Challenging the absence of observable hydrogens in the assignment of absolute configurations by NMR: application to chiral primary alcohols†

Félix Freire, José Manuel Seco, Emilio Quiñoá and Ricardo Riguera*

Received (in Cambridge, UK) 24th November 2006, Accepted 12th January 2007
First published as an Advance Article on the web 30th January 2007
DOI: 10.1039/b617184b

The absolute configuration of β-chiral primary alcohols devoid of observable hydrogens on one of the β-substituents at the asymmetric carbon (L_1/L_2) can be determined by comparison of the ^{1}H NMR of their (*R*)- and (*S*)-9-AMA ester derivatives and analysis of the $\Delta\delta^{RS}$ for the L substituent and the Cβ-H.

The most usual approach for the ^{1}H NMR assignment of the absolute configuration of organic compounds, by means of chiral derivatizing agents [CDAs; *e.g.* MPA (2-methoxy-2-phenylacetic acid), MTPA (3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid), 9-AMA (2-(anthracen-9-yl)-2-methoxyacetic acid), BPG (Boc-phenylglycine), 9-AHA (ethyl 2-(anthracen-9-yl)-2-hydroxyacetate)], requires the preparation of two diastereomeric derivatives, followed by comparison of their spectra. To be more precise, the chemical shifts of the protons placed at substituents L_1/L_2, bonded to the asymmetric carbon, must be examined and compared. The absolute configuration is then determined in accordance with the sign of their differences ($\Delta\delta^{RS}$) in both derivatives, which must be positive for one substituent (*i.e.* L_1) and negative for the other (*i.e.* L_2).[1] The requirement of obtaining data at both sides of the chiral center (L_1 and L_2) is a must in order to apply this methodology with total confidence.[2] This means that it should not be employed with compounds where either one of the substituents L_1/L_2 does not have any hydrogens to look at, or when those present are far away from the functional group.

In a monofunctional compound (*e.g.* α-chiral secondary alcohols, β-chiral primary amines or α-chiral carboxylic acids), the hydrogen bonded to the asymmetric carbon (Cα-H) does not play any role when assigning the configuration because no reliable correlation can be established between its chemical shift and the configuration (Fig. 1a). The reason is found in the proximity of Cα-H to the anisotropic cone of the carbonyl group of the ester or amide bond, which makes it highly sensitive to slight conformational changes around the Cα–O bond. As a consequence, its NMR behavior becomes unpredictable.‡

In this communication we will present experimental and theoretical evidence, together with a protocol for users, showing that the absolute configuration of a β-chiral primary alcohol devoid of protons in one of its substituents, (*i.e.* L_1) can be determined using the signals due to the other group (*i.e.* L_2) and that of the Cβ-H, provided the non-proton bearing substituent is a polar one (Pg, *i.e.* heteroatom).

The general method actually available for the assignment of configuration of β-chiral primary alcohols[5] requires the knowledge of $\Delta\delta^{RS}$ signs from the two β-substituents (L_1 and L_2) of the 9-AMA diastereotopic esters (Fig. 1a). We reasoned that if one of those two substituents were a polar group, its polarity would influence very much the conformational composition and place Cβ-H in a position less affected by the anisotropic effect of the

