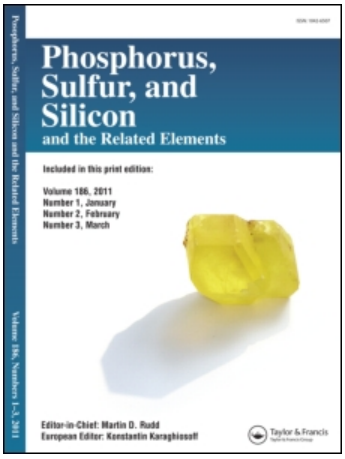


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# SYNTHESIS AND ABSOLUTE CONFIGURATION OF DIASTEREOMERIC MENTHYL BENZYLPHOSPHINATES

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# SYNTHESIS AND ABSOLUTE CONFIGURATION OF DIASTEREOMERIC MENTHYL BENZYLPHOSPHINATES

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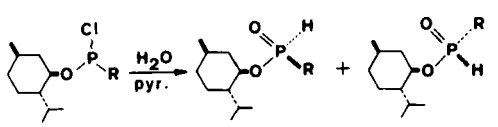
Diastereomerically pure $R_P$-menthyl benzylphosphinate (**7a**) and diastereomerically enriched $S_P$-menthyl benzylphosphinate (**7b**) have been prepared and their absolute configurations have been corroborated via chemical correlation.

*Key words:* Phosphinic acid; chiral esters, absolute configuration; thermal epimerization; alkylation; reaction with Grignard reagent; chiral phosphine oxides.



## INTRODUCTION

Menthyl alkylphosphinates and menthyl arylphosphinates of high diastereomeric purity have proven to be exceptionally useful precursors in the syntheses of various classes chiral organophosphorus compounds including optically active tertiary phosphine oxides[1] and phosphonothioates.[2] Although these syntheses are satisfactorily effective and stereoselective their general application suffers from scarce availability of a sufficiently large spectrum of the starting phosphinates possessing different substituents and defined configurations. To date only the preparations of diastereomerically pure menthyl methylphosphinates (**3**)[2] and diastereomerically enriched menthyl phenylphosphinates (**4**)[1] have been reported. The key stage of both the preparations involves hydrolysis of the appropriate menthyl phosphinochloridates **1** or **2** followed by operationally difficult and laborious separation of the resultant low melting **3a** and **3b** or **4a** and **4b** by fractional crystallization at −25°C or −78°C respectively.

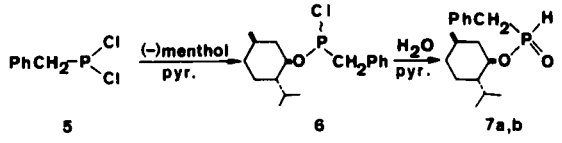



**1** **2** **3a** **4a** **3b** **4b** R = Me, R = Ph

This paper deals with the results from our studies on the synthesis and stereochemistry of the diastereomeric menthyl benzyl-phosphinates (**7a**) and (**7b**).

## RESULTS AND DISCUSSION

The synthesis of **7** follows the reaction pathway reminescent of the approach to **3** and **4**




5 6 7a,b

Thus the starting menthyl benzylphosphinochloridate (**6**) was routinely obtained by treatment of readily accessible benzydichlorophosphine (**5**) with naturally occurring (−)-menthol in the presence of pyridine. As anticipated pyridine promoted hydrolysis of **6** gave an oily mixture of **7a** and **7b** (80%) in a ratio 1:1. In contrast to the described protocols partial separation of **7** was unexpectedly straightforward. After leaving the oil for 4–5 days at 25°C only **7a** crystallized out and could be isolated by usual filtration. One recrystallization from n-hexane provided this diastereomer in a pure form ($[\alpha]_{20}^{D}$ −15.54° in methanol). Although the residual mother liquor consisted of **7b** and **7a** in a proportion 85:15 all efforts to achieve its further enrichment in **7b** by using different separation methods were unsuccessful. Attempts at fractional distillation have shown that at 120°C each of **7** is smoothly epimerized at phosphorus atom to reproduce an original mixture of **7a** and **7b** in a ratio 1:1. Utilizing the epimerization as an additional element of the preparative procedure it was possible to increase essentially the total diastereoselectivity of the synthesis. When the product of hydrolysis of **6** was subjected to several successive separations and epimerizations practically all its **7b** component was converted into **7a**. Some characteristic features of $^{31}P$ and $^{1}H$ NMR spectra of both diastereomeric **7** are summarized in Table I.

