Synthesis of Very Long Chain Fatty Acid Methyl Esters

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by

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CONTENTS

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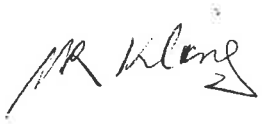
Marcel R. Kling

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.



M. R. Kling

ABSTRACT

Several methods for the total synthesis of very long chain fatty acids were investigated. The synthesis of methylene-interrupted polyalkynes by reiterative coupling of 1-heptyne with propargyl bromide under copper(I) catalysis was studied, with the aim of coupling the products with ω-haloacids. The first homologue of the reiterative coupling sequence, 1,4-decadiyne, was formed readily in a 53% isolated yield. The next homologue, 1,4,7-tridecatriyne, was formed in a 36% unisolated yield. Due to the unstable nature of these polyalkynes and the difficulties encountered in their isolation and purification, together with a literature report indicating greater difficulties in the purification of higher homologues, this approach was not taken further.

The synthesis of polyalkynes in the form of substituted propargyl bromides was also studied. Initial copper(I) catalyzed coupling of 1-heptyne with 1,4-dibromobutyne gave 1-bromo-2,5-undecadiyne in a 43% yield. Coupling of this diyne, under copper(I) catalysis, with propargyl alcohol, followed by treatment with phosphorous tribromide, gave 1-bromo-2,5,8-tridecatriyne. Similarly, 1-bromo-4,7,10-hexa-decatriyne and 1-bromo-3,6,9-pentadecatriyne were formed by the copper(I) catalyzed coupling of 1-bromo-2,5-undecadiyne with 4-pentyn-1-ol and 3-butyn-1-ol, respectively, followed by treatment with triphenylphosphine and carbon tetrabromide. These results indicated that substituted propargyl bromides were readily available from this route. The utility of 1-bromo-2,5-undecadiyne and 1-bromo-2,5,8-tridecatriyne as substrates in the copper(I) catalyzed reaction with 5-hexynoic acid or 1-(4-pentynyl)-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane was investigated. The yields of the coupled products were generally poor and the results inconsistent, therefore this method was found to be unsuitable for the synthesis of polyunsaturated very long chain fatty acids.

Cuprate methodology was shown to be effective in coupling alkyl and alkenyl bromides with ω-iodoesters to produce a range of very long chain fatty acid methyl esters. Grignard derivatives of alkyl and alkenyl bromides were reacted with methylcopper(I) (formed *in situ*), at low temperature, to form mixed dialkyl cuprate species, which were subsequently reacted with ω-iodoesters to produce a range of saturated, monounsaturated and polyunsaturated very long chain fatty acid methyl esters. A byproduct, due to competing methylation of the ω-iodoesters, was observed in all cases. Separation of the product esters from the methylated material was not achieved in some cases. To overcome this problem, alternative cuprate species were studied. Dialkyl cuprate species with two identical copper ligands were successfully employed to form pure samples of very long chain fatty acid methyl esters for the cases which could not be purified originally.

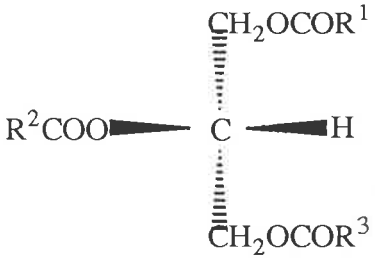
A study of the Wittig method as a means to form unsaturated very long chain fatty acid methyl esters was also undertaken. 1-Bromononane and 1-bromooctadecane were treated with triphenylphosphine in acetonitrile to produce the corresponding salts, 1-nonyl-triphenylphosphonium bromide and 1-octadecyltriphenyl-phosphonium bromide, respectively. These saturated phosphonium salts were coupled with ω-oxoesters under *cis*-Wittig conditions to produce a range of monoenoic very long chain fatty acid methyl esters with high *cis*-stereoselectivity, as shown by ^{13}C-NMR spectroscopy. In a similar fashion, 1-(*cis*-3-nonenyl)-triphenylphosphonium bromide, formed by treating commercial *cis*-3-nonen-1-ol with phosphorous tribromide followed by triphenylphosphine in acetonitrile, and 1-(*cis,cis,cis*-3,6,9-pentadecatrienyl)-triphenylphosphonium bromide, formed by reduction of 1-bromo-3,6,9-pentadecatriyne with dicyclohexylborane followed by treatment with triphenylphosphine in acetonitrile, were coupled to ω-oxoesters to produce polyunsaturated very long chain fatty acid methyl esters. In these cases, ^{13}C-NMR spectroscopic analysis indicated a significant amount of double bond isomerization.

The ω-oxoesters and ω-iodoesters used in this work were synthesized in a variety of ways, keeping the methods as general as possible. ω-Iodoesters were produced in good yield and in few steps from a range of different starting materials. ω-Hydroxyacids were treated with hydrobromic acid in acetic acid and the ω-bromoacids obtained were *trans*-halogenated with sodium iodide in acetone followed by esterification with acidic methanol to produce the required ω-iodoesters. Alternatively, ω-unsaturated acids and esters, obtained commercially or synthetically, were treated with hydrobromic acid in hexane under radical conditions, followed by *trans*-halogenation with sodium iodide in acetone and esterification of the acids with acidic methanol to provide another source of ω-iodoesters. In a different approach, 4-chlorobutyryl chloride was treated with methanol followed by *trans*-halogenation with sodium iodide in acetone to produce methyl 4-iodobutyrate.

ω-Oxoesters were formed in good yield by the ozonolysis of a number of ω-unsaturated esters.

INTRODUCTION

Interest in the area of fatty acids (FA) began as early as the beginning of the 1800s, due to the industrial uses of oils, fats and waxes, where the FA are present as triglycerides.



R^1, R^2, R^3 = alkyl

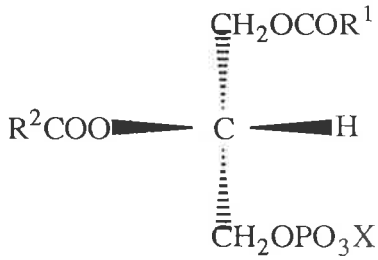
TRIGLYCERIDES

In the late 1800's, Lieben *et al.*[1,2] prepared all of the straight-chain saturated FA from acetic to heptanoic acid. A few years later, Krafft[3,4] prepared a series of FA, starting with stearic acid and, by systematic degradation, produced all of the homologous saturated acids down to nonanoic acid. Previous to these syntheses, individual acids had been prepared.[5,6]

Since the beginning of organic chemistry, FA have been one of the most intensely studied class of compounds, with hundreds of FA being identified over the years.[7] The continued interest in FA over more than a century, stems from the increasingly diverse role of FA in a vast range of biological systems. A lot is known about the metabolism of FA but still more remains unclear.

The different types of FA include straight-chain saturated and unsaturated acids, branched acids, acids with oxygen in the molecule (mostly 2-hydroxyacids) and acids containing the cyclopropane ring.[7] The work in this thesis only concerns the straight-chain acids and it is these acids only that will be discussed.

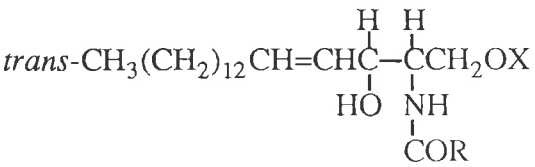
Almost all of the FA content of living organisms is lipid bound. Only a very small percentage of free FA exist in living cells. The function due to FA is either associated with lipid bound FA or to enzymatically released FA where the liberation of the free FA from the lipid is possibly the rate determining step.[8] The three major types of lipids associated with FA are the phospholipids, glycolipids and cholesterol esters, with the



X = Serine, Ethanolamine, Choline, Inositol

R^1, R^2 = alkyl

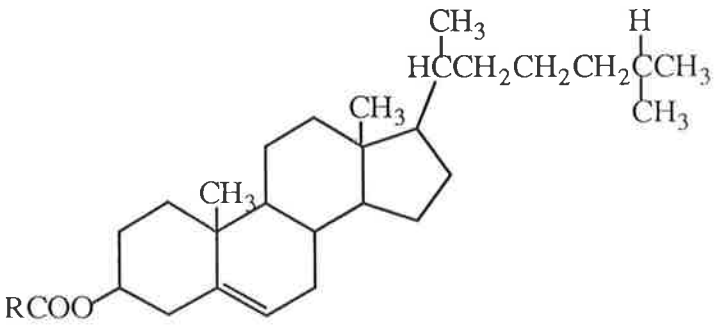
PHOSPHOLIPID



X = Sugar Unit

R = alkyl

GLYCOLIPID

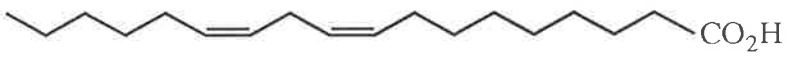


R = alkyl

CHOLESTEROL ESTER

phospholipids being by far the most abundant in all biological membranes.[9] Most of the FA incorporated in the lipids range in length from 14 – 24 carbons, typically of even numbers, with 16 and 18 carbon FA being the most common.[7] FA, as constituents of lipids, have a variety of biological roles : they serve as fuel molecules, as highly concentrated energy stores, and as components of membranes.[9]

FA were not thought to play any significant role in mammals until it was discovered in 1930 that certain FA were required in the diet to maintain animals in healthy condition.[10,11] These FA are termed the essential FA and are those that are required by, but can't be synthesized by, the organism. The most important of the mammalian essential FA are linoleic (**1**) and α-linolenic acid (**2**), which both occur in plants. A feature of these essential FA is a methylene-interrupted polyene system.



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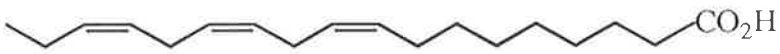

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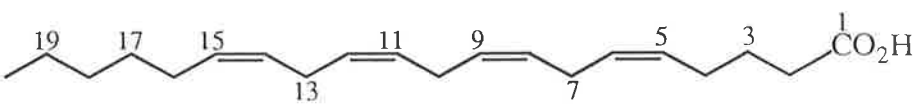
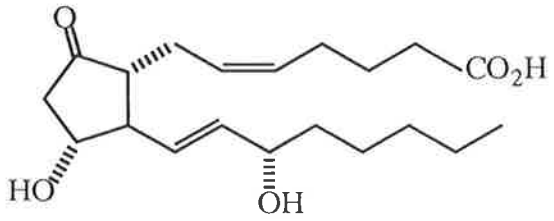
Some essential FA and in particular arachidonic acid (**3**) are precursors of many



3

different biologically active compounds, for example the prostaglandins such as PGE_2 (**4**), thromboxanes such as TXA_2 (**5**), prostacyclins such as PGI_2 (**6**) and leukotrienes

such as LTB_4 (7). These compounds have a range of biological functions, with prostaglandins having potent biological activity on almost all organs, which stimulated a lot of interest in this area.[5]



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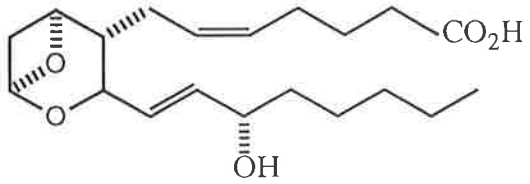

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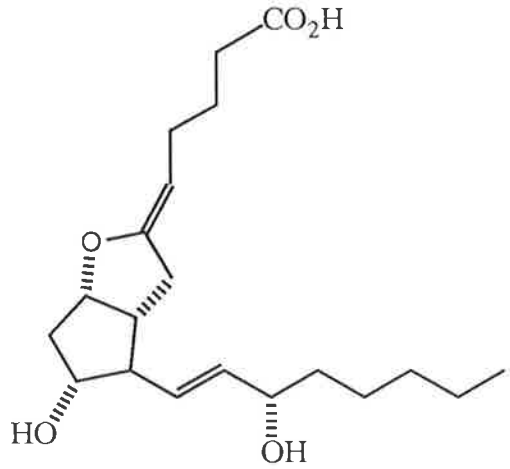

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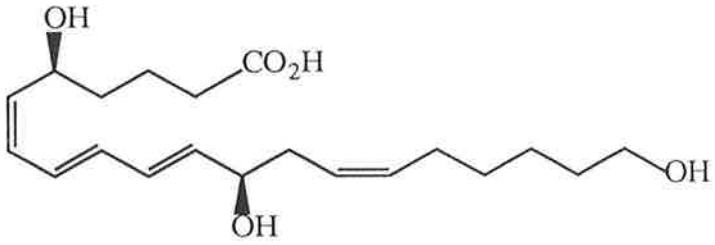

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The configuration about the double bonds of the unsaturated FA is nearly always *cis*. For most of the polyunsaturated FA, the double bonds are separated by a methylene group and are referred to as being methylene-interrupted. The unsaturated FA can be divided into different series of positional isomers. The position of the double bonds of fatty acids has been determined in a variety of ways. These include oxidative splitting,[12] using mass spectra of pyrrolidides[13,14] or picolinyl derivatives[15] and GLC-MS analysis of the dimethyl sulphide adducts to the double bonds of monoenoic FA.[16,17] The techniques of chemical ionization-MS[18] and the method of fast atom

bombardment (FAB) with MS / MS[19] have also been used. A recent method for the identification of the positional series of polyunsaturated FA has been worked out by Fellenberg *et al.*[20] The methyl esters of polyunsaturated FA are subjected to GLC-MS and the relative intensites of the peaks at m/z = 108, 150 and 192, due to cleavage in the terminal region of the molecule, determines the positional series of the FA as n–3, n–6 and n–9, respectively. The notation to indicate the positional series refers to the alkyl end of FA, as chain shortening or extension *in vivo* occurs at the carboxyl end, therefore varying the length of the carbon chain on this side of the unsaturation. Thus, arachidonic acid (**3**), which has four double bonds with the unsaturation starting at the sixth carbon in from the alkyl end, is denoted 20 : 4 (n–6). The number of carbons in arachidonic acid (**3**), 20, is followed by a figure denoting the number of double bonds. The notation in the parentheses indicates unsaturation beginning at the sixth carbon from the alkyl end. In the case of polyunsaturated FA, it is assumed that this notation refers to a methylene-interrupted polyene system. FA belong mainly to the n–3, n–6, n–7 and n–9 series, but other series are known.[7]

While the FA of the more usual chain-lengths (16 – 22 carbons) have been studied extensively over the years and therefore are the subject of many literature reports and reviews,[5,7,11] the same can not be said for FA of greater than 22 carbon-chain length. These FA are referred to as very long chain FA (VLCFA) and they are only mentioned briefly in the literature. The VLCFA occur in much smaller concentrations compared to the more common shorter chain FA[7] and, coupled with the crude analytical techniques of yesteryear, have mainly escaped detection until fairly recently. Advances in GLC at the end of the 1970s and the beginning of the 1980s, such as the routine use of capillary columns with programmed-temperature gradients, stationary phases stable at up to 350°C and the appearance of routinely applicable GLC-MS instruments, have seen an increase in the number of VLCFA reported.[7] The widespread use of HPLC has also contributed to the improved separation and detection of VLCFA.

VLCFA have been found in lower organisms, such as algae, soil microorganisms, bacteria, fungi and sponges, with carbon chain lengths of up to 36. For example, the marine protozoan *Emiliana huxley* was found to contain the unusual acids, 36 : 2 and 36 : 3, the nearest lower homologues having 14 fewer carbons.[21] GLC-MS was used to identify six VLCFA (24 : 1, 26 : 1, 28 : 2, 28 : 1, 30 : 2 and 30 : 1) contained by the fresh-water green alga *Botryococcus braunii*[22] and the amounts of the VLCFA reached 0.8 to 9.2% of the total acids. Soil extracts have been shown to contain acids of up to 30 carbons; peat was found to contain acids of 14 to 30 carbons.[23] A study of the FA content in yeasts and yeast-like organisms of the genera *Lipomyces, Saccharomyces* and *Rhodotorula*. *S. cerevisiae* showed, apart from the common 10 to 18 carbon FA, the presence of VLCFA of up to 34 carbons making up to 1 – 2% of all FA.[24] FA were also detected in certain parts of various fungi from genera *Alternaria, Botrytis* and *Neurospora*. They usually contained saturated even-numbered acids of up to 26 carbons, whereas VLCFA of up to 32 carbons were found in *Fomes igniarius*.[25] Sponges of many species have also been shown to contain VLCFA of 23 – 30 carbons and making up 1.5 – 91.0% of all FA.[26-28]

Investigations into the FA content of higher plants have also shown the widespread presence of VLCFA. The saturated acids 24 : 0, 28 : 0, 30 : 0 and 32 : 0 were detected in the needle waxes of pine and spruce trees.[29] Generally, waxes from higher plants contain mostly saturated VLCFA of up to 34 carbons. Murata *et al.*[30] have studied the tissues of 18 kinds of higher plants including potato, oat, wheat, maize and cucumber and found trace amounts of long-chain FA (saturated up to 26 carbons, monoenoic up to 24 carbons). The acids 23 : 0, 24 : 0, 26 : 0, 26 : 2 and 28 : 0 were identified in a condensate of marijuana smoke.[31] Plant-seed oils have, in general, been found to contain FA with a maximum chain-length of 22 carbons,[32] although in some cases monoenoic acids of up to 30 carbons of the n–9 series were found.[33,34]

Fish have also been studied and have been found to contain VLCFA. FA with a chain length of greater than 22 carbons have been detected in the Baltic herring.[35] The FA content of the fish was found to vary between May and September. In May the herring was found to contain FA of 24 to 32 carbons, whereas in September the FA were of only 24 to 28 carbons. Using GLC, trace amounts of the acids 24 : 1(n-12), 24 : 1(n-14), 24 : 1(n-16), 24 : 2(n-6), 24 : 3(n-3), 24 : 4(n-3) and 24 : 6(n-3) were isolated from a species of salmon.[36]

A closely studied animal, the laboratory rat, has been shown to contain saturated and monoenoic FA of up to 34 carbons in its wax secretion.[37] Monoenoic VLCFA of up to 34 carbon-chain length have also been isolated and identified from the surface of mouse skin.[38] Saturated and monoenoic VLCFA have been shown to be present in the meibomian glands, located in the lower and upper eyelid, of humans, rats, mice[39,40] and steer,[41] with chains of up to 32, 34, 29 and 27 carbons, respectively.

Recently a large group of polyunsaturated VLCFA have been discovered in the mammalian retina.[42,43] Phospholipids from bovine retina containing two polyunsaturated FA were isolated and transesterified to their methyl esters. Analysis of these FA by GLC showed that VLCFA of up to 36 carbons with 4 to 6 double bonds were present. GLC-MS and oxidative ozonolysis[43] indicated that the majority of these FA belonged to the n–3 series. The polyunsaturated VLCFA content of the retinae of the rabbit, rat, toad, and cod were also investigated. Cod retina was found to contain the highest amount of polyunsaturated VLCFA, with the content of 32 : 6(n-3) reaching 15% of the total FA of the phospholipid.

Polyunsaturated VLCFA have been isolated from rat testis.[44] Analysis of these FA confirmed that they were of the n–6 series with up to 30 carbons and containing 4 or 5 double bonds. VLCFA have also been isolated from spermatozoa obtained from the ram, bull, boar and human semen.[44] Identification by GLC-MS and determination of

the positional series by the method of Fellenberg *et al.*[20], as described previously, of these polyunsaturated VLCFA showed them to have chain-lengths of up to 34 carbons with 3 to 6 double bonds. The FA from the boar and human spermatozoa were mainly of the n-6 series, whereas the ram and bull spermatozoan FA were of the n-3 and n-6 series. A further study[45] found the predominant VLCFA of the lipids in ram spermatozoa were 28 : 4(n-3), 30 : 6(n-3), 32 : 6(n-3) and 34 : 6(n-3).

A very recent report[46] has confirmed the presence of polyunsaturated VLCFA in rat brain. These FA were shown to be predominantly of the n-3 and n-6 series, as shown by a GLC-MS technique,[20] with even-carbon chain lengths of up to 38 and containing four, five and six double bonds. Studies showed that the VLCFA composition of the lipid in rat brain varied with age.[46] The content of FA in a developing rabbit brain had also been studied[47] and the results showed that acids of up to 28 carbons were present, mainly saturated or monounsaturated. The relative proportion of VLCFA was found to rise with the increasing age of the animal. Pig brain has been shown to contain mono- and diunsaturated FA of chain lengths up to 26 carbons[48] while FA from bovine brain have been identified as being saturated or monoenoic with up to 32 carbons.[49]

Trace amounts of polyenoic VLCFA with up to 38 carbons and six double bonds have been detected in human brain.[50,51] These VLCFA were found to be predominantly of the n-6 series. In another study monoenoic FA of 16 to 28 carbons have been detected.[52] Of particular interest has been the discovery by the Poulos group of an increased concentration of polyenoic VLCFA of greater than 32 carbons in the brain of patients with peroxisomal disorders.[50,51] Many of these diseases have been known for some time[53,54] and are characterized by elevated serum metabolites such as VLCFA, but it is only recently that their molecular mechanisms are being disclosed.

The most studied peroxisomal disorder is Zellweger (cerebro-hepato-renal) syndrome, a rare inherited disorder where there is an absence of peroxisomes in the liver, kidney

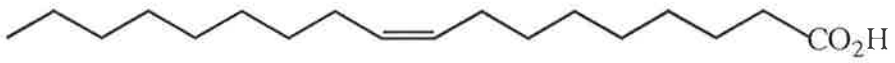
and brain of the patient.[53,54] Peroxisomes are sub-cellular organelles that are present in virtually all cell types. They contain a number of enzymes and have been found to be involved in fatty acid oxidation,[55] ether lipid synthesis[56] and bile acid synthesis.[57] Zellweger's Syndrome is a fatal disorder and diseased infants usually die within a year of birth. Characteristic clinical and pathological findings[53] include abnormal craniofacial features, severe hypotonia, epilectic seizures, ophthalmological abnormalities, hepatomegaly and severe psychomotor and sensorial retardation.

As mentioned previously, the concentration of FA containing more than 32 carbons in Zellweger brain is significantly higher than that of normal brain. The Zellweger brain VLCFA have up to 40 carbons with five or six double bonds, whereas the normal brain VLCFA have been shown to have four or five double bonds.[51] These intriguing differences indicate an abnormality in the chain elongation or degradation process of the FA or simply an increase in the biosynthesis of penta- and hexa-enoic acids.

Increased levels of polyenoic VLCFA have also been detected in the brain of patients with the peroxisomal disorders neonatal adrenoleukodystrophy (neonatal ALD) and infantile Refsum's disease (IRD).[58] In brains of patients of either of these diseases VLCFA of up to 40 carbons were detected containing up to six double bonds with the 36 carbon FA predominating and the pentaenoics being most abundant. In the case of the peroxisomal diseases X-linked ALD and adrenomyeloneuropathy (AMN) there was only a moderate increase of the polyenoic VLCFA but a noticeable increase in the 30 to 34 carbon monoenoic FA was observed.[58]

One particular peroxisomal disorder has received the attention of the media in recent years. The six-year-old son of an American couple was diagnosed as suffering from X-linked ALD. As little is known about the cause of peroxisomal diseases, there is no cure. The boy, Lorenzo, was given approximately two years to live. His parents were not willing to accept this and undertook their own research into the disease. A diet of

oleic acid (**8**) (18 : 1(n-9)) was reported to lower the high level of the saturated acid 26 : 0 in ALD patients, although the levels did not become normal. Lorenzo's parents found that addition of erucic acid (**9**) (22 : 1(n-9)) to the diet of their son, Lorenzo, brought the



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9

levels of the acid 26 : 0 to normal and seemed to halt further deterioration of his condition.[59] The media labelled erucic acid (**9**) as 'Lorenzo's oil'. Later reports on the VLCFA content of ALD brains have shown that monoenoic acids, not saturated acids, are in elevated concentrations.[58]

Thus, the occurrence of VLCFA has been found to be very widespread. They have been detected throughout the plant kingdom, the animal kingdom and in a wide variety of lower oganisms,[56] mostly bound in lipids. The quantitative proportions and qualitative compositions of FA in various organisms are characteristic for every species and genus and depend also on the environment.[56] The information to date indicates that VLCFA are almost omnipresent, the amount of VLCFA varying from the order of magnitude of 0.1% to as much as 10% of the total FA. With further development in the methods of detection and analysis, it is quite likely that VLCFA will be discovered in other sources. It is not known how or why these strange compounds are synthesized by the organisms but it seems clear that their formation is purposeful and vital for the life of the organisms. The peroxisomal diseases have also shown that abnormalities in the occurrence of VLCFA can be associated with devastating consequences. Although there is quite a lot of information on the qualitative and quantitative proportions of

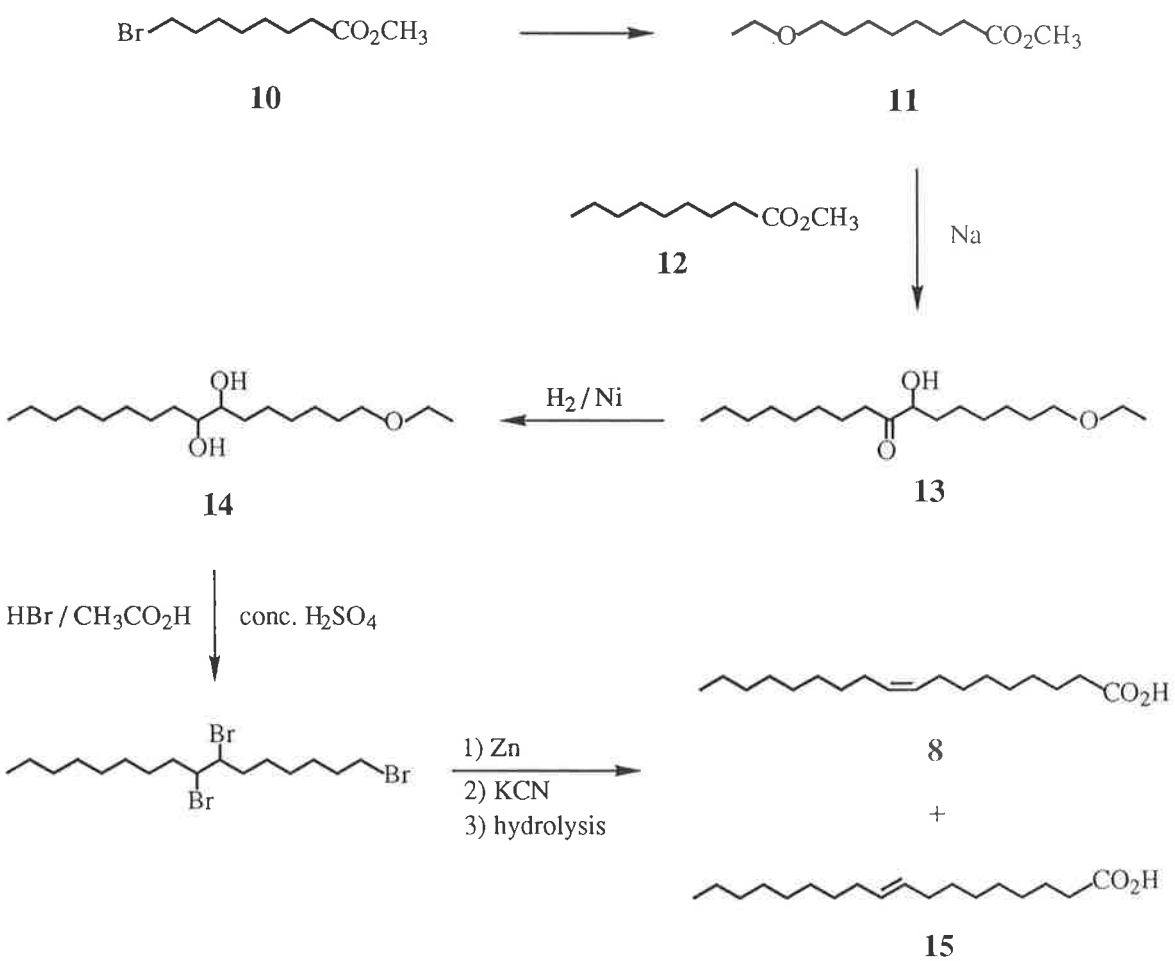
VLCFA in organisms, little is known about the biosynthesis of these FA and almost nothing about their function.

One way to elucidate the biosynthetic pathways of VLCFA and possibly shed light on their biological role is to study their metabolism *in vitro*. This is usually done by adding ^{14}C-labelled FA to appropriate cell cultures and, after an incubation period, analyzing the distribution of radioactivity in the products formed. To be able to make definite conclusions from any results obtained in this way, it is necessary to have a pure FA sample. While it is possible to isolate pure samples of some normal chain length FA, due to their larger concentrations in living organisms, this is not true for the VLCFA, particularly of greater than 30 carbons. VLCFA with 32 carbons or more exist in very low concentrations as a complex mixture of positional isomers with varying unsaturation and chain length. Even if it was possible to isolate one particular VLCFA, it would be difficult to obtain enough material for the metabolic studies.

Chemical synthesis of the VLCFA is one way to obtain a supply of pure samples with known structure. The work described in this thesis represents an investigation into the development of a general method for the synthesis of VLCFA as their methyl ester derivatives, as the ester derivatives of polyunsaturated FA are more stable.[151] In designing a synthesis of FA, the organic chemist is immediately confronted by problems relating to the stereochemistry of the double bonds in the unsaturated systems. The natural unsaturated FA possess a *cis* stereochemistry about the double bonds. *Cis* double bonds are less stable than the corresponding *trans* double bonds and isomerization of the former to the latter can occur under certain conditions. Polyunsaturated FA from a natural source also possess a methylene-interrupted polyene system. The protons on the carbon adjacent to two *cis*-double bonds are relatively acidic and strongly basic reaction conditions will result in reversible abstraction of one of these protons to produce the more stable conjugated system. Also, protonation-deprotonation of the double bond system under acidic conditions can lead

to isomerization or conjugation as well. The relatively greater stability of the conjugated double bond system is due to overlap of the π-orbitals and the resulting *trans*-stereochemistry generated. In addition, the methylene-interrupted polyene system is prone to oxidation in air, so care must be taken in the handling and storage of these compounds.

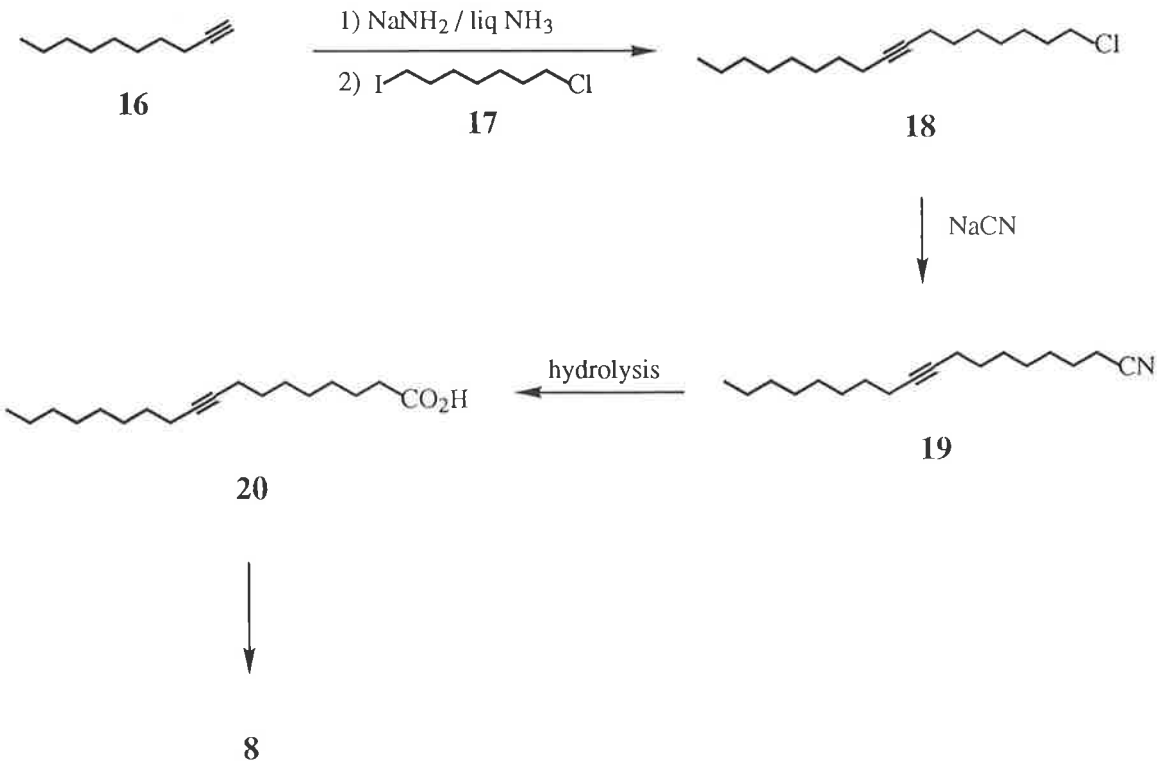
Since the early part of this century, many different syntheses of unsaturated FA have been reported. In 1943 and 1945 Baudart[60,61] reported the synthesis of oleic (*cis*-18 : 1(n-9)) (**8**) and elaidic (*trans*-18 : 1(n-9)) (**15**) acid (Scheme 1), as well as *cis*- and



SCHEME 1

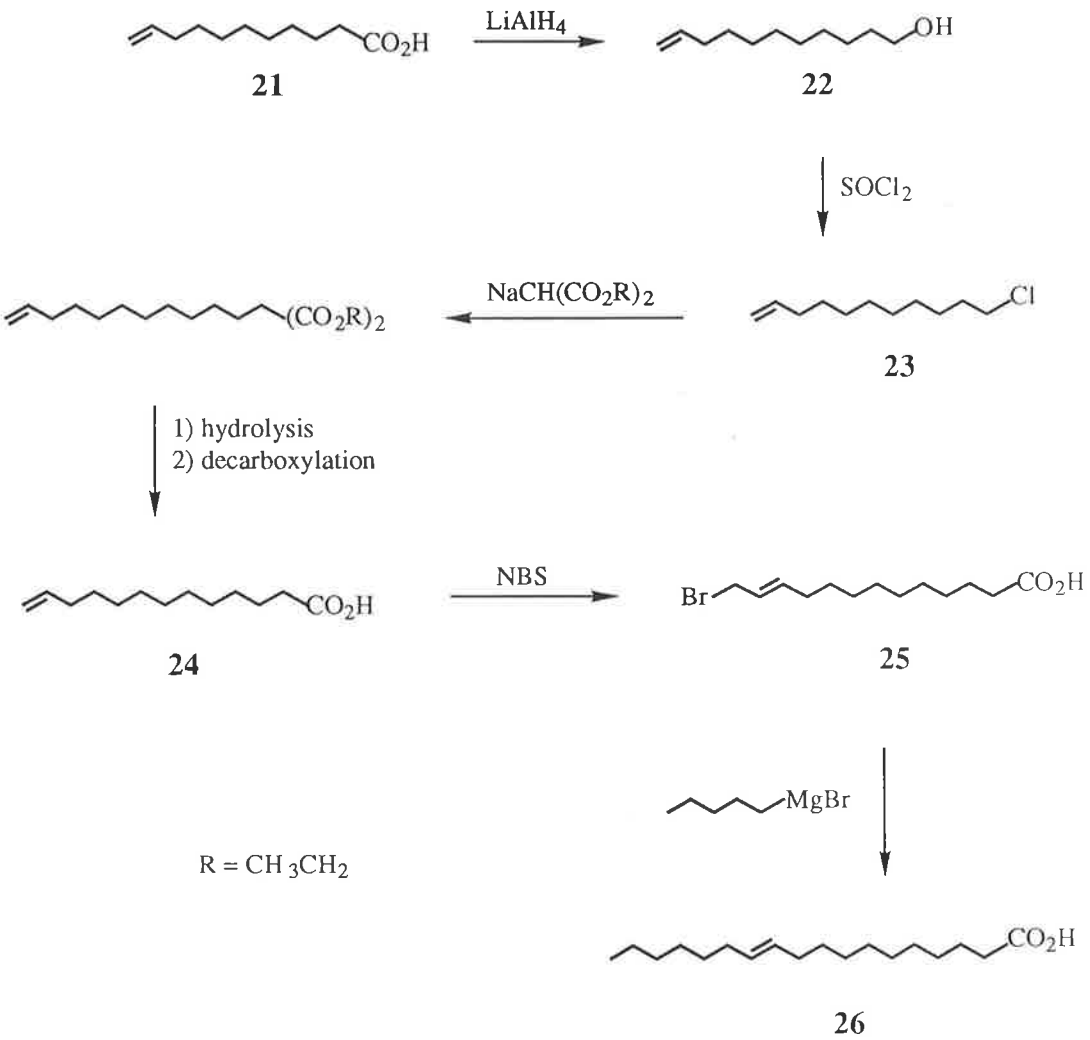
trans-5-undecenoic, 6-dodecenoic and 9-hexadecenoic acid using the acyloin synthesis. Ethyl 8-bromooctanoate (**10**) was converted to ethyl 8-ethoxyoctanoate (**11**) which was condensed with ethyl nonanoate (**12**) to obtain the acyloin product (**13**), which was reduced to the mixed isomeric 1-ethoxy-8,9-dihydroxyheptadecanes (**14**). The diastereomeric pairs of the α-glycols (**14**) were separated and the individual glycols converted to oleic (**8**)and elaidic (**15**) acid, as shown.

In a completely different way, Huber[62] synthesized all of the positional isomers of *cis*-octadecenoic acid from n–5 to n–10. For example, 1-decyne (**16**) was condensed with 1-chloro-7-iodoheptane (**17**) to give 1-chloro-8-heptadecyne (**18**), which was converted to the nitrile **19** and hydrolyzed to 9-octadecynoic acid (**20**). Partial reduction of the acetylenic acid gave oleic acid (**8**) which was separated from saturated material by fractional crystallization (Scheme 2).



SCHEME 2

A commonly used method of forming FA involves the malonic ester synthesis. In this way, Gensler *et al.*[63] formed *trans*-vaccenic acid (**26**), as shown in Scheme 3.

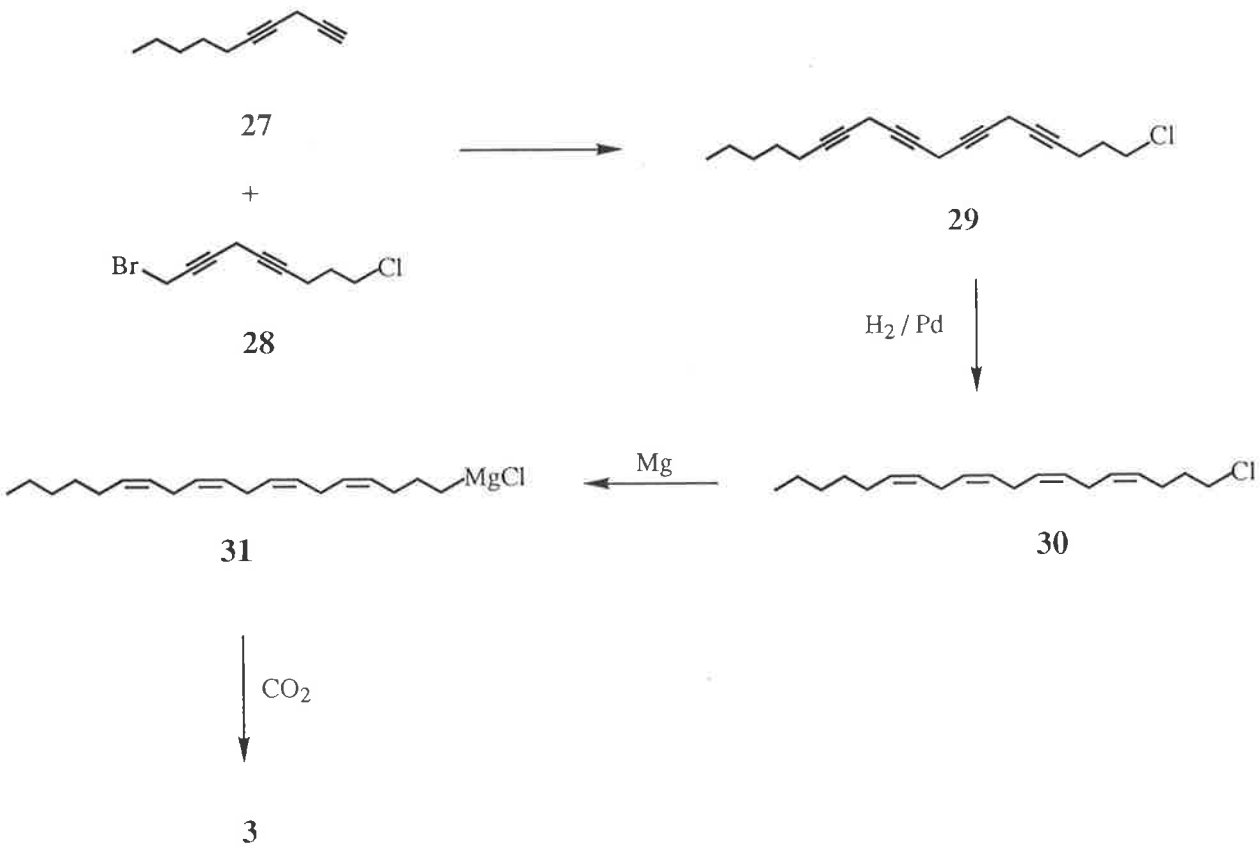


SCHEME 3

10-Undecenoic acid (**21**) was reduced to the corresponding alcohol **22** and converted to 1-chloro-10-undecene (**23**) by reaction with thionyl chloride. The chloroalkene was reacted in a malonic ester synthesis to give 12-tridecenoic acid (**24**) which was

brominated with *N*-bromosuccinimide (NBS) and the resultant bromide **25** condensed with pentylmagnesium bromide to give the desired acid **26**.

Rachlin and co-workers[64] reported a synthesis of arachidonic acid (**3**) in 1960 which involved the carbonation of the unsaturated Grignard derivative **31** (Scheme 4), a common method employed to introduce the carboxylic acid moiety. 1,4-Decadiyne (**27**) was coupled with 1-bromo-9-chloro-2,5-nonadiyne (**28**), both having being synthesized

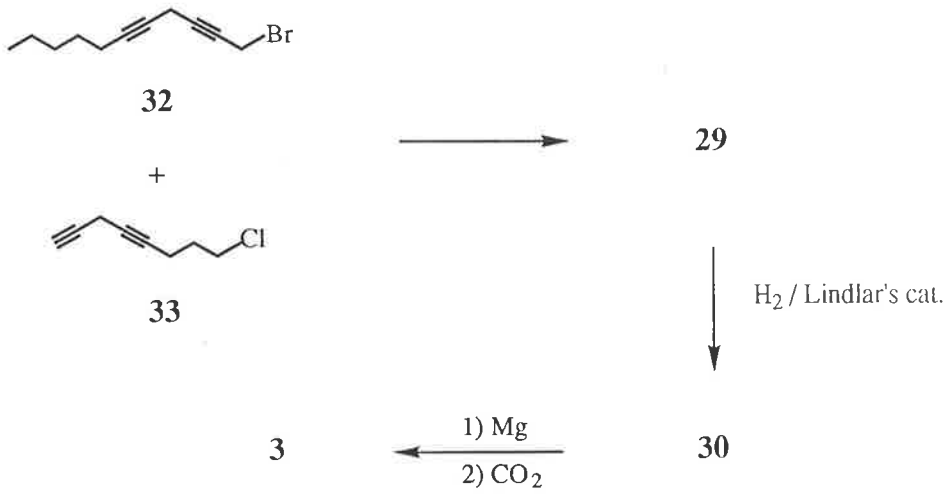


SCHEME 4

previously, to form 1-chloro-4,7,10,13-nonadecatetrayne (**29**). The tetraynyl chloride **29** was partially reduced with hydrogen over palladium to produce the corresponding

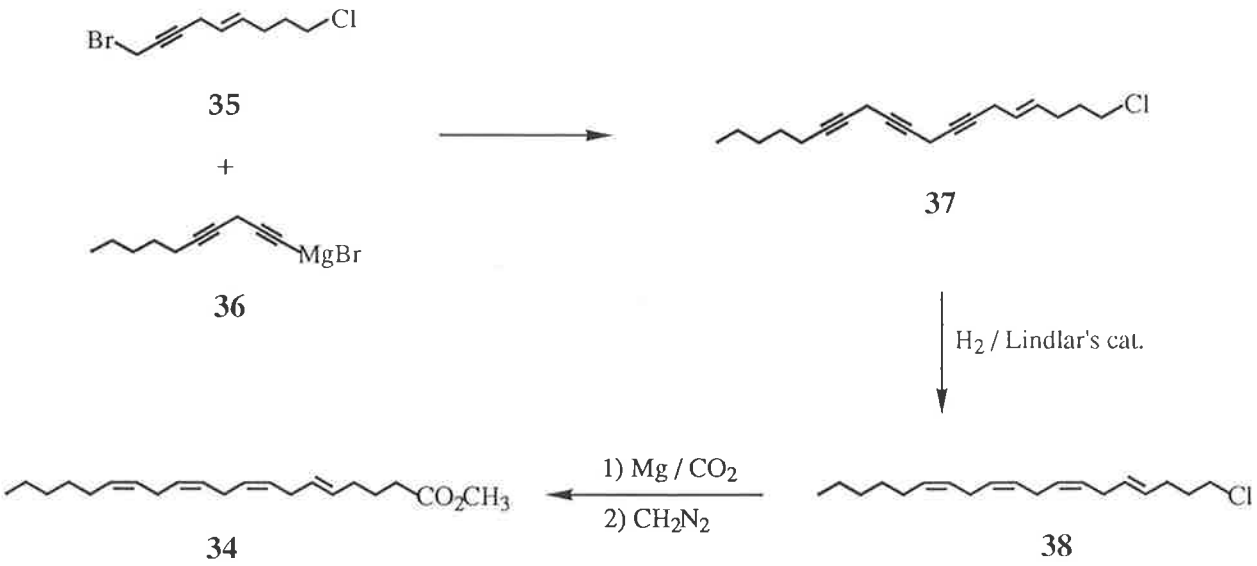
tetraenyl chloride **30**, which was treated with magnesium and carbon dioxide to give arachidonic acid (**3**).

In a similar way, Ege *et al.*[65] also formed arachidonic acid (**3**) (Scheme 5). 1-Bromo-2,5-undecadiyne (**32**) was coupled with 1-chloro-4,7-octadiyne (**33**) to form the coupled product 1-chloro-4,7,10,13-nonadecatetrayne (**29**). In this case partial reduction of the tetraynyl chloride **29** over a Lindlar's catalyst followed by metallation with magnesium and carbonation gave arachidonic acid (**3**).



SCHEME 5

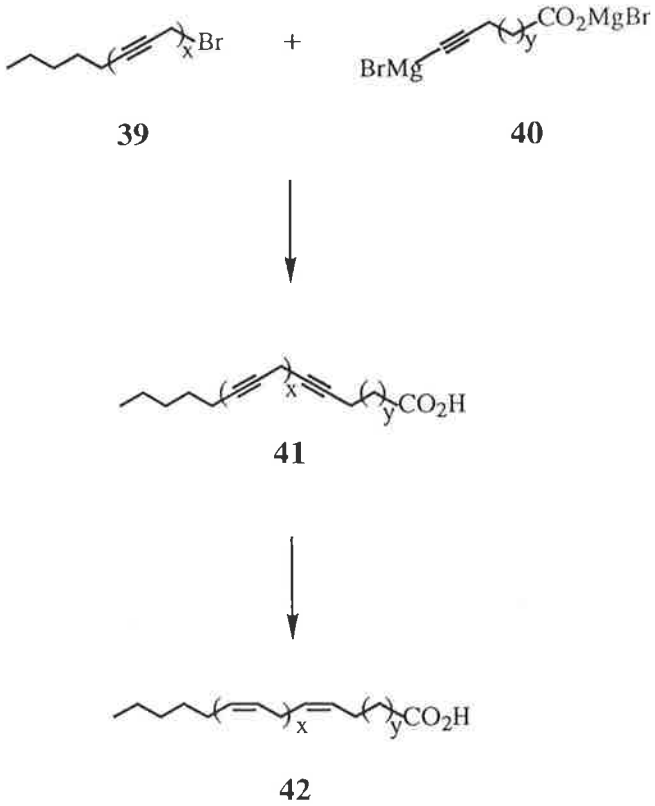
In another variation of this methodology, Egmond and co-workers[62.1] synthesized methyl *trans,cis,cis,cis*-5,8,11,14-eicosatetraenoate (**34**) (Scheme 6). *trans*-1-Bromo-9-chloro-non-5-en-2-yne (**35**) was coupled with the Grignard derivative of 1,4-decadiyne (**36**) to produce *trans*-1-chlorononadec-4-en-7,10,13-triyne (**37**), which was partially reduced over Lindlar's catalyst to the corresponding tetraenyl chloride (**38**). This latter compound was metallated with magnesium and then treated with carbon



SCHEME 6

dioxide followed by diazomethane to form the desired product. They used a very similar method to form methyl *cis,cis,cis,trans*-5,8,11,14-eicosatetraenoate and *trans,cis,cis,cis*-2,5,8,11,14-eicosa pentaenoic acid.

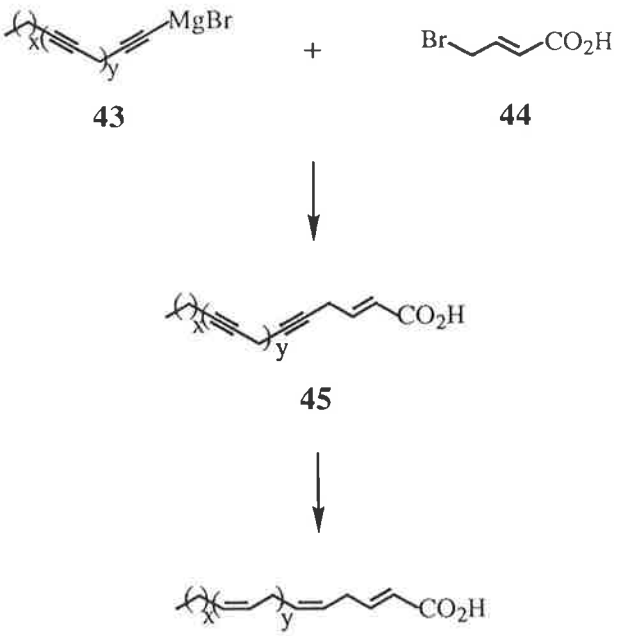
An alternative method of forming polyunsaturated FA that has seen a lot of application in the literature was developed by Osbond and co-workers[66,67] (Scheme 7). By coupling a range of substituted propargyl bromides **39** with the di-Grignard complexes of ω-acetylenic acids **40**, a number of polyalkynoic acids **41** were produced. Reduction of these polyalkynoic acids over Lindlar's catalyst gave the corresponding all *cis*-polyalkenoic acids **42**. In this way they synthesized linoleic acid (**1**), γ-linoleic acid (18 : 3(n–6)), arachidonic acid (**3**) and docosa-4,7,10,13,16-pentaenoic acid (22 : 5(n–6)).



SCHEME 7

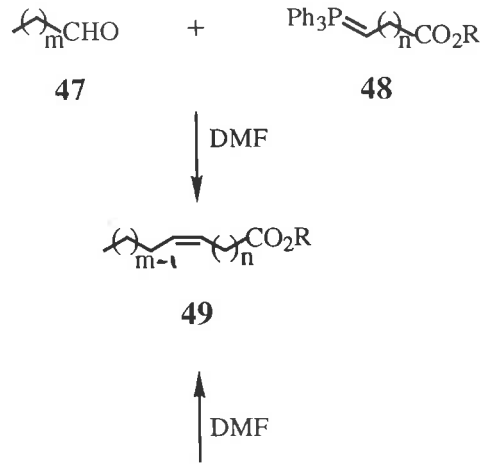
Heslinga and co-workers[68] coupled terminal acetylenes **43** with 4-bromocrotonic acid (**44**) (Scheme 8) to form *trans*-2-alkenynoic acids **45**. Terminal mono- or polyalkynes were converted to their Grignard salts and reacted with 4-bromocrotonic acid (**44**) to produce the desired acids (**45**) in good yield. These acids were then hydrogenated in the presence of Lindlar's catalyst to produce the corresponding polyenoic acids (**46**).

