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Determining the Absolute Stereochemistry of Secondary/Secondary Diols by ^{1}H NMR: Basis and Applications

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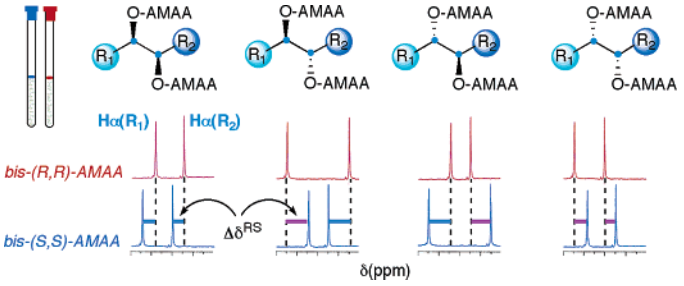

The absolute configuration of 1,2-, 1,3-, 1,4-, and 1,5-diols formed by two secondary (chiral) hydroxy groups can be deduced by comparison of the NMR spectra of the corresponding bis-(*R*)- and bis-(*S*)-MPA esters. The correlation between the NMR spectra of the bis-ester derivatives and the absolute stereochemistry of the diol involves the comparison of the chemical shifts of the signals for substituents R_1/R_2 and for the hydrogens attached to the two chiral centers [$H_\alpha(R_1)$ and $H_\alpha(R_2)$] in the bis-(*R*)- and the bis-(*S*)-ester and is expressed as $\Delta\delta^{RS}$. Theoretical calculations [energy minimization by semiempirical (AM1), ab initio (HF), DFT (B3LYP), and Onsager methods, and aromatic shielding effect calculations] and experimental data (NMR and CD spectroscopy) indicate that in these bis-MPA esters, the experimental $\Delta\delta^{RS}$ values are the result of the contribution of the shielding/deshielding effects produced by the two MPA units that combine according to the actual stereochemistry of the diol. The reliability of these correlations is demonstrated with a wide range of diols of known absolute configuration derivatized with MPA and 9-AMA as auxiliary reagents. A simple graphical model that allows the simultaneous assignment of the two asymmetric carbons of a 1,*n*-diol by comparison of the NMR spectra ($\Delta\delta^{RS}$ signs) of its bis-(*R*)- and bis-(*S*)-AMAA ester derivatives is presented.

Introduction

The assignment of the absolute configuration of monofunctional compounds by comparison of the NMR of its derivatives with the (*R*)- and the (*S*)- enantiomers of a selected auxiliary reagent is a well-established procedure due to its reliability, simplicity, and convenience. This topic was initiated by Mosher and Trost in the sixties and applied fundamentally to secondary alcohols and primary amines with the asymmetric carbon at the α-position, using α-methoxy-α-trifluoromethyl-α-phenylacetic acid (MTPA, **1**) as auxiliary.[1] In this way, the (*R*)- and the (*S*)-MTPA esters of the alcohol show NMR spectra that reflect the shielding produced by the phenyl ring of the auxiliary part selectively on each one of the substituents of the alcohol part.

In the last 10 years, the fundamental aspects of the "Mosher−Trost" method and its limitations have been studied,[1d,e] and this opened the way to the expansion of its applications to substrates containing other functional groups, to new and more efficient auxiliary reagents,[2] to optimized experimental conditions[3] that simplified its implementation to the point of using only one derivative

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instead of two,[4] or to the elimination of any manipulation of the sample, when the auxiliary is linked to a selected resin.[5]

A review on the procedures for assignment of absolute configuration by NMR of covalently bonded derivatives has recently been published.[6] It includes a critical assessment on the reliability of each application according to the number and structural variety of the substrates of known absolute configuration that have been used to validate it.

Application of this NMR procedure to polyfunctional substrates requires a much more careful analysis than for monofunctional compounds.[7] This is so because if i.e., a diol is derivatized with the (*R*)- and the (*S*)-MPA as auxiliary, it will lead to bis-MPA esters containing not one but two phenyl rings to produce shielding on the molecule. Obviously, combinations of shielding and deshielding could impede the association of the resulting spectra with the absolute configuration

Some attempts have been described in the literature, using MTPA (**1**) as auxiliary for the assignment of polyalcohols.[7b,c,8] The process involved the simultaneous esterification of all the OH groups of the substrate with the (*R*)- and the (*S*)-auxiliary and the comparison of the NMR spectra of the resulting (*R*)- and (*S*)-MTPA peresters. Unfortunately, no similar polyfunctional compounds with known absolute configuration were tested as models and therefore no experimental evidence was available that could validate the reliability of the configuration assigned in that way. An additional difficulty is that, in some cases, the signs of $\Delta\delta^{SR}$ are identical for the two substituents[7a] directly bonded to the asymmetric carbon (L_1/L_2), which makes it impossible to assign the configuration only on the basis of these data.[9,7a]

But, more importantly, even in those cases where an alternation in the signs of $\Delta\delta^{SR}$ values[10a] is observed (i.e. positive for L_1 and negative for L_2, or *vice versa*), the absolute configuration was assigned by interpretation of the $\Delta\delta^{SR}$ values as if all the auxiliaries present in the MTPA perester were completely isolated.[7b,c] This interpretation of the experimental data ignores the existence of crossed shielding and deshielding effects transmitted through the space and due to the combined action of all the auxiliaries and invalidates that analysis of the NMR data and therefore the reliability of the assignment.

In our opinion, the interpretation of the values and signs of $\Delta\delta$ must take into account the fact that each unit of the auxiliary that has been introduced on the substrate (i.e. two in the bis ester of a diol) produces shielding/deshielding not only on the protons nearest to that chiral carbon but also on substituents on the other asymmetric carbon atoms.[7a] In this way, the experimental $\Delta\delta^{SR}$ values obtained for a particular proton are the result of the combination of the shielding/deshielding effects produced by all the auxiliary reagent units present in the molecule.[7a] Evidently, the models developed for, i.e., monoalcohols are not directly applicable to polyalcohols.

In this work we will demonstrate that a correlation exists between the absolute configuration of a diol containing two secondary chiral alcohol groups and the NMR spectra of the bis esters derived from selected auxiliary reagents**.** Also**,** we will show that this correlation can be used to determine the absolute configuration of the two asymmetric centers of the diol simultaneously provided that the $\Delta\delta^{RS}$ values[10b] are interpreted as the result of the combination of the anisotropic effects of the two auxiliary reagent units present in the compound. In this way, no protecting−deprotecting operations are necessary[11] because the two hydroxyl groups of the diol are derivatized at the same time and the assignment is achieved by preparation of the bis esters of the diol with the enantiomers of an AMAA (arylmethoxyacetic acid), auxiliary reagent such as MPA (**2**), 1-NMA (**3**), 2-NMA (**4**), 9-AMA (**5**), and MTPA (**1**) as reagents (Figure 1) followed by comparison of those two ^{1}H NMR spectra.

A short account reporting only the results on symmetrical diols has been published.[12] The case of diols containing one secondary chiral and one primary alcohol group will be described elsewere.

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(10) (a) For MTPA esters $\Delta\delta^{SR}$ is defined as the difference between the chemical shift for a given substituent in the (*S*)-MTPA ester and its chemical shift in the (*R*)-MTPA derivative [i.e $\Delta\delta^{SR}L_1 = \delta L_1(S) - \delta L_1(R)$]. The same applies for the bis-MTPA-diesters. (b) For the AMAA esters (MPA, 9-AMA, etc..) $\Delta\delta^{RS}$ is defined as the difference between the chemical shift for a given substituent in the (*R*)-AMAA ester and its chemical shift in the (*S*)-AMAA derivative [i.e $\Delta\delta^{RS}L_1 = \delta L_1(R) - \delta L_1(S)$]. The same applies for the bis-AMAA-diesters.

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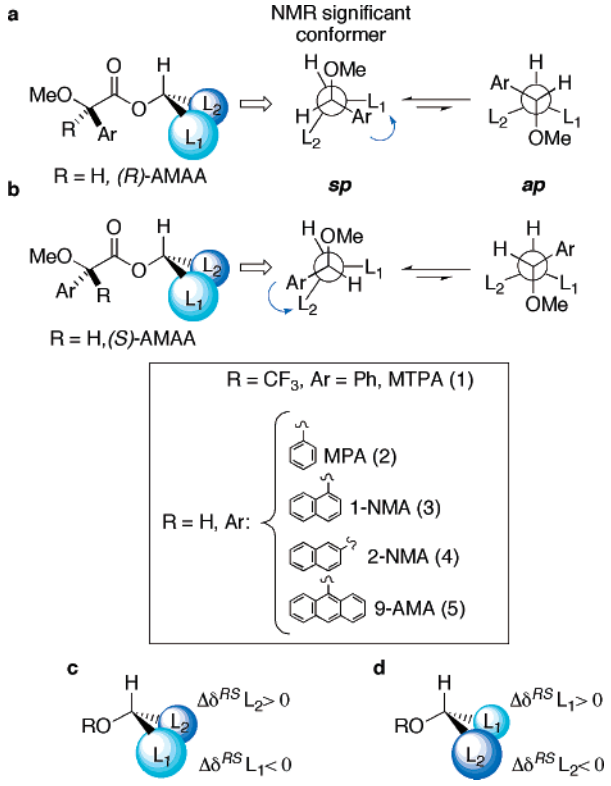

FIGURE 1. Structures and NMR correlation models for AMAA esters.

Results and Discussion

The determination of the absolute configuration by NMR of a secondary alcohol involves derivatization of the alcohol with the two enantiomers of a suitable auxiliary reagent [(*R*)- and (*S*)-AMAA] and subsequent comparison of the NMR spectra of the resulting diastereoisomers.

This NMR procedure depends on the existence of a conformational preference—the same in both the (*R*)- and the (*S*)-derivative—and on the NMR effects associated with that structure. In the case of the AMAA esters of secondary alcohols, the main conformer presents the methoxy, the carbonyl, and C(1′)H in the same plane and with the methoxy and carbonyl groups in a *synperiplanar* position so that the substituents of the alcohol (L_1/L_2) are located at both sides of that plane,[13] only one being affected by the aryl group of the auxiliary. In the (*R*)-AMAA esters (Figure 1a) of an alcohol with the stereochemistry shown, L_1 is the shielded substituent, while in the ester derivative made from the same alcohol and the (*S*)-AMAA auxiliary (Figure 1b), L_2 is the shielded one.

