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.³

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. purpurea* 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>
<thead>
<tr>
<th>Species</th>
<th>Plant part</th>
<th>Constituents</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>Aerial parts</td>
<td>Alkamides; caffeic acid ester, mainly cichoric acid, polysaccharides; polyacetylenes</td>
<td>Echinacoside is not present</td>
</tr>
<tr>
<td><em>Echinacea angustifolia</em></td>
<td>Roots</td>
<td>Alkamides; caffeic acid ester, particularly echinacoside; cynarin; polysaccharides; polyacetylenes</td>
<td>Cynarin is characteristic of <em>E. angustifolia</em></td>
</tr>
<tr>
<td><em>Echinacea pallida</em></td>
<td>Roots</td>
<td>Caffeic acid esters, particularly echinacoside; polysaccharides; polyacetylenes</td>
<td>Alkamides largely absent</td>
</tr>
</tbody>
</table>
Figure 1. Main alkamides in Echinacea species.  

1. Undeca-2E,4Z-diene-8,10-diynoic acid isobutyl-amide
2. Undeca-2Z,4E-diene-8,10-diynoic acid isobutyl-amide
3. Dodeca-2E,4Z-diene-8,10-diynoic acid isobutyl-amide
4. Undeca-2E,4Z-diene-8,10-diynoic acid (2-methyl-butyl)-amide
5. Dodeca-2E,4E,10E-trien-8-ynoic acid isobutyl-amide
6. Trideca-2E,7Z-diene-10,12-diynoic acid isobutyl-amide
7. Dodeca-2E,4Z-diene-8,10-diynoic acid (2-methyl-butyl)-amide
8. Dodeca-2E,4E,8Z,10E-tetraenoic acid isobutyl-amide
9. Dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutyl-amide
10. Dodeca-2E,4E,8Z-trienoic acid isobutyl-amide
11. Dodeca-2E,4E-dienoic acid isobutyl-amide
12. Undec-2E-ene-8,10-diynoic acid isobutyl-amide
13. Undec-2Z-ene-8,10-diynoic acid isobutyl-amide
14. Dodec-2E-ene-8,10-diynoic acid isobutyl-amide
15. Undec-2E-ene-8,10-diynoic acid (2-methyl-butyl)-amide
16. Dodec-2E-ene-8,10-diynoic acid (2-methyl-butyl)-amide
17. Dodec-2E-ene-8,10-diynoic acid (2-methyl-butyl)-amide
18. Pentadeca-2E,9Z-diene-12,14-diynoic acid isobutyl-amide
19. Hexadeca-2E,9Z-diene-12,14-diynoic acid isobutyl-amide
Alkamides have been isolated from *E. angustifolia* and *E. purpurea* roots and aerial parts, but they are largely absent from *E. pallida*. Even in the 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. purpurea*.\(^9\) Ketone compounds are shown in Figure 2.

![Ketones in Echinacea](image)

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*.\textsuperscript{10} It acts as an antioxidant, and is an inhibitor of viral integrase\textsuperscript{11} or bacterial hyaluronidase, and it has immunostimulant activity in phagocytosis tests.\textsuperscript{12}

![Cichoric Acid](image1.png)  ![Chlorgenic Acid](image2.png)  ![Echinacoside](image3.png)

**Fig 3.** Representative caffeic acid derivatives in *Echinacea*

The following polysaccharides have been identified from *E. purpurea*: an 80kDa xyloglucan, a 45kDa arabinotrehmannogalactan, and a 35kDa 4-O-methyl-glucoronarabinoxylan.\textsuperscript{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).\textsuperscript{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 °C. The α-chloroisobutylamide was refluxed with triphenylphosphine to give salt 27 in good yield. 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 methyl lithium-lithium bromide complex. Unfortunately, the alkylation failed. Only starting material 31 was recovered.

![Reaction Scheme](image)

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 CBr₄ and PPh₃ gave a complex mixture.
To circumvent the problem, we tried the very mild radical deoxygenation conditions by Gunji. First, we applied this method to a simple model system. The adduct of monoanion 32 and heptanal was treated with 1,1-thiocarbonyldiimidazole in CH₂Cl₂ at room temperature. The corresponding thiocarboimidazole 36 was treated with tributyltin hydride and AIBN at 80 °C 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. 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 tetrabutylammonium fluoride to give amide 12 and amide 13 respectively.

Amide 14 was also synthesized from acetal 43. Trimethylsilyl group was removed with tetrabutylammonium 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-Heptyl-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\textsuperscript{21} gave 40\% of a cross-coupled product, while copper chloride/piperidine conditions gave the product in 87\% yield.\textsuperscript{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).

![Chemical structures](image)

*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 (2E, 4E) and (2Z, 4E) 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.
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. Unfortunately, the reaction gave only starting material back. Also, the use of TMSCl and Pd(OAc)\(_2\) didn’t give us any promising results.

So we changed our plan of the synthesis to make phosphonium salt 55, 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. 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 (2E,4Z 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,\textsuperscript{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 (2E, 4Z) isomer 10a in 69% and 12% yields, respectively.

