Chiral Silyl Acetals as Convenient Reagents for Determining Enantiomeric Purity of Alcohols

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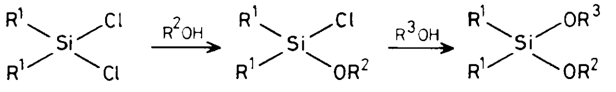
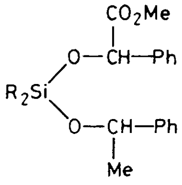
Dimethyl and diphenylsilyl acetals of structure (**3**) are convenient reagents for determining the enantiomeric purity of alcohols by n.m.r. spectroscopy.

The coupling of chiral auxiliary reagents with enantiomers to give diastereoisomeric mixtures has gained wide acceptance as a way of determining the enantiomeric purity, especially in cases where n.m.r. differentiation of the diastereoisomers is convenient and practical.[1] The problems often encountered are that the chiral auxiliary reagent is at times expensive (*cf.* trifluoromethyl-α-methoxyphenylacetyl chloride),[2] or that the coupling step is difficult (*e.g.* for hindered alcohols), or that the nuclei to be observed by n.m.r. spectroscopy are less convenient than the ^{1}H nucleus (*e.g.* ^{19}F or ^{31}P).[3,4] We now report the use of chiral silyl acetals[5] as a method for the n.m.r. determination of the enantiomeric purity of alcohols.

The silyl acetal (**3**) was prepared in a stepwise manner from the dichlorosilane (**1**; R^1 = Me or Ph). If R^2OH is an alcohol of known optical purity [near 100% (enantiomeric excess) for convenience], often derived from natural sources, then the optical purity of the chiral alcohol R^3OH can be determined if the diastereoisomers (**3**) are distinguishable by n.m.r. spectroscopy and the reaction shows no chiral recognition during silyl acetal formation. The compounds that have been used for R^2OH included methyl mandelate, quinine, and menthol. Either dimethyl or diphenylsilyl acetals can be used. Chemical shift differences depend on the R^2OH used but compare favourably with other agents used for enantiomeric purity determination. For example, the diastereoisomers (**4**) showed



(**1**) (**2**) (**3**)



(**4**) R = Ph
(**5**) R = Me

Figure 1. ^{1}H N.m.r. spectrum of (**5**) derived from (a) (±)-1-phenylethanol, (b) the (−)-isomer, and (c) the (+)-isomer.

Table 1. N.m.r. data of chiral silyl acetals (**3**) and determination of enantiomeric purity.

R^1	R^2OH	R^3OH, % E.e.[a]	^1H,[b] $\Delta\delta$/p.p.m.	Diastereoisomeric ratio of (**3**) by ^1H n.m.r. spectroscopy	^{13}C,[b] $\Delta\delta$/p.p.m.	^{29}Si [b]/p.p.m.
Me	(*S*)-(+)-Methyl mandelate	(±)-Butan-2-ol, 0	$SiCH_3$, 0.011	50:50	$SiCH_3$, 0.111	—
		(+)-Butan-2-ol, 78	$CHCH_3$, 0.059	88:12	CH_2CH_3, 0.029	
		(−)-Butan-2-ol, 92	CH_2CH_3, 0.043	3:97		
		(±)-Octan-2-ol, 0	$SiCH_3$, 0.005	48:52	$SiCH_3$, 0.106	−3.673; −3.624
		(−)-Octan-2-ol, 87	$CHCH_3$, 0.057	5:95	$CHCH_3$, 0.036	
		(+)-Octan-2-ol, 46		73:27		
		(±)-1-Phenylethanol, 0	$SiCH_3$, 0.095	50:50	$SiCH_3$, 0.160	
		(+)-1-Phenylethanol, 99	$CHCH_3$, 0.062	99:1	OCH_3, 0.082	—
		(−)-1-Phenylethanol, 97	OCH_3, 0.097	2:98		
Ph	*S*-(+)-Methyl mandelate	(±)-Butan-2-ol, 0	OCH_3, 0.010	49:51		−33.069; −33.004
		(+)-Butan-2-ol, 78	$CHCH_3$, 0.127	89:11		
		(−)-Butan-2-ol, 92	CH_2CH_3, 0.060	3:97		
		(±)-Octan-2-ol, 0	OCH_3, 0.009	49:51		−33.147; −33.003
		(+)-Octan-2-ol, 96	$CHCH_3$, 0.130	98:2		
		(+)-Octan-2-ol, 46		73:27		
		(±)-1-Phenylethanol, 0	OCH_3, 0.122	50:50		−31.954; −32.207
		(+)-1-Phenylethanol, 99	$CHCH_3$, 0.137	98:2		
		(±)-2-Methylbutanol, 0	$CHCH_3$, 0.018 CH_2CH_3, 0.016	49:51		
Me	Quinine	(±)-Hexan-2-ol	$SiCH_3$, 0.010			
		(±)-Octan-2-ol	$SiCH_3$, 0.012 $CHCH_3$, 0.060 CH_2CH_3, 0.009			
		(±)-1-Phenylethanol	$SiCH_3$, 0.059 $CHCH_3$, 0.083			
Me	Menthol	(±)-Hexan-2-ol	$SiCH_3$, 0.024			
		(±)-1-Phenylethanol	$SiCH_3$, 0.039 $CHCH_3$, 0.020			

[a] % E.e. determined by optical rotation. [b] ^1H, ^{13}C, ^{29}Si N.m.r. data measured in $CDCl_3$.

$\Delta\delta$ 0.14 p.p.m. for the alkyl methyl groups and $\Delta\delta$ 0.12 p.p.m. for the ester methyl groups ($CDCl_3$). In the case of the dimethyl acetals (**3**; R^1 = Me) the silyl methyl signals were often anisochronous for each of the two diastereoisomers. Since the signals are conveniently located in a region upfield from most ^1H signals, they can be readily used for relative intensity measurements. This is illustrated in Figure 1 with the diastereoisomers (**5**). Chiral recognition during the coupling reactions is negligible as illustrated by the agreement of the calculated and the measured e.e. values (Table 1). In addition to ^1H n.m.r. spectroscopy, ^{13}C and ^{29}Si n.m.r. spectroscopy could also be used if necessary.

The method is convenient in that no special auxiliary reagent needs to be synthesized. The coupling of alcohols to silyl chlorides has been well studied and it is likely that sterically hindered alcohols are amenable to coupling.[6]

A typical procedure to prepare a sample of the silyl acetal is as follows. To a solution of R_2SiCl_2 in benzene [or tetrahydrofuran (THF)] was added an equimolar amount of R^2OH and pyridine in benzene. The mixture was stirred for 2—3 h at room temperature. The chlorosilyl ether (**2**) could be separated by work-up at this stage if necessary. Otherwise, R^3OH and pyridine in benzene (or THF) can be added and the mixture heated to 60 °C for 4.5 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. Purification of (**3**) can be achieved by column chromatography (Al_2O_3 or SiO_2). The order of addition of R^2OH and R^3OH can be reversed if R^2OH is hindered (*e.g.* quinine) to avoid an acetal exchange reaction.

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