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Relative and Absolute Stereochemistry of Secondary/Secondary Diols: Low-Temperature ^{1}H NMR of Their bis-MPA Esters§

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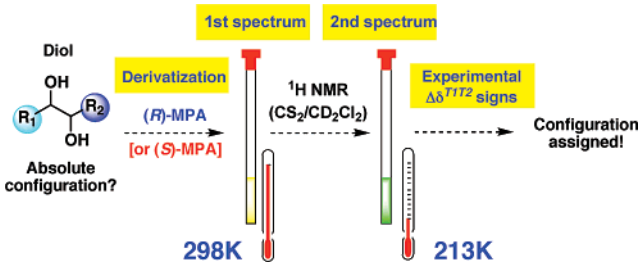

Comparison of the room- and low-temperature ^{1}H NMR spectra of the bis-(*R*)- or bis-(*S*)-MPA ester derivative of an open chain *sec*,*sec*-1,2-diol allows the easy determination of its relative stereochemistry and in some cases absolute configuration. If the diol is anti, its absolute configuration can be directly deduced from the signs of $\Delta\delta^{T1T2}$ for substituents R_1/R_2, but if the relative stereochemistry of the diol is syn, the assignment of its absolute configuration requires the preparation of two derivatives (both the bis-(*R*)- and bis-(*S*)-MPA esters), comparison of their room-temperature ^{1}H NMR spectra, and calculation of the $\Delta\delta^{RS}$ signs for the methines Hα(R_1) and Hα(R_2) and R_1/R_2 protons. The reliability of these correlations is validated with 17 diols of known absolute configuration used as model compounds.

Introduction

The reliable assignment of the absolute configuration of organic compounds by NMR is expanding from the initially studied monofunctional[1] compounds (alcohols, amines, carboxylic acids) to difunctional[1−2] (diols, aminoalcohols) and even triols.[3]

In practice, the procedure requires the preparation of two derivatives of the substrate (i.e., a secondary alcohol) with the (*R*)- and (*S*)-enantiomers of an auxiliary reagent such as α-methoxy-α-phenylacetic acid (MPA, **1**, Figure 1a) and comparison of the NMR spectra of the resulting diastereomers [(*R*)- and (*S*)-MPA esters, Figure 1b].

The assignment is based on the existence of a correlation between the chemical shifts of those derivatives and their stereochemistry (absolute configuration). More precisely, it is related to the aromatic shielding effect produced by the aryl ring of the auxiliary on the protons of the substrate part that are located within its shielding cone [i.e., for a secondary alcohol with the stereochemistry shown in Figure 1b, substituent L_1 is more shielded in the (*R*)-MPA derivative than in (*S*)-MPA and the inverse for substituent L_2]. Studies on the structure of these derivatives have shown that MPA esters are composed in solution by a mixture of essentially two conformers,[4] *sp* (major) and *ap* (minor), in equilibrium, and consideration of the relative position of the aryl ring of the auxiliary with respect to substituents L_1/L_2 of the substrate in each of those conformers allows prediction of the shifts and rationalization of the

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§ Dedicated to Prof. Miguel Yus on the occasion of his 60th birthday.
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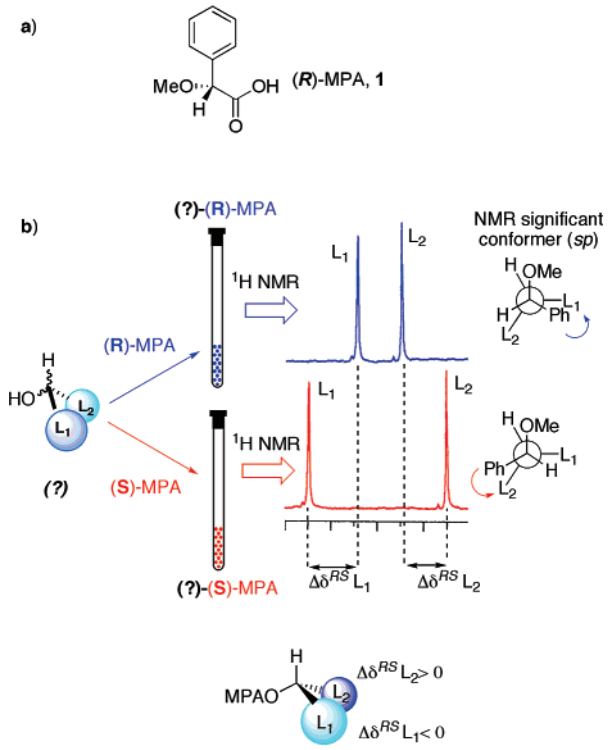

