NEW SYNTHETIC PROCEDURES FOR THE PREPARATION OF NATURAL PRODUCTS (PHEROMONES) AND THEIR INTERMEDIATES

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TO THE WOUNDERFUL WIFE FATIN AND LOVELY CHILDREN
MUSTAFA AND MUHEMIN

ACKNOWLEDGEMENTS

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The author is very grateful to his wife Fatin, and his children Mustafa and Muhemin, for their patience and for their morality.

CONTENTS

page

EXPERIMENTAL

PROLOGUE

This thesis is concerned with four topics, first reactions without solvent, second, investigation of the side product from Wittig reaction, third, one step synthesis of unsaturated aliphatic nitriles and nitrile esters from the corresponding alcohols, fourth, synthesis of one of the pheromone component of American white moth (Hyphantria cunea). The thesis is divided into three main sections, in the first main section, the introduction and background material are presented on four topics relevant to the research work described in later section: reactions without solvent, benzylation and acylation of diols, formation of esters, formation of 1-chloroacetylenes; Wittig reaction ; modification of Mitsunobu-Wilk procedure for synthesis of unsaturated nitriles; and a novel synthetic procedure of (3**Z**,6**Z**)-epoxyheneicosadiene. In the second main section , the discussion , the results are described and analysed. Finally details of the experimental work are given in the experimental section.

INTRODUCTION

1. REACTIONS WITHOUT SOLVENT

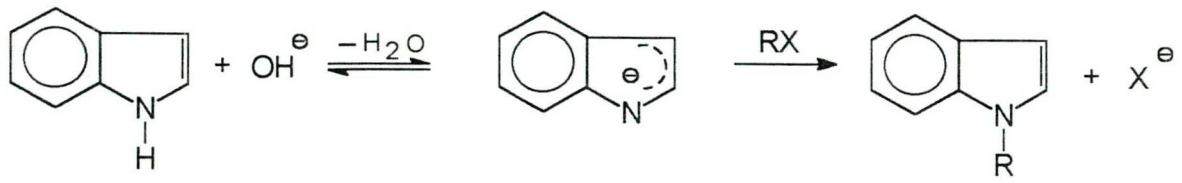
Phase transfer catalyzed (PTC) reactions in absence of organic solvent are very useful in the synthesis of organic molecules. Generally, they afford high yield under mild condition. Some cases, in presence of solvent a chemical reaction proceeds with low yield, requiring long reaction time, and side products are formed.

There are different ways in which the solvent can directly effect the course of a chemical reaction. Many solvents possess nucleophilic properties themselves and are thus able to attack the substrate directly. For example, in the uncatalyzed reaction of 1-fluoro-2,4-dinitrobenzene with thiocyanate ion in methanol the formation of 2,4-dinitroanisole is the major reaction [1].

An alternative type of solvolysis involves direct interaction of the nucleophile with solvent to form a new reagent [2].

Many different works have been performed with successful application of PTC condition, including alkylation, esterification, saponification, elimination, and S_NAr reactions.

Chemical reaction under PTC condition, in presence of a small amount of catalyst and in absence of solvent was declared efficient, economic, and easy to handle. The following review illustrates the behaviour of a chemical reaction under phase transfer condition. J.BARRY [3,4] and his coworkers had shown that the alkylation of acetate and indol anions could be achevied in high yield and short reaction time, under PTC condition with catalytic amount of $Bu_4N^{\oplus}Br^{\ominus}$ and TiO_2. The latter was used for anionic activation of $CH_3COO^{\ominus}$ and n-OctBr. Aliquat 336 was examined in this reaction, obtaining good yield and less expensive procedure, (Scheme 1).



(Scheme 1)

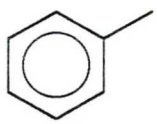
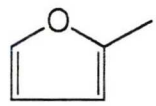
The estrification of potassium acetate by alkyl bromide was examined under PTC condition and high yield was obtained in the presence of $Bu_4N^+Br^-$ or Aliquat 336, under mild condition [5], (Scheme 2).

$$CH_3COOK + nOct\text{-}Br \xrightarrow{1\%\ Bu_4N\ Br} CH_3COOnOct + KBr$$

(Scheme 2)

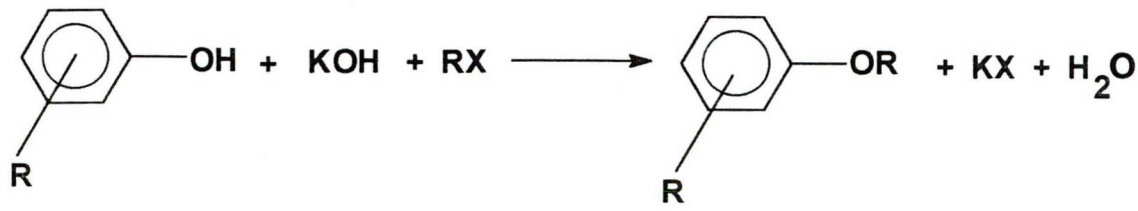
Under the same condition successful synthesis of aromatic carboxylic esters [6] were achieved with good yield by alkylation of potassium carboxylate. This work examined different potassium arenecarboxylate, (Scheme 3).

$$R^1\text{-}COOK + R\text{-}X \xrightarrow{PTC} R^1COOR + KX$$

R^1=  , 

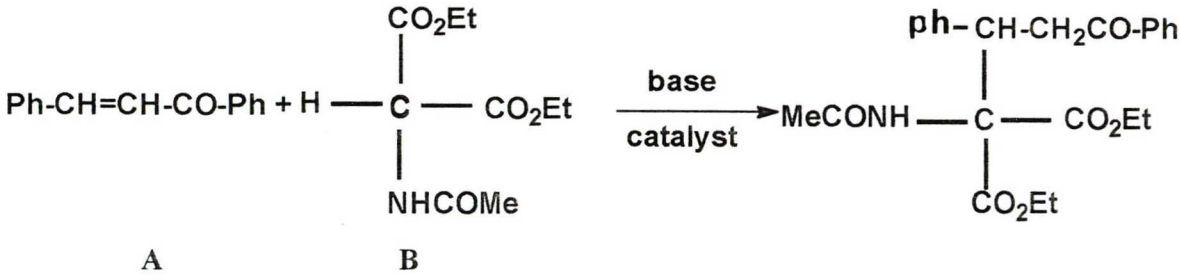
(Scheme 3)

Excellent yield of arylether compounds [7] were obtained, under PTC condition, from the reaction of phenol and alkyl bromide, (Scheme 4).



(Scheme 4)

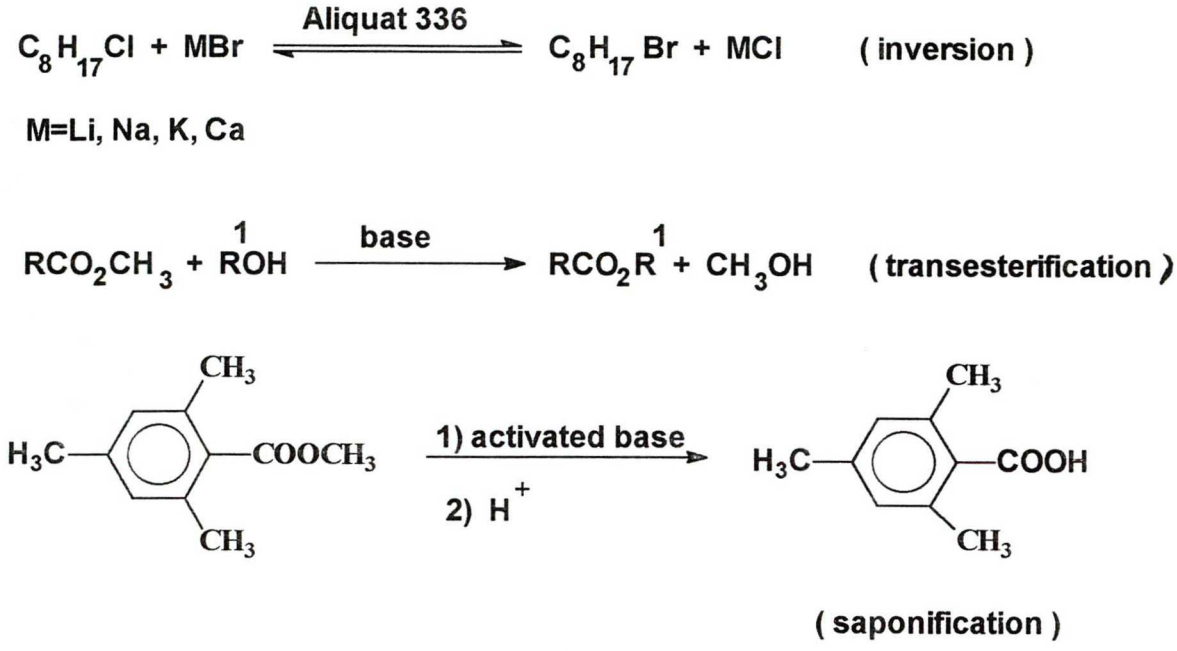
In a heterogeneous solid-liquid PTC condition, in absence of solvent, and in presence of chiral ammonium salt as a catalyst, a successful application was achieved in attempt to increase the enantiomeric excess in asymmetric Michael addition of Chalcone **A** with acetylaminomalonate **B**. It was declared that the reaction in absence of solvent could lead to the increase of system regidity, which resulted a decrease of the molecular motion and enchanced the selectivity of the reaction [8]. (Scheme 5).



A B

(Scheme 5)

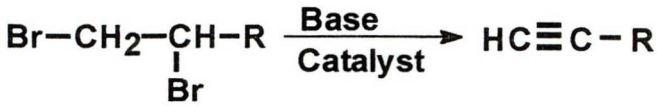
André Loupy [9] and his group have improved the yield of organic reactions, especially those involved anionic activation under PTC condition. Their observation were extended to the conversion of alkyl chloride into alkyl bromide with the inversion of configuration, transesterification, saponification, and high yield synthesis of dibenzylsulphones in one pot reaction [10](Scheme 6).



(Scheme 6)

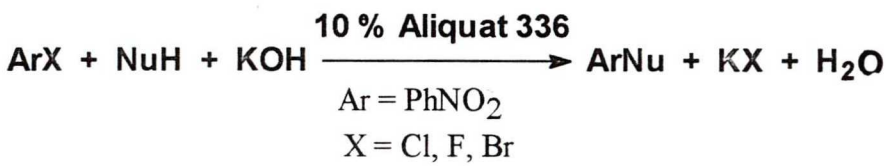
This procedure was elaborated to a new efficient and economic method for alkylation.

A successful procedure was also applied for the preparation of terminal acetylinic compound from 1,2-dibromoalkanes by elimination, under PTC condition. The reaction was performed with high yield, short time and avoided migration of C-C triple bond [11], (Scheme 7).



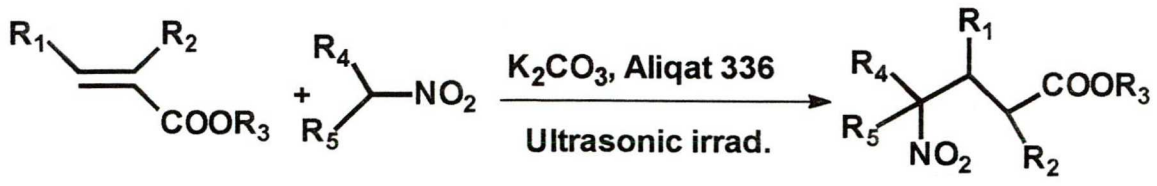
(Scheme 7)

Recently a new S_NAr reaction was also examined, in absence of solvent, for non activated aromatic systems. It has been shown that the reactions proceed with high yield, under mild condition and in the presence of tricaprylylmethylammonium chloride (Aliquat 336) or tris[2-(2-methoxyethoxy)-ethyl]amine (TDA-1 catalyst) [12], (Scheme 8).



(Scheme 8)

Another work has been done by B. Jouglet and his coworkers [13], concerning the Micheal addition reaction of nitroalkanes with monosubstituted α,ß-unsaturated esters. These reactions were catalyzed by K_2CO_3 in presence of Aliquat 336 and under ultrasonic irradiation, using unexpensive base, (Scheme 9).



R_1, R_3, R_5 =Me

R_2, R_4 = H

(Scheme 9)

In general, reaction without solvent is applied when one of the reagents is liquid playing the role of solvent, and there are significant difference between the starting material and the product either in physical state or solubility. Furthermore, it is advantageous if the product can be distilled off from the reaction mixture.

The advantages of the above procedure can be summarised as follows: The yield is better because of the more polar medium. This effect can be noticed in the esterification of salts of carboxylic acids with alkyl halides.

This application is useful in the synthesis of small molecules, when the removal of solvent is difficult.

The process takes shorter time with less byproduct. Higher conversion can be achieved when the product can continuously be removed from the reaction mixture by distilliation. Without solvent the reaction rate can be enhanced by using phase transfer catalysts, these catalysts can be devided according to their physical state into,

- Liquid, (Aliquat 336, methyltrialkylammonium chloride (Adogen 464)
- Solid (Tetrabutylammonium hydrogen sulfate).

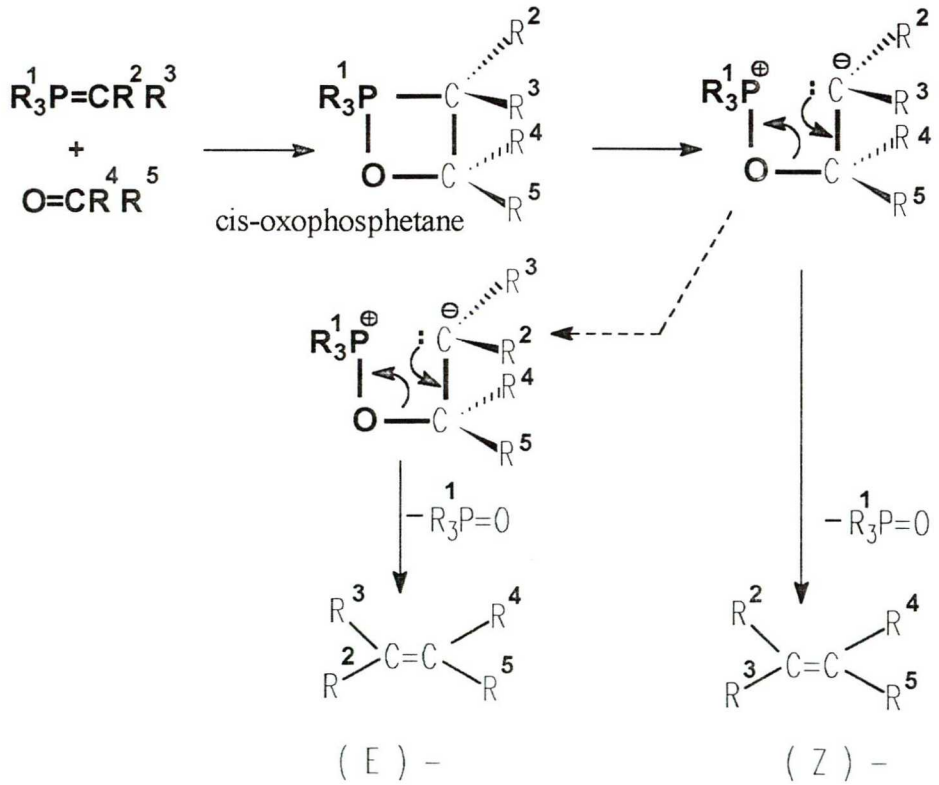
The liquid catalyst has a good solubility in the reagent, enhancing its effectivity. The reaction occurs in the liquid phase, but the removal is difficult during workup, and in case of distilliation some contamination of product occurs from the decomposition of quaterner amines to tertier ones upon heating. Solid catalysts form practically separate phases and the reaction occurs on the borderline of the solid and liquid phases. Catalysts of this type can be removed easily during workup, with either filtration or aqueous dissolution. In the latter case disadvantage is the lower rate of reaction, as a consequence of the processes on the borderline of the phases.

2. UNEXPECTED SIDE REACTION OF WITTIG COUPLING

The Wittig reaction of carbonyl compounds with nonstabilized alkylidenetriphenyl phosphoranes is an excellent and frequently used method in the synthesis of many organic compounds, a wide variety of sex pheromone components contained carbon- carbon double bond were synthesized by this method.

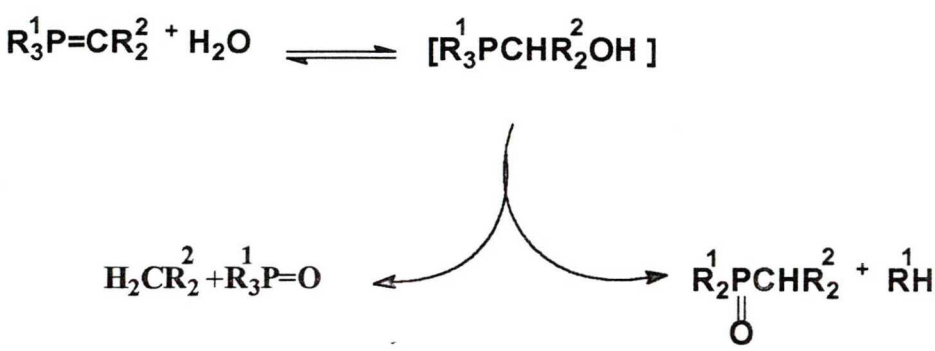
The Wittig method of olefin synthesis was extended to include many different carbonyl compounds, and great number of example can be found in the literature since the initial paper by **Wittig** and **Schollkopf** [14] in **1954**.

The carbon-carbon double bond is formed by the reaction of phosphorane with carbonyl group , the ylide has been generated by reaction of phosphonium salt with base. The general mechanism of Wittig reaction [15] is illustrated in Scheme(10).



(Scheme 10)

Electron withdrawing group on carbon atom and electron donating group on phosphorous atom, decrease the reactivity of ylide. The non stabilized ylide is very reactive and has high nucleophilicity, and it is very sensitive to water, oxygen, carbon dioxide, and alcohol. Reaction of phosphonium ylide with water produce a hydrocarbon fragment and a phosphine oxide (Scheme 11).

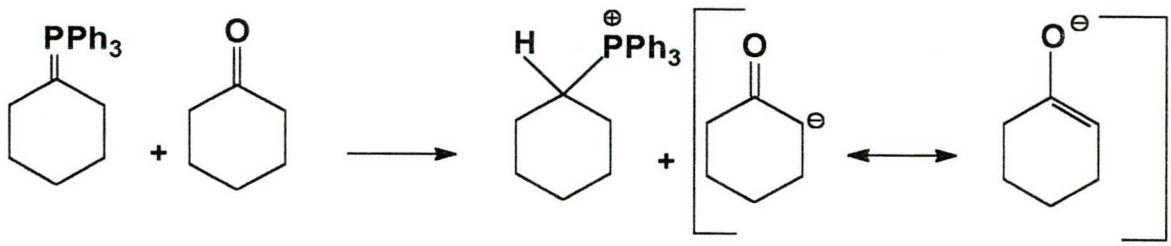


(Scheme 11)

Different reactions have been achieved in related to different molecules, but only little work has been found in the literature which concerned with the reaction of isopropylidene phosphorane with carbonyl group. For example, reaction of 3β-acetoxy-5-cholenaldehyde with isopropylidene triphenylphosphorane afforded olefin product [16].

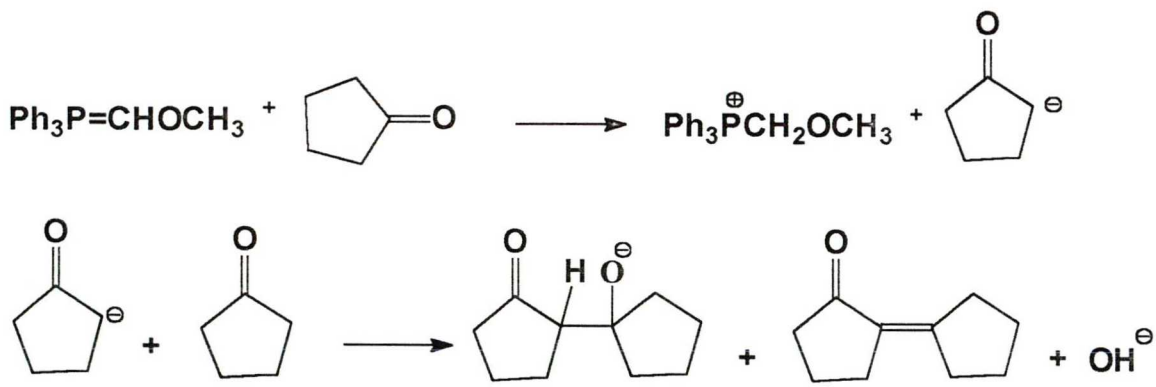
Another work was achieved by Wittig related to the reaction of isopropylidene unit with ketene [17]. Reaction of the sterically hindered tetraenedialdehyde with isopropylidene triphenylphosphorane was achieved by **Johnson.** [18] By contrast, no work was found about the reaction of isopropylidene unit with ketone.

The Wittig reaction affords side reactions, but it occures only rarely and under suitable conditions. The alkylidene phosphoranes can remove a proton from the α-position of carbonyl compound to form enol product. One of the enol products[19] is produced in the reaction between sterically hindered cyclohexanone and the cyclohexylidene ylide ,(Scheme 12).



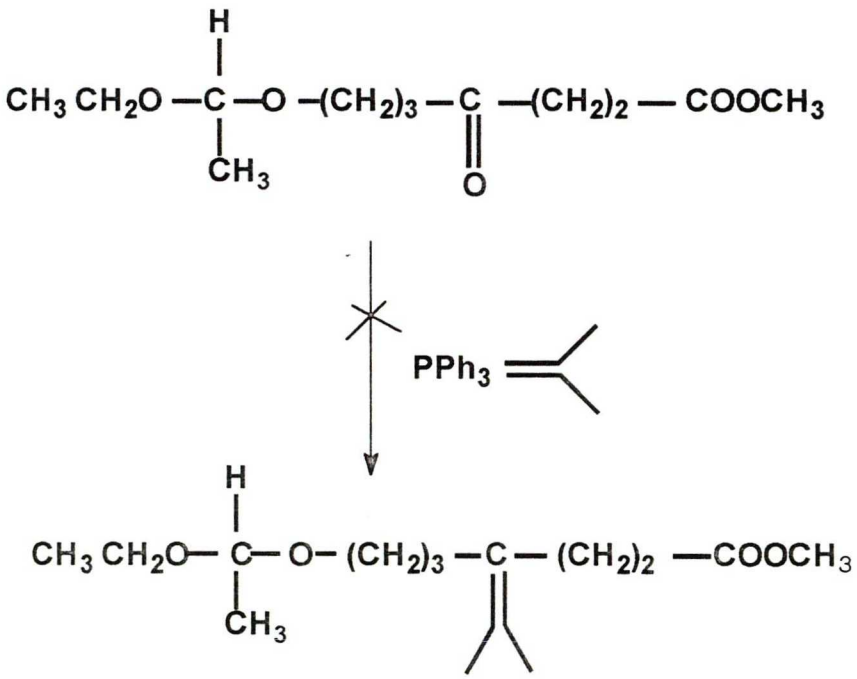
(Scheme 12)

Another aldol reaction was observed when methoxy methylene triphenylphosphor--ane was reacted with cyclopentanone [19], and 2-cyclopentylidenecyclopentanone was formed (Scheme 13).

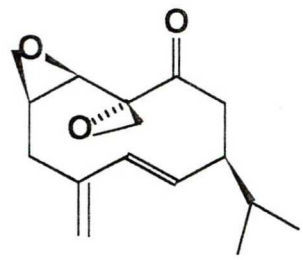


(Scheme 13)

Our work is concerned with the introduction of isopropylidene unit into carbon chain, (Scheme 14), by Wittig coupling which is used as an intermediate , in plan to prepare Periplanone B, the sex pheromone of American Cockroach.(Scheme 15).
The reaction was achieved under different conditions, but no olefinic product was observed, and the starting material was recovered. Similar result was obtained upon using isobutylidene unit. Both of them had methyl group in α-position.

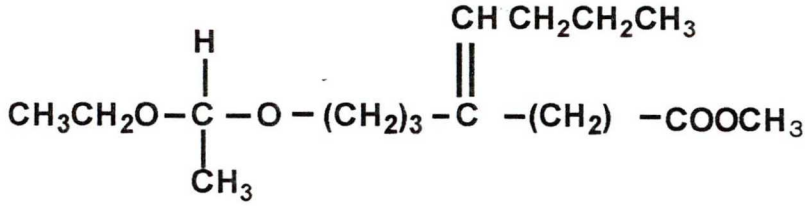


(Scheme 14)



(Scheme 15)

By contrast, another phosphorane having butylidene unit was examined with keto ester and olefin product was isolated,(Scheme 16)



(Scheme 16)

For understanding the failure of reaction of isopropylidene unit with ketoester ,we investigated the reaction of isopropylidene phosphorane with different aldehydes and ketones.The unusual results for the ketones are interpreted and the side products were identified .

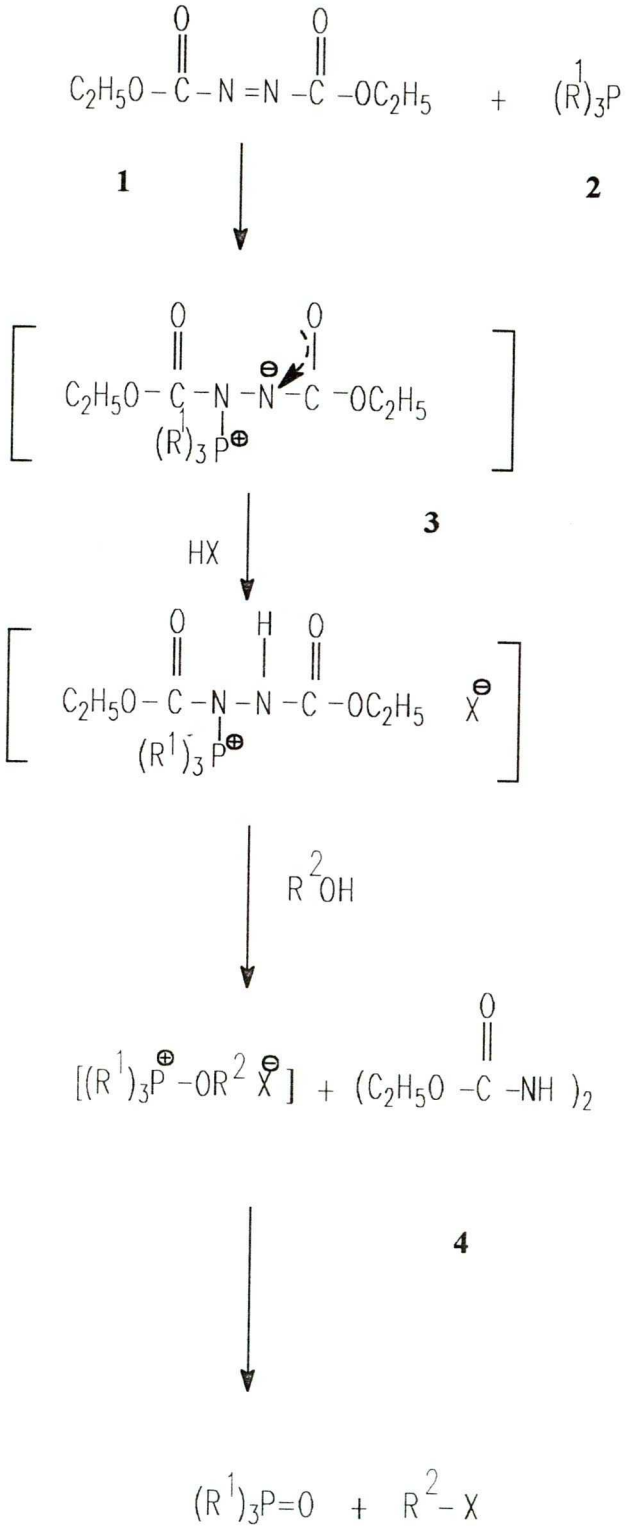
3. PREPARATION OF UNSATURATED NITRILES FROM THE CORRESPONDING ALCOHOLS.

The conversion of saturated and unsaturated alcohols into the corresponding nitriles is an important method for elongation of the chain by one carbon [20] .The resulting nitriles are useful synthetic intermediates for the synthesis of biologically active compounds[21] (e.g. sex pheromones). The nitrile is used to obtain the homologous carboxylic acid by hydrolysis of nitrile, as well as the homologous amine or aldehyde by reduction.

There are many classical methods for the conversion of alcohols to nitriles via intermediates, and they usually end with nucleophilic displacement by sodium cyanide. [22,23] These reactions are often accompanied by undesirable side reactions, and using toxic cyanide reagent. As well as the application of these methods were unsuccessful for some alcohols containing olefinic and acetylenic functional groups.

