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A.E.Favorskii's scientific legacy in modern organic chemistry: prototropic acetylene – allene isomerization and the acetylene zipper reaction

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Alexei Evgrafovich Favorskii was an outstanding organic chemist who left a great scientific legacy as a result of long time and fruitful work. Most of the theoretically and practically important discoveries of A.E.Favorskii were made in the chemistry of acetylene and its derivatives. Nowadays, the reactions discovered by him, which include acetylene – allene isomerization, the Favorskii and retro-Favorskii reactions, the Favorskii rearrangement and the vinylation reaction, are widely used in industry and in laboratory synthesis. This review summarizes the main scientific achievements of A.E.Favorskii, as well as their development in modern organic chemistry. Much consideration is given to acetylene – allene isomerization as a convenient method for the synthesis of methyl-substituted acetylenes and to the acetylene zipper reaction as a synthetic tool for obtaining terminal acetylenes. The review presents examples of the application of these reactions in modern organic synthesis of complex molecules, including natural compounds and their analogues.
The bibliography includes 266 references.

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1. Introduction

1.1. The great organic chemist A.E.Favorskii — the founder of acetylene chemistry

Alexei Evgrafovich Favorskii (1860 – 1945) was an outstanding organic chemist who left great scientific legacy as a result of a life-long and fruitful career at Saint Petersburg – Petrograd – Leningrad University and other institutions he was affiliated with.

In 1978, he began his studies at the Natural Sciences Division of the Physics and Mathematics Faculty of Saint Petersburg University. During his fourth year, aiming to complete a 'dissertation' (a requirement for the graduation from the university with a candidate degree that gave one the right to take master's exams), he was accepted to the

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Laboratory of Alexander Mikhailovich Butlerov. The work of students in the Laboratory, which occupied two small rooms in the Twelve Collegia building, was monitored by Butlerov's only assistant, Mikhail Dmitrievich L'vov. It was in that Laboratory where Favorskii s scientific career began.

After graduating from the University in 1882 with a candidate's degree, he remained in Butlerov's laboratory to carry out research towards his Master's thesis. In the course of these studies, he discovered the phenomenon of acetylene – allene isomerization, which made his name famous. Favorskii defended his Master's thesis *magna cum laude* in 1891, whereupon he assumed the privat-docent post at the Chair of Analytical and Technical Chemistry of St. Petersburg University. Four years later, Alexei Evgrafovich defended his Doctoral Dissertation entitled 'The Study of Isomeric Transformations of Carbonyl Compounds, Chlorinated Alcohols and Halogen-Substituted Oxides' and was promoted to Professor at the Chair of Analytical and Technical chemistry. The Favorskii's photograph shown in Fig. 1 was taken during the year he defended his Doctoral Dissertation (1895).

A.E.Favorskii became the Head of the Chair of Organic Chemistry at Saint Petersburg University in 1902, after the departure of the former head, Prof. N.A.Menshutkin, to the Chair of Organic Chemistry at the newly opened Polytechnic Institute. Favorskii reamined the Head of the Chair of Organic Chemistry at Saint Petersburg – Petrograd – Leningrad University until 1930, when the Chemistry Department of the Leningrad University was integrated into the newly created 'Unified Chemical Intitute' (Leningrad Chemical-Technological Institute) at the Leningrad Institute of Technology. However, the University managed to save the Favorskii's laboratory of organic chemistry, where he continued his research with graduate students.

The brief biographical information given here about the beginning of the career of Aleksei Evgrafovich is based on the material of the book by Tatyana Alekseevna Favorskaya [1] — his daughter, faithful ally and biographer. Published in 1980, the book describes the life of Favorskii, his scientific and social activities in the pre-revolutionary period and after the October Revolution of 1917. The book was published in a circulation of only 16 thousand copies and has already become a rarity.

In 2019, the Publishing house of Saint Petersburg University published another truly unique book about Favorskii — the memoirs of Tatyana Alekseevna about her father, his large family, colleagues, friends, students and all those who visited the hospitable Favorskii house.[2] Thanks to the efforts of historian Irina Ivanovna Domnina, the granddaughter of Irina Alekseevna Favorskaya, who prepared for publication the diaries of her great-aunt and photographs from the family archive, we have an opportunity to get acquainted with the living chronicle, to plunge into the university atmosphere of those years, as well as to learn many interesting facts from the biography of Alexei Evgrafovich and his close circle of family and friends.



Figure 1. Photo of A.E.Favorskii (1895).[1]

A.E.Favorskii was not only an outstanding scientist, but also a brilliant teacher. In addition to Saint Petersburg University, he taught organic chemistry at the Saint Petersburg Technological Institute, where he headed the Chair of Organic Chemistry (1887 – 1909; 1922 – 1932), the Mikhailovskii Artillery School and the Mikhailovskii Artillery Academy (1891 – 1894) and Saint Petersburg Higher Courses for Women (1900 – 1919).[1] His talent for teaching manifested itself also while he was working as a laboratory assistant at the First Petersburg Real School (1882 – 1885). At the request of his students, in addition to the obligatory laboratory course he was teaching there, he offered an elective lecture course in organic chemistry. Alexei Evgrafovich considered student's research work to be of high importance for the learning process. His own experimental skills, pedagogical talent, and the ability to inspire others with his creative enthusiasm attracted a large number of talented students. As the result of his activity, one of the largest research traditions of organic chemists was created in Russia and neighbouring countries — the former Soviet Uninon republics of Azerbaijan and Ukraine (I.A.Shikhiev, K.A.Krasuskii), Kazakhstan (I.N.Azerbaev), Tajikistan (V.I.Nikitin whose name is borne by the Institute of Chemistry of the Academy of Sciences of the Republic of Tajikistan). There are many famous names among Favorskii's students: S.V.Lebedev, V.N.Ipat'ev, G.A.Razuvaev, E.A.Porai-Koshits, I.N.Nazarov, S.N.Danilov, M.F.Shostakovskii and others.

Aleksei Evgrafovich can also rightfully be considered the founder of acetylene chemistry and the school of acetylene chemists in Russia. His students created scientific centres that continue to work fruitfully in this area. The

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Translation: G.M.Kirakosyan

notable figures include, first of all, Academician Ivan Nikolaevich Nazarov, who was founding Head of the laboratory engaged in basic and applied research in the field of acetylene and vinylacetylene chemistry at the Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow (A.E.Favorskii was the first Director of this institute in 1934–1937). I.N.Nazarov was, in turn, a mentor of many prominent chemists.

Mikhail Fyodorovich Shostakovskii, a student and ally of Aleksei Evgrafovich, became the founder of one of the leading Russian scientific centres for acetylene chemistry — the Favorskii Irkutsk Institute of Chemistry (Siberian Branch of the Russian Academy of Sciences). Significant advances in the acetylene and diacetylene chemistry resulted from the research tradition established at the Institute of Chemical Kinetics and Combustion (Siberian Branch of the Russian Academy of Sciences) by Professor Israel L'vovich Kotlyarevskii, I.N.Nazarov's student. At the Leningrad State University, research in the field of acetylene chemistry was continued by the daughters of Aleksei Evgrafovich — Professors Tatyana Alekseevna Favorskaya and Irina Alekseevna Favorskaya.

At present, the influence of A.E.Favorskii's legacy on further development of acetylene chemistry in Russia [3] and abroad is very significant. The work of Aleksei Evgrafovich served as a starting point for a number of areas in acetylene chemistry, the potential of which is rated very highly. Numerous articles on this subject published in recent years demonstrate a wide range of synthetic applications of acetylenes, unveiling acetylene chemistry as a fascinating and fruitful field of research. In particular, many classical transformations of alkynes have been the subjects of recent reviews: various cycloaddition reactions,[4–8] synthesis of functionalized alkenes [9] through alkyne hydrostannylation,[10] diboration and hydroboration,[11] chemo- and/or stereoselective hydrogenation,[12,13] addition of amides and sulfonamides [14] as well as reactions involving a carbonyl group,[15] the use of alkynes as synthetic equivalents of ketones and aldehydes,[16] alkyne radical transformations.[17] Many reviews ave devoted to the chemistry of alkynes,[18] including the use of alkynes to build complex 3D structures,[19] name reactions involving acetylene compounds [20] and the use of alkynes in commercial production.[21]

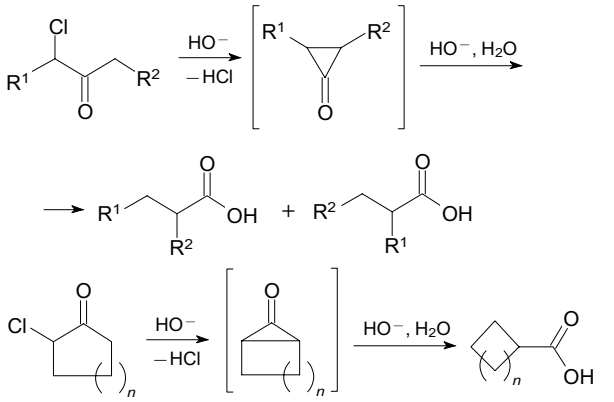
1.2. Reactions discovered by A.E.Favorskii

The contribution of Aleksei Evgrafovich Favorskii to organic chemistry is enormous. Among numerous reactions and processes invented and studied by him, the most famous are the Favorskii rearrangement, the Favorskii and retro-Favorskii reactions, as well as the vinylation reaction and acetylene–allene isomerization. These discoveries gave rise to the development of many important areas of organic chemistry that have been relevant for more than a century. The above transformations are discussed below in the reverse chronological order.

1.2.1. The Favorskii rearrangement

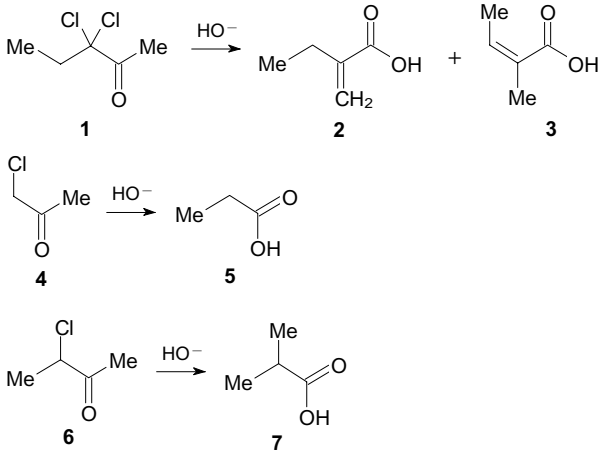
The Favorskii rearrangement is one of the reactions in which the name of the great chemist is immortalized. Research in this area laid the foundation for the Doctoral Dissertation of Aleksei Evgrafovich. Interestingly, the typical transformation — the conversion of alicyclic and cyclic α-haloketones to carboxylic acid derivatives with a modified structure of the C–C skeleton (Scheme 1) — was not the reaction that was initially discovered.

Scheme 1



In 1894, A.E.Favorskii studied the reactions of 3,3-dichloro-2-pentanone (**1**). When treated with aqueous alkali, it gave a mixture of isomeric unsaturated carboxylic acids **2** and **3** (Scheme 2).[22] It was not until 1901 when Favorskii demonstrated that chloroacetone (**4**) reacted with a 10% aqueous solution of potassium carbonate to yield propionic acid (**5**) while treatment of 3-chloro-2-butanone (**6**) gave isobutyric acid (**7**) (see Scheme 2).[23]

Scheme 2



Nowadays, the Favorskii rearrangement is a powerful synthetic tool capable of producing a wide range of organic compounds. It is applicable to acyclic and cyclic haloketones, and not only the hydroxy anions, but also thiolates and amines can serve as nucleophilic agents. The rearrangement can afford skeletally diverse caboxylic acids, esters and amides. Currently, the generally accepted mechanism for this reaction implies the initial formation of a cyclopropanone derivatives (see Scheme 1). The Favorskii rearrangement is widely used in the synthesis of natural products.[24] It is the subject of many reviews (for example, Refs 25–27), the latest one being published in 2014.

In addition to the classical version of the Favorskii rearrangement, the quasi-Favorskii rearrangement [28] and other related reactions are known; they have been covered in the above-listed reviews. In the five years that have passed since the publication of the last full review,[24] several interesting publications have appeared [29–36] which are devoted to the study of the Favorskii rearrangement and to the use of this reaction and its modifications as a

synthetic tool in the preparation of various complex molecules. In this review, they are not considered in detail.

Unfortunately, the Favorskii rearrangement is often confused with the Favorskii reaction, which is also discussed below. An example of such a confusion can be found in the recent publication[37] describing the synthesis of 2-bromocyclobutanones and their use as substrates for the Favorskii rearrangement (which the authors incorrectly termed the Favorskii reaction).

1.2.2. The Favorskii and retro-Favorskii reactions

The Favorskii reaction is the reaction of carbonyl compounds with terminal acetylenes in the presence of strong bases. This reaction was initially discovered for acetone (**8**) and phenylacetylene (**9**). The first report of the the reaction of acetylene with carbonyl compounds in the presence of powdered KOH leading to propargyl alcohols (Scheme 3) was made by A.E.Favorskii[38] on October 5, 1900, at the meeting of the Chemistry Division of the Russian Physical and Chemical Society. In the same report, A.E.Favorskii also mentioned the reverse reaction of tertiary alcohol **10** decomposition into starting compounds **8** and **9** under the action of an aqueous alkali (the retro-Favorskii reaction, *vide infra*).

In the English literature, this transformation is usually referred to as the Reppe – Favorskii reaction because much later, Reppe[39] emoloyed a copper catalyst to promote the reaction of acetylene with formaldehyde. The latter transformation provided a foundation for the commercial production of several important organic compounds such as propargyl alcohol and 2-butyne-1,4-diol.[21,40]

Alkali metal acetylenides, most frequently potassium acetylenides, which are more efficient for the addition to ketones, are used to synthesize the Favorskii carbinol — 2-methyl-3-butyn-2-ol (**11**) — by the reaction of acetylene and acetone.[21]

As noted above, the Favorskii reaction has a special significance in the industrial synthesis of propargyl alcohol[41,42] by several dozen companies in America, the European Union, China and India. The annual production of propargyl alcohol in the United States alone is estimated at 0.2 – 1.3 thousand tons.[43]

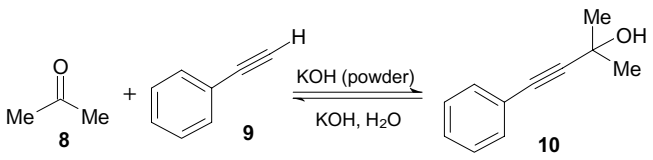
In contemporary laboratory-scale synthesis, the Favorskii reaction is essentially replaced by the reactions of various metal acetylenides with carbonyl compounds, which enables chemoselective (and even enantioselective) synthesis of propargyl alcohols with a high level of functional group tolerance.[44] However, in some cases, the Favorskii reaction and the related reaction of alkynes with carbonyl compounds in superbasic media[45] continue to be important synthetic tools. In particular, the scope of synthetic opportunities offered by this reaction have been demonstrated by B.A.Trofimov and co-workers[46 – 51] and by other researchers (see, for example, Ref. 52). Propargyl alcohols are important building blocks for modern organic synthesis, as reflected in a recent comprehensive review.[53]

The other, rather important application of the Favorskii carbinol (the product of the Favorskii reaction) is the laboratory synthesis of acetylene and diacetylene derivatives, which involves the functionalization of compound **11** at the terminal carbon atom of triple bond with subsequent elimination of acetone molecule *via* the retro-Favorskii reaction and further functionalization of the deprotected triple bond (Scheme 4). The key tools for the functionalization of terminal alkynes are the Sonogashira cross-coupling[54,55] and the Cadiot – Chodkiewicz reaction. The latter is employed in the synthesis of unsymmetrical diacetylenes.[56,57]

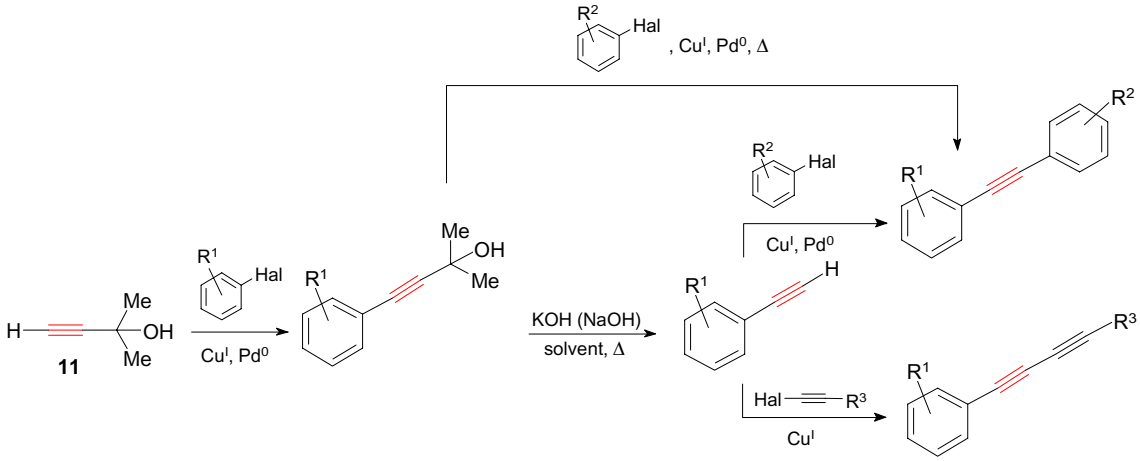
The retro-Favorskii reaction is typically carried out by heating the corresponding functionalized Favorskii carbinol in an inert hydrocarbon solvent in the presence of KOH or NaOH;[58 – 62] and the resulting terminal acetylene is directly used in next synthetic steps. However, several modifications of this approach are encountered in the literature which involve simultaneous removal of the acetone protecting group and Sonogashira reaction carried out as a one-pot process with participation of the hydroxyl group in the catalytic cycle.[63 – 67] This reaction allows introducing an additional substituent in the *ortho* position of the aromatic group, introduced in the Sonogashira step, due to CH activation.

An interesting modification of the retro-Favorskii reaction involves elimination of one protecting acetone group from the Favorskii carbinol dimer (**12**) under thermal

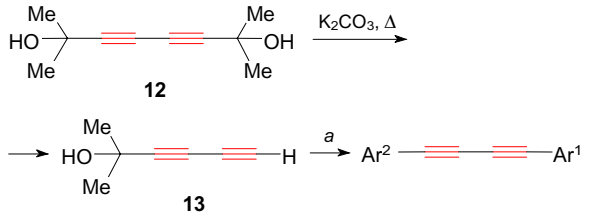
Scheme 3



Scheme 4



Scheme 5



(*a*) 1) Ar^1Hal, Cu^I, Pd^0; 2) KOH, PhH, Δ; 3) Ar^2Hal, Cu^I, Pd^0

conditions in the presence of potassium carbonate (Scheme 5).[68] The resulting monosubstituted terminal diacetylene **13** represents a redily available building block for the synthesis of unsymmetrical diacetylenes.[69, 70]

Unfortunately, this reaction usually is not associated with the Favorskii name in the English-language literature and the retro-Favorskii reaction is referred to as the process with acetone as a leaving group.[53] For this reason, publications that recognize and pay tribute to the great chemist and his discovery should be pointed out. For example, in the paper published in 2017 by Lenardao and co-workers and devoted to the use of the retro-Favorskii reaction in the synthesis of terminal ethynyl aryl selenides and sulfides,[71] a photograph of A.E.Favorskii is even shown in the graphical abstract (Fig. 2).

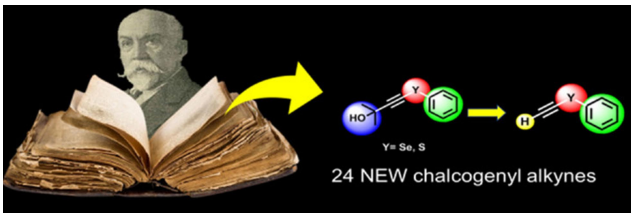


Figure 2. Graphical abstract to the paper by E.F.Lopes, B.T.Dalberto, G.Perin, D.Alves, T.Barcellos and E.J.Lenardão 'Synthesis of Terminal Ethynyl Aryl Selenides and Sulfides Based on the Retro-Favorskii Reaction of Hydroxypropargyl Precursors'. *Chem.–Eur. J.*, **23**, 13760 (2017).[71]

Thus, currently, the retro-Favorskii reaction appears to be more popular as a synthetic tool than the Favorskii reaction. In particular, its common use in the synthesis of various polyacetylene compounds deserves a separate review.

1.2.3. Vinylation reaction

The vinylation reaction discovered by Favorskii when he was studying the action of an alkaline alcohol solution on methylacetylene,[72] is another large area of acetylene chemistry associated with the synthesis of vinyl ethers and a large number of other monomers for polymer chemistry. The vinylation reaction has recently been highlighted in a review[73] dedicated to the synthesis of O-, S- and N-vinyl derivatives. Currently, the vinylation reaction is experiencing renaissance due to the implementation of green chemistry methods and the possibility of using calcium carbide as a source of acetylene.[74] It should be noted that some authors attribute the discovery of the vinylation reaction to Reppe, who, later, certainly made a huge contribution to the development of this field, especially its industry applications.[21]

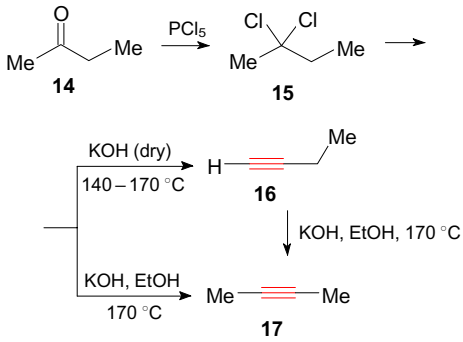
The vinylation reaction is another example of a process discovered in the first half of the 20th century which resulted in numerous practical applications. For instance, the product of the polymerization of vinyl butyl ether — the Favorskii–Shostakovsky balsam, or vinylin, has a pronounced anti-inflammatory and wound-healing effect. It had a broad medicinal use during World War II and is still in use. For example, vinylin is an ingredient of antimicrobial drug levovinisol.

1.2.4. Acetylene–allene isomerization and the acetylene zipper reaction

Acetylene–allene isomerization was the first important discovery made by A.E.Favorskii at the very beginning of his scientific activity, while he was working on his Master's thesis under the supervision of Prof. M.D.L'vov.[75] The report on the discovery of a new reaction was given by M.D.L'vov at the meeting of the Chemistry Division of the Russian Physical and Chemical Society (RPCS) on May 3, 1884 (Fig. 3 *a*).

While working on his Master's thesis, A.E.Favorskii established that, depending on the reaction conditions, treating geminal dichloride **15**, resulting from the reaction between phosphorus(V) chloride and methyl ethyl ketone (**14**), with KOH can afford both ethylacetylene (1-butyne, **16**) and dimethylacetylene (**17**) (Scheme 6) (Ref. 77, p. 98). In particular, when dry KOH is used, the reaction leads to ethylacetylene, whereas when the reaction is carried out in the presence of potassium hydroxide moistened with ethanol, dimethylacetylene is the reaction product.

Scheme 6



Further studies showed that dimethylacetylene (**17**) resulted from isomerization of compound **16** at 170 °C in alkaline alcohol solution. This transformation is rather common for terminal alkynes, and the structure of the isomerization products depends on the nature of the substituent at the triple bond. In addition, A.E.Favorskii found that disubstituted and trisubstituted allenes also underwent isomerization to give disubstituted acetylenes. The observed isomerization patterns were summarized in the Favorskii rules.[77]

A very important early discovery of A.E.Favorskii in the series of acetylene and allene hydrocarbons was the reverse process of isomerization of methylacetylenes and allenes (for example, compounds **18**, **19**) into terminal acetylenes **20**, **21** under heating in sealed tubes in the presence of sodium metal (Scheme 7).

A report on this transformation was made on May 1, 1886, at the RPCS Chemistry Division (see Fig. 3 *b*).[76]

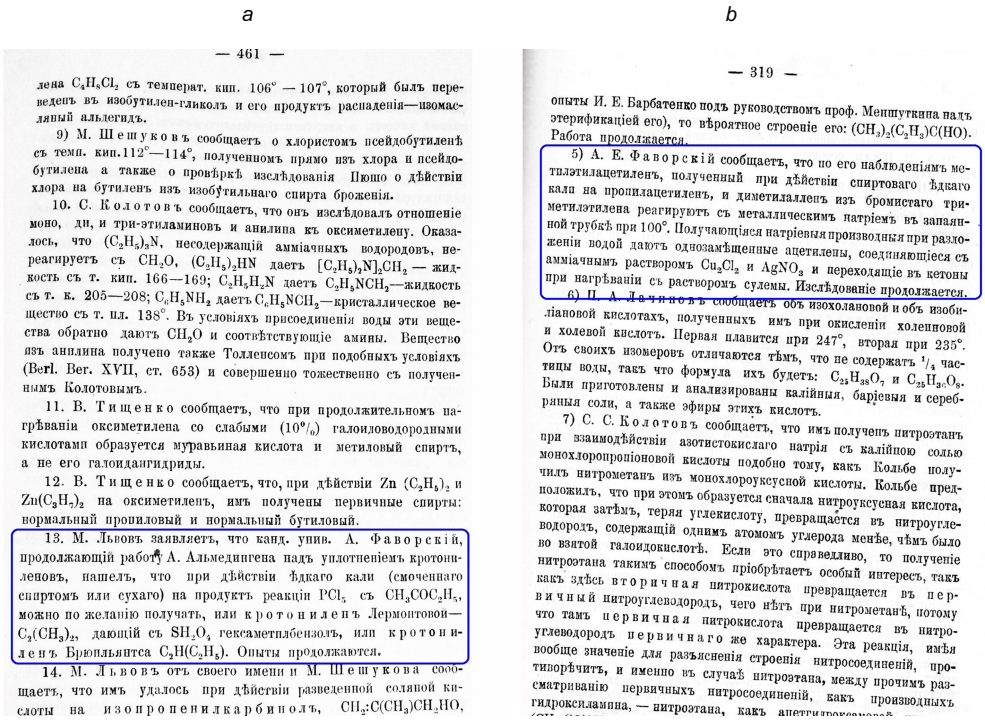
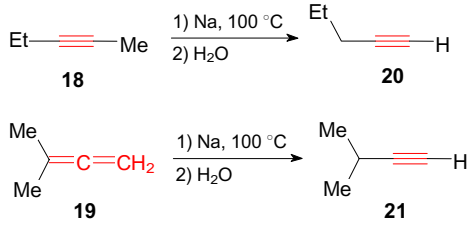


Figure 3. Photos of the original minutes of meetings of the Russian Physical and Chemical Society published in the *Journal of the Russian Physical and Chemical Society*: (*a*) first report on the observation of acetylene – allene isomerization (minutes dated May 3, 1884);[75] (*b*) first report on the observation of isomerization of internal acetylenes to terminal acetylenes (minutes dated May 1, 1886).[76]

Scheme 7



Termial alkynes play a special role in organic synthesis. They are actively used in the formation of new carbon – carbon bonds in homo-, hetero- and cross-coupling reactions, which may include preparation of a metal acetylide. The synthetic significance of the conversion of internal acetylene hydrocarbons to terminal ones was revealed after the discovery of its multipositional version under the action of superbases, such as diamine amides, the reaction dubbed the 'zipper reaction' by Brown and Yamashita.[78]

After the discovery of acetylene – allene isomerization, the isomerization of various functionalized acetylenes and its mechanism were intensively studied for many years, particularly, in search for new efficient bases capable of triggering this transformation. The available data have been summarized in a review[79] and monographs.[80,81] However, even when Bu^{t}OK in *tert*-butanol or DMSO was used, the triple bond was moved by not more than 2 or 3 carbon atoms.[82] It should also be noted that this superbasic system only led to translocation of the triple bond within a carbon chain and did not lead to the formation of a terminal alkyne.

In 1975, almost 90 years after the discovery of acetylene – allene isomerization, Brown and Yamashita reported that the use of superbasic potassium 3-aminopropylamide (KAPA) led to the migration of the triple bond in acetylene hydrocarbons by 3 – 7 carbon atoms from the internal to the terminal position.[78] This stimulated new research efforts aiming to identify new bases similar to KAPA in their ability to trigger triple bond migration and to extend the reaction to functionalized acetylenes.

Despite the widespread use of both transformations in modern organic synthesis, there are almost no review articles covering acetylene – allene isomerization and the acetylene zipper reaction. In particular, in the recent review by Avocetien *et al.*[83] devoted to the acetylene zipper reaction, this transformation was mostly discussed for substrates containing asymmetric carbon atoms. There are currently no reviews covering reactions leading to methyl-substituted acetylene compounds as a result of acetylene – allene isomerization.

Undoubtedly, special attention should be given to the research carried out at the Irkutsk Institute of Chemistry under the supervision of Academician Boris Alexandrovich Trofimov[84 – 86] as well as to the publications of other groups on acetylene – allene isomerization of heteropropargyl compounds (leading to the corresponding allene derivatives, and often culminating in the heterocycle synthesis).[87 – 89] Many of these results are summarized in the chapter on the synthesis of allenes of the review on acetylene chemistry by Trofimov and co-workers.[90]

Allenes containing heteroatom substituents are nowadays widely employed in organic synthesis, in particular, for the construction and further modification of heterocyclic compounds as detailed in a recent review.[91] Several examples of similar transformations have appeared in recent literature.[92 – 103]

The present review deals in detail with the methods of isomerization of terminal acetylenes to methylacetylenes and the reverse process, the acetylene zipper reaction as an important tool for the synthesis of terminal alkynes. It covers all publications devoted to the mechanisms of both transformations while focusing on more recent (2009–2018) publications describing synthetic applications of these reactions.

The following abbrevations are used in this review:

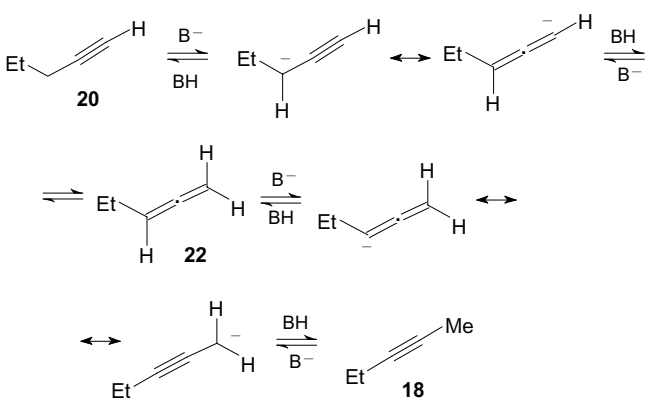
Ad — 1-adamantyl,
ADDP — 1,1′-(azodicarbonyl)dipiperidine,
B — base,
BARF — tetrakis[3,5-bis(trifuoromethyl)phehyl]borate,
BINOL — 1,1′-bi(2-naphthol),
Boc — *tert*-butoxycarbonyl,
2-BP — 2-bromopalmitic acid,
$(Bpin)_2$ — bis(pinacolato)diboron,
bipy — 2,2′-bipyridine,
C — concentration,
Cat — catalyst,
COD — 1,5-cyclooctadiene,
Cp* — pentamethylcyclopentadienyl,
CTAB — cetyltrimethylammonium bromide,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
dba — dibenzylideneacetone,
DCC — dicyclohexylcarbodiimide,
DCE — 1,2-dichloroethane,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DHP — 3,4-dihydropyran,
DIAD — diisopropylazodicarboxylate,
DIBAL-H — diisobutylaluminium hydride,
DIPEA — *N*,*N*-diisopropylethylamine,
DMAP — 4-dimethylaminopyridine,
DMDA — dimethyldiacetylene,
DME — 1,2-dimethoxyethane,
DMPS — dimethylphenylsilyl,
DMT — 4,4′-dimethoxytrityl,
DMP — Dess–Martin periodinane,
DPEphos — bis(2-diphenylphosphino)phenyl ether,
dppf — 1,1′-bis(diphenylphospino)ferrocene,
$dpppMe_2$ — dimethylbis(diphenylphosphino)methane,
dr — diastereomeric ratio,
DTBPF — 1,1′-bis(di-*tert*-butylphosphino)ferrocene,
EDA — 1,2-ethanediamine,
EDC — 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide,
EDG — electron-donating group,
ee — enantiomeric excess,
$Eu(fod)_3$ — europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate),
EWG — electron-withdrawing group,
FG — functional group,
Fu — fur-2-yl,
HOBt — 1-hydroxybenzotriazole,
HMDS — hexamethyldisilazide,
IBX — 2-iodoxybenzoic acid,
KAPA — potassium 3-aminopropylamide,
LAETA — lithium 2-aminoethylamide,
LAH — lithium aluminum hydride,
LAPA — lithium 3-aminopropylamide,
LDA — lithium diisopropylamide,
m-CPBA — *m*-chloroperoxybenzoic acid,
Mes — mesityl (2,4,6-trimethylphenyl),
MOM — methoxymethyl,
MS — molecular sieves,
Ms — methanesulfonyl (mesyl),
MTPA — α-methoxy-α-trifluoromethylphenylacetic acid,
MW — microwave radiation,
NAETA — sodium 2-aminoethylamide,
NAPA — sodium 3-aminopropylamide,
NBS — *N*-bromosuccinimide,
2-NMA-OH — α-methoxy-2-naphthylacetic acid,
NMP — *N*-methylpyrrolidone,
Nu — nucleophile,
PDA — propane-1,3-diamine,
PDC — pyridinium dichromate,
PEG — poly(ethylene glycol),
PG — protective group,
PMB — *p*-methoxybenzyl,
Py — pyridyl,
RCDEYM —cascade ring-closing dienyne metathesis,
RCM — ring-closing metathesis,
$Rh_2(S\text{-DOSP})_4$ — tetrakis[(*S*)-(+)-*N*-(*p*-dodecylbenzenesulfonyl)prolinato]dirhodium(II),
RRCM — relay ring-closing metathesis,
rt — room temperature,
TBAF — tetra-n-butylammonium fluoride,
TBAI — tetra-n-butylammonium iodide,
TBDMS — *tert*-butyldimethylsilyl,
TES — triethylsilyl,
TFA — trifluoroacetic acid,
TfO — trifluoromethanesulfonate (triflate),
THP — tetrahydropyran-2-yl,
TMEDA — *N*,*N*,*N*′,*N*′-tetramethylethylenediamine,
TMS — trimethylsilyl,
Tr — trityl (triphenylmethyl),
Ts — toluenesulfonyl (tosyl).

