JOC Notes

2-Chloro-(4*R*,5*R*)-bis[(1*R*,2*S*,5*R*)-menth-1-yloxycarbonyl)]-1,3,2-dioxaphospholane: A Practical Chiral Pool-Derived Reagent for Determining Enantiomeric Purity of Alcohols

Matthias Amberg, Uwe Bergsträsser, Georg Stapf, and Jens Hartung*

Fachbereich Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Strasse, D-67663 Kaiserslautern, Germany

hartung@chemie.uni-kl.de

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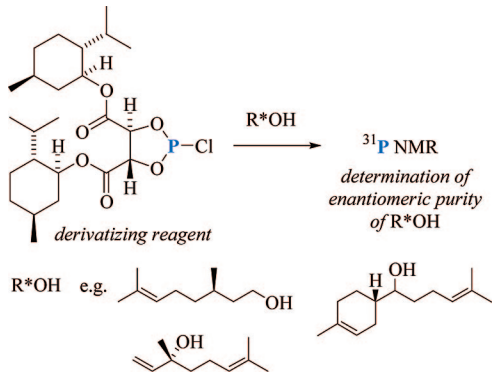

2-Chloro-(4*R*,5*R*)-bis[(1*R*,2*S*,5*R*)-menth-1-yloxycarbonyl)]-1,3,2-dioxaphospholane is a practical reagent for reliably determining enantiomeric purity of chiral alcohols via ^{31}P NMR spectroscopy. The compound is available as a crystalline solid on a 20 g scale from PCl_3 and bis[(1*R*,2*S*,5*R*)-menth-1-yl] tartrate. It is comparatively inert toward spontaneous hydrolysis under conventional laboratory conditions but undergoes quantitative substitution of alkoxide for chloride if treated with a chiral alcohol. Nonequivalent ^{31}P NMR signals of diastereomeric 2-alkoxy-1,3,2-dioxophospholanes were dispersed by ~1.4–0.1 ppm. The associated integral ratios reflected enantiomeric purities of preweighted samples of (*R*)- and (*S*)-1-phenylethanol, (+)- and (−)-menthol, and a set of primary, secondary, and tertiary alcohols with a precision of ±0.4–1.0%.

The concept of investigating enantiomeric purity of chiral alcohols in isotropic media by ^{31}P NMR was introduced by Anderson and Shapiro in 1984.[1–4] It is based on diastereomer formation from enantiomerically pure phosphorus reagents. The responsivity of the ^{31}P nucleus and the advent of high-field NMR spectrometer in most instances allows to detect nonequivalent resonances obtained from derivatizations as baseline-separated signals.[5]

Stereochemical information on phosphorus-based derivatizing reagents may, in principle, originate from substitution at the heteroatom or an inert chiral ligand attached to it. For reasons of simplicity, the use of C_n-symmetric auxiliaries ($n = 2$) is favored. It eliminates the necessity of the phosphorus atom to become a stereogenic center, which simplifies reagent preparation and mechanistic interpretation of ^{31}P NMR data.[6] In view of these arguments, it comes as no surprise that a number of chiral dioxaphospholanes and diazaphospholidines have been developed over the past decade.[1,7–11] Their potential to serve as tools in analytical chemistry has been documented in original reports and reviews.[6,12] A critical survey of the literature, however, indicates that the odds of this strategy frequently are counterbalanced by technical issues, such as an inherent hydrolytic lability of structurally simpler derivatizing reagents,[8,9] or more demanding syntheses in terms of efforts and/or cost of the more complex structures.[1,10]

Although techniques to exclude moisture from preparations nowadays are state of the art in organic synthesis, the propensity to undergo hydrolytic modifications probably is the most important drawback of chiral 2-chloro-1,3,2-dioxaphospholanes to serve as more widespread reagents in stereochemical analysis. In view of this background, we became interested in developing a low-cost crystalline phosphorus-based derivatizing reagent starting from chiral pool-derived building blocks. The major result of the present study indicates that a compound prepared from (*R*,*R*)-tartaric acid, (1*R*,2*S*,5*R*)-menthol, and PCl_3 fulfilled the given outline. The compound was available on a 20 g scale

* To whom correspondence should be addressed. Fax: +49 (0)631/205 3921.

