Total synthesis of ethyl and ortho esters of the omega-3 stearidonic and eicosapentaenoic acids

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90 ECTS thesis submitted in partial fulfillment of a
Magister Scientiarum degree in chemistry

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Reykjavik, January 2016

Total synthesis of ethyl and OBO esters of the omega-3 stearidonic and eicosapentaenoic acids
Total synthesis of ethyl and OBO esters of SDA and EPA
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Abstract

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are very important bioactive molecules. The numerous health benefits claimed to be associated with the n-3 PUFAs have greatly increased the interest in them for their production and synthesis. Applications such as research and development for drugs or as food supplements have increased the demand for a number of PUFAs, especially EPA and DHA, and possibly also SDA. After successfully synthesizing all-*cis*-(2'R)-1-O-(2´-methoxy-4,7,10,13,16,19-docosahexaenyl)-sn-glycerol, a polyunsaturated ether lipid molecule posessing a DHA-like structure, the group set out to synthesize all the major omega-3 PUFAs utilizing the methods and experience gained from that synthesis.

The work described in this thesis reveals our attempts to develop an efficient method to synthesize isomerically pure all-*cis* n-3 PUFAs, more specifically SDA and EPA. The method was based around construction of the so called ‘tail’ and ‘head’ parts intended for a highly convergent total synthesis. The tail part which incorporates the n-3 framework and methylene skipped triple bonds was successfully synthesized with successive copper mediated couplings involving propargyl subunits. The head part was synthesized from a commercially available carboxylic acid protected with an ethyl ester or a special orthoester and then lengthened via copper mediated coupling with a propargyl subunit. The head and tail were then attached together and the resulting polyyne precursor of the fatty acid was then submitted to a highly stereospecific catalytic semi-hydrogenation to afford the final product. Although this undoubtedly produced the target molecule it had a lot of impurities in the form of over-hydrogenated byproducts. The pure final product was then finally isolated via silver ion chromatography.

Útdráttur

Omega-3 fjölómettaðar fitusýrur (n-3 PUFA) eru mjög mikilvægar lífvirkar sameindir. Ýmislegir þættir í heilsu manna hafa verið tengdir við n-3 PUFA og hefur það stóraukið áhuga á nýjum leiðum til að framleiða og smíða þessi efni. Allt frá rannsóknum og þróun á lyfjum til framleiðslu fæðubótarefna hefur aukið eftirspurn eftir PUFA, sérstaklega eikósapentaensýru (EPA) og dókósahexaensýru (DHA), en mögulega einnig steridónsýru (SDA). Eftir að hafa smíðað hið fjölómettaða metoxýlaða eterlípíð all-*cis*-(2'R)-1-O-(2´-methoxy-4,7,10,13,16,19-docosahexaenyl)-*sn*-glycerol, sem hefur byggingu er svipar til DHA, lagði hópurinn af stað í efnasmíðar á öllum helstu tegundum n-3 PUFA og nýtti við það aðferðir og reynslu úr þeirri efnasmíð.

Sú vinna sem lýst er í þessari ritgerð leiðir í ljós okkar tilraunir til að þróa skilvirka aðferð til að smíða hreinar *cis*-skipaðar fjölómettaðar fitusýrur, einkum SDA og EPA. Sú leið sem varð fyrir valinu gekk út á það að smíða svokallaða hala og haus hluta samhliða sem síðan var skeytt saman. Halinn sem inniheldur n-3 endann og auk þess kolefniskeðju, þar sem skiptast á þrítengi og metylen hóp var smíðað með góðum árangri þar sem beitt var röð koparmiðlaðra tengihvarfa endastæðra þrítengja við própargýl halíð hvarfefni. Hausinn var smíðaður úr, alkýn karboxýlsýru, sem vernduð var annaðhvort sem etýlester eða s.k. OBO ortho ester og svo lengd með própargýl hóp. Hausnum og halanum var svo skeytt saman til að mynda fjölalkýn fyrirrennara fitusýrunnar sem var svo hlutvetnaður í viðurvist málmhvata til að mynda hið rúmsértæka lokamyndefni. Þó að þetta hafi án nokkurs vafa leitt til myndunar á réttu lokamyndefni, þá voru þónokkur óhreinindi á formi yfirmettaðra hliðarmyndefna til staðar. Hreint lokamyndefnið var svo loks einangrað og hreinsað með silfurjóna kísilskiljun.

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Abbreviations

PUFA	Polyunsaturated fatty acid
SDA	Stearidonic acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
LA	Linoleic acid
ALA	α-linolenic acid
OBO	4-methyl-2,6,7-tri**o**xa-**b**icycl**o**[2.2.2]octan-1-yl
TMS	Trimethylsilyl
n-BuLi	n-butyllithium
NMR	Nuclear magnetic resonance
THF	Tetrahydrofuran
DMF	N,N-dimethylformamide
TBAF	Tetra n-butylammonium fluoride
HRMS	High resolution mass spectrometry
IR	Infrared

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1 Introduction

The chief goals of this MS project was to complete the total synthesis of the ethyl ester of stearidonic acid, to design a convenient synthetic route which would be applicable to all the major omega-3 fatty acids and, specifically, find the optimal conditions for the reaction and purification of an all-*cis* semi-hydrogenation of multiple skipped triple bonds. Finally, considerable work went into design and optimization of the synthetic route of the OBO protected acid instead of the ethyl ester.

This thesis is divided into five chapters. The first chapter discusses the general background of the project such as fatty acids in general, polyunsaturated fatty acids and their synthesis until now and then stearidonic acid specifically. The second chapter is a project description where the synthetic approach is described. The third chapter provides the results and discusses them. The fourth chapter discusses the conclusion derived from this work and the fifth and final chapter provides all the experimental details.

1.1 Fatty acids

Fat is one of the main macronutrients and consists mainly of triglycerides which are the esters of three fatty acids on a glycerol backbone.[1] A fatty acid is a carboxylic acid with an aliphatic hydrocarbon chain. Fatty acids are named in a systematic way according to the IUPAC name system. Both common names usually with a historic origin and systematic nomenclatures are widely used.[2] The carbon next to the carboxylic acid group is denoted as the alpha (α) carbon and the terminal methyl group at the end of the hydrocarbon chain is denoted as the omega (ω) carbon.[2] The carboxylic acid can be called the head of the compound and is also the alpha end while the hydrocarbon chain can be called the tail and the terminal methyl group the omega end. Most naturally occurring fatty acids have an even number of carbon atoms usually between 12-22 carbons in length.[1]

Fatty acids can be saturated or unsaturated. A saturated fatty acid contains no carbon to carbon double bond. A fatty acid which contains one carbon to carbon double bond is monounsaturated (MUFA) and if it has more than one it becomes polyunsaturated (PUFA).[3] The position of a double bond is usually designated as such: X:Y n-z, where X is the number of carbons, Y is the number of double bonds and the z is the number of carbon on the first double bond counted from the omega end.[3] Figure 1 shows stearidonic acid which has the systematic name octadeca-6,9,12,15-tetraenic acid and the short hand notation 18:4 n-3.

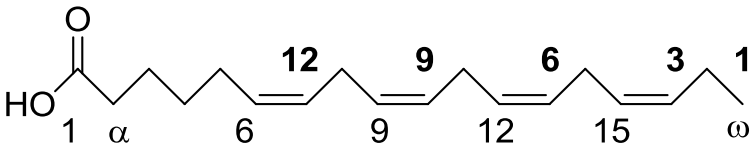


Figure 1. *Stearidonic acid (SDA), 18:4 n-3. The numbers in bold denote the number of a carbon counted from the omega end. The other numbers denote the number of a carbon counted from the alfa end.*

There are a few properties of fatty acids worth keeping in mind. Polyunsaturated fatty acids have multiple double bonds that are usually interrupted by a methylene group (skipped) and therefore it is easy to predict the position of all the double bonds from the shorthand designation. Double bonds in nature are dominantly found in the *cis* configuration though they can also be found as *trans*. The normal carbon to carbon bond has free rotation which makes saturated fatty acids extremely flexible molecules. Due to steric constrains the configuration is usually fully extended which makes them pack well together and this property gives fat with long saturated chains a high melting point. Carbon to carbon double bond does not have free rotation and causes a bend in the structure. This property has profound meaning for physiological and biological properties of unsaturated fatty acids, including reducing the melting point of fat, with a higher level of unsaturation.

1.2 Polyunsaturated fatty acids

Fatty acids are a very important energy source and have very high energy density, they are the main building-blocks of all cell membranes in the form of phospholipids and the PUFAs are also substrates for important biomolecules.[3] Linoleic acid (18:2 n-6) and α-linolenic acid (18:3 n-3) are classified as essential fatty acids (EFA) since the human body cannot synthesize them and therefore need to come from the diet. They are omega-6 and omega-3 respectively and can serve as the precursors for all other PUFAs in the body.[4]

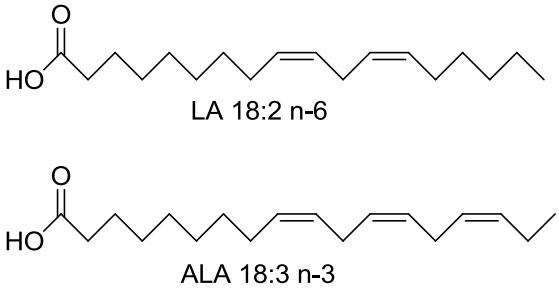


Figure 2*. The essential fatty acids linoleic acid (LA) and alpha-linolenic acid (ALA).*

The production of PUFAs in the body is facilitated through enzymes, namely elongase and desaturase. Elongase lengthens the carbon chain by two carbons and the desaturase removes two hydrogens to form a double bond. Figure 3 illustrates the enzymatic pathway that produces all the major PUFAs in plants and humans.[5] These enzymes are the reason humans cannot synthesize the essential fatty acids because humans only possess

desaturases that are capable of incorporating a double bond into the chain up to 9 carbons away from the carboxyl acid head group.[6] Plants and photoplankton on the other hand possess desaturases capable of incorporating double bonds further away from the head group as well as desaturases that incorporate double bonds from the omega end.

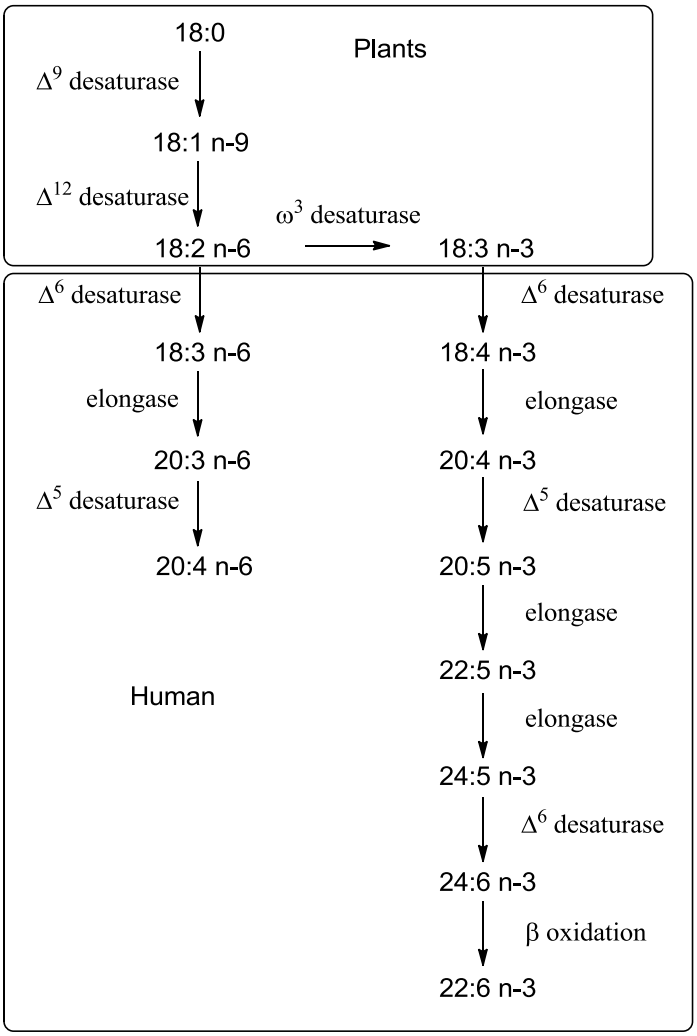


Figure 3. *The PUFA enzymatic pathway. All fatty acids are denoted by their short hand notation. Δ^x refers to the number of the carbon at which the desaturase incorporates the double bond.*

Vegetable oils are rich in the essential fatty acids, LA and ALA and is our biggest source of omega-6 and omega-3 PUFAs.[1] Marine fats and especially fish oils are a rich source of other long chain PUFAs such as EPA and DHA which make up to 20-30% of some fish oils.[7] In the body the long chain PUFAs are precursors for numerous pro-resolving and anti-inflammatory compounds such as lipoxins, resolvins and protectins and the relatively newly discovered maresins, see figure 4.[8] These compounds that derive from the omega-6 arachidonic acid (ARA) serve a key role in the promotion of inflammation which is an important process in dealing with a disease or injury.[8,9]

The omega-3 derivatives of EPA and DHA have on the other hand a key role in the resolution of inflammation and therefore the healing process.[8,9] The discovery of these compounds underlines the importance of the long chain PUFAs in the body and studies have shown numerous health benefits from consumption of EPA and DHA.

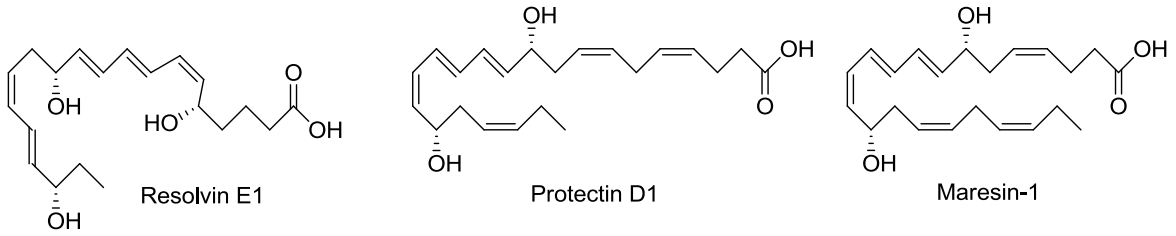


Figure 4. *An example of an EPA derived resolvin and a DHA derived protectin and maresin.*

Scientists have shown interest in the effect of PUFAs on chronic inflammatory diseases such as arthritis,[9,10,11] inflammatory bowel syndrome,[9,12] psoriasis[13] and asthma.[9,14] The beneficial effect of PUFAs in prevention and treatment of cardiovascular diseases have been known for a long time.[15] Omega-3 PUFAs have also showed beneficial effects on neurodegenerative and neurological conditions such as Alzheimer's disease,[16] depression and possibly numerous other psychiatric disorders[17,18] as well as showing protective properties for vision.[19] DHA and its derivatives have specifically showed some important neuroprotecting properties in the brain.[20] All this has created a growing interest in PUFAs as a research subject and also a growing demand for EPA and DHA concentrates in the pharmacy industry as well as its use in food supplements. On top of this there is also a growing interest in alternative options to produce and manufacture omega-3 rich oils.

1.3 Stearidonic acid

As seen above the omega-3 long chain PUFAs have numerous beneficial health effects, a charecteristic not shared with ALA. Even though the human body possesses the ability to biosynthesize these PUFAs it has been shown that this production is very limited. The transition of ALA from diet into EPA in tissues does occur in small amount but the conversion to DHA is almost non-existent.[21] This very low biosynthesis of EPA and DHA may be enough to maintain tissue function but in cases where they are needed in more quantity or possibly more generally as a beneficial health benefit it has to come from the diet. EPA and DHA in a food source is almost exclusively found in fish, seafood or fish oil. No plants produce any PUFA longer then stearidonic acid.[22]

Stearidonic acid (SDA, 18:4 n-3) can be seen in figure 1 and is a highly unsaturated fatty acid right between ALA and EPA in the PUFA enzymatic pathway. It has a lower unsaturation index than EPA and DHA which might improve its stability compared to EPA and DHA and is found generally in very low quantity (0-5 %) in fish and fish oils.[4] SDA is

the most unsaturated PUFA produced in plants and is only found in a handful of plant families whereas most plants only produce fatty acids up to 18:3. Plants of the *Echium* family have been shown to be the best producers of SDA, up to 17%.[23] SDA from diet has furthermore showed promising conversion to EPA in tissues and is 17-30% as effective as dietary EPA in increasing EPA in plasma phospholipids.[24] This is a much greater effect than for ALA and might indicate that SDA is a much better precursor for EPA from the diet. None of the DHA precursors have been found to increase DHA levels in tissues which suggests that consumption of DHA itself is the only way to effectively increase tissue levels.[24]

There is considerable interest in new alternative and sustainable ways to obtain EPA and DHA rich oils for reasons such as over-fishing, but also palatability, shelf-life and safety. Gene technology could play an important role and there is already canola oil from a modified plant which has up to 23% SDA.[24] Microorganisms such as algae produce oils containing longer PUFAs and are the main source for pure DHA today. Genetically modified microorganisms can potentially be an important method to efficiently obtain high quantities of EPA or DHA rich oils but the easiest and cheapest organisms would be plants. There have also been transgenic plants produced that accumulate EPA and DHA at high levels and they are a promising prospect for a sustainable PUFA source in the future.[25]

SDA has not received nearly as much attention as EPA or DHA and is as things are now a fatty acid from plant sources which could partially replace EPA as a dietary source for EPA and shows a similar health effects as EPA in a limited amount of studies.[24] SDA might also be more beneficial than ALA as an essential fatty acid because it bypasses the first enzymatic step which might reduce pressure on the $\Delta 6$ desaturase and therefore possibly increase DHA production.

1.4 PUFA Synthesis

Synthetic chemists have been synthesizing fatty acids for a long time, starting with the first reported synthesis of oleic acid in 1934 and linoleic acid in 1950. The first synthesized PUFAs were arachidonic acid in 1961 and DHA in 1965.[26] These early methods have since been greatly improved upon and chemists continue to work on lipid synthesis to this day.[26,27] There are many methods to produce a (Z,Z)-1,4-diene unit which is the main building block of the PUFA tail and two of them are widely used today. The substitution of propargyl halides by acetylenic organometallics followed by selective hydrogenation, which is the method used in this project, and the use of stereoselective Wittig reactions.

The acetylene chemistry using propargyl intermediates has been around for a long time and was used when the first PUFA was synthesized in 1950. This method has seen a lot of changes since then. Propargyl methanosulfonate changed to bromide and the use of copper chloride, which improved these initial procedures. In 1959 Osbond reported an iterative use of propargyl alcohol as a general procedure for the synthesis of PUFAs. The key intermediates were realized by copper catalyzed coupling of acetylenic Grignard reagents with cis-allyl bromides.[27] Later this method was improved upon further by Russian chemists which involved the condensation of a propargyl halide with a terminal acetylene facilitated by copper(I) iodide, sodium iodide and potassium carbonate.[28] This eliminated

all need for Grignard intermediates, allowing numerous other functional groups because of these relatively mild conditions.

