

USE OF SHIFT REAGENT WITH MTPA DERIVATIVES IN  $^1\text{H}$  NMR SPECTROSCOPY. III.  
 DETERMINATION OF ABSOLUTE CONFIGURATION AND ENANTIOMERIC PURITY OF  
 PRIMARY CARBINOLS WITH CHIRAL CENTER AT THE C-2 POSITION <sup>1</sup>

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There have been reported many investigations for the determination of absolute configuration and optical purity of secondary carbinols by the NMR method.<sup>2</sup> Such an attempt for primary carbinols with the chiral center at the C-2 position, however, has not been reported yet.<sup>3</sup>

As an extension of the previous method,<sup>4,5</sup> we wish to report a new simple and convenient method for determining absolute configuration and optical purity of primary carbinols with the chiral center at the C-2 position.

A partially active 2-phenyl-1-propanol [(S)-(-), 26 %ee] was quantitatively converted to the corresponding diastereomeric mixture of (R)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid [(R)-(+)-MTPA, Mosher's reagent] esters according to Mosher's method.<sup>6</sup> The magnitude of lanthanide induced shift ( $\text{LIS}_{\text{OMe}}$ ) by  $\text{Eu}(\text{fod})_3$  for the OMe group of the MTPA ester of the (R)-carbinol is larger than

that of the (S)-carbinol (Fig. 1).

The results summarized in Table 1 reveal a clear correlation of the relative magnitude of  $\text{LIS}_{\text{OMe}}$  with the absolute configuration of these primary carbinols; the diastereomeric (R)-(+)-MTPA

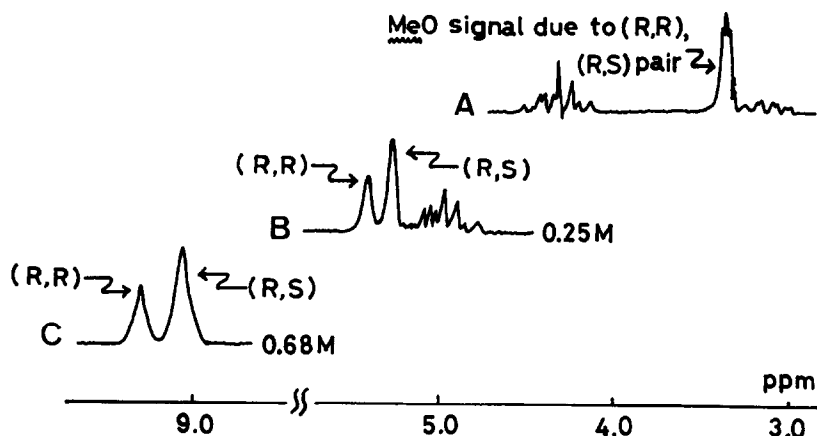


Fig. 1. 90 MHz  $^1\text{H}$  NMR spectra of (R)-(+)-MTPA esters of partially active 2-phenyl-1-propanol [(S)-(-), 26 %ee] in  $\text{CCl}_4$  containing various molar ratio of  $\text{Eu}(\text{fod})_3$ : A, 0 mol; B, 0.25 mol; C, 0.68 mol. ( See entry 6, Table 1 )

ester with the larger LIS<sub>OMe</sub> value has configuration A (where R<sub>M</sub> stands for the medium sized and R<sub>L</sub> for the large sized group)<sup>7</sup> and the alternate diastereomer with the smaller LIS<sub>OMe</sub> value has configuration B.