The Wittig reaction has also featured in syntheses of unsaturated FA. Bergelson and Shemyakin[69] used *cis*-Wittig conditions to form mono- and di-enoic FA using two approaches (Scheme 9). In one approach, ω-alkoxycarbonylalkylidenetriphenylphosphoranes **48** were coupled with aldehydes **47** in dimethylformamide (DMF) to produce monounsaturated FA esters **49**. Alternatively, alkylidenetriphenylphosphoranes **50** were coupled with ω-oxoesters **51** in DMF to form analogous mono-



x = 2, 5; y = 0
x = 4; y = 1, 2, 3

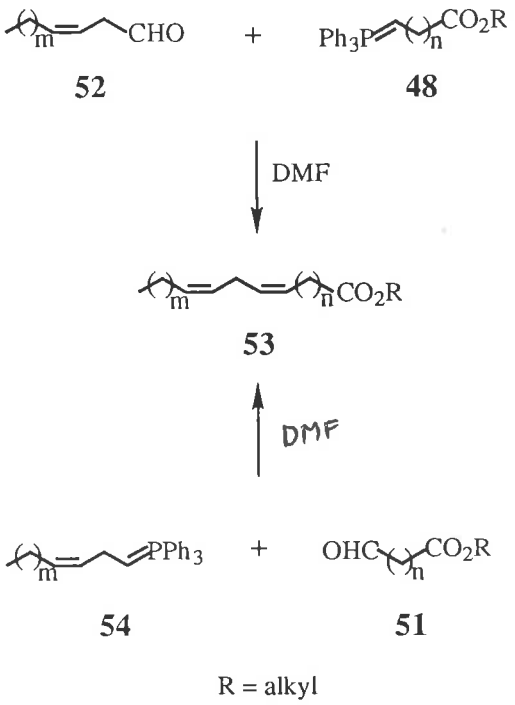
SCHEME 8



R = alkyl

SCHEME 9

unsaturated FA **49**. The authors extended this methodology to produce methylene-interrupted dienoic esters **53**, as outlined in Scheme 10. Again two methods were applied. In the first method, γ-alkenylidenetriphenyl-phosphoranes **54** were coupled with ω-oxoesters **51** in DMF and, in the second, ω-alkoxycarbonylalkylidene-triphenylphosphoranes **48** were coupled with β,γ-unsaturated aldehydes **52** in DMF, to

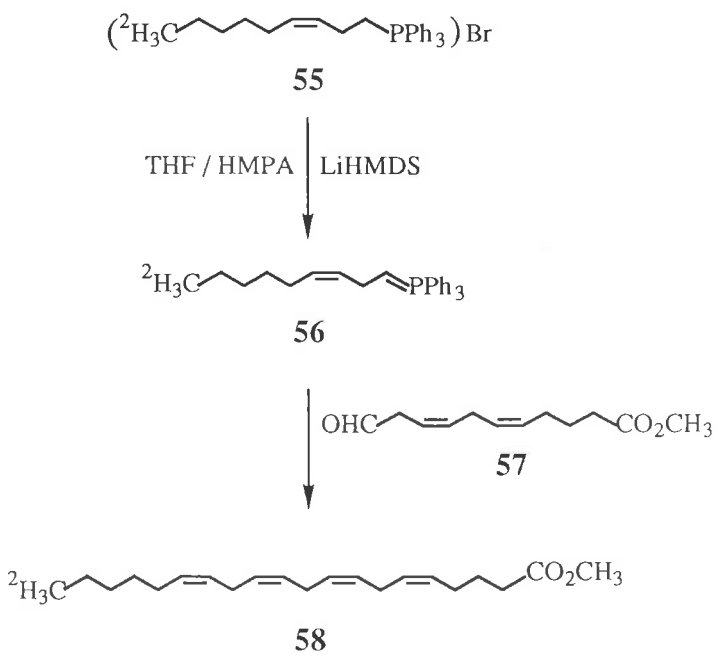


SCHEME 10

produce the diunsaturated esters **53**. In this way, Bergelson and Shemyakin[69] synthesized linoleic acid (**1**), although they reported the production of a large amount of conjugated material.

More recent applications of the Wittig reaction in the synthesis of unsaturated FA favour the use of lithium hexamethyldisilazide (LiHMDS) as the base to form the phosphoranes, in a solvent system of 20% HMPA in THF.[70,71,72] Prakash *et al.*[70] used

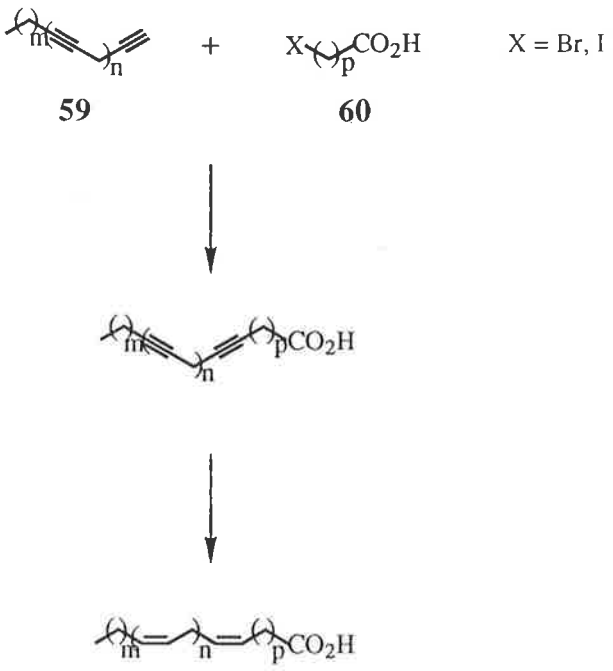
these conditions to synthesize 20-[$^2H_3$]-arachidonic acid in isomerically pure form (Scheme 11). The phosphorane **56**, generated from *cis*-9-[$^2H_3$](non-3-en-1-yl)-triphenylphosphonium bromide (**55**) and LiHMDS in THF / HMPA (4 : 1) was treated with methyl *cis,cis*-11-oxo-undeca-5,8-dienoate (**57**) to produce a good yield of the labelled product **58**.



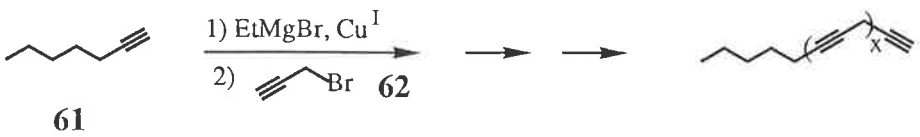
SCHEME 11

The initial investigations in the work described in this thesis concentrated on the formation of polyalkynoic acids which could be extended to the synthesis of VLCFA. An adaptation of the method of Heslinga *et al.*,[68] described above, was thought to be the most direct approach to synthesize polyenoic FA and likely to prove amenable to extension to longer chain analogues. Thus, as shown in Scheme 12, the coupling of methylene-interrupted terminal polyacetylenes **59** with ω-bromo- or ω-iodo-acids **60** was envisaged. Methylene-interrupted polyacetylenes **59** have been synthesized previously by a number of groups[64,68,73] who used a variety of conditions. Therefore, an initial study to find the optimal conditions for the reiterative coupling of 1-heptyne

(**61**) with propargyl bromide (**62**) was required (Scheme 13). 1-Heptyne (**61**) was chosen as the starting alkyne as this would lead to the formation of FA of the n–6 series, with the aim of forming arachidonic acid (**3**) as a trial. The spectral and physical properties of arachidonic acid (**3**) are well documented and therefore **3** was considered to be a good model.

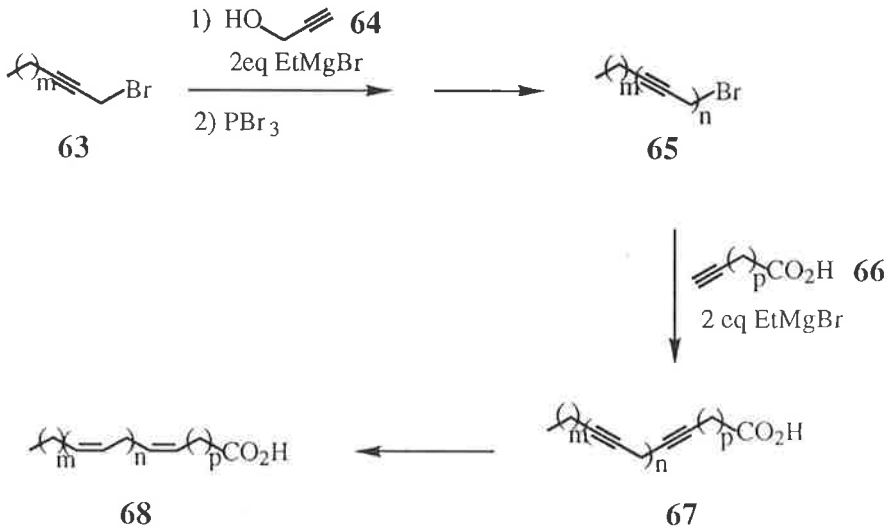


SCHEME 12



SCHEME 13

The method of Osbond *et al.*,[66,67] described above, where a substituted propargyl bromide is coupled with an ω-alkynoic acid, also lends itself to the possibility of extension by simply varying the length of the ω-alkynoic acid. A general synthesis of this type is outlined in Scheme 14. The substituted propargyl bromide **63** can be extended by reiterative coupling with propargyl alcohol (**64**) and conversion to the

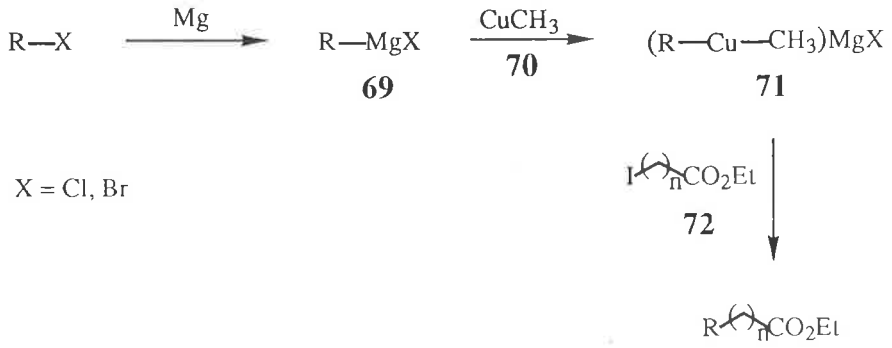


SCHEME 14

bromide **65**, as described by Osbond and co-workers.[67] The initial substituted propargyl bromide **63** can be generated by coupling a terminal alkyne with formaldehyde and converting the resultant alcohol to the bromide, in the way as Osbond *et al.*[67] have formed 1-bromooct-2-yne. The coupling of an ω-alkynoic acid **66** of desired length, *via* its di-Grignard complex, with the substituted propargyl bromide **65** containing the desired unsaturation, followed by partial hydrogenation of the polyalkynoic acid **67**, would form a general method of synthesizing VLCFA **68**.

The results of the investigations into the above two methods towards forming a general synthetic method for VLCFA are discussed in Chapter 1 of this thesis.

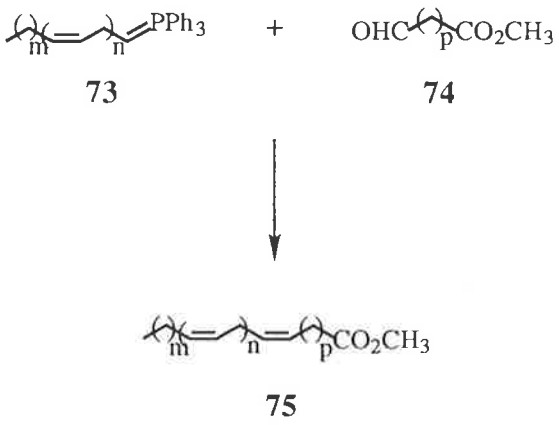
An alternative method of forming FA was thought to be possible by adapting the cuprate method of Bergbreiter and Whitesides.[74] The authors were able to couple a Grignard derivative with an ω-iodoester in high yield *via* a mixed dialkyl cuprate species. They found the procedure to be compatible with a number of functional groups and the cuprate species delivered one ligand selectively. The mixed dialkyl cuprate species **71** was generated by the addition of a Grignard species **69** to preformed methylcopper(I) **70** (Scheme 15). This complex **71** in turn reacted with an ω-iodoester **72** selectively by transfer of the alkyl group originating from the Grignard reagent **69**. The use of Grignard reagents derived from unsaturated halides in the cuprate coupling with ω-iodoesters would form the basis of a method to produce polyenoic FA esters. A



SCHEME 15

limited range of unsaturated alcohols, the reduced form of common unsaturated FA, are available commercially and can be converted by a number of reported procedures to the corresponding bromides. The bromides containing a less common structure would require synthesis. Literature reports[64,76,77] indicate that methylene-interrupted polyalkenyl halides undergo Grignard formation with minimal disruption to the all-*cis* polyene system. Therefore this methodology was deemed suitable for investigation towards the synthesis of VLCFA. The results of this investigation are discussed in Chapter 3.

The coupling of polyalkenyltriphenylphosphoranes **73** with long chain ω-oxoesters **74** *via* the Wittig method was thought to be an alternative feasible approach to forming VLCFA esters **75** (Scheme 16). *cis*-Olefination can be effected with high isomeric purity by conducting the Wittig reaction in a polar medium in the presence of bromide or iodide ions.[69,75] Prakash and co-workers[70] found a solvent system consisting of



SCHEME 16

THF : HMPA (4 : 1) and the base LiHMDS to be the best conditions for *cis*-selectivity in the Wittig reaction. The bromide anions are present upon the dehydrobromination of the phosphonium bromide. In the case of forming polyenoic esters **75**, unsaturated bromides are required where the unsaturation must begin at C3. These can be obtained by coupling the Grignard complex of 3-butyn-1-ol with a substituted propargyl bromide, followed by partial reduction of the polyalkynyl bromide. Finally, to produce a truly general synthesis of VLCFA by this method, the long chain ω-oxoesters **74** must be attainable. This can be achieved by the ozonolysis of long chain ω-unsaturated esters, which can be formed as described by Bergbreiter and Whitesides.[74] An initial investigation into the viability of the Wittig method to form unsaturated FA esters, with isomeric purity, and comparison with the cuprate method is discussed in this thesis in Chapter 4.

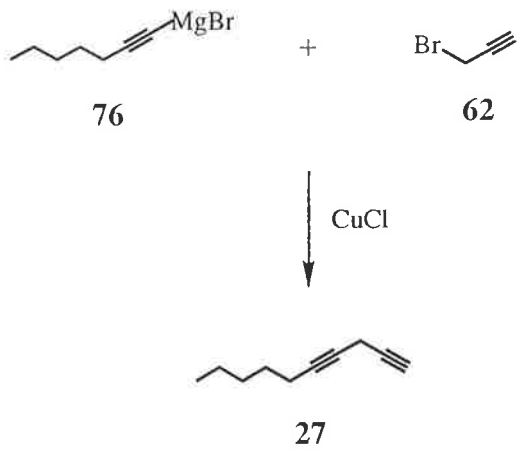
The general synthesis of ω-bromo- and ω-iodoacids and esters, from a variety of starting materials, is described in this thesis in Chapter 2. The synthesis of long-chain oxoesters, required in the synthesis of VLCFA *via* the Wittig method, are also described in Chapter 2.

RESULTS AND DISCUSSION

CHAPTER 1

Synthesis of Methylene-Interrupted Polyalkynes

The first approach to the synthesis of fatty acids involved the study of procedures for the preparation of methylene-interrupted polyalkynes. Initially the reiterative coupling of 1-heptyne (**61**) to propargyl bromide (**62**) was investigated, as a method for the synthesis of ω–6 fatty acids. 1,4-Decadiyne (**27**) had been synthesized previously by Rachlin *et al.*,[64] by coupling 1-heptynylmagnesium bromide (**76**) with propargyl bromide (**62**), using cuprous chloride as catalyst (Scheme 17). This procedure had been



76 **62** **27**

SCHEME 17

developed previously by Gensler and co-workers[73] in their synthesis of 1,4-nonadiyne, where 1-hexynylmagnesium bromide and propargyl bromide (**62**) were coupled under cuprous chloride catalysis. In both cases diethyl ether (ether) had been used as solvent. Ege *et al.*,[65] in their synthesis of methyl arachidonate, performed a cuprous chloride catalyzed coupling of 1-heptynyl-magnesium bromide (**76**) with propargyl bromide

(62) and found the best results were obtained at room temperature with tetrahydrofuran (THF) as solvent.

Preliminary experiments on the cuprous chloride catalyzed coupling of 1-heptynylmagnesium bromide (76) (formed by the addition of a standardized THF solution of ethylmagnesium bromide to 1-heptyne (61)) with propargyl bromide (62) provided results (Table 1) which were in general agreement with the findings of Ege *et al*..[65] The coupling procedure, when performed in refluxing ether with a long reaction time, gave a poor yield of the diyne **27** after isolation by distillation of the reaction mixture. Performing the coupling reaction in THF at 0°C for four hours gave yet a smaller yield of the product **27**, which was isolated in the same way. A low yield of **27** was also obtained when the reaction was performed in refluxing THF for one hour, although this latter procedure produced more allene, as shown by an absorbance at 1945 cm^{-1} in the infrared spectrum, and higher boiling byproducts, as shown by GLC analysis. The best results were obtained when the coupling reaction was performed in THF at room temperature for three hours to provide a 53% yield of the diyne **27**, after distillation.

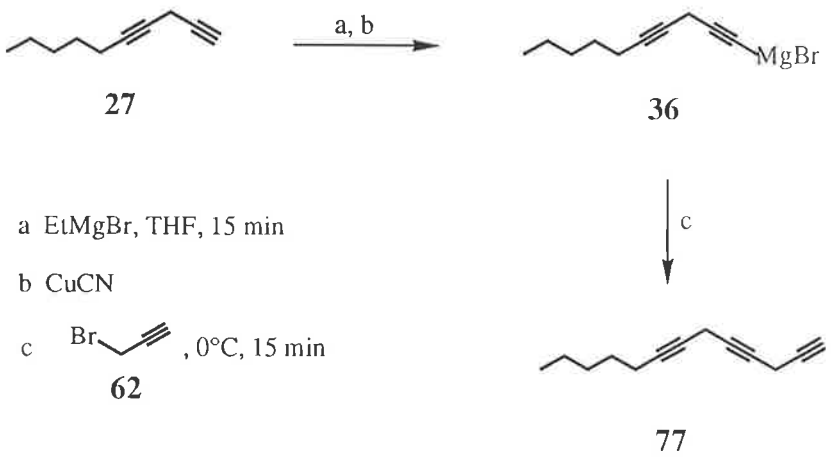
TABLE 1

Solvent	Time (h)	Temperature (°C)	Yield (%)
ether	110	35	27
THF	4	0	21
THF	3	room temp.	53
THF	1	66	20

The infrared spectrum of the diyne **27** contained a strong band for the acetylenic C–H stretch, at 3310 cm^{-1}, and weak bands at 2310, 2255 and 2150 cm^{-1}, corresponding to the C–C triple bond stretch. The ^{1}H-NMR spectrum included a triplet (*J* 2.5 Hz) at 1.88 ppm for the acetylenic proton, and a quartet (*J* 2.5 Hz) at 3.05 ppm and a triplet of

triplets (*J* 6.5, 2.5 Hz) at 2.13 ppm with equal integrations, representing the C3 and C6 protons, respectively.

The next homologue in the series of methylene-interrupted polyalkynes, formed by coupling the diyne **27** with propargyl bromide (**62**), is 1,4,7-tridecatriyne (**77**). This compound did not have much precedence in the literature. Ege *et al.*,[65] isolated the triyne **77** as a byproduct from their synthesis of the diyne **27** (although it was never isolated or identified under those circumstances in the present work) and Heslinga and co-workers[68] formed the triyne **77** in good yield using mild conditions and a short reaction time (Scheme 18). According to the latter procedure, the Grignard derivative of



SCHEME 18

the diyne **36** was treated with propargyl bromide (**62**) in THF with cuprous chloride catalysis, at 0°C for ninety minutes (Table 2). Under those conditions, the only material isolated after distillation of the reaction mixture was the starting diyne **27**. In a variation to the reaction procedure, cuprous cyanide was used instead of cuprous chloride, to give a 10% yield of a mixture of the triyne **77** and the diyne **27**, in the ratio *ca.* 7 : 3. The triyne **77** was identified by comparison with an authentic sample, obtained as described below.

Table 2

Catalyst	Time (h)	Temp (°C)	Yield*
CuCl	1.5	0	0
CuCN	1.5	0	12
CuCN	0.25	room temp	15
CuCl	5	room temp	25
CuCN	5	room temp	36
CuCl	2	50	14[a]
CuCN	2	50	20[a]
CuCN	17	room temp	18[b]

* % of reaction mixture, as shown by GLC

[a] increase in higher boiling products

[b] increase in byproducts

When the coupling of the diynylmagnesium bromide **36** with propargyl bromide (**62**) was repeated at room temperature for fifteen minutes under cuprous cyanide catalysis, a 12% yield of the triyne **77** was obtained after careful distillation of the reaction mixture. The infrared spectrum of the triyne **77** contained the expected strong band at 3310 cm^{-1}, for the acetylenic C–H absorption, and weak bands at 2295, 2220 and 2125 cm^{-1}, due to the C–C triple bond stretch. The ^{1}H-NMR spectrum included a triplet (*J* 2.5 Hz) at δ 1.92 ppm for the acetylenic proton, and a multiplet at δ 3.15 ppm and a triplet of triplets (*J* 7.0, 2.5 Hz) at δ 2.15 ppm, with integrations in the ratio 2 : 1, representing the C3 and C6, and C9 protons, respectively. GLC analysis showed one major component, contaminated with traces of other compounds with longer retention times.

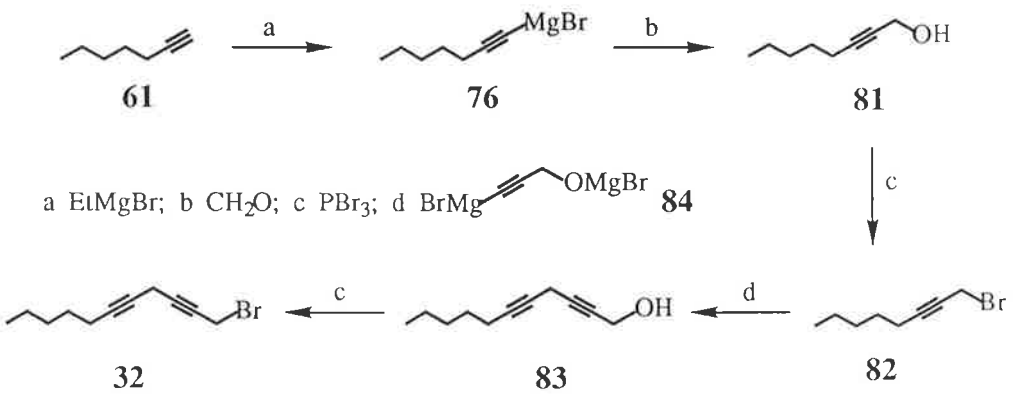
The reaction of **36** with **62** was investigated at room temperature with varying reaction times, and either cuprous chloride or cuprous cyanide as catalyst (Table 2). Although the reactions were often inconsistent, the optimum conditions involved cuprous cyanide, with a reaction time of five hours. These afforded a product mixture consisting of the diyne **27** and the triyne **77**, in the ratio *ca.* 1.6 : 1, and a trace of higher boiling byproducts. With shorter reaction times a greater proportion of the diyne **27** remained, while with longer reaction times, more byproducts were formed. Conducting the reaction at the higher temperature of 50°C gave more substantial quantities of byproducts, as indicated by GLC analysis.

The superior yields of the triyne **77** in reactions catalyzed with cuprous cyanide, as compared to cuprous chloride, are probably due to the greater solubility of the former in THF. On this basis the coupling reaction was investigated using the copper(I) catalyst, tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] (**78**),[78] which has been shown to catalyze the coupling of aryllithium reagents with allyl halides,[79] and is more soluble in THF than either cuprous cyanide or cuprous chloride.

The lithium derivative of the diyne **79** was formed from **27** in THF at –78°C, by the addition of a standardized ethereal solution of methyllithium. To this solution was added the copper(I) catalyst **78** followed by propargyl bromide (**62**). After a forty minute reaction time at –78°C, the reaction was quenched and analyzed by GLC This revealed only the unreacted diyne **27** and none of the product triyne **77**. When the reaction was repeated with the additions at 0°C and a reaction time of three hours at room temperature, the product mixture contained the diyne **27** and the triyne **77**, in the approximate ratio 4 : 1, with traces of byproducts. GLC analysis of the product mixture in this case was complicated by a broad trailing peak which was attributed to the decomposing catalyst.

Generally, the results of the above coupling reactions were highly variable. The methylene-interrupted alkynes **27** and **77** were difficult to obtain pure by distillation, which was compounded by their low yields and ~~instability~~ susceptibility towards oxidation in air. 1,4,7,10-Hexadecatetrayne (**80**) is the next homologue in the series of methylene-interrupted polyalkynes and important in the synthesis of our target VLCFA using this methodology. The difficulties experienced in the synthesis and purification of **27** and **77** would also be expected with **80**. On this basis and in view of a statement by Heslinga *et al.*,[68] that samples of **80** decomposed explosively during distillation, especially in the case of impure material, it was thought prudent to abandon this approach to the synthesis of methylene-interrupted polyalkynes.

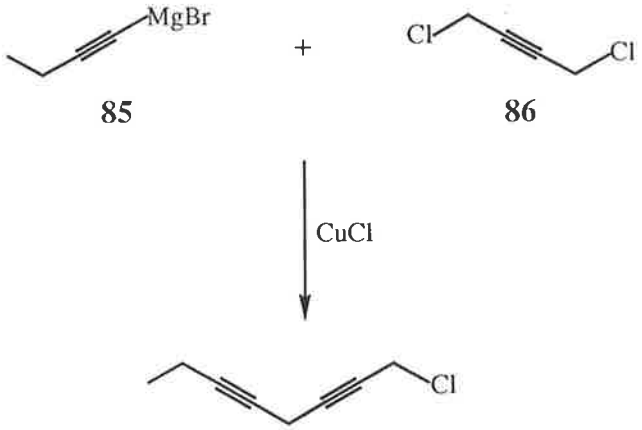
Another method of synthesizing VLCFA is by building up a methylene-interrupted polyalkyne system using the method of Osbond *et al.*,[66,67] where a substituted propargyl bromide is extended by coupling with propargyl alcohol (**64**), followed by conversion of the product to the corresponding bromide. Using this method, Osbond and co-workers[67] formed 1-bromo-2,5-undecadiyne (**32**), in a four step process (Scheme 19). Thus, the magnesium bromide derivative of 1-heptyne (**76**) was condensed with



SCHEME 19

formaldehyde to form 2-octyn-1-ol (**81**), which was converted to the corresponding bromide, 1-bromo-2-octyne (**82**). The bromide **82** was coupled with the di-Grignard complex of propargyl alcohol (**84**) to give 2,5-undecadiyn-1-ol (**83**), which was in turn converted to the corresponding bromide **32**.

In considering a shorter approach to this sequence, it was noted that Nigam and Weedon[80] had formed a low yield of 1-chloro-2,5-octadiyne (**87**), by coupling the magnesium bromide derivative of 1-butyne (**85**) with 1,4-dichloro-2-butyne (**86**), under cuprous chloride catalysis (Scheme 20). In a similar way, Pleshakov *et. al.*,[81] coupled



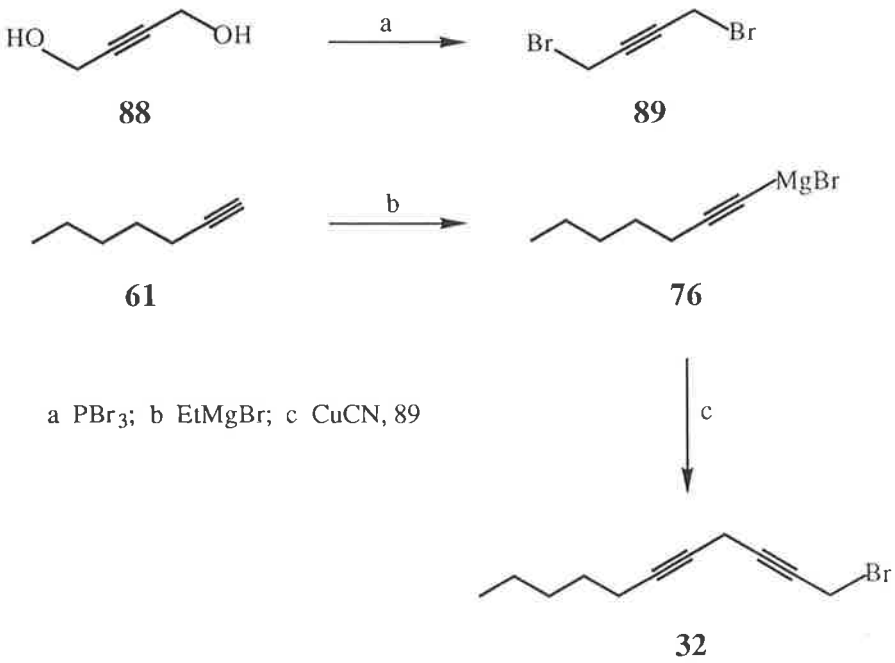
SCHEME 20

the magnesium bromide derivative of 1-heptyne (**76**) with the dichloride **86**, under cuprous chloride catalysis, to form 1-chloro-2,5-undecadiyne.[82] By analogy to these methods, the coupling of the Grignard reagent **76** with 1,4-dibromo-2-butyne (**89**) was envisaged as an alternative approach to **32**. The dibromide **89** was produced from the corresponding diol **88**, by treatment with phosphorous tribromide, according to the method of Johnson.[83] 1-Heptyne (**61**) was converted to its magnesium bromide derivative **76** by addition of a standardized THF

76

86

solution of ethylmagnesium bromide. The Grignard reagent **76** was then coupled to the dibromide **89** under cuprous cyanide catalysis, with stirring for twenty four hours at room temperature. Distillation of the crude product afforded the bromide **32** in 43% yield (Scheme 22). The infrared spectrum of the bromide **32** contained weak

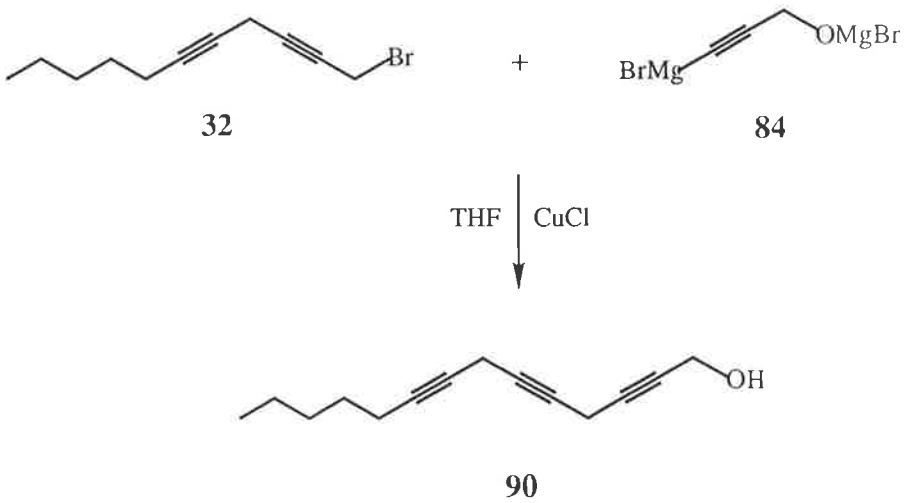


SCHEME 22

absorptions at 2260 and 2225-cm^{-1}, due to the C–C triple bond stretch, and a strong band at 614-cm^{-1}, due to the C–Br bond stretch. The characteristic signals observed in the ^{1}H-NMR spectrum were a triplet (*J* 2.5 Hz) at δ 3.92 ppm, due to the C1 protons, a pentet (*J* 2.5 Hz) at δ 3.22 ppm, due to the C4 protons, and a triplet of triplets (*J* 7.0, 2.5 Hz) at δ 2.15 ppm, due to the C7 protons.

The formation of the bromide **32** from 1-heptyne (**61**), in a one-pot process with a yield of 43%, compares well with the method undertaken by Osbond, Philpott and Wickens,[67] which gave **32** in an overall yield of approximately 30% *via* the four step process.

To examine the method of Osbond *et al.*[66,67] for the synthesis of homologous methylene-interrupted alkynes, the diynyl bromide **32** was coupled with the Grignard complex **84** (formed by the addition of propargyl alcohol (**64**) to two equivalents of ethylmagnesium bromide), in refluxing THF with cuprous chloride catalysis, and with a reaction time of thirty six hours (Scheme 23). A 49% yield of the product alcohol,

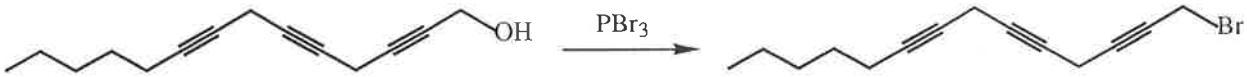


32 **84** **90**

SCHEME 23

tetradeca-2,5,8-triyn-1-ol (**90**), was obtained after purification by dry-column chromatography.[95] A strong broad absorption at 3610 – 3050 cm^{-1} for the O–H bond stretch and multiplet absorptions at 2230 – 2120 cm^{-1} for the C–C triple bond stretch were evident in the infrared spectrum of **90**. The ^{1}H-NMR spectrum contained a triplet (*J* 2.0 Hz) at δ 4.32 ppm and a multiplet at δ 3.20 ppm, due to the C1, and C4 and C7 protons, respectively, and an exchangeable singlet at δ 2.08 ppm.

Minor impurities were also evident in the ^{1}H-NMR spectrum of **90** but, since the material was found to be very unstable, no further purification was attempted. Instead the alcohol **90** was immediately converted to the corresponding bromide **91** by treatment with phosphorous tribromide in ether[67,85] (Scheme 24). The ~~crude~~ bromide

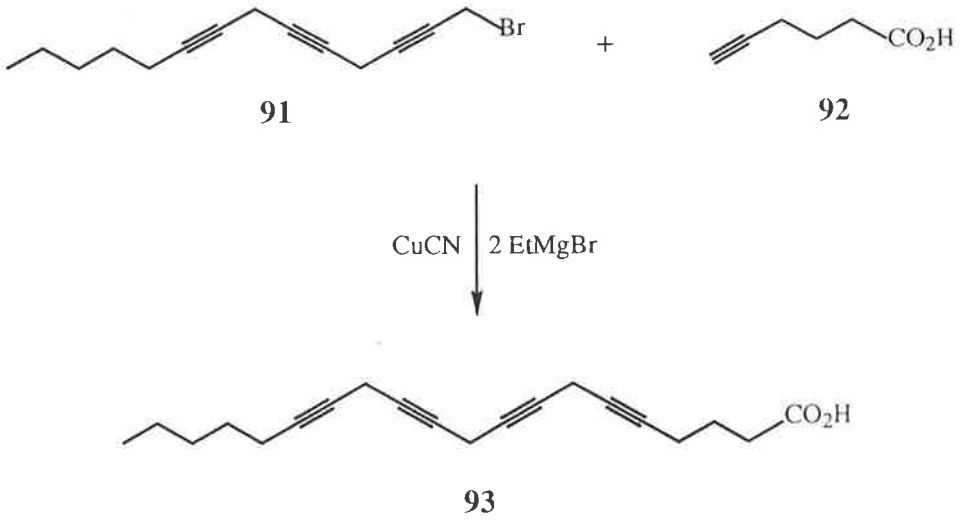


90 **91**

SCHEME 24

and obtained in
91 was purified by flash chromatography on silica ~~to give a~~ 28% yield. The ^{1}H-NMR spectrum of **91** contained a triplet (*J* 2.0 Hz) at δ 3.91 ppm and a multiplet at δ 3.13 ppm, integrating in a ratio of 1 : 2, due to the C1, and C4 and C7 protons, respectively.

One approach to the use of the diynyl bromide **32** and the triynyl bromide **91** in the synthesis of VLCFA involves their coupling with an ω-alkynoic acid.[67,85,76,87,88] An attractive feature of this approach is that an extra alkyne moiety is incorporated through the coupling procedure. As a model for the coupling of alkynyl bromides with ω-alkynoic acids, reaction of the triynyl bromide **91** with 5-hexynoic acid (**92**) was investigated (Scheme 25). Using this procedure, Osbond and co-workers[67] produced the tetraalkynoic acid **93**, which was subsequently reduced to give arachidonic acid (**3**).



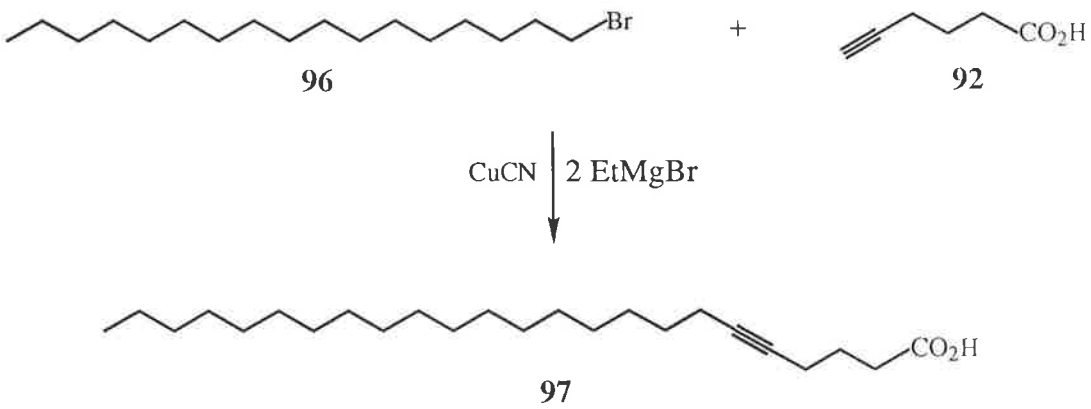
SCHEME 25

5-Hexynoic acid (**92**) was obtained in 90% yield by basic hydrolysis of 5-hexynenitrile (**94**).[88] Formation of the Grignard complex of the acetylenic acid (**95**) was achieved

by the addition of two equivalents of standardized ethylmagnesium bromide to **92** in THF. Adhering closely to the procedure specified by Osbond and co-workers,[67] it was found that the di-Grignard salt **95** became a solid mass upon formation, and extra THF was needed to form a workable slurry. To this was added the cuprous cyanide catalyst, followed by the bromide **91**. The work-up conditions of Osbond *et al.*[67] were applied to reveal an almost-solid brown mass. This material was heated with portions of hexane whilst mixing thoroughly, and when the portions were separated from insoluble material, combined and cooled, buff-coloured crystals of the tetraynoic acid **93** separated to give a 12% yield, with spectral and physical properties consistent with

those reported previously.[67,88] The ^{1}H-NMR spectrum of **93** contained a triplet of triplets (J 7.0, 2.5 Hz) at δ 2.15 ppm and another triplet of triplets (J 7.0, 2.5 Hz) at δ 2.26 ppm, due to the C16 and C4 protons, respectively, a triplet (J 7.5 Hz) at δ 2.49 ppm due to the C2 protons and a multiplet at δ 3.14 ppm due to the C7, C10 and C13 protons.

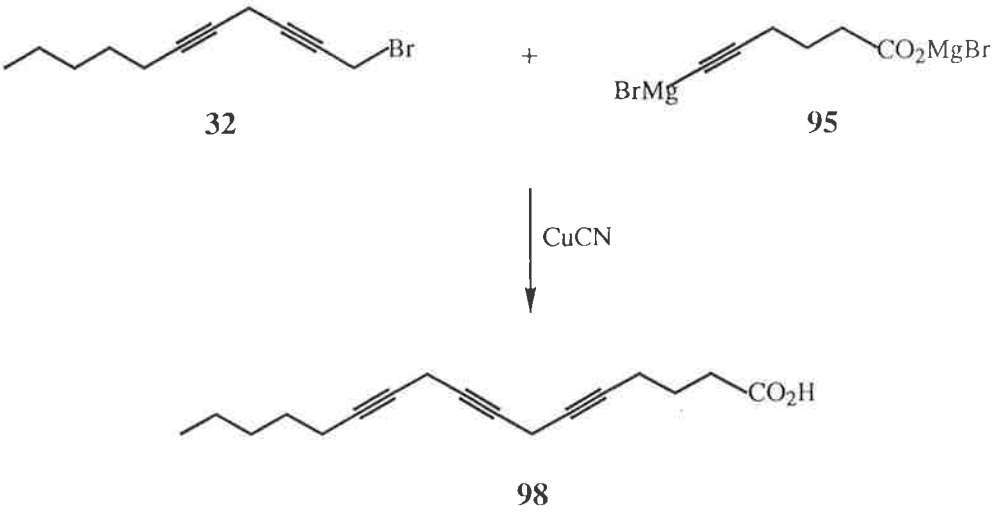
The low yield of the tetraynoic acid **93** limits the utility of this approach to the synthesis of VLCFA. In attempts to optimize the reaction conditions, in order to improve the yields, alternatives to the triynyl bromide **91** were studied, because **91** decomposes on storage and therefore needs to be synthesized each time immediately prior to use. When stearyl bromide (**96**) was used instead of **91** and the procedure was followed exactly as described above for the synthesis of **93**, none of the expected product acid **97** (Scheme 26) could be isolated and most of the stearyl bromide (**96**) was recovered. Repeating the procedure, but with longer reaction times and higher temperatures, failed to induce reaction.



SCHEME 26

The lack of reaction of **96** indicates that saturated bromides are unsuitable for coupling using this procedure. As a closer analogue of the triynyl bromide **91**, the diynyl bromide **32** was used in subsequent studies. Marcel and Holman[87] had previously

reported the coupling of the bromide **32** with **92**, and obtained good results using the method of Osbond, Philpott and Wickens.[67] Accordingly, the bromide **32** was treated with the Grignard complex **95** (Scheme 27). Again, dilution of the di-Grignard salt **95**



32 **95** **98**

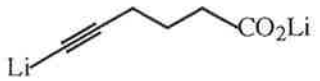
SCHEME 27

was necessary to obtain a workable slurry. Isolation of the product as described above for the synthesis of **93** gave only a 4% yield of the triynoic acid **98**, after recrystallization from hexane. The ^{1}H-NMR spectrum of **98** contained a multiplet signal at δ 3.19 ppm due to the C7 and C10 protons, and an exchangeable broad signal at δ 8.67 ppm representing the carboxylic acid proton. When the reaction was repeated in attempts to improve the yield, the procedure was found to be irreproducible, and often no trace of **98** was detected. Conducting the reaction for longer times and at higher temperatures did not improve the result.

The poor yields obtained in coupling the substituted propargylic bromides **32** and **91** with the di-Grignard derivative **95** were thought to be due to the low solubility of the latter species in THF. Egmond and co-workers[76] have also offered this explanation for the low yield obtained in their coupling of a propargylic bromide with **95** in THF. To overcome this problem, a polar aprotic solvent was required to solubilize **95**.

Accordingly, the Grignard complex **95** was formed in a solution of THF / HMPA (4 : 1), in which it was found to be totally soluble. The solution of **95** was stirred with the diynyl bromide **32**, in the presence of a catalytic amount of cuprous cyanide, overnight at room temperature. A standard work-up procedure was applied to the reaction mixture and the acidic and non-acidic components were separated by base extraction. Analysis of the acidic portion by ^{1}H-NMR spectroscopy indicated that none of the triynoic acid **98** had formed. There was no signal near δ 3.15 ppm, in the region expected for the C7 and C10 protons. The diynyl bromide **32** was recovered from the non-acidic portion.

Thus, the use of THF / HMPA achieved the solubilization of **95** but did not facilitate its reaction with **32**. As an alternative to the use of **95**, the reaction of the di-lithium derivative of 5-hexynoic acid **99**, was investigated. The salt **99** was generated in THF



99

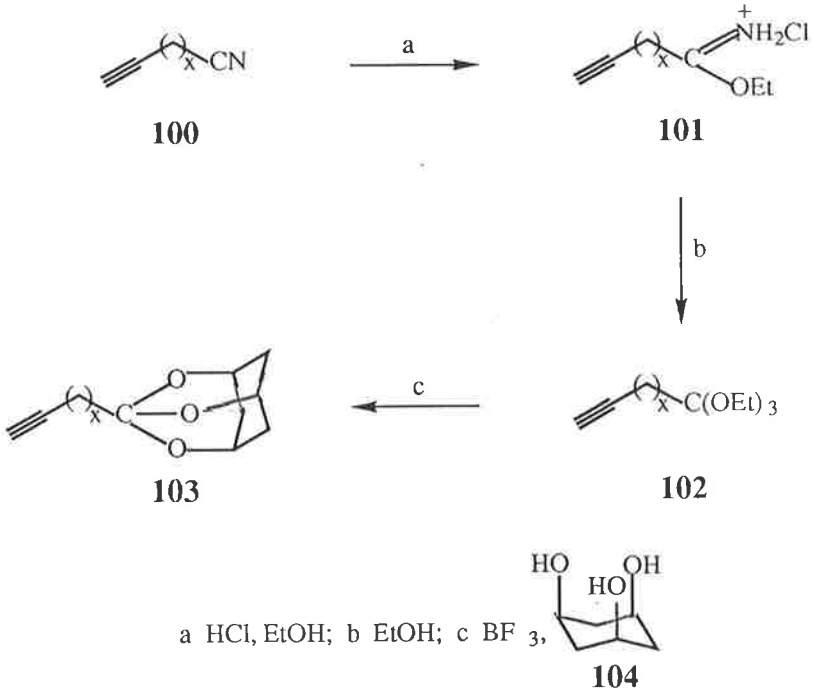
at –78°C by the addition of two equivalents of methyllithium to 5-hexynoic acid (**92**) and was completely soluble under these conditions. The solution of **99** was treated with the bromide **32** at room temperature for two hours and, after work-up, the acidic and non-acidic components were separated by base extraction. Analysis of the acidic portion by ^{1}H-NMR spectroscopy indicated that none of the triynoic acid **98** had formed, as there was no signal near δ 3.15 ppm. Only the hexynoic acid **92** was recovered from the acidic portion, while the diynyl bromide **32** was isolated from the non-acidic portion.

Initially the reaction of **99** with **32** was carried out in the absence of a copper(I) catalyst, as **99** was expected to be sufficiently nucleophilic for reaction to occur. When this was

shown not to be the case, the reaction was repeated with the inclusion of a catalytic amount of cuprous iodide. The ^{1}H-NMR spectrum of the acidic component obtained from this reaction contained a multiplet at δ 3.15 ppm, consistent for the C7 and C10 protons of the triynoic acid **98**. However, the relative integration of this peak indicated that **98** had formed in only a small amount, so isolation wasn't attempted.

The coupling of substituted propargylic bromides with lithium acetylides in THF had been shown[70] to be facilitated by the addition of HMPA. Therefore, the reaction of **99** with **32** was investigated in a solvent system consisting of THF / HMPA (4 : 1). The procedure described previously for the coupling of **99** with **32** was applied. The acidic component of the reaction mixture, obtained as previously described, was analyzed by ^{1}H-NMR spectroscopy. Formation of the triynoic acid **98** was evident by a multiplet at δ 3.15 ppm, due to the C7 and C10 protons, but again the relative integration of this peak indicated only a poor yield of **98** and inclusion of HMPA in the reaction had not significantly improved the result.

In view of the low yields obtained in the above coupling reactions with 5-hexynoic acid (**92**), the effect of protection of the carboxylic acid functionality as an orthoester was investigated. It was expected that this would simplify the reaction process, by eliminating any influence the carboxylate anion may have on unwanted side-reactions and increasing the solubilty of the reagent. There is some precedence in the literature for the coupling of ω-acetylenic orthoesters with substituted propargyl bromides. Osbond, Philpott and Wickens[67] experimented with the coupling of orthoester-protected ω-alkynoic acids with substituted propargyl bromides (Scheme 28). They converted the ω-cyanoalk-1-ynes **100** to the corresponding imidoyl ester hydrochlorides **101**, by treatment with hydrogen chloride in ethanol. The imidoyl ester hydrochlorides **101** were treated with more ethanol to form the acyclic triethyl orthoesters **102**, which were converted to the corresponding 2,8,9-trioxa-adamantanyl derivatives **103** *via*

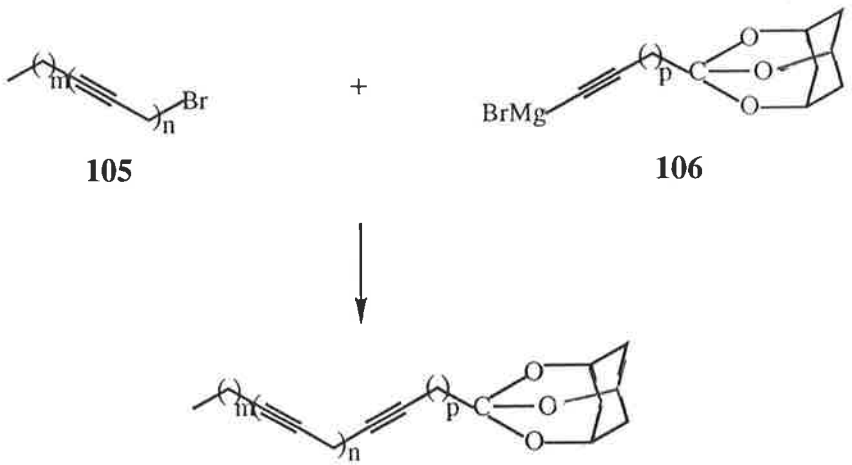


SCHEME 28

trans-esterification with *cis*-cyclohexane-1,3,5-triol (**104**) in the presence of boron trifluoride.

Osbond *et al.*,[67] formed the Grignard derivatives of the bridged orthoesters **106** and coupled them with the substituted propargyl bromides **105** which, upon hydrolysis, produced the corresponding acids **107**. (Scheme 29).

Just and Luthe,[89] as part of a synthesis of 12-hydroxyeicosatetraenoic acid, coupled the lithium salt of the orthoester, trimethyl ortho-5-hexynoate (**108**), with a propargylic iodide. They performed the reaction at –78°C in THF with cuprous iodide as catalyst. They formed the orthoester **108** by treating the appropriate nitrile **94** with hydrogen chloride and methanol in ether, which generated the imidoyl ester hydrochloride **109**.



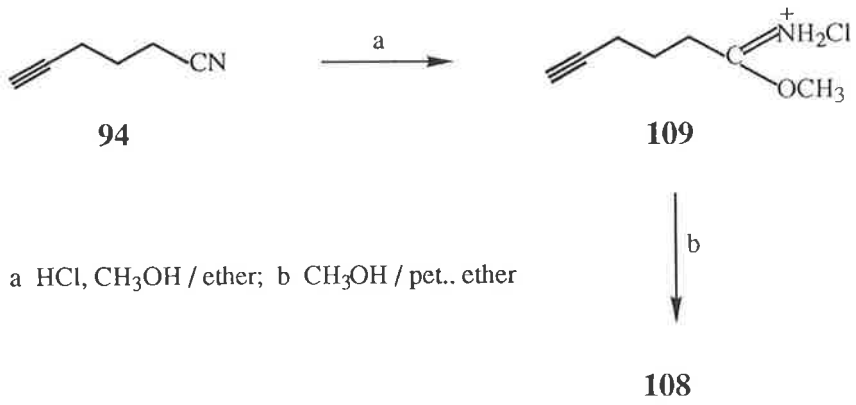
105 **106**

107

SCHEME 29

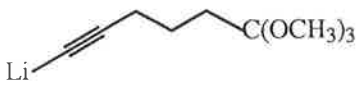
The crystalline salt **109** was then suspended in petroleum ether, and treated with methanol to form the orthoester **108** (Scheme 30).

