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USE OF SHIFT REAGENT WITH DIASTEREOMERIC MTPA ESTERS FOR DETERMINATION OF CONFIGURATION AND ENANTIOMERIC PURITY OF SECONDARY CARBINOLS IN ^{1}H NMR SPECTROSCOPY

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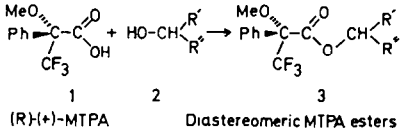
Abstract—The relative magnitude of the lanthanide induced shift(LIS) by Eu(fod)$_3$ for ^{1}H NMR spectra of the OMe group of diastereomeric (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetate esters [(*R*)-(+)-MTPA esters (**3**)] of thirty-two secondary carbinols have been measured. There is a regularity in the relative magnitudes of the LIS values of the OMe signals of the alternate diastereomers which can be correlated with their absolute configurations. This constitutes a versatile method for assigning absolute configurations to secondary carbinols. Furthermore, the relative intensity of the OMe signals can be used for determination of the composition of these diastereomeric MTPA esters and thus the enantiomeric carbinols from which they are quantitatively prepared. These studies extend the usefulness of MTPA derivatives in stereochemical studies.

THE phenomenone of chemical shift nonequivalence of diastereomeric esters and amides has been widely utilized for the analysis of enantiomeric composition of the secondary carbinols[1,2] and amides.[3] These data have also been correlated to allow the assignment of configuration based on systematic differences in the chemical shift nonequivalence of such diastereomers.[2,3] The esters of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**)



have been especially useful in these studies. The methods, however, are not applicable when the ^{1}H NMR signals of the respective diastereomers are not sufficiently separated or when the crucial signals overlap other resonances. In such cases good use has been made[4] of the ^{19}F resonances from the CF_3 group of the MTPA moiety to overcome this problem. However, the ^{19}F capability may not always be available, and in some cases the ^{19}F signals from the diastereomers may not be separated sufficiently. Thus additional methods are always desirable.

We have previously reported isolated cases[5] where the use of a lanthanide shift reagent such as Eu(fod)$_3$ with MTPA esters enhanced the substantial separation of signals from the OMe group in the MTPA acid moiety, and the carbinyl proton in the alcohol moiety so that a useful analysis could be performed. We have now completed a systematic study of this method focusing on the LIS of the OMe signal of the diastereomers represented by **3**.

We have found that the ^{1}H NMR signal from the OMe group of (*R,R*) diastereomer shifted further downfield with a specified molar ratio of Eu(fod)$_3$ than that of (*R,S*) diastereomer; the LIS values,[6] the slopes of the initial linear portion of a plot of induced chemical shift ($\delta_E - \delta$ ppm) vs molar ratio [Eu(fod)$_3$/substrate], for the OMe group of (*R,R*) diastereomers are generally larger than those for the (*R,S*) diastereomers (Fig. 1).† The

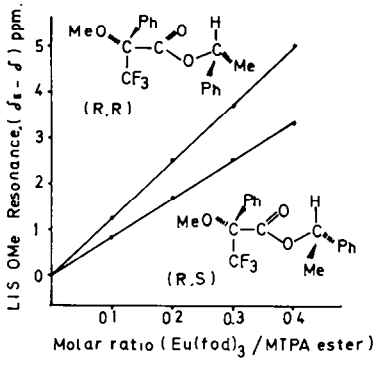


Fig. 1. Representative plots of lanthanide induced shift (LIS) of the methoxyl proton resonance vs molar ratio of Eu(fod)$_3$ for the diastereomeric MTPA esters (**3**). δ_E is the chemical shift in ppm for the OMe signal in the presence of a specified molar ratio of Eu(fod)$_3$ in CCl_4 solvent, while δ is the normal chemical shift. The difference in the slope of these two lines is designated Δ LIS value.

