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DETERMINATION OF THE ABSOLUTE CONFIGURATION OF CHIRAL SECONDARY ALCOHOLS; NEW ADVANCES USING ^{13}C- AND 2D-NMR SPECTROSCOPY

T. Pehk,[a] E. Lippmaa,[a] M. Lopp,[b] A. Paju,[b] B. C. Borer[c] and R. J. K. Taylor[c]

[a] Institute of Chemical Physics and Biophysics, EE0001 Tallinn, Rävala puiestee 10, Estonia.
[b] Institute of Chemistry, EE0108 Tallinn, Akadeemia tee 15, Estonia.
[c] School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK.

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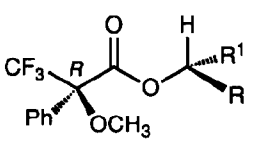
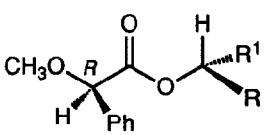
Abstract: The use of ^{1}H-^{13}C and ^{1}H-^{1}H 2D COSY correlation experiments substantially enhances the potential of the NMR procedure for determining the absolute configuration of chiral secondary alcohols *via* their diastereomeric MPA and/or MTPA esters. Phenyl ring current effects are observed over remarkably long distances and comparable effects are seen for both ^{13}C and ^{1}H chemical shifts. The use of ^{13}C chemical shifts to aid configurational assignment is particularly valuable.

The determination of the absolute configuration of chiral secondary alcohols can be achieved *via* an NMR spectroscopic investigation of the diastereomeric esters derived from the alcohol and α-methoxy-α-trifluoromethylphenylacetic (MTPA) acid and/or α-methoxyphenylacetic (MPA) acid.[1-3] This is now a widely used procedure which has been reviewed recently.[4,5] The generally accepted models for the preferred conformations of the MTPA (**A**) and MPA (**B**) esters in solution are as shown with coplanar carbinyl hydrogens, carbonyl and CF_3/OMe groups:



(**A**) *R*- MTPA ester



(**B**) *R*- MPA ester

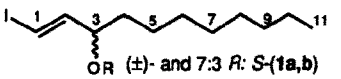
Different NMR techniques can be employed to analyse the diastereomeric esters. The use of ^{19}F NMR spectroscopy with MTPA esters[1] gives simple spectra but erroneous predictions of absolute configuration have been made using this procedure.[6,7] Alternatively, the ^{1}H chemical shift of the methoxyl singlets from

the MTPA esters has been used in conjunction with lanthanide-induced shift experiments but this procedure is rather tedious and does not always give unambiguous results.[8] The third procedure, as discussed by Mosher,[1,2] involves an analysis of the diamagnetic shielding effect of the phenyl ring on ^1H chemical shifts. R^1 in the *R*-MTPA ester (**A**) would be expected to resonate upfield relative to that of the *R*-MTPA ester of the enantiomeric alcohol. The situation is reversed in the case of the *R*-MPA ester (**B**);[3] R^1 would be expected to resonate downfield relative to that of the *R*-MPA ester of the enantiomeric alcohol. The success of the method is obviously dependent on having clearly identifiable, assigned signals from the side chains R and R^1 and this was not possible until the advent of modern NMR techniques. A recent paper[7] described the use of high field NMR spectroscopy and 2D ^1H-^1H correlation experiments to aid configurational assignment to secondary alcohols. In this *letter* we present our own results in this area. These results confirm the value of using ^1H-^1H correlation experiments but also emphasise the value of ^1H-^{13}C correlation experiments in order to guarantee the unambiguous assignment of ^1H chemical shifts from highly complex regions of the spectra. In addition, we have established that the ^{13}C chemical shifts of diastereomeric esters are influenced in the expected regular way by the diamagnetic effect of the phenyl ring; the use of ^{13}C chemical shifts to aid configurational assignment should prove to be particularly useful.[9]