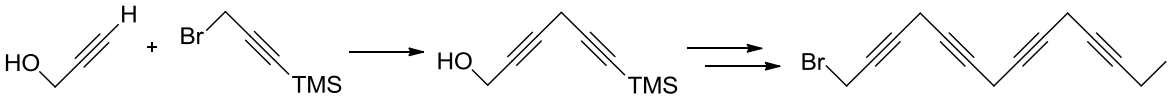


Figure 5. *An example of the acetylene approach where propargyl subunits are assembled into a methylene interrupted diyne unit that can then be lengthened by other propargyl units as desired.*

The acetylene chemistry will afford polyyne compounds that then need to be semi-hydrogenated into its polyene counterparts. This catalytic hydrogenation is generally achieved with the so-called Lindlar catalyst which consists of deactivated palladium supported on $CaCO_3$ or $BaCO_3$ and usually poisoned with lead acetate and/or quinoline.[26] For a single triple bond this method is very effective but with multiple triple bonds certain flaws become more apparent such as overhydrogenation when the triple bond is reduced all the way to a single bond as well as the appearance of the *E*-isomers. Other reduction methods exist such as hydroboration and palladium acetate with triethyloxysilane which have been tried on polyynes with varying degrees of success.[26]

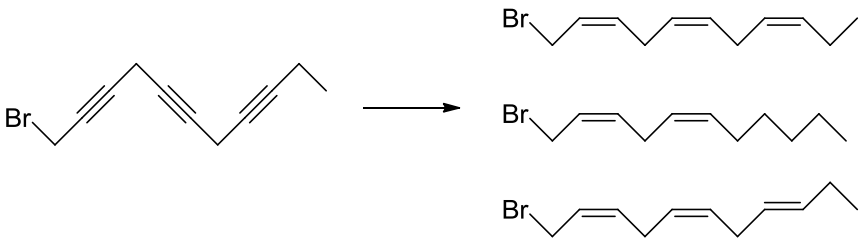


Figure 6. *An example of hydrogenation products: The desired all-cis product (top), the over-hydrogenated side product (middle) and the trans isomer side product (bottom).*

The Wittig approach has the benefit of not needing any semi-hydrogenation step and involves series of highly stereo-selective condensation of phosphonium salt and aldehyde intermediates to produce a *cis* double bond. After some sporadic use of Wittig reactions in polyene fatty acid synthesis an increase in interest rose in the 1980s. Initially the stereocontrol was less than perfect so a lot of the *trans* isomers were produced. Later with better methods and procedures the stereocontrol became much better. Another problem with the Wittig approach was the extreme conditions needed to deprotect the aldehyde groups of β,γ-ethylenic acetals which caused partial migration of double bonds resulting in conjugated isomers. Later diisopropylacetal and diethylacetals were used and could be hydrolyzed under milder conditions. A strategy for synthesizing EPA and DHA with two 6C homologating agents (Figure 7) was developed using Wittig as well as other strategies involving a mixture of the Wittig approach and the acetylene approach.[26]

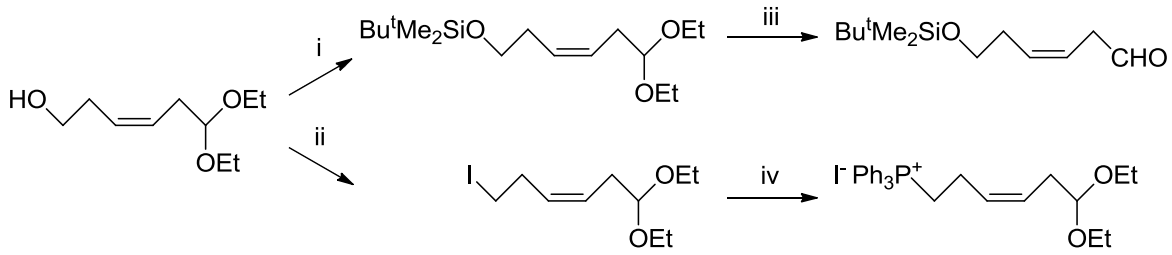


Figure 7. *These homologating agents can be used as the phosphonium salt or the aldehyde in the Wittig approuch for PUFAs. Reaction conditions: i) t-BuMe_2SiCl, imidazole, DMF; ii) 50% CF_3CO_2H, CH_2Cl_2; iii) I_2, PPh_3, imidazole; iv) PPh_3, CH_3CN, Δ, $CaCO_3$.*

2 Project description and synthesis design

The Haraldsson group had recently finished total synthesis of a naturally occurring DHA-like methoxylated alkylglycerol found in shark oil.[29] This synthesis made use of a method developed by Lapitskaya et al.[28] where terminal acetylene is attached to a propargyl halide in the presence of copper[I] ions and a base. This ether lipid had the structure of DHA attached to a glycerol only with an ether bond rather than the conventional ester bond. This spawned the question if this strategy was then not applicable to all the major omega-3 PUFAs all sharing the same structure of a terminal carboxyl acid on a long hydrocarbon chain with skipped *cis* double bonds, only differing in number of carbons and double bonds.

SDA is a convenient fatty acid to test the total synthesis for several reasons. It has only four double bonds, the head and tail groups only require a few synthetic steps and, last but not least the head group is already commercially available with the first triple bond already incorporated. Since the shelf life of the compounds is directly linked to the number of triple bonds it is also very convenient to have both head and tail groups only needing two triple bonds each. All this makes the SDA synthesis relatively easier than for the other more unsaturated PUFAs. The ethyl ester of SDA was the first to be synthesized, purified and characterized with the method described in this thesis and the total synthesis route is revealed in figure 8.

The synthesis with another protection group for the carboxylic head group was explored for reasons described in chapter 2.2. 4-Methyl-2,6,7-tri**o**xa-**b**icyclo[2.2.2]**o**ctan-1-yl (OBO) is a bicyclic ortho ester group first introduced as a protective group for carboxylic acids by Corey and Raju.[30] The total syntheses of SDA and EPA were attempted with the OBO head group, but the syntheses had to be changed marginally to accommodate for the group's weaknesses. The total syntheses based on the OBO group of SDA and EPA are shown in figures 15 and 16, respectively.

The general method used for total synthesis of SDA shown in figure 8 can be used for the other methylene interrupted unsaturated fatty acids such as other omega-3 LCPUFAs only by changing the starting compound to correspond to the number of carbons in the head of the target molecule and add triple bonds to the tail structure for the right number of double bonds in the target molecule. Figure 9 shows the total synthesis of EPA which was successfully synthesized the same way.

2.1 Retrosynthetic approach

Figure 8 shows the initial retrosynthetic approach, but as the Haraldsson group had already experienced with the DHA-like ether lipid a minor change in the strategy was much more favorable and is shown in figure 9.

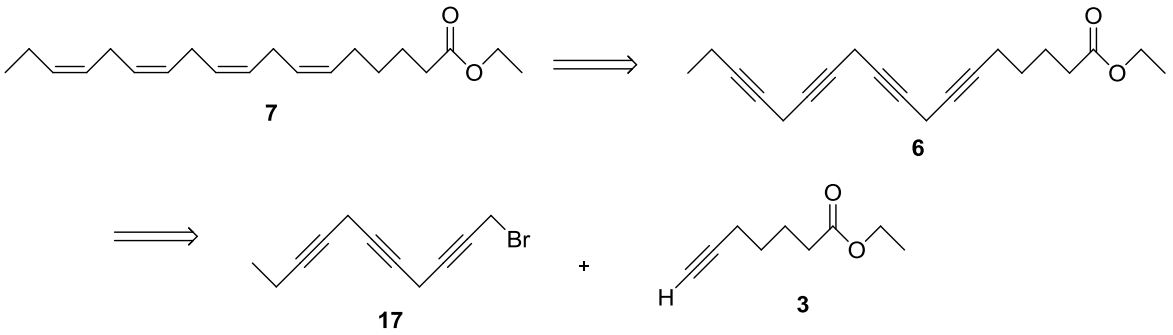


Figure 8. *The retrosynthetic approach for the 1+3 strategy for ethyl ester of SDA.*

This initial approach is a 1+3 strategy reffering to a head structure with one triple bond being attached to a tail part containing three triple bonds. This approach did not work as intended and the final attachment of head and tail afforded **7** in abysmal yields. With the small change of adding a triple bond to the head part and removing one from the tail part thus making it a 2+2 strategy, see figure 9, dramatically changed the outcome. Similarly, the 2+3 strategy for the EPA synthesis proved to be much better than the 1+4 strategy.

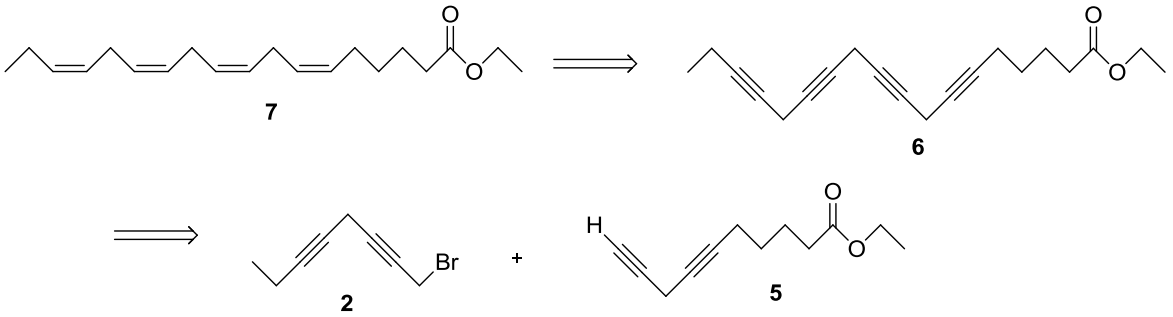


Figure 9. *The retrosynthetic approach for the 2+2 strategy for ethyl ester of SDA.*

The head part **5** can be further disconnected into its commercially available building blocks 6-heptynoic acid protected as an ethyl ester and TMS protected propargyl bromide. The tail part **2** can also be further disconnected into its commercially available materials propargyl alcohol and 1-bromopentyne which will provide the omega-3 framework. Figure 10 shows the disconnection of the diyne tail part **2** and also the triyne tail part **17** used in the 1+3 strategy and in the synthesis of EPA which consists of propargyl alcohol, TMS protected propargyl bromide and the omega-3 affording 1-bromopentyne. Figure 11 shows the disconnection of the SDA head part **5** along the very similar EPA head part **20** resulting from the 5-hexynoic acid starting material.

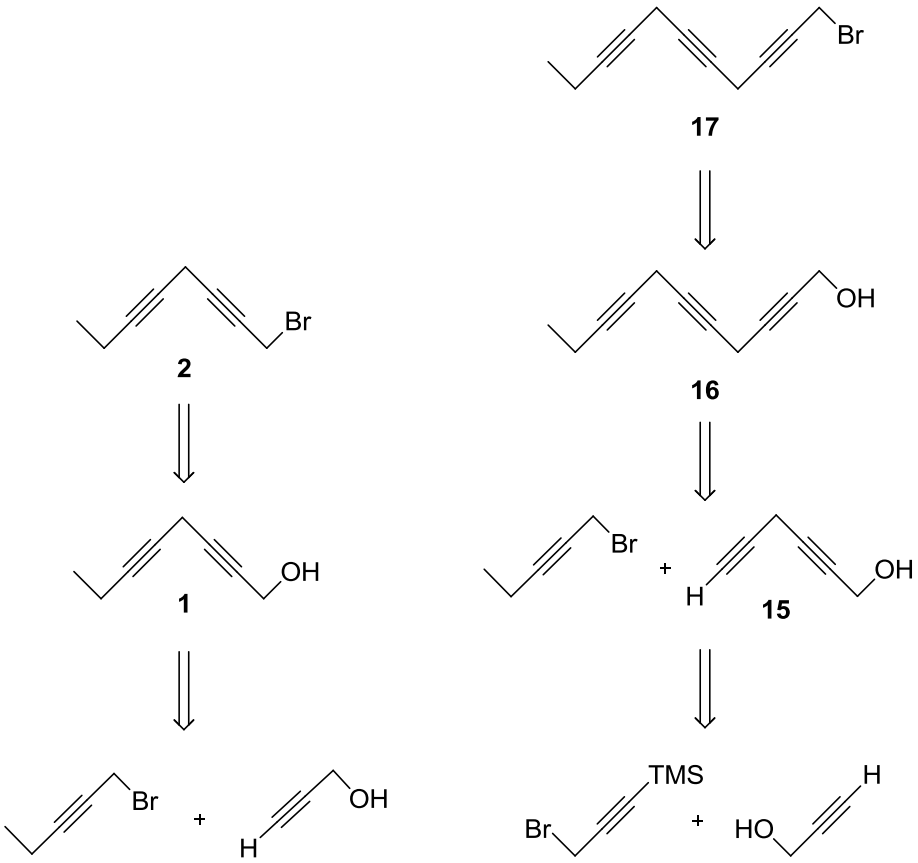


Figure 10. *Further disconnection of the diyne* ***2*** *and triyne* ***17*** *tail parts into their commercially available starting materials.*

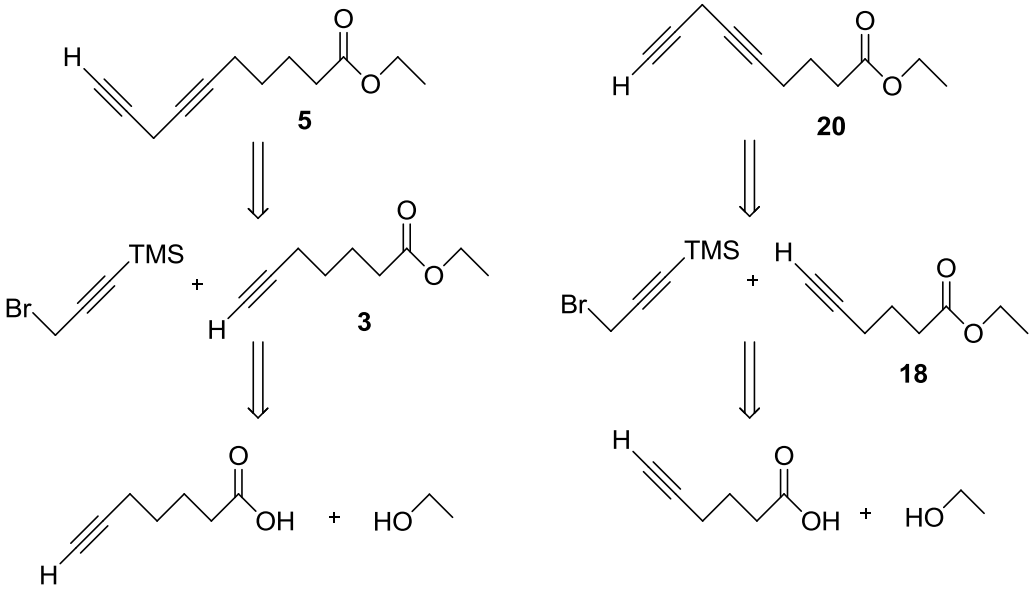


Figure 11. *Further disconnection of the diyne head parts* ***5*** *and* ***20*** *into their commercially available starting materials.*

A synthetic route was planned from commercially available substrates for all the major omega-3 PUFAs and figures 10 and 11 show the retrosynthetic approach for SDA and EPA. As mentioned above the structure for other PUFAs can be achieved in the same way by changing the head starting material and providing the tail part with the number of triple bonds that is needed. When the number of carbons between the carboxylic acid head and the first double bond exceeds four carbons the first triple bond must be implemented, since commercial resources are not available for those starting materials. This gave rise to another alternative synthesis based on another head protection group discussed in chapter 2.2. Figure 12 shows the total synthesis for the ethyl ester of SDA while figure 13 reveals the total synthesis for the ethyl ester of EPA for clarification.

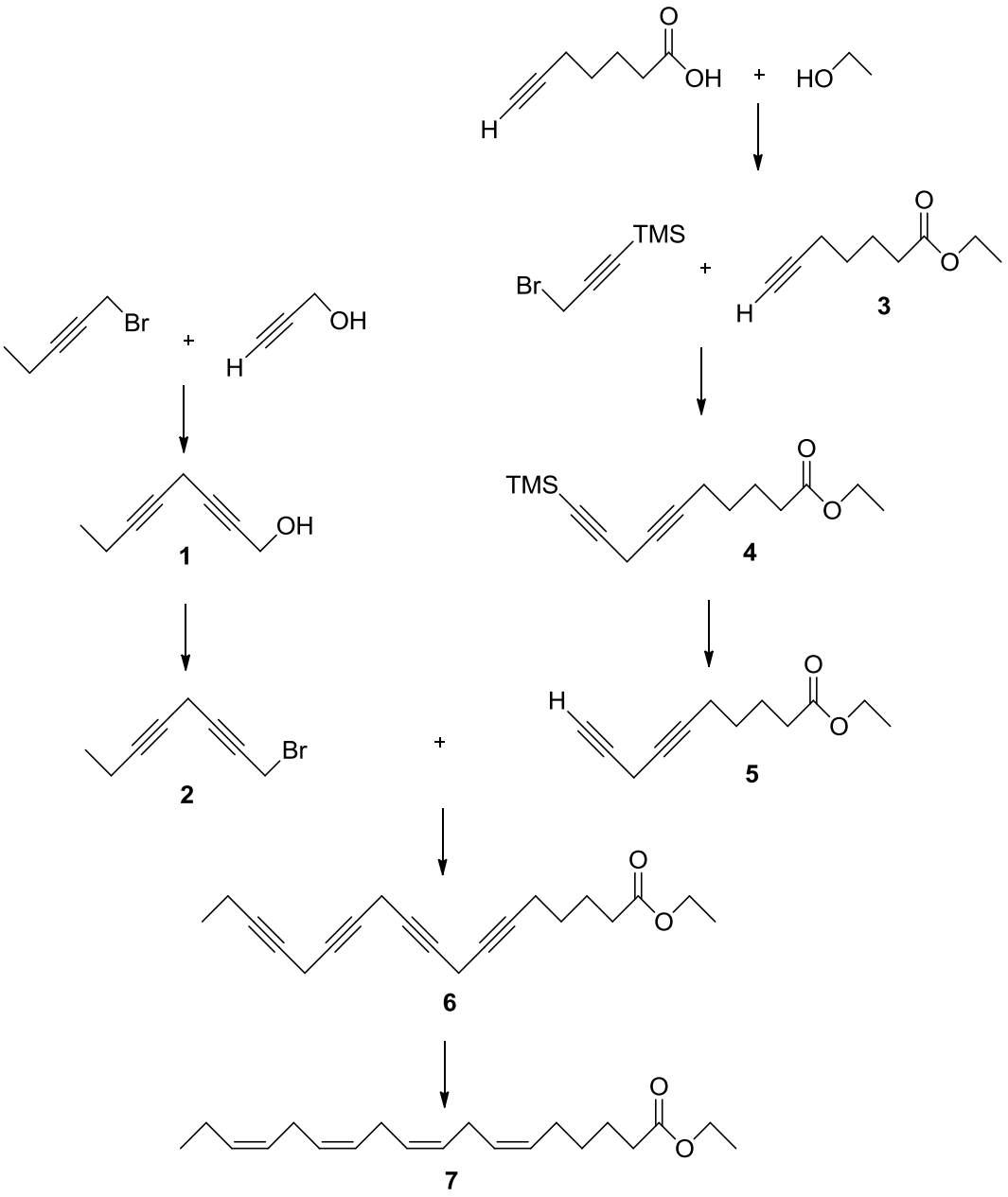


Figure 12. *Total synthesis of stearidonic acid ethyl ester (SDA).*

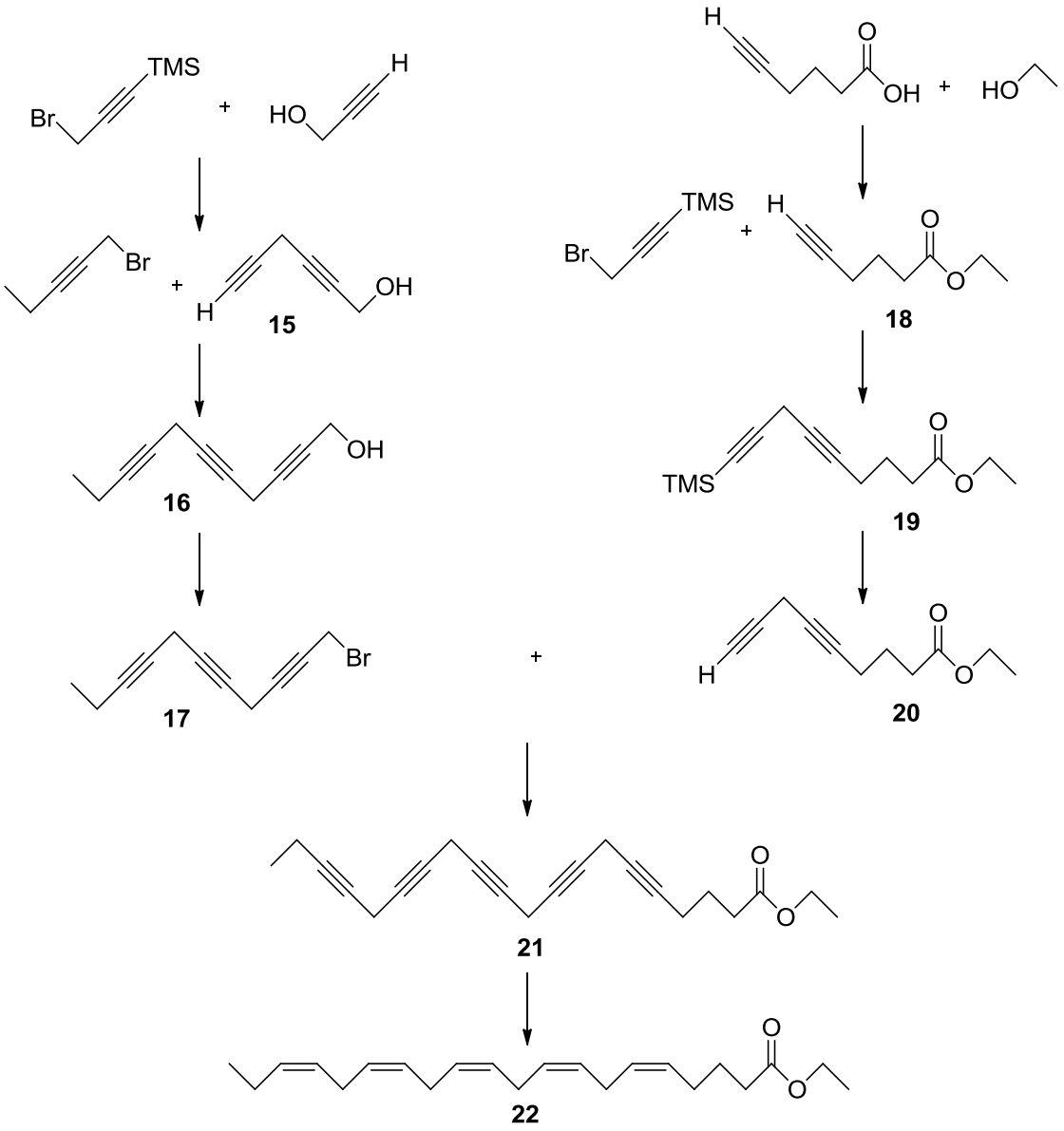


Figure 13. *Total synthesis of eicosapentenoic acid ethyl ester(EPA).*

2.2 Alternative synthesis based on OBO

For fatty acids such as ALA that have a long carbon chain between the acid group and the first double bond an n-BuLi based acetylide substitution reaction was used to incorporate the first triple bond to the head structure. An ester in the vicinity of n-BuLi results a tertiary alcohol so instead of an ethyl ester protective group an orthoester protection group for the head was used or more precisely, the bicyclic orthoester denoted as OBO (4-methyl-2,6,7-

trioxa-bicyclo[2.2.2]octan-1-yl). Orthoesters are typically used as carboxylic acid and ester protective groups, which are easily converted back into esters.

