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Review

The Alkyne Zipper Reaction: A Useful Tool in Synthetic Chemistry

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Abstract: The alkyne zipper reaction is an internal-to-terminal alkyne isomerization reaction with many interesting applications in synthetic chemistry, as it constitutes an efficient means of achieving acetylene functionalization. A review of its applications in synthesis processes is presented in this paper, with a brief overview of the mechanistic features of the alkyne zipper reaction, as well as a brief overview of its future potential.

Keywords: alkyne isomerization; acetylene isomerization; natural product synthesis; zipper; alkyne chemistry

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1. Introduction

The alkyne zipper reaction involves the migration of an internal alkyne to the terminal position in a linear hydrocarbon chain, see Scheme 1.

Scheme 1. The alkyne zipper reaction involves the isomerization of an internal triple bond to a terminal position.

Since the isomerization involves the formation of a product that is less thermodynamically stable than the original isomer, the alkyne zipper reaction has been coined a "contra-thermodynamic" process [1].

The isomerization of alkynes, under strong alkaline conditions, was first reported in the late 1800s. In the earliest reports of the reaction, the transformation was carried out using sodium amide as the base, under high reaction temperatures and long reaction times [2]. Other conditions reported include use of metallic sodium, KNH_2-NH_3-HMPA [2], alcoholic potassium hydroxide at high temperatures [3], sodium and potassium *tert*-butoxide in *tert*-butanol near 200 °C [4–6], as well as sodium amide in ethylene diamine [3,7]. The elevated temperatures required for some reactions, sometimes over several days, often resulted in side-reactions such as polymerization, or incomplete conversion from starting material [8,9]. With the introduction of the KAPA reagent (see structure in Figure 1) in the 1970s, these challenges were virtually eliminated [1], and terminal alkynes could be produced from internal alkyne starting materials at 0 °C [1,10].

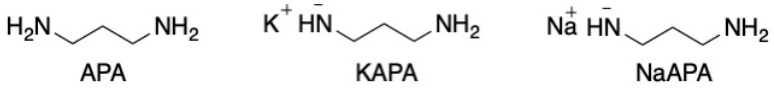


Figure 1. The structure of APA, KAPA and NaAPA.

In addition to allowing for milder reaction conditions, multilocational migration of the triple bond became achievable with the introduction of KAPA; prior to the introduction of KAPA, alkyne isomerization had been limited to rearrangements involving one or two positions—with KAPA, a migration through 10–11 carbon positions became feasible within a reasonable time span [11]; for example, Lindhoudt reported yields ranging from 80–90% in C-10 and C-11 alkynols [11].

One major drawback of KAPA is the hazard of handling KH during the preparation of the reagent [12]. Thus, investigations have resulted in the development of less hazardous alternatives. For example, Macaulay found that NaAPA can be used successfully as a safer alternative to KAPA [12]. The same research group reported that acetylene zipper reactions can be carried out using the sodium salts of 1,3-diaminopropane and 1,2-diaminoethane, in procedures that are simple, reproducible, and overall safer than using KAPA [13–16]. However, this also requires higher temperatures (50–60 °C), and longer reaction times, which stands in contrast to the efficiency of KAPA [13–16].

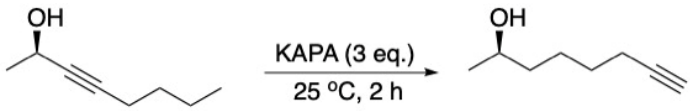
In addition to sodium salts of diaminoalkanes, Abrams also prepared the lithium salts of 1,3-diaminopropane and 1,2-diaminoethane [15]. After several hours, the terminal alkyne was the predominant isomer present in the solution, but the reaction proved to be low yielding. Addition of potassium *tert*-butoxide to the lithium salt resulted in improved yields and reduced reaction times, whereas diamine and potassium *tert*-butoxide alone did not afford any terminal alkyne [15]. It is thus assumed that the addition of potassium *tert*-butoxide to the lithium salt of 1,3-diaminopropane gives KAPA [17].

A different route to the KAPA reagent was reported by Hommes and Brandsma, who prepared KAPA by dissolving potassium or sodium amide in liquid ammonia and later replaced it with 1,3-diaminopropane [18]. Kimmel and Becker treated molten sodium or potassium with APA in an ultrasonic bath at 90 °C [19]. In both cases, the yields obtained were comparable to those obtained using the original KH/APA protocol.

Brown and Yamashita reported that hydroxyl groups will direct the reaction by transposing the alkyne to the chain terminus remote from the hydroxy function [10]. This is explained by the anionic intermediate involved in the isomerization that would be retarded by the alkoxide found in the basic conditions. The authors also suggest that the alkoxide will suppress elimination to corresponding conjugated system [10].

A few years later, it was found that the reaction does not affect the stereochemistry of optically active alcohols [20]. Brown and co-workers found that the alcohols

(*R*)-2-nonyne-4-ol and (*R*)-3-octyn-2-ol were transformed to (*R*)-1-nonyne-4-ol and (*R*)-3-octyn-7-ol without significant racemization, even when treated with 3 equivalents of KAPA at 25 °C for several hours. The latter reaction is shown in Scheme 2.



Scheme 2. The reaction of (R)-3-octyn-2-ol and KAPA to give (R)-3-octyn-7-ol, as described by Brown and coworkers is shown [20].

Furthermore, Brown and coworkers showed that the alkoxide will suppress the racemization of stereocenters positioned several carbons away. One example illustrating this is the isomerization of (*S*)-3-methyl-5-tetradecyn-1-ol, with 89% retention of configuration.

Brown and co-workers suggest that this can be explained by the fact that alkoxide has less acidic neighboring protons than the corresponding alcohol. Thus, these conditions suppress racemization [20].

Terminal alkynes are excellent starting materials for numerous reactions in which the carbon chain is elongated or modified to furnish a variety of useful products. As such, the alkyne zipper reaction has applications that range far beyond achieving acetylene functionalization in optically active alkynes. To illuminate some of the intriguing characteristics and uses of the

alkyne zipper reaction, the reaction will be the focus of this review, where the mechanistic features, and the significance of the reaction to organic synthesis, will be described.

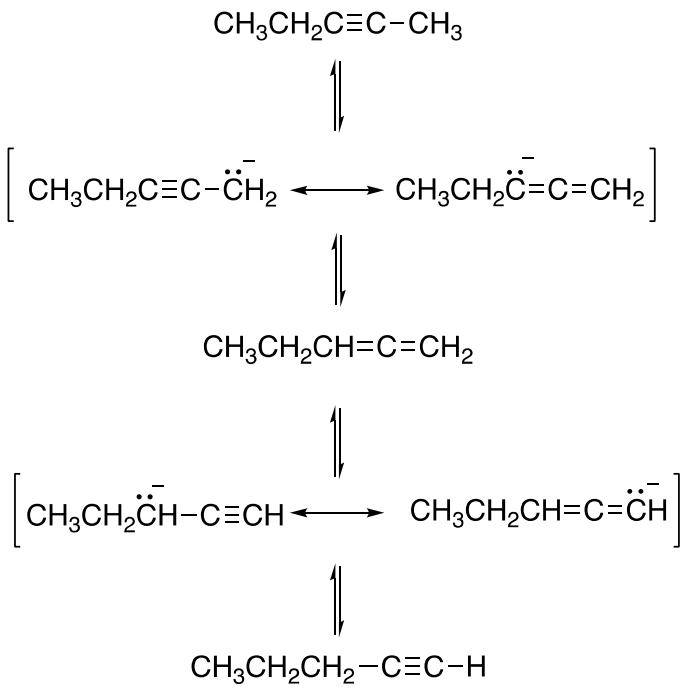
2. The Alkyne Zipper Reaction Mechanism

Few mechanistic studies exist on internal-to-terminal alkyne rearrangements. However, the reverse process, as well as the isomerization of alkynes with no methyl termini, have been under scrutiny by several research groups [7,21–25].

Alkyne isomerization have been found to follow a second order kinetics overall, being first order with respect to both the alkyne substrate and the base [9,26]. The rate at which the alkyne zipper reaction proceeds is therefore highly dependent on the type and amount of base present in the reaction medium.

Generally, the isomerization of alkynes can be viewed as a kinetically controlled process in which a proton is transferred from one site at a linear hydrocarbon to another through a series of Brønsted-Lowry acid-base exchanges. Depending on the reaction medium, these proton transfers may either be of a primarily intramolecular or an intermolecular nature [22,23].

To this end, it has been debated whether the proton transfers occur in conjugation with the base, or if the base functions solely to deprotonate the alkyne. In the case of the latter, it has been suggested that the isomerization of alkynes proceeds via allenes in a stepwise manner, through a mechanism that involves the formation of discrete carbanionic acetylene-allene intermediates, as outlined in Scheme 3 [9,21,23,27].



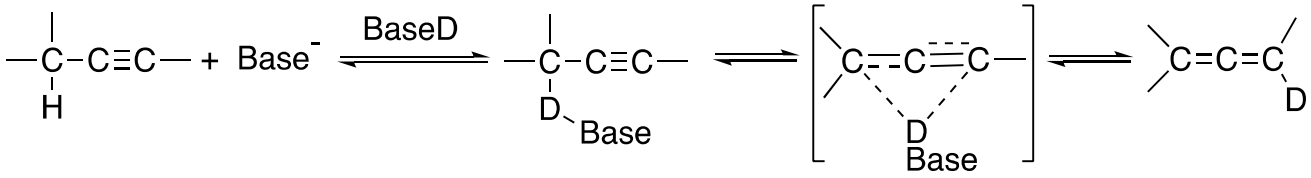
Scheme 3. The mechanism suggested by Jacobs et al. [21] In this mechanism, isomerization proceeds in steps through carbanionic species that tautomerize between the acetylenic and allenic form [21].

The isomerization reaction is initiated by the abstraction of the proton adjacent to the triple bond, by the action of the base [21,24,26,27]. This likely constitutes the rate-determining step, as the kinetic isotope effect (K_D/K_H) has been found to be significantly greater than 1 [24,26]. Upon deprotonation, the resulting carbanions tautomerize between an acetylenic and an allenic carbanion [27]. Protonation of the latter affords the allene intermediate which then isomerizes rapidly via new allene-acetylene carbanion pairs to form the corresponding alkyne isomer [27].

The fact that $K_D/K_H >> 1$ can be taken as evidence that carbanion intermediates are involved in the isomerization of alkynes [24,26]. However, allenes are rarely observed unless extreme conditions are imposed, owing to their high kinetic instability [4]. Their presence as reaction intermediates has nevertheless been acknowledged by observing the isomerization of alkynes in quasi-equilibrium mixtures, i.e., reaction mixtures in which the most thermodynamically favourable isomer is not always formed, and which therefore are not under thermodynamic control [3,21,27]. In support of the notion that alkyne rearrangements are reversible processes involving allene intermediates, allenes isomerize to form the corresponding alkynes in either direction, and vice versa [3,21,27,28].

Insofar as the carbanion mechanism involves discrete carbanionic species, it does not satisfactorily account for the observation that, depending on the solvent, the prototropic rearrangements of alkynes can exhibit a high degree of intramolecularity [22]; that is, the proton captured by the carbanion is, to varying extents, the same as the proton that was abstracted at a distinct site. Cram et al. found that when the 1,3-proton transfer in 1,3,3-triphenyl-prop-1-yne was catalyzed by triethylenediamine in a DMSO-methanol solvent mixture at 30 °C, 88% intramolecularity was obtained [22]. However, when the same compound was isomerized by potassium methoxide in methanol at 30 °C, the reaction exhibited 19% intramolecularity only [22]. Based on this, the authors concluded that the degree of intramolecularity was influenced by the polarity of the solvent, with the degree of intramolecularity being higher in less polar solvents.

To rationalize how protons may be transferred intramolecularly, it was proposed that the 1,3-proton transfers in acetylene/allene systems may proceed via a "conducted tour" mechanism, as outlined in Scheme 4 [7,22,29,30]. Deuterium labeling studies confirmed that this was a plausible pathway for alkyne rearrangements [22].

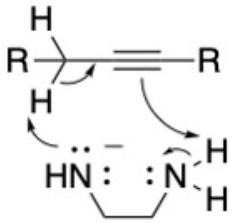


Scheme 4. Outline of the "conducted tour" mechanism [7,22,30]. In this scheme, Base is a general nitrogen- or oxygen containing base.

In this suggested mechanism, the base responsible for proton abstraction forms an ion-pair intermediate with the carbanion, such that the abstracted proton remains hydrogen-bonded to both carbanionic sites until it is recaptured at a new position further down the hydrocarbon chain [22,30]. External protons may be incorporated into the isomerization product through a proton exchange between the base hydrogen-bonded to the carbanion intermediate and the solvent, followed by further prototropic rearrangements by means of a "conducted tour" (see Scheme 4) [7,29].

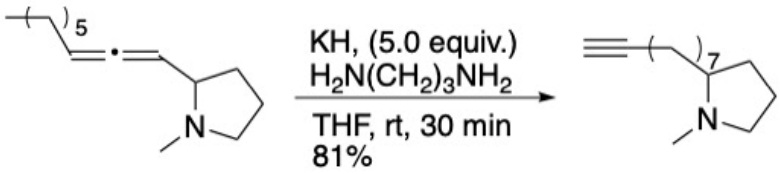
However, if an external proton were to be accepted by the carbanion at a site not involved in forming the carbanion-base complex, dissociation of the ion-pair would occur. This effect is greater in proton-rich environments, which could explain the low degree of intramolecularity observed in these types of solvents. As such, the "conducted tour" mechanism is more likely to occur only in proton-deficient solvents [23,24,30].

As an alternative to the *conducted tour* mechanism and the stepwise acetylene-allene mechanism [3,7,31] a mechanism involving the coordinated action of two amine groups in the presence of a diamine catalyst (see Scheme 5) were also proposed [2].



Scheme 5. The mechanism for the aminoalkylamide-catalyzed isomerization of an internal triple bond [7].

In this mechanism, an amide group deprotonates the carbon adjacent to the triple bond, while an amino group donates a proton to the alkyne in one concerted step [7]. The KAPA-mechanism distinguishes itself from the "conducted tour" mechanism in that it introduces the idea of a six-membered cyclic transition state in which a favorable geometry between a bidentate catalyst and the alkyne substrate is formed, as opposed to a mechanism involving monodentate base which may abstract and donate protons to the alkyne in a more arbitrary fashion. The rate-enhancing effect of the KAPA reagent [1] may thus be explained in terms of the action of the aminoalkylamide-catalyst, which, by acting as a simultaneous proton acceptor and donor, allows for a swift succession of deprotonation/re-protonation steps [8]. Each step is reversible, with the effect that isomerization may proceed randomly in either direction until the terminus is reached, at which stage the reaction is terminated by formation of the stable acetylide salt, which then precipitates out of solution [12,32,33]. The random-walk hypothesis, as well as the idea of a cyclic reaction intermediate, was strengthened by Macauley's study on isomerization of decyn-1-ols, in which all alkyne-containing isomers were identified [12,33]. However, similar to the findings of Brown and Yamashita, no allenes, which were assumed to be intermediates in the carbanion mechanism, were identified [1,12]. As such, allene intermediates appear to be omitted from depictions of the KAPA-catalyzed reaction mechanism. Nevertheless, it should be noted that Zhang et al. showed that acetylene zipper conditions can be used to transform allenes into terminal alkynes [34], as illustrated in Scheme 6.



Scheme 6. Allenes can be transformed into terminal alkynes under alkyne zipper conditions [34].

After the mid-1970s, it appears that the KAPA-mechanism has become widely accepted as the main mechanism through which alkynes isomerize under alkyne zipper conditions, as this mechanism is most frequently cited in literature. Indeed, this mechansim was adapted by Brown et al. [2] in their original report on the KAPA-catalyzed zipper reaction [2]. Since the carbanion mechanism inspired several kinetic studies relating to alkyne isomerization, which lay the foundation for understanding the mechanism governing alkyne rearrangements, it may nevertheless be viewed as an important contribution to elucidating the mechanism. Similarly, the "conducted tour" mechanism introduced the idea of a base catalyst-alkyne substrate complex, which is analogous to the cyclic alkyne-aminoalkylamide complex that is key to the KAPA mechanism. Wotiz et al. [7] argue that the three mechanisms cannot be clearly distinguished, and that all three may be operative to a certain extent under the appropriate conditions. Thus, studying the carbanion mechanism and the "conducted tour" mechanism can be supplementary to understanding the KAPA-mechanism.

As a final note on the factors that may impact the outcome of the alkyne zipper reaction, it should be noted that the presence of substituents within the chain influences the rate and direction in which the reaction proceeds [23,35]. Generally, alkyne rearrangements do

not proceed beyond a point of branching [1,3]. In cases where electron-withdrawing substituents, such as –OH, are present, the triple bond tends to migrate away from the electron-deficient carbon center, as briefly outlined in the introduction [11,23]. In comparison, electron-donating groups, such as phenyls, tend to stabilize the carbanionic intermediates to such an extent that inwards migration becomes more favorable [11,23,32].

However, when linear alkynoic acids are subjected to the same conditions that would shift the triple bond in the corresponding alkynol, conjugated 1,3-dienes are formed as the major products [11,32]. For example, Lindhoudt et al. [11] tried to isomerize alkynoic acids using KAPA and ended up with conjugated dienes. The same phenomenon was also reported by Abrams in a later publication [36]. Mechanistically, conjugated dienes may arise from deprotonation of an allene intermediate on the methylene one position away from the allene [27].

Interestingly, when Augustin and Schäfer modified the original alkyne zipper procedure to include 0.5 equivalents of iron (II) chloride in addition to 10 equivalents of KAPA in a mixture of APA and THF, they managed to isomerize internal alkynoic acids to the corresponding terminal alkyne. However, they argue that the indirect route via the alkynol constitutes a more convenient approach [37]. As the syntheses part of this paper will illustrate, this pathway appears to be preferred by most other authors as well.