Alcohol 62 could be achieved by Wittig reaction between 2-butenyldenetriphenyl 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.\(^\text{29}\)

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

![Figure 5](image)

Figure 5. New alkamides in E. purpurea 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 phosphonoacetamides 66 was reported to produce Z-\(\alpha,\beta\)-unsaturated amides in excellent
stereoselectivity. Phosphonoacetamide 66 was synthesized from bromoacetyl bromide with isobutylamine, followed by reaction with diphenylphosphate and triethylamine in 52% yield over two steps.

![Chemical structure of 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.

![Chemical structure of amide 11]

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 tetrabutylammonium 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. 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. 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. 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, which was further converted to iodide 80 with iodine, triphenylphosphine and imidazole in methylene chloride. Propargylic iodide 80 was then reacted with the anion of trimethylsilylacetylene and a copper iodide catalyst. 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. 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. Coupling of 84 with trimethylsilylacetylene using palladium catalysis afforded diacetylene 84 in 42% yield. Deprotection of the THP ether using PTSA in methanol, followed by oxidation of the resulting alcohol with PCC, led to ketone 85.

Desilylation 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 CH₂ 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. To get the aldehyde 89, 2-acetylcyclohexanone was treated with trimethyl orthoformate and PTSA in MeOH to generate ester 90 in 76% yield. 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.

![Chemical structure of ketones 20 and 21]

We started our synthesis by generating the enyne moiety in one step. Reaction of 1,4-dichloro-2-butyn with NaNH$_2$ in liquid ammonia, followed by addition of epichlorohydrin led to enynol 98. 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.
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-diynne.

![Chemical reaction diagram](image)

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 $^1$H 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$_2$O (20 mL) was slowly added chloroacetyl chloride (3.9 mL, 0.05 mol) in Et$_2$O (20 mL) over 30 min by a dropping funnel at 0 °C. 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$_3$) $\delta$ 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$_2$Cl$_2$ 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$_2$Cl$_2$ (30 mL) was added PCC (5.37 g, 25 mmol) at 0°C. After stirring at room temperature for 1 h, an excess amount of Et$_2$O 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$_3$) $\delta$ 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$_3$) $\delta$ 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 °C. The mixture was stirred for 30 min at 0 °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 NH₄Cl (1 mL) and then extracted with Et₂O (10 mL X 2). The organic layer was washed with NaHCO₃ (15 mL), brine (15 mL) and dried (MgSO₄). The residue was purified via flash column chromatography (hexane: ethyl acetate = 5:1) to give 2E isomer 29a (0.34 g, 59% yield) and 2Z isomer 29b (0.058 g, 10% yield) compound 29a: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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-2E-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 °C for 40 min. It was cooled down to room temperature then solvent was evaporated. To this mixture was added aq NaHCO₃ (1 mL) and extract with Et₂O (10 mL), then was washed with brine (10 mL) and dried (MgSO₄).
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$_2$Cl$_2$ (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$_2$Cl$_2$ (10 mL) was added PCC (0.20 g, 0.93 mmol) at 0 °C. After stirring at room temperature for 1 h, Et$_3$O 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, CDCl$_3$) δ 9.75 (t, $J = 1.5$ Hz, 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-2E-undecene-8,10-diynoic acid isobutylamide (34a) and 7-Hydroxy-2E-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 °C. The mixture was warmed to room temperature. After stirring for 3 h at room temperature, the mixture was cooled to -78 °C. To the mixture was added aldehyde 33 (0.58 g, 2.97 mmol) in THF. After stirring for 45 min at -78°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, CDCl$_3$) 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, CDCl$_3$) 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 °C. The mixture was warmed to room temperature. After stirring for 3 h at room temperature, the mixture was cooled to -78 °C. To the mixture was added heptanal (0.70 g, 0.5 mmol) in THF. After stirring for 45 min at -78 °C, water (10 mL) was added. The mixture was then extracted with ether (50 mL), washed with brine, and dried (MgSO₄). 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 \(^1\text{H NMR (300 MHz, CDCl3)}\) 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), \(^{13}\text{C NMR (75 MHz, CDCl3)}\) 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-diylnyl)heptyl] ester (36)

To a solution of compound 35 (0.63 g, 0.28 mmol) in CH₂Cl₂ (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 \(^1\text{H NMR (400 MHz, CDCl3)}\) 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 °C for 30 min then cooled down to room temperature. To the mixture, H2O (5 mL) was added then extracted with Et2O (10 mL X 2) and dried (MgSO4). The residue was purified via flash column chromatography (hexane only) to give the compound 37 (0.29 g, 54 % yield).

Compound 37 1H 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 CH2Cl2 (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 1H NMR (300 MHz, CDCl3) 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 °C for 30 min then cooled to room temperature. To the mixture, H$_2$O (1 mL) was added then extracted with Et$_2$O (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$_3$) $\delta$ 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$_2$Cl$_2$ (8 mL) and MeOH (2 mL) was blown O$_3$ at -78 °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$_2$S (1.47 mL, 20 mmol) was added and stirred for 12 h. To the mixture water was added and extracted with CH$_2$Cl$_2$ 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$_3$) $\delta$ 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 °C. The mixture was warmed to room temperature. After stirring for 3 h at room temperature, the mixture was cooled to -78 °C. To the mixture was added aldehyde 40 (0.50 g, 3.4 mmol) in THF. After stirring for 45 min at -78 °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$_3$) $\delta$ 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, CDCl$_3$) $\delta$ 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$_2$Cl$_2$ (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$_3$) $\delta$ 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$_3$SnH (0.71 mL, 2.64 mmol) at room temperature. The mixture was boiled at 80 °C 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 $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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}$O$_2$Si.