The result, in terms of the NMR spectra, is that substituent L_1 of the alcohol shown in Figure 1 is more shielded in the *(R)*- than in the (*S*)-derivative, while substituent L_2 is more shielded in the (*S*)- than in the (*R*)-derivative and thus $\Delta\delta^{RS}L_1 < 0$ and $\Delta\delta^{RS}L_2 > 0$ (Figure 1c). If the configuration of the alcohol were the opposite, the signs of $\Delta\delta^{RS}$ would be $\Delta\delta^{RS}L_1 > 0$ and $\Delta\delta^{RS}L_2 < 0$ (Figure 1d).

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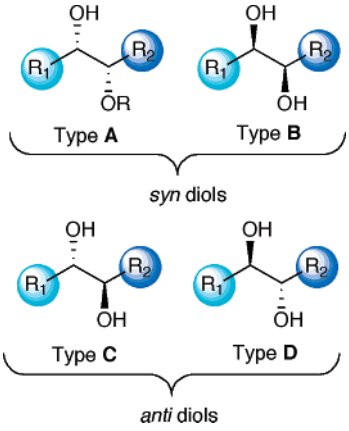

FIGURE 2. Stereochemistries for 1,2-diols with two secondary alcohol groups.

From a practical point of view, a very convenient way to extract configurational information from the average NMR spectra is to consider only the most representative conformer (*sp*) and its shielding effects, dismissing the contribution of the other (*ap*). In this manner, simplified models can be formulated to assign the absolute configuration of secondary alcohols just from the signs of $\Delta\delta^{RS}$.

In the case of a diol, triol or, more generally, a polyalcohol containing several asymmetric carbon atoms with directly attached hydroxyl groups, it should be possible to determine the absolute configuration of each asymmetric carbon in the same way, provided that only one unit of the auxiliary reagent is present at a time. This means that the other hydroxyl groups are either free or protected prior to the NMR determination.[11] This process is clearly long and experimentally laborious because the asymmetric centers are studied one by one, and efforts to explore the possibility of determining the absolute configuration of all the centers at a time, by introduction of the auxiliary in all the hydroxyl groups in a single process, are really appealing.

This would involve just two operations: derivatization of the two hydroxy groups of the diol with the (*R*)- and the (*S*)-enantiomers of the auxiliary and comparison of the NMR spectra of the bis ester derivatives.

Naturally, the values and signs of those $\Delta\delta^{RS}$ are the result of the combined action of the shielding/deshielding caused by two auxiliary reagent units present in the molecule and therefore depend on the absolute configuration at the two asymmetric carbons of the diol (Figure 2) as the absolute configuration of the two auxiliary units introduced.

In our hypothesis, the NMR spectra of the bis-(*R*)- and bis-(*S*)-ester derivatives will provide useful information to correlate the absolute configuration of the auxiliary (known) with that of the diol[14] (unknown), in a way that permits its safe assignment.

In this work, we will start describing the main conformations of the bis-AMAA-ester derivatives of the four stereoisomers of a diol with two asymmetric alcohol groups, the expected distribution of shielding and deshielding effects, and the resulting chemical shifts.

Next, a series of diols of known absolute stereochemistry and different distances between the hydroxy groups (from 1,2- to 1,*n*-diols) will be used to validate those

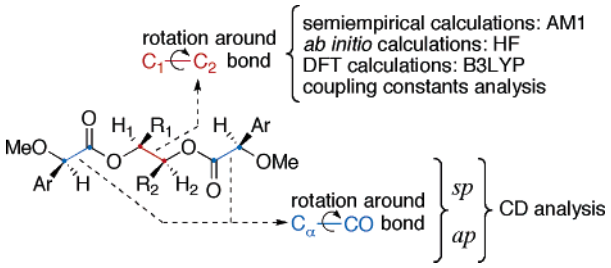

FIGURE 3. Main rotations in the conformational analysis of 1,2-diols.

predictions. Then, conclusions about how the NMR spectra of the bis esters correlate with the absolute configuration of the diol substrate will be extracted, and finally, graphical models allowing the direct assignment of the absolute configuration of a diol from the NMR data of the bis esters will be presented.

1. a. Main Conformations of the Bis-MPA and Bis-9-AMA Esters of 1,2-Diols. The NMR procedures for assignment of absolute configuration of chiral secondary alcohols depend on the existence of a conformational preference and on the NMR effects associated with that structure (Figure 1). This conformational equilibrium and the resulting NMR shifts have been studied[13] by energy minimizations, structure calculations, and shielding effect calculations, as well as by CD, low temperature, and dynamic NMR.[13]

Similarly, for the case of the bis-ester derivatives of diols, it should be possible to obtain information about the structure of the more representative conformers and the position of the aryl group with respect to the substituents of the diol by a combination of theoretical calculations and properly chosen experimental methods.

The main conformational process that should be analyzed in the bis esters of a diol are those involving rotations around the $C_\alpha-CO$ and the C_1-C_2 bonds (Figure 3): the first one relates to the auxiliary part of the molecule and is the origin of the sp (methoxy and carbonyl *synperiplanar*) and ap (methoxy and carbonyl *antiperiplanar*) conformers mentioned before and can be analyzed by CD spectroscopy.[15,4f]

For its part, the rotation around the C_1-C_2 bond determines the relative position of each AMAA reagent with respect to the other (gauche, anti, etc.) and is related to the structure of the substrate. For its study, we will carry out theoretical calculations on this rotation and compare the results with those obtained from the analysis of the coupling constants[16] between H(1′) and H(2′) (Figure 3).

1. b. Conformational Preference Around the $C_\alpha-CO$ Bond: Circular Dichroism Spectra of the Bis-AMAA Esters. The signs of the Cotton effect of the sp and ap components of the conformational equilibrium of a (*R*)-MPA ester of a secondary alcohol have been shown by CD[4f] to be negative for the sp conformer and positive for the ap [and the reverse for the (*S*)-MPA ester derivative]. As the most abundant conformer in the equilibrium is the sp, the CD spectra of all the (*R*)-MPA esters present a resulting negative Cotton effect, while the (*S*)-MPA esters present a positive sign.

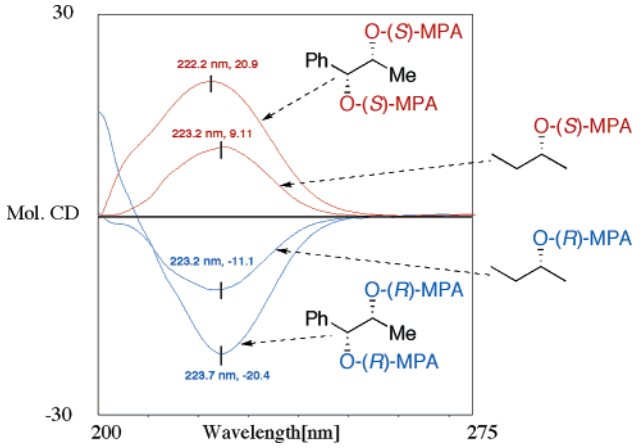

FIGURE 4. CD spectra for the bis-(*R*)- and bis-(*S*)-MPA esters of (1*R*,2*R*)-1-phenylpropane-1,2-diol (**6b**) and (*R*)- and (*S*)-MPA esters of (*R*)-butan-2-ol (**7**) [MeOH, $c = 1 \times 10^{-5}$ M].

In the case of the diols, we checked the conformational composition around the $C_\alpha-CO$ bond by examination of the CD spectra of the bis-(*R*)- and the bis-(*S*)-MPA esters of (1*R*,2*S*)-1-phenylpropane-1,2-diol (**6b**) selected as a representative substrate.

Figure 4 shows the CD spectra of the (*R*)- and (*S*)-MPA ester of (*R*)-butan-2-ol (**7**) and those of the bis-(*R*)- and bis-(*S*)-MPA esters of (1*R*,2*R*)-1-phenylpropane-1,2-diol (**6b**).

In the CD, the (*R*)-MPA ester presents a negative Cotton effect and the (*S*)-MPA ester a positive one (Figure 4). This is the consequence of the greater population of the sp conformer in those compounds.

For their part, when the bis-MPA esters of diol **6b** are examined, we observe that the bis-(*R*)-MPA ester shows a negative curve similar to that of the (*R*)-MPA ester while the bis-(*S*)-MPA of the diol presents a positive one as in the (*S*)-MPA ester of **7** (Figure 4). This coincidence in the CD curves clearly indicates that in the auxiliary part of the molecules, the main conformer is the same for MPA esters of monoalcohols (conformer sp) as for bis-MPA esters of diols.

Similarly, we investigated by CD the contribution of the conformers sp and ap to the equilibrium mixture of the bis-9-AMA esters. Figure 5 shows the CD spectra of the (*S*)-9-AMA ester of (*R*)-butan-2-ol (**7**), which presents a first positive and a second negative cotton effect as a consecuence of the major presence of sp conformer. For its part the (*R*)-9-AMA ester shows the opposite indicating a sp conformer.

In the case of a diol, we checked the conformational freedom around the $C_\alpha-CO$ bond by examination of the CD spectra of the bis-(*R*)- and the bis-(*S*)-9-AMA esters of **6b**. The spectra for the bis-(*S*)-9-AMA shown in Figure 5 presents a first positive and a second negative cotton effect indicating the presence of an sp conformer while in the bis-(*R*)-9-AMA ester the spectra shows the opposite Cotton effect as in secondary alcohols. This proves again that the main conformer is sp in both cases and that

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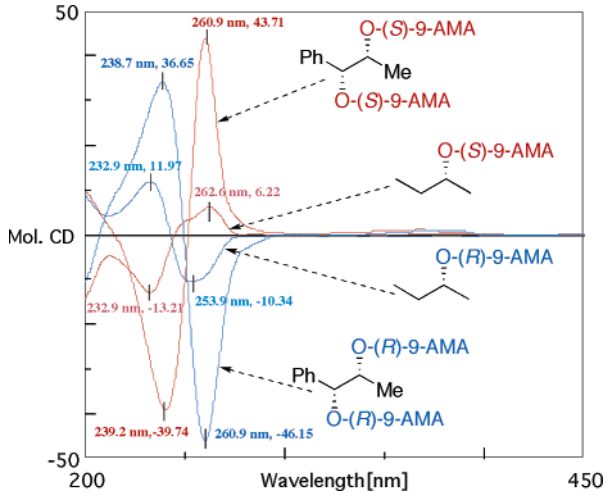

FIGURE 5. CD spectra for the bis-(*R*)- and bis-(*S*)-9-AMA esters of (1*R*,2*R*)-1-phenylpropane-1,2-diol (**6b**) and (*R*)- and (*S*)-9-AMA esters of (*R*)-butan-2-ol (**7**) [MeOH, $c = 1 \times 10^{-5}$ M].

