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Menthyldichlorophosphate: A Chiral Derivatizing Agent for Symmetrical Diols

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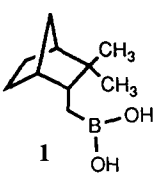
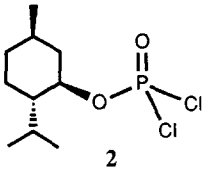
Abstract: Menthyldichlorophosphate reacts readily with a variety of C_2-chiral and meso diols to yield phosphate esters that exhibit useful diastereomeric differences in the ^{31}P NMR spectra. Meso and d,l diols are easily differentiated with this reagent. © 1997 Elsevier Science Ltd.

The need to determine enantiomeric purities of alcohols occurs frequently in synthesis. Direct chromatographic analyses by GC or HPLC on chiral stationary phases are ideal;[1] however, this approach is still of limited generality. Thus, chiral derivatizing reagents continue to serve an important function. Although there are many (perhaps dozens) of chiral derivatizing agents reported for alcohols,[2] there have been practically no such reagents designed specifically for diols. Typically, the conversion of diols to diastereomeric derivatives for optical purity analyses is simply an extension of procedures used for mono-alcohols, e.g., a diol might be treated with two equivalents of an esterification reagent to produce a diester. The disadvantages of this approach are (a) two equivalents of a possibly expensive esterification reagent are required; (b) for the diastereomer ratio to accurately reflect the original enantiomer ratio, it is necessary to ascertain that both hydroxyl groups are fully reacted; (c) any lack of enantiomeric purity in the derivatizing reagent leads to the formation of two unwanted diastereomers; (d) diesters of diols tend to be rather large molecules and generally not volatile enough for GC analyses, the highest-resolution analytical method available. The advent of the Sharpless asymmetric dihydroxylation[3] has increased the need for a more convenient and efficient chiral derivatizing agent for diols.

An ideal chiral derivatizing agent for diols would possess a single functional group capable of reacting with both diol hydroxyl groups. In addition, it should be enantiomerically pure, easily accessible, and the resulting diastereomers should be easily analyzed by chromatography (GC or HPLC) and/or by NMR. One attempt at such a reagent is the boronic acid **1**;[4] however, the resulting diastereomers were apparently amenable only to ^{13}C NMR analysis, a low-sensitivity technique not well-suited to quantitation.



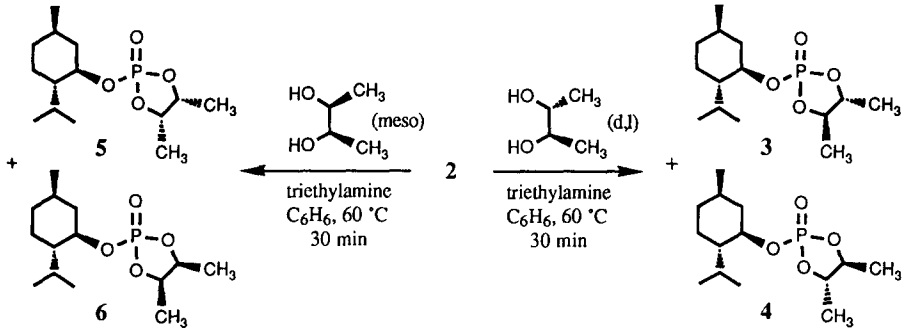
1



2

We chose to study menthyldichlorophosphate (**2**) because this reagent could react with both diol hydroxyl groups and because (-)-menthol is an inexpensive enantiomerically pure material. Compound **2** has been reported,[5a] but has not been studied as a chiral derivatizing agent. It is easily prepared[5] on a multigram scale by reaction of (-)-menthol with phosphorus oxychloride and triethylamine, and is readily purified by vacuum distillation. In $CDCl_3$ solution, the ^{31}P NMR spectrum of **2** exhibits a doublet ($^3J_{PH}$ = 9.3) at 7.5 ppm (vs. H_3PO_4) due to a coupling to the C1 proton of the menthyl group; however, proton-decoupling results in a singlet. Contrary to the original report,[5a] the undistilled material did contain a small amount of dimenthylchlorophosphate (3.9 ppm, t, J = 8.5), but this was easily removed in the purification.

