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The assignment of absolute configurations by NMR of arylmethoxyacetate derivatives: is this methodology being correctly used?

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Abstract

Examples in which Mosher's method does not allow a safe configurational assignment of absolute configuration are presented. This situation occurs when: (a) L_1 and L_2 show identical signs of $\Delta\delta^{SR}$; (b) when both positive and negative $\Delta\delta^{SR}$ values coexist for the same substituent; (c) only NMR data from one substituent of L_1 or L_2 is available; and (d) when polyalcohols are treated like monoalcohols. The requirements for the correct application of this method are discussed.

1. Introduction

In recent years, the use of ^{1}H NMR spectroscopy (Mosher's method)[1,2] for the determination of the absolute configuration[3–7] of chiral alcohols, amines and carboxylic acids has become a very popular tool and the number of papers and new compounds in which this method is applied increases dramatically every year.

A literature search indicates that often the experimental data published are not adequate or sufficient to support the configurational assignments reported, either because the method is not being correctly used or because it is applied to inappropriate cases. This may have been the cause of serious mistakes regarding stereochemistry in past and present investigations and we fear that such malpractice will continue and unsupported absolute configurations will be presented unless a note of caution on the source of these errors and a call for the rigorous application of the method is made.

In this communication we wish to call the attention of the scientific community to the risks involved in these assignments and contribute to preventing the incorrect use of this technique in the future.

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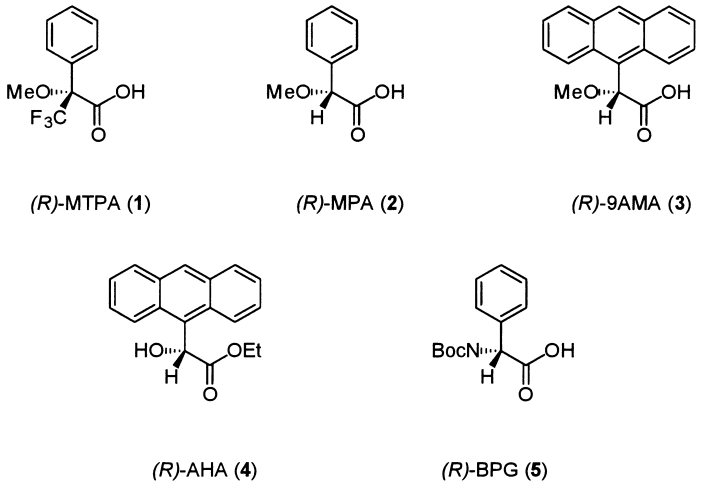
In short, the NMR methodology discussed here entails derivatization of the substrate with the two enantiomers[8–10] of a chiral auxiliary reagent, such as MTPA **1**, MPA **2**, 9-AMA **3**, AHA **4** or BPG **5** and comparison of the NMR spectra of the two diastereomeric derivatives (Scheme 1).



Scheme 1.

The success of this approach is based on the selectivity of the shielding that the aromatic group of the reagent produces on the substituents (L_1/L_2) of the substrate, where the substituent located on the same side of the plane is shielded (see Fig. 1). According to Fig. 1, the substituent L_2 is more shielded in the (*R*)-MTPA ester than in the (*S*)-MTPA ester, while L_1 is more shielded in the (*S*)-MTPA ester than in the (*R*)-MTPA ester. The difference between the experimental chemical shifts in both esters ($\Delta\delta$)[†] is the magnitude employed when analysing the data and, in the case represented above, the expected values are: $\Delta\delta^{SR}L_1 < 0$ and $\Delta\delta^{SR}L_2 > 0$. Other models similar to those shown in Fig. 1 have been established for MPA, 9-AMA and other reagents.[3–7]

In accordance with the fundamentals of the method, the $\Delta\delta^{SR}$ values must fulfil two basic conditions to be valid for configurational assignment using any of the reagents described above (MTPA, MPA, 9-AMA): (1) they should be well above the experimental error;[‡] and (2) they should take positive values on one side of the stereogenic center (i.e. L_1) and negative values on the other (i.e. L_2). Nevertheless, a literature survey on the use of this procedure shows many cases—particularly involving secondary alcohols as substrates and MTPA as the auxiliary reagent—where absolute configurations have been proposed '*on the basis of Mosher's method*' although the above conditions had clearly not been fulfilled.