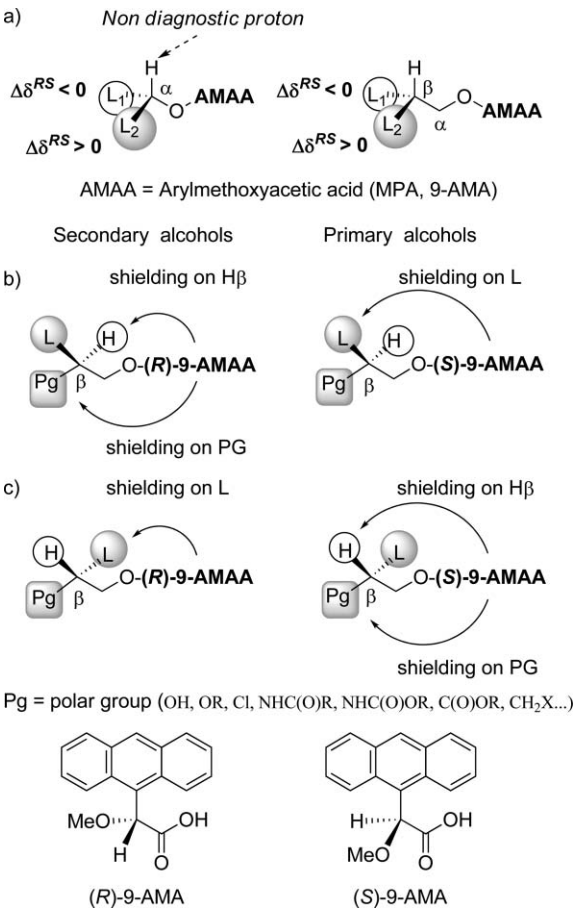

Fig. 1 (a) Assignment models for secondary and primary alcohols based on NMR data at L_1 and L_2 obtained from diastereotopic AMAA esters. (b) Expected shielding effects in the 9-AMA esters of a β-chiral primary alcohol with a Type A configuration. (c) *Idem* for a Type B configuration.

Departamento de Química Orgánica, Facultad de Química, and Unidad de RMN de Biomoléculas Asociada al CSIC, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain.
E-mail: ricardo@usc.es; Fax: +34 981591091; Tel: +34 981591091

† Electronic supplementary information (ESI) available: Experimental section, ^{1}H NMR, ^{13}C NMR spectra and additional data for selected compounds at different temperatures, conformational studies and representation of the main conformers. See DOI: 10.1039/b617184b

ester carbonyl. In this way, its chemical shift should be fully dominated by the anisotropy of the anthryl group of the auxiliary in much the same way as the L substituent. As a consequence, the Cβ-H of the 9-AMA ester derivatives of primary alcohols should serve as a diagnostic signal for assignment, and be useful as a replacement for an L substituent when this has no protons to look at.

In order to test this hypothesis, we carried out exhaustive studies on 9-AMA esters of selected β-chiral primary alcohols bearing one polar group as substituent [Pg = OH, OR, Cl, NHC(O)R, NHC(O)OR, C(O)OR, CH_2Br], including theoretical calculations, CD and NMR (low temperature, ^3J, selective deuteration…). The results, both theoretical and experimental, gave us information about the conformational composition of this family of 9-AMA esters that firmly supports the use of $\Delta\delta^{RS}$ values obtained from Cβ-H and L to assign the absolute configuration.§

Figs. 1b and 1c show a summary of the shielding effects produced by the anthryl group of the auxiliary on these compounds classified according to their configuration as Types A and B. It is necessary to point out that, in all the cases studied in this work, Type A corresponds to *S* and Type B to *R* absolute configurations. So, in order to facilitate the application of this method, both stereodescriptors will also be indicated in this communication in parentheses. Naturally, for any other compound, the stereodescriptors depend on the priority order of the substituents.

Thus, for an alcohol with a Type A (*S*) configuration (Fig. 1b), Cβ-H and Pg are more shielded in the (*R*)- than in the (*S*)-9-AMA ester. On the other hand, L (the non polar substituent) is more shielded in the (*S*)- than in the (*R*)-9-AMA derivative. As a result, both Pg and Cβ-H must present negative $\Delta\delta^{RS}$ values whereas L must present positive ones.

These considerations were fully confirmed experimentally by the NMR spectra of the 9-AMA esters of alcohols **1–6**, that showed, in all cases, $\Delta\delta^{RS}$ signs for Cβ-H and L expected for a Type A (*S*) absolute configuration (Fig. 2a).

