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Triphenylethanediol-Derived 2-Chloro-1,3,2-dioxaphospholane: Synthesis, Structure, and Reaction with Chiral Alcohols

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*The reaction of (S)-1,1,2-triphenylethanediol (**3**) with phosphorus trichloride leads to the diastereoselective formation of (S_C,R_P)-2-chloro-1,3,2-dioxaphospholane (**2**). Its configuration has been determined by single crystal X-ray diffraction. When reacted with racemic secondary alcohols, diastereomeric phosphites are obtained, which display substantial shift differences in the ^{31}P NMR spectra. Thus, chlorodioxaphospholane **2** can serve as derivatizing reagent for chiral secondary alcohols permitting to determine their enantiomeric excess.*

Keywords Chirality; crystal structure; ^{31}P NMR; phosphites; stereoselectivity

INTRODUCTION

Cyclic monochlorophosphites **1** are usually obtained from diols and phosphorus trichloride.[1–6] They frequently serve as intermediates in syntheses of chiral phophoramidites and phosphites, both versatile ligands in asymmetric catalysis.[7,8] Moreover, monochlorides of cyclic phosphites derived from chiral diols have been found to be suitable derivatizing agents for alcohols and amines.[9–11] In most cases, C_2 symmetric diols were chosen for this purpose so that the pyramidal phosphorus atom does not give rise to the formation of diastereomeric mixtures upon ring closure.[12] In this article, we report on the diastereoselective formation of the chlorodioxaphospholane **2**, the assignment of the configuration, and its reaction with secondary alcohols (Scheme 1).

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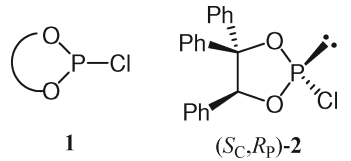
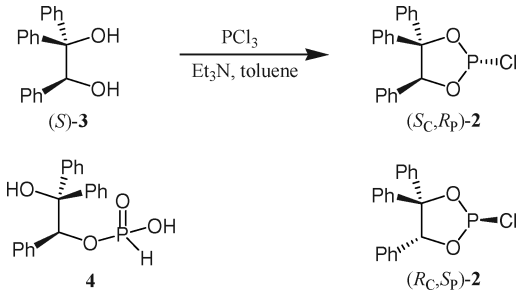


1 (S_C,R_P)-**2**

SCHEME 1

RESULTS AND DISCUSSION

Chlorodioxaphospholane **2** was obtained from (*S*)-triphenylglycol **3**, which is readily available from the corresponding enantiomer of mandelic acid.[13] Treatment of the diol **3** with phosphorus trichloride in toluene in the presence of triethylamine yielded crystalline chlorodioxaphospholane **2**, which was obtained upon concentrating the reaction mixture under reduced pressure (Scheme 2). The ^{31}P NMR spectra of



SCHEME 2

both the solid material and the solution revealed a single signal at $\delta =$ 168 ppm, indicating the stereoselective formation of the product. Crystalline **2** and its solutions must be kept under nitrogen or argon, due to its sensitivity against moisture. As shown previously,[14] ring opening of **2** occurs when it is treated with water and phosphonic acid monoester **4** forms. A crystal structure analysis unambiguously revealed the relative configuration of the heterocyclic compound **2** to be *trans*. As the synthesis started from (*S*)-diol **3**, the (S_C,R_P)-configuration is assigned to the chlorodioxaphospholane **2** (Figure 1). The enantiomeric (R_C,S_P)-**2** was obtained from (*R*)-diol **3** in an analogous way.

Chlorodioxaphospholane **2** reacts readily with secondary alcohols as demonstrated by treatment of a solution of (R_C, S_P)-**2** with (*R*)-1-phenylethanol (**5a**) to give phosphite **6a**. In the ^{31}P NMR spectra, a minor amount of a diastereomer, which is epimeric at the phosphorus atom, was detected. When the (*S*)-enantiomer of 1-phenylethanol was treated with chlorodioxaphospholane (R_C,S_P)-**2**, the phosphite **7a** was