SDA is as mentioned above an excellent candidate to test the total synthesis based on the OBO group even though the synthesis does not require it and the ethyl ester protection group is sufficient. The total synthesis route for SDA with OBO was then designed and is largely the same as with the ethyl ester protection group except for few minor changes.

Figure 14 shows the retrosynthetic approach which was the same as for the ethyl esters except involving the formation of the before mentioned OBO group. A special oxetane alcohol (3-methyloxetan-3-yl)methanol is used to form an ester which is the precursor for the actual OBO protection group which is formed in the presence of BF_3 in CH_2Cl_2 at -15°C. Certain problems arose in the final step in deprotecting the TMS protected acetylenes **10** (figure 15) and **25** (figure 16) to form the completed head groups **11** and **26** so alternative methods had to be used to obtain satisfying results, which is discussed in detail in chapter 3.3.

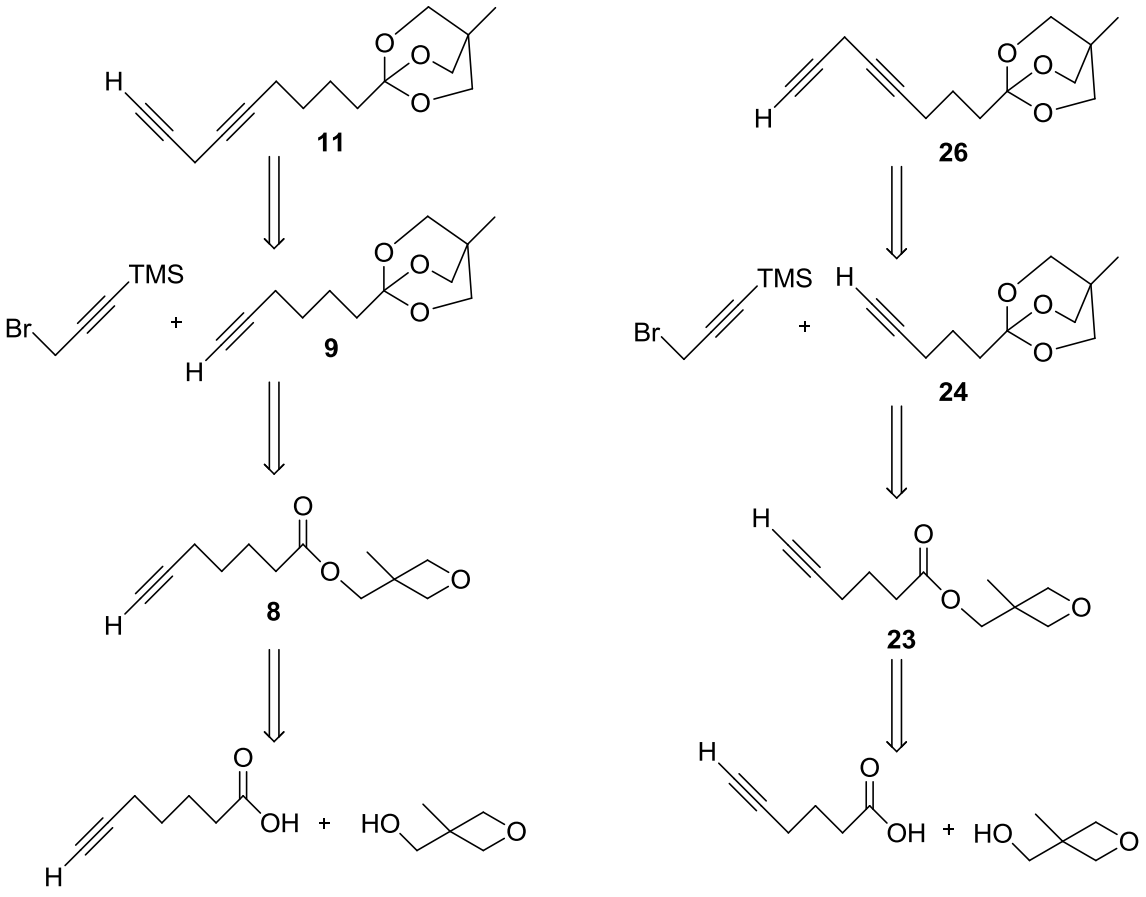


Figure 14. *Further disconnection of the OBO protected head parts **11** and **26** into their commercially available starting materials.*

Figure 15 and 16 show the resulting total syntheses of OBO protected SDA and EPA, respectively, for clarification.

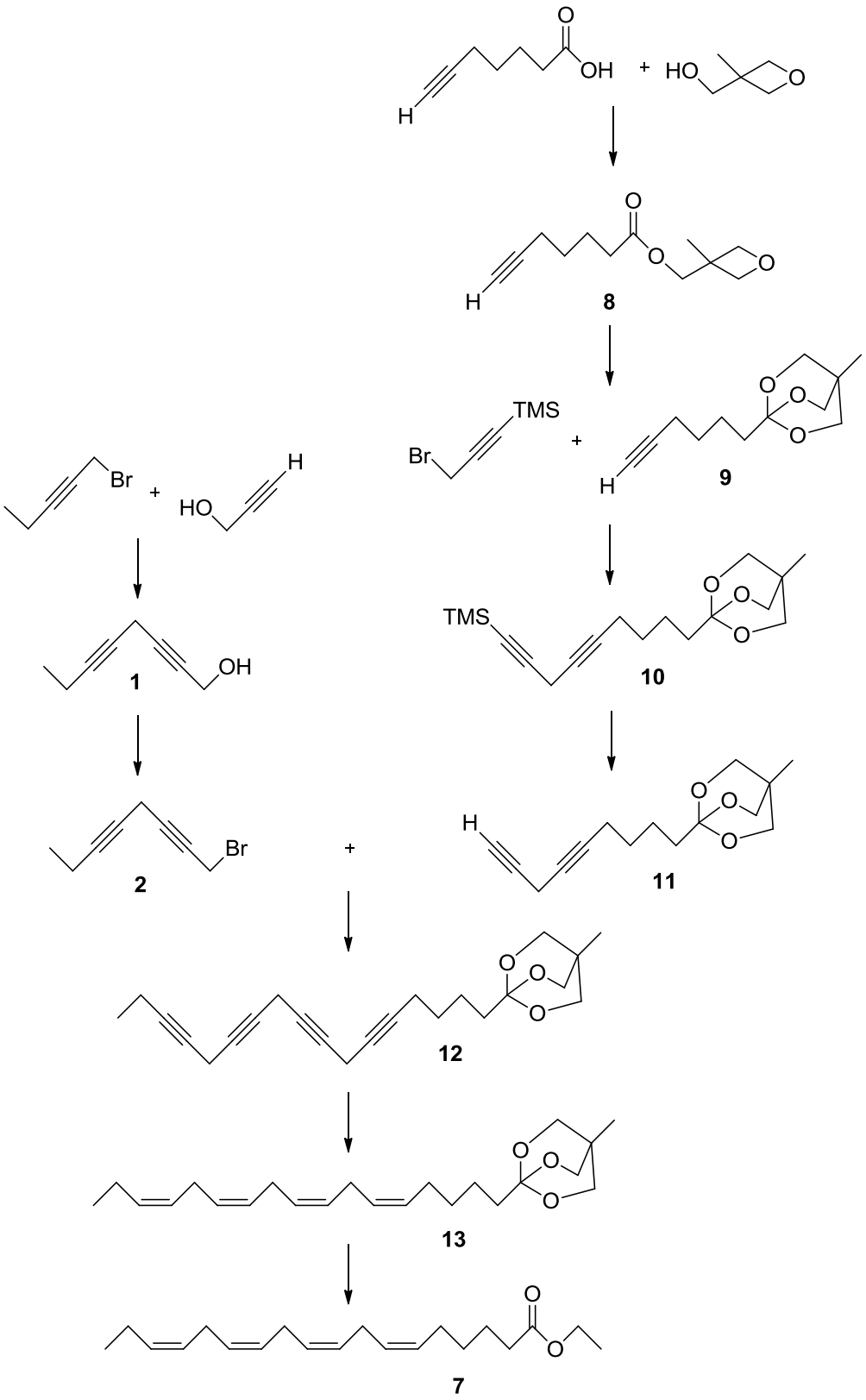


Figure 15. *Total synthesis of stearidonic acid (SDA) using OBO as a protection group.*

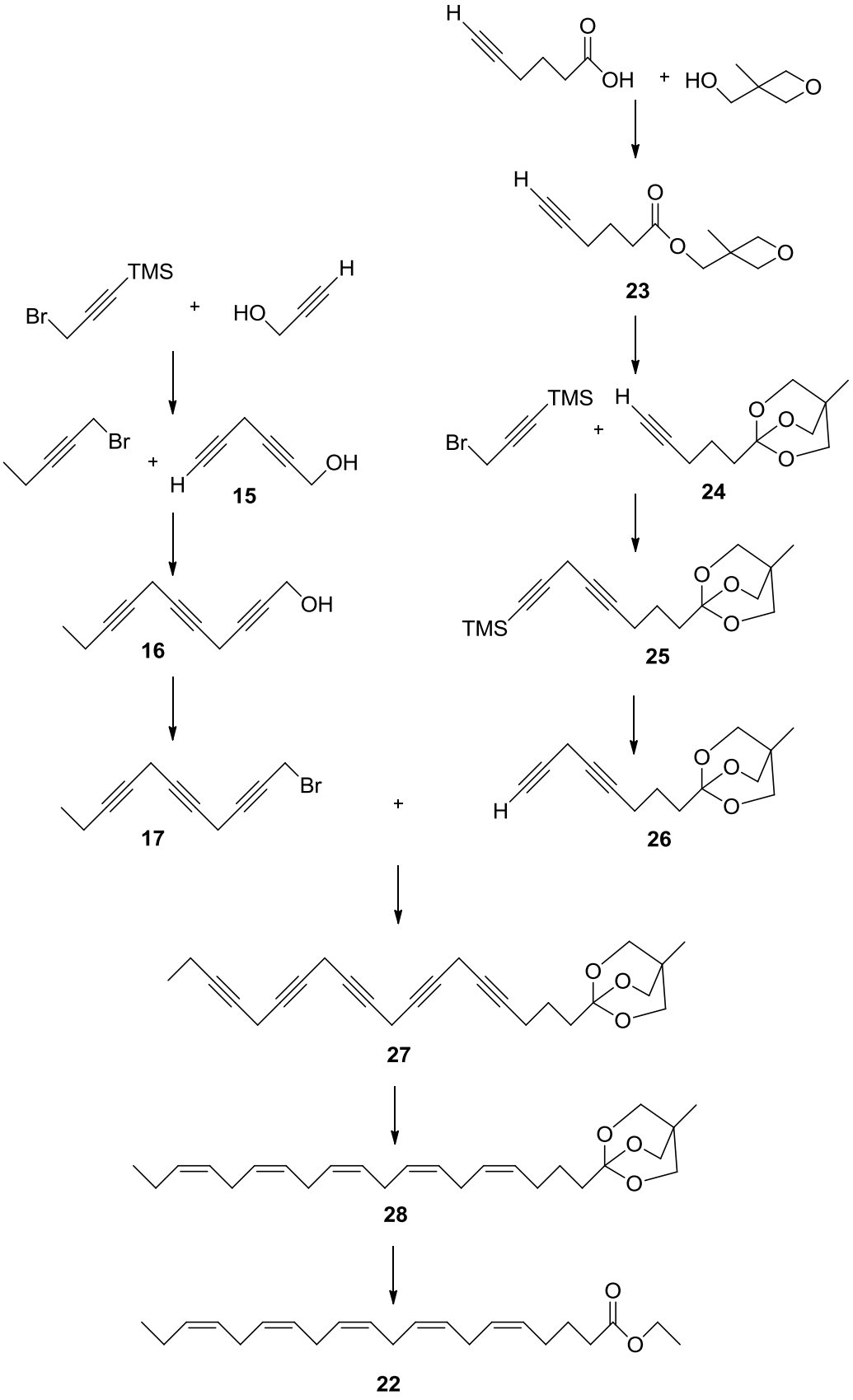


Figure 16. *Total synthesis of eicosapentenoic acid (EPA) using OBO as a protection group.*

3 Results and discussion

This chapter describes the total synthesis towards SDA and EPA in details and provides discussion of the results. It is divided into four subchapters with the first chapter describing the synthesis of the diyne **2** and triyne **17** tail parts. The second chapter describes the syntheses of the ethyl ester head groups **5** and **20**. The third chapter describes the syntheses of the OBO protected head groups **11** and **26** and, finally, the fourth chapter describes the attachment of the tail and head parts and the critical semi-hydrogenation of the tetra- and pentayn building blocks **6** and **12.** It is divided into three parts covering the ethyl esters, OBOs and, finally, a short discussion on the trans-cis assessment.

3.1 Synthesis of the tail group

Figure 17 shows the synthetic route to the diyne tail part **2** and figure 19 corresponding route to the triyne tail part **17**. As mentioned above the synthesis relies heavily up on the so called copper coupling reaction discovered by Lapitskaya et al,[28] which involves condensation of terminal acetylenes with propargyl halides at room temperature in the presence of copper[I] iodide, sodium iodide and potassium carbonate. As seen in the figures 17 and 19 the copper couplings were all accomplished in very high yields, the brominations of the propargyl alcohols by the Appel reaction to give the finished tail parts were completed in good yields, but the silver nitrate deprotection of the TMS protected terminal acetylenes took place only in moderate yields.

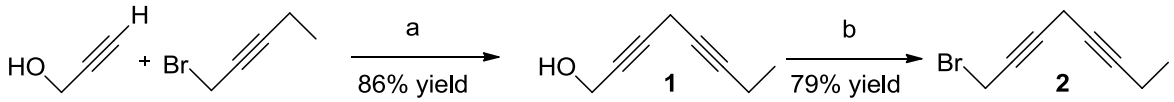


Figure 17. *Total synthesis of the diyne tail part **2**. Reaction conditions: (a) CuI, NaI K_2CO_3, DMF, r.t., 24h; (b) PPh_3, CBr_4, CH_2Cl_2, 0-25°C, 4h.*

The first step is the copper coupling of propargyl alcohol and 1-bromopent-2-yne which is the tail end and provides the all-important omega-3 framework. This reaction is a very convenient way to assemble a series of skipped triple bonds and is believed to be carried out through a copper acetylide intermediate formed when a base removes the acetylenic proton in the presence of copper(I) salt. This mechanism and the subsequent condensation with a propargyl halide are at this point in time not fully understood, but nonetheless essential for the synthetic strategy described here, see figure 18.[31] It is, however, reasonable to assume that part of the role of sodium iodide is to replace the bromide in the propargyl bromides thus rendering the system a better leaving group.

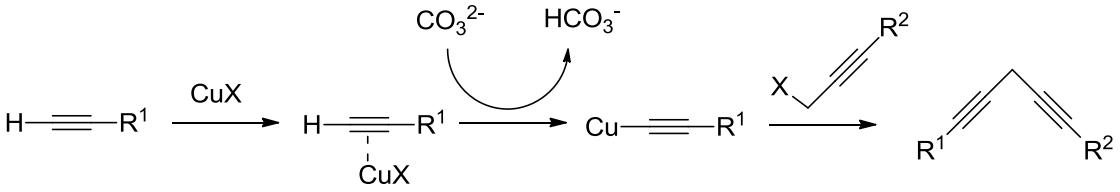


Figure 18. *Partly described copper coupling mechanism believed to occur between 1-alkynes and propargyl halides.*

The yields could be increased very slightly by extending the reaction time by approximately 24 hours. The 1-bromopent-2-yne was also used in 1.4-fold excess over the propargyl alcohol and by lowering its concentration the yields were lowered slightly. After purification on silica gel the product **1** was obtained in 86% yield.

The second step is the formation of the bromine adduct **2** from the alcohol **1** which enables it to be attached to the head parts **5** or **11** to form the skipped tetrayne frameworks **6** (ethyl ester) and **12** (OBO) which are the tetrayne precursors to the target molecule SDA. The alcohol **1** was converted into the bromide **2** via the well-known Appel reaction with triphenylphosphine and tetrabromomethane in dichloromethane at 0°C and then gradually allowed to reach 25°C. Leftover triphenylphosphine and the triphenylphosphine oxide produced in the reaction were gotten rid of by adsorbing the reaction mixture to silica gel and then flushing with a petroleum ether/dichloromethane (9:1) as an eluent leaving the triphenylphosphine and triphenylphosphine oxide adsorbed to the gel. The product **2**, an orange liquid, was obtained in 79% yield after no further purification.

For the triyne tail (see Figure 19) the alcohol part of the tail was formed first in a copper coupling of propargyl alcohol and a TMS protected propargyl bromide. As before, the product **14** was obtained in very good yields, 85% after purification on silica gel. No excess of the bromide substrate was needed for these results. The prolonged reaction time of 48 hours also gave slightly increased yields.

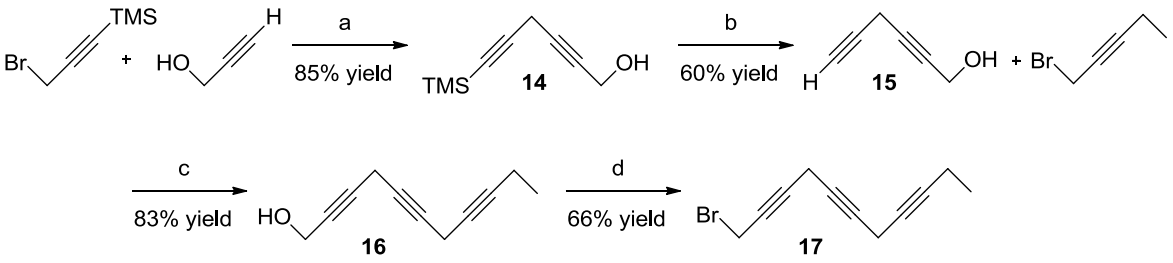


Figure 19. *Total synthesis of the triyne tail part **17**. Reaction conditions: (a) CuI, NaI K_2CO_3, DMF, r.t., 48h; (b) $AgNO_3$, $CH_2Cl_2/H_2O/MeOH(7:1:4)$, r.t. 4-5h; (c) CuI, NaI Cs_2CO_3, DMF, r.t., 48h; (d) PPh_3, CBr_4, CH_2Cl_2, 0-25°C, 4h.*

The next step involved the deprotection of the terminal acetylene and that was accomplished with silver nitrate as a catalyst in a mixture of dichloromethane, water and methanol (7:1:4).[32] Figure 20 shows the mechanism in which a HNO_3 intermediate is formed and results in the formation of the terminal acetylene and TMS-OH. The product **15**

was obtained in moderate yields of 60% after purification on silica gel. These rather poor yields can at least partly be attributed to the water soluble characteristics of the compound.

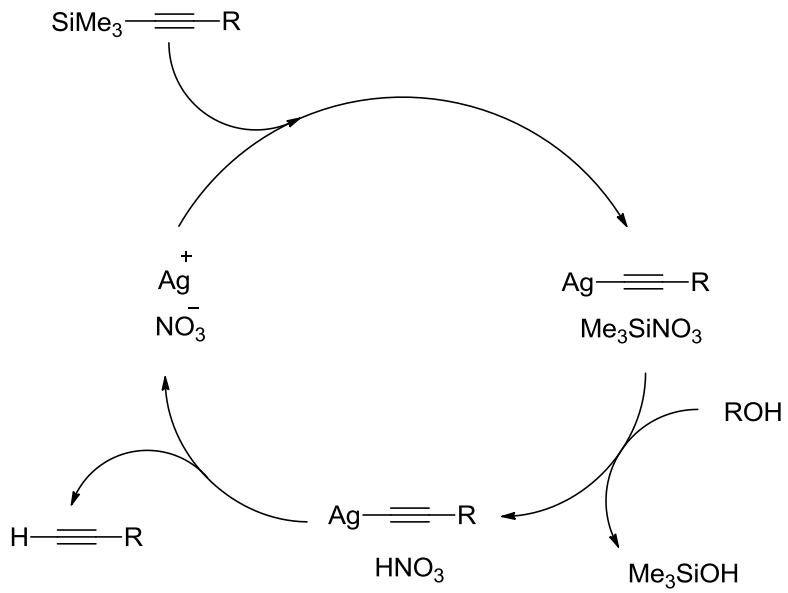


Figure 20. *Mechanistic hypothesis for selective deprotection of TMS protected 1-alkynes via silver nitrate in $CH_2Cl_2/H_2O/MeOH$ (7:1:4).*[31]

In the second copper coupling the alcohol part **15** was attached to the 1-bromopent-2-yne end part, which provided the omega-3 framework. The use of a 1.5-fold excess of the 1-bromopent-2-yne provided better yields and also the extended reaction time of 48 hours. The increased number of triple bonds required the K_2CO_3 base to be replaced with Cs_2CO_3 to obtain more favorable yields, but Cs_2CO_3 has been shown to increase yields considerably for these kinds of copper couplings and was used in all subsequent copper coupling reactions.[33] The product **16** was obtained in 83% yield after purification on silica gel.