Absolute configurations of **7a** and **7b** were deduced from simple chemical correlations.

It has been previously demonstrated that alkylation of menthyl phenylphosphinates with a variety of alkyl iodides proceeds with predominant retention of configuration at phosphorus atom and that displacement of a menthoxyl group in the resultant menthoxy alkylphenylphosphinates with Grignard and related reagents gives tertiary dialkylphenylphosphine oxides with inverted stereochemistry.[1,3,4] These findings strongly implied that the sequence of similar stereoselective transformations might be utilized to correlate the configuration of one

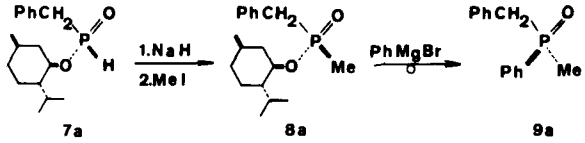
TABLE I

$^{31}P$ and $^{1}H$ NMR chemical shifts and coupling constants of menthyl benzylphosphinate (**7**) diastereomers[a]

| | $^{31}P$ NMR | PH | $^{1}H$ NMR | $PCH_2$ |
|---|---|---|---|---|
| **7a** | 38.8 | 7.05 $^{1}J_{HP} = 536$; $^{3}J_{HH} = 2.5$ | | 3.15 $^{2}J_{HP} = 19$; $^{3}J_{HP} = 2.5$ |
| **7b** | 32.5 | 8·06 $^{1}J_{HP} = 536$; $^{3}J_{HH} = 2{\cdot}5$ | | 3.12 $^{2}J_{HP} = 19$; $^{3}J_{HP} = 2.5$ |

[a] The spectra were recorded in $CDCl_3$. The chemical shift values are given in ppm and were referenced to $H_3PO_4$ and TMS respectively. The coupling constants are given in Hertz.

of the diastereomeric **7** with known optically active benzylmethylphenylphosphine oxide (**9**).[5]




**7a** **8a** **9a**

Treatment of sodium phosphinate derived from **7a** with methyl iodide gave a crystalline product (75%) whose $^1$H NMR spectrum was in excellent accord with the structure of a single diastereomer of menthyl benzylmethylphosphinate (**8**) ($[\alpha]_D^{20}$ −32.9° in methanol). High purity of **8** and stereospecificity of the methylation were additionally confirmed by $^{31}$P NMR spectra which in a variety of solvents revealed exclusively a single line absorbtion (49.7 ppm in $CHCl_3$, 47.5 ppm in benzene). Exposure of **8** to the action of phenylmagnesium bromide gave rise to the formation of a readily isolable solid compound (80%) of spectral and optical properties consistent with those reported for *R*-(+)-benzylmethylphenylphosphine oxide (**9a**).[5] Surprisingly the observed specific rotation of $[\alpha]_D^{20}$ +28.6° (methanol) corresponded to 56% optical purity of **9a** and evidenced merely moderated stereoselectivity of the designed displacement.

On the basis of the presented data stereochemistry of the intermediate **8** was identified as **8a** with R configuration of the phosphorus atom. Consequently *R* and *S* chirality could be unambiguously assigned to the phosphorus atoms of the diastereomers **7a** and **7b** respectively.

In summary an efficient procedure has been developed for the synthesis of diastereomerically pure $R_P$-**7a** and diastereomerically enriched $S_P$-**7b**. Particular preparative simplicity makes this synthesis potentially adaptable to large scale preparations without decrease in product yield or purity.



## EXPERIMENTAL

All temperatures are uncorrected. $^1$H NMR spectra were determined at 80 MHz on Tesla BS 487 instrument and were referenced to an internal standard of TMS. $^{31}$P NMR spectra were determined at 24.3 Hz on Jeol-JNM-FX-60 Fourier transform instrument with 85% $H_3PO_4$ as external standard. The chemical shifts are expressed in part per million. IR spectra were obtained on Perkin–Elmer 621 infracord spectrofotometer. Optical rotations were measured with Perkin-Elmer 241 MC polarimeter. Elemental analyses were performed by the Microanalyses Laboratory, Technical University of Łódź.

