Determination of the Absolute Configuration and Enantiomeric Purity of Allylic and Acetylenic Alcohols

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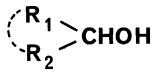
The relative magnitude of steric bulk of saturated vs. unsaturated substituents in the title compounds has been estimated by a lanthanoid induced shift (LIS) study of these (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate esters [(*R*)-(+)-MTPA esters] by ^{1}H NMR spectroscopy:

CH_2=C(Me)–>Pentyl>*n*-Pr>Et≃CH_2=CH–>Me>CH≡C–; Ph>Cyclohexyl

These results allow the assignment of the absolute configurations of both cyclic and acyclic unsaturated alcohols. Furthermore, the relative intensity of well-separated OMe signals for those diastereomeric MTPA esters can be used for the determination of the %ee of the original alcohols.

The phenomenon of the chemical shift nonequivalence of diastereomeric esters and amides has been widely used for determinations of the absolute configuration and enantiomeric purity of alcohols and amines. The method using α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA; Mosher acid) is especially useful and has been most widely employed for this purpose.[1a] This procedure, however, is not applicable when the ^{1}H NMR signals of the respective diastereomers are not sufficiently separated, or when the crucial signals overlap with other resonances. In such cases, the use of a lanthanoid shift reagent, such as Eu(fod)$_3$ (fod=6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione), with MTPA derivatives (MTPA/LSR method[1b]) often enhances the substancial separation of signals from the OMe and phenyl groups in the MTPA moiety and the methine proton in the alcohol moiety so that useful analyses can be performed.

In the course of continuing LIS studies,[2] we have become interested in extending the MTPA/LSR method to the title compounds, since these chiral unsaturated alcohols (**1** and **2**) and their related compounds are widely distributed in natural products as well as key intermediates for the synthesis of various biological active substances. In order to obtain an NMR configurational correlation scheme (Fig. 2) for predicting the absolute configuration of these alcohols by the MTPA/LSR method, it is essential to clarify the effective steric bulk of saturated vs. unsaturated substituents (R_1 vs. R_2) of the alcohol moiety in the MTPA esters for the coordinating Eu(fod)$_3$.



R_1: Alkyl, R_2: –CH=CHR (1)

R_1: Alkyl, R_2: –C≡CR (2)

Results and Discussion

The partially active alcohols employed in this study were prepared by an asymmetric reduction of the corresponding ketones with the Darvon/$LiAlH_4$ complex[3] in good enantioselectivity (e.g., 68% ee for 3-butyn-2-ol). The alcohols, thus obtained, were purified by preparative GLC, if necessary. It is worthwhile noting that the Darvon/LAH complex reduction of α,β-unsaturated carbonyl compound affords an excellent regioselectivity, giving a 1,2-addition product similar to that with $NaBH_4/CeCl_3$.[4] Some of them were obtained by the hydride reduction of the corresponding homochiral ketones with $NaBH_4/CeCl_3$ or by the optical resolution of racemic alcohols via (*S*)-1-phenylethylamine salts of phthalic acid half esters. *cis*- and *trans*-4-*p*-Menthen-3-ols (Entries 20 and 21) were separated by preparative GLC from a mixture (*cis*/*trans*=88/12) obtained by an LAH reduction of (−)-4-*p*-menthen-3-one ($[\alpha]_D^{20}$ −62.5°, neat).

Shift studies were carried out on diastereomeric mixture of the MTPA esters, as previously reported.[5] Generally, the signal due to the OMe group in the diastereomeric MTPA esters appears as a single peak, thus giving no stereochemical information about the chiral center in question. The signal, however, gave a sufficient separation by the progressive addition of Eu(fod)$_3$. Figure 1 shows a typical example of an LIS study of the (*R*)-MTPA ester of (+)-2-cyclohexen-1-ol. The results are summarised in Table 1.