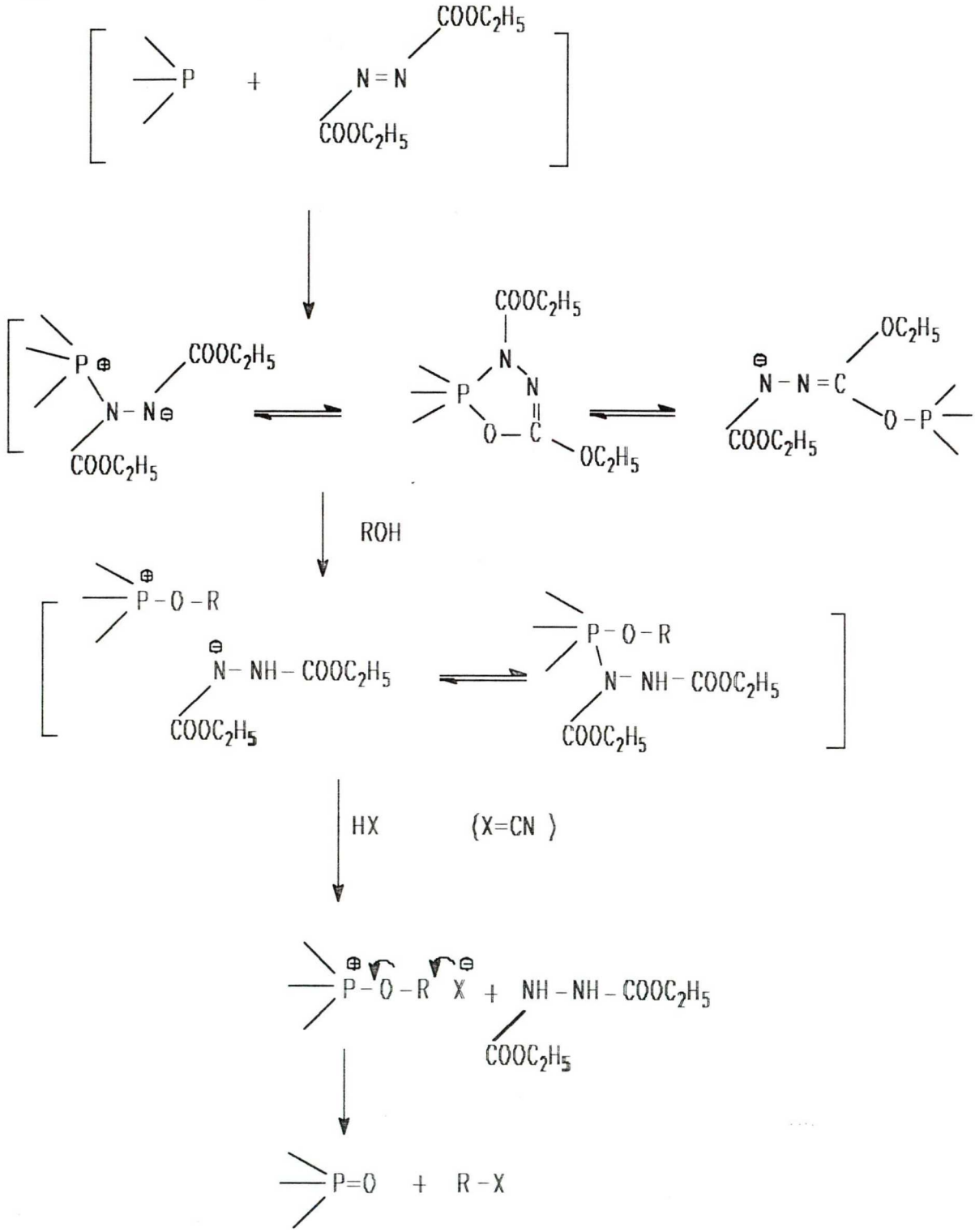
Transformation of the hydroxy group in alcohols to a variety of functional groups, was achieved by Mitsunobu[24], using triphenylphosphine **2** and diethyl azodicarboxylate **1** (DEAD) as a redox system, in which triphenylphosphine was oxidized to triphenylphosphine oxide and diethylazodicarboxylate was reduced to diethyl hydrazine dicarboxylate.(Scheme 17)

The reaction was proposed to proceed through (a) addition of **2** ($R^1=C_6H_5$) to **1** giving a quaternary phosphonium salt **3**,(b) protonation of **3**,(c) formation of an alkoxyphosphonium salt **4**,and (d) SN_2 type displacement of species **4** (Scheme 17).The reaction proceeds by intermolecular dehydration between alcohols and acidic components in the presence of DEAD and PPh_3. It was performed under mild ,neutral conditions and the result depended on the nature of nucleophilic part of the acidic component and on the structure of alcohol.



(Scheme 17)

Under the Mitsunobu condition 3β-cholestanol has been converted in 25% yield to α-cyanocholestane in the presence of HCN/PPh_3 and DEAD. A reaction mechanism was suggested by Loibner [25](Scheme 18).



{ Scheme 18 }

Another reaction was achieved by replacing HCN by LiCN, in converting oleyl alcohol to the corresponding nitrile [26].

Recently,Wilk [27] made the method more convenient by replacing HCN with acetone cyanohydrin, which acted as acidic component and source of cyanide ion. Acetone cyanohydrin is more safe than gaseous hydrogen cyanide, less toxic than alkali cyanides, and easier to handle.

However our attempts for the conversion of (**Z,Z**)-2,5-octadien-1-ol (entry 1; Table 28, page 49) to the corresponding nitrile according to the Mitsunobu-Wilk procedure, adding subsequently DEAD and acetone cyanohydrin to a solution of PPh_3 and alcohol, were unsuccessful. Here no reaction was observed and most of the starting material was recovered.

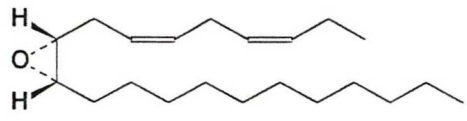
The direct transformation of acetylenic alcohol into the corresponding nitriles had been achieved by Camps and Guerrero [23] using sodium cyanide in the presence of trifluoroacetic anhydride. However, no successful work had been published for the conversion of alcohols carrying acetylenic function in β-position with respect to the corresponding acetylenenitrile.

Our attempts for cyanization of 2-dodecyne-1-ol (entry 1; Table 29, page 49) using the above procedure were unsuccessful.With the Wilk's method using acetone cyanohydrin and diethyl azodicarboxylate (DEAD) we isolated the 3-tridecynenitrile only in 20% yield. We therefore studied the transformation of unsaturated alcohols carrying conjugated or unconjugated olefinic and acetylenic functions in β-position to the corresponding nitriles, and wish to report the successful preparation of unsaturated nitriles.

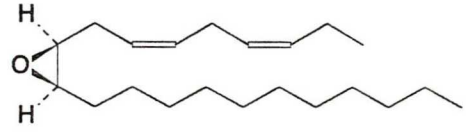
4. SYNTHESIS OF ONE OF THE PHEROMONE COMPONENTS OF HYPHANTRIA CUNEA, (3Z,6Z)-9,10-EPOXY-3,6-HENEICOSADIENE.

The fall webworm moth, Hyphantria cunea (Drury) known as the American white moth in the U.S.S.R., has been found feeding on over 100 species of deciduous trees, and it forms communal webs or tents on its hosts. In the U.S.S.R. H. cunea is an important pest of mulberry, which is used to feed the larvae of the domesticated silk moth, Bombyx mori, used to produce silk for cloth. Therefore in 1968 at Kishinev, Republic of Moldavia, studies were started to identify the sex pheromone of H. cunea and using it in control program.

The diene epoxide (3**Z**,6**Z**)-cis-(9,10)-epoxy-3,6-heneicosadiene (**5**;Scheme 19) had been isolated and identified by Hill and Roelofs in 1981, as one of the three components of the sex pheromone blend emitted by females of the salt marsh caterpillar moth Estigmene acrea Drury[28] (Scheme 19)



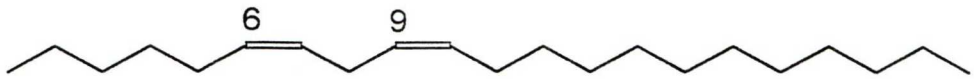
(9R,10S)-5



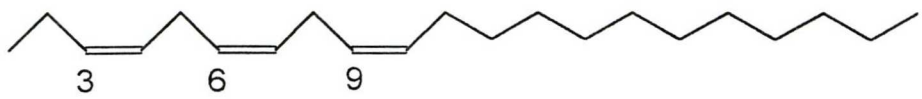
(9S,10R) -5

(Scheme 19)

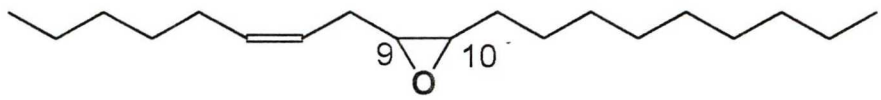
Descoins[29] , had reported that the diene epoxide (**5**; Scheme 20) was a compound of wide distribution among Arctiicae moth, and was one of the four compounds identified as a component of the sex pheromone emitted by females of the ruby tiger moth, phragmatobia fuliginosa (L). These were (6Z, 9**Z**)-heneicosadiene (**6**), (3**Z**, 6Z, 9**Z**)-heneicosatriene (**7**), (6**Z**)-cis-9,10-epoxyheneicosene (**8**), (3**Z**,6**Z**)-cis-9,10-epoxyheneicosadiene (**5**), (Scheme 20). Compound **7** and **5** were found in 15:85 ratio in female abdominal lip extract.



(6)



(7)



(8)

(5)

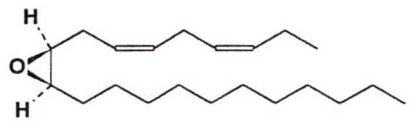
(Scheme 20)

Diene epoxide (**5**;Scheme 21) was also identified as a sex pheromone component of the fall webworm [30] (Hyphantria cunea) which was notorious pest known as Amereika-shirohitori in Japan or the American white moth in Hungary and U.S.S.R. .

Three pheromone components of the femal moth were identified ; (3**Z**, 6**Z**)-(9S,10R)-epoxy-3, 6-heneicosadiene (**5**), (9**Z**,12**Z**)-9,12-octadecadienal (**9**), and (9**Z**,12**Z**,15**Z**)-9,12,15-octadecatrienal (**10**) [31,32] (Scheme 21). A blend of **5**, **9**, and **10**, was shown inactive test against H.cunea in the U.S.S.R and in Japan.

Other two additional epoxides from the sex pheromone secretion of H. cunea ,were identified by Arn [33] and coworkers. These are (3**Z**, 6**Z**)-cis-9,10-epoxy-1, 3, 6-heneicosatriene (**11**) and (3**Z**,6**Z**)-cis-9,10-epoxy-1, 3, 6-icosatriene (**12**), (Scheme 21). These compounds were synthesized by K. Mori and T. Takeuchi.

It have been clarified that (9S,10R)-**11** and (9S,10R)-**12** are the essential components of the sex pheromone blend of H. cunea, but indeed a mixture of **5**, **9**, **10**, **11**, and **12** was attracted male H. cunea into traps both in Hungary and in Japan.[33]



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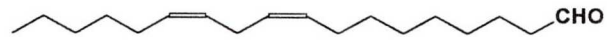

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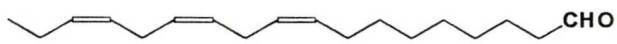

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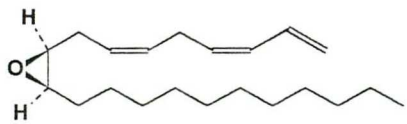
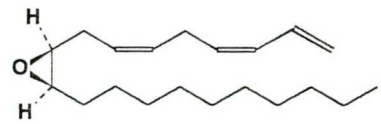


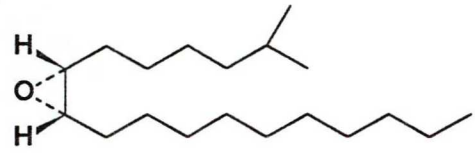
(9S,10R)-11



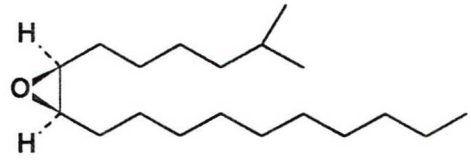
(9S,10R)-12

(Scheme 21)

The stereochemistry of the diene epoxide (**11**; Scheme 21) of Estigmene acrea was suggested first by Roelofs and his coworkers [28] as (9S,10R). This suggestion was based on the examination of an antenna of E.acrea by electroantennograph (E.A.G.). A stronger signal was registered with (7S, 8R)- (-)-disparlure (**14**), the sex attractant emitted by the femal gypsy moth (porthetria-disparl), while with (7R,8S)-(+)-disparlure (**13**)[28], a weaker signal was obtained, (Scheme 22).



(7R,8S)-(+)-13

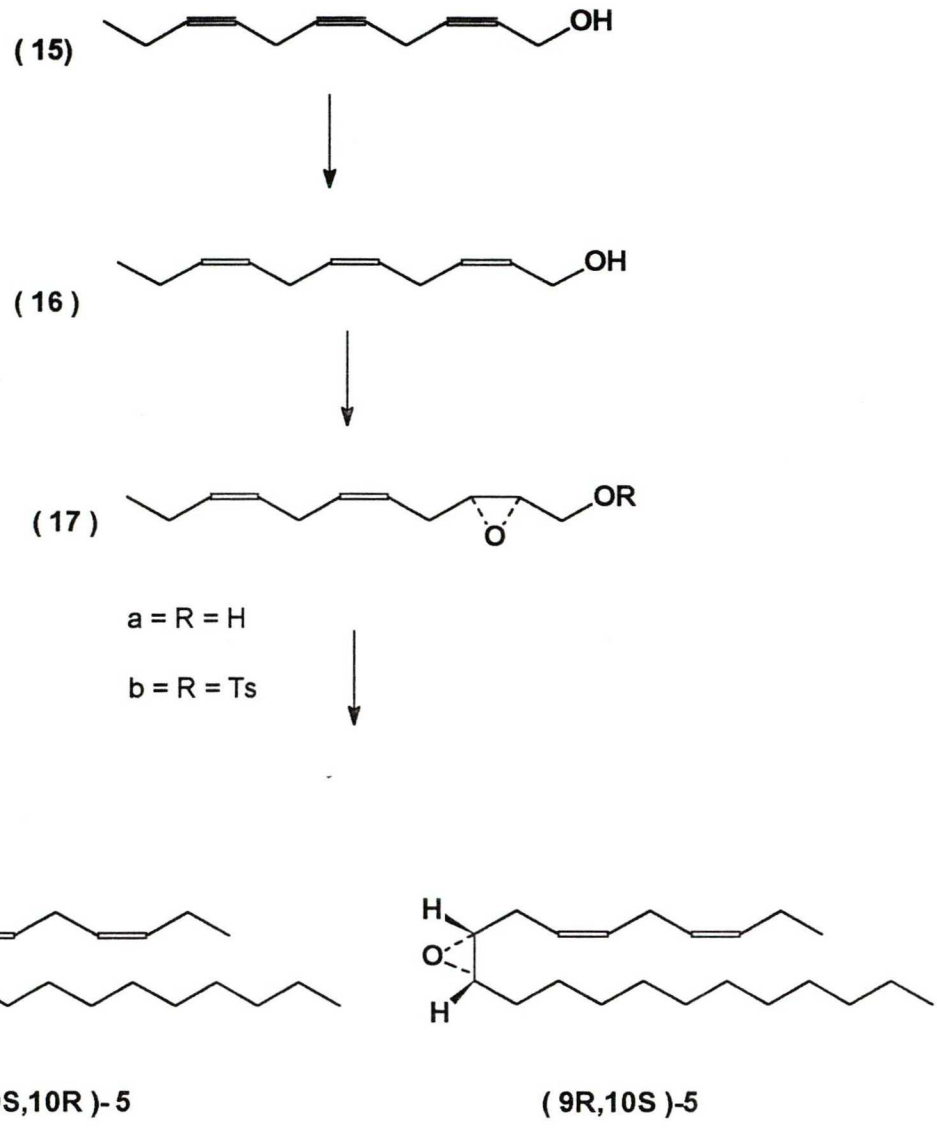


(7S,8R)-(-)-14

(Scheme 22)

Therefore the EAG analysis for both of the synthetic enantiomers of diene epoxide (5; Scheme 19) showed that the (9S,10R) isomer elicits a male antenna response 2-3 times greater than the (9R,10S) isomer with Hyphantria and with Estigime acrea [34].

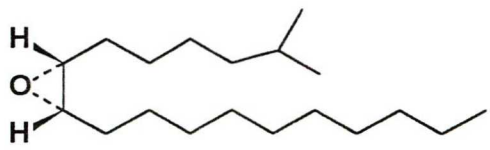
Synthesis of both (9S,10R)-**5** and (9R,10S)-**5** (Scheme 23) was achieved by K.Mori and T. Ebata [34] , using a triynal (**15**; Scheme 23) as an intermediate for the preparation of epoxide intermediate (**17**; Scheme 23), and applying the Sharpless asymmetric epoxidation [35], which dramatically facilitated the synthesis of optically active epoxides. Then an epoxy tosylate (**17b**; Scheme 23) was coupled with lithium dialkylcuprate.



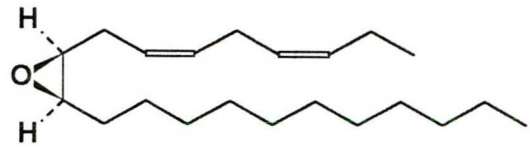
(Scheme 23)

Another work was achieved by K. Mori and T. Ebata [36], concerning with the synthesis of both the enantiomers of (3**Z**, 6**Z**)-cis-9,10-epoxy-3,6-heneicosadiene. The work based on the synthesis of (+)-disparlure (**18**; Scheme 24) was used as a model compound for the synthesis of both enantiomers (**5**; Scheme 24).

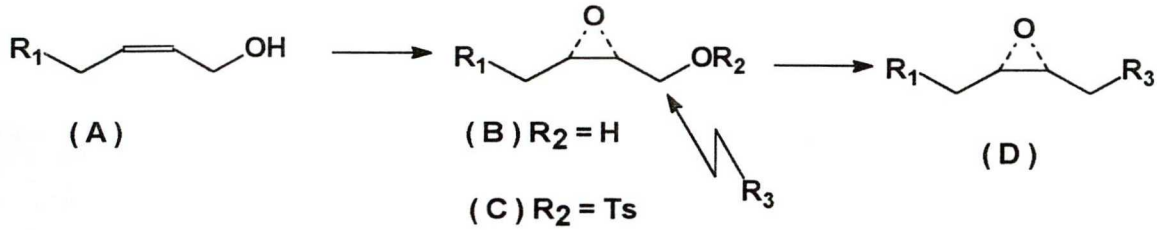
Both compounds **18** and **5** (Scheme 24), were synthesized via key intermediate, the product of the Sharpless asymmetric epoxidation (A-B; Scheme 24), and also based on the selective reaction of the tosylate group of (C) with an alkyl group to give (D) Here unexpected low optical yield by the Sharpless epoxidation was obtained.



(18)



(5)



(A) (B) R_2 = H (C) R_2 = Ts (D)

(Scheme 24)

Synthesis of racemic **5**(Scheme 24) was achieved by Kovalev [37] .The (9S,10R)-**5** (Scheme **24**),was found inactive when tested against fall webworm moth under the field condition. This was the result of the low optical purity of (9S,10R)-**5**. Therefore optically pure **5** was prepared with new synthetic procedure, by using the first chiral synthesis of both enantiomers [36] **5**. The natural pheromone was identified as (3**Z**,6**Z**)-(9S,10R)-epoxy-heneicosadiene **5**, which gave larger EAG responses when tested on both the salt marsh catorpillar moth and the fall webworm moth [31] .

RESULTS AND DISCUSSION

1. REACTIONS WITHOUT SOLVENT

Our work is extended to examine four reactions in details concerning with the reaction without solvent under phase transfer catalyst, PTC, condition. The first two reactions were benzylation and acylation of diols, and studying the most effective possible procedure for the preparation of mono derivatives. The third reaction is ester formation from the alkali metal salts of carboxylic acids with alkyl halides, and the fourth reaction is the preparation of 1-chloroalkynes from 1,1-dichloroalkenes.

Benzylation of diols.

Protection of alcohols is a widespread method in the synthesis [37-39] . It is frequently used in carbohydrate chemistry[37]

Symmetrical diols are frequent as starting materials in synthesis of aliphatic molecules. One of the key steps is differentiating the terminal hydroxyl groups by selective protection during the synthesis. Our work is concerning with the benzylation of diols. (Scheme 25).

$HO(CH_2)_6OH$ 1.benzyl chloride (A equiv.) → Products (E, F, G)
2. base (B equiv.)
3. C hr. at D °C temperature of oil bath
4. workup

product: $HO(CH_2)_6OH$ (E)
$HO(CH_2)_6OBn$ (F)
$BnO(CH_2)_6OBn$ (G)

(Scheme 25)

Benzyl chloride is used as a solvent and reagent at the same time in the above process. Powdered potassium hydroxide was used as a base, other bases were also studied; potassium carbonate, triethylamine, and pyridine.

Working up of the reaction mixture was achieved by pouring into cold water and the product was isolated by extraction. First the amount of benzylchloride and selectivity were examined, and the results are summarized in Table (**1**).

Table (**1**): Effect of quantity of benzylchloride on selectivity

$HO(CH_2)_6OH$ 1. benzyl chloride (A equiv.) → Products (E, F, G)

2. KOH (1.0 equiv.)

3. 2 hr. at 100 °C (oil bath)

4. workup.

Entry	A(equiv)	Convers. (%)	Product ratio(F/G)	Yield of monobenzyl ether (F)%
1.	1.0	74	76/24	43
2.	2.0	68	81/19	44
3.	10.0	84	71/29	48

The formation of monobenzyl ether (F) was dominated in the reaction. Increasing the amount of benzylchloride slightly increased the conversion, but it has no effect upon the ratio, and the yield.

The amount of base on the selectivity was examined and the results are presented in Table (**2**).

Table (**2**) Effect of potassium hydroxide quantity on selectivity

$HO(CH_2)_6OH$ 1. benzyl chloride (1.0 equiv.) → Products (E, F, G)

(1.0 equiv.) 2. KOH (B equiv.)

3. 10 min. at 100 °C (oil bath)

4. workup

Entry	B (equiv.)	Conversion (%)	Product ratio (F/G)	Yield of monobenzyl ether(F), %
1.	1.0	93	71/29	41
2.	2.0	92	40/60	35
3.	3.0	80	43/57	27

According to the above results, it can be shown that increasing the amount of base resulted in decreasing yield of the monobenzyl ether, and at the same time the amount of the dibenzyloxy derivative (G) increased.

The relationship between the reaction time and selectivity was examined and the results are presented in Table (**3**).

Table (**3**). Effect of the reaction time on the selectivity

$HO(CH_2)_6OH$ (1.0 equiv.) 1. benzyl chloride (1.0 equiv.) → Products (E, F, G)
2. KOH (1.0 equiv.)
3. C hr. at 100 °C (oil bath)
4. workup

Entry	C (hr.)	Conversion (%)	Product ratio (F/G)	Yield of monobenzyl ether (F), %
1.	0.2	93	71/29	41
2.	2.0	77	68/32	44
3.	5.0	71	76/24	54

Increasing the reaction time resulted a small increase of monobenzyl ether yield. In the next procedure the variation of the oil bath temperature on selectivity was examined, and the results are presented in Table (**4**).

Table (**4**). Effect of the oil bath temperature on the selectivity

$HO(CH_2)_6OH$ (1.0 equiv.) 1. benzyl chloride (A equiv.) → Products (E, F, G)
2. KOH (1.0 equiv.)
3. 2 hr. at D °C (oil bath)
4. workup

Entry	A (equiv.)	D (°C)	Conversion (%)	Product ratio(F/G)	Yield of monobenzyl ether (F), %
1.	1.0	25	28	96/4	2
2.	1.0	50	61	84/16	9
3.	1.0	100	74	76/24	43
4.	2.0	25	49	84/16	2
5.	2.0	50	75	86/14	16
6.	2.0	100	68	81/19	44

The highest yield of monobenzyl ether was achieved at 100 °C (oil bath).

Another examination has been taken in using different bases instead of potassium hydroxide. First pyridine was tested in connection with the effect of benzyl chloride quantity on selectivity. Table (**5**).

Table (**5**). Effect of the benzyl chloride quantity on selectivity

$HO(CH_2)_6OH$ 1. benzylchloride (A equiv.) → Products (E, F, G)
(1.0 equiv.) 2. pyridine (1.0 equiv.)
3. 3 hr. at 100 ^{0}C (oil bath)
4. workup

Entry	A (equiv.)	Conversion (%)	Product ratio (F/G)	Yield of monobenzyl ether (F), %
1.	1.0	14	14/86	5
2.	3.0	27	100/0	10
3.	5.0	63	79/21	49
4.	10.0	76	79/21	58

Comparing to the KOH result, the yield of monobenzyl ether (F) is lower.

An increase of the benzylchloride quantity increased the yield of half ether.(This effect were did not examined during the application of KOH.). The effect of the reaction time on the selectivity in case of pyridine is presented in Table (**6**).

Table (**6**). Effect of the reaction time on the selectivity

HO $(CH_2)_6$ OH 1. benzylchloride(10.0 equiv.) → Products (E, F, G)
(1.0 equiv.) 2. pyridine (1.0 equiv.)
3. C hr. at 100^{o}C (oil bath)
4. workup.

Entry	C (hr.)	Conversion (%)	Product ratio (F/G)	Yield of monobenzyl ether (F), %
1.	0.2	-	-	-
2.	2.0	55	98/2	17
3.	5.0	76	79/21	58

After five hour reflux, the yield and the selectivity was the same as in case of KOH under similar reaction conditions, but here the benzyl chloride was 10 equiv., while in case of KOH it was only 1 equiv. . Reduction of reaction time reduced the yield of monobenzyl ether.The results of application of potassium carbonate and triethylamine are presented in Tables (**7**) and (**8**).

Table (**7**). Application of potassium carbonate as a Base

$HO(CH_2)_6OH$ 1. benzyl chloride (A equiv.) → Products (E, F, G)
(1.0 equiv.) 2. K_2CO_3 (B equiv.)
3. C hr. at D ^{o}C (oil bath)

Entry	A (equiv.)	B (equiv.)	C (hr.)	D (°C)	Product ratio (F/G)	Yield of monobenzyl ether (F),%
1.	10.0	1.0	0.2	100	-	-
2.	10.0	1.0	2.0	100	-	-

Table (**8**). Application of triethylamine as a Base

$HO(CH_2)_6OH$ (1.0 equiv.) 1. benzyl chloride (10.0 equiv.) → Products (E, F, G)
2. Et_3N (B equiv.)
3. C hr. at 100 °C (oil bath)
4. workup

Entry	B equiv.	C hr.	Conversion (%)	Product ratio (F/G)	Yield of monobenzyl ether (F), %
1.	1.0	2.0	61	82/18	37
2.	1.0	5.0	68	60/40	40

Application of Et_3N did not give better results than the other bases. Shorter reaction time reduced the selectivity.

By contrast, the application of solvents, toluene and benzene, were examined, the results are presented in Table (**9**).

Table (**9**). Application of solvents in benzylation

$HO(CH_2)_6OH$ (1.0 equiv.) 1. benzyl chloride (1.0 equiv)/solvent → Products (E, F, G)
2. base (1.0 equiv.)
3. C hr. at D °C (oil bath)
4. workup

Entry	Solvent	C (hr.)	D (°C)	Conversion (%)	Product ratio (F/G)	Yield of monobenzyl ether (F), %
1.[a]	B	5.0	RE	78	99/1	35
2.[a]	B	2.0	RE	83	100/0	10
3.[a]	T	2.0	100	62	98/2	18
4.[a]	T	5.0	100	82	99/1	24
5.[a]	T	5.0	RE	81	95/5	35
6.[b]	T	2.0	100	1	80/20	0.4
7.[b]	T	5.0	RE	3	83/17	2

RE = reflux

a = base, KOH

b = base, pyridine

B = benzene

T = toluene

The ambiguous result of the solvent application during the benzylation, particulary in case of pyridine, was the lower yield of monobenzyl ether. Therefore the procedure without solvent is more useful.

Considering the data of Table (**1-8**). it can be concluded that the highest yield of 6-benzyloxyhexan-1-ol is obtained, when KOH (powder) is used as a base and the reaction mixture is stirred to 20-30 min. at 100 ^{o}C (oil bath). The quantity of benzyl chloride and the base are one equivalent.There is no significant change when the amount of one of the components is increased.

On the bases of obtained results, we have studied the possibility of the production of other ω -benzyloxy-alcohols. Two methods have been tested in all cases (Scheme 26), and the results are summarized in Table (**10**).

Method (A):

$HO(CH_2)_nOH$ (1.0 equiv.) — 1. pyridine (1.0 equiv.) → $HO(CH_2)nOBn$ (F)
2. benzyl chloride (1.0 equiv.)
3. 5 hr. at 100 ^{o}C (oil bath)
4. workup

Method (B):

$HO(CH_2)nOH$ (1.0 equiv.) — 1. benzyl chloride (1.05 equiv.) → $HO(CH_2)nOBn$ (F)
2. powder KOH (1.25 equiv.)
3. 30 min. at 100 ^{o}C (oil bath)
4. workup

(Scheme 26)

Table (**10**). Benzylation of different diols by A and B methods

Entry	NO. of C-atom	Method	Yield of monobenzyl ether (F)%
1.	3	A	30
2.	3	B	50
3.	4	A	20
4.	4	B	60
5.	5	A	20
6.	5	B	40
7.	6	A	35
8.	6	B	45
9.	8	A	15
10	8	B	50

The results indicated that potassium hydroxide is a more suitable base than pyridine in the benzylation of alcohols without solvent. In case of short reaction time the yields are better. While in the case of long chain diols (which are solid), the yields are better, only when the diols are soluble in benzyl chloride.

Acylation of diols.

The acylation of diols is very important step in the preparation of a number of natural products to produce asymmetric compounds.[40] Acid chlorides or anhydride are usually used as acylating agents. The acid derivatives can be formed in a short time with good yield from acid chlorides, but high reactivity of this reagent can cause some side reactions. In the case of using acid anhydride the reaction is easier [41-46] .

Acylation without solvent can only realised by acid anhydrides. Many references can be found in the literature for acylation by acetic anhydride without solvent [41,42,44,45,46] . This acylation can be performed by catalysts, most useful ones are pyridine [41,46], zinc chloride [42,44], sulphuric acid [45], and a mixture of triethylamine and dimethylaminopyridine (DMAP) [46].

Monoacylation of diols was achieved by using mainly acetic acid with concentrated sulphuric acid as a catalyst [47], ethyl acetate with aluminium oxide as a catalyst [48], and by using certain esters with inorganic metal sulphates as a catalyst precepitated on silica gel [49].

During our work we examined the dependence of the acylation selectivity on the reaction conditions, and on the chain lenght of diols, similar to benzylation. The reagent was used as a solvent, and in the presence of a co-reagent, like some bases KOH, Et_3N, pyridine, water, acetic acid, and sodium acetate. The reaction is illustrated in (Scheme 27).

$HO(CH_2)nOH$ (1.0 equiv.) — 1. $(RCO)_2O$ (A equiv.) 2. co-reagent (B. equiv.) 3. C hr. at D °C 4. workup → Products (E, F, G)

Products:		
	$HO(CH_2)n\ OH$	(E)
	$HO(CH_2)n\ O(O)CR$	(F)
	$RC(O)O(CH_2)n\ O(O)CR$	(G)

(Scheme 27)

Mono (F) and diacyl diols (G) were prepared for identification and all the products were analysed by gas chromotography. 1,4-Butanediol (E; n= 4) was acylated by acetic-, and propionic acid anhydride.