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

To a solution of acetal 43 (0.11 g, 0.44 mmol) in Acetone/ H$_2$O (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 $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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\textit{E}-ene-8,10-diynoic acid isobutyl-amide (45a) and 11-Trimethylsilyl-undec-2\textit{Z}-ene-8,10-diynoic acid isobutyl-amide (45b)

To a solution of triphenyl-(\textit{N}-isobutylcarboxamidomethyl)-phosphonium chloride 27 (0.415 g, 1.01 mmol) in THF (5 mL) was added 2.5 M \textit{n}-BuLi (0.404 mL, 1.01 mmol) at 0 °C. After stirring for 10 min at 0 °C, aldehyde 44 (0.104 g, 0.51 mmol) in THF (3 mL) was added dropwise at 0 °C. After stirring for 30 min at 0 °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 (\textit{E}) isomer 45a (112 mg, 73 % yield) and (\textit{Z}) isomer 45b (15 mg, 10 % yield).

(\textit{E}) isomer (45a): IR mmax (neat) cm$^{-1}$: 3289,2958, 2359, 2225, 2108, 1669, 1628, 844; \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 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); \textsuperscript{13}C NMR (75 MHz, CDCl$_3$) $\delta$ 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.

(\textit{Z}) isomer (45b): \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 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); \textsuperscript{13}C NMR (75 MHz, CDCl$_3$) $\delta$ 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\textit{E}-ene-8,10-diynoic acid isobutylamide (12) and Undec-2\textit{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 °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 (0.021 g, 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 °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 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) 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 °C. After 10 min, methyl iodide (0.063 mL, 1.02 mmol) was added to the mixture at -78 °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 (MgSO4). The residue was purified via flash column chromatography (hexane:ethyl acetate=3:1) to give the methylated acetylene 47 (0.027 g, 40 % yield).

Compound 47 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) 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 C12H18O2.

6,8-Decadiynal (48)

To a solution of the methylated acetylene 47 produced above (0.045 g, 0.23 mmol) in Acetone/H2O (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 NaHCO₃ (10 mL), brine (10 mL), and dried (MgSO₄). 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 ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 203.1, 77.8, 73.4, 65.3, 63.9, 44.7, 26.3, 21.4, 19.1, 4.3.

**Dodec-2E-ene-8,10-diynoic acid isobutylamide (14) and Dodec-2Z-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 °C. After stirring for 10 min at 0 °C, the aldehyde produced above (0.03 g, 0.20 mmol) in THF (1 mL) was added dropwise at 0 °C. After stirring for 30 min at 0 °C, water (25 mL) was added and the mixture was extracted with ether (50 mL), and dried (MgSO₄). 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₂₃ON
Amide **14a**: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_2$O. After 10 min, iodine (0.824 g, 3.24 mmol) was added at 0 °C 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$_2$Cl$_2$, 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$_3$) $\delta$ 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 °C. The mixture was stirred at room temperature for 30 min. The reaction was quenched with 6 mL of sat NH$_4$Cl (aq) and extracted with Et$_2$O (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-heptynl 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 Et₂O, washed with NH₄Cl solution, water and brine, dried (MgSO₄), 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 ¹H NMR (300 MHz, CDCl₃) 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 CH₂Cl₂ was added dimethyloxalyl chloride (0.263 mL, 3.7 mmol) dropwise at -78 °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 °C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH₄Cl(aq) and aqueous layer was extracted with CH₂Cl₂ (2x 20 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 to give compound 44 (0.187 g, 89 % yield)

Compound 44 ¹H NMR (300 MHz, CDCl₃) 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);
\[ ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3 \] \delta 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-heptyno1 49 (1.0 g, 4.2 mmol) and CuCl (0.043 g, 0.43 mmol) was mixed. The mixture was cooled down to -78 °C 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 °C and the sealed tube was opened. Slowly warmed to room temperature and excess propyne was evaporated. NH\(_4\)Cl (aq) (50 mL) was added to the mixture then extracted with Et\(_2\)O (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 \(^1\text{H} \text{NMR (300 MHz, CDCl}_3 \) \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-2E,4E-dienoic acid isobutylamide (11) and Dodeca-2Z,4E-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 °C. After stirring for 10 min at 0 °C, trans-2-decenal (0.095mL, 0.5 mmol) in THF (3 mL) was added dropwise at 0 °C. After stirring for 30 min at 0°C, water (5 mL) was added. The solution was then extracted with ether (30 mL) and dried
(MgSO₄). 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 ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75MHz, CDCl₃) 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 C₁₆H₂₉NO (M)⁺ calcld 251.2249, measured 251.2243.