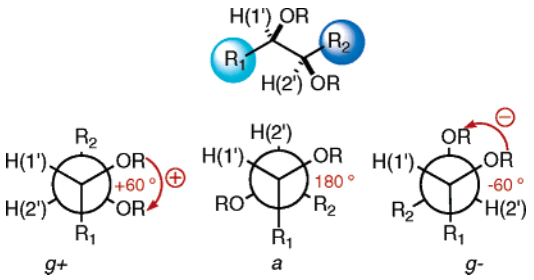

FIGURE 6. Main conformers for the bis-AMAA esters of a *syn*-diol type B.

rotation around the C_α−CO bond of 9-AMA bis esters follows the same trend as in the bis-MPA esters and, as in the monoesters of secondary alcohols, with the methoxy and the carbonyl groups in a *synperiplanar* disposition.

1. c. Conformational Preference Around the C_1−C_2 Bond: Semiempirical (AM1), ab Initio (HF) DFT (B3LYP), and Onsager Calculations. Coupling Constants Analysis. In accordance with studies carried out on the conformational composition of diols, rotation around the C_1−C_2 bond can give three main conformers[16] named as *g*+, *g*−, and *a*: Conformer *g*+ has the two ester groups at 60°, conformer *g*− has the two ester groups at −60°, and conformer *a* has the two ester groups at 180°. The number of gauche interactions will depend on the absolute configuration of the diol that it is going to be studied. For example, for the diol shown in Figure 6, the conformer *g*+ presents three gauche interactions, the *g*− presents two gauche interactions, and the *a* conformer presents three gauche interactions.

In the case of the bis AMAA esters the number and type of the gauche interactions will depend not only on the configuration of the diol but on that of the auxiliary too. To obtain information about the rotation around the C1−C2 bond, energy calculations by different methods[17] on the AMAA bis esters were carried out.

The resulting energy data show that in fact conformers *a*, *g*+, and *g*− are the more representative ones but that their energy is practically the same for the three rotamers. In contrast, rotation around the C_α−CO bond (in the auxiliary units) presents in all the cases and according to the CD studies a clear preference for the sp conformer.

TABLE 1. $^3J_{H1-H2}$ Experimental Values Obtained for the Bis-(*R*)-MPA and (*R*)-9-AMA Esters of the Following Diols with Their Respective Angles[a]

		diol number		
AMAA	rel configuration	(10)	(14)	(11)
(*R*)-MPA	*syn*-type A	4.4 (46)	7.6 (146)	5.3 (39)
	syn-type B	4.1 (49)	5.8 (34)	7.8 (147)
	anti-type C	3.1 (57)	4.2 (49)	
	anti-type D	5.1 (40)	4.6 (44)	
(*R*)−9-AMA	*syn*-type A	5.6 (36)	7.2 (143)	5.3 (39)
	syn-type B	3.1 (57)	5.6 (51)	7.5 (145)
	anti-type C	4.4 (46)	3.4 (54)	
	anti-type D	3.8 (51)	4.1 (48)	

[a] The angles were obtained by using the Altona−Karplus equation with the Sweet Jppc program. The angle can be positive or negative for each *J* value.

Experimental information was obtained by analysis of the coupling constants between H(1′) and H(2′) in MPA and 9-AMAA bis esters of diols **10**, **11**, and **14** of known absolute configuration.

Table 1 shows the coupling constant values and the resulting dihedral angles[18]obtained. As can be seen, the *J* values vary considerably with the structure within a single diol type. For instance in a bis-(*R*)-MPA ester of a *syn*-diol type A, the observed *J* goes from 4.1 Hz in the heptane-2,3-diol (**10**) up to 7.6 Hz in the 3-phenyl-2,3-dihydroxymethylpropionate (**11**). This clearly proves that there are conformational differences between those two compounds: In the first one the dihedral angle is +49° or −49° (corresponding to the *a* and the *g*+ conformers, respectively), while for the second compound the *J* value suggests an angle of 147° or −147° indicative of a quasieclipsed conformation. A similar result is observed in a bis-(*R*)-9-AMA ester (Table 1).

These results indicate that there is no a single preferred conformation around the C_1−C_2 bond representative for diols A−D. Fortunately, an analysis of the NMR consequences of the two processes just discussed (rotation around C1−C2 and C_α−CO) shows that only rotation around the C_α−CO in the auxiliary parts of the bis esters is really important.

In fact, if we examine the geometry of the bis-AMAA esters, find that the pattern of shielding/deshielding of substituents R_1/R_2 is exclusively determined by the absolute configuration at the asymmetric carbons of the diol and at the AMAA units and of the preferred conformation around C_α−CO.

For instance, in the bis-(*R*)-AMAA ester (MPA and 9-AMA) of the type A diol shown in Figure 7a, only substituents R_1 and R_2 are shielded by the aryl rings, and this is independent of the rotamer considered around the C1−C2 bond. The same conclusion is obtained analyzing the bis-(S)-AMAA ester, where, R_1, H(1′), R_2, and H(2′) are shielded (Figure 7b).

(17) Theoretical calculations [energy minimization by semiempirical (AM1), ab initio (HF), DFT (B3LYP), and Onsager methods, and aromatic shielding effect calculations] were performed using Gaussian 98.

(18) The dihedral angle is defined by H1−C1−C2−H2 atoms.

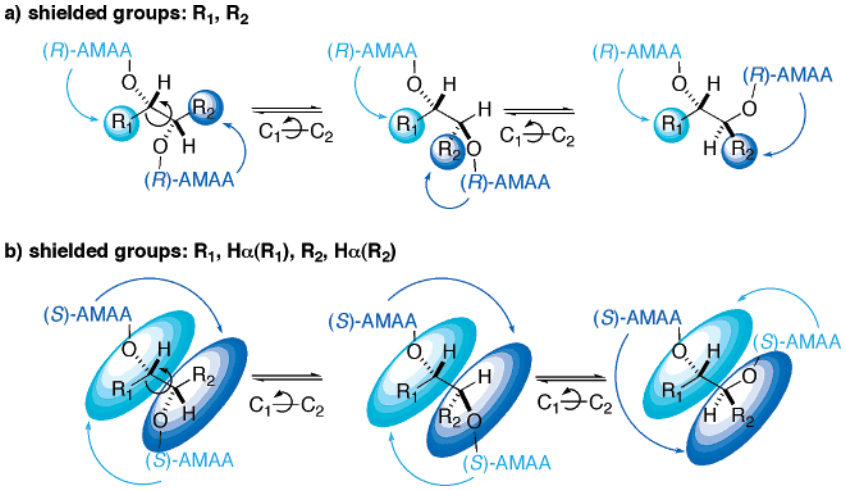

FIGURE 7. Shielded groups in the three main conformers by C1−C2 rotation: (a) bis-(*R*)-AMAA and (b) bis-(*S*)-AMAA esters, respectively.

Similar analysis for diol types B, C, and D leads us to conclude that there is in all cases a group of protons that are more shielded in one of the bis-AMAA ester derivatives than in the other and that allows a correlation to be established between the NMR spectra ($\Delta\delta^{RS}$) and the structural type of the diol (absolute confguration)

2. a. The Expected Shielding in the Bis-AMAA Esters of *syn*-1,2-Diols. In accordance with those results, representative pictures of the bis-AMAA esters of diols with structural types A−D can be formulated that include the spatial orientation of the aryl rings of each AMAA unit and the direction of its anisotropic effect. This will allow us to evaluate the participation of each reagent unit into the overall combined shielding/deshielding and to predict the differences between the spectra of the bis-(*R*)- and the bis-(*S*)-derivatives of a diol.

Thus, in the bis-(*R*)-MPA ester of a *syn*-1,2-diol with structure type A (Figure 8a), substituents R_1 and R_2 are both shielded by the phenyl ring, while in the bis-(*S*)-MPA ester (Figure 8b) the groups that are shielded are R_1, R_2, $H_\alpha(R_1)$, and $H_\alpha(R_2)$. Therefore, in the bis-(*S*)-AMAA esters of a *syn*-diol of type A, protons $H_\alpha(R_1)$ and $H_\alpha(R_2)$ are more shielded than in the bis-(*R*)-AMAA ester (Figure 8c,d), whereas substituents R_1 and R_2 are shielded in both the bis-(*R*)- and the bis-(*S*)-AMAA esters. Comparison of the two NMR spectra will show differences of chemical shifts[10b] leading to the following: $\Delta\delta^{RS}[H_\alpha(R_1)] > 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] > 0$ (Figure 8e).

For their part, as substituents R_1 and R_2 are shielded in both the bis-(*R*)- and the bis-(*S*)-ester derivatives and it is not possible to know the exact amount of those shifts, and no reliable correlation can be established between their chemical shifts and the configuration.

The same reasoning applied to the enantiomeric diol (type B configuration, Figure 8e) that leads to $\Delta\delta^{RS}$ signs[10b] opposite to those of type A discussed above: $H_\alpha(R_1)$ and $H_\alpha(R_2)$ are more shielded in the bis-(*R*)-AMAA ester than in the bis-(*S*)-AMAA derivative leading to $\Delta\delta^{RS}[H_\alpha(R_1)] < 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] < 0$ (Figure 8f). Once again, R_1 and R_2 are shielded in both the bis-(*R*)- and the bis-(*S*)-AMAA esters and their chemical shifts (or $\Delta\delta^{RS}$ signs) cannot be correlated to the absolute configuration of the diol.

In conclusion, for type A *syn*-diol the following $\Delta\delta^{RS}$ signs result: $\Delta\delta^{RS}[H_\alpha(R_1)] > 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] > 0$. While for a type B *syn*-diol the characteristic signs are $\Delta\delta^{RS}[H_\alpha(R_1)] < 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] < 0$.