In the course of our present studies a series of secondary alcohols and their MPA and MTPA esters have been investigated. In all cases the unambiguous determination of absolute configuration has been achieved. Representative examples, (±)-(**1**)-(**6**), (-)-menthol (**7**) and (-)-cholesterol (**8**), are presented in this *letter*. Alcohols were converted into MTPA (**a**) and MPA (**b**) esters, shown in the Scheme, using standard literature procedures.[3] For the racemates, the configurational conclusions were confirmed by comparison with the corresponding spectra obtained from derivatisation of pure/enriched enantiomers, where available [*R*- (**3**), *S*-(**4**), *R*-(**5**), *S*-(**6**) and an enriched sample of *R*-(**1**) were employed].[10] For a typical NMR experiment an ester sample of *ca.*10 mg was employed. NMR studies were performed in $CDCl_3$ solution on a Bruker AM-500 instrument at 125.7 MHz for ^{13}C and 500 MHz for ^1H nuclei. Standard pulse programmes were used for the 2D correlation experiments. For the most critical ^1H-^{13}C COSY experiments several hundred scans were obtained in the F_2 dimension and the acquisition time was chosen to resolve diastereomeric ^{13}C absorptions. In the F_1 dimension, only 32-64 data points were accumulated giving *ca.* 30 Hz resolution which was enough to differentiate beween the diastereomeric ^1H chemical shifts.

A comparison of the differential shielding effects from MTPA and MPA esters is presented in the Table for 1-iodo-3-hydroxy-1*E*-undecene (**1**). The data for the other compounds is shown in the Scheme. In all cases, the observed differential shielding values accord with the proposed models (**A**) and (**B**), for MTPA and MPA esters, respectively. Earlier observations[5] concerning the larger ^1H shielding of MPA esters compared to MTPA esters are confirmed by the data in the Table. The same trends are seen for ^{13}C chemical shifts. The ^{13}C and ^1H differential shieldings for the MPA esters (**1b**) shown in the Table are particularly noteworthy: the separation of the diastereomeric methyl protons 9 bonds removed from the chiral centre, is 2.7 Hz at 500 MHz. It should also be noted that the greatest shielding effects are observed for both ^1H and ^{13}C at the positions β- to the carbinyl carbon.

Table Differential shielding on ^{1}H and ^{13}C nuclei in diastereomeric *R*-MTPA (1a) and *R*-MPA (1b) esters.[a]



(±)- and 7:3 *R*: *S*-(1a,b)

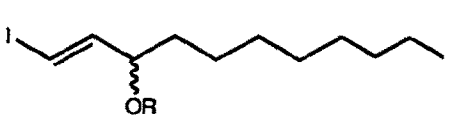
Compound		Atoms 1	2	4	5	6	7	8	9	10	11
(1a)	$\Delta\delta_H$	-0.12	-0.13	0.04	0.11	0.05	0.05	0.04	b	b	b
	$\Delta\delta_C$	-0.43	-0.24	0.09	0.32	0.06	0.04	0.03	b	b	b
(1b)	$\Delta\delta_H$	-0.46	-0.15	0.10	0.25	0.14	0.13	0.07	0.05	0.01	0.01[c]
	$\Delta\delta_C$	-1.06	-0.37	0.16	0.41	0.18	0.10	0.07	0.01	0.02	b

[a]For MTPA esters $\Delta\delta = \delta_S - \delta_R$, for MPA esters $\Delta\delta = \delta_R - \delta_S$ (in ppm). Underlined values indicate the maximum shielding region of the phenyl ring.
[b]Difference not resolved.
cThe separation of the methyl protons 9 bonds removed from the chiral centre (13 bonds from the phenyl ring) is 2.7 Hz at 500 MHz.

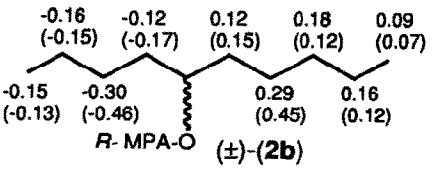
The data for 5-decanol (**2**) illustrates the power of the method proposed herein using ^{1}H-^{13}C COSY correlation. The two alkyl substituents at the chiral centre are butyl and amyl groups but, despite this small difference, distinct chemical shifts are observed for all ^{1}H and ^{13}C nuclei in the MPA diastereomers (**2b**) as shown in the Scheme. Unambiguous assignment of all carbon resonances of the parent alcohol was made by 2D ^{13}C-^{13}C INADEQUATE correlation. This then provides a convenient means of assigning all of the ^{1}H chemical shifts in the diastereomeric ester derivatives using ^{1}H and ^{13}C chemical shift correlation. In this instance the chemical shift assignments were confirmed by chromatographic separation of the diastereomers (**2b**) followed by NMR analysis of the individual diastereomers.

