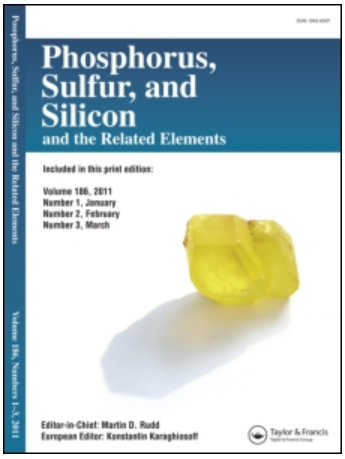

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SYNTHESIS OF OPTICALLY ACTIVE 4-OXO-1-PHENYL-2-PHOSPHOLENE-1-OXIDE AND THE DETERMINATION OF ITS CONFIGURATION

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SYNTHESIS OF OPTICALLY ACTIVE 4-OXO-1-PHENYL-2-PHOSPHOLENE-1-OXIDE AND THE DETERMINATION OF ITS CONFIGURATION

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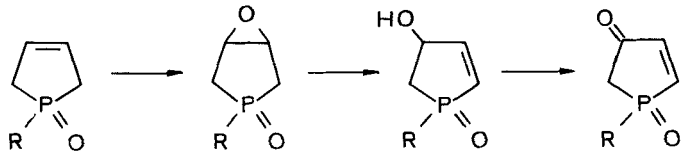
(+)-(1*S*,4*R*)-4-hydroxy-1-phenyl-2-phospholene-1-oxide (+)-(**4a**) was obtained by optical resolution of the corresponding ω-camphanates **5a** and converted into (+)-(S)-4-oxo-1-phenyl-2-phospholene-1-oxide (+)-(**1a**). The absolute stereochemistry of (+)-(**4a**) was determined by a single-crystal X-ray analysis.

INTRODUCTION

The commonly known utility of 2-cyclopenten-1-one as a versatile unit for the synthesis of a variety of carbocyclic compounds[1,2] stimulates considerable interest in the chemistry of five membered cyclic unsaturated ketones containing a heteroatom in the ring. These ketones constitute potential precursors of different mono- and polyheterocycles.[3–8] Among the organophosphorus analogues of 2-cyclopenten-1-one 4-oxo-2-phospholene-1-oxides (**1**) with a chiral tetracoordinate phosphorus are particularly attractive.[9,10] [4 + 2]Cycloaddition of **1** to conjugate dienes has been successfully used for highly regio and stereoselective syntheses of substituted tetrahydrophosphindoles and phosphasteroids.[10]

In an attempt to extend the applicability of **1** as chiral reagents we undertook investigations on the preparation and absolute stereochemistry of the enantiomeric 4-oxo-1-phenyl-2-phospholene-1-oxide (**1a**).

A simple route to **1** is represented by the reaction sequence consisting in: (i) epoxidation of 3-phospholenes **2** to the corresponding oxiranes **3**, (ii) isomerization of **3** affording allyl alcoholes **4**, (iii) oxidation of **4**.



2 3 4 1

	a	b	c
R	Ph	Me	OMe

SCHEME 1

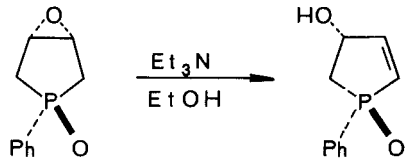
Although such an approach has been effectively employed in the preparation of the racemic **1a** no details concerning particular steps and intermediates in this synthesis have been reported.[10]

The strategy we chose to prepare the enantiomeric **1a** was based on the sequence **2a** → **3a** → **4a** → **1a** completed with an optical resolution of one of the diastereomeric **4a**. We anticipated that oxidation of the enantiomeric **4a** to the optically active **1a** would not affect the stereochemistry at phosphorus.

