ABSTRACT

SYNTHETIC STUDIES TOWARD ENETRIYNE NATURAL PRODUCTS
& EXAMINATION OF THE SYNTHETIC SCOPE AND
MECHANISM OF DMDS ADDITION TO 1,4-ENYNES

by Gordon Victor Givan

A general, convenient route to enetriyne natural products, exemplified by several Fistulina hepatica metabolites, has been developed. The method is advantageous for the synthesis of conjugated polyynes as compared to traditional methods. The synthetic scheme is highlighted by the coupling of a triyne and alkenyl halide segment by a modified Stille reaction. Three enetriynes were synthesized for comparison with natural products isolated from F. hepatica shake cultures.

The scope and utility of the reaction between DMDS and 1,4-enynes was explored. Successful syntheses of a number of 1,4-enynes were realized in good yield, however, varied yields were obtained for DMDS derivatization of the 1,4-enynes. A tether of less than five methylene groups between distal functional groups and the enyne appears to significantly diminish the formation of 2,5-disubstituted thiophenes. Possible pathways for the mechanism of the reaction were investigated. Current evidence suggests the mechanism for the reaction between DMDS and 1,4-enyne may proceed through either an enyne-MeSI adduct or allene intermediate.
SYNTHETIC STUDIES TOWARD ENETRIYNE NATURAL PRODUCTS &
EXAMINATION OF THE SYNTHETIC SCOPE AND MECHANISM
OF DMDS ADDITION TO 1,4-ENYNES

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LIST OF ABBREVIATIONS

CAN  ammonium cerium(IV) nitrate
m-CPBA  3-chloroperoxybenzoic acid
DIAD  diisopropyl azodicarboxylate
DIBAL-H  diisobutylaluminum hydride
DMAP  4-(dimethylamino)pyridine
DMDS  dimethyl disulfide
DMF  $N,N$-dimethylformamide
DPPA  diphenylphosphoryl azide
EI  electron impact ionization
ESI  electrospray ionization
GC-MS  gas chromatography-mass spectrometry
HMPA  hexamethylphosphoric triamide
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrometry
IR  infrared spectroscopy
LAH  lithium aluminum hydride
LDA  lithium diisopropylamide
MeCN  acetonitrile
p-MPM  $p$-methoxyphenylmethyl
NMR  nuclear magnetic resonance
PE  petroleum ether
PCC  pyridinium chlorochromate
PDC  pyridinium dichromate
RBF  round bottom flask
$R_f$  retention factor (for TLC)
rt  room temperature
TBAF  tetrabutylammonium fluoride
TBDMSCl  $tert$-butyldimethylsilyl chloride
TBDPSCl  $tert$-butyldiphenylsilyl chloride
TFA  trifluoroacetic acid
THF  tetrahydrofuran
THP  2-tetrahydropyranyl
TLC  thin-layer chromatography
TMSCl  trimethylsilyl chloride
$t_R$  retention time (for gas chromatography)
TsCl  tosyl chloride
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I want to give my most heartfelt thanks to my family, especially mom and dad, whose infinite love and support have helped me through the good and bad times. Not a day goes by that I do not give thanks for being blessed with such a wonderful family. Love you all.

Finally, I wanna give a shout out to the crew. Holla. I’m out.

“Free like OJ, all day”

- T. Shakur
Chapter 1. Development of a new synthetic pathway to enetriynes exemplified by the *Fistulina hepatica* metabolite (Z)-3-tridecene-5,7,9-triyne-1,11-diol

1-1. Introduction

In 1892, the first acetylenic compound, tariric acid 1, was isolated from the seed oil of *Picramnia tariri* DC.\(^1,2\) Since then, many classes of naturally occurring acetylenic metabolites have been discovered. One such class of acetylenic secondary metabolites is the polyacetylenes, which possess conjugated triple bonds. Polyacetylenes are common constituents of many natural products and are derived from a broad range of phyla representing plants, fungi, bryophytes, amphibians, and algae as well as marine and terrestrial microorganisms.\(^3\) Antiviral and antitumor activities have been attributed to many of these metabolites.\(^3-5\) Some examples of naturally occurring linear polyacetylenes with diverse biological activities are illustrated in Scheme 1. Cicutoxin 2 is a neurotoxin found in water hemlock,\(^6\) while the *Ochanostachys amentaca* metabolite minquartynoic acid 4 possesses antitumor properties.\(^7\) Compound 3 is commonly found in the Asteraceae family, especially in tribes Cynareae and Heliantheae.\(^8\) Work on *Artemisia vulgaris* L. and related species resulted in the unambiguous identification of 5 and 6.\(^9\) Polyacetylenes with ene-tetrayne-ene, ene-triyne-diene 7, and triynediene chromophores are characteristic of the genus Dahlia.\(^10\)

In fact, over 600 naturally occurring acetylenic compounds had been isolated by 1970, largely from plants and basidiomycete fungi.\(^11\) Approximately 70% of the fungal acetylenes contain 9 or 10 carbon chains. Included among these simple polyacetylenes are derivatives that possess antimicrobial activities (Scheme 2). Agrocybin 8 is a phytotoxic compound responsible for killing grass in fairy rings, *Marasmius oreades*.\(^12\) Biformin 9 and marasin 10 have been reported to be active against some kinds of bacteria and fungi.\(^13-16\)

In 1966, Jones *et al.* isolated five metabolites produced by the fungus *Fistulina hepatica* (beefsteak mushroom).\(^17\) Each was a polyyne with an unbranched 10 and 13 carbon chain (Scheme 3). The tetraol (15) exhibited modest antibacterial activity comparable to cephalosporin C against *Staphylococcus aureus* (Oxford strain) and *Salmonella typhi* (strain Miss S.).
Scheme 1. Selected examples of naturally occurring polyacetylenes

1. MeO\(\text{C(C\(\equiv\)C)}_3\text{H}_9\)

2. HO\(\text{C(C\(\equiv\)C)}_2\text{H}_7\text{OH}\)

3. H\(_3\text{C}\)\text{C(C\(\equiv\)C)}_3\text{H}_2\text{OH}\)

4. OH\(\text{C(C\(\equiv\)C)}_2\text{H}_7\text{CO}_2\text{H}\)

5. H\(_3\text{C}\)\text{C(C\(\equiv\)C)}_2\text{E/Z}\text{H}_3\text{CO}_2\text{H}\)

6. H\(_3\text{C}\)\text{C(C\(\equiv\)C)}_3\text{E/Z}\text{H}_3\text{CO}_2\text{H}\)

7. H\(_3\text{C}\)\text{C(C\(\equiv\)C)}_2\text{H}_3\text{CO}_2\text{H}\)

Scheme 2. Examples of simple biologically active polyyne natural products

Agrocybin (8) Biformin (9) Marasin (10)
Additional work on *F. hepatica* has been done by Farrell. Farrell reported the isolation of two additional compounds from culture extracts (Scheme 4, 16 and 17). Cinnatriacetin A and B isolated from *F. hepatica* fruiting bodies have also been reported (Scheme 4, 18 and 19). They were active against gram positive bacteria, however, they proved inactive against gram negative bacteria, yeast, and other fungi. The isolation of cinnatriacetin was unique in that it contained a cinnamate moiety and a C14 polyacetylene chain, which is very uncommon from the Basidiomycete fungi.

Scheme 3. *Fistulina hepatica* metabolites isolated by original Jones

![Chemical structures](image)

Recent work by our group revealed through time-course analysis that at least 20 polyenynes, all of which are thought to be biosynthetically related, are produced by *F. hepatica*. 3
Polyenynes produce intense, distinct ultraviolet (UV) spectra unique to each conjugation pattern. As such, UV spectroscopy is an extremely valuable tool in detecting the presence of polyenynes in solution. Even with optimized culture conditions, these metabolites are typically produced by *F. hepatica* in quantities of only 0.1 mg/L to 2 mg/L. Because of the extremely low recoveries, an efficient synthetic procedure was sought for both biological testing and structure verification.

Scheme 4. Additional metabolites isolated from *Fistulina hepatica*.

It was our goal to synthesize one such metabolite, (Z)-3-tridecene-5,7,9-triyne-1,11-diol 20 (Scheme 5). The isolation and characterization of a compound that was tentatively assigned this structure had been reported by Huffman based on LC-MS, UV, and $^1$H NMR spectroscopic data. A comparison of the synthetic compound with the natural product can then be made to verify the structure of 20. Upon development of a generalized, convergent synthetic route to various Fistulina metabolites, the biological properties, biosynthesis, and antibacterial
effectiveness of these polyynes may be studied more comprehensively. A desirable procedure
will have sufficient flexibility to allow the synthesis of other widely-found enetriyne structures.

Scheme 5. Initial synthetic target: \((Z)\)-3-tridecene-5,7,9-triyne-1,11-diol \(^3\)

Several methods are available for the synthesis of polyenynes. Mainly, these include the
use of Cu(I)/Cu(II) catalysts for oxidative homocoupling of terminal acetylenes\(^{20-22}\) or Pd-
catalyzed cross-coupling reaction of terminal acetylenes with alkynyl bromides or iodides.\(^{22-24}\)
Each method has potential disadvantages for the synthesis of unsymmetrical polyynes including
production of complex mixtures of products and manipulation of highly unstable acetylenic
precursors. A recently developed methodology for the synthesis of tetraacetylenic compounds
utilizes a three component Cadiot-Chodkiewicz reaction to avoid diyne or triyne
intermediates.\(^{25,26}\) On the other hand, the convergent coupling of vinyl and acetylenic segments,
where the triyne is prepared using the Tykwinski modification of the FBW rearrangement, is
easily accessible for a wide variety of starting materials.\(^{27}\) The Tykwinski rearrangement
provides a convenient route to functionalized triynes without the production of complex mixtures
or isolation of very unstable terminal polyacetylenes.\(^{28}\) Published examples of this
rearrangement methodology have focused upon the preparation of materials with novel
electronic and optical properties.\(^{27,29,30}\) The scope and utility of the Tykwinski method has not
been fully explored for oxygenated, functionalized intermediates and could provide
complications in the syntheses of triyne segments in natural products. A modified Stille method
for coupling of stannanes to haloalkenes should provide for the construction of the enetriyne
backbone. The limited precedent for use of the Stille reaction in triyne-alkenyl halide coupling
presents a new area of exploration.

This chapter explores the convergent assembly of alkene and polyyne building blocks
from inexpensive, commercially available starting materials leading to structure \(20\) and analogs.
Multiple entry points through simple precursors will be advantageous for radiochemical
syntheses. Good yields and stereocontrol of the alkene are generally possible by the Stille procedure with an appropriate catalyst system. A differential protection scheme was devised that may be useful in the synthesis of other derivatives, such as carboxylic acids.

1-2. Results and Discussion

1-2.1 Synthesis of (Z)-3-tridecene-5,7,9-triyne-1,11-diol

It was hypothesized that a convergent synthesis using the Tykwinski modification of the Fritisch-Buttenberg-Wieshell (FBW) rearrangement would be a flexible, efficient pathway to the Fistulina natural products. Retrosynthetic analysis of a polyenyne, proposed as the structure of a natural product isolated by Huffman, is outlined in Scheme 6. The target diol (20) was to be formed by a Stille coupling of the cis-butene-1-ol derivative (21) and the Bu₃Sn-triyne (22). Triyne segment 22 was further disconnected into trimethylsilylpropynal 23 and terminal acetylene 24, which were to be coupled through lithiation of 24 and subsequent addition to 23 to form the basis of the triyne backbone.

Scheme 6. Retrosynthesis of (Z)-3-tridecene-5,7,9-triyne-1,11-diol

A primary requirement in the proposed synthesis was easy access to trimethylsilylpropynal 23. This was achieved by the preparation of 3-trimethylsilylprop-2-ynol 26 from propargyl alcohol 25 as described in the literature. The oxidation of 26 was performed using a literature method, which employed K₂CrO₄ dissolved in H₂SO₄ and a phase-transfer catalyst, tetrabutylammonium hydrogen sulfate (Scheme 7).
Scheme 7. Preparation of trimethylsilylpropynal 23

\[ \text{Reagents and conditions: (a) (i) EtMgBr, THF, (ii) TMSCl, (iii) 1.4 M } \text{H}_2\text{SO}_4, 20 \, ^\circ\text{C}; \) (b) \((n-\text{Bu})_4\text{N}^+\text{HSO}_4^{-}, \text{K}_2\text{CrO}_4, \text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C}\]

However, the reported distillation of 23 proved difficult due to polymerization and violent bumping of the distillate. An effective and reliable purification utilized flash column chromatography (10:1 PE/Et\textsubscript{2}O), even though a lower yield than that obtained in the literature was found. A short plug of silica and a fast flow rate were essential as the acetylenic aldehyde readily decomposed upon contact with silica. With these precautions, purification by flash column chromatography produced a consistent yield of 55-60%. The crude TMS-aldehyde, obtained in 86% yield, was tested in the subsequent acetylide anion additions but resulted in unsatisfactory yields. Drying the crude TMS-aldehyde over molecular sieves or MgSO\textsubscript{4} did not improve the viability of the crude TMS-aldehyde for alknylations.

A second concern early in our studies was the choice of alcohol protecting groups for the commercially available starting alkynols. Various ether and silyl ether protective groups were explored, namely TBDMS, \(p\)-MPM, and TBDPS. Through preliminary experiments, the first two protective groups proved incompatible with most methods for 1,1-dibromoalkene formation. As reported by Mattes, TBDMS protected alcohols when treated with CBr\textsubscript{4} and PPh\textsubscript{3} in dichloromethane yielded a mixture of two compounds.\(^{33}\) The mixture was comprised of the dibromoalkene product and the compound resulting from the replacement of the TBDMS ether with bromide. Similar results were observed with our TBDMS ether as cleavage to the alkyl bromide by the triphenylphosphine dibromide occurred. Furthermore, \(p\)-MPM ethers consistently gave lower reaction yields for each step leading up to the dialkynyl ketone and were also problematic under Corey-Fuchs reaction conditions in that no dibromoalkene formation was observed by \(^1\text{H} \text{NMR} \text{spectroscopy.} \) TBDPS was found to be an effective protective group as little to no premature cleavage occurred throughout the sequence, leading to acceptable yields.
Two methods were used for the protection of the terminal alkynol. The first method used pyridine, in conjunction with DMAP, as the base. This method gave yields of 85-95% but residual tert-butylchlorodiphenylsilane (TBDPSCl) was not easily eliminated, although many attempts were made by flash column chromatography. The second method, which was used later in the project, involved using imidazole as base. This method was found to work best as purification was easier and a quantitative yield was obtained.

The lithiation of the protected terminal alkyne (24) and the subsequent coupling reaction with purified TMS-aldehyde 23 to form secondary alcohol 27 were straightforward (Scheme 8). Alkyne 24 was reacted with n-BuLi at -78 °C in THF, which was followed by the addition of 23 in THF at -78 °C. The reaction was then warmed to 0 °C for an additional period of time. The best yields were obtained by decreasing the lithiation time at -78 °C to 15 min and the reaction time after addition of the TMS-aldehyde to 30 min versus similar literature methods. Under the aforementioned conditions, an 83% yield was obtained.

Secondary alcohol 27 was then oxidized for 1.5 h using 3 weight equivalents (min.) of manganese dioxide. This was an extremely facile and clean reaction with no purification necessary after vacuum-filtration through a pad of Celite. A crude yield of 95% was obtained for ketone 28. The next step in the synthesis, formation of the dibromoalkene 29, proved difficult and a number of potential methods were explored. Details will be discussed below, but for now, let it suffice to say that the Corey-Fuchs method using a mixture of CBr₄ and PPh₃ proved to be the optimal approach and formed dibromoalkene 29 in 69% yield. Executing a successful FBW rearrangement to the triyne constituted a second major hurdle in the synthesis and its development will be discussed in detail later in this section. After substantial optimization attempts, 29 was efficiently converted to the corresponding triyne (30) using n-BuLi in anhydrous hexanes in an 83% yield (Scheme 8). Upon reaction with tributyltin oxide and a catalytic amount of tetrabutylammonium fluoride, 30 was converted to the Bu₃Sn-triyne (22).

(Z)-Haloalkene 21a, the second fragment for the Stille coupling, was synthesized from readily available materials through literature methods, which will be discussed in detail in a later section. Since the target molecule (20) was a diol, protection of the hydroxyl functionality in iodoalkene 21a before coupling was expected to be necessary, as the hydroxyl group was close enough to the coupling locus to potentially interfere with the assembly. It was our goal to be able to sequentially deprotect the diol at the end of the synthesis, which increases the flexibility
of the synthesis. To this effect, the (Z)-haloalkene 21a was protected with the acid-sensitive THP group which is orthogonal to a bulky silyl ether.\textsuperscript{39}

Scheme 8. Synthetic route to triyne 30\textsuperscript{a}

\textsuperscript{a} Reagents and conditions: (a) TBDPSCl, imidazole, CH\textsubscript{2}Cl\textsubscript{2}; (b) (i) n-BuLi, THF -78 °C, (ii) 23, THF; (c) MnO\textsubscript{2}, hexanes, rt; (d) CBr\textsubscript{4}, PPh\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}; (e) n-BuLi, hexanes, -78 °C to -10 °C

With segments 21a and 22 in hand, the completion of the enetriyne skeleton could be undertaken (Scheme 9). Optimization of the reaction conditions was necessary and is detailed in a later section. The best reaction conditions found were 5 mol% Pd(dbam)\textsubscript{2} and 10 mol% P(furyl)\textsubscript{3} in THF. When 1.25 equivalents of 22 were used, a 56% yield of the ene-triyne (31) was obtained. The stepwise deprotection of the enetriyne backbone led to the corresponding diol (20). Dowex-50W resin was used to remove the THP group to yield 32, which was used without purification. Finally, desilylation with an equimolar amount of TBAF at 0 °C gave 20 in 54% yield over the two deprotection steps. A 14% overall yield of 20 was obtained with six purifications being performed over nine steps.
Scheme 9. Formation and deprotection of the enetriyne backbone of 20

\[ \text{OTBDPS} + \text{SnBu}_3 \xrightarrow{\text{a}} \text{56\%} \text{OTBDPS} \]

\[ \text{22} \xrightarrow{\text{b}} \text{32} \]

\[ \text{54\% over b and c} \]

\[ \text{20} \]

\[ \text{TBAF, THF, 0 °C} \]

\[ \text{Reagents and conditions: (a) 21a, Pd(dba)}_2, \text{P(furyl)}_3, \text{THF; (b) Dowex-50W, MeOH/Et}_2\text{O; (c) TBAF, THF, 0 °C} \]

1-2.2 Formation of dibromoalkene

Ketone 28c was synthesized to explore optimized conditions in the formation of the dibromoalkene compounds. However, the transformation of ketone 28c to geminal dibromoalkene 29c proved difficult, and required a considerable amount of time to develop a satisfactory route. Ketones had been reported to be more difficult than aldehydes upon which to effect the formation of dibromoalkenes. As previously mentioned, the Corey-Fuchs reaction, in which carbon tetrabromide and triphenylphosphine are used, was originally employed. Initial attempts proved unsuccessful with TBDMS silyl ethers and alternative approaches were then sought. At this point it was not known that a TBDPS ether could withstand the reaction conditions. In fact, the TBDPS ether (28c) directly gave a 55% yield, which was similar to literature values for related CBr\textsubscript{4}/PPh\textsubscript{3} reactions. Prior to the identification of this method, a comparison of the different reactions available for the formation of geminal dibromoalkenes were explored using the TBDPS protecting group (Scheme 10).

The first alternative to the CBr\textsubscript{4}/PPh\textsubscript{3} method was a direct Wittig approach in which a standard base-formed ylide was reacted with the ketone. Michel had reported a similar reaction
in the conversion of aldehydes to terminal alkynes via intermediate dibromoalkenes. A slight excess of dibromomethyltriphenylphosphine was reacted with \( t\)-BuOK in THF at rt, followed by the addition of aldehyde. The required dibromomethyltriphenylphosphine bromide was synthesized in acetonitrile according to Wolkoff. The level of water present in the reaction mixture is critical to the success of the Wolkoff method, although this parameter was not addressed in the original reference. It was found that the addition of 2% \( \text{H}_2\text{O} \) (v/v) resulted in a 68% yield. Before use, the Wittig salt was dried by heating under vacuum in a drying pistol warmed by refluxing xylenes. It was initially found that Michel’s method worked for the formation of geminal dibromoalkene \( 29c \), but not very effectively. A series of experiments were then conducted to optimize the conditions for the Wittig reaction to form dibromoalkene \( 29c \). Acetophenone was used as the model ketone for all optimization reactions. First, the temperature used during the deprotonation of the phosphonium salt was varied between -78 °C and +25 °C, with formation of the ylide occurring most readily at rt. The use of different bases was explored next. \( t\)-BuOK, NaHMDS, NaH, and \( n\)-BuLi in THF solution were all employed with \( n\)-BuLi proving best. THF/HMPA and \( \text{Et}_2\text{O} \) had proven effective in other Wittig reactions carried out in our lab, but neither offered any additional benefits in this particular instance. To summarize, the use of \( n\)-BuLi in THF at rt gave a 49% optimized yield of \( 29c \) from the base-generated ylide reaction.

As a second alternative, Normant had reported a three-step sequence utilizing gem-trihalomethyl intermediates for the efficient transformation of linear and cyclic alkyl ketones to geminal dibromoalkenes. Normant’s sequence was followed directly with the exception of using the Lewis acid catalyst, \( \text{CeCl}_3 \), for the activation of the carbonyl group in place of \( \text{BF}_3 \cdot \text{Et}_2\text{O} \). The Normant strategy relied on the formation of a reactive carbanion via reaction of lithium diisopropylamine (LDA) and bromoform (CHBr)\( _3 \). The addition to the activated ketone was carried out at -100 °C resulting in a gem-tribromomethyl tertiary alcohol \( 33 \), which was used directly without further purification. The alcohol was transformed into the corresponding geminal tribromomethyl ester \( 34 \) by reacting with isopropenyl acetate and \( p\)-TsOH·\( \text{H}_2\text{O} \) at 30 °C. Finally, the formal elimination of BrOAc from \( 34 \) yielded the geminal dibromoalkene \( 29c \), a process mediated by 1 equivalent of ethylmagnesium bromide (EtMgBr) at -78 °C for 30 min. The overall yield for the three step sequence was 53%.
In summary, the use of TBDPS ether as the protecting group allowed the use of three different approaches to 29c in comparable yields, with CBr₄/PPh₃ being the easiest and most direct route.

It was our thought that perhaps tribromo ester 34, accessible by Normant’s method, could be converted directly to triyne 30c via geminal dibromoalkene 29c in a one pot process. However, all attempts at this transformation were unsuccessful (Scheme 11). Normant had originally used 4 equivalents of EtMgBr to affect the formation of dibromoalkene, but the temperature of the reaction was maintained at -95 °C for 30 min and the mixture was quenched at -100 °C. As reported earlier, the elimination of 34 to 29c was found to work using 1 equivalent of EtMgBr in THF at -78 °C. When more than 1 equivalent of EtMgBr was used in THF and the temperature was warmed from -78 °C to -10 °C, as required for triyne formation, protonated intermediate 36 (Scheme 12) was observed with little to no rearrangement observed. While the formation of the geminal dibromoalkene was possible under these conditions, it was known through Tykwinski’s work that the FBW rearrangement would not occur in THF. Therefore, it was thought that the most likely conditions for a one-pot process would be to use 2 equivalents of n-BuLi in hexanes as the temperature was increased from -78 °C to -10 °C in 30
min. One equivalent of \( n \)-BuLi would be necessary for dibromoalkene formation, followed by an additional equivalent of \( n \)-BuLi to initiate metal-halogen exchange of 29c. However, under this set of conditions, a complex mixture of 3-4 side-products was observed by \( ^1H \) NMR spectroscopy that could not be separated by chromatography and analyzed due to their similar \( R_f \) values.

Scheme 11. Attempted conversion of 34 to triyne 30c in one-pot process

![Scheme 11. Attempted conversion of 34 to triyne 30c in one-pot process](image)

1-2.3 Triyne Rearrangement

The variation of Fritisch-Buttenberg-Wiechell rearrangement as reported by Tykwinski for use with dialkynyl alkenes was a technically difficult step in the synthetic scheme.\(^{27}\) At the outset, it was unknown through Tykwinski’s publications whether the TBDPS terminal group would be compatible with the rearrangement. In other words, the effect of steric and/or electronic differences around the alkene, particularly for more functionally rich derivatives, was unknown. Numerous rearrangement attempts were originally made on dibromoalkene 29c. It was observed that the metal-halogen exchange proceeded without complication, but protonation of the lithiated intermediate (35) prior to rearrangement regularly occurred resulting in a mixture of bromoalkenes 36. Since attempts with 29c were met with resistance, the corresponding alkyl dibromoalkene (29b) was synthesized (Scheme 13). At about the same time, it was found that the TBDPS was not the problem.

Scheme 12. Protonation of lithiated intermediate during FBW rearrangement

![Scheme 12. Protonation of lithiated intermediate during FBW rearrangement](image)
Through helpful discussions with Tykwinski,\textsuperscript{45} it was felt that the most likely difficulty was the reaction’s extreme sensitivity to moisture. By recharging the H$_2$SO$_4$ nitrogen bubbler and KOH trap used to purify our N$_2$ and flushing the nitrogen line while heating, the successful rearrangement to the triyne was realized in good yield both for examples of $n$-propyl and TBDPS precursors (30b and 30c). It followed that extreme care should be taken to ensure scrupulously dry reaction conditions. To this effect, all glassware was flame-dried and cooled under a stream of nitrogen gas. A functional, uncontaminated nitrogen line was essential, with preferably, no other reactions run simultaneously on the nitrogen line.