FIGURE 1. (a) Structure of MPA. (b) General procedure for assignment of the absolute configuration of a secondary alcohol.

assignment. Naturally if the substrate contains more than one derivatizable group, (i.e., a 1,2-*sec*,*sec*-diol or 1,2,3-triol), the easiest way is to derivatize all of them in a single operation and find a way to assign the configuration of the two asymmetric carbons at the same time.[2] Unfortunately, analysis of the NMR data is far more complex because the bis-MPA esters contain not one but two phenyl rings and the observed chemical shifts are the result of a combination of the shielding/deshielding originated by those two auxiliaries.[2,5]

In the case of some monofunctional compounds (i.e., secondary alcohols and primary amines), it is possible to assign the absolute configuration using only one derivative [prepared from either (*R*)- or (*S*)-MPA] instead of two[6] by modification of the probe temperature[6a−b] or selective complexation[6c−i] that modifies the relative populations of the *sp*/*ap* conformers.

In this paper we present the application of this concept to polyfunctional compounds, namely, 1,2-secondary/secondary diols (Figure 2), and report the application of the low-temperature NMR of the bis-(*R*)- and bis-(*S*)-MPA esters for assignment of their absolute configuration using only one derivative.

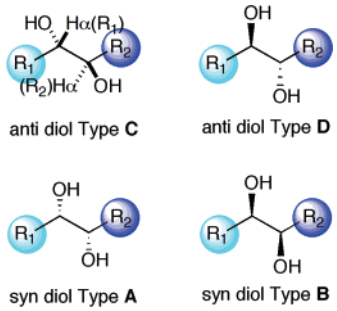

FIGURE 2. Four stereoisomers of 1,2-secondary/secondary diols.

Results and Discussion

***anti*-1,2-Diols.** Figure 3 shows the structure of the1,2-secondary/secondary diols **2**−**17** of known absolute configuration used in this work[7] that are representative of the four possible stereoisomers (syn A−B and anti C−D, Figure 2). Their bis-(*R*)- and bis-(*S*)-MPA ester derivatives were prepared, their ^{1}H NMR spectra taken at different temperatures[8] (298−183 K), and the changes in chemical shifts calculated and expressed as $\Delta\delta^{T1T2}$ values.[9]

The data obtained for the bis-(*R*)-MPA ester derivatives of diols **2**−**5** (anti type C) shows that in all cases substituent R_1 has a positive $\Delta\delta^{T1T2}$ and substituent R_2 a negative one, while the bis-(*R*)-MPA esters of diols **6**−**8** (anti type D) have the opposite distribution of signs. With the bis-(*S*)-MPA esters of the same diols **2**−**8** opposite signs are obtained [negative for R_1 and positive for R_2 in the case of **2**−**5** (anti type C), and positive for R_1 and negative for R_2 in **6**−**8** (anti type D)]. Thus, there is a correlation between the distribution of $\Delta\delta^{T1T2}$ signs of R_1/R_2 and the absolute stereochemistry of those anti C and anti D diols.

A rational explanation of those results can be obtained by consideration of the relative stability and structure of the *sp*/*ap* conformers[10] (Figure 4a).

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(7) (a) For experimental details on diols **3**−**7**, see: Calderón, F.; Doyaguez, E. G.; Fenández-Mayoralas, A. *J. Org. Chem.* **2006**, *71*, 6258−6261 and Calderón, F.; Fernández, R.; Sánchez, F.; Fenández-Mayoralas, A. *Adv. Synth. Catal.* **2005**, *347*, 1395−1403. (b) For experimental details on diols **2**, **8**−**17** see ref 2a.