In this note we will illustrate, with examples taken from the literature, some of these questionable situations. In some cases, the authors were perfectly aware of the problem and cautiously proposed

[†] $\Delta\delta^{SR}$ for L_1 (or L_2) represents the difference between the chemical shift of the substituent L_1 (or L_2) of the chiral substrate when it is derivatized with the (*S*)-chiral auxiliary reagent [i.e. (*R*)-MTPA] and the shift when the substrate is derivatized with the (*R*)-chiral auxiliary reagent [i.e. (*S*)-MTPA]. With MPA and similar auxiliary reagents (AMAAs), $\Delta\delta^{RS}$ is usually employed.

[‡] In addition to the experimental error limit that can be ascribed to the characteristics of the NMR spectrometer, special care should be taken with experimental variables such as temperature variations either during the acquisition or between different NMR experiments, changes in solvent composition (dielectric constant, dipole moment), etc. (see Ref. 3).

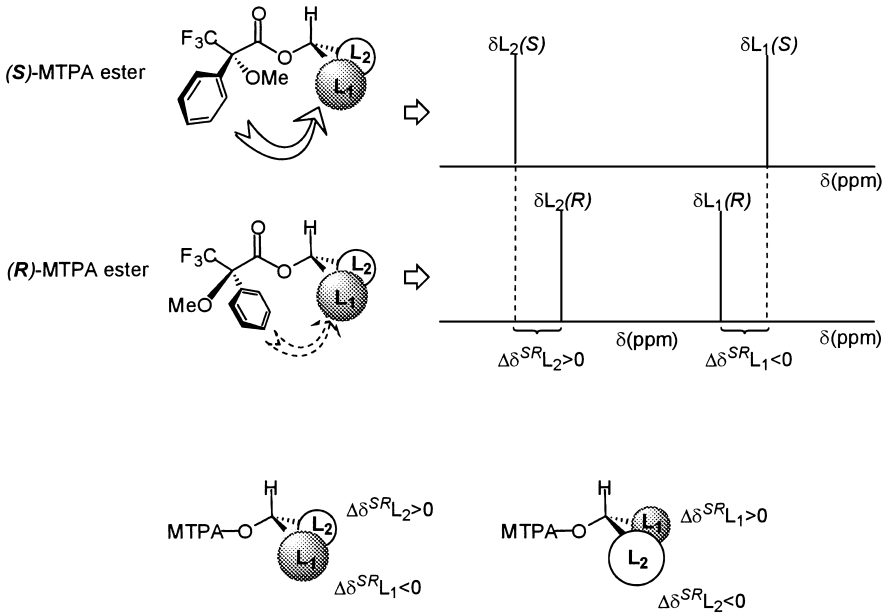


Figure 1. Conformational models for MTPA esters with their NMR spectra and the meaning of the $\Delta\delta^{SR}$ magnitudes. Arrows indicate the predominant shielding effect caused by the aromatic systems

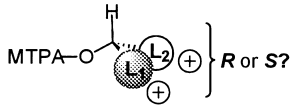
a tentative absolute configuration.[12–17] However, this is not always the situation and, in many cases, $\Delta\delta^{SR}$ values that should be considered useless have been employed to derive absolute configurations.

The majority of misuses arise because the second condition discussed above is not observed, i.e. the need to obtain coherent $\Delta\delta^{SR}$ values from both L_1 and L_2, and we will center our discussion on this point by distinguishing two main scenarios. Firstly, we will describe cases in which Mosher's method produces experimental data ($\Delta\delta^{SR}$) that do not allow a safe configurational assignment. This situation occurs when: (a) L_1 and L_2 show identical signs of $\Delta\delta^{SR}$; or (b) when both positive and negative $\Delta\delta^{SR}$ values coexist for the same substituent.

