

A modular and flexible total synthesis of YC-17 has been developed featuring a catalytic-nickel ynal cyclization. Synthetic derived YC-17 was subjected to a biocatalytic C-H activation to generate methymycin and neomethymycin. Leveraging key intermediates towards a diverted total synthesis[168] effort will provide substrates that will be utilized in studying hydroxylation pattern in PikC catalyzed reactions. Ultimately we hope to develop a series of rules governing PikC C-H oxidations, and applying this knowledge towards the development of more efficient routes towards analogs of macrolide antibiotics. In addition studies described in this dissertation demonstrated that electronically biased complex substrates can have their inherent bias overridden by appropriate choice of catalyst. Substrates synthesized using this general scheme may provide an avenue to understanding PikC.

In addition, we have developed an efficient approach to the 1,1- disubstituted allylic alcohol moiety; however we have only demonstrated this application in two complex substrates. Future students in the Montgomery laboratory will examine the generality of these findings towards a range of macrocycles containing limited functionality and ring size. A general method to this motif would be a highly desirable outcome.

Future students in the Sherman-Montgomery laboratory will synthesize substrates to probe the hydroxylation pattern in PikC. A general and modular strategy has been developed and can be leveraged to reach substrates that can be utilized to interrogate PikC reactivity patterns. One proposed substrate is presented in Figure 22.

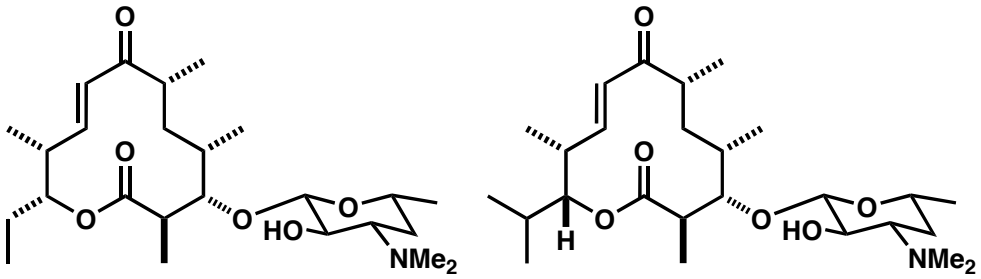


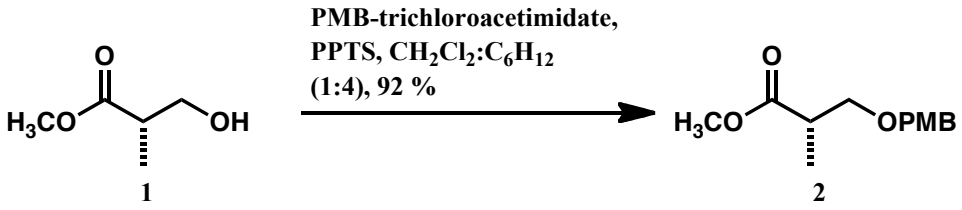
Figure 22. Proposed analog of YC-17.

In conclusion, a total synthesis of methymycin and neomethymycin has been achieved whereby a simpler starting material was transformed utilizing an enzyme to reach fully oxidized final natural products. All previous approaches to methymycin/neomethymycin have utilized the strategy whereby fully oxidized and protected subunits were coupled together followed by macrocyclization and deprotected to produce a final natural product. In addition we have applied a nickel catalyzed macrocyclization utilizing stereo-undefined alkynes to prepare stereo-defined allylic alcohols along with a novel nickel catalyzed macrocyclization to produce 1,1-

disubstituted allylic alcohol containing motifs. Previous approaches utilized prefunctionalized olefins or a multi-step synthesis.

Chapter 4

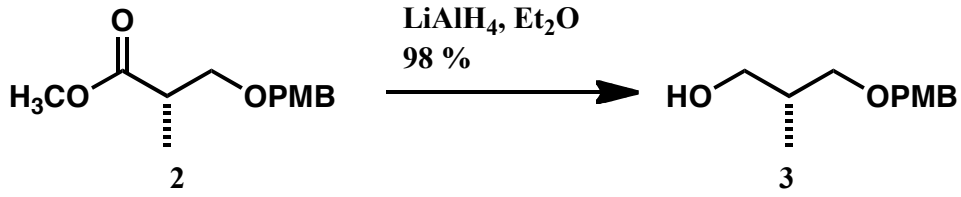
EXPERIMENTAL



(S)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate
To a stirred solution of NaH (0.24 g, 0.010 mmol) in MTBE (75 mL) was added PMB-OH (12 mL, 101. mmol) (neat and dropwise) and stirred at rt for 90 min. Subsequently re-cooled to 0°C, and trichloroacetonitrile (10.2 mL, 101.6 mmol) was added dropwise. The reaction was stirred for 90 min at 0°C, and 30 min at rt. Solvents were removed under reduced pressure. To the resulting crude mixture, a solution of 0.5 mL of MeOH in 250 mL of hexanes was added slowly. Filtered through Celite, solvents were removed under reduced pressure, and used directly without further purification.

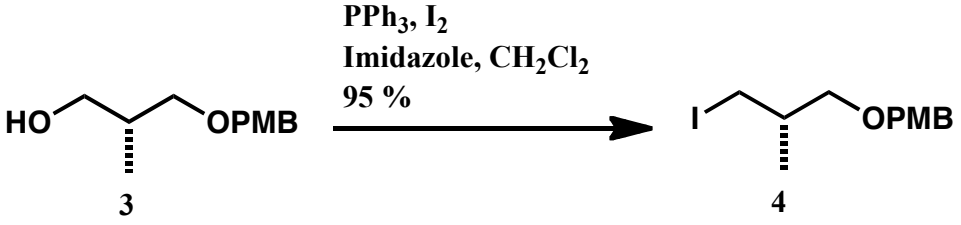
1 (8.0 g, 68 mmol) was dissolved in 100 mL of cyclohexane, and PPTS (1.7 g, 6.8 mmol) was added at rt. Imidate prepared in previous step was dissolved in CH_2Cl_2 (25 mL) and added via cannula. The resulting solution was stirred overnight, and TLC indicated an incomplete reaction; therefore, additional PPTS (1.7 g, 6.8 mmol) was added and stirred for 12 h. An additional portion of PPTS was added (1.7 g, 6.8 mmol) and stirred for 2 h. TLC indicated completion, and crude reaction mixture was filtered through Celite:Silica gel bed with 1:5 EtOAc:hexanes, and concentrated under reduced pressure. The residue

was purified by flash chromatography (1:20 EtOAc:hexanes) to afford the title compound (15 g, 92 %) as a colorless oil. Matched all data as previously reported by Boger and colleagues.[169]



(S)-3-((4-methoxybenzyl)oxy)-2-methylpropan-1-ol

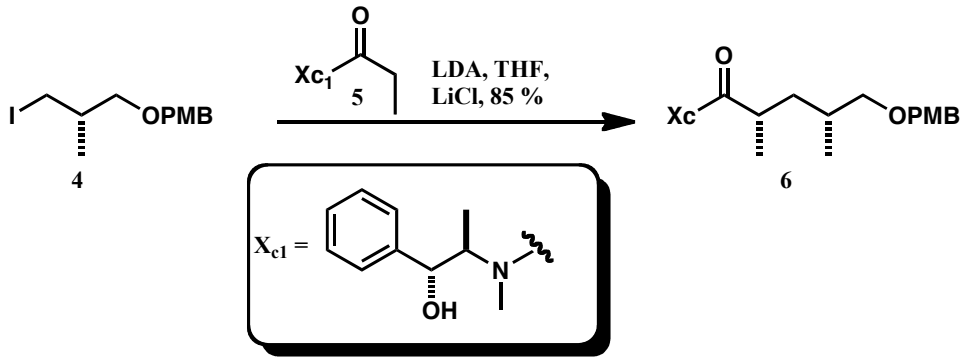
To a suspension of $LiAlH_4$ (4.0 g, 0.11 mol) in Et_2O (50 mL) at 0 °C was added a solution of **2** (10 g, 44 mmol) in Et_2O (50 mL) via cannula. The resulting solution was warmed to rt, and stirred for 18 h. The solution was cooled to 0°C, and reaction was terminated by slow addition of H_2O (25 mL), followed by 1N NaOH (25 mL), during which grey $LiAlH_4$ was converted into white $Al(OH)_3$, and removed via filtration, washed with Et_2O (~300 mL), H_2O (100 mL) was added, and extracted with EtO_2, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5:10 EtOAc:hexanes) to afford the title compound (7.83 g, 98 %) as a colorless oil. Matched all data as previously reported by Boger and colleagues.[169]



(S)-1-((3-iodo-2-methylpropoxy)methyl)-4-methoxybenzene

To a stirred solution of **3** (5.4 g, 30 mmol) in CH_2Cl_2 (150 mL) was added imidazole (5.1 g, 75 mmol), PPh_3 (20 g, 75 mmol), and I_2 (15 g, 60 mmol) at 0 °C, and stirred for 10

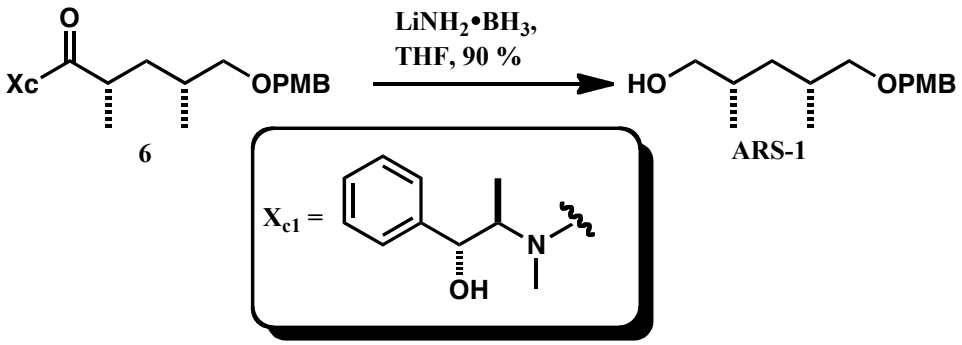
minutes, allowed to warm to rt, and stirred for 6 h. The reaction was terminated by addition of half saturated $Na_2S_2O_3$, extracted with ethyl acetate, washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and purified by flash chromatography (1:15 EtOAc:hexanes) to afford the title compound (8.27 g, 95 %) as a colorless oil. Matched all data as previously reported by Carter and colleagues.[170]



(2S,4R)-5-((4-methoxybenzyl)oxy)-N,2,4-trimethyl-N-((2R,3R)-3-phenylbutan-2-yl)pentanamide

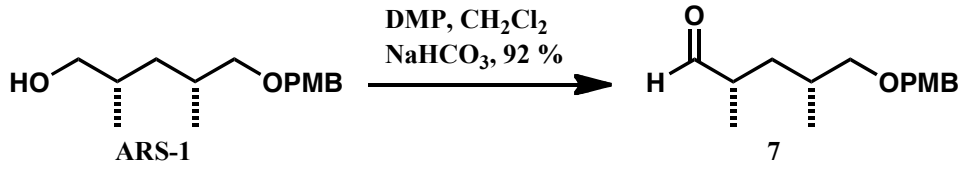
A solution of BuLi (42 mL, 2.5 M) was added to LiCl (11 g, 0.27 mol) and *i*-Pr_2NH (15 mL, 0.11 mol in THF (10 mL) at -78°C. The resulting solution was warmed to 0 °C, and stirred for 15 min, re-cooled to -78 °C to which an ice cooled solution of **5** (12 g, 53 mmol) in THF (50 mL) was added via cannula (slowly dripped down side of flask). The mixture was stirred for 1 h at -78 °C, 0 °C for 15 min, rt for 5 min; after which the flask is re-cooled to 0 °C. A solution of **4** (7.7 g, 26 mmol) in THF (10 mL) is added via cannula, stirred for 30 min at 0 °C, warmed to rt and stirred for 18 h. The flask was cooled to 0 °C and half saturated ammonium chloride was added, extracted with ethyl acetate, washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution from 1:5

EtOAc:hexanes to 2:3 EtOAc:hexanes) to afford the title compound (9.4 g, 85 %) as a colorless oil. Matched all data as previously reported by Carter and colleagues.[170]



(2S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol

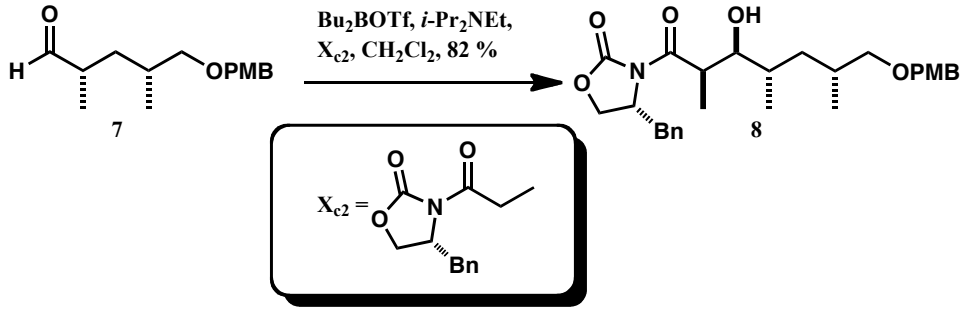
A solution of BuLi (17 mL, 2.5M) was added to a stirred solution of THF (5 mL) and *i*-Pr_2NH (6.1 mL, 44 mmol) at -78 °C, and stirred at -78 °C for 10 min, 0°C for 5 min, and re-cooled to -78 °C. A separate flask was charged with $BH_3•NH_3$ (1.4 g, 44 mmol) and cooled to -78 °C, and previously prepared solution of LDA was added via cannula. The resulting solution was warmed to 0 °C and stirred for 20 min. The cooling bath was removed, and resulting solution was warmed to rt, and stirred for 20 min during which the solution became easy to stir, and was re-cooled to 0°C, and **6** (4.5 g, 11 mmol) in THF (25 mL) was added via cannula, stirred for 20 minutes at 0°C, the cooling bath was removed and stirred at rt for 2 h. The reaction was terminated by addition of 3N HCl (added slowly), extracted with EtOAc, washed combined organic extracts with 2N NaOH, water, dried with MgSO4, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (2.5 g, 90 %) as a colorless oil. Matched all data as previously reported by Sherman and colleagues.[7]



ARS-1 7

(2*S*,4*R*)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal

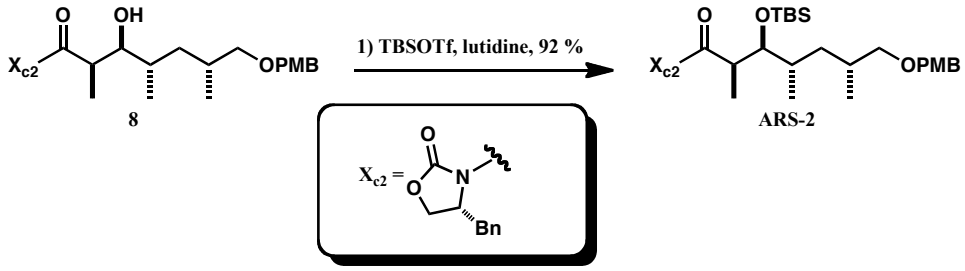
A solution of **ARS-1** (1.4 g, 5.6 mmol) and $NaHCO_3$ (2.4 g, 29 mmol) in CH_2Cl_2 (70 mL, non anhydrous) was cooled to 0 °C, and DMP (3.0 g, 8.4 mmol) was added slowly and stirred for 3 h. The reaction was terminated by addition of a 1:1 solution of half-saturated aqueous $Na_2S_2O_3$ and half-saturated aqueous $NaHCO_3$ and vigorously stirred for 0.5 h, extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (1.3 g, 92 %) as a colorless oil. Matched all data as previously reported by Kang and colleagues.[172]



(*R*)-4-benzyl-3-((2*R*,3*S*,4*S*,6*R*)-3-hydroxy-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoyl)oxazolidin-2-one

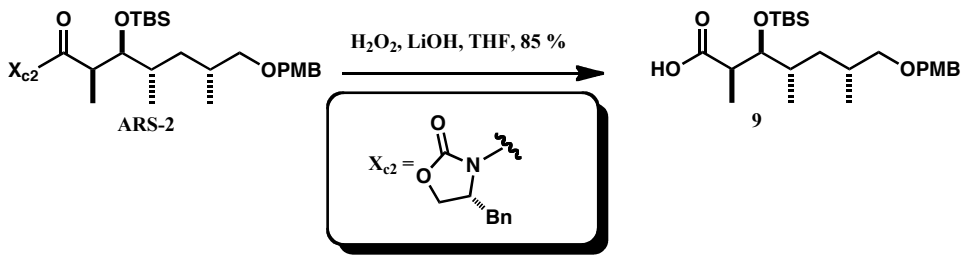
To a solution of $\mathbf{X_{c2}}$ (1.6 g, 6.84 mmol) in CH_2Cl_2 (30 mL) at 0 °C, was added neat dibutylboron triflate (2.3 mL, 9.10 mmol), and stirred for 15 min. The solution was cooled to -78 °C, *i*-Pr_2NEt (1.6 mL, 9.1 mmol) was added drop-wise, stirred for 15 min, warmed to 0 °C, and stirred for 1 h, followed by cooling to -78 °C. An ice-cooled

solution of **7** (1.1 g, 4.6 mmol) in CH_2Cl_2 (5 mL) was added drop-wise (dripped down side of flask). The solution was stirred at -78 °C for 2 h, at -20 °C for 1 h, and was terminated by addition of pH = 7 phosphate buffer. To this cloudy solution was added 50 mL of (1:3) 30 % hydrogen peroxide:MeOH solution, the reaction vessel was removed from cooling bath and stirred for 3 h at rt, extracted with CH_2Cl_2, washed with half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (3.5:10 EtOAc:hexanes) to afford the title compound (1.8 g, 82 %) as a colorless oil. Matched data as previously reported by Kang and colleagues.[172]



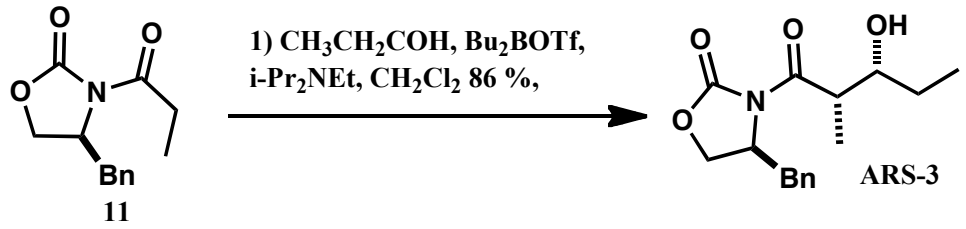
(*R*)-4-benzyl-3-((2*R*,3*S*,4*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoyl)oxazolidin-2-one

To a solution of **8** (1.5 g, 3.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added 2,6-lutidine (0.69 mL, 5.9 mmol) and TBSOTf (1.1 mL, 4.7 mmol). The reaction mixture was stirred at 0 °C for 4 h, terminated by addition of half-saturated aqueous $NaHCO_3$, and allowed to warm to rt. Extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:10 EtOAc:hexanes) to afford the title compound (1.7 g, 92 %) as a colorless oil. Matched data as previously reported by Kang and colleagues.[172]



(2*R*,3*S*,4*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoic acid

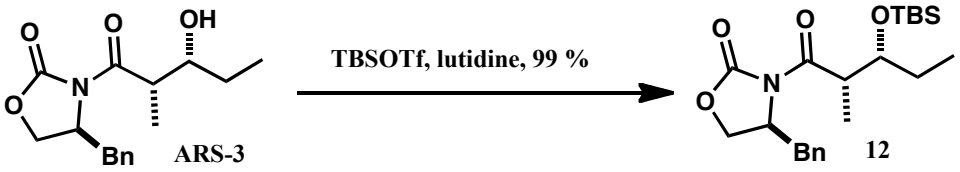
To a solution of **ARS-2** (0.71 g, 1.2 mmol) in (4:1) THF:water (2 mL) to was added 30% H_2O_2 (600 μL) and 0.8M LiOH (0.08 g, 1.9 mmol) at 0 °C and stirred for 5 h, quenched by adding aqueous Na_2SO_3 (1.3 M, 3 mL) and half-saturated aqueous NH_4Cl (4 mL). Extracted with ethyl acetate, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5:10 EtOAc:hexanes) to afford the title compound (0.44 g, 85 %) as a colorless oil. Matched data as previously reported by Kang and colleagues.[172]



(S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one

To a solution of **11** (12 g, 52 mmol) in CH_2Cl_2 (75 mL) at 0 °C was added Bu_2BOTf (20 mL, 78 mmol), and stirred for 5 min, followed by slow addition of *i*-Pr_2NEt (18 mL, 0.10 mol). The resulting mixture was stirred at 0 °C for 30 min followed by cooling to -78 °C. A solution of propanal (7.6 mL, 0.10 mol) in CH_2Cl_2 (5 mL) was added slowly (dripped down side of flask), and stirred at -78 °C for 30 min, and 1 h at 0 °C. Reaction was

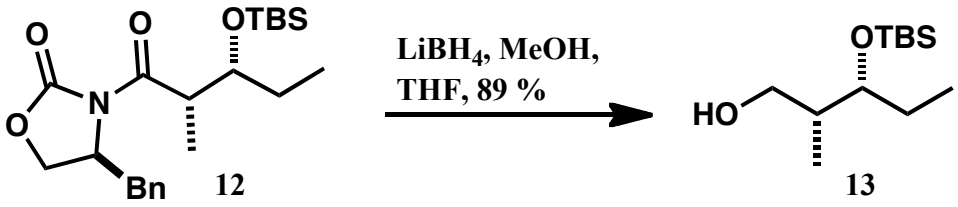
terminated by addition of pH = 7 phosphate buffer, followed by slow addition of a 30 % H_2O_2:MeOH (1:3, 40 mL), and stirred at rt for 3 h, extracted with ethyl acetate, washed with half-saturated aqueous NaCl, dried with $MgSO_4$, and solvents were removed under reduced pressure. The crude solid was recrystallized using EtOAc:hexanes (1:2) solvents were removed from mother liquor and the residue was purified by flash chromatography (3:20 EtOAc:hexanes) to afford title compound as a colorless solid, (13 g, 86%). Matched data as reported by Evans and colleagues.[173]



(S)-4-benzyl-3-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentanoyl)oxazolidin-2-one

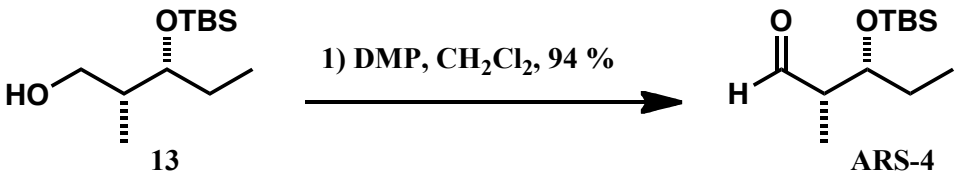
To a solution of **ARS-3** (9.2 g, 32 mmol) in CH_2Cl_2 (115 mL) at 0°C was added 2,6-lutidine (7.4 mL, 64 mmol) and TBSOTf (16 mL, 64 mmol). The reaction mixture was stirred at 0°C for 4 h, quenched with half-saturated aqueous $NaHCO_3$, and allowed to warm to rt. Extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (13 g, 99 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.21, (m, 5H), 4.60 (ddd, *J* = 3, 6.5, 9.5 Hz, 1H), 4.18-4.14 (m, 2H), 3.96 (app. q, J = 5.5, 11 Hz, 1H), 3.89 (app. q, J = 6.5, 11Hz, 1H), 3.31 (dd, *J* = 3, 13.5 Hz, 1H), 2.77 (dd, *J* = 9.5, 13 Hz, 1H), 1.61-1.53 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.91-0.88 (m, 12H), 0.03 (s, 3H), 0.01 (s, 3H)^{13}C NMR (126 MHz, $CDCl_3$) δ 175.59, 153.27, 135.61, 129.67, 129.15, 127.53, 73.98, 66.19, 56.03, 42.44, 37.82, 28.35, 26.02, 18.26, 11.67, 9.58, -3.94,

-4.66. Also reported by Liu, H.-W.[174]



(2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentan-1-ol

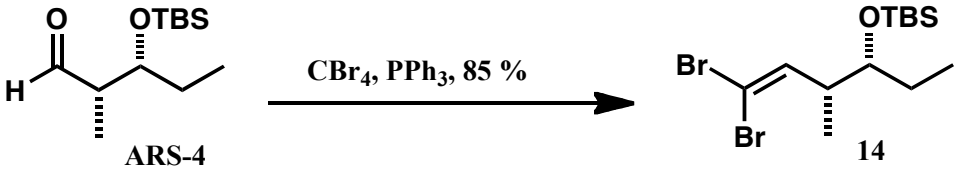
To a stirred solution of **12** (4 g, 9.9 mmol) in THF at 0 °C was added MeOH (1.2 mL, 30 mmol) followed by slow addition of $LiBH_4$ (15 mL, 30 mmol), during which evolution of gas was observed. The resulting mixture was stirred at 0 °C for 10 min, and stirred at rt for 2 h. The reaction was terminated by addition of 1N NaOH (30 mL), poured into water (30 mL), extracted with ethyl acetate, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (2.0 g, 89 %) as a colorless oil. Matched data as previously reported by Das, P.[175]



(2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentanal

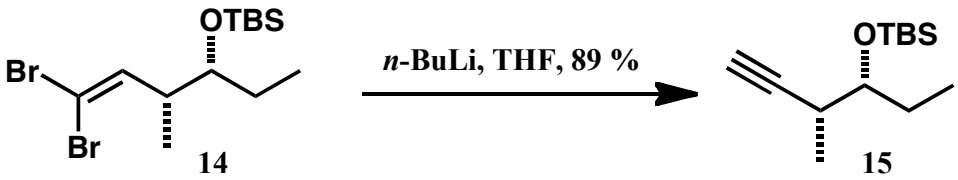
To a solution of **13** (1.1 g, 4.7 mmol) and $NaHCO_3$ (1.9 g, 24 mmol) in CH_2Cl_2 (30 mL, non anhydrous) cooled to 0°C, was added DMP (3.2 g, 7.5 mmol) (slowly added portion

wise) and stirred for 3 h. The reaction was terminated by addition of a 1:1 solution of half-saturated aqueous $Na_2S_2O_3$ and half-saturated aqueous $NaHCO_3$ and vigorously stirred for 0.5 h, extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (1:5 EtOAc:hexanes) to afford the title compound (1.0 g, 94%) as a colorless oil. The title compound was used immediately as chiral alpha branched aldehydes tend to be unstable.



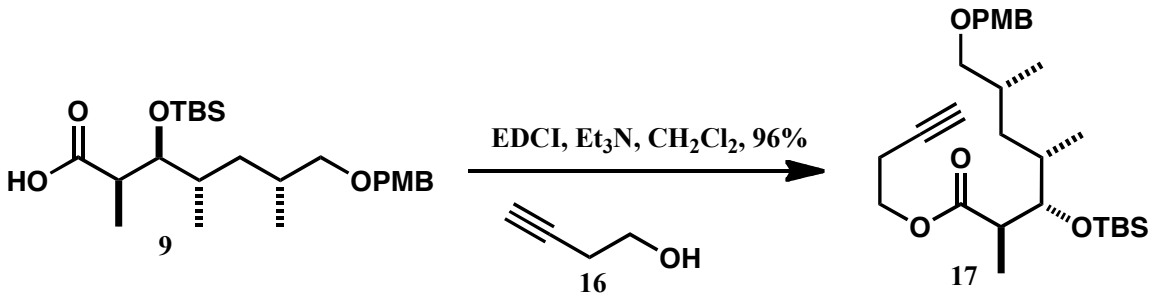
tert-butyl((3R,4R)-6,6-dibromo-4-methylhex-5-en-3-yloxy)dimethylsilane

To a solution of PPh_3 (2.3 g, 8.2 mmol) and Zn dust (0.54 g, 8.2 mmol) in 50 mL of CH_2Cl_2 was added CBr_4 (2.7 g, 4.1 mmol) and stirred for 15 min at rt. A solution of **ARS-4** (0.94 g, 4.1 mmol) in 10 mL of CH_2Cl_2 was added drop-wise, and stirred for 18 h, poured into hexanes, filtered through Celite and purified by flash chromatography (100 % hexanes) to afford title compound as a colorless oil (1.3 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, *J* = 9.5 Hz, 1H), 3.53 (app. q, J = 5.5, 1H), 2.54 (dquint., *J* = 2.5, 7.0 Hz, 1H), 1.45 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 – 0.85 (m, 12H), 0.03 (s, *3*H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 87.6, 75.4, 42.4, 27.7, 26.1, 18.3, 13.3, 9.7, -4.0, -4.5. HMRS calcd for $C_{13}H_{26}Br_2OSi$ $[M - H]^+$ 383.0052, found 383.0041.



