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TADDOL organophosphorus derivatising agents for the determination of the enantiomeric excess of chiral alcohols and carboxylic acids by ^{31}P and ^{1}H NMR spectroscopy

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Abstract

The use of an organophosphorus derivatisation agent prepared from TADDOL for the NMR determination of enantiomeric composition of chiral alcohols and carboxylic acids is described.

The determination of enantiomeric purity is of considerable importance. NMR and chromatographic methods are widely used.[1] They are based on the formation of diastereomeric complexes or derivatives. Among these methods, ^{31}P is a very attractive nucleus for NMR analysis because of the large chemical dispersion and the simplicity of the spectra.[2] In the past two decades, several chiral phosphorous-P(III) chemical derivatisation agents (CDAs) have been developed. Most of them contain an amine or a C_2 symmetric diamine moiety, but less attention has been paid to C_2 symmetric diols.[3,4] Furthermore, all of these CDAs have been applied to the determination of the enantiomeric excess of various chiral alcohols,[3,5–22] amines,[7,15,16,23,24] thiols[5,12,14,15,24,25] and aminoacids;[23,26,27] however, there are no examples reported with carboxylic acids, the usual method being determination by salt formation with chiral amines or diamines.[28,29] In addition, it would be desirable to be able to determine the enantiomeric composition by the simplest NMR method, i.e. ^{1}H NMR.[11,30] Here we wish to report the results obtained with diol CDAs (especially TADDOL CDAs) for the ee determination of chiral alcohols and carboxylic acids, using ^{31}P and *even* ^{1}H NMR spectroscopy.

Many P(III)-diol derivatives with an exocyclic chiral alcohol have been used as chiral phosphorus ligands in asymmetric synthesis.[31–35] ^{31}P chemical shifts recorded with dioxazaphospholane, dioxazaphosphinane, or TADDOL-P(III) and menthol[17] are presented in Table 1. The average shift difference between the two diastereoisomers is 0.4 ppm, except in the case of

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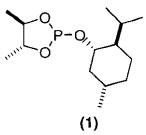
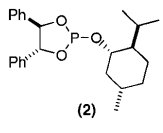
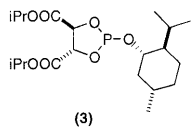
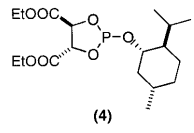
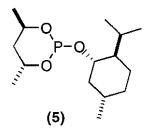
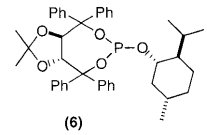
dioxazaphospholane (**1**). We decided to focus on TADDOL-P(III) derivatives because of the non-equivalence of the acetallic-methyl ^{1}H NMR chemical shift in the range 0–1 ppm, an area usually devoid of signals, which can allow the determination of ee by integration.

Table 1
^{31}P shift differences $\Delta\delta$ (ppm) of some menthol derivatives

 (1)	 (2)	 (3)	 (4)	 (5)	 (6)
$\Delta\delta = 1.1$[a]	$\Delta\delta = 0.5$[a]	$\Delta\delta = 0.4$[b]	$\Delta\delta = 0.3$[b]	$\Delta\delta = 0.3$[a]	$\Delta\delta = 0.4$[a]

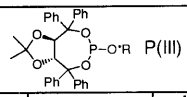
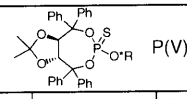
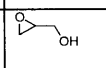
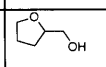
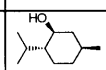
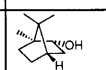
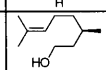
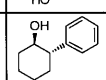
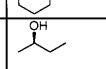
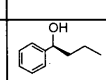
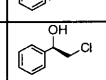
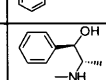
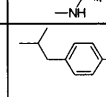
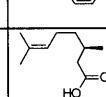
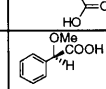
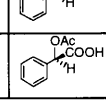
[a] In $CDCl_3$.[36]
[b] In C_6D_6.[3]

Typical procedure: Reaction can be performed easily in an NMR tube by adding one equivalent of anhydrous TADDOL (0.1 mmol) in $CDCl_3$ solution with five equivalents of a base and one equivalent of PCl_3. Either *N*,*N*-diethylaniline or pyridine can be used as a base, but pyridine was more convenient for the interpretation of ^{1}H NMR spectra. To this solution was added the chiral alcohol or carboxylic acid (0.1 mmol) and reaction occurred instantaneously, such that the ^{31}P and ^{1}H NMR spectra could be recorded immediately. Sulphur may be added directly to the NMR tube and the spectra were recorded again after shaking the tube, without any further purification. In the cases where the ^{1}H NMR spectra were not sufficiently clear for interpretation owing to the presence of phosphonate by-product (^{31}P $\delta = -4.1$ ppm, ^{1}H $\delta = 0.95$ ppm), the sulphated product could be purified by rapid silica gel chromatography (hexane/AcOEt 95/5). Chemical shifts and shift differences are given for primary alcohols, secondary alcohols and carboxylic acids in Table 2.

