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OPTICALLY ACTIVE TRIVALENT PHOSPHORUS ACID ESTERS: SYNTHESIS, CHIRALITY AT PHOSPHORUS AND SOME TRANSFORMATIONS

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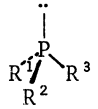
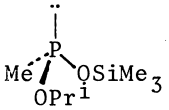
Abstract - Optically active trivalent phosphorus acid esters and thioesters have been obtained by three different methods: (a) asymmetric condensation of racemic trivalent phosphorus chlorides with achiral alcohols or thiols in the presence of optically active tertiary amines, (b) asymmetric reaction of racemic chlorophosphines with optically active alcohols (menthol), (c) stereospecific synthesis from optically active methylthio-alkoxy-phosphonium triflates. Chirality at phosphorus in and optical purity of the chiral trivalent phosphorus acid esters have been determined by chemical correlations. It has been demonstrated that nucleophilic substitution at chiral trivalent phosphorus occurs stereospecifically with inversion of configuration at phosphorus. A new synthesis of chiral tertiary phosphines of high optical purity has also been devised.

INTRODUCTION

Trigonal-pyramidal, tri-coordinate phosphorus compounds with three different substituents, $R^1R^2R^3P$:, are chiral at phosphorus and can in principle be resolved into enantiomers or prepared in an optically active form. For a long time the only known optically active trivalent phosphorus compounds were tertiary phosphines first prepared by Horner (Refs. 1 and 2) in 1961. Chiral tertiary phosphines still occupy a central position in the study of dynamic phosphorus stereochemistry. Recently chiral phosphines have found very important applications as ligands for the catalysts employed in asymmetric, homogeneous hydrogenation (Ref.3). The efficiency of this process was found to be strongly dependent upon the structure of chiral phosphorus ligand. In this connection the synthesis of other classes of chiral trivalent phosphorus compounds is of great interest.



R=alkyl, aryl
(L.Horner,1961)



(H.Benschop,1971)

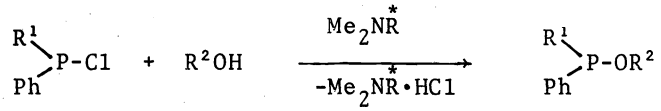
Especially interesting are optically active trivalent phosphorus acid esters because the great majority of organophosphorus reactions are based on their conversion into tetra-, penta- and hexa-coordinate phosphorus compounds. Benschop et.al. (Ref.4) recently synthesized optically active O-trimethylsilyl O-isopropyl methylphosphonite, the first example of an optically active trivalent phosphorus compounds containing a phosphorus-oxygen bond. However, this compound ,apart from the sensitivity to moisture, was unsuitable for studies of organophosphorus reaction mechanisms since nucleophilic reagents react preferentially at silicon rather than phosphorus.
For the past few years, work in this Laboratory (Refs.5 to 9) has centered on the preparation and reactions of optically active trivalent phosphorus acid esters and thioesters, especially those with the phosphorus atom as the sole centre of chirality. Progress in these studies is reported in the present paper. The following topics will be discussed in detail:
(a) asymmetric synthesis of optically active trivalent phosphorus acid esters and thiesters,
(b) stereochemistry of nucleophilic substitution at chiral, trivalent phosphorus,

(c) synthesis and reactions of diastereoisomeric O-menthyl ethylphenylphosphinites,
(d) stereospecific synthesis of optically active phosphinites and reactivity of alkylthio- and alkylseleno-phosphonium salts

ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE TRIVALENT PHOSPHORUS ACID ESTERS AND THIOESTERS

Our first approach to the synthesis of optically active trivalent phosphorus acid esters (1) and thioesters (2) was based on the reaction between racemic, chiral chlorophosphines and achiral alcohols or thiols in the presence of optically active (-)- or (+)-N,N-dimethyl-(1-phenylethyl)amine (see Note a). The asymmetric condensations were carried out in ether at -70÷-78° using equimolar amounts of the reagents. The resulting optically active esters (1) and (2) were purified by distillation. Some representative examples are shown in Scheme I, together with their optical rotation values.

Scheme I. Asymmetric Synthesis of Chiral Trivalent Phosphorus Acid Esters 1 and 2



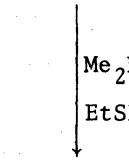
(±) (1)

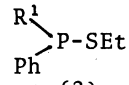
a, R^1=Et, R^2=Me, $[\alpha]_{589}$+30.5°

b, R^1=Et, R^2=Pr^n, $[\alpha]_{589}$+17.1°

c, R^1=Me, R^2=Me, $[\alpha]_{589}$+15.8°

d R^1=Me, R^2=Pr^n, $[\alpha]_{589}$+27.2°

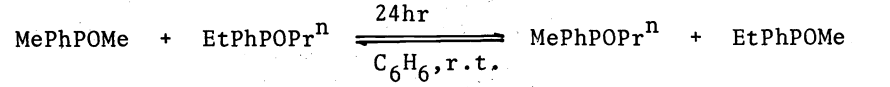




(2)

R^1=Et, $[\alpha]_{589}$+9.7°

The optical stability of chiral esters (1) is not very high. They undergo slow racemisation at room temperature. It was also observed that racemisation of esters (1) is accelerated by traces of amine hydrochlorides which are present in the distilled esters. However , it is noteworthy that this racemisation process is not due to pyramidal inversion at phosphorus but is a consequence of the intermolecular exchange of the alkoxy groups at phosphorus accompanied by inversion of configuration. This view was confirmed by the fact that a mixture of four possible phosphinites (1 a-d) is formed from an equimolar mixture of O-methyl methylphenylphosphinite (1c) and O-propyl ethylphenylphosphinite (1b) as evidenced by ^{31}P-NMR spectra.



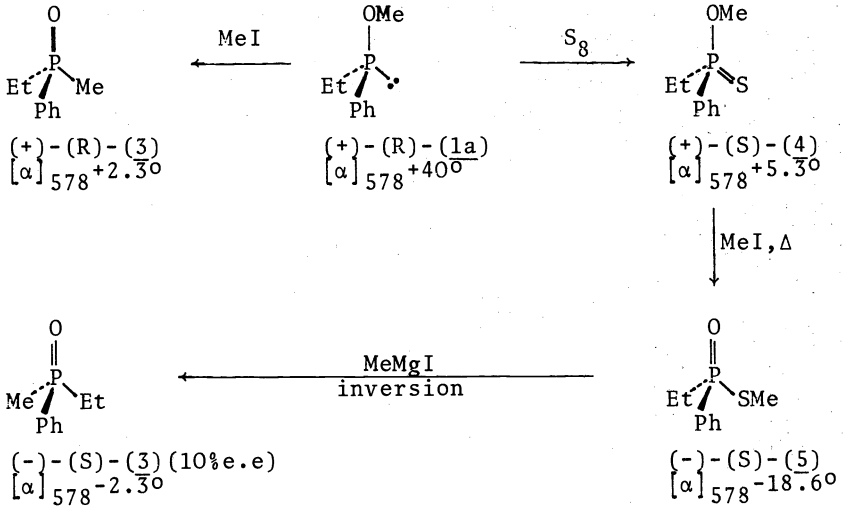
(1c) (1b) (1d) (1a)