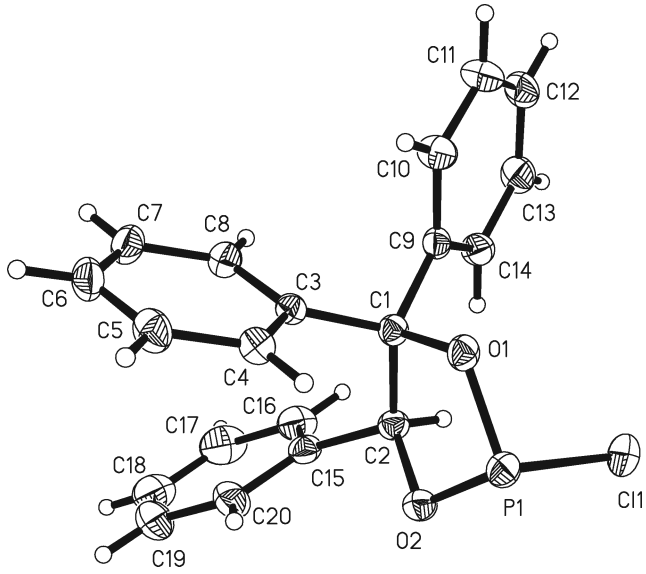
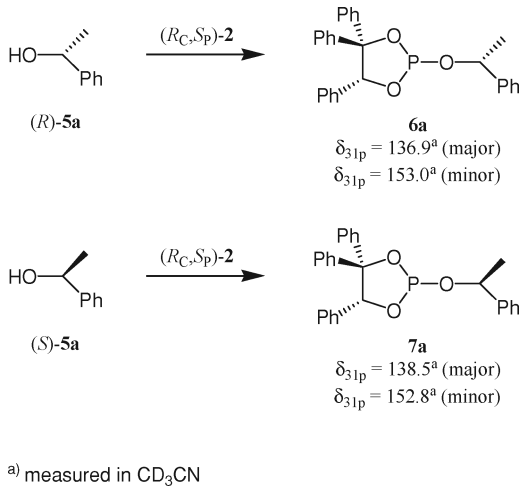


FIGURE 1 ORTEP view of the molecular structure of (*2R,5S*)-**2** in the crystal. Displacement ellipsoids are drawn at the 50% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. Selected geometric parameters [Å] and [°]: P1–Cl1 2.1094(7), P1–O1 1.6054(12), P1–O2 1.6060(13), O1–C1 1.480(2), O2–C2 1.4525(19), C1–C2 1.570(2), C1–C3 1.519(2), C1–C9 1.532(2), C2–C15 1.499(2), C3–C4 1.385(2), C3–C8 1.390(2), C4–C5 1.389(3), C5–C6 1.374(3), C6–C7 1.379(3), C7–C8 1.379(3), C9–C10 1.387(2), C9–C14 1.377(3), C10–C11 1.387(3), C11–C12 1.372(3), C12–C13 1.367(3), C13–C14 1.388(2), C15–C16 1.378(3), C15–C20 1.378(3), C16–C17 1.380(3), C17–C18 1.369(4), C18–C19 1.366(4), C19–C20 1.381(3), Cl1–P1–O1 100.82(5), Cl1–P1–O2 99.65(5), O1–P1–O2 95.09(6), P1–O1–C1 114.39(10), P1–O2–C2 110.51(10), O1–C1–C3 107.53(13), O1–C1–C9 105.37(12), C3–C1–C9 112.96(13), O1–C1–C2 103.48(12), C3–C1–C2 111.46(13), C9–C1–C2 115.09(14), O2–C2–C15 109.20(13), O2–C2–C1 104.88(13), C1–C2–C15 117.38(14).

obtained. Its ^{31}P NMR data clearly differ from those of **6a**. Again, a minor product, epimeric at the phosphorus atom, also formed (Scheme 3).

The substantial shift differences in the ^{31}P NMR spectra, which are easily obtained from the reaction mixture, suggest the idea to use enantiomerically pure chlorodioxaphospholanes **2** as a tool for derivatizing chiral alcohols in order to determine their enantiomeric excess. For this purpose, the commercially available secondary alcohols **5a–c** in their



a) measured in CD_3CN

SCHEME 3

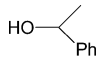
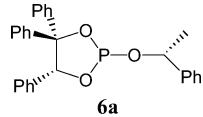
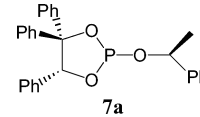
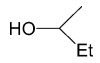
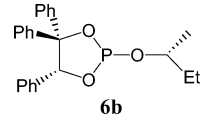
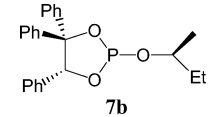
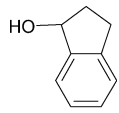
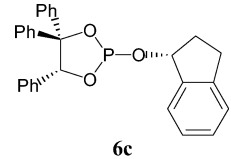
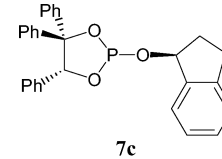
racemic as well as enantiomerically pure form were treated with a solution of **2** in the presence of triethylamine, and the ^{31}P NMR spectra of the products **6** and/or **7** were measured directly from the reaction mixture. The chemical shifts of the ^{31}P resonances are given in Table I for the major and the minor epimer at the phosphorus atom. Except for the phosphites **6b/7b** derived from 2-butanol (**5b**), not only the major epimers but also the minor ones showed sufficiently large shift differences. Their formation is not necessarily a drawback inasmuch as its ^{31}P MNR signals serve as an additional probe to determine the enantiomeric excess of the alcohol. The derivatization of racemic carbinols **5** clearly indicates that no kinetic resolution has occurred upon reaction with chlorodioxaphospholane **2**.

