Stereospecific Synthesis of Diastereoisomerically Pure (−)-(R_p)-*O*-Menthyl Methylphenylphosphinite and Ethylphenylphosphinite: Key Intermediates in Synthesis of Chiral Tertiary Phosphines

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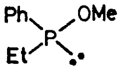
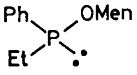
Summary The reaction of the diastereoisomerically pure (−)-(R_P)-O-menthyl methylphenylphosphinite (**9**) and (−)-(R_P)-*O*-menthyl ethylphenylphosphinite (**2**) with organolithium reagents has been found to give chiral tertiary phosphines (**10**) and (**11**) with a very high optical purity.

The importance of chiral tertiary phosphines in stereochemical studies and especially their successful use in the homogeneous catalysis of asymmetric synthesis has prompted us to search for new methods of resolution and synthesis of chiral phosphines.[1] Recently we reported[2,3] a new synthetic approach to chiral tertiary phosphines based on the stereospecific reaction of optically active phosphinites with organolithium reagents. However, this method was limited by the low optical purity at phosphorus of the starting chiral *O*-methyl ethylphenylphosphinite (**1**) and the diastereoisomeric mixture of *O*-menthyl ethylphenylphosphinites (**2**). Using this method, Chodkiewicz *et al.*[4] obtained chiral tertiary phosphines with higher optical purities (18—80%) *via* diastereoisomeric cinchonine phosphinites (**3**). We also developed a new and general approach to chiral tervalent phosphorus esters, exemplified by the stereospecific synthesis of *O*-methyl t-butylphenylphosphinite (**4**).[5] We report here the stereospecific synthesis of the diastereoisomerically pure *O*-menthyl methylphenylphosphinite (**9**) and *O*-menthyl ethylphenylphosphinite (**2**) and their conversion into chiral tertiary phosphines of very high optical purity.


(1)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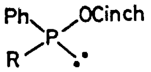
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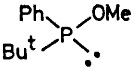
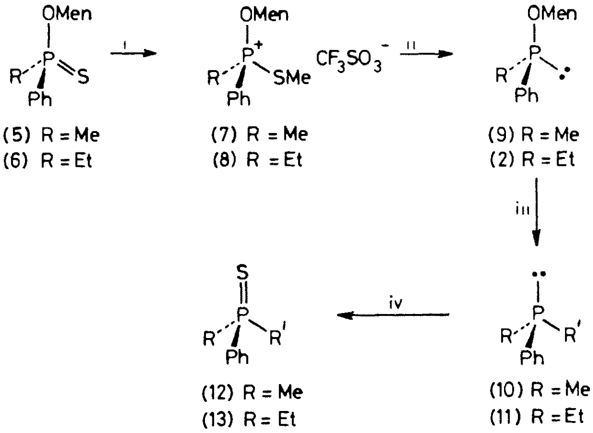

(4)

Men = (−)-menthyl; Cinch = cinchonine, R = Me, Ph, *o*-MeC_6H_4, or α-naphthyl.

Compound (−)-(R_P)-(**9**) was prepared as outlined in the Scheme. Diastereoisomerically pure (−)-(S_P)-*O*-menthyl methylphenylphosphinothionate (**5**)[6] [m.p. 88—91 °C, $\delta(^{31}P)$ 85·9 p.p.m.] reacted with methyl trifluoromethanesulphonate at room temperature in CH_2Cl_2 solution to give, after removal of the solvent, (−)-(*S*)-menthyloxy(methylthio)methyl(phenyl)phosphonium trifluoromethanesulphonate (**7**) [$\delta(^{31}P)$ 88·9 p.p.m.] in quantitative yield. This phosphonium salt, on treatment with t-butyl-lithium mercaptide at −70 °C in Et_2O–CH_2Cl_2 solution afforded one, laevorotatory diastereoisomer of *O*-menthyl methylphenylphosphinite (**9**) [$\delta(^{31}P)$ 109·8 p.p.m.].† Since the latter reaction involves nucleophilic attack of the Bu^tS^- anion on the sulphur atom of (−)-(S_P)-(**7**), the phosphinite (**9**) was formed with retention of configuration at phosphorus and, was accordingly assigned the *R* configuration.