108



SCHEME 30

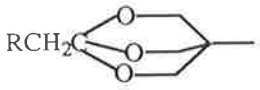
A similar methodology was used by Prakash *et al.*[70] in their synthesis of [$^2H_3$]-arachidonic acid. As part of their synthetic scheme, the lithium salt of the acetylenic orthoester **110** was coupled with a substituted propargylic bromide. They



110

prepared **108** by the method of Just and Luthe[89] and also applied the same coupling procedure, but obtained low yields in THF. However, by changing the solvent system from THF to THF : HMPA (5 : 1), they obtained a good yield of coupled product.

Bridged ortho esters are more stable to hydrolysis compared to the acyclic ortho esters and are less prone to nucleophilic attack.[93,94] Corey and Raju[91] have developed a novel method of forming bridged, bicyclic ortho esters of the 2,6,7-trioxabicyclo[2.2.2]octane series (**111**). The bridged ortho esters **111** were formed by esterification of the desired



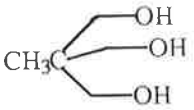
R = alkyl

111

carboxylic acid chloride with the oxetanyl alcohol **112**, followed by rearrangement of the resultant ester **113** with boron trifluoride. The facile procedure for the synthesis of bridged orthoesters and the relative attributes of cyclic versus acyclic orthoester functionality made this an attractive method for masking the carboxyl moiety in 5-hexynoic acid (**92**).

112

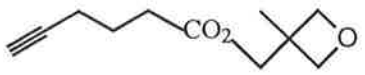
113



114

Thus, inexpensive, commercial 1,1,1-tris(hydroxymethyl)ethane (**114**) was converted to 3-methyl-3-hydroxymethyloxetane (**112**) in 54% yield by heating with ethyl carbonate and potassium hydroxide, followed by purification *via* distillation. The infrared spectrum of the oxetanyl alcohol **112** contained a strong broad band at 3700 – 3050 cm^{-1} due to the O–H stretch. The ^{1}H-NMR spectrum consisted of a singlet at δ 1.33 ppm due to the methyl group, a singlet at δ 3.67 ppm due to the hydroxy-substituted methylene group, an exchangeable broad singlet at δ 3.78 ppm, due to the hydroxy proton, and an AB ~~ab~~ quartet (*J* 6.0 Hz) at δ 4.90 ppm, produced by the protons of the ring methylene groups.

The alcohol **112** was treated with 5-hexynoyl chloride (generated in 86% yield by heating the acetylenic acid **92** with oxalyl chloride), to form the ester **115** in 80% yield,



115

after distillation. A strong absorption at 1736 cm^{-1}, due to the carbonyl stretch, a strong absorbance at 3292 cm^{-1}, due to the acetylenic C–H stretch, and an absorbance at 2116 cm^{-1}, due to the C–C triple bond stretch, were observed in the infrared spectrum of **115**. The ^{1}H-NMR spectrum contained a singlet at δ 4.14 ppm, due to the protons on the acyclic oxygen-substituted methylene group, and an ab quartet (*J* 6.0 Hz) at δ 4.33 ppm, due to the protons of the ring methylene groups.

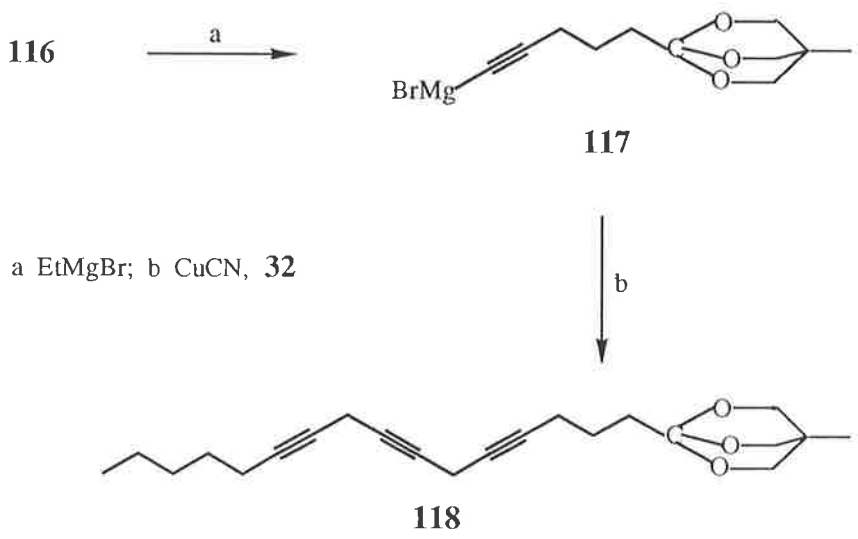
Treatment of the oxetanyl ester **115** with 0.25 equivalents of boron trifluoride etherate in dichloromethane caused rearrangement to the desired orthoester **116** (Scheme 31).

116

SCHEME 31

The isolated yield of **116** after dry-column flash chromatography[95] over triethylamine pretreated silica was 57%. The infrared spectrum of **116** contained a strong band at 3312 cm^{-1}, due to the acetylenic C–H stretch, and a weak band at 2125 cm^{-1}, due to the C–C triple bond stretch. The ^{1}H-NMR spectrum contained a singlet at δ 0.78 ppm, due to the bridgehead methyl group, and a singlet at δ 3.83 ppm due to the methylene groups in the orthoester moiety.

The first trials for coupling the orthoester protected acetylene **116** with the diynyl bromide **32**, as outlined in Scheme 32, were attempted using the Grignard derivative **117**. The salt **117**, formed by the addition of a standardized THF solution of ethylmagnesium bromide to the orthoester **116** at 0°C, was treated with the bromide **32**, in the presence of cuprous cyanide, at room temperature for twenty four hours. After a



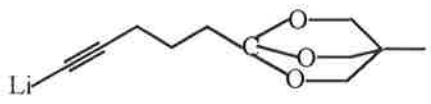
SCHEME 32

standard work-up procedure, the reaction was analyzed by TLC and ^{1}H-NMR spectroscopy, which showed that no **118** had formed. The only components present on the thin layer chromatogram of the crude reaction mixture were **32** and **116**, with a small amount of decomposition evident. The ^{1}H-NMR spectrum of the crude reaction mixture also indicated that **118** had not formed. The resonances at δ 3.90 and 3.15 ppm were of equal integration, as expected for the C1 and C4 protons of the bromide **32**, whereas **118** would be expected to show a signal near δ 3.10 ppm, due to the C7 and C10 protons, but no signal at δ 3.90 ppm.

When the coupling of the Grignard derivative **117** with the bromide **32** under cuprous cyanide catalysis was conducted in a solvent system of THF : HMPA (5 : 1) for twenty

four hours at room temperature, again no **118** was detected by TLC or ^{1}H-NMR analysis. Performing the coupling procedure at higher temperatures produced the same result.

Reactions of the bromide **32** with the lithium acetylide **119** were also studied. The method of Just and Luthe[89] was applied to **116** and the bromide **32**. The acetylenic orthoester **116** was deprotonated at −78°C with *n*-butyllithium, followed by the



119

addition of cuprous iodide. The bromide **32** was then added and the solution was allowed to stir at room temperature for two hours. Analysis of the crude mixture by TLC showed the presence of the orthoester **116** and a trace of the bromide **32**, but again no **118** was detected.

The reaction was modified by the addition of HMPA, as Prakash and co-workers[70] obtained improved results in this way in a similar system. Therefore, the lithium acetylide **119** was generated in a solution of THF : HMPA (5 : 1), and treated with the bromide **32** and cuprous iodide. After a reaction time of twenty four hours at room temperature, the crude product was analyzed by TLC and ^{1}H-NMR spectroscopy. The thin layer chromatogram contained **116**, a trace of the bromide **32**, and a new component, migrating closely to **116**. ^{1}H-NMR analysis of the crude reaction mixture again showed only weak signals at δ 3.88 and 3.14 ppm, due to the protons at C1 and C4 of the bromide **32**, respectively, but a new multiplet signal was evident at δ 3.05 ppm, presumably due to the protons at C7 and C10 of the product **118**. This ^{1}H-NMR spectral evidence indicated that the product orthoester **118** had formed, but

integration of the spectrum suggested the yield was fairly low. For this reason, no attempt was made to isolate the product.

The results discussed in this Chapter have shown that bromides such as **32** and **91** can be synthesized fairly easily, in relatively few steps. However, their coupling with the hexynoic acid **92** or its orthoester derivative **116**, were fairly unsuccessful. On this basis the method was considered unsuitable for the synthesis of VLCFA.

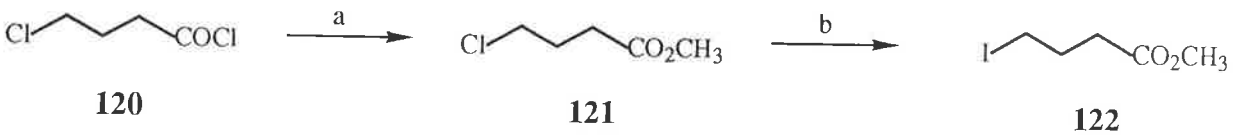
RESULTS AND DISCUSSION

CHAPTER 2

Synthesis of ω-Iodoesters and ω-Oxoesters

Due to the lack of success in the coupling of ω-alkynoic acids with substituted propargylic bromides, alternative methods for the synthesis of VLCFAs were required. The methods studied in the work described in the remainder of this thesis involved the coupling of polyalkenyl halides, *via* cuprate species, with ω-iodoesters, and the coupling of polyalkenyl halides, *via* alkylphosphonium species, with ω-oxoesters. In this Chapter, the synthesis of a range of ω-iodoesters and ω-oxoesters, used in those studies, is discussed.

One method of forming ω-iodoesters is by *trans*-halogenation of ω-chloride or ω-bromide precursors with sodium iodide. In this way, methyl 4-iodobutyrate (**122**) was prepared from readily available 4-chlorobutyryl chloride (**120**) in two steps, as shown in Scheme 33. The acid chloride **120** was esterified with methanol. After



120 **121** **122**

a CH_3OH; b NaI, acetone

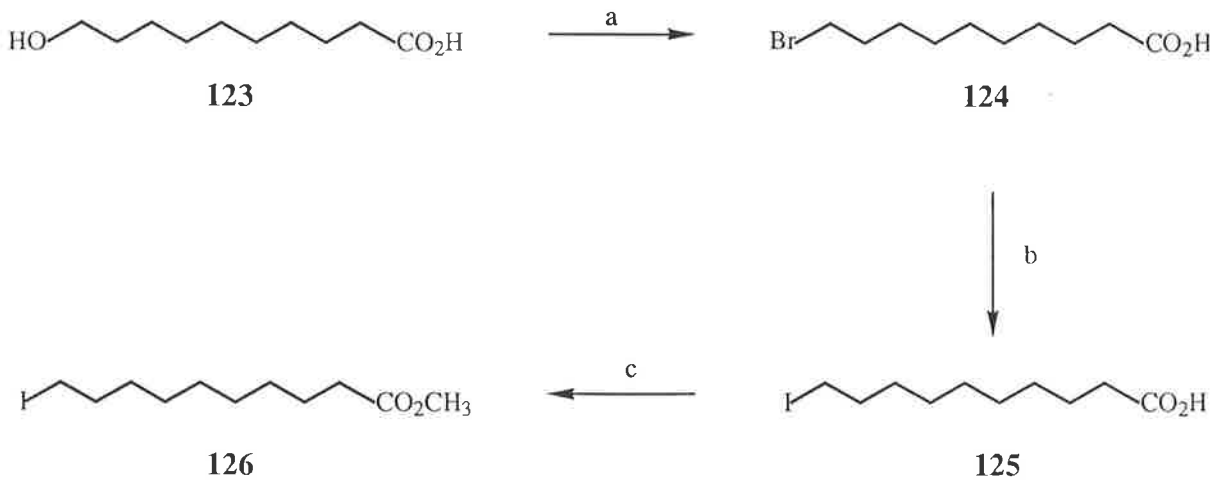
SCHEME 33

removal of the solvent under reduced pressure, the residue was distilled to give a 79% yield of methyl 4-chlorobutyrate (**121**). The infrared spectrum of the ester **121** contained a strong absorption at 1736 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR

spectrum contained a triplet (*J* 6.5 Hz) at δ 3.60 ppm, due to the protons on C4, and a singlet at δ 3.70 ppm, due to the ester methyl group.

The chloroester **121** was *trans*-halogenated with sodium iodide in refluxing acetone, to produce the iodoester **122** in an 85% yield, after distillation. A strong absorption at 1736 cm^{-1}, due to the C–O double bond stretch, was observed in the infrared spectrum of the iodoester **122**. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.25 ppm, due to the protons on C4, and a singlet at δ 3.70 ppm, due to the protons of the ester methyl group.

Another method of forming ω-iodoesters is by converting ω-hydroxyacids to the corresponding ω-bromoacids, followed by *trans*-halogenation, with sodium iodide, and esterification. An example of this is the conversion of commercially available 10-hydroxydecanoic acid (**123**) to methyl 10-iododecanoate (**126**), in three steps (Scheme 34). The hydroxy acid **123** was treated with 33% hydrobromic acid in acetic



123 **124** **126** **125**

a HBr, AcOH; b NaI, acetone; c CH_3OH, HCl

SCHEME 34

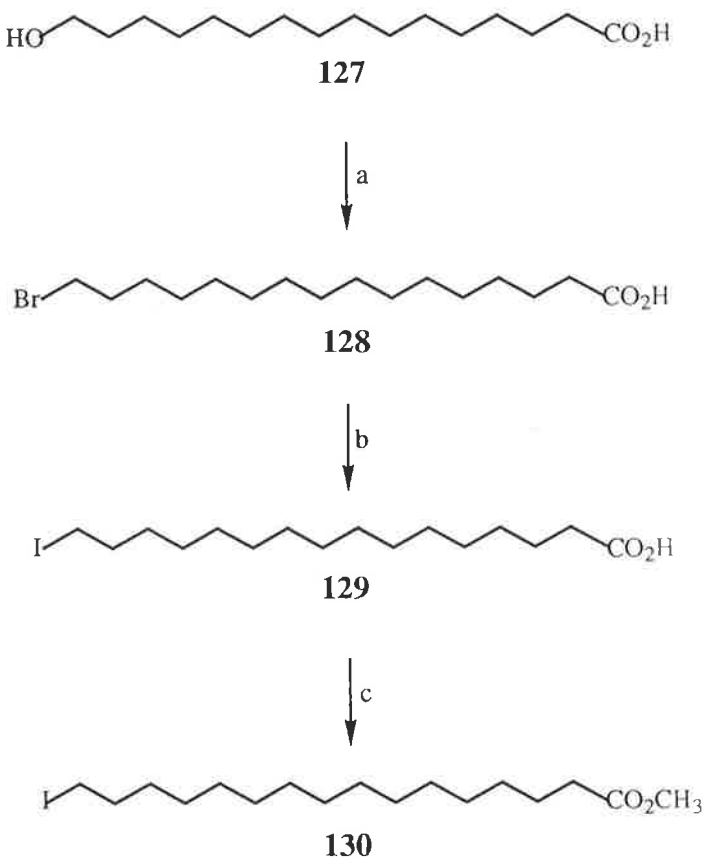
acid, at room temperature overnight, followed by heating at 100°C for four hours. After removal of the solvent under reduced pressure, and recrystallization of the residue from hexane, a 75% yield of 10-bromodecanoic acid (**124**) was obtained. The infrared spectrum of the bromoacid **124** contained a broad absorption at 3500 – 2350 cm^{-1}, due to the carboxylic acid O–H bond stretch, and a strong absorption at 1706 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.34 ppm, due to the protons on C10, and an exchangeable broad singlet at δ 11.77 ppm, due to the carboxylic acid proton.

The bromoacid **124** was *trans*-halogenated by treatment with sodium iodide in refluxing acetone. After dilution of the solvent with water, the precipitate which formed was collected and recrystallized from hexane, to give a 90% yield of 10-iododecanoic acid (**125**). The infrared spectrum of the iodoacid **125** contained a broad absorption at 3400 – 2400 cm^{-1}, due to the carboxylic acid O–H bond stretch, and a strong absorption at 1712 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.13 ppm, due to the protons on C10, and an exchangeable broad singlet at δ 11.71 ppm, due to the carboxylic acid proton.

The iodoacid **125** was readily esterified by treatment with a methanolic solution of hydrogen chloride for four hours. Removal of the solvent under reduced pressure, followed by distillation of the residue, afforded methyl 10-iododecanoate (**126**) in an 89% yield. The infrared spectrum of the iodoester **126** contained a strong absorption at 1736 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.18 ppm, due to the protons on C10, and a singlet at δ 3.67 ppm, due to the ester methyl group.

Using the same approach as described for the synthesis of the iodoester **126**, commercially available 16-hydroxyhexadecanoic acid (**127**) was converted to methyl 16-iodohexadecanoate (**130**) (Scheme 35). Thus, treatment of the hydroxyacid **127** with

33% hydrobromic acid in acetic acid, in the same manner as described for the reaction of **123**, produced an 87% yield of 16-bromohexadecanoic acid (**128**), after



a HBr, AcOH; b NaI, acetone; c CH_3OH, HCl

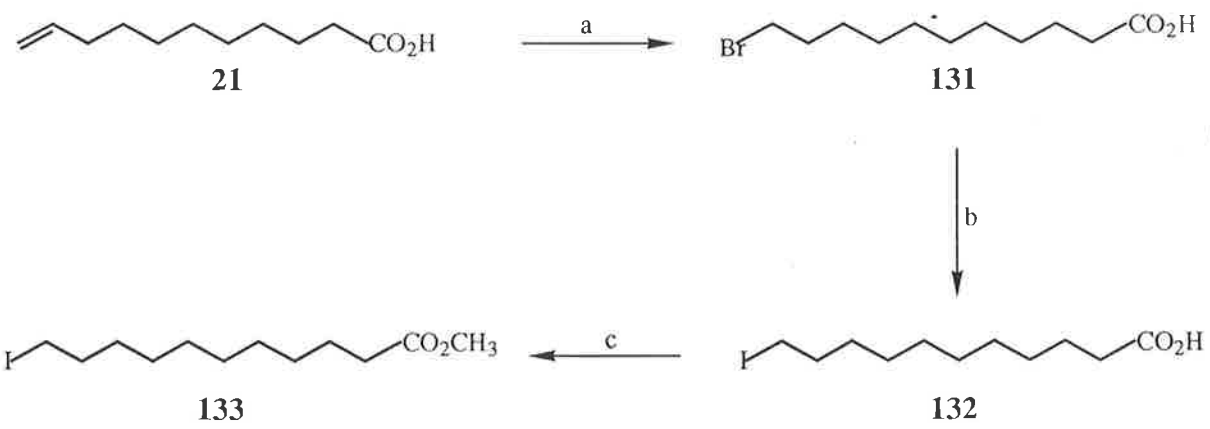
SCHEME 35

recrystallization from hexane. A broad absorption at 3650 – 2425 cm^{-1}, due to the carboxylic acid O–H bond stretch, and a strong absorption at 1712 cm^{-1}, due to the C–O double bond stretch, were observed in the infrared spectrum of the acid **128**. The ^{1}H-NMR spectrum contained a triplet (J 6.5 Hz) at δ 3.43 ppm, due to the protons on C16.

16-Iodohexadecanoic acid (**129**) was obtained in a 90% yield after recrystallization from hexane, upon treatment of the bromoacid **128** with sodium iodide in refluxing acetone. The infrared spectrum of the iodoacid **129** contained a broad absorption at 3600 – 2500 cm^{-1}, due to the carboxylic acid O–H stretch, and a strong absorption at 1710 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.20 ppm, due to the protons on C16.

Esterification of the iodoacid **129** with methanolic hydrogen chloride, afforded an 84% yield of methyl 16-iodohexadecanoate (**130**), after recrystallization from methanol. A strong absorption at 1730 cm^{-1}, due to the C–O double bond stretch, was observed in the infrared spectrum of the ester **130**. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.22 ppm, due to the protons on C16, and a singlet at δ 3.70 ppm, due to the ester methyl group.

In an alternative approach, ω-iodoesters can also be formed in a few steps, by starting with the corresponding ω-unsaturated acids. This method was used in the conversion of commercially available 10-undecenoic acid (**21**) to methyl 11-iodoundecanoate (**133**), in three steps, as shown in Scheme 36. The unsaturated acid **21** was suspended in hexane saturated with hydrogen bromide and containing a catalytic amount of azobisisobutyronitrile (AIBN). The suspension was irradiated with a 300W sun-lamp for thirty minutes and then the solid was collected by filtration after cooling the mixture to –10°C. Recrystallization of the solid from hexane revealed a 67% yield of 11-bromoundecanoic acid (**131**). The infrared spectrum of the bromoacid **131** contained a broad absorption at 3300 – 2500 cm^{-1}, due to the carboxylic acid O–H stretch, and a strong absorption at 1712 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.44 ppm, due to the protons on C11, and a broad signal at δ 10.40 ppm, due to the carboxylic acid proton.



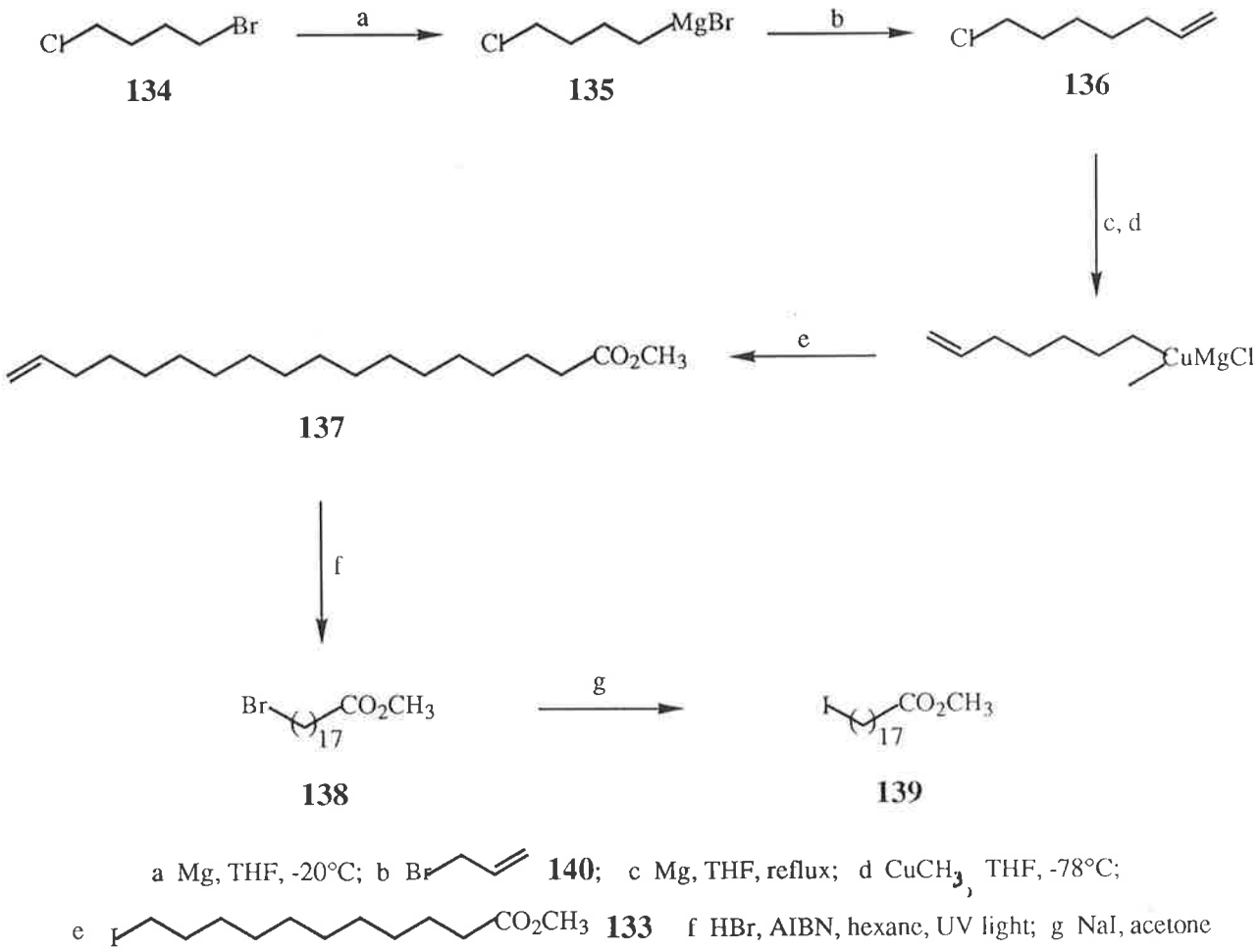
a HBr, AIBN, hexane, UV light; b NaI, acetone; c CH_3OH, HCl

SCHEME 36

The bromoacid **131** was *trans*-halogenated by treatment with sodium iodide in refluxing acetone. The product, which precipitated after dilution of the solvent with water, was collected and recrystallized from hexane, to yield 76% of 11-iodoundecanoic acid (**132**). A broad absorption at 3100 – 2400 cm^{-1}, due to the carboxylic acid O–H stretch, and a strong absorption at 1710 cm^{-1}, due to the C–O double bond stretch, were observed in the infrared spectrum of iodoacid **132**. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.15 ppm, due to the protons on C11, and a broad exchangeable singlet at δ 11.83 ppm, due to the carboxylic acid proton.

The iodoacid **132** was esterified with methanolic hydrogen chloride. Distillation of the residue, after removal of the solvent under reduced pressure, produced a 95% yield of methyl 11-iodoundecanoate (**133**). A strong absorption at 1738 cm^{-1}, due to the C–O double bond stretch, was present in the infrared spectrum. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.20 ppm, due to the protons on C11, and a singlet at δ 3.70 ppm, due to the protons on the ester methyl group.

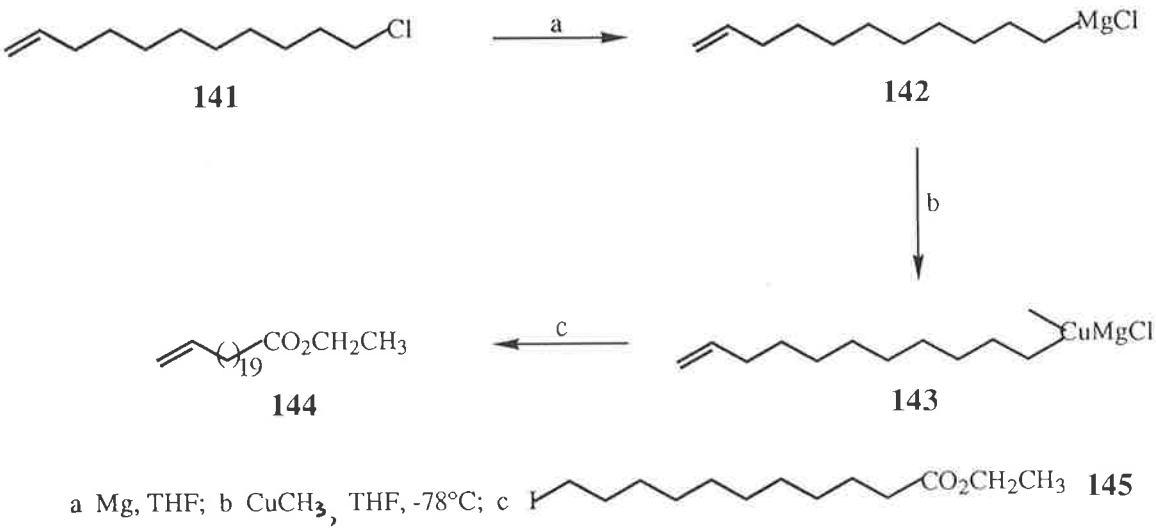
The above syntheses of the ω-iodoesters **122, 126, 130** and **133** involve functional group manipulations. An alternative and more general method of forming ω-iodoesters is by chain-elongation. An approach considered for the synthesis of the ω-iodoester **139** by this method is outlined in Scheme 37. The approach is based on methodology



SCHEME 37

developed by Bergbreiter and Whitesides[74] to couple alkylmagnesium halides with ω-iodoesters, *via* mixed copper(I) ate complexes. Their procedure is compatible with a number of functional groups and reportedly produces coupled products in high yields. To exemplify their procedure, Bergbreiter and Whitesides[74] described the synthesis of ethyl 21-docosenoate (**144**) (Scheme 38). 11-Chloroundecene (**141**) was metallated with

magnesium in THF to form the Grignard reagent **142**, which was added to a solution of methylcopper(I) in THF at –78°C (formed by the addition of one equivalent of methyllithium to cuprous iodide in THF at –78°C) to generate the mixed copper(I) ate complex **143**. The complex **143** reacted with ethyl 11-iodoundecanoate (**145**) at –78°C to yield, after isolation, 79% of the ester **144**. This procedure was considered suitable as a



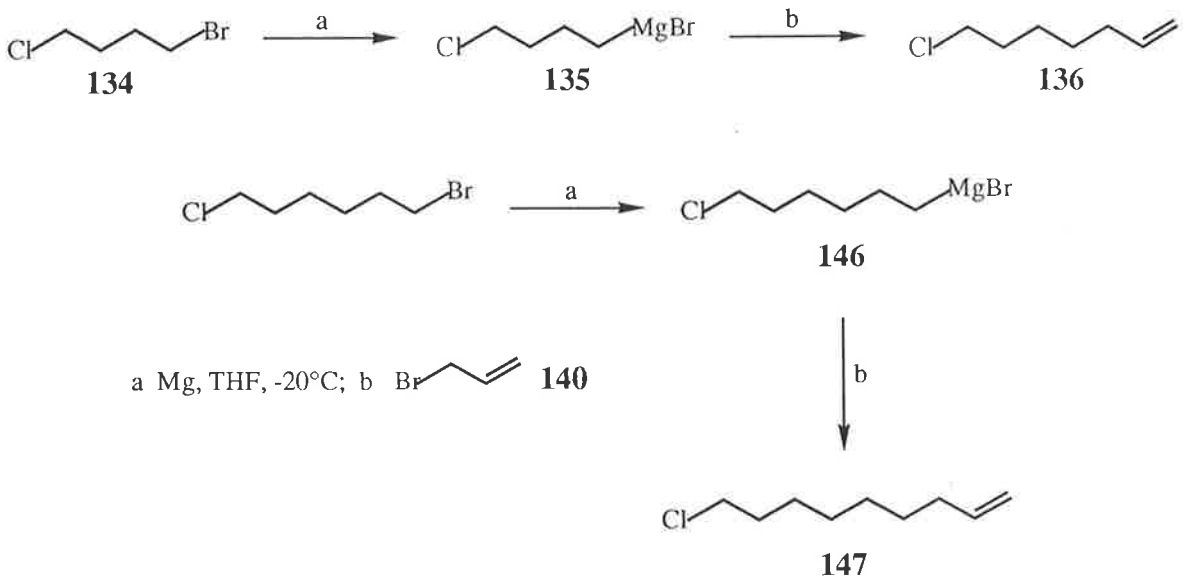
SCHEME 38

general method for the synthesis of a range of ω-unsaturated esters, which could be converted to the corresponding ω-iodoesters using the methodology described above for the synthesis of **133**.

To keep the method of formation of the ω-unsaturated esters completely general, using the approach of Bergbreiter and Whitesides,[74] a general method was required to form ω-unsaturated halides of varying length. ω-Unsaturated halides are usually formed by reacting the Grignard derivatives of shorter homologues with ethylene oxide,[96,97,~~72.3~~ 93] oxetane[~~72.4~~ 99,100] or formaldehyde[98], to form the corresponding longer chain alcohols, followed by conversion to the corresponding halides. These reactions are quite often moderate in yield. Synthesis of a substantially elongated ω-unsaturated halide using

this approach would require a long, reiterative procedure, resulting in an overall low yield. Consequently, alternative procedures were investigated.

One method reported for forming ω-unsaturated halides is by condensation of mono-Grignard species of 1-bromo-ω-chloroalkanes with allyl bromide (**140**). Noël and co-workers[101] have reported the selective metallation of 1-bromo-ω-chloroalkanes with magnesium at low temperatures to form the corresponding mono-magnesium derivatives, utilizing the greater reactivity of the bromide with respect to the chloride. They ~~functionalized~~ reacted these Grignard reagents with a variety of electrophiles, leaving the chloro moiety intact. Among the compounds they obtained using this approach were 7-chlorohept-1-ene (**136**) and 9-chloronon-1-ene (**147**) (Scheme 39). The chloride **136**



SCHEME 39

was formed in 45% yield by condensing the mono-Grignard derivative of 1-bromo-4-chlorobutane (**135**) with allyl bromide (**140**). Analogously, the chloride **147** was prepared in 60% yield by coupling the mono-Grignard derivative of 1-bromo-6-chlorohexane (**146**) with allyl bromide (**140**). Unfortunately, the paper gave no

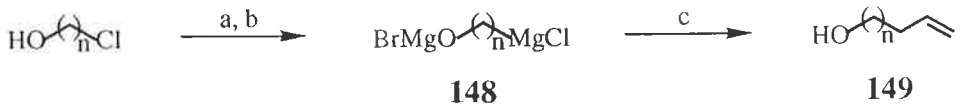
experimental details, and a search through the literature failed to reveal further details on this work.

The method of Noël *et al.*[101] appeared suitable as a general method for the synthesis of a range of ω-unsaturated alkyl halides, as the 1–bromo-ω-chloroalkanes of varying chain-length are commercially available. Initial attempts at forming a Grignard reagent from 1-bromo-4-chlorobutane (**134**) at low temperature, however, proved unsuccessful. Magnesium in THF, initially activated at room temperature with 1,2-dibromoethane, was cooled to –20°C and 1-bromo-4-chlorobutane (**134**) was added. No reaction was observed at this temperature, even after vigorous stirring for three hours. It was considered that allowing the reaction mixture to warm very slowly to room temperature overnight would enable reaction to occur, with selectivity for the bromide in the presence of the chloride. Under these conditons reaction did proceed and most of the magnesium was used up. The reaction mixture obtained in this way was treated with allyl bromide (**140**) for a short time, with warming of the reaction mixture. However, ^{1}H-NMR spectroscopic analysis of the crude product gave a spectrum which contained no discernable peaks between δ 4.8 and 6.2 ppm corresponding to the vinylic protons of the expected product **136**.

In a modification of the above procedure, the entrainment method[102] was employed. The dihalide **134** was added with 1,2-dibromoethane to magnesium in THF at –20°C. Again no reaction occurred at this temperature. As previously described, the mixture was allowed to warm very slowly to room temperature, during which reaction occurred and most of the magnesium was used up. This mixture was stirred with allyl bromide (**140**) overnight. However, ^{1}H-NMR analysis of the crude product mixture again showed no signals between δ 4.8 and 6.2 ppm, corresponding to the vinylic protons of the expected product **136**.

Oppolzer and Schneider[103] have reported the generation of Grignard reagents at –65°C using slurries of highly active, precondensed magnesium in THF, or anthracene-activated magnesium in THF. Also, the introduction of a copper(I) catalyst would probably facilitate reaction between the Grignard derivative **135** and allyl bromide (**140**). These alternatives were not investigated, however, as an easier method was successfully applied to form the ω-unsaturated halides, as described in the following paragraphs.

An alternative method for the formation of ω-unsaturated halides is *via* the corresponding ω-unsaturated alcohols (**149**), which can be prepared by the condensation of the di-Grignard complexes of polymethylene chlorohydrins (**148**) with allyl bromide (**140**) (Scheme 40). The preparation and reaction of the di-Grignard

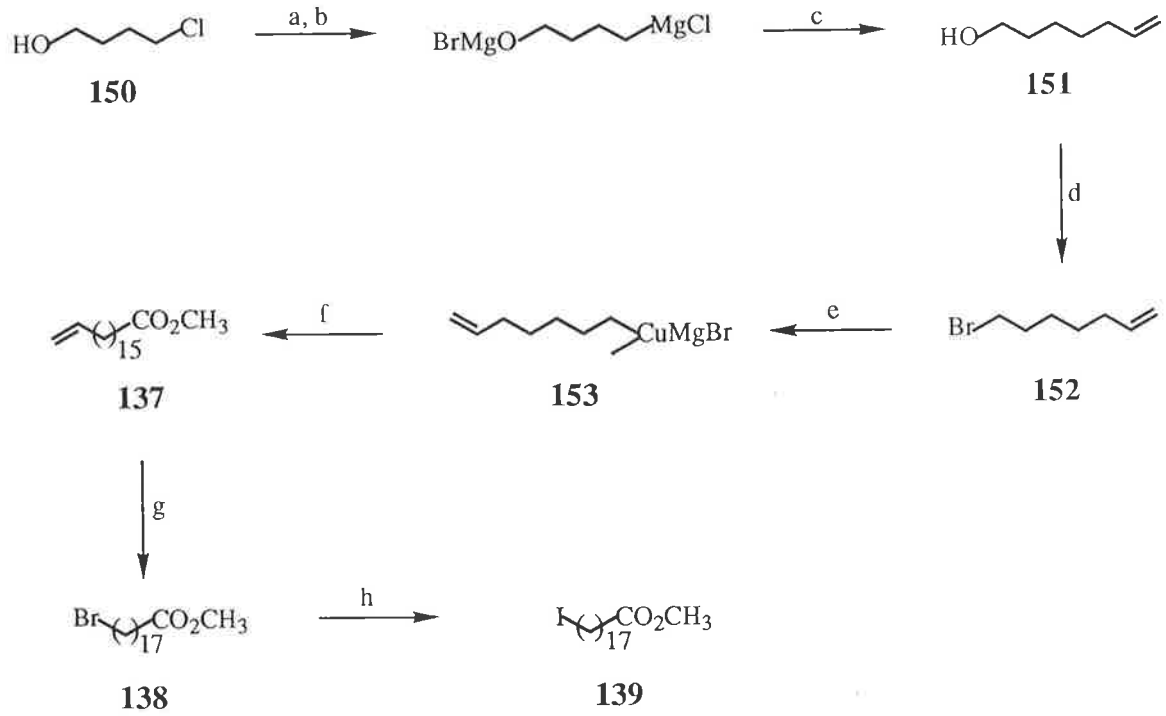


a EtMgBr, THF, -20°C; b Mg, reflux; c CuBr, Br  **140**

SCHEME 40

complexes of certain chlorohydrins have been reported by Cahiez *et al.*[104] They briefly touched upon the coupling of polymethylene chlorohydrins with allyl bromide (**140**), *via* the di-Grignard complexes of the former compounds, under copper(I) catalysis. The product ω-unsaturated alcohols were reportedly formed in excellent yields. Conversion of the ω-unsaturated alcohols, produced by this method, to the corresponding bromides, would form a general synthesis of the required ω-alkenyl halides. Consequently, the synthesis of the ω-iodoester **139** was performed as shown in Scheme 41.

The chlorohydrin, 4-chorobutan-1-ol (**150**) was not formed in the conventional way. Usually, the chlorohydrin **150** is formed by bubbling anhydrous hydrogen chloride gas through THF, followed by removal of the excess THF and distillation of



150 **151** **152** **153** **137** **138** **139**

a EtMgBr, THF, -20°C; b Mg, reflux; c CuBr, **140**; d PBr_3; e CH_3Cu, -78°C; f **133**; g HBr, AIBN, hexane, UV light; h NaI, acetone

SCHEME 41

the residue.[105,106] The generality of this process is limited to the availability of cyclic ethers. To form longer chain polymethylene chlorohydrins, an alternative synthesis is required, as the corresponding cyclic ethers are not readily available. To keep every aspect of the synthesis of the target ω-unsaturated halides completely general, the method of Coleman and Bywater[107] for the synthesis of hexamethylene chlorohydrin, was adapted. Therefore, to synthesize the chlorohydrin **150**, tetramethylene glycol was initially refluxed for two hours with concentrated aqueous hydrogen chloride, containing a catalytic amount of cuprous chloride, then the mixture was continuously

extracted with toluene for eighteen hours while being heated at 90°C. In this way, a 51% yield of the chlorohydrin **150** was achieved after distillation. A broad absorption at 3700 – 3000 cm^{-1}, for the O–H bond stretch, and a strong absorption at 650 cm^{-1}, corresponding to the C–Cl bond stretch, were present in the infrared spectrum of **150**. The ^{1}H-NMR spectrum contained an exchangeable singlet at δ 1.92 ppm, due to the alcohol proton, a multiplet at δ 1.81 ppm, due to the C2 and C3 protons, a triplet (*J* 6.5 Hz) at δ 3.61 ppm, due to the protons on C4, and a triplet (*J* 6.5 Hz) at δ 3.71 ppm, due to the protons on C1. GLC analysis indicated the presence of a small amount of 1,4-dichlorobutane, as a contaminant in **150**, by comparison with an authentic sample.

The method of Cahiez *et al.*,[104] was applied in the present work to form 6-hepten-1-ol (**151**). Thus, 4-chorobutan-1-ol (**150**) was deprotonated with ethylmagnesium bromide in THF at −15 to −20°C, so as to avoid ring closure of the resultant alkoxide. Magnesium turnings were then added to the mixture and heating was commenced immediately. Addition of a catalytic amount of cuprous bromide to the cooled solution formed a brown / purple complex. Allyl bromide (**140**) was added in an exothermic process and the reaction was allowed to proceed overnight at room temperature. An 81% yield of 6-hepten-1-ol (**151**) was thus obtained after isolation. The infrared spectrum of **151** contained a broad band at 3650 – 3000 cm^{-1}, due to the O–H bond stretch, and a band at 1642 cm^{-1}, due to the alkene double bond stretch. The ^{1}H-NMR spectrum contained a singlet for an exchangeable proton at δ 1.63 ppm, a triplet (*J* 6.5 Hz) at δ 3.67 ppm, due to the C1 protons, and characteristic multiplets between δ 4.83 and 6.23 ppm, due to the vinylic protons.

Conversion of the ω-unsaturated alcohol **151** to its bromide derivative **152** was found to be not as trivial as expected for such a simple compound. Derivatization to the bromide **152** was chosen, above other halides, as bromides are generally easier to form and conversion to the corresponding Grignard reagents is normally fairly facile. The alcohol **151** was initially treated with phosphorous tribromide in ether, with a trace of

pyridine. After a three hour reflux followed by stirring overnight at room temperature, the reaction mixture was subjected to a basic work-up procedure and chromatography on silica to yield, at best, 28% of the bromide **152**. This procedure was modified by carrying out the reaction with no solvent and a shorter reaction time, but a similar yield, 31%, of the bromide **152** was obtained. The infrared spectrum of the bromide **152** contained the alkene C–H bands at 3076, 994 and 912 cm^{-1} and a band representing the C–C double bond stretch at 1640 cm^{-1}. A triplet (*J* 6.5 Hz) at δ 3.35 ppm, due to the C1 protons, and the characteristic vinylic proton multiplets between δ 4.80 and 6.22 ppm, were observed in the ^{1}H-NMR spectrum.

In an attempt to improve the yield of the bromide **152**, the method used by Beckwith *et al.*[99] (an adaption of the procedure of Hooz and Gilani[84]) to convert alcohols to the corresponding bromides, similar to **152**, was employed. The alcohol **151** was mixed with triphenylphosphine and tetrabromomethane in dichloromethane, and stirred overnight at room temperature. Separation of the product from the triphenylphosphine oxide byproduct, by hexane extraction, was followed by chromatography on silica, to reveal a good yield of the bromide **152**, but contaminated with a significant amount of bromoform byproduct, as shown by a large singlet at δ 6.87 ppm in the ^{1}H-NMR spectrum. A further attempt at purification, by distillation, failed as bromoform co-distilled with the product **152**. An attempt to azeotrope the bromoform with formic acid[108] also failed, as the bromide **152** also azeotropically distilled with formic acid.

To avoid the problem of bromoform formation, triphenylphosphine dibromide was utilized, as described by Rakoff.[109] Triphenylphosphine dibromide was generated by addition of molecular bromine to a dichloromethane solution of triphenylphosphine at 0°C. To this slurry was added the alcohol **151** and, after a reaction time of two hours at 0°C, the product was separated from the triphenylphosphine oxide byproduct, by hexane extraction, and distilled, to yield 50% of the bromide **152**.

While this last method gave an improved yield of **152**, it was thought likely that other methods could give even better yields. Another variation of forming bromides utilizing triphenylphosphine is by activation of the latter compound with *N*-bromosuccinimide.[110] This method was applied to the alcohol **151** using the procedure described by Bose and Lal.[111] Triphenylphosphine was added to a THF solution of *N*-bromosuccinimide, whereupon an exothermic reaction occurred with separation of a solid. To this mixture was added the alcohol **151**, and after stirring for three hours at room temperature, the mixture was filtered, to remove the succinimide byproduct, and concentrated. Analysis of the residue by TLC on silica and ^{1}H-NMR spectroscopy revealed a complex mixture of compounds with little of the bromide **152** having formed, as shown by comparison to a previously synthesized sample.

The best result of forming the bromide **152** was obtained *via* the simple method of Gaubert, Linstead and Rydon.[112] The alcohol **151** and pyridine were added slowly to phosphorous tribromide and, after addition was complete, the mixture was immediately distilled until thick white fumes evolved. The distillate was base-washed, dried, and redistilled to afford 74% of the bromide **152**.

The method of Bergbreiter and Whitesides[74] was applied in an attempt to couple the bromide **152** with methyl 11-iodoundecanoate (**133**). Initially the bromide **152** was added to magnesium turnings in THF. After the magnesium had been consumed, the mixture was added to pre-formed methylcopper(I) at –78°C in THF, and after stirring for one hour, the temperature was raised to 10°C. No colour change from yellow to light pink / purple[74] was observed, as expected upon formation of the cuprate **153**. The mixture was recooled to –78°C and the iodoester **133** was added. After stirring for one hour at this temperature and three hours at room temperature, a standard work-up procedure was applied. ^{1}H-NMR spectroscopic analysis of the crude mixture showed an absence of signals in the vinylic region, indicating that no **137** was present. GLC

analysis showed the presence of unreacted **133**, but no **137**, by comparison with an authentic sample obtained as described below. Mass spectral analysis gave an ion at m/z 224, which indicated that some methylation of the ω-iodoester **133** had occurred, to form methyl dodecanoate **154**.

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To further investigate the coupling procedure, it was decided to study the reaction of 1-bromoheptane with the iodoester **133**. Analysis by TLC on silica of the resultant product mixture indicated that no methyl octadecanoate (**155**) had formed, as seen by comparison with an authentic sample obtained by esterification of commercially available octadecanoic acid. GLC analysis indicated that the only product formed in the reaction was the byproduct ester **154**.

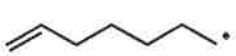
To simplify the system even further, 1-iodopentane was substituted for the iodoester **133**. 1-Bromoheptane was treated with magnesium in THF, and the solution was added to a suspension of methylcopper(I) at –78°C. This mixture was warmed to 0°C whereupon the suspension changed colour from yellow to a very pale pink. This colour change is indicative of the formation of the mixed dialkylcuprate.[74] 1-Iodopentane was added to this suspension at –78°C and after stirring at room temperature for three hours a standard work-up procedure was applied. Under these conditions, the desired product, dodecane (**156**), was obtained in a 35% yield. The identity of dodecane (**156**) was determined by GLC and ^{1}H-NMR spectroscopic analysis, and comparison with an authentic sample.

The reaction of the 1-bromoheptane with 1-iodopentane had been performed at a higher concentration than the above reaction of the 1-bromoheptane with the ω-iodoester **133**. To see if the reactions were sensitive to concentration effects, the

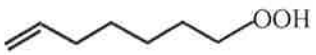
reaction of the 1-bromoheptane with the iodoester **133** was repeated at a higher concentration. This produced a best yield of 26% of the methyl octadecanoate (**155**), with physical and spectral properties identical to those of an authentic sample. However, the reproducibility of this reaction was found to be poor.

The reaction of the bromide **152** with the iodoester **133** was also attempted at higher concentrations. Otherwise the conditions used were the same as before. However, again none of the ester **137** was observed by TLC of the product on silica, or by ^{1}H-NMR spectroscopic or GLC analysis. The only product isolated from the reaction was the alcohol **151**. The infrared spectrum of the alcohol **151** contained a strong, broad absorption at 3700 – 3000 cm^{-1}. Also contained in the infrared spectrum were a sharp absorption at 3095 cm^{-1}, due to the alkene C–H bond stretch, and the corresponding C–C double bond stretch at 1646 cm^{-1}. The ^{1}H-NMR spectrum contained a triplet (J 6.5 Hz) at δ 3.63 ppm and an exchangeable singlet at δ 1.92 ppm, and complex multiplets between δ 4.80 and 6.23 ppm characteristic of a terminal alkene. Further, comparison of the spectral data of the alcohol **151** with that of an authentic sample, and GLC comparison, confirmed the structure.

It was believed that formation of the alcohol **151** probably occurred during metallation of the bromide **152** with magnesium. This most likely occurs by reaction of the intermediate radical species **157** with oxygen, producing a peroxide **158**. The peroxide **158** then breaks down to form the alcohol **151**. It has been shown that, during Grignard



157



158

formation, a substantial amount of alkyl radicals escape and return to the surface of the magnesium.[113] The diffused radicals can dimerize, react with species present in the solvent, or return to the magnesium surface. The above reactions were conducted

under an atmoshpere of industrial grade nitrogen, which contains a small amount of oxygen.

To prove that formation of the alcohol **151** does indeed occur during the metallation of the bromide **152**, and not during the alkylation step, the reaction of the bromide **152** with magnesium was studied separately. Thus, a sample of the bromide **152** was added to magnesium in THF in the usual way and, after one hour at reflux, the solution was quenched with saturated aqueous ammonium chloride solution and the solvent removed. The crude product mixture was subjected to dry-column flash chromatography on silica to reveal the same alcohol **151**, as identified by its spectral properties and GLC retention time. This result verified that the alcohol **151** was formed during metallation of the bromide **152** with magnesium.

Alcohol formation was not just confined to reaction of the bromide **152** with magnesium, but was observed after metallation with magnesium and quenching of a number of alkyl halides. The halides studied were 1-bromo-4-pentene, 1-bromo-5-hexene, 1-bromobutane, 1-bromooctane and 1-chlorobutane. In all cases, the reactions were conducted in THF under industrial grade nitrogen. The halides were added to the magnesium and THF and, after the initial vigorous reaction had subsided, the solutions were refluxed for one hour. Under these conditions, 4-penten-1-ol, 5-hexen-1-ol and octan-1-ol were formed by metallation of 1-bromo-4-pentene, 1-bromo-5-hexene and 1-bromooctane, respectively, and butan-1-ol was formed by metallation of 1-bromobutane and 1-chlorobutane. These alcohols were analyzed by infrared spectroscopy, ^{1}H-NMR spectroscopy, and GLC and found to be identical to authentic samples. One molar concentrations of the halides were used. The Grignard content was determined by using the direct titration method of Watson and Eastham,[114] with 2,2'-biquinoline as indicator. Using this procedure, the concentration of the Grignard solutions was shown to vary between 0 – 0.30 M. When the reactions were repeated, but under high purity

nitrogen, which contains only a trace of oxygen, surprisingly no increase in Grignard content was observed, and alcohol formation still occurred.

It was thought unusual that reaction with oxygen, during formation of the Grignard reagents, would occur to such an extent. The possibility of a contaminant causing the excessive reaction was investigated. One possible source of contamination was the solvent, THF. The THF used in this work was distilled from sodium and benzophenone ketyl immediately prior to use. To eliminate the possibility of the THF being the source of contamination, THF from various sources was used. However, no increase in the amount of active Grignard reagent was observed, as shown by titration values. Grignard reagents, when generated in THF distilled from lithium aluminium hydride, also gave low titration values. When ether (distilled from sodium and benzophenone ketyl) was substituted for THF as solvent for the Grignard formation, the active Grignard content was generally higher, as determined by titration, but alcohol formation still occurred. The Grignard reactions were also performed using new glassware, to eliminate the possibility of a contaminant being present on the glassware. Again, no increase in the concentration of the Grignard content was observed.