2. Mechanism of the acetylene–allene isomerization and the acetylene zipper reaction

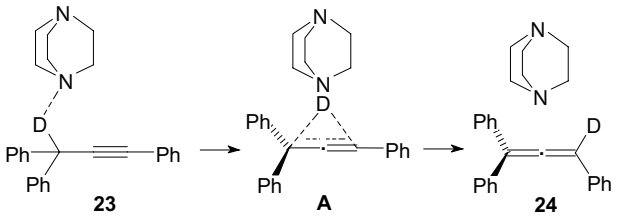
In studies dealing with acetylene–allene isomerization, the mechanism of proton transfer and the formation or absence of anionic intermediates in this process have been repeatedly discussed. Favorskii believed that proton transfer coud be intramolecular.[104] Later, Jacobs *et al.*[105] have suggested a carbanion mechanism through the formation of allene **22** (Scheme 8).

In 1964, when studying the isomerization of 3-deuterio-1,3,3-triphenylprop-1-yne (**23**) to allene **24** under the action of different bases, Cram *et al.*[106] have demonstrated that

Scheme 8



Scheme 9



1,3-proton transfer can be both intra- and intermolecular depending on the base used (Scheme 9). For example, upon the treatment with MeOK in methanol, allene retained only 19% of deuterium. If 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as a base, the reaction product retained 88% of deuterium atoms. Deuterium was retained in the molecule in the course of isomerization even in the presence of proton donors — *tert*-butyl alcohol or DABCO hydroiodide. The authors have suggested that, in the presence of amines, proton transfer occurs through the formation of bimolecular intermediate species **A** and have coined the name 'conducted tour' mechanism for this process (Scheme 9).

According to Carr *et al.*,[107] acetylene–allene isomerization is a kinetically controlled process; therefore, the thermodynamically most favourable diene isomers is usualy not formed. After the isomerization of alkyne to allene, further transformation involves elimination of allene protons (labelled with I in Scheme 10), which have higher kinetic acidity than the methylene protons (labelled with II). The formation of dienes upon isomerization of alkyne in the presence of Bu^{t}OK has been detected only at 250 °C.[82]

However, in the presence of electron-withdrawing substituents at the triple bond such as aryl[108] and carboxyl groups,[109] the acidity of methylene protons II increases, and methylene group deprotonation can compete with elimination of the allene proton. In this case, the reaction gives diene isomers.

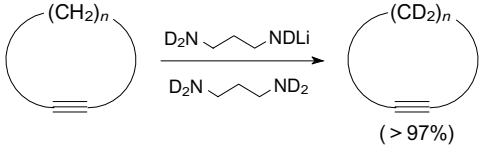
Multipositional acetylene–allene isomerization seems also to be a kinetically controlled process. In the acetylene zipper reaction of hydrocarbons and alcohols, the formation of the most thermodynamically stable diene isomers has not been observed.

Diene isomers have been identified only upon isomerization of acetylenic amines and acids.[110–113]

It is suggested that, in the process of multipositional isomerization, the triple bond undergoes random migration along the carbon chain through the formation of intermediate allene isomers until the formation of poorly soluble acetylenide removes the terminal isomer from the reaction.[114]

Another experimental proof was provided by the treatment of cycloalkynes by lithium 3-aminopropylamide (LAPA) at 0 °C in *N*,*N*,*N*′,*N*′-d_4-propane-1,3-diamine.[115] The reaction afforded 97% substitution of protons with deuterium and was proposed as a method for the deuterated cycloalkyne generation (Scheme 11). For cyclododecyne, the reaction gave, in addition to the corresponding alkyne, the allene isomer (in the 2 : 3 ratio), while the increase in temperature gave a conjugated diene. 1,3-Cyclododecadiene was also synthesized when a stronger base — the sodium salt of 1,3-diaminopropane (PDA) — was used.

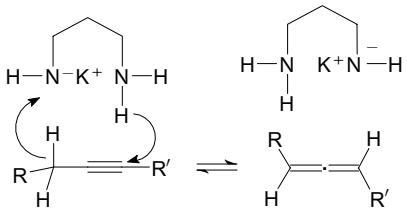
Scheme 11



n = 10–13

The high isomerization rate of alkynes in the KAPA-catalyzed acetylene zipper reaction (2–10 min) was explained by Brown and Yamashita [78] by concerted proton transfer in a cyclic transition state in which the amide group accepts a proton and the amino group donates a proton (Scheme 12). This proton transfer mechanism of prototropic isomerization involving amides of diamines was suggested for the first time by Wotiz *et al.*[116]

Scheme 12

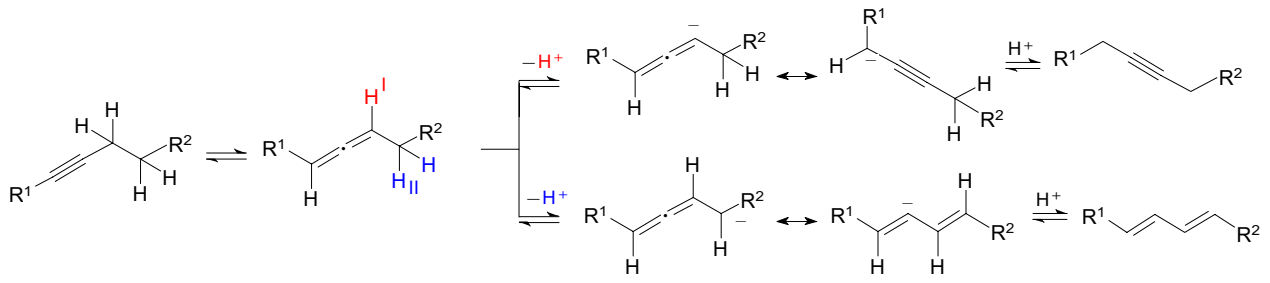


The triple bond shift by one carbon atom during the isomerization of 2-alkyn-1-ol to 3-alkyn-1-ol also occurred in the presence of monoamine amides.[117]

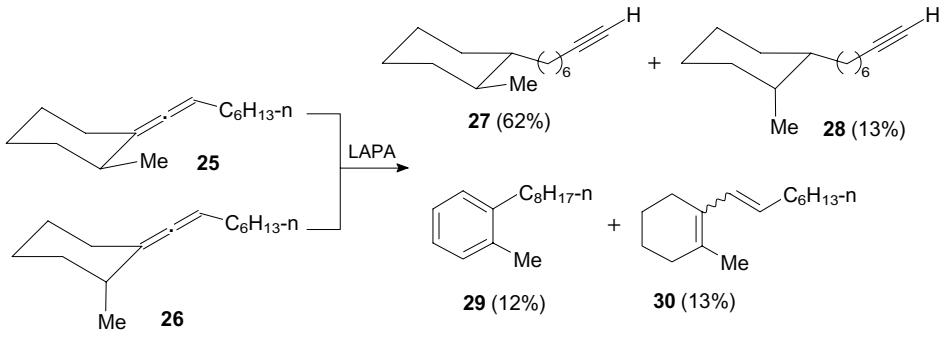
Later, Abrams and Shaw [118] have studied the mechanism of the 1,3-proton shift in acetylene–allene isomerization under the action of LAPA using a mixture of diastereomeric allenes **25** and **26**. The major product in the mixture of compounds **27**–**30** was terminal acetylene **27** with a *trans* arrangement of the substituents in the cyclohexane moiety (Scheme 13).

The formation of thermodynamically more favourable isomer **27** has been explained by the existence of a carba-

Scheme 10



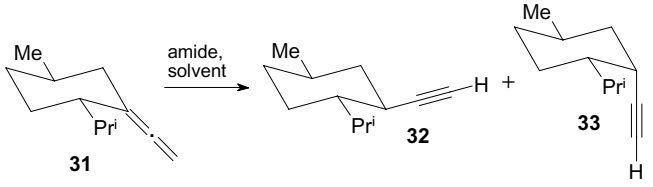
Scheme 13



nionic intermediate generated at the first stage after removal of the allene proton.

The isomerization of vinylidene-substituted cyclohexanes in the presence of amides of di- and monoamines has been studied by Nantz and co-workers [119] to accomplish the stereoselective synthesis of ethynylcyclohexanes (Scheme 14). For allene **31** as an example, a correlation has been found between the ratio of *trans* and *cis* isomers **32** and **33** and the nature of the base and solvent used. In experiments with potassium n-butylmethylamide, the predominant formation of thermodynamically more stable isomer **32** has been observed, which can be interpreted in favour of the existence of a carbanionic intermediate in this transformation.

Scheme 14



Amide	R	Solvent	**32** : **33** ratio
H_2N N$^-$K$^+$ H	–	PDA	1.2 : 1
	–	THF	1.3 : 1
HN N$^-$K$^+$ R Me	H	EDA	1.1 : 1
	Me	THF	1.8 : 1
K$^+$N$^-$ Bu^n Me	–	THF	7 : 1

EDA is ethane-1,2-diamine

At the same time, under the action of diamine amides, mixtures of isomers **32** and **33** were obtained in almost equal amounts, with the lowest stereoselectivity being observed for reactions carried out in diamines. Therefore, in processes mediated by diamine amides, proton abstraction and addition occur with equal probability within both sides of the vinylidene moiety, which can be realized in a cyclic transition state.

From the analysis of published data, it can be concluded that proton transfer in acetylene–allene isomerization follows various mechanisms depending on the reaction conditions and the nature of the base and substrates. Available indirect evidence supports concerted 1,3-proton transfer through the cyclic transition state proposed by Wotiz *et al.*[116] when amides of diamine are used as a base.

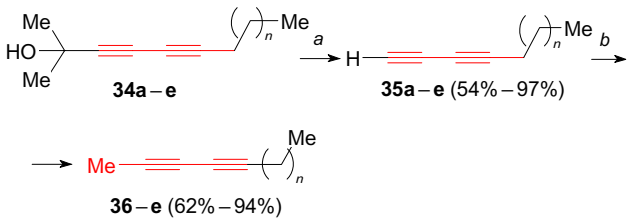
3. Acetylene–allene isomerization in synthesis of methylacetylenes

3.1. Modern research on the acetylene–allene isomerization

Despite the fact that in most of the recent works, acetylene–allene isomerization serves as a synthetic tool for creating methylethynyl moieties in molecules of various complexity, there are publications devoted exclusively to studying this process.

The acetylene–allene isomerizations of derivatives produced from diacetylenes **34a–e** have been studied, and optimal conditions for the transformation of terminal diacetylenes **35a–e** to isomeric methyldiacetylenes **36a–e** have been selected [120] (Scheme 15).

Scheme 15

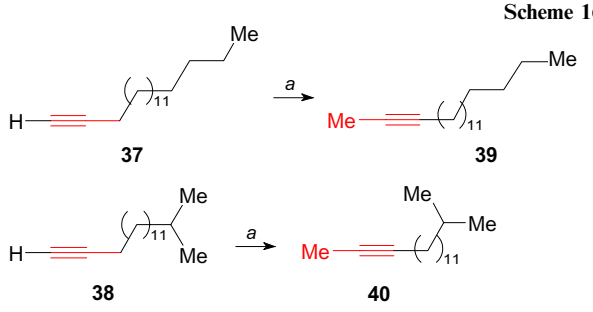


(*a*) is NaOH, xylene or PhMe, Δ; (*b*) is NaOH or KOH, CTAB, xylene, or PhMe, or hexane, Δ; CTAB is cetyltrimethylammonium bromide; n = 1 (**a**), 2 (**b**), 4 (**c**), 5 (**d**), 8 (**e**)

This work was prompted by an unexpected isomerization of undeca-1,3-diyne **35d** observed during an attempt to optimize conditions of its synthesis by the retro-Favorskii reaction; as a result, undeca-2,4-diyne **36d** was isolated. It turned out that alka-1,3-diynes in the reacion with a base (NaOH or KOH) under reflux in xylene or toluene in the presence of a phase transfer catalyst — cetyltrimethylammonium bromide — underwent acetylene–allene isomerization to give methyl-substituted diacetylenes **36** in high yields. For more volatile diacetylenes, higher yields were achieved using hexane as a solvent and KOH as a base.

The publication of Mohammad *et al.*[121] is one of the few works devoted exclusively to the use of acetylene–allene isomerization for the synthesis of methylacetylenes. The major objective of the authors was to study the influence of the nature of the alkyl substituent, namely, the presence of branching remote from the triple bond in the hydrocarbon chain of terminal acetylenes **37** and **38**, on the rate

Scheme 16



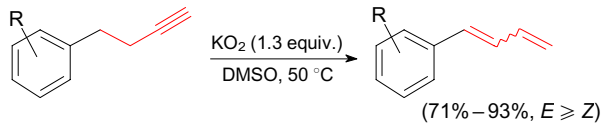
(*a*) Bu^{t}OK (1 equiv.), DMSO, 50 or 70 °C

and direction of the triple bond isomerization to give methylacetylenes **39** and **40** (Scheme 16).

It has been demonstrated that the presence of an isopropyl moiety is responsible for twofold acceleration of isomerization; the reaction rate is described by the pseudo-first order equation. This fact can be explained by different packing of alkyl substituents, which results in a different spatial arrangement of the remote linear alkyl and isopropyl moieties relative to the triple bond. In this case, the isopropyl substituent makes the packing less tight and facilitates the access of the base to the propargyl protons, thereby promoting isomerization.

The work by Khan and Budanur [122] should also be attributed to a focused study of the isomerization of homopropargylarenes under the action of potassium superoxide as a base. The authors selected optimal conditions for isomerization: 1.3 equiv. superoxide in DMSO at 50 °C. Under these conditions, all homopropargylarenes gave buta-1,3-dienylarenes as a mixture of diastereomers with the predominance of the *E* isomer (Scheme 17).

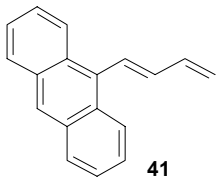
Scheme 17



R = Alk, $(MeO)_n$ (n = 1–3), benzo

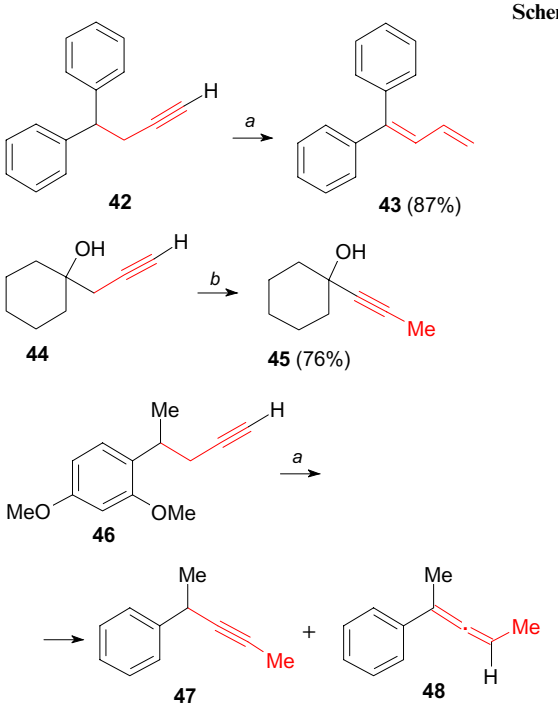
Only in the case of homopropargylanthracene, the process was highly stereoselective to give exclusively the *E* isomer of diene **41** in 77% yield.

Structure 41



It has also been shown that one of the hydrogen atoms in the benzyl position can be substituted by a phenyl group without interfering into the isomerization process: compound **42** gives product **43** in high yield. On going to cyclohexanol derivatives **44**, the reaction stops at the stage of formation of exclusively methylacetylene **45**. If a methyl substituent is introduced into the benzyl position (compound **46**), the reaction gives a 2 : 3 mixture of product **47**,

Scheme 18

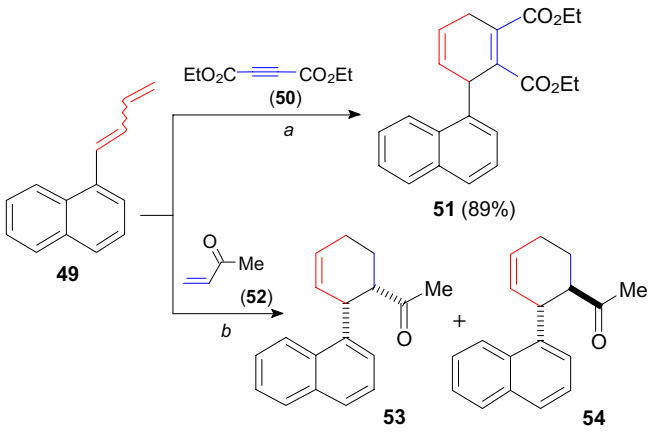


(*a*) KO_2, DMSO, 50 °C; (*b*) KO_2, DMSO, 60 °C

as a result of the triple bond shift by one carbon atom, and allene **48** in an overall yield of 83% (Scheme 18).

The synthetic significance of 1,3-dienes was demonstrated by the example of the isomerized naphthalene derivative **49**. It undergoes the Diels–Alder reaction with alkyne **50** to form product **51** in the presence of hydroquinone as a catalyst. The reaction with alkene **52** under similar conditions afforded a 2 : 1 mixture of diastereomers **53** and **54** in a total yield of 85% (Scheme 19).

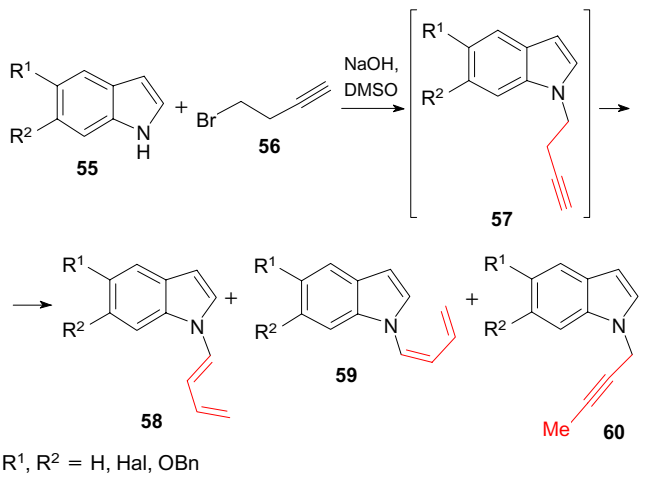
Scheme 19



(*a*) 1,4-$(HO)_2C_6H_4$, PhMe, 130 °C, 19 h; (*b*) 1,4-$(HO)_2C_6H_4$, PhMe, 130 °C, 46 h

Pis Diez *et al.* [123] have carried out alkylation of indoles **55** with homopropargyl bromide **56** catalyzed by a superbase (NaOH in DMSO) and have comprehensively studied the isomerization of intermediate homopropargylindoles **57** under these conditions (Scheme 20). The alkylation unexpectedly affords a mixture of *E* (**58**) and *Z* isomers (**59**) of

Scheme 20

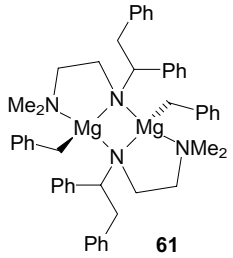


N-butadienylindoles under rather mild conditions (at 70 °C in 2 h). The study of this reaction can be considered as the first investigation of acetylene–allene isomerization for N-homopropargyl-substituted nitrogenous heterocycles. It has been demonstrated that butadienes **58** and **59** are thermodynamically controlled products, while methylpropargylindole **60** can be isolated under kinetic control conditions. Scheme 21 shows the mechanism of the conversion of unsubstituted propargylindole **57a** to products **58a**–**60a** through the formation of intermediates **A**–**D**. The formation of dienes is facilitated by stabilization of carbanion **C** formed from allene **B** after the first stage of acetylene–allene isomerization.

An analogous reaction has been revealed for carbazole. It is worth noting that the alkylation of indole with 5-chloro-1-pentyne afforfs exclusively a nonisomerized alkylation product. The data obtained are consistent with the patterns discussed in the section devoted to the isomerization mechanism. The synthetic potential of the resulting dienes has been demonstrated by the example of the Diels–Alder reaction with quinone.

Rochat *et al.*[124] were the first to propose the use of homogeneous catalysis of acetylene–allene isomerization by organomagnesium complexes with amine ligands. In particular, complex **61** proved to be the most efficient catalyst.

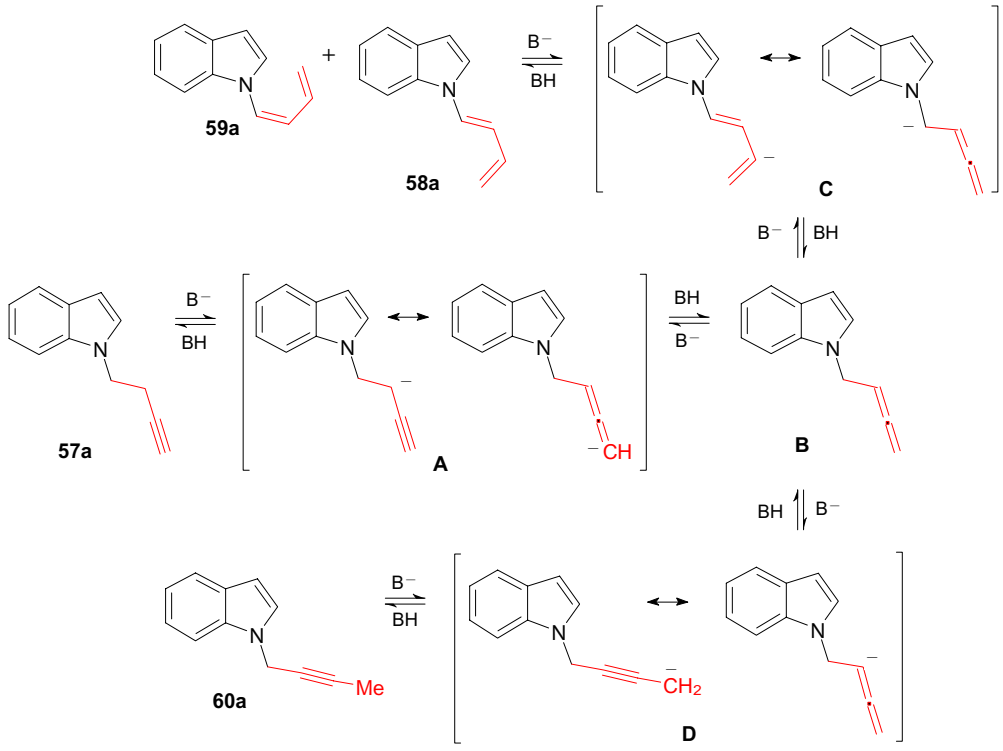
Structure 61



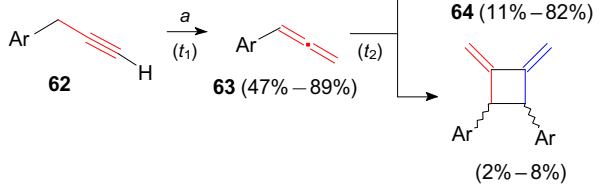
The entire process (Scheme 22) can be clearly separated into two stages — the isomerization of the terminal triple bond in acetylene **62** to give allene **63** (in time t_1) and subsequent isomerization of allene **63** to methylacetylene **64** (t_2).

This process was defined by the authors as temporally separated autotandem catalysis. The presence of electron-withdrawing groups in the aromatic ring promoted the isomerization to allene, while the nature of the group did not affect further isomerization to methylacetylene. In all cases, the mixture contained up to 10% of the dimers of the initially formed allenes as by-products. To describe this process, the authors have suggested the following mechanism: at the first stage of transformations, terminal acetylene **62a** (Ar = Ph) forms the corresponding magnesium

Scheme 21



Scheme 22

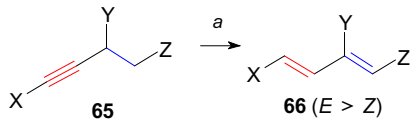


(*a*) **61** (4.8 mol.%), [D$_8$]PhMe, 80 °C;
Ar = RC$_6$H$_4$ (R = EWG, EDG); EWG is electron-withdrawing groups; EDG is electron-donating groups

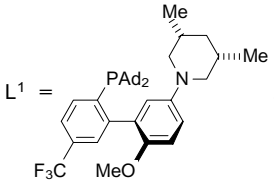
acetylenide **A**, then the second acetylene molecule is activated to give three key tautomeric complexes **B** – **D** being in equilibrium due to the 1,3-hydride shift (Scheme 23).

Wang *et al.*[125] have focused on the design of a push – pull catalyst for mild isomerization of alkynes **65** to butadienes **66**. The idea of the authors was to combine, in one molecular framework, a Lewis acid centre for coordination to the triple bond and a basic amino group for deprotonation of the propargyl position, which somewhat resembles similar systems for the soft generation of enolate ions. The AuCl complex with the L^1 ligand after the subsequent replacement of the chloride anion by tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) proved to be most efficient for implementing this strategy. These isomerization conditions have been tested on a variety of substrates **65** — arylalkynes, heteroarylalkynes, enynes and even terminal acetylenes. In all cases, isomerization afforded high yields of the product and occurred with high stereoselectivity, with the predominant formation of the corresponding *E*,*E* isomer **66** (Scheme 24).

Scheme 24



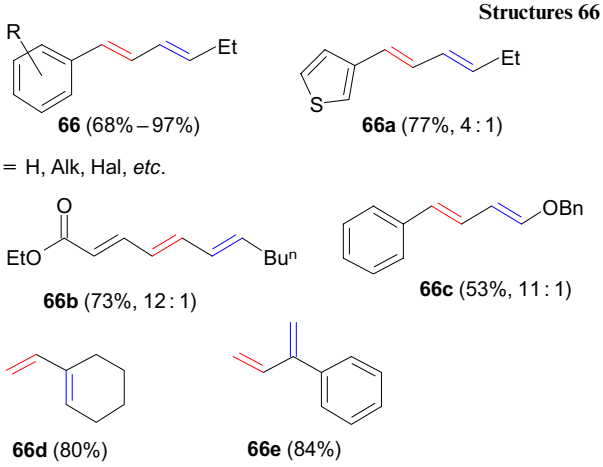
(*a*) L^{1}AuCl (2 mol.% – 5 mol.%), NaBARF (10 mol.%), PhCF$_3$, 60 °C;



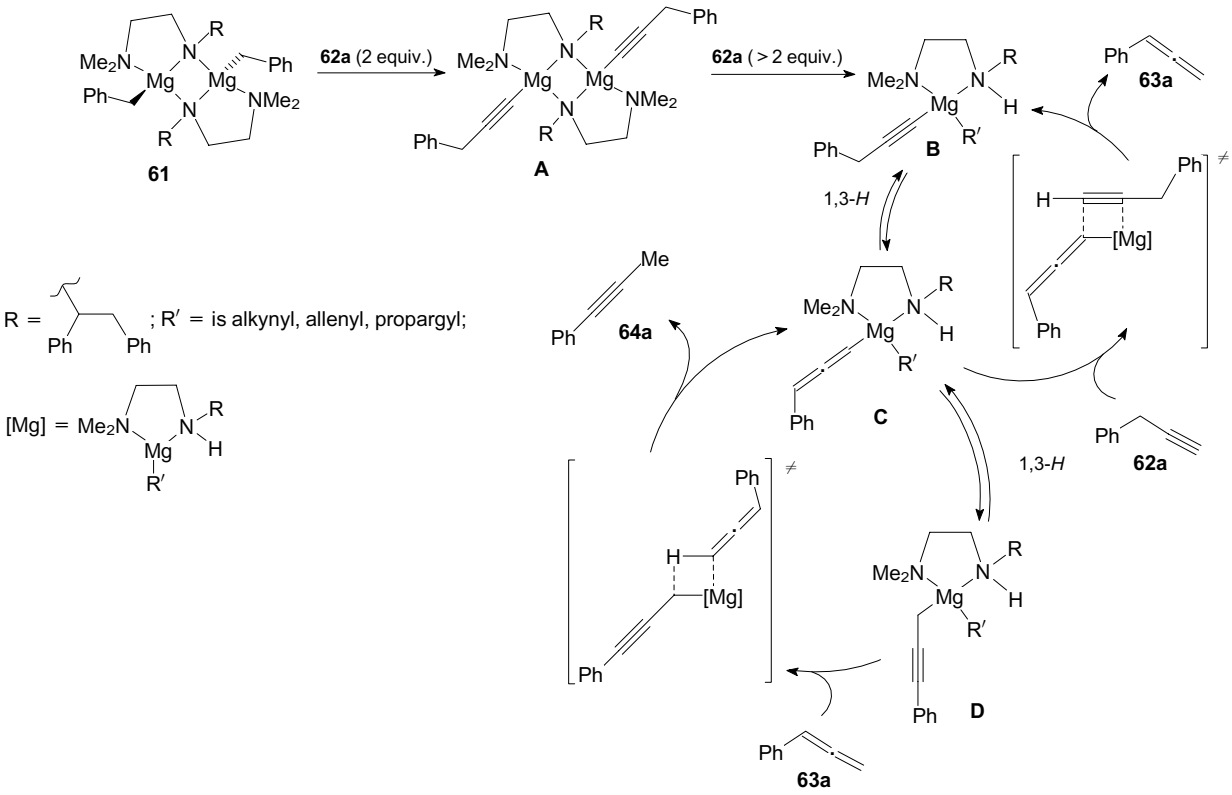
; Ad is 1-adamantyl

The examples of dienes **66** obtained under these conditions, with indication of the yields and *E*,*E*/*E*,*Z* ratios are given below.

Structures 66



Scheme 23

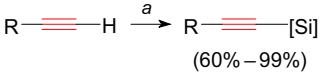


Thus, despite more than a century of history and numerous publications devoted to acetylene–allene isomerization, new directions for studying this reaction are currently developed: the use of new substrates, the use of new bases and the targeted design of catalysts that make it possible to carry out acetylene–allene isomerization under mild conditions and shift the equilibrium towards acetylene–diene isomerization.

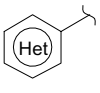
3.2. Isomerization of unfunctionalized acetylenes in synthesis of methylacetylenes

The acetylene–allene isomerization is not always a desired process. In particular, a unique catalytic method has been developed for the silylation of terminal alkynes, which opens the possibility of producing ethynylsilanes without the use of metal acetylides.[126] The following conditions have been selected for the successful implementation of the process: 10 mol.% KOH or NaOH, an excess of trialkylsilane and 1,2-dimethoxyethane (DME) as a solvent. Depending on the nature of the substrate, the reaction either occured at room temperature or required heating to 40–60 °C. The process is almost universal and can be used for the synthesis of silyl-substituted aryl-, heteroaryl-, ferrocenyl- and alkylacetylenes (Scheme 25).

Scheme 25



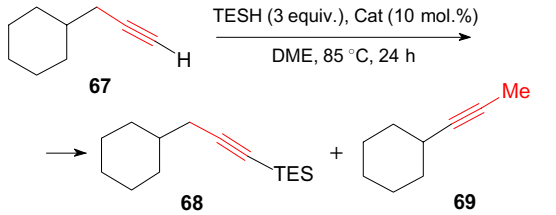
(*a*) [Si]H (3 equiv.), KOH or NaOH (10 mol.%), DME, 25–85 °C, 24–48 h;

R =  (R′ = H, Alk, Hal, *etc.*), , ,

Alk, FG–CH_2; [Si] = $SiEt_3$ (TES), $SiMe_2Ph$, $SiMe_2Et$, $SiBu^t_3$, $Si(OEt)_3$, $SiMe_2$(Py-2), $SiMe_2H$, $SiPhMe_2$; FG is functional group, Py is pyridyl

It is important that, for alkyl-substituted acetylenes, the authors were able to optimize conditions which allowed avoiding the acetylene–allene isomerization. This process was observed as a side one upon silylation of cyclohexylmethylacetylene **67** only when stronger bases, such as sodium or potassium *tert*-butoxide, were used: in addition to product **68**, methylacetylene **69** was identified (Scheme 26).