In summary, the triphenylglycol motif, frequently applied as an auxiliary group in asymmetric synthesis,[15] is now used to generate chlorodioxaphospholane **2**, which forms in a diastereoselective manner. The chlorophosphite **2** readily reacts with chiral secondary alcohols and permits determination of their optical purity by simply taking the ^{31}P NMR spectra of the reaction mixture.

EXPERIMENTAL

Specific rotations were determined with a Perkin-Elmer 341 polarimeter. NMR spectra were determined using a Bruker DRX 200 and DRX 500. Toluene was distilled from sodium wire under nitrogen and was taken from the receiving flask with syringes. Triethylamine was

TABLE I ^{31}P Chemical Shifts[a] of Phosphites 6/7 Obtained from Alcohols 5 with Chlorodioxaphospholane 2

Enantiomer of **2**	Chiral Alcohol **5**	Phosponites **6/7** ^{31}P Chemical Shifts	
(R_C,S_P)-**2**	 **5a**	 **6a** δ_{31p} = 136.8 (major) δ_{31p} = 150.9 (minor)	 **7a** δ_{31p} = 138.2 (major) δ_{31p} = 150.5 (minor)
(R_C,S_P)-**2**	 **5b**	 **6b** δ_{31p} = 138.3 (major) δ_{31p} = 150.3 (minor)	 **7b** δ_{31p} = 137.3 (major) δ_{31p} = 150.3 (minor)
(S_C,R_P)-**2**	 **5c**	 **6c** δ_{31p} = 139.1 (major) δ_{31p} = 150.1 (minor)	 **7c** δ_{31p} = 138.1 (major) δ_{31p} = 150.8 (minor)

[a] ^{31}P{^{1}H}NMR-data, measured in toluene.

refluxed over CaH_2 for several hours and distilled under nitrogen. The receiving flask was closed thereafter with a septum and rinsed with nitrogen. All reactions were carried out under an atmosphere of anhydrous argon. Reaction temperatures below 0°C were monitored by a thermocouple connected to a resistance thermometer (Ebro).

(*2R,5S*)-2-Chloro-4,4,5-triphenyl-1,3,2-dioxaphospholane (2)

A 250-mL flask was equipped with a stirring bar, and a connection to a combined argon/vacuum line and was closed with a septum. The air in the flask was replaced by argon, PCl_3 (1.53 mL, 17.5 mmol) and triethylamine (4.86 mL, 34.9 mmol) were injected by syringes, and the mixture was cooled to –78°C. Triphenylglycol (*S*)-**3** (5.08 g, 17.5 mmol) was suspended in toluene (100 mL) under argon and added through

a cannula under stirring at such a rate that the temperature did not exceed −60°C. The mixture was slowly warmed up to room temperature and stirred for 60 h. The precipitate that formed during the reaction was removed by filtration through a frit under argon. The residue was rinsed twice with toluene (10 mL each time). The combined filtrates were concentrated under reduced pressure at room temperature. In the course of this, crystalline (*2R,5S*)-**2** formed gradually and was used for single crystal X-ray diffraction. $[\alpha]^{D}_{25} = +123.6$ (*c* 3.9 in toluene);^{1}H NMR (C_6D_6, 200 MHz): $\delta = 6.69$ (d, $J = 1.7$ Hz, 1H, 5-H), 6.87–7.08 (m, 9H), 7.12–7.31 (m, 4H), 7.76–7.83 (m, 2H) (arom-H). ^{31}P NMR (C_6D_6, 81 MHz): $\delta = 168$ (broad s). ^{13}C{^{1}H} NMR (C_6D_6, 125 MHz): $\delta = 85.5$ (d, $J = 7.0$ Hz, C-5), 92.5 (d, $J = 7.1$ Hz, C-4), 126.3–127.6 (C_{arom}), 133.2 (d, $J = 5.7$ Hz), 138.2 (d, $J = 2.5$ Hz), 140.5 (s, C-*i*).