The remaining examples in the Scheme illustrate that this method works successfully for allylic, homoallylic and acetylenic alcohols (**3-5**). Regular long range effects are even observed on the protons and carbons of silyl protecting groups (*e.g.* **6**). There are a small number of irregularities on the carbons adjacent to the carbinyl carbon in MTPA esters (**4**) and (**6**) but these do not invalidate the general trends. Menthol (**7**) deserves special mention as its MTPA and MPA esters have been studied previously.[7,11] We find some differences to the published data, presumably resulting from the overlap of signals in the 1D spectra and even on 500 MHz 2D ^{1}H-^{1}H COSY diagrams. For example, in our work on MTPA esters (Scheme), H_{4e} has a differential shielding value of +0.01 ppm (*vs.* -0.03 ppm[7]), H_{4a} is +0.02 ppm (*vs.* 0 ppm[7]) and H_5 is +0.02 ppm (*vs.* +0.04 ppm[7]). In addition, pro-*R* and pro-*S* isopropyl methyl carbon shieldings differ by 5.2 ppm. In the most likely conformation, shown in the Scheme, the isopropyl methine proton is pointing towards the oxygen thereby minimising interaction with 2-H. In this conformation the pro-*S* methyl has two gauche interactions and the pro-*R* methyl one gauche interaction, which explains the 5 ppm chemical

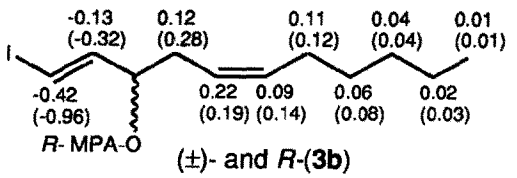
Scheme: *Differential ^1H (^{13}C) shieldings from diastereomeric pairs of esters.* [For MTPA esters, (**a**), $\Delta\delta = \delta_S - \delta_R$, for MPA esters, (**b**), $\Delta\delta = \delta_R - \delta_S$ (in ppm)]



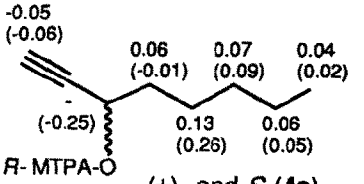
(±)- and 7:3 *R:S*-(**1a,b**): see Table for data



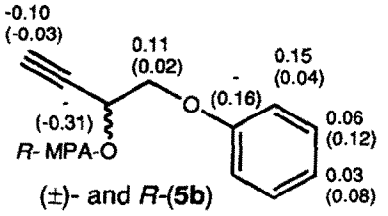
(±)-(**2b**)



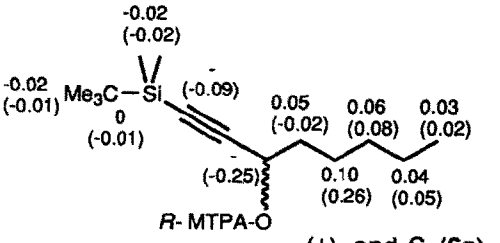
(±)- and *R*-(**3b**)



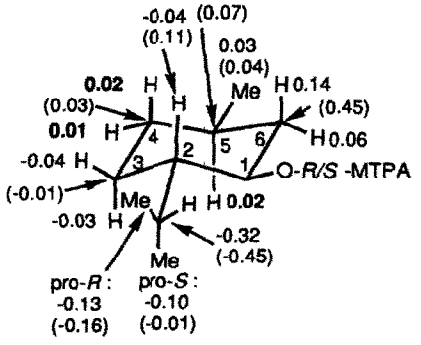
(±)- and *S*-(**4a**)



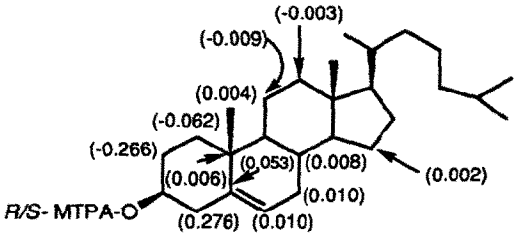
(±)- and *R*-(**5b**)



(±)- and *S*- (**6a**)



(-)-(**7a**)



(-)-(**8a**)

shift difference and enables the diastereomeric methyl carbons and, by ^{1}H-^{13}C correlation experiments, the corresponding methyl protons, to be assigned. This information reverses the isopropyl methyl group assignment reported in the literature.[7] The methyl group assignment for the *S*-MPA ester of menthol has to be corrected also. This follows from the parallelism between the long range effects of MTPA and MPA esters (see Table and Scheme) and was confirmed by remeasuring the 2D NMR spectra of the *R*- and *S*-MPA esters of menthol. The reported[11] chemical shift values for the *S*-MPA ester of menthol of δ0.84 (isopropyl-methyls) and δ0.69 (5-Me) should therefore be replaced by δ0.85 (pro-*R*-Me), δ0.69 (pro-*S*-Me) and δ0.82 (5-Me).