2. b. The Expected Shielding in the Bis-AMAA Esters of *anti*-1,2-Diols. Similar analysis of the distribution of the shielding effects in the bis-(*R*)- and bis-(*S*)-MPA ester derivatives of *anti*-1,2-diols of structural types C and D show the following results: (a) In the bis-(*R*)-MPA bis of the *anti*-diol with type C configuration, the two phenyl groups shield the substituents R_1 and $H_\alpha(R_1)$ (Figure 9a,c) while the substituents R_2 and $H_\alpha(R_2)$ remain unaffected. (b) In the bis-(*S*)-MPA bis the aromatic rings shield R_2 and $H_\alpha(R_2)$ (Figure 9b,d) while R_1 and $H_\alpha(R_1)$ are unchanged.

Therefore, type C configuration will be characterized by R_1 and $H_\alpha(R_1)$ being shielded to a greater extent in the bis-(*R*)-AMAA than in the bis-(*S*)-AMAA ester and $\Delta\delta^{RS}(R_1) < 0$ and $\Delta\delta^{RS}[H_\alpha(R_1)] < 0$ (Figure 9e), and by R_2 and $H_\alpha(R_2)$ being shielded to a greater extent in the bis-(*S*)-AMAA than in the bis-(*R*)-AMAA ester: $\Delta\delta^{RS}(R_2) > 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] > 0$ (Figure 9e).

The enant*i*omeric diol (type D configuration) will be characterized by opposite signs: $\Delta\delta^{RS}(R_1) > 0$ and $\Delta\delta^{RS}[H_\alpha(R_1)] > 0$,and $\Delta\delta^{RS}(R_2) < 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] < 0$ (Figure 9f).

Figure 10a,b illustrates graphically these conclusions indicating the $\Delta\delta^{RS}$ sign characteristics for the four isomers of a diol.

2. c. The Shielding Effect and $\Delta\delta^{RS}$ Sign Calculations on the Bis-AMAA Esters of 1,2-Diols. The reliability of those predictions is based on two assumptions: (a) that the two AMAA parts of the bis ester are both in a *synperiplanar* disposition and (b) that rotation around the C(1′)−C(2′) bond has no influence on the expected shifts for $H_\alpha(R_1)$, $H_\alpha(R_2)$, R_1, and R_2, because in every one of the three main conformers generated (a, $g+$, $g-$) the groups under the shielding cones of the auxiliaries are the same.

To check the validity of those assumptions and evaluate their consequences on the NMR spectra, we decided

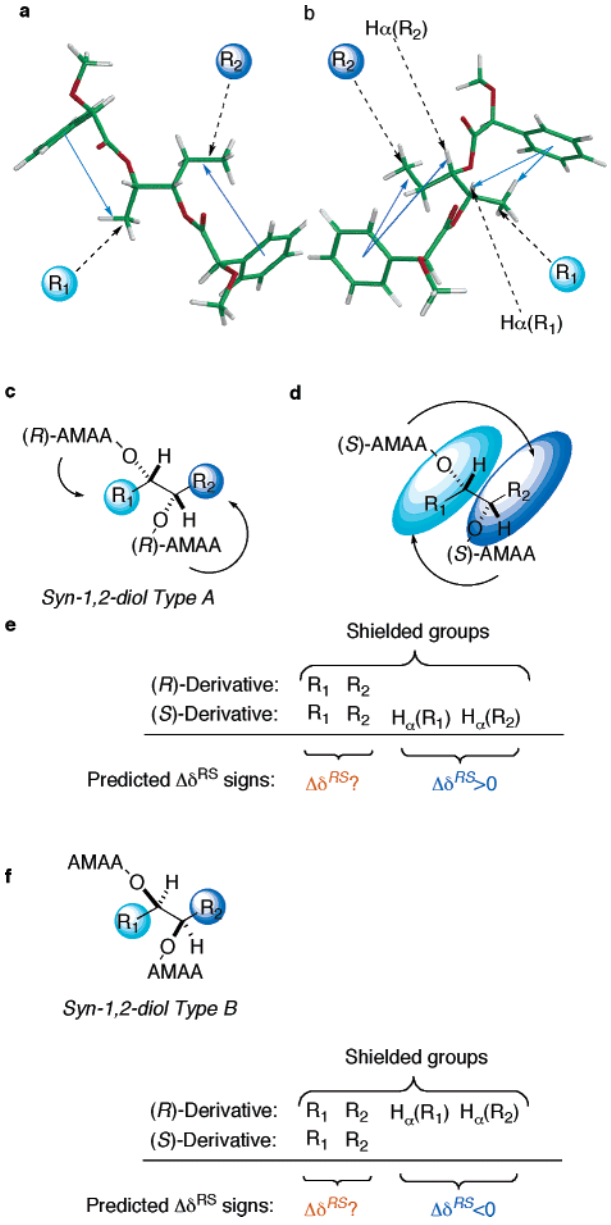

FIGURE 8. Distribution of the shielding effects and signs of$\Delta\delta^{RS}$ for the bis-AMAA esters of *syn*-1,2-diols.

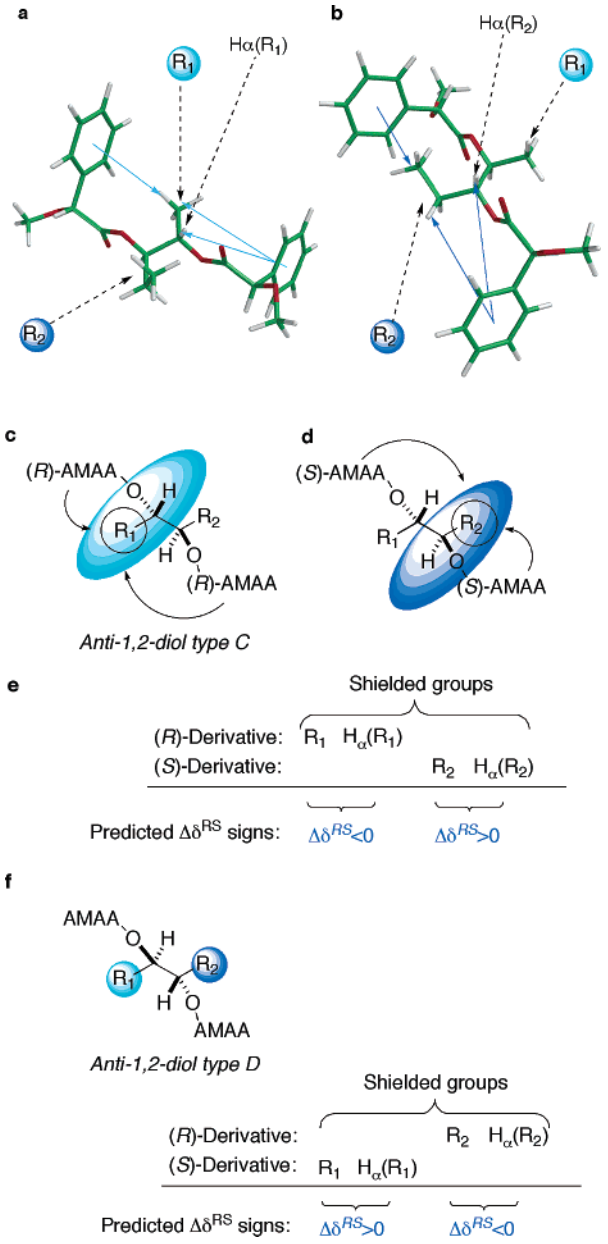

FIGURE 9. Distribution of the shielding effects and signs of $\Delta\delta^{RS}$ for the bis-AMAA esters of *anti*-1,2-diols.

to carry out shielding effect calculations[19] on the bis-(*R*)- and bis-(*S*)-MPA esters of all the stereoisomers of pentane-2,3-diol (**8**) and butane-2,3-diol (**9**) taken as model compounds.

Table 2 shows the chemical shifts of protons H(2′), H(3′), the methyl and the ethyl groups (R_1, R_2), calculated for the three main conformers (*a*, *g*+, *g*−) of those bis-esters.

When the $\Delta\delta^{RS}$ values are calculated by subtraction considering all nine possible combinations of conformers [(*a*)−(*a*), (*a*)−(*g*+), (*a*)−(*g*−), etc.], the resulting signs are identical for all the combinations in a given compound, and coincident with the experimental one. Thus, i.e., for the *syn*-diol type A, the calculated $\Delta\delta^{RS}$ are positive for H(2′) and H(3′) in all nine possible combinations (for the experimental signs see Figures 8, 9, and 10) and the same is observed in the other compounds examined.

As for the signs obtained for R_1 and R_2 some bis-MPA esters show no homogeneous signs (i.e., in a *syn*-type A diol, subtracting (*a*−)(*a*) or (*g*+)−(*g*+) gives a negative $\Delta\delta^{RS}$ sign but the difference is positive when (*g*−)−(*g*−) are subtracted. This occurs in the cases where the signals

(19) (a) Cheeseman, J. R.; Trucks, G. W.; Keith, T. A.; Frisch, M. J. *J. Chem. Phys.* **1996**, *104*, 5497−5509. (b) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

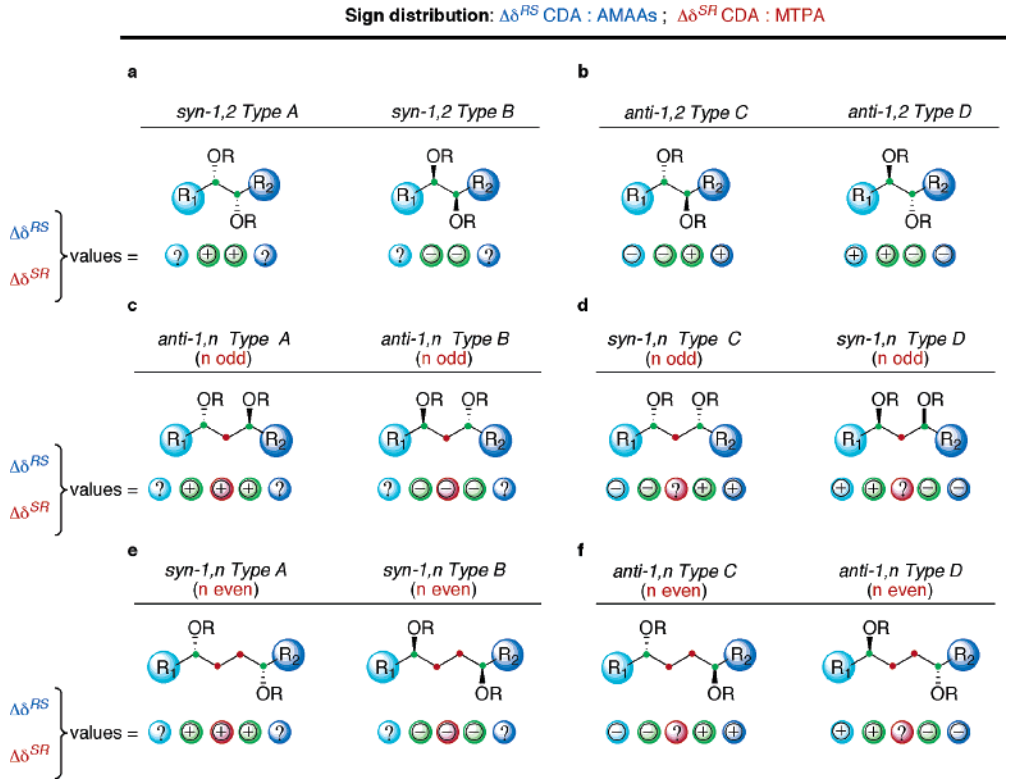

FIGURE 10. Δδ sign distribution for the bis-AMAA ($\Delta\delta^{RS}$) and bis-MTPA esters ($\Delta\delta^{SR}$) of the four possibilities of a 1,*n*-diol.