First the amount of base used as co-reagent was examined, and has been found that one equivalent of any bases used cause the exclusive formation of diacetates. (G; n=4; R=CH_3-).Using 0.1 equivalent of KOH gave the same result (Table **11**). Using catalytic amounts of co-reagents (0.05 eq.) increase the yields of mono acetates (F).(Table **12**).

Table (**11**). Acylation of butanediol using 1.0 equiv. of base

$HO(CH_2)_4OH$ 1. acetic anhydride (10 ml/g OH) → Products (E, F, G)

(1.0 equiv.) 2. base (1.0 equiv.)

3. 2 hr. at 25 °C)

4. workup

Entry	Base	Conversion (%)	Product ratio (F/G)	Yield of mono acylated product (F), %
1.	KOH	100	0/100	0
2.	Pyridine	100	0/100	0
3.	Et_3N	100	0/100	0
4.	KOH (0.1equiv)	100	0/100	0

Table (**12**). Acylation with using catalytic amount of co-reagents

$HO(CH_2)_4OH$ 1. acetic acid anhydride (10 ml/g OH) → Products (E, F, G)

(1.0 equiv.) 2. co-reagent (0.05 eq.)

3. 3 hr. at 25 °C

4. workup

Entry	Co-reagent	Conversion (%)	Product ratio (F/G) %	Yield of mono acylated product (F), %
1.	Water	54	85/15	40
2.	Acetic acid	58	83/17	45
3.	Pyridine	100	47/53	45
4.	Sodium acetate	85	64/31	55
5.	Potassium hydroxide	85	60/40	50

Increasing the reaction time of acylation resulted 100% conversion, and the product rate was shifted very intensively to the direction of diacyl products (G). It seemed to be obvious, that the undesired decrease of the product ratio, was the result of the excess of the anhydride used. The decrease of the amount of anhydride led to the decrease of the concentration and a similar results like in Table (**13**) were obtained, because anhydride is used as a solvent, and decrease of the amount of solvent will slow down the reaction because of anhydride destruction is decreasing. By contrast, increasing the amount of solvent which means an increase of the amount of anhydride, it is a faster reaction, and we found that the monoacyl derivative of diol is formed easier than the diacyl derivative .

Table (**13**). Effect of reaction time on selectivity

$HO(CH_2)_4OH$ 1. acetic anhydride(10 ml/g OH) ► Products (E, F, G)

(1.0 equiv.) 2. co-reagent (0.05 eq.)

3. C hr. at 25 °C

4. workup

Entry	Co-reagent	Reaction time (hr.)	Conversion (%)	Product ratio (F/G)	Yield of mono acylated product (F), %
1.	Water	3	54	85/15	40
2.	Water	24	100	15/85	13
3.	Acetic acid	3	58	83/17	45
4.	Acetic acid	24	100	15/85	12

Increasing the temperature of reaction also improved the conversion, but the product ratio was shifted in direction of the undesired diacylated derivative (G). The same result was produced at 25 °C and 100 °C. Here, equivalent amount of anhydride was used, and the reaction was performed with liquid diols. The heat evolved in the reaction can cause a significant changes in the product ratio. Table (**14**)

Table (**14**). Effect of temperature on selectivity

$HO(CH_2)_4OH$ 1. acetic anhydride (A) ► Products (E, F, G)

(1.0 equiv.) 2. KOH (0.05 eq.)

3. 4 hr. at D °C

4. workup

Entry	Amount of anhydride (A)	Temp.D (°C)	Conversion (%)	Product ratio (F/G)	Yield of mono acylated product (F), %
1.	10 ml/g OH	0	92	53/47	48
2.	10 ml/g OH	25	85	60/40	50
3.	10 ml/g OH	100[a]	100	0/100	0
4.	1.0 equiv.	25	80	66/34	50
5.	1.0 equiv.	100[a]	67	73/27	49

a= oil bath temperature.

Lower amount of anhydride gave moderate conversion Table (**15**). This is compaired with the temperature experiment performed at 100 °C resulting further decrease in yield. At room temperature KOH gave the best result. Table (**14**, entry 2.)

Table (**15**). Effect the amount of acetic anhydride on selectivity

$HO(CH_2)_4OH$ 1. acetic anhydride (A) ► Products (E, F, G)

(1.0 equiv.) 2. co-reagent (0.05 eq.)

3. 4 hr. at 100 °C

4. workup

Entry	Amount of anhydride (A)	Co-reagent	Conversion (%)	Product ratio (F/G)	Yield of mono acylated product (F), (%)
1.	10 ml/g OH	KOH	100	0/100	0
2.	1.0 equiv.	KOH	67	73/27	49
3.	1.0 equiv.	H_2O	76	72/28	53
4.	0.5 equiv.	H_2O	46	89/11	38

Propionic anhydride was examined instead of acetic anhydride and the results are presented in Table (**16 - 20**). The tendencies are parallel to those obtained with acetic anhydride.Duing to lower reactivity of propionic acid anhydride, conversion was reduced.

Table (**16**). Acylation with 1.0 equiv. base

$HO(CH_2)_4OH$ 1.Propionic anhydride (10 ml/ g OH) ► Products (E, F, G)

(1.0 equiv.) 2. base (1.0 equiv.)

3. 2 hr. at 25 °C

4. workup

Entry	Base	Conversion (%)	Product ratio (F/G)	Yield of mono acylated product (F), (%)
1.	KOH	100	0/100	0
2.	Pyridine	94	0/100	0
3.	Et_3N	95	6/94	5

Table (**17**). Acylation with catalytic amount of co-reagent

$HO(CH_2)_4OH$ 1. propionic anhydride (10 ml/g OH) ► Products

(1.0 equiv.) 2. co-reagent (0.05 eq.)

3. 3 hr. 25 °C

4. workup

Entry	Co-reagent	Conversion (%)	Product ratio (F/G)	Yield of mono acyled (F), (%)
1.	KOH	90	60/40	54
2.	Pyridine	90	64/36	55
3.	Et_3N	87	69/31	50

Table (**18**). Effect of reaction time on selectivity

$HO(CH_2)_4OH$ 1. propionic acid anhydride (10 ml/g OH) → Products (E, F, G)

(1.0 equiv.) 2. co-reagent (0.05 eq.)

3. C hr. 25 oC

4. workup

Entry	Co-reagent	Reaction time (hr.)	Conversion	Product ratio (F/G)	Yield of mono acylated product (F), (%)
1.	KOH	3	90	60/40	54
2.	KOH	24	97	5/95	3
3.	Pyridine	3	90	64/36	55
4.	Pyridine	24	100	0/100	0
5.	Et_3N	2	87	69/31	50
6.	Et_3N	24	93	14/86	11

Table (**19**). Effect of temperature on selectivity

$HO(CH_2)_4OH$ 1. propionic anhydride (A) → Products (E, F, G)

(1.0 equiv.) 2. co-reagent (0.05 eq.)

3. 3 hr. at (D) ^oC

4. workup

Entry	Amount of anhydride (A)	Co-reagent	D (^oC)	Conversion (%)	Product ratio (F/G)	Yield of mono acylated product (F), (%)
1.	1.0 equiv.	KOH	25	66	77/23	51
2.	1.0 equiv.	KOH	100[a]	100	49/51	45
3.	10ml/g OH	Pyridine	25	90	64/36	55
4.	10ml/g OH	Pyridine	100[a]	96	0/100	0
5.	10ml/g OH	Et_3N	25	87	69/31	50
6.	10ml/g OH	Et_3N	100[a]	100	0/100	0
7.	1.0 equiv.	Et_3N	25	75	80/20	55
8.	1.0 equiv.	Et_3N	100[a]	100	43/57	40
9.	10ml/g OH	H_2O	25	94	47/53	40
10.	10ml/g OH	H_2O	100[a]	100	0/100	0

a = oil bath

Table (**20**). Effect of amount of propionic anhydride on selectivity

$HO(CH_2)_4OH$ (1.0 equiv.) 1. propionic anhydride (A) → Products (E, F, G)
2. co-reagent (0.05 eq.)
3. 3 hr. at 25°C
4. workup

Entry	Amount of anhydride (A)	Co-reagent	Conversion (%)	Product ratio %, (F/G)	Yield of mono acylated product (F), %
1.	1.0 equiv.	KOH	66	77/23	51
2.	10ml/g OH	KOH	90	60/40	54
3.	10ml/g OH	Pyridine	90	64/36	55
4.	10ml/g OH	Et_3N	87	69/31	50
5.	1.0 equiv.	Et_3N	75	80/20	55

Finally, effect of the chain lenght of the diols on the conversion and yield was investigated. Solubility problems may arise in the case of diols with higher chain lenght more than five carbon atoms, because they are solids.

Afterwards, acylation of 1,6-hexanediol and 1,8-octandiol with acetic or propionic anhydride in presence of several co-reagent was examined based on the previous results. The previous optimum reaction time 3 hr., was kept at room temperature, a slight, but not significant, decrease of the conversion was observed. The yield of mono acylated derivative (F) showed more significant decrease with increasing chain lenght, Table (**21**).

Other observation was made from the summary of the results.Reaction without solvent is useful for the preparation of mono acylated diols with anhydrides.- The process requires co-reagent which accelerate the acylation KOH, pyridine, Et_3N, NaOAc, H_2O can be applied. From the point of view of conversion and yield of monoacylated product (F), in practice, KOH proved to be the most suitable one. In this process catalytic amount of co-reagent is used.

Table (**21**). Effect of chain lenght of diol on selectivity of acylation

$HO(CH_2)_4OH$ (1.0 equiv.) 1. $(RCO_2)O$ (A equiv.) → Products (E, F, G)
2. co-reagent (cat.)
3. 3 hr. at 25 °C
4. workup

Entry	n	R	Amount of anhydride (A)	Co-reagent	Conv. (%)	Product ratio (F/G)	Yield of mono acylated product (F), (%)
1.	6	Me	10 ml/g OH	Acetic acid	68	72/28	45
2.	6	Me	10 ml/g OH	KOH	88	51/49	41
3.	6	Me	1.0 equiv.	KOH	67	72/28	45
4.	6	Me	10 ml/g OH	NaOAC	75	68/32	48
5.	6	Et	10 ml/g OH	Et_3N	62	77/23	45
6.	6	Et	1.0 equiv.	Et_3N	38	87/13	30
7.	6	Et	1.0 equiv.	KOH	67	70/30	45
8.	6	Et	10 ml/g OH	KOH	90	50/50	41
9.	8	Me	10 ml/g OH	Acetic acid	76	66/34	42
10.	8	Me	10 ml/g OH	KOH	95	36/64	30
11.	8	Me	1.0 equiv.	KOH	59	58/42	30
12.	8	Me	10 ml/g OH	NaOAC	82	60/40	45
13.	8	Et	10 ml/g OH	Et_3N	51	73/27	37
14.	8	Et	1.0 equiv.	Et_3N	11	73/27	5
15.	8	Et	1.0 equiv.	KOH	66	53/47	31
16.	8	Et	10 ml/g OH	KOH	89	46/54	38

The best result of monoacylated derivative (F) was achieved after 3 hr. at room temperature. If the carbon chain of diol is longer, a small reduction in the yield of the monoacylated derivative (F) is observed, and this is due to the solubility problems. It is desired to enhance the amount of anhydride in case of solid diol, and the scale of procedure is accompained with more problem than in case of liquid diol. According to the experiment, the following mechanism can be proposed.

Method (A): (Potassium hydroxide, water and sodium acetate.)

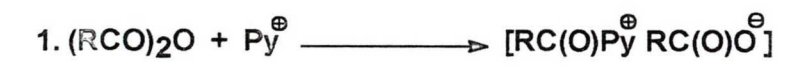
1. $(RCO)_2O + MB \longrightarrow RC(O)B + RC(O)OM$

2. $RC(O)OM + \overset{/}{R}B \longrightarrow RC(O)O\overset{/}{R} + MB$

Total: $(RCO)_2O + \overset{/}{R}B \longrightarrow RC(O)O\overset{/}{R} + RC(O)B$

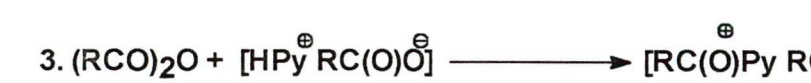
When B = $O\overset{\ominus}{H}$, $OAC^{\ominus}$; M = K,Na .

Method (B) : (Pyridine ,and triethylamine .)

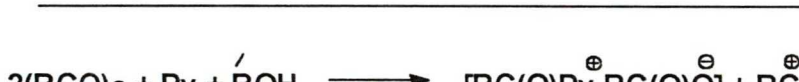


1. $(RCO)_2O + P\overset{\oplus}{y} \longrightarrow [RC(O)P\overset{\oplus}{y}\ RC(O)O\overset{\ominus}{]}$

2. $[RC(O)P\overset{\oplus}{y}\ RC(O)O\overset{\ominus}{]} + \overset{/}{R}OH \longrightarrow [HP\overset{\oplus}{y}\ RC(O)O\overset{\ominus}{]} + RC(O)O\overset{/}{R}$



3. $(RCO)_2O + [HP\overset{\oplus}{y}\ RC(O)O\overset{\ominus}{]} \longrightarrow [RC(\overset{\oplus}{O})Py\ RC(O)O\overset{\ominus}{]} + RCOOH$



Total: $2(RCO)_2 + Py + \overset{/}{R}OH \longrightarrow [RC(O)P\overset{\oplus}{y}\ RC(O)O\overset{\ominus}{]} + R\overset{\oplus}{C}(O)O\overset{/}{R} + RCOOH$

Esterification of carboxylic acid salts

Ester formation is often used in organic synthesis starting with carboxylic acid [50-61] or their salts [62-68]. Applying phase transfer condition, the esterification can be achieved without solvent if one of the reactants is liquid [63,68]. This process was developed for the synthesis of acetates [5,69] and aromatic carboxylic esters [6].

The reaction of sodium salts of carboxylic acids with alkyl bromides under PTC condition was achieved in the presence of Aliquot 336 (FLUKA) as a catalyst, with vigorous stirring and heating, and the esters could be obtained by distillation of the reaction mixture. The results are presented in Table (**22**). This process can be applied when the alkyl bromides are liquid and the esters formed can be purified by distillation. A good yield was achieved applying alkyl bromide with low volatility. Generally the amount of alkyl bromide used was 2 ml/g of salt of carboxylic acid. In case of methyl iodide and ethyl bromide it was 5 ml/g of salt of carboxylic acid.

Table (**22**). Esterification of carboxylic acid salts

R^1-COONa 1. R^2-Br/Aliquot 336 (cat.) → R^1-COOR^2
2. 5 - 24 hr. at 120 °C (oil bath)
3. distillation

R^1	R^2	Yield of esters (%)
CH_3-	C_4H_9	90
C_2H_5-	C_4H_9	95
CH_3-	C_5H_{11}-	85
$HO(CH_2)_{10}$	C_4H_9-	85
CH_3CH=CHCH=CH-(E,E)	CH_3-	90
CH_3CH=CHCH=CH-(E,E)	C_2H_5-	85
CH_3CH=CHCH=CH-(E,E)	C_3H_7-	90
CH_3CH=CHCH=CH-(E,E)	C_4H_9-	90
CH_3CH=CHCH=CH-(E,E)	C_5H_{11}-	90

(2**E**, 4**E**) - propyl-(2,4-hexadienoate) formation under PTC condition was investigated with different type of catalyst. Table (**23**).

Table (**23**). Investigation of formation of ester from carboxylic acid salt

$CH_3CH=CHCH=CHCOONa$ 1. PrBr/solvent → $CH_3CH=CHCH=CHCOOPr$
2. catalyst
3. 5 - 8 hr. at 120 °C (oil bath)

Entry	Solvent	PTC catalyst	Yield of ester (%)
1.	-	-	5
2.	-	Aliquot 336	90
3.	-	$Bu_4N^+HSO_4^-$	90
4.	-	Triton X-100[e]	50[a]
5.	Dichloromethane[b]	Aliquot 336	15
6.	DMF[b]	Aliquat 336	45
7.	H_2O[c]	Aliquot 336	99
8.	H_2O[d]	$Bu_4N^+HSO_4^-$	93

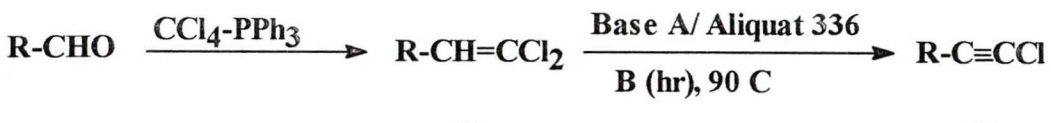
a= difficult to isolate the product
b= 3 ml/g RCOONa
c= 0.2 ml/g RCOONa after 3 hr.
d= 0.15 ml/g RCOONa after 3 hr.
e= polyoxyethylene ethers with other surface active compounds

Table (**23**), shows that the reaction without catalyst gave a very low yield (entry 1.). The yield is decreased when solvent is used (entry 5,6). In this process alkyl bromide was more polar than solvent, and could help to make a homogeneous reaction, therefore the yield of product was higher. In case of using quaternary ammonium salt as a catalyst good yields were obtained (entry 3,8).

During the reaction, sodium bromide formed has precipitated and the density of the mixture changed. A reaction was checked by gas chromatography showing a 70% of yield after 3 hr., and required another 3 hr. to complete. After 3 hr., water was added to the reaction mixture to dissolve sodium bromide. The reaction time was decreased and a good yield was obtained (entry 7,8).

Preparation of 1-chloro-1-alkynes from 1,1-dichloro-1-alkenes.

Several methods are known for the preparation of 1-chloro-1-alkynes (**20**), (Scheme 28.), which are important intermediates for a number of syntheses [70-83]. We developed an effective synthesis for the preparation of 1-chloro-1-alkynes from 1,1-dichloro-1-alkenes (**19**) [84,85], (Scheme 28). This procedure was achieved without solvent and under PTC conditions [86].The results are presented in Table (**24**).



19 **20**

(Scheme 28)

Table(**24**). Hydrogen chloride elimination from 1,1-dichloro-1-alkenes.

Entry[a]	Base	A(equiv.)	B(hr.)	Catalyst (ml/gof 19)	Product contents %[b] 19	20	RC=CH
1.	KOH	2	0.5	0.2	4	80	2
2.	KOH	2	0[c]	0.2	5	80	1
3.	KOH	1	0.5	0.2	21	60	1
4.	KOH	2	2.0	0.2	-	70	1
5.	KOH	1	2.0	0.2	4	80	-
6.	KOH	2	2.0	0.5	-	60	10
7.	KOH	4	24.0	0.2	-	60	30
8.	KOH	2	24.0	0.2	-	80	3
9.	NaOH	2	2.0	0.2	-	60	5
10.	$Ca(OH)_2$	2	2.0	0.2	40	40	1
11.	KOH	1	0.5	0.2	20	70	-
12.	KOH	2	0[c]	0.2	2	70	5
13.	KOH	2	2.0	0.2	2	70	4
14.	KOH	1	2.0	0.2	4	80	-

When a = 1-10 entry; R = $CH_3(CH_2)_5$ and /or $CH_3(CH_2)_6$-

11-14 entry; R = $CH_3(CH_2)_3$-

b = analysed by gas chromotagraphy.

c = the product was distilled off just after mixing the reactants.

This method is based on the synthesis of terminal acetylene derivative from 1,2-dibromo-alkenes formerly developed[11]. Butyllithium is widely used as a base in the synthesis of acetylenes (if R = aliphatic chain) from 1,1-dihalo-alkenes. This usually gives good results in case of bromo derivatives, though bromo compound is much more expensive than the corresponding chloro compound. Applying butyllithium in case of chloro derivatives gives the required 1-chloro-alkyne derivatives only in low yield.

Our method was better when the product could be distilled. We examined the application of many bases and found that KOH is the best one. NaOH and $Ca(OH)_2$ formed from CaO with equivalent H_2O in situ. gave lower yields, see Table (**24**). When the temperature of the reaction mixture increased above 100 ^oC the quaternary ammonium salt catalyst decomposed to tertiary amine within an hour.

Discussion of results

Benzylation and acylation of aliphatic diols, esterification of carboxylic acids salts with alkyl halides and formation of 1-chloro-1-alkynes were investigated using reaction without solvent. One of the reagents was liquid and applied in excess in all experiments.

During the benzylation of diols the aim was to reach the highest yield for monobenzylated derivatives. The best results were obtained applying potassium hydroxide as a base at 100 ^oC (oil bath temperature). In this case the yields of monobenzyl ethers were 50-60 %.

During the acylation of diol the aim was to get the best yield of monoacylated derivatives using acetic and propionic anhydrides. These processes needed co-reagents having catalytic effect.

The best co-reagent was potassium hydroxide. Highest yields 45-55% were achieved after 3 hours at room temperature.

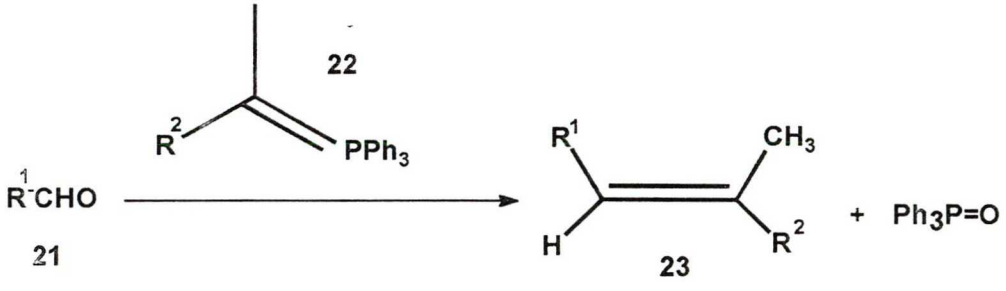
The esterification of carboxylic acids sodium salts was performed by alkyl halides using Aliquot 336 (FLUKA) as PTC catalyst. The esters were produced after 5-24 hours with 80-95% yields.

1-Chloro-1-alkynes were formed from 1,1-dichloro-1-alkenes by hydrogen chloride elimination. Applying potassium hydroxide as a base the highest yields of products were 70-80 %. In all cases the yields were better than those of the common methods.

2. INTERPRETATION OF THE SIDE REACTION OF WITTIG COUPLING

A number of side reactions have been observed during Wittig coupling reactions. One of them is the aldol condensation of carbonyl compounds which is the result of excess base used for the generation of phosphorane.This side reaction was observed using sterically hindered carbonyl compounds, or the phosphorane contaning side chain in α-position.

Introduction of isopropylidene and isobutylidene units are important steps in the synthesis of natural products. However, the Wittig coupling with isopropylidenphosphorane (Scheme 29),was rarely used for this purpose, because low yield was achieved [16-18], or only the starting material was recovered. We reinvestigated the Wittig reaction of the phosphoranes **22** and identified the structure of side products. The reaction between phosphoranes **22** and aldehydes (**21a-e**) afforded the alkenes (**23a-j**) in moderate yield (Scheme 29 and Table **25**)



21	R^1
a	Bu
b	-$(CH_2)_5$-CH_3
c	-$(CH_2)_6$-CH_3
d	2-cyclohexenyl
e	phenyl

22	R^2
a	Me
b	Et

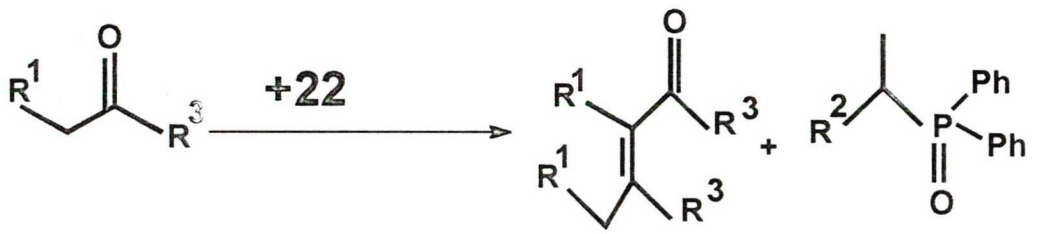
23	R^1	R^2
a	Bu	Me
b	Bu	Et
c	-$(CH_2)_5$-CH_3	Me
d	-$(CH_2)_5$-CH_3	Et
e	-$(CH_2)_6$-CH_3	Me
f	-$(CH_2)_6$-CH_3	Et
g	2-cyclohexenyl	Me
h	2-cyclohexenyl	Et
i	phenyl	Me
j	phenyl	Et

(Scheme 29)

Table(25); Reaction of aldehydes (**21**) with phosphoranes (**22**).

Entry	Aldehyde (**21**)	Yields of products (%) (**23**)	
		$R^2=CH_3$	$R^2=C_2H_5$
1.	Pentanal	40	35
2.	Heptanal	30	20
3.	Octanal	20	15
4.	2-Cyclohexene-1-carboxaldehyde	40	30
5.	Benzaldehyde	30	30

The reaction of phosphoranes **22** with ketones (**24a-d**) yielded α,β-unsaturated ketones (**25a-c**) and diphenylphosphine oxide derivatives (**26a-b**) (Scheme 30, Table **26**).



24 **25** **26**

24	R^1	R^3
a	Bu	Me
b	Pr	$-CH_2-CH_2-COOCH_3$
c		$-(CH_2)_3-$
d		$-(CH_2)_4-$

25	R^1	R^3
a	Bu	Me
b		$-(CH_2)_3-$
c		$-(CH_2)_4-$

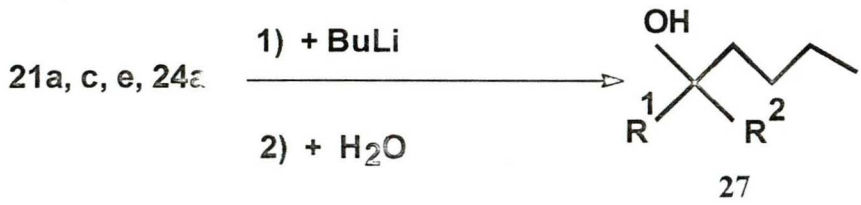
26	R^2
a	Me
b	Et

(Scheme 30)

Table (**26**): Reaction of ketone (**24**) with phosphorane (**22**)

Entry	Ketone (24)	Yields of product (%)	
		R^2=CH_3	R^2= C_2H_5
1.	2-Heptanone (24a)	50	45
2.	Methyl-4-oxooctanonate (24b)	0	0
3.	Cyclopentanone (24e)	40	35
4	Cyclohexanone (24d)	20	20

At first we thought that the aldol condensation products were the result of the excess of butyllithium used as a base for generation of phosphoranes. To prove this hypothesis, carbonyl compounds were reacted with butyllithium (Scheme 31),but in accordance with the previous study [87] the reaction afforded secondary or tertiary alcohols (**27a-d**), and no trace of aldol condensation products were detected ,(Table **27**).



27

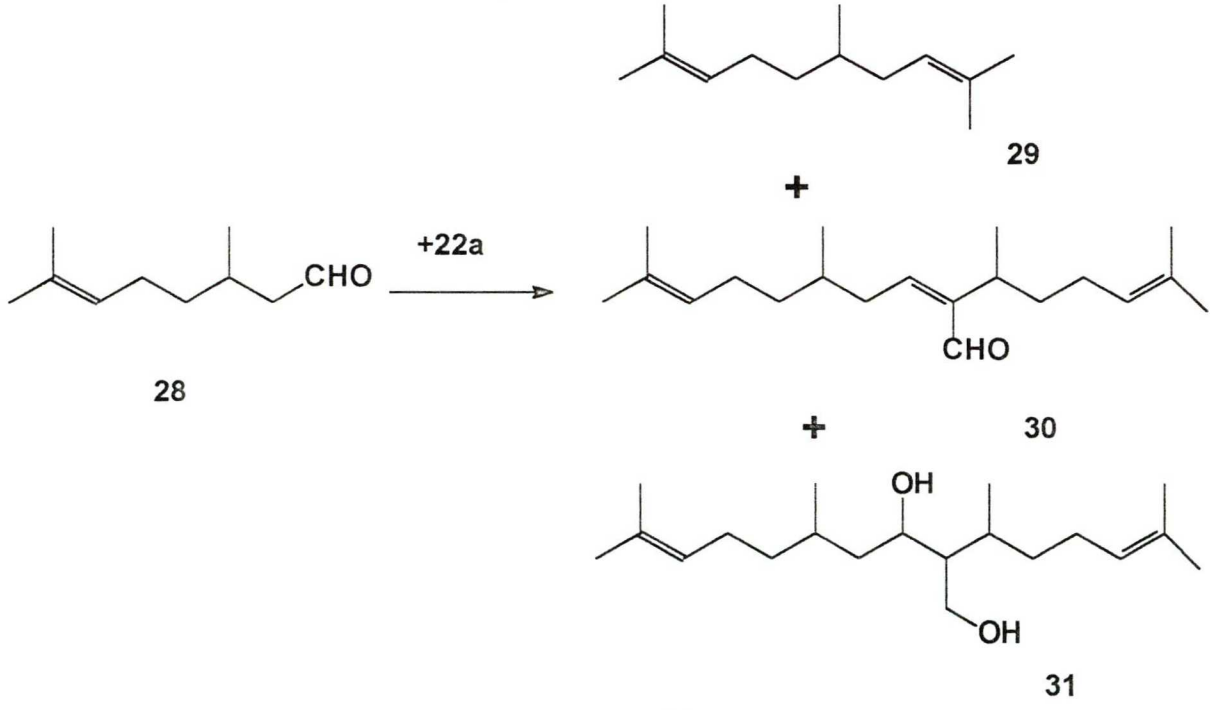
27	R^1	R^2
a	-$(CH_2)_3$-CH_3	H
b	-$(CH_2)_6$-CH_3	H
c	Phenyl	H
d	-$(CH_2)_4$-CH_3	Me

(Scheme 31)

Table (**27**): Reaction of butyllithium with carbonyl compound(**21**)

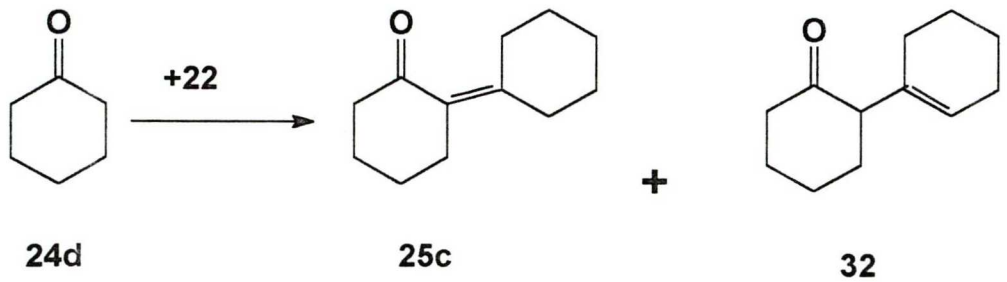
Entry	Carbonyl compound	Product (27)	Yield%
1.	Pentanal	5-hydroxynonane (**27a**)	60
2.	Octanal	5-hydroxydodecane (**27b**)	45
3.	Benzaldehyde	1-hydroxy-1-phenylpentane (**27c**)	50
4.	2-Heptanone	5-hydroxy-5-methyldecane (**27d**)	40

The reaction between the branched chain citronellal (**28**) and phosphorane **22a** afforded both aldol condensation (**30**) and Wittig (**29**) products, in ratio 2:1. A third compound (**31**) was also isolated ,(Scheme 32) .



