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A NEW ^{31}P NMR METHOD FOR THE ENANTIOMERIC EXCESS DETERMINATION OF DIOLS AND SECONDARY DIAMINES WITH C_2 SYMMETRY

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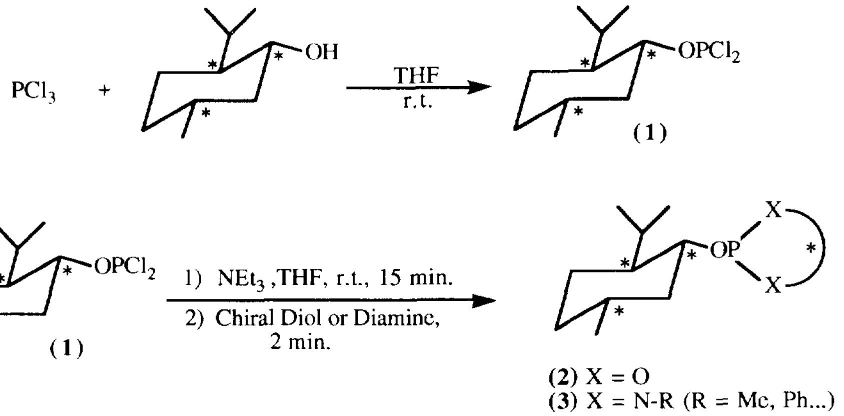
Abstract : A new reagent for the determination of enantiomeric excess of chiral diols and diamines with C_2 symmetry is described. This derivatizing agent easily prepared from PCl_3 and (1*R*,2*S*,5*R*)-(-)-menthol allows an accurate analysis of the diastereomeric derivatives by ^{31}P NMR spectroscopy.

Over the past decade, there has been a great surge of interest in enantioselective synthesis which has led to an increased demand for accurate, reliable and convenient methods of measuring enantiomeric purity[1]. Thus, the increasing use of enantiomerically pure diols and diamines possessing a C_2 axis of symmetry, as chiral building blocks or chiral ligands in numerous asymmetric synthesis, demands new methodologies for the enantiomeric excess (ee) determination[2,3]. Indeed, the enantiomeric purity of these compounds is routinely measured by gas or liquid chromatography through the use of chiral stationnary phases[4]. Enantiomeric excess determination by ^{1}H NMR spectroscopy of some 1,2 and 1,3 diols can be performed using chiral lanthanide shift reagents due to the nonequivalence of enantiotopic hydroxyl groups resonances[5]. ^{31}P NMR spectroscopy provides the most convenient method for determining the enantiomeric purity of chiral phophorus compounds because the chemical shift dispersion is usually large and spectra are simple when broad band proton decoupling is applied[6]. Although several chiral phosphoryl or thiophosphoryl chlorides have been examined as chiral derivatizing agents for alcohols and amines[7], no method has been developed for the ee determination of diols and diamines.

We wish to report now the first, simple and very efficient ^{31}P NMR method for the determination of the ee of various chiral diols and diamines possessing a C_2 axis of symmetry which is based on the use of (-)-dichloromenthylphosphine **1** as new chiral derivatizing agent.

1 is quantitatively prepared by reaction of PCl_3 with (1*R*,2*S*,5*R*)-(-)-menthol in THF at room temperature (Scheme 1). This reagent is stable for weeks under an inert atmosphere but is very sensitive to moisture. For this reason, **1** may be conveniently stored as *ca.* 2 M solutions in THF under nitrogen and samples taken by syringe when needed. All of the diols (or secondary diamines) examined react with **1** quantitatively in a few minutes at room temperature in the presence of 3 equivalents of NEt_3, providing the corresponding compounds **2** (respectively **3**)[8].



Scheme 1

Analysis of the diastereomeric derivatives is performed by ^{31}P NMR spectroscopy and the results obtained with different diols or diamines are summarized in Table I.

Due to the C_2 symmetry of the chiral diol, a single diastereomer is obtained after derivatization of the enantiomerically pure compound. Using a mixture of the racemic diol or diamine, the ^{31}P NMR spectra show two well separated singlets corresponding to the two diastereomers and in some cases (entries 1, 2 and 3) another signal corresponding to the meso compound. The enantiomeric purity can be accurately measured and no kinetic resolution has been observed. Thus, integration of the two signals for the racemic mixtures always corresponds to 50:50 (± 2%).

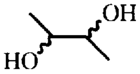
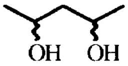
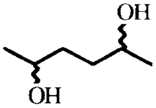
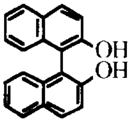
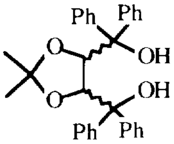
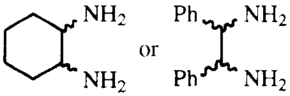
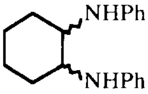
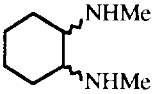
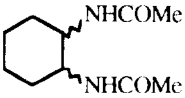
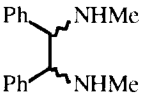
All diols displayed in entries 1-5 are easily analyzed through their derivatives. Primary diamines represent the most difficult case, leading to various products during the derivatization and no exploitable results. On the other hand, secondary diamines reacted quantitatively with **1** and the enantiomeric purity of these compounds can be accurately measured. Noteworthy in some cases, compounds **2** or **3** oxidize slowly (entry 4) and ee can also be measured on the corresponding oxides. However, lower chemical shift difference of the ^{31}P NMR signals is observed.

