# SYNTHESIS OF 9-OXO- AND 10-HYDROXY-2E-DECENOIC ACIDS

**G. Yu. Ishmuratov, R. Ya. Kharisov, O. V. Botsman, N. M. Ishmuratova, and G. A. Tolstikov**

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*Experimental methods of synthesizing 9-oxo- and 10-hydroxy-2E-decenoic acids, biologically active compounds of the bee family (*Apis mellifera *L.), are reviewed.*

**Key words:** 10-hydroxy-2E-decenoic acid, 9-oxo-2E-decenoic acid, synthetic methods.

The most important components identified in honeybee (*Apis mellifera* L.) queen substance and royal jelly are 9-oxo-2E-decenoic (**1**, 9-ODA) and 10-hydroxy-2E-decenoic (10-HDA) acids. 10-HDA acts as a bectericide, fungicide, and antitumor substance [1]. Oxoacid **1** regulates the behavior and metabolism of the bee family by attracting drones and young workers, inhibiting sexual development in workers, preventing the emergence of a new queen, and assisting the gathering and migration of swarming bees [2].

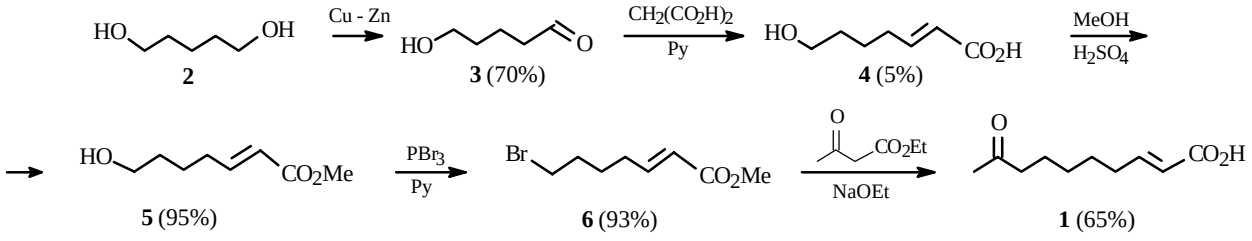
These biologically active compounds are isolated from bees in quantities insufficient for practical application. Therefore, the only method for preparing them is organic synthesis.

Several approaches to the synthesis of 9-ODA and 10-HDA are known. These can be divided into methods for introducing oxo-, hydroxy-, and $\alpha,\beta$-unsaturated carboxylic acid groups.

In this review, we examine various approaches to forming the conjugated acid.

## SYNTHESIS OF 9-OXO-2E-DECENOIC ACID

**Synthesis Using the Doebner Reaction.** The Doebner reaction involves condensation of aldehydes with malonic acid accompanied by decarboxylation and is widely used to introduce the $\alpha,\beta$-unsaturated carboxylic acid in syntheses of 9-ODA (**1**). For example, 1,5-pentandiol (**2**) was selectively oxidized at one of the hydroxyls to give 5-hydroxypentanal (**3**), which reacted with malonic acid in the presence of pyridine to give 7-hydroxy-2E-heptenoic acid (**4**). Then, **4** was transformed into methyl ester **5** and converted to bromide **6** [3]. Condensation of **6** with sodium acetoacetic ester completed the synthesis of the desired pheromone **1** (Scheme 1).




**2** **3** (70%) **4** (5%) **5** (95%) **6** (93%) **1** (65%)

Scheme 1.

Institute of Organic Chemistry, Ufa Scientific Center of the Russian Academy of Sciences, Russian Federation, 450054, Ufa, pr. Oktyabrya, 71, fax (3472) 35 60 66, e-mail: kharis@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 3-18, January-February, 2002. Original article submitted January 3, 2002.

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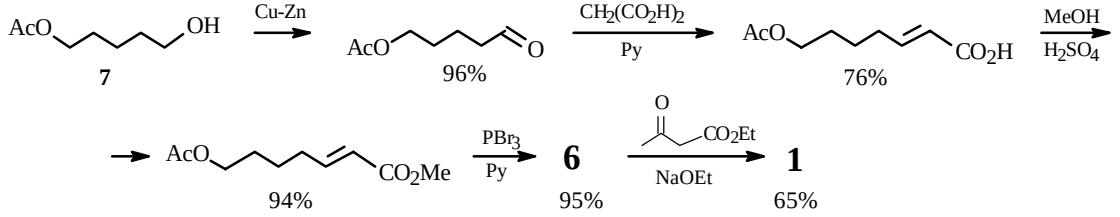
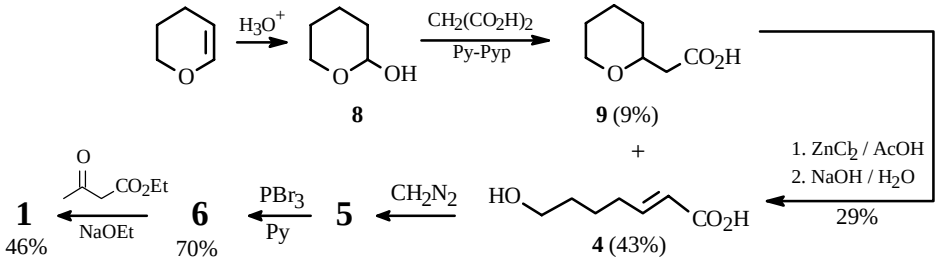
Replacing the starting diol **2** by monoacetate **7** can substantially increase the product yield [3] (Scheme 2).



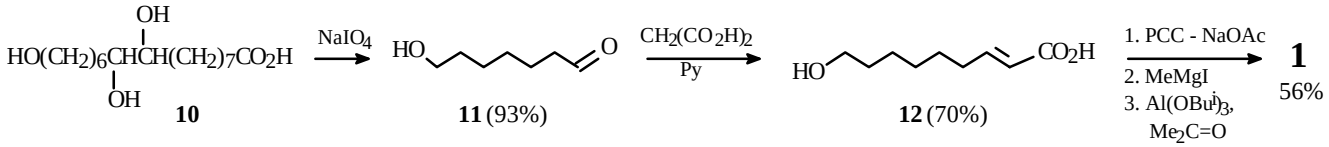

Scheme 2.

Lactols are the cyclized form of hydroxyaldehydes. Therefore, the Doebner condensation can be performed using these compounds. Thus, 2-hydroxytetrahydropyran (**8**) was used to synthesize 2E-unsaturated hydroxyacid **4**. 2-Tetrahydropyranylacetic acid (**9**), which was formed as an impurity, was converted in two steps into **4** [4] (Scheme 3).



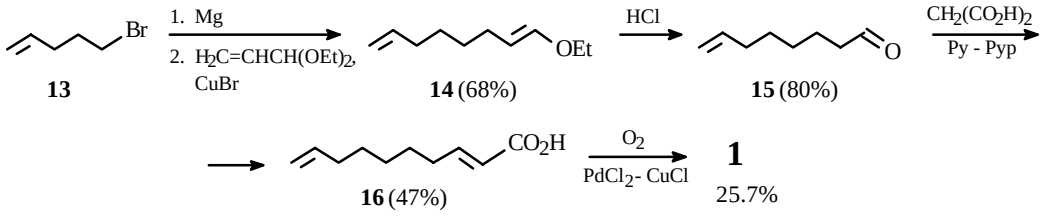

Scheme 3.

Aleuritic acid (**10**) was cleaved to give 7-hydroxyheptanal (**11**), which reacted with malonic acid to form 9-hydroxy-2E-nonenoic acid (**12**). The 9-oxo group was introduced into the pheromone by oxidation of the hydroxyl in **12** to the aldehyde, reaction with the Grignard reagent from methyliodide at the carbonyl, and subsequent Oppenauer oxidation [5] (Scheme 4).



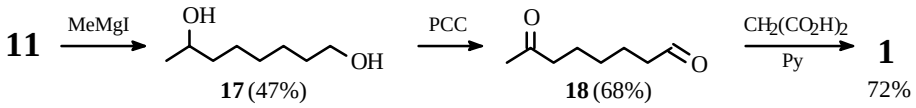

Scheme 4.

A method was proposed for synthesizing 9-ODA from 7-octenal (**15**) by reaction with the Grignard reagent from 4-pentenylbromide (**13**) with the diethylacetal of acrolein and subsequent acid hydrolysis of the resulting enol ether **14** [6]. Doebner condensation of **15** with malonic acid gave 2E,9-decadienoic acid (**16**), Wacker—Tsuji oxidation of which gave the pheromone **1** (Scheme 5).



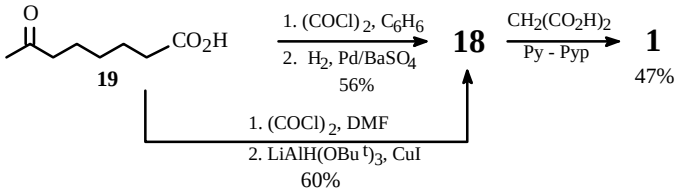

Scheme 5.

However, condensation of malonic acid with 7-oxooctanal (**18**) is more often used in practice [7, 8]. We will present examples that demonstrate various approaches to synthesizing this ketoaldehyde. Thus, hydroxyaldehyde **11** was obtained from aleuritic acid (**10**) and reacted with methylmagnesium iodide. Then, both alcohols were oxidized to give 1,7-octandiol (**17**) [9] (Scheme 6).



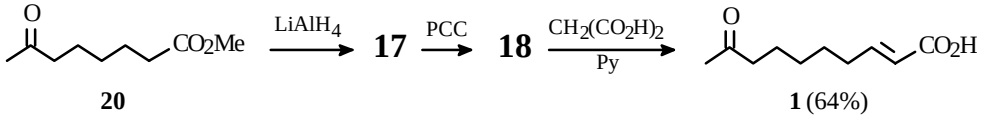

Scheme 6.

Syntheses of **18** from 7-oxooctanoic acid (**19**) by selective reduction of its acid chloride have been reported [10, 11] (Scheme 7).



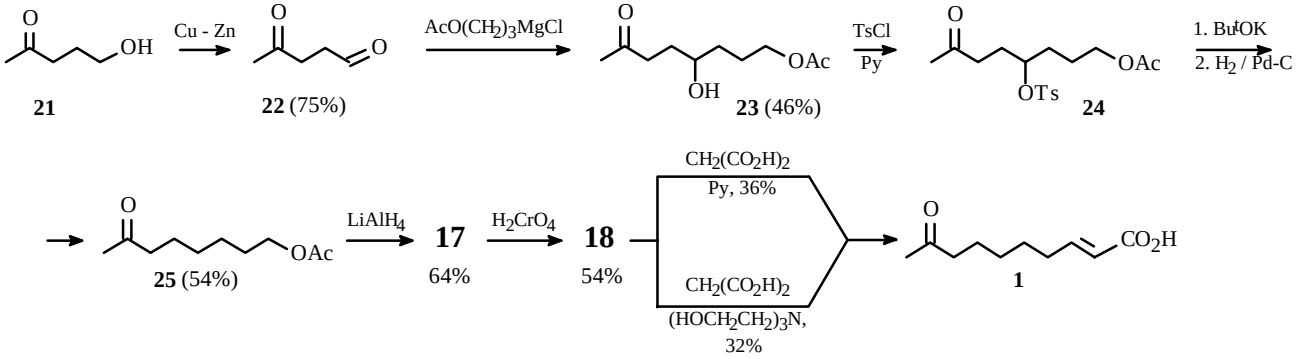

Scheme 7.