It is well-known that the order of the steric requirement of the alkyl, alkenyl and alkynyl groups varies appreciably with the reaction mode; for instance, the magnitude of the conformational free energy of the substituent on the cyclohexane ring is of the order of

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Et>Me>CH_2=CH–>CH≡C–; *t*-Bu>Ph.[6]

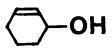
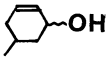
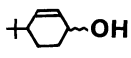
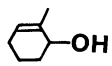
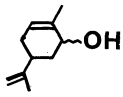
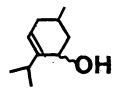
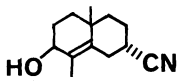
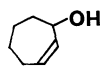
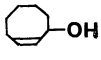
On the other hand, a partly reversed order,

Ph>*t*-Bu; CH≡C–>CH_2=CH–>Et>Me,[7]

has been observed for the chiral hydride reduction of carbonyl compounds by modified $LiAlH_4$ complexes, probably because of an electronic effect which plays a more important role than does the van der Waals repulsion. However, it has been reported that the relative magnitude of the steric requirement of several substituents in the MTPA/LSR study is of the order of

Ph>*t*-Bu>*i*-Pr>Et>Me;[5] COOMe>Ph>Alkyl;[8]

Table 1. Lanthanoid Induced Shift of Methoxyl Group in the Acid Moiety for Diastereomeric (*R*)-MTPA Esters of Allylic and Acetylenic Alcohols

Entry	(*R*)-MTPA-O-CH(M)-L		LIS_{OMe}		ΔLIS_{OMe}	Config. with Larger LIS_{OMe}	Remarks
	L	M	LIS^A	LIS^B	LIS^A-LIS^B		
1	Me	CH≡C–	7.8		0	—	
			(0.16)[a]	(−0.22)[a]	(0.38)[a]	(*S*)[a]	
2	Et	CH≡C–	4.8	3.8	1.0	(*S*)	
			(0.07)[a]	(−0.19)[a]	(0.26)[a]	(*S*)[a]	
3	CH_2=CH–	Me	6.8	5.8	1.0	(*R*)	
4	Et ≃	CH_2=CH–	14.8		0	—	
5	*n*-Pr	CH_2=CH–	9.7	9.5	0.2	(*S*)	
6	*i*-Pr	CH_2=CH–	6.8	5.8	1.0	(*S*)	
7	Pentyl	CH_2=CH–	7.1	6.4	0.7	(*S*)	
8	Hexyl	CH_2=CH–	10.5	9.6	1.0	(*S*)	
9	CH_2=CHCH_2–	Me	8.2	6.8	1.4	(*R*)	
10	CH_2=C(Me)–	Et	8.8	6.9	1.9	(*R*)	
11	Ph	Cyclohexyl	8.8	7.7	1.1	(*R*)	
12	···CH_2–CH_2–	···CH=CH–	8.7	7.4	1.3	(*S*)	
13	···CH(Me)–CH_2–	···CH=CH–	9.3	8.6	0.7	(*S*) (*cis*)	
14	···CH(Me)–CH_2–	···CH=CH–	10.1	7.8	2.3	(*S*) (*trans*)	
15	···CH_2–CH_2–	···CH=CH–	8.0	7.5	0.5	(*S*)[b] (*cis*)	
16	···CH_2–CH_2–	···CH=CH–	7.4	6.9	0.5	(*S*)[b] (*trans*)	
17	···CH=C(Me)–	···CH_2–CH_2–	10.1	9.2	0.9	(*R*)[c]	
18	···CH=C(Me)–	···(*i*-Pr*)CH–CH_2–	11.4	7.9	3.5	(*R*) (*cis*)	
19	···CH=C(Me)–	···(*i*-Pr*)CH–CH_2–	14.1	18.3	−4.2	(*S*) (*trans*)[d]	
	(*i*-Pr*: *i*-Propenyl)						
20	···CH=C(*i*-Pr)–	···CH(Me)–CH_2–	13.9	6.8	7.1	(*R*) (*cis*)	
21	···CH=C(*i*-Pr)–	···CH(Me)–CH_2–	11.5	10.5	1.0	(*R*) (*trans*)	
22	···C(···C=C(Me)–)(···CH_2–CH_2–)		[6.3] / [4.9] (Racemate)		|1.4|		
23	···CH_2–CH_2–	···CH=CH–	8.3	8.9	−0.6	(*R*)	
24	···CH_2–CH_2–	···CH=CH–	8.4	8.5	−0.1	(*R*)	

a) Determined by LIS value of the ethynyl proton. b) Configurations not previously reported. These configurations agrees with those predicted from the sense of asymmetric induction by Darvon/LAH complex.[3] c) The assignment is consistent with that presumed from the steric course of asymmetric reduction via hydrosilylation (T. Kogure and I. Ojima, *J. Organomet. Chem.*, **234**, 249 (1982)). d) The result was obtained by repeated run (Ref. 5).