$\delta_{^{31}P}$ 122.4ppm $\delta_{^{31}P}$ 125.8ppm $\delta_{^{31}P}$ 115.8 $\delta_{^{31}P}$ 130.0ppm

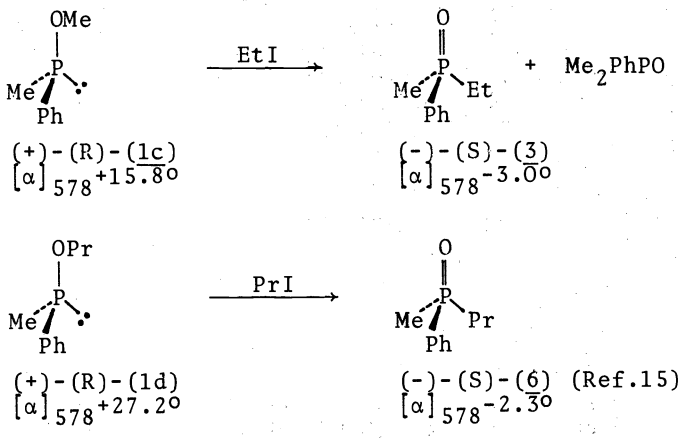
Note a. For our previous work on the use of optically active N,N-dimethyl-(1-phenylethyl)amine in the asymmetric synthesis of chiral sulphinic acid esters see Ref. 10.

The equilibrium in this system is attained after 24hr in benzene solution at room temperature.
Since the optically active esters (1) and (2) have been obtained for the first time, it was necessary to establish their absolute configurations as well as their optical purity. In the case of esters (1) this problem was easily solved by converting them stereospecifically into known, chiral phosphine oxides. For example, the chirality at phosphorus in the ester (+)-(1a) follows from chemical correlation with the well known (-)-(S)-or (+)-(R)-methylethylphenylphosphine oxide (3) (Ref.11) shown in Scheme II.

Scheme II. Determination of Chirality at Phosphorus in (+)-O-Methyl Ethylphenylphosphinite (1a)

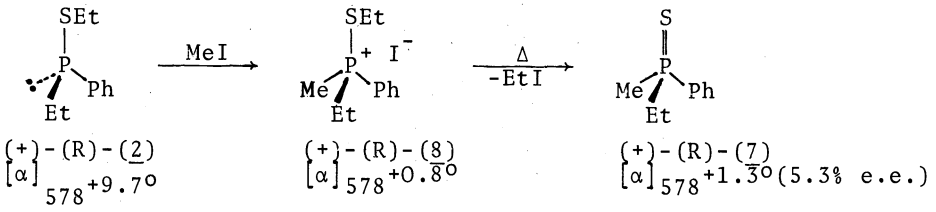


The first method, which links up the chirality at phosphorus in (+)-(1a) with (-)-(S)-(3), consists of three reactions: addition of sulphur to (+)-(1a), isomerisation of the phosphinothionate (+)-(4) into the corresponding phosphinothiolate (-)-(5) and reaction of (-)-(5) with methylmagnesium iodide. Since sulphur addition to trivalent phosphorus compounds proceeds with retention of configuration (Ref.12), and during the thiono-thiolo isomerisation (+)-(4)→(-)-(5) there is no bond breaking at phosphorus (Ref.13) and since reactions of Grignard reagents with phosphinothiolates occur with predominant inversion of configuration (Ref.14), the chirality at phosphorus in (+)-(1a) is assigned as (R). It is interesting to note that independent support of this conclusion comes from the Arbusov reaction of (+)-(1a) with methyl iodide affording directly the phosphine oxide (+)-(3) with the (R) configuration. The configuration at phosphorus in (+)-(1c) and (+)-(1d) was similarly assigned as (R) based on the results of the Arbusov reactions shown below.



The absolute configuration of (+)-(2) has been established chemically by its stereospecific conversion into optically active (+)-(R)-methylethylphenylphosphine sulphide (7) (Ref.16) as shown in Scheme III.

Scheme III. Determination of Chirality at Phosphorus in (+)-S-Ethyl Ethylphenylthiophosphinite (2)



(+)-(R)-(2) $[\alpha]_{578}$ +9.7°

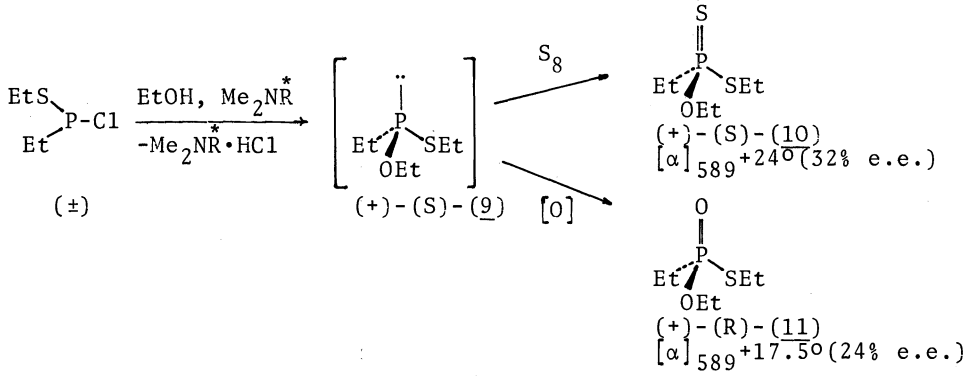
(+)-(R)-(8) $[\alpha]_{578}$ +0.8°

(+)-(R)-(7) $[\alpha]_{578}$ +1.3° (5.3% e.e.)

The thioester (+)-(2) was treated with an excess of methyl iodide under reflux to give the corresponding phosphonium salt (+)-(8), which was subsequently converted on heating into the phosphine sulphide (+)-(7) having the (R) chirality at phosphorus. Since methylation of (+)-(2) occurs with retention of configuration at phosphorus and in the second step the bonds around phosphorus are not broken, the chirality at phosphorus in (+)-(2) is assigned as (R).

From the chemical correlations shown above it is also possible to estimate the optical purity of the chiral esters (1) and (2). They are rather low (ca.10%). However, much higher extent of asymmetric induction (ca.30%) was observed during the condensation of (±)-S-ethyl ethylphosphonochloridite with ethanol in the presence of (-)-N,N-dimethyl-(1-phenylethyl)amine. The optically active ester (+)-(9) formed in this reaction was converted without isolation into well known esters (10) (Ref.17) and (11) (Ref.18) by treatment with sulphur and m-chloroperbenzoic acid, respectively. The synthesis and reactions of (+)-(9) are shown in Scheme IV which depicts also configurational relationships.