Exhaustive reduction of methyl-7-oxooctanate (**20**) with subsequent oxidation of the resulting diol **17** was used to prepare **18** [12] (Scheme 8).



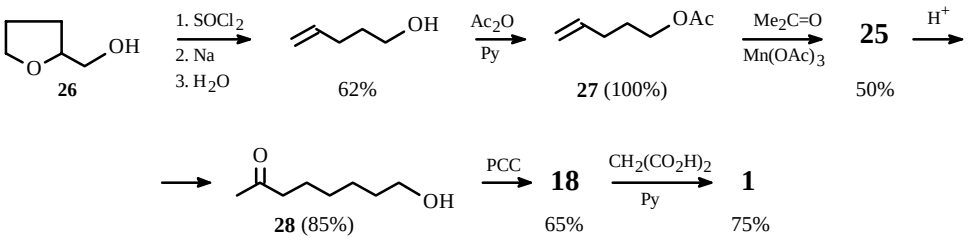

Scheme 8.

Japanese researchers prepared 4-oxopentanal (**22**) via dehydrogenation of 2-oxopentan-5-ol (**21**) [13]. Reaction of the Grignard reagent from 1-acetoxy-3-chloropropane with **22** gave 8-acetoxy-5-hydroxyoctan-2-one (**23**). The alcohol of **23** was hydrogenated as the corresponding tosylate **24**. Further transformations included reduction of the oxo- and acetoxy to hydroxyls and subsequent oxidation of them to oxo groups. The resulting **18** was condensed in the presence of triethanolamine or pyridine to give **1** in yields of 32 and 36%, respectively (Scheme 9).



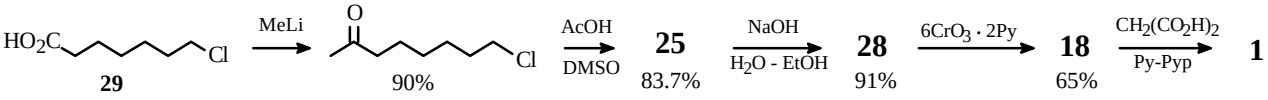

Scheme 9.

Reaction of 4-pentenylacetate (**27**) with acetone in the presence of Mn(III) occurred by a radical mechanism and was used as a key step in the synthesis of **18** from starting tetrahydrofurfuryl alcohol (**26**) [14] (Scheme 10).



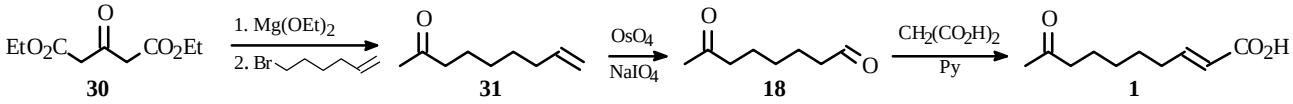

Scheme 10.

Selective reaction of 7-chloroheptanoic acid (**29**) with methyllithium directly introduced the $\omega$-acetyl and was used to synthesize **18** [15] (Scheme 11).



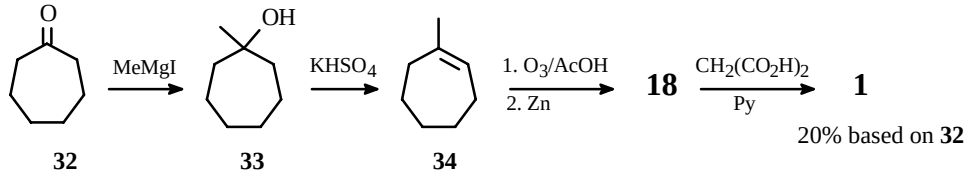

Scheme 11.

The enolate obtained from the diethyl ester of 3-oxoglutaric acid (**30**) was monoalkylated by magnesium ethoxide and 5-hexenylbromide and decarboxylated to give 2-oxo-8-nonene (**31**), periodate oxidation of which in the presence of $OsO_4$ gave **18** [16] (Scheme 12).



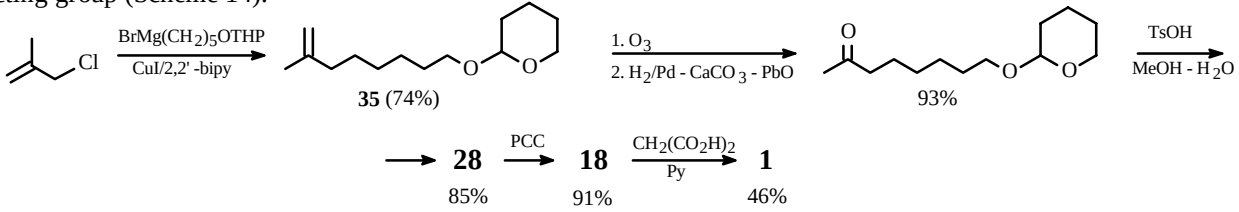

Scheme 12.

9-ODA was synthesized by converting cycloheptanone (**32**) through tertiary alcohol **33** into 1-methylcycloheptene (**34**) followed by decyclization by reductive ozonation [17] (Scheme 13).



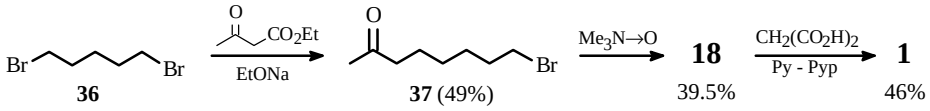

Scheme 13.

Ozonolytic cleavage of a double bond was also used with methylallylchloride as starting material [18]. Catalyzed reaction of the Grignard reagent from the tetrahydropyranyl ester of 5-bromopentan-1-ol with methylallylchloride gave the corresponding derivative 7-methyl-7-octen-1-ol (**35**), reductive ozonolysis of which gave hydroxyketone **28** after removal of the protecting group (Scheme 14).



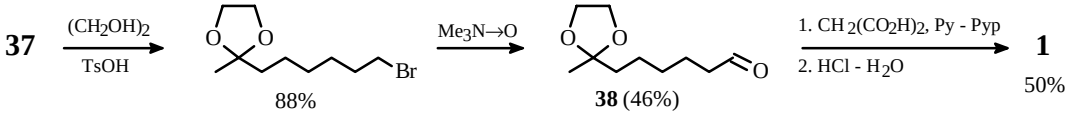

Scheme 14.

The possibility of preparing **18** from 1,5-dihalopentanes was studied [19]. It was shown that the yields are highest if dibromide **36** is used. This was condensed with acetoacetic ester. The halo group in the intermediate 8-bromooctan-2-one (**37**) was oxidized by triethylamine oxide or pyridine into the oxo group (Scheme 15).



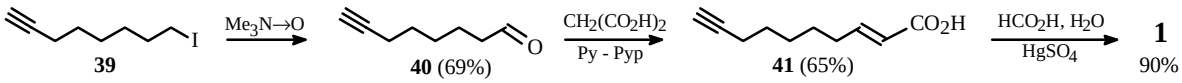

Scheme 15.

Ketoaldehyde **18** was stabilized by first protecting the ketone in **37** [19, 20]. Oxidation gave the oxoacetal **38**, which then underwent Doebner condensation to give **1**. The yield increased from 46 to 50% based on **37** (Scheme 16).



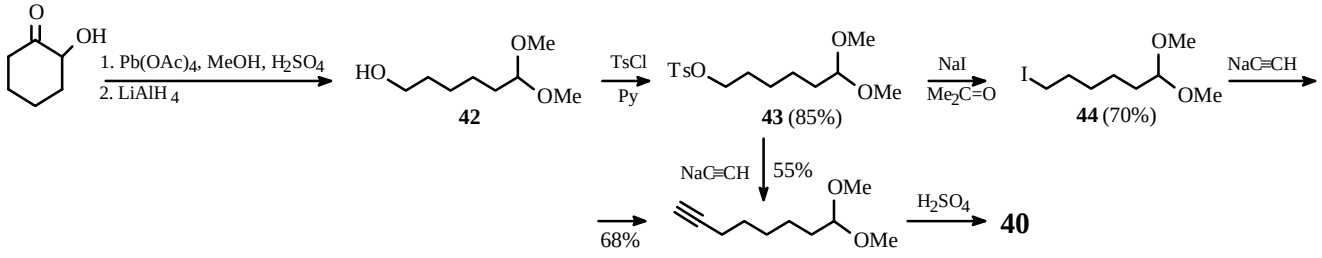

Scheme 16.

Hydration of a terminal acetylene was used to introduce the *ω*-acetyl in 9-ODA. The key enyne acid **41** was synthesized from 8-iodo-1-octyne (**39**) via the following sequence of reactions. The halogenated C was oxidized to give 7-octynal (**40**), condensation of which with malonic acid gave **41** [21] (Scheme 17).




Scheme 17.

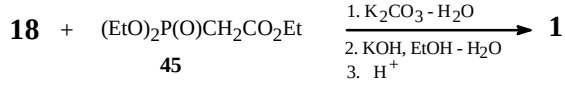
Furthermore, aldehyde **40** was synthesized from 1-hydroxycyclohexanone via the intermediate tosylate **43** of the dimethylacetal of ω-hydroxycaproic aldehyde (**42**). Ether **43** or the corresponding iodide **44** was reacted with sodium acetylide [22] (Scheme 18).




Scheme 18.

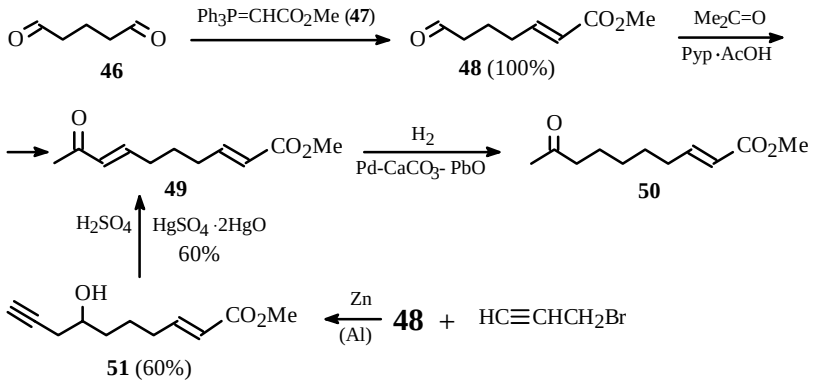
**Syntheses Based on Olefination of Aliphatic Aldehydes.** Another common method for introducing the double bond in 9-ODA is olefination of aliphatic aldehydes by the Wittig—Horner—Emmons reaction [23, 24].

The Horner—Emmons reaction of **18** with a phosphonoacetate (**45**) in the presence of weak base occurred selectively at the aldehyde [25]. Products of double olefination were not observed (Scheme 19).