(Scheme 32)

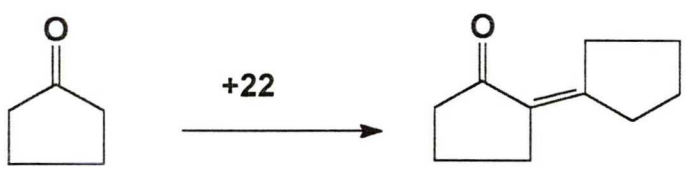
Only aldol products were formed using cylic ketones (cyclopentanone and cyclohexanone. In case of cyclohexanone (**24d**) ,two isomers of α,β-unsaturated ketone were formed (**25C** and **32**) with a ratio 1:1 (Scheme 33).



24d **25c** **32**

(Scheme 33)

2-Cyclopentylidencyclopentanone (**25b**) was formed from cyclopentanone (**24c**),(Scheme 34)



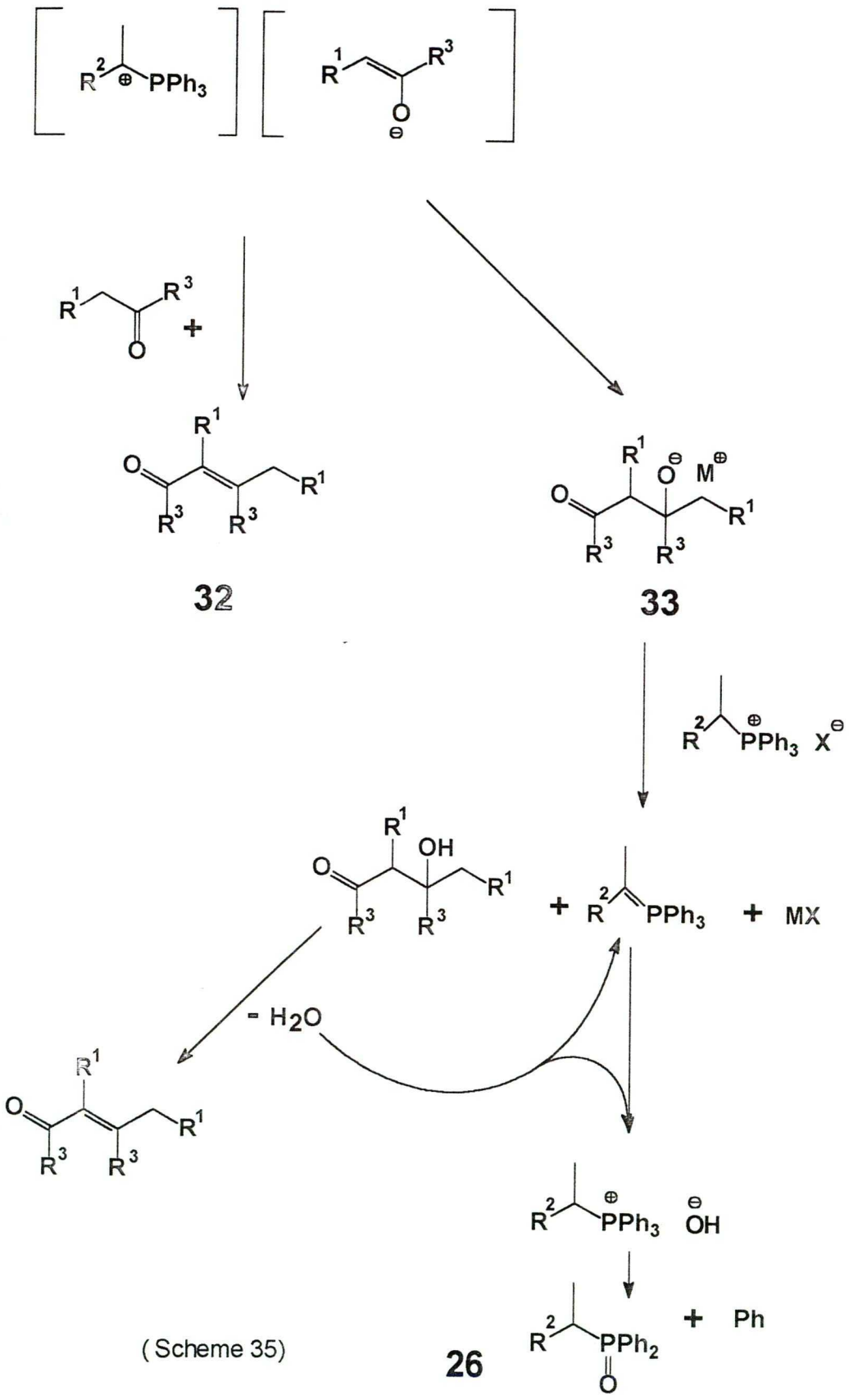
24c **25b**

(Scheme 34)

An unexpected observation has been made also by Imamato[88] and his group for isopropylmagnesium chloride in reaction with cyclopentanone and cyclohexanone, the aldol product was the major one rather than the addition product. They have examined the reaction in the presence of cerium chloride provided the addition product in a good yield rather than aldol product. We examined cerium chloride methodology in Wittig reaction, but only the decomposition of the ylide was observed without coupling reaction.

The lack of reaction between ketoester **24b** and **22a** indicates that the phosphorane **22a** is a strong base enough to initiate aldol condensation of unhindered carbonyl compounds, but its nucleophilicity is too weak for the Wittig coupling, (Scheme 30). The formation of phosphine oxide derivative **26** suggests the following mechanism, (Scheme 35). In acid-base mechanism, the aldol products from the ketone, induced by base, presumably served by the basic phosphorane reagent rather than some unreacted butyllithium or other bases e.g.LiOH.This phosphorane reagent deprotonate ketone to generate the enolate. This enolate is well disposed to condense with starting ketone, to give an aldol adduct in the standard route (**32**). However it is possible that the aldol alkoxide (**33**) deprotonates the phosphonium salt to generate the ylide and then loses water. Hydroxide ion could cleave phenyl phosphonium salts easily to give phosphine oxide (Scheme 35).

Summarizing our results, the isopropylidene and isobutylidene ylides are stable enough and can act as a base under Wittig condition to generate aldol product with ketone, and the yield of olefin product is very low or undetectable.



(Scheme 35)

3. PREPARATION OF UNSATURATED NITRILES BY THE MODIFICATION OF MITSUNOBU-WILK PROCEDURE.

Wilk procedure[27] was applied for converting the saturated alcohol to the corresponding nitrile.Subsequent addition of DEAD and acetone cyanohydrin to a solution of PPh_3 and alcohol at 0 °C, and then the reaction mixture was stirred at room temperature.This procedure was unsuccessful for converting of unsaturated alcohol to nitrile.

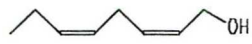
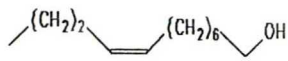
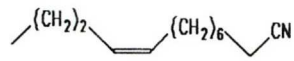
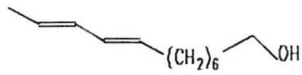
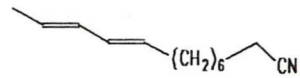
Mitsunobu[24] had observed unexpected result during the alkylation of active methylene compounds.When ethyl cyanoacetate was allowed to react with 1-propanol in the usual procedure (Wilk procedure) , no alkylated products could be isolated and 45% of the ester was recovered.

A slight modification of Wilk procedure was applied for unsaturated alcohols carrying olefinic function , namely subsequent addition of DEAD , alcohol and acetone cyanohydrin to a cold solution (-20 to -30 °C) of PPh_3 and stirring at this temperature for some hours, followed by stirring at room temperature.Here, we observed smooth reaction and the unsaturated nitriles were isolated in good yield, (Table **28**).This sequence of addition at low temperature had been used to diminish undesirable side products.

We have also applied this procedure for the conversion of diphenylcarbinol into diphenylacetonitrile.This transformation had been performed by Wilk in 10% yield. With the above modification we obtained the desired product in 30% yield (Table **28**,entry 5).

Unsaturated alcohols carrying acetylenic function in β-position was also converted to the corresponding nitriles at low temperature , under the same sequence of addition.Here the alcohol was stirred with PPh_3-DEAD mixture for 1-2 hours followed by addition of acetone cyanohydrin (Table **29**).

Table **28** : Conversion of olefenic alcohols to nitriles.

Entry	Substrate	Time(h)	Product	Yield(%)[a]
1		10		70
2		3		50
3		16		61
4		20		59
5	$Ph_2CH.OH$	20	$Ph_2CH.CN$	30

a Yields refer to isolated,chromatographically homogeneous material

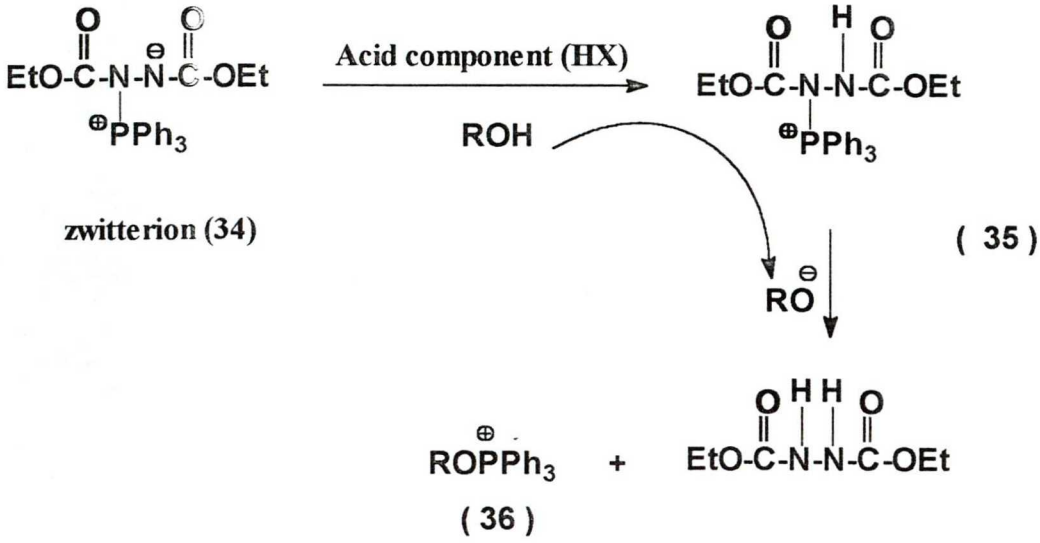
Table **29** :Conversion of β-acetylenic alcohols to nitriles

Entry	Substrate	Product	Yield%[a]
1.	CH_3-$(CH_2)_8$-C≡C-CH_2-OH	CH_3-$(CH_2)_8$-C≡C-CH_2-CN	66%
2.	CH_3-$(CH_2)_7$-C≡C-CH_2-OH	CH_3-$(CH_2)_7$-C≡C-CH_2-CN	55%
3	CH_3-$(CH_2)_4$-C≡C-CH_2-OH	CH_3-$(CH_2)_4$-C≡C-CH_2-CN	50%

a Yields refer to isolated,chromotographically homogenous material.

A detailed mechanistic information was suggested in the Mitsunobu esterification of alcohols[89] , applying triphenylphosphin-diisopropyl azodicarboxylate (PPh_3-DIAD) in presence of acid component (carboxylic acid).

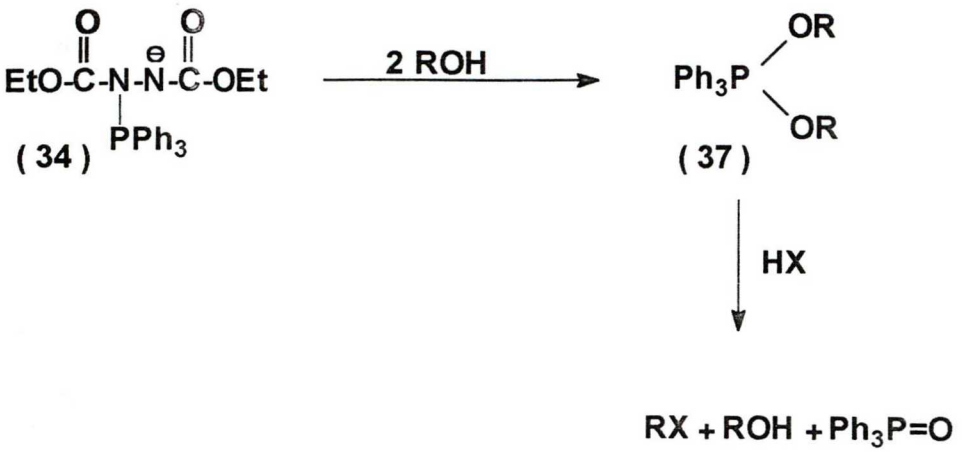
The first step of this reaction was the formation of adduct (**34**;Scheme 36) between DIAD or DEAD and PPh_3. This adduct was formed within second at -20 °C as evidenced by decolorization of DIAD upon addition. It was declaried that the phosphorus is bonded to the nitrogen and not oxygen in the adduct, called Zwitterion (**34**;Scheme 36).The Zwitterion will be protonated during the addition of acid component, which was used up at the same time to deprotonate the alcohol to form alkoxyphosphonium salt (Scheme 36).



(Scheme 36)

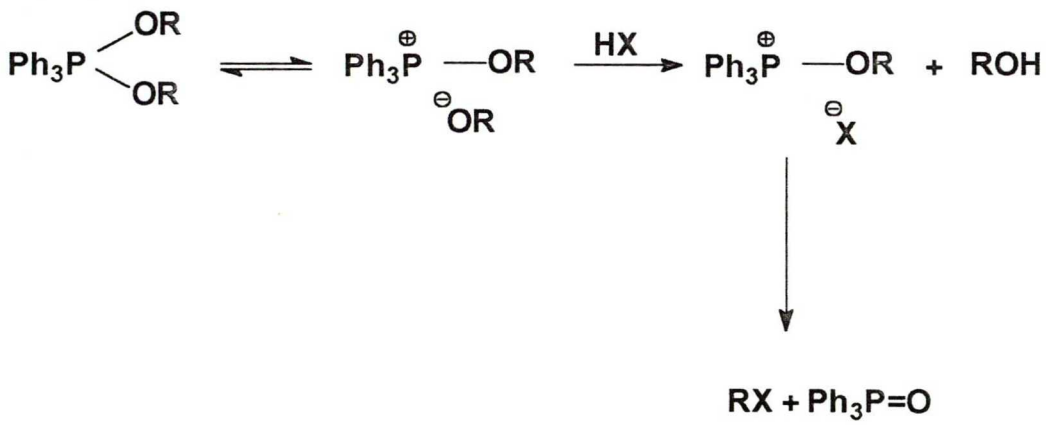
The second step of this reaction was the transfer of PPh_3 group from the DEAD-PPh_3 adduct to the alcohol in order to form phosphonium salt.

On the basis of ^{31}P NMR both Grochowski [90] and Jenkins [91] declared that the true intermediate was the dialkoxyphosphorane $Ph_3P(OR)_2$ (**37**;Scheme 37) which was formed in the absence of acid component.



(Scheme 37)

Decomposition of dialkoxyphosphorane to the product was considered to be alkoxyphosphonium salt by Jenkins [91] (Scheme 38).



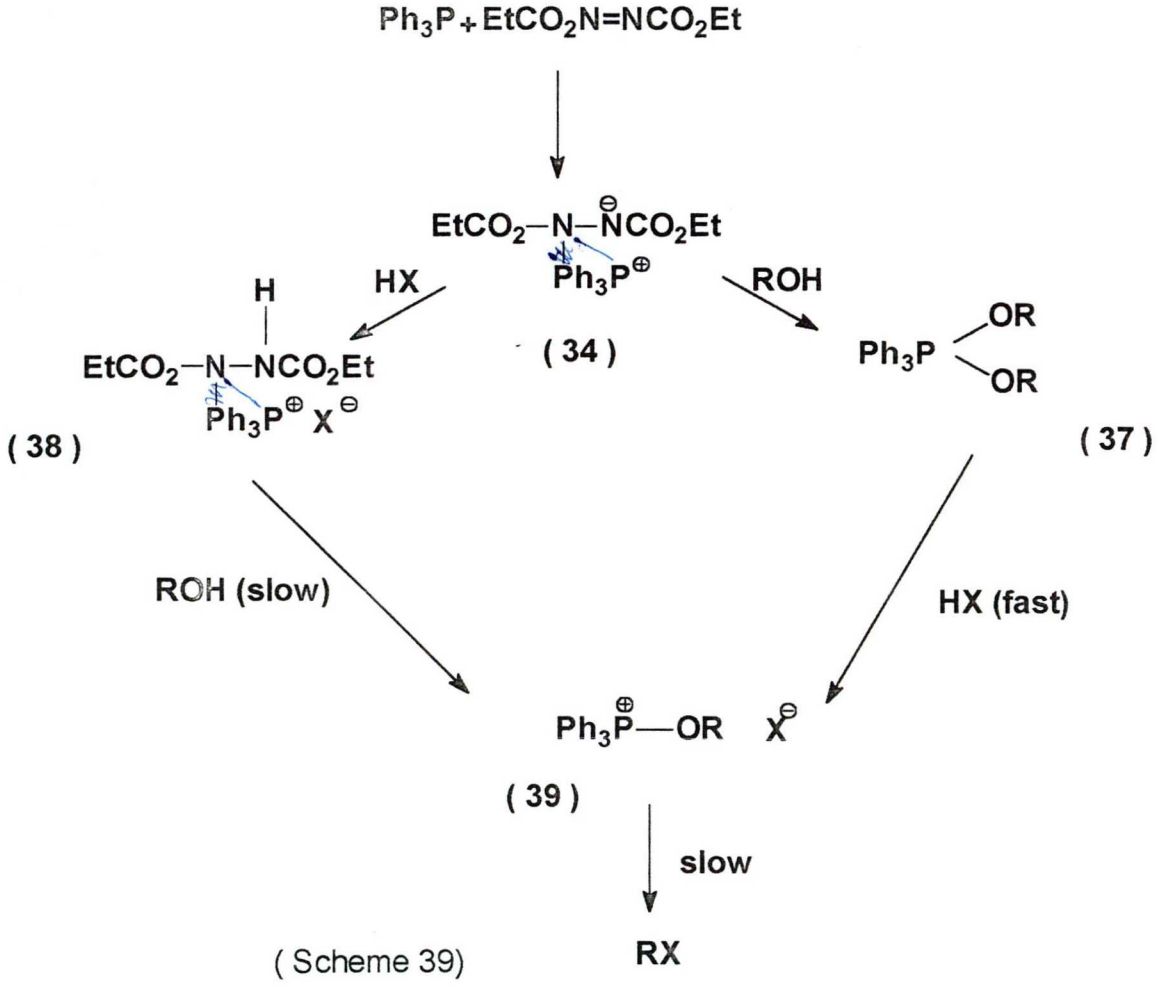
(Scheme 38)

Recently Hughes[89] and his coworkers have not observed phosphorane in the absence of acid and the major product was $Ph_3P=O$, but in presence of acid component oxyphosphonium intermediate was indicated (**36**;Scheme 36).

Formation of oxyphosphonium intermediate was also proved by Walker[92] and coworkers and they found that the stable phosphorane was formed in absence of acid component and was converted to the phosphonium salt upon addition of acid component.

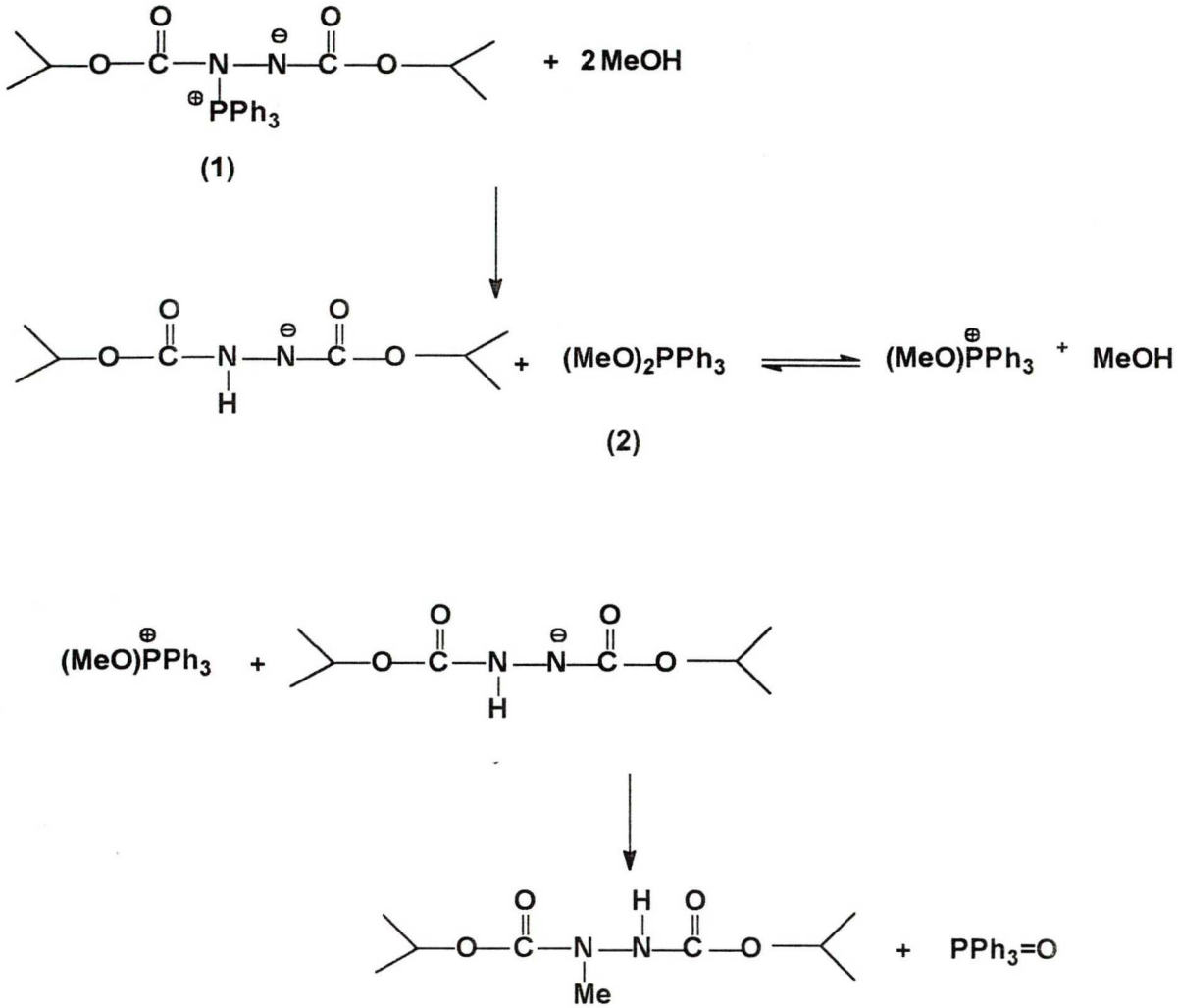
Walker[92] discussed his observation reffering to his experimental results and others, assumed that the betaine(**34**; Scheme 39) was present in the PPh_3-DEAD mixture, then protonation accured immediatly to give the conjugated acid phosphonium salt (**38**; Scheme 39). On addition of ROH this salt will undergoes slow conversion to the phosphonium salt **39**. But in the absence of acid component half of betain **34** was reacted

with alcohol to give dialkoxyphosphorane (**37**; Scheme 39), addition of acid component caused protonation of half of the betaine **34**, and also caused the conversion of dialkoxyphosphorane (**37**) to the phosphonium salt (**39**) instantaneously (Scheme 39). It was also assumed that the liberation of the second molecule of alcohol as suggested by Jenkins from the phosphorane (**37**) on treatment with acid, was incorrect, and further consumption of unreacted alcohol takes place via **38**→**39** and not through **37**. Walker suggested that the phosphorane **37** was the only intermediate formed when the acid was added in the last step.



(Scheme 39)

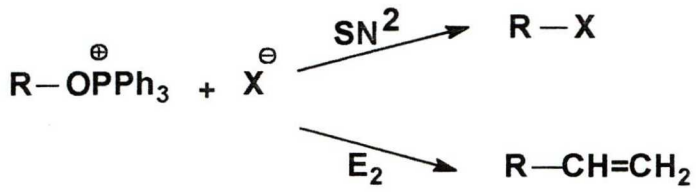
To sort out the above results, Hughes[89] examined the reaction of simple alcohol, methanol and 2-butanol, with PPh_3-DIAD mixture in the absence of acid component, no phosphorane intermediates were observed at room temperature, but at -20 °C the phosphorane of 2-butanol was stable for several hours. The major degradation product was formed from methanol reaction , and a mechanism was suggested (Scheme 40). Therefore in absence of acid component phosphoranes of different stability were formed.



(Scheme 40)

Hughes[89] had suggested that the transfer of PPh_3 group from the adduct (**34**;Scheme 36) depended on the bascity of genereted counter ion $X^{\ominus}$ and on the extent of hydrogen bonding to this counter ion. The function of counter ion was to deprotonate the alcohol which must accrue before $PPh_3^{\oplus}$ transfer from the adduct **35** (Scheme 36). So $X^{\ominus}$ was assumed as a base and a nucleophile in the first two step of Mitsunobu reaction.

The last step of this reaction was the SN_2 reaction between the nucleophile $X^{\ominus}$ and the phosphonium salt. Elimination reaction was also a competitive process and depending on the reaction condition (Scheme 41).



(Scheme 41)

The SN_2 step was very slow and the reaction was followed by the formation of phosphonium salt intermediate at low temperature.

From the above argument we can conclude that the phosphorane or the alkoxyphosphonium intermediate were not stable and could decomposed at room temperature to $Ph_3P=O$.

The mechanism of Mitsunobu reaction depends on the order of mixing of the reagents and consequently this effect the reaction pathway. Also the product and side product depend on the reaction condition, sequence of reagents addition, and on the structure of alcohol.

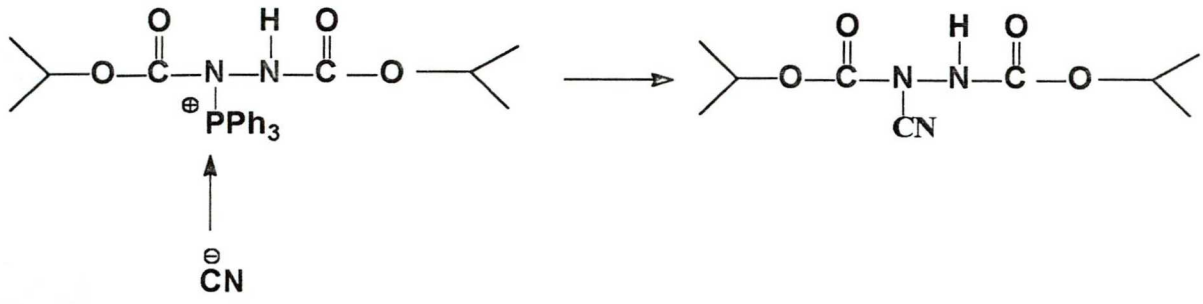
Our interpretation of successful reaction for conversion of unsaturated alcohol to the corresponding nitrile was based on change in reaction conditions and sequence of reagent addition.

Unsuccessful results for conversion of unsaturated alcohols carrying olefinic function and for β-acetylenic alcohols into the corresponding nitriles by applying Wilk procedure, could be assumed to a different possibilites in related to the previous discussion, as following;

1. A degradation product could be formed at room temperature from the ROH and the phosphonium salt.

2. Unsaturated alcohol could be formed phosphorane intermediate with PPh_3-DEAD adduct.These intermediates are not stable at room temperature and consequently decompose to starting material and $PPh_3=O$.

3. From the previous discussion the nucleophile CN^- acted as a base and nucleophile and there is a competitive reaction between CN^- ion and alcohol may take place to attack the PPh_3 -DEAD adduct. Therefore some side product could be formed rapidly at r.t. as was described by Hughes[89] (Scheme 42).

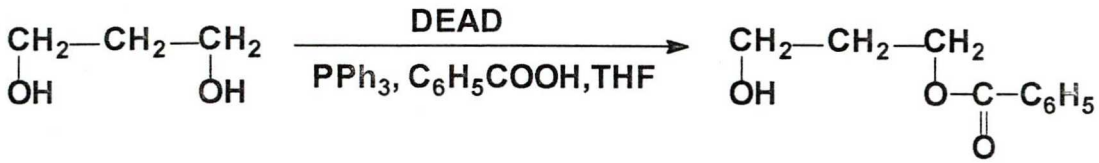


(Scheme 42)

Our modification for Wilk procedure was to change the sequence of addition and the conditions of the reaction , where the temperature was kept at -20 °C in order to avoide the mentioned possibilites for uncuccessful results. In case of β-acetylenic alcohols, the reaction was stirred at -20 °C for 1-2 hours after addition of ROH , to secure the complete reaction of alcohol with PPh_3-DEAD adduct and stablize the phosphorane intermediate. We have observed that the reaction of longer β-acetylenic alcohols with PPh_3-DEAD proceeded rapidly and afforded the nitriles in good yields. This may be due to the more stable intermediate formed during the reaction.

