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Synthesis of natural compounds in Echinacea

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Synthesis of natural compounds in *Echinacea*

by

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GENERAL INTRODUCTION

Over the last decades, organic synthesis has been one of the central parts of chemistry. Discovery and invention of new synthetic strategies and technologies have enriched the field of organic synthesis. These novel methods allow us to approach complex natural products in a direct and efficient way. The synthesis of biologically active natural compounds and their analogs have become an important role in drug discovery studies. Especially, approaches to these molecules in a concise manner are highly desirable. In this context, we have investigated direct routes to natural products.

Chapter one describes a synthesis of natural compounds in *Echinacea,* which is an important botanical supplement in the market. The synthesis of components in Echinacea will help us to understand their biological activities.

Chapter two describes the new synthetic strategy to construct complex molecules using Diels-Alder/ene cyclization and its application to a natural product. The numbering of the compounds, figures and references used are independent in each chapter.

CHAPTER 1. SYNTHESIS OF NATURAL COMPOUNDS IN *ECHINACEA*

Introduction

Echinacea is a perennial herb with purple, daisy-like flowers, which are hardy, herbaceous plants, native to parts of North America. There are nine known species of *Echinacea*, but only three of these are used for medicinal purposes. These three species are *E. angustifolia*, *E. pallida*, and *E. purpurea*. [1]

Echinacea has a long history of medicinal use by Native Americans for a wide variety of infections, such as septic wounds, but also as an anti-toxin for snakebites and blood poisoning.[2] Traditionally, *Echinacea* was described as an anti-infective agent, and was used in bacterial and viral infections, furunculosis, mild septicemia and other skin conditions, including boils, carbuncles and abscesses.[3] Other traditional uses include nasopharyngeal catarrh, tonsillitis, as a supportive treatment for influenza-like infections and recurrent infections of respiratory tract and lower urinary tract and for poorly-healing superficial wounds.[3b]

The fresh or dried underground parts (roots, rhizomes) of all of the three species are used medicinally. In addition, the fresh or dried flowering tops and the fresh pressed juice from the flowering tops of *E. pupurea* are used.[1]

In 2005, *Echinacea* products ranked among the top botanical supplements sold in the United States. Commercial *Echinacea* products often are mixtures of the three main medicinal species and there is no regulation of the amounts of the chemical constituents.

There are some differences in the constituents of *Echinacea* across the species and their respective plant parts (Table 1).

A wide range of compounds in *Echinacea* species has been reported to have pharmacological activity.[4] These active constituents can be divided into three major groups, namely the alkamides and polyenynes, caffeic acid derivatives and polysaccharides.[5] There is, however, still debate on the relative importance of these groups. It is generally thought that no single constituent or group of constituents is responsible for the activities of *Echinacea*.

Alkamides and polyenynes are main lipophilic components of *Echinacea*. There are at least 20 alkamides present, mainly isobutylamides of straight chain fatty acids with double bonds and triple bonds. The pioneering studies of both Bohlmann and Bauer have revealed the structure, chemistry and biological activities of these alkamides.[6] Figure 1 shows the alkamide constituents in *Echinacea* extracts.[8]

Table 1. Major constituents of Echinacea species used medicinally [7]

Species	**Plant part**	**Constituents**	**Comments**
Echinacea purpurea	Aerial parts	Alkamides; caffeic acid ester, mainly cichoric acid, polysaccharides; polyacetylenes	Echinacoside is not present
Echinacea angustifolia	Roots	Alkamides; caffeic acid ester, particularly echinacoside; cynarin; polysaccharides; polyacetylenes	Cynarin is characteristic of *E. angustifolia*
Echinacea pallida	Roots	Caffeic acid esters, particulary echinacoside; polysaccharides; polyacetylenes	Alkamides largely absent

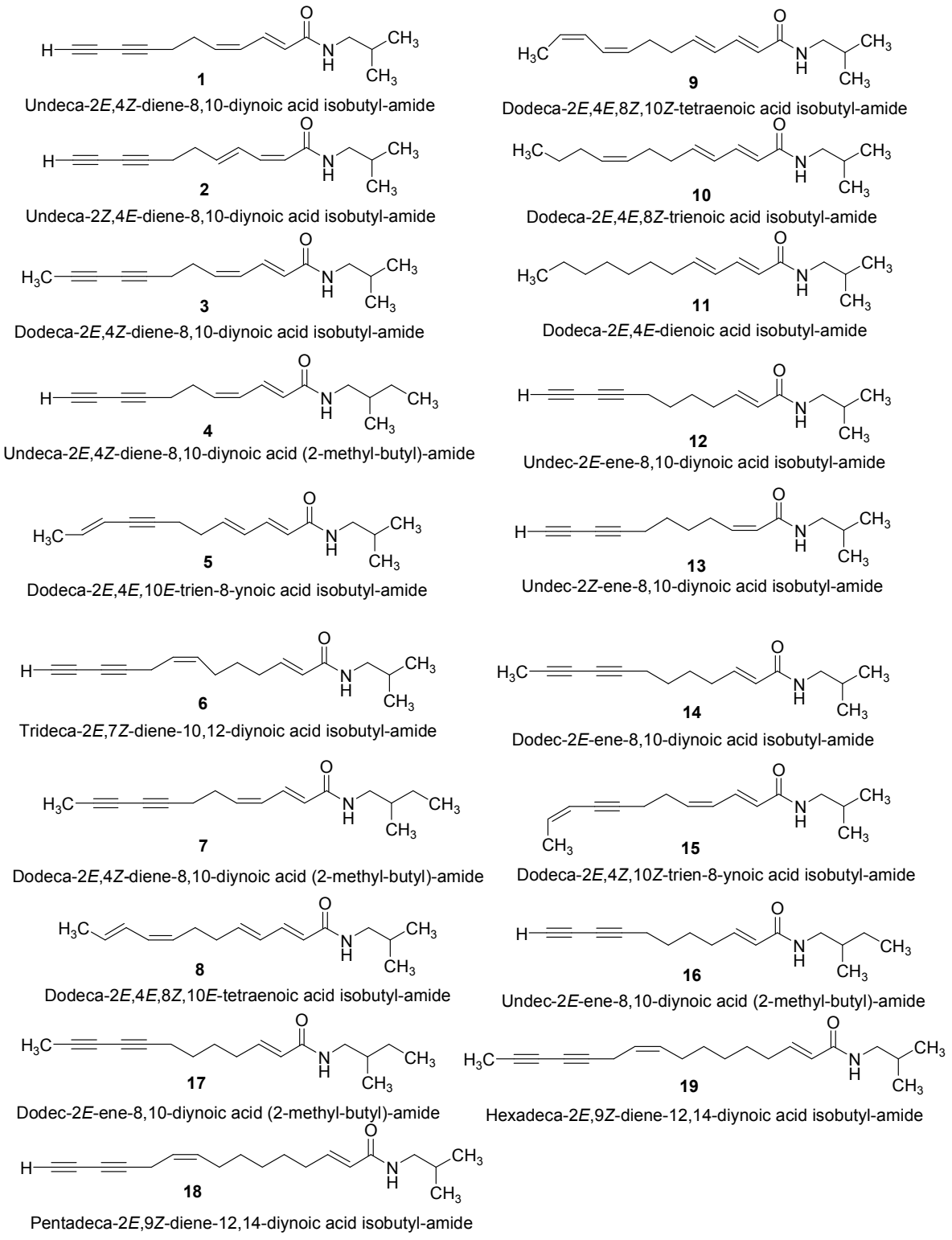


Figure 1. Main alkamides in Echinacea species.[8]

Alkamides have been isolated from *E. angustifolia* and *E. purpurea* roots and arial parts, but they are largely absent from *E. pallida*. Even in same species, alkamide levels differ significantly in different parts. For example, in *E. purpurea*, the roots have higher levels of the C12 diene-diyne alkamides, whereas levels of the C12 tetraene alkamides and C11 diene-diynes are highest in stems. The major constituents of the roots of *E. pallida* are ketone compounds, which can be a marker for *E. pallida,* since it is not found in *E. angustifolia* and *E. pupurea*.[9] Ketone compounds are shown in Figure 2.

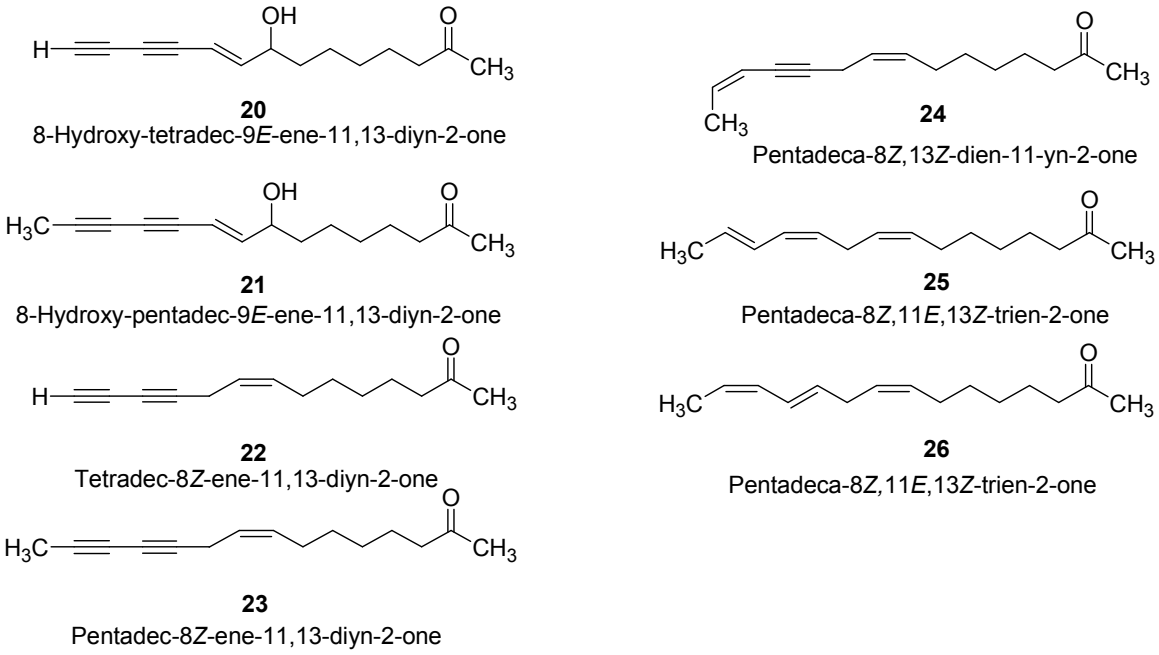


Figure 2. Ketones in *Echinacea*

Caffeic acid derivatives are another major constituents of *Echinacea*. The basic structures of caffeic acid derivatives consist of one or two caffeoyl moieties with a linking molecule, such as tartaric acid, quinic acid or a sugar residue. Examples of caffeic acid derivatives are shown in Figure 3. Of the common caffeic acid derivatives, cichoric acid

appears to have the greatest reported activity. It is found in appreciable amounts in *E. purpurea*[10]. It acts as an antioxidant, and is an inhibitor of viral integrase[11] or bacterial hyaluronidase, and it has immunostimulant activity in phagocytosis tests.[12]

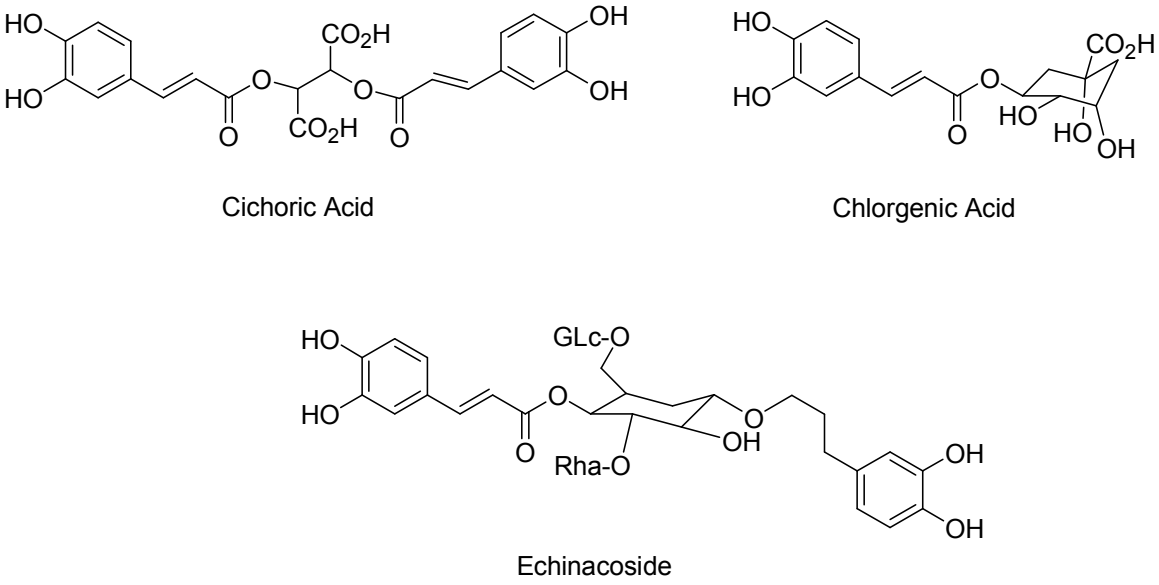


Fig 3. Representative caffeic acid derivatives in *Echinacea*

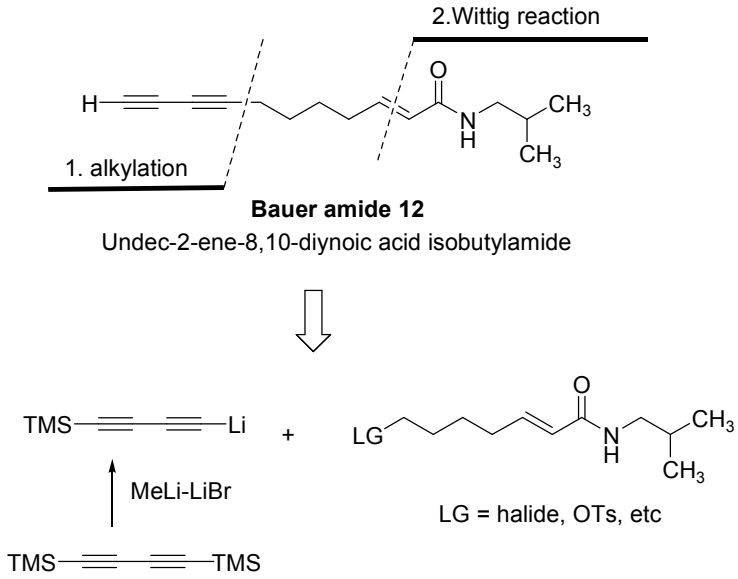
The following polysaccharides have been identified from *E. purpurea*: an 80kDa xyloglucan, a 45kDa arabinotrhamnogalactan, and a 35kDa 4-O-methyl-glucoronoarabinoxylan.[13] Additional polysaccharides and glycoproteins have been characterized from *Echinacea* cell cultures. Polysaccharides from *Echinacea* have potent immunostimulant activity, i.e., macrophage activation and cytokine production (IL-1, IL-6, IL-10 TNF-alpha). [14]

Although there are lots of studies for *Echinacea* and its bioactive constituents in the literature, synthesis of its natural components, especially alkamides and ketones have not been explored. Synthesis of compounds in *Echinacea* will allow us to understand more clearly its bioactive components and also helps to identify the biologically active natural compounds that can be leads for useful drugs. So we describe in this chapter the synthesis of alkamides and ketones of *Echinacea*. The object of this synthesis is to establish a flexible and general synthetic route to alkamides and ketones. The synthesized amides and ketones were tested for their biological activities and compared with natural *Echinacea* extracts as the authentic standards.

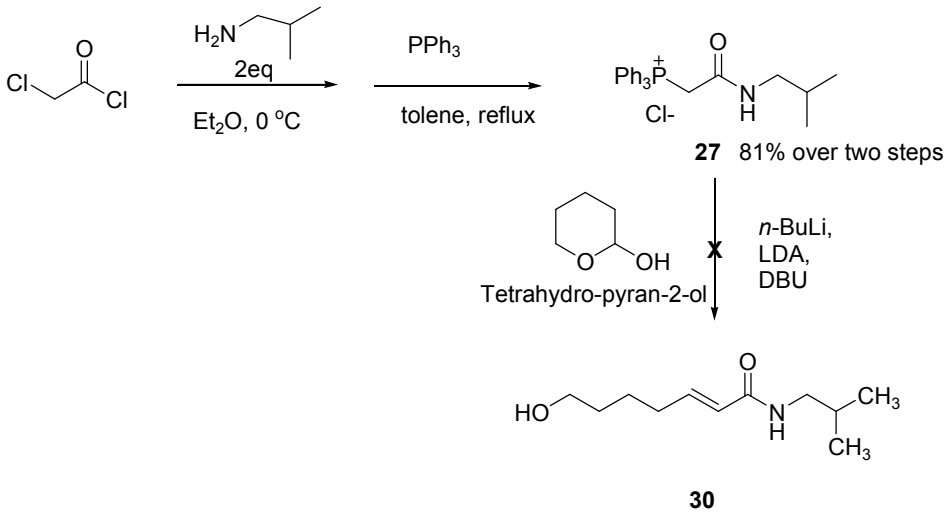
Results and Discussion

We commenced our study with amides **12**, **13** and **14** as our target compounds. These amides have been shown to be active against A. *aegyptii* larvae and H. *zea* neonates at the microgram per milliliter level.[15]

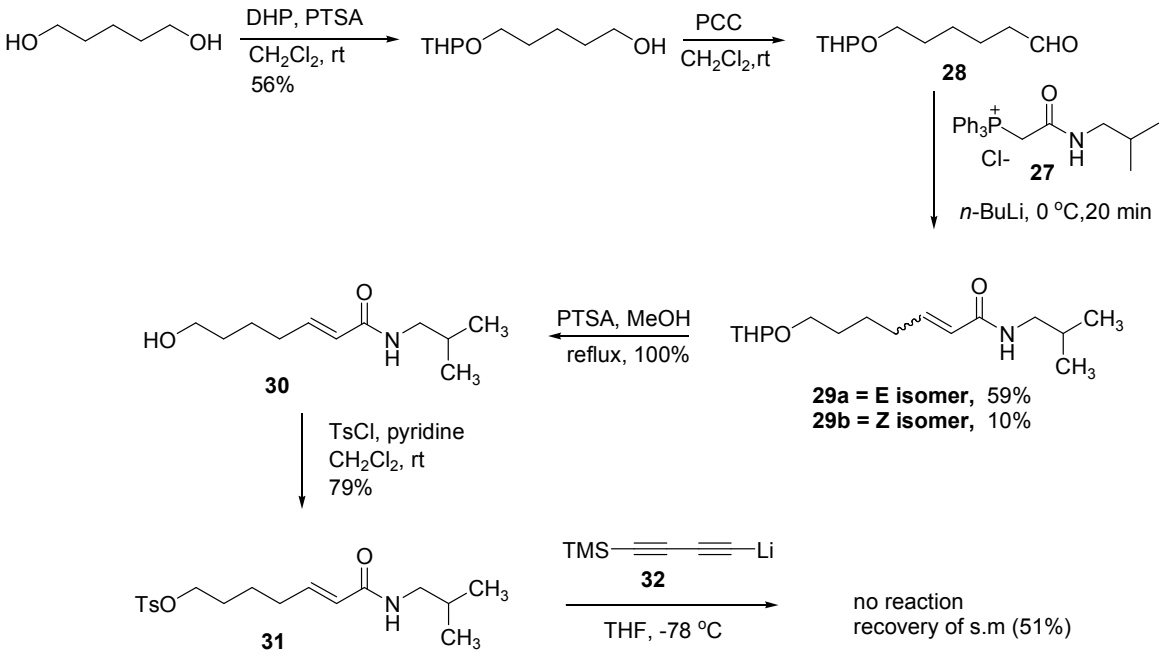
Our first approach to amide **12** is shown below. As illustrated in the retrosynthetic scheme, target molecule might be achieved by alkylation between a lithium diacetylide and the isobutylamide. Generation of a monoanion from commercially available 1,4-bis-trimethylsilyl-1,3-butadiyne by methyl lithium-lithium bromide complex has been reported.[16]



Chloroacetyl chloride was coupled with isobutyl amine in diethyl ether at 0 ^{o}C. The α-chloroisobutylamide was refluxed with triphenylphosphine to give salt **27** in good yield.[17] To achieve amide **30**, we tried a Wittig reaction between phosphonium salt **27** and tetrahydropyran-2-ol. Unfortunately, several bases, such as *n*-BuLi, LDA or DBU, were not successful, but only gave unreacted starting material.

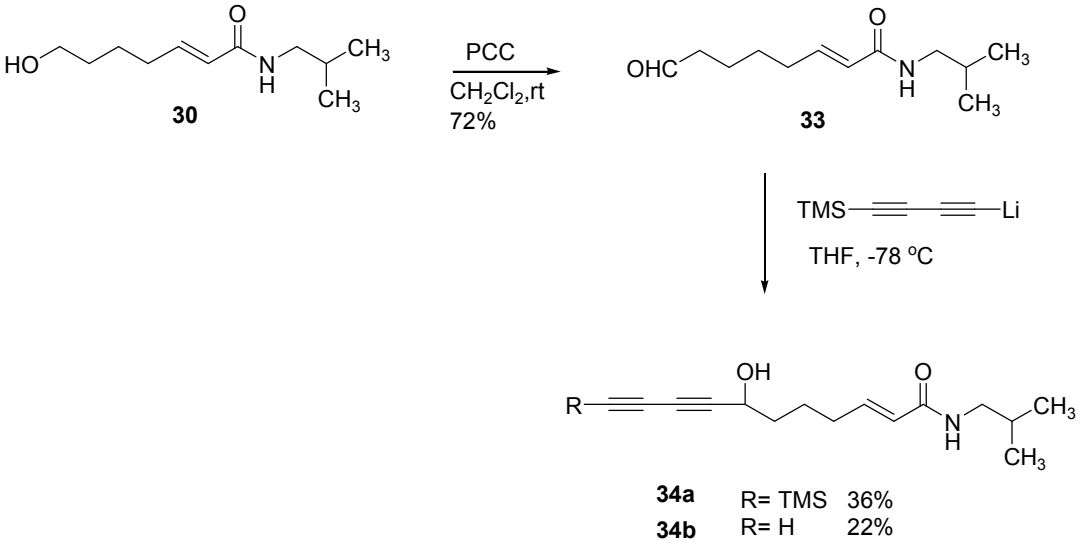


The THP-protected aldehyde **28** was subjected to Wittig reaction and the reaction was successful to give separable mixture of α,β-unsaturated amide **29a** (*E*-isomer) and **29b** (*Z*-isomer) in 59% and 10% yields, respectively. With amide **29a** in hand, deprotection of the THP protected alcohol and tosylation of the primary alcohol provided tosylate **31** in 79 % yield over two steps. Tosylate **31** was subjected to alkylation by the monoanion of 1,4-bistrimethylsilyl-1,3-butadiyne generated by the methyllithium-litium bromide complex. Unfortunately, the alkylation failed. Only starting material **31** was recovered.

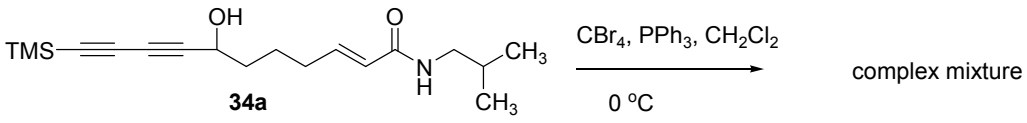


We thought that the poor nucleophilicity of anion **32** caused the failure of alkylation. So we changed our electrophile from tosylate to an aldehyde to enable C-C bond formation. Aldehyde **33** was made from alcohol **30** by PCC oxidation in a moderate yield. To our delight, alkylation between monoanion and aldehyde was successful to give alcohol **34a** in

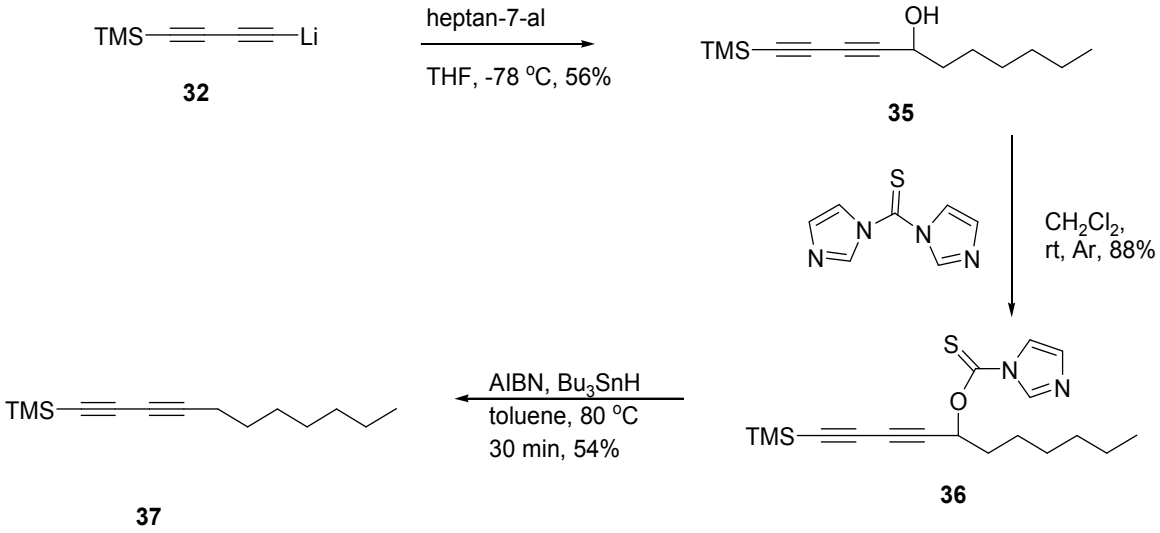
36% yield. At the same time, removal of the TMS group from the acetylene occurred to give alcohol **34b** in 22% yield.



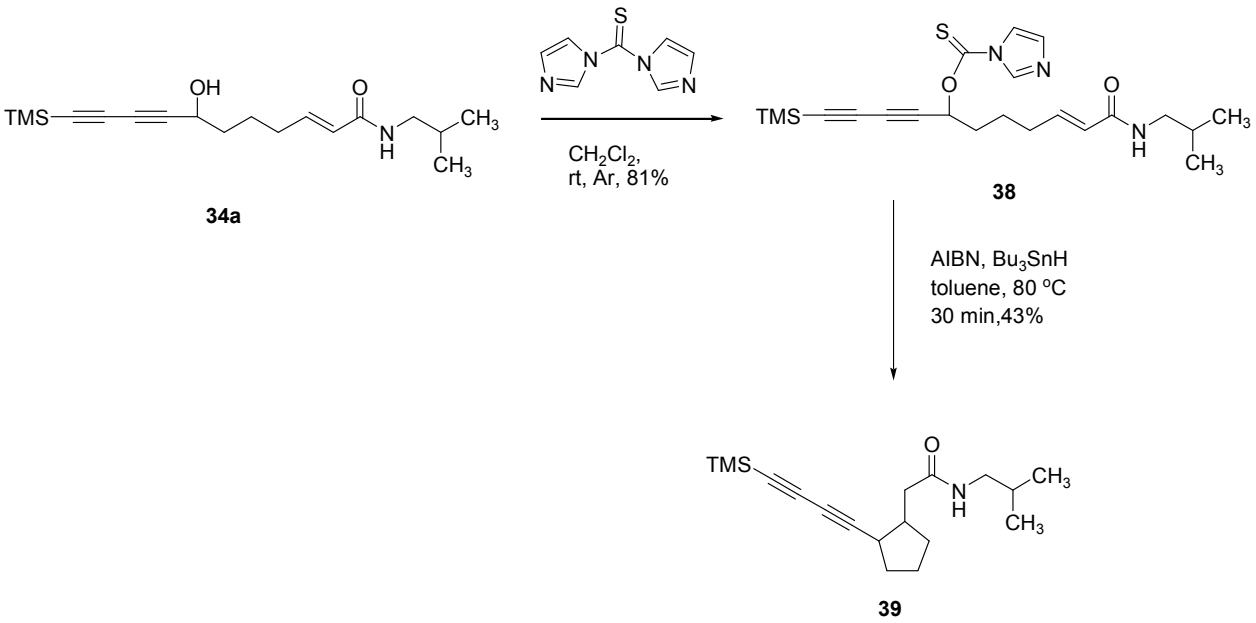
To remove the secondary hydroxyl group, a radical reaction was applied. First attempt was bromination of secondary alcohol, followed by treatment with tributyltin hydride and AIBN. Bromination by CBr_4 and PPh_3 gave a complex mixture.



To circumvent the problem, we tried the very mild radical deoxygenation conditions by Gunji.[18] First, we applied this method to a simple model system. The adduct of monoanion **32** and heptanal was treated with 1,1-thiocarbonyldiimidazole in CH_2Cl_2 at room temperature. The corresponding thiocarboimidazole **36** was treated with tribuyltin hydride and AIBN at 80 ^oC in toluene to produce deoxygenated diyne **37** in 54% yield.