Similarly, the diastereoisomerically pure (−)-(R_P)-*O*-menthyl ethylphenylphosphinite (**2**) [$\delta(^{31}P)$ 116·6 p.p.m.] was prepared from (−)-(S_P)-*O*-menthyl ethylphenylphosphinothioate (**6**)[3] [m.p. 108—110 °C, $\delta(^{31}P)$ 90·5 p.p.m.] *via* (−)-(S_P)-menthyloxy(methylthio)ethylphenylphosphonium trifluoromethanesulphonate (**8**) [$\delta(^{31}P)$ 95·2 p.p.m.] (Scheme)



Scheme. Reagents, i, CF_3SO_3Me; ii, Bu^tSLi or EtSNa; iii, R′Li; iv, S_8. Men = (−)-menthyl.

Since both esters (**9**) and (**2**) are prone to oxidation, they could not be isolated in the pure state.‡ However, the ethereal solutions of the crude phosphinites (**9**) and (**2**) were found to be suitable for the synthesis of chiral phosphines. Thus, (−)-(R_P)-(**9**) in Et_2O was added to a solution of an alkyl-lithium in Et_2O at −50 °C. The mixture was then refluxed for 0·5—1 h and left overnight at room temperature. After the usual work-up, methylalkylphenylphosphines (**10**) were separated from menthol by column chromatography on silica gel using hexane as eluant. Ethylalkylphenylphosphines (**11**) were similarly obtained from (−)-(*R*)-(**2**).

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† The S_P isomer of (**9**) absorbs in the ^{31}P n.m.r. spectrum at δ 107·0 p.p.m.

‡ For this reason we could not estimate the specific optical rotation for (−)-(R_P)-(**9**) and (−)-(R_P)-(**2**).

TABLE

Compound	Configuration	$[\alpha]_{589}$/°(Solvent)	R′
(5)	(−)-(S_P)	−52 5 (MeOH)	—
(6)	(−)-(S_P)	−45 9 (PhH)[a]	—
(7)	(−) (S_P)	−65 0 (CH_2Cl_2)	—
(8)	(−)-(S_P)	−41 5 (CH_2Cl_2)	—
(9)	(−)-(R_P)	—	—
(2)	(−)-(R_P)	—	—
(10a)	(−)-(*R*)	−18 4 (MePh)	Pr^n
(10b)	(−)-(*R*)	−20 6 (MePh)	Bu^n
(11a)	(+) (*S*)	+3 4 (MePh)	Me
(11b)	(−)-(*R*)	−10 8 (PhH)	Bu^n
(11c)	(+) (*R*)	+109 4 (neat)	Bu^t
(12a)	(−)-(*S*)	−20 6 (MeOH)	Pr^n
(12b)	(−)-(*S*)	−22 1 (MeOH)	Bu^n
(13a)	(+)-(*R*)	−22 3 (MeOH)	Me
(13b)	(+)-(*S*)	+0 94 (MeOH)	Bu^n
(13c)	(+)-(*S*)	+6 3 (MeOH)	Bu^t

[a] In ref 3 (Scheme 2) the value of the optical rotation for (−)-(S_P)-(**6**) was erroneously given as $[\alpha]_D$ −49 5°

The yields of the phosphines (**10**) and (**11**) were in the range 30—70% with respect to the starting phosphinothioates (**5**) and (**6**) No attempt has been made yet to improve the yields Optical rotations and absolute configurations of the chiral phosphines (**10**) and (**11**) as well as of the corresponding sulphides (**12**) and (**13**) are summarised in the Table

The reactions of the phosphinites (−)-(**9**) and (−)-(**2**) with alkyl-lithium reagents occur with inversion of configuration at phosphorus and with a high stereospecificity. For instance, (−)-(*R*)-methyl-n-propylphenylphosphine (**10a**) has been obtained from (−)-(R_P)-(**9**) with 94% optical purity§ and (+)-(*S*)-methylethylphenylphosphine (**11a**) prepared from (−)-(R_P)-(**2**) was at least 91% optically pure ¶ It is believed that other phosphines (**10**) and (**11**), which have been synthesised for the first time by our method, exhibit the same degree of optical purity The n m r experiments to confirm this view are underway in our laboratory

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§ The optical purity of (−)-(**10a**) was calculated on the basis of data in ref 7

¶ The optical purity of (+) (**11a**) was calculated on the basis of the data for the phosphine sulphide (+)-(**13a**) in ref 8 assuming that the sulphur addition is fully stereospecific

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