(8) A 1:4 mixture of CD_2Cl_2/CS_2 is a very convenient NMR solvent for these experiments.

(9) $\Delta\delta^{T1T2}$ values are defined as the difference between δ at the higher temperature (T_1, 298 K in this paper) minus δ at the lower temperature (T_2, 183 K).

(10) (a) The *sp* conformer has the methoxy and carbonyl groups in a synperiplanar disposition (in the same plane), while in the *ap* conformer those groups are antiperiplanar (see ref 4). (b) Theoretical calculations on bis-MPA esters of 1,2-diols [energy minimization by semiempirical (AM1) and DFT (B3LYP)] were performed using Gaussian 98; for experimental details on those calculations, see ref 2a.

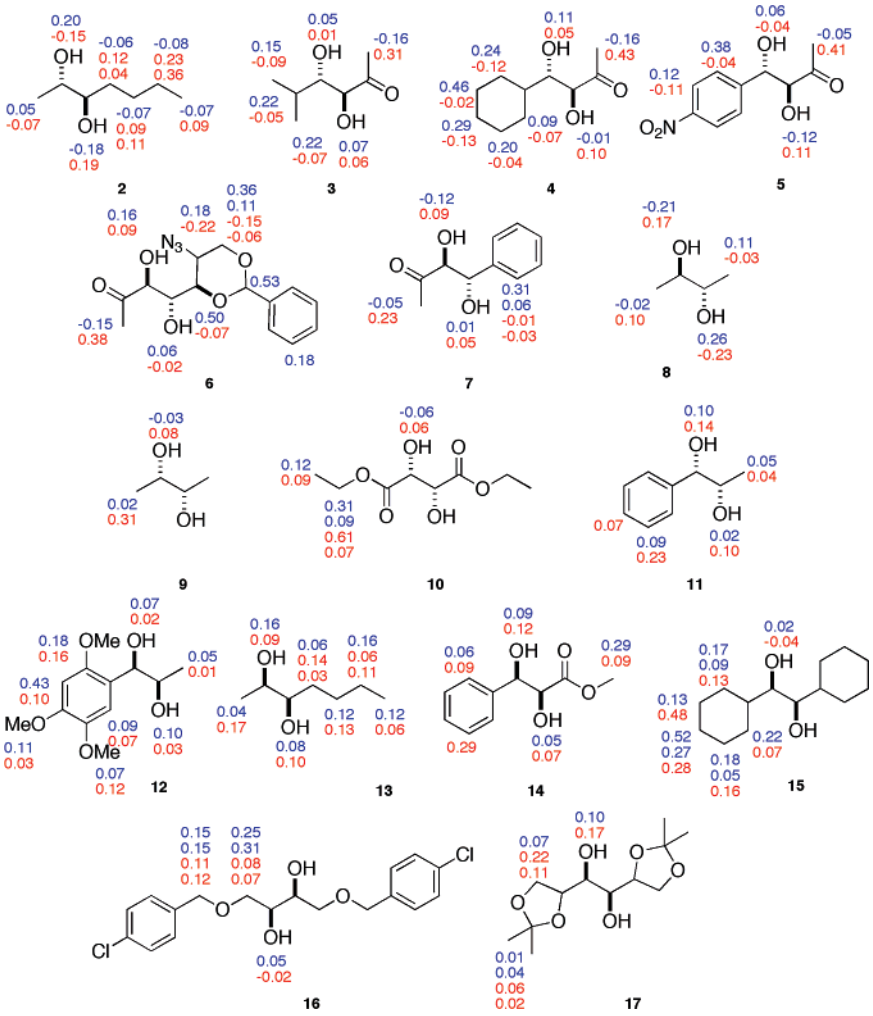

FIGURE 3. Selection of 1,2-secondary/secondary diols employed in this study, and $\Delta\delta^{T1T2}$ values (ppm, 298−183 K, CS_2/CD_2Cl_2, 4:1) obtained for their bis-(*R*)-MPA (blue) and bis-(*S*)-MPA esters (red).