Compound 11a ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75MHz, CDCl₃) 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-6E-en-4-yn-1-ol (57)

To a solution of Pd(PPh₃)₂Cl₂ (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 °C in Ar. After stirring at room temperature for 2 h, the reaction was quenched with sat NH₄Cl (aq), extracted with ether, washed with brine, and dried (MgSO₄). The residue was purified via flash column chromatography to give compound 57 (230 mg, 74 % yield).
Compound 57 $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 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-6E-en-4-ynal (58)**

To a solution of compound 57 (0.20 g, 1.61 mmol) in CH$_2$Cl$_2$ (10 mL) was added PCC (0.695 g, 3.2 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, then Et$_2$O (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$_3$) $\delta$ 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$_3$) $\delta$ 200.9, 139.1, 110.8, 86.0, 80.3, 42.9, 18.7, 12.8

**Dodeca-2E,4E,10E-trien-8-ynoic acid isobutylamide (5) and Dodeca-2E,4Z,10E-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 °C. After stirring for 10 min at 0 °C, aldehyde 58 (0.10 g, 0.82 mmol) in THF (5 mL) was added dropwise at 0 °C. After stirring for 30 min at 0 °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\(_3\)) \(\delta 7.19\) (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\(_3\)) \(\delta 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\(_3\)) \(\delta 7.52\) (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\(_3\)) \(\delta 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-4Z-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\(_3\)) \(\delta 5.43-5.35\) (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)
4Z-Octenal (61)

To a solution of oxalyl chloride (0.27 mL, 3.12 mmol) in 10 mL of CH₂Cl₂ was added dimethylsulfoxide (0.44 mL, 6.24 mmol) dropwise at -78°C. 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°C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH₄Cl(aq) and aqueous layer was extracted with CH₂Cl₂ (2x 20 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= 4:1) to give compound 61 (165 mg, 84 % yield).

Compound 61 ¹H NMR (300 MHz, CDCl₃) 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-2E,4E,8Z-trienoic acid isobutylamide (10) and Dodeca-2E,4Z,8Z-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 °C. After stirring for 10 min at 0 °C, aldehyde 61 (0.10 mg, 0.79 mmol) in THF (3 mL) was added dropwise at 0 °C. After stirring for 1 h at 0 °C, water (5 mL) was added. The solution was then extracted with ether (30 mL) and dried over MgSO₄. 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$_3$) $\delta$  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$_3$) $\delta$  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 °C. 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$_4$Cl (5 mL), extract with Et$_2$O, 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$_3$) $\delta$  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$_2$Cl$_2$ (10 mL) was added PCC (1.37 g, 6.34 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, then Et$_2$O (20 mL) was added. The solution was filtered through celite and solvent was removed. The residue was purified via flash column chromatography (hexane:ethyl acetate= 4:1) to give compound 63 (296 mg, 76 % yield)

Compound 63 $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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 °C. After stirring for 10 min at 0 °C, aldehyde 63 (250 mg, 2.0 mmol) in THF (2 mL) was added dropwise at 0 °C. After stirring for 30 min at 0 °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 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$_2$Cl$_2$ (20 mL) was added bromoacetyl chloride (1.25 mL, 15 mmol) in CH$_2$Cl$_2$ (20 mL) by dropping funnel at 0 °C. 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 CH₂Cl₂ (20 mL) followed by addition of Et₃N (3
mL, 21 mmol) at 0 °C. 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, CDCl₃) 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°C. The mixture was stirred at room temperature for 0.5 h. The reaction was quenched with
6 mL of sat NH₄Cl (aq) and extracted with Et₂O (10 mL x 3). Organic layer was washed
with brine (20 mL x 2), dried (MgSO₄), 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, CDCl₃) 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); ¹³C NMR (75MHz, CDCl₃) δ 88.5, 83.5,
79.4, 66.1, 61.3, 30.9, 15.9, 14.4, -0.16 ; HRMS m/e (EI) for C₁₀H₁₆OSi (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 CH₂Cl₂ was added
dimethylsulfoxide (0.766 mL, 10.8 mmol) dropwise at -78 °C. 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 °C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH₄Cl(aq) and aqueous layer was extracted with CH₂Cl₂ (2x 20 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 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 °C in Ar. The mixture was stirred for 20 min at 0 °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 NH₄Cl(aq) and extracted with Et₂O (3x 30 mL), dried (MgSO₄), 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 ¹H NMR (300MHz, CDCl₃) 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 °C in Ar. After stirring for 2 h at -78 °C, reaction was quenched with excess of EtOAc (30 mL) at -78 °C and warmed to room temperature. The
mixture was washed with 10% HCl (aq) (10 mL), brine (10 mL), dried (MgSO₄), 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 CH₂Cl₂ was added dimethylsulfoxide (0.178 mL, 2.46 mmol) dropwise at -78 °C. 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 °C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH₄Cl(aq) and aqueous layer was extracted with CH₂Cl₂ (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 to give compound 71a (0.106 g, 81 % yield)