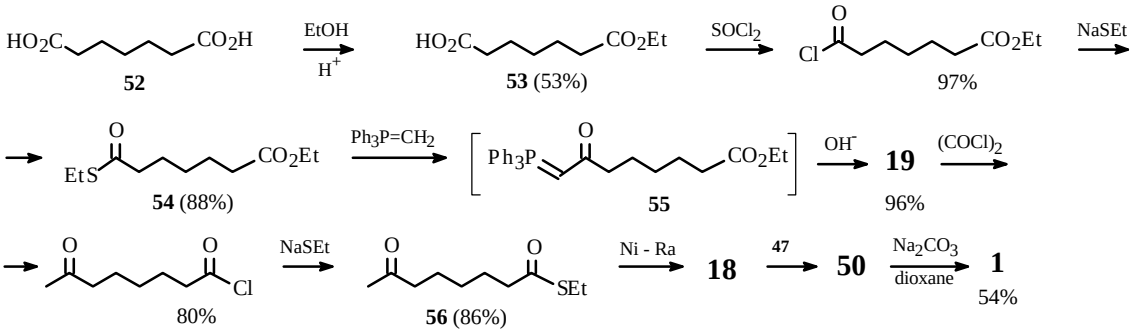

Scheme 19.

Glutaric aldehyde (**46**) was used as starting material. It reacted with carbomethoxymethylidenetriphenylphosphorane (**47**) at one of the carbonyls to give the methyl ester of 7-oxo-2E-heptenoic acid (**48**) in quantitative yield [26]. Subsequent transformations followed two pathways. First, condensation of **48** with acetone gave in low yield the methyl ester of 9-oxo-2,7-decadienecarboxylic acid (**49**), the $\Delta^7$-double bond of which is extremely reactive and was hydrogenated over poisoned catalyst (in particular, Lindlar catalyst) to give the methyl ester of 9-ODA (**50**). Second, **48** underwent a Reformatskii—Hodemar reaction with propargylbromide in the presence of Zn or Al to give (in 60% yield) the methyl ester of 7-hydroxy-2-decen-9-ynoic acid (**51**). Dehydration and subsequent addition of water in the presence of acid with mercury-ion catalysis also gave unsaturated ketone **49** (Scheme 20).



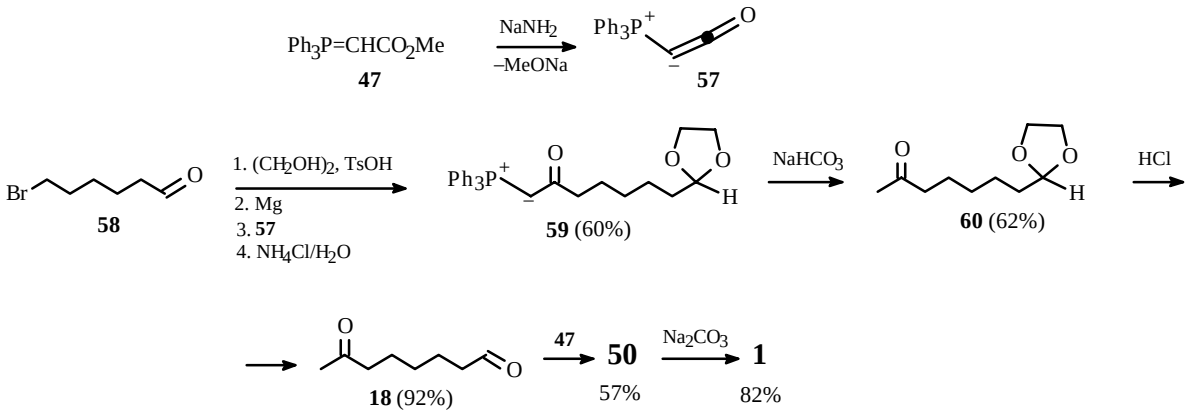

Scheme 20.

An interesting approach to the synthesis of 9-ODA from pimelic acid (**52**) has been proposed [27]. First, monoester **53** was converted to diester **54**, containing one thioester and by which was acylated of methylidenetriphenylphosphorane. Hydrolysis of the resulting acylylide **55** gave oxoacid **19**. Reduction of the carboxylic acid to the aldehyde went through the corresponding thioester **56**. The synthesis of **1** was completed by regioselective olefination of the aldehyde in **18** by phosphorane **47** (Scheme 21).



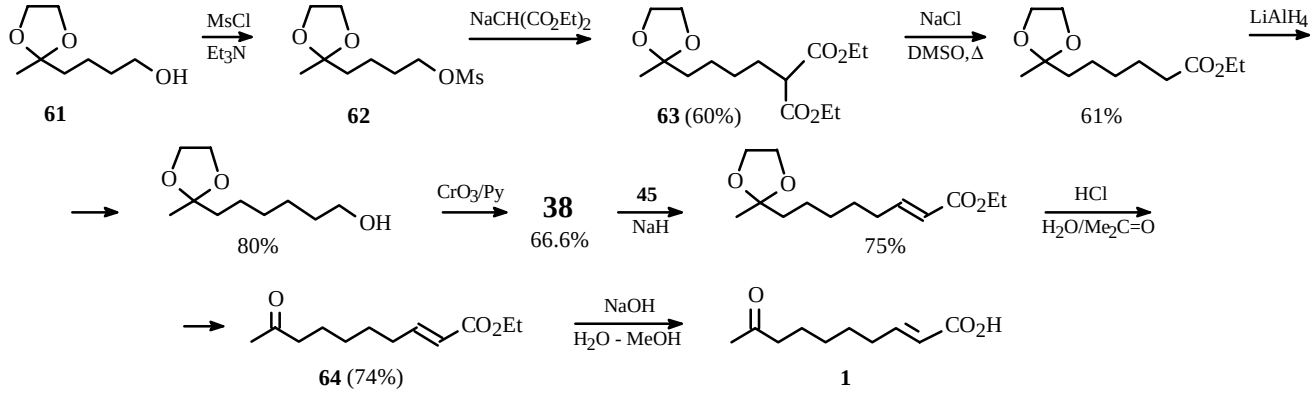

Scheme 21.

Furthermore, a method has been described in which **47** was successfully used to introduce both the oxo- and $\alpha,\beta$-unsaturated carboxylic acids [28]. Ketenylidenetriphenylphosphorane (**57**) was formed by treatment of **47** with base and reacted with the Grignard reagent from 1-bromohexanal acetal (**58**). Workup of the reaction mixture with aqueous $NH_4Cl$ isolated acylylide **59**. Base hydrolysis of **59** gave acetal **60**, which was olefinated by **47** after removal of the protecting group. The synthesis was completed by base hydrolysis of the intermediate **50** (Scheme 22).



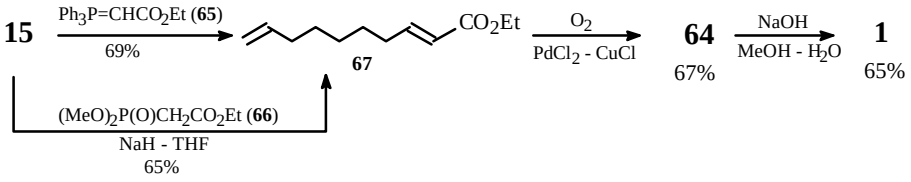

Scheme 22.

A method was proposed for preparing oxoketal **38**, which was then transformed by a Horner—Emmons reaction with phosphonoacetate **45** into the ethyl ester of 9-ODA (**64**) [29]. For this, the acetal of 5-oxohexan-1-ol (**61**) was esterified to the corresponding mesylate **62** and reacted with sodium diethylmalonate in a Knoevenagel condensation. The substituted malonate **63** was converted by standard reactions into the key intermediate **38** (Scheme 23).



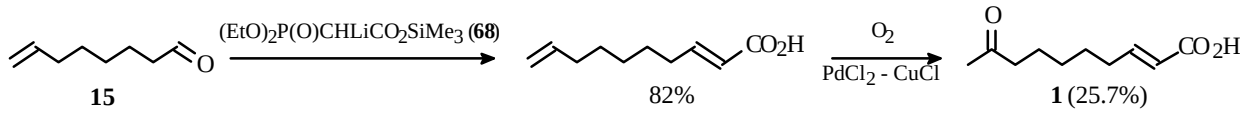

Scheme 23.

Wittig olefination by carboethoxymethylidenetriphenylphosphorane (**65**) [30] or a Horner—Emmons reaction using phosphonoacetate (**66**) [29] introduced an olefin into octenal **15** to give the ethyl ester of 2E,9-decadienoic acid (**67**). Wacker—Tsuji oxidation of the terminal double bond followed by saponification of **64** gave **1** (Scheme 24).



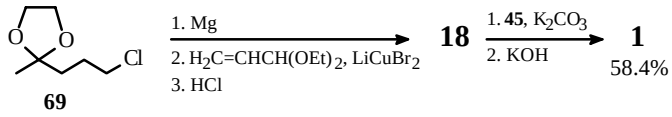

Scheme 24.

If metallated diethyltrimethylsiloxycarbonylmethanephosphonate (**68**) is used to form the olefin, then the saponification can be avoided (Scheme 25).



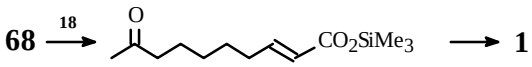

Scheme 25.

Catalyzed reaction of the Grignard reagent from chlorodioxolane **69** with acrolein acetal gave ketoaldehyde **18** after acid hydrolysis. The reaction occurred selectively at the aldehyde if a weak base was used to form the olefin via a Wittig—Horner reaction of phosphonoacetate **45** with dicarbonyl **18** [31] (Scheme 26).



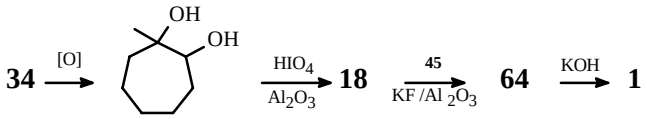

Scheme 26.

Using silyl phosphonate **68** instead of $(EtO)_2P(O)CH_2CO_2R$ (where R = alkyl) in the Horner—Emmons reaction increased the yield of **1** to 70% [32] (Scheme 27).



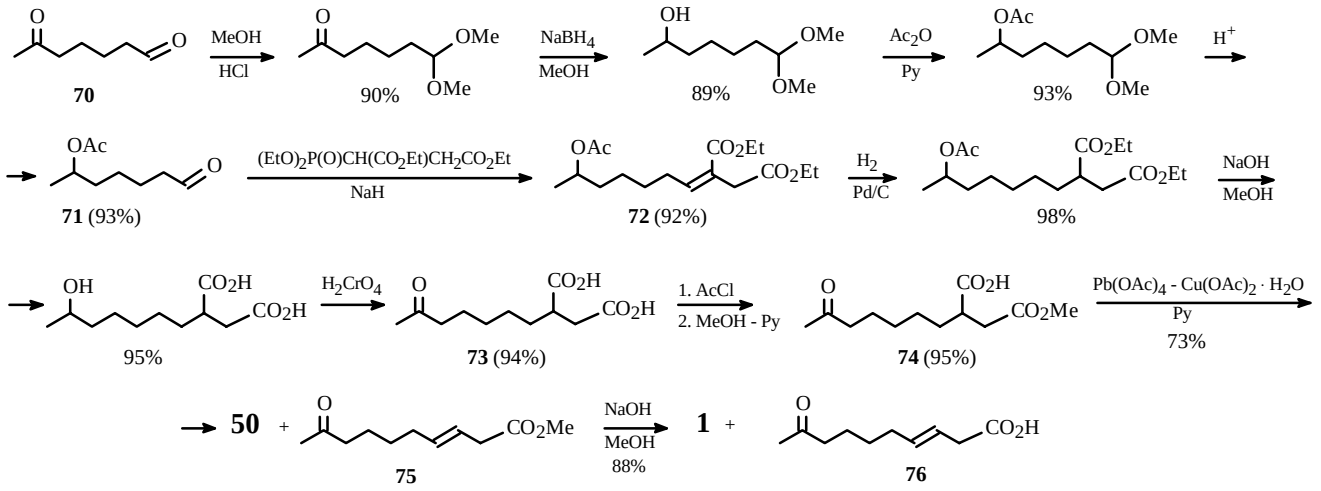

Scheme 27.

