POLYMER-BOUND WITTIG REAGENTS IN THE SYNTHESIS OF OLEFINS AND ETHYL RETINOATE

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CHAPTER I

HISTORICAL

Wittig Reaction[1]

In 1953 Wittig and Geissler prepared methylenetriphenylphosphorane from triphenylmethylphosphonium bromide and phenyllithium, reacted it with benzophenone, and obtained 1,1-diphenylethylene and triphenylphosphine oxide in quantitative yield,[2] as shown below.

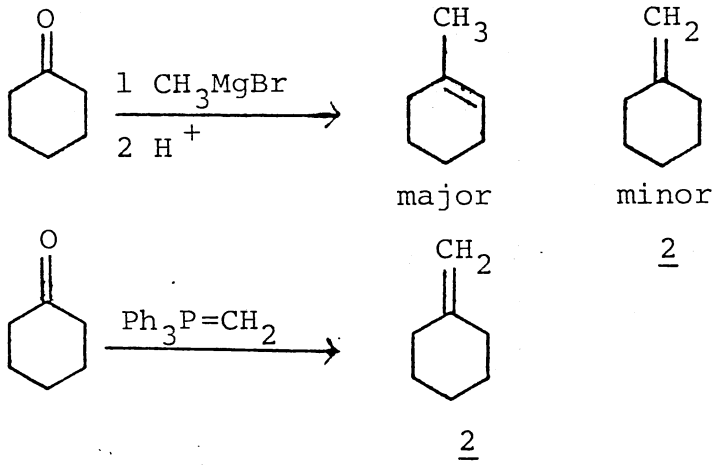
$$Ph_3P{=}CH_2 + Ph_2C{=}O \longrightarrow Ph_2C{=}CH_2 + Ph_3P{=}O$$

1

This discovery led in the following years to the development of a new method for the synthesis of olefins[3-6] which, under the name Wittig reaction, soon attained importance in preparative organic chemistry.

The two distinct advantages of this method are (i) structural specificity; the carbonyl group is replaced specifically by a carbon-carbon double bond without the formation of isomeric olefins. In contrast, the older method of converting carbonyl compounds to olefins using the Grignard reaction followed by dehydration of the resulting carbinol as given in the following illustration usually gives mixture of isomeric olefins. The illustration also shows that the Wittig reaction is the best available method for the introduction of an exocyclic double bond. (ii) the reaction is carried out in alkaline medium and under mild conditions. Consequently it is one of the best

methods for the preparation of sensitive olefins such as retinoids, carotenoids and other natural products.



Preparation of Wittig Reagents

The Wittig reagents or phosphoranes are generally prepared by the action of bases on triphenylalkylphosphonium halides, with a suitable solvent, in an inert atmosphere. Commonly used bases are alkali metal hydroxides and alkoxides, organo metallic compounds and bases such as sodium amide. As solvents, alcohol, tetrahydrofuran, diethyl ether and dimethylformamide are used. The choice of a base and solvent is very critical and depend on the nature of the desired Wittig reagent. Wittig reagents may be divided into two groups according to their reactivity. The first and larger group includes the alkylidene phosphoranes of low stability and high reactivity which are generated by bases such as organometallic compounds or alkoxides. The second group comprises the less reactive resonance-stablized alkylidene phosphoranes, and these are generally formed by the action of alkali metal hydroxides.

Structures and Properties of Phosphoranes

Phosphoranes can be considered as resonance hybrids of two limiting structures, the ylide form (a) and the ylene form (b)

$$R_3\overset{+}{P}-\overset{-}{C}R^1R^2 \longrightarrow R_3P=CR^1R^2$$

(a) (b)

This stabilization is attributed to valence shell expansion of the phosphorous atom with concomitant overlap of a vacant 3d-orbital on phosphorous with a filled 2p-orbital on carbon, of the carbanion intermediate (a).

The reactivity of the phosphorane is determined by the distribution of the negative charge in the molecule, which in turn depends on the nature of the substituents R^1 and R^2 on carbon as well as R on phosphrous. More commonly, electron-withdrawing substituents R^1 and R^2 will stabilize the negative charge and consequently reduce the reactivity of the ylide, by decreasing its nucleophilic character. In contrast, electron-releasing groups will increase the nucleophilicity of the ylide. Electron-withdrawing group R on phosphorous will, other things being equal, increase the d-orbital resonance and therefore favor the ylene form (b), whereas electron-releasing groups will increase the importance of the ylide form (a). The above mentioned hypotheses are further supported by the positive inductive effect studies of the substituents on phosphorous. Substituents with increased +I effect will stabilize the ylide form making it more reactive and substituents with -I effect will stabilize the ylene form.

Mechanism and Stereochemistry

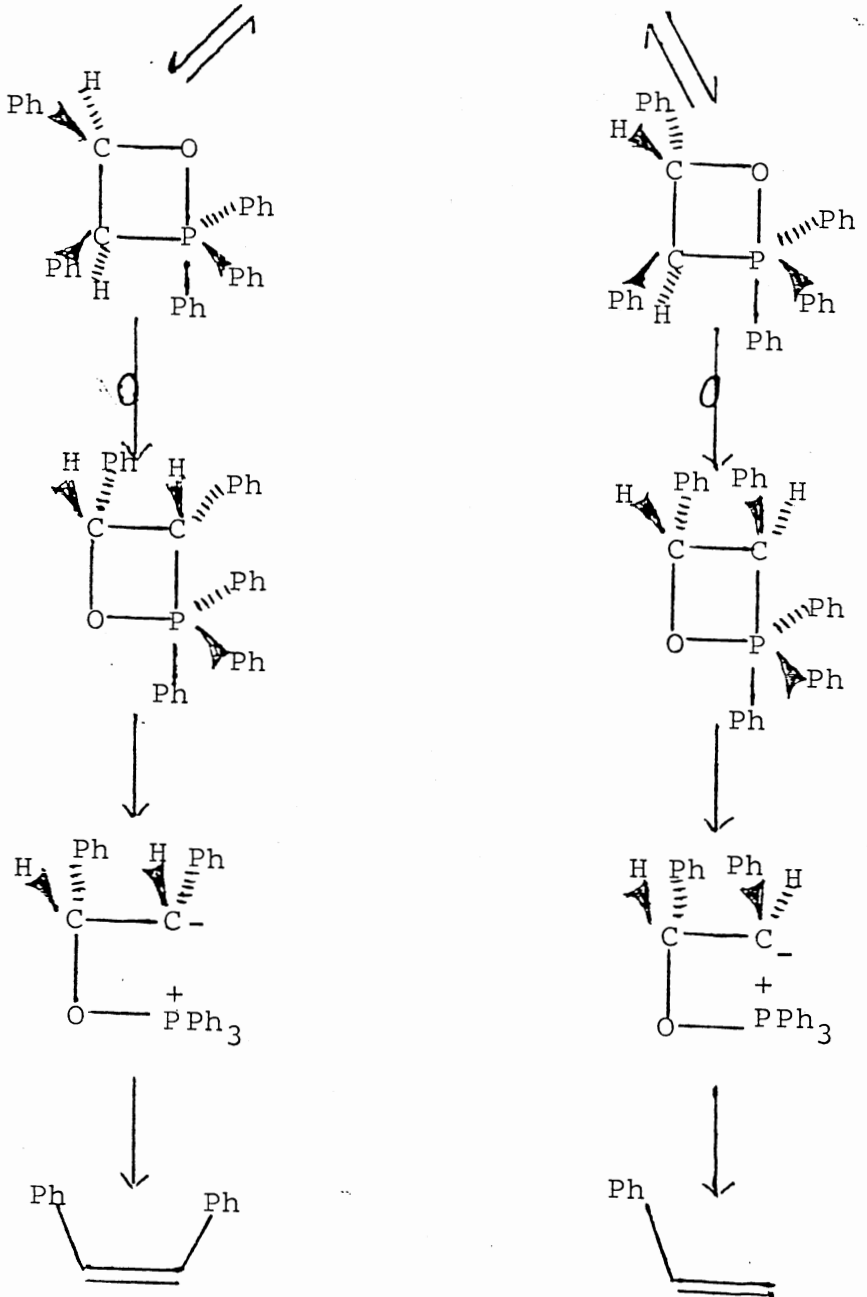
The mechanism of the Wittig reaction depends on the structure of the ylide and the conditions of the reaction.[7] No single mechanism holds for all reactions. A recent mechanism by Bestmann[8] is given on page 5.

The phosphorane reacts with the carbonyl compound forming a cyclic oxaphosphetane intermediate in step one. In order to facilitate Wittig olefination, the C-P bond becomes axial by rearrangement of the ligands around phosphorous by pseudorotation. After this rearrangement, the C-P bond collapses to form the betaine. The lifetime of the betaine being very short, elimination of the triphenylphosphine oxide occurs readily, leading to the formation of the olefin.

Wittig olefination can lead to the formation of both cis and trans olefins, depending on the orientation of the subsitutents on the newly formed double bond.[9] In general trans-selectivity predominates because of the thermodynamic stability of the sterically less hindered product.[10] However it has been shown by Schlosser,[9] and by Bergelson and co-workers[11,12] that the stereochemical course of the Wittig reaction can be reversed or changed by appropriate selection of environmental conditions including solvent, base, presence or absence of salts, and the structure of the reactant.[9] For example, in the formation of stilbene from benzylidenetriphenylphosphorane and benzaldehyde, use of ether as solvent gives 30:70, Z:E isomers, where as DMF gives 75:25, Z:Eisomers.[11]

Recent work on nonstabilized salt free ylides, ($CH_3CH{=}PPh_3$) indicated the formation of >90% Z-alkene in polar as well as nonpolar

$Ph_3P{=}CHPh + PhCHO$



aprotic solvents, with aldehydes.[7] Under these conditions oxaphosphetane is the only intermediate observed by ^{31}P NMR analysis.[7] For the same phosphorane generated by n-BuLi, E:Z ratios of the olefin formed were found to be low.[7,9]

Nonstabilized phosphoranes in general react with both aldehydes and ketones, whereas resonance stabilized phosphoranes react with aldehydes and not ketones. For example, benzylidenephosphorane does not react with cyclohexanone whereas methylidenephosphorane reacts readily to form methylenecyclohexane.

The scope of Wittig reaction is extended by the use of phosphonate carbanions which is referred to as the Horner-Emmons or the Wadsworth-Emmons modification of the Wittig reaction.[13] Carbanions of this type gain stability by delocalization of the charge through the phosphoryl group. They are more nucleophilic than the corresponding phosphoranes. P(O)-stabilized anions show less delocalization because of a small positive charge on phosphorous, a result of back donation from oxygen. This results in a strongly increased contribution of the limiting structure (b) to the resonance hybrid.

$$(EtO)_2\overset{\overset{O^-}{|}}{P}{=}CHCOOEt \longrightarrow (EtO)_2\overset{\overset{O\,-}{\|}}{P}{-}CHCOOEt$$

4 (a) 4 (b)

Because of higher nucleophilicity phosphonate carbanions with their negative charge stabilized by a carbonyl group react readily with ketones as given below, whereas their phosphorane counterparts are much less reactive.

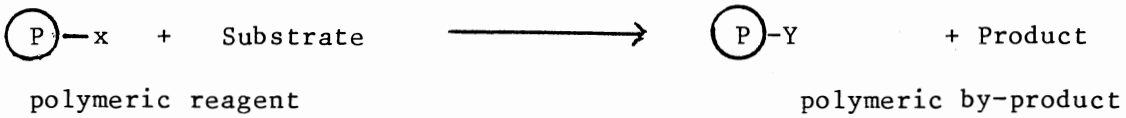
$$C_6H_5COC_6H_5 + \underset{4}{(EtO)_2P(O)CH_2COOEt} \longrightarrow (C_6H_5)_2C{=}CHCOOEt$$

Higher trans-selectivity is the rule, which is another advantage over conventional Wittig reaction in the carbonyl olefinations using P(O) activated phosphoryl carbanions. However, but for ketones, phosphoranes are still preferred for reactions with aldehydes.

Polymer-Bound Reagents[14]

Many areas of scientific endeavor have felt the effect of the utilization of insoluble polymeric materials. Organic chemistry is no exception. Polymer chemistry bears a close analogy to organic chemistry wherein polymeric hydrocarbons can be considered parent polymers from which other functionalized polymers are derived, with only few exceptions. In general insoluble polymers undergo chemical reactions in much the same way as low-molecular weight compounds. For example benzene rings in styrene polymers can undergo halogenation, alkylation, acylation, and sulfonation. Many of these reactions have been used for preparing functionalized insoluble polystyrene-based reagents. Two factors which affect the polymer reactivity are rate of diffusion and the pore size. The rate of diffusion of molecules through the polymer matrix is slower than in solution reactions and is overcome by the use of good swelling solvents. The problem of smaller pore size is taken care of by the use of macroporous polymers.

A polymeric reagent is an insoluble polymer bearing a reactive group, which reacts stoichiometrically to achieve chemical modification of an added substrate as illustrated below.



Polymer mediated reactions are broadly classified into three categories: (1) reactions in which the insoluble polymer acts as a carrier for the substrate. The product remains attached to the support while the by-products, excess of reagents and solvents all remain in solution and can be removed by filtration. The last stage in such a synthesis involves cleavage of the product from the polymer backbone. (2) Reactions in which a polymer incorporating a conventional synthetic reagent is reacted with a low-molecular weight substrate which is transformed into the product. The excess of the polymeric reagent and the spent polymer remain insoluble whereas the product goes into solution. Polymer supported Wittig reactions fall under this type. (3) Reactions of insoluble polymers carrying catalytic groups. Here, the reacted polymer is the same as the functionalized polymer.

Use of insoluble polymeric reagents offer certain advantages over conventional low-molecular weight reagents. (1) Ease of processing: This is usually the most important consideration as work-up or purification of the product of a polymer-supported reaction is often reduced to simple filtrations. This advantage alone is often sufficient to justify the use of a functional polymer. In Wittig synthesis, the by-product phosphine oxide offers separation problems in certain solution reactions whereas in a polymeric Wittig reaction, the phosphine oxide by-product being insoluble is easily separated by simple filtration. Polymer-supported reagents may also be used more conveniently in excess to drive the reactions to completion, without incurring a penalty in the work-up procedure. (2) Ease of handling: The reactivity of an unstable reagent or catalyst may be attenuated when supported on a polymer, and toxic and malodorous materials can be rendered environmentally

more acceptable. Polymeric phosphine, presents an example of being non-toxic and odorless when compared with monomeric phosphine. (3) Improved yields and selectivity of product formation: Side reactions associated with the solution reactions can be minimized by the use of polymeric reagents thereby improving the yields. Polystyrene-bound 3-phenylpropanoic ester enolate, under partial conversion conditions, gives increased yields of acylation product with p-nitrobenzoyl chloride[15] and decreased yields of self condensation of the ester. By the control of the degree of cross-linking and the choice of the polymeric backbone it is sometimes possible to create special electronic and steric conditions significantly different from those existing in bulk solution, thus changing the reaction path. In the formation of stilbene from benzylidenephosphorane and benzaldehyde, the ratio of E:Z isomer increases in the order 20%>8%>2% cross-linked polymer (see Results and Discussion). (4) Ability of the polymer to be recovered, regenerated and reused: This is a critical feature which often compensates for the time and capital investment required for preparing the polymeric reagents. In a Wittig reaction, the insoluble phosphine oxide by-product, easily separated by simple filtration can be readily reduced to the phosphine and be reused repeatedly.

Among the disadvantages, the additional steps and the cost involved in synthesizing functional polymers are the major factors. As mentioned earlier, this may well be offset by the potential advantages, and certainly in the case of regenerable and recyclable polymers this objection essentially disappears. The occurrence of slow reaction and poor yields in certain cases, however, can be overcome by appropriate choice of support and reaction conditions.[15] The overall chemical

and mechanical stability of the support can often be limiting but this is overcome by increasing the degree of cross-linking of the polymers. The ultimate capacity of a functionalized polymer is restricted in that, for the same stoichiometric quantities, the polymeric reagent weighs more than the analogous monomeric reagent. The higher weight of the polymeric reagent, however, offers no hindrance to the reactivity. Finally, it is difficult to characterize the side reactions associated with polymeric reactions, though they seldom occur. Proper solution for this is still under investigation.

The most widely used insoluble polymers in organic synthesis are styrene-based with divinylbenzene as the cross-linking agent.[14] They are produced by heterogeneous suspension polymerisation techniques either in the presence or absence of an organic solvent, depending on the type of resin needed. The polymer forms as tough, insouble and spherical cross-linked beads whose size depend on the extent of dispersion in solution, the amount of agitation, the temperature, the interfacial tension and the initiator used during polymerization.

Styrene-based polymers have many advantages over other resins. Aromatic ring functionalization is achieved easily to give reactive, yet selective styrene-based reagents. The type and degree of cross-linking can be easily controlled. Since the degree of cross-linking of the polymer controls its ability to swell in solvents, polymer beads of both good swelling and less swelling characteristics can be made. Being hydrocarbon-like, these polymers are compatible with organic solvents so that functional groups are easily accessible to organic reagents and solvents. Polystyrene is not degraded by most chemical reagents under ordinary conditions and can withstand the chemical

treatments and physical handling required in sequential syntheses. Pore dimensions can be easily controlled during synthesis by regulating the concentration of divinylbenzene, thereby allowing a wide choice of pore dimensions.

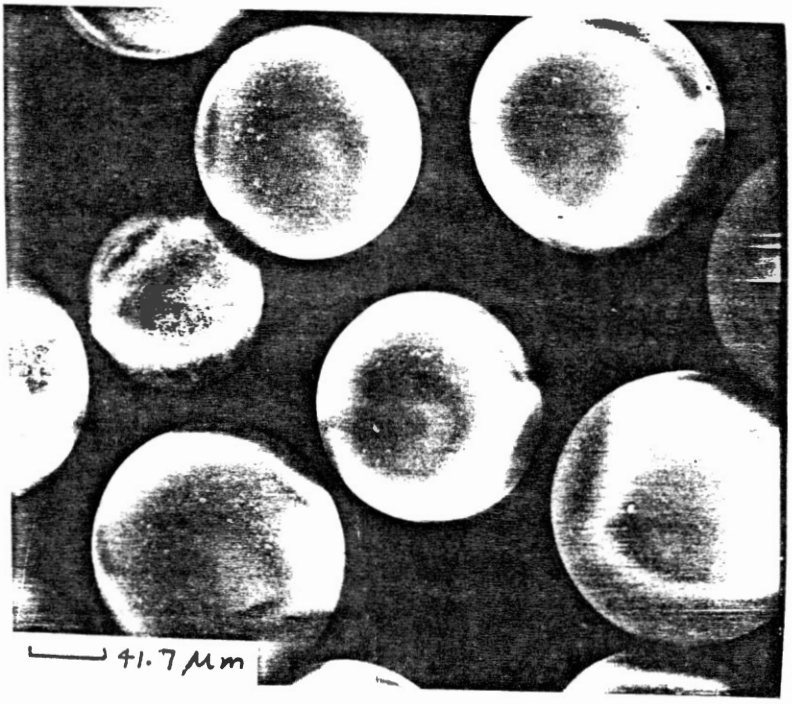
The two types of insoluble polymers generally encountered in organic syntheses are (1) lightly cross-linked swellable polystyrene resins referred to as gel polymers. (2) highly cross-linked less swellable polystyrene resins commonly referred to as macroporous or macroreticular polymers.[14]

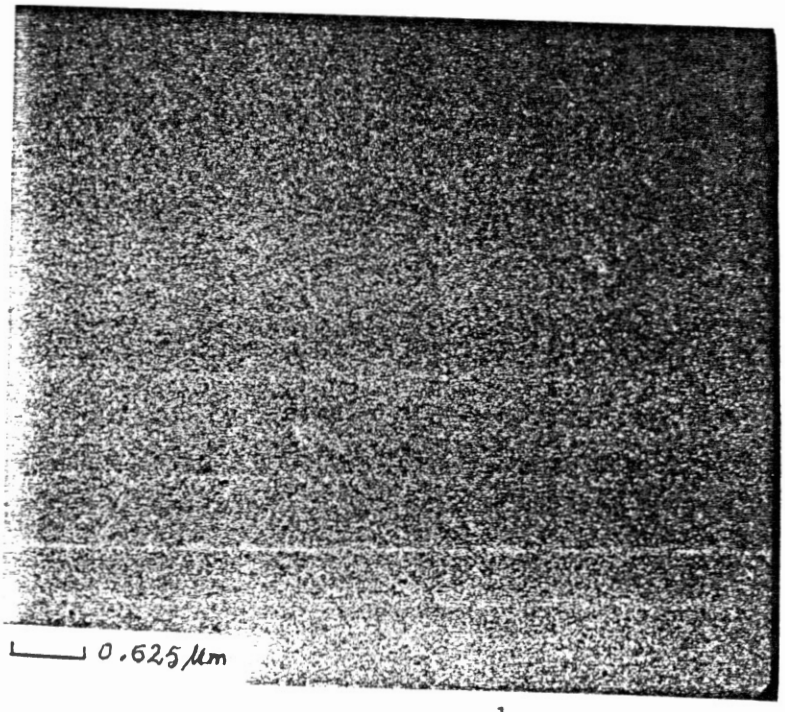
Gel polymers are obtained in the absence of a solvent during polymerization. The polymer beads in the dry state are non-porous. For this reason they are also referred to as microporous, where the pores are the spaces between polymer chains in the solvent-swollen beads. In a scanning electron microscope the bead has a pearly appearance with a relatively smooth surface and looks undivided (single) (Figure 1). Macroporous polymers are synthesized in the presence of a solvent, which results in an expanded network with definite and permanent internal porous structure.[14d] Pore diameters as high as several thousand angstroms can be achieved. The size and shape of the pores are retained even in the dry state. A scanning electron micrograph shows the bead to be composed of a large number of microparticles fused together such that the bead contains about 50% pores by volume. The bead is opaque with a characteristic matt appearance (Figure 2).

Lightly cross-linked gel polymers are less fragile; require less care in handling. Higher reaction rates can be achieved during the reactions of polymer functionalization, and their loading capacity is

higher. Highly cross-linked macroporous polymers have the advantages of ease of filtration from the reaction medium, and large pore sizes which offer less hindrance to the diffusion of the reactants. While reactivity with gel polymer is a function of swelling, requiring good swelling solvents such as THF, CH_2Cl_2, etc., with macroporous polymers reactions can be carried out in a variety of solvents without appreciable changes in reaction rates.[14]

Active functional groups may be incorporated into the polymer chains (i) by direct polymerisation and copolymerisation of monomers containing the desired functional groups; (ii) by chemcial modification of a preformed polymer, and (iii) by a combination of (i) and (ii). The difficulty with the first method is that considerable manipulation of the copolymerisation procedure may be necessary to ensure a good yield of the required copolymer in a satisfactory physical form. In the second method preformed resins of high quality are normally employed and the desired functional groups introduced by using standard organic synthetic procedures. This ensures a product with good physical form. Functional group distribution, however, is not well understood whatever be the method of forming the functional polymers. This still remains an area requiring more detailed investigation and the development of more suitable analytical procedures. Standard elemental analysis with supporting IR and NMR spectra generally provides satisfactory evidence for chemical modification besides weight gain/loss and allows calculation of the degree of substitution or functionalization of a polymer expressed in milliequivalents per gram of polymer.

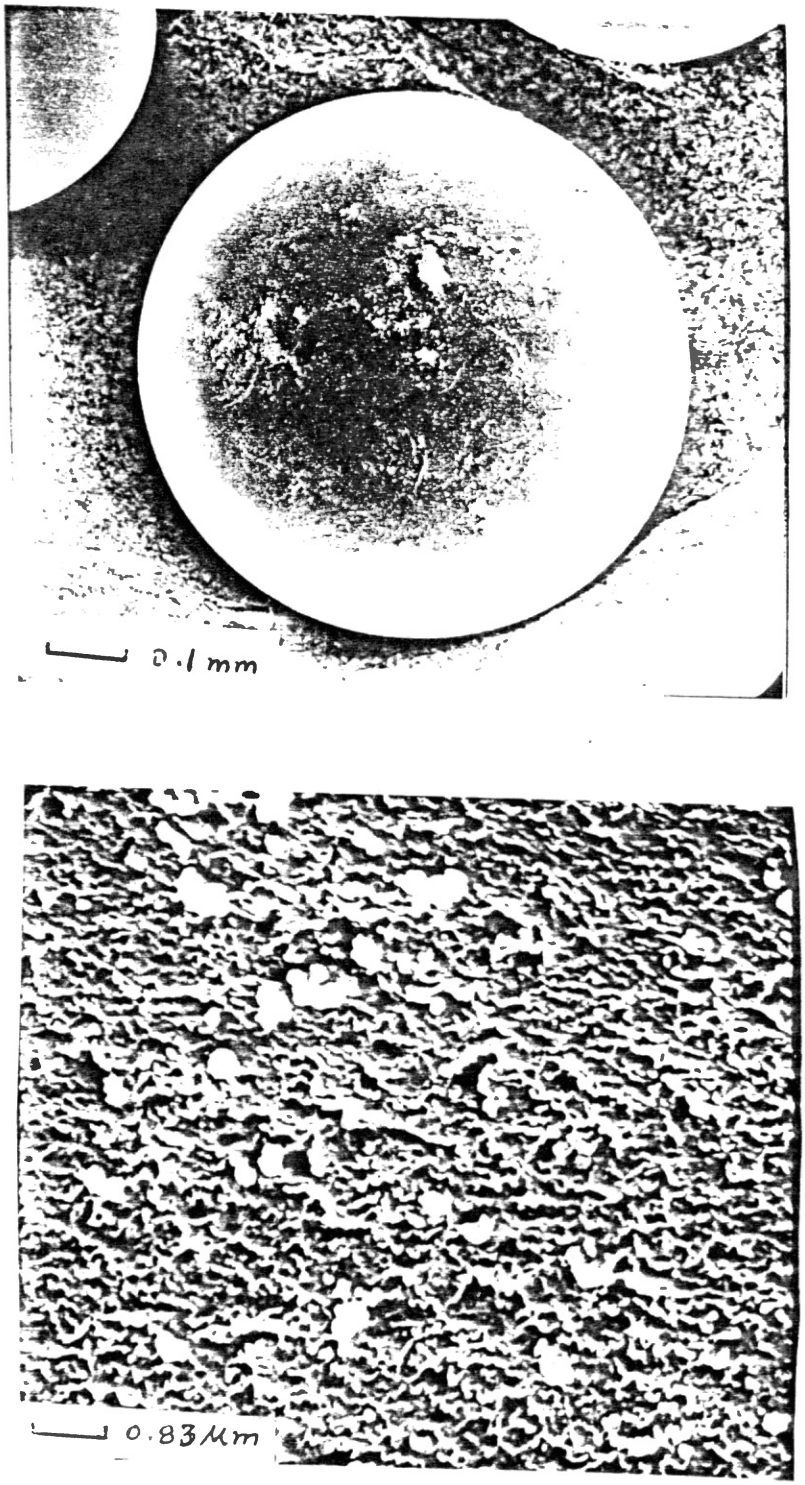




TOP: Magnification 24 x 10^1

BOTTOM: Magnification 16 x 10^3

Figure 1. Scanning Electron Micrographs of 2% DVB Cross-linked Gel Polymer.



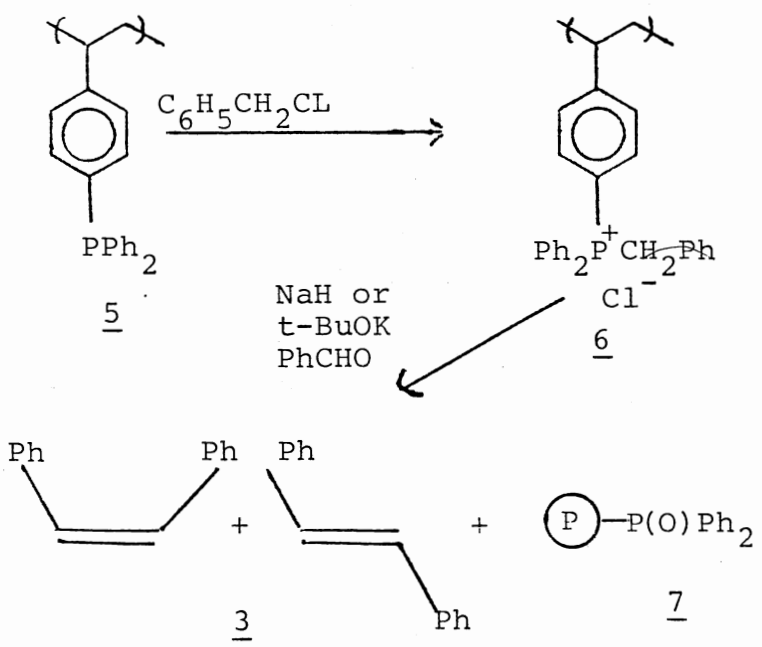
TOP: Magnification 94.
BOTTOM: Magnification 12 x 10^3.

Figure 2. Scanning Electron Micrographs of 20% DVB Cross-linked Macroporous Polymer.

Polymer-Bound Wittig Reagents

The first application of functional polymers in organic synthesis began with the pioneering work of Merrifield[16], who successfully synthesized polypeptides by the use of insoluble 2% divinylbenzene cross-linked polystyrene as a support. Almost simultaneously, Letsinger's group[17] reported the synthesis of a dipeptide on "popcorn polymer support". The efforts of Merrifield and Letsinger served as an impetus to many workers in the fields of chemistry, biochemistry, pharmaceuticals and medical sciences and the utilization of functional polymers in synthetic work has become an ever growing field.[14]

In an attempt to study the scope of solid phase method for Wittig olefinations, Camps, and co-workers,[18] prepared the first polystyrene-supported phosphonium salt. Polystyryldiphenylphosphine 5, was obtained by the copolymerization of 3:1 styrene: p-styryldiphenylphosphine containing 2% divinylbenzene (DVB) as cross-linking agent. As can be seen later in Results and Discussion, such a procedure would put the functional groups in the hindered, highly cross-linked regions of the polymer backbone, making the polymer less reactive than expected. Treatment of 5 (60-140 mesh) with benzyl chloride afforded polystyryldiphenylbenzylphosphonium chloride, 6. A suspension of 6 in THF was treated with equimolar amount of base followed by an equivalent amount of benzaldehyde to give Z- and E- stilbenes 3. A 40% yield was obtained with t-BuOK as base and a 60% yield with NaH. The product mixture contained unreacted aldehyde and side products benzyl alcohol and benzoic acid, which resulted from a Cannizzaro reaction. Use of excess base, such as n-BuLi, and its removal by filtration increased the amount of side products.



In the following year, Heitz and Michaels[19] came out with their independent contribution to the solid phase Wittig synthesis in a comprehensive manner. Cross-linked polymers with 0.5% and 2% DVB were used. Polystyryldiphenylphosphine 5 was obtained by two routes: (1) copolymerization of monomers as discussed earlier and (2) bromination of polystyrene using ferric chloride as catalyst, followed by treatment with sodium diphenylphosphide. Bromination using $FeCl_3$ as catalyst, has been reported to give nonreproducible results with a colored resin of low quality and lacking homogeneity.[20] It has also been observed that in a number of cases, the bromo polymer prepared by using ferric chloride as catalyst, is less reactive than that prepared by using thallium acetate as catalyst. A number of alkylpolystyryldiphenylphosphonium bromides were prepared. These were made to react with a number of aryl carbonyl compounds using excess n-BuLi for phosphorane generation. For the same combination of phosphonium salt and carbonyl

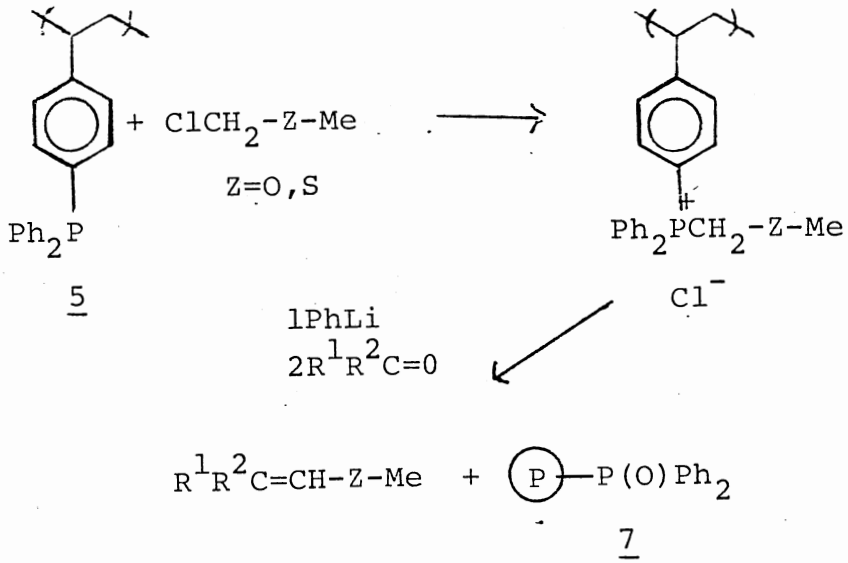
compound the yields varied in the order 48, 26, and 86% with 0.5% and 11, 32 and 68% with 2% cross-linked polymer. Lower yields in the latter case were attributed to the higher degree of cross-linking which, according to the authors, rendered the functional groups on the polymer less accessible to the carbonyl compound. Side products were observed if n-BuLi was not removed prior to the addition of the carbonyl compound.

