A CONVENIENT METHOD FOR THE DETERMINATION OF
ABSOLUTE CONFIGURATION AND ENANTIOMERIC EXCESS
OF BICYCLIC SECONDARY CARBINOLS

N. Kalyanam and D. A. Lightner[*]
Department of Chemistry, University of Nevada
Reno, Nevada 89557 USA

Methods based on nmr spectroscopy are becoming increasingly important in the determination of absolute configuration and enantiomeric excess (e.e.) of optically active compounds. These involve either examination of nmr spectra of partially active compounds in a chiral media or conversion of partially active compounds to diasteromers (using an optically pure auxiliary compound) whose nmr spectra are examined with or without added shift reagent[1,2]. Yamaguchi *et.al.* have described[3] an ^{1}H-nmr method of determination of absolute configuration and e.e. of secondary carbinols using MTPA derivatives[4] in the presence of added Eu(fod)$_3$ shift reagent. But no systematic study on the stereochemically important bicyclic secondary carbinols has appeared. We report here the determination of absolute configuration and e.e. of bicyclic carbinols through the study of both ^{19}F and ^{1}H nmr spectra of their MTPA derivatives in the presence of Eu(fod)$_3$.

The induced shifts for -OCH$_3$ ([LIS]$_{-OCH_3}$) and -CF$_3$ ([LIS]$_{-CF_3}$) signals in ^{1}H nmr and ^{19}F nmr respectively are summarized in the Table. It is evident that R-(+)-MTPA[5] derivatives of B-R alcohols[6] have higher [LIS]$_{-OCH_3}$ and [LIS]$_{-CF_3}$ values than R-(+)-MTPA derivatives of B-S alcohols.[6] This can be rationalized using the following empirical models.[3,7]

11

12

R - (+) - B-R

13

R - (+) - B-S

14
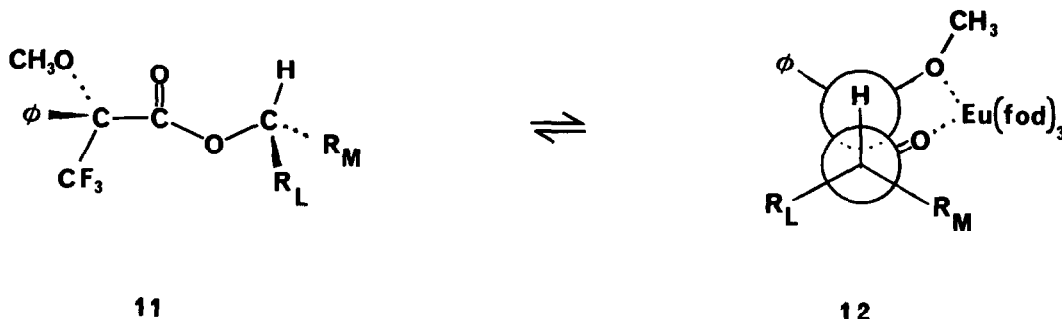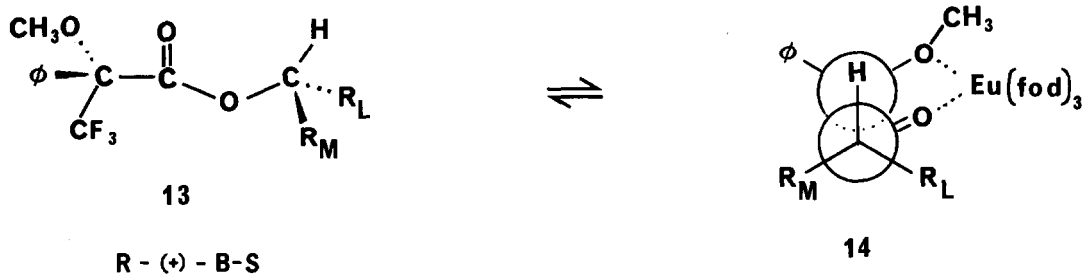
The lower steric hindrance experienced by the complexing shift reagent in 12 than in 14 should increase the steady state concentration of 12 over 14; hence, $[LIS]_{-OCH_3}$ and $[LIS]_{-CF_3}$ for R(+)-B-R (11) must be larger than those for R-(+)-B-S (13). However, for 3, 4 and 5 no useful separation of -OCH₃ groups for the diastereomers 11 and 13 is obtained in the [1]H-nmr [(i.e.) $\Delta[LIS]_{-OCH_3}$ = 0], but the -CF₃ signals for the corresponding diastereomers are well separated. Thus ^{19}F-nmr offers a distinct advantage over [1]H-nmr. The simple two line spectrum for the diastereotopic -CF₃ signals in ^{19}F-nmr with no interfering signals is clearly preferable to [1]H-nmr method in which the carbinyl, olefinic and aromatic hydrogens interfere with the downfield-shifting signals for -OCH₃ groups. Also in most cases $[LIS]_{-CF_3}$ are generally larger than $[LIS]_{-OCH_3}$.