results for more than thirty different diastereomeric pairs of MTPA esters are tabulated in Table 1. Since the Cahn-Ingold-Prelog *R,S* nomenclature scheme is based on arbitrary rules, such a correlation must be a superficial manifestation of a more fundamental phenomenon. This correlation, however, can be rationalized based on the observation that for simple system the priorities in the *R,S* nomenclature scheme generally follow the order of increasing steric bulk, and it may well be that the steric bulk of the R′ and R″ groups in the diastereomeric esters **3** is the determining factor in most of these cases. Thus those compounds in Table 1 which conform to diastereomer A (where R_M stands for medium-sized R group and R_L for the large sized R group) have larger LIS

†In cases where the OMe signal of (*R,R*) diastereomer appears at higher field than that of (*R,S*) diastereomer in the absence of Eu(fod)$_3$, as is often the case with the MTPA esters having Ph group on carbinyl carbon,[2b] the OMe signal of (*R,R*) diastereomer shifts further downfield passing over the signal of (*R,S*) diastereomer by the progressive addition of Eu(fod)$_3$.

Table 1. Chemical shift nonequivalences of methoxyl group in the acid moiety for diastereomeric (*R*)-(+)-MTPA esters induced by Eu(fod)$_3$

Entry	(R)-(+)-MTPA esters Carbinyl moiety R_L	R_M	LIS values of MeO signals of MTPA esters Compds.A : Compds.B LIS_A : LIS_B	ΔLIS values (LIS_A-LIS_B)	Config. of carbinols with larger LIS value
1	Ph	Me	12.6 : 8.6	4.0	(R)-(+)[a]
2	Ph	CF_3	6.1 : 2.3	3.8	(S)-(+)[b,j]
3	Ph	Et	9.6 : 7.5	2.1	(R)-(+)[a]
4	Ph	n-Pr	9.6 : 7.5	2.1	(R)-(+)[c]
5	Ph	i-Pr	10.4 : 9.0	1.4	(R)-(+)[d]
6	Ph	t-Bu	10.6 : 9.2	1.4	(R)-(+)[e]
7	neo-Pentyl	Me	17.3 : 7.8	9.5	(R)-(-)[f]
8	t-Bu	Me	17.0 : 9.5	7.5	(R)-(-)[g]
9	i-Pr	Me	13.7 : 9.1	4.6	(R)-(-)[a]
10	Et	Me	12.7 : 10.0	2.7	(R)-(-)[a]
11	n-Bu	n-Pr	11.8 : 10.4	1.4	(R)-(-)[a]
12	i-Pr	n-Pr	6.2 : 5.4	0.8	(R)-(+)[a]
13	t-Bu	n-Bu	10.1 : 9.2	0.9	(R)-(+)[h]
14	Ph	CH_2OMe	7.1 : 4.9	2.2	(S)-(+)[i,j]
15	Ph	CH_2SMe	8.4 : 6.4	2.0	(S)-(+)[i,j]
16	Ph	CH_2NMe_2	4.4 : 4.2	0.2	(S)-(-)[j,k]
17	Ph	$(CH_2)_2OEt$	6.7 : 5.3	1.4	(R)-(+)[l]
18	$(CH_2)_2OEt$	Et	8.2 : 7.8	0.4	(R)-(+)[l]
19	1-Indanol o-Phenylene C-2		9.6 : 9.4	0.2	(R)-(-)[m]
20	α-Tetralol o-Phenylene C-2		9.4 : 10.4	-1.0	(S)-(-)[n]
21	β-Tetralol Benzyl C-3		7.0 : 7.9	-0.9	(S)-(+)[o]
22	trans-2-Me-CYHL[p] C-2	C-6	12.4 : 11.6	0.8	(R)-(-)[q]
23	cis-3-Me-CYHL[p] C-2,C-3	C-6	8.4 : 8.5	-0.1	(S)-(-)[r]
24	trans-3-Me-CYHL[p] C-2,C-3	C-6	12.0 : 11.6	0.4	(R)-(-)[s]
25	cis-Carveol C-1	C-3	11.4 : 7.9	3.5	(R)-(-)[t]
26	trans-Carveol C-1	C-3	14.1 : 18.3	-4.2	(S)-(-)[t]
27	Borneol C-1	C-3	11.1 : 10.9	0.2	(R)-(-)
28	Menthol C-4	C-2	13.0 : 5.3	7.7	(R)-(-)
29	Neomenthol C-4	C-2	10.2 : 9.6	0.6	(S)-(+)[u]
30	3-α-Cholestanol C-4,C-5	C-2	12.7 : 8.6	4.1	(R)-(+)
31	3-β-Cholestanol C-4,C-5	C-2	9.3 : 9.2	0.1	(S)-(+)[u]
32	Testosterone C-13	C-16	5.6 : 4.8	0.8	(S)-(+)[u,v]
33	Ph	Me	10.9 : 10.5[w]	0.4	(R)-(+)