***tert*-butyldimethyl(((3*R*,4*R*)-4-methylhex-5-yn-3-yl)oxy)silane**

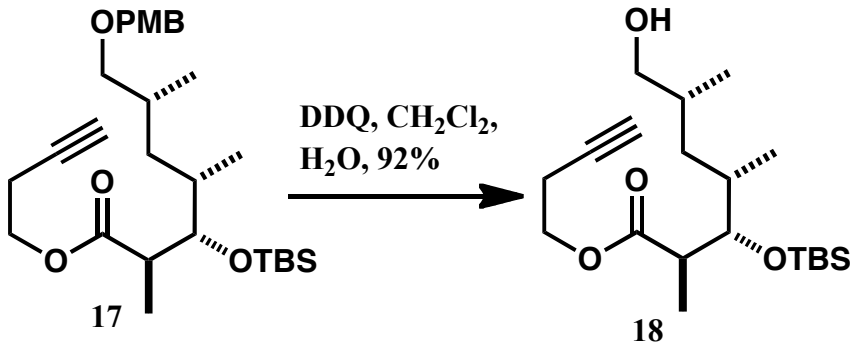
To a solution of **14** (1.60 g, 4.1 mmol) in THF (40 mL) cooled to -78 °C was added butyl lithium (7.0 mL, 2.4M) drop-wise. Reaction was stirred at -78 °C for 3 h and 0 °C for 3 h, terminated by addition water, extracted with ethyl acetate, washed with half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:20 EtOAc:hexanes) to afford the title compound (0.89 g, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) 3.58 (app. q, J = 5.5, 11 Hz) 2.56 (dquint., *J* = 2.0, 5.6 Hz, 1H), 2.04 (d, *J* = 2.4 Hz, 1H), 1.74 (m, 1H), 1.58 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.92 (m, 12H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 87.58, 76.26, 69.64, 31.58, 27.41, 26.27, 18.54, 17.41, 9.05, -3.95, -4.14. HMRS calcd for $C_{13}H_{26}OSi$ $[M - {}^tBu]^+$ 169.1049, found 169.1052.



(2*R*,3*S*,4*S*,6*R*)-but-3-yn-1-yl 3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoate

To a solution of **16** (0.740 g, 1.05 mmol) DMAP (1 crystal), **EDCI** (0.100 g, 0.522 mmol), and Et_3N (60.0 μL, 0.520 mmol) in 2 mL of CH_2Cl_2 was added a solution of **9** (0.183 g, 0.417 mmol) in 0.5 mL of CH_2Cl_2. The resulting solution was stirred at rt of 6 h, and the reaction was terminated by addition of 1N HCl (2 mL), extracted with ethyl acetate, washed with half-saturated NaCl, 1N HCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography

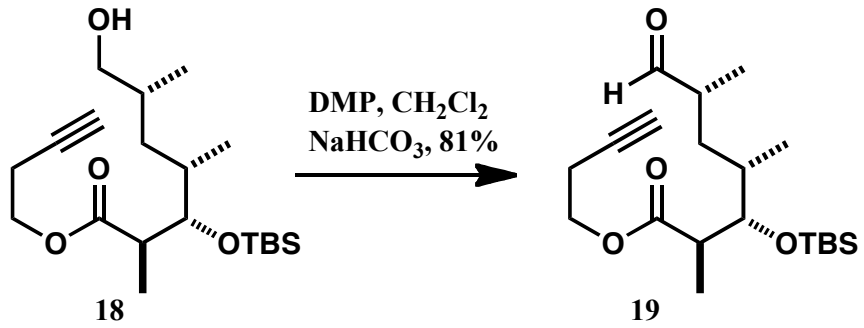
(1:10 EtOAc:hexanes) to afford the title compound (0.196 g, 96%) as a colorless oil. ^{1}H NMR ^{1}H NMR (400 MHz, $CDCl_3$) 7.24 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 4.41 (app. t, J = 12.4 Hz, 2H, 4.18-4.07 (m, 2H), 3.81 (app. t, J = 4.8 Hz, 1H), 3.81 (s, 3H), 3.31 (dd, J = 9.0, 4.6 Hz), 3.13 (dd, J = 7.2, 2Hz, 1H), 2.61 (quint. J = 6.6 Hz, 1H), 2.50 (dquint. J = 2.8, 7.2 Hz, 2H), 1.98, (t, 2.6 Hz, 1H), 1.85-1.8 (m, 1H), 1.71-1.67 (m, 1H), 1.56 (s, 3H), 1.43 (ddd, J = 4.8, 8.0, 13.4 Hz, 1H), 1.15 (d, J = 7.2 Hz, 2H), 0.97-0.88 (m, 16H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 159.2, 131.1, 129.3, 113.9, 80.3, 75.5, 72.9, 70.1, 62.2, 55.5, 42.4, 37.1, 36.8, 31.2, 26.2, 19.1, 19.0, 18.5, 16.3, 13.6, -3.9, -4.1. HMRS calcd for $[C_{28}H_{46}O_5SiNa]^+$ 513.3007, found 555.3009.



(2*R*,3*S*,4*S*,6*R*)-but-3-yn-1-yl 3-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-2,4,6-trimethylheptanoate

To a solution of **17** (0.178 g, 0.363 mmol) in H_2O (0.3 mL) and CH_2Cl_2 (3 mL) was added DDQ (0.164 g, 0.726 mmol) at rt and the resulting solution was stirred for 4 h, diluted with CH_2Cl_2 (5 mL), aqueous half saturated $NaHCO_3$, and extracted with CH_2Cl_2, washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution from 1:10 EtOAc:hexanes to 1:5 EtOAc:hexanes) to afford the title compound (0.124 g, 92%) as a colorless oil. ^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$) 4.13 (ddddd, J = 7.5, 10.5, 13.3, 17.3, 23.7 Hz, 2H),

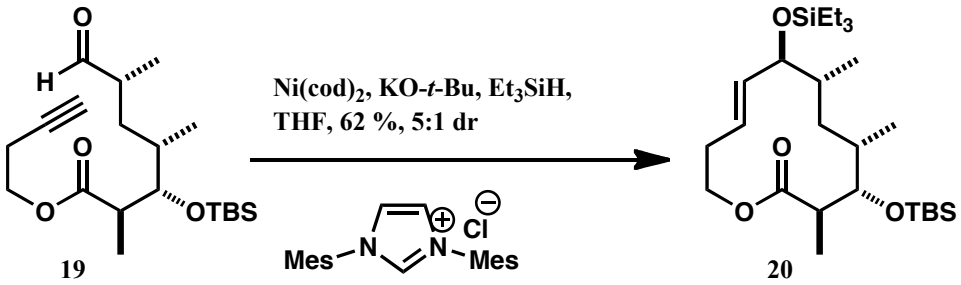
3.83 (dd, *J* = 3.5, 6.0 Hz), 3.45-3.37 (m, 2H), 2.63 (quint. *J* = 7 Hz, 1H), 2.51 (ddd, *J* = 3, 7, 9.5 Hz), 1.97 (t, *J* = 2.5 Hz, 1H), 1.66-1.63 (m, 3H), 1.44 (ddd, *J* = 5.5, 8.5, 14.0 Hz, 1H), 1.23 (s, 1H), 1.13 (d, *J* = 7 Hz, 3H), 0.94-0.87 (m, 16H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 80.3, 70.1, 67.6, 62.4, 42.8, 36.3, 35.8, 33.2, 29.9, 26.2, 19.1, 18.5, 18.3, 16.9, 14.1, -3.8, -4.0. HMRS calcd for $[C_{20}H_{38}O_4Si]^+$ 370.2539, found 370.2540.



18 19

(2*R*,3*S*,4*S*,6*R*)-but-3-yn-1-yl 3-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethyl-7-oxoheptanoate

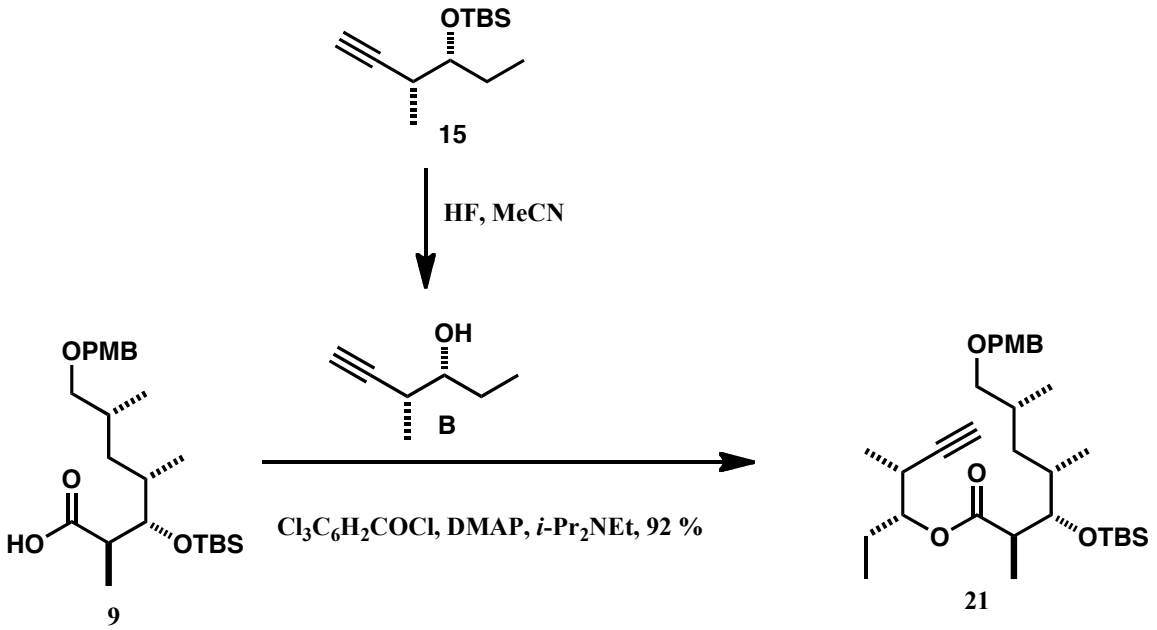
To a solution of **18** (0.059 g, 0.159 mmol) and NaHCO3 (0.63 g, 0.795 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added DMP (0.122 g, 0.287 mmol) in one portion. The reaction was stirred for 4 h at 0 °C, and terminated by addition of 1:1 solution of half-saturated $Na_2S_2O_3$ and half-saturated $NaHCO_3$ (5 mL) and then vigorously stirred for 0.5 h, extracted with CH_2Cl_2, washed with half-saturated $NaHCO_3$, half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure to yield crude **19** (0.047 g, 81 %) as a colorless oil. The produce was used immediately without characterization as chiral alpha branched aldehydes are often unstable.



(3*R*,4*S*,5*S*,7*R*,8*S*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-3,5,7-trimethyl-8-((triethylsilyl)oxy)oxacyclododec-9-en-2-one

In a glovebox $Ni(cod)_2$ (0.005 g, 30 mol %), **A** (IMes-HCl) (0.006 g, 29 mol %), and KO-*t*-Bu (0.002 g, 40 mol %), were charged to a round-bottom flask, removed from the glovebox, THF (2 mL) was added and stirred for 10 min at rt. Neat triethylsilane (17 μL, 0.11 mmol) was added, followed by syringe drive addition of **19** (0.020 g, 0.054 mmol) in THF (2 mL) over three hours, the reaction was stirred for 12 h at rt. The septum was removed from the round bottom, stirred for 1 h in open atmosphere. Solvents were concentrated, and the residue was purified by flash chromatography (1:50 EtOAc:hexanes) to afford the title compound {a 5:1 mixture of C7 diastereomers as judged by comparing integration of the signals at 4.90 (major) 4.65 (minor)} (0.026 g, 62 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56-5.51 (m 1H), 5.3.4-5.28 (m, 1H), 4-94-4.90 (m, 1H), 4.30-4.26 (m, 1H), 3.99 (dd, J = 5.0 9.0 Hz, 1H), 3.63 (d, *J* = 9 Hz), 2.58-2.52 (m, 1H), 2.38-2.33 (m, 3H), 1.73-1.70 (m, 2H), 1.63-1.53 (m, 5H), 1.35-1.31 (m, 7H), 1.17-1.1 (m, 6H), 0.9-0.86 (m, 37H), 0.56-0.51 (m, 8H), 0.05 (s, 3H), 0.04 (s, 3H). Combined integrals for major and minor isomers are reported in regions where resolution is poor. ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 131.1, 129.0, 74.2, 68.37, 60.41, 44.1, 39.0, 32.3, 30.6, 29.3, 29.1, 26.4, 23.2, 18.8, 17.2, 15.5, 14.3, 11.2, 7.1, 5.2, 1.3, -3.0, -3.1. All resolved carbon signals for the major and minor diastereomers are

reported, and unless noted, integrations refer to mixture of C7 diastereomers. HMRS calcd for : $C_{29}H_{58}O_4Si_2$ 526.3874 found 526.3866.

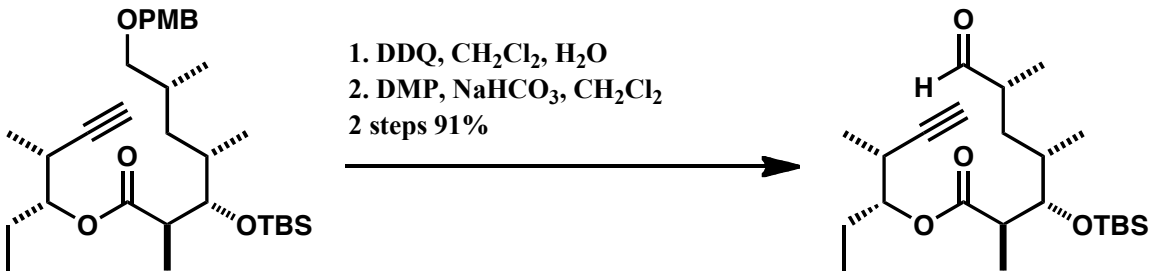


(2*R*,3*S*,4*S*,6*R*)-(3*R*,4*R*)-4-methylhex-5-yn-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoate

To a solution of 48% HF (3.2 mL), MeCN (5 mL), and water (2 mL) at 0 °C was added **15** (0.64 g, 2.8 mmol), in MeCN (10 mL). The resulting solution was removed from ice bath and stirred at rt for 3 h, and carefully transferred to a separatory funnel, washed with half-saturated aqueous $NaHCO_3$, extracted with diethyl ether, dried with $MgSO_4$, and concentrated under reduced pressure while cooling flask in an ice bath (CAUTION: resulting alkyne was volatile, caution must be exercised when removing solvents). The residue is dissolved in THF, dried with molecular sieves, and used without characterization.

To a solution of **9** (0.22 g, 0.50 mmol) in THF (2 mL) at rt was added *i*-Pr_2NEt (96 μL, 0.55 mmol), trichlorobenzoyl chloride (78 μL, 0.5 mmol) and stirred for 1 h. A separate flask was charged with **B** and DMAP (0.122 g, 1.0 mmol) in THF (1.5 mL) and was

added via cannula to activated acid. The resulting solution was stirred for 18 h, quenched with aqueous half-saturated NH_4Cl, extracted with EtOAc, washed with half-saturated aqueous NaCl, dried with $MgSO_4$, and solvents were removed under reduced pressure. The residue was purified by flash chromatography (1:10 EtOAc:hexanes) to afford the title compound (0.24 g, 92 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.71 (app. q, J = 6.0, 1H), 4.39 (s, 2H), 3.88 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.78 (s, 3H), 3.31 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.10 (app. t, *J* = 7.4 Hz, 1H), 2.73 (dquint., *J* = 2.4, 6.8 Hz, 1H), 2.59 (quint., *J* = 6.8 Hz, 1H), 2.03 (d, *J* = 2.8 Hz, 1H), 1.86-1.76 (m, 2H), 1.74-1.69 (m, 3H), 1.39 (ddd, *J* = 4.8, 8.0, 13.4 Hz, 1H), 1.14 (d, *J* = 8 Hz, 6H), 0.95 – 0.9 (m, 9H), 0.87-0.86 (m, 9H), 0.034 (s, 3H), 0.026 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 159.0, 131.0, 129.1, 113.8, 85.1, 76.8, 76.0, 75.4, 72.7, 70.3, 55.3, 42.6, 36.9, 36.5, 31.1, 29.7, 26.1, 23.7, 18.9, 18.4, 17.2, 16.4, 14.6, 9.6, -4.06, -4.08. HMRS calcd for $[C_{31}H_{52}O_5SiNa]^+$ 555.3476, found 555.3476.



21 **22**

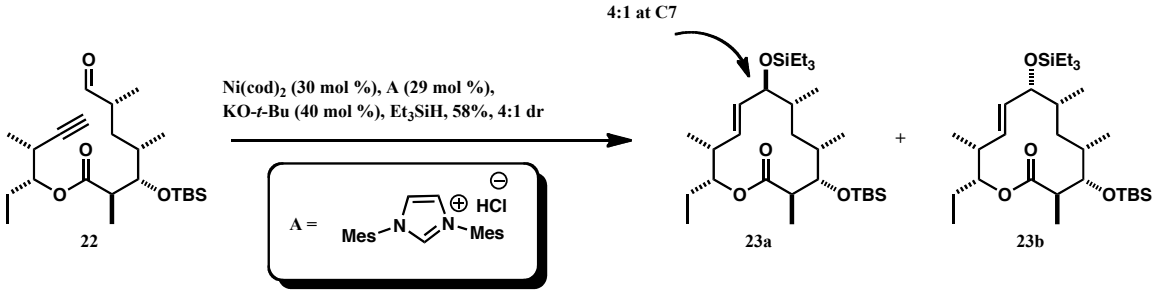
(2*R*,3*S*,4*S*,6*R*)-(3*R*,4*R*)-4-methylhex-5-yn-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethyl-7-oxoheptanoate

To a solution of **21** (0.12 g, 0.22 mmol) in water (0.5 mL), and CH_2Cl_2 (5 mL) at rt was added DDQ (0.10 g, 0.45 mmol), the biphasic mixture was stirred for 4 h, diluted with CH_2Cl_2 (5 mL), and washed with aqueous half-saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with water, dried with $MgSO_4$, and solvents were removed under

reduced pressure. The residue was purified by flash chromatography (1:20 hexanes:EtOAC); however, desired compound co-eluted with anisaldehyde and contaminated material was carried forward.

To a solution of previously prepared mixture in CH_2Cl_2 (10 mL, non-anhydrous) and $NaHCO_3$ (0.092 g, 1.1 mmol), at 0 °C was added DMP (0.168 g, 0.40 mmol) in one portion, and was stirred at 0 °C for 4 hours. The reaction was quenched by addition a 1:1 solution of half-saturated $Na_2S_2O_3$ and half-saturated $NaHCO_3$ (5 mL) and then vigorously stirred for 0.5 h, extracted with CH_2Cl_2, washed with half-saturated $NaHCO_3$, half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:20 EtOAc:hexanes) to afford the title compound (0.082 g, 91 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 2.4 Hz, 1H), 4.69 (ddd, *J* = 4.8, 6.0, 7.6 Hz, 1H), 3.87 (dd, *J* = 7.2, 4.0 Hz, 1H), 2.75 (ddq, *J* = 2.4, 6.9, 13.0, 1H), 2.62 (quint., *J* = 7.0 Hz, 1H), 2.42 (m, 1H), 2.04 (d, *J* = 2.8 Hz, 1H), 1.84 (ddd, *J* = 4.0, 8.8, 13.6 Hz, 1H), 1.72- 1.60 (m, 4H), 1.17-1.14 (m, 6H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.93 – 0.87 (m, 15H), 0.05 (s, *3*H), 0.04 (s, 3H).

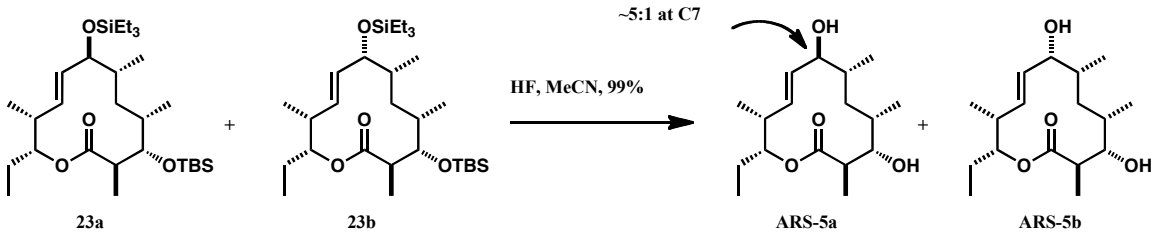
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3, 175.6, 85.1, 77.2, 76.4, 70.4, 44.3, 43.2, 36.8, 33.2, 29.8, 26.3, 23.7, 18.6, 17.2, 16.6, 15.0, 14.8, 9.88, -3.79, -3.84. HMRS calcd for $[C_{23}H_{42}O_4SiNa]^+$ 433.2745, found 433.2746. Note: Title compound was only isolated and characterized as previous compound was impure; chiral alpha branched aldehydes are often unstable. Care should be exercised when handling enantio-enriched aldehydes.



(3*R*,4*S*,5*S*,7*R*,11*R*,12*R*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-12-ethyl-3,5,7,11-tetramethyl-8-((triethylsilyl)oxy)oxacyclododec-9-en-2-one

In a glovebox $Ni(cod)_2$ (0.007 g, 30 mol %), **A** (IMes-HCl) (0.008 g, 29 mol %), and KO-*t*-Bu (0.004 g, 40 mol %), were charged to a round-bottom flask, removed from the glovebox, THF (9 mL) was added and stirred for 10 min at rt. Neat triethylsilane (27 μL, 0.17 mmol) was added, followed by syringe drive addition of **22** (0.035 g, 0.085 mmol) in THF (1 mL) over three hours, the reaction was stirred for 12 h at rt. The septum was removed from the round bottom, stirred for 1 h in open atmosphere. Solvents were concentrated, and the residue was purified by flash chromatography (1:50 EtOAc:hexanes) to afford the title compound {a 4:1 mixture of C7 diastereomers as judged by comparing integration of the signals at 5.00 (major) 5.05 (minor)} (0.026 g, 58 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (dd, J = 15.4, 4.2 Hz, 1H), 5.41 (dd, J = 15.6, 1.8 Hz, 1H), 5.01 – 4.97 (m, 1H), 4.00 (m, 1H), 3.63 (d, J = 9.6 Hz, 1H), 2.58 – 2.41 (m, 2H), 1.89-1.85 (m, 1H), 1.80 – 1.76 (m, 2H), 1.67 – 1.48 (m, 5H), 1.34–1.24 (m, 3H), 1.03 –1.01 (m, 4H), 0.96 – 0.94 (m, 3H), 0.93-0.92 (m, 8H), 0.91-0.89 (m, 8H), 0.88-0.86 (m, 16H), 0.62 – 0.45 (m, 9H), 0.05-0.04 (m, 9H). Combined integrals for major and minor isomers are reported in regions where resolution is poor. ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 131.5, 128.6, 79.5, 77.4, 75.6, 44.1, 37.8, 36.5, 33.6, 32.8, 26.5, 26.47, 24.9, 20.6, 18.8, 18.4, 17.6, 10.8, 10.6, 7.2, 7.1, 5.22, 5.08, -2.98, -3.09. Diagnostic signals for the minor diastereomer include the following: 5.51-5.48 (m, 2H)

and 5.10 (m, 1H), and for major diastereomer include 5.66 (dd, J = 15.6, 4.2 Hz, 1H), 5.41 (dd, J = 15.5, 1.6 Hz, 1H), and 5.01-4.97 (m, 1H). All resolved carbon signals for the major and minor diastereomers are reported, and unless noted, integrations refer to mixture of C7 diastereomers. HMRS calcd for : $C_{29}H_{58}O_4Si_2$ 526.3874 found 526.3866.

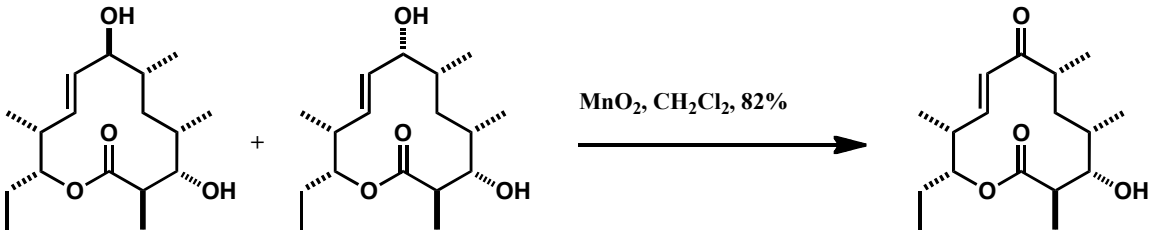


(3*R*,4*S*,5*S*,7*R*,11*R*,12*R*,*E*)-12-ethyl-4,8-dihydroxy-3,5,7,11-tetramethyloxacyclododec-9-en-2-one

To a solution of 48% HF (0.3 mL), MeCN (0.5 mL), and water (0.2 mL) at 0 °C, was added **23a and 23b** (0.022 g, 0.042 mmol) in MeCN (0.5 mL). Reaction was removed from cooling bath, and stirred at rt for 3 h. Diluted with MeCN (5 mL), carefully transferred to a separatory funnel, washed with half-saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (3:10 EtOAc:hexanes) to afford the title compound {a 5:1 mixture of C7 diastereomers as judged by comparing integration of the signals at 4.99 (major) 5.09 (minor)} (0.012 g, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71- 5.66 (m, 1H), 5.50-5.46 (m, 1H), 4.99 (ddd, J = 3.5, 5.0, 8.8 Hz, 1H), 4.14-4.11 (m, 1H), 3.55-3.51 (m, 1H), 2.59-2.55 (m, 1H), 2.54-2.47 (m, 1H), 1.95-1.87 (m, 2H), 1.69-1.51 (m, 7H), 1.29-1.21 (m, 8H), 1.05-1.00 (m, 7H), 0.98-0.96 (m, 6H), 0.91-0.84 (m, 5H). Combined integrals for major and minor isomers are reported in regions where resolution is poor.

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 131.2, 128.6, 79.1, 77.4, 76.2, 43.9, 38.0, 35.6, 32.8, 32.1, 24.6, 20.8, 17.4, 16.7, 11.1, 10.6. Diagnostic signal for the minor diastereomer: 5.09 (ddd, *J* = 3.0, 5.5, 8.8, 1H) and for major diastereomer is 4.99 (ddd, *J* = 3.5, 5.0, 8.3 Hz, 1H).