Scheme 26



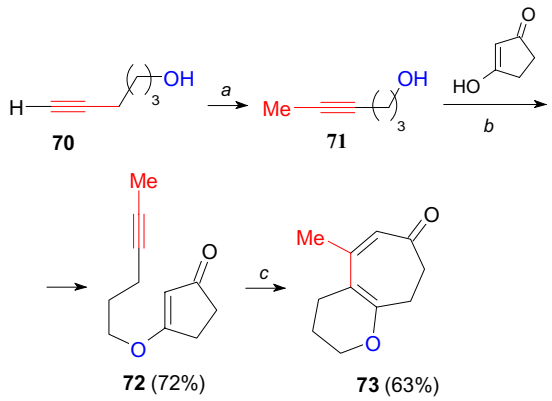
Catalyst (Cat)	Content of **68** (%)	Content of **69** (%)
Bu^tOK	89	9
Bu^tONa	46	52

3.3. Isomerization of acetylenic alcohols and ethers

3.3.1 Achiral alcohols and ethers

Tyman *et al.*[127] have developed for the first time an intramolecular alkyne-de Mayo reaction, which affords medium-sized fused carbocycles annulated to O- and N-heterocycles. The acetylene–allene isomerization of hex-5-yn-1-ol (**70**) under commom superbasic conditions (potassium *tert*-butoxide in DMSO) led to methylacetylene **71**, which was used for synthesizing compound **72** — one of the substrates for preparing bicycle **73** by the mentioned reaction (Scheme 27).

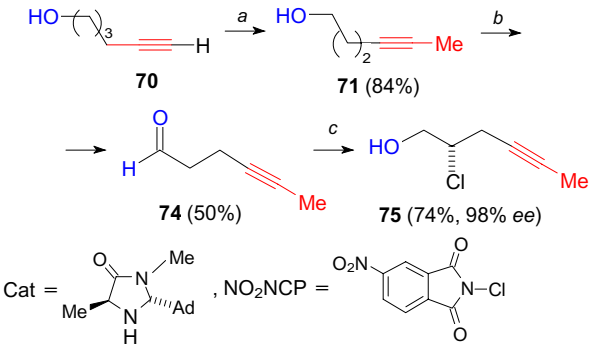
Scheme 27



(*a*) Bu^tOK, DMSO, rt; (*b*) $TsOH \cdot H_2O$ (0.05 equiv.), PhMe, 130 °C, 20 h; (*c*) *hν* (λ = 254 nm), CF_3CH_2OH (*C* = 0.03 M), rt, 9 h;
rt is room temperature, Ts is toluenesulfonyl (tosyl),
C is concentration

Ponath *et al.*[128] have studied enantioselective organocatalytic α-chlorination of aldehydes, using imidazolidinones as catalysts and N-chloroimides as chlorinating agents. One of the substrates was hex-4-ynal (**74**), which was obtained from hex-5-yn-1-ol (**70**) through acetylene–allene isomerization to hex-4-yn-1-ol (**71**) in the Bu^tOK–DMSO system and the subsequent Swern oxidation of the OH group. It was shown that the triple bond — an important functional group — is not affected under these conditions of enantioselective chlorination, which leads to the formation of product **75** (Scheme 28).

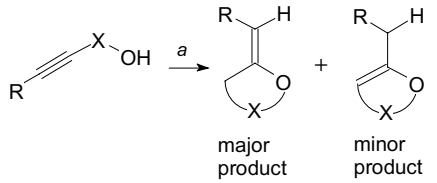
Scheme 28

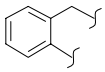


(*a*) Bu^tOK, DMSO, 22 °C, 15 h; (*b*) $(COCl)_2$, Et_3N, DMSO;
(*c*) 1) NO_2NCP (1.2 equiv), Cat (5 mol.%), TFA (5 mol.%), AcOH (10 mol.%), MeCN, −30 °C, 48 h; 2) $NaBH_4$, EtOH, 0 °C, 30 min;
TFA is trifluoroacetic acid, *ee* is enantiomeric excess

Acetylene – allene isomerization was found to be a side process,[129] like in the synthesis of ethynylsilanes mentioned above (see Scheme 26). The authors studied the intramolecular addition of OH group to the triple bond and allene moiety catalyzed by alkaline earth metals amides. The optimal conditions found allowed *exo*-dig nucleophilic cyclization of various acetylenic alcohols to proceed avoiding the isomerization of the triple bond and formation of products with an endocyclic double bond (Scheme 29).

Scheme 29



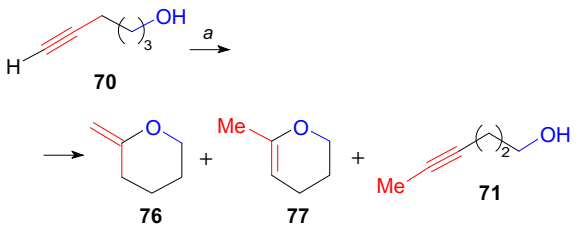
X = $(CH_2)_n$,  ; R = H, Alk, Ar;

(*a*) $[M\{N(TMS)_2\}_2]_2$ (5 mol.% – 10 mol.%), benzene-d_6, 80 – 120 °C; M = Ca, Sr, Ba; TMS is trimethylsilyl

However, while optimizing the conditions for the cyclization of hex-5-yn-1-ol (**70**) catalyzed by Sr and Ba amides, the authors identified a by-product of acetylene – allene isomerization — hex-4-yn-1-ol (**71**) along with the target cyclic product **76** and its isomer **77** (Scheme 30). Interestingly, hex-4-yn-1-ol (**71**) was also used as a substrate in the process studied, but, unlike the two previous works, it was produced by methylation of protected pen-4-tyn-1-ol.

Shulz and co-workers[130] developed the synthesis of macrolide pheromones of the sawtoothed grain beetle *Oryzaephilus Surinamensis* and the frog *Spinomantis Aglavei*. The key step of the synthesis of pheromones is the ring-closing alkyne metathesis. This reaction uses methylalkyne derivatives and is catalyzed by an alkylidyne tungsten complex containing the imidazolidin-2-iminum ligand. Thus, the presence of two methylethynyl moieties is the key success factor of the entire synthetic chain. Acetylene – allene isomerization is an extremely convenient route to this moiety. In particular, at the first stages of the synthesis, the isomerization of hex-5-yn-1-ol (**70**) — the displacement of the triple bond by one carbon atom — was carried out under the above-described conditions (see Scheme 28). Then, the hydroxyl group of isomerized alcohol **71** was used to build up the carbon chain through its oxidation to aldehyde **74** followed by the enantioselective addition of diethylzinc to the carbonyl group (Scheme 31). The resulting alcohols **78a**,**b** were reacted with acid **79** to introduce a

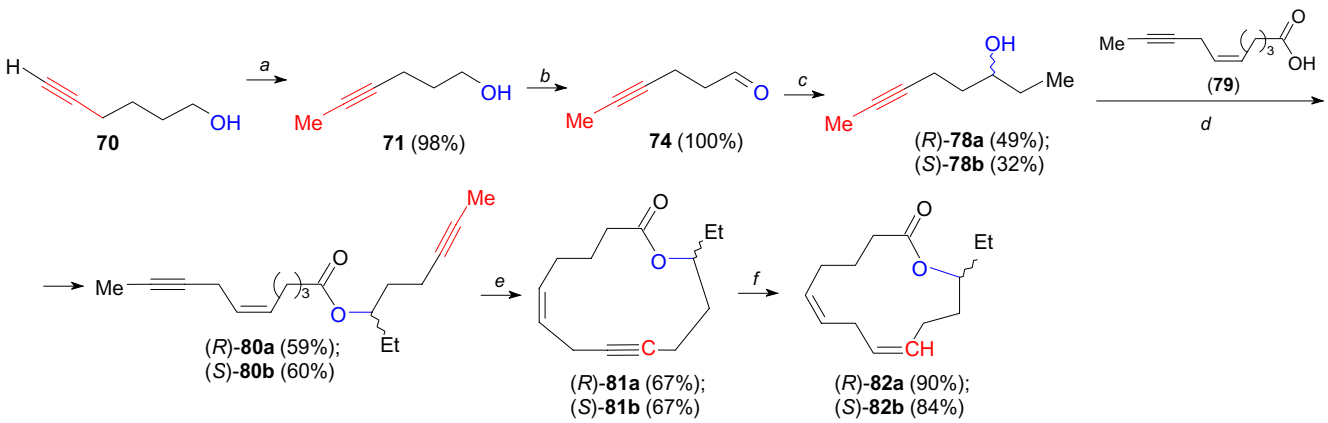
Scheme 30



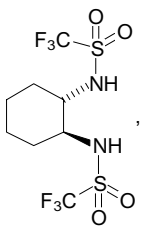
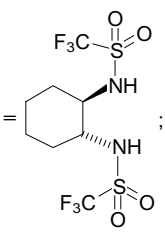
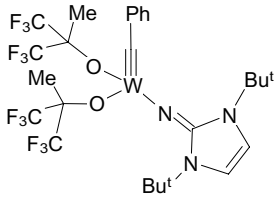
(*a*) $[M\{N(TMS)_2\}_2]_2$ (10 mol.%), benzene-d_6, 110 – 120 °C

M	*T*/°C	**76** : **77** : **71** ratio
Sr	120	49 : 7 : 44
Ba	110	10 : 11 : 79
Ba	120	28 : 4 : 67

Scheme 31



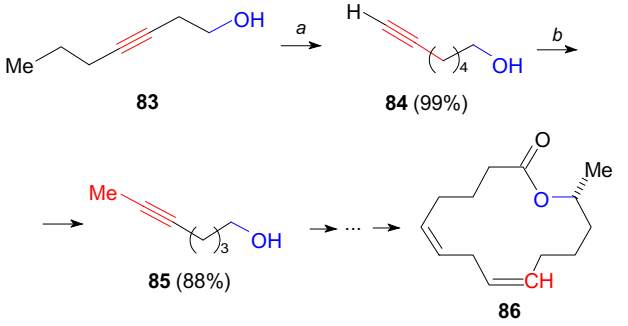
(*a*) Bu^tOK, DMSO, rt, 3 h; (*b*) $(COCl)_2$, Et_3N, DMSO; (*c*) (*S*,*S*)-L^2 or (*R*,*R*)-L^2, $Ti(OPr^i)_4$, Et_2Zn; (*d*) DMAP, EDC; (*e*) Cat (5 mol.%), PhMe, MS 5 Å, rt; (*f*) H_2, Lindlar catalyst, MeOH; DMAP is 4-dimethylaminopyridine, EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; MS is molecular sieves;

(*S*,*S*)-L^2 = , (*R*,*R*)-L^2 = ; Cat = 

moiety containing the second methylethynyl group into esters **80a**,**b**. The final steps of the synthetic chain were ring-closing metathesis (RCM) and the Lindlar-catalyzed hydrogenation of the triple bond in metathesis products **81a**,**b**, which led to target macrocyclic lactones **82a**,**b** — enantiomers of the 13-membered pheromone cucujolide X.

It is noteworthy that the approach to the synthesis of a ring with a larger number of carbon atoms than in cucujolide X (see Scheme 31) differs from the above-described one in that both types of isomerizations of acetylene compounds considered in this review (Scheme 32) are used at the early stages.[130] In particular, commercially available hept-3-yn-1-ol (**83**) was first converted to a terminal alcohol under the action of sodium 3-aminopropylamide (NAPA). At the next stage, the triple bond in alcohol **84** was isomerized by one carbon atom under the action of potassium *tert*-butoxide to give the desired methylacetylene **85**, from which the 14-membered pheromone cucujolide V (**86**) was synthesized.

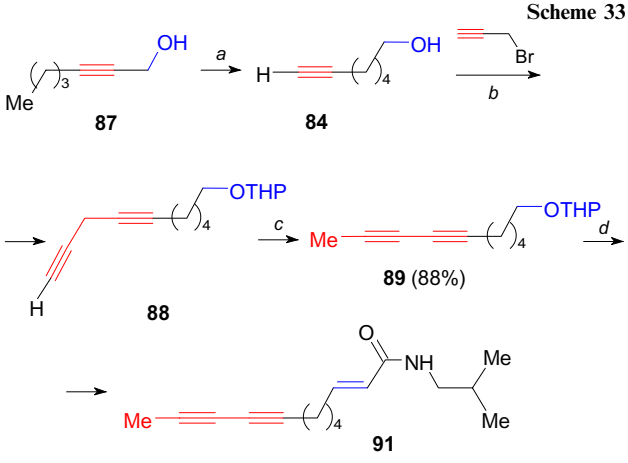
Scheme 32



(*a*) NaH, PDA; (*b*) Bu^{t}OK, DMSO, rt, 3 h

A similar synthetic scheme involving both acetylene–allene isomerization and the acetylene zipper reaction was described in the work [131] devoted to the synthesis of polyunsaturated N-alkylamides of echinacea and their analogues (Scheme 33). At one of the early stages, hept-2-yn-1-ol (**87**) was subjected to the acetylene zipper reaction

Scheme 33

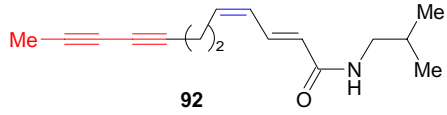


(*a*) NaH, EDA, 60 °C; (*b*) 1) DHP, TsOH (86% yield); 2) EtMgBr, CuCl (75% yield); (*c*) Bu^{t}OK, THF, DMSO, −40 °C; (*d*) 1) TsOH, MeOH (93% yield); 2) Swern oxidation; 3) Bu^{i}NHC(O)CH$_2$PPh$_3^+$Cl$^-$ (**90**), Bu^{t}OK (59% yield); DHP is 3,4-dihydropyran, THP is tetrahydropyran-2-yl

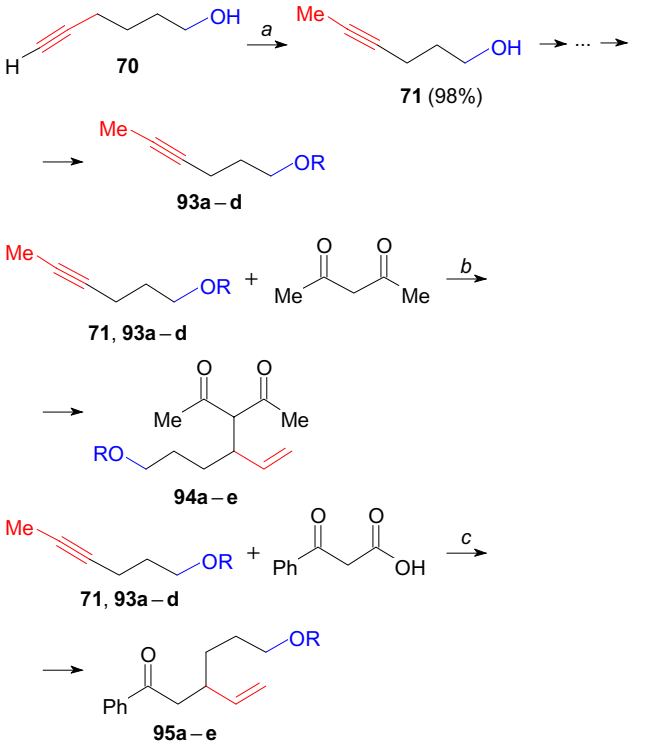
under the action of sodium 2-aminoethylamide (NAETA), and then the protected alcohol was subjected to C-alkylation with propargyl bromide to form diyne **88** with the triple bonds separated by a methylene group. The next stage involved acetylene–allene isomerization to give a conjugated methyldiacetylene moiety: for substrate **88**, the reaction was catalyzed by potassium *tert*-butoxide in a DMSO–THF mixture and gave protected alcohol **89**. The product obtained after removal of the protective group was subjected to the Swern oxidation and introduced as a carbonyl component into the Wittig alkenylation with phosphine **90**, which gave target enediyne amide **91**.

Acetylene–allene isomerization was also used to create a pentadiyne moiety in the synthesis of amide **92**.[131]

Structure 92



Scheme 34



(*a*) Bu^{t}OK, DMSO, rt; (*b*) [Rh(COD)Cl]$_2$ (5 mol.%), DPEphos (12 mol.%), Yb(OTf)$_3$ (6 mol.%), DCE, 70 °C; (*c*) [Rh(COD)Cl]$_2$ (4 mol.%), DPEphos (8 mol.%), 2-methyltetrahydrofuran (C = 0.5 mol L^{-1}), 60 °C, 24 h; TBDMS is *tert*-butyldimethylsilyl, COD 1,5-diene, DPEphos is bis(2-diphenylphosphino)phenyl ether, TfO is trifluoromethanesulfonate (triflate), DCE is 1,2-dichloroethane; **93**: R = Bn (**a**), Bz (**b**), TBDMS (**c**), Ts (**d**)

Compound **94**, **95**	R	Yield of **94** (%)	Yield of **95** (%)
a	Bn	95	90
b	Bz	90	51
c	TBDMS	76	58
d	Ts	80	85
e	H	57	53

The procedure described in Ref. 130 was used to synthesize key starting compounds — methyl-substituted acetylenic alcohol **71** and its derivatives **93a–d**, which are substrates for studying the Rh-catalyzed addition of 1,3-dicarbonyl compounds to acetylenes (mainly to methylacetylenes),[132] as well as the Rh-catalyzed coupling of β-keto acids with methylacetylenes, which occurs in tandem with decarboxylation (Scheme 34).[133] The first approach is a mild method for the synthesis of β-allyl-1,3-dicarbonyl compounds **94a–e**, not requiring the use of bases. The second reaction opens up wide possibilities for the synthesis of branched γ,δ-unsaturated ketones **95a–e**, also without the use of basic reagents.

Alkene metathesis was used for developing stereoselective synthesis of macrocycles with *E*-configuration of the endocyclic double bond.[134] To obtain the required substrates, the acetylene–allene isomerization of terminal acetylenic alcohols **96**, **97** to methylacetylenes **98**, **99** turned out to be indispensable. The subsequent reduction of methylacetylenes with lithium in liquid ammonia and Jones oxidation of the resulting *E*-alkenes led to acids **100a**,**b** containing a methyl-substituted double bond with the *E* configuration; the latter were used for the acylation of alcohols **101a–c** to give substrates **102a–c**, required for the key metathesis stage. The desired ring-closing stereoselectivity (the content of *E* isomer >98%) was achieved by using starting methyl-substituted *E*-alkenes **102a–c** and catalyst **103** (Scheme 35). Acetylene–allene isomerization has been used in synthesis of three macrocyclic structures **104–106** with the content of the *E* isomer > 99%. It is worth noting that macrolactone **104** is the natural antibiotic recifeiolide.

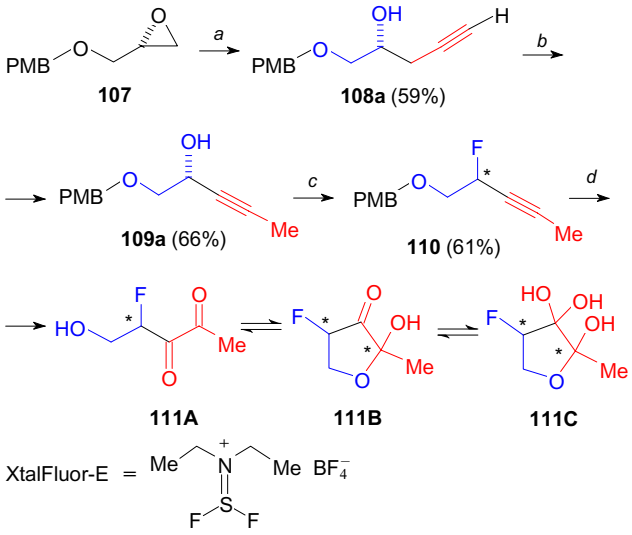
3.3.2. Chiral alcohols and their derivatives

Isomerization of acetylenic alcohols occurs, as a rule, with retention of configuration of asymmetric carbon atoms at the hydroxyl group, which is actively used in stereoselective syntheses of biologically active compounds.

Acetylene–allene isomerization was used at the early stages of synthesis of the fluorinated analogue of (*S*)-4,5-dihydroxypentane-2,3-dione [(S)-DPD] acting as a quorum sensing signalling molecule for bacterial communication.[135] To this end, oxirane **107** was converted to optically active (*R*)-pent-4-yne-1,2-diol with the protected OH group at the C(1) atom (**108a**), which was subjected to acetylene–allene isomerization. Although isomerization of the substrate to methylacetylene **109a** under common conditions — Bu^{t}OK, DMSO, room temperature — occurred, as expected, with retention of optical purity, the presence of a fluorine atom in the target product facilitated its rapid racemization; therefore, the repeated synthesis was started from racemic epoxide. At next stages, the free OH group was substituted by a fluorine atom with the use of the XtalFluor-E reagent, and the triple bond of acetylene **110** was oxidized to the corresponding diketone using the $NaIO_4$–RuO_2 system. Deprotection by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave target F-DPD (±)-(**111**), which completely inhibited bacterial growth of *Vibrio harveyi* (Scheme 36).

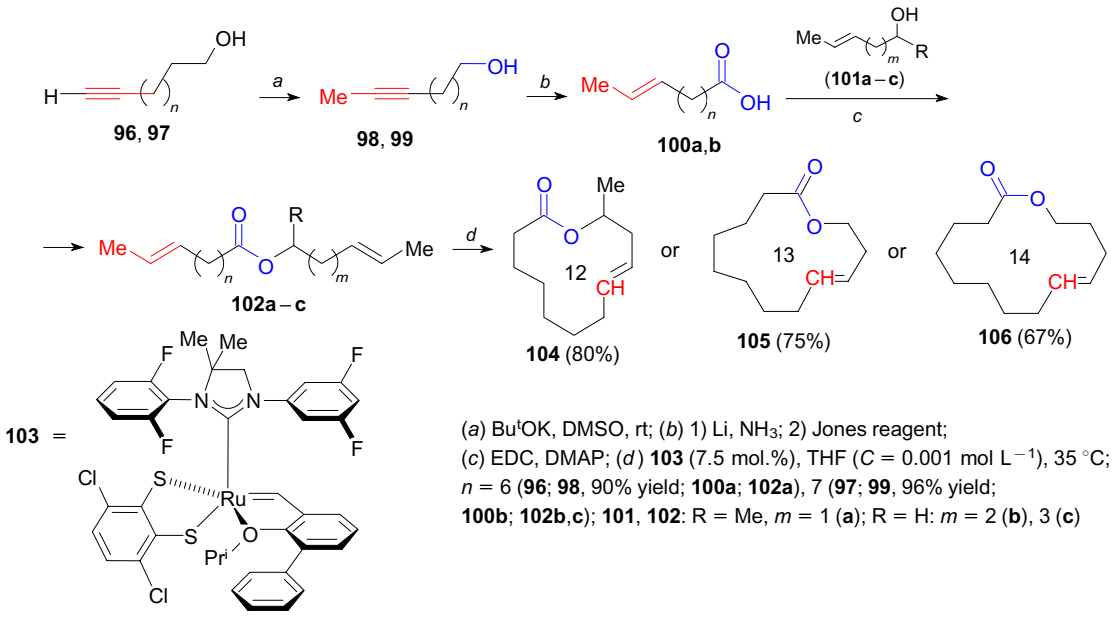
Tandem stereoselective formation of a new C–C bond through the reaction of Rh carbenoids and chiral allyl

Scheme 36



(*a*) HC≡CLi·EDA, DMSO; (*b*) Bu^{t}OK, DMSO; (*c*) XtalFluor-E, $Et_3N·HF$, Et_3N; (*d*) 1) $RuO_2·H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O (82% yield); 2) DDQ (40% yield); PMB is *p*-methoxybenzyl

Scheme 35



(*a*) Bu^{t}OK, DMSO, rt; (*b*) 1) Li, NH_3; 2) Jones reagent; (*c*) EDC, DMAP; (*d*) **103** (7.5 mol.%), THF (C = 0.001 mol L^{-1}), 35 °C; n = 6 (**96**; **98**, 90% yield; **100a**; **102a**), 7 (**97**; **99**, 96% yield; **100b**; **102b**,**c**); **101**, **102**: R = Me, m = 1 (**a**); R = H: m = 2 (**b**), 3 (**c**)

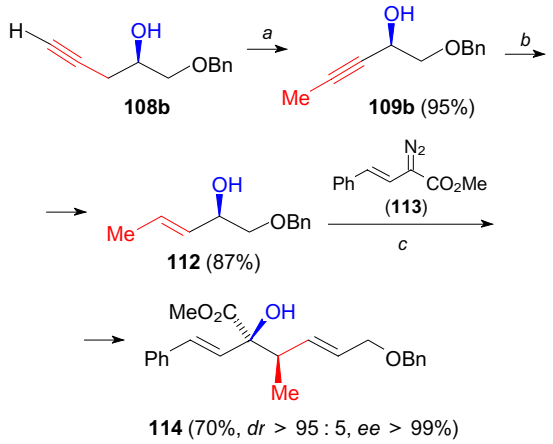
alcohols has been studied by Li, Parr and Davies.[136] The stereochemistry of catalyst ligands and the configuration of the stereo centre in allyl alcohol are essential for the stereochemical outcome. As one of the starting compounds, (*R*,*E*)-1-(benzyloxy)pent-3-en-2-ol (**112**) was used, which was synthesized by acetylene–allene isomerization of the benzyl analogue **108b** of the above-mentioned terminal alcohol with subsequent reduction of the triple bond. The reaction of alcohol **112** with benzylidenediazopropanoate **113** catalyzed by tetrakis[(*S*)-(+)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]dirhodium(II), Rh_2[(*S*)-DOSP]$_4$, afforded product **114** with high enantioselectivity (Scheme 37).

In the method suggested for synthesis of a bicyclic aldehyde, an intermediate in the proposed total synthesis of natural diterpenoid elisabethin A,[137] the early stages involved acetylene–allene isomerization of chiral alcohol **115** (Scheme 38). The resulting Me–C≡C moiety in alcohol **116** was reduced to a double bond with the *E* configuration to give compound **117**. The Mitsunobu reaction involving phenol **118** and Claisen rearrangement of ether **119** involving the former isomerized triple bond afforded the starting compound **120** for the key stage — relay ring-closing metathesis (RRCM). Ring closing in compound **120** afforded a 1.4 : 1 mixture of diastereomers **121** and **122** (in a total yield of 85%), which was separated, and the isolated *trans* isomer was converted to the target bicyclic aldehyde **123**.

Farcet *et al.*[138] described an approach to the total synthesis of diterpene bielschowskysin, which is probably the most complex natural product of the furanocembranoid group. This is one of a few works where acetylene–allene isomerization was applied to intermediate **124** with a complex structure rather than at the beginning of the synthetic path. Despite a large number of stereo centres and functional groups, the reaction proceeded smoothly and chemoselectively to give isomerization product **125** in high yield (Scheme 39). The subsequent reduction of the triple bond with simultaneous introduction of a iodine atom, the Nozaki–Hiyama–Kishi reaction of iodide **126** and aldehyde **127** and the oxidation of the newly formed OH group in compound **128** to a carbonyl group with simultaneous formation of a cyclic hemiacetal gave the target synthetic intermediate **129** as a mixture of anomers (5 : 1) — an essential substrate for the further synthesis of bielschowskysin.

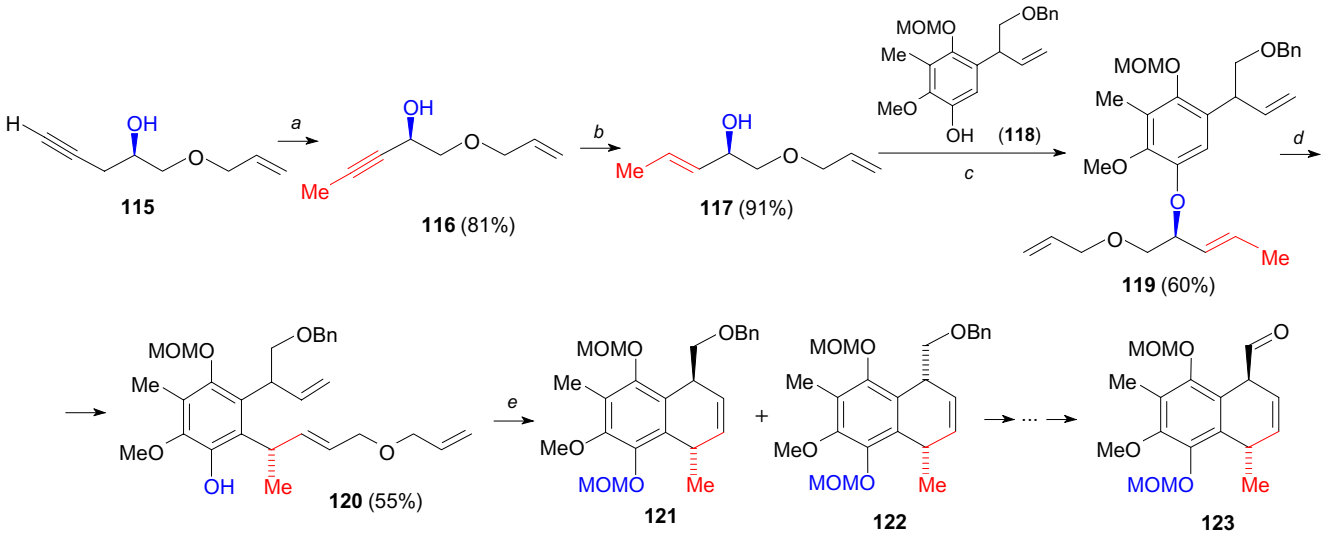
The isomerization of penta-1,4-diyne derivatives is a key step in the synthesis of methyldiacetylene compounds containing both aryl and hydroxyalkyl substituents (Scheme 40).[139] The resulting methylacetylenes were used as substrates in alkyne metathesis. Initially, the authors assumed that the metathesis of methyldiacetylenes with the participation of the tungsten carbyne complex **130** should give the corresponding triacetylene. It turned out that the reaction proceeded in high yields and led to the formation of dimethyldiacetylene (DMDA), which could be efficiently adsorbed by molecular sieves 5 Å to shift the metathesis equilibrium towards the reaction products. It was demonstrated that this reaction can be carried out either intra- or intermolecularly for substrates **131**, **132**, respectively to

Scheme 37



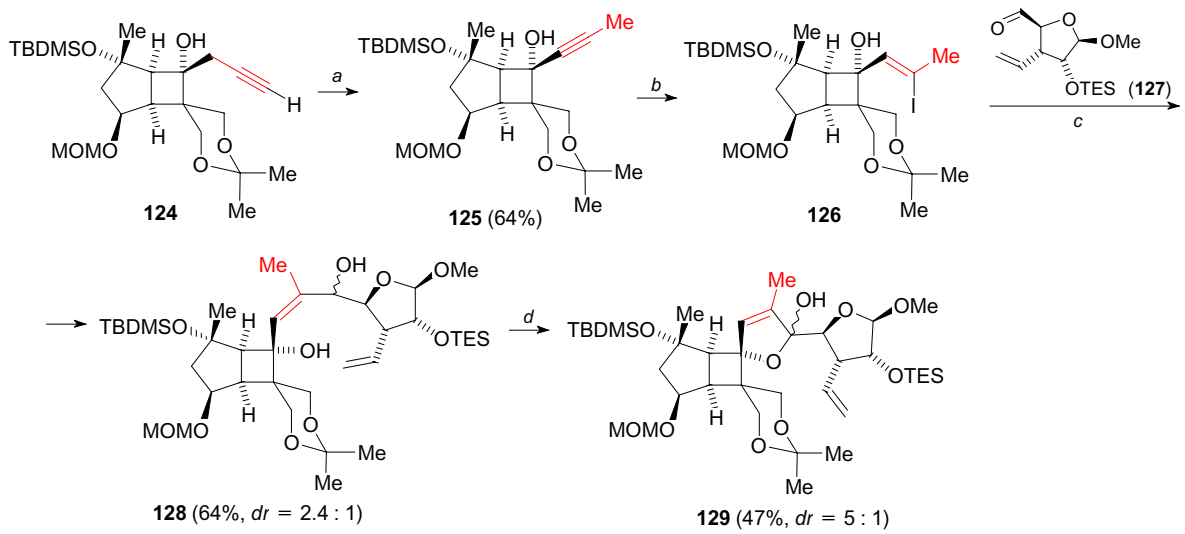
(*a*) Bu^{t}OK, DMSO; (*b*) LAH; (*c*) Rh_2[(*S*)-DOSP]$_4$ (1 mol.%), pentane, 0 °C; LAH is lithium aluminium hydride, *dr* is diastereomeric ratio

Scheme 38



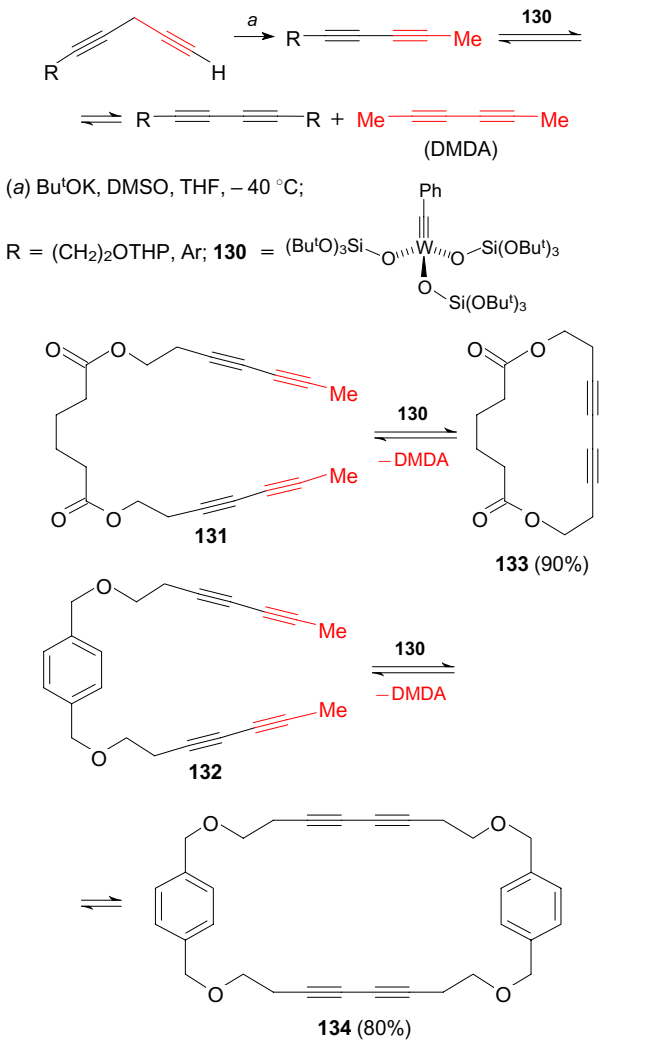
(*a*) Bu^{t}OK, DMSO, rt; (*b*) LAH, THF; (*c*) ADDP, PBu$^n_3$; (*d*) Eu(fod)$_3$; (*e*) 1) Grubbs II catalyst (4 mol.%), 2) Bu^{n}Li, MOMCl; 3) separation; Eu(fod)$_3$ is europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate), ADDP is 1,1′-(azodicarbonyl)dipiperidine, MOM is methoxymethyl

Scheme 39



(*a*) Bu^{t}OK, DMSO, rt; (*b*) 1) LAH, MeONa; 2) I_2, THF; (*c*) $CrCl_2$ – $NiCl_2$ (3 equiv.), DMSO; (*d*) Swern oxidation

Scheme 40



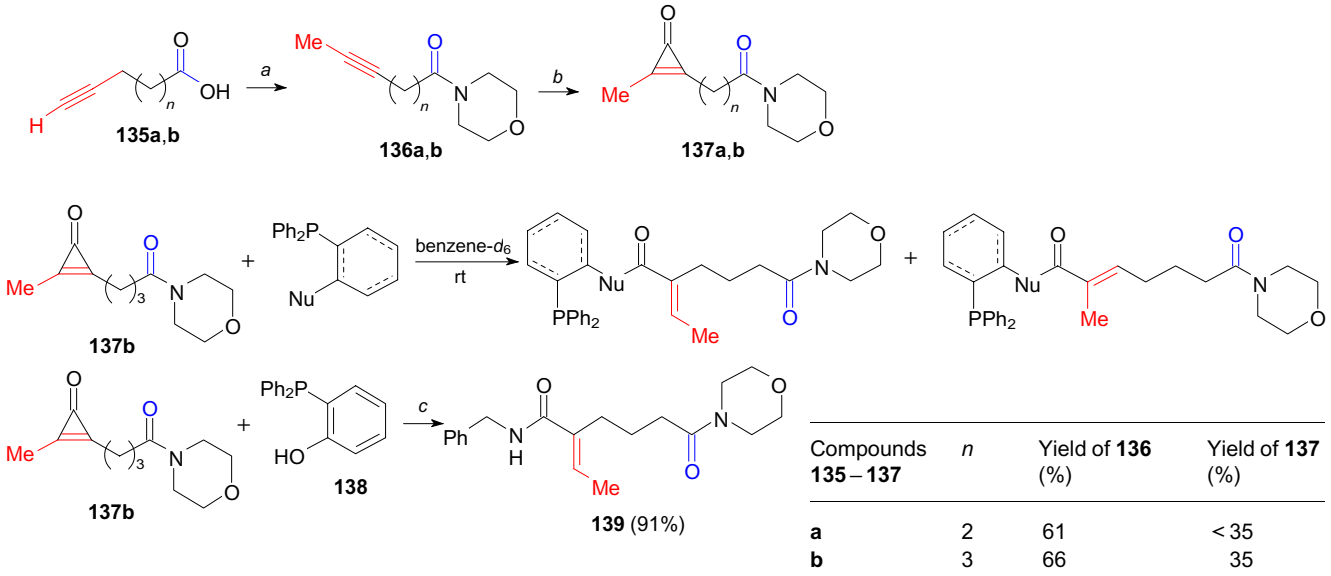
obtain macrocycles **133** and **134** with a conjugated diacetylene system (see Scheme 40).

