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OPTICALLY ACTIVE PHOSPHINE OXIDES

SYNTHESIS AND ABSOLUTE CONFIGURATION OF (MENTHOXYCARBONYLMETHYL) PHENYLVINYL PHOSPHINE OXIDE

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Abstract The enantiomeric (−)-(menthoxycarbonylmethyl)phenylvinylphosphine oxide **1b** has been prepared and its absolute configuration rigorously established *via* chemical correlation. One-step decarbalkoxylation of (−)-ethyl(methoxycarbonylmethyl)phenyphosphine oxide **6** was effected with LiCl-H$_2$O-DMSO and shown to proceed without concomitant racemization at phosphorus.

Besides being a class of compounds which has occupied a central position in the study of organophosphorus reaction mechanisms and stereochemistry, the optically active phosphine oxides are also of some importance from the standpoint of synthetic organophosphorus chemistry. Presently, this importance lies solely in the observation that the optically active phosphine oxides are prone to undergo a stereospecific reduction[1] and can therefore provide optically active phosphines. Surprisingly, other synthetic transformations of optically active phosphine oxides have not received attention. This may be due to the fact, that optically active phosphine oxides bearing carbon functionalities are rare and rather difficult to obtain.[2] Hence, the development of a reliable synthesis for doubly functionalized enantiomeric phosphine oxides seemed to us highly desirable. In this paper we report the preparation of the first representative of this class of compounds and the assessment of its absolute configuration by means of chemical correlation.

RESULTS AND DISCUSSION

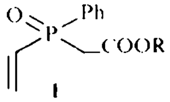

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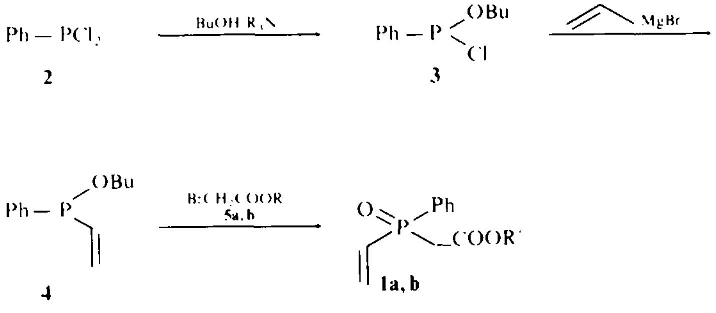
Figure 1

The activating effects of the phosphoryl group allow many synthetic transformations of the adjacent functionalities. A vinyl function activated by the phosphoryl group is known to be susceptible to conjugate addition,[3,4] cycloaddition,[5] addition-alkylation,[4] etc.[6] Also, enhanced nucleophilic reactivity of the α-phosphorylated carbanions is amply evidenced.[7] In our opinion, the combination of these two functions in one molecule, such as **1**, has warranted the creation of a species of extremely high synthetic maneuverability, and, particularly attractive, whilst optically active at phosphorus. To obtain phosphine oxide **1** the reaction sequence shown in Scheme I was followed.

Treatment of phenylphosphonous dichloride **2** with butanol/amine[8] and subsequently with vinylmagnesium bromide[9] resulted in the formation of butyl phenylvinylphosphonite **4** in 48.5% overall yield. Phosphinite **4** was further reacted with both methyl bromoacetate **5a** and with menthyl bromoacetate **5b**.



(a) R' = CH$_3$, (b) R' = Men

Scheme I

The former reaction gave a very viscous material apparently indicating that considerable polymerization accompanies the Michaelis-Arbusov process. Small portions of this material were distilled *in vacuo* and gave, in *ca* 30% total yield, oily colorless **1a** which, however, showed a tendency toward further polymerization on standing. It was hoped, that our target molecule **1b** would appear crystalline which would therefore render its handling and storage after isolation possible.

Heating equimolar amounts of butyl phenylvinylphosphonite **4** with (−)-menthyl bromoacetate **5b**[10] produced a pale yellow oil from which white flaky crystals started to precipitate slowly upon cooling to room temperature. After 2–3 days the precipitate was separated from the mother liquor and analysed. Its ^{1}H NMR spectrum was in excellent agreement with the structure expected of compound **1b**. Moreover, the clarity of this spectrum argued for a high degree of diastereomeric purity of the sample. This point, being of prime importance to the subject of this work, was further substantiated by the occurrence of single lines in the ^{31}P NMR spectra of **1b** in $CHCl_3$ (22.1 ppm) and benzene (19.01 ppm) solutions.