3. The Alkyne Zipper Reaction in Synthesis

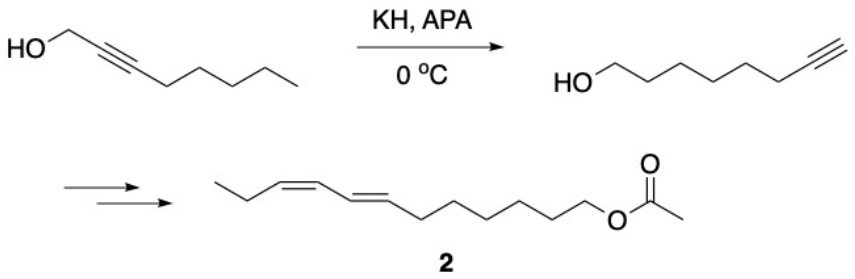
Alkynes are found in numerous organic compounds, including several natural products and analogues of these [38–42], synthetic intermediates [43], and liquid crystalline gigantocycles [44]. Terminal alkynes are particularly useful scaffolds in organic synthetic chemistry [45] where they can act as nucleophiles, be reduced to alkenes or alkanes, or be oxidized to produce carboxylic acids. Their versatility is illustrated by the multitude of reactions they may participate in, including addition reactions, cross-coupling reactions (e.g., references [46,47]), alkyne metathesis (read more in e.g., [48,49]), and enyne metathesis reactions [50,51]. Moreover, terminal alkynes may have applications in click chemistry reactions, as exemplified with the copper catalyzed azide–alkyne cycloaddition [52–54].

In the following sections, we will highlight several examples of syntheses where the alkyne zipper reaction is applied to obtain the functionalization required for these types of reactions.

3.1. Pheromones and Long Chained Alcohols

Brown and Yamashita predicted that the alkyne zipper reaction would become a useful tool to functionalize long hydrocarbon to prepare lipid compounds [10]. Brown and Yamashita listed bombykol (**1**) and dodeca-7,9-dien-l-y1 acetate (**2**), the sex pheromone of the European grape vine moth (*Lobesia botrana*), as examples of synthetic targets [10].

The latter was prepared by Negishi and Ahramovitch shortly after [55], see Scheme 7. The authors are not reporting reaction time or yield.



Scheme 7. The alkyne zipper reaction in Negishi and Ahramovitch's synthesis of dodeca-7,9-dien-l-y1 acetate) (**2**), the sex pheromone of the European grape vine moth (*Lobesia botrana*).

Related compound (2*E*,13*Z*)-2,13-octadecadien-1-yl acetate (3), pheromone structure from Sesiid moths [56], (11*Z*,14*E*)- and (11*E*,14*E*)-11,14-octadecadienal (4 and 5, respec-

tively), sex pheromone components of female tea cluster caterpillar, *Andraca bipunctata* [57], were prepared by similar use of alkyne zipper reaction. Camps et al. also used the method to prepare analogues sex pheromone of processionary moth, *Thaumetopoea pityocampa*, (6 and 7) [58]. All compounds listed in this paragraph are shown in Figure 2.

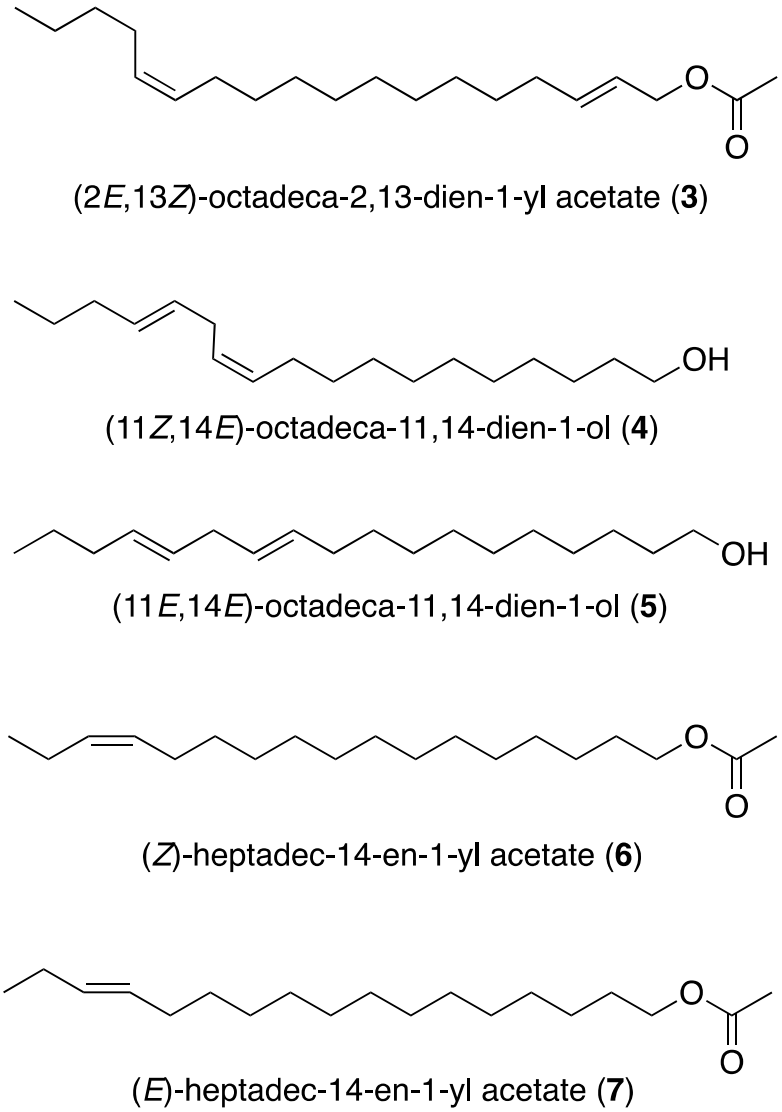
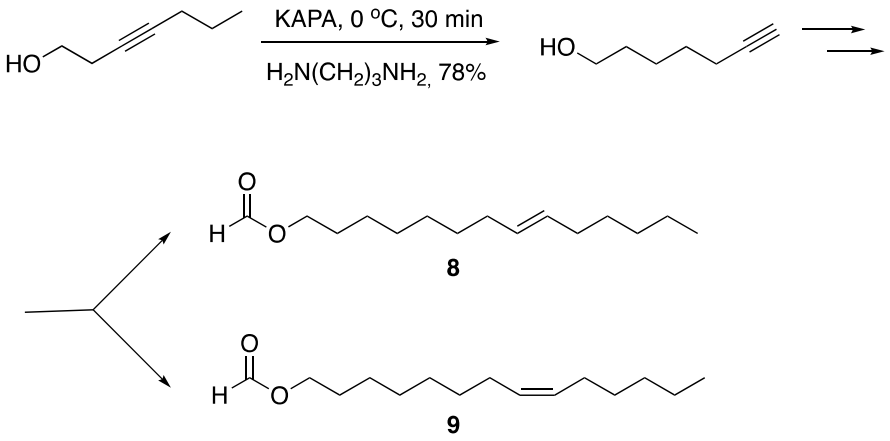


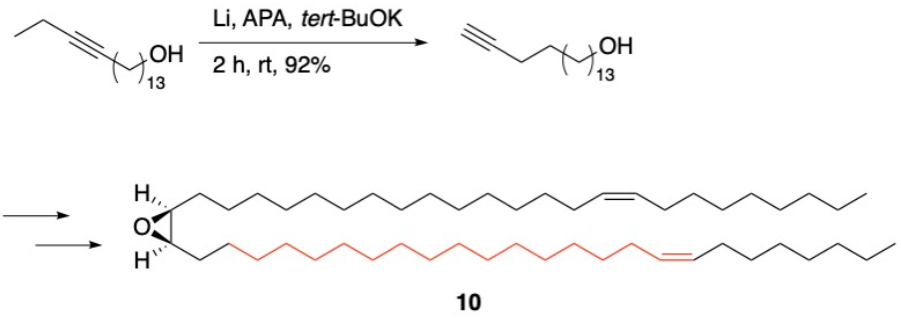
Figure 2. Structures of (E)-2-(Z)-13-octadecadien-1-ol acetate [56], (Z,E)- and (E,E)-11,14-octadecadienal [57] and (Z)- and (E)-heptadec-14-en-1-yl acetate [58]. All compounds were synthesized with alkyne zipper reaction as part of the synthesis.

Mori also used the alkyne zipper reaction in the synthesis of sex pheromone mimics **8** and **9** against the yellow peach moth [59]. In this synthesis, the resulting terminal alkyne was alkylated, followed by reduction of the alkyne to *E*- and *Z*-alkenes using lithium tetrahydridoaluminate or Lindlar catalyst and hydrogen, respectively. These were transformed into the corresponding formats, see Scheme 8. Bioassay of a 10:1 mixture of E and Z against the male *Dichocrocis punctiferalis* demonstrated it to be as active as the natural product in low dose experiment. However, the natural pheromone was more active at higher dose [59].



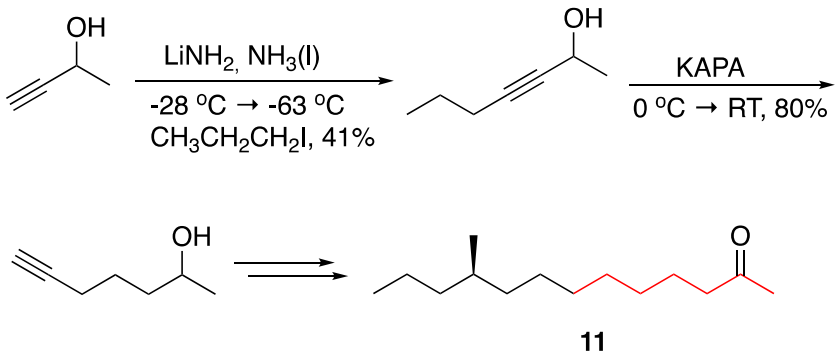
Scheme 8. Mori's short synthesis of sex pheromone mimics against the yellow peach moth [59].

Mori and Argadel used the reaction in their synthesis of (9*Z*,25*S*,26*R*,43*Z*)-25,26-epoxy-9,43-henpentacontadiene (**10**), a component of the nymph recognition pheromone produced by cinereous cockroach *Nauphoeta cinerea* [60]. The alkyne zipper reaction in this synthesis was accomplished with the constellation of Li, 1,3-diamoproapane, *tert*-BuOK at room temperature for 2 h to give the terminal alkyne in excellent yield, 92%. This synthesis also illustrates how well the alkyne zipper reaction can work even though the hydroxyl is several atoms away (here thirteen methylenes between the triple bond and the hydroxyl), see Scheme 9.



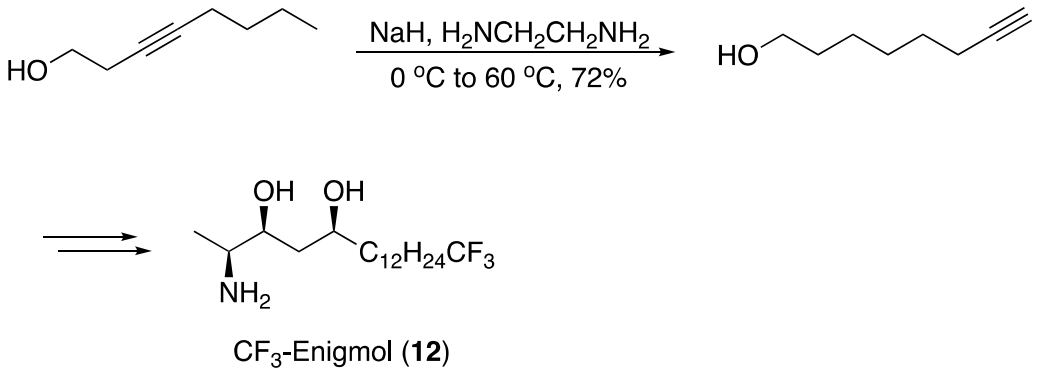
Scheme 9. The alkyne zipper reaction in Mori and Argadel's synthesis of (9Z,25S,26R,43Z)-25,26-Epoxy-9,43-henpentacontadiene [60]. The fragment from the zipper reaction is marked in red.

Mori and Senda used the reaction in their synthesis of (*R*)-(−)-10-methyl-2-tridecanone (**11**), the pheromone of the southern corn rootworm, see outline in Scheme 10. They employed the traditional Brown and Yamashita method for the KAPA preparation [61].



Scheme 10. Synthesis of *(R)*-(−)-10-methyl-2-tridecanone, the pheromone of the southern corn rootworm [61].

Enigmol is a sphingolipid derived structure that exhibited broad-spectrum cytotoxicity against human cancer cell lines in vivo without causing systemic toxicity. Miller et al. synthesized fluorinated analogues of enigmol to increase lipophilicity to increase tumor uptake. CF_3-enigmol (**12**) (trifluorination at C-18) and CF_2-enigmol (difluorination at C-6) were both prepared [62]. For the former an alkyne zipper reaction was used, see Scheme 11. Despite good IC_{90} values in tumor, CF_3-enigmol did not significantly inhibit tumor growth. Also, the compound led to significant weight loss in mice [62].

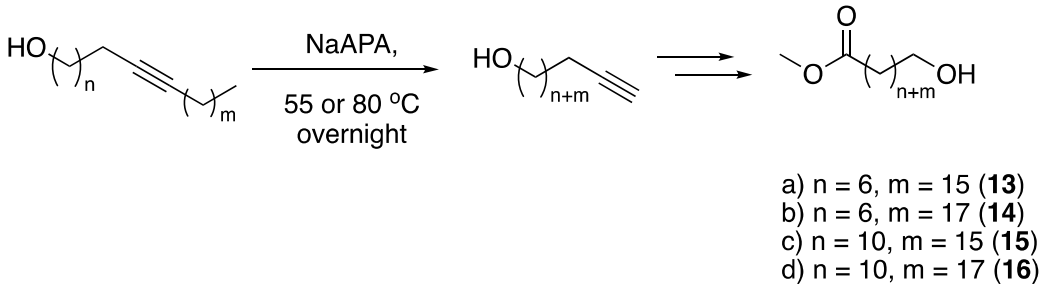


Scheme 11. The alkyne zipper reaction used in the synthesis of CF_3-enigmol [62].

3.2. Fatty Acids and Derived Structures

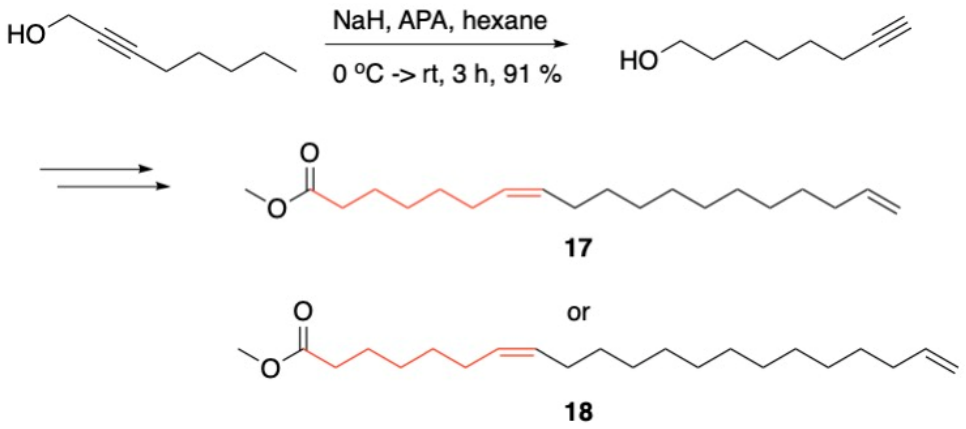
The alkyne zipper reaction has also been employed in numerous long chained fatty acid derivatives, as illustrated in the following section.

An early use of alkyne zippe reaction in the sytnehsis of fatty acids is reported by Abrams [14]. As part of her development of safer methods for alkyne zipper isomerization, she demonstrated her method with NaAPA in the synthesize of a series of ω-hydroxy esters, structures **13–16**, see Scheme 12 [14].



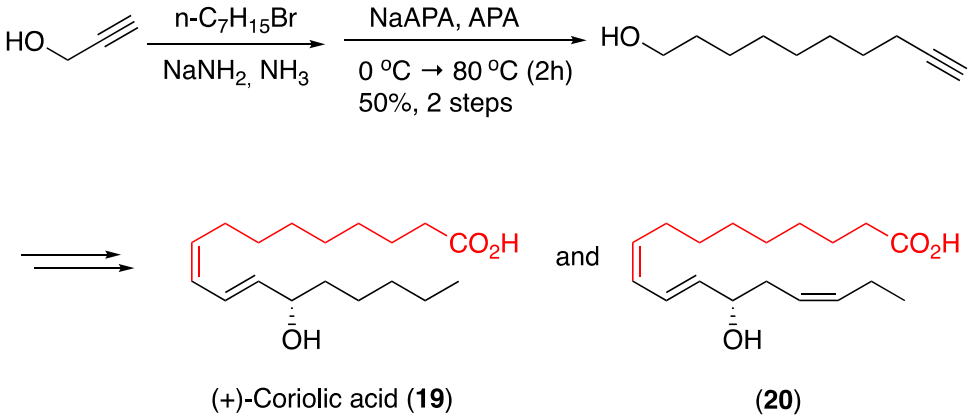
Scheme 12. The synthesis of ω-hydroxy esters **13–16** [14].