In the final step the alcohol **16** was converted to the corresponding bromide to form the final tail product **17** which is then ready to be attached to the terminal acetylene of the head groups **20** or **26** via copper coupling to form the pentayne precursors **21** (ethyl ester) or **27** (OBO) of the target molecule EPA. The reaction was accomplished as before via the Appel reaction and the product was obtained in 66% yield after purification on silica gel.

3.2 Synthesis of the ester head group

Figure 21 shows the synthetic route to the head group **5** which is the head part corresponding to SDA. Figure 22 shows the very similar way **20** was synthesized which is the head part corresponding to EPA. All products were obtained in excellent yields.

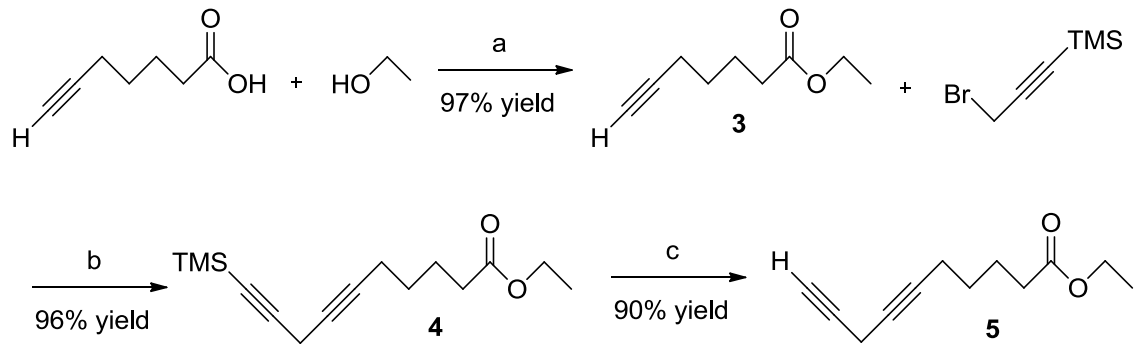


Figure 21. *Synthesis of the SDA head group **5**. Reaction conditions: (a) EDCI, DMAP, CH_2Cl_2, r.t., 4h. (b) CuI, NaI, Cs_2CO_3, DMF, r.t., 24h. (c) $AgNO_3$, $CH_2Cl_2/H_2O/MeOH$ (7:1:4), r.t., 8h.*

The starting material was chosen such that the number of carbons between the terminal carboxylic acid and the triple bond corresponded to the target molecule. In the case of SDA the starting material is 6-heptynoic acid. In the first step it was converted into an ethyl ester under inert conditions with ethanol at room temperature using EDCI as a coupling agent and DMAP as catalytic base in CH_2Cl_2. The product **3** was obtained as a colorless liquid in almost quantitative yields after separation of the product and the EDCI/DMAP suspension after filtering through a short silica gel layer.

The resulting ester protected head group **3** was then elongated by the copper coupling with TMS protected propargyl bromide in 96% yield after purification on silica gel. To obtain optimal yields 1.3-fold excess of the bromide was required and a reaction time up to 48 hours. In the final step deprotection of the terminal TMS protected acetylene afforded the head part **5**, which was then ready to be attached to the diyne tail **2** to form the tetrayne precursor **6** for SDA. This was accomplished by the silver nitrate procedure mentioned above (figure 20) in 90% yield after purification on silica gel. Equally good yields were obtained when the crude product **4** was submitted to the silver nitrate deprotection without any purification on silica gel and the deprotected head group **5** then obtained in 86% yield over two steps after purification on silica gel.

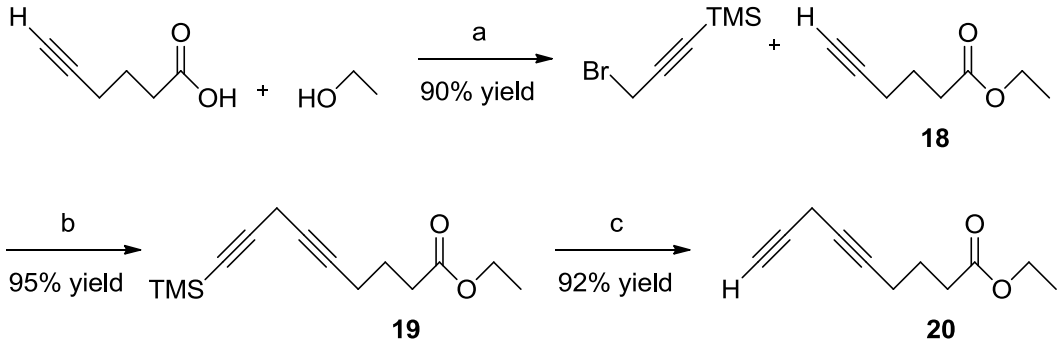


Figure 22. *Synthesis of the EPA head group **20**. Reaction conditions: (a) EDCI, DMAP, CH_2Cl_2, r.t., 4h. (b) CuI, NaI, Cs_2CO_3, DMF, r.t., 24h. (c) $AgNO_3$, $CH_2Cl_2/H_2O/MeOH$ (7:1:4), r.t., 8h.*

For the EPA case the 5-hexynoic acid was converted into its ethyl ester under similar conditions as described earlier with EDCI and DMAP in CH_2Cl_2. The product **18** was obtained in 90% yield after separation on a short silica gel layer. Then the second triple bond was added to the structure with a TMS protected propargyl bromide copper coupled to the terminal acetylene to form the TMS protected diyne **19** in 95% yield after purification on silica gel. Finally, the TMS group was removed by the $AgNO_3$ deprotection reaction to obtain **20** in 92% yield after purification on silica gel. As for the SDA head similar yields were obtained when the crude **19** was deprotected and then purified on a silica gel.

3.3 Synthesis of the OBO head group

The alternative to the ethyl ester synthesis described in the previous section 3.2 is the OBO protected head group synthesis. Figure 24 shows the synthetic route to **11** using 6-heptynonic acid as the starting material for the SDA synthesis and the synthetic route to **26** is described in figure 26 using the 5-hexynoic acid as starting material for the EPA synthesis. Similar to the ethyl esters the synthesis starts with a formation of an ester but using 3-methyl-3-oxetanemethanol instead of ethanol as the alcohol substrate. The OBO group is then formed in an intramolecular reconfiguration by activating the oxetane ring with BF_3. The OBO was observed to be very unstable and was readily converted back to an ester under mildly acidic conditions and extreme care had to be taken to avoid breakdown in later steps. Figure 23 shows the degradation of the OBO group into its diol ester breakdown product when exposed to acidic environment.

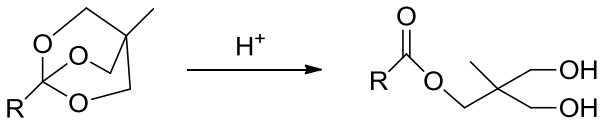


Figure 23. *Observed breakdown of the OBO-group in acidic conditions.*

The copper promoted coupling reaction involving the TMS-protected propargyl bromide to form **10** (SDA) and **25** (EPA) was done similar to what was described for the ethyl esters but the then subsequent TMS deprotection of **10** and **25** had to be redesigned completely since the very minor acidic aqueous conditions involved in the silver nitrate reaction were enough to completely destroy the OBO group.

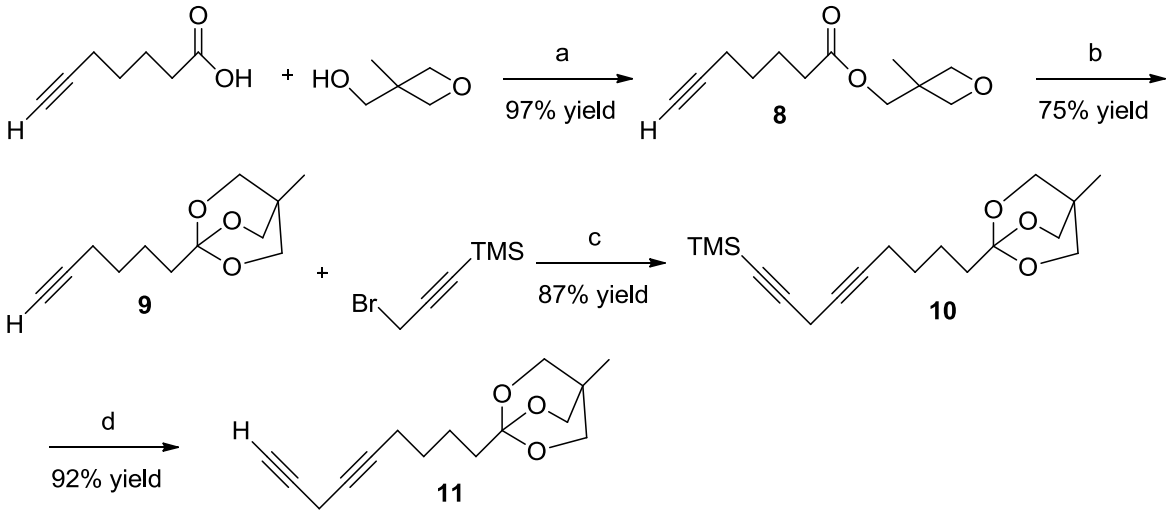


Figure 24. *Synthesis of the OBO protected SDA head group **11**. Reaction conditions: (a) EDCI, DMAP, CH_2Cl_2, r.t., 4h. (b) BF_3-etherate, CH_2Cl_2, -15°C, 8h. (c) CuI, NaI, Cs_2CO_3, DMF, r.t., 48h. (d) TBAF, THF, -78°C, 24h.*

The first step was an esterification of the 6-heptynoic acid with the oxetane alcohol which formed the oxetane ester **8** in the same way the ethyl esters **3** and **18** were formed in the presence of EDCI and DMAP in CH_2Cl_2 in inert conditions at room temperature**.** The afforded product **8** was obtained in 97% yields after being passed through a short silica gel layer.

The OBO-group was then formed in the presence of BF_3 in CH_2Cl_2 at -15°C, see figure 25. The BF_3 serving as a Lewis acid coordinates with the oxetane oxygen which increases the ring strain in the four-membered ring which in turns pushes for heterolysis of the C-O bond. This makes the carbon more susceptible to a nucleophilic attack from the carbonyl which forms a zwitterion that collapses into the isomeric bicyclic OBO-group, driven by the formation of a six-membered ring from a four-membered ring.[30]

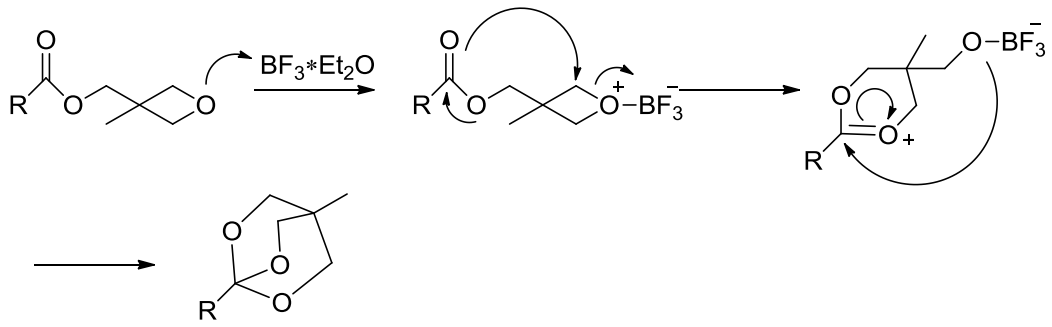


Figure 25. *Reaction mechanism of the OBO-group formation.*

The OBO orthoester **9** was collected in up to 75% yield after purification on a neutral alumina gel. Neutral or basic alumina gel or triethylamine doped silica gel was necessary for all chromatography to prevent breakdown due to the acidic conditions present in normal silica gel. Some considerable drop in yields were still observed on alumina gel, and the breakdown product of OBO was established on a neutral alumina gel column after isolating **9** in poor yield and then flush the column with the more polar ethyl acetate and analyze the resulting solution on ^{1}H NMR spectra which indicates some instability on alumina. Other precautions that had to be taken were for example filtration of deuterated chloroform on basic alumina before being used as a solvent for NMR spectroscopy and to stop using ammonium chloride to quench reactions for all OBO-group protected compounds.

The copper coupling of **9** and TMS-protected propargyl bromide to form **10** was done under same conditions as for the ethyl ester **3** with the exception in the quenching of the reaction which was done with ionized water instead of the normally used saturated aqueous NH_4Cl solution which forms mildly acidic conditions. The resulting reaction mixture created an emulsion slurry which made extraction into diethyl ether very difficult and might explain the slightly lower yield of 87% after purification on alumina compared to its ethyl ester counterpart **4**. In an effort to reduce the formation of the slurry the amount of the copper and sodium salts as well as the cesium carbonate were halved which did not seem to affect yields but might play part in the increased reaction time.

The previously used silver nitrate deprotection of TMS was not applicable to the OBO protected head as was mentioned above. When the deprotection was tried in methanol under mildly basic conditions a significant formation of an allene side-product was observed. A different approach was then tried which involved TBAF in dry THF at -78°C. With this method the allene product was still observed in the ^{1}H NMR spectra, but by adapting the method carefully, which included very exact temperature control and elusion of the reaction mixture on a cooled alumina column with cooled solvent, the product was afforded in 92% yield with roughly 2% allene still present as estimated from the ^{1}H NMR spectra.

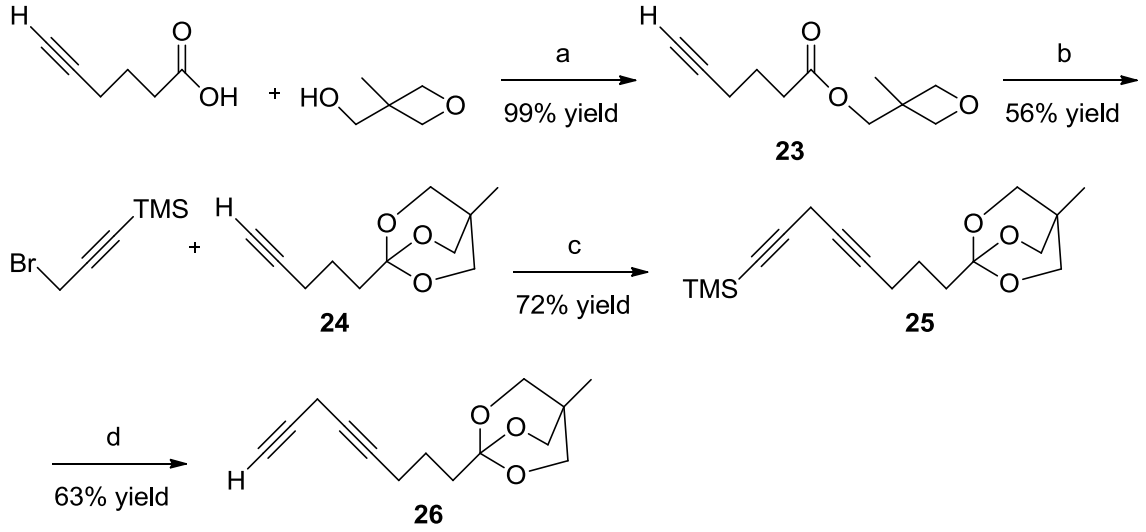


Figure 26. *Synthesis of the OBO protected EPA head group* ***26*** *. Reaction conditions: (a) EDCI, DMAP, CH_2Cl_2, r.t., 4h. (b) BF_3-etherate, CH_2Cl_2, -15°C, 10h. (c) CuI, NaI, Cs_2CO_3, DMF, r.t., 48h. (d) TBAF, THF, -78 (-) -25°C, 24h.*

In the EPA head synthesis the 5-hexynoic acid was condensed to the oxetane alcohol in the same fashion as before with EDCI and DMAP. The product **23** was obtained in 99% yield after purification on a short silica layer. The oxetane ester was then reconfigured into OBO via BF_3 in CH_2Cl_2 at -15°C with the product **24** obtained in 56% yield after purification on a triethylamine impregnated silica gel and then on neutral alumina. The yields were very low compared to the SDA head which is most likely connected to the purification on the alumina column which was a reoccurring problem troughout the OBO synthesis where the yields dropped significantly. TMS protected propargyl alcohol was then attached to the head with the copper coupling reaction and the product **25** was obtained in 72% yield after purification on neutral alumina. Finally, the TMS protected diyne was deprotected via TBAF in THF at -78°C which afforded the product in 63% yield after treatment on a short cooled basic alumina column. The overall yields were considerably lower than in the SDA head group **11** synthesis, and there seems to be a trend between shorter starting acid and lower yields. But the SDA head was made more often and the reactions and work-up better optimized.

The OBO protected head piece was obtained in significantly lower yield than its ethyl ester counterpart, the synthesis was also more difficult and vulnerable to breakdown and production of byproducts. The OBO group can easily be converted into its ethyl ester counterpart as has been demonstrated on a head group corresponding to ALA where it was put under reflux with p-toluenesulfonic acid in ethanol affording the ethyl ester product in 95% crude yield.[34] The OBO group can be converted to the much more convenient ethyl ester after the OBO group has served its purpose i. e. to protect while incorporating the first triple bond to the head part.

3.4 Attachment and hydrogenation

In the final steps in the synthesis the head and tail parts were assembled to afford the polyyne structure that was then subjected to a stereospecific catalytic semi-hydrogenation to afford the desired ester or OBO protected PUFA. The literature[35] as well as our former synthesis[29] has taught us much about over-hydrogenation so considerable amount of effort went into finding/designing ways to minimize that. A few kinds of catalysts were tried as well as many different solvents and amount of the surface-poisoning agents such as quinoline and ethylene diamine adjusted. Finally, the resulting product needs to be purified and all over-hydrogenated byproducts separated from the target molecule. That was achieved with a specific separation on a $AgNO_3$ impregnated silica preparative TLC plates, a technique which has been known for a long time[36] and is a good method to separate lipids according to their unsaturation.[37]

3.4.1 Ethyl ester

Figures 27 and 28 show the final two steps in the syntheses for SDA and EPA, respectively.

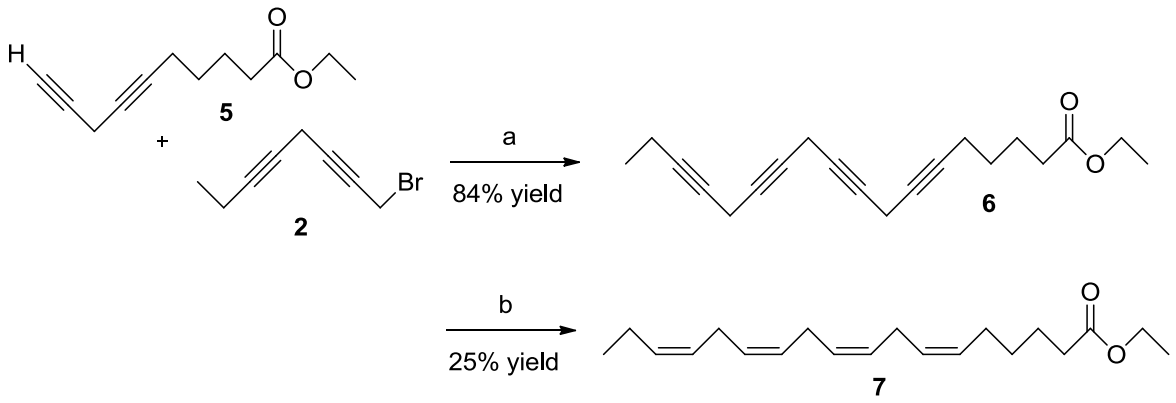


Figure 27. *Final steps in the total synthesis of the ester of SDA **7** . Reaction conditions: (a) CuI, NaI, Cs_2CO_3, DMF, r.t., 48h. (b) Lindlar, quinoline, toluene, H_2, 0°C, 30 min.*

In the first step the head and tail parts were coupled together and that was achieved the same way as before with the same standard copper coupling. Reaction conditions were unchanged from before with a total reaction time of about 48 hours to afford **6** in 84% yield after purification on silica gel. At this point it came apparent that the shelf life of the compound was not good and the formation of an insoluble mass was observed. Loss of material was observed for all the polyynes and it proved to be exponentially faster with increasing number of triple bonds, sometimes a matter of hours for the hexayne compounds. Storage at -87°C under nitrogen kept the compounds stable for much longer. This instability might play a significant role in the product recovery for the subsequent reduction reaction and it is likely paramount to immediately reduce **6** to**7** for optimal yields.

