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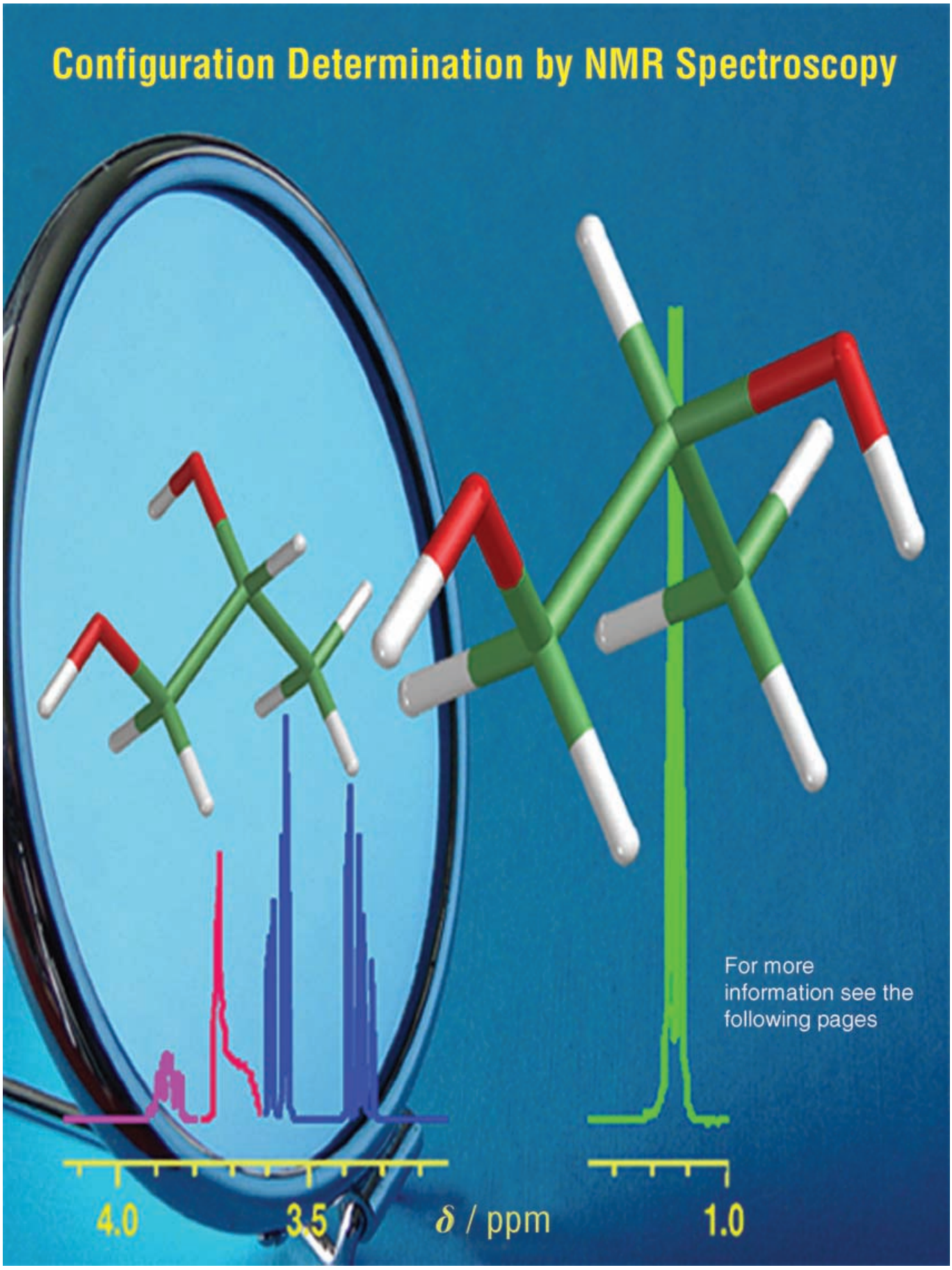

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The Prediction of the Absolute Stereochemistry of Primary and Secondary 1,2-Diols by ^{1}H NMR Spectroscopy: Principles and Applications

Félix Freire, José M. Seco, Emilio Quiñoá, and Ricardo Riguera*[a]

Dedicated to Professor Joaquín Plumet and Professor Rafael Suau on the occasion of their 60th birthdays

Abstract: The absolute configuration of 1,2-diols formed by a primary and a secondary (chiral) hydroxyl group can be deduced by comparison of the ^{1}H NMR spectra of the corresponding (*R*)- and bis-(*S*)-MPA esters (MPA = methoxyphenylacetic acid). This method involves the use of the chemical shifts of substituents L^1/L^2 attached to the secondary (chiral) carbon, and of the hydrogen atom linked to the chiral center (Cα–H) as diagnostic signals. Theoretical (AM1, HF, and B3LYP calculations) and experimental data (dynamic and low-temperature NMR spectroscopy, studies on deuterated derivatives, constant coupling analysis, circular dichroism (CD) spectra, and NMR studies with a number of diols of known absolute configuration) prove that the signs of the $\Delta\delta^{RS}$ obtained for those signals correlate with the absolute configuration of the diol. A graphical model for the reliable assignment of the absolute configuration of a 1,2-diol by comparison of the NMR spectra of its bis-(*R*)- and bis-(*S*)-MPA esters is presented.

Keywords: chirality · configuration determination · methoxyphenylacetic acid · NMR spectroscopy · stereochemistry

Introduction

The use of NMR methods for the assignment of the absolute configuration of organic compounds is particularly useful to researchers who need a simple, rapid, and economical procedure that works in solution and only requires access to an NMR spectrometer. Experimentally, all that is needed is to derivatize the chiral substrate with the two enantiomers, (or just one, depending on the methodology used), of the appropriate auxiliary reagent, that is, the (*R*)- and the (*S*)-enantiomers of α-methoxyphenylacetic acid[1a,b] (MPA, **1**), 9-anthrylmethoxyacetic acid[1b] (9-AMA, **2**), or α-methoxy-α-(trifluoromethyl)phenylacetic acid[1c–j] (MTPA, **3**) for the study of chiral secondary alcohols (Figure 1a), and to compare the NMR spectra of the resulting diasteroisomeric derivatives. In practice, the location in the space of the substituents L^1 and L^2 around the asymmetric carbon atom of the alcohol is decided on the basis of their chemical shifts and expressed by the signs of their $\Delta\delta^{RS}$ values.[2] The scheme in Figure 1b graphically illustrates this procedure as applied to a monofunctional compound.

This procedure is based on two assumptions: the existence in the two derivatives of the same conformational preference and the presence in the reagent of an anisotropic group that produces selective shielding or deshielding on L^1 and L^2. Information about the nature of the different auxiliary reagents used and on the limitations and reliability of the assignment for several families of chiral substrates have been the object of a recent and extensive review.[3a] Guides for the selection of the most appropriate reagent[3b] and the procedure for the assignment of the absolute configuration of alcohols,[3,4] amines,[3,4] and carboxylic acids,[3,4] for establishing criteria in order to get a reliable assignment,[3c] and adaptations to microscale and automatized assignment have recently been published.[5]

In general, the correlations between the NMR spectra of the derivatives and the absolute configuration of the substrates have only been established for monofunctional compounds (alcohols, amines, carboxylic acids, etc.) and therefore, if this methodology was used for the assignment of the configuration of a polyhydroxylated compound with several hydroxylated asymmetric carbon atoms (e.g., a secondary

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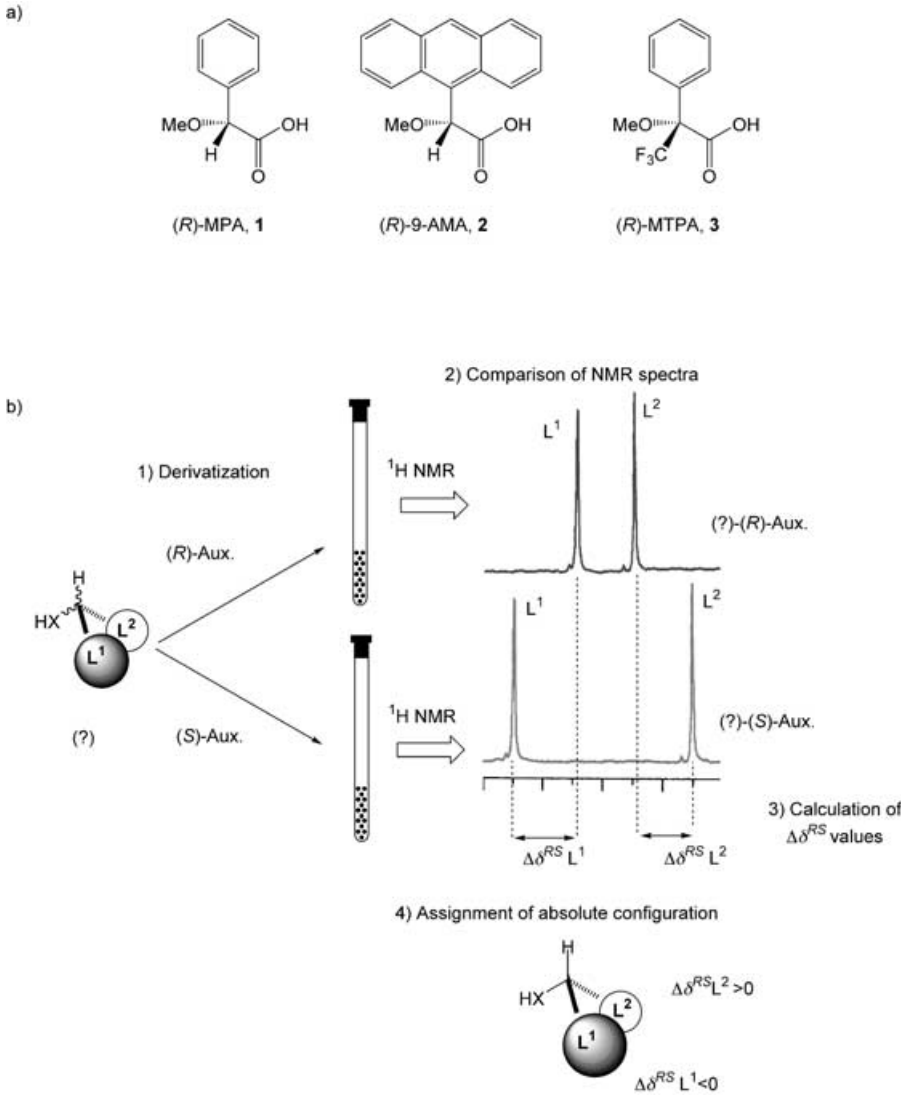