Reagent **2** reacts readily[6] with symmetrical 1,2-diols to yield diastereomeric phosphate esters, as shown below for the d,l and meso 2,3-butanediols. The products could be analyzed by ^{31}P NMR without further purification, though the peaks were somewhat narrower and better resolved if the triethylamine hydrochloride precipitate was removed by filtration and/or water workup. The ^{31}P resonances of the diastereomers (**3** and **4**) were separated by 0.16 ppm,[7] which is approximately "baseline resolved". Further, we found that reagent **2** could be used to distinguish between d,l and meso diols: while the reaction of meso diols also produced two products (e.g., **5** and **6**), they exhibited resonances that were (a) more downfield than those of the d,l diols, (b) better separated than those of the d,l diols, and (c) not necessarily formed in equal amounts.

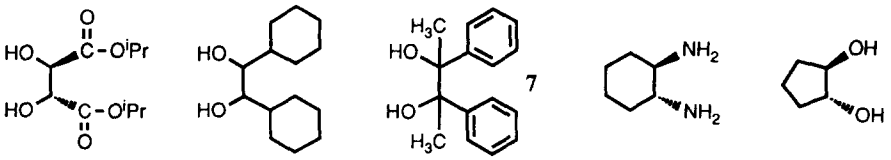


^{31}P NMR: 14.63 and 15.75 ppm

^{31}P NMR: 14.09 and 14.26 ppm

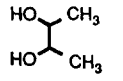
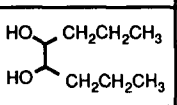
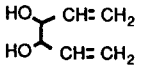
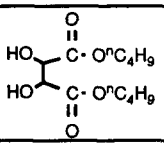
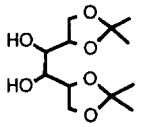
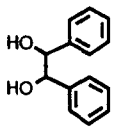
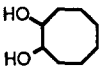
The ^{31}P NMR data (in C_6H_6) for the derivatives of a series of diols (d,l and meso) are given in Table 1. In general, the diastereomeric differences in the ^{31}P spectra are sufficient for the determination of a wide range of enantiomeric purities. In the case of d,l-stilbene diol, the separation is large enough (0.29 ppm) for determination of rather high enantiomeric purities. For example, we were able to confirm that the Sharpless asymmetric dihydroxylation converts *trans*-stilbene into the diol in >99% ee.[8] In several cases (a-c in Table 1) the derivatives were amenable to gas chromatography, which exhibited (on SE-54) a resolution equal to or somewhat better than that observed in the ^{31}P NMR. Much like the ^{31}P NMR spectra, the GC chromatograms always have the derivatives of meso diols at longer retention time and better resolved than the derivatives of d,l diols. The derivatives are easily isolated by column chromatography on silica gel with little or no diastereomeric separation observed. We found that proton and carbon NMR and reverse-phase HPLC (C-18) were not generally useful for enantiomeric purity analyses.

The only 1,3-diols studied, d,l and meso 2,4-pentanediol, yielded derivatives at quite different chemical shift (-3 to -7 ppm) and significantly larger separation in both cases. However, (d,l)-2,4-pentanediol gave some indication of possible non-cyclic phosphate ester formation (four small "doublets" in the range of -12 to -16 ppm). The derivatives of several 1,2-diols and one 1,2-diamine (below) failed to exhibit significant ^{31}P NMR



separation.[9] Also, trans-1,2-cyclopentanediol apparently failed to form a cyclic phosphate ester. This procedure was not useful with non-symmetrical diols (e.g., propylene glycol) because complex and poorly-resolved spectra resulted; this was also the case with 2-amino alcohols.

Table 1: Diastereomeric Differences in ^{31}P NMR Spectra of (-)-menthyldichlorophosphate Derivatives of Various Diols (C_6H_6 solution).