71a ¹H NMR (300 MHz, CDCl₃) 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-2Z,4E-diene-8,10-diynoic acid isobutylamide (72a) and 11-Trimethylsilyl-undeca-2E,4E-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 °C 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 °C over 2 h. The reaction was quenched with NH₄Cl(aq), washed with water, brine, dried (MgSO₄), 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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-2Z,4E-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 °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$_3$) $\delta$ 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, CDCl₃) 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 C₁₅H₁₀NO (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 °C 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 °C and the sealed tube was opened. The mixture was warmed to room temperature slowly to evaporate excess propyne. NH₄Cl (aq) (20 mL) was added to the mixture then extracted with Et₂O (3 x 20 mL). Organic layer was washed with water, brine, dried (MgSO₄), 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 76.1, 66.0, 64.6, 61.7, 31.2, 15.9, 4.47 ; HRMS m/e (EI) for C₆H₁₀O (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 CH₂Cl₂ was added dimethylsulfoxide (1.63 mL, 22.9 mmol) dropwise at -78 °C. 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 °C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH₄Cl (aq) (10 mL) and aqueous layer was extracted with CH₂Cl₂ (2 x 30 mL). Combined organic layer was washed with water (2 x 20 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 aldehyde 68b (0.55 g, 80 % yield)

1H NMR (300 MHz, CDCl₃) 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); 13C NMR (75 MHz, CDCl₃) δ 199.9, 74.4, 74.2, 66.5, 64.4, 42.4, 12.6, 4.3

Dec-2E-ene-6,8-diyanoic 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 °C in Ar. The mixture was stirred for 20 min at 0 °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 NH₄Cl (aq) and extracted with ethyl ether (3x 30 mL), dried (MgSO₄), 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)

1H NMR (300 MHz, CDCl₃) 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-2E-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 °C in Ar. After stirring for 2 h at -78 °C, reaction was quenched with excess of ethylacetate (30 mL) at -78 °C and warmed to room temperature. The mixture was washed with 10% HCl (aq) (10 mL), brine, dried (MgSO₄), 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 CH₂Cl₂ was added dimethylsulfoxide (0.530 mL, 7.48 mmol) dropwise at -78 °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 °C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH₄Cl (aq) and aqueous layer was extracted with CH₂Cl₂ (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)

¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 193.9, 155.4, 134.0, 74.3, 74.3, 67.0, 60.6, 31.4, 18.2, 4.3

**Dodeca-2Z,4E-diene-8,10-diynoic acid isobutylamide (64) and Dodeca-2E,4E-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 °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 °C over 2 h. The reaction was quenched with NH₄Cl (aq), washed with water, brine, dried (MgSO₄), 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 ¹H NMR (300 MHz, CDCl₃) 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), 13C NMR (75 MHz, CDCl₃) 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-6Z-en-4-yn-1-ol (74)

To a solution of Pd(PPh₃)₂Cl₂ (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 °C in Ar. After stirring at room temperature for 2 h, the reaction was quenched with sat NH₄Cl (aq), extracted with ether, washed with brine, and dried (MgSO₄). The residue was purified via flash column chromatography (hexane:ethyl acetate= 2:1) to give compound 74 (545 mg, 88 % yield)

Compound 74 ¹H NMR (300MHz, CDCl₃) 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-6Z-en-4-ynal (75)

To a solution of compound 74 (500 mg, 4.03 mmol) in CH$_2$Cl$_2$ (20 mL) was added PCC (1.56 g, 7.2 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, then Et$_2$O (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 $^1$H 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-2E,8Z-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 °C in Ar. The mixture was stirred for 20 min at 0 °C 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$_4$Cl (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 °C in Ar. After stirring for 2 h at -78 °C, reaction was quenched with excess of ethylacetate (30 mL) at -78°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 to give allylic alcohol (0.430 g, 81 % yield).
To a solution of oxaly chloride (0.498 mL, 5.72 mmol) in 20 mL of CH$_2$Cl$_2$ was added dimethylsulfoxide (0.812 mL, 11.44 mmol) dropwise at -78 °C. 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 °C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH$_4$Cl (aq) and aqueous layer was extracted with CH$_2$Cl$_2$ (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 $^1$H 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-2Z,4E,10Z-trien-8-ynoic acid isobutylamide (65) and Dodeca-2E,4E,10Z-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 °C 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 °C over 2 h. The reaction was quenched with NH$_4$Cl(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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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 °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\(_2\)O (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\(_3\)) \(\delta\) 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-octynoxy)tetrahydropyran (79)

To a solution of compound 78 (0.41 g, 2.95 mmol) in CH$_2$Cl$_2$ (10 mL) was added 3,4-dihydro-2H-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$_2$Cl$_2$ (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$_3$) $\delta$ 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-nonynoxy)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$_2$Cl$_2$, 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$_3$P (1.1 g, 4.2 mmol) in Et$_2$O–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 Et2O (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 NaHCO3, brine, dried (MgSO4), 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**

1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) 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 (El): m/z calcd for C15H25IO2: 364.0899; found: 364.0906.