Figure 1. a) Structures of arylmethoxyacetic acids. b) General procedure for the assignment of the absolute configuration of a chiral substrate.

diol), the stereochemistry at the two chiral hydroxylated carbon atoms should be examined and assigned separately. This means that selective protection/deprotection of the hydroxyl groups would be necessary and several steps would be required to obtain the absolute configuration of one chiral center at a time.[6]

We previously showed that the absolute configuration of the two asymmetric carbon atoms of a diol formed by two secondary alcohol groups can be determined in a single process by comparison of the NMR spectra of the corresponding bis-MPA or bis-9-AMA esters if the differences in the chemical shifts of the derivatives were interpreted as the result of the combined action of the two reagent units present in the molecule.[7]

This approach is much more convenient, because the two alcohol groups are derivatized and assigned at the same time in a single operation, but specific models for configuration assignment (different than those operatives for monofunctional alcohols) need to be used. This is because the aromatic shielding effect produced by the reagent unit linked to each one of the hydroxyl groups of the diol affects not only the substituents on that asymmetric carbon atom, but also the substituents of the second asymmetric carbon atom and therefore the chemical shifts observed result from the combined action of those shielding–deshielding effects.

A particularly interesting class of diols is that formed by a chiral secondary alcohol and a primary alcohol group (a beta-chiral 1,2-diol). This structural fragment is present in many relevant natural products (for example, sugars, nucleosides, glycerides) and it is produced in the laboratory by common important reactions including the reduction of carbonyl compounds (ketoaldehydes, ketoacids, ketoalcohols, hydroxyaldehydes), the dihydroxylation of monosubstituted alkenes, the opening of epoxides, and the hydroxylation of allylic alcohols.

The assignment of their absolute configuration by comparison of the NMR spectra of the corresponding bis-(*R*) and bis-(*S*)-MPA ester derivatives should be possible by considering the combined action of the shielding–deshielding effects of the two reagent units, in a way similar to the one successfully employed with chiral secondary–secondary diols.[7]

In fact, when the NMR spectra of the bis-(*R*)- and bis-(*S*)-MPA esters of the beta-chiral 1,2-diols of known absolute configuration **4**–**14** shown in Figure 2a were compared, we found that the substituent L (Figure 2b) and one of the methylene protons located on the other substituent of the asymmetric carbon show a distribution of $\Delta\delta^{RS}$ signs that correlate perfectly with the absolute configuration of the diols for all those compounds.

Thus, all the protons of substituent L have the same $\Delta\delta^{RS}$ sign. This should be opposite to the sign obtained for the other substituent (the methylene group); however, only one

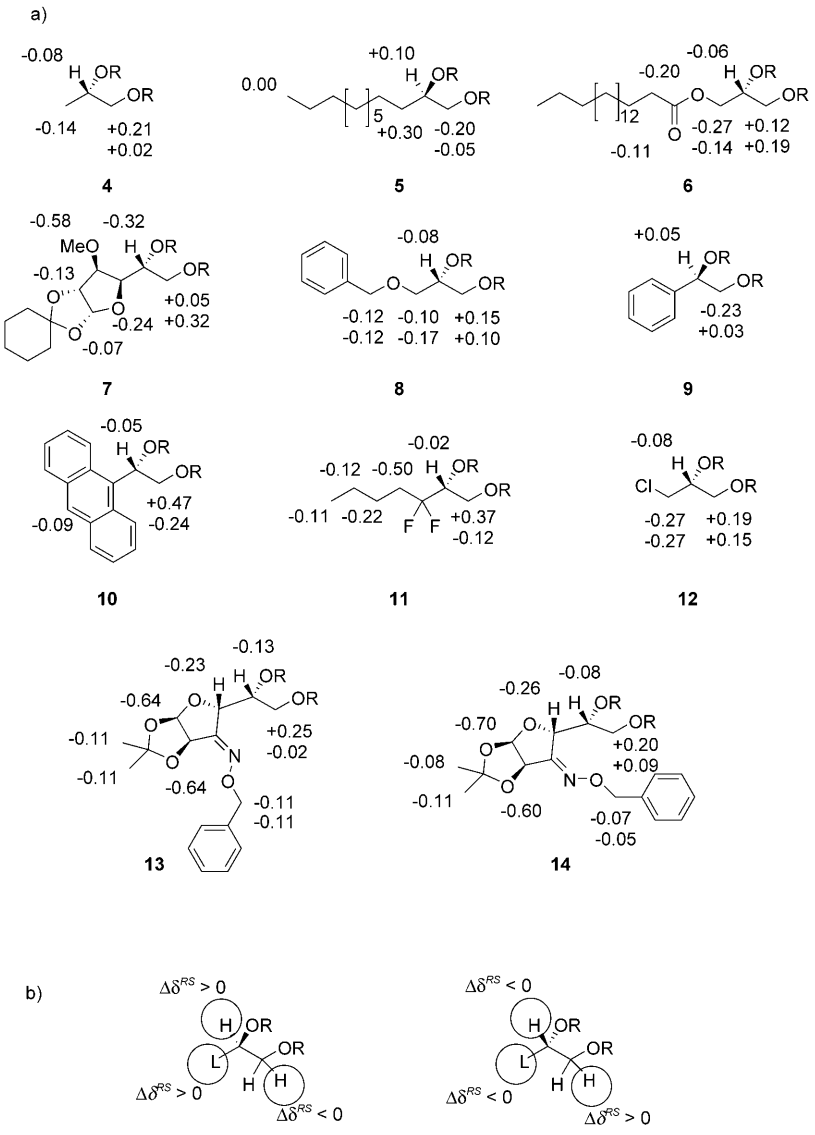


Figure 2. a) Selected $\Delta\delta^{RS}$ values for bis-MPA esters of beta-chiral–1,2-diols **4**–**14**. b) Empirical model to assign the absolute configuration of beta-chiral 1,2-diols.

of the two methylene protons show the expected $\Delta\delta^{RS}$ sign, while the other presented a very small $\Delta\delta^{RS}$ absolute value, so close to the experimental error that its sign has no significance for stereochemical assignment (**4**–**5**, **7**, **14**), or a sign opposite to that of the other geminal hydrogen (**9**–**11**, **13**). The distribution of the $\Delta\delta^{RS}$ signs of proton H(2′) is also coherent with the absolute configuration of the diols.

This pattern is graphically illustrated in Figure 2b and apparently indicates that there is a correlation between the NMR data and the absolute configuration of the diols.

In this paper, we present theoretical and experimental data that fully explain the NMR spectra of the bis-MPA esters of beta-chiral 1,2-diols, and demonstrate the relationship between the absolute configuration and the spectra, and its use for configurational assignment purposes.

Results and Discussion

NMR analysis—shielding–deshielding contributions of the MPA units: To evaluate the contribution of each MPA unit of the bis-MPA ester of a beta-chiral 1,2-diol, we first compared the NMR spectra of the MPA esters of (*S*)-1-acetoxypropan-2-ol (**16**) and of (*S*)-2-acetoxypropan-1-ol (**17**) with those of the bis-acetate of (*S*)-propane-1,2-diol (**15**) (which has the same skeleton and stereochemistry but lacks the phenyl group), and the bis-MPA esters of (*S*)-propane-1,2-diol (**4**) (Figure 3). For such a comparison, we checked the changes in the chemical shifts of the methyl Me(3′) and the methylene CH_2(1′) protons caused by the controlled introduction of the MPA units.