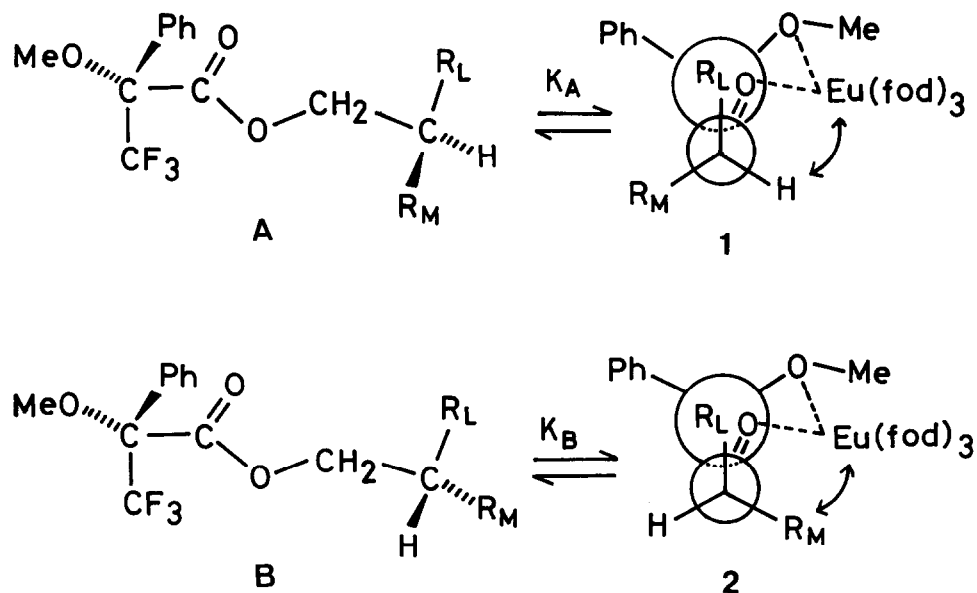
As is seen in the last column of Table 1, there is perfect agreement between this correlation scheme and the results for all of the twelve primary carbinols tested so far.

Table 1. Lanthanide Induced Shift of the Methoxyl Group in the Acid Moiety for Diastereomeric (R)-(+)-MTPA Esters in the Presence of Eu(fod)<sub>3</sub>

Entry	(R)-(+)-MTPA esters Carbinyl moiety		LIS <sub>OMe</sub> of MTPA esters		Δ LIS <sub>OMe</sub> (LIS <sub>A</sub> -LIS <sub>B</sub> )	Config. of carbinols with larger LIS <sub>OMe</sub>
	R <sub>L</sub>	R <sub>M</sub>	Compds.A Compds.B			
			LIS <sub>A</sub>	LIS <sub>B</sub>		
1	Et	Me	9.95	9.75	0.20	(R)-(+) <sup>a</sup>
2	n-Pr	Me	8.82	8.57	0.25	(R)-(+) <sup>b</sup>
3	i-Pr	Me	9.56	9.41	0.15	(R)-(+) <sup>c</sup>
4	n-Bu	Me	9.13	8.90	0.23	(R)-(+) <sup>a</sup>
5	t-Bu	Me	8.78	8.63	0.15	(R)-(-) <sup>c</sup>
6	Ph	Me	9.88	9.41	0.47	(R)-(+) <sup>d</sup>
7	Ph	CF <sub>3</sub>	7.00	5.89	1.11	(R)-(+) <sup>e</sup>
8	Ph	Et	7.71	7.48	0.23	(R)-(-) <sup>f</sup>
9	Ph	i-Pr	7.60	6.80	0.80	(R)-(-) <sup>g</sup>
10	Ph	t-Bu	8.70	8.00	0.70	(R)-(+) <sup>h</sup>
11	(+)-(4R,8R)-p-Menth- 1-en-9-ol		8.80	8.72	0.08	(R)-(+) <sup>i</sup>
12	C-4	Me				
	Ph	OMe	7.45	7.38	0.07	(R)-(-) <sup>j</sup>

<sup>a</sup> P. A. Levene and A. Rothen, *J. Org. Chem.*, 1, 76 (1936). <sup>b</sup> G. I. Fray and S. R. Robinson, *Tetrahedron*, 18, 261 (1962). <sup>c</sup> G. Zweifel, N. R. Ayyanger, T. Munakata and H. C. Brown, *J. Amer. Chem. Soc.*, 86, 1076 (1964). <sup>d</sup> S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 171 (1961). <sup>e</sup> D. Dull, Ph. D. thesis, Stanford University, 1967. <sup>f</sup> M. J. Brienne, C. Ouannes and J. Jaques, *Bull. Soc. Chem. Fr.*, 34, 613 (1967). <sup>g</sup> J. L. Schmiegel, Ph. D. thesis, Stanford University, 1967. <sup>h</sup> D. R. Clark and H. S. Mosher, *J. Org. Chem.*, 35, 1114 (1970). <sup>i</sup> B. A. Paeson, H. C. Cheung, S. Gurbaxani and G. Saucy, *J. Amer. Chem. Soc.*, 92, 336 (1970). <sup>j</sup> D. M. Feigl and H. S. Mosher, *J. Org. Chem.*, 33, 4242 (1968).