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

To a solution of K2CO3 (326 mg, 2.36 mmol, freshly dried over P2O5) 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 Et2O (10 mL) and aq NH4Cl (10 mL). The aqueous layer was extracted with CH2Cl2, dried (MgSO4), 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**

1H NMR (300MHz, CDCl3) δ 4.71–4.60 (m, 1 H), 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$_3$) $\delta$ 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-4Z-en-1-yne (82)

To a solution of Ni(OAc)$_2$·4H$_2$O (47 mg, 0.19 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$_3$) $\delta$ 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$_3$) $\delta$ 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-7Z-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$_2$O (5 mL) was added. The aqueous layer was extracted with Et$_2$O, 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-6Z-en-1,3-diyne (84)

To a solution of the bromoacetylene (100 mg, 0.29 mmol), trimethylsilylacetylene (83
mL, 0.58 mmol), (PPh$_3$)$_2$PdCl$_2$ (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 NH$_4$Cl (3 mL)
and the aqueous layer was extracted with Et$_2$O, 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-Trimethylsilyl-tetradec-8Z-ene-11,13-diyne-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 H₂O. The aqueous layer was extracted with Et₂O, washed with aq NaHCO₃, dried (MgSO₄), filtered and concentrated. The residue was dissolved in CH₂Cl₂ (5 mL) and pyridinium chlorochromate (117 mg, 0.56 mmol) was added at room temperature. After 1 h, Et₂O (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 ¹H NMR (300 MHz, CDCl₃) 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-8Z-ene-11,13-diyne-2-one (22)**

To a solution of the diyne (10 mg, 0.036 mmol) in MeOH (2 mL) was slowly added AgNO₃ (8 mg, 0.047 mmol) in H₂O (1 mL) and MeOH (3 mL) at room temperature. After 15 min, KCN (14 mg, 0.216 mmol) in H₂O (2 mL) was added, and the solution was stirred for 10 min. The mixture was extracted with Et₂O, dried (MgSO₄), 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$_3$) $\delta$ 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$_3$) $\delta$ 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 (El) 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$_2$O (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 °C with vigorous stirring for 6 h. The mixture was cooled to room temperature then water (5 mL) was added and extracted with Et$_2$O (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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O (20 mL) was added lithium aluminum hydride (0.330 g, 3.47 mmol) at 0 °C in Ar. After stirring at 0 °C for 2 h, the mixture was warmed to room temperature. To the mixture was added H$_2$O (0.33 mL), 15% NaOH(aq)
(0.33 mL) and H₂O (1 mL) successively at room temperature, then the mixture was filtered and organic layer was washed with H₂O, brine, dried (MgSO₄) 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 CH₂Cl₂ was added dimethylsulfoxide (1.21 mL, 17.0 mmol) dropwise at -78 °C. 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 °C and stirred for 80 min while slowly warmed to room temperature. The reaction was quenched with sat NH₄Cl(aq) and aqueous layer was extracted with CH₂Cl₂ (2x 30 mL). Combined organic layer was washed with water (2x 20 mL), dried (MgSO₄), 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, CDCl₃) 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 °C. The mixture was stirred for 20 min at -78 °C, 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 NH₄Cl (5 mL) and extracted with Et₂O (20 mL). The organic layer was washed with water, brine, dried (MgSO₄) 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$_3$) $\delta$ 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 °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 °C. After 5 min, iodine in THF (2 mL) was added to a mixture then stirred at -78 °C for 30 min. The mixture was warmed to room temperature and quenched with NH$_4$Cl, extracted with Et$_2$O, 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$_3$) $\delta$ 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\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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\(_3\)P (1.44 g, 5.5 mmol) in Et\(_2\)O–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\(_2\)O (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\(_3\)) \( \delta \) 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 PPh₃ (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, CDCl₃) \(\delta\) 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-6Z-ene-9,11-diynyl-[1,3]dioxolane (97)

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

\(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 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, CDCl₃) \(\delta\) 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-diyyn-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 °C for 3 h and extracted with diethyl ether. Organic layer was washed with brine (2x 20 mL), dried (MgSO₄), 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, CDCl₃) \(\delta\) 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, CDCl₃) \(\delta\) 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 °C in Ar. The mixture was warmed to room temperature and stirred for 4 h. The mixture was cooled to -78 °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 NH₄Cl (aq) and aqueous layer was extracted with ethyl ether. Combined organic layer was washed with water, brine, dried (MgSO₄), 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, CDCl₃) 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 °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 (MgSO₄), 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).
\( ^1H \text{NMR (300 MHz, CDCl}_3 \delta \ 6.19 \ (dd, J = 15.9, 6.0 \text{ Hz, 1H}), 5.72 \ (d, J = 15.9 \text{ Hz, 1H}), 4.28-4.10 \ (m, 1H), 3.96-3.87 \ (m, 4H), 1.68-1.47 \ (m, 6H), 1.42-1.32 \ (m, 5H), 1.30 \ (s, 3H), 0.19 \ (s, 9H); ^{13}C \text{NMR (75 MHz, CDCl}_3 \delta \ 147.0, 110.3, 110.0, 72.4, 66.1, 64.8, 39.3, 36.9, 29.8, 25.4, 24.2, 23.9, 15.5, 0.1; HRMS m/e (EI) for } C_{17}H_{30}O_3Si (M)^+ \text{ calcd 310.1964, measured 310.1921.} \)

**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 1 h at room temperature, the mixture was cooled to 0 \(^\circ\)C and cold H\(_2\)O (5 mL) was added. The aqueous layer was extracted with Et\(_2\)O, 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 %)

