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USE OF SHIFT REAGENT WITH MTPA DERIVATIVES IN ^{1}H NMR SPECTROSCOPY. II. DETERMINATION OF ABSOLUTE CONFIGURATION AND DIASTEREOMERIC COMPOSITION OF SECONDARY CARBINOLS IN EPIMERIC MIXTURE

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Determination of absolute configuration and optical purity of partially active secondary carbinols by NMR spectroscopy has been the subject of many investigations.[1-3] However, configurational assignment of secondary carbinols in an epimeric mixture has so far been limited to the case where the definite configurational relationship of a hydroxyl group in question with a neighboring chiral center having known absolute stereochemistry can be established.

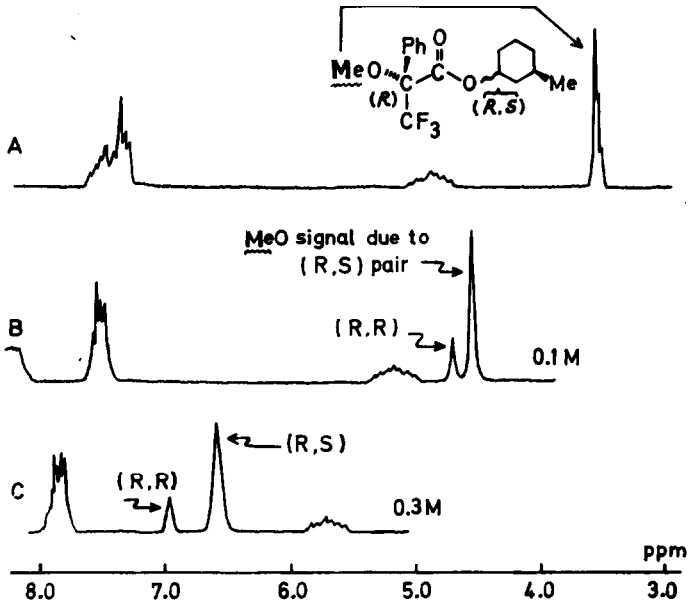


Fig. 1. 90 MHz ^{1}H NMR spectra of (R)-(+)-MTPA esters of (-)-cis-(1S,3R)-, and (-)-trans-(1R, 3R)-3-methylcyclohexanols (cis/trans=74/26) in CCl_4 containing various molar ratios of $Eu(fod)_3$: A, 0 mol; B, 0.1 mol; C, 0.3 mol.

To overcome this limitation, we have developed a convenient general method which enables determination of the absolute configuration and the diastereomeric composition of secondary carbinols in an epimeric mixture without any stereochemical information about the neighboring chiral center.

An epimeric mixture of secondary carbinols, (-)-cis-(1S,3R)-, and (-)-trans-(1R,3R)-3-methylcyclohexanols (cis/trans=74/26), was quantitatively converted to the corresponding (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid[(R)-(+)-MTPA, Mosher's Reagent] esters by the method previ-

TABLE

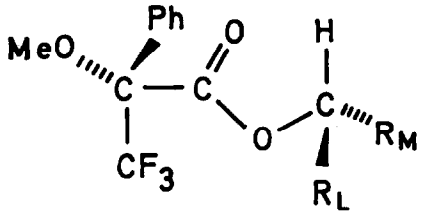
LIS Values of the Methoxyl Group in the Acid Moiety in (R)-(+)-MTPA Esters of Secondary Carbinols in Diastereomeric Relation

Entry	(R)-(+)-MTPA ester: Carbinyl moiety	R_L	R_M	LIS value of OMe signal (LIS_{OMe})	Absolute configuration of carbinol	Preferred conformation of OH
1	(-)-trans-3-MeCYHL[a]	C-2,C-3	C-6	11.2	(R)[f]	ax (trans)
	(-)-cis-3-MeCYHL			10.1	(S)[g]	eq (cis)
2	(-)-Menthol	C-4	C-2	12.4	(R)	eq (trans)
	(+)-Neomenthol			9.0	(S)	ax (cis)
3	(-)-cis-Menthenol	C-4	C-2	13.3	(R)[h]	eq' (cis)
	(-)-trans-Menthenol			10.0	(S)[h]	ax' (trans)
4	(+)-NeoisoCVMTL[b]	C-1	C-3	12.0	(R)[g]	eq (cis)
	(+)-IsoCVMTL			9.8	(S)[g]	ax (trans)
5	(-)-CVMTL	C-1	C-3	8.1	(R)[g]	eq (trans)
	(+)-NeoCVMTL			7.1	(S)[g]	ax (cis)
6	(-)-cis-Carveol	C-1	C-3	12.7	(R)[g]	eq' (cis)
	(-)-trans-Carveol			11.2	(S)[g]	ax' (trans)
7	(-)-Isoborneol	C-1	C-3	11.1	(R)[g]	exo
	(+)-Borneol			8.3	(S)[g]	endo
8	(-)-IsoPCPHL[c]	C-2	C-4	10.0	(R)[g]	ax' (trans)[i]
	(+)-NeoisoPCPHL			9.7	(S)[g]	eq' (cis)
9	(-)-NeoPCPHL	C-2	C-4	15.8	(R)[g]	ax' (cis)[i]
	(+)-PCPHL			9.7	(S)[g]	eq' (trans)[i]
10	(-)-α-Nopinol	C-1	C-3	11.5	(R)[i]	eq' (cis)[i]
	(-)-β-Nopinol			9.2	(S)[i]	eq' (trans)[i]
11	3α-Cholestanol	C-4,C-5	C-2	13.3	(R)	eq (trans)
	3β-Cholestanol			8.3	(S)	ax (cis)
12	α-ESTDL[d]-3-Me ether	C-13	C-16	13.5	(R)	ax (trans)
	β-ESTDL-3-Me ether			7.2	(S)	eq (cis)
13	Androsterone	C-4,C-5	C-2	8.3	(R)	ax (trans)
	Epiandrosterone			5.7	(S)	eq (cis)
14	3β-AcO-PRGN[e]-20β-ol	C-17	C-21	8.3	(R)[j]	
	3β-AcO-PRGN-20α-ol			4.1	(S)[j]	