It is known that magnesium contains trace amounts of other transition metals and that the ratios of metal contaminants vary in magnesium from different sources.[115] It has also been shown that these metal contaminants can catalyze different reactions during Grignard formation.[115] To investigate the possibility of contaminants in the magnesium contributing to alcohol formation, magnesium turnings from three different sources, and magnesium powder from a fourth source, were compared in standard Grignard reagent forming reactions. In all cases, titration values for the Grignard content were low and alcohol formation was occurring. In another attempt to overcome the problem of alcohol formation, Rieke magnesium[116] was formed in THF and 1-bromo-4-pentene was added to the suspension of magnesium. Direct titration[114]

of the solution, after the suspension had settled, showed that no Grignard reagent was present.

Consequently, to overcome the problem of alcohol production during Grignard reagent formation, all oxygen needed to be removed from the nitrogen atmosphere. This was accomplished by using a manganese(II) oxide oxygen trap.[117] High purity nitrogen was passed through a column of green manganese(II) oxide supported on vermiculite, followed by passage through a column of silica gel, before entering the reaction vessel where Grignard formation was to take place. The green manganese(II) oxide is oxidized to brown / black manganese dioxide in the presence of oxygen. When the oxygen trap is exhausted, manganese dioxide can be converted back to manganese(II) oxide by passing hydrogen through the column at high temperature. When the bromide **152** was metallated with magnesium in THF using oxygen-free nitrogen, the Grignard reagent was formed and gave a titration value 80% of the theoretical value.

Having established conditions for Grignard formation, the coupling of the bromide **152** with the iodoester **133** to form the ω-unsaturated ester **137**, was retried. Initial trials at sub-millimole scale gave poor yields with the methylated material **154** greatly predominating. When the coupling reaction was conducted on an approximate ten millimole scale, or greater, good yields of the product ester **137** were obtained. Thus, the bromide **152** was coupled with the iodoester **133**, using the method as described previously, with the exception of generating the Grignard reagent under an atmosphere of oxygen-free nitrogen. The ester **137** was obtained in a 74% yield, after purification by flash chromatography on silica. The infrared spectrum of **137** contained absorptions at 3076 and 1642 cm^{-1}, due to the vinylic C–H bond stretch and the C–C double bond stretch, respectively, and a strong absorption at 1742 cm^{-1} due to the C–O double bond stretch. ^{1}H-NMR spectral analysis revealed a singlet at δ 3.63 ppm, due to the ester methyl group, and the characteristic group of multiplets between δ 4.77 and 6.20 ppm, due to the protons on the terminal double bond.

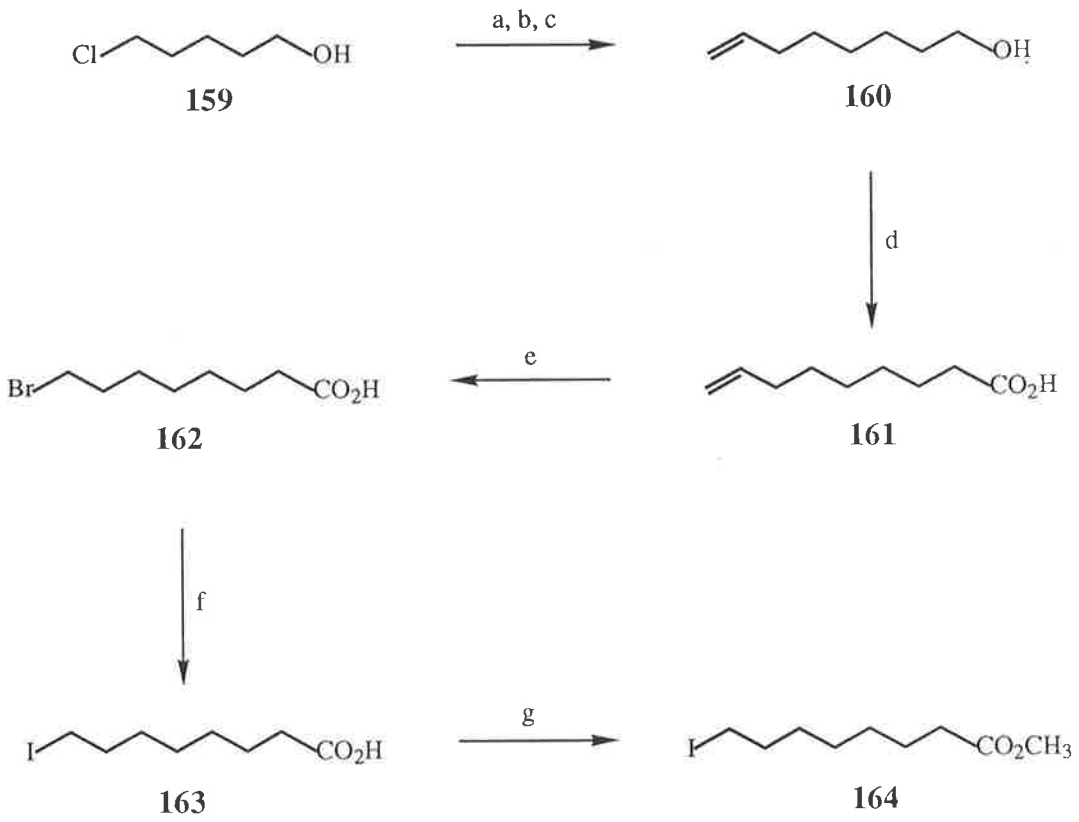
When the reaction to give the ester **137** was repeated, in some cases significant amounts of methyl dodecanoate (**154**) were produced, due to transfer of the methyl group of the cuprate species **153** to the iodoester **133** or by methylation of **133** by residual methylcopper(I). The byproduct ester **154** and the ester **137** had very similar chromatographic properties and could not be separated. Therefore, in these cases the ester **137** was used without further purification.

Methyl 18-iodooctadecanoate (**139**) was formed from methyl 17-octadecenoate (**137**), in a similar way as described for the synthesis of the iodoester **133**. A sample of **137**, contaminated with approximately 30% of methyl dodecanoate (**154**) (GLC analysis), was radically hydrobrominated, in the same way as described for the acid **21**, to give methyl 18-bromooctadecanoate (**138**) in a 66% yield, after recrystallization from methanol. The infrared spectrum of the bromoester **138** contained a strong absorption at 1730 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (J 6.5 Hz) at δ 3.38 ppm, due to the protons on C18, and a sharp singlet at δ 3.65 ppm, due to the ester methyl group. The contaminant **154** used in the reaction to give **138**, was separated from the product through the recrystallization.

trans-Halogenation of the bromoester **138** was performed with sodium iodide in refluxing acetone. The product iodoester **139** was obtained in a 73% yield after recrystallization from methanol. A strong absorption at 1730-cm^{-1}, due to the C–O double bond stretch, was observed in the infrared spectrum of **139**. The ^{1}H-NMR spectrum contained a triplet (J 6.5 Hz) at δ 3.22 ppm, due to the protons on C18, and a sharp singlet at δ 3.71 ppm, due to the ester methyl group.

Access to ω-alkenols as described above for 6-hepten-1-ol (**151**), offers yet another approach to ω-iodoesters. Accordingly, the iodoester **164** was synthesized as shown in Scheme 42. Thus, the pentamethylene chlorohydrin **159** was obtained in a 45% yield,

using an identical procedure to that described above for the formation of the chlorohydrin **150**. The infrared spectrum of the chlorohydrin **159** contained a broad



a EtMgBr, THF, -20°C; b Mg, reflux; c CuBr, **140**; d Jones reagent;
e HBr, AIBN, hexane, UV light; f NaI, acetone; g CH_3OH, HCl

SCHEME 42

band at 3650 – 3000 cm^{-1}, for the O–H bond stretch, and a C–Cl bond stretch at 652 cm^{-1}. A multiplet signal at δ 1.61 ppm, due to the C2, C3 and C4 protons, an exchangeable singlet signal at δ 2.57 ppm, due to the alcohol proton, a triplet (*J* 6.5 Hz) at δ 3.56 ppm, due to the protons on C5, and a triplet (*J* 6.5 Hz) at δ 3.66 ppm, due to the protons on C1, were observed in the ^{1}H-NMR spectrum. GLC analysis showed that a trace of a contaminant was present in **159**. This was probably 1,5-dichloropentane, as,

by analogy, the chlorohydrin **150** was contaminated with 1,4-dichlorobutane when prepared by a similar procedure.

5-Chloropentan-1-ol (**159**) was coupled with allyl bromide (**140**), to form 7-octen-1-ol (**160**) in a 66% yield, by applying an identical procedure to that described above for the formation of the alcohol **151**. The infrared spectrum of **160** contained bands for the O–H bond stretch at 3600 – 3000 cm^{-1} and the alkene C–C double bond stretch at 1640 cm^{-1}. A singlet at δ 1.98 ppm for an exchangeable proton, a triplet (*J* 6.5 Hz) at δ 3.61 ppm, due to the C1 protons, and the characteristic vinylic proton multiplets between δ 4.77 and 6.18 ppm were observed in the ^{1}H-NMR spectrum.

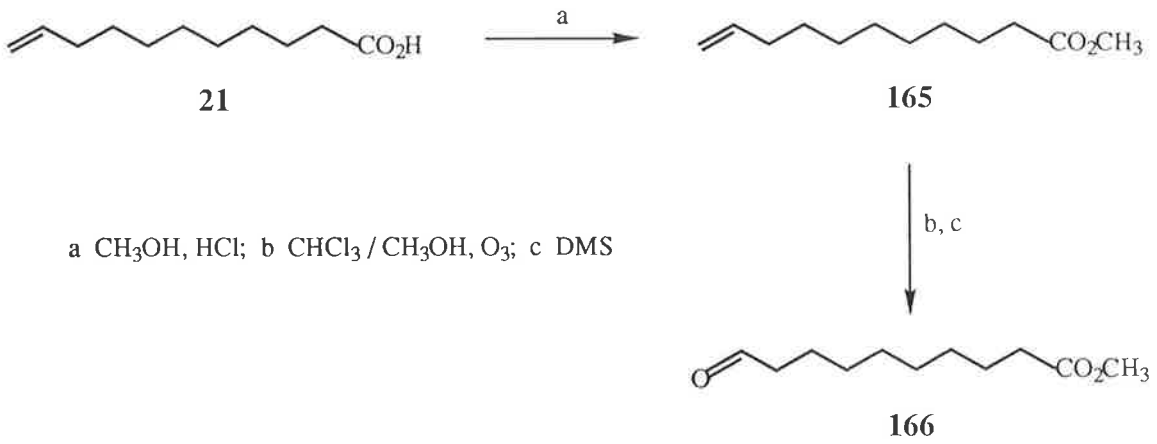
Oxidation of the ω-unsaturated alcohol **160** with Jones reagent[121] provided 7-octenoic acid (**161**) in a 63% yield, after purification by chromatography. The infrared spectrum of **161** contained a broad absorption at 3400 – 2400 cm^{-1}, due to the carboxylic acid O–H stretch, a strong absorption at 1710 cm^{-1}, due to the C–O double bond stretch, and an absorption at 1642 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained the characteristic multiplets between δ 4.74 and 6.12 ppm, due to the terminal alkene protons, and a broad exchangeable singlet at δ 11.32 ppm, due to the carboxylic acid proton.

The acid **161** was hydrobrominated, as described for the acid **21**, to form 8-bromooctanoic acid (**162**), in a 69% yield after recrystallization from hexane. The infrared spectrum of **162** contained a broad absorption at 3450 – 2400 cm^{-1}, due to the carboxylic acid O–H bond stretch, and a strong absorption at 1710 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.41 ppm, due to the protons on C8, and a broad signal at δ 10.42 ppm, due to the carboxylic acid proton.

trans-Halogenation of the bromoacid **162** was performed with sodium iodide in refluxing acetone, as for the bromoacid **131**. 8-Iodooctanoic acid (**163**) was produced in an 83% yield, after recrystallization from hexane. The infrared spectrum of **163** contained a broad absorption at 3450 – 2400 cm^{-1}, due to the carboxylic acid O–H bond stretch, and a strong absorption at 1710 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.18 ppm, due to the protons on C8, and a broad exchangeable signal at δ 9.05 ppm, due to the carboxylic acid proton. Methyl 8-iodooctanoate (**164**) was produced in an 88% yield after distillation, by treatment of the iodoacid **163** with methanolic hydrogen chloride. The infrared spectrum of the ester **164** contained a strong absorption at 1738 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.15 ppm, due to the protons on C8, and a sharp singlet at δ 3.64 ppm, due to the ester methyl group.

The ω-oxoesters required for the studies described in the subsequent sections of this thesis were conveniently prepared by ozonolysis of the corresponding ω-unsaturated esters, using an adaption of the method of Gokhali *et al.*[122] In this way, methyl 10-oxodecanoate (**166**) was readily prepared from the acid **21** *via* methyl 10-undecenoate (**165**), as shown in Scheme 43. Thus, the commercially available acid **21** was esterified by treatment with methanolic hydrogen chloride to give the ester **165**, in 80% yield after distillation. The infrared spectrum of **165** contained a strong absorption at 1744 cm^{-1}, due to the C–O double bond stretch, an absorption at 3076 cm^{-1}, due to the alkene C–H bond stretch, and an absorption at 1640 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a sharp singlet at δ 3.70 ppm, due to the ester methyl group, and characteristic multiplets between δ 4.77 and 6.23 ppm.

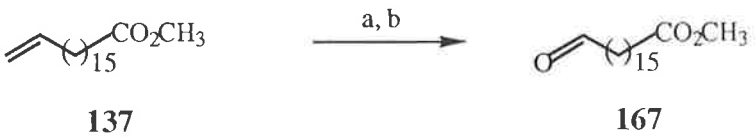
The ester **165** was dissolved in methanol / chloroform (1 : 1), and a stream of ozonized oxygen was passed through the solution at –20°C for three hours. A reductive work-up



SCHEME 43

with dimethyl sulphide produced the oxoester **166** in a 49% yield, after flash chromatography. The infrared spectrum of **166** contained an absorption at 2720 cm^{-1} due to the aldehydic C–H stretch, and a strong absorption at 1736 cm^{-1}, due to the C–O double bonds stretches. The ^{1}H-NMR spectrum contained a sharp singlet at δ 3.65 ppm, due to the ester methyl group, and a triplet (*J* 1.8 Hz) at δ 9.85 ppm, due to the aldehydic proton.

Methyl 17-octadecenoate (**137**) was also conveniently converted to the corresponding ω-oxoester **167** by ozonolysis (Scheme 44), using the same method as described for the

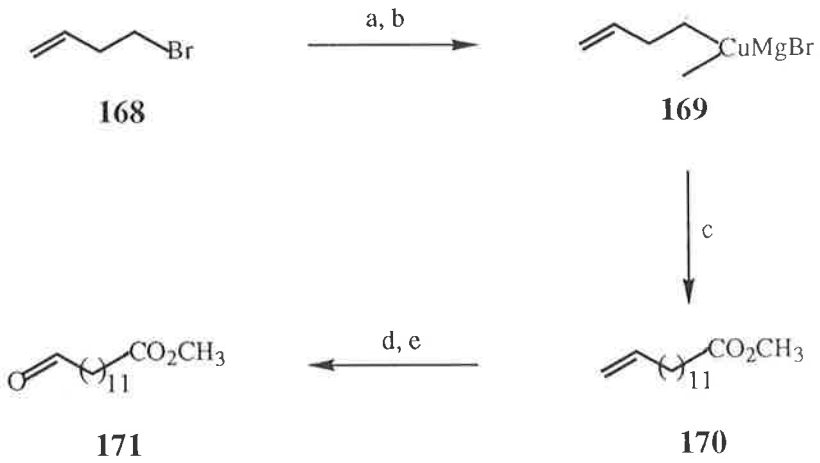


a $CHCl_3$ / CH_3OH, O_3; b DMS

SCHEME 44

formation of **166**. Thus, a sample of the ester **137**, contaminated with approximately 30% of methyl dodecanoate (**154**) (GLC analysis), was ozonized followed by a reductive work-up, to produce a mixture containing unchanged ester **154** and methyl 17-oxoheptadecanoate (**166**). Purification of this mixture by flash chromatography allowed separation of **154** and **166**. The yield of the oxoester **166**, based on ozonolizable material, was 67%. The infrared spectrum of **166** contained an absorption at 2728 cm^{-1}, due to the aldehydic C–H stretch, and a strong absorption at 1724 cm^{-1}, due to the C–O double bonds stretches. The ^{1}H-NMR spectrum contained a sharp singlet at δ 3.65 ppm, due to the ester methyl group, and a triplet (*J* 1.8 Hz) at δ 9.83 ppm, due to the aldehydic proton.

The ω-oxoester, methyl 13-oxotridecanoate (**171**), was prepared by combining the cuprate methodology discussed above, with the ozonolysis procedure described for **166** and **167**, as shown in Scheme 45. Thus, using the same procedure as described



168 **169** **171** **170**

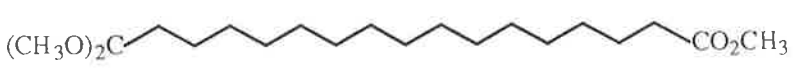
a Mg, THF; b CH_3Cu, THF, -78°C; c **126**;
d $CHCl_3$ / CH_3OH, O_3; e DMS

SCHEME 45

previously for the synthesis of the ester **137**, 1-bromo-3-butene (**168**) was coupled to methyl 10-iododecanoate (**126**) to form the ester, methyl 13-tetradecenoate (**170**), in a 76% yield. The infrared spectrum of **170** contained the absorptions characteristic of an alkene functionality at 3074 and 1640 cm^{-1}, and a strong band at 1744 cm^{-1} due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a sharp singlet at δ 3.65 ppm, due to the ester methyl group, and the characteristic group of multiplets between δ 4.75 and 6.24 ppm due to the protons on the terminal double bond. The ester **170** was contaminated with a substantial amount of methyl undecanoate, formed by methyl transfer from the cuprate species **169** to the ω-iodoester **126**, or by methylation of **126** by residual methylcopper(I). The yield of the ester **170** given above is based on GLC analysis. Due to the closely similar chromatographic behaviour of **170** and methyl undecanoate, they were not separated and the mixture was used without further purification.

Ozonolysis of a sample of methyl 13-tetradecenoate (**170**) contaminated with approximately 30% of methyl undecanoate (GLC analysis), in the same way as described for the formation of **166**, was followed by purification by flash chromatography. Unreacted methyl undecanoate was recovered from the reaction and, based on this, a yield of 68% of methyl 13-oxotridecanoate (**171**) was obtained. The infrared spectrum of **171** contained an absorption at 2716 cm^{-1} due to the aldehydic C–H stretch, and a strong absorption at 1740 cm^{-1}, due to the C–O double bonds stretches. The ^{1}H-NMR spectrum contained a sharp singlet at δ 3.67 ppm, due to the ester methyl group, and a triplet (*J* 1.8 Hz) at δ 9.85 ppm,. due to the aldehydic proton.

In one of the attempts to ozonize the ester **137**, the only product formed was methyl 17-oxoheptadecanoate dimethyl acetal (**172**), which was isolated in a 73% yield. No



172

oxoester **167** was detected by ^{1}H-NMR or infrared spectroscopy. The infrared spectrum of **172** contained a strong absorption at 1730 cm^{-1}, due to the C–O double bond stretch. The ^{1}H-NMR spectrum contained a singlet at δ 3.32 ppm, due to the protons of the acetal methoxy groups, a singlet at δ 3.67 ppm, due to the ester methyl group, with the peaks integrating in a ratio of 2 : 1, respectively, and a multiplet at δ 4.36 ppm, due to the proton on C17.

The acetal **172** was dissolved in a mixture of methanol and 10% aqueous hydrogen chloride, and heated overnight at 50°C. The ^{1}H-NMR spectrum of the crude material obtained from this reaction indicated the presence of unreacted **172**, and the corresponding aldehyde **167**. This was further proof of the structure of the acetal **172**.

The formation of a dimethyl acetal from ozonoysis of an olefin is precedented in the literature. Schmitz and co-workers[152] formed a dimethyl acetal upon ozonolysis of a diterpene, using conditions very similar to those used in this work. They do not comment on the formation of the dimethyl acetal instead of the aldehyde. The reference[153] cited by Schmitz and co-workers for the ozonolysis procedure does not contain any discussion on the possibility of forming dimethyl acetals instead of the carbonyl compounds.

RESULTS AND DISCUSSION

CHAPTER 3

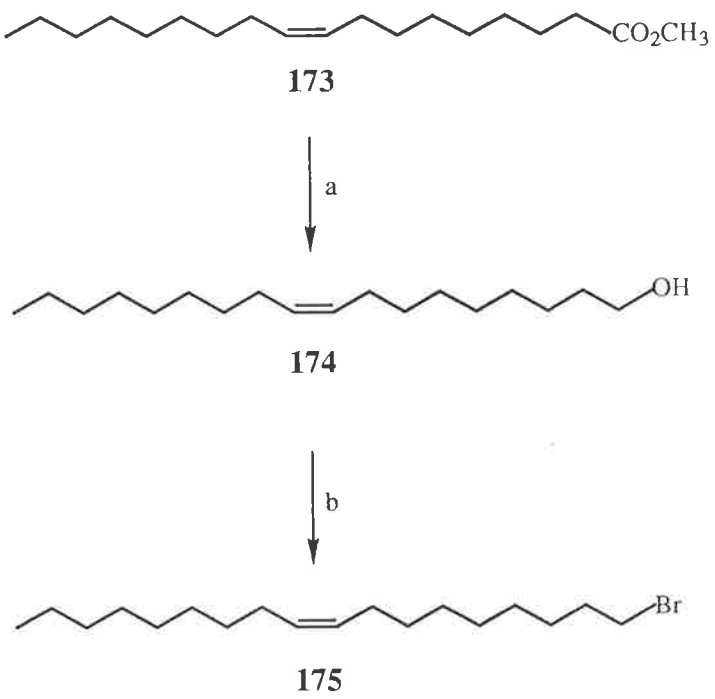
Synthesis of VLCFA *via* Cuprate Methodology

With the ω-iodoesters **122, 126, 130, 133, 139** and **164** available from the work described in Chapter 2, it was envisaged that the mixed dialkyl cuprate methodology could be employed in the synthesis of VLCFA. This would require the coupling of alkenyl bromides with the ω-iodoesters **122, 126, 130, 133, 139** and **164** to form a range of fatty acids as their methyl ester derivatives, of varying length, unsaturation, and series.

The unsaturated bromides used in this work were produced in high yields by treating the corresponding alcohols, obtained commercially or by reduction of the appropriate methyl esters, with triphenylphosphine and carbon tetrabromide. Thus, 1-bromo-9-octadecene (**175**) was synthesized from methyl 9-octadecenoate (**173**), *via* the alcohol **174**, as shown in Scheme 46. The ester **173** was reduced with lithium aluminium hydride in ether, to give 9-octadecen-1-ol (**174**) in a 78% yield after distillation. The infrared spectrum of the alcohol **174** contained a broad band at 3352 cm^{-1}, due to the O–H bond stretch, an absorption at 3004 cm^{-1}, due to the olefinic C–H bond stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. An exchangeable singlet at δ 1.52 ppm, due to the alcohol proton, and a triplet (*J* 6.0 Hz) at δ 3.53 ppm, due to the protons on C1, were observed in the ^{1}H-NMR spectrum.

The alcohol **174** was treated with triphenylphosphine and carbon tetrabromide in dichloromethane to produce the bromide **175** in a 91% yield, after chromatography. The infrared spectrum of the bromide **175** contained an absorption at 3004 cm^{-1}, due to the olefinic C–H bond stretch, and a weak absorption at 1680 cm^{-1}, due to the C–C double bond stretch. A triplet (*J* 6.5 Hz) at δ 3.31 ppm, due to the protons on C1, and a

triplet (*J* 4.5 Hz) at δ 5.24 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum.

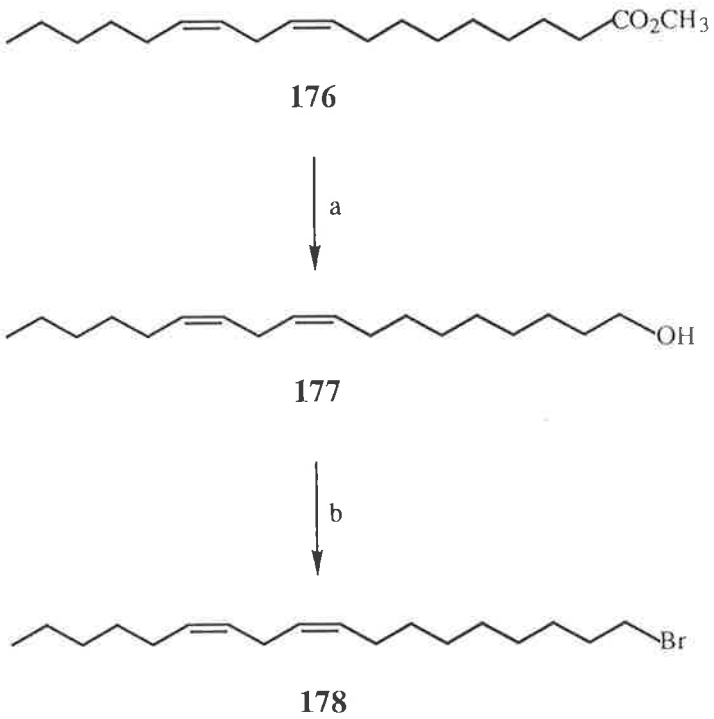


a $LiAlH_4$, ether; b PPh_3, CBr_4, CH_2Cl_2

SCHEME 46

In a similar way, the dienyl bromide **178** was synthesized from the ester **176**, as shown in Scheme 47. The commercially available ester **176** was treated with lithium aluminium hydride in ether, in an analogous way as for the ester **173**, to produce the corresponding alcohol **177** in an 80% yield, after distillation. The infrared spectrum of the alcohol **177** contained a broad absorption at 3336 cm^{-1}, due to the O–H bond stretch, a sharp absorption at 3008 cm^{-1}, due to the alkene C–H stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a broad, exchangeable singlet at δ 2.08 ppm, due to the alcohol proton, a

triplet (*J* 6.0 Hz) at δ 3.62 ppm, due to the protons on C1, and a multiplet at δ 5.35 ppm, due to the olefinic protons.



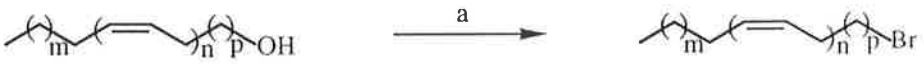
a $LiAlH_4$, ether; b PPh_3, CBr_4, CH_2Cl_2

SCHEME 47

The bromide **178** was formed in a 95% yield, after chromatography, upon treatment of the alcohol **177** with triphenylphosphine and carbon tetrabromide. A sharp absorption at 3008 cm^{-1}, due to the olefinic C–H stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch, were present in the infrared spectrum of the bromide **178**. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.34 ppm, due to the protons on C1, and a multiplet at δ 5.29 ppm, due to the olefinic protons.

Other unsaturated bromides, used in this work, were formed by treating the corresponding commercially available alcohols with triphenylphosphine and carbon

tetrabromide, as shown in Scheme 48. In this way, 1-bromo-9-hexadecene (**180**) was obtained in a 94% yield after chromatography, from the alcohol **179**. The infrared



179 : m = 4, n = 1, p = 7
181 : m = 0, n = 3, p = 7
183 : m = 3, n = 4, p = 3
185 : m = 0, n = 6, p = 2

180 : m = 4, n = 1, p = 7
182 : m = 0, n = 3, p = 7
184 : m = 3, n = 4, p = 3
186 : m = 0, n = 6, p = 2

a Ph_3P, CBr_4, CH_2Cl_2

SCHEME 48

spectrum of the bromide **180** contained an absorption at 3000 cm^{-1}, due to the olefinic C–H stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.32 ppm, due to the protons on C1, and a triplet (*J* 4.5 Hz) at δ 5.25 ppm, due to the olefinic protons.

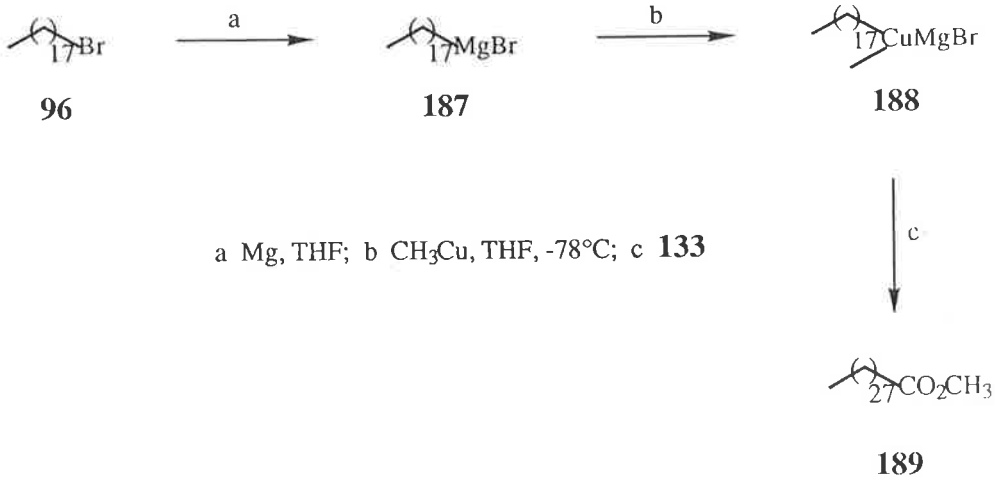
In an analogous way, the alcohol **181** was converted to the trienyl bromide **182** in a 92% isolated yield. The infrared spectrum of the bromide **182** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. A triplet (*J* 6.5 Hz) at δ 3.30 ppm, due to the protons on C1, and a multiplet at δ 5.26 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum.

The tetraenyl bromide **184** was produced in a 77% isolated yield, from the alcohol **183**, as by the method described for the bromides **175, 178, 180** and **182** above. The infrared spectrum of the bromide **184** contained an absorption at 3012 cm^{-1}, due to the olefinic C–H bond stretch, and a weak C–C double bond stretch absorption at 1650 cm^{-1}. A

triplet (*J* 6.5 Hz) at δ 3.39 ppm, due to the protons on C1, and a multiplet at δ 5.37 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum.
In a completely identical fashion, the hexaenyl bromide **186** was formed from the alcohol **185**, in a 77% yield after chromatography. A strong olefinic C–H bond stretch absorption at 3012 cm^{-1}, and an absorption at 1650 cm^{-1}, due to the C–C double bond stretch, were apparent in the infrared spectrum of the bromide **186**. The ^{1}H-NMR spectrum contained a triplet (*J* 6.5 Hz) at δ 3.33 ppm, due to the protons on C1, and a multiplet at δ 5.31 ppm, due to the olefinic protons.

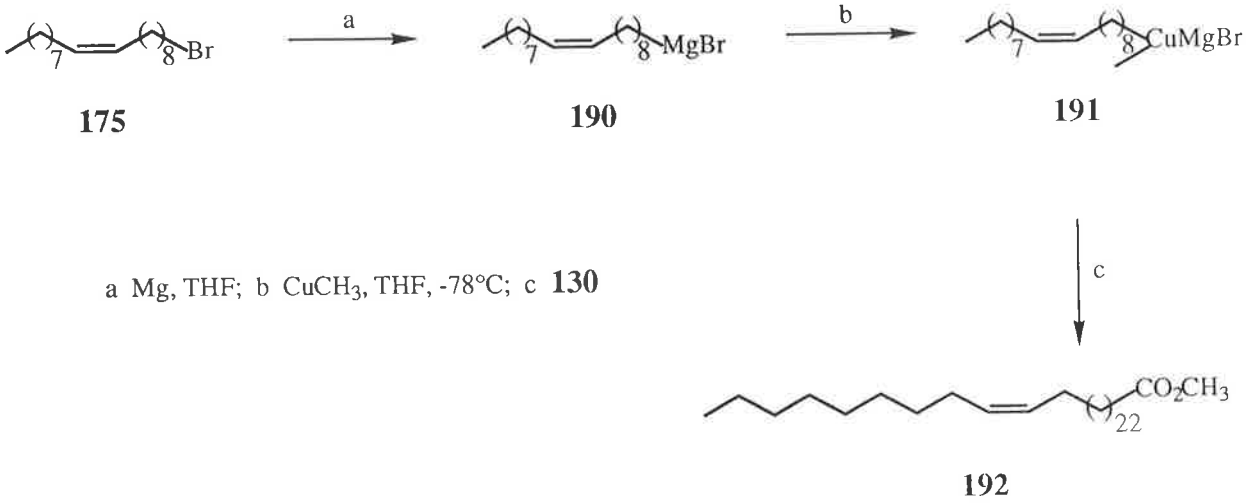
The alkenyl bromides **175, 178, 180, 182, 184,** and **186,** obtained as described above, contain the unsaturation that will be incorporated into the VLCFA, upon coupling with the appropriate ω-iodoesters. The bromides **175, 178, 180, 182, 184,** and **186** are of known regio- and stereo-chemistry about the double bonds and the cuprate coupling conditions were not expected to affect their integrity, therefore producing product esters of predetermined structure.

To investigate the suitability of the mixed dialkyl cuprate methodology for the synthesis of VLCFA esters, a trial was performed to generate methyl nonacosanoate (**189**), as shown in Scheme 49. Thus, the bromide **96** was metallated with magnesium in THF, and the Grignard derivative **187** so formed was added to an equimolar amount of preformed methylcopper(I) in THF at –78°C. After the mixture was briefly warmed to 0°C to ensure complete formation of the cuprate **188**, the ω-iodoester **133** was added and stirring was continued for one hour at –78°C, followed by two hours at room temperature. A standard work-up procedure was applied. Isolation of the ester **189** by flash chromatography on silica, followed by recrystallization from hexane, produced a 23% yield. The ester **189** had a melting point which agreed with the literature value,[140] and its spectral properties were as expected.



SCHEME 49

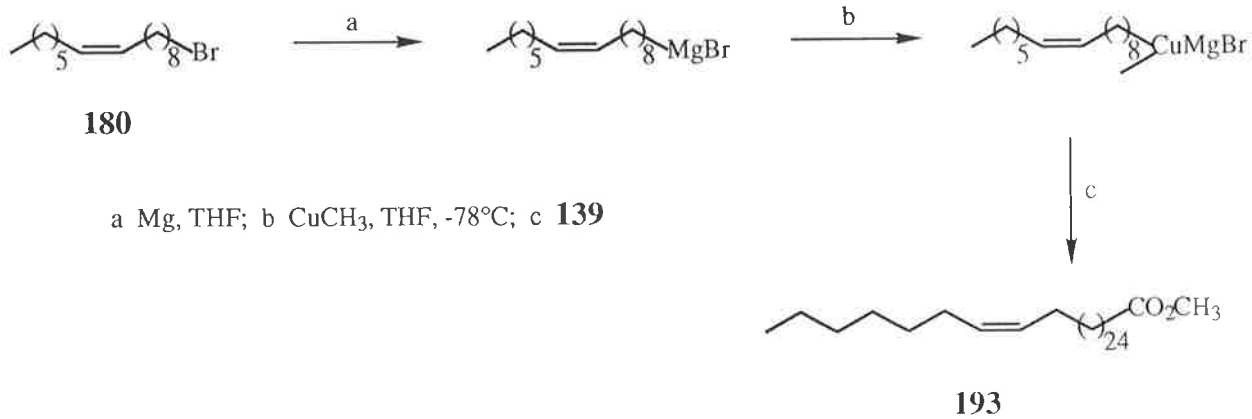
The formation of the ester **189**, though in modest yield, showed the validity of the mixed dialkyl cuprate method as a means of forming VLCFA esters. This method was then applied to the synthesis of the monoenoic ester **192,** by coupling the bromide **175** with the ω-iodoester **130** as shown in Scheme 50. The bromide **175** was treated with



SCHEME 50

magnesium in THF to form the Grignard derivative **190**. The Grignard derivative **190** was added to a suspension of preformed methylcopper(I), as previously described, to form the mixed dialkyl cuprate species **191**. Reaction of the cuprate species **191** with the ω-iodoester **130**, followed by a standard work-up procedure and purification by flash chromatography on silica, produced the desired VLCFA ester **192** in a 13% yield. The infrared spectrum of the ester **192** contained an absorption at 3004 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1742 cm^{-1}, due to the C–O double bond stretch, and a very weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a singlet at δ 3.67 ppm, due to the ester methyl group, and a triplet (*J* 4.6 Hz) at δ 5.35 ppm, due to the olefinic protons. The ^{13}C-NMR spectrum contained a peak at δ 27.19 ppm, due to the allylic carbons C24 and C27, a peak at δ 51.46 ppm, due to the ester methyl carbon, a peak at δ 129.88 ppm, due to the sp^2 carbons C25 and C26, and a small peak at δ 174.39 ppm, due to the sp^2 carbon C1.

To test the generality of the cuprate coupling method, a mono-unsaturated VLCFA ester of a different series was formed by coupling the bromide **180** with the ω-iodoester **139**, as shown in Scheme 51. Therefore, using identical conditions as described for the



180

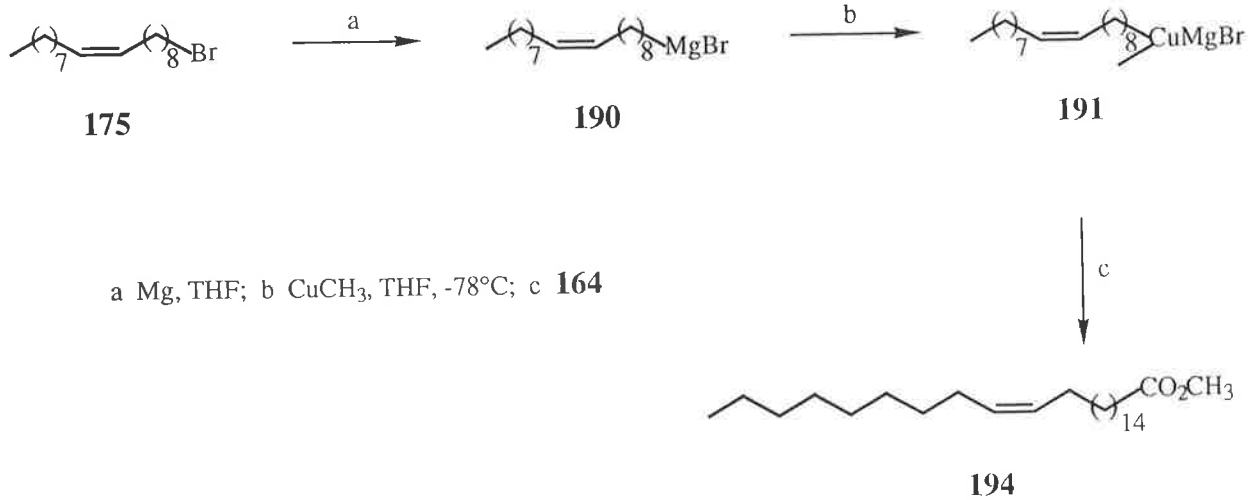
a Mg, THF; b $CuCH_3$, THF, -78°C; c **139**

193

SCHEME 51

formation of the VLCFA ester **192**, the monoenoic ester **193** was synthesized in a 10% yield, after purification by flash chromatography on silica. The infrared spectrum of the ester **193** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1742 cm^{-1}, due to the C–O double bond stretch, and a very weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a singlet at δ 3.66 ppm, due to the ester methyl group, and a triplet (*J* 4.7 Hz) at δ 5.35 ppm, due to the olefinic protons. The ^{13}C-NMR spectrum contained a peak at δ 27.21 ppm, due to the allylic carbons C26 and C29, a peak at δ 51.40 ppm, due to the ester methyl carbon, a peak at δ 129.88 ppm, due to the sp^2 carbons C27 and C28, and a small peak at δ 174.32 ppm, due to the sp^2 carbon C1.

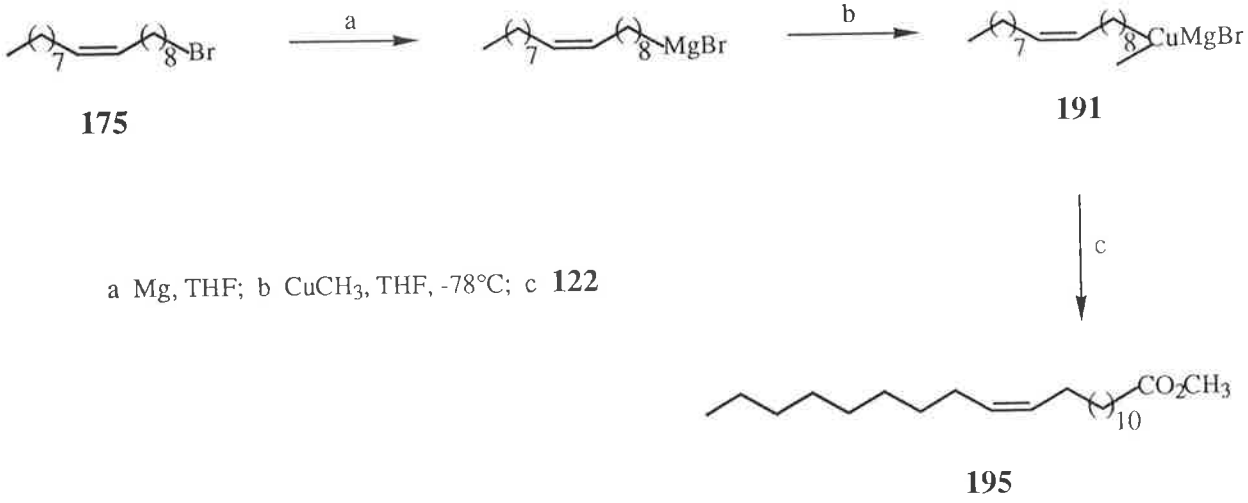
Another monoenoic ester successfully synthesized by the mixed dialkyl cuprate method, as shown in Scheme 52, was the ester **194**. The cuprate species **191**, formed by the addition of the Grignard derivative **190** to a suspension of methylcopper(I) in THF, was treated with the ω-iodoester **164** under the same conditions as described for the synthesis of **192** and **193**. In this way, a 14% yield of the ester **194** was obtained, after



SCHEME 52

isolation by flash chromatography on silica. The infrared spectrum of the ester **194** contained an absorption at 3004 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1744 cm^{-1}, due to the C–O double bond stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. A singlet at δ 3.67 ppm, due to the ester methyl group, and a triplet (*J* 4.7 Hz) at δ 5.35 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum contained a peak at δ 27.17 ppm, due to the allylic carbons C16 and C19, a peak at δ 51.38 ppm, due to the ester methyl carbon, a peak at δ 129.83 ppm, due to the sp^2 carbons C17 and C18, and a small peak at δ 174.29 ppm, due to the sp^2 carbon C1.

A slightly shorter chain monoenoic ester, methyl erucate (**195**), was also synthesized, as shown in Scheme 53. The monoenoic ester **195** is the methyl ester derivative of

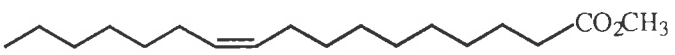


SCHEME 53

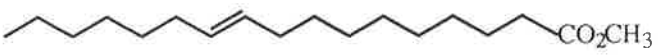
'Lorenzo's oil', which has been shown to stabilize patients mildly affected by the peroxisomal disorder X-linked ALD[59], when added to their diet. The same method, as applied in the synthesis of the esters just discussed, was applied to couple the bromide **175**, *via* the cuprate species **191**, to the ω-iodoester **122**. The ester **195** was formed in an 18% yield,

after purification by flash chromatography. The infrared spectrum of the ester **195** contained an absorption at 3004 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1744 cm^{-1}, due to the C–O double bond stretch, and a very weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a singlet at δ 3.67 ppm, due to the ester methyl group, and a triplet (*J* 4.6 Hz) at δ 5.35 ppm, due to the olefinic protons. A peak at δ 27.186 ppm, due to the allylic carbons C12 and C15, a peak at δ 51.421 ppm, due to the ester methyl carbon, a peak at δ 129.865 ppm, due to the sp^2 carbons C13 and C14, and a small peak at δ 174.348 ppm, due to the sp^2 carbon C1, were present in the ^{13}C-NMR spectrum. The ^{13}C-NMR spectrum of the ester **195** compared well with that of a literature report.[124]

An important aspect in this study of the synthesis of VLCFA was to maintain the all-*cis* geometry of the double bonds. The isomeric purity of monoenoic esters in general can be determined quite easily from the ^{13}C-NMR spectra. The signal for an allylic carbon atom has been reported[125] to fall in the range δ 27.22 – 27.39 ppm for a *cis* double bond, and in the range δ 32.64 – 32.69 ppm for a *trans* double bond. These assignments were confirmed further by the comparison of the ^{13}C-NMR spectra of commercial samples of methyl *cis*-10-heptadecenoate (**196**) and methyl *trans*-10-heptadecenoate (**197**). The ^{13}C-NMR spectrum of the ester **196** contained peaks at δ 27.14 and



196



197

27.17 ppm, corresponding to the allylic carbons C9 and C12 adjacent to the *cis* double bond, while the ^{13}C-NMR spectrum of the ester **197** contained a peak at δ 32.57 ppm,

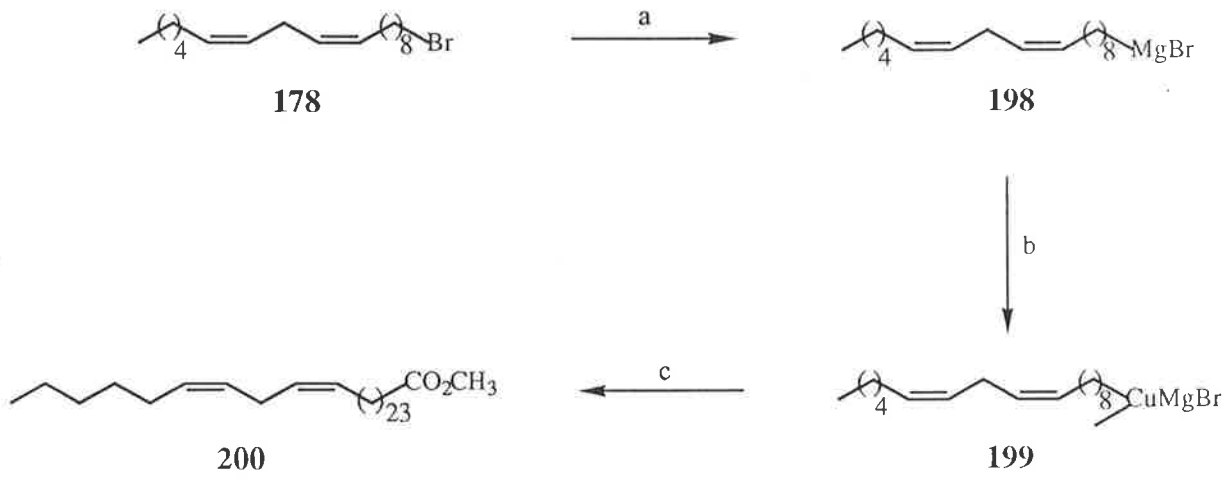
due to the carbons C9 and C12 adjacent to the *trans* double bond. This trend is in general agreement with that reported.[125] The ^{13}C-NMR spectra of the monoenoic esters **192, 193, 194** and **195**, synthesized in this study, contained peaks at δ 27.19, 27.19, 27.17 and 27.19 ppm, respectively, and no discernable peaks were observed in the region corresponding to an allylic carbon of a *trans* double bond. There was no evidence for isomerization of the *cis* double bond occurring during the formation of the esters **192, 193, 194** and **195**.

The reactions discussed above to form the esters **192, 193, 194** and **195** have shown that monoenoic VLCFA esters can be effectively synthesized using the cuprate methodology. Studies of these monoenoic esters by ^{13}C-NMR spectroscopy have revealed that no detectable isomerization of the double bond takes place under the reaction conditions used.

In the above reactions to give the esters **189, 192, 193, 194** and **195**, methyl transfer to the iodoesters **122, 130, 133, 139**, and **164** was always observed to be a significant competing reaction. The reactions also afforded products of reduction and dimerization of the alkyl halides **96, 175**, and **180**. For example, methyl heptadecanoate, methyl nonadecanoate and methyl nonanoate were isolated from the reactions to form the esters **192, 193** and **194**, respectively. The esters were identified by ^{1}H-NMR spectroscopy and mass spectrometry. Methylation of the ω-iodoesters **122, 130, 133, 139** and **164**, can be attributed to methyl transfer from the corresponding cuprate species, or to methylation of the ω-iodoesters **122, 130, 133, 139** and **164** by residual methylcopper(I).[131,132] As a particular example, methyl nonanoate was isolated in a 58% yield from the reaction to form the ester **194**. Also isolated from this reaction was the reduced alkyl halide 9-octadecene and a small amount of the dimerized alkyl halide, 9,27-hexatriacontadiene, as identified by ^{1}H-NMR spectroscopy and mass spectrometry. In another case, methyl heptadecanoate was isolated in a 43% yield from the reaction to form **192**, along with the reduced alkyl halide,9-octadecene,

and a small amount of the dimerized alkyl halide, 9,27-hexa-triacontadiene. In all the reactions described above, the unreacted ω-iodoesters **122**, **130**, **133**, **139** and **164** were recovered.

Having established that the cuprate coupling methodology can effectively produce monoenoic VLCFA esters isomerically pure, the methodology was then extended to the formation of VLCFA esters containing multiple unsaturation. To this end, the dienyl bromide **178** was coupled with the ω-iodoester **130**, as shown in Scheme 54. The



178 **198** **200** **199**

a Mg, THF; b CH_3Cu, THF, -78°C; c **130**

SCHEME 54

cuprate species **199**, formed in the usual way by addition of the Grignard derivative **198** to a THF suspension of methylcopper(I) at –78°C, was treated with the ω-iodoester **130** and allowed to stir for one hour at –78°C and two hours at room temperature. After a standard work-up procedure, the crude reaction mixture was purified by flash chromatography on silica to reveal a 22% yield of the dienoic ester **200**. The infrared spectrum of the ester **200** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1742 cm^{-1}, due to the C–O double bond stretch,

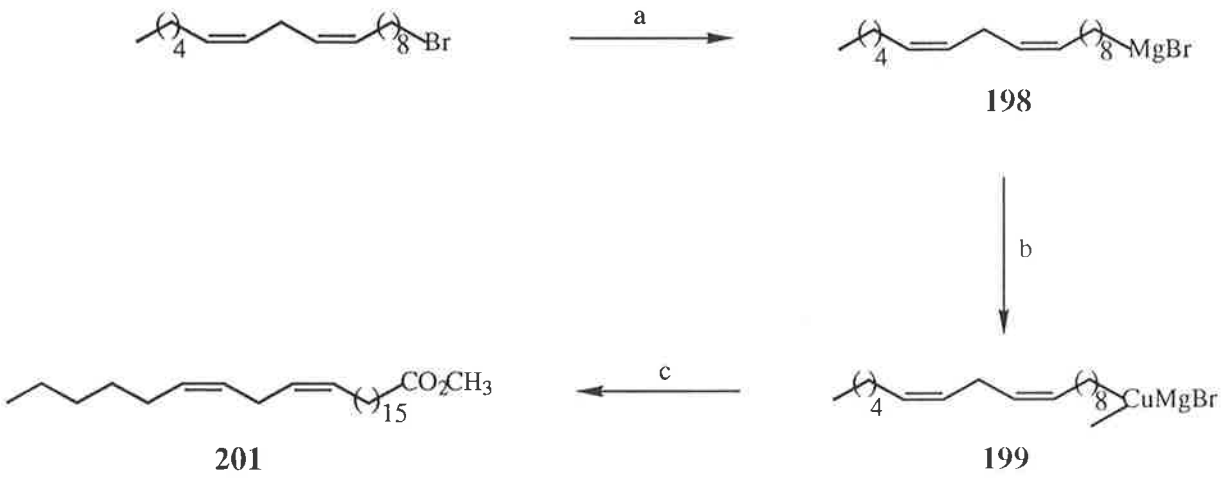
and a very weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. A triplet (*J* 5.9 Hz) at δ 2.77 ppm, due to the protons on C27, a singlet at δ 3.66 ppm, due to the ester methyl group, and a multiplet at δ 5.35 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum contained a peak at δ 25.61 ppm, due to the doubly allylic carbon C27, a peak at δ 27.22 ppm, due to the allylic carbons C24 and C30, a peak at δ 51.36 ppm, due to the ester methyl carbon, peaks at δ 127.92 and 130.13 ppm, due to the sp^2 carbons C26, C28 and C25, C29 respectively, and a peak at δ 174.25 ppm due to the sp^2 carbon C1.