RESULTS AND DISCUSSION

1-Phenyl-3-phospholene-1-oxide (**2a**) was prepared according to the known procedure[11] comprising addition of phenyldibromophosphine to 1,3-butadiene and subsequent hydrolysis of the resulting adduct. The phospholene **2a** was converted into oxirane **3a** on treatment with *m*-chloroperbenzoic acid in refluxing chloroform. As it could be expected on the ground of stereochemistry of similar reactions, the epoxidation was completely stereoselective.[12,13] On the basis of ^{31}P-NMR spectra **3a** was identified as an individual diastereomer, however its ^{1}H-NMR spectra appeared to be sufficiently ambiguous to prohibit configurational assignments. The *trans*-stereochemistry of the epoxidation was eventually verified with confidence by dipol moment measurements. The experimentally found value of 2.8 D for **3a** corresponded satisfactorily to 2.97 D reported for the closely related *trans*-3,4-epoxy-3,4-dimethyl-1-phenylphospholane-1-oxide and was far removed from 5.8 D attributed to the *cis*-isomer of this compound.[12]

The isomerization of **3a** was accomplished in high yield in the presence of triethylamine in ethanol affording *trans*-allyl alcohol **4a** exclusively. The ^{1}H-NMR spectrum of **4a** (in $DCCl_3$) revealed $^{3}J_{H-H}$ and $^{2}J_{(O)P-H}$ for one of the methylene protons being 3.5 Hz and 8.5 Hz, respectively (Table I). In the light of known relations between coupling constants and the corresponding dihedral angles[14–16] these values argued predominance of an envelope conformation with pseudoequatorial disposition of phenyl and hydroxyl groups.



3a (±)-4a

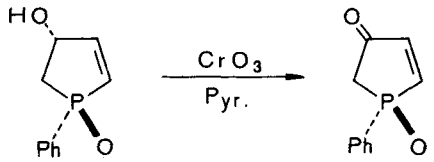
SCHEME 2

The preparation of the enantiomeric **4a** was performed conventionally by working with ω-camphanyl chloride as a resolving agent.[17] When the racemic **4a** was treated with this chloride under standard conditions, a 1:1 mixture of diastereomeric ω-camphanates **5a** was obtained in excellent yield. The ratio of diastereomers could be precisely evaluated on the basis of the ^{31}P-NMR spectrum (δ 55.5 ppm; δ 55.7 ppm). Fractional crystallization of the mixture from benzene/hexane (1:1) allowed to isolate the pure enantiomer (+)-**5a** (δ 55.7 ppm). The ^{1}H-NMR spectrum of this isomer was routinely consistent with its structural framework (Table I). Finally hy-

drolysis of (+)-**5a** under generally employed basic conditions provided the desired alcohol (+)-**4a** in high yield.

The crucial step of the discussed synthesis involving oxidation of the enantiomeric (+)-**4a** was satisfactorily realized using Collins reagent.[18]

The choice of this particular oxidant resulted from predicted preparative advantages as well as from the need to avoid strongly acidic conditions that usually promote facile racemization of optically active phosphine oxides.[19] The alcohol (+)-**4a** treated with chromium trioxide in pyridine gave rise to 4-hydroxy-1-phenyl-2-phospholene-1-oxide (+)-(**1a**) in moderate yield. ^{31}P-NMR and ^{1}H-NMR (Table I) spectra of (+)-**1a** were quite in line with the expected structure.



(+)-4a (+)-1a

SCHEME 3

Despite of prolonged exposure to the oxidizing reagent the ketone (+)-**1a** was not found to change its specific rotation. The observed configurational stability allowed to expect a high optical purity of this compound.

Being unable to assign the absolute configuration to any of the obtained optically active compounds by the appropriate chemical correlations we turned arbitrarily to single crystal X-ray analysis of (+)-**4a**.

The alcohol (+)-**4a** crystallized in orthorombic system, space group P 2_1 2_1 2_1 with unit cell parameters $a = 10.246$ (3); $b = 9.416$ (3); $c = 9.978$ (3) Å^3; $Z = 4.779$. Independent reflexions were collected on a Synthex P 2_1 diffractometer using CuK_α radiation. Of these 758 were classified as observable above background radiation levels [$F_o \geq 2\sigma(F_o)$]. The crystal structure was determined by direct methods and refined by standard Fourier procedure and full-matrix least squares technique to *the final agreement factors; conventional* $R = 0.041$ *and weighted* $R_w = 0.046$[20] (Tables II, III and IV).

The factors R and R_w decreased to 0.037 and 0.041 respectively after two additional cycles of refinement when the anomalous scattering components f' and f'' for phosphorus and oxygen were included.[21] The factors slightly increased to 0.042 and 0.046 respectively after refinement of the molecule positional parameters taken with opposite sign. The significance test on the R factors[22] showed that probability of error in determination of the absolute configuration was less than 0.5%.