Scheme IV. Synthesis of and Determination of Chirality at Phosphorus in (+)-O-Ethyl-S-ethyl Ethylphosphonite (9)



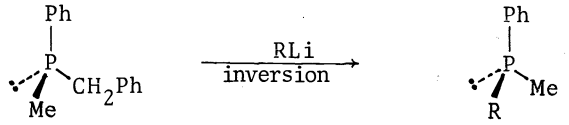
(+)-(S)-(10) $[\alpha]_{589}$ +24° (32% e.e.)

(+)-(R)-(11) $[\alpha]_{589}$ +17.5° (24% e.e.)

STEREOCHEMISTRY OF NUCLEOPHILIC SUBSTITUTION AT AN OPTICALLY ACTIVE TRIVALENT PHOSPHORUS ATOM

In contrast to the widely investigated stereochemistry of nucleophilic substitution at optically active tetracoordinate phosphorus (Ref.19), similar studies with optically active trivalent phosphorus systems are only in the initial stage. One of the most important questions is whether nucleophilic displacement reactions at the optically active P^{III} centre occur synchronously according to a S_N2-P^{III} mechanism or by an addition-elimination (A-E) mechanism involving tetracoordinate phosphorane intermediate. The second closely related problem concerns the relationship between the structure of a transition state or intermediate and the steric course of nucleophilic substitution at trivalent phosphorus.

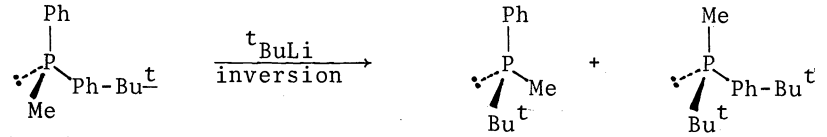
Studies on the stereochemistry of nucleophilic substitution at the chiral P^{III} centre have been initiated by Kyba (Ref.20) who found that replacement of the benzyl group by n-butyl and t-butyl in (+)-(R)-methylbenzylphenylphosphine occurs with complete inversion of configuration at phosphorus.



(+)-(R) (+)-(S)

R=Bu^{n}, Bu^{t}

(E.P.Kyba, 1975)

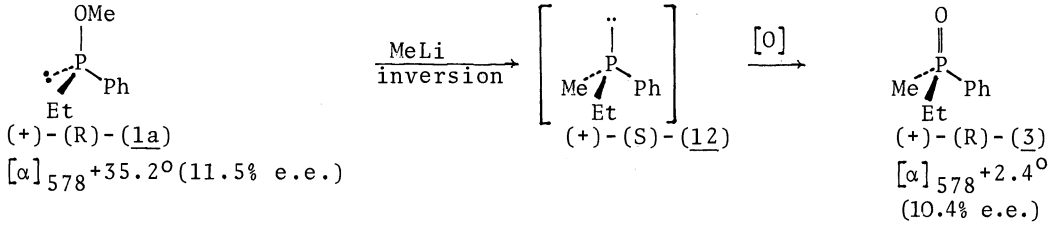


(+)-(S) (S) (R)

(E.P.Kyba, 1976)

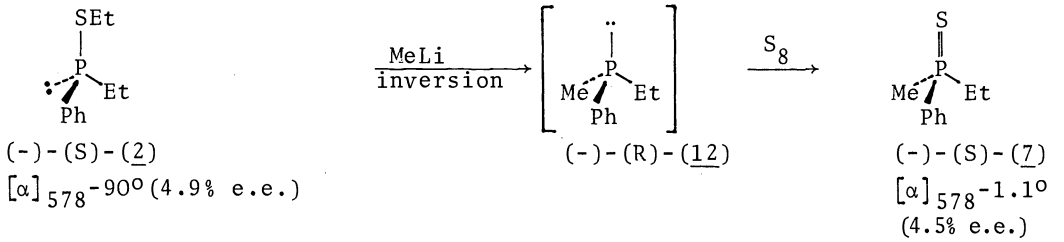
In further work (Ref.21) Kyba demonstrated that the treatment of (+)-(S)-methylpheny1-4-t-butylphenylphosphine with t-butyllithium resulted in displa - cement of phenyl and 4-t-butylphenyl anions in comparable amounts with complete inversion of configiration at phosphorus with both leaving groups. This result was considered as an evidence against pseudorotation in the potential valence-expanded anionic intermediate and led Kyba to the conclusion that nucleophilic substitution at phosphorus in chiral tertiary phosphines is a classical S_N2 process which can not proceed through an intermediate.
Our successful asymmetric synthesis of the optically active trivalent phosphorus acid esters (1) and thioester (2) and their relative optical stability enabled us to extend the studies on nucleophilic substitution at the trivalent phosphorus atom to other leaving groups and nucleophiles. Thus, the ester (+)-(R)-(1a) was treated with methyllithium to give the optically active methylethylphenylphosphine (12). Its optical purity was estimated and its absolute configuration established by the conversion into the optically active phosphine oxide (+)-(R)-(3). Similarly, the thioester (-)-(S)-(2) gave on treatment with methyllithium the optically active phosphine (12) which was transformed into the optically active phosphine sulphide (-)-(S)-(7). In both cases the replacement of the methoxy or ethylthio group by methyllithium occurs with inversion of configuration at the chiral trivalent phosphorus atom and with high stereospecificity. We have also demonstrated that the transesterification of (-)-(S)-(2) with sodium methoxide in methanol under very mild conditions (-65°C, 3 min) resulted in the formation of optically active ester (1a) with predominant inversion of configuration. All nucleophilic displacement reactions discussed above are summarized in Scheme V.

Scheme V. Nucleophilic Displacement Reactions at Trivalent Phosphorus in Esters (1) and (2)



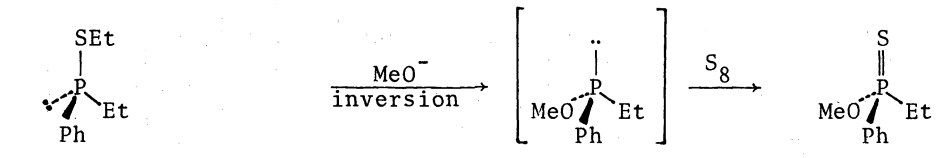
(+)-(R)-(1a) (+)-(S)-(12) (+)-(R)-(3)

$[\alpha]_{578}$ +35.2°(11.5% e.e.) $[\alpha]_{578}$ +2.4° (10.4% e.e.)



(-)-(S)-(2) (-)-(R)-(12) (-)-(S)-(7)

$[\alpha]_{578}$ -90°(4.9% e.e.) $[\alpha]_{578}$ -1.1° (4.5% e.e.)