Shimada et al. used the alkyne zipper reaction in their synthesis of two non-methylene-interrupted fatty acids with terminal olefin, structures **17** and **18**, isolated as minor components of ovarian lipids of the limpet *Cellana toreuma.* In this synthesis, NaAPA in hexane was reacted with a propargylic alcohol to give the corresponding terminal alkyne in 91% yield. Over several more reactions, both fatty acid esters **17** and **18** were made, see Scheme 13, and by that the suggested structures for the natural products were confirmed.



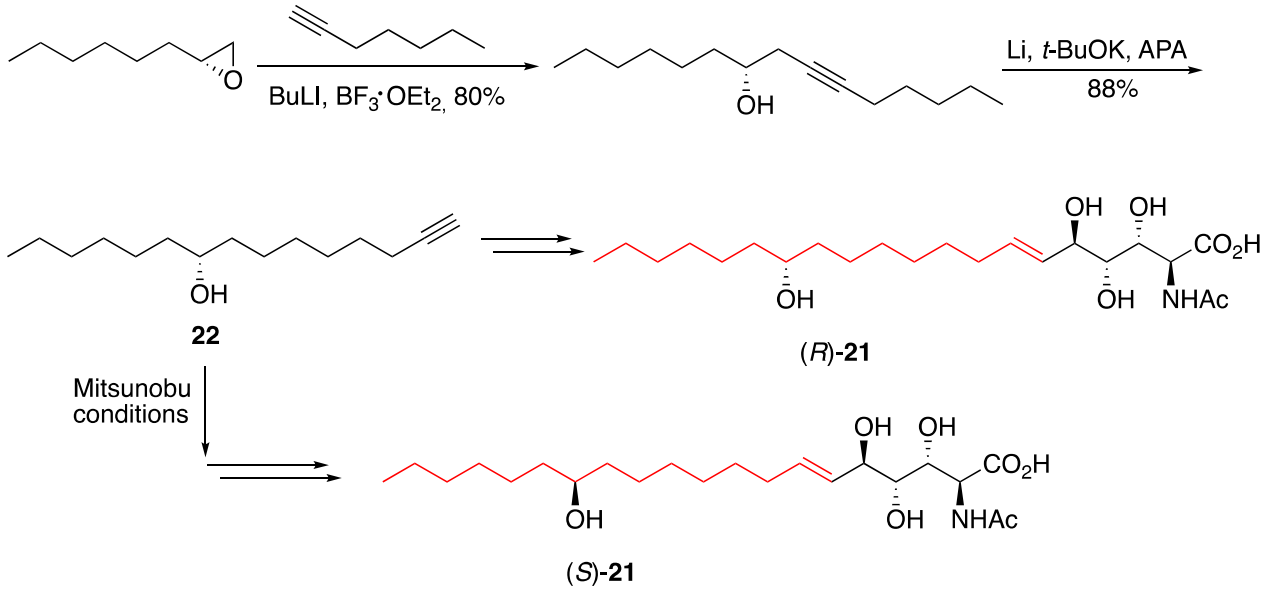
Scheme 13. The syntheses of methyl esters of fatty acids Y and Z.

Yadav et al. synthesized (*S*)-coriolic acid (**19**) and (*S*)-15,16-didehydrocoriolic acid (**20**) using the alkyne zipper reaction as a key step [63]. In their synthesis, NaAPA is prepared from $NaNH_2$ in APA, heated at 60 °C for 25 min. The mixture was cooled to 0 °C and internal alkyne was added. The mixture was reacted at 80 °C for 2 h to give the terminal alkyne in 82% yield. Both fatty acids were synthesized with similar synthesis sequences, as depicted in Scheme 14.



Scheme 14. The syntheses of methyl esters of fatty acids 19 and 20 [63].

Otaka and Mori used the alkyne zipper in theis synthesis of the sphingolipid sphingofungin D (**21**), antifungal metaboiites produced by *Aspergillus fumigatis* ATCC 20857. KAPA was prepared from Li, APA and *tert*-BuOK, and gave terminal alkyne (*R*)-**22** in 88% yield, and without affecting the stereochemistry of the starting material. More reactions gave C14 (*R*)-isomer of sphingofungin D ((*R*)-**21**) [64,65]. Data did not match with the natural product, thus a Mitsunobu inversion was used to prepare (*S*)-**22**. From (*S*)-**22**, the natural product, C14 (*S*)-isomer of sphingofungin D ((*S*)-**21**), was synthesized, see Scheme 15. A similar strategy was also used to give its three stereoisomers [65].



Scheme 15. The synthesis of sphingofungin D (**21**) by Otaka and Mori [64,65].

Chida and co-workers have previosly reported the transformation from sphingofungin D to sphingofungin A (**23**) and B (**24**), see stuctures in Figure 3, [66], thus making Otaka and Mori's strategy a formal synthesis of these as well.

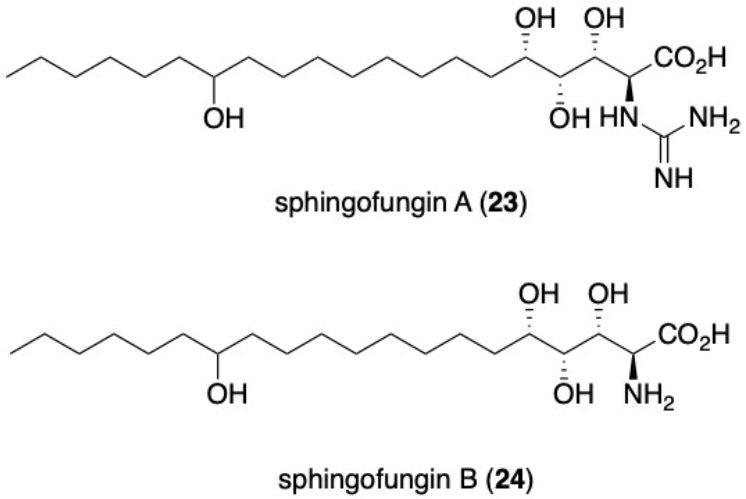
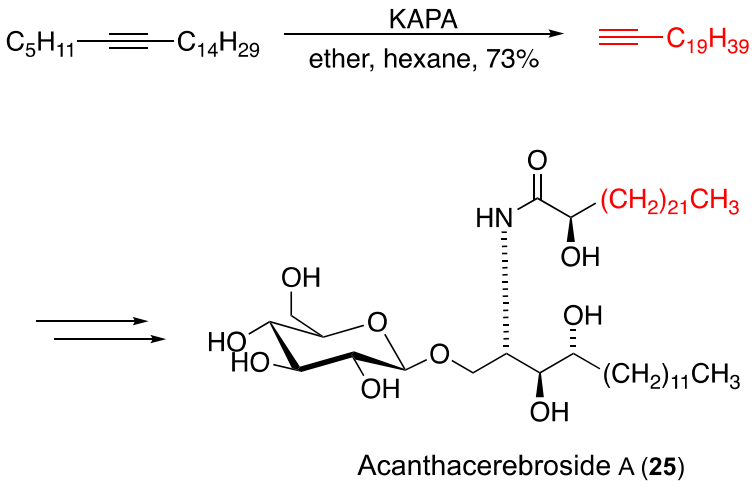


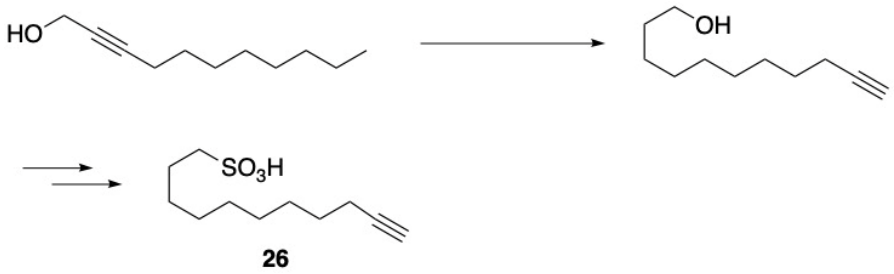
Figure 3. The stuctures of sphingofungin A (**23**) and B (**24**) [66].

Sugiyama et al. reported the absolute stereochemistry of the ceramide part of achanthacerebroside A (**25**) by preparing the corresponding sphingosine base [67]. In the total synthesis of the cerebroside **25**, an alkyne zipper reaction was used to prepare the lipophlic part of the structure, see Scheme 16. KAPA was prepared from KH and APA, and the reaction was carried out in a solvent mixture of diethyl ether and hexane to give the desired terminal alkyne in 73% yield [68].



Scheme 16. The alkyne zipper reaction used in the achanthacerebroside A (**25**) [68].

Helvig et al. studied the correlation of cytochrome P450, naturally involved in lauric acid oxidation, and hydroxylation of pesticide diclofop in wheat. They developed a series of inhibitors of diclofop metabolism. As part of this study, the water-soluble sodium salt of undec-9-yne-1-sulfonic acid (**26**) was synthesized, see Scheme 17. In this synthesis, the alkyne zipper reaction is a key reaction. However, there are no data given about reactions conditions, but the authors are citing Macaulay's article on NaAPA [69], and are assumed to use NaAPA protocol. Yield is reported to be 73% yield.



Scheme 17. Part of the synthesis of sodium salt of undec-9-yne-1-sulfonic acid (**26**).

Another interesting example involves the synthetic route for the quorum sensing molecule *diffusible signal factor* (DSF) (**27**) (Figure 4), in which the alkyne zipper reaction became key to efficiently obtain the biologically active stereoisomer.

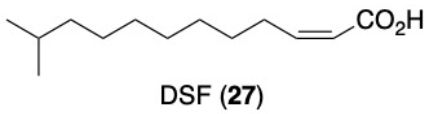
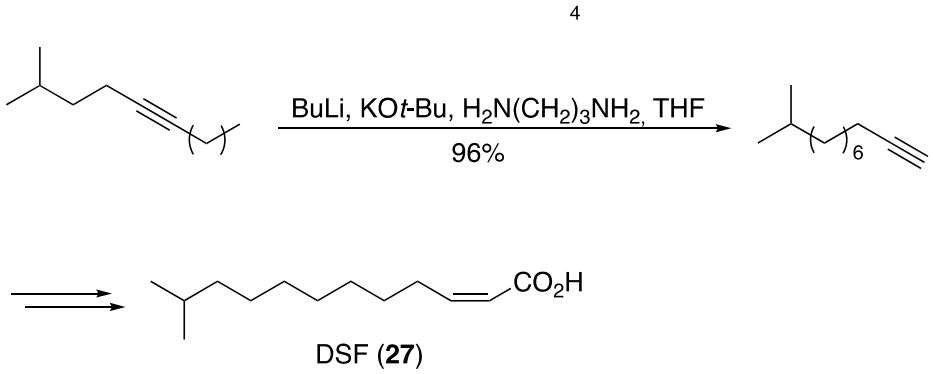


Figure 4. Shows the structure of cis-11-methyl-2-dodecenoic acid (**27**) [70].

While the *cis*-unsaturated isomer effectively mediates intercell communications, the *trans*-unsaturated has no known biological effect, whereas the biological activity of the saturated derivative is significantly lower than the biosynthesized compound [70]. Thus, finding a pathway that primarily yielded the *cis*-unsaturated isomer was essential.

It is interesting to note that this is an example of high yielding regiospecific reaction on a pure non-symmetric hydrocarbon. The synthetic pathway is outlined in Scheme 18.

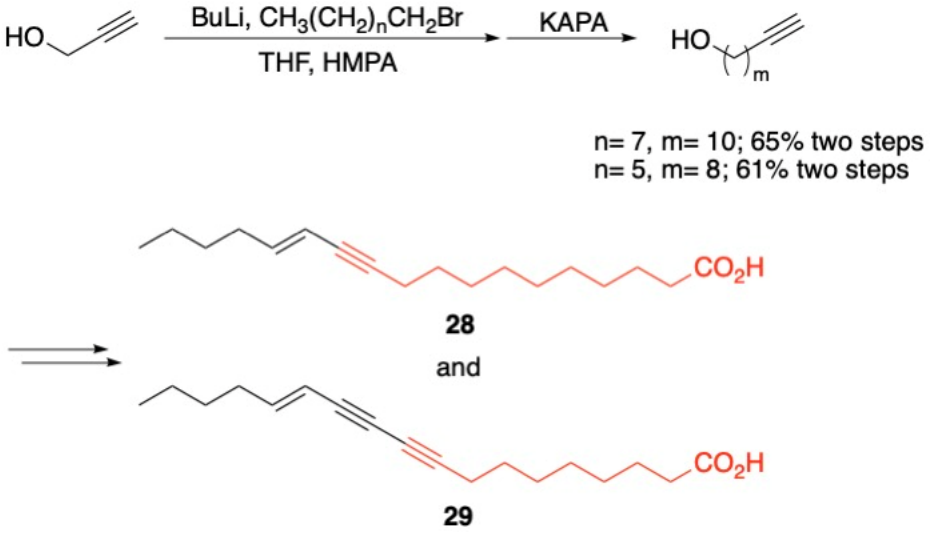


Scheme 18. Outline of the synthesis route in which the alkyne zipper reaction played an essential part [70].

An internal alkyne was generated through the alkylation of 1-hexyne with 4-bromo-2-methyl butane. The alkyne zipper reaction was then performed using a mixture of *n*-butyllithium, potassium *tert*-butoxide, and 1,3-diaminopropane in THF, to obtain a terminal alkyne in 96% yield. Finally, DSF was obtained in 89% yield by the addition of gaseous carbon dioxide to **61**, and the partial hydrogenation of the resulting carboxylic acid [70].

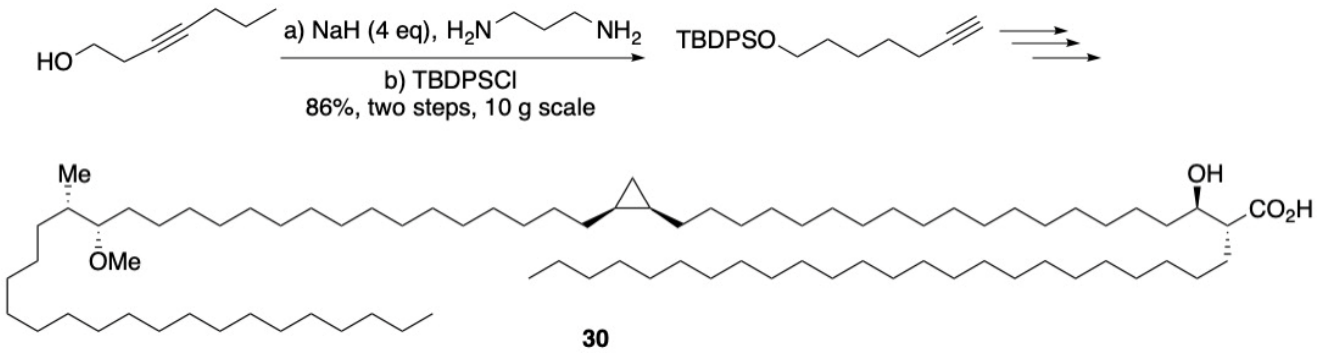
An interesting feature of this pathway is that two of the steps involved the carbon-carbon addition to terminal alkynes in high yields, which illustrates the effectiveness of using terminal alkynes in synthesis processes.

Alves et al. used alkyne zipper reaction the synthesis of polyacetylenic acids **28** and **29** isolated from *Nanodea muscosa* [71], see Scheme 19. The same group also synthesized other polyacetylenic acids, isolated from *Heisteria acuminata*, using the same strategy [72]. The group used KAPA to prepare the terminal alkyne, followed by a cross coupling reaction to obtain the target molecule. Alves et al. do not list reaction conditions, but they are referring to Abrams [15] in their preparation of KAPA, thus it is assumed that they use the "mixed alkali metal amides" method, in which lithium salt of 1,3-dipropanediamine is treated with KO*t*Bu to give a cleaner and safer conditions.



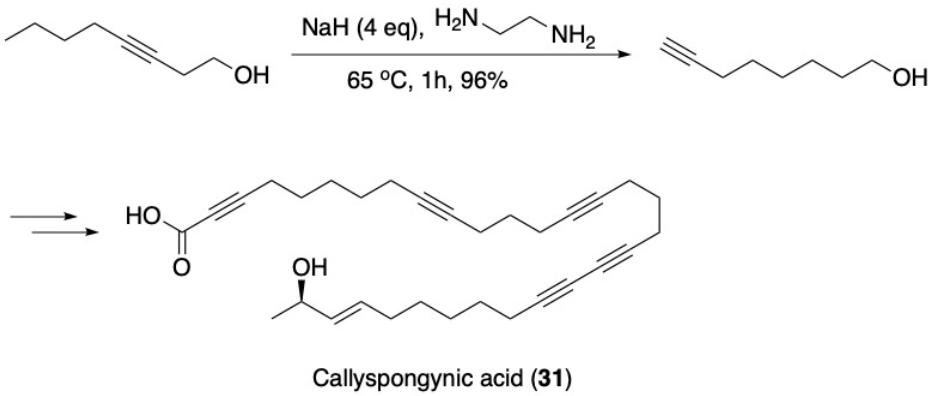
Scheme 19. Synthesis of two polyacetylenic acids **28** and **29** by Alves et al. [71].

In the synthesis of a mycolic acid (**30**) from *Mycobacterium tuberculosis* [73], the isomerization reaction, employing NaH and diaminopropane, is performed on a homopropargylic alcohol, to give a terminal alkyne in good yield. The hydroxyl group is protected as a silyl ether and over several reaction steps transformed into the natural product mycolic acid (**30**), as depicted in Scheme 20.