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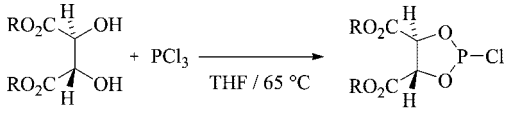
TABLE 1. Preparation of Chiral 2-Chloro-1,3,2-dioxaphospholanes 5–8



1–4 **5–8**

entry	1–8	R	yield of 5–8 (%)	δ ^{31}P NMR[a]
1	**1**, **5**	C_2H_5	92	176.1
2	**2**, **6**	$C_6H_5CH_2$	87	175.4
3	**3**, **7**	cC_6H_{11}	84	175.8
4	**4**, **8**	(1*R*,2*S*,5*R*)-menth-1-yl	86	175.6

[a] Referenced versus 85% (w/w) aqueous H_3PO_4 in a sealed ampule as internal standard.

as a colorless crystalline solid. It showed no apparent kinetic resolution in standard manipulations performed prior to ^{31}P NMR analysis and was largely inert toward moisture. Its synthesis and utility for determining enantiomeric purity of chiral alcohols are reported in the following sections.

Preparation of 2-Chloro-1,3,2-dioxaphospholanes. Four 2-chloro-1,3,2-dioxophospholanes were prepared from PCl_3 and dialkyltartrates **1**–**4**. Diethyl (*R*,*R*)-tartrate (**1**) was commercially available. Dialkyl (*R*,*R*)-tartrates **2**–**4** were prepared in extension to literature procedures[13–16] upon treatment of (*R*,*R*)-tartaric acid (<95% purity) with the corresponding alcohol in hot toluene using *p*-toluene sulfonic acid monohydrate as catalyst. The use of TsOH instead of MsOH as catalyst and hot toluene as solvent constituted useful modifications for increasing the reported yield of bis[(1*R*,2*S*,5*R*)-menth-1-yl] tartrate **4** from 33 to 74%. Esterification was performed on a ~50 g scale to furnish upon recrystallization analytically pure **4** as colorless needles. The yields of esters **2** (82%) and **3** (84%) closely followed the information provided in the original reports,[13–15] although some published procedures relied on alternative acids for catalyzing esterification of tartaric acid [e.g., $B(OH)_3$ for **2**].

The synthesis of 2-chloro-1,3,2-dioxaphospholanes **5**–**8** (Table 1) was preferentially performed in refluxing THF using a 7–8-fold excess of PCl_3 in order to ensure selective monoadduct formation with the tartaric acid ester. We refrained from applying a base in order to reduce the amount of required PCl_3 for the following reasons. (i) An excess of PCl_3 was recovered by distillation. Its purity was sufficiently high for preparation of a further batch of reagent **8**. (ii) The use of, for example, NEt_3 as auxiliary base was inevitably associated with salt formation. Removal of triethylammonium hydrochloride by filtration posed a time-consuming process, which was associated with a considerable drop in yields of heterocycles **5**–**8**. We therefore refrained from further pursuing this strategy. (iii) The efficiency for the preparation of **5** using an excess of PCl_3 exceeded that of the original protocol[7] using an equimolar amount of phosphorus reagent and diethyl tartrate in the presence of $PhNEt_2$ (compare 87 to 56%).[17]

Chlorodioxaphospholanes **5**–**8** were purified via distillation (**5**)[7] or low-temperature crystallization from petroleum ether

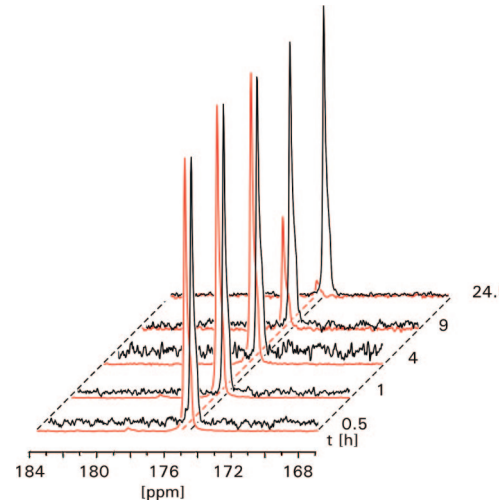
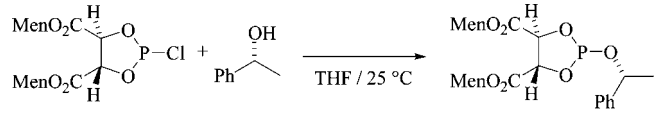