The reduction of **6** to **7** involved considerable experimental work since numerous variations of all parameters were explored. Type of catalyst, temperature, amount of poisoning agent, solvent, addition of cyclohexene and reaction time were all tested in varied combinations to try to find optimal reaction condition for minimal over-hydrogenation. Over-hydrogenation was estimated from ^{1}H NMR spectra of the resulting crude solutions.

Three different stereoselective semi-hydrogenating catalysts were tested to try to determine the optimal conditions for the polyyne hydrogenation. The Lindlar and Rosenmund catalysts, both commercially available palladium based catalysts, and the Brown catalyst which is nickel based and prepared *in situ*. The fourth catalyst tried was essentially a Lindar catalyst without the lead poisoning. Overall the Rosenmund and Brown catalysts showed a higher degree of over-hydrogenation than the Lindlar catalyst and the unleaded Lindlar catalyst showed a significantly higher over-hydrogenation. The Lindlar catalyst did still show over-hydrogenation which was dealt with by using the silver ion chromatography.

The most optimal condition achieved of those tried for reduction of **6** was Lindlar catalyst poisoned with 0.5 equivalents of quinoline in toluene at 0°C. A mixture of the target

molecule **7** and its byproducts was afforded in approximately 60% crude yield after purification on silica gel. This mixture was then applied to a 5% silver nitrate impregnated preparative silica TLC plate which afforded **7** in 40% yield. Overall the reduction of **6** to **7** was accomplished in 25% yield. The final step of deprotecting the ester head group to afford SDA was not attempted since that is a very well established method for all fatty acids and the ethyl ester of fatty acids is also used in numerous applications and can be metabolized in humans.

For EPA the head **20** and tail **17** were similarly coupled together under the same copper promoted conditions as for SDA and the product **21** obtained in 89% yield after purification on silica gel (Figure 28) that product was then hydrogenated with the Lindlar catalyst in toluene with no quinoline which afforded a product that was heavily over-hydrogenated according to its ^{1}H-NMR spectrum. No further attempts to obtain better results were tried in this thesis project but **22** has since been obtained inn around 25% yield under the same conditions and with the same purification method that afforded **7**.

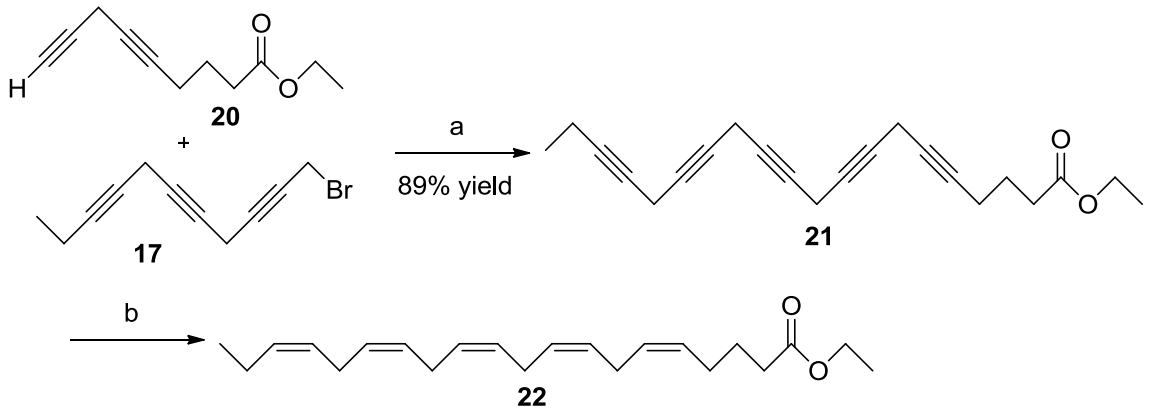


Figure 28. *Final steps in the total synthesis of the ester of EPA **22** . Reaction conditions: (a) CuI, NaI, Cs2CO3, DMF, r.t., 48h. (b) Lindlar, toluen, H_2, r.t., 60 min.*

3.4.2 OBO

Figure 29 shows the final two steps in the synthesis of OBO protected SDA and figure 30 the corresponding steps for EPA. The first step involves attaching the head and tail parts together with the same copper coupling reaction as before, and the second step the hydrogenation of the resulting polyyne products.

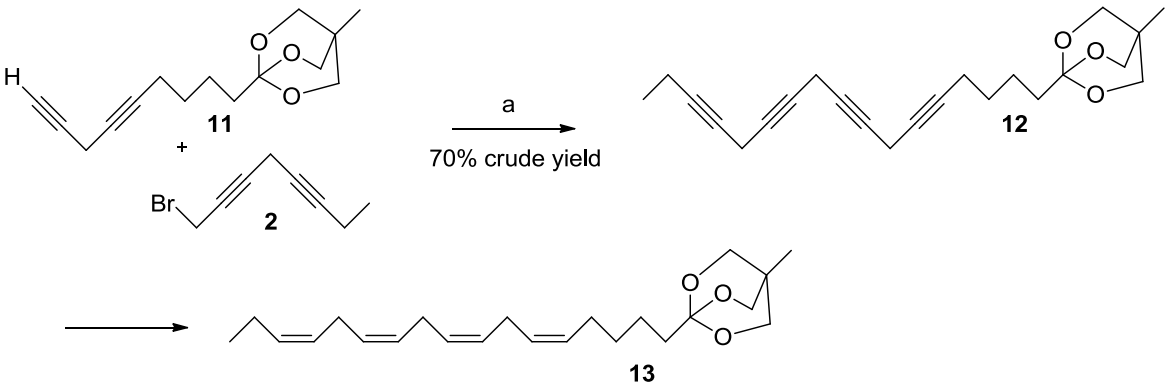


Figure 29. *The final steps in the total synthesis of OBO protected SDA* ***13****. Reaction conditions: (a) CuI, NaI, Cs_2CO_3, DMF, r.t., 48h.*

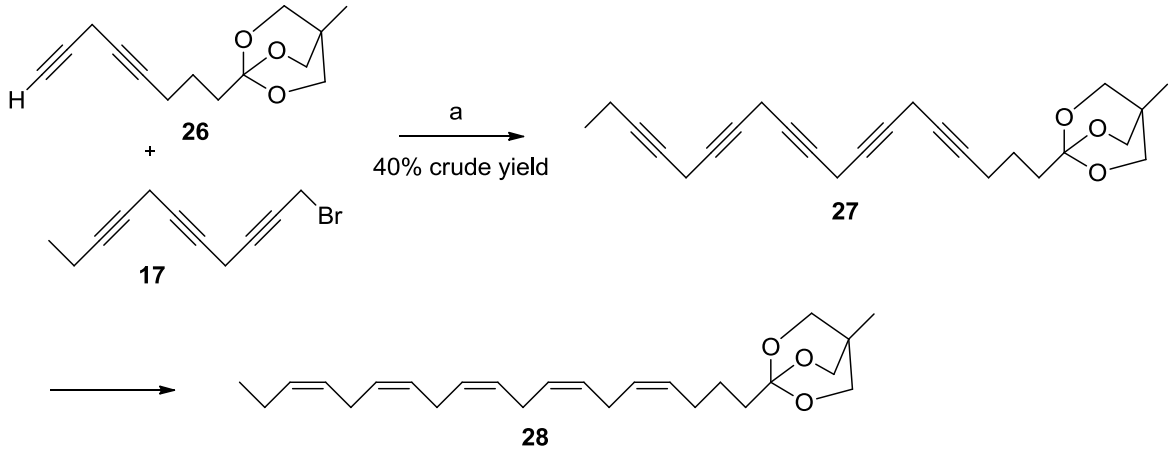


Figure 30. *The final steps in the total synthesis of OBO protected EPA* ***28****. Reaction conditions: (a) CuI, NaI, Cs_2CO_3, DMF, r.t., 48h.*

The tail **2** and the head **11** parts corresponding to SDA were copper coupled together under the same conditions as for the ethyl ester. The reaction was quenched with deionized water and extracted into diethyl ether with the aforementioned slurry formation which negatively affected the yields and the product **12** was obtained in 70% crude yield with no further purification. Any attempts to purify it on basic or neutral alumina did not succeed and evidence seems to suggest breakdown of the OBO group. The tail **17** and head **26** parts corresponding to EPA were similarily copper coupled to form the pentayne **28** in 40% yields after purification on neutral alumina.

No satisfying results were obtained from the hydrogenation attempts involving **12** and **27** and further attempts were abandoned after the easy and straightforward conversion of the OBO protecting moiety to ethyl esters was demonstrated with the ethyl esters much more convenient to work with. The OBO group did survive the hydrogenation process as evidenced by the ^{1}H NMR spectra of the product. Further purification was difficult since the OBO group could not withstand the $AgNO_3$ impregnated preparative silica TLC plates. The purification was however demonstrated by the separation of the OBO protected ALA and its over-hydrogenation byproducts on an $AgNO_3$ impregnated neutral alumina column.[34]

3.4.3 Trans measurements

The desired compound is the pure all-*cis*-isomer and the amount of *trans*-isomers in the final product is of a serious concern. The amount of *trans* double bonds formed is mostly determined by the catalyst and different catalysts are stereospecific to various degree. The catalyst that proved most efficient in reducing over-hydrogenation was the Lindlar catalyst. To try to estimate the amount of trans isomers in the Lindlar reaction product an IR transmittance calibration curve was made using a series of solutions with varying proportions of methyl oleidate and methyl elaidate, which are methyl esters of oleic acid (*cis*-18:1n-9) and elaidic acid(*trans*-18:1n-9), respectively.

The amount of *trans*-fatty acids in a sample is most commonly measured by gas chromatography (GC) methods, but it is also possible to distinguish between the two isomers in an IR spectra. The out-of-plane C−H deformation band at 966 cm^{-1} is very characteristic of *trans* double bonds, while the *cis* double bonds have a medium band at 3010 cm^{-1} and a weak band at 1645 cm^{-1}. These differences in the *cis* and *trans* absorption were used to make a calibration curve and then estimate roughly the proportions of *cis* and *trans* double bonds in the final product.

The rough estimate of *trans* content in the final product **7** suggests around 6-10% *trans* configuration in the double bonds when the IR-spectrum is compared to the calibration curve mentioned above.

4 Conclusions

The synthesis of the tail part **2** was completed in good to very good yields (79-86%) and **17** was completed in fair to very good yields (60-85%)in individual steps. The ethyl ester head **5** for SDA was obtained in 84% total yield overall in three steps and the ethyl ester head group **20** for EPA in 79% overall yield. Their OBO protected counterparts **11** and **26** were completed in 58% and 25% overall yield respectively, in four steps.

The synthesis of the tetraynes **6** and **12** and the pentaynes **21** and **27** were successfully completed. Storage problems started to arise at this point, most likely related to the high level of unsaturation. Immediate hydrogenation of these polyyne compounds might be necessary to ensure optimal yields. The ethyl ester of SDA **7** was the only hydrogenated compound that was obtained pure after treatment on $AgNO_3$ impregnated preparative silica TLC plate in 26% yield. Obtaining **7** in 18% overall yield.

The silver ion chromatography proved to be a very successful way to accurately separate the hydrogenated products based on their over-hydrogenation and to achieve a final product with no over-hydrogenated byproducts. Preparative TLC was used in this thesis work but the general method could be applied to a liquid chromatography application with a silver ion impregnated column and the purification process would without a doubt benefit greatly.

All the hydrogenation catalysts tested in this thesis showed varying degrees of over-hydrogenation with the main product still being the compound with all the double bonds intact. Lindlar catalyst was the catalyst that showed the lowest percentage of over-hydrogenation. In the case of *trans* isomers in the final product **7**, which was hydrogenated with the Lindlar catalyst the amount estimated was 6-10%. The tetrayne products **6** and **21** were obtained in good yields and the success of this method is therefore based entirely on the catalyst's ability to hydrogenate the compound stereospecifically and without any over-hydrogenation. The catalysts tried in this thesis did not work optimally on these polyyne compounds and other known or possibly unknown catalysts might enable the synthesis to be completed in much higher yield and purity.

The synthesis of the polyyne OBO protected compounds were completed, but in much lower yields than their ethyl ester counterparts. The synthesis was also more difficult and much harder to purify the compounds compared to the ethyl esters. The conversion of OBO to ethyl ester was demonstrated to be possible in good yields and that would be the recommended solution to the synthesis of the PUFAs that need to have the first triple bond incorporated into the head structure.

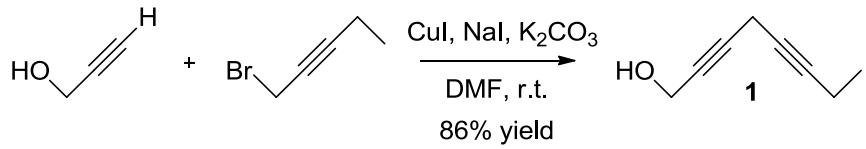
5 Materials and methods

5.1 Materials and equipments

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 spectrometer in deuterated chloroform as solvent, at 400.12 and 100.61 MHz respectively. Chemical shift (δ) are quoted in parts per million (ppm) and the coupling constant (J) in hertz (Hz). The following abbreviations are used to describe the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, bs = broad singlet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, qt = quartet of triplets, m = multiplet. All ^{1}H spectra ppm measured from the $CDCl_3$ singlet at 7.26 as the reference peak. All ^{13}C spectra ppm measured from the $CDCl_3$ triplet at 70.0 as the reference peak. All infrared spectra (when measured) were conducted on a Nicolet Avatar 360 FT-IR (E.S.P.) Spectrophotometer on a NaCl plate or grounded in a KBr tablet. Melting points were determined on a Büchi m-560 melting point apparatus and are uncorrected. The high-resolution mass spectra (HRMS) were acquired on a Bruker micrOTOF-Q mass spectrometer equipped with E-spray atmospheric pressure ionization chamber (ESI). Cases where no ^{13}C, IR or HRMS results were included involve compounds that have already been made and fully characterized, unless otherwise stated.

All chemicals and solvents were used without further purification unless otherwise stated. Tetrahydrofuran was dried over Na wire in the presence of benzophenone under dry nitrogen atmosphere. 6-heptynoic acid (90%), 5-hexynoic acid (97%), 3-methyl-3-oxetanemethanol (98%), Propargyl alcohol (99%), 3-bromo-1-(trimethylsilyl)-1-propyne (98%), 1-bromo-2-pentyne (97%), EDCI (98%), DMAP (>99%), sodium iodide (≥99%), copper(I) iodide (99.5%), cecium carbonate (99.9%) anhydrous potassium carbonate, ethanol absolute (≥99.8%), triphenylphosphine (99%), tetrabromomethane (99%), silver nitrate (≥99.8), Quinoline (98%), Lindlar catalyst, palladium on calcium carbonate 5% wt. poisoned with lead, palladium on calcium carbonate 5% wt. not poisoned, palladium on barium sulfate 5% wt., nickel(II) acetate tetrahydrate (98%), sodium borohydride (98%), deutarated chloroform (99.8% D), aluminum oxide activated neutral 58Å, aluminum oxide activated basic 58Å as well as all the solvents tetrahydrofuran (≥99.9%), dichloromethane (≥99.8%), diethyl ether (≥99.8%), ethyl acetate (≥99.7%), methanol (≥99.9%), anhydrous toluene (99%), anhydrous N,N-dimethylformamide (98%) and petroleum ether 90% fraction with boiling range 40-60°C were purchased from Sigma-Aldrich. Cyclohexene (99%) was purchased from Acros. Boron trifluoride etherate (~50%) was purchased from Merck. Silica gel 40-60 µm F60 and preparative silica TLC plates (250µm, F-254) were obtained from Silicycle.

5.2 Experimental



Synthesis of octa-2,5-diyn-1-ol (1)

Into a suspension of CuI (0.980 g, 5.0 mmol), NaI (1.488 g, 10.0 mmol) and finely ground K_2CO_3 (0.691 g, 5.0 mmol) in dry DMF (10 mL) at room temperature the reactants 1-bromopent-2-yne (1.029 g, 7.0 mmol) and propargyl alcohol (0.280 g, 5.0 mmol) were added. The reaction mixture was stirred for 24 hours and then quenched with a sat. $NH_4Cl_{(aq)}$ solution, extracted 3x into diethyl ether and the combined ether extracts washed 2x with a sat. $NH_4Cl_{(aq)}$ solution, 2x with brine, dried over $MgSO_4$, filtered and concentrated. The crude concentrate was then applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent yielding the product as a yellow liquid (0.528 g, 4.30 mmol, 86% yield).

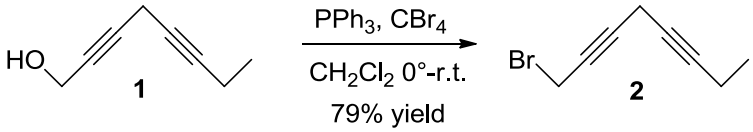
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_101]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (t, *J* = 2.1 Hz, 2H, C**H**$_2$OH), 3.18 (quin, *J* = 2.1 Hz, 2H, ≡CC**H**$_2$C≡), 2.17 (qt, *J* = 2.3, 7.6 Hz, 2H, C**H**$_2$$CH_3$), 1.55-1.62 (bs, 1H, O**H**), 1.12 (t, *J* = 7.5 Hz, 3H, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$): δ 82.45 (**C**≡), 80.83 (**C**≡), 78.35 (**C**≡), 72.65 (**C**≡), 51.29 (**C**OH), 13.80 (**C**H_3), 12.33 (**C**H_2), 9.80 (**C**H_2) ppm.

IR (NaCl): 3346 (O−H), 2976 and 2878 (C−H in CH_3), 2938 (C−H in CH_2), 2259 (C≡C) 1012 (C−O) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_8H_{10}O$+Li 129.0886; found 129.0890 amu.[29]



Synthesis of 1-bromoocta-2,5-diyne (2)

A round bottom flask containing PPh_3 (2.802 g, 10.7 mmol) and dichloromethane (20 mL) was cooled to 0-4°C with a water/ice bath. Into the cooled solution CBr_4 (1.535 g, 4.63 mmol) was added and the mixture stirred for 10 minutes. Finally octa-2,5-diyn-1-ol **1** (0.435 g, 3.56 mmol) dissolved in dichloromethane (5 mL) was added drop wise and the solution stirred at 0-4°C for 45 minutes when the cooling bath was removed and the solution allowed to reach room temperature and further stirred for 3 hours. The reaction was discontinued by addition of silica gel (40 – 60 µm, 60A) into the reaction mixture until formation of a slurry appeared which was then followed by removal of the solvent in vacuo. The resulting brown silica gel was then washed with dichloromethane/petroleum ether (1:9) for elution affording the product as a yellow liquid (0.520 g, 2.81 mmol, 79% yield).

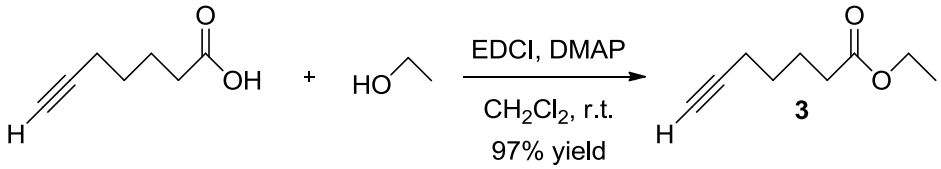
[Notebook reference to ^{1}H NMR and ^{13}C spectra: SVSIII_105]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (t, *J* = 2.3 Hz, 2H, C**H$_2$**Br), 3.21 (quin, *J* = 2.3 Hz, 2H, CC**H$_2$**C), 2.14-2.20 (qt, *J* = 2.4, 7.5 Hz, 2H, C**H$_2$**CH_3), 1.12 (t, *J* = 7.5 Hz, 3H, C**H$_3$**) ppm.

^{13}C NMR ($CDCl_3$): δ 82.67 (**C**≡), 82.07 (**C**≡), 75.24 (**C**≡), 72.16 (**C**≡), 14.83 (**C**H_2Br), 13.78 (**C**H_3), 12.34 (**C**H_2), 10.06 (**C**H_2) ppm.

IR (NaCl): 2976 and 2878 (C−H in CH_3), 2937 (C−H in CH_2), 2234 (C≡C), 1210 (C−H in CH_2Br) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_8H_{10}Br$+Li 222.9729; found 222.9727 amu.[29]



Synthesis of ethyl hept-6-ynoate (3)

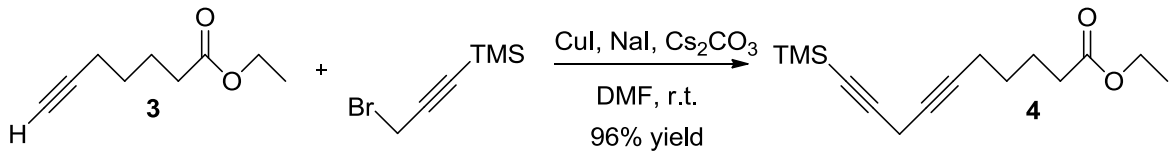
Into a 25 mL round bottom flask under nitrogen atmosphere containing EDCI (0.930 g, 4.85 mmol) and DMAP (0.198 g, 1.62 mmol) dissolved in CH_2Cl_2 (15 mL), 6-heptynoic acid (0.510 g, 4.04 mmol) was added. Subsequently EtOH (0.372 g, 8.08 mmol) was added and the solution stirred for 4 hours at room temperature. The whole reaction mixture was then washed through a 1 cm thick silica gel cake using diethyl ether/petroleum ether (1:1) as an eluent and finally concentrated affording the product as a colorless and clear liquid (0.609 g, 3.90 mmol, 97% yield).