Thus, if we examine the structure of the bis-(*R*)-MPA esters of a diol anti C and place the auxiliaries in the more stable conformer[10] *sp*, the orientation of the phenyl ring of one of the MPA units is shielding R_1 while the phenyl ring of the other unit is shielding both R_1 and H$\alpha(R_1)$. In the less populated conformer *ap*, one MPA unit is shielding R_2 and the other shields both R_2 and H$\alpha(R_2)$ (Figure 4b). When the temperature decreases, the equilibrium is shifted and the number of molecules in the *sp* conformation increases and those in *ap* decrease.

The average NMR spectrum reflects those changes, showing the signals for R_1 moved to higher field and those of R_2 to lower field as temperature diminishes. This means that R_1 has a $\Delta\delta^{T1T2}$ positive and R_2 a negative sign. The experimental results[11] obtained for **2**−**5** (Figure 3) are in perfect agreement with that prediction.

Figure 5 shows the evolution of the NMR spectra of the bis-(*R*)-MPA ester of compound **3** with temperature. In the *sp* conformer the two phenyl rings shield Me(6′), Me(7′), and H(5′); therefore, the average NMR spectrum at lower temperatures (from 298 to 183 K) shows an upfield shift for these protons (positive $\Delta\delta^{T1T2}$). For its part Me(1′) is shielded in the minor conformation *ap*, and its signal shifts downfield (negative $\Delta\delta^{T1T2}$ sign) at lower temperature because the number of molecules in the *ap* conformer as well as its contribution to the average NMR spectrum are lower (Figure 3).

Similar analysis of the distribution of the shielding effects in the bis-(*R*)-MPA ester derivative of the anti-1,2-diols of structural type D show that in the *sp* conformation one of the auxiliaries shields R_2 and the other shields both R_2 and H$\alpha(R_2)$ while in the *ap* conformation one auxiliary shields R_1 and the other shields both R1 and H$\alpha(R_1)$. Thus, at lower temperature the increasing *sp* population leads to R_2 becoming more heavily shielded (positive $\Delta\delta^{T1T2}$) and R_1 less shielded (negative $\Delta\delta^{T1T2}$) than at higher temperature, as experimentally[11] shown by compounds **6**−**8** in Figure 3.

Identical reasoning applied to the bis-(*S*)-MPA esters of the same diols **2**−**8**, leads to a distribution of $\Delta\delta^{T1T2}$ signs opposite to that obtained from the bis-(*R*)-MPA of the same compound[11] (Figure 3). A resume of the $\Delta\delta^{T1T2}$ signs of R_1/R_2, characteristic of each enantiomer of the anti diols, is shown in Figure 6.

Interestingly, although the methine protons H$\alpha(R_1)$ and Hα-(R_2) are subjected to the same shielding effects as R_1 and R_2, no correlation between their shifts and the stereochemistry was found (i.e., compounds **3**, **4**, **6**, and **7** in Figure 3). This apparent

(11) ^{1}H NMR spectra of bis-MPA esters of diols **2**−**17** taken at different temperatures are included in the Supporting Information as Figures 5S−20S.

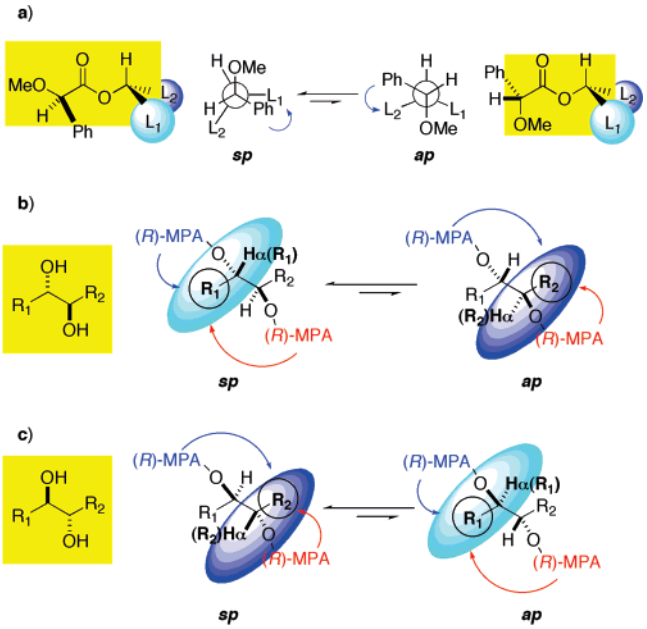

FIGURE 4. (a) Structure and equilibrium between the *sp* and *ap* conformers of the (*R*)-MPA ester of a secondary alcohol. (b and c) Distribution of the shielding effects for the bis-(*R*)-MPA esters of anti *C* and anti D diols, respectively.