Thus, examination of the spectra a–d and more precisely, comparison of the chemical shifts of the Me(3′) in the diacetate **15** (spectrum a, Figure 3) with the same signal in the mono- (**16**, **17**) and bis-(*R*)-MPA esters (**4**) (spectra b–d, Figure 3), indicates that the methyl group is subjected to the aromatic shielding of the MPA unit in **16**, **17**, and **4**, and that this shielding effect is more intense in the bis-(*R*)-MPA ester (**4**, spectrum d) than in the two mono-MPA esters (**16**, **17**, spectra b and c, respectively). These results suggest that both MPA units in the bis-MPA ester shield those protons, and their additivity is the cause of the increased shift to higher field in **4**.

Similar comparison of the spectra of the diacetate **15** with those of the (*S*)-MPA ester series (spectra e–g, Figure 3) shows that the Me(3′) of the bis-(*S*)-MPA ester (**4**, spectrum g) presents the same chemical shift as for the monoester **17** (spectrum f), being only slightly more shielded than in the bis-acetate **15** (spectrum a). These results suggest that Me(3′) is, in the bis-(*S*)-MPA ester, subjected only to the aromatic shielding due to the MPA unit linked to the primary alcohol group, and that the MPA unit linked to the secondary alcohol does not affect this group in an observable way (spectrum e versus a and g).

We compared the chemical shifts of the methylene protons at C(1′) in the a–d series of spectra. The comparison

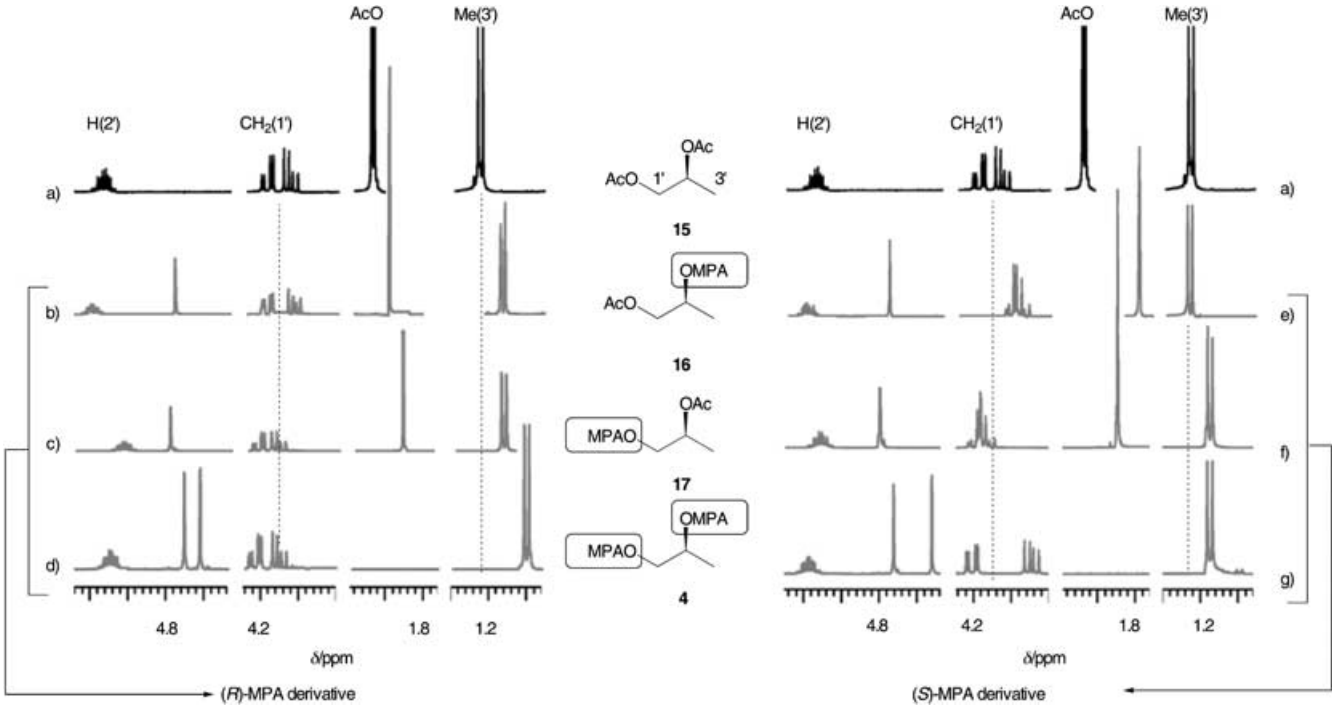


Figure 3. Partial ^{1}H NMR spectra (250.13 MHz in $CDCl_3$) of a) the bis-acetate of (*S*)-propane-1,2-diol; b, e) the (*R*)- and (*S*)-MPA ester of (*S*)-1-acetoxypropan-2-ol respectively; c, f) the (*R*)- and (*S*)-MPA ester of (*S*)-2-acetoxypropan-1-ol respectively; d, g) the bis-(*R*)- and bis-(*S*)-MPA esters of (*S*)-propane-1,2-diol, respectively.

shows that substitution of the acetate at position C(2′) of **15** (spectrum a) by (*R*)-MPA produces no changes in the methylene proton chemical shifts (**16**, spectrum b) and that small shifts to lower field are observed when the MPA units are incorporated either into the primary alcohol group (**17**, spectrum c) or into both hydroxyl groups (**4**, spectrum d). These results indicate that the two methylene protons are equally affected by the MPA unit on the primary alcohol group in the (*R*)-MPA esters and are not affected by the MPA unit on the secondary alcohol.

Furthermore, a similar comparison of the bis-acetate **15** with the mono and bis-(*S*)-MPA esters (**16**, **17**, **4**; spectra e, f and g respectively) shows that the two methylene protons present now display a different behavior. When the acetate at C(2′) is replaced by (*S*)-MPA (**16**, spectrum e), both methylene proton resonances move to higher field. On the other hand, when the substitution is carried out on the primary position, both protons are slightly deshielded (**17**, spectrum f). However, in the bis-MPA ester (**4**, spectrum g), the methylene proton that resonates at higher field shows the expected shielding, as in the case of **16** (spectrum e), while the proton at lower field undergoes a deshielding effect that must be caused by the (*S*)-MPA unit linked at C(1′). As a result, in the bis-(*S*)-MPA ester the two methylene protons are clearly more separated than in the bis-acetate **15**.

In conclusion, the spectra of the bis-MPA esters (spectra d and g) shown on Figure 3 clearly demonstrate that the two MPA units contribute to the chemical shifts associated with the substituents of the asymmetric carbon at C(2′), that is, the methylene and methyl protons at C(1′) and C(3′), respectively.

These results lead us to examine the conformational composition of the bis-MPA esters and more precisely, to study the role of the MPA unit linked to the primary alcohol.

Conformational composition of the bis-MPA esters of beta-chiral 1,2-diols: Bis-MPA esters of (*S*)-propane-1,2-diol were selected as model compounds to perform the corresponding conformational analysis. The main conformational processes studied and the conformers associated to them are shown in Figure 4 and comprise: 1) rotation around the C(1′)–C(2′) bond: conformers *gg*, *gt* and *tg*; 2) rotation around the Cα–CO bond: conformers *sp* and *ap*; and 3) rotation around the O–C(1′) bond: conformers I and II.

The values of the vicinal coupling constants between H(2′) and H(1′) were employed for the study of the rotation around the C(1′)–C(2′) bond. The rotation around the Cα–CO bond was analyzed by CD spectroscopy. For the last process, that is, the rotation around the O–C(1′) bond, we resorted to theoretical calculations: semiempirical, ab initio, and DFT methods (AM1, HF, and B3LYP, respectively). Finally, experimental evidence about the conformation of the compounds in solution was obtained from the studies of the evolution of the NMR spectra with temperature and from selective deuteration of the methylene protons.

Preference around the C(1′)–C(2′) bond; CD and NMR (^3J) studies: The conformational preference around the C(1′)–C(2′) bond in the dibenzoate of (*S*)-propane-1,2-diol has

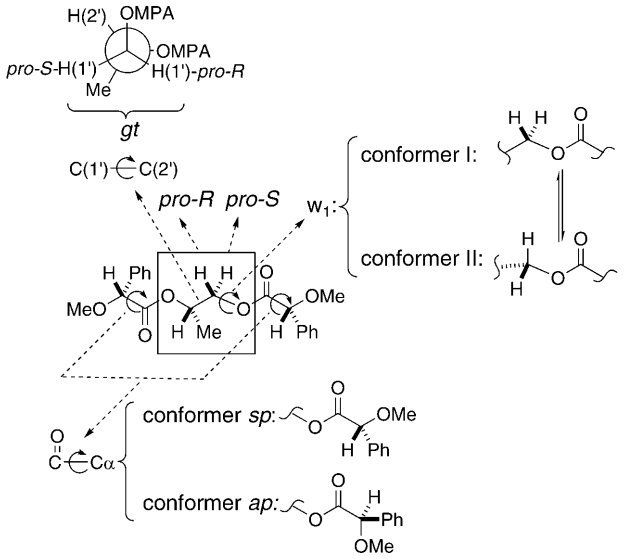


Figure 4. Generation of the main conformers for the bis-(*R*)-MPA esters of (*S*)-propane-1,2-diol by rotation around the highlighted bonds.