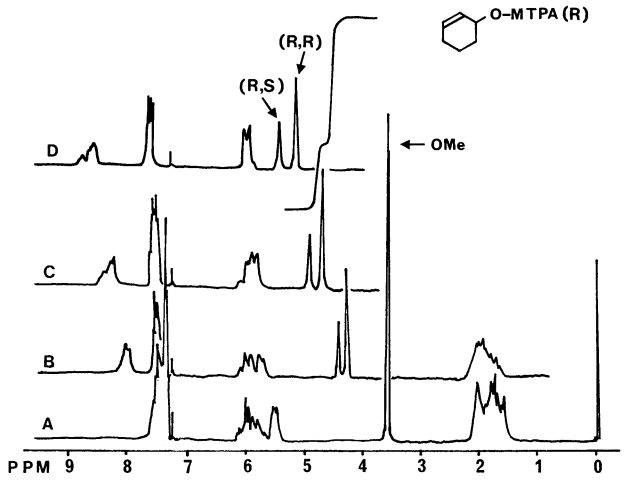


Fig. 1. ^{1}H NMR spectra of the (*R*)-(+)-MTPA ester of 2-cyclohexen-1-ol [(*R*)-(+), 27% ee] in the presence of a specified molar ratio of Eu(fod)$_3$ to the MTPA ester in $CDCl_3$. A, 0; B, 0.1; C, 0.16; D, 0.22.

no systematic investigation has been carried out for those of unsaturated substituents.

The results given in Table 1 clearly indicate that, in contrast to the above two cases,[6,7] the order of effective steric bulk of the substituents in coordination with Eu(fod)$_3$ is as follows:

(a) acyclic alcohols

CH_2=C(Me)–>Pentyl>*n*-Pr>Et≃CH_2=CH–>Me>CH≡C–; CH_2=$CHCH_2$–>Et, Me; Ph>Cyclohexyl

(b) cyclic alcohols

···CH=C(*i*-Pr)–>···CH=C(Me)–>···CH(Me)–CH_2–, CH_2–CH_2–; ···CH_2–CH(Me)–>···CH_2–CH_2–>···CH=CH–

These observations strongly suggest that the electronic interaction between the unsaturated substituent and the three heptafluoropropyl groups in Eu(fod)$_3$ is not a dominant factor, but that an extension effect[9] of the substituents is effective (e.g the ethynyl and vinyl groups vs. the methyl group; Entries 1 and 3).

As reported previously,[5] since Eu(fod)$_3$ approaches to the *si*-face side of the ester carbonyl group, the LIS_{OMe} due to compounds (**A**) is consistently larger than that of the compounds (**B**). This correlation scheme enables the determination of the absolute configuration of original alcohols by considering the relative magnitude of the substituents.

Furthermore, the relative intensity of well-separated OMe signals for the diastereomeric MTPA esters can be used to determine the diastereomeric ratio of MTPA esters and, hence, the enantiomeric purity of the original alcohols. The experimental deviations from those obtained by measurements of specific rotation were within ±2%.

Previously,[5] we have observed that substrates with a quasi-axial hydroxyl group, such as *trans*-carveol (Entry

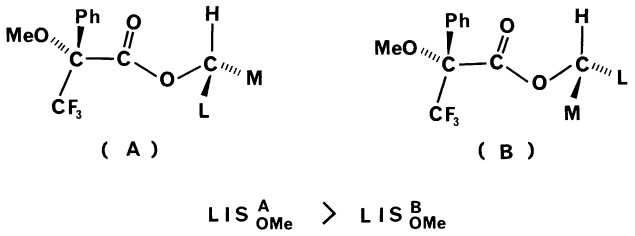


Fig. 2. NMR configurational correlation scheme.

