REVIEW

Construction of (*Z*,*Z*) skipped 1,4-dienes. Application to the synthesis of polyunsaturated fatty acids and derivatives †

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Covering: 1957 to the end of 1998.

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1 Introduction

During the last three decades, numerous studies have emphasised the major role of the polyunsaturated fatty acid (PUFA) in the physiology and biochemistry of organisms (furthermore, isolation of numerous pheromones has shown that they derive from PUFA).[1]

This review covers the literature from 1957 to the end of 1998. It focuses on the preparations of the skipped diene moiety and their application to the synthesis of natural products such as polyunsaturated fatty acids and metabolites (Fig. 1).[2]

Four classes of PUFA derive from four different precursors: linoleic, linolenic, oleic and palmitoleic acids. Those deriving from linoleic (*n*-6 acids series) and linolenic acids are essential, and are not synthesised and must be present in the diet.[3] The nutritional effects and metabolism of these two series of essential fatty acids are different.[4]

From arachidonic acid, the lipoxygenase enzymatic systems lead to three hydroperoxyeicosatetraenoic acids (HPETE) which are precursors of the corresponding hydroxyeicosatetraenoic acids (HETE).[5,6] In particular, leukotriene A4, obtained from HPETE, leads to leukotriene B4, to lipotoxins and mainly, after addition of glutathione, to leukotriene C4, D4 and E4.[7,8] Docosahexaenoic acid **12** has been proposed as an active molecule against prostate cancer.[9] DHA is also a strong competitive inhibitor of the conversion of arachidonate to prostaglandins by the prostaglandin synthetase but exhibits little interference to the conversion of arachidonate to metabolites on the leukotriene pathway.[10]

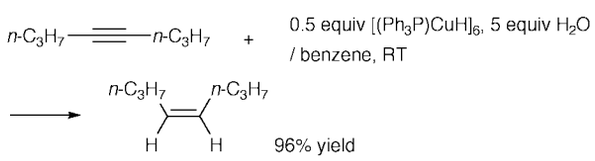
† Dedicated to the memory of Professor R. A. Raphael.

2 Preparation of PUFA and metabolites from the polyyne synthesis–semi-hydrogenation sequence

2.1 Synthesis of the 1,4-diene moiety from cross-coupling between propargyl halides and acetylide organometallic reagents

For a long time, the sole method leading to pure (*Z*)-olefins was the semi-hydrogenation of the corresponding alkynes.[11] In 1952, Lindlar reported that hydrogenation of alkynes under palladium catalysis (palladium oxide deposited on calcium carbonate and poisoned with lead acetate and quinoline) led to (*Z*)-alkenes with high selectivities.[12,13] Dideutero (*Z*)-alkenes were elaborated by this method.[14] Next, Brown proposed another selective catalyst (P-2 Ni) generated *in situ* by reduction of nickel acetate with sodium borohydride in ethanol.[15] Addition of 1,2-diaminoethane increased significantly the selectivities (*Z*-alkenes *vs.* alkanes). Finally, hydroboration followed by protolysis is more and more used.[16]

Recently, numerous systems have been reported for reduction of a triple bond to a (*Z*)-double bond. For instance, triphenylphosphinecopper hydride leads to (*Z*)-alkenes with high selectivities and yields (Scheme 1).[17]



Scheme 1

(*Z*)-Alkenes and dideutero (*Z*)-alkenes may be obtained from alkynes and a low valent transition metal. The metallacyclopropene intermediates give after protolysis the (*Z*)-double bond. So, the tantalum chloride–zinc couple reacts with dodecyne **13** and gives after deuterium oxide treatment the (*Z*)-dideuterododecene **14** (Scheme 2).[18]

Similar results were obtained by Sato *et al.* by using the couple titanium tetraisopropoxide–isopropylmagnesium chloride.[19] A titanacyclopropene intermediate is evidenced by its reaction with deuterium oxide (Scheme 3).

This method was then simplified by Kitching for the preparation of a deuterated trienic ether **16** from triyne **15**.[20] Neverthe-

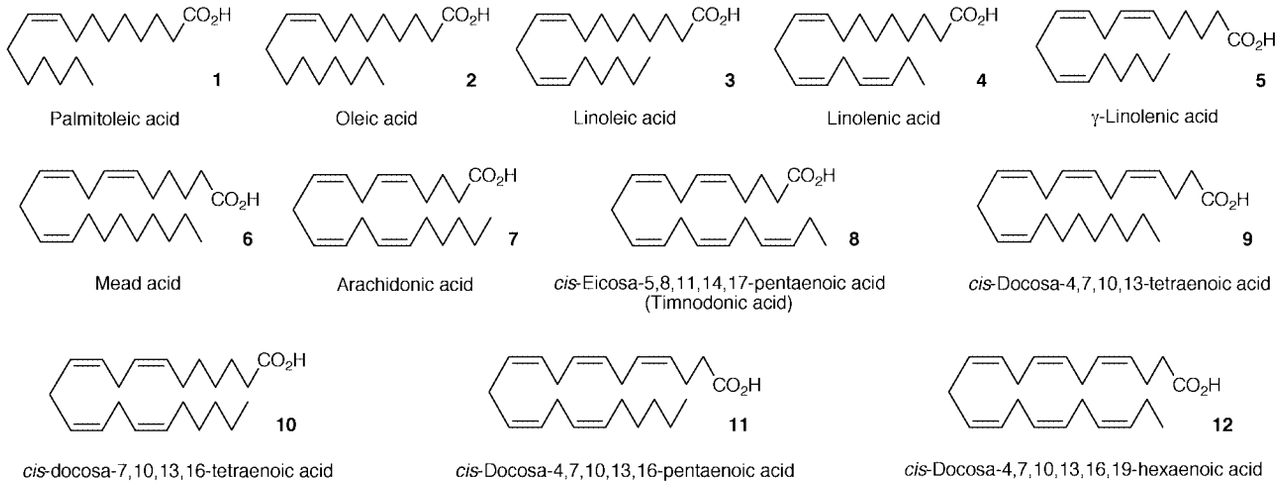
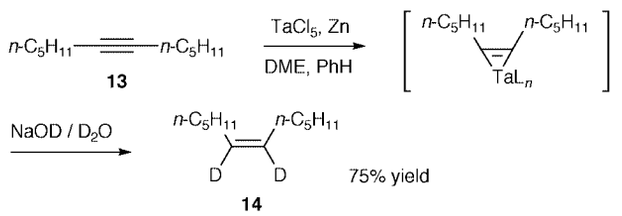
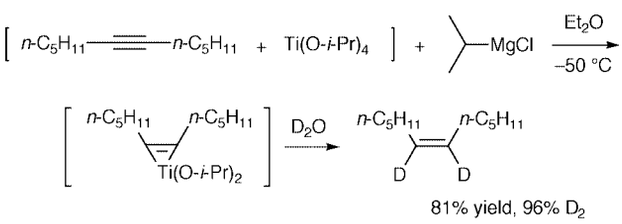


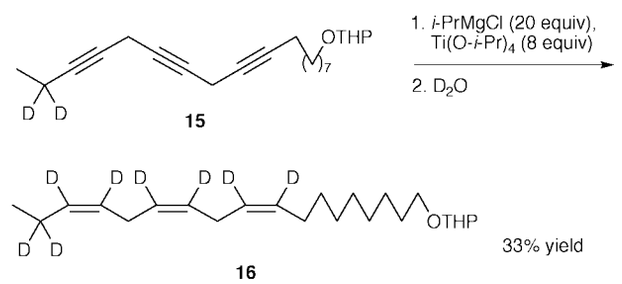
Fig. 1



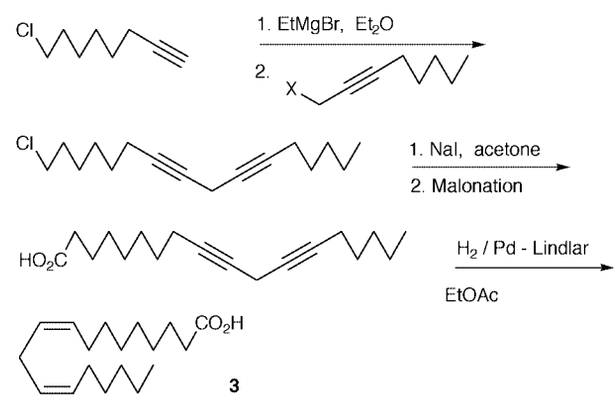
Scheme 2



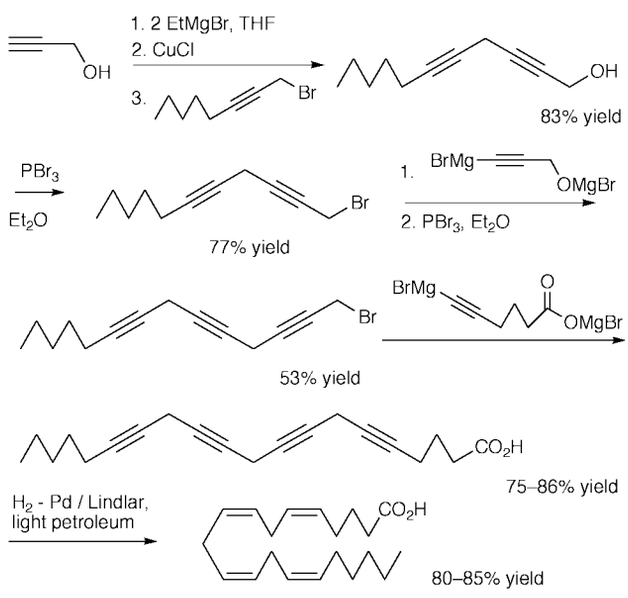
Scheme 3



Scheme 4



Scheme 5



Scheme 6

less, the large excess of Grignard reagent does not allow the presence of functional groups such as esters (Scheme 4).

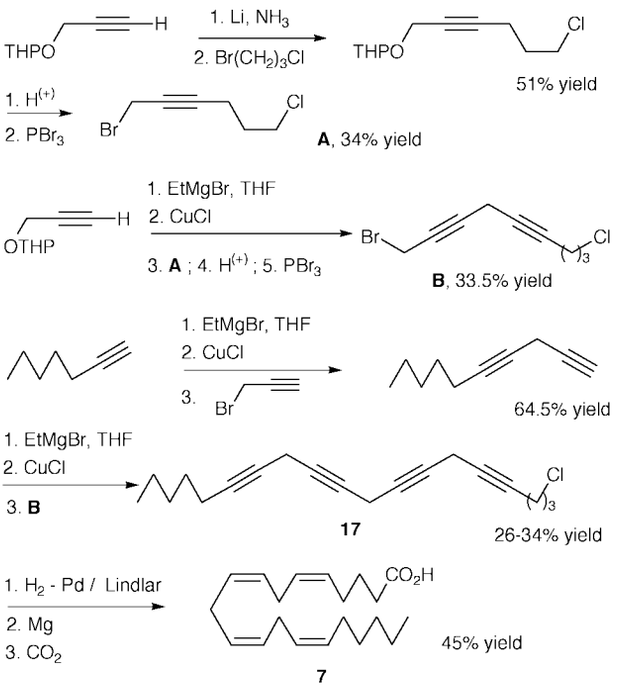
2.1.a Synthesis of PUFA

As early as 1951, numerous natural monoethylenic acids were prepared by acetylene chemistry followed by selective hydrogenation.[21,22] Although the first PUFA (linoleic acid **3**) was synthesised by Raphael and Sondheimer in 1950,[23] the change of X = methanesulfonate to bromide and the use of copper chloride have improved this procedure which is, now, a classical and a very often used method. One year later, Gensler and Thomas reported a similar approach to the same acid (Scheme 5).[24,25]

In 1959, Osbond reported a general route to PUFA, based on the iterative use of propargyl alcohol. Arachidonic **7** (Scheme 6) and docosahexaenoic acids **12** were prepared by this procedure.[26,27]

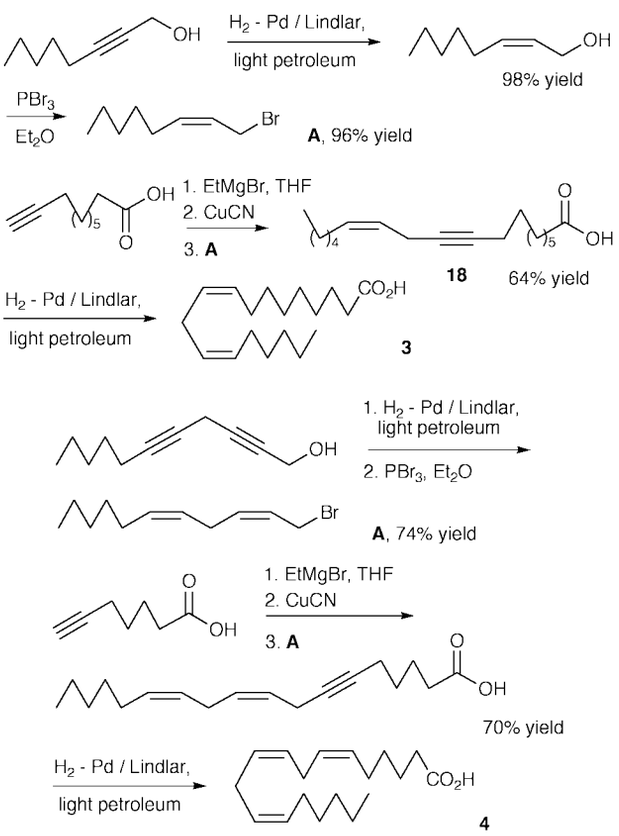
Eicosa-5,8,11,14-tetraynoic acid is a strong inhibitor of the biosynthesis of leukotriene and 5-HETE.[28] In contrast to the preceding scheme, the iterative way was abandoned in favour of the combination of two diyne synthons to achieve the chlorotetrayne **17**. Arachidonic acid **7** was synthesised, at the same time, by similar routes. In the synthesis developed by Gensler, the THP derivative of propargyl alcohol was used as the C_3 homologating agent to achieve one of the two synthons (Scheme 7)[29] (see also the Hoffmann-La Roche method[30]).