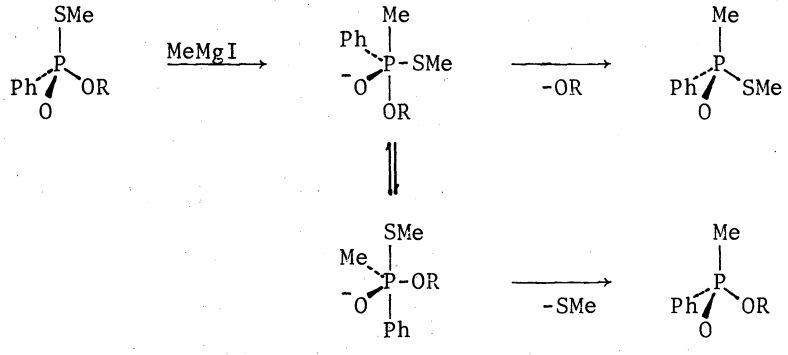


(-)-(S)-(2) $[\alpha]_{578}$ -7.2° (3.9% e.e.)

(+)-(R)-(1a)

(+)-(S)-(4) $[\alpha]_{578}$ +0.6°

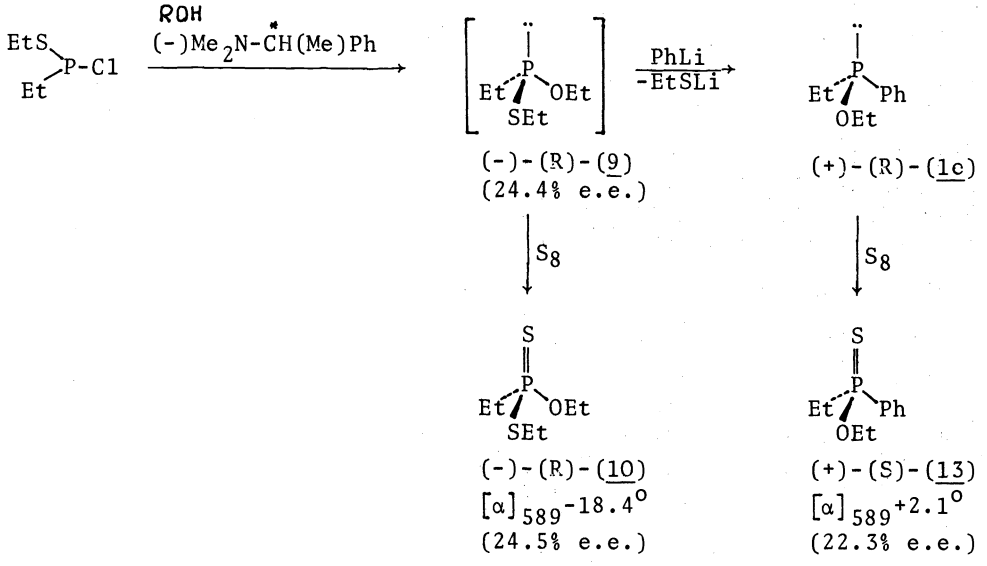
In continuation of our studies nucleophilic substitution at phosphorus in the optically active O-ethyl S-ethyl ethylphosphonite (9) was investigated. In this substrate two potential leaving groups are present which show different leaving group ability; the ethylthio group is expected to be a better leaving group than the ethoxy group.
However, before discussing our experiments it is interesting to describe briefly the results obtained by DeBruin and Johnson (Ref.22) concerning the stereochemistry of nucleophilic substitution at the chiral tetracoordinate phosphorus atom in the optically active O-alkyl S-methyl phenylphosphono - thiolates. They found that methylmagnesium iodode reacted with O-alkyl S-methyl phenylphosphonothiolates to displace either the methylthio group with retention of configuration at phosphorus or the alkoxy group with inversion and the competition was dependent on the nature of the alkoxy group. According to DeBruin this result can be rationalized by formation of a phosphorane intermediate in which the alkoxy group and the thioalkoxy group occupy apical and equatorial positions, respectively. Decomposition of this intermediate results in the formation of phosphinothiolate with inversion of configuration at phosphorus. This process is competitive with isomerisation to a new phosphorane intermediate, which decomposes to form phosphinate with retention of configuration.



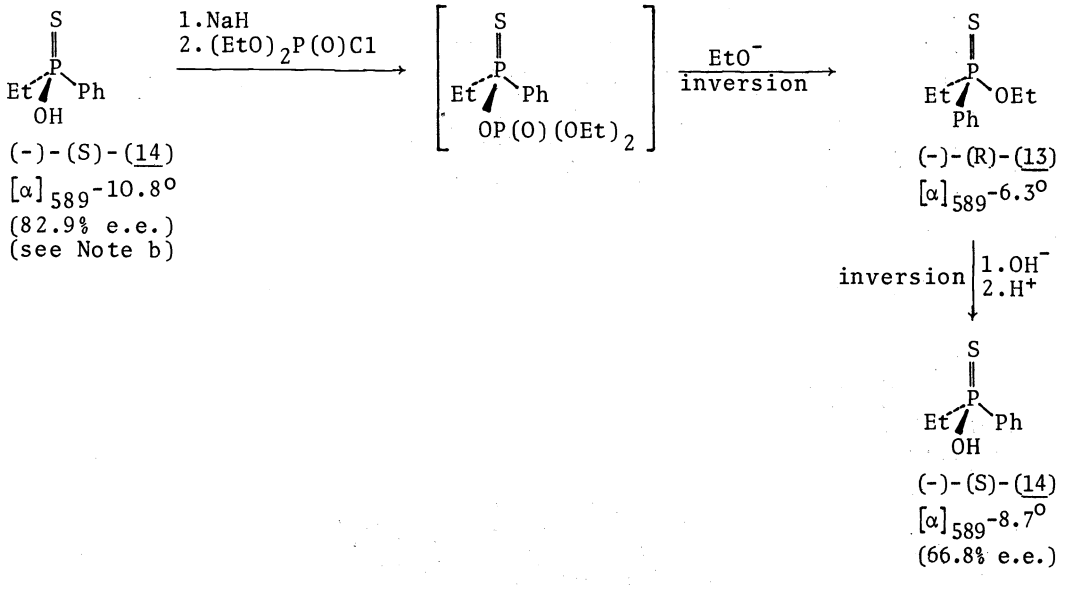
(K.E.DeBruin, 1975)

It is interesting to note that in O-alkyl S-methyl phenylphosphonothiolates, which are similar in some respects to (9), displacement of the alkoxy group occurs more readily than that of the methylthio group and that the methylthio group is displaced with retention of configuration at phosphorus.
We found that the reaction of the optically active thioester (-)-(R)-(9) with phenyllithium in ether at -50° followed by treatment of the reaction mixture with elemental sulphur gave (+)-O-ethyl ethylphenylphosphinothionate (13). According to ^{31}P NMR spectra no S-ethyl ethylphenylphosphinodithioate was observed demonstrating that in the reaction of (9) with phenyllithium the ethylthio group is selectively displaced. Furthermore, since the absolute configuration of (+)-(13) can be easily assigned as (S) based on the chemical correlation shown in Scheme VIII (Ref.23) and since the sulphur addition to trivalent phosphorus compounds occurs with retention of configuration at phosphorus, the absolute configuration of O-ethyl ethylphenylphosphinite (1c) formed in the reaction between (-)-(R)-(9) and phenyllithium should be (R). Thus, the replacement of the ethylthiogroup in (9) by phenyl occurs with almost complete inversion of configuration at phosphorus as shown in Scheme VI.