The peak at δ 25.61 ppm in the ^{13}C-NMR spectrum of the ester **200** is as expected for a carbon adjacent to two *cis* double bonds.[125] No peak was observed at approximately δ 35.7 ppm, corresponding to a carbon adjacent to two *trans* double bonds,[125] and no peak could be detected at approximately δ 30.6 ppm, corresponding to a carbon adjacent to both a *cis* double bond and a *trans* double bond.[125] Any conjugation of the double bonds under the reaction conditions would be expected to produce significant changes in the ^{13}C-NMR spectrum. No such changes were observed. This indicated that, within the limits of detection using ^{13}C-NMR spectroscopy, no isomerization or conjugation of the double bonds had occurred during formation of the dienoic ester **200**.

A significant amount of the ester methyl heptadecanoate, due to methylation of the ω-iodoester **130**, was also isolated from the reaction mixture, as well as a small amount of unreacted ω-iodoester **130**. In addition, the reduced dienyl halide 6,9-octadecadiene was isolated with a small amount of the dimerized dienyl halide, 6,9,27,30-hexatriacontatetraene, as identified by ^{1}H-NMR spectroscopy and mass spectrometry.

Another dienoic ester that was synthesized was the shorter chain ester **201**, as shown in Scheme 55. The cuprate species **199** was generated in the usual way from methylcopper(I) and the Grignard reagent **198**, and treated with the ω-iodoester **164**.

After a standard work-up procedure, the crude reaction mixture was purified by chromatography on silica. Analysis of the product ester component, which was homogenous by TLC on silica, by ^{1}H-NMR spectroscopy indicated that the ester **201**



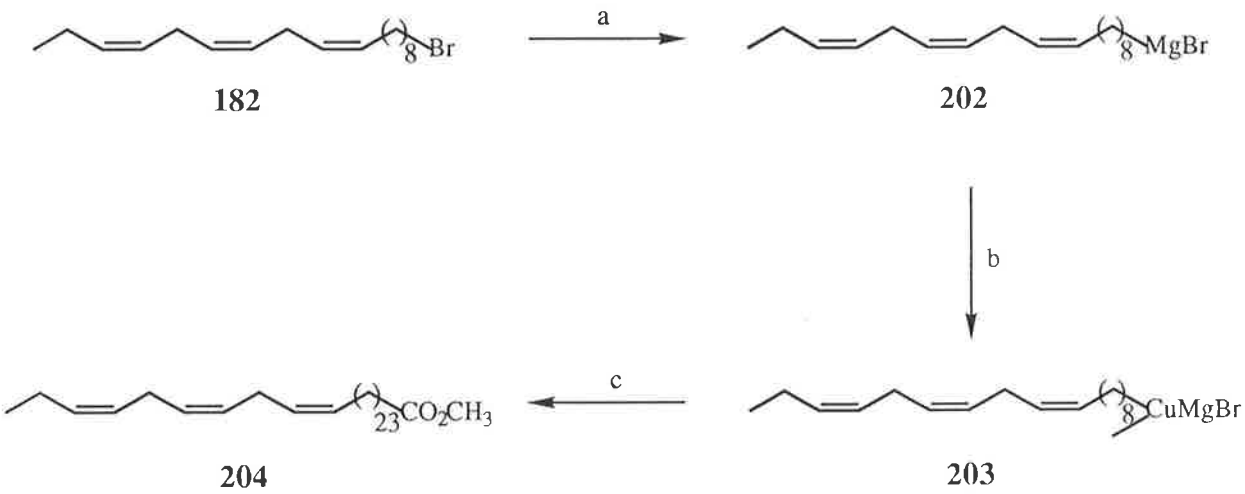
a Mg, THF; b CH_3Cu, THF, -78°C; c **164**

SCHEME 55

had formed, but was contaminated with a substantial amount of the byproduct ester, methyl nonanoate. The ^{1}H-NMR spectrum contained a multiplet at δ 5.36 ppm, due to the olefinic protons of the ester **201**, and a singlet at δ 3.67 ppm, due to an ester methyl group. The ratio of the integrations of the multiplet to the singlet was approximately 7 : 10, rather than the expected 4 : 3. The presence of methyl nonanoate was confirmed by mass spectrometry. Attempts to separate the ester **201** from methyl nonanoate by chromatography on silver nitrate impregnated silica[126] proved ineffective, as substantial decomposition of the ester **201** was observed.

The VLCFA trienoic ester **204** was formed by the cuprate coupling of the bromide **182** to the ω-iodoester **130**, as shown in Scheme 56. The trienyl bromide **182** was metallated

with magnesium in THF and the resultant Grignard reagent **202** was added to a suspension of methylcopper(I) in THF at –78°C. Warming of the mixture to 0°C ensured complete formation of the cuprate species **203**, which was immediately



182 **202** **204** **203**

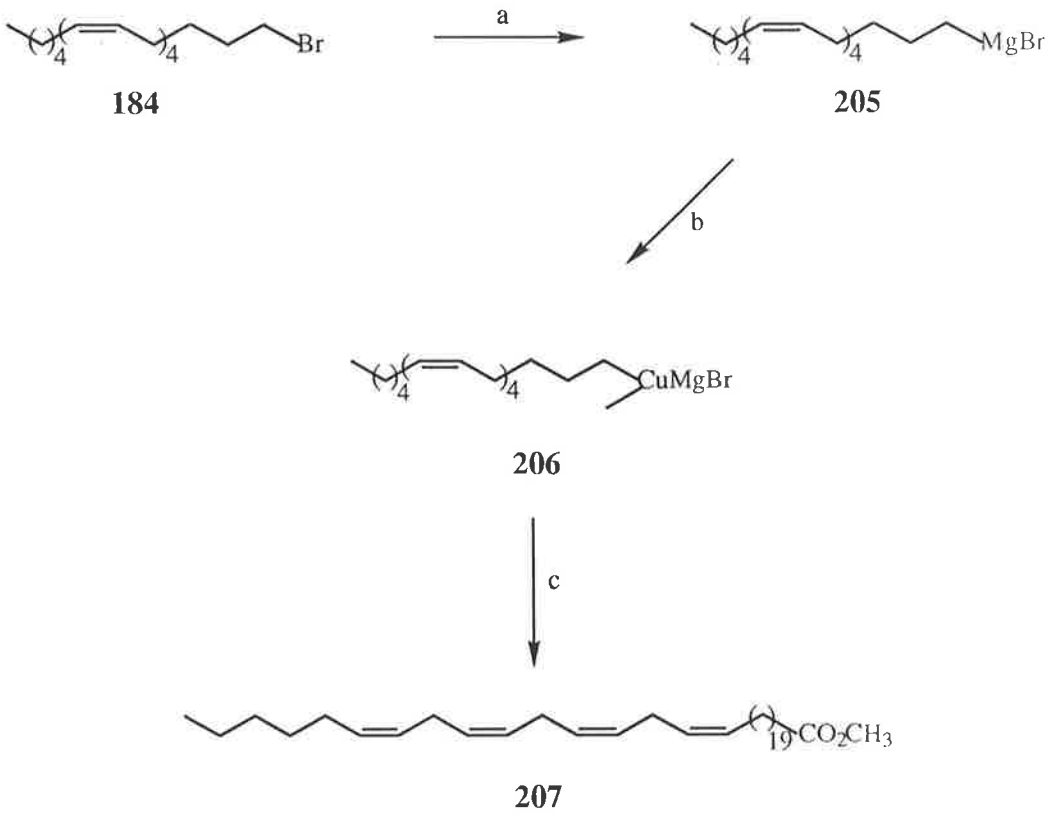
a Mg, THF; b CH_3Cu, THF, -78°C; c **130**

SCHEME 56

recooled to –78°C and reacted with the ω-iodoester **130**. A standard work-up procedure was followed by purification of the crude material by chromatography on silica. The ^{1}H-NMR spectrum of the product ester component, homogenous by TLC on silica, contained a singlet at δ3.68 ppm, due to the ester methyl group, and a multiplet at δ 5.38 ppm, due to the olefinic protons of the ester **204**. The integration of the singlet and the multiplet was in the ratio of 6 : 7 respectively, rather than the expected ratio of 2 : 1. This indicated that a substantial amount of methyl heptadecanoate, formed by methylation of the ω-iodoester **130**, was present with the ester **204**. Again, attempts to separate the ester **204** from methyl heptadecanoate by chromatography on silver nitrate impregnated silica[126] proved ineffective, due to substantial decomposition of the ester **204** during the purification process. A hydrocarbon component was also isolated from

the crude reaction mixture and was shown to consist mainly of the reduced trienyl halide 3,6,9-octadecatriene, with a small amount of the dimerized halide, 3,6,9,27,30,33-hexatriacontahexene, also present. Unreacted ω-iodoester **130** was recovered.

The mixed dialkyl cuprate methodology was also applied to the coupling of the tetraenyl bromide **184** with the ω-iodoester **130,** in an attempt to form the tetraenoate ester **207,** as shown in Scheme 57. The bromide **184** was metallated with magnesium in



a Mg, THF; b CH_3Cu, THF, -78°C; c **130**

SCHEME 57

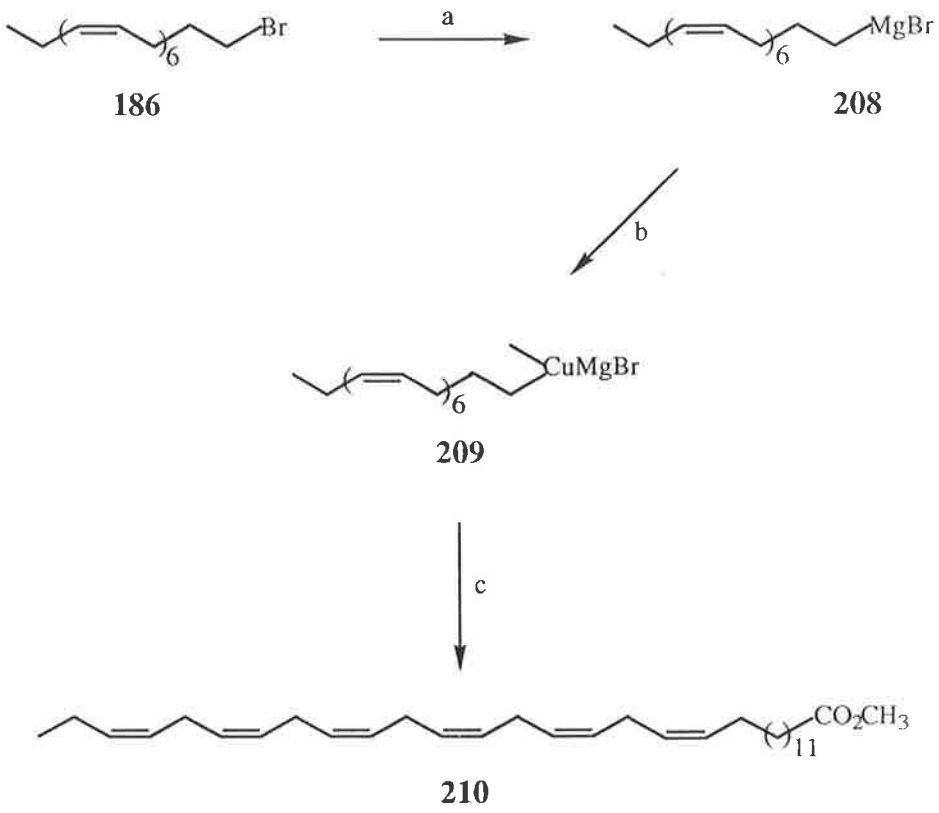
THF and the resulting Grignard reagent **205** was added to a suspension of methylcopper(I) in THF at –78°C. After stirring the mixture at this temperature for one

hour, it was allowed to warm to 0°C in an attempt to form the cuprate species **206**. No colour change from yellow / brown to a pale pink was observed, as expected on cuprate formation, so the reaction temperature was raised to 20°C. Still no colour change of the mixture was evident, but the mixture was cooled to 0°C and stirred for twenty five minutes, then cooled further to –78°C. The reaction mixture was treated with the ω-iodoester **130** and stirred for one hour at –78°C, followed by two hours at room temperature. The product mixture was purified by chromatography, after a standard work-up procedure had been applied. The only ester isolated was the unreacted starting material **130**. The identity of the recovered ester **130** was confirmed by comparison of its migratory properties by TLC on silica and the ^{1}H-NMR and mass spectra, with an authentic sample. The ^{1}H-NMR spectrum would be expected to contain a multiplet at δ 5.38 ppm, due to the olefinic protons of the ester **207**, had it formed. No such signal in the ^{1}H-NMR spectrum was observed. A hydrocarbon component was also isolated and consisted mainly of the reduced halide 5,8,11,14-eicosatetraene, with a small amount of the dimerized halide, 6,9,12,15,25,28,31,34-tetracontaoctene, present, as shown by ^{1}H-NMR spectroscopic and mass spectrometric analysis.

Repeated attempts at coupling the bromide **184** with the ω-iodoester **130** failed to produce any of the ester **207**. This may be attributed to the inability to form the mixed dialkyl cuprate **206**, due to its instability with the larger alkyl group, or possibly the tetraenyl Grignard derivative **205** adopts a folded geometry and therefore its reactivity towards cuprate formation is reduced.

The coupling of the hexaenyl bromide **186** with the ω-iodoester **126** was attempted, as shown in Scheme 58, with the aim of forming the ester **210**. The bromide **186** was metallated with magnesium in THF and the Grignard reagent **208** was added to a suspension of methylcopper(I), as described for the previous reactions. No colour change of the reaction suspension to indicate formation of the cuprate species **209** was

observed, even upon warming of the reaction mixture to 20°C. The solution was subsequently cooled to –78°C and treated with the ω-iodoester **126**. After a standard work-up procedure, the only ester component isolated was recovered ω-iodoester **126**, as identified by comparison of its chromatographic properties and spectral data with an



186 **208** **209** **210**

a Mg, THF; b CH_3Cu, THF, -78°C; c **126**

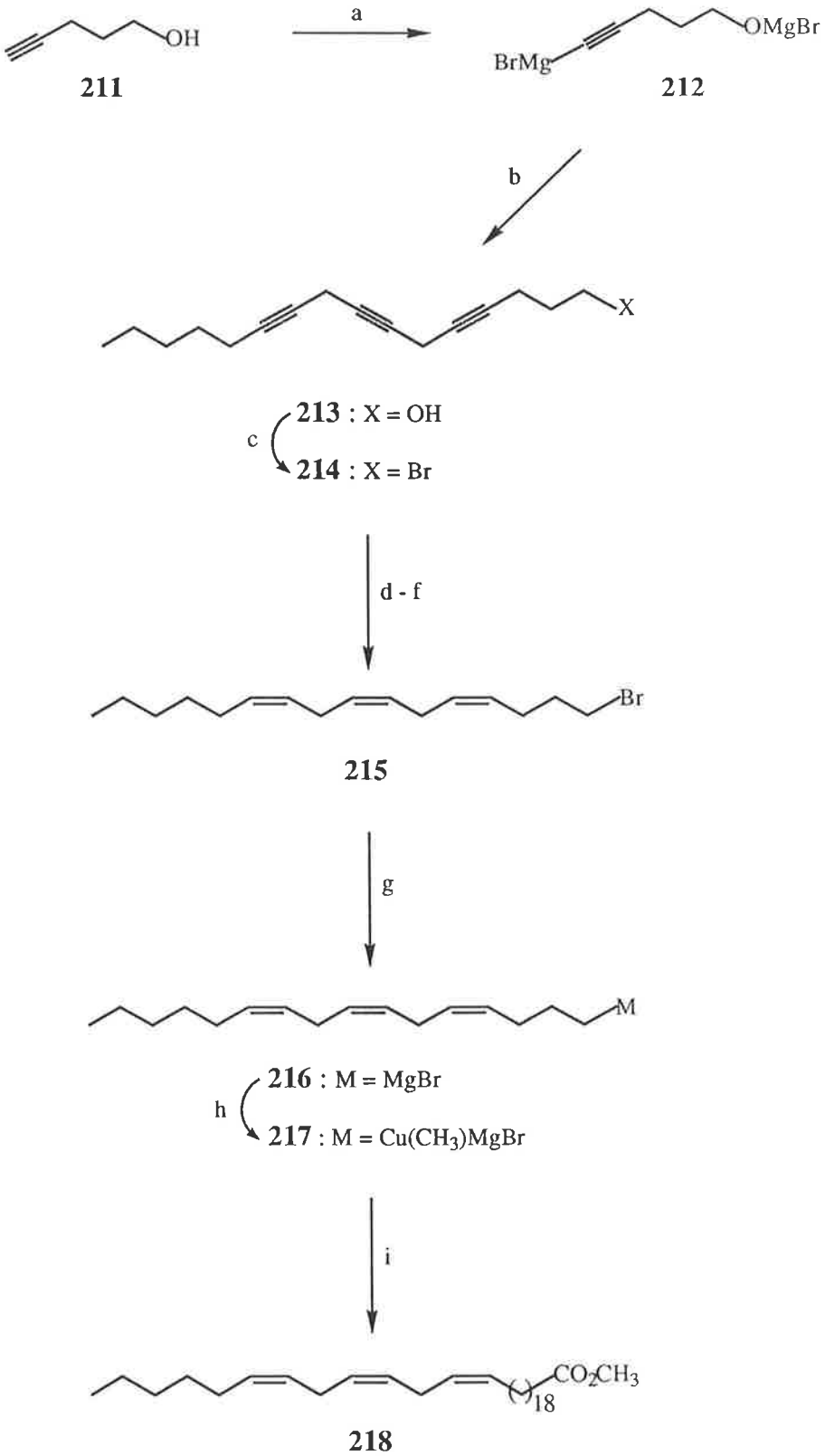
SCHEME 58

authentic sample. Also isolated were the reduced halide, 3,6,9,12,15,18-docosahexene, and a small amount of the dimerized halide, 3,6,9,12,15,18,26,,29,32,35,38,41-tetratetracontadodecene, identified by ^{1}H-NMR spectroscopy and mass spectrometry.

Application of the cuprate methodology to the formation of polyunsaturated esters resulted in the successful formation of the dienoic esters **200** and **201**, and the trienoic ester **204**. A limitation to this methodology appears to be either the length of the alkyl halide used in the formation of the corresponding cuprate species, or the degree of unsaturation of this same halide as shown by the inability to form the esters **207** and **210**.

In all the procedures described above, an unsaturated bromide derived from a commerical source was coupled with an ω-iodoester. Only a limited number of unsaturated precursors of varying unsaturation and positional series can be purchased commercially. This restricts the generality of this method for the synthesis of VLCFA. To overcome this limitation, unsaturated bromides can be synthesized fairly readily from inexpensive materials. As an example of this, the VLCFA ester **218** was synthesized, as outlined in Scheme 59. Thus, the Grignard complex **212**, generated by the addition of the alkynol **211** to two equivalents of ethylmagnesium bromide in THF, was coupled with the diynyl bromide **32** under cuprous chloride catalysis, using the general method of Osbond *et at.*[67] as applied in Chapter 1. The crude material was purified by chromatography on silica followed by distillation, to provide a 43% yield of the triynyl alcohol **213**. The infrared spectrum of the alcohol **213** contained a broad absorption at 3440cm^{-1}, due to the O–H bond stretch, and a weak absorption at 2225 cm^{-1}, due to the C–C triple bond stretch. The ^{1}H-NMR spectrum contained a multiplet at δ 3.17 ppm, due to the protons on C6 and C9, and a triplet (*J* 6.5 Hz) at δ 3.77 ppm, due to the protons on C1.

Treatment of the alcohol **213** with triphenylphosphine and carbon tetrabromide in dichloromethane produced the triynyl bromide **214** in a 76% yield, after purification by chromatography. The infrared spectrum of the bromide **214** contained a weak absorption at 2225 cm^{-1}, due to the C–C triple bond stretch, and an absorption at 670 cm^{-1}, due to the C–Br bond stretch. A multiplet at δ 3.07 ppm, due to the protons



a 2 EtMgBr, THF; b CuCl, **32**; c CBr_4, Ph_3P, CH_2Cl_2; d $(\bigcirc)_2BH$; e AcOH
f NaOH, HOOH, H_2O; g Mg, THF; h CH_3Cu, THF, -78°C; i **130**

SCHEME 59

on C6 and C9, and a triplet (*J* 6.5 Hz) at δ 3.47 ppm, due to the protons on C1, were observed in the ^{1}H-NMR spectrum.

The triynyl bromide **214** was partially reduced to the corresponding all-*cis* trienyl bromide **215**, by following the method described by Millar and Underhill.[139] The bromide **214** was added to a suspension of dicyclohexylborane, formed by the addition of two equivalents of cyclohexene to a THF solution of borane-dimethylsulfide complex, and after a four hour reaction period, glacial acetic acid was added and the solution allowed to stir overnight. The mixture was subjected to a basic oxidative work-up with aqueous sodium hydroxide and aqueous hydroperoxide, and the crude material obtained was purified by chromatography and distillation. In this way, the bromide **215** was obtained in a 56% yield. The infrared spectrum of the bromide **215** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. A triplet (*J* 6.5 Hz) at δ 3.35 ppm, due to the ~~olefinic~~ C-1 protons, was evident in the ^{1}H-NMR spectrum.

The coupling of the bromide **215** with the ω-iodoester **130** was achieved *via* the mixed dialkyl cuprate species **217**. The Grignard reagent **216**, formed in the usual way from the bromide **215**, was added to methylcopper(I) at –78°C and on warming of this mixture to 5°C, a colour change from yellow to very pale pink was observed, indicative of cuprate formation. The mixture was immediately cooled to –78°C and treated with the ω-iodoester **130**. A reaction time of one hour at –78°C and two hours at room temperature was followed by a standard work-up procedure and chromatography on silica. ^{1}H-NMR spectral analysis of the product ester component revealed a singlet at δ 3.64 ppm, due to an ester methyl group, and a multiplet at δ 5.33 ppm, due to olefinic protons, with integrations of the signals in the ratio of 2.8 : 1.0, respectively. The expected integration ratio of the methyl ester singlet to the olefinic proton multiplet of the ester **218** was 1 : 2 respectively. Therefore, this indicated a substantial amount of the saturated ester, methyl heptadecanoate, to be present. Mass spectral analysis of the

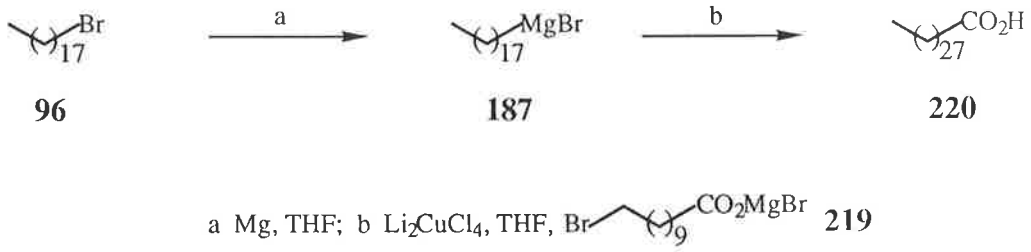
product ester component confirmed the presence of the ester **218** and a large amount of methyl heptadecanoate. Unreacted ω-iodoester **130** was also isolated from the reaction mixture, as well as a component consisting of the reduced halide 4, 7, 10-hexadecatriene with a small amount of the dimerized halide 6,9,12,20,23,26-dotriacontahexene, as shown by ^{1}H-NMR spectroscopy and mass spectrometry.

The successful synthesis of the trienoate ester **218** showed that VLCFA can be formed from synthetic alkenyl halides as well as those derived from commercial sources. This makes the synthesis of VLCFA completely general, subject to the limitations observed in the attempted couplings of **184** with **130** and **186** with **126**.

Formation of VLCFA by the mixed dialkyl cuprate method has generally been quite successful, as shown by the formation of the esters **189, 192, 193, 194, 195, 200, 201, 204** and **218**, as described above. In all the reactions to form these esters, methylation of the corresponding ω-iodoesters, due to methyl transfer from the cuprate species or methylation by residual methylcopper(I), arising due to incomplete cuprate formation, was observed. In most cases the product ester could be separated from the methylated material. Separation of the esters **201, 204** and **218** from the byproduct esters methyl undecanoate, methyl heptadecanoate and methyl heptadecanoate, respectively, was not achieved, highlighting the problem brought about by methylation. Therefore, the methylation of ω-iodoesters should preferably be avoided. It was noted in Chapter 2 that, in attempts to form the ω-unsaturated ester **137** on a sub-millimole scale, the methylated byproduct **154** greatly predominated, whereas on a larger scale, good yields of the ester **137** were obtained, with methylation of the ω-iodoester **133** occurring to a lesser extent. Bergbreiter and Whitesides[74] performed their coupling reactions on a twenty five to two hundred millimole scale and obtained good yields of the desired coupling products, with no mention of any methylated material being formed. In a report on the synthesis of meromycolic acid, Gensler *et al*[127] described the coupling of a long-chain ω-iodoester with a long-chain bromide, *via* the mixed dialkyl cuprate

method, to form methyl meromycolate. This reaction had been performed on a millimole scale and they obtained a modest yield (28%) of methyl meromycolate, with a substantial amount of methylated material being isolated.

As the scaling up of the reactions conducted in this work would be costly and methylation would probably still occur to some extent, making the purification of the esters **201, 204** and **218** difficult, an alternative method needed to be found. Mirviss[128] has recently reported the synthesis of ω-unsaturated acids based on the coupling method of Baer and Carney.[129] The ω-unsaturated acids were formed by the coupling of the Grignard derivatives of ω-unsaturated halides with the magnesium bromide salt of ω-bromoacids, in the presence of dilithium tetrachlorocuprate in THF. The method of Mirviss[128] was applied in this work in one attempt to form nonacosanoic acid (**220**) in a trial reaction, as shown in Scheme 60. The Grignard derivative **187**, formed from

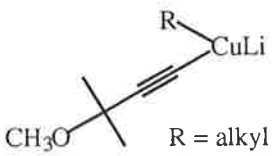


SCHEME 60

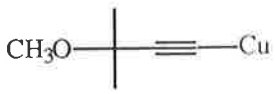
the bromide **96** and magnesium in THF, was added to the blue solution of the magnesium bromide salt **219** (formed by addition of one equivalent of ethylmagnesium bromide to 11-bromoundecanoic acid, in THF) containing a catalytic amount of dilithium tetrachlorocuprate.[130] The reaction mixture was stirred at –20°C for two hours and a further two hours at room temperature. After an acidic work-up and separation of the reaction components by chromatography, the acidic component was purified by further chromatography to reveal a 4% yield of the slightly impure acid **220**. Due to the poor yield, no further investigation of this method was conducted.

The methylation of the ω-iodoesters encountered in almost all of the reactions involving the mixed dialkyl cuprate species, was thought to be due to the insolubility of the cuprate complex and its precursor, methylcopper(I), in THF under reaction temperatures. This insolubility of the latter complex probably results in incomplete cuprate formation upon addition of a Grignard reagent, and the residual methylcopper(I) in the reaction mixture may cause methylation[131,132] of the ω-iodoester present. Methylation of the ω-iodoesters may also be due to methyl transfer from the cuprate species during the last stage of the reaction.

A mixed cuprate species was required which would be soluble in THF at low temperature and contain one strongly bound ligand, allowing selective transfer of the other ligand. These requirements are fulfilled by the cuprate species **221**, developed by Corey.[133,134] The cuprous acetylide **222** is easily generated and is totally soluble in THF at –78°C. Addition of an alkyllithium reagent to **222** produces the THF soluble

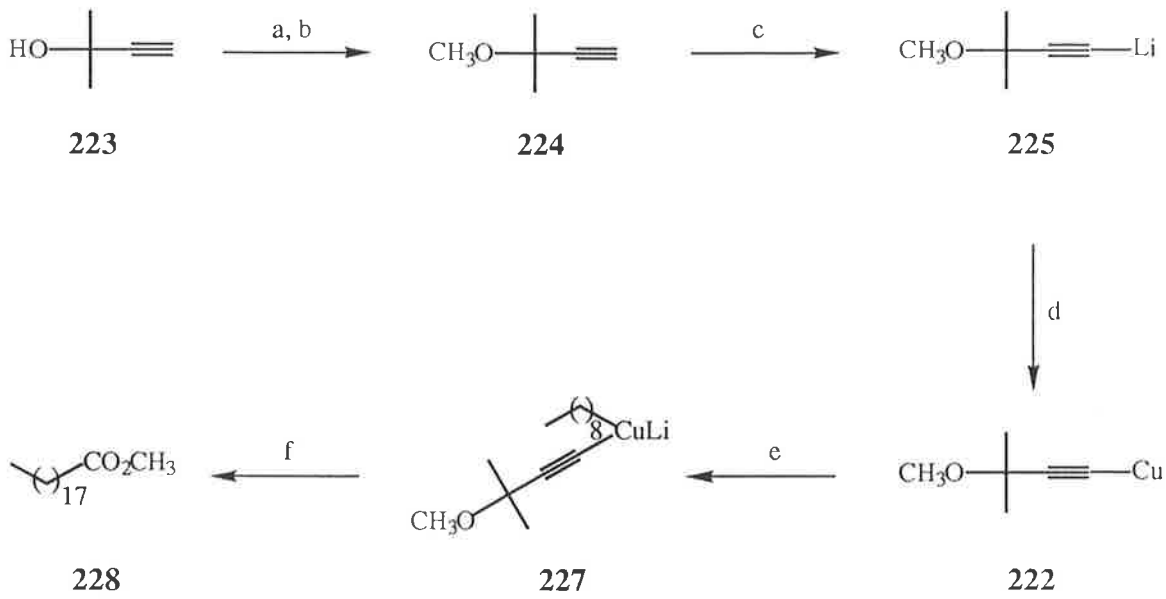


221



222

cuprate **221**. Alkynyl ligands are tightly bound to copper, allowing the selective transfer of the alkyl group from the cuprate species.[74,135,136] To investigate the viability of coupling an alkyl halide with an ω-iodoester *via* the cuprate species **221**, methyl nonadecanoate (**228**) was synthesized, as shown in Scheme 61. Thus, the acetylene **224**, easily prepared by the methylation of the commercial alcohol **223**,[134] was converted to the corresponding lithium salt **225** by the addition of one equivalent of *n*-butyllithium. Addition of cuprous iodide to the THF solution of **225** at 0°C produced a red-orange solution of **222**. The solution of the cuprous acetylide **222** was added to a

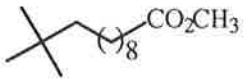


a NaH, DMF; b $(EtO)_2CO$; c ^nBuLi, THF; d CuI, 0°C; e **226**; f **126**

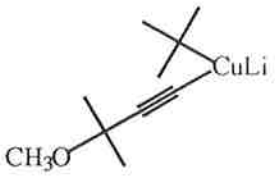
SCHEME 61

−78°C solution of nonyllithium **226** (formed by adding two equivalents of *t*-butyllithuim to a −78°C ether solution of nonyl iodide[137,138]) which reacted immediately to produce a pale yellow solution of the cuprate **227**. The ω-iodoester **126** was added to the reaction mixture and, after allowing the reaction mixture to warm to room temperature over four hours followed by stirring for a further two hours, a standard work-up procedure was applied. Analysis of the crude reaction mixture by TLC on silica revealed one major component, with the ω-iodoester **126** barely detectable and a very mobile faint component, probably hydrocarbon. The mixture was purified by chromatography. ^{1}H-NMR spectroscopic analysis of the main reaction component confirmed the presence of a methyl ester (singlet at δ 3.68 ppm) but a large singlet at δ 0.87 ppm indicated incorporation of a *t*-butyl group. Mass spectrometrical analysis confirmed that the ester **228** had formed (M^+ = 312 m/e) and an ion at M^+ = 242 m/e suggested the presence of the ester **229**. That is, residual *t*-butyllithium had combined with the cuprous acetylide **222** to form the cuprate species **230**, which then reacted with

the ω-iodoester **126** to form the ester **229**. When an excess of nonyl iodide was used, with respect to the *t*-butyllithium, and a longer reaction time was allowed for iodine-lithium exchange, the formation of the ester **229** was still observed. Since the



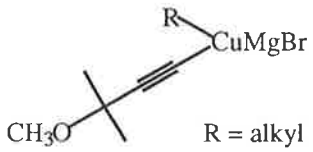
229



230

products formed due to alkylation of ω-iodoesters with the *t*-butyl group are expected to have similar chromatographic properties to the desired coupled products, no further use was made of this method, due to the predicted purification difficulties.

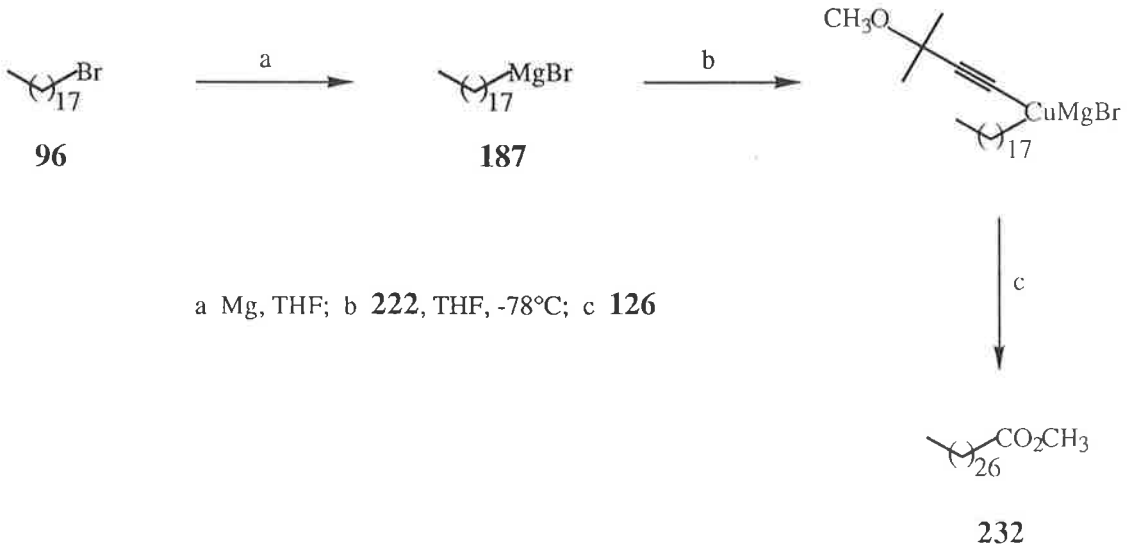
To avoid the complications caused by residual *t*-butyllithium from the incomplete iodine-lithium exchange of alkyl iodides, an alternative is to form the cuprate species **231** by addition of a Grignard reagent to the cuprous acetylide **222**. Bergbreiter and



231

Whitesides[74] had briefly investigated the utility of alkyl(alkynyl) cuprates in coupling reactions with alkyl halides and found them to be unsatisfactory. They did, however, obtain a moderate yield when an alkyl iodide was used as a substrate. This result was encouraging enough to prompt investigation in this work into the possible utility of this method for the formation of VLCFA.

Therefore, the synthesis of methyl octacosanoate (**232**) was attempted *via* the cuprate species **231**, as shown in Scheme 62. The commercial bromide **96** was metallated with magnesium in THF and the Grignard reagent **187** produced was added to a –78°C THF solution of the cuprous acetylide **222**, formed as previously described. The reaction mixture was warmed slowly to 10°C, during which a colour change from red-orange to yellow was observed. The mixture was recooled to –78°C and a THF solution of the ω-iodoester **126** was added. The reaction mixture was allowed to slowly warm to room

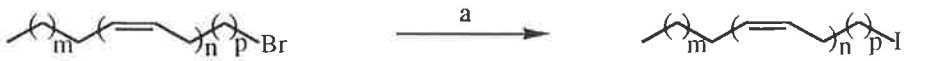


SCHEME 62

temperature and then stirred at this temperature for three hours. A standard work-up procedure was then applied. TLC analysis on silica of the crude reaction mixture revealed a very mobile component, probably hydrocarbon, and unreacted ω-iodoester **126**, as indicated by comparison to an authentic sample. No other component was evident. This result indicated that this method was unsuitable for the formation of VLCFA, and no further use was made of it.

The cuprate coupling reactions described in the following paragraphs require the lithiation of alkyl iodides as a preliminary step in the formation of the cuprate species.

The alkyl iodides required were formed by treatment of the corresponding alkyl bromides with sodium iodide in reluxing acetone, as shown in Scheme 63.Therefore, the bromide **178** was dissolved in acetone and treated with 2.5 equivalents of sodium



178 : m = 3, n = 2, p = 7
182 : m = 0, n = 3, p = 7

233 : m = 3, n = 2, p = 7
234 : m = 0, n = 3, p = 7

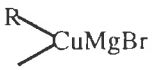
a NaI, acetone, reflux

SCHEME 63

iodide. After refluxing the solution overnight, the iodide **233** was isolated in a 78% yield, after chromatography. A sharp absorption at 3004cm^{-1}, due to the olefinic C–H bond stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch, were present in the infrared spectrum of the iodide **233**. The ^{1}H-NMR spectrum contained a triplet (J 6.5 Hz) at δ 3.12 ppm, due to the protons on C1, and a multiplet at δ 5.25 ppm, due to the olefinic protons.

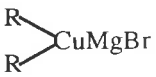
Similarly, treatment of the bromide **182** with sodium iodide in refluxing acetone, produced the iodide **234** in a 75% yield, after chromatography. The infrared spectrum of the iodide **234** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H bond stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. A triplet (J 6.5 Hz) at δ 3.12 ppm, due to the protons on C1, and a multiplet at δ 5.29 ppm, due to the olefinic protons, were present in the ^{1}H-NMR spectrum.

The unwanted methylation encountered in reactions involving the mixed cuprate species **235** could be avoided by forming the cuprate species **236** instead, where both



R = alkyl

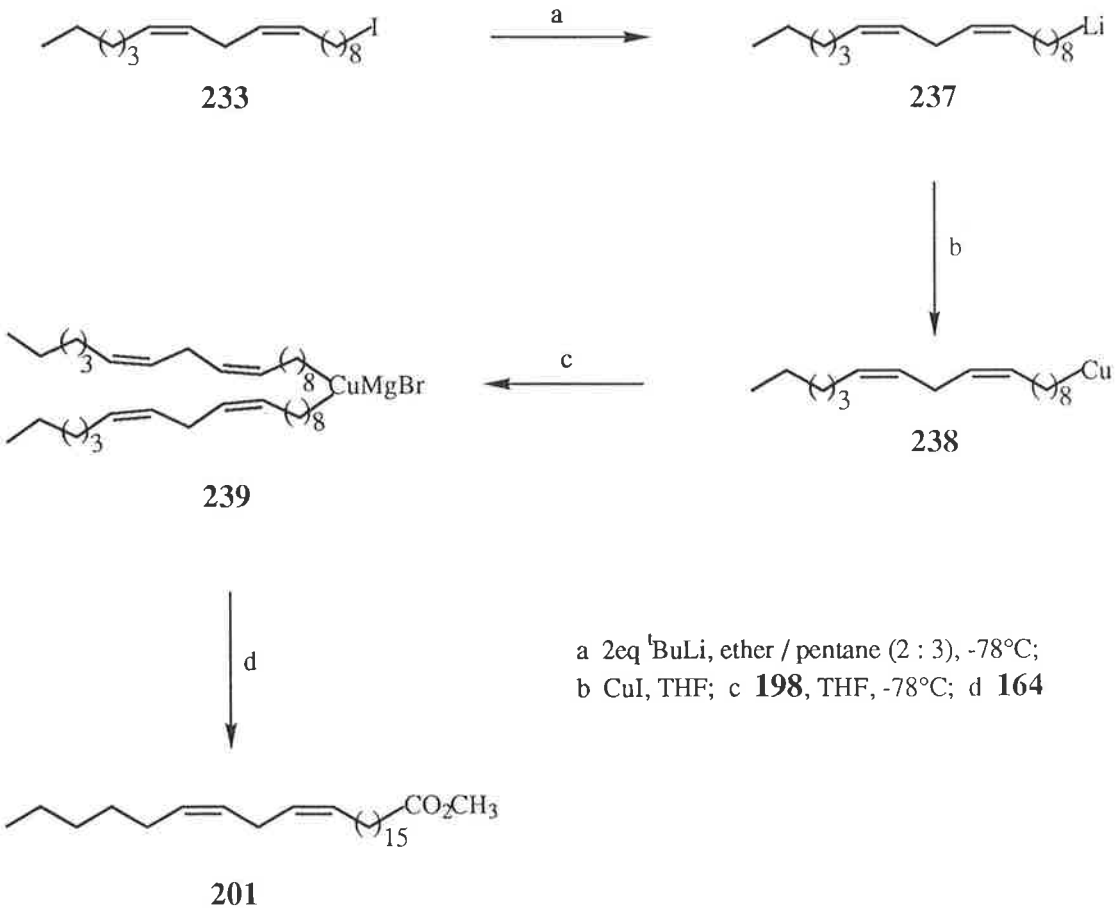
235



R = alkyl

236

alkyl ligands are the same. The dialkyl cuprate **236** lacks efficiency in reaction, as only one alkyl group is transferred while the other identical ligand is not utilized. However, reactions involving the cuprate **236** produced product esters without any purification problems, due to competing alkylation, demonstrated by the formation of the dienoic ester **201**, as outlined in Scheme 64. Thus, a THF solution of the dienyl iodide **233** was



233 **237** **238** **239** **201**

a 2eq ^{t}BuLi, ether / pentane (2 : 3), -78°C;
b CuI, THF; c **198**, THF, -78°C; d **164**

SCHEME 64

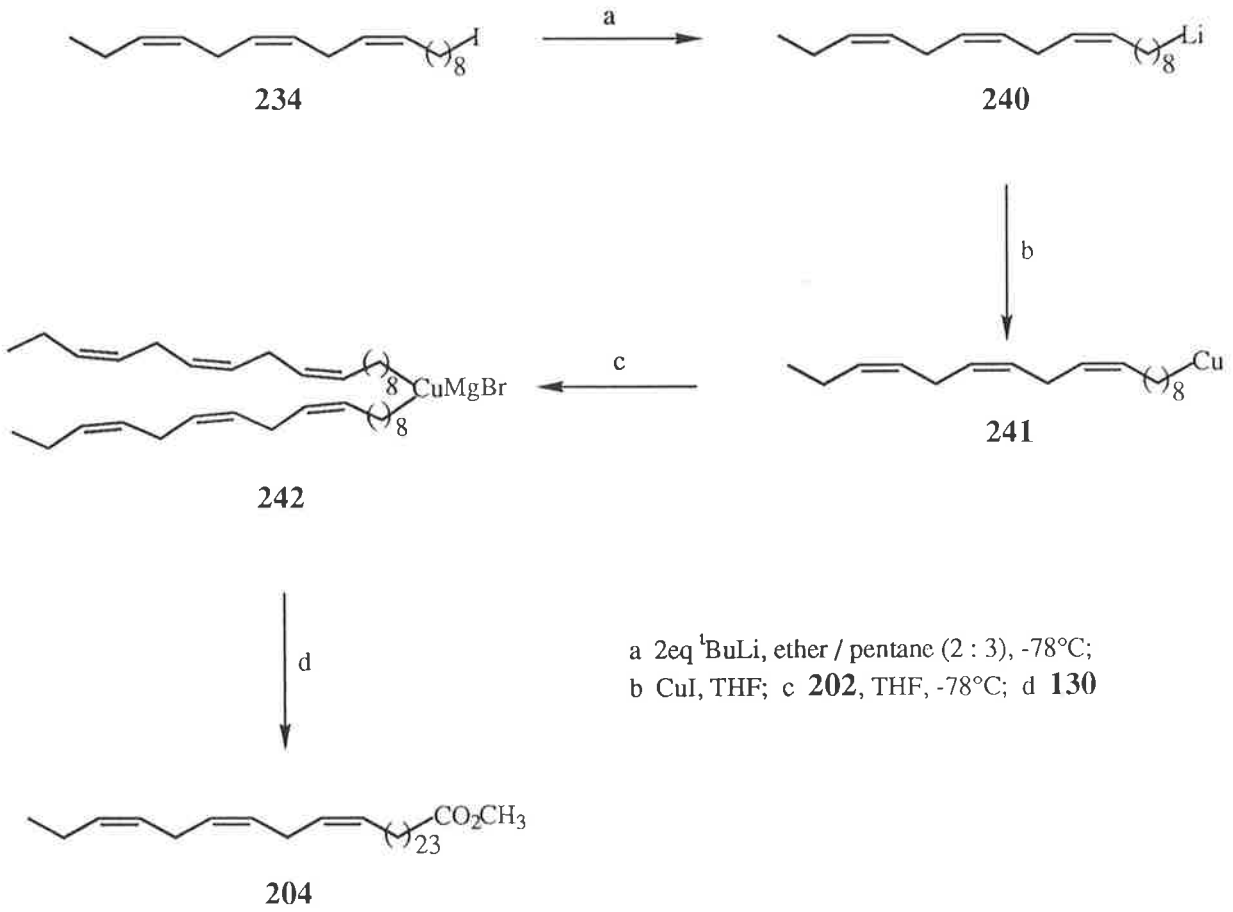
converted to the lithium reagent **237**, by treatment with two equivalents of *t*-butyllithium[137,138] at –78°C. Addition of one equivalent of cuprous iodide generated the black, solid alkylcopper(I) species **238**. The Grignard reagent **198**, generated by treating a THF solution of the bromide **178** with magnesium, was added to the alkylcopper(I) **238** at –78°C. Warming of the mixture to 0°C produced a black suspension of the dialkyl cuprate **239**, which was immediately recooled to –78°C. A THF solution of the ω-iodoester **164** was added to the cuprate **239** at –78°C, which was then allowed to warm to room temperature over three hours followed by stirring at this temperature for a further two hours. After a standard work-up procedure, the crude material was purified by chromatography, to reveal a 12% yield of the dienoic ester **201**. The infrared spectrum of the ester **201** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1742 cm^{-1}, due to the C–O double bond stretch, and a very weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. A singlet at δ 3.67 ppm, due to the ester methyl group, and a multiplet at δ 5.36 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum contained a peak at δ 25.60 ppm, due to the doubly allylic carbon C19, peaks at δ 27.18 and 27.22 ppm, due to the allylic carbons C16 and C22, a peak at δ 51.46 ppm, due to the ester methyl carbon, peaks at δ 127.90 and δ130.17 ppm, due to the sp^2 carbons C18, C20 and C17, C21, respectively, and a small peak at δ 174.38 ppm, due to the sp^2 carbon C1.

In the same way as discussed for the dienoic ester **200**, the peak at δ 25.60 ppm in the ^{13}C-NMR spectrum of the ester **201** had a typical chemical shift for a carbon adjacent to two *cis* double bonds. No peaks were observed to indicate isomerization or conjugation of the methylene-interrupted diene system

Other components isolated from the reaction mixture were unreacted ω-iodoester **164** and a substantial amount of hydrocarbon, shown to consist mainly of the reduced halide 6,9-octadecadiene with a small amount of the dimerized halide, 6,9,27,30-hexa-

triacontatetraene, also present, as shown by ^{1}H-NMR spectroscopy and mass spectrometry.

The same cuprate methodology, as used to form the ester **201**, was applied to the formation of the trienoate ester **204**, as shown in Scheme 65. The iodide **234** was



SCHEME 65

converted to the lithium reagent **240**, as described for the iodide **233**. Addition of cuprous iodide to this solution produced the alkylcopper(I) species **241**, as a black, insoluble solid. The Grignard reagent **202**, formed from the bromide **182** and magnesium in THF, was added to the mixture of **241** in THF at –78°C and after stirring at this temperature for one hour, the mixture was warmed to 0°C to form a black

suspension of the cuprate **242**. The suspension was immediately recooled to –78°C and a solution of the ω-iodoester **130** in THF was added. An identical reaction time as used in the synthesis of the ester **201** was applied in this case, followed by a standard work-up procedure. Purification of the crude reaction mixture revealed a 10% yield of the trienoic ester **204**. The infrared spectrum of the ester **204** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1742 cm^{-1}, due to the C–O double bond stretch, and a very weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a singlet at δ 3.67 ppm, due to the ester methyl group, a triplet (*J* 5.8 Hz) at δ 2.82 ppm, due to the protons on C27 and C30, and a multiplet at δ 5.37 ppm, due to the olefinic protons. Peaks at δ 25.52 and 25.60 ppm, due to the carbons C27 and C30, peaks at δ 20.55 and 27.25 ppm, due to the carbons C33 and C24, respectively, a peak at δ 51.40 ppm, due to the ester methyl carbon, peaks at δ 127.11, 127.60, 128.23, 128.29, 130.39 and 131.92 ppm, due to the sp^2 carbons C31, C26, C28, C29, C25 and C32, respectively, and a peak at δ 174.36 ppm, due to the sp^2 carbon C1, were observed in the ^{13}C-NMR spectrum.

The allylic carbon C24 of the trienoic ester **204**, gave a peak at δ 27.25 ppm in the ^{13}C-NMR spectrum, which is the expected value of a carbon adjacent to a *cis* double bond. The other allylic carbon of **204**, C33, produced a peak at δ 20.55 ppm, the signal appearing more downfield than that of C24, due to the influence of the methyl group, which usually extends to the ω4 carbon. The chemical shift value of C33 is consistent with values reported for fatty acids belonging to the n–3 series[125], to which **204** belongs. No peak was observed with a value corresponding to a carbon adjacent to a *trans* double bond. The peaks at δ 25.52 and 25.60 ppm are consistent chemical shift values for carbons allylic to two *cis* double bonds and no peaks were observed due to carbons allylic to two *trans* double bonds, or allylic to a *cis* and a *trans* double bond. The chemical shift values of the sp^2 carbons C25, C26, C28, C29, C31 and C32 of the ester **204** were very similar to fatty acids of the same series.[125] Therefore, within the

limits of detection by ^{13}C-NMR spectroscopy, the integrity of the all-*cis* triene system had been unaffected by the reaction conditions.

The results of this study have shown the mixed dialkyl cuprate method of coupling an alkenyl halide with an ω-iodoester to be a viable route to a range of VLCFA esters of varying length, series and unsaturation. For all the VLCFA esters formed, analysis by ^{13}C-NMR spectroscopy confirmed that no perturbation of the *cis* stereochemistry about the double bonds had occurred. A methylation byproduct was formed in all the reactions involving a mixed dialkyl cuprate species generated from methylcopper(I) and proved to be problematic in some cases. For example, the esters **201**, **204** and **218** were not separated from the corresponding saturated byproduct ester. The problem was successfully overcome by synthesizing the required ester *via* a dialkyl cuprate species, as demonstrated by the syntheses of the esters **201** and **204**.

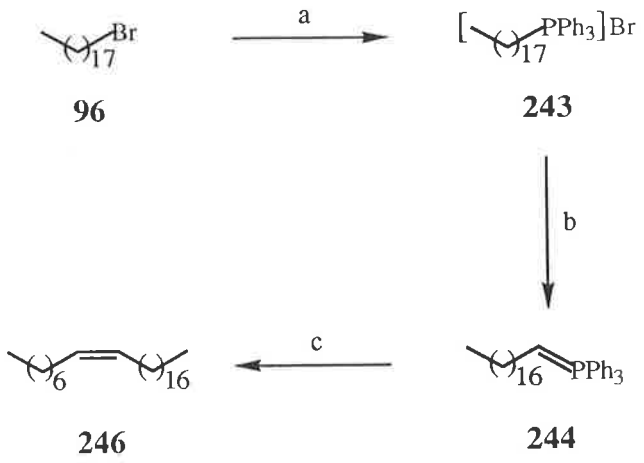
RESULTS AND DISCUSSION

CHAPTER 4

Synthesis of VLCFA *via* Wittig Methodology

The coupling of unsaturated halides with ω-iodoesters *via* a cuprate species has been shown in Chapter 3 to be a viable method of forming unsaturated VLCFA esters. An alternative method available to form unsaturated VLCFA esters is the Wittig method. The reaction of carbonyl compounds with alkylidene phosphoranes has been used quite commonly to synthesize fatty acids.[69,70,72,75,89,109,141] Particularly, the use of lithium hexamethyldisilazide (LiHMDS) in phosphorane formation, and low temperatures during the coupling process have been reported to produce *cis* double bonds with high isomeric purity.[70,72,141] In this study, the viability of the Wittig methodology was investigated towards the synthesis of unsaturated fatty acids, with direct comparisons to the cuprate methodology described in Chapter 3.