Oxidative decyclization of methylcycloalkene **34** produced **18**, which gave precursor **64** after olefination [33] (Scheme 28).



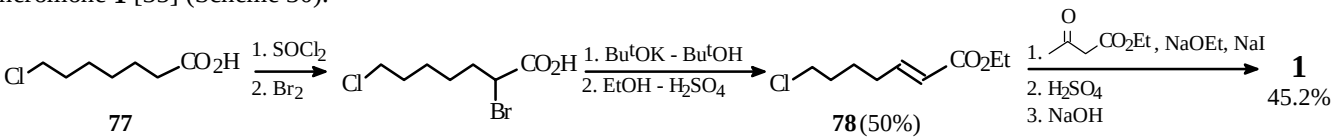

Scheme 28.

**Other Syntheses.** Oxidative decarboxylation of monoesters of 1,4-dicarboxylic acids can also introduce the double bond into 9-ODA. Such a derivative of succinic acid (**74**) was synthesized by using the phosphonate of the diethyl ester of 2-(diethoxyphosphonyl)-butanedicarboxylic acid to form an olefin from acetoxyheptanal (**71**), which was prepared from 6-oxoheptanal (**70**) via a standard reaction sequence [34]. The resulting unsaturated triester **72** was transformed into the saturated oxodicarboxylic acid **73**, selective methylation of which through the corresponding acyl chloride gave monomethyl ester **74**. Oxidative decarboxylation of **74** produced methyl esters **75** and **50** as a mixture (3:1) of double-bond positional isomers, hydrolysis of which gave the corresponding acids **76** and **1** (Scheme 29).



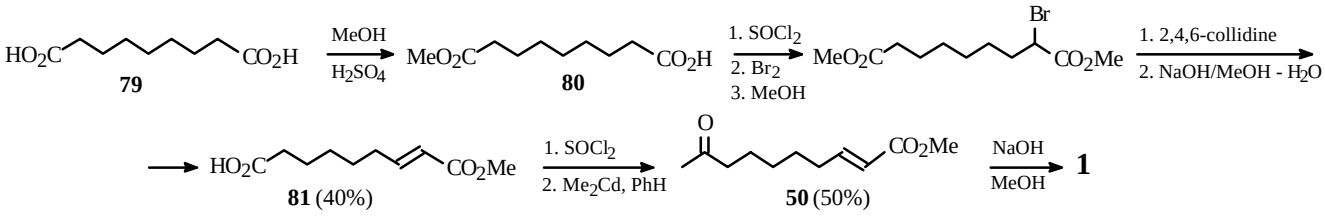

Scheme 29.

Dehydrobromination of $\alpha$-bromoacids is one method for preparing $\alpha,\beta$-unsaturated acids. The use of ω-chloroalkanoic acids is promising for the synthesis of this class of compounds because they are readily prepared via hydrolysis of trichloroalkanes, products of ethylene telomerization. Thus, bromination and dehydrobromination of 7-chloroheptanoic acid (**77**) formed an ester of 7-chloro-2E-heptenoic acid (**78**), which was condensed with sodium acetoacetic ester to give the pheromone **1** [35] (Scheme 30).



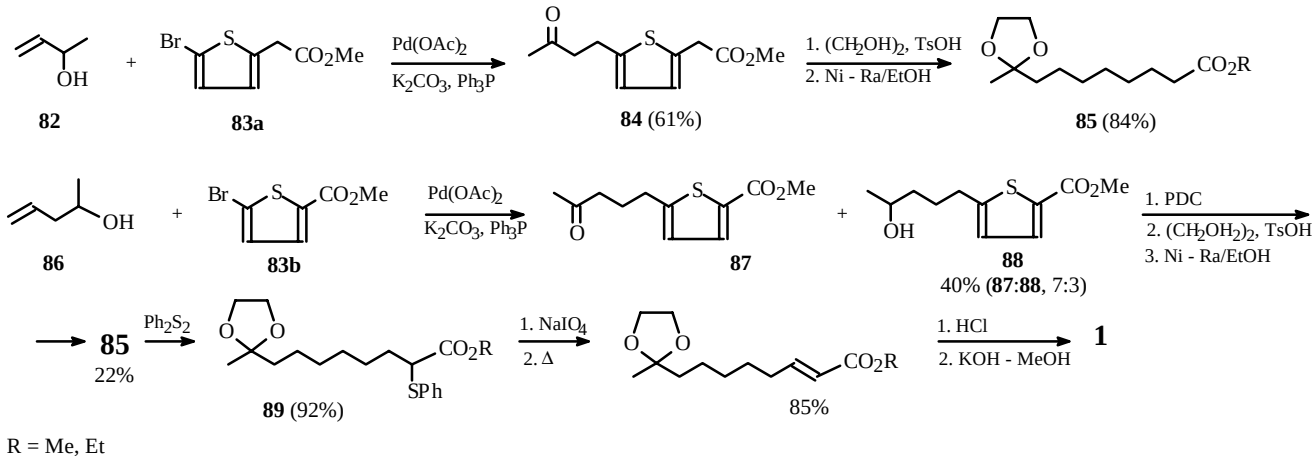

Scheme 30.

Azelaic acid (**79**) was used to synthesize 9-ODA [36]. The monoester **80** was prepared to differentiate the carboxylic groups. Further successive bromination and dehydrobromination led to its 2E-unsaturated analog **81**, the acyl chloride of which reacted with dimethylcadmium to give precursor **50** (Scheme 31).



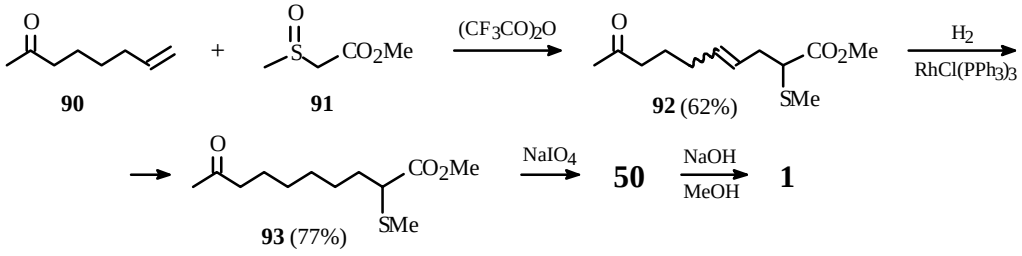

Scheme 31.

The best method for introducing the $\alpha,\beta$-double bond into an available saturated ester is considered to be a method based on the ability of sulfoxides and selenoxides to effect *syn*-1,2-elimination. Several selective methods are known for synthesizing the starting $\alpha$-sulfenyl and $\alpha$-selenyl compounds. Thus, the required S-containing compound was prepared by using Pd-catalyzed thienylation of $\alpha$-methylallyl alcohol (**82**) by a 2-bromothiophene derivative (**83a**) [37]. The resulting disubstituted thiophene **84** was converted to the ketal and desulfided to a mixture (1:3.5) of methyl and ethyl esters of 9-oxodecanoic acid ketal (**85**). Furthermore, the mixture of **87** and **88** that was obtained via thienylation of 2-hydroxy-4-pentene (**86**) by another brominated thiophene **83b** was oxidized by Collins reagent, converted to the ketal, and desulfided to give the key compound **85**, which was transformed by the Trost method through phenylsulfide **89** into **1** (Scheme 32).



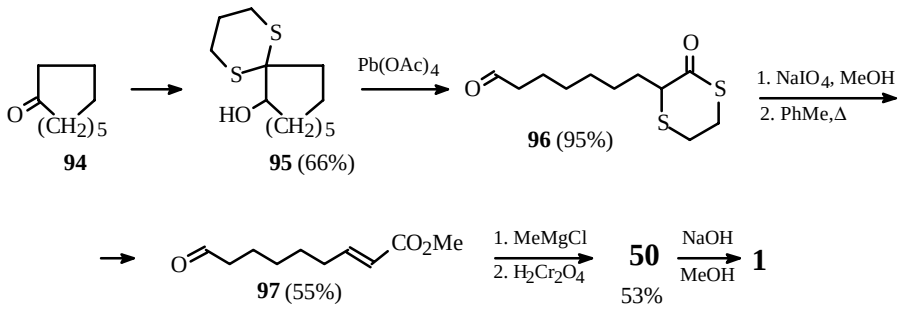

Scheme 32.

The Pummerer condensation of 2-oxo-7-octene (**90**) with sulfoxide **91** is interesting. It gave methyl-2-methylthio-9-oxo-4-decenoate (**92**) [38]. Oxidative *syn*-elimination of its saturated analog **93** gave the precursor of pheromone **50** (Scheme 33).




Scheme 33.

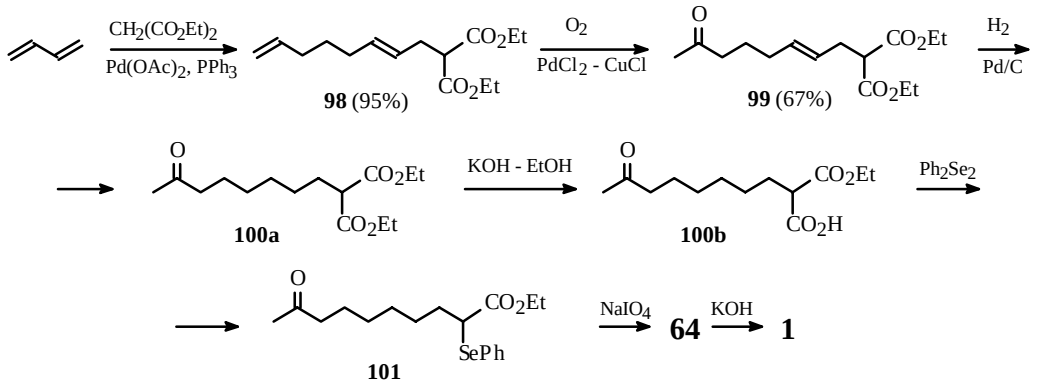
Cyclononanone **94** was also used as starting material to synthesize 9-ODA. Thiylation gave 1,3-dithiane **95**, oxidation of which by lead tetraacetate caused rearrangement and formation of 1,4-dithiane **96**. Periodate oxidation of **96** in methanol gave the methyl ester of 9-oxo-2E-nonenoic acid (**97**) as the result of *trans*-esterification and thermal *syn*-elimination. The oxo of **1** was introduced by a selective reaction of the Grignard reagent from methylchloride with aldehyde **97** and subsequent oxidation [39] (Scheme 34).




Scheme 34.