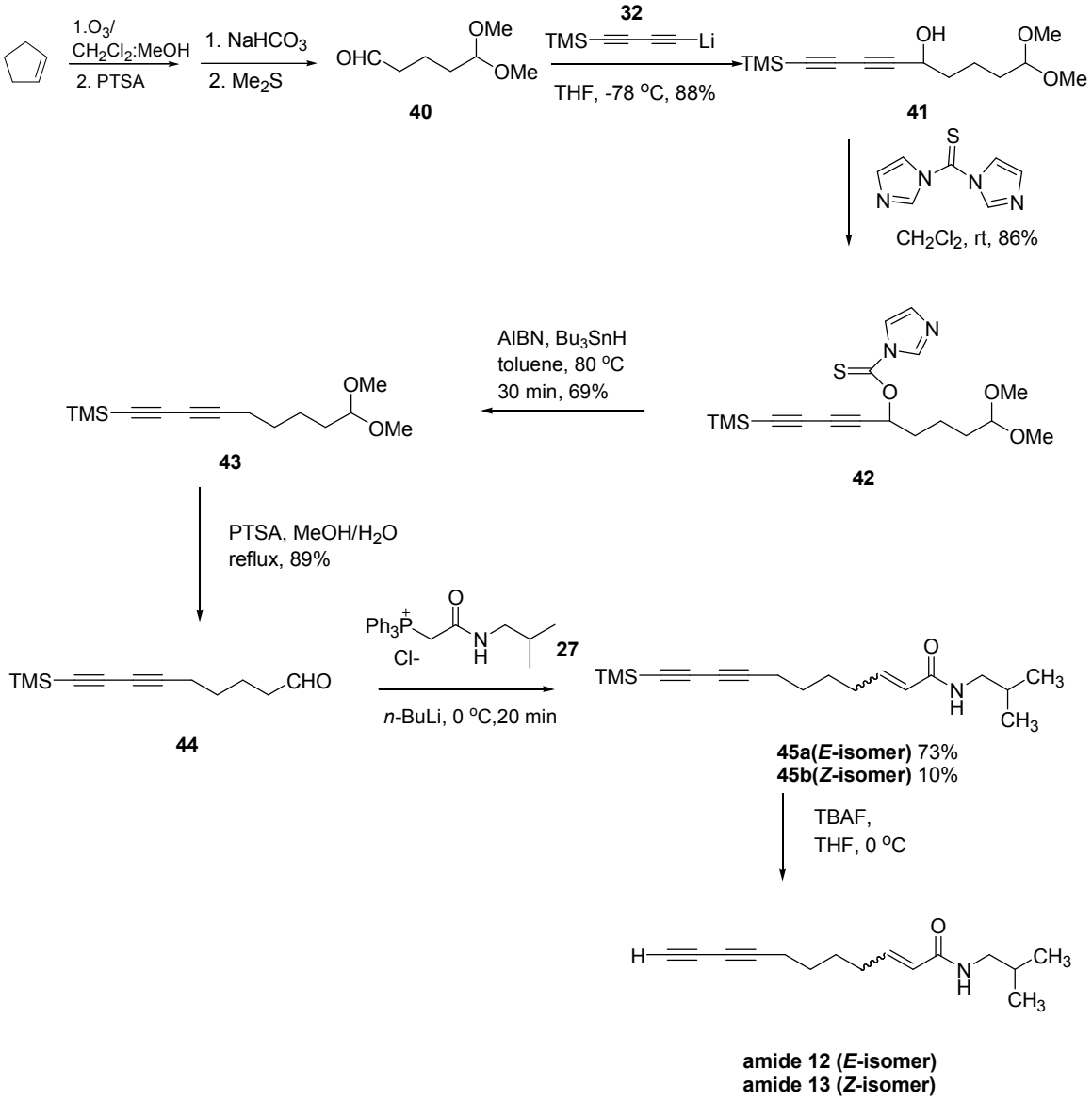
With this result, compound **34a** was subjected to deoxygenation. Thiocarboimidazole **38** was achieved in good yield. Unfortunately, radical deoxygenation reaction gave the intramolecular cyclization product **39** as the major product (43% yield).



After we discovered the problematic deoxygenation step, we changed the order of the synthetic steps. To avoid intramolecular radical cyclization, α,β-unsaturated amide moiety should be introduced at the last step.

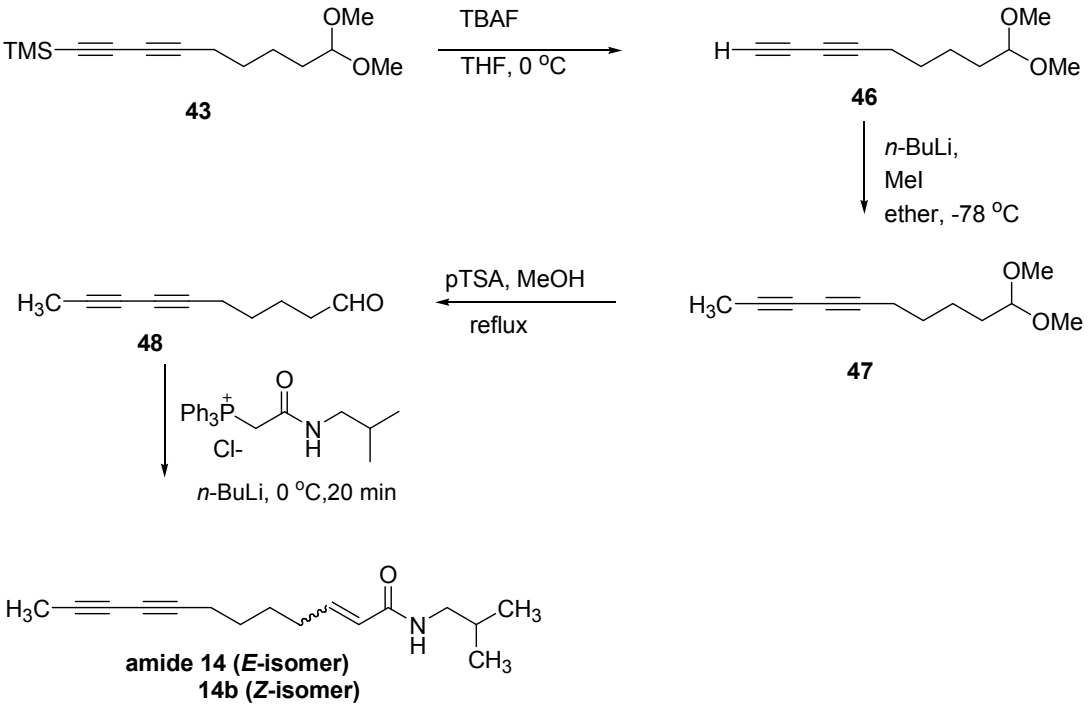
The new synthetic route began with the construction of acetal **41** from 1,4-bis-trimethylsilyl-1,3-butadiyne and aldehyde **40**, readily available from the ozonolysis of cyclopentene by the method of Schreiber.[19] Anion **32** was reacted with aldehyde **40** at -78 °C to afford a propargylic alcohol **41** in 88% isolated yield. Deoxygenation was successful to give acetal **43** in 54% yield in two steps. The acetal protection was cleaved with PTSA in good yield and aldehyde **44** was subjected to Wittig reaction with phosphonium salt **27** to give amide **45a** (*E*-isomer) and **45b** (*Z*-isomer) in 73% and 10% yields, respectively. Compounds **45a** and **45b** were easily separated by flash silica gel chromatography.

Compounds **45a** and **45b** were desilylated with tetrabutylamonium fluoride to give amide **12** and amide **13** respectively.



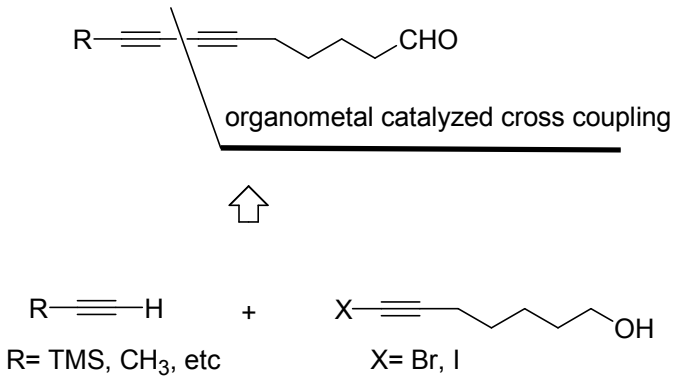
Amide **14** was also synthesized from acetal **43**. Trimethylsilyl group was removed with tetrabutylamonium fluoride in excellent yield. Diacetylene **46** was treated with *n*-BuLi and MeI to give acetal **47** in 40 % yield. Although the yield was not excellent, we proceeded to

the next step to get the aldehyde **48** with PTSA in water. The aldehyde **48** was again subjected to Wittig reaction to get the mixture of amide **14** (*E*-isomer) and **14a** (*Z*-isomer) in 69 % and 12% yields, respectively.

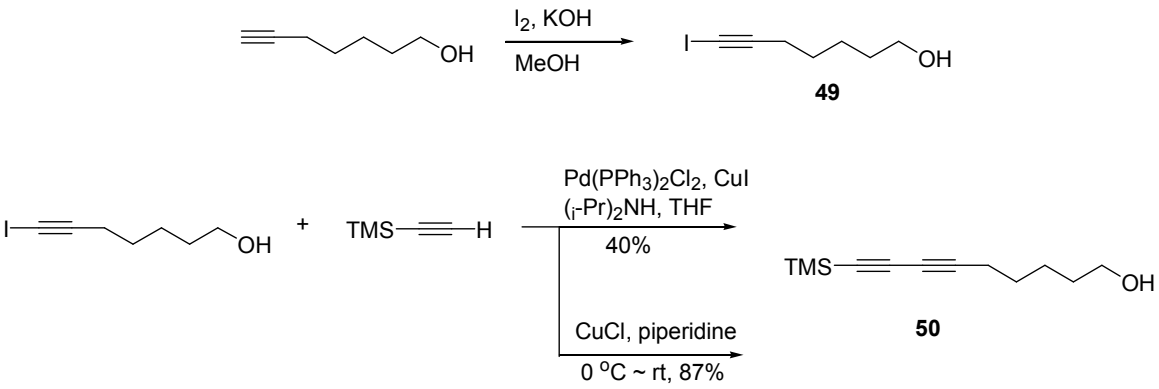


Improved syntheses of amides 12, 13 and 14

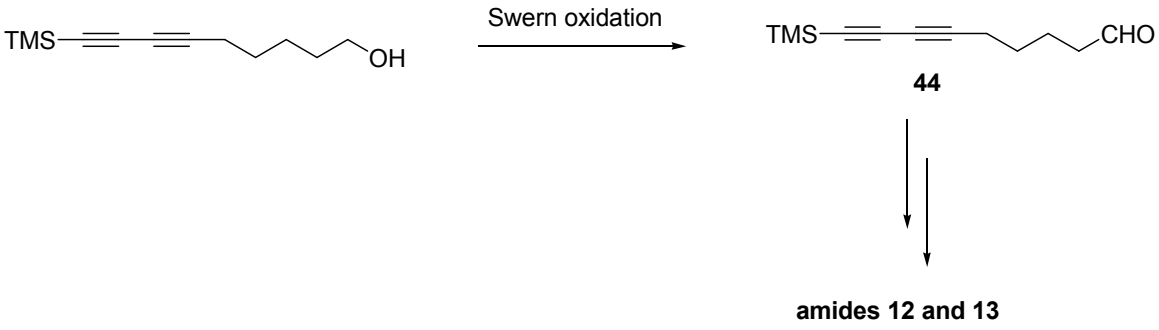
Amide **12** was later synthesized by another synthetic route. Instead of using 1,4-bis trimethylsilyl-1,3-butadiyne, the 1,3-diyne moiety was introduced by coupling of two acetylene units. This approach allowed a more flexible route to synthesize 1,3-diyne part of the molecule. In the literature, the Cadiot-Chodkiewicz cross-coupling reaction and the palladium-copper catalytic reaction have been reported.[20]



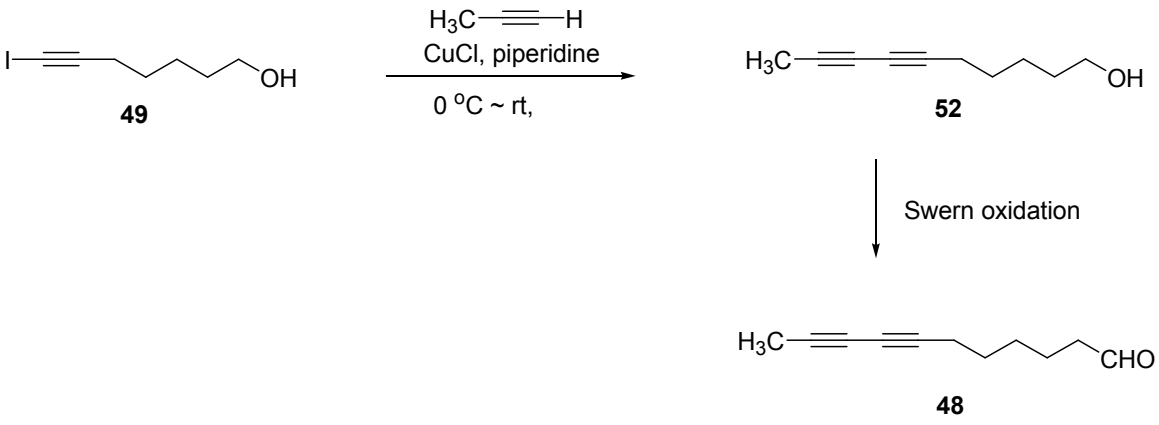
7-Heptyn-1-ol was converted to iodo compound **49** with iodine and potassium hydroxide in methanol in excellent yield. Iodo alcohol **49** was then coupled with trimethylsilylacetylene under two conditions. A palladium-copper catalyzed reaction[21] gave 40% of a cross-coupled product, while copper chloride/piperidine conditions gave the product in 87% yield.[22]



With the diynol **50** in hand, the next steps were straightforward to finish the synthesis of amides **12** and **13**. Swern oxidation of alcohol **50** produced aldehyde **44**. The rest of the syntheses were the same as mentioned previously.



The same synthetic route was applied to synthesize amide **14**. The copper-catalyzed reaction of propyne with iodo alcohol **49** generated alcohol **52** in 82% yields. The improved yield of intermediate **52** made this route more efficient to get amide **14**. Oxidation and a Wittig reaction of aldehyde **48** led to amides **14** and **14a.**



In summary, the improved synthetic route by utilizing a copper-catalyzed acetylene cross coupling reaction[23] enabled us to introduce the 1,3-diyne unit in a more flexible and efficient way.

Synthesis of α,β,γ,δ-unsaturated amides

There are a series of α,β,γ,δ-unsaturated amides in *Echinacea*, which are interesting targets to investigate (Figure 4).

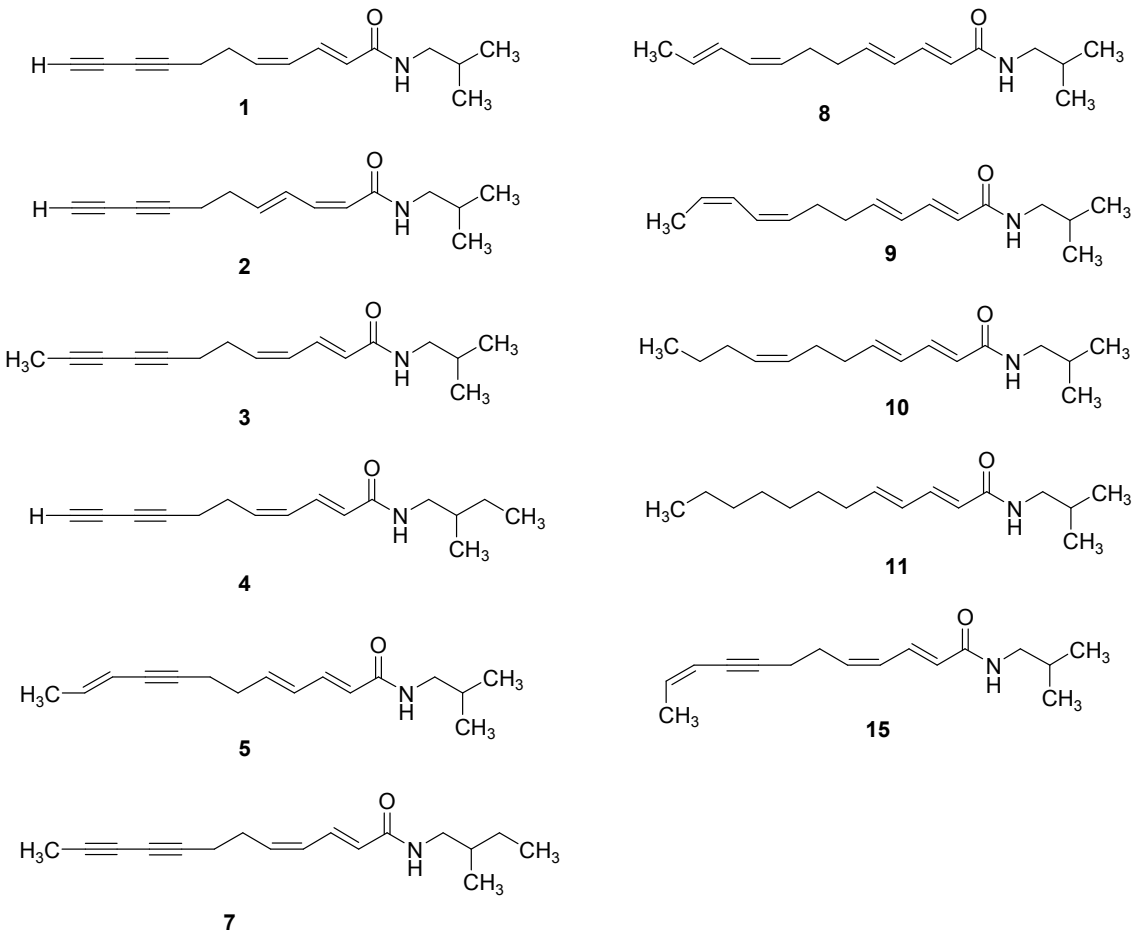
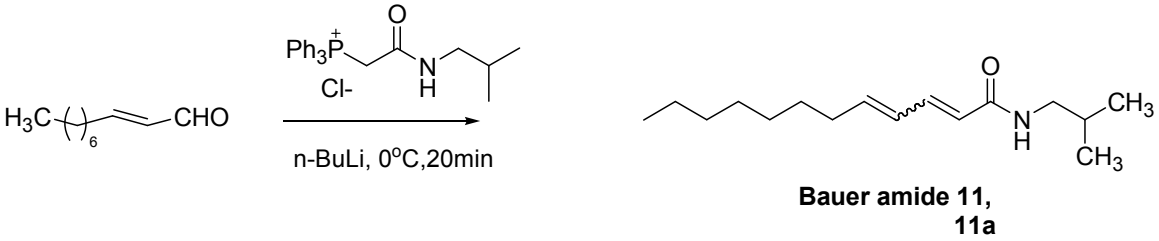


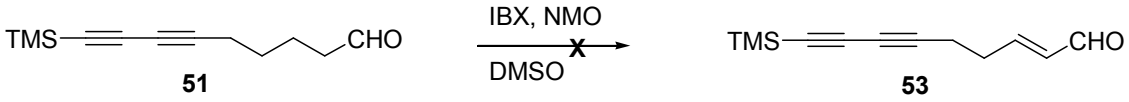
Figure 4. α,β,γ,δ-Unsaturated Bauer amides

First, amide **11** was synthesized by a Wittig reaction between commercially available *trans*-2-decenal and phosphonium salt **27**. The reaction produced both (2*E*, 4*E*) and (2*Z*, 4*E*) amides **11** and **11a** in 64% and 20% yields, respectively. This was the first synthesis of this series of α,β,γ,δ-unsaturated amides.



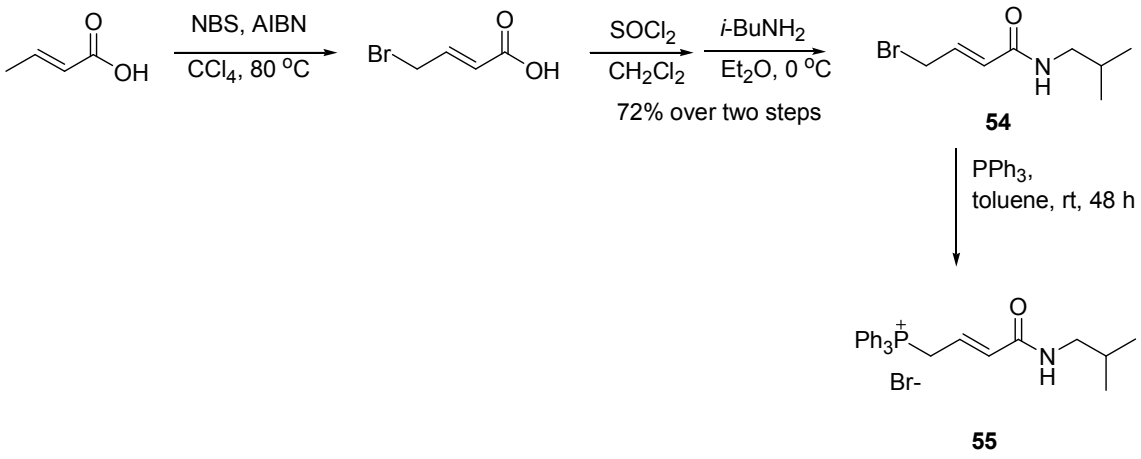
Bauer amide 11, 11a

Since we have achieved a successful route to introduce the diacetylene moiety, we tried to expand our route to synthesize α,β,γ,δ-unsaturated amides. To achieve Bauer amide **2**, we tried to synthesize α,β-unsaturated aldehyde **53** from the aldehyde **51** by the method of Nicolau.[24] Unfortunately, the reaction gave only starting material back. Also, the use of TMSCl and $Pd(OAc)_2$[25] didn't give us any promising results.

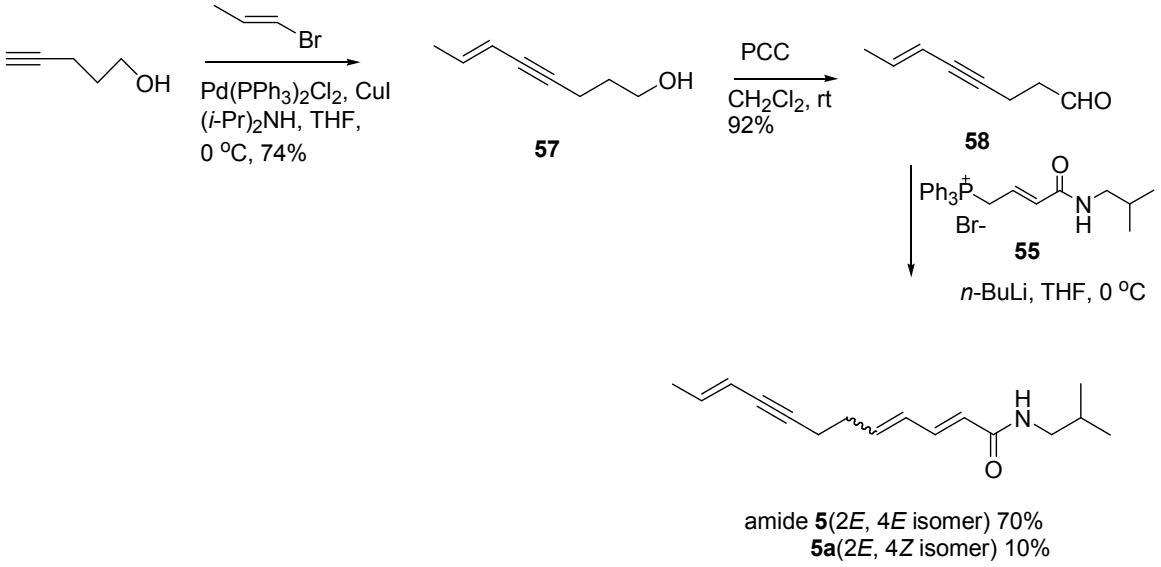


51 **53**

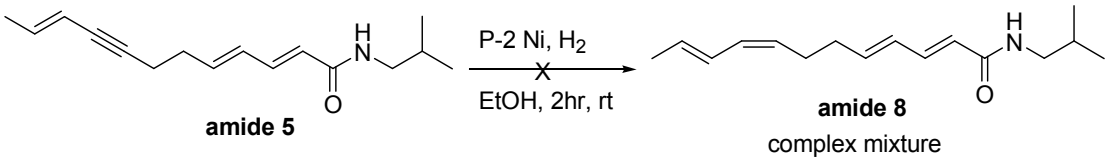
So we changed our plan of the synthesis to make phosphonium salt **55,**[26] which possesses the α,β-unsaturated amide moiety. Allylic bromination of crotonic acid by NBS and AIBN in refluxed CCl_4 gives the bromoacid, which is converted into the acid chloride, followed by addition of isobutyl amine to produce bromo amide **54** in 72% yield over two steps. Wittig salt **55** was achieved by stirring with PPh_3 in toluene at room temperature. The formation of salt was best at room temperature. When the reaction was heated to reflux, a dark polymerized solid was formed.



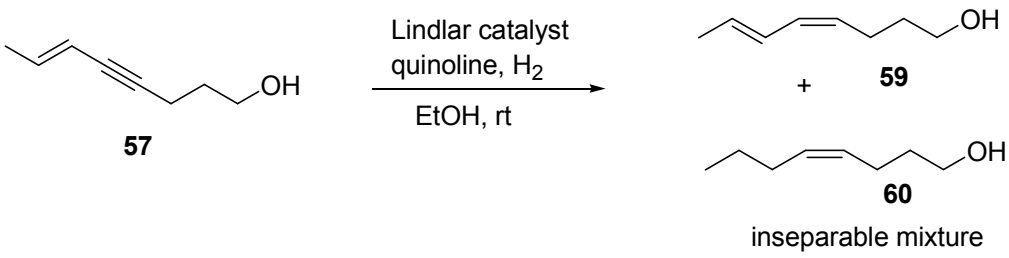
Among many α,β,γ,δ-unsaturated amides, amides **5** and **8** could be synthesized by using a common intermediate. Amide **8** could be achieved by hydrogenation of amide **5**. Synthesis of amide **5** commenced with 4-pentynol. It was coupled with trans-3-bromopropene by a palladium-mediated Sonogashira reaction.[27] Enynol **57** was produced in good yield. Then oxidation of **57** by PCC gave rise to aldehyde **58** in 92 % yield. Wittig reaction between aldehyde **58** and salt **55** produced a mixture of amides **5** and **5a** (2*E*,4*Z* isomer) in 70 % and 11 % yields, respectively, which could be separated by silica gel column chromatography. The stereochemistry of the conjugated double bonds was conformed by the distinctive chemical shifts and coupling constants.



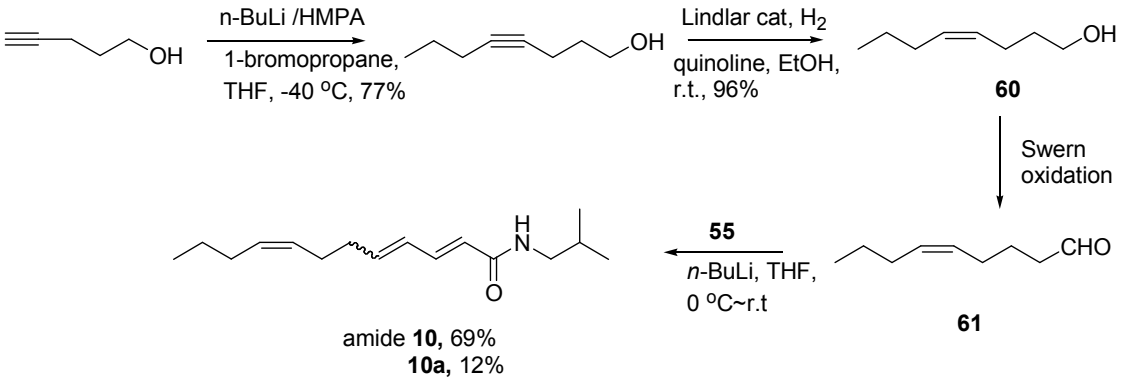
Amide **5** was treated with P-2 nickel,[28] but unfortunately, the reaction gave only a complex mixture. We attribute this failure to the presence of the unsaturated amide moiety which may be susceptible to hydrogenation.



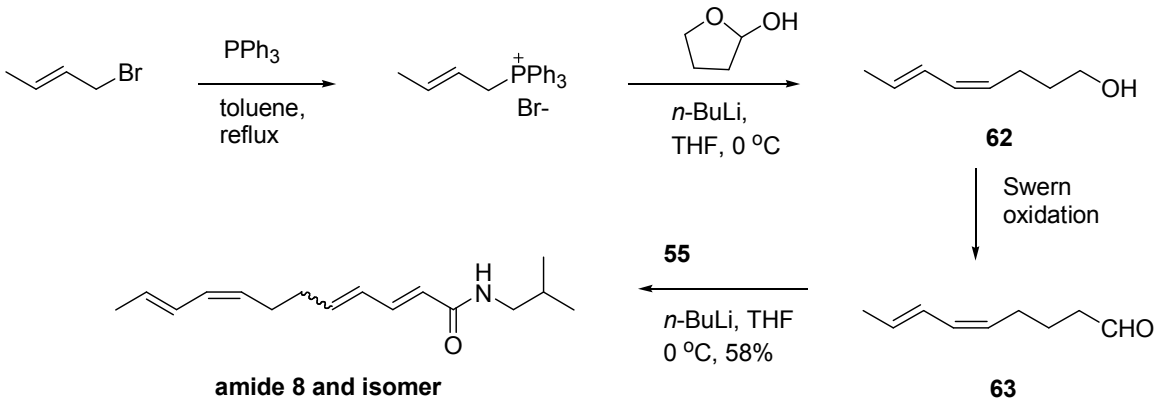
After we experienced difficulties in the hydrogenation step of amide **5**, we tried to hydrogenate alcohol **57**, which could be a much more straightforward reaction. When alcohol **57** was treated with Lindlar catalyst condition, an inseparable mixture of alcohols **59** and **60** was achieved. Although both alcohols could be used as precursors of amides **8** and **10**, the difficulty of separation forced us to find alternative ways of synthesis.



Alcohol **60** was synthesized from 4-pentyn-1-ol by alkylation with 1-bromopropane in 77% yield. Triple bond was hydrogenated by Lindlar catalyst to give exclusively the *Z*-isomer of alcohol **60.** Swern oxidation and Wittig reaction with salt **55** gave amide **10** and its (2*E*, 4*Z*) isomer **10a** in 69 % and 12 % yields, respectively.



Alcohol **62** could be achieved by Wittig reaction between 2-butenylidenetriphenyl phosphorane and 2-hydroxytetrahydrofuran. The Wittig reaction proceeded smoothly to give diene alcohol **62** in 68 % yield. Alcohol **62** was oxidized to aldehyde **63** and underwent a Wittig reaction with salt **55** to give amide **8** and its isomer in 58% yield. The mixture of isomers was hard to separate.



Recently, Chan *et al* reported alkamides **64** and **65** from *E. purpurea* and *E. pallida,* which inhibited LPS-mediated activation of a murine macrophage line RAW264.7, suggesting that these alkamides may have anti-inflammatory activity.[29]

As well as showing those biological activities, the new alkamides and amide **2** have interesting unsaturated amide moieties in common.