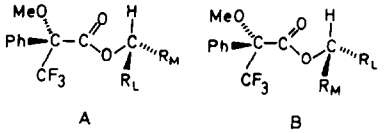
[a] P. A. Levene, and A. Rothen, J. Org. Chem., 1, 76(1936). [b] H. Peters, D. Feigl, and H. S. Mosher, J. Org. Chem., 33, 4245(1968). [c] J. Kenyon, and S. M. Partridge, J. Chem. Soc., 128(1936). [d] P. A. Levene, and J. Mikeska, J. Biol. Chem., 70, 355(1926). [e] R. MacLeod, F. J. Welch, and H. S. Mosher, J. Amer. Chem. Soc., 82, 876(1960). [f] K. Mislow, R. E. O'Brien, and H. Schaefer, J. Amer. Chem. Soc., 84, 1 0(1962). [g] R. W. Pickerd, and J. Kenyon, J. Chem. Soc., 105, 1121(1914). [h] W. M. Foley, F. J. Welch, E. M. LaCombe, and H. S. Mosher, J. Amer. Chem. Soc., 81, 2779(1959). [i] Ref. 10. [j] These carbinols are configurationally related to the other (R)-carbinols because CF_3, CH_2X(X=OMe, SMe, NMe_2) take nomenclatural preference over Ph group according to the Cahn-Ingold-Preloq sequence rule. [k] Ref. 11., Specific rotation has been taken on its hydrochloride. [l] Configurations not previously reported. These configurations tentatively assigned based on the method described in this paper. [m] J. H. Brewster, and J. G. Buta, J. Amer. Chem. Soc., 88, 2233(1966). [n] Ref. 12. [o] H. Arakawa, N. Torimoto, and Y. Masui, Tetrahedron Lett., 4115(1968). [p] CYHL: Stands for cyclohexanol. [q] C. Beard, C. Djerassi, T. Elliott, and R. C. C. Tao, J. Amer. Chem. Soc., 84, 874(1962). [r] R. K. Hill, P. J. Foley and L. A. Gardello, J. Org. Chem., 32,2330(1967). [s] B. K. Mcbeth, and J. A. Mills, J. Chem. Soc., 205(1947). [t] S. H. Schroeter, and E. L. Eliel, J. Org. Chem., 30, 1(1965). [u] Configuration with smaller LIS value. [v] Eu(fod)$_3$ seems to coordinate more preferentially with α,β-unsaturated carbonyl group of carbinyl moiety(testosterone) than the MeO group of acid moiety, and hence LIS value for the MeO group are considerably smaller until molar ratio (Eu(fod)$_3$/substrate) exceeds ~0.8. Since linear relationship between the induced shifts and molar ratios of Eu(fod)$_3$ was not observed until the ratio exceeds ~1.1, the determinations of LIS values were done with the molar ratios of 1.2~1.9 in which range the induced shifts were essentially linear with respect to molar ratio of reagent. [w] Values for the MTPA amide.

‡Although the magnitudes of LIS values for MTPA esters change to some extent with concentration of substrate in CCl_4 solution, ΔLIS values remain almost invariably.

