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NOE CORRELATIONS IN MTPA, MNCB AND MBNC ESTERS

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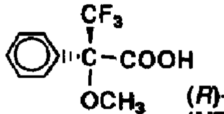
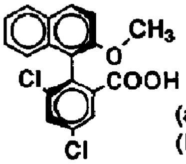
Abstract : NOEs are observed between the protons of the acid moieties and the protons of the alcohol moieties in some α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**), 2-(2'-methoxy-1'-naphthyl)-3,5-dichlorobenzoic acid (MNCB, **2**), and 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (MBNC, **3**) esters. This initial observation could be another clue to determine the absolute configurations of chiral alcohols.

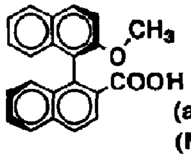
The nonequivalence of NMR chemical shifts for diastereomeric α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**) esters has been utilized for determination of the absolute configuration of chiral alcohols and amines[1]. Previously we reported on the application of axially chiral 2-(2'-methoxy-1'-naphthyl)-3,5-dichlorobenzoic acid (MNCB, **2**) and 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (MBNC, **3**) for the same purpose[2]. Herein we wish to show that stereochemically significant NOEs are observed between the protons of the acid moieties and the protons of the alcohol moieties in some esters of these three acids.



(*R*)-1
(MTPA)



(a*S*)-2
(MNCB)



(a*R*)-3
(MBNC)

On MTPA esters, Mosher proposed that, in solution, the carbinyl proton, ester carbonyl and trifluoromethyl groups of the MTPA moiety lie in the same plane (Figure **1A**)[3]. The PCILO calculation on a MTPA ester demonstrates that there are two stable conformations (Figures **1A** and **1B**)[4]. Furthermore, the band profile analysis of IR adsorptions (in CCl_4) on the (*R*)-MTPA esters of several cyclohexanols exhibits that the conformation of **1A** is preferable (*ca.*7:3) to that of **1B**[4]. When the MTPA group is in the two stable conformations in solution, NOEs will be observed between the methoxy protons of the MTPA moiety and the Hb proton, and also between the phenyl protons and the Ha proton in the conformation of **1A** for (*R*)-MTPA esters. On the other hand, weak or no NOEs will be observed between the methoxy protons of the MTPA moiety and the Ha proton, and also between the phenyl protons and the Hb proton in the conformation of **1B**. The reverse should hold true for (*S*)-MTPA esters. After all, in order to determine the absolute configurations of alcohols, it is essential to compare the strength of the NOEs between the protons of the MTPA moieties and the protons of the alcohol moieties in the two diastereomers.

On MBNC and MNCB esters, when these esters are in the idealized conformations (Figures **2A** and **2B**)[2], NOEs will be observed between the methoxy protons of the acid moieties and the Hb proton in (a*S*)-MNCB and (a*R*)[5]-MBNC esters (Figure **2A**). Contrarily, NOEs will be observed between the methoxy protons of the acid moieties and the Ha proton in (a*R*)-MNCB and (a*S*)-MBNC esters (Figure **2B**). Some NOEs could be observed between the proton(s) of the naphthalene faced the alcohol moiety and the proton(s) of the alcohol moiety in each ester.

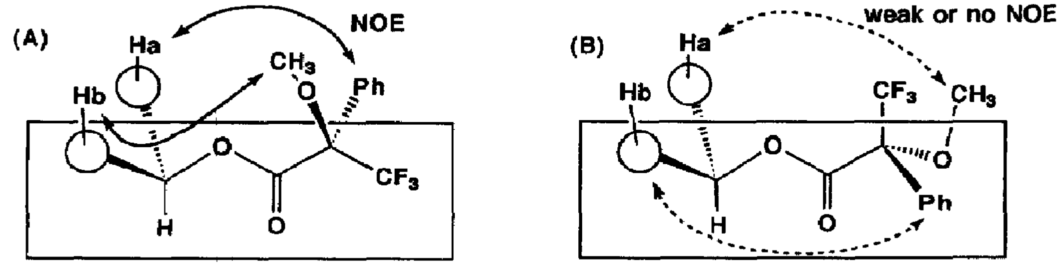


Figure 1. Two stable conformation models for (*R*)-MTPA ester of a secondary alcohol and possible NOE correlations.

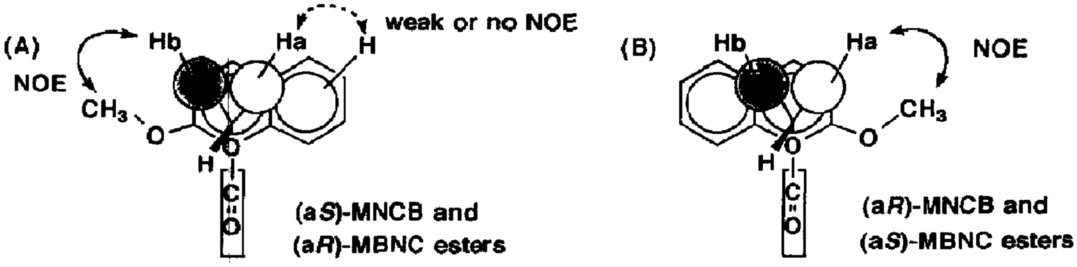
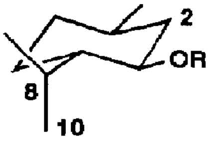
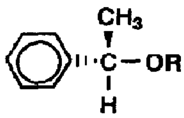


Figure 2. Configurational correlation models for MNCB and MBNC esters of a secondary alcohol and possible NOE correlations.