FIGURE 1. Monitoring relative signal intensity (^{31}P NMR, 162.0 MHz, $CDCl_3$) of chlorodioxaphospholane **5** (red line) and **8** (black line), upon exposure of neat samples to laboratory atmosphere (~50–80% relative humidity, ~20–25 °C).

SCHEME 1. Formation of 1-Phenylethoxy-1,3,2-dioxaphospholane (*R*)-(10a) [Men = (1*R*,2*S*,5*R*)-menth-1-yl)]



8 (*R*)-**9a** (*R*)-**10a** (95 %)

(**6**–**8**). Compounds **6** and **7** melted upon warming to room temperature, whereas menthol deriviative **8** (mp 72 °C) remained a colorless crystalline solid. It was air-stable for months if stored at 20 °C in a stop-cocked round-bottomed flask without the necessity of excluding moisture.

Reactivity of 2-Chloro-1,3,2-dioxaphospholanes. The stability of phosphorus reagents **5**–**8** upon exposure to laboratory atmosphere (~50–80% relative humidity, ~20–25 °C) increased along the sequence of ester substituents $C_2H_5 \ll C_6H_5CH_2 < c\text{-}C_6H_{11} \sim$ (1*R*,2*S*,5*R*)-menth-1-yl (for **5** and **8**, see Figure 1). Diethyl derivative **5** was almost completely decomposed within 24.5 h, as evident from a gradual decrease of its ^{31}P NMR resonance at 176.1 ppm. Di-*O*-benzyl derivative **6** showed a qualitatively comparable but less extensive deterioration if exposed as neat a sample to atmosphere. Its ^{31}P NMR signal at 175.4 ppm decreased to approximately a third of its original intensity after 24.5 h. In the same time, new signals appeared at δ = 22.3, 18.1, 15.3, 9.6, 4.4, and −20.8. Similar signs of chlorodioxaphospholane modification were not evident from ^{31}P NMR spectra of dicyclohexyl ester **7** and dimenthyl derivative **8** over a period of 24 h.

In view of its aparent stability and convenience in handling, all succeeding experiments were restricted to the use of menthyl-substituted 2-chloro-1,3,2-dioxaphospholane **8** as derivatizing reagent. The compound was preferentially applied in a 0.2 M solution of anhydrous THF that was stored in an atmosphere of dry nitrogen. A typical batch was consumed within 14 days. No signs of deterioration or loss in efficiency of the reagent were encountered within this time span (^{31}P NMR).

Aliquots of (*R*)-α-phenylethanol (*R*)-**9a**, chlorodioxaphospholane **8**, and NEt_3 in THF furnished mixed diester (*R*)-**10a** in 95% yield (^{31}P and ^{1}H NMR) as a colorless solid (Scheme 1

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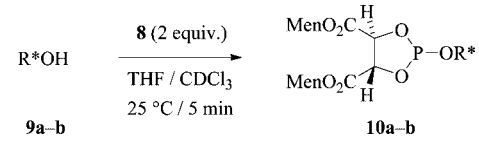
TABLE 2. Reproducing Enantiomeric Ratios of Chiral Secondary Alcohols 9a–b via ^{31}P NMR Analysis of Derived Alkoxydioxaphospholanes 10a,b[a]



9a–b **10a–b**

entry	**9/10**	er[b]	dr[c]
1	**a**	95.1: 4.9	95.4: 4.6
2	**a**	71.0: 29.0	70.4: 29.6
3	**a**	47.0: 53.0	47.1: 52.9
4	**a**	29.4: 70.6	29.5: 70.5
5	**a**	4.9: 95.1	5.0: 95.0
6	**b**	94.7: 5.3	94.9: 5.1
7	**b**	69.4: 30.6	68.6: 31.4
8	**b**	50.0: 50.0	50.4: 49.6
9	**b**	29.9: 70.1	29.6: 70.4
10	**b**	5.0: 95.0	5.4: 94.6