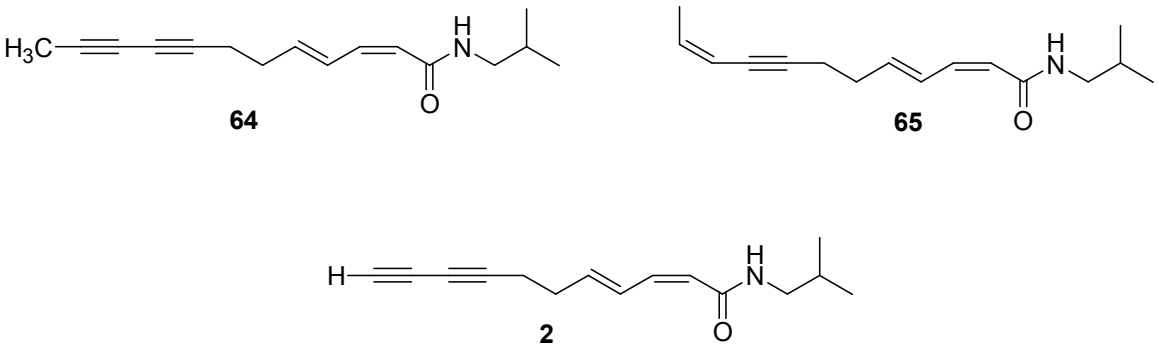
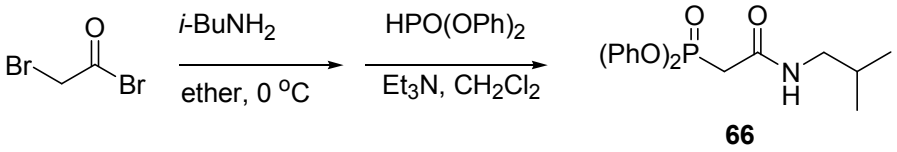


Figure 5. New alkamides in *E. pupurea* and *E. pallida*

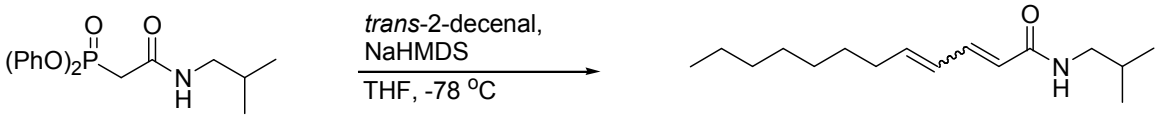
We applied the cis-selective Horner-Wadsworth-Emmons reaction as the key step for the synthesis of these amides. The Horner-Wadsworth-Emmons reaction of diphenyl phosphono acetamides **66** was reported to produce *Z*- α,β-unsaturated amides in excellent

stereoselectivity.[30] Phosphonoacetamide **66** was synthesized from bromoacetyl bromide with isobutylamine, followed by reaction with diphenylphosphate and triethylamine in 52 % yield over two steps.[15]



66

The Horner-Wadsworth-Emmons reaction with **66** was tested with *trans*-2-decenal to check the *cis*-selectivity. The reaction gave the *cis*-diene as the major product as expected, although the selectivity was not excellent.

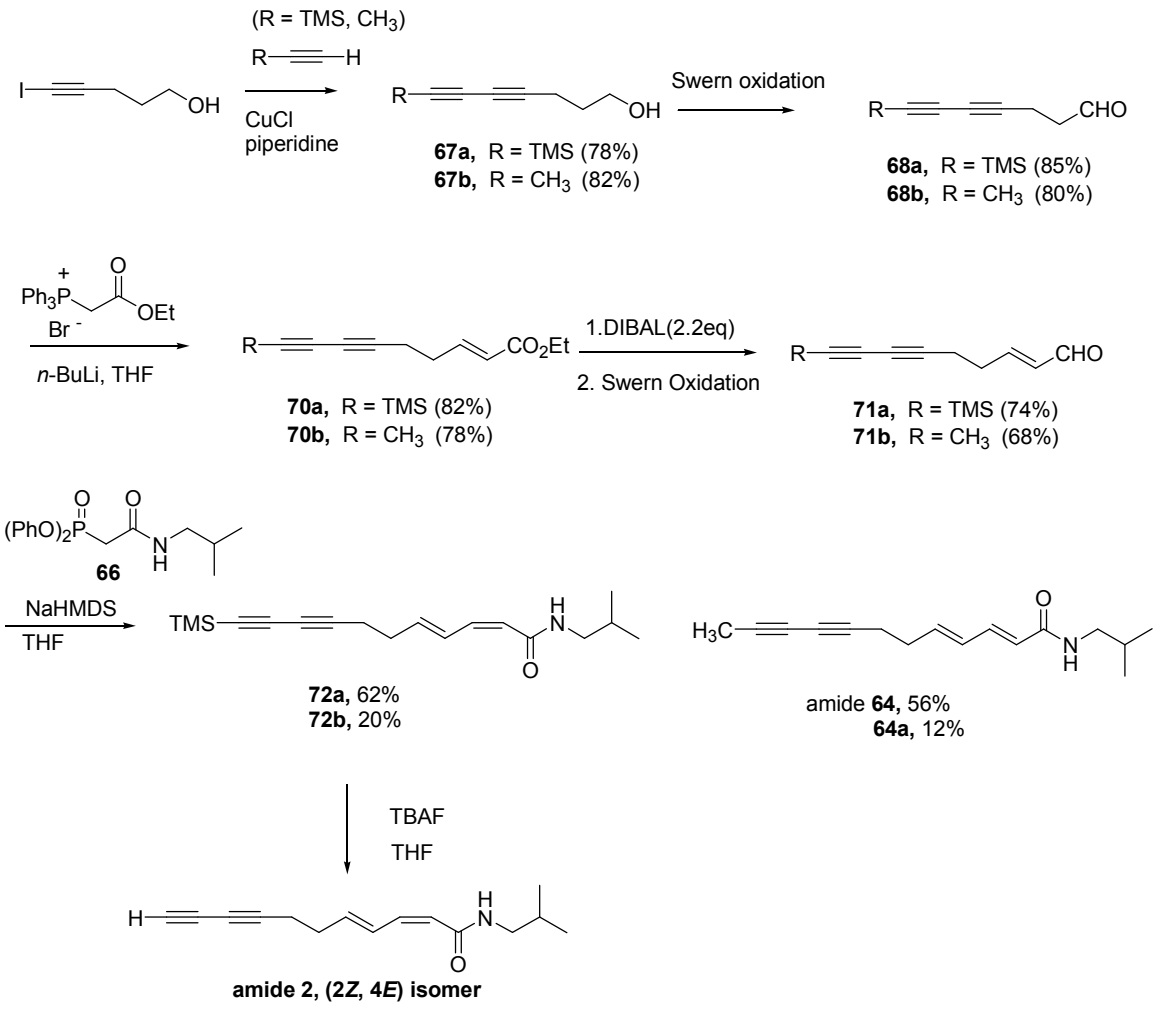


66

amide **11** (2*Z*, 4*E* isomer), 50%
11a(2*E*, 4*E* isomer), 17%

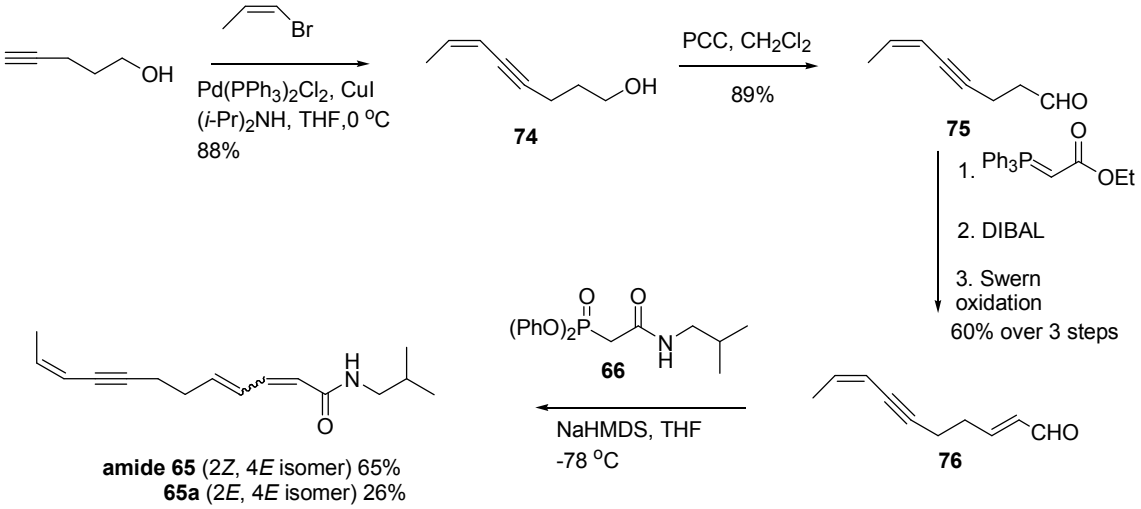
Our synthesis of amides **2** and **64** began with 5-iodo-4-pentyn-1-ol. Copper-catalyzed coupling reaction with propyne and trimethylsilyl acetylene gave alcohols **67a** and **67b** in 82% and 78% yields, respectively. Oxidation of alcohols **67a** and **67b** in Swern oxidation produces the corresponding aldehydes **68a** and **68b** smoothly. To achieve extended α,β-unsaturated aldehydes, aldehydes **68a** and **68b** were subjected to a Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane to give esters **70a** and **70b** in good yields. Esters **70a** and **70b** were converted into corresponding aldehydes **71a** and **71b** by DIBAL

reduction followed by Swern oxidation. Finally, Horner-Wadsworth-Emmons reaction of aldehyde **71a** and **71b** with **66** produced amides **72a** and **64** as the major products along with amides **73a** and **64a** as minor products. Amide **72a** was converted to Bauer amide **2** by removing the TMS group with tetrabutylamonium fluoride in excellent yield.



Another natural compound **65** was also synthesized by a similar route from enynol **74** which could be made from 5-pentynol and cis-3-bromopropene by a Sonogashira reaction in 88 % yield. Aldehyde **75** (by PCC oxidation of **74**) was subjected to Wittig reaction, DIBAL

reduction and Swern oxidation to generate aldehyde **76** in a moderate yield. Compound **76** was treated with phosphonate **66** to give amide **65** and its isomer **65a** in 65 % and 26 % yields, respectively.

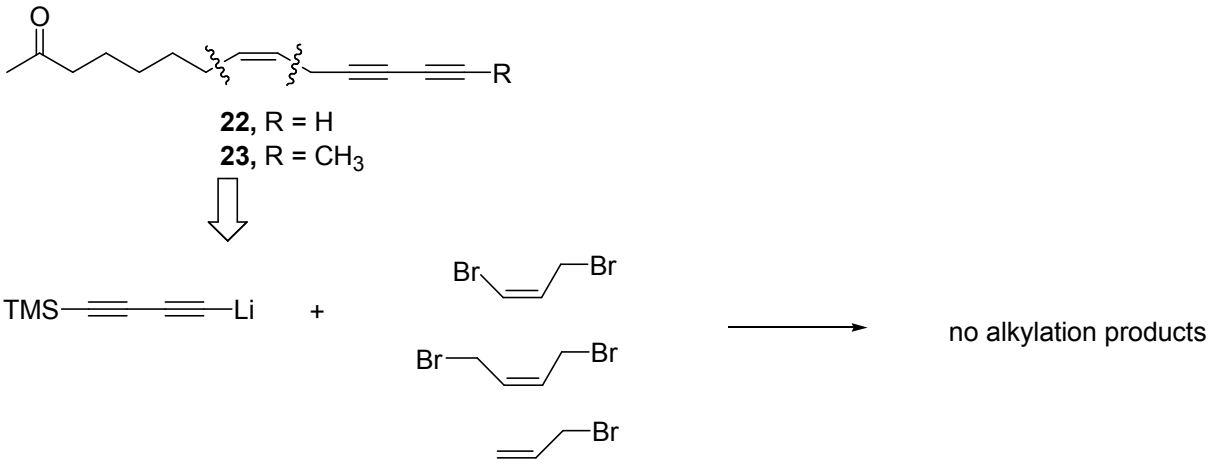


Synthesis of ketones in Echinacea

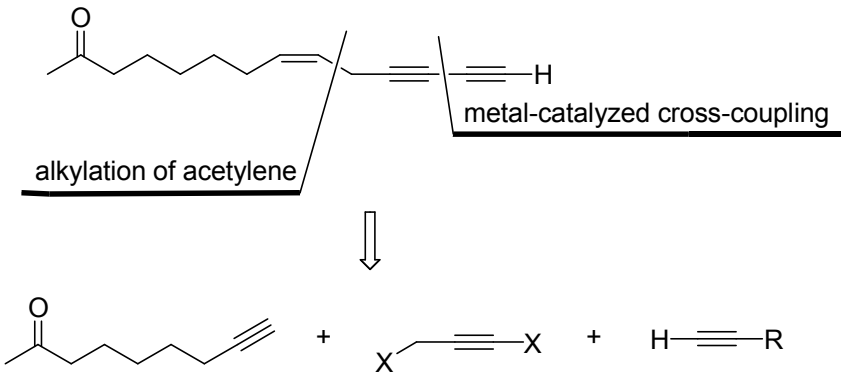
E. pallida contains acetylenic ketones as the major hydrophobic constituents. Ketone **22** is one of major constituents of *E. pallida*. These compounds have been shown to be potent antifungal agents.[31] However, the full range of biological activity is not known, primarily due to the difficulty in obtaining pure **22** from plant extracts.

As we started the synthesis of ketone **22**, our first strategy of synthesis was using 1,4-bistrimethylsilyl-1,3-butadiyne as the source of the diacetylene unit. We tried several alkylation conditions using *cis*-1,3-dibromopropene, *cis*-1,4-dibromobut-2-ene or allyl bromide as electrophiles with a monoanion of 1,4-bistrimethylsilyl-1,3-butadiyne, but all

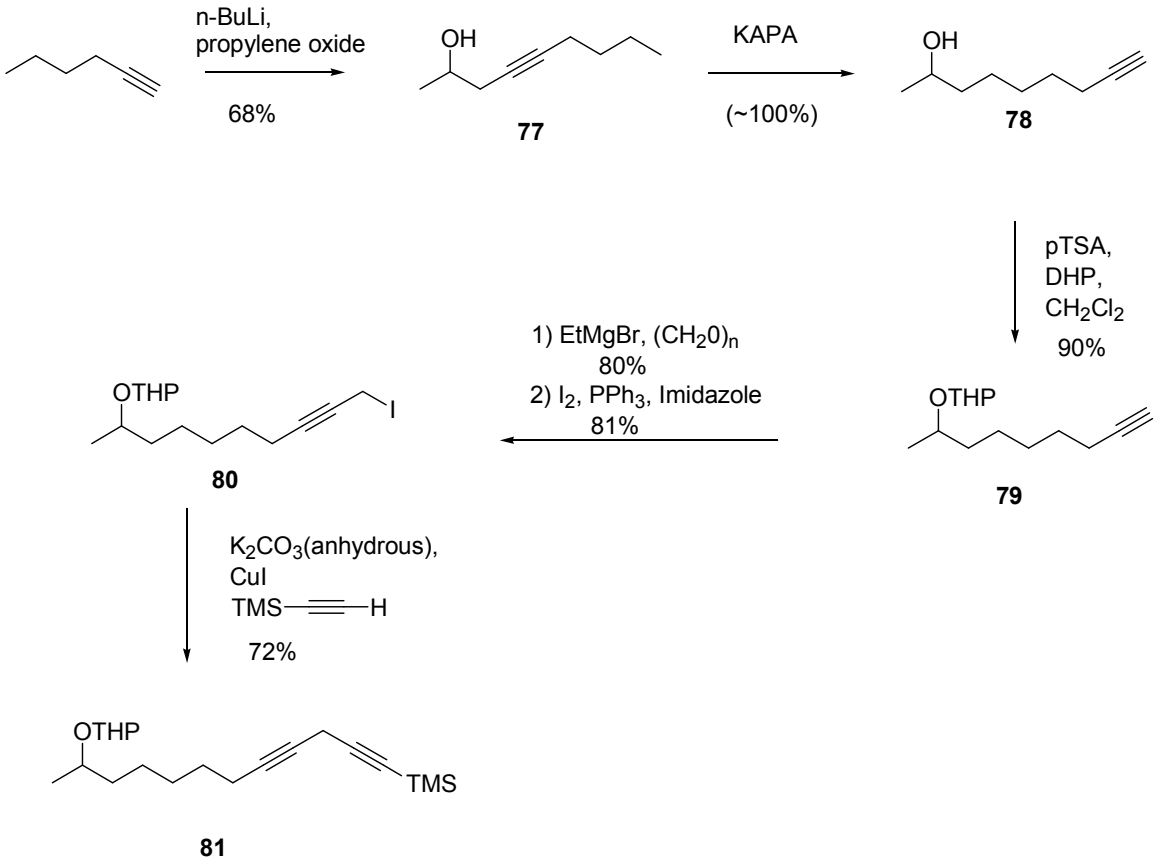
attempts failed. Again, the poor reactivity of the monoanion of butadiyne forced an alternative approach to synthesis.



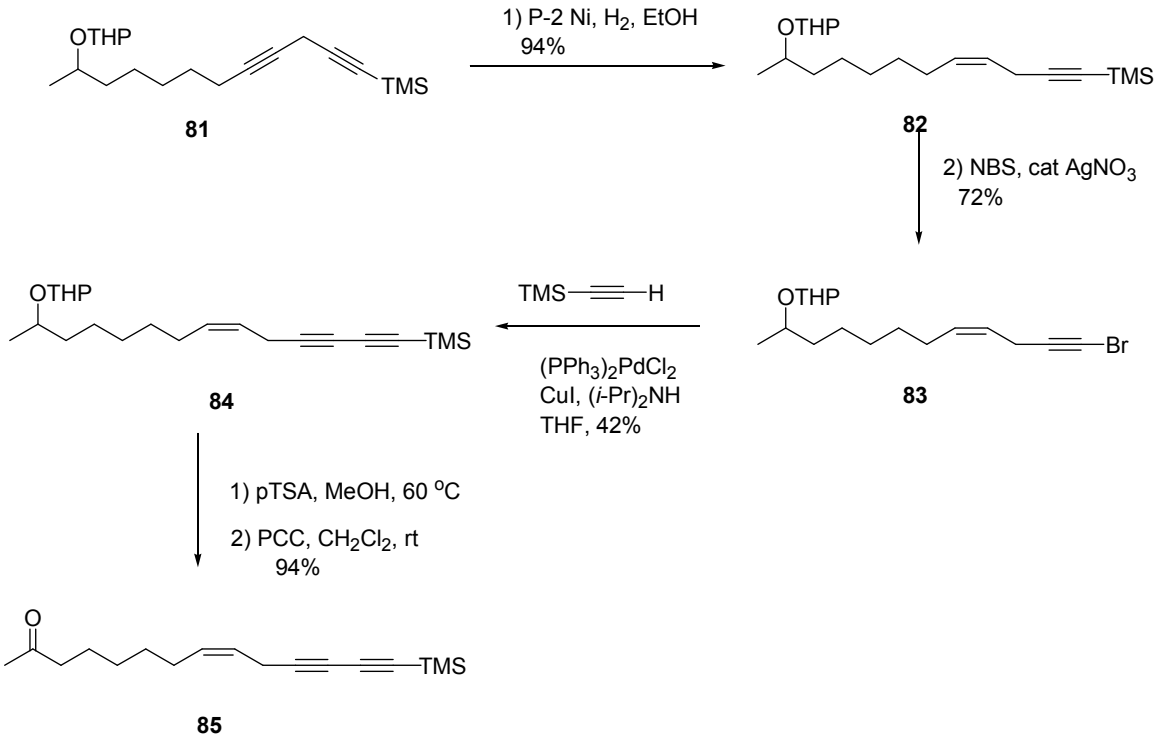
As illustrated in the retrosynthetic route below, we changed our strategy to build the diyne moiety by a cross-coupling reaction.



The new synthetic route to ketone **22** was commenced with known acetylenic alcohol **78**.[32] Hexyne was activated with *n*-butyl lithium and coupled with propylene oxide to give homoproparglyic alcohol **77** in good yield. The triple bond migration reaction was carried out via KAPA conditions to give an excellent yield of the acetylenic alcohol **78**.[33] Secondary alcohol was protected with 2,3-dihydrofuran to give acetylene **79**. It was treated with ethylmagnesium bromide and paraformaldehyde to produce a propargyl alcohol,[34] which was further converted to iodide **80** with iodine, triphenylphosphine and imidazole in methylene chloride.[35] Propargylic iodide **80** was then reacted with the anion of trimethylsilylacetylene and a copper iodide catalyst.[36] Surprisingly, this reaction was very slow and the yields of 72% required potassium carbonate that was dried over phosphorus pentoxide.

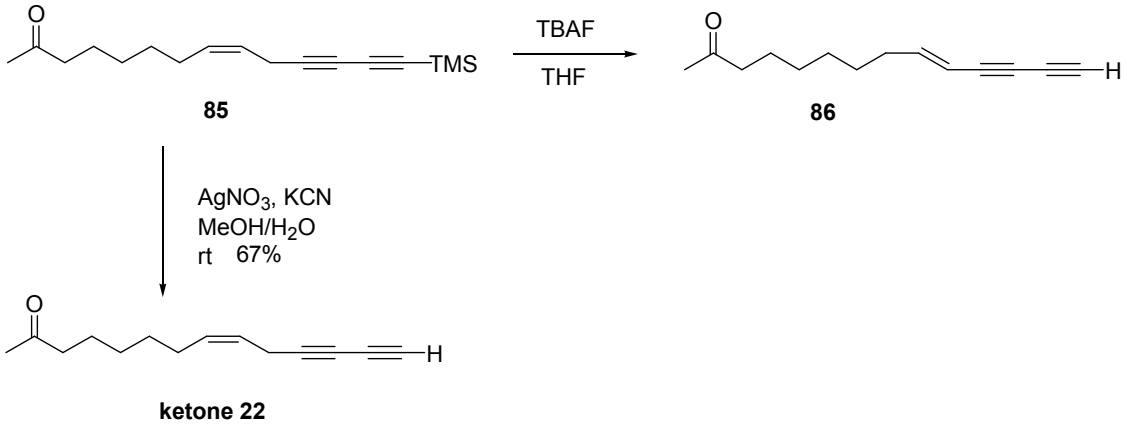


Selective reduction of the internal acetylene in **81** was achieved with P-2 nickel according to the method of Larcheveque in 94% yield.[37] The bulky trimethylsilyl group undoubtedly played a key role in the regioselectivity. Bromination of the acetylene **82** with NBS in acetone at 25 °C provided bromoacetylene **84** in 72% yield.[38] Coupling of **84** with trimethylsilylacetylene using palladium catalysis afforded diacetylene **84** in 42% yield.[39] Deprotection of the THP ether using PTSA in methanol, followed by oxidation of the resulting alcohol with PCC, led to ketone **85**.



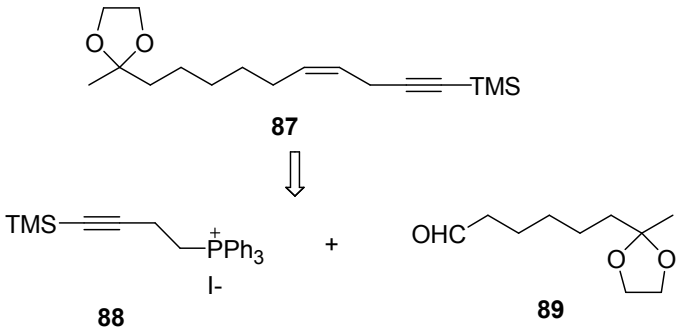
Desilylation[40] using silver nitrate and potassium cyanide produced ketone **22** in 60% yield from **84**. Attempted desilylation using tetrabutylammonium fluoride with either the

ketone **85** or the protected alcohol **84** led to isomerization of the double bond to a conjugated enyne **86**, as evidenced by the disappearance of the CH_2 resonance around δ 3.00.

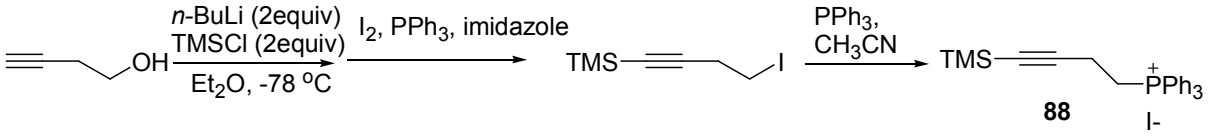


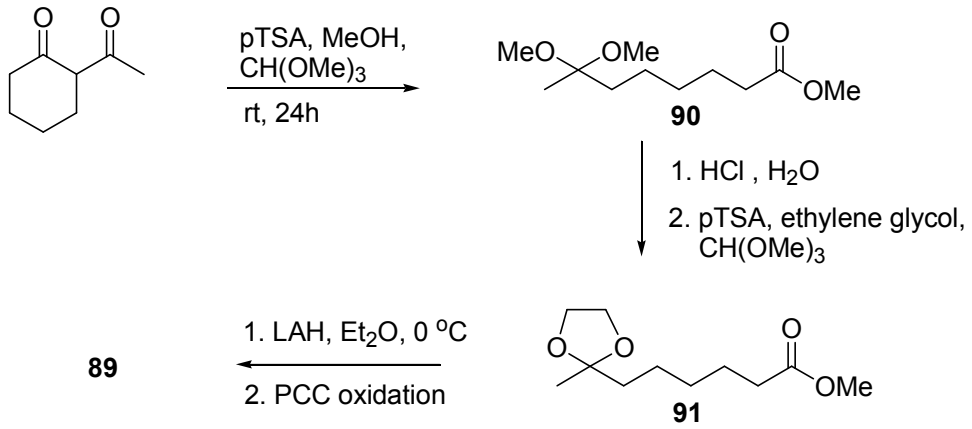
Improved synthesis of ketones 22 and 23

Although ketone **22** was synthesized successfully, the number of steps and low overall yield of **22** prompted an alternative synthetic route. So, a new synthetic route to the ketones **22** and **23** was explored. As shown in retrosynthetic scheme below, the enyne **87**, an intermediate of our previous ketone **22** synthesis, could be generated by a Wittig reaction between phosphonium salt **88** and aldehyde **89**. This new route could shorten the synthesis significantly.

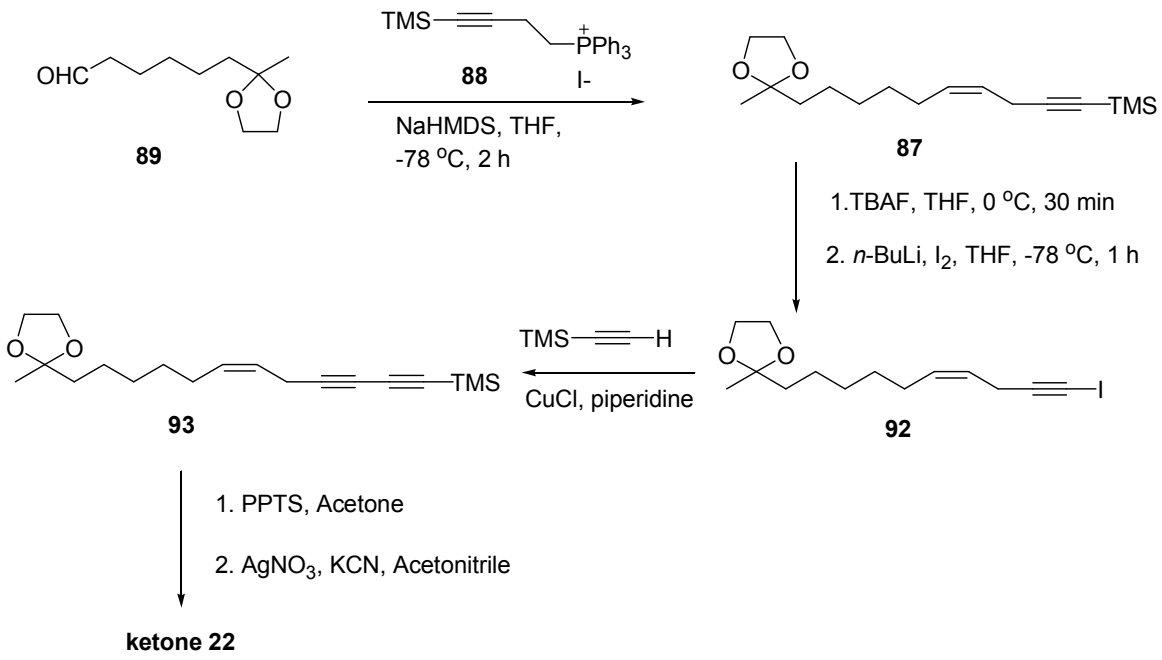


Wittig salt **88** was made by a known procedure from butyn-1-ol.[41] To get the aldehyde **89**, 2-acetylcyclohexanone was treated with trimethyl orthoformate and PTSA in MeOH to generate ester **90** in 76% yield.[42] Dimethyl acetal was converted into 1,3-dioxolane in a two step conversion to get ester **91**. Change of the protecting group from the dimethyl acetal to the dioxolane was due to the liability of the dimethyl acetal in later steps. Ester **91** was converted into aldehyde **89** by reduction and oxidation.