When the alcohols have the enantiomeric structure represented by Type B (*R*), Cβ-H and Pg are more shielded in the (*S*)- than in the (*R*)-9-AMA derivative, and L is more shielded in the (*R*)- than in the (*S*)-9-AMA ester (Fig. 1c). Therefore, Cβ-H and Pg present a positive $\Delta\delta^{RS}$ value and L a negative one (the opposite set to those obtained from a Type A (*S*) configuration).

This distribution of signs is, in fact, experimentally confirmed and observed in the NMR spectra of the series of alcohols **7–10** with Type B (*R*) configuration, shown in Fig. 2b.¶

The above results, taken as a whole, prove that there does exist a correlation between the signs of $\Delta\delta^{RS}$ from Cβ-H and L and the configuration at the β position, graphically expressed by the drawings in Fig. 2. This behavior of Cβ-H is particularly useful not only because it complements those obtained from L_1/L_2 but also because it allows the configurational assignment of alcohols where one of the L_1/L_2 substituents has no protons to look at in the NMR spectra. Illustrative examples are compounds **1–10**. In all those cases, the configuration matches perfectly the distribution of signs expected for L and Cβ-H and therefore the assignment of configuration of such a compound can be carried out just by examination of those two groups.

In summary, the fact that Cβ-H and Pg are under analogous anisotropic influence and thus present the same $\Delta\delta^{RS}$ sign

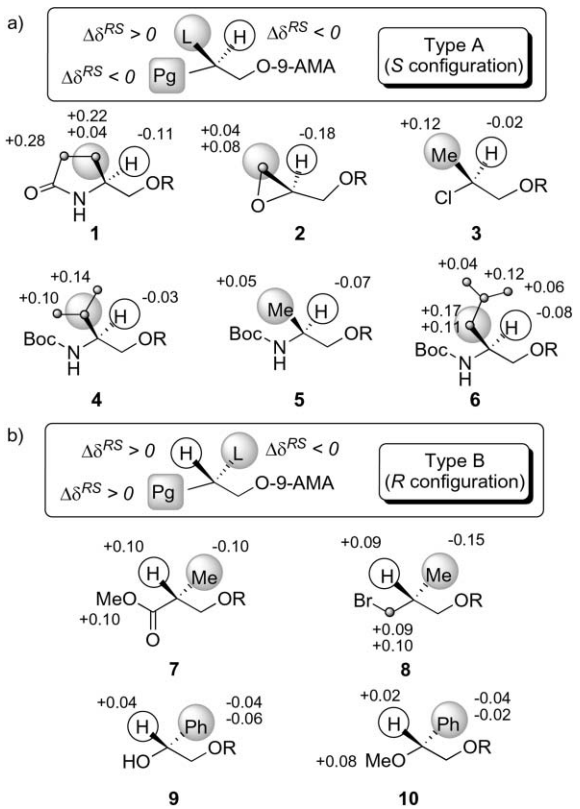

Fig. 2 (a) $\Delta\delta^{RS}$ values (ppm) for 9-AMA esters of Type A (*S*) β-chiral primary alcohols. (b) *Idem* for Type B (*R*).

represents a major practical advance in order to assign confidently the configuration in these compounds: when no NMR information can be obtained from Pg due to the lack of hydrogens, Cβ-H does provide it.

As may be expected from a compound where the L_1/L_2 groups and Cβ-H are at β from the functional group bearing the auxiliary, the $\Delta\delta^{RS}$ values obtained from the 9-AMA esters of primary alcohols are usually small due to the distance and in several cases close to the experimental error, clearly diminishing the reliability of the assignment (*i.e.* **3**, Fig. 2a).

