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Characterization of an Optically Active Pentacoordinate Phosphorane with Asymmetry Only at Phosphorus

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Abstract: By treating diastereomeric [*o*-OC(CF₃)₂C₆H₄]₂PCH₂CO₂(-)-menthyl] (2-(**R**)**P** and 2-(**S**)**P**) with LiAlH₄, a pair of enantiomerically pure phosphoranes, [*o*-OC(CF₃)₂C₆H₄]₂PCH₂C₂HOH (3-(**R**)**P** and 3-(**S**)**P**), having asymmetry only at phosphorus were obtained.

In order to investigate the stereochemistry of pentacoordinate phosphorus, which is believed to be involved in biological phosphoryl transfer processes,¹ a wide range of model pentacoordinate phosphorus compounds have been devised and utilized.² Although the number is small among them are optically active compounds, which incorporate optically active alcohols or aminoalcohols.³ But as for optically active pentacoordinate compounds bearing chirality only at the central phosphorus atom, the only example we are aware of is a pentaarylphosphorus compound prepared by Hellwinkel.⁴ However, since this fascinating compound exhibits residual optical activity, there is no precedence for compounds with a rigid and definable absolute stereochemistry with asymmetry only at phosphorus. By utilizing Martin's phosphorane **1**⁵ we have succeeded in obtaining such a compound and herein we report the details of its stereochemical characterization.

Phosphorane **1** was prepared by combining published procedures.^{5,6} The attachment of the chiral auxiliary to phosphorane **1** was achieved by treating the phosphorane with NaH in THF, followed by the addition of (-)-menthyl chloroacetate as shown in scheme 1, furnishing a 1:1 diastereomeric mixture of phosphorane **2** in 87 % combined yield. Fortunately, the diastereomers could be resolved as prisms and needles by recrystallization from MeOH-H₂O. The separated crystals were repeatedly recrystallized to assure diastereomeric purity giving the compounds in 25 % and 22 % yields, respectively. The diastereomers showed distinctive signals in both ¹H and ³¹P NMR (δ -25.6 and -25.3 in acetone-d₆, respectively) and these signals were used to determine purity of the diastereomers.

In order to determine the absolute stereochemistry of the diastereomers, X-ray crystal structure analysis was conducted on the prism-shaped crystal.⁷ The ORTEP

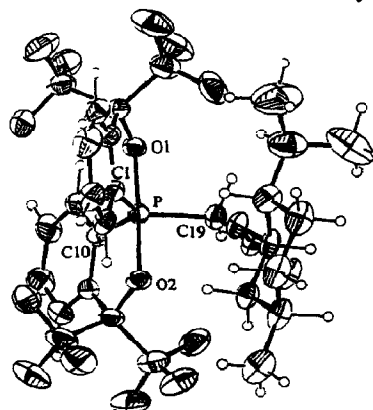
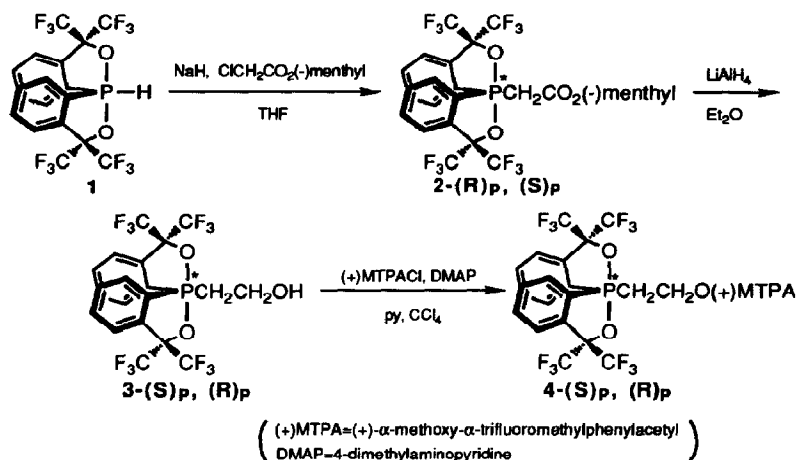


Figure 1. ORTEP drawing of 2-(**R**)**P** showing the thermal ellipsoids at the 30 % probability level.

structure is shown in Fig. 1. The absolute stereochemistry of the phosphorus atom determined from its relative stereochemistry to the known (-)-menthyl moiety turned out to be (R)_P.⁸