A parallel effort was by McKinley and Rakshys.[21] Copolymerisation of styrene with p-styryldiphenylphosphine containing 2% DVB led to good yields of 5. Whereas, copolymerization of p-bromostyrene with styrene containing 2% DVB to give bromopolystyrene and treatment of the latter with n-BuLi followed by chlorodiphenylphosphine gave only 60% of 5. Phosphonium salt formation proceeded in yields of 85-100% with benzyl bromide, methyl iodide and ethyl iodide. Phosphoranes were generated by adding an excess of methysulfinylcarbanion and filtering the excess reagent. Wittig olefinations were effected by adding stoichiometric amounts of various aromatic and aliphatic carbonyl compounds with yields ranging from 14-72%. Unreacted carbonyl compounds were recovered in all reactions which again led to the conclusion that a portion of polymer sites was inaccessible to reaction with carbonyl compound. In the products stilbene and ß-methyl styrene E/Z isomer ratios were found to be the same as in monomeric Wittig reactions, under similar conditions.

Hodge and co-workers reported a phase transfer catalyzed method on polymer-supported Wittig reagents.[22] The triphase Wittig reaction was carried out by vigorously stirring a mixture of the phosphonium salt, the carbonyl compound, methylene chloride and 50% aqueous sodium

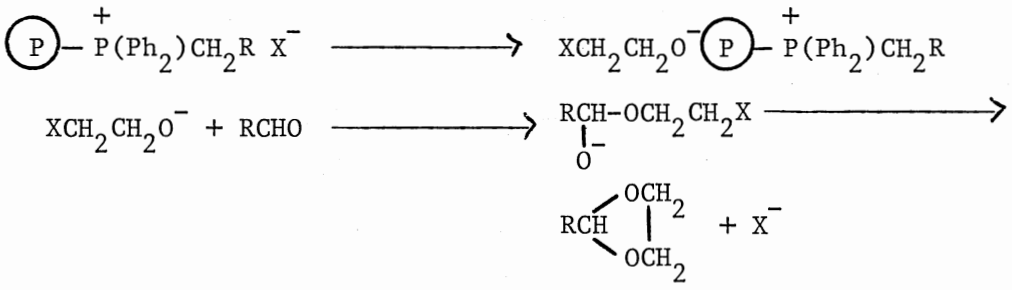
hydroxide with an added phase transfer catalyst. Good yields were obtained from benzylphosphonium salts and aldehydes and moderate yields from allylphosphonium salts and aldehydes. Alkylphosphonium salts failed to react under these conditions. Besides, phase transfer conditions were not successful with ketones. Hydrolysis of the phosphonium salt was found to be a side reaction in most cases.

In a recent investigation by Akelah[23], 2% cross-linked methoxymethyl- and methylthiomethylpolystyryldiphenylphosphonium chlorides were successfully used for Wittig olefination of carbonyl compounds to substituted vinyl ethers and thio ethers as illustrated below.

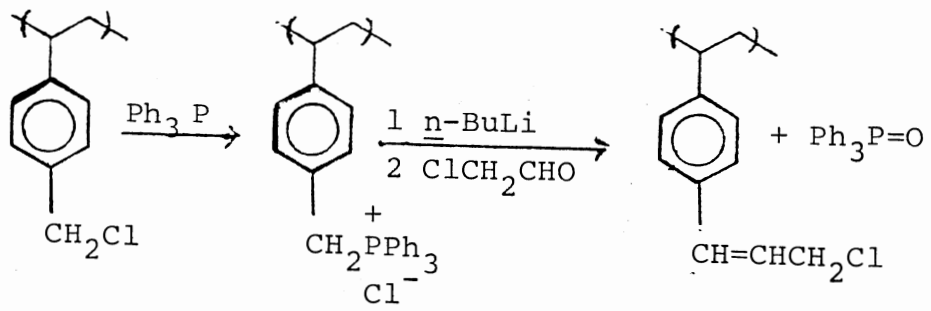


A different concept was the use of 2% DVB cross-linked polystyrene-supported symmetrical diols as monoblocking agents for symmetrical dialdehydes in Wittig olefinations so that only one aldehyde function takes part in the reaction.[24-26] By this approach unsymmetrical carotenoids and insect sex attractants were synthesized in improved yields without symmetrical by-products and with the total recovery of starting material when compared with solution reactions. More

systematic study of the solid phase technique in mono-olefinations came from the work of Castells, Font and Virgili.[27] By use of a molar ratio of 1:1 of the polymeric phosphorane and the dialdehyde they were able to get exclusively mono-olefination product. Different reaction conditions were used for phosphorane generation. The authors claim, that <u>in situ</u> generation of the phosphorane with polymeric phosphine, alkyl halide and ethylene oxide in the presence of dialdehyde was the method of choice for solid phase Wittig reactions. One of the drawbacks, however was formation of ethylene acetal of the aldehyde used as shown below.



A modification of the solid phase Wittig olefination was the preparation of olefins attached to the polymeric-support.[28] Chloromethylpolystyrene was treated with triphenylphosphine to give the polymeric phosphonium salt. The latter was treated with <u>n</u>-BuLi followed by chloroacetaldehyde to give the polymer-bound allyl chloride as illustrated below.



A recent paper by Hodge and Waterhouse[29] reported a phase transfer catalyzed method for polymer-bound olefins. As in other phase transfer Wittig reactions,[22] a portion of the phosphonium salt was hydrolysed to give the phosphine oxide and a hydrocarbon. However this approach provides a versatile method for the preparation of cross-linked polystyrenes with a wide range of pendant groups which could undergo further useful transformations. For example, polymer-supported transition metal complex catalysts can be prepared in this way.[29]

Synthesis of Retinoids by Wittig Reaction and Other Methods

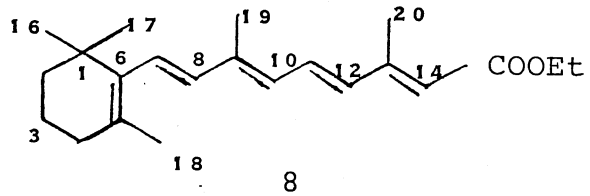
Retinoic acid and its analogues have received considerable attention for their importance in controlling the normal growth, development, and differentiation of epithelial cells.[30] Chemoprevention of cancer by retinoids is currently an active area of research of considerable importance.[31] Natural retinoids are toxic and have an inadequate tissue distribution. Attention was therefore directed towards synthetic retinoids which were more active and less toxic and which had a high degree of tissue specificity for protection against cancer at any particular organ site.[32]

All-*trans*-retinoic acid and its methyl and ethyl esters have carcinostatic activity in the hamster tracheal organ culture assay.[33] Our long range goal is to develop new methods for the synthesis of heteroretinoic acids or the methyl or ethyl esters in an effort to improve the carcinostatic activity and/or to lower the toxicity compared with that of all-*trans*-retinoic acid and its derivatives. The primary research was aimed at synthesizing all *E*-ethyl retinoate

by means of polymer-supported Wittig reagents, which can pave the way for heteroretinoids.

Grignard[34-37] and Reformatzkii reactions were the early routes reported for the synthesis of retinoids. The discovery of Wittig reaction provided a convenient method for the synthesis of retinoids and carotenoids on an industrial scale.[39] Soon Wittig reaction proved to be the most practical and the preferred method for the production of Vitamin A and its derivatives.

Ethyl retinoate 8 has four double bonds in the polyene side chain.



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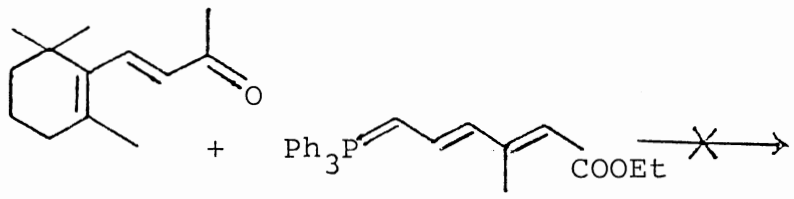
Any of the polyene side chain double bonds could be formed by Wittig condensation in the final step of a retinoid synthesis. The Wittig reaction route to the synthesis of retinoids enabled the exploration of various combinations of different coupling reactions[1,39,40] which eventually were patented.[1,41-43] The two different fragments tried for Wittig olefination were $C_{18} + C_2$, $C_{13} + C_7$, $C_{15} + C_5$ and $C_{10} + C_{10}$, of which any one served as the phosphonium salt and the other as the carbonyl compound.

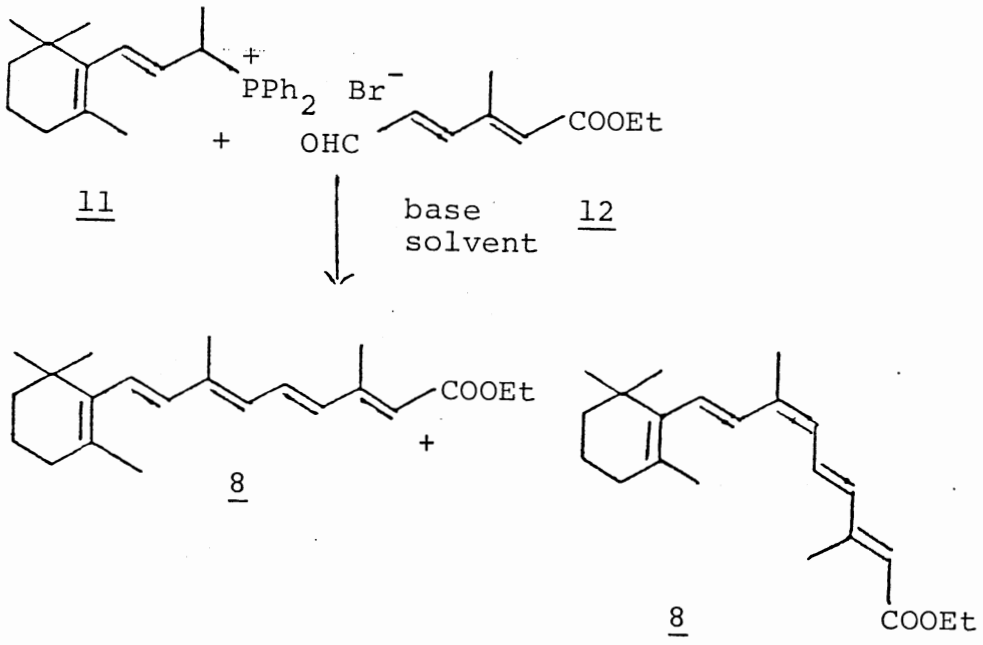
Wittig condensation of a C_{18} ketone with a C_2 phosphonium salt carrying different functional groups such as acetate, alcohol, nitrile, ester resulted in poor yields (3-15%) in most cases.[39]

Of the two possible $C_{13} + C_7$ combinations, ß-ionone 9 (a C_{13} Ketone) showed no reactivity towards a C_7 phosphorane 10.[40]



9 10

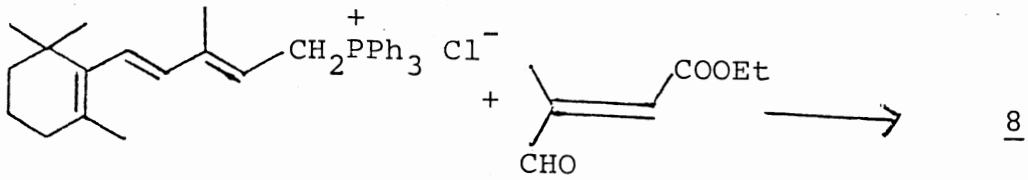
In contrast the C_{13} phosphonium salt, ß-ionyltriphenylphosphonium bromide (11) readily reacted with the all-trans C_7 aldehydic ester 12 to give a mixture of all-trans and 9-cis ethyl retinoate 8.(29)[39,40,44]



11 12 8 8

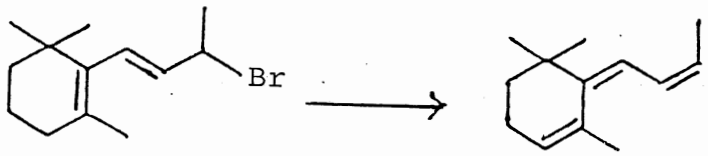
In general, good yields (60-70%) were obtained but the method gained little practical importance because of the presence of 9-cis isomer which could not be converted to the all-trans isomer.

The technical manufacturing procedure of Vitamin A, Vitamin A acid and the corresponding ethyl ester developed by Pommer,[39b] was based on the Wittig reaction of a ß-ionylideneethyltriphenylphosphonium halide 13 with a C_5 aldehyde function 14[14] in the presence of sodium methoxide.[45] The product from 13 and trans-ethyl ß-formylcrotonate 14 was a mixture of all-trans and 11-cis ethyl retinoate from which the all-trans isomer could be obtained by subsequent iodine catalyzed isomerization.

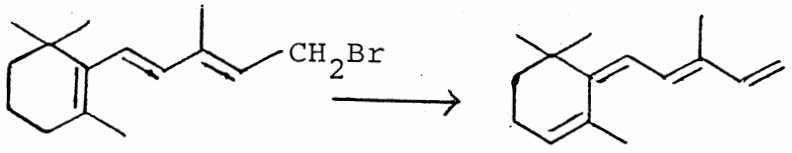


13 14

ß-Ionyl halide (15) and ß-ionylideneethyl halide (17) necessary for the corresponding phosphonium salts were unstable and readily eliminated hydrogen bromide at room temperature to form the triene (16) and the tetraene (18) respectively.[39b]



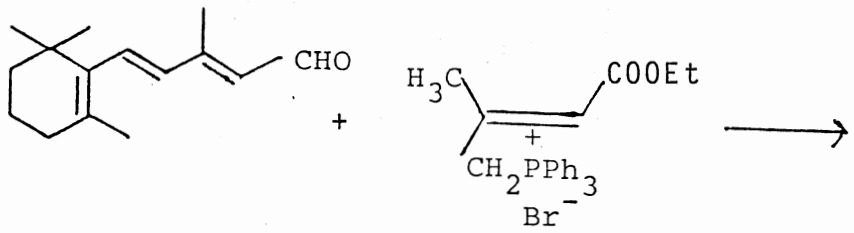
15 16



17 18

The phosphonium salts 11 and 13 were made by treating the respective alcohols with triphenylphosphonium bromide. Even the phosphonium salts 11 and 13 in solution existed in equilibrium with triphenylphosphonium bromide and alkenes as (16) and (18). Therefore 11 and 13 were used as prepared and not isolated.[33b]

Improved yields (40%) were reported for the reaction between ß-ionylidene acetaldehyde (19) and the C_5 ester phosphonium salt (20).[39b,41]

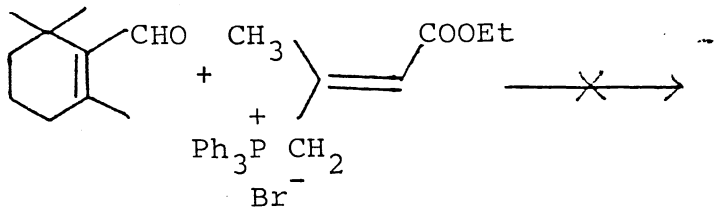


8

19 20

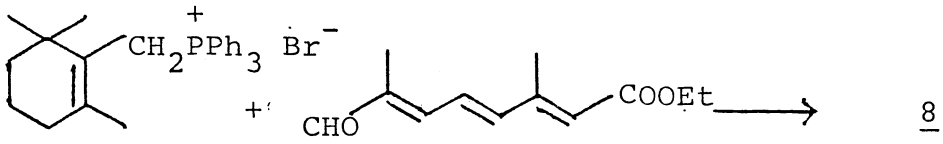
Use of isomeric mixtures of 19 and 20, resulted in a mixture of isomeric products: 9-cis, 11-cis, and 13-cis in addition to the all-trans isomer. It was easy to isomerise the 11-cis and 13-cis double bonds but the 9-cis double bond remained unaffected by iodine.[39b] The C_{15} aldehyde, (ß-ionylideneacetaldehyde) (19) was extremely unstable, undergoing decomposition unless used immediately. The ^1H NMR spectral analysis indicated that the phosphorane generated from phosphonium salt 20 contained Z- and E- isomers in the ratio 2:1.[46]

Initial attempts of a Wittig condensation between ß-cyclocitral (21), a C_{10} aldehyde and a C_5 ester phosphonium salt 20 were unsuccessful due to the lack of reactivity of hindered aldehyde.[46b]



21 20

The phosphonium salt ß-cyclogeranylphosphonium halide (22) readily reacted with C_{10} triene aldehydic ester 22 to give all-trans-ethyl retinoate 8 as the major product (65%).[39b,42].

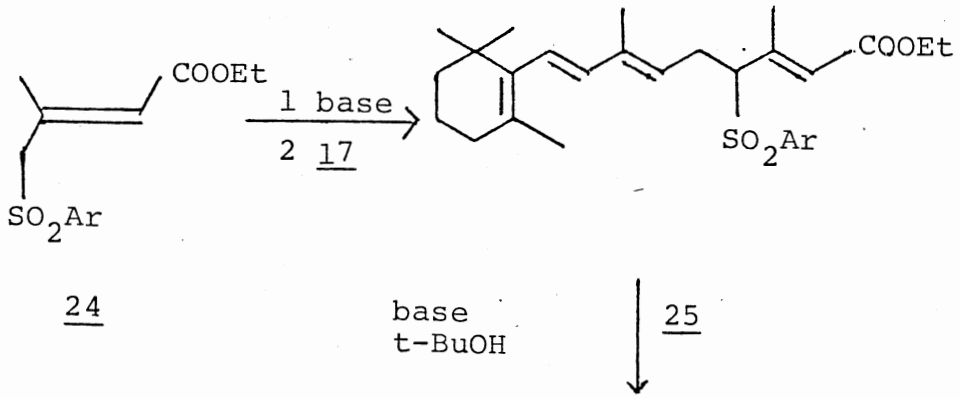


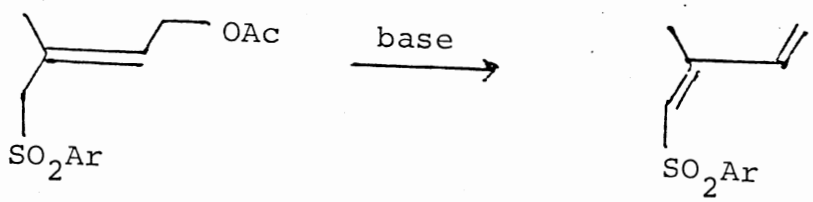
22 23 8

Strongly polar solvents such as dimethylformamide, methanol and ethanol served better than less polar solvents for the above mentioned Wittig condensations and in most cases sodium alkoxide was used as the base.[43] Other bases such as sodium acetylide and phenyllithium were also used in some instances.[42] One of the major problems encountered in the Wittig reaction route to retinoids was the separation of the triphenylphosphine oxide by-product. The separation of the phosphine oxide was accomplished on an industrial scale[39a] by a lengthy countercurrent extraction using hydrocarbon solvents and aqueous alcohol, which is cumbersome and there is a likely tendency for the retinoid to undergo decomposition. For example the acidification step prior to

extraction can cause partial decomposition of the product retinoid and the longer time involved in the extraction process may lead to isomerization of the retinoid.

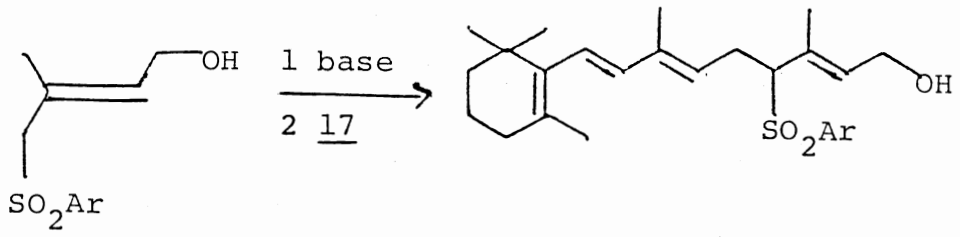
The undesirability of the triphenylphosphine oxide as a by-product and the desirability of enhancing the stereoselectivity of alkene forming process, has prompted the investigation of alternative approaches to the synthesis of retinoids. Reports of recent origin include sulfone alkylation-elimination route[47] isonitrile anion route[48], and palladium induced decarboxylative elimination reaction[49] as alternatives to Wittig reaction. For example, exclusive formation of 11, 12-trans double bond was effected by sulfone route[47a] by using all-trans-C_{15} bromide 17 and trans- sulfone ester 24. As mentioned earlier, good yields of the unstable 17 could not be obtained. Around 40% of 17 underwent elimination to the tetraene 18.[47a] Depending on the functional group at the allylic sulfone 26, elimination to the diene 27 has sometimes been observed under the conditions of alkylation.[47c]





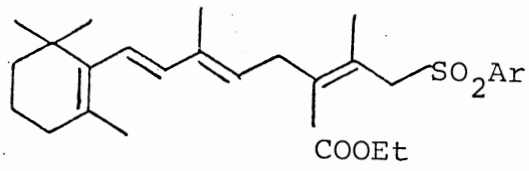
26 27

Besides, the functional group at the sulfone also had some influence on the orientation of the alkyl substituent. For example, the hydroxy sulfone 28 gave exclusively α-alkylation product 29.



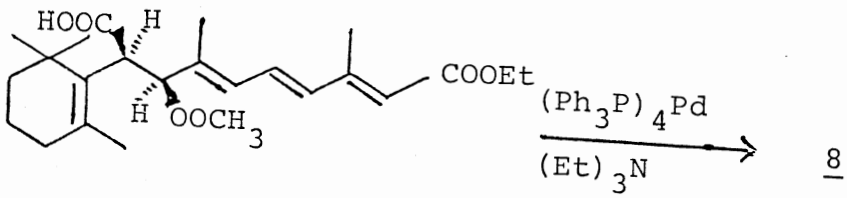
28 29

whereas 24 gave both α- and γ-alkylation products 25, and 30.[47c]



30

Trost and Fortunak[49] accomplished exclusive trans-geometry at the 7,8-double bond by decarboxylative elimination of acetoxy acid 31 using $(Ph_3P)_4Pd$.



31 8

The number of steps involved in the work of Trost reduced the overall yield from 35 to 40% from 2,2,6-trimethylcyclohexanone to 8.

In view of the side reactions and lower yields confronted with sulfone[47] and decarboxylative elimination[49] routes to ethyl retinoate, the polymer-bound Wittig reaction route appears more promising due to the quick and convenient separation of the phosphine oxide by-product. In addition, an increased degree of cross-linking of the polymer, can promote trans-selectivity in the olefination step as can be seen in the Results and Discussion. Use of phosphonate ester carbanions instead of phosphoranes, can also improve the stereospecificity as mentioned earlier.

CHAPTER II

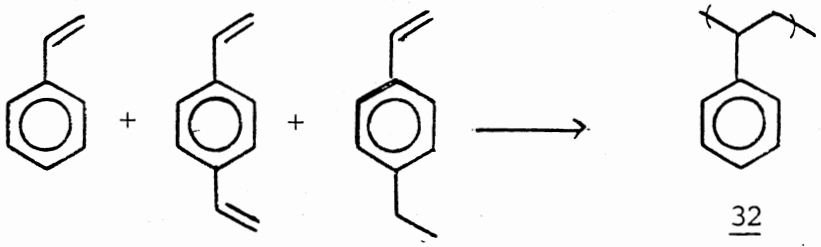
RESULTS AND DISCUSSION

Although Wittig olefinations by the use of polymeric phosphoranes have been studied,[18,19,21-23] no attempt was made to optimize the conditions for specific phosphonium salts. A search of the literature revealed that no study on the effect of higher (>2%) degree of cross-linking and the effect of macroporosity of the polymer in Wittig olefinations has ever been reported. Accessibility of the large molecules to the polymeric phosphorane remained unexplored because penetration of large molecules through a polymer matrix was thought to be very difficult. Though the reduction of the polymeric phosphine oxide was mentioned,[18b] its reusability was not established. Stimulated by these observations and in an effort to synthesize light and air sensitive ethyl retinoate which shows prophylactic activity in the treatment of cancer,[35] we attempted to study the polymer-bound Wittig reagents in a broader outlook.

Polystyrene (32) Gel Polymers Cross-linked with 2% and 8% Divinylbenzene (DVB), and Macroporous polymer with 20% DVB

The 2% and the 8% DVB cross-linked polystyrenes (32) were prepared by suspension techniques, using azobis (isobutyronitrile) (AIBN) as the free radical initiator. It was necessary to distill the styrene

and the divinylbenzene prior to polymerization, to remove the inhibitor and small quantities of polymer formed in storage. Addition of anionic surfactant sodium dodecylbenzenesulfonate (SDBS) gave sizable amount of fibrous material and clustered beads, in the product polymer which considerably reduced the yield (61%). Separation of single beads from the mixture was difficult.[50] Polymerization in the absence of SDBS gave better yields of polystyrene (80-88%). Use of teflon blade stirrer was more convenient than the stainless steel one, with the optimum stirring rate of 340-380 rpm, for maximizing the yield of 60/100 mesh particles. To effect better dispersion in the reaction mixture, the position of the blade was adjusted at the interface of organic and the aqueous layers. Polymerization was complete in about 36 h, at 70°C. Macroporous 20% DVB cross-linked polystyrene was obtained from Rohm and Haas. The most probable pore size of the macroporous polystyrene used in this research is 900 Å (in dry form measured by mercury penetration porosimetry).[51] The microparticles are approximately the same size as the pores. With 2% and 8% cross-linked polystyrene 60/100 mesh beads and with 20% DVB macroporous polystyrene 25/60 mesh beads were used for Wittig olefinations.



32

Bromination of Polystyrene

The method developed by Heitz and Michels[52] for the bromination of 32 gave orange yellow colored bromo polymer 33. As mentioned earlier in the introductory part this method leads to nonreproducible results with reduced reactivity of 33. Ferric chloride-catalyzed bromination of toluene in nitromethane produced 36% ortho-and 64% para-bromotoluene.[53a] Initial functionalization of the polystyrene at the hindered ortho position may affect the polymer reactivity for further functionalization. Whereas functionalization at the para position would make the functional group more accessible for further ring modifications. It is known from literature[53b] that thallium acetate catalyzed bromination of anisole in CCl_4 yielded 91% para substituted product and of o-xylene gave 85% of para substituted product. We expect a similar behavior with polystyrene. Thus bromination by bromine in CCl_4 with catalytic amounts of thallic acetate sesquihydrate[20] (Scheme 1 shows the reaction sequence for the formation of alkylpolystyryldiphenylphosphonium salts 34 and 35 from cross-linked polystyrenes 32.) resulted in 100% conversions for all the three types of polymers, the only limiting factor being the amount of bromine added (Table I). The bromopolymer 33 obtained had a cleaner appearance than that obtained by $Br_2/FeCl_3$ method. The reaction proceeded more easily with the smooth disappearance of bromine color as the sample was refluxed. Elemental analysis confirmed the required amount of bromine (3.00 mequiv/g) in 33. (Table I)

TABLE I

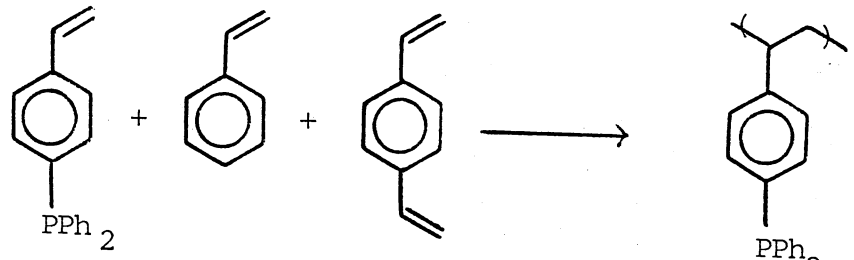
BROMINATION OF POLYSTYRENE

Copolymer, % Cross-linking	Moles of $Tl(OAC)_3$ per mole of PS	Moles of Br/mole of PS	mequiv Br/g	% Conversion	% RS[a]
2	0.02	0.43	3.10	100	44.0
2	0.02	0.43	3.05	99	43.0
8	0.02	0.44	3.03	98	43.0
8	0.02	0.42	2.94	96	42.0
20	0.02	0.43	3.08	100	46.0

[a]Percentage ring substitution

Phosphination of Bromopolystyrene (33)

In some of the earlier lnvestigations the polystyryldiphenylphosphine (5) was prepared by copolymerization of p-styryldiphenylphosphine, styrene and divinylbenzene.[17,21] as shown below.



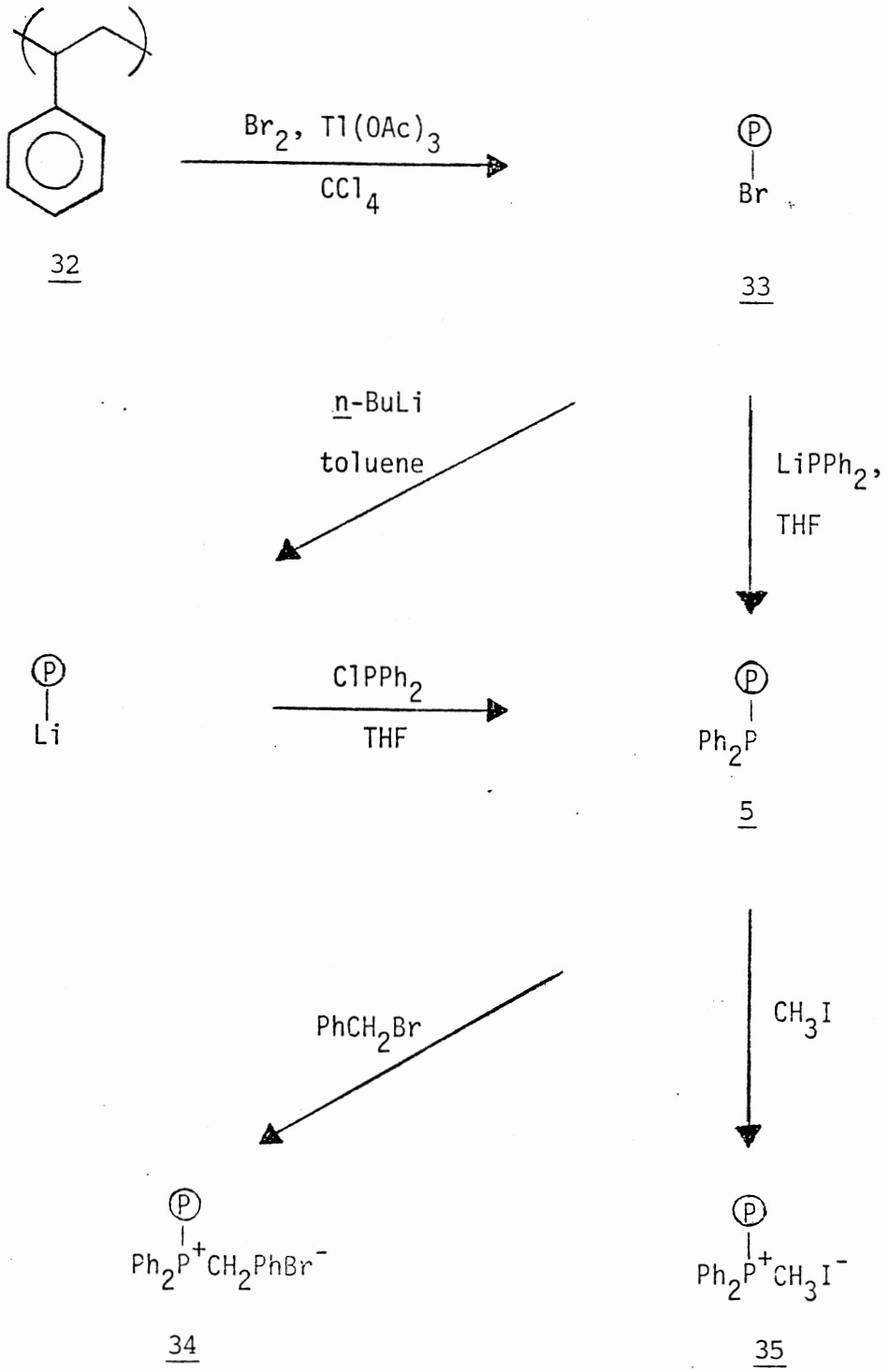
5

The copolymer reactivity ratios for styrene (m_1) and p-styryldiphenylphosphine, (m_2) are r_1=0.46-0.53, and r_2=1.11-1.43.[54] Those for styrene and m-divinylbenzene (m_2) are r_1=0.5-0.9 and r_2=0.6-1.1, and for styrene and p-divinylbenzene (m_2) are r_1=0.2-0.7 and r_2=1.0-1.2.[55] The values imply that both p-styryldiphenylphosphine and divinylbenzene are incorporated into the polymer faster than styrene itself during free radical polymerization. The phosphine groups are preferentially incorporated into the more highly cross-linked regions of nonuniformally cross-linked polymers. In subsequent reactions some of these sites are difficult or impossible for an external reagent to reach even when the 2% cross-linked polymer is swollen. In contrast, when bromination of cross-linked polystyrene is the initial method of functionalization, any selectivity leads to bromine incorporation at the more accessible sites in the polymer matrix.