Osbond has also described the synthesis of linoleic **3** and



Scheme 7

linolenic acids **4**. The key intermediates in these synthesis were realised by copper catalysed coupling of acetylenic Grignard reagents with (*Z*)-allyl bromides providing 1,4-enynes (Scheme 8).[31]



Scheme 8

From dehydrolinoleic acid **18**, (±)-vernolic acid **19** was prepared using an epoxidation–semi-hydrogenation sequence (Scheme 9).[31]

In order to study their metabolism, Sprecher has prepared three non-natural *n*-7 acids **20**, **21**, **22** using Osbond's strategy (Fig. 2).[32]

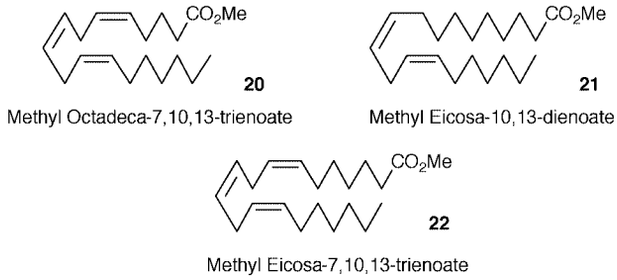
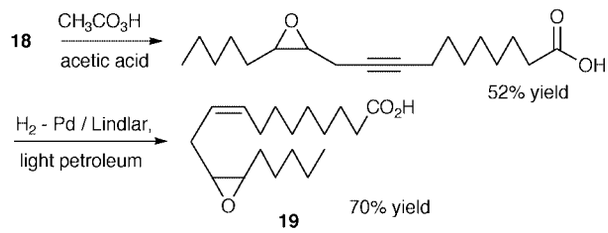
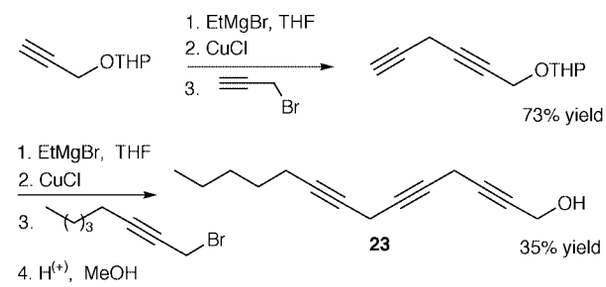


Fig. 2



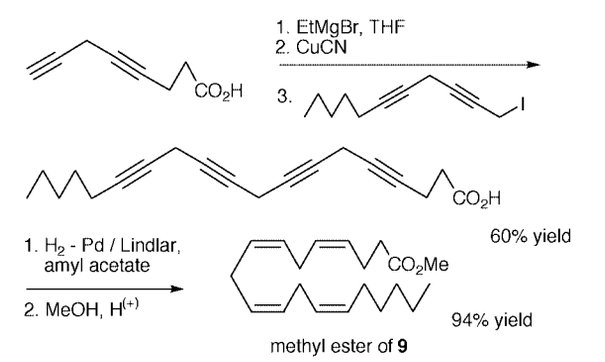
Scheme 9

The Unilever team has equally developed the chemistry of 1,4-diynes. So triynol **23** constitutes a good synthon giving an easy access to numerous PUFA, especially arachidonic acid **7** and DHA **12** (Scheme 10).[33]



Scheme 10

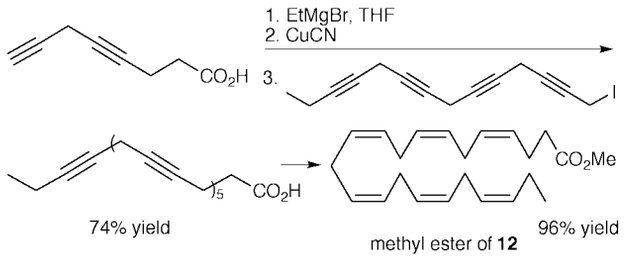
Kunau's work has illustrated the efficiency of these synthetic methods by the preparation of methyl esters of docosa-4,7,10,13-tetraenoic acid **9**, docosa-7,10,13,16-tetraenoic acid **10**, and docosa-4,7,10,13,16-pentaenoic **11** (Scheme 11). The procedure was finally highlighted for the synthesis of methyl DHA **12** (methyl docosa-4,7,10,13,16,19-hexaenoate) (Scheme 12).[34]



Scheme 11

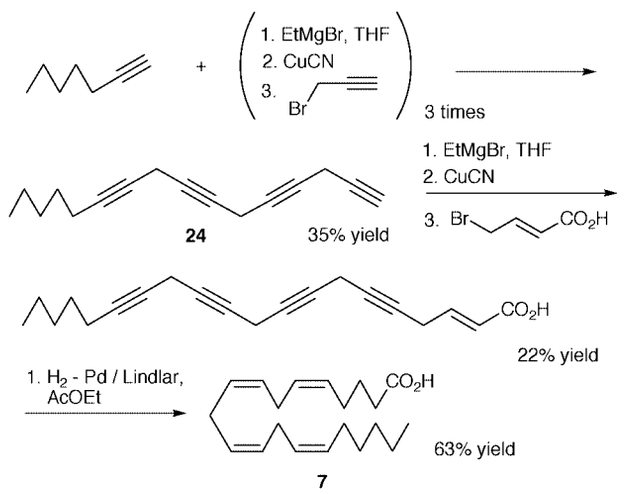
The propargylic iodides were prepared from the corresponding methanesulfonate with sodium iodide in acetone or magnesium iodide in a benzene–diethyl ether mixture.[35] Using a similar procedure, ^{14}C labelled linoleic, γ-linolenic and homo γ-linolenic have been prepared.[36]

Using skipped terminal tetrayne **24** prepared by iterative propargylation of terminal alkynes, the Unilever team has



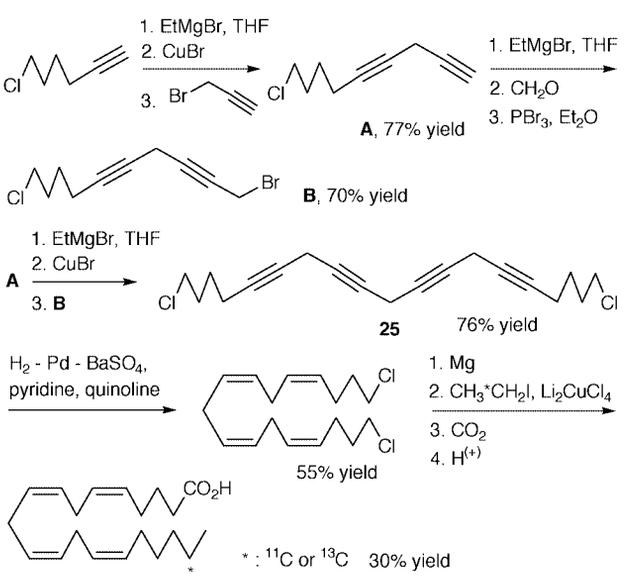
Scheme 12

shown that C_4 homologation with γ-bromocrotonic acid followed by hydrogenation with Lindlar catalyst led to arachidonic acid **7**. It should be noted that the hydrogenation reaction proceeds also on the α-double bond of the carboxylic acid function (Scheme 13).[37]



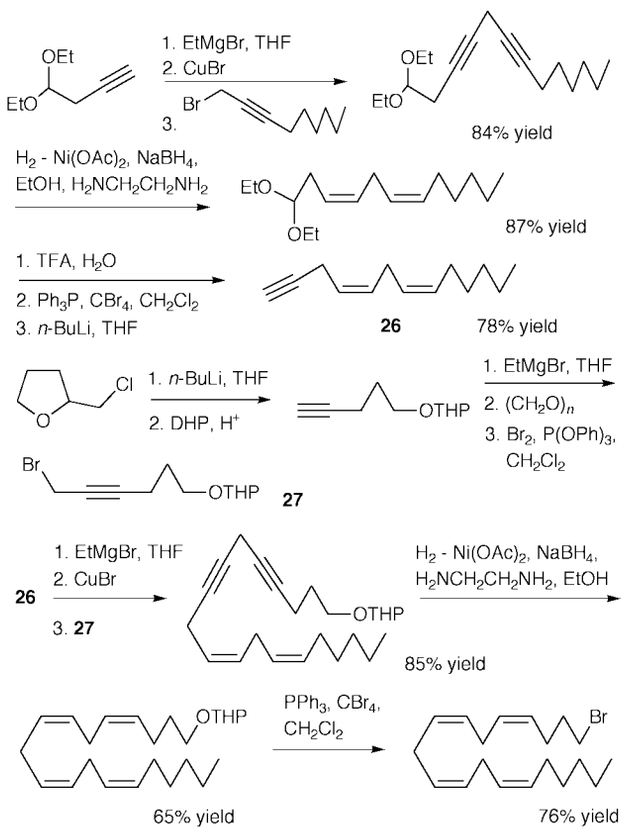
Scheme 13

Another original and efficient synthesis of ^{13}C and ^{11}C labelled arachidonic acids has also been recently published. These were prepared *via* the cross-coupling of the symmetrical diorganomagnesium reagent derived from dichloride **25** with respectively ^{13}C or ^{11}C iodoethane and carbon dioxide (Scheme 14).[38]



Scheme 14

Mioskowski has proposed the all (*Z*)-1-bromononadeca-4,7,10,13-tetraene as a key intermediate in the synthesis of arachidonic acid labelled on C1.[39] It should be noticed that skipped diynes were reduced using the Brown P-2 nickel catalyst system. Because of the extreme instability of these polyacetylenic intermediates (two triple bonds), these authors have elaborated—through acetylenic chemistry—the tridecadienyne **26**. The Grignard reagent of **26** was then alkylated with propargyl bromide **27** (Scheme 15).



Scheme 15

A combination of yne cross coupling and Wittig reaction was employed in the synthesis of the ethyl ester of docosahexaenoic acid **12**. The final coupling was realised from a skipped diene phosphorane and a triene aldehyde generated by oxidative cleavage of the vicinal diol **28** (Scheme 16).[40]

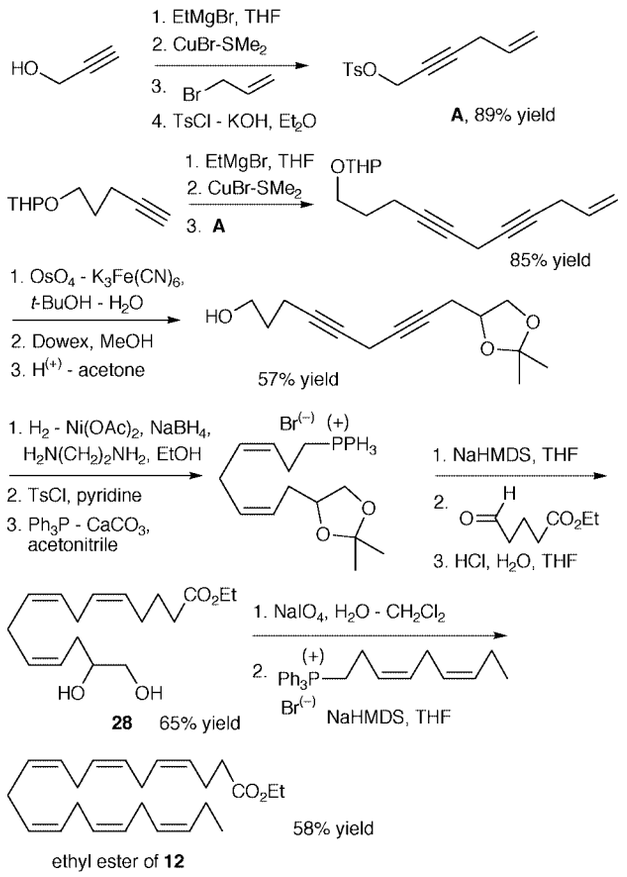
In order to study the transformation mechanism induced by lipoxygenase of flax, Crombie and co-workers have synthesised the d_2-linolenic acid from d_2-pentynol **29** which was prepared by alkynylation of d_2-formaldehyde (Scheme 17). Osbond methodology was then used for the construction of the triyne skeleton.[41]

In the same way, the biosynthesis of calendic acid was studied from polydeuterated palmitoic acid.[42] To clarify the biosynthesis of arachidonic acid, numerous analogues have been prepared; for example, the 16-methylarachidonic acid **30** was prepared *via* the polyyne route in 25% overall yield (Scheme 18).[43]

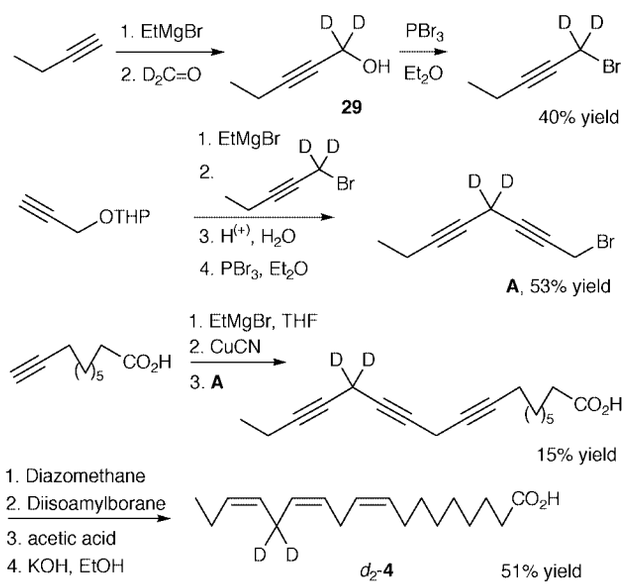
For identical reasons, the Unilever team has synthesised numerous eicosa-8,11,14-trienoic acids containing methyl, dimethyl and cyclopropyl substituents (Fig. 3).[44]

Mioskowski *et al.* have prepared 5- or 6-*exo*-methylene-arachidonic acid analogues which strongly inhibit the formation of LTB_4 and 5-HETE at 10^{-5} M in human PMN. It should be noticed that the coupling of the lithiodienyne derived from **31** with an allylic chloride, which gave the desired skeleton, was not copper catalysed (Scheme 19).[45]

On the other hand, structures containing an (*E*)-double bond have also been proposed as competitive analogues of linolenic acid. The introduction of the (*E*)-double bond results from the coupling of the mono Grignard reagent of acetylene with



Scheme 16



Scheme 17

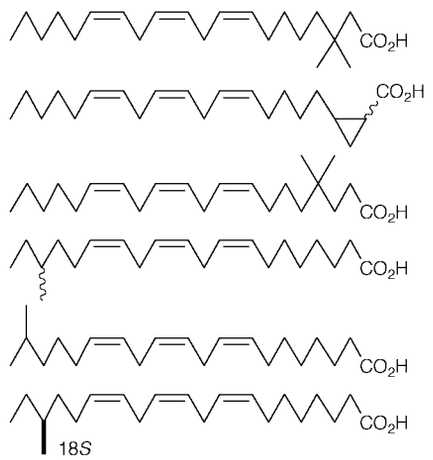
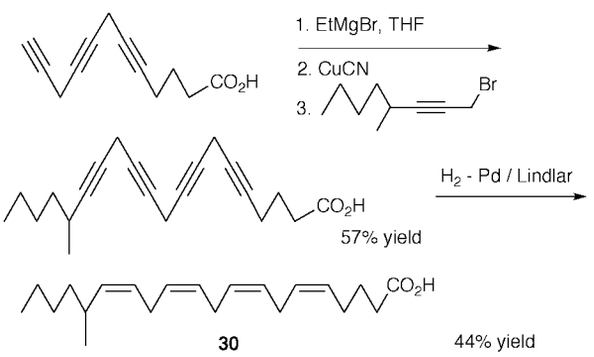
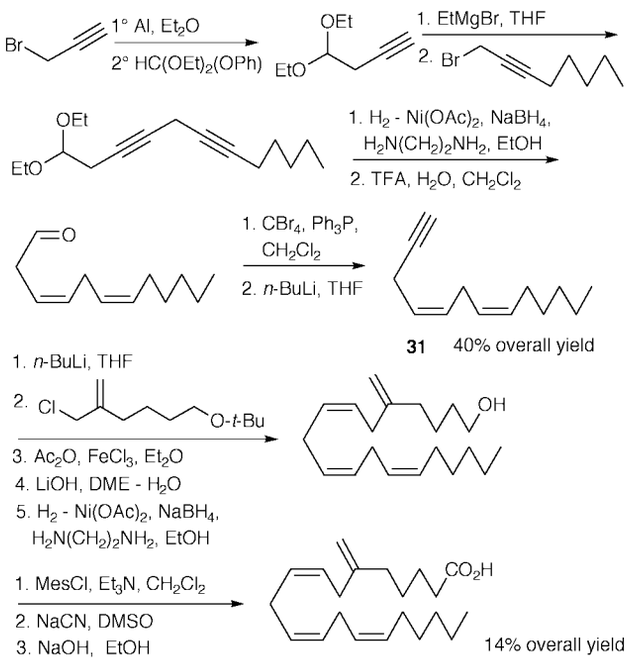


Fig. 3



Scheme 18



Scheme 19

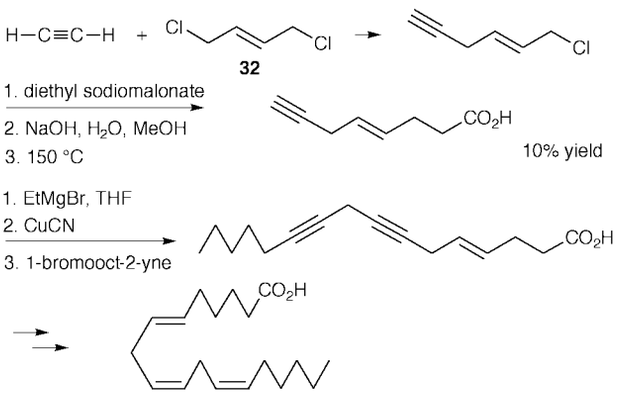
(*E*)-1,4-dichlorobut-2-ene **32** which gives the chloroenyne. This was then alkylated with diethyl sodiomalonate giving, after decarboxylation, the acid terminus (Scheme 20).[46]

In the synthesis of (*E*,*Z*,*Z*)-octa-5,9,12-trienoic acid (colombinic acid) **33** (Scheme 21), the (*E*)-double bond and the acid function were introduced through a Claisen transposition with triethyl orthoacetate.[47]

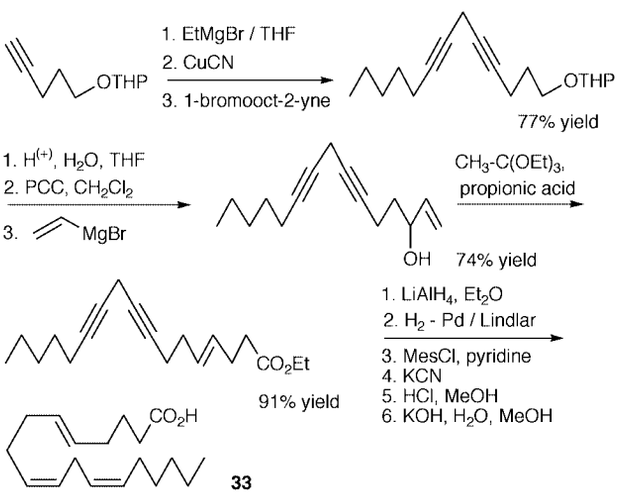
Among the analogues of polyunsaturated acids, the synthesis of PUFA bearing a cyclopropyl ring has received great interest. This was suggested by biosynthetic considerations. In particular the peroxidation pathways of arachidonic acid leading to thromboxanes, prostaglandins, leukotrienes and (mono and poly) hydroxy arachidonic acids, begin with an enzymatic abstraction of an hydrogen atom from the bis allylic position 7, 10 or 13.