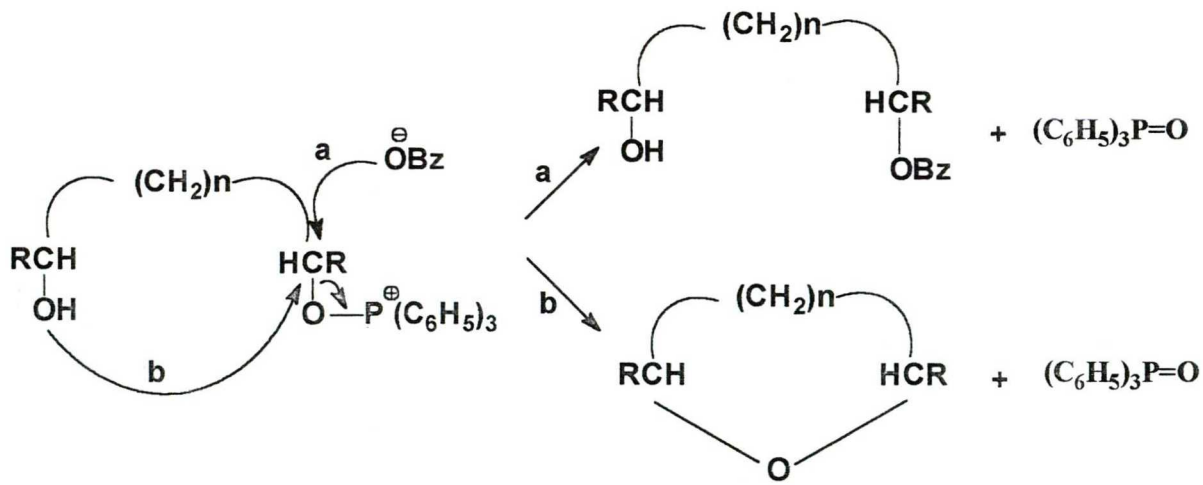
Unsuccessful results for cyanzation of diols.

In using the hydration system of PPh_3-DEAD in presence of acid component , Mitsunobu[93] and his coworkers, had achieved a selective esterification of 1,3-propane diol and 1,4-butandiol, with an equimolar amount of benzoic acid, as acidic component.The yield of half benzoylation was 66% (Scheme 43).



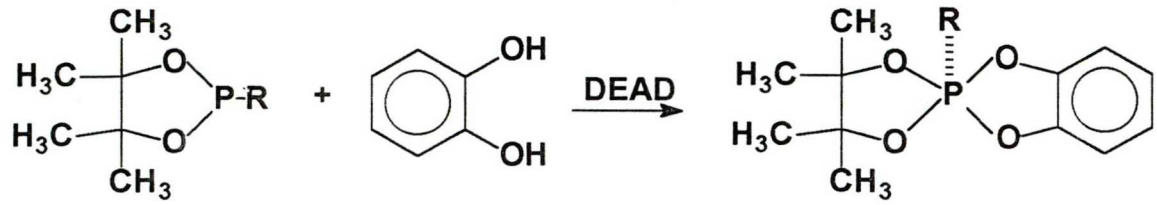
(Scheme 43)

The corresponding cyclic ethers were obtained, when diols were allowed to react with PPh_3-DEAD, in the absence of an acidic component. The cyclization took place because of intramolecular participation by a neighbouring hydroxyl group in the initially formed alkoxyphosphonium salt (Scheme 44).



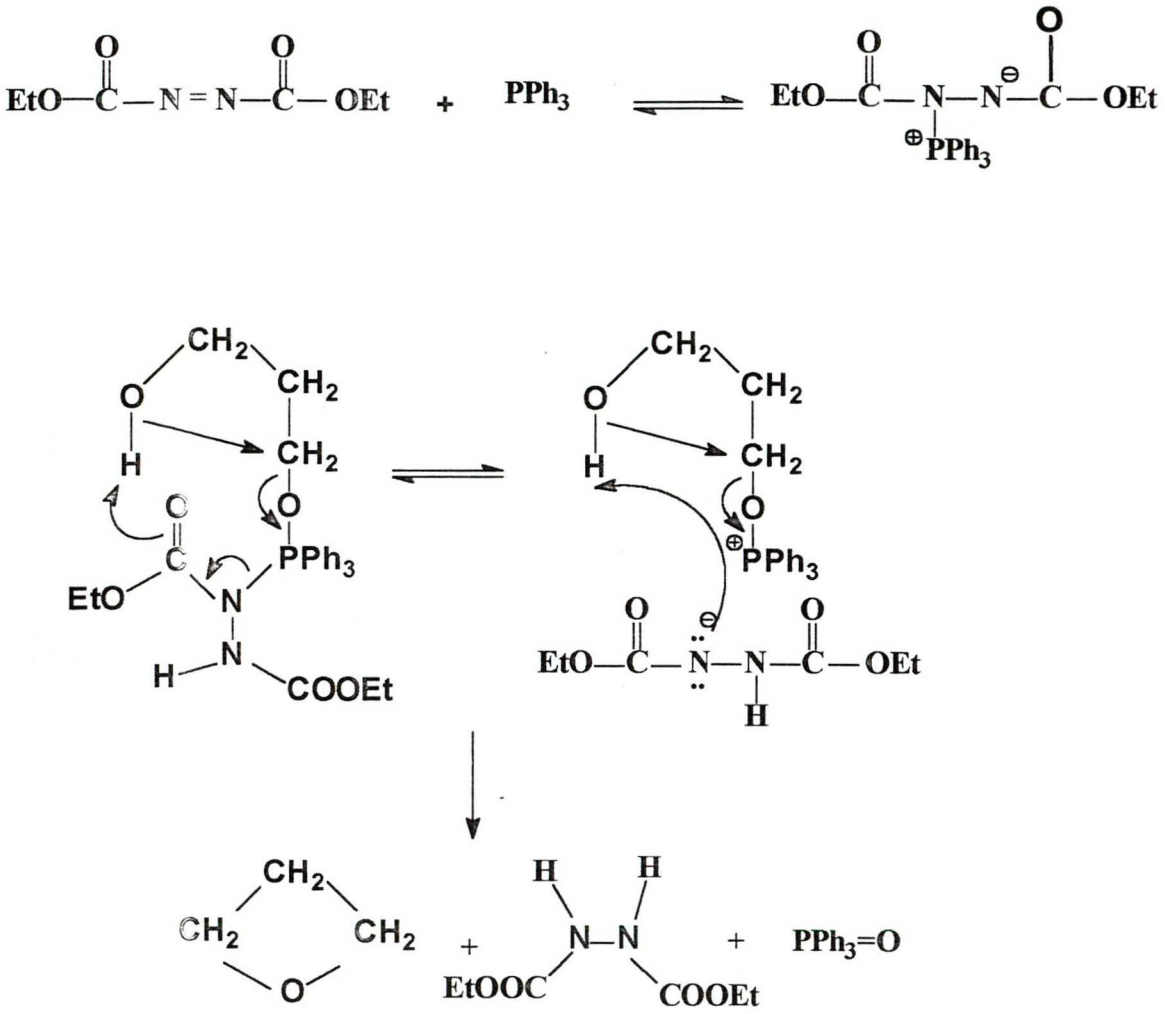
(Scheme 44)

Spirophosphoranes were synthesized by Bone and Trippett[94] by reacting the cyclic phosphorus (lll) compounds with DEAD and 1,2-diols,1,3-diols, or catechol (Scheme 45).



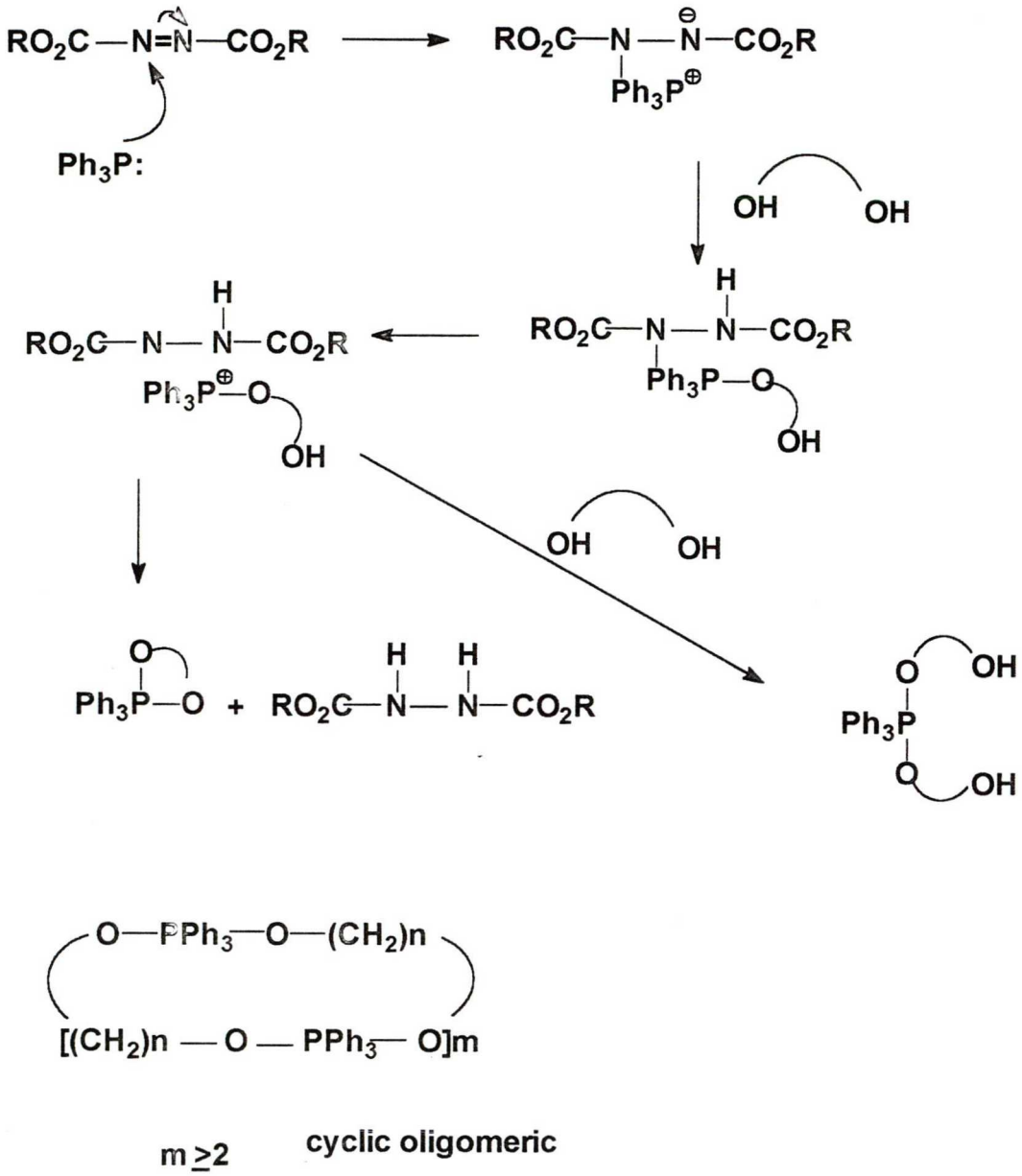
(Scheme 45)

J.Carlock and M.Mack[95] had also suggested a mechanism for the formation of cyclic polyethers from the corresponding diols by using PPh_3-DEAD system (Scheme 46).



(Scheme 46)

Recently[96] cyclic dioxytriphenylphosphoranes was obtained upon the addition of di-isopropyl azodicarboxylate or DEAD to the mixture of PPh_3, acid component and diol in THF at 0°C. This work was extended for longer carbon diol under the same condition[97]. The phosphoranes obtained from these reactions were oligomeric (Scheme 47).

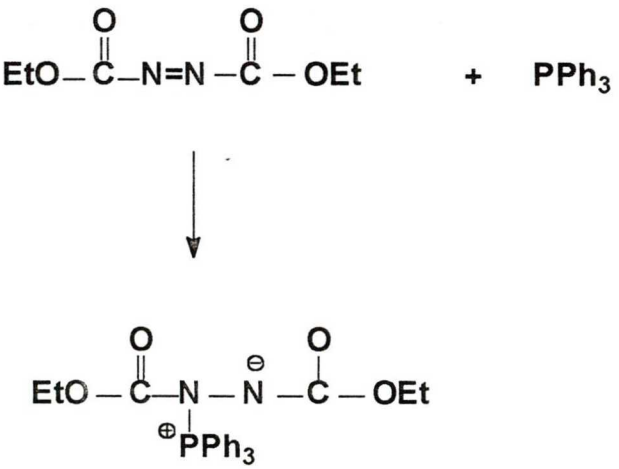


(Scheme 47)

The phosphoranes products were detected by ^{1}H-NMR ,^{13}C-NMR, and ^{31}P-NMR at 10 °C. Isolation of these various phosphoranes was not attempted due to their extreme sensitivity to moisture and to their rapid thermal decomposition at room temperature.

Referring to the benzoylation of diols[93], our work was extended to cyanization of diols, using PPh_3-DEAD dehydration system in presence of acetone cyanohydrin as acidic component.

1,3-propandiol, 1,4-butandiol,1,5-propandiol,and 1,8-octandiol were reacted with PPh_3-DEAD in presence and in absence of acetone cyanohydrine and under the same condition of benzoylation .Also a different conditions of addition and molar of reactants were applied. Unsuccessful attempts for cyanization of diols were obtained.The reactions were followed by gas chromotography and only one signal was observed in all cases.This signal was examined under the reaction condition of PPh_3 and DEAD to form the intermediate complex (**34**; Scheme 48), which had exactly the same signal at the same retention time.



34

(Scheme 48)

It seems that the reaction of diols with PPh_3-DEAD adduct in presence of acetone cyanohydrin, affords type of phosphorane products, which were decomposed at r.t. to PPh_3=O. Duo to the instability of these phosphorane, we were unable to follow the reaction by gas chromotography.

Unsuccessful attempts for cyanization of diols may due to weak nucleophile CN^- ion and also to the thermaly instable phosphorane intermediates. Therefore the nature of anion derived from acidic compound and the structure of alcohol have been found to play an important role in the reaction path.

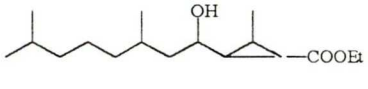
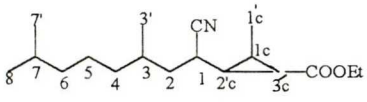
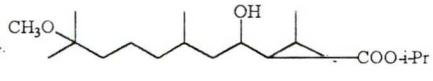
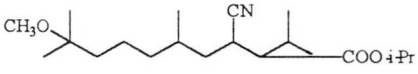
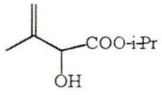
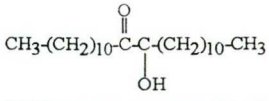
Carbon elongation of hydroxy esters

The direct transformation of ester compounds containing terminal or secondary hydroxyl group into the corresponding nitrile esters have been achieved successfully applying our procedure with a change of reaction conditions under the same sequence of addition . Here the hydroxy ester was stirred with PPh_3-DEAD mixture for 30 min., followed by addition of acetone cyanohydrin and the reaction mixture was stirred at low temp. for 6 hr., and then at r.t. Usual workup afforded the corresponding nitrile in good or acceptable yields (Table **30**; entries 1-3).

However, no nitrile products were observed in the reactions of sterically hindered α-hydroxy ester and α-hydroxy acid (Table **30**, entry 5 and 6). We also failed to perform the carbon elongation with amino alcohol and α-hydroxy ketone (Table **30**; entries 7 and 8). In these cases, the starting compounds decomposed during the above reaction conditions.

In summary , under modified conditions described above, hydroxy esters can be converted conveniently into the corresponding nitriles by Mitsunobu-Wilk method.

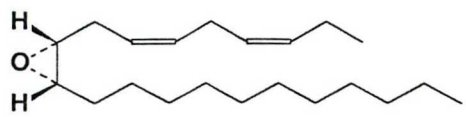
Table **30**: Conversion of Alcohols to Nitriles.

Entry	Substrate	Product	Yield [a] %
1.	HO-$(CH_2)_8$-$COOCH_3$	NC-$(CH_2)_8$-$COOCH_3$	70
2.	HO-$(CH_2)_{10}$-$COOCH_3$	NC-$(CH_2)_{10}$-$COOCH_3$	75
3.			55
4.			48
5.		NO REACTION/ DECOMP..	
6.	CH_3-CH(OH)-COOH	NO REACTION/DECOMP.	
7.	CH_3-C(CH_3)(NH_2)-CH_2-OH	NO REACTION/DECOMP.	
8.		NO REACTION/DECOMP.	

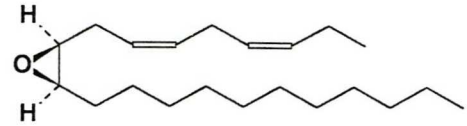
a Yields refer to isolated, chromatographically homogenous material.

4. SYNTHESIS OF(3Z, 6Z)-9, 10-EPOXY-3, 6-HENEICOSADIENE.

Synthesis the diene epoxide (9S, 10R)- and (9R, 10S) (Scheme 49) was achieved by K. Mori and T. Ebata[34], using a triynal as an intermediate, and applying the Sharpless asymmetric epoxidation[35].



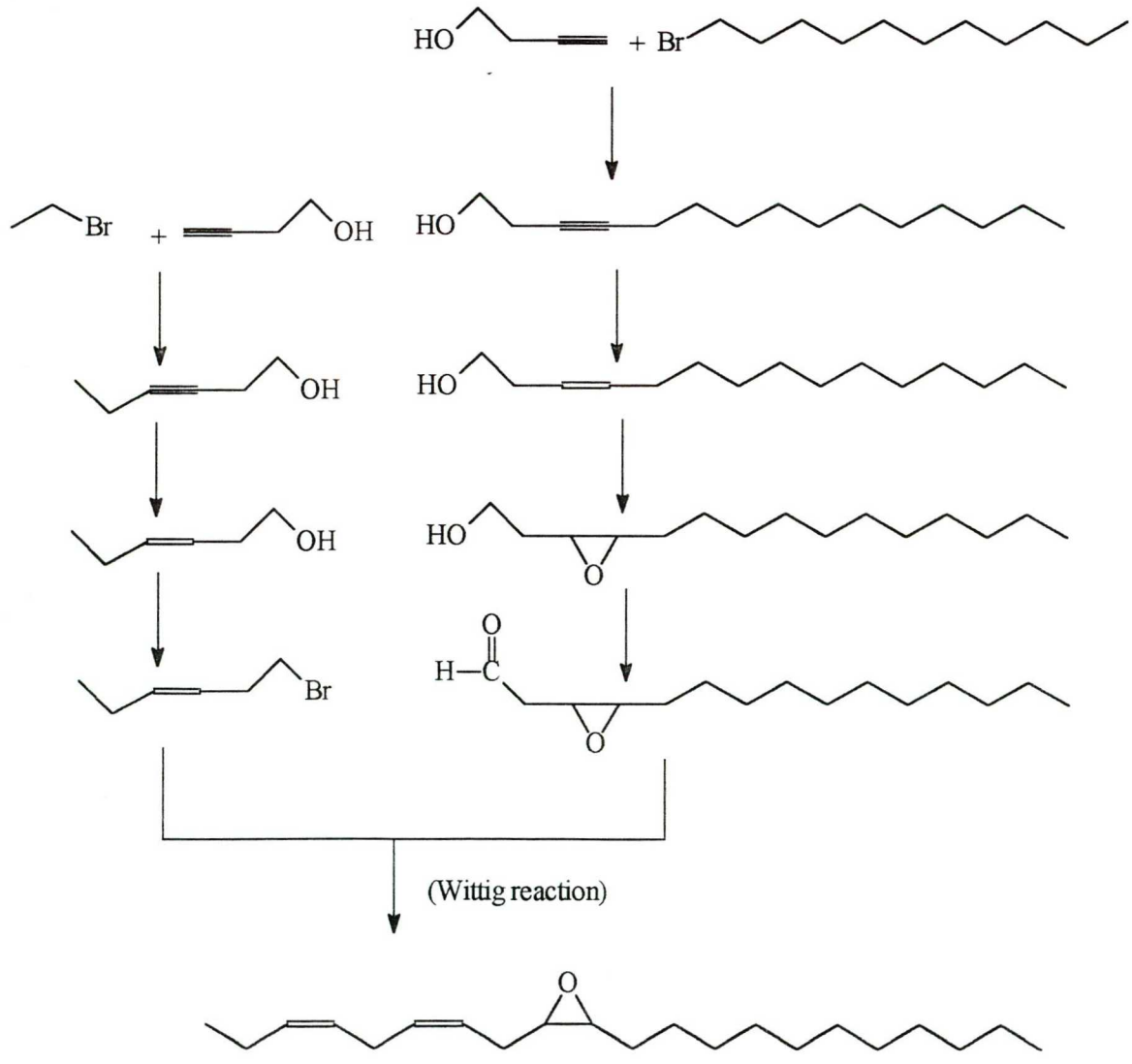
(9R,10S)-epoxide



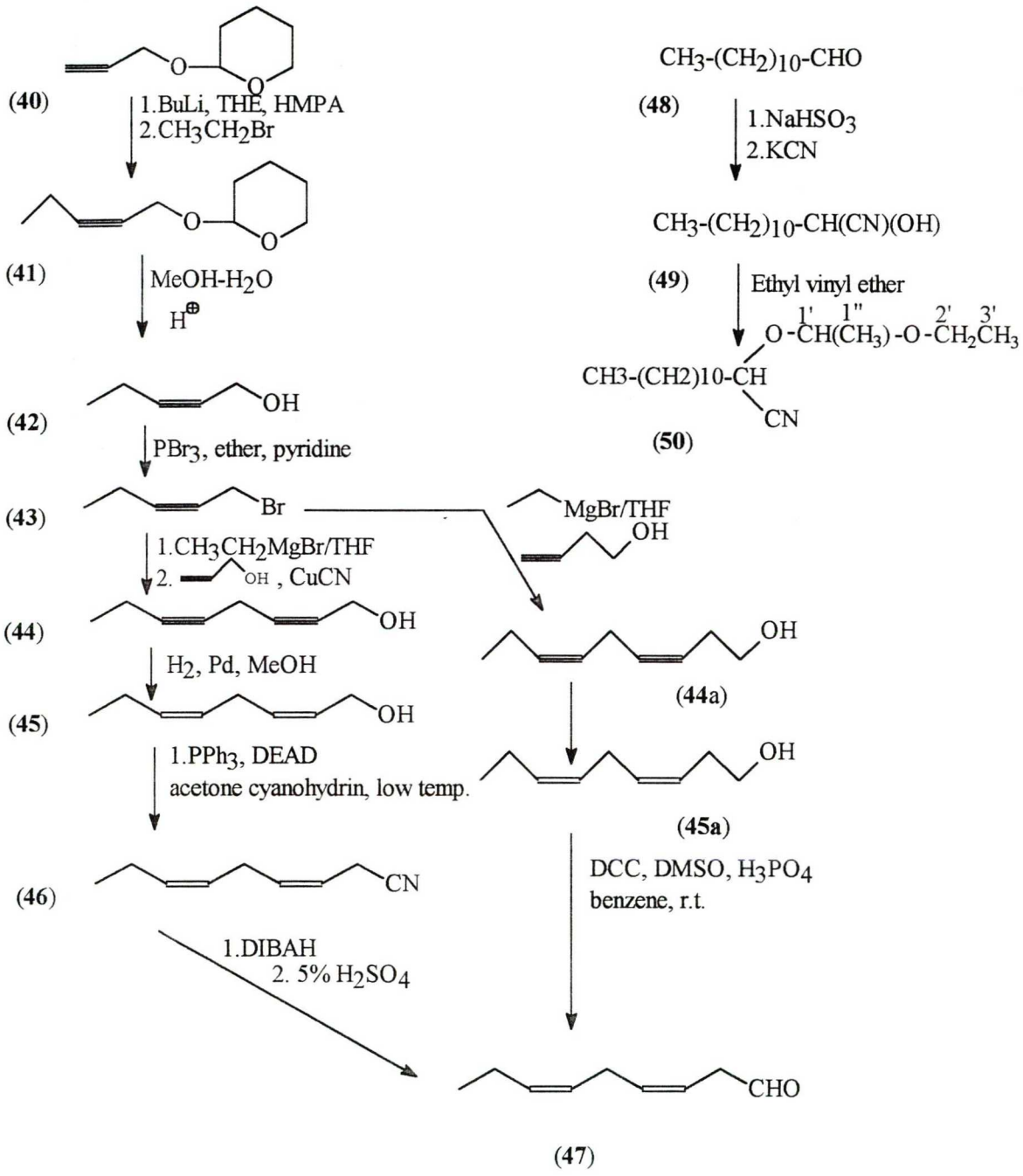
(9S,10R) -epoxide

(Scheme 49)

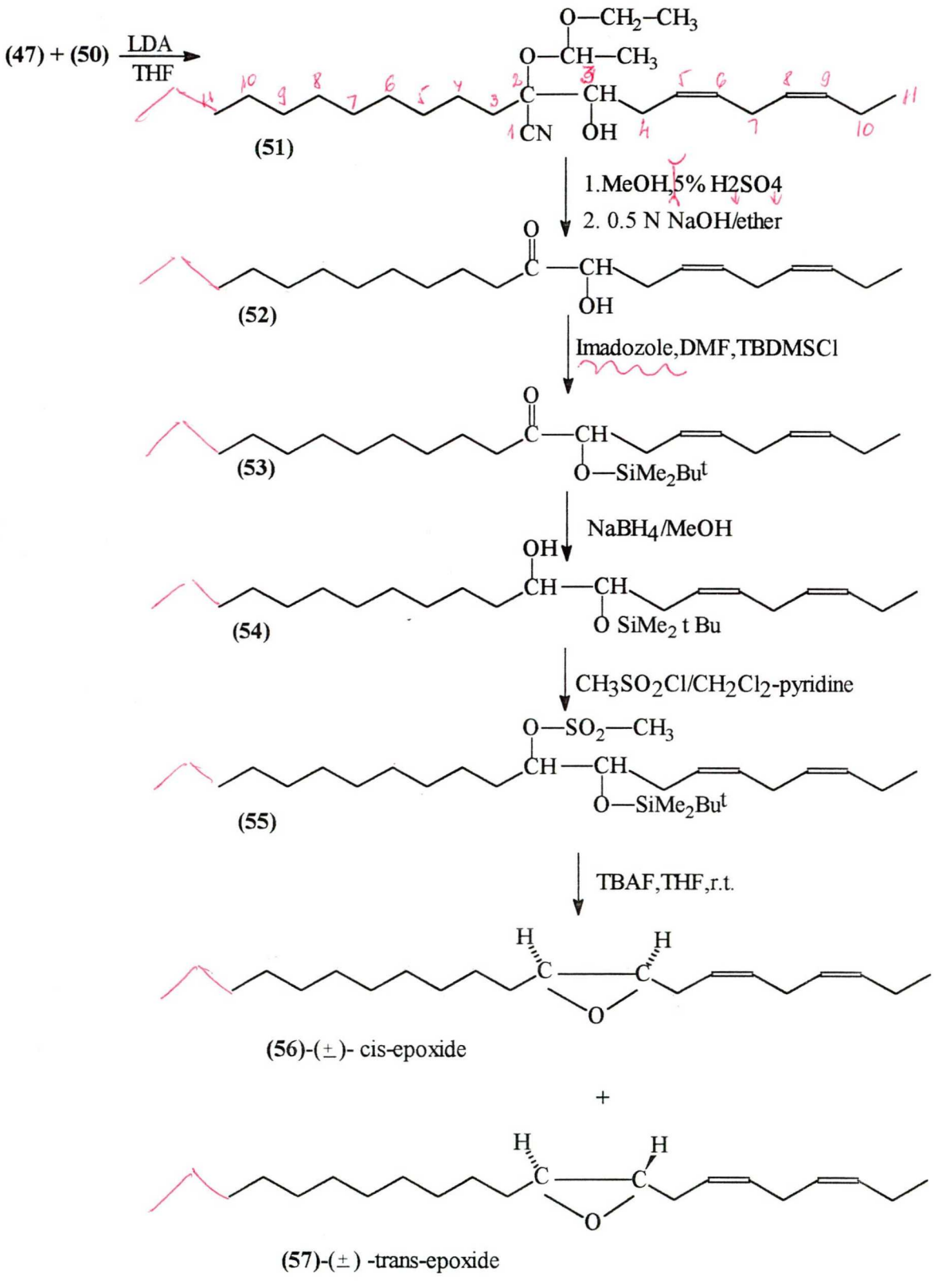
Synthesis of racemic diene epoxide was achieved by Kovalev[31] and the general outline of the synthetic route is shown in (Scheme 50).



(Scheme 50)


(40)
1.BuLi, THE, HMPA
2.CH3CH2Br
(41)
MeOH-H2O
H⊕
(42)
OH
PBr3, ether, pyridine
(43)
Br
1.CH3CH2MgBr/THF
2.
OH , CuCN
(44)
OH
H2, Pd, MeOH
(45)
OH
1.PPh3, DEAD
acetone cyanohydrin, low temp.
(46)
CN
1.DIBAH
2. 5% H2SO4
CHO
(47)
CH3-(CH2)10-CHO
(48)
1.NaHSO3
2.KCN
CH3-(CH2)10-CH(CN)(OH)
(49)
Ethyl vinyl ether
1' 1"
O-CH(CH3)-O-CH2CH3
2' 3'
CH3-(CH2)10-CH
CN
(50)
MgBr/THF
OH
OH
(44a)
OH
(45a)
DCC, DMSO, H3PO4
benzene, r.t.