In our investigations conversion of bromo polymer 33 to phosphine 5 (Scheme 1) appeared to be the most critical step in the reaction sequence, in that it proceeded with increasing difficulty in the order 2% < 8% < 20% macroporous 33. Two main reaction routes have been studied. Treatment of 2% DVB cross-linked bromo polymer 33 in THF with chlorodiphenylphosphine followed by lithium metal gave 64% conversion to 5 with no residual bromine.[56] Following the method of Regen and Lee,[57] by adding preformed lithium diphenylphosphide to the THF swollen 33 and stirring at room temperature for 48 h. afforded >90%, 65% and 35% conversions with 2%, 8% and 20% macroporous DVB cross-linked 33. Added 6 h heating at 65°C increased the percentage conversion to 83 with 8% DVB cross-linked 33, but had no effect on 20% macroporous 33 (Scheme 1) (Table II). Elemental analysis of 5 from 8% and 20% macroporous DVB crosslinked polymers confirmed the presence of residual bromine which accounted for all of the sites that were not transformed to phosphine. (See experimental section for a sample calculation of % conversion). This revealed that some of the active sites in the more highly cross-linked 33 failed to react with the bulky lithium diphenylphosphide.

In the second approach bromopolystyrene (33) in toluene was treated with excess n-BuLi to give the lithiated polymer, which in turn was treated with chlorodiphenylphosphine in THF[20] to give 80% and 38% conversion to 5 with 2% and 20 % DVB cross-linked 33. (Scheme 1). Elemental analysis of the phosphine 5 showed the absence of bromine in 2% DVB cross-linked polymer and an insignificant amount (2.42%, 0.03 mequiv/g) in 20% DVB cross-linked polymer. This implies that, the lithiation step was quantitative but apparently the

Scheme 1.

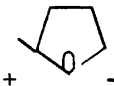

Br2, Tl(OAc)3
CCl4
32
33
n-BuLi
toluene
LiPPh2,
THF
ClPPh2
THF
Li
Ph2P
5
PhCH2Br
CH3I
Ph2P+CH2PhBr-
Ph2P+CH3I-
34
35

chlorodiphenylphosphine failed to reach all of the lithiated sites. Overall loss of bromine without incorporation of phosphorous could have occurred by protonation of residual polystyryllithium during the H_2O/acetone washing of the phosphine product. Alternatively some replacement of hydrogen by bromine could occur by a side reaction accompanying $S_{RN}1$ subsitution in which an aryl free radical abstracts a hydrogen atom from the THF solvent.[58] A speculative radical pathway for

$ArLi \longrightarrow ArH$ is,

$$ArLi + ClPPh_2 \longrightarrow Ar^{\cdot} + LiCl + {}^{\cdot}PPh_2$$

$$Ar^{\cdot} + {}^{\cdot}PPh_2 \longrightarrow ArPPh_2$$

$$Ar^{\cdot} + \text{  } \longrightarrow ArH + \cdot\text{  }$$

As the degree of cross-linking is increased the polymer becomes more rigid with a tight network which may hinder the approach of considerably larger ions or molecules such as diphenylphosphide ion or chlorodiphenylphosphine, to the reactive site in the polymer. This may be ascribed as one of the probable reasons for low % conversions in phosphination with 20% DVB cross-linked macroporous polymer. Besides different polymer morphology of the 20% macroporous polymer may also have its contribution.

Formation of Phosphonium Salts 34 and 35

Functional modification of all the three types of phosphines to the benzyl- and methylpolystyryldiphenylphosphonium salts (34) and (35) (Scheme 1) proceeded with good yields (80-93%) (Scheme 1) (Table III). Phosphonium salts 34 and 35 were formed by treating the phosphines

TABLE II

PHOSPHINATION OF BROMOPOLYSTYRENE

Copolymer, % Cross-linking	Brominated copolymer, mequiv Br/g[a]	Phosphine polymer mequiv Br/g[a]	Phosphine polymer mequiv P/g[a]	% Conversion	% RS
A. Lithium diphenylphoshide method					
2	3.05	0.00	2.09	91	39.0
2	3.10	0.00	2.40	100	44.0
2	3.05	0.05	2.12	92	40.0
8	2.94	0.63	1.60	65	27.0
8[b]	3.00	0.02	2.01	83	36.0
20	3.08	1.63	0.97	35	16.0
20	3.08	1.64	0.70	25	12.0
B. n-Butyllithium/chlordiphenylphosphine method					
2	3.10	0.00	0.00	80	35.0
20	3.08	0.03	1.13	38	18.0

[a]By elemental analysis.

[b]The reaction mixture was heated at reflux an additional 6 h.

TABLE III

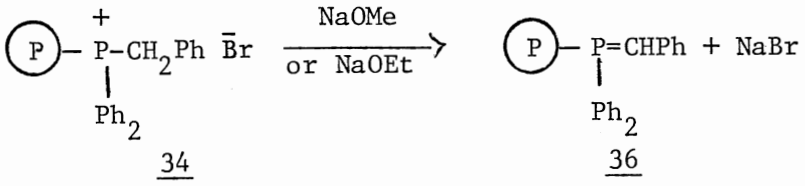
FORMATION OF BENZYL- AND METHYLPOLY-STYRYLDIPHENYLPHOSPHONIUM SALTS 34 (A) AND 35 (B)

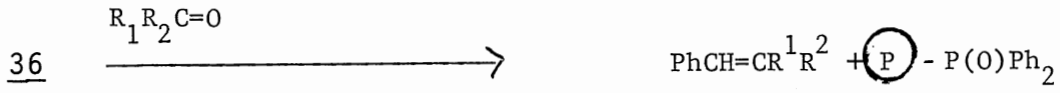
Copolymer % Cross-linking	Phosphine mequiv P/g	Phosphonium salt mequiv Br/g	% Conversion	% RS
A.				
2	2.09	1.23	80.0	31.0
2	2.40	1.41	86.0	38.0
2	2.09	1.36	93.0	36.5
8	1.60	1.00	80.0	22.0
20	1.13	0.69	83.0	15.0
B.				
2	2.09	1.25	78.0	30.5
2	2.09	1.38	85.0	33.0
8	2.01	1.38	88.0	31.5
20	0.97	0.66	81.0	13.0
20	0.70	0.63	100.0	20.0

with benzyl bromide and methyl iodide respectively using either benzene or dimethylformamide as solvents. Use of Me_2SO as solvent[21] retained some solvent in the polymer in spite of vacuum drying at 60°C for two days, and the polymer beads were partially fractured into powder, which rendered it difficult to handle for further operations. The percentage conversions in the phosphonium salts were determined by the ion exchange (titrimetric) determination of the bromide and iodide contents of 34 and 35 (Table III). In some cases the percentage conversion to 34 and 35 were also counterchecked by elemental analysis for phosphorous and halogen (Br or I).

Phosphorane Generation and Wittig Olefination of 34 and 35

In previous reports,[18,21] benzylidenepolystyryldiphenylphosphoranes (36) were generated by bases such as NaH, t-BuOK and dimethylsulfinyl carbanion, and were treated with benzaldehyde to give yields of stilbene 60%, 40% and 35% respectively. Since 34 is an activated salt with acidic protons, it was found advantageous to use sodium alkoxide as the base for phosphorane 36 generation. By this approach use of excess base, filtration and washing of the resin after the phosphorane generation was unnecessary since filtration of NaBr prior to carbonyl addition resulted in poor yields of the olefin. Phosphonium salt 34 in THF was treated with equimolar amounts of sodium methoxide in methanol or sodium ethoxide in ethanol to obtain 36. The 2% and macroporous 20% DVB cross-linked polymers attained the characteristic orange-red phosphorane color in 3-4 h of stirring at room temperature. The 8% DVB cross-linked sample required 12-16 h to attain full color.





Wittig olefination of 36 with aldehydes were complete after 16 h at room temperature and 2-4 h at 60°C with 2% and macroporous 20% cross-linked polymers, and 24 h at room temperature and 4 h at 60°C with the 8% cross-linked polymer. With different carbonyl compounds the yields of olefins ranged from 72 to 93% by GLC analysis (Table IV). With 2% cross-linked polymers the extent of phosphorane generation was determined by washing the NaBr from the polymer after the reaction and titrating the solution for bromide ion.

Trans-Cinnamaldehyde and trans-α-methylcinnamaldehyde were used for the synthesis of 38 and 39. GLC analysis of the product olefins 38 and 39 showed the presence of only the E,E- and E,Z-olefins. This was further confirmed by ^{1}H NMR spectral analysis. In our reactions with cinnamaldehyde and α-methylcinnamaldehyde no side products of Cannizzarro reaction were observed as found in earlier reports. Addition of benzaldehyde after generation of phosphorane 36 gave 2% benzyl alcohol by GLC analysis. Whereas simultaneous addition of benzaldehyde and sodium ethoxide to the phosphonium salt 34 gave no benzyl alcohol in the product olefin 3 by GLC analysis.

The yields of olefins and amounts of recovered aldehyde in Table IV indicate that the rates of phosphorane generation and/or olefin formation decrease in the order 2% > macroporous 20% > 8% cross-linked polymer. The higher yields with 2% cross-linked polymer indicate that some of the phosphonium sites did not react with the base, sodium alkoxide or with the aldehydes in the 8% and macroporous 20% cross-linked polymer. The Z:E product ratios decrease in the order 2% > 8% > macroporous 20% cross-linked polymer. This brings to light an important consideration in the stereoselectivity of Wittig olefinations, wherein we can effect increased trans-selectivity by the use of macroporous 20% cross-linked polymers.

The methylidenepolystyryldiphenylphosphoranes (37) were generated by the addition of three molar equivalents of the sodium salt of dimethylsulfoxide to 35 swollen in a 1:1 (V:V) mixture of THF and Me_2SO. The phosphorane generation was complete after 6 h of stirring with the formation of green black color with 2% and macroporous 20% cross-linked polymers, whereas with 8% cross-linked polymer the phosphorane generation was incomplete even after 16 h of stirring as evidenced by iodide determination of the recovered polymer by titrimetric method. The excess base and the solvents were filtered and the polymer was washed with THF prior to the addition of the carbonyl compound. The rest of the procedure with 37 was similar to the procedure used for benzylidenephosphorane 36. A 5-25% excess of phosphonium salt was used with cyclohexanone, cinnamaldehyde and benzophenone. A 40-50% excess of phosphonium salt was used and the mixture was kept at 60°C for 24 h with the larger ketones, 10-nonadecanone and cholest-4-en-3-one. The extent of phosphorane generation was

TABLE IV

OLEFINS FROM POLYMER-SUPPORTED BENZYLPHOSPHONIUM SALT 34

Copolymer, % Cross-linking	mequiv P^+	aldehyde	mequiv aldehyde	product	% Yield[a]	isomer ratio Z/E, or Z,E/E,E	% recovered aldehyde	% NaBr Released[b]
2	2.42	PhCHO	2.50	PhCH=CHPh	93	57/43	0.50[c]	100.00
				3				
8	2.60		2.23		73	48/52	16.0	d
20[e]	2.38		1.86		80	28/72	18.0	d
2	2.45	PhCH=CHCHO	3.27	PhCH=CHCH=CHPh	89	40/60	2.5[c]	95.00
				38				
8	2.00		1.85		77[f]	35/65	0.5[c]	d
20[e]	2.06		2.09		72[g]	17/83	10.5	d
2	2.53	$PhCH=C(CH_3)CHO$	2.53	$PhCH=C(CH_3)CH=CHPh$	89	30/70	6.0	92.00
				39				

TABLE IV (Continued)

Copolymer, % Cross-linking	mequiv P^+	aldehyde	mequiv aldehyde	product	% Yield	isomer ratio Z/E, or Z,E/E,E	% Recovered aldehyde	% NaBr Released
2	3.20	n-$C_{11}H_{23}CHO$	3.07	n-$C_{11}H_{23}CH{=}CHPh$	d	43/57	2.5	d

[a] By GLC analysis unless noted otherwise.

[b] By Mohr titration of the NaBr washed from recovered polymer.

[c] Based on calculated amount that could react with phosphorane.

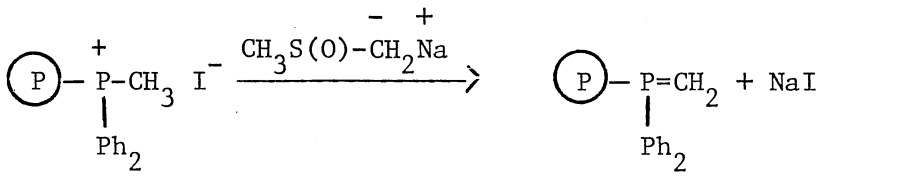
[d] Not determined.

[e] Macroporous.

[f] Recrystallized yield.

[g] Yield based on ^1H NMR integration.

established by the titrimetric determination of the residual iodide in the recovered polymer.



35 37

7

The yields of Wittig reaction of the phosphorane 37 ranged from 52% to 99% by GLC analysis (Table V) higher than in an earlier report (14-72%).[21] Here again yields of olefins in all cases depended on the polymer: 2% > macroporous 20% > 8% cross-linked polymer. The recovered polymeric phosphine oxides with 8% cross-linking contained 39% and 47% of the original iodide ion (Table V) indicating incomplete phosphorane generation. The sodium salt of the dimethylsufoxide in dimethylsulfoxide failed to penetrate to some of the phosphonium sites. This accounts for the lowest yields with the 8% cross-linked polymer.

With macroporous 20% cross-linked polymer, penetration of a reagent to a reactive site requires transport from bulk liquid to the particle surface, transport through the liquidfilled macropores of the polymer, and transport through a path of less than 900 Å of the 20% cross-linked polymer matrix. Diffusion through the macropores should proceed at the same rate as diffusion through a quiet liquid. Diffusion through the polymer matrix will be much slower. Transport of molecules to the reactive sites in a macroporous polymer is much faster

TABLE V

OLEFINS FROM POLYMER-SUPPORTED METHYLPHOSPHONIUM SALT 35[a]

Copolymer, % Cross-linking	mequiv P^+	carbonyl compound	mequiv carbonyl compd	product	% Yield[b]	% recovered carbonyl compd[c]	I^- left in polymer, mequiv[d]
2	2.55	$(CH_2)_5CO$	2.42	$(CH_2)_5C{=}CH_2$	99	0.0	0.00
				2			
2	2.75	PhCH=CHCHO	2.63	$PhCH{=}CHCH{=}CH_2$	95	0.0	0.00
				41			
8	3.22		2.73		52(72)[e]	7.0	1.25
20[f]	3.15	Ph_2CO	2.65		83	0.0	g
2	2.75	Ph_2CO	2.52	$Ph_2C{=}CH_2$	94	0.0	g
				1			
8	3.48		2.78		61(92)[e]	34.0	1.63
20[f]	2.45		2.30		74	10.0	0.00
2	3.79	$(n\text{-}C_9H_{19})_2CO$	2.52	$(n\text{-}C_9H_{19})_2C{=}CH_2$	96[h]	0.4	0.00
				42			

TABLE V (Continued)

Copolymer, % Cross-linking	mequiv P^+	carbonyl compound	mequiv carbonyl compd	product	% Yield[b]	% recovered carbonyl compd[c]	I^- left in polymer, mequiv[d]
20[f]	2.47		1.74		62[h]	34[i]	0.00
2	3.74	cholest-4-en-3-one	2.48	3-methylenecholest-4-ene	91[h]	0.0	0.00
				43			
20[f]	2.40		1.62		87[h]	9.5	[g]

[a] The phosphorane was generated by adding 3 equiv. of the sodium salt of Me_2SO to a mixture of the polymer in Me_2SO at -10°C and warming to room temperature. The carbonyl compound was added, and the mixture was stirred 16 h at 20°C and 4 h at 60°C.

[b] By GLC analysis.

[c] Area % of (reactant and products) in GLC analysis.

[d] By ion exchange analysis.

[e] Yield in parenthesis based on phosphonium salt consumed.

[f] Macroporous.

[g] Not determined.

[h] After addition of ketone was stirred and heated for 24 h at 60°C and stirred 24 h at 20°C.

[i] Phosphorane was partially decomposed by accidental exposure to air before addition of 10-nonadecanone.

than in a non-macroporous polymer of the same macroparticle size and degree of cross-linking because most of the transport occurs through liquid-filled pores rather than through the cross-linked matrix. Evidently the much shorter diffusion path required to reach the active sites in the macroporous polymer enabled higher conversion to phosphorane at 20% cross-linking than at 8% cross-linking without macroporosity. The 20% cross-linked polymer, however, gave lower yields of olefins than the 2% cross-linked polymer even though it contained no residual iodide ion. This must be due to a failure of the aldehydes and ketones to penetrate to all of the phosphorane sites in the 20% cross-linked polymer. We presume at this point, that longer reaction times might have afforded higher yields. Even the larger ketones 10-nonadecanone, and cholest-4-en-3-one penetrated the 20% cross-linked macroporous polymer to give good yields from reactions with 37.

The maximum unreacted carbonyl compound observed with 2% cross-linked polymer was 6 area % by GLC analysis (Table V) much less than previous observations.[21] By maintaining a ratio of 2:3 for carbonyl compound and phosphonium salt as is usually done in Wittig olefinations, the unreacted carbonyl compound was found to be almost absent (Table V).

Recycling of Phosphine Oxide 7 to Phosphine 5

Reduction of 2% and macroporous 20% cross-linked phosphine oxide 7 to phosphine 5 were successfully carried out by refluxing 7 in benzene with Cl_3SiH and N,N-dimethylaniline.[18b,57,59] By substituting triethylamine[57] with N, N-dimethylaniline,[59] we believed that the latter would serve as a swelling solvent and enhance

the transport properties of the polymer. Huge excess of $HSiCl_3$ and longer reaction times as reported by previous workers,[57] were found unnecessary, Using 1.5 moles of Cl_3SiH and refluxing the mixture for 16 h 92% yield of 5 was obtained, established by quantitative ^{31}P NMR analysis. Treatment of the product mixture with aqueous NaOH is an essential step in the solution reaction[59] to separate the phosphine from the trichlorosilane by-products. In a polymeric reaction this was found unnecessary if the $HSiCl_3$ used is < 2 moles per mole of phosphine oxide.[57] The siloxane side products from trichlorosilane remain in solution in the presence of benzene and N,N-dimethylaniline and are removed by repeated washings with benzene, THF and ether in nitrogen atmosphere. The recycled 2% cross-linked phosphine 5 gave the phosphonium salt 34 and E- and Z-stibenes (3) by Wittig reactions with benzaldehyde with no reduction in yield over three cycles (Table VI). The recycled macroporous 20% crosslinked phosphine 5 gave a 75% yield of stilbene (Table VI).

Ethyl Retinoate

The facile separation of phosphine oxide by-product from the Wittig olefination product mixture, its recovery and reusability, besides enhanced trans-selectivity in the product olefins with 20% cross-linked polymer, motivated us to explore the polymer-bound Wittig reaction route to the synthesis of ethyl retinoate (8). Retinoids in general are sensitive to light, thermally unstable, readily oxidized and easily isomerized and their separation from reaction mixtures is difficult.

TABLE VI

RECYCLING OF POLYMERS FOR WITTIG SYNTHESES OF STILBENE

Cross-linking, %	Cycle	g $Ar_3P{=}O$ polymer used	g Ar_3P polymer recovered	g Ar_3P polymer used	g $Ar_3\overset{+}{P}CH_2Ph$ polymer recovered	mequiv P^+/g	g P^+ polymer used	g $Ar_3P{=}O$ polymer recovered	% yield stilbenes
2	1	-	-	-	-	1.24	1.97	1.69	93[a]
	2	11.10[b]	10.70	8.10	10.80	1.24	1.94	1.55	93[c]
	3	2.39[d]	2.30	2.30	2.91	1.30	2.28	1.76	97[c]
20	1	-	-	-	-	0.69	3.45	e	80
	2	5.99[b]	5.80	5.24	5.99	0.64	1.83	1.62	75

[a] Phosphorane was generated before benzaldehyde was added.

[b] Combined phosphine oxide polymer from four different experiments.

[c] Sodium ethoxide to generate phosphorane and benzaldehyde were added at the same time.

[d] Part of the polymer recovered from cycle 2 shown and polymer from a duplicate of cycle 2 were used.

[e] Not determined.

The two phosphonium salts which attracted our attention as retinoid precursors were 3-ethoxycarbonyl-2-methylallylpolystyryldiphenylphosphonium bromide (46), a C_5 ester phosphonium salt, and polystyryldiphenylß-cyclogeranylphosphonium bromide (49), a C_{10} compound. Better reactivity was anticipated of these compounds than of C_{13} and C_{15} phosphonium salts 11 and 13 in which the conjugated double bonds make the phosphoranes less reactive due to resonance stabilization. It has been reported[39b] that the halide precursors of 11 and 13, though easy to form, are very unstable and eliminate hydrogen halide forming the corresponding triene 16 and tetraene 18. The C_5 bromo ester 45 and the C_{10} bromide 48 are stable when stored in the refrigerator.

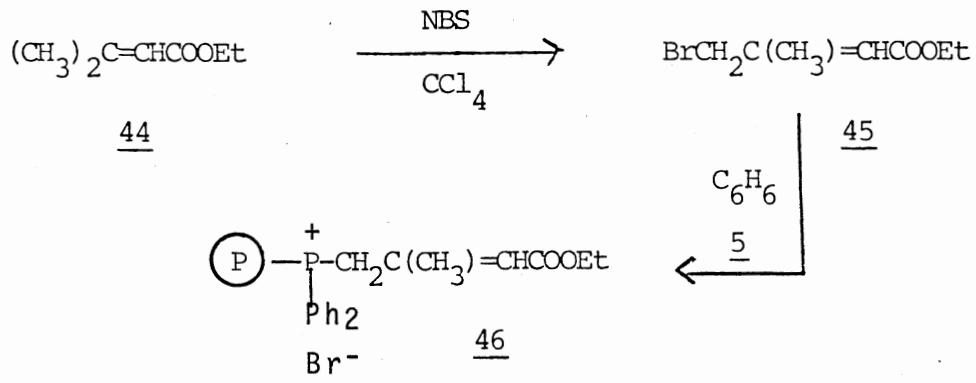
Preparation of Phosphonium Bromides 46 and 49

Polymer-bound C_5 and C_{10} phosphonium bromides 46 and 49 were prepared as per schemes II and III.

Allylic bromination of ethyl-3-methyl-2-butenoate 44 with N-bromosuccinimide (NBS) in CCl_4, in the presence of catalytic amounts of azobis (isobutyronitrile) (AIBN) proceeded in 74% yield of the bromo ester 45.[60] GLC analysis of the product revealed two major peaks in the ratio 41:59 corresponding to Z and E isomers of 45 and a small peak of longer retention time indicative of some dibromo compound, which was separated by distillation.
No attempt was made to separate the E-and Z-bromo esters 45 as it was known from previous literature[46] that both E-and Z-phosphonium salts with benzaldehyde lead to the same isomeric mixture (2:1) of the product olefins. The mixture of E-and Z-45 was

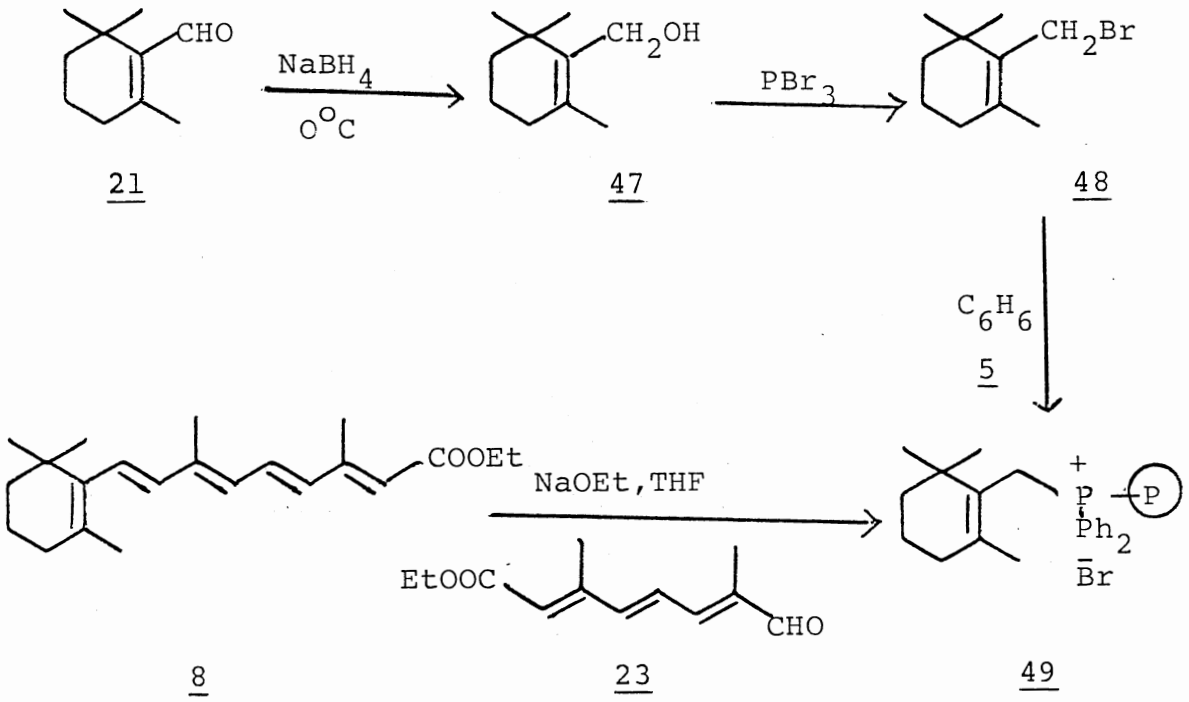
treated with 2% and 20% DVB cross-linked phosphine 5 to give the corresponding phosphonium salt 46 with 84% and 78% conversions respectively (Table VII). ^{31}P NMR analysis of the phosphonium salt 46 showed 2 signals very close to each other at ∂ 21.79 and at δ 21.95 ppm indicative of two isomers.

Scheme II.



Reduction of ß-cyclocitral (21) with $NaBH_4$ in CH_3OH at 0°C resulted in 80% yield of ß-cyclogeraniol (47).[61,62] ^1H NMR spectral analysis of the compound was indicative of a single isomer. Reduction with aluminum isopropoxide[61] was found to give ∝-cyclogeraniol as a minor product. Phosphorous tribromide treatment of 47 in the presence of catalytic amounts of pyridine led to ß-cyclogeranyl bromide 48 in 92% crude yield.[61] The compound 48 without further purification was treated with phosphine 5 in DMF which gave polystyryldiphenyl-ß-cyclogeranylphosphonium bromide 49[63] in 78.5% conversion based on bromide analysis (Table VII). ^{31}P NMR analysis showed a signal at δ 18.74 ppm confirming the phosphonium salt formation.

Scheme III.



Compound 49 could also be formed by the reaction of 47 with polystyryldiphenylphosphine hydrobromide (50).[39b,43]

5 50

Attempts to prepare 50 by treating 5 with methanolic hydrobromic acid in methanol or methanolic hydrochloric acid in methanol[39b,43] at room temperature gave the corresponding methylphosphonium salt (P--P(Ph_2)CH_3Br) and unreacted 5 which gave signals in ^{31}P NMR spectrum at 21.4 and δ -6.2 respectively. Use of ethyl acetate as solvent and purging the reaction mixture with hydrogen bromide[64] at

TABLE VII

FORMATION OF 3-ETHOXYCARBONYL-2-METHYLALLYL- AND ß-CYCLOGERANYLPOLYSTYRYLDIPHENYLPHOSPHONIUM BROMIDES 46 (A) AND 49 (B)

Copolymer % cross-linking	Phosphine mequiv P/g	Phosphonium salt, mequiv Br/g	% Conversion	% RS
A.				
2	2.09	1.22	84.0	33.0
2	2.09	1.16	80.0	31.0
20	0.70	0.48	78.0	10.0
B.				
2	2.09	1.11	79.0	31.0
2	2.09	0.95 (1.25)[c]	88.0	35.0

[a] By elemental analysis

[b] By bromide determination

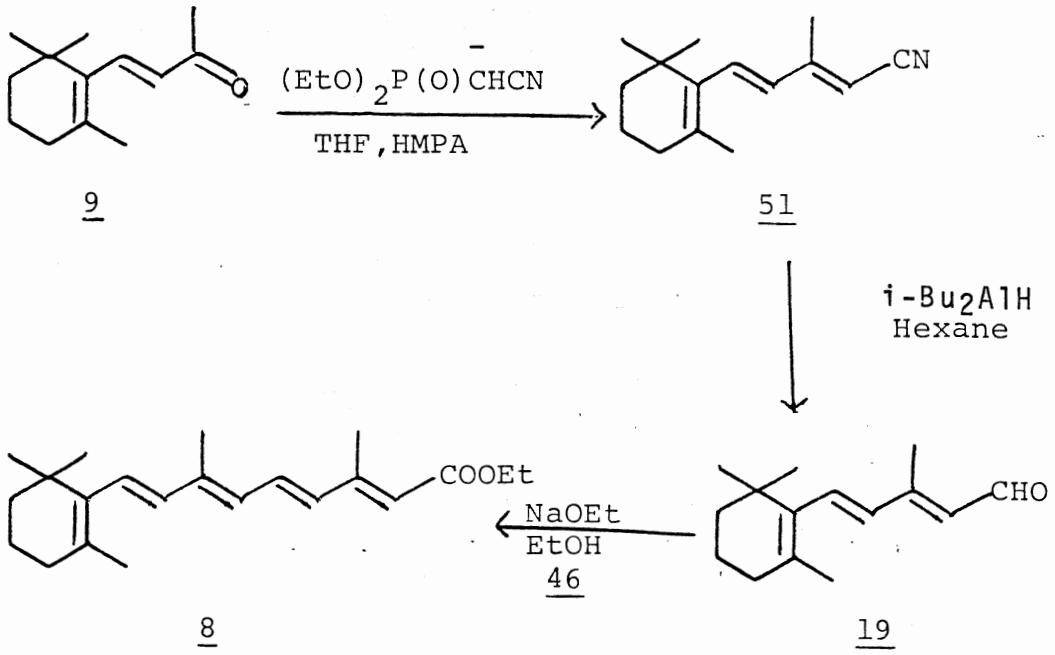
[c] Triarylphosphine hydrobromide

0°C and then warming to room temperature resulted in the corresponding ethylphosphonium salt (P -$P(Ph_2)C_2H_5Br$) which showed a peak at ∂25.45 in ^{31}P NMR spectrum besides the peak for unreacted phosphine. Phosphine 5 failed to react with HBr when DMF was the solvent. Treatment of phosphine 5 with aqueous hydrobromic acid in THF solvent also showed no reactivity.[65] Taking 5 in benzene and passing hydrogen bromide for five minutes at 0°C and then warming to room temperature and stirring for 24 h resulted in 79% of 50 established by bromide determination. ^{31}P NMR analysis gave a signal at δ -9.09 ppm. The hydrobromide reacted with 47 to give 49 in 87.8% yield.

Preparation of ß-Ionylideneacetaldehyde (19)

ß-Ionylideneacetaldehyde (19) was obtained in two steps from ß-ionone (9) (Scheme IV).

Scheme IV.