[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_97]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, *J* = 7.1 Hz, 2H, COOC**H₂**CH_3), 2.32 (t, *J* = 7.4 Hz, 2H, C=OC**H₂**CH_2), 2.19-2.24 (td, *J* = 2.6, 7.0 Hz, 2H, ≡CC**H₂**), 1.95 (t, *J* = 2.6 Hz, 1H, **H**C≡), 1.75 (quin, *J* = 7.4 Hz, 2H, C=OCH_2C**H₂**), 1.57 (quin, *J* = 7.1 Hz, 2H, ≡CCH_2C**H₂**), 1.26 (t, *J* = 7.1 Hz, 3H, CH_2C**H₃**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.36 (**C**=O), 83.94 (≡**C**CH_2), 68.53 (≡**C**H), 60.26 (O**C**H_2CH_3), 33.78 (C=O**C**H_2), 27.85 (**C**H_2), 24.01 (**C**H_2), 18.12 (**C**H_2), 14.23 (**C**H_3) ppm.

IR (NaCl): 3295 (≡C−H), 2941 (C−H in CH_2), 2869 (C−H in CH_3), 2117 (C≡C), 1732 (C=O), 645 (C≡C−H bend) cm^{-1}.



Synthesis of ethyl 10-(trimethylsilyl) deca-6,9-diynoate (4)

Into a solution of CuI (0.358 g, 1.88 mmol) and NaI (0.700 g, 4.7 mmol) in dry DMF (8 mL), $CsCO_3$ (1.225 g, 3.76 mmol) was added. Into that suspension ethyl hept-6-ynoat **3** (0.290 g, 1.88 mmol) in DMF (2 mL) and 3-bromo-1-(trimethylsilyl)-1-propyne (0.467 g, 2.44 mmol) were added respectively and the resulting mixture was stirred for 48 h under nitrogen atmosphere at room temperature. The reaction was quenched with sat. $NH_4Cl_{(aq)}$, extracted with Et_2O and the combined ether extracts washed 1x with sat. $NH_4Cl_{(aq)}$, 1x with water and 1x with a brine solution. The ether extract was then dried over $MgSO_4$, filtered and concentrated which afforded the crude product which was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent affording the product as a yellowish liquid (0.475 g, 1.80 mmol, 96% yield). Purifying the product on a silica gel column was usually skipped and the crude concentrate used in the next reaction.

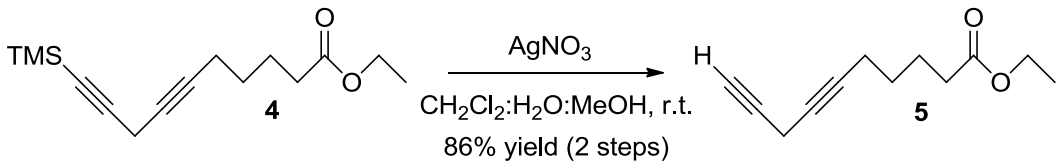
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_99]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10-4.15 (q, *J* = 7.1 Hz, 2H, COOC**H$_2$**CH_3), 3.18 (t, *J* = 2.4 Hz, 2H, ≡CC**H$_2$**C≡), 2.31 (t, *J* = 7.5 Hz, 2H, C=OC**H$_2$**CH_2), 2.19 (tt, *J* = 2.4, 7.0 Hz, 2H, ≡CC**H$_2$**CH_2), 1.72 (quin, *J* = 7.4 Hz, 2H, C=OCH_2C**H$_2$**), 1.53 (quin, *J* = 7.2 Hz, 2H, ≡CCH_2C**H$_2$**), 1.26 (t, *J* = 7.1 Hz, 3H, CH_2C**H$_3$**), 0.16 (s, 9H, TMS) ppm.

^{13}C NMR ($CDCl_3$): δ 173.48 (**C**=O), 100.63 (**C**≡), 84.71 (**C**≡), 80.33 (**C**≡), 73.78 (**C**≡), 60.24 (O**C**H_2), 33.85 (C=O**C**H_2), 28.06 (**C**H_2), 24.13 (**C**H_2), 18.47 (**C**H_2), 14.24 (**C**H_3), 10.87 (≡C**C**H_2C≡), 0.09 (TMS) ppm.

IR (NaCl): 2958 (C−H), 2182 (C≡C), 1735 (C=O) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{15}H_{24}O_2Si$+Na 287.1443; found 287.1441 amu.



Synthesis of ethyl deca-6,9-diynoate (5)

Crude ethyl 10-(trimethylsilyl) deca-6,9-diynoate **4** (1.0 g, 3.92 mmol) was dissolved in a mixture of dichloromethane/water/methanol (7:1:4; 40 mL). $AgNO_3$ (0.096 g; 0.565 mmol) was added to the solution and stirred for 8 hours at room temperature. The reaction was then quenched with a saturated $NH_4Cl_{(aq)}$ solution. The resulting solution was extracted 3x into dichloromethane and the combined extracts washed 1x with a saturated $NH_4Cl_{(aq)}$ solution, then 1x with a brine solution and dried over $MgSO_4$, filtered and concentrated. The crude product concentrate was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent affording the product as a clear yellowish liquid (0.646 g, 3.36 mmol, 86% yield over two steps).

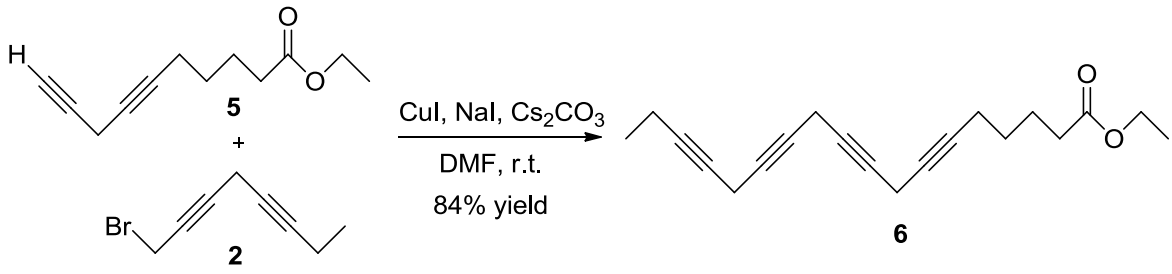
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_103]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09-4.15 (q, *J* = 7.1 Hz, 2H, OC**H₂**CH_3), 3.13-3.15 (q, *J* = 2.5 Hz, 2H, ≡CC**H₂**C≡), 2.31 (t, *J* = 7.5 Hz, 2H, C=OC**H₂**CH_2), 2.19 (tt, *J* = 2.4, 7.0 Hz, 2H, ≡CC**H₂**CH_2), 2.05 (t, *J* = 2.7 Hz, 1H, **H**C≡), 1.71 (quin, *J* = 7.4 Hz, 2H, C=OCH_2C**H₂**), 1.53 (quin, *J* = 7.1 Hz, 2H, ≡CCH_2C**H₂**), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2C**H₃**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.45 (**C**=O), 80.56 (**C**≡), 78.83 (**C**≡), 73.46 (**C**≡), 68.43 (H**C**≡), 60.25 (O**C**H_2), 33.84 (C=O**C**H_2), 28.04 (**C**H_2), 24.13 (**C**H_2), 18.40 (**C**H_2), 14.23 (**C**H_3), 9.54 (≡C**C**H_2C≡) ppm.

IR (NaCl): 3292 (≡C−H), 2981 and 2868 (C−H in CH_3), 2940 (C−H in CH_2), 2125 (C≡C), 1732 (C=O), 650 (≡C−H bend) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{12}H_{16}O_2$+Na 215.1048; found 215.1043 amu.



Synthesis of ethyl octadeca-6,9,12,15-tetraynoate (6)

Into a solution of CuI (0.625 g, 3.28 mmol) and NaI (1.220 g, 8.20 mmol) in dry DMF (12 mL), $CsCO_3$ (2.136 g, 6.56 mmol) was added. Into that suspension ethyl deca-6,9-diynoate **5** (0.315 g, 1.64 mmol) in DMF (2 mL) and 1-bromoocta-2,5-diyne **2** (0.426 g, 2.30 mmol) in DMF (2 mL) were added, respectively, and the resulting mixture was stirred for 64h under nitrogen atmosphere at room temperature. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, extracted into diethyl ether and the combined ether extracts washed 1x with saturated $NH_4Cl_{(aq)}$, 1x with water and 1x with a brine solution. After drying the solution over $MgSO_4$ and filtering the solvent was evaporated, to afford the crude product which was applied to a silica gel chromatography using petroleum ether/ethyl acetate (4:1) as an eluent. This afforded the product as a yellow liquid (0.406 g, 1.37 mmol, 84% yield).

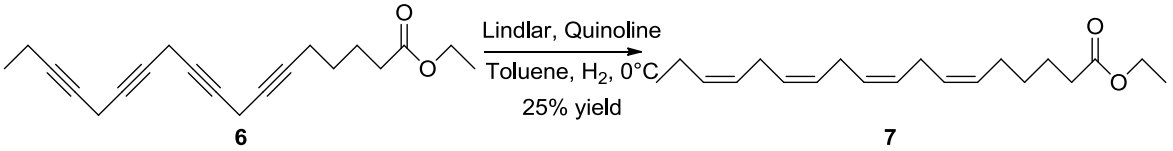
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_107]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96-4.02 (q, *J* = 7.1 Hz, 2H, OC**H₂**CH_3), 2.97-3.03 (m, 6H, ≡CC**H₂**C≡), 2.17 (t, *J* = 7.5 Hz, 2H, C=OC**H₂**CH_2), 2.00-2.07 (m, 4H, ≡CC**H₂**CH_3, ≡CC**H₂**CH_2), 1.58 (quin, *J* = 7.4 Hz, 2H, C=OCH_2C**H₂**), 1.39 (quin, *J* = 7.2 Hz, 2H, ≡CCH_2C**H₂**), 1.12 (t, *J* = 7.1 Hz, 3H, OCH_2C**H₃**), 0.98 (t, *J* = 7.5 Hz, 3H, ≡CCH_2C**H₃**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.48 (**C**=O), 82.18 (≡**C**CH_2), 80.18 (≡**C**CH_2), 75.17 (**C**≡), 75.07 (**C**≡), 74.18 (**C**≡), 74.12 (2**C**≡), 73.03 (**C**≡), 60.25 (O**C**H_2CH_3), 33.85 (C=O**C**H_2CH_2), 28.10 (C=OCH_2CH_2**C**H_2), 24.16 (C=OCH_2**C**H_2), 18.43 (≡C**C**H_2), 14.24 (OCH_2**C**H_3), 13.84 (≡CH_2**C**H_3), 12.36 (≡C**C**H_2), 9.83 (≡C**C**H_2C≡), 9.75 (≡C**C**H_2C≡), 9.72 (≡C**C**H_2C≡) ppm.

IR (NaCl): 2977 and 2877 (C−H in CH_3), 2937 (C−H in CH_2), 2215 (C≡C), 1732 (C=O) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{20}H_{24}O_2$+Na 319.1674; found 319.1669 amu.



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Synthesis of (6Z,9Z,12Z,15Z)-ethyl octadeca-6,9,12,15-tetraenoate (7)

A suspension of Lindlar catalyst in dry toluene (25 mL) was saturated with hydrogen gas. Ethyl octadeca-6,9,12,15-tetraynoate **6** (0.100 g; 0.38 mmol) and quinoline (0.021 g; 0.17 mmol) was then added into the suspension and stirred at 0°C. By monitoring the reaction with TLC the reaction was ended after 46 min and the mixture filtered through a thin celite layer, flushed with dichloromethane and then concentrated. The crude mixture was then applied to a silica gel chromatography using petroleum ether/ethyl acetate (9:1) as eluent. Evaporation of the solvent afforded mixture of the product and all its over-hydrogenated by-products which was then applied to a 5% $AgNO_3$ doped preparative silica TLC plates using acetone/petroleum ether (4:25) as eluent affording the clear liquid/oil product (0.026 g, 0.085 mmol 25% yield).

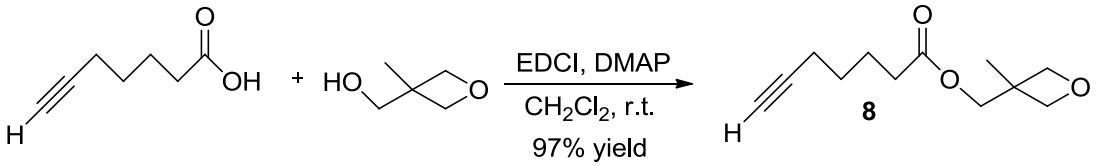
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSII_179_B2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.28-5.44 (m, 8H, C=C**H**) 4.10-4.15 (q, *J* = 7.1 Hz, 2H, OC**H₂**CH_3), 2.78-2.86 (m, 6H, =CC**H₂**C=), 2.30 (t, *J* = 7.5 Hz, 2H, C=OC**H₂**CH_2), 2.08 (quin, *J* = 6.9 Hz, 4H, =CHC**H₂**CH_3, =CHC**H₂**CH_2), 1.65 (quin, *J* = 7.5 Hz, 2H, C=OCH_2C**H₂**), 1.40 (quin, *J* = 7.6 Hz, 2H, =CHCH_2C**H₂**), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2C**H₃**), 0.98 (t, *J* = 7.5 Hz, 3H, =CHCH_2C**H₃**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.66 (**C**=O), 132.01 (=**C**H), 129.68 (=**C**H), 128.51 (=**C**H), 128.30 (=**C**H), 128.11 (=**C**H), 128.07 (=**C**H), 127.91 (=**C**H), 127.02 (=**C**H), 60.18 (O**C**H_2CH_3), 34.25 (C=O**C**H_2CH_2), 29.09 (=CHCH_2**C**H_2), 26.87 (=CH**C**H_2CH_2), 25.62 (=CH**C**H_2CH=), 25.61 (=CH**C**H_2CH=), 25.54 (=CH**C**H_2CH=), 24.61 (C=OCH_2**C**H_2), 20.55 (=CH**C**H_2CH_3), 14.26 (OCH_2**C**H_3), 14.26 (=CHCH_2**C**H_3) ppm.

IR (NaCl): 3011 (C−H alkenes), 2963 and 2872 (C−H, CH_3), 2933 (C−H, CH_2), 1736 (C=O), 1653 (C=C), 715 (=C−H bend) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{25}H_{28}O_3$+Na 327.2300; found 327.2292 amu.



Synthesis of (3-methyloxetan-3-yl)methyl hept-6-ynoate (8)

Into a round bottom flask under nitrogen atmosphere containing EDCI (0.966 g, 5.04 mmol) and DMAP (0.204 g, 1.68 mmol) dissolved in CH_2Cl_2 (15 mL), 6-heptynoic acid (0.530 g, 4.2 mmol) was added. Subsequently 3-methyloxetan-3-yl methanol (0.429 g, 4.2 mmol) was added and the solution stirred for 4 hours at room temperature. Then the whole reaction mixture was poured unto a 1 cm thick silica gel layer and washed through with diethyl ether/petroleum ether (1:1) and finally concentrated affording the product as a colorless and clear liquid (0.859 g, 4.09 mmol, 97% yield).

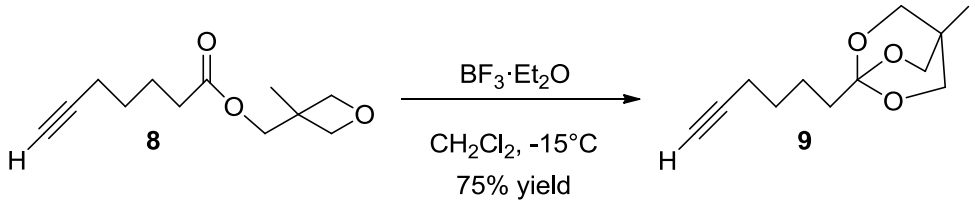
[Notebook reference to ^{1}H NMR spectra: SVSI_169]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51 (d, *J* = 6.0 Hz, 2H, C**H$_2$**OC**H$_2$**), 4.37 (d, *J* = 6.0 Hz, 2H, C**H$_2$**OC**H$_2$**), 4.17 (s, 2H, C=OOC**H$_2$**C), 2.39 (t, *J* = 7.4 Hz, 2H, C=OC**H$_2$**CH_2), 2.20-2.24 (td, *J* = 2.6, 7.0 Hz, 2H, ≡CC**H$_2$**), 1.95 (t, *J* = 2.6 Hz, 1H, ≡C**H**), 1.77 (quin, *J* = 7.4 Hz, 2H, C=OCH_2C**H$_2$**), 1.57 (quin, *J* = 7.1 Hz, 2H, ≡CCH_2C**H$_2$**), 1.33 (s, 3H, CC**H$_3$**) ppm.

^{13}C NMR ($CDCl_3$) Pending.

IR (NaCl) Pending.

HRMS (ESI): *m/z* calculated for $C_{12}H_{18}O_3$+Na 233.1154; found 233.1148 amu.



Synthesis of 1-(hex-5-yn-1-yl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (9)

(3-Methyloxetan-3-yl)methyl hept-6-ynoate **8** (0.859 g, 4.09 mmol) in dry CH_2Cl_2 (10 mL) was placed in a previously dried round bottom flask. The solution was then cooled down to -15°C with an acetone/ice bath. Finally $BF_3{\cdot}Et_2O$ (0.290 g, 2.04 mmol) was added and the mixture stirred for 6 hours at -15°C and then slowly allowed to reach room temperature. The reaction was quenched with triethylamine (0.35 mL) and stirred for 10 minutes until diethyl ether (20 mL) was added. This resulted in the formation of a BF_3/triethylamine complex which was then filtered off with gravity filtration and the resulting solution applied to a 1 cm long 5% triethylamine doped silica gel cake using CH_2Cl_2 as an eluent which afforded oily crystals with the evaporation of the solvent. To further purify the product and remove all traces of triethylamine the crystals were applied to a neutral alumina chromatography using petroleum ether/ethyl acetate (7:3) as an eluent affording the product as white crystals (0.648 g, 3.07 mmol, 75% yield).

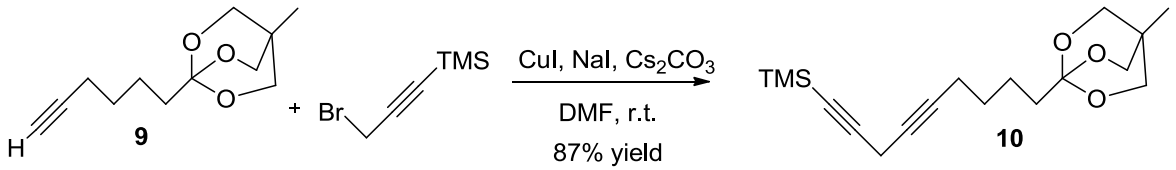
[Notebook reference to ^{1}H NMR spectra: SVSI_129]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 6H, OC**H$_2$**CCH_3), 2.15-2.19 (m, 2H, ≡CC**H$_2$**CH_2), 1.92 (t, *J* = 2.6 Hz, 1H, ≡C**H**), 1.65-1.70 (m, 2H, CH_2C**H$_2$**CO_3), 1.51-1.56 (m, 4H, ≡CCH_2C**H$_2$**C**H$_2$**), 0.79 (s, 3H, C**H$_3$**) ppm.

^{13}C NMR ($CDCl_3$): Pending.

IR (NaCl): Pending.

HRMS (ESI): Pending.



Synthesis of trimethyl(9-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)nona-1,4-diyn-1-yl)silane (10)

Into a solution of CuI (0.269 g, 1.41 mmol) and NaI (0.524 g, 3.52 mmol) in dry DMF (8 mL), $CsCO_3$ (0.919 g, 2.82 mmol) was added. Into that suspension 1-(hex-5-yn-1-yl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane **9** (0.296 g, 1.41 mmol) in DMF (2 mL) and 3-bromo-1-(trimethylsilyl)-1-propyne (0.539 g, 2.82 mmol) were added, respectively, and the resulting mixture was stirred for 48 h under nitrogen atmosphere at room temperature. The reaction was then quenched with water and extracted into Et_2O which resulted in formation of a brown slurry. The water was slowly drained off and the brown slurry/ether layer was filtered through a short 1 cm celite layer using Et_2O as solvent. The resulting ether solution was washed 3x with water/brine (1:1), 1x with brine, dried over $MgSO_4$, filtered and concentrated. This crude solution was applied to a basic alumina chromatography using petroleum ether/ethyl acetate (7:3) as an eluent, which afforded the product as a yellowish liquid (0.393 g, 1.23 mmol, 87% yield).