3.4. Isomerization of acetylene carboxylic acid derivatives

Row *et al.*[140] have reported cyclopropenones with improved stability that maintain robust reactivity with nucleophilic agents as potential new click reagents for bioorthogonal reactions. Methylcyclopropenones were recommended by the authors for this purpose (Scheme 41). First, acetylene – allene isomerization of acetylenic acids **135a**,**b** was used to obtain methylacetylenic amides **136a**,**b**. The isomerization of the acids occurred at higher temperature than in the case of acetylenic alcohols. Then, compounds **136a**,**b** were converted to methylcyclopropenones **137a**,**b**. The model compound **137b** allowed one to select conditions for using the methylcyclopropenone ring as a new functional group for accomplishing click reactions in living systems. In particular, disubstituted methylcyclopropenones turned out to be significantly more stable than monosubstituted analogues and, at the same time, were prone to undergo ring opening under the action of aromatic and aliphatic O-, N- and S-nucleophiles. Applying 2-(diphenylphosphanyl)phenol (**138**) as a nucleophilic agent afforded tandem transformations — cyclopropenone ring opening and Staudinger ligation — to form product **139**. In addition, it was demonstrated that cyclopropenone modified with lysine residue can be used for recombinant protein production. Thus, a new type of stable cyclopropenones, which can be easily obtained from acetylene precursors, opens the way to the development of new tandem bioorthogonal transformations for fluorescent labelling.

Isomerization of acid **135b** (Scheme 42) led to acid **140b**, which was converted to important substrates (for example, compounds **141**, **142**) for studying copper-catalyzed carboboration of internal acetylenic compounds containing substituents with different steric demands.[141] A copper complex with a cyclic diaminocarbene ligand fused with a naphthoquinone moiety, ^{NQ}IMesCuCl, was suggested as an optimal catalyst. The reaction of alkynes **141** and **142** with bis(pinacolato)diboron, $(Bpin)_2$, and alkyl iodides in the presence of potassium *tert*-butoxide and the copper catalyst in DMF at room temperature was highly regio- and stereoselective to give carboboration products (for example, compounds **143**, **144**) in moderate to high yield (a major regioisomer is shown for products **143**, **144**).

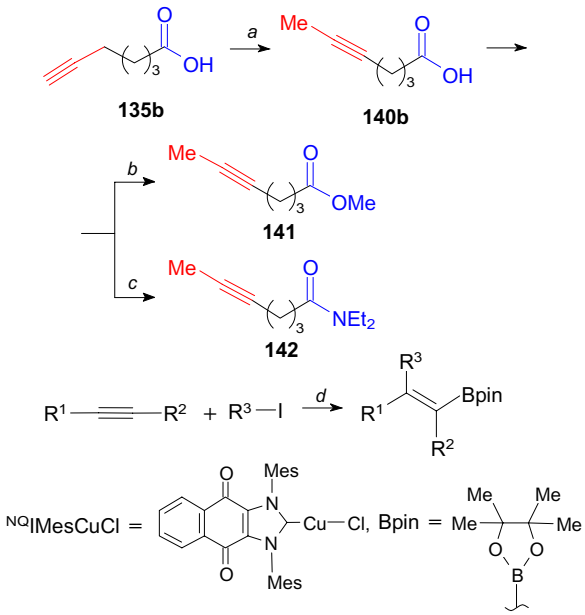
Scheme 41



Compounds **135–137**	*n*	Yield of **136** (%)	Yield of **137** (%)
a	2	61	< 35
b	3	66	35

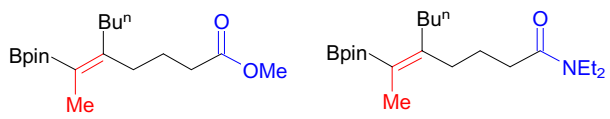
(*a*) 1) Bu^{t}OK, DMSO, 75 °C ; 2) EDC, morpholine, CH_2Cl_2, rt; (*b*) 1) $TMSCF_3$, NaI, THF, rt; 2) H_2O;
(*c*) 1) benzene-d_6, rt; 2) BnN_3, DMF – H_2O (95 : 5), rt; Nu is nucleophile

Scheme 42



(*a*) Bu^{t}OK, DMSO, 75 °C; (*b*) MeI, K_2CO_3, DMF, rt, 27 h;
(*c*) Et_2NH, EDC, DMAP, CH_2Cl_2, rt, 27 h; (*d*) ^{NQ}IMesCuCl (10 mol.%), $(Bpin)_2$, Bu^{t}OK, DMF, rt, 4 h; Mes is mesityl (2,4,6-trimethylphenyl)

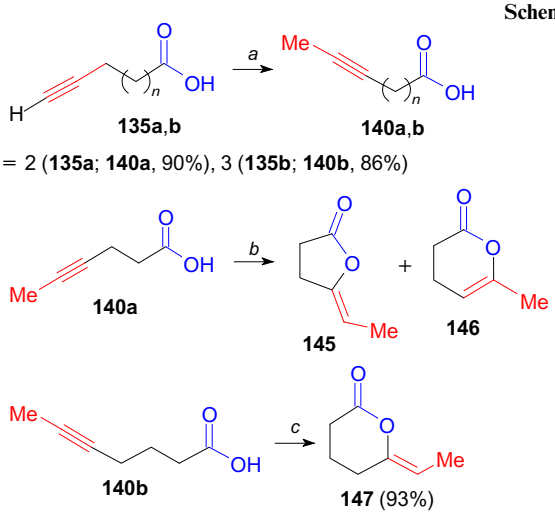
Structures 143, 144



143 (79%, *Z* : *E* = 10 : 1) **144** (89%, *Z* : *E* = 9.1 : 1)

A mild method of gold-catalyzed intramolecular cyclization of acetylenic carboxylic acids to give γ-, δ- and ε-lactones was reported.[142] The reaction regioselectivity (the *exo*-to-*endo* ratio) was mainly affected by the substrate nature. Acids **140a**,**b** containing a methylethynyl moiety were used as substrates. They were synthesized through isomerization of the corresponding terminal acetylenic acids **135a**,**b**. It is worth noting that, in contrast to the above examples, the isomerization occurred at room temperature, rather than on heating, and gave desired products **140a**,**b** in high yield (Scheme 43). The latter were converted to lactones **145** and **146** (in the 7 : 1 ratio and overall yield of 94%), as well as to δ-lactone **147**.

Scheme 43

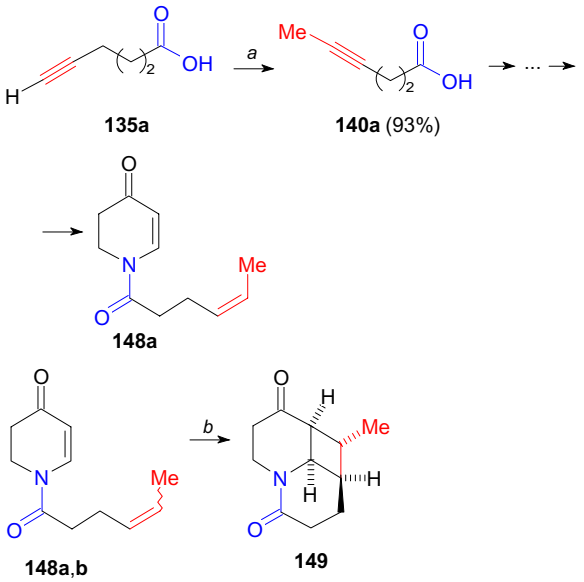


(*a*) Bu^{t}OK, DMSO, rt; (*b*) $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$ (0.1 mol.%), rt, 5 min; (*c*) $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$ (0.1 mol.%), 65 °C, 10 min

Intramolecular [2 + 2] photocycloaddition in the presence of a chiral Lewis acid as a catalyst was studied by Brimioulle *et al.*[143] Substrates for this transformation were (*Z*)- and (*E*)-alkenoyldihydropyridones **148a**,**b**. *Z* isomer **148a** was synthesized by acylation of dihydropyridone with

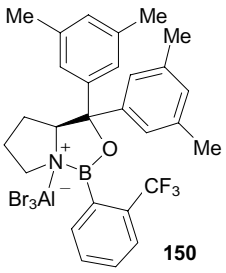
(*Z*)-hex-4-enoic acid; the synthesis of the latter began with acetylene–allene isomerization of hex-5-ynoic acid (**135a**) under rather uncommon severe conditions (aqueous KOH solution, 170 °C) followed by hydrogenation of isomerization product **140a** on the Lindlar catalyst (Scheme 44). The cycloaddition of both isomers occurred diastereoselectively with the predominant formation of *trans*-diastereomer **149**, either in the presence of catalyst **150** (for 20 h) or without the catalyst (for 1.5 h). At the same time, the catalyzed reaction of the *Z* substrate gave mainly one enantiomer, and its structure is shown in Scheme 44. The reasons for the observed stereoselectivity are discussed in the cited work.

Scheme 44



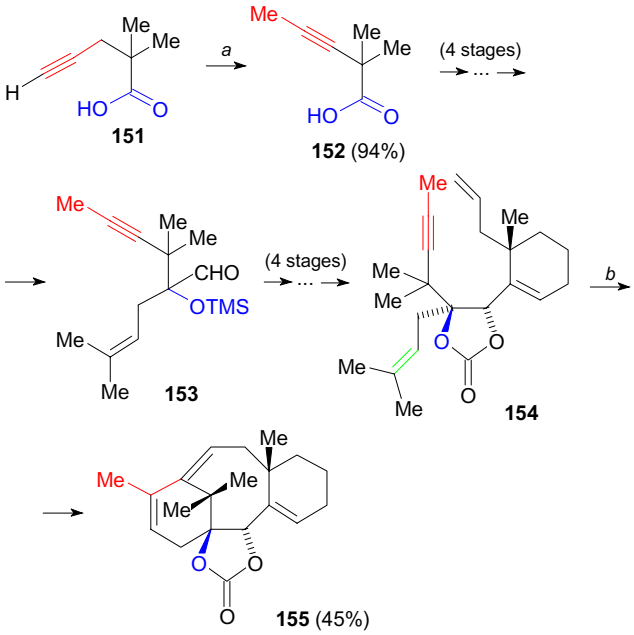
(*a*) KOH, H_2O, 170 °C; (*b*) *hν* (λ = 366 nm), CH_2Cl_2, −70 °C

Structure 150



An original method of synthesis of the tricyclic taxol core was reported.[144, 145] To form a tricyclic system, ring-closing dienyne metathesis (RCDEYM) was used. One of the key reagents in this synthesis is 2,2-dimethyl-4-pentynoic acid (**151**); its isomerization in DMSO is induced by potassium *tert*-butoxide on heating and gives 2,2-dimethyl-3-pentynoic acid (**152**). The triple bond remains intact during further transformations (see, *e.g.*, structures of compounds **153**, **154**) up to the metathesis stage, while the carboxyl group is a key structural moiety for the preparation of two substrates for the final stage, which differ in steric loading of the highlighted double bond. For the substrate with higher steric demands **154**, the intended RCDEYM process was realized to give the target product **155** (Scheme 45).

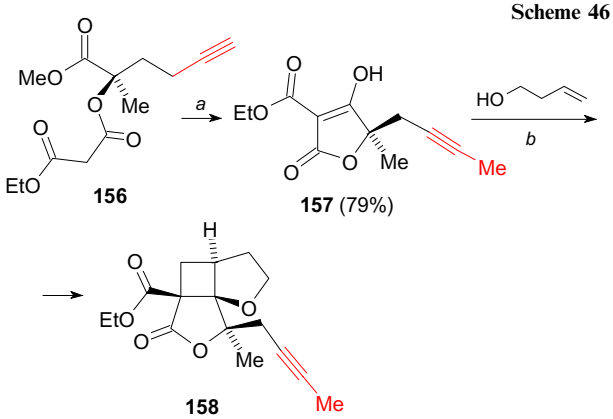
Scheme 45



(*a*) Bu^{t}OK, DMSO, 75 °C; (*b*) 1) Grubbs II catalyst (10 mol.%), PhMe, 110 °C, 24 h

Weixler and Bach [146] synthesized cembranoid diterpenes through intramolecular [2 + 2] photocycloaddition in a series of tetronic acid derivatives. The synthesis of one of the initial substrates for this reaction containing the methylethynyl moiety also involved acetylene–allene isomerization (Scheme 46).

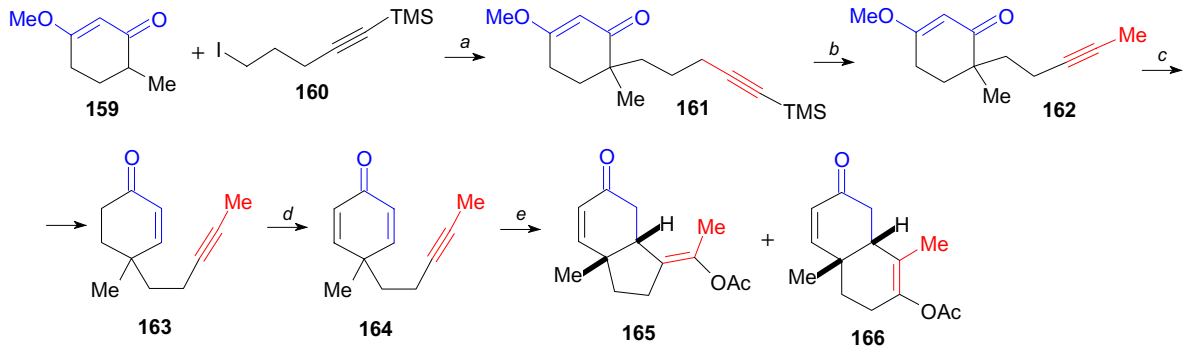
Scheme 46



(*a*) 1) Bu^{t}OK, DMF, 0 °C; 2) NaOH, Et_2O, rt;
(*b*) 1) Mitsunobu reaction (51% yield); 2) [2 + 2] cycloaddition, *hν* (λ = 254 nm) (72% yield)

In particular, the isomerization of polyfunctional ester **156** occurred in tandem with the Dieckmann condensation under the action of potassium *tert*-butoxide in DMF followed by treatment with the NaOH–Et_2O system for the complete transformation of the terminal triple bond to the internal one, which led to the tetronic acid derivative with a methylethynyl moiety **157** in high yield. Then, a homoallyl fragment necessary for cycloaddition was introduced by the Mitsunobu reaction. The key reaction for the resulting substrate was smooth, did not affect the triple bond and

Scheme 47



(*a*) LDA, THF, −78 °C; (*b*) 1) K_2CO_3, MeOH (91% yield); 2) Bu^{t}OK, DMSO (84% yield); (*c*) 1) DIBAL-H, THF, −78–20 °C; 2) 10% HCl (aq.); (*d*) DDQ, TsOH, dioxane, Δ; (*e*) $Pd(OAc)_2$ (5 mol.%), bipy (10 mol.%), AcOH, 80 °C; LDA is lithium diisopropylamide, bipy is 2,2′-bipyridine, DIBAL-H is diisobutylaluminum hydride

gave the tricyclic product of [2 + 2] addition **158** with high regio- and stereoselectivity.

3.5. Isomerization of acetylene ketones

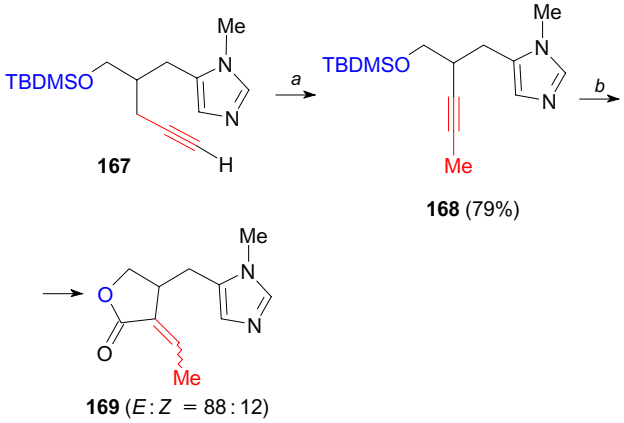
Pd-catalyzed cyclization of cyclohexa-2,5-dien-1-ones containing ethynylalkyl substituents at the C(4) atom has been studied.[147] In the synthesis of one of the substrates at the initial stage, acetylene–allene isomerization was used. This example illustrates that isomerization can occur in a series of non-enolizable methyl ethers of 1,3-dicarbonyl enols. Compounds **159** and **160** served as substrates for the synthesis of the starting compound for isomerization, and the obtained ether **161** was isomerized to give **162** under the action of Bu^{t}OK in DMSO after preliminary removal of the TMS group. Compound **162** was first converted to enone **163** and then to dienone **164**. Carbocyclization of compound **164** using palladium acetate and bipyridine as a ligand led to a mixture of products of exo- (**165**) and endocyclization (**166**) in a ratio of 1.9 : 1 (and 67% total yield), which was due to the regioselectivity of the addition of Pd to the triple bond at the first stage of the process (Scheme 47).

3.6. Isomerization of acetylenic N-heterocycles, amines and amides

Davies *et al.*[148, 149] have described the synthesis of pilocarpine alkaloids. One of the approaches ruled out stereoselective synthesis, but generated the desired molecular core. At the initial stage of acetylene–allene isomerization of the imidazole derivative **167**, the methylethynyl moiety was formed in compound **168**, which was further subjected to Pd-catalyzed carbonylation simultaneously with the formation of lactone **169**. Despite the good yield of the product at the stage of acetylene–allene isomerization, carbonylation occurred in a low yield (10%), which was the reason for the development of an alternative synthetic route (Scheme 48).

In synthesis of *N*-arenesulfonamido-*N*′-arylpiperazines, which are cytosolic glucokinase inhibitors due to their ability to bind to glucokinase regulatory protein, one of the first stages involved acetylene–allene isomerization of propynylpiperazine **170** to methylacetylene **171** occurring under very mild conditions upon treatment of the substrate with potassium *tert*-butoxide in THF at room temperature.[150, 151] Then, to synthesize a library of compounds, the Buchwald–Hartwig N-arylation followed by benzyl

Scheme 48



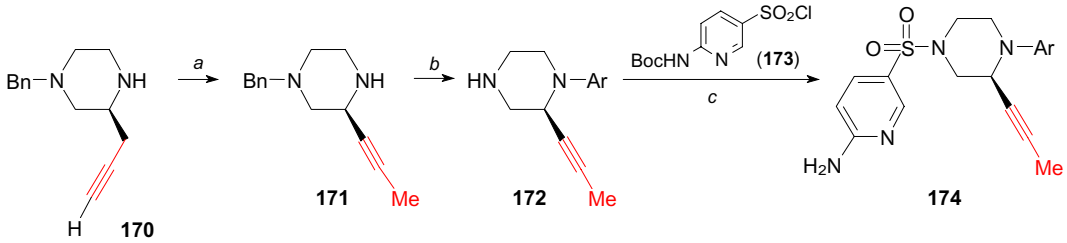
(*a*) Bu^{t}OK, Bu^{t}OH, 82 °C, 24 h; (*b*) 1) HF, MeCN; then HCl (92% yield); 2) CO, $PdCl_2(PPh_3)_2$, $SnCl_2$, DMF, 110 °C (10% yield)

protective group cleavage were carried out. This procedure afforded a series of *N*-arylpiperazines **172**, which were coupled with *N*-Boc-2-aminopyridine-3-sulfonyl chloride (**173**) and, after removal of the Boc protective group, gave target piperazines **174** (Scheme 49).

High-yield isomerization of the triple bond from the terminal position to the internal one for *N*-arylamide **175** was described.[152] The resulting isomerized amide **176** was used, along with a series of other amides and ureas, in two-stage tandem hydroamidation–Pd-catalyzed cyclization to give indole. It turned out that, in contrast to acetylenic amides with a terminal triple bond and aryl-substituted triple bond, substrate **176** with a methylacetylene moiety did not enter into these transformations and formed neither the amidation product **177** nor the corresponding indole **178** (Scheme 50). Thus, this is an example of a limitation of the proposed method.

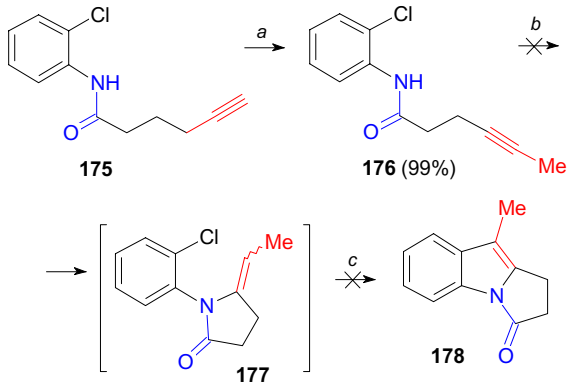
Isomerization of *N*-arylamide **179** to methylacetylene **180** was also used for producing, for example, compound **181** in the development of a universal approach to the synthesis of indolines (**183**) and tetrahydroquinolines (**184**) from acetylenic amines and 1,3-diketones catalyzed by potassium tetrachloroplatinate.[153] Isomerization proceeded smoothly at room temperature under standard conditions (DMSO–potassium *tert*-butoxide) (Scheme 51).

Scheme 49



(*a*) Bu^{t}OK, THF, rt; (*b*) 1) Buchwald – Hartwig reaction; 2) 1-chloroethyl chloroformate, K_2CO_3; (*c*) 1) DIPEA; 2) TFA; DIPEA is diisopropylethylamine, Boc is *tert*-butoxycarbonyl

Scheme 50



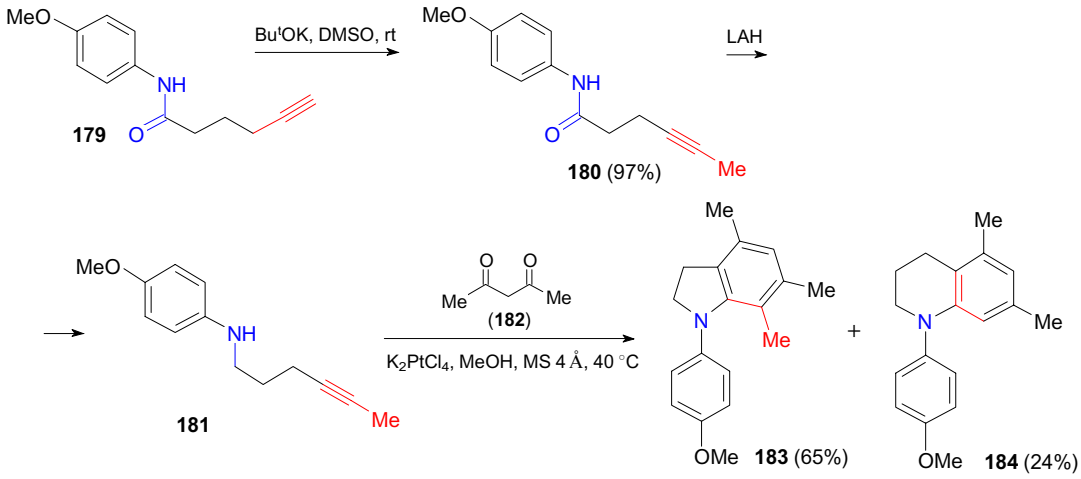
(*a*) Bu^{t}OK, DMSO, rt; (*b*) K_2CO_3 (5 equiv.), NMP, 180 °C, 3 h; (*c*) $Pd(OAc)_2$ (5 mol.%), DTBPF (10 mol.%); NMP is *N*-methylpyrrolidone, DTBPF is 1,1′-bis(di-*tert*-butylphosphino)ferrocene

Thus, acetylene – allene isomerization is a convenient and sometimes indispensable method for producing methylacetylenes and is used in various fields of modern organic synthesis. Of special note are the preparation of substrates for various metathesis variants, the isomerization of chiral alcohols, which is often used at the initial stages of the synthesis of natural molecules, as well as the targeted synthesis of methylacetylenes with various functional groups for studying new types of cyclization of alkynes. It is essential that, in most cases, regardless of the nature of the functional group in terminal alkynes, the optimal conditions for acetylene – allene isomerization are provided by the superbasic potassium *tert*-butoxide – DMSO system. In the synthesis of the initial terminal acetylenes, the acetylene zipper reaction can be used; this reaction, in combination with the subsequent isomerization of terminal alkynes to methylacetylenes, is carried out as a tandem process.

4. The use of the acetylene zipper reaction in synthesis of terminal acetylenes

Since its discovery, the acetylene zipper reaction has been a convenient synthetic tool in organic chemistry for the preparation of molecules containing long polymethylene chains. This reaction proceeds under fairly mild conditions with high yields of products, while the terminal triple bond can then be transformed to various functional groups, selectively reduced, or used to create a new carbon – carbon bond. It should also be noted that, in contrast to the acetylene – allene isomerization of terminal acetylenes to methyl-substituted acetylenes, the multipositional isomerization of functionalized internal alkynes to terminal isomers turned out to be applicable only to hydrocarbons and alcohols. The acetylene zipper reaction involving acetylene alcohols has become the most popular in organic synthesis, since in this case it affords α,ω-bifunctional compounds. Due to the retention of configuration of asymmetric carbon atoms upon isomerization, this transformation is actively used in stereoselective syntheses of natural compounds, which was the subject of consideration of the aforementioned review.[83] It is important that alk-2-yn-1-ols, the most commonly used starting compounds for the acetylene zipper reaction, can be easily synthesized by alkylation of an O-protected propargyl alcohol. The starting internal acetylene alcohols of the second type, alk-3-yn-1-ols, are produced either by a similar reaction from but-2-yn-1-ol or

Scheme 51



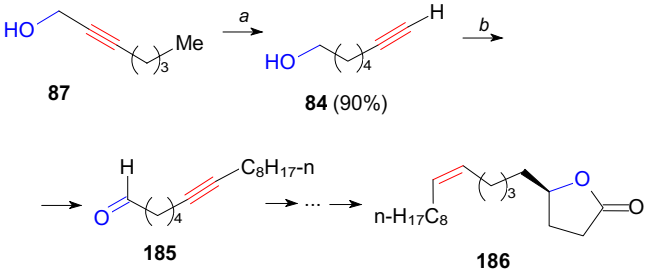
(more often) by oxirane ring opening with the corresponding acetylides.

4.1. Isomerization of acetylenic alcohols

4.1.1. Achiral alcohols

At one of the initial stages of the synthesis of the currant stem girdler pheromone, belonging to the class of butyrolactones, the acetylene zipper reaction involving hept-2-yn-1-ol (**87**) was used.[154] Treatment with LAPA, synthesized from lithium in propane-1,3-diamine in the presence of potassium *tert*-butoxide, gives hept-6-yn-1-ol (**84**). This system of bases for carrying out the acetylene zipper reaction was first proposed by Abrams and Shaw.[118] Probably the true base in this system is KAPA, but in the future, when discussing similar basic systems, we will indicate the reagents used for their preparation and specified by the authors in the reaction schemes. Further selective C-alkylation of acetylenic alcohol with octyl bromide and the Swern oxidation yielded key intermediate aldehyde **185**, which was ultimately converted to the desired chiral butyrolactone **186** (Scheme 52).

Scheme 52

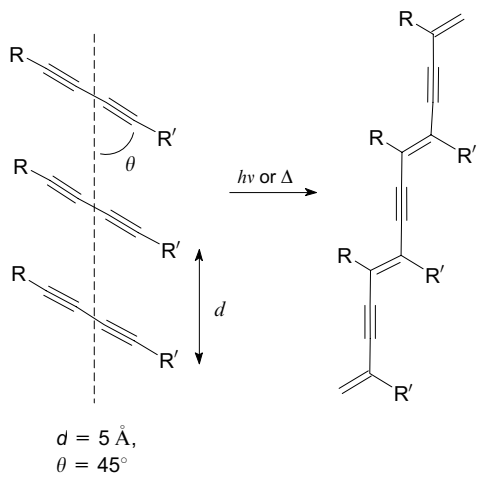


(*a*) Li, Bu^{t}OK, PDA, rt; (*b*) 1) Bu^{n}Li (1.5 equiv.), n-C_8H_{17}Br (95% yield); 2) $(COCl)_2$, Et_3N, DMSO (95% yield)

An important field of using conjugated diacetylenes is due to the possibility of involving them in solid-state topochemical photopolymerization (Scheme 53).[155–159] Of particular interest are amphiphilic diacetylene monomers capable of forming micelles and films on the interface. In the synthesis of such compounds, the acetylene zipper reaction is often used.

Properties of products of topochemical photopolymerization of butadiynes containing amide groups and methylene chains as linkers between butadiyne and tris(dodecyloxy)phenyl moieties were studied.[160] To obtain methylene chains of necessary length, the acetylene zipper

Scheme 53



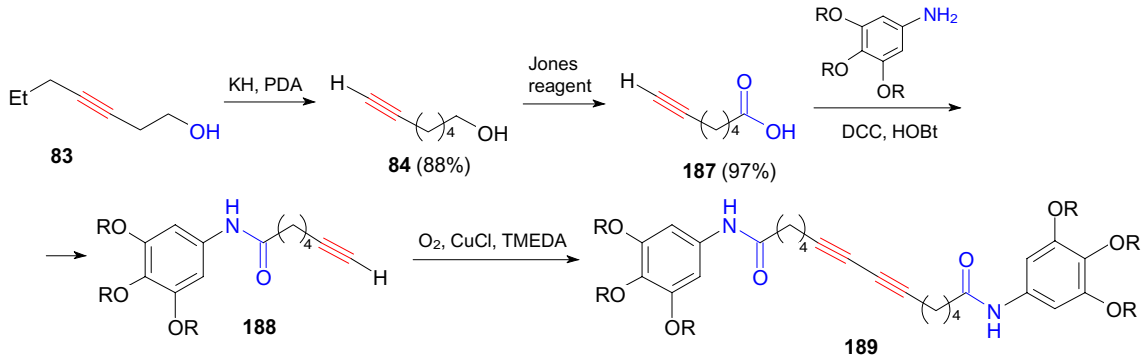
reaction of hept-3-yn-1-ol (**83**) under the action of KAPA followed by oxidation of the primary alcohol group to hept-6-ynoic acid **187** was used (Scheme 54). The latter was transformed to amide **188** and its dimer **189**.