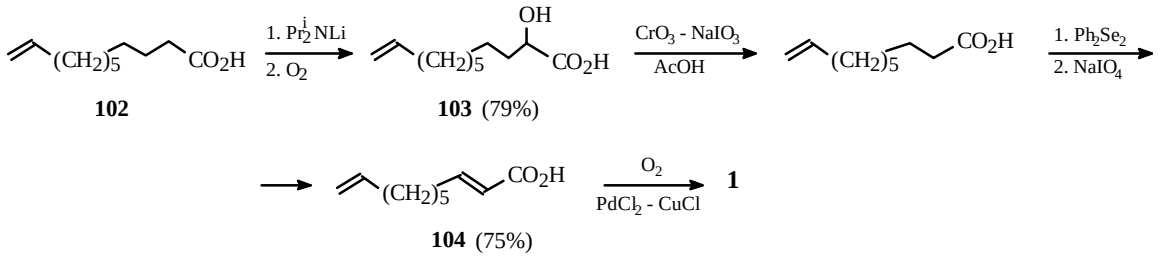
Selenoxides effect *syn*-elimination under milder conditions than sulfoxides and were used to introduce the E-double bond into the backbone of 9-ODA [40]. The key ethyl-9-keto-2-phenylselenyldecanoate (**101**) was prepared from the diethyl ester of 2E,7-octadienylmalonic acid (**98**), the telomerization product of butadiene and diethylmalonate. For this, the terminal

double bond was selectively oxidized. The resulting methylketone **99** was hydrogenated at the unaffected double bond to give the saturated ketodiester **100a**, which was then selectively hydrolyzed to monoester **100b**. Introduction of the phenylselenyl group into **100b** was accompanied by decarboxylation of the unprotected carboxylic acid. Periodate oxidation of the resulting selenide **101** led to unsaturated ester **64**, base hydrolysis of which completed the synthesis (Scheme 35).



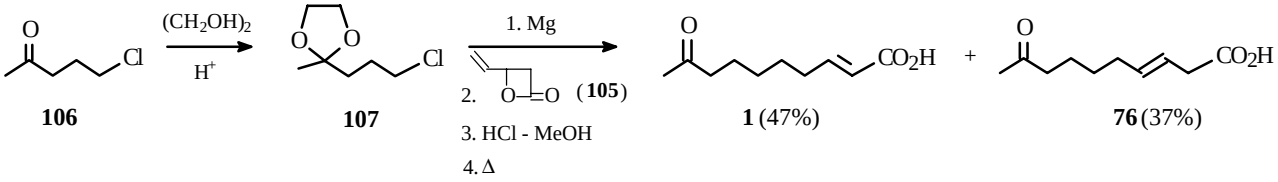

Scheme 35.

A method for preparing **1** from 10-undecenoic acid (**102**) by shortening the chain through the corresponding $\alpha$-hydroxyacid **103** has been proposed [41]. The double bond was introduced by oxidative elimination of the intermediate selenide; the oxo, by Wacker—Tsuji oxidation of the terminal double bond in **104** (Scheme 36).



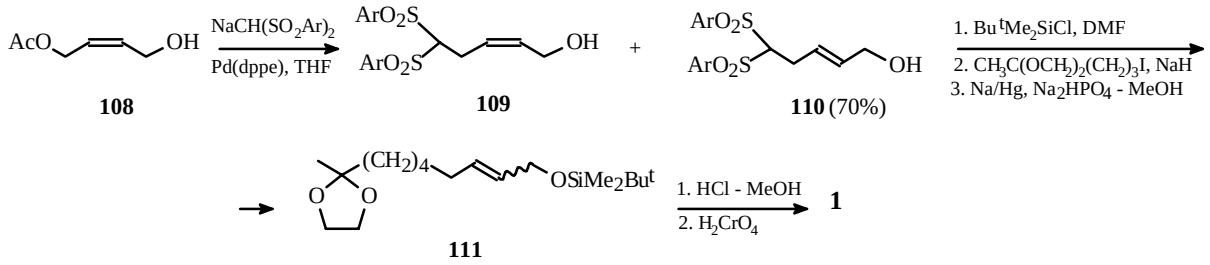

Scheme 36.

A mixture of 9-ODA and its $\Delta^3$-isomer **76** was formed via reaction of the Grignard reagent from 5-chloro-2-oxopentane ethyleneketal (**107**) with $\beta$-vinyl-$\beta$-propiolactone (**105**) and subsequent thermal isomerization [42] (Scheme 37).




Scheme 37.

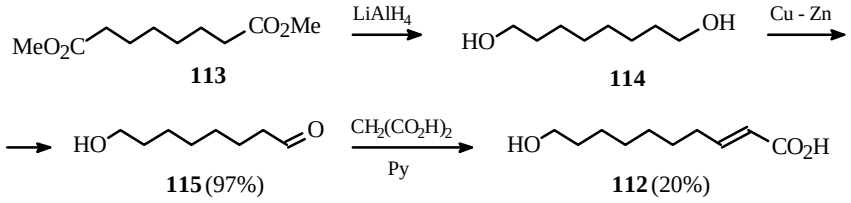
The high reactivity of allyl acetates for nucleophilic substitution was used in the synthesis of 9-ODA from (Z)-2-buten-1,4-diol monoacetate (**108**) [43]. For example, catalyzed reaction of **108** with the sodium salt of bisphenylsulfonylmethane afforded an isomeric mixture (83:17) of Z-(**109**) and E-(**110**) sulfonoalcohols. Repeated alkylation of the silyl derivatives of these by 4,4-ethylenedioxypentyliodide gave after desulfonation allyl siloxane **111**, which was readily transformed into the desired product (Scheme 38).



Scheme 38.

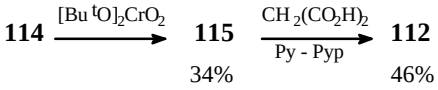
## SYNTHESIS OF 10-HYDROXY-2E-DECENOIC ACID

**Syntheses Using Doebner Condensation.** Doebner condensation of malonic acid with 8-hydroxyoctanal (**115**) is quite frequently used to synthesize 10-HDA (**112**). Various approaches to the synthesis of the hydroxyaldehyde have been reported. It was synthesized [44, 45] from 1,8-octanediol (**114**), which was prepared by hydride reduction of the dimethyl ester of suberic acid (**113**) via partial catalytic dehydrogenation over zinc—copper (Scheme 39).



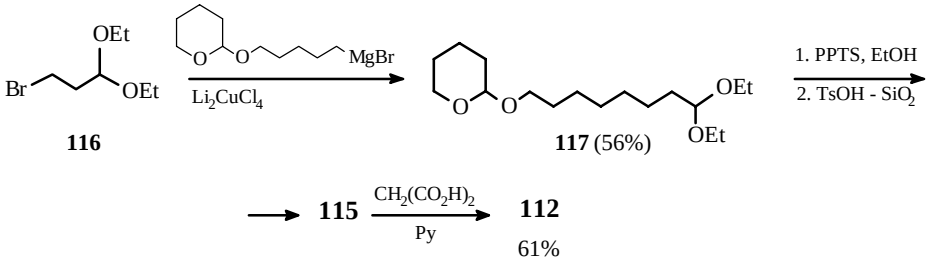
Scheme 39.

Another method is based on selective oxidation of diol **114** by *t*-butylchromate, which produced **115** [46] (Scheme 40).



Scheme 40.

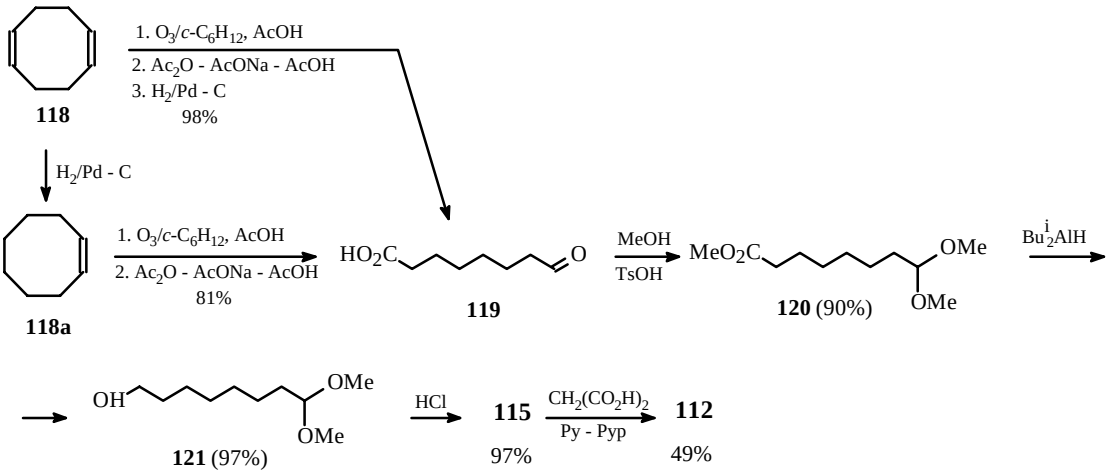
Reaction of 3-bromopropanal (**116**) with 5-(2-tetrahydropyranyloxy)pentylmagnesium bromide catalyzed by dilithium tetrachlorocuprate gave diacetal **117**, which was hydrolyzed stepwise by acid to give the key aldehyde **115** [47] (Scheme 41).



Scheme 41.

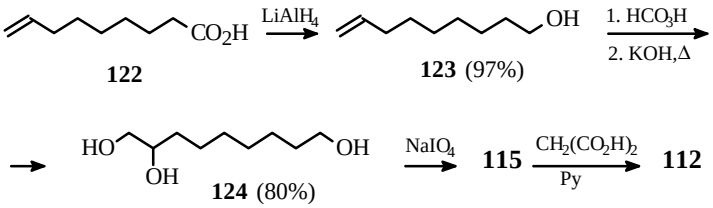
An effective synthesis of **115** is based on the available cyclic dimer of butadiene, 1Z,5Z-cyclooctadiene (**118**) [48] and

its product of selective hydrogenation, *cis*-cyclooctene (**118a**). The key 8-oxoacid (**119**) was prepared by partial ozonolysis—acidolysis of **118** with subsequent hydrogenation of the remaining double bond or exhaustive ozonolysis—acidolysis of **118a**. Methanolysis in the presence of TsOH converted **119** into acetalester **120**, hydride reduction of which and hydrolysis of the intermediate 8,8-dimethoxyoctan-1-ol (**121**) gave **115** (Scheme 42).



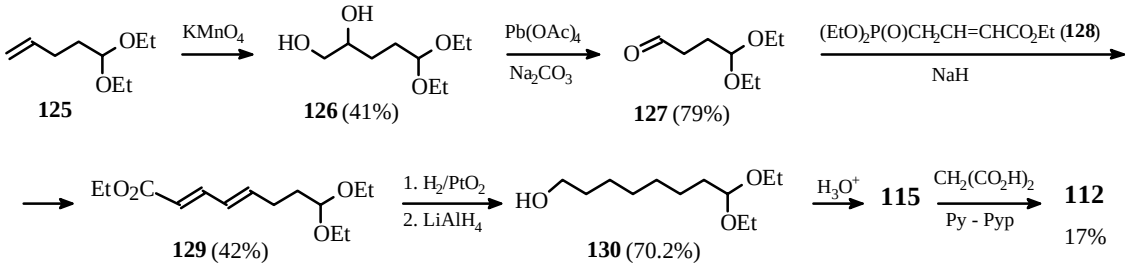

Scheme 42.