As an initial trial to establish the effectiveness of the Wittig reaction in the formation of isomerically pure *cis* double bonds, octanal (**245**) was coupled with the phosphonium salt **243** to produce 8-hexacosene (**246**), as shown in Scheme 66. Thus, the commercially available bromide **96** was treated with triphenylphosphine in acetonitrile, to produce the phosphonium salt **243** in a 54% yield, after recrystallization. The melting point of the salt **243** agreed with a literature report.[142] The Wittig procedure used to couple **243** with **245**, and all subsequent Wittig reactions performed in this work, were based on the procedure described by Prakash et al.[70] Accordingly, a suspension of the phosphonium salt **243** in THF containing 20% hexamethylphosphoramide (HMPA) was treated with a THF solution of LiHMDS (formed by the addition of one equivalent of *n*-butyllithium to hexamethyldisilazane in THF) at 0°C to produce an orange solution of



a PPh_3, CH_3CN, reflux 36h; b LiHMDS, THF / HMPA (4 : 1);
c $CH_3(CH_2)_6CHO$ **245**

SCHEME 66

the ylid **244**. Octanal (**245**) was added to the mixture at –78°C followed by stirring at 0°C for one hour. A mildly acidic workup was followed by purification of the reaction material by chromatography, to give an 82% yield of the alkene **246**. The infrared spectrum of **246** contained a weak absorption at 3004 cm^{-1}, due to the olefinic C–H bond stretch. The C–C double bond stretch absorption was not visible. The ^{1}H-NMR spectrum contained a multiplet at δ 2.01 ppm, due to the protons on C7 and C10, and a triplet (*J* 4.7 Hz) at δ 5.34 ppm, due to the olefinic protons. A peak at δ 27.21 ppm, due to the carbons C7 and C10, and a peak at δ 129.87 ppm, due to the sp^2 carbons C8 and C9, were observed in the ^{13}C-NMR spectrum.

The isomeric purity of the alkene **246** was determined in the same way as described for the monoenoic esters in Chapter 3. A direct comparison of the chemical shifts of the peaks due to the allylic and olefinic carbons of the alkene **246** with reported suitable monoenoic esters determined the isomeric purity of the former compound. The chemical shifts of the allylic and olefinic carbons of monoenoic esters, where the double

bond is separated from the ester functionality by several carbons, are essentially the same in the ^{13}C-NMR spectrum, as for a monoene hydrocarbon. Therefore, the peak at δ 27.21 ppm, due to the allylic carbons C7 and C10, confirmed the *cis* stereochemistry of **246**. No peaks were observed between δ 32.64 and 32.69 ppm to indicate the presence of the *trans* isomer. The peak at δ 129.87 ppm in the ^{13}C-NMR spectrum of **246** is typical for olefinic carbons of a *cis* double bond, the signal for *trans* olefinic carbons generally appearing slightly more downfield. This implied that the Wittig reaction to form the alkene **246** went with complete *cis* selectivity.

To form the unsaturated esters described in the rest of this Chapter, the oxoesters **166**, **167** and **171**, obtained as described in Chapter 2, and the phosphonium salts **243**, 1-nonyltriphenylphosphonium bromide (**248**) and 1-(*cis*-3-nonenyl)triphenyl-phosphonium bromide (**251**), were utilized. The synthesis of the phosphonium salt **243** has already been described. The phosphonium salt **248** was formed, as outlined in Scheme 67, by heating a solution of 1-bromononane (**247**) and triphenylphosphine in

247 **248**

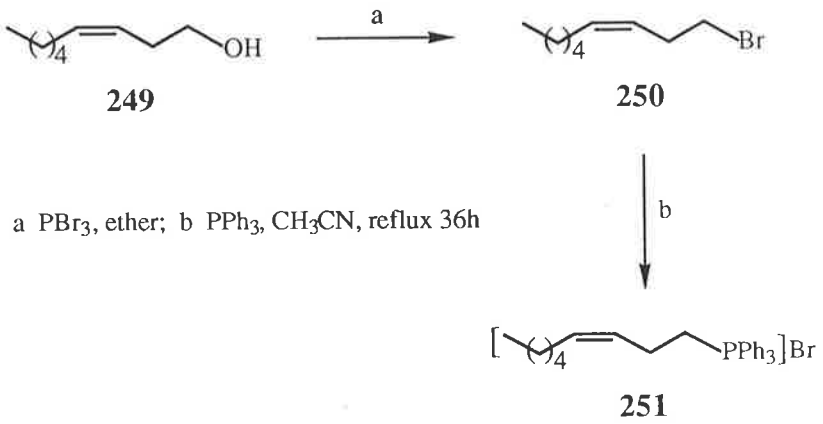
a PPh_3, CH_3CN, reflux 36h

SCHEME 67

acetonitrile at reflux for thirty six hours. Removal of the solvent under reduced pressure left a gummy material, which was triturated with ether and then placed under a high vacuum for six hours. In this way, the salt **248** was formed in a 96% yield as a clear, colourless glass, which was found to be moisture sensitive, as exposure to the air caused the salt **248** to change from a glass to a gummy material. For this reason, the phosphonium salt **248** was stored under nitrogen as a solution in dimethyl formamide (DMF). HMPA would have been preferred as the solvent, as it was required in the

Wittig reaction, but the salt **248** dissolved very slowly in HMPA to form a thick solution which was difficult to transfer by syringe. DMF was chosen above other solvents, as previous reports have used DMF as a solvent in Wittig reactions to give high *cis* selectivity.[75]

The phosphonium salt **251** was formed as shown in Scheme 68. The commercially

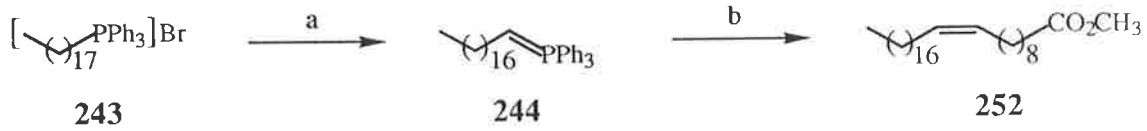


SCHEME 68

available unsaturated alcohol **249** was treated with phosphorous tribromide in ether to produce the bromide **250** in a 59% yield, after chromatography. The infrared spectrum of the bromide **250** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H stretch, and a weak absorption at 1660 cm^{-1}, due to the C–C double bond stretch. A triplet (*J* 6.5 Hz) at δ 3.37 ppm, due to the protons on C1, and a multiplet at δ 5.44 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum.

The bromide **250** was treated with triphenylphosphine in acetonitrile, in the same way as described for the reaction of the bromide **247**. The phosphonium salt **251** was formed in a 92% yield as a clear, colourless glass, and was stored as a solution in DMF, for the same reasons as given for the salt **248**.

To test the applicability of the Wittig method to the formation of unsaturated fatty acid esters, the monoenoic ester **252** was synthesized, as shown in Scheme 69. The ylid **244**



243 **244** **252**

a LiHMDS, THF / HMPA (4 : 1); b **166**

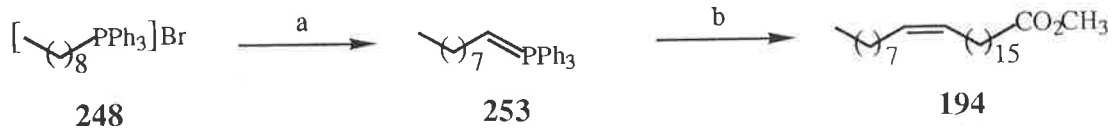
SCHEME 69

was generated from the phosphonium salt **243** and LiHMDS, in a solvent system of THF containing 20% HMPA, in the same way as described for the alkene **246**. Addition of the oxoester **166** to the orange ylid mixture **244** at −78°C, followed by stirring at 0°C for one hour and a weakly acidic work-up, produced the monoenoic ester **252** in a 67% yield, after chromatography. The infrared spectrum of the ester **252** contained an absorption at 2996 cm^{-1}, due to the olefinic C–H bond stretch, and a strong absorption at 1730 cm^{-1}, due to the C–O double bond stretch. The C–C double bond stretch absorption wasn't visible. The ^{1}H-NMR spectrum contained a singlet at δ 3.67 ppm, due to the ester methyl group, and a triplet (*J* 5.3 Hz) at δ 5.34 ppm, due to the olefinic protons. Peaks at δ 27.17 and 27.19 ppm, due to C9 and C12, a peak at δ 51.43 ppm, due to the ester methyl carbon, peaks at δ 129.78 and 129.93 ppm, due to the sp^2 carbons C10 and C11, and a peak at δ 174.33 ppm, due to the sp^2 carbon C1, were observed in the ^{13}C-NMR spectrum.

The peaks observed at δ 27.11 and 27.19 ppm in the ^{13}C-NMR spectrum of the ester **252**, are typical values for carbons allylic to a *cis* double bond, as described previously. No peaks were observed in the range δ 32.64 – 32.69 ppm, attributable to carbons allylic to a *trans* double bond. This indicated that the ester **252** was not contaminated by any detectable amount of the *trans* isomer.

The results from the formation of **246** and **252** showed that the Wittig reaction could be used successfully to form alkenes of high stereochemical integrity. The Wittig method was then applied to form monoenoic and dienoic esters, to be directly compared to those formed *via* the cuprate method, discussed in Chapter 3. The esters chosen, for simplicity, were methyl 17-hexacosenoate (**194**), methyl 13-docosenoate (**195**), and methyl 17,20-hexacosadienoate (**201**).

An analogous procedure as used to form the alkene **246** and the ester **252**, was applied to couple the oxoester **167** with the phosphonium salt **248**, to synthesize the monoenoic ester **194**, as shown in Scheme 70. Thus, a solution of LiHMDS in THF, generated



248 **253** **194**

a LiHMDS, THF / DMF / HMPA (3.5 : 2 : 1); b **167**

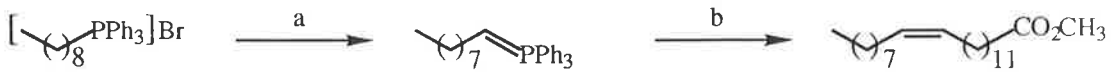
SCHEME 70

immediately prior to use as described earlier, was added to a THF / HMPA / DMF solution of the phosphonium salt **248** at 0°C. The orange solution of the ylid **253**, so formed, was cooled to −78°C and treated with the oxoester **167**. After a one hour reaction time at room temperature, a weakly acidic work-up with ammonium chloride solution was followed by purification *via* chromatography, to produce a 13% yield of the ester **194**. The infrared and ^{1}H-NMR spectra of the ester **194** were identical to those of **194** formed by the cuprate methodology, as discussed in Chapter 3. The ^{13}C-NMR spectrum of the ester **194** formed by the Wittig method, contained all the peaks expected for the *cis* monoenoic ester **194**. Also observed in this spectrum was a small peak at δ 32.62 ppm. This is the expected chemical shift of a carbon adjacent to a *trans* double bond[125], indicating that, in this case, a small amount of the *trans* isomer had also formed. The ratio of the peaks at δ 27.21 and 32.62 ppm was approximately 21 : 1

respectively, indicating the *cis* isomer to be contaminated with about 5% of the corresponding *trans* isomer. The corresponding signal for an olefinic carbon of a *trans* double bond, characteristically downfield of the analogous carbons of a *cis* double bond,[125] was observed at δ 130.35 ppm. The ratio of the peaks at δ 129.89 and 130.35 ppm also indicated the presence of approximately 5% of the *trans* isomer.

The moderate yield obtained in the formation of the ester **194**, in contrast to the good yields realized for the ester **252** and the alkene **246**, is thought to be due to the lack of purity of the phosphonium salt **248**, as only the crystalline salt **243** was properly isolable. Therefore, a better purification method for the salt **248** is desirable, but was not found in this study.

The same procedure was followed, as described above, to couple the phosphonium salt **248** with the oxoester **171** to form the monoenoic ester **195**, the methyl ester derivative of 'Lorenzo's oil'. So, as outlined in Scheme 71, a DMF / HMPA / THF solution of the salt **248** was treated with LiHMDS at 0°C to form the phosphorane **253**, which was



248 **253** **195**

a LiHMDS, THF / DMF / HMPA (5 : 1.5 : 1); b **171**

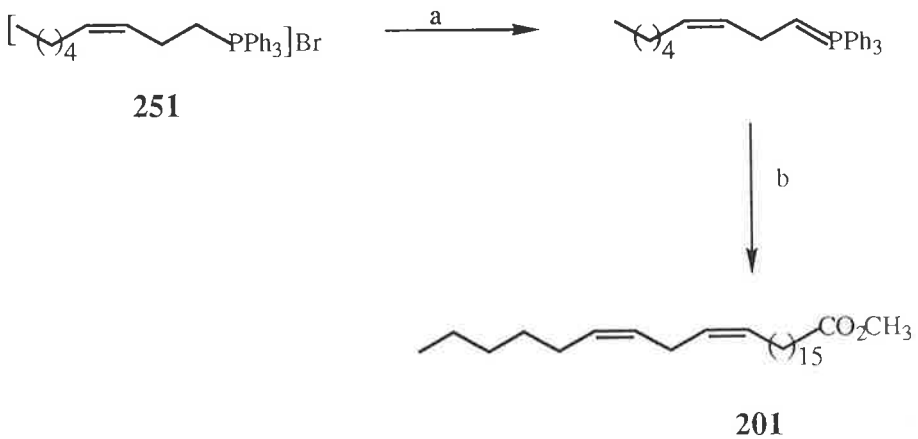
SCHEME 71

subsequently treated with the oxoester **171** at −78°C. After a one hour reaction period at room temperature, the reaction mixture was quenched and the crude material obtained was purified by chromatography to give a 12% yield of the ester **195**. Again, the moderate yield of **195** can be attributed to the suspect purity of the salt **248**, as explained previously. A comparison of the infrared, ^{1}H-NMR and ^{13}C-NMR spectra of

the monoenoic ester **195** obtained by the Wittig reaction, with that of the same ester formed by the cuprate method, described in Chapter 3, showed them to be identical.

In the case of the ester **195** formed by the Wittig method, a peak at δ 27.21 ppm in the ^{13}C-NMR spectrum, due to the allylic carbons C12 and C15, indicated the *cis* stereochemistry of the double bond formed. No peak was observed at approximately δ 32.6 ppm, as would indicate the presence of any *trans* isomer, as previously discussed. Also, no peak at approximately δ 130.4 ppm, due to the sp^2 carbons of a *trans* double bond, was evident in the spectrum. Therefore, in this case, the Wittig reaction went with complete stereoselectivity to form the isomerically pure *cis* ester **195**.

Formation of the dienoic ester **201** was achieved by coupling the phosphonium salt **251** to the oxoester **167**, as outlined in Scheme 72. Using the same method as applied to the synthesis of the monoenoic esters **194** and **195**, the dienoic ester **201** was formed in a 10% yield, after chromatography. The moderate yield obtained is again thought to be due to the lack of purity of the phosphonium salt **251**. The infrared spectrum of the



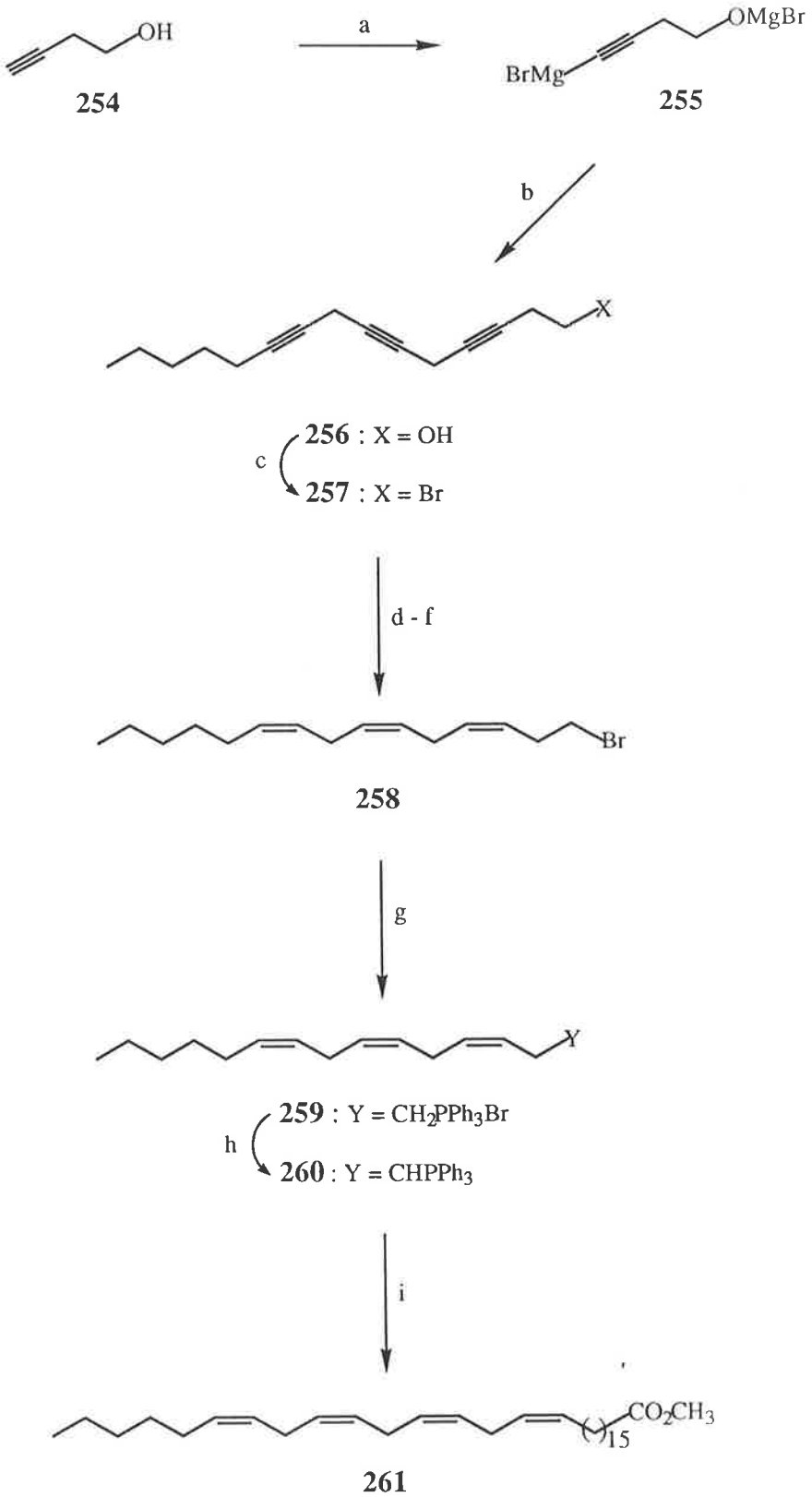
a LiHMDS, THF / DMF / HMPA (5 : 1.5 : 1); b **167**

SCHEME 72

ester **201** contained an absorption at 3008 cm^{-1}, due to the olefinic C–H bond stretch, a strong absorption at 1742 cm^{-1}, due to the C–O double bond stretch, and a very weak absorption at 1660 cm^{-1}, due to the C–C double bond stretch. The ^{1}H-NMR spectrum contained a triplet (*J* 5.9 Hz) at δ 2.78 ppm, due to the protons on C19, a singlet at δ 3.67 ppm, due to the ester methyl group, and a multiplet at δ 5.36 ppm, due to the olefinic protons. Also observed in the ^{1}H-NMR spectrum were a small triplet (*J* 5.9 Hz) at δ 2.72 ppm, a multiplet at δ 2.0 ppm and a multiplet at δ 0.89 ppm, indicating the presence of one or more contaminants.

The ^{13}C-NMR spectrum of **201**, formed as described above, contained all the peaks expected for the *cis* isomer, as compared to the spectrum of the ester **201**, synthesized by the cuprate method. The ^{13}C-NMR spectrum also contained extra small peaks at δ 30.45 ppm, characteristic for a carbon adjacent to a *cis* and a *trans* double bond,[125] and at δ 32.55 ppm, typical for a carbon adjacent to a *trans* double bond.[125] Comparison of the heights of the peaks at δ 30.45 and 32.55 ppm indicated the presence of approximately 20% of the *cis, trans* isomer and / or material containing a conjugated diene system. Extra peaks were also observed at δ 127.70, 128.28, 130.48 and 130.83 ppm, due to the olefinic carbons of the *cis, trans* isomer and / or conjugated material. No peak was observed at approximately δ 35.7 ppm, a typical value for a carbon adjacent to two *trans* double bonds,[125] indicating that no *trans, trans* isomer was present.

To investigate the generality of the Wittig method of forming unsaturated esters, one attempt at the total synthesis of the tetraenoic ester **261**, as shown in Scheme 73, was undertaken. Thus, using the same procedure used to form the alcohols **90** and **213** as described in Chapters 1 and 2, respectively, the alkynol **254** was added to two equivalents of ethylmagnesium bromide in THF at 0°C, to form the Grignard complex



a 2 EtMgBr, THF; b CuCl, **32**; c CBr_4, Ph_3P, CH_2Cl_2; d $(\bigcirc)_2BH$;
e AcOH; f NaOH, HOOH, H_2O; g PPh_3, CH_3CN, reflux 36h;
h LiHMDS, THF / DMF / HMPA (3.5 : 2 : 1); i **167**

SCHEME 73

255, and was followed by the addition of the diynyl bromide **32**. The resulting mixture was refluxed for twenty four hours, with more cuprous chloride being added after sixteen hours. An acidic work-up with aqueous sulphuric acid was followed by purification of the crude reaction material *via* chromatography and distillation, to produce the triynyl alcohol **256** in a 24% yield. The infrared spectrum of **256** contained a broad absorption at 3440 cm^{-1}, due to the O–H bond stretch, and an absorption at 2212 cm^{-1}, due to the C–C triple bond stretch. A multiplet at δ 3.07 ppm, due to the protons on C5 and C8, and a triplet (*J* 6.5 Hz) at δ 3.62 ppm, due to the protons on C1, were observed in the ^{1}H-NMR spectrum.

In an attempt to recrystallize the alcohol **256** from hexane, as had been reported for similar alcohols,[67] some decomposition of the material was produced. This had the effect of lowering the yield of the next step. Thus, the partially decomposed alcohol **256** was treated with carbon tetrabromide and triphenylphosphine in dichloromethane, as for the bromide **214** described in Chapter 3, and the mixture was stirred overnight at room temperature, to produce the triynyl bromide **257** in a 46% yield, after isolation followed by purification by chromatography. The infrared spectrum of the bromide **257** contained a weak absorption at 2210 cm^{-1}, due to the C–C triple bond stretch, and an absorption at 670 cm^{-1}, due to the C–Br bond stretch. The ^{1}H-NMR spectrum contained a multiplet at δ 3.07 ppm, due to the protons on C5 and C8, and a triplet (*J* 7.0 Hz) at δ 3.39 ppm, due to the protons on C1.

The triynyl bromide **257** was reduced to the all-*cis* trienyl bromide **258** using the method described by Millar and Underhill,[139] which had been successfully employed in the formation of the bromide **215**, discussed in Chapter 3. Thus, the bromide **257** was added to a suspension of dicyclohexylborane in THF (prepared by adding two equivalents of cyclohexene to a solution of borane-dimethylsulfide complex in THF) at 0°C. After a reaction time of four hours, glacial acetic acid was added and the mixture was stirred overnight. A basic oxidative work-up with aqueous sodium hydroxide

solution and aqueous hydrogen peroxide solution, was followed by extractive isolation and purification of the crude product by distillation and chromatography. The trienyl bromide **258** was afforded in a 29% yield. The infrared spectrum of **258** contained an absorption at 3004 cm^{-1}, due to the olefinic C–H bond stretch, and a weak absorption at 1650 cm^{-1}, due to the C–C double bond stretch. A triplet (*J* 6.5 Hz) at δ 3.31 ppm, due to the protons on C1, and a multiplet at δ 5.37 ppm, due to the olefinic protons, were observed in the ^{1}H-NMR spectrum.

Treatment of the bromide **258**, as for the bromides **247** and **250**, with triphenylphosphine in acetonitrile produced the phosphonium salt **259** in a 73% yield. The salt **259** was immediately dissolved in DMF and diluted with THF and HMPA. Addition of a freshly generated solution of LiHMDS in THF to the solution of **259** produced an orange solution of the ylid **260**, which was subsequently reacted with the oxoester **167** at –78°C, as described for the esters **194** and **195**. The crude reaction mixture was purified by chromatography to give a small amount of material which had ^{1}H-NMR spectral characteristics of an unsaturated fatty ester. That is, a multiplet at δ 3.81 ppm, a singlet at δ 3.67 ppm, and a multiplet at δ 5.37 ppm, were present in the ^{1}H-NMR spectrum. The ratio of integration of these signals was incorrect for the expected ester **261**.

Analysis by ^{13}C-NMR spectroscopy of the ester component resulting from the coupling of **167** with **259** revealed the presence of a large number of double bond isomers. In the olefinic carbon region of the ^{13}C-NMR spectrum, from δ 125.7 - 134.7 ppm, there existed many peaks, implying a large number of isomers present in the mixture. Also, in the region δ 30.4 – 34.1 ppm, there was observed numerous peaks, indicating the existence of carbons adjacent to *trans* double bonds and carbons adjacent to both a *cis* and a *trans* double bond. These peaks could be due to material containing a *cis-trans* methylene interrupted diene system, a conjugated polyene system, or both. There were no peaks at approximately δ 35.7 ppm, due to carbons adjacent to two trans double bonds.

The Wittig reaction has been shown to be quite useful in the formation of monoenoic esters, with little or no contamination by the *trans* isomer being observed, as exemplified by the syntheses of the esters **194, 195** and **252**. The yield of the Wittig reaction has the potential to be much higher than obtained in some of the cases described above, as shown by the 67% yield of the monoenoic ester **252**. However, when the Wittig method was employed in the synthesis of the dienoic ester **201** and the tetraenoic ester **261**, a substantial amount of isomerization and / or conjugation of the double bonds was observed. Therefore, the cuprate methodology of Chapter 3 has proven to be far superior. The monoenoic esters **194** and **195** and the dienoic ester **201** were formed isomerically pure by this method.

CONCLUSION

In this study, the copper(I) catalyzed coupling of the substituted propargyl bromides, 1-bromo-2,5-undecadiyne and 1-bromo-2,5,8-tridecatriyne, with 5-hexynoic acid or its orthoester protected derivative, 1-(4-pentynyl)-4-methyl-2,6,7-trioxobicyclo[2.2.2]-octane, gave poor results and therefore this route to the synthesis of very long chain fatty acids was found to be unsuitable. The polyalkynyl bromides themselves were formed readily in a few steps. 1-Bromo-2,5-undecadiyne was produced by the copper(I) catalyzed coupling of 1-heptyne with 1,4-dibromobutyne. The copper(I) catalyzed coupling of 1-bromo-2,5-undecadiyne with propargyl alcohol, followed by treatment with phosphorous tribromide produced 1-bromo-2,5,8-tridecatriyne. In a similar fashion, 1-bromo-2,5-undecadiyne was coupled , under copper(I) catalysis, with 4-pentyn-1-ol and 3-butyn-1-ol, followed by treatment with triphenyl-phosphine and carbon tetrabromide, to produce 1-bromo-4,7,10-hexadecatriyne and 1-bromo-3,6,9-pentadecatriyne, respectively.

Wittig methodology has been shown to be quite effective in coupling alkyltriphenyl-phosphonium bromides with ω-oxoesters to produce mono-unsaturated very long chain fatty acid methyl esters with high *cis* double bond selectivity, as shown by ^{13}C-NMR spectroscopy. However, the coupling of alkenyltriphenylphosphonium bromides with ω-oxoesters, under the same conditions, proved less successful as significant isomerization of the double bonds of the product very long chain fatty acid methyl esters was observed by ^{13}C-NMR spectroscopic analysis. The yields of the Wittig products are potentially much higher than those generally observed. The use of the crystalline 1-octadecyl-triphenylphosphonium bromide in the Wittig reactions produced good yields of products. In contrast, when either the hygroscopic 1-nonyltriphenylphosphonium bromide, 1-(*cis*-3-nonenyl)triphenylphosphonium bromide or 1-(*cis,cis,cis*,3,6,9-pentadecatrienyl)-triphenylphosphonium bromide were

used, considerably lower yields of coupled products were obtained. This is believed to be due to the difficulty in obtaining pure samples of these salts.

The coupling of alkyl bromides, *via* mixed dialkyl cuprate species, with ω-iodoesters has proven to be the most effective method to form very long chain fatty acid methyl esters. A number of saturated, monounsaturated and polyunsaturated very long chain fatty acid methyl esters have been formed in this way, consisting of up to 34 carbons and containing up to 3 *cis* double bonds. These very long chain methyl esters were formed in moderate yields of 10 – 28%. Analysis of the unsaturated very long chain fatty acid methyl esters formed by this method by ^{13}C-NMR spectroscopy indicated no isomerization or migration of the *cis* double bonds under the reaction conditions used, but the results indicate that this methodology is limited by either the length or extent of unsaturation of the alkyl bromide, as cuprate formation was not achieved with 1-bromo-5,8,11,14-eicosatetraene and 1-bromo-4,7,10,13,16,19-docosahexaene. In all the mixed dialkyl cuprate coupling reactions involving the methyl alkyl cuprate species, methylation of the ω-iodoester was observed as a competing reaction. In a few cases, separation of the product very long chain fatty acid methyl esters from the methylated material was not achieved. This problem was successfully overcome by forming the analogous dialkyl cuprate species.

EXPERIMENTAL

GENERAL

Melting points were determined using a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by Canadian Microanalytical Service Ltd., New Westminster, British Columbia, Canada, or by Chemical and Micro Analytical Services Pty. Ltd., North Essendon, Victoria, Australia.

Infrared Spectra were recorded as films or solutions, as indicated, on a Hitachi 270-30 spectrometer. The signals have been designated b (broad); s (strong); m (medium) and w (weak).

(unless otherwise indicated)

^{1}H-NMR spectra were recorded at 60 MHz on a Varian T60 spectrometer. 300 MHz ^{1}H-NMR spectra were recorded on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer. ^{13}C-NMR spectra were recorded on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer. Chemical shifts have been quoted in parts per million (ppm) downfield from tetramethylsilane and coupling constants (*J*) are given in Hertz (Hz). Peak multiplicities have been abbreviated to b (broad); bs (broad singlet); s (singlet); d (doublet); t (triplet); q (quartet); p (pentet); m (multiplet); tt (triplet of triplets) and ddt (doublet of doublet of triplets).

Electron impact mass spectra were recorded with an AEI MS-30 double focussing mass spectrometer operating at 70 eV. Chemical Ionization (CI) mass spectra were recorded with a ZAB 2HF spectrometer, as were the collisionally activated (CA) spectra.

All thin layer chromatography (TLC) was performed on Merck DC-Alufolien Kieselgel 60 F_{254} Art. 5554. TLC plates were visualized by dipping in a solution of phosphomolybdic acid in 95% ethanol (4% w / v) followed by heating. Flash column chromatography[155] was performed on Merck Kieselgel 60 (230-400 mesh ASTM). Dry-column flash chromatography[95] was performed on Merck Kieselgel 60 HF_{254} Art. 7739.

Analytical gas-liquid chromatography was carried out using either a Pye Unicam 104 or a Pye Unicam G.C.D. gas chromatograph, each equipped with a flame ionization detector. Nitrogen was used as the carrier gas. The column used was 12.5% OV17 on Varaport 30, 70-80 mesh, 4 mm x 1.5 m, with a carrier gas flow rate of 30 ml min^{-1}.

All solvents were distilled before use. Anhydrous diethyl ether (ether) and tetrahydrofuran (THF) were obtained by distillation from benzophenone ketyl. Hexane refers to the fraction of light petroleum of b.p. = 66 – 68°C. All reactions were conducted under an atmosphere of nitrogen and moisture sensitive reactions were conducted in flame-dried glassware. 9-Hexadecen-1-ol (**179**), 9,12,15-octadecatrien-1-ol (**181**), 5,8,11,14-eicosatetraen-1-ol (**183**) and 4,7,10,13,16,19-docosa-hexaen-1-ol (**185**) were purchased from Nu-Chek-Prep, Inc., Elysian, Minnesota, U.S.A.

1,4-Decadiyne (27)

A solution of 1-heptyne (**61**) (20.0 g, 0.208 mol) in THF (200 ml) was added to a stirred solution of 1.95M ethylmagnesium bromide in THF (106.0 ml, 0.207 mol) and the resultant solution was refluxed under nitrogen for 1 h. Cuprous chloride (0.50 g, 5.05 mmol) was then added and the solution was refluxed for a further 15 min. Upon cooling, a solution of propargyl bromide (**62**) (27.0 g, 0.227 mol) in THF (100 ml) was added and the resultant solution was stirred for a further 3 h at room temperature. The reaction mixture was then poured into a saturated aqueous ammonium chloride solution (200 ml) and layers separated. The aqueous layer was extracted with ether (2 x 50 ml) and the combined organic layers were washed with saturated aqueous sodium chloride (2 x 50 ml), dried ($MgSO_4$) and solvent removed *in vacuo*. The orange residue was distilled *via* kügelrohr to give 14.75 g (53%) of the *title compound* as a light yellow oil (b.p. = 150°C / 20 mm (block); lit.[65] b.p. = 60 – 62°C / 5 mm) which darkened immediately on exposure to air.

IR(neat) : 3310s, 2990s, 2955s, 2880s, 2310w, 2255w, 2150w, 1473m cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.93 (t, *J* 6.5 Hz, 3H, CH_3), 1.2 – 1.6 (m, 6H, $CH_3(CH_2)_3$), 1.88 (t, *J* 2.5 Hz, 1H, ≡CH), 2.13 (tt, *J* 6.5, 2.5 Hz, 2H, $CH_2CH_2C\equiv$), 3.05 (q, *J* 2.5 Hz, 2H, $\equiv CCH_2C\equiv$) ppm. A small peak at 1945 cm^{-1} in the IR spectrum indicated the presence of a small amount of allene impurity.

When the reaction was conducted in ether with a reaction time of 110 h at reflux, a 27% yield of the *diyne* **27** was obtained. Using the same procedure as described above, but with a reaction time of 4 h at 0°C, gave a 21% yield of **27**. Conducting the reaction for 1 h at reflux produced a 20% yield of the *diyne* **27**, with increased amounts of allene, as shown by an increased absorption at 1945 cm^{-1}, and higher boiling products, as shown by GLC.

1-Bromo-2,5-undecadiyne (32)

The method of Pleshakov *et al.*[81] to synthesize 1-chloro-2,5-undecadiyne (87) (which is mistakenly reported as 1-chloro-2,5-decadiyne) was modified.

1-Heptyne (**61**) (0.205 g, 2.14 mmol) was added to a solution of ethyl magnesium bromide (2.0 mmol) in THF (20 ml) with stirring. The solution was refluxed for 30 min after which cuprous cyanide (0.15 g, 0.168 mmol) was added and the solution refluxed for a further 15 min. To the cooled solution was added the dibromide **89** (1.39 g, 6.56 mmol) and the resulting yellow mixture was allowed to stir overnight at room temperature. The orange solution was poured into saturated aqueous ammonium chloride solution (20 ml) and the layers were separated. The aqueous layer was extracted with ether (2 x 10 ml) and the organic layers combined, washed with 1 : 5 ammonium hydroxide solution : saturated aqueous ammonium chloride solution (20 ml), followed by brine (20 ml), dried ($MgSO_4$), and the solvent removed *in vacuo*. Most of the unreacted dibromide **89** was removed by kügelrohr distillation (b.p. = 100°C / 0.07 mm (block)) and the residue was purified by flash chromatography on silica (2% ethyl acetate / hexane) to give 0.195 g (43%) of the *bromide* **32** as a light yellow oil which darkened immediately on exposure to air. The *bromide* **32** was found to have a b.p = 84 – 90°C / 0.015 mm (lit.[65] b.p. = 78 – 79°C / 0.01 mm).

IR(neat) : 2928s, 2856s, 2260w, 2225w, 1468s, 1314s, 1210s, 614s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.90 (t, *J* 7.0 Hz, 3H, CH_3), 1.2 – 1.58 (m, 6H, $CH_3(\mathbf{CH_2})_3$), 2.15 (tt, *J* 7.0, 2.5 Hz, 2H, $CH_2\mathbf{CH_2}C{\equiv}$), 3.22 (p, *J* 2.5 Hz, 2H, $\equiv CCH_2C{\equiv}$), 3.92 (t, *J* 2.5Hz, 2H, $\equiv CCH_2Br$) ppm.

1,4,7-Tridecatriyne (77)

To a solution of the alkyne **27** (1.0 g, 7.46 mmol) in THF at 0°C under nitrogen was added a 1.85 M solution of ethylmagnesium bromide in THF (3.90 ml, 7.22 mmol). The solution was stirred for 15 min at 0°C during which the solution went red/brown in colour. Cuprous cyanide (0.03 g, 0.335 mmol) was then added and the solution was

stirred for a further 15 min at 0°C. Addition of a solution of propargyl bromide (**62**) (0.85 g, 7.14 mmol) in THF (10 ml) was followed by stirring for 90 min at 0°C and then the mixture was poured into a 1 : 5 solution of ammonium hydroxide : saturated ammonium chloride solution (30 ml). Layers were separated and the aqueous layer was extracted with ether (2 x 20 ml). The organic material was combined and washed with brine (2 x 20 ml), dried ($MgSO_4$), and solvent removed *in vacuo*. The orange residue was distilled *via* kügelrohr to yield 0.168 g (14%) of the *title compound* (B.p. = 120° / 0.045 mm (block)). Redistillation of the alkyne **77** *via* sublimation block gave a 12% overall yield (b.p. = 120°C / 0.05 mm (block), lit.[68] b.p. = 69 – 71°C / 0.001 mm). The light yellow liquid darkened immediately on exposure to air.

IR(neat) : 3310s, 2960s, 2925s, 2860s, 2295w, 2220w, 2125w, 1465s, 1310s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.90 (t, *J* 7.0 Hz, 3H, CH_3), 1.24 – 1.60 (m, 6H, $CH_3(CH_2)_3$), 1.92 (t, *J* 2.5 Hz, 1H, ≡CH), 2.15 (tt, *J* 7.0, 2.5 Hz, 2H, $CH_2CH_2C\equiv$), 3.15 (m, 4H, $\equiv CCH_2C\equiv$) ppm.

Conducting the reaction, as described above, with cuprous chloride as catalyst produced no *triyne* **77**, as shown by GLC analysis. When the reaction was performed at room temperature, a non-isolated yield of 15% was obtained, and the reaction conditions of 5 h at room temperature produced a non-isolated yield of 36%. Increasing the reaction time to 17 h at room temperature produced a non-isolated yield of 18%, with an increased amount of byproduct. With cuprous chloride as catalyst, a reaction time of 5 h at room temperature produced a 25% non-isolated yield of the *triyne* **77**, and conducting the reaction at 50°C for 2 h gave a 14% yield with an increase in higher boiling products. Conducting the reaction at 50°C for 2 h with cuprous cyanide as catalyst also produced an increase in higher boiling products, with the *triyne* **77** formed in an non-isolated yield of 20%. All yields were determined by GLC analysis.

Attempted formation of *1,4,7-Tridecatriyne (77)* with tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] (78) as catalyst.

The method of Raner[79] was adapted to this system.

To a solution of the diyne **27** (0.406 g, 3.03 mmol) in THF (10 ml) cooled to –78°C (dry ice / acetone) was added a 1.5 M solution of methyllithium in ether (2.0 ml, 3.0 mmol). The solution was stirred for 5 min, then tetrakis[iodo(tri-*n*-butyl-phosphine)copper(I)][78] (78) was added and the solution was stirred for a further 5 min. Propargyl bromide (62) (0.386 g, 3.24 mmol) in THF (10 ml) was added to the solution, at a rate to maintain a temperature below –60°C. The solution was stirred at –78°C for 40 min then poured into saturated aqueous ammonium chloride solution (20 ml). The layers were separated and the organic layer was dried ($MgSO_4$) and analyzed by GLC. No *triyne* 77 was detected.

The reaction described above was repeated with the additions at 0°C and the final reaction mixture stirred for 3 h at room temperature. GLC analysis showed an approximate 18% yield of the *triyne* 77, but this was complicated by a broad trailing peak, probably due to the catalyst **78** decomposing.

Tetrakis[iodo(tri-n-butylphosphine)copper (I) (78)

The *title compound* was formed in a 53% yield, following the method of Kauffman and Teter.[78] M.p. = 75 – 76°C (lit.[78] m.p. = 75°C).

1,4-Dibromo-2-butyne (89)

The method of Johnson[83] was followed to obtain an 85% yield of the *title compound* , b.p. = 96 – 102°C / 16 mm (lit.[83] b.p. = 60°C / 0.07 mm)
IR(neat) : 3004s, 2285w, 1422s, 1206s, 612s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 3.97 (s, 4H, $BrCH_2C\equiv$) ppm.

Tetradeca-2,5,8-triyn-1-ol (90)

The method of Osbond, Philpott and Wickens[67] was applied. The crude product **90** was purified by dry-column flash chromatography[95] (ethyl acetate / hexane gradient) to obtain a buff coloured solid (49%).
IR(neat) : 3350b, 2960s, 2930s, 2860s, 2230-2120w, 1025s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.92 (m, 3H, CH_3), 1.20 – 1.65 (m, 6H, $CH_3(\mathbf{CH_2})_3$), 1.60 (m, 2H, $CH_2\mathbf{CH_2}C\equiv$), 2.08 (s, 1H, exch, OH), 3.20 (m, 4H, $\equiv CCH_2C\equiv$), 4.32 (t, *J* 2.0 Hz, 2H, $\equiv CCH_2O$) ppm. The *alcohol* ***90*** contained minor impurities, but was not purified further.

1-Bromo-2,5,8-tetradecatriyne (91)

The method of Osbond, Philpott and Wickens[67] was applied. The crude *title compound* was purified by flash chromatography on silica (10% dichloromethane / hexane) to yield the *bromide* ***91*** as a yellow oil (28%) which darkened on exposure to air.
^{1}H-NMR(CCl_4) : δ 0.93 (m, 3H, CH_3), 1.13 – 1.57 (m, 6H, $CH_3(\mathbf{CH_2})_3$), 2.13 (m, 2H, $CH_2\mathbf{CH_2}C\equiv$), 3.13 (m, 4H, $\equiv CCH_2C\equiv$), 3.91 (t, *J* 2.2 Hz, 2H, $\equiv CCH_2Br$) ppm.

5-Hexynoic acid (92)

Commercially available 5-hexynenitrile (**94**) was hydrolyzed *via* the method of Pyatnova *et al.*[88] Yield = 90%. b.p. = 120 – 121°C / 21 mm (lit.[88] b.p. = 111 – 112°C / 14 mm).

IR(neat) : 3300s, 2924b, 2120w, 1712s, 1418s, 1246s, 642s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.70 – 2.12 (m, 3H, $CH_2CH_2CH_2$, ≡CH), 2.16 – 2.73 (m, 4H, $CH_2C\equiv$, CH_2CO_2), 11.04 (s, 1H, exch, CO_2H) ppm.

Eicosa-5,8,11,14-tetraynoic acid (93)

The method of Osbond, Philpott and Wickens[67] and Pyatnova *et al.*[88] was applied. Some dilution and warming on formation of the di-Grignard complex of 5-hexynoic acid (**95**) was required to facilitate stirring. The crude, almost solid, compound obtained was heated with petroleum ether (b.p. = 40 – 60°C) whilst swirling vigorously, and the solvent pipetted away. This was repeated thrice more with portions of petroleum ether. On cooling the combined petroleum ether portions, buff-coloured crystals were deposited which were collected and dried in a dessicator under vacuum. Yield = 12%, m.p. = 77.5 – 79°C (lit.[88] m.p. = 79.8 – 80.5°C).

^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.90 (t, *J* 6.5 Hz, 3H, CH_3), 1.35 (m, 4H, $CH_3(CH_2)_2CH_2$), 1.49 (p, *J* 7.0 Hz, 2H, $CH_3(CH_2)_2CH_2$). 1.84 (p, *J* 7.0 Hz, 2H, $\equiv CCH_2CH_2CH_2CO_2$), 2.15 (tt, *J* 7.0, 2.5 Hz, 2H, $CH_3(CH_2)_3CH_2C\equiv$) 2.26 (tt, *J* 7.0, 2.5 Hz, 2H, $\equiv CCH_2(CH_2)_2CO_2$), 2.49 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 3.14 (m, 6H, $\equiv CCH_2C\equiv$) ppm, carboxylic acid proton not visible.

Attempted formation of *Tetracosa-5-ynoic acid (97)*

The coupling of stearyl bromide (**96**) with 5-hexynoic acid (**92**) was performed using the procedure of Osbond, Philpott and Wickens.[67] Dilution and warming of the di-Grignard complex of 5-hexynoic acid **95** was necessary to obtain a workable slurry. No **97** was isolated, using the same procedure as applied for **93**.

The reaction above was repeated with the final reaction conducted at reflux. No **97** was isolated.

Attempted formation of *Heptadeca-5,8,11-triynoic acid (98)* by the reaction of the Grignard complex **95** with the bromide **32**

The method of Marcel and Holman[87] was applied to couple diynyl bromide **32** with hexynoic acid **92**. Dilution and heating was required to obtain a workable slurry of **95**. Isolation with hexane, as for **93**, revealed a 4% yield of the *acid 98*.
^{1}H-NMR($CDCl_3$) : δ 0.73 – 2.67 (m, 17H, $CH_3(CH_2)_4$, $(CH_2)_3CO_2$), 3.19 (m, 4H, $\equiv CCH_2C\equiv$), 8.67 (b, 1H, CO_2H) ppm.

When the reaction to couple **92** with **32** was repeated as above, but with final reactions conducted overnight at reflux, no *acid 98* was isolated.

The procedure, as described above, was applied to couple **92** and **32** in a solvent system of THF / HMPA (4 : 1). The reaction mixture was then poured into 10% aqueous sulphuric acid and extracted with ether (3x). The organic material was washed with brine (2x), then extracted with 10% aqueous sodium hydroxide solution (3x). The combined basic aqueous material was reacidified by addition of concentrated hydrochloric acid and extracted with ether (3x). These ether extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. ^{1}H-NMR spectroscopic analysis of

this material contained no signal at δ 3.19 ppm, indicating no *acid 98* had formed. The original organic material, from before the base extractions, was dried ($MgSO_4$), and concentrated to reveal recovered bromide **32**.

Attempted formation of *Heptadeca-5,8,11-triynoic acid (98)* by the reaction of the lithium complex **99** with the bromide **32**

A 1.3 M solution of methyllithium in ether (2.0 ml, 2.6 mmol) was added to 5-hexynoic acid (**92**) (0.30 g, 2.679 mmol) in THF (7 ml) at –78°C and stirred for 30 min, followed by stirring at room temperature for 1 h. After cooling the solution to –78°C, 1-bromo-2,5-undecadiyne (**32**) (0.307 g, 1.352 mmol) was added and washed through with THF (2 x 1 ml). Stirring was continued at –78°C for 45 min followed by 2 h at room temperature. The brown solution was poured into saturated aqueous ammonium chloride solution (20 ml) and 10% aqueous sulphuric acid (5 ml) was added. The layers were separated and the aqueous portion was extracted with ether (3 x 15 ml). The combined organic material was extracted with 10% aqueous sodium hydroxide solution (3 x 20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*, to recover the diynyl bromide **32**. The basic aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether (3 x 20 ml). The extracts were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure. The ^{1}H-NMR spectrum of this material did not contain a signal at δ 3.15 ppm, indicating that no **98** had formed.

In a variation of the above procedure, a 1.0 M solution of methyllithium in ether (7.9 ml, 7.9 mmol) was added to 5-hexynoic acid (**92**) (0.45 g, 4.02 mmol) in THF (8 ml) at –78°C. After stirring the solution at this temperature for 15 min, it was allowed to warm to room temperature, and stirring was continued for 30 min. The solution was then cooled to 0°C (ice bath), and cuprous iodide (0.13 g, 0.68 mmol) was added, followed by stirring for 10 min. The bromide **32** (0.30 g, 1.32 mmol) was then added and the

solution was allowed to stir at room temperature for 2 h. The work-up conditions, as described above, were applied. The bromide **32** was recovered. The ^{1}H-NMR spectrum of the acidic component contained a multiplet at δ 3.15 ppm, indicating a small amount of the *title compound* had formed. No attempt at isolation was made.

This latter procedure was repeated, but with a solvent system of THF / HMPA (4 : 1). The bromide **32** was recovered. The ^{1}H-NMR spectrum of the acidic component contained a multiplet at δ 3.15 ppm, indicating a small amount of **98** had formed. Again, no attempt at isolation was made.

3-Methyl-3-hydroxymethyloxetane (112)

The method of Corey and Raju[91] was applied to form the *oxetanyl alcohol* ***112*** in a 54% yield. B.p. = 120 – 123°C / 44 mm (lit.[154] b.p. = 80°C / 4 mm).
IR(neat) : 3428b, 2956s, 2868s, 1456s, 1050s, 978s, 830s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.33 (s, 3H, CH_3), 3.67 (s, 2H, CH_2OH), 3.78 (bs, 1H, exch, OH), 4.38 (d, *J* 6.0 Hz, 2H, CH_2OC), 4.58 (d, *J* 6.0 Hz, 2H, CH_2OC) ppm; MS (CA, m/e) : 103 $(M+H)^+$, 85, 72, 57, 43.

Oxetane-3-methyl-3-methylenyl 5-hexynoate (115)

5-Hexynoyl chloride (generated by refluxing 1 equivalent of 5-hexynoic acid (**92**) with 2.5 equivalents of oxalyl chloride for 2 h, followed by distillation. Yield = 86%. B.p. = 79 - 80°C / 4 mm) was esterified with **112**, following the method of Corey and Raju.[91] The crude compound was distilled *via* kügelrohr to give an 80% yield of the *ester* ***115*** as a colourless oil (b.p. = 180°C / 20 mm (block)).

IR(neat) : 3292s, 2960s, 2872s, 2116w, 1736s, 1156s, 982s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 1.33 (s, 3H, CH_3), 1.63 – 2.63 (m, 7H, $HC{\equiv}C(CH_2)_3$), 4.14 (s, 2H, CO_2CH_2), 4.24 (d, *J* 6.0 Hz, 2H, CH_2OC), 4.41 (d, *J* 6.0 Hz, 2H, CH_2OC) ppm; MS(m/e) : 196 (M^+), 168, 144, 95, 55, 41.

1-(4-Pentynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (116)

The ester **115** was treated with boron trifluoride, as described by Corey and Raju[91]. The *title compound* was obtained in a 57% yield, after purification by dry-column chromatography[95] over triethylamine pretreated silica.
IR(CCl_4) : 3312s, 2964s, 2928s, 2872s, 2120w, 1398s, 1064s, 632s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.78 (s, 3H, CH_3), 1.52 – 1.85 (m, 5H, HC≡, $(CH_2)_2CO_3$), 2.01 (m, 2H, $\equiv CCH_2$), 3.83 (s, 6H, CH_2O) ppm.

Attempted formation of ***1-(4,7,10-hexadecatriynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (118)***, by coupling the Grignard derivative **117** with the bromide **32**

To a solution of ethylmagnesium bromide in THF (1.46 ml, 0.759 mmol) at 0°C was added a solution of **116** (0.15 g, 0.765 mmol) in THF (0.5 ml), with a further 0.5 ml THF used to wash it through. The mixture was stirred at 0°C for 2 h. Cuprous cyanide (0.02 g, 0.223 mmol) was then added to the solution, followed by stirring at room temperature for 10 min. A solution of the bromide **32** (0.19 g, 0.837 mmol) in THF (0.5 ml) was added, washed through with THF (0.5 ml), and the mixture was allowed to stir at room temperature for 24 h. The solution was then poured into ether (20 ml) / water (30 ml) and shaken. The layers were separated and the aqueous layer was extracted with ether (2 x 20 ml). The combined organic material was washed with ammonium hydroxide solution (20 ml), water (20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. TLC analysis of the crude mixture on silica (40% ethyl acetate /

hexane) revealed components which, with comparison to authentic materials, were shown to be the bromide **32** and the orthoester **116**. A small amount of decomposition was observed. No **118** was detected. ^{1}H-NMR spectrometric analysis of the crude reaction mixture revealed signals attributable to **32** and **116** but no signals corresponding to the *orthoester 118*.