During the course of the rearrangement, $n$-BuLi was reacted with the geminal dibromoalkene (29) in anhydrous hexanes at -78 °C. As reported in Tykwinski’s later publications,\textsuperscript{29,30} the best yields were obtained by warming the reaction from -78 °C to -10 °C over 30 min. Typical yields for rearrangements leading to 30 and related oxygenated triynes ranged from 70-85%, which were comparable to the reported literature values. As previously reported, the choice of solvent was very important to the success of this reaction.\textsuperscript{27} Reactions in THF, irregardless of temperature, resulted in a protonated intermediate, in similar fashion to 36, presumably due to the basicity of the intermediate. Hexanes, with its poor solvating ability, favor the initiation of the FBW rearrangement.\textsuperscript{27}

The close relationship between the *F. hepatica* metabolites and those of many other plants and fungi required for the rearrangement to be an effective, yet broad method for formation of the triyne backbone. These new examples proved informative as we were able to expand on the original ideas of Tykwinski to produce oxygenated triyne skeletons.
Scheme 13. Syntheses of additional triynes 30b-e

\[
\text{24b-e} \xrightarrow{a} \text{27b-e} \xrightarrow{b} \text{28b-e} \xrightarrow{c} \text{29b-e} \xrightarrow{d} \text{30b-e}
\]

\[\text{b R = } n\text{-propyl} \]
\[\text{c R = } \text{TBDPSO} \]
\[\text{d R = } \text{TBDPSO} \]
\[\text{e R = } n\text{-butyl} \]

\(^a\) Reagents and conditions: (a) (i) \(n\)-BuLi, THF, -78 °C, (ii) 23, THF, -78 °C to 0 °C; (b) MnO\(_2\), hexanes; (c) CBr\(_4\)/PPh\(_3\), CH\(_2\)Cl\(_2\); (d) \(n\)-BuLi, hexanes, -78 °C to -10 °C

Table 1. Yields for compounds 27-30

<table>
<thead>
<tr>
<th>Compound</th>
<th>27 (^a) Yield (%)</th>
<th>28 (^b) Yield (%)</th>
<th>29 (^a) Yield (%)</th>
<th>30 (^a) Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>83</td>
<td>76</td>
<td>63</td>
<td>76</td>
</tr>
<tr>
<td>c</td>
<td>93</td>
<td>83</td>
<td>55</td>
<td>83</td>
</tr>
<tr>
<td>d</td>
<td>76</td>
<td>89</td>
<td>59</td>
<td>82</td>
</tr>
<tr>
<td>e</td>
<td>79</td>
<td>54</td>
<td>83</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after flash column chromatography

\(^b\) Crude yield after vacuum filtration through a pad of Celite

1-2.4 Syntheses of (Z)-haloalkenes

(Z)-Haloalkene fragments (21a-c) for the Stille coupling convergent synthesis were synthesized from readily available materials through literature methods (Scheme 14). Iodination of tetrahydro-\(2H\)-pyran-2-yl (THP)-protected 3-butyn-1-ol 37 with \(n\)-butyllithium and iodine afforded iodoalkyne 38 in an 83\% yield after flash column chromatography. Iodoalkyne 38 was
then subjected to a stereospecific hydroboration to produce 21a in a 66% isolated yield.\textsuperscript{5}

Haloalkenes 21b and 21c were synthesized in identical fashion through the reduction of the respective ethyl esters 39b,c with LiAlH\textsubscript{4} and subsequent reaction of alcohols 40b,c with dihydropyran to give the THP-protected haloalkenes.\textsuperscript{39,46}

Scheme 14. Syntheses of haloalkenes\textsuperscript{a}

\[
\begin{align*}
\text{THPO} & \quad \text{THPO} \quad \text{THPO} \\
\text{37} & \quad \text{38} & \quad \text{21a} \\
\text{X} & \quad \text{X} \quad \text{X} \\
\text{39b or c} & \quad \text{40b or c} & \quad \text{21b: } X = \text{I} \\
& & \quad \text{21c: } X = \text{Br}
\end{align*}
\]

\textsuperscript{a} Reagents and conditions: (a) (i) \textit{n}-BuLi, THF, -78 °C, (ii) I\textsubscript{2}, THF; (b) (i) cyclohexene, Me\textsubscript{2}S-BH\textsubscript{3}, (ii) AcOH, 2-aminoethanol; (c) (i) LiAlH\textsubscript{4}, Et\textsubscript{2}O, 0 °C, (ii) H\textsubscript{2}O; (d) dihydropyran, \textit{p}-TsOH, CH\textsubscript{2}Cl\textsubscript{2}

1.2.5 Formation of enetriyne backbone

With the protected triyne segment completed, the coupling of the triyne and vinyl halide segment to form the complete enetriyne backbone was explored. It was anticipated that this could be accomplished using a variation on Stille’s method,\textsuperscript{47-49} in which a TMS-triyne (e.g. 30) would be converted to a Bu\textsubscript{3}Sn-triyne by a transmetallation and subsequently coupled to the appropriate (Z)-haloalkene (21). Prior to the Stille coupling, the terminal diyne and triyne species was protected with trimethylsilyl (TMS) for stability. Terminal or Bu\textsubscript{3}Sn- triynes are too susceptible to decomposition and undesirable side reactions to manipulate through a multi-step synthesis.\textsuperscript{28}

Sn-Si Exchange

The TBDPS ether in our triyne presented a potential problem in the Sn-Si exchange. According to Buchwald, Sn-Si exchange using a catalytic amount of TBAF and 0.5 equivalents
(Bu₃Sn)₂O in THF at 60 °C, can be effected in good yield. However, due to the potentially labile TBDPS protecting group, the reaction was carried out at room temperature for 3.5 h. Since the TMS alkynyl group is more readily displaced by F⁻ than the TBDPS ether, minimal cleavage of the TBDPS ether occurred. Carbon-13 NMR spectra of the crude Bu₃Sn-triyne (22) showed effective exchange as signaled by the appearance of tin satellite peaks. Crude 22, after *in vacuo* removal of the solvent, was used directly in the Stille coupling without further purification.

### Stille Coupling

According to the sole literature precedent, synthesis of (-)-ichthyothereol, 10 equivalents of crude Bu₃Sn-triyne were used during the Stille coupling. Unlike the published example, the triyne fragment in our synthesis was the more precious component and such an excess was not desirable. Therefore, 1.25 equivalents of crude Bu₃Sn-triyne 22, based on limiting (Z)-iodoalkene 21, were used in the Stille reaction. The initial conditions employed in the Stille coupling, 5 mol % PdCl₂(PPh₃)₂ (based on iodoalkene 21) in THF did not prove very successful.

Experiments to optimize the Stille coupling by varying the catalyst and solvent were performed. From the literature, plausible catalysts included PdCl₂(PPh₃)₂, Pd(CH₃CN)₂Cl₂, and Pd(dba)₂/triphenylarsine. In the last case, AsPh₃ was shown to be effective in increasing the yield and accelerating the reaction rate 10²-10³ fold over triphenylphosphine ligands. Kinetic data showed evidence that the ease by which a ligand dissociates from the proposed Pd(II) intermediate to form a Pd-stannane π-complex is reflected in the rate-determining transmetallation step. Poor electron-donor ligands, such as AsPh₃ and tri-2-furylphosphine (P(furyl)₃), dissociate more readily than PPh₃. This set of optimization experiments is summarized in Table 2. It was found that the use of Pd(dba)₂/AsPh₃ in THF (Table 2, Entry 5) improved the yield significantly (44%) over the other two conditions in either THF or DMF (7-18%). A second set of optimization experiments were then performed to determine the effect of decreasing the amount of palladium and increasing the amount of AsPh₃. Due to the toxicity of AsPh₃, an additional experiment was set up to determine if P(furyl)₃ could be used in place of AsPh₃ (Table 2). From these experiments, it was found that by decreasing the amount of palladium, the yield of the reaction decreased (Table 2, Entry 7). Also, increasing the amount of AsPh₃ beyond 10% had no meaningful effect on the reaction (Table 2, Entry 8). Most notably,
however, was the successful substitution of AsPh$_3$ with P(furyl)$_3$, which resulted in coupling yields of 25% to 28%, respectively (Table 2, Entry 9). The use of $N$, $N$-dimethylformamide (DMF) as solvent was considered in the PdCl$_2$(PPh$_3$)$_2$ and Pd(CH$_3$CN)$_2$Cl$_2$ cases.$^{47,49}$ The use of DMF as a solvent (~10%) with either of the catalysts did not prove as successful as THF (~20%).

Table 2. Optimization of catalysts and solvent for Stille coupling $^{a,b}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst(s)</th>
<th>Solvent</th>
<th>% Yield $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% PdCl$_2$(PPh$_3$)$_2$</td>
<td>THF</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>5% PdCl$_2$(PPh$_3$)$_2$</td>
<td>DMF</td>
<td>8%</td>
</tr>
<tr>
<td>3</td>
<td>5% Pd(CH$_3$CN)$_2$Cl$_2$</td>
<td>THF</td>
<td>18%</td>
</tr>
<tr>
<td>4</td>
<td>5% Pd(CH$_3$CN)$_2$Cl$_2$</td>
<td>DMF</td>
<td>7%</td>
</tr>
<tr>
<td>5</td>
<td>5% Pd(dba)$_2$, 10% AsPh$_3$</td>
<td>THF</td>
<td>44%</td>
</tr>
<tr>
<td>6</td>
<td>5% Pd(dba)$_2$, 10% AsPh$_3$</td>
<td>THF</td>
<td>25%</td>
</tr>
<tr>
<td>7</td>
<td>1% Pd(dba)$_2$, 10% AsPh$_3$</td>
<td>THF</td>
<td>12%</td>
</tr>
<tr>
<td>8</td>
<td>5% Pd(dba)$_2$, 20% AsPh$_3$</td>
<td>THF</td>
<td>28%</td>
</tr>
<tr>
<td>9</td>
<td>5% Pd(dba)$_2$, 10% P(furyl)$_3$</td>
<td>THF</td>
<td>28%</td>
</tr>
</tbody>
</table>

$^a$ 0.236 mmol of crude Bu$_3$Sn-triyne were used in 1.85 mL of the indicated solvent for entries 1-5. 0.308 mmol of crude Bu$_3$Sn-triyne were used in 2.4 mL of the indicated solvent for entries 6-9.

$^b$ All reactions were stirred in the dark at rt for 16 h

$^c$ Isolated yield after flash column chromatography

The effect of the leaving group in the (Z)-alkenyl halides was investigated. It was found that bromoalkene 21c did not react with the Bu$_3$Sn-triyne (Table 3, Entry 1). A final large-scale comparison including 10 mol% AsPh$_3$ or 10 mol% P(furyl)$_3$ in a coupling reaction with 22d and
5 mol% Pd(dba)$_2$ in THF was performed (Table 3, Entries 2 and 3). The P(furyl)$_3$ reaction gave a considerably higher yield at 61% versus 41% for the AsPh$_3$. Hence, conditions for the Stille coupling were optimized and as reported in the synthesis of 20.

Table 3. Optimization of halogen leaving group for Stille Coupling $^{a,b}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>X =</th>
<th>Catalyst(s) $^c$</th>
<th>Solvent</th>
<th>% Yield $^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>Pd(dba)$_2$, AsPh$_3$</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>Pd(dba)$_2$, AsPh$_3$</td>
<td>THF</td>
<td>36-41%</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>Pd(dba)$_2$, P(furyl)$_3$</td>
<td>THF</td>
<td>61%</td>
</tr>
</tbody>
</table>

$^a$ 0.770 mmol of crude Bu$_3$Sn-triyne was used in 6.0 mL THF

$^b$ All reactions were stirred in the dark at rt for 16 h

$^c$ 5% Pd and 10% of AsPh$_3$ or P(furyl)$_3$ were used

$^d$ Isolated yield after flash chromatography

Improved yields were observed for reactions carried out on larger scales (~1.75 mmol) than the optimization experiments, but results varied between sets of coupling partners. A 56% isolated yield for secondary TBDPS ether 31 (Scheme 9) was obtained, whereas primary TBDPS ether 41 proceeded in 71% (Scheme 16). A very large excess (10 equivalents) of Bu$_3$Sn-triyne was used in the literature example, therefore, our optimized yields were much higher than the ichthyothereol precedent per mmol triyne.

It should be noted that no (E,Z)-isomerization of the allylic alcohol was evident in the crude $^1$H spectra of coupling products. It was found that the use of CDCl$_3$ as the NMR solvent affected the degree of isomerization in the alkenes, particularly the allylic alcohols and their derivatives (e.g. 41). The presence of dissolved HCl in the CDCl$_3$ NMR solvent was thought to
be the cause for the observed isomerization. When discovered, all subsequent NMR spectra were obtained using acetone-\(\text{d}_6\) as the NMR solvent.

### 1-2.6 Deprotection of enetriyne backbone

With the assembly of the enetriyne backbone completed, our focus moved to selectively deprotecting the TBDPS and THP groups. Orthogonal deprotection was desirable that may ultimately allow for the preparation of carboxylic acids 42 and 44-45 and ketone 43 derivatives of the diols (Scheme 15). These more highly oxidized polyacetylenes are commonly observed as natural products and often have substantial biological activities.

Initially, desilylation proceeded with mixed results. It was found that the addition of an equimolar amount of TBAF at rt led to the decomposition of the sensitive enetriyne backbone. The addition of TBAF at 0 °C and stirring for 2 h at 0 °C gave better results in that fewer side products were observed by \(^1\text{H}\) NMR spectroscopy, but reaction times and yields (35-90%) of 46 varied considerably between reactions for unknown reasons (Scheme 16). Incomplete reactions after 2 h were observed in some instances, highlighting the importance of monitoring the reaction course by TLC. Removal of the THP protecting group to produce 32 proved less difficult and more reliable through the use of Dowex-50W resin in a 3:1 mixture of MeOH/Et\(_2\)O. The Et\(_2\)O was required due to the poor solubility of the compounds in MeOH. Near quantitative yields, often recounted in the literature, were not attained, presumably due to the acid-sensitivity of the enetriyne backbone. A maximum yield of 39% was attained from several purification attempts by flash column chromatography with silica gel.

It was found during the synthesis of 20 that the removal of the THP group followed by desilylation without intermediate purification, provided for better overall yields (54%) of diol 20. For 20, order of deprotection was found to be important with cleavage of the acetal and then desilylation providing better yields as compared to the reverse order. Nevertheless, it was shown that the protecting groups could be selectively removed which will be useful in future syntheses of additional derivatives.
Scheme 15. Potential oxidative targets of enetriynediols

**Scheme 16. Orthogonal deprotection of the enetriyne backbone**

Reagents and conditions: (a) Dowex-50W, MeOH/Et₂O; (b) TBAF, THF, 0 °C
1-2.7 Spectroscopic data of (Z)-3-tridecene-5,7,9-triyne-1,11-diol

Characterization of synthetic 20 through NMR spectroscopy revealed that the data did not correspond to the natural product data reported by Huffman. Although many resonances between the two compounds did approximately correlate, the multiplicity of the two spectra differed substantially at positions 2 and 11 (Table 4). Namely, the methylene groups originally presumed to neighbor the double bond and the primary alcohol were not consistent in terms of chemical shift or multiplicity with synthetic 20. Of note, was position 11 in which a triplet was observed versus a doublet of doublets. No observable coupling across the triyne backbone ($J < 0.3$ Hz) was present in synthetic 20, which was in direct conflict with the original explanation by Huffman for the doublet of doublets in the natural product.

Table 4. $^1H$ NMR comparison of isolated natural product and synthetic 20

<table>
<thead>
<tr>
<th>Position</th>
<th>Natural Product $^a$</th>
<th>Synthetic Product 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^\delta H$</td>
<td>$J$ (Hz)</td>
</tr>
<tr>
<td>1</td>
<td>3.72, $t$</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>2.38, $t$</td>
<td>6.6</td>
</tr>
<tr>
<td>3</td>
<td>6.28, $dt$</td>
<td>11.2, 6.4</td>
</tr>
<tr>
<td>4</td>
<td>5.59, $dm$</td>
<td>10.4</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
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<td>7</td>
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<td>8</td>
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<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4.41, $dd$</td>
<td>6.4, 1.5</td>
</tr>
<tr>
<td>12</td>
<td>1.75, $m$</td>
<td>1.75, v. quintet</td>
</tr>
<tr>
<td>13</td>
<td>1.01, $dd$</td>
<td>6.8, 4.8</td>
</tr>
</tbody>
</table>

$^a$ NMR data for natural product isolated by Huffman (2002)
Further inspection of the natural product data and research of literature spectra, led us to believe that the true structure of the natural product was in part, an allylic alcohol. Similar chemical shifts, multiplicities, and coupling constants for allylic alcohols were found. This data, in conjunction with the belief that the observation by liquid chromatography/mass spectrometry (LC/MS) of an ion with \( m/z \) 202 for the natural product observed by Huffman was accurate, led us to a likely revision to the structure (47) of the isolated natural product. In this case, the multiplicities observed for each methylene group would be reduced, given the loss of the asymmetric center. Finally, it should be noted that while 47 was expected to be a better fit for the collected data, both the LC-MS and NMR spectra originally obtained were of very low quality.

![Structure](image)

**1-2.8 Syntheses of additional enetriyne compounds**

It was decided to pursue the synthesis of a number of enetriyne skeletons to further explore the utility of our rearrangement/coupling strategy. The b and c series analogs, primarily used for the optimization experiments of dibromoalkene 29 and triyne 30 formations, were not carried past triyne 30 (Scheme 13). Included in these experiments, the synthesis of analog 47, the revised structure for the enetriyne natural product, was undertaken (Schemes 13 and 17). Following the same synthetic pathway presented for 20, commercially available 5-hexyn-1-ol was protected in quantitative yield using imidazole and TBDPSCI in CH\(_2\)Cl\(_2\) to give 24d. The remaining transformations leading from terminal alkyne 24d to triyne 30d are summarized in Scheme 13. Comparable yields to the original synthesis of 20 were obtained for each step in the sequence leading to 30d (Table 1). Triyne 30d was then coupled to alkenyl segment 21b using the optimized Stille conditions in a 71% yield. Successive deprotection with Dowex-50W and TBAF gave diol 47 in 54% yield over the two steps.
Scheme 17. Syntheses of enetriyne compounds 47 and 50<sup>a</sup>

\[
\begin{align*}
30d,e & \quad 21b \\
\text{a} & \longrightarrow \\
41 \text{ from } 30d & \quad 48 \text{ from } 30e \\
\text{b} & \\
\text{d} & \quad R = \text{TBDPSO} \quad \text{e} \quad R = \text{n-butyl} \\
49 \text{ from } 41 & \quad 50 \text{ from } 48 \\
\text{c} & \\
41 & \quad 51 \\
c & \\
\text{Comparison of 47 to the Fistulina metabolites was made on several levels. Through an examination of the } ^1\text{H NMR data, 47 was indiscernible from natural product isolated by Huffman. In the natural product’s } ^1\text{H NMR spectrum, the alkyl region from 1.0 to 2.0 ppm was obscured by peaks belonging to solvents and impurities in the sample, preventing an unambiguous assignment. However, differences between the retention times of the natural product (8.23 and 9.21 min) and 47 (5.66 min) observed during analytical HPLC experiments were not consistent with the identification of 47 as the natural product. There are several explanations for this discrepancy. Synthetic 47 was compared by HPLC to natural products.}}
\end{align*}
\]
isolated from recently grown *F. hepatica* culture extracts using a new isolation procedure and culture medium. The original Huffman product was isolated by liquid-liquid extraction and HPLC from 20-40 day 2.5% malt extract broth shake cultures. It is possible that the compound isolated from culture growths recently collected by Minto was different, either due to the use of a Sephadex LH-20 chromatography for the isolation or due to a medium change to YM broth cultures. Variation of the growth conditions may have resulted in a different secondary metabolite being formed. Finally, the poor quality of the LC-MS provided for reasonable uncertainty that the natural product isolated by Huffman was not correctly identified.

Since diol 47 was more polar by reverse-phase HPLC than the natural product isolated by Huffman, an alkyl-allylic alcohol system was considered for a potential structure and the synthesis of 50 was performed. Effecting the reductive elimination of a tosylate by Superhydride to directly convert 47 to alcohol 50 was attempted (Scheme 18). Therefore, 41 was deprotected with TBAF to give mono-deprotected enetriyne 51. Reacting 51 with TsCl provided for 52 in 62% yield. However, the final transformation, in which the tosyl group is substituted with a hydride ion, did not work. By inspection of the crude 1H NMR, it appeared the reaction caused decomposition of the enetriyne backbone and cleavage of the allylic THP group also occurred with no methyl groups being formed. Nevertheless, the successful synthesis of 50 was accomplished. Using the synthetic scheme developed and previously described, 1-hexyne was carried through to 50 (Schemes 13 and 17). After coupling of 1-hexyne to 23, dialkynyl alcohol 27e was carried through the reaction scheme to give triyne 30e, with yields provided in Table 1. Coupling of triyne 30e to alkenyl segment 21b provided for the enetriyne (48) in quantitative yield. Deprotection with Dowex-50W removed the THP group to give enetriyne 50 in 70% yield.

The 1H NMR spectrum of 50 also correlated well with the natural product data. However, the analytical HPLC data did not match with the natural product. Definitive conclusions to the correct structure of the natural product will be accomplished in the future following spectroscopic recharacterization of the natural product.
Scheme 18. Attempted synthesis of $50$ from $47^a$

\[
\begin{align*}
51 & \xrightarrow{a} 62\%\quad 52 \\
\text{HO} & \quad \text{TsO} \\
\text{3} & \quad \text{3}
\end{align*}
\]

\[
\begin{align*}
48 & \xrightarrow{b} 50 \\
\text{OH} & \quad \text{TsO} \\
\text{3} & \quad \text{3}
\end{align*}
\]

$^a$ Reagents and conditions: (a) TsCl, pyridine, CH$_2$Cl$_2$, 0 °C; (b) Super-hydride, THF, 0 °C; (c) Dowex-50W, MeOH/Et$_2$O

1-3. Conclusion

A concise, efficient synthetic scheme has been developed for the construction of enetriyne backbones, exemplified by several *F. hepatica* metabolites. Existing literature techniques were expanded through our work allowing the preparation of oxygenated triynes. A modified Stille reaction using Pd(dba)$_2$ and tris(2-furyl)phosphine was developed for the construction of enetriyne backbones providing good coupling yields without requiring a large excess of triyne. Using these methods, an enetriynediol that was proposed as the structure of a *F. hepatica* natural product was prepared in 14% yield over nine steps. Validation of this approach provided an invaluable blueprint towards the syntheses of additional enetriyne analogs in future studies of the biosynthesis and bioactivity of Fistulina metabolites. In spite of conflicting results, mainly due to the quality of the natural product data, several revised structures ($47$ and $50$) for Fistulina natural products isolated by Huffman and Minto were prepared for future comparison to isolates from fungal extracts. Reisolation of the natural products, taking advantage of a higher field NMR, should allow complete characterization of the biological enetriynes.
1-4. Experimental Methods

1-4.1 General procedures

All reactions were carried out under N₂ gas in oven-dried or flame-dried glassware, where noted. The glassware was cooled under a dry stream of N₂ before use. The N₂ line was equipped with a concentrated H₂SO₄ trap and KOH bubbler. Glass syringes were used to transfer all solvents and solutions. For the triyne rearrangement, it was found that no special treatment of the syringes was required beyond oven-drying and cooling in a dessicator. Flash column chromatography was performed with silica gel (Natland International, 230-400 mesh) using petroleum ether (PE)/diethyl ether (Et₂O) or hexanes/ethyl acetate (EtOAc) in the indicated ratios. TLC analyses were conducted using pre-coated silica gel plates with aluminum backings (Whatman, Al Sil G/UV). UV light and 0.5% KMnO₄/2.5% Na₂CO₃ stain were used to detect products on TLC plates. IR spectra were obtained on a Perkin Elmer 1600 FT-IR spectrophotometer as a neat film on NaCl plates or as a solution (solvent as indicated). ¹H and ¹³C NMR spectral data were recorded on either a 200 or 300 MHz FT-NMR spectrometer (Bruker, Avance Series). HRMS samples were carried out at the Mass Spectrometry Lab, Department of Chemistry, The Ohio State University, Columbus, OH.

1-4.2 Materials

The solvents were dried by distillation under N₂ from the drying agents specified: CH₂Cl₂ (CaH₂); THF, Et₂O, and hexanes (Na/benzophenone ketyl). For the triyne rearrangement reaction, anhydrous hexanes were purchased from Aldrich. Pd(CH₃CN)₂Cl₂, AsPh₃, and P( furyl)₃ were purchased from Aldrich. Pd(dbă)₂ was purchased from Acros. All other commercially available reagents were reagent grade and were used as received. BuLi was titrated using 1,2-dichloroethane and phenolphthalein periodically to verify the concentration.⁵⁷ Activated manganese dioxide was prepared by oven-drying the product from the reaction of manganese chloride with potassium permanganate according to the literature method.³⁸ The dibromomethyltriphenylphosphine bromide required for Michel’s method was synthesized in acetonitrile according to Wolkoff.⁴⁴ The level of water present in the reaction mixture is critical. It was found that the addition of 2% H₂O (v/v) resulted in a maximum yield. Before use, the
Wittig salt was dried by heating under vacuum in a drying pistol warmed by refluxing xylenes. Pd(Ph₃)₂Cl₂ was prepared through a literature method.⁵⁸

1-4.3 Synthesis of (Z)-3-tridecene-5,7,9-triyne-1,11-diol

Trimethylsilylpropynal (23). In a 1000 mL 3N RBF was stirred a solution of alcohol 26 (10.05 g, 78.5 mmol) and tetrabutylammonium hydrogen sulfate (2.69 g, 7.92 mmol) in CH₂Cl₂ (150 mL). The solution was cooled to 0 °C. To this mixture was added dropwise via an additional funnel, a solution of K₂CrO₄ (10.05 g, 51.8 mmol) in 30% (v/v) H₂SO₄ (122 mL) at 0 °C over 45 min. The mixture was stirred for an additional 15 minutes and quenched with 10% (w/v) FeSO₄ solution (78 mL). The layers were separated and the organic phase was washed with H₂O (80 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (20:1 PE/Et₂O) with a fast solvent flow and a short plug of silica afforded 5.92 g of 23 as a yellow oil (60%): IR (neat) 2964, 2902, 2859, 2154, 1669, 1254, 1002, 851, 763 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.24 (s, 9H), 9.22 (s, 1H).

