

PREPARATION OF OPTICALLY ACTIVE 1,3,2-OXATHIAPHOSPHORINANES USING
 (-)-10-MERCAPTOISOBORNEOL AS A CHIRAL SOURCE[†]

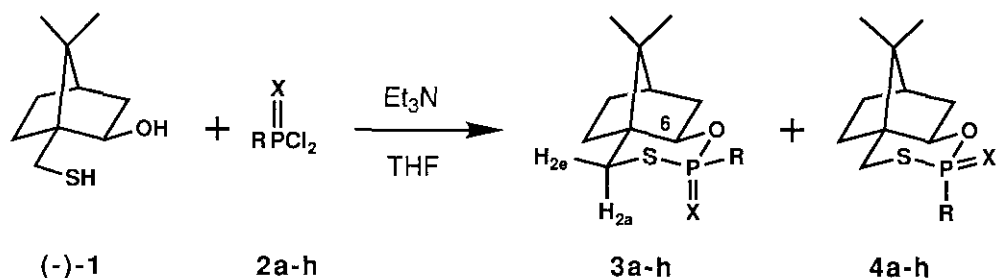
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Abstract—Optically active 1,3,2-oxathiaphosphorinanes (3) and (4) were prepared from (-)-10-mercaptoisoborneol (1) and phosphorus dichlorides [RP(X)Cl₂] (2). The configuration at phosphorus in these derivatives was assigned on the basis of their ¹H nmr spectral data and X-ray diffraction analysis of 4f.

For the preparation of chiral phosphorus compounds, simple and practical methods have so far been established using optically active amines, such as (-)-ephedrine,¹ L-proline ethyl ester,² and L-prolinol,³ as chiral sources. The diastereomeric phosphorus amides [N-P(X)<], thus obtained from these amines, were separated and subjected to stereoselective P-N bond fission to give simple chiral phosphorus esters. However, there has been little information available concerning the use of other chiral sources, such as diols and hydroxy-thiols, for the practical synthesis. For hydroxy-thiols, there has been only one report with D-glucopyranoside derivatives giving 1,3,2-oxathiaphosphorinanes.⁴ The method requires four steps to get the starting chiral thiols from methyl 2,3-di-O-methyl-α-D-glucopyranoside and does not seem to be a practical method to obtain optically active phosphorus compounds in general. Recently, Modena *et al.*⁵ and we⁶ have indicated that (-)-10-mercaptoisoborneol (1) is a valuable chiral source for the preparation of optically active sulfoxides. The hydroxy-thiol (1) is obtained quite easily in two steps from commercially available (+)-10-camphorsulfonic acid. We thus planned to prove that 1 is useful for obtaining chiral phosphorus compounds. In the present studies, we found that the reaction of 1 with phosphorus dichlorides [RP(X)Cl₂] (2) gave 1,3,2-oxathiaphosphorinanes as a mixture of diastereomers in fair yield and that the optically active oxathiaphosphorinanes (3) and (4) were separated readily by column and/or thin layer chromatography (silica gel). In addition, we determined the absolute configuration at phosphorus of 3 and 4.

A mixture of (-)-10-mercaptoisoborneol (1) and phosphorus dichlorides [RP(X)Cl₂] (2) (1 equivalent) was stirred in anhydrous tetrahydrofuran (THF) in the presence of triethylamine (2 equivalents) (Scheme 1). The diastereomeric 1,3,2-oxathiaphosphorinanes (3) and (4) were obtained and separated readily.⁷ Yield, melting

[†] This paper is dedicated to the memory of the late Professor Tetsuji Kametani.



Scheme 1

Table 1. Yield, mp, and optical rotations of 1,3,2-oxathiaphosphorinanes (3) and (4)

Compound	R	X	Yield(%)	mp (°C)	$[\alpha]_D$ deg.
<u>3a</u>	Ph	O	21	135-136	+98.0
<u>4a</u>	Ph	O	29	160-161	-40.9
<u>3b</u>	PhO	O	27	130-131	-205.7
<u>4b</u>	PhO	O	24	81-82	+152.7
<u>3c</u>	PhCH ₂	O	17	192-193	+104.8
<u>4c</u>	PhCH ₂	O	15	163-164	-26.3
<u>3d</u>	CH ₂ =CHCH ₂	O	24	syrup	+67.4
<u>4d</u>	CH ₂ =CHCH ₂	O	15	76-78	-1.6
<u>3e</u>	CH ₂ =C=CH	O	22	69-70	+113.6
<u>4e</u>	CH ₂ =C=CH	O	13	97-99	-106.5
<u>3f</u>	EtOC(O)CH ₂	O	17	syrup	+54.6
<u>4f</u>	EtOC(O)CH ₂	O	13	91-92	-8.2
<u>3g</u>	PhSCH ₂	O	49	80-81	+80.5
<u>4g</u>	PhSCH ₂	O	12	94-97	-8.9
<u>3h</u>	Ph	S	29	syrup	+50.2
<u>4h</u>	Ph	S	20	133-135	-45.8