A very effective way to obtain greater $\Delta\delta^{RS}$ values and therefore a higher guarantee of the reliability of their signs, is to record the NMR spectra at a lower temperature. Fig. 3 shows a bar diagram with the $\Delta\delta^{RS}$ values at two temperatures for compounds **2**, **3**, **8**, **9** and **10**. The values are significantly higher at lower temperature for all the alcohols investigated, in accordance with the conformational composition of the 9-AMA esters.[5] This outcome has important practical applications for assignment purposes: for instance, in the case of **3**, the $\Delta\delta^{RS}$ for Cβ-H is so small at 300 K ($\Delta\delta^{RS} = -0.02$ ppm) that a fully reliable sign cannot be inferred from that value, while at 213 K, the sign is clearly identified as negative ($\Delta\delta^{RS} = -0.21$ ppm). In addition to this advantage, the increase of $\Delta\delta^{RS}$ values at lower temperature constitutes an experimental way to check that the conformational composition of the 9-AMA esters is just as expected: when higher consistent $\Delta\delta^{RS}$ values are obtained, the experiment confirms both the assignment and the conformational behavior of the esters. However, when no coherent increments for L_1/L_2 and Cβ-H are observed, it indicates that the NMR method is not appropriate for the compound under

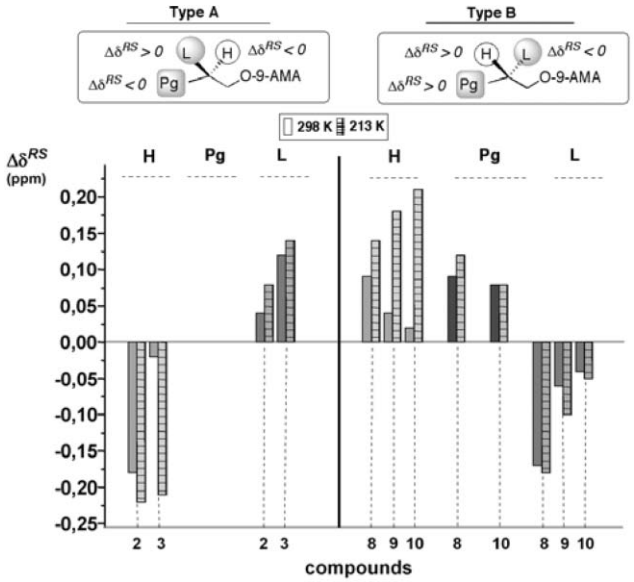

Fig. 3 Temperature variations of $\Delta\delta^{RS}$ for the compounds indicated.

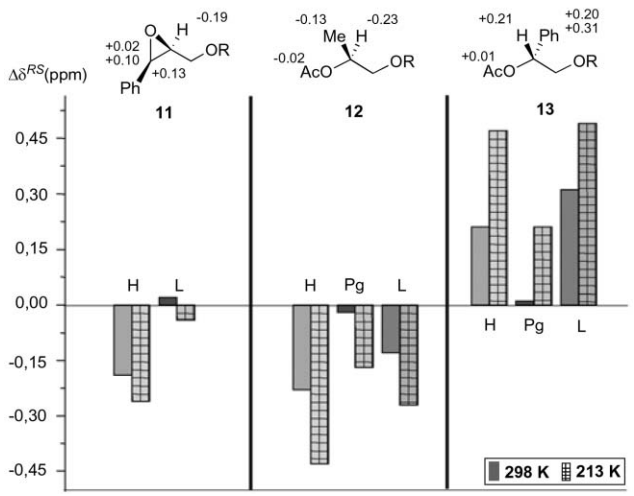

Fig. 4 Temperature variations of $\Delta\delta^{RS}$ for the compounds shown.

study and that the signs of $\Delta\delta^{RS}$ do not generate a reliable assignment of configuration.

In order to evaluate if the low temperature NMR experiments serve to detect those structures that are inappropriate for configurational assignment, we tested alcohols **11–13** (Fig. 4), whose special conformational and structural characteristics make them problematic.[5]

Epoxide **11** (Fig. 4, Type B (*R*)) has observable protons only at one side of the chiral center (L). The $\Delta\delta^{RS}$ signs at rt for L and for Cβ-H suggest a Type A (*S*) configuration. The low temperature NMR shows an unusual behavior of $\Delta\delta^{RS}$ values that places a warning sign on that erroneous assignment. Simply, the NMR method is not reliable for this compound because the anisotropy of its phenyl group competes with the anisotropy from the anthryl group of the auxiliary.