For demonstration of these hypotheses, (-)-menthol derivatives (**4a-c**) and (*S*)-1-phenethol derivatives (**5a,b**) were subjected to NMR analyses[6]



4a ; R = (*S*)-MTPA
4b ; R = (*R*)-MTPA
4c ; R = (a*R*)-MNCB



5a ; R = (a*S*)-MBNC
5b ; R = (a*R*)-MBNC

On the (-)-menthol derivatives (**4a,b**), irradiation of the *ortho* protons of the phenyl group in each diastereomer resulted in the enhancement of the proton signals of H-2ax,eq, H-8, H-10 and some others (Figure 3, spectra **C** and **F**) The patterns of these spectra are about the same. On the other hand, the NOE enhancement data from the irradiation of the methoxy protons (Figure 3, spectra **B** and **E**) cleary suggest that the methoxy group is in proximity to the H-8 proton in the case of the (*R*)-MTPA ester, and the distances between the methoxy group and the H-2 protons of the (*S*)-MTPA ester are short compared with those of the (*R*)-MTPA ester. These results revealed that the NOEs between the methoxy protons of the MTPA moiety and the protons of the alcohol moiety in the respective diastereomers are available to determine the absolute configurations of alcohols of this type.

The NOEs observed in the phase-sensitive NOESY spectrum of the (a*R*)-MNCB ester of (-)-menthol (**4c**) support the validity of the hypothesis stated above (Figure 4 and **4c'**)[7]. The MBNC esters of (*S*)-1-phenethol (**5a,b**) also exhibit expected NOE correlations (**5a',b'**)