The scope of tandem processes — the Nicholas and Pauson–Khand cyclizations — for the synthesis of oxa- and azapolycyclic molecules has been studied by Closser *et al.*[161] Hept-3-yn-1-ol (**83**) and its homologue **190** were used to synthesize hept-6-yn-1-ol (**84**) and oct-7-yn-1-ol (**191**), respectively, which were further converted to $Co_2(CO)_6$ complexes intended for tandem cyclization. Both alcohols were isomerized by treatment with NAETA obtained from ethane-1,2-diamine and sodium hydride. Subsequent introduction of the THP protective group, the Iotsich reaction with pent-4-enal, O-methylation, removal of the THP group and complexation with $Co_2(CO)_8$ led to the target Co complexes **192a**,**b** (Scheme 55). This combination of structural fragments revealed the limitation of the proposed method: the target [5.9.5]-tricyclic ether **193** was formed in low yield (19%–27%) at both stages (in the Nicholas and the Pauson–Khand reactions), but with high diastereoselectivity at the stage of the Pauson–Khand reaction — the *trans* isomer **193** was the major one.

An attempt to synthesize the homologue of compound **193** — [5.10.5]-tricyclic ether — failed because of the formation of 20-membered dimer **194** (rather than a 10-membered ether) in the Nicholas reaction stage.

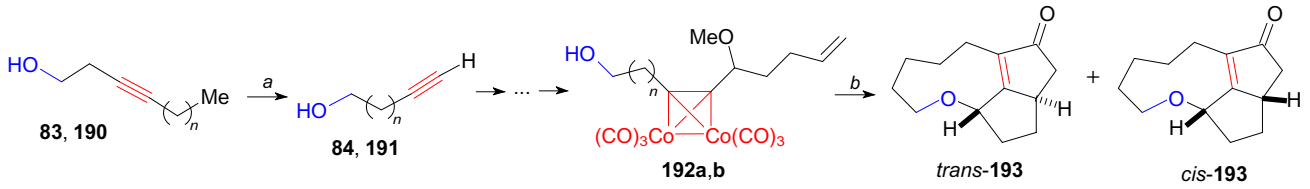
Terminal hept-6-yn-1-ol (**84**) obtained from hept-3-yn-1-ol (**83**) was used to synthesize the corresponding aldehyde **195** by carbonylation of a PMB-protected alcohol.[162] The

Scheme 54



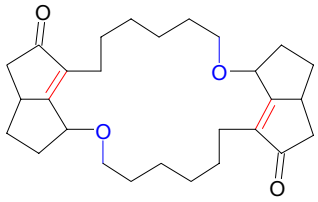
DCC is dicyclohexylcarbodiimide, HOBt is 1-hydroxybenzotriazole, TMEDA is *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

Scheme 55



(*a*) NaH, EDA, rt; (*b*) 1) Nicholas reaction; 2) Pauson–Khand reaction; *n* = 2 (**83**), 3 (**190**), 4 (**84**, 64%; **192a**), 5 (**191**, 59%; **192b**)

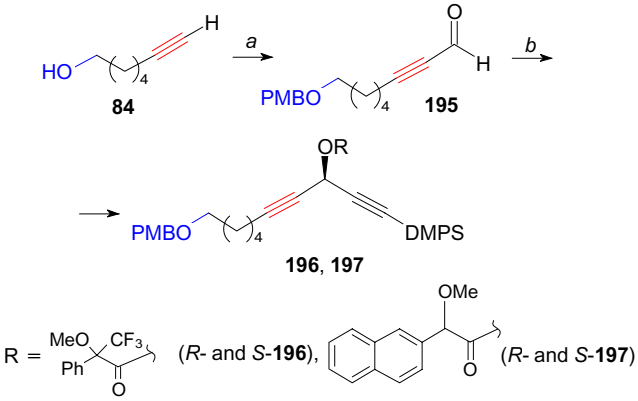
Structure 194



194

latter was necessary to obtain model Mosher's esters (**196**), as well as α-methoxy-2-naphthylacetic acid esters **197** in order to establish the absolute configuration of petrocortyne A, the natural acetylene compound produced by sea sponges (Scheme 56).

Scheme 56

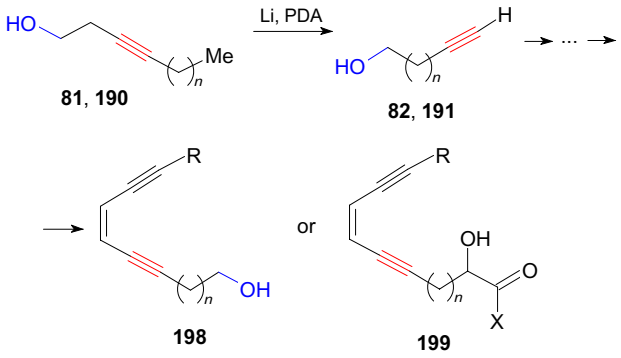


(*a*) 1) PMBCl, NaH, TBAI (92% yield); 2) Bu^{n}Li, DMF (88% yield); (*b*) 1) DMPSC≡CH, Et_2Zn, BINOL, $Ti(OPr^i)_4$ (92% yield); 2) chromatography (HPLC); 3) MTPA-Cl or 2-NMA-OH, DCC, DMAP; TBAI is tetra-n-butylammonium iodide, BINOL is 1,1′-bi-(2-naphthol), DMPS is dimethylphenylsilyl, HPLC is high performance liquid chromatography, MTPA is α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid), 2-NMA-OH is α-methoxy-2-naphthylacetic acid

The NAETA-controlled acetylene zipper reaction of hept-3-yn-1-ol (**83**) was used to produce 4-oxonon-2-en-8-ynal, which acts as an ethynyl-containing analogue of endogenic electrophile 4-oxonon-2-enal (4-ONE), a product of lipid peroxidation.[163] The NAETA-controlled isomerization of oct-3-yn-1-ol (**190**) was also used in synthesis of polyacetylene callyspongynic acid. The latter was utilized for elucidating potential protein targets of polyacetylene natural products:[164] for producing a silyl analogue of oleoylethanolamide (OEA), a peroxisome proliferator-activated receptor alfa (PPARα),[165] as well as in synthesis of fluorinated enigmol analogues with enhanced antitumour activity.[166]

Isomerization of both alcohols — hept-3-yn-1-ol (**83**) and oct-3-yn-1-ol (**190**) — under the action of LAPA afforded somewhat lower yields; however, scale-up of this process to >10 g made it possible to isolate terminal acetylenes **82**, **191** in preparative (gram) amounts.[167] It should be noted that terminal alcohols were purified by a classical method, through the formation of corresponding silver acetylenides. Terminal acetylenic alcohols **82**, **191** were used in synthesis of acyclic enediyne compounds **198**, **199**, exhibiting high antibacterial activity (Scheme 57).

Scheme 57



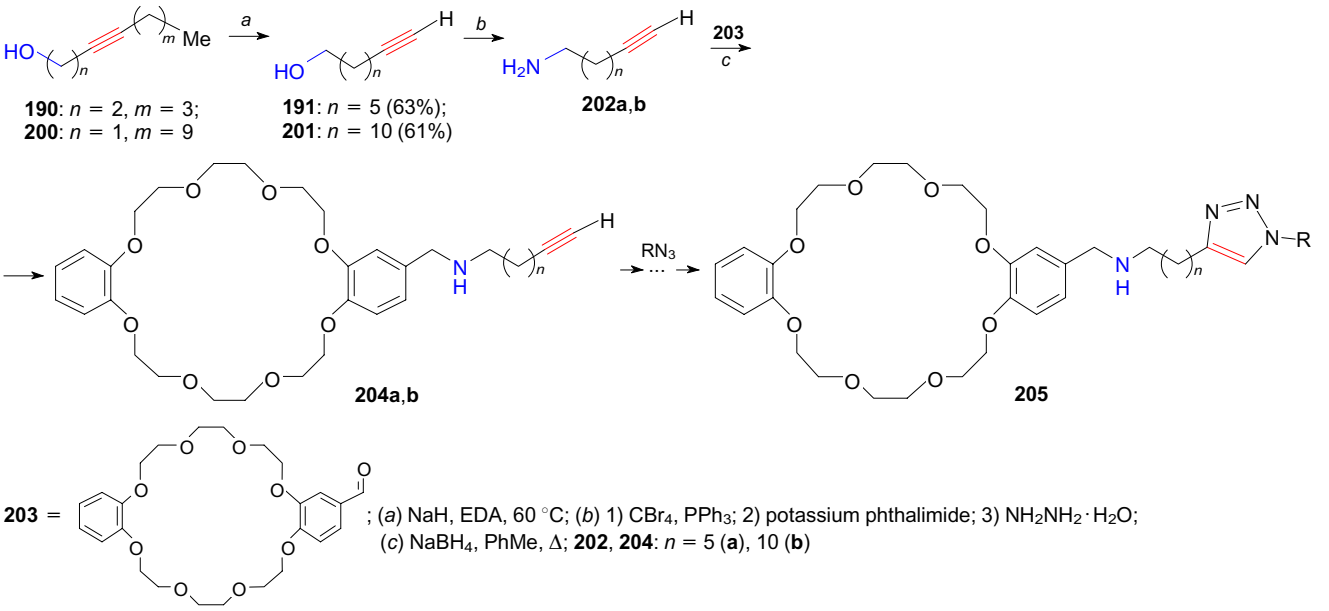
n = 2 (**81**), 3 (**190**), 4 (**82**, 48%), 5 (**191**, 48%); R = 2-Fu, Pr^n, Bu^n; X = OH, OAc, NHBn; Fu is furyl

Isomerization of oct-3-yn-1-ol (**190**) to a terminal acetylide under the action of NAETA, prepared from sodium hydride and EDA, gave terminal acetylene **191** in moderate yield.[168] Under similar conditions, tridec-2-yn-1-ol (**200**) converted to tridec-12-yn-1-ol (**201**).[169] Amino derivatives of these terminal acetylenes have interesting applications: compounds **202a**,**b** were used in the reaction with dibenzo-24-crown-8 (**203**) affording macrocyclic crown ethers **204a**,**b** modified by alkylamino groups. The subsequent click reaction of these macromolecules with azides allowed functionalized crown ethers **205** to be synthesized. Compounds **205** differing in the length of the spacer between the nitrogen atom and the triazole ring (6 or 11 carbon atoms) were conceived for design of molecular machines (Scheme 58).

Isomerization of oct-3-yn-1-ol, non-2-yn-1-ol, and dec-2-yn-1-ol under the same conditions was used to synthesize a library of nicotinamide phosphoribosyltransferase inhibitors based on 1,2,3-triazole rings.[170]

Under the action of lithium 2-aminopropylamide (LAETA) in the presence of potassium *tert*-butoxide, oct-3-yn-1-ol (**190**) isomerized at room temperature in 3 h, the yield of the terminal acetylenic alcohol **191** was 65%.[171] Then, the isomerization product was used in the synthesis of

Scheme 58



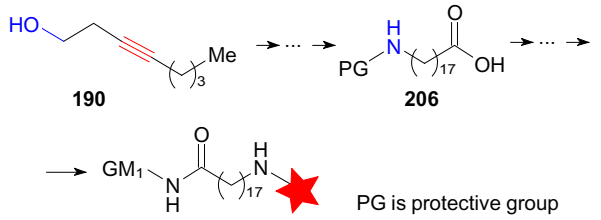
(*S*)-(oct-7-yn-1-yl)-2,2,2-trifluoroethanethioate required for studying the reactivity of the triple bond in the hydrosilylation reaction that occurs upon the formation of monolayers with the hydrogenized silicon (100) surface.

Polyakova *et al.*[172] carried out the isomerization of oct-3-yn-1-ol (**190**) under different conditions — under the action of KAPA at 80 °C. The resulting terminal alcohol **191** was used to prepare N-protected ω-amino stearic acid **206** (Scheme 59). It can be used to introduce a fluorescent label (indicated by an asterisk in Scheme 59) into GM1 ganglioside analogues, which is important for studying the dynamics of these glycosphingolipids in living systems.

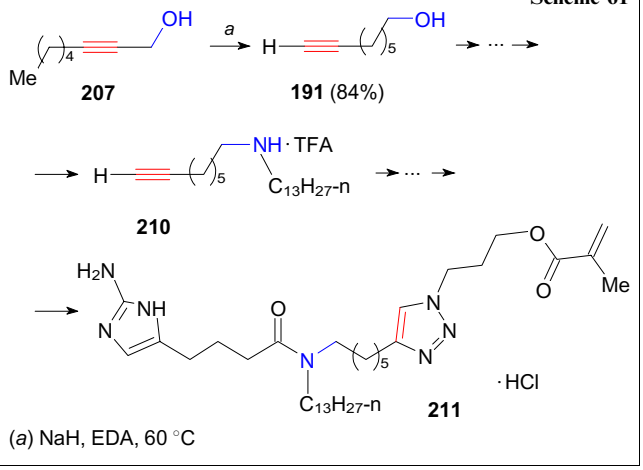
The acetylene zipper reaction involving the isomer of alcohol **190**, oct-2-yn-1-ol (**207**), was carried out under the action of LAPA in the presence of potassium *tert*-butoxide, which quantitatively led to the same oct-7-yn-1-ol (**191**).[173] The substitution of the OH group in this alcohol with a bromine atom and subsequent alkylation of hydroxymethyldipyridine derivative **208** afforded bipyridine ligand **209** containing an ethynyl moiety (Scheme 60).

The isomerization of oct-2-yn-1-ol (**207**) under the action of another base, NAETA, afforded a lower yield of the product (77%).[174] Nevertheless, these conditions were suitable for significant scale-up of the process (substrate loading 25 g). The obtained oct-7-yn-1-ol (**191**) was converted to amine **210**, which was used in the synthesis of the 2-aminoimidazole derivative **211** (Scheme 61). The triple bond in the substituent served to introduce the methacrylate moiety by means of a click reaction with azide and to obtain

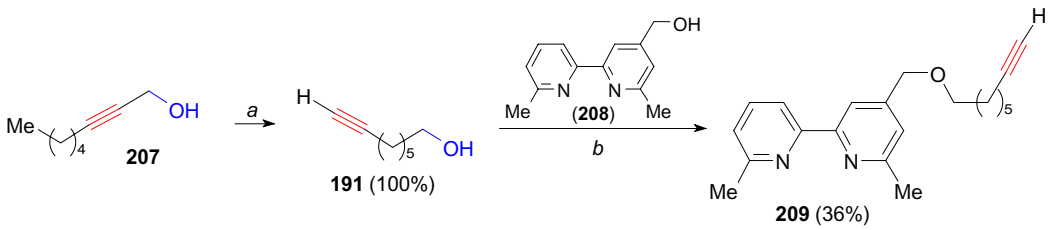
Scheme 59



Scheme 61

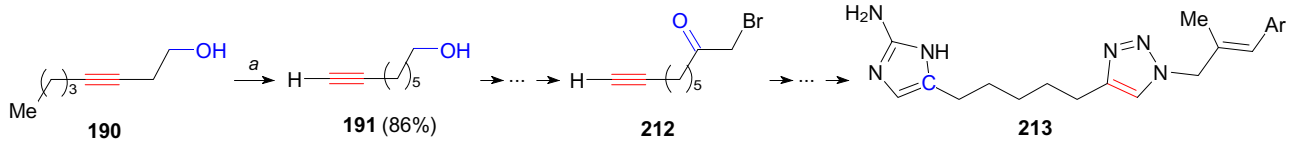


Scheme 60



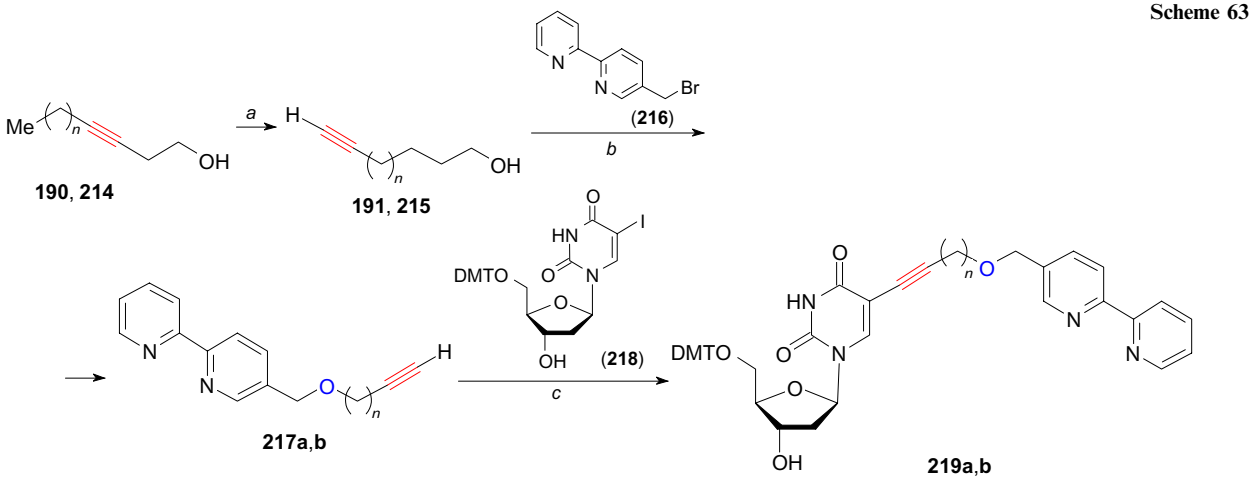
(*a*) Li, Bu^{t}OK, PDA; (*b*) 1) NBS, PPh_3 (60% yield); 2) NaH; NBS is *N*-bromosuccinimide

Scheme 62



(*a*) NaH, EDA, 40 – 65 °C

Scheme 63



(*a*) NaH, EDA, 60 °C, 15 h; (*b*) NaH, 18-crown-6, THF, MS 4 Å; (*c*) CuI, Pd(dppf)Cl_2, Et_3N, DMF, 60 °C; *n* = 3 (**190**; **191**, 51%), 4 (**214**; **215**, 61%;), 6 (**217a**, 62%; **219a**, 79%), 7 (**217b**, 61%; **219b**, 77%); DMT is 4,4′-dimethoxytrityl, dppf is 1,1′-bis(diphenylphosphino)ferrocene

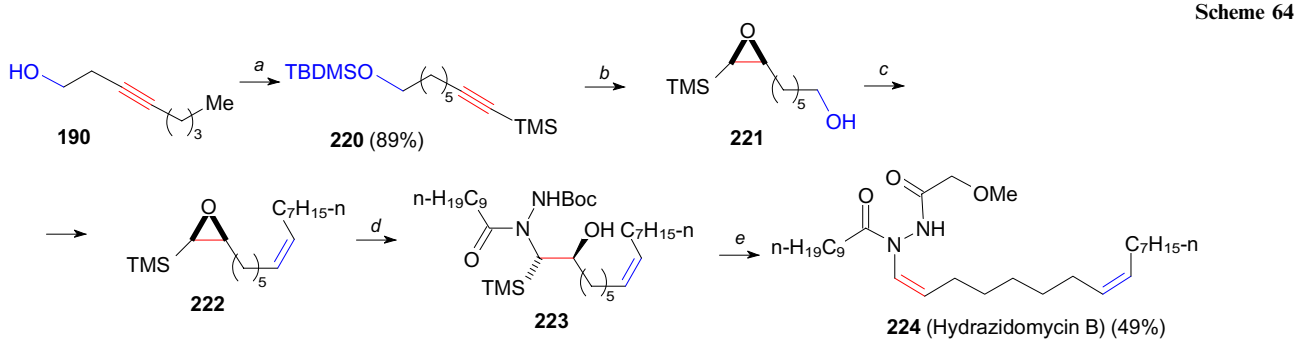
polymer materials with a pronounced antibiotic effect, tested on *Acinetobacter baumannii* bacteria.

The acetylene zipper reaction of oct-3-yn-1-ol (**190**) under the action of NAETA gave alcohol **191**, which was converted to bromide **212**.[175] The latter was used in the synthesis of 2-aminobenzimidazole derivatives **213** with a somewhat different linker between the imidazole and triazole rings exhibiting antibiofilm and antibacterial activity. In this case, the C(1) atom of the alcohol is involved in the formation of the imidazole ring, while the triple bond is involved in the formation of the triazole ring (Scheme 62).

Jäschke and co-workers [176] also carried out the acetylene zipper reaction of oct-3-yn-1-ol (**190**) and non-3-yn-1-ol (**214**) under the action of NAETA. Terminal alcohols **191**, **215** functioned as linkers between the bipyridine chelating ligand **216** (from which alkynes **217a**,**b** were produced) and pyrimidine nucleoside **218** (Scheme 63). The resulting nucleosides **219a**,**b** were used in synthesis of modified G-quadruplex DNA with covalently attached bipyridine ligands and their copper complexes. The latter showed high activity as catalysts in the asymmetric Michael addition. In this case, the linker chain length has a significant effect on the stereoselectivity of the process.

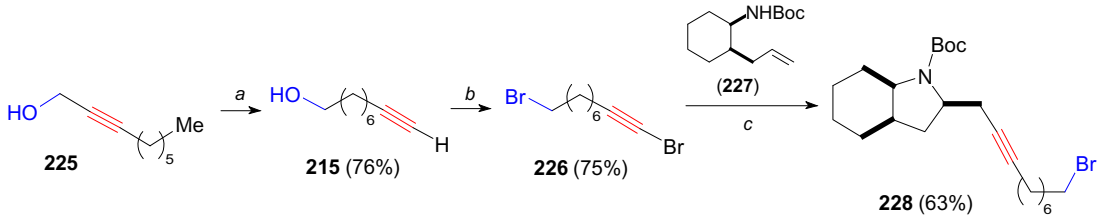
Under analogous conditions, the isomerization of compound **190** (NAETA, 65 °C) afforded the desired oct-7-yn-1-ol (**191**) in quantitative yield. The latter was used, without further purification, in the synthesis of a natural compound containing a *Z*-enehydrazide moiety.[177] In total synthesis of

Scheme 64



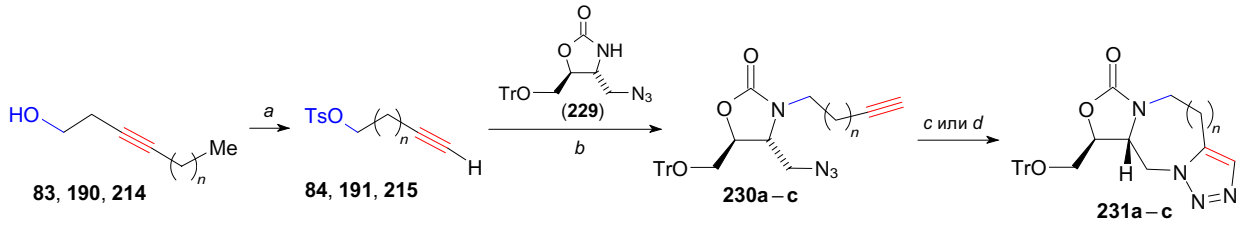
(*a*) 1) NaH, EDA (100% yield); 2) TBDMSCl, imidazole; 3) TMSCl, Bu^nLi; (*b*) 1) DIBAL-H (54% yield, ratio *Z* : *E* = > 15 : 1); 2) m-CPBA (88% yield); (*c*) 1) DMP; 2) Bu^nLi; 3) n-$C_7H_{15}PPh_3^+Br^-$; (*d*) 1) $BocNHNH_2$, $BF_3 \cdot Et_2O$ (79% yield); 2) n-$C_9H_{19}C(O)Cl$, Et_3N (82% yield); (*e*) 1) Peterson elimination, Bu^tOK, THF; 2) $MeOCH_2C(O)Cl$, KHMDS; 3) $Mg(ClO_4)_2$ (10 mol.%); m-CPBA is *m*-chloroperoxybenzoic acid, DMP is Dess – Martin periodinane, HMDS is hexamethyldisilazide

Scheme 65



(*a*) NaH, EDA, 60 °C; (*b*) 1) CBr_4, PPh_3; 2) NBS, $AgNO_3$; (*c*) $Pd(dba)_2$ (5 mol.%), DPEphos (7.5 mol.%), Bu^{t}ONa, PhMe, 80 °C; dba is dibenzylideneacetone

Scheme 66



(*a*) 1) NaH, EDA (81%–82% yield); 2) TsCl, Et_3N, DMAP (84%–90% yield); (*b*) NaH; (*c*) MW, 160 °C; (*d*) Cp*RuCl$(PPh_3)_2$, 80 °C; n = 2 (**83**), 3 (**190**), 4 (**84**, **214**, **230a**, **231a**), 5 (**191**, **230b**, **231b**), 6 (**215**, **230c**, **231c**); MW is microwave radiation, Tr is trityl (triphenylmethyl)

this compound, both the triple bond and the hydroxyl group played a key role. Scheme 64 shows the sequence of transformations and the structures of intermediates **220**–**223**. In particular, the triple bond is necessary to obtain the *Z*-enehydrazide part through the synthesis of (*Z*)-TMS-alkyne, epoxidation, epoxide ring opening with Boc-hydrazine, and stereoselective Peterson elimination. The hydroxyl group was used to create the second *Z*-alkene moiety through the Wittig olefination. This sequence of transformations afforded hydrazidomycin B (**224**).

The first palladium-catalyzed oxy- and aminoalkynylation of alkenes using 1-bromoacetylenes was reported.[178] The acetylene zipper reaction of non-2-yn-1-ol (**225**) was used as a tool for synthesis of bromoalkyne **226** — one of the substrates for aminoalkynylation. In particular, the isomerized product, non-8-yl-1-ol **215**, was transformed to 1,9-dibromonon-1-yne (**226**), which reacted with *tert*-butyl-2-allylcyclohexylcarbamate (**227**) to form the corresponding octahydroindole **228**. The aminoethynylation reaction proceeded with high diastereoselectivity — *dr* is >95 : 5 (Scheme 65).

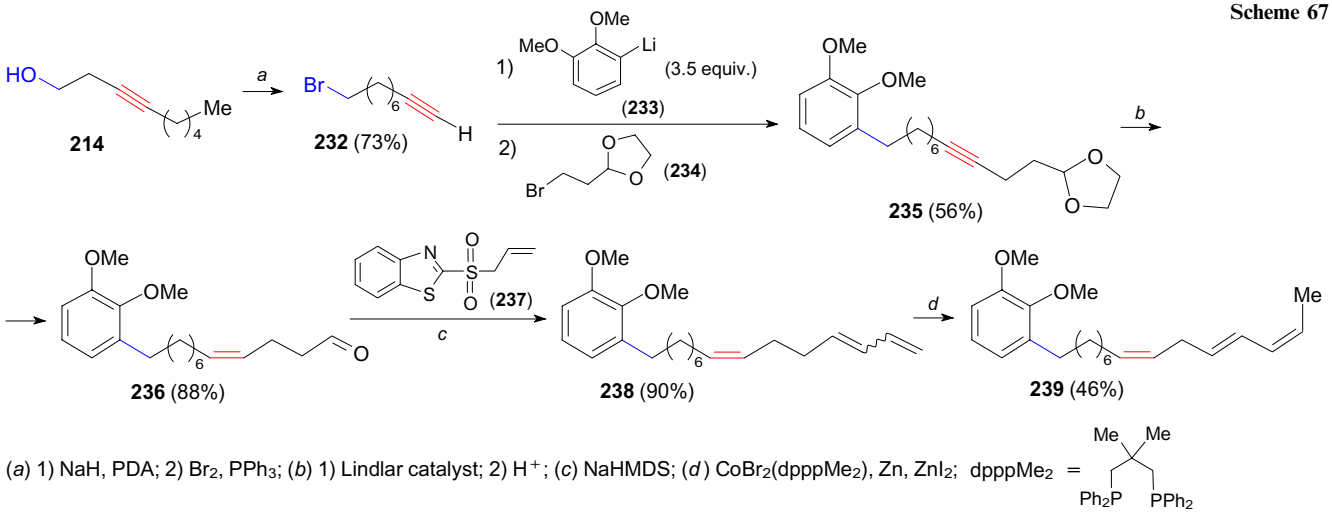
The isomerization of three alcohols — hept-3-yn-1-ol (**83**), oct-3-yn-1-ol (**190**) and non-3-yn-1-ol (**214**) — has been described.[179] The reactions occurred in the presence of NAETA. The resulting alcohols, after conversion to the corresponding tosylates **84**, **191**, **215**, were used for N-alkylation of azidomethyl oxazolidinone **229**, and then the reactivity of products **230a**–**c** in the 1,3-cycloaddition reaction was studied. It was demonstrated that the number of methylene groups and, hence, the size of the forming diazaheterocycle, has a key effect on the reactivity of the substrates and the process direction. In particular, the microwave-induced cyclization of azidoacetylene **230a**, generated from heptynol **83**, gave target triazole **231a** with the concurrent formation of a ten-membered fused ring under severe conditions but in good yield (76%). Its homologue **231b** under was obtained in 52% yield the same conditions. With increasing number of methylene groups, the yields of the products decreased. In the case of azidoacetylene **230c** with seven methylene groups, the yield of the 12-membered ring **231c** was only 32% (in addition, 20% of the 1,5-isomer was isolated); however, the use of Cp*RuCl$(PPh_3)_2$ (Cp* is pentamethylcyclopentadienyl) as a catalyst increased the yield to 71% (Scheme 66).

A method of isomerization of 1,3-alkadienes containing an additional double bond in the 7-position of the carbon chain to the corresponding (2*Z*,4*E*)-alka-2,4,7-trienes with the use of the $CoBr_2(dpppMe_2)$–Zn–ZnI_2 catalytic system was described.[180] The developed procedure was applied to synthesize the natural compound urushiol. At the first stage, non-3-yn-1-ol (**214**) was isomerized in high yield under the action of NAPA to the corresponding terminal acetylenic alcohol **215**, which was used to prepare 9-bromonon-1-yne (**232**) without further purification (Scheme 67). Then, arylation and alkylation proceeding in one stage under the action of excess dimethoxyphenyllithium **233** and bromopropionaldehyde acetal **234** gave product **235**. A series of subsequent stages involving Lindlar hydrogenation to form aldehyde **236** and its further Julia–Kocienski olefination with allyl sulfone **237** led to the diene moiety required for isomerization (compound **238**). Triene **239** (dimethyl-substituted urushiol) was isolated in a moderate yield (see Scheme 67).

In the method developed for producing metabolites of unsaturated biologically active acids, one of which is 12-hydroxyheptadecatrienoic acid, the acetylene zipper reaction involving non-3-yn-1-ol (**214**) was used at the first stage under the conditions differing from those described in the previous work. Isomerization was performed under the action of LAPA in the presence of potassium *tert*-butoxide, which gave the target non-8-yn-1-ol (**215**) in 95% yield.

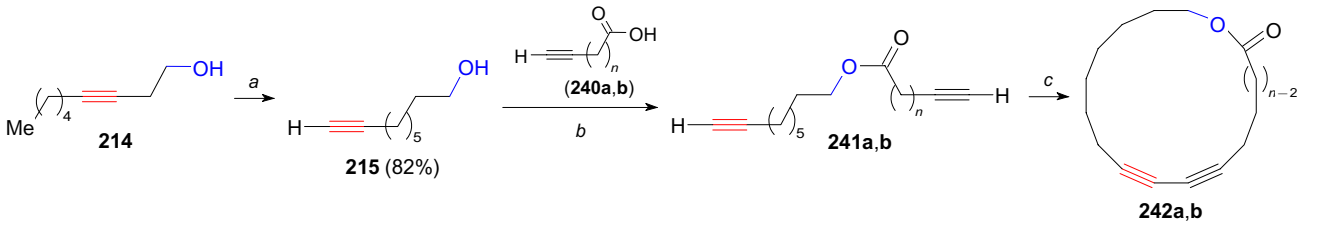
It is worth highlighting the studies where the acetylene zipper reaction served as a tool for obtaining the starting compounds in the synthesis of O-containing macrocycles and medium-sized rings. Bedard and Collins,[182] at the first stage of this approach to macrocycles, used the isomer-

Scheme 67



(*a*) 1) NaH, PDA; 2) Br_2, PPh_3; (*b*) 1) Lindlar catalyst; 2) H^+; (*c*) NaHMDS; (*d*) $CoBr_2(dpppMe_2)$, Zn, ZnI_2; dpppMe$_2$ =

Scheme 68



(*a*) NaH, EDA, 60 °C; (*b*) DCC, DMAP; (*c*) CuCl (100 mol.%), $Ni(NO_3)_2$ (100 mol.%), PEG 400 – MeOH (2 : 1), PyH, Et_3N, O_2, rt, then 60 °C, 1–2 days; n = 3 (**241a**, 85%; **242a**, 83%), 8 (**241b**, 65%; **242b**, 87%)

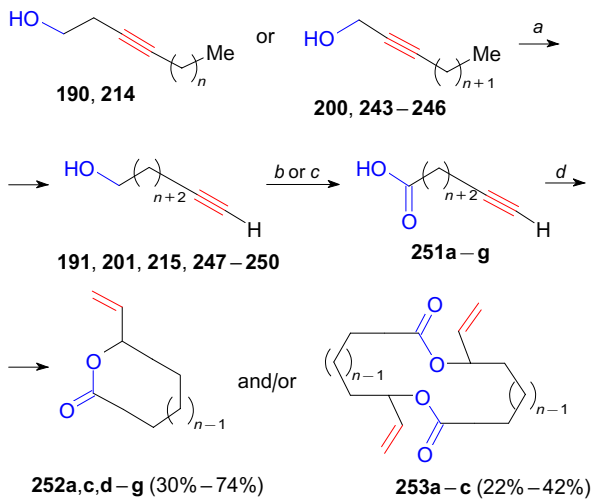
ization of non-3-yn-1-ol (**214**). The reaction proceeded under the action of NAETA at 60 °C for 15 h. This work is worth noting because the resulting terminal acetylene alcohol was involved in the synthesis of substrates for Glaser–Hay macrocyclization using a phase separation strategy. In particular, this alcohol was converted to two esters by acylation with acids **240a**,**b** (Scheme 68). Esters **241a**,**b** were substrates for optimizing macrocyclization conditions, avoiding the use of traditional tactics of high dilutions and slow addition of reactants. The authors proposed a radically new approach based on the use of the polyethylene glycol (PEG)–ether two-phase system, the $CuCl_2$ catalyst and the $Ni(NO_3)_2 \cdot 6H_2O$ co-catalyst with pyridine as a ligand. The Glaser macrocyclization at the interface ensured high yields of 83% and 87% for the target macrocycles **242a**,**b**, respectively, when operating in the centimolar concentration range (C = 0.02 mol L^{-1}) (see Scheme 68).