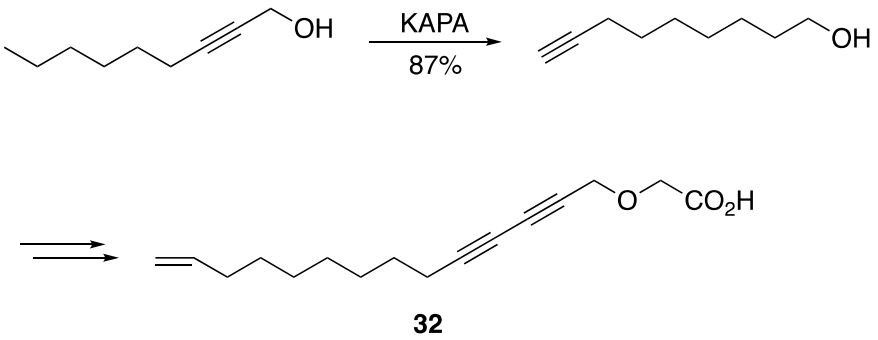
Scheme 20. The alkyne zipper reaction from the synthesis of a mycolic acid from Mycobacterium tuberculosis [73].

1,2-Ethylenediamine can be used as a substitute for 1,3-propandiamine, as depicted in the synthesis of the polyacetylene callyspongynic acid (**31**) [74]. The isomerization was accomplished in excellent yield, 96%, see Scheme 21.



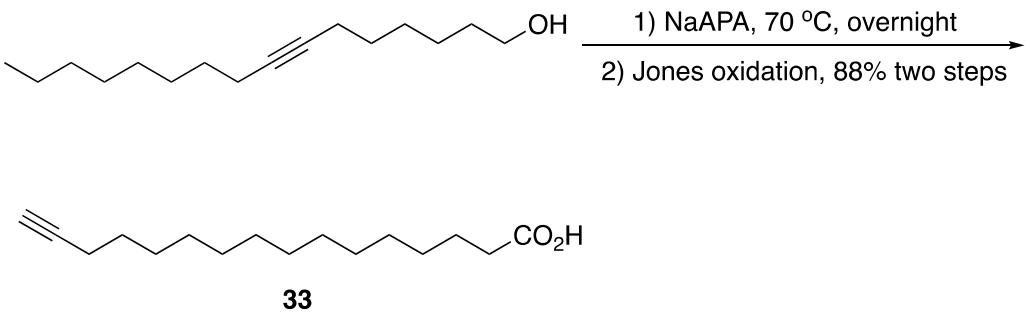
Scheme 21. Synthesis of Callyspongynic acid (**31**) [74].

Several other syntheses use similar strategies, including Stefani's synthesis of polyacetylenic montiporic acids B (**32**), with antibiotic effects. The acetylene zipper reaction is shown in Scheme 22 [75].



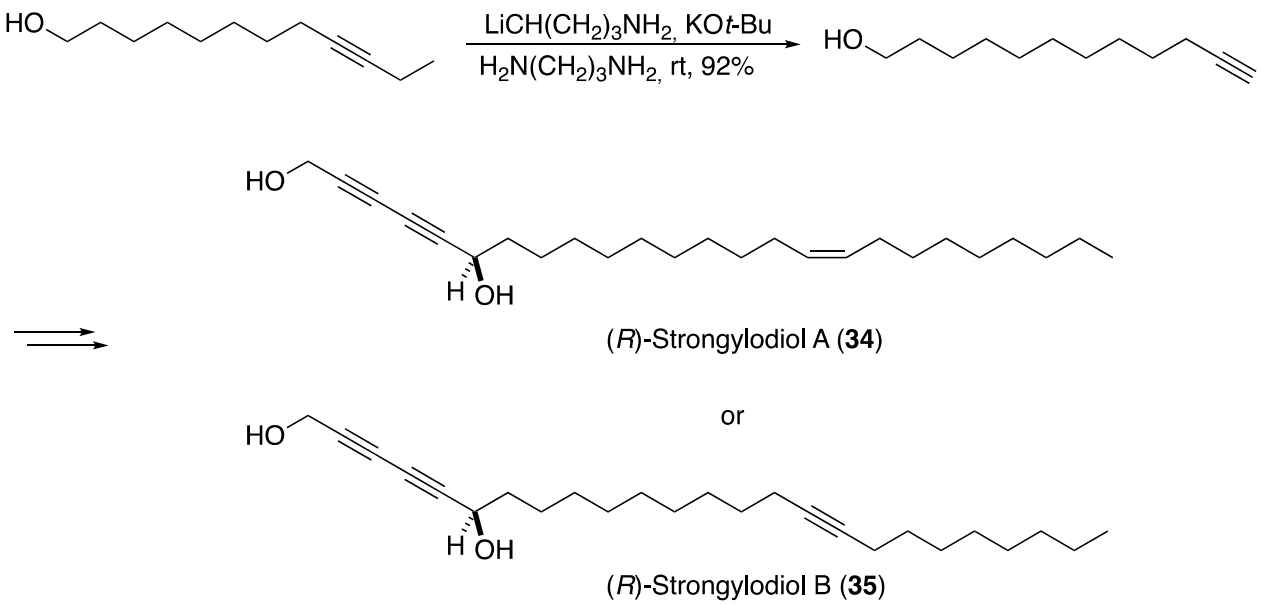
Scheme 22. The acetylene zipper reaction in Stefani's synthesis of polyacetylenic montiporic acids B [75].

Hannoush and Arenas-Ramirez prepared ω-alkynyl analogues of fatty acids, exemplified by compound **33** [76]. What should be noted here is, the distance between the hydroxyl group and the alkyne. Even though six methylenes separate the two functionalities, the alkyne zipper reaction was still successful and high yielding, see exemplified with fatty acid Scheme 23.



Scheme 23. The synthesis of ω-alkynyl analogues of fatty acids illustrates that the alkyne and hydroxyl can be far apart.

Another synthesis illustrating the same phenomenon, but to an even more extreme degree, is the asymmetric synthesis of cytotoxic sponge metabolites (*R*)-strongylodiols A (**34**) and B (**35**) by Kirkham et al. [77], see Scheme 24. In this synthesis, 9-dodecyn-1-ol is transformed into 11-dodecyn-1-ol, even with eight methylenes separating hydroxyl group and alkyne in the starting material.



Scheme 24. The synthesis of cytotoxic sponge metabolites R-strongylodiols A (**34**) and B (**35**) by Kirkham et al. [77].

Two related structures, the long-chain acetylenic alcohols (*R*)-Strongylodiols C (**36**) and D (**37**), see structures in Figure 5, both isolated from Okinawan marine sponge of the genus *Strongylophora*, were also synthesized using a similar approach [78].

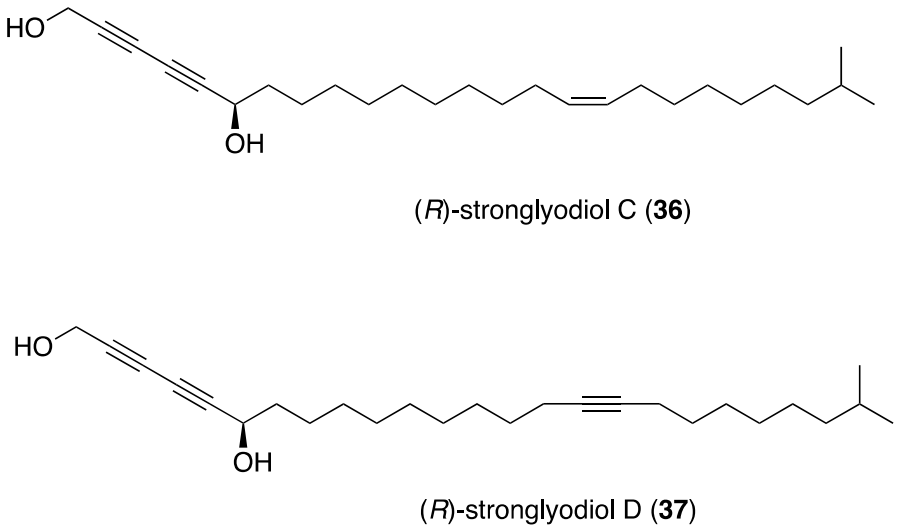
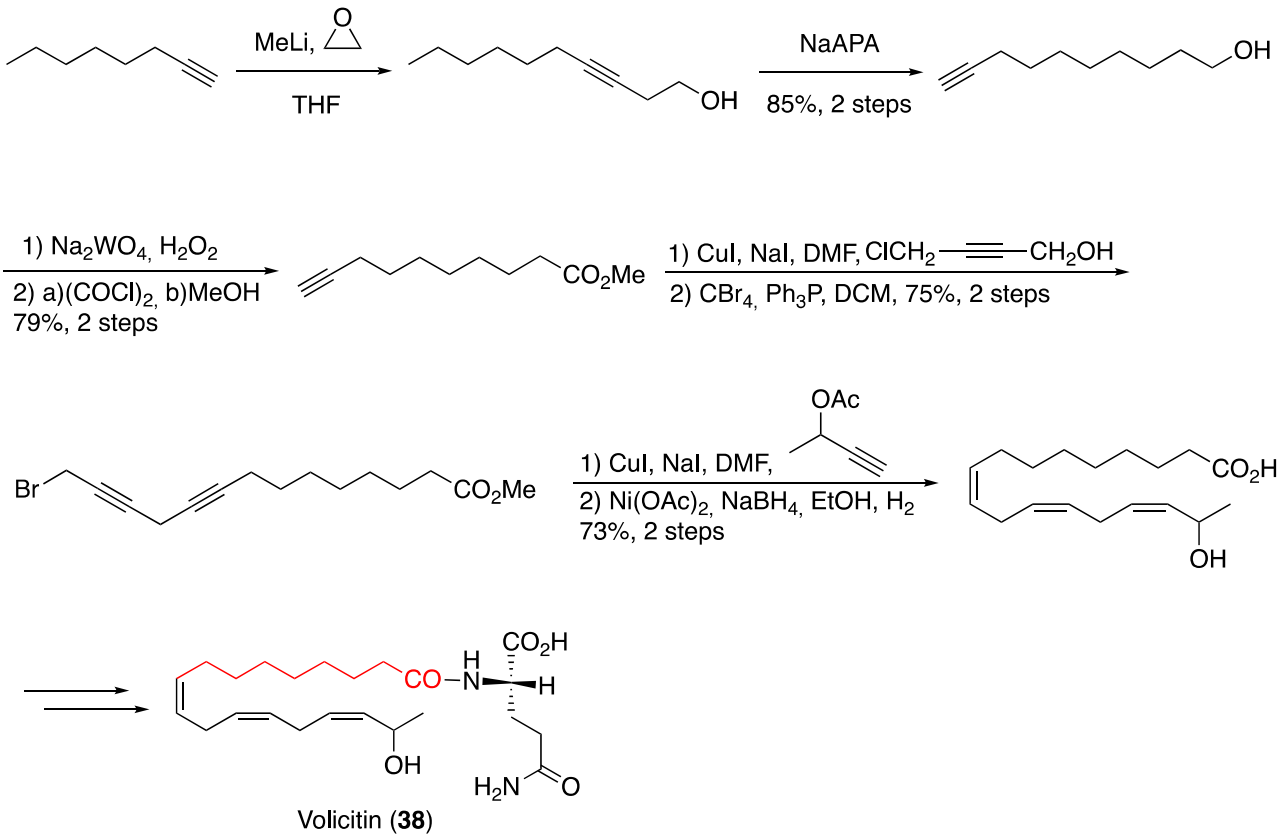


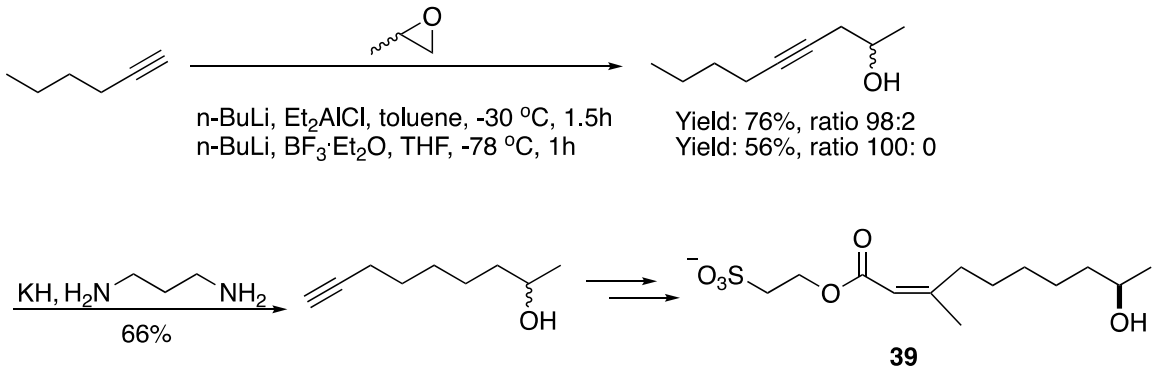
Figure 5. The structures of (R)-Strongylodiols C and D (**36** and **37**, respectively).

We also used the alkyne zipper reaction in our formal synthesis of volicitin (**38**) [79], see Scheme 25. In this synthesis, 1-octyne, treated with MeLi, is reacted with oxirane to give 3-decanyl-1-ol. This compound was treated with NaAPA to isomerize. Over a few reactions, including the coupling to the amino acid [80], the natural product volicitin was synthesized.



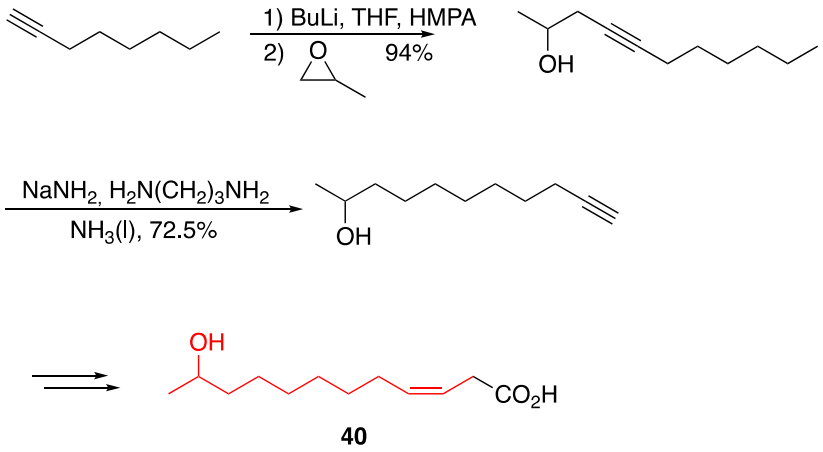
Scheme 25. The formal synthesis of Volicitin by Hansen and Stenstrøm [79].

The same type of strategy was performed by Dobbs et al. in their total synthesis of the Irciniasulfonic Acids (**39**), which also happens to be the first published synthesis of the compound, see Scheme 26 [81].



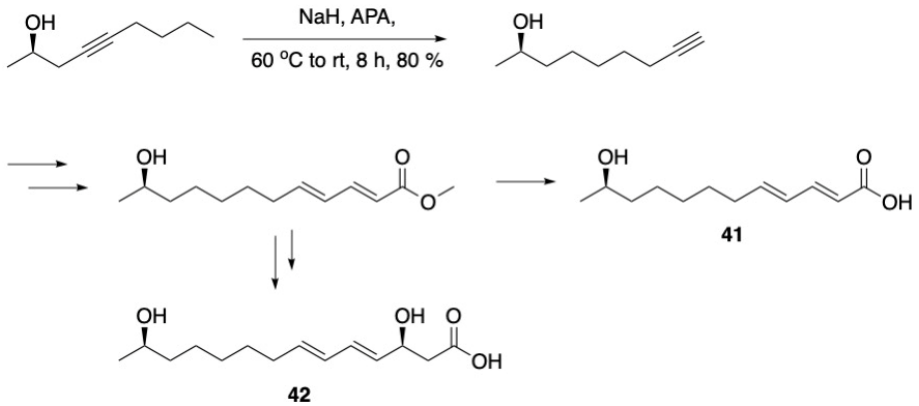
Scheme 26. The synthesis of Irciniasulfonic Acids [81].

Oehlschlager et al. used the alkyne zipper reaction as a key transformation in a formal synthesis of naturally occurring macrolide from cucujid grain beetles (**40**) [82], see Scheme 27. The prepared intermediates are synthesized in overall yields of 40–50% over five steps, which is reported to be a 2- to 3-fold improvement upon previously reported syntheses.