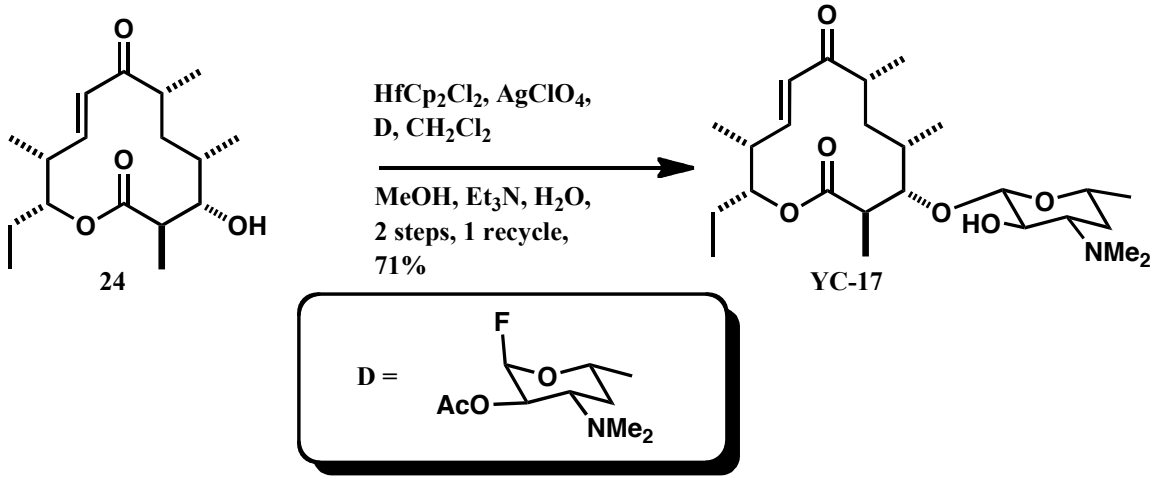
Assignment of stereochemistry at C7 was done by correlation with known compound from the Sherman lab[7] and from Cane lab.[12]



ARS-5a **ARS-5b** **24**

(3*R*,4*S*,5*S*,7*S*,11*R*,12*R*,*E*)-12-ethyl-4-hydroxy-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione

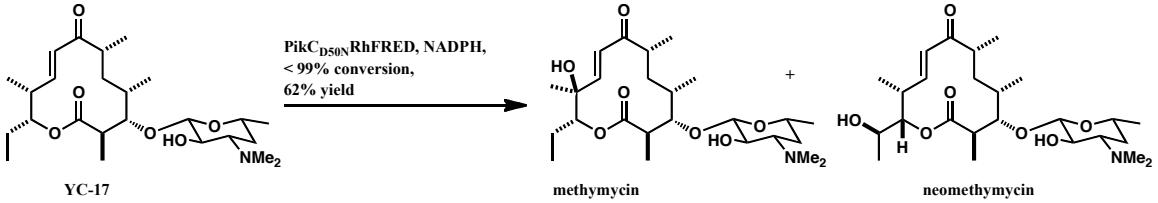
To a solution of **ARS-5a** and **ARS-5b** (0.008 g, 0.027 mmol) in CH_2Cl_2, was added MnO_2 (0.047g, 0.54 mmol), and stirred at rt for 2 h. Filtered through a pad of Celite, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5:10 EtOAc:hexanes) to afford the title compound (0.0066 g, 82%) as a colorless oil. Matched data as previously reported by Pilli and colleagues.[13]



(3*R*,4*S*,5*S*,7*R*,11*R*,12*R*,*E*)-4-(((2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-12-ethyl-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione

In a glovebox, $HfCp_2Cl_2$ (0.064g, 0.17 mmol), $AgClO_4$ (0.035 g, 0.17 mmol), and 4 Å powered molecular sieves (0.1 g) were charged to a round bottom flask, the flask was removed from the glovebox, CH_2Cl_2 (2 mL) was added, stirred for 10 minutes, **D** (0.010g, 0.042 mmol) in CH_2Cl_2 (0.8 mL) was added, and stirred for 0.5 h. A solution of **24** (0.005 g, 0.017 mmol) in CH_2Cl_2 (0.5 mL) was added, and reaction was allowed to stir for 48 h, quenched by addition of aqueous half-saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with half-saturated $NaHCO_3$, half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. Analysis of crude reaction mixture presented starting material **24,** acetylated **YC-17** (C2' on desosamine) and **YC-17**. The residue was purified by flash chromatography (MeOH:CH_2Cl_2 = 1:50) and starting material was subjected to one round of recycle, batches were combined, and dissolved in MeOH (1 mL), Et_3N (0.5 mL), and water (0.5 mL). The resulting mixture was heated to 40 °C for 3 h, solvents were concentrated, and the residue was purified by flash chromatography (2:25 MeOH:CH_2Cl_2) to afford the title compound (0.005 g, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 5.6, 15.6 Hz, 1H), 6.40 (d,

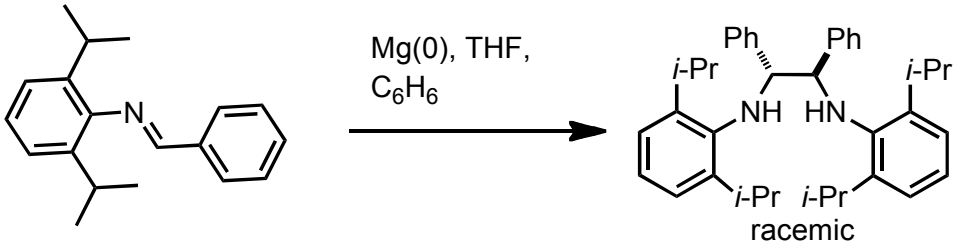
J = 16.4 Hz, 1H), 4.90 (ddd, *J* = 2.2, 6.0, 8.2 Hz, 1H), 4.22 (d, *J* = 7.2 Hz, 1H), 3.56 (d, *J* = 10.4 Hz, 1H), 3.49-3.42 (m, 1H), 3.31-3.23 (m, 1H), 2.83-2.78 (m, 1H), 2.61-2.56 (m, 1H), 2.50-2.46 (m, 1H), 2.35 (broad s, 6H), 1.77-1.64 (m, 3H), 1.56-1.50 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.15-1.13 (m, 3H), 1.1 (d, *J* = 4.0 Hz, 3H), 0.96-0.94 (m, 3H), 0.88-0.82 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4, 175.3, 147.6, 126.2, 104.9, 85.9, 73.9, 70.5, 69.4, 66.3, 45.3, 44.2, 40.6, 38.1, 34.3, 33.7, 29.9, 29.4, 25.4, 21.3, 17.9, 17.6, 16.3, 10.5, 9.8. HMRS calcd for : $C_{25}H_{43}NO_6$ $[M + H]^+$ 454.3163 found 454.3168. Also reported by Cane and colleagues,[9] Isolation of natural product YC-17 can be found by: Kinumaki, A.; Suzuki, M.[10]



Mixture of (3*R*,4*S*,5*S*,7*R*,11*S*,12*R*,*E*)-4-(((2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-12-ethyl-11-hydroxy-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione and (3*R*,4*S*,5*S*,7*R*,11*R*,12*S*,*E*)-4-(((2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-12-((*R*)-1-hydroxyethyl)-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione

To a 125 mL Erlenmeyer flask (Caution: DO NOT use a stir bar!) reaction buffer (30 mL), is added, followed by NADPH (0.043 g in 1 mL of water) and gently swirled, next PikC$_{D50N}$RhFRED (2 mL, with 0.024% being active PikC$_{D50N}$RhFRED) was added and gently swirled, **YC-17** (0.002 g), in MeOH (300 µL, CAUTION: MeOH is partially toxic to proteins, care must be taken to minimize amount and dilute with reaction buffer) and flask was gently swirled. The flask is placed in a 30 °C incubator overnight. Protein is precipitated by addition of $CHCl_3$ (25 mL). Crude mixture is filtered through a pad of Celite, and concentrated under reduced pressure, and analyzed using LC/MS. Crude

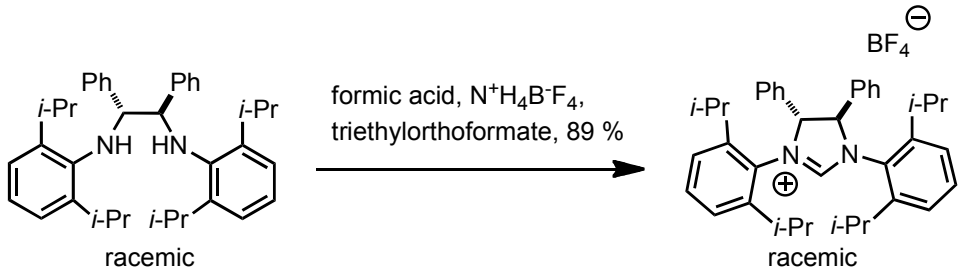
reaction mixture analysis by LC/MS indicated approximately a 1:1 ratio between methymycin and neomethymycin. The residue was purified by flash chromatography (1:10 MeOH:CH_2Cl_2) to afford the title compound (0.0015 g, 62%) as a colorless oil; during purification the mixture was enriched to a 4:3 ratio of methymycin:neomethymycin as judged by comparing integration of the signals at 6.76 (methymycin) and 6.59 (neomethymycin) by integration. Matched data as previously reported by Cane and colleagues,[11]



(+/-)-(1R,2R)-N1,N2-bis(2,6-diisopropylphenyl)-1,2-diphenylethane-1,2-diamine

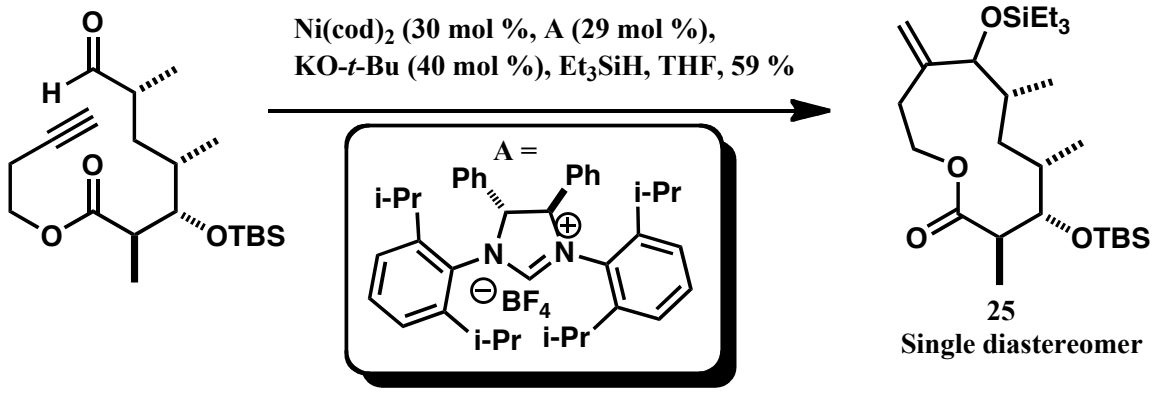
N-Benzylidene-2,6-diisopropylaniline (10.0 g, 37.7 mmol), magnesium powder (Aldrich reagent plus 99.5% purity, 2.75 g, 113 mmol) and of benzene (120 mL) were combined in 1.0 L flame dried round-bottom flask with a stir bar under nitrogen. Trifluoroacetic acid (17.4 mL, 226 mmol) was then dispensed by syringe drive over 1 h and stirred overnight at ambient temperature. The reaction was terminated with sat. $NaHCO_3$ (250 mL) and stirred for 1 h. The two layers were separated, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were then dried with Na_2SO_4 and concentrated under reduced pressure to yield crude brown colored oil. The oil was then dissolved in methanol (40 mL) and placed in a freezer (-20 °C) overnight. The solvent was then decanted from the precipitate, affording 7.0 g as a mixture of

racemic and meso products. The precipitate was then dissolved in refluxing methanol (250 mL) and undissolved solids remaining after 1 h were removed by filtration. The filtered methanol solution cooled overnight at room temperature. The solvent was then decanted from the resulting 2.5 g of white crystalline solid (meso isomer). The mother liquor was then concentrated to 125 mL and heated to reflux until all solids dissolved. The solution was then cooled to RT and placed in a -20 °C freezer overnight. The solvent was decanted to afford 3.2 g of white solid (>98:2 racemic:meso). Matched data as previously reported by Sigman and colleagues.[14]

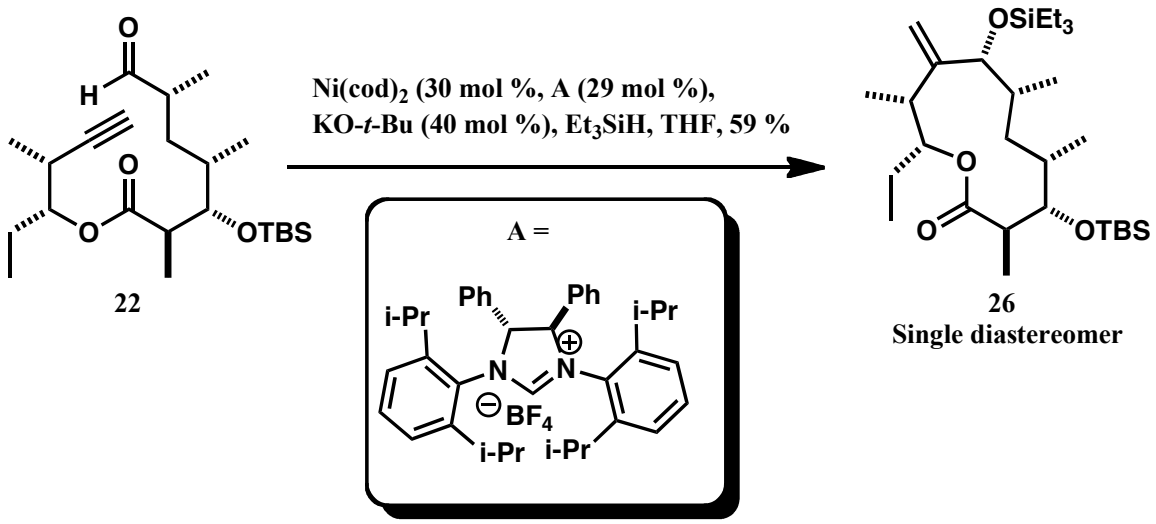


(±)-(4R,5R)-1,3-Bis(2,6-diisopropylphenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate (DP-IPr)

(±)-(1R, 2R)-N1, N2-Bis(2,6-diisopropylphenyl)-1,2-diphenylethane-1,2-diamine (0.580 g, 0.940 mmol), ammonium tetrafluoroborate (98 mg, 0.94 mmol), triethylorthoformate (1.11 g, 7.52 mmol), and formic acid (1 drop) were combined in a dry 25 mL round-bottom flask with a reflux condenser under nitrogen. The reaction was then heated to 120 °C with stirring for 24 h. The reaction mixture cooled to room temperature and was then concentrated under high vacuum. The reaction mixture was purified by flash column chromatography (SiO_2, 80% v/v EtOAc/Hexanes, R_f = 0.2) to afford title compound (0.530 g, 0.84 mmol, 89% yield) as a pale yellow solid. This material was then heated at 40 °C overnight, under reduced pressure. Matched data as previously reported by Montgomery and colleagues.[15]



In a glovebox $Ni(cod)_2$ (0.0085 g, 30 mol %), **A** (0.018 g, 29 mol %), and KO-*t*-Bu (0.004g, 39 mol %), were charged to a round-bottom flask, the flask was removed from the glovebox, THF (8 mL) was added and stirred for 10 min at rt. Neat triethylsilane (33 μL, 0.21 mmol) was added, followed by syringe drive addition of **22** (0.042 g, 0.103 mmol) in THF (2 mL) over three hours, the reaction was stirred for 12 h at rt. The septum was removed from the round bottom, stirred for 1 h in open atmosphere. Solvents were concentrated, and the residue was purified by flash chromatography (1:50 EtOAc:hexanes) to afford the title compound (0.031 g, 59%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.11 (s, 1H), 4.66-4.61 (m, 1H), 3.89 (dd, J = 4.4, 8.0 Hz, 1H), 3.76 (s, 1H), 2.56 (quintet, J = 7.2 Hz, 2H), 1.87-1.78 (m, 3H), 1.57-1.49 (m, 1H), 1.42-1.34 (m, 1H), 1.24-1.13 (m, 2H), 1.05-1.00 (m, 5H), 0.94-0.87 (m, 25H), 0.84-0.83, (m, 2H), 0.58-0.52 (m, 6H), 0.1 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 147.5, 129.3, 129.0, 112.6, 80.4, 72.5, 64.5, 42.0, 36.7, 31.8, 30.9, 26.4, 26.0, 18.3, 18.2, 17.3, 15.0, -4.1, -4.3. HMRS calcd for : $C_{29}H_{58}O_4Si_2$ 526.3874, found 526.3877.



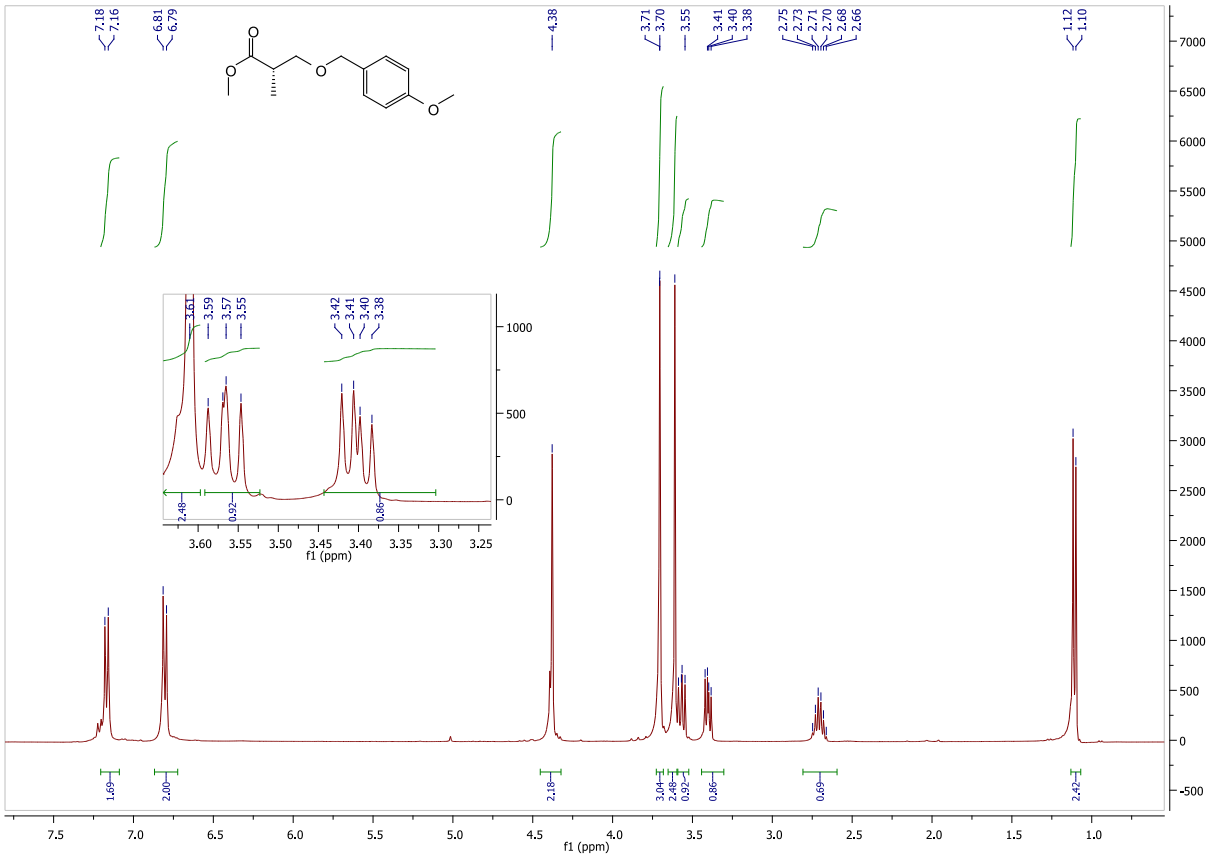
(3R,4S,5S,7R,8S,10R,11R)-4-((tert-butyldimethylsilyl)oxy)-11-ethyl-3,5,7,10-tetramethyl-9-methylene-8-((triethylsilyl)oxy)oxacycloundecan-2-one

In a glovebox $Ni(cod)_2$ (0.0085 g, 30 mol %), **A** (0.018 g, 29 mol %), and KO-*t*-Bu (0.004g, 39 mol %), were charged to a round-bottom flask, the flask was removed from the glovebox, THF (8 mL) was added and stirred for 10 min at rt. Neat triethylsilane (33 μL, 0.21 mmol) was added, followed by syringe drive addition of **22** (0.042 g, 0.103 mmol) in THF (2 mL) over three hours, the reaction was stirred for 12 h at rt. The septum was removed from the round bottom, stirred for 1 h in open atmosphere. Solvents were concentrated, and the residue was purified by flash chromatography (1:50 EtOAc:hexanes) to afford the title compound (0.031 g, 59%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.11 (s, 1H), 4.66-4.61 (m, 1H), 3.89 (dd, J = 4.4, 8.0 Hz, 1H), 3.76 (s, 1H), 2.56 (quintet, J = 7.2 Hz, 2H), 1.87-1.78 (m, 3H), 1.57-1.49 (m, 1H), 1.42-1.34 (m, 1H), 1.24-1.13 (m, 2H), 1.05-1.00 (m, 5H), 0.94-0.87 (m, 25H), 0.84-0.83, (m, 2H), 0.58-0.52 (m, 6H), 0.1 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 152.3, 111.2, 80.3, 80.1, 72.2, 40.0, 36.6, 36.1, 30.9, 30.8, 26.1, 21.7, 19.9, 18.5,

18.3, 16.1, 14.4, 11.7, 7.3, 5.1, -4.4, -4.5. HMRS calcd for : $C_{29}H_{58}O_4Si_2$ 526.3874, found 526.3877.