[(*R*)-(+)-MTPA—OCH(Ph/Me)]	LIS_A	LIS_B	ΔLIS
0.1 mmol/0.4 ml CCl_4	12.7	8.5	4.2
0.1 mmol/0.8 ml CCl_4	12.0	8.0	4.0

§The application of such an empirical correlation requires careful consideration of demonstrable difference in steric bulk between the R_M and R_L groups. It is also requires careful consideration of other factors such as attractive or repulsive forces which may be introduced if the group posses unsaturation or heteroatoms. It is basically an empirical correlation and as such is valid only when used to assign the configuration of a new compound in a group of closely related compounds whose configuration are known to follow the correlation. It would be a mistake to assume that other lanthanide shift reagents follow the same empirical correlation. We have only studied the effect of Eu(fod)$_3$. Nevertheless if in any specific case the induced shifts are such that there is insufficient separation of OMe signals, shift reagents other than Eu(fod)$_3$ should be tried. Use could be made of chiral shift reagents[7] as well as the achiral Eu(fod)$_3$.

values‡ (LIS_A) of the OMe resonance than those diastereomers which clearly conform to formula **B**.



A B

There is little question concerning the assignment of R_L and R_M as shown for the first 13 entries in Table 1. The question of which acts as the larger group on other stereochemical situations,§ Ph or t-Bu (entry 6) has been discussed and tested experimentally; generally Ph acts as the sterically large group.[8] Similarly the case of t-Bu vs n-Bu (entry 13) has been tested;[9] generally t-Bu appears to be larger than n-Bu although there is an exception of this. As is seen in the last column there is perfect agreement between this correlation scheme and the results for these first 13 entries.

Entries 14–18 contain an extra heteroatom in the substrate. In these cases, the presence of additional

functional groups such as NMe_2, OMe, OEt and SMe in the carbinyl moiety does not interfere with the application of this method because LIS values of the protons attached to these additional groups in the carbinyl moiety (Table 2) are considerably smaller than those of OMe group of the MTPA moiety. This clearly indicate that the major

Table 2. Induced chemical shift nonequivalences of group X and carbinyl proton for diastereomeric (*R*)-(+)-MTPA esters in the presence of Eu(fod)$_3$

(R)-(+)-MTPA-CO-CH(Ph)(X)

Entry	X	LIS values of methyl signals in group X LIS_A	LIS_B	Entry	X	LIS values of carbinyl proton signals LIS_A	LIS_B
1	CH_2OMe	2.2 (7.1)[a];	1.0 (4.9)[a]	4	Me	3.6(12.6)[a];	3.5(8.6)[a]
2	CH_2SMe	-0.01(8.4)[a];	-0.45(6.4)[a]	5	CF_3	1.6(6.1)[a];	1.5(2.3)[a]
3	CH_2NMe_2	—[b](4.4)[a];	—[b](4.2)[a]	6	t-Bu	2.8(10.6)[a];	2.2(9.2)[a]

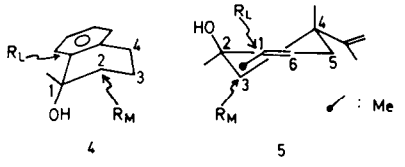
[a] Those in parentheses are for the OMe group in the MTPA acid moiety.

[b] The LIS values for NMe_2 group are considerably smaller than those for the OMe group in the acid moiety, however, accurate values were not obtained because of rapid line broadning.

complexing of the Eu(fod)$_3$ is the same in these compounds as in the first 13 entries. Without the precedence of examples with known configuration it would be unwise to try to apply a correlation scheme based on R_L vs R_M to such compounds. The first three of these ($PhCH(OH)CH_2OMe$,[10] $PhCH(OH)CH_2SMe$,[10] and $PhCH(OH)CH_2NMe_2$[11]) are correctly correlated by assuming that Ph acts as R_L in the correlation scheme. In entry 17, if Ph acts as if it is larger than $EtOCH_2CH_2$–, as shown by the entries in columns 2 and 3 of example 17 and if this correlation holds for this substrate then (*R*)-1-phenyl-2-ethoxy-ethanol should be dextrorotatory. Similarly, for example 18, if $EtOCH_2CH_2$– acts as though it is larger than Et, then (*R*)-1-ethoxy-3-pentanol is dextrorotatory.

Entries 22–32 are examples with more than one chiral center. In such cases it may be that one or more of these additional asymmetric centers is influential in determining the chemical shift nonequivalence. In spite of this, except for two instances (entries 20† and 26), these MTPA esters fit the correlation scheme in which R_L and R_M are being designated as shown in the second and third columns of Table 1.