Lumbroso *et al.*[183] used an atom-economic method for closing macrocycles and medium-sized rings based on the Rh-catalyzed propargylic CH oxidation. The acetylene zipper reaction of alcohols and subsequent oxidation of primary alcohol groups with the Jones reagent or pyridinium dichromate (PDC) were key tools in the synthesis of initial compounds. In particular, the isomerization of alcohols **190**, **200**, **214**, **243**–**246** containing 8 to 21 carbon atoms was promoted by NAETA. The subsequent oxidation of compounds **191**, **201**, **215**, **247**–**250** gave substrates **251a**–**g** for intramolecular lactonization. It was estimated that the macrolactonization direction depends on the size of the forming ring. Macrocyclization leading to macrolactones **252d**–**g** with 14-, 16-, 18- and 20-membered rings occurred smoothly in high yields in centimolar solutions. For the 12-membered lactone **252c** and for the seven-membered ring **252a**, the reaction gave a mixture of intramolecular cyclization and dimerization products (compounds **253a**,**c**), while no eight-membered lactone (as well as nine-and ten-membered rings) was detected; rather, only dimerization product **252b** was isolated (Scheme 69). It is worth noting that the reaction occurred with high regioselectivity through the formation of an intermediate Markovnikov product of hydrometalation of the triple bond. The reaction turned out to be applicable for producing functionalized macrolactones.

Cyclization for producing macrocyclic lactones was also studied by Santandrea *et al.*[184] who have used the Castro–Stephens cross-coupling for the first time as a synthetic method for macrocyclic ring closing. Substrates in this transformation were esters **254a**–**f** — the products of acylation of terminal acetylenic alcohols with *o*-iodobenzoic acid. These alcohols were synthesized using the acetylene zipper reaction by the above-described procedures.[182, 183] The developed approach turned out to be applicable for synthesis of acetylenic lactones **255a**–**f** with a ring size of 10 to 25 units where CuCl was used as a catalyst and phenanthroline served as a ligand in the presence of caesium carbonate in toluene (Scheme 70).

A combination of acetylene zipper and macrocyclization was also used to synthesize macrocyclic diacetylenic lactones.[185] The key stage of macrocyclic ring closing is a new procedure of oxidative coupling of alkynes promoted by iodine and Cu^I and Au^I catalysts. The acetylene zipper reaction involving alcohol **200** is a convenient tool for synthesis of initial tridec-12-ynoic acid (**251c**). This acid is

Scheme 69



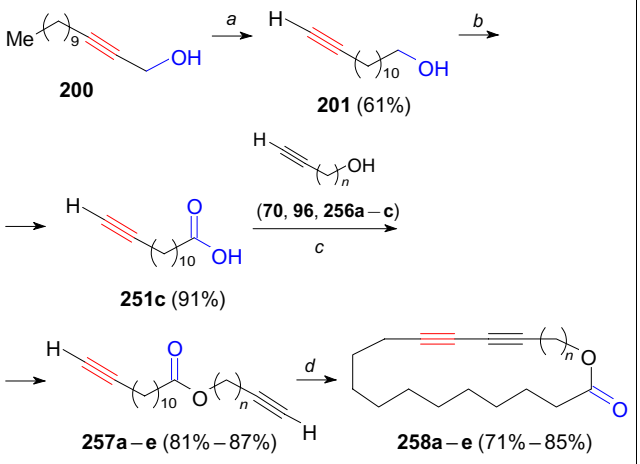
(*a*) NaH, EDA, 70 °C; (*b*) for *n* = 3, 4 (compounds **191**, **215**): Jones reagent (45%–48% yield); (*c*) for *n* > 4 (compounds **201**, **247**–**250**): PDC, DMF (45%–48% yield); (*d*) $[Rh(COD)Cl]_2$, DPEphos, 70 °C, *C* = 0.01 mol L^{-1}

Substrate	*n*	Alcohol [yield (%)]	Acid	Lactone (ring size)	Dimer
190	3	**191** (65)	**251a**	**252a** (7)	**253a**
214	4	**215** (75)	**251b**	– (8)	**253b**
200	8	**201** (71)	**251c**	**252c** (12)	**253c**
243	10	**247** (55)	**251d**	**252d** (14)	–
244	12	**248** (54)	**251e**	**252e** (16)	–
245	14	**249** (78)	**251f**	**252f** (18)	–
246	16	**250** (77)	**251g**	**252g** (20)	–

used to convert various acetylenic alcohols (**70**, **96**, **256a**–**c**) to esters **257a**–**e** — the starting compounds for macrocyclization, which provides diacetylenic lactones **258a**–**e** in high yields (Scheme 71). The developed approach has been successfully applied in synthesis of the natural compound ivorenolide B exhibiting immunosuppressive activity.

Xue and Zimmt[186] studied self-organization of 1,5-bis(alkadiynyloxy)anthracenes on the surface of highly oriented pyrolytic graphite (HOPG) and the structure of the deposited monolayers. To this end, the acetylene zipper reaction of methylacetylenes **259**–**261** was accomplished under the action of a mixture of LAPA and potassium *tert*-butoxide to give long-chain terminal acetylenic alcohols **96** (C_{10}), **97** (C_{11}) and **262** (C_{14}), which were further alkylated with 1,5-bis(chloromethyl)anthracene (**263**). The reaction products **264a**–**c** containing a terminal triple bond

Scheme 71



(*a*) NaH, EDA, 60 °C; (*b*) Jones reagent; (*c*) EDC, DMAP, CH_2Cl_2; (*d*) PPh_3AuCl (10 mol.%), CuI (30 mol.%), I_2 (2.5 equiv.), Pr^i_2NH (1.2 equiv.), PhMe, *C* = 0.01 mol L^{-1}; *n* = 1 (**256a**, **257a**, **258a**), 2 (**256b**, **257b**, **258b**), 3 (**256c**, **257c**, **258c**), 4 (**70**, **257d**, **258d**), 8 (**96**, **257e**, **258e**)

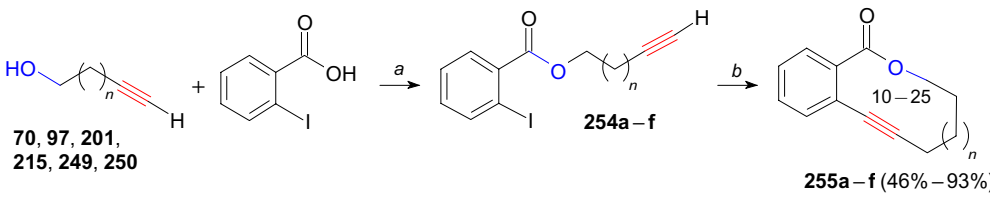
were used as initial compounds in the Cadiot–Chodkiewicz coupling with iodoalkynes **265a**–**c**, which led to the target bis(diynes) **266** (Scheme 72).

To synthesize 1,5-bis(alkadiynyloxy)anthracene derivatives with similar structures, isomerizations of oct-2-yn-1-ol (**207**) and pentadec-2-yn-1-ol (**243**) were carried out under analogous conditions.[187,188] In synthesis of hybrid kabiramide C analogues with affinity for G-actin,[189] as well in synthesis of triazole- and ditriazole-based nicotinamide phosphoribosyltransferase (NAMPT) inhibitors with antiproliferative and antiinflammatory activity,[190] the isomerization of dec-2-yn-1-ol (**259**) to terminal dec-9-yn-1-ol (**96**) has been accomplished under the conditions most frequently used for octynol and heptynol (NAETA, 60 °C).

The isomerization of an internal alcohol containing ten C atoms, dec-3-yn-1-ol (**267**), under the action of NAPA at 100 °C to give terminal dec-1-yn-9-ol (**96**) in high yield has been described.[191] Then, the latter was either converted to mesylate **268** or oxidized to acid **269** (Scheme 73).

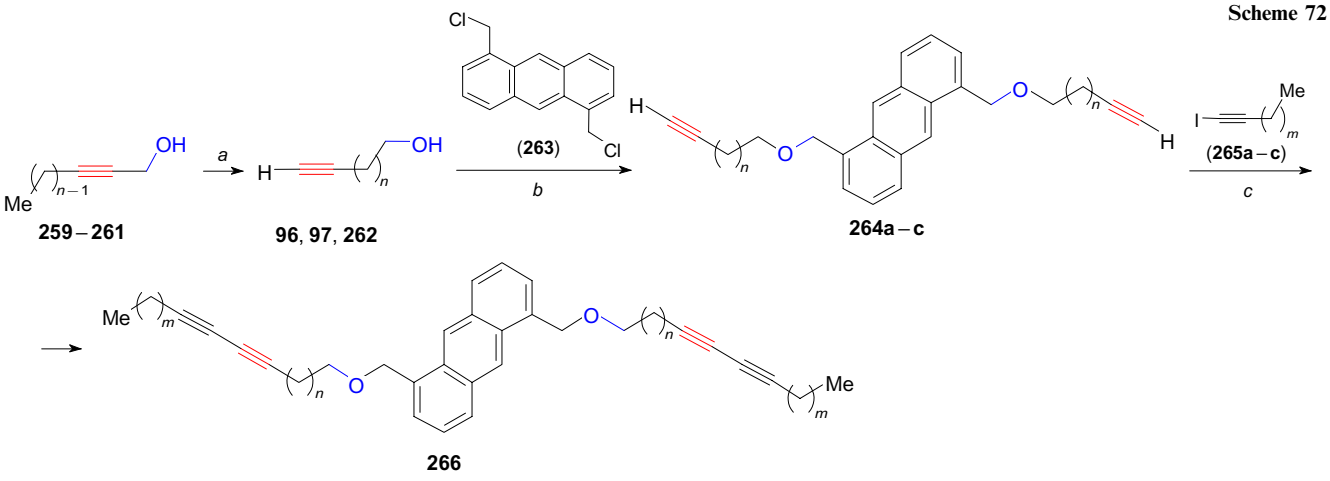
Alkylating and acylating C_{10} fragments (compounds **268**, **269**) with a terminal triple bond were used to synthesize a 48-membered cyclic lipid containing ether and amide bonds separated by alkadiynyl moieties. The key stages of this synthesis are alkylation of diprotected glycerol **270** to give diyne **271**, generation of amino groups by reduction of azide functions and acylation of dialcohol **271** with acid **269** to give tetrayne **272**, Glaser oxidative coupling of acetylene fragments leading to compound **271** and the use of the same

Scheme 70



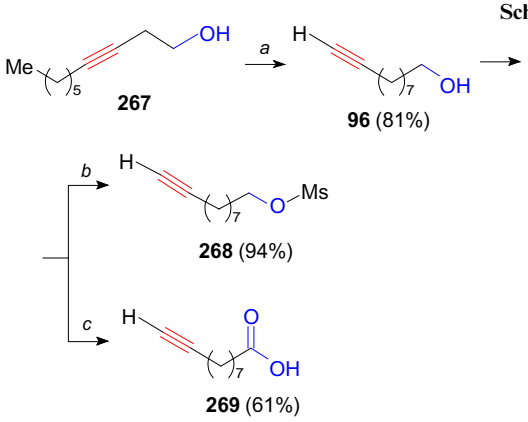
(*a*) DCC, DMAP; (*b*) CuCl (5 mol.%), phenanthroline (30 mol.%), Cs_2CO_3, PhMe, 135 °C, *C* = 0.024 mol L^{-1}; *n* = 3 (**70**, **254a**, **255a**), 6 (**215**, **254b**, **255b**), 8 (**97**, **254c**, **255c**), 10 (**201**, **254d**, **255d**), 16 (**249**, **254e**, **255e**), 18 (**250**, **254f**, **255f**)

Scheme 72



(*a*) Li, PDA, Bu^{t}OK; (*b*) NaH; (*c*) CuI, pyrrolidine; *n* = 7 (**96**, **259**, **264a**), 8 (**97**, **260**, **264b**), 11 (**261**, **262**, **264c**); **265**: *m* = 4 (**a**), 8 (**b**), 9 (**c**)

Scheme 73



(*a*) NaH, PDA, 100 °C; (*b*) MsCl, Et_3N; (*c*) Jones reagent; Ms is methanesulfonyl (mesyl)

reaction for macrocyclization affording target macrocycle **273** in 62% yield. This sequence of transformations is shown in Scheme 74. It has been discovered that the target compound **273** can self-organize to form helical ribbons.

Different conditions were used for isomerization of undec-2-yn-1-ol (**260**):[192] to prepare a superbase from PDA, n-butyllithium and potassium *tert*-butoxide, THF was additionally used as a solvent. The use of a fourfold excess of the base made it possible to carry out isomerization in 3 h and isolate terminal acetylene **97** in 87% yield. The subsequent stages included Sonogashira cross-coupling with iodoalkenes **274a**,**b**, conversion of coupling products **275a**,**b** to tosylates and alkylation by the resulting tosylates of *N*,*N*′-dimethylethylenediamine (**276**). As a result, the target products, natural compounds clathculins A (**277a**) and B (**277b**), were isolated in 77% yield in both cases (Scheme 75).

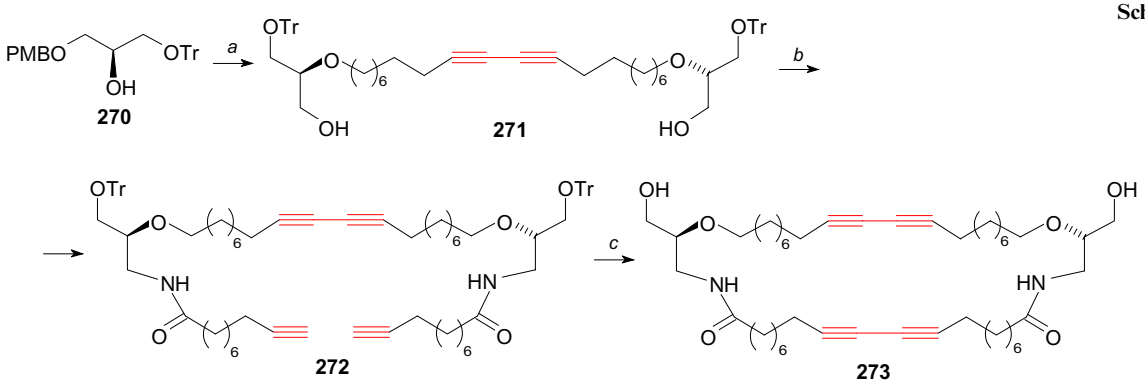
In addition to publications dealing with the application of the acetylene zipper reaction in synthesis of macrocyclic acetylene compounds, there are investigations where this reaction has been used to produce biologically active deuterium-labelled compounds.

The acetylene zipper reaction involving dec-2-yn-1-ol (**259**) promoted by NAPA gave dec-9-yn-1-ol (**96**) in high yield (90%). The resulting terminal decynol was used in synthesis of [9,10,11,11-D_4]-oleic acid **278** (Scheme 76).[193]

Long-chain internal acetylenic alcohol **279** was isomerized to terminal dodec-11-yn-1-ol (**280**) for further synthesis of pentadeuterated fatty carboxylic acids **281** – **283**, which are precursors in the pheromone biosynthesis of the Egyptian armyworm.[194] The isomerization was promoted by LAPA in the presence of potassium *tert*-butoxide to give the product in high yield (Scheme 77).

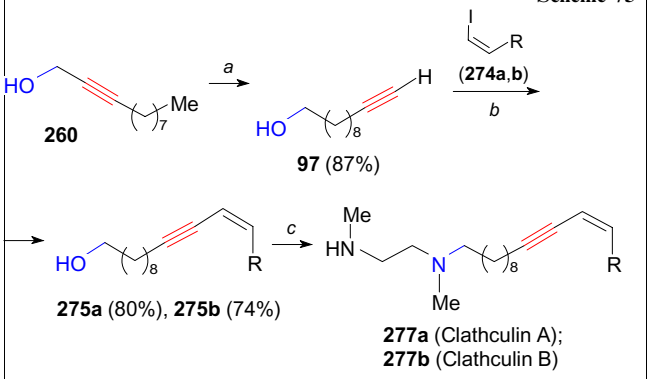
In the synthesis of deuterated palmitic acid, the acetylene zipper reaction of non-2-yn-1-ol (**225**) was used under

Scheme 74



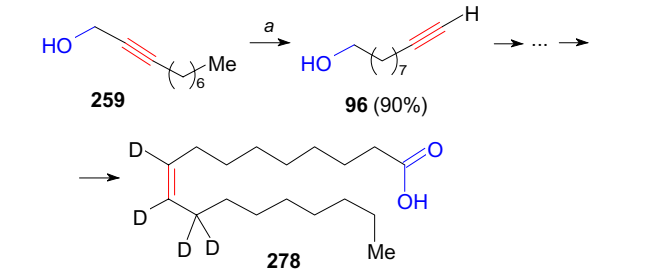
(*a*) 1) alkylation of **268**; 2) Glaser reaction; 3) PMB deprotection; (*b*) 1) synthesis of diamine through diazide; 2) acylation of **269**; (*c*) 1) Glaser reaction; 2) Tr group elimination

Scheme 75



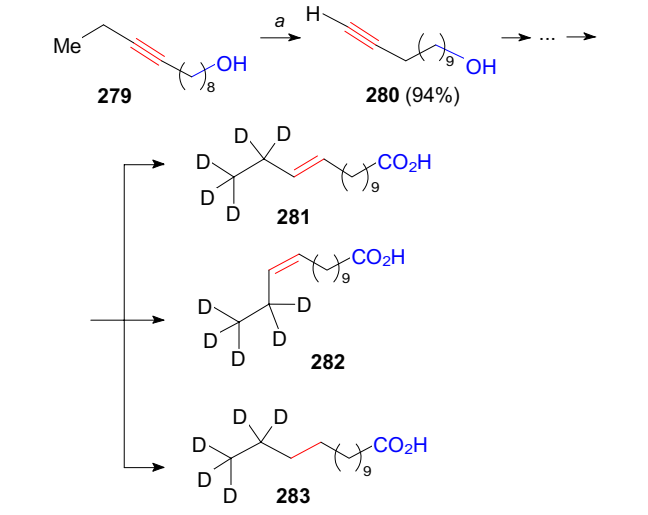
(*a*) Bu^{n}Li, Bu^{t}OK, PDA, THF, rt; (*b*) $PdCl_2(PhCN)_2$, CuI, pyrrolidine; (*c*) 1) TsCl, Et_3N, DMAP; 2) $MeNH(CH_2)_2NHMe$ (**276**); R = $(CH_2)_2CH{=}CH_2$ (**a**), Bu^n (**b**)

Scheme 76



(*a*) NaH, PDA

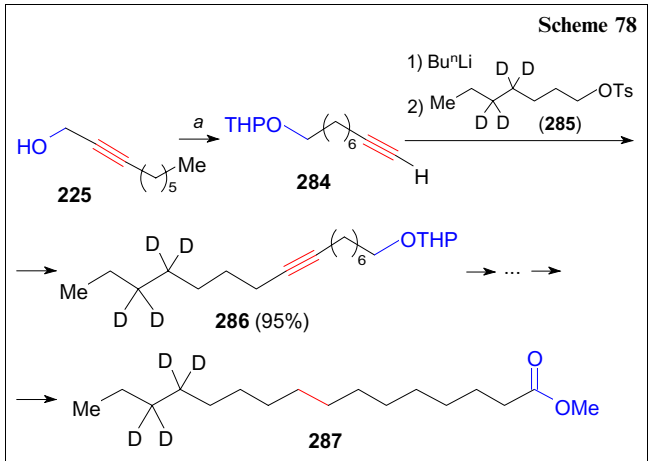
Scheme 77



(*a*) LAPA, Bu^{t}OK

similar conditions.[195] The OH group in the intermediate terminal acetylenic alcohol was protected, and the THP-protected alcohol **284** was alkylated at the C atom with tetradeuterioheptyl tosylate **285**. The protected deuterated alcohol **286** was then converted to the target [13,13,14,14-D_4]-palmitic acid **287** (Scheme 78).

Scheme 78



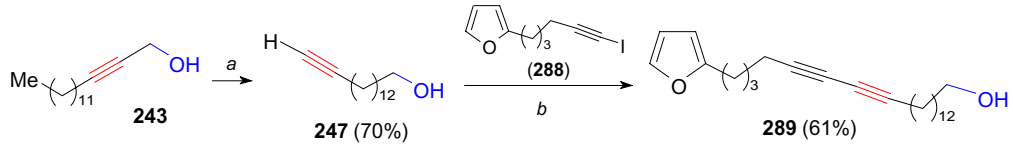
(*a*) 1) Li, PDA, Bu^{t}OK (66% yield); 2) DHP, TsOH

The reaction involving acetylenic alcohols consisting of more than 10 carbon atoms is used in the total synthesis of natural compounds and their synthetic analogues. In particular, a method has been developed for producing natural acetylenes bearing a furan ring.[196] In the synthesis of one of the derivatives, isomerization of the long-chain (C_{15}) acetylenic alcohol **243** under the action of KAPA at room temperature was used. The Cadiot–Chodkiewicz reaction of the resulting terminal acetylene **247** with iodoacetylene component **288** led to the target product, 21-(2-furyl)henicosa-14,16-diyn-1-ol (**289**) (Scheme 79).

The acetylene zipper reaction of hexadec-7-yn-1-ol (**290**) was used at the early stages of the total synthesis of one of the main virulence factors of *Mycobacterium tuberculosis*.[197] The isomerization of hexadec-7-yn-1-ol (**290**) occurred under the action of NAPA to give hexadec-15-yn-1-ol in a good yield (**291**). Then, a TMS group was introduced at the terminal atom of the triple bond, and the hydroxyl group was replaced by a iodine atom. The halogen–lithium exchange in iodide **292** and *tert*-butyllithium followed by the reaction of the resulting organolithium compound with Weinreb amide **293** led to β-hydroxyketone **294**; the stereoselective Evans reduction of **294** and TMS-deprotection afforded important intermediate **295.** Further transformations led to the target triglycosyl phenolic glycolipid PGL-tb1 — compound **296** (Scheme 80).

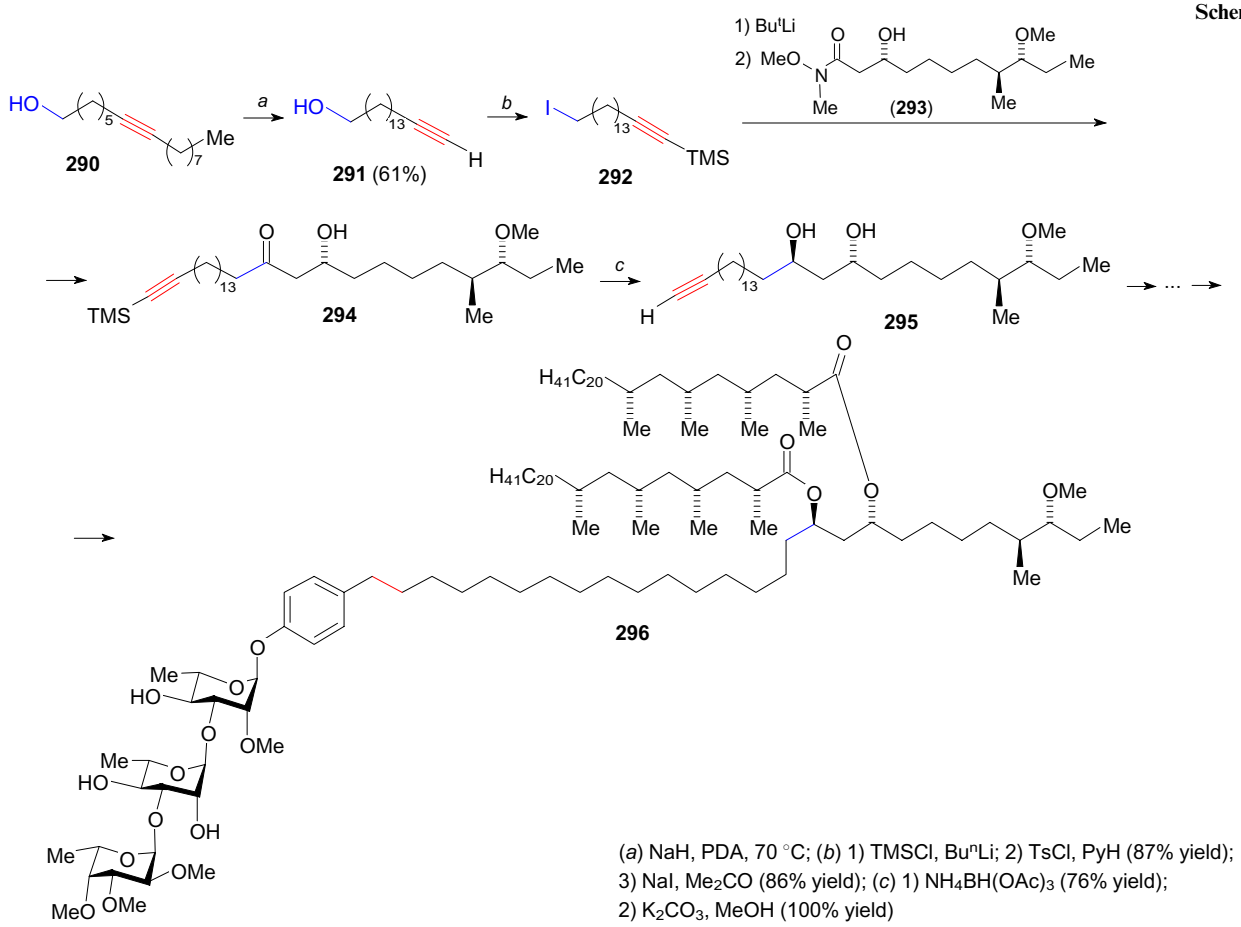
Hannoush and Arenas-Ramirez[198] studied the possibility of biochemical detection and visualization of lipoproteins containing synthetic fatty acids modified with ethynyl moieties at the terminal ω-position. A series of fatty acids have been studied, two of them being obtained by isomerization of corresponding alcohols, tetradec-3-yn-1-ol (**297**) and hexadec-7-yn-1-ol (**290**), with subsequent Jones oxidation. ω-Ethynylmyristic acid (**298**) and ω-ethynylpalmitic

Scheme 79



(*a*) KAPA; (*b*) CuI, piperidine

Scheme 80

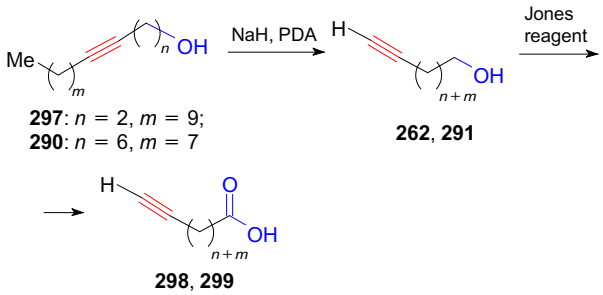


acid (**299**) were metabolically incorporated into lipoproteins of different cell lines and visualized by means of the azide click reaction (Scheme 81).

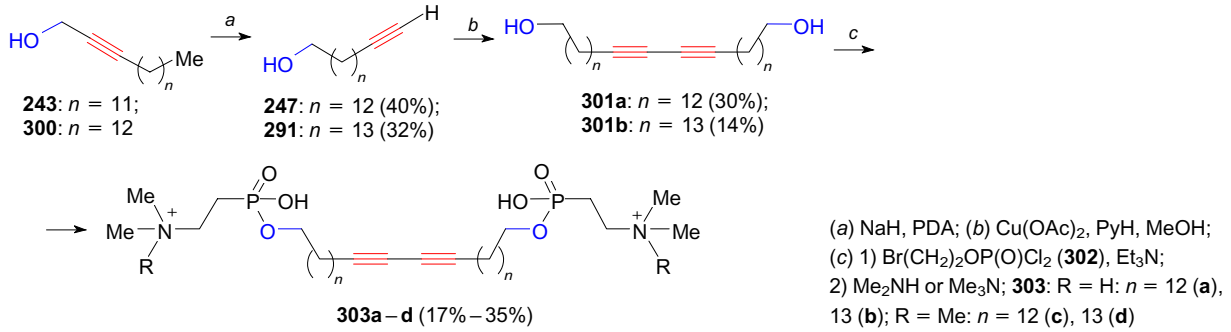
The isomerization of higher acetylenic alcohols — penta- (**243**) and hexadecynol (**300**) — was also accomplished under the action of NAPA.[199] As in other cases, these conditions afforded acetylene zipper products in moderate yields. (As an alternative to this approach, the authors proposed a scheme based on the alkylation of trimethylsilyl acetylide with THP-protected bromoalkanols.) Terminal acetylenic alcohols **247** and **291** were subjected to the Eglinton homocoupling to give diynes **301a**,**b**, which were phosphorylated with β-bromoethylphosphonic dichloride (**302**), and the resulting dibromides were used to alkylate dimethylamine and trimethylamine. This allowed the authors to obtain the target bipolar phospholipids **303a**–**d** (Scheme 82).

The highest yield of the isomerization product of hexadec-7-yn-1-ol (**290**) was achieved,[200] which is attributable to the fact that the reaction was carried out overnight. The authors used terminal hexadec-16-yn-1-ol (**291**) in synthesis

Scheme 81

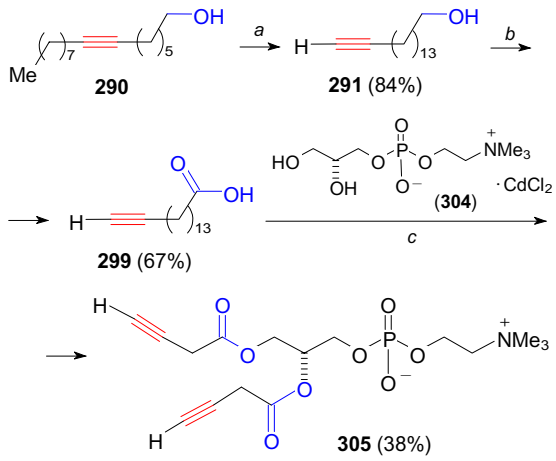


Scheme 82



of the corresponding carboxylic acid **299**. The acid was necessary for accomplishing the reaction with betaine **304** to synthesize ethynyl-modified phospholipid **305** (Scheme 83), which was further transformed to the corresponding $Co_2(CO)_6$ complex. Such a seemingly unusual modification for biological systems made it possible to quickly and efficiently detect modified phospholipids in complex mixtures using tandem mass spectrometry.

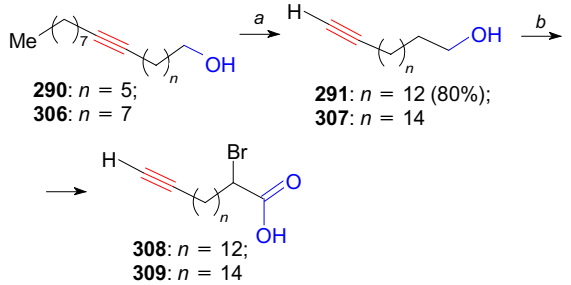
Scheme 83



(*a*) NaH, PDA, 55 °C; (*b*) PDC; (*c*) DCC, DMAP

Analogous isomerization of hexadec-7-yn-1-ol (**290**) and octadec-9-yn-1-ol (**306**) was used in synthesis of ethynyl analogues of 2-bromopalmitic acid (2-BP), an irreversible inhibitor of palmitoyl acyltransferase.[201] The synthesis of the acids involves the oxidation of alcohols **291**, **307** with iodoxybenzoic acid (IBX), the bromination of the resulting aldehydes at the α-position through the reaction with NBS and the oxidation with pyridinium dichromate (Scheme 84). The presence of a triple bond in the synthesized 2-BP analogues **308**, **309** and, therefore, the ability to visualize objects with built-in acids using click reactions allowed the authors to use the obtained compounds as chemical markers to elucidate the mechanism and nature of 2 -BP binding to palmitoyl acyltransferase DHHC4.