Surprisingly, the ^{31}P NMR spectrum of the crude oil in $CHCl_3$ showed the same sharp single line at 22.4 ppm in addition to some intractable noise-like signals of polymeric origin. However, another measurement in benzene solution revealed the existence of two equally intense signals at ca 19.8 ppm, which was more in line with expectation. The separation of those lines was 0.98 Hz and the addition of crystalline **1b** to the sample caused only the low-field signal to increase. Examination of a benzene solution of the mother liquor showed among some noise-like signals a single line absorption at 19.6 ppm, to which another line at slightly lower field had been added after addition of crystalline **1b**. It was therefore reasonable to assume that crystalline **1b** presents itself as a single diastereomer enantiomeric at both menthyl and phosphorus residues.†

In order to assign the absolute configuration to the phosphorus atom of **1b** chemical correlation with optically active ethylmethylphenylphosphine oxide **7** was carried out according to Scheme II.

Low pressure hydrogenation of **1b** over $Pd/CaCO_3$ in methanol gave the saturated oxide **6** in 88% yield. The conversion of the oxide **6** into the oxide **7** required however further investigation since 48% aq. HBr, which was shown recently to be effective in such a transformation,[11] had to be avoided for optically active phosphine oxides are known to undergo extensive racemization under acidic conditions.[12] Decarbalkoxylation of **6** by use of Me_3SiCl/NaI[13] or Al_2O_3/dioxane[14] had failed, but the procedure utilizing a $LiCl–H_2O–DMSO$ system[15] was successfully adapted. Compound **7** was isolated in 60% yield and its optical and spectral properties agreed with those reported for *S*-(−)ethylmethylphenylphosphine oxide.[2b]

The formation of *S*-(−)-**7** in such a reaction sequence establishes unequivocally the same *S* configuration of phosphorus atom in (−)-**1b** since neither the hydrogenation nor the decarbalkoxylation step involves breakage of any of the phosphorus bonds. Accordingly, the *R* configuration is assigned to the P of (−)-**6**.

It is worthwhile to note that the rotation observed for **7** $[\alpha]_{589}$ −**23.1**/ agrees well with its highest reported rotation $[\alpha]_{589}$ −23[2b] and therefore strongly suggests, finally, ~100% optical purity of **1b** and also of **6** and **7**.

CONCLUSIONS

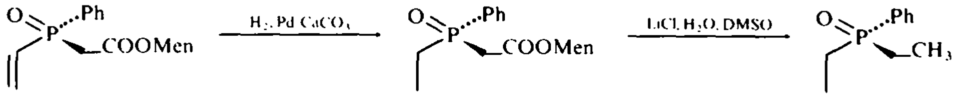
The synthetic route presented herein provides a simple access to the optically pure bifunctionalised phosphine oxide **1b**. The synthetic importance of this compound follows from the fact that all non-aromatic carbons in this system may be activated under different reaction conditions. We believe that **1b** will prove very useful as a building block in the construction of a variety of new systems containing optically active phosphorus atoms of known configuration. Application of **1b** along this line will be the subject of future reports from this Laboratory.

EXPERIMENTAL

All m.p.'s and b.p.'s are uncorrected. ^{1}H NMR spectra were recorded at 80 MHz with Tesla BS 487 Spectrometer using TMS as internal standard. ^{31}P NMR spectra were obtained on a Jeol-JNM-FX 60 Fourier transform spectrometer at 24.3 MHz with 85% H_3PO_4 as external standard. Positive ^{31}P NMR signals were assigned to low field from H_3PO_4. Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter (sensitivity ± 0.002°). Elemental analyses were performed at Microanalyses Laboratory of Technical University of Łódź.

Phenylphosphonous dichloride **2** and methyl bromoacetate **5a** were commercially available. Compounds **3**[7], **4**[8] and **5b**[10] were obtained accordingly to the literature procedures.

(*Methoxycarbonylmethyl)phenylvinylphosphine oxide* (**1a**). To butyl phenylvinylphosphonite **4** (40.5 g, 0.194 mol) warmed to 40°C under nitrogen was added gradually methyl



1b (S) $[\alpha]_D = -68.7$

6 (R) $[\alpha]_D = -32.4$

7 (S) $[\alpha]_D = -23.1$

Scheme II

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† The isolation of another diastereomer from polymeric material is underway.