(Scheme 51)

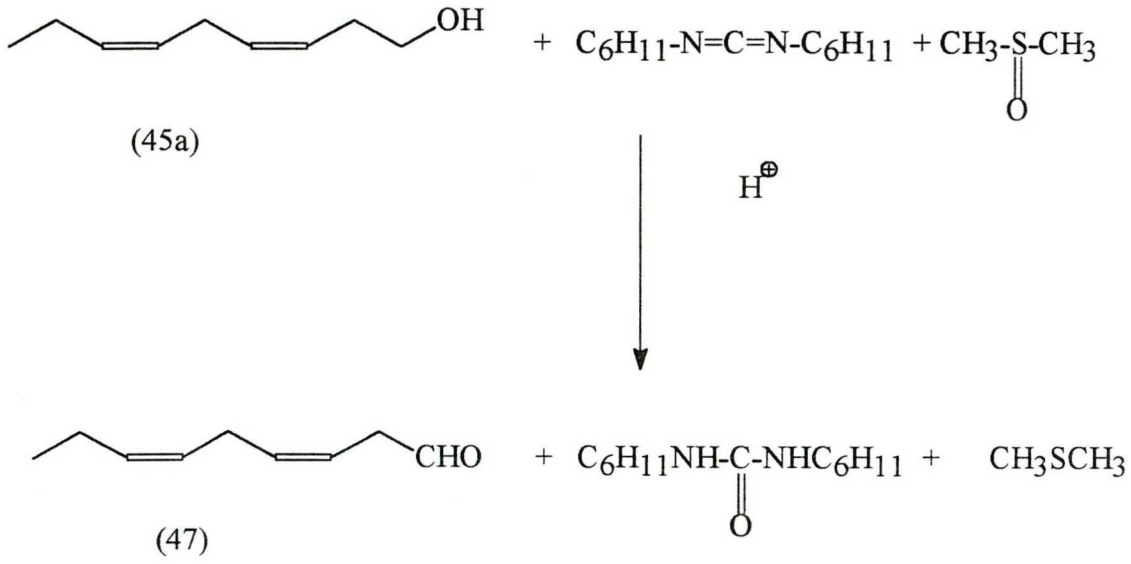

(47) + (50)
LDA
THF
(51)
1.MeOH,5% H2SO4
2. 0.5 N NaOH/ether
(52)
Imadozole,DMF,TBDMSCl
(53)
NaBH4/MeOH
(54)
CH3SO2Cl/CH2Cl2-pyridine
(55)
TBAF,THF,r.t.
(56)-(±)- cis-epoxide
+
(57)-(±) -trans-epoxide

(Scheme 52)

Our synthetic target was the preparation of the diene epoxide by new methodology. The key step of our synthesis was the nucleophilic acylation of homoallylic aldehyde (**47**) by protected cyanohydrin (**50**) (Scheme 52).

The aldehyde intermediate (**47**) was synthesized from the protected propargylic alcohol[98] (**40**), which was reacted with ethyl bromide and butyllithium in THF-HMPA[99] to give (**41**), which was treated with p-toluenesulfonic acid in a mixture of methanol and water to recover acetylenic alcohol (**42**). The corresponding bromide (**43**) was prepared from (**42**) using PBr_3 in ether and pyridine[100]. The Grignard coupling reaction[100,101] of (**43**) with propargyl alcohol-CuCN catalyst in THF gave compound (**44**).Under the same procedure, compound (**44a**) was prepared from (**43**) and 3-butyn-1-ol in THF-HMPA in the presence of CuCl catalyst[102,103]. Semihydrogenation of (**44**) and (**44a**) using (H_2 / Pd-$BaSO_4$ / quinoline) in methanol afforded pure (**Z**, **Z**)-diene alcohols (**45**) and (**45a**), respectively (Scheme 51).

A novel procedure for converting olefinic alcohol (**45**) to the corresponding nitrile (**46**) was elaboreted by us[104], using PPh_3, diethyl azodicarboxylate, and acetone cyanohydrin, at -20 °C. Reduction of the nitrile group in (**46**) by diisobutylaluminum hydride in toluene at -40 °C gave the corresponding imine[105]. Then the hydrolysis of the formed imine by treatment with aqueous acid afforded aldehyde (**47**). Here we achieved only low yield ,probably because of the homoallylic bond migration[105] and the low stability of β,γ- unsaturated aldehyde (**47**). Therefore another procedure was used to synthesized (**47**) (yield 75%). This was achieved by Pfitzner and Moffatt oxidation[106] of compound (**45a**), using dimethyl sulfoxide, dicyclohexylcarbodiimide in the presence of orthophosphoric acid (Scheme 53).



(Scheme 53)

In the preparation of intermediate (**50**), dodecanal (**48**) was reacted with sodium bisulfite and potassium cyanide to give cyanohydrin[107] (**49**), which was reacted with ethyl vinyl ether[108] to yield (**50**) (Scheme 51).

Using Stork's methodology for the reaction of (**50**) and (**47**) in the presence of lithium diisopropylamide in THF-HMPA, under carefully controlled conditions[109] yielded (**51**). In this reaction the protected aldehyde cyanohydrin (**50**) was transformed into ~~their~~ anion with LDA, then addition of aldehyde (**47**) formed the wanted C-C bond by nucleophilic acylation (**51**). The product (**51**) was treated with 5% H_2SO_4 in methanol, to cleave the protection group, then treatment with 0.5N NaOH in ether furnished hydroxy ketone (**52**) in 40 % yield. Protection of the free hydroxyl group in (**52**) with t-butyldimethylsilyl chloride in the presence of imadozole-DMF afforded the coressponding silly ether (**53**). This was converted to epoxide (**56** and **57**), via a three step sequence. First partial reduction of (**53**) with $NaBH_4$ in methanol, then mesylation of the alcohol formed (**54**),using methansulfonyl chloride in methylene chloride and pyridine to give a diasteromeric mixture of (**55**), which was desilylated with tetrabutylammonium flouride in THF[110]. The diene epoxides (**56** and **57**) were identified from NMR spectrum as a mixture of (3**Z**, **6Z**)-9,10-epoxyheneicosadiene cis and trans, in ratio (65:35)(Scheme 52). This identification based on the general information of NMR spectra, that the hydrogen in cis epoxide has higher chemical shift than those of the trans epoxide[111].

EXPERIMENTAL

Instrumentation

Proton nuclear magnetic resonance spectra and ^{13}C nuclear magnetic resonance spectra were recorded with a Varian WXR-400 instrument at 400 and 100 MHz: internal standard TMS. The following abbreviations are used : singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b). Infrared spectra were determined using Nicolet 205 FT.IR spectrometer. Gas chromatographic analysis were conducted on Hewlett-Packard 5890 instrument equipped with a flame -ionization detector and employing a silica capillary coloumn (5m x 0.53 mm ID).

Reagents

Coloumn chromatography was carried out using silica gel 60 (REANAL, HUNGARY). Thin lyaer chromatography was carried out using either aluminium oxide G.(Merck) or silica gel. The following materials were commercially available: benzyl chloride, butyllithium (Merck), triphenylphosphine, diethyl azodicarboxylate, acetone cyanohydrin, propergyl alcohol, 3-butyen-1-ol, palladium on $BaSO_4$ (Aldrich). DIBAH, and HMPA (Fluka).

Purification of solvents.

Diethylether and benzene.

These were dried by storage over sodium.

Pyridine.

This was dried by refluxing and distilling over potassium hydroxide.

HMPA

This was purified by distillation over calacium hydride under reduced pressure , and was then stored over Type 4A molecular sieves.

Dimethylsulphoxide (DMSO).

This was dried overnight over calacium sulphate. The filtered solvent was fractionally distilled over calacium hydride under reduced pressure and was then stored over Type 4A molecular sieves.

Tetrahydrofurane (THF).

This was dried by distillation over calacium hydried or sodium / benzophenone.

Dimethylformamide (DMF).

This was purified by azeotropic distillation with benzene , at atmospheric pressure , then at reduced pressure, B.p. 76 °C / 39 mm Hg.

Dichloromethane.

This was purified by washing with 5% Na_2CO_3, water, dried over calacium chlorde, then distilled B.p. 40 °C .

Methanol.

This was dried by fractional distillation and storage over Type 4A molecular seives, B.p. 65 °C /760 mmHg.

Acetone.

This was purified by refluxing with potassium permanganate. The filtrate dried over anhydrous K_2CO_3, filtered , and distilled, B.p. 56 °C /760 mm Hg, and storaed over Type 4A molecular sieves.

Hexane.

This was dried by distillation over sodium , and storaed over Type 4A molecular sieves.

Purification of reagents.

Diisopropylamine

This was purified by distillation over potassium hydroxide , collected at B.p. 83 °C / 760 mmHg.

Triethylamine.

This was purified by distillation over potassium hydroxide, B.p. 89 °C.

General procedure for benzylation of alcohols

Alcohol (1.0 equivalent) was dissolved in benzyl chloride (1.05 equiv.) with stirring and warming if necessary, and powdered potassium hydroxide (1.25 equiv.) was added into the mixture immersed in 100 °C (oil bath). The resulting suspension was stirred for 30 min. at 100 °C, then cool to room temperature, and the mixture was poured into cold water (20 ml/g alcohol). The organic material was extracted with ether, dried over natrium sulfate, and concentrated in vacuum. The product was purified by distillation, coloumn chromatagraphy or recrystillization, depending upon the mass and poiling point of the residue.

Boiling point data:

3-Benzyloxy-1-propanol	120°C/1 torr
4-Benzyloxy-1-butanol	134-135°C/1.5 torr
5-Benzyloxy-1-pentanol	143-144°C/1 torr
6-Benzyloxy-1-hexanol	154°C/0-8 tor
8-Benzyloxy-1-octanol	179°C/2 torr.

1.6-Dibenzyloxy-hexane

This was prepared according to the general procedure from hexandiol and benzyl chloride. IR(Vmax): 2850, 1500, 1450, 1260, 1100. **^{1}H-NMR(100 MHz; $CDCl_3$)**; 1.3-1.4 (m, 8H, $(CH_2)_4$-); 3.46(m, 4H, 2x-OCH_2-); 4.49(m, 4H, 2x-OCH_2Ph); 7.25-7.40(m, 10H, aromatic protons).

6-Benzyloxy-1-hexanol

This was prepared according to the general procedure from hexandiol and benzyl chloride.IR(Vmax):3400, 1440, 1100, 780, 680. **^{1}H-NMR($CDCl_3$);** 1.31(m, H, OH); 1.3-1.7(m, 8H, 4xCH_2); 3.47(t, 2H, O-CH_2-); 3.63(t, 2H, CH_2-OH); 4.50(s, 2H, OCH_2 Ph); 7.25-7.40(m, 5H, aromatic proton).

General procedure for acylation of alcohols

Alcohol was dissolved in acid anhydride, and the mixture was stirred at right temperature and time after adding the co-reagent.

Working up:

(A): If the co-reagent is potassium hydroxide, the mixture was filtered and concentrated in vacuum. Product was obtained by distillation or coloumn chromatagraphy.

(B): If the co-reagent is pyridine or triethylamine, the mixture was poured into 1N HCl solution and stirred, extracted by ether, and the ether solution was washed with 1N HCl to get rid off pyridine. The solution was neutralized by 5% $NaHCO_3$, washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated in vacuum. Product was obtained by distillation or coloumn chromatagraphy.

(C): If the co-reagent is water. The mixture was poured into cold 30% NaOH solution (3 ml/ml anhydride) with stirring and cooling. After 10 min. stirring, the organic material was extracted with ether and dried over dry potassium carbonate, filtered and the friltrate was concentrated in vacuum. The product was obtained from the residue by distilliation or coloumn chromotagraphy.

1,4-Diacetoxybutane

This was procedured based on the general method. **^{1}H-NMR ($CDCl_3$)**: 1.71(m,4H,-$(CH_2)_2$-); 2.05 (s, 6H,2x -CH_3); 4.10 (m, 4H, 2x -OCH_2-).
^{13}C-NMR($CDCl_3$).: 63.9 (C-1 and C-4); 25.2 (C-2 and C-3); 20.9 (CH_3); 174.14 (C=O). IR (KBr film), ν max; 2850-2950 (-CH_2); 1740 (C=O); 1230 (C-O-C), cm^{-1}.

4-Acetoxy-1-butanol

This was procedured based on the general method. **^{1}H-NMR($CDCl_3$);** 1.30 (m, H, OH); 1.70 (m, 2H, CH_2); 2.05 (s, 3H, CH_3); 3.62 (t, 2H, CH_2OH); 4.10 (m, 2H, OCH_2).

General procedure for preparation of carboxylic acids sodium salt

Sodium metal (1.0 equiv.) was dissolved in water free methanol (50 ml/g), and the carboxylic acid (1.0 equiv.) was added into the stirred mixture. The resulting mixture was concentrated in vacuum to produce solid product of sodium salt of the carboxylic acid, which is used for ester synthesis.

General procedure for esterification of carboxylic acids salts

Aliquat 336 (0.07 ml/g RCOONa) was dissolved in a certain alkylhalogenide (2-5 ml/g RCOONa) and sodium salt of carboxylic acid was added to the solution under vigorous stirring. The resulted suspension was vigorously stirred at 120 ^oC (oil bath) for 5-24 hr. The reaction was followed by TLC and GC analysis. In case of larger amounts of (RCOONa > 500 g), water (0.2 ml/g RCOONa) was added in the 3rd. hour of boiling,and

then it was boiled furtherward. At the end of reaction, the mixture was filtered or separated in case of two phases, and the product was obtained from the reaction mixture by distillation. The unchanged alkylhalogenide can be reobtained during distillation.

Butyl acetate: ($R^1 = CH_3$-; $R^2 = C_4H_9$-)

This was synthesized on the bases of the general procedure from sodium acetate and butyl bromide in 90% yield, B.p. ; 123-125 ^oC.

Butyl propionate: ($R^1 = C_2H_5$-; $R^2 = C_4H_9$-)

This was produced from sodium propionate and butyl bromide in 95% yield, B.p., 144-146 ^oC.

Pentyl acetate: ($R^1 = CH_3$-; $R^2 = C_5H_{11}$-)

This was produced from sodium acetate and pentyl bromide in 95% yield, B.p., 141-143 ^oC.

Pentyl propionate: ($R^1 = C_3H_7$-; $R^2 = C_5H_{11}$-)

This was produced from sodium propionate and pentyl bromide in 85% yield, B.p. 66 ^oC/14 torr.

Butyl-(11-hydroxyundecanoate): (R^1 =HO $(CH_2)_{10}$ -; R^2 =C_4H_9-)

This was produced from sodium salt of 11-hydroxy-undecanoic acid and butyl bromide in 85% yield, B.p 166 ^oC/0.3 torr.

^{1}H-NMR($CDCl_3$) : 0.93 (t,J=7Hz, 3H,-CH_3); 1.25-1.70 (m,20H, 10xCH_2); 2.29 (t,J=7.5 Hz,2H,CH_2C=O); 3,64 (t,J = 6Hz, 2H, CH_2OH); 4.09 (t,J=6Hz, 2H,CH_2OC=O). **^{13}C-NMR** ($CDCl_3$); 174.07 (C-1); 34.42 (C-2); 25.04 (C-3); 25.83 (C-9); 32.08 (C-10); 62.80 (C-11); 64.15 (C-1); 30.77 (C-2); 19.9 (C-3); 13.71 (C-4).

(2E,4E)-Butyl-(2,4-Hexadienoate): R^1 =CH_3CH=CHCH=CH-; R^2 = C_4H_9-)

This was produced from sodium salt of (2E, 4E)-hexadieonic acid and butyl bromide in 90% yield, B.p., 108-110 ^oC/14 torr. ^{1}H - NMR ($CDCl_3$); 0.92 (t, J = 7Hz, 3H, -CH_3); 1.2-1.8 (m, 4H, 2xCH_2); 1.83 (dd, J_1= 5Hz, J_2 = 0.5 Hz, 3H, CH_3C=); 4.14 (t, J=6Hz,2H, -OCH_2); 5.80 (dd, J_1=15 Hz, J_2=1 Hz, H, =C^2HC=O);
6.11 (m,H,-C^5H =); 6.24 (m,H, = C^4H -); 7.28 (dd + I.r., J_1=15 Hz, J_2=10 Hz,
H, -C^3H =). **^{13}C - NMR($CDCl_3$)**: 167.28 (C-1); 119.25 (C-2); 144.83 (C-3); 129.97 (C-4); 139.00 (C-5); 18.59 (C-6); 64.06 (C-1′); 30.91 (C-2′); 19.27 (C-3′);
13.76 (C-4′).

quantity ?

General procedure for preparation of 1,1-dichloro-alkenes:

Triphenyl phosphine (4.0 equiv.) was dissolved in a mixture of water and alcohol free dichloromethane (1.5 ml/g PPh_3),and the aldehyde $CH_3(CH_2)n$ CHO (1.0 equiv.), and CCl_4(2.0 equiv.) were added to the solution, The resulting mixture was stirred at 25 ^oC for 2 hours. The product was purified by semi-dry column chromatagraphy[112,113], but in case of large amount, the product 1,1-dichloro-1-alkene were distilled. The reaction mixture was concentrated in vacuum, and the residue was suspended in hexane (1.0 ml/g), the precipitate was filtered off and the product was fractionally distilled.

1,1-Dichloro-1-hexene (n=3):

This is prepared from pentanal in 60% yield. **^{1}H-NMR ($CDCl_3$)**; 5.86 (t, J = 7 Hz, H, -CH=); 2.14 (m,2H -CH_2C=); 1.30 (br.s., 4H, -$(CH_2)_2$-); 0.80 (t, J= 6Hz, 3H, -CH_3). **^{13}C -NMR ($CDCl_3$):** 119.5 (C-1); 130.11 (C-2); 28.2 (C-3); 29.3 (C-4); 32.7 (C-5); 14.1 (C-6).

1,1-Dichloro-1-octene (n=5):

This is prepared from heptanal in 70% yield. **^{1}H-NMR($CDCl_3$):** 5.87 (t, J= 7 Hz, H, -CH=); 2.10 (m, 2H, -CH_2C=); 1.30 (br.s., 8H, -$(CH_2)_4$-); 0.85 (t, J= 6Hz, 3H, -CH_3). **^{13}C -NMR ($CDCl_3$)**: 119.65 (C-1); 130.10 (C-2); 28.2 (C-3); 29.2, 29.5 (C-4,5); 31.9 (C-6); 27.7 (C-7); 14.0 (C-8).

1,1-Dichloro-1-nonene(n=6):

This is prepared from octanal in 65% yield. **^{1}H-NMR ($CDCl_3$)**: 5.89 (t, J=7Hz, H, -CH=); 2.12 (m, 2H, -CH_2C=); 1.31 (br.s. 10H, -$(CH_2)_5$-); 0.80 (t, J= 6 Hz, 3H, -CH_3). **^{13}C -NMR ($CDCl_3$):** 119.86 (C-1); 130.08 (C-2); 28.2 (C-3); 29.11, 29.27, 29.67 (C-4,5,6); 31.88 (C-7); 22.71 (C-8); 14.09 (C-9).

General procedure for preparation of distillable-1-chloro-alkynes

1,1-Dichloro-alkene (1.0 equiv.) was mixed with well powdered potassium hydroxide (1.0 equiv.), and with Aliquat 336 phase transfer catalyst (0.2 ml/g 1,1-dichloro-alkene). The mixture was stirred at 90 ^oC for 2 hours. The product was purified by distilliation.

1-Chloro-1-hexyne (n=3)

This is prepared from 1,1-dichloro-1-hexene in 80% yield, B.p. 115-117 °C/760 torr (lit [114]., 115-116 °C/760 torr). **^{1}H-NMR ($CDCCl_3$)**: 2.15 (m,2H, -$CH_2C\equiv$); 1.2-1.6 (br.s., 4H, -$(CH_2)_2$-); 0.9 (t, J= 7Hz,3H, -CH_3). **^{13}C-NMR ($CDCl_3$):** 56.93 (C-1); 69.73 (C-2); 18.46 (C-3); 30.47 (C-4); 21.91 (C-5); 13.56 (C-6).

1-Chloro-1-octyne (n=5)

This is prepared from 1,1-dichloro-1-nonene in 70% yield, B.p. 70 °C/20 torr, (lit [70]., 61-62 °C/torr). **^{1}H-NMR ($CDCl_3$):** 2.14 (m,2H, -$CH_2C\equiv$); 1.2-1.6 (br.s., 8H, -$(CH_2)_4$-); 0.9 (t, J= 7Hz, 3H, -CH_3). **^{13}C-NMR ($CDCl_3$)**: 56.89 (C-1); 69.68 (C-2); 18.51 (C-3); 28.80 (C-4); 28.9, 28.4 (C-5,6); 22.5 (C-7); 14.10 (C-8).

1-Chloro-1-nonyne (n=6)

This is prepared from 1,1-dichloro-1-nonene in 80% yield, B.p., 82 °C/20 torr (lit [115]., 75-80 °C/17.5 torr). **^{1}H-NMR ($CDCl_3$):** 2.18 (t, J= 4Hz,2h, -$CH_2C\equiv$); 1.2-1.55 (br.s., 10H, -$(CH_2)_5$-); 0.85 (t, J=7Hz, 3H, -CH_3); **^{13}C-NMR ($CDCl_3$)**: 56.91 (C-1); 69.8 (C-2); 18.75 (C-3); 28.7 (C-4); 28.9 (C-5); 28.38 (C-6); 31.7 (C-7); 22.6(C-8); 14.08 (C-9).

Gas chromatography analysis data

The analysis was made on HP.5890 series II equipment with HP-1 capillary coloumn 5m x 0.53 mm i.d.; df=2.65/um, and FID detector. The temperature of the injector was 200 °C and for the detector was 280 °C. Nitrogen was the carrier gas (13 ml/min.); split = 1:10. Retention times are given in minute.

Benzylation: retention time(min.)

Coloumn temperature, after 2 min. at 100 °C was heated to 250 °C at 10 °C/min., speed. Table (**31**).

Table (**31**)

n	$HO(CH_2)_nOH$	$HO(CH_2)_nOBn$	$BnO(CH_2)nOBn$
3	a	3.5	6.2
4	a	5.1	11.3
5	a	6.2	12.2
6	0.9	7.3	13.1
8	2.9	9.6	14.9

a = product come together with solvent.

Benzylchloride 0.54 min.

Acylation: Retention time(min)

Coloumn temperature, after 2 min. at 50 °C, was heated to 250 °C at 10 °C/min, speed. Table **(32)**.

Table **(32)**.

n	X	$HO(CH_2)_4OH$	$HO(CH_2)_nOX$	$XO(CH_2)_nOX$
4	Ac	2.4	4.3	5.7
4	EtCO	2.4	5.3	6.9
6	Ac	4.7	6.0	7.0
6	EtCO	4.7	6.7	8.2
8	Ac	6.5	7.4	8.3
8	EtCO	6.5	8.0	9.3

Acetic anhydride 0.45 min.; Propionic anhydride 1.28 min.

1-Chloro-1-alkynes: Retention time

The analysis was made by Perkin-Elmer F22 equipment SPB-1 (SUPELCO) capillary coloumn 60m x 0.25 mm i.d. and FID detector. The temperature of the injector and the detector was 240 °C, temperature of the coloumn was 90 °C, for 8 min., then it was heated at 8 °C/min. speed to 240 °C. The carrier gas was nitrogen (2 ml/min.; split = 1:100).Retention times are presented in Table **(33)**.

Table **(33)**.: Retention time(min.) of $CH_3(CH_2)_n$-Z

Z	n=3	n=5	n=6
CHO	6	11	13
$CH=CCl_2$	13	18	21
C≡CH	4	8	10
C≡CCl	7	14	16

General procedure for reaction of carbonyl compound with butyllithium

To a solution of carbonyl compound (1.0 eqiv.; **21a, c, e, 24a**)in dry THF (40 ml /gm **21** or **24**), butyllithium (1.0 equiv. 1,6 N in hexane) was added dropwise at 0°C. The resulted mixture was stirred for 3 hrs at room temperature and poured into saturated ammonium chloride solution (4 ml /ml butyllithium). After extraction with ether, the organic layer was successively washed with water, 5% $NaHCO_3$›and brine. Drying over Na_2SO_4, the solvent was concentrated and the product was isolated by column chromatography.

5-Hydroxynonane(27a).

This was synthesized according to the general procedure from pentanal(**21a**).The product was isolated by column chromatography(benzene/acetone 10:2) in 60 % yield
νmax(KBr); 3400(OH) cm^{-1}.^{1}**H-NMR(CDCl$_3$)**: 0.91(t, J=6 Hz, 6H, 2x-CH_3);1.2-1.5(m, 12H, 6x -CH_2-); 3.59 (m, H, -CH-O). ^{13}C-NMR($CDCl_3$): 14.11(C-1, C-9);57.18(C-4, C-6); 27.87(C-3, C-7); 22.80(C-2, C-8);
72.02(C-5).

5-Hydroxy-5-methyldecane (27d)

This was synthesized according to the general procedure from 2-heptanone (**24a**). The product was isolated by column chromatography(benzene/acetone 10:2) in 40 % yield.ν max (KBr) ;3420,1463,1380 cm^{-1}. **^{1}H-NMR(CDCl$_3$)**; 0.89+0.91(s; 6H,-C^1H_3 ,- $C^{10}H_3$); 1.15 (s,3H,-$C^{5'}H_3$); 1.25-1.50(m,14H,7x-CH_2-). **^{13}C-NMR($CDCl_3$);** 14.08(C-1); 23.22(C-2); 23.59(C-3); 41.59(C-4); 72.81(C-5); 26.97(C-5′); 41.84(C-6); 22.68(C-7); 32.47(C-8); 22.68(C-9); 14.13(C-10).

*Isopropyltriphenylphosphonium bromide(**22a**)*

Isopropyl bromide (6.2 gm;0.05 mol) was refluxed with triphenylphosphin(12.2 gm;0.047 mol) for 48 hrs. White precipitate formed as isopropyl triphenylphosphonium bromide,white crystals from ether-ethanol, m.p 238°C (lit.[16]238-239°C).ν max(KBr);1580, 1430, 1100, 1000, 680 cm $^{-1}$ **^{1}H-NMR($CDCl_3$)**; 1.35(dd, 6H, 2x -CH_3); 5.35(m, H, -CH-); 7.7-8.0 (m, 15H, 3Ph).

*Isobutyltriphenylphosphonium bromide(**22b**).*

Isobutyl bromide (3.14 gm;0.023mol) was refluxed with triphenylphosphine(6.0 gm;0.023mol) for 24 hrs.white precipitate formed. The product isolated as white crystals(ether-ethanol), m.p, 225-226 °C (lit[15]. 225-227 °C).

General procedure for the Wittig coupling

To the suspension of phosphonium salt (1.0 eqiv.) in dry THF(10 ml/gm salt) butyllithium (1.0 equiv.;1.6 N in hexane) was added dropwise at 0 °C. The resulted suspension was stirred at 0°C for 30 min., then the carbonyl compound(1.0 equiv.; **21**or **24** in dry THE (3ml/gm **21** or **24**) was added slowely at -78 °C. The mixture was stirred at room temperature overnight. Dilute with hexane (20ml /gm phosphonium salt), filtered, and the filterate concentrated in vacuo.The residue was dissolved in ether and the products were separated by column chromatography.

*1-(Cyclohex-2-enyl)-2-methyl-2-propene(**23d**).*

This was synthesized according to the general procedure by the reaction of 2-cyclohexene-1-carboxaldehyde (**21d**) and the phosphorane generated from isopropyl triphenylphosphonium bromide. The product was isolated by two flash chromatography on silica gel,70-230 mesh,eluent:ether /pentane (1:10) and 230-400 mesh ,eluent: ether /pentane (1:80) provide olefin compound as colourless oil in 40 % yield. ν_{max} (KBr);1380,1440,1650 cm^{-1}. **^{1}H-NMR ($CDCl_3$)** ; 1.3-1.4 (m,4H,-$C^{5'}H_2$ - $C^{6'}H_2$-);1.63-1.69 (m, 6H, 2x-CH_3);2.05(m, 2H, -$C^{4'}H_2$-); 3.47(m,H,-$C^{1'}$H-); 5.02(m, H,- =$C^{2'}$ H-); 5.05(m, H, =$C^{3'}$H-); 5.67(m, H, =C^{1}H-). **^{13}C-NMR(CDCl3)** ; 126.82 (C-1); 130.29 (C-2); 17.83 and 25.79 (C-3 andC-2″); 31.86, 29.06 and 24.09 (C-4′,C-5′, and C-6′); 32.81 (C-1′); 126.8 (C-3′); 130.28 (C-2′).

*2-Methyl-1-phenyl-1-propene(**23j**)*

This was synthesized according to the general procedure from the reaction of benzaldehyde(**21e**) and the phosphorane generated from isopropyltriphenylphosphonium bromide.The product was isolated by two flash chromatography on silica gel,70-230 mesh, eluent: ether /pentane(1:10) and 230-400 mesh, eluent, ether /pentane (1:80) provide olefin compound as colourless oil in 30 % yield. ν max(KBr); 1650, 1560, 1480, 1430 cm^{-1}
^{1}H-NMR($CDCl_3$);1.86,1.90(ss, 2x3H, 2x-CH_3); 6.27(s, H, -CH=); 7.17-7.31(m, 5H, aromatic proton).

*6-Oxo-8-methyl-7-tridecene(**25a**)*[116]

This was synthesized according to the general procedure from 2-heptanone(**24a**) and the phosphorane generated from isopropyl and isobutyltriphenylphosphonium bromide in 50 % and 45 % yields, respectively. The product was isolated by flash chromatography,eluent:ether /pentane (1:10). ν max(KBr); 1680,1616(-CO-C=C-) cm^{-1}.
^{1}H-NMR($CDCl_3$) ; 0.89(t, J=7Hz , 2x3H, -C^1H_3 and -$C^{13}H_3$); 1.2-1.37(m, 8H, -C^2H_2-C^3H_2- and -$C^{11}H_2$-$C^{12}H_2$-); 1.58(m, 2H, -C^4H_2-); 1.44(m, 2H, -$C^{10}H_2$-); 1.86(s, 3H, =C-C^8H_3); 2.39(m, 2H, O=C-C^5H_2-); 2.57(m, 2H, =C-C^9H_3-);6.04(s, H, =CH-).
^{13}C-NMR(CDCL3); 14.01(C-1); 22.55 (C-2); 31.50 (C-3); 23.97 (C-4); 44.39 (C-5); 201.05 (C-6); 123.69 (C-7); 159.29 (C-8); 33.70 (C-9); 27.92 (C-10); 31.99 (C-11); 22.53 (C-12); 13.96 (C-13); 25.44 (C-8′) .

*2-Cyclopentyliden cyclopentanone (**25b**).*[117]

This was synthesized according to the general procedure from cyclopentanone (**24c**) and the phosphorane (**22**) generated from isopropyl or isobutyl triphenylphosphonium bromide in 40 % and 35 % yield,respectively. The product was isolated by column chromatography (benzene /acetone 10:1) to give colourless oil.ν max (KBr):1706,1635 cm^{-1}. **^{1}H-NMR ($CDCl_3$)** ; 1.65-1.77(m, 4H, -$C^{4'}H_2$-$C^{3'}H_2$-);1.92 (m,2H,-C^4H_2-); 2.29(m, 2H, -$C^{2'}H_2$-$C^{1'}$=); 2.31(t, J=6Hz, 2H, -C^5H_2-C=O); 2.54 (m, 2H, -C^3H_2-C^2=) ; 2.79(m, 2H, -$C^{5'}H_2$-$C^{1'}$ =). **^{13}C-NMR($CDCl_3$)** ; 204.59(C-1); 127.93(C-2); 29.50(C-3); 20.06(C-4); 39.79 (C-5); 158.79 (C-1′); 34.30 (C-2′); 25.21 (C-3′); 26.92 (C-4′); 32.55 (C-5′).