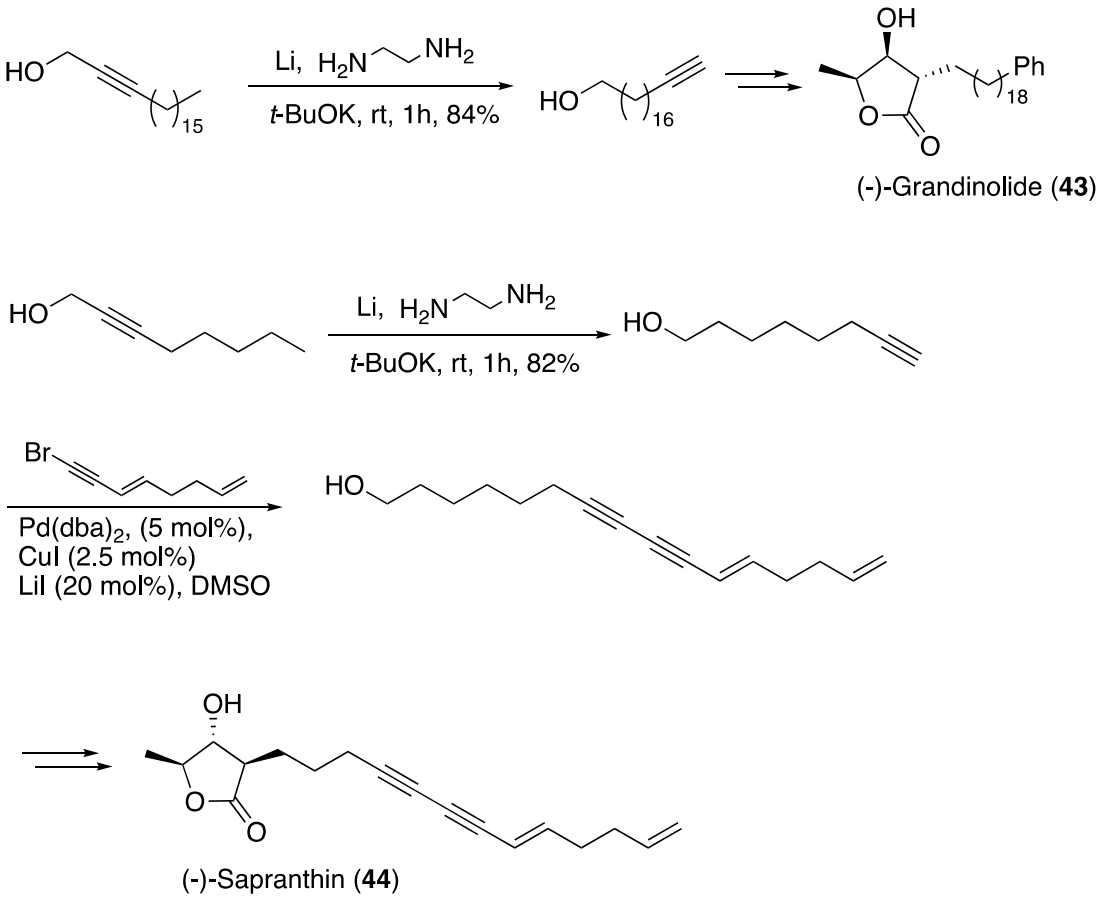
Scheme 27. Outline of the synthesis of naturally occurring macrolide pheromones of cucujid grain beetles [82].

A very similar strategy was also in Chinnababu's synthesis of unsaturated fatty acid leodomycin C (**41**) and D (**42**), see Scheme 28 [83].



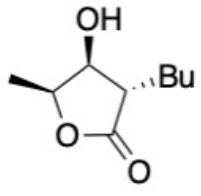
Scheme 28. The synthesis of leodomycin C (**41**) and D (**42**). Both were synthesized with alkyne zipper as a key reaction [83].

Harcken et al. synthesized related structures (-)-grandinolide (**43**) and (-)-sapranthin (**44**) [84]. The structures were assumed to differ only in the lipophilic alkyl chains, while consisting of the same blastmycinolactol core-structure. The absolute configuration for (-)-grandinolide was already established, but it was unknown for (-)-sapranthin. Synthesis proved that the suggested structure for (-)-sapranthin was incorrect. The zipper reactions were achieved with KAPA, prepared from Li, APA and *tert*-BuOK in 1 h at room temperature in good yields, see Scheme 29.



Scheme 29. The synthesis of (-)-grandinolide and (-)-sapranthin [84].

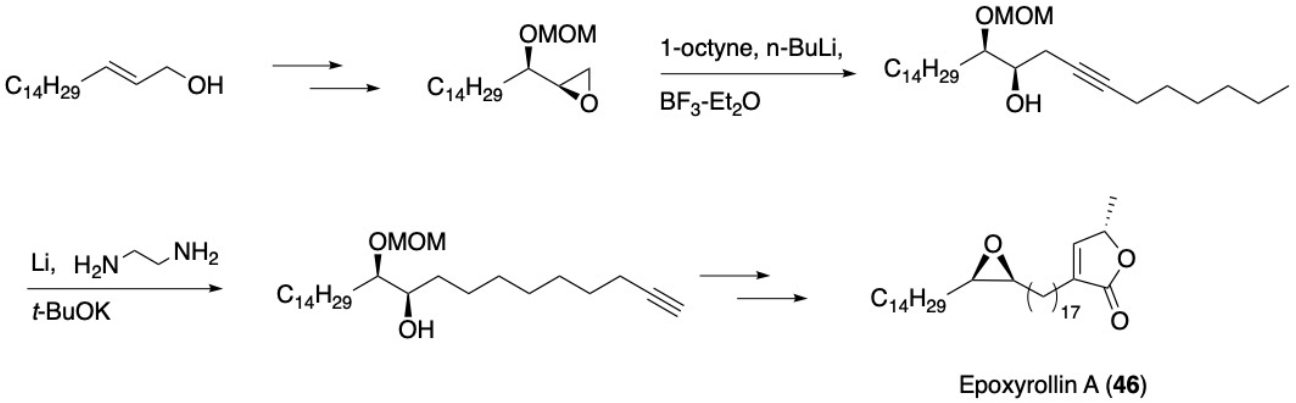
However, comparison of NMR data from the isolated sample of (-)-sapranthin with all epimers of blastmycinolactol (see structure **45** in Figure 6), revealed that natural (-)-sapranthin was almost identical with one of the epimers of blastmycinolactol. Based on this, an epimer of (-)-sapranthin was prepared, and the NMR data was matching. Thus, the true structure of (-)-sapranthin was corrected.



epi-blastomycinolactol (**45**)

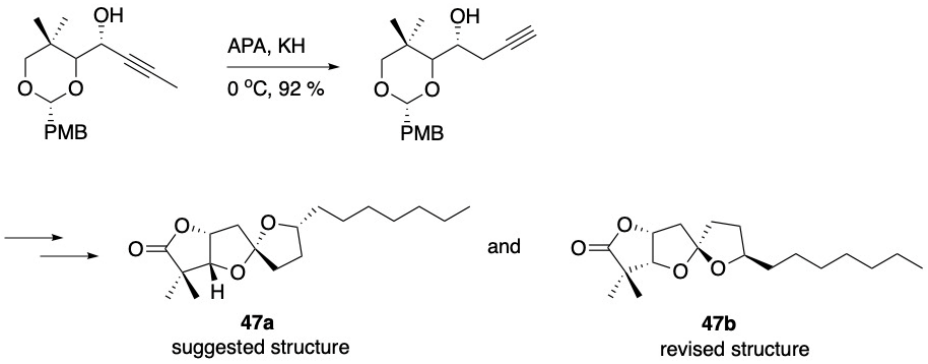
Figure 6. The structure of epi-blastmycinolactol (**45**) [84].

Konno et al. used the acetylene zipper reaction in their synthesis of the proposed structure of epoxy lactone epoxyrollin A (**46**). In this synthesis the lithium acetylide from octyne is reacted with epoxide followed by isomerization with KAPA, prepared from Li, APA, and potassium *tert*-butoxide, see Scheme 30. The terminal alkyne thus formed was used in a cross coupling, and both the unsaturated motifs were reduced. However, the spectroscopic data acquired for **46** did not match with those obtained for the natural product, and the conclusion was therefore that the structure needs revision [85]. To the best of our knowledge, no follow-up studies have been published.



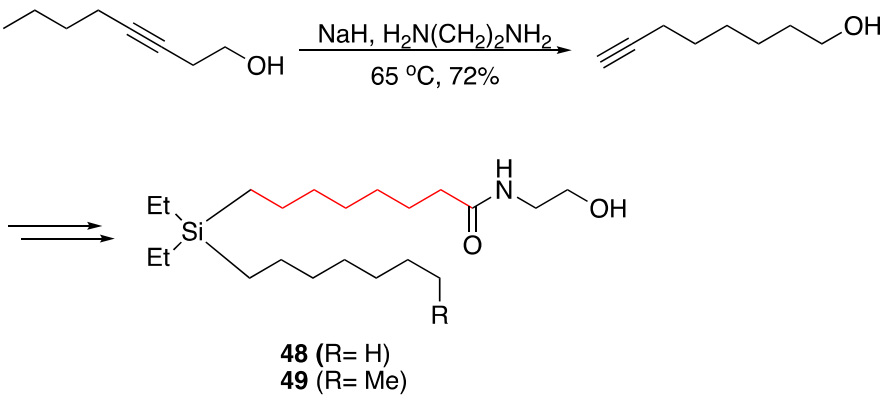
Scheme 30. An outline of the synthesis of the suggested structure of epoxyrollin A [85].

Thais and Dudley used the zipper reaction as part of their synthesis of cephalosporolide H (**47**), isolated from the culture broth of the marine fungus *Penicillium* sp. [86,87]. The compound displays anti-inflammatory activity against 3R-hydroxysteroid dehydrogenase (3R-HSD). Their first approach revealed the suggested structure to be incorrect. However, they were able to find the correct structure, which was the epimer. Both the suggested and the revised structure were synthesized with the alkyne zipper reaction as a key step, see Scheme 31 [86,87].



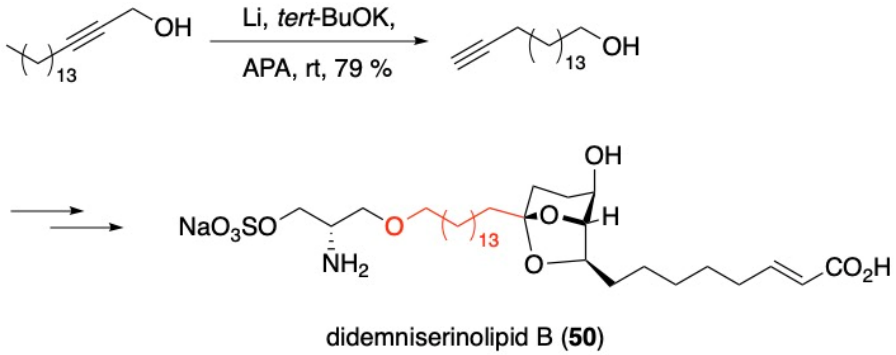
Scheme 31. The alkyne zipper reaction in the synthesis of the suggested and the revised structure of cephalosporolide H [86,87].

The alkyne zipper reaction was also used as part of the synthesis of silicon-containing fatty acid amide derivatives (see examples **48** and **49** in Scheme 32). These were demonstrated to be as novel peroxisome proliferator-activated receptor (PPAR) agonists [88].



Scheme 32. Synthesis of silicon-containing fatty acid amides [88].

Ramana applied an alkyne zipper reaction in their formal synthesis of (+)-didemniserinolipid B (**50**), see Scheme 33 [89].

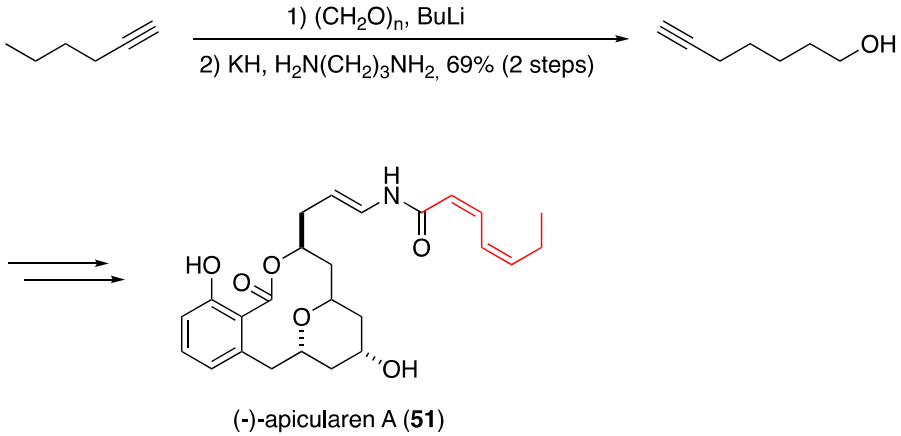


Scheme 33. Outline of the synthesis of (+)-didemniserinolipid B [89].

3.3. Macrocycles

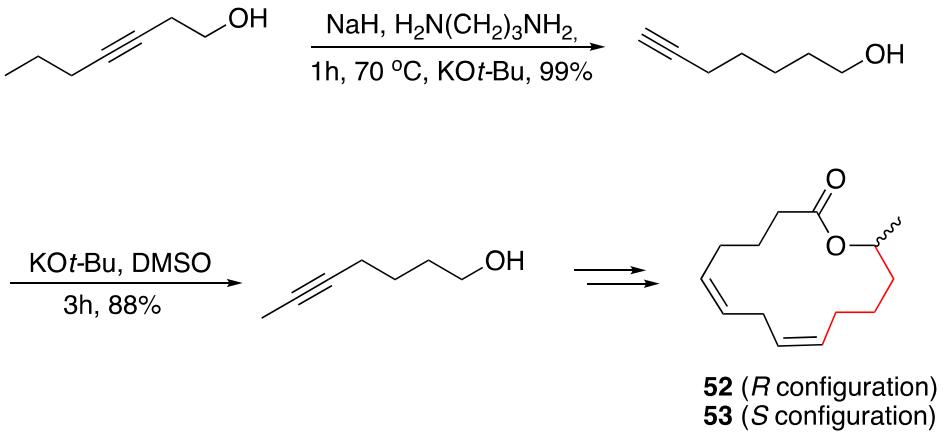
A large number of natural products are cyclic. Many examples utilize the zipper reaction for part of the ring where the trippel bond has been reduced to either the alkene with the correct stereochemistry, or to the corresponding fully saturated compound as can be seen in the following examles.

The synthesis of macrolide (-)-apicularen A (**51**) starts with reaction of lithium acetylide of 1-nonyne with (*S*)-propylene oxide, followed by acetylene zipper reaction [90], as depicted in Scheme 34.



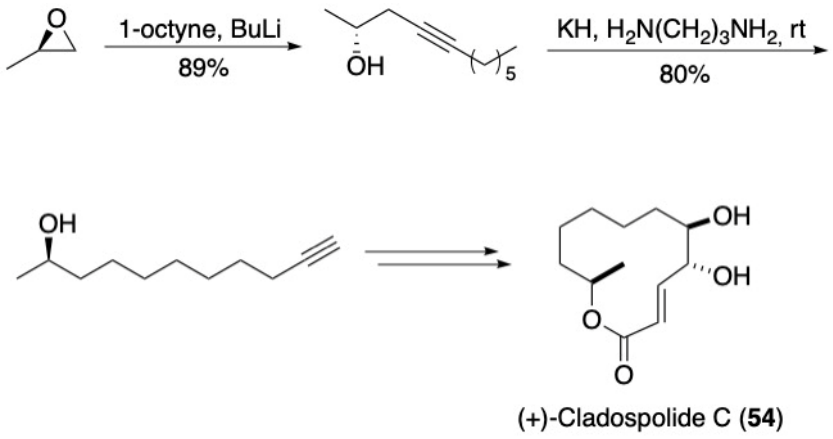
Scheme 34. The zipper reaction in the synthesis of (−)-apicularen A [90].

An interesting twist regarding the use of the alkyne zipper reaction can be found in the synthesis where the terminal triple bond is formed in a classic zipper reaction followed by isomerization to the corresponding ω-2 alkyne as exemplified in the publication by Hötling et al. The authors identified and synthesized the macrolide pheromones of the grain beetle *Oryzaephilus surinamensis* and the frog *Spinomantis aglavei* (**52** and **53**) [91]. In this synthesis, see Scheme 35, the terminal alkyne hept-6-yn-1-ol is formed quantitatively by using NaH, KOtBu and 1,3-diaminopropane, with subsequent isomerization to the internal alkyne, hept-6-yn-1-ol, with KotBu in DMSO.



Scheme 35. The use of acetylene zipper reaction to form terminal alkyne, with a subsequent isomerization to internal alkyne [91].

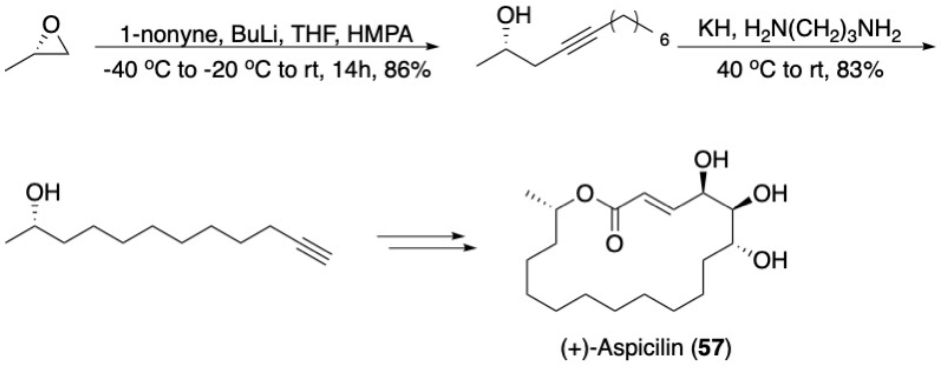
The efficient total synthesis of (+)-Cladospolide C (**54**) starts with (*R*)-propylene oxide and giving the target molecule in a total yield of 26% over 11 steps [92], see part of the synthesis in Scheme 36. The same group also synthesized cladospolides A and B (**55** and **56**, respectively) [93] and related compounds, (4S,5S,11R)- and (4S,5S,11S)-iso-Cladospolide B with similar approach [94].



Scheme 36. An outline of the synthesis of (+)-Cladospolide C [92].