The introduction of the cyclopropyl skipped dienic moiety was realised from a functionalised cyclopropyl aldehyde **34** (Scheme 22).[48]

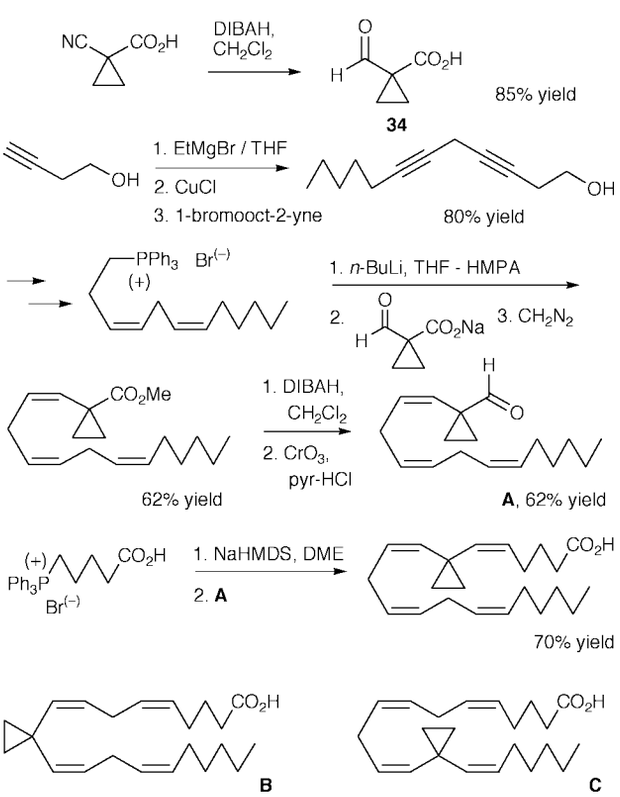
A combination of acetylenic coupling and Wittig reaction gave easy access to this class of analogues. Nicolaou *et al.* have prepared identical structures bearing two or three cyclopropyl



Scheme 20



Scheme 21



Scheme 22

rings on the arachidonic acid (AA) skeleton. Cyclopropyl phosphonium salt **35** or aldehyde **34** were used to achieve the synthesis of a series of AA cascade modulators (Fig. 4).[49]

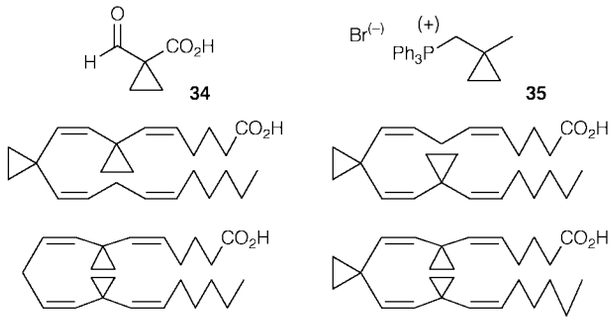


Fig. 4

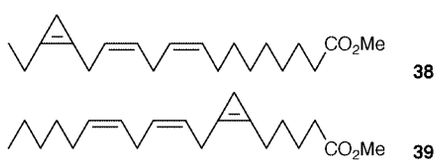
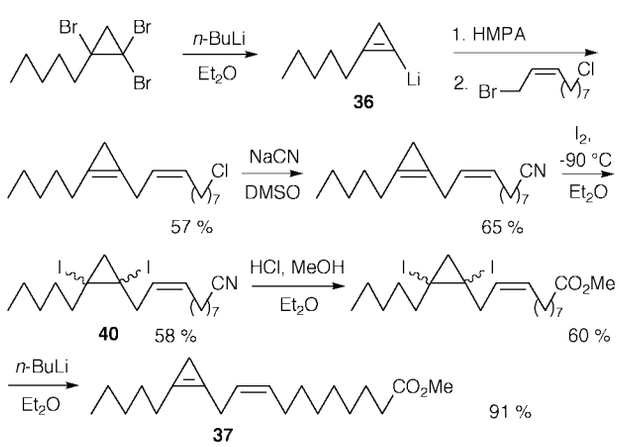


Fig. 5

Sterculic acid, a naturally occurring cyclopropene fatty acid, is a potent inhibitor of Δ^9-desaturase which converts stearic acid into oleic acid. To better understand the mechanism of inhibition and to propose other inhibitors of Δ^6-, Δ^{12}- and Δ^{15}-desaturase, Baird *et al.* have prepared cyclopropenyl analogues **37**, **38** and **39** (Fig. 5) of α- and γ-linolenic acids from cyclopropenyllithium reagent **36**. It should be noticed that the cyclopropene ring, sensitive to acidic conditions, must be protected as the corresponding diiodocyclopropane **40**. Butyllithium mediated β-elimination cleanly restores the fragile cyclopropene ring in high yield (Scheme 23).[50]

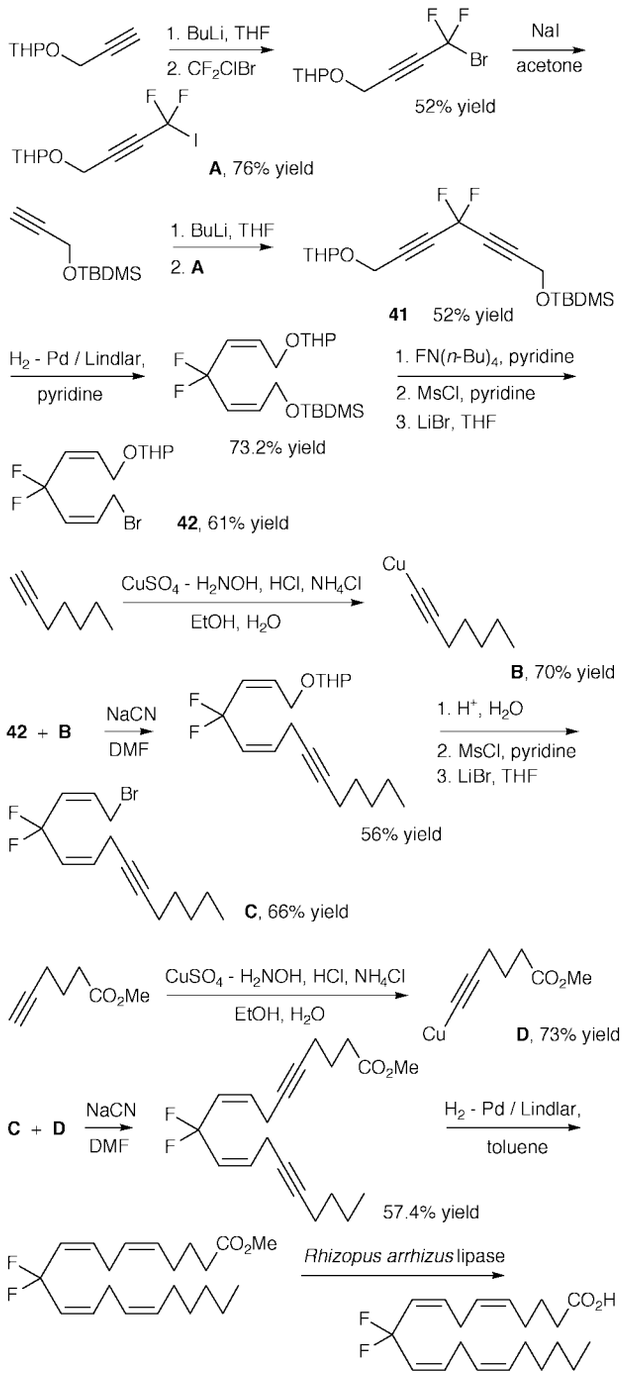


Scheme 23

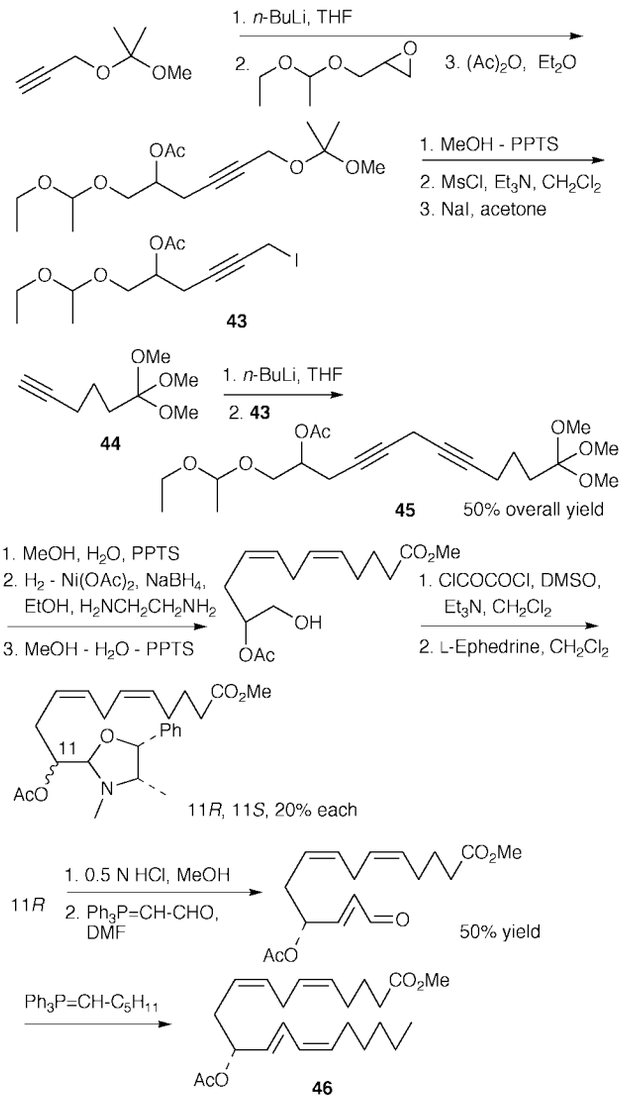
In order to elaborate inhibitors of degradation of AA, Fried *et al.* have suggested replacing the bis allylic hydrogen atoms by fluorine atoms. The carbon skeletons of such components were achieved through the construction of a difluoro skipped diyne **41**. This was realised by two successive couplings of alkynyllithium reagents derived from the propargyl alcohol and the bromochlorodifluoromethane. Diprotected difluoroheptadiynediol **41** was then semi-hydrogenated, monodeprotected and brominated leading to allylic bromide **42** which was alkylated with alkynylcopper in the presence of sodium cyanide. It should be noted that hydrolysis of the ester function was realised using a *Rhizopus arrhizus* lipase because basic or acidic hydrolysis had given unsatisfactory results (Scheme 24).[51]

2.1.b Synthesis of PUFA metabolites

Numerous total syntheses of PUFA metabolites from skipped polyynes have been reported.



Scheme 24



Scheme 25

Just *et al.* have reported the synthesis of (11*RS*)-HETE **46**, and methyl (11*RS*,5*Z*,8*Z*,12*E*,14*Z*)-hydroxyeicosa-5,8,12,14-tetraenoate from racemic glycidol. The (*Z*)-skipped diene moiety was introduced from the skipped diyne **45** generated by cross coupling of an alkynyllithium reagent bearing an ortho-ester function **44** with a functionalised propargyl iodide **43** (Scheme 25).[52]

Using a similar strategy, (11*R*)-HETE **49** was prepared from isopropylidene D-glyceraldehyde. It should be noted that the 1,4-diyne unit was constructed by coupling a mixed acetylenic Gilman reagent derived from lithiodienyne **47** with a bromo allene **48** which prevents the formation of allenyne by-products (Scheme 26).[53]

Using the Wittig reaction, leukotriene C4 was synthesised from a dialkynylphosphonium salt and a dienic functional aldehyde previously prepared by Corey (see ref. 93).[54]

5-Oxo-ETE **52**, a potential chemotactic for human neutrophils, was synthesised by Rokach *et al.* This metabolite deriving from (5*S*)-HETE was found to be about 100 times more active than its precursor. A convergent synthesis is accomplished *via* two synthons, a dithiolane-aldehyde **50** and a dienyl phosphonium bromide **51** (Scheme 27).[55] A similar strategy has been applied to the synthesis of the deuterated or tritiated analogues.[56]

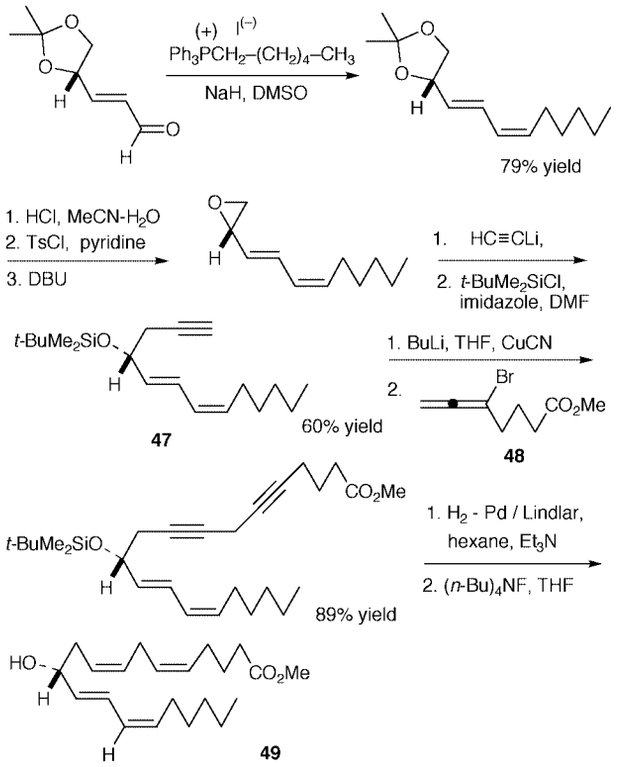
Finally, anacardic acids which have been isolated from various plants are derived from salicylic acids. This was thought to explain the antimold and antibacterial activity of the anacardic acid **53** (Scheme 28).[57]

2.1.c Synthesis of pheromones

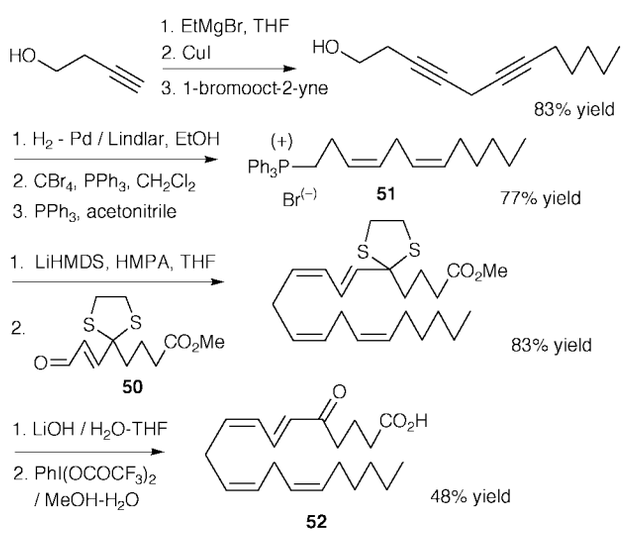
The major constituents of sex pheromones of certain female lepidopterans are dienes, trienes and tetraenes which always contain the skipped diene moiety.