2-Cyclohexyliden cyclohexanone (25c)[118].

This was synthesized according to the general procedure from cyclohexanone(**24d**) and the phosphorane(**22**) generated from isopropyl or isobutyl triphenylphosphonium bromide in 10 % yield.The product was isolated by column chromatography benzene /acetone (10:1).ν max (KBr); 1700,1680,1430 cm^{-1}.
^{13}C-NMR($CDCl_3$) ; 206.56 (C-1); 130.80 (C-2); 43.53 (C-6); 146.46 (C-1′).

2-(Cyclohex-1-enyl)-cyclohexanone(32)[119]

This compound was isolated with 10 % yield during the formation of compound (5c). **^{1}H-NMR($CDCl_3$)** ;2.88 (m, H, -CH-); 5.43 (m, H, -CH=). **^{13}C-NMR($CDCl_3$)**; 211.76 (C-1); 42.13 (C-6) ; 58.75 (C-2); 135.83 (C-1′); 123.65 (C-2′).

2,6,9-Trimethyl-2,8-decadiene (29).

This was synthesized according to the general procedure from citronellal (**28**) and the phosphorane generated from isopropyl triphenylphosphonium bromide. The product was isolated by two flash chromatography on silica gel 70-230 mesh, eluent:ether /pentane (1:10) and 230-400 mesh, eluent: ether /pentane (1:80) providing olefin compound as colourless oil in 10 % yield. ν max(KBr); 1450,1380,760 cm^{-1} .**^{1}H-NMR($CDCl_3$)** ; 1.59 and 1.68 (s+s, 2x3H, $(CH_3)_2C=$); 1.61 and 1.70 (s+s, 2x3H, $(CH_3)_2C=$); 1.75(m, 2H, $=C^3\text{-}C^4H_2\text{-}$); 2.05(m, 2H, $=C^8\text{-}C^7H_2\text{-}$); 1.44 (m, H, C^6H-); 1.13-1.34(m, 2H, $-C^5H_2\text{-}$); 5.10-5.18(m, 2H, $-C^3H= + -C^8H=$).

9-Formyl-2,6,10,14-tetramethyl-pentadeca-2,8,13-triene(30)

This compound was synthesized from the reaction of citronellal (**28**) and the phosphorane generated from isopropyl or isobutyl triphenylphosphonium bromide. The product was isolated by column chromatography ,benzene /acetone (10:1) as colourless oil in 10 % yield. **^{1}H-NMR($CDCl_3$)**; 0.94 (m, 3H, $-C^{6'}H_3$); 1.15(m, 3H, $-C^{10'}H_3$); 1.22 and 1.33 (m, 2H, $-C^5H_2\text{-}$); 1,53 and 1.75 (m, 2H, $-C^{11}H_2\text{-}$); 1.60 and 1.66(m, 12H, $2x(CH_3)_2C=$); 1.87 (m, 2H, $-C^{12}H_2\text{-}$); 1.98 (m, 2H, $-C^4H_2\text{-}$); 2.26 and 2.33 (m, 2H, $-C^7H_2\text{-}C=$); 2.03 (m,

H, -C^6H-); 2.69 (m, H, -C^{10}H-); 5.09 (m, 2H, -C^3H= + -C^{13}H=); 6.42 (m, H, -C^8H=); 9.35 (t, J=1.5Hz, H, -CHO). **^{13}C-NMR($CDCl_3$)** ; 25.76 (C-1); 131.55 (C-2); 124.32 (C-3); 25.45 (C-4); 36.81 (C-5); 30.09 (C-6); 36.19 (C-7); 135.33 (C-8); 147.45(C-9); 32.82 (C-10); 36.81(C-11); 25.45 (C-12); 124.32 (C-13); 131.55 (C-14); 25.76 (C-15); 17.68 (C-2′ and C-14′);19.05 (C-6′ and C-10′); 195.01(CHO).

*8-Hydroxy-9-hydroxymethyl-2,6,10,14-tetramethyl-pentadeca-2,13-diene(**31**)*

This was synthesized in 10 % yield during the formation of compound (**30**).The product was isolated by column chromatography,benzene/acetone (10:1).
^{1}H-NMR($CDCl_3$); 0,86(m,3H,-$C^{10'}H_3$); 0.92(m,3H,-$C^{6'}H_3$); 1.25-1.32(m,2H,-C^5H_2-); 1.28-1.55 (m, 2H, -C^7H_2-); 1.30-1.45 (m, 2H, -$C^{11}H_2$-); 1.38 (m, H, -C^9H-); 1.61 (m, 6H,-$C^{2'}H_3$ + -$C^{14'}H_3$); 1.66 (m, H, -C_{10}H-); 1.69 (m, 6H, -C^1H_3 + -$C^{15}H_3$); 1.70 (m, H, -C_6H-); 2.00 (m, 2H, -C^4H_2-); 2.02 (m, 2H, -$C^{12}H_2$-); 3.81 and 3.87(m, 2H, -$C^{9'}H_2$-); 3.95 m, H, -C^8H-); 5.09 and 5.10 (m, 2H, =C^3H + -C^{13}H=). **^{13}C-NMR($CDCl_3$)**; 25.73 (C-1); 131.38 and 131.66 (C-2 and C-14); 124.54 and 124.74 (C-3 andC-13); 25.52 (C-4); 38.15(C-5); 31.24(C-6); 43.61 (C-7); 72.60 (C-8); 49.26 (C-9); 28.71 (C-10); 35.34 (C-11); 25.80(C-12); 25.73 (C-15); 17.69 (C-14′); 15.72 (C-10′); 19.06 (C-6′) ; 17.69 (C-2′); 62.42(C-9′).

*Isopropyl diphenylphosphine oxide (**26 a**)*[120]

To a suspension of isopropyl triphenylphosphonium bromide(0.3 gm;0.0007 mol) in benzene(10 ml),30 % NaOH aqueous solution (4 ml) was added.The resulting mixture was refluxed for 2 hrs. After cooling,the benzene was evaporated and the residue was extracted with chloroform, drying over Na_2SO_4,the filtrate was concentrated in vacuo to produce white powder in 80 % yield. **^{1}H-NMR($CDCl_3$)** ; 1.196 (d, J=17Hz, J_{PH}=16.2Hz, 3H, -CH_3); 1.179(d, J=17Hz, J_{PH}=16.2Hz, 3H, -CH_3); 2.54(m, H, J_{PH}=6.3Hz, -CH-P); 7.35-7.75(m, 10H, aromatic protons). **^{13}C-NMR($CDCl_3$)** ; 27.10(C-1, $J_{C(1)P}$=72.73 Hz); 15.27(C-2 + C-1″, $J_{C(2)P}$=17.96Hz); 132.27(C-1′, $J_{C(1')P}$=94.6Hz); 131.02(C-2′ +C-6′; $J_{C(2'+6')P}$=8.5Hz); 128.54(C-3′+C-5′;$J_{C(3'+5')P}$=11.3Hz); 131.47(C-4′,$J_{C(4')P}$=2.7Hz).

*1-Methyl propyl diphenylphosphine oxide (**26 b**).*[121]

This was formed from isobutyl triphenylphosphonium bromide in the same procedure as described in(6a). **^{1}H-NMR($CDCl_3$)**; 0.975 (t, J=7Hz, 3H, $-CH_3$); 1.17(dd, J=11.5Hz, 3H, $-C^{1''}H_3$); 1,46 and 1.73(m, 2H, $-CH_2$); 2.27(m, H, -CH-); 7.4-7.55 (m, 10H, aromatic protons). **^{13}C-NMR($CDCl_3$)**; 33.7 (C-1, $J_{C(1)P}$=72.3Hz); 22.06 (C-2, $J_{C(2)P}$=1.6Hz); 12.25 (C-3, $J_{C(3)P}$=13.3Hz); 11.5(C-1″, $J_{C(1)P}$=2.5Hz); 132.3 (C-1′, $J_{C(1')P}$=94.4Hz); 130.94 (C-2′ +C-6′, $J_{C(2'+6')P}$=8.6Hz); 128.5(C-3′+C-5′, $J_{C(3'+5')P}$=11.2Hz); 131.4 (C-4′, $J_{C(4')P}$=2.7Hz).

Gas chromatography data.

The gas chromatagraphy analysis were performed by HP-5890 series 11 equipment using capillary coloumn (HP-1; 5m x 0.53 mm i.d; df=2.65 μm),and FID detector. Temperature of injector was 200°C,and the detector 280°C. Temperature of coloumn was 100°C for 2 min.,then heating for 250°C with 10°C / min. Carrier; N_2 (13 ml/ min., split=1:10) .

Time of retention (min.):

21,1.1; **21e**, 1.5; **28**, 0.95; **23e**, 0.92; **23i**; 1.72; **29**, 1.75; **25a**, 13.88; **30**, 10.3; **26b**, 11.0; **26a**, 10.26; **27b**, 3.47; **31**, 12.57; (Temperature of coloumn was 50°C for 2 min.); **25c**, 9.63; **23g**, 3.213.

General procedure for preparation of unsaturated nitriles.

To a stirred solution of triphenylphosphin(1.0 g;3.8 mmol) in dry ether(10 ml) was added dropwise diethyl azodicarboxylate (0.66 gm; 3.8 mmol) at -20 °C, under nitrogen. The resulting mixture was stirred for 20 min. under cooling,then alcohol (2.5 mmol) was added dropwise at -20 °C. After stirring for 20 min. at -20 °C, a solution of acetone cyanohydrin(0.32 g;3.75 mmol) in dry ether(1.0 ml) was added slowly and the mixture was stirred at this temperature for 4 hours.The reaction mixture was allowed to warm to r.t. and stirred for the time indicated in Table. The white precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (hexane:acetone 10:0.5) to afford pure nitriles (Table **28**,entries 1-5).

*(Z,Z)-Nona-3,6-dienenitrile.(Table **28**,entry 1)*

This was prepared by the general procedure from 2,5-octadiene-1-ol.

GC: R_t=4.96 min.

^{1}H-NMR($CDCl_3$) ; 0.99 (t, 3H, J=7Hz, CH_3); 2.07(m, 2H, CH_2); 2.89 (m, 2H, CH_2); 3.12 (dt, 2H, J=7Hz, CH_2); 5.25-5.75 (m, 4H, 2CH=CH). **^{13}C-NMR($CDCl_3$)** ; 14.14(C-9); 15.59 (C-8); 20.63 (C-2); 25.51 (C-5); 118.51 (C-N); 124.936 (C-7 and C-6); 133.34 (C-4); 134 (C-3).

*(E,E)-Hepta-3,5-dienenitrile.(Table **28** ,entry 2)*

This was prepared according to the general procedure from 2,4-hexadiene-1-ol

GC: R_t= 2.55 min.

^{1}H-NMR($CDCl_3$); 1.77(dm, 3H, J=6.5Hz, CH_3); 3.14(dm, 2H, J=6Hz, CH_2); 5.4(dt, 1H, J=15 and 6Hz,=CH); 5.77(dq, 1H, J=4.5 and 7Hz, =CH); 6.04 (ddq, 1H, J=15.10 and 2Hz, =CH); 6.33(ddt, 1H, J=15.10 and 1Hz, =CH). **^{13}C-NMR($CDCl_3$)** ;18.14(C-7); 20.35(C-2); 119.14(C-N); 127.95(C-5); 129.66(C-4); 131.49(C-6); 134.98(C-3).

*(Z)-Tridec-9-enenitrile.(Table **28** , entry 3)*

This was prepared according to the general procedure from **Z**-9-octadiene-1-ol.

GC: R_t=5.44 min.

^{1}H-NMR($CDCl_3$) ;0.9(t, 3H, J=6Hz, CH_3); 1.37(m, 2H, CH_2); 1.25-1.5 (m, 8H, $4CH_2$); 1.65 (m, 2H, CH_2); 2.0 (m, 2H, CH_2); 2.35 (t, 2H, J=7Hz, CH_2); 5.36 (m, 2H, CH=CH). **^{13}C-NMR($CDCl_3$)** ; 13.82 (C-13); 17.13 (C-12); 22.89 (C-11); 25.37 (C-5); 27.11(C-4); 28.65 (C-6); 28.67 (C-3); 28.92 (C-2); 29.31(C-7); 29.58 (C-8); 119.84 (C-N); 129.77 (C-10); 129.87 (C-9).

*(E,E)-Trideca-9,11-dienenitrile.(Table **28** , entry 4).*

This was prepared according to the general procedure from **Z,Z**-8,10-dodcadiene-1-ol.

GC:R_t= 6.15 min.

^{1}H-NMR($CDCl_3$); 1.25-1.5(m, 8H, $4CH_2$); 1.65 (m, 2H, CH_2); 1.73 (d, 3H, J=7Hz, CH_3); 2.05 (m, 2H, CH_2); 2.33(t, 2H, J=7Hz, CH_2); 5.48-5.65 and 5.95-6.06(m,-CH=CH-CH=CH-). **^{13}C-NMR($CDCl_3$)** ; 13.82 (C-13); 17.12 (C-5); 18.01 (C-4); 25.35 (C-5); 28.61 (C-3); 28.79 (C-2); 29.24 (C-7); 32.44 (C-8); 119.83 (C-N); 28.65 (C-6); 126.87 (C-11); 130.42 (C-10); 131.62 (C-9); 131.81 (C-12).

General procedure for conversion of β-acetylenic alcohols to nitriles.

To a stirred solution of triphenylphosphin (1.0 g; 3.8 mmol) in dry ether (10 ml) was added dropwise diethyl azodicarboxylate (0.66 g; 3.88 mmol) at -20°C, under N_2.The resulting mixture was stirred for 20 min under cooling, and then the alcohol (2.5 mmol) was added dropwise at -20°C. After stirring for 1 hr at -20°C, a solution of acetone cyanohydrin (0.32 g; 3.75 mmol) in dry ether (2 ml) was added slowly and the mixture was stirred at this temperature for 4 hr.The reaction mixture was allowed to warm to room temperature and stirred overnight. The white precipitate was filtered and the filtrate was concentrated in vacuo.The residue was purified by coloumn chromotography (hexane;acetone 2:1) to afford pure nitriles (Table **29**).

*3-Tridecynenitrile.(Table **29** , entry 1)*

GC:Rt= 5.87 min.

^{1}H-NMR ($CDCl_3$):0.89 (t, 3H, J=7Hz, CH_3); 1.2-1.4 (m, 12H ,$6xCH_2$); 1.48 (m, 2H, CH_2); 2.16 (tt, 2H, J=7.1+2.5Hz, CH_2-C≡C); 3.31 (t, 2H, J=2.5Hz, C≡C-CH_2).

^{13}C-NMR ($CDCl_3$): 9.30 (C-2); 14.12 (C-13); 18.51 (C-5); 22.68 (C-12); 28.26 (C-8); 28.82 (C-9); 29.10 (C-6); 29.28 (C-7); 29.46 (C-10); 31.87 (C-11); 66.57 (C-3); 84.68 (C-4); 115.09 (C-1).

*3-Dodecynenitrile.(Table **29** ,entry 2)*

GC: Rt= 4.56 min

^{1}H-NMR ($CDCl_3$): 0.89 (t, 3H, J=7Hz, CH_3); 1.2-1.4 (m, 10H, 5xCH_2); 1.48 (tt, 2H, CH_2); 2.16 (tt, 2H, J=7.1+2.5Hz, CH_2-C≡C); 3.30 (t, 2H, J=2.5Hz, C≡C-CH_2).

^{13}C-NMR ($CDCl_3$): 9.26 (C-2); 14.11 (C-12); 18.51 (C-5); 22.66 (C-11); 28.25 (C-8); 28.82 (C-9); 29.06 (C-6); 29.17 (C-7); 31.83 (C-10); 68.58 (C-3); 84.65 (C-4); 115.08 (C-1).

*3-Nonynenitrile.(Table **29** , entry3).*

GC: Rt= 1.12 min.

^{1}H-NMR ($CDCl_3$): 0.88 (t, 3H, J=7Hz, CH_3); 1.2-1.4 (m, 4H, 2xCH_2); 1.48 (tt, 2H, CH_2); 2.16 (tt, 2H, J=7.1+2.5 Hz, CH_2-C≡C); 3.29 (t, 2H, J=2.5Hz, C≡C-CH_2).

^{13}C-NMR ($CDCl_3$): 9.26 (C-2); 14.13 (C-9); 18.48 (C-5); 22.68 (C-8); 27.95 (C-6); 30.99 (C-7); 66.60 (C-3); 84.65 (C-4); 115 (C-1).

General procedure for conversion of hydroxy esters to nitrile esters.

To a stirred solution of triphenylphosphin (1.0 g; 3.8 mmol) in dry ether (10 ml) was added dropwise diethyl azodicarboxylate (0.66 g; 3.8 mmol) at - 20 °C , under nitrogen. The resulting mixture was stirred for 20 min. under cooling , and then the alcohol (2.5 mmol) was added dropwise at - 20 °C. After stirring for 30 min at this temperature , a solution of acetone cyanohydrin (0.32 g; 3.75 mmol) in dry ether (5 ml) was added slowly and the mixture was stirred at this temp. for 6 hr. . The reaction mixture was allowed to warm to r.t. and stirred overnight The white precipitate was filtered and the filtrate was concentrated in vaccuo The residue was purified by coloumn chromatography (hexane / acetone 10:0.5) to afford pure nitrile (Table **30**).

*9-Cyanononanoic acid methyl ester.(Table **30**; entry1)*

GC:Rt=6.3 min.

^{1}H-NMR($CDCl_3$): 1.25-1.5 (m ,8H ,4xCH_2); 1.55-1.7 (m, 4H, 2xCH_2); 2.29 (t, 2H ,CH_2); 2.32 (t, 2H, CH_2); 3.66 (s, 3H, CH_3); **^{13}C-NMR($CDCl_3$)**: 17.10 (C-9); 24.90 (C-3); 25.33 (C-8); 28.72 (C-4); 29.09 (C-5); 29.22 (C-6); 29.23 (C-7); 34.04 (C-2); 52.10 (CH_3); 119.84 (C-N); 174.28 (COO).

*11-Cyanoundecanoic acid methyl ester.(Table **30** , entry 2)*

GC:Rt= 8.016 min.

^{1}H-NMR($CDCl_3$): 1.25-1.5 (m, 12H, 6xCH_2); 1.55-1.7 (m, 4H, 2xCH_2); 2.30 (t, 2H ,CH_2); 2.34 (t, 2H, CH_2); 3.67 (s, 3H, CH_3); **^{13}C-NMR($CDCl_3$)**: 17.12 (C-11); 24.92 (C-3); 25.37 (C-10); 28.65 (C-4); 28.73 (C-5); 29.09 (C-6); 29.18 (C-7); 29.22 (C-8); 29.27 (C-9); 34.08 (C-2); 52.15 (CH_3); 119.84 (C-N); 174.28 (COO).

*2-(1-Cyano-3,7-dimethyloctyl) 1-methyl-cyclopropane-carboxylic acid ethyl ester. .(Table **30** ,entry 3)*

GC:Rt=9.4 min.

^{1}H-NMR($CDCl_3$): 0.83 (d, 3h, J=7Hz, 7′-H); 0.93 (t, 3H, COO-C-CH_3); 1.05-1.9 (m, 13H, 4xCH_2+5xCH); 1.12 (s, 6H, 11′,12-H); 1.24 (d, 3H, J=7Hz, 3-H); 3.20 (m, H , CHCN); 4.07 (m, 2H, $COOCH_2$). **^{13}C-NMR($CDCl_3$)**: 11.3 (C-3′); 13.8 (OCH_2-$\underline{CH_3}$); 15.8 (C-12); 17.9 (C-11′); 19.9 (C-5); 19.95 (C-7′); 22.7 (C-10); 24.5 (C-11); 25.6 (C-9); 25.7 (C-3); 27.9 (C-7); 30.2 (C-2); 36.21 (C-8); 35.8 (C-4); 51.7 (C-6); 63.5 ($O-CH_2$); 119.6 (C-N); 169.8 (C-1).

*2-(1-Cano-3,7-dimethyl-7-methoxyoctyl) 1-methyl-cyclopropane-carboxylic acid isopropyl ester.(Table **30** ,entry 4)*

GC:Rt=11.3 min.

^{1}H-NMR($CDCl_3$): 0.83 (d, 3H, J7Hz, 7′-H); 1.05-1.9 (m, 12H, 4xCH_2+4xCH); 1.12 (s , 6H, 11′, 12-H); 1.21 (d, 6H, J=6Hz , ispro-H); 1.24 (d, 3H J=7Hz, 3-H); 3.15 (m, H ,CHCN); 3.16 (s, 3H, CH_3O); 4.98 (t, H, J=6Hz,COOCH). ^{13}C-NMR ($CDCl_3$): 11.3 (C-3′); 15.8 (C-12); 17.9 (C-11′); 19.9 (C-5); 19.95 (C-7′); 22.2,22.5 (CH-($\underline{CH_3}$)$_2$); 22.7 (C-10); 24.5 (C-11); 25.6 (C-9); 25.7 (C-3); 27.9 (C-7); 30.2 (C-2); 35.8 (C-4); 36.21 (C-8); 51.7 (C-6); 95.2 (O-CH); 119.5 (C-N); 169.8 (C-1).

Synthesis of (3Z,6Z)-9,10-epoxy-3,6-heneicosadiene.

2-(Prop-2-ynyloxy)tetrahydropyran (40).

GC: Rt= 3.17 min.

Tetrahydropyran(32 g; 0.38 mol) was added slowly with vigrous stirring, at 0 °C, to propergyl alcohol (20 g; 0.37 mol) contained crystals of p-toluenesulfonic acid.The resulting mixture was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with ether, washed successively with 20% K_2CO_3 solution, water,and brine. Dried over Na_2SO_4, and then concentrated to give pure **40** (62.0 g: 96%).GC:97% purity. IR (film) ν_{max} ;2200,1000-1200,cm $^{-1}$. **^{1}H-NMR ($CDCl_3$)**:1.5-1.9(m, 6H ,3xCH_2); 2.41(t ,H ,CH);3.54+3.84(m, 2H, O-CH_2); 4.24+4.29(qt, 2H, J=16 and 2.4 Hz,CH_2);4.82(t ,H ,O-CH-).

2-(Pent-2-ynyloxy)tetrahydropyran (41)

GC: Rt= 6.814 min.

A solution of butyllithium (80 ml; 1.6 N in hexane) was added dropwise at 0 °C with stirring ,under argon, to a solution of 2-(prop-2-ynyloxy)tetrahydropyran (20 g; 0.142 mol) in dry THF(200 ml) and HMPA (30 ml). The reaction mixture was stirred at 0 °C for 30 min. Ethyl bromide (20 g; 0.183 mol) was then added slowly at 0-5 °C , and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quanched with 10% NH_4Cl (200 ml), and the organic product was extracted with hexane. The organic layer was successively washed with 10% NH_4Cl (2x100 ml) , 5% $NaHCO_3$ (2x100 ml) , water (2x100 ml) , brine , and dried over Na_2SO4, and concentrated in vaccuo. The crude product was eluted through a short silica gel coloumn (benzene/ acetone 10:1) to afford pure **41** (21 g; 88%):(GC; 97.5% purity). IR (film) ν_{max}: 2200,1000-1200,cm^{-1}. **^{1}H-NMR($CDCl_3$)**: 1.14(t, H, CH_3); 1.5-1.9 (m, 6H, 3xCH_2) ; 2.24(qt, 2H, 4-H); 3.84-3.53 (m, 2H, O-CH_2-); 4.19+4.29 (qt, 2H, J=14.8+ 2.2 Hz,1-H); 4.81 (t, J=3.4Hz ,)-CH-). **^{13}C-NMR($CDCl_3$)**: 12.52(C-4); 13.78 (C-5); 19.13 (C-3′); 25.41 (C-4′); 30.31(C-2′); 54.67 (C-1); 61.96 (C-5′); 75.11 (C-3); 88.0 (C-2); 96.7(C-1′).

2-Pentyne-1-ol(42).

GC: Rt= 0.599 min.

A mixture of 2-(pent-2-ynyloxy)tetrahydropyran (20 g; 0.119 mol), methanol (200 ml), water (20 ml), and p-toluensulfonic acid (2.26 g; 0.0119 mol) ,was heated at 60 °C for 3 hr. The reaction mixture was cooled , concentrated in vaccum, diluted with ether and the ether layer was successively washed with 5% $NaHCO_3$, water, brine, dried over

Na_2SO_4, and concentrated .The crude product (8.5 g; 86%), was purified by distillation to give pure **42** (B.p 70 °C/30 mm). IR (film) ν_{max}: 3400 (OH); 2230 (C≡C) cm^{-1}. **^{1}H-NMR($CDCl_3$)**: 1.15(t, 3H, CH_3); 1.60 (b, H, OH); 2.23 (qt, 2H, 4-H); 4.25 (m, 2H, 1-H). **^{13}C-NMR(CDCL3)**: 12.43(C-4); 13.78(C-5); 51(C-1); 87.7(C-2); 87.72(C-3).

1-Bromo-2-pentyne (43).

GC: Rt=1.067 min.

Phosphoroustribromide (25.76 g; 0.095 mol) in dry ether (10 ml) was added dropwise, with stirring, at -30 °C, under argon, to the mixture of 2-pentyne-1-ol (20 g; 0.238 mol) in dry ether (40 ml) and dry pyridine (9 ml) . The reaction mixture was stirred for 30 min. at -30 °C, then refluxed for 3 hr. After cooling the reaction mixture was poured into crushed ice , extracted with ether, washed with cooled saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vaccum to give crude product, which was distilled to afford **43** as colourless oil (17.2 g; 50%).(B.p 65 °C/30 mm). IR(film) νmax: 2235(C≡C); 603(Br) cm^{-1}. **^{1}H-NMR($CDCl_3$)**: 1.14(t, 3H, CH_3); 2.26 (t, 2H, J=7.5+2.4 Hz, 4-H); 3.93 (t, 2H, J=2.4Hz, 1-H). **^{13}C-NMR($CDCl_3$)**; 12.66 (C-4); 13.48(C-5); 15.73 (C-Br); 74.62 (C-2); 89.44 (C-3).

2,5-Octadiyn-1-ol (44).

GC: Rt= 5.59 min.

A solution of ethyl magnesium bromide in dry THF was prepared in the usual manner from ethyl bromide (38.8 g; 0.356 mol), magnesium turnings (7.689 g; 0.32 mol), and crystals of iodine in dry THF (150 ml). A solution of propergyl alcohol (9.13 g; 0.163 mol) in dry THF(10 ml) was added dropwise during 40 min. to the stirred solution of ethyl magnesium bromide at 0-5 °C. The reaction mixture was stirred at room temperature for 2 hr. Cuprous cyanide (0.5 g) was then added at 5 °C, and stirring was continued for 20 min.. A solution of 1-bromo-2-pentyne (15 g; 0.102 mol) in dry THF (15 ml) was added slowly during 30 min. at 0-5 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into cooled 10% NH_4Cl (160 ml) ,the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were successively washed with 10 %NH_4Cl,water, 5%$NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromotography on silica gel (benzene/ acetone 10:1) to yield pure **44** (20 g; 82%) (GC;90% purity). IR(film) ν_{max}: 3400 (OH), 2230 (C≡C) cm^{-1}. **^{1}H-NMR($CDCl_3$):** 1.13(t,3H,CH_3) ;1.71(t ,H ,J=5.5 Hz, OH); 2.18(qt ,2H ,J=7.4 and 2.2 Hz , 7-H); 3.19(tt , 2H , J=2.2Hz , 4-H); 4.27(dt, 2H, J=5.5 and 2.2 Hz, 1-H). **^{13}C-NMR(CDCl3):** 9.82(C-4); 12.35 (C-7); 13.82 (C-8); 51.29 (C-1); 72.60 (C-6); 78.37 (C-5); 82.47(C-2); 80.81(C-3).

(Z,Z)-2,5-Octadien-1-ol (45).

GC: Rt= 3.7 min.

To a solution of 2,5-octadiyn-1-ol (2.0 g; 0.016 mol) in dry methanol (40 ml) was added palladium catalyst (10% on $BaSO_4$) (0.050 g) and quinoline (5 ml). The mixture was vigorously stirred under slight pressure of hydrogen until hydrogen absorption ceased. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in ether. The ethereal solution was successively washed with 1N Hcl (2x20 ml), 5% $NaHCO_3$ (2x20 ml), water, brine, dried over Na_2SO_4, and concentrated to give **45** (1.7 g;82%)(GC;90% purity). IR(film)ν_{max}: 3400(OH), 3020(C=C) cm $^{-1}$. **^{1}H-NMR($CDCl_3$)**:0.98(t, 3H, CH_3);1.51 (b, H, OH); 2.07 (m, 2H, 7-H); 2.83 (m, 2H, 4-H); 4.23 (m, 2H, 1-H); 5.30-5.56 (m, 4H, 2xCH=CH).

^{13}C-NMR(CDCl3):14.21 (C-8); 20.55 (C-7); 25.70 (C-4); 58 55 (C-1); 126.42 (C-5); 128.53 (C-3); 131.27 (C-2); 132.49 (C-6).

3,6-Nonadiyn-1-ol (44a).

GC :Rt= 10.57 min.

A solution of ethyl magnnesium bromide in dry THF was prepared in the usual manner from ethyl bromide (6.3 g; 0.062 mol),magnesium turnings (1.3 g; 0.054 mol), and crystal of iodine in dry THF (40 ml). A solution of 3-butyn-1-ol (1.9 g; 0.027 mol) in dry THF (3 ml) was added dropwise during 40 min. to the stirred solution of ethyl magnesium bromide at 0-5 °C. The reaction mixture was stirred at room temerature for 30 min., then refluxed for 2 hr. Cooled to r.t. and cuprous chloride (2.0 g; 0.02 mol) was added and the mixture was stirred for 30 min. A solution of 1-bromo-2-pentyne (2.2 g; 0.014 mol) in dry HMPA (10 ml) was added slowly during 30 min. at 0-5 °C.The reaction mixture was stirred at r.t. overnight, then poured into cooled saturated NH_4Cl (25 ml), the organic layer was separated and the aqueous layer was extracted with ether . The combined organic layers were successively washed with saturated NH_4Cl, water, 5% $NaHCO_3$, brine , dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromotography on silica gel (benzene /acetone 10:1) to yield **44a** (2.5 g; 68%)(GC ;93% purity) IR(film) ν_{max}:3400(OH), 2230(C≡C) cm $^{-1}$.