Scheme VI. Steric Course of the Reaction of O-Ethyl S-Ethyl Ethylphosphonite (9) with Phenyllithium

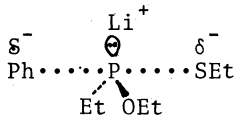


Scheme VII. Determination of Chirality at Phosphorus in O-Ethyl Ethylphenylphosphinothionate (13)

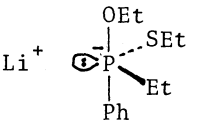


Our results, which are in sharp contrast with those obtained by DeBruin, can be best explained by assuming that nucleophilic substitution at phosphorus in (9) proceeds synchronously according to a classical S_N2 mechanism involving transition state (15) shown below

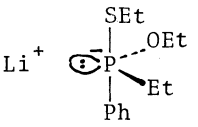
Note b. Optical purity of the optically active thioacid (14) was determined by NMR method via the diastereomeric salts with optically active α-naphtylethylamine (ref.24)



(15)



(16)

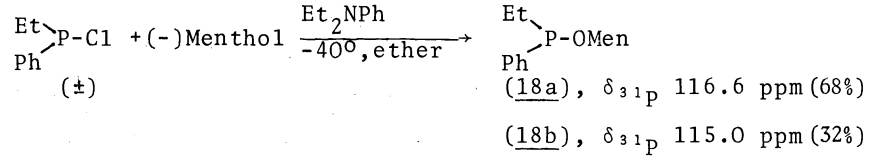


(17)

Formation of the valency-expanded anionic intermediates (16) and (17) in the reaction under consideration seems less likely. If (16) were the intermediate, the displacement of the ethylthio group by phenyl would be expected to take place with retention of configuration at phosphorus after one pseudorotation of (16) and decomposition. Moreover, displacement of the ethoxy group should also be observed. Although formation of intermediate (17) and its fast decomposition to the substitution product (1e) with inversion at phosphorus is an alternative explanation of the stereochemistry, all the data (Ref.25) on nucleophilic substitution at the tetracoordinate phosphorus atom bearing an alkoxy and thioalkoxy groups indicate the strong preference of the latter for an equatorial position in the transient phosphorane species. Therefore, it is reasonable to expect that formation of (17) will be less favourable than that of (16).

SYNTHESIS, CHIRALITY AT PHOSPHORUS AND REACTIONS OF O-MENTHYL ETHYLPHENYLPHOSPHINITES (18)

In the next part of this study our attention was directed toward the possible generation of optical activity at trivalent phosphorus by formation of diastereoisomeric esters with optically active alcohols. Since diastereoisomeric menthyl esters of methylphenylphosphinic acid (Ref.26) and p-toluenesulphinic acid (Ref.27) are important precursors to many optically active phosphorus and sulphur compounds we decided to investigate O-menthyl ethylphenylphosphinite (18) which should exist in two diastereoisomeric forms due to chiral centres at phosphorus and in the menthyl moiety.



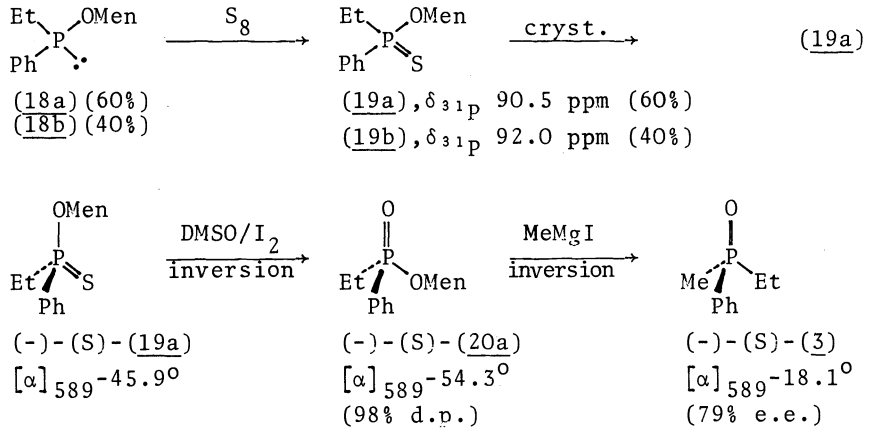
(±)

(18a), δ_{31P} 116.6 ppm (68%)

(18b), δ_{31P} 115.0 ppm (32%)

As expected, the low temperature condensation of racemic ethylphenylchlorophosphine with menthol in the presence of N,N-diethylaniline resulted in the formation of a mixture of the diastereoisomeric phosphinites (18a) and (18b) in a ratio 68:32. The ratio of diastereoisomers was found to be controlled by kinetic factors and strongly dependent on the nature of the tertiary amine used for condensation. It affects not only the diastereoisomeric purity of the ester (18) but also the chirality at phosphorus of the major diastereoisomer formed. For instance, the reaction in the presence of triethylamine produced a mixture of (18a) and (18b) in a ratio 29:71.
Since the ester (18) is a liquid, its separation into pure diastereoisomers was rather difficult. However, we were able to assign the absolute configurations to both diastereoisomers and to connect them with the ^{31}P NMR chemical shifts by chemical correlation as shown in Scheme VIII.
In the first step, a mixture of (18a) and (18b) was treated with sulphur to give with retention of configuration at phosphorus a mixture of the corresponding O-menthyl ethylphenylphosphinothionates (19). The pure diastereo - isomer (19a) obtained by fractional crystallisation was oxidised with dimethylsulphoxide in the presence of iodine to O-menthyl ethylphenylphosphinate (20a) with inversion of configuration at phosphorus (Ref.7 and 28).

Scheme VIII. Chemical Assignment of Chirality at Phosphorus in O-Menthyl Ethylphenylphosphinites (18)



Finally, the ester (20a) was reacted with methylmagnesium iodide to give the phosphine oxide (-)-(S)-(3). Since the last reaction is also accompanied by inversion at phosphorus it follows that the (S)- configuration should be assigned to (-)-(19a). Therefore, the ester (18a) and (18b) have the configurations (R) and (S), respectively (see Note c).

