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(1*S*,2*S*)-(-)-1,2-Diphenylethylenediamine; A Good Chiral Solvating Agent for the Determination of Enantiomeric Purity of Chiral Alcohols by ^{1}H NMR

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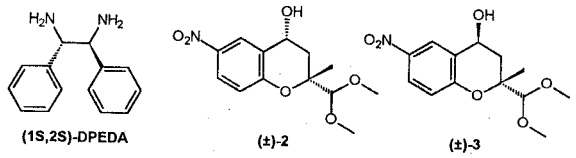
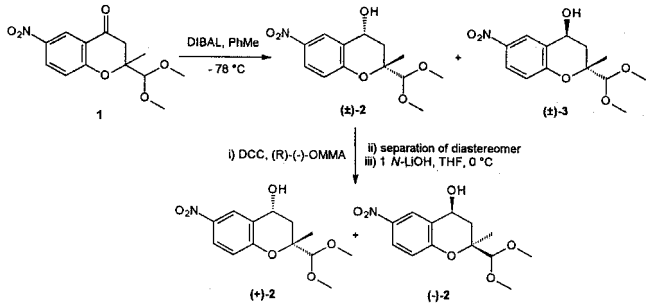
A majority of biologically important compounds are chiral and in many cases only one enantiomer exhibits desired activities. Although in the past it has been common to commerciallize the compounds in a racemic form, it is now required to have a single enantiomer for more selective activities. Therefore, it becomes more important than ever to determine the optical purity of the compounds.

Over the years, several techniques have been developed for the purpose of the determination of enantiomeric purity of chiral compounds. Among those, the NMR method became the subject for extensive studies because of its simplicity and non-destructive nature. For this purpose, chiral derivating agents (CDA),[1] chiral lanthanide shift reagents (CLSR),[2] and chiral solvating agent (CSA)[3] have been developed and all these approaches were based on the diastereoisomeric non-equivalency in NMR spectra. Although substantial developments have been made in these approaches, further improvements are necessary to cover wider range of compounds.

During the course of our research programs, we needed to determine the optical purity of several chiral alcohols and acids. For this purpose we have investigated various chiral solvating agents and found that (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (DPEDA) possesses an excellent property for the NMR determination of the enantiomeric purity for various alcohols and we would like to report the results of the study.



The compound, (±)-2, is a key intermediate for the potassium channel activator (PCA)[4] we have developed. This compound was prepared according to the procedure described in Scheme 1.



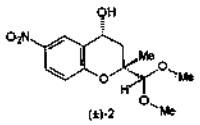
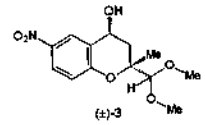
Scheme 1. Preparation of (−)-2 and (+)-2 by optical resolution

The reduction of ketone **1** with DIBAL in toluene −78 ℃ gave a diastereomeric mixture (9 : 1) in 94% yield and the diastereomers **2** and **3** were separated by column chromatography. The resolution of racemic **2** was carried out by forming the corresponding O-methyl mandelate, separating diastereomeric mandelates by column chromatography, and hydrolyzing the corresponding mandelate with 1 N *aqueous* LiOH in THF to give optically pure alcohol **2**. At this time it became necessary to determine the optical purity of the alcohol **2** and the typical procedure is described below.

In 0.1 molar solution of the alcohols and (1*S*,2*S*)-(−)-diphenylethylenediamine in $CDCl_3$ was directly prepared in a NMR tube and its ^{1}H NMR (500 MHz) spectrum was recorded at ambient temperature. The alcohols examined and the chemical shifts of the protons showing non-equivalency are listed in Table 1. Although there are numerous cases reported for the interaction between acids and the chiral bases, however, there are not many examples known for the case of alcohols where the interaction is expected to be much weaker. Nontheless, we found that even in this case the non-equivalency is large enough for the accurate determination of the optical purity as shown in Table 1.

In Figure 1, the regions corresponding to the $\underline{CH}(OMe)_2$ resonances of (a) free (±)-2, (b) the mixture of (±)-2 and 3 equimolar CSA, (c) 80% ee of (−)-2 , (d) 95% ee of (+)-2, enantiomerically pure of (+)-2 are shown, respectively. The concentration of (1*S*,2*S*)-DPEDA also substantially influences the degree of non-equivalency. Non-equivalency increases with an increase of (1*S*,2*S*)-DPEDA until the alcohol

Table 1. Non-equivalent chemical shifts in a mixture of (1*S*,2*S*)-(−)-DPEDA and alcohols

Substrate	CSA (molar ratio)	Δδ (Hz)	Proton	Solvent
 (±)-2	0.5	1.8	CH(OMe)$_2$	$CDCl_3$
	0.8	1.4		
	1.0	1.5		
	1.6	2.9		
	2.0	3.7		
	3.0	4.4		
 (±)-3	1.0	2.5	Me	$CDCl_3$
	1.6	3.0		
	2.0	3.5		
	3.0	4.0		

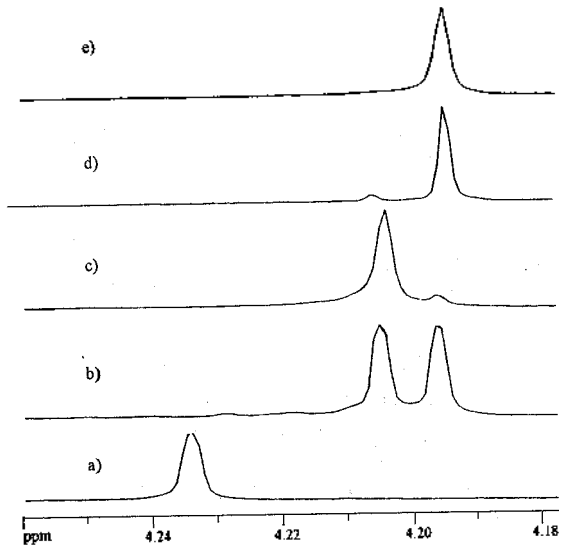


Figure 1. ^{1}H NMR resonances (500 MHz, $CDCl_3$) of CH(OMe)$_2$ acetal in; (a) free (±)-2. (b) the mixture of (±)-2 and 3 equimolar of (1*S*,2*S*)-DPEDA. (c) the mixture of (−)-2 enriched and 3 equimolar of (1*S*,2*S*)-DPEDA. (d) the mixtute of (+)-2 enriched and 3 equimolar of (2*S*,2*S*)-DPEDA. (e) the mixture of enantiomerically pure (+)-2 and 3 equimolar of (1*S*,2*S*)-DPEDA.

is completely saturated with (1*S*,2*S*)-DPEDA. Although the amount of (1*S*,2*S*)-DPEDA required to exhibit this effect depends on the interaction strength of the alcohol-amine pair, many alcohols have association constants great enough in a typical NMR amine concentration and enough non-equivalency normally observed when the chiral sovating agent and the alcohol ratio is between 2 and 3.

In conclusion, this study shows that (1*S*,2*S*)-(−)-diphenylethylenediamine is a convenient and effective chiral solvating agent for the *in situ* NMR determination of the enantiomeric purity of chiral alcohols. This agent is found be advantageous over other chiral amines such as (*R*)-(+)-α-methylbenzylamine or (*R*)-(+)-1-(1-naphthyl)ethylamine for this purpose.

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Syn-Selectivity in Titanium (IV) Mediated Aldol Condensation of the Silyl Ketene Acetal of S-2-Pyridyl Thioester with Aldehydes

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Over the past decade, a variety of Lewis acid mediated aldol condensation methods between ester or thioester silyl