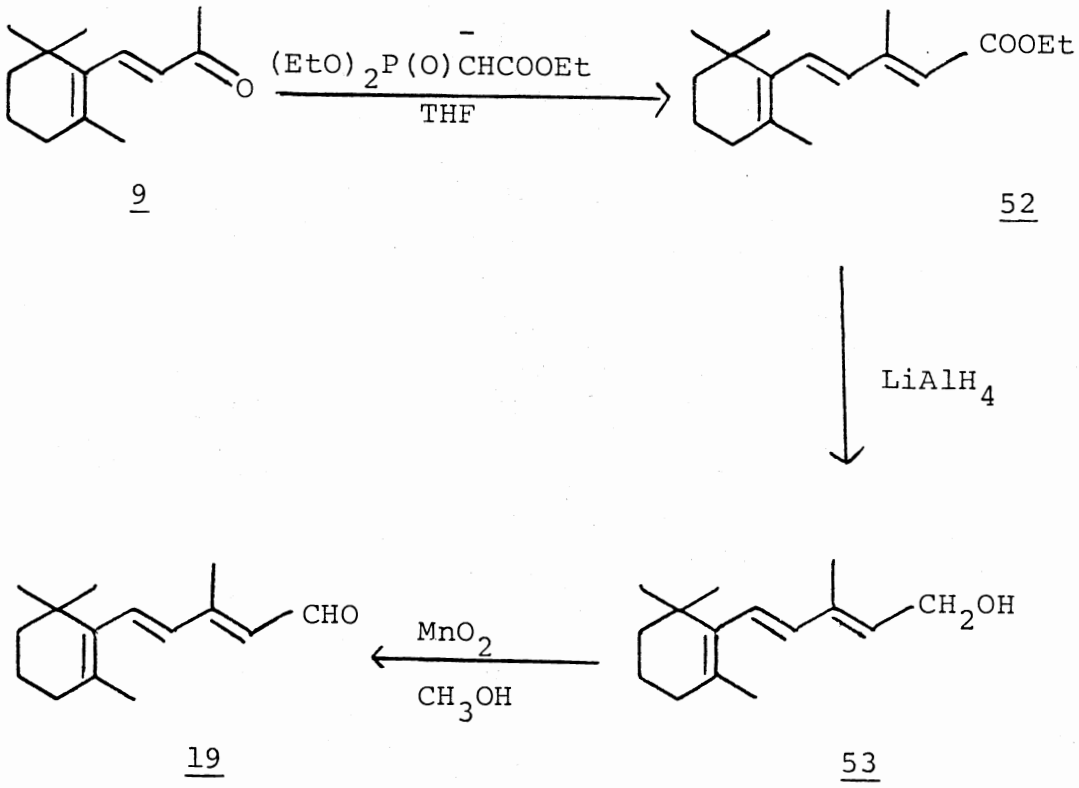


9 51 8 19

ß-Ionone 9 readily reacted with the sodium salt of diethyl cyanomethylphosphonate in THF to give ß-ionylideneacetonitrile (51) in 90% yield.[66] GLC analysis and ^1H NMR data of 51 indicated the presence of two isomers, namely 7(E),9(E) and 7(E),9(Z), in the ratio 60:40. Preparation of 19 with added hexamethylphosphoramide (HMPA) (1.5 moles/mole of 9) under otherwise the same conditions gave 80:20 mixture of E,E- and E,Z-nitriles 51 from 9 and diethyl cyanomethylphosphonate. Reduction of 51 with diisobutylaluminum hydride (DIBAL-H) in hexane proceeded smoothly and the highly unstable ß-ionylideneacetaldehyde 19 could be isolated in 87% crude yield by breaking the aldimine complex with silica gel (20% water) in 1:1 (v/v) mixture of ether/hexanes.[67] Our previous attempts to break the complex with CH_3OH containing small amounts of water, acidification by 10% HCl[68a] or 10% H_2SO_4[68b] and then extraction partly decomposed the product aldehyde to an orange red viscous oil, lowering the yield to around 40%.

A three step reaction sequence to obtain 19 from 9 was first to effect the chain extension of 9 by triethylphosphonoacetate which gives ethyl-ß-ionylideneacetate (52). The ester 52 is then reduced in the second step by lithium aluminum hydride, to the alcohol 53 which in turn is oxidized by MnO_2 to give 19.[69] The MnO_2 oxidation of 53 to 19 was not complete in our attempts. Despite stirring the reaction mixture for six days in the dark, only 50% conversion to 19 was seen by GLC (Scheme V).

Scheme V



9 52 19 53

Wittig Olefination of Phosphonium Salts 46 and 49 leading to Ethyl Retinoate (8)

The carbonyl olefinations of 19 to 8 were effected by simultaneous addition of 19 and NaOEt in approximately stoichiometric amounts to 2% and to macroporous 20% cross-linked C_5 phosphonium salts 46 in absolute ethanol and stirring the mixture at room temperature for 20 h. The products were purified by filtration through Waters SEP-PAK C_{18} cartridges. Correlation of the weight of the product with ^1H NMR integration data afforded 70% yield in the case of 2% and 65.4% yield in the case of macroporous 20% cross-linked polymer (Table VIII).

TABLE VIII

ETHYL RETINOATE 8 FROM 46 AND 49

Copolymer % Cross-linking	P^+	mequiv P^+	aldehyde	mequiv aldehyde	% Yield
2	46	2.16	19	2.00	70[a] (92)[b]
20	46	1.20	19	1.00	65.4[a] (100)[b]
2	49	1.67	23	1.00	55[c]
2	49[e]	2.80	23	1.90	50[d]

[a] Yield after SEP-PAK purification.

[b] Yield based on ^1H NMR integration.

[c] Crude Yield.

[d] Yield based on recrystallized retinoic acid.

[e] Not isolated.

The product was analyzed by HPLC to be a mixture of 7 isomers. The 7 isomers were separated into 5 fractions by HPLC and identified by ^{1}H and ^{13}C NMR (Tables X and XI) analyses to be all-trans, 9-cis, 11-cis, 9,13-di-cis, 13-cis, 11,13-di-cis, and 9,11,13-tri-cis isomers of ethyl retinoate (8). The isomer distributions according to HPLC peak areas with 2% and macroporous 20% cross-linked polymers are presented in Table IX. It becomes evident from the data that 46% of the product had 11-cis double bond when the phosphonium salt 46 was the 2% cross-linked polymer. The amount of 11-cis double bond isomers in the product considerably reduced to 26% when 46 was macroporous 20% cross-linked polymer, thereby implying increased stereoselectivity in the olefination step. Interestingly the proportion of biologically active 13-cis and all-trans[70] isomers of 8 changed from 36% in 2% cross-linked polymer to 49% in 20% macroporous cross-linked polymer. The percentage of 9-cis isomers was found to be 30%, 10% more than what is expected from a 80:20 ratio of E,E- and E,Z-C_{15} nitriles 51. This might have occurred by stereomutation during the diisobutylaluminum hydride reduction of 51. It is worth mentioning that the isomeric mixture of 46 produced 13-cis and 13-trans double bonds in the ratio 62.5:37.5 with 2% cross-linked polymer and 58:42 with 20% cross-linked polymer, an observation in close agreement with the 60:40 ratio previously reported[46a] for the reaction of benzaldehyde with monomeric C_5 phosphonium salt 20.

Addition of aldehyde 19 after phosphorane generation from 46 led to poor yields (<30%), maybe due to the resonance stabilization of the ylide from 46, which is slow to react.

Iodine catalyzed isomerization of 8 from macroporous 20% cross-

TABLE IX

ETHYL RETINOATE (8) FROM 46 AND 19 ISOMER DISTRIBUTION

Isomer	Copolymer % Cross-linking 2	20	After I_2 Isomerization
all-trans	15.2	21.8	41.3
9-cis	8.0	12.0	12.5
11-cis	14.3	8.4	4.2
9,13-di-cis	9.7	12.0	5.0
13-cis	20.6	27.3	31.2
11,13-di-cis	21.1	11.9	2.5
9,11,13-tri-cis	10.9	5.9	3.2

linked polymer, in ether/benzene (1:1) for three days under refrigeration at 0°C reduced the number of major isomers to three, as listed in Table IX.

Two sets of experiments were tried on C_{10} phosphonium salt 49. In the first, the phosphonium salt 49 formed from 48 and 5 was used for Wittig olefination without isolation in THF, by the simultaneous addition of C_{10} aldehydic ester 23 in THF and NaOEt in ethanol (Scheme III). HPLC of the crude product showed 2 peaks in the ratio 77:23 which were identified and characterized by ^1H NMR to be all-trans and 7-cis isomers of ethyl retinoate (8) (Table VIII). The esters 8 were hydrolyzed to the acids by refluxing with ethanolic KOH. All-trans-retinoic acid (38%) was separated by recrystallization from CH_3OH. In the second experiment the phosphonium salt 49 was separated from the reaction mixture by filtration, purified by washing and dried at 50°C. This afforded 78.5% conversion to 49. Wittig olefination of 49 with 23 gave 55% yield of the crude ethyl retinoate 8 consisting of all-trans and 7-cis isomers in the same ratio 77:23 (Table VIII). Iodine catalyzed isomerization of 8 obtained from 49 and 23, in 1:1 ether/benzene gave 13-cis and all-trans 8 with the HPLC relative areas 25:75.

Spectra 5 and 6 represent the ^1H NMR and ^{13}C NMR of all-trans-retinoic acid. The chemical shifts values in the spectra agree with the literature values.[70]

Study of the ^1H NMR data of the ethyl retinoate isomers revealed that the methyl proton chemical shifts of all the 7 isomers (excluding the ester proton chemical shifts) agreed within $\pm$0.03 ppm with the methyl shifts previously reported[70] for methyl retinoate (Table X).

Spectrum 7 is the ^1H NMR of the combined all-trans and 9-cis isomers of ethyl retinoate (8). The ester proton chemical shifts were at ∂ 1.35 for the CH_3 and at ∂ 4.20 for the OCH_2 protons. The vinyl proton chemical shifts of all-trans isomer agreed well within ± 0.03 ppm with the reported values for the corresponding methyl ester. In the 9-cis isomer slightly different chemical shifts were observed for H-7 and H-12. H-7 of the 9-cis isomer was at ∂ 6.28 rather than at ∂ 6.23 assigned earlier.[70] Irradiation of the doublet of doublets of H-11 at ∂ 7.08 collapsed the doublets of H-10 and H-12 to singlets at ∂ 6.05 and at δ 6.21. H-12 was at ∂ 6.27 in earlier report.[70]

Spectrum 8 shows the ^1H NMR of the 11-cis isomer. The ester protons were seen at ∂ 1.30 and at ∂ 4.20. As is evident from the spectrum H-7 and H-8 had slightly upfield shifts at ∂ 6.29 and at ∂ 6.15 compared with ∂ 6.35 and ∂ 6.21 observed earlier.[70] The values observed in our spectrum look reasonable based on the chemical shifts observed for H-7 and H-8 at ∂ 6.26 and at ∂ 6.12 in 11,13-di-cis isomer. In the coupled spectrum a multiplet was observed for H-10 and H-11 with sharp peaks at ∂ 6.56 and ∂ 6.58. Irradiation of the H-12 multiplet between ∂ 5.9 - 5.94, caused the multiplet of H-10 and H-11 to collapse to a broad singlet at ∂ 6.57, indicating that both H-10 and H-11 had the same chemical shift. Irradiation of the signal at ∂ 6.57 resulted in a singlet for H-12 whose signal was at ∂ 5.92, slightly upfield compared to ∂ 6.0 reported earlier. Coupling constant $J_{11,12}$ was 8 Hz, and $J_{10,11}$ was not possible to measure because of the broad singlet for H-10 and H-11 in the decoupling experiment.

Spectrum 9 is the ^1H NMR of the combined 13-cis and 9,13,di-cis isomers of ethyl retinoate (8). The ester protons showed up at

TABLE X

^{1}H NMR CHEMICAL SHIFTS AND COUPLING CONSTANTS OF ETHYL RETINOATE ISOMERS AND ALL-TRANS RETINOIC ACID

Isomer	Vinyl Proton Chemical Shifts						Methyl Proton Chemical Shifts				∂ of Ester Protons		J, Hz		
	7	8	10	11	12	14	16,17	18	19	20	OCH_2	CH_3	7,8	10,11	11,12
All-trans-acid	6.30	6.17	6.16	7.06	6.33	5.81	1.03	1.72	2.02	2.38	----	----	16	11	15.5
All-trans-ester	6.28	6.14	6.15	7.00	6.27	5.77	1.03	1.73	2.02	2.37	4.20	1.31	16	11-11.5	15
9-cis-ester	6.28	6.65	6.05	7.08	6.21	5.77	1.05	1.75	2.02	2.36	4.20	1.31	16	11.5	15
11-cis-ester	6.29	6.17	6.57	6.57	5.92	5.88	1.02	1.72	1.97	2.37	4.20	1.30	16	------	8
9,13,-di-cis-ester	6.29	6.65	6.18	7.09	7.74	5.66	1.02	1.72	2.00	2.06	4.18	1.28	16	10-11	15
13-cis-ester	6.26	6.16	6.26	6.99	7.80	5.66	1.03	1.75	2.00	2.07	4.18	1.28	16.5	12	15
11,13,-di-cis-ester	6.26	6.12	6.41	6.62	6.97	5.71	1.02	1.71	1.96	2.17	4.16	1.26	16	12	12
9,11,13,tri-cis-ester	6.28	6.67	6.30	6.71	6.88	5.72	1.02	1.73	1.99	2.18	4.15	1.26	16	12	12

∂ 1.28 and at ∂ 4.28. Otherwise the spectrum looked identical with that of the corresponding methyl ester within ± 0.03 ppm experimental error.

Spectrum 10 is the ^{1}H NMR of the 11,13-di-cis isomer, with the ester proton chemical shifts at ∂ 1.26 and at ∂ 4.16. The methyl and the vinyl proton chemical shifts were in agreement with the values observed earlier within ± 0.03 ppm experimental error.

Spectrum 11 is the ^{1}H NMR of the 9,11,13-tri-cis-ethyl retinoate 8 isomer. But for the ester protons which had chemical shifts at ∂ 1.26 and at ∂ 4.15 the chemical shifts of other regions were in conformity with the values assigned earlier[70] within ± 0.03 ppm allowable limits.

The ^{13}C NMR spectral data for the all-trans retinoic acid and the 7 isomers of ethyl retinoate are presented in Table XI. The chemical shift values for the all-trans-acid and the all-trans- and 13-cis-ethyl esters were in good agreement with literature values, within ± 0.5 ppm for the analogous methyl ester.[70b]

It was not possible to make all the assignments for the 9-cis isomer since the spectrum represented both 9-cis- and all-trans-esters, of which all-trans isomer was predominant.

Chemical shift assignments for 11-cis-isomer were based on the literature values[70b] for the corresponding acetate.

For the 9,13-di-cis, 11,13,-di-cis and 9,11,13-tri-cis isomers, chemical shift assignments were made by approximating the effect of a cis double bond compared to a trans double bond in each of the 9-cis, 11-cis, and 13-cis analogous compounds such as methyl ester or alcohol.[70b]

TABLE XI

^{13}C NMR CHEMICAL SHIFTS OF ETHYL RETINOATE ISOMERS AND ALL-TRANS RETINOIC ACID

Isomers	Carbon Numbers										
	1	2	3	4	5	6	7	8	9	10	11
All-trans-acid	34.22	39.59	19.20	33.09	129.94	137.47	128.83	137.00	140.01	129.20	131.61
All-trans-ethyl ester	34.24	39.59	19.21	33.10	129.99	137.69	128.62	137.26	139.54	129.50	130.90
9-cis-ester	34.24	39.59	19.21	33.10	130.13	138.10	130.13	129.50	------	------	129.99
11-cis-ester	34.26	39.51	19.21	30.04	129.83	137.68 or 137.63	128.52 or 128.97	137.68	139.83	125.83	131.40 or 128.97 or 128.53
9,13-di-cis-ester	34.25	39.50	19.22	33.08	129.91	138.58	128.44	129.91	138.58	129.31 or 128.85	130.95
13-cis-ester	34.25	39.59	19.22	33.11	129.97	137.67	128.60	137.46	139.71	130.33	132.12
11,13-di-cis-ester	34.25	39.51	19.21	33.02	129.69	137.78 or 137.73	128.41	137.73 or 137.78	139.46	126.38 or 126.65	129.14
9,11,13-tri-cis-ester	34.22	39.52	19.25	33.05	130.06 or 130.15	137.91 or 137.88	127.94	130.06 or 129.08	137.88 or 137.91	124.58 or 125.97	130.15 or 130.06

TABLE XI (Continued)

Isomers	Carbon Numbers									
	12	13	14	16,17	18	19	20	C=O	OCH_2	$OCH_2\underline{CH_3}$
All-trans-acid	134.70	154.97	117.48	28.92	21.71	12.92	14.06	------	-----	-------
All-trans-ethyl ester	135.16	152.80	118.58	28.94	21.73	12.89	13.82	167.20	59.64	14.35
9-cis-ester	------	------	118.20	-----	21.73	-----	13.82	167.20	59.64	14.35
11-cis-ester	131.40	153.51	119.25	28.95	21.78	12.36	15.28	167.02	59.69	14.34
9,13-di-cis-ester	128.85 or 129.31	151.04	116.55	28.97	21.85	20.98	-----	166.42	59.62	14.35
13-cis-ester	129.58	154.04	116.55	28.97	21.74	12.88	20.98	166.42	59.62	14.35
11,13-di-cis-ester	126.65 or 126.38	152.42	118.52	28.93	21.74	12.23	25.59	166.09	59.72	14.30
9,11,13-tri-cis	124.58 or 125.97	152.48	118.55	28.97	21.83	-----	25.64	166.12	59.72	14.29

Summary and Conclusions

Successful polymer-supported syntheses require penetration of the reagents from solution into all of the functional sites in the polymer gel. The method by which the potential reactive sites are introduced, the swelling of the polymer matrix, the size of the penetrating reagent and the affinity of the reagent for the polymer all influence the accessibility of potential reactive sites.[14k] The key to success in our polymer-supported Wittig olefinations may be attributed to two major factors: the method of original functionalization of the polystyrene and the method of phosphorane generation. Functionalization via bromination and phosphination of a cross-linked polystyrene, rather than by a copolymerization using p-styryldiphenylphosphine, incorporates the functional group at the more accessible sites in the polymer matrix. In our investigations the reagent which had most difficulty in penetrating the cross-linked polymers was lithium diphenylphosphide or chlorodiphenylphosphine. In the subsequent phosphonium salt formation, phosphorane generation, and olefination, the alkyl halide, the base and the carbonyl compound only needed to penetrate to reactive sites in the polymer that had already been reached by lithium diphenylphosphide. Consequently the Wittig reactions gave higher yields than in previous investigations in which the original functionalization was performed by copolymerization with p-styryldiphenylphosphine.[18,21]

The second factor which is crucial for high-yield in polymer-supported Wittig reactions is use of a solvent/base system that promotes transport of the base to the phosphonium sites. Previous workers used NaH or t-BuOK in THF[18] or n-BuLi in dioxane[19] and obtained apparently incomplete phosphorane formation. The sodium

alkoxide/alcohol/THF method works well for the benzyl and C_{10} phosphonium salts 34 and 49. For the C_5 phosphonium salt 46 sodium alkoxide/alcohol method was found suitable. We suspect that the use of methanol or ethanol promotes swelling of the phosponium ion sites within the polymer matrix, whereas use of only THF as the solvent fails to swell the potentially reactive sites enough for the base to penetrate to all of them. With methylphosphonium salt 35 the use of dimethylsulfoxide as solvent should enable swelling of all of the phosphonium sites.

Previously Heitz and Michels[19] compared 0.5% and 2% cross-linked polystyrenes as supports for Wittig reagents and obtained higher yields with the 0.5% cross-linked polymer using excess n-BuLi in hexane for phosphorane generation. Although their polymers were functionalized by bromination and sodium diphenylphosphide treatment of the crosslinked polystyrene some sites failed to react with n-BuLi. Our results demonstrate that the use of more highly cross-linked polystyrenes is no barrier to high yield olefinations with polymer-supported Wittig reagents. Even large ketones such as 10-nonadecanone and cholest-4-en-3-one reacted with 37 in high yield and precious conjugated aldehydes ß-ionylideneacetaldehyde (19) and 2,6-dimethyl-7-ethoxycarbonyl-2,4,6-heptatrienal 23 reacted with polymer-bound phosphoranes from 46 and 49 in reasonable yields. Moreover, on a large scale the more highly cross-linked, more rigid polymers are much easier to filter from reaction mixtures than the highly gelatinous solvent-swollen 0.5% and 2% cross-linked polystyrenes.

With the 20% cross-linked support the lithium diphenylphosphide reaction defined the number of sites in the polymer to be used in the

subsequent Wittig reaction. Even though the phosphination proceeded in 35% yield, the subsequent steps with less bulky reagents gave good yields.

Polymer-bound Wittig reagents offer a more convenient method than the soluble Wittig reagents for the synthesis of light and air sensitive retinoids, with reasonable yields, and easy separation of the phosphine oxide by-product.

A puzzling but synthetically useful result of this investigation is the marked increase in the fraction of E olefins with increased cross-linking of the polystyrene support. The results might be due to different solvation of the reactive sites in the different supports, but we have no really satisfactory explanation.

The by-product phosphine oxides are reduced to phosphines and reused for Wittig reaction with no reduction in yield.

Other Attempted Work

Polymer-bound Phosphonite Esters 55 and 56

Due to the better reactivity of the resonance stabilized, carbonyl containing phosphoryl carbanions than of phosphoranes with ketones and their ability to promote trans-selectivity in the product olefin, we considered the preparation of polymerbound phosphonite esters.[13]

Though phosphonate esters are well documented in the literature, articles on phosphonite esters are scarce and most of the work in this area comes from Russian journals.

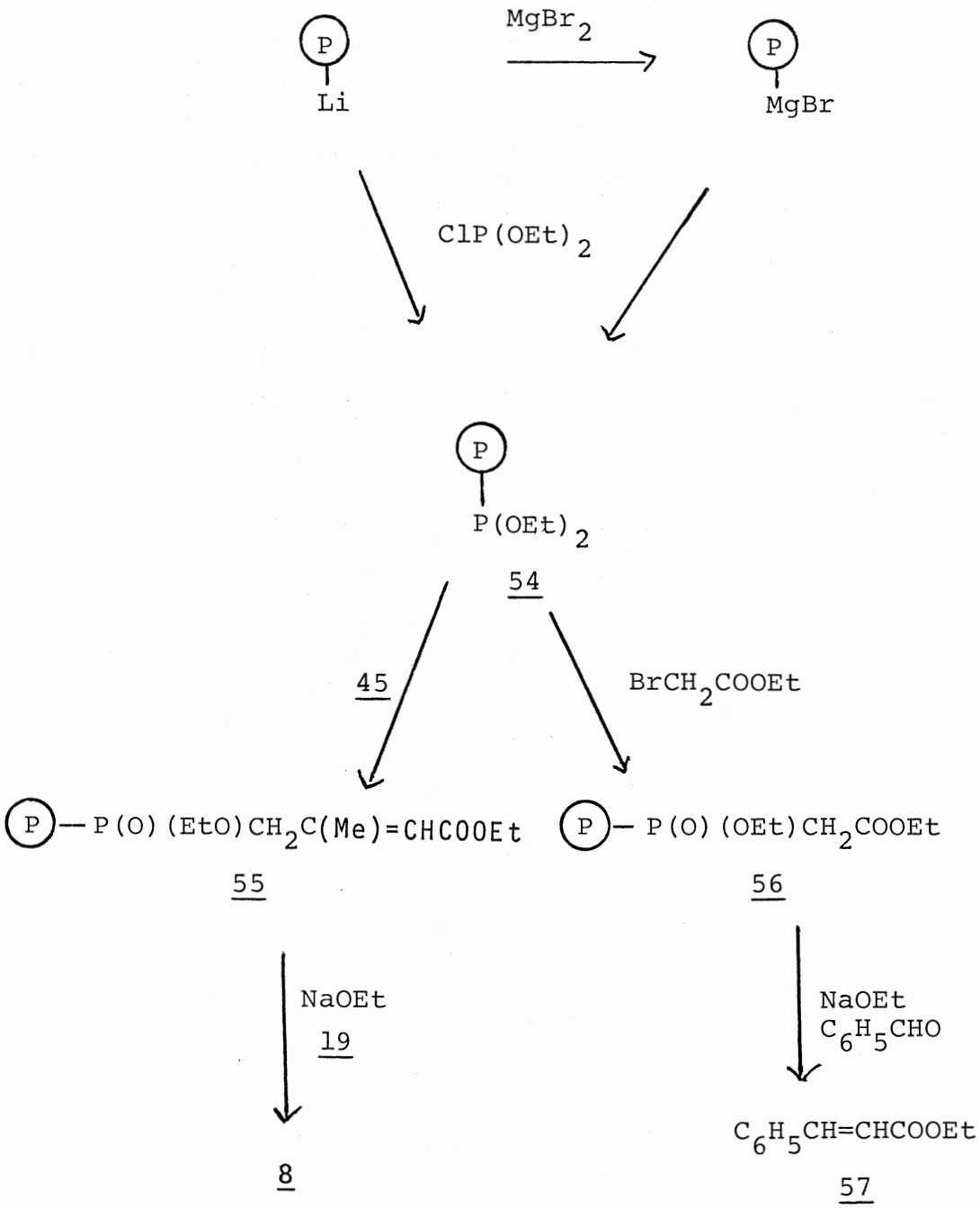
Addition of chlorodiethylphosphite in THF to lithium metal gave a red colored solution with which bromopolystyrene 33 failed to react. This procedure is analogous to lithium diphenylphosphide method for

phosphine 5. Reaction of polystyryllithium (from 33 and n-BuLi) with one equivalent of $ClP(OEt)_2$ at dry ice temperature proceeded in partial conversion to the polystyryldiethylphosphonite 54[71] (Scheme VI). Elemental analysis showed 4.00% P (8.2 expected) and 1.55% Br (24% in 33) in 54. ^{31}P NMR spectrum revealed two broad signals at ∂ 159 and at ∂ 25.8 with relative areas of 55.5% and 44.5%. The above chemical shift values were in good agreement with the literature[71b] values of ∂ 158.5 for the trivalent phosphorous compound $(C_6H_5)P(OC_2H_5)_2$ and at ∂ 20-32 for the compounds of the general formula $OP(R)(OR)_2$.This was further confirmed by IR spectral analysis where the band at 1235 cm^{-1} was due to -P=O and bands at 965, 1030, 1050, and 1160 cm^{-1} were indicative of P-O-C linkage and 1450 cm^{-1} band confirmed P-Ph linkage.[72] In another approach, by converting the lithiopolymer to the Grignard reagent by treatment with freshly formed $MgBr_2$ in THF and then adding $ClP(OEt)_2$[73] at dry ice temperature gave 4.4% P and 1.0% Br in the product 54. ^{31}P NMR and IR spectral data were identical with the previously prepared 54 direct from polystyryllithium, showing the presence of both tri- and pentavalent phosphorous species in the sample.

Michaelis-Arbuzov reaction of 54 with the C_5 bromo ester 45 and with ethyl bromoacetate gave a polymer with a single broad signal at ∂ 30 ppm in ^{31}P NMR spectrum indicative of the formation of phosphinate esters 55 and 56. A band at 1715 cm^{-1} and 1725 cm^{-1} was seen in the IR spectrum for both 55 and 56, confirming the presence of ester carbonyl.

Carbonyl olefination of 56 with benzaldehyde followed by NaoEt gave by GLC analysis 7.5% ethyl cinnamate and 89.7% unreacted benzal-

Scheme VI.


P
Li
MgBr2
P
MgBr
ClP(OEt)2
P
P(OEt)2
54
45
BrCH2COOEt
P— P(O)(EtO)CH2C(Me)=CHCOOEt
55
P— P(O)(OEt)CH2COOEt
56
NaOEt
19
8
NaOEt
C6H5CHO
C6H5CH=CHCOOEt
57

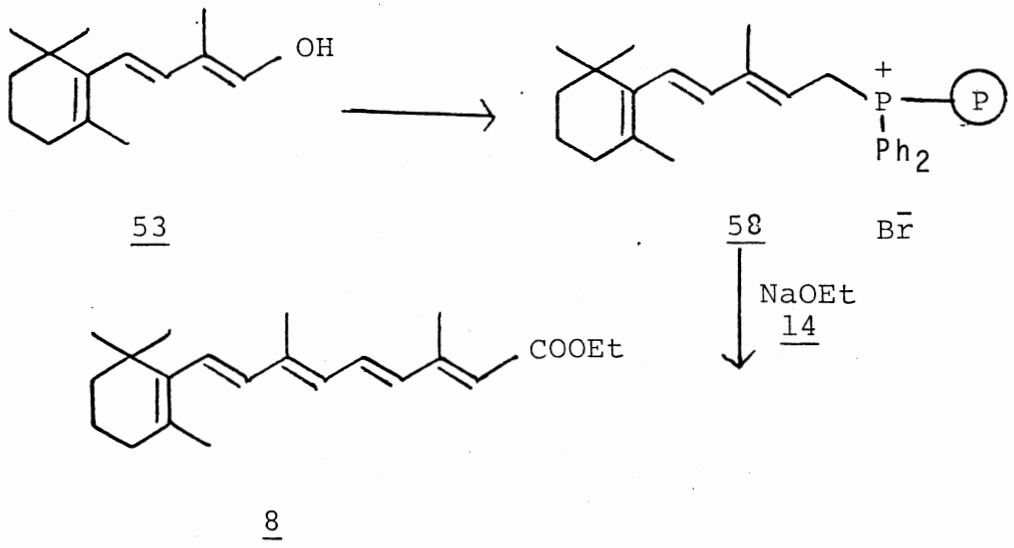
dehyde. The ^{1}H NMR spectrum of the product from 55 and 19 was too complicated to analyze but the IR spectrum revealed the presence of ester carbonyl band at 1715 cm^{-1}. It was not possible to determine the yield because a major portion of the product was the decomposed 19 and it was not possible to study the ^{1}H NMR (Scheme VI).

Polymer-Bound C_{15} and C_{13} Phosphonium Bromides 58 and 60

It has been known from solution reactions[33b] that a Wittig coupling between the C_{15} phosphonium salt 13 and the C_5 aldehyde ester 14 leads to all-trans-ethyl retinoate 8 as the major product. This offers a way to prevent 9-cis double bond in the product. The C_{13} phosphonium salt 11 is more reactive than the C_{13} ketone 9 in Wittig reactions.

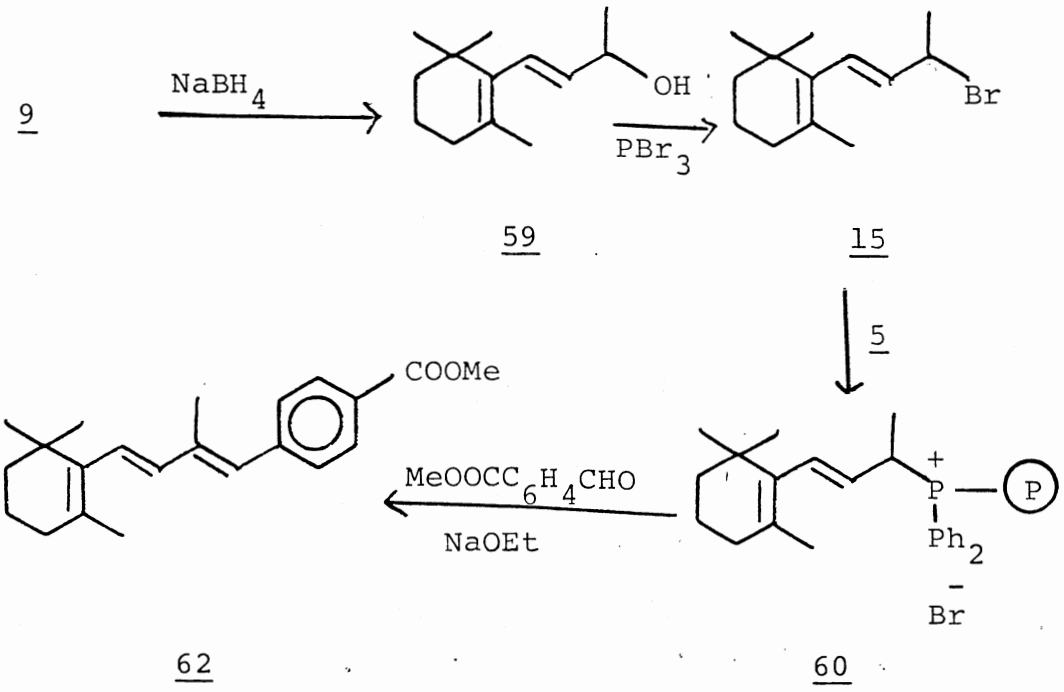
We attempted the preparation of the polymeric C_{15} phosphonium salt 58 by treating C_{15} alcohol 53 with phosphine hydrobromide 50 in benzene. (Scheme VII). The ^{31}P NMR spectrum of the product gave two signals at ∂ 25.4 for 58 and at ∂ -9.1 for the unreacted 50 with the relative areas of 60:40. Bromide analysis of 58 compared with ^{31}P NMR integration data revealed 46% conversion to 58. Wittig olefination of 58 with 14 using NaOEt as base did not proceed to the desired product 8. Polymer 58 beads turned red brown after the addition of base indicating the phosphorane generation but the ^{1}H NMR of the product showed only the presence of starting material 14. At this point it is reasonable to assume that the phosphorane from 58 due to resonance stabilization lacked reactivity towards 14 requiring different conditions for the reaction to go.

Scheme VII.



The C_{13} phosphonium salt 60 was obtained as per scheme VIII.

Scheme VIII.



