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Chiral 1,2-Diols: The Assignment of Their Absolute Configuration by NMR Made Easy

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

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

ricardo.riguera@usc.es

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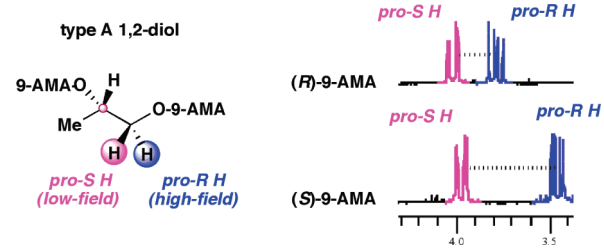
ABSTRACT



The absolute configuration of a 1,2-primary/secondary diol can be easily determined by preparation of its bis-(*R*)- and bis-(*S*)-9-AMA ester derivatives, followed by comparison of the NMR chemical shifts of the diastereotopic methylene protons in the two derivatives. Alternatively, the assignment can be carried out using only one derivative if the evolution with temperature of the signals corresponding to the CαH protons is analyzed.

The assignment of the absolute configuration of a chiral substrate by ^{1}H NMR using a chiral derivatizating agent (CDA) is a well-established technique.[1]

The general method, derived from the pioneering "Mosher−Trost Method",[1,2] consists of the derivatization of the chiral substrate (i.e., alcohol, amine, thiol, etc.) with the two enantiomers of a CDA (i.e., MPA: 2-methoxy-2-phenylacetic acid; 9-AMA: 2-(anthracen-9-yl)-2-methoxy-acetic acid; MTPA: 2-methoxy-2-trifluoromethyl-2-phenyl-acetic acid), followed by the comparison of the chemical shifts of the protons in the substrate moiety of the two resulting derivatives.[1]

The full proton assignment in molecules with complex structure (sugars, policyclic compounds, etc.) usually requires the combination of multiple NMR techniques such as TOCSY, COSY, NOESY, etc., a fact that can make tedious the assignment of the absolute configuration by NMR. A second limitation is the need to prepare two diastereomeric derivatives from a sample that sometimes is very small. Fortunately, for some functional groups, the configuration can be determined by using only one derivative with an appropriate CDA.[3]

In this communication, we will demonstrate with the help of theoretical and empirical studies that in the case of chiral 1,2-primary/secondary diols both limitations can be circum-

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(2) (a) Dale, A. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

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vented by using 9-AMA as the CDA of choice and just looking at the chemical shifts of the diastereotopic methylene protons (Figure 1).

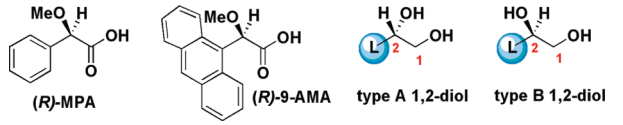

Figure 1. Structures of MPA, 9-AMA, and types A and B 1,2-diols.

Thus, conformational analysis of the bis-(*R*)- and bis-(*S*)-9-AMA esters of (*S*)-propane-1,2-diol (configuration type A, Figure 2), using a combination of theoretical and experimental data,[4] indicated that in both the bis-(*R*)- and the bis-(*S*)-9-AMA derivatives there is a conformational equilibrium between two main conformers: II-sp and II-ap (Figure 2). In these conformers, the O−C(1′) bond adopts a II conformation with the carbonyl of the 9-AMA at C(1′) coplanar to the *pro-S*-methylene proton[5] at C(1), and the C(1′)−C(2′) bond is in a *gt* (gauche-*trans*) conformation.[6] For its part, the 9-AMA moieties adopt two possible orientations: an sp orientation (the carbonyl and the OMe are *synperiplanar*) or an ap orientation (the carbonyl and the OMe are *antiperiplanar*).

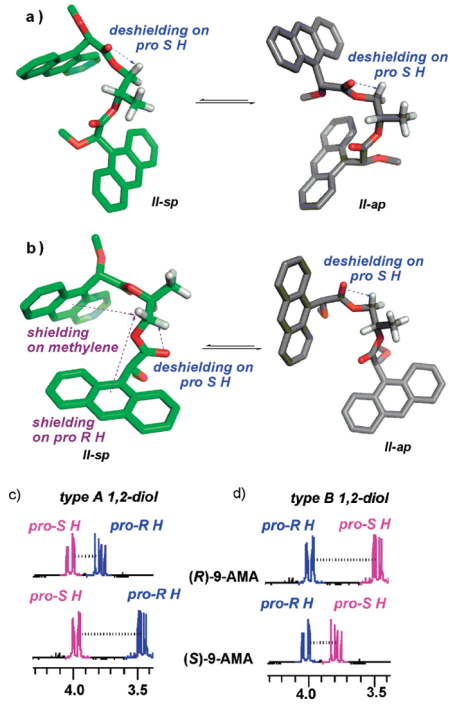

Figure 2. Representative conformers of the (a) bis-(*R*)- and (b) bis-(*S*)-9-AMA esters of (*S*)-propane-1,2-diol. Partial ^{1}H NMR showing the methylene protons in the bis-9-AMA esters of (c) (*S*)- and (d) (*R*)-propane-1,2-diol, types A and B, respectively.