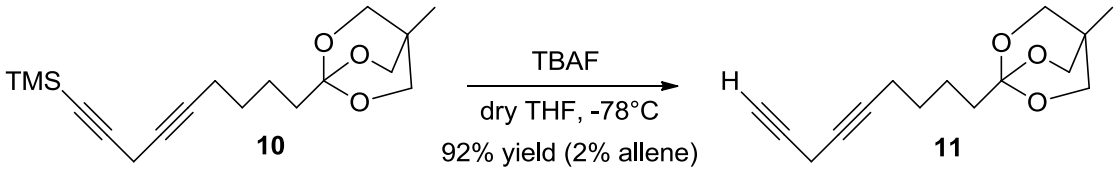
[Notebook reference to ^{1}H NMR spectra: SVSI_175]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 6H, $OC\mathbf{H_2}CCH_3$), 3.18 (t, *J* = 2.4 Hz, 2H, $\equiv CC\mathbf{H_2}C\equiv$), 2.12-2.17 (m, 2H, $\equiv CC\mathbf{H_2}CH_2$), 1.64-1.69 (m, 2H, $CH_2C\mathbf{H_2}CO_3$), 1.48-1.55 (m, 4H, $C\mathbf{H_2}C\mathbf{H_2}CH_2CO_3$), 0.79 (s, 3H, $CC\mathbf{H_3}$), 0.16 (s, 9H, TMS) ppm.

^{13}C NMR ($CDCl_3$): Pending.

IR (NaCl): Pending.

HRMS (ESI): Pending.



Synthesis of 4-methyl-1-(nona-5,8-diyn-1-yl)-2,6,7-trioxabicyclo[2.2.2]octane (11)

Trimethyl(9-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)nona-1,4-diyn-1-yl)silane **10** (0.062 g, 0.19 mmol) in dry THF (3 mL) was placed in a previously dried two necked round bottom flask under nitrogen. This flask and another round bottom flask containing tetra-*n*-butylammonium fluoride in THF (0.190 mL, 1 M, 0.19 mmol) with added dry THF (2 mL) were cooled down to -78°C in a dry ice/acetone bath. When adequately cooled the contents of the TBAF containing flask were transferred to the other flask very slowly with a cooled syringe. The solution was stirred for 4 hours under nitrogen at -78°C and then very slowly allowed to reach -25°C over 4 hours and kept at -25°C over night until the reaction was concluded to be finished by monitoring on TLC. Then the still cold contents of the flask were applied straight to a neutral alumina chromatography using cooled petroleum ether/ethyl acetate (1:1) as an eluent, affording the product as a yellowish liquid (0.043 g, 0.17 mmol 92% yield, 2% allene).

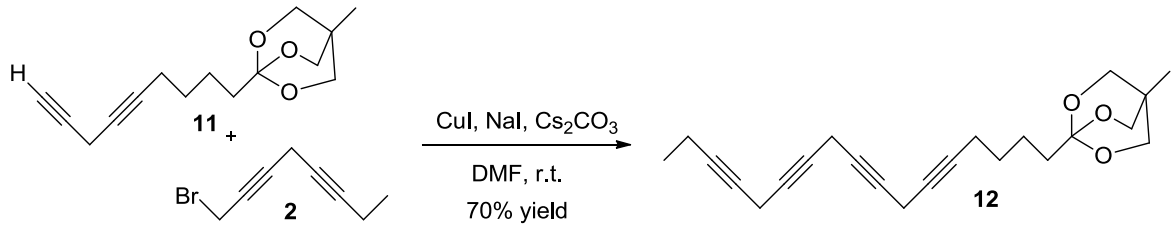
[Notebook reference to ^{1}H NMR spectra: SVSI_143]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 6H, $OC\mathbf{H_2}CCH_3$), 3.13-3.15 (q, *J* = 2.4 Hz, 2H, $\equiv C\mathbf{H_2}C\equiv$), 2.13-2.18 (m, 2H, $\equiv CC\mathbf{H_2}CH_2$), 2.05 (t, *J* = 2.6 Hz, 1H, $\equiv C\mathbf{H}$), 1.64-1.70 (m, 2H, $CH_2C\mathbf{H_2}CO_3$), 1.48-1.55 (m, 4H, $\equiv CCH_2C\mathbf{H_2}C\mathbf{H_2}$), 0.80 (s, 3H, $CC\mathbf{H_3}$) ppm.

^{13}C NMR ($CDCl_3$): Pending.

IR (NaCl): Pending.

HRMS (ESI): Pending.



Synthesis of 1-(heptadeca-5,8,11,14-tetrayn-1-yl)-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (12)

Into a solution of CuI (0.075 g, 0.40 mmol) and NaI (0.1474 g, 0.99 mmol) in dry DMF (8 mL), $CsCO_3$ (0.257 g, 0.79 mmol) was added. Into that suspension 4-methyl-1-(nona-5,8-diyn-1-yl)-2,6,7-trioxabicyclo[2.2.2]octane **11** (0.048 g, 0.20 mmol) in DMF (2 mL) and 1-bromoocta-2,5-diyne **2** (0.073 g, 0.40 mmol) were added respectively and the resulting mixture was stirred for a few days under nitrogen atmosphere at room temperature and monitored by TLC. The reaction was quenched with water extracted into Et_2O which resulted in formation of a brown slurry. The water was slowly drained off and the brown slurry/ether layer was filtered through a short 1 cm celite layer using Et_2O as a solvent. The resulting ether solution was washed 2x with water/brine (1:1), 2x with brine, dried over $MgSO_4$, filtered and concentrated. This orange/brown crude product was not purified further (0.048 g, 0.14 mmol, 70% crude yield).

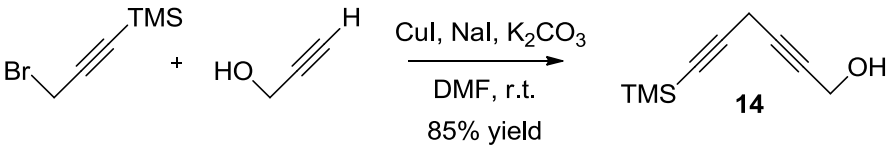
[Notebook reference to ^{1}H NMR spectra: SVSII_17B]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 6H, $OC\mathbf{H_2}CCH_3$), 3.11-3.20 (m, 6H, $\equiv CC\mathbf{H_2}C\equiv$), 2.12-2.20 (m, 4H, $\equiv C\mathbf{H_2}CH_2$, $\equiv C\mathbf{H_2}CH_3$), 1.65-1.68 (m, 2H, $C\mathbf{H_2}C(OCH_2)_3$), 1.48-1.53 (m, 4H, $C\mathbf{H_2}C\mathbf{H_2}CH_2C(OCH_2)_3$), 1.12 (t, 3H, $\equiv CCH_2C\mathbf{H_3}$), 0.79 (s, 3H, $C(OCH_2)_3CC\mathbf{H_3}$) ppm.

^{13}C NMR ($CDCl_3$): Pending.

IR (NaCl): Pending.

HRMS (ESI): *m/z* calculated for $C_{23}H_{28}O_3$+Na 375.1936; found 375.1931 amu.

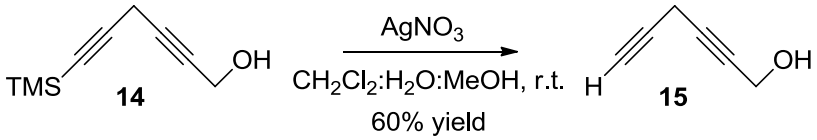


Synthesis of 1-(trimethylsilyl)hex-1,4-diyn-6-ol (14)

Into a suspension of CuI (0.953 g, 5.0 mmol), NaI (1.525 g, 10.0 mmol) and finely ground K_2CO_3 (0.691 g, 5.0 mmol) in dry DMF (10 mL) at room temperature the reactants 3-bromo-1-(trimethylsilyl)prop-1-yne (1.00 g, 5.0 mmol) and propargyl alcohol (0.267 g, 5.0 mmol) were added. The reaction mixture was stirred for 48 hours and then quenched with a sat. $NH_4Cl_{(aq)}$ solution, extracted 4x into diethyl ether and the combined ether extracts washed 2x with a sat. $NH_4Cl_{(aq)}$ solution, 2x brine, dried over $MgSO_4$, filtered and concentrated. The crude concentrate was then applied to a silica gel chromatography using petroleum ether/ethyl acetate (6:4) as an eluent yielding the product as an orange liquid (0.710 g, 4.25 mmol, 85% yield). Purifying the product on a silica gel column was usually skipped and the crude concentrate used in the next reaction.

[Notebook reference to ^{1}H NMR spectra: TKKI-249]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (t, *J* = 2.2 Hz, 2H HOC**H$_2$**≡), 3.25 (t, *J* = 2.2 Hz, 2H, ≡C**H$_2$**≡), 1.54 (bs, 1H, -O**H**), 0.16 (s, 9H, TMS) ppm.



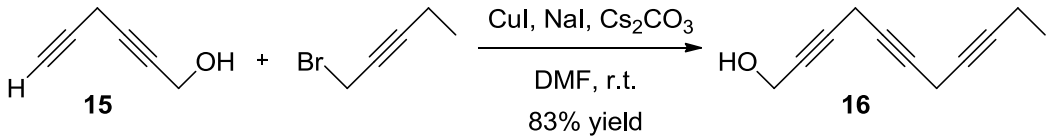
Synthesis of hex-2,5-diyn-1-ol (15)

1-(Trimethylsilyl)hex-1,4-diyn-6-ol **14** (0.710 g, 4.27 mmol) was dissolved in a mixture of dichloromethane/water/methanol (7:1:4) to which $AgNO_3$ was added. The mixture was stirred at room temperature for up to 5 hours. If the reaction did not show completion monitored with TLC (petroleum ether/ethyl acetate; 7:3) a few grains of $AgNO_3$ could be added. The reaction mixture was then quenched with a saturated $NH_4Cl_{(aq)}$ solution and extracted into diethyl ether. The combined diethyl ether extracts were then washed with a saturated $NH_4Cl_{(aq)}$ solution, brine solution, dried over $MgSO_4$, filtered and concentrated. The crude concentrate was then applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent, affording the product as a clear yellow liquid (0.241 g, 2.56 mmol, 60% yield).

[Notebook reference to ^{1}H NMR spectra: SVSII_25]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (t, *J* = 2.2 Hz, 2H, C**H**$_2$OH), 3.22 (q, *J* = 2.3 Hz, 2H, CC**H**$_2$C), 2.09 (t, *J* = 2.7 Hz, 1H, ≡C**H**), 1.57-1.64 (bs, 1H, CH_2O**H**) ppm.

HRMS (ESI): *m/z* calculated for $C_9H_{14}O$+Li 173.0968; found 173.0963 amu.[29]

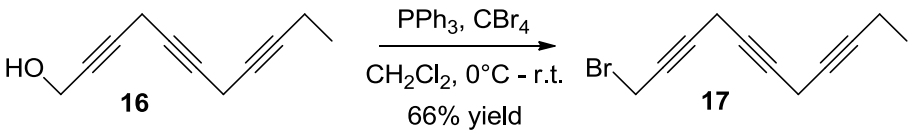


Synthesis of undeca-2,5,8-triyn-1-ol (16)

Into a suspension of CuI (0.988 g, 5.19 mmol), NaI (2.100 g, 14.0 mmol) and Cs_2CO_3 (3.382 g, 10.1 mmol) in dry DMF (15 mL) at room temperature hex-2,5-diyn-1-ol **15** (0.488 g, 5.19 mmol) in DMF (2 mL) and 1-bromopent-2-yne (1.144 g, 7.79 mmol) were added. The reaction mixture was stirred for 48 hours and then quenched with a sat. $NH_4Cl_{(aq)}$ solution, extracted 3x into diethyl ether and the combined ether extracts washed 1x with a sat. $NH_4Cl_{(aq)}$ solution, 2x with brine, dried over $MgSO_4$, filtered and concentrated. The crude concentrate was then applied to a silica gel chromatography using petroleum ether/diethyl ether (1:1) as an eluent, yielding the product as an orange liquid (0.686 g, 4.31 mmol, 83% yield).

[Notebook reference to ^{1}H NMR spectra: SVSII_27]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (t, *J* = 2.1 Hz, 2H, C**H$_2$**OH), 3.20 (quin, *J* = 2.2 Hz, 2H, C**H$_2$**C≡CCH_2OH), 3.13 (quin, *J* = 2.4 Hz, 2H, C**H$_2$**C≡CCH_2CH_3), 2.17 (qt, *J* = 2.4, 7.5 Hz, 2H, C**H$_2$**CH_3), 1.58-1.70 (bs, 1H, CH_2O**H**), 1.12 (t, *J* = 7.5 Hz, 3H, CH_2C**H$_3$**) ppm.

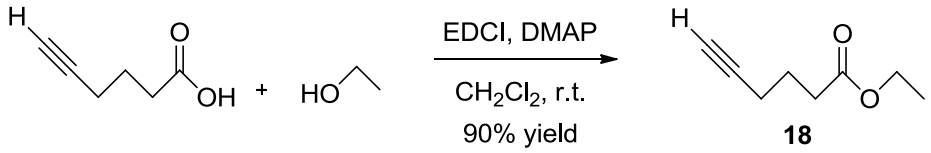


Synthesis of 1-bromoundeca-2,5,8-triyne (17)

A round bottom flask containing PPh_3 (3.371 g, 12.5 mmol) and dichloromethane (35 mL) was cooled to 0-4°C with a water/ice bath. Into the cooled solution CBr_4 (1.845 g, 5.56 mmol) was added and the mixture stirred for 10 minutes. Finally undeca-2,5,8-triyn-1-ol **16** (0.686 g, 4.28 mmol) dissolved in CH_2Cl_2 (5 mL) was added drop wise and the solution stirred at 0-4°C for 45 minutes. The cooling bath was removed and the solution allowed to reach room temperature and further stirred for 3 hours. The reaction was discontinued by addition of silica gel (40 – 60 µm, 60A) into the reaction mixture until formation of a slurry appeared, which was then followed by removal of the solvent in vacuo. The resulting brown silica gel was then washed with dichloromethane/petroleum ether (1:9) for elution affording the product as a brown liquid (0.628 g, 2.82 mmol, 66% yield).

[Notebook reference to ^{1}H NMR spectra: EKRV_76B_150714]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (t, J= 2.3 Hz, 2H, C**H$_2$**Br), 3.23 (quin, *J* = 2.3, 2H, C**H$_2$**C≡CH_2Br), 3.14 (quin, *J* =2.3 Hz, 2H, C**H$_2$**C≡CH_2CH_3), 2.14-2.21 (qt, *J* = 2.4, 7.5, 2H, C**H$_2$**CH_3), 1.12 (t, *J* = 7.5, 3H, C**H$_3$**) ppm.



Synthesis of ethyl hex-5-ynoate (18)

Into a 25 mL round bottom flask under nitrogen atmosphere containing EDCI (0.966 g, 5.04 mmol) and DMAP (0.205 g, 1.68 mmol) dissolved in CH_2Cl_2 (15 mL), 5-hexynoic acid (0.471 g, 4.20 mmol) was added. Subsequently ethanol (0.387 g, 8.40 mmol) was added and the solution stirred for 4 hours at room temperature. The whole reaction mixture was then washed through 1 cm thick silica gel cake using diethyl ether/petroleum ether (1:1) as an eluent and finally concentrated affording the product as a colorless and clear liquid (0.530 g, 3.78 mmol, 90% yield).

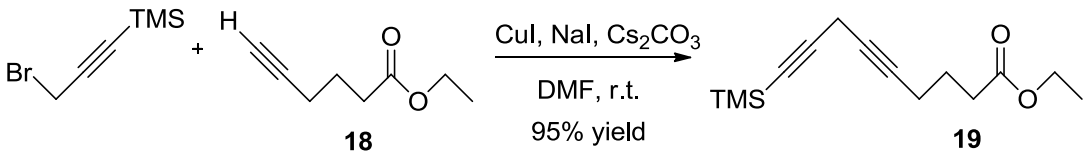
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_13]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11-4.16 (q, *J* = 7.1 Hz, 2H, COOC**H₂**CH_3), 2.44 (t, *J* = 7.4 Hz, 2H, C=OC**H₂**CH_2), 2.24-2.28 (td, *J* = 2.6, 7.0 Hz, 2H, ≡CC**H₂**), 1.96 (t, *J* = 2.6 Hz, 1H, **H**C≡), 1.85 (quin, *J* = 7.2 Hz, 2H, C=OCH_2C**H₂**), 1.27 (t, *J* = 7.1 Hz, 3H, CH_2C**H₃**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.2 (**C**=O), 83.5 (≡**C**CH_2), 69.2 (≡**C**H), 60.5 (O**C**H_2), 33.1 (C=O**C**H_2), 23.8 (**C**H_2), 18.0 (**C**H_2), 14.4 (**C**H_3) ppm.

IR (NaCl): 3329 (≡C−H), 2987 (C−H in CH_2), 2937 (C−H in CH_3), 2119 (C≡C), 1733 (C=O), 640 (C≡C−H bend) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_8H_{12}O_2$+Na 163.0735; found 163.0730 amu.



Synthesis of ethyl 9-(trimethylsilyl) nona-5,8-diynoate (19)

Into a solution of CuI (0.588 g, 3.09 mmol) and NaI (1.150 g, 7.73 mmol) in dry DMF (15 mL), $CsCO_3$ (2.010 g, 6.18 mmol) was added. Into that suspension ethyl hex-5-ynoate **18** (0.433 g, 3.09 mmol) in DMF (2 mL) and 3-bromo-1-(trimethylsilyl)-1-propyne (1.181 g, 6.18 mmol) were added respectively and the resulting mixture was stirred for 48 h under nitrogen atmosphere at room temperature. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, extracted with Et_2O and the combined ether extracts washed 1x with saturated $NH_4Cl_{(aq)}$, 1x with water and 1x with a brine solution. The ether extract was then dried over $MgSO_4$, filtered and concentrated. The crude product was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent affording the product as a yellow liquid (0.734 g, 2.94 mmol, 95% yield).

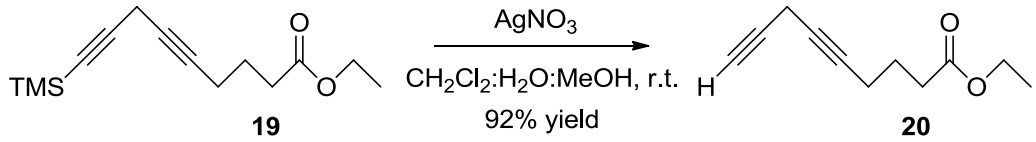
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11-4.16 (q, *J* = 7.1 Hz, 2H, COOC**H$_2$**CH_3), 3.18 (t, *J* = 2.4 Hz, 2H, ≡CC**H$_2$**C≡), 2.42 (t, *J* = 7.5 Hz, 2H, C=OC**H$_2$**CH_2), 2.24 (tt, *J* = 2.4, 7.0 Hz, 2H, ≡CC**H$_2$**CH_2), 1.82 (quin, *J* = 7.2 Hz, 2H, C=OCH_2C**H$_2$**), 1.26 (t, *J* = 7.1 Hz, 3H, CH_2C**H$_3$**), 0.16 (s, 9H, TMS) ppm.

^{13}C NMR ($CDCl_3$): δ 173.19 (**C**=O), 100.52 (**C**≡), 84.82 (**C**≡), 79.74 (**C**≡), 74.37 (**C**≡), 60.31 (O**C**H_2), 33.13 (C=O**C**H_2), 23.87 (**C**H_2), 23.85 (**C**H_2), 18.22 (**C**H_3), 10.87 (≡C**C**H_2C≡), 0.07 (TMS) ppm.

IR (NaCl): 2960 (C−H), 2183 (C≡C), 1736 (C=O) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{14}H_{22}O_2Si$+Na 273.1287; found 273.1282 amu.