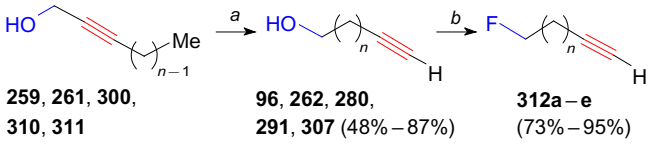
Scheme 84



(*a*) NaH, PDA, 55 °C; (*b*) 1) IBX (for n = 12, 90% yield); 2) NBS, proline (for n = 12, 74% yield); 3) PDC (for n = 12, 71% yield)

Isomerization of five different acetylenic alcohols **259**, **261**, **300**, **310**, **311** with an even number of C atoms (from 10 to 18) has been reported.[202] The reaction was promoted by LAPA in the presence of potassium *tert*-butoxide and afforded terminal acetylenic alcohols **96**, **262**, **280**, **291**, **307**, mos often in high yields (Scheme 85). The latter were converted, through the formation of the corresponding tosylates, to the target ω-fluoroacetylene compounds **312a**–**e**. These compounds were used to prepare fluoroalkyl monolayers on oxide-free Si(111) surfaces, resulting in changes in the physical and electronic properties of the surface.

Scheme 85



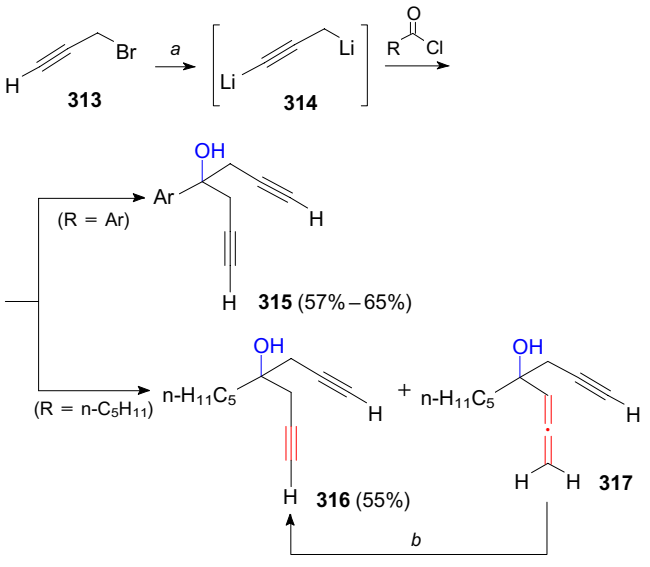
259, **261**, **300**, **310**, **311** — **96**, **262**, **280**, **291**, **307** (48%–87%) — **312a**–**e** (73%–95%)

(*a*) Li, PDA, Bu^{t}OK, rt; (*b*) 1) TsCl, PyH; 2) KF, 18-crown-6, MeCN; n = 7 (**96**, **259**, **312a**), 9 (**280**, **310**, **312b**), 11 (**261**, **262**, **312c**), 13 (**291**, **300**, **312d**), 15 (**307**, **311**, **312e**)

The isomerization of octadec-4-yn-1-ol, which occurred in the LAPA–potassium *tert*-butoxide system, was used in synthesis of octadec-17-ynoic acid necessary for producing photoreactive cardiolipins for photoaffinity labelling.[203]

In contrast to the above studies, Vasquez and Cabezas[204] developed a method for the preparation of bis(homopropargyl) alcohols from acyl chlorides. The synthesis involved the conversion of propargyl bromide **313** to dianion **314** and its reaction with acyl chlorides (Scheme 86). In the case of aromatic acyl chlorides (R = Ar), this method afforded the corresponding bis(homopropargyl) alcohols **315** in yields from 57% to 65%. However, the reaction with hexanoyl chloride (R = n-C_5H_{11}) gave a 1 : 1 mixture of the target alcohol **316** and alcohol **317** with the propargyl substituent isomerized to the allene moiety. To prepare exclusively the target n-pentylbis(homopropargyl) alcohol **316**, this mixture was treated with KAPA, which promoted the isomerization of allene **317**. This transformation afforded the target product in 55% yield, avoiding the separation of the isomer mixture (at the propargylation stage) (see Scheme 86).

Scheme 86



(*a*) Bu^{n}Li (2 equiv.), TMEDA; (*b*) KAPA

4.1.2. Chiral alcohols

In the first total synthesis of chaetoglogin A,[205] the initial compound was (*S*)-hept-4-yn-2-ol (**318a**), generated by the opening of (*S*)-2-methyloxirane with but-1-yne under the action of n-butyllithium. The acetylene zipper reaction of alcohol **318a** with the use of LAPA in the presence of potassium *tert*-butoxide gave an intermediate terminal acetylenic alcohol, which was acetylated to produce (*S*)-hept-6-yn-2-ol acetate (**319**) in high overall yield (74% for three stages). This was followed by the Sonogashira reaction with aryl iodide **320** (Scheme 87). The key stages of the entire process are the antroposelective oxidative coupling of the Sonogashira reaction product **321** with a chiral ligand promoted by vanadium catalyst **322** to give compound **323** and the oxidative dearomatization of the diformyldiethynylbiphenyl moiety, produced at the next stage, under the action of the IBX–silver triflate system (not shown in the scheme). Further transformations led to the target product **324**.

The acetylene zipper reaction was used in the total synthesis of another biologically active natural macrocycle.[206] (*S*)-Hept-3-yn-2-ol (**318b**), obtained *via* enantioselective Noyori hydrogenation of the corresponding ketone **325**, was used to synthesize chiral (*S*)-hept-3-yn-2-yl benzoate **326**. The isomerization of alcohol **318b** in the presence of KAPA occurred smoothly without loss of optical purity. The next key stage in the synthesis of aspergillide B was Zn-ProPhenol (L^3)-catalyzed enantioselective ethynylation of aldehyde **327**. This unsaturated aldehyde was not chosen by chance: the highest yields and ethynylation stereoselectivity were achieved precisely for this compound. The addition product **328** was further converted in several stages into aldehyde **329**, which was used as a substrate in repeated Zn-ProPhenol-catalyzed ethynylation with methyl propiolate (**330**). The resulting carbinol **331** formed the target aspergillide B (**332**) as a result of six additional stages, the key stage being the chemoselective reduction of the triple bond using the hydrosilylation–protodesilylation protocol (Scheme 88).

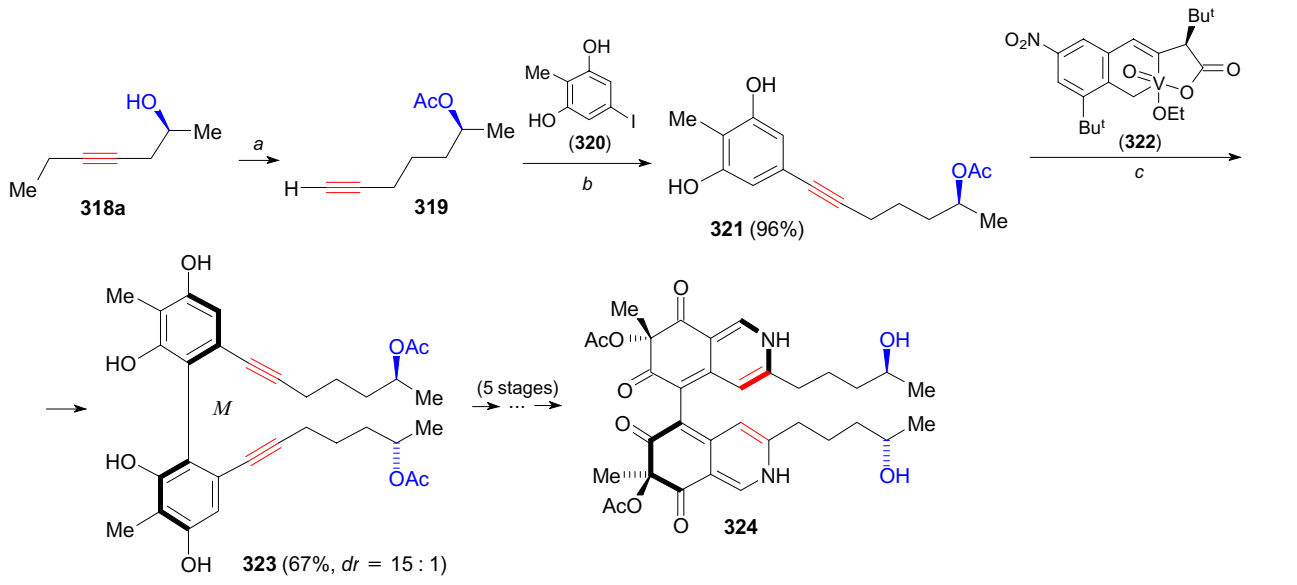
The synthesis of a natural macrolactone isomeric to (−)-aspergillide B has been reported.[207] The synthesis commenced with the opening of the three-membered ring in (*R*)-2-methyloxirane **333** with lithium ethylacetylide; then, the acetylene zipper reaction of (*R*)-hept-4-yn-2-ol (**334**) was accomplished. The isomerization promoted by LAPA in the presence of potassium *tert*-butoxide occurred smoothly and afforded high yield of the product. The introduction of required protective groups into the resulting terminal acetylenic alcohol and C-glycosylation of compound **335** with D-tri-*O*-acetylgalactal **336** gave the key intermediate **337**, which was further transformed, through the stages of Ru-catalyzed *trans*-hydrosilylation–desilylation and homologization as a result of nucleophilic substitution using the cyanide anion, to the (−)-aspergillide C precursor **338**. The last macrolactonization stage, leading to the target product **339**, was not carried out by the authors (denoted by the dashed arrow in Scheme 89).

The acetylene zipper reaction of (*R*)-hept-4-yn-2-ol (**334**) under similar conditions was also applied in total synthesis of the natural compound tubelactomicin A.[208]

The isomerization of (*R*)-undec-3-yn-2-ol (**340**) under the action of KAPA occurred smoothly and gave the terminal optically active alcohol **341** in high yield without loss of enantiomeric purity.[209–211] The resulting terminal acetylenic alcohol was the key starting compound in the synthesis of a number of cladospolides, 12-membered biologically active macrolactones. The following stages included the protection of the OH group, carboxylation and isomerization developed by Trost leading to the corresponding (*E*,*E*)-dienoate **342**. The latter, after a series of stages with Sharpless dihydroxylation and macrolactonization being the key ones, were converted to cladospolides C (**343**) and B (**344**) (Scheme 90).

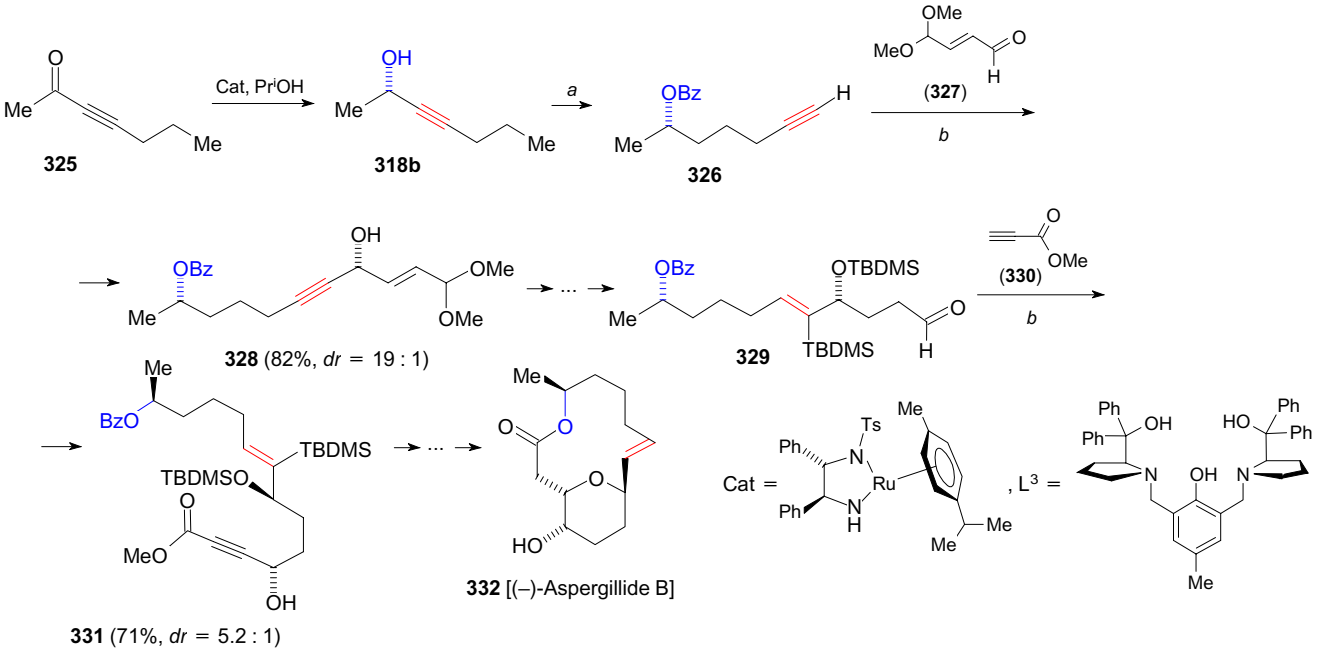
The isomerization of the same alcohol **340** was described in the aforementioned paper by Santandrea, Bedard and Collins[184] (see Scheme 70) dealing with the synthesis of macrocyclic lactones. The reaction was promoted by NAETA. The terminal acetylenic alcohol **341** underwent the Mitsunobu reaction with 2-iodo-4,5-dimethoxybenzoic

Scheme 87



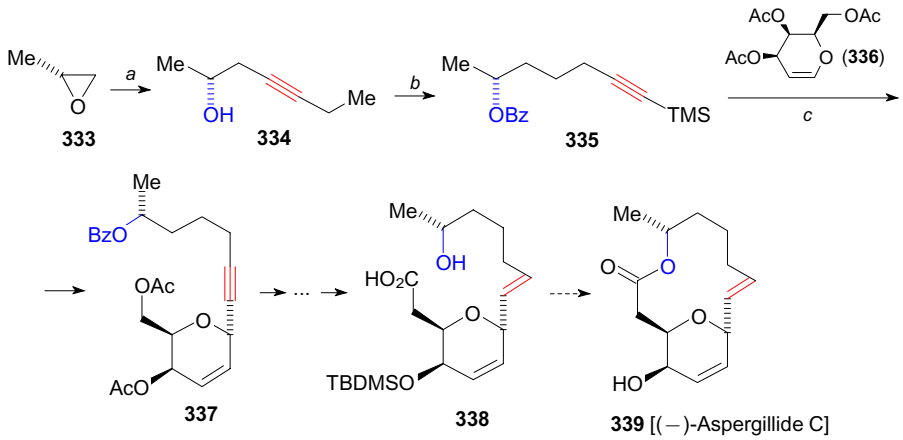
(*a*) 1) Li, PDA, Bu^{t}OK; 2) Ac_2O, DMAP, PyH; (*b*) $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, DMF, 65 °C; (*c*) O_2, AcOH, PhCl, 0 °C, 48 h

Scheme 88



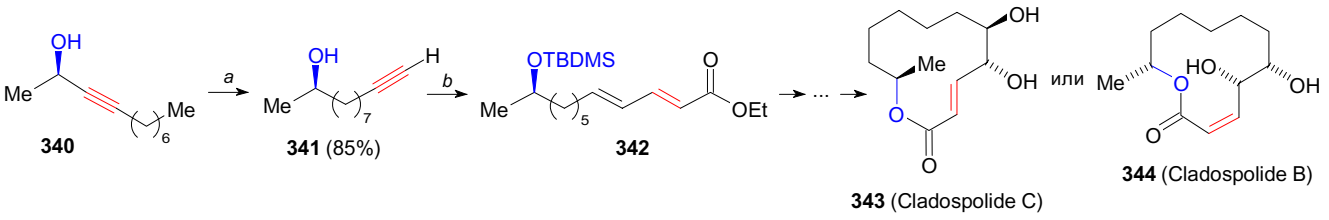
(*a*) 1) KH, PDA (81% yield); 2) BzCl, DMAP, Et_3N (84% yield); (*b*) Me_2Zn, L^3

Scheme 89



(*a*) Bu^nLi, EtC≡CH; (*b*) 1) Li, PDA, Bu^tOK (92% yield); 2) Bu^nLi, TMSCl; 3) BzCl, PyH (98% yield); (*c*) $SnCl_4$

Scheme 90

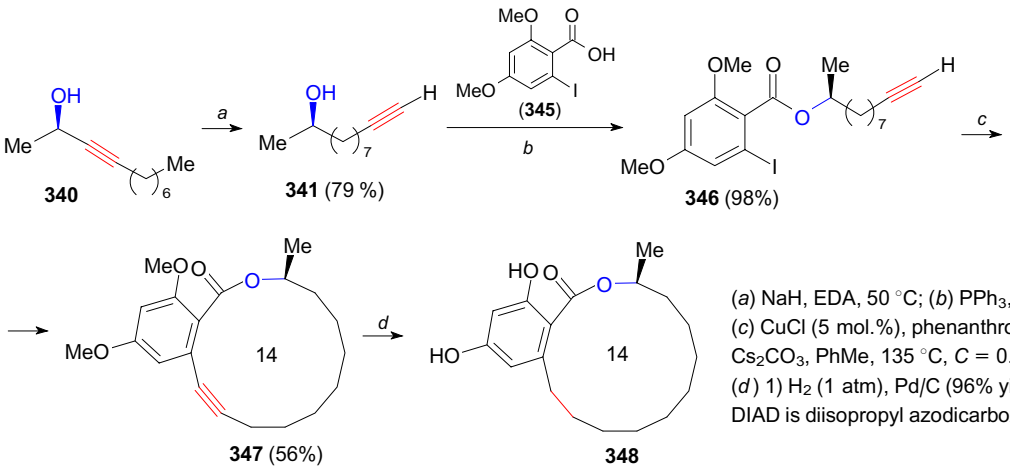


(*a*) KH, PDA; (*b*) 1) Bu^nLi, TBDMSCl, $ClCO_2Et$ (81% yield); 2) PhOH, PPh_3 (90% yield)

acid (**345**) to give (*S*)-alkylbenzoate **346** — the starting compound for macrocyclization. The cyclization under the selected conditions led to macrocyclic acetylenic lactone **347**; the reduction of the intramolecular triple bond and removal of Me protective groups led to the target product — the natural compound zearalane (**348**) (Scheme 91).

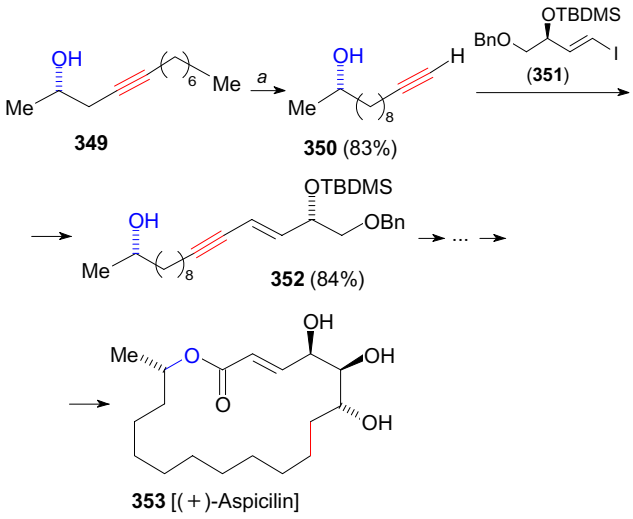
The synthesis of yet another macrolide lactone also included the isomerization of chiral (*S*)-dodec-4-yn-2-ol (**349**) promoted by KAPA and the Sonogashira reaction of alcohol **350** and disubstituted (*S*,*E*)-4-iodobut-3-ene-1,2-diol **351** to give enyne **352** (Scheme 92).[212]

Scheme 91



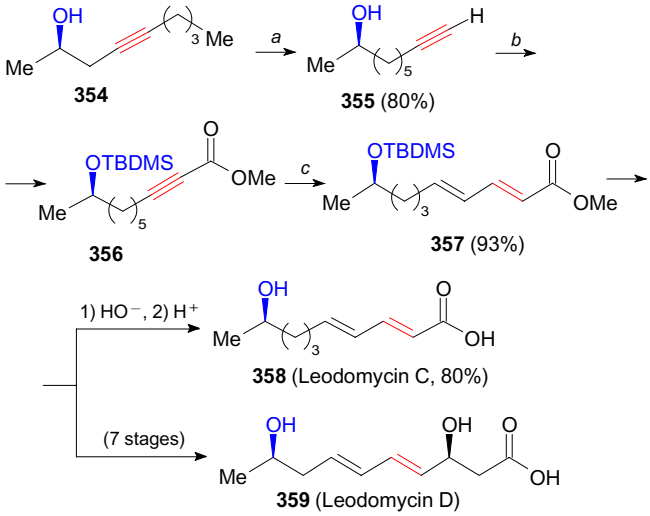
(*a*) NaH, EDA, 50 °C; (*b*) PPh_3, DIAD;
(*c*) CuCl (5 mol.%), phenanthroline (30 mol.%), Cs_2CO_3, PhMe, 135 °C, C = 0.024 mol L^{-1};
(*d*) 1) H_2 (1 atm), Pd/C (96% yield); 2) BBr_3 (38% yield);
DIAD is diisopropyl azodicarboxylate

Scheme 92



(*a*) KH, PDA, rt; (*b*) Sonogashira reaction

Scheme 93



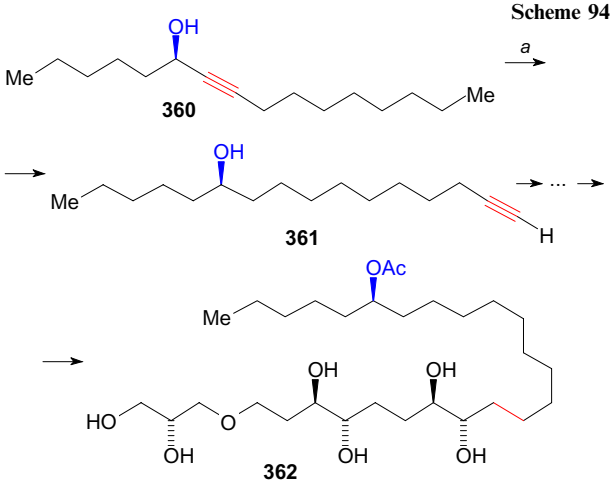
(*a*) NaH, PDA, rt; (*b*) 1) TBDMSCl, imidazole (96% yield); 2) Bu^nLi, $ClCO_2Me$ (92% yield); (*c*) PPh_3, PhOH, Δ

The subsequent Sharpless asymmetric dihydroxylation, the Wittig reaction and ring closing through macrolactonization using intermediate O-protection and deprotection afforded the target (+)-aspicilin (**353**).

The acetylene zipper reaction of (*R*)-non-4-yn-2-ol (**354**) promoted by NAPA gave terminal acetylenic alcohol **355** in 80% yield.[213] This alcohol was used in synthesis of natural compounds isolated from marine bacteria. Further methylcarbonylation of terminal acetylene **355**, Trost isomerization of methoxycarbonylacetylene **356** to the corresponding diene **357** and hydrolysis at the final stage led to leodomycin C (**358**). Leodomycin D (**359**) was synthesized from ester **357** through seven additional synthetic stages (Scheme 93).

The isomerization of (*R*)-hexadec-7-yn-6-ol (**360**) under the action of NAPA gave the terminal acetylenic alcohol (*R*)-hexadec-15-yn-6-ol (**361**), which was used in total synthesis of the anticancer marine natural compound mycalol **362** (Scheme 94).[214] The structure of this compound, namely, the configuration of two chiral centres, was refined.

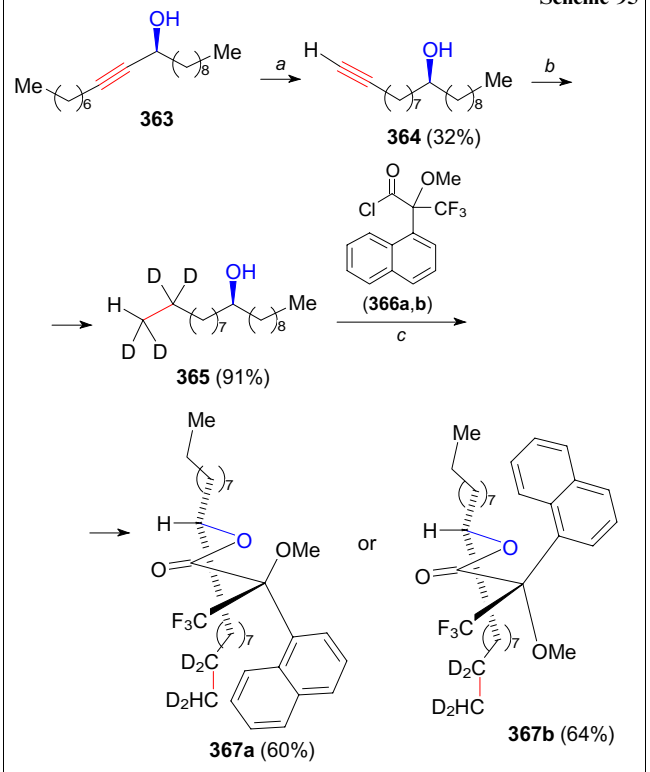
Scheme 94



(*a*) NaH, PDA

A method for diastereomeric discrimination of methyl group signals in the ^1H NMR spectra of the reaction products of higher secondary alcohols with chiral derivatizing acids — Mosher's acid analogues — have been reported.[215] The starting compound was alcohol **363**, converted into isomer **364** *via* the acetylene zipper reaction. Next, d_4-(*S*)-nonadecan-9-ol **365** was synthesized and derivatized with the *R* and *S* isomers of α-naphthyl Mosher's acid analogues **366a**,**b** to give diastereomers **367a**,**b**

Scheme 95



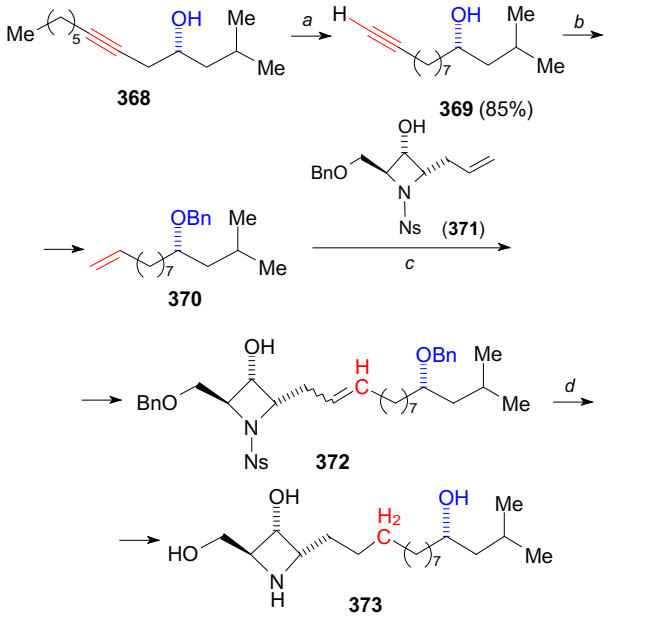
(*a*) KH, PDA, rt; (*b*) D_2, 5% Pd/C, rt; (*c*) $(COCl)_2$, DMF, hexane–CH_2Cl_2 (1 : 1), 0 °C; **366**: *R* isomer (**a**), *S* isomer (**b**); **367**: *S*,*R* isomer (**a**), *S*,*S* isomer (**b**)

(Scheme 95). For the latter, pronounced diastereomeric discrimination of the methyl group signals in the ^1H NMR spectra was observed.

Fujiwara *et al.*[216] proposed a general method for the synthesis of penaresidin B with actomyosin ATPase-activating properties and cytotoxicity. The method is based on the use of the RCM reaction to introduce a side-chain hydroxydodecyl moiety. The initial acetylene zipper reaction for chiral alcohol **368**, as in the previous example, proceeded under the action of KAPA and yielded terminal acetylene **369**. Next, a six-step general approach developed by the authors was used, which involved the RCM of alkenes **370** and **371** in the presence of the Grubbs II catalyst to give product **372** and the hydrogenation of its multiple bond. At the final stage, penaresidin B (**373**) was formed by deprotection. The advantage of this approach is that it can afford penarezidin side-chain analogues (Scheme 96).

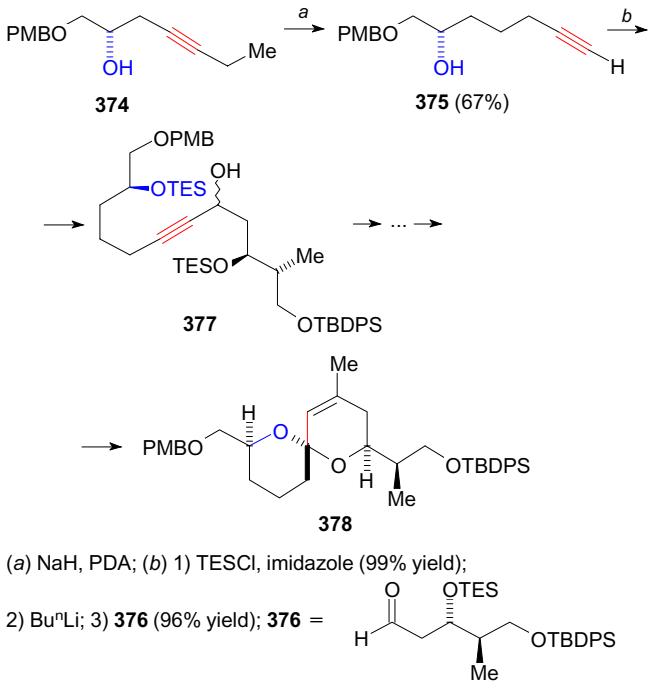
An approach to the synthesis of 7-deoxyocadaic acid, an inhibitor of serine/threonine phosphatase, have been reported.[217] The authors developed an efficient method for the formation of the C(3)–C(14) domain of this acid (Scheme 97). The isomerization of a mixture of enantiomers of monoprotected glycol **374** (the *S*/*R* ratio ~6.4 : 1, the major enantiomer is shown) proceeded under the action of NAPA in propane-1,3-diamine on heating to 70 °C and led to terminal alcohol **375** in 67% yield. It should be noted that the authors did not succeed in isomerization of the protected glycol; therefore, the free OH group was protected with TESCl after the acetylene zipper reaction. Intermediate diprotected acetylene glycol was converted to lithium acetylide and coupled with aldehyde **376**. Oxidation of the obtained propargyl alcohol **377** to ketone with the Dess–

Scheme 96



(*a*) KH, PDA; (*b*) 1) H_2, Lindlar catalyst, quinoline, CH_2Cl_2 (96% yield); 2) NaH, BnBr, TBAI (80% yield); (*c*) Grubbs II catalyst; (*d*) 1) PhSH, Cs_2CO_3 (97% yield); 2) Boc_2O, Et_3N (82% yield); 3) H_2/Pd (96% yield); 4) HCl, MeOH (92% yield)

Scheme 97



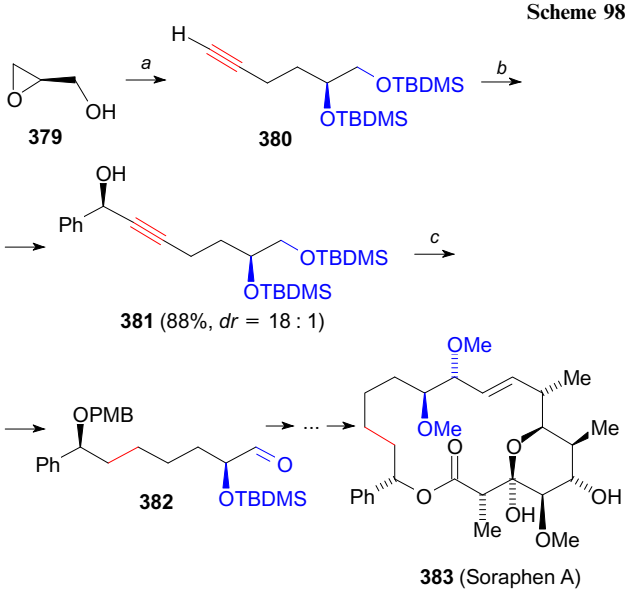
(*a*) NaH, PDA; (*b*) 1) TESCl, imidazole (99% yield); 2) Bu^nLi; 3) **376** (96% yield); **376** =

Martin periodinane, chromatographic isolation of the major *S* diastereomer, and double intramolecular hetero-Michael addition and isomerization of the exocyclic double bond afforded the target spiroketal **378**.

The acetylene zipper reaction has been used at the initial stage of the total synthesis of natural macrocycle, which included 34 stages and demonstrated the unique possibilities of the chemistry of acetylenes. In particular, an optically

active diol resulting from the epoxide ring opening reaction of (*R*)-glycidol **379** with lithium propynylide was isomerized under the action of LAPA in the presence of potassium *tert*-butoxide, that led to a terminal glycol without loss of enantiomeric purity. Protection of both OH groups to form diprotected glycol **380** and enantioselective ethynylation of benzaldehyde catalyzed by dimethylzinc in the presence of the ProPhenol ligand (L^3) gave the product **381**. The subsequent steps of triple bond hydrogenation, protectiion and deprotection and the Swern oxidation led to compound **382**, which acted as a key block in further transformations to form the target soraphen A (**383**) (Scheme 98).