The arotinoid 62 (Wittig olefination product) attempted in this work was known to possess carcinostatic activity.[74]

Sodium borohydride reduction of 9 gave ß-ionol (59) in 96% crude yield. ^{1}H NMR of 59 was indicative of a single isomer. PBr_3 treatment of 59 with catalytic amounts of pyridine afforded ß-ionyl bromide 15 (90%) which eliminated HBr readily forming the triene 16. Bromide 15 without further purification was converted to polystyrylphosphonium salt 60 with phosphine 5 immediately. Phosphonium salt 60 was not isolated and was treated with the aldehyde ester 61 and $NaOCH_3$. The reaction mixture attained intense red brown color within 1 h after the addition of $NaOCH_3$ confirming the formation of phosphorane. ^{1}H NMR analysis of the product showed signals in the aromatic and aliphatic regions. The vinyl region was complicated. However, the chemical shift values were not in agreement with the previously reported values for the desired arotenoid 62.[74]

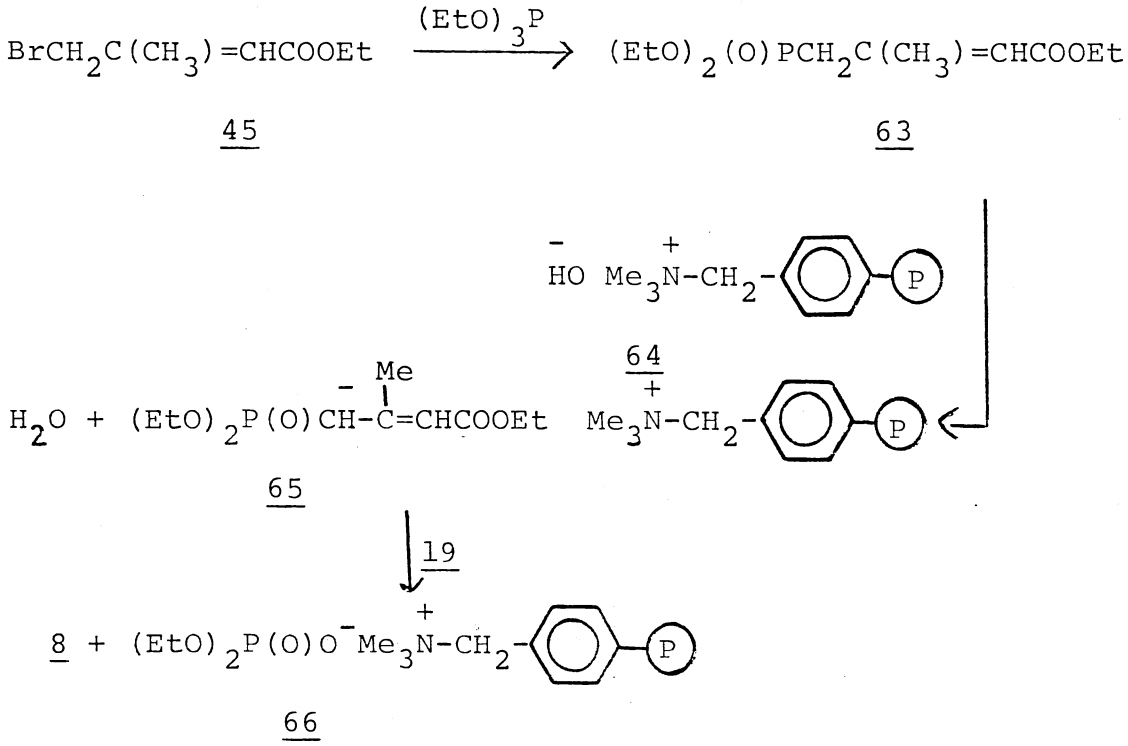
Suggestions for Future Work

Synthesis of ethyl retinoate 8 from isomeric mixtures of C_{15} aldehyde 19 and C_5 phosphonium salt 46 produces seven isomers. Iodine catalyzed isomerization reduces the number of major isomers to three, 9-cis, 13-cis and all-trans 8. The formation of 9-cis isomers of 8 could be avoided by the use of all-trans aldehyde 19. A convenient method to obtain all-trans 19 is to separate the two isomers of 19 from diisobutylaluminum hydride reduction of 51, by HPLC over a silica gel column with ether/hexane as solvents.[75] Such a procedure would give only four isomers in the product of 8, 11-cis, 11,13-di-cis, 13-cis and all-trans. This isomeric mixture could be

easily converted to the two biologically active 13-cis and all-trans 8 by iodine catalyzed isomerization[70,76] as is evident from our experiments. Hydrolysis of 8 and fractional crystallization should then enable complete separation of the two isomers. Otherwise, as esters they could also be separated by HPLC by the use of Whatman Magnum-20 column.

A synthetic approach that can promote 13-trans double bond in the product 8 is the use of phosphonate ester of the C_5 fragment in the form of an ion exchange resin 65, which could undergo condensation with all-trans 19 to give all-trans 8. The reaction sequence for such an approach is given in Scheme IX.

Scheme IX.



Michaelis-Arbuzov reaction of 45 with triethyl phosphite would give the phosphonate ester 63 as an isomeric mixture, which could be separated into Z- and E- isomers by fractional distillation and

preparative GLC.[77] The E-isomer of 63 can then be percolated through a column filled with Amberlyst A-26, a macroreticular anion exchange resin, in the OH^- form (64), to give the polymer-supported phosphonate 65.

Condensation of either E- or Z-phosphonate 63 with benzaldehyde produced a 4:1 mixture of E,E- and Z,E-isomers of methyl 3-methyl-5-phenylpenta-2,4-dienoate.[46b] Addition of 63 to ß-cyclocitral yielded a 5:1 mixture of E,E-and Z,E-dienoic esters.[46b] The ion exchange resin/phosphonate method gave good yields of α,ß-unsaturated esters and nitriles from the reactions of carbonyl compounds with diethylmethyl phosphonoacetate and with diethyl cyanomethylphosphonate.[78] In the product, α,ß-unsaturated nitriles the E:Z ratio depended on the carbonyl compound. Whereas with α,ß-unsaturated esters the products were exclusively all-trans compounds. Based on these observations we would expect that the carbonyl olefination of all-trans 19 with the E-phosphonate of 65 will lead to all-trans 8 as the sole product. Even if the olefination step is not stereospecific, resulting in 11-cis along with all-trans 8, the mixture may be isomerized to all-trans 8 by catalytic amounts of bis(benzonitrile)palladium dichloride and triethylamine in acetonitrile.[79] As in our previous experiments, iodine catalysis can effect the conversion of 11-cis to 11-trans quantitatively.

The advantages of 63 in an ion exchange resin over soluble 63 and over the polymer-bound C_5-phosphorane 46 are: (1) the ion exchange resin will trap the by-product anion as 66 thus facilitating a quicker separation of the retinoid from 66 by simple filtration. (2) The phosphonate ester modification of the Wittig reaction in an ion

exchange resin will promote the formation of E-alkene in its entirety.

CHAPTER III

EXPERIMENTAL

Reagents and Solvents

Benzene and toluene were distilled from CaH_2. Diethyl ether was distilled from $LiAlH_4$. Tetrahydrofuran was dried over anhyd. $MgSO_4$ and distilled from sodium ketyl of benzophenone under nitrogen. Dimethylsulfoxide was vacuum distilled from CaH_2 under nitrogen. Styrene, divinylbenzene, chlorodiphenylphosphine, ethyl 3-methyl-2-butenoate, ß-cyclocitral, ß-ionone, methyl iodide and chlorodiethylphosphite were distilled under vacuum prior to use. N-Bromosuccinimide was purified by recrystallization. Solvents such as dichloromethane, methanol, acetone, carbon tetra chloride, hexanes and other chemicals used in this research such as benzaldehyde, cinnamaldehyde, cyclohexanone, α-methylcinnamaldehyde, dodecyl aldehyde, 10-nonadecanone, chlolest-4-en-3-one, silver nitrate, ammonium thiocynate, N,N-dimethylaniline, Cl_3SiH, PBr_3, $NaBH_4$, HBr, diisobutylaluminum hydride, 2,6-dimethyl-7-ethoxycarbonyl-2,4,6-heptatrienal, HMPA, silica gel, triethyl phosphonoacetate, $LiAlH_4$, MnO_2, Mg turnings, dibromoethane, NaH, and ethyl bromoacetate were reagent grade and were used without further purification. Sodium methoxide and sodium ethoxide were prepared by dissolving a weighed amount of freshly cut sodium in a measured volume of the alcohol in a nitrogen atmosphere. Dimethylsulfinyl carbanion was generated in a nitrogen atmosphere by adding a

weighed quantity of dry sodium hydride to dimethylsulfoxide and heating the mixture to 50-65°C until the NaH dissolved.[80]

3-Ethoxycarbonyl-2-methylpropenal and 2,6-dimethyl-7-ethoxycarbonyl-2,4,6-heptatrienal were received as gifts from Dr. Michael Rosenberger from Hoffmann-La Roche, Inc. ß-Cyclocitral was a gift from Dr. Rautenstrauch, Firmenich SA, Geneva, Switzerland.

Analyses

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard model 5840A instrument with a 6 ft. x 0.125 in. o.d. nickel column of 20% SE-30 on 80/100 mesh chromosorb Q and a thermal conductivity detector. Preparative GLC was done on an Aerograph model A90-P instrument operated isothermally with a 6 ft. x 1/4 in. o.d. copper column of 15% SE-30 on 80/100 mesh Gas Chrom Q. HPLC analysis were accomplished with a Spectra Physics model 8700 solvent delivery system, a 254 nm uv detector from a DuPont model 830 LC, and a Hewlett-Packard strip chart recorder model 7123A. Partisil M9 10/50 ODS-2 column was used with a solution of 90% CH_3OH and 10% 0.01 M HOAC in water (v/v) as the solvent and a flow rate of 2 mL/min. Electron micrographs were obtained on a JEOL model JSM-35 Scanning Electron Microscope by coating the polymer with Au/Pd alloy. Mass spectral analyses were done on a high resolution double focusing mass spectrometer CEC model 21-110B with Data General DS-50S data system at 70 eV. ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra were obtained in $CDCl_3$ solvent on varian model XL-100(15) and XL-300 instruments with $(CH_3)_4Si$ as internal standard for ^1H and ^{13}C and 85% H_3PO_4

as external standard for ^{31}P. ^{1}H NMR spectra were recorded at 100 MHz and at 300 MHz, ^{13}C NMR at 25.2 MHz and at 75.5 MHz, and ^{31}P NMR at 40.5 MHz and at 121.5 MHz. IR spectra were recorded on a Perkin-Elmer model 681 instrument. Elemental analyses were carried out by Midwest Micro Labs (Indianapolis, IN) or by Galbraith Laboratories (Knoxville, TN).

General Procedures with Polymeric Reagents

All polymer samples were washed and dried in a vacuum oven immediately before use. All reactions were conducted under nitrogen or argon in 3-necked round bottomed flasks equipped with overhead stirrer, serum stopper, nitrogen inlet, and reflux condenser (whenever needed). Reactions involving retinoids were performed in a curtained area protected from light and in some cases using dim red lights. Polymer samples were allowed to swell in the solvent for 0.5 h without stirring before starting a reaction. The teflon blade of the stirrer was positioned high enough to avoid friction between the beads and the walls of the flask. These precautions with swelling and stirring enabled us to recover the reacted polymers with little or no breakage of beads. All polymer filtration and washing was performed in medium porosity fritted funnels from Kimble Glass Co. Reaction temperatures of Ca -10°C were achieved by use of an ice/salt bath.

General Procedure for the Suspension Polymerization of Styrene Containing DVB as Cross-linker.[50] Two Percent Cross-Linked Polystyrene (32)

Gelatin, 2.7 g, was dissolved in 60 mL of deionized water at 50-60°C with magnetic stirring. In 390 mL of deionized water 24.6 g of poly(diallyldimethylammonium chloride) (Catfloc T® from Calgon Corp.) and 5.1 g of boric acid were dissolved (in that order) at room temperature. After adjusting the pH to 10.0 with 25% KOH, 0.1 g. of $NaNO_2$ was added, followed by hot gelatin solution. The entire mixture of aqueous phase after thorough mixing was transferred carefully (to prevent foaming) to a 1000 mL 3-necked round bottomed flask fitted with reflux condenser, mechanical stirrer, and thermocouple connected to a proportional temperature controller. A solution of 151.5 g of styrene, 5.7 g of DVB (55% active divinylbenzene from Polysciences, Inc.) and 0.825 g of AIBN (from Aldrich Chemical Co.) was added slowly to the flask. Nitrogen was swept through the flask for 0.5 h, and slight positive pressure of nitrogen was maintained throughout the polymerization. The teflon blade was positioned such that the mid portion of the blade was at the aqueous/organic interface of the quiet mixture. The mixture was stirred at 340 rpm for 10 min., heated to 70°C over a period of 40-60 min., and maintained at this temperature for 36 h. The polymer mixture was then cooled and separated into different fractions by wet filtration through 40, 60, 100, 200, 325 and 400 mesh U.S. standard sieves. The fractions on different sieves were then transferred into medium and fine porosity fritted disc funnels, filtered and washed successively with water, CH_3OH, CH_2Cl_2, acetone and

finally with CH_3OH. The polymer beads were dried at 60°C under vacuum and weighed. Total weight of the polymer was 133 g. (80%) with the following particle size distribution: 9.8% on 40, 25.6% on 60, 39.8% on 100, 21.8% on 200, 2.2% on 325 and 0.8% on 400 mesh sieve.

Preparation of 8% Cross-linked Polystyrene (32)

The general procedure was followed with the monomer mixture composition of 140.0 g styrene, 24.10 g DVB, and 0.825 g AIBN. Total weight of the polymer was 144.0 g (88%) with the following particle size distribution 8.30% on 40, 40.10 on 60, 40.80 on 100, 9.3 on 200, 0.7 on each 325 and 400 mesh sieves.

General Procedure for the Bromination of Polystyrene (32). Bromination of 2% Cross-linked Polystyrene (32)

To 60.0 g of 32 in 700 mL of CCl_4 was added 4.67 g (11.44 mmole) of $Tl(OAc)_3$ sesquihydrate. After 0.5 h of stirring 39.03 g (0.22 mole) of bromine in 50 mL of CCl_4 was added dropwise by means of a pressure equalizing addition funnel. The mixture was refluxed for 2 h (protected from light), cooled and filtered. The polymer was successively washed with 30 mL each of CCl_4, acetone, 2N methanolic hydrochloric acid, acetone and finally with 50 mL of absolute methanol and dried at 80°C under vacuum to give 80.0 g (100%) of bromopolystyrene (33).

Anal. Found: Br 27.96% (3.10 mequiv/g), (100%); (%RS 44).

Bromination of 8% Cross-linked Polystyene (32)

The general procedure was used with 26.00 g. of 8% cross-linked polystyrene (32), 2.24 g (5.48 mmole) of $Tl(OAc)_3$ and 20.0 g (0.125 mole) of bromine in 300 mL of CCl_4 to give 34.75 g of 33.

Anal. Found: Br 24.31% (3.03 mequiv/g); (98%); (% RS 43).

Bromination of 20% Cross-linked Macroporous Polystyrene (32)

Macroporous polystyrene (32) (from Rohm & Haas Company), 59.50 g, in 750 mL of CCl_4 was brominated following the general procedure with 4.62 g (11.31 mmole) of $Tl(OAc)_3$ and 36.90 g (0.205 mole) of bromine to yield 77.30 g of bromopolystyrene 33.

Anal. Found: Br 24.68% (3.08 mequiv/g), (100%); (% RS 46).

General Procedure for the Phosphination of Bromopolystyrene (33). Phosphination of 2% Cross-linked Bromopolystyrene (33).

Lithium Diphenylphosphide Method[52]

A solution of 50 mL of THF and 16 mL (0.086 mole) of chlorodiphenylphosphine was added dropwise at -10°C to 1.55 g. (0.223 g-atom) of lithium metal ribbon (99.9%, 19 mm wide x 0.75 mm thick from Alfa Products) which was cut into pieces about 3 x 4 mm in size. The mixture was stirred for 16 h at room temperature. The lithium diphenylphosphide solution was transferred by syringe to a pressure-equalizing addition funnel and added dropwise to a stirred mixture of 10.0 g (31.0 mequiv.) of 2% cross-linked bromopolystyrene (33) in 50 mL of THF at

-10°C. Another 50 mL of THF was added and the mixture was stirred for 48 h at 20°C. A nitrogen-purged mixture of acetone: water, 2:1 by volume, 50 mL, was added, and the mixture was stirred for 15 min. The solution was decanted, another 50 mL of acetone: water was added, and the mixture was transferred with acetone washing to a filter funnel under nitrogen.[81] The mixture was filtered under a slight pressure of nitrogen. The polymer was washed sequentially with 15 mL of acetone, 10 mL of THF, and 10 mL of diethyl ether seven times and dried at 100°C under vacuum to give 13.1 g of polystyryldiphenylphosphine (5).

Anal. Found: P 6.47% (2.09 mequiv/g), (91%) (% RS 37).

n-Butyllithium Method

The 3-neck flask had a glass frit, a stopcock and a 24/40 joint at the bottom. To 10.0 g (31.0 mequiv) of 2% cross-linked 33 in 50 mL of toluene at -10°C was added dropwise 60 mL (96 mmole) of 1.6 M n-BuLi in hexane. The mixture was stirred for 1 h at room temperature and for 10 h at 70°C. The mixture was cooled and filtered through the frit under slight nitrogen pressure. The polymer was washed five times with toluene (50 mL). The flask was cooled to -10°C, 80 mL of THF was added, and then 30 mL (167 mmole) of chlorodiphenylphosphine dropwise. The mixture was stirred for 4 h, filtered, and washed and dried as in method A to give 12.4 g of phosphine polymer 5.

Anal. Found: P 5.77% (1.86 mequiv/g); Br 0.00 (80%) (% RS 35).

Phosphination of 8% Cross-linked Bromopolystyrene (33)

The general procedure A was followed with 25.10 g (77.80 mequiv) of 8% cross-linked 33, 70 mL (0.39 mole) of $ClPPh_2$ and 7.42 g (1.07 g-atom) of Li metal to give 30.52 g of phosphine 5.

Anal. Found: P 4.97% (1.60 mequiv/g); Br 5.02% (0.63 mequiv/g), (65%); (%RS 27 P, 9 Br).

In a second experiment 48.50 g (146.0 mequiv) of the 8% cross-linked 33 and lithium diphenylphosphide [prepared from 84.5 mL (470 mequiv) of $ClPPh_2$ and 10.3 g of Li (1.48 g-atoms)] in THF were refluxed for 6 h after stirring at 20°C for 48 h to yield 60.4 g of phosphine 5.

Anal. Found: P 6.26% (2.02 mequiv/g); Br 1.82% (0.022 mequiv/g); (83%), (%RS 36 P, 3.3 Br).

Phosphination of 20% Cross-linked Macroporous Bromopolystyrene (33)

By the general procedure A 15.0 g (46.20 mequiv) of 20% cross-linked macroporous 33 with ca 113 mequiv of $LiPPh_2$ gave 15.70 g (35%) of 5 (after some accidental loss during filtration). A second trial which employed 48 h stirring at 20°C and 6 h at reflux gave the same phosphine content.

Anal. Found: P 3.0% (0.97 mequiv/g); Br 13.07% (1.63 mequiv/g), (35%), (%RS 16 P, 24.4 Br).

With 10.0 g of the 20% cross-linked macroporous 33 the general procedure B was used (except heating at 70°C lasted 24 h) to give 10.9 g of phosphine 5.

Anal. Found: P 3.5% (1.13 mequiv/g); Br 2.42% (0.03 mequiv/g) (38%); (%RS 18 P, 4.5 Br).

Calculation of % Conversion

For the partial conversion of bromostyrene repeat units to styryldiphenylphosphine units by the lithium diphenylphosphide method with 20% crosslinked macroporous polystyrene % conversion was calculated as follows. 1) With 20% DVB cross-linking the copolymer also contains 16% ethylvinylbenzene (EVB) and 64% styrene (St) by weight, since the divinylbenzene monomer contained 55% DVB and 44% EVB by weight. The average molecular weight of one repeat unit is [(.20 DVB)(1mmole/130.2 mg DVB) + (0.16 EVB) (1 mmole/132.2 mg EVB) + (0.64 St) (1 mmole/104.1 mg St)]$^{-1}$ = 112.4 mg monomer/mmole repeat units. 2) Assume all three kinds of repeat units are equally reactive with bromine. The brominated copolymer by elemental analysis contains 3.08 mequiv brominated repeat units (BrSt)/g and [1000 mg - (3.08 mequiv)(191.4 mg BrSt/mequiv)][112.4 mg/mequiv non-brominated repeat unit]$^{-1}$ = 3.65 mequiv non-brominated repeat units/g. The brominated polystyrene has [3.08/(3.08 + 3.65)] x 100 = 46% ring substitution. 3) After phosphination the polymer contains by elemental analysis 1.63 mequiv BrSt/g and 0.97 phospinated repeat units (Ph_2PSt)/g. Therefore [1000 mg - (1.63 mequiv)(191.4 mg BrSt/mequiv) - (0.97 mequiv Ph_2PSt)(296.7 mg Ph_2PSt/mequiv)] [112.4 mg/mequiv unsubstituted repeat unit]$^{-1}$ = 3.56 mequiv unsubsituted repeat units/g. The polymer contains (1.63 + 0.97 + 3.56) = 6.16 mequiv of repeat units/g, of which (1.63/6.16)(100) = 26% are BrSt, (0.97/6.16)(100) = 16% are Ph_2PSt, and 58% are unsubstituted. The 42% of substituted repeat units agrees within

experimental error with 46% of BrSt units in the starting brominated polystyrene. The % conversion of BrSt to Ph_2PSt repeat units was (16/46)(100) = 35%.

Another calculation, which assumed that only styrene repeat units reacted with bromine, gave 27% BrSt, 16% Ph_2PSt, and 57% unsubstituted repeat units.

General Procedure for the Formation of Phosphonium Salts 34 and 35. Benzylpolystyryldiphenylphosphonium Bromide (34) from 2% Cross-linked Phosphine 5

Benzylbromide, 5.0 mL (42.0 mmole), was added dropwise with stirring to a suspension of 10.0 g (21.0 mequiv) of the 2% cross-linked 5 in 70 mL of N,N-dimethylformamide. The mixture was stirred for 48 h at 70°C, cooled, filtered, washed sequentially with 10 mL each of benzene, CH_2Cl_2, and $(Et)_2O$ ten times over 4-6 h and dried at 60°C under vacuum to give 13.50 g (93%) of phosphonium salt 34. ^{31}P NMR (Spectrum 1) showed a signal at 22.88 supporting the formation of 34.

Anal. Found: Br^- 1.36 (mequiv/g) 93% yield by ion exchange analysis.

Preparation of Phosphonium Salt 34 from 8% Cross-linked Phosphine 5

By the general procedure 6.97 g (11.15 mequiv) of 8% cross-linked phosphine 5 with 4 mL (33.60 mmole) of benzyl bromide gave 8.67 g of phosphonium salt 34.

Anal. Found: Br^- 1.00 mequiv/g (80%).

Preparation of Phosphonium Salt 34 from 20% Cross-linked Macroporous Phosphine 5

The general procedure was followed with 15.0 g (10.50 mequiv) of 20% cross-linked macroporous phosphine 5 and 10 mL (84 mmole) of benzyl bromide to give 16.3 g of phosphonium salt 34.

Anal. Found: Br^- 0.57 (mequiv/g) (91%).

Preparation of Methylpolystyryldiphenylphosphonium Iodide 35 from 2% Cross-linked Phosphine 5

The general procedure used for the phosphonium salt 34 was followed at 40°C with 8.40 g (17.60 mequiv) of 2% cross-linked phosphine 5 and 2 mL (42.10 mmole) of CH_3I to give 11.0 g of phosphonium salt 35. ^{31}P NMR (Spectrum II) showed a signal at δ 21.03 supporting the formation of 35.

Anal. Found: I^- 1.38 (mequiv/g) (85% by ion exchange analysis).

Preparation of Phosphonium Salt 35 from 8% Cross-linked Phosphine 5

By the same general procedure 20.9 g (42.0 mequiv) of 8% cross-linked phosphine 5 with 4 mL (84.20 mmole) of CH_3I gave 28.40 g of phosphonium salt.

Anal. Found: I^- 1.38 (mequiv/g) (88%).

Preparation of Phosphonium Salt 35 from 20% Cross-linked Phosphine 5

The general procedure used for 34 was followed with 16.00 g (11.20 mequiv) of 20% cross-linked macroporous phosphine 5 and 2 mL (42.10 mmole) of CH_3I to afford 17.50 g of phosphonium salt 35.

Anal. Found: I^- 0.63 mequiv/g (100%).

General Procedure for the Ion Exchange Analysis of Phosphonium Salts 34 and 35

The phosphonium salt was powdered in a "Wig-L-bug", and a weighed 0.2-0.3 g amount was transferred to a dry 250 mL Erlenmeyer flask. DMF, 5 mL, was added. After 0.25-0.5 h a solution of 3-5 drops of 8M HNO_3 in 5 mL of 50% $NaNO_3$ was added. After 3 h the mixture was diluted with 100 mL of water for bromides (200 mL of water for iodides), 5 mL of 8 M HNO_3 was added, and the mixture was titrated by the Volhard method.

General Procedure for the Wittig Olefination with Phosphonium Salt 34

Z- and E-stilbenes (3) from 2% Cross-linked Benzylphosphonium Salt 34. To 1.97 g (2.42 mequiv) of 2% cross-linked benzylphosphonium salt 34 in 30 mL of THF at -10°C was added 1.2 mL of 2.03 M sodium methoxide in methanol (2.44 mmole) dropwise with a syringe. The mixture was orange-red after 2 h of stirring at 20°C. After another 1 h the mixture was cooled to -10°C, and 0.265 g (2.5 mmole) of benzaldehyde was added dropwise. The mixture was stirred for 16 h at 20°C, refluxed for 2 h, filtered, and washed sequentially with 5 mL

portions of THF, dichloromethane, and $(Et)_2O$, ten times over 2 h. The combined filtrate was evaporated on a rotary evaporator. The residue was taken in CH_2Cl_2, filtered through Whatman 40 filter paper giving CH_2Cl_2 washes and was evaporated again on a rotary evaporator. The residue was weighed and analyzed by GLC with diphenyl ether as an internal standard, which gave 93% yield of the olefin 3. The phosphine oxide by-product 0.23 g was tested for residual bromide which revealed complete phosphorane generation. With other samples wherever mentioned the NaBr by-product of phosphorane generation was recovered by washing the filtered polymer on a fritted funnel and on the Whatman 40 filter paper with deionized water. The aqueous filtrate was analyzed for bromide ion by Mohr titration.

GLC conditions (common to all samples): Attenuation 2^6, Injector temperature 200°C, TCD temperature 250°C, the flow rate 40 mL/-min., and the sample injection size 1-2 μL.

Stilbene analysis was done by temperature programming, with the initial temperature of 150°C for 2 minutes, rate of increase 20°C/min., and the final temperataure of 180°C for 10 minutes. Retention times (minutes): Benzaldehyde 0.88, benzyl alcohol 1.12, diphenyl ether 4.07, cis-stilbene 5.54, and trans-stilbene 9.10.

Synthesis of 3 from 8% Cross-linked Benzylphosphonium Salt 34

With 2.63 g (2.60 mequiv) of phosphonium salt 34, 2.40 mL (2.60 mmole) of NaOEt and 0.237g (2.23 mmole) of benzaldehyde, the general procedure was followed except that 16 h of stirring was allowed for phosphorane generation and 24 h of stirring at room temperature and 4 h

at reflux were allowed for olefin formation. GLC analysis yielded 73% of the olefin 3.

Synthesis of 3 from 20% Cross-linked Macroporous Benzylphosphonium Salt 34

The general procedure was followed with 3.46 g (2.38 mequiv) of 20% cross-linked macroporous phosphonium salt 34, 2.10 mL (2.4 mmole) of NaOEt, and 0.198 g (1.86 mmole) of benzaldehyde to yield 80% of the olefin 3 by GLC analysis.

Synthesis of Z,E-and E,E-1,4-Diphenyl-1,3-Butadiene (38) from 2% Cross-linked Benzylphosphonium Salt 34

The general procedure for Wittig olefination was followed with 1.99 g (2.45 mequiv) of 2% cross-linked phosphonium salt 34, 1.20 mL (2.45 mmole) of NaOEt and 0.43 g (3.27mmole) of cinnamaldehyde. For GLC analysis octadecane was used as internal standard and the yield was 89%. The E,E isomer of 38 was crystallized from a solution of the product mixture in methanol: mp 151-152°C (lit.[81] 152-153°C). ^{1}H NMR ($CDCl_3$: δ 6.46-7.12 (AA^1 BB^1, 4 H), 7.20-7.46 (m, 10 H). Titration of the aqueous filtrate of the NaBr, released 2.32 mequiv of bromide implying 94.4% conversion to the phosphorane.

GLC conditions: The olefin 38 was analyzed by temperature programming, with the initial temperature of 200°C for 4 minutes, rate of increase 25°C/min., final temperature of 250°C for 12 minutes. Retention times (minutes): Cinnamaldehyde 0.96, cinnamyl alcohol 2.12, octadecane 5.6, cis-olefin 38 6.33, and trans olefin 38 7.96.

Synthesis of 38 from 8% Cross-linked

Benzylphosphonium Salt 34

The procedure used for stilbene 3 was followed with 2.01 g (2.01 mequiv) of 8% cross-linked phosphonium salt 34, 0.80 mL (2.00 mequiv) of $NaOCH_3$, and 0.245 g (1.85 mequiv) of cinnamaldehyde to afford 77% yield of the olefin 38 by recrystallization.

Synthesis of 38 from 20% Cross-linked Macroporous

Benzylphosphonium Salt 34

By the same general procedure, 3.02 g (2.06 mequiv) of 20% cross-linked macroporous phosphonium salt 34, 2.60 mL (2.20 mequiv) of NaOEt and 0.276 g (2.09 mequiv) of cinnamaldehyde yielded 72% of 38 based on ^1H NMR integration.

Synthesis of 2-Methyl-1,4-diphenyl-1,3-

butadiene (39) from 2% Cross-linked

Benzylphosphonium salt 34

The general procedure for Wittig olefination was followed with 2.06 g (2.53 mequiv) of 2% cross-linked phosphonium salt 34, 1.25 mL (2.53 mequiv) of NaOEt, and 0.37 g (2.53 mequiv) of -methylcinnamaldehyde. GLC analysis of the product gave 89% yield. The E,E-isomer of 39 was isolated as white crystals from methanol, mp 81-83°C. ^1H NMR ($CDCl_3$): δ 2.1 (,3 H), 6.64 (,1 H), 6.66 (d,1 H,J = 16 Hz), 6.94 (d,1 H,J = 16 Hz), 7.2-7.5 (m,10 H). Mohr titration of the aqueous filtrate of NaBr, released 2.31 mequiv of bromide indicative of 91% conversion to the phosphorane.

GLC conditions were similar to 38. Retention times (minutes): α-Methyl cinnamaldehyde 1.11, cis-olefin 39 5.43; and trans-olefin 39 7.04.

Synthesis of 1-Phenyl-1-tridecene (40) from 2% Cross-linked Benzylphosphonium Salt 34

By the same general procedure, 2.37 g (3.20 mequiv) of 2% cross-linked phosphonium salt 34, 3.20 mL (3.20 mequiv) of NaOEt, 0.57g (3.07 mmole) of dodecanal gave 72 area % of the olefin 40 by GLC analysis. The relative amounts of Z-and E-isomers were determined by assuming equal thermal-conductivity response factors. The Z-isomer was confirmed as the minor product from the vinyl hydrogen region of the ^{1}H NMR spectrum of the mixture. ^{1}H NMR ($CDCl_3$): ∂0.96 (m,3 H), 1.3-1.5 (m,18 H), 2.2-2.4 (m,2 H), 5.62 (d of t, 0.43 H, H-2 of Z-isomer, J=12 Hz, J=7 Hz), 6.00-6.55 (m,1.57 H,H-1 of Z-isomer, and H-1 and H-2 of E-isomer), 7.0-7.5 (m,5 H).

GLC conditions: The olefin 1-phenyl-1-tridecene (40) was analyzed by temperature programming with the initial temperature of 170°C for 6 minutes, rate of increase 25°C/min., and the final temperature of 250°C for 12 min. Retention times (minutes): Dodecanal 2.75, cis-olefin 40 9.68, trans olefin 40 10.23.

General Procedure for Wittig Olefinations with Methylphosphonium Salt 35. Methylenecyclohexane (2) from 2% Crosslinked Methylpolystyryldiphenylphosphonium Iodide (35)

To 2.04 g (2.55 mequiv) of 2% cross-linked methylphosphonium

salt 35 in 30 mL of a (1:1) (v:v) mixture of THF and Me_2SO at -10°C was added 5.0 mL (6.75 mequiv) of the sodium salt of Me_2SO in Me_2SO. The mixture was stirred for 6 h. The polymer turned a green-black color. The polymer was filtered under nitrogen pressure, washed with THF (100 mL), and cooled to -10°C. Cyclohexanone, 0.237g (2.42 mmole), was added dropwise. The mixture was stirred for 16 h at 20°C and refluxed for 2 h. The polymer was filtered and washed with THF, CH_2Cl_2 and $(Et)_2O$ as in the general procedure for 34. The filtrate was partially distilled, and the remaining liquid was analyzed by GLC using decane as an internal standard (99.1% yield). A small amount of sample was purified by preparative GLC at 80°C and identified from its ^1H NMR. ^1H NMR ($CDCl_3$): ∂ 1.45 (br s,6 H), 2.1 (br s,4 H) 4.55 (s,2 H). With other samples the combined filtrate after washing was evaporated on a rotary evaporator, weighed and analyzed by GLC by using suitable internal standards. After the Wittig reaction the residual I^- in the phosphine-oxide polymer was determined by ion exchange analysis with 0.18 g of the sample. The analysis indicated no iodide.