Aldehyde **115** was also prepared using 8-nonenoic acid (**122**). For this, the reaction sequence in Scheme 43 was used. This included reduction of the carboxylic acid, hydroxylation of the terminal double bond, and oxidative cleavage of the intermediate 1,2-diol [21].



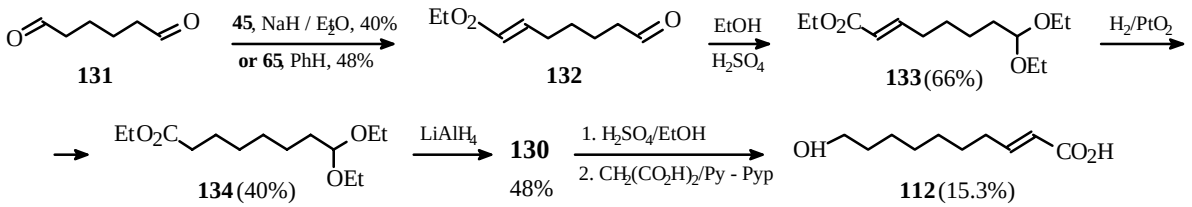

Scheme 43.

The synthesis of key aldehyde **115** from 4-pentenal diethoxyacetal (**125**) involved Wagner hydroxylation of the double bond and oxidative cleavage of the resulting diol **126** to succinaldehyde monoacetal (**127**) [49]. Then successive olefination of **127** by phosphonate **128**, catalytic hydrogenation of dienoate **129**, and hydride reduction afforded 1,1-diethoxy-8-octanol (**130**), which gave **112** after acid hydrolysis and Doebner condensation (Scheme 44).



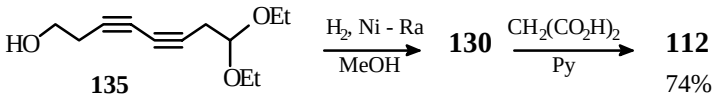

Scheme 44.

Hydroxyacetal **130** can also be prepared from adipoaldehyde (**131**) [50]. Horner—Emmons mono-olefination was the key step in the synthesis through the intermediates **132**, **133**, and **134** (Scheme 45).



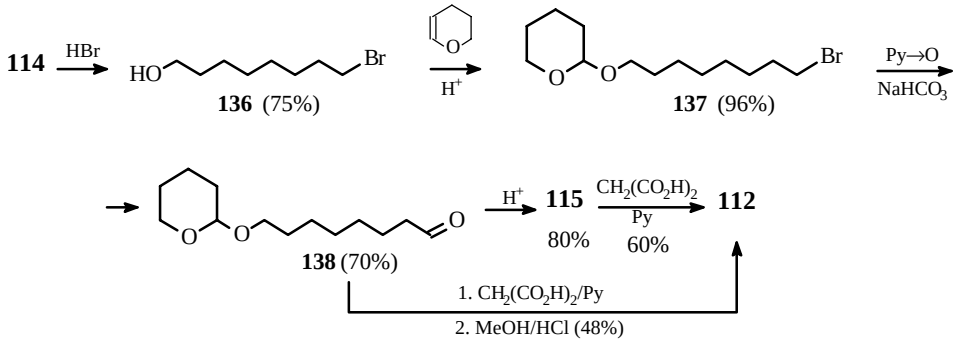

Scheme 45.

Condensation with malonic acid included also a precursor of **115**, hydroxyacetal **130**, which was obtained by exhaustive hydrogenation of 1,1-diethoxy-8-hydroxy-3,5-octadiyne (**135**) over Raney nickel [51] (Scheme 46).



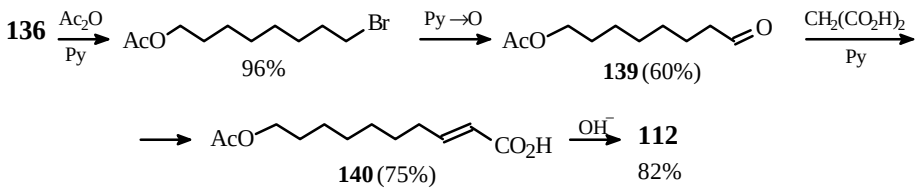

Scheme 46.

Selective bromination of diol **114** gave a bromohydrin (**136**) that was converted to the tetrahydropyranyl ester (**137**) and oxidized at the halogenated C. The resulting protected hydroxyaldehyde (**138**) was converted to the desired product **112** either traditionally through intermediate **115** or in one procedure by successive condensation and hydrolysis. Protecting **138** with tetrahydropyranyl decreased the yield of **112** via the second route [52] (Scheme 47).




Scheme 47.

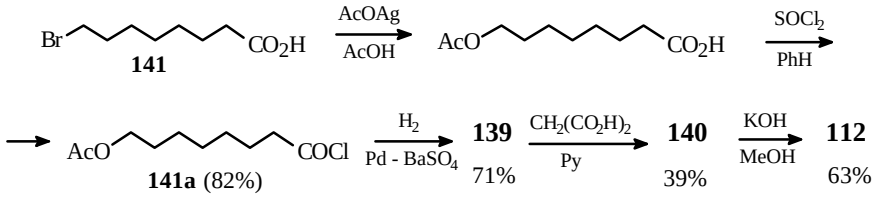
Using acyl protection slightly increased the yield of the condensation product **140** (Scheme 48).




Scheme 48.

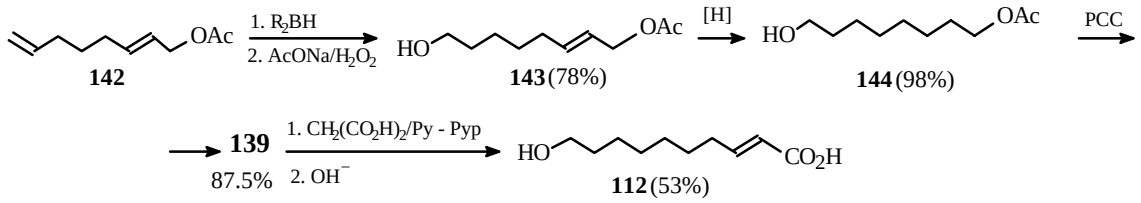
Synthesis of **112** from 8-bromooctanoic acid (**141**) by successive substitution of the Br by acyloxy in the presence of

silver acetate and Rosenmund reduction of the intermediate acyl chloride **141a** to acetoxyaldehyde **139** has been reported [53] (Scheme 49).



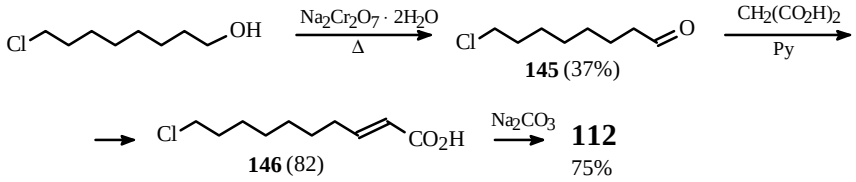

Scheme 49.

A Japanese patent contains a description of the preparation of **112** through aldehydoacetate **139** from an available butadiene telomer and acetic acid, 2E,7-octadien-1-ylacetate (**142**), which was transformed through the corresponding organoboron intermediate into unsaturated **143** and then saturated **144** hydroxyacetates [54] (Scheme 50).



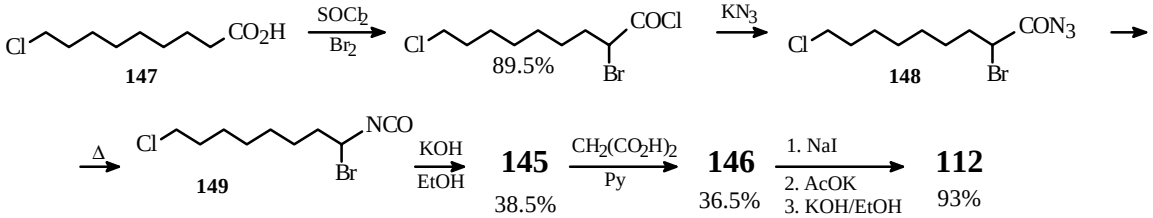

Scheme 50.

In addition to 8-hydroxyoctanal (**115**), the corresponding chloro compound **145** can also undergo Doebner condensation [55]. The halide in intermediate 10-chloro-2E-decenoic acid (**146**) was readily replaced by hydroxyl upon treatment with mild base (Scheme 51).




Scheme 51.

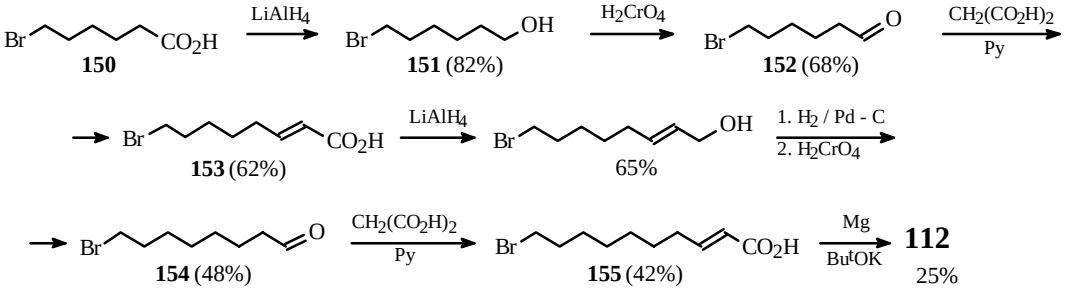
Hydroxyacid **112** can be prepared by a method based on industrial 9-chlorononanoic acid (**147**) using Curtius rearrangement of azide **148** into isocyanate **149** in the key step followed by hydrolysis to 8-chlorooctanal **145** [56] (Scheme 52).




Scheme 52.

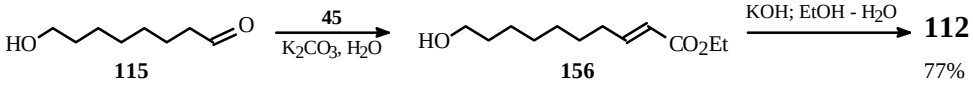
The carbon chain of **112** was constructed from 6-bromohexanoic acid (**150**) after its conversion to bromohydrin (**151**)

and two Doebner condensations of homologous bromaldehydes **152** and **154** to give the corresponding *ω*-bromosubstituted 2E-unsaturated acids **153** and **155**. The latter was hydrolyzed to the desired product [57] (Scheme 53).



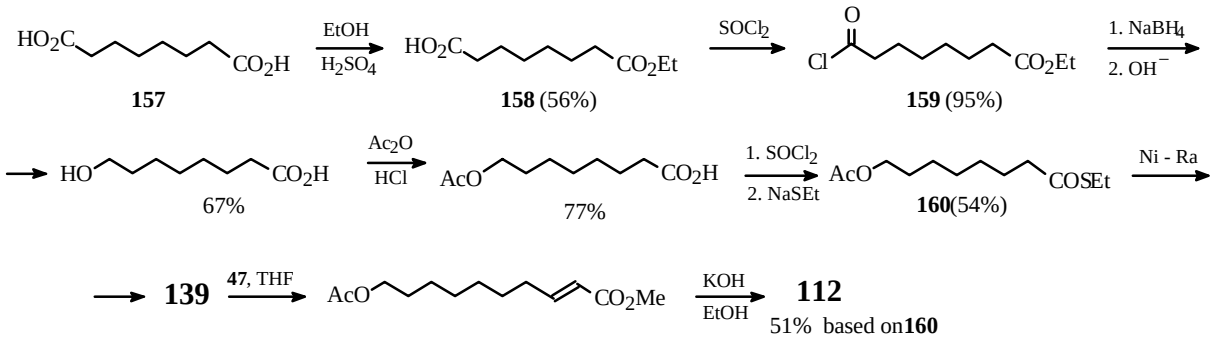

Scheme 53.