TABLE 2. Chemical Shifts (δ) and $\Delta\delta^{RS}$ Signs Theoretically Calculated[a] for All Three Conformers of the Bis-(*R*) and Bis-(*S*)-MPA Esters of Pentane-2,3-diol (8) and Butane-2,3-diol (9)

			calcd		$\Delta\delta^{RS}$ predicted[e]		calcd			$\Delta\delta^{RS}$ predicted[e,f]	
diol	type/aux	C(1′)−C(2′)	H(2′)	H(3′)	R_1	R_2	R_1[b]	R_{2a}[c]	R_{2b}[d]	R_1	R_2
8		*a*	5.404	4.939			1.816	1.007	0.95		
	syn-type A	*g*+	5.650	5.349			1.668	1.007	1.08		
	(*R*)-MPA	*g*−	5.707	4.997	>0	>0	1.560	1.367	1.497	–	–
		a	4.687	4.814			2.020	1.656	1.085		
	syn-type A	*g*+	5.291	4.690			1.798	0.824	1.217		
	(*S*)-MPA	*g*−	4.807	4.805			1.480	0.798	1.145		
		a	5.128	4.623			2.088	1.788	−0.322		
	anti-type C	*g*+	4.851	4.831			2.241	1.446	3.18		
	(*R*)-MPA	*g*−	4.875	5.822	<0	>0	1.990	1.480	0.098	<0	>0
		a	4.839	5.130			1.103	0.475	1.555		
	anti-type C	*g*+	5.371	4.995			1.528	0.740	1.502		
	(*S*)-MPA	*g*−	5.986	4.500			1.408	1.328	1.465		
9		*a*	5.283	5.283			1.357	0.863			
	syn-type A	*g*+	5.317	5.314			1.251	0.797			
	(*R*)-MPA	*g*−	5.521	5.521	>0	>0	1.417	1.133		–	–
		a	4.645	4.646			1.823	0.883			
	syn-type A	*g*+	4.805	4.807			1.260	0.927			
	(*S*)-MPA	*g*−	4.917	4.916			1.437	0.883			
		a	4.924	5.023			0.800	0.384			
	anti-type C	*g*+	4.758	5.749			1.306	0.192			
	(*R*)-MPA	*g*−	4.682	6.016	<0	>0	1.184	0.120		<0	>0
		a	5.026	4.925			1.877	1.574			
	anti-type C	*g*+	6.010	4.686			1.670	1.520			
	(*R*)-MPA	*g*−	5.110	5.102			1.762	1.498			

[a] Calculations performed in Gaussian 98.[17,19] [b] R_1 = Me(1′). [c] R_{2a} = Me(5′) for compound **8** and Me(4′) for compound **9**. [d] R_{2b} = CH_2(4′) for compound **8**. [e] $\Delta\delta^{RS}$ signs predicted by the model shown in Figure 13. [f] As R_1 and R_2 are shielded in the bis-(R) and bis-(S)-MPA esters of diols **8** and **9** (types A) no reliable prediction of the resulting signs can be made.

considered have no diagnostic value (see Figure 8). In those diols where R_1/R_2 are of diagnostic value (i.e., *anti*-type C) the sign of the differences is homogeneous and coincident with the experimental ones.

This coincidence between the experimental and the calculated $\Delta\delta^{RS}$ signs proves the reliability of the conformational description of the bis MPA esters, particularly, the existence of a shielding affecting selectively to

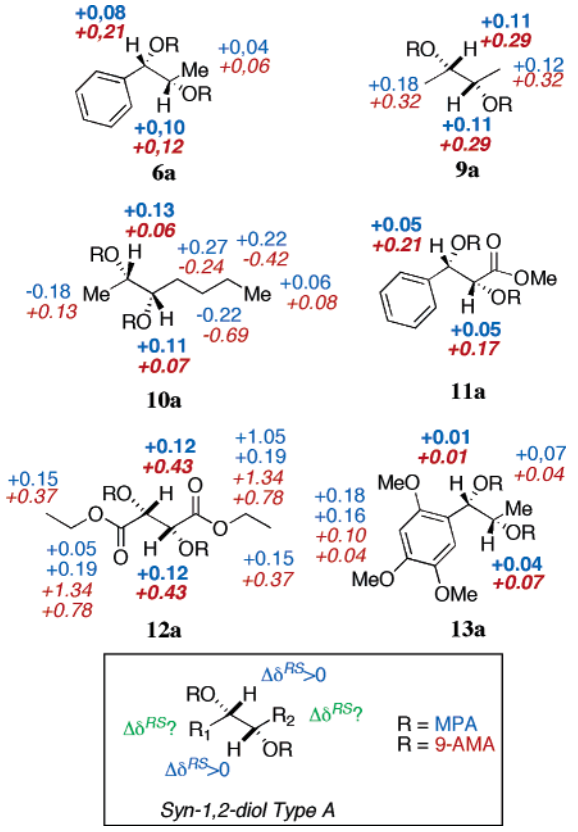

FIGURE 11. $\Delta\delta^{RS}$ values for the bis-9-AMA (red and italic values) and bis-MPA esters (blue values) of *syn*-diols type A: **6a**, **9a**−**13a**.

certain substituents and ensures that the rotation around C(1′)−C(2′) is not relevant for the resulting $\Delta\delta^{RS}$.

3. a. The NMR Spectra of *syn*-1,2-Diols. Experimental verification of the above predictions was carried out by checking the NMR spectra of the bis-(*R*)- and bis-(*S*)-9-AMA and bis-(*R*)- and bis-(*S*)-MPA esters derived from a series of *syn*- and *anti*-1,2-diols of known absolute configuration, such as diols respectively (1*S*,2*S*)- and (1*R*,2*R*)-1-phenyl-propane-1,2-diol (**6a** and **6b**, types A and B, respectively), (2*S*,3*S*)- and (2*R*,3*R*)-butane-2,3-diol (**9a** and **9b**, types A and B, respectively), (2*S*,3*S*)- and (2*R*,3*R*)-heptane-2,3-diol (**10a** and **10b**, types A and B, respectively), (2*S*,3*S*)- and (2*R*,3*R*)-3-phenyl-2,3-dihydroxymethylpropionate (**11a** and **11b**, types A and B, respectively), L- and D-ethyl tartrate (**12a** and **12b**, configuration types A and B, respectively), (2*S*,3*S*)- and (2*R*,3*R*)-dihydroxyasarone (**13a** and **13b**, types A and B), and 1,2:5,6-diisopropylidene D-mannitol (**14b**, type B). Their $\Delta\delta^{RS}$ values are shown in Figures 11 and 13, and the NMR spectra of the bis-(*R*)- and bis-(*S*)-MPA ester of **10a** and **10b** are shown in Figure 12.

In all the examples examined, the distribution of the signs of $\Delta\delta^{RS}$ for protons $H_\alpha(R_1)$ and $H_\alpha(R_2)$ corresponds perfectly with those discussed above for the *syn*-1,2-diols. Indeed, the *syn*-1,2-diols of Figure 11 (configuration type A) show in all cases positive $\Delta\delta^{RS}$ values for $H_\alpha(R_1)$ and $H_\alpha(R_2)$ while the diols shown in Figure 13, which have type B configuration, give negative values. This trend demonstrates experimentally the correlation between the absolute configuration and the signs of $\Delta\delta^{RS}$ and also the usefulness of this procedure to distinguish the two

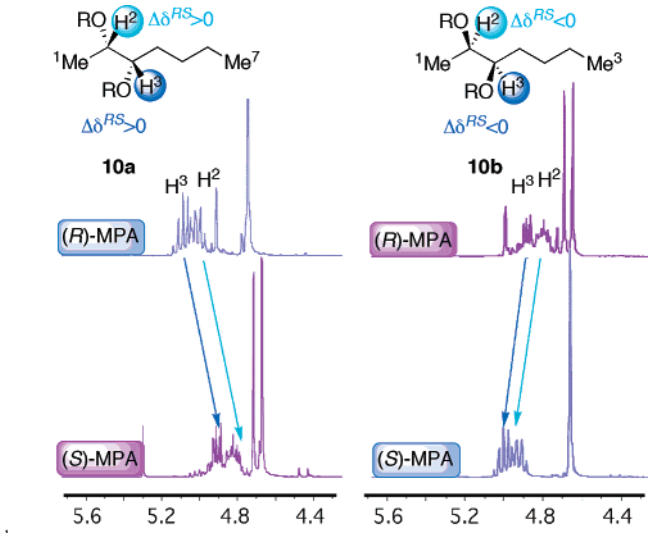

FIGURE 12. Partial ^{1}H NMR spectra of bis-(*R*)- and bis-(*S*)-MPA esters of (2*S*,3*S*)-heptane-2,3-diol (**10a**) and (2*R*,3R)-heptane-2,3-diol (**10b**).