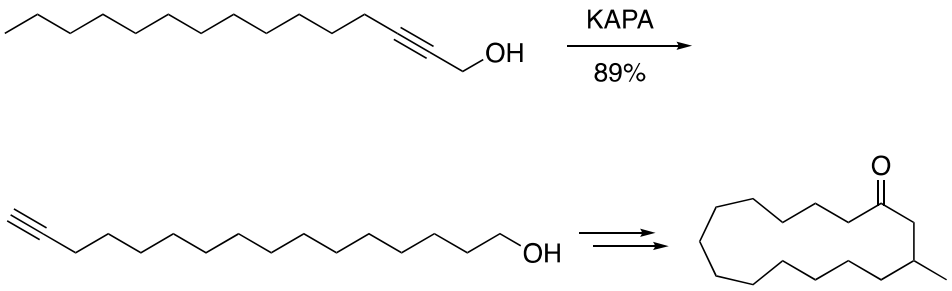
The synthesis of macrolide (+)-aspicillin (**57**) starts with reaction of lithium acetylide of 1-pentyne with *para*formaldehyde to give hept-3-yne-2-ol. The compound is oxidized to the corresponding ketone, which is reduced with Noyori conditions to give (*S*)-hept-3-yne-2-ol, followed by acetylene zipper reaction [95], as depicted in Scheme 37. The compound has been of interest to synthetic chemist since the absolute configuration was determined in the 1980s [96,97]. After successfully synthesizing the compound, it was evaluated against various cancer cell lines and evaluated for antibacterial and antifungal effects. Promising

in vitro inhibitory activity on proliferation of A549, HeLa and MCF7 cell-lines, but no cytotoxicity towards Neuro2a and MDA-MB-231. No potential antibacterial or antifungal activities were found [95].



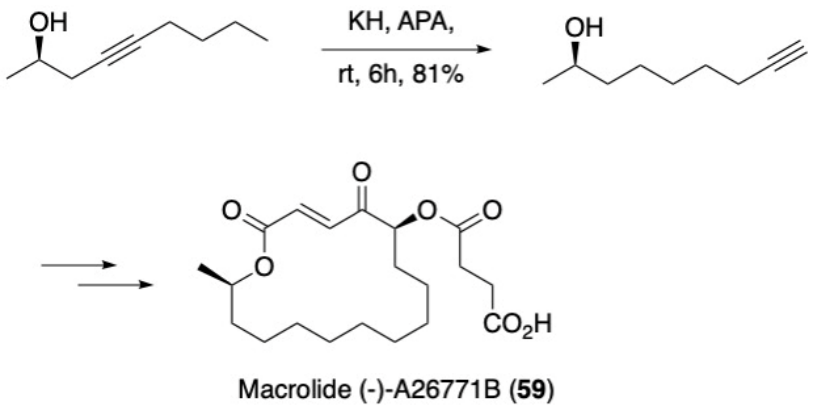
Scheme 37. Depiction of the synthesis of (+)-Aspicillin.

Utimoto et al. used the zipper reaction as part of their synthesis towards large ring ynone, exemplified with racemic muscone (**58**), see Scheme 38. No details other than the yield and isomerization catalyst (KAPA) are listed [98].



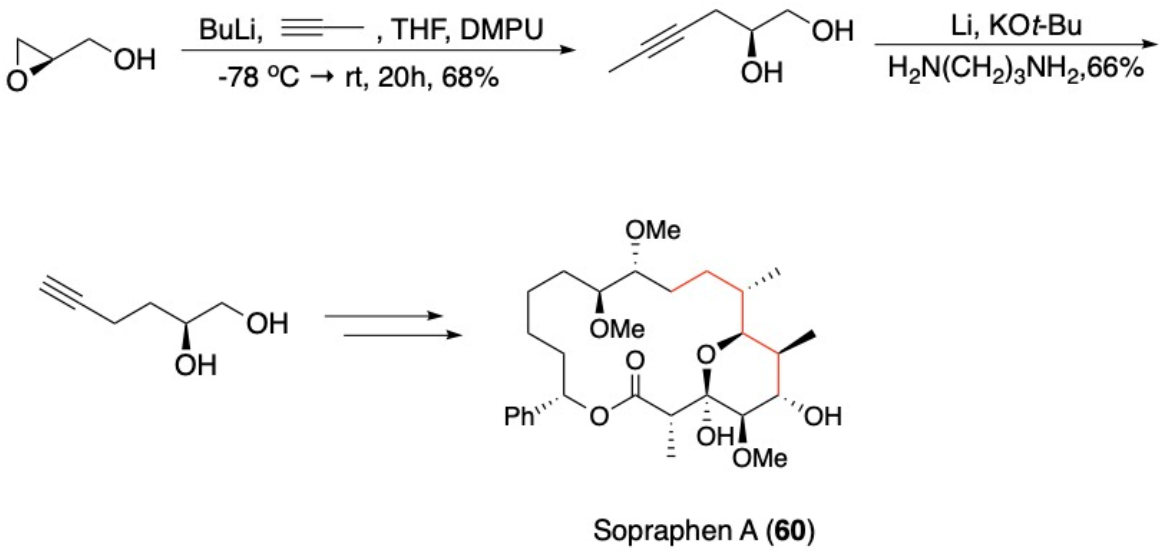
Scheme 38. The synthesis of racemic muscone (**58**).

Reddy et al. used the zipper reaction in their formal synthesis of antibiotic macrolide (-)-A26771B (**59**), see Scheme 39 [99].



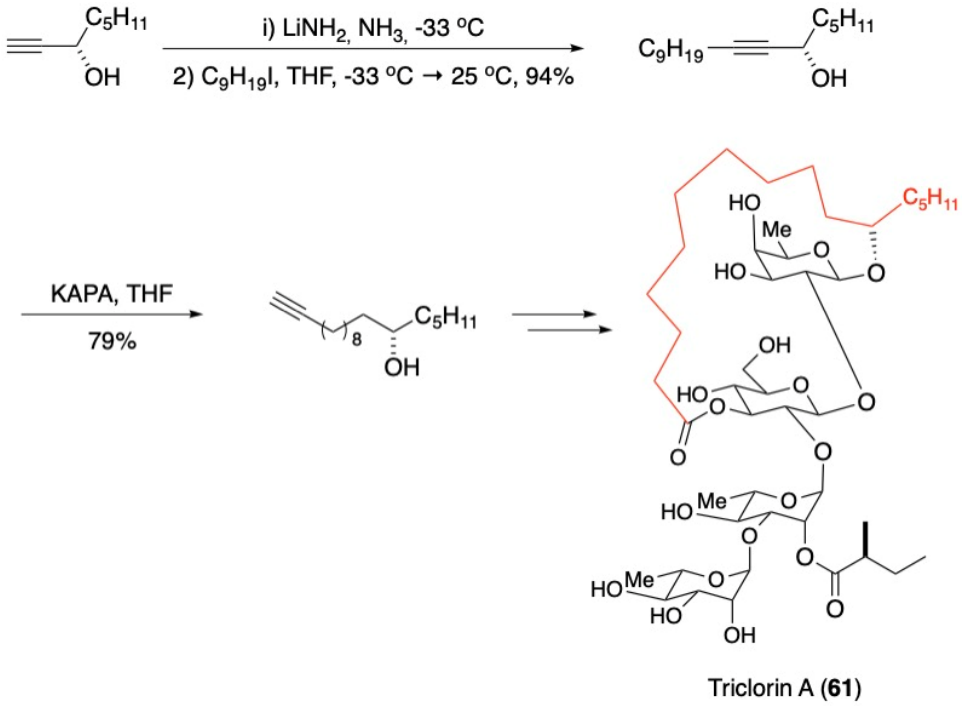
Scheme 39. The alkyne zipper reaction in the synthesis of macrolactone (-)-A26771B [99].

Sopraphen A (**60**) is a complex macrocyclic polyketide structure with potent antifungal activity [100]. Due to an interesting mode of action, selective inhibition of acetyl CoA carboxylase enzyme of fungus, the compound is of interesting for treatment of obesity, diabetes, and cancer. Trost and coworkers approached this by reacting (*S*)-glycol with the acetylide of propyne, followed by acetylene zipper reaction, see Scheme 40.



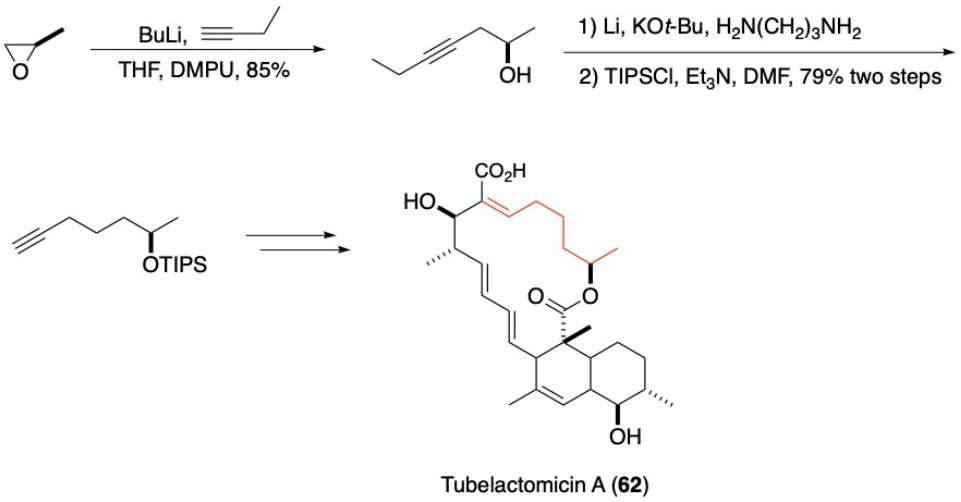
Scheme 40. Part of the synthesis of sopraphen A [100].

Tetrasaccharide macrolactone tricolorin A (**61**) was synthezied by Larson and Heathcock [101]. The natural product is of interest to scientist as it is a herbicide, and thus of interest. In their synthesis the alkyne zipper was done on a propargylic alcohol, which was alkylated prior to the zipper reaction. The zipper reaction, shown in Scheme 41, was repoted to be good yielding, 79%, by KAPA, prepared from KH and APA, in THF. The alkyne zipper reaction was one of 39 reactions to synthesize the target molecule—total yield was reported to 6%.



Scheme 41. The alkyne zipper reaction in Larson and Heathcock's synthesis of triclorin A [101].

Sommer and Fürstner employed a alkyne zipper reaction as part of their formal synthesis of macrolide antibiotic Tubelactomicin A (**62**) [102]. Their reaction conditions were Li and APA, followed by *tert*-BuOK, see Scheme 42.



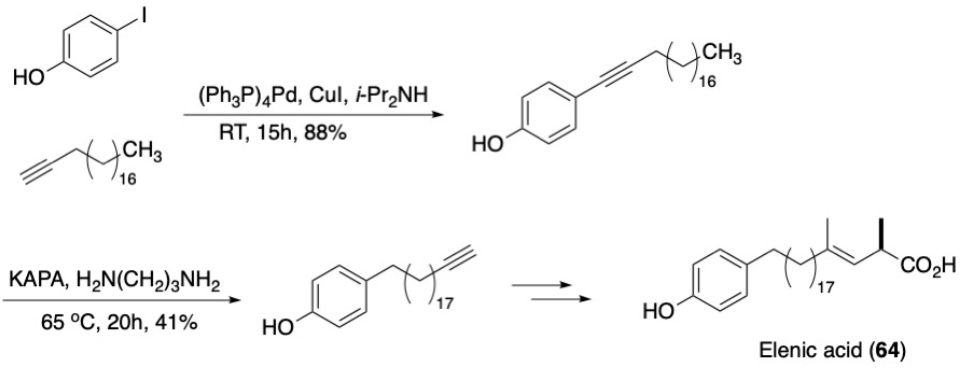
Scheme 42. An Outline from the formal synthesis of macrolide antibiotic Tubelactomicin A [102].

3.4. Other Natural Product Classes

Even though the most obvious synthetic targets are long chained alcohols, the alkyne zipper reaction is found as part of other compound classes as well. As shown in the following section, published literature evidence the wide spectrum of different compound classes that have been prepared.

One noteworthy example is elenic acid (**63**), an inhibitor of topoisomerase II. The compound was synthesized Hoye et al. [103], see Scheme 43. This is an interesting example of synthetic use of the acetylene zipper reaction, as the isomerization is conducted from a conjugated system, and the fact that the hydroxyl group is a phenol, and not an alcohol, as in the previous examples.

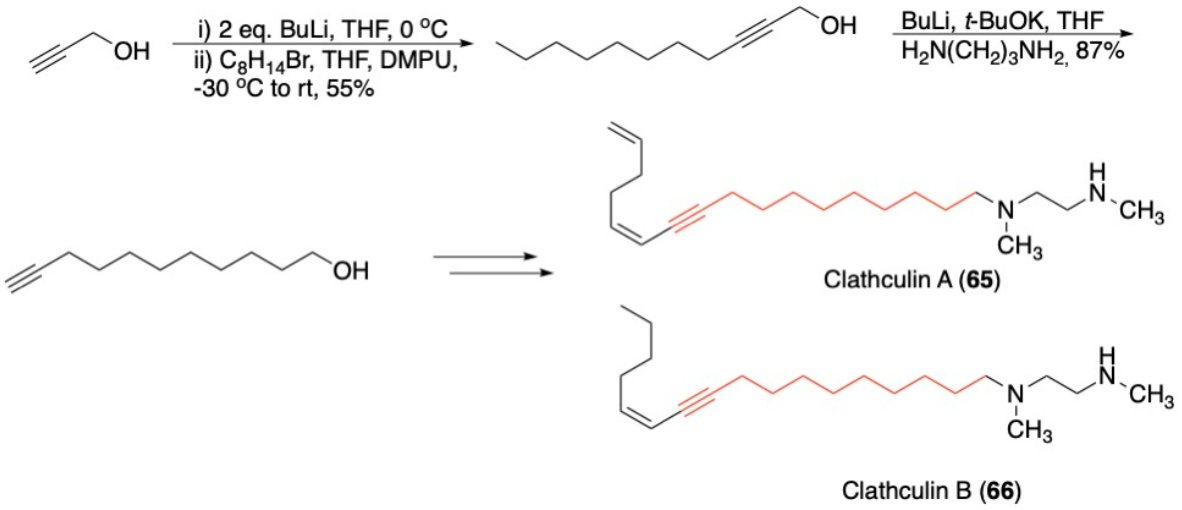
Isomerization with KAPA at 65 °C, gave the terminal alkyne in moderate yield of 41%. This was the first time that alkyne zipper reaction was used on an acetylene conjugated to an aromatic moiety, which can explain the modest yield, compared to the reactions previously listed. The authors do not explain whether they tried to improve the yield. They did not report whether the remaining 59% was unreacted starting material or transformed into biproducts.



Scheme 43. Synthesis of elenic acid, an inhibitor of topoisomerase II [103].

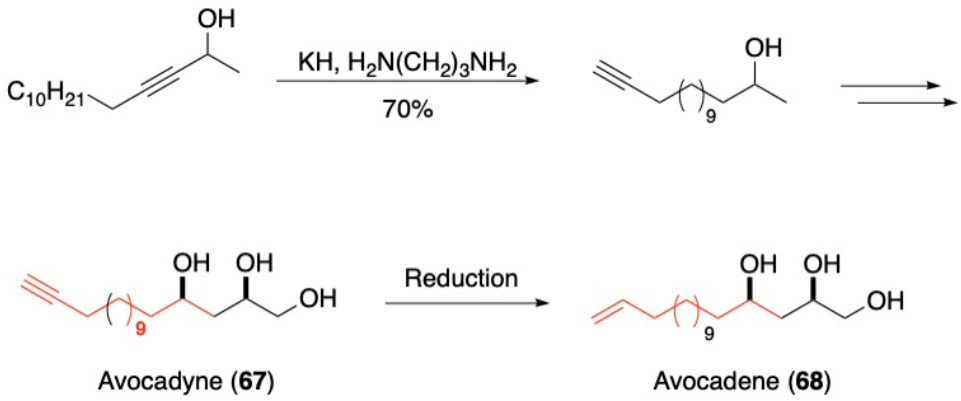
Clathculins A and B (**65** and **66**, respectively), nitrogen-containing metabolites from the sponge of genus *Clathrina* were also synthesized by Hoye [104]. The compounds are quite unique as they are acyclic, long chained containing a 1,2-diaminoethane moiety. The alkyne zipper reaction was achieved with 5.0 equivalence of diaminopropane in the presence of 4.0 equivalence of butyllithium and 4.0 equivalents of *tert*-BuOK. The authors report that the reaction conditions are "operationally simpler than the standard zipper isomerization

conditions and also avoid the use of noxious 1,3-diaminopropane as the reaction solvent" when using THF as solvent [104]. The reported yield is 87%. See Scheme 44.



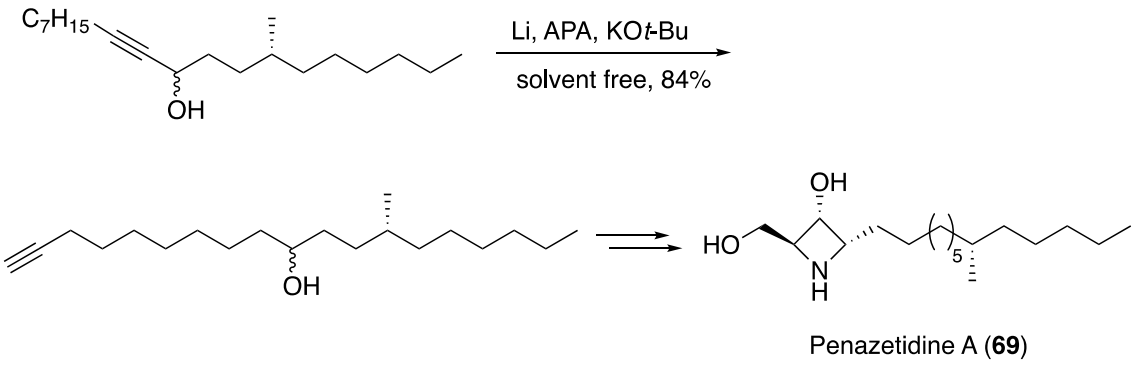
Scheme 44. An Outline of the synthesis of clathculin A and B using alkyne zipper reaction [104].