The ^{13}C NMR studies are particularly useful for large molecules. This is illustrated in the Scheme for the differential ^{13}C shieldings observed from a 2:1 mixture of *R*-:*S*- MTPA esters (**8a**) of cholesterol. In this example, regular effects are measurable even into ring D. Data for differential ^{1}H shielding effects were in accord with literature values.[7]

On the basis of these results a general strategy for the determination of the absolute configuration of secondary alcohols by NMR spectroscopy can be formulated, (a) for a pure enantiomer, and (b) for a mixture of enantiomers. In case (a), esters with both *R*- and *S*-MPA acids (preferred) or MTPA acids should be prepared and the resulting spectra assigned by 1D and 2D methods. A comparison of ^{1}H and ^{13}C chemical shifts from both diastereomeric esters, and a consideration of the diamagnetic effect of the phenyl rings in preferred conformations (**A** or **B**), should enable the absolute configuration to be determined.

In case (b), only the *R*- or *S*-MPA ester (preferred), or *R*- or *S*-MTPA ester needs to be prepared. If the quantity of enantiomers is unequal, 2D NMR assignments and the interpretation of the observed differences of ^{1}H and ^{13}C chemical shifts should be sufficient to determine the absolute configurations and ratio of the two enantiomers. In the case of a racemate, the separation of the diastereomeric esters and assignment of configuration as in case (a) is recommended. Even if only partial separation of diastereomeric esters is achieved, a comparison of the ^{1}H and ^{13}C 1D spectra of the original and enhanced mixtures gives the configurational assignment.

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References and notes

1. J. A. Dale, D. L. Dull and S. H. Mosher, *J. Org. Chem.*, **1969**, *34*, 2543;
   G. R. Sullivan, J. A. Dale and S. H. Mosher, *J. Org. Chem.*, **1973**, *38*, 2143.
2. J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **1973**, *95*, 512.

3. B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christie, G. S. Ponticello, S. L. Varga and J. P. Springer, *J. Org. Chem.*, **1986**, *51*, 2370.
4. S. Yamaguchi, Ch. 7 in Asymmetric Synthesis, Vol. 1, Ed. J. D. Morrison, Academic Press, New York, 1983.
5. D. Parker, *Chem. Rev.*, **1991**, *91*, 1441.
6. T. Kusumi, I. Ohtani, Y. Inouye and H. Kakisawa, *Tetrahedron Lett.*, **1988**, *29*, 4731.
7. I. Ohtani, T. Kusumi, M. O. Ishitsuka and H. Kakisawa, *Tetrahedron Lett.*, **1989**, *30*, 3147;
   I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, **1991**, *113*, 4092.
8. S. Yamaguchi, F. Yasuhara, and K. Kabuto, *Tetrahedron*, **1976**, *32*, 1363.
9. J. K. Whitesell and D. Reynolds, *J. Org. Chem.*, **1983**, *48*, 3548.
10. *R*-(**3**): B. C. Borer and R. J. K. Taylor, *Synlett*, **1992**, 117;
    S-(**4**): J. Fried, C. H. Lin, J. H. Sih, P. Dalven and G. F. Cooper, *J. Am. Chem. Soc.*, **1972**, *94*, 4343;
    R-(**5**): P. Niidas, T. Kanger, M. Lopp and Ü. Lille, *Proc. Estonian Acad. Sci., Chem.*, **1989**, *38*, 285 (*Chem. Abstr.*, **1990**, *113*, 40047d);
    S-(**6**): M. Lopp, T. Kanger, A. Müraus, T. Pehk and Ü. Lille, *Tetrahedron Asymmetry*, **1991**, *2*, 943;
    An enantiomerically enriched sample of alcohol (**1**) (3*R* : 3*S* = *ca.* 7:3) was prepared from racemic (**1**) using *Candida cylindricea* lipase (Sigma) and decanoic acid via Klibanov's procedure (G. Kirchner, M. P. Scollar and A. M. Klibanov, *J. Am. Chem. Soc.*, **1985**, *107*, 7072), the resulting mixture of decanoate esters being hydrolysed under standard conditions (NaOH, aq. MeOH). Racemic (**1**) was made *via* a modification of a literature procedure (E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **1972**, *94*, 2506).
11. M. Adamczeski, E. Quinoa and P. Crews, *J. Org. Chem.*, **1990**, *55*, 240.