APPENDIX

On the forthcoming pages are proton and carbon NMR spectra for compounds synthesized during dissertation studies: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3.40
3.38
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2.71
2.70
2.68
2.66
1.12
1.10
3.61
3.59
3.57
3.55
3.42
3.41
3.40
3.38
2.48
0.92
0.86
f1 (ppm)
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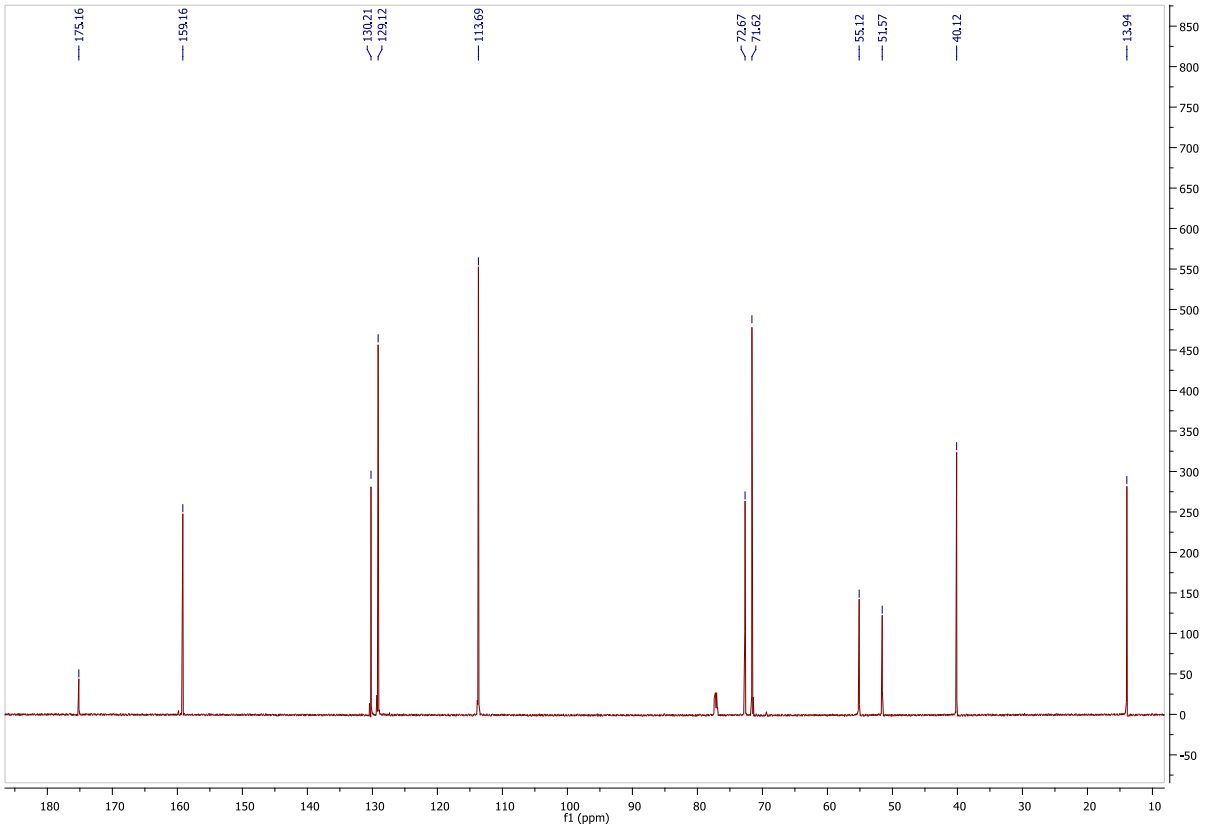
0.86
0.69
2.42
f1 (ppm)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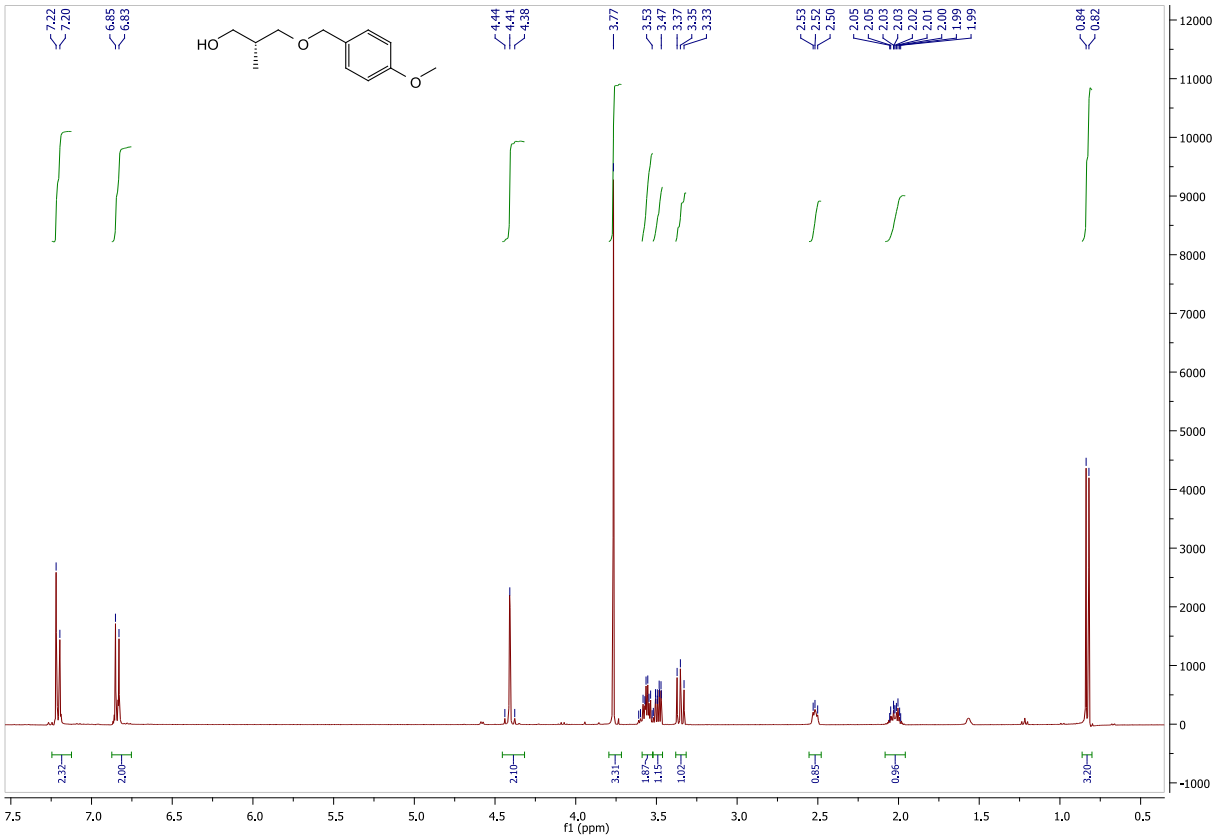
51.57
40.12
13.94
f1 (ppm)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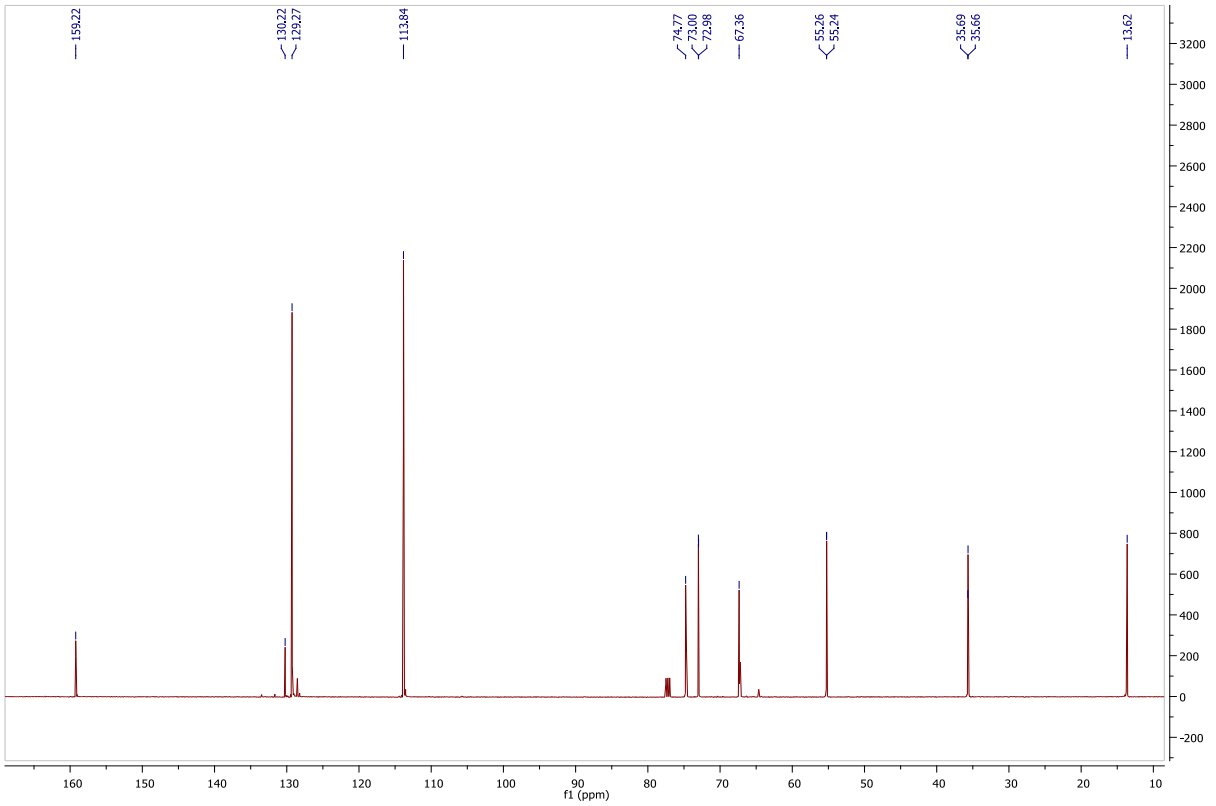
7.20
6.85
6.83
HO
O
O
4.44
4.41
4.38
3.77
3.53
3.47
3.37
3.35
3.33
2.53
2.52
2.50
2.05
2.05
2.03
2.03
2.02
2.01
2.00
1.99
1.99
0.84
0.82
2.32
2.00
2.10
3.31
1.87
1.15
1.02
0.85
0.96
3.20
f1 (ppm)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55.24
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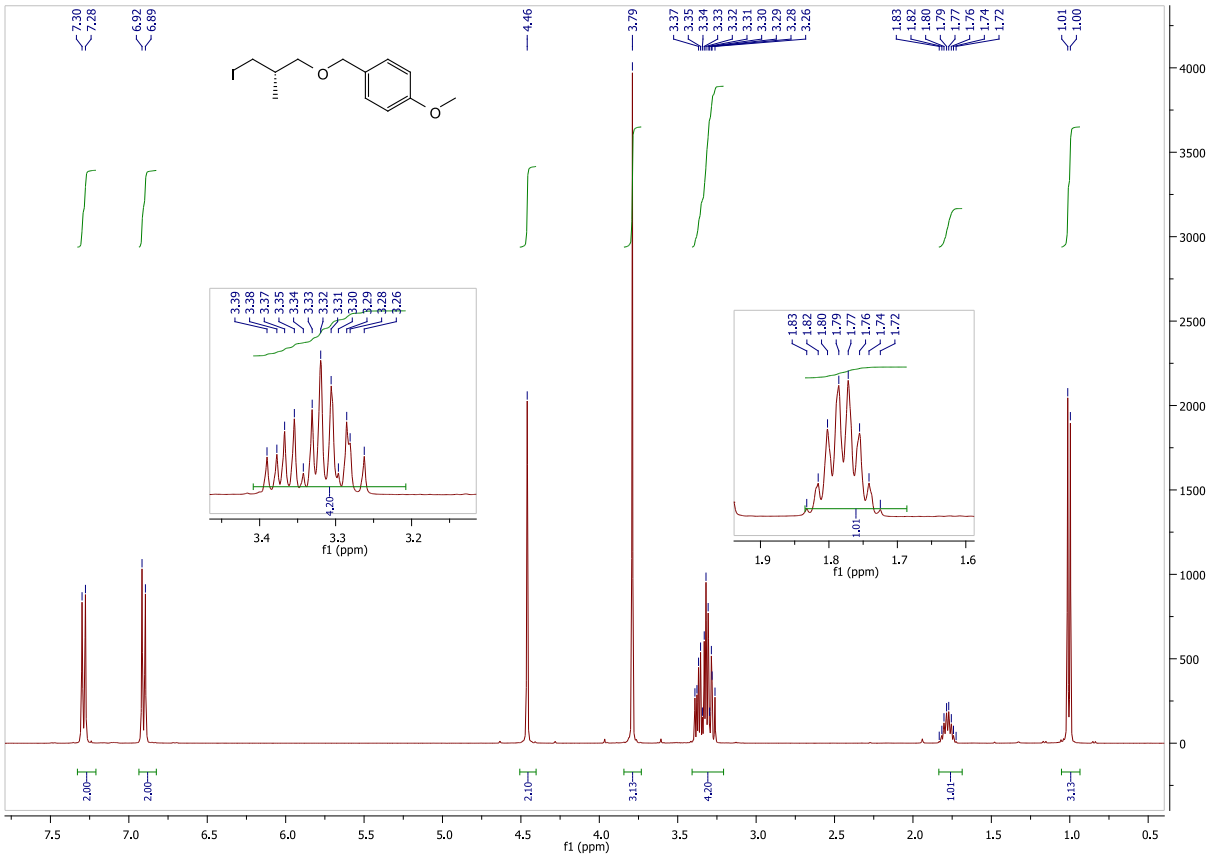
13.62
f1 (ppm)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3.37
3.35
3.34
3.33
3.32
3.31
3.30
3.29
3.28
3.26
1.83
1.82
1.80
1.79
1.77
1.76
1.74
1.72
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1.00
2.00
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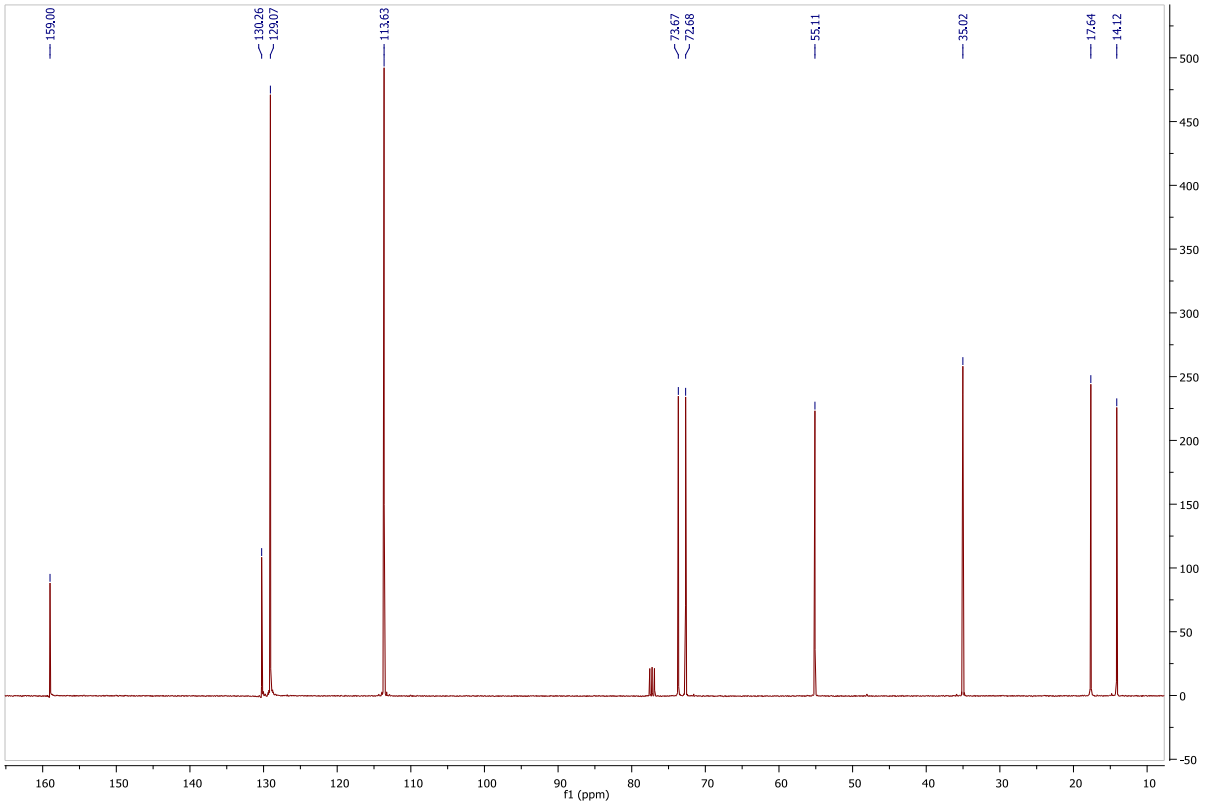
3.13
4.20
1.01
3.13
f1 (ppm)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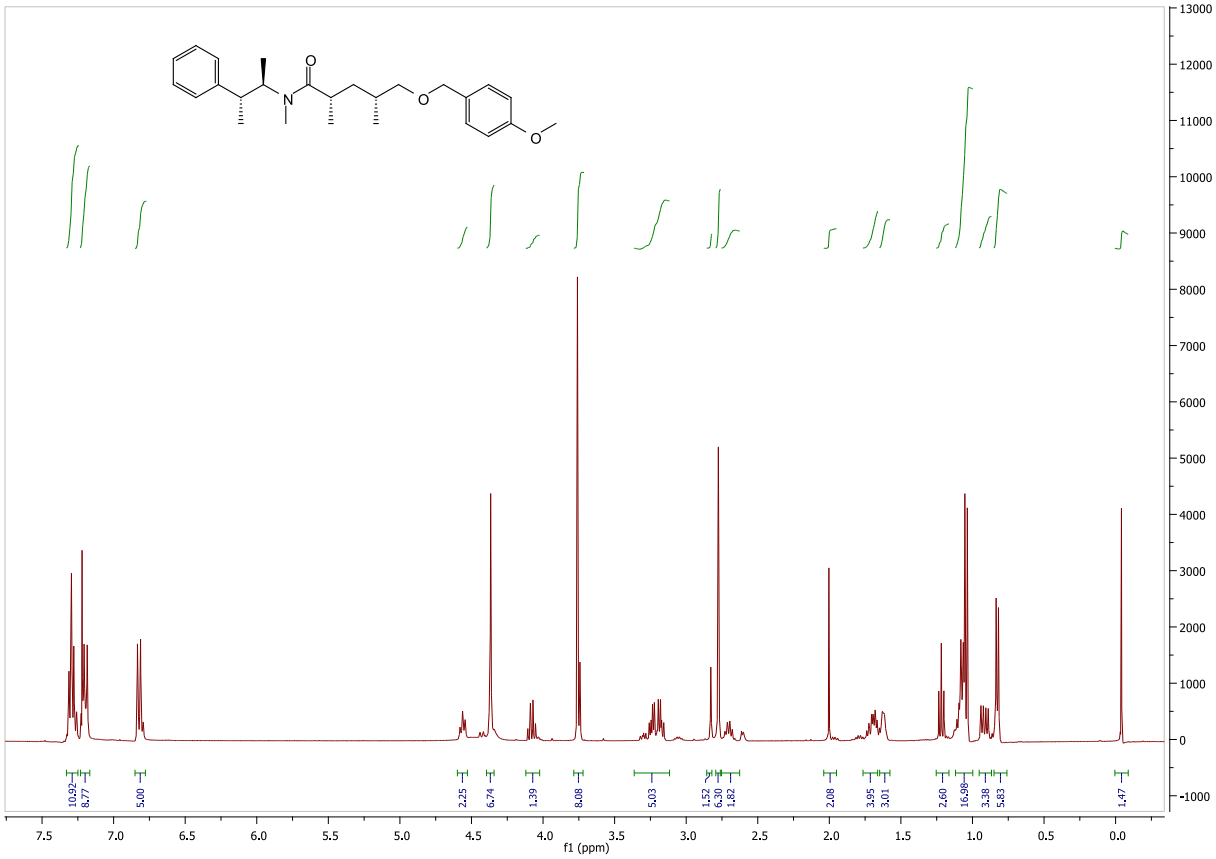
f1 (ppm)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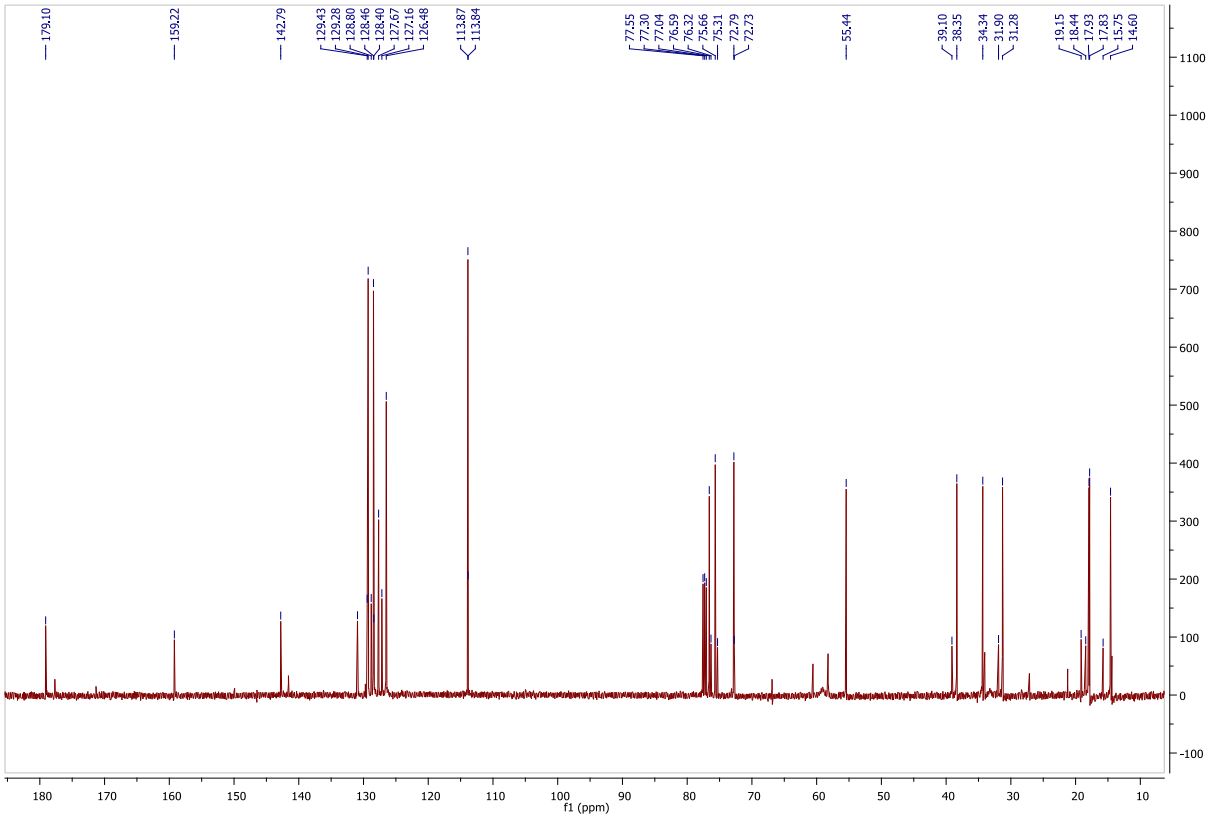
5.83
1.47
f1 (ppm)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77.04
76.59
76.32
75.66
75.31
72.79
72.73
55.44
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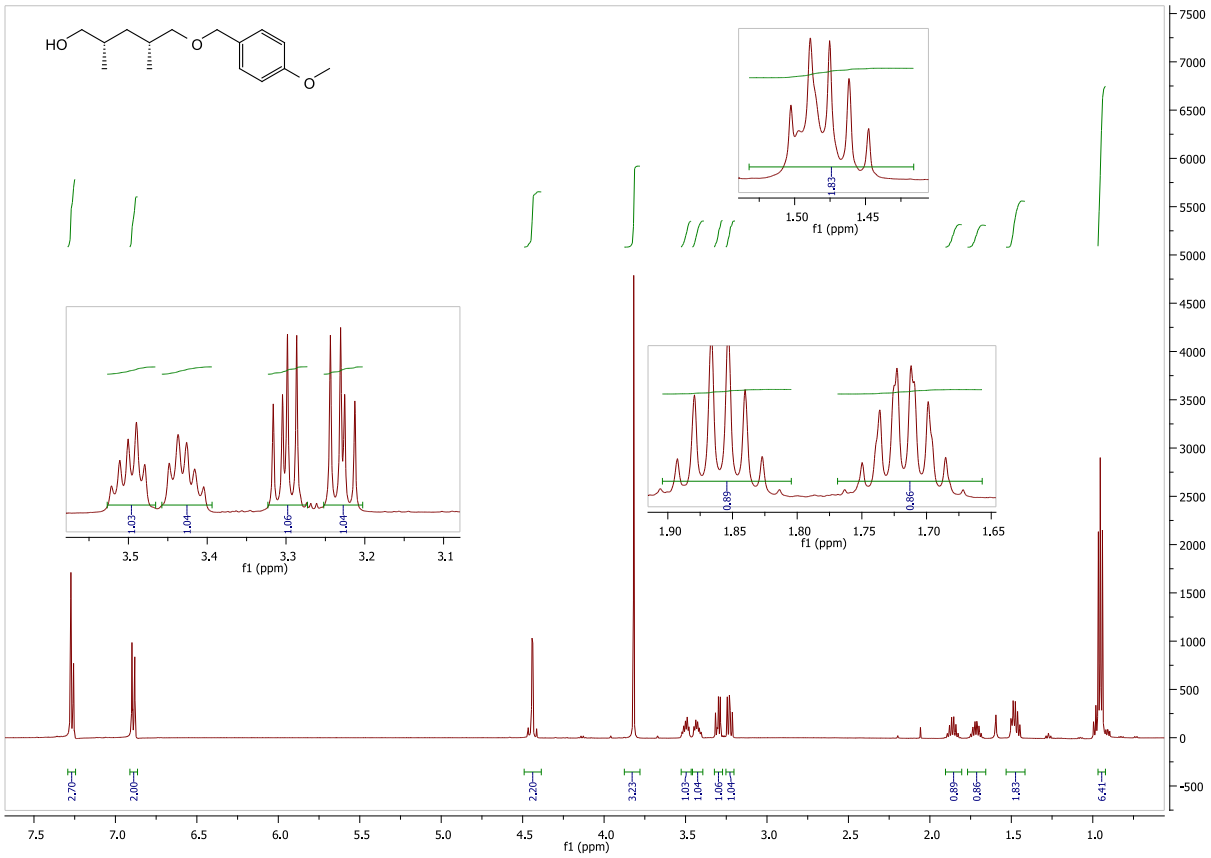
17.83
15.75
14.60
f1 (ppm)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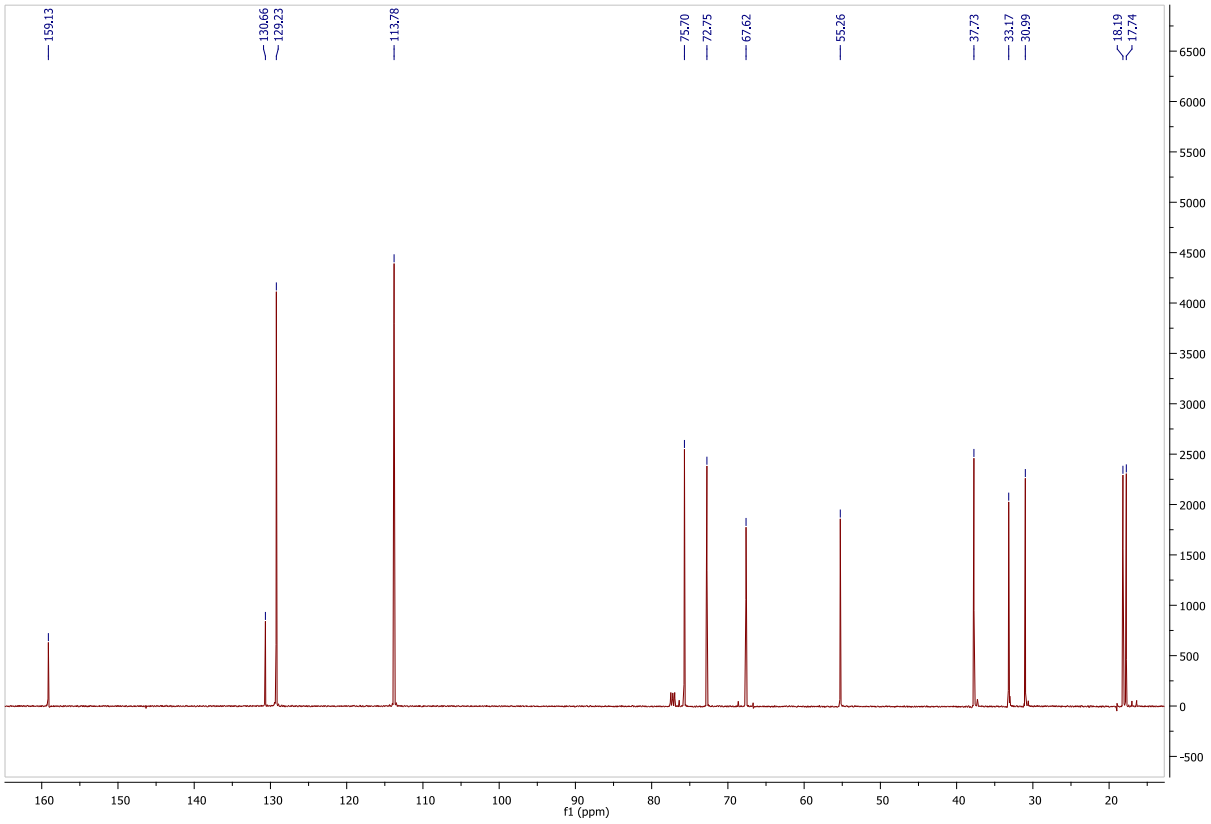
O
O
f1 (ppm)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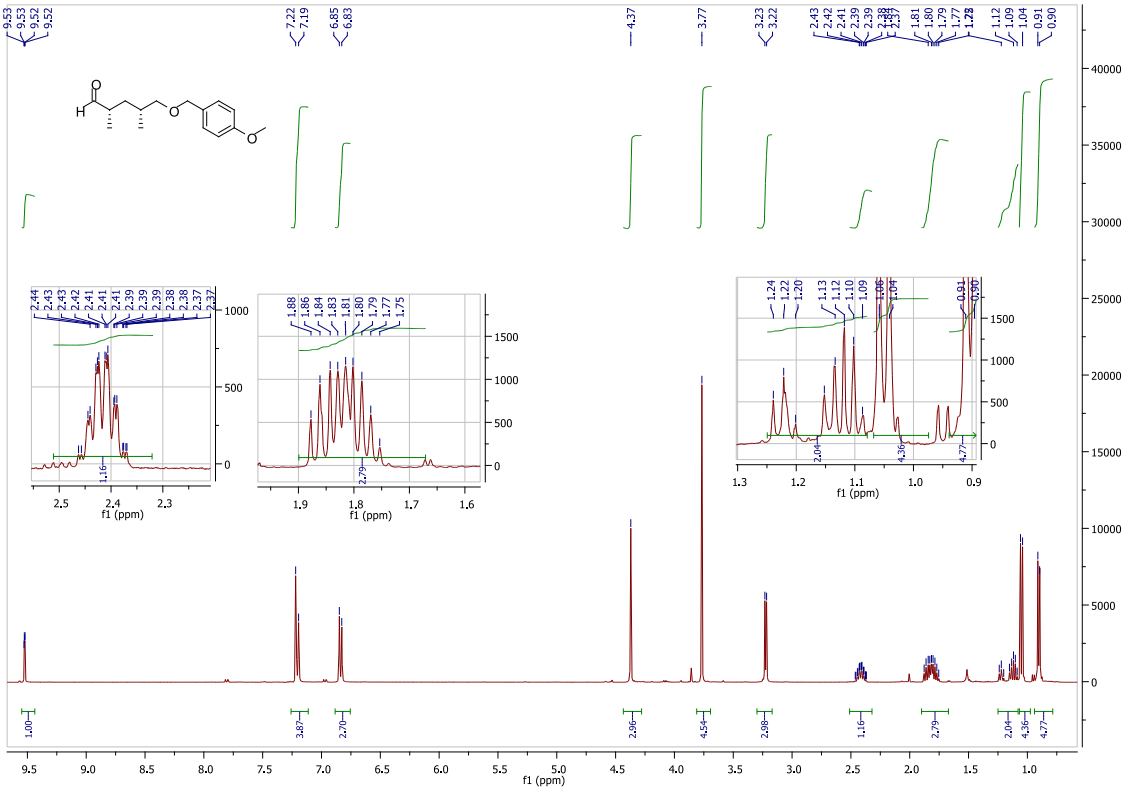
f1 (ppm)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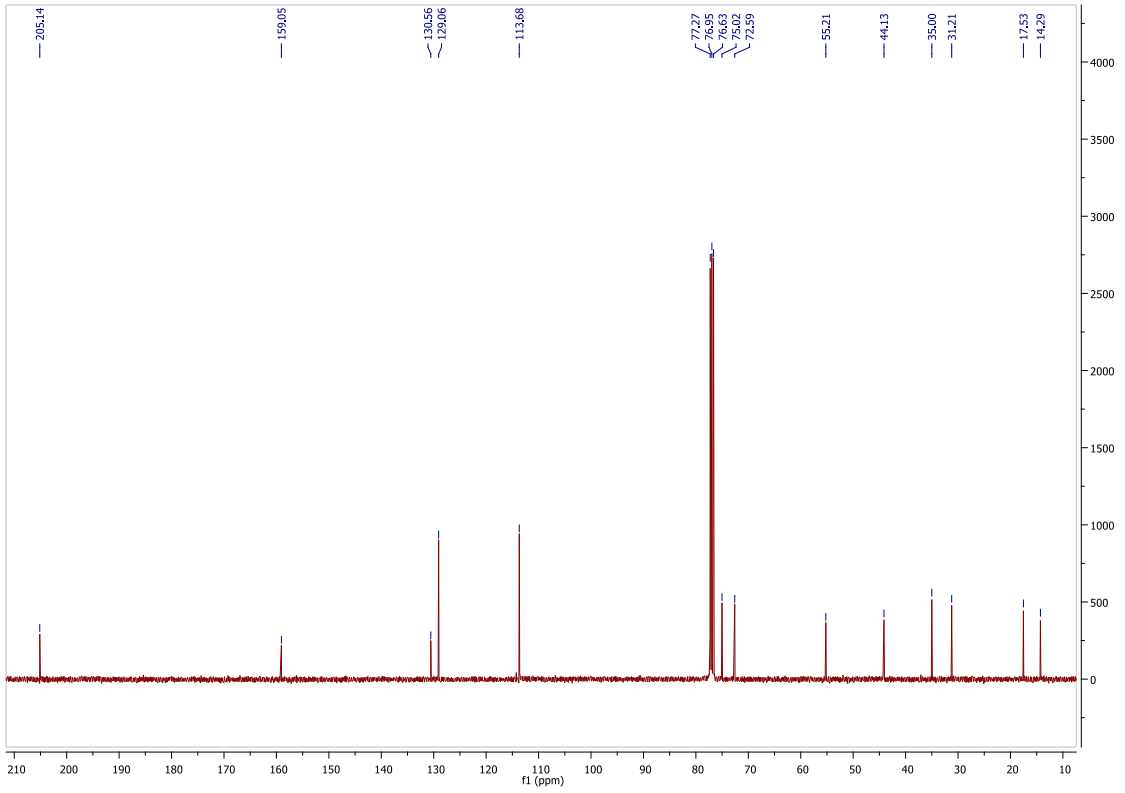
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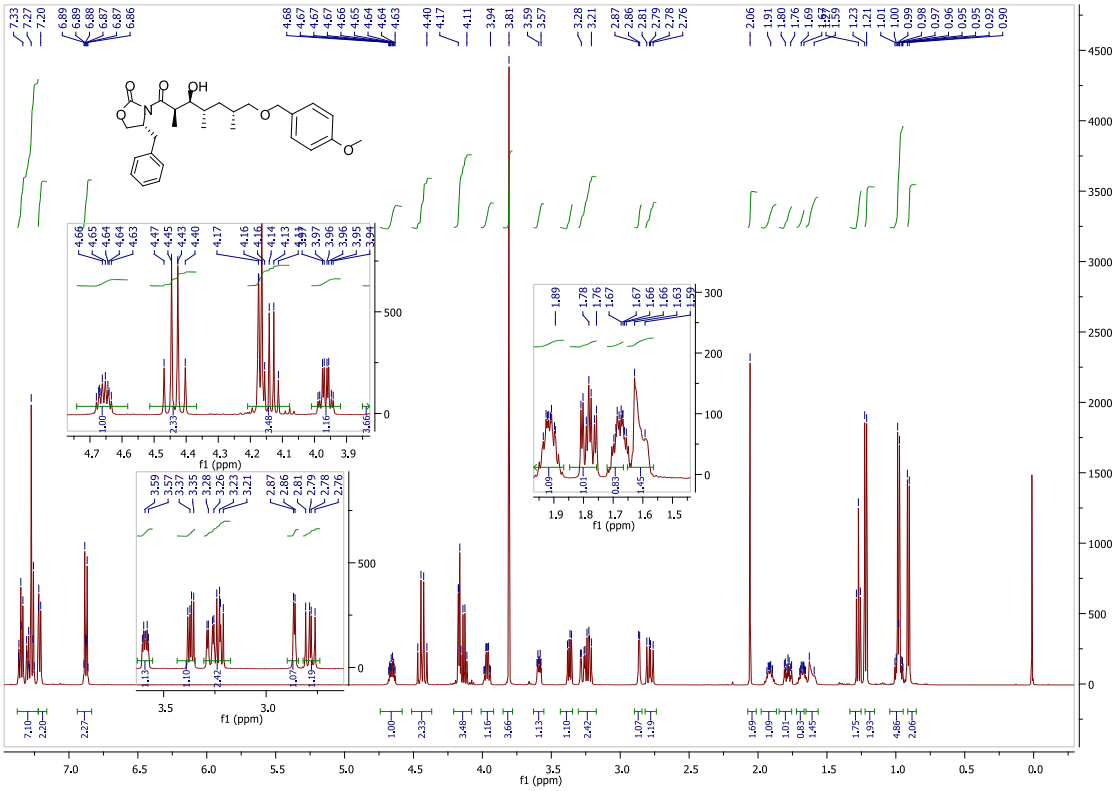