With regard to compounds **12–13**, both show identical $\Delta\delta^{RS}$ signs for Cβ-H and L, making the assignment untenable. In the low temperature experiments the signs did not change (Fig. 4), thus confirming that the method cannot be applied to these compounds.‖

A protocol for the assignment of absolute configuration of β-chiral primary alcohols follows:

1) Preparation of the (*R*)- and (*S*)-9-AMA esters.

2) Comparison of their ^{1}H-NMR spectra.

3) Calculation of the $\Delta\delta^{RS}$ values for Cβ-H and L.

4) If the $\Delta\delta^{RS}$ values are negative for Cβ-H and positive for L, the alcohol presents a Type A (*S*) configuration. If Cβ-H is positive and L negative, the alcohol belongs to Type B (*R*).

5) The calculation of the $\Delta\delta^{RS}$ values at lower temperature confirms the correctness of the absolute configuration assigned.

To sum up, the use of the Cβ-H and L signals allows the assignment of the absolute configuration of β-primary alcohols with no protons at one of the substituents. In addition, repeating the spectrum at lower temperature serves to check out the reliability of the assignment.

We thank the Ministerio de Educación y Ciencia (MEC) and the Xunta de Galicia for financial support (CTQ2005-05296/BQU; SAF2003-08765-C03-01; PGIDIT06PXIB209029PR) and the Centro de Supercomputación de Galicia (CESGA) for their assistance with the computational work.

Notes and references

‡ A different situation holds for polyfunctional compounds, such as diols and amino alcohols, where the hydrogens directly bound to the asymmetric centers do generate the diagnostic shifts for assignment. In those cases, the shift of a given Cα-H is caused by the adjacent CDA unit and not by the one placed at the same carbon. For diols see: refs. 3*a–c*. For amino alcohols see: ref. 4.

§ Descriptions of the main conformers found for Type A (*S*) and Type B (*R*) (*R*)- and (*S*)-9-AMA esters can be found in the Electronic Supplementary Information (ESI). Theoretical calculations [energy minimization by semiempirical (AM1), and DFT (B3LYP)] were performed using Gaussian 98. (1*S*)-deuterated (*R*)-3-bromo-2-methylpropan-1-ol was synthesized and used in the ^3J and low temperature NMR experiments.

¶ It is necessary to consider that the enantiomers of the Type A (*S*) alcohols tested experimentally belong to Type B (*R*) and present the opposite set of signs to those shown in Fig. 2a. Similarly, the enantiomers of the Type B (*R*) alcohols tested experimentally belong to Type A (*S*) and present the opposite set of signs to those shown in Fig. 2b.

‖ The main conformers of compounds **12–13**—and correspondingly, their chemical shifts—are analogous to those found for the bis-AMAA esters of β-chiral 1,2-diols, as shown by constant coupling and low temperature studies. For β-chiral 1,2-diols see: ref. 3*b*.

1 For reviews see: J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17; J. M. Seco, E. Quiñoá and R. Riguera, *Tetrahedron: Asymmetry*, 2001, **12**, 2915.

2 J. M. Seco, E. Quiñoá and R. Riguera, *Tetrahedron: Asymmetry*, 2000, **11**, 2781.

3 (*a*) F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 2005, **70**, 3778; (*b*) F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *Chem.–Eur. J.*, 2005, **11**, 5509; (*c*) J. M. Seco, M. Martino, E. Quiñoá and R. Riguera, *Org. Lett.*, 2000, **2**, 3261.

4 V. Leiro, F. Freire, E. Quiñoá and R. Riguera, *Chem. Commun.*, 2005, 5554.

5 S. K. Latypov, M. J. Ferreiro, E. Quiñoá and R. Riguera, *J. Am. Chem. Soc.*, 1998, **120**, 4741.