It can be seen from the table that $\Delta[LIS]_{-OCH_3}$ and $\Delta[LIS]_{-CF_3}$ are of the same magnitude for 3, 4 and 5. The results are readily explicable in terms of the models proposed (vide supra). For 3 and 4, R_L and R_M are of the same magnitude and hence $\Delta[LIS]$ values must be similar. For 5, both R_L and R_M become equally sterically congested in going from 3/4 to 5. Higher increases in $\Delta[LIS]_{-OCH_3}$ and $\Delta[LIS]_{-CF_3}$ for 6 and 7 can also be explained by the models proposed. For example, the diastereomer R-(+)-B-R of 6 derives additional stabilization in 12 because the syn -OCH₃ group is sterically disposed to coordinate with Eu(fod)₃ (see 15), whereas such a situation does not exist for R-(+)-B-S isomer of 6. The increased coordination of Eu(fod)₃ with the B-R isomer relative to the B-S isomer is expected to give increased $\Delta[LIS]_{-OCH_3}$ and $\Delta[LIS]_{-CF_3}$. This conclusion is supported by the fact that $[LIS]_{syn-OCH_3}$ for R-(+)-B-R isomer (1.03) is greater than $[LIS]_{syn-OCH_3}$ for R-(+)-B-S isomer (0.96).
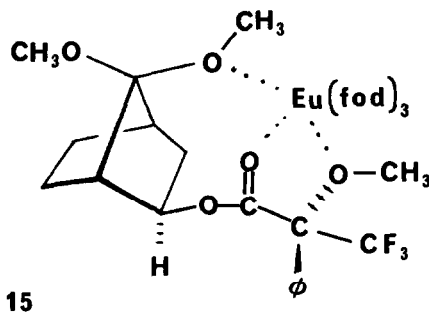

15

Table: Lanthanide Induced Shifts of the Methoxy and Trifluoromethyl
Groups in the Acid Moiety for the Diastereomeric R-(+)-MTPA
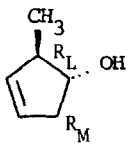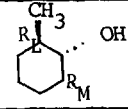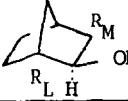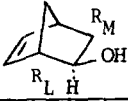Esters in the Presence of $Eu(fod)_3$
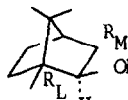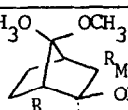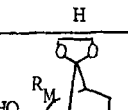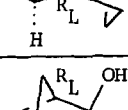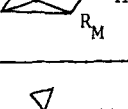
Entry	Structure of the Carbinyl Moiety[a]	^1H-nmr Data[b]			^{19}F-nmr Data[b]		
		$[LIS]_{-OCH_3}$ for R-(+)-B-R Derivative	$[LIS]_{-OCH_3}$ for R-(+)-B-S Derivative	$\Delta[LIS]_{-OCH_3}$	$[LIS]_{-CF_3}$ for R-(+)-B-R Derivative	$[LIS]_{-CF_3}$ for R-(+)-B-S Derivative	$\Delta[LIS]_{-CF_3}$
1[c]	(structure: CH_3, R_L, OH, R_M)	5.7	-	-	3.7	-	-
2[d]	(structure: CH_3, R_L, OH, R_M)	18.7	14.7	4.0	22.3	18.7	3.6
3[e]	(structure: R_M, OH, R_L, H)	10.9	10.9	0	14.2	13.9	0.3
4[f]	(structure: R_M, OH, R_L, H)	11.6	11.6	0	14.7	14.3	0.4
5[g]	(structure: R_M, OH, R_L, H)	15.2	15.2	0	13.3	12.7	0.6
6[h]	(structure: CH_3O, OCH_3, R_M, OH, R_L, H)	4.8	4.4	0.4	7.9	7.0	0.9
7[i]	(structure: R_M, HO, R_L, H)	8.2	6.9	1.3	10.6	9.4	1.2
8[j]	(structure: R_L, OH, H, R_M)	17.5	14.2	3.3	19.9	17.3	2.6
9[k]	(structure: R_L, H, OH, R_M)	14.2	11.8	2.4	15.5	13.5	2.0
10[k]	(structure: OH, R_L, H, R_M)	12.8	11.2	1.6	15.9	13.9	2.0