points, and optical rotations of 3 and 4 are shown in Table 1. Ir, ¹H nmr, and ³¹P nmr spectral data are summarized in Table 2. The configuration at phosphorus was assigned from the chemical shifts of H-6 signals in the ¹H nmr spectra. H-6 signal of 3 appeared at lower field than that of 4. In other words, the P=X (X=O, S) group must be oriented *cis* to H-6 in 3.¹ This assignment was confirmed by a single-crystal X-ray diffraction study of 4f (Figure 1).⁸ The configurational assignment to the 2-sulfides (3h) and (4h) was evidenced by chemical correlations with the corresponding 1,3,2-oxathiaphosphorinane 2-oxides; oxidation with *m*-chloroperbenzoic acid converted 3h and 4h into 3a and 4a, respectively, under the conditions known to give configurationally retained products.⁹

Table 2. Ir, ^1H nmr, and ^{31}P nmr spectral data of 1,3,2-oxathiaphosphorinanes (3) and (4)

Compound	Ir $\nu_{P=O}$ (cm^{-1})	^1H nmr ^c (δ)			Coupling constants (Hz)			^{31}P nmr ^{c,d} (δ)
		H _{2e}	H _{2a}	H ₆	P, H _{2e}	P, H _{2a}	P, H ₆	
<u>3a</u>	1235 ^a	2.74	2.88	4.72	22.2	8.1	8.4	-41.61
<u>4a</u>	1235 ^a	2.84	3.28	4.21	14.2	14.2	3.7	-41.47
<u>3b</u>	1270 ^a	2.88	3.21	4.71	23.7	6.4	0	-13.51
<u>4b</u>	1255 ^a	2.58	2.87	4.54	28.3	10.0	6.4	-24.04
<u>3c</u>	1220 ^a	2.40	2.26	4.50	23.0	5.7	8.9	-48.79
<u>4c</u>	1220 ^a	2.72	3.20	3.79	15.6	12.0	4.0	-52.27
<u>3d</u>	1240 ^b	2.60	2.88	4.51	23.6	5.5	8.7	-52.82
<u>4d</u>	1230 ^a	2.82	3.21	4.17	14.5	12.9	3.9	-48.51
<u>3e</u>	1260 ^b	2.64	2.86	4.54	25.4	7.8	8.6	-37.82
<u>4e</u>	1225 ^a	3.16	2.92	4.31	15.9	13.4	4.2	-34.07
<u>3f</u>	1245 ^b	2.65	3.00	4.53	26.1	6.4	8.8	-44.68
<u>4f</u>	1255 ^b	2.90	3.24	4.32	14.5	14.5	3.9	-39.21
<u>3g</u>	1240 ^a	2.64	3.15	4.52	24.4	5.4	8.8	-48.77
<u>4g</u>	1240 ^a	2.84	3.21	4.13	15.4	12.7	3.8	-45.34
<u>3h</u>	1260 ^b	2.92	2.96	4.76	14.2	0	8.8	33.03
<u>4h</u>	1260 ^a	3.11	2.95	4.15	17.0	11.0	3.2	37.02

a: KBr, b: neat, c: measured in CDCl_3 , d: from 85% H_3PO_4 (low field negative)