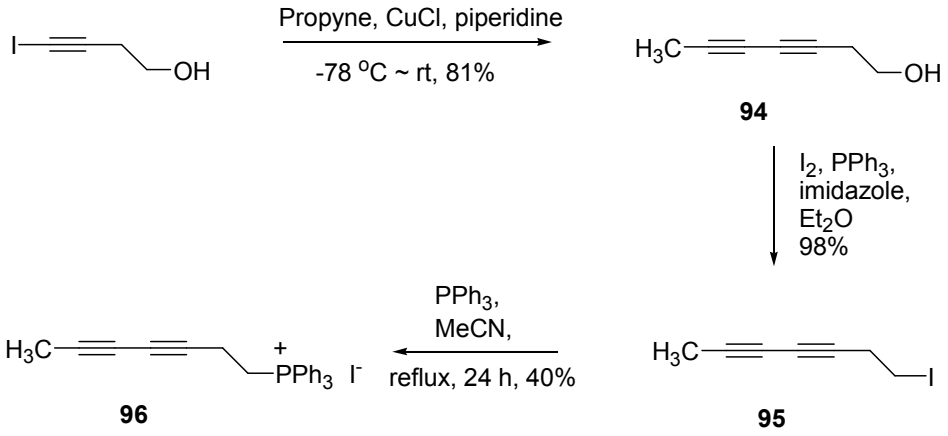




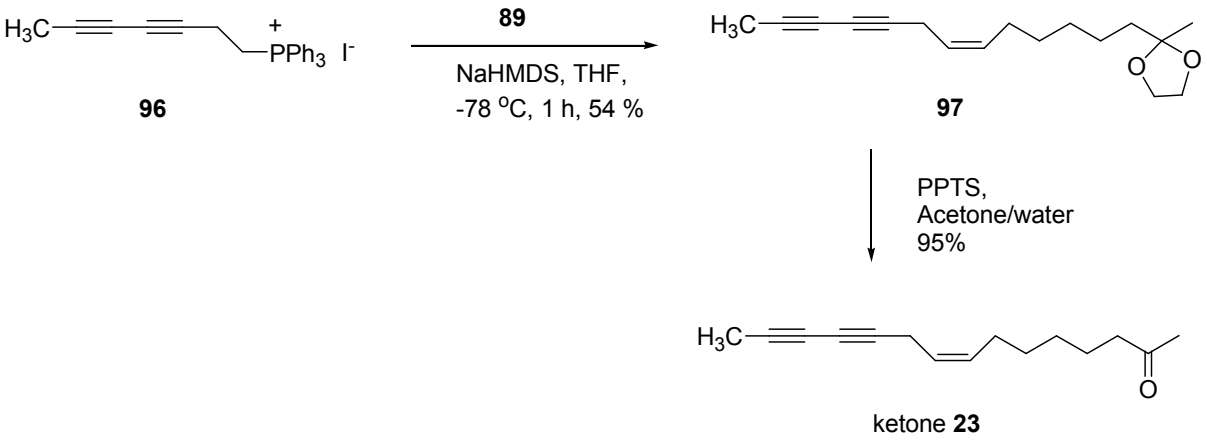
A Wittig reaction between salt **88** and aldehyde **89** proceeded smoothly to generate enyne **87**. The stereochemistry of the alkene was characterized by its coupling constant (J = 10.4 Hz). Enyne **87** was converted into **92** by a two step sequence. Direct conversion to **92** by NBS and silver nitrate gave undesired side products. Compound **92** was coupled with trimethylsilylacetylene by a copper-catalyzed reaction to generate **93**. The ketal protecting group and silyl protecting group of **93** were removed by previous reaction conditions to afford ketone **22**.



Although we have achieved an improved synthetic route to ketone **22**, the problematic step of this route was the acetylene coupling step. The yield of this step was lower than other cases. Since a copper-catalyzed acetylene coupling reaction was good with 4-iodobutyn-1-ol, we changed the route to introduce the acetylene coupling step in its earlier stage. 4-Iodobutyn-1-ol was coupled with propyne in good yield. Diynol **94** was then converted into Wittig salt **96** in two steps.

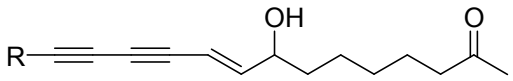


Compound **96** underwent Wittig reaction with aldehyde **89** to generate enyne **97** in 54 % yield. This reaction also gave the *cis*-alkene exclusively. Removal of a ketal protection group (PPTS, water) gave ketone **23** in good yield.



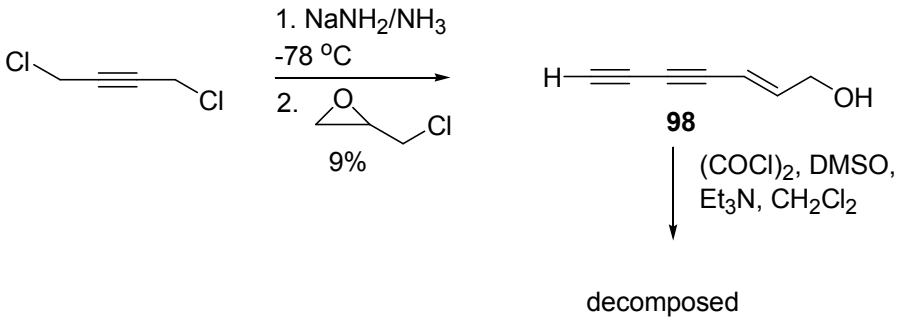
Synthesis of ketones 20 and 21

Other main ketones in *Echinacea* are ketones **20** and **21**. These ketones have a conjugated enyne moiety, which is the key to the synthesis.

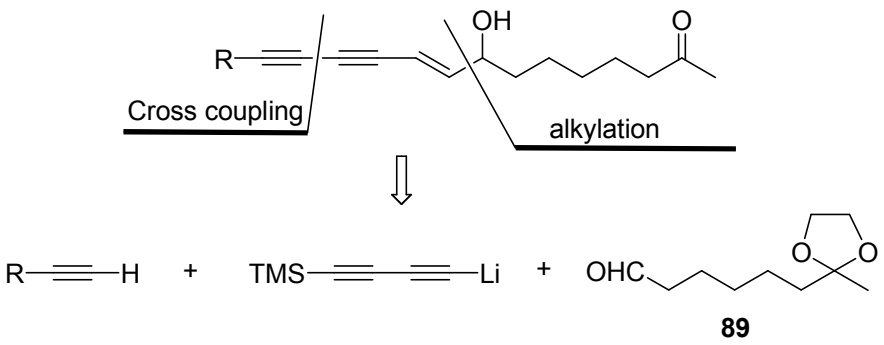


R= H ketone **20**
R= CH_3 ketone **21**

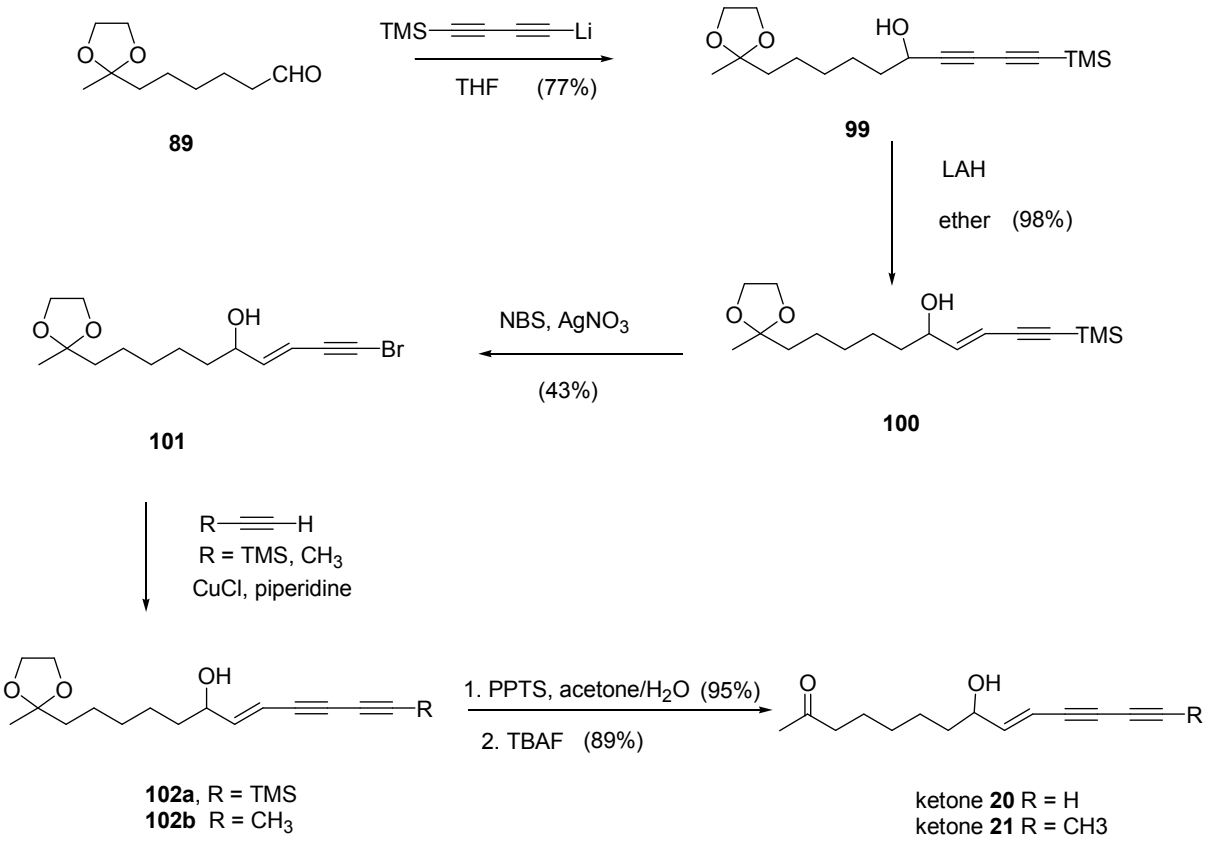
We started our synthesis by generating the enyne moiety in one step. Reaction of 1,4-dichloro-2-butyne with $NaNH_2$ in liquid ammonia, followed by addition of epichlorohydrin led to enynol **98**.[43] Although the yield was poor (9 %), it was a very straightforward route to get the key structure for the target molecule. We tried to oxidize enynol **98**, but, unfortunately, the reaction only led to a decomposed mixture. In the literature, we found that the corresponding aldehyde is very unstable even at lower temperature.[44]



So we changed the strategy to build the diyne moiety by using a copper-catalyzed coupling reaction. The conjugated enyne was introduced by a selective reduction of a 1,3-diyne.



Aldehyde **89** was treated with the monoanion of 1,4-bistrimethylsilyl-1,3-butadiyne to give adduct **99** in a moderate yield. Selective reduction of the diyne to the olefinylic acetylene **100** was achieved by lithium aluminum hydride in excellent yield. The selective reduction is the result of an intramolecular hydroalumination reaction, which involves the hydroxyl group. Enynol **100** was then converted into the bromo compound by NBS under silver nitrate catalyst. Bromo compound was coupled with both trimethylsilylacetylene and propyne by a copper-mediated cross-coupling reaction to generate **101a** and **101b**. The ketal protecting group of the resulting diacetylenes can be removed using mild aqueous acid (PPTS, water) to afford compound **21** in 95% yield from **101b**. The silyl protecting group can be removed with tetrabutylammonium fluoride at ambient temperature to provide **20** in 84% overall yield from **101a**.



In conclusion, we have synthesized some of the natural compounds of *Echinacea*, amides **2**, **5**, **8**, **10**, **11**, **12**, **13**, **14**, **64** and **65**. In the synthesis of these amides, we have developed general and flexible synthetic routes to the amides. As well as the natural compounds, we also prepared the isomers of natural amides, which could be utilized to discover new natural constituents of *Echinacea* as standards for identification. Ketones **20**, **21**, **22** and **23** have also been synthesized in direct and efficient synthetic routes.

Experimental section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under an argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz and reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for all flash column chromatography.

(Isobutylcarbamoylmethyl) triphenylphosphonium bromide (27)

To a solution of isobutylamine (9.9 mL, 0.1 mol) in Et_2O (20 mL) was slowly added chloroacetyl chloride (3.9 mL, 0.05 mol) in Et_2O (20 mL) over 30 min by a dropping funnel at 0 ^oC. After the addition was complete, the mixture was stirred for 1 h at the same temperature. The precipitate was filtered off and the filtrate was evaporated *in vacuo*. The residual colorless oil was purified by vacuum distillation to get the 2-chloro-N-isopropylacetamide (6.05 g, 81%). The 2-chloro-N-isopropylacetamide (2.8 g, 18.7 mmol) was refluxed with triphenylphosphine (4.91 g, 18.8 mmol) in toluene for 24 h to get the phosphonium salt **27** (7.69 g, 100 % yield).

Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.55 (m, 12H), 7.22-7.10 (m, 3H), 5.10 (d, *J* = 14.4 Hz, 2H), 2.90 (t, *J* = 6.0 Hz, 2H), 0.78 (d, *J* = 6.6 Hz, 6H)

6-(Tetrahydropyran-2-yloxy)hexanal (28)

To a solution of 1,5-pentanediol (3.14 mL, 30 mmol) in 60 mL of CH_2Cl_2 was added 3,4-dihydro-2*H*-pyran (2.73 mL, 30 mmol) and PTSA (0.29 g, 1.5 mmol) at room temperature. The mixture was stirred for 5 h and washed with $NaHCO_3$ (30 mL), brine (20 mL) and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate = 4:1) to give the 5-(tetrahydropyran-2-yloxy)pentan-1-ol (3.13 g, 55 % yield).

To a solution of the above alcohol (3.13 g, 16.6 mmol) in CH_2Cl_2 (30 mL) was added PCC (5.37 g, 25 mmol) at 0 ^{o}C. After stirring at room temperature for 1 h, an excess amount of Et_2O was added then filtered through celite. The solvent was removed and the residue was purified via flash column chromatography (hexane: ethyl acetate = 4:1) to give aldehyde **28** (2.12 g, 69%).

Compound **28**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.7 Hz, 1H), 4.56 (m, 1H), 3.85 (m, 1H), 3.71 (dt, *J* = 9.8, 6.3 Hz, 1H), 3.49 (m, 1H), 3.38 (dt, J = 9.8, 6.2 Hz, 2H), 2.46 (dt, *J* = 7.1, 1.7 Hz, 2H), 1.97-1.55 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 98.1, 62.4, 43.1, 30.4, 28.9, 25.1, 19.2, 18.7

7-(Tetrahydropyran-2-yloxy)-2*E*-heptenoic acid isobutylamide (29a) and 7-(Tetrahydropyran-2-yloxy)-2*Z*-heptenoic acid isobutylamide (29b)

To the Wittig salt **27** (1.59 g, 3.0 mmol) in anhydrous THF (10 mL) was added *n*-BuLi (1.2 mL, 2.5M in hexane) at 0 ^{o}C. The mixture was stirred for 30 min at 0 ^{o}C and then aldehyde **28** (0.37 g, 2.0 mmol) in THF (3 mL) was added by cannula. The mixture was slowly warmed to room temperature and stirred for 2 h. The reaction was quenched with satd aq NH_4Cl (1 mL) and then extracted with Et_2O (10 mL X 2). The organic layer was washed with $NaHCO_3$ (15 mL), brine (15 mL) and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate = 5:1) to give 2*E* isomer **29a** (0.34 g, 59% yield) and 2*Z* isomer **29b** (0.058 g, 10% yield) compound **29a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dt, *J* = 15.3, 6.9 Hz, 1H), 6.29 (brs, 1H), 5.77 (d, *J* = 15.3 Hz, 1H), 4.70 (t, *J* = 4.2 Hz, 1H), 3.80-3.61 (m, 2H), 3.45-3.21 (m, 2H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.10 (dt, *J* = 6.9, 6.3 Hz, 2H), 1.75-1.42 (m, 7H), 0.81 (d, *J* = 6.8 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 143.9, 124.3, 99.1, 67.4, 62.5, 47.1, 31.9, 30.9, 29.4, 28.7, 25.6, 25.2, 20.4, 19.8; compound **29b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 11.4, 7.2 Hz, 1H), 5.65 (br, 1H), 5.67 (d, *J* = 11.4 Hz, 1H), 4.53 (t, *J* = 4.5 Hz, 1H), 3.83-3.67 (m, 2H), 3.47-3.33 (m, 2H), 3.08 (t, *J* = 6.0 Hz, 2H), 2.65 (dt, *J* = 6.9, 6.3 Hz, 2H), 1.80-1.41 (m, 7H), 0.89 (d, *J* = 6.8 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 145.2, 122.8, 99.1, 67.6, 62.6, 46.8, 30.9, 29.6, 28.8, 28.7, 26.3, 25.7, 20.4, 19.9.

7-Hydroxy-2*E*-heptenoic acid isobutylamide (30)

To a solution of a *trans* isomer **29a** (0.143 g, 0.51 mmol) in MeOH (5 mL) was added PTSA (0.005 g, 0.51mmol). The mixture was heated at 50 ^{o}C for 40 min. It was cooled down to room temperature then solvent was evaporated. To this mixture was added aq $NaHCO_3$ (1 mL) and extract with Et_2O (10 mL), then was washed with brine (10 mL) and dried ($MgSO_4$).

The residue was purified via flash column chromatography (hexane: ethyl acetate = 2:1) to give the alcohol **30** (0.102 g, 100 % yield)

Compound **30** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (dt, *J* = 15.3, 6.9 Hz, 1H), 6.05 (br, 1H), 5.80 (d, *J* = 15.3 Hz, 1H), 3.59 (t, *J* = 6 Hz, 2H), 3.09 (t, *J* = 6.6 Hz, 2H), 2.59 (br, 1H), 2.18 (dt, *J* = 8.1, 6.0 Hz, 2H), 1.81-1.72 (m, 1H), 1.60-1.39 (m, 4H), 0.88 (d, *J* = 6.6 Hz, 6H)

Toluene-4-sulfonic acid 6-isobutylcarbamoyl-5*E*-hexenyl ester (31)

To a solution of compound **30** (0.124 g, 0.623 mmol) and pyridine (0.151 mL, 1.87 mmol) in CH_2Cl_2 (5 mL) was added TsCl (0.357 g, 1.87 mmol) at room temperature The mixture was stirred for 3 h and washed with 10 % HCl (10 mL), $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate=1:1) to give the compound **31** (0.165 g, 79%);

Compound **31** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.70 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.89 (br, 1H), 5.76 (d, *J* = 15.3 Hz, 1H), 3.98 (t, *J* = 6.3 Hz, 2H), 3.09 (t, *J* = 6.3 Hz, 2H), 2.42 (s, 3H), 2.10 (dt, *J* = 7.5, 7.2 Hz, 2H), 1.81-1.69 (m, 1H), 1.68-1.57 (m, 2H), 1.40-1.38 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)

8-Oxo-2*E*-octenoic acid isobutylamide (33)

To a solution of alcohol **30** (0.12 g, 0.62 mmol) in CH_2Cl_2 (10 mL) was added PCC (0.20 g, 0.93 mmol) at 0 ^oC. After stirring at room temperature for 1 h, Et_2O was added and the mixture was filtered through Celite. Solvent was removed and the residue was purified via flash column chromatography (hexane: ethyl acetate = 4:1) to give aldehyde **33** (0.87 g, 72 %).

Compound **33** ^{1}H NMR (300 MHz, CDCl3) δ 9.75 (t, *J* = 1.5Hz, 1H), 6.76 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.79 (d, *J* = 15.3 Hz, 1H), 5.77 (br, 1H), 3.12 (t, *J* = 6.3 Hz, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.20 (dt, *J* = 7.8, 7.2 Hz, 2H), 1.82-1.72 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 6H). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 166.0, 143.1, 124.9, 47.1, 43.2, 31.3, 28.8, 20.8, 20.3

7-Hydroxy-11-trimethylsilanyl-2*E*-undecene-8,10-diynoic acid isobutylamide (34a) and **7-Hydroxy-2*E*-undecene-8,10-diynoic acid isobutylamide (34b)**

To a solution of 1,4-bistrimethylsilyl-1,3-butadiyne (1.44 g, 7.4 mmol) in 10 mL of THF was added MeLi−LiBr (1.5 M solution, 4.94 mL) at 0 ^{o}C. The mixture was warmed to room temperature. After stirring for 3 h at room temperature, the mixture was cooled to -78 ^{o}C. To the mixture was added aldehyde **33** (0.58 g, 2.97 mmol) in THF. After stirring for 45 min at -78^{o}C, water (10 mL) was added. The mixture was then extracted with ether (50 mL), washed with brine, and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate= 4:1) to give the product **34a** (0.26 g, 36 % yield) and **34b** (0.12 g, 22 % yield).

Compound **34a** ^{1}H NMR (300 MHz, CDCl3) δ 6.80 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.79 (d, *J* = 15.3 Hz, 1H), 5.63 (br, 1H), 4.42 (t, *J* = 6 Hz, 1H), 3.14 (t, *J* = 6 Hz, 2H), 2.21 (dt, *J* = 8.1, 7.5 Hz, 2H), 1.84-1.60 (m, 5H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.19 (s, 9H) ;

Compound **34b** ^{1}H NMR (300 MHz, CDCl3) δ 6.81 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.80 (d, *J* = 15.3 Hz, 1H), 5.64 (br, 1H), 4.18 (td, *J* = 6.3, 1.2 Hz, 1H), 3.14 (t, *J* = 6.3 Hz, 2H), 2.22 (dt, *J* = 8.4, 6.0 Hz, 2H), 2.20 (d, *J* = 1.2 Hz, 1H), 1.84-1.61 (m, 5H), 0.91 (d, *J* = 6.6 Hz, 6H)

1-Trimethylsilyl-1,3-undecadiyn-5-ol (35)

To a solution of 1,4-bistrimethylsilylbutadiyne (0.24 g, 1.25 mmol) in 5 mL of THF was added MeLi−LiBr (1.5 M solution, 0.83 mL) at 0 ^{o}C. The mixture was warmed to room temperature. After stirring for 3 h at room temperature, the mixture was cooled to -78 ^{o}C. To the mixture was added heptanal (0.70 g, 0.5 mmol) in THF. After stirring for 45 min at -78 ^{o}C, water (10 mL) was added. The mixture was then extracted with ether (50 mL), washed with brine, and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate =4:1) to give the product **35** (0.64 g, 56 % yield).

Compound **35** ^{1}H NMR (300 MHz, CDCl3) δ 4.40 (t, *J* = 6 Hz, 1H), 1.96 (br, 1H), 1.74-1.66(m, 2H), 1.45-1.25 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H), 0.29 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.8, 87.4, 78.9, 69.9, 63.1, 37.9, 31.9, 29.1, 25.2, 22.8, 14.3, 0.1.

Imidazole-1-carbothioic acid O-[1-(4-trimethylsilanylbuta-1,3-diynyl)heptyl] ester (36)

To a solution of compound **35** (0.63 g, 0.28 mmol) in CH_2Cl_2 (5 mL) was added 1,1-thiocarbonyldiimidazole (0.98 g, 0.55 mmol) at room temperature. The mixture was stirred overnight then solvent was removed. The residue was purified via flash column chromatography (hexane:ethyl acetate = 5:1) to give the compound **36** (0.84 g, 88 % yield).

Compound **36** ^{1}H NMR (400 MHz, CDCl3) δ 8.31 (s, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.01 (t, *J* = 6.4 Hz, 1H), 2.01-1.96 (m, 2H), 1.52-1.46 (m, 2H), 1.37-1.24 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.18 (s, 9H).

1-Trimethylsilyl-1,3-undecadiyne (37)

To a solution of compound **36** (0.84 g, 0.24 mmol) in toluene (5 mL) was added tributyltinhydride (0.13 mL, 0.49 mmol) and AIBN (0.004 g, 0.024 mmol) at room temperature. The mixture was heated at 80 ^{o}C for 30 min then cooled down to room temperature. To the mixture, H_2O (5 mL) was added then extracted with Et_2O (10 mL X 2) and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane only) to give the compound **37** (0.29 g, 54 % yield).

Compound **37** ^{1}H NMR (400 MHz, CDCl3) δ 2.62 (t, *J* = 6.8 Hz, 2H), 1.57-1.49 (m, 2H), 1.37-1.32 (m, 2H), 1.29-1.23 (m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H), 0.18 (s, 9H).

Imidazole-1-carbothioic acid O-[6-isobutylcarbamoyl-1-(4-trimethylsilyl-1,3-butadiynyl)-hex-5-enyl] ester (38)

To a solution of compound **34a** (0.023 g, 0.072 mmol) in CH_2Cl_2 (2 mL) was added 1,1-thiocarbonyldiimidazole (0.026 g, 0.144 mmol) at room temperature The mixture was stirred overnight then remove solvent. The residue was purified via flash column chromatography (hexane:ethyl acetate=5:1) to give the compound **38** (0.025 g, 81% yield).

Compound **38** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.60 (s, 1H), 7.04 (s, 1H), 6.78 (dt, *J* = 15.3, 7.2 Hz, 1H), 6.05 (t, *J* = 6.6 Hz, 1H), 5.79 (d, *J* = 15.3 Hz, 1H), 5.54 (br, 1H), 3.15 (t, *J* = 6.3 Hz, 2H), 2.26 (dt, *J* = 7.2, 6.9 Hz, 2H), 2.09-1.98 (m, 2H), 1.82-1.65 (m, 3H), 0.92 (d, *J* = 6.3 Hz, 6H), 0.19 (s, 9H)

N-Isobutyl-2-[2-(4-trimethylsilyl-1,3-butadiynyl) cyclopentyl]acetamide (39)

To a solution of compound **38** (0.025 g, 0.058 mmol) in toluene (5 mL) was added tributyltinhydride (0.31 mL, 0.12 mmol) and AIBN (0.001 g, 0.006 mmol) at room temperature. The mixture was heated at 80 ^{o}C for 30 min then cooled to room temperature. To the mixture, H_2O (1 mL) was added then extracted with Et_2O (10 mL X 2) and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane:ethyl acetate=5:1) to give the compound **39** (0.008 g, 43 % yield).

Compound **39** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (br, 1H), 3.08 (t, *J* = 6.0 Hz, 2H), 2.55 (dd, *J* = 13.8, 4.5 Hz, 1H), 2.39-2.19 (m, 3H), 2.09-1.96 (m, 3H), 1.84-1.62 (m, 5H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.17 (s, 9H)

5,5-Dimethoxypentanal (40)

To a solution of cyclopentene (0.88 mL, 0.01 mol) in mixture of CH_2Cl_2 (8 mL) and MeOH (2 mL) was blown O_3 at -78 ^{o}C. When light blue color appeared, stopped blowing O_3 then the mixture was flushed with O_2 till the blue color discharged at same temperature. To the mixture PTSA (0.08 g, 0.42 mmol) was added and warmed to room temperature then stirred for 2 h. $NaHCO_3$ (0.042 g) was added to the mixture, then Me_2S (1.47 mL, 20 mmol) was added and stirred for 12 h. To the mixture water was added and extracted with CH_2Cl_2 and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate=5:1) to give the product **40** (1.05 g, 72 %).

Compound **40** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.2 Hz, 1H), 4.34 (t, *J* = 5.4 Hz, 1H), 3.29 (s, 6H), 2.46 (t, *J* = 5.7 Hz, 2H), 1.71-1.59 (m, 4H)

9,9-Dimethoxy-1-trimethylsilyl-1,3-nonadiyn-5-ol (41)

To a solution of 1,4-bistrimethylsilyl-1,3-butadiyne (1.63 g, 8.4 mmol) in 10 mL of THF was added MeLi−LiBr (1.5 M solution, 5.58 mL) at 0 ^{o}C. The mixture was warmed to room temperature. After stirring for 3 h at room temperature, the mixture was cooled to -78 ^{o}C. To the mixture was added aldehyde **40** (0.50 g, 3.4 mmol) in THF. After stirring for 45 min at -78 ^{o}C, water (10 mL) was added. The mixture was then extracted with ether (50 mL), washed with brine, and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane:ethyl acetate=4:1) to give the product **41** (0.793 g, 88 % yield).

Compound **41** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43(q, *J* = 5.1 Hz, 1H), 4.37 (t, *J* =5.7 Hz, 1H), 3.32 (s, 6H), 1.87 (brs, 1H), 1.71−1.78 (m, 2H), 1.58−1.68 (m, 2H), 1.48−1.56 (m, 4H), 0.19 (s, 9H); ^{13}C NMR (75MHz, CDCl3) δ 104.5, 87.6, 87.5, 78.9, 69.9, 62.6, 52.9, 37.3, 32.2, 20.4, -0.29.

Imidazole-1-carbothioic acid O-[1-(4,4-dimethoxybutyl)-5-trimethylsilyl-2,4-pentadiynyl] ester (42)

To a solution of the compound **41** (0.71 g, 2.65 mmol) in CH_2Cl_2 (10 mL) was added 1,1-thiocarbonyldiimidazole (0.94 g, 5.3 mmol) at room temperature. After stirring for 12 h, the solvent was removed in vacuo. The residue was purified via flash column chromatography (hexane:ethyl acetate=3:1) to give the product (0.86 g, 86 % yield).

Compound **42** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (t, *J* = 0.9 Hz, 1H), 7.56 (t, *J* = 1.5 Hz, 1H), 6.98 (q, *J* = 0.9 Hz, 1H), 5.99 (t, *J* = 6.6 Hz, 1H), 4.33 (t, *J* = 5.1 Hz, 1H), 3.27 (s, 6H), 1.98−2.01 (m, 2H), 1.55−1.64 (m, 4H), 0.15 (s, 9H).

(9,9-Dimethoxy-1,3-nonadiynyl)trimethylsilane (43)

To a solution of the thioimidazolide produced above (0.91 g, 2.4 mmol) in toluene was added AIBN (0.039 g, 0.24 mmol) and Bu_3SnH (0.71 mL, 2.64 mmol) at room temperature. The mixture was boiled at 80 ^oC for 1 h. It was cooled to room temperature and solvent was removed in vacuo. The residue was purified via flash column chromatography (hexane:ethyl acetate=10:1) to give the acetal **43** (0.42 g, 69 % yield).

Compound **43** ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (t, *J* = 5.6 Hz, 1H), 3.30 (s, 6H), 2.27 (t, *J* = 6.8 Hz, 1H), 1.46−1.61 (m, 4H), 1.39−1.45 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.5, 88.6, 83.3, 79.9, 65.9, 52.9, 32.2, 28.1, 24.1, 19.4, -0.12; HREIMS [M]+ m/z: 252.1549 (Calc. 252.1546) for $C_{14}H_{24}O_2Si$.

9-Trimethylsilyl-6,8-nonadiynal (44)

To a solution of acetal **43** (0.11 g, 0.44 mmol) in Acetone/ H_2O (5 mL/ 0.5 mL) was added PTSA (0.009 g, 0.044 mmol) at room temperature. After stirring for 12 h at room temperature, the solvent was removed. Water (25 mL) was added and the mixture was extracted with ether (50 mL), washed with sat $NaHCO_3$, brine, and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate=4:1) to give an aldehyde **44** (0.081g, 89 % yield).

Compound **44** ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, J = 1.8 Hz, 1H), 2.45 (td, J = 6.9, 1.8 Hz, 2H), 2.30 (t, J = 6.9 Hz, 2H), 1.68−1.78 (m, 2H), 1.50−1.60 (m, 2H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 88.5, 83.7, 79.3, 66.2, 43.4, 27.7, 21.4, 19.3, -0.1; HREIMS [M]+ m/z: 206.1130 (Calc. 206.1127) for $C_{12}H_{18}OSi$.