Meinwald and workers have described numerous syntheses of these components. In the synthesis of (*Z*)-heneicosa-1,3,6,9-tetraene **54**, they reported two strategies for obtaining the terminal conjugated diene moiety. The first approach leads to a homopropargyl alcohol **55** which, after bromination and treatment under basic conditions, gives the desired polyene (Scheme 29).[58]

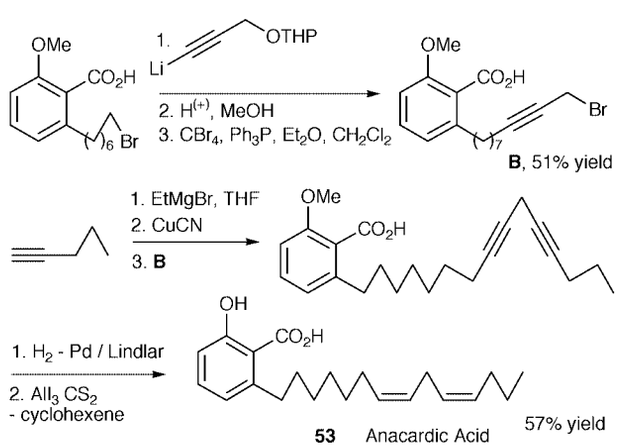
An alternative to the basic elimination has also been proposed by the same authors and used a Wittig olefination of a dienic aldehyde with the phosphorane deriving from allyl-(triphenyl)phosphonium bromide.[59]



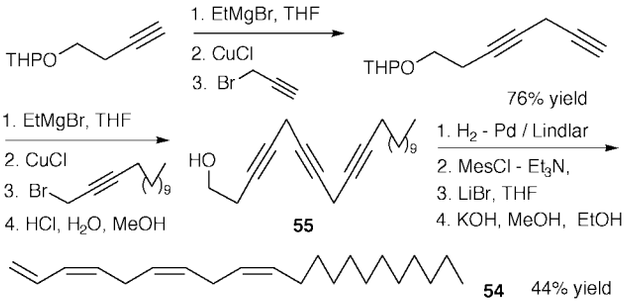
Scheme 26



Scheme 27

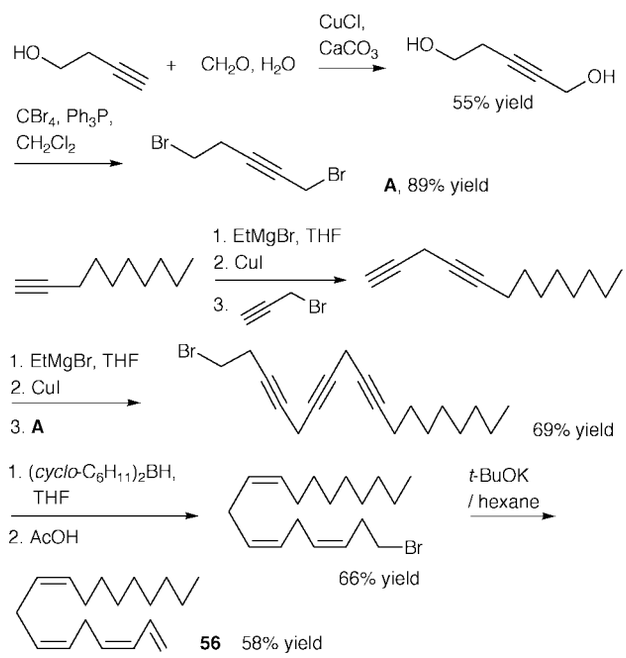


Scheme 28



Scheme 29

Using a similar strategy, an olefin bearing a (3*Z*,6*Z*,9*Z*)-1,3,6,9-tetraene moiety **56** (sex pheromone of lepidopterans) has been prepared by Millar. It should be noted that reduction of the triple bond was achieved using dicyclohexylborane instead of transition metal mediated hydrogenation as it tolerates the homoallyl bromide function (Scheme 30).[60]



Scheme 30

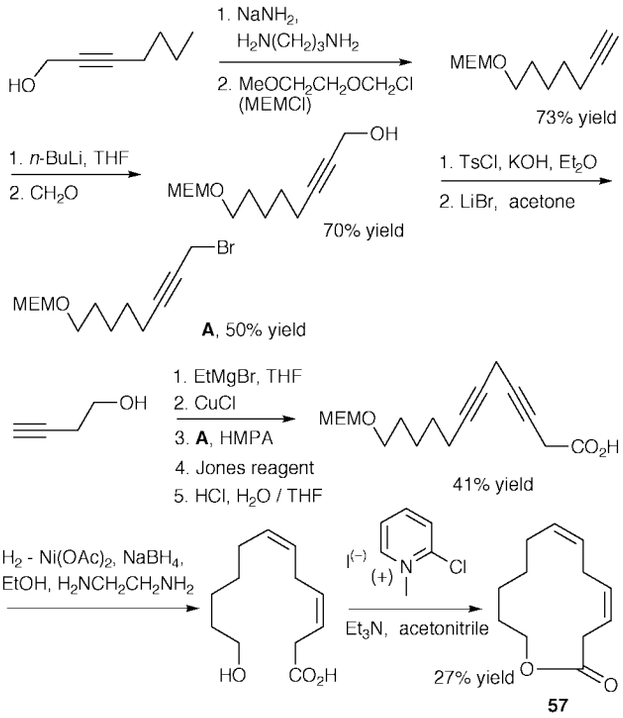
Some dienic macrolides such as **57**, aggregation pheromones of coleopterans (a major world wide pest of stored grain) have been synthesised by Oehschlager (Scheme 31).[61,62]

C_{21} polyunsaturated fatty acids have been observed in essential oil of brown algae. Oxidation products of these give characteristic seaweed or algae odours. In order to clarify the odour activity relationship, Narden Int. chemists have prepared (all-*Z*)-heneicosa-1,6,9,12,15-pentaene from arachidonic acid (Scheme 32).

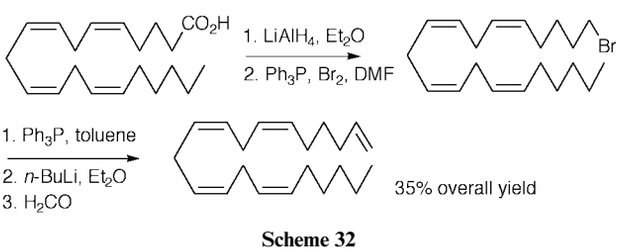
They achieved the synthesis of numerous aldehydes potentially responsible for the odour. For example, the dodecatrienal **58** has been prepared *via* the coupling of the Grignard reagent derived from the diethoxybutyne and the appropriate propargyl tosylate **59** (Scheme 33).[63]

(All-*Z*)-dodeca-3,6,9-trienic acid **60** was proposed as a possible precursor of algal sex attractants from female gametes of *Analipus japonicus*. The synthesis of this acid was realised by Ishihara using a classical route (Scheme 34).[64]

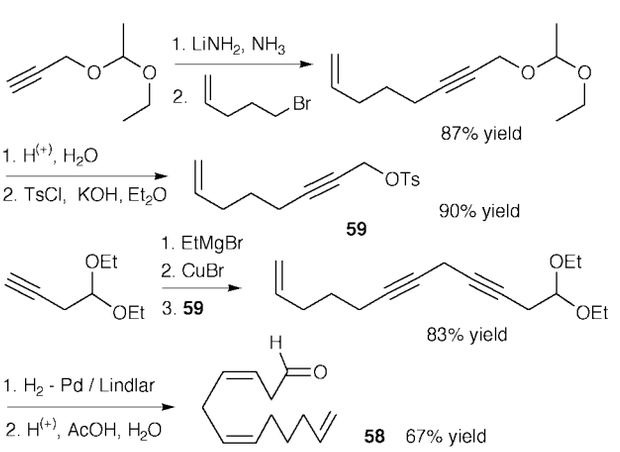
To study the biosynthesis of pheromones in female gametes of marine brown algae, Boland has prepared the (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid **61** deuterated on the vinylic



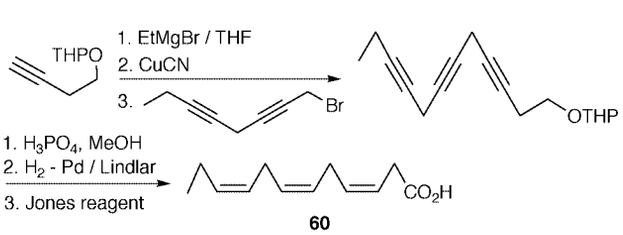
Scheme 31



Scheme 32

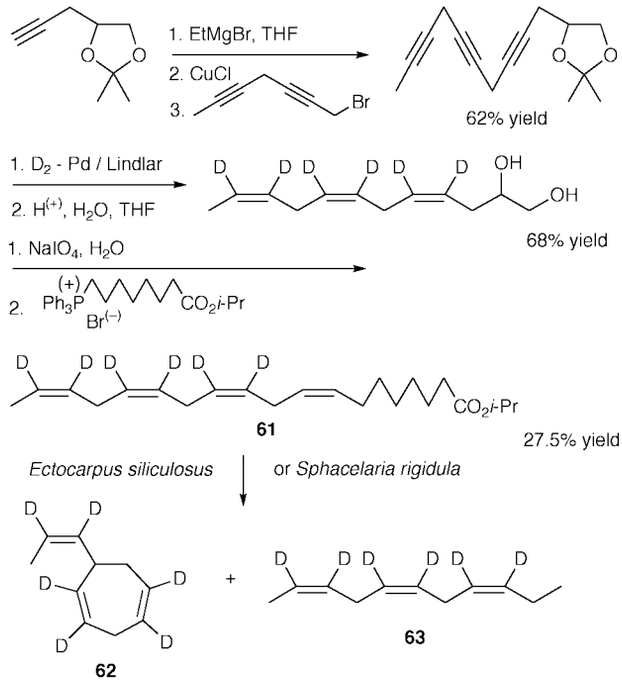


Scheme 33



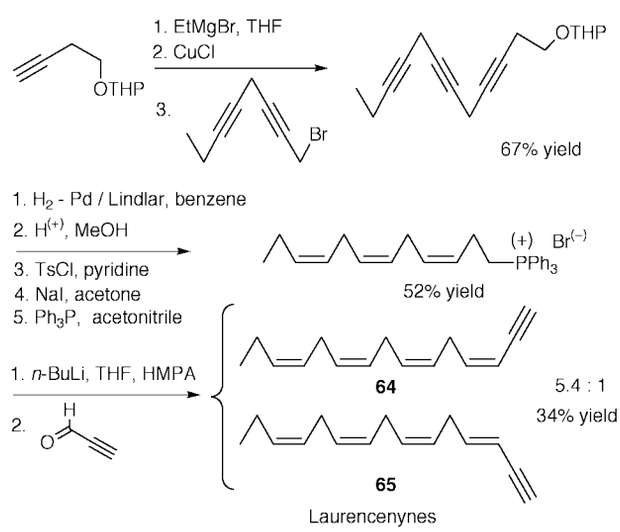
Scheme 34

positions during partial reduction over a Lindlar catalyst. This was then bio-transformed with different algae into deuterated pheromones **62** and **63** (Scheme 35).[65]



Scheme 35

The red alga *Laurencia okamurai* contains acetylenic polyenes such as laurencenynes **64** and **65**. To confirm their structures, Yamada has realised their synthesis by a combination of copper catalysed polyyne synthesis and Wittig reaction (Scheme 36).[66]



Scheme 36

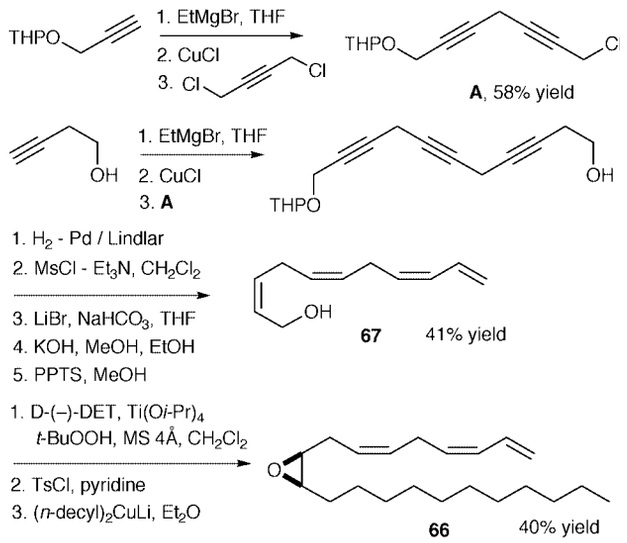
(*Z*)- and (*E*)-undeca-1,3,5,8-tetraenes, the odorous principles of the gametes of the brown alga *Spermatochnus paradoxus* have been prepared using a similar route to that above.[67]

Among the three pheromone components of female Fall webworm moth which contain a skipped diene moiety, Mori *et al.* have synthesised each enantiomer of (3*Z*,6*Z*)-*cis*-9,10-epoxyhenicosa-3,6-diene. Selective introduction of chirality was achieved employing the asymmetric Sharpless epoxidation of tetraenol **67** (Scheme 37).[68]

2.2 Synthesis of the 1,4-diene moiety from cross-coupling between propargyl halides and terminal alkynes

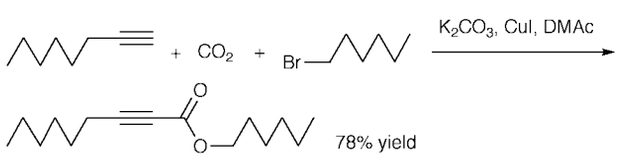
2.2.a Synthesis of PUFA

Terminal alkynes react with copper salts in weakly basic media to afford copper acetylides which can react with methanal to give substituted propargyl alcohols.[69] This methodology has



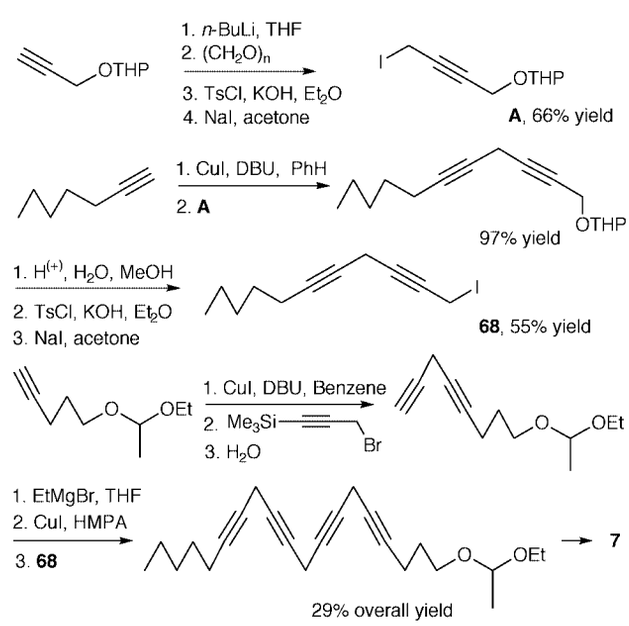
Scheme 37

been used in numerous industrial processes. Recently, it was shown that alkyl alk-2-ynoates could be directly generated from terminal alkynes, CO_2 and alkyl bromide in the presence of potassium carbonate and a catalytic amount of Cu(I) or Ag(I) in dimethylacetamide (Scheme 38).[70]



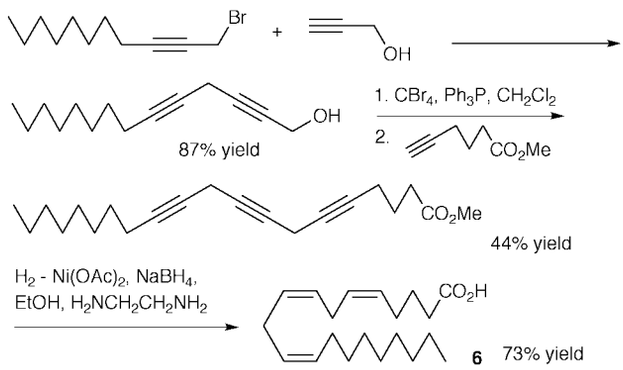
Scheme 38

Eiter has reported that the cross-coupling between terminal alkynes and propargyl iodides mediated by copper iodide in the presence of DBU (or DBN) in benzene led to skipped 1,4-diynes. This reaction has been successfully applied in the synthesis of arachidonic acid **7**.[71] It should be noted that the tetrayne synthesis was achieved using a cross-coupling reaction between a diyne Grignard reagent and propargyl iodide **68** instead of direct coupling of the terminal alkyne under DBU–CuI conditions which gave numerous allenic impurities (Scheme 39).