Column chromatrography was performed by using E. Merck silica gel 60 (70–230 mesh A STM). All solvents were reagent grade materials purified by standard methods and redistilled before use.

Benzyldichlorophosphine was prepared according to known method.[6]

*$R_P$-(−)-Menthyl benzylphosphinate* (**7a**) *and diastereomerically enriched $S_P$-menthyl benzylphosphinate* (**7b**). To a solution of **5** (57.9 g, 0.30 mol) in diethyl ether (150 mL) cooled in an ice-water bath was added slowly a solution of (−)-menthol (46.9 g, 0.30 mol) and pyridine (24.5 g, 0.31 mol) in diethyl ether (150 mL) so that the reaction temperature remained 8–10°C. After the reaction was completed stirring was continued for 30 min and then a solution of water (5.9 g, 0.30 mol) and pyridine (24.5 g, 0.31 mol) in diethyl ether (150 mL) was added. The reaction mixture was allowed to warm to 20°C and the precipitate of pyridinium hydrochloride was separated by filtration. The filtrate was washed with 10% aqueous $NaHCO_3$ (3 × 100 mL) and water (3 × 100 mL), dried over $MgSO_4$ and evaporated in vacuo. Distillation of the residue under reduced pressure gave a 1:1 mixture of diastereometric **7a** and **7b** (by $^{31}$P NMR spectrum in $CHCl_3$) as a pale yellow oil (70.6 g, 80.0%): B.p.

148–150/0.2 torr. On standing for 5 days at 25°C the oil deposited a precipitate which was filtered off and washed with a small amount of cold n-hexane. One recrystallization of this material from n-hexane provided analytically pure **7a** (24 g) as colorless plates: M.p. 74.5–75.0°C; $[\alpha]_D^{20}$ −15.4° (c = 2.03, methanol); $^{31}$P NMR ($CHCl_3$): $\delta$ 38.8; $^1$H NMR ($CDCl_3$): $\delta$ 0.5–2.4 (m, 18H, menthyl), 3.15 (dd, $^2J_{HP}$ = 19.0 Hz, $^3J_{HH}$ = 2.5 Hz, 2H, P(O)$CH_2$), 3.93–4.24 (m, 1H, CHO), 7.05 (dt, $^1J_{HP}$ = 536 Hz, $^3H_{HH}$ = 2.5 Hz, 1H, PH), 7.1–7.3 (m, 5H, Ph). IR (KBr) 1220 $cm^{-1}$ (P═O), 2350 $cm^{-1}$ (PH). Anal. Calcd. for C, H, O, P: C, 69.35; H, 9.26; P, 10.52. Found: C, 69.02; H, 9.34; P, 10.49. The combined filtrates were evaporated in vacuo at 25°C to give 85:15 mixture of **7b**:**7a** (41.0 g) as a pale yellow oil: $^{31}$P NMR ($CHCl_3$) (for **7b**): $\delta$ 32.5; $^1$H NMR ($CDCl_3$) (for **7b**): $\delta$ 0.5–2.4 (m, 18H menthyl), 3.12 (dd, $2J_{PH}$ = 19.0 Hz, $^3J_{HH}$ = 2.5 Hz, 2H, P(O)$CH_2$), 3.93–4.24 (m, 1H, CHO), 8.06 (dt, $^1J_{HP}$ = 536 Hz, $J_{HH}$ = 2.5 Hz, 1H, PH), 7.1–7.3 (m, 5H, Ph). IR (film) 1220 $cm^{-1}$ (P═O); 2350 $cm^{-1}$ (PH). Anal. Calcd for C, H, O, P: C, 69.35; H, 9.26; P, 10.52. Found: C, 69.10; H, 9.50; P, 10.37.