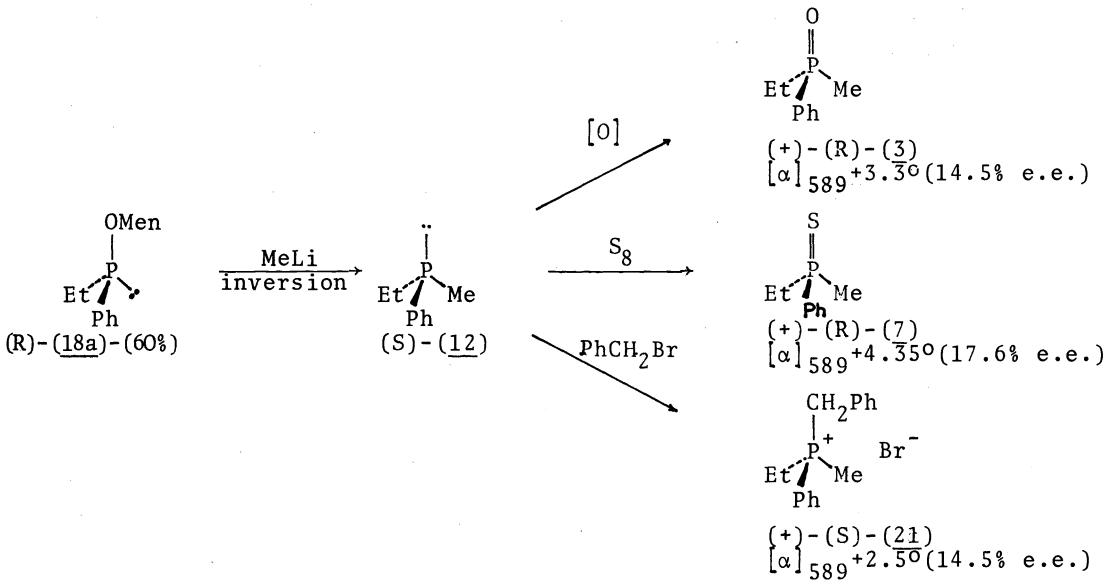
(R)-(18a) δ_{31P} 116.6 ppm

(S)-(18b) δ_{31P} 115.0 ppm

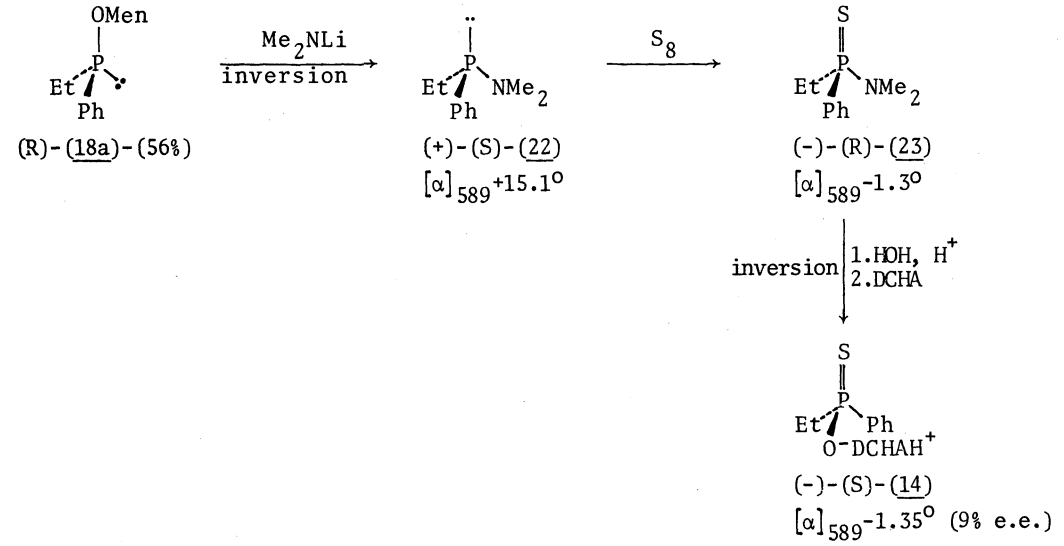
In extension of our studies on the stereochemistry of nucleophilic substitution at chiral, trivalent phosphorus we examined the reaction of the diastereoisomeric menthyl esters (18) with methyllithium and dimethylaminolithium. Reaction of a 60:40 mixture of the esters (18a) and (18b) with methyllithium gave optically active methylethylphenylphosphine (12) which was converted into the corresponding phosphine oxide (+)-(R)-(3), phosphine sulphide (+)-(R)-(7) and benzylphosphonium bromide (+)-(R)-(21). Since the optical properties and absolute configurations of (3), (7) and (21) (Ref.29) are known and since the oxidation, sulphurisation and quaternisation of the phosphine (3) occur with retention of configuration, it was demonstrated that the replacement of the menthoxy group by methyl occurs with inversion of configuration and with almost complete stereospecificity. All the reactions discussed above are shown in Scheme IX. Similarly, the reaction of a mixture of (18a) and (18b) [56:44] with dimethylaminolithium was also found to take place with inversion of configuration. It afforded the optically active (+)-N,N-dimethyl ethylphenylphosphinoamidite (22) configuration of which was established chemically as shown in Scheme X. In this context it is interesting to note that the acid-catalysed hydrolysis of the optically active N,N-dimethyl ethylphenylphosphinoamidothionate (23) occurs with inversion of configuration at the thiophosphoryl centre.

Note c. The same conclusion can be drawn from the analysis of the ^{1}H-NMR spectra of (19a) and (19b) (Ref.7).

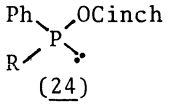
Scheme IX. Steric Course of the Reaction of O-Menthyl Ethylphenylphosphinites (18) with Methyllithium



Scheme X. Steric Course of the Reaction of O-Menthyl Ethylphenylphosphinites (18) with Dimethylaminolithium



The results presented above clearly show that the optical purity of the phosphine (3) and amide (22) is only dependent on the diastereoisomeric purity of the menthyl esters (18). Recently, Chodkiewicz, Jore and Wodzki (Ref.30) applying the same approach obtained optically active tertiary phosphines with the optical purity values from 18 to 80% via diastereoisomeric cinchonine phosphinites (24)

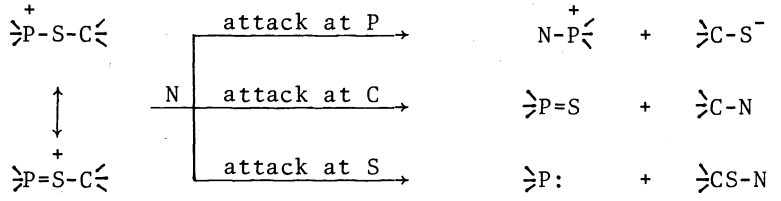


(24)

R=Me, Ph, o-MePh, α-Np
Cinch=Cinchonine

STEREOSPECIFIC SYNTHESIS OF OPTICALLY ACTIVE PHOSPHINITES

Athough optically active trivalent phosphorus acid esters and thioesters may be easily obtained by the asymmetric syntheses described above a major limitation of this approach consists in the low optical purity at phosphorus of these esters. Therefore, we decided to look for a stereospecific method for their preparation. Our attention was directed toward alkylthio- and alkylseleno-phosphonium salts as a possible precursors of trivalent phosphorus compounds.
Generally, phosphonium salts bearing the alkylthio group might react with a nucleophile via the three pathways shown schematically below.