Synthesis of ethyl nona-5,8-diynoat (20)

Crude ethyl 9-(trimethylsilyl)nona-5,8-diynoate **19** (0.704 g, 2.81 mmol) was dissolved in a mixture of dichloromethane/water/methanol (7:1:4; 35 mL). $AgNO_3$ (0.143 g; 0.840 mmol) was added to the solution and stirred for 8 hours at room temperature. The reaction was then quenched with a saturated $NH_4Cl_{(aq)}$ solution. The resulting solution was extracted 3x into dichloromethane and the combined extracts washed 1x with a saturated $NH_4Cl_{(aq)}$ solution, then 1x with a brine solution and dried over $MgSO_4$, filtered and concentrated. The crude concentrate was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent affording the product as a clear yellowish liquid (0.506 g, 2.59 mmol, 92% yield)

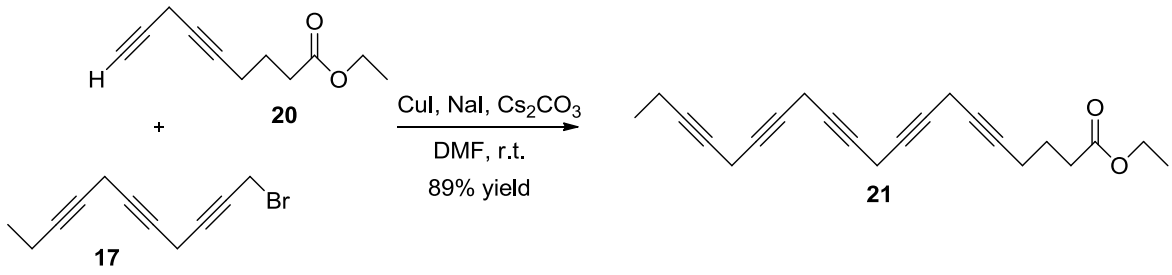
[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSIII_31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10-4.16 (q, *J* = 7.1 Hz, 2H, OC**H$_2$**CH_3), 3.13-3.15 (q, *J* = 2.5 Hz, 2H, ≡CC**H$_2$**C≡), 2.41 (t, *J* = 7.5 Hz, 2H, C=OC**H$_2$**CH_2), 2.24 (tt, *J* = 2.4, 6.9 Hz, 2H, ≡CC**H$_2$**CH_2), 2.05 (t, *J* = 2.7 Hz, 1H, **H**C≡), 1.81 (quin, *J* = 7.2 Hz, 2H, C=OCH_2C**H$_2$**), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2C**H$_3$**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.2 (**C**=O), 80.0 (**C**≡), 78.8 (**C**≡), 74.0 (**C**≡), 68.5 (H**C**≡), 60.4 (O**C**H_2), 33.2 (C=O**C**H_2), 23.9 (**C**H_2), 18.2 (**C**H_2), 14.2 (**C**H_3), 9.60 (≡C**C**H_2C≡) ppm.

IR (NaCl): 3292 (≡C−H), 2980 (C−H in CH_3), 2940 (C−H in CH_2), 1931 (C≡C), 1730 (C=O), 746 (≡C−H bend) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{11}H_{14}O_2$+Na 201.0892; found 201.0886 amu.



Synthesis of ethyl icosa-5,8,11,14,17-pentaynoate (21)

Into a solution of CuI (0.107 g, 0.561 mmol) and NaI (0.209 g, 1.403 mmol) in dry DMF (5 mL), $CsCO_3$ (0.366 g, 1.122 mmol) was added. Into that suspension ethyl nona-5,8-diynoat **20** (0.035 g, 0.196 mmol) in DMF (2 mL) and 1-bromoundeca-2,5,8-triyne **17** (0.104 g, 0.446 mmol) in DMF (2 mL) were added respectively and the resulting mixture was stirred for 4 days under nitrogen atmosphere at room temperature. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, extracted into diethyl ether and the combined ether extracts washed 1x with saturated $NH_4Cl_{(aq)}$, 1x with water and 1x with a brine solution. After drying the solution over $MgSO_4$ and filtering, the solvent was evaporated. The crude product was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent, affording the product as a yellow liquid (0.056 g, 0.174 mmol, 89% yield).

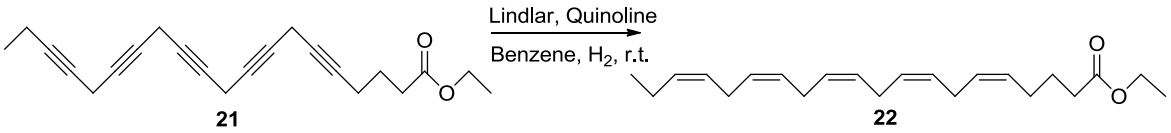
[Notebook reference to ^{1}H NMR spectra: SVSII_35]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10-4.16 (q, *J* = 7.1 Hz, 2H, OC**H$_2$**CH_3), 3.12-3.15 (m, 6H, ≡CC**H$_2$**C≡), 2.41 (t, *J* = 7.5 Hz, 2H, C=OC**H$_2$**CH_2), 2.23(tt, *J* = 6.9, 2.2, 2H, ≡CC**H$_2$**CH_2), 2.13-2.20 (qt, *J* = 7.5, 2.2, 2H, ≡CC**H$_2$**CH_3), 1.81 (quin, *J* = 7.2 Hz, 2H, C=OCH_2C**H$_2$**), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2C**H$_3$**), 1.12 (t, *J* = 7.5 Hz, 3H, ≡CCH_2C**H$_3$**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.12 (**C**=O), 82.14 (≡**C**), 79.52 (≡**C**), 75.19 (**C**≡), 74.99 (**C**≡), 74.57 (**C**≡), 74.46 (**C**≡), 74.39 (**C**≡), 74.11 (**C**≡), 73.98 (**C**≡), 72.96 (**C**≡), 61.27 (O**C**H_2), 33.11 (C=O**C**H_2CH_2), 23.84 (**C**H_2), 18.14 (≡C**C**H_2), 14.19 (**C**H_3), 13.79 (**C**H_3), 12.31 (≡C**C**H_2), 9.76 (≡C**C**H_2C≡), 9.75 (≡C**C**H_2C≡), 9.69 (≡C**C**H_2C≡), 9.67 (≡C**C**H_2C≡) ppm.

IR (NaCl): 2980 (C−H in CH_3), 2939 (C−H in CH_2), 2251 (C≡C), 1728 (C=O) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{22}H_{24}O_2$+Na 343.1674; found 343.1669 amu.



21 22

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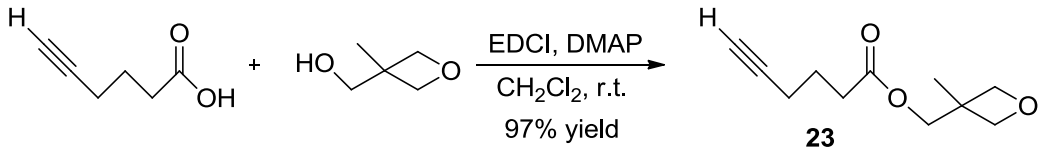
Synthesis of all-*cis*-ethyl icosa-5,8,11,14,17-pentaenoate (22)

A suspension of a Lindlar catalyst in dry benzene (10 mL) was saturated with hydrogen gas. Ethyl icosa-5,8,11,14,17-pentaynoate **21** (0.015 g; 0.34 mmol) and quinoline (0.033 g; 0.257 mmol) were then added into the suspension and stirred at room temperature. By monitoring the reaction with TLC the reaction was ended after 1 hour and the mixture filtered through a thin celite layer, flushed with dichloromethane and then concentrated. The crude mixture was then applied to a silica gel chromatography using petroleum ether/ethyl acetate (9:1) as an eluent. Evaporation of the solvent afforded a mixture of the product and all its over-hydrogenated byproducts that was not purified any further. ^{1}H NMR spectra still showed traces of triple bonds in the mixture indicating that the reaction had not proceeded to completion. This was completed at another time in 40% yield.[38]

[Notebook reference to ^{1}H NMR spectra: SVSII_49]



Synthesis of (3-methyloxetan-3-yl)methyl hex-5-ynoate (23)

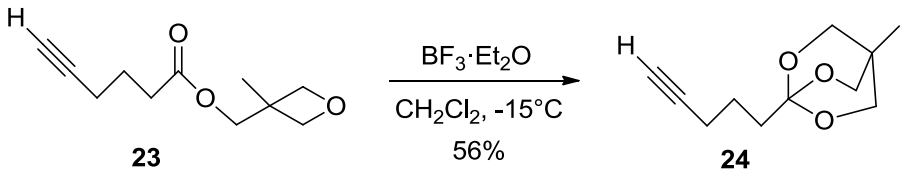
Into a 25 mL round bottom flask under nitrogen atmosphere containing EDCI (0.930 g, 4.85 mmol) and DMAP (0.198 g, 1.62 mmol) dissolved in CH_2Cl_2 (15 mL), 5-hexynoic acid (0.510 g, 4.04 mmol) was added. Subsequently 3-methyloxetan-3-yl methanol (0.372 g, 8.08 mmol) was added and the solution stirred for 4 hours at room temperature. Then the whole reaction mixture was poured unto a 1 cm thick silica gel layer and washed through with diethyl ether/petroleum ether (1:1) and finally concentrated affording the product as a colorless and clear liquid (0.609 g, 3.96 mmol, 97% yield).

[Notebook reference to ^{1}H and ^{13}C NMR spectra: SVSII_11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51-4.52 (d, *J* = 6.0 Hz, 2H, C**H₂**OC**H₂**), 4.37-4.39 (d, *J* = 6.0 Hz, 2H, C**H₂**OC**H₂**), 4.17 (s, 2H, C=OOC**H₂**C), 2.51 (t, *J* = 7.0 Hz, 2H, C=OC**H₂**CH_2), 2.26-2.30 (td, *J* = 2.7, 6.9 Hz, 2H, ≡CC**H₂**), 1.97 (t, *J* = 2.7 Hz, 1H, ≡C**H**), 1.87 (quin, *J* = 7.1 Hz, 2H, C=OCH_2C**H₂**), 1.33 (s, 3H, CC**H₃**) ppm.

^{13}C NMR ($CDCl_3$): δ 173.08 (**C**=O), 83.08 (≡**C**CH_2), 79.54 (2C, C**C**H_2O), 69.22 (≡**C**H), 68.64 (C=OO**C**H_2), 39.08 (C=OOCH_2**C**CH_3), 32.76 (C=O**C**H_2CH_2), 23.55 (C=OCH_2**C**H_2), 21.17 (≡C**C**H_2), 17.83 (**C**H_3) ppm.

IR (NaCl): 3289 (≡C-H), 2118 (C≡C), 1736 (C=O) 645 (≡C-H bend) cm^{-1}.



Synthesis of 4-methyl-1-(pent-4-yn-1-yl)-2,6,7-trioxabicyclo[2.2.2]octane (24)

(3-Methyloxetan-3-yl)methyl hex-5-ynoate **23** (0.777 g, 3.96 mmol) in dry CH_2Cl_2 (10 mL) was placed in a previously dried round bottom flask. The solution was then cooled down to -15°C with an acetone/ice bath. Finally $BF_3{\cdot}Et_2O$ (0.281 g, 1.98 mmol) was added and the mixture stirred for 7 hours at -15°C and then slowly allowed to reach room temperature. The reaction was quenched with triethylamine (0.35 mL) and stirred for 10 minutes until diethyl ether (20 mL) was added. This resulted in the formation of a BF_3/triethylamine complex which was then filtered away with gravity filtration and the resulting solution applied to a 1 cm long 5% triethylamine doped silica gel cake using CH_2Cl_2 as eluent which afforded oily crystal with the evaporation of the solvent. To further purify the product and remove all traces of triethylamine the crystals were applied to a neutral alumina chromatography using petroleum ether/ethyl acetate (7:3) as an eluent affording the product as a white crystal (0.433 g, 2.22 mmol, 56% yield).

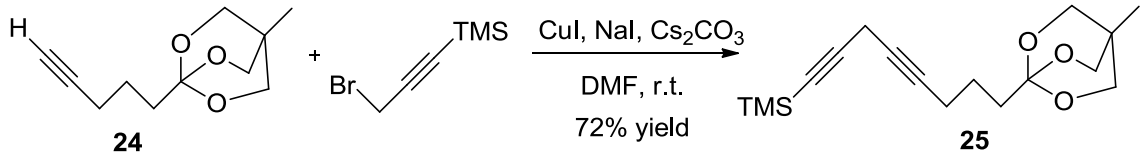
[Notebook reference to ^{1}H NMR spectra: SVSIII_93]

Melting point: 49.9 – 50.6 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 6H, $C(OC\mathbf{H_2})_3CCH_3$), 2.19-2.23 (td, *J* = 2.7, 7.0 Hz, 2H, $\equiv C\mathbf{H_2}$), 1.93 (t, *J* = 2.7 Hz, 1H, $\equiv C\mathbf{H}$), 1.76-1.81 (m, 2H, $C\mathbf{H_2}C(OCH_2)_3CCH_3$), 1.64-1.73 (m, 2H, $C\mathbf{H_2}CH_2(OCH_2)_3CCH_3$), 0.79 (s, 3H, $C(OCH_2)_3CC\mathbf{H_3}$) ppm.

^{13}C NMR ($CDCl_3$): δ 108.89 ($\mathbf{C}(OCH_2)_3$), 84.26 ($CH_2\mathbf{C}\equiv$), 72.57 ($C(O\mathbf{C}H_2)_3CCH_3$), 68.39 ($\equiv\mathbf{C}H$), 35.51 ($\mathbf{C}H_2C(OCH_2)_3$), 30.24 ($CH_2C(OCH_2)_3\mathbf{C}CH_3$), 22.42 ($\mathbf{C}H_2CH_2C(OCH_2)_3$), 18.20 ($\equiv C\mathbf{C}H_2$), 14.54 ($\mathbf{C}H_3$) ppm.

IR (NaCl): 3289 (≡C−H), 2934-2974 (C−H in CH_2), 2881 (C−H in CH_3), 2115 (C≡C) cm^{-1}.



Synthesis of trimethyl(8-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)octa-1,4-diyn-1-yl)silane (25)

Into a solution of CuI (0.175 g, 0.917 mmol) and NaI (0.341 g, 2.29 mmol) in dry DMF (4 mL), $CsCO_3$ (0.598 g, 1.83 mmol) was added. Into that suspension 4-methyl-1-(pent-4-yn-1-yl)-2,6,7-trioxabicyclo[2.2.2]octane **24** (0.170 g, 0.866 mmol) in DMF (2 mL) and 3-bromo-1-(trimethylsilyl)-1-propyne (0.228 g, 1.19 mmol) were added respectively and the resulting mixture was stirred for 48 h under nitrogen atmosphere at room temperature. The reaction was then quenched with water and extracted into Et_2O which resulted in a formation of a brown slurry. The water was slowly drained away and the brown slurry/ether layer was filtered through a short 1 cm celite layer using Et_2O as a solvent. The resulting ether solution was washed 3x with water/brine (1:1), 1x with brine, dried over $MgSO_4$, filtered and concentrated. This crude solution was applied to a basic alumina chromatography using petroleum ether/ethyl acetate (4:1) as an eluent which afforded the product as an orange liquid (0.190 g, 0.638 mmol, 72% yield).

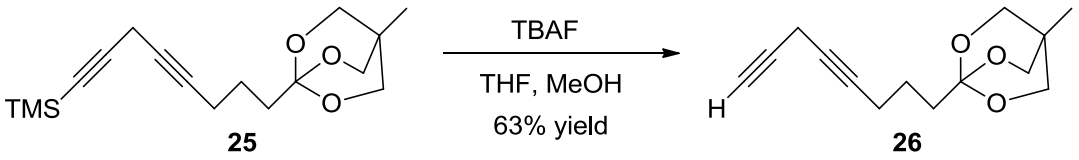
[Notebook reference to ^{1}H NMR spectra: SVSI_165]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 6H, $C(OC\mathbf{H_2})_3CCH_3$), 3.16 (t, *J* = 2.4 Hz, 2H, $\equiv CC\mathbf{H_2}C\equiv$), 2.16-2.21 (tt, *J* = 2.4, 6.9 Hz, 2H, $\equiv CC\mathbf{H_2}CH_2$), 1.73-1.78 (m, 2H, $C\mathbf{H_2}C(OCH_2)_3CCH_3$), 1.60-1.69 (m, 2H, $C\mathbf{H_2}CH_2C(OCH_2)_3CCH_3$), 0.79 (s, 3H, $C(OCH_2)_3CC\mathbf{H_3}$), 0.16 (s, 9H, TMS) ppm.

^{13}C NMR ($CDCl_3$): Pending.

IR (NaCl) 2932-2959 (C−H in CH_2), 2877 (C−H in CH_3), 2182 (C≡C) cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{25}H_{28}O_3$+Na 329.1549; found 329.1543 amu.



Synthesis of 4-methyl-1-(octa-4,7-diyn-1-yl)-2,6,7-trioxabicycl[2.2.2]octane (26)

trimethyl(8-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)octa-1,4-diyn-1-yl)silane **25** (0.074 g, 0.24 mmol) in dry THF (3 mL) and methanol (10 µL) was placed in a previously dried two necked round bottom flask under nitrogen. This flask and another round bottom flask containing tetra-*n*-butylammonium fluoride in THF (0.24 mL, 1M, 0.24 mmol) with added dry THF (2 mL) were cooled down to -78°C in a dry ice/acetone bath. When adequately cooled, the contents of the TBAF containing flask were transferred to the other flask very slowly with a cooled syringe. The solution was stirred for 4 hours under nitrogen at -78°C and then very slowly allowed to reach -25° over 4 hours. Then kept at -25°C over night until the reaction was concluded to be finished by monitoring on TLC. Then the still cold contents of the flask were applied straight to a neutral alumina chromatography, using cooled petroleum ether/ethyl acetate (1:1) as an eluent, affording the product as a yellowish liquid (0.035 g, 0.15 mmol, 63% yield, 4% allene).

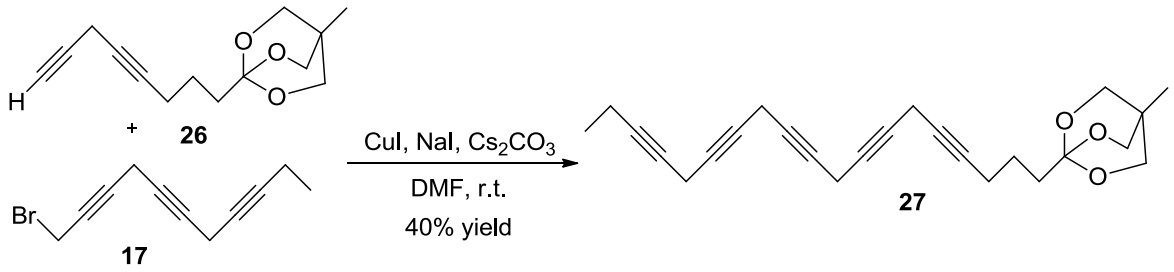
[Notebook reference to ^{1}H NMR spectra: SVSII_41]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 6H, $C(OC\mathbf{H_2})_3CCH_3$), 3.12-3.14 (q, *J* = 2.5 Hz, 2H, $\equiv CC\mathbf{H_2}C\equiv$), 2.17-2.22 (tt, *J* = 2.4, 6.9 Hz, 2H, $\equiv CC\mathbf{H_2}CH_2$), 2.04 (t, *J* = 2.7 Hz, 1H, $\equiv C\mathbf{H}$), 1.73-1.78 (m, 2H, $C\mathbf{H_2}C(OCH_2)_3CCH_3$), 1.61-1.70 (m, 2H, $C\mathbf{H_2}CH_2C(OCH_2)_3CCH_3$), 1.54 (s, H_2O) 0.79 (s, 3H, $C(OCH_2)_3CC\mathbf{H_3}$) ppm.

^{13}C NMR ($CDCl_3$): Pending.

IR (NaCl): Pending.

HRMS (ESI): Pending.



Synthesis of 4-methyl-1-(nonadeca-4,7,10,13,16-pentyn-1-yl)-2,6,7-trioxabicyclo [2.2.2]octane (27)

Into a solution of CuI (0.107 g, 0.56 mmol) and NaI (0.210 g, 1.41 mmol) in dry DMF (8 mL), $CsCO_3$ (0.368 g, 1.13 mmol) was added. Into that suspension 4-methyl-1-(octa-4,7-diyn-1-yl)-2,6,7-trioxabicycl[2.2.2]octane **26** (0.064 g, 0.27 mmol) in DMF (2 mL) and 1-bromoundeca-2,5,8-triyne **17** (0.112 g, 0.50 mmol) in DMF (2 mL) were added respectively and the resulting mixture was stirred for a few days under nitrogen atmosphere at room temperature and monitored by TLC. The reaction was quenched with water, extracted into Et_2O which resulted in a formation of a brown slurry. The water was slowly drained away and the brown slurry/ether layer was filtered through a short 1 cm celite layer using Et_2O as a solvent. The resulting ether solution was washed 2x with water/brine (1:1), 2x with brine, dried over $MgSO_4$, filtered and concentrated. This orange/brown crude product was applied to a neutral alumina chromatography using petroleum ether/ethyl acetate (7:3) as an eluent, which afforded the product as a yellow liquid (0.041 g, 0.108 mmol, 40% yield).

[Notebook reference to ^{1}H NMR spectra: SVSII_45]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 6H, $C(OC\mathbf{H_2})_3CCH_3$), 3.10-3.51 (m, 8H, $\equiv CC\mathbf{H_2}C\equiv$), 2.1-2.21 (m, 4H, $\equiv CC\mathbf{H_2}CH_2$, $\equiv CC\mathbf{H_2}CH_3$), 1.74-1.78 (m, 2H, $C\mathbf{H_2}C(OCH_2)_3CCH_3$), 1.62-1.68 (m, 2H, $C\mathbf{H_2}CH_2C(OCH_2)_3CCH_3$), 1.54 (bs, H_2O), 1.12 (t, J = Hz, 3H, $\equiv CCH_2C\mathbf{H_3}$), 0.79 (s, 3H, $C(OCH_2)_3CC\mathbf{H_3}$) ppm.

^{13}C NMR ($CDCl_3$): Pending.

IR (NaCl): Pending.

HRMS (ESI): *m/z* calculated for $C_{25}H_{28}O_3$+Na 399.1936; found 399.1931 amu.

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