GLC conditions: Methylenecyclohexane (2) was analyzed by temperature programming with the initial temperature of 60°C for 5 minutes; rate of increase 25°C/min., and the final temperature of 120° for 10 minutes. Retention times: Methylenecyclohexane 2.95, and decane 8.14.

Synthesis of 1-Phenyl-1,3-butadiene (41) from 2% Crosslinked Methylphosphonium Salt 35

The general procedure described for 2 was followed with 2.21 g (2.75 mequiv) of 2% cross-linked phosphonium salt 35, 9 mL (7.95

mequiv) of dimethylsulfinylcarbanion (sodium salt), and 0.347 g (2.53 mequiv) of cinnamaldehyde. The product was purified by preparative GLC at 180°C and analyzed by GLC using tetradecene as the internal standard which gave 95% yield of the olefin 41. It was stored with a small amount of 4-t-butylcatechol as a polymerization inhibitor. ^{1}H NMR ($CDCl_3$): ∂ 5.04-5.30 (m,2 H), 6.2-6.6 (m,2 H), 6.68-6.84 (m,1 H), 7.1-7.4 (m,5 H). Phosphine oxide by-product, 0.156 g on ion exchange analysis contained no residual iodide.

GLC conditons: The olefin 1-Phenyl-1,3-butadiene (41) was analyzed by temperature programming with the initial temperature of 140°C for 4 minutes, rate of increase 25°C/min., and the final temperature of 200°C for 10 minutes. Retention times (minutes): cinnamaldehyde 4.10, 1-phenyl-1,3-butadiene 2.50, and tetradecane 5.81.

Synthesis of 41 from 8% Cross-linked Methylphosphonium Salt 35

The procedure used for 2% cross-linked phosphonium salt 35 was followed except that 16 h of stirring at room temperature was allowed for phosphorane generation and 24 h of stirring at room temperature and 4 h at reflux were allowed for olefin formation. Wittig reaction with 2.35 g (3.22 mequiv) of 8% cross-linked phosphonium salt 35, 8.0 mL (10.0 mequiv) of dimethysulfinyl carbanion (sodium salt) and 0.36g (2.73 mequiv) of cinnamaldehyde provided 52% yield of the olefin 41 based on the aldehyde added and 72% based on phosphonium salt 35 consumed. The polymeric phosphine oxide, 0.357g on ion exchange analysis contained 0.52 mequiv/g of the residual iodide.

Synthesis of 41 from 20% Cross-linked Macroporous Methylphosphonium Salt 35

The general procedure was followed with 4.92 g (3.15 mequiv) of 20% cross-linked phosphonium salt 35, 12.0 mL (10.0 mequiv) of dimethylsulfinyl carbanion (sodium salt) and 0.35 g (2.65 mmole) of cinnamaldehyde to yield 83% of the olefin 41.

Synthesis of 1,1-Diphenylethylene (1) from 2% Cross-linked Methylphosphonium Salt 35

Wittig olefination of 0.46 g (2.52 mmole) of benzophenone, with 2.20 g (2.75 mequiv) of 2% cross-linked phosphonium salt 35 and 9 mL (7.95 mequiv) of dimethylsulfinyl carbanion (sodium salt) was carried out by following the general procedure. The product was analyzed by GLC using octadecane as internal standard. A small amount of sample was purified by preparative GLC at 240°C and was identified by ^1H NMR and IR spectra. ^1H NMR ($CDCl_3$): δ 5.38 (s,2 H), 7.2 (m,10 H). Ion exchange analysis of 0.36 g of the phosphine oxide revealed the absence of residual iodide.

GLC conditions: The olefin 1,1-diphenylethylene (1) was analyzed isothermally at temperature 180°C for 12 minutes. Retention times (minutes): Octadecane 10.32, and 1,1-diphenylethylene 3.68.

Synthesis of 1 from 8% Cross-linked Methylphosphonium salt 35

The same procedure as with 41 was followed using 2.52 g (3.48 mequiv) of 8% cross-linked phosphonium salt 35, 9.0 mL (11.25 mequiv) of dimethylsulfinyl carbanion (sodium salt), and 0.51 g (2.79 mmole) of

benzaldehyde. The product was analyzed in an analogous manner to the synthesis of 1 using 2% cross-linked phosphonium salt 35. A 92% yield was obtained based on the phosphonium salt 35 consumed and 61% based on the benzophenone added. Ion exchange analysis of 0.29 g of the phosphine oxide by-product gave 0.63 mequiv/g (14% RS) of the iodide ion, supporting incomplete phosphorane generation.

Synthesis of 1 from 20% Cross-linked Macroporous Methylphosphonium Salt 35

Wittig olefination of 0.42 g (2.30 mmole) of benzophenone with 3.91 g (2.45 mequiv) of 20% cross-linked phosphonium salt 35 and 10 mL (7.5 mequiv) of dimethylsulfinyl carbanion (sodium salt) was successful by following the general procedure. GLC analysis afforded 74% of the olefin 1. Phosphine oxide 0.152 g on ion exchange analysis contained no residual iodide.

Synthesis of 2-Nonyl-1-undecene (42) from 2% Cross-linked Methylphosphonium Salt 35

The general procedure was followed except that for olefin formation 24 h at 60°C was allowed. Wittig reaction was performed with 2.76 g (3.76 mequiv) of 2% cross-linked phosphonium salt 35, 17.7 mL (15.2 mequiv) of dimethylsulfinyl carbanion (sodium salt) and 0.71 g (2.52 mmole) of 10-nonadecanone. The product was analyzed by GLC using hexadecane as the internal standard, which yielded 94% of the olefin 42. A small amount of 42 was purified by preparative GLC at 270°C and was identified from its ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$): δ 0.81-1.0 (m,6 H), 1.15-1.55 (m,28 H), 1.8-2.1 (m,4 H),

4.68 (br s, 2 H) IR (neat) 3070, 1645 cm^{-1}.

GLC conditions: The olefin 2-nonyl-1-undecene (42) was analyzed by temperature programming with the initial temperature of 200°C, rate of increase 25°C/min., and the final temperature of 220°C for 10 minutes. Retention times (minutes): Hexadecane 2.49, 2-nonyl-1-undecene 5.60, and 10-nonadecanone 7.19.

Synthesis of 42 from 20% Cross-linked Methylphosphonium Salt 35

The procedure used for 2% cross-linked phosphonium salt 35 was followed, the quantities of the 20% cross-linked phosphonium salt 35, base and the ketone were, 3.90 g (2.47 mequiv) 10.40 mL (7.40 mequiv), and 0.49 g (1.74 mequiv) respectively. Before the addition of the ketone, the ylide was decomposed partially due to accidental air exposure. GLC analysis of the product showed 62.2% yield of the olefin 42. Phosphine oxide by-product 0.19 g, on ion exchange analysis contained no residual iodide.

Synthesis of 3-Methylene-4-cholestene 43 from 2% Cross-linked Methylphosphonium Salt 35

Wittig olefination conditions were the same as for 42. The amounts of phosphonium salt 35, base and cholest-4-en-3-one used were, 2.73 g (3.74 mequiv), 17.0 mL (14.60 mequiv), and 0.956 g (2.48 mmole) respectively. The product was recrystallized from methanol/acetone to give (0.871 g) 91% yield of 43 as white needles, mp 69-70.5°C. ^1H NMR ($CDCl_3$): δ 0.7-2.5 (m,43 H), 4.55-4.75 (m,2 H), 5.8-5.9 (m, 0 H). IR (KBr) 3080, 1640, 1600 cm^{-1}.

Synthesis of 43 from 20% Cross-linked Methylphosphonium Salt 35

The same procedure described under 2% cross-linked phosphonium salt 35 was followed with 3.80 g (2.40 mequiv) of 20% cross-linked phosphonium salt 35, 10.20 mL (7.24 mequiv) of dimethylsulfinyl carbanion (sodium salt) and 0.62 g (1.62 mmole) of cholest-4-en-3-one. The product on recrystallization gave an yield of 87.1% (0.542 g) for the olefin 43. Ion exchange analysis of 0.21 g of the phosphine oxide by-product revealed the absence of residual iodide in the sample.

General Procedure for the Reduction of Polystyryldiphenylphosphine Oxide (7) to Polystyryldiphenylphosphine (5). Reduction of 2% Cross-linked Phosphine Oxide 7

To a stirred mixture of 11.10 g (22.60 mequiv) of 2% cross-linked phosphine oxide 7 in 50 mL of benzene was added dropwise 4.50 mL (35.0 mequiv) of N,N-dimethylaniline followed by 3.50 mL (35.0 mequiv) of trichlorosilane. The mixture was refluxed for 12-16 h, cooled, filtered and washed sequentially with 15 mL portions of benzene, THF, and diethyl ether a total of 12 times over 3 h. The phosphine 5 was dried at 80°C under vacuum to give 10.70 g. ^{31}P NMR analysis showed 92% phosphine and 8% phosphine oxide sites.

^{31}P NMR Analysis of $CDCl_3$-Swollen Polymer

Pulsed Fourier transform spectra were obtained at 40.5 MHz using a 90° pulse width, 10,000 Hz frequency range, 8192 data points, 0.82 s

acquisition time, 6.0 s delay time between pulses, and 240-600 acquisitions per spectrum. No ^{1}H decoupling was employed to eliminate the nuclear Overhauser effect. Observed chemical shifts relative to external 85% H_3PO_4, peak widths at half height, and T_1 values measured by the fast inversion recovery method were obtained as follows under ^{1}H-decoupled conditions. Phosphine: ∂ -6.3 ppm; 100-130 Hz; 2.6 s; Phosphine oxide: ∂ +28.8 ppm; 164-260 Hz; 2.0 s.

Reduction of 20% Cross-linked Phosphine Oxide 7 to Phosphine 5

The general procedure was employed with 5.99 g (ca 6 mequiv) of the phosphine oxide 7, 1.2 mL (9.50 mequiv) of N,N-dimethylaniline and 1 mL (10.0 mequiv) of $HSiCl_3$ to give 5.80 g of the phosphine 5. ^{31}P NMR analysis showed a single peak at ∂ -6.3 ppm; with 60 Hz peak width at half height supporting total conversion to the phosphine.

Preparation of 2% Cross-linked Benzylpolystyryldiphenylphosphonium Bromide (34) from Phosphine 5 of Recycle 1

By following the general procedure, 8.10 g (15.71 mequiv) of the recycled phosphine 5 and 5 mL (42.0 mmole) of benzyl bromide gave 10.80 g of the phosphonium salt 34.

Anal. Found: Br^- 1.24 mequiv/g (89%) based on ion exchange analysis.

Preparation of 20% Cross-linked Benzylpoly-styryldiphenylphosphonium Bromide (34) from Recycled Phosphine 5

The general procedure was followed by taking 5.24 g (ca 4.72 mequiv) of the recycled phosphine 5 and 3.0 mL (25.20 mmole) of benzyl bromide to yield 5.99 g of the phosphonium salt 34.

Anal. Found: Br^- 0.64 mequiv/g (83%).

Synthesis of Z-and E-Stilbenes (3) from Recycled 2% Cross-linked Benzyl-phosphonium Salt 34

Wittig olefination was performed by following the general procedure except that the carbonyl compound and the base were added simultaneously. By taking 1.94 g (2.41 mequiv) of the recycled phosphonium salt 34, 1.90 mL (2.45 mequiv) of NaOEt and 0.245 g (2.35 mmole) of benzaldehyde, 97% of stilbene (3) was obtained by GLC analysis.

Synthesis of 3 from Recycled 20% Cross-linked Benzylphosphonium Salt 34

By the same general procedure as above 1.83 g (1.08 mequiv) of the recycled phosphonium salt 34, 0.8 mL (1.1 mequiv) of NaOEt and 0.093 g (0.87 mmole) of benzaldehyde afforded 75% of stilbene by GLC analysis.

Reduction of 2% Cross-linked Phosphine Oxide 7 (Recycle II) to Phosphine 5

Reduction was accomplished by the general procedure, taking 2.39 g (4.70 mequiv) of the 2% cross-linked phosphine oxide 7 (Recycle I), 0.70 mL (6.0 mequiv) of N,N-dimethylaniline, and 0.6 mL (6.0 mequiv) of $HSiCl_3$. The phosphine 5 weighed 2.30 g and ^{31}P NMR analysis revealed 90% phosphine and 10% phosphine oxide.

Preparation of Benzylphosphonium Salt 34 from Phosphine 5 of Recycle II

The general procedure was employed with 2.30 g (4.36 mequiv) of the phosphine 5 from recycle II, 2.0 mL (16.8 mmole) of benzylbromide and 30 mL of DMF. This gave 2.91 g of the phosphonium salt 34.

Anal. Found: Br^- 1.31 mequiv/g (92%).

Synthesis of Z- and E-Stilbenes (3) from 2% Cross-linked Benzylphosphonium Salt 34 (Recycle II)

Wittig olefination conditions were the same as for the first recycle. Reaction of 2.28 g (2.87 mequiv) of the phosphonium salt 34 with 2.44 mL (2.90 mequiv) of NaOEt and with 0.28 g (2.64 mmole) of benzaldehyde gave a 97.4% yield of the olefin 3.

Preparation of E- and Z-Ethyl 4-bromo-3-methyl-2-butenoate (45)[60]

To a solution containing 38.60 g (0.30 mmole) of ethyl 3-methyl-2-butenoate (44) in 150 mL of CCl_4 were added 51.60 g (0.30 mmole)

of freshly purified NBS and 0.20 g of AIBN. The mixture was heated at reflux for 2 h, cooled, filtered and washed 6 times with 15 mL portions of CCl_4. The solvent was evaporated on a rotary evaporator, and the residue was distilled to give 56.0 g (74%) of 45, b.p. 51-55°C/0.55 mm. The Z:E isomer ratio was 41:59 by GLC analysis. ^1H NMR spectral data of 45 agreed with the literature values[60] of the corresponding methyl ester. ^1H NMR ($CDCl_3$): δ 1.1-1.35 (t,3 H), 2.0 and 2.25 (2d, 3 H,J = 2), 3.95 and 4.55 (2 s,2 H), 4.0-4.2 (q,2 H,J = 6.5), 5.7 and 5.9 (2 s, 1 H).

Preparation of E- and Z- 3-Ethoxycarbonyl-2 Methylallylpolystyryldiphenylphosphonium Bromide 46. Preparation of 2% Cross-linked Phosphonium Bromide 46

By employing the general procedure 4.92 g (10.30 mequiv) of 2% cross-linked phosphine 5 with 3.30 g (15.0 mequiv) of 45 in 50 mL of benzene provided 6.83 g of the phosphonium salt 46. ^{31}P NMR analysis (Spectrum III) showed two peaks at δ21.79 ppm and at δ 20.95 ppm indicative of phosphonium salt 46 formation.

Anal. Found: Br^- 1.22 mequiv/g (84%) by ion exchange analysis.

Preparation of 20% Cross-linked Phosphonium Bromide 46

By the same general procedure, from 8.70 g (6.08 mequiv) of 20% cross-linked phosphine 5 and 3 mL (14.0 mequiv) of 45 in 60 mL of

DMF, was obtained 10.0 g of the phosphonium salt 46.

Anal. Found: Br^- 0.48 mequiv/g (78% yield) by ion exchange analysis.

Preparation of ß-Cyclogeraniol (47)[61]

To a solution containing 20.0 mL (ca 140.0 mequiv) of ß-cyclocitral (21)in CH_3OH (30 mL) at 0°C was added portionwise 3.40 g (89.90 mmole) of $NaBH_4$ over a period of 1 h. The reaction mixture was stirred for 3 h, poured over ice containing 25 mL of 5N HCl and extracted with ether. The ether layer was washed with saturated solution of $NaHCO_3$, water, dried over $MgSo_4$ and the solvent was evaporated. Vacuum distillation of the residue afforded 15.83 g (80%) of 47, b.p. 87-89°C/3.8 mm (lit[61] 101-102°C/11 mm). ^1H NMR and IR spectral data confirmed the formation of 47. ^1H NMR ($CDCl_3$): ∂ 1.04 (6 H), 1.72 (s, 3 H), 1.88-2.05 (br t, 2 H), 2.66-3.26 (br t,1 H), 4.08 (2 H). IR (neat) 3380, 1385, 1020 cm^{-1}.

Preparation of ß-Cyclogeranyl Bromide (48)[61]

To 5.61 g (39.0 mequiv) of 47 in 30 mL of 1:5 (v/v) ether/hexanes at 0°C was added four drops of pyridine and then 1.7 mL (53 mequiv) of PBr_3 over a period of 0.5 h. The reaction mixture was stirred for 3 h, poured over ice and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$ and the solvents were evaporated. The residue was weighed to give 7.44 g (92%) in crude yield of 48. The bromide was used without further purification. ^1H NMR ($CDCl_3$): ∂ 1.1 (s,6 H), 1.8 (s,3 H), 1.9-2.1 (br t,2 H), 4.03 (s, 2 H).

Preparation of ß-Cyclogeranylpolystyryldiphenylphosphonium Bromide (49)[42,66]

To 3.50 g (7.30 mequiv) of phosphine 5 in 30 mL of DMF was added 2.04 g (9.0 mequiv) of 48. The mixture was stirred at room temperature for 20 h, at 50°C for 6 h and again at room temperature for 16 h. The polymer was filtered, washed and dried as in the general procedure which yielded 4.79 g of the phosphonium salt 49. ^{31}P NMR spectrum (Spectrum IV) showed a signal at δ 18.74 supporting the formation of 49.

Anal. Found: Br^- 1.11 mequiv/g (78.50 % yield) by ion exchange analysis.

Preparation of Polystyryldiphenylphosphonium Bromide (50)[39b,43]

To 2.0 g (3.6 mequiv) (partially oxidised to the phosphine oxide 7 by impure THF washing) of phosphine 5 in 15 mL of benzene, was passed hydrogen bromide gas for five minutes. The reaction mixture was stirred under room temperature for 24 h, filtered and washed 8 times with 5 mL portions of benzene and then with 10 mL of diethyl ether. The polymer was dried under vacuum at 40°C to give 2.45 g of the phosphine hydrobromide 50. ^{31}P NMR spectrum showed a signal at δ -9.09 for the phosphine hydrobromide 50.

Anal. Found: Br^- 1.25 mequiv/g (79%) by ion exchange analysis.

Preparation of 49 from 50

To 2.01 g (2.50 mequiv) of the phosphine hydrobromide 50 in 7 mL of DMF was added 0.648 g (4.60 mequiv) of C_{10} alcohol 47. The mixture was stirred at 50°C for 16 h and at room temperature overnight. The polymer was filtered, washed and dried as in the general procedure to give 2.30 g of the phosphonium salt 49. ^{31}P NMR analysis indicated a single peak at δ 18.74 for the phosphonium salt 49.

Anal. Found: Br^- 0.95 mequiv/g (88%) by ion exchange analysis.

Preparation of ß-Ionylideneacetonitrile (51)[66]

To a mixture containing 10.50 mL (51.50 mequiv) of ß-ionone (9), 9.0 mL (55.60 mequiv) of diethyl cyanomethylphosphonate, 17 mL of HMPA and 30 mL of THF at -10°C was added dropwise 54 mL (56 mequiv) of NaOEt. The mixture was warmed to room temperature and stirred overnight. It was neutralized with 1:10 (v/v) (ca 2N) HOAc to pH 7 and after adding 50 mL of 50% CH_3OH was extracted with ether. The ether layer was washed with saturated NaCl and H_2O and dried over $MgSO_4$ and the solvents were evaporated. The residue was vacuum distilled to afford 9.96 g (90.5%) of 51, b.p. 100-103°C/0.25 mm. GLC analysis of 51 showed 2 isomers, 7(E),9(Z) and 7(E),9(E) in the ratio 20:80. ^1H NMR data agreed with the literature values.[68a]

Preparation of ß-Ionylideneacetaldehyde (19) From 51[67]

To a solution of 51 (0.687 g, 3.16 mequiv) in THF (10 mL) at -78°C, under argon atmosphere was added dropwise a hexane solution of

diisobutylaluminum hydride (1M,46mL,4.60 mmole). After 3 h of stirring at 0°C a few drops were removed and tested by IR analysis for the disappearance of the nitrile band at 2230 cm^{-1}. After ensuring total disappearance of the nitrile band the solution was cooled to -78°C and hydrolyzed by the slow addition of a slurry of silica gel (10 g, 75-250 μm) deactivated with water (2 mL) in 1:1 v/v deoxygenated ether/hexanes (30 mL). The resultant mixture was stirred at 0°C for 1 h and transferred into a 50 mL centrifuge tube with deoxygenated ether washings. The tube was capped immediately with serum stopper and centrifuged for 10 minutes. The solution was decanted into a nitrogen flushed 100 mL round-bottomed flask. The tube containing the silica gel was centrifuged two more times with fresh deoxygenated ether and the supernatent transferred to the flask. Solvents were evaporated with a stream of nitrogen, and the residue was weighed to give 0.59 g (87%) crude yield of the aldehyde 19. The sample was used immediately for Wittig reaction without further purification.

Synthesis of Ethyl Retinoate (8) from 2% Cross-linked Phosphonium Salt 46 and the C_{15} Aldehyde 19

To 1.87 g (2.16 mequiv) of the phosphonium salt 46 in absolute ethanol (20 mL) at -10°C were added dropwise and simultaneously 1.25 mL (2.20 mequiv) of NaOEt and (2.70 mL, ca 2.0 mequiv) of an ethanolic solution of 19. The mixture was stirred overnight in the dark, filtered under nitrogen pressure and washed 9 times sequentially with 10 mL portions of deoxygenated ethanol, CH_2Cl_2, and diethyl ether. Solvents were evaporated on a rotary evaporator and the residue

was dissolved in CH_2Cl_2, filtered once again and the filtrate concentrated on a rotary evaporator. The residue was dissolved in HPLC grade methanol, filtered through Water's SEP-PAK C_{18} catridge giving methanol washes. The solvent was evaporated with a stream of nitrogen and the residue was weighed to give 0.53 g (70% yield by ^1H NMR integration). The product was analyzed by HPLC to contain 7 isomers of ethyl retinoate which were isolated and characterized by ^1H NMR spectral data (Table X). The isomer distribution is given in Table IX. Spectra 7-11 represent the ^1H NMR of different isomers.

The ester 8, (0.1 g) was dissolved in 2 mL of methanolic solution (90% CH_3OH and 10% 0.01 M HOAc). A sample volume of 0.1 mL/2mL was injected at 24°C with the attenuation of 0.64. The different isomers eluted in the following order: 9,11,13-tri-cis at 78.5 min., 11,13-di-cis at 85 min., 9,13-cis at 95.5 min., 13-di-cis at 99.5 min., 11-cis at 108.5 min., 9-cis at 118 min., and all-trans at 122 min. A 0.4 mL/2mL was injected for sample collection, at attenuation 1.28. The 7 isomers were collected in 5 fractions for 4 times. The first fraction was 9,11,13-tri-cis isomer, 2nd fraction 11,13-di-cis, 3rd fraction 13-cis and 9,13-di-cis, 4th fraction 11-cis and the last fraction was 9-cis and all-trans isomers of ethyl retinoate 8. After each collectionthe solvents were evaporated with a stream of nitrogen in a warm water bath. This was followed by repeated evaporations with HPLC grade methanol for 5 times. The different fractions were then taken for ^1H and ^{13}C NMR analysis in 100% $CDCl_3$ (Table X and XI).

Synthesis of Ethyl Retinoate (8) from 20% Cross-linked Phosphonium Salt 46

The same procedure as in the previous experiment was repeated with 3.48 g (1.66 mequiv) of 20% cross-linked phosphonium salt 46, 1.10 mL (1.70 mequiv) of NaOEt, and an ethanolic solution of 19 (2.0 mL, ca 1.50 mequiv). The product after SEP-PAK purification yielded 0.345 g which, by ^{1}H NMR integration corresponded with 65% yield. HPLC analysis revealed the presence of the same 7 isomers with different isomer distribution (Table VIII).

Iodine Catalyzed Isomerization of 8

The ester 8 (0.0452 g) in ether/benzene (2.0 mL, 1:1) was treated with 0.2 mL of 0.5% iodine in benzene[77] and kept in the refrigerator (0°C) for 3 days. The solvents were evaporated with a stream of nitrogen and warming the sample with warm water bath. HPLC grade methanol (2.0 mL) was added and evaporated 5 times to remove the iodine, and the sample was dissolved in 2 mL solution of 90% methanol and 10% 0.01 M HOAc. HPLC analysis of the sample showed 3 major peaks corresponding to all-trans, 9-cis and 13-cis isomers of 8 in the proportions 41.3%, 12.5%, and 31.2% respectively. The percentages of minor isomers were: 11-cis 4.2%, 9,13di-cis 5.0%, 11,13-di-cis 2.5%, and 9,11,13-tri-cis 3.2%.

Synthesis of 8 from C_{10} Phosphonium Bromide 49 and C_{10} aldehyde 23

Wittig Reaction of 49 Without Isolation

To 2.26 g (4.75 mequiv) of phosphine 5 in THF (20.0 mL) was added 0.825 g (3.6 mequiv) of the C_{10} bromide 48. The mixture was stirred under room temperature for 36 h and at 50°C for 2 h. To this reaction mixture at -10°C was added dropwise and simultaneously 0.414 g (1.90 mequiv) of C_{10} aldehyde 23 and 1.8 mL (3.0 mequiv) of NaOEt. It was stirred under room temperature for 24 h, filtered and washed as in the previous experiment. The filtrate was concentrated on a rotary evaporator and the residue was extracted with ether. The ether layer was washed with saturated NaCl, dried and evaporated to give 0.58 g of the product which contained some unreacted aldehyde 23. HPLC analysis indicated 2 isomers in the ratio 77:23 which were characterized by ^1H NMR to be all-trans and 7-cis isomers of 8.

The product ester 8 (0.58 g) in ethanol (2.0 mL) was hydrolyzed to the acid by refluxing for 2 h with 0.208 g (3.5 mequiv) of KOH in ethanol (2 mL) and water (0.5 mL). The resultant mixture was cooled, diluted with water (10 mL), neutralized with Ca 8 N HOAc and extracted with CH_2Cl_2. The organic layer was washed several times with water, dried and evaporated to give 0.47g of the acid. This on recrystallization from methanol provided 0.20 g (38% overall yield) of all-trans-retinoic acid, m.p. 179-180°C (lit[43] 179-181°C). From the recrystallization yield the total yield was calculated to be 50%. Spectra 5 and 6 correspond with the ^1H NMR and ^{13}C NMR of all-trans retinoid acid.

Wittig Reaction of 49 after Isolation

Wittig olefination conditions were similar to the previous experiment. From 1.52 g (1.67 mequiv) of 49 in THF (15.0 mL), 0.22 g (1.00 mequiv) of 23 and 1 mL (1.67 mequiv) of NaOEt was obtained 0.18 g (55%) of the product 8 in crude yield. Mass spectral analysis showed M^+ at m/e 328 and the fragmentation pattern agreed with the corresponding methyl ester reported earlier.[83] HPLC analysis showed 2 peaks in agreement with 7-cis and all-trans isomers of 8 which were further confirmed by ^1H NMR data. The ester 8 (0.10 g) in ether/benzene (4 mL, 1:1) was treated with 0.4 mL of 0.5% iodine in benzene and kept in the refrigerator (0°C) for 3 days. The solvents were evaporated and the iodine was removed as described in an earlier experiment for 8. HPLC analysis of the sample showd 2 peaks corresponding to 13-cis and all-trans ethyl retinoate 8, in the ratio 25:75.

Preparation of Ethyl ß-Ionylidene-acetate (52)[69]

To 0.70 g (30.0 mmole) of NaH in THF (30.0 mL) was added HMPA (9.0 mL) and triethylphosphonoacetate (6.5 mL, ca 30.0 mmole). The resultant mixture was stirred for 1 h, cooled to -10°C and 5.0 g (25.0 mmole) of ß-ionone was added dropwise. It was stirred at 40°C for 4 h and at room temperature for 16 h. The reaction mixture was poured over ice and extracted with ether. The ether layer was washed with water until the aqueous extract was neutral to phenolphthalein, dried and the solvents evaporated on a rotary evaporator. The residue on

vacuum distillation afforded 5.91 g (81%) of 52, b.p. 125-130°C/0.5 mm (lit[84], 118-120°C/0.3 mm). GLC analysis of the product showed two isomers, E,Z and E,E in the ratio 20:80. The IR and the ^{1}H NMR data were in conformity with the literature values.[68a,84]

Reduction of 52 to ß-Ionylideneethanol (53)[84]

To a suspension of 1.72 g (45.30 mmole) of $LiAlH_4$ in diethyl ether (30.0 mL) at -10°C was added dropwise an ether solution of 52 (7.50 g, 28.50 mmole). The reaction mixture was stirred for 2 h at 0°C. The complex was decomposed by the addition of wet methanol (30 mL) followed by 10% NH_4Cl (150 mL) and extracted with diethyl ether. The ether layer was washed several times with water, dried and the solvents evaporated on a rotary evaporator. The residue was weighed to give 6.0 g (90% crude yield) of 53. IR and ^{1}H NMR spectral data were in agreement with the previous report.[84]

Oxidation of 53 to ß-Ionylideneacetaldehyde (19)[69]

To 100 mL of CH_3OH at -5°C was added in small portions 15.0 g (0.17 mole) of active MnO_2 (Aldrich Chemical Co.). After stirring for 10 minutes, 5.10 g (23.40 mmole) of 53 in methanol (20 mL) was added. The resultant mixture was stirred for 6 days under room temperature. The progress of the reaction was followed by TLC (pet. ether/acetone 9:1 V/V; 13181 silica gel sheet with fluorescent indicator from Eastman Kodak) by the disappearance of the spot at R_f = 0.36 and appearance of a spot at R_f = 0.57 , which indicated incompleteness of the reaction even after 6 days. The reaction mixture was filtered, washed several times with CH_3OH and the solvents evaporated

on a rotary evaporator. The residue, on IR and ^1H NMR analysis showed the presence of unreacted alcohol. ^1H NMR integration (CH_2OH:CHO) gave 3:2 ratio for the alcohol and the aldehyde.

Synthesis of 8 From 46 and 19 (Obtained by the Oxidation of 53)

Wittig olefination conditions were the same as in previous experiments. The reaction was carried out with 2.60 g (3.0 mequiv) of 46, 1.70 mL (3.10 mequiv) of NaOEt and 0.80 g of 19. Quantification of the product was not done. IR showed ester carbonyl band at 1715 cm^{-1}, and mass spectral analysis gave M^+ at m/e 328.

Preparation of Diethylpolystyrylphosphonite 54

n-BuLi Method[71]

Polystyryllithium was prepared as in the procedure for phosphine 5, with 7.06 g (28.10 mequiv) of bromopolymer 33 and 35.0 mL (56.0 mmole) of 1.60 M n-BuLi in hexane. To the lithiopolymer in THF (40 mL) at -78°C was added dropwise 7.0 mL (28.0 mmole) of chlorodiethylphosphite. The mixture was stirred for 3 h, filtered under argon pressure and washed 6 times with 15 mL portions of deoxygenated THF and diethyl ether. The polymer was dried under vacuum at 70°C to give 7.1 g of the product. ^{31}P NMR spectrum showed two peaks at +159 ppm and at +25.8 ppm with the relative areas 55.5:44.5 for tri- and pentavalent phosphorous. IR (KBr) 965, 1030, 1050, 1160, 1235, 1450 cm^{-1}.[71]

Anal. Found: P 4.00%, (29% RS) Br 1.55% (3% RS) by elemental analysis.

Grignard Method[73]

Polystyryllithium was prepared as before by taking 6.96 g (28.0 mequiv) of bromopolymer 33 and 35 mL (56.0 mequiv) of 1.6 M n-BuLi in hexane. To the lithiopolymer in THF (40.0 mL) at 0°C was added dropwise a freshly prepared THF solution of $MgBr_2$ (200 mL, 41.0 mmole) (from $BrCH_2CH_2Br$ and Magnesium turnings). The reaction mixture was stirred for 3 h, filtered under argon pressure and washed twice with THF (20 mL). After adding THF (40 mL), 7.0 mL (28.0 mmole) of chlorodiethylphosphite was added dropwise. The resultant mixture was stirred for 5 h and then at 0°C for 3 h, filtered, washed and dried as in the previous experiment. The product showed no weight gain again. ^{31}P NMR showed two peaks as before at +159 ppm and at +25.8 ppm. IR spectrum also looked identical.

Anal. Found: P 4.48% (32.5% RS); Br 1.00% (2% RS) by elemental analysis.

Michaelis-Arbuzov Reaction of 54 with the Bromo Ester 45

To 4.58 g of 54 (Method A) (ca 3.30 mmole) in 60 mL of DMF was added the bromo ester 45 (2.0 mL). The mixture was stirred at 140°C for 7 h and at room temperature for 16 h. The polymer was filtered under nitrogen atmosphere, washed 6 times with 10.0 mL portions of CH_2Cl_2, THF and diethyl ether, dried at 70°C under vacuum to give 4.7 g of the phosphinate 55. ^{31}P NMR analysis showed a single broad peak at +30 ppm indicative of pentavalent phosporous species. IR spectrum displayed a carbonyl band at 1715 cm^{-1}.

