Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 919–921

TETRAHEDRON: *ASYMMETRY*

Incorrect procedure for the assignment of the absolute configuration of carbonucleosides by NMR: MPA must not be used with primary alcohols

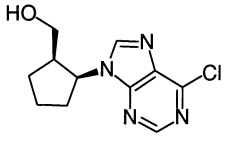
José Manuel Seco, Emilio Quiñoá and Ricardo Riguera*

Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago de Compostela, 15706, Santiago de Compostela, Spain

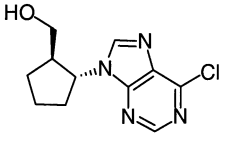
Received 4 April 2002; accepted 29 April 2002

Abstract—The absolute stereochemistry proposed for the enantiomers of the carbonucleosides *cis*- and *trans*-6-chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine, **1** and **2**, respectively, should be questioned because of the erroneous use of the auxiliary reagent methoxyphenylacetic acid (MPA, **3**), and the low quality of the NMR data used for the assignment. For a rigorous application of the NMR method to those primary alcohols, 9-anthrylmethoxyacetic acid (9-AMA, **4**) should be used as the auxiliary reagent and structural calculations should be carried out to validate the NMR model.

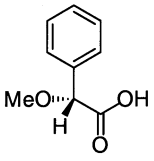
Methoxyphenylacetic acid (MPA, **3**), is one of the auxiliary reagents most commonly used for the assignment of the absolute configuration of chiral secondary alcohols by NMR, but it has been proven[1,2] that it cannot be employed for the study of chiral primary alcohols. Despite this well-established fact, two recent papers describe the assignment of the absolute configuration of the four enantiomers of carbonucleosides (±)-**1** and (±)-**2** making use of NMR methodology but employing MPA **3** as reagent instead of the auxiliary of choice, 9-AMA **4**.[3,4] Herein, we wish to alert readers that MPA is known to produce the incorrect configurational assignment and that therefore the configurations assigned to **1** and **2** are not supported by the experimental data provided in those papers and should be taken as purely arbitrary.[5]



(±)-**1**

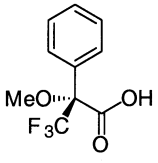


(±)-**2**



3 *(R)*-MPA,

4 *(R)*-9-AMA



5 *(R)*-MTPA

* Corresponding author. Fax: +34-981-591091.

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00209-4

In the methodology developed for the assignment of the absolute configuration of chiral alcohols by NMR,[6] the substrate is divided into two parts. One is esterified with the appropriate (*R*)-auxiliary reagent and the other with the (*S*)-enantiomer. The spectra of both diasteromeric esters are recorded and compared, the $\Delta\delta^{RS}$ determined and the substituents L_1 and L_2 of the alcohol placed in space in accordance with the corresponding signs of $\Delta\delta^{RS}$.

Our studies on the application of this methodology to a series of primary alcohols of diverse structures and with the asymmetric carbon in the β-position[1] have unambiguously shown that only the auxiliary reagent 9-anthrylmethoxyacetic acid (9-AMA, **4**), could be safely trusted to assign their configuration, while other reagents such as methoxyphenylacetic acid (MPA, **3**) and methoxytrifluoromethylphenylacetic acid (MTPA, **5**) do not generate $\Delta\delta^{RS}$ values/signs useful for a reliable assignment.

Fig. 1 shows three examples taken from that paper[1] indicating that MPA generates: (a) different signs for protons of the same substituent, (b) identical signs for different substituents and (c) sign distributions incoherent with the model and the absolute configuration of the alcohol as indicated by the results obtained with **4**.

Despite these facts that clearly prohibit the use of **3** with chiral primary alcohols, this was the auxiliary reagent employed in the papers[3,4] that originate this communication, although the literature containing the relevant information is in fact included in the reference list of these publications. Thus, the enantiomers of *cis*- and *trans*-6-chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine (±)-**1** and (±)-**2**, respectively, were transformed into the corresponding (*R*)- and (*S*)-MPA esters **6**–**9** and their absolute configurations assigned using the model developed by us for 9-AMA esters but with the NMR data from the MPA esters. This incorrect choice of auxiliary reagent, known to give unreliable data with primary alcohols, is enough by itself to invalidate the assignment.

In addition to the high risk of misassignment associated with the use of MPA, a raw examination of the NMR data obtained should be enough for the authors to doubt the value of the configurational assignment (Fig. 2). In all four cases, only data for H1′ and H3′ are considered for the assignments, the values being small (i.e. ±0.01 for H1′ in the *cis* isomers **6** and **7**) and always obtained from complex multiplets. In the case of the *cis* carbonucleosides, other $\Delta\delta$ values can be calculated from the data published in the experimental part[6] and an incoherent distribution of the signs of $\Delta\delta$ result for H5′, H2 and H8. In the case of the *trans* compounds, no chemical shifts for protons other than H1′ and H3′ are reported. These contradictory results are concordant with those shown in Fig. 1 and are fully illustrative of the limitations of this reagent and confirm its unreliability.

In consequence, the absolute configuration assigned for carbonucleosides **1** and **2** in those two concurrent papers must therefore be considered as purely arbitrary because the severe alterations of the procedure invalidate the results.