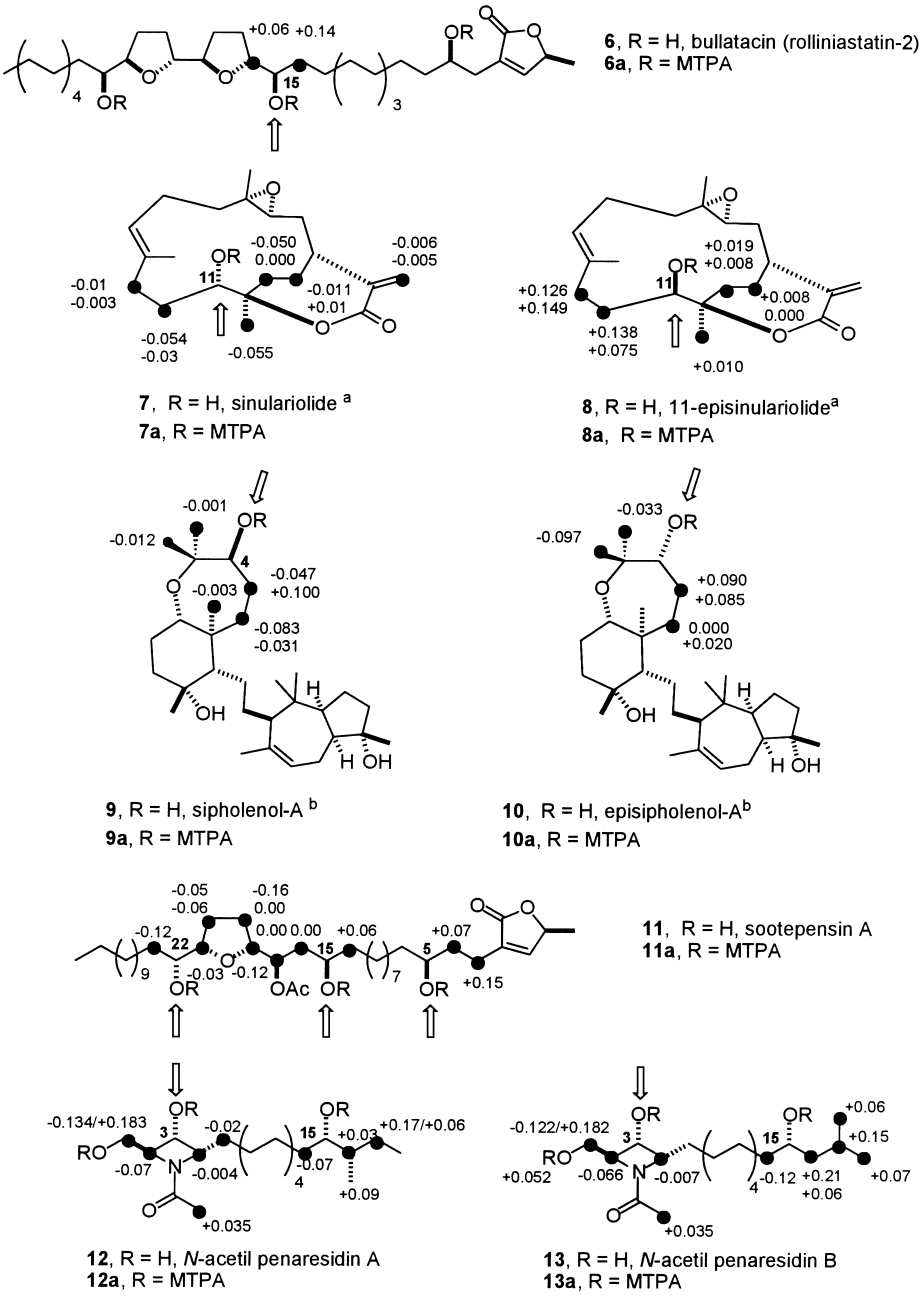
Secondly, we will discuss cases where the structure of the substrate precludes the use of Mosher's method and thus it is being incorrectly used. More precisely, the problems arise when: (c) only NMR data from one substituent of the stereogenic center (L_1 or L_2) is available; and (d) when poly-alcohols are studied and the $\Delta\delta^{SR}$ values obtained are interpreted as in the case of monoalcohols.

2. Case (a): Identical signs of $\Delta\delta^{SR}$ for both substituents

Selected literature examples in which MTPA esters show identical signs for $\Delta\delta^{SR}$ of L_1 and L_2 (Scheme 2) are shown in Fig. 2 [see, for instance the $\Delta\delta$ data around C-15 in bullatacin (roll-iniastatin-2, **6**);[18,19] C-11 in sinulariolide **7** and its epimer episinulariolide **8**;[11] C-4 in sipholenol A



Scheme 2.



[a]Only values close to the stereogenic center are shown. For a complete set of data see ref. 11.

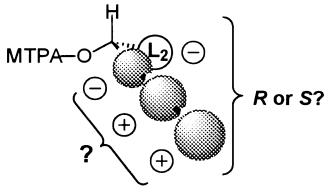
[b]Idem, see ref. 12. Original δ^{SR} values reported in Hertz at 500 MHz.