Michaelis-Arbuzov Reaction of 54 with Ethyl Bromoacetate[73]

The reaction was performed as before with 5.47 g (ca 3.90 mmole) of 54 (Method B) and 1.5 mL of ethylbromoacetate in DMF (60 mL) which gave 5.2 g of the product 56 (some samples was lost while transferring). Again ^{31}P NMR analysis displayed a single signal at δ +30 ppm. IR spectrum showed a carbonyl band at 1725 cm^{-1}.

Synthesis of 8 From 55 and 19

Wittig olefination conditions were the same as in previous experiments for 8 except that the base was added after the addition of the carbonyl compound. The reaction was carried out with 2.68 g of 55, 0.36 g (1.65 mequiv) of C_{15} aldehyde 19 and 2.7 mL (3 mequiv) of NaOEt. IR spectrum of the product displayed a band for ester carbonyl at 1715 cm^{-1}. It was not possible to study the ^{1}H NMR.

Synthesis of Ethyl Cinnamate (57) From 56 and Benzaldehyde

The same conditions as above were followed with 2.71 g of 56, 0.26 g (2.47 mmole) of benzaldehyde and 3.9 mL (4.30 mequiv) of NaOEt. GLC analysis of the product gave 7.5 area % for 57 and 89.7 area % for unreacted benzaldehyde.

Preparation of Polymer-Bound C_{15} Phosphonium Bromide 58

To 2.90 g (6.0 mequiv) of phosphine 5 in benzene (20 mL) was passed hydrogen bromide gas for 10 minutes and the mixture was stirred

for 1 h. Alcohol 53 (0.79 g, 3.5 mmole) was then added, and the mixture was stirred at 50°C for 20 h. The polymer was filtered and washed as in 46. It was dried at 40°C under vacuum to give 3.40 g of 58. ^{31}P NMR spectrum displayed 2 signals at ∂ -9.91 ppm for the hydrobromide 50 and at ∂ +25.4 ppm for the C_{15} phosphonium bromide 58, in the proportion 40:60.

Anal. Found: Br^- 0.97 mequiv/g (17.5% RS) by ion exchange analysis.

Subtracting 40% for 50 the % conversion to 58 was 46%. (Calculation is only approximate since some phosphine 5 may also be present at δ - 9.1 ppm, the peak being broad).

Wittig Olefination of 58 with C_5 Aldehyde 14

The same conditions as in other experiments for 8 were followed with 2.05 g (1.20 mequiv) of 58, 1.20 mL (1.2 mequiv) of NaOEt and an ethanolic solution of C_5 aldehyde 14 (1.60 mL, 0.19 g, 1.40 mequiv). Polymer mixture showed some signs of phosphorane generation (light red brown color) but ^1H NMR of the product revealed only the starting material.

Reduction of ß-Ionone (9) to ß-Ionol (59)

The procedure described under 47 was repeated. From 10.0 g (50.0 mmole) of 9, and 1.29 g (34.0 mmole) of $NaBH_4$ was obtained 9.60 g (96%) of 59. ^1H NMR ($CDCl_3$): ∂ 0.99 (s, 6, 2 C-1 CH_3, s) 1.25-1.36 (d,3,C-9 CH_3,J=7 Hz), 1.67 (s,3,C-5 CH_3), 1.92-2.06 (t,2,C-4 CH_2), 3.88 (br,s,1,OH), 4.32 (m,1, H-9), 5.37-5.6 (dd,1,H-8,J=16 Hz, $J_{8,9}$=6 Hz) 5.92-6.14 (s, 1,H-7, $J_{7,8}$=17 Hz).

Preparation of ß-Ionyl Bromide (15)

The procedure described under 48 was repeated. From 4.97 g (24.0 mmole) of 59, 1.1 mL (34 mequiv) of PBr_3, and 4 drops of pyridine in 30 mL of ether/hexanes (1:5) was obtained 6.05 g (91% crude yield) of 15. The bromide was taken immediately for further reaction.

Preparation of ß-Ionylpolystyryldipheny-phosphonium Bromide 60 and Wittig Olefination with 61

Phosphonium salt 60 was formed as in 49 with 1.52 g (3.2 mequiv) of phosphine 5 and 1.44 g (ca, 3.4 mmole) of 15 in 20 mL of THF. The reaction mixture was proceeded for Wittig reaction by the same procedure as in 8 with 1.5 mL (2.35 mequiv) of NaOEt and 0.22 g (1.4 mmole) of aldehyde 61. The ^1H NMR spctrum showed the absence of aldehyde signal, but the chemical shift values in the aromatic and aliphatic regions were not in agreement with the desired product.[74]

BIBLIOGRAPHY

1. (a) Maercker, A. Org. Reactions. 1965, 14, 270-490; (b) Johnson, A. W. "Ylid Chemistry", Academic Press, New York, 1966. Part I; (c) Grosney, I.; Rowley, A. G. "Organophosphorous Reagents in Organic Synthesis", Cadogan, J. I. G. Ed., Academic Press, New York, 1979, Chapter 2; (d) Bestmann, H. J. Pure Appl. Chem. 1980, 52, p. 771.

2. Wittig, G.; Geissler, G. Ann. 1953, 580, p. 44.

3. Wittig, G.; Schollkopf, U. Chem. Ber. 1954, 87, 1318.

4. Wittig, G.; Haag, W. Chem Ber. 1955, 88, 1654.

5. Wittig, G. Angew. Chem. 1956, 68, 505.

6. Wittig, G. Experientia. 1956, 12, 41.

7. Vedejs, E.; Meier, G. P.; Snoble, K. A. J. J. Am. Chem. Soc. 1981, 103, 2823-2831.

8. Bestmann, H. J. Pure Appl. Chem. 1979, 51, 515-533.

9. Schlosser, M. Topics in Stereochemistry. 5, Eliel, E. L.; Allinger, N. L.; Eds., John Wiley and Sons, Inc., New York, NY 1970, 1-34.

10. Trippett, S. Adv. Org. Chemistry. 1960. 1, 83.

11. Bergelson, L.D.; Vauver, V. A.; Shemyakin, M. M. Izvest. Akad. Nauk SSR, Otdel, Khim. Nauk, 1961, 729.

12. (a) Bergelson, L.D.; Vauver, V.A.; Barsukov, L. I.; Shemyakin, M. M. Dokl Akad. Nauk SSSR. 1962. 143, 111-114; (b) Tetrahedron Lett. 1964, 38, 2669-2674.

13. (a) Wadsworth, W. S. Org. Reactions. 1978, 25, 73; (b) Walker, B. J. in "Organophosphorous Reagents in Organic Synthesis", J. I. G.Cadogan, Ed., Academic Press, New York, 1979, Chapter 3; (c) Bergelson, L. D.; Shemyakin, M. M. Tetrahedron, 1963, 19, 149-159.

14. For reviews see (a) Akelah, A.; Sherrington, D.C. Chem. Review. 1981, 81, 557-587; (b) Frechet, J. M. J. Tetrahedron, 1981, 37, 663-683; (c) Akelah, A. Synethesis, 1981, 413-438; (d) Hodge, P. in "Polymer-Supported Reactions in Organic Synthesis",

Hodge, P.; Sherrington, D.C. eds., John Wiley and Sons, New York, 1980; pp. 83-155; (e) Mathur, N. K.; Narang, C. K.; Williams, R. E. "Polymers as Aids in Organic Chemistry", Academic Press, New York, 1980; (f)
Kraus, M. A.; Patchornik, A. Macromol. Rev. 1980, 15, 55-106. (g) Manecke, G.; Reuter, P. Pure Appl. Chem. 1979, 51, 2373-2330; (h) Warshawsky, A. Isr. J. Chem. 1979, 18, 318-324. (i) Daly, W. H. Makromol. Chem., Supp. 2. 1979, 3-25. (j) Leznoff, C. E. Acc. Chem. Res. 1978, 11, 327-333; (k) Heitz, W. Adv. Polym. Sci. 1977, 23, 1-23.

15. Chang, Y. H.; Ford, W. T. J. Org. Chem. 1981, 46, 5364-5371.

16. Merrifield, R. B. J. Am. Chem. Soc., 1963, 85, 2149-2154.

17. Letsinger, R. L.; Koronet, J. J. Am. Chem. Soc. 1963, 95, 3045.

18. Camps, F.; Castells, L.; Font, J.; Vela. F. Tetrahedron Lett. 1971. 1715-1716.

19. (a) Heitz, W.; Michels, R. Angew. Chem. Int. E. Engl. 1972, 11, 298-299; (b) Heitz, W., Michels, R. Liebigs Ann. Chem. 1973, 227-230.

20. Farrell, M. J.; Frechet, J. M. J. J. Org. Chem. 1976, 41, 3877-3882.

21. McKinley, S. V., Rakshys, J. W. J. Chem. Soc., Chem. Comm., 1972, 134-135.

22. Clarke, S. D.; Harrison, C. R.; Hodge, P. Tetrahedron Lett. 1980. 21, 1375-1378.

23. Akelah, A. Eur. Polym. J. 1982, 18, 559-561.

24. Leznoff, C. C.; Greenburg, S. Can. J. Chem. 1976, 54, 3824-3829.

25. Leznoff, C. C.; Fyles, T. M. J. Chem. Soc. Chem. Comm., 1976, 251.

26. Leznoff, C. C.; Sywanyk, W. J. Org. Chem. 1977, 42, 3203-3204.

27. Castello, J., Font, F; Virgili, A. J. Chem. Soc. Perkin Trans. 1. 1979, 1-6.

28. Frechet, J. M.; Schuerch, C. J. Am. Chem. Soc., 1971, 93, 492-496.

29. (a) Hodge, P.; Waterhouse, J. Polym. Commun. 1981, 3861-62. (b) Pittmann, C. U. "Polymer-Supported Reactions in Organic Synthesis", Hodge, P.; Sherrington, D.C. Eds., John Wiley and Sons, New York, 1980. Chapter 5.

30. Boutwell, R. K. "Oncology Overview: Selected Abstracts on Vitamin A in Cancer Biology", U.S. Department of Health, Education, and Welfare, National Cancer Institute: Washington, D.C., September, 1979.

31. (a) Newton, D. L.; Henderson, W. R., Sporn, M. B. Cancer Res. 1980, 40 3413-3425; (b) Sporn, M. B.; Newton, D. L. Fed. Proc., Fed. Am. Soc. Exp. Biol., 1979, 38, 2528-2534; (c) Sporn, M. B.; Dunlap, N. A.; Newton, D. L.; Smith, M. B.; Dunlap, N. M.; Newton, D. L.; Henderson, W. R. Nature (London), 1976, 263, 110-113.

32. (a) Bollag, W. Eur. J. Cancer. 1974, 10, 731-736; (b) Bollag, W. Chemother. Basel. 1975, 21, 236-247.

33. Newton, D. L.; Henderson, W. R.; Sporn, M. B. "Structure Activity Relationships of Retinoids", published by the National Cancer Institute, Revised Edition, Feb. 26, 1980.

34. Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A., Walker, T. J. Chem. Soc. 1952, 1094.

35. Isler, O.; Ronco, A.; Guey, W.; Hindley, N. C.; Huber, W.; Draler, K.; Kofler, M. Helv. Chim. Acta., 1969, 32, 489.

36. Oroshnik, W., J. Amer. Chem. Soc. 1956, 78, 2651.

37. Eiter, K.; Truscheit, E. Ger. Pat, 1,110,156, 1961, Chem. Abstr. 1962 57, 4567.

38. Gedye, R. N., Arora, P.; Khalil, A. H. Can. J. Chem., 1975, 53, 1943-1948; (b) Rathke, M. W. Org. Reactions, 1975, 22, 423; (c) Santaniello, E.; Manzoechi, A. Synthesis, 1977, 698.

39. (a) Pommer, H. Angew. Chem. Int. Ed. Eng. 1977, 16, 423-429. (b) Pommer, H. Angew. Chem., 1960, 72, 811-819 and 911.

40. Isler, O.; Mayer, H. in "Carotenoids", Isler, O.,Ed., Halted Press, A Division of John Wiley and Sons, Inc., New York, 1971. pp. 373-388.

41. Wittig, G.; Pommer, H. Ger. Pat. 950,552, 1956; Chem. Abstr. 1954, 53 436.

42. Pommer, H.; Wittig, G. Ger. Pat., 951,212, 1956; Chem. Abstr. 1959, 53, 437.

43. Pommer, H., Sarnecki, W. U.S. Patent, 3006939, 1961.

44. (a) Pommer, H.; Wittig,G. Ger. Pat. 1,001,256, 1959; Chem. Abstr. 1959, 53, 13081e; (b) Pommer, H.; Sarnecki, W. Ger. Pat. 1,050,763, (1959). Chem. Abstr. 1961, 55, 5572g.

45. (a) Pommer, H.; Sarnecki, W. Ger. Pat. 1,068,710, 1959; Chem. Abstr. 1961, 55, 12446; (b) Pommer, H.; Sarnecki, W., Ger. Pat., 1,046,612, 1958; Chem. Abstr. 1961, 55, 5573; (c) Pommer, H.; Sarnecki, W. Ger. Pat. 1,059,900, 1959; Chem. Abstr. 1961, 55, 14511; (d) Pommer, H.; Sarnecki, W. Ger. Pat. 1,068,702, 1959, Chem. Abstr. 1961, 55, 10,812.

46. (a) Howe, R. K., J. Am. Chem. Soc. 1971, 93, 3457. (b) Gedye, R. N.; Westaway, K. C.; Arora, P.; Bisson, R.; Khalil, A. H. Can. J. Chem. 1977, 55, 1218-1228.

47. (a) Julia, M.; Arnold, D. Bull. Chem. Fr. 1973, 743-750; (b) Manchand, P. S., Rosenberger, M.; Saucy G.; Wehrli, P. A.; Wong, H.; Chambers, L.; Ferro, M. P.; Jackson, W. Helv. Chem. Acta 1976, 59, 387-396; (c) Olson, G. L., Ho-cheun Cheung; Morgan, K. D.; Neukom, C.; Saucy, G. J. Org. Chem. 1976, 41, 3281-3293. (d) Miller, D.; Trammel, M.; Kini, A.; Liu, R. S. H. Tetrahedron Lett. 1981, 22, 409-412.

48. Kienzle, F. Helv. Chim. Acta 1973. 56, 1671.

49. Trost, B. M., Fortunak, J. M. D. Tetrahedron Lett. 1981, 22, 3459-3462.

50. (a) Balakrishnan, T.; Ford, W. T. J. Appl. Poly. Sci. 1982, 27, 133-138; (b) Balakrishnan, T.; Lee, J.; Ford, W. T. Submitted to Macromolecular Synthesis.

51. Porosity data provided by the Rohm and Haas Company.

52. Heitz, W.; Michels, R. Makromol. Chem. 1971, 148, 9.

53. (a) Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Hardie, B. A. J. Am. Chem. Soc. 1964, 86, 1039-1044. (b) McKillop, A.; Bromley, D. Tetrahedron Lett. 1969, 1623-1626.

54. Young, L. J. in "Polymer Handbook", Brandrup, J.; Immergut, E. J., Eds., New York: John Wiley and Sons, Inc. 1975, pp. 11-323.

55. Ref. 51, p. 95.

56. Relles, H. M.; Schluenz, R. W. J. Am. Chem. Soc. 1974, 96, 6469-6475.

57. Regen, S. L.; Lee, D. P. J. Org. Chem. 1975, 40, 1669-1670.

58. Swartz, J. E.; Bunnett, J. F. J. Org. Chem. 1979, 44, 340-346.

59. Fritzsche, H.; Hasserodt, U.; Korte, F. Chem. Ber. 1965, 98, 171-174.

60. Ahmed, I.; Gedye, R. N.; Nechwatel, A. J. Chem. Soc. (C). 1968, 185-187.

61. Kuhn, V. R.; Hoffer, M. Chem. Ber. 1934, 67, 357-361.

62. Loeliger, P.; Bollag, W.; Mayer, H. Eur. J. Med. Chem.-Chem. Ther. 1980, 15, pp. 9-15.

63. Brit. Pat. (BASF) 817884, 1959; Chem. Abstr. 1960, 54, 11074b.

64. Surmatis, J. D.; Ofner, A. J. Org. Chem. 1963, 28, 2735-2739.

65. Widmer, E.; Lukac, T.; Bernhard, K.; Zell, R. Helv. Chim. Acta. 1982, 65, 671-683.

66. (a) Stilz, W.; Pommer, H. U. S. Pat. 3,157,660, 1964; (b) Pommer, H.; Stilz, W. Ger. Pat. 1,116,653, 1961.

67. Liu, R. S. H.; Matsumoto, H.; Asato, A. H. D.; Dinny, M.; Shichida, Y.; Yoshizawa, T.; Dahlquist, F. W. J. Am. Chem. Soc. 1981, 103, 7195-7201.

68. (a) Ramamurthy, V.; Tustin, G.; Yau, C. C.; Liu, R. S. H. Tetrahedron, 1975, 31, 193-199. (b) Samokvolov, G. I.; Zakharkin, L. I.; Davydova, L. P.; Khorlina, I. M. Akad. Nauk SSR. Dok. Khim. 1959, 126, 1013-1026. Eng. 447-450.

69. (a) Bu'Lock, J. D.; Quarrie, S. A.; Taylor, D. A. J. Labelled Compd. 1972, 9, 311-320. (b) Robeson, C. D.; Cawley, J. D.,; Eddinger, C. C.; Checkak, A. J. J. Am. Chem. Soc. 1955, 77, 4111-4119.

70. Halley, B. A.; Nelson, E. C. J. Chrom. 1979, 179, 113-123.

71. (a) Kapachnik, M. I.; Tsvetkov, E. N. Izv. Akad. Nauk SSR, Otd. Khim. Nauk. 1960, 133-134. Eng. 122-123; (b) Crutchfield, M. M.; Dungan, C. H.; Letcher, J. H.; Mark V.; Van Wazer, J. R. "Topics in Phosphorous Chemistry". Vol. 5, ^{31}P Nuclear Magnetic Resonance, Interscience Publishers, New York, 1967, p. 255, 296.

72. Thomas, L. C. "Interpretation of the Infrared Spectra of Organophosphorous Compounds", Heyden, New York, 1974, Chapters 4, 5, 9.

73. (a) Kabachnik, M. I.; Tsvetkov, E. N. Zh. Obshch. Khim. 1960, 30, 3227-3233. Eng. 3197-3202; (b) Sander, M. Chem. Ber. 1960, 93, 1220-1231; (c) Kabachnik, M. I.; Tsvetkov, E. N. Akad-Nauk SSSR. Proceedings, Chemistry Section 1957, 117, 1063-1066.

74. Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.; Fung, V. A. J. Med. Chem. 1982, 24, 583-592.

75. Dugger, R. W.; Heathcock, C. H. Synth. Commun. 1980, 10, 509-515.

76. Isler, O. Pure Appl. Chem. 1979, 51, 447.

77. Pattenden, G.; Weedon, B. C. L. J. Chem. Soc. (C) 1968, 1984-1997.

78. Cainelli, G.; Contento, M.; Manescalchi, F.; Ragnoli, R. J. Chem. Soc. Perkin I 1980, 2516-2519.

79. Rosenberger, M.; Neukom, C. J. Org. Chem. 1982, 47, 1782.

80. Corey, E. J.; Chaykovsky, M. J. Am. Chem. Soc. 1962, 84, 866-867.

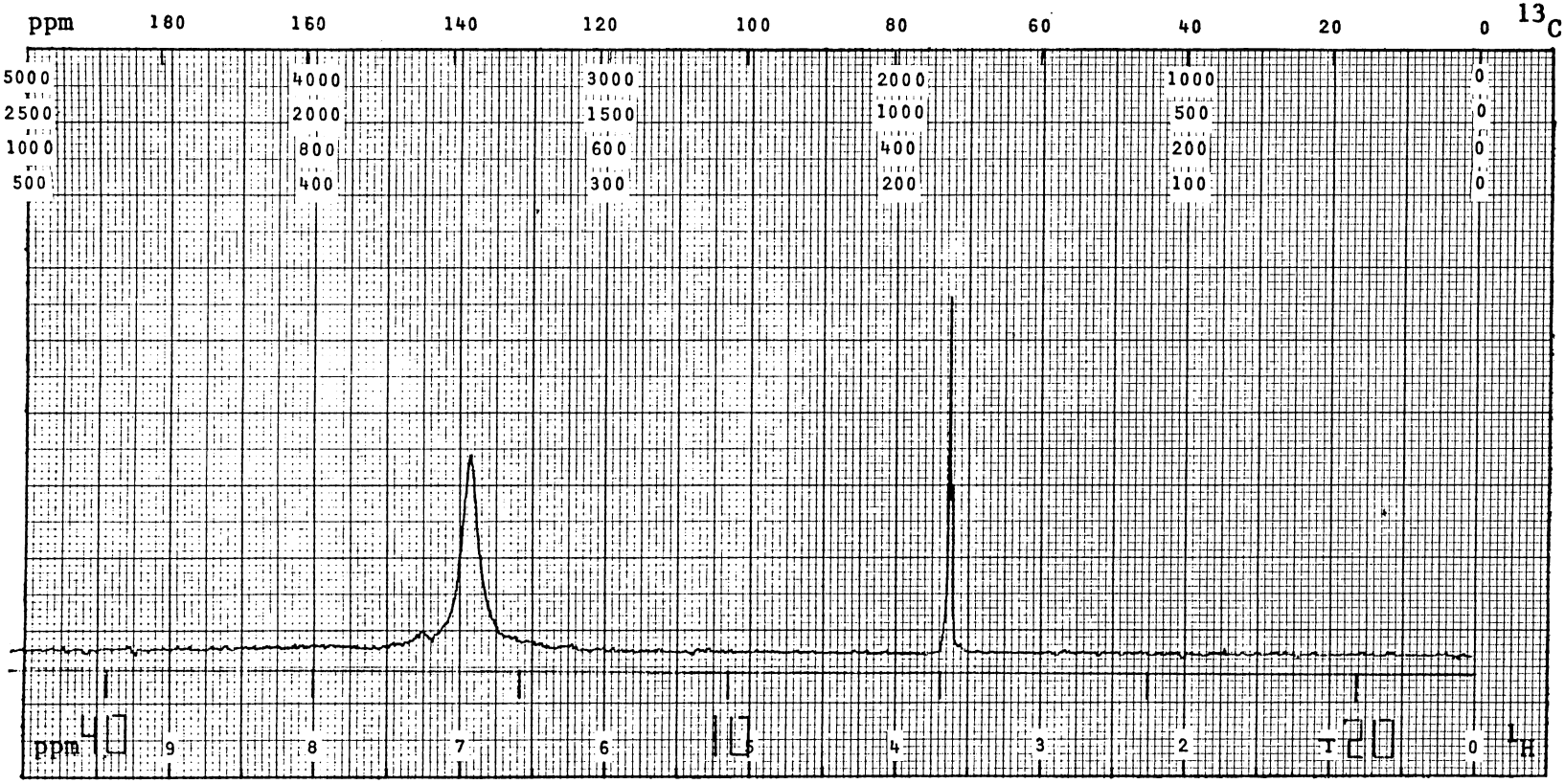
81. Colwell, A. R.; Duckwall, L. R.; Brooks, R.; McManus, S. P. J. Org. Chem. 1981, 46, 3097-3102.

82. Aldrich Chemical Company Handbook of Organic Chemicals, 1981-82.

83. Reid, R.; Nelson, E. C.; Mitchell, E. D.; McGregor, M. L.; Waller, G. R.; John, K. V. Lipids, 1973, 8, 558-565.

84. Andrewes, A. G.; Jensen, S. L. Acta. Chem. Scand. 1973, 27, 1401-1409.

APPENDIX

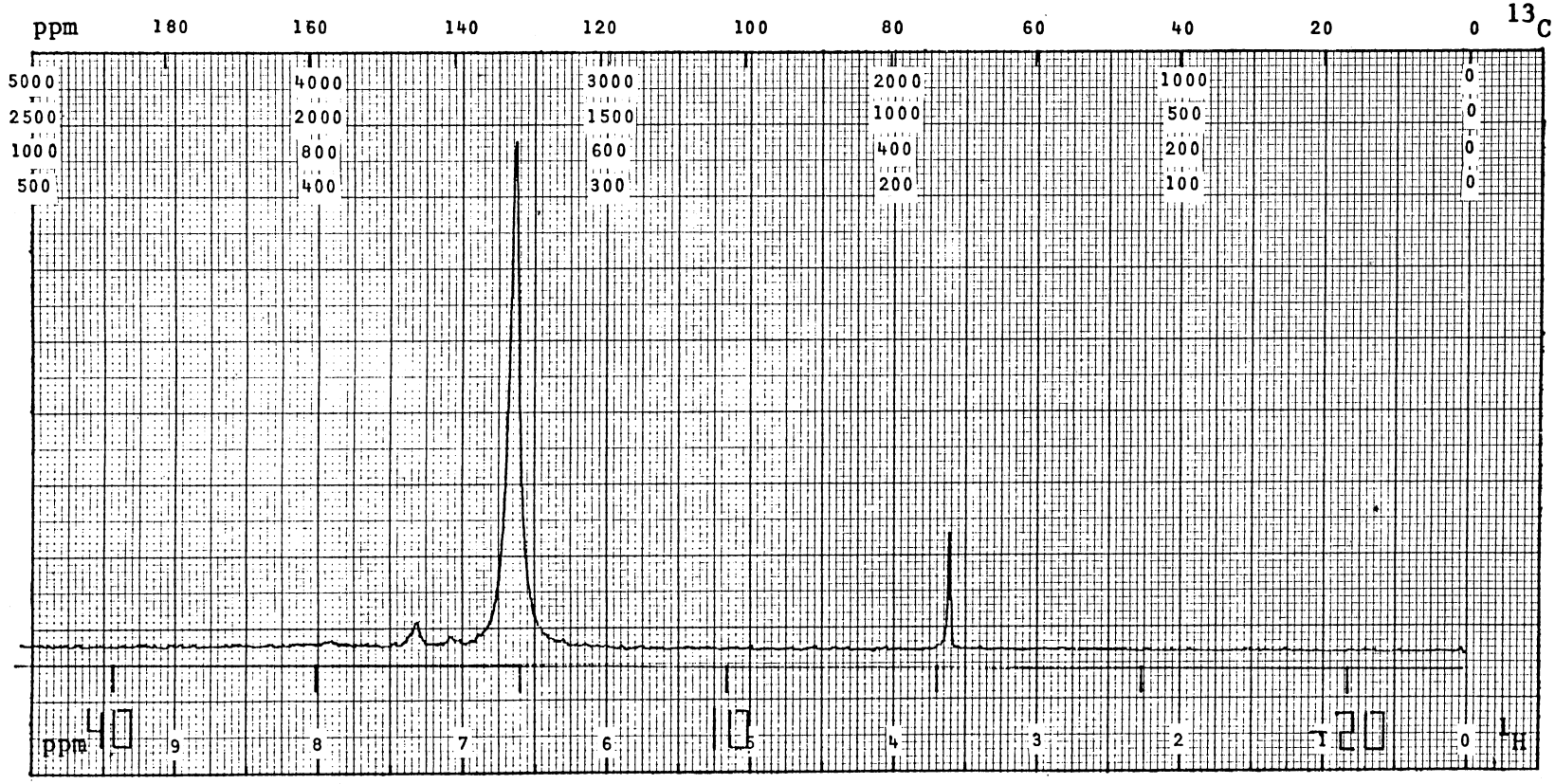


Spectrum 1. ^{31}P NMR of Benzylphosphonium Salt 34.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 6600 Hz; PW. .8499.5Hz; T. . 20 °C; Acq/SA. . 500

Size. .16 K; P2/RF. .12 µs/dB; SF. .121.42 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 0.10 s

DC. . ^1H ; Gated Off. . NA ; Offset. . 0 Hz; RF. .5 W/dB; NBW. . 100 Hz

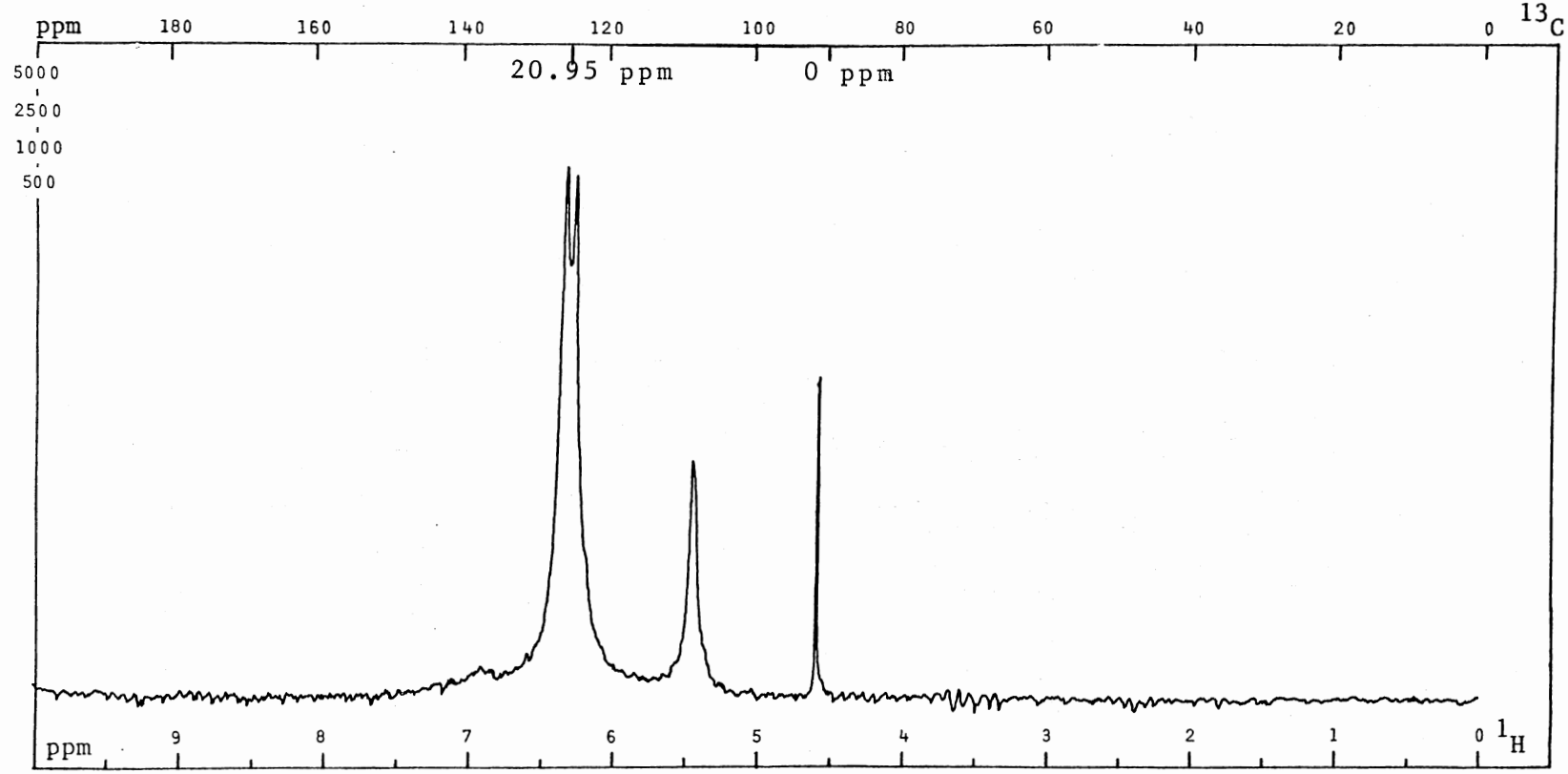


Spectrum 2. ^{31}P NMR of Methylphosphonium Salt 35.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 6600 Hz; PW. .8499.5Hz; T. . 20 °C; Acq/SA. . 100

Size. . 16 K; P2/RF. . 10 µs/dB; SF. .121.42 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 1.0 s