*Thermal epimerization of $R_P$-(−)-menthyl benzylphosphinate* (**7a**) *and $S_P$-menthyl benzylphosphinate* (**7b**). Diastereomerically pure **7a** or alternatively diastereomerically enriched **7b** (85%) (38.0 g, 0.13 mol) were heated with stirring at 120°C under dry nitrogen for 0.5 h. The resulting oil was distilled under reduced pressure to afford the 1:1 mixture of **7a** and **7b** (36.0 g, 95%): B.p. 148–150/0.2 torr; $^{31}$P NMR ($CHCl_3$): $\delta$ 38.8 (for **7a**), 32.5 (for **7b**).

*$R_P$-(−)-Menthyl benzylmethylphosphinate* (**8a**). To a stirred suspension of sodium hydride (0.5 g, 0.02 mol) in DMF (20 mL) was added a solution of **7a** (6 g, 0.02 mol) and methyl iodide (28.4 g, 0.2 mol) in DMF (20 mL). After stirring for 30 min. at 55°C the reaction mixture was concentrated to a small volume in vacuo. The residue was dissolved in benzene (100 mL) and washed with water (3 × 20 mL). Drying the organic phase with $MgSO_4$ and evaporation of the solvent in vacuo gave a solid which was recrystallized from n-hexane to afford **8a** (4.6 g, 75.0%) as colorless plates: M.p. 109.5–110.0°C; $[\alpha]_D^{20}$ −32.9° (c = 1.5, methanol); $^{31}$P NMR: ($CHCl_3$) $\delta$ 49.7, (benzene) 47.5; $^1$H NMR ($CDCl_3$): $\delta$ 0.6–2.25 (m, 18H, menthyl), 1.51 (d, $^2J_{HP}$ = 14.7 Hz, 3H, P(O)$CH_3$), 3.12 (d, $^2J_{HP}$ = 18.8 Hz, 2H, P(O)$CH_2$), 4.07–4.25 (m, 1H, CHO), 7.2–7.3 (m, 5H, Ph). IR (KBr) 1200 $cm^{-1}$ (P═O). Anal. Calcd. for C, H, O, P: C, 70.00; H, 9.50; P, 10.04. Found: C, 69.80; H, 9.62; P, 9.94.

*$R_P$-(+)-Benzylmethylphenylphosphine oxide* (**9a**). To magnesium turnings (0.49 g, 20.0 mmol) suspended in diethyl ether (40 mL) bromobenzene (3.1 g, 20.0 mmol) was added and the mixture was refluxed until most of the magnesium had been consumed. Then a solution of **8a** (3.1 g, 10.0 mmol) in diethyl ether (20 mL) was added and refluxing was continued for 30 min. After cooling to 20°C the reaction mixture was quenched with 5% aqueous $NH_4Cl$ solution (30 mL). The organic phase was separated, washed with water (2 × 15 mL) dried over $MgSO_4$ and concentrated in vacuo. The resultant solid was purified by column chromatography on silica gel with benzene as eluent to give **9a** (1.84 g, 80.0%) as colorless prisms; M.p. 137–138°C; $[\alpha]_D^{20}$ + 28.6°C (c = 1.3, methanol); $^{31}$P NMR ($CHCl_3$): $\delta$ 35.2; $^1$H NMR ($CDCl_3$): $\delta$ 1.64 (d, $^2H_{HP}$ = 14.0 Hz, 3H, P(O)$CH_3$), 3.30 (d, $^2J_{HP}$ = 15.0 Hz, 2H, P(O)$CH_2$), 7.0–7.85 ppm (m, 10H, Ph). IR (KBr) 1180 $cm^{-1}$ (P═O).



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## REFERENCES

1. W. B. Farnham, R. K. Murray, Jr. and K. Mislow, *J. Am. Chem. Soc.*, **92,** 5809 (1970).
2. H. P. Benschop, D. H. J. M. Platenburg, F. H. Meppelder and H. J. Boter, *Chem. Commun.*, **33,** (1970).
3. O. Korpiun, R. A. Lewis, J. Chickos and K. Mislow, *J. Am. Chem. Soc.*, **90,** 4842 (1968).
4. R. A. Lewis and K. Mislow, *J. Am. Chem. Soc.*, **91,** 7009 (1969).
5. O. Korpiun and K. Mislow, *J. Am. Chem. Soc.*, **89,** 4784 (1967).
6. T. Weil, B. Prijs and H. Erlenmeyer, *Helv. Chim. Acta*, **36,** 1314 (1953).