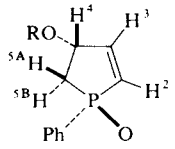
$$R_{1,596,0.005} = 1.007\left(\frac{R_1}{R_2} = 1.135;\ \frac{R_{w1}}{R_{w2}} = 1.122\right)$$

The obtained values were satisfactory explicit to prove $(S)_p$ and $(R)_c$ configurations of the respective chiral centers in the examined molecule (Figure 1).

Since phosphorus chirality of (+)-**4a** and (+)-**1a** was expected to be identical the established stereochemistry of (+)-**4a** allowed for unquestionable assignment of $(S)_p$ configuration to (+)-**1a**.

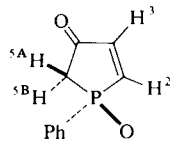
TABLE I

Spectral data for **1a**, **4a** and **5a**



4a R = H

5a R = -camphanyl



1a

Compd.	^{1}H-NMR[a,c]					^{31}P-NMR[b,c]
	H^2	H^3	H^4	H^{5A}	H^{5B}	
1a	7.54–7.81 (m) together with aromatic protons	7.05 (d d, $J_{H^2-H^3} = 8.0$, $J_{H^3-P} = 42.0$)		2.91 (d, $J_{H^{5A}-P} = 12.0$)	2.88 (d, $J_{H^{5B}-P} = 7.0$)	36.4
4a	6.22 (d d d, $J_{H^2-H^3} = 8.0$, $J_{H^2-H^4} = 1.0$, $J_{H^2-P} = 24.0$)	7.08 (dd d, $J_{H^2-H^3} = 8.0$, $J_{H^3-H^4} = 3.0$, $J_{H^3-P} = 45.0$)	5.18–5.21 (m)	2.54 (d d d, $J_{H^4-H^{5A}} = 8.0$, $J_{H^{5A}-H^{5B}} = 16.0$, $J_{H^{5A}-P} = 15.0$)	2.07 (d d d, $J_{H^4-H^{5B}} = 3.5$, $J_{H^{5A}-H^{5B}} = 16.0$, $J_{H^{5B}-P} = 8.5$)	59.1
5a	6.10–7.42 (m)		3.61–3.91 (m)	0.80–3.05 (m) together with camphanyl protons		55.5 55.7

[a] In $CDCl_3$ with Me_4Si used as an internal reference.
[b] In $CHCl_3$ with 85% H_3PO_4 as an external reference.
[c] J values are given in hertz, chemical shifts are given in ppm.

TABLE II

Coordinates ($\times 10^4$) and isotropic temperature factors for non-hydrogen atoms with e.s.d.'s in parentheses

	x	y	z	B_{iso}(Å^2)
P(1)	7872 (1)	2305 (1)	5685 (1)	3.5 (1)
O(1)	6838 (3)	1210 (3)	5833 (4)	4.6 (2)
O(2)	9632 (4)	4079 (6)	2682 (4)	6.7 (2)
C(2)	7332 (5)	4056 (6)	5271 (6)	4.8 (3)
C(3)	7741 (6)	4439 (6)	4087 (6)	5.7 (3)
C(4)	8540 (3)	3402 (7)	3280 (6)	5.2 (3)
C(5)	8885 (5)	2143 (7)	4197 (7)	5.0 (3)
C(11)	8835 (4)	2438 (5)	7183 (4)	3.1 (2)
C(12)	8451 (5)	1700 (5)	8327 (5)	3.8 (2)
C(13)	9149 (6)	1838 (6)	9501 (5)	5.2 (3)
C(14)	10226 (5)	2704 (6)	9560 (6)	4.8 (3)
C(15)	10607 (5)	3435 (6)	8441 (6)	4.7 (3)
C(16)	9937 (5)	3300 (5)	7251 (5)	4.1 (2)

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-NMR spectra were recorded with a Brucker HFX 72 at 90 MHz using 5–10% solutions with TMS as an internal standard.

^{31}P-NMR spectra were taken on a Brucker HFX 72 at 36.43 MHz with 85% H_3PO_4 as an external standard, utilizing broad band proton decoupling. Mass spectra were obtained on a LKB GCMS model 2091 with 70 eV ionization potential. Specific rotations were measured on a Perkin–Elmer Polarimeter 241 MC.

