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THE USE OF (4R,5R)-DICARBOALKOXY 2-CHLORO 1,3,2-DIOXAPHOSPHOLANES AS NEW CHIRAL DERIVATIZING AGENTS FOR THE DETERMINATION OF ENANTIOMERIC PURITY OF ALCOHOLS BY ^{31}P NMR.

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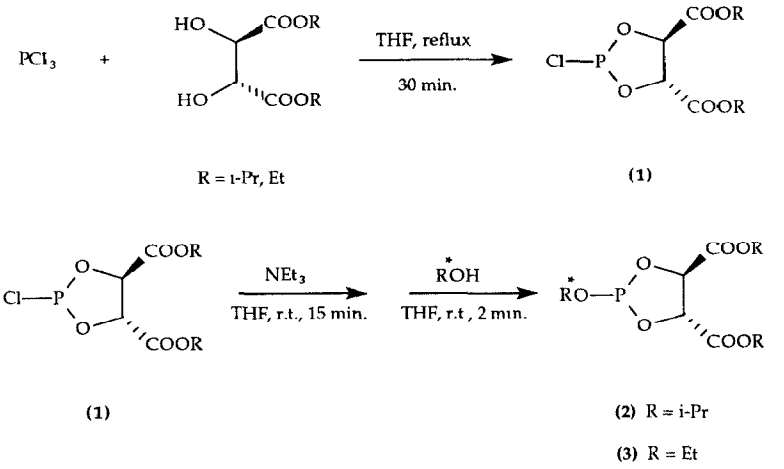
Abstract: The title compounds are prepared from a dialkyl tartrate and PCl_3. Their use as chiral derivatizing agents for the determination of enantiomeric excess of primary, secondary and tertiary alcohols by ^{31}P NMR is described.

In the past twenty years, remarkable improvements in enantioselective synthesis with the aim to prepare chiral compounds have been described[1,2]. One of the most important problems in this field is to measure their enantiomeric purity. NMR and chromatographic methods based on the formation of diastereomeric complexes or derivatives are widely used[3-5]. ^{31}P NMR spectroscopy provides a very convenient method for determining the optical purity of chiral phosphorus compounds because the chemical shift dispersion is usually large and spectra are simple, when broad band proton decoupling is applied[6]. Several organophosphorus chiral derivatizing agents[7] (CDA) as well as achiral reagents[8] for the analysis of chiral alcohols by ^{31}P NMR have been successfully used. Recently, Alexakis has prepared a diazaphospholidine possessing a C_2 axis of symmetry from hexamethylphosphorous triamide and (1R, 2R) N, N'- dimethylcyclohexane- 1, 2- diamine[9]. This CDA allows an accurate analysis by ^{31}P NMR and was successfully tested on a large array of primary, secondary and tertiary alcohols, functionalized or not.

We wish to report herein new cheap and efficient chiral derivatizing agents **1** for the determination of e.e. of chiral alcohols. **1** are quantitatively prepared by reaction of PCl_3 with a dialkyl tartrate in refluxing THF[10] (scheme 1). Analysis of the diastereomeric derivatives is performed by ^{31}P NMR spectroscopy. The reagents are unique in that either retention or inversion at phosphorus during derivatization of an enantiomerically pure alcohol yields a single diastereomer due to the C_2 symmetry of the chiral dialkyl tartrate ligand on phosphorus.



Scheme 1

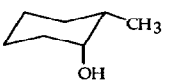
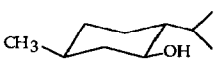
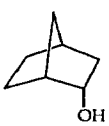
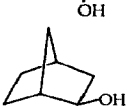
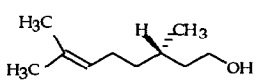
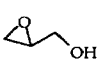
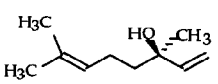
The reagents are stable for weeks under inert atmosphere, but very sensitive to moisture : they cannot be purified and are to be used crude. For this reason, compounds **1** were conveniently stored as ca. 0.5 M solutions in THF under nitrogen and taken by syringe when needed. The reaction between CDA **1** and an alcohol is quantitative, instantaneous, and the e.e. can be determined by ^{31}P NMR. CDA **1** oxidize rapidly, but e.e. can also be measured on the corresponding oxides, however, a loss of chemical shift difference of the ^{31}P NMR signals is observed.The diastereomeric pairs of derivatives exhibit typical NMR shift differences between 0.2 and 1.5 ppm and the results obtained with different alcohols are summarized in table I. It is worth mentioning that the presence of a lone pair of electrons on phosphorus tends to increase the chemical shift difference, as already described [9].