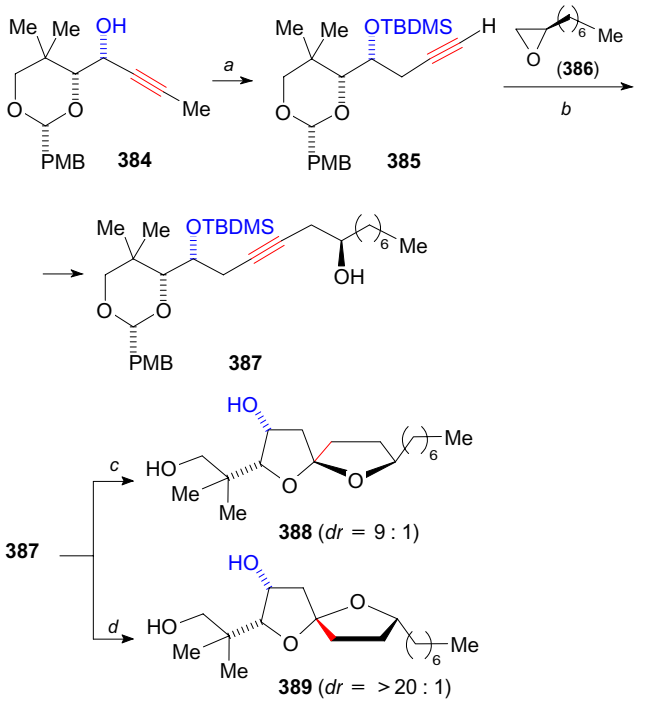
Scheme 98



(*a*) 1) CH≡CMe, Bu^{n}Li (68% yield); 2) LAPA, Bu^{t}OK (66% yield); 3) TBDMSCl, imidazole (78% yield); (*b*) BzH, L^3, Me_2Zn; (*c*) 1) H_2, $PtO_2 \cdot H_2O$ (92% yield); 2) TBAI, KHMDS, PMBCl (90% yield); 3) HF · PyH (50% yield); 4) Swern oxidation (98% yield)

In the synthesis of 5,5-spiroketals being the core of the natural product cephalosporolide H, one of the stages was the acetylene zipper reaction of chiral alcohol **384** promoted by KAPA, which occurred without loss of enantiomeric purity.[219] After installation of the TBDMS protective group, terminal acetylene **385** reacted with oxirane **386** to form the key intermediate — acetylenic alcohol **387**. Depending on the cyclization conditions (Pd^{II}- or Au^{I}-induced cyclization in the presence of $ZnCl_2$), alcohol **387** gave epimeric 5,5-spiroketals **388** or **389**, respectively. It is essential that the formation of the required epimer **389**,

Scheme 99



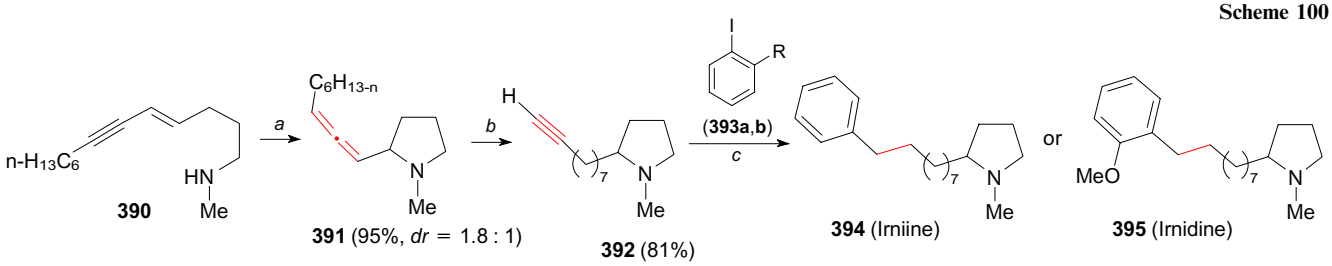
(*a*) 1) KAPA (92% yield); 2) TBDMSCl, imidazole (yield 93%); (*b*) Bu^{n}Li, $BF_3 \cdot Et_2O$; (*c*) 1) $Pd(MeCN)_2Cl_2$, MeCN, rt (42% yield); 2) TBAF (73% yield); (*d*) 1) AuCl, MeOH, rt (42% yield); 2) $ZnCl_2$, MgO, CH_2Cl_2 (73% yield); TBAF is tetra-n-butylammonium fluoride

which was then converted to the target cephalosporolide H, is controlled by chelation of the hydroxyl group and the ketal oxygen atom with $ZnCl_2$ (Scheme 99).

4.2. Acetylene zipper reaction for N-derivatives

An unusual example is the acetylene zipper reaction for pyrrolidine derivatives containing an internal allene fragment. Zhang, Werness and Tang[220] selected conditions for the intramolecular hydroamination of conjugated enynes, which proceeded under the action of n-butyllithium in THF for a wide range of amines. In particular, the reaction of amine **390** afforded the allene-substituted *N*-methylpyrrolidine **391** in good yield. Isomerization of this pyrrolidine under the action of KAPA at room temperature in THF led to terminal alkynylpyrrolidine **392** in good yield. The latter was subjected to Sonogashira cross-coupling with iodarenes **393a**,**b** with subsequent reduction of the triple bond, that allowed the authors to obtain alkaloids of the plant *Arisarum vulgare* **394** and **395**, demonstrating the relevance of the developed methodology (Scheme 100).

Scheme 100



(*a*) Bu^{n}Li, THF; (*b*) KAPA, THF, rt; (*c*) 1) Sonogashira reaction (for **a**, 52% yield, for **b**, 55% yield); 2) H_2, Pd/C (10 mol.%), MeOH (for **a**, 72% yield, for **b**, 57% yield); R = H (**393a**), OMe (**393b**)

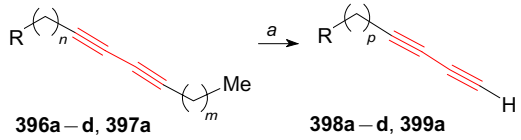
The analysis of the literature shows that the acetylene zipper reaction is widely used in modern organic synthesis, mainly for the production of a variety of terminal acetylenic alcohols, including alcohols with stereocentres. This process is often used in the synthesis of natural compounds and their analogues, containing both long linear fragments in the carbon skeleton and rings, including macrocycles or heterocycles. The presented data demonstrate that the entire set of bases suitable for isomerization can be used for the same alcohols. However, the most commonly used systems are sodium aminoethylamide and potassium aminopropylamide. Usually, lithium aminopropylamide, which is less hazardous in operation, is first prepared and then treated with potassium *tert*-butoxide to form *in situ* the most efficient superbase KAPA. Despite the fact that the most available base is NAETA, which is formed in the reaction of sodium hydride with ethanediamine, isomerization promoted by NAETA usually requires prolonged heating to 60 °C, whereas when KAPA is used, the acetylene zipper reaction usually proceeds at room temperature.

4.3. Diacetylene zipper reaction

The study of multipositional prototropic isomerization of diacetylenic hydrocarbons and alcohols (the diacetylene zipper reaction) was started in the laboratory of I.A.Favorskaya under the supervision of L.A.Remizova and has been studied in detail in the group of I.A.Balova. A detailed optimization of the conditions for the simultaneous isomerization of two triple bonds from the internal to the terminal position under the action of lithium 2-aminoethylamide led to the creation of a method for the synthesis of terminal diacetylenic hydrocarbons and their further functionalization for the production of diacetylenic alcohols, acids, ketones, arenes and hetarenes.

The first report on the diacetylene zipper reaction described the isomerization of diacetylenic hydrocarbons **396a–d** and nona-2,4-diyn-1-ol (**397a**) under the action of a seven-fold excess of LAETA in the ethanediamine–benzene–hexane (1 : 2 : 2) solvent system. The terminal diacetylenes **398a–d** were isolated in high yields (70%–80%), while the yield of terminal diacetylenic alcohol **399a** was only 20% (Scheme 101).

Scheme 101



396a–d, 397a **398a–d, 399a**

(*a*) 1) LAETA (7 equiv.), EDA, PhH, hexane; 2) H_2O;
R = Me (**396**, **398**), OH (**397a**, **399a**); *m* = 3: *n* = 2 (**396a**), 3 (**396b**); *n* = 3, *m* = 4 (**396c**); *n* = *m* = 5 (**396d**); *n* = 1, *m* = 3 (**397a**); *p* = 5 (**399a**, 19%), 6 (**398a**, 76%), 7 (**398b**, 74%), 8 (**398c**, 72%), 11 (**398d**, 71%)

Since the diacetylene zipper reaction affords lithium derivatives of terminal isomers, it was decided to introduce reactive 1-lithioalka-1,3-diynes into the reaction with various C-electrophilic agents without preliminary isolation of unstable terminal diacetylenes. In one of the first studies devoted to these transformations,[222] dialkynylide anions **400** were alkylated with THP-protected bromine-substituted alcohols **401a**,**b**. It is important that after the isomerization process, THF or dioxane was introduced into the reaction mixture before the addition of the alkylating agent to destroy the associates of organolithium compounds. After removal of the THP protection, this two-stage process afforded long-chain diacetylenic alcohols **402a–c** in 35%, 20% and 47% yield, respectively; the latter were oxidized with Jones reagent to give acids **403a–c** (Scheme 102).

To obtain a variety of secondary and tertiary diacetylenic alcohols **404**, **405**, oxiranes and ketones, respectively, have been used as electrophilic agents.[223] It is worth noting that the authors proposed to exclude EDA from the solvent system, that made it possible to minimize the side reaction of diamine with the electrophilic component (Scheme 103). However, homopropargyl alcohols like **406** were still isolated as by-products; their formation was attributed to the isomerization of the initially forming alcohols **405** under the action of LAETA.

The conditions for the synthesis of diacetylenic ketones **407** through the reaction of lithium dialkynylides **400** with Weinreb amides were reported (see Scheme 103).[224]

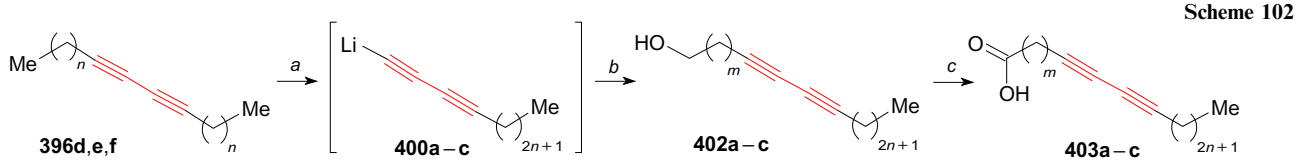
The Sonogashira–Hagihara reaction — the Cu^{I}/Pd^{0}-catalyzed cross coupling of terminal acetylenes with halides with a $C(sp^2)$–Hal bond — is a unique tool in the synthesis of aryl and hetaryl-substituted alkynes, as well as enyne derivatives.[54, 55] The possibility to use unstable diacetylene compounds, obtained by the diacetylene zipper reaction, in the Sonogashira coupling without isolation and purification has been demonstrated [225–227] (Scheme 104).

In particular, it was shown that the diacetylene zipper reaction followed by quenching of diacetylide anion with water and Sonogashira reaction in one-pot mode is an efficient method for the synthesis of *o*-(buta-1,3-diynyl)anilines, aminopyridines and naphthylamines.[225]

This procedure was extended to a number of other aromatic and heterocyclic iodides, which afforded various mono- and di(alka-1,3-diynyl)arenes **408** and heteroarenes **409–411** in good and high yields in most cases.[226, 227]

Since diacetylenic alcohols are of great interest for further functionalization of the OH group, the isomerization conditions for this family of compounds have been optimized.[228] It was demonstrated that, in contrast to diacetylenic hydrocarbons, isomerization of alcohols **397a**, **412a**,**b** should be accomplished for 5 min in an EDA–THF mixture without adding nonpolar solvents (Scheme 105). However, even under these conditions, preparatively significant isomerization to terminal isomers **413a**,**b** is possible only for tertiary diacetylenic alcohols **412a**,**b**, while primary

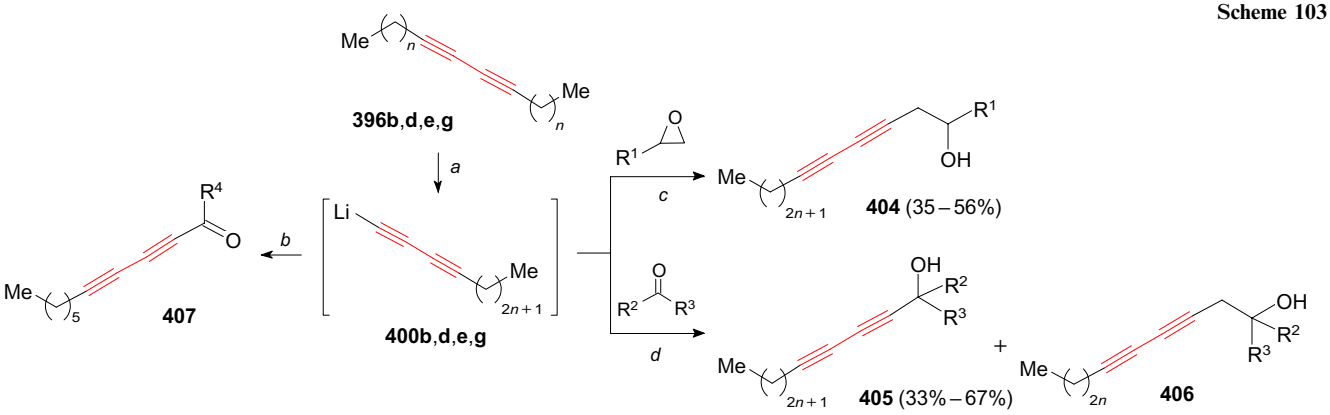
Scheme 102



396d,e,f **400a–c** **402a–c** **403a–c**

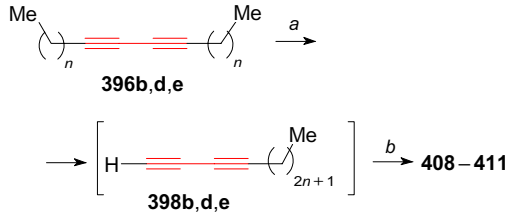
(*a*) LAETA (3 equiv.), EDA, PhH, hexane; (*b*) 1) THF; 2) $Br(CH_2)_mCH_2OTHP$ (**401a**,**b**); 3) HCl; (*c*) Jones oxidation;
n = 2 (**396e**, **400a**, **402a**, **403a**), 4 (**396f**, **400b**, **402b**, **403b**), 5 (**396d**, **400c**, **402c**, **403c**); *m* = 5 (**401a**, **402b**,**c**, **403b**,**c**), 9 (**401b**, **402a**, **403a**)

Scheme 103



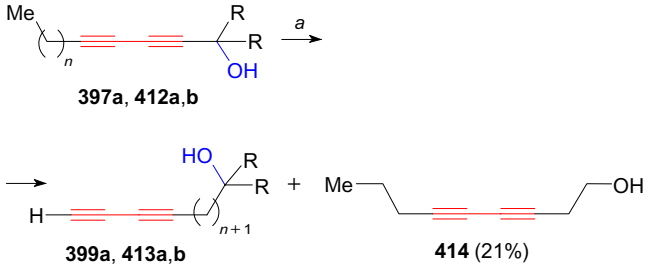
(*a*) LAETA (3 equiv.), THF, PhH, hexane; (*b*) for *n* = 3: $R^1C(O)N(Me)OMe$, THF; (*c*) for *n* = 2, 3, 5: THF ; (*d*) for *n* = 0, 2, 3, 5: THF; **396**, **400**: *n* = 0 (**g**), 2 (**e**), 3 (**b**), 5 (**d**); **404**: R^1 = H, Ph, 2-$MeC_6H_4OCH_2$; **405**: R^2, R^3 = Me, Ph, 2-Py, 3-Py, 4-Py; **406**: R^2 = Me, R^3 = 2-Py, *n* = 3 (7%); R^2 = Ph, R^3 = 4-Py: *n* = 2, 3, 5 (6% – 15%); **407**: R^4 = Me (52%), Ph (64%), PhCH═CH (45%)

Scheme 104



(*a*) 1) LAETA (3 equiv.), THF, PhH, hexane; 2) H_2O; (*b*) Sonogashira reaction: XI or IYI, Cu^I, Pd^0 (36% – 96% yield); **396**, **398**: *n* = 2 (**e**), 3 (**b**), 5 (**d**); X = Ar, Het; Y is arylene, hetarylene

Scheme 105



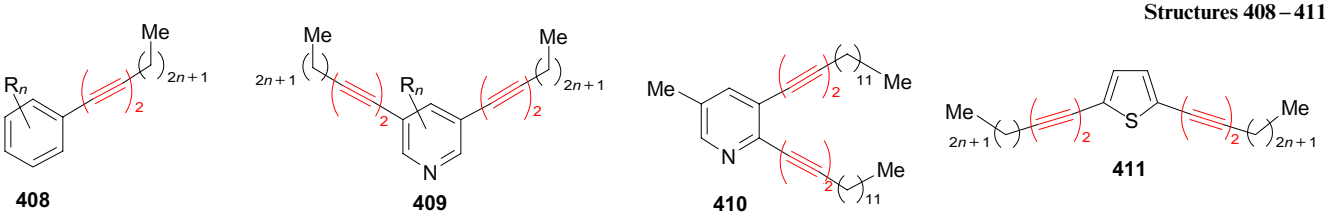
(*a*) LAETA, EDA, THF; R = H, *n* = 3 (**397a**; **399a**, 4%); R = Me: *n* = 2 (**412a**; **413a**, 42%), 5 (**412b**; **413b**, 21%)

alcohol **397a** is resinified during the reaction and the yield of terminal diacetylene **399a** does not exceed 4%. The authors explain such a different behaviour of primary monoacetylenic and diacetylenic alcohols by the higher acidity of the propargyl H atoms and the undesirable reverse shift of the isomerized triple bonds towards the OH group with the formation of unstable cumulene structures and subsequent destruction of the molecule. It should be noted that when the reaction time for the substrate **397a** was decreased to 1.5 min, alcohol **414** containing triple bonds in the homopropargyl position was isolated as the major product.

The isomerization of diacetylenic alcohols was described in a paper [229] devoted to the synthesis of diacetylene azides. For example, the diacetylene zipper reaction of alcohols **412b**,**c** occurred under the action of LAETA in the benzene – hexane system. However, the yields of target terminal diacetylenes were low, and reaction conditions have not been optimized. The resulting diacetylenes **413b**,**c** were used in the Cadiot – Chodkiewicz reaction to synthesize triacetylenes **415b**,**c** (Scheme 106).

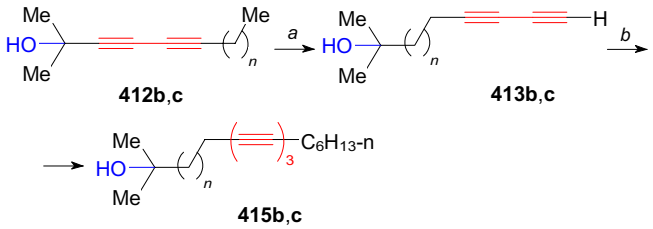
A revisited study of the diacetylene zipper reaction for a series of diacetylenic alcohols has been published in 2013. [230] As in the previous examples, the process was promoted by LAETA in the EDA – THF solvent system. It was shown that for the complete conversion of the starting internal diacetylene alcohols to terminal alcohols, the EDA-to-THF ratio is of crucial importance. It was found that the optimal ratio of these solvents is 1 : 2. In this case, the formation of isomerization by-products, the corresponding homopropargyl alcohols, was not observed. The resulting alcohols **399a**,**b**, **413c** were introduced without purification into the Sonogashira reaction with various *ortho*-functionalized iodoarenes. When this reaction was carried out in the presence of diisopropanolamine in DMF and with an excess (3 – 5 equiv.) of the starting internal alcohols, the target buta-1,3-diynylarenes **416** were isolated in moderate to high yields (Scheme 107).

Structures 408 – 411



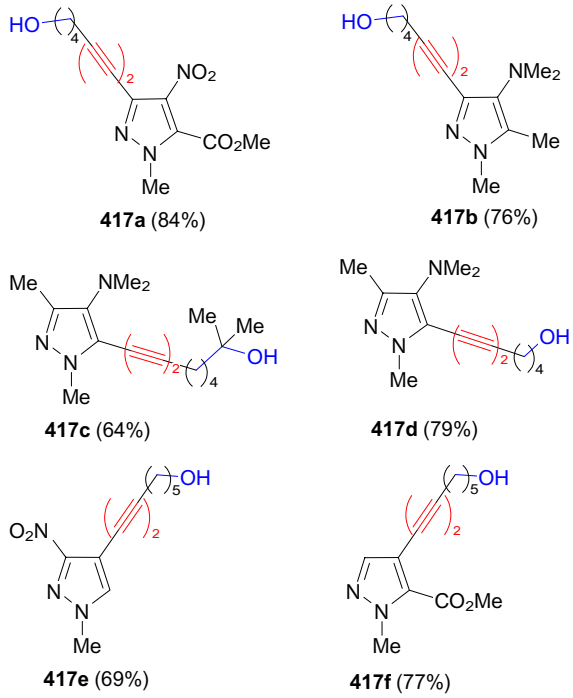
408: R_n = H, NH_2, NO_2, CN, Br, OMe, C(O)H, Ac; **409**: R = NH_2, Cl; **408**, **409**, **411**: *n* = 2, 3, 5

Scheme 106



(*a*) LAETA, PhH, hexane; (*b*) Cadiot–Chodkiewicz reaction: BrC≡CC$_6$H$_{13}$-n; *n* = 5 (**412b**; **413b**, 21%; **415b**, 69%), 3 (**412c**; **413c**, 43%; **415c**, 78%)

Structures 417



The diacetylenic zipper reaction of the above diacetylenic alcohols followed by the Sonogashira reaction was used in synthesis of (buta-1,3-diynyl)-substituted pyrazoles **417a**–**f**.[231]

Cyclization of functionalized diynes is an important method of synthesis of heterocyclic compounds, including ethynyl-substituted heterocycles.[232] Thus, the next step of applying the diacetylene zipper reaction–Sonogashira cross-coupling sequence is the use of the resulting *ortho*-functionalized (buta-1,3-diynyl)arenes in synthesis of ethynyl-substituted heterocycles.

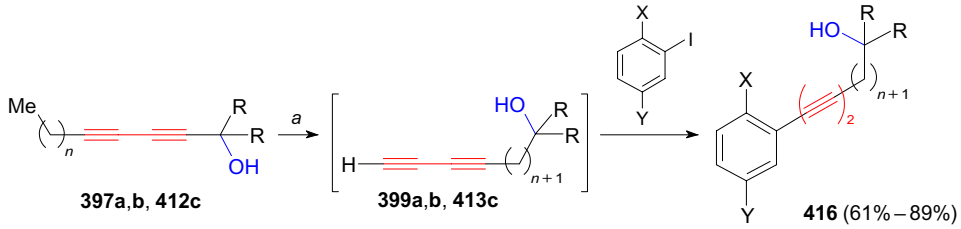
The Richter cyclization of *o*-(buta-1,3-diynyl)anilines **418** through the formation of diazonium salts **419** leads to 4-bromo(chloro)-3-ethynylcinnolines **420**, containing different substituents in the cinnoline ring (Scheme 108).[233,234]

Analogous products were also synthesized from the corresponding triazenes **421**. The substitution of the bromine atom by an ethynyl moiety through the Sonogashira reaction gives the enediyne system **422** with the annulated cinnoline ring.[234]

The substitution of the bromine atom by a nucleophilic moiety in cinnoline **419** with R = CO_2Me, *n* = 7 followed by cyclization affords polyheterocyclic systems **423**–**426**.[233–235]

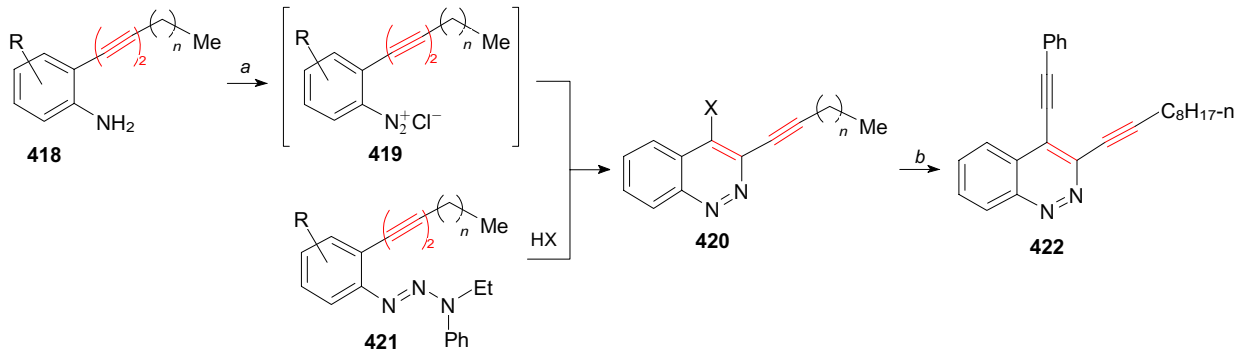
Another type of intramolecular cyclization of *ortho*-functionalized (buta-1,3-diynyl)arenes **416** — electrophile-promoted cyclization — was used to synthesize 3-iodo-2-ethynylheteroindenes **427** (Scheme 109). It is worth noting that in the case of N-cyclization, the hydroxyl group should be protected with TBDMSCl. The resulting iodoethynylhe-

Scheme 107



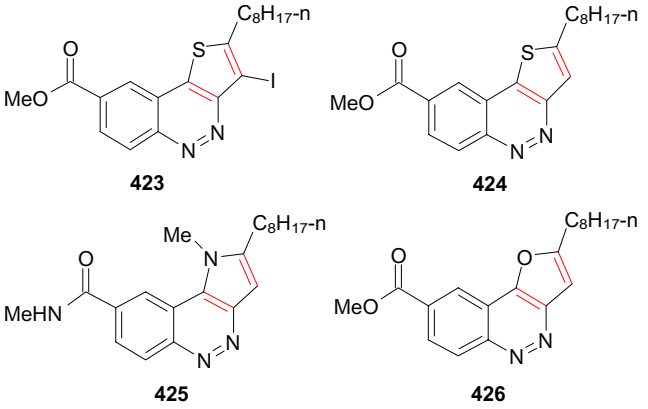
(*a*) LAETA, EDA–THF (1 : 2); R = H: *n* = 3 (**397a**, **399a**), 2 (**397b**, **399b**); R = Me, *n* = 3 (**412c**, **413c**); X = SMe, NH_2, NO_2, NMe_2; Y = H, CO_2Et

Scheme 108



(*a*) $NaNO_2$, HCl; (*b*) Sonogashira reaction (for R = H, X = Br, *n* = 7): PhC≡CH; *n* = 5, 7, 9; X = Cl, Br

Structures 423 – 426



terocycles **427** were converted to acyclic enediyne systems **428**.[236]

Compound **429** was used as a starting compound in the synthesis of a 12-membered enediyne system annulated with indole through the RCM at the stage of macrocyclization. To this end, both hydroxyl groups were modified to give the acyclic diene substrate **430**. Ring closing catalyzed by the Grubbs II catalyst was smooth, as in the case of the previously described benzothiophene analogue,[237] and led to the target dienediyne as a mixture of *E* (**431a**) and *Z* isomers (**431b**) in 6 : 1 ratio (in 78% total yield), and the major *E* isomer **431b** was isolated in the individual form in 34% yield (Scheme 110).[236]

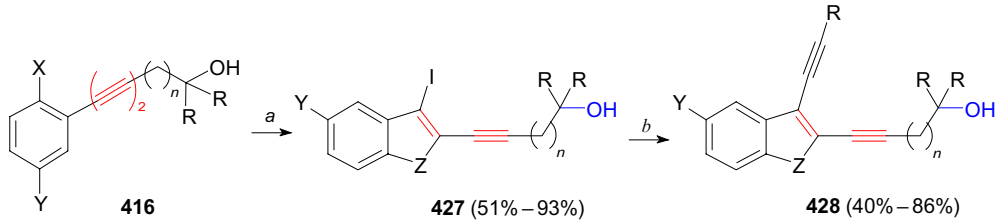
Thus, the use of the diacetylene zipper reaction in combination with subsequent modifications of the terminal diacetylene moiety is an efficient method for the synthesis of unsymmetrically substituted diacetylene compounds, including those containing different functional groups. This synthetic approach should be considered as an alternative supplement to other widely used methods for the preparation of non-symmetric diacetylene compounds — the Cadiot – Chodkiewicz and dehydrodimerization of non-equivalent acetylene alcohols under Glaser conditions. The choice between these two synthetic sequences and the diacetylene zipper reaction depends primarily on the nature of the substituents, as well as on the availability of the starting reactants and the scale of the synthesis. It should be understood that to obtain diacetylene substrates for the diacetylene zipper reaction, both of the above methods are used, and the starting compounds in these transformations are cheap and available terminal acetylene hydrocarbons, propargyl alcohol and Favorskii carbinol.

5. Conclusion

The chemistry of mono-, di- and polyacetylene molecules is extremely diverse and multifaceted. The contribution of A.E.Favorskii to the formation and development of organic chemistry and, in particular, the chemistry of acetylene compounds, is difficult to overestimate. The reactions that he discovered more than 100 years ago have not lost their relevance. On the contrary, they are actively developed and evolve with modern organic synthesis. All the reactions discussed in the Introduction, especially acetylene – allene isomerization and the acetylene zipper reaction, are used in the synthesis of a wide variety of compounds as a convenient tool for the formation of the carbon skeleton of complex molecules. In this case, the triple bond can be both retained in the target molecules and used for further functionalization.

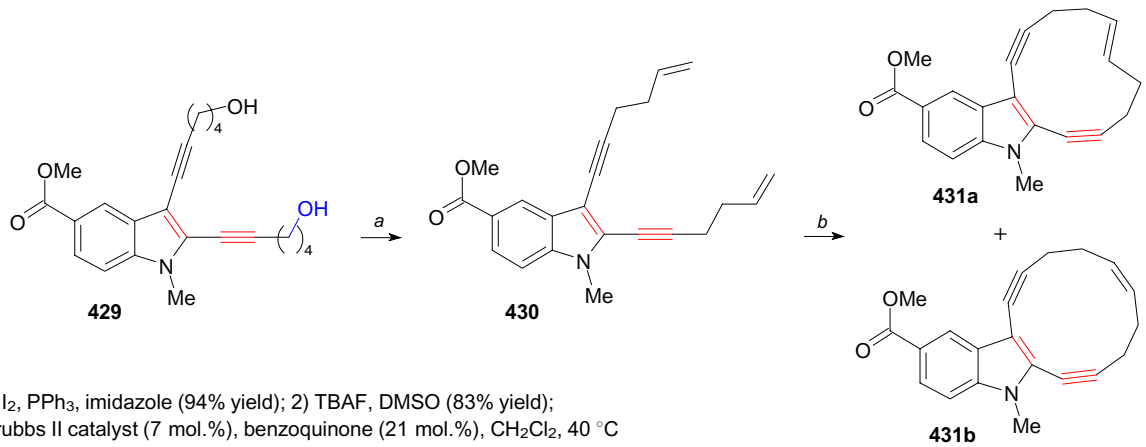
In recent years, the chemistry of acetylenes has received tremendous development. Radically new fields have been

Scheme 109



(*a*) I_2, CH_2Cl_2; (*b*) Sonogashira reaction: RC≡CH; *n* = 5, 7, 9; X = SMe, NMe_2; Y = H, CO_2Et; Z = S, NMe; R = Alk, Ar

Scheme 110



(*a*) 1) I_2, PPh_3, imidazole (94% yield); 2) TBAF, DMSO (83% yield);
(*b*) Grubbs II catalyst (7 mol.%), benzoquinone (21 mol.%), CH_2Cl_2, 40 °C

discovered in the chemistry of acetylene compounds, which are reflected in the cited reviews: Cu-catalyzed azide–alkyne cycloaddition[238] and strain-promoted azide–alkyne cycloaddition (SPAAC) for use in biology;[239,240] different alkyne reactions catalyzed by metal complexes,[241] including gold,[242–244] silver,[245] palladium,[246] ruthenium,[247,248] rhodium,[249] manganese complexes;[250] activation of alkynes by superelectrophiles.[251,252] New mild methods of ethynylation using Cu/Pd-catalyzed cross coupling[55] and C—H activation;[253] alkyne metathesis,[254] including carbene–alkyne metathesis;[255] synthesis of heterocyclic systems,[256] including iodine-promoted alkyne cyclizations;[257] synthesis of polyaromatic systems,[258,259] alkenylation of arenes and heteroarenes under the action of acids;[260] various functionalization methods for terminal alkynes,[261] including A3 reactions (metal-catalyzed coupling of aldehyde, amine and alkyne),[262,263] allenation of terminal alkynes[264] and other methods of triple bond modification have been developed.[265,266]

In summary, we can be sure that the strong foundation of the chemistry of acetylenes laid by A.E.Favorskii is the scientific basis for both the reactions and synthetic sequences described in this review, and for new transformations that will be discovered in the future.

Figure 2 is courtesy of the Wiley-VCH Verlag.

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