3-(tert-Butyldiphenylsiloxy)-1-pentyne (24). Method A: To a stirred solution of 1-pentyn-3-ol (0.825 g, 9.81 mmol) in dry CH₂Cl₂ (16.5 mL) was added pyridine (0.99 mL, 10.3 mmol) and DMAP (0.12 g, 0.98 mmol). TBDPSCl (2.942 g, 10.7 mmol) was then added via a syringe at 0 °C. The mixture was allowed to warm to rt and stirred for 1.5 days. The reaction was quenched with 1 M HCl (9 mL) and the aqueous phase was extracted with CH₂Cl₂ (2 x 15 mL). The combined organic phases were then dried over MgSO₄ and concentrated under vacuum to give the crude product. The crude product was purified by flash column chromatography (20:1
PE/Et₂O) to afford 2.993 g of a light yellow oil (95%), which typically contained ~5% TBDPSCl. Characterization is provided below.

Method B: In a 250 mL RBF was stirred a solution of 1-pentyn-3-ol (2.518 g, 29.9 mmol) and imidazole (6.107 g, 89.7 mmol) in dry CH₂Cl₂ (130 mL). TBDPSCl (9.755 g, 35.5 mmol) was rapidly added via a syringe in one portion. White solids immediately formed upon addition of TBDPSCl. The reaction was stirred at rt for 16 h and was then diluted with Et₂O (240 mL). After the layers were separated, the organic phase was washed with brine (150 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (PE then 50:1 PE/Et₂O) afforded 9.644 g of 24 (100%): IR (neat) 3306, 3071, 3049, 2963, 2932, 2858, 2360, 1428, 1111, 701, 505 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.94 (t, J = 7.3 Hz, 3H), 1.07 (s, 9H), 1.65 (m, 2H), 2.29 (d, J = 2.0 Hz, 1H), 4.29 (dt, J = 7.3 Hz, 2.0 Hz, 1H), 7.38 (m, 6H), 7.70 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ 9.01, 19.30, 26.88, 31.32, 64.85, 72.50, 84.86, 127.40, 127.57, 129.62, 129.70, 133.56, 133.70, 135.82, 136.03; HRMS (ESI) calcd m/z for C₂₁H₂₆OSiNa⁺ 345.1645, found m/z 345.1651.

6-(tert-Butyldiphenylsiloxy)-1-trimethylsilyl-1,4-octadiyne-3-ol (27). To a stirred solution of terminal alkyne 24 (9.640 g, 29.9 mmol) in dry THF (230 mL) at -78 °C was added n-BuLi (1.24 M, 25.3 mL, 31.4 mmol) dropwise via a syringe. The mixture was stirred at -78 °C for 15 min, followed by the slow addition of 23 (4.146 g, 32.9 mmol) in THF (15 mL) over 5 min. The reaction mixture was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with aqueous NH₄Cl solution (115 mL) and the layers were separated. The aqueous phase was extracted with ether (3 x 75 mL). The combined organic phases were then washed with brine (150 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (50:1 then 20:1 PE/Et₂O) afforded diynol 27 as a mixture of diastereomers (11.125 g, 83%) as a yellow oil: IR (neat) 3394, 3072, 3050, 2962, 2896, 2858, 2176, 1590, 1463, 1428, 1251, 1150, 1113, 1060, 845, 741, 702, 622, 506 cm⁻¹.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.16 (s, 5H), 0.17 (s, 4H), 0.95 (dt, $J = 7.3, 1.6$ Hz, 3H), 1.07 (s, 9H), 1.71 (m, 2H), 4.34 (m, 1H), 4.88 (dd, $J = 6.9, 1.6$ Hz, 1H), 7.39 (m, 6H), 7.71 (m, 4H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ -0.33, 9.22, 19.27, 26.92, 31.13, 31.17, 52.46, 64.92, 64.94, 81.82, 85.87, 89.07, 101.67, 101.79, 127.37, 127.40, 127.59, 129.60, 129.62, 129.71, 133.62, 133.65, 133.96, 135.85, 135.88, 136.16, 136.22; HRMS (ESI) calcd $m/z$ for C$_{27}$H$_{36}$O$_2$Si$_2$Na$^+$ 471.2146, found $m/z$ 471.2135.

6-($tert$-Butyldiphenylsiloxy)-1-trimethylsilyl-1,4-octadiyn-3-one (28). In a 1000 mL RBF, a solution of 27 (11.125 g, 24.8 mmol) in dry hexanes (530 mL) was stirred. To this solution was added MnO$_2$ (33.2 g) as a solid in one portion. The resulting black suspension was stirred at rt for 1.5 h and was then vacuum-filtered through a pad of Celite. The solids were washed with hexanes (4 x 50 mL) and the filtrate concentrated under vacuum to give 9.060 g of crude product 28 (82%), which was used without further purification: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.24 (s, 9H), 0.96 (t, $J = 7.4$ Hz, 3H), 1.09 (s, 9H), 1.74 (m, 2H), 4.41 (t, $J = 6.2$ Hz, 1 H), 7.40 (m, 6H), 7.69 (m, 4H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ -0.91, 9.06, 19.33, 26.82, 30.70, 64.83, 84.64, 94.14, 98.91, 102.39, 127.66, 127.71, 129.93, 132.76, 133.14, 135.75, 136.02, 160.22. On a 0.238 g scale, this reaction proceeded in 95% yield.

3-(Dibromomethylidene)-6-($tert$-butyldiphenylsiloxy)-1-trimethylsilyl-1,4-octadiyne (29). Carbon tetrabromide (8.440 g, 25.5 mmol) and triphenylphosphine (13.388 g, 51.0 mmol) were added to CH$_2$Cl$_2$ (280 mL) and stirred at rt for 5 min. To this mixture was rapidly added the ketone 28 (9.060 g, 20.3 mmol) in CH$_2$Cl$_2$ (28 mL) via syringe. The reaction was stirred at rt for
3 h and was then concentrated under vacuum to approximately 10 mL. Hexanes (150 mL) were used to dilute the reaction mixture and the resulting yellow-brown suspension was vacuum-filtered through a pad of Celite using hexanes (4 x 50 mL) to wash the solid by-products. The filtrate was then concentrated under vacuum to give the crude product. Purification by flash column chromatography (PE then 50:1 PE/Et₂O) afforded 8.366 g of 29 as a yellow oil (69%):

IR (neat) 3071, 3049, 2962, 2932, 2895, 2858, 2219, 2152, 1590, 1428, 1347, 1251, 1107, 1086, 1067, 1025, 874, 845, 739, 701, 612, 506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.21 (s, 9H), 0.96 (t, J = 7.3 Hz, 3H), 1.07 (s, 9H), 1.72 (m, 2H), 4.39 (dd, J = 6.6, 5.4 Hz, 1H), 7.38 (m, 6H), 7.70 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.46, 9.08, 19.35, 26.92, 31.08, 65.53, 81.07, 97.52, 100.26, 102.13, 108.62, 114.06, 127.51, 127.59, 129.65, 129.71, 133.31, 133.65, 135.80, 136.06; HRMS (ESI) calcd m/z for C₂₈H₃₄Br₂Si₂Na⁺ 625.0387, found m/z 625.0416.

7-(tert-Butyldiphenylsiloxy)-1-trimethylsilyl-1,3,5-nonatriyne (30). In a flame-dried 500 mL RBF, was stirred a solution of dibromoenediyne compound 29 (4.880 g, 8.10 mmol) in anhydrous hexanes (224 mL). To this solution was added n-BuLi (1.24 M, 7.84 mL, 9.72 mmol) dropwise via syringe at -78 °C. The mixture was allowed to warm to approximately -10 °C over a 30 min period and was then quenched with saturated NH₄Cl solution (140 mL). The aqueous layer was extracted with ether (3 x 50 mL). The combined organic phases were washed with H₂O (100 mL), brine (100 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. The crude product was purified by flash column chromatography (PE then 100:1 PE/Et₂O) to afford triyne 30 (2.626 g, 73%) as an orange-yellow oil: IR (neat) 3072, 3050, 2963, 2933, 2896, 2859, 2208, 2170, 2079, 1590, 1472, 1428, 1347, 1252, 1112, 1064, 1017, 847, 701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.19 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H), 1.05 (s, 9H), 1.67 (m, 2H), 4.30 (t, J = 6.0 Hz, 1H), 7.39 (m, 6H), 7.67 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.53, 9.04, 19.31, 26.85, 31.22, 61.48, 63.03, 65.43, 69.53, 79.68, 87.08, 88.03, 127.56, 127.65, 129.83, 133.01, 133.31, 135.76, 135.96; HRMS (ESI) calcd m/z for C₂₈H₃₄OSi₂Na⁺ 465.2040, found m/z 465.2058. A small scale (75.0 mg of 29) reaction gave an 83% yield.

![Diagram](image-url)
(Z)-11-(tert-Butyldiphenylsiloxy)-1-(tetrahydro-2H-pyran-2-yl)oxy)-3-tridecene-5,7,9-triyne (31). To a stirred solution of TMS-triyne 30 (1.117 g, 2.52 mmol) and (Bu$_3$Sn)$_2$O (0.642 mL, 1.26 mmol) in dry THF (25.5 mL) was added TBAF (1.0 M, 47 µL, 0.047 mmol) via syringe at rt. The mixture was stirred for 3.5 h at rt and was then concentrated under vacuum to afford crude product 22, which was used without further purification.

A solution of iodoalkene 21a (0.569 g, 2.02 mmol), Pd(dba)$_2$ (58.0 mg, 0.05 mmol), and P(furyl)$_3$ (46.8 mg, 0.10 mmol) in THF (19.5 mL) was stirred at rt. To the mixture was added the crude Bu$_3$Sn-triyne 22 via syringe. The reaction was stirred in the dark at rt for 16 h. The reaction mixture was then concentrated under vacuum to give the crude product as a dark brown oil. Purification by flash column chromatography (20:1 PE/Et$_2$O) afforded 0.590 g of 31 as a reddish-brown viscous oil (56%): IR (neat) 3070, 2937, 2861, 2246, 2184, 2102, 1592, 1464, 1429, 1388, 1350, 1197, 1111, 1073, 1034, 908, 821, 735, 704, 506 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 0.93 (t, $J = 7.4$ Hz, 3H), 1.06 (s, 9H), 1.68 (m, 8H), 2.64 (q, $J = 6.8$ Hz, 2H), 3.49 (m, 2H), 3.80 (m, 2H), 4.33 (t, $J = 6.0$ Hz, 1H), 4.60 (m, 1H), 5.57 (d, $J = 10.9$ Hz, 1H), 6.25 (dt, $J = 10.9$ Hz, 7.4 Hz, 1H), 7.39 (m, 6H), 7.66 (m, 4H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 9.06, 19.31, 19.48, 25.44, 26.86, 30.62, 31.25, 31.50, 62.29, 62.63, 65.50, 65.81, 66.79, 69.69, 73.92, 78.54, 81.56, 98.64, 109.14, 127.54, 127.64, 129.81, 133.05, 133.34, 135.77, 135.97, 146.75; HRMS (ESI) calcd m/z for C$_{34}$H$_{40}$O$_3$SiNa$^+$ 547.2639, found m/z 547.2656.

1) (Bu$_3$Sn)$_2$O cat. TBAF, THF
2) 21a, Pd(dba)$_2$, P(furyl)$_3$

[OHTPH]

Dowex-50W MeOH/Et$_2$O

OTBDPS 31

OH

Dowex-50W MeOH/Et$_2$O

OTBDPS 32
(Z)-11-(tert-Butyldiphenylsiloxy)-3-tridecene-5,7,9-triyn-1-ol (32). In a 50 mL RBF was stirred a solution of enetriyne 31 (48.5 mg, 9.20*10^{-2} mmol) in MeOH/Et_{2}O (3:1) (2 mL). To this solution was added Dowex-50W resin (50 mg) as a solid in one portion. The reaction was stirred in the dark for 36 h. The reaction mixture was then filtered by gravity and the solids washed with Et_{2}O (3 x 10 mL). The filtrate was concentrated under vacuum to give the crude product, which was used in the subsequent desilylation without further purification. For characterization purposes, the crude product of a separate reaction was purified by flash column chromatography (5:1 PE/Et_{2}O) to afford 32 as a viscous oil (39%): IR (neat) 3354, 3072, 3051, 2964, 2957, 2859, 2242, 2210, 1590, 1472, 1428, 1349, 1108, 1065, 1007, 909, 823, 737, 702, 614, 506 cm^{-1}; ^{1}H NMR (300 MHz, CDCl_{3}) δ 0.93 (t, J = 7.3 Hz, 3H), 1.06 (s, 9H), 1.69 (m, 2H), 2.61 (qd, J = 7.0, 1.3 Hz, 2H), 3.73 (t, J = 6.4 Hz, 2H), 4.33 (t, J = 6.0 Hz, 1H), 5.63 (d, J = 10.9 Hz, 1H), 6.23 (dt, J = 10.9, 7.5 Hz, 1H), 7.38 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (75.5 MHz, CDCl_{3}) δ 9.05, 19.31, 26.85, 31.25, 34.37, 61.54, 62.50, 65.50, 66.97, 69.63, 73.68, 78.68, 81.69, 110.01, 127.55, 127.65, 129.82, 133.05, 133.32, 135.77, 135.97, 145.90; HRMS (ESI) calcd m/z for C_{29}H_{32}O_{2}SiNa^+ 463.2064, found m/z 463.2070.

![Chemical structure](attachment:image)

(Z)-3-Tridecene-5,7,9-triyn-1,11-diol (20). To a stirred solution of crude enetriyne 32 (40.5 mg, 9.20*10^{-2} mmol) in THF (2.0 mL) at 0 °C was added TBAF (1.0 M in THF, 0.092 mL, 9.20*10^{-2} mmol) dropwise by syringe. The reaction was stirred in the dark at 0 °C for 2 h and was then quenched with brine (2 mL). The aqueous layer was extracted with Et_{2}O (3 x 5 mL). The combined organic phases were dried over MgSO_{4} and concentrated under vacuum to give the crude product. Purification by flash column chromatography (1:1 PE/Et_{2}O) afforded 10.1 mg of 20 as a dark red oil (54% yield over two steps): IR (in CDCl_{3}) 3694, 3608, 2968, 2881, 2252, 2206, 2190, 1602, 1379, 1036, 960 cm^{-1}; IR (neat) 3339, 2968, 2935, 2878, 2209, 2185, 2103, 1697, 1607, 1463, 1403, 1344, 1257, 1115, 1052, 968, 738, 710 cm^{-1}; ^{1}H NMR (300 MHz, CDCl_{3}) δ 1.00 (t, J = 7.4 Hz, 3H), 1.75 (v. quintet, J = 7.2 Hz, 2H), 2.61 (tdd, J = 7.5,
6.4, 1.3 Hz, 2H), 3.73 (t, J = 6.4 Hz, 2H), 4.40 (t, J = 6.5 Hz, 1H), 5.63 (dt, J = 10.9, 1.3 Hz, 1H),
6.24 (dt, J = 10.9, 7.5 Hz, 1H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 9.29, 30.60, 34.41, 61.54,
63.18, 64.17, 66.48, 69.94, 74.12, 78.44, 80.99, 109.88, 146.27; HRMS (ESI) calcd m/z for
C\(_{13}\)H\(_{14}\)O\(_2\)Na\(^+\) 225.0886, found m/z 225.0885.

Second set of data for secondary diol: \(^1\)H NMR (300 MHz, acetone-d\(_6\)) \(\delta\) 0.98 (t, J = 7.4 Hz,
3H), 1.70 (quintet of d, J = 7.2, 1.3 Hz, 2H), 2.55 (tdd, J = 7.5, 6.5, 1.5 Hz, 2H), 3.62 (t, J = 6.4
Hz, 2H), 4.40 (t, J = 6.4 Hz, 1H), 5.68 (dt, J = 11.0, 1.4 Hz, 1H), 6.40 (dt, 11.0, 7.5 Hz, 1H); \(^{13}\)C
NMR (75.5 MHz, acetone-d\(_6\)) \(\delta\) 9.71, 31.38, 35.58, 61.23, 62.86, 63.86, 67.12, 68.62, 75.34,
78.13, 84.23, 108.94, 149.39.

(Z)-13-(Tetrahydro-2\(H\)-pyran-2-yloxy)-10-tridecene-4,6,8-triyn-3-ol (46). To a stirred
solution of enetriyne 31 (0.234 g, 0.455 mmol) in THF (5 mL) at 0 °C was added TBAF (1.0 M
in THF, 0.50 mL, 0.50 mmol) dropwise by syringe. The reaction was stirred in the dark at 0 °C
for 2 h and was then quenched with brine (5 mL). The aqueous layer was extracted with Et\(_2\)O (3
x 10 mL). The combined organic phases were dried over MgSO\(_4\) and concentrated under
vacuum to give the crude product. Purification by flash column chromatography afforded 45.0
mg of 46 as a dark red-brown oil (35%): IR (neat) 3402, 2941, 2874, 2208, 2185, 2103, 1645,
1608, 1464, 1404, 1347, 1275, 1200, 1137, 1120, 1075, 1033, 984, 905, 868, 810, 741 cm\(^{-1}\); \(^1\)H
NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.00 (t, J = 7.4 Hz, 3H), 1.56 (m, 6H), 1.75 (m, 4H), 2.63 (q, J = 6.9
Hz, 2H), 3.48 (m, 2H), 3.79 (m, 2H), 4.40 (t, J = 6.5 Hz, 1H), 4.59 (m, 1H), 5.57 (dt, J = 10.9,
1.4 Hz, 1H), 6.26 (dt, J = 10.9, 7.4 Hz, 1H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 9.29, 19.47,
25.44, 30.61, 31.54, 52.12, 62.30, 63.31, 64.19, 65.78, 66.30, 69.98, 74.36, 78.30, 80.88, 98.66,
109.02, 147.11; HRMS (ESI) calcd m/z for C\(_{18}\)H\(_{22}\)O\(_3\)Na\(^+\) 309.1461, found m/z 309.1463.
1-4.4 Syntheses of 1,4-diyn-3-one derivatives

4-(tert-Butyldiphenylsiloxy)-1-butyne (24c). To a stirred solution of 3-butyn-1-ol (0.898 g, 12.8 mmol) in dry CH₂Cl₂ (21.5 mL) was added pyridine (1.35 mL, 14.1 mmol) and DMAP (0.155 g, 1.27 mmol). TBDPSCI (4.172 g, 15.2 mmol) was then added at 0 °C and the mixture was allowed to warm to rt for 1.5 days. The reaction was quenched with 1 M HCl (12 mL) and the aqueous phase extracted with CH₂Cl₂ (2 x 20 mL). The combined organic phases were then dried over MgSO₄ and concentrated under vacuum to give the crude product. The pale yellow oil was purified by flash column chromatography (50:1 PE/Et₂O) to afford 3.352 g of 24c (85%): IR (neat) 3306, 3070, 2957, 2931, 2857, 2122, 1472, 1428, 1112, 823, 738, 702, 506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.04 (s, 9H), 1.93 (t, J = 2.6 Hz, 1H), 2.43 (dt, J = 7.0, 2.6 Hz, 2H), 3.76 (t, J = 7.0 Hz, 2H), 7.38 (m, 6H), 7.67 (m, 4H).

6-(tert-Butyldiphenylsiloxy)-1-hexyne (24d). To a solution of 5-hexyn-1-ol (2.943 g, 30.0 mmol) and imidazole (6.114 g, 89.8 mmol) in dry CH₂Cl₂ (130 mL) was added TBDPSCI (9.892 g, 36.0 mmol). The reaction was stirred at rt for 16 h and then diluted with Et₂O (240 mL). The organic layer was washed with brine (150 mL) and concentrated under vacuum to give crude product. The yellow oil was purified by flash column chromatography (PE to 50:1 PE/Et₂O) to afford 24d (10.063 g, 99%): IR (neat) 3308, 3071, 2957, 2931, 2859, 2361, 1428, 1112, 702, 506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.03 (s, 9H), 1.63 (m, 4H), 1.92 (t, J = 2.7 Hz, 1H), 2.17 (dt, J = 6.8, 2.7 Hz, 2H), 3.66 (t, J = 5.9 Hz, 2H), 7.38 (m, 6H), 7.65 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ 18.17, 19.21, 24.94, 26.85, 31.55, 63.31, 68.24, 84.53, 127.60, 129.53, 133.99, 135.56; HRMS (ESI) calcd m/z for C₂₂H₂₈OSiNa⁺ 359.1802, found m/z 359.1793.
1-Trimethylsilyl-1,4-octadiyn-3-one (28b). To a stirred solution of 1-pentyne (0.201 g, 2.96 mmol) in dry THF (25 mL) at -78 °C was added n-BuLi (1.6 M, 1.85 mL, 2.96 mmol) dropwise via a syringe. The mixture was stirred at -78 °C for 15 min, followed by the addition of 3 (0.392 g, 3.11 mmol) in THF (2 mL) slowly over 5 min. The reaction mixture was warmed to 0 °C and stirred for an additional 30 min. The reaction was then quenched with aqueous NH₄Cl solution (12 mL) and the layers were separated. The aqueous phase was extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (25 mL), dried over MgSO₄, and concentrated under vacuum to give 0.511 g of 27b (89%), which was used without further purification.

To a stirred solution of secondary alcohol 27b (0.511 g, 2.63 mmol) in anhydrous hexanes (85 mL) was added MnO₂ (3.548 g) as a solid in one portion. The resulting black suspension was stirred at rt for 1.5 h and then vacuum-filtered through a pad of Celite. The solids were washed with hexanes (4 x 25 mL). The filtrate was concentrated under vacuum to give the crude product. Purification by flash column chromatography (PE) afforded 0.430 g of 28b as a yellow oil (76% over 2 steps): IR (neat) 2966, 2937, 2224, 2149, 1629, 1253, 1215, 848 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.23 (s, 9H), 1.00 (t, J = 7.4 Hz, 3H), 1.62 (sextet, J = 7.2 Hz, 2H), 2.36 (t, J = 7.1 Hz, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.91, 13.42, 21.04, 21.08, 82.28, 95.86, 97.89, 102.76, 160.82; HRMS (ESI) calcd m/z for C₁₁H₁₆SiONa⁺ 215.0863, found m/z 215.0865.

7-(tert-Butyldiphenylsiloxy)-1-trimethylsilyl-1,4-heptadiyn-3-ol (27c). To a stirred solution of terminal alkyne 24c (1.567 g, 5.08 mmol) in dry THF (41.5 mL) at -78 °C was added n-BuLi (1.6 M, 3.18 mL, 5.09 mmol). The mixture was stirred at -78 °C for 15 min, followed by the dropwise addition of 23 (0.674 g, 5.35 mmol) in THF (3 mL) over 5 min. The resulting orange
reaction mixture was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with aqueous NH₄Cl solution (20 mL), causing the reaction mixture to turn red, and the layers were separated. The aqueous phase was extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (25 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (10:1 PE/Et₂O) afforded 1.830 g of oil (83%): IR (neat) 3396, 3071, 3049, 2958, 2858, 2234, 2176, 1589, 1472, 1428, 1250, 1112, 1036, 845, 703, 506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.17 (s, 9H), 1.06 (s, 9H), 2.50 (dt, J = 6.9, 2.0 Hz, 2H), 3.78 (t, J = 6.9 Hz, 2H), 5.07 (t, J = 2.0 Hz, 1H), 7.41 (m, 6H), 7.69 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.34, 19.15, 22.86, 26.77, 52.65, 62.01, 78.32, 82.63, 88.95, 102.22, 127.68, 129.67, 133.47, 135.56; HRMS (ESI) calcd m/z for C₂₆H₃₄Si₂O₂Na⁺ 457.1990, found m/z 457.1990.

9-(tert-Butyldiphenylsiloxy)-1-trimethylsilyl-1,4-nonadiyn-3-ol (27d). To a stirred solution of terminal alkyne 24d (6.000 g, 17.8 mmol) in dry THF (130 mL) at -78 °C was added n-BuLi (1.24 M, 15.1 mL, 18.7 mmol). The mixture was stirred at -78 °C for 15 min, followed by the slow addition of 23 (2.476 g, 19.7 mmol) in THF (10 mL) over 5 min. The reaction mixture was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched with aqueous NH₄Cl solution (70 mL) and the layers were separated. The aqueous phase was extracted with ether (3 x 40 mL). The combined organic phases were washed with brine (75 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (50:1 then 20:1 PE/Et₂O) afforded 6.248 g of product (76%): IR (neat) 3392, 3071, 3050, 2957, 2898, 2859, 2233, 2174, 1428, 1251, 1112, 1033, 845, 703, 506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.17 (s, 9H), 1.03 (s, 9H), 1.62 (m, 4H), 2.21 (dt, J = 6.8, 2.1 Hz, 2H), 3.65 (t, J = 5.8 Hz, 2H), 5.06 (t, J = 2.1 Hz, 1H), 7.39 (m, 6H), 7.65 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.31, 18.50, 19.20, 24.75, 26.86, 31.61, 52.74, 63.30, 85.58, 88.90, 102.48, 127.61, 129.55, 133.96, 135.56; ¹³C NMR (75.5 MHz, acetone-d₆) δ -0.19, 18.73,
To a stirred solution of 1-hexyne (0.625 g, 7.61 mmol) in dry THF (55 mL) at -78 °C was added n-BuLi (1.24 M, 6.44 mL, 7.99 mmol) dropwise. The mixture was stirred at -78 °C for 15 min, followed by the slow addition of 23 (1.052 g, 8.35 mmol) in THF (5 mL) over 5 min. The reaction mixture was warmed to 0 °C and stirred for an additional 30 min. The resulting orange reaction mixture was quenched with aqueous NH₄Cl solution (30 mL) and the layers were separated. The aqueous phase was extracted with ether (3 x 25 mL). The combined organic phases were washed with brine (40 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (10:1 PE/Et₂O) afforded 1.476 g of 27e as a pale yellow oil (93%): IR (neat) 3360, 2960, 2935, 2874, 2233, 2177, 1251, 1034, 845, 761 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.17 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H), 1.42 (m, 4H), 2.21 (dt, J = 6.9, 2.1 Hz, 2H), 5.07 (t, J = 2.1 Hz, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.32, 13.55, 18.41, 21.90, 30.33, 52.77, 77.29, 85.81, 88.87, 102.54; HRMS (ESI) calcd m/z for C₁₂H₂₀OSiNa⁺ 231.1176, found m/z 231.1184.