This regularity can be qualitatively rationalized in terms of the following empirical models. The preferred conformations of the (R)-(+)-MTPA esters may be such that the ester group and the  $R_L$  group exist in the anticonformation. Diastereomeric (R)-(+)-MTPA esters A and B coordinate with  $\text{Eu}(\text{fod})_3$  with both oxygen atoms from the carbonyl and OMe group. If the complexation constant  $K_A$  for the formation of 1 from A is larger than the constant  $K_B$  for the formation of 2 from B,



B, then the steady state concentration of 1 should exceed that of 2 so that a larger chemical shift should be induced in A than B as is observed. It is proposed that this happens because of the lesser steric interaction of the  $\text{Eu}(\text{fod})_3$  with the hydrogen atom on the chiral center in 1 than with  $R_M$  in 2.

The experimental support for the present model is that the magnitudes of  $\Delta\text{LIS}_{\text{OMe}}$  for the esters of 2-*i*-Pr- and 2-*t*-butyl-2-phenylethanols (entries 9, 10) are larger than those for the Me and Et derivatives (entries 6, 8). That is to say, contrary to the case of secondary carbinols,<sup>4</sup> the magnitudes of  $\Delta\text{LIS}_{\text{OMe}}$  are influenced by the steric bulk difference not between two larger groups ( $R_L$  versus  $R_M$ ) but between two smaller groups ( $R_M$  versus H). The presence of additional OMe group in the carbinyl moiety does not interfere with the application of this method because  $\text{LIS}_{\text{OMe}}$  in the carbinyl moiety (0.8) is considerably smaller than that of  $\text{LIS}_{\text{OMe}}$  of the MTPA acid moiety (Table 1, entry 12).

The enantiomeric purity of original carbinols can be determined<sup>8</sup> from the ratio of peak areas of the OMe signals except in the case where the  $\Delta\text{LIS}_{\text{OMe}}$  is

too small to afford the correct enantiomeric purity (entries 11, 12).

Since the reduction of an optical active carboxylic acid having the chiral center at the  $\alpha$ -position with  $\text{LiAlH}_4$  affords the corresponding carbinol without any racemization,<sup>9</sup> the present method is also applicable to these types of active or partially active carboxylic acids, and aldehydes.

Further investigation to explore the limitation of the present technique is in progress.

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#### REFERENCES AND NOTES

1. Presented at the 35th Annual Meeting of the Chemical Society of Japan, Sapporo, August 1976.
2. M. Raban and K. Mislow, Top. Stereochem., 2, 199 (1967); W. H. Pirkle and S. D. Beare, J. Amer. Chem. Soc., 89, 5485 (1967); G. M. Whitesides and D. W. Lewis, ibid., 92, 6979 (1970); R. R. Fraser, M. A. Petit and J. K. Saunders, Chem. Comm., 1450 (1971); K. Ajisaka, M. Kamisaku and M. Kainosho, Chem. Lett., 857 (1972); H. Gerlach and B. Zagalak, Chem. Comm., 274 (1973); G. R. Sullivan, J. A. Dale and H. S. Mosher, J. Org. Chem., 38, 2143 (1973); G. Helmchen, Tetrahedron Lett., 1527 (1974); M. D. McCreary, D. W. Lewis, D. L. Wernick and G. M. Whitesides, J. Amer. Chem. Soc., 96, 1083 (1974) and references therein.
3. After this work has been completed, the determination of enantiomeric purity of 2-phenylethanol-1,1,2- $\text{d}_3$  in the presence of  $\text{Eu}(\text{dcm})_3$  was reported. J. D. Morrison, J. E. Tomaszewski, H. S. Mosher, J. Dale, D. Miller and R. L. Elsenbaumer, J. Amer. Chem. Soc., 99, 3167 (1977).
4. S. Yamaguchi, F. Yasuhara and K. Kabuto, Tetrahedron, 32, 1363 (1976).
5. S. Yamaguchi and F. Yasuhara, Tetrahedron Lett., 89 (1977).
6. J. A. Dale and H. S. Mosher, J. Amer. Chem. Soc., 95, 512 (1973).
7. The order of steric requirements of  $R_L$  and  $R_M$  on the chiral center was considered to be the same as has been discussed on the MTPA esters of secondary carbinols. (reference 4)
8. The experimental deviations from those obtained by the measurement of specific rotations were within  $\pm 2\%$ .
9. J. A. Dale and H. S. Mosher, J. Org. Chem., 35, 4002 (1970).