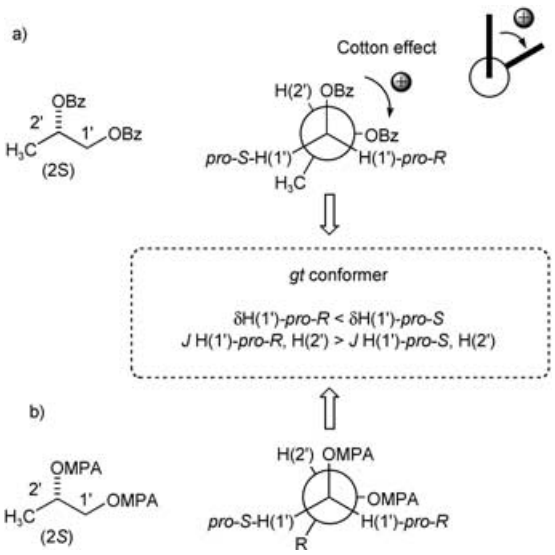


Figure 5. Structure and NMR characteristics of the *gt* conformer for a) the dibenzoate and b) the bis-MPA esters of (*S*)-propane-1,2-diol.

been studied by AM1 calculations, CD, and NMR spectroscopy.[8] We found that *gt* is the most abundant conformer in the equilibrium (Figure 5). Also, the use of deuterated derivatives allowed the identification of the *pro-R* and *pro-S* methylene protons at C(1′) in this conformation,[9] which is characterized by those protons forming different dihedral angles with H(2′) ($J = 6.8$ Hz for *pro-R* and 3.6 Hz for *pro-S*), the *pro-R* being the most shielded proton.

NMR data (δ and J values) of the bis-MPA esters of (*S*)-propane-1,2-diol[10] show a very close coincidence with the above results, suggesting that the main rotamer around the C(1′)–C(2′) bond is in both cases (dibenzoates and bis-MPA esters) the same (*gt*). The NMR spectra of the bis-MPA esters of the (1*S*) deuterated diol (Figure 6) confirmed that the *pro-R* proton has the largest J value and is more shielded than the *pro-S* proton. In addition, the *pro-S* proton produced the smaller $\Delta\delta^{RS}$ value, often with the opposite sign to that of the other geminal proton. Similar J values have been obtained for the bis-MPA esters of diols **5**–**14**.

A comparative NMR study (δ and J values) of the MPA esters of chiral diols **5**–**14** reinforces the prevalence of a conformational preference (*gt*) in this family of compounds.

The (1*S*)-deuterated (*S*)-propane-1,2-diol was prepared by the following six-step sequence (Scheme 1):

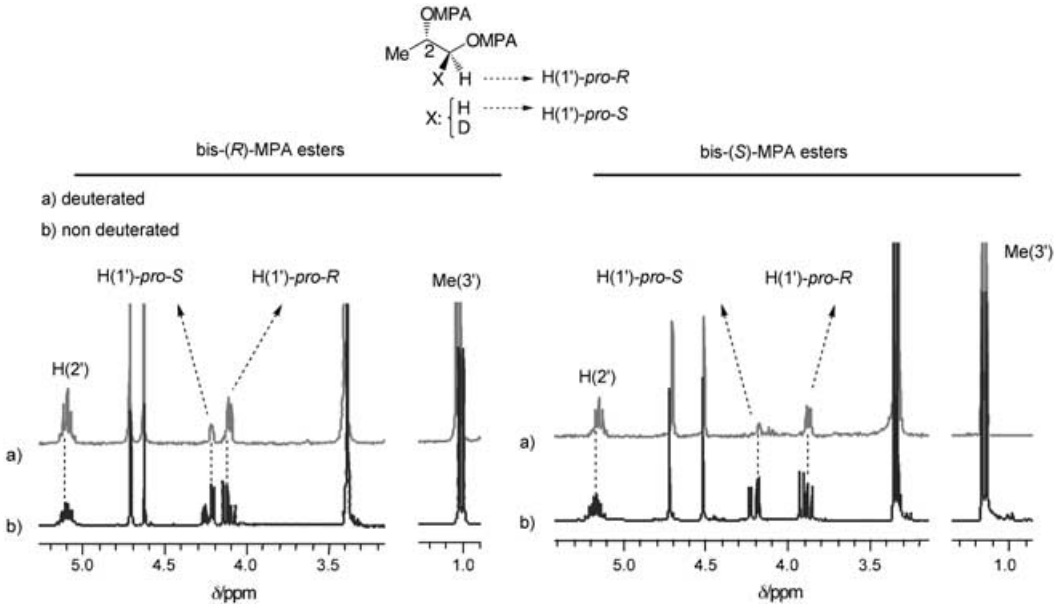
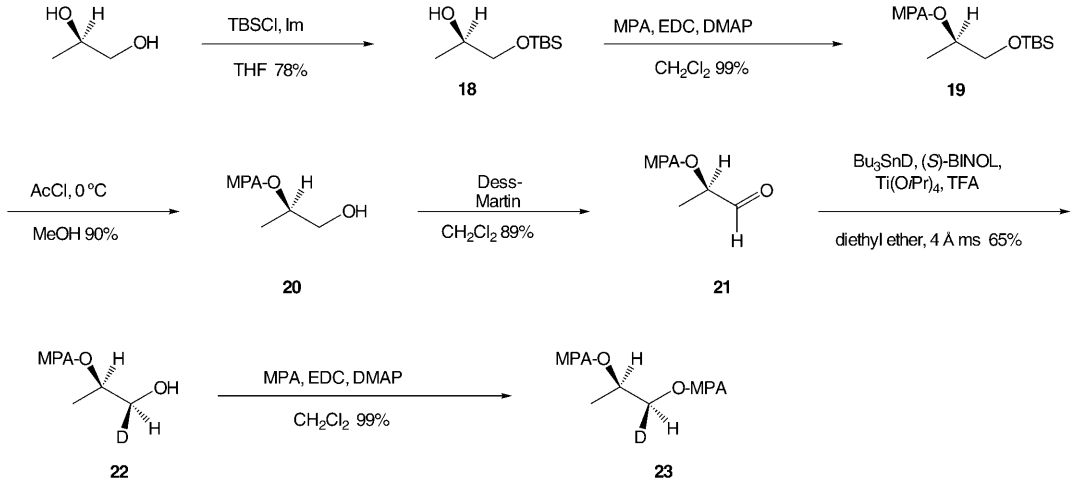


Figure 6. Partial NMR spectra of the bis-MPA-esters of (*S*)-propane-1,2-diol and its (1*S*)-deuterated analogue.



Scheme 1.

1) Protection of the primary alcohol with TBSCl (TBSCl = *tert*-butyl dimethyl silyl chloride).[11]
2) Esterification of the secondary alcohol with MPA.
3) Selective deprotection of the primary hydroxyl group with acetyl chloride.[12]
4) Oxidation to the aldehyde with Dess–Martin reagent.[13]
5) Asymmetric reduction to the (1*S*)-deuterated derivative with (*S*)-BINOL and tributyltin deuteride.[14]
6) Esterification of the hydroxyl group at C(1′) with MPA.

The preference around the Cα–CO bond—CD studies: The conformational preference in the MPA fragment was studied through the CD spectra of the MPA esters of (*S*)-propane-1,2-diol, (*S*)-1-acetoxypropan-2-ol, and (*S*)-2-acetoxypropan-1-ol.

We know from previous work[5f] that the contribution and sign of the CD band of an MPA ester is related to the relative position of the phenyl group with respect to the carbonyl group in each conformation. In the case of an (*R*)-MPA ester, the CD band is negative for the *sp* conformer and positive for *ap*, and the opposite situation holds for the (*S*)-MPA esters (positive band in the *sp* conformation and negative in *ap*).

Experimentally, we found that the (*R*)-MPA esters of the above compounds have a negative Cotton effect band, while the corresponding (*S*)-MPA esters have a positive band (Figure 7). This is associated with the predominance of the *sp* over the *ap* conformations in those derivatives.

The intensity of the band is greater for the bis-(*R*)-MPA ester of (*S*)-propane-1,2-diol than for the bis-(*S*)-MPA ester ($\Delta\varepsilon = -33.78$ and $24.62\,cm^{-2}mol^{-1}$ respectively), indicating that the conformational preference for the *sp* conformer is greater in the bis-(*R*)- than in the bis-(*S*)-MPA ester. As expected, the CD spectra of the bis-MPA esters of (*R*)-propane-1,2-diol show the opposite behavior: the more intense CD band is observed in the bis-(*S*)-MPA ester ($\Delta\varepsilon = 29.45$ versus $-24.95\,cm^{-2}mol^{-1}$).