To a stirred solution of secondary alcohol 27c (0.256 g, 0.590 mmol) in dry hexanes (18 mL) was added MnO₂ (0.714 g) as a solid in one portion. The resulting black suspension was stirred at rt for 1.5 h and then vacuum-filtered through a pad of Celite. The solids were washed with hexanes (4 x 25 mL). The filtrate was concentrated under vacuum to give 0.211 g of crude oil (83%), which was used without further purification: IR (neat) 3071, 3050, 2959, 2858, 2213, 2154, 1628, 1428, 1253,
1215, 1113, 1021, 912, 848, 703, 506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.24 (s, 9H), 1.07 (s, 9H), 2.65 (t, J = 6.6 Hz, 2H), 3.82 (t, J = 6.6 Hz, 2H), 7.40 (m, 6H), 7.68 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.93, 19.13, 23.32, 26.72, 61.00, 82.68, 92.72, 98.11, 102.60, 127.76, 129.79, 133.10, 135.52, 160.57; HRMS (ESI) calcd m/z for C₂₆H₃₂Si₂O₂Na⁺ 455.1833, found m/z 455.1839.

9-(tert-Butyldiphenylsiloxy)-1-trimethylsilyl-1,4-nonadiyn-3-one (28d). To a stirred solution of secondary alcohol 27d (6.248 g, 13.51 mmol) in dry hexanes (290 mL) was added MnO₂ (18.1 g) as a solid in one portion. The resulting black suspension was stirred at rt for 1.5 h and was then vacuum-filtered through a pad of Celite. The solids were washed with hexanes (4 x 50 mL). The filtrate was concentrated under vacuum to give 5.507 g of crude product (89%), which was used without further purification: IR (neat) 3072, 2966, 2931, 2861, 2238, 2216, 1630, 1254, 1217, 1113, 848, 704, 504 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.23 (s, 9H), 1.03 (s, 9H), 1.67 (m, 4H), 2.39 (t, J = 6.7 Hz, 2H), 3.66 (t, J = 5.8 Hz, 2H), 7.38 (m, 6H), 7.64 (m, 4H).

1-Trimethylsilyl-1,4-nonadiyn-3-one (28e). To a stirred solution of secondary alcohol (1.459 g, 7.01 mmol) in anhydrous hexanes (150 mL) was added MnO₂ (9.4 g) as a solid in one portion. The resulting black suspension was stirred at rt for 1.5 h and then vacuum-filtered through a pad of Celite. The solids were washed with hexanes (4 x 25 mL). The filtrate was concentrated under vacuum to give 1.138 g of crude product, which was used without further purification (79%): IR (neat) 2961, 2936, 2875, 2222, 2149, 1633, 1253, 1216, 1013, 848, 762 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.24 (s, 9H), 0.91 (t, J = 7.3 Hz, 3H), 1.42 (sextet, J = 7.4 Hz, 2H), 1.58 (quintet, J = 7.1 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H).
1-4.5 Dibromoalkene synthetic techniques

\[ \begin{align*}
\text{TBDPSO} & \quad \text{O} & \quad \text{Br} \\
\text{28c} & \quad \text{n-BuLi, THF} & \quad \text{29c}
\end{align*} \]

3-(Dibromomethylidene)-7-(tert-butylidiphenylsiloxy)-1-trimethylsilyl-1,4-heptadiyne (29c).

Method A:
To a stirred solution of \( n\)-BuLi (1.6 M, 0.58 mL, 0.93 mmol) in dry THF (24 mL) at rt was added \((\text{Ph}_3\text{PCHBr}_2)\text{Br}\) (0.477 g, 0.927 mmol) as a solid in one portion. The mixture turned yellow and was stirred for 5 min, followed by the addition of the ketone \(28c\) (0.200 g, 0.462 mmol) in THF (2.4 mL). The resulting mixture was stirred for 30 min. The reaction was then quenched with \(\text{H}_2\text{O}\) (10 mL) and the layers were separated. The aqueous phase was extracted with ether (3 x 15 mL). The combined organic phases were dried over MgSO\(_4\) and concentrated under vacuum to give crude product. Purification by flash column chromatography (100:1 PE/Et\(_2\)O) afforded 0.132 g of product (49%): IR (neat) 3071, 2958, 2858, 2231, 2154, 1472, 1428, 1251, 1112, 875, 845, 702 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.19 (s, 9H), 1.04 (s, 9H), 2.59 (t, \(J = 6.7\) Hz, 2H), 3.80 (t, \(J = 6.8\) Hz, 2H), 7.39 (m, 6H), 7.68 (m, 4H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) -0.46, 19.17, 23.95, 26.79, 61.71, 78.25, 95.18, 100.57, 101.88, 108.34, 114.28, 127.70, 129.69, 133.45, 135.59; HRMS (ESI) calcd \(m/z\) for C\(_{27}\)H\(_{32}\)Br\(_2\)OSi\(_2\)Na\(^+\) 611.0230, found \(m/z\) 611.0212.

Method B:
Carbon tetrabromide (0.420 g, 1.26 mmol) and triphenylphosphine (0.654 g, 2.49 mmol) were added to CH\(_2\)Cl\(_2\) (13 mL) and the orange solution was stirred at rt for 5 min. To this mixture the ketone \(28c\) (0.427 g, 0.99 mmol) in CH\(_2\)Cl\(_2\) (1.3 mL) was added. The reaction was stirred at rt for 3 h, by which time the reaction had turned to a deep red solution, and was then concentrated under vacuum to approximately 10 mL. Hexanes (25 mL) were used to dilute the reaction mixture. The resulting suspension was vacuum-filtered through a pad of Celite using hexanes (4 x 25 mL) to wash the solid by-products. The filtrate was then concentrated under vacuum to
give the crude product. Purification by flash column chromatography (100:1 PE/Et₂O) afforded 0.322 g of a pale yellow oil (55%). Characterization was identical to that provided above.

Method C:

7-(tert-Butyldiphenylsiloxy)-3-(tribromomethyl)-1-trimethylsilyl-1,4-heptadiyn-3-ol (33). In a 10 mL RBF, a solution of diisopropylamine (90.3 mg, 0.892 mmol) in dry THF (1.35 mL) was stirred at -30 °C. To the reaction mixture was added n-BuLi (1.24 M, 0.72 mL, 0.89 mmol). The mixture was warmed to 0 °C, stirred for 10 min, and then cooled to -100 °C. Bromoform (0.225 g, 0.890 mmol) in THF (0.7 mL) was then added dropwise via syringe. After 10 min at -100 °C, a solution of ketone 28c (0.193 g, 0.445 mmol) in dry Et₂O (0.7 mL) was slowly added, followed by the addition of CeCl₃ (0.107 g, 0.435 mmol) as a solid in one portion. The reaction mixture was stirred at approximately -90 °C for 45 min and was then quenched with aqueous saturated NH₄Cl solution (3 mL). Upon warming to rt, the aqueous layer was extracted with ether (3 x 5 mL). The combined organic phases were washed with 0.5 M HCl (5 mL), saturated NaHCO₃ solution (5 mL), dried over MgSO₄, and concentrated under vacuum to afford 0.332 g of the crude product, which was used without purification in the following step: ¹H NMR (300 MHz, CDCl₃) δ 0.19 (s, 9H), 1.05 (s, 9H), 2.55 (t, J = 6.7 Hz, 2H), 3.81 (t, J = 6.7 Hz, 2H), 7.38 (m, 6H), 7.67 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.66, 19.11, 23.06, 26.75, 56.02, 61.55, 75.94, 85.47, 92.13, 99.57, 127.68, 129.52, 133.31, 134.76, 135.51.

7-(tert-Butyldiphenylsiloxy)-3-(tribromomethyl)-1-(trimethylsilyl)-3-acetoxy-1,4-heptadiyne (34). To a solution of the crude tribromomethyl alcohol 33 (0.332 g, 0.586 mmol) in isopropenyl acetate (5 mL) was added p-TsOH (0.645 g, 3.39 mmol) as a solid in one portion at 30 °C and
stirred for 1.5 days. The reaction mixture was concentrated under vacuum to approximately 1 mL and ether (10 mL) was added. While stirring at 0 °C, aqueous saturated NaHCO₃ was slowly added until gas evolution ceased. The mixture was warmed to rt and stirred for an additional 30 min. The layers were separated and the aqueous phase was extracted with ether (3 x 15 mL). The combined organic phases were washed with saturated NaHCO₃ solution (20 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (15:1 PE/Et₂O) afforded 0.249 g of 34 as an oil (79% over two steps): IR (neat) 3049, 2958, 2931, 2895, 2857, 1773, 1428, 1251, 1207, 1112, 1004, 847, 736, 704, 506 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.18 (s, 9H), 1.02 (s, 9H), 2.13 (s, 3H), 2.55 (t, J = 6.8 Hz, 2H), 3.79 (t, J = 6.8 Hz, 2H), 7.39 (m, 6H), 7.65 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.68, 19.14, 21.28, 23.26, 26.77, 49.77, 61.49, 74.38, 86.70, 93.77, 97.14, 127.71, 129.67, 133.44, 133.46, 135.57, 166.64; HRMS (ESI) calcd m/z for C₂₉H₃₅Br₃O₃Si₂Na⁺ 748.9547, found m/z 748.9564.

In a 25 mL RBF under a N₂ atmosphere, a solution of tertiary acetate 34 (0.154 g, 0.21 mmol) in dry ether (6.1 mL) was stirred at -78 °C. To this solution was added dropwise a solution of EtMgBr (1.0 M, 0.21 mL, 0.21 mmol). The resulting mixture was stirred at -78 °C for 30 min and was then quenched with saturated NH₄Cl solution (5 mL). The aqueous phase was extracted with ether (3 x 10 mL). The combined organic phases were washed with saturated NaHCO₃ solution (10 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (100:1 PE/Et₂O) afforded 82.9 mg of product (67% for this step and 53% over three steps). The product was spectroscopically identical to 29c described earlier.
1-4.6 Dibromoalkenes via Corey-Fuchs method

![Chemical structure of 28b and 29b](image)

3-(Dibromomethylidene)-1-trimethylsilyl-1,4-octadiyne (29b). Carbon tetrabromide (2.328 g, 7.02 mmol) and triphenylphosphine (3.677 g, 14.0 mmol) were added to CH$_2$Cl$_2$ (70 mL) and stirred at rt for 5 min. To this mixture was added ketone 28b (1.078 g, 5.61 mmol) in CH$_2$Cl$_2$ (7 mL). The reaction was stirred at rt for 3 h and was then concentrated under vacuum to approximately 10 mL. Hexanes (50 mL) were used to dilute the reaction mixture and the resulting suspension was vacuum-filtered through a pad of Celite. The filtrate was concentrated under vacuum to give crude product, which was purified by flash column chromatography (PE) to afford 1.229 g of product (63%): IR (neat) 2963, 2934, 2222, 2156, 1251, 875, 845, 760 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.20 (s, 9H), 1.00 (t, $J = 7.4$ Hz, 3H), 1.59 (sextet, $J = 7.3$ Hz, 2H), 2.30 (t, $J = 7$ Hz, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ -0.44, 13.47, 21.58, 21.73, 77.69, 98.21, 100.73, 101.71, 107.71, 114.48; HRMS (EI) calcd m/z for C$_{12}$H$_{16}$Br$_2$Si$^+$ 347.9362, found m/z 347.9332.

![Chemical structure of 28d and 29d](image)

3-(Dibromomethylidene)-9-(tert-butyldiphenylsiloxy)-1-trimethylsilyl-1,4-nonadiyne (29d). Carbon tetrabromide (2.877 g, 8.67 mmol) and triphenylphosphine (4.556 g, 17.4 mmol) were added to CH$_2$Cl$_2$ (96 mL) and stirred at rt for 5 min. To this mixture was added the ketone 28d (3.197 g, 6.94 mmol) in CH$_2$Cl$_2$ (9.6 mL). The reaction was stirred at rt for 3 h and was then concentrated under vacuum to approximately 10 mL. Hexanes (50 mL) were used to dilute the reaction mixture. The resulting residue was vacuum-filtered through a pad of Celite and the solids washed with hexanes (4 x 50 mL). The filtrate was concentrated under vacuum to give crude product. Purification by flash column chromatography (100:1 PE/Et$_2$O) afforded 2.522 g of 29d (59%): IR (neat) 3071, 3050, 2957, 2932, 2898, 2858, 2224, 2156, 1428, 1251, 1112,

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3-(Dibromomethylidene)-1-trimethylsilyl-1,4-nonadiyne (29e). Carbon tetrabromide (2.264 g, 6.83 mmol) and triphenylphosphine (3.588 g, 13.7 mmol) were added to CH₂Cl₂ (75 mL) and stirred at rt for 5 min. To this mixture was added ketone 28e (1.126 g, 5.46 mmol) in CH₂Cl₂ (7.5 mL). The reaction was stirred at rt for 3 h and was then concentrated under vacuum to approximately 10 mL. Hexanes (50 mL) were used to dilute the reaction mixture and the resulting residue was vacuum-filtered through a pad of Celite. The solids were washed with hexanes (4 x 25 mL) and the combined filtrates were concentrated under vacuum to give crude product. Purification by flash column chromatography (PE then 100:1 PE/Et₂O) afforded 1.058 g of product (54%): IR (neat) 2959, 2929, 2859, 2283, 1660, 1466, 1250, 884, 867, 845, 760 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.20 (s, 9H), 0.90 (t, J = 7.2 Hz, 3H), 1.43 (sextet, J = 7.1 Hz, 2H), 1.55 (quintet, J = 6.8 Hz, 2H), 2.32 (t, J = 6.9 Hz, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.44, 13.53, 19.45, 21.91, 30.11, 77.54, 98.36, 100.73, 101.70, 107.67, 114.48; HRMS (EI) calcd m/z for C₁₃H₁₈Br₂Si⁺ 361.9518, found m/z 361.9517.

1-4.7 Triynes via Tykwinski rearrangement
1-Trimethylsilyl-1,3,5-nonatriyne (30b). To a stirred solution of dibromoenediyne 29b (0.876 g, 2.52 mmol) in anhydrous hexanes (60 mL) was added n-BuLi (1.6 M, 1.89 mL, 3.02 mmol) dropwise via a syringe at -78 °C. The mixture was allowed to warm to approximately -10 °C over a 30 min period and was then quenched with saturated NH₄Cl solution (10 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic phases were washed with H₂O (20 mL), brine (20 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (PE) afforded 0.360 g of 30b as a light yellow oil (76%): IR (neat) 2965, 2936, 2212, 2168, 2079, 1340, 1252, 847, 760 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.17 (s, 9H), 0.97 (t, J = 7.3 Hz, 3H), 1.53 (sextet, J = 7.2 Hz, 2H); 13C NMR (75.5 MHz, CDCl₃) δ -0.49, 13.42, 21.39, 21.54, 59.91, 62.53, 65.60, 80.90, 85.44, 88.35; HRMS (EI) calcd m/z for C₁₂H₁₆Si⁺ 188.1016, found m/z 188.1023.

8-((tert-Butyldiphenylsiloxy)-1-trimethylsilyl-1,3,5-octatriyne (30c). To a solution of dibromoenediyne 29c (0.198 g, 0.337 mmol) in anhydrous hexanes (9.2 mL) was added n-BuLi (1.6 M, 0.253 mL, 0.41 mmol) dropwise via a syringe at -78 °C while stirring. The mixture was allowed to warm to approximately -10 °C over a 30 min period and was then quenched with saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with ether (3 x 10 mL). The combined organic phases were washed with H₂O (10 mL), brine (10 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (PE then 100:1 PE/Et₂O) afforded 0.120 g of a yellow oil (83%): IR (in Et₂O) 3073, 3050, 2218, 2168, 2079, 1589, 1473 ,1428, 1406, 1361, 1334, 1307 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.18 (s, 9H), 1.03 (s, 9H), 2.52 (t, J = 6.7 Hz, 2H), 3.74 (t, J = 6.7 Hz, 2H), 7.40 (m, 6H), 7.65 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.49, 19.17, 23.66, 26.75, 60.11, 61.64, 62.34, 66.56, 78.00, 85.62, 88.30, 127.74, 129.77, 133.29, 135.57; HRMS (ESI) calcd m/z for C₂₇H₃₂OSi₂Na⁺ 451.1884, found m/z 451.1886.
10-(tert-Butyldiphenylsiloxy)-1-trimethylsilyl-1,3,5-decatriyne (30d). To a stirred solution of dibromoenediyne 29d (2.517 g, 4.08 mmol) in anhydrous hexanes (110 mL) was added \( n\)-BuLi (1.24 M, 3.95 mL, 4.90 mmol) at -78 °C. The mixture was allowed to warm to approximately -10 °C over a 30 min period and was subsequently quenched with saturated \( \text{NH}_4\text{Cl} \) solution (70 mL). The aqueous layer was extracted with ether (3 x 40 mL). The combined organic phases were washed with \( \text{H}_2\text{O} \) (50 mL), brine (50 mL), dried over \( \text{MgSO}_4 \), and concentrated under vacuum to give the crude product. Purification by flash column chromatography (PE then 100:1 PE/E\( \text{t}_2\text{O} \)) afforded 1.417 g of product (76%) as an oil: IR (neat) 3073, 3054, 2959, 2931, 2860, 2212, 2167, 2079, 1472, 1252, 1111 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.18 (s, 9H), 1.03 (s, 9H), 1.63 (m, 4H), 2.28 (t, \( J = 6.6 \) Hz, 2H), 3.64 (t, \( J = 5.8 \) Hz, 2H), 7.39 (m, 6H), 7.64 (m, 4H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 19.20, 24.54, 26.86, 31.49, 60.00, 62.52, 63.10, 65.66, 80.85, 85.49, 88.36, 127.64, 129.59, 133.86, 135.55; \(^{13}\)C NMR (75.5 MHz, acetone-\( d_6 \)) \( \delta \) 0.61, 19.36, 19.70, 25.25, 27.19, 32.25, 60.42, 63.05, 63.90, 65.68, 82.60, 86.52, 86.65, 128.59, 130.56, 134.51, 136.22; HRMS (ESI) calcd \( m/z \) for C\(_{29}\)H\(_{36}\)OSi\(_2\)Na\(^+\) 479.2197, found \( m/z \) 479.2196. The yields for this rearrangement ranged from 76-82%.

1-Trimethylsilyl-1,3,5-decatriyne (30e). To a stirred solution of dibromoenediyne 29e (1.040 g, 2.87 mmol) in anhydrous hexanes (78 mL) was slowly added \( n\)-BuLi (1.24 M, 2.78mL, 3.45 mmol) at -78 °C. The mixture was allowed to warm to approximately -10 °C over a 30 min period followed by a saturated \( \text{NH}_4\text{Cl} \) solution quench (50 mL). The aqueous layer was extracted with ether (3 x 25 mL). The combined organic phases were washed with \( \text{H}_2\text{O} \) (25 mL),
brine (25 mL), dried over MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (PE) afforded 0.479 g of 30e as a light yellow oil (83%): IR (neat) 2961, 2936, 2874, 2212, 2168, 2080, 1466, 1331, 1252, 1014, 942, 845, 760 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.17 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H), 1.40 (sextet, J = 7.1 Hz, 2H), 1.50 (quintet, J = 7.0 Hz, 2H), 2.28 (t, J = 7.0 Hz, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ -0.49, 13.45, 19.12, 21.91, 30.00, 59.90, 62.55, 65.46, 81.05, 85.43, 88.36; HRMS (EI) calcd m/z for C₁₃H₁₈Si⁺ 202.1172, found m/z 202.1205.

1-4.8 Syntheses of haloalkene segments

2-(4-Iodo-3-butenyloxy)tetrahydro-2H-pyran (38).⁶¹ To a stirred solution of terminal alkyne 37 (1.870 g, 12.1 mmol) in THF (18 mL) at -78 °C was added n-BuLi (11.7 mL, 1.24 M, 14.5 mmol) slowly via syringe. After 30 min at -78 °C, a solution of I₂ (3.636 g, 14.3 mmol) in THF (18 mL) was added dropwise. A white precipitate formed and the reaction mixture was stirred at -78 °C for 15 min. The reaction was allowed to warm to rt and stirred for an additional 30 min. The reaction was quenched with a 20% Na₂S₂O₃ aqueous solution (12 mL) and the layers were separated. The aqueous layer was extracted with hexanes (3 x 15 mL). The combined organic phases were dried over MgSO₄ and concentrated under vacuum to afford the crude product. Purification by flash column chromatography (15:1 PE/Et₂O) gave 2.833 g of a dark yellow oil (83%): IR (neat) 2942, 2873, 1440, 1352, 1200, 1136, 1122, 1070, 1033 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.62 (m, 6H), 2.64 (t, J = 7.0 Hz, 2H), 3.49 (m, 2H), 3.80 (m, 2H), 4.61 (m, 1H).

2-(4-Iodo-3-butenyloxy)tetrahydro-2H-pyran (21a).⁶² In a 100 mL RBF was stirred a solution of cyclohexene (2.05 mL, 20.2 mmol) in dry n-pentane (30.3 mL) cooled to -78 °C. Me₂S-BH₃
(1.01 mL, 10 M, 10.1 mmol) was added to the solution and stirred for 10 min at -78 °C. The reaction was then warmed to rt and stirred for 1 h. Iodoalkyne 38 (2.828 g, 10.1 mmol) was added slowly via syringe, upon which the reaction mixture turned yellow. After an additional 3 h at rt, AcOH (1.52 mL) was added dropwise via a syringe to quench the reaction. After 15 min, 2-aminoethanol (1.52 mL) was added via a syringe and the reaction was stirred overnight. The reaction mixture was poured into a separatory funnel and washed with brine (3 x 15 mL). The organic phase was dried over MgSO$_4$ and concentrated under vacuum to afford the crude product. Purification by flash column chromatography (20:1 PE/Et$_2$O) afforded 1.887 g of 21a as a yellow oil (66%): IR (neat) 2941, 2870, 1610, 1440, 1352, 1284, 1259, 1136, 1121, 1080, 1034, 984 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.67 (m, 6H), 2.42 (q, $J = 5.6$ Hz, 2H), 3.47 (m, 2H), 3.81 (m, 2H), 4.59 (m, 2H).

(Z)-3-Iodo-2-propenol (40b).\textsuperscript{63} In a 250 mL RBF was stirred a mixture of LiAlH$_4$ (1.010 g, 27.5 mmol) in Et$_2$O (82.5 mL) at 0 °C. To this mixture was added a solution of ethyl ester 39b (9.375 g, 41.5 mmol) in Et$_2$O (22 mL) dropwise via syringe and stirred for 1 h at 0 °C. The reaction was sequentially quenched at 0 °C with H$_2$O (1 mL) and 15% NaOH (w/v) (1 mL) added dropwise by syringe. An additional 3 mL of H$_2$O was added prior filtration by gravity. The filtrate was diluted with Et$_2$O (100 mL). The organic phase was then washed with saturated NaHCO$_3$ solution (40 mL) and dried over MgSO$_4$. After concentration under vacuum, the crude product was purified by flash column chromatography (10:1 PE/Et$_2$O) to afford 3.236 g of product as a light yellow oil (42%): IR (neat) 3321, 3069, 2921, 2869, 1610, 1449, 1280, 1043, 1010, 648, 618, 522 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.23 (dd, $J = 5.7, 1.4$ Hz, 2H), 6.35 (dt, $J = 7.7, 1.4$ Hz, 1H), 6.48 (dt, $J = 7.7, 5.7$ Hz, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 66.09, 83.09, 140.38.
(Z)-2-(3-Iodo-2-propenyloxy)tetrahydro-2H-pyran (21b). To a stirred solution of dihydropyran (1.552 g, 18.5 mmol) in CH$_2$Cl$_2$ (42 mL) was added p-TsOH (0.234 g, 1.23 mmol) as a solid in one portion. The reaction mixture was cooled to 0 °C and the allylic alcohol 40b (3.231 g, 17.6 mmol) in CH$_2$Cl$_2$ (21 mL) was then added rapidly at 0 °C. The reaction was allowed to warm to rt and stirred overnight. The solvent was removed under vacuum to afford crude product, which was purified by flash column chromatography (35:1 PE/Et$_2$O) to afford 3.731 g of 21b as an oil (79%): IR (neat) 3070, 2941, 2870, 1613, 1448, 1347, 1280, 1200, 1124, 1068, 1031, 964, 905, 872, 815, 643 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.65 (m, 6H), 3.52 (m, 1H), 3.86 (m, 2H), 4.10 (ddt, $J$ = 13.5, 5.2, 1.2 Hz, 1H), 4.64 (m, 1H), 6.42 (m, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 19.38, 25.37, 30.52, 62.31, 70.03, 82.75, 98.53, 138.31.