Scheme 1

The optical rotation values were $[\alpha]_{436}^{21} +11.1^\circ$ (c 1.02, CHCl_3) for 2-(R)_P and $[\alpha]_{436}^{21} -70.0^\circ$ (c 1.02, CHCl_3) for 2-(S)_P. Since benzene rings were attached directly to the asymmetric phosphorus atom in a C_2 symmetry style, it was speculated that a Cotton effect arising from the isoenergetic exciton dipole coupling of π - π^* transition of the two benzene rings would be observed with opposite sign between the two diastereomers in CD spectroscopy.⁹ The results are shown in Fig. 2. The measured spectra of 2-(R)_P and 2-(S)_P have been calibrated so that the vertical coordinate gives the $\Delta\epsilon$ values as shown in Fig. 2. The major peaks of 2-(R)_P are λ ($\Delta\epsilon$) = 214 (+8.2), 229 (-5.4), 235 (+3.5), 265 (+1.7), and 271 nm (+1.3), while those for 2-(S)_P are 213 (-6.5), 228 (+8.2), 234 (-3.5), 265 (-2.0), and 271 nm (-1.5), thus showing the expected trend. The large differences in intensity at 214 and 229 nm can be ascribed to the overlap of the (-)-menthyl moiety, which shows a monotonic positive Cotton effect. These large Cotton effects imply that 2-(R)_P has an overall left-handed helical electron transition moment, while that of 2-(S)_P is the opposite.

The epimerization rates of the compounds were measured at 100°C using toluene and pyridine as solvents by monitoring ³¹P NMR. The rates turned out to be $1.3 \times 10^{-7} \text{ s}^{-1}$ in toluene, and $1.9 \times 10^{-7} \text{ s}^{-1}$ in pyridine, corresponding to activation free energies of $\Delta G^\ddagger_{373} = 33.8 \text{ kcal mol}^{-1}$ and $33.5 \text{ kcal mol}^{-1}$, respectively. These results show that the process is very slow and that there is little dependence on solvent polarity or donor ability upon the rate. Thus it was concluded that epimerization could be avoided under usual conditions.

The removal of the chiral auxiliary was effected by treating the diastereomers with LiAlH_4 in refluxed Et_2O as depicted in scheme 1, thereby generating the first example of a pair of enantiomeric single structured optically active phosphoranes 3 with asymmetry only at phosphorus. The yields of 3-(R)_P and 3-(S)_P were 81 % and 84 %, respectively. Due to the difficulties encountered in complete removal of (-)-menthol from the product mixture using chromatographic means, the final purification of the alcohols 3-(R)_P and 3-(S)_P was carried out by sublimation under reduced pressure at temperatures at or below 50°C. Partial

epimerization could be detected when the heating temperature was raised. ^1H , ^{13}C , and ^{31}P NMR showed identical spectra for the two enantiomeric compounds thus verifying their identity.¹⁰

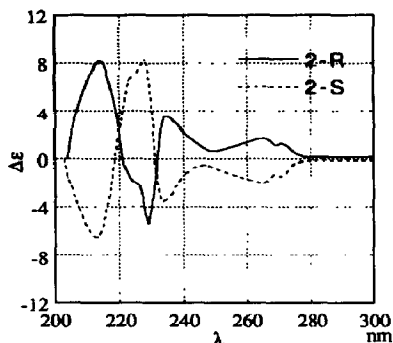


Figure 2. CD spectra of 2-(R)P (solid line, 4.98×10^{-5} M) and 2-(S)P (broken line, 5.38×10^{-5} M) in cyclohexane. The original data has been replotted in terms of $\Delta\epsilon$. The random noise level in the <230 nm region was $\Delta\epsilon = \text{ca.} \pm 1$ while in the >230 nm region it was $\Delta\epsilon = \text{ca.} \pm 0.3$.

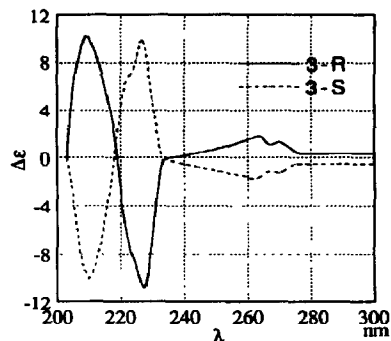


Figure 3. CD spectra of 3-(R)P (solid line, 1.73×10^{-5} M) and 3-(S)P (broken line, 1.26×10^{-5} M) in cyclohexane. The original data has been replotted in terms of $\Delta\epsilon$. The random noise level in the <230 nm region was $\Delta\epsilon = \text{ca.} \pm 1$ while in the >230 nm region it was $\Delta\epsilon = \text{ca.} \pm 0.3$.

The optical rotation values of 3-(R)P and 3-(S)P were $[\alpha]^{21}_{436} +108^\circ$ (c 1.02, CHCl_3) and $[\alpha]^{21}_{436} -107^\circ$ (c 0.83, CHCl_3), respectively. The CD spectra (Fig. 3) of 3-(R)P showed peaks at 210 (+10.2), 227 (-10.9), 264 (+1.8), and 270 (+1.3), while that of 3-(S)P showed peaks at the same wavelengths with identical magnitudes of opposite sign.