Figure 2. Selected $\Delta\delta^{SR}$ values for MTPA derivatives of compounds **6**–**13**. Arrows show the studied stereogenic centers. Dots show the positions where data were obtained from

9;[12] C-22 in sootepensin A **11**,[13] C-3 in *N*-acetyl penaresidin A **12** and B **13**,[14] and C-20 in compound **21** (Fig. 5)].[20] In these compounds, identical signs of $\Delta\delta^{SR}$ were obtained at both sides of the asymmetric centers and therefore this information cannot be used for configurational assignment of the corresponding carbon atoms. In contrast to sipholenol A **9**, its epimer episipholenol A **10** shows the expected positive/negative alternation of signs (Fig. 2)[12] that guarantees the applicability of the NMR method in that case. Although the examples only show MTPA as the auxiliary reagent, the need for opposite signs to be obtained for both substituents is a general requirement whatever the arylmethoxyacetic acid employed.

3. Case (b): One substituent presents both positive and negative $\Delta\delta^{SR}$ values

Some examples of compounds that produce both positive and negative $\Delta\delta^{SR}$ values (Scheme 3) for the same substituent are shown in Fig. 3. Thus, the MTPA ester of scanlonenyne **14** showed an apparently arbitrary distribution of $\Delta\delta^{SR}$ signs that precluded the application of the NMR method.[15] A similar case is that of a degradation product **16** of kulolide **15**, where the distribution of signs takes the expected pattern in the surroundings of the asymmetric carbon (positive on one side and negative on the other). However, anomalous positive values appear for the protons located at the far right-hand side of the molecule (Fig. 3).[21] Additional examples include the dilkamural derivative **17**,[16] and the alcohol **18** resulting from the reduction of cystalgerone.[22]

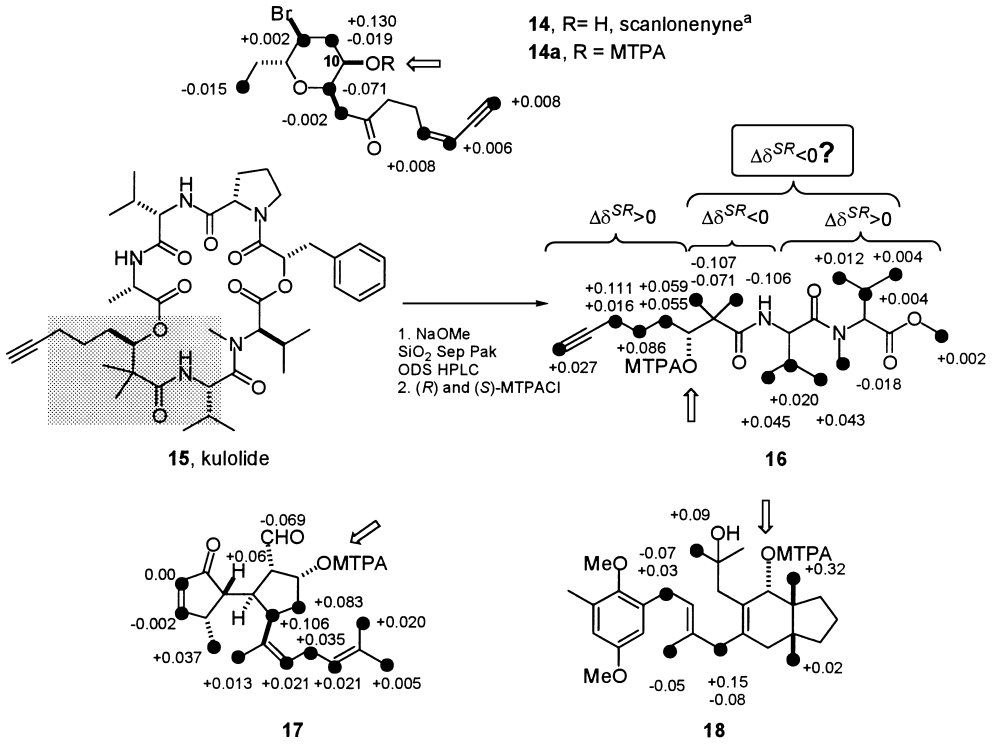


Scheme 3.