(Z)-3-Bromo-2-propenol (40c). In a 250 mL RBF was stirred a mixture of LiAlH$_4$ (0.303 g, 7.58 mmol) in Et$_2$O (23 mL) at 0 °C. To this mixture was added a solution of ethyl ester 39c (2.042 g, 11.4 mmol) in Et$_2$O (6 mL) dropwise via syringe and stirred for 1 h at 0 °C. The reaction was sequentially quenched at 0 °C with H$_2$O (0.3 mL) and 15% NaOH (w/v) (0.3 mL) added dropwise by syringe. An additional 0.9 mL of H$_2$O was added prior to filtration by gravity. The filtrate was diluted with Et$_2$O (40 mL). The organic phase was then washed with saturated NaHCO$_3$ solution (12 mL) and dried over MgSO$_4$. After concentration under vacuum, the crude product was purified by flash column chromatography (10:1 PE/Et$_2$O) to afford 0.751 g of product as a light yellow oil (48%): IR (neat) 3326, 3085, 2927, 2877, 1623, 1453, 1292, 1047, 1015, 959, 663 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.31 (dd, $J$ = 5.3, 1.0 Hz, 2H), 6.31 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 60.95, 108.94, 133.85.
(Z)-2-(3-Bromo-2-propenyloxy)tetrahydro-2H-pyran (21c). To a stirred solution of dihydropyran (0.472 g, 5.32 mmol) in CH₂Cl₂ (12.5 mL) was added p-TsOH (71 mg, 0.37 mmol) as a solid in one portion. The reaction mixture was cooled to 0 °C and the allylic alcohol 40c (0.729 g, 17.6 mmol) in CH₂Cl₂ (6.25 mL) was then added rapidly at 0 °C. The reaction was allowed to warm to rt and stirred overnight. The solvent was removed under vacuum to afford crude product, which was purified by flash column chromatography (50:1 then 35:1 PE/Et₂O) to afford 0.899 g of 21c as an oil (76%): IR (neat) 3084, 2943, 2870, 1627, 1350, 1291, 1201, 1125, 1071, 1031, 964, 872, 815, 670 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.64 (m, 6H), 3.51 (m, 1H), 3.85 (m, 1H), 4.18 (ddd, J = 14.1, 5.8, 0.9 Hz, 1H), 4.33 (ddd, J = 13.8, 5.1, 1.3 Hz, 1H), 4.62 (m, 1H), 6.29 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 19.35, 25.33, 30.50, 62.25, 65.31, 98.48, 109.01, 132.09.

1-4.9 Syntheses of enetriynes 47 and 50: Stille coupling and deprotection

(Z)-13-(tert-Butyldiphenylsiloxy)-1-(tetrahydro-2H-pyran-2-yloxy)-2-tridecene-4,6,8-triyne (41). To a stirred solution of TMS-triyne 30d (0.989 g, 2.17 mmol) and (Bu₃Sn)₂O (0.553 mL, 1.08 mmol) in dry THF (21.7 mL) was added TBAF (1.0 M, 43.4 μL, 0.043 mmol) at rt. The mixture was stirred for 3.5 h and was then concentrated under vacuum to afford crude product, which was used without further purification. No spectroscopic data were collected for this intermediate.
To a stirred solution of THP-protected iodoalkene 21b (0.465 g, 1.74 mmol), Pd(dba)$_2$ (49.9 mg, 0.05 mmol), and P(furyl)$_3$ (40.4 mg, 0.10 mmol) in THF (16.8 mL) was added the crude Bu$_3$Sn-triyne. The reaction was stirred in the dark at room temperature for 16 h. The reaction mixture was then concentrated under vacuum to give crude product as a dark brown oil. Purification by flash column chromatography (50:1 then 20:1 PE/Et$_2$O) afforded 0.644 g of product (71%) as a dark reddish-brown oil: IR (neat) 3071, 3049, 2932, 2858, 2248, 2213, 2184, 1590, 1472, 1428, 1389, 1201, 1112, 1032, 907, 823, 736, 702, 614, 506 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-d$_6$) $\delta$ 1.04 (s, 9H), 1.51 (m, 6H), 1.70 (m, 4H), 2.43 (t, $J = 6.3$ Hz, 2H), 3.46 (m, 1H), 3.73 (t, $J = 5.7$ Hz, 2H), 3.80 (m, 1H), 4.26 (ddd, $J = 14.0$, 6.6, 1.6 Hz, 1H), 4.42 (ddd, $J = 14.0$, 6.0, 1.8 Hz, 1H), 4.64 (t, $J = 3.4$ Hz, 1H), 5.75 (dt, $J = 11.2$, 1.5 Hz, 1H), 6.40 (dt, $J = 11.0$, 6.5 Hz, 1H), 7.44 (m, 6H), 7.69 (m, 4H); $^{13}$C NMR (75.5 MHz, acetone-d$_6$) $\delta$ 19.52, 19.73, 19.97, 25.31, 26.18, 27.22, 31.23, 32.29, 59.69, 62.33, 63.96, 65.73, 65.87, 68.94, 72.80, 79.83, 84.75, 99.03, 109.19, 128.61, 130.58, 134.58, 136.26, 147.55; HRMS (ESI) calcd m/z for C$_{34}$H$_{40}$O$_3$SiNa$^+$ 547.2639, found m/z 547.2622.

$\text{(Z)-13-(Tetrahydro-2H-pyran-2-yl oxy)-11-tridecene-5,7,9-triyn-1-ol (51).}$ To a stirred solution of enetriyne 41 (0.151 g, 0.287 mmol) in THF (5.5 mL) at 0 °C was added TBAF (1.0 M in THF, 0.28 mL, 0.280 mmol). The reaction was stirred in the dark at 0 °C for 2 h and was then quenched with brine (10 mL). The aqueous layer was extracted with Et$_2$O (3 x 15 mL). The combined organic phases were dried over MgSO$_4$ and concentrated under vacuum to give the crude product, which was used without further purification in the subsequent deprotection. Purification of a reaction by flash column chromatography (2:1 PE/Et$_2$O) afforded 51 in 87% yield: IR (neat) 3390, 2943, 2870, 2213, 2183, 1627, 1455, 1442, 1201, 1136, 1120, 1076, 1032, 980, 903, 868, 704 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.52 (m, 4H), 1.63 (m, 4H), 1.78 (m, 2H), 2.35 (t, $J = 6.6$ Hz, 2H), 3.49 (m, 1H), 3.63 (t, $J = 6.0$ Hz, 2H), 3.84 (m, 1H), 4.27 (ddd, $J =$
14.0, 6.8, 1.5 Hz, 1H), 4.43 (ddd, \(J = 13.8, 6.0, 1.5\) Hz, 1H), 4.61 (m, 1H), 5.59 (dt, \(J = 11.0, 1.7\) Hz, 1H), 6.26 (dt, \(J = 11.2, 6.4\) Hz, 1H).

**(Z)-2-Tridecene-4,6,8-triyne-1,13-diol (47).** To a stirred solution of crude THP-protected enetriyne 51 (82.1 mg, 0.287 mmol) in 3:1 MeOH/Et\(_2\)O (6.3 mL) was added Dowex-50W resin (0.161 g) as a solid in one portion. The reaction was stirred in the dark for 36 h. The reaction mixture was then filtered by gravity and the solids washed with Et\(_2\)O (3 x 20 mL). The filtrate was concentrated under vacuum to give the crude product, which was purified by flash column chromatography (1:2 PE/Et\(_2\)O) to afford 31.2 mg of 47 as an oil (54% over two steps): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.63 (m, 4H), 2.36 (t, \(J = 6.4\) Hz, 2H), 3.65 (t, \(J = 6.0\) Hz, 2H), 4.38 (dd, \(J = 6.4, 1.5\) Hz, 2H), 5.57 (dt, \(J = 11.0, 1.3\) Hz, 1H), 6.27 (dt, \(J = 11.0, 6.4\) Hz, 1H).

**TBDPSO**

![Diagram](image)

**(Z)-13-(tert-Butyldiphenylsiloxy)-2-tridecene-4,6,8-triyn-1-ol (49).** To a stirred solution of THP-protected enetriyne 41 (0.221 g, 0.421 mmol) in 3:1 MeOH/Et\(_2\)O (7.5 mL) was added Dowex-50W resin (0.240 g) as a solid in one portion. The reaction was stirred in the dark for 36 h. The reaction mixture was then filtered by gravity and the solids washed with Et\(_2\)O (3 x 25 mL). The filtrate was concentrated under vacuum to give the crude product, which was purified by flash column chromatography (2:1 PE/Et\(_2\)O) to afford 91.7 mg of 49 as an oil (49%): IR (neat) 3360, 3071, 3050, 2932, 2858, 2213, 2184, 1698, 1590, 1472, 1428, 1390, 1111, 1010, 824, 741, 703, 614, 506 cm\(^{-1}\); \(^1\)H NMR (300 MHz, acetone-\(d_6\)) \(\delta\) 1.06 (s, 9H), 1.72 (m, 4H), 2.46 (t, \(J = 6.3\) Hz, 2H), 3.76 (t, \(J = 5.8\) Hz, 2H), 4.36 (m, 2H), 5.67 (dt, \(J = 11.1, 1.5\) Hz, 1H),
6.41 (dt, J = 11.1, 6.3 Hz, 1H), 7.46 (m, 6H), 7.72 (m, 4H); $^{13}$C NMR (75.5 MHz, acetone-d$_6$) δ 19.51, 19.73, 25.32, 27.22, 32.29, 59.74, 60.96, 61.08, 63.97, 65.88, 68.71, 73.00, 79.43, 84.60, 107.43, 128.61, 130.59, 134.59, 136.27, 151.22; HRMS (ESI) calcd m/z for C$_{29}$H$_{32}$O$_2$SiNa$^+$ 463.2064, found m/z 463.2075.

(Z)-1-(Tetrahydro-2H-pyran-2-yloxy)-2-tridecene-5,7,9-triyne (48). To a solution of TMS-triyne 30e (0.454 g, 2.27 mmol) and (Bu$_3$Sn)$_2$O (0.58 mL, 1.14 mmol) in dry THF (23 mL) was added TBAF (1.0 M, 0.042 mL, 0.042 mmol) at rt. The mixture was stirred for 3.5 h and was then concentrated under vacuum to afford crude product, which was used without further purification. No spectroscopic data were collected for this intermediate.

To a stirred solution of THP-protected allylic iodoalkene 21b (0.481 g, 1.79 mmol), Pd(dba)$_2$ (51.5 mg, 0.05 mmol), and P(furyl)$_3$ (41.6 mg, 0.10 mmol) in THF (17.6 mL) was added the crude Bu$_3$Sn-triyne. The reaction was stirred in the dark at room temperature for 16 h. The reaction mixture was then concentrated under vacuum to give crude product as a dark brown oil. Purification by flash column chromatography (50:1 hexanes/EtOAc) afforded 0.493 g of a reddish-brown oil (100%): IR (neat) 2939, 2872, 2214, 1455, 1342, 1201, 1133, 1078, 1029, 906, 734 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-d$_6$) δ 0.90 (t, J = 7.2 Hz, 3H), 1.39 (m, 2H), 1.50 (m, 4H), 1.58 (m, 2H), 1.79 (m, 2H), 2.40 (t, J = 6.8 Hz, 2H), 3.46 (m, 1H), 3.78 (m, 1H), 4.29 (m, 1H), 4.42 (ddd, J = 14.0, 6.0, 1.7 Hz, 1H), 4.63 (m, 1H), 5.75 (dt, J = 11.3, 1.7 Hz, 1H), 6.40 (dt, J = 11.3, 6.4 Hz, 1H); $^{13}$C NMR (75.5 MHz, acetone-d$_6$) δ 13.68, 19.34, 19.97, 22.53, 26.17, 30.71, 31.23, 60.01, 62.27, 65.73, 67.39, 72.74, 75.33, 79.81, 83.95, 98.77, 108.45, 147.52; HRMS (ESI) calcd m/z for C$_{18}$H$_{22}$O$_2$Na$^+$ 293.1512, found m/z 293.1541.
(Z)-2-Tridecene-4,6,8-triyne-1-ol (50). To a stirred solution of THP-protected enetriyne 48 (0.380 g, 1.41 mmol) in 3:1 MeOH/Et₂O (25 mL) was added Dowex-50W resin (0.80 g) as a solid in one portion. The reaction was stirred in the dark for 36 h. The reaction mixture was then filtered by gravity and the solids washed with Et₂O (3 x 25 mL). The filtrate was concentrated under vacuum to give the crude product. Purification by flash column chromatography (5:1 PE/Et₂O) afforded 0.185 g of 50 (70%) as an oil: IR (neat) 3326, 2959, 2933, 2872, 2214, 1459, 1422, 1041, 1019, 735 cm⁻¹, ¹H NMR (300 MHz, acetone-d₆) δ 0.90 (t, J = 7.3 Hz, 3H), 1.46 (m, 4H), 2.40 (t, J = 6.8 Hz, 2H), 4.32 (m, 2H), 5.64 (d, J = 11.1 Hz, 1H), 6.38 (dt, J = 11.1, 6.3 Hz, 1H); ¹³C NMR (75.5 MHz, acetone-d₆) δ 13.20, 18.89, 22.06, 30.24, 59.16, 60.47, 60.59, 65.20, 68.21, 72.46, 78.94, 84.18, 106.96, 150.69; HRMS (ESI) calcd m/z for C₁₃H₁₄ONa⁺ 209.0937, found m/z 209.0930.
References


45. Tykwinski, R. R., personal communication.


Chapter 2. Synthetic and mechanistic studies of dimethyl disulfide addition to 1,4-enynes

2-1. Introduction

Characterization of unsaturated fatty acids by GC-MS methods requires the formation of a derivative to prevent migration of the C=C double bond. Dimethyl disulfide (DMDS) derivatization of unsaturated fatty acids, especially for monoenoic fatty acids, is a widely used method for the mass spectrometric location of the C=C double bond (Scheme 19). DMDS is added stereoselectively across the double bond of a monounsaturated alkene, yielding suitable adducts for GC-MS analysis without isolation or purification. Cleavage of the radical cation during an electron-impact MS analysis subsequently occurs between the carbons that originally constituted the double bond to yield two intense fragment ions that serve to locate the unsaturated positions.

Scheme 19. Dimethyl disulfide derivatization of a monoenoic methyl ester

DMDS derivatization of polyunsaturated fatty acids presents more difficulties than monoenes due to the formation of a complex array of heterocyclic structures. When the double bonds are separated by more than four carbon atoms, independent derivatization of the alkenes occurs, but fatty acids with this unsaturation pattern are relatively rare in nature. When the double bonds are closer together, such as methyl linoleate, a complex product mixture is possible. DMDS derivatization reactions at higher temperatures (60 °C) and longer reaction times (40 h) result in cyclization to give heterocycles containing with thietane, tetrahydrothiophene and tetrahydrothiopyran structures (4, 5, 6-membered rings). These compounds do not fragment into ions with easily interpretable mass spectra (Scheme 20). GC-MS analysis can be simplified by partial hydrogenation of the C=C double bonds in polyunsaturated fatty acids to generate monoenoic fatty acids prior to the DMDS derivation.
Consequently, the formation of 1,2-di(thiomethyl) ethers can be expanded to locate the C=C double bonds in polyunsaturated fatty acids (Scheme 21).

Scheme 20. DMDS derivatization of a dienoic ester with proximate double bonds

\[
\text{R} - \text{C} = \text{C} - \text{R}' 
\text{DMDS, I}_2 
\text{cyclohexane} \quad 35-60 \, ^\circ \text{C}
\]

In order for this method to be a useful analytical technique for the analysis of unknown samples, a comprehensive spectral library was needed. This has been done for a variety of simple 1,3-dienoate esters, but to date, no examples of 1,4-enyne derivatives have been reported. As such, we set out to explore the feasibility of using the DMDS derivatization method for the analysis of acetylenic fatty acids, as exemplified by crepenynic acid. Crepenynic acid is a constituent of certain seed oils and the biosynthetic precursor to a large family of acetylenic secondary metabolites in plants. When methyl crepenynate, produced by transesterification of Crepis alpina seed oil, was subjected to the literature DMDS derivatization conditions, a high yield of 2,5-disubstituted thiophene was isolated (Scheme 22). Product characterization verified that the cyclization occurred by the regioselective insertion of a sulfur atom between C9 and C12 of the crepenynate backbone.

Encouraged by these results, methyl 6-tridecen-9-ynoate was synthesized as a model compound to study this reaction. Again, cyclization to the corresponding thiophene was observed (Scheme 22). Two aspects of the thiophene-forming reaction were then examined. Firstly, the scope of the new DMDS derivatization of 1,4-enynes for the production of 2,5-disubstituted thiophenes was explored. The effects of functionality and chain length from the enyne on the yield of the reaction were examined. A series of 6-tridecen-9-yne derivatives were synthesized to compare functional group effects. Also, a series of 1,4-enynes consisting of four and five carbons between the distal functional groups and the enyne were synthesized to study
the effect of tether length on the reaction. In this chapter, the synthetic scope of this reaction will be outlined.

Scheme 21. Partial hydrogenation before DMDS derivatization for the analysis of dienoic esters

Secondly, a series of experiments focusing upon the reaction mechanism were undertaken. Isotopic labeling and trapping experiments were carried out and reported.\(^{23}\) In addition, optimization of preparative reaction conditions and the syntheses of several hypothetical reaction intermediates for the DMDS-mediated heterocyclization have also been explored. In this chapter, the syntheses of two intermediates for potential thiophene-forming mechanisms, their testing, and the results of these experiments will be presented. Attempts to uncover an acid-catalyzed allene mechanism will be also be explored and discussed.

Scheme 22. DMDS derivatization of acetylenic methyl esters\(^d\)

\(^d\) Reagents and conditions: DMDS, \(\text{I}_2\), MeOH, 60 °C, 6 h
2-2. Results and Discussion

2-2.1 Syntheses of 1,4-enynes

DMDS derivatization, in which DMDS and I$_2$ were reacted with C$_{13}$ methyl ester 55, produced thiophene 56 as the major product in 56% yield (Scheme 22).

This reaction defined a new route to 2,5-disubstituted thiophenes. A goal of my studies was to determine the scope and utility of DMDS derivatization for the synthesis of 2,5-disubstituted thiophenes. To this effect, various 1,4-enynes were constructed for subsequent reactions with DMDS/I$_2$. Two variables were considered with respect to their influence on the reaction – type of remote functionality and tether chain length. A series of 6-tridecene-9-yne compounds were made to compare the effect of various functional groups on DMDS derivatization. The chain length (Scheme 24, n = 4, 3, 2) was varied for benzoate ester 63a-c and enynol derivatives 64a-c.

An efficient methodology for the synthesis of 1,4-enynes had already been developed by Zhu for the C$_{13}$ methyl ester (55) (Scheme 23). Expansion of this strategy led to the general route outlined in Scheme 24. The construction of the enyne occurred through a Wittig reaction (Scheme 23, reaction c). Deprotonation of 59 resulted in a un-stabilized ylide that coupled with an appropriate aldehyde and formed the desired (Z)-alkene. The ease of this synthesis lay in the fact that a collection of 1,4-enynes could be made through variation of only the aldehyde segment. Still, it was necessary for an efficient and facile route to the corresponding phosphonium salt 59. Commercially available 3-heptyn-1-ol 57 was reacted with a triphenylphosphine-bromine complex to convert the alcohol to bromide 58. Phosphonium salt 59 was then produced from the reaction of 58 with triphenylphosphine in methanol while stirring for 20 h at 110 °C.

For the 6-tridecen-9-yne series of compounds, commercially available 1,6-hexanediol 60a was monoprotected through reaction with pyridine and benzoyl chloride to afford desymmetrized alcohol 61a. To favor mono-esterification, a large excess of 60a was used. The addition of benzoyl chloride in three small portions over 1 h versus a large portion at once provided the highest yield of 61a (86%). The oxidation of 61a to benzoyl aldehyde 62a was straightforward. Reaction with pyridinium chlorochromate (PCC) and silica gel as a ground admixture, followed by vacuum-filtration through a pad of Celite and silica gel resulted in crude aldehyde. Purified 62a was then obtained after flash column chromatography (81%).
Scheme 23. Synthesis of methyl 6-tridecen-9-ynoate $55 \text{(C}_{13}\text{ methyl ester)}$

\[
\begin{align*}
\text{HO} & \quad \text{a} \quad \text{86\%} \quad \text{Br} & \quad \text{b} \quad \text{97\%} \quad \text{BrPh}_3\text{P} \\
57 & \quad 58 & \quad 59 \\
\text{c} \quad 54\% & \quad \text{MeO} & \quad \text{55}
\end{align*}
\]

Reagents and conditions: (a) PPh$_3$·Br$_2$, pyridine, CH$_2$Cl$_2$, 0 °C; (b) PPh$_3$, MeOH, 110 °C, 20 h; (c) MeOOC(CH$_2$)$_4$CHO, NaH, THF/HMPA, rt, 20 h

The successful coupling of the two segments via a Wittig reaction assembled the 6-tridecen-9-yne chain. This step proved to be the most cumbersome as the careful selection of solvent and base played a significant role in the success of the reaction. First of all, the best results were achieved when a solvent was chosen that completely dissolved the phosphonium salt (59) before the addition of base. It was found that while 59 was slightly soluble in both Et$_2$O and THF, HMPA increased the solubility of the salt immensely. It was found that a 10:1 mixture of THF/HMPA provided for complete dissolution. Secondly, the choice of base influenced the reaction to a degree. It was found that the use of sodium hydride (NaH), as a 95% powder, gave the best results. The condition of the phosphonium salt was found to be important. Phosphonium salt 59 was extremely hygroscopic and even minimal air-exposure was detrimental to its condition. To summarize, the best yields (65%) of 63a were obtained using NaH in a 10:1 THF/HMPA mixture with recently prepared 59. The final step for the realization of 6-tridecen-9-yne-1-ol 64a was base-mediated ester hydrolysis in which 63a was reacted with a 1% NaOH methanol solution. A nearly quantitative yield (99%) for enynol 64a was obtained (Scheme 24).

As presented in Schemes 25 and 26, 64a was a versatile intermediate for the syntheses of other 1,4-enynes. It was envisioned that enynol 64a could be transformed into the analogous tosyl, thiol, amine, and carboxylic acid. Of particular importance to us, were the amine and carboxylic acid derivatives, as in the developing stages of this project, it was found that acidic conditions favored the formation of thiophene while basic conditions appeared to terminate the
reaction. With the amine and carboxylic acid derivatives, the proximity effect of the two functional groups on the course of the DMDS reaction were to be determined. However, these two derivatives proved difficult to synthesize (Scheme 25). Conversion of 64a to azide 65 was accomplished in 76% yield, but numerous attempts to reduce the azide to the amine (66) were unsuccessful. Using lithium aluminum hydride (LiAlH4) to reduce 65 failed. Also, a literature method in which ammonium formate is used as the reducing agent did not provide for the successful reduction of 65. The direct oxidation of 64a with both PCC and pyridinium dichlorochromate (PDC) failed to produce carboxylic acid 67. As an alternative, C13 model ester 55 was prepared as previously described and then a base-catalyzed ester hydrolysis utilizing LiOH in acetone proved successful in the synthesis of 67 in a 99% yield.

Scheme 24. Synthetic route to 1,4-enynols

![Scheme 24](image)

Reagents and conditions: (a) PPh3· Br2, pyridine, CH2Cl2; (b) PPh3, MeOH, 110 °C, 20 h; (c) BzCl, pyridine, CH2Cl2; (d) PCC/silica gel, CH2Cl2; (e) 59, NaH, THF/HMPA, rt, 20 h; (f) 1% NaOH in MeOH

Tosyl enyne 68 and thiol enyne 70 were easily synthesized in good yield (Scheme 26). p-TsCl and pyridine were successfully used to convert enynol 64a to 68 in a 91% yield. A Mitsunobu reaction, employing triphenylphosphine, DIAD and thiolacetic acid, were used for the conversion of 64a to the corresponding thiolester enyne (69) in 97% isolated yield. Subsequent reduction of the thioester with LiAlH4 resulted in a 91% yield of thiol 70. To summarize the 6-
tridecen-9-yne series, the benzoate ester 63a, alcohol 64a, tosyl 68, thiol 70, and the acid 67 were all synthesized in good yields with only one target molecule, the amine 66, failing to be produced.

Scheme 25. Attempted syntheses of amine and carboxylic acid derivatives

\[ \text{Scheme 25. Attempted syntheses of amine and carboxylic acid derivatives}^{a} \]

\[ \begin{align*}
64a & \xrightarrow{a} 76\% \quad \text{N}_3 \\
64a & \xrightarrow{b} \quad \text{H}_2\text{N} \\
64a & \xrightarrow{c} \quad \text{O}
\end{align*} \]

\( a \) Reagents and conditions: (a) PPh\(_3\), DPPA, DIAD, THF; (b) LiAlH\(_4\) or ammonium formate, 5\% Pd-C; (c) PCC in CH\(_2\)Cl\(_2\) or PDC in DMF

As mentioned earlier, the effect of chain length on the DMDS derivatization was another important constraint to be examined. Chain length was varied from \( n = 4 \) to \( n = 2 \) in Scheme 24 by following an analogous sequence to that used with 1,6-hexanediol 60a starting from the commercially available diols, 1,5-pentanediol 60b and 1,4-butanediol 60c. The range of yields for the syntheses of the three chain length derivatives are given in Scheme 24. Enynols 64b and 64c were of particular interest. If the mechanism of the reaction proceeded via an intermediate with cationic character at one of the alkene carbons, it was postulated that enynols 64b and 64c could effectively trap the cation, resulting in five- or six-membered cyclic ethers.