Table (continued)

a. Absolute configuration for all the compounds are known except for 7 and 8. The absolute configuration of 7 is established in this work.

b. The spectra were obtained on a JEOL FX-100 Fourier transform spectrometer in CDCl$_3$ solvent with TMS and CFCl$_3$ as internal standards for ^{1}H- and ^{19}F-nmr respectively; [LIS] values were evaluated using (Eu(fod)$_3$/Mosher esters) molar ratios from 0.1-0.5.

c. Only the pure (1R, 2R) isomer used; C. S. Pak, Ph.D. dissertation, University of Nevada, Reno, 1977.

d. Prepared by C. S. Pak according to H. C. Brown and N. M. Yoon, J. Am. Chem. Soc., 99, 5514 (1977).

e. Prepared by B. V. Crist according to the procedure described by H. C. Brown, N. R. Ayyangar and G. Zweifel, J. Am. Chem. Soc., 86, 403 (1964).

f. C. S. Pak, Ph.D. dissertation, University of Nevada, 1977.

g. Prepared by the reduction of a mixture of d- and dl-camphor by K-Selectride according to the procedure described by B. Ganem, J. Org. Chem., 40, 146 (1975).

h. Prepared by G. L. Landen and J. Gawronski; originally described by D. A. Lightner and D. E. Jackman, J. Am. Chem. Soc., 96, 1938 (1974).

i. Prepared by the oxymercuration of 8-ethylenedioxy-[3.2.1]-bicyclooct-6-ene and resolved as the half acid-phthalate; L. May and N. Kalyanam.

j. Prepared by W. K. Yokoyama according to the procedure by J. Meinwald, J. Crandall and E. Hymans, Org. Synthesis, 5, 86 (1973).

k. D. A. Lightner and W. A. Beavers, J. Am. Chem. Soc., 93, 2677 (1971).

References

 1. For reviews on the determination of optical purity see: (a) M. Raban and K. Mislow, Top. Stereochem., 2, 199 (1967), and (b) Y. Izumi and A. Tai, Stereo-Differentiating Reactions, Academic Press, New York, 1977, Chapter 8.

 2. For leading references on the determination of absolute configuration of carbinols by NMR methods see: (a) S. Seo, Y. Tomita, K. Tori and Y. Yoshimura, J. Am. Chem. Soc., 100, 3331 (1978), and (b) G. Helmchen, Tetrahedron Lett., 1527 (1974).

 3. S. Yamaguchi, F. Yasuhara and K. Kabuto, Tetrahedron, 32, 1363 (1976).

 4. R-(+)-MTPA=R-(+)-α-methoxy-α-trifluoromethylphenylacetic acid is available as 99+% enantiomerically pure from Aldrich Chemical Co. Its diasteromeric esters (Mosher esters) were first described by J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).

 5. All Mosher esters were prepared using R-(+)-MTPA[4] via its acid chloride. In this work they are called R-(+)-MTPA esters or derivatives. In a typical preparation, to a solution of R-(+)MTPA-Cl (0.14 mmol) in dry pyridine (300 µl), carbon tetrachloride (200 µl) and the substrate alcohol (0.10 mmol in 100 µl CCl$_4$) were injected successively. There was immediate precipitation of pyridine hydrochloride. After the reaction was complete (as evidenced by no more formation pyridine hydrochloride), the solution was shaken with 3-dimethylamino-1-propylamine (24 µl). The solution was then diluted with ether and washed with dilute HCl, saturated Na$_2$CO$_3$ and saturated NaCl successively. After drying over MgSO$_4$, the solvents were removed to yield the Mosher derivative which was utilized for nmr spectral measurements. J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., 95, 512 (1973).

 6. The letter B is an indication of the 'bulkiness sequence subrule' (priority sequence: oxygen atom > large group (R$_L$) > medium group (R$_M$) > hydrogen atom. For the proposal and use of this nomenclature see, M. Nakazaki, H. Chikamatzu, K. Naemura, M. Nishimo, H. Murakami and M. Asao, J. Chem. Soc., Chem. Comm., 667 (1978).

 7. However, use of a single conformation to explain LIS must be done with caution. G. R. Sullivan, J. Am. Chem. Soc., 96, 7162 (1976); D. H. Williams, Pure and Appl. Chem., 40, 25 (1974).