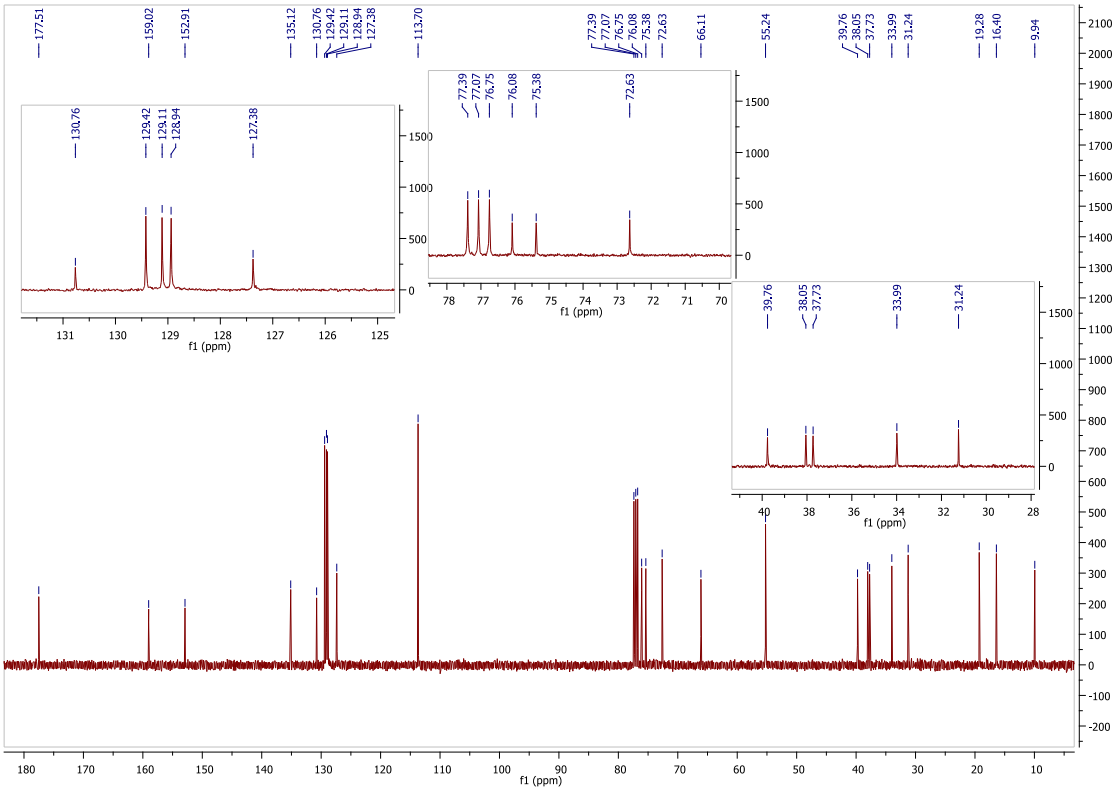

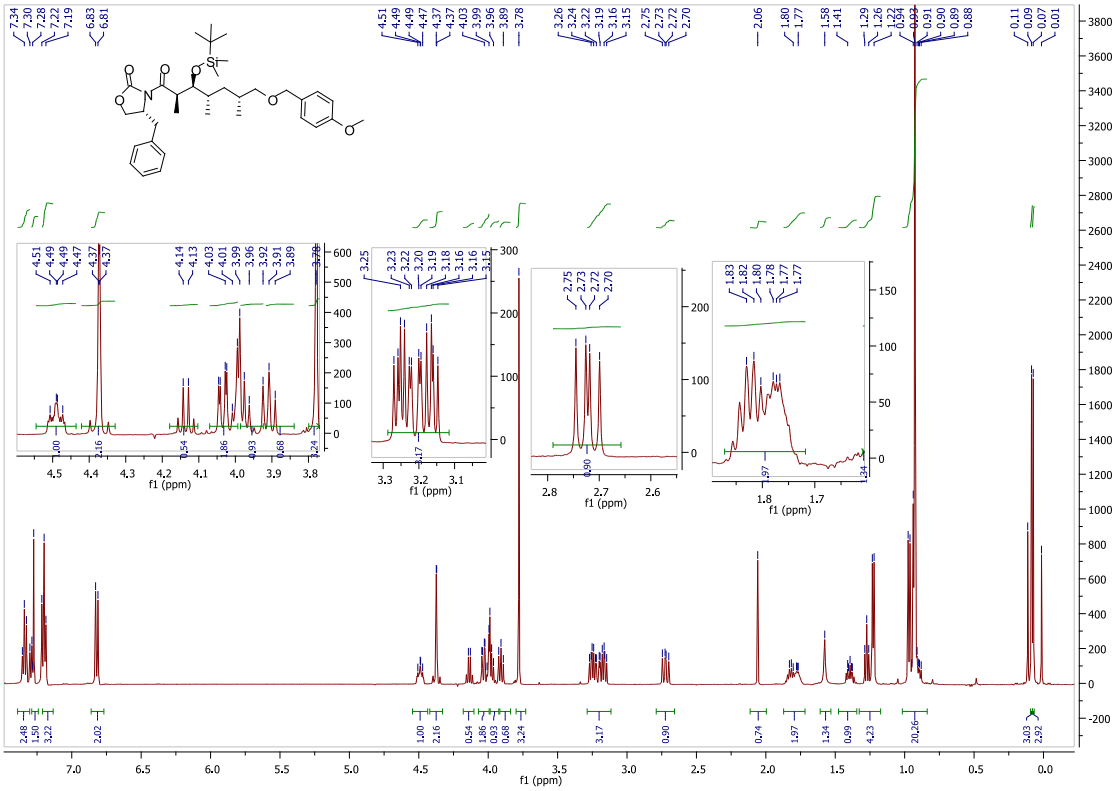

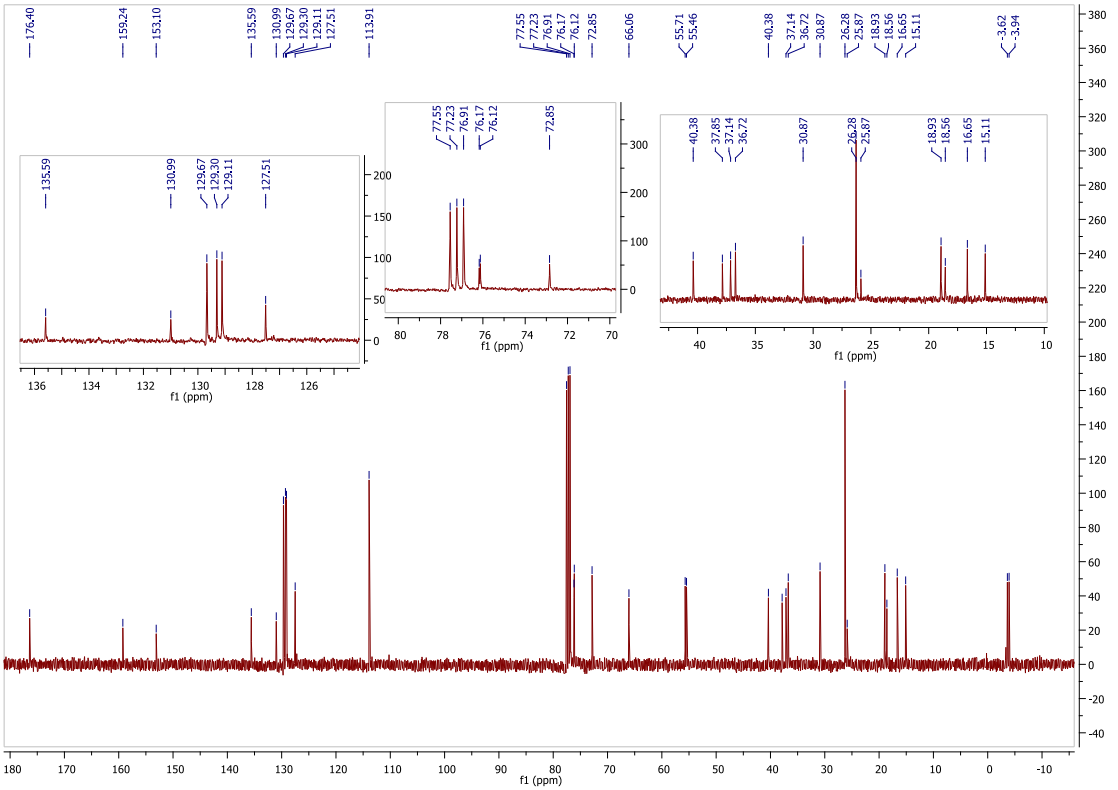

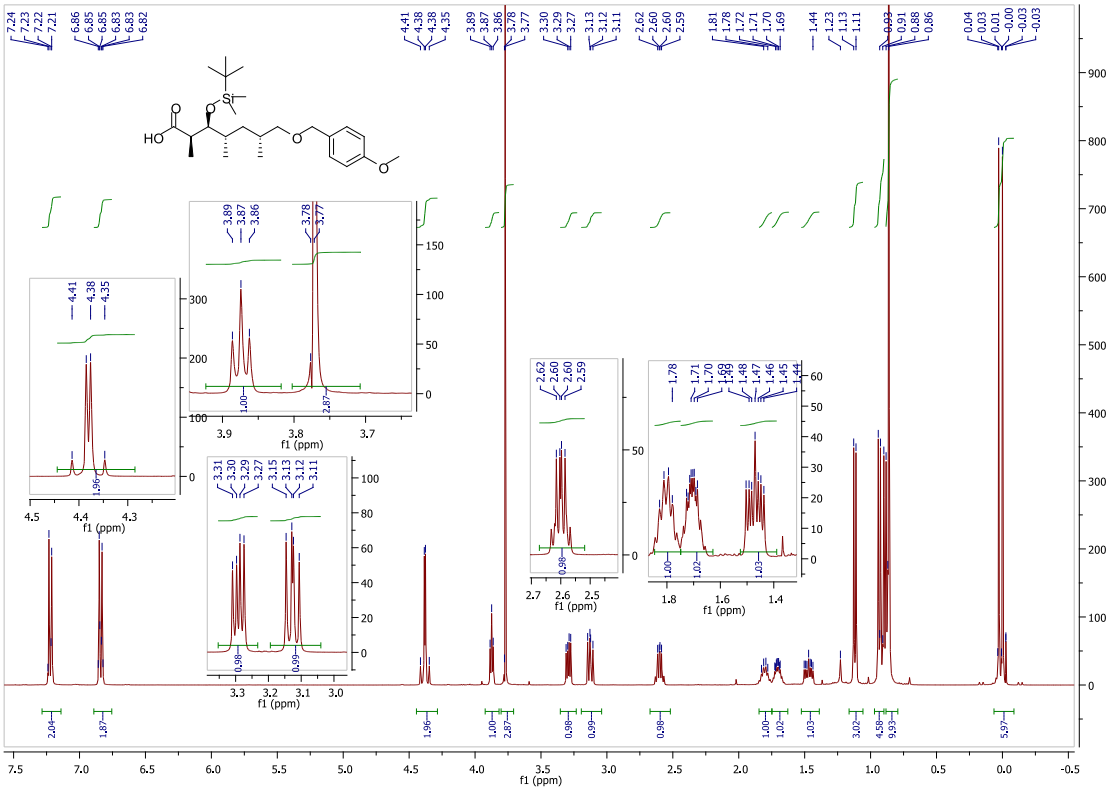

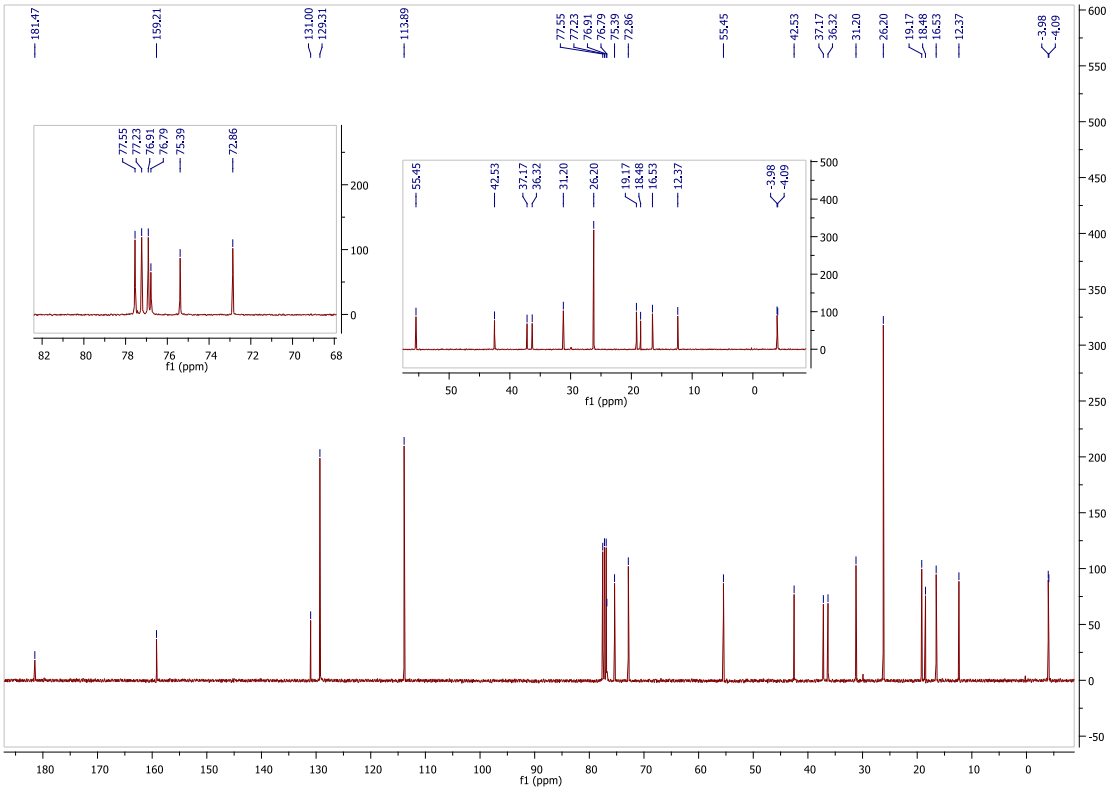

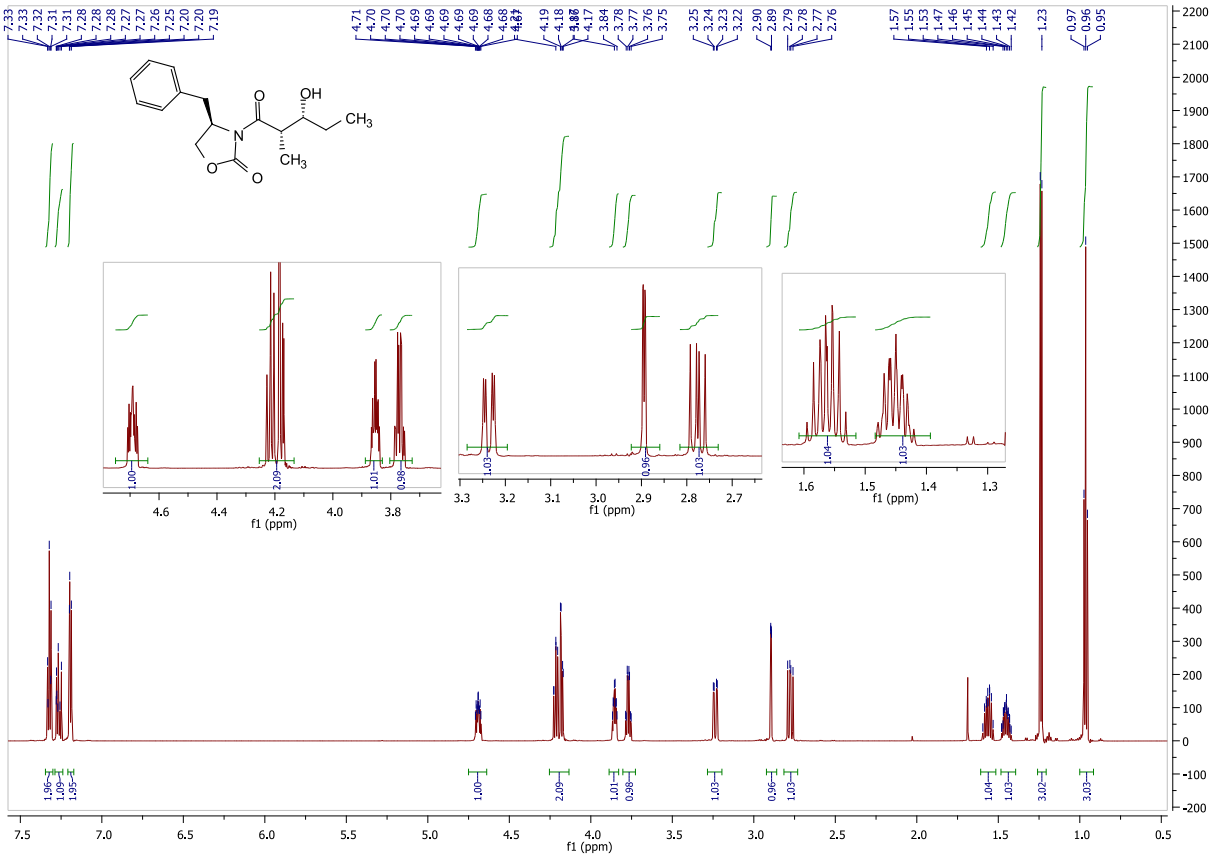
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N
O
O
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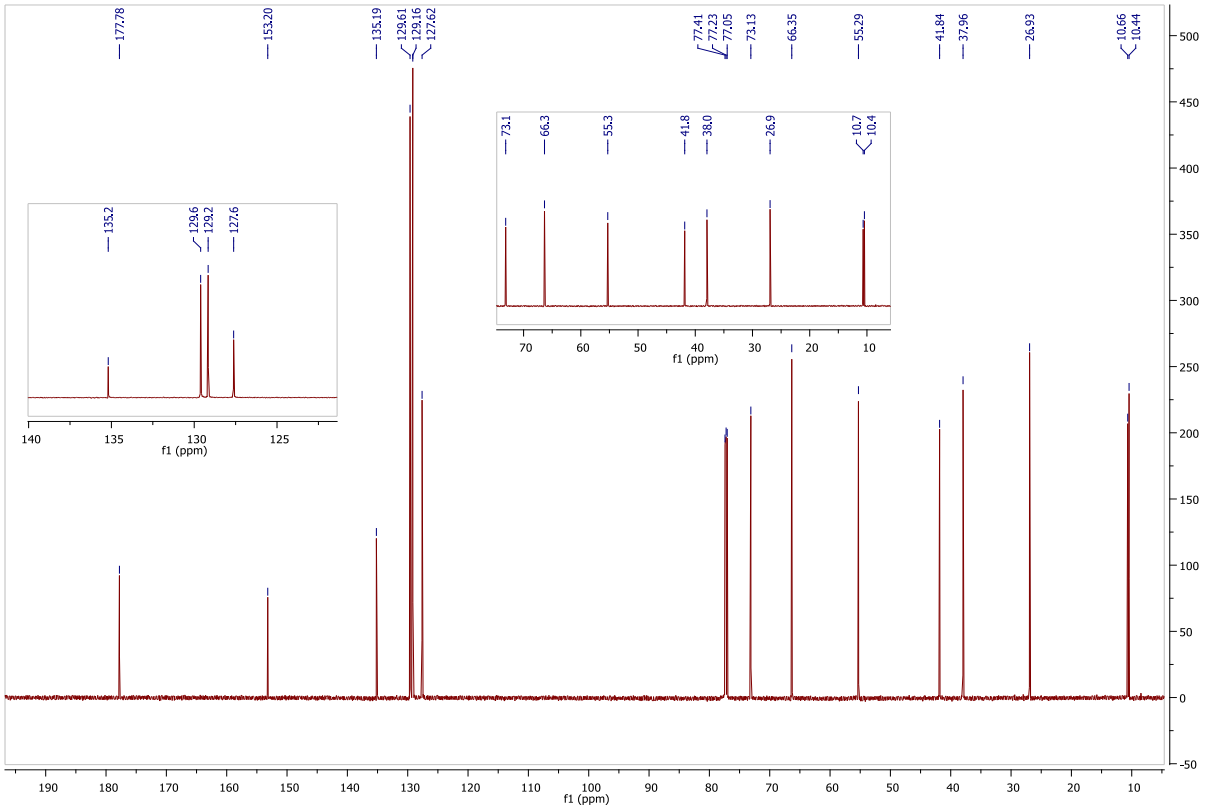
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10.44
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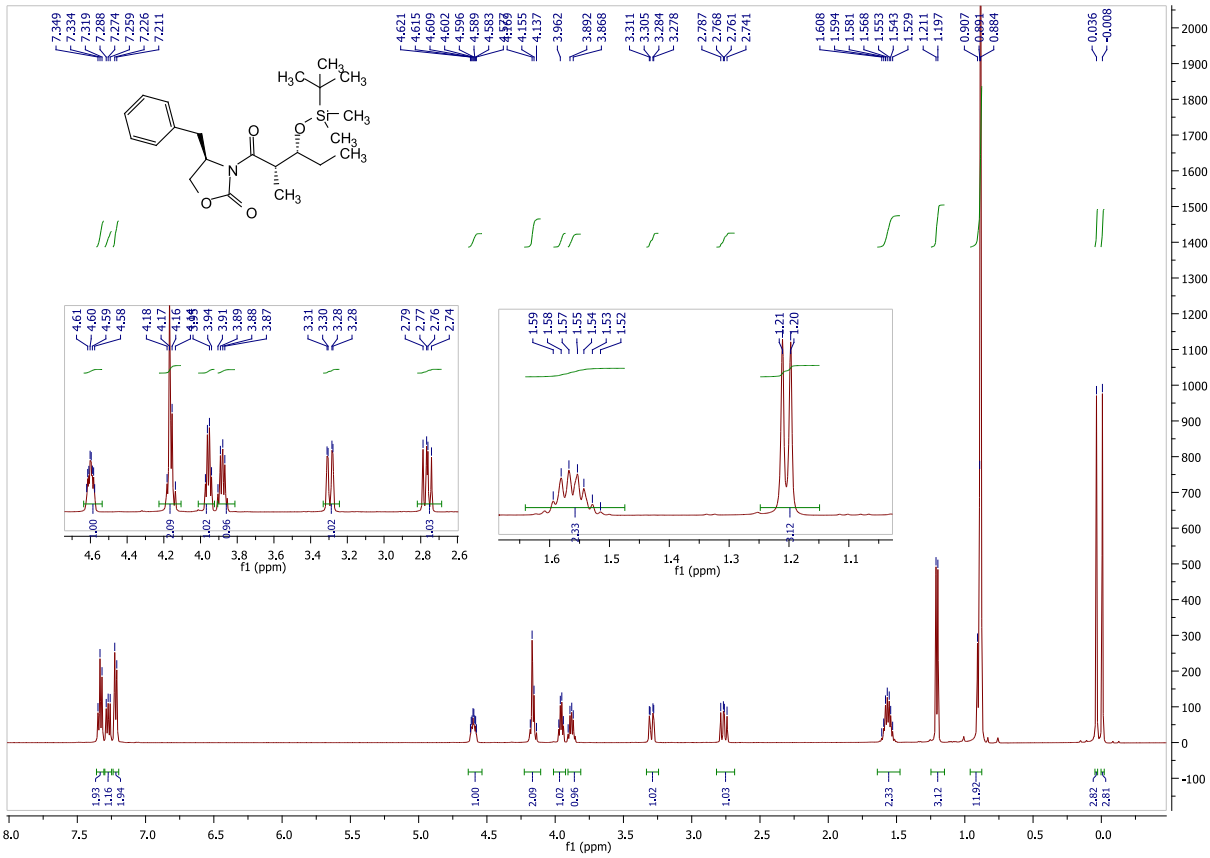
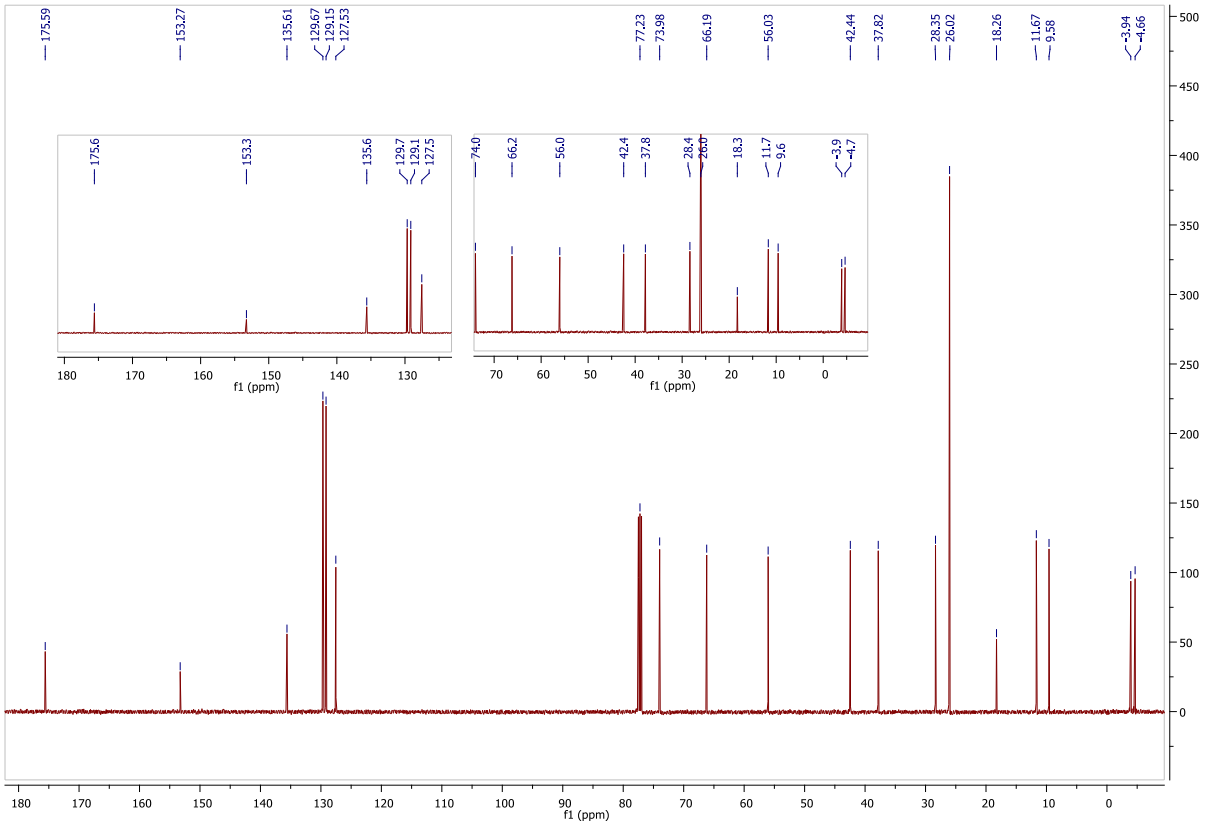
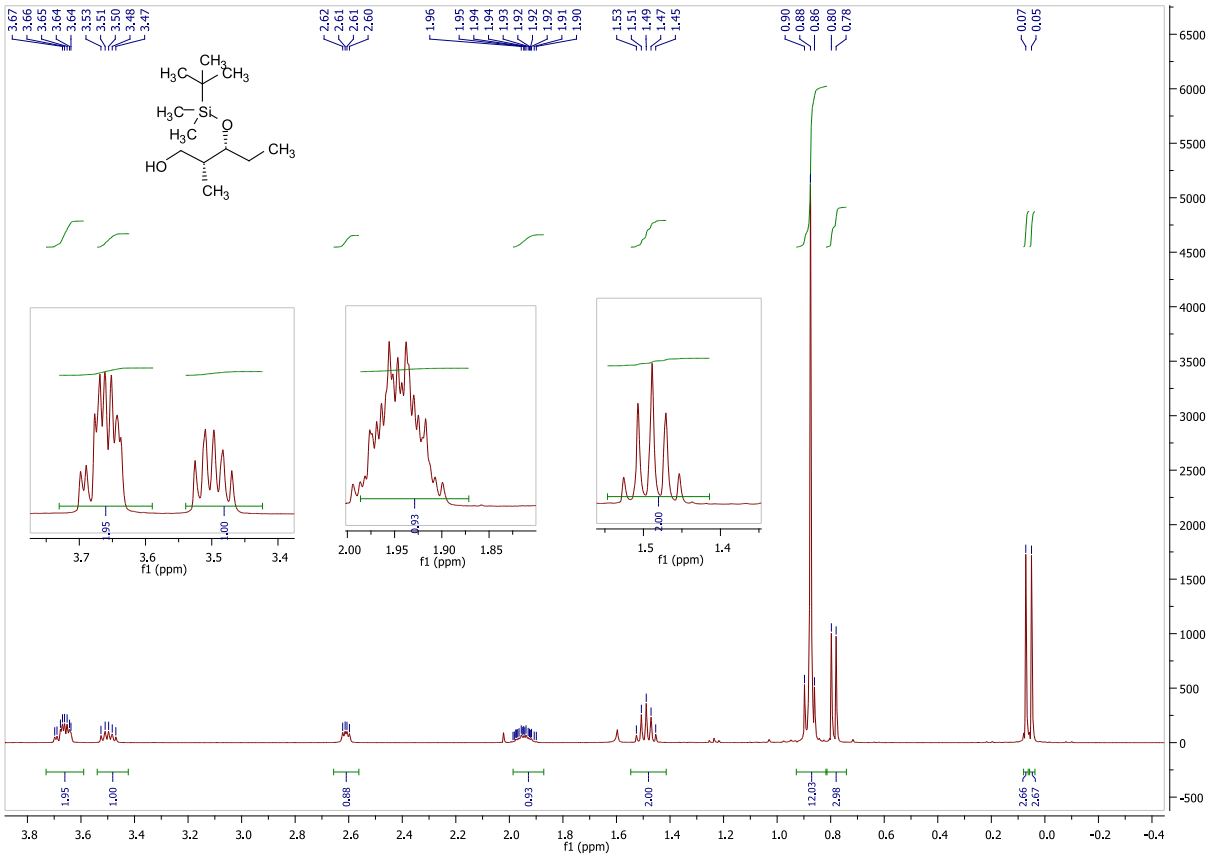
f1 (ppm)