\( ^1H \text{NMR (300MHz, CDCl}_3 \delta \ 6.19 \ (dd, J = 15.9, 6.0 \text{ Hz, 1H}), 5.67(dd, J = 15.9, 1.5 \text{ Hz, 1H}), 4.15-4.09 \ (m, 1H), 3.95-3.89 \ (m, 4H), 1.70-1.45 \ (m, 6H), 1.43-1.32 \ (m, 5H), 1.29 \ (s, 3H); ^{13}C \text{NMR (75 MHz, CDCl}_3 \delta \ 147.7, 110.3, 109.4, 78.3, 72.2, 66.1, 64.8, 39.3, 36.9, 29.8, 25.4, 24.2, 23.9, 15.5; HRMS m/e (EI) for } C_{14}H_{21}BrO_3 (M)^+ \text{ calcd 316.0674, measured 316.0761} \)

**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 \(^\circ\)C. The mixture was stirred at room temperature for 0.5 h. The reaction was quenched
with 1 mL of sat NH₄Cl (aq) and extracted with ethyl ether (3x 10 mL). Organic layer was washed with brine (2x 10 mL), dried (MgSO₄), 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 %)

_H NMR (300 MHz, CDCl₃) 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); _C NMR (75 MHz, CDCl₃) 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 C₁₀H₁₉O₃Si (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 °C for 3 h and extracted with diethyl ether. Organic layer was washed with brine (2x 20 mL), dried (MgSO₄), 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 °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)

_H NMR (400MHz, CDCl₃) 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); _C NMR (100MHz, CDCl₃) δ  209.4, 150.6, 108.0, 74.3, 73.9, 72.1,
8-Hydroxy-pentadec-9E-ene-11,13-diyne-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 °C 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 °C and the sealed tube was opened. The mixture was slowly warmed to room temperature while excess propyne was evaporated. Sat NH₄Cl (aq) was added to the mixture then extracted with ethyl ether. Organic layer was washed with 10% HCl (aq), brine, dried (MgSO₄), 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 °C for 3 h and extracted with diethyl ether. Organic layer was washed with brine (2x 20 mL), dried (MgSO₄), 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₉O₂ (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. They often enable the generation of multiple stereogenic centers in a single operation. In the context of developing new tandem radical reactions, Kraus et al. discovered a novel tandem reaction involving a Diels-Alder reaction, followed by an ene reaction. Initial study commenced with an attempt to generate bromo aldehyde 3, a precursor for a radical reaction. Diels-Alder reaction between 2-bromoacrolein (1) 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.
In the literature, Heathcock, in his elegant synthesis of *Daphniphyllum* alkaloids, employed a hetero-Diels-Alder/ene sequence. There are also a few examples of tandem Diels-Alder/Diels-Alder reactions and tandem ene/ene reactions. 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. 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.
<table>
<thead>
<tr>
<th>aldehyde</th>
<th>diene</th>
<th>reaction conditions</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCHO</td>
<td>R₃ = Me</td>
<td>toluene 80 °C, 24 h 0 °C to 25 °C, 6 h</td>
<td><img src="image1.png" alt="Product Image" /></td>
<td>56</td>
</tr>
<tr>
<td>HCHBr</td>
<td>R₃ = Me</td>
<td>BF₃OEt₂,Et₂O</td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>82</td>
</tr>
<tr>
<td>HCHMe</td>
<td>R₃ = Me</td>
<td>BF₃OEt₂,Et₂O</td>
<td><img src="image3.png" alt="Product Image" /></td>
<td>77</td>
</tr>
<tr>
<td>HCHO</td>
<td>R₃ = Me</td>
<td>BF₃OEt₂,Et₂O</td>
<td><img src="image4.png" alt="Product Image" /></td>
<td>56</td>
</tr>
<tr>
<td>HCHMe</td>
<td>R₃ = Me</td>
<td>Et₂AlCl, CH₂Cl₂ -78 °C to 0 °C, 2 h</td>
<td><img src="image5.png" alt="Product Image" /></td>
<td>34</td>
</tr>
<tr>
<td>HCHOC₅H₅</td>
<td>R₃ = Me</td>
<td>BF₃OEt₂,Et₂O</td>
<td><img src="image6.png" alt="Product Image" /></td>
<td>46</td>
</tr>
<tr>
<td>HCHO</td>
<td>R₃ = H</td>
<td>BF₃OEt₂,Et₂O</td>
<td><img src="image7.png" alt="Product Image" /></td>
<td>41</td>
</tr>
<tr>
<td>HCO₂S</td>
<td>R₃ = Me</td>
<td>Et₂AlCl, CH₂Cl₂ -78 °C to 0 °C, 2 h</td>
<td><img src="image8.png" alt="Product Image" /></td>
<td>55</td>
</tr>
</tbody>
</table>

Figure 1. Examples of tandem Diels-Alder/ene reaction
3-Bromobut-3-en-2-one $^9$ 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.