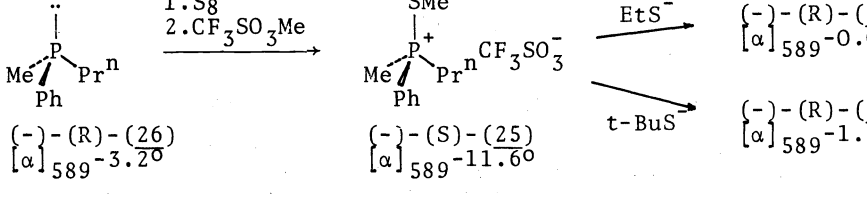
In contrast to the well-known nucleophilic attack at phosphorus (Ref.32) attack at sulphur leading to trivalent phosphorus compounds has not been, to our knowledge, clearly demonstrated (Ref.33) and has received no attention. Preliminary experiments with simple methylthiotriphenylphosphonium triflate and ethylmercaptide anion as a highly "thiophilic" nucleophile revealed that triphenylphosphine is formed in this reaction as the sole phosphorus containing product together with a mixture of disulphides (eq.1). Formation of three possible disulphides strongly suggests that the initial reaction stage involves a fast exchange of the alkylthio groups at phosphorus leading to dynamic equilibrium (eq.2) and then nucleophilic attack of ethylmercaptide and methylmercaptide anions on sulphur in both phosphonium cations results in the formation of triphenylphosphine and a mixture of disulphides.

$$Ph_3\overset{+}{P}SMe\ CF_3SO_3^- \xrightarrow[Et_2O\text{-}CH_2Cl_2]{EtSNa} Ph_3P + (MeS)_2 + (EtS)_2 + MeS_2Et \quad \text{(eq.1)}$$

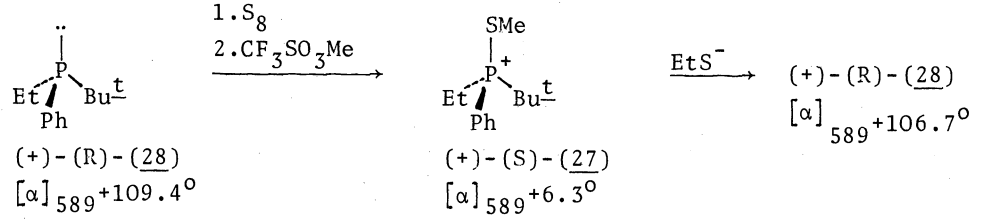
$$Ph_3\overset{+}{P}SMe + EtS^- \rightleftharpoons Ph_3\overset{+}{P}SEt + MeS^- \quad \text{(eq.2)}$$

Such a mechanistic picture is supported by the fact that treatment of (-)-(S)-methylthio-methyl-n-propylphenylphosphonium triflate (25) with sodium ethylmercaptide at -75° in ether-methylene chloride solution gave almost racemic phosphine (26) (see Scheme XI). Racemisation must be a consequence of a fast alkylthio-alkylthio exchange at chiral phosphorus in (25) occuring with inversion of configuration.
However, if our mechanistic proposals concerning the reaction of alkylthio-phosphonium salts with alkylmercapto anions are correct, one would expect that a stereospecific synthesis of phosphines or other trivalent phosphorus compounds would be possible provided that nucleophilic attack at phosphorus could be avoided. In order to accomplish this we conducted the reaction of (-)-(S)-(25) with t-butylmercapto anion and found that it gave the optically active phosphine (26) with 59% of the initial optical activity. This experiment clearly demostrated that nucleophilic attack at the tetrahedral phosphorus atom in (25) by t-butylmercaptide anion is sterically hindered and that the more easily accessible sulphur atom is preferentially attacked. As a consequence chiral phosphine (26), becomes the leaving group and is formed from (25) with retention of configuration at phosphorus. The experiments discussed above are summarised in Scheme XI.

Scheme XI. Synthesis and Reaction of Optically Active Methylthio-methyl-n-propylphenylphosphonium Triflate (25) with Alkylmercaptide Anions

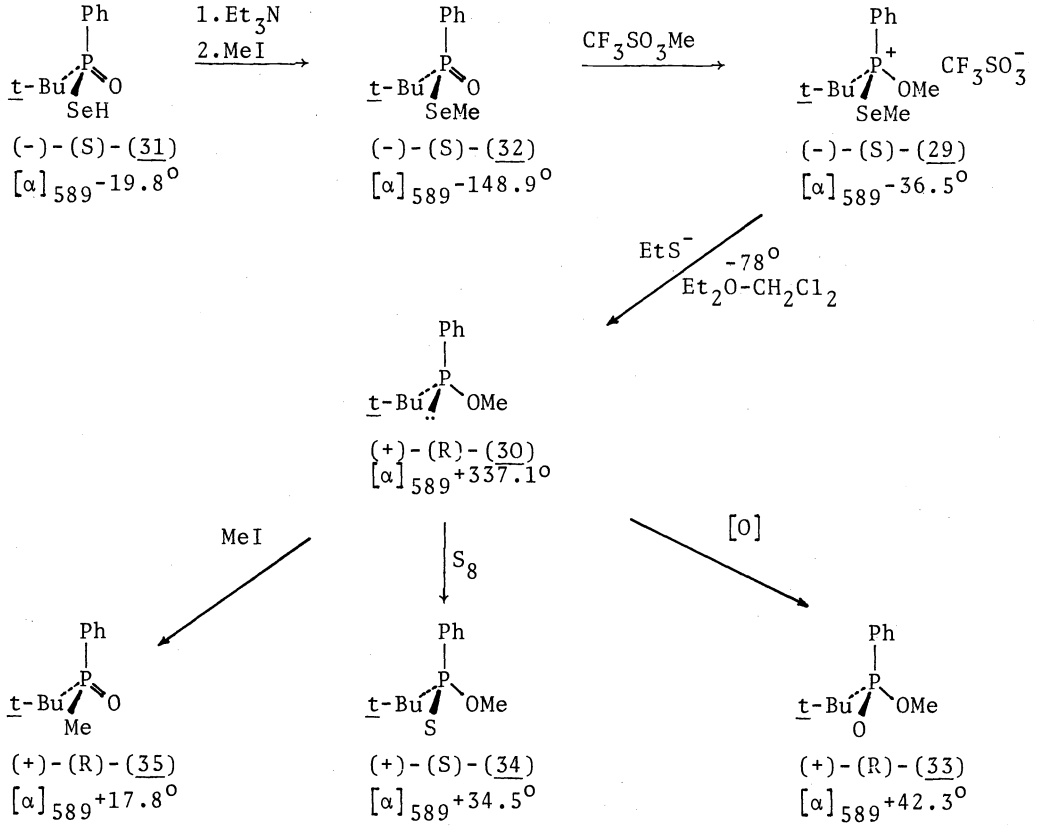


Scheme XII. Synthesis and Reaction of Optically Active Methylthioethyl-t-butylphenylphosphonium Triflate (27) with Sodium Ethylmercaptide