As can be seen from the negative sign of Δ LIS values (entries 20, 21, 23 and 26), there are four examples which do not follow this correlation scheme. In α-tetraol **4**, the methylene group at C-2 may be clearly designated R_M, while the *ortho* phenylene group is R_L. In (−)-*trans*-carveol **5**, the greater branching at C-1 would be determining in designating the C-1 branch as R_L over the C-3, C-4 branch as R_M, and this assumption seems to be



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correct by inspecting Dreiding models. Therefore, these examples are clear exceptions to this general correlation scheme. Although, there are several common structural features‡ for these exceptional cases, these features might be superficial manifestation and further detailed study would be necessary for the elucidation of this problem.

Furthermore, we have observed that when the differences in the LIS values of the OMe resonance of (*R,R*) and (*R,S*) diastereomers are 0.2 or greater, the separation of resonance signals of the usual line width is such that we can make practical use of the data to determine quantitatively the diastereomeric ratio of MTPA esters, and thereby enantiomeric purity of original carbinols from which these stereoisomers were prepared. The experimental deviations from those obtained by the measurement of specific rotation were within ±2%.

The explicit directions for use of this correlation for prediction of the configuration of a secondary carbinol are as follows: only secondary carbinols are chosen which have R′ and R″ groups which can clearly be designated R_L and R_M. Such a carbinol which is practically active whose rotation has been taken is quantitatively converted by treatment with excess of the acid chloride from (*R*)-(+)-MTPA into a mixture of diastereomers by the previously described method.[2b] The LIS values for the OMe signals of the two diastereomers are determined in the presence of Eu(fod)$_3$ as indicated in Fig. 1. The observed rotation of the original carbinol mixture and its LIS value are clearly associated with the major OMe signal. This correlation derived from the data in Table 1 predicts that the diastereomer with the larger LIS value will have configuration **A** and the alternate diastereomer with the smaller LIS value will have configuration **B**. If R_L takes precedence over R_M in the *R,S* nomenclature scheme, then that diastereomeric MTPA ester with the larger LIS value will be (*R,R*) if (*R*)-(+)-MPTA was used (or (*S,S*) if (*S*)-(−)-MTPA was used). In cases where only one pure isomer of the carbinal is available, as is often the case with natural products, diastereomeric MTPA esters can be generated from the same carbinol using both (*R*)-(+)- and (*S*)-(−)-MTPA. Since NMR spectra of (*R,S*) and (*S,R*) or (*R,R*) and (*S,S*) enantiomers are indistinguishable, an application of symmetry principles will give the necessary information.§

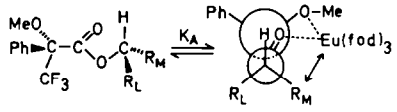
The above NMR configurational correlation can be

†The configuration of α-tetralol with a larger LIS value was assigned as (*S*)-(−) by Horeau's method in agreement with the result reported in the literature.[12]

‡(i) The all of these four compounds belong to cyclic modification. (ii) Two of these (entries 20 and 26) have quasiaxial OH group at allylic or benzylic position as preferred conformation (S. Yamaguchi *et al., Bull. Chem. Soc. Japan* **43**, 3952 (1970); **44**, 3487 (1971).). (iii) In addition to the small steric bulk difference between R_L and R_M (entries 21 and 23), preferred conformation of the OH group in these compounds is equatorial. The small Δ LIS value for 3-β-cholestanol (entry 31) may be attributable to the small steric bulk difference between R_L and R_M. (J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions*, p. 58. Prentice-Hall, Englewood Cliffs, New Jersey (1970).) Since 3-β-cholestanol possesses an equatorial OH group, example 31 seems to be a marginal example which follows this correlation scheme.