To provide additional examples and insight into the effect of chain length, C\(_{12}\) 74a and C\(_{11}\) 74b methyl esters were synthesized in a similar fashion to the C\(_{13}\) model methyl ester 55. First, \( \gamma \)-valerolactone 71a and \( \delta \)-butyrolactone 71b were subjected to methanolysis in refluxing 5\% H\(_2\)SO\(_4\)/methanol solution. The respective methyl ester alcohols (72a, \( n = 3 \) and 72b, \( n = 2 \)) were reacted as described earlier in the syntheses of the 6-tridecen-9-yne compounds to provide 74a and 74b in moderate yields (Scheme 27).
Scheme 26. Syntheses of additional 6-tridecen-9-yne

\[ \text{Scheme 26. Syntheses of additional 6-tridecen-9-yne}^{a} \]

\[ \begin{align*}
\text{64a} & \xrightarrow{\text{a}} 91\% \quad \text{TsO} \quad \text{68} \\
\text{64a} & \xrightarrow{\text{b}} 97\% \quad \text{SO} \quad \text{69} \\
\text{55} & \xrightarrow{\text{d}} 99\% \quad \text{HO} \quad \text{67}
\end{align*} \]

\[ \begin{align*}
\text{Reagents and conditions: (a) } p\text{-TsCl, pyridine, CH}_2\text{Cl}_2, 0^\circ \text{C}; \text{ (b) PPh}_3, \text{ DIAD, thiolacetic acid,} \\
\text{THF; (c) LiAlH}_4, \text{ Et}_2\text{O; (d) (i) LiOH, acetone, (ii) 1 N HCl} \]

Several additional 1,4-enynes were synthesized to determine the effect of an aryl or unsubstituted alkyl group. Three commercially available aldehydes were chosen so that only one step, the Wittig reaction, would need to be completed for each 1,4-enyne, allowing direct enyne syntheses. 1,4-Enynes 75, 76, and 77 were synthesized in moderate yield (Scheme 28).

Scheme 27. Syntheses of methyl ester 1,4-enynes

\[ \text{Scheme 27. Syntheses of methyl ester 1,4-enyne}^{a} \]

\[ \begin{align*}
\text{n = 3} & \quad \text{71a} \\
\text{n = 2} & \quad \text{71b} \\
\text{72a,b} & \xrightarrow{\text{a}} 60\% \quad \text{MeO} \quad \text{73a,b} \\
\text{74a,b} & \xrightarrow{\text{c}} 60\%
\end{align*} \]

\[ \begin{align*}
\text{Reagents and conditions: (a) } 5\% \text{ H}_2\text{SO}_4/\text{MeOH, reflux, 70 }^\circ \text{C, overnight; (b) PCC/silica gel,} \\
\text{CH}_2\text{Cl}_2; \text{ (c) 59, NaH, THF/HMPA, rt, 20 h} \]

67
Scheme 28. Additional enynes from commercially available aldehydes\textsuperscript{a}

\begin{align*}
\text{PhCH}_2\text{CHO} & \xrightarrow{54\%} \text{Ph}\text{CH}═\text{C}═\text{C}═\text{CH}_2 \\
\text{PhC}═\text{CHCHO} & \xrightarrow{56\%} \text{Ph}\text{C}═\text{C}═\text{C}═\text{CH}_2 \\
\text{CH}_3\text{C}═\text{CHCO}_2\text{H} & \xrightarrow{49\%} \text{CH}_3\text{C}═\text{C}═\text{C}═\text{CH}_2
\end{align*}

\textsuperscript{a} Reagents and conditions: 59, NaH, THF/HMPA, rt, 20 h

2-2.2 DMDS derivatization of 1,4-enynes

With the 6-tridecen-9-ynes and additional 1,4-enynes synthesized, DMDS derivatization was undertaken. Optimized DMDS derivatization, previously reported by our lab,\textsuperscript{23} was used as standard conditions and are as follows. A 10 mg/mL solution of 1,4-enyne in MeOH was reacted with 10 equivalents of DMDS and 3 equivalents of I\textsubscript{2} in the dark at 60 °C for 6 h (Scheme 29). After standard work-up as described in the Experimental Section, the crude product was purified by flash column chromatography. Purification of thiophenes 78a-k were on occasion difficult by flash column chromatography using silica gel, as the crude mixtures were very complex with several spots having similar \textit{R}_{f} values. Hence, after initial flash column chromatography, the resulting mixture still needed to be separated using HPLC to obtain pure, isolated thiophene products 78a-k. The HPLC setup as described in the general procedures of the Experimental Section was used. The results of the DMDS derivatizations are summarized in Table 5 as isolated yields after flash column chromatography and HPLC. DMDS derivatization of the 1,4-enynes consistently resulted in low to moderate yields of 2,5-disubstituted thiophene product 78a-k. Carboxylic acid derivative 67 proceeded in the highest yield (28\%), followed by enynol 64a (25\%). However, the average yield was closer to 10\% for many of the enynes.

Several generalizations were inferred from the results. It appeared that the reaction was very sensitive to functionality. When the functional group of the 1,4-enynes was varied, each
gave considerably lower results when compared to either C\textsubscript{13} methyl ester 55 or methyl crepenynate 53. The sensitive nature of the reversible addition of the sulfur electrophile to the \(\pi\)-system was likely affected\textsuperscript{32,33}. The presence of functional groups other than a methyl ester altered this equilibrium, decreasing the yield of productive reactions. Many of the 1,4-enynes contained nucleophilic functionalities, which may not favor thiophene formation. The chain length also appeared to affect the yield of thiophene product. As the number of methylenes that link the 1,4-enzyme moiety to the terminal functional group was decreased, the yield of the reaction also decreased. Steric effects may also interfere with the addition of DMDS as the functional group was moved closer to the reaction center. The thiophenes, produced by the DMDS derivatization of benzoate ester 63c and enynols 64b and 64c, were not isolated by HPLC. These reactions were only analyzed by GC-MS to determine if nucleophilic trapping of a cationic intermediate by oxygen nucleophile could be observed. When enynols 64b and 64c were reacted with DMDS/I\textsubscript{2}, no evidence was found for the formation of cyclic ethers. Implied in these results was that the mechanism for this reaction was not consistent with a cationic intermediate that could be trapped by cyclization of enynols 64b and 64c. While nucleophilic attack of the alcohol on an electron-deficient sulfur may compete for trapping at carbon, MeS\textsuperscript{+} addition to the alkyne provides an alternative explanation.

Scheme 29. 1,4-Enyne reactions with DMDS\textsuperscript{a}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {R-\hspace{1cm}C=C-C=C-S-\hspace{1cm}R}
\end{tikzpicture}
\end{center}

\textsuperscript{a} Reagents and conditions: DMDS (10 eq), I\textsubscript{2} (3 eq), MeOH, 60 °C, 6 h
Table 5. Results of DMDS derivatizations of 1,4- enyne derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,4-Enyne Precursor</th>
<th>Thiophene Product 78</th>
<th>R =</th>
<th>% Yield $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63a</td>
<td>a</td>
<td>BzO(CH$_2$)$_5$-</td>
<td>7%</td>
</tr>
<tr>
<td>2</td>
<td>64a</td>
<td>b</td>
<td>HO(CH$_2$)$_5$-</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>c</td>
<td>TsO(CH$_2$)$_5$-</td>
<td>13%</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>d</td>
<td>HS(CH$_2$)$_5$-</td>
<td>21%</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>e</td>
<td>HOOC(CH$_2$)$_4$-</td>
<td>28%</td>
</tr>
<tr>
<td>6</td>
<td>74a</td>
<td>f</td>
<td>MeOOC(CH$_2$)$_3$-</td>
<td>7%</td>
</tr>
<tr>
<td>7</td>
<td>74b</td>
<td>g</td>
<td>MeOOC(CH$_2$)$_2$-</td>
<td>7%</td>
</tr>
<tr>
<td>8</td>
<td>63b</td>
<td>h</td>
<td>BzO(CH$_2$)$_4$-</td>
<td>8%</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>i</td>
<td>CH$_3$(CH$_2$)$_3$-</td>
<td>0%$^b$</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>j</td>
<td>Phenyl-(CH$_2$)$_2$-</td>
<td>17%</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>k</td>
<td>Phenyl-CHCH-</td>
<td>8%</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after flash column chromatography and HPLC

$^b$ 78i was major product by GC-MS, but no product was isolated after flash column chromatography and HPLC

An additional factor that may have contributed to the overall yield decrease of the 1,4-enyne derivatives as compared to the initial C$_{13}$ methyl ester and methyl crepenynate examples was the fact that all were purified by HPLC in addition to flash column chromatography. The C$_{13}$ methyl ester was purified by flash column chromatography only and additional purifications may have contributed to a decrease in the amount of isolated product.

2-2.3 Mechanistic studies

From previous mechanistic work, reasonable mechanisms for the DMDS derivatization reaction were proposed (Scheme 30).$^{23}$ First, iodine reacts with DMDS to produce MeSI, which then adds to the C=C double bond to form an episulfonium ion. From the episulfonium ion, three different pathways were hypothesized for the generation of thiophene product. It was determined that pathway b was not likely as synthesized cis- and trans-enynethiol ethers were
not converted to thiophene under standard DMDS conditions.\textsuperscript{23} However, neither the possibility of pathway c nor the potential involvement of allenes had been explored.

\textbf{Testing of thiirane pathway}

In the proposed mechanism (Scheme 30), it was hypothesized that the thiophene could be formed via a thiirane intermediate 79. In the proposed mechanism, the methyl group of episulfonium ion intermediate is cleaved by iodide to produce thiirane, which was consistent with the observation of MeI formed during the course of the reaction.\textsuperscript{23} Acid-catalyzed cyclization of the thiirane could occur and subsequent rearrangement would produce thiophene product. A similar transformation had been reported in the literature.\textsuperscript{34} A thiirane with a \(\beta,\gamma\)-alkynyl substituent was observed to cyclize to form the thiophene under acidic conditions. To test this hypothesis, thiirane 79 was synthesized from ethyl crepenynate (Scheme 31) in order to differentiate thiophene product formed from the thiirane 79 versus C\textsubscript{13} methyl ester 55 by GC-MS methods. To this end, \textit{Crepis alpina} seed oil 80 was transesterified with a 2\% H\textsubscript{2}SO\textsubscript{4} ethanol solution. The seed oil was a mixture of crepenynic and linoleic acids in an approximate 80:20 ratio. The crude mixture (81) contained both ethyl crepenynate and ethyl lineolate and was used directly in the next step. Epoxidation of the crude mixture with \(m\)-CPBA proved to be a facile reaction that proceeded at rt in 2 h. At this point, the mixture of epoxides was separated by flash column chromatography to give isolated ethyl crepenynate oxirane 82. The conversion of epoxide 82 to thiirane 79 was carried out by the method of Iranpoor.\textsuperscript{35} Cerium (IV) as ceric ammonium nitrate (CAN), in the presence of ammonium thiocyanate (NH\textsubscript{4}SCN), was used to catalyze the metathesis reaction with thiourea in a 66\% yield.

Experiments were conducted to determine whether synthesized thiirane 79 could be converted to thiophene using conditions similar to the DMDS protocol. A number of reaction conditions in methanol solvent were employed which included: (i) standard DMDS derivatization conditions with varying amounts of I\(_2\) (3 eq and 1 eq), (ii) HI (0.1 eq and 1 eq) and DMDS, (iii) HI only (0.1 eq and 1 eq), (iv) DMDS only, (v) and methanol only (Scheme 32). For the experiments involving HI, DMDS, and methanol, the reactions were analyzed after 2 h at rt, followed by reaction at 60 °C. At 60 °C, the experiments were analyzed after 3 and 6 h. Each set of experiments, which included either thiirane 79, C\textsubscript{13} methyl ester 55, or a mixture of both, was run in triplicate. It was observed that no thiophene product was formed from the thiirane.
intermediate when reacted by itself or in a mixture with \( \text{C}_{13} \) methyl ester under any of the reaction conditions tested. But, \( \text{55} \) was observed to form thiophene product \( \text{56} \) under condition (a) (Scheme 32).

These results support a mechanism for thiophene formation that is insensitive to the thiirane, and importantly, does not involve the thiirane as an intermediate on the path to thiophene. Thus, pathway c in Figure 30 was not consistent with the collected data relating to thiophene formation.

Scheme 30. Potential pathways of DMDS reaction mechanism\(^{23}\)
Scheme 31. Synthesis of thiirane as a potential intermediate\(^a\)

**Reagents and conditions:** (a) 2\% \(\text{H}_2\text{SO}_4/\text{EtOH}\), reflux, 80 °C, 2 h; (b) \(\text{m-CPBA}, \text{CH}_2\text{Cl}_2\); (c) \(\text{NH}_4\text{SCN}, \text{CAN}, t\text{-BuOH}, 50 \degree \text{C}\)

Scheme 32. Experiments to convert thiirane intermediate to thiophene\(^a\)

**Reagents and conditions:** (a) Standard DMDS derivatization conditions using 3 eq and 1 eq of \(\text{I}_2\); (b) HI with DMDS in MeOH; (c) HI only in MeOH; (d) DMDS only in MeOH; (e) MeOH only

**Synthesis and isolation of MeSI adduct**

The addition of \(\text{K}_2\text{CO}_3\) and 18-crown-6 to the standard DMDS derivatization reaction conditions resulted in only a trace amount of thiophene being formed.\(^{23}\) The major product,
adduct 83, by GC-MS had m/z 396 with a significant amount of starting material also remaining. Initially, no attempts were made to characterize this product as the observed m/z led us to believe that MeSI had simply added across the double bond of the enyne. This assumption was in part due to literature citations concerning the relative ease upon which MeSI adds across double bonds.\textsuperscript{32,33} The reaction was also originally run in MeOD. No deuterium incorporation was observed, which was expected as the only chemistry apparently involved MeSI addition to the π-bond.\textsuperscript{23} The limited, interpretable data available from the mass spectrum did not provide enough evidence for the full determination of the adduct’s structure.

A large-scale reaction of 83 was carried out for isolation and characterization of the MeSI adduct. The reagents and conditions for the synthesis of 83 are outlined in Scheme 33. Standard DMDS derivatization conditions were used, but K\textsubscript{2}CO\textsubscript{3} (3 eq) and 18-crown-6 (3 eq) were also added to the reaction mixture. After stirring in the dark for 6 h at 60 °C, the reaction mixture was extracted directly into hexanes. After standard work-up, the crude residue was initially passed through a flash column to remove the baseline impurities. In order to confidently assign a structure for the m/z 396 compound, substantial purification of 83 had to be accomplished prior to characterization by NMR spectroscopy. It was observed that all three compounds present in the mixture after flash column chromatography, namely, C\textsubscript{13} methyl ester 55, thiophene 56, and MeSI adduct 83 had a similar R\textsubscript{f} from TLC analyses.

Scheme 33. Reaction for the synthesis of MeSI adduct\textsuperscript{a}

\[ \text{MeO} \quad \xrightarrow{\text{Adduct}} \quad 55 \rightarrow 83 \]

\textsuperscript{a} Reagents and conditions: DMDS, I\textsubscript{2}, 18-crown-6, K\textsubscript{2}CO\textsubscript{3}, MeOH, 60 °C, 6 h

High-performance liquid chromatography (HPLC) was used to purify 83. No trifluoroacetic acid (TFA) was used in the eluent due to the potential acid sensitivity of 83. After injection of the sample, the solvent gradient was increased linearly from 50:50 to 0:100 A/B
(water/acetonitrile) over 20 min. Aided by GC-MS, fractions containing the adduct with $m/z$ 396 were found. Isolation was straightforward as the MeSI adduct (83) eluted in pure acetonitrile. The adduct solution was concentrated under vacuum and dissolved in acetone-d$_6$ for NMR analysis.

**Structure elucidation of MeSI adduct**

A considerable amount of work was required to assign the correct structure for the MeSI adduct (83). IR spectroscopy provided little direction towards the structure. Absorptions at 2958 and 2869 cm$^{-1}$ were consistent with sp$^3$–CH stretching and a strong absorbance at 1738 cm$^{-1}$ indicated the presence of an ester. High resolution-mass spectrometry (HRMS) with electrospray ionization (ESI) resulted in an observed $m/z$ 419.0493, consistent with a calculated $m/z$ 419.0512 for C$_{15}$H$_{25}$O$_2$SINa$^+$. Complete assignments could not be made from the one-dimensional $^1$H and $^{13}$C NMR data. Interestingly, the $^{13}$C NMR spectrum revealed 4 sp$^2$ carbons in addition to the carbonyl carbon. To assign the resonances, DEPT (90 and 135), HETCOR, $^1$H-$^1$H COSY, gradient HSQC, gradient HMBC, and 1-D NOE difference spectroscopic experiments were performed. The tabulated NMR data are summarized in Table 6.

Distortionless enhancement by polarization transfer (DEPT) experiments showed two of the sp$^2$ carbons were not attached to a proton, providing evidence for a tetra-substituted alkene. Correlation spectroscopy (COSY) was informative for the two spin systems and connectivity on either side of the tetra-substituted alkene. Heteronuclear chemical shift correlation (HETCOR) corroborated HSQC data whereby all $^1$H and $^{13}$C resonances were assigned with no evidence of diastereotopic hydrogens. HMBC revealed that C-14 had a strong crosspeak with C-2 and a weak interaction with C-5 consistent with the point of thiomethyl ether attachment. The NOE difference experiments showed that H-8 was in close proximity to H-4 and H-14 (Scheme 34, a and b), while H-14 and H-7 showed reciprocal NOE enhancement (Scheme 34, c). From the collected data, the structure of MeSI adduct 83 was determined specifying both the stereo- and regiochemical relationships around the tetra-substituted alkene (Scheme 34).
Through these experiments, NMR spectroscopy provided evidence for the anti-addition of MeSI to the carbon-carbon triple bond when subjected to basic conditions. Apparently, only one regioisomer was produced from the reaction. The additional C=C double bond may have a significant regiochemical influence on the production of 83. A possible explanation is that the π-complex formed between the carbon-carbon double bond and MeS⁺ blocks I⁻ attack at C-12 (in methyl crepenynate) (Scheme 35). No evidence for d-incorporation into 83 was observed under basic conditions in MeOD, which precludes the involvement of an ene-allene intermediate in adduct formation.
Table 6. Tabulated NMR data for MeSI adduct

<table>
<thead>
<tr>
<th>$^{13}$C assignment</th>
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<td>7, 13</td>
<td>13</td>
<td></td>
<td>t, $J = 7.5$ Hz</td>
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*w = weak; s = strong
Experiments on isolated MeSI adduct intermediate

After isolated MeSI adduct 83 was obtained, experiments were conducted to determine whether 83 could be affected to produce thiophene 56. Adduct 83 was subjected to a set of three different reaction conditions performed in duplicate, as outlined in Scheme 35. They were: (i) standard DMDS derivatization conditions, (ii) HI (2 eq.) and DMDS (10 eq.) in MeOH, (iii) and HI (2 eq.) only in MeOH. The indicated reagents were added to a 10 mg/mL solution of 83 and mixed. Finally, the test tubes were placed in a 60 °C water-bath for 6 h. After the reactions were completed, an aliquot from each flask was analyzed by GC-MS.

It was found that under standard DMDS derivatization conditions, the MeSI adduct 83 effectively proceeded to the thiophene product 56. The reaction was fairly clean by GC-MS as 56 and an unknown impurity with m/z 382 were the only major peaks in the mass spectrum. Only a trace amount of MeSI adduct 83 remained in the reaction mixture. However, the other two reaction conditions proceeded differently from the standard DMDS derivatization condition, but in practically the same manner to each other as only a small amount of thiophene 56 was observed. It appeared that the presence of DMDS had little effect on the outcome of the experiments involving HI. Side-products observed by GC-MS analysis were not characterized, however, a cursory search did not identify product with likely masses for constitutional isomers of 83, DMDS or I2 adducts. Also, an incomplete reaction was observed as a significant amount of starting MeSI adduct 83 remained in the mixture.

An additional experiment was performed in which conditions for the MeSI adduct formation were originally employed. After 5 h at 60 °C, formation of MeSI adduct was verified by GC/MS. HI (3 eq.) was then added to the reaction mixture and stirred for 2 h at 60 °C. From this experiment, it was found that thiophene 56 was formed in a 28% yield after flash column chromatography.

Isolated 83 was successfully converted to thiophene when subjected to standard DMDS derivatization conditions. However, it was not explicitly determined if the MeSI adduct 83 was a bona fide intermediate. It is plausible that an equilibrium exists between the 1,4-enyne and 83 as illustrated in Scheme 30. The MeSI adduct was only observed to form under basic conditions. Basic conditions effectively trapped the MeSI adduct 83, allowing it to accumulate. Due to the likely reversibility, isolated 83 allowed for the production of thiophene when subjected to DMDS derivatization conditions. Consumption of K2CO3 by the addition of HI to a reaction in
progress allowed the adduct’s conversion to 56. It should be noted that no MS evidence for the expected addition of DMDS to a 1,4-enyne leading to the vicinal bis(thiomethyl)ether has been found to date. As an intermediate, adduct 83 may be proposed to transform to thiophene as presented in Scheme 37.

Scheme 36. Experiments attempting the conversion of isolated MeSI adduct to thiophene 56

\[ \text{MeO} \quad \text{Me} \quad \text{S} \quad \text{Me} \quad \text{I} \quad \xrightarrow{a \text{ or } b \text{ or } c} \quad \text{MeO} \quad \text{Me} \quad \text{S} \quad \text{Me} \quad \text{Thiophene} \]

\(^a\) Reagents and conditions: (a) standard DMDS derivatization; (b) HI and DMDS in MeOH; (c) HI only in MeOH

Scheme 37. Rearrangement of MeSI adduct to thiophene under acidic conditions

Hypothetical acid-catalyzed allene mechanism

A set of experiments was developed to test the hypothesized acid-catalyzed allene mechanism (Scheme 38), which had not been explored by previous mechanistic work. Methyl crepenynate 53 and \(C_{13}\) thiophene 56 were subjected to standard DMDS derivatization conditions in MeOD. Performing the experiments in MeOD determined which positions were deuterated during the course of the reaction. As previously reported, deuterium incorporation at the \(\alpha\)-
position of the $n$-butyl side chain was observed when C$_{13}$ methyl ester 55 was subjected to DMDS derivatization in MeOD.$^{23}$ It was also known that deuteriation of the thiophene ring occurred, presumably by acid-catalyzed electrophilic substitution. Hence, thiophene 53' derived from methyl crepenynate 53 possessed four possible sites for deuterium incorporation. In contrast, after thiophene formation has occurred, only two sites were labile as seen in 56' derived from 56 (Scheme 39). H/D exchange efficiency before and after ring formation were to be explored.

Scheme 38. Hypothetical acid-catalyzed allene mechanism

Three reactions were tested, which included: (1) methyl crepenynate 53, (2) C$_{13}$ thiophene 56, (3) and a 1:1 mixture of 53 and 56. The three different reactions were performed in triplicate (Scheme 39). After reacting for 6 h at 60 °C, each sample was analyzed by GC/MS in triplicate. To determine the amount of deuterium incorporation, natural abundance samples with no deuteration had to be analyzed to provide isotopomer distributions. To this effect, thiophene 56 isolated from previous DMDS reactions in MeOH and thiophene 54 prepared from DMDS derivatization of 53 in MeOH were analyzed in triplicate by GC/MS. Using the envelope of isotopic peak intensities, isotopomer distribution could be extracted and the results are summarized in Table 7. It was concluded that variable amounts of DI present, likely formed through elimination processes from iodinated enynes, causes a wide variation in H/D exchange rates. Under the reaction conditions, H/D exchange into preexisting thiophene occurs. This process masks any deuteration at position $\Delta$ that may occur via an allenic intermediate.
Scheme 39. Experiments to determine allene pathway and sites of deuteration

![Diagram of chemical structures](image)

\[ a \] Reagents and conditions: DMDS (10 eq), I\(_2\) (3 eq), MeOD, 60 °C, 6 h

Table 7. GC-MS data for deuterium incorporation into \( 53' \) and \( 56' \)

<table>
<thead>
<tr>
<th></th>
<th>( d_0 )</th>
<th>( d_1 )</th>
<th>( d_2 )</th>
<th>( d_3 )</th>
<th>( d_4 )</th>
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<tbody>
<tr>
<td>( 53' ) from ( 53+56 )</td>
<td>4.9±1.7</td>
<td>14.0±5.3</td>
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<td>26.6±4.2</td>
<td>21.8±13.4</td>
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<td>( 53' ) from ( 53 )</td>
<td>2.5±0.5</td>
<td>10.3±2.8</td>
<td>46.6±12.8</td>
<td>24.2±3.7</td>
<td>16.3±12.3</td>
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<tr>
<td>( 56' ) from ( 53+56 )</td>
<td>31.2±18.1</td>
<td>30.9±5.4</td>
<td>37.9±20.7</td>
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<td>0</td>
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<tr>
<td>( 56' ) from DMDS/MeOD/I(_2)</td>
<td>28.3±13.4</td>
<td>31.6±7.3</td>
<td>40.1±20.2</td>
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</table>

MS analysis of the reaction mixture for the incorporation of deuterium in the residual starting material (53) in MeOD could identify the equilibration between starting 1,4-ene and allene (Scheme 40). The experiment was performed in triplicate by subjecting methyl crepenynate 53 to DMDS derivatization conditions in MeOD. After 1 h at 60 °C, the reaction was stopped and analyzed in duplicate by GC/MS (Table 8). By GC/MS, deuteration was not observed in the starting material (methyl crepenynate 53) after reaction in MeOD for 1 h at 60 °C by comparison with unreacted 53.

In the proposed acid-catalyzed allene mechanism, the allene would be in equilibrium with the starting 1,4-ene (Scheme 40). Isomerization to the conjugated isomer is expected to be thermodynamically favored. The lack of observed deuterium incorporation into 53 would only
be consistent for thiophene formation mechanism if the attack of MeS⁺ upon the ene-allene was rapid and irreversible under acid-catalyzed conditions. Allene formation is expected to be slow under basic conditions and no deuteration of the MeSI adduct was detected. While adduct 83 may be an intermediate, its reversible formation under reaction conditions would allow an allene mechanism to remain operative. An allene mechanism is enticing because the conjugated allene could direct the reaction to specifically introduce MeS⁺ at C-12 (in methyl crepenynate) (path a in Scheme 38). Literature precedence exists for directed addition of a sulfenyl halide to the central carbon of an allene,³⁶,³⁷ however, addition of MeS⁺ to the alkene cannot be eliminated as a possibility from the collected data (path b, Scheme 38). No d-exchange into the 1,4-enzyme occurs, but enyne – ene-allene rearrangement may not be reversible due to the attack of MeS⁺ and conversion of this intermediate to the initial dihydrothiophene.