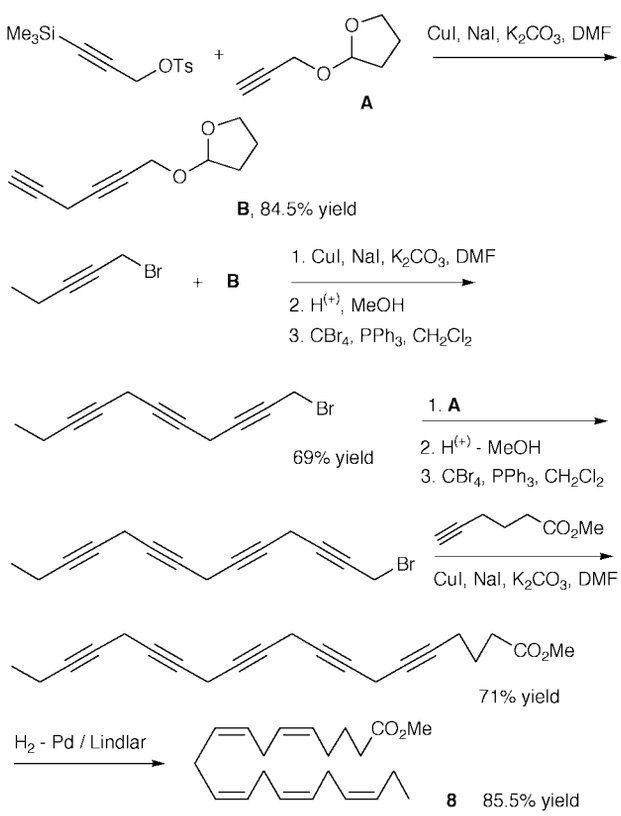
Scheme 39

From results concerning the coupling of a terminal alkyne with an allylic bromide,[72] Jeffery and Linstrumelle have proposed new, simple and cheap conditions for preparing skipped diynes. This reaction mediated by copper iodide and quaternary ammonium salt was exemplified by a short synthesis of Mead acid **6** (Scheme 40).[73]



Scheme 40

Pivnitsky has equally applied this method to the preparation of numerous synthons having a 1,4-diyne fragment. It should be noted that this reaction tolerates functions such as esters, alcohols or epoxides.[74] This reaction was also applied to the synthesis of (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid (timnodonic acid) **8** (Scheme 41), linoleic acid **3** and γ-linolenic acid **5**.[75,76]

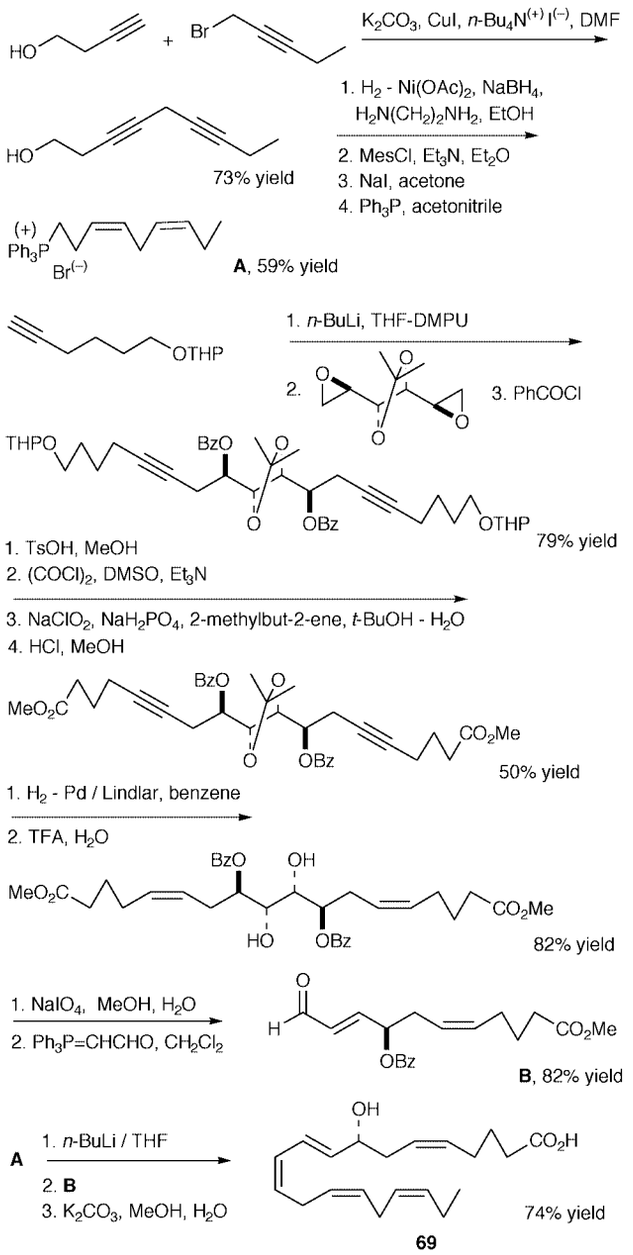


Scheme 41

2.2.b Synthesis of PUFA metabolites

Hydroxyeicosapentaenic acid has been isolated in small quantities from barnacles and has been named as an eclosion factor of barnacles. Its structure, (8*R*)-HEPE **69**, has been proposed on the basis of biogenetic considerations and from its mass spectrum. Shing *et al.* have reported its synthesis where the chiral centre derives from D-mannitol (Scheme 42).[77]

Hepoxilin B3 **70**, an arachidonic acid metabolite, is present in mammalian tissues as mixture of two epimers at the 10-hydroxy



Scheme 42

group. Pivnitsky *et al.* have synthesised the two different epimers in order to assign precisely their structures.[78] The hexatritiated analogue of hepoxilin B3 has also been prepared.[79] The final chain elongation to reach the 20-carbon chain was performed by reaction of methyl hex-5-ynoate with propargyl chloride **71**. The mildness of the experimental conditions preserves the epoxyalcohol function of the both diyne **71** and the resulting triyne (Scheme 43).

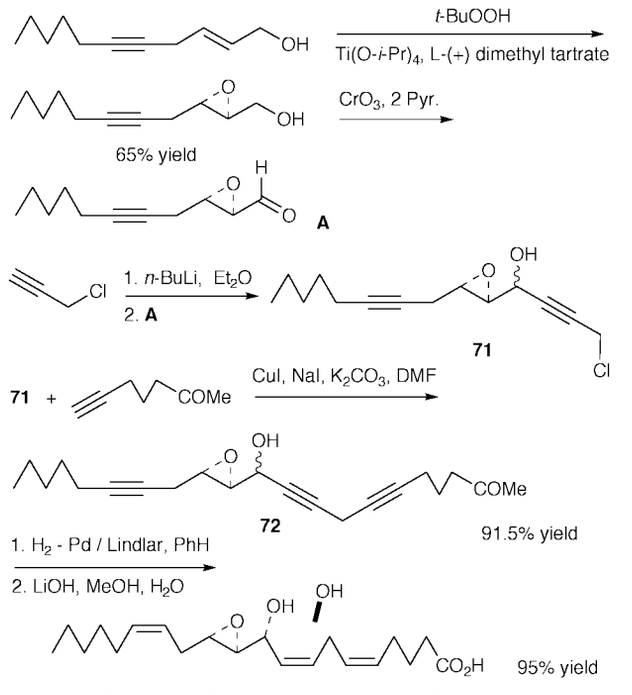
Dussault has also used the hydroperoxide derived from linoleic acid to prepare aldehyde **72**[80] which has permitted an efficient synthesis of 15-HPETE.[81]

Through a Sonogashira cross-coupling as a key step, Linstrumelle and Larchevêque have prepared (5*S*)-HETE **73**. It should be noted that the alkyne function bearing a trimethylsilyl group is not reduced during hydrogenation of **74** over Brown P-2 Ni (Scheme 44).[82]

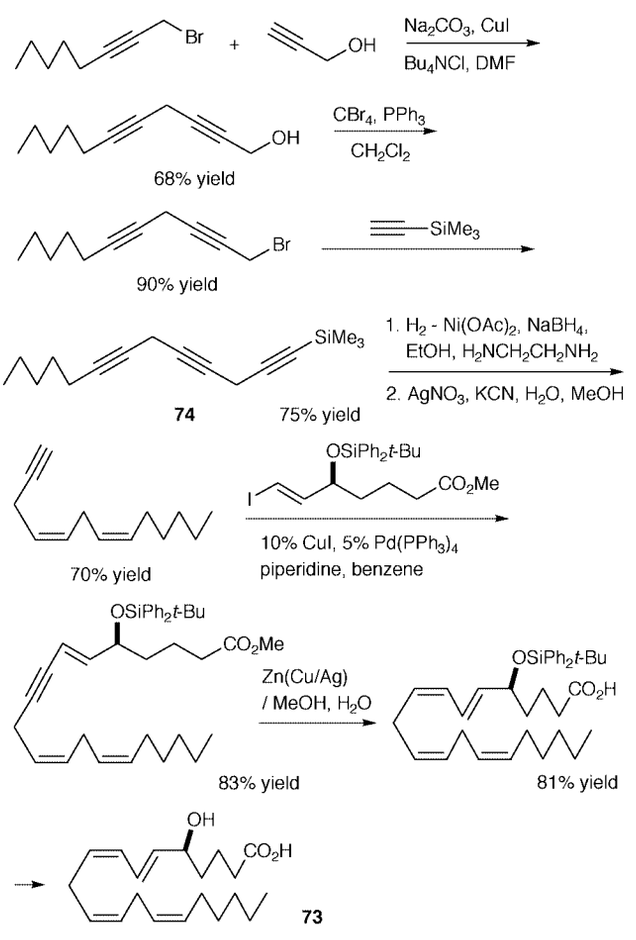
Finally, to obtain tetrahydrofurans from skipped epoxides, Capon has used the methodology reported by Jeffery to prepare some (*Z*)- or (*E*)-1,4-enynes.[83]

2.2.c Synthesis of pheromones

For biosynthetic studies, Meinwald has prepared different



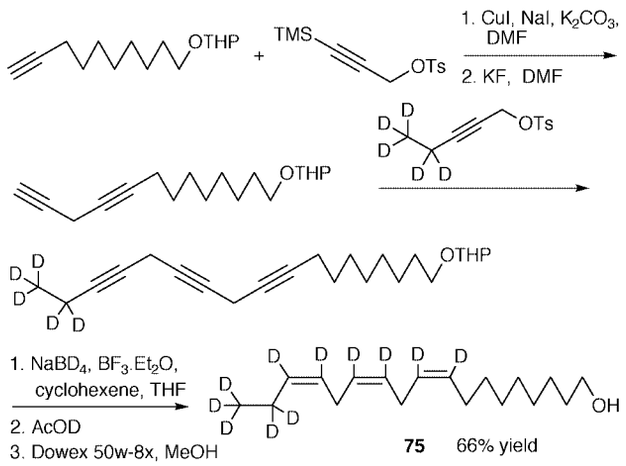
Scheme 43



Scheme 44

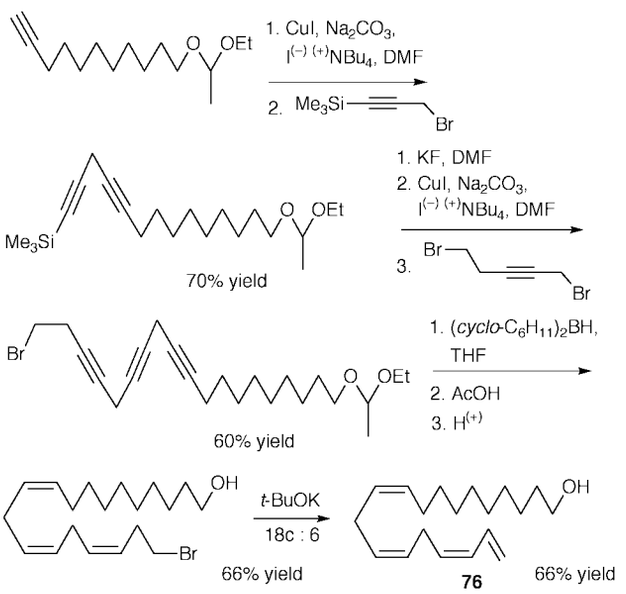
polydeuterated pheromones (Scheme 45).[84] To introduce cleanly deuterium atoms on the vinylic positions, once again, the Brown hydroboration procedure was found to be the most efficient.

(10*Z*,13*Z*)-Nonadeca-10,13,18-tetraen-16-ol **76**, a pheromone of *Leucoptera scitella*, was obtained by successive

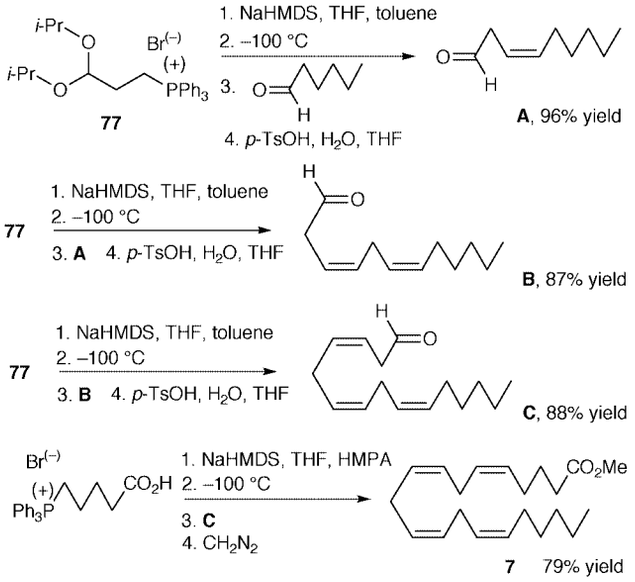


Scheme 45

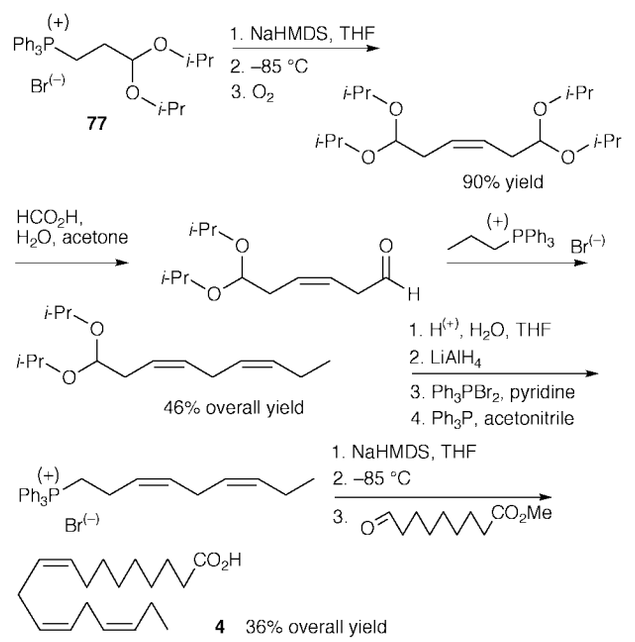
coupling between propargylic bromides and terminal alkynes. The mildness of the Linstrumelle–Jeffery conditions allows the coupling of the 1,5-dibromopent-2-yne only on the propargyl position without affecting the alkyl bromide function (Scheme 46).[85]



Scheme 46



Scheme 47



Scheme 48

3 Direct preparation of PUFA and metabolites

3.1 Synthesis of the 1,4-diene moiety *via* Wittig reaction

The Wittig reaction performed under specific conditions (absence of lithium cation, high dilution, low temperature) stereoselectively gives access to a *Z*-double bond with perfect control.