These examples introduce a degree of uncertainty as to which parts of L_1 and L_2 should be considered to obtain $\Delta\delta^{SR}$ and this obviously reduces the level of confidence in the configuration assigned. The use of other AMAA reagents, which generate more homogeneous $\Delta\delta^{SR}$ values, would be advisable in situations like these.

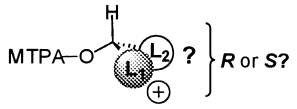
4. Case (c): Use of $\Delta\delta^{SR}$ data from a single substituent

Literature reports are also found where NMR data from only one of the substituents (L_1/L_2) around the stereogenic center have been used to derive the absolute configuration (Scheme 4). Illustrative examples, shown in Fig. 4, are: 4-deoxyannomontacin **19** and (2,4-*cis* and *trans*)-annomontacinone **20**,[23] where the absolute configuration at C-10 was proposed on the basis of NMR data from only one side of the asymmetric carbon; the donnaienins, whose stereochemistries at C-4 and C-15 were assigned from derivatives **21** and **22**,[20] cimicidanol and cimicidol derivatives **23**, **24**, and **25**, where only the signals of the triterpenoid side chain terminal methyl groups were considered;[24] and soulattrolide **26**, where the configuration at C-12 could not be safely assigned by this method[17] (Fig. 5). The assignment of C-5 in sootepensin A (**11**, Fig. 2) can also be included in this class.[13]



[a] Original $\Delta\delta^{SR}$ values reported in hertz at 400 MHz.

Figure 3. Selected $\Delta\delta^{SR}$ values for MTPA derivatives of compounds **14**–**18**



Scheme 4.

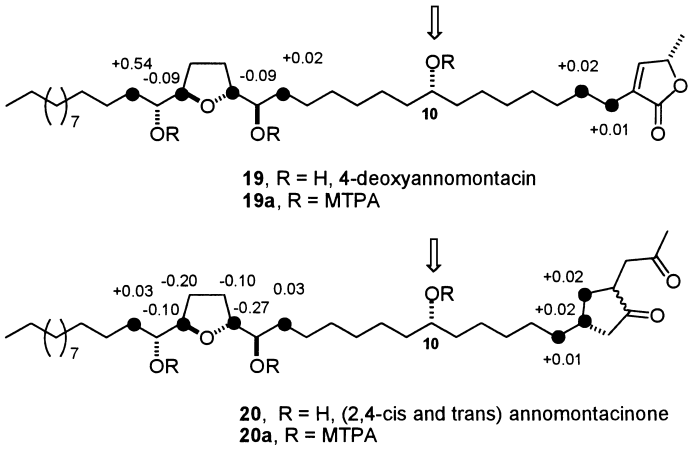


Figure 4. $\Delta\delta^{SR}$ values for MTPA derivatives of compounds **19** and **20**

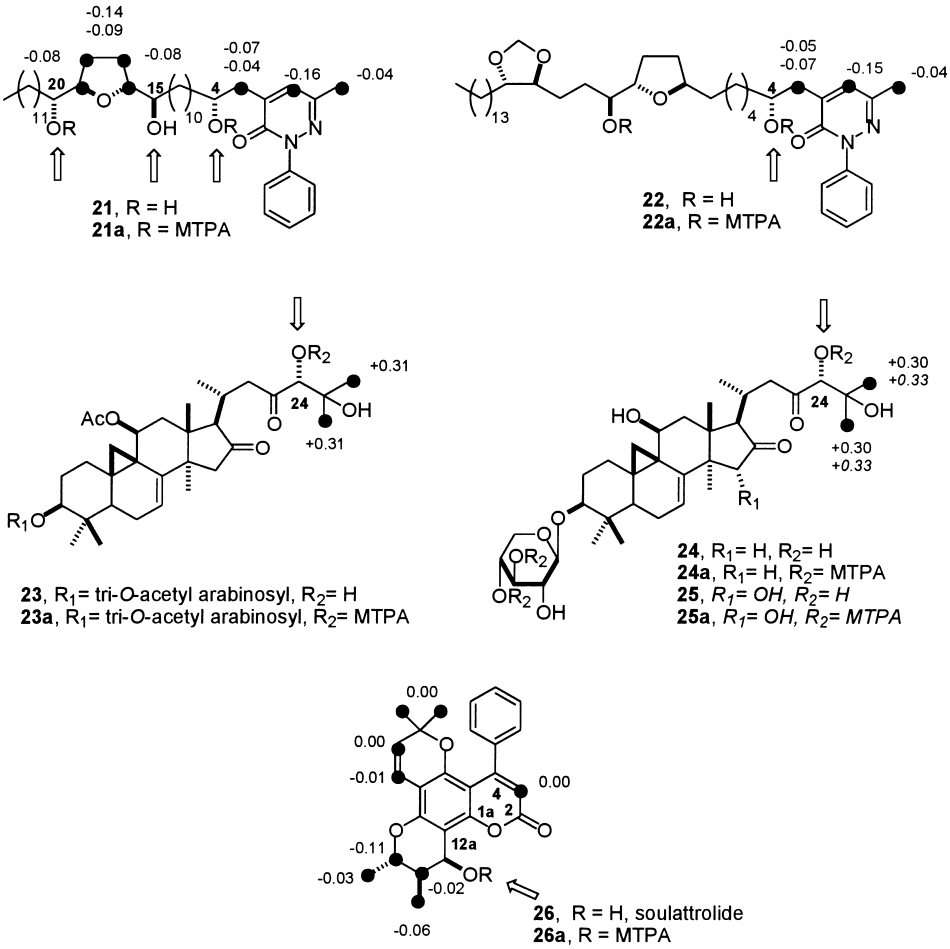
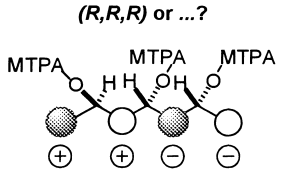