Since the t-butyl group directly attached to phosphorus strongly decreases the rate of nucleophilic substitution at phosphorus (Ref.34), we prepared (+)-(S)-methylthio-ethyl-t-butylphenylphosphonium triflate (27) from the corresponding phosphine (28). As expected, the reaction of the triflate (27) with sodium ethylmercaptide resulted in the formation of phosphine (28) with almost full optical activity and retained configuration (see Scheme XII). After establishing the relationship between the structure of alkylthio-phosphonium salts and optical purity of the resulting chiral phosphines we could procede to the stereospecific synthesis of optically active phosphinites. Thus, O-methyl-Se-methyl-t-butylphenylphosphonium triflate (29) was chosen as a starting meterial for optically active O-methyl t-butylphenylphosphinite (30).

Scheme XIII. Stereospecific Synthesis of Optically Active O-Methyl t-Butylphenylphosphinite (30)



In this case the undesired nucleophilic attack at phosphorus by mercaptide anion should be prevented by the bulky t-butyl group directly attached to it. The triflate (29) was prepared from the known (-)-(S)-t-butylphenylphosphinoselenoic acid (31) (Ref.35) as outlined in Scheme XIII and on treatment with sodium ethylmercaptide it gave the optically active phosphinite (30). The latter was in turn coverted into the corresponding chiral derivatives (33), (34) and (35) in order to estimate its optical purity. If one assumes

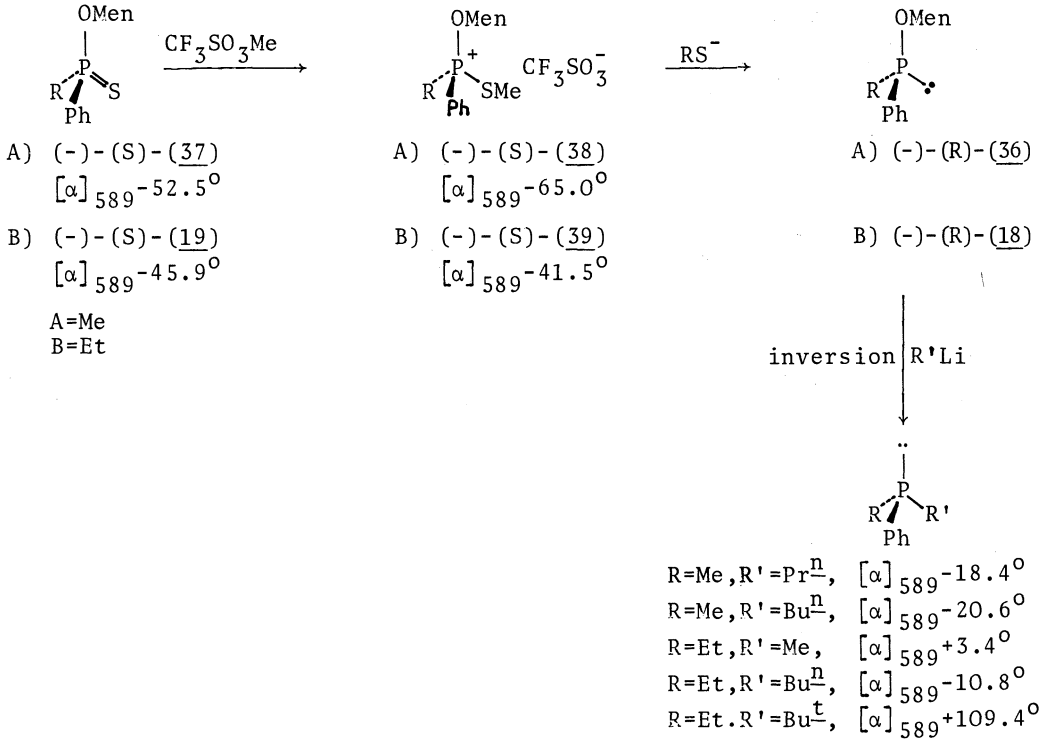
that the Arbusov reaction of (30) with methyl iodide is fully stereospecific it follows that the optical purity of the product should be 85%. The synthesis of opticaly active phosphinite (30) represents the first stereospecific synthesis of chiral trivalent phosphorus ester and opens new possibilities for a stereochemical studies (see Note d).

Our approach to stereospecific synthesis of chiral trivalent phosphorus acid esters is further illustrated by the stereospecific synthesis of the diastereoisomerically pure O-menthyl methylphenylphosphinite (36) and O-menthyl ethylphenylphosphinite (18).

The ester (-)-(R)-(36) was prepared in the following way. Diastereoisomerically pure (-)-(S)-O-menthyl methylphenylphosphinothionate (37) (Ref.37) was treated with methyl triflate to give the corresponding phosphonium salts (38) which on treatment with lithium t-butylmercaptide gave the diastereoisomerically pure (-)-(S)-(36). Similarly, the diastereoisomerically pure (-)-(R)-(18) was prepared from (-)-(S)-O-menthyl ethylphenylphosphinothionate (19) via (-)-(S)-O-menthyl-S-methyl ethylphenylphosphonium triflate (39). In this context, it is interesting to note that the sterically bulky menthoxy group functions effectively to retard nucleophilic attack at phosphorus and directing it toward sulphur.

Both O-menthyl phosphinites (36) and (18) were used as starting materials for synthesis of chiral phosphines of high optical purity (see Scheme XIV).

Scheme XIV. Stereospecific Synthesis of Diastereoisomerically Pure O-Menthyl Methylphenylphosphinite (18) and Chiral Tertiary Phosphines



Further studies on stereospecific synthesis of other classes of chiral trivalent phosphorus acid derivatives are underway in our laboratory.

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Note d. Very recently Horner and Jordan (Ref.36) prepared optically active O-p-cresyl ethylphenylphosphinite by the reaction of p-cresyl trifluoroacetate with optically active N,N-diethyl ethylphenylphosphinoamidite.

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