11-Trimethylsilyl-undec-2*E*-ene-8,10-diynoic acid isobutyl-amide (45a) and 11-Trimethylsilyl-undec-2*Z*-ene-8,10-diynoic acid isobutyl-amide (45b)

To a solution of triphenyl-(*N*-isobutylcarboxamidomethyl)-phosphonium chloride **27** (0.415 g, 1.01 mmol) in THF (5 mL) was added 2.5 M *n*-BuLi (0.404 mL, 1.01 mmol) at 0 ^{o}C. After stirring for 10 min at 0 ^{o}C, aldehyde **44** (0.104 g, 0.51 mmol) in THF (3 mL) was added dropwise at 0 ^{o}C. After stirring for 30 min at 0 ^{o}C, water (25 mL) was added. The solution was then extracted with ether (50 mL) and dried over $MgSO_4$. The residue was purified via flash column chromatography (hexane:ethyl acetate=10:1) to give (*E*) isomer **45a** (112 mg, 73 % yield) and (*Z*) isomer **45b** (15 mg, 10 % yield).

(*E*) isomer (**45a**): IR mmax (neat) cm^{-1}: 3289,2958, 2359, 2225, 2108, 1669, 1628, 844; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.78 (d, *J* =15.3 Hz, 1H), 5.67 (br, 1H), 3.13 (t, *J* =6.3 Hz, 2H), 2.25−2.29 (m, 2H), 2.14−2.20 (m, 2H), 1.74−1.83 (m, 1H), 1.52−1.56 (m, 4H), 0.91 (d, *J* =6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1,143.9, 124.3, 88.6, 83.5, 79.8, 66.0, 47.1, 31.5, 28.8, 27.7, 27.5, 20.4, 19.2,-0.2; HRMS [M]+ m/z: for $C_{18}H_{29}NOSi$ Calculated: 303.2018; found:303.2023 .

(*Z*) isomer **(45b)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dt, *J* = 11.4, 7.5 Hz, 1H), 5.69 (d, *J* =11.4 Hz, 1H), 5.50 (br, 1H), 3.11 (t, *J* =6.3 Hz, 2H), 2.63−2.70 (m, 2H), 2.27−2.31 (m, 2H), 1.74−1.83 (m, 1H), 1.49−1.64 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 145.0, 122.9, 88.7, 83.3, 80.1, 65.8, 46.8, 28.8, 28.6, 28.2, 27.9, 20.4, 19.2, -0.1.

Undec-2*E*-ene-8,10-diynoic acid isobutylamide (12) and Undec-2*Z*-ene-8,10-diynoic acid isobutylamide (13)

To a solution of amide **45a** (0.029 g, 0.096 mmol) in THF (1 mL) was added 1 M TBAF (0.144 mL, 0.144 mmol) at 0 ^{o}C. After stirring for 30 min, the solvent was removed in vacuo. The residue was purified via flash column chromatography (hexane:ethyl acetate=10:1) to give amide **12** (0.021g, 95%).

Amide **12** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 15.3, 6.6 Hz, 1H), 5.79 (d, *J* = 15.3 Hz, 1H), 5.62 (br, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.23−2.29 (m, 2H), 2.16−2.22 (m, 2H), 1.97 (t, *J* = 0.9 Hz, 1H) 1.74−1.83 (m, 1H), 1.52−1.59 (m, 4H), 0.91 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 143.8, 124.3, 78.1, 68.6, 65.2, 64.9, 47.1, 31.5, 28.8, 27.6, 27.5, 20.3, 19.0; HREIMS [M]+ m/z: 231.16260 (Calc. 231.16231) for $C_{15}H_{21}$ NO.

Amide **13** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (dt, *J* = 11.4, 7.5 Hz, 1H), 5.69 (d, *J* = 11.4 Hz, 1H), 5.49 (br, 1H), 3.11 (t, *J* = 6.9 Hz, 2H), 2.64−2.72 (m, 2H), 2.57−2.30 (m, 2H), 1.95 (t, *J* = 1.2 Hz, 1H), 1.72−1.86 (m, 1H), 1.50−1.63 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 145.0, 122.9, 78.5, 68.7, 65.0, 64.7, 46.8, 28.8, 28.5, 28.2, 27.8, 20.4, 19.1.

9,9-Dimethoxy-1,3-nonadiyne (46)

To a solution of acetal **43** (0.09 g, 0.36 mmol) in THF (5 mL) was added TBAF (1 M solution, 0.542 mL) at 0 ^{o}C. The mixture was warmed to room temperature and stirred for 30 min. Solvent was removed in vacuo. The residue was purified via flash column

chromatography (hexane: ethylacetate=2:1) to give a terminal acetylene that was taken immediately to the next step (0.062 g, 96 % yield).

Compound **46** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (t, *J* = 5.4 Hz, 1H), 3.31 (s, 6H), 2.27 (t, *J* = 6.6 Hz, 2H), 1.96 (t, *J* = 1.2 Hz, 1H), 1.53−1.65 (m, 4H), 1.41−1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.5, 78.3, 68.6, 65.1, 64.8, 52.9, 31.8, 28.0, 24.1, 19.2.

10,10-Dimethoxy-2,4-decadiyne (**47**)

To a solution of the terminal acetylene **46** produced above (0.053 g, 0.29 mmol) in THF (3 mL) was added *n*-BuLi (2.5 M solution, 0.119 mL) at -78 ^{o}C. After 10 min, methyl iodide (0.063 mL, 1.02 mmol) was added to the mixture at -78 ^{o}C. The mixture was warmed to room temperature then HMPA (1.5 mL) was added. After stirring 12 h at room temperature, ice water (10 mL) was added ,extracted with ether (20 mL x 3). The organic layer was washed with water and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane:ethyl aetate=3:1) to give the methylated acetylene **47** (0.027 g, 40 % yield).

Compound **47** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (t, *J* = 5.7 Hz, 1H), 3.26 (s, 3H), 2.20 (t, *J* = 6.9 Hz, 2H), 1.84 (s, 3H), 1.49−1.59 (m, 4H), 1.33−1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.9, 77.6, 72.8, 65.5, 64.0, 51.2, 33.1, 28.6, 23.4, 18.7, 4.2; HREIMS [M]+ m/z: 194.1314 (Calc. 194.1307) for $C_{12}H_{18}O_2$.

6,8-Decadiynal (48)

To a solution of the methylated acetylene **47** produced above (0.045 g, 0.23 mmol) in Acetone/H_2O (5 mL/0.5 mL) was added PTSA (0.01 g, 0.05 mmol) at room temperature

After stirring for 12 h at room temperature, the solvent was removed. Water (30 mL) was added and the mixture extracted with ether (20 mL), washed with sat $NaHCO_3$ (10 mL), brine (10 mL), and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate=4:1) to give an aldehyde **48** (0.030 g, 87 % yield).

Compound **48** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H), 2.45 (td, *J* = 7.2, 1.5 Hz, 1H), 2.27 (t, *J* = 6.9 Hz, 2H), 1.84 (s, 3H), 1.49−1.59 (m, 4H), 1.33−1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 77.8, 73.4, 65.3, 63.9, 44.7, 26.3, 21.4, 19.1, 4.3.

Dodec-2*E*-ene-8,10-diynoic acid isobutylamide (14) and **Dodec-2*Z*-ene-8,10-diynoic acid isobutylamide (14a)**

To a solution of triphenyl-(N-isobutylcarboxamidomethyl)-phosphonium chloride **27** (0.165 g, 0.4 mmol) in THF (2 mL) was added n-BuLi (2.5 M, 0.16 mL) at 0 ^{o}C. After stirring for 10 min at 0 ^{o}C, the aldehyde produced above (0.03 g, 0.20 mmol) in THF (1 mL) was added dropwise at 0 ^{o}C. After stirring for 30 min at 0 ^{o}C, water (25 mL) was added and the mixture was extracted with ether (50 mL), and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate=10:1) to give **14** (0.033 g, 68 % yield) and **14a** (0.009 g, 18 % yield).

Amide **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.78 (d, *J* = 15.5 Hz, 1H), 5.56 (br, 1H), 3.14 (t, *J* = 6.3 Hz, 2H), 2.15−2.27 (m, 4H), 1.90 (s, 3H), 1.73, 1.83 (m, 1H), 1.53−1.59 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 144.1, 124.2, 76.5, 73.5, 65.9, 64.7, 47.1, 31.6, 28.8, 27.9, 27.4, 20.4, 19.2, 4.4; HREIMS [M]+ m/z: 245.1784 (Calc. 245.1780) for $C_{16}H_{23}ON$

Amide **14a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dt, *J* = 11.4, 7.5 Hz, 1H), 5.67 (d, *J* = 11.4 Hz, 1H), 5.54 (br, 1H), 3.10 (t, *J* = 6.9 Hz, 2H), 2.69 −2.62 (m, 2H), 2.27-2.23 (m, 2H), 1.92 (s, 3H), 1.85-1.73 (m, 1H), 1.59−1.51 (m, 4H), 0.91 (d, *J* = 6.6 Hz, 6H).

7-iodo-6-heptyn-1-ol (49)

To a solution of 6-heptynol (0.331 g, 2.95 mmol) in 10 mL of methanol was added KOH in 5 mL of H_2O. After 10 min, iodine (0.824 g, 3.24 mmol) was added at 0 ^oC and warmed to room temperature and stirred for 2 h. The reaction was then quenched with water and extracted with ether (20 mL x 3). The solvent was removed in vacuo, the residue dissolved in CH_2Cl_2, washed with brine (15 mL) and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane: ethyl acetate= 4:1) to give **49** (0.498 g, 71%).

Compound **49** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (t, J = 6.5 Hz, 2H), 2.47 (t, J = 6.9 Hz), 1.64-1.51 (m, 4H), 1.50-1.42 (m, 2H).

9-Trimethylsilyl-6,8-nonadiyn-1-ol (50)

Method (a): To a solution of trimethylsilylacetylene (0.45 mL, 3.15 mmol) and 7-iodo-6-heptynol **49** (0.250 g, 1.05 mmol) in degassed piperidine (2 mL) was added CuCl (0.010 g, 0.105 mmol) at 0 ^oC. The mixture was stirred at room temperature for 30 min. The reaction was quenched with 6 mL of sat NH_4Cl (aq) and extracted with Et_2O (10 mL x 3). Organic layer was washed with brine (20 mL x 2), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **50** (0.213 g, 87 %)

Method (b): To a solution of 7-iodo-6-heptynol **49** (0.1 g, 0.42 mmol), trimethylsilylacetylene (0.072 mL, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (10 mg) and copper iodide (3 mg) in 5 mL of THF was added diisopropylamine (0.150 mL) at room temperature in Ar. After stirring 1 h at room temperature, the mixture was diluted with Et_2O, washed with NH_4Cl solution, water and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **50** (0.04 g, 40 % yield).

Compound **50** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (t, *J* = 6.0 Hz, 2H), 2.02 (t, *J* = 6.9 Hz, 2H), 2.02 (brs, 1H), 1.56-1.41 (m, 6H), 0.16 (s, 9H)

9-Trimethylsilyl-6,8-nonadiynal (44)

To a solution of oxalyl chloride (0.160 mL, 1.84 mmol) in 10 mL of CH_2Cl_2 was added dimethylsulfoxide (0.263 mL, 3.7 mmol) dropwise at -78 ^{o}C. The mixture was stirred at same temp for 20 min and triethylamine (0.766 mL, 5.51 mmol) was added dropwise and stirred at same temperature for 20 min. To the mixture was added compound **50** (0.213 mg, 0.918 mmol) at -78 ^{o}C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl(aq) and aqueous layer was extracted with CH_2Cl_2 (2x 20 mL). Combined organic layer was washed with water (2x 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **44** (0.187 g, 89 % yield)

Compound **44** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.8 Hz, 1H), 2.45 (td, *J* = 6.9, 1.8 Hz, 2H), 2.30 (t, *J* = 6.9 Hz, 2H), 1.68−1.78 (m, 2H), 1.50−1.60 (m, 2H), 0.14 (s, 9H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 88.5, 83.7, 79.3, 66.2, 43.4, 27.7, 21.4, 19.3, -0.1; HREIMS [M]+ m/z: 206.1130 (Calc. 206.1127) for $C_{12}H_{18}OSi$.

6,8-Decadiyn-1-ol (52)

In a sealed tube, degassed piperidine (7 mL), 7-iodo-6-heptynol **49** (1.0 g, 4.2 mmol) and CuCl (0.043 g, 0.43 mmol) was mixed. The mixture was cooled down to -78 ^oC and excess propyne gas was added by blowing along the wall of the tube. Propyne gas was condensed to liquid (3 mL) in sealed tube and the tube was closed. The mixture was slowly warmed to room temperature. After stirring for 2 h at room temperature, the mixture was cooled to -78 ^oC and the sealed tube was opened. Slowly warmed to room temperature and excess propyne was evaporated. NH_4Cl (aq) (50 mL) was added to the mixture then extracted with Et_2O (3 x 30 mL). Organic layer was washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **52** (0.472 g, 75 % yield)

Compound **52** ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (t, J = 6.6 Hz, 2H), 2.25 (t, J = 6.0 Hz, 2H), 1.89 (s, 3H), 1.63−1.47 (m, 6H), 1.32 (brs, 1H).

Dodeca-2*E*,4*E*-dienoic acid isobutylamide (11) and **Dodeca-2*Z*,4*E*-dienoic acid isobutylamide (11a)**

To a solution of Wittig salt **27** (0.412 g, 1.0 mmol) in THF (5 mL) was added 2.5 M n-BuLi (0.40 mL, 1.0 mmol) at 0 ^oC. After stirring for 10 min at 0 ^oC, trans-2-decenal (0.095mL, 0.5 mmol) in THF (3 mL) was added dropwise at 0 ^oC. After stirring for 30 min at 0^oC, water (5 mL) was added. The solution was then extracted with ether (30 mL) and dried

($MgSO_4$). The residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give (E) isomer **11** (81 mg, 64 % yield) and (Z) isomer **11a** (25 mg, 21 % yield).

Compound **11** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 15.0, 9.9 Hz, 1H), 6.14-5.97 (m, 2H), 5.87 (br, 1H), 5.78 (d, *J* = 15.0 Hz, 1H), 3.13 (t, *J* = 6.3 Hz, 2H), 2.11 (dt, *J* = 13.2, 6.6 Hz, 2H), 1.80-1.71 (m, 1H), 1.43-1.18 (m, 10H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 164.9, 141.9, 140.7, 128.7, 122.9, 46.8, 32.9, 31.8, 29.2, 29.1, 28.8, 28.7, 22.7, 19.9, 13.9 ; HRMS *m/e* (EI) for $C_{16}H_{29}NO$ $(M)^+$ calcd 251.2249, measured 251.2243.

Compound **11a** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.36 (dd, *J* = 11.4, 11.4 Hz, 1H), 5.95 (dt, *J* = 15.3, 7.8, 1H), 5.65 (br, 1H), 5.46 (d, *J* = 11.1 Hz, 1H), 3.12 (t, *J* = 6.3 Hz, 2H), 2.15 (dt, *J* = 13.8, 6.9 Hz, 2H), 1.84-1.75 (m, 1H), 1.43-1.22 (m, 10H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 167.1, 144.4, 142.0, 127.0, 118.4, 47.0, 33.2, 32.0, 29.5, 29.4, 29.1, 28.8, 22.9, 20.4, 14.3

Oct-6*E*-en-4-yn-1-ol (57)

To a solution of $Pd(PPh_3)_2Cl_2$ (56 mg, 0.08 mmol), CuI (15.2 mg, 0.08 mmol) in THF (5 mL) was added 4-pentynol (0.23 mL, 2.48 mmol), trans-bromopropene (0.21 mL, 2.48 mmol) and diisopropylamine (0.97 mL, 7.44 mmol) successively at 0 ^{o}C in Ar. After stirring at room temperature for 2 h, the reaction was quenched with sat NH_4Cl (aq), extracted with ether, washed with brine, and dried ($MgSO_4$). The residue was purified via flash column chromatography to give compound **57** (230 mg, 74 % yield).

Compound **57** ^{1}H NMR (300MHz, $CDCl_3$) δ 6.05 (dq, *J* = 15.9, 6.9 Hz, 1H), 5.40 (dq, *J* = 15.9, 1.8 Hz, 1H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.41 (t, *J* = 6.9 Hz, 2H), 1.81-1.73 (m, 5H), 1.52 (brs, 1H)

Oct-6*E*-en-4-ynal (58)

To a solution of compound **57** (0.20 g, 1.61 mmol) in CH_2Cl_2 (10 mL) was added PCC (0.695 g, 3.2 mmol) at 0 ^{o}C. The mixture was stirred for 1 h at room temperature, then Et_2O (20 mL) was added. The solution was filtered through celite and solvent was removed. The residue was purified via via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **58** (183 mg, 92 % yield).

Compound **58** ^{1}H NMR (300MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.2 Hz, 1H), 6.02 (dq, *J* = 15.9, 6.9 Hz, 1H), 5.40 (dq, *J* = 15.9, 1.8 Hz, 1H), 2.67-2.61 (m, 2H), 2.59-2.54 (m, 2H), 1.71 (dd, J = 6.6, 1.8 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 200.9, 139.1, 110.8, 86.0, 80.3, 42.9, 18.7, 12.8

Dodeca-2*E*,4*E*,10*E*-trien-8-ynoic acid isobutylamide (5) and Dodeca-2*E*,4*Z*,10*E*-trien-8-ynoic acid isobutylamide (5a)

To a solution of compound **55** (0.59 g, 1.23 mmol) in THF (5 mL) was added 2.5 M *n*-BuLi (0.42 mL, 1.06 mmol) at 0 ^{o}C. After stirring for 10 min at 0 ^{o}C, aldehyde **58** (0.10 g, 0.82 mmol) in THF (5 mL) was added dropwise at 0 ^{o}C. After stirring for 30 min at 0 ^{o}C, water (5 mL) was added. The solution was then extracted with ether (30 mL) and dried over $MgSO_4$. The residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give (*E*) isomer **5** (140 mg, 70 %) and (*Z*) isomer **5a** (20 mg, 10 %).

Compound **5** ^{1}H NMR (300MHz, $CDCl_3$) δ 7.19 (dd, *J* = 15.0, 10.2 Hz, 1H), 6.23-6.09 (m, 1H), 6.15 (dd, *J* = 10.2, 10.2 Hz, 1H), 6.07 (dq, *J* = 15.6, 6.9 Hz, 1H), 5.78 (d, *J* = 15.0 Hz, 1H), 5.49 (br, 1H), 5.45 (ddt, *J* = 15.9, 1.8, 1.8 Hz, 1H), 3.17 (t, *J* = 6.6 Hz, 2H), 2.40-2.34 (m, 4H), 1.84-1.76 (m, 1H), 1.75 (dd, *J* = 6.6, 1.8 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 141.0, 140.6, 138.8, 129.5, 122.9, 111.0, 87.2, 80.2, 47.2, 32.4, 28.9, 20.4, 19.3, 18.8

Compound **5a** ^{1}H NMR (300MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 14.7, 10.8, 1.2 Hz, 1H), 6.15 (dd, *J* = 10.8, 10.8 Hz, 1H), 6.04 (dq, *J* = 15.3, 6.9 Hz, 1H), 5.86-5.7 (m, 1H), 5.85 (d, *J* = 14.7 Hz, 1H), 5.57 (br, 1H), 5.44 (ddt, *J* = 15.6, 1.8, 1.8 Hz, 1H), 3.17 (t, *J* = 6.6 Hz, 2H), 2.55-2.48 (m, 2H), 2.40-2.35 (m, 2H), 1.74 (dd, *J* = 6.6, 1.8 Hz, 3H), 1.87-1.77 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 166.3, 138.7, 137.8, 135.8, 127.7, 124.7, 111.0, 87.2, 80.3, 47.2, 31.6, 28.9, 19.7, 18.7, 16.2.

Oct-4*Z*-en-1-ol (60)

To a solution of 4-octyn-1-ol (252 mg, 2 mmol) in EtOH (5 mL) was added Lindlar catalyst (67 mg) and the flask was filled with H_2. To a mixture was added quinoline (0.33 mL) then the mixture was stirred for 1 h at room temperature. After 1 h, the mixture was filtered and the residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **60** (240 mg, 94 % yield).

Compound **60** ^{1}H NMR (300MHz, $CDCl_3$) δ 5.43-5.35 (m, 2H), 3.66 (t, *J* = 6.6 Hz, 2H), 2.16-2.09 (m, 2H), 2.05-1.98 (m, 2H), 1.67-1.58 (m, 2H), 1.43-1.25 (m, 3H), 0.90 (t, *J* = 7.2 Hz, 3H)

4*Z*-Octenal (61)

To a solution of oxalyl chloride (0.27 mL, 3.12 mmol) in 10 mL of CH_2Cl_2 was added dimethylsulfoxide (0.44 mL, 6.24 mmol) dropwise at -78^oC. The mixture was stirred at same temp for 20 min and triethylamine (1.30 mL, 9.36 mmol) was added dropwise and stirred at same temp for 20 min. To the mixture was added compound **60** (200 mg, 1.56 mmol) at -78^oC and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl(aq) and aqueous layer was extracted with CH_2Cl_2 (2x 20 mL). Combined organic layer was washed with water (2x 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **61** (165 mg, 84 % yield).

Compound **61** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.2 Hz, 1H), 5.44-5.28 (m, 2H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.34 (dt, *J* = 10.8, 7.2 Hz, 2H), 2.00 (dt, *J* = 10.8, 7.2 Hz, 2H), 1.40-1.31 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H)

Dodeca-2*E*,4*E*,8*Z*-trienoic acid isobutylamide (10) and Dodeca-2*E*,4*Z*,8*Z*-trienoic acid isobutylamide (10a)

To a solution of compound **55** (0.77 g, 1.59 mmol) in THF (5 mL) was added 2.5 M *n*-BuLi (0.63 mL, 1.59 mmol) at 0 ^oC. After stirring for 10 min at 0 ^oC, aldehyde **61** (0.10 mg, 0.79 mmol) in THF (3 mL) was added dropwise at 0 ^oC. After stirring for 1 h at 0 ^oC, water (5 mL) was added. The solution was then extracted with ether (30 mL) and dried over $MgSO_4$. The residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **10** (135 mg, 69 %) and compound **10a** (24 mg, 12 %).

Compound **10** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (ddd, *J* = 14.7, 11.4, 1.2 Hz, 1H), 6.10 (dd, *J* = 11.4, 10.8 Hz, 1H), 5.83 (d, *J* = 15.0 Hz, 1H), 5.77 (dq, *J* = 10.8, 7.8 Hz, 1H), 5.45 (br, 1H), 5.44-5.32 (m, 2H), 3.17 (t, *J* = 6.6 Hz, 2H), 2.39-2.32 (m, 2H), 2.18-2.10 (m, 2H), 2.02-1.96 (m, 2H), 1.85-1.75 (m, 1H), 1.42-1.29 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.87 (t, *J* = 7.2 Hz, 3H)

Compound **10a** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 15.0, 9.9 Hz, 1H), 6.19-6.03 (m, 2H), 5.75 (d, *J* = 15.0 Hz, 1H), 5.47 (br, 1H), 5.44-5.32 (m, 2H), 3.16 (t, *J* = 6.6 Hz, 2H), 2.21-2.14 (m, 4H), 2.00 (dt, *J* = 6.9, 7.0 Hz, 2H), 1.84-1.75 (m, 2H), 1.42-1.26 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.92 (t, *J* = 6.6 Hz, 3H)

4Z,6E-Octadien-1-ol (59)

To a solution of crotyl triphenylphosphonium bromide (3.73 g, 9.4 mmol) in THF (20 mL) was added *n*-BuLi (3.76 mL, 2.5M in hexane, 9.4 mmol) at 0 ^oC. The mixture was stirred for 30 min, then 2-hydroxytetrahydrofuran (552 mg, 6.27 mmol) was added at the same temperature. The mixture was warmed to room temperature, then stirred overnight. The reaction was quenched with aq NH_4Cl (5 mL), extract with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified via via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **59** (505 mg , 64% yield).

Compound **59** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 15.3, 10.8 Hz, 1H), 5.98 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.69 (dq, *J* = 15.3, 6.8 Hz, 1H), 5.27 (m, 1H), 3.67 (t, *J* = 6.8 Hz, 2H), 2.27 (td, *J* = 7.2, 7.2 Hz, 2H), 1.77 (d, *J* = 6.8 Hz, 3H), 1.70-1.59 (m, 2H).

4Z,6E-Octadienal (63)

To a solution of compound **59** (400 mg, 3.17 mmol) in CH_2Cl_2 (10 mL) was added PCC (1.37 g, 6.34 mmol) at 0 ^oC. The mixture was stirred for 1 h at room temperature, then Et_2O (20 mL) was added. The solution was filtered through celite and solvent was removed. The residue was purified via via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **63** (296 mg, 76 % yield)

Compound **63** ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, *J* = 1.2 Hz, 1H), 6.26 (dd, *J* = 15.3, 10.8 Hz, 1H), 5.68 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.44 (dq, *J* = 15.3, 6.8 Hz, 1H), 5.20 (m, 1H), 2.35 (td, *J* = 6.8, 1.2 Hz, 2H), 2.20 (td, *J* = 7.2, 7.2 Hz, 2H), 1.87 (d, *J* = 6.8 Hz, 3H), 1.72-1.60 (m, 2H).

Dodeca-2,4,8,10-tetraenoic acid isobutyl-amide (8) , (8a)

To a solution of compound **55** (1.4 g, 3.0 mmol) in THF (10 mL) was added 2.5 M n-BuLi (1.2 mL, 3.0 mmol) at 0 ^oC. After stirring for 10 min at 0 ^oC, aldehyde **63** (250 mg, 2.0 mmol) in THF (2 mL) was added dropwise at 0 ^oC. After stirring for 30 min at 0 ^oC, water (5 mL) was added. The solution was then extracted with ether (30 mL) and dried over $MgSO_4$. The residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give the mixture of amide **8** and **8a**. (460 mg , 62% yield)

(Isobutylcarbamoylmethyl)-phosphonic acid diphenyl ester (66)

To a solution of isobutylamine (3 mL, 30 mmol) in CH_2Cl_2 (20 mL) was added bromoacetyl chloride (1.25 mL, 15 mmol) in CH_2Cl_2 (20 mL) by dropping funnel at 0 ^oC. The mixture was stirred for 1 h while slowly warmed to room temperature. The mixture was

filtered, then solvent was removed. The crude residue was added to a solution of diphenylphosphite (3.46 mL, 15 mmol) in CH_2Cl_2 (20 mL) followed by addition of Et3N (3 mL, 21 mmol) at 0 ^oC. After stirring 12 h at room temperature, the mixture was filtered and concentrated. The residue was purified via flash column chromatography (hexane:ethyl acetate= 1:1) to give compound **66** (2.7 g, 52% yield).

Compound **66** ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 4H), 7.19-7.15 (m, 6H), 3.15 (d, *J* = 20.0 Hz, 2H), 3.02 (t, *J* = 6.0 Hz, 2H), 1.69-1.67 (m, 1H), 0.83 (d, *J* = 6.8 Hz, 6H).

7-Trimethylsilyl-4,6-heptadiyn-1-ol (67a)

To a solution of trimethylsilylacetylene(0.5 mL, 3.51 mmol) and 5-iodo-4-pentynol **1** (0.281 g, 1.34 mmol) in degassed piperidine (2 mL) was added CuCl (0.014 g, 0.14 mmol) at 0^oC. The mixture was stirred at room temperature for 0.5 h. The reaction was quenched with 6 mL of sat NH_4Cl (aq) and extracted with Et_2O (10 mL x 3). Organic layer was washed with brine (20 mL x 2), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **67a** (0.188 g, 78%)

Compound **67a** ^1H NMR (300MHz, $CDCl_3$) δ 3.69 (t, *J* = 6 Hz, 2H), 2.37 (t, *J* = 6.9 Hz, 2H), 2.12 (brs, 1H), 1.77-1.70 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (75MHz, $CDCl_3$) δ 88.5, 83.5, 79.4, 66.1, 61.3, 30.9, 15.9, 14.4, -0.16 ; HRMS *m/e* (EI) for $C_{10}H_{16}OSi$ $(M)^+$ calcd 180.0970, measured 180.0956.