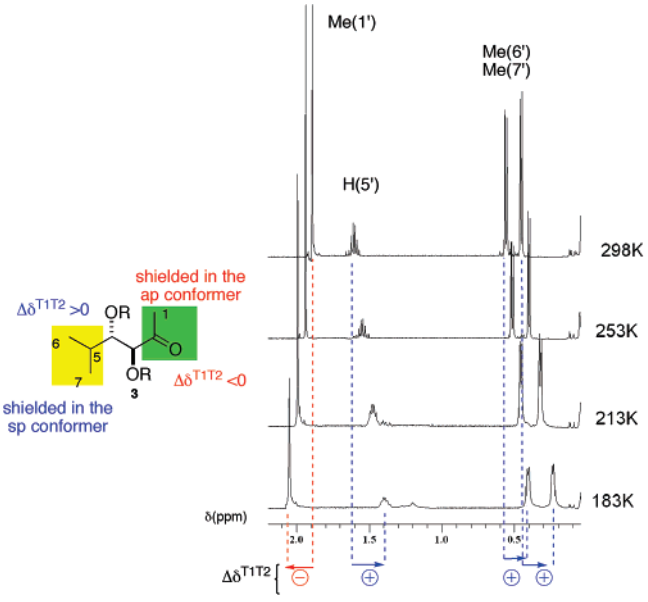

FIGURE 5. Partial NMR spectra of the bis-(*R*)-MPA ester of compound **3** at different temperatures.

inconsistency can nevertheless be explained because the methine protons are subjected to the effect of only one phenyl group, not two, and the magnitude of this effect can be in the same quantitative range as the anisotropic effect due to the ester carbonyl group. The final result of all these influences is unpredictable, thus rendering protons Hα(R_1) and Hα(R_2) no diagnostic value for assignment.

***syn*-1,2-Diols.** In the case of the *syn*-1,2-diols the situation is quite different because the shielding/deshielding predicted for substituents R_1 and R_2 leads to the same sign distribution of $\Delta\delta^{T1T2}$ in both enantiomers (types A and B); only quantitative differences can be expected, and no application to configurational assignment can be derived.

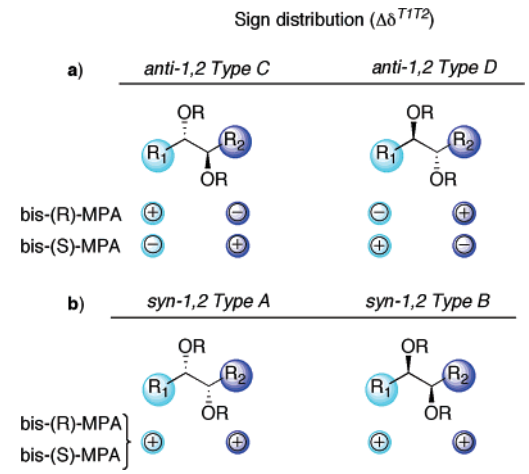

FIGURE 6. $\Delta\delta^{T1T2}$ sign distributions for the bis-(*R*)- and (*S*)-MPA esters of anti (a) and syn (b) 1,2-secondary/secondary diols