[a] Men = (1*R*,2*S*,5*R*)-menth-1-yl; R* = 1-phenyleth-1-yl for **9a** and **10a** and R* = menth-1-yl for **9b** and **10b**. [b] Refers to ratios of (*R*)-**9a** versus (*S*)-**9a** and (1*R*,2*S*,5*R*)-**9b** versus (1S*R*,2*R*,5*S*)-**9b**. [c] At 242.9 MHz ^{31}P NMR in $CDCl_3$/THF = 1/2 (v/v), refers to ratios of (*R*)-**10a** versus (*S*)-**10a** and (1*R*,2*S*,5*R*)-**10b** versus (1S*R*,2*R*,5*S*)-**10b**.

and Supporting Information). Attempts to further purify the material by recrystallization resulted in decomposition of the material.

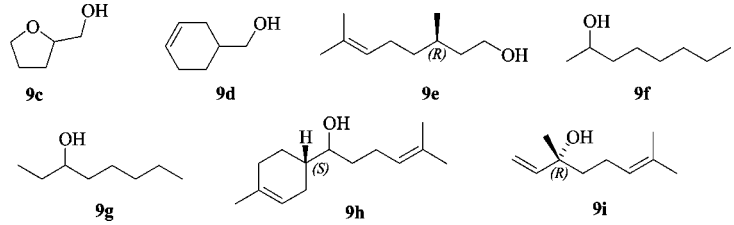
The precision for determining enantiomeric purity of alcohols via ^{31}P NMR was checked by mixing solutions of preweighted samples of (*S*)-**9a** and (*R*)-**9a** in spectroscopic grade $CDCl_3$ with aliquots of NEt_3 and **8** in THF directly in an NMR tube (Supporting Information). The sample was agitated for approximately 5 min (20 °C). A ^{31}P NMR spectrum (162.0 MHz) recorded from the mixture showed baseline-separated resonances at 145.5 [(*R*)-**10a**] and 144.1 ppm [(*S*)-**10a**]. In a similar way, preweighted samples of (*S*)-**9a** and (*R*)-**9a** were treated with (i) aliquots of NEt_3 and **8** (Supporting Information) or (ii) 2 equiv of **8** in the absence of NEt_3 (Table 2). A gradual increase of (*S*)-**9a** from 4.9 to 95.1% was reproduced within an an error range of ±0.4 on the basis of relative ^{31}P NMR signal intensities of (*R*)-**10a**/(*S*)-**10a** (Table 2, entries 1–5, and Supporting Information).

Menthol **9b** was quantitatively converted into **10b** upon treatment with a 2-fold excess of **8** in the absence of NEt_3, as determined by ^{31}P NMR using triphenylphosphine oxide as internal standard (δ = 27.2). Mixed esters of (1*R*,2*S*,5*R*)-**10b** (146.9 ppm) and (1*S*,2*R*,5*S*)-**10b** (146.6 ppm) were characterized by baseline-separated ^{31}P NMR resonances (242.9 MHz). Ratios of (1*R*,2*S*,5*R*)-**9b**/(1*S*,2*R*,5*S*)-**9b** ranging from 94.7/5.3 to 5.0/95.0 were reproduced by relative signal intensities of (1*R*,2*S*,5*R*)-**10b**/(1*S*,2*R*,5*S*)-**10b** within a precision of ±0.4% (Table 2, entries 6–10). An increase in reaction temperature from 20 to 40 °C was found to accelerate alcohol derivatization in instances where NEt_3 served as an auxiliary base. The temperature effect was related to a reaction between alcohol **10b** and an adduct (δ ^{31}P = 132.3; not shown) that is formed from of reagent **8** and NEt_3.