§Standard precautions must be taken to prevent kinetic resolutions by either making the two diastereomers separately or by preparing quantitatively with a mixture of a unequal amount of the mixture of (*R*)- and (*S*)-MTPA in the presence of an excess of the chiral carbinol.

qualitatively rationalized by empirical models represented by formulas **6** and **7** in which the diastereomeric MTPA esters **A** and **B** coordinate with Eu(fod)$_3$ with both the O atoms from the carbonyl and OMe group. The steric interactions of the R_M and R_L groups will be different in these two complexes. If the complexation constant K_A for the formation of **6** from **A** is larger than the constant K_B for the formation of **7** from **B**, then the steady state concentration of **6** should exceed that of **7** so that a larger chemical shift should be induced in **A** than **B** as is



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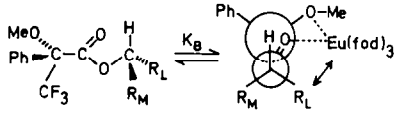

B 7

observed. It is proposed that this happens because of the lesser steric interaction of R_M with the Eu(fod)$_3$ in complex **6** than with R_L in complex **7**. In the model this depends upon the choice of the conformation of the carbinyl moiety with respect to rotation about the carbinyl oxygen axis. The experimental support for the present models is that the magnitude of ΔLIS value decreases with decreasing steric bulk differences between the two substituents (R_L and R_M) on carbinyl carbon of phenylalkyl carbinyl (Table 1, entries 1–6) and dialkylcarbinyl (Table 1, entries 7–10) esters. The observation that the LIS values for the OMe group in the MTPA acid moiety are considerably larger than those for the carbinyl proton in the alcohol moiety (Table 2, entries 4–6) would also support this postulation indicating that the complexing of Eu(fod)$_3$ with the ester groups makes little contribution in this instance.

Most of the partially active carbinols used in these studies were prepared by asymmetric reduction using the chiral reducing agent formed by the reaction of one mole of LAH with 2.3 moles of (−)-(2*R*,3*S*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol. The reactions were done in an ether solvent at 0°C according to the previously published method.[5] It is noteworthy that this is a convenient, rapid, practical method for obtaining a variety of partially active secondary carbinols with substantial enantiomeric purities. Those substrates with aliphatic groups only (Table 3, first 5 entries) were reduced with stereoslectivities from 8 to 52% while those containing an aromatic moiety were reduced with stereosectivities of from 37 to 76% (Table 3, last 5 entries).

The above NMR configurational correlation has also been found to hold well for the MTPA esters of enantiomeric primary carbinols with the chiral center at the C-2 position, and of α-hydroxylic acid esters. Further systematic investigations to extend the application for these types of compounds are now in progress.

EXPERIMENTAL

Instruments. NMR spectra were measured on Varian A-60 and Hitachi R-22 (90 MHz) instruments in CCl_4 with TMS as an internal standard. Optical rotations were determined on Perkin-Elmer 141 and 241 electronic polarimeters using 1-dm and 0.1-dm thermostated cells. Preparative VPC were carried out on a Varian Aerograph (model 700) using PEG 20M or Erythritol (1 ~ 2 meter × 4 mm column).

Table 3. Asymmetric reduction of ketones with LiAlH$_4$—(−)-(2*R*,3*S*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol reagent[a]

$$R_1COR_2 + LiAlH_2(OR^*)_2 \xrightarrow[0°C]{Et_2O} \xrightarrow{H_3O^+} R_1^*CH(OH)R_2$$

Ketones		Carbinols	
R_1	R_2	Enantiomeric purity[b] % ee	Configuration
Me	Et	8 (7)	(S)-(+)
Me	i-Pr	25 (24)	(S)-(+)
Me	Neopentyl	52 (51)	(S)-(+)
n-Pr	i-Pr	20 (18)	(S)-(−)
Et	CH_2CH_2OEt	17	(R)-(+)[c]
Et	Ph	76 (78)	(S)-(−)
CH_2CH_2OEt	Ph	54	(S)-(−)[c]
α-Tetralone		39 (40)	(S)-(+)
β-Tetralone		37 (38)	(R)-(+)
1-Indanone		43 (45)	(S)-(+)

[a] Asymmetric reductions by the LiAlH$_2$(OR*)$_2$ reagent described in reference 5 using method A.

[b] Values based on the relative areas of the MeO nmr signals of diastereomeric MTPA derivatives in the presence of Eu(fod)$_3$. Values in parentheses based upon optical rotation.[4,5]

[c] Configurations not previously reported. These configurations tentatively assigned based on the method described in this paper.