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1.94
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1.92
1.91
1.90
1.53
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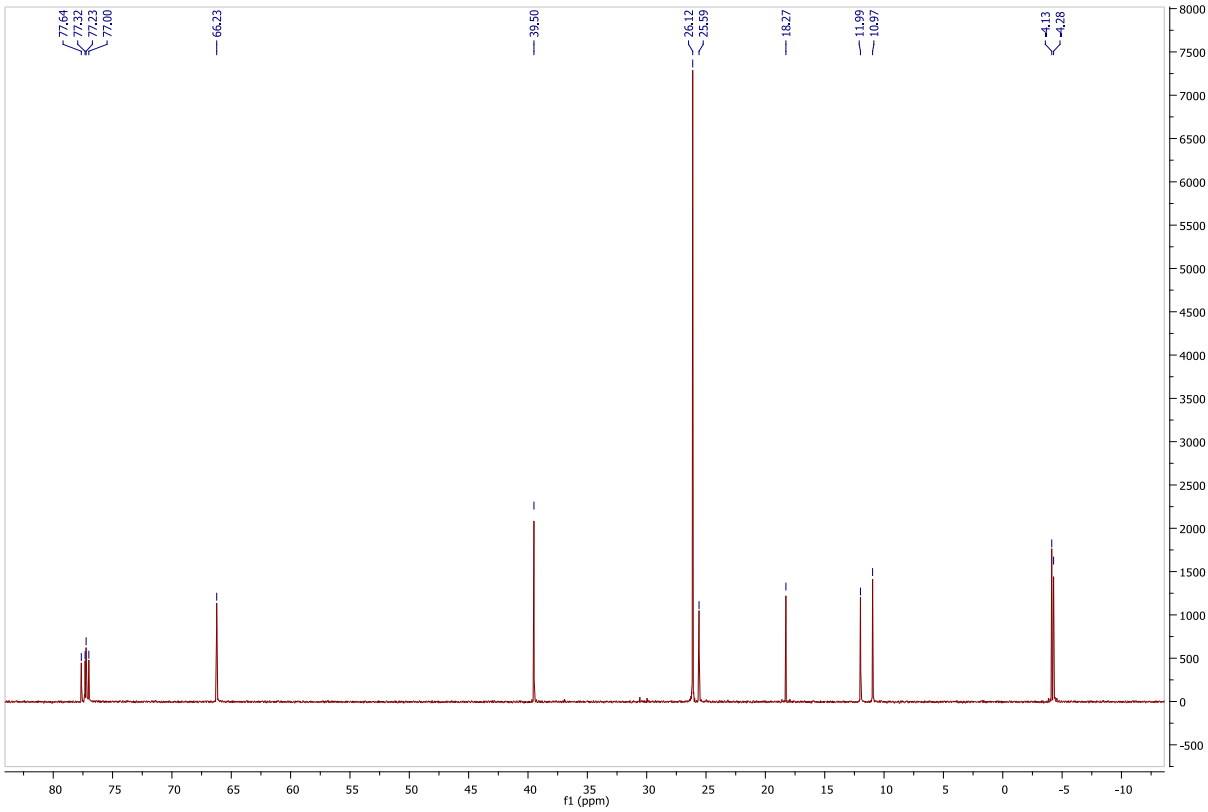
0.05
f1 (ppm)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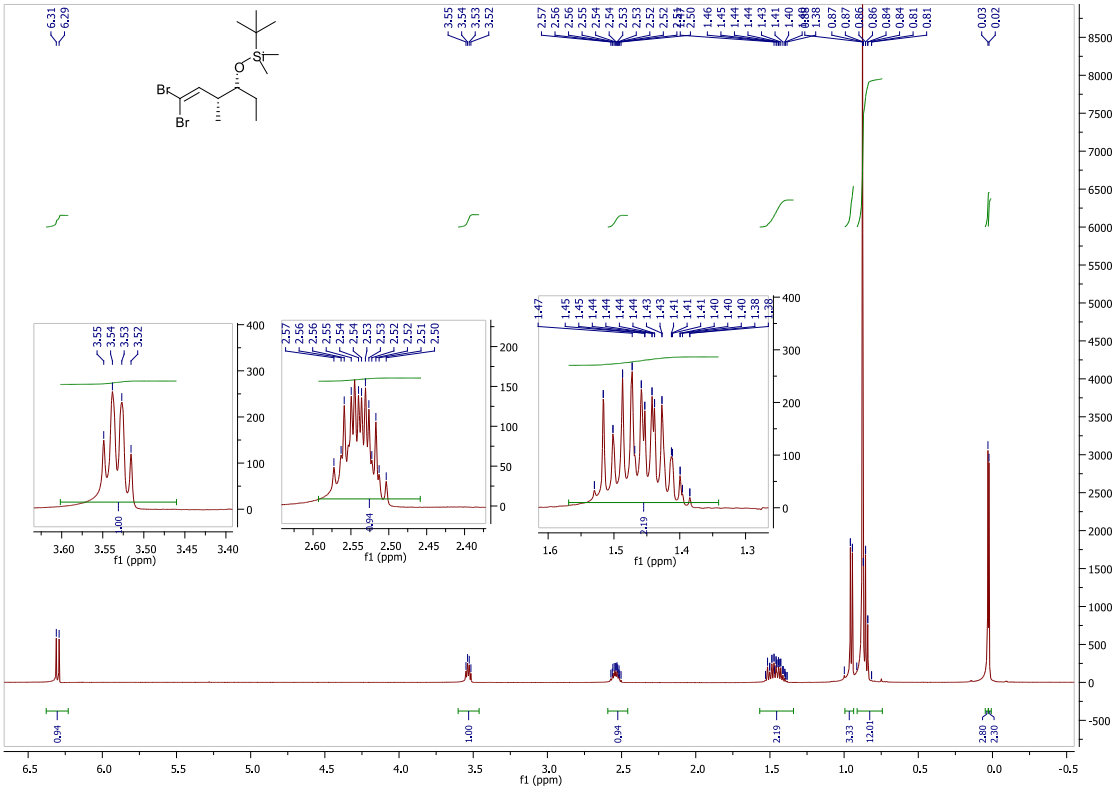
f1 (ppm)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Br
Si
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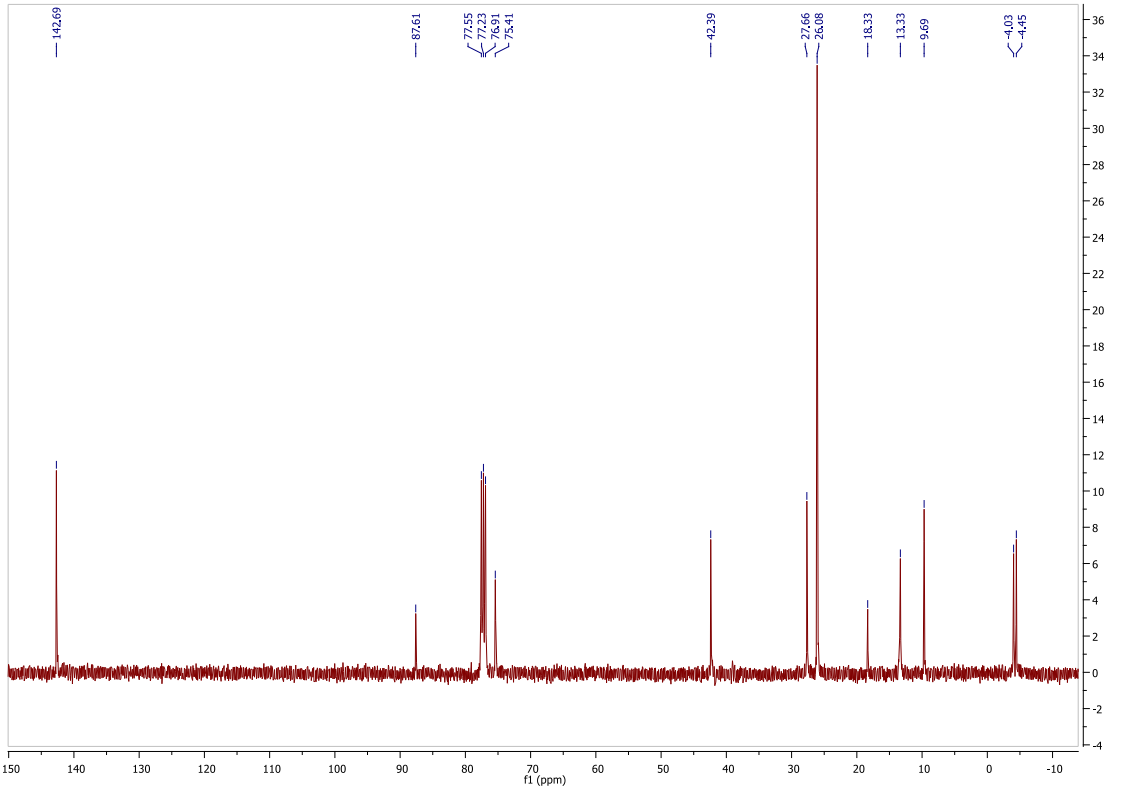
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9.69
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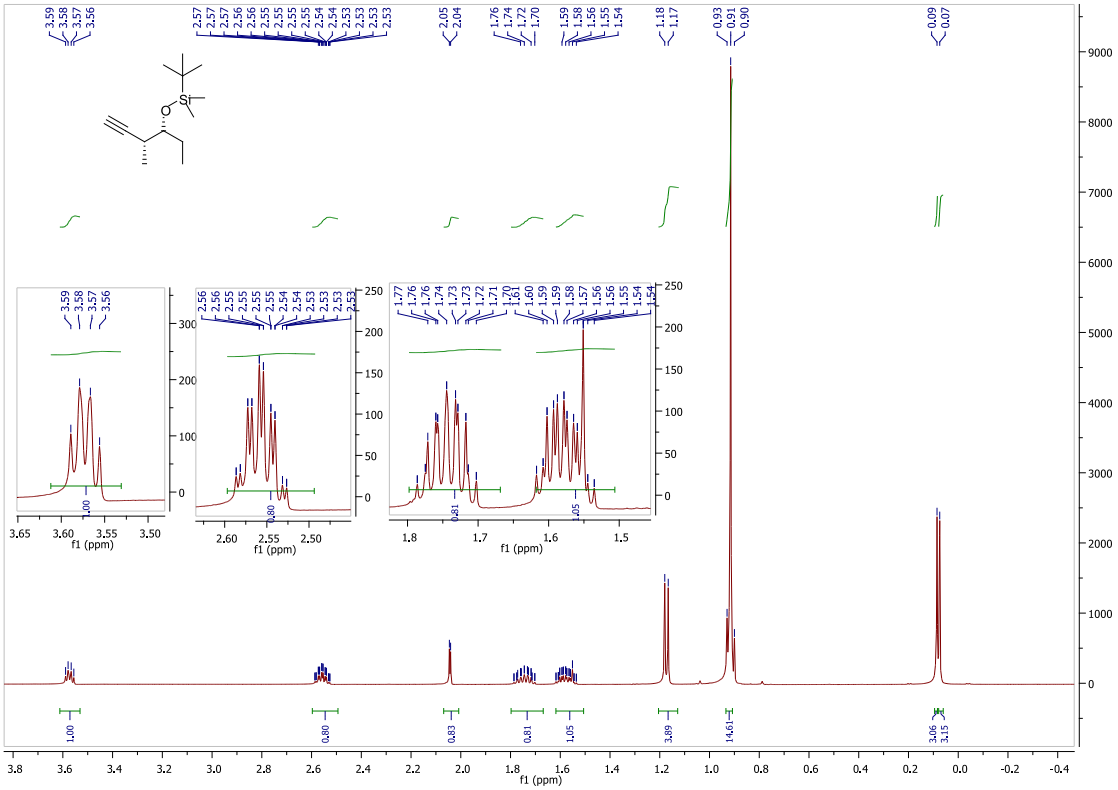
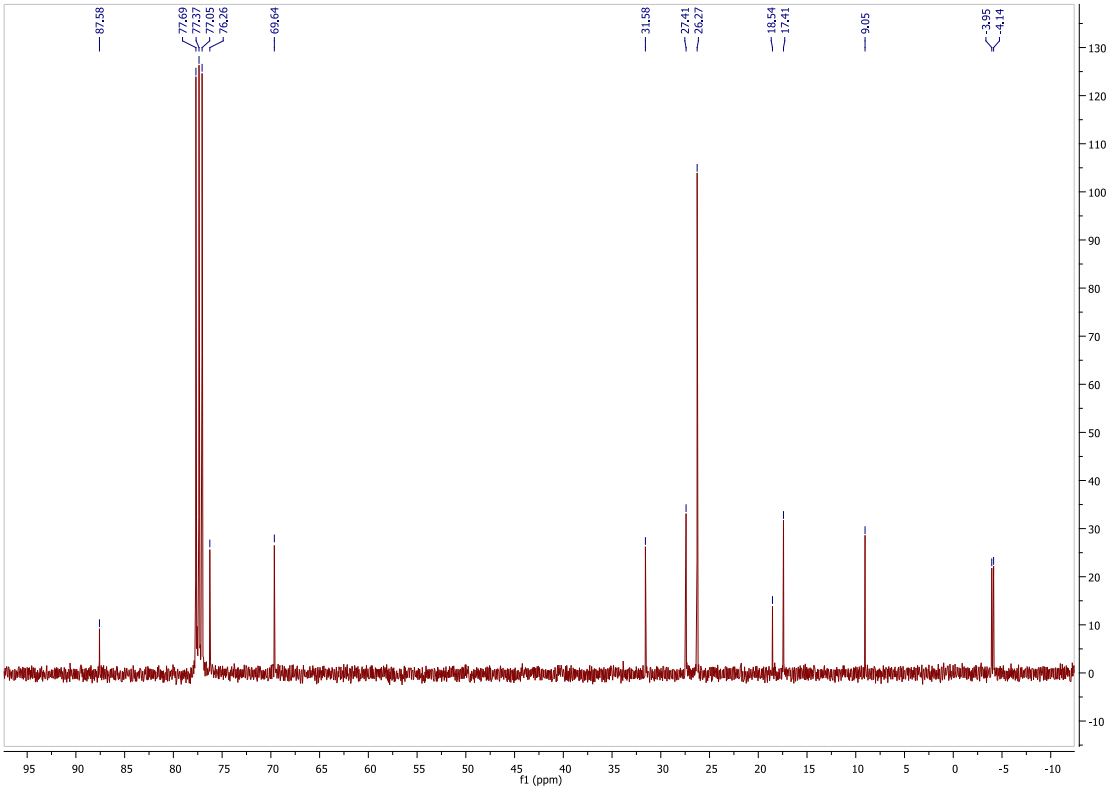
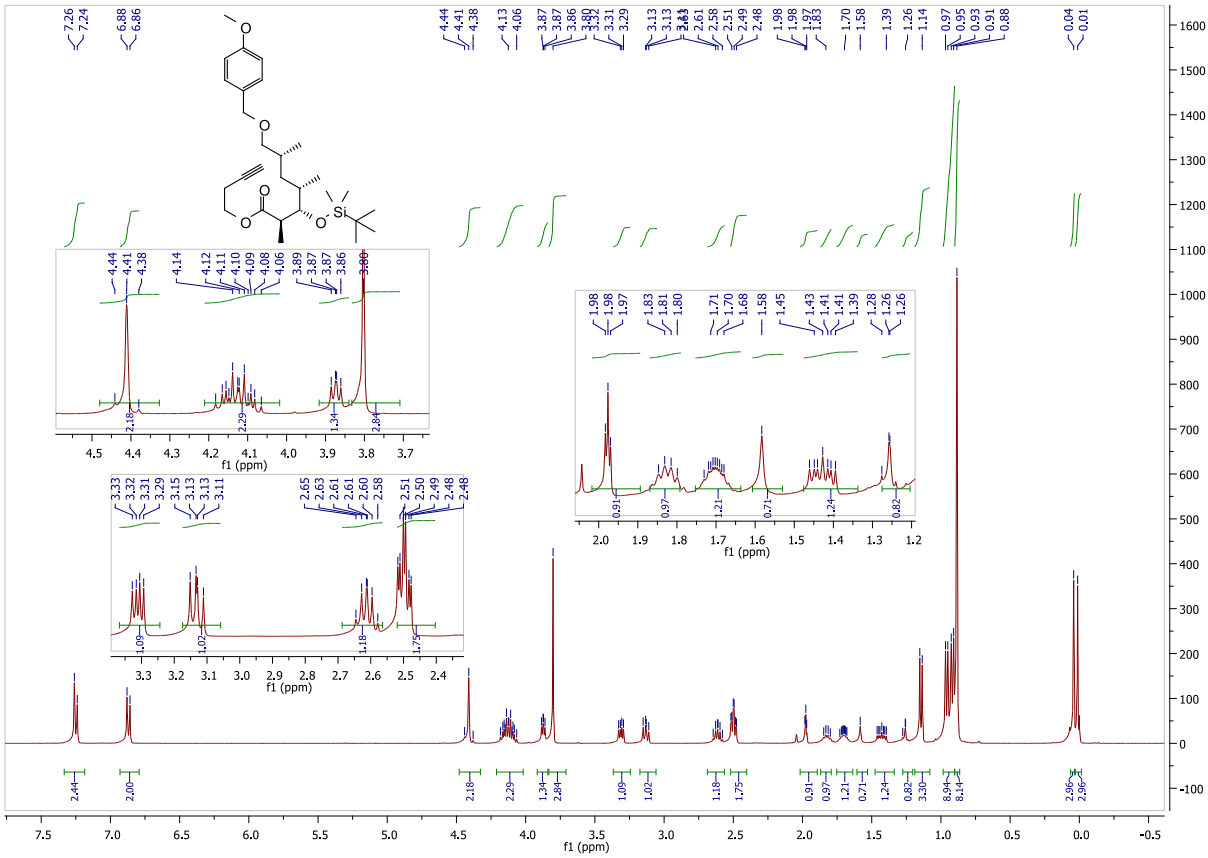
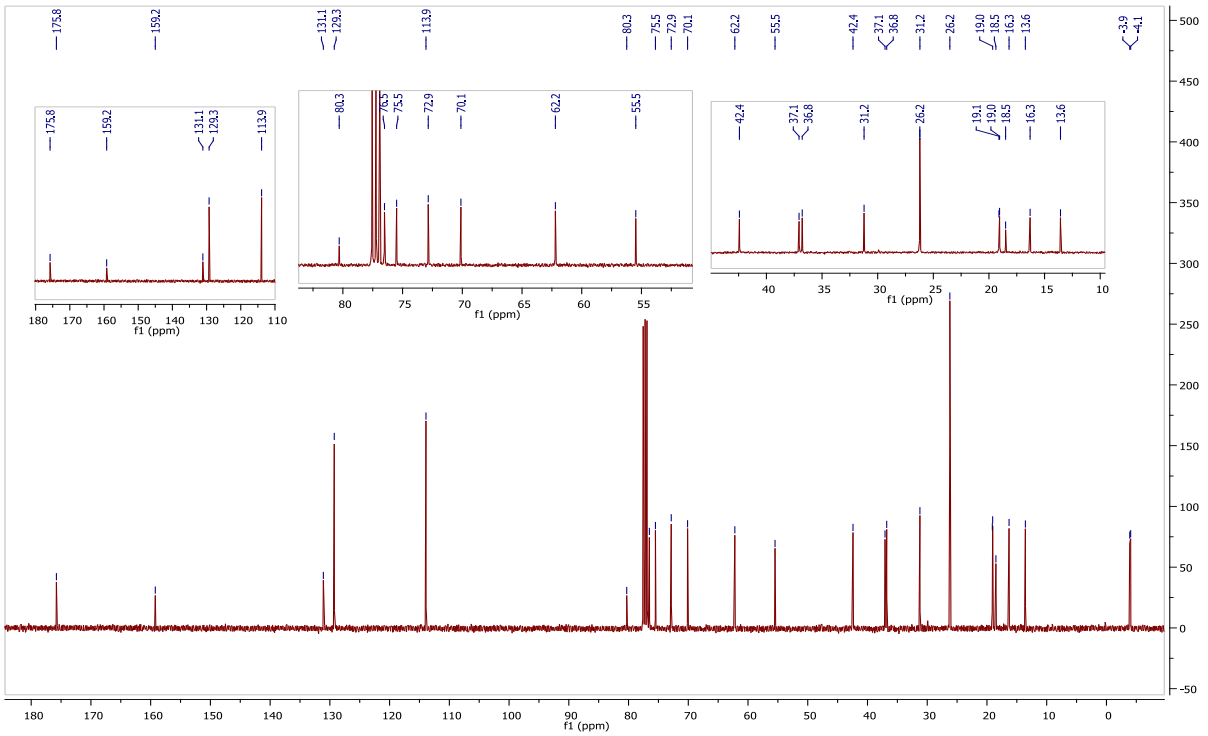
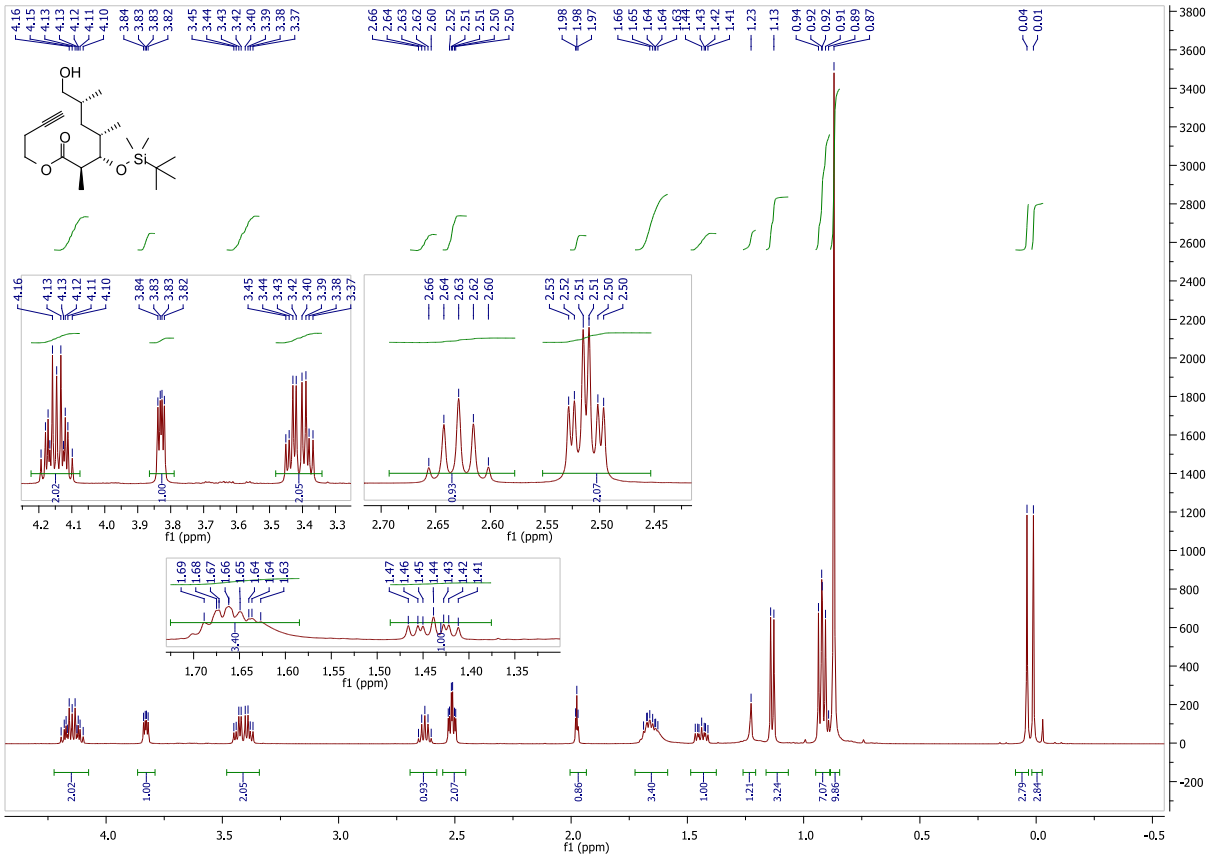
f1 (ppm)