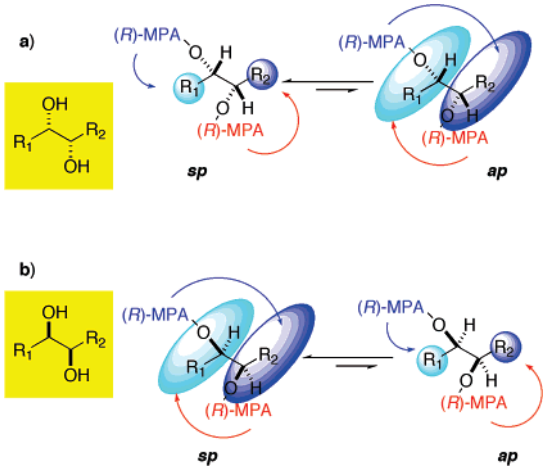

FIGURE 7. Distribution of the shielding effects for the bis-(*R*)-MPA esters of syn A (a) and syn B (b) 1,2-secondary/secondary diols.

Thus, in a type A *syn*-1,2-diol derivatized as the bis-(*R*)-MPA ester, the *sp* conformer has one of the MPA units oriented to shield R_1 while the other MPA unit is shielding R_2 (Figure 7a). Similarly, in the *ap* conformer each substituent is selectively shielded by one of the MPA units, so that a change in the *sp*/*ap* ratio with temperature leads to the same effect on R_1 and R_2 (both more shielded) and a positive $\Delta\delta^{T1T2}$ for both R_1 and R_2 is obtained. Experimentally, this is demonstrated[11] on compounds **9**−**11** (Figure 3).

Exactly the same thing occurs in the bis-(*R*)-MPA ester of a type B syn diol: in the *sp* conformer one of the MPA units is oriented to shield R_1 while the other MPA unit is shielding R_2 (Figure 7b), as temperature diminishes the *sp* population is increased as well the shielding on R_1 and R_2, and this leads to a positive $\Delta\delta^{T1T2}$ sign for R_1 and R_2 in perfect agreement with the experimental results obtained for **12**−**17** (Figure 3).

Identical reasoning applied to the bis-(*S*)-MPA esters of the same diols **9**−**17** leads to a distribution of $\Delta\delta^{T1T2}$ signs identical to those obtained from the bis-(*R*)-MPA esters: positive $\Delta\delta^{T1T2}$ for R_1 and R_2 in both syn A and B diols as experimentally shown[11] for compounds **9**−**17** in Figure 3.

As before, in the syn diols the signs of $\Delta\delta^{T1T2}$ of Hα(R_1) and Hα(R_2) show no correlation with their stereochemistry.

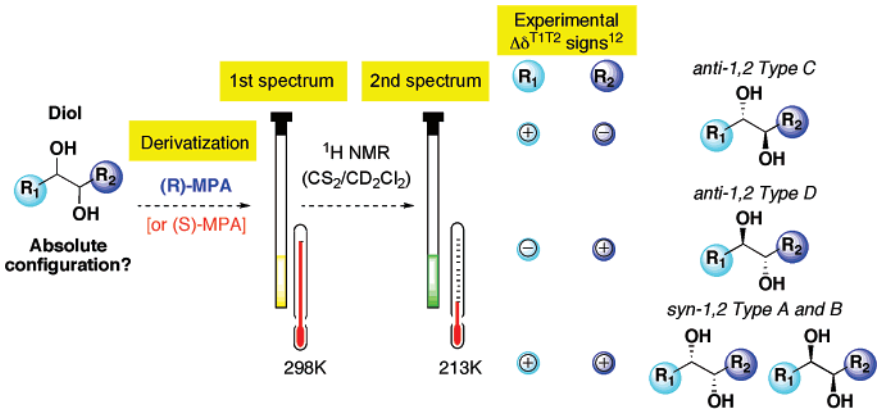

FIGURE 8. Diagram for assignment of the absolute configuration of anti secondary/secondary 1,2-diols from the $\Delta\delta^{T1T2}$ signs.

A resume of the $\Delta\delta^{T1T2}$ signs of R_1/R_2, characteristic of each enantiomer of the syn diols, is graphically shown in Figure 6.

In conclusion, while the low-temperature NMR pattern due to the signals of substituents R_1/R_2 in the two enantiomers of an anti diol are different, the signs of $\Delta\delta^{T1T2}$ for the two enantiomers of the syn diol pair are identical and therefore cannot be distinguished by this procedure.