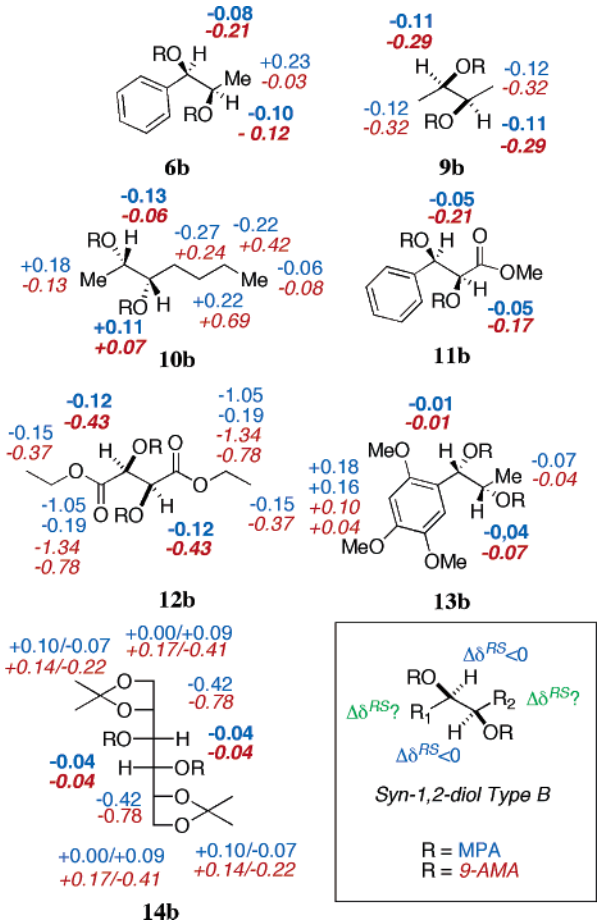

FIGURE 13. $\Delta\delta^{RS}$ values for the bis-9-AMA (red and italic values) and bis-MPA esters (blue values) of *syn*-diols type B: **6b**, **9b**−**14b**.

enantiomers of a *syn*-1,2-diol on the basis of the chemical shifts of protons $H_\alpha(R_1)$ and $H_\alpha(R_2)$.

The data presented in the Figures 11 and 13 also confirm that such correlation cannot be established with the $\Delta\delta^{RS}$ of R_1 and R_2: the majority of the compounds

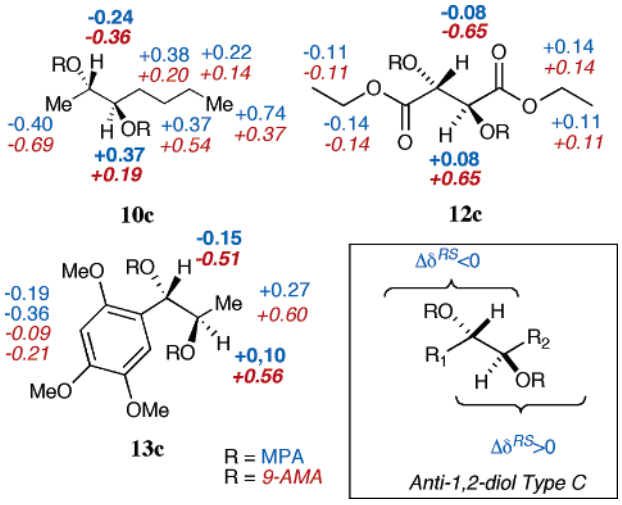

FIGURE 14. $\Delta\delta^{RS}$ values for the bis-9-AMA (red and italic values) and bis-MPA esters (blue values) of *anti*-diols type C: **10c**, **12c**, and **13c**.

studied (**9**, **12**, **13**) present identical signs of $\Delta\delta^{RS}$ for substituents R_1 and R_2, while in the cases of (2*S*,3*S*)- and (2*R*,3*R*)-heptane-2,3-diol (**10a**, **10b**) and of 1,2:5,6-diisopropylidene D-mannitol (**14**) positive and negative signs of $\Delta\delta^{RS}$ coexist in the same substituent. It is clear that in these situations it is not possible to associate the signs of $\Delta\delta^{RS}$ with a particular spatial arrangement, and that the signals due to R_1 and R_2 are not valid for assignment purposes.

Moreover, the absence of reliability of the configuration assigned by applying separately to each hydroxy group of a diol the model for monoalcohols is evident from several of the examples in Figures 11 and 13. Thus, compounds **6**, **9**, **12**, **13**, and **14** show identical $\Delta\delta^{RS}$ signs for the two substituents directly bonded to the asymmetric carbon and, therefore, no reliable configuration can ever be extracted from that data.

3. b. The NMR Spectra of *anti*-1,2-Diols. Similarly, the NMR spectra of the bis-MPA and bis-9-AMA esters of (2*S*,3*R*)-heptane-2,3-diol (**10c**), diethyl *meso*-tartrate (**12c**), and (2*S*,3*R*)-dihydroxyasarone (**13c**) (Figure 14) show signs of $\Delta\delta^{RS}$ in perfect agreement with those predicted for *anti*-1,2-diols with type C configuration: $\Delta\delta^{RS}(R_1) < 0$ and $\Delta\delta^{RS}[H_\alpha(R_1)] < 0$, and $\Delta\delta^{RS}(R_2) > 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] > 0$.

The NMR spectra of the bis-(*R*)- and bis-(*S*)-MPA esters of a type C *syn*-diol as (2*S*,3*R*)-heptane-2,3-diol (**10c**) are shown in Figure 15 and serve to illustrate these results.

The $\Delta\delta^{RS}$ obtained for the bis-MPA and bis-9-AMA esters of diethyl (2*R*,3*S*)-heptane-2,3-diol (**10d**) and (2*R*,3*S*)-dihydroxyasarone (**13d**), representative of *anti*-1,2-diols with type D configuration, are shown in Figure 16. As expected, the signs of $\Delta\delta^{RS}$ are the opposite to those of the *anti*-1,2-diols of type C, and are in perfect agreement with the following predictions: $\Delta\delta^{RS}(R_1) > 0$ and $\Delta\delta^{RS}[H_\alpha(R_1)] > 0$, and $\Delta\delta^{RS}(R_2) < 0$ and $\Delta\delta^{RS}[H_\alpha(R_2)] < 0$.

The NMR spectra of the bis-(*R*)- and bis-(*S*)-MPA ester of (2*R*,3*S*)-heptane-2,3-diol (**10d**), a *syn*-diol type D, are presented in Figure 17 to illustrate the shifts of the selected signals.

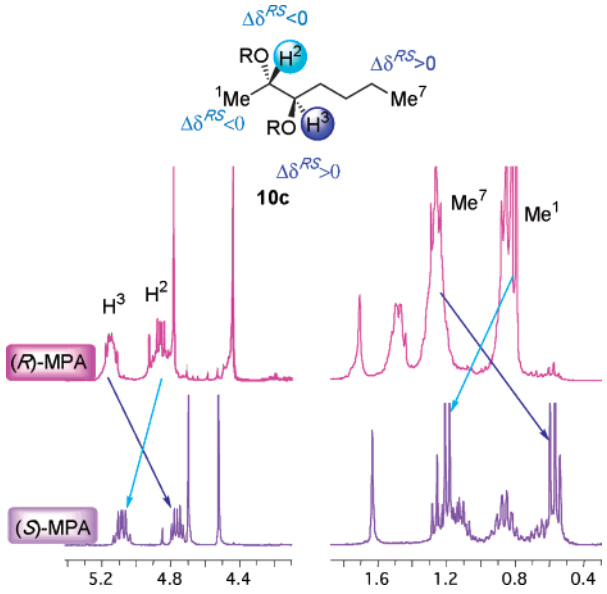

FIGURE 15. Partial ^{1}H NMR spectra of bis-(*R*) and bis-(*S*)-MPA esters of (2*S*,3*R*)-heptane-2,3-diol (**10c**).

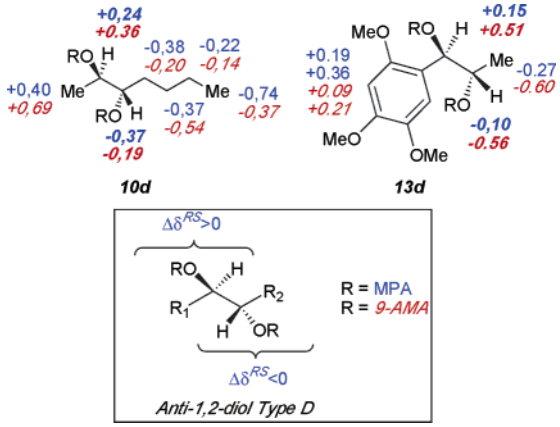

FIGURE 16. $\Delta\delta^{RS}$ values for the bis-9-AMA (red and italic values) and bis-MPA esters (blue values) of *anti*-diols type D: **10d** and **13d**.

4. a. The $\Delta\delta^{RS}$ Sign Distribution in 1,*n*-Diols (*n* > 2). It has been demonstrated that the combined shielding of two auxiliary reagents is predictable in 1,2-diols and that the chemical shifts of the bis-ester derivatives can be associated to a certain configuration, and we will now consider the more general case in which the two OH groups are separated by one or more carbon atoms, i.e., linear 1,*n*-diols in which $n > 2$.

A comparison of the conformational possibilities of the bis-esters of 1,2-diols with those of 1,*n*-diols indicates the existence of some relationships quite significant from the NMR point of view.

Thus, the spatial disposition of the aromatic rings of the AMAA reagents with respect to the rest of the molecule in the bis-esters of *syn*-1,*n*-diols with an even number of methylene groups between the two hydroxy groups is identical with that found in the bis-esters of *anti*-1,*n*-diols with an odd number of methylene groups separating the hydroxy groups and, therefore, the distribution of $\Delta\delta^{RS}$ signs for "even" *syn*-1,*n*-diols and for "odd" *anti*-1,*n*-diols must be the same.