7-Trimethylsilyl-4,6-heptadiynal (68a)

To a solution of oxalyl chloride (0.471 mL, 5.4 mmol) in 10 mL of CH_2Cl_2 was added dimethylsulfoxide (0.766 mL, 10.8 mmol) dropwise at -78 ^oC. The mixture was stirred at

same temp for 20 min and triethylamine (2.25 mL, 16.2 mmol) was added dropwise and stirred at same temp for 20 min. To the mixture was added compound **67a** (0.487 mg, 2.7 mmol) at -78 ^{o}C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl(aq) and aqueous layer was extracted with CH_2Cl_2 (2x 20 mL). Combined organic layer was washed with water (2x 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **68a** (0.409g, 85 % yield)

9-Trimethylsilyl-non-2E-ene-6,8-diynoic acid ethyl ester (70a)

To a solution of carbethoxymethyl(triphenyl)phosphonium bromide (3.94 g, 9.19 mmol) in 30 mL of THF was added *n*-BuLi (3.67 mL, 2.5M soln in Hexane) at 0 ^{o}C in Ar. The mixture was stirred for 20 min at 0 ^{o}C and added compound **3a** (0.409 g, 2.29 mmol) at same temp. After 1 h of stirring at room temperature, reaction was quenched with sat NH_4Cl(aq) and extracted with Et_2O (3x 30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **70a** (0.465 g, 82% yield)

Compound **70a** ^{1}H NMR (300MHz, $CDCl_3$) δ 6.94-6.89 (m, 1H), 5.86 (d, J = 15.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.43 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H), 0.18(s, 9H)

9-Trimethylsilyl-non-2E-ene-6,8-diynal (71a)

To a solution of compound **70a** (0.341 g, 1.37 mmol) in 10 mL of THF was added DIBAL-H (4.12 mL, 1M soln) at -78 ^{o}C in Ar. After stirring for 2 h at -78 ^{o}C, reaction was quenched with excess of EtOAc (30 mL) at -78 ^{o}C and warmed to room temperature. The

mixture was washed with 10% HCl (aq) (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give allyl alcohol (0.260 g, 92 % yield)

To a solution of oxalyl chloride (0.110 mL, 1.23 mmol) in 5 mL of CH_2Cl_2 was added dimethylsulfoxide (0.178 mL, 2.46 mmol) dropwise at -78 ^oC. The mixture was stirred at same temp for 20 min and triethylamine (0.526 mL, 3.69 mmol) was added dropwise and stirred at same temperature for 20 min. To the mixture was added above alcohol (0.127 mg, 0.616 mmol) at -78 ^oC and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl(aq) and aqueous layer was extracted with CH_2Cl_2 (2x 10 mL). Combined organic layer was washed with water (2x 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **71a** (0.106 g, 81 % yield)

71a ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H), 6.84 (dt, *J* = 15.6, 6.3 Hz, 1H), 6.16 (dd, *J* = 15.6, 7.8 Hz, 1H), 2.59-2.47 (m, 4H), 0.17 (s, 9H)

11-Trimethylsilyl-undeca-2*Z*,4*E*-diene-8,10-diynoic acid isobutylamide (72a) and 11-Trimethylsilyl-undeca-2*E*,4*E*-diene-8,10-diynoic acid isobutylamide (72b)

To a solution of diphenylphosphonoacetamide **66** (0.187 g, 0.539 mmol) in 10 mL of THF was added NaHMDS (0.735 mL, 1 M soln in THF) at -78 ^oC and stirred at the same temperature for 20 min. To the mixture was added aldehyde **71a** (0.1 g, 0.49 mmol) in 2 mL of THF via cannula and resulting mixture was warmed to 10 ^oC over 2 h. The reaction was quenched with NH_4Cl(aq), washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography

(hexane:ethyl acetate= 5:1) to give compound **72a** (0.090 g, 62 % yield) and compound **72b** (0.029 g, 20 % yield)

Compound **72a** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 15.3, 11.4 Hz, 1H), 6.37 (t, *J* = 11.4 Hz, 1H), 6.05-5.90 (m, 1H), 5.58 (brs, 1H), 5.52 (d, *J* = 12.9 Hz, 1H), 3.12 (t, *J* = 6.9 Hz, 2H), 2.39-2.38 (m, 4H), 1.84-1.75 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 140.9, 140.0, 128.5, 119.9, 88.5, 82.3, 79.1, 66.2, 46.9, 31.6, 28.8, 20.4, 19.4, -0.13; HRMS *m/e* (EI) for $C_{18}H_{27}NOSi$ $(M)^+$ calcd 301.1862, measured 301.1843

Compound **72b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.17 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.08-5.98 (m, 1H), 5.80 (d, *J* = 14.8 Hz, 1H),5.59 (brs, 1H), 3.15 (t, *J* = 6.4 Hz, 2H), 2.42-2.35 (m, 4H), 1.83-1.76 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 6H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 140.7, 139.5, 129.9, 123.3, 88.4, 84.0, 78.7, 66.4, 47.2, 31.6, 28.9, 20.4, 19.3, -0.10

Undeca-2*Z*,4*E*-diene-8,10-diynoic acid isobutylamide (2)

To a solution of compound **72a** (0.032 g, 0.106 mmol) in 2 mL of THF was added TBAF (0.159 mL, 1.16 mmol) at 0 ^{o}C. The mixture was stirred for 1 h at room temperature and solvent was removed. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **2** (0.024 g, 99 % yield)

Amide 2 ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 14.7, 11.4 Hz, 1H), 6.37 (t, *J* = 11.4 Hz, 1H), 6.02-5.89 (m, 1H), 5.63 (brs, 1H), 5.53 (d, *J* = 11.4 Hz, 1H), 3.12 (t, *J* = 6.6 Hz, 2H), 2.49-2.31 (m, 4H), 1.97 (s, 1H), 1.84-1.74 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H);^{13}C

NMR (75 MHz, $CDCl_3$) δ 166.5, 140.9, 139.8, 128.5, 119.9, 82.3, 77.5, 65.2, 65.1, 46.9, 31.4, 28.8, 20.4, 19.1; HRMS *m/e* (EI) for $C_{15}H_{19}NO$ $(M)^+$ calcd 229.1467, measured 229.1579.

4,6-Octadiyn-1-ol (67b)

In a sealed tube, degassed piperidine (5.5 mL), 5-iodo-4-pentynol (1.74 g, 8.49 mmol) and CuCl (0.086 g, 0.85 mmol) was mixed. The mixture was cooled to -78 ^oC and excess propyne gas was added by blowing along the wall of the tube. Propyne gas was condensed to liquid (2 mL) in sealed tube and the tube was closed. The mixture was slowly warmed to room temperature. After stirring for 2 h at room temperature, the mixture was cooled to -78 ^oC and the sealed tube was opened. The mixture was warmed to room temperature slowly to evaporate excess propyne. NH_4Cl (aq) (20 mL) was added to the mixture then extracted with Et_2O (3 x 20 mL). Organic layer was washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **67b** (0.847 g, 82 % yield)

Compound **67b** ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (t, J = 6.3 Hz, 2H), 2.34 (t, J = 7.2 Hz, 2H), 2.17 (brs, 1H), 1.87 (s, 3H), 1.78-1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.1, 66.0, 64.6, 61.7, 31.2, 15.9, 4.47 ; HRMS *m/e* (EI) for $C_8H_{10}O$ $(M)^+$ calcd 122.0732, measured 122.0799.

4,6-Octadiynal (68b)

To a solution of oxalyl chloride (1 mL, 11.5 mmol) in 60 mL of CH_2Cl_2 was added dimethylsulfoxide (1.63 mL, 22.9 mmol) dropwise at -78 ^oC. The mixture was stirred at same temperature for 20 min and triethylamine (4.78 mL, 34.4 mmol) was added dropwise

and stirred at same temperature for 20 min. To the mixture was added compound **67b** (0.70 g, 5.73 mmol) at -78 ^{o}C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl (aq) (10 mL) and aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). Combined organic layer was washed with water (2 x 20 mL) , dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 5:1) to give compound aldehyde **68b** (0.55 g, 80 % yield)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.54 (t, *J* = 6.6 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 74.4, 74.2, 66.5, 64.4, 42.4, 12.6, 4.3

Dec-2E-ene-6,8-diynoic acid ethyl ester (70b)

To a solution of carbethoxymethyl(triphenyl)phosphonium bromide (5.26 g, 12.37 mmol) in 40 mL of THF was added *n*-BuLi (4.95 mL, 2.5M soln in hexane) at 0 ^{o}C in Ar. The mixture was stirred for 20 min at 0 ^{o}C and added compound **68b** (0.59 g, 4.95 mmol) at same temperature. After 1 h of stirring at room temperature, the reaction was quenched with sat NH_4Cl (aq) and extracted with ethyl ether (3x 30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **70b** (0.73 g, 78 % yield)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01-6.85 (m, 1H), 5.86 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.43-2.40 (m, 4H), 1.90 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H)

Dec-2*E*-ene-6,8-diynal (71b)

To a solution of compound **70b** (0.437 g, 2.3 mmol) in 20 mL of THF was added DIBAL-H (4.6 mL, 1.0 M soln) at -78 ^{o}C in Ar. After stirring for 2 h at -78 ^{o}C, reaction was quenched with excess of ethylacetate (30 mL) at -78 ^{o}C and warmed to room temperature. The mixture was washed with 10% HCl (aq) (10 mL), brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 3:1) to give allylic alcohol (0.28 g, 81 % yield)

To a solution of oxalyl chloride (0.326 mL, 3.74 mmol) in 20 mL of CH_2Cl_2 was added dimethylsulfoxide (0.530 mL, 7.48 mmol) dropwise at -78 ^{o}C. The mixture was stirred at same temperature for 20 min and triethylamine (1.56 mL, 11.2 mmol) was added dropwise and stirred at same temperature for 20 min. To the mixture was added above alcohol (0.277 g, 1.87 mmol) at -78 ^{o}C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl (aq) and aqueous layer was extracted with CH_2Cl_2 (2x 10 mL). Combined organic layer was washed with water (2x 10 mL), dried (MgSO4), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 5:1) to give compound **71b** (0.229 g, 84 % yield)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, *J* = 7.8 Hz, 1H), 6.83 (dt, *J* = 15.6, 6.0 Hz, 1H), 6.14 (dd, *J* = 15.6, 7.8 Hz, 1H), 2.58-2.40 (m, 4H), 1.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 155.4, 134.0, 74.3, 74.3, 67.0, 60.6, 31.4, 18.2, 4.3

Dodeca-2*Z*,4*E*-diene-8,10-diynoic acid isobutylamide (64) and Dodeca-2*E*,4*E*-diene-8,10-diynoic acid isobutylamide (64a)

To a solution of diphenylphosphonoacetamide **66** (0.370 g, 1.06 mmol) in 10 mL of THF was added NaHMDS (1.06 mL, 1M soln in THF) at -78 ^{o}C and stirred at same temperature

for 20 min. To the mixture was added aldehyde **71b** (0.140 g, 0.97 mmol) in 2 mL of THF via cannula and resulting mixture was warmed to 10 ^{o}C over 2 h. The reaction was quenched with NH_4Cl (aq), washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **64** (0.131 g, 56 % yield) and compound **64a** (0.028 g, 12 % yield)

Compound **64** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 15.3, 11.4 Hz, 1H), 6.34 (t, *J* = 11.4 Hz, 1H), 5.99-5.87 (m, 1H), 5.78 (brs, 1H), 5.52 (d, *J* = 11.4 Hz, 1H), 3.09 (t, *J* = 6.6 Hz, 2H), 2.37-2.32 (m, 4H), 1.87 (s, 3H), 1.82-1.73 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7,140.9, 140.3, 128.4, 119.9, 75,8, 73,7, 66.2, 64.7, 46.9, 31.8, 28.8, 20.4, 19.3, 4.4

Oct-6*Z*-en-4-yn-1-ol (74)

To a solution of $Pd(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol), CuI (28.5 mg, 0.15 mmol) in THF (10 mL) was added 4-pentynol (0.93 mL, 10 mmol), cis-bromopropene (0.426 mL, 5 mmol) and diisopropylamine (1.96 mL, 15 mmol) successively at 0 ^{o}C in Ar. After stirring at room temperature for 2 h, the reaction was quenched with sat NH_4Cl (aq), extracted with ether, washed with brine, and dried ($MgSO_4$). The residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **74** (545 mg, 88 % yield)
Compound **74** ^{1}H NMR (300MHz, $CDCl_3$) δ 5.89 (dq, *J* = 10.8, 6.9 Hz, 1H), 5.45 (dq, *J* = 10.8, 1.8 Hz, 1H), 3.78 (dt, J = 6.0, 6.0 Hz, 2H), 2.48 (td, *J* = 6.6, 2.1 Hz, 2H), 1.84 (dd, J = 6.9, 2.1 Hz, 3H), 1.83-1.76 (m, 2H), 1.54 (brs, 1H)

Oct-6*Z*-en-4-ynal (75)

To a solution of compound **74** (500 mg, 4.03 mmol) in CH_2Cl_2 (20 mL) was added PCC (1.56 g, 7.2 mmol) at 0 ^oC. The mixture was stirred for 1 h at room temperature, then Et_2O (40 mL) was added. The solution was filtered through celite and solvent was removed. The residue was purified via via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **75** (438 mg, 89 % yield).

Compound **75** ^1H NMR (300MHz, $CDCl_3$) δ 9.78 (d, *J* = 7.8 Hz, 1H), 5.86 (dq, *J* = 10.8, 6.9 Hz, 1H), 5.41 (dq, *J* = 10.8, 1.8 Hz, 1H), 2.41 (td, *J* = 6.6, 2.1 Hz, 2H), 2.34 (td, *J* = 7.8, 6.8 Hz, 2H), 1.81 (dd, *J* = 6.9, 2.1 Hz, 3H), 1.81-1.69 (m, 2H)

Deca-2*E*,8*Z*-dien-6-ynal (76)

To a solution of carbethoxymethyl(triphenyl)phosphonium bromide (3.43 g, 8 mmol) in THF (20 mL) was added *n*-BuLi (3.2 mL, 2.5M soln in hexane) at 0 ^oC in Ar. The mixture was stirred for 20 min at 0 ^oC and added compound **75** (0.50 g, 4.03 mmol) at same temperature. After 1 h of stirring at room temperature, reaction was quenched with sat NH_4Cl (aq) and extracted with ethyl ether (3x 30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give ester compound (0.68 g, 88 %). To a solution of above ester (0.68 g, 3.54 mmol) in 20 mL of THF was added DIBAL-H (8.8 mL,1.0 M soln, 8.8 mmol) at -78 ^oC in Ar. After stirring for 2 h at -78 ^oC, reaction was quenched with excess of ethylacetate (30 mL) at -78^oC and warmed to room temperature. The mixture was washed with 10% HCl (aq) (10 mL), brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give allylic alcohol (0.430 g, 81 % yield).

To a solution of oxalyl chloride (0.498 mL, 5.72 mmol) in 20 mL of CH_2Cl_2 was added dimethylsulfoxide (0.812 mL, 11.44 mmol) dropwise at -78 ^oC. The mixture was stirred at same temp for 20 min and triethylamine (2.39 mL, 17.16 mmol) was added dropwise and stirred at same temp for 20 min. To the mixture was added above allylic alcohol (0.430 g, 2.86 mmol) at -78 ^oC and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl (aq) and aqueous layer was extracted with CH_2Cl_2 (2x 10 mL). Combined organic layer was washed with water (2x 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **76** (0.355 g, 84 % yield) Compound **76** ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, *J* = 7.6 Hz, 1H), 6.86 (dq, *J* = 15.6, 6.4 Hz, 1H), 6.14 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.89-5.83 (m, 1H), 5.38 (d, *J* = 9.6 Hz, 1H), 2.54-2.51(m, 4H), 1.77 (d, *J* = 6.8 Hz, 3H)

Dodeca-2*Z*,4*E*,10*Z*-trien-8-ynoic acid isobutylamide (65) and Dodeca-2*E*,4*E*,10*Z*-trien-8-ynoic acid isobutylamide (65a)

To a solution of diphenylphosphonoacetamide **66** (0.228 g, 0.67 mmol) in 6 mL of THF was added NaHMDS (1 mL, 1M soln in THF) at -78 ^oC and stirred at same temp for 20 min. To the mixture was added aldehyde **76** (0.100 g, 0.67 mmol) in 2 mL of THF via cannula and resulting mixture was warmed to 10 ^oC over 2 h. The reaction was quenched with NH_4Cl(aq), washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 3:1) to give compound **65** (0.106 g, 65% yield) and compound **65a** (0.042 g, 26% yield)

Amide 65 ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 14.1, 11.1 Hz, 1H), 6.38 (t, *J* = 11.1 Hz, 1H), 6.02 (dt, J = 15.3, 6.6 Hz, 1H), 5.92-5.84 (m, 1H), 5.54 (brs, 1H), 5.50 (d, *J* = 11.4 Hz, 1H), 5.44 (dt, J = 10.8, 1.8 Hz, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.51-2.39 (m, 4H), 1.76 (d, J = 6.6 Hz, 3H), 1.79-1.71 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 166.2, 141.0, 140.8, 137.2, 127.8, 119.3, 110.2, 93.6, 77.5, 47.0, 32.4, 28.6, 20.1, 19.1, 5.7 ; HRMS *m/e* (EI) for $C_{16}H_{23}NO$ $(M)^+$ calcd 245.1780, measured 245.1782.

Amide 65a ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 15.0, 10.2 Hz, 1H), 6.26-6.09 (m, 2H), 5.90 (dq, *J* = 10.8, 6.9 Hz, 1H), 5.78 (d, *J* = 14.7 Hz, 1H), 5.49 (brs, 1H), 5.44 (dt, *J* = 10.5, 1.8 Hz, 1H), 3.16 (t, *J* = 6.6 Hz, 2H), 2.51-2.39 (m, 4H), 1.83 (d, *J* = 6.9 Hz, 3H), 1.82-1.72 (m, 1H), 0.92 (d, *J* = 6.3 Hz, 6H)

8-Nonyn-2-ol (78)

To 1,3-diaminopropane (10 mL) was added lithium (0.14 g, 20 mmol) in Ar. The mixture was heated at 70 ^{o}C with vigorous stirring for 2 h. After blue color discharged, the mixture was cooled to room temperature then potassium *tert*-butoxide (1.3 g, 12 mmol) was added in one portion. After 15 min of stirring, compound **77** (0.46 g, 3 mmol) was added to the mixture at room temperature. The mixture turned into red color. After 1 h stirring, the reaction was quenched with water (15 mL), extracted with Et_2O (20 mL x 3), washed with 10% HCl, brine, and dried ($MgSO_4$). The residue was used for next step without purification. (0.43 g, 95% yield)

Compound **78** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85-3.72 (m, 1H), 2.19 (td, *J* = 6.8, 2.8 Hz, 2H), 1.94 (t, *J* = 2.8 Hz, 1H), 1.59-1.50 (m, 2H), 1.48- 1.37 (m, 6H), 1.19 (d, *J* = 6.8 Hz, 3H).

2-(1-Methyl-7-octynyloxy)tetrahydropyran (79)

To a solution of comound **78** (0.41g, 2.95 mmol) in CH_2Cl_2 (10 mL) was added 3,4-dihydro-2*H*-pyran (0.29 mL, 3.25 mmol) and PTSA (56 mg, 0.3 mmol) at room temperature. The mixture was stirred for 8 h. The reaction was quenched with aqueous $NaHCO_3$ then extracted with CH_2Cl_2 (20 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **79** (0.59 g, 90 % yield)

Compound 79 ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70-4.61 (m, 1H), 3.92-3.85(m, 1H), 3.78-3.70 (m, 1 H), 3.51–3.44 (m, 1 H), 2.17 (td, J = 6.9, 2.7 Hz), 1.94 (t, J = 2.7 Hz, 1H), 1.87-1.65 (m, 2H), 1.62-1.48 (m, 8H), 1.46-1.30 (m, 4H), 1.22, 1.10 (d, J = 6.2 Hz, 3 H)

2-(9-Iodo-1-methyl-7-nonynyloxy)tetrahydropyran (80)

To a solution of ethyl magnesium bromide (5.4 mL, 16.3 mmol) in anhydrous THF (20 mL) was added a solution of compound **79** (2.44 g, 10.9 mmol) in THF (10 mL) at room temperature. The solution was refluxed for 1 h, then cooled to 0 °C and paraformaldehyde (490 mg, 16.3 mmol) was added. The mixture was refluxed for 1 h, then cooled to room temperature and stirred for 12 h. The reaction was quenched with $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexanes–EtOAc, 2:1) to provide the propargyl alcohol (2.00 g, 72%).

To a solution of imidazole (284 mg, 4.2 mmol) and Ph_3P (1.1 g, 4.2 mmol) in Et_2O–MeCN (12 mL/4 mL) was slowly added iodine (1.1 g, 4.2 mmol) at 0 °C. The resulting slurry

was warmed to room temperature and then stirred for 20 min. The slurry was cooled to 0 °C and the propargyl alcohol (964 mg, 3.8 mmol) was added in Et_2O (10 mL) at 0 °C. The solution was slowly warmed to room temperature and then stirred for 1 h. The reaction was quenched by adding hexane (30 mL). The organic layer was washed with aq $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give **80** (1.18 g, 85%).

Compound 80 ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69–4.61 (m, 1 H), 3.94–3.70 (m, 2 H), 3.69 (s, 2 H), 3.50–3.46 (m, 1 H), 2.20–2.16 (m, 2 H), 1.83– 1.79 (m, 1 H), 1.72–1.65 (m, 1 H), 1.65–1.33 (m, 12 H), 1.20, 1.11 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.9, 95.9, 87.0, 86.9, 74.1, 71.3, 63.1, 62.8, 37.6, 36.6, 31.5, 31.4, 29.1, 28.6, 28.5, 25.8, 25.7, 25.6, 25.2, 21.9, 20.4, 20.1, 19.4, 19.3, 19.2, –16.3, –16.4. HRMS (EI): *m*/*z* calcd for $C_{15}H_{25}IO_2$: 364.0899; found: 364.0906.

1-Trimethylsilyl-11-(2-oxacyclohexyl)oxydodeca-1,4-diyne (81)

To a solution of K_2CO_3 (326 mg, 2.36 mmol, freshly dried over P_2O_5) and CuI (205 mg, 1.1 mmol) in DMF (5 mL) was added trimethylsilylacetylene (1.22 mL, 8.6 mmol) and compound **80** (784 mg, 2.15 mmol) in DMF (2 mL) at 0 °C. The solution was warmed to room temperature and stirred for 24 h. The solution was diluted with Et_2O (10 mL) and aq NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 10:1) to give compound **81** (514 mg, 72 % yield).

Compound **81** ^{1}H NMR (300MHz, $CDCl_3$) δ 4.71~4.60 (m, 1H), 3.92~3.69 (m, 2H), 3.50~3.46 (m, 1H), 3.19~3.17 (m, 2H), 2.19~2.10 (m, 2H), 1.82~1.30 (m, 14H), 1.20,1.07(d,

J = 6.3 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.9, 98.8, 95.7, 84.7, 84.6, 81.2, 81.1, 74.1, 73.6, 73.5, 71.2, 62.9, 62.6, 37.6, 36.6, 31.4, 31.3, 29.1, 28.8, 25.8, 25.6, 25.2, 21.9, 20.3, 19.9, 19.3, 18.9, 18.8, 11.0, 0.2, 0.1; HRMS (EI) m/z calcd 334.5683 found 334.5425

1-Trimethylsilyl-11-(2-oxacyclohexyl)oxydodeca-4*Z*-en-1-yne (82)

To a solution of $Ni(OAc)_2 \cdot 4H_2O$ (47 mg, 019 mmol) in EtOH (2 mL) was rapidly added $NaBH_4$ (8 mg, 0.19 mmol) at room temperature under argon. The flask was filled with H_2 gas and when the gas evolution ceased the active catalyst was poisoned with ethylenediamine (0.025 mL, 0.37 mmol). A solution diyne **81** (313 mg, 0.937 mmol) in EtOH (2 mL) was injected via cannula. The solution was stirred for 2 h and then filtered through Celite. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 10:1) to give compound **82** (289 mg, 94 % yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46~5.36 (m, 2H), 4.69~4.59 (m, 1H), 3.89~3.67 (m, 2H), 3.49~3.42 (m, 1H), 2.94 (d, *J* = 5.4 Hz, 2H), 2.04~1.97 (m, 2H), 1.81~1.21 (m, 14H), 1.20,1.08 (d, *J* = 6.3 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 132.0, 124.1, 124.0, 105.6, 98.8, 95.8, 84.2, 84.1, 74.1, 74.0, 71.3, 63.0, 62.6, 37.7, 36.7, 31.4, 31.3, 29.6, 29.5, 29.4, 27.3, 27.2, 25.9, 25.8, 25.7, 25.5, 22.8, 21.8, 20.3, 19.9, 19.3, 18.6, 0.2; HRMS (EI) m/z calcd 336.5814 found 336.5528

2-(11-Bromo-1-methyl-undec-7*Z*-en-10-ynyloxy)tetrahydropyran (83)

To a solution of compound **82** (265 mg, 0.79 mmol) in acetone (5 mL) was added *N*-bromosuccinimide (210 mg, 1.18 mmol) and $AgNO_3$ (27 mg, 0.16 mmol) at room

temperature. After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and cold H_2O (5 mL) was added. The aqueous layer was extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (hexane:ethyl acetate= 10:1) to give the bromoacetylene compound **83** (204 mg, 72 % yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49~5.31 (m, 2H), 4.68~4.57 (m, 1H), 3.95~3.80 (m, 1H), 3.76~3.62 (m, 1H), 3.49~3.41 (m, 1H), 2.92 (d, *J* = 6.6 Hz, 2H), 2.04~1.99 (m, 2H), 1.85~1.62 (m, 2H), 1.52~1.25 (m, 12H), 1.21,1.11 (d, *J* = 6.3 Hz, 3H)

1-Trimethylsilyl-13-(2-oxacyclohexyl)oxytetradeca-6*Z*-en-1,3-diyne (84)

To a solution of the bromoacetylene (100 mg, 0.29 mmol), trimethylsilylacetylene (83 mL, 0.58 mmol), $(PPh_3)_2PdCl_2$ (8 mg, 0.011 mmol), and CuI (2 mg, 0.011 mmol) in THF (6 mL), was added isopropylamine (70 mL, 0.58 mmol) at room temperature under argon. After stirring for 2 h at room temperature, the reaction was quenched by adding aq NH4Cl (3 mL) and the aqueous layer was extracted with Et_2O, washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 5:1) to give compound **84** (44 mg, 42 % yield).

Compound **84** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57~5.30 (m, 2H), 4.72~4.58 (m, 1H), 3.92~3.68 (m, 2H), 3.00 (d, *J* = 5.4 Hz, 2H), 2.08~1.99 (m, 2H), 1.82~1.23 (m, 14H), 1.21,1.05 (d, *J* = 6.2 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 132.5, 123.8, 122.3, 98.8, 95.9, 83.2, 83.1, 78.2, 78.1, 74.1, 74.0, 71.3, 71.2, 68.2, 68.1, 63.1, 62.7, 37.7, 37.6, 36.6, 31.5, 31.2, 29.5, 29.4, 29.3, 27.4, 27.3, 25.9, 25.8, 25.7, 25.5, 21.8, 20.3, 20.0, 19.3, 17.8, 17.1, 0.1 ; HRMS (EI) m/z calcd 360.6055 found 360.5938

14-Trimethylsilanyl-tetradec-8*Z*-ene-11,13-diyn-2-one (85)

To a solution of compound **84** (100 mg, 0.28 mmol) in MeOH (5 mL) was added *p*-toluenesulfonic acid (12 mg, 0.014 mmol). The solution was heated at 60 °C for 1 h. It was then cooled to room temperature, concentrated, and diluted with H_2O. The aqueous layer was extracted with Et_2O, washed with aq $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and pyridinium chlorochromate (117 mg, 0.56 mmol) was added at room temperature. After 1 h, Et_2O (10 mL) was added and the suspension was filtered through Celite. The solvent was concentrated in vacuo and the crude residue was purified via flash column chromatography (hexane:ethyl acetate= 5:1) to give compound **85** (68 mg, 89 % yield).

Compound **85** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49-5.32 (m, 2H), 3.00 (d, J = 6.9 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 2.13 (s, 3H), 2.01 (m, 2H), 1.67-1.48 (m, 2H), 1.42-1.21 (m, 4H), 0.17 (s, 9H)

Tetradec-8*Z*-ene-11,13-diyn-2-one (22)

To a solution of the diyne (10 mg, 0.036 mmol) in MeOH (2 mL) was slowly added $AgNO_3$ (8 mg, 0.047 mmol) in H_2O (1 mL) and MeOH (3 mL) at room temperature. After 15 min, KCN (14 mg, 0.216 mmol) in H_2O (2 mL) was added, and the solution was stirred for 10 min. The mixture was extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified via flash column chromatography (hexanes–EtOAc, 2:1) to give compound **22** (5 mg, 67 % yield) as a light yellow liquid.

Compound **22** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51~5.37 (m, 2H), 2.99 (d, *J* = 6.9 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 2.08~2.01 (m, 2H), 1.97 (t, *J* = 1.2 Hz, 1H), 1.43~1.26(m, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 209.3, 133.0, 122.2, 77.4, 76.5, 68.6, 65.1, 43.9, 30.1, 29.2, 28.9, 27.2, 23.9, 17.7; HRMS (EI) m/z calcd 202.2921 found 202.2806

6-(2-Methyl-[1,3]dioxolan-2-yl) hexanoic acid methyl ester (91)

To a solution of compound **90** (500 mg, 2.29 mmol) in MeOH (3 mL) was added 2N HCl solution (5 mL) at room temperature. The mixture was stirred for 4 h at room temperature and extracted with Et_2O (20 mL). The organic layer was washed with $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The crude residue, ethylene glycol (0.557 mL, 10 mmol), PTSA (28 mg, 0.15 mmol) and molecular sieves were heated at 50 ^{o}C with vigorous stirring for 6 h. The mixture was cooled to room temperature then water (5 mL) was added and extracted with Et_2O (20 mL). The organic layer was washed with $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The crude residue went to next step without purification. (395 mg, 80% yield in 2 steps)

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95-3.89 (m, 4H), 3.66 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.65-1.58 (m, 4H), 1.43-1.32 (m, 4H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 110.3, 64.9, 51.7, 39.2, 34.2, 29.5, 25.1, 23.9, 23.9.

6-(2-Methyl-[1,3]dioxolan-2-yl)-hexanal (89)

To a compound **91** (1.25 g, 4.6 mmol) in Et_2O (20 mL) was added lithium aluminum hydride (0.330 g, 3.47 mmol) at 0 ^{o}C in Ar. After stirring at 0 ^{o}C for 2 h, the mixture was warmed to room temperature. To the mixture was added H_2O (0.33 mL), 15% NaOH(aq)

(0.33 mL) and H_2O (1 mL) successively at room temperature, then the mixture was filtered and organic layer was washed with H_2O, brine, dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified via flash column chromatography to give alcohol (0.800 g, 93 % yield). To a solution of oxalyl chloride (0.741 mL, 8.5 mmol) in 20 mL of CH_2Cl_2 was added dimethylsulfoxide (1.21 mL, 17.0 mmol) dropwise at -78 ^oC. The mixture was stirred at same temp for 20 min and triethylamine (3.55 mL, 25.5 mmol) was added dropwise and stirred at same temp for 20 min. To the mixture was added above alcohol (0.800 g, 4.25 mmol) at -78 ^oC and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH_4Cl(aq) and aqueous layer was extracted with CH_2Cl_2 (2x 30 mL). Combined organic layer was washed with water (2x 20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **89** (0.729 g, 92 % yield).

Compound **89** ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1H), 3.95-3.89 (m, 4H), 2.43 (t, J = 7.2 Hz, 2H), 1.66-1.59 (m, 5H), 1.44-1.32 (m, 4H), 1.30 (s, 3H)

Trimethyl[10-(2-methyl-[1,3]dioxolan-2-yl)dec-4-en-1-ynyl]silane (87)

To a solution of compound **88** (612 mg, 1.19 mmol) in THF (10 mL) was added NaHMDS (1.19 mL, 1M in THF) at -78 ^oC. The mixture was stirred for 20 min at -78 ^oC, then aldehyde **89** (201 mg, 1.08 mmol) in THF (3 mL) was added by cannular. The mixture was slowly warmed to room temperature then stirred for 12 h. The reaction was quenched with NH_4Cl (5 mL) and extracted with Et_2O (20 mL). The organic layer was washed with water, brine, dried ($MgSO_4$) and concentrated. The crude residue was purified via flash

column chromatography (hexane:ethyl acetate= 2:1) to give compound **87** (275 mg, 86 % yield).