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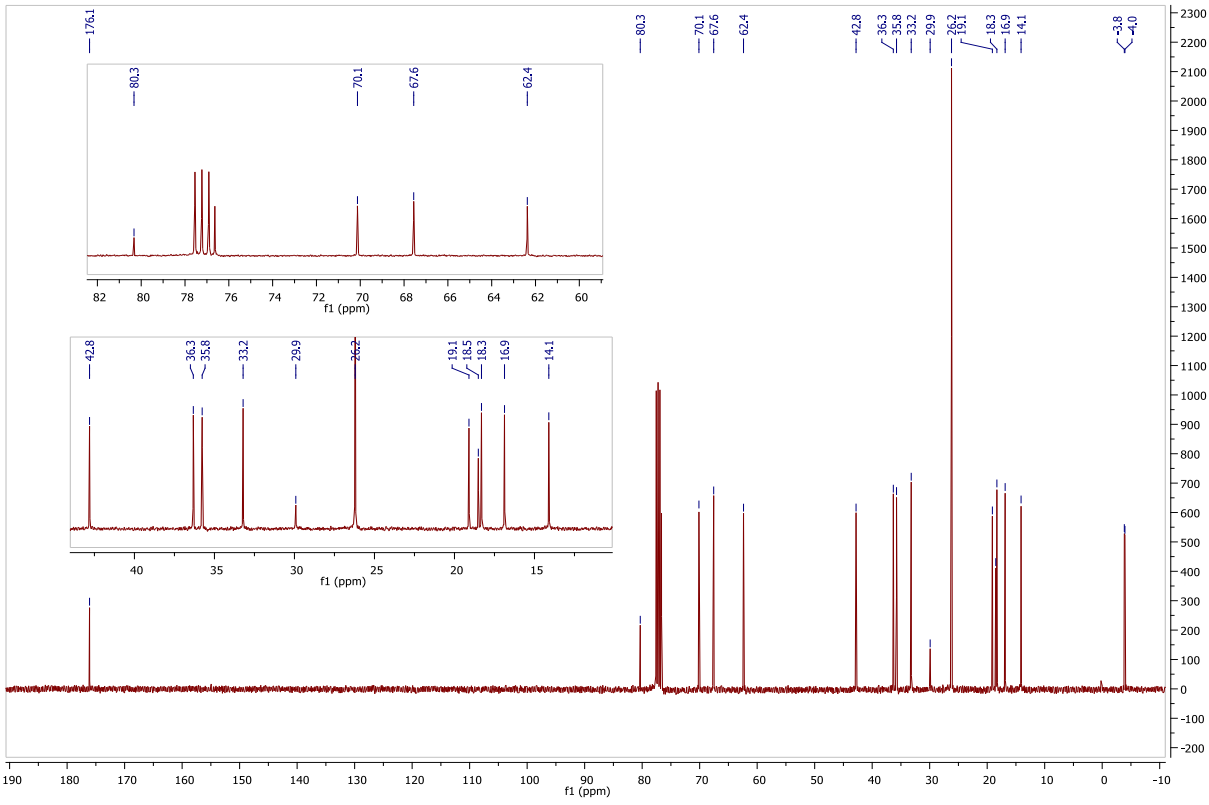
O
O
Si
f1 (ppm)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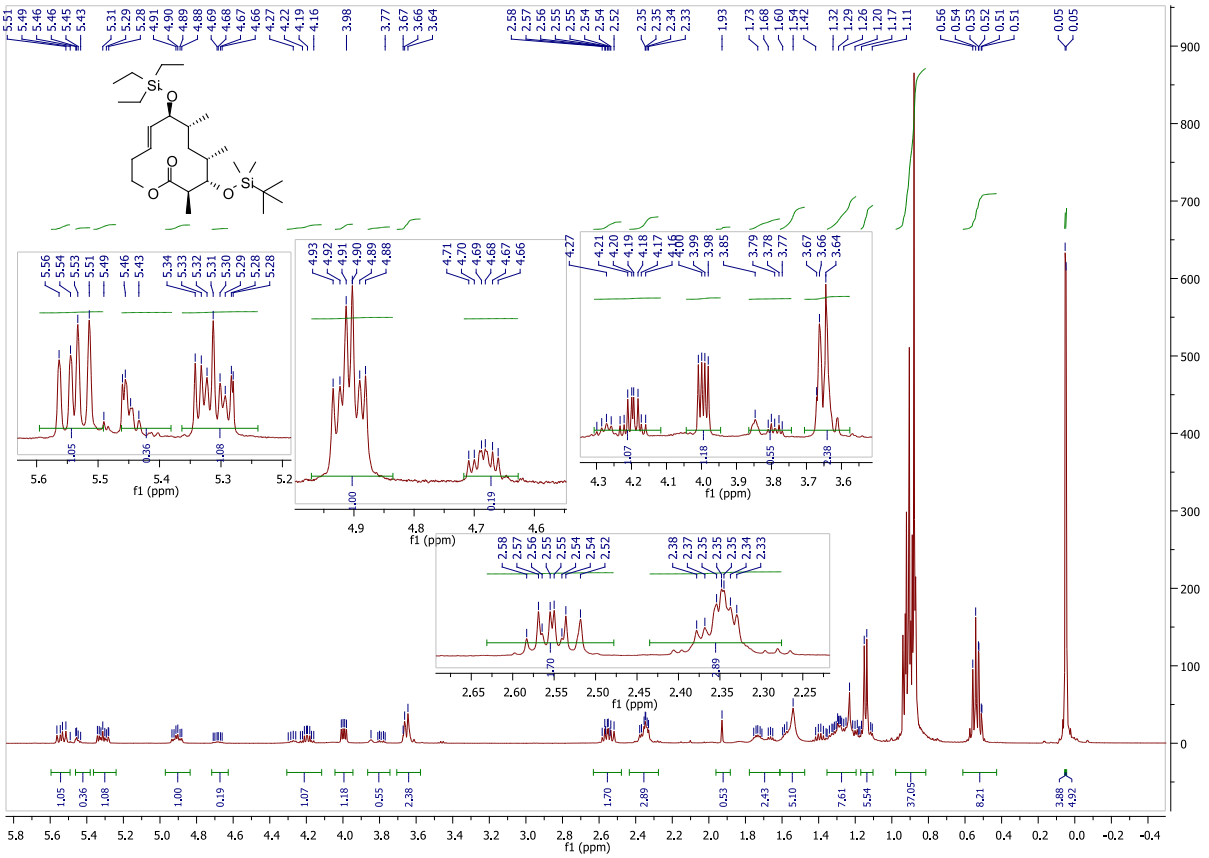
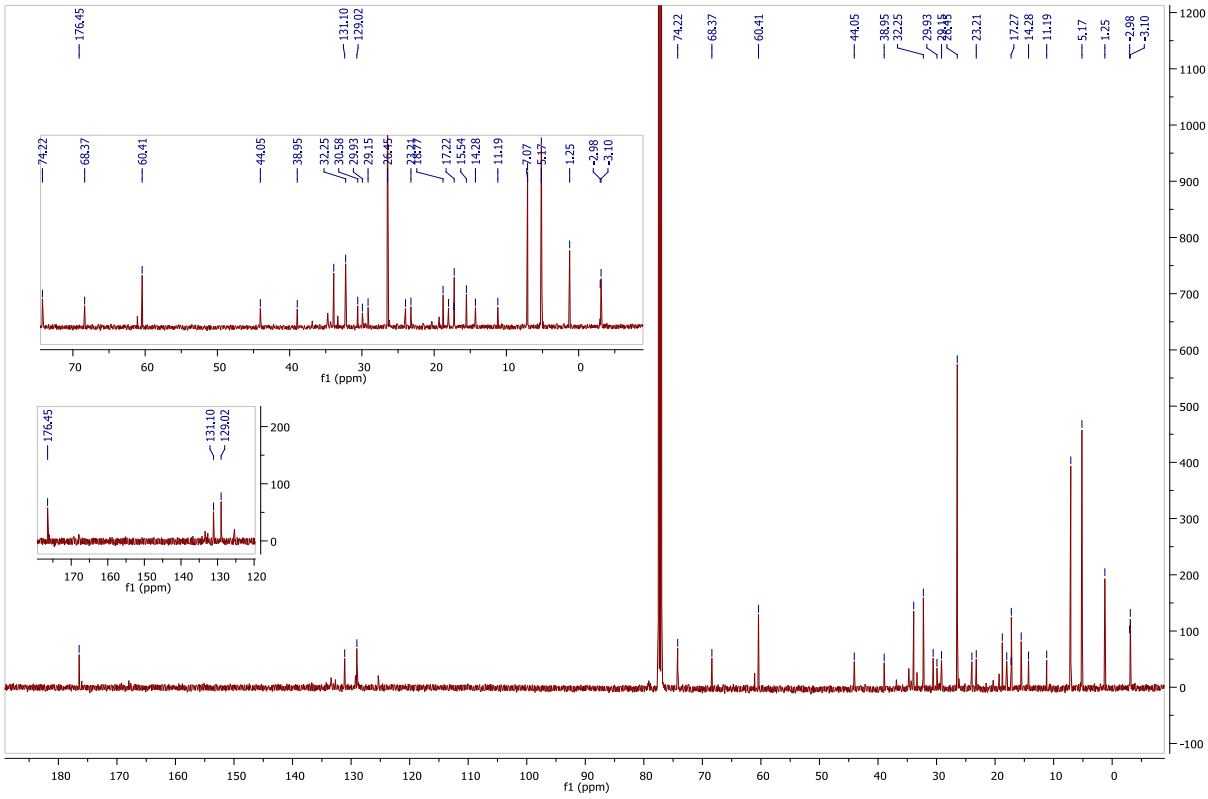
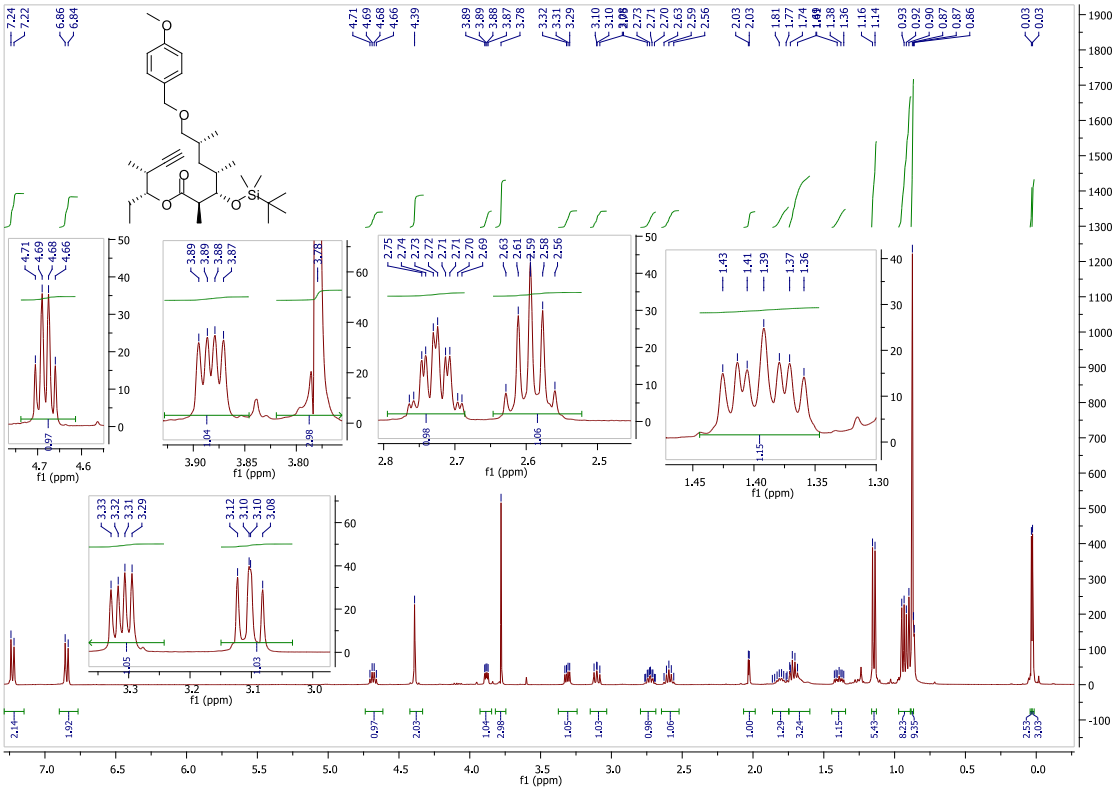
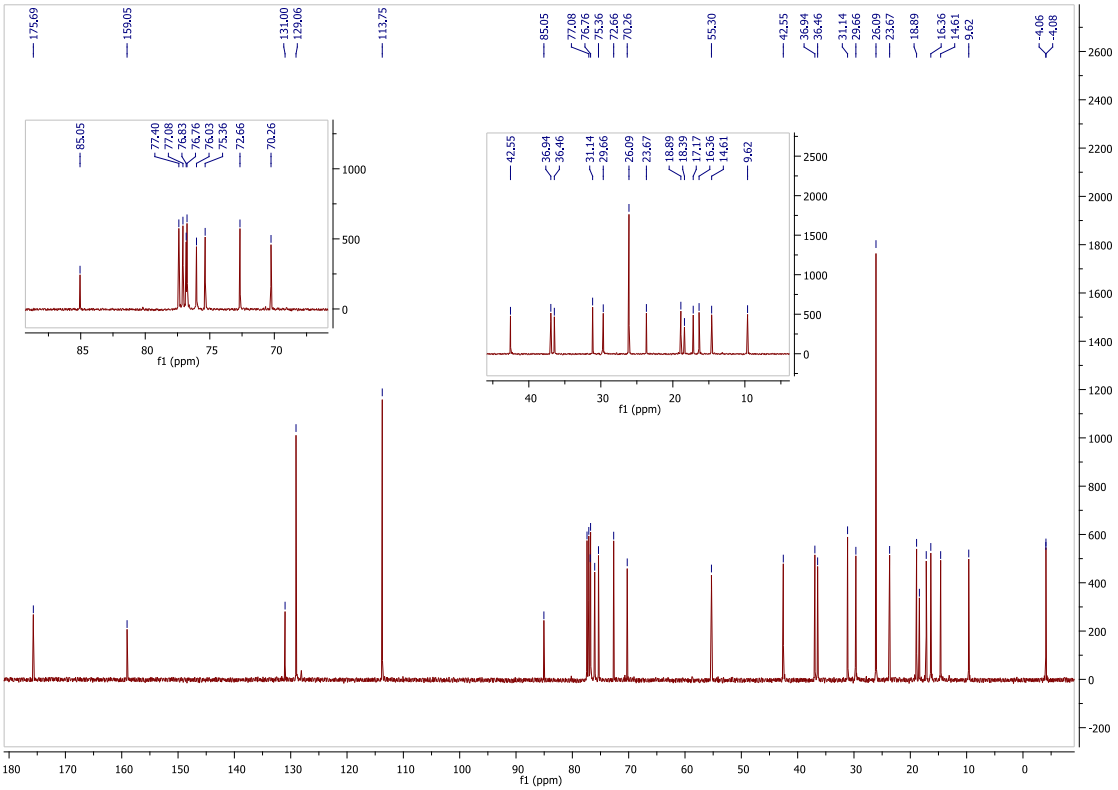
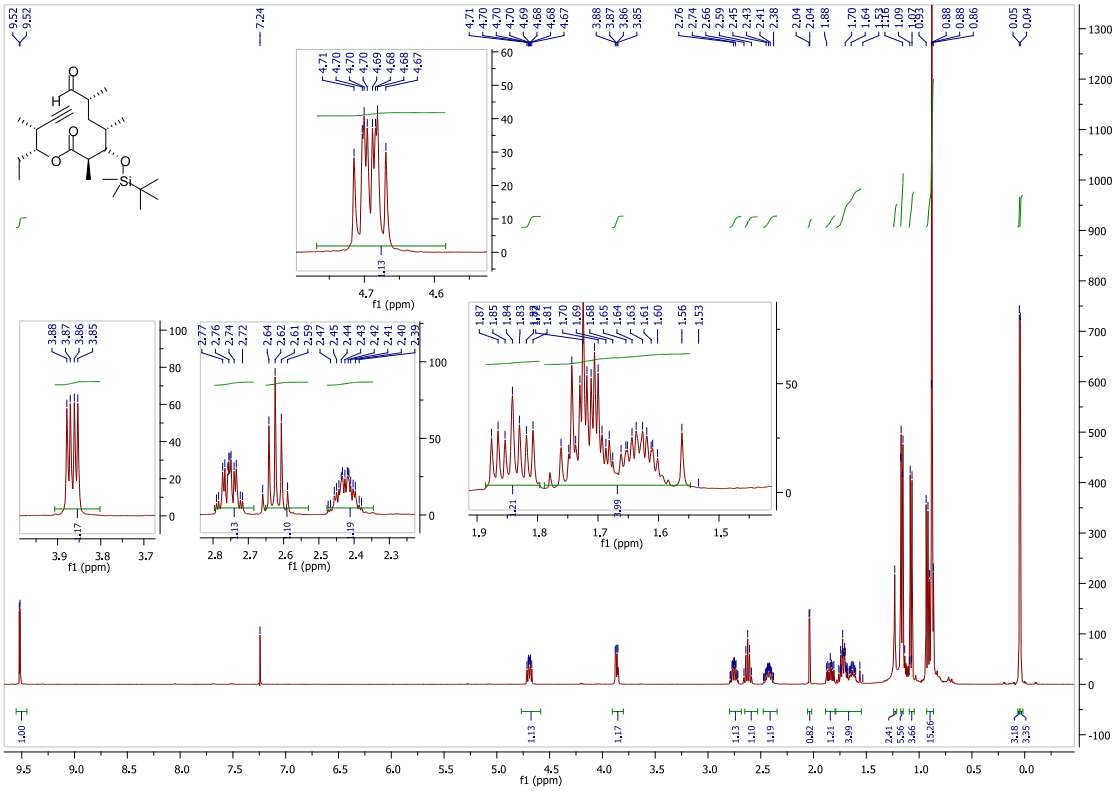
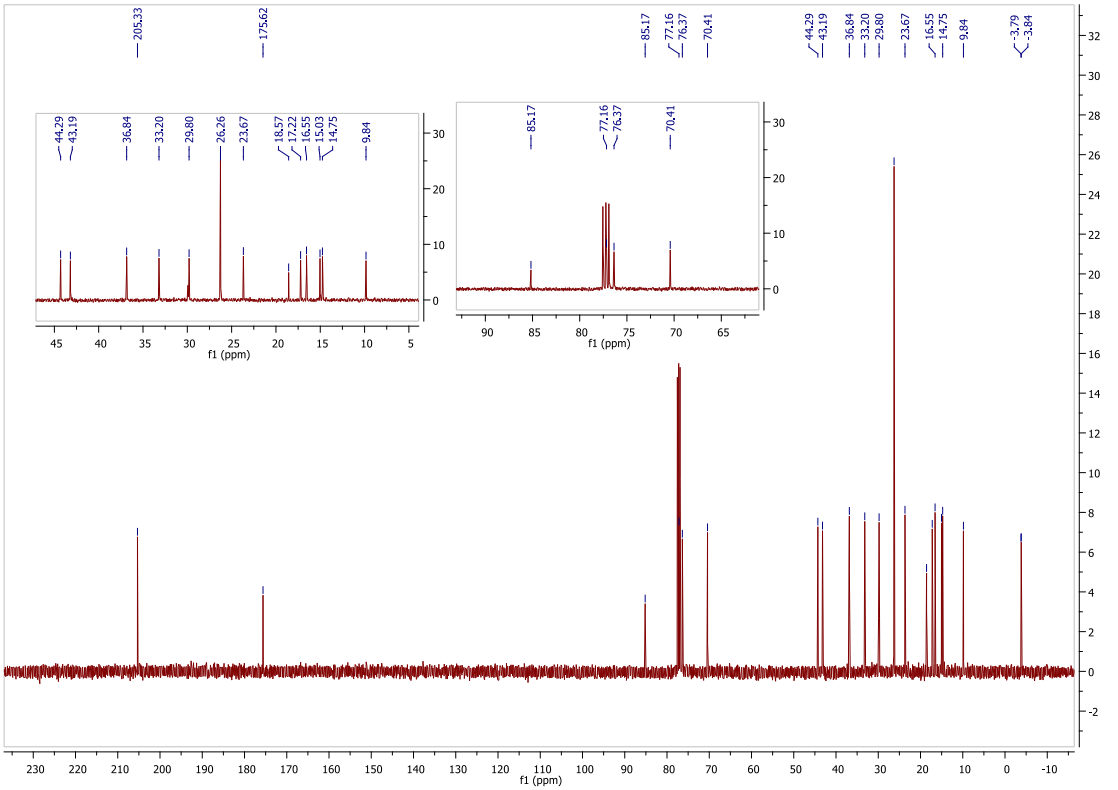