Table 8. Comparison of isotopic peak intensities for methyl crepenynate during DMDS derivatization in MeOD. Intensities were normalized to the m/z 236 ion for samples before and after a 60 °C/1 h derivatization (10 mg/mL enyne, 10 eq. DMDS, 3 eq. I₂). Under these reaction conditions, the enyne was approximately 50% consumed.

<table>
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<tr>
<th>m/z</th>
<th>Normalized intensity prior to DMDS reaction in MeOD (±std dev)</th>
<th>Normalized intensity following DMDS reaction in MeOD (±std dev)</th>
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<td>236.1</td>
<td>100.00</td>
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<tr>
<td>327.2</td>
<td>1.89±0.07</td>
<td>2.16±0.09</td>
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</table>

Scheme 40. Potential equilibrium between 1,4-enzyme and allene
2-3. Conclusion

In summary, the scope and utility of the reaction between DMDS and 1,4-enynes were explored. The successful syntheses of a number of 1,4-enynes in good yield were realized. However, deviation from the initial methyl esters, e.g. 53 and 55, and the use of ethers containing less than six carbons between the functional group and the 1,4-enyne resulted in dramatically decreased yields of the DMDS derivatization reaction. The reaction was relatively insensitive to COOH, OH, and SH indicating that thiophenes of moderate complexity may be generated. Possible reaction mechanisms were investigated. Evidence discounted the thiirane as a potential reaction intermediate. Isolation and elucidation of the correct structure of MeSI adduct 83 was accomplished. Results suggested that the MeSI adduct was likely in equilibrium with starting 1,4-enyne and not a central intermediate, but a plausible mechanism for direct conversion of the MeSI adduct to thiophene product remained. An acid-catalyzed allene reaction mechanism is very attractive and has not been eliminated as the reaction mechanism. From current evidence, the mechanism for the reaction between DMDS and 1,4-enyne may proceed through either a MeSI adduct or the allene intermediate. A third possibility, initially presented by L. Zhu, involves a Wagner-Meerwein rearrangement leading to ring expansion to a cationic thietane intermediate. The four-membered ring is opened by nucleophilic attack of iodide to give a MeSI adduct, a congener of 83. Acid-catalyzed activation of the triple bond promotes transformation to thiophene.

2-4 Experimental Methods

2-4.1 General procedures

Unless otherwise mentioned, all reactions were performed under a N₂ atmosphere. All glassware was oven-dried and cooled under a dry stream of N₂ before use. Glass syringes were used to transfer all solvents and solutions. Flash column chromatography was performed with silica gel (230-400 mesh, Natland International, Morrisville, NC), using petroleum ether (PE)/diethyl ether or hexanes/ethyl acetate in the indicated ratio. A chromatotron (Model 8924, Harrison Research, Palo Alto, CA), which is a preparative, radial, thin-layer chromatograph, was used for specific purifications with the solvent and ratio indicated. TLC analyses were conducted using pre-coated silica gel plates with aluminum backings (Whatman, Al Sil G/UV).
UV light and 0.5% KMnO$_4$/2.5% Na$_2$CO$_3$ stain were used to detect products on TLC plates. IR spectra were obtained on a Perkin Elmer 1600 FT-IR spectrophotometer as a neat film (on NaCl plates) or in solution (solvent as indicated). $^1$H and $^{13}$C NMR spectral data were recorded on either a 200 or 300 MHz FT-NMR spectrometer (Bruker, Avance Series). HRMS samples were carried out at the Mass Spectrometry Lab, Department of Chemistry, The Ohio State University, Columbus, OH. GC-MS was performed on HP-5890 II gas chromatograph with a DB5 column (15 m, 0.25 mm ID, J&B Scientific, Folsom, CA). The GC oven temperature was programmed to ramp from 100 °C to 300 °C, beginning and ending with 100 °C isothermal segments. HPLC was performed on ÄKTA Explorer (Amersham Pharmacia Biotech, Uppsala, SE) with an Econosil C18 column (10 µ, 250 mm x 10 mm, Alltech, Deerfield, IL). Elution was performed at a flow rate of 5 mL/min at room temperature using a water (A) and acetonitrile (B) gradient. After injection of the sample, the solvent gradient was increased linearly from 50:50 to 0:100 A/B over 20 min. The column was equilibrated with 50:50 A/B to start and finish each injection. The eluent was monitored at 210, 220, and 250 nm. For each tube that had the expected absorption ratios, an aliquot was injected onto the GC-MS to determine which contained the purified material.

2-4.2 Materials

Dimethyl disulfide (DMDS) and 18-crown-6 were purchased from Aldrich Inc. and used directly. 3-Heptyn-1-ol was purchased from Lancaster. MeOD was purchased from Isotec. All other commercially available reagents were reagent grade and were used as received. HPLC-grade acetonitrile was obtained from Pharmco (Brookfield, CT). The solvents were dried by distillation under N$_2$ from the drying reagents specified: CH$_2$Cl$_2$ (CaH$_2$); THF and Et$_2$O (Na/benzophenone ketyl).

3-Heptynyltriphenylphosphonium bromide 59 was synthesized as previously described by Zhu. Crepis alpina seed oil was obtained as a gracious gift from Dr. Richard Adlof, USDA, Peoria, IL. The main component, tricrepenynin 80, was transesterified by refluxing the seed oil with 2% solution of H$_2$SO$_4$ in ethanol for 2 h to afford ethyl crepenynate 81, which was used without further purification. Methyl crepenynate 53 was synthesized in the same manner but with a 2% methanolic H$_2$SO$_4$ solution. $\gamma$-Valerolactone and $\delta$-butyrolactone were refluxed with
5% solution of H$_2$SO$_4$ in methanol to give methyl 5-hydroxypentanoate $71a$ and methyl 4-hydroxybutanoate $71b$, respectively. Literature oxidation of $71a$ and $71b$ with PCC$^{40}$ gave aldehydes $71a$ and $71b$, respectively.$^{41}$

2-4.3 Syntheses of 1,4-enynes

\[ \text{BrPh}_3\text{P} \xrightarrow{\text{MeO} \text{O} \text{H}, \text{NaH}} \text{MeO} \xrightarrow{\text{THF/HMPA, rt, 20 h}} \]

\[ 59 \quad 55 \]

**Methyl 6-tridecen-9-ynoate (55).**$^{23}$ To a stirred solution of phosphonium salt $59$ (1.896 g, 4.34 mmol) in a 10:1 mixture of dry THF/HMPA (30.8 mL) was added aldehyde (0.961 g, 6.67 mmol) by syringe. NaH (100 mg, 4.17 mmol) was added as a powder (95%) in one portion to the reaction mixture. The resulting suspension was stirred at rt for 20 h. Celite was then added to the flask and the suspension was vacuum-filtered using ether (4 x 25 mL) to wash the retained solids. The filtrate was washed with brine (50 mL) and the aqueous phase was extracted with ether (3 x 25 mL). The combined organic phases were dried over MgSO$_4$ and concentrated under vacuum to give the crude product. Purification by flash column chromatography (35:1 hexanes/EtOAc) afforded 0.504 g of $55$ as a yellow oil (54%). Spectroscopic data was identical to previously reported C$_{13}$ methyl ester.

\[ \text{HO} \xrightarrow{\text{BzCl, pyridine}} \text{BzOH} \]

\[ \text{CH}_2\text{Cl}_2 \quad \text{CH}_2\text{Cl}_2 \]

\[ 60a-c \quad 61a-c \]

**6-Benzyloxynhex-1-ol (61a).**$^{42}$ A solution of 1,6-hexanediol $60a$ (16.881 g, 0.143 mol) in dry CH$_2$Cl$_2$ (24 mL) and pyridine (16 mL) was stirred at 0 °C. Benzoyl chloride (3.60 mL, 31.0 mmol) was added to the reaction mixture in three equal portions over 1 h with a syringe. The mixture was then warmed to rt and stirred for an additional 3 h. The reaction was quenched with cold H$_2$O (300 mL) and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic phases were washed with 1 M HCl (2 x 150 mL), brine (150 mL), dried over
MgSO₄, and concentrated under vacuum to give the crude product. Purification by flash column chromatography (2:1 hexanes/EtOAc) afforded 5.890 g of 61a (86%) as an oil: IR (neat) 3376, 3063, 2935, 2860, 1719, 1602, 1452, 1315, 1277, 1116, 712 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.43 (m, 4H), 1.58 (m, 2H), 1.76 (m, 2H), 3.63 (t, J = 6.2 Hz, 2H), 4.30 (t, J = 6.5 Hz, 2H), 7.45 (m, 3H), 8.01 (m, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 25.38, 25.80, 28.66, 32.55, 62.75, 64.90, 128.29, 129.48, 130.38, 132.81, 166.68. Several additional compounds were prepared using the above procedure.

5-Benzoylpentan-1-ol (61b). Purification by flash column chromatography (1:1 hexanes/EtOAc) afforded a light yellow oil in 78% yield: IR (neat) 3421, 3064, 3034, 2940, 2866, 1721, 1602, 1452, 1389, 1316, 1276, 1177, 1118, 1071, 1027, 712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.51 (m, 2H), 1.60 (m, 2H), 1.77 (quintet, J = 7.3 Hz, 2H), 2.34 (s, 1H), 3.63 (t, J = 6.4 Hz, 2H), 4.29 (t, J = 6.6 Hz, 2H), 7.40 (m, 2H), 7.50 (m, 1H), 8.00 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 22.27, 28.46, 32.19, 62.51, 64.86, 128.26, 129.45, 130.29, 132.80, 166.67.

4-Benzoylbutan-1-ol (61c). Purification by flash column chromatography (2:1 hexanes/EtOAc) afforded a light yellow oil in 88% yield: IR (neat) 3418, 3064, 3035, 2949, 2874, 1719, 1602, 1452, 1388, 1316, 1274, 1177, 1119, 1070, 1028, 946, 712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.68 (quintet, J = 6.8 Hz, 2H), 1.82 (quintet, J = 6.8 Hz, 2H), 2.39 (s, 1H), 3.67 (t, J = 6.4 Hz, 2H), 4.31 (t, J = 6.4 Hz, 2H), 7.39 (m, 2H), 7.50 (m, 1H), 8.00 (m, 2H).

6-Benzoylhexanal (62a). To a stirred solution of benzoyl alcohol 61a (4.171 g, 18.8 mmol) in dry CH₂Cl₂ (63 mL) was added a ground admixture of PCC (8.303 g, 38.6 mmol) and silica gel (8.3 g) in one portion. The resulting brown suspension was stirred at rt for 2 h and the reaction was then diluted with ether (50 mL). The solids were vacuum-filtered through a fritted-glass funnel packed with a lower layer of Celite (0.5 cm deep) covered with silica gel (2 cm deep).
The solids were washed with ether (4 x 25 mL) and the filtrate was concentrated under vacuum to give an orange-brown oil. The crude oil was purified by flash column chromatography (7.5:1 PE/Et₂O) to give 3.354 g of aldehyde \(62a\) (81\%): IR (neat) 3062, 2941, 2864, 1719, 1601, 1451, 1314, 1276, 1116, 1070, 1026, 713 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl₃) \(\delta\) 1.46 (m, 2H), 1.73 (m, 4H), 2.44 (t, \(J = 7.3\) Hz, 2H), 4.30 (t, \(J = 6.4\) Hz, 2H), 7.40 (m, 2H), 7.50 (m, 1H), 8.00 (m, 2H), 9.76 (s, 1H). Several additional compounds were prepared using the above procedure.

**5-Benzoylpentanal (62b).**\(^{43}\) Purification by flash column chromatography (4:1 hexanes/EtOAc) afforded aldehyde \(62b\) in 86\% yield: \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 1.78 (m, 4H), 2.51 (m, 2H), 4.31 (t, \(J = 6.0\) Hz, 2H), 7.41 (m, 2H), 7.53 (m, 1H), 8.01 (m, 2H), 9.78 (t, \(J = 1.3\) Hz, 1H).

**4-Benzoylbutanal (62c).**\(^{43}\) Purification by flash chromatography (10:1 hexanes/EtOAc) afforded aldehyde \(62c\) in 84\% yield: IR (neat) 3064, 2962, 2900, 2836, 1720, 1602, 1452, 1388, 1316, 1277, 1177, 1119, 1071, 1027, 713 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl₃) \(\delta\) 2.10 (quintet, \(J = 6.7\) Hz, 2H), 2.62 (t, \(J = 7.2\) Hz, 2H), 4.34 (t, \(J = 6.3\) Hz, 2H), 7.48 (m, 3H), 8.00 (m, 2H), 9.82 (s, 1H).

\[\text{BrPh}_3\text{P} \rightarrow \begin{array}{c} \text{THF/HMPA, rt, 20 h} \\ \text{NaH} \end{array} \rightarrow \text{BzO} \]

\(62a-c, n = 2-4\)  

**6-Tridecen-9-ynyl benzoate 63a.** To a stirred solution of phosphonium salt \(59\) (1.013 g, 2.32 mmol) in a 10:1 mixture of dry THF (16.5 mL)/HMPA (1.65 mL), was added benzoyl aldehyde \(62a\) (0.562 g, 2.55 mmol) by syringe. NaH (53 mg, 2.21 mmol) was added as a solid in one portion to the reaction mixture. The resulting suspension was stirred at rt for 20 h. Celite was added to the flask and the suspension was vacuum-filtered using ether (4 x 15 mL) to wash solids. The filtrate was washed with brine (25 mL) and the aqueous phase extracted with ether (3 x 25 mL). The combined organic phases were dried over MgSO₄ and concentrated under vacuum to give the crude product. Purification by chromatotron (20:1 hexanes/EtOAc) afforded 0.429 g of enyne \(63a\) (65\%): IR (neat) 3062, 3018, 2960, 2932, 2859, 1721, 1602, 1452, 1275, 1116, 712 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 0.93 (t, \(J = 7.3\) Hz, 3H), 1.46 (m, 6H), 1.74 (m,
2H), 2.06 (m, 2H), 2.09 (tt, J = 7.1, 2.5 Hz, 2H), 2.88 (m, 2H), 4.29 (t, J = 6.6 Hz, 2H), 5.42 (m, 2H), 7.42 (m, 2H), 7.54 (m, 1H), 8.03 (m, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 13.46, 17.16, 20.74, 22.39, 25.63, 26.93, 28.58, 28.99, 64.98, 78.39, 79.92, 125.35, 128.30, 129.50, 130.45, 130.80, 132.79, 166.64; HRMS (ESI) calcd m/z for C₂₀H₂₆O₂Na⁺ 321.1825, found m/z 321.1844. Several additional compounds were prepared using the above procedure.

5-Dodecen-8-ynyl benzoate (63b). Purification by flash column chromatography (35:1 hexanes/EtOAc) afforded enyne as an oil in 69% yield: IR (neat) 3018, 2959, 2932, 2869, 1720, 1602, 1451, 1274, 1116, 712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.93 (t, J = 7.3 Hz, 3H), 1.49 (m, 4H), 1.77 (m, 2H), 2.11 (m, 4H), 2.90 (m, 2H), 4.30 (t, J = 6.5 Hz, 2H), 5.43 (m, 2H), 7.42 (m, 2H), 7.53 (m, 1H), 8.02 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.46, 17.19, 20.76, 22.40, 25.82, 26.68, 28.32, 64.86, 78.31, 80.00, 125.73, 128.31, 129.52, 130.46, 130.49, 132.81, 166.64; HRMS (EI) calcd m/z for C₁₉H₂₄O₂⁺· 284.1776, found m/z 284.1443.

4-Undecen-7-ynyl benzoate (63c). Purification by flash column chromatography (35:1 hexanes/EtOAc) afforded enyne 63c in 51% yield: IR (neat) 3064, 2962, 2934, 2874, 1714, 1602, 1453, 1385, 1316, 1275, 1177, 1115, 1071, 1027, 957, 713 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, J = 7.3 Hz, 3H), 1.45 (sextet, J = 7.3 Hz, 2H), 1.82 (quintet, J = 6.8 Hz, 2H), 2.08 (tt, J = 7.1, 2.4 Hz, 2H), 2.21 (quartet, J = 6.8 Hz, 2H), 2.88 (m, 2H), 4.30 (t, J = 6.5 Hz, 2H), 5.47 (m, 2H), 7.41 (m, 2H), 7.54 (m, 1H), 8.02 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.41, 17.10, 20.69, 22.32, 23.55, 28.34, 64.23, 78.08, 80.02, 126.28, 128.27, 129.46, 129.52, 130.34, 132.77, 166.49; HRMS (ESI) calcd m/z for C₁₈H₂₂O₂Na⁺ 293.1512, found m/z 293.1500.

6-Tridecen-9-yn-1-ol (64a). A solution of benzoyl enyne 63a (0.487 g, 1.63 mmol) in 1% NaOH in MeOH (w/v) solution (20 mL) was stirred at rt for 3 h. The reaction was quenched
with H₂O (15 mL) and the aqueous phase extracted with ether (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO₄, and concentrated under vacuum to give crude product as a pale yellow oil. The crude oil was purified by flash column chromatography (3:1 PE/Et₂O) to afford 0.313 g of enynol **64a** as an oil (99%): IR (neat) 3346, 2960, 2932, 2860, 1458, 1073, 1054 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.94 (t, J = 7.3 Hz, 3H), 1.36 (m, 4H), 1.47 (sextet, J = 7.2 Hz, 2H), 1.55 (m, 2H), 2.03 (m, 2H), 2.10 (tt, J = 7.0, 2.5 Hz, 2H), 2.89 (m, 2H), 3.61 (t, J = 6.6 Hz, 2H), 5.41 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.45, 17.14, 20.74, 22.40, 25.30, 26.98, 29.10, 32.60, 62.90, 78.46, 79.90, 125.26, 130.92; HRMS (ESI) calcd m/z for C₁₃H₂₂ONa⁺ 217.1563, found m/z 217.1550. Several additional compounds were prepared using the above procedure.

**5-Dodecen-8-yn-1-ol (64b).** Purification by flash column chromatography (10:1 hexanes/EtOAc) afforded enynol **64b** in 86% yield: IR (neat) 3343, 2960, 2933, 2870, 1459, 1069 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.94 (t, J = 7.3, 3H), 1.49 (m, 6H), 2.06 (m, 2H), 2.10 (tt, J = 7.1, 2.5 Hz, 2H), 2.88 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 5.41 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.47, 17.17, 20.76, 22.41, 25.50, 26.77, 32.26, 62.81, 78.40, 79.97, 125.48, 130.74; HRMS (ESI) calcd m/z for C₁₂H₂₀ONa⁺ 203.1406, found m/z 203.1416.

**4-Undecen-7-yn-1-ol (64c).** Purification by flash column chromatography (6:1 hexanes/EtOAc) afforded enynol **64c** in 96% yield: IR (neat) 3339, 2962, 2934, 2862, 1461, 1433, 1379, 1338, 1288, 1073, 1054, 736, 689 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, J = 7.3 Hz, 3H), 1.46 (sextet, J = 7.2 Hz, 2H), 1.60 (quintet, J = 6.6 Hz, 2H), 1.91 (s, 1H), 2.08 (tt, J = 7.1, 2.4 Hz, 2H), 2.11 (m, 2H), 2.87 (m, 2H), 3.61 (t, J = 6.4 Hz, 2H), 5.43 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.42, 17.03, 20.70, 22.34, 23.29, 32.03, 62.07, 78.34, 80.04, 125.77, 130.30; HRMS (ESI) calcd m/z for C₁₁H₁₈ONa⁺ 189.1250, found m/z 189.1237.

**13-Azido-7-tridecen-4-yne (65).** To a stirred solution of enynol **64a** (0.178 g, 0.92 mmol) in dry THF (20 mL) were added PPh₃ (0.966 g, 3.68 mmol) and DPPA (0.79 mL, 3.67 mmol).
DIAD (0.72 mL, 3.66 mmol) was then added dropwise via syringe and the resulting mixture was stirred at rt for 1.5 h. The solvent was removed in vacuo and the residues washed with ethyl acetate (50 mL) through a short pad of silica gel. The filtrate was diluted with ethyl acetate (50 mL), washed with 1 M HCl (50 mL) and brine (50 mL). The solution was then dried over MgSO\textsubscript{4} and concentrated under vacuum to give the crude product, which was purified by flash column chromatography (20:1 PE/Et\textsubscript{2}O) to afford 0.154 g of azide 65 (76%): IR (neat) 2961, 2933, 2861, 2096, 1461, 1348, 1288 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 0.94 (t, J = 7.3 Hz, 3H), 1.37 (m, 4H), 1.48 (sextet, J = 7.2 Hz, 2H), 1.58 (m, 2H), 2.04 (m, 2H), 2.10 (tt, J = 7.1, 2.4 Hz, 2H), 2.88 (m, 2H), 3.24 (t, J = 6.9 Hz, 2H), 5.41 (m, 2H); \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}) δ 13.47, 17.18, 20.77, 22.42, 26.30, 26.89, 28.73, 28.87, 51.42, 78.38, 79.97, 125.48, 130.69; HRMS (ESI) calcd \m/z for C\textsubscript{13}H\textsubscript{21}N\textsubscript{3}Na\textsuperscript{+} 242.1628, found \m/z 242.1626.

6-Tridecen-9-ynyl tosylate (68). To a solution of enynol 64a (0.136 g, 0.70 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (1 mL) at 0 °C was added pyridine (0.134 mL, 1.39 mmol) followed by p-TsCl (0.201 g, 1.06 mmol) over a 1 h period. The reaction mixture was stirred at 0 °C for an additional 2 h and then warmed to rt for 8 h. The reaction was quenched with H\textsubscript{2}O (10 mL) and aqueous phase was extracted with ether (3 x 15 mL). The combined organic phases were washed with 1 M HCl, brine, and dried over MgSO\textsubscript{4}. The solution was concentrated under vacuum to give crude product as oil, which was purified by chromatotron (15:1 hexanes/EtOAc) to afford 0.221 g of product (91%) as an oil: IR (neat) 3027, 2932, 2869, 1462, 1284 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 0.93 (t, J = 7.3 Hz, 3H), 1.28 (m, 4H), 1.47 (sextet, J = 7.3 Hz, 2H), 1.61 (m, 2H), 1.96 (m, 2H), 2.09 (tt, J = 7.0, 2.5 Hz, 2H), 2.43 (s, 3H), 2.84 (m, 2H), 3.99 (t, J = 6.6 Hz, 2H), 5.37 (m, 2H), 7.32 (dd, J = 8.0, 0.6 Hz, 2H), 7.77 (dt, J = 8.3, 2.0 Hz, 2H); \textsuperscript{13}C NMR (50 MHz, CDCl\textsubscript{3}) δ 13.44, 17.10, 20.71, 21.58, 22.36, 24.88, 26.74, 28.59, 28.64, 70.48, 78.29, 79.93, 125.43, 127.82, 129.76, 130.52, 133.13, 144.63; HRMS (ESI) calcd \m/z for C\textsubscript{20}H\textsubscript{28}O\textsubscript{3}SNa\textsuperscript{+} 371.1651, found \m/z 371.1663.
6-Tridecen-9-ynyl thioacetate (69). To a stirred solution of PPh$_3$ (0.332 g, 1.27 mmol) in dry THF (2.3 mL) at 0 °C was added DIAD (0.25 mL, 1.27 mmol) dropwise via syringe. The resulting thick, white slurry was stirred at 0 °C for 30 min. A solution of enynol 64a (0.122 g, 0.63 mmol) and thiolacetic acid (90 µL, 1.26 mmol) in dry THF (1.5 mL) was added dropwise via syringe to the reaction flask. The mixture was stirred at 0 °C for 1 h and then warmed to rt for an additional 1 h. The reaction was diluted with ether (20 mL) and washed with NaHCO$_3$ (4 x 10 mL). The organic phase was dried over MgSO$_4$ and concentrated under vacuum to give crude product. Purification by flash column chromatography (50:1 hexanes/EtOAc) afforded 0.154 g of 69 (97%): IR (neat) 2963, 2932, 2858, 1694, 1459, 1432, 1353, 1135, 1109, 956, 627 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.94 (t, $J = 7.3$ Hz, 3H), 1.35 (m, 4H), 1.48 (sextet, $J = 7.3$ Hz, 2H), 1.55 (m, 2H), 2.01 (m, 2H), 2.10 (tt, $J = 7.1$ Hz, 2.4 Hz, 2H), 2.30 (s, 3H), 2.84 (t, $J = 7.4$ Hz, 2H), 2.89 (m, 2H), 5.40 (m, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 13.47, 17.16, 20.77, 22.42, 26.88, 28.37, 29.82, 29.06, 29.37, 30.62, 78.43, 79.92, 125.33, 130.83, 195.97; HRMS (ESI) calcd m/z for C$_{15}$H$_{24}$OSNa$^+$ 275.1440, found m/z 275.1452.