DC. . ^{1}H ; Gated Off. . NA ; Offset. . 0 Hz; RF. . 5 W/dB; NBW. . 100 Hz

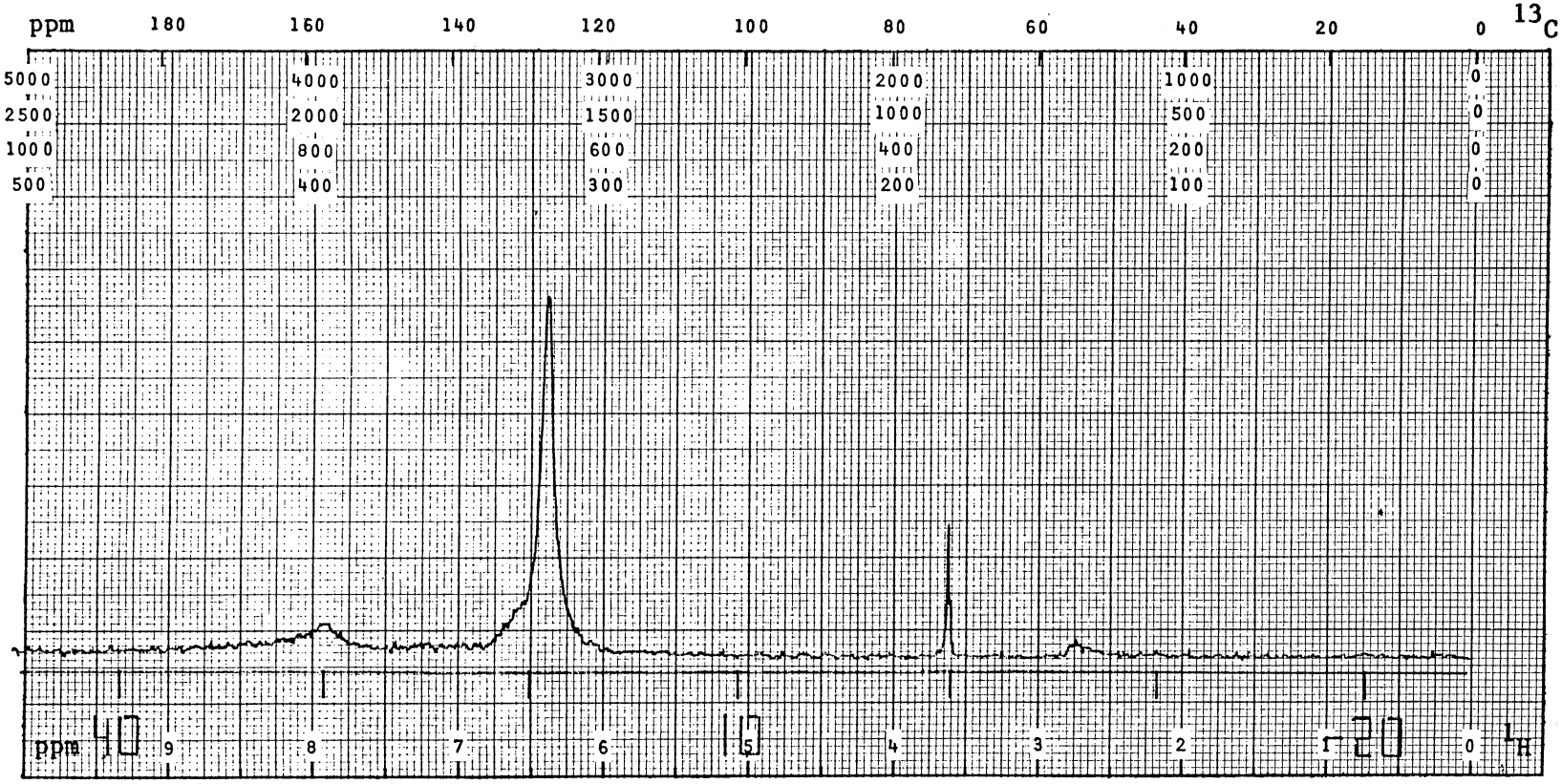


Sprectrum 3. ^{31}P NMR of C_5 Phosphonium Salt 46.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 49201 Hz; PW. . 6000 Hz; T. . 20 °C; Acq/SA. . 100

Size. . 16 K; P2/RF. . 10 µs/~~dB~~; SF. . 40.54 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 5.0 s

DC. . ^1H ; Gated Off. . NA ; Offset. . 45316 Hz; RF. . 9 W/~~dB~~; NBW. . 100 Hz

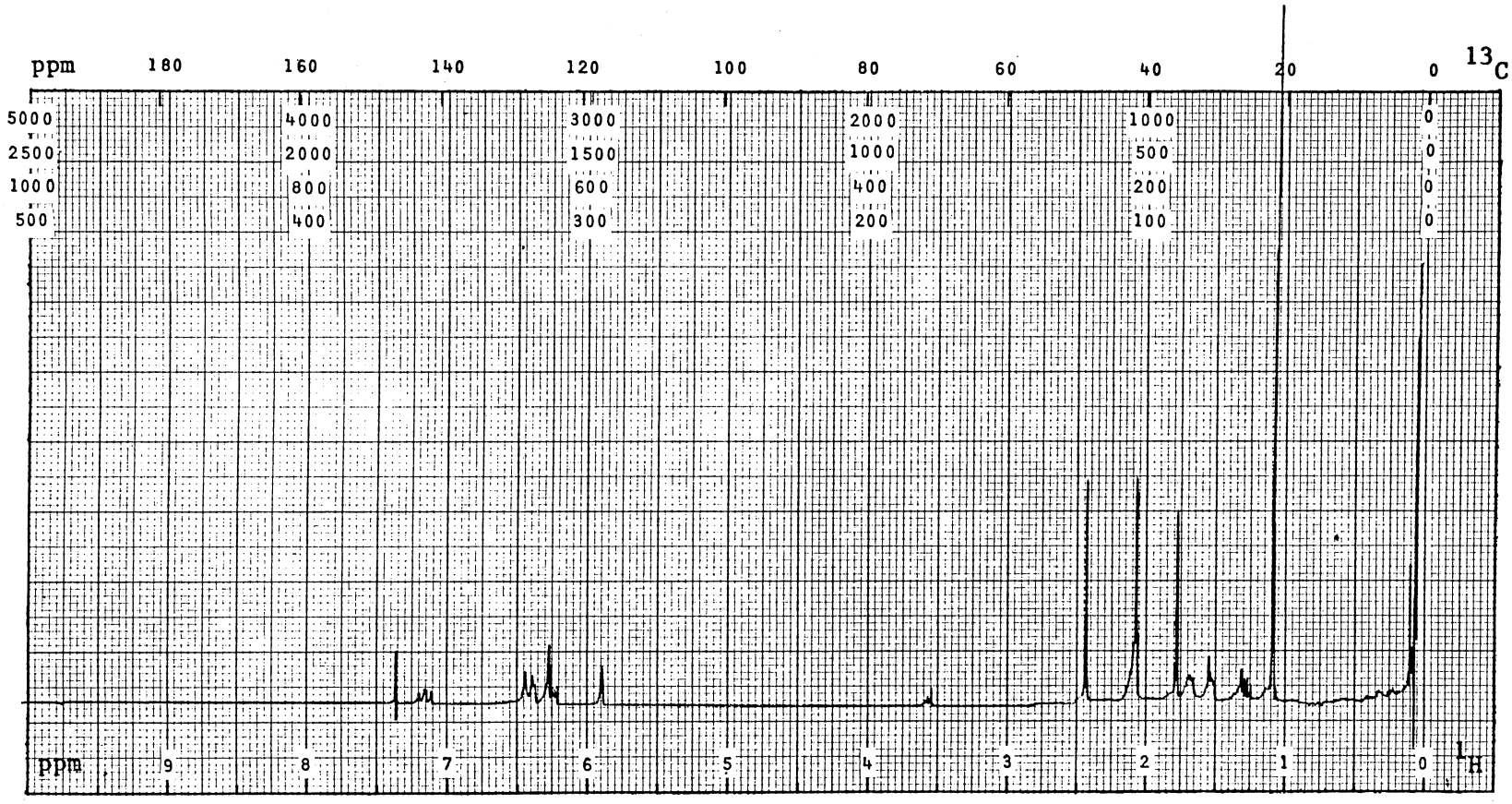


Spectrum 4. ^{31}P NMR of C_{10} Phosphonium Salt 49.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 6600 Hz; PW. .8499.5Hz; T. . 20 °C; Acq/SA. . 500

Size. . 16 K; P2/RF. . 10 µs/dB; SF. .121.42 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 0.10 s

DC. . ^{1}H; Gated Off. . NA ; Offset. . 0 Hz; RF. . 5 W/dB; NBW. . 100 Hz

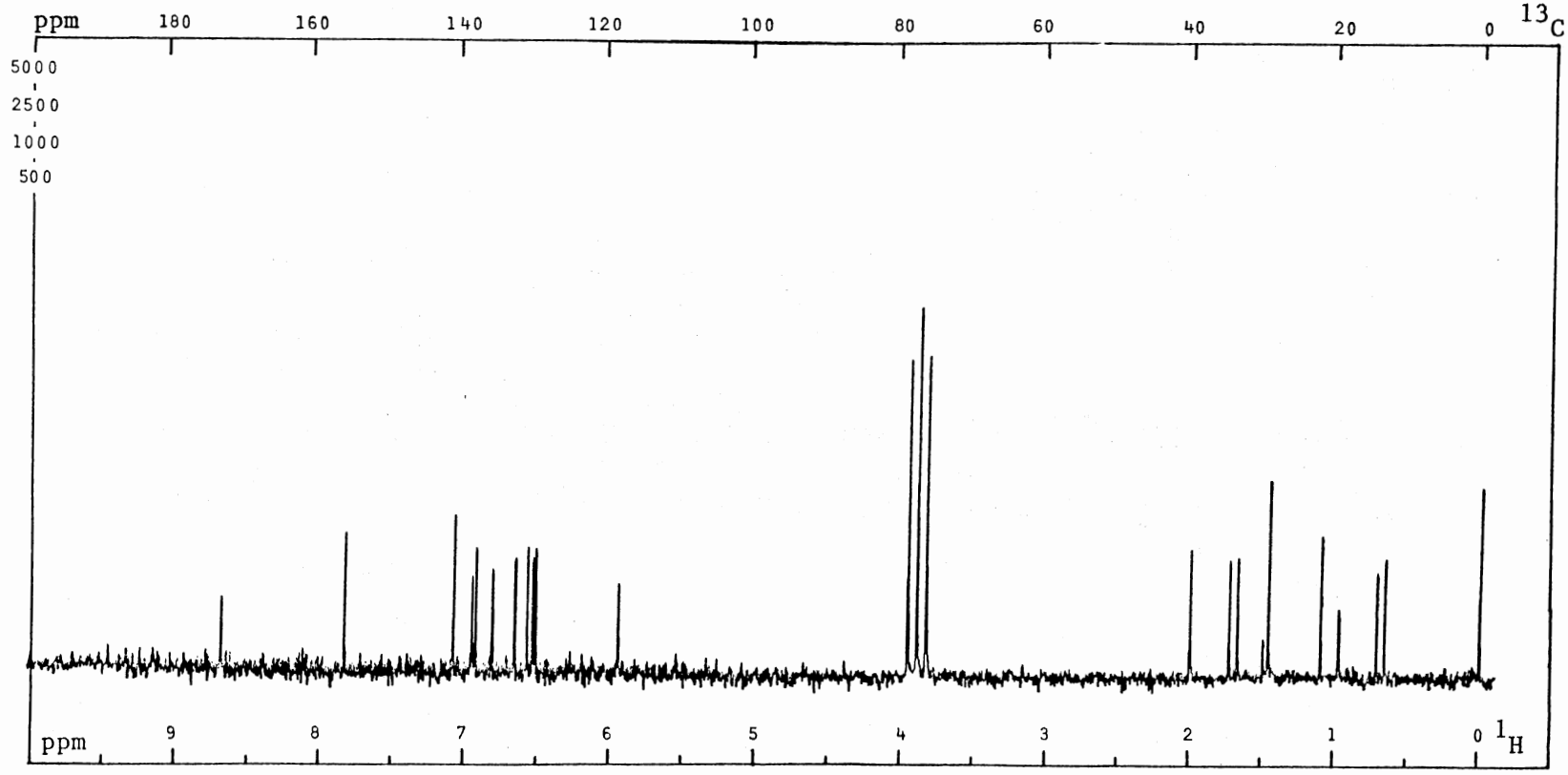


Sprectrum 5. ^{1}H NMR of All-Trans-Retinoic Acid.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 1000 Hz; PW. . 3000 Hz; T. . 18 °C; Acq/SA. . 140

Size. . 10K; P2/RF. . 20 µs/dB; SF. . 300 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 1.0 s

DC. . NA ; Gated Off. . NA ; Offset. . NA Hz; RF. . NA W/dB; NBW. . NA Hz

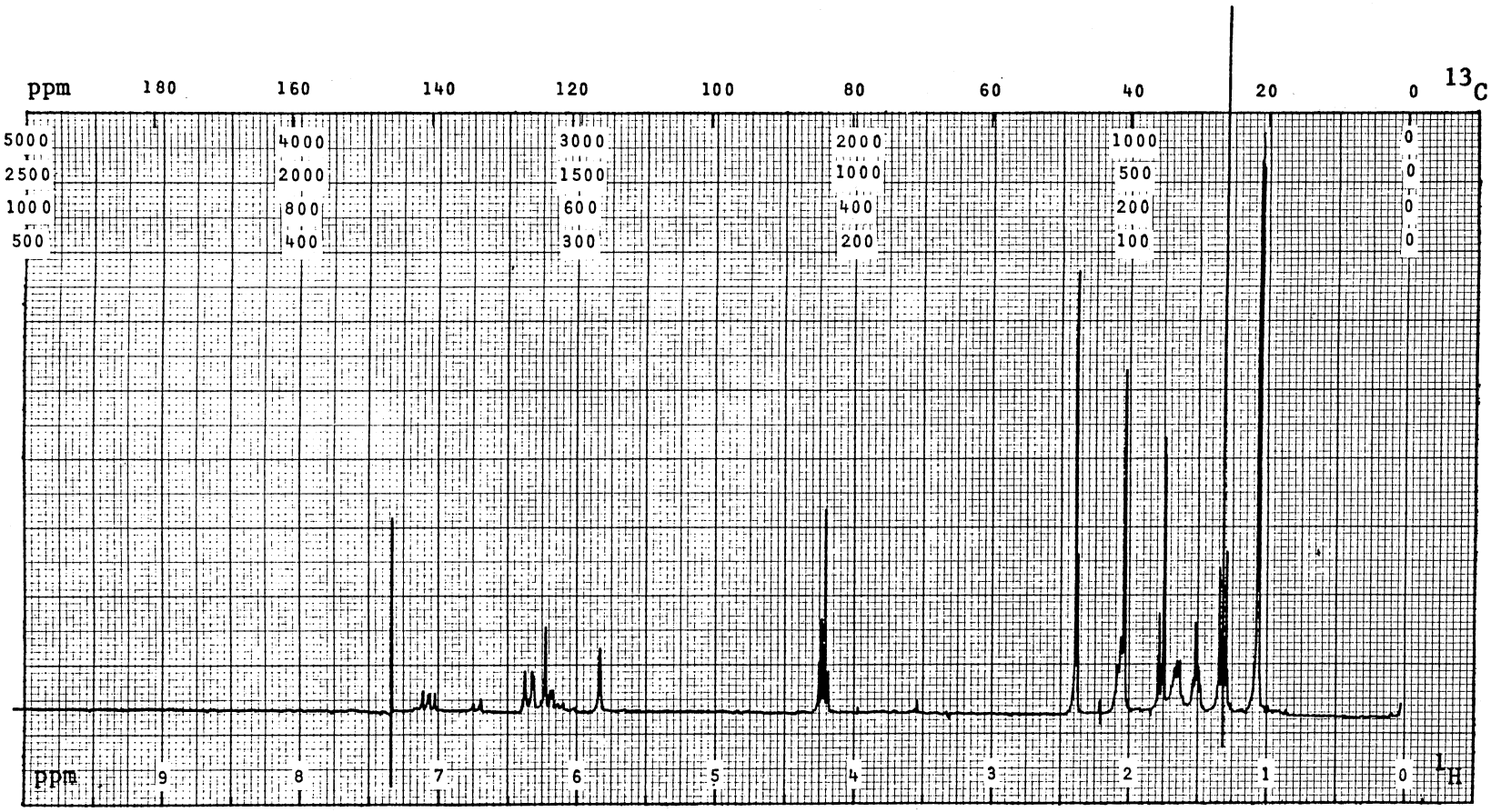


Spectrum 6. ^{13}C NMR of All-trans Retinoic Acid.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 0 Hz; PW. .5000 Hz; T. . 20 °C; Acq/SA. . 8500

Size. .8 K; P2/RF. . 10 µs/dB; SF. . 25.2 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 5.0 s

DC. . ^{1}H ; Gated Off. . NA ; Offset. . NA Hz; RF. .10 W/dB; NBW. . 0 Hz

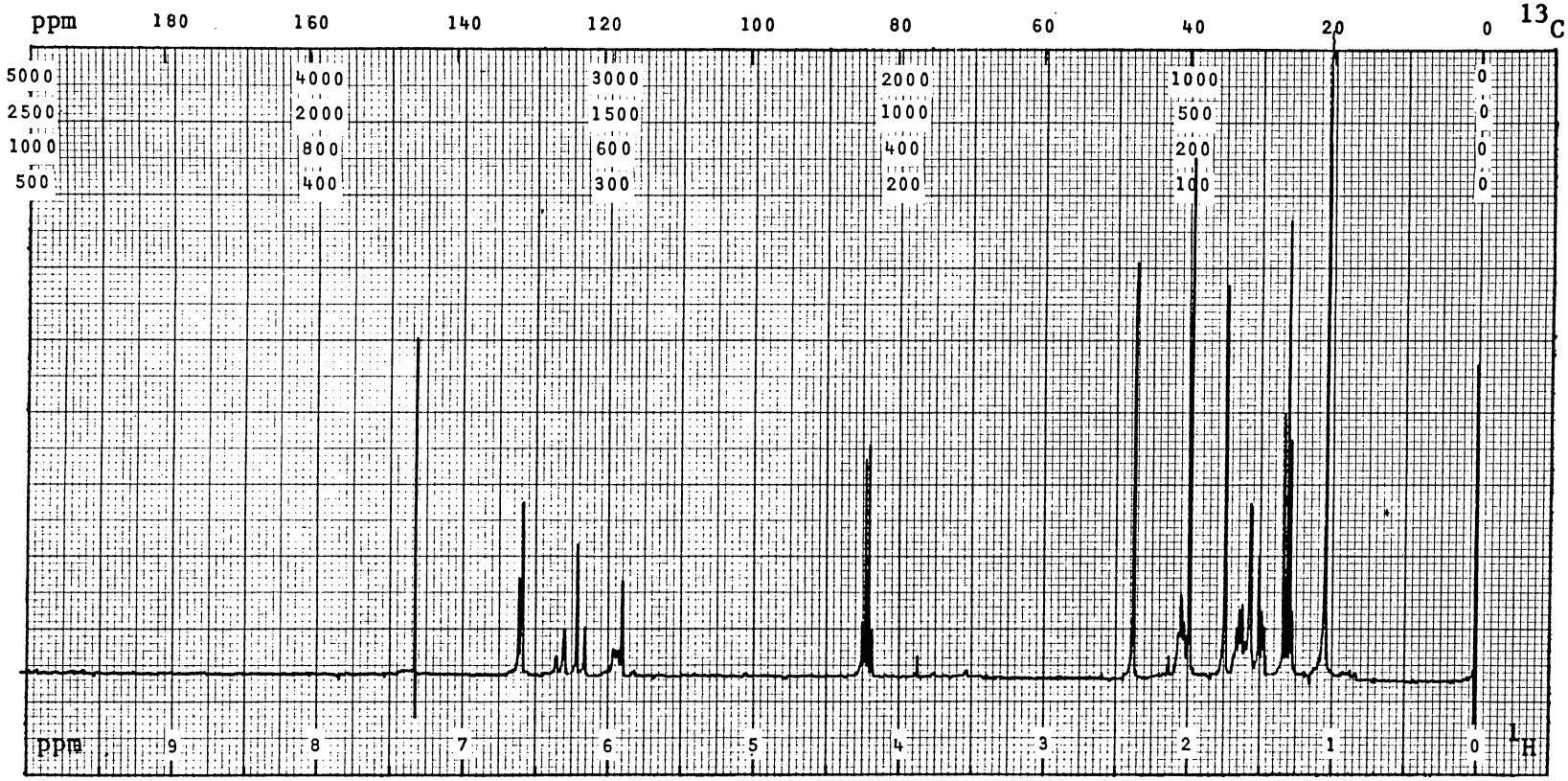


Spectrum 7. ^{1}H NMR of All-trans and 9-cis-Ethyl Retinoate.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 0 Hz; PW. . 3000 Hz; T. . 18°C; Acq/SA. . 40

Size. . 8K; P2/RF. . 5.0 µs/dB; SF. . 300 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 1.0 s

DC. . NA ; Gated Off. . NA ; Offset. . NA Hz; RF. . NA W/dB; NBW. . NA Hz

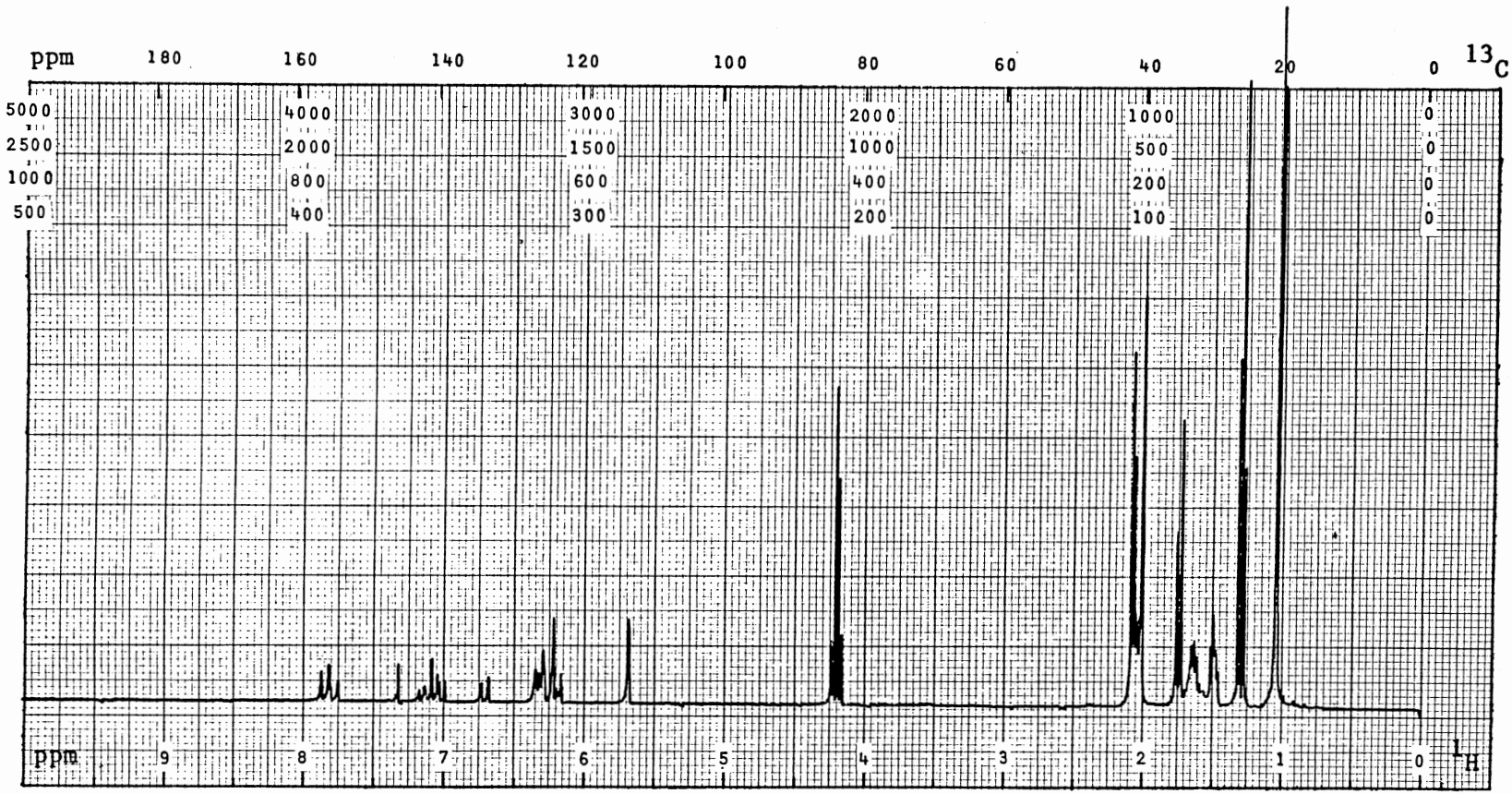


Spectrum 8. ^{1}H NMR of 11-*cis*- Ethyl Retinoate.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 0 Hz; PW. . 3000 Hz; T. . 18°C; Acq/SA. . 260

Size. . 16K; P2/RF. . 4 µs/dB; SF. . 300 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 1.0 s

DC. . NA; Gated Off. . NA ; Offset. . NA Hz; RF. . NA W/dB; NBW. . NA Hz

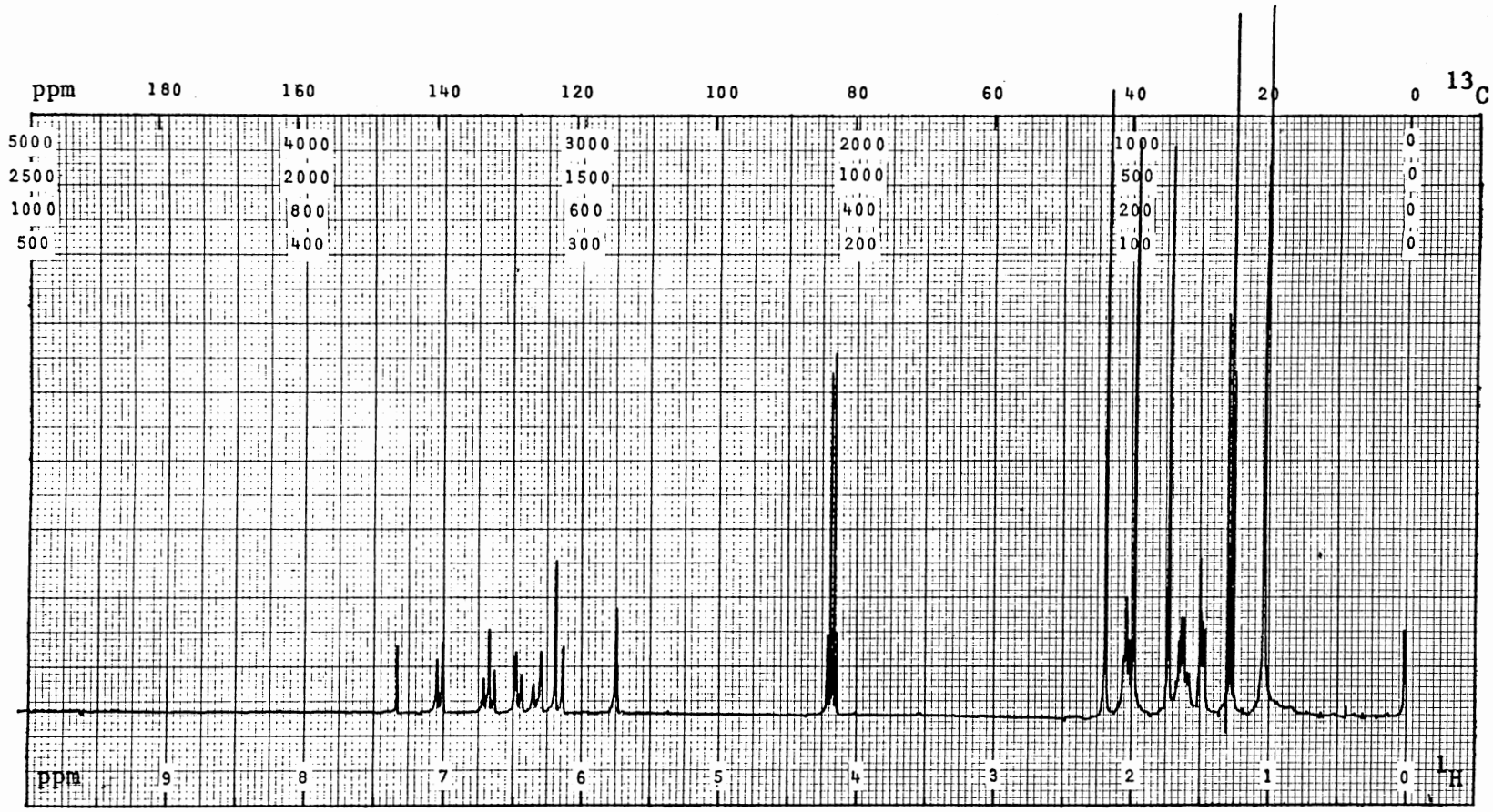


Spectrum 9. ^{1}H NMR of 9,13-di-cis-Ethyl Retinoate.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 0 Hz; PW. . 3000 Hz; T. . 18°C; Acq/SA. . 40

Size. . 16K; P2/RF. . 4 µs/dB; SF. . 300 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 1.0 s

DC. . NA; Gated Off. . NA ; Offset. . NA Hz; RF. . NA W/dB; NBW. . NA Hz

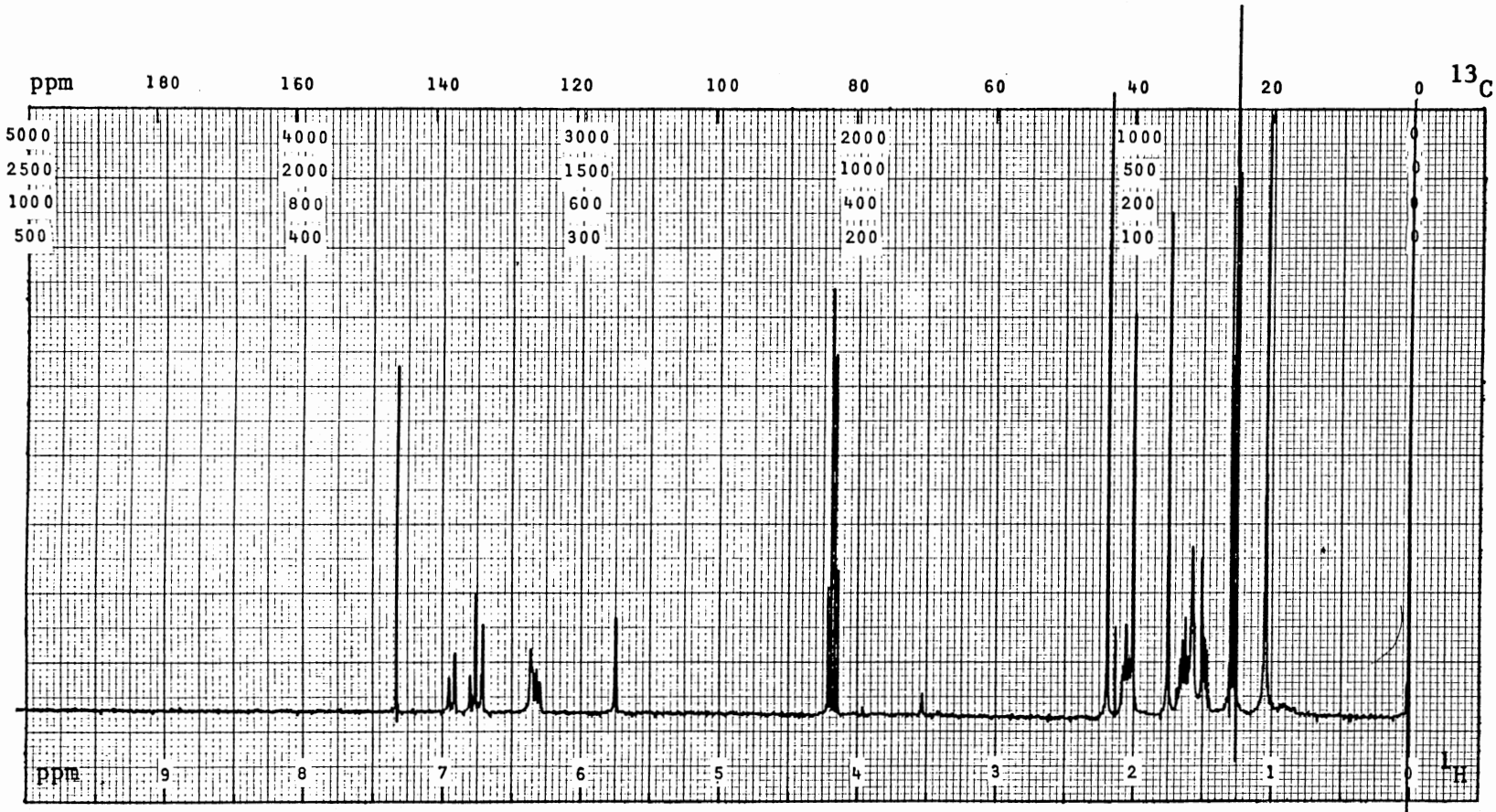


Spectrum 10. ^{1}H NMR of 11,13-di-cis-Ethyl Retinoate.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 0 Hz; PW. . 3000 Hz; T. . 18°C; Acq/SA. . 100

Size. . 16K; P2/RF. . 4 µs/dB; SF. . 300 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 1.0 s

DC. . NA; Gated Off. . NA ; Offset. . NA Hz; RF. . NA W/dB; NBW. . NA Hz



Spectrum 11. ^{1}H NMR of 9,11,13-tri-cis-Ethyl Retinoate.

PFT X CW _ ; Solvent. . $CDCl_3$; SO. . 0 Hz; PW. . 3000 Hz; T. . 18 °C; Acq/SA. . 200

Size. . 16K; P2/RF. . 4 µs/dB; SF. . 300 Hz; FB. . NA Hz; Lock. . D ; D5/ST. . 1.0 s

DC. . NA ; Gated Off. . NA ; Offset. . NA Hz; RF. . NA W/dB; NBW. . NA Hz

VITA

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Doctor of Philosophy

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