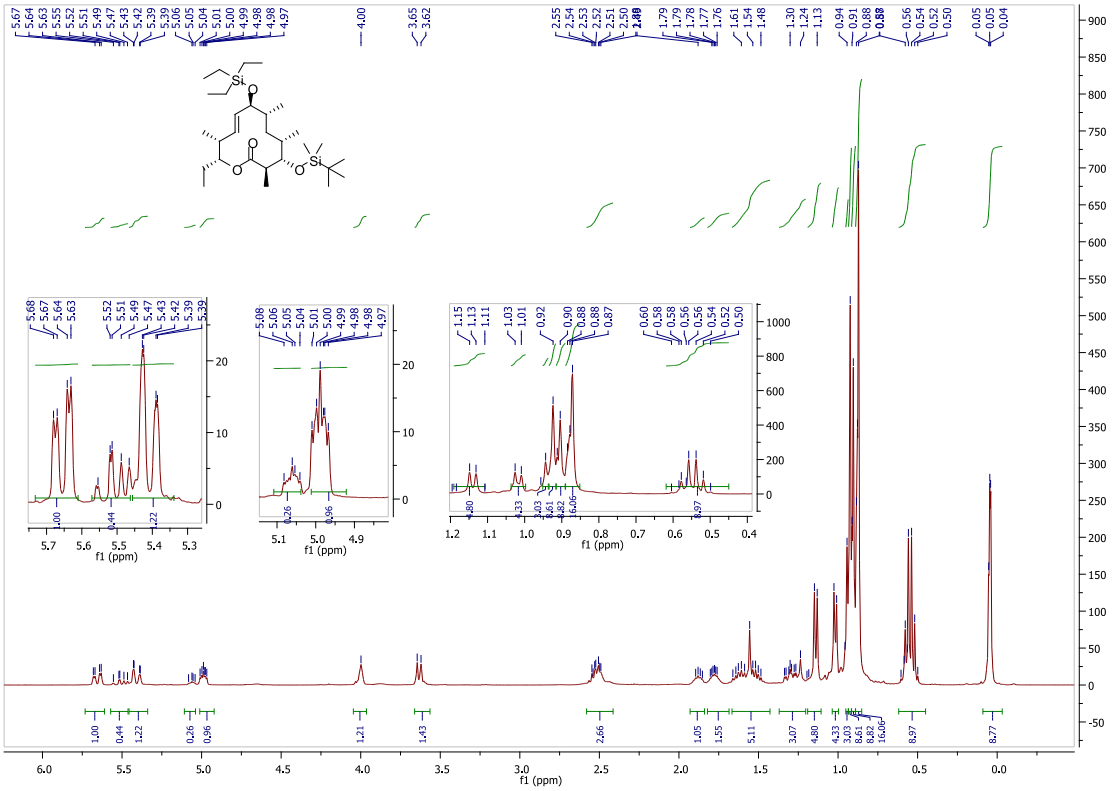


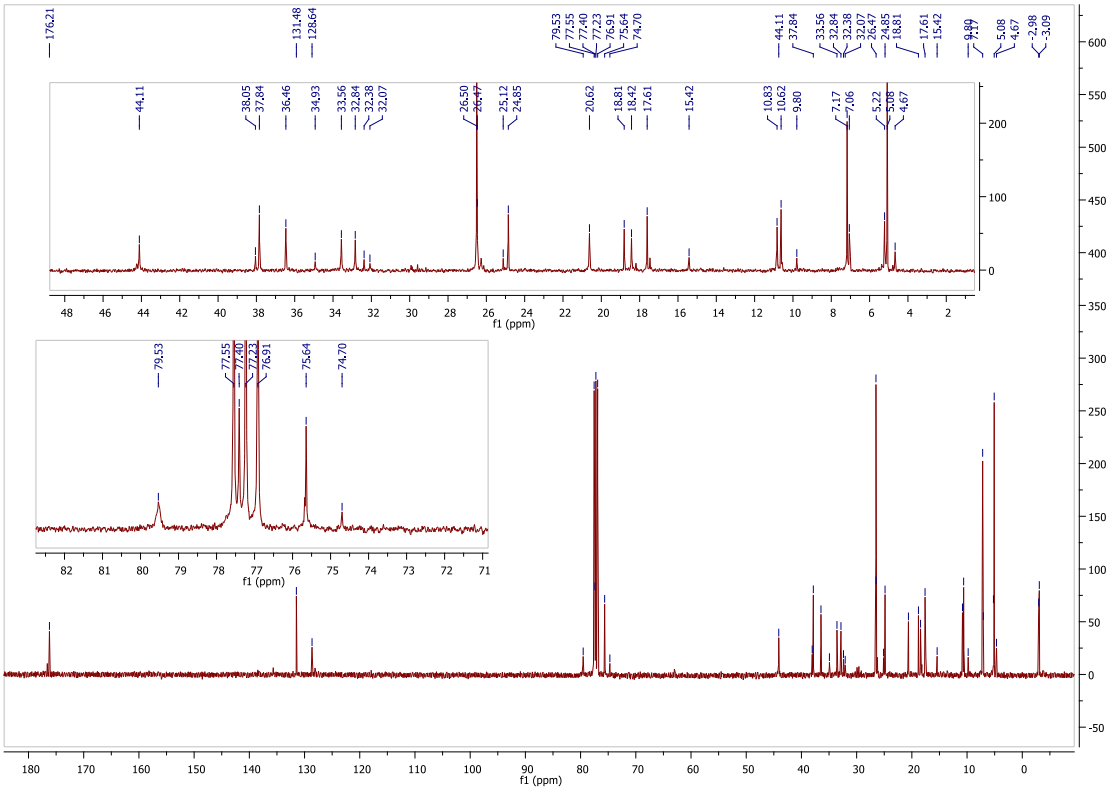


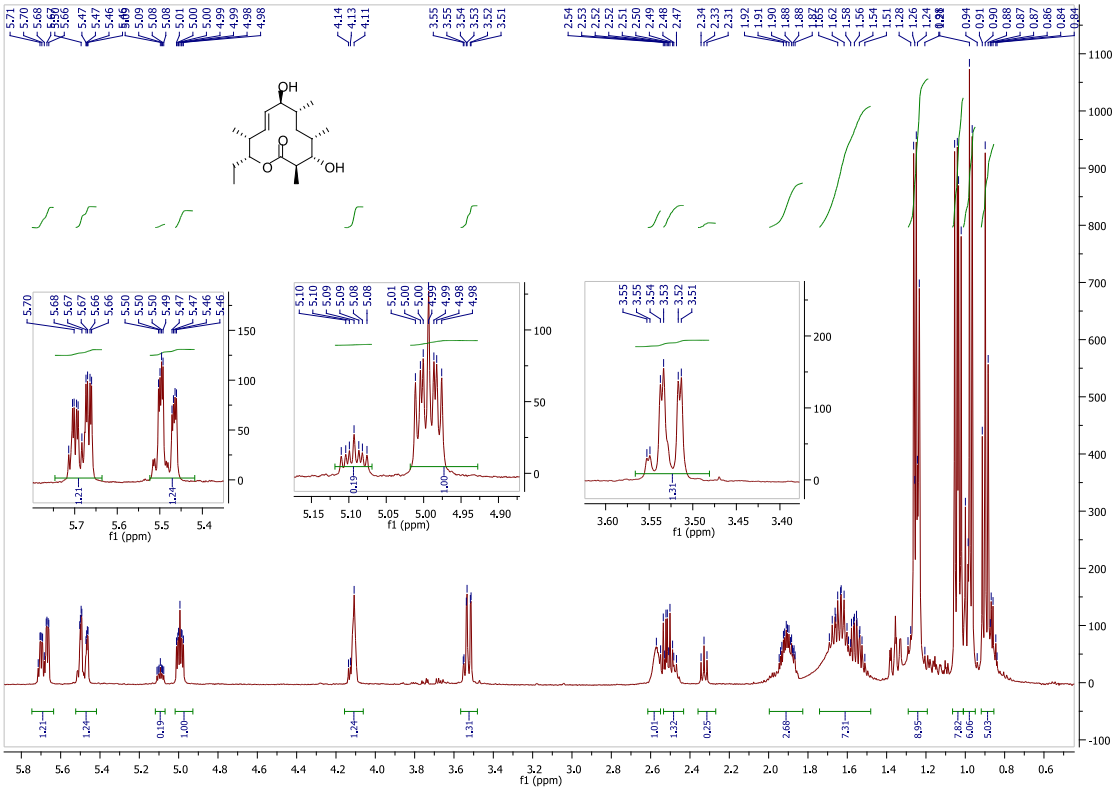


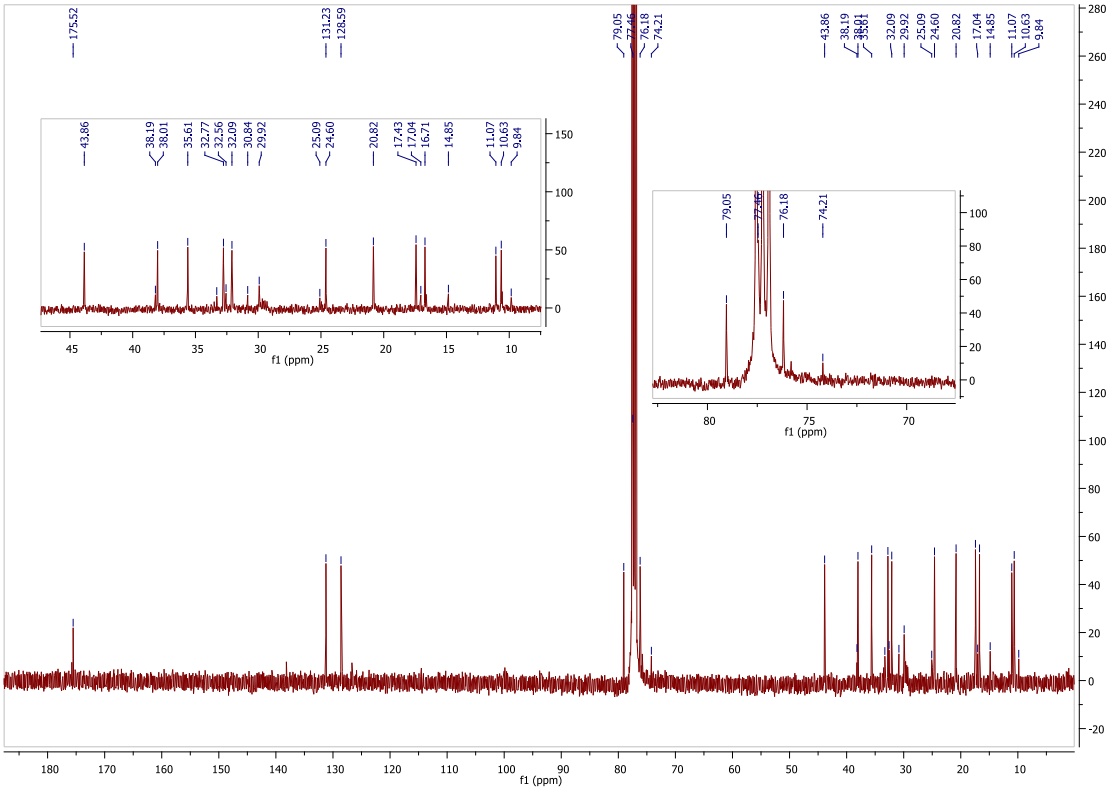


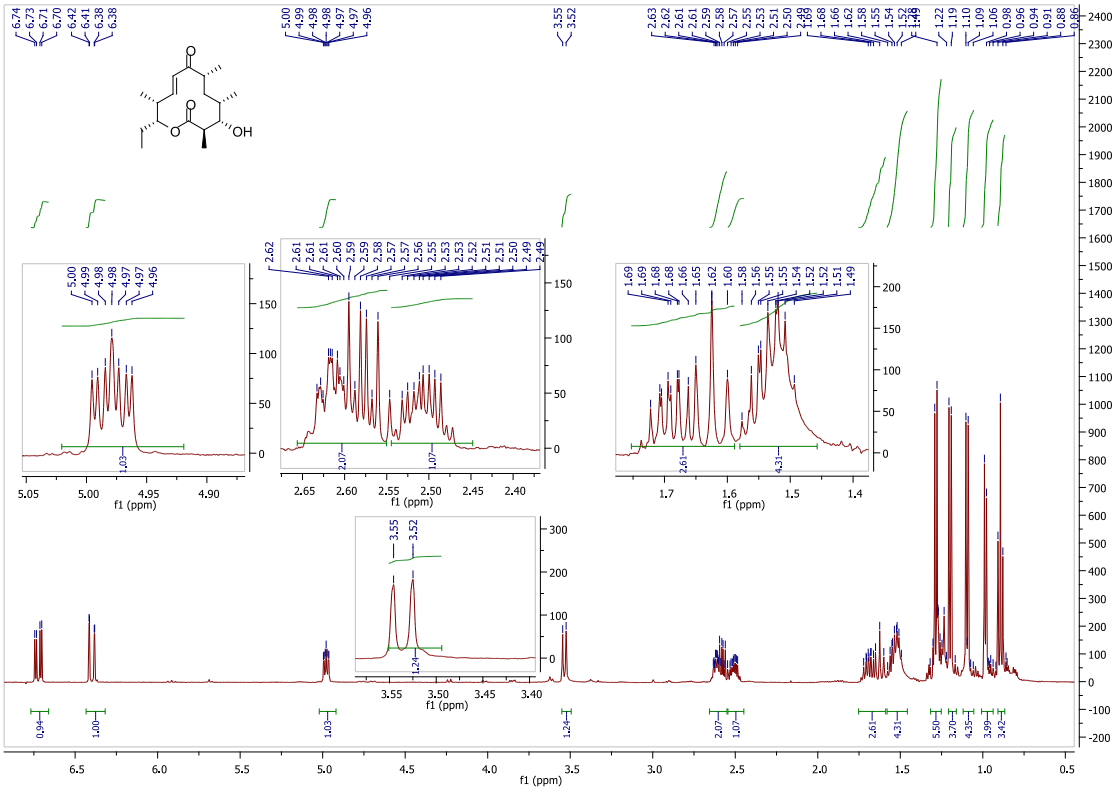


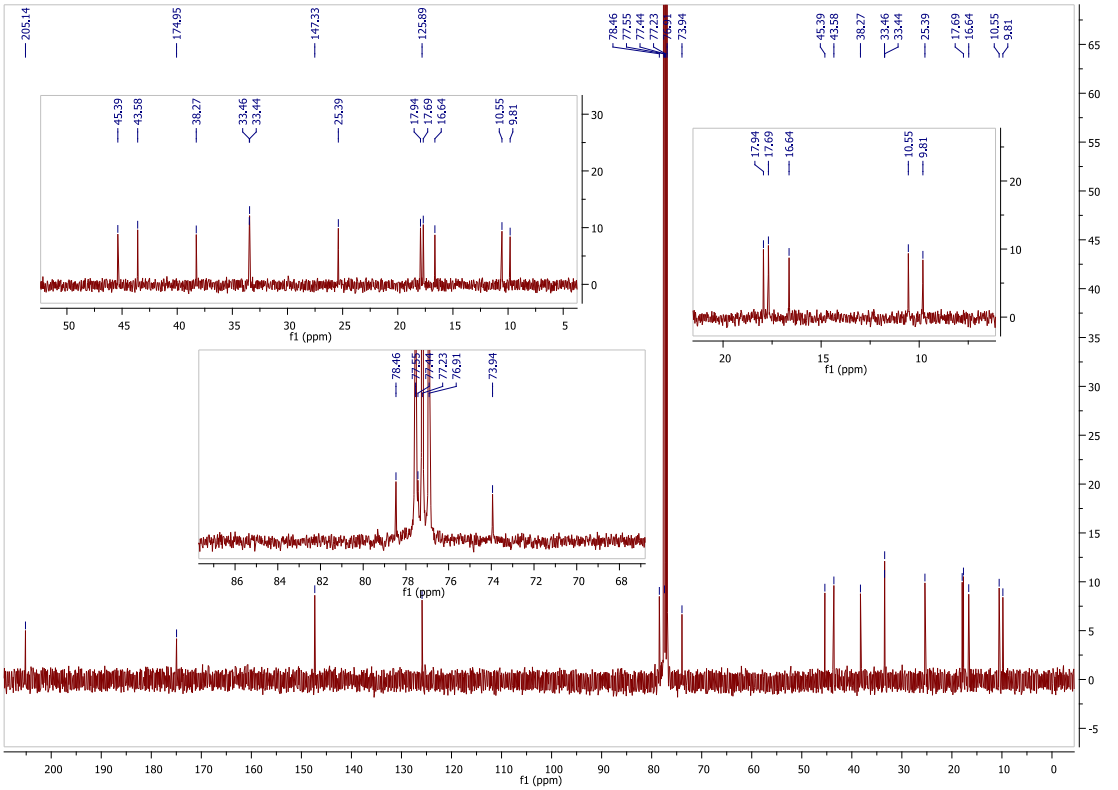




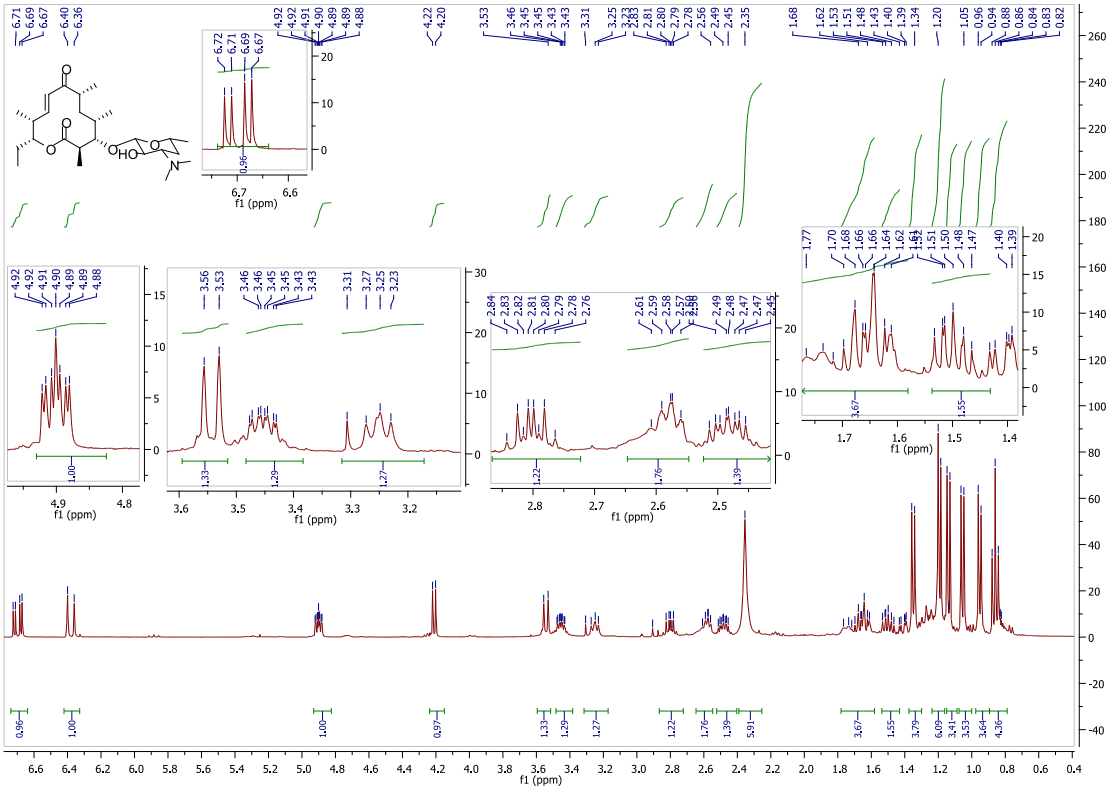


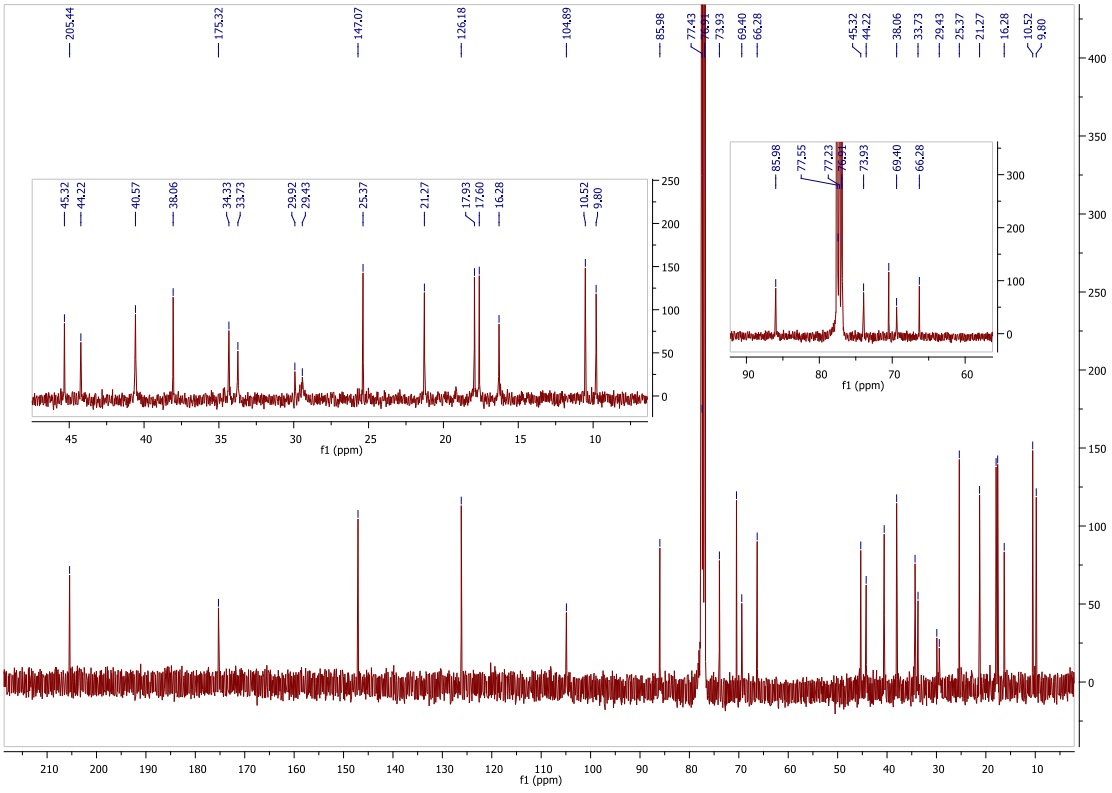




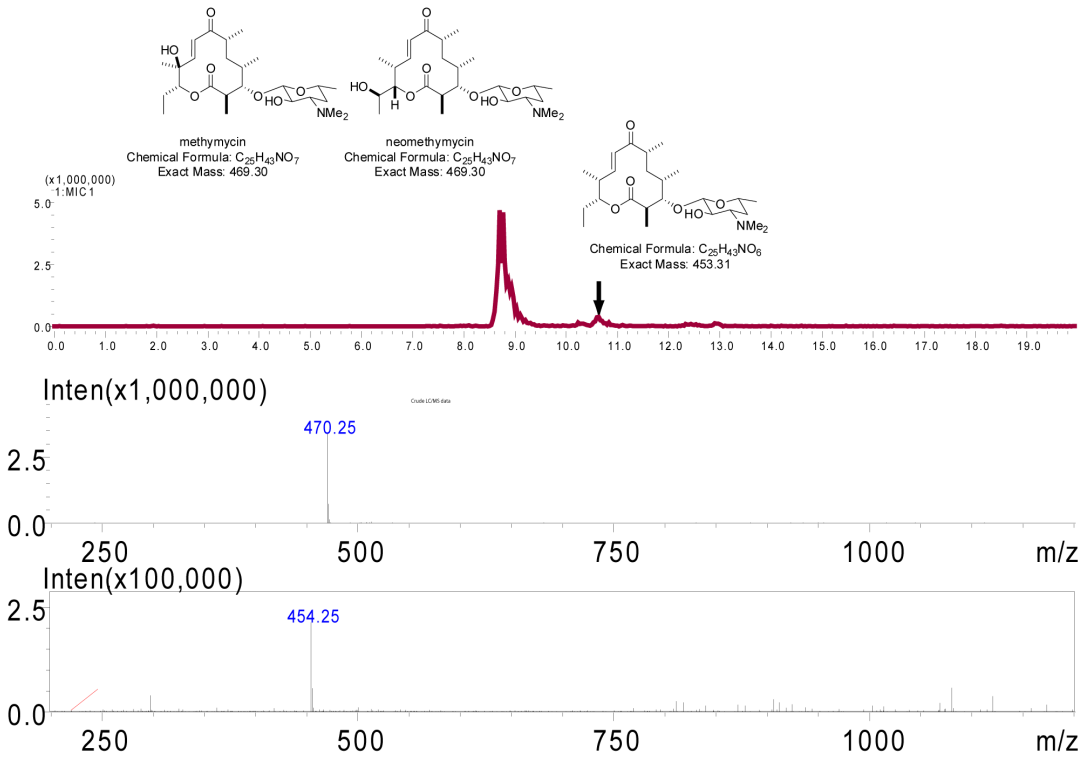


Please see *JACS*, **1998**, *120*, 2682-2683, *supporting info* for spectral comparison and please see Kinumaki, A.; Suzuki, M. for isolation of natural product YC-17.[10]

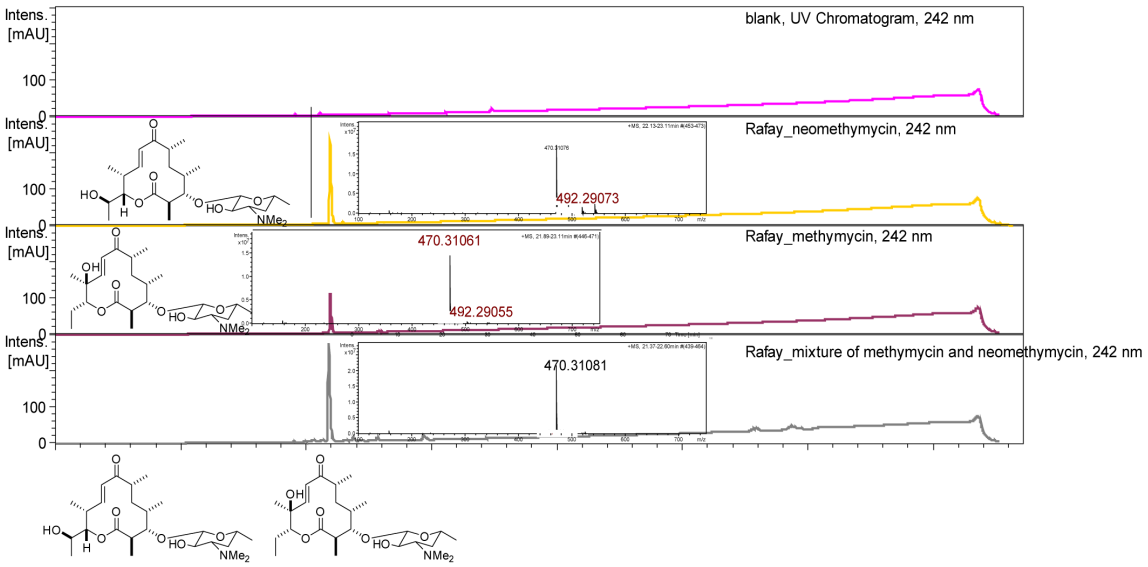




Crude LC/MS data after reaction mixture was filtered through Celite. Large Peak at 8.5-9.2 minutes is mixture of methymycin and neomethymycin $[M + H]^+$ 470.3
Peak at 10.6 indicated by arrow is remaining YC-17 $[M + H]^+$ 454.3

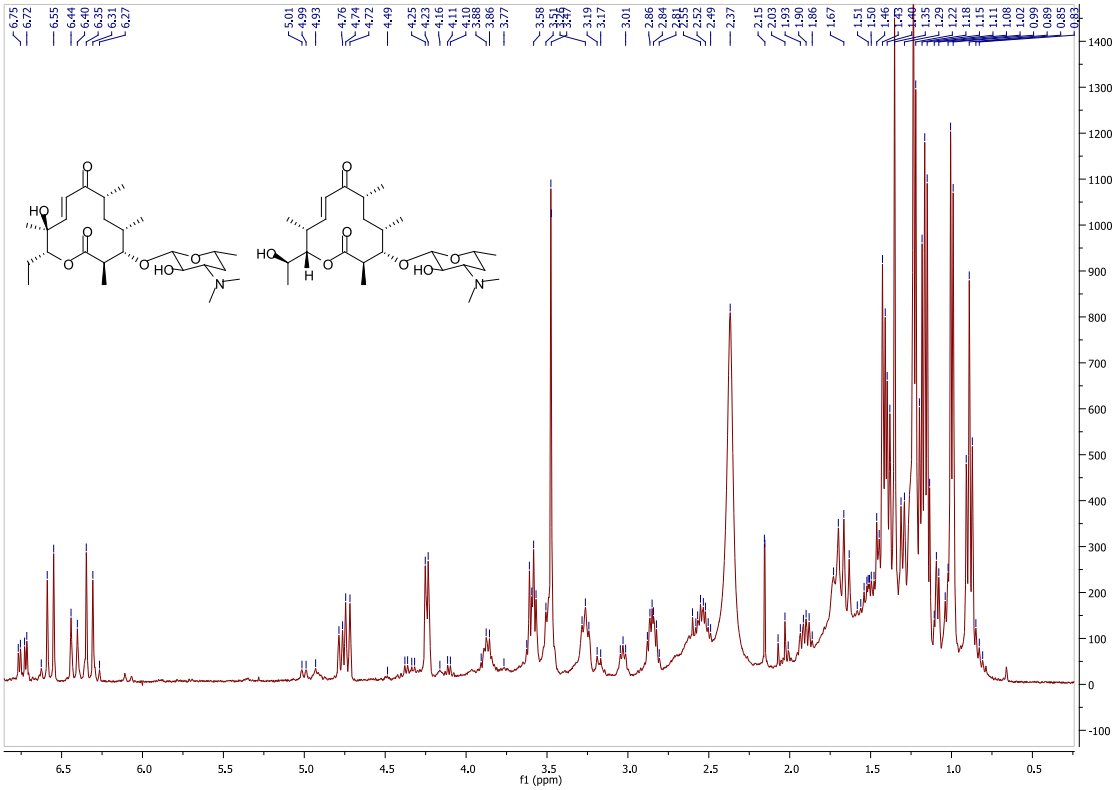


Purified methymycin and neomethymycin analyzed using FTICR-MS. Compared against standards derived from fermentation.

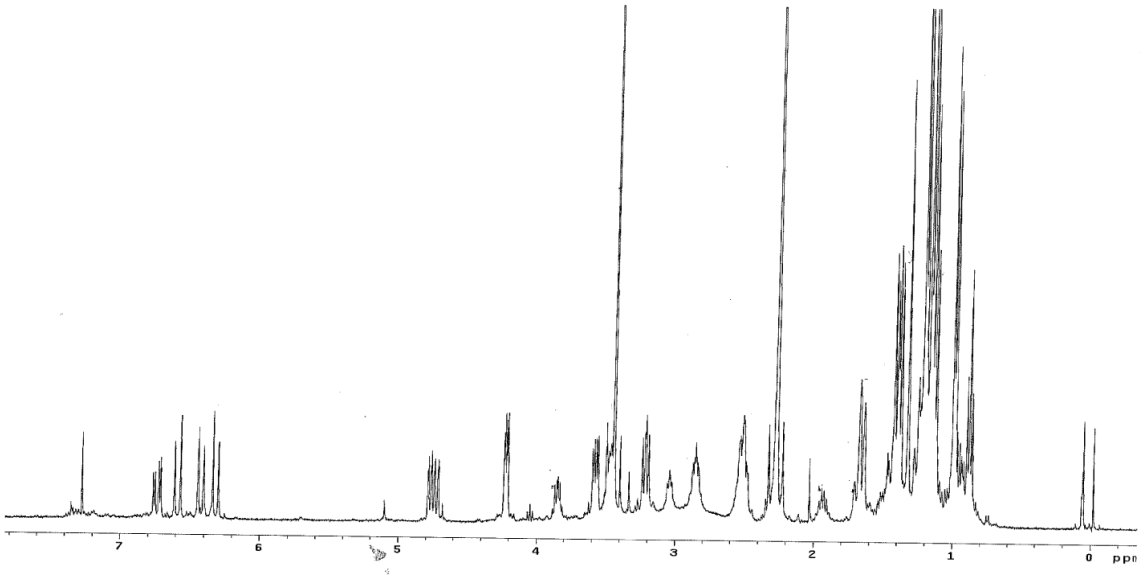


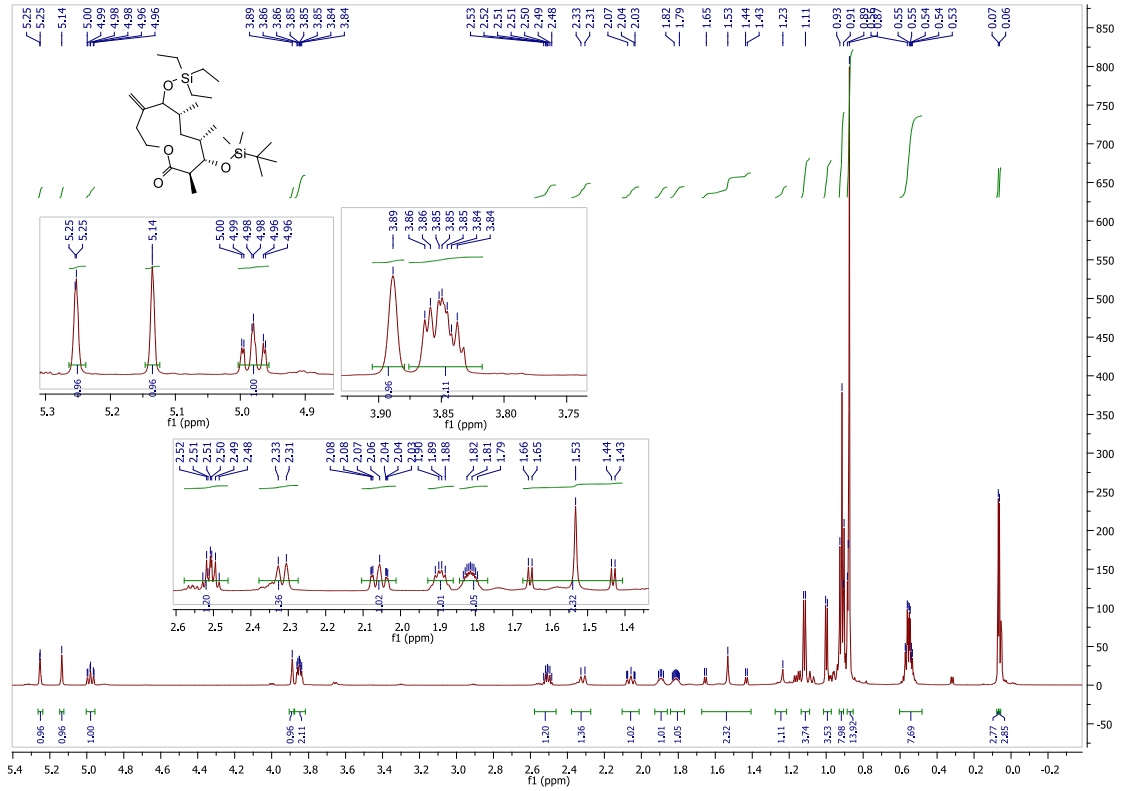
Lane 1, blank. Lane 2 contains authentic neomethymycin isolated from fermentation.[12] Lane 3 contains authentic methymycin isolated from fermentation.[12] Lane 4 contains synthetic methymycin and neomethymycin prepared through total synthesis.

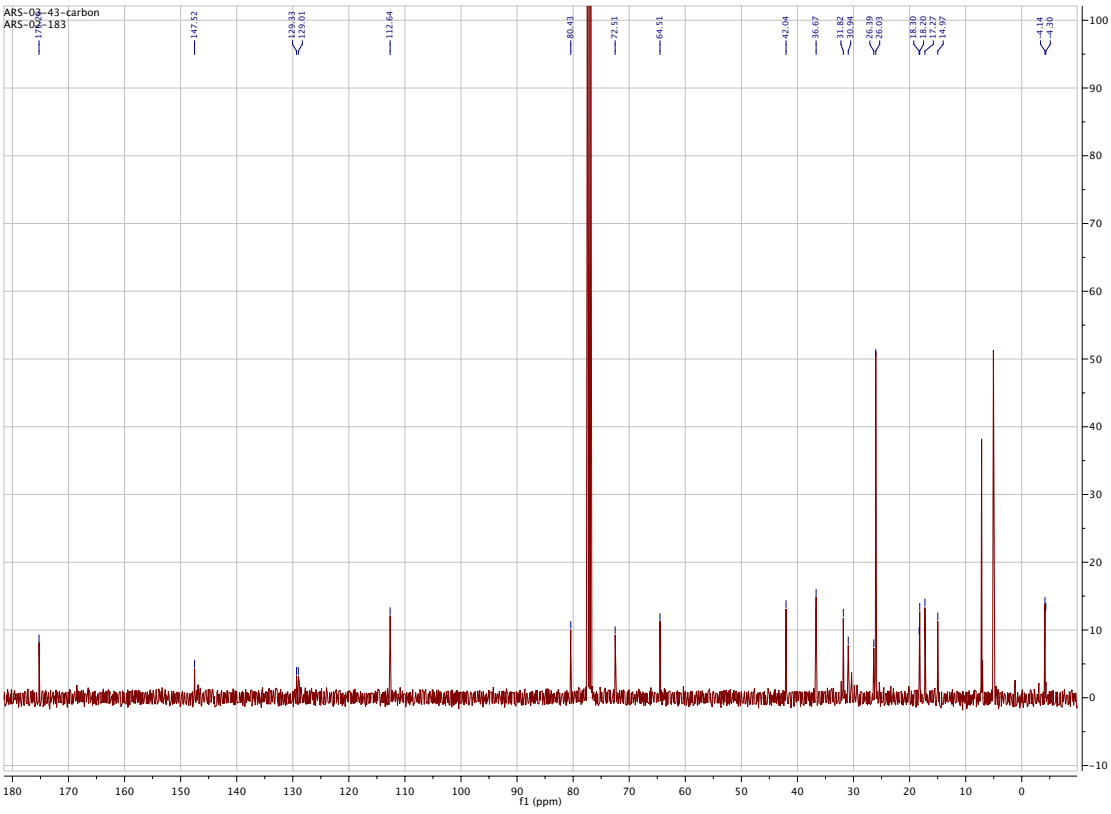
Synthetic methymycin and neomethymycin:

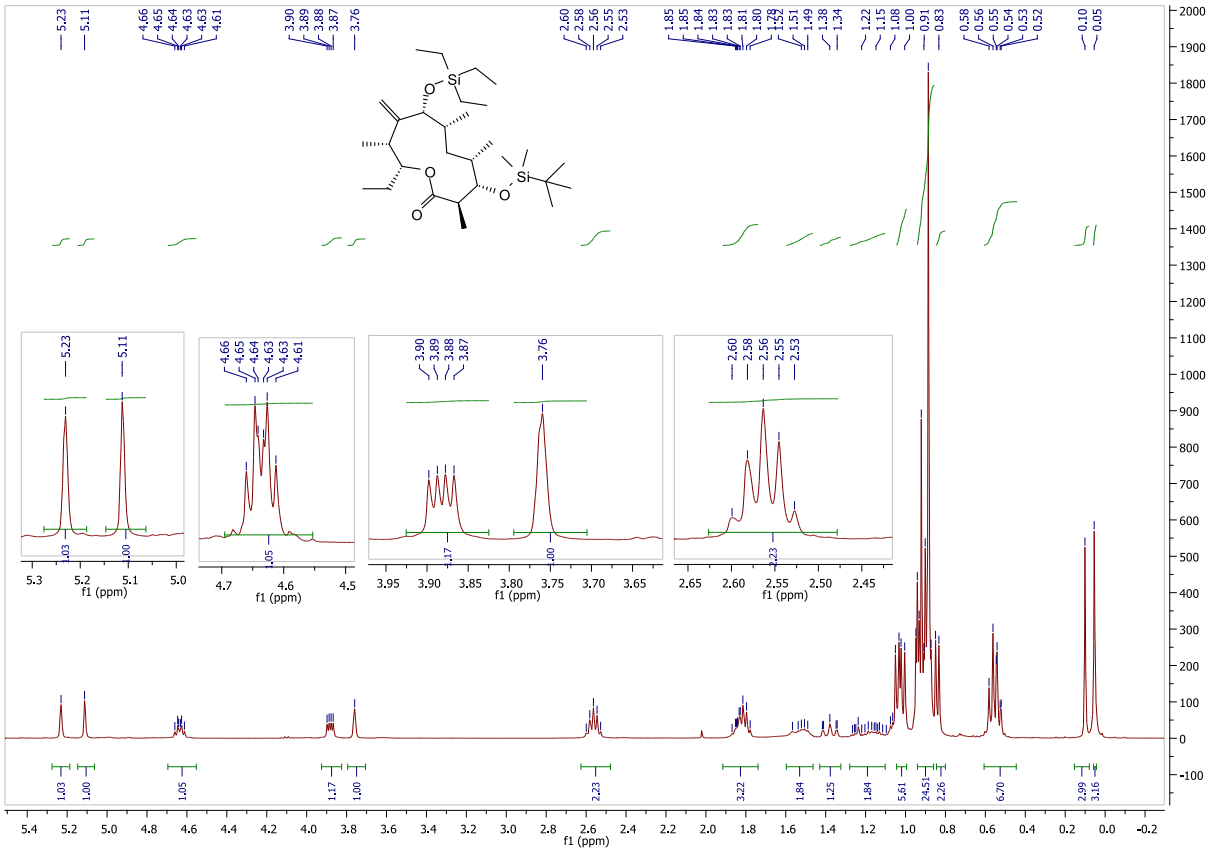


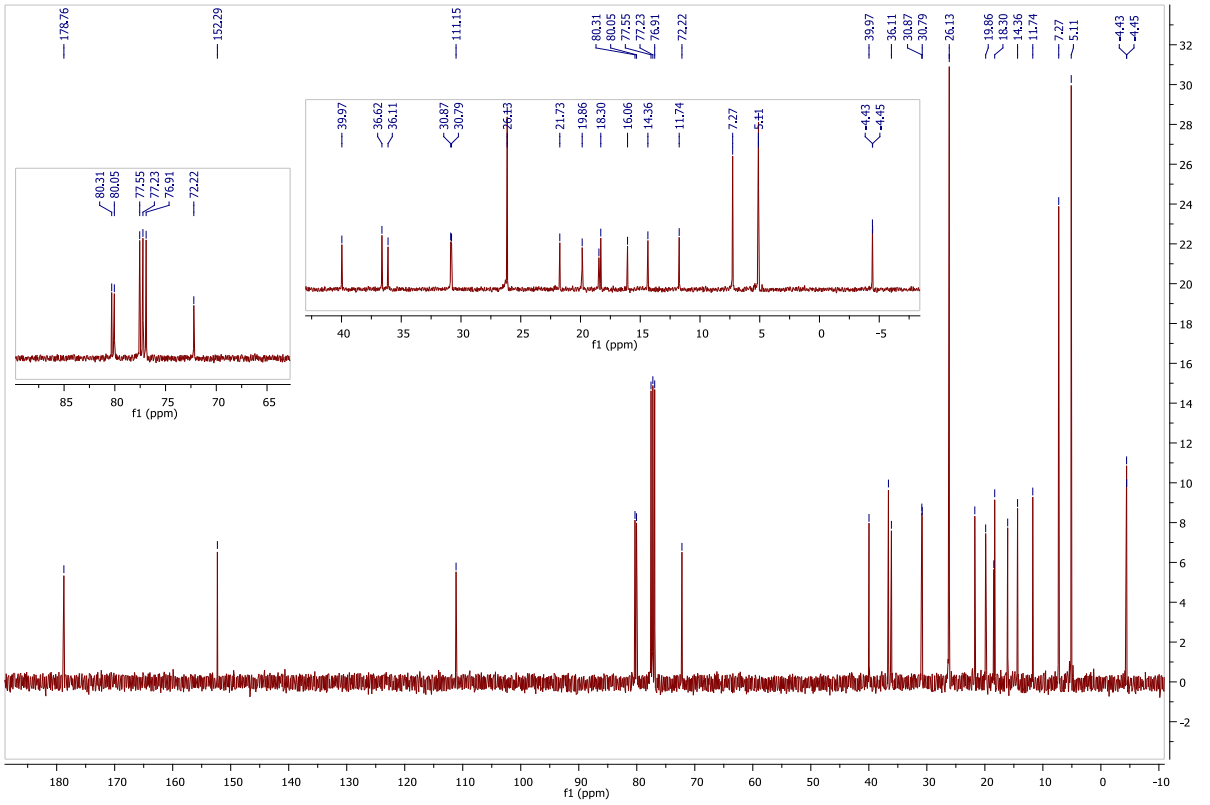
Fermentation derived methymycin and neomethymycin:






ARS-03-43-carbon
ARS-02-183





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