^{1}H-NMR($CDCl_3$): 1.12(t, 3H, J=7.5Hz, CH_3); 1.51(b, H, OH); 2.18 (qt, 2H , J=7.5 and 2.4Hz, 8-H); 2.45 (tt, 2H, J=6.3 and 2.4 Hz, 2-H); 3.14 (tt, 2H, J=2.4 and 2.4 Hz, 5-H); 3.71 (t, 2H, J=6.3Hz,1-H). **^{13}C-NMR($CDCl_3$)**: 9.72 (C-5); 12.36 (C-8); 13.85 (C-9); 23.03 (C-2); 61.08 (C-1); 73.40 (C-7); 76.83 (C-6); 76.83 (C-4); 82.13 (C-3).

(Z,Z)-Nona-3,6-dien-1-ol (45a).

GC: Rt= 8.95 min.

To a solution of 3,6-nonadiyn-1-ol (2.0 g; 0.014 mol) in dry methanol (40 ml) was added 10% palldium catalyst on $BaSO_4$ (0.1 g) and quinoline (0.75 ml). The reaction mixture was vigorously stirred under slight pressure of hydrogen until hydrogen absorption ceased . The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in ether . The etheral solution was successively washed with 1N Hcl (2x20 ml); 5% $NaHCO_3$ (2x20 ml), water, brine, dried over Na_2SO_4, and concentrated to give olefinic product **45a** (1.4 g; 68%)(GC; 90% purity). IR(film) ν_{max}:3400, 3020, cm $^{-1}$. **^{1}H-NMR($CDCl_3$)**: 0.97(t, 3H, J=7Hz, CH_3); 1.51(b, H, OH); 2.07 (qd, 2H, J=7.6 and 7.1 Hz, 8-H); 2.36(td, 2H, J=6.5 and 7.5 Hz, 2-H); 2.82(t, 2H, J=7.3Hz, 5-H); 3.65 (t ,2H, J=6.5 Hz, 1-H); 5.3-5.56 (m, 4H, 2xCH=CH). **^{13}C-NMR($CDCl_3$):** 14.25 (C-9); 20.58 (C-8); 25.66 (C-5); 30.78 (C-2); 62.23 (C-1); 125.34 (C-7); 126.85 (C-6); 131.52 (C-4); 132.19 (C-3).

(Z,Z)-Nona-3,6-dienenitrile (46).

GC : Rt= 4.96 min.

To a stirred solution of triphenylphosphin (7.8 g; 0.029 mol) in dry ether (50 ml) was added dropwise diethyl azodicarboxlate (5.17 g; 0.029 mol) at -20 °C, under nitrogen. The resulting mixture was stirred for 20 min. under cooling, then alcohol (2.5 g; 0.0198 mol) was added dropwise at -20 °C. After stirring for 20 min.,a solution of acetone cyanohydrin (2.52 g; 0.029 mol) in dry ether (10 ml) was added slowly and the mixture was stirred at this temperature for 4 hours.. After warming to r.t. , the mixture was stirred overnight . The white precipitate formed was filtered off and the filtrate was concentrated in vacuo. The residue was purified by flash chromotography (hexane/ acetone 10 :0.5) to afford pure nitrile **46** (1.8 g ;68%). IR (film) ν_{max}: 2220 (CN), cm $^{-1}$. **^{1}H-NMR($CDCl_3$)**: 0.99 (t, 3H, J=7Hz, CH_3); 2.07(m, 2H, 8-H); 2.89 (m, 2H, 5-H); 3.12(dt, 2H, J=7Hz, 2-H); 5.25-5.75 (m, 4H, 2xCH=CH).

^{13}C-NMR($CDCl_3$): 14.14 (C-9); 15.59 (C-8); 20.63 (C-2); 25.51 (C-5); 118.51 (C-N); 124.9 (C-7 +C-6); 133.34 (C-4); 134 (C-3).

(Z,Z)-Nona-3,6-dienal (47).

GC : Rt= 7.93 min.

This compound was synthesized by two different methods:

Method A : **(Z,Z)**-Nona-3,6-dienenitrile **46** (0.2 g; 1.5 mmol) was stirred in dry toluene (4 ml) under argon , and diisobutylaluminium hydride (2.4 ml; 3 mmol) was added dropwise at -40 °C . After stirring one houre at - 40 °C, then 2 hr. at 0°C. , methanol (2 ml) was added , and stirring was countinued for 2 hr.. Then 1N H_2SO_4 (1 ml) was added and the mixture was stirred vigorously at 0°C for 1 hr. The reaction mixture was extracted with ether , the organic layer was washed successively with water, brine, dried over Na_2SO_4 , and then concentrated. The crude product was purified by silica-gel coloumn chromatography to afford aldehyde **47** (0.04 g;20%). IR (film) ν_{max}:2820 , 1715 cm^{-1}. **^{1}H-NMR($CDCl_3$)**: 0.98(t ,3H ,J=7.5 Hz,CH_3); 2.06(m ,2H ,8-H) ; 2.79 (m, 2H, 5-H); 3.23 (dm, 2H, J=7 Hz, 2-H); 5.25-5.75 (m, 4H , 2xCH=CH); 9.68 (t,H , J=1.9 Hz, CHO). **^{13}C-NMR(CDCl3)**: 14.18 (C-9); 20.60 (C-8); 25.87(C-4); 42.50 (C-2); 118.25 (C-7); 125.94 (C-6); 132.68 (C-4); 135.57(C-2).199.44 (CHO).

Method B : **(Z,Z)**-Nona-3,6-dien-1-ol **45a** (0.3 g; 2 mmol) was added to dry benzene (2 ml) contaning Dicyclohexylcarbodiimide (1.24 g ;6 mmol) and dry dimethyl sulfoxide (DMSO) (1.0 g; 1 mmol). Anhydrous orthophosphoric acid (0.1 g ; 1mmol) was then added at r.t. ,under argon, and the resulting mixture was stirred at r.t. for 2-3 hr.. The progress of the reaction was followed by TLC. At the end of the reaction ,the dicyclohexylurea was removed by filtration , and washed with ethyl acetate . Then water added , and the ethyl acetate layer was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel coloumn chromatography to yield pure aldehyde **47** (0.230 g ;75%)(GC; 85% purity).

2-Hydroxytridecanenitril (49)..

GC: Rt= 3.54 min.

To a solution of sodium bisulfite (22.4 g; 0.216 mol) in water (100 ml) was added dropwise at 0°C with stirring , under argon, a solution of dodecanal **48** (20 g; 0.108 mol) in methanol (62 ml), then the mixture was stirred at r.t. overnight The white preciptitate formed , was filtered off and washed with ether and dried over P_2O_5. The above bisulfite adduct (10 g; 0.035 mol) was dissolved in water (20 ml) , and a solution of KCN (2.27 g; 0.035 mol) in water (8 ml) was added dropwise at 0-5 °C. The mixture was stirred for 30 min. at r.t. The oil layer was extracted with ether , and the ethereal solution was washed successively with a solution of sodium bisulfite, water, 5% $NaHCO_3$, water, brine, dried over Na_2SO_4 , and concentrated in vacuo to give **49** (6.2 g; 84%) as an oil IR (film) ν_{max}:3400(OH),2200(CN) cm^{-1}. **^{1}H-NMR($CDCl_3$):** 0.88 (t, 3H , CH_3); 1.2-1.8 (m, 20H ,10xCH_2); 2.27 (b, H, OH); 4.48 (t, H, J=6.6Hz,CH).

^{13}C-NMR($CDCl_3$): 14.13 (C-13); 22.69 (C-12); 24.5 (C-4); 28.97 (C-10); 29.30 (C-9); 29.32 (C-8); 29.46 (C-7); 29.57 (C-6); 29.59 (C-5); 31.90 (C-11); 35.29 (C-3); 61.44 (C-2); 119.84 (C-N).

*2-(1-Ethoxyethoxy)tridecanenitrile (**50**).*

GC: Rt= 9.015 and 9.285 min.

Ethyl vinyl ether (2.65 g; 0.036 mol) was added dropwise at 0°C to the solution of 2-hydroxytridecanenitrile **49** (5.0 g; 0.023 mol) in benzene (10 ml) and one drop of conc. HCl . The reaction mixture was stirred at r.t. and controlled by TLC At the end of the reaction , the mixture was extracted with ether. The ethereal solution was successively washed with 20% K_2CO_3 solution , water, brine dried over Na_2SO_4 , and concentrated to give a diasteromeric mixture of **50** (6.0 g; 90 %)(GC: 90% purity) IR (film) ν_{max}: 2200 (CN), 1000-1100, cm $^{-1}$. **^{1}H-NMR($CDCl_3$)**: 0.88(t, 3H, CH_3); 1.23 (1.22) (t, 3H, '3-H); 1.36(1.39) (d, 3H,"1-H); 1.2-1.4 (m, 20H,10xCH2); 3.46-3.75 (m, 2H, '2-H); 4.46 (4.28) (t ,H, CH); 4.92 (4.83) (q, H,'ł-H). **^{13}C-NMR(CDCl3):** 14.09 (C-13); 15(14.90) (C-'3); 19.50(19.54) (C-"1); 22.66 (C-12); 24.77(24.64) (C-4); 28 97(C-10); 29.30 (C-9); 29.32 (C-8); 29.46 (C-7); 29.57 (C-6); 29.59 (C-5) ; 31.88 (C-11); 33.57 (34.02) (C-3); 60.93(61.47) (C-'2); 63.00 (C-2); 98.8 (100.38) (C-'1).; 118.89(119.55) (C-N).

*2-(1-Ethoxyethoxy)-3- hydroxy-2-undecylundeca-5,8-dienenitrile (**51**).*

GC: Rt= 18.1 min.

To a solution of lithium diisopropylamide (1.7 mmol) in dry THF (5 ml), under argon, and at - 78°C, a freshly prepared 2-(1-ethoxyethoxy)tridecanenitrile **50** (0.5 g;1.7 mmol) in dry hexamethylphosphoramide (0.75 g),was added dropwise with vigorous stirring for 10 min., and then (**Z**,**Z**)-nona-3,6-dienal (**47**) (0.250 g;1.8 mmol) in dry THF (1 ml) was added dropwise over one hour at -78 °C. The reaction mixture was stirred at -78 °C for 2 hr., then at r.t. overnight. Water was added and stirring was continued for 5 min. . The solvent was concentrated , and the residue was extracted twice with ether. The combined ethereal solution were washed with 5% $NaHSO_3$, brine ,dried over Na_2SO_4 , and concentrated to give crude product , which was purified by silica-gel coloumn chromatograohy benzene / acetone (10 :0.5) to afford **51** .(0.350 g; 47%). IR (film) ν_{max}: 3400(OH), 2220(CN) cm $^{-1}$.

^{1}H-NMR($CDCl_3$): 0.87 (t, 3H, CH_3); 0.98 (t, 3H, CH_3); 1.22 (t, 3H , 3'-H); 1.2-1.7 (m, 18 H, 9xCH2); 1.4 (d, 3H, 1''-H); 1.70-2.3 (m, 6H, 11-H, 2-H and 8-H); 2.33 (2.15)(d , H ,OH); 2.69 (m, 2H ,5-H); 3.46-3.7 (m, 2H ,2'-H); ; 3.55-3.7 (m, H, 9-H); 5.1(5.07)(q , H,1'-H); 5.25-5.5 (m, 4H, 2xCH=CH);

^{13}C-NMR($CDCl_3$): 14.09 (C-21); 14.12 (C-1); 15.3 (C-3′); 20.6 (C-2); 20.8(21.2) (C-1″); 22.76 (C-20); 23.7 (C-12); 25.8 (C-5); 28.9-29.0 (C_{13}-C_{18}); 31.2 (C-19); 31.9 (C-11); 42.5 (C-8); 60.89 (C-2′); 74.1(73.7) (C-9); 81(80.9) (C-10); 98.3(98.4) (C-1′); 118.6 (C-N); 125.3 (C-3); 125.9 (C-4); 131.5 (C-6); 132.1 (C-7).

*9-Hydroxyheneicosa-3,6-dien-10-one (**52**).*

GC: Rt=15.09 and 15.9 min.

A mixture of compound (**51**) (0.3 g; 0.7 mmol) in methanol (1.5 ml) and 5% H_2SO_4 (0.25 ml), was stirred for 10 min. at r.t., and the progress of the reaction was followed by TLC. The solvent was evaporated , and the residue was extracted with ether . The ethereal solution was washed with brine. To the ethereal solution 0.5 N NaOH (10 ml)was added , and the mixture was stirred for 20 min. The organic layer was separated , washed with brine , dried over Na_2SO_4 , and concentrated to give crude product which was purified by coloumn chromatography (benzene / acetone 10 :0.5 as eluent) to give pure **52** (0.100 g ; 43%). IR (film) ν_{max}: 3450 (OH), 1715 (C=O) cm $^{-1}$. **^{1}H-NMR($CDCl_3$)**: 0.94 (t, 3H, CH_3); 0.98 (t , 3H, CH_3); 1.2-1.65 (m,18H, 9xCH_2); 1.78-2.32 (m, 4H, 2-H and 8-H); 2.45 (m ,2H ,11-H); 2.69 (m, 2H, 5-H); 3.5 (d, H, OH); 4.17 (m, H, 9-H); 5.25-5.6 (m, 4H , 2xCH=CH). **^{13}C-NMR($CDCl_3$):** 14.08 (C-21); 14.12 (C-1); 22.05 (C-2); 22.5 (C-20); 23.7 (C-12); 25.8 (C-5); 28.9-29.0 (C_{13}-C_{18}); 31.2 (C-19); 37.5 (C-11); 40 3 (C-8); 76.4 (C-9); 125.3 (C-3); 125.9 (C-4); 131.5 (C-6); 132.1 (C-7); 212.5 (C=O).

*9-(tert-Butyldimethylsilanyloxy)heneicosa-3,6-dien-10-one (**53**).*

GC: Rt= 17.9 min.

To a solution of imadozol (0.267 g; 3.88 mmol) in dry dimethylformamide (4 ml), under argon, and at 0°C , was added t-butyldimethylsilyl chloride (0.271 g ;1.8 mmol) ,the resulting mixture was stirred for 15 min. at 0 °C, then a solution of compound (**52**) (0.5 g; 1.5 mmol) in dry methylene chloride (2 ml) was added dropwise. The reaction mixture was stirred at r.t.overnight., and then poured into a mixture of ether and water. The organic layer was separated and then washed successively with 5% $NaHSO_3$, water, 5% $NaHCO_3$,water, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was eluted through a short silica-gel coloumn using hexane, then hexan/ acetone (10:0.5) to get compound **53** (0.615 g ;90 %). IR (film) ν_{max}: 1715 (C=O) cm $^{-1}$.

^{1}H-NMR($CDCl_3$):0.07 (s, 6H, 2xCH_3) 0.90 (s, 9H, 3xCH_3); 0.85 (t, 3H, CH_3); 0.92 (t , 3H, CH_3); 1.2-1.65 (m,18H, 9xCH_2); 1.78-2.3 (m, 4H, 2-H and 8-H); 2.45 (m, 2H, 11-H); 2.67-2.8 (m, 2H , 5-H); 3.98 (m, H, 9-H); 5.25-5.6 (m , 4H , 2xCH=CH).

^{13}C-NMR($CDCl_3$): - 4(si-2Me); 14.08 (C-21); 14.12 (C-1); 18.16 (C-3Me) 22.05 (C-2); 22.5 (C-20); 23.7 (C-12); 25.8 (C-5); 25.9 (3xCH_3); 28.9-29.0 (C_{13}-C_{18}); 31.2 (C-19); 37.5 (C-11); 40.3 (C-8); 75.4 (C-9); 125.1 (C-3); 125.9 (C-4); 131.5 (C-6); 132.1 (C-7); 212.5 (C=O).

*9-(tert-Butyldimethylsilanyloxy) heneicosa-3,6-dien-10-ol (**54**).*

GC: Rt= 18.29 min.

To a solution of compound (**53**) (0.9 g; 2.06 mmol) in dry methanol (10 ml) , under argon, and at 0°C , was added a solution of sodium borohydride (0.05 g; 1.5 mmol) in methanol (2 ml). The reaction mixture was stirred at r.t. for 5-6 hr. A solution of 5% $NaHSO_4$ (5 ml) was added ,extracted with ether . The ethereal solution was successively washed with water ,5% $NaHCO_3$, water, brine, dried over Na_2SO_4, and concentrated to give diastereomeric mixture of **54** (0.8 g; 88%)(GC;85% purity). IR (film)ν_{max}: 3400 ,2820 ,1460 ,1240 , 820 , 760. cm $^{-1}$. **^{1}H-NMR($CDCl_3$)**: 0.07 (s, 6H, 2xCH_3);0.90 (s ,9H , 3xCH3); 0.90 (t, 3H, CH_3); 0.92 (t, 3H, CH_3); 1.2-1.7 (m , 20H, 10xCH_2); 1.8-2.1 (m ,4H, 2-H and 8-H); 2.14 (2.143) (d, H, J=7(3.4) Hz, OH); 2.6-2.8 (m, 2H, 5-H); 3.42 (3.57) (m, H, 10-H); 3.49 (3.60) (m, H, 9-H); 5.25-5.54 (m, 4H, 2xCH=CH). **^{13}C-NMR($CDCl_3$)**: -4 (si-2Me); 14.08 (C-21); 14.12 (C-1); 18.16 (C-3Me); 22.05 (C-2); 22.5 (C-20); 23.7 (C-12); 25.8 (C-5); 25.9 (3xCH_3); 28.9-29.0 (C_{13}-C_{18}); 31.2 (C-19); 37.5 (C-11); 40.3 (C-8); 72.6 (74.7) (C-10); 75.4 (75.2) (C-9); 125.3 (C-3); 125.9 (C-4); 131.5 (C-6); 132.15 (C-7).

*[2-(tert-Butyldimethylsilanyloxy)-1-undecyldeca-4,7-dienyl]methan sulfonate (**55**).*

GC: Rt= 16.69 min.

Methanesulfonyl chloride (0.163 g; 1.4 mmol) was added to a mixture of compound (**54**) (0.5 g; 1.1 mmol) in dry methylene chloride (10 ml) and dry pyridine (3 ml), at 0 °C and under argon. The reaction mixture was stirred at r.t. for 6 hr. Then methylene chloride was added ,washed successively with water (3 ml), 1N HCl (3 ml), water (3 ml), 5% $NaHCO_3$ (3 ml), water, brine, dried and concentrated to give semi-oil product , which was purified over silica-gel coloumn benzene / acetone (10:0.5) to give pure **55** (0.45 g; 75%). IR (film) ν_{max}: 2820, 1460, 1380, 1180 ,840 ,760 , cm $^{-1}$.
^{1}H-NMR($CDCl_3$): 0.07 (s,6H,2xCH_3);0.90 (s, 9H, 3xCH_3); 0.90 (t, 3H, CH_3); 0.92 (t ,3H, CH_3); 1.15-1.85 (m, 20H, 10xCH_2); 1.8-2.3 (m, 4H, 2-H and 8-H); 3.00 (3.05) (s ,3H , SO_2-CH_3); 2.75 (m, 2H, 5-H); 3.87 (m ,H, 9-H); 4.52 (m, H, 10-H); 5.25-5.54 (m ,4H , 2xCH=CH).

^{13}C-NMR($CDCl_3$): - 4.63 (- 4.41) (si-2Me); 14.08 (C-21); 14.12 (C-1); 18.2 (17.98) (C-3M); 22.05 (C-2); 22.5 (C-20); 23.7 (C-12); 25.8 (C-5); 25.82(25.80) (3xCH_3); 28.9-29.0 (C_{13}-C_{18}); 31.0(C-11); 31.2 (C-19); 38.53 (38.73)(C-SO2); 40.3 (C-8); 72.4(74.5)(C-9); 84.61(87.30) (C-10); 125.3 (C-3); 125.8 (C-4); 131.3 (C-6); 132.1(C-7).

*(3Z,6Z)-9,10-Epoxyheneicosadiene (**56**).*

GC: Rt= 24.06 and 24.6 min.

To a solution of compound (**55**)(0.265 g; 5 mmol) in dry THF (10 ml) was added tetrabutylammonium flouride (0.236 g;7.5 mmol) at r.t., and the resulting mixture was stirred for 24 hr at r.t.. Water was then added ,and the reaction mixture was extracted twice with ether . The combined ethereal solutions were washed with brine , dried over Na_2SO_4, and concentrated in vacuo to give crude product , which was purified over silica gel coloumn (hexane / acetone 10:2) to give pure epoxide **56** and **57** as a mixture of (cis and trans isomers (ratio 3:2) (0.100 g; 63% yield).IR (film)ν_{max}: 3040 , 2980 , 2950, 2880 ,1655 ,1465 ,1400 ,1205 ,1000 ,910 ,820, cm^{-1}.

^{1}H-NMR($CDCl_3$): 0.84 (t, 3H, J=7Hz , CH_3); 0.88 (t, 3H, CH_3); 1.12-1.5 (m, 20H , 10xCH_2); 1.8-2.4 (m, 4H, 2-H and 8-H); 2.75 (m, 2H, 5-H); 2.92 (m, 2H 9,10-cis H); .2.58 (m , 2H , 9,10-trans H); 5.25-5.6 (m, 4H, 2xCH=CH). **^{13}C-NMR($CDCl_3$)**: 14.1 (C-1); 14.2 (C-21); 20.58 (C-2); 22.69 (C-20); 25.6(C-5); 26.3 (C-13); 26.7 (C-14); 27.8 (C-11); 28.3 (C-18); 29.32 (C-17); 29.5 (C-15); 29.59 (C-14); 29.6 (C-8); 29.96 (C-16); 31.9 (C-19); 57.25 (C-9); 56.3 (C-10); 124.1 (C-3); 126.8 (C-4); 130.9 (C-6); 132.19 (C-7).

SUMMARY

This thesis is concerned with the investigation of new reactions without solvent: Benzylation and acylation of alipatic diols, esterification of carboxylic acid salts, and formation of 1-chloro-1-alkynes. Interpretation of the side product of Wittig reaction is also concerned. A novel synthetic procedure for preparation of unsaturated nitriles from the corresponding alcohols is discussed. A new synthetic procedure for the preparation of the pheromone component of Hyphantria cunea is described.

In the benzylation of diols the aim was to achieve the highest possible yield of monobenzylated derivatives using benzyl chloride. The best results were obtained applying KOH as a base at 100 °C, in yield 50-60 %.

$$\mathbf{HO-(CH_2)n-OH} \xrightarrow[\text{2. powderd KOH}\\\text{3. 30 min. at 100 °C}]{\text{1. benzyl chloride}} \mathbf{HO-(CH_2)n-OBn}$$

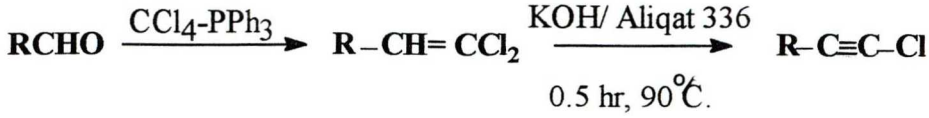
In the acylation of diols the aim was to achieve good yield of monoacylated derivatives using acetic acid and propionic anhydride in the presence of co-reagent KOH: 45-55 % yield was achieved after 3 hr at r.t.

$$\mathbf{HO-(CH_2)n-OH} \xrightarrow[\text{2. KOH}\\\text{3. 3 hr. r.t.}]{\text{1. } (RCO)_2O} \mathbf{HO-(CH_2)n-O-C(=O)-R}$$

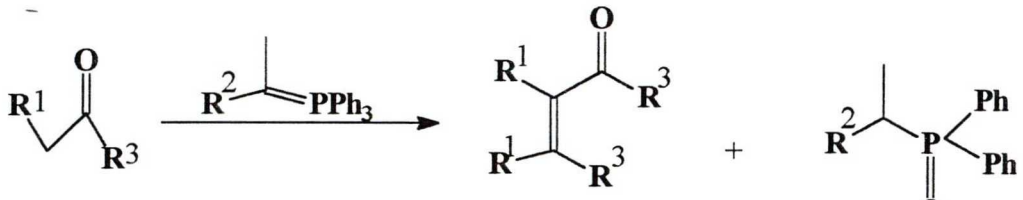
The esterification of carboxylic acid sodium salts was performed by alkyl bromide, using Aliquat 336 under phase transfer condition. The esters were obtained in 80-95 % yield.

$$\mathbf{R^1-COONa} \xrightarrow[\text{2. 5-24 hr. at 120 °C}]{\text{1. } R^2\text{-Br/ Aliqat 336}} \mathbf{R^1-COO-R^2}$$

1-Chloro-1-alkynes were formed from 1,1-dichloro-1-alkenes by hydrogen chloride elimination, applying KOH as a base , 70-80 % yield was obtained.

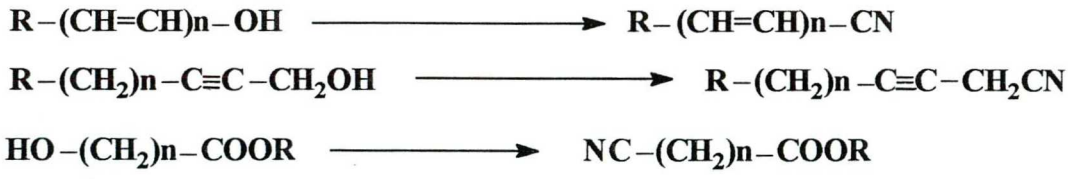


Introduction of isopropylidene and isobutylidene units is important step in the synthesis of natural products, through reaction between phosphorane (**22**) and ketone (**24**).However, in this reaction we got aldol condensation. The aldol condensation was not the result of the excess of butyllithium used. The isopropylidene and isobutylidene ylides are stable enough and can act as a base under Wittig condition to generate aldol product with ketone.

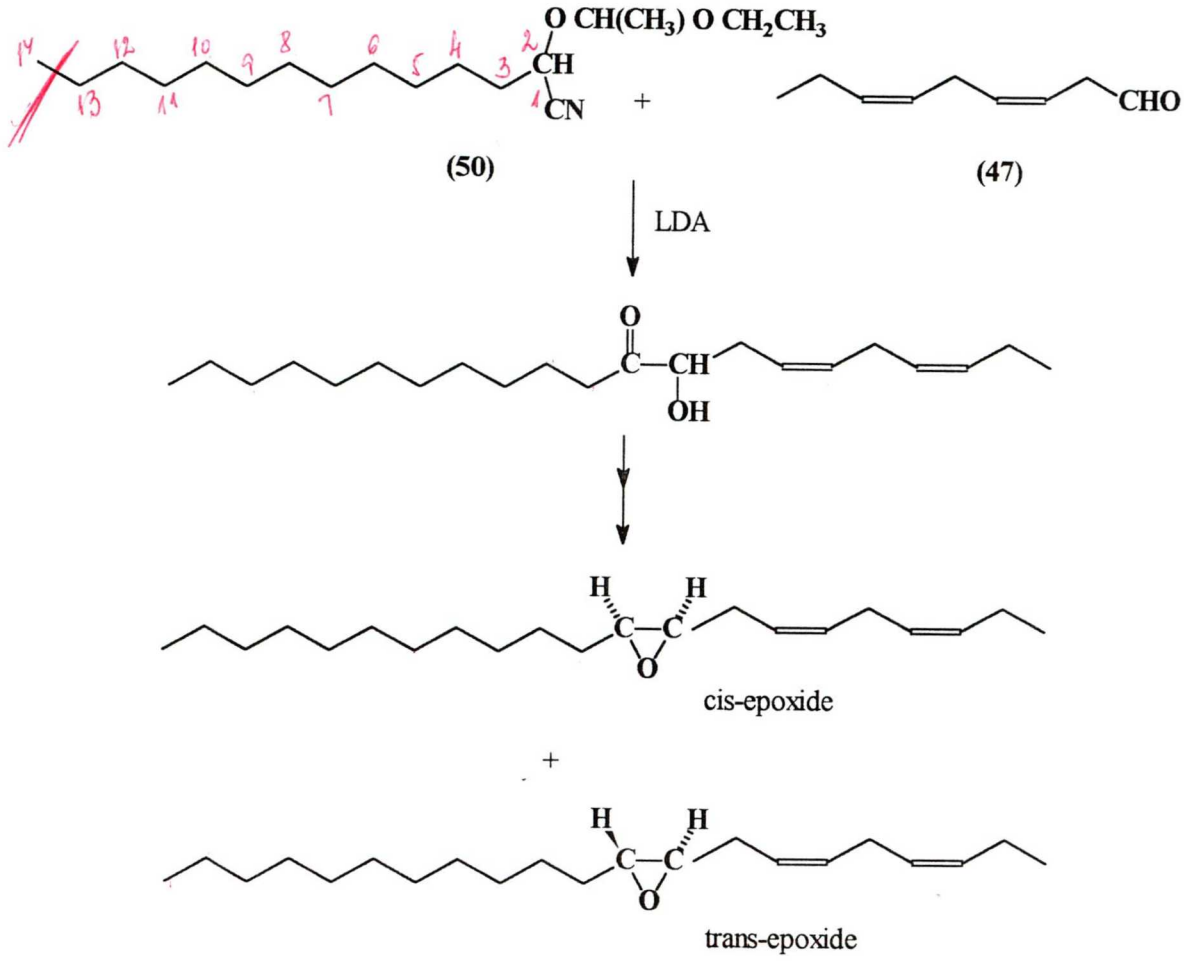


24 **22**

A novel procedure was elaborated for the conversion of olefinic alcohols, β-acetylenic alcohols, and hydroxy esters to the corresponding nitriles by the modification of Mitsunobu-Wilk procedure, by using PPh_3-DEAD mixture in the presence of acetone cyanohydrin at low temperature (yields 50-75 %).



Finally a novel synthesis of one of the Hyphantria cunea pheromone - (3**Z**,6**Z**)-9,10-epoxy-3,6-heneicosadiene- was elaborated in which the key step was the nucleophilic acylation of homoallylic aldehyde (**47**) by protected cyanohydrin (**50**). The product was identified from NMR spectrum as a cis-trans mixture in ratio 65:35.


O CH(CH3) O CH2CH3
CH
CN
CHO
(50)
(47)
LDA
O
C
CH
OH
H
H
C
C
O
cis-epoxide
+
trans-epoxide

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