Compound **87** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46-5.38 (m, 2H), 3.95-3.87 (m, 4H), 2.96 (d, *J* = 6.0 Hz, 2H), 2.04-1.96 (m, 2H), 1.63-1.49 (m, 2H), 1.41-1.32 (m, 6H), 1.28 (s, 3H), 0.13 (s, 9H).

2-(10-Iododec-6-en-9-ynyl)-2-methyl-[1,3]dioxolane (92)

To a solution of compound 87 (115 mg, 0.39 mmol) in THF (5 mL) was added TBAF (0.430 mL, 1M soln in THF) at 0 ^{o}C. The mixture was stirred for 1h at room temperature and solvent was removed. The crude residue was purified via flash column chromatography to give acetylene compound (85 mg, 97% yield). To a solution of acetylene (99 mg, 0.45 mmol) in THF (5 mL) was added *n*-BuLi (0.187 mL, 2.5 M in hexane) at -78 ^{o}C. After 5 min, iodine in THF (2 mL) was added to a mixture then stirred at -78 ^{o}C for 30 min. The mixture was warmed to room temperature and quenched with NH_4Cl, extracted with Et_2O, washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 3:1) to give compound **92** (108 mg, 87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50-5.35 (m, 2H), 3.96-3.88 (m, 4H), 3.08 (d, *J* = 6.8 Hz, 2H), 1.99 (dt, *J* = 7.2, 6.8 Hz, 2H), 1.69-1.57 (m, 2H), 1.42-1.28 (m, 6H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 132.6, 123.3, 110.4, 92.9, 64.9, 39.4, 29.7, 29.5, 27.3, 24.2, 23.9, 19.4, -6.5

Trimethyl-[12-(2-methyl-[1,3]dioxolan-2-yl)-dodec-6-ene-1,3-diynyl]-silane (93)

The same procedure for **67a** was applied. (35 % yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54-5.30 (m, 2H), 4.02-3.98 (m, 4H), 3.02 (d, *J* = 6.8 Hz, 2H), 2.09 (dt, *J* = 7.2, 6.8 Hz, 2H), 1.66-1.52 (m, 2H), 1.49-1.30 (m, 6H), 1.27 (s, 3H), 0.19 (s, 9H)

3,5-Heptadiyn-1-ol (94)

The same procedure for **67b** was applied. (538 mg, 81 % yield).

Compound **94** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74-3.71 (m, 2H), 2.51 (t, *J* = 6.8 Hz, 2H), 1.91 (s, 3H)

3,5-Heptadiynal (95)

To a solution of imidazole (374 mg, 5.5 mmol) and Ph_3P (1.44 g, 5.5 mmol) in Et_2O–MeCN (12 mL/4 mL) was slowly added iodine (1.40 g, 5.5 mmol) at 0 °C. The resulting slurry was warmed to room temperature and then stirred for 20 min. The slurry was cooled to 0 °C and the alcohol **94** (538 mg, 4.9 mmol) was added in Et_2O (10 mL) at 0 °C. The solution was slowly warmed to room temperature and then stirred for 1 h. The reaction was quenched by adding hexane (30 mL). The organic layer was washed with aq $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexanes–EtOAc, 2:1) to give **95** (1.04 g, 98 % yield).

Compound **95** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 1.83 (s, 3H)

Triphenyl(hepta-3,5-diynyl)phosphonium Iodide (96)

To a solution of PPh_3 (0.793 g, 3.03 mmol) in acetonitrile was added compound **95** (0.60 g**,** 2.75 mmol) and refluxed for 24 h. The mixture was cooled to room temperature and the solvent was removed to give compound 96 as yellowish oil. (1.02 g, 78% yield)

Compound **96** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.53 (m, 15H), 3.86-3.80 (m, 2H), 2.79 (dt, *J* = 20.8, 6.4 Hz, 2H), 1.87 (s, 3H)

2-Methyl-2-tridec-6*Z*-ene-9,11-diynyl-[1,3]dioxolane (97)

The same procedure for **87** was applied. 54% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dt, *J* = 10.4, 7.2 Hz, 1H), 5.36 (dt, *J* = 10.4, 7.2 Hz, 1H), 3.96-3.88 (m, 4H), 2.98 (d, *J* = 7.2 Hz, 2H), 2.01 (td, *J* = 7.2, 6.0 Hz, 2H), 1.89 (s, 3H), 1.63-1.59 (m, 2H), 1.41-1.29 (m, 6H), 1.30 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 122.9, 110.4, 75.0, 73.6, 65.3, 64.8, 64.7, 39.4, 29.7, 29.5, 27.3, 24.2, 24.0, 17.8, 4.4.

Pentadec-8Z-ene-11,13-diyn-2-one (23)

To a solution of compound 97 (56 mg, 0.22 mmol) in acetone/water (1 mL/ 1 mL) was added PPTS (4.6 mg, 0.022 mmol) at room temperature. The mixture was heated at 40 ^{o}C for 3 h and extracted with diethyl ether. Organic layer was washed with brine (2x 20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **23** (43mg, 93% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.34 (m, 2H), 2.96 (d, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 2.01 (td, *J* = 7.2, 6.0 Hz, 2H), 1.88 (s, 3H), 1.60-1.51 (m, 2H), 1.42-1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 132.5, 123.1, 74.9, 73.6, 65.3, 64.8,

43.9, 30.1, 29.2, 28.9, 27.2, 23.9, 17.8, 4.4; HRMS (EI): *m/z* calcd for $C_{15}H_{20}O$: 216.1514; found: 216.1510.

10-(2-Methyl-[1,3]dioxolan-2-yl)-1-trimethylsilyldeca-1,3-diyn-5-ol (99)

To a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (1.46 g, 7.5 mmol) in 10 mL of THF was added MeLi-LiBr complex (5 mL, 1.5 M soln) at 0 ^{o}C in Ar. The mixture was warmed to room temperatuer and stirred for 4 h. The mixture was cooled to -78 ^{o}C and aldehyde **89** (0.700 g, 3.76 mmol) in 4 mL of THF was added via cannula. The mixture was stirred for 1 h while warmed to room temperature. The reaction was quenched with saturated NH_4Cl (aq) and aqueous layer was extracted with ethyl ether. Combined organic layer was washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give compound **99** (0.890 g, 77 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45-4.38 (m, 1H), 3.97-3.89 (m, 4H), 1.89-1.80 (brs, 1H), 1.74-1.60 (m, 4H), 1.48-1.32 (m, 6H), 1.31 (s, 3H), 0.19 (s, 9H)

10-(2-Methyl-[1,3]dioxolan-2-yl)-1-trimethylsilyldec-3-en-1-yn-5-ol (100)

To a solution of compound **99** (0.600 g, 1.94 mmol) in 20 mL of diethyl ether was added LAH (0.088 g, 2.33 mmol) at 0 ^{o}C and the mixture was stirred for 2 h while warmed to room temperature. The mixture was poured into ice cold water (5 mL) then extracted with diethyl ether. Organic layers was washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound **100** (0.590 g, 98 % yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 15.9, 6.0 Hz, 1H), 5.72 (d, *J* = 15.9 Hz, 1H), 4.28-4.10 (m, 1H), 3.96-3.87 (m, 4H), 1.68-1.47 (m, 6H), 1.42-1.32 (m, 5H), 1.30 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 110.3, 110.0, 72.4, 66.1, 64.8, 39.3, 36.9, 29.8, 25.4, 24.2, 23.9, 15.5, 0.1; HRMS *m/e* (EI) for $C_{17}H_{30}O_3Si$ $(M)^+$ calcd 310.1964, measured 310.1921.

1-Bromo-10-(2-methyl-[1,3]dioxolan-2-yl)-dec-3-en-1-yn-5-ol (101)

To a solution of compound **100** (0.125 g, 0.40 mmol) in acetone (10 mL) was added NBS (0.086 g, 0.48 mmol) and $AgNO_3$ (0.004 g, 0.02 mmol) at room temperature. After stirring for 1h at room temperature, the mixture was cooled to 0 ^{o}C and cold H_2O (5 mL) was added. The aqueous layer was extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (Hexane-EtOAc = 4:1) to give the bromoacetylene compound **101** (0.055 g, 43 %)

^{1}H NMR (300MHz, $CDCl_3$) δ 6.19 (dd, *J* = 15.9, 6.0 Hz, 1H), 5.67(dd, *J* = 15.9, 1.5 Hz, 1H), 4.15-4.09 (m, 1H), 3.95-3.89 (m, 4H), 1.70-1.45 (m, 6H), 1.43-1.32 (m, 5H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 110.3, 109.4, 78.3, 72.2, 66.1, 64.8, 39.3, 36.9, 29.8, 25.4, 24.2, 23.9, 15.5 ; HRMS *m/e* (EI) for $C_{14}H_{21}BrO_3$ $(M)^+$ calcd 316.0674, measured 316.0761

1-(2-Methyl-[1,3]dioxolan-2-yl)-12-trimethylsilanyldodec-7-ene-9,11-diyn-6-ol (102a)

To a solution of trimethylsilylacetylene (0.052 mL, 0.37 mmol) and compound **100** (0.040 g, 0.126 mmol) in degassed piperidine (1 mL) was added CuCl (0.002 g, 0.013 mmol) at 0 ^{o}C. The mixture was stirred at room temperature for 0.5 h. The reaction was quenched

with 1 mL of sat NH_4Cl (aq) and extracted with ethyl ether (3x 10 mL). Organic layer was washed with brine (2x 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **102a** (0.035 g, 83 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 15.9, 5.7 Hz, 1H), 5.73 (d, *J* = 15.9 Hz, 1H), 4.18-4.10 (m, 1H), 3.95-3.90 (m, 4H), 1.65-1.38 (m, 6H), 1.42-1.31 (m, 5H), 1.30 (s, 3H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 110.3, 108.3, 90.6, 87.9, 75.3, 72.2, 64.8, 39.3, 36.9, 31.8, 25.3, 24.1, 14.3, -0.17 ; HRMS *m/e* (EI) for $C_{19}H_{30}O_3Si$ $(M)^+$ calcd 334.1964, measured 334.1798

8-Hydroxy-tetradec-9E-ene-11,13-diyn-2-one (20)

To a solution of compound **102a** (0.030 g, 0.08 mmol) in water/acetone (1 mL/1 mL) was added PPTS (0.002 g, 0.008 mmol) at room temperature. The mixture was heated at 40 ^{o}C for 3 h and extracted with diethyl ether. Organic layer was washed with brine (2x 20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give ketone (0.022 g, 95 % yield). To a solution of above ketone (0.022g, 0.076mmol) in 5mL of THF was added TBAF (0.114 mL, 1M soln in THF) at 0 ^{o}C. The mixture was stirred for 1h at room temperature and solvent was removed. The crude residue was purified via flash column chromatography to give ketone **20** (0.015 g, 89 % yield)

^{1}H NMR (400MHz, $CDCl_3$) δ 6.34 (dd, *J* = 16.5, 5.6 Hz, 1H), 5.73 (d, *J* = 16 Hz, 1H), 4.22-4.17 (m, 1H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 1H), 1.60 (brs, 1H), 1.62-1.50 (m, 6H), 1.40-1.30 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 209.4, 150.6, 108.0, 74.3, 73.9, 72.1,

71.3, 68.3, 43.8, 36.8, 30.2, 29.2, 25.2, 23.8 ; HRMS *m/e* (EI) for $C_{14}H_{18}O_2$ $(M)^+$ calcd 218.1307, measured 218.1229

8-Hydroxy-pentadec-9E-ene-11,13-diyn-2-one (21)

In a sealed tube, degassed piperidine (2 mL), compound **101** (0.060 g, 0.189 mmol) and CuCl (0.003 g, 0.019 mmol) was mixed. The mixture was cooled down to -78 ^oC and excess propyne gas was added by blowing along the wall of the tube. Propyne gas was condensed to liquid in sealed tube and the tube was closed. The mixture was slowly warmed to room temperature. After stirring for 2 h at room temperature, the mixture was cooled to -78 ^oC and the sealed tube was opened. The mixture was slowly warmed to room temperature while excess propyne was evaporated. Sat NH_4Cl (aq) was added to the mixture then extracted with ethyl ether. Organic layer was washed with 10% HCl (aq), brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was dissolved in acetone/water (1 mL/ 1 mL) then added PPTS (0.002 g, 0.008 mmol) at room temperature. The mixture was heated at 40 ^oC for 3 h and extracted with diethyl ether. Organic layer was washed with brine (2x 20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound **21** (0.027 mg, 63 % yield in two steps)

^1H NMR (300MHz, $CDCl_3$) δ 6.26 (dd, *J* = 15.9, 6.0 Hz, 1H), 5.71(d, *J* = 15.9 Hz, 1H), 4.20-4.12 (m, 1H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.98 (s, 3H), 1.62-1.49 (m, 4H), 1.39-1.24 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 148.7, 109.1, 81.8, 80.4, 76.8, 72.2, 64.5, 43.8, 36.8, 30.1, 29.2, 25.2, 23.8, 4.8; HRMS *m/e* (EI) for $C_{15}H_{20}O_2$ $(M)^+$ calcd 232.1463, measured 232.1497

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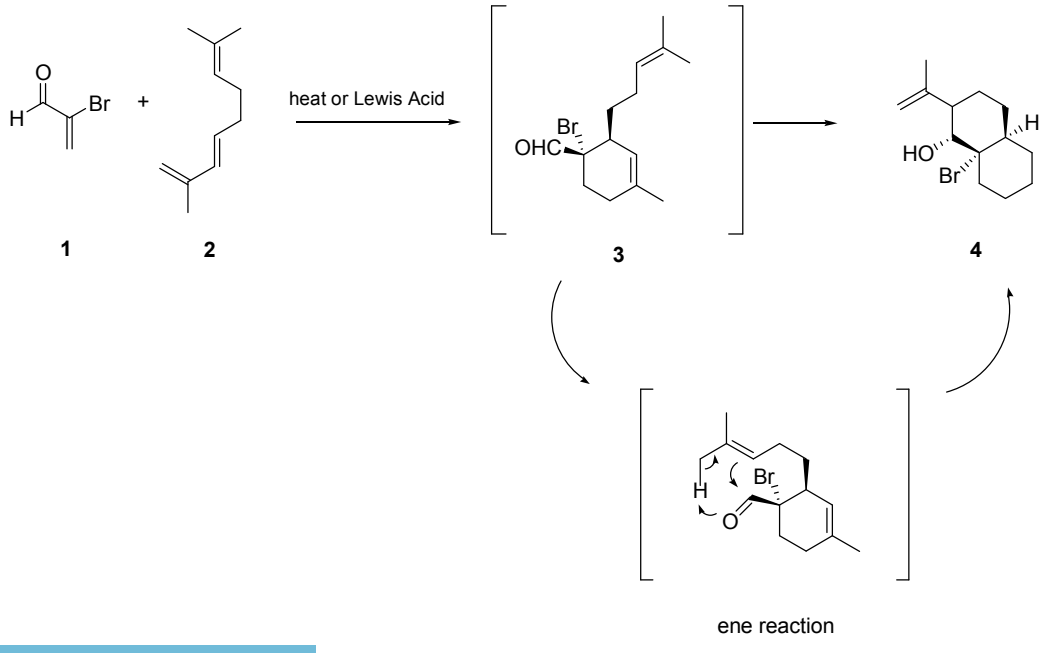
CHAPTER 2. TANDEM DIELS-ALDER/ENE REACTIONS IN ORGANIC SYNTHESIS: A SYNTHESIS OF ISOLIGULARONE

Introduction

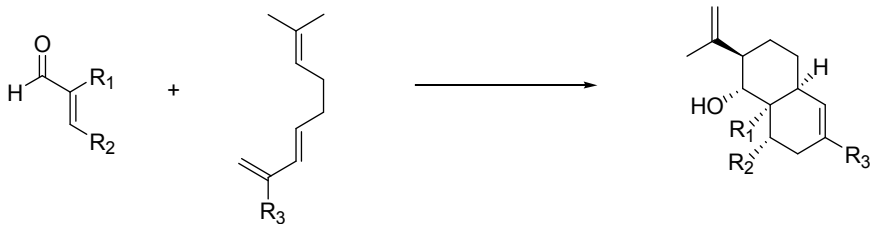
Tandem reactions have become a powerful tool for the synthetic chemist.[1] They often enable the generation of multiple stereogenic centers in a single operation. In the context of developing new tandem radical reactions,[2] Kraus *at al* discovered a novel tandem reaction involving a Diels-Alder reaction, followed by an ene reaction.[3] Initial study commenced with an attempt to generate bromo aldehyde **3**, a precursor for a radical reaction. Diels-Alder reaction between 2-bromoacrolein (**1**)[4] and diene **2** did not yield **3,** either by a thermal or by a Lewis acid-catalyzed pathway. Instead of **3**, alcohol **4** was generated as a single diastereomer by a tandem Diels-Alder/ene reaction.[5]



In the literature, Heathcock, in his elegant synthesis of *Daphniphyllum* alkaloids, employed a hetero-Diels-Alder/ene sequence.[6] There are also a few examples of tandem Diels-Alder/Diels-Alder reactions and tandem ene/ene reactions.[7] But this kind of tandem Diels-Alder/ene reaction was not known in the literature.

The stereochemistry of bromo alcohol **4** was determined by chemical and spectral methods. First, the alcohol was assumed to be syn to the bromine in the ring juncture, because attempts to generate epoxide from bromo alcohol **4** by conventional methods failed.[8] NOESY NMR experiments showed strong interactions between the carbinol hydrogen and the methyl of the isopropenyl group, indicating that the isopropenyl group was syn to the methine. No NOE interaction was observed between the carbinol hydrogen and the methine at the ring juncture. Also, the structure of the adduct from 2,5-dihydrothiophene-3-carboxaldehyde and diene **2** was determined by X-ray crystallography. The product stereochemistries are consistent with an endo-selective Diels-Alder reaction, followed by an ene reaction via a chair-like conformation.

There are several examples of this tandem reaction in Figure 1. Although the initial system studied (**1** and **2**) underwent the tandem reaction either at 80 °C in 56% yield or at 0 °C with catalysis by boron trifluoride etherate in 82 % yield, less reactive aldehydes required Lewis acid catalysis.



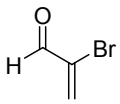
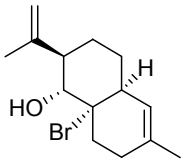
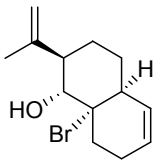
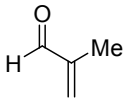
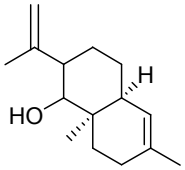
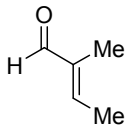
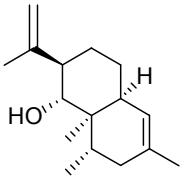
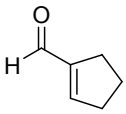
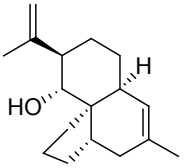
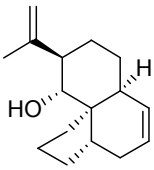
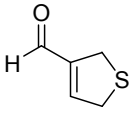
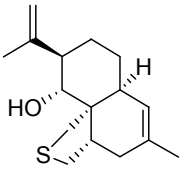
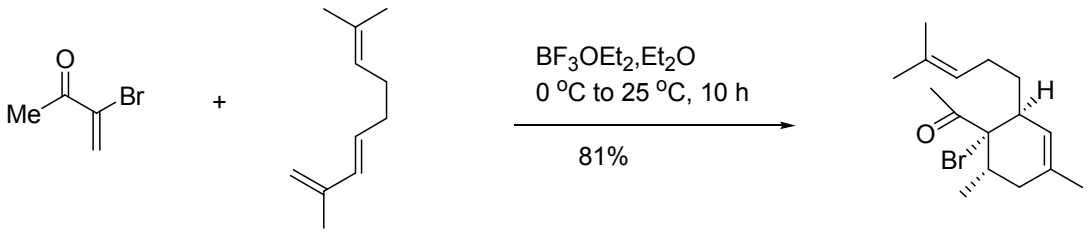
aldehyde	diene	reaction conditions	product	% yield
	R_3 = Me	toluene 80 °C, 24 h		56
		BF_3OEt_2,Et_2O 0 °C to 25 °C, 6 h		82
	R_3 = H	BF_3OEt_2,Et_2O 0 °C to 25 °C, 6 h		77
	R_3 = Me	BF_3OEt_2,Et_2O 0 °C to 25 °C, 10 h		56
	R_3 = Me	Et_2AlCl, CH_2Cl_2 -78 °C to 0 °C, 2 h		34
	R_3 = Me	BF_3OEt_2,Et_2O 0 °C to 25 °C, 12 h		46
	R_3 = H	BF_3OEt_2,Et_2O 0 °C to 25 °C, 19 h		41
	R_3 = Me	Et_2AlCl, CH_2Cl_2 -78 °C to 0 °C, 2 h		55

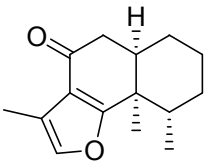
Figure 1. Examples of tandem Diels-Alder/ene reaction

3-Bromobut-3-en-2-one **5** [9] was synthesized and reacted with diene **2** at 0 °C in the presence of boron trifluoride diethyl etherate to determine whether unsaturated ketones could participate in the tandem reaction. Unfortunately, the only product was the Diels-Alder adduct **6** in 81 % yield.



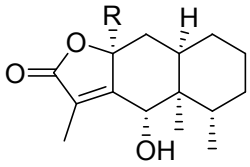
5 **2** **6**

One application of this methodology might be to the synthesis of eremophilane sesquiterpenes. The sesquiterpene Isoligularone (**7**)[10], and eremophilanolides (**8**)[11] and (**9**)[12] have been reported.



Isoligularone

7



R= H, OH

eremophilanolides

8,9

Isoligularone has been synthesized by Yoshikoshi and by Tobinaga using novel Michael addition protocols.[13] Yoshikoshi's synthesis commenced with a known diketone **10,**[14] which was converted into a enone **11** in 5 steps with a 56 % overall yield. Enone **11** was converted

into a dione **12** by a 3 step conversion. Compound **12** was the key intermediate to the novel annulation with the nitro alkene. The key annulation produced dihydrofuran compound **13** in 22 % yield with its isomer. Compound **13** was then transformed to Isoligularone by oxidation and desulfoxidation in 47% yield in two steps (Figure 2).

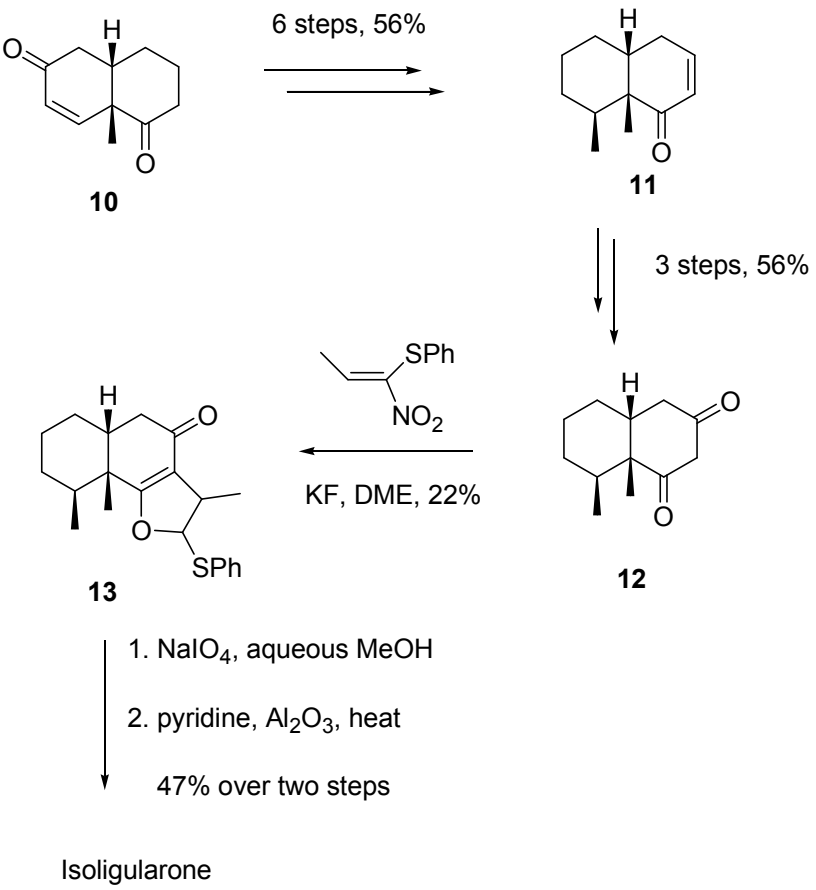


Figure 2. Synthesis of Isoligularone by Yoshikoshi.

Although Isoligularone has been synthesized, application of our tandem reaction would give a more efficient and direct route for its synthesis. In this chapter, we will discuss a

direct approach to eremophilane sesquiterpenes via the tandem Diels-Alder/ene reaction strategy.

Result and Discussion

As illustrated in the retrosynthetic scheme, the decalin skeleton of eremopholides would be accessible from the tandem Diels-Alder/ene reaction between triene **15** and *trans*-2-methyl-2-butenal as a diene and dienophile (Figure 3).

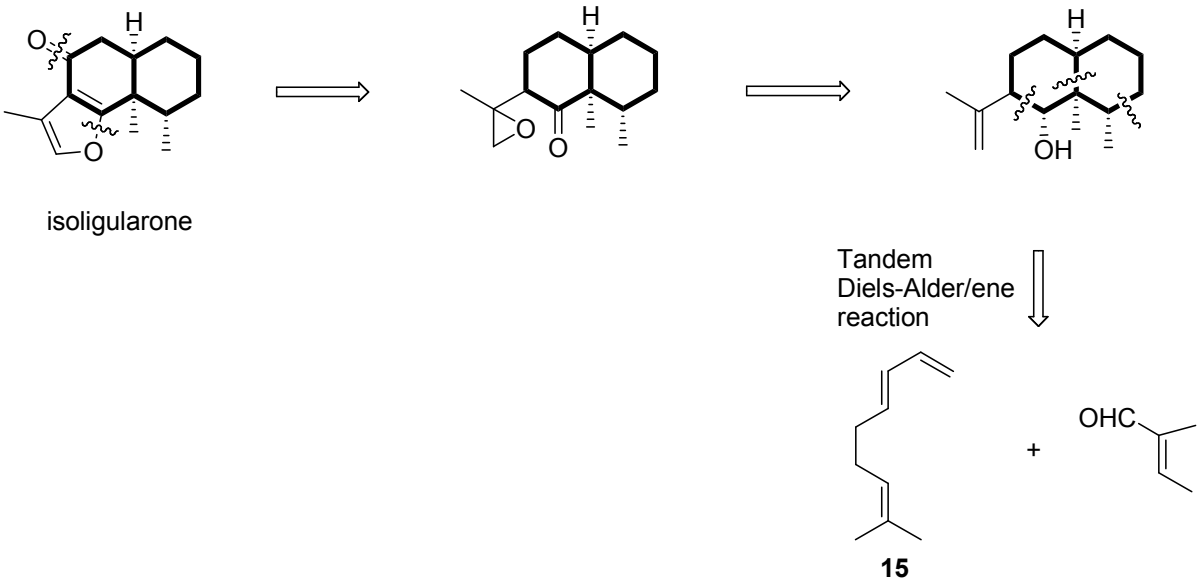
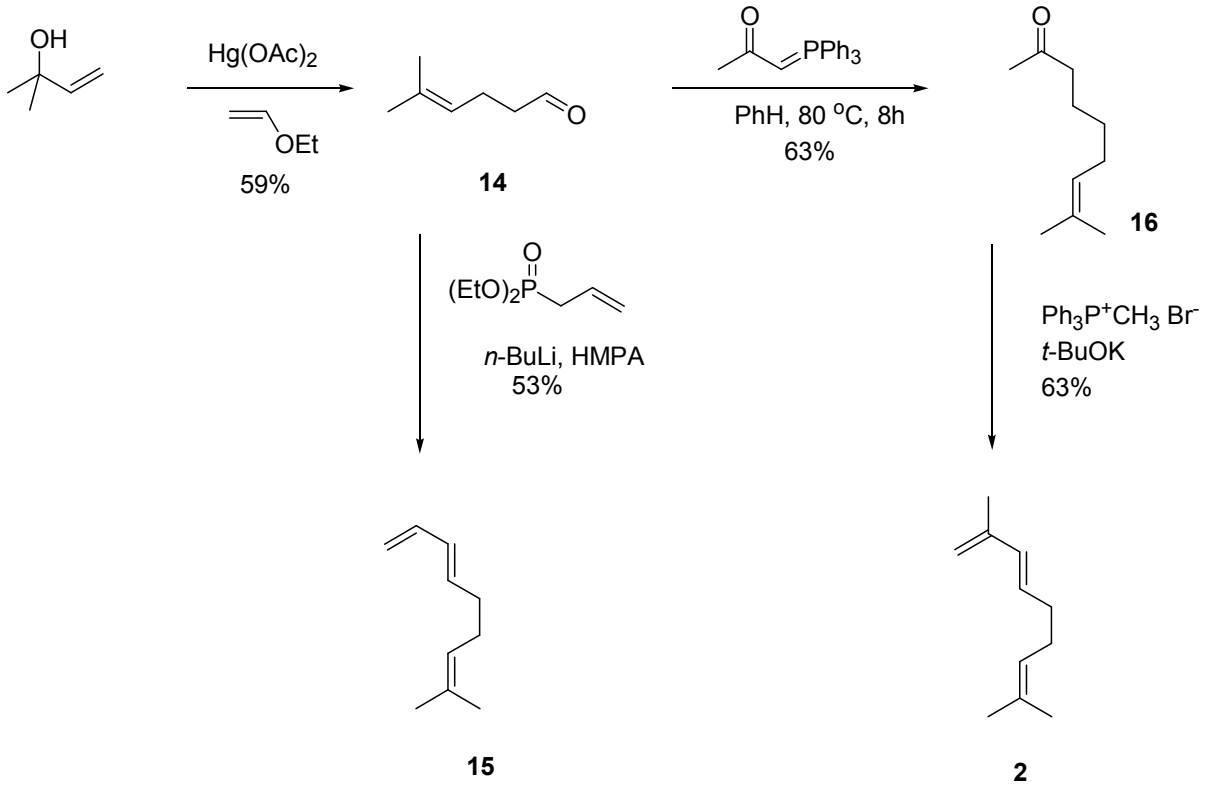


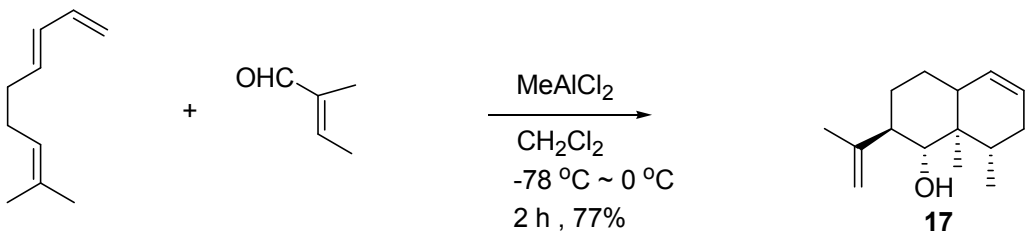
Figure 3. Retrosynthetic analysis of Isoligularone.