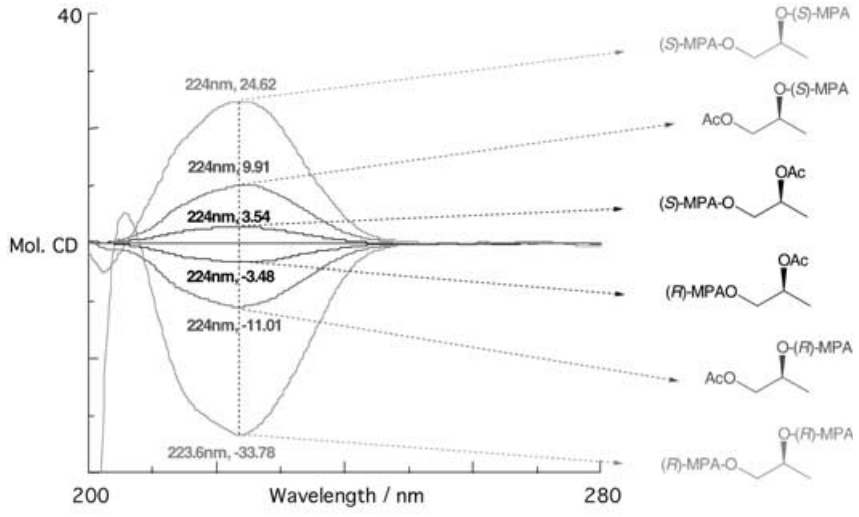


Figure 7. CD spectra of MPA esters of (*S*)-propane-1,2-diol, (*S*)-1-acetoxypropan-2-ol, and (*S*)-2-acetoxypropan-1-ol ($c = 1 \times 10^{-5}$ in MeOH).

The preference around the O–C(1′) bond—energy calculations: The energy variations involved in the rotation around the O–C(1′) (Figure 4) were obtained by semiempirical (AM1), ab initio (HF), and DFT (B3LYP) calculations[15] with the bis-MPA esters of (*S*)-propane-1,2-diol taken as model compounds (Table 1).

In the case of the bis-(*R*)-MPA ester, the three types of calculations pointed to the existence of a minimum energy structure with the two MPA units in a synperiplanar disposition of the MeO and carbonyl groups (*sp*; in full agreement with the CD results) and with

Table 1. Relative energies and dihedral angles for representative conformations of the bis-(*R*) and bis-(*S*)-MPA esters of (*S*)-propane-1,2-diol. The minimum energy conformers are shown in bold.

Derivative	Conformer		Dihedral angle[a]		Energy [kJ mol^{-1}]		
	Cα–CO	O–C(1′)	*pro-S*	*pro-R*	AM1	B3LYP[b]	HF[b]
bis-(*R*)-MPA	*ap*	*I*	+59	−59	3.74	3.71	10.40
	sp	*II*	−37	−155	1.35	2.37	1.02
	sp	***I***	+44	−74	**0**	**0**	**0**
bis-(*S*)-MPA	*ap*	*I*	+42	−76	8.67	4.18	2.16
	sp	***II***	−38	−157	**0**	**0**	**0.68**
	sp	*I*[c]			3.90	0	0

[a] Dihedral angle between the carbonyl (C=O) and *pro-S*- and *pro-R*-H(1′), respectively. [b] Density functional and ab initio methods were conducted with 6-311+G(2d,p) and 6-31G(d) basis sets, respectively. [c] This structure evolves from a type I to a type II conformation.

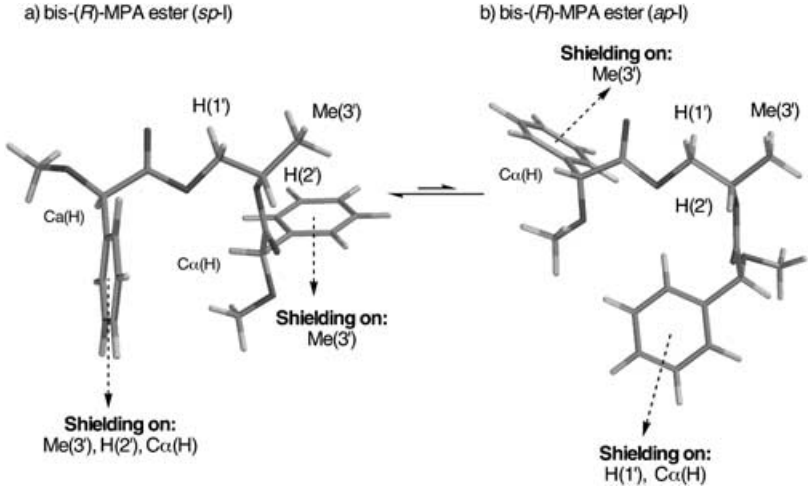


Figure 8. Conformational equilibrium between conformers *sp*-I and *ap*-I in the bis-(*R*)-MPA esters of (*S*)-1,2-propanediol.

the O–C(1′) bond in conformation I (*sp*-I; Figure 8a). This form is characterized by the *pro-S*- and *pro-R*-H(1′) protons forming dihedral angles of +44° and −74°, respectively, with the carbonyl group.

The last representative conformer[16] in order of stability has the two MPA units in the *ap* conformation (MeO and carbonyl groups in antiperiplanar disposition) and the O–C(1′) bond in conformation I, with both methylene hydrogen atoms forming practically 60° angles with the carbonyl group (*ap*-I; Figure 8b).

The calculations for the bis-(*S*)-MPA esters show that the minimum energy form has the MPA fragments in the *sp* conformation, but the most stable rotamer around the O–C(1′) bond is now conformation II (Figure 9a), with the carbonyl group practically coplanar with the *pro-S*-H(1′) hydrogen. The second relevant conformer has the MPA units in an *ap* conformation, while bond O–C(1′) adopts conformation I (Figure 9b).

These calculations show that, in the bis-(*R*)-MPA esters, the carbonyl group bisects the angle formed by the two methylene hydrogen atoms (CH_2(1′), conformation I), and that in the bis-(*S*)-MPA esters, the carbonyl group is coplanar with one of them (*pro-S*-H(1′), conformation II).

These geometries are especially relevant to explain the NMR shifts of the methylene protons: they are affected by the anisotropy generated by the carbonyl groups in the *R* and *S* derivatives in a clearly different way.

The NMR representative conformation in the bis-MPA esters of beta-chiral 1,2-diols: All the information presented below allow us to elucidate the full conformational characteristics of the bis-MPA esters of beta-chiral 1,2-diols, and to explain their NMR spectra.

In the case of the bis-(*R*)-MPA ester of (*S*)-propane-1,2-diol (Figure 8), the main process is the equilibrium between two conformers (*sp*-I and *ap*-I). In both conformers the C(1′)–C(2′) bond is rotated to adopt the *gauche* form (*gt*), but they are different regarding the other bonds (Figure 8).

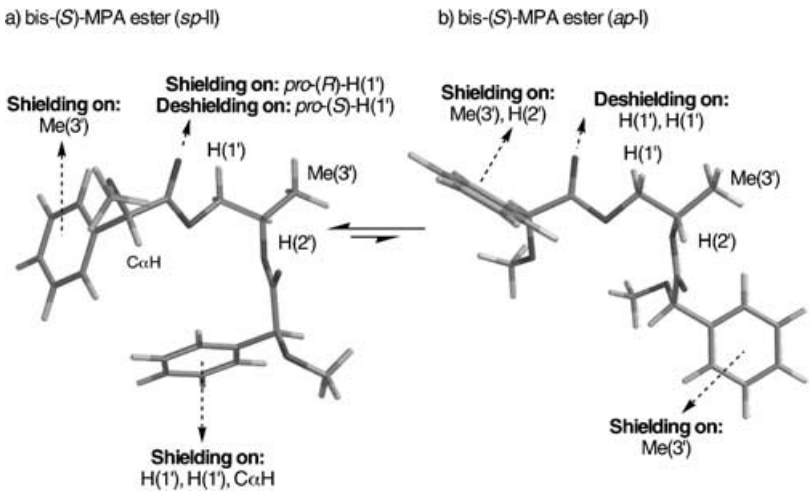


Figure 9. Conformational equilibrium between conformer *sp*-II and *ap*-I in the bis-(*S*)-MPA esters of (*S*)-propane-1,2-diol.

In accordance with that equilibrium, the NMR of the bis-(*R*)-MPA esters should be dominated by the shielding/deshielding effects produced by the phenyl groups of the two MPA units on Me(3′), H(1′), and H(2′), because the anisotropy of the carbonyl group will have an identical effect on the two methylene protons (H(1′)) in both conformers.

Thus, in conformer *sp*-I the phenyl group of the MPA unit linked to the primary alcohol projects its shielding cone on Me(3′) and H(2′), while the MPA unit bonded to the secondary one shields Me(3′); this results in double shielding (Figure 8a and Figure 4d). In the *ap*-I conformation the phenyl group of the MPA unit bonded to the primary alcohol shields the Me(3′) group and the MPA unit on the secondary alcohol shields the methylene protons, H(1′), (Figure 8).