**Syntheses Based on Olefination of Aliphatic Aldehydes.** Other effective methods for introducing the 2E-double bond into 10-HDA are based on the Wittig—Horner—Emmons reaction. For example, the Wittig—Horner reaction of hydroxyaldehyde **115** with phosphonate **45** and subsequent hydrolysis afforded **112** in high yield [56] (Scheme 54).



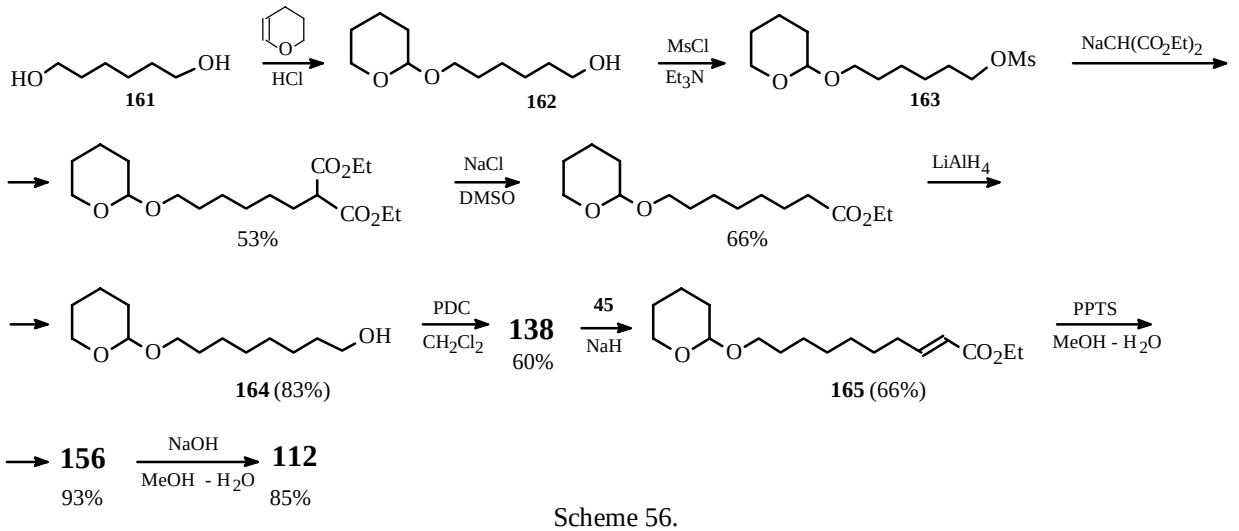

Scheme 54.

Synthesis of **112** from dicaboxylic acid **157** through its monoester **158** has been reported [59]. Aldehyde **139**, which was used in the key step of olefination by phosphorane **47**, was prepared via several successive selective transformations of the carboxylic and ethoxycarbonyl groups. The former was converted by hydride reduction of acyl chloride **159** into hydroxyl; the latter, by treatment with Raney nickel of intermediate thioester **160** into carbonyl (Scheme 55).



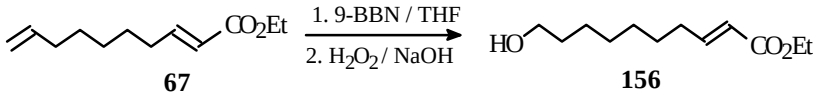

Scheme 55.

Monotetrahydropyranyl ester **162** was prepared by selective protection of 1,6-hexandiol (**161**), transformed into mesylate **163**, and converted using diethylmalonate into the bis-homolog **164**, which was readily olefinated to the corresponding aldehyde **138** and exhaustively hydrolyzed to **112** [60] (Scheme 56).



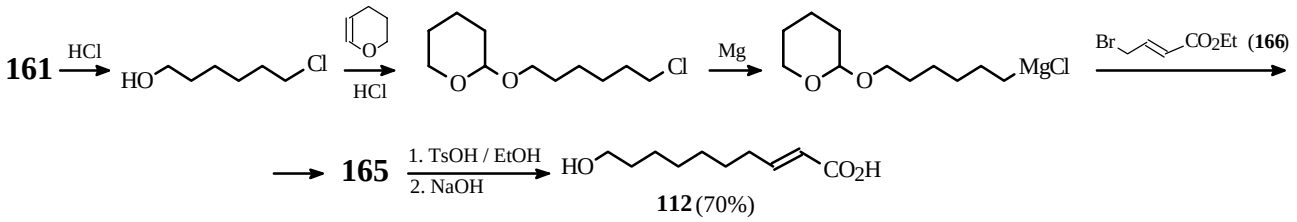

Scheme 56.

Hydroboration of dienoate **67** using 9-borabicyclo[3.3.1]nonane, which occurred regioselectively and chemically selectively at the terminal double bond, followed by oxidation of the organoboron intermediate was used to synthesize the ethyl ester of 10-hydroxy-2E-decenoic acid (**156**) [29] (Scheme 57).



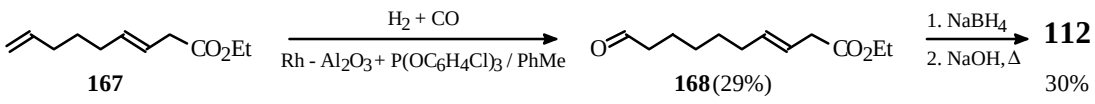

Scheme 57.

**Other Synthetic Methods.** In addition to the above methods for preparing the E-double bond in 10-HDA, approaches based on the use of already unsaturated starting materials are known. Thus, French researchers synthesized **112** using the E-double bond of ethyl-γ-bromocrotonate (**166**), which reacted with 6-(2-tetrahydropyranyloxy)hexylmagnesium chloride [61] (Scheme 58).



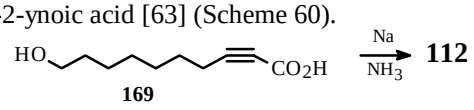

Scheme 58.

Catalytic hydroformylation of the vinyl group of ethyl-3E,8-nonadienoate (**167**), the product of hydroesterification of butadiene, produced aldehydoester **168**, which was isomerized after hydride reduction of the oxo group by heating in the presence of base into the desired 2E-unsaturated acid **112** [62] (Scheme 59).



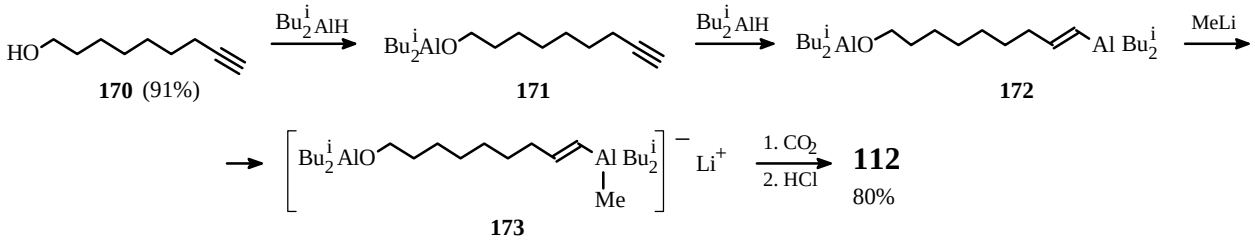

Scheme 59.

Furthermore, examples are known of syntheses of 10-HDA based on partial 2E-stereoselective reduction of acetylene precursors, for example, 10-hydroxydec-2-ynoic acid [63] (Scheme 60).



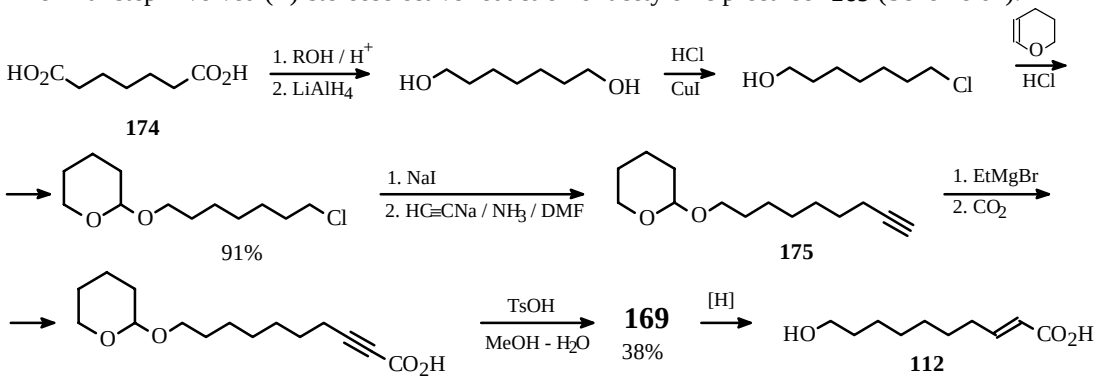

Scheme 60.

A one-step process was developed for preparing **112** from 8-nonyn-1-ol (**170**), treatment of which with diisobutylaluminumhydride in hydrocarbon solvent converted it initially to the alcoholate **171** and then to the *trans*-vinylalane **172**. Reaction of **172** with methyllithium in ether gave the complexed vinyllithium alanate **173**, carboxylation of which by $CO_2$ followed by hydrolysis completed this novel synthesis [64] (Scheme 61).



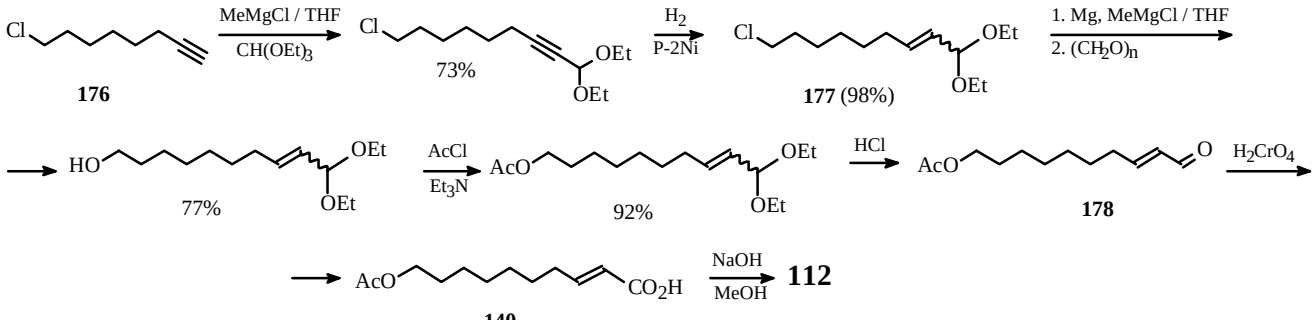

Scheme 61.