For expanding the scope of the procedure, racemates of primary alcohols having a stereogenic center located in β-(**9c**,**d**) or in γ-position (**9e**), secondary aliphatic alcohols (**9f**–**h**), or a tertiary alcohol (**9i**) in solutions of $CHCl_3$ were derivatized upon treatment with chloro-1,3,2-dioxaphospholane **8** and NEt_3 in THF to furnish solutions that were investigated by ^{31}P NMR spectroscopy (Table 3, entries 1–3, 5, and 7–9). This information was supplemented by data from experiments using enantiomerically enriched samples of citronellol **9e** (Table 3, entry 4) and 2-octanol **9f** (Table 3, entry 6). Diastereomeric 2-alkoxydioxaphospholanes obtained from this set of experiments showed ^{31}P NMR shift dispersions ranging between 0.1 to 0.4 ppm. Baseline separation was attainable in the latter but not in the former instances (Table 3). We therefore refrained from oxidizing phosphorus(III) compounds **10** to phosphorus(V) derivatives (not shown) for obtaining additional analytical information.[1,7,8] Enantiomeric ratios of the alcohols were reproduced in all instances within satisfactory error ranges [±0.3% (**9e**,**h**), ±0.4% (**9i**), ±0.5% (**9g**), ±0.6% (**9d**) to ±1.0 (**9f**)].

In conclusion, 2-chloro-(4*R*,5*R*)-bis[(1*R*,2*S*,5*R*)-menth-1-yloxycarbonyl)]-1,3,2-dioxaphospholane (**8**) is a C_2-symmetric, air-stable reagent, which was prepared on a 20 g scale. The compound **8** was applied to quantitatively convert racemic or enantiomerically enriched (e.g., er = 95:5) chiral alcohols in a

TABLE 3. Reproducing Enantiomeric Ratios of Selected Chiral Primary, Secondary, and Tertiary Alcohols 9c–i via ^{31}P NMR of Derived Dioxaphospholanes (not shown)



entry	**9–10**	er[a]	dr [^{31}P NMR][b]	δ ^{31}P[c]	$\Delta\delta$
1	**c**	50: 50	49.2: 50.8	145.1/144.9	0.2
2	**d**	50: 50	49.4: 50.6	143.9/143.8	0.1
3	**e**	50: 50	50.8: 49.2	143.9/143.7	0.2
4	**e**	90.3: 9.7	89.7: 10.3	*143.9*/143.7	0.2
5	**f**	50: 50	48.2: 51.8	144.9/144.7	0.2
6	**f**	90.2: 9.8	89.2: 10.8	*144.9*/144.7	0.2
7	**g**	50: 50	50.5: 49.5	145.5/145.3	0.2
8	**h**	50: 50	49.7: 50.3	143.7/143.6	0.1
9	**i**	50: 50	49.6: 50.4	143.6/143.5	0.1

[a] Refers to (*S*)-**9c–g**/(*R*)-**9c–g**, (*S*,*S*)-**9h**/(*R*,*S*)-**9h**, (*S*)-**9h**,**i**/(*R*)-**9h**,**i**. [b] Dioxaphospholanes **10**. [c] ^{31}P NMR (242.9 MHz) in $CDCl_3$/THF [1/2 (v/v)]; major signals are in italics.

solution of 1/2 (v/v) $CDCl_3$/THF to furnish diastereomeric 2-alkoxy-1,3,2-dioxaphospholanes. Reactions were complete within a few minutes without using specialized equipment for excluding air or moisture. Enantiomeric purity of chiral alcohols was reproduced with a precision of ±0.4% if baseline separation of nonequivalent ^{31}P NMR signals was attainable. The reagent was applicable for determining enantiomeric ratios of primary, secondary, and tertiary alcohols. Observed $\Delta\delta$ ^{31}P values decreased, as the distance between the stereogenic center and the hydroxyl group increased or differences in steric sizes of substituents attached to a secondary or tertiary stereocenters became small. The performance of reagent **8** for analyzing chiral carboxylic acids, amines, and/or thiols poses a straightforward extension to the present report, which is being extensively pursued at the moment in this laboratory.

Experimental Section

Instrumentation and general remarks have been disclosed previously[18] (see also Supporting Information).