6-Tridecen-9-yn-1-thiol (70). To a stirred suspension of LiAlH$_4$ (22.0 mg, 0.58 mmol) in dry ether (2.5 mL) at 0 °C was added dropwise a solution of thiolester enyne 66 (0.146 g, 0.58 mmol) in ether (2.5 mL). The reaction mixture was stirred at 0 °C for 1 h and then warmed to rt for additional 3 h. The reaction flask was cooled to 0 °C and the reaction was quenched with 3N HCl (3 mL). The layers were separated and the aqueous phase extracted with ether (3 x 5 mL). The combined organic phases were washed with a sat. NaHCO$_3$ solution (20 mL), dried over MgSO$_4$, and concentrated under vacuum to give crude product, which was purified by flash column chromatography (98:2 PE/Et$_2$O) to afford 0.111 g of a pale yellow oil (91%): $^1$H NMR (300 MHz, acetone-$_d_6$) $\delta$ 0.96 (t, $J = 7.3$ Hz, 3H), 1.42 (m, 4H), 1.47 (sextet, $J = 7.3$ Hz, 2H),
1.59 (m, 2H), 2.06 (m, 2H), 2.11 (tt, \( J = 7.1, 2.4 \) Hz, 2H), 2.53 (q, \( J = 7.4 \) Hz, 2H), 2.91 (m, 2H), 5.42 (m, 2H); \(^{13}\)C NMR (75.5 MHz, acetone-d\(_6\)) \( \delta \) 13.63, 17.49, 21.12, 23.11, 24.75, 27.48, 28.55, 29.03, 34.68, 79.17, 80.18, 126.28, 131.47; HRMS (EI) calcd \( m/z \) for C\(_{13}\)H\(_{22}\)S\(^+\) 210.1437, [M\(^+\)] was not found, but the possibility of disulfide formation was not reported.

### 6-Tridecen-9-ynoic acid (67).

To a stirred solution of methyl ester 55 (88.2 mg, 0.40 mmol) in acetone (7 mL) was added 5 M LiOH (5 mL). The reaction was stirred for 3 h and then diluted with ether (20 mL). HCl (1 N) was added until the pH was ~ 4.0. The layers were separated and the organic phase was washed with brine (20 mL) and H\(_2\)O (20 mL), dried over MgSO\(_4\), and concentrated under vacuum to give the crude product. Purification by flash column chromatography (7:1 hexanes/EtOAc) with 0.5\% AcOH afforded 82.0 mg of 67 (99\%) as an oil:

\( \stackrel{\text{1H NMR (300 MHz, CDCl}_3}{\text{d}} \) 0.94 (t, \( J = 7.3 \) Hz, 3H), 1.40 (m, 2H), 1.47 (sextet, \( J = 7.2 \) Hz, 2H), 1.63 (quintet, \( J = 7.6 \) Hz, 2H), 2.06 (m, 2H), 2.10 (tt, \( J = 7.2, 2.3 \) Hz, 2H), 2.34 (t, \( J = 7.6 \) Hz, 2H), 2.88 (m, 2H), 5.42 (m, 2H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 13.46, 17.16, 20.75, 22.40, 24.21, 26.67, 28.71, 33.81, 78.32, 80.00, 125.63, 130.43, 179.61; HRMS (EI) calcd \( m/z \) for C\(_{13}\)H\(_{20}\)O\(_2\)Na\(^+\) 231.1355, found \( m/z \) 231.1364.

The following five compounds were prepared using the general procedure described for 60a. Purification methods and analytical data are presented for each compound.

### Methyl 5-dodecen-8-ynoate (74a).

Purification by flash column chromatography (30:1 hexanes/EtOAc) afforded 74a as a yellow oil in 60\% yield: IR (neat) 2962, 2935, 2872, 1741, 1458, 1437, 1365, 1244, 1202, 1157, 1089, 1026 cm\(^{-1}\); \( \stackrel{\text{1H NMR (300 MHz, CDCl}_3}{\text{d}} \) 0.94 (t, \( J \) \) \( J = 7.4 \) Hz, 2H), 1.40 (m, 2H), 1.47 (sextet, \( J = 7.2 \) Hz, 2H), 1.63 (quintet, \( J = 7.6 \) Hz, 2H), 2.06 (m, 2H), 2.10 (tt, \( J = 7.2, 2.3 \) Hz, 2H), 2.34 (t, \( J = 7.6 \) Hz, 2H), 2.88 (m, 2H), 5.42 (m, 2H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 13.46, 17.16, 20.75, 22.40, 24.21, 26.67, 28.71, 33.81, 78.32, 80.00, 125.63, 130.43, 179.61; HRMS (EI) calcd \( m/z \) for C\(_{13}\)H\(_{20}\)O\(_2\)Na\(^+\) 231.1355, found \( m/z \) 231.1364.
= 7.3 Hz, 3H), 1.47 (sextet, \( J = 7.2 \) Hz, 2H), 1.68 (quintet, \( J = 7.4 \) Hz, 2H), 2.04 (m, 2H), 2.09 (tt, \( J = 7.1 \), 2.5 Hz, 2H), 2.30 (t, \( J = 7.4 \) Hz, 2H), 2.87 (m, 2H), 3.64 (s, 3H), 5.43 (m, 2H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 13.46, 17.16, 20.75, 22.40, 24.55, 26.40, 33.40, 51.47, 78.23, 80.04, 126.27, 129.78, 174.00; HRMS (ESI) calcd \( m/z \) for C\(_{13}\)H\(_{20}\)O\(_2\)Na\(^+\) 231.1355, found \( m/z \) 231.1358.

**Methyl 4-undecen-7-ynoate (74b).** Purification by flash column chromatography (30:1 hexanes/EtOAc) afforded 74b as a yellow oil in 22% yield. The reported yield is not accurate as a large portion of the sample was spilled during purification and the reaction was only performed once: IR (neat) 2963, 2874, 1740, 1437, 1363, 1198, 1164, 1078, 1028, 909, 692 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.93 (t, \( J = 7.3 \) Hz, 3H), 1.47 (sextet, \( J = 7.3 \) Hz, 2H), 2.09 (tt, \( J = 7.1 \), 2.4 Hz, 2H), 2.35 (m, 4H), 2.89 (m, 2H), 3.65 (s, 3H), 5.43 (m, 2H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 13.46, 17.09, 20.74, 22.37, 22.63, 33.73, 51.56, 78.07, 80.10, 126.74, 128.72, 173.42; HRMS (ESI) calcd \( m/z \) for C\(_{12}\)H\(_{18}\)O\(_2\)Na\(^+\) 217.1199, found \( m/z \) 217.1200.

\[
\begin{align*}
\text{BrP}_{3} \text{H} & \quad \text{O} \\
& \quad \text{NaH} \\
\text{THF/HMPA, rt, 20 h} \\
\end{align*}
\]

**1-Phenyl-3-decen-6-yne (75).** Purification by flash column chromatography using petroleum ether as the eluent afforded 75 as a yellow oil in 54% yield: IR (neat) 3086, 3062, 3025, 2962, 2932, 2871, 1604, 1496, 1454, 1290, 746, 699 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta \) 1.01 (t, \( J = 7.2 \) Hz, 3H), 1.55 (sextet, \( J = 7.3 \) Hz, 2H), 2.17 (tt, \( J = 7.1 \), 2.4 Hz, 2H), 2.43 (m, 2H), 2.74 (t, \( J = 7.1 \) Hz, 2H), 2.89 (m, 2H), 5.52 (m, 2H), 7.29 (m, 5H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \( \delta \) 13.48, 17.09, 20.75, 22.39, 28.99, 35.55, 78.29, 79.95, 125.82, 128.28, 128.40, 130.02, 141.76; HETCOR showed the overlap of two \(^{13}\)C NMR peaks at \( \delta \) 125.82; HRMS (EI) calcd \( m/z \) for C\(_{16}\)H\(_{20}\)Na\(^+\) 212.1560, found \( m/z \) 212.1554.
(E,Z)-1-Phenyldec-1,3-diene-9-yne (76). Purification by flash column chromatography using petroleum ether as the eluent afforded 76 as a yellow oil in 56% yield: IR (neat) 3059, 3028, 2962, 2932, 2871, 2839, 1596, 1492, 1449, 1287, 984, 946, 697 cm\(^{-1}\); \(^{1}\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.02 (t, \(J = 7.4\) Hz, 3H), 1.57 (sextet, \(J = 7.2\) Hz, 2H), 2.20 (tt, \(J = 7.1, 2.4\) Hz, 2H), 3.21 (m, 2H), 5.59 (dt, \(J = 10.4, 7.3\) Hz, 1H), 6.25 (t, \(J = 10.8\) Hz, 1H), 6.61 (d, \(J = 15.5\) Hz, 1H), 7.10 (dd, \(J = 15.5, 11.1\) Hz, 1H), 7.37 (m, 5H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\) 13.95, 18.34, 21.23, 22.82, 78.26, 81.10, 123.92, 126.90, 127.66, 128.09, 129.05, 130.02, 133.78, 137.71; HRMS (EI) calcld \(m/z\) for C\(_{16}\)H\(_{18}\)+ 210.1403, found \(m/z\) 210.1423.

7-Dodecen-4-yne (77). Purification by flash column chromatography using petroleum ether as the eluent afforded 77 as a yellow oil in 49% yield: IR (neat) 2960, 2931, 2873, 1459, 1379, 1287 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.87 (t, \(J = 7.0\) Hz, 3H), 0.94 (t, \(J = 7.3\) Hz, 3H), 1.30 (m, 4H), 1.48 (sextet, \(J = 7.2\) Hz, 2H), 2.01 (m, 2H), 2.10 (tt, \(J = 7.1\) Hz, 2.4 Hz, 2H), 2.88 (m, 2H), 5.40 (m, 2H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 13.45, 13.92, 17.13, 20.78, 22.30, 22.43, 26.80, 31.56, 78.55, 79.82, 125.00, 131.25; HRMS (EI) calcld \(m/z\) for C\(_{12}\)H\(_{20}\)+ 164.1560, possessed hydrocarbon pattern but [M\(^{+}\)] could not be identified.

2.4.4 Reaction of 1,4-enynes with DMDS

General procedure for 78a-k

In a 50 mL RBF with a stir bar was placed a solution of 1,4-enyne in MeOH. To this flask, DMDS (10 equivalents) and I\(_2\) (3 equivalents) were added. Additional MeOH was added to bring the concentration of 1,4-enyne to 10 mg/mL of MeOH. The flask was then sealed under
N₂ with a wired rubber septum and placed in a 60 °C oil-bath. After stirring in the dark for 6 h and cooling to rt, the reaction was quenched with a 20% aqueous Na₂S₂O₃ solution. The aqueous phase was extracted with ether (4 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated under vacuum to afford the crude product. An initial purification was performed by flash column chromatography with the indicated solvent. The material obtained after column chromatography was then purified by the HPLC method, as described in the General Procedure section. Fractionation began at 50:50 A/B and the eluent was collected in 10 mL aliquots. Concentration under vacuum afforded the isolated thiophenes, which were then characterized through standard spectroscopic methods.

**5-(5-Butylthiophen-2-yl)pentyl benzoate (78a).** Thiophene 78a was afforded in a 7% isolated yield after flash column chromatography (20:1 hexanes/EtOAc) and HPLC: IR (in CDCl₃) 3064, 2960, 2934, 2860, 2258, 2246, 1714, 1602, 1452, 1316, 1279, 1119, 1071, 1027 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.90 (t, J = 7.4 Hz, 3H), 1.36 (sextet, J = 7.5 Hz, 2H), 1.67 (m, 8H), 2.72 (t, J = 7.3 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 4.30 (t, J = 6.5 Hz, 2H), 6.53 (m, 2H), 7.41 (m, 2H), 7.54 (m, 1H), 8.02 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.81, 22.20, 25.50, 28.46, 29.82, 29.97, 31.27, 33.81, 64.92, 123.32, 123.49, 128.31, 129.54, 130.47, 132.80, 142.61, 143.43, 166.67; HRMS (ESI) calcd m/z for C₂₀H₂₆O₂SNa⁺ 353.1546, found m/z 353.1555.

**5-(5-Butylthiophen-2-yl)pentan-1-ol (78b).** Thiophene 78b was afforded in a 25% isolated yield after flash column chromatography (4:1 hexanes/EtOAc) and HPLC: IR (in CDCl₃) 3064, 2935, 2860, 2246, 1603, 1461, 1438, 1350, 1225, 1174, 1044, 1019 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.90 (t, J = 7.3 Hz, 3H), 1.37 (m, 4H), 1.58 (m, 6H), 1.87 (s, 1H), 2.72 (t, J = 7.4 Hz, 2H), 2.74 (t, J = 7.4 Hz, 2H), 3.63 (t, J = 6.5 Hz, 2H), 6.53 (s, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.81, 22.21, 25.20, 29.82, 30.07, 31.43, 32.44, 33.81, 62.87,
123.31, 123.43, 142.78, 143.38; HRMS (ESI) calcd m/z for C_{13}H_{22}OSNa^+ 249.1284, found m/z 249.1288.

5-(5-Butylthiophen-2-yl)pentyl tosylate (78c). Thiophene 78c was afforded in a 13% isolated yield after flash column chromatography (35:1 hexanes/EtOAc) and HPLC: IR (in CDCl$_3$) 3064, 2960, 2933, 2861, 2245, 1600, 1459, 1359, 1262, 1190, 1177, 1098, 1020 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J = 7.3$ Hz, 3H), 1.35 (m, 4H), 1.60 (m, 6H), 2.42 (s, 3H), 2.69 (quintet, $J = 7.5$ Hz, 4H), 3.99 (t, $J = 6.5$ Hz, 2H), 6.51 (m, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.76 (d, $J = 8.3$ Hz, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 13.82, 21.63, 22.21, 24.82, 28.59, 29.82, 29.85, 30.94, 33.81, 70.43, 123.34, 123.52, 127.88, 129.82, 133.19, 142.33, 143.48, 144.67; HRMS (ESI) calcd m/z for C$_{20}$H$_{28}$O$_3$S$_2$Na$^+$ 403.1372, found m/z 403.1398.

5-(5-Butylthiophen-2-yl)pentane-1-thiol (78d). Thiophene 78d was afforded in a 21% isolated yield after flash column chromatography (50:1 hexanes/EtOAc) and HPLC: IR (in CDCl$_3$) 2959, 2932, 2858, 2244, 1459, 1438, 1261, 1176, 1102, 1015 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J = 7.2$ Hz, 3H), 1.39 (m, 4H), 1.64 (m, 6H), 2.68 (m, 6H), 6.53 (s, 2H); HRMS (ESI) disulfide formed upon electrospray ionization, calcd m/z for C$_{26}$H$_{42}$S$_4$Na$^+$ 505.2061, found m/z 505.2051.

5-(5-Butylthiophen-2-yl)pentanoic acid (78e). Thiophene 78e was afforded in a 28% isolated yield after flash column chromatography (2:1 hexanes/EtOAc with 0.5% AcOH) and HPLC: IR (in CDCl$_3$) 3642, 2956, 2940, 2862, 2245, 1732, 1458, 1438, 1214, 1174, 1114 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J = 7.1$ Hz, 3H), 1.37 (sextet, $J = 7.6$ Hz, 2H), 1.65 (m, 6H), 2.32 (t, $J = 7.2$ Hz, 2H), 2.72 (m, 4H), 4.15 (s, 1H), 6.53 (s, 2H).
Methyl 4-(5-butylthiophen-2-yl)butanoate (78f). Thiophene 78f was afforded in a 7% isolated yield after flash column chromatography (30:1 hexanes/EtOAc) and HPLC: IR (in CDCl$_3$) 2958, 2932, 2873, 2246, 1731, 1454, 1439, 1278, 1175, 1120 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J = 7.2$ Hz, 3H), 1.35 (sextet, $J = 7.2$ Hz, 2H), 1.60 (quintet, $J = 7.3$ Hz, 2H), 1.95 (m, 2H), 2.35 (t, $J = 7.4$ Hz, 2H), 2.75 (m, 4H), 3.65 (s, 3H), 6.56 (s, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 14.26, 22.63, 27.12, 29.78, 30.25, 33.60, 34.24, 52.01, 123.86, 124.42, 141.83, 144.25, 172.63.

Methyl 3-(5-Butylthiophen-2-yl)propanoate (78g). Thiophene 78g was afforded in a 7% isolated yield after flash column chromatography (30:1 hexanes/EtOAc) and HPLC: IR (in CDCl$_3$) 2959, 2932, 2874, 2258, 2246, 1734, 1603, 1438, 1366, 1262, 1201, 1173, 1103, 1022 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J = 7.2$ Hz, 3H), 1.35 (sextet, $J = 7.4$ Hz, 2H), 1.60 (quintet, $J = 7.6$ Hz, 2H), 2.64 (t, $J = 7.4$ Hz, 2H), 2.72 (t, $J = 7.5$ Hz, 2H), 3.07 (t, $J = 7.5$ Hz, 2H), 3.67 (s, 3H), 6.56 (m, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 13.79, 22.18, 25.39, 29.78, 33.76, 35.92, 51.68, 123.49, 124.06, 140.36, 144.11, 172.97; HRMS (ESI) calcd m/z for C$_{12}$H$_{18}$O$_2$SNa$^+$ 249.0920, found m/z 249.0910.

4-(5-Butylthiophen-2-yl)butyl benzoate (78h). Thiophene 78h was afforded in a 8% isolated yield after flash column chromatography (20:1 hexanes/EtOAc) and HPLC: IR (in CDCl$_3$) 3062, 2975, 2959, 2872, 2245, 1715, 1466, 1454, 1316, 1278, 1119 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J = 7.4$ Hz, 3H), 1.36 (sextet, $J = 7.6$ Hz, 2H), 1.61 (quintet, $J = 7.4$ Hz, 2H), 1.81 (m, 4H), 2.73 (t, $J = 7.6$ Hz, 2H), 2.81 (t, $J = 6.8$ Hz, 2H), 4.33 (t, $J = 6.1$ Hz, 2H), 6.55 (m, 2H), 7.42 (m, 2H), 7.54 (m, 1H), 8.01 (m, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 13.81, 22.20, 28.11,
28.14, 29.74, 29.82, 33.80, 64.71, 123.37, 123.69, 128.32, 129.54, 130.42, 132.82, 142.20, 143.62, 166.63; HRMS (ESI) calcd m/z for C_{19}H_{24}O_{2}SNa^+ 339.1389, found m/z 339.1390.

2-Butyl-5-(2-phenylethyl)thiophene (78j). Thiophene 78j was afforded in a 17% isolated yield after flash column chromatography (PE solvent) and HPLC: IR (in CDCl₃) 3066, 3030, 2960, 2932, 2859, 2246, 1603, 1496, 1454, 1175, 1030 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.92 (t, J = 7.2 Hz, 3H), 1.37 (sextet, J = 7.3 Hz, 2H), 1.62 (quintet, J = 7.4 Hz, 2H), 2.74 (t, J = 7.5 Hz, 2H), 2.99 (m, 4H), 6.55 (s, 2H), 7.23 (m, 5H); ¹³C NMR (50 MHz, CDCl₃) δ 13.85, 22.19, 29.83, 32.12, 33.84, 38.05, 123.39, 123.72, 126.04, 128.35, 128.41, 141.33, 141.92, 143.63.

2-Butyl-5-[(E)-2-phenylethyl]thiophene (78k). Thiophene 78k was afforded in an 8% isolated yield after flash column chromatography (PE solvent) and HPLC: IR (in CDCl₃) 3027, 2963, 2931, 2874, 2257, 2246, 1598, 1449, 1262, 1096, 990 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.93 (t, J = 7.2 Hz, 3H), 1.39 (sextet, J = 7.3 Hz, 2H), 1.65 (quintet, J = 7.1 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 6.65 (d, J = 3.5 Hz, 2H), 6.84 (m, 2H), 7.32 (m, 5H); ¹³C NMR (50 MHz, CDCl₃) δ 13.81, 22.14, 30.06, 33.62, 122.21, 124.56, 126.11, 126.21, 126.96, 127.25, 128.62, 137.20, 140.44, 145.44.

2-4.5 Syntheses of potential intermediates to test thiophene-forming mechanism

Ethyl 9,10-epoxyoctadecan-12-ynoate (82). To a stirred solution of crude ethyl crepenynate 81 (0.235 g, containing ~20% ethyl linoleate) in CH₂Cl₂ (9 mL) was added m-CPBA (0.196 g, 1.14 mmol) as a solid in one portion. The reaction was stirred at rt for 2 h. Ca(OH)₂ (57 mg) was
added and the reaction mixture was cooled to 0 °C for 1 h. The precipitates were then vacuum-filtered through a pad of Celite with a 0.5 cm deep layer of Ca(OH)$_2$ on top. The filtrate was concentrated under vacuum to afford the crude product. Purification by flash column chromatography (10:1 PE/Et$_2$O) afforded 0.187 g of an oil. A yield was not calculated as the starting material was a mixture of the ethyl esters of crepenynic and linoleic acids: IR (neat) 2930, 2857, 1738, 1465, 1374, 1246, 1179, 1035 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.80 (t, $J = 7.2$ Hz, 3H), 1.16 (t, $J = 7.1$ Hz, 3H), 1.38 (m, 18H), 2.05 (tt, $J = 7.1$, 2.3 Hz, 2H), 2.15 (m, 1H), 2.19 (t, $J = 7.4$ Hz, 2H), 2.47 (m, 1H), 2.85 (m, 1H), 3.00 (m, 1H), 4.03 (q, $J = 7.1$ Hz, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 13.99, 14.26, 18.72, 18.81, 22.22, 24.94, 26.44, 27.52, 28.61, 29.04, 29.19, 29.31, 31.07, 34.36, 55.44, 57.05, 60.18, 74.85, 82.52, 173.83; HRMS (ESI) calcd m/z for C$_{20}$H$_{34}$O$_3$Na$^+$ 345.2400, found m/z 345.2397.

**Ethyl 9,10-epithiooctadecan-12-ynoate (79).** To a stirred solution of epoxide 82 (0.187 g, 0.581 mmol) in t-BuOH (1.82 mL) was added NH$_4$SCN (0.134 g, 1.77 mmol) as a solid in one portion, followed by cerium ammonium nitrate (64.0 mg, 0.12 mmol). The mixture was warmed to 50 °C and stirred overnight. The solvent was removed in vacuo and CHCl$_3$ (2 x 15 mL) was added to the residue. The suspension was filtered and the filtrate concentrated under vacuum to afford the crude product. Purification by flash column chromatography (50:1 PE/Et$_2$O) afforded 0.129 g of 79 (66%) as an oil: IR (neat) 2931, 2857, 1737, 1465, 1373, 1246, 1182, 1036, 733 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.88 (t, $J = 7.0$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.46 (m, 18H), 1.89 (m, 1H), 2.14 (tt, $J = 6.9$, 2.3 Hz, 2H), 2.27 (t, $J = 7.5$ Hz, 2H), 2.34 (m, 1H), 2.69 (m, 1H), 2.95 (m, 1H), 3.08 (m, 1H), 4.10 (q, $J = 7.1$ Hz, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 14.02, 14.27, 18.73, 21.58, 22.23, 24.95, 28.62, 29.07, 29.14, 29.18, 29.55, 30.50, 31.08, 34.37, 38.86, 41.65, 60.18, 76.97, 82.33, 173.85; HRMS (ESI) calcd m/z for C$_{20}$H$_{34}$O$_3$SNa$^+$ 361.2172, found m/z 361.2177.
Methyl 10-iodo-9-thiomethyl-(Z,E)-trideca-6,9-dien-oate (83). In a 50 mL RBF with a stir bar was dissolved a solution of C\textsubscript{13} methyl ester 55 (0.118 g, 0.533 mmol) in MeOH (5.0 mL). To this solution was added DMDS (0.48 mL, 5.33 mmol) by syringe and an additional portion of MeOH (4.0 mL). K\textsubscript{2}CO\textsubscript{3} (0.224 g, mmol) and 18-crown-6 (0.423 g, mmol) were then added as solids in one portion, followed by I\textsubscript{2} (0.409 g, mmol) and additional MeOH (2.8 mL) to bring the concentration of 55 to 10 mg/mL MeOH. The flask was sealed under N\textsubscript{2} and a rubber septum attached tightly with a small piece of wire. The flask was placed in a 60 °C oil-bath and stirred for 6 h in the dark. After 6 h, the reaction mixture was extracted with hexanes (4 x 15 mL). The combined organic phases were dried over MgSO\textsubscript{4} and concentrated under vacuum to afford the crude product. Initially, the crude mixture was purified by flash column chromatography (20:1 hexanes/EtOAc) to eliminate baseline impurities. The resulting material was then dissolved in acetonitrile (2.0 mL) and purified by HPLC as described in the General Procedure section. No trifluoroacetic acid (TFA) was used due to the potential acid-sensitivity of 83. The sample was divided into two equal portions (1.0 mL) and sequentially injected. Fractionation began at 20:80 A/B and the eluent was collected in 5 mL aliquots. After fractions containing solutes which produced the m/z 396 ion during GC/MS analysis were found, which occurred at 100% acetonitrile, the aliquots were collected and concentrated under vacuum. Isolated MeSI adduct 83 (17.5 mg) was obtained after HPLC for characterization and testing: IR (neat) 2958, 2869, 1738, 1456, 1435, 1362, 1204, 1172, 1019, 967, 744 cm\textsuperscript{-1}; HRMS (ESI) calcd m/z for C\textsubscript{15}H\textsubscript{25}O\textsubscript{2}SINa\textsuperscript{+} 419.0512, found m/z 419.0493. NMR data is presented in Table 6.
References


APPENDIX

APPENDICES

A $^1$H NMR spectrum of (Z)-3-tridecene-5,7,9-triyne-1,11-diol 20
B $^{13}$C NMR spectrum of (Z)-3-tridecene-5,7,9-triyne-1,11-diol 20
C $^1$H NMR spectrum of (Z)-2-tridecene-4,6,8-triyne-1,13-diol 47
D $^{13}$C NMR spectrum of (Z)-2-tridecene-4,6,8-triyne-1,13-diol 47
E $^1$H NMR spectrum of (Z)-2-tridecene-4,6,8-triyne-1-ol 50
F $^{13}$C NMR spectrum of (Z)-2-tridecene-4,6,8-triyne-1-ol 50
Proton NMR of (2)-2-tridecene-4,6,8-triyne-1,13-diol in acetone-d6
$^{13}$C{IH} spectrum of (Z)-2-tridecene-4,6,8-triyn-1,13-diol in acetone-d6