The procedure above was repeated but modified by conducting the final 24 h reaction time at 66°C. TLC analysis of the crude mixture on silica (40% ethyl acetate / hexane) revealed that the bromide **32** and the orthoester **116** were the only components present. The ^{1}H-NMR spectrum contained signals corresponding to **32** and **116**. No signals corresponding to the *orthoester 118* were observed.

When the coupling of **32** with **116** was conducted in a solvent system of THF / HMPA (5 : 1) using the first described procedure, TLC analysis of the crude reaction mixture on silica (40% ethyl acetate / hexane) again revealed only bromide **32** and orthoester **116** present on the chromatogram, although the bromide **32** component was very faint. The ^{1}H-NMR spectrum contained signals attributable to the bromide **32** and the orthoester **116**, but not ~~the~~ due to the *orthoester 118*.

Attempted formation of *1-(4,7,10-hexadecatriynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (118)* by coupling the lithium derivative **119** with the bromide **32**

The procedure of Just and Luthe[89] was modified for the coupling of **32** with **116**.
To a solution of **116** (0.15 g, 0.765 mmol) in THF (1.5 ml) cooled to −78°C (dry-ice / acetone) was added a 2.2 M solution of *n*-butyllithium in hexanes (0.35 ml, 0.77 mmol). The mixture was stirred for 10 min at this temperature, then for a further 15 min at −20°C (dry-ice / CCl_4). Cuprous iodide (0.073 g, 0.383 mmol) was added and, after stirring for 10 min, a solution of bromide **32** (0.19 g, 0.837 mmol) in THF (0.25 ml)

was added and washed through with THF (0.25 ml). The solution was allowed to stir at room temperature for 2 h. The reaction mixture was quenched by pouring into ice / ether. The layers were separated and the aqueous material was extracted with ether (2 x 10 ml). The organic material was combined, washed successively with ammonium hydroxide solution (2 x 15 ml) and water (20 ml), dried ($MgSO_4$), and concentrated under reduced pressure. TLC analysis of the crude mixture on silica (40% ethyl acetate / hexane) revealed only components corresponding to **32** and **116**, with **32** present in a trace amount. Some decomposition was evident. ^{1}H-NMR analysis of the crude reaction mixture revealed signals consistent for the presence of **116**. Signals attributable to the bromide **32** were barely discernable, and no multiplet at approximately δ 3.05 ppm was visable, indicating no *orthoester **118*** had formed.

The reaction was repeated with the modifications described by Prakash *et al.*[70] Thus the bromide **32** was treated with the lithium acetylide **119**, in a solvent system of THF / HMPA (5 : 1), using the same procedure as described above. TLC analysis of the crude mixture on silica (40% ethyl acetate / hexane) and alumina (hexane) produced chromatograms containing a faint component corresponding to **32**, a component corresponding to **116**, and a closely migrating new component. ^{1}H-NMR spectroscopic analysis of the crude reaction mixture produced a spectrum with weak signals attributable to the bromide **32**, signals corresponding to **116**, and a multiplet at δ 3.05 ppm, due to the protons at C7 and C10 of the *product **118***. Integration of the signal revealed **118** had formed in a small yield. No attempt at isolation was made.

Methyl 4-chlorobutyrate (121)

Thionyl chloride (0.10 ml, 1.39 mmol) was added to dry methanol (20 ml), followed by the acid chloride **120** (3.01 g, 21.35 mmol). The solution was refluxed for 20 hours. The cooled solution was concentrated under reduced pressure and then diluted with

dichloromethane (20 ml). The dichloromethane solution was washed with saturated aqueous sodium bicarbonate solution (20 ml), water (20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude oil was distilled *via* kügelrohr, to give 2.30 g (79%) of the *ester* **121** (b.p. = 150°C / 22 mm (block), lit.[143] b.p. = 173 – 174°C).

IR(neat) : 2952s, 1736s, 1440s, 1214s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.82 – 2.67 (m, 4H, $(CH_2)_2CO_2$), 3.60 (t, *J* 6.5 Hz, 2H, CH_2Cl), 3.70 (s, 3H, OCH_3) ppm; MS(m/e) : 138(M^+), 136(M^+), 106, 104, 100, 66, 63, 48.

Methyl 4-iodobutyrate (122)

A solution of the chloroester **121** (2.20 g, 16.11 mmol) and sodium iodide (6.0 g, 40.0 mmol) in acetone (65 ml) was refluxed overnight. The cooled reaction mixture was poured into water (400 ml) followed by the addition of dichloromethane (50 ml). The layers were shaken and separated and the aqueous layer was extracted with dichloromethane (3 x 50 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was distilled *via* kügelrohr, to give 3.11 g (85%) of the *title compound*, b.p. = 190°C / 22 mm (block) (lit.[144] b.p. = 198 – 200°C).

IR(neat) : 2948s, 1736s, 1438s, 1200s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.83 – 2.63 (m, 4H, $(CH_2)_2CO_2$), 3.25 (t, *J* 6.5 Hz, 2H, CH_2I), 3.70 (s, 3H, OCH_3) ppm; MS(m/e) : 228(M^+), 197, 169, 142, 127, 105, 101, 74.

10-Bromodecanoic acid (124)

The procedure, as outlined by Chuit and Hauser,[123] was applied. The hydroxyacid **123** (5.03 g, 26.72 mmol) was suspended in a solution of 33% hydrobromic acid in acetic acid (70 ml) and stirred overnight at room temperature, followed by heating at 100°C

for 4 h. The mixture was cooled and the solvent removed under reduced pressure. The crude product was dissolved in dichloromethane (40 ml) and washed with water (2 x 20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from hexane to produce 5.06 g (75%) of the *bromoacid* ***124***. M.p. = 36.5 – 38°C (lit.[120] m.p. = 37 – 38°C).

IR(CCl_4) : 3500 - 2350, 2932s, 2852s, 1706s cm^{-1}; ^{1}H-NMR(CCl_4) : 1.17 – 2.50 (m, 16H, $(CH_2)_8CO_2$), 3.34 (t, *J* 6.5 Hz, 2H, CH_2Br), 11.77 (bs, 1H, exch, CO_2H) ppm; MS(m/e) : 252(M^+), 250(M^+), 235, 233, 223, 221, 209, 207, 193, 191, 171, 153, 129.

10-Iododecanoic acid (125)

The bromoacid **124** (5.0 g, 19.91 mmol) and sodium iodide (7.50 g, 50.04 mmol) were placed in dry acetone (100 ml), and the mixture was refluxed overnight. The cooled solution was poured into water (500 ml) and the precipitate collected by büchner filtration. The solid was dissolved in dichloromethane (30 ml), and washed with 10% aqueous sodium thiosulphate solution (1 x 20 ml), water (1 x 20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The white solid was recrystallized from hexane to yield 5.36 g (90%) of the *title compound*. M.p. = 49 – 50°C (Lit.[120] m.p. = 49 – 50°C).

IR(CCl_4) : 3400 - 2400, 2928s, 2852s, 1712s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 1.20 – 2.03 (m, 14H, $(CH_2)_7CH_2CO_2$, 2.30 (m, 2H, CH_2CO_2), 3.13 (t, *J* 6.5 Hz, 2H, CH_2I), 11.71 (bs, 1H, exch, CO_2H) ppm; MS(m/e) : 298(M^+), 281, 171, 135, 128, 111, 97, 83.

Methyl 10-iododecanoate (126)

Thionyl chloride (0.3 ml, 4.17 mmol) was added *via* syringe to dry methanol (60 ml). A solution of the iodoacid **125** (1.20 g, 4.02 mmol) in methanol (10 ml) was added to the methanolic hydrogen chloride solution and the mixture was stirred at room

temperature for 4 h. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane (40 ml), washed with a saturated aqueous sodium bicarbonate solution (20 ml), dried ($MgSO_4$) and the solvent again removed under reduced pressure. The residual oil was distilled *via* kügelrohr to produce 1.12 g (89%) of the *ester* ***126***, b.p. = 140°C / 0.03 mm (block) (lit.[145] b.p. = 139 – 141°C / 0.15 mm).

IR(neat) : 2924s, 2852s, 1736s, 1436s, 1172s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.10 – 2.07 (m, 14H, CH_2), 2.31 (m, 2H, CH_2CO_2), 3.18 (t, *J* 6.5 Hz, 2H, CH_2I), 3.67 (s, 3H, OCH_3) ppm; MS(m/e) : 312(M^+), 281, 269, 185,153, 135, 111, 97, 83.

16-Bromohexadecanoic acid (128)

The hydroxyacid **127** (2.50 g, 9.18 mmol) was treated with a solution of 33% hydrobromic acid in acetic acid (25 ml), as described for the formation of the bromoacid **124**. The crude product was recrystallized from hexane to produce 2.69 g (87%) of the *bromoacid* ***128***, m.p. = 68 – 69.5°C (lit.[143] m.p. = 70 – 70.5°C).

IR($CHCl_3$) : 3650 – 2425, 2928s, 2852s, 1712s cm^{-1}; ^{1}H-NMR($CDCl_3$) : 1.17 – 2.20 (m, 26H, $(CH_2)_{13}CH_2CO_2$), 2.37 (m, 2H, CH_2CO_2), 3.43 (t, *J* 6.5 Hz, 2H, CH_2Br) ppm; MS(m/e) : 336(M^+), 334(M^+), 318, 316, 306, 304, 292, 290, 254, 184, 128, 82.

16-Iodohexadecanoic acid (129)

The bromoacid **128** (5.06 g, 15.09 mmol) was *trans*-halogenated with sodium iodide (5.60 g, 37.36 mmol) in acetone (100 ml), as described for the formation of the iodoacid **125**. After recrystallization from hexane, 5.18 g (90%) of the *iodoacid* ***129*** was obtained. M.p. = 71- 73°C (lit.[144] m.p. = 76°C).

IR($CHCl_3$) : 3600 – 2500, 2928s, 2852s, 1710s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.18 - 2.03 (m, 26H, $(CH_2)_{13}CH_2CO_2$), 2.37 (m, 2H, CH_2CO_2), 3.21 (t, *J* 6.5 Hz, 2H, CH_2I) ppm; MS(m/e) : 382(M^+), 365, 255, 254, 237, 219, 139, 125, 111, 97, 83, 69.

Methyl 16-iodohexadecanoate (130)

The iodoacid **129** (5.0 g, 13.08 mmol) was esterified by stirring in methanolic hydrogen chloride solution (1.0 ml thionyl chloride in 200 ml methanol), as described for the formation of the iodoester **126**. The crude compound was recrystallized from methanol, to yield 4.38 g (84%) of the *title compound*. M.p. = 37.5 – 38°C.
IR($CHCl_3$) : 2928s, 2852s, 1730s, 1174s cm^{-1}; ^{1}H-NMR($CDCl_3$) : 1.17 – 2.07 (m, 26H, $(CH_2)_{13}CH_2CO_2$, 2.31 (m, 2H, CH_2CO_2), 3.22 (t, *J* 6.5Hz, 2H, CH_2I), 3.70 (s, 3H, OCH_3) ppm; MS(m/e) : 396(M^+), 364, 259, 226, 208.

11-Bromoundecanoic acid (131)

10-Undecenoic acid (**21**) (20.0 g, 0.109 mmol), azobisisobutyronitrile (AIBN) (ca 0.40 g) and hexane (160 ml) were placed in a 250 ml 3-neck round-bottom flask equipped with a condensor, calcium chloride drying tube, magnetic stirrer and a gas inlet. Anhydrous hydrogen bromide gas was bubbled into the mixture for 15 min whilst the mixture was illuminated with a 300 W UV lamp. The flow of gas was stopped and the mixture was irradiated for a further 15 min. The solution was then cooled to –10°C (ice-salt bath) and the precipitate was collected by büchner filtration. Concentration and cooling of the filtrate produced some more precipitate, which was collected in the same way. The crude solid was recrystallized from hexane, to produce 19.25 g (67%) of the *bromoacid 131*. M.p. = 44 – 47°C (lit.[146] m.p. = 49 – 50°C).

IR(nujol mull) : 3300 – 2500, 2925s, 1712s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.22 – 2.07 (m, 16H, $(CH_2)_8CH_2CO_2$), 2.37 (m, 2H, CH_2CO_2), 3.44 (t, *J* 6.5 Hz, 2H, CH_2Br), 10.40 (b, 1H, exch, CO_2H) ppm; MS(m/e) : 266(M^+), 264(M^+), 249, 237, 235, 223, 221, 207, 205, 185, 167.

11-Iodoundecanoic acid (132)

In the same manner as described for the formation of the iodoacid **125**, bromoacid **131** (10.0 g, 38 mmol) was *trans*-halogenated with sodium iodide (13.5 g, 90 mmol) in acetone (200 ml). The crude product was recrystallized from hexane, to produce 8.88 g (75%) of the *acid* **132**. M.p. = 64.5 – 65°C (lit.[120] m.p. = 64 – 65°C).
IR(mull) : 3100 – 2400, 2950s, 2875s, 1710s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 1.37 – 2.03 (m, 16H, $(CH_2)_8CH_2CO_2$), 2.32 (m, 2H, CH_2CO_2), 3.15 (t, *J* 6.5 Hz, 2H, CH_2Br), 11.83 (b, 1H, exch, CO_2H) ppm; MS(m/e) : 312(M^+), 295, 185, 167, 149.

Methyl 11-iodoundecanoate (133)

The iodoacid **132** (4.61 g, 14.78 mmol) was esterified by treatment with methanolic hydrogen chloride (0.4 ml thionyl chloride in 150 ml methanol), as described for the formation of the iodoester **126**. The crude product was distilled *via* kügelrohr to produce 4.59 g (95%) of the *title compound*, b.p. = 180°C / 0.04 mm (block) (lit.[74] b.p. = 98 – 102°C / 0.15 mm). The oil solidified on standing. M.p. = 24 – 25°C.
IR(neat) : 2924s, 2852s, 1738s, 1436s, 1170s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.18 – 2.03 (m, 16H, $(CH_2)_8CH_2CO_2$), 2.32 (m, 2H, CH_2CO_2), 3.20 (t, *J* 6.5 Hz, 2H, CH_2I), 3.69 (s, 3H, OCH_3) ppm (lit.[72] ^{1}H-NMR(CCl_4) : δ 1.0 – 2.0 (m, 16H), 2.2 (t, 2H), 3.15 (t, 2H), 3.62 (s, 3H) ppm); MS(m/e) : 326(M^+), 295, 199, 167, 149.

Attempted formation of *7-chlorohept-1-ene (136)*

The procedure outlined by Noël *et al.*[101] was used.

(a) To a flame-dried 3-necked flask, fitted with a dropping funnel and a thermometer, and containing magnesium turnings (0.137 g, 5.636 mmol) and THF (10 ml), was added 1,2-dibromoethane (0.02 ml, 0.232 mmol). When the vigorous reaction had subsided the mixture was cooled to −20°C (CCl_4 / dry-ice). A solution of 1,4-bromochlorobutane (**134**) (1.0 g, 5.83 mmol) in THF (5 ml) was added to the mixture, whilst maintaining a temperature of approximately −20°C. No reaction of the dihalide **134** with the magnesium was observed. The mixture was vigorously stirred for a further 3 h at −20°C but no reaction was visible. The solution was then allowed to warm to room temperature very slowly overnight, during which time reaction of **134** with the magnesium had occurred. Allyl bromide (**140**) (0.48 ml, 5.545 mmol) was added to the solution and the mixture was stirred at room temperature for 30 min, followed by heating (hot-water bath) for 15 min. The cooled solution was poured into a saturated ammonium chloride solution (30 ml) and the layers were separated. The aqueous layer was extracted with ether (2 x 20 ml). The combined organic material was washed with water (20 ml), dried ($MgSO_4$) and the solvent removed by fractional distillation. ^{1}H-NMR analysis fo the crude material revealed no vinylic protons were present. Therefore **136** had not formed.

(b) The above procedure was modified by using the method of entrainment[102].
A solution of the dihalide **134** (1.0 g, 5.833 mmol), 1,2-dibromoethane (0.53 ml, 6.14 mmol) and THF (10 ml) was added to magnesium turnings (0.29 g, 11.93 mmol) in THF (20 ml), which had been previously activated with 1,2-dibromoethane (0.02 ml, 0.232 mmol), at −20°C (CCl_4 / dry-ice). No reaction was observed at this temperature. The mixture was allowed to warm very slowly to room temperature whereupon reaction took place and the mixture refluxed

vigorously. When reaction had subsided, the solution was allowed to cool and allyl bromide (**140**) (0.48 ml, 5.545 mmol) was added. The solution was heated (hot-water bath) for 15 min, then allowed to stir at room temperature overnight. The solution was worked-up as described in (a). ^{1}H-NMR spectroscopic analysis of the crude material showed no signals between δ 5.0 and 6.0 ppm, expected for the vinylic protons of **136**.

Methyl 17-octadecenoate (137)

The method of Bergbreiter and Whitesides[74] was applied.

A 1.2 M ethereal solution of methyllithium (3.2 ml, 3.84 mmol) was added slowly to a suspension of cuprous iodide (0.867 g, 4.55 mmol) in THF (4.5 ml) at –78°C, while maintaining a solution temperature below –60°C. The resultant mixture was stirred at –78°C for 1 h, then slowly warmed to 0°C, whereupon a bright yellow suspension formed. The mixture was immediately cooled to –78°C and a solution of 7-heptenylmagnesium bromide (formed by the addition of the bromide **152** (1.61 g, 9.096 mmol) to magnesium (0.24 g, 9.87 mmol) and iodine (a crystal) in THF (7 ml) under an atmosphere of oxygen-free nitrogen[117] was added, while maintaining the reaction temperature below –60°C. After stirring the mixture at –78°C for 1 h, the reaction was allowed to warm until a distinct purple colouration appeared (0° – 10°C), upon which the solution was immediately cooled to –78°C. Methyl 11-iodoundecanoate (**133**) (1.44 g, 4.42 mmol) in THF (15 ml) was added to the mixture, again while maintaining a reaction temperature below –60°C. Stirring was continued at –78°C for 1 h, after which the solution was allowed to warm to room temperature. The reaction mixture was stirred at this temperature for 2 h and then quenched by pouring into a saturated aqueous solution of ammonium chloride (20 ml). The layers were separated and the aqueous layer was extracted with ether (3 x 15 ml). The combined organic material was washed with brine (30 ml), dried ($MgSO_4$) and the

solvent removed *in vacuo*. The crude oil was purified by flash chromatography on silica (2.5% ether / hexane) to yield 0.837 g (74%) of the *title compound* as a white solid, m.p. = 24 – 26°C. A small amount was hydrolyzed[74] for characterization, m.p. = 56 – 56.5°C (lit.[62] m.p. = 55.5 – 56.1°C).

IR(neat) : 3076m, 2924s, 2848s, 1742s, 1642m, 1466m, 1438s, 1176s, 910s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 1.31 (s, 26H, $(CH_2)_{13}CH_2CO_2$), 1.96 – 2.48 (m, 4H, CH_2CH=CH, CH_2CO_2), 3.63 (s, 3H, OCH_3), 4.77 – 5.20 (m, 1H, CH_2=CH), 5.83 (ddt, *J* 16.5, 9.0, 6.5 Hz, 2H, CH_2=CH) ppm; M.S (m/e) : 2.96 (M^+), 265, 264, 222, 87, 74.

Methyl 18-bromooctadecanoate (138)

A portion, 1.60 g, of the ester **137** contaminated with 30% of the saturated ester **154** (GLC), was hydrobrominated in hexane (10 ml) containing AIBN (ca. 20 mg), using the same method as described for the formation of the bromoacid **131**. After reaction was complete, the solvent was removed under reduced pressure. The residue was redissolved in dichloromethane (20 ml) and washed with saturated aqueous sodium bicarbonate solution (15 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The solid residue was recrystallized from methanol, producing 1.02 g (66% adjusted yield) of the *bromoester 138*. M.p. = 36 – 37°C (lit.[148] m.p. = 35 - 36°C).

IR($CDCl_3$) : 2928s, 2852s, 1730s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.17 – 1.73 (m, 30H, $(CH_2)_{15}CH_2CO_2$), 2.28 (m, 2H, CH_2CO_2), 3.38 (t, *J* 6.5 Hz, 2H, CH_2Br), 3.65 (s, 3H, OCH_3) ppm; MS(m/e) : 378(M^+), 376 (M^+), 347, 345, 335, 333, 297, 265, 143.

Methyl 18-iodooctadecanoate (139)

The bromoester **138** (1.0 g, 2.65 mmol) was *trans*-halogenated with sodium iodide (1.0 g, 6.67 mmol) in acetone (15 ml), as described for the formation of the iodoester **122**. On

completion of the reaction, the mixture was gravity filtered to remove the sodium bromide and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (20 ml) and washed with 10% aqueous sodium thiosulphate solution (10 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was recrystallized from methanol to yield 0.82 g (73%) of the *title compound*. M.p. = 44 – 44.5°C.

IR($CDCl_3$) : 2924s, 2852s, 1730s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.12 – 1.98 (m, 30H, $(CH_2)_{15}CH_2CO_2$), 2.28 (m, 2H, CH_2CO_2), 3.22 (t, *J* 6.5 Hz, 2H, CH_2I), 3.71 (s, 3H, OCH_3) ppm; MS(m/e) : 424(M^+), 393, 293, 265, 247, 155.

4-Chlorobutan-1-ol (150)

The method of Coleman and Bywater[107] to form 6-chlorohexan-1-ol, was adapted.

Yield : 51% (GLC : 95% purity). B.p. = 80 – 82°C / 15 mm (lit.[119] 84 – 85°C / 16 mm).

IR(neat) : 3344b, 2940s, 2868s, 1448s, 1062s, 650s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.81 (m, 4H, $CH_2(CH_2)_2CH_2$), 1.92 (s, 1H, OH), 3.68 (m, 4H, CH_2O, CH_2Cl) ppm.

6-Hepten-1-ol (151)

The procedure outlined by Cahiez *et al*[104] was applied.

To a solution of the chlorohydrin **150** (3.511 g, 32.33 mmol) in THF (45 ml) at –20°C (CCl_4 / dry-ice), was added a 1.6 M solution of ethylmagnesium bromide in THF (25.0 ml, 40 mmol), whilst maintaining the temperature between –20 and –15°C. After stirring for an additional 15 min, magnesium (1.176 g, 48.38 mmol) and iodine (2 crystals) were added to the solution, and it was immediately heated to reflux. During the 4 h reflux of the mixture, two aliquots of 1,2-dibromoethane (0.10 ml, 1.16 mmol) were added at 1.0 h intervals. The cooled solution was removed from the

excess magnesium by cannulation to another flask. Cuprous bromide (0.24 g, 1.673 mmol) was added and the solution was stirred for 15 min at room temperature, during which time it changed colour from a light grey / brown to a dark purple / brown. To this mixture was added allyl bromide (**140**) (7.83 g, 64.72 mmol) dropwise, and stirring was continued overnight at room temperature. The mixture was then refluxed for 1 h, cooled, and poured into a saturated aqueous solution of ammonium chloride (50 ml). The layers were separated and the aqueous layer was extracted with ether (2 x 20 ml). The combined organic material was washed with brine (30 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification of the crude material by dry-column chromatography[95] on silica (40% ethyl acetate / hexane) was followed by distillation at reduced pressure to yield 2.98 g (81%) of the *title compound*, b.p. = 78 – 82°C / 16 mm (lit[98] b.p. = 105 – 107°C / 21 mm).

IR(neat) : 3336b, 3076m, 2928s, 2856s, 1642m, 1056s, 910s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.23 – 2.72 (m, 8H, $(CH_2)_4CH_2O$), 1.63 (s, 1H, exch, OH), 3.67 (m, 2H, CH_2O), 4.80 – 5.22 (m, 2H, CH_2=CH), 5.88 (ddt, *J* 16.5, 9.0, 6.5 Hz, 1H, CH_2=CH) ppm.

6-Hepten-1-ol (151), isolated from the cuprate reaction

The alcohol **151** was isolated from an attempted coupling of the bromide **152** and the iodoester **133**, using the method of Bergbreiter and Whitesides[74], as described for the formation of methyl octadecanoate (**155**). The *title compound* was purified by dry-column chromatography (ethyl acetate / hexane gradient).

IR(neat) : 3360b, 3075m, 2930s, 2855s, 1640m, 1055s, 910s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.20 – 2.36 (m, 8H, $(CH_2)_4CH_2O$), 1.90 (s, 1H, exch, OH), 3.64 (m, 2H, CH_2O), 4.80 – 5.20 (m, 2H, CH_2=CH), 5.85 (ddt, *J* 16.5, 9.0, 6.5 Hz, 1H, CH_2=CH) ppm.

The compound **151** had an identical retention time to an authentic sample, as shown by GLC analysis.

6-Hepten-1-ol (151) from metallation of **152** with magnesium

The bromide **152** (1.170 g, 6.61 mmol) in THF (1 ml) was added slowly to magnesium (0.33 g, 13.58 mmol) and iodine (a crystal) in THF (3 ml), maintaining a gentle reflux. The solution initially became clear and colourless, then went yellow. After the vigorous reaction had subsided, THF (3.5 ml) was added and the mixture was refluxed for a further 2 h. A 1 ml aliquot of the resultant solution was added to 2,2'-biquinoline (a few crystals) in dry benzene (20 ml)[114], in an attempt to titrate the Grignard content, but no coloured charge transfer complex was observed. The remaining reaction solution was stripped of solvent (rotary evaporator) to leave a yellow solid, which was found to be soluble in ethanol and methanol but not very soluble in water. The solid was dissolved in saturated aqueous ammonium chloride solution and extracted with dichloromethane (3x). The combined organic material was dried ($MgSO_4$) and solvent removed *in vacuo* to reveal a yellow oil. The compound was purified by dry-column chromatrography on silica (ethyl acetate / hexane gradient).

The spectral data were identical to an authentic sample of the *alcohol* ***151***, and GLC analysis of the *alcohol* ***151***, isolated as above, had the same retention time as the authentic material.

1-Bromo-6-heptene (152)

(a) Phosphorous tribromide (3.0 ml, 31.61 mmol) was added slowly to an ice-cold solution of **151** (2.40 g, 21.05 mmol) and pyridine (10 drops) in ether (40 ml). A white precipitate formed immediately. The mixture was refluxed for 3 h, then stirred overnight at room temperature. The mixture was cooled to 0°C (ice-bath) and poured slowly onto ice. The layers were separated, and the aqueous layer was extracted with ether (2 x 20 ml). The combined organic material was washed with saturated aqueous sodium bicarbonate solution (1 x 20 ml) and water

(1 x 20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by dry-column chromatography (ethyl acetate / hexane gradient) to reveal 1.03 g (28%) of the *bromide* **152** as a colourless oil.

IR(neat) : 3076m, 2928s, 2852s, 1640m, 994m, 912s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.25 – 2.35 (m, 8H, $(CH_2)_4CH_2Br$), 3.45 (t, *J* 6.5 Hz, 2H, CH_2Br), 4.80 – 5.22 (m, 2H, CH_2=CH), 5.85 (ddt, *J* 16.5, 9.0, 6.0 Hz, 1H, CH_2=CH) ppm.

(b) A mixture of pyridine (1.40 ml, 17.40 mmol) and alcohol **151** (7.0 g, 61.40 mmol) was added to phosphorous tribromide (2.40 ml, 25.26 mmol) slowly during ice-cooling. The mixture was stirred for 6 h at room temperature, then poured onto ice. The layers were separated and the aqueous portion was extracted with ether (3 x 20 ml). The organic material was combined, washed with saturated aqueous sodium bicarbonate solution (2 x 20 ml) followed by water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by dry-column chromatography (ethyl acetate / hexane gradient) to reveal 3.01 g (31%) of the *title compound*.

The spectral data for the *bromide* **152** were the same as described in (a).

(c) An adaption of the method of Hooz and Gilani[84], used by Beckwith *et al*[99] to form similar bromides, was applied.

To an ice-cooled solution of alcohol **151** (1.50 g, 13.16 mmol) and triphenylphosphine (3.53 g, 13.45 mmol) in dichloromethane (8 ml) was added tetrabromomethane (4.95 g, 14.93 mmol) in small portions. The mixture was allowed to stir at room temperature overnight. The yellow solution was concentrated under reduced pressure and distilled *via* kügelrohr (b.p. = 150°C / 20 mm (block)). The clear distillate was purified further by dry-column chromatography (ethyl acetate / hexane gradient) to provide 2.015 g of a clear liquid. The ^{1}H-NMR spectrum was identical to that described in (a), except for a large singlet at δ 6.87 ppm, indicating the presence of a substantial

amount of bromoform. The liquid was redistilled and small fractions taken. ^{1}H-NMR analysis showed the same ratio of bromoform in each fraction, indicating that bromoform co-distilled with the *bromide 152*. An attempt to azeotropically distill off the bromoform with formic acid[108] failed as all three components distilled together.

(d) The method, as described by Rakoff,[109] was applied.

To an ice-cooled solution of triphenylphosphine (13.56 g, 51.76 mmol) in dichloromethane (35 ml) was added bromine (2.65 ml, 51.66 mmol) dropwise. Alcohol **151** (5.64 g, 49.45 mmol) in dichloromethane (5 ml) was added slowly to the slurry, maintaining the temperature below 5°C. Upon addition, the ice-bath was removed and stirring continued at room temperature for 2 h. The solvent was removed under reduced pressure, and the solid residue was washed with portions of hexane. The combined hexane washings was concentrated *in vacuo* and the residue distilled *via* kügelrohr (b.p. = 160°C / 25 mm (block)). The distillate was further purified by dry-column chromatography (ethyl acetate / hexane gradient) to yield 4.43 g (50%) of the *bromide 152*, with spectral data as described in (a).

(e) The method described by Bose and Lal[111] was applied.

Triphenylphosphine (1.15 g, 4.39 mmol) in THF (10 ml) was added slowly to a solution of *N*-bromosuccinimide (0.78 g, 4.39 mmol) in THF (10 ml) at 0°C (ice-bath). An exothermic reaction occurred with the formation of a gummy solid. The alcohol **151** (0.50 g, 4.39 mmol) in THF (5 ml) was added, and the resulting mixture was stirred for 3 h. The solution was gravity filtered to remove the succinimide and the solvent was removed under reduced pressure. The gummy residue was washed with several portions of hexane and the combined washings were concentrated *in vacuo*. TLC analysis of the crude mixture on silica (hexane; 5% ether / hexane; 20% ethyl acetate / hexane) revealed a complex mixture. The

alcohol **151** was present and very little of the *bromide* **152** had formed. The ^{1}H-NMR spectrum of the crude material contained an exchangeable singlet at δ 2.63 ppm, a complex multiplet at δ 3.47 ppm, the characteristic vinylic multiplets at δ 4.73 – 6.15 ppm and aromatic signals at δ 7.50 ppm. No further purification of the material was attempted.

(f) The method of Gaubert *et al*[112] was applied.

A mixture of the alcohol **151** (7.0 g, 61.40 mmol) and pyridine (1.5 ml, 18.64 mmol) was added dropwise to phosphorous tribromide (2.50 ml, 26.31 mmol). Upon completion of addition, the mixture was immediately distilled under water pump reduced pressure until white fumes evolved (bath temperature 160°C). The crude distillate was diluted with dichloromethane (30 ml) and washed successively with water (20 ml), aqueous saturated sodium bicarbonate solution (20 ml), and water (20 ml). The solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled to obtain 8.032 g (74%) of the *bromide* **152**, b.p. = 73 – 76°C / 18 mm (lit.[112] b.p. = 77 – 81°C / 20 mm), with the same spectral data as described in (a).

Methyl Octadecanoate (155)

The coupling procedure of Bergbreiter and Whitesides[74] was applied.

To a suspension of cuprous iodide (1.65 g, 8.66 mmol) in THF (20 ml) at –78°C was added a 1.6 M solution of methyllithium in ether (5.35 ml, 8.56 mmol), while maintaining a temperature below –60°C. The pale yellow suspension was stirred at –78°C for 1 h, then was allowed to warm to 0°C, whereupon the suspension became a bright yellow colour. The mixture was immediately cooled to –78°C. A THF solution of heptylmagnesium bromide (formed previously by adding a solution of 1-bromoheptane (1.54 g, 8.60 mmol) in THF (5 ml) to magnesium turnings (0.22 g,

9.05 mmol) in THF (5 ml) and heating at reflux for a further 1 h) was added to the suspension of methylcopper(I), again while maintaining a temperature below –60°C. After stirring the suspension for 1 h at –78°C, the mixture was allowed to warm until the colour changed from yellow to a very pale pink (approx. 10°C), and then immediately cooled to –78°C. The ω-iodoester **133** (3.29 g, 10.10 mmol) in THF (1 ml) was added slowly to the reaction mixture and, after stirring for 1 h at –78°C, the mixture was allowed to warm to room temperature and stirred for a further 2 h. During this time, the mixture went black. The mixture was then poured into a saturated aqueous solution of ammonium chloride (30 ml), and the layers were separated. The aqueous layer was extracted with ether (3 x 20 ml). The combined organic material was washed with brine (20 ml), dried ($MgSO_4$) and the solvent was removed *in vacuo*. The solid residue was recrystallized from methanol to provide 0.66 g (26%) of the *title compound* as a white solid, m.p. = 38 – 39°C (lit.[119] m.p. = 39.1°C). The product had an identical retention time to an authentic sample by GLC analysis.

^{1}H-NMR(CCl_4) : δ 0.92 (m, 3H, CH_3), 1.30 (s, 30H, $(\mathbf{CH_2})_{15}CH_2CO_2$), 2.38 (m, 2H, CH_2CO_2), 3.65 (s, 3H, OCH_3) ppm.

Dodecane (156)

The procedure of Bergbreiter and Whitesides[74], as described for the synthesis of methyl octadecanoate (**155**), was applied to couple 1-bromoheptane with 1-iodopentane. The *title compound* was isolated in a 38% crude yield. GLC comparison with an authentic sample showed the residue was *dodecane (**156**)*. ^{1}H-NMR(CCl_4) : δ 0.86 (m, 6H, CH_3), 1.28 (s, 20H, CH_2) ppm.

5-Chloropentan-1-ol (159)

The method of Coleman and Bywater,[107] to form 6-chlorohexan-1-ol, was applied. Yield : 45% (GLC : 97% purity). B.p. = 110 – 114°C / 15 mm (lit.[119] b.p. = 112°C / 12 mm).

IR(neat) : 3348b, 2936s, 2864s, 1054s, 652s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.37 – 1.97 (m, 6H, $(CH_2)_3CH_2O$), 2.57 (s, 1H, OH), 2.59 (m, 4H, CH_2O, CH_2Cl) ppm.

7-Octen-1-ol (160)

The *title compound* was afforded in a 66% yield from the chlorohydrin **159**, following the same procedure as described for the alcohol **151**. B.p. = 100 – 103°C / 24 mm (lit.[118] b.p. = 127°C / 88 mm).

IR(neat) : 3340b, 3076m, 2928s, 2852s, 1640m, 1056s, 910s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.21 – 2.28 (m, 10H, $(CH_2)_5CH_2O$), 1.98 (s, 1H, exch, OH), 3.61 (m, 2H, CH_2O), 4.78 – 5.18 (m, 2H, CH_2=CH), 5.84 (ddt, *J* 16.5, 9.0, 6.5 Hz, 1H, CH_2=CH) ppm.

7-Octenoic acid (161)

Jones reagent[121] was added dropwise to a cooled (ice-bath), stirred solution of the alcohol **160** (3.72 g, 29.0 mmol) in acetone (100 ml), until an orange colour persisted. The mixture was then poured into water (400 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic material was extracted with saturated aqueous sodium bicarbonate solution (3 x 30 ml). The basic extracts were combined and acidified by addition of concentrated hydrochloric acid. The acidic aqueous solution was extracted with dichloromethane (3 x 30 ml) and the combined organic extracts was

dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was purified by dry-column flash chromatography on silica, to produce 2.61 g (63%) of the *acid* ***161***.
IR(neat) : 3400 – 2400, 2928s, 2856s, 1710s, 1642m, 9125 cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.17 – 2.48 (m, 10H, $(CH_2)_5$), 4.74 – 5.17 (m, 2H, CH_2=CH), 5.48 (ddt, *J* 16.5, 9.0, 6.5 Hz, 1H, CH_2=C**H**), 11.32 (b, 1H, exch, CO_2H) ppm; MS(m/e) : 143$(M+1)^+$, 125, 96, 82, 55.

8-Bromooctanoic acid (162)

The acid **161** (2.46 g, 17.30 mmol) and AIBN (ca. 0.20 mg) were suspended in hexane (25 ml) and hydrobrominated, as described for the formation of bromoacid **131**. The crude product was recrystallized from hexane, to afford 2.66 g (69%) of the *title compound*. M.p. = 33 – 36°C (lit.[120] m.p. = 36 – 37°C).
IR($CDCl_3$) : 3450 – 2400, 2932s, 2856s, 1710s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.20 – 2.53 (m, 12H, $(CH_2)_6CO_2$), 3.41 (t, *J* 6.5 Hz, 2H, CH_2Br), 10.42 (b, 1H, exch, CO_2H) ppm; MS(m/e) : 224(M^+), 222(M^+), 206, 204, 194, 192, 180, 178, 164, 162, 143, 125, 83, 73.

8-Iodooctanoic acid (163)

The bromoacid **162** (2.50 g, 11.20 mmol) was *trans*-halogenated with sodium iodide (4.20 g, 28.02 mmol) in acetone (55 ml), as described for the formation of the iodoacid **125**. After recrystallization from hexane, 2.51 g (83%) of the *iodoacid* ***163*** was obtained. M.p. = 42.5 – 44°C.
IR($CDCl_3$) : 3450 – 2400, 2932s, 2856s, 1710s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.17 – 2.50 (m, 12H, $(CH_2)_6CO_2$), 3.18 (t, *J* 6.5 Hz, 2H, CH_2I), 9.05 (b, 1H, exch, CO_2H) ppm; MS(m/e) : 270(M^+), 252, 143, 125, 97, 83, 55.

Methyl 8-iodooctanoate (164)

Using the procedure described for the formation of the iodoester **126**, the iodoacid **163** (2.40 g, 8.84 mmol) was esterified to produce, after kügelrohr distillation, 2.22 g (88%) of the *iodoester* ***164***, b.p. = 150°C / 0.2 mm (block).
IR(neat) : 2928s, 2852s, 1738s, 1436s, 1174s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 1.20 – 2.38 (m, 12H, $(CH_2)_6CO_2$), 3.15 (t, *J* 6.5 Hz, 2H, CH_2I), 3.64 (s, 3H, OCH_3) ppm; MS(m/e) : 285$(M+1)^+$, 253, 183, 169, 157, 125, 97, 83.

Methyl 10-undecenoate (165)

The commercial acid **21** (3.02 g, 16.39 mmol) was esterified by treatment with methanolic hydrogen chloride (1.0 ml thionyl chloride in 200 ml methanol), as described for the formation of the ester **126**. Distillation of the crude oil *via* kügelrohr provided 2.60 g (80%) of the *ester* ***165***, b.p. = 130°C / 0.05 mm (block), (lit.[147] b.p. = 247°C).
IR(neat) : 3076m, 2925s, 2852s, 1744s, 1640m, 1438s, 1198s, 910s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.10 – 2.47 (m, 16H, $(CH_2)_8CO_2$), 3.70 (s, 3H, OCH_3), 4.77 – 5.20 (m, 2H, CH_2=CH), 5.85 (ddt, *J* 16.5, 9.0, 6.5 Hz, 1H, CH_2=CH) ppm; MS(m/e) : 198 (M^+), 166, 137, 110, 86, 73.

Methyl 10-oxodecanoate (166)

Ozone-containing oxygen was bubbled through a solution of the ester **165** (1.0 g, 5.04 mmol) in chloroform (50 ml) for 5 h, maintaining the solution temperature between –20 and –10°C. Dimethyl sulfide (0.31 ml, 7.21 mmol) was added *via* syringe to the reaction mixture and it was allowed to stir at room temperature overnight. The

resulting yellow solution was concentrated *in vacuo*. The residue was dissolved in dichloromethane (30 ml), washed with water (2 x 20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification of the residue by flash chromatography on silica (20% ethyl acetate / hexane) afforded 0.49 g (49%) of the *title compound* as a clear, colourless oil.

IR(neat) : 2928s, 2852s, 2720m, 1736s, 1438s, 1172s cm^{-1}; ^1H-NMR(CCl_4) : δ 1.07 – 1.97 (m, 12H, $(CH_2)_6CH_2CO_2$), 2.05 – 2.55 (m, 4H, CH_2CO_2, CH_2CHO), 3.65 (s, 3H, OCH_3), 9.85 (t, *J* 1.8 Hz, 1H, CHO) ppm (lit.[149] ^1H-NMR : δ 1.3 (bs, $(CH_2)_7$), 2.3 (m, $CH_2C{=}O$), 3.6 (s, OCH_3), 9.7 (t, CHO) ppm); MS(m/e) : 201$(M+1)^+$, 172, 169, 157, 125.

Methyl 17-oxoheptadecanoate (167)

The bromide **152** (1.29 g, 7.28 mmol) was coupled with the iodoester **133** (2.60 g, 7.97 mmol), as previously described, to produce 1.74 g of an inseparable mixture of the esters **137** and **154**, in the ratio of 1.6 : 1 (GLC) respectively, after isolation by flash chromatography on silica (2.5% ether / hexane).

A portion of the mixture of **137** and **154** (1.01 g) was dissolved in chloroform / methanol (1 : 1, 20 ml) and cooled to –15°C. Ozone-containing oxygen was bubbled fairly rapidly through the solution for 3 h, keeping the solution temperature between –15 and –5°C. The gas flow was then stopped and dimethyl sulfide (0.30 ml, 3.41 mmol) was added by syringe. The reaction was allowed to warm to room temperature and stirring was continued at this temperature overnight. The solvent was removed from the yellow solution under reduced pressure and the residue was taken up in dichloromethane (20 ml). This solution was washed with water (2 x 20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The yellow oil was purified by flash chromatography (10% ethyl acetate / hexane) to afford 0.48 g (1.61 mmol) of the *oxoester* ***167*** as a white solid, m.p. = 38 – 39.5°C. The ester **154**

(0.30 g) was also recovered. The yield of the *oxoester* **167**, based on ozonolizable material (0.71 g, 2.39 mmol), was 67%.

IR($CDCl_3$) : 2928s, 2852s, 2728m, 1724s, 14409s, 1176s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.13 – 1.96 (m, 26H, $(CH_2)_{13}CH_2CO_2$), 2.33 (m, 4H, CH_2CHO, CH_2CO_2), 3.65 (s, 3H, OCH_3), 9.83 (t, *J* 1.8 Hz, 1H, CHO) ppm; MS(m/e) : 298(M^+), 266, 254, 222, 122, 98, 74; high-resolution mass measurement : M^+ 298.24973, $C_{18}H_{34}O_3$ requires 298.25079.

Spectral data for the ester **154**.

^{1}H-NMR($CDCl_3$) : δ 0.88 (m, 3H, CH_3), 1.12 – 1.82 (m, 18H, $CH_3(CH_2)_9$), 2.30 (m, 2H, CH_2CO_2), 3.66 (s, 3H, OCH_3) ppm; MS(m/e) : 214(M^+), 183, 171, 143, 87, 74.

Methyl 13-oxotridecanoate (171)

The bromide **168** (0.98 g, 7.26 mmol) and the iodoester **126** (2.49 g, 7.98 mmol) were coupled in the same way as described for the formation of **137**. Isolation by flash column chromatography on silica (3% ether / hexane) provided 1.65 g of an inseparable mixture of the esters **170** and methyl undecanoate. GLC analysis showed **170** and methyl undecanoate to be in the ratio 2.3 : 1. The following data is for the ester **170**.

IR(neat) : 3074w, 2924s, 2852s, 1744s, 1640m, 1468m, 1438s, 1196m, 910m cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.30 (s, 18H, $(CH_2)_9CH_2CO_2$), 1.93 – 2.47 (m, 4H, CH_2C=, CH_2CO_2), 3.65 (s, 3H, OCH_3), 4.75 – 5.17 (m, 1H, CH_2=CH), 5.83 (ddt, *J* 16.5, 9.0, 6.5 Hz, 2H, CH_2=CH) ppm; MS(m/e) : 240 (M^+), 208, 207, 165, 87, 74, 55.

A portion of the mixture (0.70 g) was ozonized as described for the formation of the oxoester **167**. The crude product mixture was purified by flash chromatography on silica (10% ethyl acetate / hexane) to reveal 0.359 g (1.44 mmol) of the *title compound* as

a clear, colourless liquid. Methyl undecanoate (0.19 g) was also recovered. The yield of the *oxoester 171* based on ozonolizable material (0.51 g, 2.12 mmol) was 68%.
IR(neat) : 2924s, 2852s, 2716m, 1740s, 1466s, 1438s, 1172s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.15 – 2.57 (m, 22H, $(CH_2)_{11}$), 3.67 (s, 3H, OCH_3), 9.85 (t, *J* 1.8 Hz, 1H, CHO) ppm (lit.[150] ^{1}H-NMR($CDCl_3$) : δ 1.2 – 1.7 (m, 18H, $(CH_2)_9$), 2.2 – 2.5 (m, 4H, CH_2CO_2, CH_2CHO), 3.66 (s, 3H, OCH_3), 9.74 (t, 1H, CHO) ppm); MS(m/e) : 242 (M^+), 214, 211, 199, 167, 54; high resolution mass measurement : M^+ 242.18745, $C_{14}H_{26}O_3$ requires 242.18819

Spectral data for methyl undecanoate.
^{1}H-NMR($CDC1_3$) : δ 0.87 (m, 3H, CH_3), 1.27 (s, 16H, $CH_3(CH_2)_8$), 2.29 (m, 2H, CH_2CO_2), 3.66 (s, 3H, OCH_3) ppm; MS(m/e) : 200(M^+), 169, 157, 143, 87, 74.

Methyl 17-Oxoheptadecanoate dimethyl acetal (172)

A mixture of the esters **137** and **154** (0.35 g, 1.6 :`1 by GLC) was ozonized as described for the formation of the oxoester **167**. The crude product mixture was purified by flash chromatography on silica (10% ethyl acetate / hexane) to reveal 0.206 g (0.60 mmol) of the *acetal 172*, as a white solid (m.p. = 25 – 25.5°C). The unchanged ester **154** (0.106 g) was also recovered. Therefore, the yield of the *acetal 172*, based on ozonolizable material (0.244 g, 0.82 mmol), was 74%.
IR($CHCl_3$) : 2928s, 2852s, 1730s, 1124 cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.10 – 1.82 (m, 28H, $(CH_2)_{14}CH_2CO_2$), 2.31 (m, 2H, CH_2CO_2), 3.32 (s, 6H, $CHOCH_3$), 3.67 (s, 3H, CO_2CH_3), 4.36 (m, 1H, $CH(OCH_3)_2$) ppm; MS(m/e) : 344(M^+), 343(M-1)$^+$, 327, 313, 281, 199, 75, 71, 55, 41; high-resolution mass measurement : M^+ 344.29177, $C_{20}H_{40}O_4$ requires 344.29266.

Hydrolysis of the *Acetal 172*

The acetal **172** (98 mg) was dissolved in methanol (5 ml) and 10% aqueous hydrogen chloride solution (5 ml) was added. The mixture was stirred overnight at 50°C. The cooled mixture was concentrated *in vacuo*, followed by the addition of dichloromethane (10 ml). The layers were shaken and separated. The organic material was washed with saturated aqueous sodium bicarbonate solution (10 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. ^{1}H-NMR spectroscopic analysis of the crude material showed that the methyl ester singlet at δ 3.67 ppm and the acetal methoxy singlet at δ 3.32 ppm were in a ratio of approximately 2 : 1. A triplet (*J* 1.8 Hz) at δ 9.85 ppm was also visible.

9-Octadecen-1-ol (174)

A solution of the ester **173** (3.00 g, 10.12 mmol) in ether (20 ml) was added slowly to a stirred suspension of lithium aluminium hydride (0.77 g, 20.29 mmol) in ether (20 ml). After the vigorous reaction had subsided, the mixture was heated at reflux for 3 h. The cooled solution was then poured into saturated aqueous ammonium chloride solution (100 ml) and the mixture was diluted with water (20 ml). The layers were separated and the aqueous layer was extracted with ether (3 x 20 ml). The combined organic material was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled *via* kügelrohr to give 2.13 g (78%) of the *alcohol* ***174***, b.p. = 200°C / 0.03 mm (block) (lit.[119] b.p. = 205 – 210°C / 15 mm).

IR(neat) : 3700 – 3000, 3004m, 2924s, 2852s, 1660w, 1466s, 1058s, 722s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.89 (m, 3H, CH_3), 1.33 (s, 24H, $CH_3(CH_2)_6$, $(CH_2)_6CH_2O$), 1.52 (s, 1H, exch, OH), 1.77 – 2.23 (m, 4H, CH_2C=), 3.53 (t, *J* 6.0 Hz, 2H, CH_2O), 5.29 (t, *J* 4.5 Hz, 2H, CH=CH) ppm; MS(m/e) : 268 (M^+), 207, 183, 166, 152, 142, 127.

1-Bromo-9-octadecene (175)

To a cooled (ice bath) solution of the alcohol **174** (1.17 g, 4.36 mmol) and triphenylphosphine (1.16 g, 4.42 mmol) in dichloromethane (8 ml) was added carbon tetrabromide (1.45 g, 4.37 mmol), in small portions. The solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the solid residue was washed with hexane (4x). The hexane washings were combined and concentrated *in vacuo*. Dry-column flash chromatography on silica (hexane) of the residue produced 1.32 g (91%) of the *title compound* as a clear, colourless oil.
IR(neat) : 3004m, 2924s, 2848s, 1660w, 12466s, 722m, 658s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.88 (m, 3H, CH_3), 1.10 – 2.27 (m, 28H, $CH_3(CH_2)_7$, $(CH_2)_7CH_2Br$), 3.31 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.24 (t, *J* 4.5 Hz, 2H, CH=CH) ppm; MS(m/e) : 332 (M^+), 330 (M^+), 164, 162, 150, 148, 111, 97, 83, 69.

9, 12-Octadecadien-1-ol (177)

The ester **176** (2.03 g, 6.89 mmol) was treated with lithium aluminium hydride (0.52 g, 13.70 mmol) in ether (20 ml), as described for the formation of the alcohol **174**. The *dienol* **177** (1.47 g, 5.52 mmol) was afforded in an 80% yield as a clear, colourless oil, after distillation *via* kügelrohr, b.p. = 230°C / 0.03 mm (block) (lit.[144] b.p. = 148 – 150°C / 1 mm).
IR(neat) : 3650 – 3075, 3008m, 2924s, 2852s, 1660w, 1466m, 962m, 735m cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.86 (m, 3H, CH_3), 10.7 – 1.77 (m, 18H, $CH_3(CH_2)_3$, $(CH_2)_6CH_2O$), 2.08 (s, 1H, exch, OH), 1.82 – 2.77 (m, 4H, CH_2C=), 2.75 (m, 2H, =CCH_2C=), 3.62 (t, *J* 6.0 Hz, 2H, CH_2O), 5.35 (m, 4H, CH=CH) ppm; MS(m/e) : 266 (M^+), 251, 249, 219, 207, 173, 171, 127.