With these results in hand, the orientation of the anthryl and carbonyl groups toward the methylene protons can be visualized, and therefore, the anisotropic effects over those protons are predicted for each derivative.

Thus, in the bis-(*R*)-9-AMA ester of a type A diol, the carbonyl group on the primary alcohol is oriented in such a way that induces a deshielding effect over the *pro-S* proton and a shielding effect over the *pro-R* proton. For its part, the anthryl groups of the two auxiliary units are not well oriented toward the methylene group, so their anisotropic effects do not influence significantly those two protons (Figure 2a).

In the case of the bis-(*S*)-9-AMA ester of the same diol, the situation is more complex: the carbonyl group at C(1′) is oriented to cause shielding on *pro-R* H and deshielding on *pro-S* H in both conformers sp and ap, but the anthryl groups of the two 9-AMA auxiliaries are also well oriented to act on the methylene protons producing the following effects: in the sp conformer, *pro-R* H is shielded by the two anthryl units, while the *pro-S* H is shielded by only the anthryl moiety of the 9-AMA at C(1′) (Figure 2b).

In this way, the methylene protons of a 1,2-diol are subjected in every derivative to very different shielding/deshielding effects that should produce very different spectral patterns for the bis-(*R*)-9-AMA and the bis-(*S*)-9-AMA derivatives (Figure 2c). These results are summarized as follows: in a type A 1,2-diol, the methylene protons should resonate at closer frequencies in the bis-(*R*)-9-AMA than in the bis-(*S*)-9-AMA derivative (Figure 2c).

Similar analysis on the relative orientation of the anisotropic groups with respect to the methylene protons in the enantiomeric 1,2-diol (configuration type B) shows the reverse distribution of shielding/deshielding effects (Figure 2d). This means that in a type B diol the methylene protons should resonate at closer frequencies in the bis-(*S*)-9-AMA than in the bis-(*R*)-9-AMA derivative (Figure 2d). Figures 2c and 2d show the actual NMR spectra of the bis-9-AMA esters of (*S*)- and (*R*)-propane-1,2-diol (types A and B, respectively).

Theoretical chemical shift calculations (GIAO)[7] on the sp-II and ap-II conformers of the bis-(*R*)- and bis-(*S*)-9-AMA esters of (*S*)-propane-1,2-diol showed data in very good agreement with the experimental chemical shifts.

Experimental demonstration of the general character of this correlation between absolute configuration of the diol and the spectra of the methylene protons was obtained with a series of 1,2-diols of known absolute configuration (**1**−**9**,

(4) For conformational studies by CD, structure calculations, coupling constants analysis, and selective deuteration, see Supporting Information for details.

(5) The pro-*R* and pro-*S*-methylene protons have been assigned by means of deuteration experiments (See Figure S5 in Supporting Information). Note that in a type A 1,2-diol, the pro-*S*-proton resonates at lower field and the pro-*R* at higher field, while in a type B 1,2-diol, the pro-*S* resonates at higher field and the pro-*R* at lower field.

(6) H(2)−C(2)−C(1)−H *proR* in *gauche* and C(3)−C(2)−C(1)−O in *trans* conformations.

(7) Aromatic shielding effect calculations were performed using Gaussian 98. See Supporting Information.