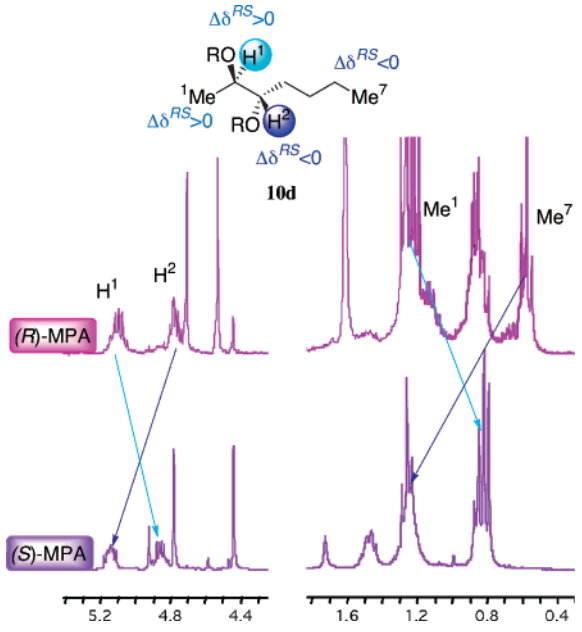

FIGURE 17. Partial ^{1}H NMR spectra of bis-(*R*)- and bis-(*S*)-MPA esters of (2*R*,3*S*)-heptane-2,3-diol (**10d**).

Indeed, this disposition of the aryl rings is coincident with the one described already for the bis-esters of *syn*-1,2-diols (Figure 10a). Consequently, the distribution of the signs of $\Delta\delta^{RS}$ for "even" *syn*-1,*n*-diols (Figure 10c) and for "odd" *anti*-1,*n*-diols must be the same as those for *syn*-1,2-diols (Figure 10e).

Similarly, the bis-esters of *anti*-1,*n*-diols with an even number of methylene groups separating the hydroxy groups (Figure 10f) and the bis-esters of *syn*-1,*n*-diols with an odd number of methylene groups between the hydroxy groups (Figure 10d) present the same relative disposition of the aromatic rings of the AMAA reagents as seen previously in the *anti*-1,2-diols (Figure 10b). Therefore the distribution of the shielding effects and signs of $\Delta\delta^{RS}$ for "even" *anti*-1,*n*-diols and for "odd" *syn*-1,*n*-diols are the same as those for *anti*-1,2-diols (Figure 10b,d,f).

In accordance with those equivalences, and for the sake of simplicity, we will refer in the following discussion to the cases of "odd" *anti*-1,*n*-diols and *syn*-1,*n*-diols ($n > 2$) only, and will broaden the conclusions to include the corresponding "even" 1,*n*-diols, as shown in Figure 10.

4. b. The NMR Spectra of the Bis-AMAA Esters of 1,*n*-Diols. Experimental confirmation of these predictions has been obtained from the NMR of the bis-AMAA ester derivatives of several 1,*n*-diols of known absolute configuration.

Figure 18 shows the structure and $\Delta\delta^{RS}$ values reported in the literature[20] for the bis esters of 9-AMA and MPA as auxiliaries with (2*S*,4*S*)- and (2*R*,4*R*)-pentane-2,4-diol (**15a** and **15b**), for the bis esters of MPA with onchitriol I (**16a**),[20a] and for the bis esters of 2-NMA with the acetogenins asimicin (**17b**) and rolliniastatin-2 (**18d**). In all these cases, the $\Delta\delta^{RS}$ signs reported[20b] are in full

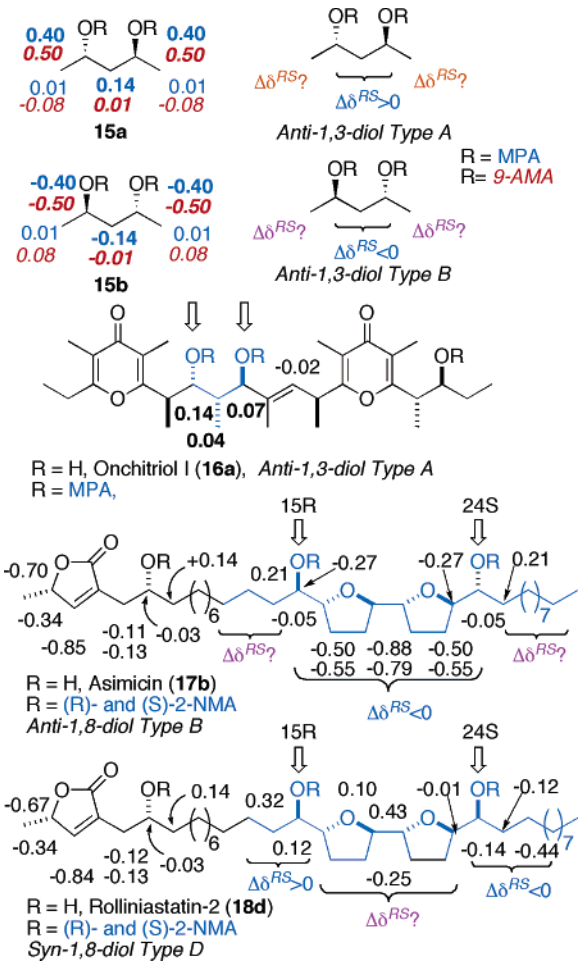

FIGURE 18. Values for $\Delta\delta^{RS}$ of the bis-9-AMA (red and italic values) and bis-MPA (blue plain values) esters of (2*S*,4*S*)- and (2*R*,4*R*)-pentane-2,4-diol (**15a** and **15b**); bis-MPA esters of onchitriol I (**16a**) and bis-2-NMA esters of asimicin (**17b**) and rolliniastatin-2 (**18d**).

agreement with the absolute configuration of the compounds and with the rules presented in Figure 18. Thus, compounds **15a** and **16a** are examples of *anti*-1,3-diols with configuration type A and present, as expected, positive $\Delta\delta^{RS}$ for $H_\alpha(R_1)$, $H_\alpha(R_2)$, and R_3. Compound **15b** is an *anti*-1,3-diol with configuration type B, and accordingly it presents negative $\Delta\delta^{RS}$ for $H_\alpha(R_1)$, $H_\alpha(R_2)$, and R_3. Similarly, asimicin (**17b**) presents $\{\Delta\delta^{RS}[R_3,H_\alpha(R_1),H_\alpha(R_2)] < 0\}$, corresponding to its type B diol structure.

Finally, rolliniastatin-2 (**18d**) represents an example of a type D 1,*n*-diol and in agreement with the predictions presents $\Delta\delta^{RS}[R_1,H_\alpha(R_1)] > 0$ and $\Delta\delta^{RS}[R_2,H_\alpha(R_2)] < 0$ (Figure 10f).

On the Use of MTPA as Auxiliary Reagent for 1,*n*-Diols. In the previous sections we have described the rules relating the absolute configuration of diols with the chemical shifts of their AMAAs bis-esters (MPA, 1-NMA, 2-NMA, and 9-AMA).

When a diol is derivatized with MTPA as auxiliary, the combination of the shielding/deshielding effects generated by each reagent unit is operative too and the reasoning followed to explain and predict the $\Delta\delta$ signs in bis-AMAA esters should also be of use in bis-MTPA

(20) (a) For NMR data of MPA esters of compounds **16a** see: Rodríguez, J.; Riguera, R.; Débitus, C. *J. Org. Chem.* **1992**, *57*, 4624–4632. (b) For NMR data of 2-NMA esters of compounds **17b** and **18d** and MTPA esters of **17b** and **18d** see ref 9f.

esters, provided that the conformational differences[1d,e] between the AMAA and bis-MTPA esters are taken into account.

These differences involve important changes in the shielding/deshielding distribution but can be summarized very easily: Thus, if in the (*R*)-AMAA ester of a secondary alcohol substituent L_1 is shielded and L_2 unaffected (Figure 1), in the corresponding (*R*)-MTPA ester, the situation is reversed (L_2 is shielded and L_1 is unaffected, Figure 1). As a result, the signs of $\Delta\delta^{RS}$ obtained with MTPA are the opposite of those obtained for the same configuration, using AMAA reagents.[10]

When MTPA is used as an auxiliary reagent, it is common to express the shift differences in the form of $\Delta\delta^{SR}$ instead of $\Delta\delta^{RS}$. In these conditions and for the same diol, the signs of $\Delta\delta^{SR}$ obtained with MTPA are coincident with the signs of $\Delta\delta^{RS}$ obtained with AMAA, and the general patterns represented in Figure 10 for AMAA esters are also applicable to MTPA esters by simply replacing in the tables the $\Delta\delta^{RS}$(AMAA) by $\Delta\delta^{SR}$(MTPA).

A model has recently been proposed[21] that is in agreement with the above predictions for 1,2-diols.

Experimental proof of the value of those rules can be obtained from the literature data published for MTPA bis esters of the series of diols shown in Figures 19 and 20.

Thus, the NMR data of all the compounds[22] in Figure 19 give rise to negative $\Delta\delta^{SR}$ for $H_\alpha(R_1)$, $H_\alpha(R_2)$, and R_3 and this is in accordance with their structural type (*anti*-type B diols). Furthermore, all the compounds in Figure 20 show a distribution of the signs of $\Delta\delta^{SR}$ indicative of a *syn*-diol type D configuration: $\Delta\delta^{SR}[H_\alpha(R_1),R_1] > 0$ and $\Delta\delta^{SR}[H_\alpha(R_2),R_2] < 0$.

Practical Applications: The Assignment of the Absolute Configuration of a Diol with Two Asymmetric Secondary Carbons. Throughout this work it has been demonstrated that a correlation exists between the absolute configuration of the two asymmetric carbons of a diol and the NMR spectra of its bis-(*R*)- and bis-(*S*)-ester derivatives of a selected auxiliary reagent (AMAAs or MTPA). This correlation is conveniently expressed by the signs of the $\Delta\delta^{RS}$ or $\Delta\delta^{SR}$ parameter of the substituents of the bis-ester. We also have shown that any one of the four possible stereoisomers of a diol with two asymmetric carbons has a specific and characteristic distribution of $\Delta\delta$ signs. Therefore, it is possible to deduce the absolute configuration of any diol just by comparison of the observed $\Delta\delta$ signs of the bis-derivatives with the patterns characteristic for the four possible isomers.