Solvents and reagent. Ether was distilled over LAH and stored over Linde molecular sieve 3A. Spectrograde CCl_4 was dried with molecular sieve 3A. Pyridine was dried with BaO, distilled and stored over molecular sieve 3A. A stock LAH soln in ether was passed through a glass filter unter N_2 and stored in a flask closed with a rubber septum. It was analysed[13] by iodometry immediately prior to use. Aliquots were removed by syringe as needed.

Chiral carbinols. Several partially active carbinols employed in this experiment were prepared by asymmetric reduction of corresponding ketones with (−)-(2*R*,3*S*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol[14]—LAH complex according to the procedure (A) reported previously.[5] The chemical yields were essentially quantitative. The carbinols thus obtained were purified by preparative VPC, if necessary. The enantiomeric purities and configurations are collected in Table 3.

Partially active (+)-*trans*-2-methylcyclohexanol ($[\alpha]_D^{25}$ + 5.04° (*c*, 0.4, cyclopentane)) was prepared by asymmetric reduction[5] of racemic 2-methylcyclohexanone followed by preparative VPC separation from the *cis* isomer.

(−)-*cis*-(1*S*,3*R*)- ($[\alpha]_D^{25}$ − 2.27° (*c*, 1.54, cyclopentane)), and (−)-*trans*-(1*R*,3*R*)-3-Methylcyclohexanols ($[\alpha]_D^{25}$ − 1.07° (c, 1.31, cyclopentane)) were isolated by preparative VPC from a mixture of 3-methylcyclohexanols (*cis*/*trans* = 68/32) prepared by reduction of (*R*)-(+)-3-methylcyclohexanone ($[\alpha]_D^{25}$ + 13.5° (neat))[14] with LiAlH(OMe)$_3$ in anhydrous ether.

(−)-*cis*- ($[\alpha]_D^{25}$ − 23.7° (neat)) and (−)-*trans*- ($[\alpha]_D^{25}$ − 199.0° (neat)) Carveols were separated by preparative VPC from a mixture of carveol (*cis*/*trans* = 69/31) prepared by Meerwein-Ponndorf reduction of (−)-carvone ($[\alpha]_D^{25}$ − 61.4° (neat)).[15]

2-Substituted-1-phenylethanols were prepared by asymmetric reduction of corresponding ω-substituted acetophenones with LAH-(−)-menthol complex.[10] The absolute configurations of OMe and SMe derives (Table 1, entries 14, and 15) have been assigned as (*S*)-(+) by correlating them chemically to (*S*)-(+)-mandelic acid.[10]

MTPA esters. 0.1 mmole of partially active carbinols were converted to diastereomeric mixture of (*R*)-(+)-MTPA esters with excess MTPA chloride made from (*R*)-(+)-MTPA according to the usual method.[2b]

Shift studies (representative example). NMR spectra of (*R*)-(+)-MTPA esters of partially active phenylethylcarbinol ($[\alpha]_D^{20}$ − 21.54° (neat), 78%ee, Table 3) were taken with molar ratio of $Eu(fod)_3$ to MTPA ester of 0.1–0.3 in CCl_4, and the magnitudes of induced chemical shift of OMe signals were plotted vs molar ratio ($Eu(fod)_3$/MTPA ester). In this range the induced shifts were essentially linear with respect to molar ratio of reagent. The ratio of peak areas of well separated OMe signals with larger and smaller LIS value was (12/88). Therefore, (−)-phenylethylcarbinol will have (*S*)-configuration.

Assignment of absolute configuration of (+)-α-tetralol by Horeau's method.[16a,b] 81.4 mg of partially active (+)-α-tetralol ($[\alpha]_D^{25}$ + 10.65° (*c*, 6.60, benzene), 40%ee, Table 3) was treated with 507 mg of racemic α-phenylbutyric anhydride according to the procedure reported in the literature.[16b] The specific rotation of recovered α-phenylbutyric acid (345 mg) was $[\alpha]_D^{25}$ − 0.452° (*c*, 27.4, benzene) indicating that (+)-α-tetralol has (*S*)-configuration.

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