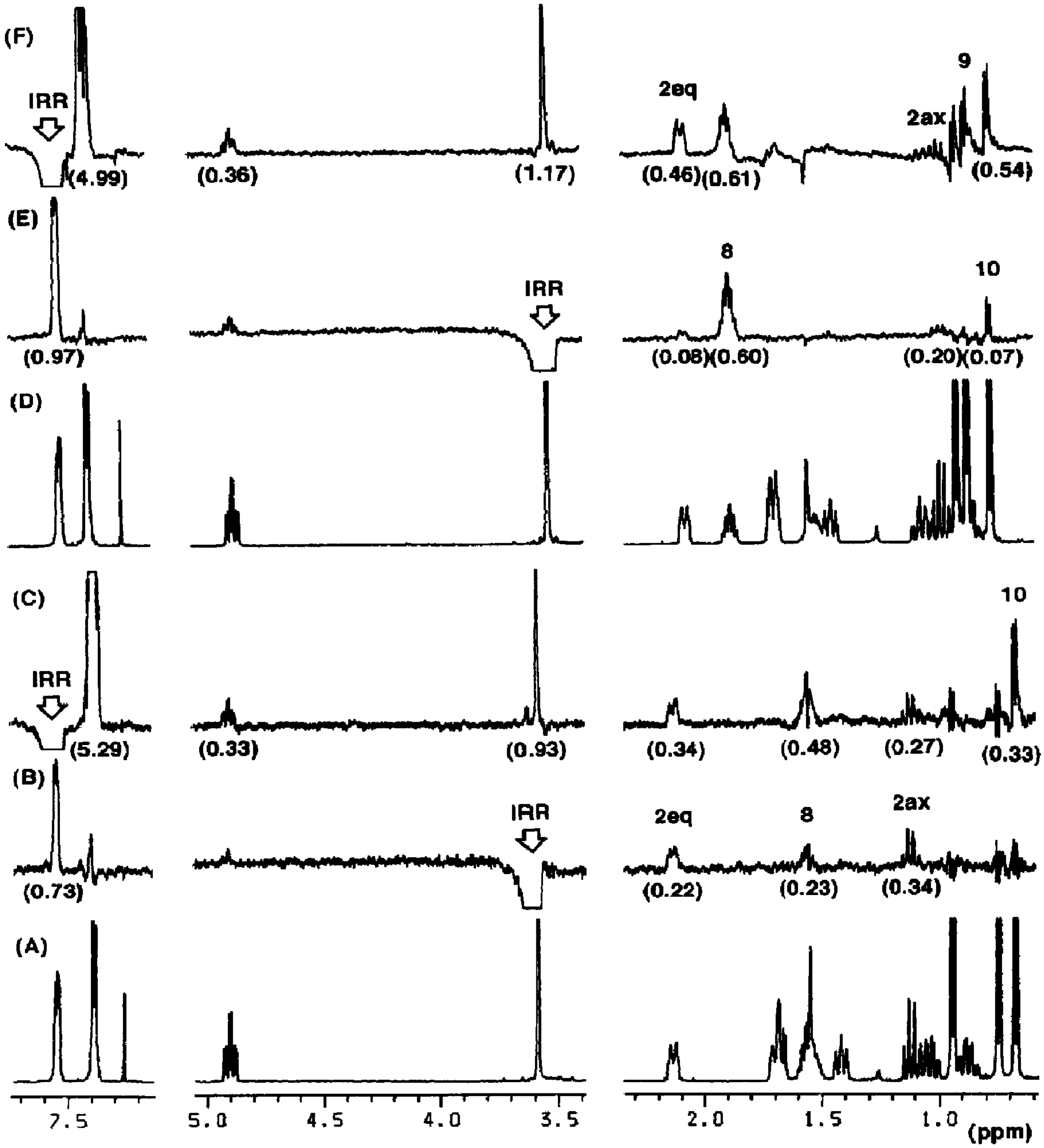


Figure 3. ^{1}H-NMR and NOE Difference Spectra (CDCl$_3$; 500MHz) of the (*S*)- and (*R*)-MTPA esters of (-)-menthol (**4a,b**). (A) The (*S*)-MTPA ester (**4a**), non-irradiated spectrum; (B) irradiation of the methoxy protons of **4a**; (C) irradiation of *o*-H-Ar protons of **4a**; (D) the (*R*)-MTPA ester (**4b**), non-irradiated spectrum, (E) irradiation of the methoxy protons of **4b**; (F) irradiation of *o*-H-Ar protons of **4b**. The values in the parentheses are the percentages of NOE enhancements.

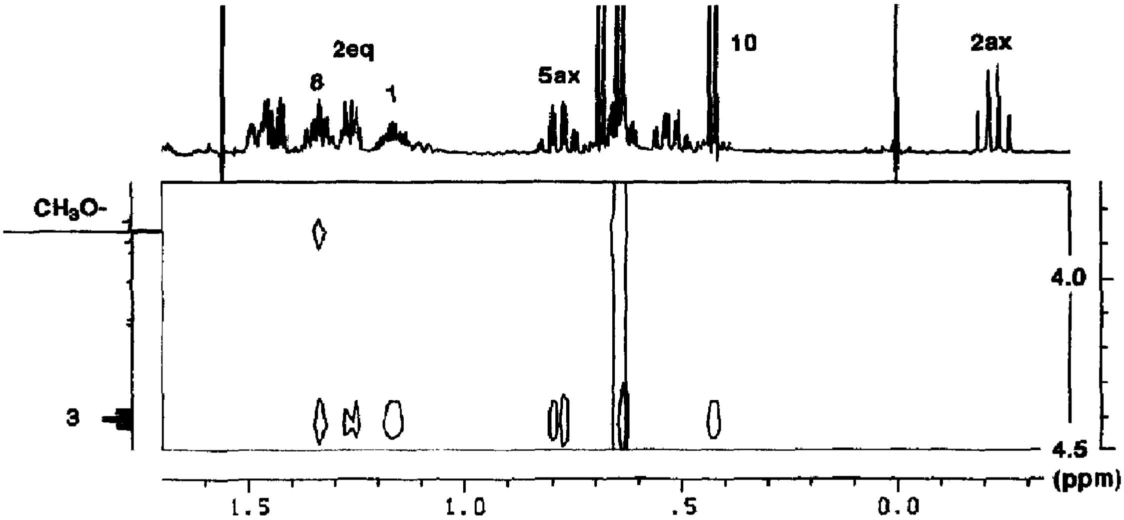
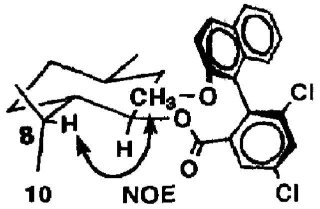
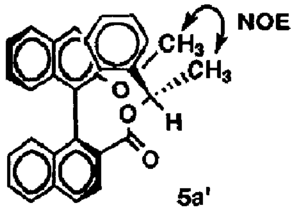


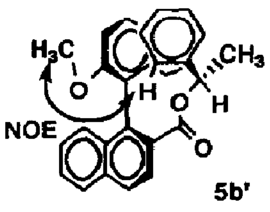
Figure 4. Selected Phase-Sensitive NOESY Spectrum ($CDCl_3$; 500MHz) of the (a*R*)-MNCB ester of (-)-menthol (**4c**).



4c'



5a'



5b'

Since the distances between the observed protons are long (~3Å), these NOE correlations are weak (~1%), but distinct enough to compare between the diastereomers. More appropriate and versatile reagents for NOE experiments are under preparation.

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5. The descriptors (a*R*) and (a*S*) refer to axial chirality.
6. A Bruker AM 500 spectrometer was used to record proton, phase-sensitive NOESY, and NOE difference spectra in $CDCl_3$ (ambient temperature).
7. In the (a*S*)-MNCB ester of (-)-menthol, no cross peak between the methoxy protons and the H-8 proton but the weak one between the methoxy protons and the H-2eq proton was observed.

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