19), do not follow the correlation scheme and that the steric bulk of the substituent on the carbinyl carbon atom of the original alcohol is of the order of

···(*i*-Pr*)CH–CH_2–>···CH=C(Me)–,

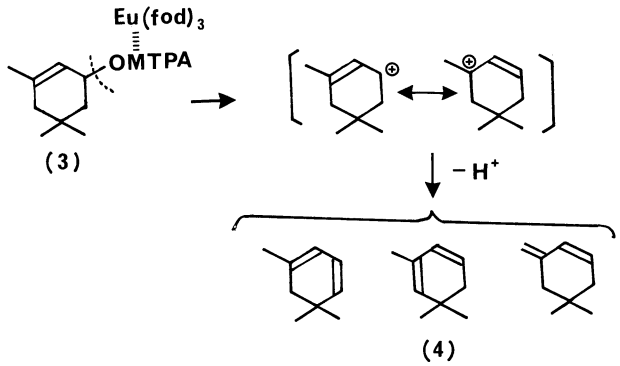
contrary to the usual order. As can be seen in the case of *trans*-4-*p*-menthen-3-ol (Entry 21), however, this irregularity disappeared when the methyl group was substituted by a more bulky isopropyl group.

In cases where only one enantiomer of the concerned alcohol is available (as is often the case with natural products) two diastereomeric MTPA esters can be generated from the same alcohol using both (*R*)-(+)- and (*S*)-(−)-MTPA. Since the NMR spectra of (*R*,*S*) and (*S*,*R*) or (*R*,*R*) and (*S*,*S*) enantiomers are indistinguishable, an application of symmetry principles should provide the necessary information.

Entries 23 and 24 are clear exceptions to this correlation scheme. Although the preferred conformation of these substrates seems to be responsible for this irregularity,[10] a further detailed study would be necessary for an elucidation of this problem.

An MTPA ester of 3,5,5-trimethyl-2-cyclohexen-1-ol (**3**) decomposed immediately upon the addition of a catalytic amount of Eu(fod)$_3$ to a $CDCl_3$ solution, giving three elimination products [one of which was separated (GLC), and identified as 2,6,6-trimethyl-1,3-cyclohexadiene (**4**)[11]] under ordinary NMR measurement conditions ($CDCl_3$, at ambient temperature).

A similar phenomenon was also observed for the MTPA esters of 3-methyl-2-cyclohexen-1-ol, *cis*- and *trans*-piperitols, β-ionol, 2,3,4,4a,5,6,7,8-octahydro-4a-



methyl-2-naphthol, and 4-methyl-3-penten-2-ol. Although this mild elimination reaction caused by the Lewis acid character of $Eu(fod)_3$ is strictly a characteristic of the compounds which afford a tertiary carbocation intermediate, the reaction seems to be inhibited by the adjacent alkyl group on the sp^2 carbon atom (Entry 22), which prevents access[12] of $Eu(fod)_3$. A further investigation of this unique elimination reaction is in progress.

Experimental

Instruments. NMR spectra were taken on a Hitachi R-90H FT spectrometer in $CDCl_3$ with TMS as an internal standard. Optical rotations were determined on Perkin-Elmer 241 electronic polarimeter using 1-dm and 0.1-dm thermostated microcells. GLC analyses were made on Shimadzu GC-7A using PEG 20M column (3 mm×2.0 m). Preparative GLC was carried out on a Varian Aerograph (model 700) using the same stationary phase (column: 4 mm×2.0 m).

Solvents and Reagents. Ether was distilled over $LiAlH_4$. Pyridine was dried over BaO and distilled. All of the solvents were stored over a Linde molecular sieve 4A. A stock $LiAlH_4$ solution in ether was passed through a glass filter under nitrogen and stored in a flask closed with a rubber septum. It was analyzed by iodometry immediately prior to use.[13] Aliquots were removed by a syringe, as needed.

Synthesis of Substrate (Representative Example). Optically active (+)-(1*R*,4*S*)- and (+)-(1*R*,4*R*)-4-*t*-butyl-2-cyclohexen-1-ols (a) 2-Bromo-4-*t*-butylcyclohexanones (**5**). To a stirred solution of 15.4 g of 4-*t*-butylcyclohexanone in 50 ml of CCl_4 was added dropwise 15.1 g of bromine in 15 ml CCl_4. The reaction flask was cooled to 15—30 °C and the rate of addition was adjusted so as to maintain a faint coloration of bromine at all times (ca. 2 h). The reaction product was washed with water, sodium carbonate solution, and saturated brine, successively, and dried over magnesium sulfate. The solvent was evaporated to give 20.5 g of crude (**5**) as a yellow oil.