O'Doherty and co-workers used the alkyne zipper reaction as part of their enantio- and diastereoselective synthesis of polyketide natural products avocadyne (**67**) and avocadene (**68**) [105]. Overall, the synthesis were high yielding and step efficient. The alkyne zipper reaction proceeded in 70% yield with KAPA, prepared from KH and APA, and is shown in Scheme 45.

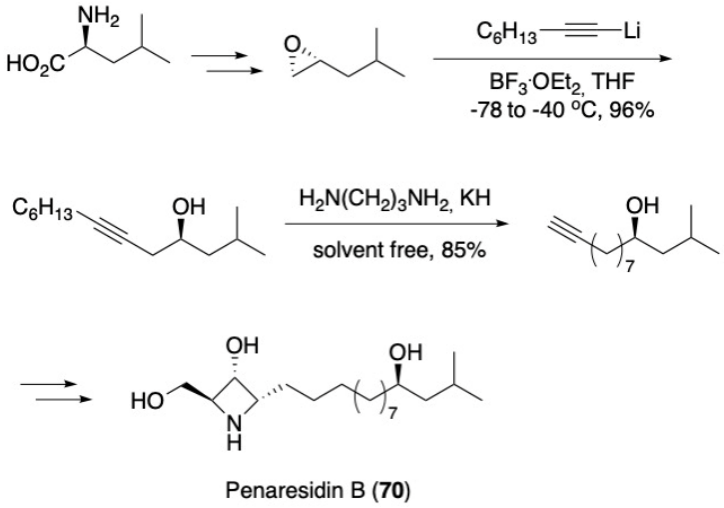


Scheme 45. An outline of O'Doherty and co-workers' synthesis of avocadyne and avocadene [105].

The alkyne zipper reaction was used in several syntheses of the azetidine sphingolipid derived natural products penazetidines, e.g., penazetidine A (**69**) [106], penaresidin B (**70**) [107,108] and analogues [109]. The acetylene zipper reactions from Mori's synthesis and Takayuki's synthesis are depicted in Schemes 46 and 47, respectively.



Scheme 46. The acetylene zipper reaction from Mori's synthesis of pentazetidine A (**69**) [106].



Scheme 47. The synthesis of penaresidin B (**70**) [109].

Amiclenomycin (**71**), isolated from cultures of different *Streptomyces* strains, is a potent mechanism-based inhibitor of BioA. However, due to amiclenomycin's low chemical stability, development of analogues is of interest. Structure of amiclenomycin is shown in Figure 7.

Shi and Aldrich developed four analogues of amiclenomycin. One of these, M-1 (**72**), was prepared using an alkyne zipper reaction as one of the key reactions, see Scheme 48 [110]. During biological testing, the compound demonstrated no biological activity.

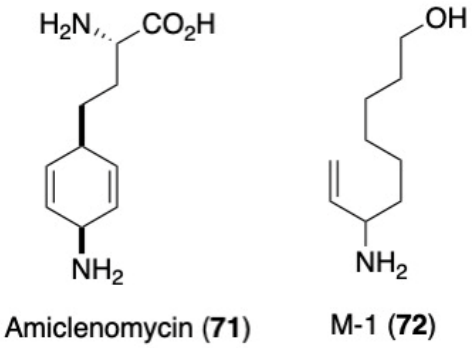
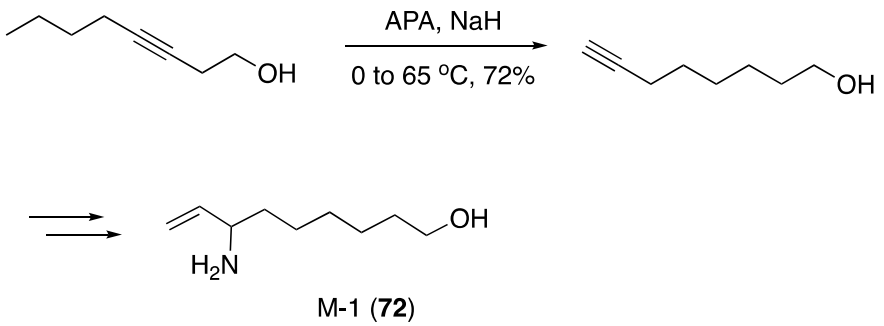


Figure 7. The structure of amiclenomycin and analogue M-1 [110].



Scheme 48. The alkyne zipper reaction in Shi and Aldrich's synthesis of M-1 [110].

Several other different compounds have been prepared with similar alkyne zipper conditions. A few more examples are polyalkyne furane adociacetylene B (**73**) [111], irisquinone (**74**) [112], cyclic tripeptide beauveamide A (**75**) [113], piperamide guineesine (**76**) [114] (all listed structures shown in Figure 8).

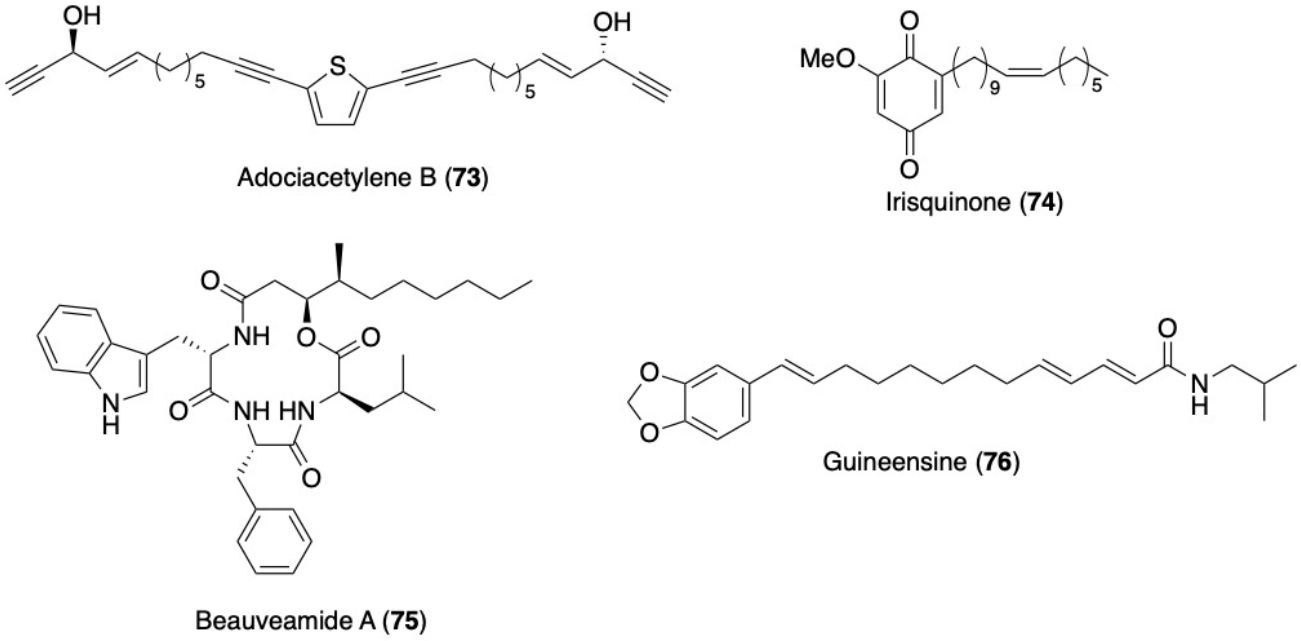
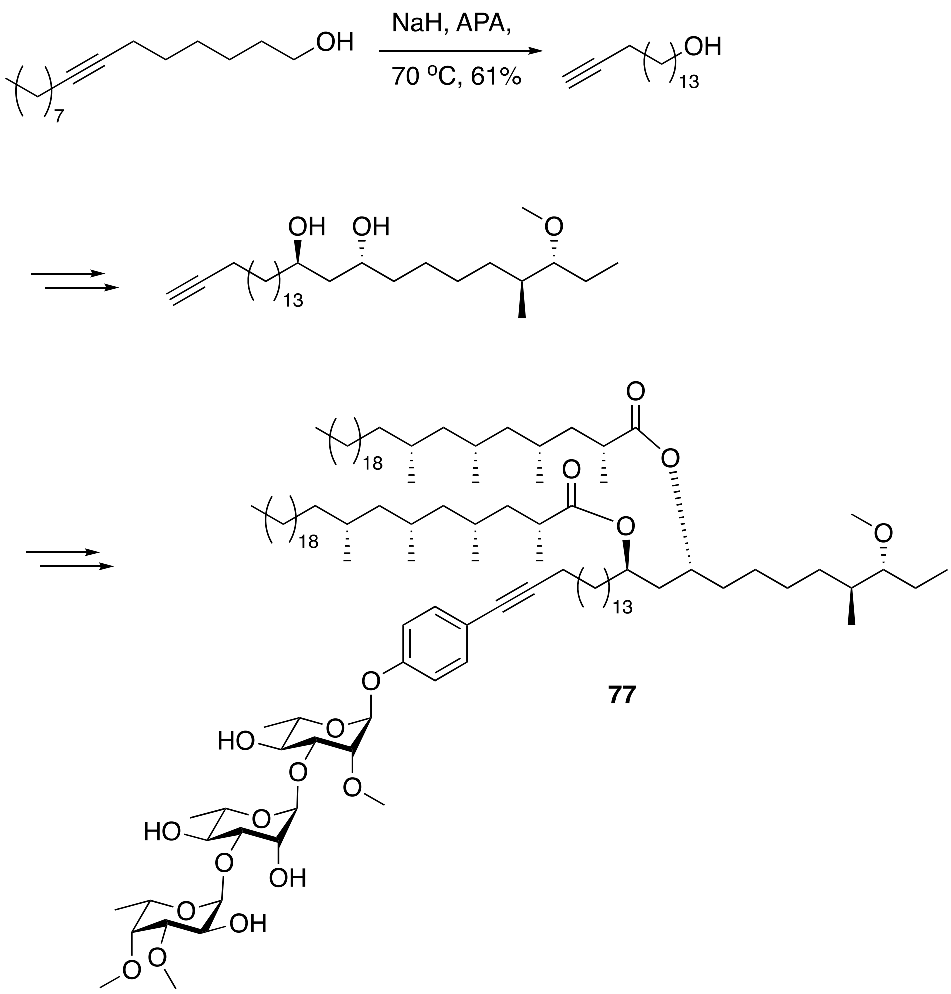


Figure 8. The structures of different classes that have all prepared with the alkyne zipper reaction as part of the synthesis.

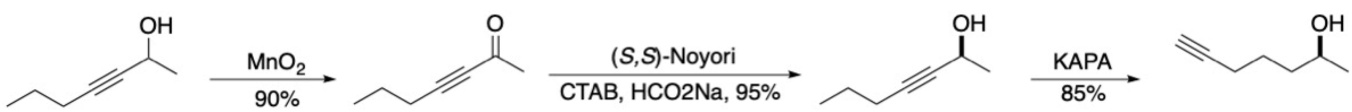
The first total Synthesis of glycolipid PGL-tb1 (**77**) from *Mycobacterium tuberculosis* was reported by Barroso et al. [115]. In the strategy, an alkyne zipper reaction is used to prepare part of the complex natural product's framework. The authors used NaAPA at 70 °C for 24 h giving the corresponding terminal alkyne in moderate yield, 61%, see Scheme 49. It is not mentioned whether optimalizations to improve yield was done or not.



Scheme 49. The zipper reaction from the total synthesis of glycolipid PGL-tb1 from Mycobacterium tuberculosis [115].

3.5. Noyori Reduction/Acetylene Zipper Combination

Combining Noyori reduction of ketones to chiral alcohols, followed by the acetylene zipper reaction is an approach used in several syntheses. As the acetylene zipper reaction is not affecting the stereochemistry of the hydroxyl group, as discussed above, this approach has proved to be very useful in asymmetric synthesis [116]. Scheme 50 show an example of this strategy, and how optical building blocks can be made from racemic starting materials. Even though the examples in the following sections could have been described in other sections, we decided to collect them as the strategy has been successfully used in several asymmetric syntheses.

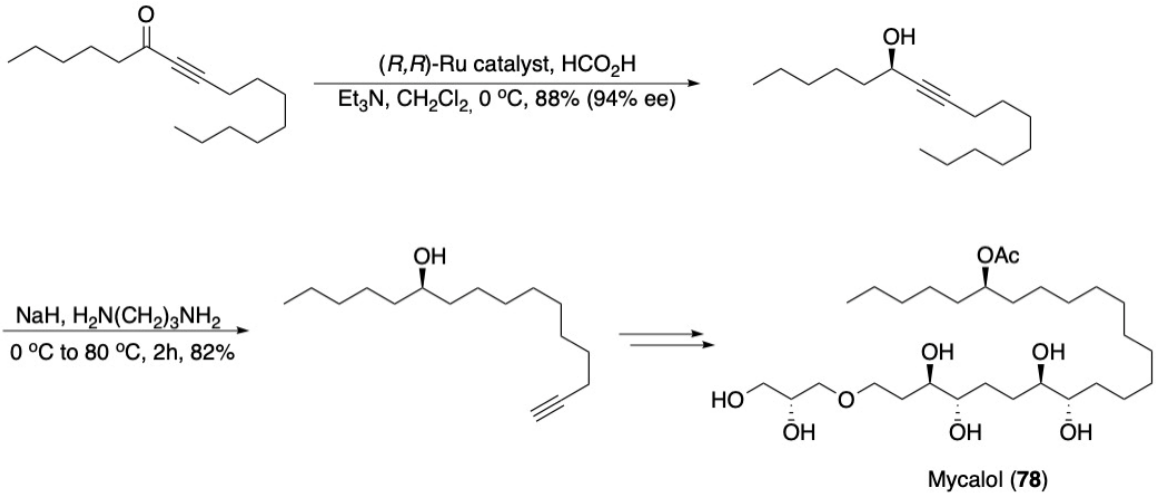


Scheme 50. A generic example of combination of Noyori reduction of alkyne zipper reaction.

The combination of Noyori reduction of a ketone into an optically active alcohol followed by zipper reaction have been utilized in several syntheses [87,117–128], here exemplified with natural products mycalol (**78**) [129,130] and broussonetine G (**79**) [131,132].

Das et al. used the alkyne zipper reaction to form one of the key fragments used in their synthesis of isomers of the promising anticancer natural lipid mycalol (**78**) [129].

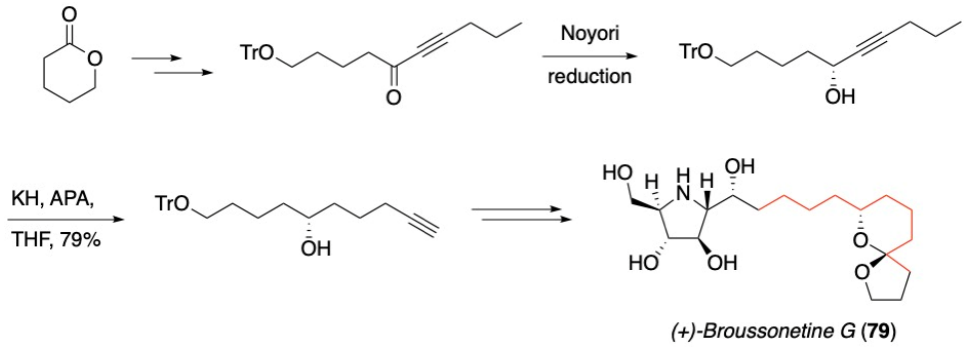
Comparison of the spectroscopic data revealed that the structure, suggested by Reddy and co-workers [133], had to be revised [129]. Nageswara Rao et al. also synthesized the same compound using a Noyori/zipper approach. Their approach is outlined in Scheme 51 from the chiral propargylic alcohol [130].



Scheme 51. The zipper reaction in the synthesis of mycalol (**78**) [130].

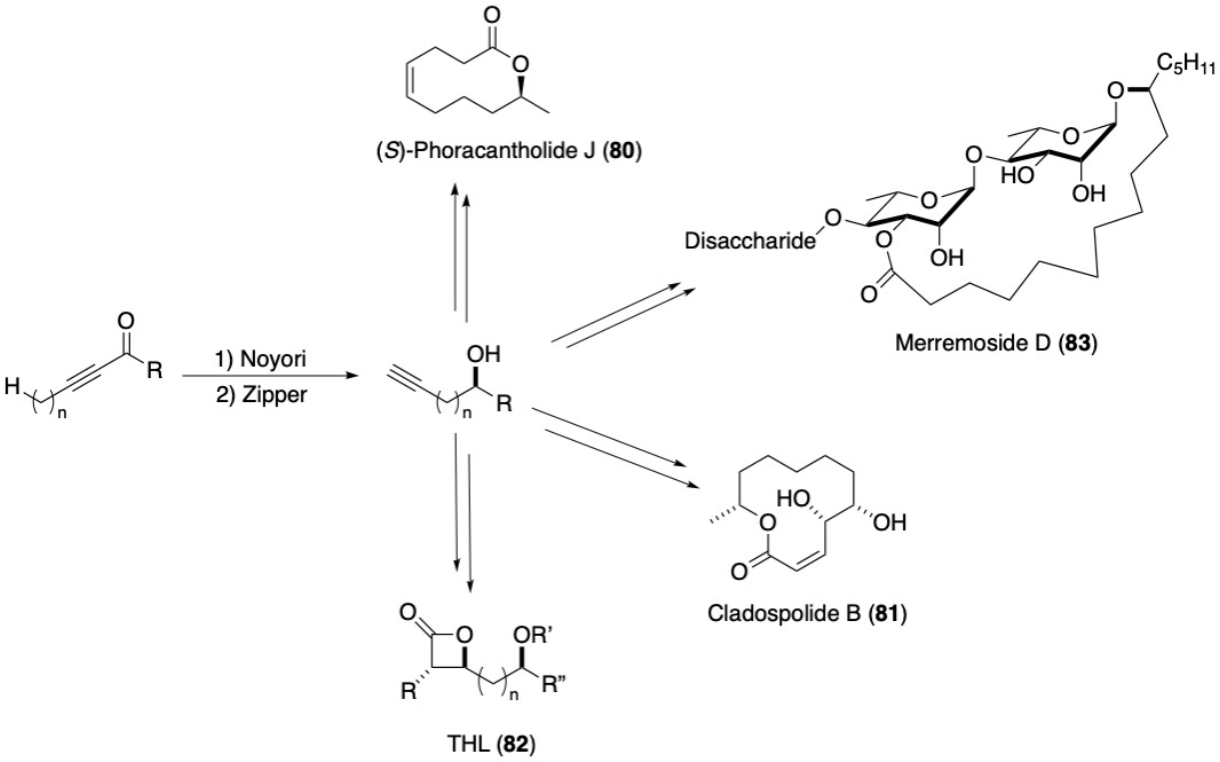
Broussonetine G (**79**) (see Scheme 52), a potent glycosidase-inhibitory natural product, was synthesized by Trost et al. [131,132]. The compound was of interest, due to its potential as antitumor and anti-HIV agents. Trost et al. prepared KAPA from KH and APA, with THF as solvent. The reaction was left stirring for 24 h at room temperature to give the product in 79% yield.