3.1.a Synthesis of PUFA

Starting with a C_3-homologating agent **77**, Santelli *et al.* have prepared in four steps the arachidonic acid **7** (Scheme 47).[86]

Oxidative duplication of the phosphorane deriving from this C_3 homologating agent **77** led to a novel C_6 protected dialdehyde where, under slightly acidic conditions, only one aldehyde function could be generated. This methodology, developed by Viala, was applied in the synthesis of linolenic acid **4** (Scheme 48).[87]

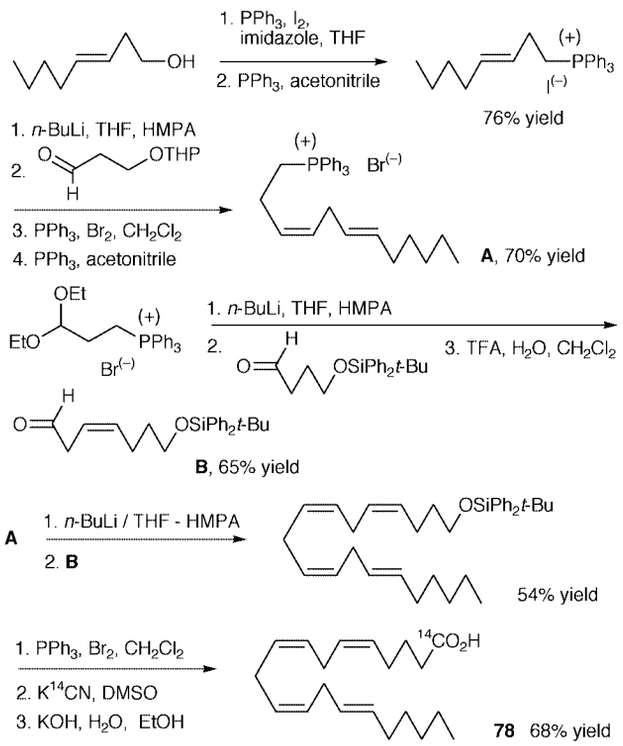
In addition to the use of the C_6 homologating agent highlighted above, eicosapentaenoic (EPA) **8** and docosahexaenoic (DHA) **12** acids were efficiently prepared.[88] *Via* successive Wittig reaction, Vatèle *et al.* prepared a ^{14}C labelled analogue **78** of linolenic and arachidonic acid **7** (Scheme 49).[89]

Following reduction of 1,4-diyne moiety by Wittig coupling, a synthesis of arachidonic-d_5 **7** was proposed (Scheme 50).[90]

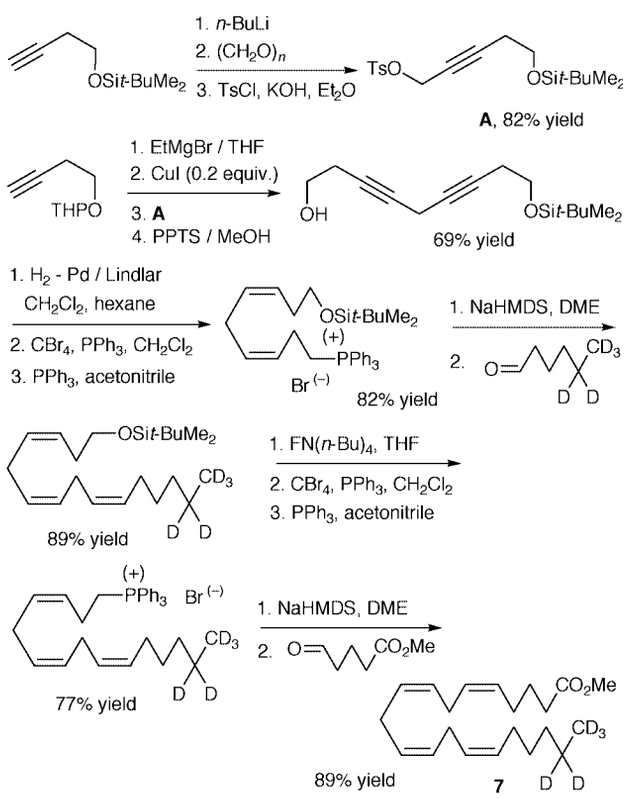
α-Amino arachidonic acid **79**, a non natural amino acid, was obtained by Wittig coupling between a trienic phosphorane and an aldehyde derived from (*S*)-glutamic acid. It should be noted that, in this case and in numerous others, the polyenic phosphorane used derives from the alkyne chemistry (Scheme 51).[91]

3.1.b Synthesis of PUFA metabolites

The first enantioselective synthesis of leukotriene C1 **80**, a "slow reacting substance" of anaphylaxis, was described by Corey from D-(−)-ribose. Carbon skeleton formation was elaborated *via* a Wittig reaction between a phosphorane and the functionalised aldehyde **83**. The latter was synthesised from epoxyaldehyde **81** which was C_4 homologated by the Wollenberg reagent **82** (Scheme 52).[92]



Scheme 49



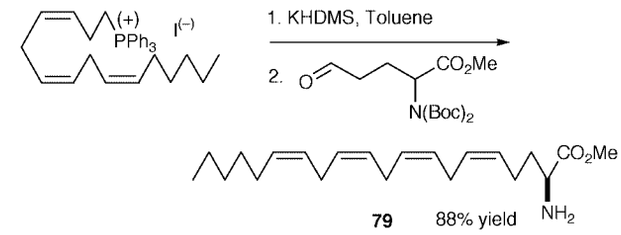
Scheme 50

3.1.c Synthesis of pheromones

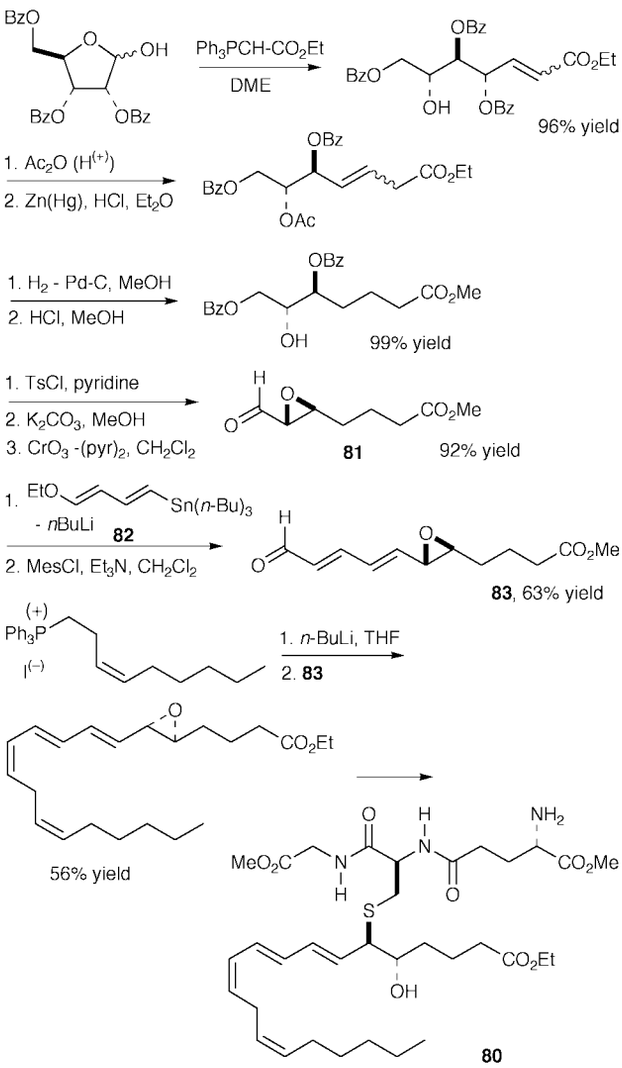
Sex pheromones of lepidopterans are often polyunsaturated compounds and their biosynthesis derives from PUFA. Viala has reported the synthesis of three pheromones (**83**) by using the C_3 homologating agent **77** (Scheme 53).[93]

Using the same homologating agent, Stevens has synthesised a macrolide component **85** of the pheromones of grain beetles of *Oryzaephilus* and *Cryptolestes* (Scheme 54).[94]

A series of unsaturated fluorinated and tritiated analogues of



Scheme 51



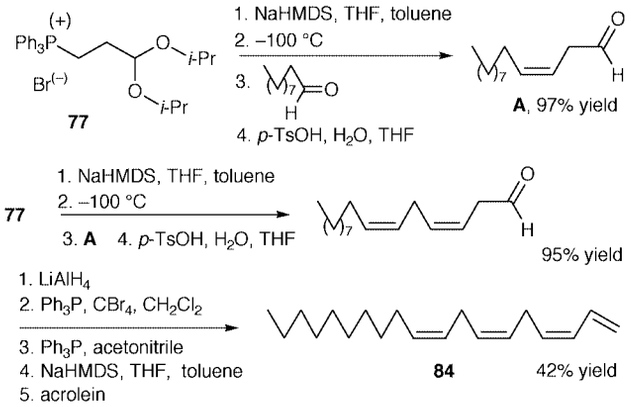
Scheme 52

the trail pheromones **86**–**89** of subterranean termites have been prepared by Prestwich *et al.* An original strategy to prepare the phosphonium salt was investigated from methoxyhexa-1,4-diene (Scheme 55).[95]

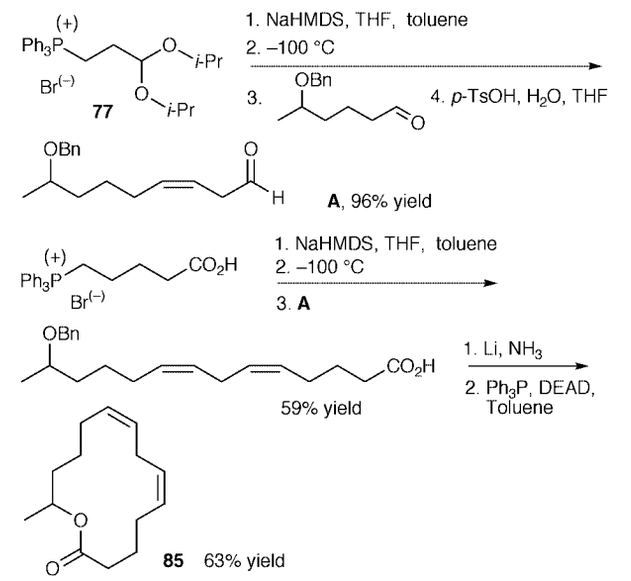
3.2 Synthesis of PUFA metabolites mediated by vinylstannanes

The fact that vinylstannanes generally react with a clean retention of configuration of the double bond has attracted numerous organic chemists to introduce a vinyl moiety as, for example, a key step of total synthesis. First, Corey has developed this methodology in the synthesis of PUFA. An efficient synthesis of 1-acetoxy-3-tributylstannylprop-2-ene **90** from propargyl alcohol was achieved by stereoselective hydroalumination (Scheme 56).

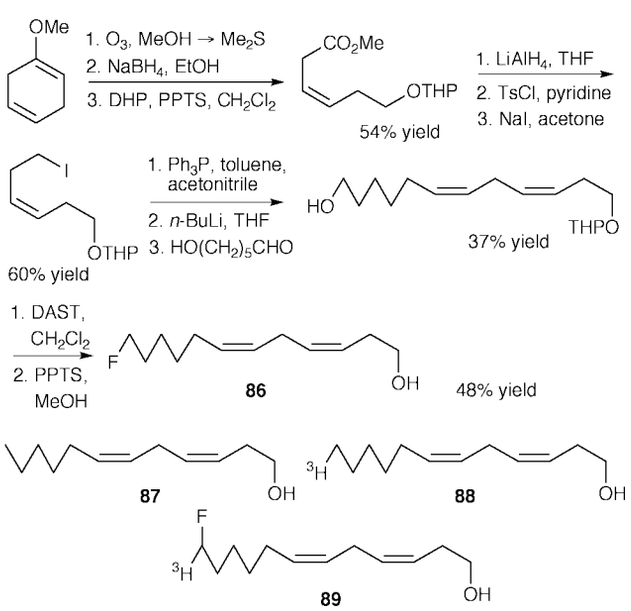
This vinyltin acts as a C_3 homologating agent and has been used in the synthesis of 5,6-didehydroarachidonic acid **91**



Scheme 53

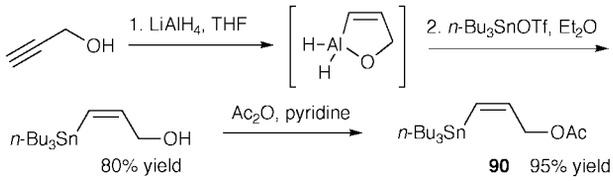


Scheme 54

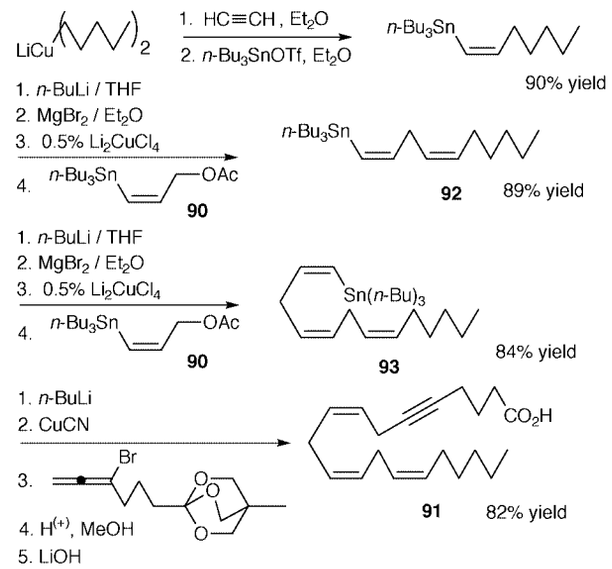


Scheme 55

(Scheme 57). The (*Z*)-vinylcuprate reagent resulting from the carbocupration reaction of acetylene led to a (*Z*)-vinylstannane which, after transmetallation with butyllithium and magnesium salt exchange, reacts with the C_3 (*Z*)-vinylstannane under



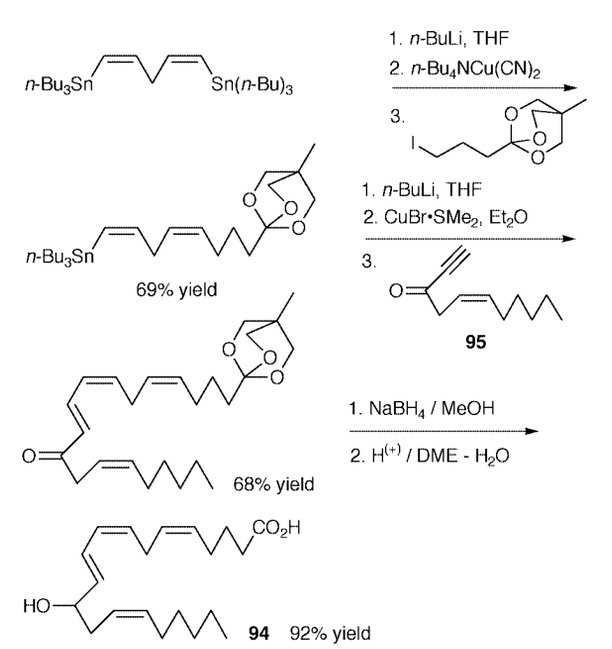
Scheme 56



Scheme 57

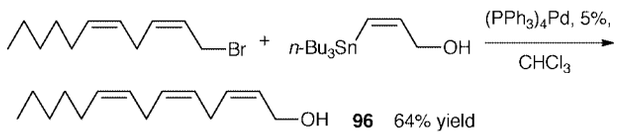
copper catalysis to afford a new (all-*Z*) skipped dienic vinyltin **92**. Another iterative process leads to a novel vinyl tin precursor **93** of a vinyllithium reagent.[96]

This strategy was applied by Corey for the synthesis of (±)-12-HETE **94**.[97] The 1,3-diene moiety was achieved during the final step of the carbon skeleton formation through a 1,4-conjugated addition of a vinylcuprate on the enone **95** (Scheme 58).