Thus, a protocol for assignment of the absolute configuration of a 1,*n*-diol requires the following steps: (a) to separately prepare the bis-(*R*)- and bis-(*S*)-ester derivatives of the "unknown diol" with the (*R*)- and (*S*)-

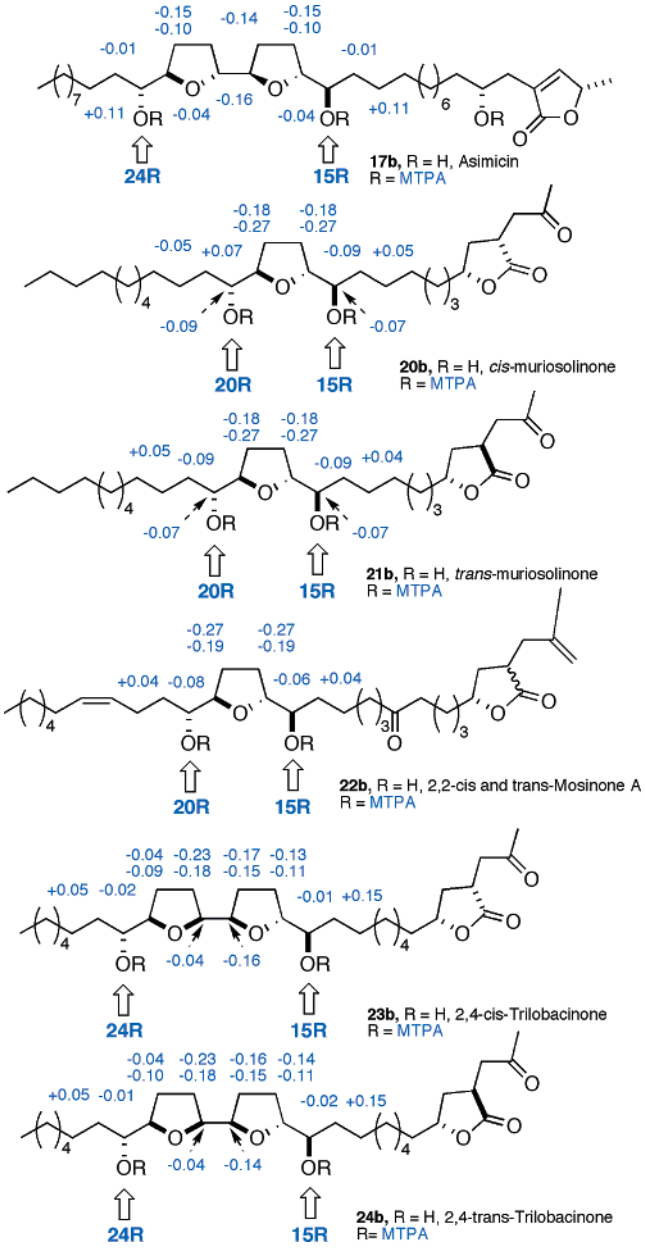

FIGURE 19. $\Delta\delta^{SR}$ values of different *anti*-type B 1,*n*-diols esterified with MTPA.

enantiomers of the auxiliary reagent, (b) to compare the ^{1}H NMR spectra of those two bis-esters, (c) to assign the spectra and measure the differences $\Delta\delta^{RS}$ [or $\Delta\delta^{SR}$ in the case of MTPA (1)] of the substituents [H(1′), H(2′), and/or R_1, R_2], and (d) to compare the signs of the $\Delta\delta^{RS}$ observed with those shown in Figure 10.

The simplicity and usefulness of this procedure is demonstrated by the fact that two NMR spectra are enough to obtain in a single operation the absolute configuration at the two asymmetric carbons of the diol. The reliability of the assignment is secured by its validation with the study of several diols of absolute configuration known by independent ways.

Conclusions

In this work, we have demonstrated that there is a correlation between the absolute configuration of the two

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(22) (a) For NMR data of MTPA esters of compound **22** see: Craig, D.; Zeng, L.; Gu, Z.; Kozlowski, J. F.; McLaughlin, J. L. *J. Nat. Prod.* **1997**, *60*, 581−586. (b) For NMR data of MTPA esters of compounds **20** and **21** see: Woo, M.; Yol, K.; Cho, Y.; Zhang, Y.; Zeng, L.; Gu, Z.; McLaughlin, J. L. *J. Nat. Prod.* **1995**, *58*, 1533−1542 and ref 22a. (c) For NMR data of MTPA esters of compound **19d** see: Craig, D.; Alali, F. Q.; Gu, Z.; McLaughlin, J. L. *Bioorg. Med. Chem.* **1998**, *6*, 569−575. (d) For NMR data of MTPA esters of compounds **23** and **24** see: He, K.; Zhao, G.; Shi, G.; Zeng, L.; Chao, J.; McLaughlin, J. L. *Bioorg. Med. Chem.* **1997**, *5*, 501−506.

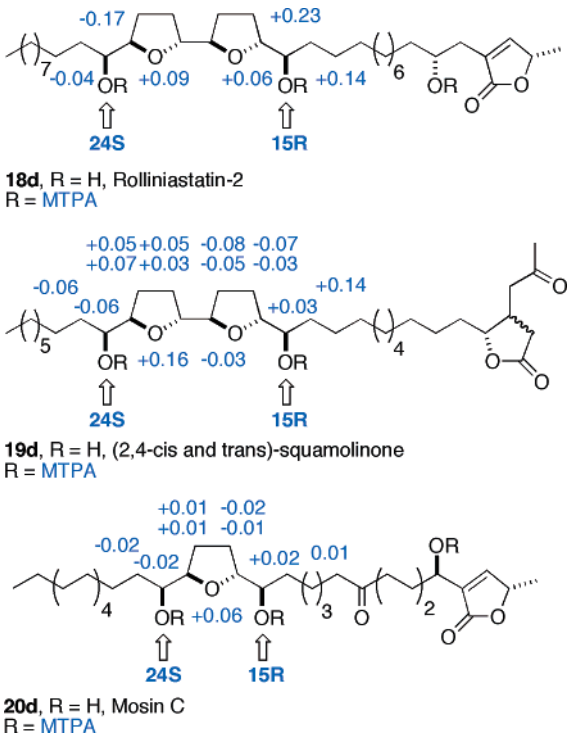

FIGURE 20. $\Delta\delta^{SR}$ values of different *syn*-type D 1,*n*-diols esterified with MTPA.

asymmetric carbons of a diol and the NMR spectra of their bis-(*R*)- and bis-(*S*)-ester derivatives of selected auxiliary reagents. The presence of two units of the auxiliary reagent in the bis-ester causes the chemical shift of the substituents to depend on the combined action of the shielding effects of the two auxiliaries and therefore the signs of $\Delta\delta^{RS}$ cannot be interpreted by using the model designed for the AMAA esters of a monoalcohol. The reliability of these correlations and of the general interpretation of the NMR spectra of the bis-ester derivatives has been demonstrated with a wide range of diols of known absolute configuration and supported by high-level energy and shielding effect calculations.

Simple graphical models that allow the simultaneous assignment of the two asymmetric carbons of a 1,*n*-diol with unknown configuration just by comparison of the NMR spectra ($\Delta\delta^{RS}$ signs) of its bis-(*R*)- and bis-(*S*)-AMAA ester derivatives are presented.

Experimental Section

General Procedures. The diols **6a**,**b**, **10a**−**d**, and **11a**,**b** were prepared according to the osmium-catalyzed asymmetric dihydroxylation,[23] and their spectroscopic data are coincident with those reported in the literature.[23,24] The diols **13a**−**d** derived from 2,3-dihydroxyasarone are reported here for the first time and were prepared by the same procedure. The esters were prepared by treatment of the diol (**6**, **9**−**15**) (1 equiv) with the corresponding arylmethoxyacetic acid (2.5 equiv) in the presence of EDC[24a] (2.5 equiv) and DMAP (catalytic) in CH_2Cl_2, and nitrogen atmosphere. The reaction was stirred at room temperature for 2 h. The organic layer was then washed with water, HCl (1M), water, $NaHCO_3$(sat), and water, then dried (Na_2SO_4) and concentrated under reduced pressure to obtain the diester. Final purification was achieved by HPLC (μ-Porasil, 3 mm × 250 mm or Spherisorb S5W 5 μm, hexane−ethyl acetate). All the compounds were characterized by optical rotation, NMR (1D,2D), and MS(EI).

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded at 500 and 250 MHz. Chemical shifts (ppm) are internally referenced to the TMS signal (0 ppm) in all cases. *J* values are recorded in Hz.

1D ^{1}H NMR spectra: Size 32 K, pulse length 2.8 μs (30°), 16 acquisitions.

1D ^{13}C NMR spectra: Size 64 K, pulse length 3.5 μs (30°), 1024 acquisitions.

2D COSY spectra: Sequence D1−90−t1−90−t2; relaxation delay D1 = 0.5 s; 90° pulse 8.5 μs.

2D NOESY spectra: Sequence D1−90−t1−90−τ_{mix}−90−t2; relaxation delay D1 = 0.5 s; mixing time (τ_{mix}) 0.5 s, 90° pulse 8.5 μs; TPPI-mode, NS = 64.

Computational Methods. Ab initio Hartree−Fock (HF) and density functional theory (DFT) calculations were performed to elucidate the conformational preferences of the bis-MPA esters of butanediol and pentanediol, taken as model compounds. We used the standard 6-31G(d) and 6-311+G(2d,p) basis set. The geometries of the most relevant conformations of the MPA ester, selected from our previous work,[13] were first optimized at the HF/6-31G(d) level. Because of the size of the system, the calculations were restricted to conformations with the $C_{\alpha'}$−O−C=O skeletal fragment in its most stable orientation: i.e., the *Z* conformation. For the determination of more accurate energies, single-point calculations at the HF optimized geometries were carried out with the DFT/B3LYP approach. For the *bis*-MPA esters, solvent effects were considered using two continuum models: the Onsager model,[25a−c] and the isodensity surface-polarized continuum model (IPCM).[25d] NMR calculations were carried out with the GIAO method.[19] All the calculations were performed with the Gaussian98 series of programs.[19b]

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Supporting Information Available: Experimental data (HPLC, NMR, MS, etc.) relative to diols **6a**,**b**, **10a**−**d**,**11a**,**b**, **13a**−**d**, and the bis-MPA and 9-AMA esters of diols **6a**,**b**, **9a**,**b**, **10a**−**d**, **11a**,**b**, **12a**−**c, 13a**−**d**, **14b**, and **15a**,**b**; conformational energy distribution around the $C_{1'}$ − $C_{2'}$ bond for model compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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