Crystal Structure Determination of (*2R,5S*)-2

A well-shaped crystal of the compound was selected by means of an optical microscope, sealed in a thin-walled glass capillary (Hilgenberg GmbH, Germany). Data collection was performed at –40°C on an STOE IPDS diffractometer, using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). Unit cell parameters were determined by least-squares refinement on the positions of 8000 strong reflections, distributed equally in reciprocal space in the range $2.05° < \Theta < 25.95°$. An orthorhombic lattice was found, and by inspection of the systematic extinctions space group, $P2_12_12_1$ was uniquely determined. Crystal data, as well as details of data collection and structure refinement, are listed in Table II. LP corrections were applied to the collected data, and the structure was solved by direct methods[16] and subsequent Fourier syntheses. Approximate positions of all hydrogen atoms were found via difference Fourier syntheses. Refinement by full-matrix least-squares calculations on F^2 [17] converged (max. shift/esd: 0.000) to the final indicators given in Table II. Refined parameters include anisotropic displacement parameters for all the atoms heavier than hydrogen. The H atoms were treated as riding on their parent carbon atoms in idealized positions. Isotropic displacement parameters were kept equal to 120% of the equivalent isotropic displacement parameters of the parent carbon atom. The refined Flack parameter (–0.01(6)) clearly indicated the choice of the correct enantiomorph. Scattering factors, dispersion corrections, and absorption coefficients were taken from International Tables for Crystallography (1992, Vol. C, Tables 6.114, 4.268, and 4.2.4.2). Crystallographic data (excluding structure factors) for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no.

TABLE II Crystal Data, X-Ray Measurement, and Structure Determination Summary for Compound (*2R,5S*)-2

Empirical formula	$C_{20}H_{16}ClO_2P$
Formula weight	354.75
Crystal color; habit	colorless, prism
Crystal size (mm^3)	$0.38 \times 0.22 \times 0.18$
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 9.4185(5)$ Å
	$b = 9.7205(6)$ Å
	$c = 18.7925(10)$ Å
Volume ($Å^3$)	1720.50(17)
Z	4
Density (calcd.; $g \cdot cm^{-3}$)	1.370
Temperature (K)	233(2)
Diffractometer	STOE IPDS
Wavelength (Å)	Mo-K_α, $\lambda = 0.71073$
Absorption coefficient (mm^{-1})	0.324
$F(000)$	736
Data collection mode	ϕ-scans
θ Range (°)	$2.17 \leq \theta \leq 25.96$
Index ranges	$-11 \leq h \leq 11$;
	$-11 \leq k \leq 11$;
	$-23 \leq l \leq 23$
Reflections collected/unique	24638/3359;
	($R_{int} = 0.044$)
Observed reflections [$I > 2\sigma(I)$]	3064
Data/parameters	3359/217
Goodness of fit on F^2	0.998
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.026$;
	$wR_2 = 0.059$
R indices (all data)	$R_1 = 0.029$;
	$wR_2 = 0.060$
Largest diff. peak/hole ($e \cdot Å^{-3}$)	0.214/−0.153

CCDC 666785. Copies of the data can be obtained free of charge upon application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: int. +1223/336–033; E-mail: teched@chemcrys.cam.ac.uk) or via the Internet at http://www.ccdc.cam.ac.uk.

Preparation of a Stock Solution of 2 and Derivatization of Chiral Alcohols

As described above, to a solution of PCl_3 (1.6 mL, 18.34 mmol) and triethylamine (5.0 mL, 35.87 mmol), a suspension of (*S*)-**3** (4.99 g, 17.19

mmol) in toluene was added through a thick cannula at –78°C within 45 min. The flask containing the diol (*S*)-**3** was thereafter rinsed twice with toluene (15 mL each time), and both portions were added. The mixture stirred under argon was allowed to reach room temperature overnight and was stirred for 48 h. The precipitate was removed by suction filtration under argon and washed with toluene (20 mL). The combined filtrates were concentrated under reduced pressure at room temperature. To the residue, 100 mL of toluene were added. By means of a cannula, 40 mL of this solution was transferred into a second flask under argon. A slight white solid material on the bottom of the first flask must not be transferred. The clear solution was again concentrated at room temperature under reduced pressure and the residue thus obtained was dissolved in 50 mL of toluene so that a clear colorless solution formed that contained **2** (6.87 mmol); 0.137 M solution. In order to determine the enantiomeric excess, the corresponding secondary alcohol (1.0 mmol) was dissolved in toluene (2 mL) and added to a mixture of the stock solution of **2** (5 mL, 0.69 mmol) and triethylamine (0.5 mL, 3.59 mmol) at room temperature. The sample was filtrated under argon through a syringe filter and subjected to ^{31}P NMR spectroscopy. When the derivatization is performed at lower temperatures, the products, which are diastereomeric at the phosphorus center, form in a different ratio.

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