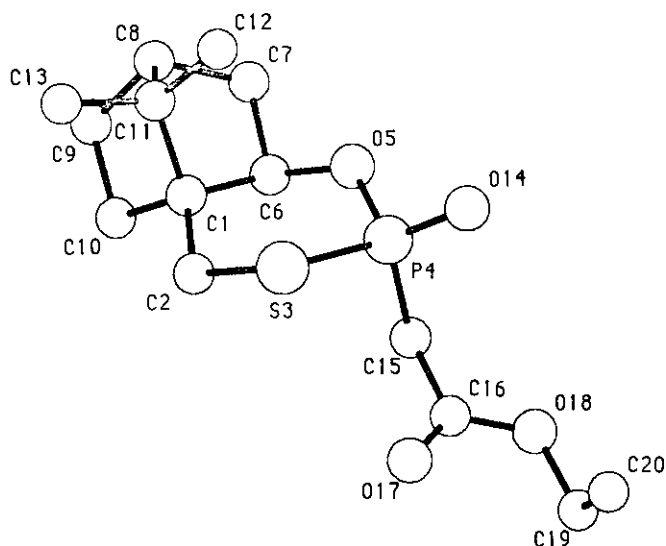
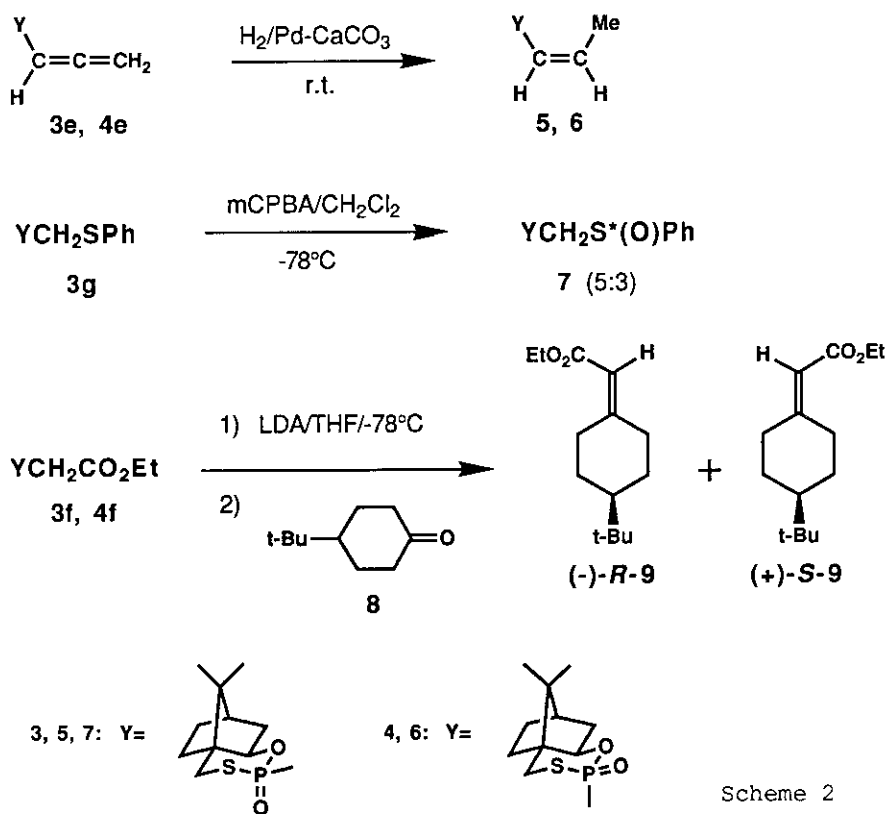


Figure 1. Perspective Structure of **4f**

The optically active oxathiaphosphorinanes thus obtained may be applied to the synthesis of other chiral compounds in two ways: (i) a transformation to simple chiral phosphorus compounds by the known P-O and P-S bond fission⁴ and (ii) an application to diastereoselective reactions¹⁰ without cleavage of the phosphorinane ring. We investigated along the latter line and obtained several results in the preliminary experiments (Scheme 2). Hydrogenation of the allene phosphonates (**3e**) and (**4e**)¹¹ proceeded stereoselectively in the presence of Lindlar catalyst to give *cis*-1-propene phosphonates (**5**) and (**6**), respectively.¹² *cis*-Olefins (**5**) and (**6**) would be desirable for a chiral synthesis of fosfomycin.¹³ Oxidation of the sulfinylmethane-phosphonate (**3g**) with *m*-chloroperbenzoic acid gave the sulfinylmethanephosphonate (**7**)¹⁴ as a mixture of diastereomers (5:3). Moreover, an attempt to apply the chiral phosphorinanes to an asymmetric Emmons-Horner reaction was performed with the anion of **3f** and 4-*tert*-butylcyclohexanone (**8**) in THF. A mixture of *R* and *S* olefins (**9**) was obtained in 59% yield corresponding to an optical purity of 16% e.e.¹⁵ in favor of the (-)-*R* isomer.¹⁶ The ratio was reversed with the diastereomer **4f**. We are currently studying the reactions with **3** and **4**.



Scheme 2

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