We began our study with the synthesis of triene **15**. Pure 2-methyl-3-butenol was heated to 140 ^{o}C for 5 hours with freshly recrystallized $Hg(OAc)_2$ and ethyl vinyl ether in a sealed tube to generate a γ,δ-unsaturated aldehyde **16** via Claisen rearrangement. Extension of the

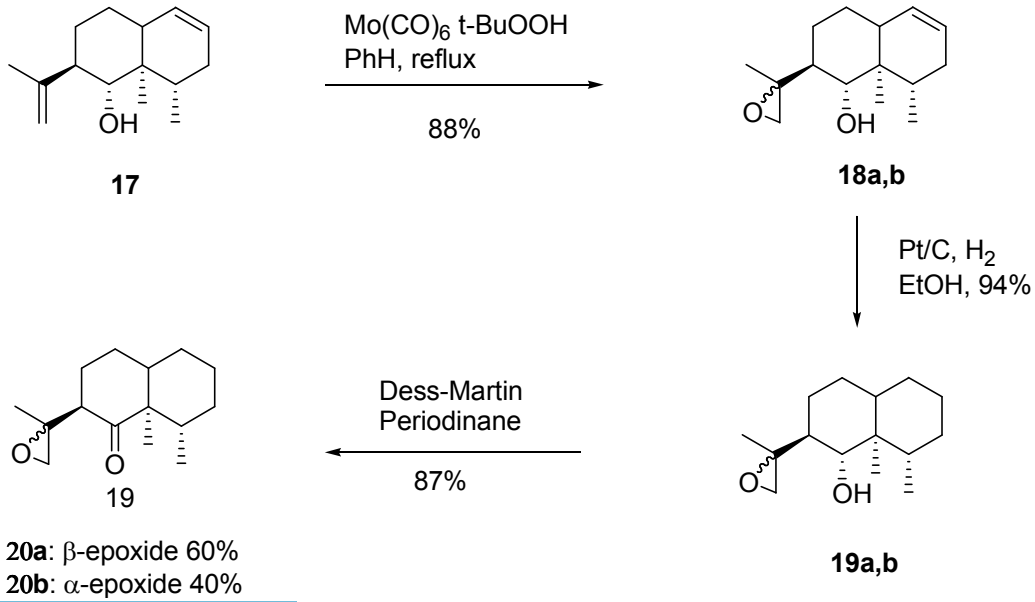
reaction time gave an increased amount of the inseparable side products. Aldehyde **16** was then treated with the anion formed by reacting diethyl allylphosphonate with *n*-BuLi to afford desired triene **15**.



To achieve the key Diels-Alder/ene adduct **17**, various Lewis acid catalysts and reaction temperature conditions were examined. Successful Lewis acids for the previous reactions, such as $BF_3{\cdot}OEt_2$ and Et_2AlCl, didn't give promising results, but only low yields of the product. But, with $MeAlCl_2$ in methylene chloride, this tandem reaction proceeded smoothly to give an alcohol **17** in 77 % yield as a single isomer. The reaction should be done at low temperature (-78 °C to 0 °C), because when the temperature went to room temperature, undesirable side products were formed.

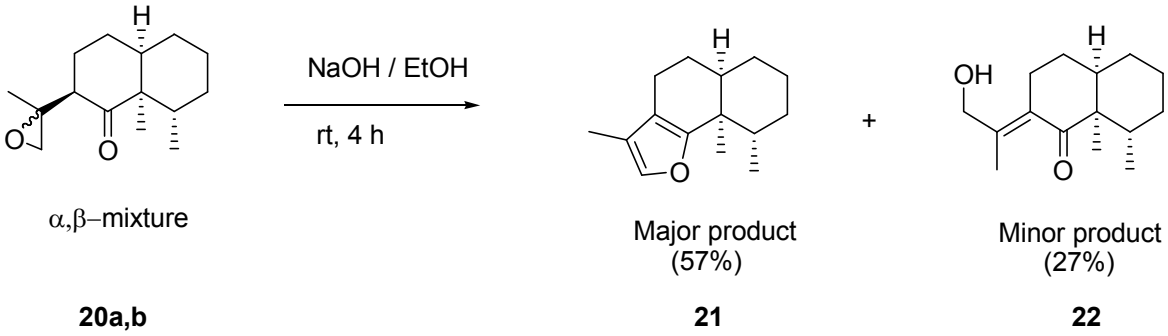


With the adduct **17** in hand, we tried hydroxyl-directed epoxidation. We tried both vanadyl acetylacetonate and molybdenum hexacarbonyl as catalysts with *tert*-butyl hydroperoxide. Molybdenum catalyst gave a better yield than a vanadium catalyst at low temperature. Surprisingly, the epoxide formation was still regioselective at a higher temperature (80 °C) and even gave better yields than a room temperature reaction. This epoxidation provided a separable mixture of two epoxides **18a** and **18b** in a ratio of 60:40 in 88 % yield. These epoxides underwent hydrogenation without separation with Pt/H_2 to give **19a** and **19b**, which could be oxidized with Dess-Martin periodinane to yield **20a** and **20b** in 87% yield.



The major epoxide **20a** was treated with sodium hydroxide in ethanol at room temperature, followed by acidification to afford furan **21** in 82% yield. A small amount of enone **22** was also isolated. The minor epoxide isomer **20b** produced **21** and **22** in 20% and 60% yields, respectively. On the basis of these results and the selectivities reported for molybdenum hexacarbonyl-catalyzed epoxidation of (-)- isopulegol,[15] we tentatively assign the structures of **20a** and **20b**.

Since both epoxides **20a** and **20b** gave the same compounds **21** and **22** of a different ratio, we preceded to the next step without purification of compounds **20a** and **20b**. The epoxide opening reaction gave 57 % yield of furan **21** and 27% of enone **22**.



α,β–mixture

20a,b

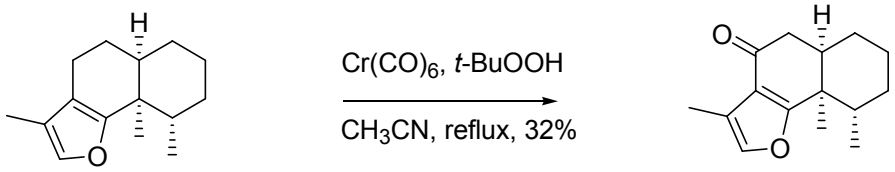
Major product (57%)

21

Minor product (27%)

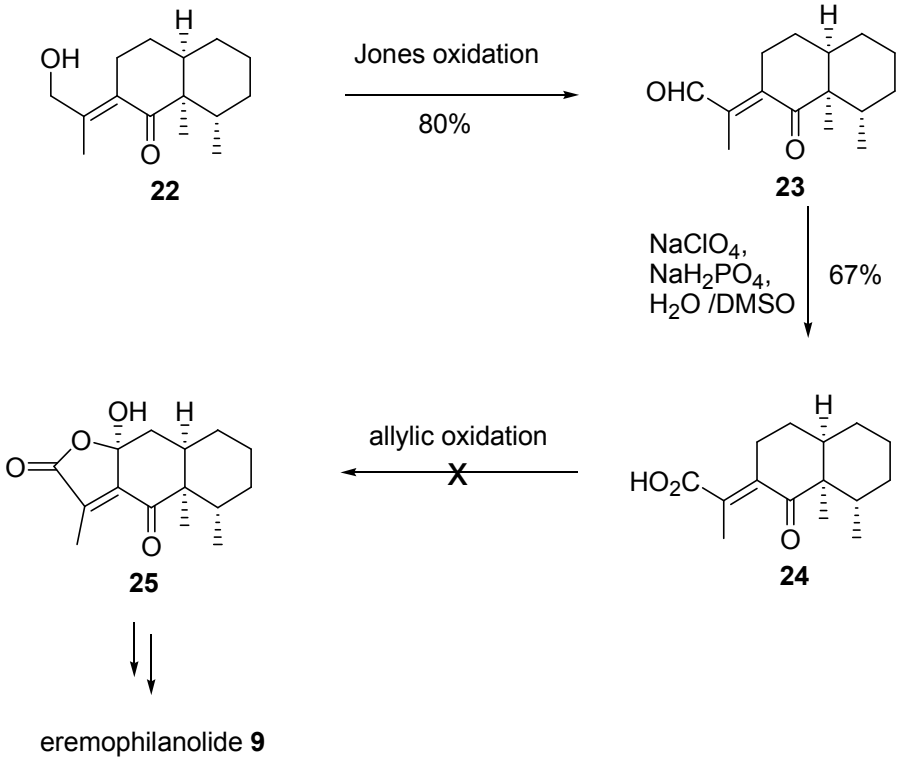
22

With furan **21** in hand, we continued our synthesis. The conversion of furan **21** into isolingularone required a benzylic oxidation. Although several methods have been advanced for this transformation,[16] the application of most of these methods [CrO_3, $Pb(OAc)_4$, SeO_2] to **21** led to decomposition of the furan subunit. Fortunately, the use of chromium hexacarbonyl and *tert*-butyl hydroperoxide in boiling acetonitrile afforded a 32% yield of compound **7**.[17] The proton NMR and ^{13}C NMR spectra for **7** matched the literature spectra[18] for isolingularone.

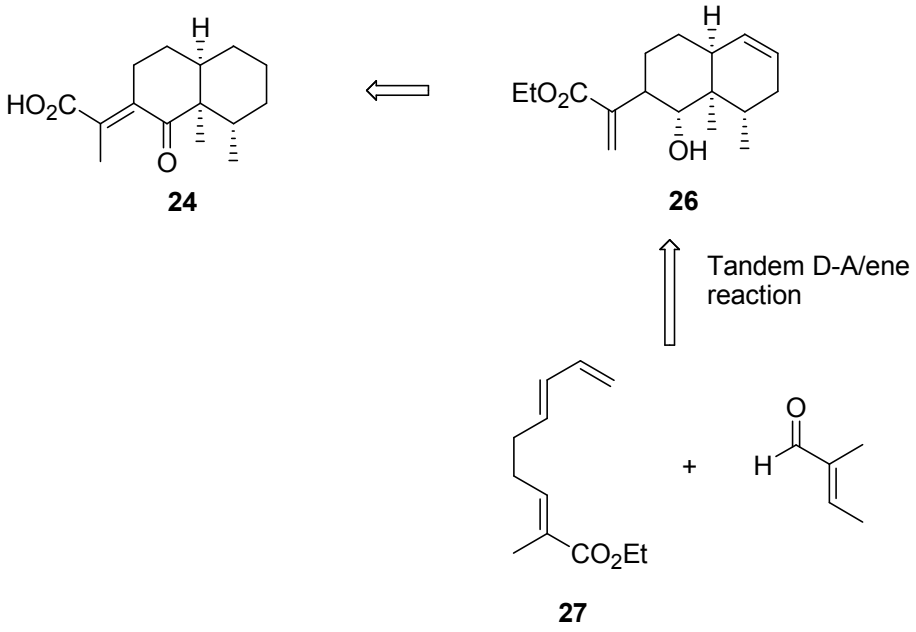


21 Isoligularone

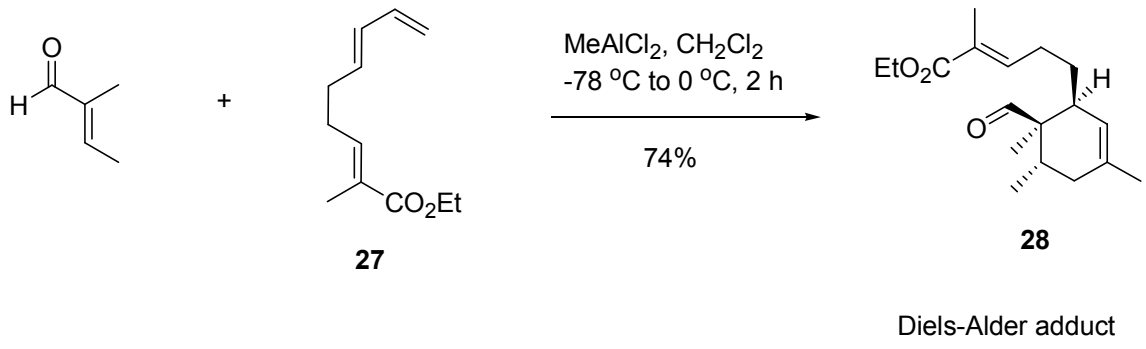
Enone **22** could be a suitable intermediate for eremophilanolides **8** and **9**. Enone **22** was treated with Jones reagent to give aldehyde **23** in 80 % yield. Aldehyde **23** was then oxidized to acid **24** by $NaClO_4$ and NaH_2PO_4 in H_2O/DMSO at room temperature in 67 % yield. With acid **24** in hand, we tried various allylic oxidations, which could lead to hydroxy lactone **25**, but all attempts were failed.



Since enone **22** was a minor product, we tried another synthetic route to aldehyde **23**. We thought introduction of a ester group in the tandem reaction stage could provide a very efficient route to generate acid **24**.



Known ester **27** was synthesized by the method of Parker.[19] When **27** was reacted with *trans*-2-methyl-2-butenal at -78 °C in the presence of methylaluminum dichloride, the reaction gave only Diels-Alder adduct **28** in 74 % yield.



In conclusion, we have developed a tandem Diels-Alder/ ene reaction, which can create as many as five stereogenic centers in a single reaction. The efficient synthesis of isoligularone nicely demonstrates the utility of this tandem Diels-Alder/ene reaction sequence for the synthesis of natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

5-Methylhex-4-enal (14)

Pure 2-methyl-but-3-en-2-ol (4.85 mL, 46.4 mmol), ethyl vinyl ether (13.3 mL, 139.3 mmol), and freshly recrystallized $Hg(OAc)_2$ (2.96 g, 9.29 mmol) were heated in a sealed tube for 5 h at 130 °C (*extended reaction time will increase the amount of inseparable side product*). The reaction mixture was concentrated to remove volatiles and then purified via flash column chromatography (hexane: EtOAc = 50:1 to 30:1) to give rather volatile γ,δ-unsaturated aldehyde **14** (3.05 g, 59 % yield) as a pale yellow oil;

^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.5 Hz 1H), 5.12-5.09 (m, 1H), 2.50-2.32 (m, 4H), 1.61 (s, 3H), 1.56 (s, 3H);

8-Methyl-1,3,7-nonatriene (15)

To a -78 °C solution of diethyl allylphosphonate (2.5 mL, 14.3 mmol) in THF (40 mL) was added dropwise *n*-BuLi (5.74 mL, 2.5 M in hexanes, 14.3 mmol). After stirring for 15 min, a solution of the aldehyde (1.34 g, 11.9 mmol) in HMPA (5 mL, plus 1 mL THF rinse) was added dropwise via cannula. The resulting solution was stirred for 2 h at –78 °C, and then allowed to warm to 25 °C. After 12 h at 25 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL). The mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (hexane only) to give triene **15** (861 mg, 53 % yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.3, 10.8 Hz, 1H), 5.72 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.14-5.08 (m, 2H), 4.97 (d, *J* = 10.4 Hz 1H), 2.13-2.08 (m, 4H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.2, 132.1, 131.2, 124.0, 114.9, 33.0, 28.0, 25.9, 17.9; HRMS *m/e* (EI) for $C_{10}H_{16}$ $(M)^+$ calcd 136.1252, measured 136.1255.

2-Isopropenyl-8,8a-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (17)

To a -78 °C solution of trans-2-methyl-2-butenal (1.1 mmol) in Et_2O (3.5 mL) was added $MeAlCl_2$ (1.5 mmol) and stirred for 10 min at -78 °C. To the resulting yellow solution was added via cannula a solution of triene **15** (1 mmol) in Et_2O (1 mL plus 0.5 mL rinse). After 10 min at -78 °C, the reaction was warmed to 0 °C and further stirred for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2.

The organic layer was dried over $MgSO_4$, filtered, and was concentrated in vacuo. The residue was purified via silica gel flash chromatography (hexane-EtOAc= 5:1) to give the Diels-Alder/ene adduct **17**. (890 mg, 77 % yield)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66-5.61 (m, 1H), 5.34-5.28 (m, 1H), 4.85 (d, J = 9 Hz, 2H), 3.57 (d, J = 10.5 Hz, 1H), 2.52-2.38 (m, 1H), 2.28-1.95 (m, 2H), 1.80-1.71 (m, 2H), 1.67 (s, 3H), 1.51-1.32 (m, 4H), 0.97 (s, 3H), 0.91 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 130.8, 126.2, 113.1, 70.0, 49.2, 38.7, 32.3, 30.5, 26.9, 26.7, 19.2, 18.1, 15.4; HRMS *m/e* (EI) for $C_{15}H_{24}O$ $(M)^+$ calcd 220.1827, measured 220.1820.

8,8a-Dimethyl-2-(2-methyl-oxiranyl)-1,2,3,4,4a,7,8,8a-octahydro-naphthalen-1-ol (18a,18b)

To a solution of alcohol **17** (0.89 g, 4.1 mmol) and $Mo(CO)_6$ (96 mg, 0.36 mmol) in 10 mL of benzene was added *tert*-butylhydroperoxide (0.84 mL, 5.5 M solution in decane) at room temperature under argon. The reaction was heated to reflux for 1 h and then cooled to room temperature. To the reaction was added 5 mL of 10% $Na_2S_2O_4$ (aq). It was extracted with ethyl acetate (3x 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via silica gel flash chromatography (hexane-EtOAc= 5:1) to give epoxide **18a** and **18b** (850 mg, 80 % yield).

18a ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61-5.72 (m, 1H), 5.25 (d, J = 10.0 Hz, 1H), 3.97 (d, J = 10.4 Hz, 1H), 2.85 (brs, 1H), 2.81 (d, J = 4.4 Hz, 1H), 2.61 (d, J = 4.4 Hz, 1H), 2.40-2.35 (m, 1H), 2.15 (brs, 1H), 2.06-2.03 (m, 1H), 1.73-1.63 (m, 4H), 1.49-1.41 (m, 2H), 1.31 (s, 3H), 0.92 (s, 3H), 0.85 (d, J = 7.2 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.5, 126.3,

70.3, 60.6, 53.1, 44.5, 38.9, 37.6, 31.8, 30.4, 26.5, 24.6, 20.6, 18.3, 15.3; HRMS *m/e* (EI) for $C_{15}H_{24}O_2$ $(M)^+$ calcd 236.1776, measured 236.1774

18b ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67-5.63 (m, 1H), 5.29 (d, J = 9.6 Hz, 1H), 3.80 (d, J = 10.8 Hz, 1H), 2.56 (d, J = 4.5 Hz, 1H), 2.48 (d, J = 4.5 Hz, 1H), 2.25-2.20 (m, 1H), 2.14 (brs, 1H), 2.11-1.98 (m, 1H), 1.80-1.62 (m, 4H), 1.52-1.43 (m, 2H), 1.27 (s, 3H), 0.90 (s, 3H), 0.88 (d, J = 7.2 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 126.5, 71.2, 60.3, 53.0, 46.9, 39.7, 37.5, 31.7, 30.5, 26.7, 25.0, 18.0, 16.7, 15.4;

8,8a-Dimethyl-2-(2-methyl-oxiranyl)-decahydro-naphthalen-1-ol (19a, 19b)

To a solution of epoxides **18a,b** (850 mg, 3.6 mmol) in 10 mL of tetrahydrofuran was added Pt-C (1 %, 200 mg) and the flask was charged with H_2 gas. The mixture was stirred at room temperature for 1 h and then was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified via silica gel flash chromatography (hexane-EtOAc= 5:1) to give epoxide **19a** and **19b** (809 mg, 94 % yield).

Compound **19a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (d, *J* = 10.4 Hz, 1H), 2.91 (d, *J* = 4.4 Hz, 1H), 2.80 (brs, 1H), 2.65 (d, *J* = 4.4 Hz, 1H), 1.85-1.72 (m, 4H), 1.69-1.61 (m, 2H), 1.52-1.39 (m, 4H), 1.36 (s, 3H), 1.30-1.13 (m, 5H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.9, 60.8, 53.1, 44.8, 40.0, 36.9, 31.8, 28.9, 27.4, 26.3, 23.3, 20.8, 20.5, 19.4, 15.3; HRMS *m/e* (EI) for $C_{15}H_{26}O_2$ $(M)^+$ calcd 238.1933, measured 238.1928.

Compound **19b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, *J* = 10.8 Hz, 1H), 2.56 (d, J = 4.4 Hz, 1H), 2.49 (d, *J* = 4.4 Hz, 1H), 2.75 (brs, 1H), 2.18-1.98 (m, 1H), 1.92-1.82 (m, 2H), 1.79-1.68 (m, 2H), 1.57-1.42 (m, 4H), 1.34 (s, 3H), 1.25-1.15 (m, 4H), 0.92 (d, *J* = 7.2 Hz,

3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.9, 59.7, 53.1, 47.2, 40.1, 36.7, 31.7, 28.9, 27.5, 26.4, 23.5, 20.5, 19.1, 16.8, 15.4;

2-(1-Methyl-2-oxacyclopropyl)-8,8a-dimethyldecahydronaphthalen-1-one (20a, 20b)

To a solution of above crude compounds **19a, 19b** (809 mg, 3.4 mmol) in 20 mL of CH_2Cl_2 was added the Dess-Martin periodinane (1.58 g, 3.7 mmol) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 8 h. To the mixture was added 20 mL of saturated $NaHCO_3$ (aq) and 20 mL of 10 % $Na_2S_2O_3$ (aq). It was then extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and was concentrated in vacuo. The residue was purified via silica gel flash chromatography (hexane-EtOAc= 5:1) to give epoxides **20a** (418 mg, 52 % yield) and **20b** (280 mg, 35 % yield).

Compound 20a

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (d, J = 4.5 Hz, 1H), 2.55 (d, J = 4.5 Hz, 1H), 2.40-2.29 (m, 2H), 2.20-1.91 (m, 5H), 1.49-1.33 (m, 5H), 1.30 (s, 3H), 1.25-1.18 (m, 1H), 1.12 (s, 3H), 0.88 (d, J = 6.8 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 57.1, 55.9, 53.1, 45.4, 39.4, 31.4, 30.6, 29.7, 26.7, 23.5, 20.5, 17.7, 14.8 ; HRMS *m/e* (EI) for $C_{15}H_{24}O_2$ $(M)^+$ calcd 236.1776 , measured 236.1771

Compound 20b

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71-2.62 (m, 1H), 2.60 (d, J = 4.5 Hz, 1H), 2.49 (d, J = 4.5 Hz, 1H), 2.41-2.28 (m, 2H), 2.21-1.81(m, 5H), 1.50-1.40 (m, 5H) 1.37 (s, 3H), 1.16 (s, 3H), 0.88 (d, J = 6.8 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 56.5, 52.0, 51.5, 51.2, 39.6, 31.5, 30.6, 29.7, 25.5, 23.9, 20.8, 20.6, 20.5, 15.0 ;

3,9,9a-Trimethyl-4,5,5a,6,7,8,9,9a-octahydronaphtho[1,2-b]furan (21) and 2-(2-Hydroxy-1-methylethylidene)-8,8a-dimethyloctahydronaphthalen-1-one (22)

To a solution of compounds **20a** and **20b** (0.24 g, 1 mmol) in 5 mL of ethanol was added NaOH (4 mg, 0.1 mmol) at room temperature. The solution was stirred for 8 h at room temperature. To the solution was added 2 mL of 10% HCl (aq) and it was extracted with ethyl ether (2x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via silica gel flash chromatography (hexane-EtOAc= 2:1) to give compound **21** (124 mg, 57 % yield) and **22** (63 mg, 27 % yield).

Compound **21** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 1.2 Hz, 1H), 2.41-2.26 (m, 2H), 2.09-2.04 (m, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.85-1.25 (m, 9H), 1.19 (s, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.1, 119.5, 116.4, 42.5, 38.9, 36.6, 31.2, 29.9, 27.8, 25.5, 21.5, 20.7, 17.8, 8.4 ; HRMS *m/e* (EI) for $C_{15}H_{22}O$ $(M)^+$ calcd 218.1670 , measured 218.1665

Compound **22** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 2H), 2.95-2.82 (m, 1H), 2.19-1.95 (m, 4H), 1.85 (s, 3H), 1.70-1.25 (m, 8H), 1.09 (s, 3H), 0.67 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 142.0, 131.1, 62.4, 47.6, 40.2, 33.7, 30.1, 29.2, 28.4, 25.2, 24.0, 18.8, 10.4;

Isoligularone (7)

To a solution of compound **21** (73 mg, 0.33 mmol) in 2 mL of acetonitrile was added $Cr(CO)_6$ (31 mg, 0.17 mmol) and *tert*-butylhydroperoxide (0.073 mL, 5.5 M solution in decane) and then heated to reflux for 7 h. The mixture was cooled to room temperature and then diluted with ethyl ether (10 mL). It was washed with H_2O, sat $NaHCO_3$ (aq) and brine.

The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via preparative thin layer chromatography (hexane-EtOAc= 5:1) to give compound **7** (24 mg, 32 % yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 1.2 Hz, 1H), 2.85 (m, 1H), 2.25-2.20 (m, 2H), 2.19 (d, *J* = 1.2 Hz, 3H), 1.61-1.26 (m, 8H), 1.30 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ196.3, 174.8, 139.3, 119.2, 118.7, 42.3, 41.4, 39.9, 35.0, 30.1, 26.3, 20.6, 17.3, 16.2, 9.4 ; HRMS *m/e* (EI) for $C_{15}H_{20}O_2$ $(M)^+$ calcd 232.1463 , measured 232.1466.

2-(8,8a-Dimethyl-1-oxooctahydronaphthalen-2-ylidene)propionaldehyde (23)

To a solution of enone **22** (63 mg, 0.267 mmol) in 2 mL of acetone was added Jones reagent (66 μmL, 8 N solution) slowly at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 2 h then warmed to room temperature. Ethyl ether (10 mL) was added to a mixture and washed with brine solution until blue color is removed in water layer. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified via preparative thin layer chromatography to give compound **23** (50 mg, 80 % yield)

Compound **23** ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.2 (s, 1H), 3.63 (dt, *J* = 14.3, 3.6 Hz, 1H), 2.39 (td, *J* = 14.1, 3.6 Hz, 1H), 2.28-2.12 (m, 1H), 2.12-1.87 (m, 2H), 1.78 (d, *J* = 1.8 Hz, 3H), 1.79- 1.65 (m, 3H), 1.64-1.52 (m, 4H), 1.78 (s, 3H), 0.70 (d, *J* = 6.9 Hz, 3H)

2-(8,8a-Dimethyl-1-oxooctahydronaphthalen-2-ylidene) propionic acid (24)

To a solution of $NaClO_4$ (54 mg, 0.6 mmol) and NaH_2PO_4 (54 mg, 0.4 mmol) in 2 mL of H_2O was added aldehyde **23** (10 mg, 0.04 mmol) in 2 mL of DMSO at room temperature. The mixture was stirred at room temperature for 8 h. Ethyl ether (8 mL) was added then

washed with water, brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was subjected to next step without purification. (67 % yield)

Compound **24** ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.2 (brs, 1H), 3.42 (dt, *J* = 14.4, 3.6 Hz, 1H), 2.31-2.21 (m, 1H), 2.19-2.17 (m, 2H), 1.95 (d, *J* = 1.5 Hz, 3H), 1.92-1.83 (m, 1H), 1.72-1.48 (m, 7H), 1.12 (s, 3H), 0.69 (d, *J* = 7.0 Hz, 3H)

5-(6-Formyl-3,5,6-trimethylcyclohex-2-enyl)-2-methylpent-2-enoic acid ethyl ester (28)

To a -78 ^oC solution of trans-2-methyl-2-butenal (0.10 mL, 1.03 mmol) in Et_2O (3.5 mL) was added $MeAlCl_2$ (1.03 mL, 1M soln in hexane, 1.03 mmol) and stirred for 10 min at -78 °C. To the resulting yellow solution was added via cannula a solution of ester **27** (0.10 g, 0.51 mmol) in Et_2O (2 mL). After 10 min at -78 °C, the reaction was warmed to 0 °C and further stirred for 1 h. The reaction was quenched by the addition of 10 % aqueous NaOH (3 mL) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and was concentrated in vacuo. The residue was purified via silica gel flash chromatography (hexane-EtOAc= 5:1) to give the Diels-Alder adduct **28**. (96 mg, 74 % yield)

Compound **28** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 6.68 (td, *J* = 7.8, 1.5 Hz, 1H), 5.71-5.65 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.35-2.21 (m, 1H), 2.20-2.08 (m, 4H), 2.03-2.01 (m, 1H), 1.81 (s, 3H), 1.62-1.45 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H)

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GENERAL CONCLUSIONS

In this dissertation, we have investigated the direct and efficient synthetic route to biologically active natural products.

Chapter 1 describes the synthesis of some of the natural compounds in *Echinacea.* Several main constituents of the plant *Echinacea* have been synthesized for the first time. We have developed a direct and flexible route to amides and ketones in *Echinacea*. The synthesized natural products have been used for standard samples for the biological studies.

Chapter 2 describes the new tandem strategy to construct bicyclic systems by a Diels-Alder/ ene reaction and its application for the synthesis of Isoligularone. During this tandem reaction, as many as five stereogenic centers can be created in a single reaction. The efficient synthesis of Isoligularone nicely demonstrates the utility of this tandem Diels-Alder/ene reaction sequence for the synthesis of natural products.

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