Reagents **1** show excellent reactivity toward primary, secondary and tertiary alcohols and optical purity can be accurately measured. It is important to note that kinetic resolution is not observed. Derivatives **2** and **3** appear as two singlets (P-H decoupled) corresponding to each diastereomer. Integration of these signals for the racemic mixtures always corresponds to 50:50 (± 2%).

Alcohols displayed in entries 10-14 are easily analyzed through their derivatives. Tertiary alcohols represent the most difficult case, normally giving rise to elimination products and displaying strong kinetic resolution[3]. Yet, with **1**, linalool (entry 14) reacted quantitatively and gave complete baseline separation and correct 50/50 ratio for the racemic compound. Noteworthy are the primary alcohols such as glycidol (entry 13) and citronellol (entry 12) having an α or β stereogenic center respectively, which are successfully analyzed. For most cases, we could compare the e.e.'s found with those obtained by other methods[11]. An excellent agreement in all cases can be stated.

Various chiral alcohols have been probed via derivatization with reagent **1** and subsequent ^{31}P NMR analysis. It should be noticed that **1** can be used in slight excess, since its chemical shift (δ = 174 ppm) does not interfere with those of **2** and **3** (δ range between 140 and 145 ppm). Extension of this study to other functional groups such as amines is in progress.

TABLE I : ^{31}P NMR CHEMICAL SHIFT DIFFERENCES $\Delta\delta$ (ppm) OF SOME ALCOHOLS' DERIVATIVES .

Entry	Chiral Compound	(2)	(3)	(4) [a]
1	$tBuCH(OH)CH_3$	1.5	1.4	1.1
2	$CH_3(CH_2)_5CH(OH)CH_3$	0.3 [b]	- [c]	- [c]
3	$CH_3(CH_2)_4CH(OH)CH_2CH_3$	0.4 [b]	0.2	- [c]
4	$PhCH(OH)CH_3$	1.4	1.3	1.0
5	$PhCH(OH)CH_2Cl$	1.5	1.2	1.0
6	$PhCH(OH)CH_2Br$	1.5	1.2	1.0
7		0.7	0.4	- [b]
8		0.7	0.7	- [b]
9		0.4	0.3	0.3
10		0.4	0.2	- [b]
11		0.4	0.3	- [b]
12		1.5	- [b]	0.5
13		1.1	1,2	1.1
14		1.5	- [c]	- [b]

a: oxide of the alcohol derivative **2** (δ range between 2 and 5 ppm).

b : no return to the baseline.

c : not performed.

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10. Typical procedure: A solution of diisopropyl tartrate (1.17 g, 1.5 mmol) in dry THF (5 ml) is added dropwise under N_2 atmosphere via syringe to a solution of PCl_3 (1.08 ml, 1.5 mmol) in THF (4 ml) under stirring at room temperature, the mixture is then refluxed for 0.5 hours. After cooling to room temperature, 1 ml of this solution is introduced into a small round bottomed flask under N_2, and NEt_3 (0.15 mmol) is added. The mixture is stirred for 15 minutes, then R*OH (0.2 mmol) is added slowly. When the formation of the derivatives **2** is complete (usually 3-5 min), 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 at 40.539 MHz. Chemical shifts are reported using 85% H_3PO_4 as external standard (reference $\delta = 0$).

11. E.e. for alcohols displayed in entries 7, 8 and 9 have been measured by GLC analysis after derivatization with isopropyl isocyanate, see : Konig, W.A.; Francke W.; Benecke I.; *J. Chromatogr.*, **1982**, 239, 227.