In order to assure the high enantiomeric purity of the chiral alcohols, the alcohols 3 were converted to their *R*-(+)-Mosher ester as described in the scheme. The yields were at best 54 and 31 %, respectively, and were not optimized. A mixture of 2-(R)P and 2-(S)P was subjected to the same sequence of reactions, to give racemic 4 in 52 % overall yield. Fortunately, resolution of the ^{31}P NMR signals could be achieved in acetone with signals at -24.5 and -24.7, respectively. As shown in the ^{31}P NMR charts in Fig. 4, the high diastereomeric purity of 4-(R)P and 4-(S)P could thus be confirmed. This establishes the fact that no epimerization had occurred during the two consecutive transformations of esters 2-(R)P and 2-(S)P or during purification procedures and that the alcohols 3-(R)P and 3-(S)P are of high enantiomeric purity.

X-Ray structural analysis carried out upon a recrystallized sample of 4-(R)P confirmed the *R* configuration upon phosphorus.

In summary, we have established for the first time the absolute stereochemistry of the first chiral pentacoordinate phosphorus compound with asymmetry located solely on the phosphorus atom, and in the

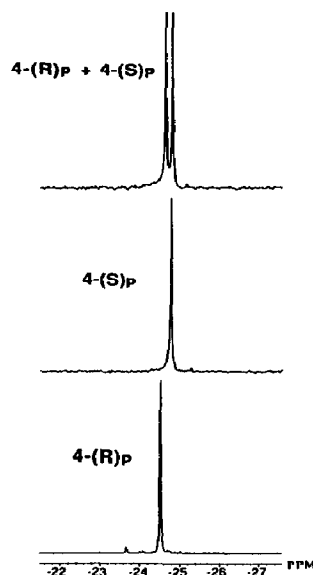


Figure 4. ^{31}P NMR of a mixture of 4-(R)P+4-(S)P (upper chart), 4-(S)P (middle chart), and 4-(R)P (lower chart).

course of it have successfully converted (reduction and esterification) optically active compounds without the accompaniment of epimerization.

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- (7) Crystal data for **2-(R)P**: data were collected on a Mac Science MXC3 diffractometer. $C_{30}H_{29}F_{12}O_4P$, $M=712.50$, orthorhombic, space group $P2_12_12_1$, $a=16.922(4)$, $b=19.322(7)$, $c=10.036(3)$ Å, $\alpha=90.05(3)^\circ$, $\beta=89.92(2)^\circ$, $\gamma=90.03(2)^\circ$, $V=3281(2)$ Å³, $Z=4$, $D_c=1.43$ g/cm³, $F(000)=1456$, Mo K α ($\lambda=0.71073$ Å); 4217 unique reflections measured; 3059 reflections with $I>3\sigma(I)$ used in refinement. $R=0.078$, $R_w=0.060$. The supplementary material has been deposited at the Cambridge Crystallographic Data Center.
- (8) for proposed nomenclature see: Martin, J. C.; Balthazor, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 152.
- (9) Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations*; Cambridge University Press: Cambridge, 1982.
- (10) **3-(R)P** and **3-(S)P**: ¹H NMR (CDCl₃) δ 8.42-8.38 (m, 2 H), 7.74-7.67 (m, 6 H), 3.84 (ddt, ³J_{PH} = 4.88 Hz, J = 13.7, 6.8 Hz, 2 H), 2.75 (ddt, ²J_{PH} = 17.1 Hz, J = 13.7, 6.8 Hz, 1 H), 2.60 (ddt, ²J_{PH} = 13.2 Hz, J = 13.7, 6.8 Hz, 1 H), 1.79 (bs, 1 H); ¹³C NMR (acetone-d₆) δ 138.3 (d, ³J_{PC} = 9.2 Hz), 137.1 (d, ²J_{PC} = 20.2 Hz), 135.9, 133.3 (d, ²J_{PC} = 12.9 Hz), 131.3 (d, ¹J_{PC} = 160 Hz), 126.4 (d, J_{PC} = 14.7 Hz), 124.1 (q, J_{FC} = 288.6 Hz), 123.9 (q, J_{FC} = 288.6 Hz), 82.8 (sept, J_{FC} = 31.3 Hz), 58.2, 44.0 (d, ¹J_{PC} = 114.0 Hz). ¹⁹F NMR (CDCl₃) -74.9 (q, J = 9.8 Hz, 3F), -75.1 (q, J = 9.8 Hz, 3F). ³¹P NMR (acetone-d₆) δ -22.7, (CDCl₃) δ -21.5.
- (11) Analytical and spectral data for all optically active compounds, **2**, **3**, and **4**, were fully compatible with the given assignments. Mp: **2-(R)P** 127-128°C; **2-(S)P** 125-127°C; **3-(R)P** 103-105°C; **3-(S)P** 103-105°C; **4-(R)P** 128-130°C; **4-(S)P** 128-129°C.

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