Prior to this synthesis, shown in Scheme 52, the relative stereochemistry of the spiroketal and the 1′-hydroxyl group system (marked in blue in Scheme 52) were unknown. The four stereoisomers were synthesized, and NMR and optical rotation data were compared, to reveal the true structure of the natural product.



Scheme 52. A partof the synthesis of (+)-Broussonetine G [131,132]. The fragment from the zipper reaction is marked in read in the product. The hydroxyl group marked in blue had unknown relative stereochemistry prior to this synthesis.

The same approach was used in the syntheses of phoracantholide J (**80**) [122] cladospolide B (**81**) [120], tetrahydrolipstatin (also known as THL and Orlistat) (**82**) [118,119], and merremoside D (**83**) [117], all structures shown in Scheme 53.



Scheme 53. The scheme shows examples of products formed with the Noyori reduction/alkyne zipper combination. Illustration is based on Avocetien et al. [122].

Menezes' group used the same type of strategy to successfully build fragments of (-)-macrolactin F (**84**) [134], but to the best of our knowledge, the group has not reported a total synthesis where these fragments are being used.

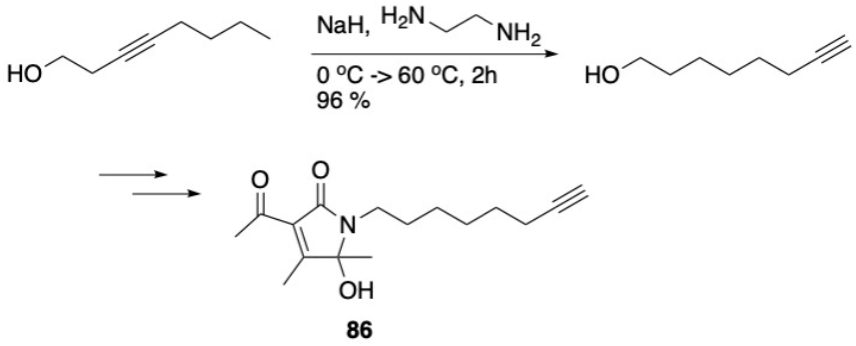
3.6. Probes via Copper Catalyzed Azide–Alkyne Cycloaddition (Click Chemistry)

As with most useful synthetic chemistry, the acetylene zipper reaction has found its way to other disciplines of science. In the next section we will list a few examples where terminal alkynes were used to perform click chemistry to prepare probes used in biotechnological research.

Hannoush and Arenas-Ramirez prepared ω-alkynyl analogues of fatty acids, shown previously in Scheme 23. These were added to the cultured cells and incorporated into acylated proteins. Subsequently, the alkyne group was used to ligate with azide-tagged biotin or fluorophorse via click chemistry reaction [76].

During a study of neurotrophic agent MT-21 (**85**), a structural analogue of natural product pyrrocidine A, it was demonstrated that the hemiaminal group is activated under acidic conditions to react with thiols, such as the one found in biological nucleophiles, such as cysteine containing proteins. The formed products were of interest, as understanding these could contribute to an overall understanding of the activation mechanism. For this purpose, the group prepared an analogue, MT-21 alk (**86**), with an alkyne functionality.

Another analogue, MT-21 alk (**86**), was prepared as shown in Scheme 54. MT-21 alk (**86**) was used to investigate the formed products. The formed products were conjugated with TAMRA-N_3 with Click chemistry reaction (copper catalyzed azide–alkyne cycloaddition (CuAAC)) and the proteins were separated by SDS-PAGE [135].

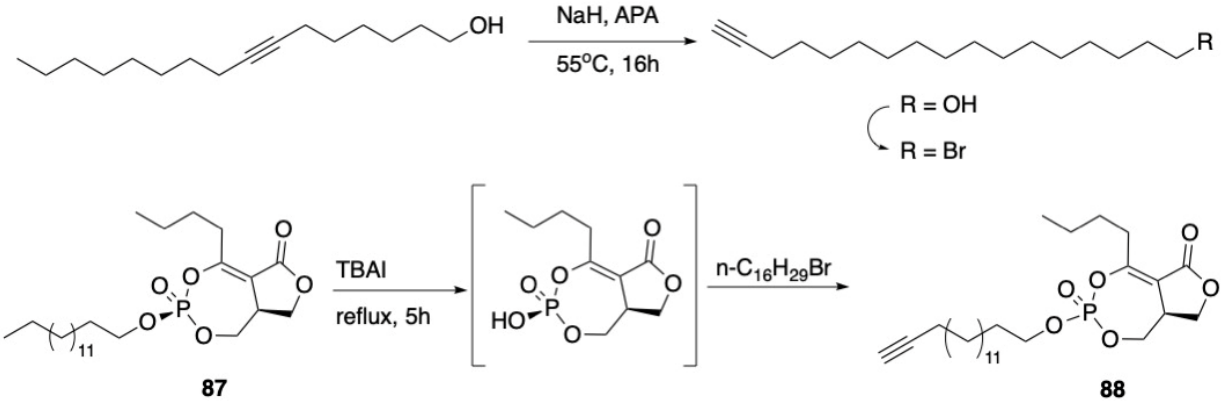


Scheme 54. An outline of the synthesis of MT-21 alk (**86**) [135].

Salinipostin A (**87**) is highly potent and selective antimalaria agent. However, the mechanism of action was not known. Yoo et al. used a hemi-synthesis method to prepare an analogue of Salinipostin A containing a terminal alkyne, coined Sal A alk (**88**), for target identifications studies. Synthesis of Sal A alk is depicted in Scheme 55.

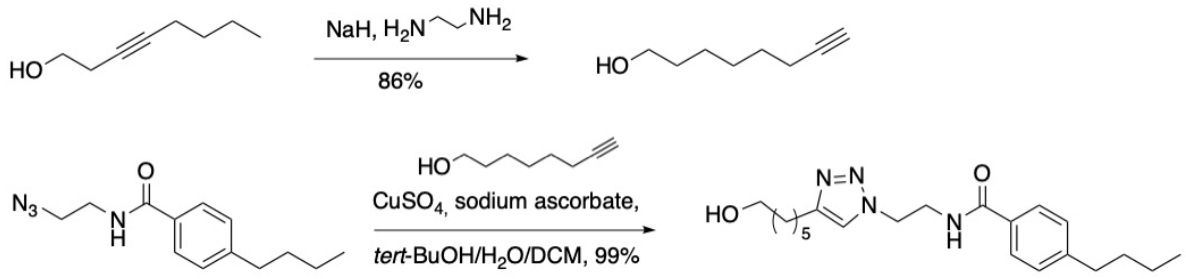
It was confirmed that the activity was retained in the analogue. The click reaction, alkene, and azide [3+2] cycloaddition, between TAMRA-azide and Sal A alk demonstrated that the analogue labeled multiple proteins in a dose-dependent manner.

Sal A alk (**88**) was then used as a probe to affinity purify targets. Using this probe, a group of largely uncharacterized serine hydrolases were identified in P. falciparum parasites. Several of these proteins are vital for parasite growth and probably important in lipid metabolism and signaling [136].



Scheme 55. The synthesis of Sal A alk (**88**) [136].

Furlani et al. reported the synthesis of 1,4-di-substituted 2-aminoimidazoles (**89a-l**), shown in Figure 9, that inhibit and disperse biofilms [137]. These compounds were identified via structure-activity relationship (SAR) studies as analogues of marine metabolite oroidin [138]. The triazole compounds also demonstrated to improve the effect of β-lactams against multi-drug resistant bacteria. Also in this synthesis, the alkyne zipper reaction demonstrates how well-suited it is for coupling with alkene and azide [3+2] cycloaddition click chemistry, giving access to several new compounds. The alkyne zipper reaction and the subsequent click chemistry is depicted in Scheme 56.



Scheme 56. The alkyne zipper reaction and the subsequent click chemistry from Furlani et al. [137].

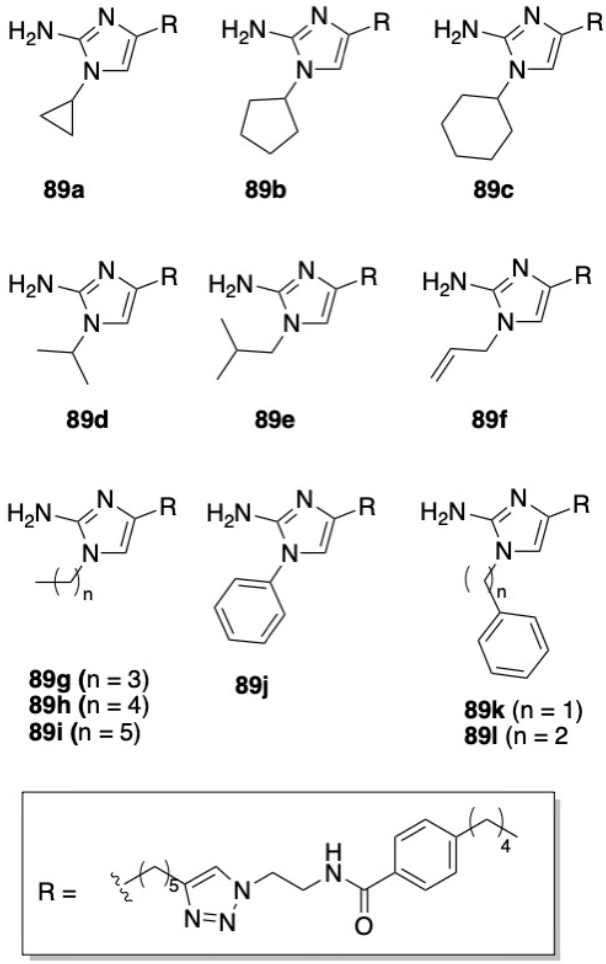
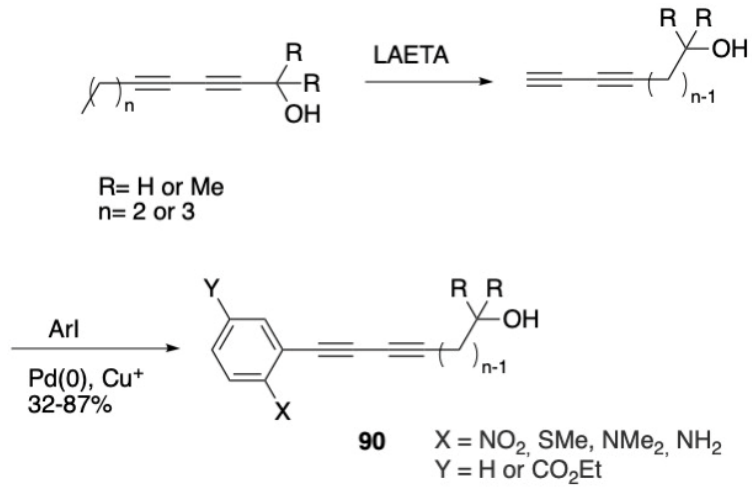


Figure 9. Triazoles **89a-l** prepared by Furlani et al. [137].

3.7. Synthesis of Arylalkadiynols via an Acetylene Zipper-Sonogashira Reaction Sequence

The alkyne zipper reaction also became central in the synthesis of arylalkadiynols in a pathway employing successive alkyne zipper-Sonogashira reactions instead of the Cadiot-Chodkiewicz coupling reaction, which is more commonly used to obtain non-symmetrical diynes [139]. The role of the alkyne zipper reaction was to isomerize an internal diyne to a 1,3-diyne to make the terminal triple bond available for Sonogashira coupling to an iodoarene (**90**) [139].

Anyway, Sonogashira coupling was then performed, with the diacetylene present in excess due to competitive Glaser couplings [139]. The diacetylene zipper reaction and the subsequent Sonogashira coupling are outlined in Scheme 57.



Scheme 57. The lithium 2-aminoethylamide (LAETA) catalyzed diacetylene zipper reaction and the subsequent Sonogashira coupling to a disubstituted arene [139].

The coupling reaction proved successful with both electron withdrawing and electron donating substituents on the arene. An interesting feature of this reaction pathway is that it shows that the alkyne zipper reaction may also effectively be applied to conjugated diyne systems, and not just molecules containing a single triple bond. All the same, the purpose of the zipper reaction was to obtain a terminal alkyne so that further carbon extensions could be achieved [139–143].

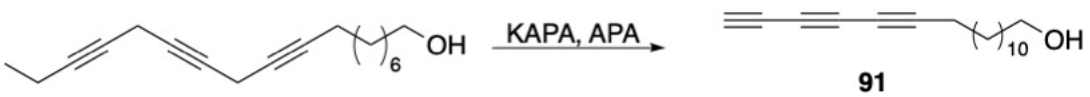
Mäeorg et al. reported that enynes can be isomerized in the same manner with NaAPA [144,145].

3.8. Polyurethane Materials

Another synthetic route in which the alkyne zipper reaction proved highly advantageous was in a patent concerning the process of synthesizing polyurethane (PU) materials from unsaturated plant oils [146]. Attempts at synthesizing PU from renewable sources often lead to materials with mechanical properties that are unsatisfactory compared to the petroleum-derived alternatives [146].

These lacking material properties are believed to be caused in part by the low ratio of primary to secondary alcohols that are generated from bio-based PUs [146].

Furthermore, PUs derived from biomass feedstock often contain terminal saturated hydrocarbon chains of 6–18 carbons, which reduce the polymer rigidity by plasticizing the network structure [147]. Thus, biomass-derived PU materials are often blended with PUs acquired from fossil feedstock to compensate for the substandard qualities of the bio-based materials [146], making the effort of producing bio-renewable PUs to little avail. In this patent, the use of the alkyne zipper reaction circumvented these challenges as it provided a way of targeting the ends of the PU building blocks; terminal alkynes were generated from internal alkynols (Scheme 58), which were originally derived from dehydrogenated unsaturated plant oils [146].



Scheme 58. An example of an alkyne zipper reaction involved in the synthesis pathway for polyurethane from plant oils [146].

Subsequently, the terminal alkynes were oxidized to afford terminal, primary hydroxyl groups instead of the unsaturated hydrocarbon chains, thus improving the mechanistic properties of the bio-renewable PU materials [146]. As such, a demonstration of how

the zipper reaction provided an efficient means to the production of bio-renewable PU materials of higher quality is given by this example. In contrast to the above examples, the zipper reaction was in this case used to modify the terminus of a hydrocarbon chain rather than being a means of extending the carbon chain. With the rearrangement of three unconjugated triple bonds, this example also shows how the alkyne zipper reaction is effective at isomerizing multiple triple bonds within the same molecule.

4. Conclusions and Future Perspectives

As this review demonstrates, the alkyne zipper reaction has constituted a key step in several syntheses of natural products, analogues of these, and other useful compounds. In addition to providing a means of obtaining the building blocks needed to synthetize these structurally divergent compounds, the alkyne zipper reaction is relatively easy to perform in a laboratory setting, which makes it a valuable member of the organic chemistry toolbox.

However, despite its potential usefulness, the alkyne zipper is currently an underappreciated tool in organic synthesis [148]. This might be due to the limitations regarding its need for highly basic conditions.

Perhaps equally crucial, the reaction seems to have limited functional group selectivity beyond alkynes, as pointed out by Brown and Negishi [149]. Even though Augustin managed to perform alkyne zipper reactions on carboxylic acids [37] and Brown and Negishi managed to transpose the alkyne on alkynyl boranes [149], both studies also underline the given limitations.

Nonetheless, with the recent Nobel Prize in chemistry for the development of click chemistry and bioorthogonal chemistry, and numerous papers and review papers on the importance of click chemistry in medicinal science and drug discovery [54,150,151], material science and polymer chemistry [53,152–154], the need for reliable methods to prepare terminal alkynes is evident and more relevant than ever. The acetylene zipper reaction is indeed an important part of the reaction toolbox that may be used to achieve this.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

APA	1,3-Diaminopropane
CTAB	Cetyltrimethylammonium bromide
CuAAC	Copper catalyzed azide–alkyne cycloaddition
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DSF	Diffusible signal factor
HMPA	Hexamethylphosphoramide
KAPA/PAPA	Potassium 3-aminopropylamide
KOt-Bu	Potassium *tert*-butoxide
LAETA	Lithium 2-aminoethylamide
MOM	Methoxymethyl
NaAPA	Sodium 3-aminopropylamide

PU	Polyurethane
rt	Room temperature
SDS-PAGE	Sodium dodecyl sulfate–polyacrylamide gel electrophoresis
TAMRA-N_3	Tetramethylrhodamine azide
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
THF	Tetrahydrofuran

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