Future researchers interested in the assignment of configuration of primary alcohols should avoid repeating such an erroneous protocol and use the appropriate reagent (*R*)-**4**. In the particular case of carbonucleosides **5**–**9**, attention should also be paid to the cyclic nature of the substrates and the large size of the heterocyclic purine system. The studies that established the methodology for configurational assignments of primary alcohols by NMR pointed out[1] that if the stereogenic center of the alcohol is part of a ring, or when strong steric interactions are present, the NMR data of the 9-AMA derivatives should be complemented with ab initio or molecular mechanics calculations to ensure that unexpected conformational changes have not been introduced by those interactions.

A good example of the correct use of the methodology for primary alcohols can be found in the recent work of Fatorrusso and co-workers[7] where the configuration of oxacinin-1 **10**, also a cyclic, hindered primary alcohol,

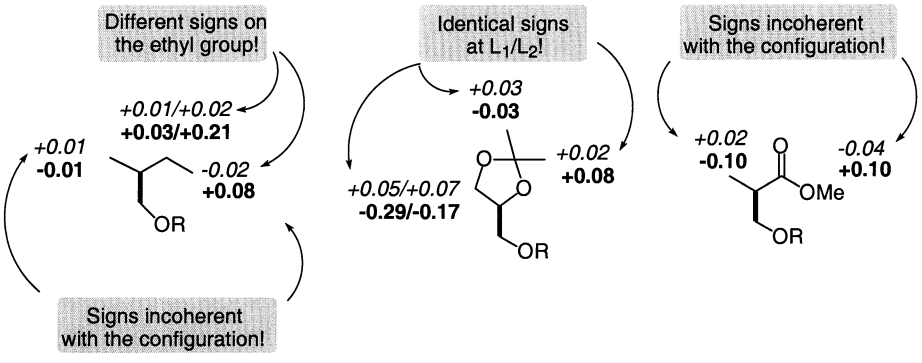


Figure 1. $\Delta\delta^{RS}$ values for the 9-AMA (in **bold**) and MPA (in *italics*) esters of the corresponding alcohols. The discrepancies in the case of MPA esters are pointed out.

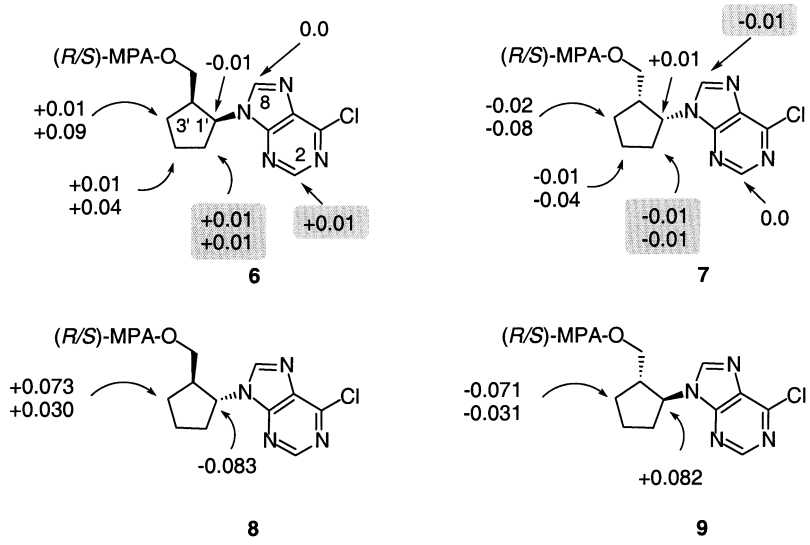
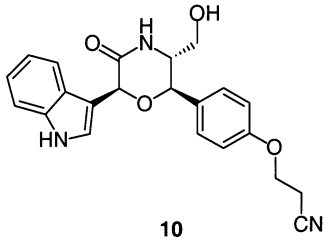


Figure 2. Reported $\Delta\delta^{RS}$ values for MPA derivatives of carbonucleosides **6**–**9**. Discrepancies in the signs are highlighted. Only data for 1′ and 3′ were given for **8** and **9**.

was elucidated following the recommended and tested procedure. A guide on the use of the NMR methods for the assignment of absolute configurations has been published recently and may help all those interested in their application.[6]



10

To summarize: if the absolute configuration of a primary alcohol is to be assigned by NMR, the following points must be taken into account: (1) **4** must necessarily be employed as the auxiliary reagent, (2) MPA should not be used and (3) if the stereogenic center belongs to a ring and/or has nearby bulky groups, theoretical calculations should be performed and should complement the NMR data for the 9-AMA derivatives.

Acknowledgements

This work was supported by grants from CICYT (PM98-0227, FEDER-CICYT 1FD97-2157) and from Xunta de Galicia (XUGA-PGIDT99PXI20906B and XUGA-PGIDT99BIO20901).

References

1. Latypov, S. K.; Ferreiro, M. J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 4741–4751.
2. Ferreiro, M. J.; Latypov, S. K.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **1996**, *7*, 2195–2198.
3. Quezada, E.; Santana, L.; Uriarte, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2637–2639.
4. Besada, P.; Terán, C.; Quezada, E.; Seco, J. M.; Uriarte, E. *Nucleosides Nucleotides & Nucleic Acids* **2001**, *20*, 1359–1361.
5. The general requirements for a correct application of these NMR methods can be found in: Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781–2791.
6. Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925.
7. Ciminiello, P.; Dell'Aversano, C.; Fattorrusso, C.; Fattorrusso, E.; Forino, M.; Magno, S. *Tetrahedron* **2001**, *57*, 8189–8192.