Dielectric Constans were measured on a Radelkis type OH-302. Calculations were carried out on a RIAD 32 computer using the X-ray 70 system.[23]

Trans-3,4-Epoxy-1-Phenylphospholane-1-Oxide (3a). To a solution of **2a** (20.0 g; 0.112 mol) in chloroform (100 ml) 85% *m*-chloroperbenzoic acid (31.0 g; 0.152 mol) was added. The mixture was heated at reflux for 10h washed with 10% $Na_2S_2O_5$ aq (2 × 100 ml), saturated Na_2CO_3 aq (2 × 100 ml) and water (100 ml), dried over $MgSO_4$ and concentrated in vacuo. Recrystallization from CCl_4—light petroleum gave pure **3a** (18.2 g; 84%): m.p. 118–120°C; ^{1}H-MNR spectrum ($CDCl_3$): δ 2.37–2.67 (m, 4H, 2-CH_2-), δ 3.77 (d, J_{P-H} = 26.0 Hz, 2H, 2-CH), δ 7.32–7.97 (m, 5H, Ph). ^{31}P-NMR spectrum ($CHCl_3$): δ 58.4* MS: m/e 194 (M^+). Anal. Calcd. for $C_{10}H_{11}O_2P$: C, 61.84; H, 5.71; P, 15.95. Found: C, 61.85; H, 5.87; P, 15.82.

4-Hydroxy-1-Phenyl-2-Phospholene-1-Oxide (4a). A solution of **3a** (10.0 g; 0.052 mol) and Et_3N (7 ml) in EtOH (100 ml) was heated at reflux for 20 h. The reaction mixture was then evaporated and the residue was recrystallized from EtOAc to afford **4a** (9.0 g; 90%): m.p. 88–90°C; MS: m/e 194 (M^+). Anal. Calcd. for $C_{10}H_{11}O_2P$: C, 61.84; H, 5.71; P, 15.95. Found: C, 62.10; H, 5.90; P, 16.04.

TABLE III

Final atomic parameters ($\times 10^3$) for H atoms and H—C (H—O) bond lengths (Å)

	x	y	z	B_{iso}(Å^2)	Bonded to	Bond length
H(1)	1023 (6)	401 (7)	325 (6)	4 (2)	O (2)	0.84 (6)
H(2)	670 (6)	472 (6)	586 (6)	5 (2)	C(2)	1.07 (6)
H(3)	764 (7)	552 (6)	369 (7)	6 (2)	C(3)	1.09 (7)
H(4)	806 (5)	312 (5)	251 (4)	2 (1)	C(4)	0.95 (5)
H(51)	894 (4)	118 (5)	404 (4)	1 (1)	C(5)	0.92 (4)
H(52)	987 (6)	217 (6)	447 (5)	5 (1)	C(5)	1.04 (6)
H(12)	774 (5)	107 (5)	829 (4)	2 (1)	C(12)	0.94 (5)
H(13)	886 (4)	140 (4)	1025 (4)	1 (1)	C(13)	0.90 (4)
H(14)	1077 (4)	270 (5)	1031 (5)	2 (1)	C(14)	0.93 (5)
H(15)	1133 (4)	397 (4)	845 (4)	1 (1)	C(15)	0.90 (4)
H(16)	1012 (4)	381 (5)	657 (4)	1 (1)	C(16)	0.85 (4)

TABLE IV

Bond lengths (Å) and angles (°)

Bond lengths		Bond angles	
P(1)—O(1)	1.486 (3)	O(1)—P(1)—C(2)	116.3 (2)
P(1)—C(2)	1.787 (5)	O(1)—P(1)—C(5)	115.5 (3)
P(1)—C(5)	1.818 (6)	O(1)—P(1)—C(11)	110.9 (2)
P(1)—C(11)	1.795 (4)	C(2)—P(1)—C(5)	93.8 (3)
C(2)—C(3)	1.305 (8)	C(2)—P(1)—C(11)	107.3 (2)
C(3)—C(4)	1.508(8)	C(5)—P(1)—C(11)	111.9 (2)
C(4)—C(5)	1.539 (9)	P(1)—C(2)—C(3)	111.4 (4)
C(4)—O(2)	1.420 (7)	P(1)—C(5)—C(4)	106.8 (4)
C(11)—C(12)	1.393 (7)	C(2)—C(3)—C(4)	118.6 (5)
C(12)—C(13)	1.378 (8)	C(3)—C(4)—C(5)	107.9 (5)
C(13)—C(14)	1.373 (8)	C(3)—C(4)—O(2)	111.2 (5)
C(14)—C(15)	1.368 (8)	C(5)—C(4)—O(2)	114.5 (5)
C(15)—C(16)	1.378 (8)	P(1)—C(11)—C(12)	119.5 (3)
C(16)—C(11)	1.392 (7)	P(1)—C(11)—C(16)	121.8 (4)
		C(11)—C(12)—C(13)	120.2 (5)
		C(12)—C(13)—C(14)	120.6 (5)
		C(13)—C(14)—C(15)	119.5 (5)
		C(14)—C(15)—C(16)	121.0 (5)
		C(15)—C(16)—C(11)	120.0 (5)
		C(16)—C(11)—C(12)	118.6 (4)