Scheme 58

Only one example using vinyltin reagent and using the Stille reaction was reported in the synthesis of (all-*Z*)-tetradeca-2,5,8-trienol **96** (Scheme 59).[98]



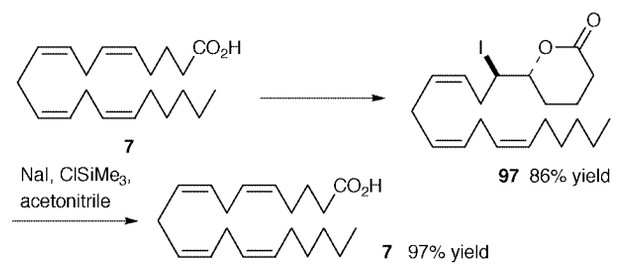
Scheme 59

4 Hemisynthesis of PUFA and metabolites from PUFA

4.1 Chemical studies

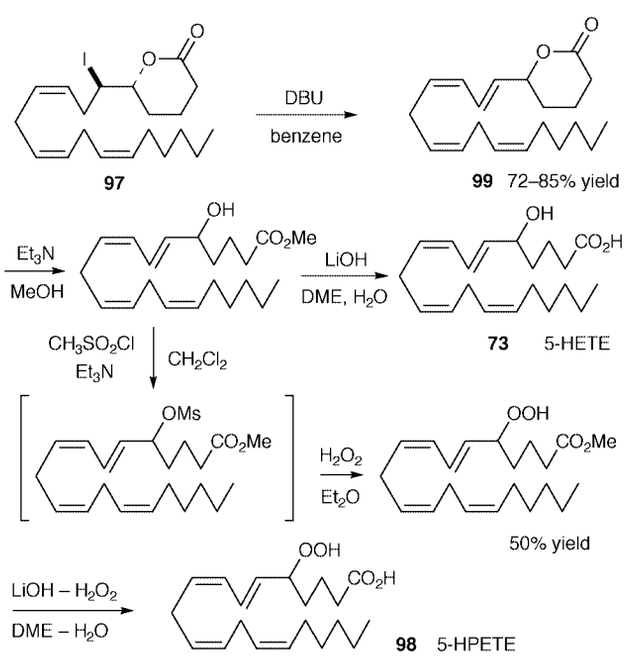
Certain PUFA from animal or vegetable origin could be obtained by classical purification methods.

Corey has proposed an efficient method to purify arachidonic acid. Iodolactonisation of arachidonic acid **7** leads to δ-lactone **97** which can selectively regenerate **7** by elimination (Scheme 60).[99] Identically, DHA (docosahexaeneoic acid) **12** could be purified *via* a γ-lactone.[100]



Scheme 60

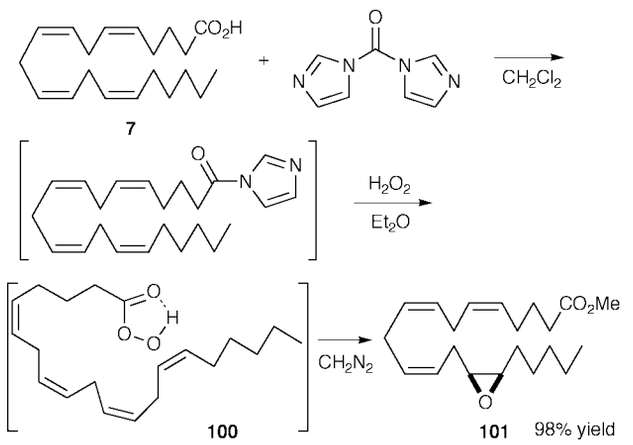
From the aformentioned δ-lactone **97**, 5-HETE and 5-HPETE **98** were prepared by Corey. DBU treatment led to the tetraene lactone **99** precursor to 5-HETE **73** (Scheme 61).



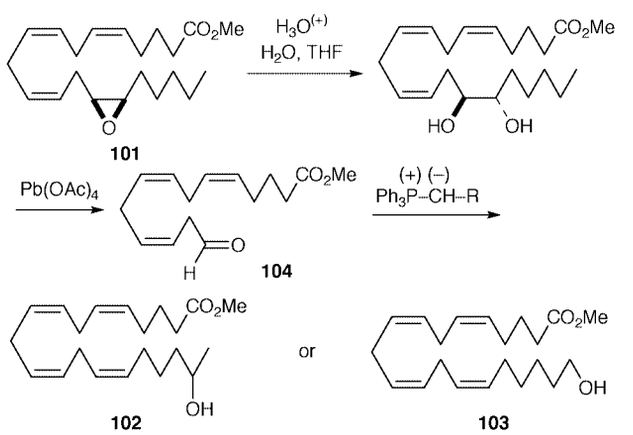
Scheme 61

Perarachidonic acid **100** was selectively transformed into the epoxide **101** on the final double bond.[101] This intramolecular oxygen transfer pathway results from the "linear attack" of the C=C π orbital on the O–O peroxidic bond (S_N2 like) and of the tendency of the molecule to adopt a strongly bent, "J" like shape (Scheme 62).

The arachidonic acid epoxide **101** was transformed into 19- or 20-hydroxyarachidonic acids **102** and **103** which are biosynthetically produced during the NADPH dependent cyto-



Scheme 62



Scheme 63

chrome P-450 mediating oxidative pathway (Scheme 63).[102] Using the same strategy, Perrier *et al.* have obtained labelled compounds.[103] The 20-hydroxyarachidonic acid **103** led easily to the corresponding lactones confirming the existence of a preferential hairpin conformation in this series.[104]

To study the formation mechanism of 15-HPETE, Corey has prepared, from aldehyde ester **104**, the methyl esters of eicosapentaenoic **105** and eicosahexaenoic acids **106**. This series was also completed by the synthesis of a corresponding cyclopropyl derivative **107** (Scheme 64).[105]

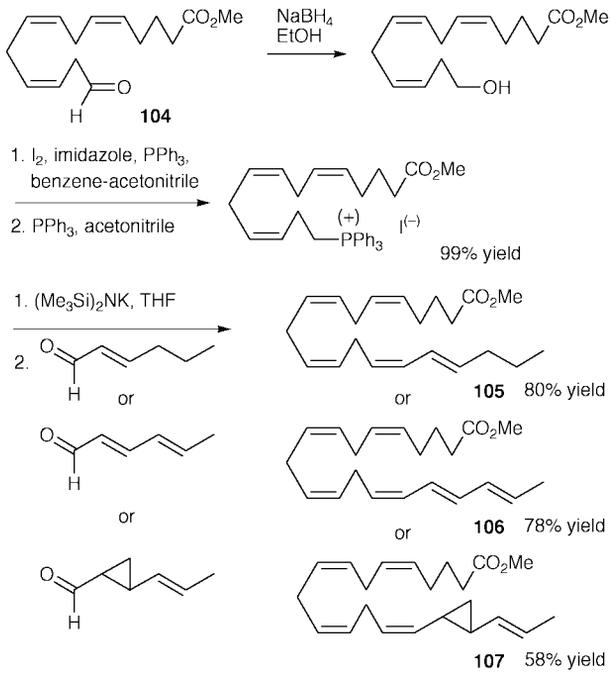
The epoxide **101** of arachidonic acid treated with the magnesium salt of cyclohexylisopropylamine led to 15-HETE **108** which was then transformed into 15-HPETE **109** (Scheme 65).

12-HETE **94** has also been synthesised from epoxide **101** using a sequence including epoxide ring opening with potassium bromide, a vanadium mediated selective epoxidation followed by the regeneration of the double bond. It should be noted that this problematical reaction has been solved by the use of trifluoromethanesulfonic anhydride–tris(dimethylamino)phosphine (Scheme 66).[106]

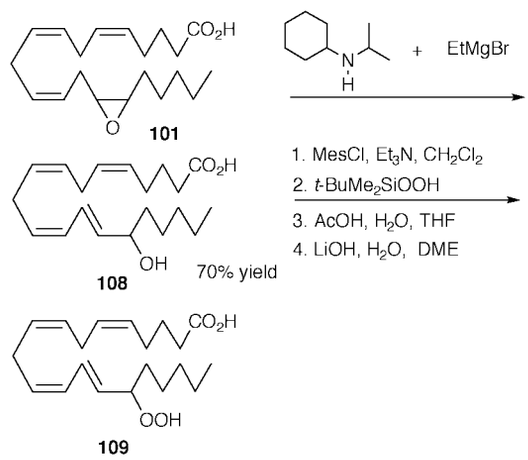
For identical reasons, acids **111** bearing an alkylidene cyclopropane moiety have been prepared by Misra from aldehyde **110** derived from arachidonic acid using the Peterson elimination reaction (Scheme 67).[107]

From the epoxide **112** of arachidonic acid, Ennis has prepared the analogues of peptidoleukotrienes **114** (Scheme 68).[108]

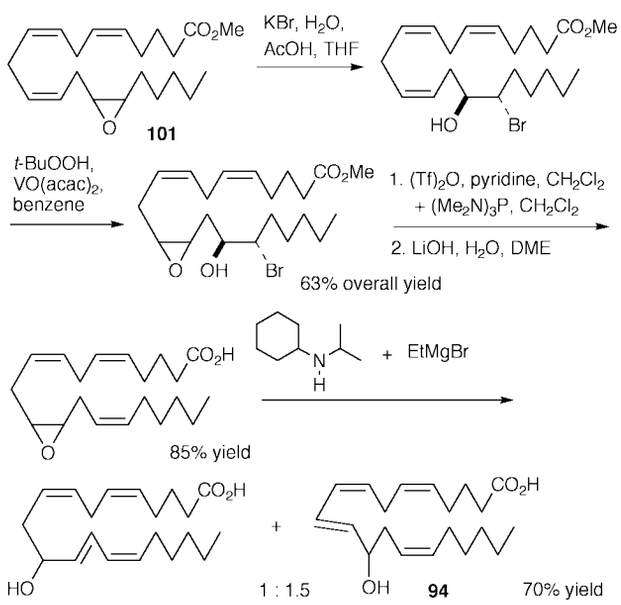
Labelled arachidonic acid **7** was also obtained from the natural product **7**. Barton has proposed a radical method for exchanging the acid function. Photolytic cleavage of the Barton ester **115** in the presence of ^{13}C labelled *p*-nitrophenyl isocyanate led, after saponification, to ^{13}C enriched arachidonic acid (Scheme 69).[109]



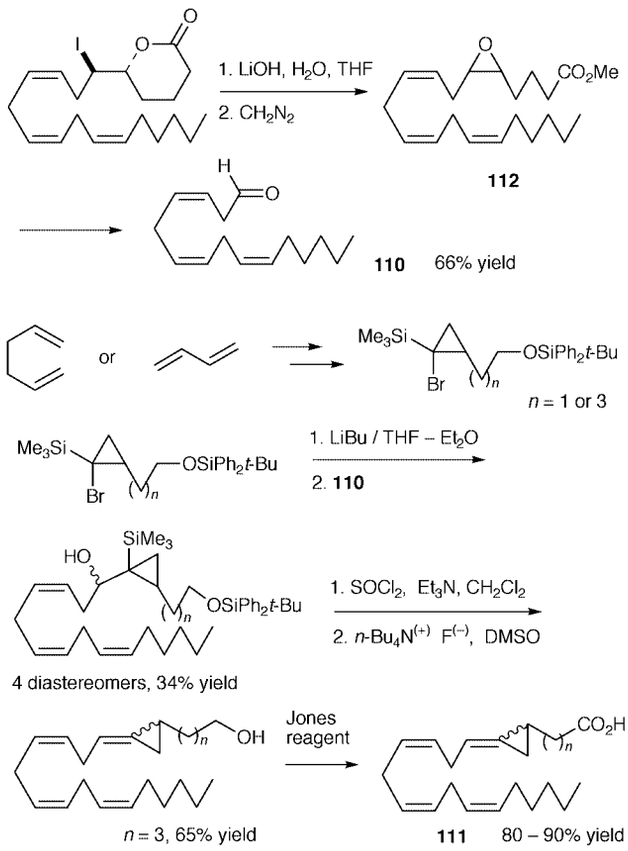
Scheme 64



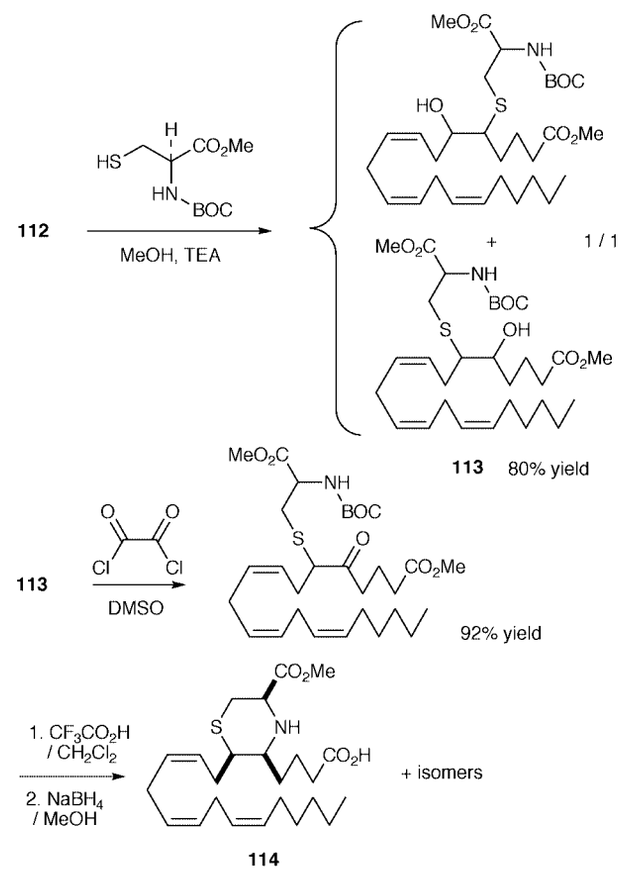
Scheme 65



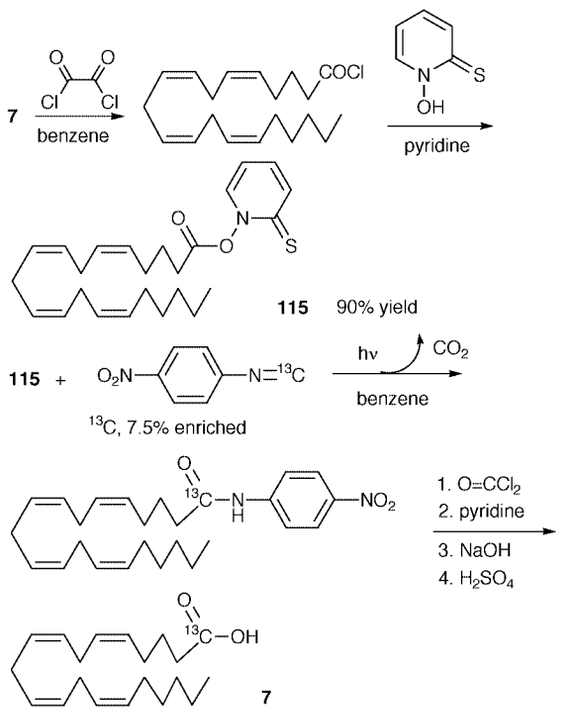
Scheme 66



Scheme 67

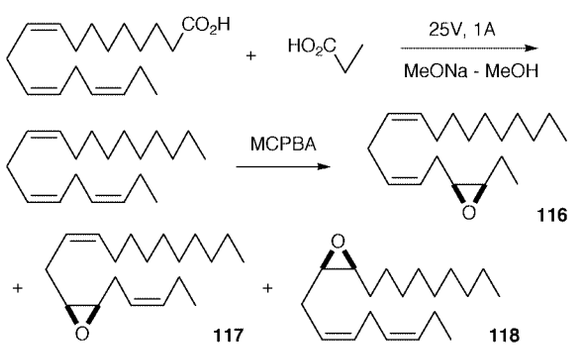


Scheme 68



Scheme 69

(All-*Z*)-nonadeca-3,6,9-triene, previously identified in extracts of virgin female ovipositor tips and suspected to be a sex pheromone, failed to attract any male moths. Becker has shown that (3*S*,4*R*,6*Z*,9*Z*)-*cis*-3,4-epoxynonadeca-6,9-diene **116** exhibited biological activity. The triene was synthesised from α-linolenic acid and propionic acid *via* Kolbe electrosynthesis. Random epoxidation leads to the three possible monoepoxides of which only one enantiomer of **116** was found to be an active compound (Scheme 70).