(b) dl-4-*t*-Butyl-2-cyclohexen-1-one (**6**). The dehydrobromination was carried out as described by Miyano.[14] Under a nitrogen atmosphere, to a hot stirred suspension (140 °C) of 1.6 g of magnesium oxide in 45 ml *N*,*N*-dimethylformamide was added 7.0 g of (**5**) in 5 ml of *N*,*N*-dimethylformamide; the reaction mixture was stirred for 1 h. After it was cooled with an ice-bath, the magnesium oxide was dissolved by adding 100 ml of dil. hydrochloric acid and extracted several times with ether. The combined ether extract was washed with brine, sodium carbonate, and saturated brine, successively, and the solution was dried over magnesium sulfate. After the solvent was evaporated, the residue was distilled under reduced pressure to give 3.7 g of crude product as a colorless oil (bp 80—83 °C/8 Torr, 1 Torr=133.322 Pa). GLC analysis showed that the product contains 11% of 4-*t*-butylcyclohexanone and 89% of (**6**); it was purified by liquid chromatography (silica gel; hexane–ethyl acetate=10/2) to give (**6**). Compound (**6**): Colorless oil, ^1H NMR ($CDCl_3$) δ=0.98 (s, 9H), 6.02 (d of d, J=10 and 2 Hz, 1H), 7.00 (d of t, J=10 and 2 Hz, 1H). These spectra data were consistent with the literature.[15]

(c) (+)-(1*R*,4*S*)-(**7**) and (+)-(1*R*,4*R*)-4-*t*-Butyl-2-cyclohexen-1-ol(**8**). These alcohols were obtained by an asymmetric reduction of (**6**) with a Darvon/LAH complex according to the procedure reported previously.[3] GLC analysis indicated that the product contains sole 1,2-addition products [**7**: 15%, **8**: 85%]; and no other isomer was detected. The separation of *cis* and *trans* mixture was performed by preparative GLC.{(**7**): $[\alpha]_D^{25}$ +31.7° (*c* 0.68 methanol), mp 54.5 °C. Found: C, 77.36: H, 11.85%. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76%. ^1H NMR ($CDCl_3$) δ=0.91 (s, 9H), 4.02—4.19 (m, 1H), 5.91 (s, 2H); (**8**): $[\alpha]_D^{25}$ +5.14° (*c* 1.07 methanol) mp 38 °C. Found: C, 77.57; H, 11.91%. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76%. ^1H NMR ($CDCl_3$) δ=0.87 (s, 9H), 4.02—4.31 (m, 1H), 5.74 (s, 2H)].

MTPA Esters. 0.1 mmol of partially active unsaturated alcohols were converted to a diastereomeric mixture of (*R*)-(+)-MTPA esters with excess MTPA chloride made from (*R*)-(+)-MTPA according to the usual method.[1]

NMR Shift Studies (Representative Example). NMR spectra of the (*R*)-(+)-MTPA ester of partially active 2-cyclohexen-1-ol ($[\alpha]_D^{25}$ +40.3° (*c* 1.11, $CHCl_3$) 27% ee) were taken with a molar ratio of $Eu(fod)_3$ to the MTPA ester ranging over 0.1—0.3 in $CDCl_3$ (Fig. 1); the magnitudes of the induced chemical shift of the OMe signals were plotted vs. the molar ratio [$Eu(fod)_3$/MTPA ester]. In this range the induced shifts were essentially linear with respect to the molar ratio of the reagent. The ratio of the peak areas of well-separated OMe signals with larger and smaller LIS values was (36/64). From the results of Table 1, (-CH=CH-<-CH_2-CH_2-), (+)-2-cyclohexen-1-ol has the *R*-configuration.[16]

The authors express their sincere thanks to Dr. Masayoshi Ando for his generous gift of valuable samples (Entry 22 and 2,3,4,4a,5,6,7,8-octahydro-4a-methyl-2-naphthol).

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