Resolution of (±)-4-Hydroxy-1-Phenyl-2-Phospholene-1-Oxide (4a) into Enantiomers. To a solution of (−) ω-camphanic acid chloride (8.1 g; 0.375 mol) in pyridine (50 ml) **4a** (5.0 g; 0.258 mol) was added and the mixture was stirred for 20 h at room temperature. Completion of the reaction was confirmed by T.L.C. (EtOAc: C_6H_6, 4:1). The mixture was poured into ice/water (1000 ml) and extracted with $CHCl_3$ (3 × 300 ml). The combined extracts were washed with saturated $NaHCO_3$ aq (100 ml) and water (100 ml), dried over $MgSO_4$ and traces of pyridine were evaporated in vacuo. Recrystallization of the residue consisting of two diastereomeric ω-camphanates (9.5 g; 98%) (^{31}P-NMR, $CHCl_3$: δ 55.5 and 55.7) from benzene-hexane (1:0.5) gave a single diastereomer (+) **5a** (3.6 g; 38%), (^{31}P-NMR, $CHCl_3$: δ 55.7): m.p. 166–168°C, $[\alpha]_D^{20}$ +68.8° (c = 1.12, $CHCl_3$). The other diastereomer was not separated. ω-Camphanate (+)-**5a** (2.2 g: 0.0058 mol) was treated with 1.5 normal NaOH aq (15 ml) for 1 h at room temperature. Completion of the reaction was confirmed by TLC (EtOAc—MeOH 9:1). Then the mixture was extracted with $CHCl_3$ (6 × 15 ml), dried over $MgSO_4$ and evaporated to dryness. The resulting solid after crystallization from EtOAc afforded a single enantiomeric (+)-**4a** (0.96 g; 86%); m.p. 108–110°C, $[\alpha]_D^{20}$ +184.8° (c = 1.98, $CHCl_3$).

4-Oxo-1-Phenyl-2-Phospholene-1-Oxide (+)-(1a). Enantiomeric (+)-**4a** (1.0 g; 0.0052 mol) in pyridine (3 ml) was added to the Collins reagent (3.5 g CrO_3 in 90 ml of pyridine) and stirred at room tempera-

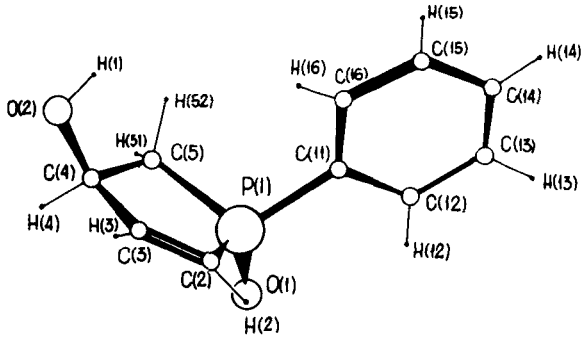


FIGURE 1 Stereoview of (+)-**4a**.

ture for 24 h. After conventional work up the crude product was recrystallized from ether to give (+)-**1a** (0.5 g; 50%); m.p. 91–93°C, $[\alpha]_D^{20}$ +285.5° (c = 2.65, $CHCl_3$); MS: m/e 192 (M^+). Anal. Calcd. for $C_{10}H_9O_2P$: C, 62.51; H, 4.72; P, 16.12. Found: C, 62.50; H, 4.70; P, 15.98.

ACKNOWLEDGMENTS

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