Scheme 70

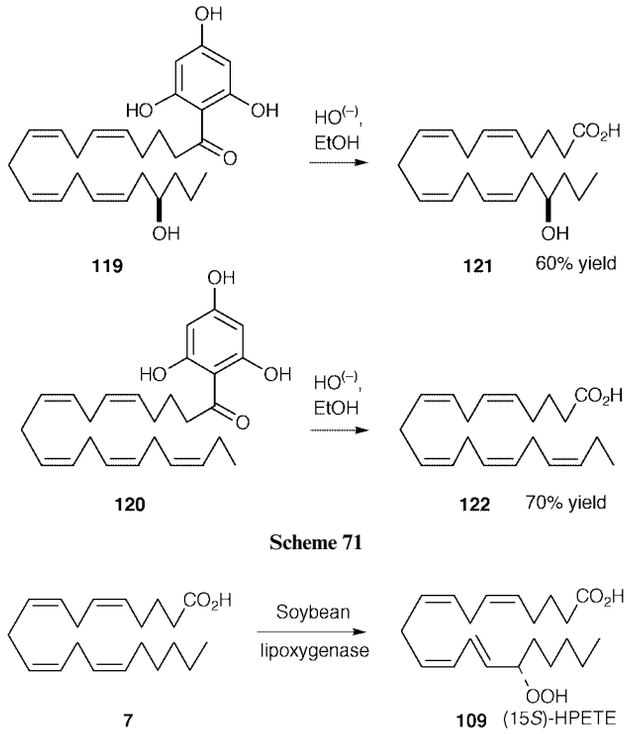
Subsequently, enantioselective syntheses of active dienic epoxides were achieved using a route similar to those reported by Mori.[110]

Finally, brown algae contain eicosanoyl phloroglucinols **119** or **120** which, under basic treatment, lead to the corresponding acids **121** or **122** (Scheme 71).[111]

4.2 Enzyme mediated synthesis

Soybean lipoxygenase, in the presence of oxygen, brought about the introduction of a hydroperoxide function after abstraction of a hydrogen atom from the skipped methylene carbon between the last two double bonds. Thus, the arachidonic acid **7** was converted into (15*S*)-hydroperoxyeicosatetraenoic acid [(15*S*)-HPETE] **109** (Scheme 72).

In the same way, soybean lipoxygenase mediated the preparation of (13*S*)-hydroperoxide from linoleic acid. Increasing

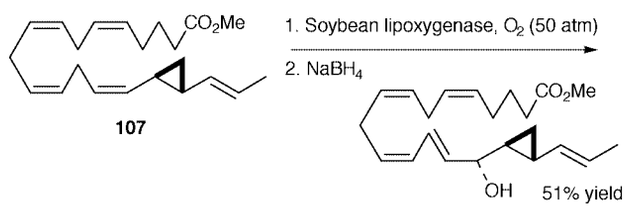


Scheme 71

Scheme 72

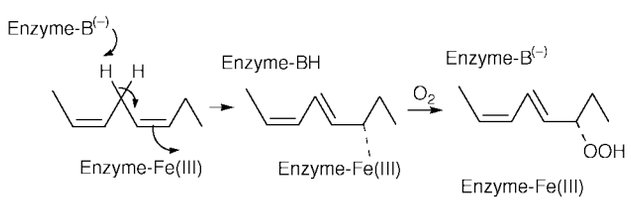
the O_2 pressure was also found to be favourable in terms of yields.[112]

In order to study the oxidation mechanism, Corey has used the cyclopropane acid **107**. Hydroperoxidation occurs without the formation of a cyclopropylmethyl radical which, if it was present, would isomerise into a homoallyl radical (Scheme 73).[113]



Scheme 73

This observation and others have allowed the proposal of a pathway where the hydroperoxide formation results from oxygen incorporation into a carbon–iron bond (Scheme 74).[114]



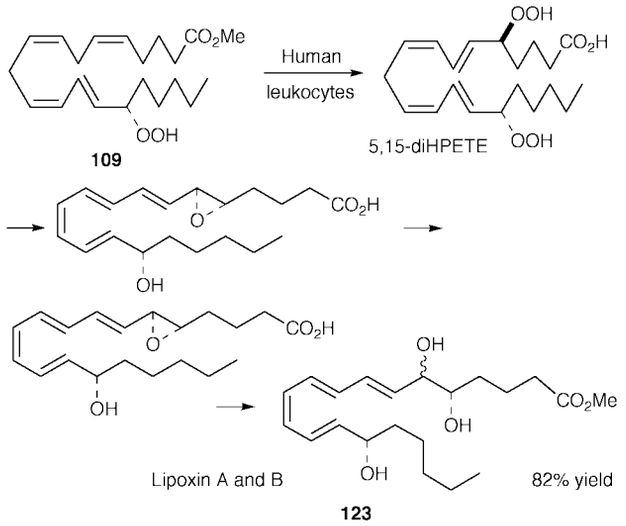
Scheme 74

Lipoxins A and B **123** are obtained when (15*S*)-HPETE **109** was submitted to the action of human leukocytes (Scheme 75).[115]

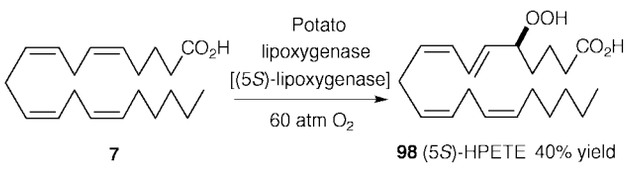
Potato lipoxygenase, under O_2 pressure, transforms arachidonic acid **7** into (5*S*)-HPETE **98** (Scheme 76).

Then, used in anaerobic media, it converts (5*S*)-HPETE **98** into leukotriene A_4 **124** *via* an organoiron intermediate **125** (Scheme 77).[116]

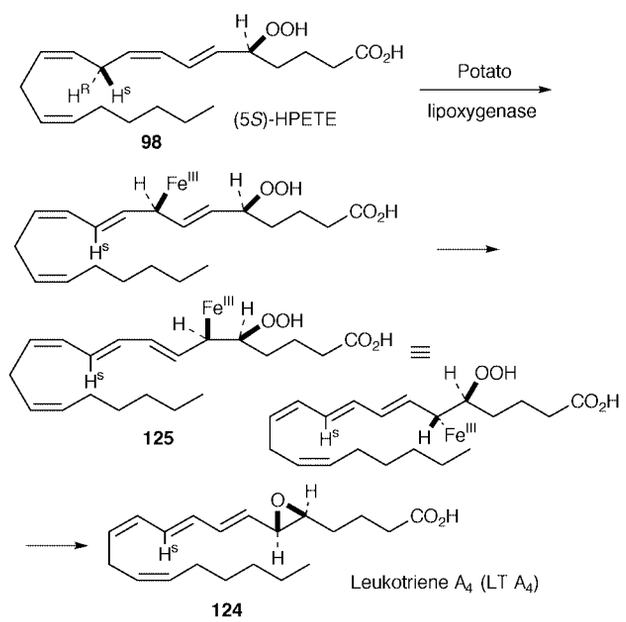
In the same study, Corey has shown that lipoxygenase



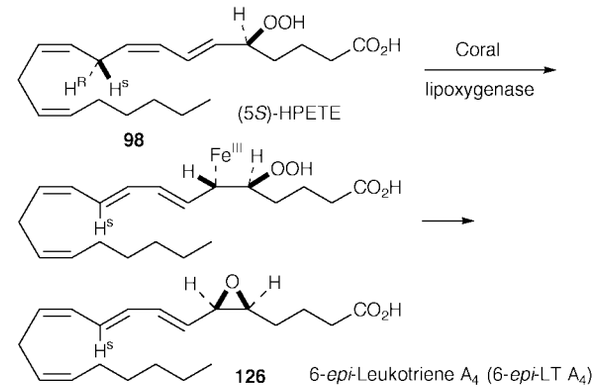
Scheme 75



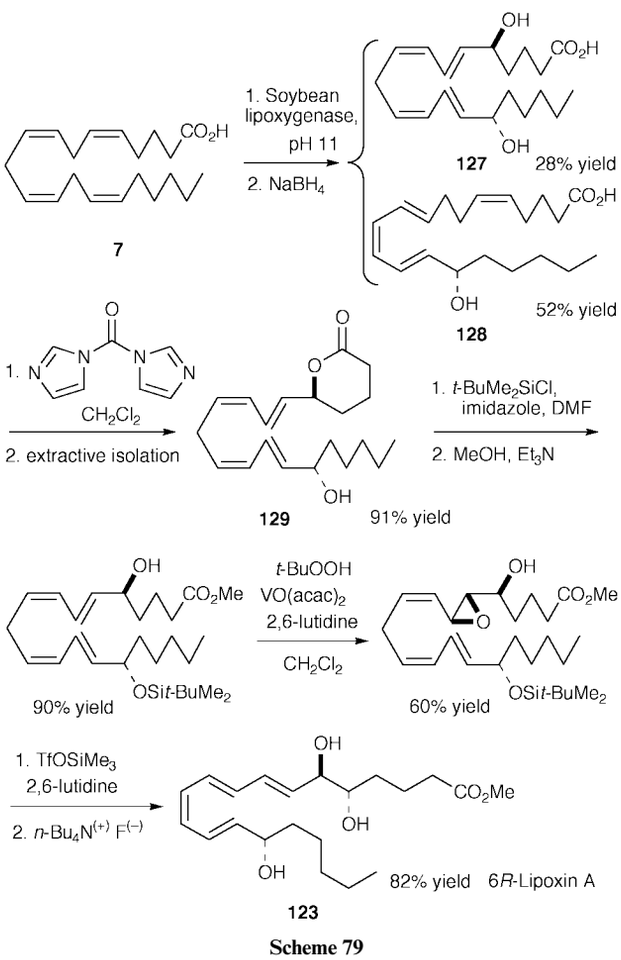
Scheme 76



Scheme 77



Scheme 78



Scheme 79

normally acting as an (8*R*)-HPETE promoter, gives mainly, from (5*S*)-HPETE **98**, the 6-*epi*-leukotriene A_4 **126**. These two results are in accord with the intervention of an organoiron intermediate (Scheme 78).

From the arachidonic acid **7**, soybean lipoxygenase, in the presence of oxygen, catalysed the formation of two bis hydroperoxides which after reduction gave the two acids **127** and **128**. The mixture of these metabolites was treated with 1,1′-carbonyldiimidazole and only (5*S*,15*S*)-diHETE was converted to a δ-lactone **129**. This was then transformed, after selective epoxidation of the double bond with an α-hydroxy function, into lipoxin A **123** (Scheme 79).[117]

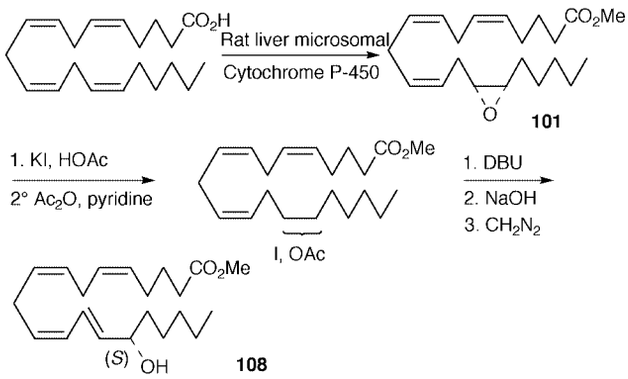
Arachidonic acid **7** could also be selectively epoxidised by purified rat liver microsomal cytochrome P-450 to afford 14,15-epoxyeicosatrienoic acid **101** in which the absolute configuration was established by conversion to the corresponding (15*S*)-hydroxyeicosatetraenoic acid (HETE) **108** (Scheme 80).[118]

Oxidation of linolenic acid **5**, by a preparation of red alga, gave rise to a tetraenoic acid and a hydroxyacid **130**. In this last case, only the *pro*-(*S*) hydrogen is eliminated (Scheme 81).[119]

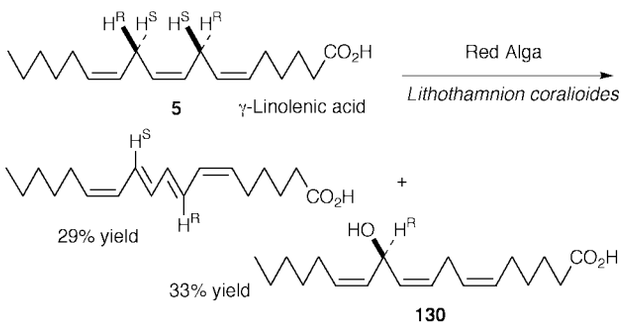
5 Synthesis of cyclic skipped polyenes

Musso has prepared the (all-*Z*)-cyclododeca-1,4,7,10-tetraene **131** which would form new organometallic π-complexes. Nevertheless, the cyclisation reaction (McMurry cross coupling) occurred in a very low yield (Scheme 82).[120]

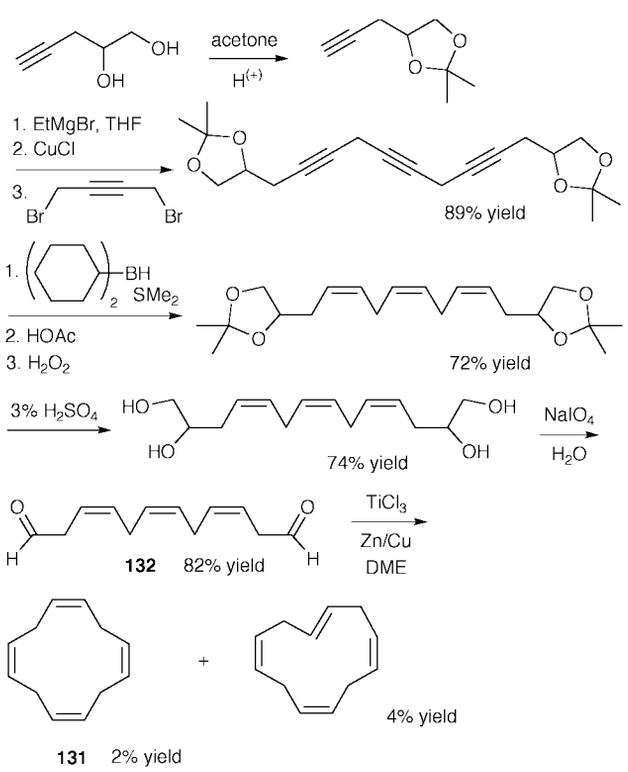
Using a similar approach, Musso has prepared the thiacyclotridecatriene from trienic dialdehyde **132**.[121] The fascinating cyclododecatetraene **131** was also prepared by Gleiter by cross-coupling the dilithium reagent of the skipped enediyne with (*Z*)-1,4-dibromobut-2-ene. However, due to the ring strain, the



Scheme 80



Scheme 81



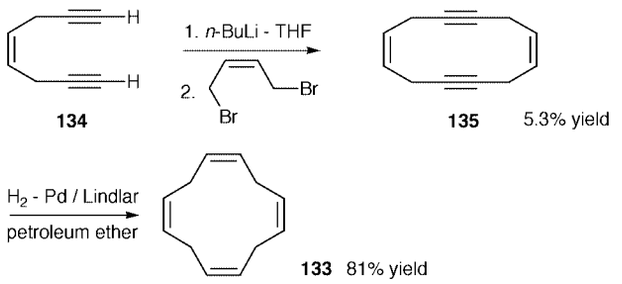
Scheme 82

cyclisation reaction afforded dienediyne **135** in only 5% yield (Scheme 83).[122]

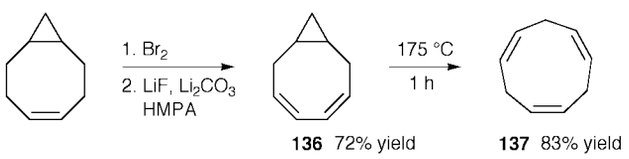
Finally, Paquette, using a sequence involving bromination, dehydrobromination reaction and thermolytic ring opening of bicyclo[6.1.0]non-4-ene **136** has realised the most efficient synthesis of (all-*Z*)-cyclononatriene **137** (Scheme 84).[123]

6 Conclusion

In the two last decades, remarkable advances have been achieved in the preparation of the skipped diene moiety



Scheme 83



Scheme 84

directed toward the total synthesis of pheromones, polyunsaturated fatty acids and their metabolites. Acetylene chemistry was initially very often used, but the Wittig approach has permitted the synthesis of numerous highly polyunsaturated compounds such as DHA or HETE. Nevertheless, due to its tolerance toward numerous functional groups, the novel method using *in situ* formed copper acetylides has led to a renewal of interest in the acetylenic route. This was reinforced by the possibility of introducing deuterium or tritium atoms on sp^2 carbons with high selectivities through borane or low valent transition metal mediated reduction. In addition to these two major methods and in spite of their low use, vinyltin reagents have proven their efficiency in the synthesis of PUFA metabolites. Finally, PUFA have also emerged as carriers of the skipped diene moiety both for PUFA metabolites synthesis and for biosynthetic studies.

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