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 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.](image_url)

We began our study with the synthesis of triene 15. Pure 2-methyl-3-butenol was heated to 140 °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 \textbf{16} was then treated with the anion formed by reacting diethyl allylphosphonate with \textit{n}-BuLi to afford desired triene \textbf{15}.

\begin{align*}
\text{OH} & \xrightarrow{\text{Hg(OAc)$_2$}} \text{OEt} \\
& \xrightarrow{\text{Ph, 80 °C, 8h}} \text{(EtO)$_2$P} \xrightarrow{\text{n-BuLi, HMPA}} \text{PhH, 80 °C, 8h} \\
& \xrightarrow{\text{Ph$_3$P$^+$CH$_3$Br}, t$-$BuOK}} \text{Ph}_3 \text{P}
\end{align*}

To achieve the key Diels-Alder/ene adduct \textbf{17}, various Lewis acid catalysts and reaction temperature conditions were examined. Successful Lewis acids for the previous reactions, such as BF$_3$ OEt$_2$ and Et$_2$AlCl, 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 \textbf{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/H₂ 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,\textsuperscript{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.

\[ \text{NaOH / EtOH} \quad \text{rt, 4 h} \]

With furan 21 in hand, we continued our synthesis. The conversion of furan 21 into isoligularone required a benzylic oxidation. Although several methods have been advanced for this transformation,\textsuperscript{16} the application of most of these methods [CrO\textsubscript{3}, Pb(OAc)\textsubscript{4}, SeO\textsubscript{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.\textsuperscript{17} The proton NMR and \textsuperscript{13}C NMR spectra for 7 matched the literature spectra\textsuperscript{18} for 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 NaClO₄ and NaH₂PO₄ in H₂O/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 an ester group in the tandem reaction stage could provide a very efficient route to generate acid 24.

\[
\begin{align*}
\text{HO}_2\text{C-} & \quad \leftrightarrow \\
\text{EtO}_2\text{C-} & \\
\text{24} & \quad \text{26}
\end{align*}
\]

Tandem D-A/ene reaction

\[
\begin{align*}
\text{MeAlCl}_2, \text{CH}_2\text{Cl}_2 \\
-78 \degree \text{C to } 0 \degree \text{C, } 2 \text{ h}
\end{align*}
\]

74% yield

Known ester 27 was synthesized by the method of Parker.\(^\text{19}\) When 27 was reacted with \textit{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.

\[
\begin{align*}
\text{MeAlCl}_2, \text{CH}_2\text{Cl}_2 \\
-78 \degree \text{C to } 0 \degree \text{C, } 2 \text{ h}
\end{align*}
\]

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 CDCl₃ (7.27 ppm for ^1^H 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 Å, 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;

^1^H NMR (300 MHz, CDCl₃) 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 NH₄Cl (15 mL). The mixture was extracted with Et₂O (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, 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.

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₀H₁₆(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 Et₂O (3.5 mL) was added MeAlCl₂ (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 Et₂O (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 NH₄Cl (3 mL) and extracted with CH₂Cl₂.
The organic layer was dried over MgSO₄, 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)

1H NMR (300 MHz, CDCl₃) 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); 13C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₄O (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% Na₂S₂O₄ (aq). It was extracted with ethyl acetate (3x 20 mL). The organic layer was dried over MgSO₄, 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 1H NMR (400 MHz, CDCl₃) 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); 13C NMR (100 MHz, CDCl₃) 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_{13}H_{26}O_{2} (M)^{+} calcd 238.1933, measured 238.1928.

**18b** ^1^H NMR (400 MHz, CDCl₃) 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); ^1^C NMR (100 MHz, CDCl₃) 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 H₂ 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, CDCl₃) 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); ^1^C NMR (100 MHz, CDCl₃) 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_{13}H_{26}O_{2} (M)^{+} calcd 238.1933, measured 238.1928.

**Compound 19b** ^1^H NMR (400 MHz, CDCl₃) 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-oxacyclopentyl)-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$_2$Cl$_2$ was added the Dess-Martin periodinane (1.58 g, 3.7 mmol) at 0 °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$_2$S$_2$O$_3$ (aq). It was then extracted with CH$_2$Cl$_2$. 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 MgSO₄, 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 ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₁H₂₂O (M)⁺ calcd 218.1670, measured 218.1665

Compound 22 ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 H₂O, sat NaHCO₃ (aq) and brine.
The organic layer was dried over MgSO₄, 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)

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 196.3, 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 C₁₅H₂₆O₂ (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 °C. The reaction mixture was stirred at 0 °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 (MgSO₄), filtered and concentrated in vacuo. The residue was purified via preparative thin layer chromatography to give compound 23 (50 mg, 80 % yield)

Compound 23 ¹H NMR (300 MHz, CDCl₃) 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 NaClO₄ (54 mg, 0.6 mmol) and NaH₂PO₄ (54 mg, 0.4 mmol) in 2 mL of H₂O 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 MgSO₄, filtered and concentrated in vacuo. The crude product was subjected to next step without purification. (67 % yield)

Compound 24 ¹H NMR (400 MHz, CDCl₃) 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 °C solution of trans-2-methyl-2-butenal (0.10 mL, 1.03 mmol) in Et₂O (3.5 mL) was added MeAlCl₂ (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 Et₂O (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 CH₂Cl₂. The organic layer was dried over MgSO₄, 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 ¹H NMR (300 MHz, CDCl₃) 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)
References


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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