	(-)-menthyldichlorophosphate derivative ^{31}P $\Delta\delta$ [a]			
	d,l-diol		meso diol	
Diol	chemical shifts	separation	chemical shifts	separation
(a) 	14.09, 14.25	0.16	14.63, 15.75	1.12
(b) 			14.72, 15.84	1.12
(c) 	14.11, 14.31	0.20	14.82, 15.77	0.95
(d) 	15.43,15.56	0.13		
(e) 	16.62, 16.73	0.11		
(f) 	13.70, 13.99	0.29	2.02, 15.56	13.54
(g) 	13.96, 14.03	0.07	15.48, 16.55	1.07
(h) 	12.96, 13.03	0.07	12.85, 13.97	1.12
(i) 	-6.15, -6.54	0.49	-3.66, -7.68	4.02

We also briefly evaluated the corresponding dichlorophosphate reagents **8** and **9** (see Table 2) prepared from racemic *trans*-2-phenylcyclohexanol[10] and *trans*-2-(1-naphthyl)cyclohexanol for comparison to the menthyl reagent. These reagents were prepared in a manner identical to that for the (-)-menthyl derivative except that

vacuum distillation was omitted because these dichlorophosphates are less volatile and more susceptible to thermal decomposition. These reagents did give larger $\delta\Delta$ values but were not easily purified nor as inexpensively available in optically pure form as is (-)-menthol. Note that for the menthyl derivatives C_6H_6 solvent (Table 1) gives a better separation for derivatives of the d,l isomers, but that $CDCl_3$ (Table 2) gives a somewhat better separation for the meso derivatives.

Table 2: Diastereomeric Differences in ^{31}P NMR Spectra of Phosphate Ester Derivatives.

Reagent R*O–P(=O)(Cl)–Cl	Diol ^{31}P $\Delta\delta$ (d,l / meso)[a]				
	2,3-butanediol	stilbenediol	1,5-hexadiene-3,4-diol	trans-1,2-cyclo-hexanediol	cyclo-octanediol
R* = menthyl (2)	0.07 / 1.24	0.24 / -	012 / 1.16	0 / 1.14	0.03 / 1.2
= trans-2-phenyl-cyclohexyl (8)	0.26 / 1.76	0.24 / -	0.06 / 1.17	0.31 / 1.42	0.10 / -
= trans-2-(1-naphthyl)-cyclohexyl (9)	0.30 / 1.81	0.25, 0.24[b] / -	0.14 / 0	0.26 / 1.42	0.08, 0.19[b] / -

[a] $CDCl_3$ solvent; [b] apparently separate signals for each of two rotamers.

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REFERENCES AND NOTES

1. Schurig, V. *J. Chromatogr. A* **1994**, *666*, 111-29.
2. For a review of NMR methods, see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441-57.
3. For a review of the Sharpless asymmetric dihydroxylation, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.
4. Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1988**, 6063.
5. a. Cremlyn, R. J. W.; Ellam, R. M.; Akhtar, N *Phosphorus and Sulfur* **1978**, *5*, 1-14. b. We used hexanes as the reaction solvent instead of diethyl ether, which made a second filtration unnecessary. Bulb-to-bulb distillation (0.1 mmHg, ~ 80 °C) provided high purity (> 97% by ^{31}P NMR) product in 74% yield on a 22 mmol scale. This reagent is also known as menthylphosphorodichloridate.
6. Derivatization was accomplished by treating a mixture of the diol (25 mg, 1 equiv.), triethylamine (2.2 equiv.) and benzene (0.8 mL) with menthyldichlorophosphate (1.5 equiv), followed by heating at 60 °C for 30 minutes. Filtration or (preferably) a water workup prior to NMR analysis is recommended.
7. Diastereomers **3** and **4** have been reported in the context of a reagent for alcohol derivatization, with a reported ^{31}P $\delta\Delta$ of 0.14 ppm: Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304-5.
8. Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302-3.
9. Derivatization of the 3° diol **7** required reaction at room temperature for several hours. Heating resulted in decomposition.
10. Schwatz, A.; Madan, P.; Whitesell, J.K.; Lawrence, R.M. *Org. Synth.* **1990**, *69*, 1.

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