Another method for preparing 10-HDA is also based on carboxylation [65, 66]. Iotsich reagent from protected $\omega$-alkynol **175**, which is available through simple transformations of pimelic acid (**174**), was used as the organometallic compound. The final step involved (E)-stereoselective reduction of acetylenic precursor **169** (Scheme 62).



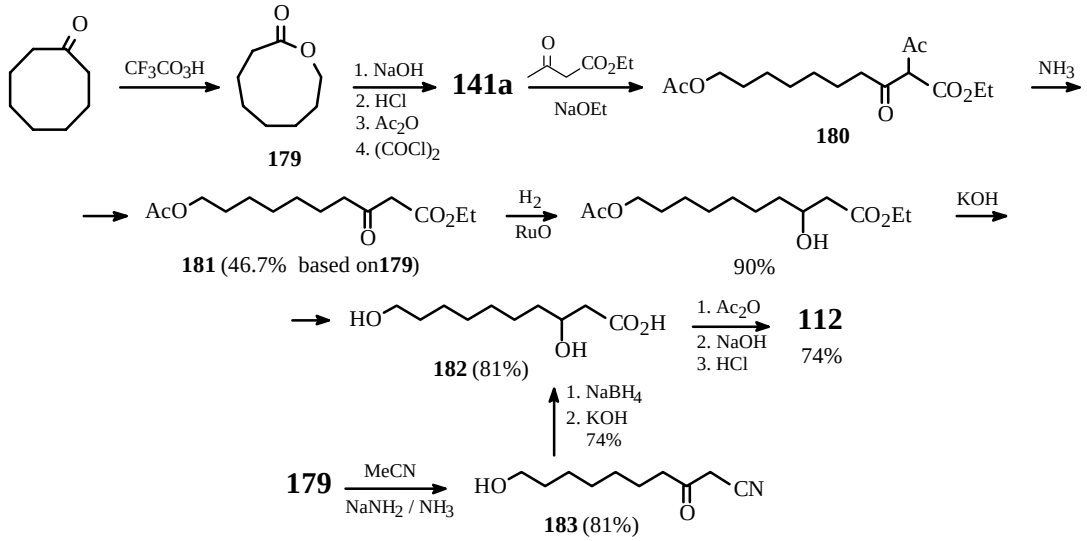

Scheme 62.

The carbon skeleton of **112** was also constructed by successive extension of starting $\omega$-chlorooctyne **176** (initially through Iotsich reagent) by triethylorthoformate and then (using the Grignard reagent from the partially reduced condensation product **177**) by paraformaldehyde. Further selective transformations, including formation of intermediate (E)-$\alpha,\beta$-unsaturated aldehyde **178**, gave the desired hydroxyacid [67] (Scheme 63).




Scheme 63.

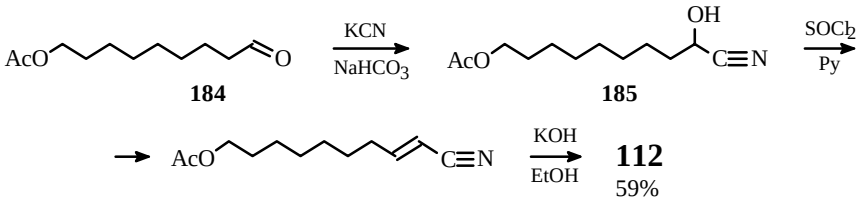
Dehydration of $\alpha$- and $\beta$-hydroxyacids and their derivatives is sometimes used to introduce the $\alpha,\beta$-unsaturated carboxylic acid into **112**. For example, selective dehydration of 3,10-dihydroxydecanoic acid (**182**) was effected using acetic anhydride [68]. Also, two approaches based on transformations of octanolide **179**, which can be prepared from cyclooctanone by a Bayer—Villager reaction, were proposed for preparing of $\beta$-hydroxyacid **182**. One of these converted **179** by unique transformations into the acid chloride of 8-acetoxyoctanoic acid (**141a**), condensation of which with sodium acetoacetic ester and subsequent ammonolysis of the resulting diketoester **180** gave the $\beta$-oxoester **181**, which was reduced and saponified to the key acid **182** (Scheme 64).




Scheme 64.

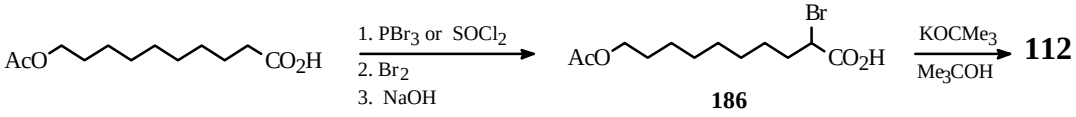
An alternate approach to the synthesis of **182** includes condensation of lactone **179** with sodium acetonitrile, reduction of the oxo group in the intermediate **183**, and subsequent saponification (Scheme 64).

The double bond can be introduced in the synthesis of 10-HDA by dehydration with thionylchloride of an $\alpha$-hydroxynitrile (**185**), prepared by condensation of 9-acetoxynonanal (**184**) with potassium cyanide [69] (Scheme 65).



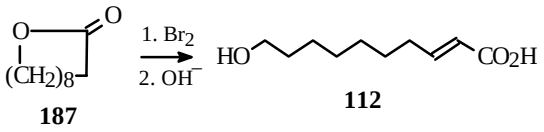

Scheme 65.

In addition to dehydration to introduce the (E)-double bond, 1,2-elimination of α-bromoacids (for example, treatment of 10-acetoxy-2-bromodecanoic acid **186** with potassium *t*-butoxide) has been used. The acids were prepared by regioselective bromination of acid halides of the corresponding carboxylic acids [70, 71] (Scheme 66).



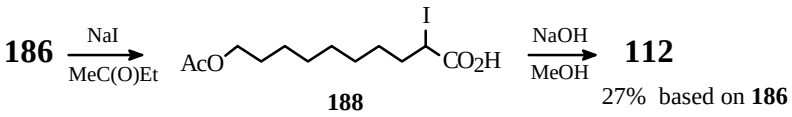

Scheme 66.

$\alpha$-Bromination of decanolide **187** with subsequent treatment with base also gave **112** [72] (Scheme 67).



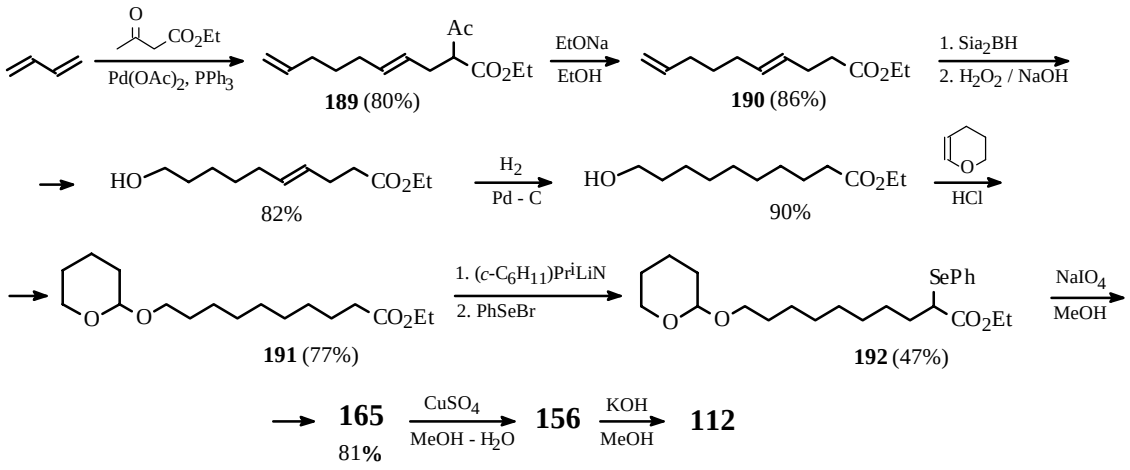

Scheme 67.

Dehyhdroiodination of 10-acetoxy-2-iododecanoic acid (**188**), obtained by transhalogenation of the corresponding bromide **186**, has been used [54]. This enabled the elimination conditions to be milder (Scheme 68).



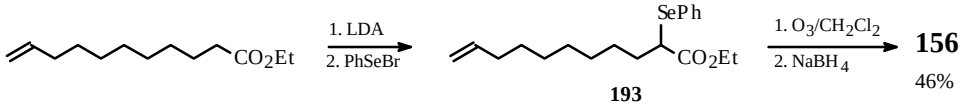

Scheme 68.

*syn*-Elimination of selenoxides has been used for stereoselective introduction of the (E)-double bond into 10-HDA. This process occurs under very mild conditions whereas oxidation of a selenide, for example **192**, usually leads directly to the elimination product **165**. Precursor **191** of the key compound **192** was synthesized from the product of catalytic telomerization of butadiene and acetoacetic ester, i.e., diene ketoester **189**, by selective deacetylation and anti-Markovnikov hydrogenation of intermediate **190** through an organoboron intermediate [73] (Scheme 69).



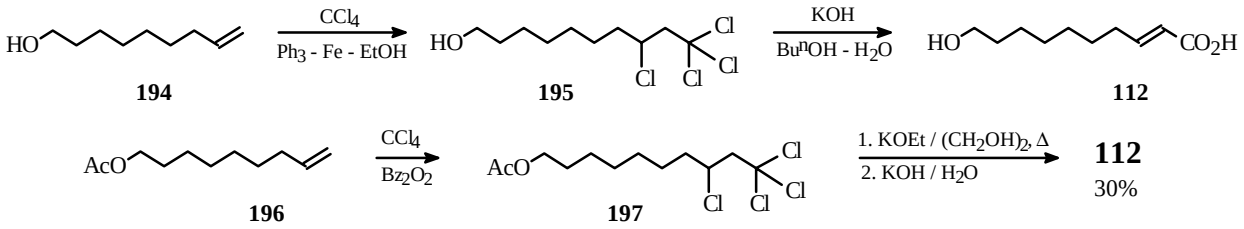

Scheme 69.

Another proposed synthesis [74] is interesting because ozonolysis of the double bond involves simultaneous oxidation of the selenide **193** to form 2E-unsaturated hydroxyester **156** (Scheme 70).



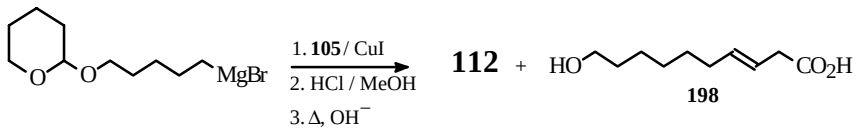

Scheme 70.

Saponification of 1,1,1,3-tetrachloroalkyl derivatives **195** and **197**, products of radical addition of $CCl_4$ to 8-nonenol **194** and its corresponding acetate **196**, was convenient for introducing the $\alpha,\beta$-unsaturated carboxylic acid into **112** [75, 76] (Scheme 71).




Scheme 71.

Finally, reaction of $\beta$-vinyl-$\beta$-propiolactone **105** with 5-(2-tetrahydropyranyloxy)pentylmagnesium bromide catalyzed by CuI gave a mixture (2:3) of 10-HDA and isomer **198** after deprotection and heating in the presence of base [42] (Scheme 72).




Scheme 72.

Thus, the literature review clearly shows that the syntheses of highly biologically active 9-oxo- and 10-hydroxy-2E-decenoic acids are definitely interesting.

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