In the case of the bis-(*S*)-MPA ester of (*S*)-propane-1,2-diol (Figure 9), the conformational equilibrium is also characterized by two main components *sp*-II and *ap*-I, which share identical disposition around the C(1′)–C(2′) bond (*gt* rotamer) but show differences regarding the other bonds. The most representative conformer is *sp*-II and has the two MPA units in the *sp* disposition and the O–C(1′) bond rotated to adopt conformation II (carbonyl coplanar to *pro-S*-H(1′), Figure 9a). The second representative conformer, *ap*-I, has the two MPA units in the *ap* conformation and the O–C(1′) bond rotated to adopt conformation I (Figure 9b). The shielding/deshielding effects on these conformers are illustrated in Figure 9.

Variable-temperature NMR experiments: Lowering the temperature of the NMR probe should produce an increase in the relative population of the more stable conformer that should manifest itself in the NMR spectra. Experimental evidence to support this and identify the most stable conformer in equilibrium was obtained from low-temperature NMR experiments carried out on the bis-MPA esters of (*S*)-propane-1,2-diol.

Thus, comparison of the NMR spectra of the bis-(*R*)-MPA ester of (*S*)-propane-1,2-diol taken at different temperatures (from 300–183 K) (Figure 10a) showed no significant changes, while a comparison of the spectra of the bis-(*S*)-MPA ester showed important shifts (Figure 10b) that are summarized in the following points:

1) The Me(3′) and H(2′) signals suffer a slight deshielding.
2) The two methylene CH_2(1′) proton resonances shift in opposite directions: *pro-S*-H(1′) is deshielded at lower temperature while *pro-R*-H(1′) is strongly shielded.
3) One of the Hα protons shows a resonance that is shifted to higher field at lower temperature.

These facts are coherent with the results of the calculations (Table 1), the CD and the *J* analysis as shown before: in the bis-(*R*)-MPA esters, the equilibrium is heavily shifted towards the most stable conformer and the decrease of temperature is not enough to produce significant changes in the population ratio (Figure 10a). For the bis-(*S*)-MPA ester, the energies between the main populations are closer. Consequently, the change of temperature is more effective in changing the relative populations and also the resulting NMR spectra (Figure 10b).

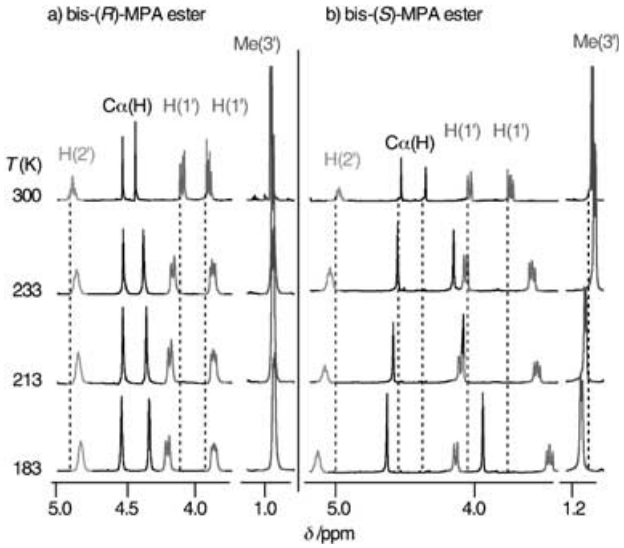


Figure 10. Evolution with the temperature of the NMR spectra of a) bis-(*R*)- and b) bis-(*S*)-MPA esters of (*S*)-propane-1,2-diol.

It is particularly important to point out that the two methylenic protons (CH_2(1′)) are affected in opposite ways: the *pro-R*-H(1′) is more affected by the magnetic anisotropy of the MPA unit linked to the secondary alcohol and moves upfield, while the *pro-S*-H(1′) proton is affected by the magnetic anisotropy of the carbonyl linked to the primary alcohol group and moves downfield.

The correlation between the absolute configuration of beta-chiral 1,2-diols and the NMR spectra of their bis-MPA esters—a graphical model for assignment: Above we have shown that the NMR of the bis-MPA esters of 1,2-diols can be fully interpreted on the basis of their conformational composition and that there is a correlation between the signs of $\Delta\delta^{RS}$ and the absolute configuration of the diol. From a practical point of view, the spectra can be more easily interpreted just by considering the more abundant conformer in each derivative and neglecting the contributions of the minor components.

According to this simplification, in the bis-(*R*)-MPA ester of (*S*)-propane-1,2-diol (Figure 11a) the Me(3′) group is shielded by the two MPA units, while in the bis-(*S*)-MPA ester (Figure 11b), Me(3′) is shielded only by the MPA unit linked to the primary alcohol; therefore Me(3′) should be more shielded in the bis-(*R*)-MPA ester than in the bis-(*S*)-MPA ester and will produce a negative $\Delta\delta^{RS}$ value[2] (Figure 11c).

The signal due to proton H(2′) is not affected in the bis-(*S*)-MPA while in the bis-(*R*)-MPA ester it is shielded by the MPA unit linked to the primary alcohol, this should produce a negative $\Delta\delta^{RS}$ value (Figure 11c).

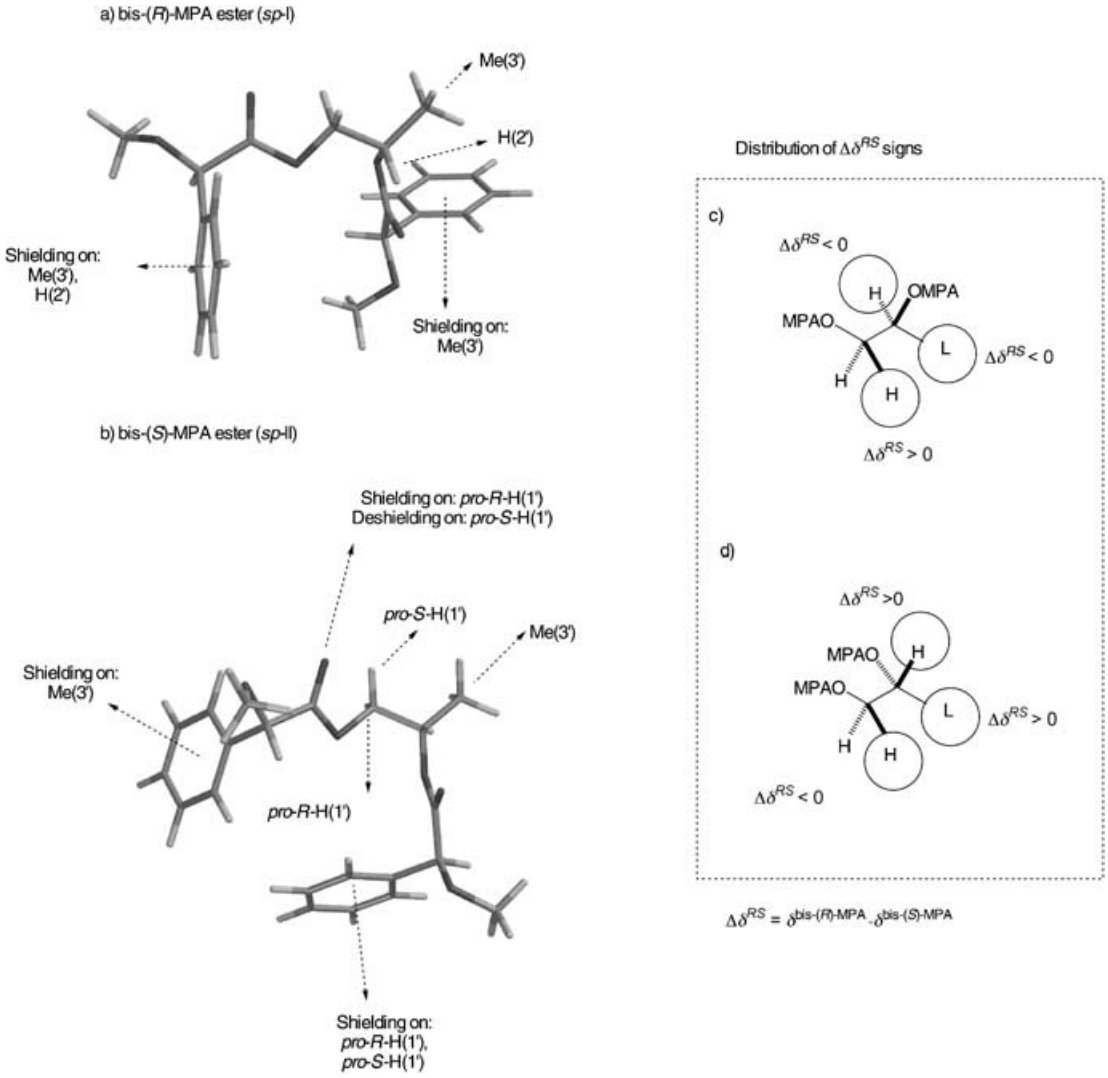


Figure 11. Shielded/deshielded groups in the bis-(*R*)- and bis-(*S*)-MPA esters of (*S*)-propane-1,2-diol (a,b) and $\Delta\delta^{RS}$ sign distribution for bis-MPA esters of beta-chiral 1,2-diols (c,d).