The enantiomeric purity of various chiral diol and diamines has been probed via derivatization with reagent **1** and subsequent ^{31}P NMR analysis. An excellent agreement occurred in all cases with the ee measured *via* other analytical methods such as chiral HPLC or chiral gas chromatography. Although the limit of detection of this method was lower than in the case of HPLC, **1** was found as a convenient derivatizing reagent for the determination of the enantiomeric purity of a large class of compounds.

Experimental Section

Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl. ^{31}P NMR (40.54 MHz) data were recorded with a AC 100 Bruker spectrometer using 85% H_3PO_4 as external standard. Reagents were prepared according to standard procedures or were obtained from commercial sources and used as received.

Table I : ^{31}P NMR chemical shift differences $\Delta\delta$ (ppm) of some diols or diamines' derivatives.

Entry	Chiral Diol or Diamine	$\Delta\delta^{31}$P (ppm)	Peak ratio
1		1.28	26 : 24 : 50^{a}
2		0.95	25 : 25 : 50^{a}
3		0.459	25 : 25 : 50^{a}
4		14.03 4.89^{b}	51 : 49 51 : 49
5		1.42	50 : 50
6		-^{c}	-^{c}
7		1.18	51 : 49
8		1.26	50 : 50
9		1.91	51 . 49
10		1.28	50 : 50

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[a] : percentage corresponding to the proportion of the two diastereomers and to the meso compound.

[b] : $\Delta\delta^{31}$P measured on the corresponding oxides.

[c] : no exploitable results.

Preparation of menthylphosphorodichloridite (1). A solution of phosphorus trichloride (5.0 g, 38 mmol) in dry THF (10 mL) was added dropwise under N_2 atmosphere to a solution of (1*R*,2*S*,5*R*)-(-)-menthol (6.0 g, 38 mmol) in THF (10 mL). The mixture was stirred at room temperature for 1 hour. Compound **1** cannot be isolated in pure form and was used in solution without further purification. ^{31}P NMR ($CDCl_3$): δ 175.1 ppm (single signal).

Typical procedure for the determination of enantiomeric purity of chiral diols or diamines. 1 mL of the previous solution containing menthylphosphorodichloridite **1** is introduced into a small round bottomed flask under N_2 and 0.63 mL of NEt_3 (4.5 mmol) is added. After the addition was complete, the mixture was stirred at room temperature for 15 minutes and racemic diol or diamine (2 mmol) was added slowly. When the formation of the derivatives **2** or **3** is complete (usually 3-5 minutes), the suspension is filtered, transferred into a 5 mm NMR tube along with 100 µl of C_6D_6 and the ^{31}P NMR spectrum is recorded.

Notes and References

1. Parker, D. *Chem. Rev.* **1991**, 91, 1441 and references therein.
2. Morrison, J. D. *"Asymmetric Synthesis"*, Academic Press : New York, **1983**, Vol.5.
3. Martens, J. *"Topics in Current Chemistry"*, Springer Verlag : Berlin **1984**, 125, 165.
4. Allenmark, S. G. *"Chromatographic Enantioseparation"*, Ellis Horwood : Chichester, **1988**.
   Schurig, V.; Nowotny, H. P. *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 939.
   Pirkle, W. H.; Finn, J. *"Asymmetric Synthesis"*, Academic Press : New York **1983**, Vol. 1, Chapter 5.
5. Sweeting, L. M.; Crans, D. C.; Whitesides, G. M. *J. Org. Chem.* **1987**, 52, 2273.
   Miyano, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1981**, 54, 3522.
6. Verkade, J. G.; Quin, L. D. *"Phosphorus-31 NMR spectroscopy in Stereochemical Analysis : Organic Compounds and Metal complexes"*, VCH Publishers, Inc. : Deerfield Beach, Florida, **1987**, Vol. 8.
7. Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, 49, 1304.
   Kato, N. *J. Am. Chem. Soc.* **1990**, 112, 254.
   Johnson, C. R.; Elliot, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, 106, 5019.
   Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron Asymmetry* **1990**, 1, 437.
   Brunel, J. M.; Pardigon, O.; Maffei, M.; Buono, G. *Tetrahedron Asymmetry* **1992**, 3, 1243.
8. Reactive **1** was previously used for the resolution of 1,1'-binaphthalene-2,2'-diol giving enantiomerically pure diastereomers separated by simple crystallization. Brunel, J. M.; Buono, G. *J. Org. Chem.* **1993**, 58, 7313.

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