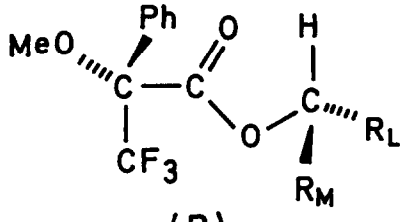
[a]CYHL:Cyclohexanol, [b]CVMTL:Carvomenthol, [c]PCPHL:Pinocampheol, [d]ESTDL:Estradiol [e]PRGN:Pregn-5-en-, [f]B. K. Macbeth and J. A. Mills, J. Chem. Soc. 205 (1947). [g]W. Klyne and J. Buckingham, "Atlas of Stereochemistry" p. 77-87, Chapman and Hall, London (1974). [h]J. Katsuhara, H. Yamasaki and N. Yamamoto, Bull. Chem. Soc. Japan 43, 1584 (1970). [i]D. V. Banthorpe and D. Whittaker, Chem. Rev. 66, 643 (1966). [j]L. F. Fieser and M. Fieser, "Steroids" p. 568, Reinhold Publishing Corporation, New York (1959).

ously described.[1] The magnitude of LIS_{OMe}[3,4] of the (1R)-carbinol is larger than that of the (1S)-carbinol (see Fig. 1). The ratio of peak areas of the well separated OMe signals with larger and smaller LIS_{OMe} values (75/25) affords the diastereomeric composition of the original carbinols. All the 14 examples tested (see the Table) completely agree with the NMR-configurational correlation scheme which can be rationalized by the same empirical models proposed in a previous paper.[3]

This correlation derived from the data listed in the Table predicts that the diastereomer having a larger LIS_{OMe} value should have configuration (A), while the alternate diastereomer having a smaller LIS_{OMe} value should have configuration (B). If R_L takes precedence over R_M in the R, S nomenclature scheme, the diastereomeric MTPA ester having the larger LIS_{OMe} value should be (R,R), if (R)-(+)-MTPA was used(or (S,S), if (S)-(-)-MTPA was used).



(A)



(B)

It is worthwhile to note that the present method also affords a reliable result for the carbinols in epimeric mixtures (see entries 1-cis and 6-trans) whose configurational assignments (in enantiomeric mixture) had not afforded any satisfactory results.[3]

As can be seen from the fourth and the fifth column of the Table, the relative magnitudes of LIS_{OMe} values are governed solely by the absolute configuration of the carbinyl carbon atom in question, while the other stereochemical features of the hydroxyl group, such as the preferred conformation and/or the relative configuration to the substituent attached to the neighboring chiral center, are not influential in determining the relative magnitude of the induced chemical-shift nonequivalence. This method, therefore, is also applicable to the epimeric mixture of secondary carbinols produced by diastereoselective reduction of the chiral ketone having unknown absolute stereochemistry.

Furthermore, this technique would provide an useful tool for determining absolute configuration of the chiral center other than the hydroxyl group of secondary carbinols in an epimeric mixture, and hence, for determining that of the original chiral ketone, if the relative configuration of the substituent on

the chiral center in question to the hydroxyl group is known.

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4. NMR sepctra of the (R)-(+)-MTPA esters (mixture of (R,R) and (R,S) pair) were taken with molar ratio of $Eu(fod)_3$ to the MTPA esters of 0.1-0.3 in CCl_4, and the magnitudes of induced chemical shift in ppm for the OMe signal were plotted vs. molar ratio of $Eu(fod)_3$. In this range the induced shifts are essentially linear with respect to molar ratio of $Eu(fod)_3$ and the slope of this line is designated LIS_{OMe}.