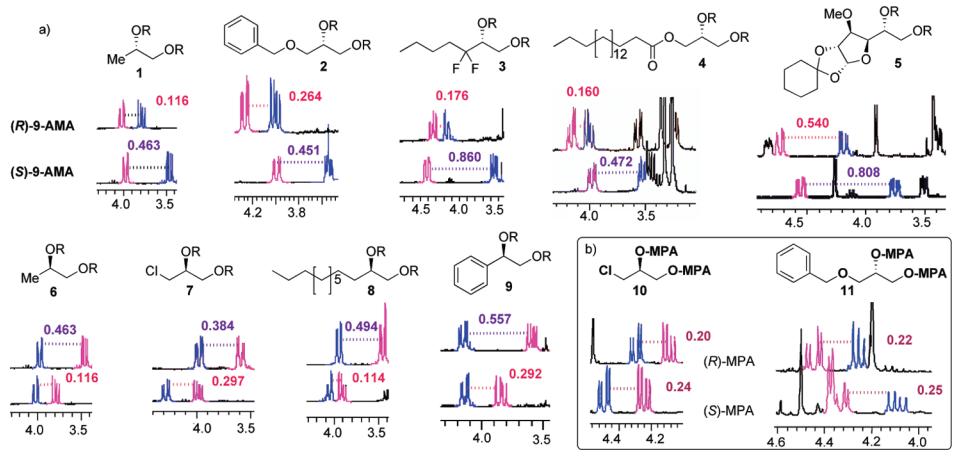

Figure 3. (a) Partial ^{1}H NMR spectra showing the diastereotopic methylene protons of the bis-9-AMA esters **1**−**5** (type B) and **6**−**9** (type A). (b) Partial ^{1}H NMR spectra showing the diastereotopic methylene protons of the bis-MPA esters **10** and **11**.

Figure 3). In all cases, the absolute configuration of the diol correlates with the pattern of the methylene protons of Figure 2 for the bis-(*R*)- and bis-(*S*)-9-AMA derivatives, demonstrating the usefulness of this correlation for the assignment of the absolute configuration by NMR of the bis-9-AMA derivatives.

It should be pointed out that when 9-AMA is replaced by MPA the shielding/deshieldings observed for the methylenes are so small that no useful differences are obtained (see **10**−**11** in Figure 3).[8]

Single Derivatization Method. In previous papers,[3] we have described the use of low-temperature NMR as a way to obtain the absolute configuration using only one MPA derivative. This requires the analysis of the evolution with temperature of the chemical shift values for the L_1/L_2 groups. It is based on the changes on relative populations of the main conformers induced by temperature modification and its translation to the NMR spectra via the anisotropic effects of the phenyl ring of MPA on L_1/L_2.

In the case of the bis-9-AMA ester derivatives of 1,2-diols, the groups better oriented for this purpose are the CαH protons on the 9-AMA moieties, and in fact, we observed a perfect correlation between the evolution with temperature of those signals and the absolute configuration of the diol.

In this way, when the NMR spectra of the bis-(*R*)-9-AMA ester of (*S*)-propane-1,2-diol (**1**, type A) are registered at decreasing temperatures, both CαH protons are shifted to higher field (Figure 4c and 4d). In the bis-(*S*)-9-AMA ester of the same diol, the CαHs are shifted in opposite directions (one to higher field and the other to lower field), and the same pattern of evolution was observed for all the bis-9-AMA esters of compounds **2**−**5** (type A, Figure 3).

These shifts with temperature can be explained by the shieldings/deshieldings effect suffered by the CαH in each conformer and the change of their relative populations with temperature.

Thus, in the bis-(*R*)-9-AMA ester of the (*S*)-1,2-propanediol (type A), we observe the following anisotropic effects: (a) in the II-sp conformer, the 9-AMA unit on the primary alcohol shields the CαH of the 9-AMA unit on the secondary alcohol (Figure 4a); (b) in the II-ap conformer, the opposite effect happens, and the 9-AMA on the secondary alcohol shields the CαH of the 9-AMA on the primary alcohol (Figure 4a).

As a consequence, a drop of the NMR probe temperature compels the CαH protons of both 9-AMA units to move upfield providing a positive $\Delta\delta^{T1T2}$ value[9] (Figure 4c).

For its part, in the bis-(*S*)-9-AMA ester of the same diol [(*S*)-propane-1,2-diol, Type A], the distribution of anisotropic

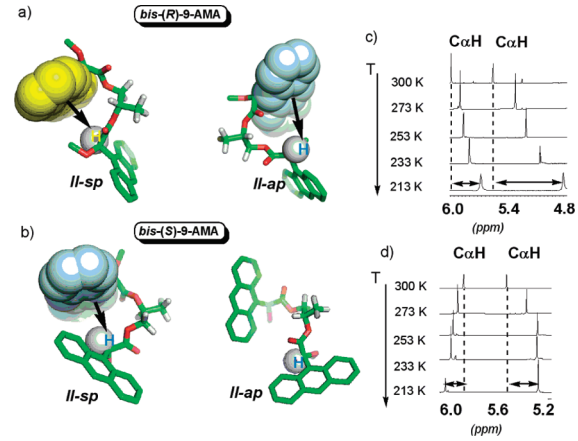

Figure 4. Shielding effects over the CHα protons at the 9-AMA moieties in the main conformers of (a) bis-(*R*)- and (b) bis-(*S*)-9-AMA esters of (*S*)-propane-1,2-diol and evolution with the temperature of their spectra (c,d).

(8) If MPA is the reagent of choice, the "classical" approximation is a reliable alternative. For details, see: Freire, F.; Seco, J. M.; Quiñoa, E.; Riguera, R. *Chem.—Eur. J.* **2005**, *11*, 5509, reference 3b.