The two methylenic protons H(1′) are not affected in the bis-(*R*)-MPA esters, while in the bis-(*S*)-MPA ester they are shielded by the MPA unit linked to the secondary alcohol and affected by the carbonyl linked to the primary alcohol. This group deshields the *pro-S*-H(1′) and shields the *pro-R*-H(1′) protons (Figure 11b); therefore *pro-R*-H(1′) is more shielded in the bis-(*S*)- than in the bis-(*R*)-MPA ester and will result in a very intense and positive $\Delta\delta^{RS}$ sign, while the *pro-S*-H(1′) proton either be shielded or deshielded (positive or negative $\Delta\delta^{RS}$ sign) depending on the exact balance between the opposite effects of the phenyl of the MPA bonded to the secondary and the carbonyl of the other MPA unit. This eliminates the methylene proton with the smaller $\Delta\delta^{RS}$ value for stereochemical diagnosis. An illustration of the distribution of $\Delta\delta^{RS}$ signs for each configuration is shown in Figure 11. It is applicable to the series of diols of known absolute configuration shown in Figure 2 (compounds **4**–**14**) and can therefore be used for the assignment of absolute configuration of any 1,2-diol.

The procedure for assignment is quite simple and requires the following steps:

1) The bis-(*R*)- and the bis-(*S*)-MPA derivatives should be prepared, their proton NMR spectra assigned and the $\Delta\delta^{RS}$ values and signs measured for the signals of L, H(2′), and H(1′), and then be compared with those of Figure 11.
2) If the $\Delta\delta^{RS}$ signs of both the L substituents and the H(2′) proton are negative and that of the methylene proton of diagnostic value (the one with the higher $\Delta\delta^{RS}$) is positive, the absolute configuration at the asymmetric carbon of the diol is the one shown in Figure 11c.
3) If the signs of both L substituent and the H(2′) proton are positive and that of the methylene proton of diagnostic value (the one with the higher $\Delta\delta^{RS}$ value) is negative, then the absolute configuration is the one shown in Figure 11d.

Experimental Section

General procedures: The esters **4**–**14**, were prepared in CH_2Cl_2 by treatment of the corresponding diol (1 equiv) with (*R*)- and (*S*)-MPA (2.5 equiv) in the presence of EDC[17] (2.5 equiv) and DMAP (catalytic) (EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP = 4-dimethylaminopyridine). All the reactions were carried out under nitrogen atmosphere. The mixtures were stirred at room temperature for 2 h. The organic layers were washed with water, HCl (1 M), water, $NaHCO_3$ (sat), and water, and were then dried (Na_2SO_4) and concentrated under reduced pressure to yield the diesters. The bis-acetate ester (**15**) of **4** was prepared following an analogous procedure with acetic acid. The esters **16** and **17** were prepared by selective esterification of the primary hydroxyl groups with either acetic acid (**16**) or MPA (**17**) followed by the esterification of the secondary hydroxyl groups with either MPA (**16**) or acetic acid (**17**). Compound **23** was prepared by protection of the primary hydroxyl group with TBSCl[11] (**18**) followed by esterification of the secondary alcohol with MPA (**19**), a selective deprotection of the primary hydroxyl group[12] (**20**), and oxidation[13] to the aldehyde (**21**). Next, the aldehyde was reduced to a chiral deuterated primary alcohol[14] (**22**) followed by its esterification with MPA (**23**).

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: *D*1-90-*t*1-90-*t*2; relaxation delay *D*1 = 0.5 s; pulse length 8.5 μs (90°); 2D NOESY spectra: sequence: *D*1-90-*t*1-90-τ_{mix}-90-*t*2; relaxation delay *D*1 = 0.5 s; mixing time (τ_{mix}) 0.5 s, pulse length 8.5 μs (90°); TPPI-mode, NS = 64.

Computational methods: Ab initio Hartree–Fock (HF) and DFT calculations were performed to elucidate the conformational preferences of the bis-MPA esters of (*S*)-propane-1,2-diol, taken as a model compound. 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,[18] 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_α–O–C=O skeletal fragment in its most stable orientation; that is, the *Z* conformation. For the determination of more accurate energies, single-point calculations at the HF-optimized geometries were carried out using the DFT/B3LYP approach. All the calculations were performed with the Gaussian 98 series of programs.[15]

Bis-(*R*)-MPA ester of (*S*)-propane-1,2-diol ((*R*)-4): $[\alpha]_D = -37.69$ (*c* = 2.78 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 1.00$ (d, *J* = 6.4 Hz, 3H), 3.38 (s, 3H), 3.39 (s, 3H), 4.10 (dd, *J* = 6.4 Hz, 11.9 Hz, 1H), 4.23 (dd, *J* = 3.6 Hz, 11.9 Hz, 1H), 4.52 (s, 1H), 4.72 (s, 1H), 5.03–5.15 (m, 1H), 7.23–7.43 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 15.8$, 57.3, 60.1, 68.9, 82.2, 82.3, 127.1, 127.2, 128.6, 126.6, 128.7, 128.8, 135.9, 136.0, 169.9, 170.3 ppm; MS (EI): *m*/*z*: 372 [M^+].

Bis-(*S*)-MPA ester of (*S*)-propane-1,2-diol ((*S*)-4): $[\alpha]_D = +35.72$ (*c* = 2.65 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 1.15$ (d, *J* = 6.5 Hz, 3H), 3.33 (s, 3H), 3.36 (s, 3H), 3.89 (dd, *J* = 6.7 Hz, 11.9 Hz, 1H), 4.21 (dd, *J* = 3.3 Hz, 11.9 Hz, 1H), 4.51 (s, 1H), 4.72 (s, 1H), 5.11–5.23 (m, 1H), 7.28–7.46 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 16.1$, 57.2, 57.3, 66.1, 68.9, 81.9, 82.3, 127.0, 128.5, 128.6, 135.9, 136.0, 170.0, 170.1 ppm; MS (EI): *m*/*z*: 372 [M^+].

Bis-(*R*)-MPA ester of (*R*)-dodecane-1,2-diol ((*R*)-5): $[\alpha]_D = -56.10$ (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 0.88$ (t, *J* = 6.3 Hz, 3H), 1.10–1.21 (m, 2H), 1.21–1.35 (m, 2H), 1.42–1.44 (m, 2H), 1.36–1.50 (m, 12H), 1.42–1.44 (m, 2H), 3.34 (s, 3H), 3.36 (s, 1H), 3.89 (dd, *J* = 6.9 Hz, 11.9 Hz, 1H), 4.23 (dd, *J* = 3.2 Hz, 11.9 Hz, 1H), 4.50 (s, 1H), 4.74 (s, 1H), 5.11 (m, 1H), 7.26–7.49 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 14.5$, 23.1, 23.2, 29.6, 29.7, 29.7, 29.8, 29.9, 30.7, 32.3, 57.7, 57.8, 65.7, 72.8, 82.5, 83.0, 127.4, 127.5, 128.9, 128.9, 129.1, 136.5, 136.7, 170.7, 170.8 ppm; MS (EI): *m*/*z*: 498 [M^+].

Bis-(*S*)-MPA ester of (*R*)-dodecane-1,2-diol ((*S*)-5): $[\alpha]_D = +67.76$ (*c* = 2.00 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 0.88$ (t, *J* = 6.7 Hz, 3H), 0.92–1.06 (m, 14H), 1.04–1.23 (m, 2H), 1,24–1.33 (m, 2H), 3.39 (s, 3H), 3.39 (s, 1H), 4.09 (dd, *J* = 6.1 Hz, 11.8 Hz, 1H), 4.28 (dd, *J* = 3.1 Hz, 11.9 Hz, 1H), 4.62 (s, 1H), 4.70 (s, 1H), 5.01 (m, 1H), 7.31–7.43 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 14.5$, 23.1, 24.8, 29.4, 29.6, 29.7, 29.8, 29.9, 30.6, 32.3, 57.7, 65.6, 72.4, 82.7, 83.7, 127.6, 128.9, 129.0, 129.1, 129.1, 136.5, 136.7, 170.5, 170.7 ppm; MS (EI): *m*/*z*: 498 [M^+].

Bis-(*R*)-MPA ester of 3-estearoyl-*sn*-glycerol ((*R*)-6): $[\alpha]_D = -17.67$ (*c* = 6.82 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 0.89$ (t, *J* = 6.59 Hz, 3H), 1.09–1.36 (m, 28H), 1.37–1.42 (m, 2H), 1.42–1.47 (m, 2H), 2.00 (dt, *J* = 2.3, 7.5 Hz, 2H), 3.38 (s, 3H), 3.40 (s, 3H), 3.85 (dd, *J* = 6.6 Hz, 11.9 Hz, 1H), 4.03 (dd, *J* = 4.1 Hz, 11.9 Hz, 1H), 4.18 (dd, *J* = 5.3 Hz, 12.2 Hz, 1H), 4.42 (dd, *J* = 4.1 Hz, 12.2 Hz, 1H), 4.6 (s, 1H), 4.74 (s, 1H), 5.17–5.25 (m, 1H), 7.30–7.45 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 23.9$, 24.4, 25.2, 36.1, 37.0, 57.2, 57.8, 58.0, 62.9, 69.1, 80.9, 82.0, 82.7, 105.1, 113.0, 127.5, 127.7, 128.9, 129.0, 129.2, 136.7, 136.9, 169.2, 170.8 ppm; MS (EI): *m*/*z*: 654 [M^+].