Figure 5. $\Delta\delta^{SR}$ values for MTPA derivatives of compounds **21**–**26**

It is evident that, at times, information from both sides of the asymmetric carbon is simply unavailable due to signal overlap, impracticable identification of the signals (i.e. interference of small shifts produced by the reagent) or because the compound has no protons in L_1 or in L_2. Nevertheless, it should be stressed that the absolute configuration can never be safely derived from the NMR data of only one substituent because the assumption that the other substituent will show the opposite sign is no more than a guess that has often been disproved by experimental data (vide infra). Those researchers confronted with this type of molecule should deduce and accept that the NMR method is not suited for such structures.

5. Case (d): Application to polyfunctionalized substrates

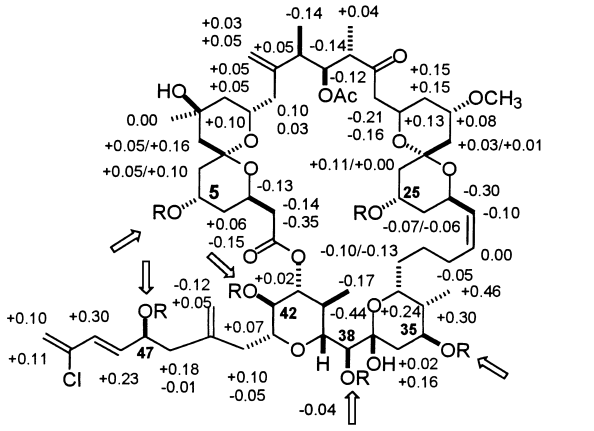
Another situation where the assignment of stereochemistry by the NMR method is inappropriate involves the direct application to polyalcohols of the models originally developed for mono-alcohols (Scheme 5).



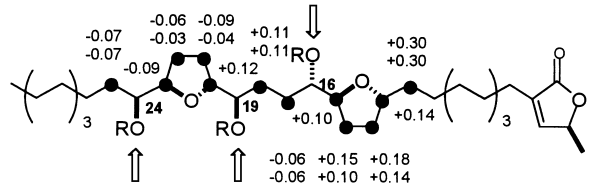
Scheme 5.

Several attempts to assign the absolute configuration of all the asymmetric centers of a polyalcohol by application of the NMR method to the fully esterified derivatives with (*R*)- and (*S*)-MTPA have been reported but, in general, the $\Delta\delta^{SR}$ data obtained does not allow a completely unambiguous assignment of configuration.

Significant cases are represented in Fig. 6. For example, in the hexa-MTPA ester of 5-desacetylaltohyrtin A **27**,[25] the $\Delta\delta$ values around C-5, C-35, C-38, C-42 and C-47 do not present the necessary alternation of signs (which are identical for L_1 and L_2), and the same situation occurs with C-16, C-19 and C-24 of squamostatin D **28**.[26] Compounds **6**, **11**, **12** and **13** in Fig. 2, and compounds **20** and **21** in Figs. 4 and 5, represent additional examples of this limitation.