(9) The $\Delta\delta^{T1T2}$ values are defined as δ at the higher temperature (T1) minus δ at the lower temperature (T2).

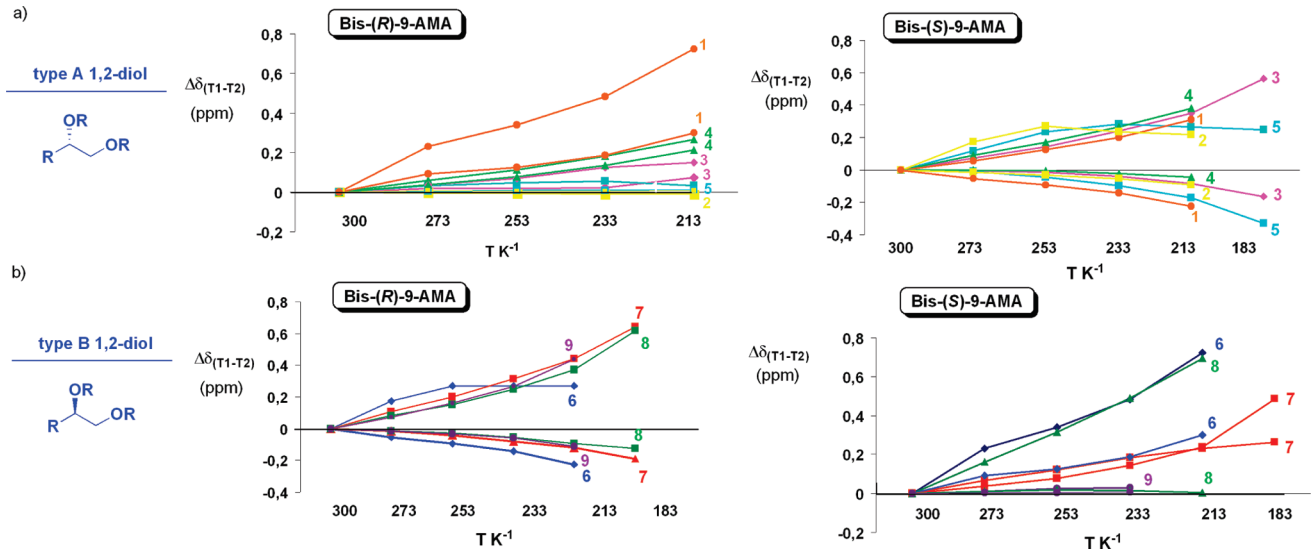

Figure 5. Evolution with the temperature of the CHα protons of the 9-AMA moieties of the bis-(*R*)- and bis-(*S*)-9-AMA **1**−**9**.

effects is the following: (a) in the II-sp conformer, the 9-AMA unit on the secondary alcohol shields the CαH proton of the other 9-AMA; (b) in the II-ap conformer, the two 9-AMA units are oriented in such a way that they do not affect any CαH proton.

When the NMR spectra are taken at lower temperatures, the CαH of the 9-AMA on the primary alcohol (higher-field CαH proton) moves upfield (positive $\Delta\delta^{T1T2}$), while the CαH proton of the other 9-AMA (the one that resonates at lower field) moves downfield (negative $\Delta\delta^{T1T2}$) (Figures 4b and 4d).

Similar analysis in the enantiomeric diol (type B) reveals the opposite pattern in the NMR spectra for the shifts of the CαH protons of the bis-9-AMA esters when the temperature decreases. In this way, when the NMR spectra of the bis-(*R*)-9-AMA ester of (*R*)-propane-1,2-diol (**6**, type B) are registered at decreasing temperatures, the CαHs are shifted in opposite directions (one to high-field and the other to low field), while in the bis-(*S*)-9-AMA ester of the same diol, both CαH protons are shifted to high field. The same pattern of evolution was observed for all the bis-9-AMA esters of compounds **6**−**9** (type B, Figure 3).

Plots showing the evolution with temperature of the CαHs of the bis-(*R*)- and bis-(*S*)-9-AMA esters of compounds **1**−**9** are shown in Figure 5.

In conclusion, the absolute configuration of 1,2-primary/secondary diols can be easily determined by two different and complementary ways: (a) the comparison of the methylene protons in both derivatives, bis-(*R*)- and bis-(*S*)-9-AMA esters, or (b) by using a single derivative, where the movement of the CαH protons of the 9-AMA moieties in the NMR spectra when the temperature decreases is related to the absolute configuration of the diol. This is the first time that the chiral auxiliary 9-AMA is applied in a single derivatization method.

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Supporting Information Available: Conformational analysis (energy calculations, CD, selective deuteration, dynamic NMR, experimental and theoretical chemical shifts), general experimental procedures, synthesis of 9-AMA, and spectroscopic data of compounds **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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