(*R*,*R*)-Bis[(1*R*,2*S*,5*R*)-menth-1-yl] tartrate (4). A solution of (*R*,*R*)-tartaric acid (24.9 g, 166 mmol), (1*R*,2*S*,5*R*)-menthol (1*R*,2*S*,5*R*)-**9b** (64.9 g, 415 mmol), $TsOH \cdot H_2O$ (4.83 g, 25.4 mmol), and toluene (260 mL) was refluxed for 20 h with the reaction water being azeotropically removed. The mixture was washed with 5% $NaHCO_3$ (2 × 90 mL), brine (2 × 90 mL), and H_2O (2 × 90 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The excess of alcohol (1*R*,2*S*,5*R*)-**9b** was distilled off (65 °C, 60 mbar) to afford an oil that was dissolved in hexane (90 mL) at 70 °C. The solution was kept at –20 °C. The solids that precipitated were collected by filtration and washed with cold hexane (−20 °C) to afford 52.5 g (123 mmol, 74%) of **4** as colorless needles.

2-Chloro-(4*R*,5*R*)-bis[(1*R*,2*S*,5*R*)-menth-1-yloxycarbonyl)]-1,3,2-dioxaphospholane (8). A solution of dialkyl tartrate **4** (6.29 g, 14.8 mmol) in anhydrous THF (10 mL) was added to a solution of PCl_3 (115 mmol) in dry THF (10 mL). The solution was stirred for 1 h at 65 °C and hereafter concentrated under reduced pressure. The residual oil was dissolved in a minimum volume of petroleum ether and kept at −20 °C. The crop of crystals that separated from the solution was collected and dried to furnish 6.19 g (86%) of compound **8** as colorless solid: mp 71.8–72 °C; ^{31}P NMR (162 MHz, C_6D_6) δ 175.6; ^1H NMR (600 MHz, C_6D_6) δ 5.71 (d, 1H, J = 7.0 Hz), 5.08 (dd, 1H, $J_{H,P}$ = 8.6 Hz, $J_{H,H}$ = 7.1 Hz), 4.95 (dt, 1H, J_d = 4.4 Hz, J_t = 10.6 Hz), 4.86 (dt, 1H, J_d = 4.4 Hz, J_t = 10.9 Hz), 1.98 (m, 4H), 1.37 (m, 7H), 1.07 (m, 3H), 0.90 (m, 2H), 0.84 (dd, 6H, J = 7.0, 3.0 Hz), 0.79 (d, 3H, J = 7.0 Hz), 0.76 (d, 3H, J = 7.0 Hz), 0.72 (dd, 6H, J = 6.4, 4.2 Hz), 0.59 (m, 2H); ^{13}C NMR (150 MHz, C_6D_6) δ 167.1, 166.7 (d, $J_{P,C}$ = 5.3 Hz), 78.9 (d, $J_{P,C}$ = 9.1 Hz), 77.7 (d, $J_{P,C}$ = 8.9 Hz), 77.0 (d, $J_{P,C}$ = 6.9 Hz), 47.0 (d, $J_{P,C}$ = 18.2 Hz), 40.6 (d, $J_{P,C}$ = 12.6 Hz), 34.1 (d, $J_{P,C}$ = 7.1 Hz), 31.3 (d, $J_{P,C}$ = 2.6 Hz), 26.5 (d, $J_{P,C}$ = 14.9 Hz), 23.4 (d, $J_{P,C}$ = 7.9 Hz), 21.9, 20.8. Anal. Calcd for $C_{24}H_{40}ClO_6P$ (491 g/mol): C, 58.71; H, 8.21. Found: C, 58.55; H, 8.26.

Derivatization of Chiral Alcohols: General Procedure. Solutions of compound **8** (250 μL of a 0.2 M solution in THF) and NEt_3 (250 μL of a 0.2 M solution in THF) are added to a solution of alcohol **9** (0.05 mmol) in $CDCl_3$ (250 μL) in an NMR tube. The tube is stop-cocked, shaken for 5 min, and subjected to a ^{31}P NMR experiment.

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Supporting Information Available: Experimental procedures for the synthesis of 2-chloro-1,3,2-dioxaphospholanes **6** and **7**, spectral data of compound **4**, **8**, and (*R*)-**10a**, results from derivatization of preweighted mixtures of enantiomers of **9a**,**b**, and ^{31}P NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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