27, R=H,5-desacetyl altohyrtin A
27a, R = MTPA



28, R = H, squamostatin-D
28a, R = MTPA

Figure 6. $\Delta\delta^{SR}$ values for MTPA derivatives of compounds **27** and **28**

In this context, we would like to point out that the fundamentals of the NMR method under discussion relate to aromatic shielding, a through-space phenomenon affecting protons several bonds away from the hydroxylic carbon bearing the auxiliary reagent. Therefore, the $\Delta\delta^{SR}$

observed in a compound having several non-isolated MTPA esters is the result of the combined effects (shielding/deshielding) of all these aryl rings and cannot be interpreted as if it were produced by just one of them.

Therefore, in the application of the NMR method to fully derivatized polyalcohols, the model developed for monoalcohols cannot be directly applied and the effect of such a structural combination on the sign of $\Delta\delta^{SR}$ should be taken into account. New efforts are needed in this field in order to deduce an acceptable model for the correct interpretation of $\Delta\delta^{SR}$ values and safer configurational assignment.

6. The role of the auxiliary reagent

It is clear that some of the problems described above (i.e. when the compound under study has no protons at one side of the stereogenic center) have no easy solution, but many others could probably be solved by a more appropriate choice of auxiliary reagent. Thus, when $\Delta\delta^{SR}$ is too small to guarantee the reliability of the assignment, more powerful auxiliary reagents should be tried.[1,2,27] This situation is frequently observed when the shifts of protons that are far remote from the asymmetric carbon bearing the reagent are used. Two such cases are 4-deoxyannomontacin **19** and annomontacinone **20** (Fig. 4),[23] where the $\Delta\delta$ values are small and correspond to protons situated 6–7 bonds away in an open chain with a large degree of conformational freedom, a factor that further increases the uncertainty of the assignment.

For its part, the seemingly arbitrary distribution of signs is clearly related to the use of MTPA, which in our opinion should be abandoned[§] in favor of alternative reagents (MPA, 9-AMA) that generate a simpler and more reliable conformer composition. Indeed, it is not casual coincidence that all the examples described in this paper correspond to the use of MTPA as the auxiliary reagent. The tendency of this compound to produce shifts that are useless for configurational assignments was already noted in 1991.[28] In 1996, we reported theoretical and experimental evidence showing that the conformational complexity of MTPA esters (three main conformers) could lead, in some cases, to an anomalous distribution of $\Delta\delta^{SR}$ signs that renders the prediction of absolute configuration impossible or extremely risky.[29]

7. Concluding remarks

The determination of absolute configurations by NMR is being successfully employed in an increasing number of investigations. Our understanding of the molecular (conformational) behavior that explains the effectiveness of this method, as well as the large number of compounds with known absolute configuration that have been used to test the method, has afforded strong foundations to this chemical tool and gives confidence to the researcher regarding the reliability of the stereochemical results obtained. However, it is worrying to observe that the method is

[§] Some alleged advantages of MTPA over MPA presented in the past include: (a) the lack of risk of racemization; and (b) the possibility of using ^{19}F NMR in addition to ^{1}H NMR for the stereochemical assignment, both of which have proven to be unjustified: in fact, MPA acids do not racemize during esterification (see Refs. 1b and 15) and ^{19}F NMR of MTPA esters/amides has proven to produce erroneous absolute configuration determinations (see Ref. 28).

often applied without paying heed to the fundamental requirements. In summary, we propose that the following requirements should be fulfilled for the correct application of this method:

(i) The choice of an auxiliary reagent that generates the largest and most homogenous $\Delta\delta$ values, i.e. MPA or 9-AMAA in the case of alcohols. The examples we have presented provide unequivocal proof of the limitations of MTPA.
(ii) The need to obtain significant $\Delta\delta$ data for both L_1 and L_2, which should correspond to protons as close as possible to the chiral center.
(iii) The signs of $\Delta\delta$ must be positive at one side and negative at the other for an acceptable configurational assignment.
(iv) Special care must be taken with substrates where the scope and limitations of the method have not yet been well established; i.e. polyfunctional compounds.

The only objective of this work is to send a warning signal about the need for rigorous application of the NMR method if safe configurational assignments are to be obtained. The use of examples from the literature to illustrate the message does not imply that we believe those configurations to be either right or wrong—we cannot know that!—but solely that the NMR data used is neither sufficient nor adequate for stereochemical assignment.

Acknowledgements

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