1-Bromo-9,12-octadecadiene (178)

Using an identical procedure as described for the formation of the bromide **175**, the *title bromide* (1.60 g, 4.85 mmol) was produced in a 90% yield, by treatment of the alcohol **177** (1.36 g, 5.09 mmol) with triphenylphosphine (1.34 g, 5.11 mmol) and carbon tetrabromide (1.09 g, 5.10 mmol) in dichloromethane (8 ml), followed by purification by dry-column flash chromatography on silica (hexane).
IR(neat) : 3008m, 2924s, 2852s, 1466m, 724m, 660m cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.90 (m, 3H, CH_3), 1.07 – 2.27 (m, 22H, $CH_3(CH_2)_4$, $(CH_2)_7CH_2Br$), 2.72 (m, 2H, $=CCH_2C=$), 3.34 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.29 (m, 4H, CH=CH) ppm; MS(m/e) : 330 (M^+), 328 (M^+), 137, 123, 109, 95.

1-Bromo-9-hexadecene (180)

The alcohol **179** (1.07g, 4.45 mmol) was treated with triphenylphosphine (1.19 g, 4.54 mmol) and carbon tetrabromide (1.51 g, 4.54 mmol) in dichloromethane (8 ml), as described for the bromide **175**, to provide 1.27 g (94%) of the *bromide **180*** after purification by dry-column flash chromatography on silica (hexane).
IR(neat) : 3000m, 2924s, 2848s, 1650w, 1466m, 725m, 658s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.89 (m, 3H, CH_3), 1.08 – 2.22 (m, 24H, $CH_3(CH_2)_6$, $(CH_2)_6CH_2Br$), 3.32 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.25 (t, *J* 4.5 Hz, 2H, CH=CH) ppm; MS(m/e) : 304 (M^+), 302 (M^+), 150, 148, 111, 97, 83, 69, 55.

1-Bromo-9, 12, 15-octadecatriene (182)

In the same way as described for the bromide **175**, the alcohol **181** (1.15 g, 4.35 mmol) was treated with triphenylphosphine (1.14 g, 4.35 mmol) and carbon tetrabromide

(1.44 g, 4.35 mmol) in dichloromethane (8 ml) to produce 1.31 g (92%) of the *title bromide* after dry-column flash chromatography on silica (hexane).

IR(neat) : 3008s, 2924s, 2852s, 1650w, 1464m, 720m, 658s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.97 (t, *J* 7.5 Hz, 3H, CH_3), 1.13 – 2.23 (m, 16H, $CH_3\mathbf{CH_2}$, $(\mathbf{CH_2})_7CH_2Br$), 2.73 (m, 4H, $=CCH_2C=$), 3.30 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.26 (m, 6H, CH=CH) ppm; MS(m/e) : 328 (M^+), 326 (M^+), 272, 270, 135, 121, 108, 95, 93, 79, 67.

1-Bromo-5, 8, 11, 14-eicosatetraene (184)

The alcohol **183** (0.90 g, 3.10 mmol) was treated with triphenylphosphine (0.83 g, 3.16 mmol) and carbon tetrabromide (1.05 g, 3.17 mmol) in dichloromethane (10 ml), as described for the bromide **175**, to yield 0.78 g (71%) of the *title compound*, after dry-column flash chromatography on silica (hexane).

IR(neat) : 3012s, 2924s, 2825s, 1650w, 1456sm, 714m, 655m cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.91 (m, 3H, CH_3), 1.13 – 2.37 (m, 14H, $CH_3(\mathbf{CH_2})_4$, $(\mathbf{CH_2})_3CH_2Br$), 2.83 (m, 6H, $=CCH_2C=$), 3.39 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.37 (m, 8H, CH=CH) ppm; MS(m/e) : 354 (M^+), 352 (M^+), 216, 214, 150, 79, 65, 55.

1-Bromo-4, 7, 10, 13, 16, 19-docosahexaene (186)

Analogous to the formation of the bromide **175**, the alcohol **185** (1.00 g, 3.18 mmol) was reacted with triphenylphosphine (0.84 g, 3.20 mmol) and carbon tetrabromide (1.06 g, 3.20 mmol) in dichloromethane (10 ml) to give 0.93 g (77%) of the *bromide 186* after dry-column flash chromatography on silica (hexane).

IR(neat) : 3012s, 2960s, 2928s, 1650m, 1436s, 714s, 656 cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.97 (t, *J* 7.5 Hz, 3H, CH_3), 1.58 – 2.42 (m, 6H, $CH_3C\mathbf{H_2}$, $(\mathbf{CH_2})_2CH_2Br$), 2.81 (m, 10H,

$=CCH_2C=$), 3.33 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.31 (m, 12H, CH=CH) ppm; MS(m/e) : 378 (M^+), 376 (M^+), 309, 307, 255, 253, 202, 200, 119, 105, 91.

Methyl nonacosanoate (189)

The mixed dialkyl cuprate coupling method described by Bergbreiter and Whitesides[74] was applied.

Octadecylmagnesium bromide (**187**) was prepared from the bromide **96** (0.35 g, 1.05 mmol) and magnesium (0.03 g, 1.31 mmol) in THF (1.5 ml) containing 1,2-dibromoethane (0.04 g, 0.21 mmol) and a crystal of iodine. After the initial vigorous reaction subsided, the mixture was refluxed for 2 h. To a suspension of cuprous iodide (0.20 g, 1.05 mmol) in THF (3.0 ml) at –78°C was added a 1.15 M ethereal solution of methyllithium (0.92 ml, 1.06 mmol), taking care to maintain the reaction temperature below –50°C. The reaction mixture was stirred at –78°C for 1 h. The resultant light yellow suspension was allowed to gradually warm to 0°C with stirring. A bright yellow suspension of methylcopper(I) formed which was immediately cooled to –78°C. The Grignard reagent **187**, generated as described above, was added *via* syringe to the methylcopper(I) suspension, while maintaining a reaction temperature below –50°C. The reaction mixture was allowed to stir for another 1 h at –78°C and then was warmed until a distinct pale pink colouration of the reaction mixture was observed (approximately 0°C). As soon as this colour was observed the mixture was cooled to –78°C. A solution of methyl 11-iodoundecanoate (**133**) (0.42 g, 1.29 mmol) in THF (1.0 ml) was added by syringe and the resulting mixture was stirred at –78°C for 1 h, followed by 2 h at room temperature. The black mixture was quenched by pouring into saturated aqueous ammonium chloride (20 ml) and extracted with ether (3 x 15 ml). The combined extracts was washed with saturated sodium chloride (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The *ester (189)* was isolated by dry-column flash

chromatography on silica (ethyl acetate / hexane gradient) and recrystallized from hexane to give 0.11 g (23%). M.p. = 69 – 70°C (lit.[140] m.p. = 68.8°C).
IR($CHCl_3$) : 2924s, 2852s, 1730s, 1468m, 1194m cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ 0.88 (t, *J* 6.4 Hz, 3H, CH_3), 1.25 (s, 50H, $CH_3(CH_2)_{25}$), 1.60 (m, 2H, $CH_2CH_2CO_2$), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 3.67 (s, 3H, OCH_3) ppm; MS(m/e) : 452 (M^+), 420, 409, 395, 381, 367, 353, 199, 185, 143, 129, 87, 74.

Methyl 25-tetratriacontenoate (192)

Using the procedure described for methyl nonacosanoate (**189**), 9-octadecenylmagnesium bromide (**190**) was prepared from bromide **175** (0.40 g, 1.21 mmol) and magnesium (0.06 g, 2.47 mmol) in THF (1.5 ml) and allowed to react with methylcopper(I) (0.92 mmol) and the ω-iodoester **130** (0.40 g, 1.01 mmol) to give 63 mg (13%) of the *title compound* as a white wax. M.p. = 45.5 – 46°C.
IR(CCl_4) : 3004m, 2928s, 21848s, 1742s, 1650w, 1468s, 1172s cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ 0.88 (t, *J* 6.5 Hz, 3H, CH_3), 1.25 (s, 52H, $CH_3(CH_2)_6$, $(CH_2)_{20}(CH_2)_2CO_2$), 1.60 (m, 2H, $CH_2CH_2CO_2$), 2.01 (m, 4H, CH_2C=), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 3.67 (s, 3H, OCH_3), 5.35 (t, *J* 4.6 Hz, 2H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, 300 MHz) : δ14.20 (C34), 22.69 (C33), 29.94 (C3), 27.19 (C24, C27), 29.14 – 29.76 (C4 – C23, C28 – C32), 31.90 (C32), 34.11 (C2), 51.45 (OCH_3), 129.88 (C25, C26), 174.39 (C1) ppm; MS(m/e) : 521 $(M+1)^+$, 520 (M^+), 489, 488, 446, 415, 97, 83, 74, 69, 57, 55; high-resolution mass measurement : M^+ 520.51925, $C_{35}H_{68}O_2$ requires 520.52193; Anal. calcd for $C_{35}H_{68}O_2$: C, 80.7; H, 13.2. Found C, 81.1; H, 13.7.

Methyl 27-tetratriacontenoate (193)

9-Hexadecenylmagnesium bromide was prepared from the bromide **180** (0.26 g, 0.86 mmol) and magnesium (0.03 g, 1.31 mmol) in THF (1.5 ml) and allowed to react with methylcopper(I) (0.69 mmol) and the ω-iodoester **139** (0.30 g, 0.71 mmol), using the procedure described for methyl nonacosanoate **(189)**, to give 35 mg (10%) of the *ester* ***193*** as a white wax. M.p. = 46 – 47°C.

IR(CCl_4) : 3008m, 2924s, 2852s, 1742s, 1650w, 1468s, 21262s, 1172s, 1116s, 1014s cm^{-1}; ^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.88 (t, *J* 6.2 Hz, 3H, CH_3), 1.25 (s, 52H, $CH_3(CH_2)_4$, $(CH_2)_{22}(CH_2)_2CO_2CH_2$), 1.60 (m, 2H, $CH_2CH_2CO_2$), 2.01 (m, 4H, CH_2C=), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 3.67 (s, 3H, OCH_3), 5.25 (t, *J* 4.6 Hz, 2H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, 300 MHz) : δ 14.10 (C34), 22.67 (C33), 24.97 (C3), 27.21 (C26, C29), 28.99 – 29.70 (C4 – C25, C30 – C31), 31.80 (C32), 34.13 (C2), 51.40 (OCH_3), 129.88 (C27, C28), 174.32 (C1) ppm; MS(m/e) : 521 $(M+1)^+$, 520 (M^+), 489, 488, 446, 404, 143, 125, 111, 97, 83, 74, 69, 57, 55, 43; high-resolution mass measurement : M^+ 520.51977, $C_{35}H_{68}O_2$ requires 520.52193; Anal. calcd for $C_{35}H_{68}O_2$: C, 80.7; H, 13.2. Found C, 80.4; H, 13.1.

Methyl 17-Hexacosenoate (194) via Mixed Dialkyl Cuprate Method

The copper complex **191** was prepared from methylcopper(I) (1.00 mmol) and 9-octadecenylmagnesium bromide **(190)** (1.06 mmol), as described for the ester **189**. The cuprate **191** was reacted with the ω-iodoester **164** (0.34 g, 1.20 mmol) using the procedure described for the ester **189**, to provide 58 mg (14%) of the *ester* ***194***, as a colourless oil.

IR(neat) : 3004m, 2924s, 2852s, 1744s, 1650w, 1468s, 1264s cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ 0.88 (t, *J* 6.5 Hz, 3H, CH_3), 1.25 (s, 36H, $CH_3(CH_2)_6$, $(CH_2)_{12}(CH_2)_2CO_2$), 1.62 (m, 2H, $CH_2CH_2CO_2$), 2.01 (m, 4H, CH_2C=), 2.30 (t, *J* 4.7 Hz, 2H, CH_2CO_2), 3.66 (s,

3H, OCH_3), 5.34 (t, *J* 4.7 Hz, 2H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, 300 MHz) : δ 14.08 (C26), 22.67 (C25), 24.92 (C3), 27.17 (C16, C19), 29.13 – 29.75 (C4 – C15, C20 – C23), 31.89 (C24), 34.06 (C2), 51.38 (OCH_3), 129.83 (C17, C18), 174.29 (C1) ppm; MS(m/e) : 409 $(M+1)^+$, 408 (M^+), 377, 376, 334, 292, 172, 143, 141, 129, 119, 117, 87, 74, 55, 43, 41; high-resolution mass measurement : M^+ 408.39564, $C_{27}H_{52}O_2$ requires 408.39673; Anal. calcd for $C_{27}H_{52}O_2$: C, 79.3; H, 12.8. Found C, 79.1; H, 12.4.

Methyl 17-hexacosenoate (194) via Wittig Method

1-Nonyltriphenylphosphonium bromide **(248)** was formed in the following way. A solution of 1-bromononane (**247**) (1.0 g, 4.83 mmol) and triphenylphosphine (1.40 g, 5.34 mmol) in acetonitrile (4 ml) was heated at reflux for 36 h. The solvent was then removed under reduced pressure and the gummy residue was washed thoroughly with several portions of ether. The colourless gum was heated briefly under high vacuum, then kept under high vacuum at room temperature for 6 h, to give 4.9 g (96%) of the phosphonium salt **248** as a clear, colourless glass. The hygroscopic salt **248** was stored under nitrogen as a 1.0 M solution in DMF.

A solution of LiHMDS (0.46 mmol) in THF (0.5 ml) was generated by the addition of a 2 M solution of *n*-butyllithium in hexanes (0.23 ml, 0.46 mmol) to hexamethyldisilazane (0.10 ml, 0.47 mmol) in THF at 0°C. The solution of LiHMDS (0.46 mmol) was added to **248** (0.42 mmol) in DMF : THF : HMPA (1.3 ml, 2 : 3.5 : 1) at 0°C to form an orange solution, which was cooled to –78°C after 10 min. The oxoester **167** (0.10 g, 0.34 mmol) in THF (0.50 ml) was added and the resultant solution was allowed to warm to room temperature and was stirred at this temperature for 1 h. The solution was poured into saturated aqueous ammonium chloride solution (20 ml) and extracted with ethyl acetate (3 x 15 ml). The combined extracts was washed with water (20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual oil was purified by flash column chromatography on silica (2.5% ether / hexane) to give 16 mg (13%) of

the *title compound*. The physical and spectral data were as for **194** formed by the mixed dialkyl cuprate method.

Methyl 13-docosenoate (195) via Mixed Dialkyl Cuprate Method

9-Octadecenylmagnesium bromide (**190**), formed from the bromide **175** (0.35 g, 1.06 mmol) and magnesium (0.06 g, 2.47 mmol) in THF (1.5 ml), was added to methylcopper(I) (1.00 mmol) to form the cuprate **191**, which was reacted with the ω-iodoester **122** (0.28 g, 1.23 mmol) using the procedure described for the ester **189**. The *title compound* was formed in an 18% yield as a colourless oil.

IR(neat) : 3004m, 2920s, 2842s, 1744s, 1650w, 1466m, 1170m cm^{-1}; ^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.88 (t, *J* 6.5 Hz, 3H, CH_3), 1.27 (s, 28H, $CH_3(CH_2)_6$, $(CH_2)_8(CH_2)_2CO_2$), 1.62 (m, 2H, $CH_2CH_2CO_2$), 2.01 (m, 4H, CH_2C=), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 3.66 (s, 3H, OCH_3), 5.35 (t, *J* 4.6 Hz, 2H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, ~~300~~ 75 MHz) : δ 14.13 (C22), 22.72 (C21), 25.00 (C3), 27.24 (C12, C15), 29.10 – 29.82 (C4 – C11, C16 – C19), 31.96 (C20), 34.14 (C2), 51.43 (OCH_3), 129.90 (C13, C14), 174.35 (C1) ppm (lit.[124] ^{13}C-NMR : δ 14.07 (C22), 22.69 (C21), 25.02 (C3), 27.24 (C12, C15), 29.19 – 29.79 (C4 – C11, C16 – C19), 31.92 (C20), 34.12 (C2), 129.73 (C14), 129.75 (C13) ppm); MS(m/e) : 353 $(M+1)^+$, 352 (M^+), 321, 320, 278, 253, 236, 157, 125, 97; high-resolution mass measurement : M^+ 352.33592, $C_{23}H_{44}O_2$ requires 352.33413.

Methyl 13-docosenoate (195) via the Wittig Method

The phosphonium salt **248** (0.42 mmol), generated as described in the synthesis of **194**, was reacted with LiHMDS (0.42 mmol) and the oxoester **171** (0.11 g, 0.45 mmol) in DMF : THF : HMPA (2.2 ml, 1.5 : 5 : 1), as described for **194**. Purification of the crude product by flash column chromatography on silica (2.5% ether / hexane) gave 19 mg

(12%) of the *ester* ***195***. The infrared and ^{1}H-NMR spectra were the same as for **195** synthesized by the cuprate method. The ^{13}C-NMR spectrum contained all the peaks for the *cis* isomer **195** and, in addition, contained small peaks at δ 32.62 and 130.35 ppm, due to the presence of approximately 5% of the *trans* isomer.

Methyl 25, 28-tetratriacontadienoate (200)

The bromide **178** (0.32 g, 0.97 mmol) was treated with magnesium (0.06 g, 2.47 mmol) to form the Grignard reagent **198**, which was added to methylcopper(I) (0.92 mmol) and then reacted with the ω-iodoester **130**, as described for the ester **189**. From the reaction was obtained 107 mg (22%) of the *dienoate ester* ***200*** as a white wax, m.p. = 43 – 43.5°C. IR(CCl_4) : 3008m, 2924s, 2848s, 1742s, 1650w, 1468s, 1172s cm^{-1}; ^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.89 (t, *J* 6.5 Hz, 3H, CH_3), 1.25 (s, 46H, $CH_3(CH_2)_3$, $(CH_2)_{20}(CH_2)_2CO_2$), 1.62 (m, 2H, $CH_2CH_2CO_2$), 2.05 (m, 4H, CH_2C=), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 2.77 (t, *J*5.9 Hz, 2H, $=CCH_2C=$), 3.66 (s, 3H, OCH_3), 5.35 (m, 4H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, ~~300~~ 75 MHz) : δ 14.03 (C34), 22.56 (C33), 24.95 (C3), 25.61 (C27), 27.22 (C24, C30), 29.14 – 29.68 (C4 – C23, C31), 31.53 (C32), 34.08 (C2), 51.36 (OCH_3), 127.92 (C26, C28), 130.13 (C25, C29), 174.25 (C1) ppm; MS(m/e) : 519 $(M+1)^+$, 518 (M^+), 517 $(M-1)^+$, 487, 486, 284, 279, 253, 241, 227, 199, 185, 143, 129, 87; high-resolution mass measurement : M^+ 518.50362, $C_{35}H_{66}O_2$ requires 518.50628.

Methyl 17,20-Hexacosadienoate (201) via Mixed Dialkyl Cuprate Method

The Grignard reagent **198** was generated from the bromide **178** (0.20 g, 0.61 mmol) and magnesium (0.30 g, 1.23 mmol) in THF (1.20 ml) and reacted with methylcopper(I) (0.58 mmol) to form the cuprate **199**, which was subsequently reacted with the ω-iodoester **164** (0.20 g, 0.70 mmol), following the procedure described for the ester **189**.

Purification of the crude material by flash column chromatography on silica (2.5% ether / hexane) provided 89 mg of a mixture of the esters methyl nonanoate and **201**, which was homogenous by TLC on silica. The ^{1}H-NMR spectrum of the mixture was identical to that of the *ester* ***201***, (see below) except the integration ratio of the multiplet at δ 5.36 ppm to the singlet at δ 3.67 ppm was 7 : 10, respectively, instead of the expected 4 : 3. An attempted purification by column chromatography on silver nitrate impregnated silica[126] caused loss of the ester **201** due to decomposition.

Methyl 17,20-Hexacosadienoate (201) via Dialkyl Cuprate Method

A solution of 1.6M *t*-butyllithium in pentane (1.0 ml, 1.60 mmol) was added to the iodide **233** (0.30 g, 0.80 mmol) in ether (0.80 ml) at –78°C[137,138] and the mixture was allowed to stir for 15 min. Cuprous iodide (0.15 g, 0.80 mmol) was added to the mixture and a black solid formed. Stirring was continued at –78°C for 1 h, then the temperature of the mixture was allowed to warm to 0°C to ensure complete formation of the alkylcopper(I) species **238**, followed by recooling of the mixture to –78°C. The Grignard reagent **198**, generated from the bromide **178** (0.32 g, 0.97 mmol) and magnesium (0.06 g, 2.47 mmol) in THF (1.5 ml), was added to the mixture at –78°C and stirring was continued for 1 h. Warming of the mixture to 0°C formed the black suspension of the cuprate **239** and the mixture was again recooled to –78°C. Addition of a solution of the ω-iodoester **164** (0.41 g, 1.44 mmol) in THF (1 ml) was followed by stirring of the mixture for 1 h at –78°C. The mixture was allowed to warm to room temperature over 3 h and then stirred for a further 2 h. The mixture was poured into aqueous ammonium chloride solution (20 ml) and the layers separated. The aqueous layer was extracted with ether (3 x 10 ml). The combined organic material was washed with brine (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification of the crude material by flash column chromatography on silica (2.5% ether / hexane) provided 37 mg (12%) of the *ester* ***201***. as an oil

IR(CCl_4) : 3008m, 2928s, 2852s, 1742s, 1650w, 1466m, 1172m cm^{-1}; ^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.89 (t, *J* 6.6 Hz, 3H, CH_3), 1.25 (s, 30H, $CH_3(\mathbf{CH_2})_3$, $(CH_2)_{12}(CH_2)_2CO_2$), 1.62 (m, 2H, $CH_2CH_2CO_2$), 2.05 (m, 4H, CH_2C=), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 2.78 (t, *J* 5.9 Hz, 2H, =CCH_2C=), 3.67 (s, 3H, OCH_3), 5.36 (m, 4H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, 300 MHz) : δ 14.08 (C26), 22.57 (C25), 24.94 (C3), 25.60 (C19), 27.18, 27.21 (C16, C22), 29.14 – 29.67 (C4 – C15, C23), 31.52 (C24), 34.10 (C2), 51.46 (OCH_3), 127.90 (C18, C20), 130.17 (C17, C21), 174.38 (C1) ppm; MS(m/e) : 407 $(M+1)^+$, 406 (M^+), 375, 374, 123, 109, 85, 81, 67, 55, 41; high-resolution mass measurement : M^+ 406.37964, $C_{27}H_{50}O_2$ requires 406.38108; Anal. calcd for $C_{27}H_{50}O_2$: C, 79.7; H, 12.4. Found C, 80.1; H, 12.3.

Methyl 17,20-hexacosadienoate (201) via the Wittig Method

1-(3-nonenyl)triphenylphosphonium bromide (**251**) was formed in a 92% yield as a clear, colourless glass, by reacting the bromide **250** (0.51 g, 2.48 mmol) and triphenylphosphine (0.72 g, 2.75 mmol) in acetonitrile (2 ml), in the same way as for the the formation of the salt **248**. The salt **251** was stored as a 0.90 M solution in DMF under nitrogen. In the same way as described for the ester **194**, a solution of the phosphonium salt **251** (0.34 mmol) in DMF : THF : HMPA (2.0 ml, 1.5 : 5 : 1) was reacted with LiHMDS (0.35 mmol) followed by the oxoester **167** (0.11 g, 0.35 mmol). The crude material obtained was purified by flash column chromatography on silica (2.5% ether / hexane) to give 15 mg (10%) of the ester **201**. The infrared spectrum was the same as previously described for **201**. The ^{1}H-NMR spectrum contained all the signals corresponding to **201**, but also contained the anomolous signals at δ 2.0 ppm (m) and δ 2.72 ppm (t, *J* 5.9 Hz). The ^{13}C-NMR spectrum contained all the peaks for **201** with extra peaks at δ 30.45, 32.55, 127.70, 128.28, 130.48 and 130.83 ppm.

Methyl 25,28,31-tetratriacontatrienoate (204) via Mixed Dialkyl Cuprate Method

The bromide **182** (0.36 g, 1.10 mmol) was treated with magnesium (0.06 g, 2.47 mmol) in THF (2 ml) in the usual way to form the Grignard reagent **202**. Reaction of **202** with methylcopper(I) (1.06 mmol) followed by treatment with the ω-iodoester **130** (0.50 g, 1.26 mmol), in the manner described for **189**, produced 0.16 g of product material, after purification by flash column chromatography on silica (2.5% ether / hexane). The ^{1}H-NMR spectrum of the material was as expected for the ester **204** except the ratio of integration of the singlet at δ 3.66 ppm to the multiplet at δ 5.37 ppm was 5 : 7, rather than the expected ratio of 2 : 1. An extra triplet (*J* 6.5 Hz) was also observed at δ 0.88 ppm. This indicated that the ester **204** was contaminated with a substantial amount of a saturated ester, presumably methyl heptadecanoate, due to methylationof the ω-iodoester **130**.

Methyl 25, 28, 31-tetratriacontatrienoate (204) via Dialkyl Cuprate Method

Cuprous iodide (0.18 g, 0.95 mmol) was added to a solution of the lithium reagent **240**, formed by addition of a 1.60 M pentane solution of *t*-butyllithium (1.18 ml, 1.89 mmol) to the iodide **234** (0.36 g, 0.96 mmol) in ether (0.80 ml) at –78°C,[137,138] and stirred at this temperature for 1 h. The resulting dark-orange mixture was warmed to 0°C to form the dark orange-black alkylcopper(I) species **241**. The mixture was immediately cooled to –78°C and the Grignard reagent **202**, formed by adding a solution of the bromide **182** (0.37 g, 1.13 mmol) in THF (0.5 ml) to magnesium (0.06 g, 2.47 mmol) and a crystal of iodine in THF (1.0 ml) and refluxing for 1 h, was added at –78°C. The brown mixture was warmed to 0°C, whereupon a black suspension of the cuprate species **242** formed which was cooled immediately to –78°C. Addition of a solution of the ω-iodoester **130** (0.46 g, 1.15 mmol) in THF (1.0 ml) to the cuprate mixture at –78°C was followed by stirring at this temperature for 1 h and 3 h at room temperature. The reaction mixture

was poured into saturated aqueous ammonium chloride solution (20 ml) and the layers separated. The aqueous layer was extracted with ether (3 x 15 ml) and the combined organic material was washed with brine (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification of the crude material afforded 48 mg (10%) of the *trienoate ester* **204** as a white wax, m.p. = 39 – 41°C.

IR(CCl_4) : 3008m, 2924s, 2848s, 1742s, 1650w, 1466m, 1172 cm^{-1}; ^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.98 (t, *J* 7.5 Hz, 3H, CH_3), 1.25 (s, 40H, $(CH_2)_{20}(CH_2)_2CO_2$), 1.62 (m, 2H, $CH_2CH_2CO_2$), 2.06 (m, 4H, CH_2C=), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 2.81 (t, *J* 5.6 Hz, 4H, =CCH_2C=), 3.67 (s, 3H, OCH_3), 5.37 (m, 6H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, 300 MHz) : δ 14.27 (C34), 20.54 (C33), 24.97 (C3), 25.53 (C27 or C30), 25.62 (C27 or C30), 27.25 (C24), 29.15 – 29.69 (C4 – C23), 34.13 (C2), 51.40 (OCH_3), 127.62 (C26, C31), 128.24 (C28, C29), 130.40 (C25, C32), 174.33 (C1) ppm; MS (m/e) : 516 (M^+), 515 $(M-1)^+$, 284, 270, 253, 141, 227, 199, 185, 143, 129; high-resolution mass measurement : M^+ 516.48820, $C_{35}H_{64}O_2$ requires 516.49063; Anal. calcd for $C_{35}H_{64}O_2$: C, 81.3; H, 12.5. Found C, 81.4; H, 12.5.

Hexadeca-4,7,10-triyn-1-ol (213)

The method of Osbond *et al.*[67] was adapted.

A solution of the alkynol **211** (2.25 ml, 24.18 mmol) in THF (1 ml) was added to a 1.65 M solution of ethylmagnesium bromide in THF (31.5 ml, 51.98 mmol) at 0°C (ice-bath) and then stirred at room temperature for 2 h. The mixture was cooled to 0°C, cuprous chloride (0.05 g, 0.51 mmol) was added and, after stirring for 15 min, the diynyl bromide **32** (2.75 g, 12.11 mmol) in THF (1 ml) was added dropwise. The solution was refluxed for 24 h, more cuprous chloride (0.03 g, 0.30 mmol) being added after 19 h. The cooled solution was poured into 10% aqueous sulphuric acid (50 ml) and ice and the layers were separated. The aqueous layer was extracted with ether (3 x 20 ml) and the combined organic material was washed with a 1 : 4 ammonium

hydroxide : saturated ammonium chloride solution (2 x 25 ml), water (20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Unreacted bromide **32** was removed from the crude mixture by dry-column flash chromatography on silica (40% ethyl acetate / hexane) and the more polar component was distilled *via* kügelrohr to provide 1.19 g (43%) of the alcohol **213**, b.p. = 250°C / 0.08 mm (block).

IR(neat) : 3650 – 3075, 2928s, 2852s, 2225w, 1318s, 1058s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.89 (m, 3H, CH_3), 1.07 – 2.47 (m, 13H, $CH_3(CH_2)_4$, $(CH_2)_2CH_2O$, OH), 3.17 (m, 4H, $\equiv CCH_2C\equiv$), 3.77 (t, *J* 6.5 Hz, 2H, CH_2O) ppm.

1-Bromo-4,7,10-hexadecatriyne (214)

The triynyl alcohol **213** (0.76 g, 3.30 mmol) and triphenylphosphine (0.87 g, 3.32 mmol) were dissolved in dichloromethane (8 ml) and cooled to 0°C (ice bath). Carbon tetrabromide (1.10 g, 3.32 mmol) was added in portions to the solution and stirring was continued overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The solid residue was washed with hexane (4x) and the combined washings were again concentrated *in vacuo*. The residual oil was purified by dry-column flash chromatography on silica (hexane) to give 0.74 g (76%) of the *title compound*.

IR(neat) : 2928s, 2856s, 2225w, 1434s, 1318s, 1246s, 670s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.92 (m, 3H, CH_3), 1.40 (m, 6H, $CH_3(CH_2)_3$), 1.83 – 2.52 (m, 6H, $CH_2C\equiv$, CH_2CH_2Br), 3.07 (m, 4H, $\equiv CCH_2C\equiv$), 3.47 (t, *J* 6.5 Hz, 2H, CH_2Br) ppm.

1-Bromo-4, 7, 10-hexadecatriene (215)

The method of Millar and Underhill,[139] for the reduction of similar triynes, was adapted.

A suspension of dicyclohexylborane (9.60 mmol) was prepared by dropwise addition of cyclohexene (1.95 ml, 19.23 mmol) to a solution of borane-dimethylsulfide complex (2.0 M, 4.8 ml, 9.60 mmol) in THF (1.5 ml) whilst maintaining the temperature between 0 – 5°C (ice-bath). The resulting mixture was warmed to 20°C and stirred for 2 h, then cooled to 0°C again. The bromotriyne **214** (0.66 g, 2.25 mmol) in THF (2.0 ml) was added to the mixture at 0°C and, upon completion of the addition, the temperature of the mixture was allowed to warm to room temperature over 2 h, followed by stirring at this temperature for an additional 2 h. Glacial acetic acid (3.8 ml) was then added dropwise and the resulting solution was stirred overnight. To the cooled solution (ice-bath) was added aqueous sodium hydroxide (5 M, 13.6 ml) followed by the dropwise addition of 30% aqueous hydrogen peroxide (3.7 ml). The resultant mixture was diluted with water (50 ml) and extracted with hexane (3 x 20 ml). The combined organic extracts was dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was purified by dry-column flash chromatography on silica (hexane) followed by kügelrohr distillation to give 0.38 g (56%) of the *bromotriene (215)*, b.p. = 250° / 0.05 mm (block).

IR(neat) : 3008m, 2924s, 2848s, 1650w, 1450m cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.73 – 2.40 (m, 11H, $CH_3(CH_2)_3$, $BrCH_2CH_2$), 2.78 (m, 6H, CH_2C=), 3.35 (t, *J* 6.5 Hz, 2H, CH_2Br), δ 5.29 (m, 6H, CH=CH) ppm.

Methyl 20, 23, 26-dotriacontatrienoate (218)

The Grignard reagent **216** was generated by adding the bromide **215** (0.15 g, 0.50 mmol) and 1,2-dibromoethane (0.03 g, 0.16 mmol) in THF (0.3 ml) to magnesium (25 mg, 1.03 mmol) and iodine (a small crystal) in THF (0.3 ml) and heating the resultant mixture at reflux for 1 h. Addition of the Grignard reagent **216** to methylcopper(I) (0.33 mmol) was followed by treatment with the ω-iodoester **130** (0.16 g, 0.40 mmol), as described for the ester **189**. The reaction mixture was quenched with aqueous

ammonium chloride solution and the aqueous phase extracted with ether (3x), dried ($MgSO_4$) and concentrated *in vacuo*, analogously as described for the ester **189**. The residual oil was purified by flash column chromatography on silica (2.5% ether / hexane) to give 55 mg of a mixture of the *title compound* and methyl heptadecanoate. No attempt was made to separate the two compounds.

^{1}H-NMR($CDCl_3$) : δ 0.87 (m, CH_3), 1.27 (s, CH_2), 2.30 (t, *J* 7.0 Hz, CH_2CO_2), 3.64 (s, OCH_3), 5.33 (m, CH=CH) ppm.

The ratio of the integrations of the signals at δ 3.64 and 5.33 ppm was 2.8 : 1, respectively. The expected ratio of these peaks for **208** is 1 : 2, respectively.

MS(m/e) : 488 (M^+ for ester 156), 284 (M^+ for ester 105); high-resolution mass measurement : M^+ 488.45820, $C_{33}H_{60}O_2$ requires 488.45933.

Nonacosanoic acid (220)

The method of Mirviss[128] was applied.

To a solution of the bromoacid **131** (0.29 g, 1.09 mmol) in THF (1.2 ml) at 0°C was added a 1.1 M THF solution of ethylmagnesium bromide (1.0 ml, 1.1 mmol) and the mixture was stirred for 1 h. A 0.2 M solution of Li_2CuCl_4 in THF[101] (0.15 ml, 0.003 mmol) was added to the mixture at –10°C The resultant solution was cooled to –20°C and a THF solution of the Grignard reagent **187** (1.05 mmol), formed by treating the bromide **96** (0.35 g, 1.05 mmol) with magnesium (0.05 g, 2.06 mmol) in THF (1.25 ml) in the usual way, was added slowly. The solution was stirred at –20°C for 1.5 h and then for 2 h at room temperature. The blue reaction mixture was poured into 10% aqueous sulphuric acid (20 ml) and the resultant mixture was extracted with toluene (3 x 15 ml). The combined toluene extracts was washed with 5% aqueous sulphuric acid (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The solid residue was purified first by dry-column flash chromatography on

silica (ethyl acetate gradient in hexane) and then by flash column chromatography on silica (20% ethyl acetate / hexane) to give 20 mg (4%) of slightly impure *acid 220*. ^{1}H-NMR($CDCl_3$) : δ 0.87 (m, 3H, CH_3), 1.33 (s, 52H, $(CH_2)_{26}$), 2.36 (m, CH_2CO_2) ppm; MS(m/e) : 438 (M^+), 410, 395, 306, 215, 187.

3-Methoxy-3-methyl-1-butyne (224)

Prepared by the method of Corey *et al.*[134] in a 61% yield. B.p. = 76 – 80°C (lit.[134] b.p. = 77 – 80°C).
IR(neat) : 3300s, 2980s, 2936s, 2828m, 2100w, 1176s, 1076s, 844s cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 1.48 (s, 6H, CH_3), 2.42 (s, 1H, ≡CH), 3.37 (s, 3H, OCH_3) ppm; MS(m/e) : 97 $(M–H)^+$, 83, 67, 51, 43.

Methyl nonadecanoate (228)

The method of Corey *et al.*[134] applied.
A solution of the alkyne **224** (0.09 g, 0.90 mmol) in THF (0.90 ml) at 0°C was treated with *n*-butyllithium (2.5 M in hexanes, 0.35 ml, 0.88 mmol). The solution was stirred for 10 min, then cuprous iodide (0.17 g, 0.90 mmol) was added and washed through with THF (0.90 ml). The resultant red / orange solution of **222** was stirred at 0°C for 30 min, then transferred to a solution of nonyllithium (**226**) in THF at –78°C, formed previously by treating nonyl iodide (0.23 g, 0.90 mmol) in ether (0.50 ml) with *t*-butyllithium (1.60 M in pentane, 1.25 ml, 2.0 mmol),[137,138] causing an immediate change in colour from red / orange to yellow. The solution was briefly warmed to –20°C then recooled to –78°C. The ω-iodoester **126** (0.34 g, 1.09 mmol) in THF (0.25 ml) was added and the mixture was stirred for 30 min at –78°C, 5 h at –20°C and finally 1 h at room temperature. The reaction mixture was poured into saturated aqueous ammonium

chloride solution (30 ml) and extracted with ether (3 x 20 ml). The combined ether extracts was washed with brine (20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography on silica (2.5% ether / hexane) to give 0.15 g of material, homogenous by TLC on silica.

The ^{1}H-NMR spectrum contained : δ 0.87 (large singlet), 1.31 (s, CH_2), 2.31 (m, CH_2CO_2), 3.68 (s, OCH_3) ppm; The singlet at δ 0.87 ppm indicated incorporation of a *t*-butyl group. MS(m/e) : 312 (M^+ for **228**), 280, 268, 242 (M^+ for **229**), 143, 87, 74.

Attempted formation of *methyl octacosanoate (232)*

The method of Bergbreiter and Whitesides[72] was adapted.

A solution of the cuprous acetylide **222** (0.90 mmol) in THF (0.80 ml) was generated as described for the synthesis of **228**. This solution was cooled to –78°C and the Grignard reagent **187** (1.05 mmol), formed by reacting the bromide **96** (0.35 g, 1.05 mmol) with magnesium (0.06 g, 2.47 mmol) in THF (1.5 ml) in the usual way, was added. The mixture was stirred for 1 h at –78°C, then warmed to 10°C, during which the solution changed colour from red / orange to yellow. The reaction mixture was immediately cooled to –78°C and a solution of the ω-iodoester **126** (0.35 g, 1.11 mmol) in THF (0.50 ml) was added. After stirring for 1 h at –78°C and 3 h at room temperature, the mixture was poured into saturated aqueous ammonium chloride solution (40 ml) and extracted with ether (2 x 20 ml). The combined extracts was washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Analysis of the reaction mixture by TLC on silica showed only a mobile component (hydrocarbon) and unreacted ω-iodoester **126** being present on the chromatogram, indicating that no ester **232** had formed.

1-Iodo-9,12-octadecadiene (233)

A solution of the bromide **178** (0.50 g, 1.52 mmol) and sodium iodide (0.57 g, 3.80 mmol) in acetone (10 ml) was refluxed overnight. The solution was allowed to cool to room temperature and then was poured into water (200 ml) and extracted with dichloromethane (3 x 30 ml). The combined extracts was washed with 10% aqueous sodium thiosulphate solution (30 ml), dried (MgSO4) and the solvent removed *in vacuo*. The crude sample was purified by dry-column flash chromatography on silica (hexane) to give 0.45 g (78%) of the *iodide* **233**.

IR(neat) : 3004m, 2924s, 2848s, 1650w, 1464m, 722m cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.90 (m, 3H, CH_3), 1.07 – 2.27 (m, 22H, $CH_3(CH_2)_4$, $(CH_2)_7CH_2I$), 2.71 (m, 2H, $=CCH_2C=$), 3.12 (t, *J* 6.5 Hz, 2H, CH_2I), 5.25 (m, 4H, CH=CH) ppm; MS(m/e) : 376 (M^+), 196, 156, 110, 95, 81, 67, 55, 41; high-resolution mass measurement : M^+ 376.16164, $C_{18}H_{33}I$ requires 376.1627.

1-Iodo-9, 12, 15-octadecatriene (234)

The bromide **182** (0.50 g, 1.53 mmol) was treated with sodium iodide (0.58 g, 3.87 mmol) in acetone (10 ml), as described for the iodide **233**, to give 0.40 g (70%) of the *iodide* **234**, after purification by dry-column flash chromatography on silica (hexane).

IR(neat) : 3008s, 2924s, 2848s, 1650w, 1464m, 718m cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.98 (t, *J* 7.5 Hz, 3H, CH_3), 1.15 – 2.33 (m, 16H, CH_3CH_2, $(CH_2)_7CH_2I$), 2.75 (m, 4H, $=CCH_2C$), 3.12 (t, *J* 6.5 Hz, 2H, CH_2I), 5.29 (m, 6H, CH=CH) ppm; MS(m/e) : 374 (M^+), 345, 317, 183, 155, 136, 121, 109, 107, 94, 91, 79, 55; high-resolution mass measurement : M^+ 374.14555, $C_{18}H_{31}I$ requires 374.14705.

1-Octadecyltriphenylphosphonium bromide (243)

A mixture of the bromide **96** (2.05 g, 6.15 mmol), triphenylphosphine (3.78 g, 14.41 mmol) and acetonitrile (20 ml) was refluxed overnight. The resulting mixture was concentrated *in vacuo* to reveal a white solid. This solid was washed several times with ethyl acetate and then recrystallized from hexane / dichloromethane to give 1.98 g (54%) of the *title compound* as a white crystalline solid. M.p. = 98 – 99.5°C (lit.[142] m.p. = 99 – 100°C).

^{1}H-NMR($CDCl_3$) : δ 0.88 (m, 3H, CH_3), 1.1 – 1.8 (m, 32H, $CH_3(CH_2)_{16}$), 3.83 (b, 2H, CH_2P), 7.80 (m, 15H, aromatic) ppm.

8-Hexacosene (246)

A THF solution of LiHMDS (1.57 mmol) was generated by the addition of *n*-butyllithium (1.50 M, 1.05 ml, 1.58 mmol) to hexamethyldisilazane (0.33 ml, 1.57 mol) in THF (1.55 ml) at 0°C. The phosphonium salt **243** (0.93 g, 1.56 mmol) was suspended in THF : HMPA (3.1 ml, 4 : 1) and cooled to 0°C. Addition of the solution of LiHMDS produced an orange solution of the ylid **244** which, after stirring for 10 min at 0°C, was cooled to –78°C. The aldehyde **245** (0.11 g, 0.86 mmol) in THF (3 ml) was added to the mixture, which was subsequently allowed to warm to 0°C and was stirred at this temperature for 1 h. The resultant solution was poured into saturated aqueous ammonium chloride solution (20 ml) and extracted with ethyl acetate (3 x 15 ml). The combined ethyl acetate extracts was washed with water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification of the residue by dry-column flash chromatography on silica (hexane) gave 0.25 g (82%) of the alkene **246** as an oil.

IR(neat) : 3004w, 2924s, 2848s, 1462m cm^{-1}; ^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.88 (t, *J* 6.5 Hz, 6H, CH_3), 1.26 (s, 40H, $CH_3(CH_2)_5$, $(CH_2)_{15}CH_3$), 2.01 (m, 4H, CH_2C=), 5.34 (t, *J* 4.7 Hz, 2H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, 300 MHz) : δ 14.13 (C1, C26), 22.70 (C2,

C25), 27.21 (C7, C10), 29.25 – 29.78 (C4 – C6, C11 – C23), 31.90 (C3 or C24), 31.94 (C3 or C24), 129.87 (C8, C9) ppm; MS(m/e) ; 364 (M^+), 125, 111, 97, 83, 66, 52, 49, 39; high-resolution mass measurement : M^+ 364.40868, $C_{26}H_{52}$ requires 364.40690; Anal. calcd for $C_{26}H_{52}$: C, 85.6; H, 14.4. Found : C, 85.3, H, 14.3.

1-Bromo-cis-3-nonene (250)

Phosphorous tribromide (0.70 ml, 7.38 mmol) was added to a solution of the alcohol **249** (2.0 g, 14.06 mmol) and pyridine (5 drops) in ether and the mixture was heated at reflux overnight. The cool mixture was poured into water (20 ml) and the layers were separated. The aqueous layer was extracted with ether (2 x 20 ml). The combined organic material was washed with saturated aqueous sodium bicarbonate solution (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification of the crude oil by dry-column flash chromatography on silica (hexane) gave 1.69 g (59%) of the bromide **250**.

IR(neat) : 3008m, 2952s, 2924s, 2852s, 1660w, 1466m, 1266, 1208m cm^{-1}; ^{1}H-NMR($CDCl_3$) : δ 0.91 (m, 3H, CH_3), 1.12 – 1.63 (m, 6H, $CH_3(CH_2)_3$), 2.03 (m, 2H, $=CCH_2(CH_2)_2$), 2.62 (m, 2H, $=CCH_2CH_2Br$), 3.37 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.44 (m, 2H, CH=CH) ppm; MS(m/e) : 206 (M^+), 204 (M^+), 164, 162, 150, 148, 83, 69, 55, 41.

Methyl 10-octacosenoate (252)

A solution of LiHMDS (2.03 mmol) was generated from hexamethyldisilazane (0.43 ml, 2.04 mmol) and *n*-butyllithium (1.50 M in hexanes, 1.35 ml, 2.03 mmol) in THF (1.6 ml) at 0°C, as described for the formation of the alkene **246**. Addition of the solution of LiHMDS to a suspension of the phosphonium salt **243** (1.20 g, 2.01 mmol) in THF : HMPA (3.0 ml, 4 : 1) at 0°C produced an orange solution which was cooled to

–78°C and reacted with the oxoester **166** (0.20 g, 1.00 mmol), as described for the alkene **246**. The reaction mixture was poured into saturated aqueous ammonium chloride solution (10 ml) and extracted with ethyl acetate (3 x 10 ml). The combined extracts was washed with water (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by dry-column flash chromatography on silica (2.5% ether / hexane) followed by recrystallization from acetone, to give 0.29 g (67%) of the *monoenoic ester* **252** as a white solid, m.p. = 36 – 37°C.

IR($CHCl_3$) : 2996m, 2928s, 2848s, 1730s, 1466s, 1440s, 1176s cm^{-1}; ^{1}H-NMR($CDCl_3$, 300 MHz) : δ 0.88 (t, *J* 6.5 Hz, 3H, CH_3), 1.25 (s, 40H, $CH_3(CH_2)_{15}$, $(CH_2)_5(CH_2)_2CO_2$), 1.61 (m, 2H, $CH_2CH_2CO_2$), 2.01 (m, 4H, CH_2C=), 2.30 (t, *J* 7.5 Hz, 2H, CH_2CO_2), 3.67 (s, 3H, OCH_3), 5.34 (t, *J* 5.3 Hz, 2H, CH=CH) ppm; ^{13}C-NMR($CDCl_3$, 300 MHz) : 14.12 (C28), 22.69 (C27), 24.93 (C3), 27.17 (C9 or C12), 27.19 (C9 or C12), 29.13 – 29.75 (C4 – C8, C13 – C25), 31.92 (C26), 34.09 (C2), 51.43 (OCH_3), 129.78 (C10), 129.93 (C11), 174.33 (C1) ppm; MS(m/e) : 437 $(M+1)^+$, 436 (M^+), 405, 404, 362, 320, 228, 213, 199, 185, 171, 111, 97, 83, 69, 55, 43, 41; high-resolution mass measurement : M^+ 436.42620, $C_{29}H_{56}O_2$ requires 436.42803; Anal. calcd for $C_{29}H_{56}O_2$: C, 79.8; H, 12.9. Found C, 79.7; H, 13.2.

Pentadeca-3,6,9-triyn-1-ol (256)

The Grignard complex **255** (39.2 mmol), generated by the addition of a solution of 3-butyn-1-ol (**254**) (2.75 g, 39.24 mmol) in THF (20 ml) to a 1.60 M THF solution of ethylmagnesium bromide (49 ml, 78.4 mmol), was treated with cuprous chloride (0.20 g, 2.02 mmol) and then reacted with the diynyl bromide **32** (3.0 g, 13.2 mmol), using the method of Osbond *et al.*[67] and as described for the triynyl alcohol **213**. The crude material obtained was distilled *via* kügelrohr to remove the excess alcohol **254** (b.p. = 170°C / 14 mm (block)) and the residue was purified further by dry-column flash chromatography on silica (ethyl acetate / hexane gradient) to give 0.69 g (24%) of

the *triynyl alcohol* **256**. An attempt to recrystallize the low melting solid resulted in some decomposition of the material.

IR(CCl_4) : 3700 – 3050, 2932s, 2858s, 2212w, 1318s, 1052s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.93 (m, 3H, CH_3), 1.10 – 1.77 (m, 6H, $CH_3(CH_2)_3$), 1.93 – 2.57 (m, 5H, $CH_2C{\equiv}$, OH), 3.07 (m, 4H, $\equiv CCH_2C{\equiv}$), 3.62 (t, *J* 6.5 Hz, 2H, CH_2O) ppm.

1-Bromo-3,6,9-pentadecatriyne (257)

To an ice-cooled solution of the alcohol **256** (0.59 g, 2.73 mmol) and triphenylphosphine (0.72 g, 2.75 mmol) in dichloromethane (7 ml) was added carbon tetrabromide (0.91 g, 2.74 mmol) portionwise. The solution was stirred at room temperature overnight and then concentrated under reduced pressure. The solid residue was washed with hexane (7x) and the combined washings was concentrated *in vacuo*. The residual oil was purified by dry-column chromatography on silica (hexane) to give 0.35 g (46%) of the *bromide* **257**.

IR(neat) : 2928s, 2856s, 2210w, 1416m, 670s cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.92 (m, 3H, CH_3), 1.08 – 1.67 (m, 6H, $CH_3(CH_2)_3$), 1.90 – 2.40 (m, 2H, $CH_2C{\equiv}$), 2.70 (t, *J* 6.5 Hz, 2H, $\equiv CCH_2CH_2Br$), 3.07 (m, 4H, $\equiv CCH_2C{\equiv}$), 3.39 (t, *J* 6.5 Hz, 2H, CH_2Br) ppm.

1-Bromo-3,6,9-pentadecatriene (258)

The method of Millar and Underhill[139] and as dicussed for the trienyl bromide **215**, was followed.

The triynyl bromide **257** (0.32 g, 1.13 mmol) in THF (1.5 ml) was added to a suspension of dicyclohexylborane (9.88 mmol) at 0°C, as described previously. After an identical procedure to that of the bromide **215** was followed, the crude material obtained was purified *via* dry-column flash chromatography on silica (hexane) to give 0.17 g of

material. Further purification of this material by kügelrohr distillation gave 93 mg (29%) of the bromide **258**, b.p. = 200°C / 0.05 mm (block).

IR(neat) : 3004m, 2928s, 2852s, 1650w, 1452m cm^{-1}; ^{1}H-NMR(CCl_4) : δ 0.70 – 2.23 (m, 13H, $CH_3(CH_2)_3$, CH_2C=), 2.75 (m, 4H, =CCH_2C=), 3.31 (t, *J* 6.5 Hz, 2H, CH_2Br), 5.37 (m, 6H, CH=CH) ppm.

Attempted formation of ***methyl 17,20,23,26-dotriacontatetraenoate (261)***

The phosphonium bromide **259** (89 mg, 0.16 mmol) was formed by treating the bromide **258** (64 mg, 0.22 mmol) with triphenylphosphine (0.66 g, 0.25 mmol) in acetonitrile (0.20 ml), as described for the formation of **248**. The solution of **259** in DMF : THF : HMPA (0.65 ml, 2 : 3.5 : 1) was treated with LiHMDS (0.16 mmol) followed by the oxoester **167** (42 mg, 0.14 mmol) in the same way as described for the synthesis of the ester **194**. Purification of the crude mixture by flash column chromatography on silica (3.0% ether / hexane) gave 6 mg of material.

^{1}H-NMR($CDCl_3$) consisted of : δ 0.89 (t, *J* 6.5 Hz), 1.25 (s), 1.62 (m), 1.95 – 2.18 (m), 2.30 (t, *J* 7.5 Hz), 2.81 (m), 3.67 (s), 5.37 (m) ppm. The ratio of integrations of the signals were not correct for **254**.

^{13}C-NMR($CDCl_3$) consisted of : δ 14.08, 22.56, 24.95, 25.62, 27.25, 28.88 – 29.68, 34.11, 51.45, 174.37 ppm. There were also many small peaks between δ 22.61 – 27.67 ppm, δ 30.38 – 33.00 ppm and δ 125.68 – 134.66 ppm indicating a substantial amount of double bond isomers present. No further purification was undertaken.

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