The average chemical shift of TADDOL-P(III)-alcohol or acid derivatives is in the same area as those observed with diamine-P(III)-alcohols derivatives (130–150 ppm), while the P(V)-TADDOL compounds (the sulphated compounds) are shifted to higher fields (50–60 ppm) compared with those of P(V)-diamine compounds (80–90 ppm).[14] The chemical shift difference between two diastereoisomers is between 0.1 and 1.2 ppm for alcohol-P(III) derivatives, the resolution usually being better with secondary alcohols compared with primary alcohols. When the chirality is in the γ position, for example in the case of citronellol (entry 5), no resolution was detected.

Interestingly, the resolution and chemical shift difference can be higher for P(V) compared with P(III) derivatives, i.e. in the case of menthol (entry 3), despite reports that the presence of a lone pair of electrons on phosphorus tends to increase the chemical shift difference.[3,14] For this reason recording both P(III) and P(V) phosphorus NMR spectra could be convenient for an accurate ee determination. Another way of ee determination consists of recording ^{1}H NMR spectra and integrating the TADDOL methyl chemical shifts. For each diastereoisomer the two methyl substituents are non-equivalent and two singlets are observed in an area between 0 and 0.9 ppm, as presented in Table 2.

Table 2
^{31}P and ^{1}H chemical shift and shift differences $\Delta\delta$ (ppm) of some alcohol derivatives[a]

	alcohols	 P(III)			 P(V)		
		$\delta\ ^{31}P$	$\Delta\delta$	$\delta\ ^{1}H$	$\delta\ ^{31}P$	$\Delta\delta$	$\delta\ ^{1}H$
1		131.99 131.86	0.13	0.70, 0.38 0.61, 0.43	55.91 55.72	0.19	0.88, 0.35 0.81, 0.40
2		131.94 131.92	0.02	0.88, 0.32 0.67, 0.52	55.73 55.63	0.10	0.75, 0.39 0.65, 0.51
3		143.50 143.10	0.40	0.97, 0.58 1.06, 0.43	54.39 51.83	2.56	
4		135.10 134.62	0.48	0.70, 0.41 0.68, 0.52	54.02 53.77	0.25	0.69, 0.47 0.60, 0.54
5		132.06	0	0.82, 0.52	55.54	0	0.83, 0.35
6		140.95 139.19	1.76	0.96, 0.24 0.68, 0.53	51.84 51.58	0.26	0.67, 0.39 0.60, 0.43
7		136.03 135.81	0.22	0.98, 0.40 0.99, 0.40			
8		136.42 135.31	1.11	0.32, 0.87 0.42, 0.81	53.85 52.26	1.59	0.56, 0.41 0.37, 0.34
9		133.41 134.77	1.34	0.78, 0.35 0.58, 0.44	51.90 53.76	1.86	0.54, 0.51 0.44, 0.39
10		140.32 142.51	2.31	0.88, 0.19 1.07, 0.38			
11		118.22 116.98	1.24	0.88, 0.33 0.68, 0.52	55.87	0	
12		114.09 113.65	0.44		52.50	0	0.24, 0.53
13		122.79 120.48	2.31	0.87, 0.38 0.60, 0.43	52.51	0	0.68, 0.52
14		123.94 122.74	1.2	0.72, 0.39 0.64, 0.57	53.22 52.49	0.73	0.67, 0.53 0.60, 0.42

[a] The underlined values are those of the major enantiomer.

In the case of carboxylic acids (entries 11–14), accurate ee determination could be achieved when the chirality is α to the carboxylate moiety. The chemical shift difference is even greater than that recorded with some secondary alcohols.

In conclusion, enantiomeric excess determination of a series of chiral alcohols and carboxylic acids can be achieved easily with TADDOL phosphorus derivatives using ^{31}P or even ^{1}H NMR. Work is in progress to extend this methodology to a wide range of alcohols, amines, thiols and acids.

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