Thus, from a practical point of view, if we had one of the four possible isomers of an 1,2-secondary/secondary diol and wished to know which is it, using a minimum amount of sample, the low-temperature NMR of the (*R*)- or (*S*)-bis-MPA ester derivative would allow us to unambiguously distinguish the relative stereochemistry of the diol (syn or anti) and if it happens to be an anti diol assign its absolute configuration, distinguishing enantiomer type C from type D (opposite signs for R_1 and R_2, Figure 6). If the NMR data indicated that our diol is syn (same signs for R_1 and R_2), then assignment of its absolute configuration requires the preparation of the other MPA derivative and comparison of the $\Delta\delta^{RS}$ signs for the H$\alpha(R_1)$ and H$\alpha(R_2)$ and R_1/R_2 substituents.[2a]

A step-by-step procedure for assignment together with a ready to use graphical scheme follows: (1) The diol sample should be converted into either the (*R*)- or the (*S*)-bis-MPA-ester derivative, its ^{1}H NMR taken at two sufficiently different temperatures (i.e., 298 and 213 K), the signals for R_1/R_2 assigned, and their $\Delta\delta^{T1T2}$ calculated. (2) If the signs obtained for $\Delta\delta^{T1T2}$ are positive for one substituent and negative for the other, it is an anti diol, while if the signs are the same, the diol is syn. (3) The absolute configuration of the anti diol is obtained by comparison of the signs with those indicated in the graphical scheme shown in Figure 8. (4) If the relative stereochemistry of the diol is syn, its absolute configuration can only be obtained after preparation of the other MPA derivative, comparison of the room-temperature NMR spectra of the bis-(*R*)- and bis-(*S*)-MPA esters, calculation of the $\Delta\delta^{RS}$ for the methines H$\alpha(R_1)$ and H$\alpha(R_2)$ and R_1/R_2 protons, and comparison of the signs with those described in ref 2a.

Experimental Section

General Esterification Procedure. Esters **2**−**17** were prepared by treatment of the diol (1 equiv) with the corresponding (*R*)- and (*S*)-α-methoxy-α-phenylacetic acid (MPA; 2.2 equiv) in the presence of EDC[13] (2.2 equiv) and DMAP (catalytic) in dry CH_2Cl_2 under a nitrogen atmosphere. The reaction was stirred at room temperature for 3−8 h. The organic layer was sequentially washed with water, HCl (1 M), water, $NaHCO_3$(satd), and water and then dried (Na_2SO_4) and concentrated under reduced pressure to obtain the bis ester. Final purification was achieved by flash column chromatography on silica gel 230−400 mesh (elution with 8:2 to 7:3 hexane/ethyl acetate mixtures, 90−95% yields after purification). All compounds were characterized by optical rotation, NMR (1D, 2D), and MS(EI).

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra of samples were recorded at 500 and 250 MHz. ^{1}H chemical shifts are internally referenced to the TMS signal (0.00 ppm) for spectra recorded in CD_2Cl_2/CS_2 (1:4). ^{13}C chemical shifts are internally referenced to $CDCl_3$ (77.0 ppm). *J* values are recorded in Hertz. Low-temperature ^{1}H spectra were recorded at 500 MHz (500.13 MHz). The solvent used was a mixture of CD_2Cl_2/CS_2 in a 1:4 ratio.

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Supporting Information Available: Experimental data (NMR, MS, etc.) relative to bis-MPA esters of diols **15** and **16**; experimental data (NMR) relative to bis-MPA esters of diols **2**−**17** at room and low temperature (298−213 K); proton and carbon spectra of bis-(*R*) and bis-(*S*)-MPA esters of diols **15** and **16** (Figures 1S−4S); ^{1}H NMR spectra of bis-(*R*)- and bis-(*S*)-MPA esters of diols **2**−**17** recorded at different temperatures (298, 253, 213, and 183 K, Figures 5S−20S). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The $\Delta\delta^{T1T2}$ signs shown correspond to the bis-(*R*)-MPA esters. The corresponding $\Delta\delta^{T1T2}$ signs for the bis-(*S*)-MPA esters can be found in Figure 6.

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