bromoacetate **5a** (29.75 g, 0.194 mol) at such a rate as to maintain the reaction temperature in the range of 100–105°C. After the addition was complete, the reaction mixture was kept at this temperature for an additional 0.5 h. Small portions of this mixture were distilled *in vacuo* and gave **1a** (19.9 g, 46.2%). B.p. = 140–3°C/0.1 mmHg; ^{31}P NMR-($CHCl_3$): $\delta = 22.39$ ppm; ^{1}H NMR ($CDCl_3$): 3.24 ppm (d, 3H, $^2J_{PH} = 16$ Hz, CH_3), 3.63 ppm (s, 3H, OCH_3), 5.9–6.9 ppm (m, 3H, $CH{=}CH_2$), 7.25–8.0 ppm (m, 5H, C_6H_5). [Found: C 59.0; H 6.00; P 12.99; Calc. for $C_{11}H_{13}O_3P$ (224,19), C 58.93; H 5.84; P 13.21.]

(−)-*(Menthoxycarbonylmethyl)phenylvinylphosphine oxide* **1b**. Butyl phenylvinylphosphonite **4** (52 g, 0.25 mol) was reacted with (−)-menthyl bromoacetate **5b** ($[\alpha]_{589} = -72.63$, neat; $[\alpha]_{589} = -61.72$, $CHCl_3$; 69.3 g 0.25 mol) in the manner described above. Volatile by-products (**BuBr**) were removed on a rotary evaporator under vacuum and the residual oily mixture was allowed to stand for crystallization at room temperature. The white precipitate was filtered off, washed with cold benzene and dried in a dessicator. The crystalline **1b** thus obtained (26 g, 30%) was of sufficiently high purity for further use. Recrystallization from benzene gives an analytically pure sample of **1b**. M.p. 152°C; $[\alpha]_{589} = -87.2$ (c, 6.4, $CHCl_3$); ^{31}P NMR ($CHCl_3$): $\delta = 22.1$ ppm, (C_6H_6): $\delta = 19.0$ ppm; ^{1}H NMR ($CDCl_3$): 0.55 1.0 ppm (m, 9H, 3 × CH_3), 1.0–2.05 ppm (m, 9H, menthyl), 3.25 ppm (d, 2H $^2I_{PH} = 16$ Hz, P-CH_2), 4.68 ppm (m, 1H, OCH) 5.9–6.9 ppm (m, 3H, $CH{=}CH_2$) 7.35–8.0 (m, 5H, C_6H_5). [Found: C 68.59, H 8.24, P 8.77. Calc. for $C_{20}H_{29}O_3P$ (348.42) C 68.94; H 8.39; P 8.89.]

(−)-*Ethyl(Menthoxycarbonylmethyl)phenylphosphine oxide* (**6**). Low pressure hydrogenation of **1b** (2.5 g, 0.007 mol) in methanol (25 mL) with Pd/$CaCO_3$ as a catalyst was carried out at room temperature for 20 min. (hydrogen uptake 161 mL). Removal of MeOH and the catalyst gave crystalline **6** (2.2 g, 88%). M.p. 92–3°C; $[\alpha]_{589} = -50.7$ (c, 4.85, $CHCl_3$); ^{31}P NMR ($CHCl_3$): $\delta = 36$ ppm; ^{1}H NMR ($CDCl_3$): 0.55–2.45 ppm (m, 23H); 3.16 ppm (d, 2H, $^2J_{PH} = 15$ Hz, P–CH_2–CO) 4.68 ppm (m, 1H, OCH) 7.35–7.95 ppm (m, 5H, C_6H_5). [Found: C 68.21; H 8.36; P 8.50. Calc. for $C_{20}H_{31}O_3P$ (350.44) C 68.55; H 8.92; P 8.84.]

(−)-*Ethylmethylphenylphosphine oxide* (**7**). A mixture of **6** (1.05 g, 0.003 mol), DMSO (5 mL), H_2O (0.05 g, 0.003 mol) and LiCl (0.25 g, 0.006 mol) was refluxed for 12 h. 10 mL of saturated. NaCl solution was added after cooling and the resulted mixture was extracted several times with $CHCl_3$. The extracts were combined, dried ($MgSO_4$) and the solvent evaporated. Purification of crude material by column chromatography (benzene-aceton-methanol 2:1:1) provided **7** (0.3 g, 60%). M.p. 46–48°C (lit.[2b] 50–52°C); $[\alpha]_{589} = -28.3$ (c, 3.44, $CHCl_3$); $[\alpha]_{589} = -23.1$ (c, 6.13, MeOH) (lit.[2b] −23, MeOH); ^{31}P NMR (MeOH): $\delta = 38.3$ ppm (lit.[16] 37.5 ppm, CD_3OD).

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