Bis-(*S*)-MPA ester of 3-estearoyl-*sn*-glycerol ((*S*)-6): $[\alpha]_D = +18.20$ (*c* = 7.84 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 0.89$ (t, *J* = 6,6 Hz, 3H), 1.11–1.33 (m, 28H), 1.51–1.57 (m, 2H), 2.20 (t, *J* = 7.8 Hz, 2H), 3.34 (s, 3H), 3.37 (s, 3H), 3.99 (dd, *J* = 6.9 Hz, 11.9 Hz, 1H), 4.04 (dd, *J* = 6.6 Hz, 11.9 Hz, 1H), 4.19 (dd, *J* = 4.1 Hz, 11.9 Hz, 1H), 4.30 (dd, *J* = 4.08 Hz, 11.9 Hz, 1H), 4.55 (s, 1H), 4.74 (s, 1H), 5.22–5.33 (m, 1H), 7.29–7.44 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 23.9$, 24.3, 25.2, 36.1, 36.9, 57.8, 57.9, 64.6, 69.4, 76.9, 80.9, 82.5, 83.1, 83.5, 105.2, 113.8, 127.3, 127.6, 128.9, 128.9, 129.0, 129.1, 136.4, 136.5, 169.8, 170.5 ppm; MS (EI): *m*/*z*: 654 [M^+].

Bis-(*R*)-MPA ester of 1,2-*O*-cyclohexiliden-3-*O*-methyl-α-D-glucofuranose ((*R*)-7): $[\alpha]_D = -41.88$ (*c* = 3.42 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 1.14$–1.79 (m, 10H), 2.56 (s, 3H), 2.90 (d, *J* = 3.1 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 4.01 (dd, *J* = 3.1, 9.4 Hz, 1H), 4.12 (dd, *J* = 3.1 Hz, 12.2 Hz, 1H), 4.33 (d, *J* = 3.7 Hz, 1H), 4.34 (s, 1H), 4.95 (dd, *J* = 2.5 Hz, 12.2 Hz, 1H), 5.06 (ddd, *J* = 2.5, 3.1, 5.6 Hz, 1H), 5.75 (d, *J* = 3.7 Hz, 1H), 7.18–7.56 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 23.9$, 24.3, 25.2, 36.0, 37.0, 57.1, 57.7, 58.0, 62.9, 69.1, 80.9, 82.0, 82.6, 82.7, 105.1, 112.9, 127.5, 127.7, 128.9, 129.0, 129.1, 136.7, 136.9, 169.2, 170.8 ppm; MS (EI): *m*/*z*: 570 [M^+].

Bis-(*S*)-MPA ester of 1,2-*O*-cyclohexiliden-3-*O*-methyl-α-D-glucofuranose ((*S*)-7): $[\alpha]_D = +24.64$ (*c* = 2.94 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 1.39$–1.75 (m, 10H), 3.00 (s, 3H), 3.29 (s, 3H), 3.36 (s, 3H), 3.48 (dd, *J* = 3.1 Hz, 12.2 Hz, 1H), 4.07 (dd, *J* = 6.6 Hz, 12.2 Hz, 1H), 4.25 (dd, *J* = 3.14, 8.10 Hz, 1H), 4.46 (d, *J* = 3.7 Hz, 1H), 4.55 (s, 1H), 4.63 (dd, *J* = 2.2 Hz, 12.2 Hz, 1H), 4.74 (s, 1H), 5.38 (ddd, *J* = 1.8, 4.7, 6.3 Hz, 1H), 5.82 (d, *J* = 3.5 Hz, 1H), 7.23–7.53 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 23.9$, 24.3, 25.2, 36.0, 36.9, 57.8, 57.9, 64.6, 69.4, 80.9, 82.5, 83.1, 83.5, 105.2, 113.1, 127.3, 127.6, 128.9, 128.9, 129.0, 129.1, 136.5, 136.6, 169.8, 170.5 ppm; MS (EI): *m*/*z*: 570 [M^+].

Bis-(*R*)-MPA ester of (*R*)-3-benzyloxipropane-1,2-diol ((*R*)-8): $[\alpha]_D = -60.11$ (*c* = 5.19 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 3.29$ (d, 5.6 Hz, 1H), 3.29 (d, 5.0 Hz, 1H), 3.38 (s, 3H), 3.39 (s, 3H), 4.24 (dd, *J* = 5.9 Hz, 11.9 Hz, 1H), 4.44 (dd, *J* = 3.4 Hz, 11.9 Hz, 1H), 4.63 (s, 1H), 4.69 (s, 1H), 5.14–5.22 (m, 1H), 7.09 (d, *J* = 6.9 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.24–7.42 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 57.7$, 57.8, 63.3, 68.2, 71.4, 73.6, 82.6, 82.7, 127.7, 128.9, 129.0, 129.1, 129.2, 136.4, 136.5, 137.9, 170.3, 170.6 ppm; MS (EI): *m*/*z*: 480 [M^+].

Bis-(*S*)-MPA ester of (*R*)-3-benzyloxipropane-1,2-diol ((*S*)-8): $[\alpha]_D = +35.07$ (*c* = 2.82 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): $\delta = 3.34$ (s, 3H), 3.35 (s, 3H), 3.45 (d, *J* = 5.0 Hz, 1H), 3.46 (d, *J* = 5.0 Hz, 1H), 4.09 (dd, *J* = 6.3 Hz, 11.9 Hz, 1H), 4.34 (dd, *J* = 3.7 Hz, 16.6 Hz, 1H), 4.50 (s, 1H), 4.75 (s, 1H), 5.21–5.29 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.25–7.46 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 57.7$, 57.8, 63.4, 68.3, 71.4, 73.7, 82.5, 82.8, 127.6, 127.6, 127.8, 128.0, 128.2, 128.8, 129.0, 129.0, 129.1, 129.2, 129.2, 130.1, 136.5, 136.5, 137.9, 170.5, 170.6 ppm; MS (EI): *m*/*z*: 480 [M^+].

Bis-(*R*)-MPA ester of (*R*)-1-phenylethane-1,2-diol ((*R*)-9): $[\alpha]_D = -83.44$ (*c* = 2.46 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ (ppm): 3.30 (s, 3H), 3.33 (s, 3H), 4.08 (dd, *J* = 8.1 Hz, 11.9 Hz, 1H), 4.39 (dd, *J* = 3.7 Hz,

11.9 Hz, 1H), 4.46 (s, 1H), 4.8 (s, 1H), 6.06 (dd, J=3.8, 8.2 Hz, 1H), 7.20–7.50 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=57.8, 57.8, 66.6, 74.2, 82.5, 82.9, 127.0, 127.6, 127.6, 127.8, 128.9, 129.1, 129.1, 129.2, 129.2, 135.9, 136.4, 136.6, 170.2, 170.6 ppm; MS (EI): m/z: 434 [M^+].

Bis-(*S*)-MPA ester of (*R*)-1-phenylethane-1,2-diol ((*S*)-9): $[\alpha]_D$=+42.67 (c=1.21 in $CHCl_3$); ^{1}H NMR (250.17 MHz $CDCl_3$) δ=3.36 (s, 3H), 3.37 (s, 3H), 4.31 (dd, J=4.1 Hz, 11.9 Hz, 1H), 4.36 (dd, J=6.6 Hz, 11.9 Hz, 1H), 4.68 (s, 2H), 5.95 (dd, J=4.6, 6.5 Hz, 1H), 6.89–7.36 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=57.6, 57.7, 66.6, 74.1, 82.7, 126.6, 127.6, 127.8, 128.8, 128.8, 129.1, 129.2, 129.3, 129.8, 136.3, 136.4, 169.8, 170.6 ppm; MS (EI): m/z: 434 [M^+].

Bis-(*R*)-MPA ester of (*R*)-1-(9-anthryl)ethane-1,2-diol ((*R*)-10): $[\alpha]_D$=−5.71 (c=3.12 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=3.27 (s, 3H), 3.37 (s, 3H), 4.39 (dd, J=3.7 Hz, 12.2 Hz, 1H), 4.62 (s, 1H), 4.73 (s, 1H), 5.15 (dd, J=10.0 Hz, 12.2 Hz, 1H), 7.48 (dd, J=3.7 Hz, 10.0 Hz, 1H), 7.01–7.42 (m, 13H), 7.91–7.94 (m, 2H), 8.30–8.38 ppm (m, 3H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=57.7, 57.8, 65.8, 71.6, 82.8, 82.8, 125.2, 125.8, 127.6, 127.8, 128.9, 129.0, 129.4, 129.3, 129.5, 130.1, 130.2, 131.7, 135.9, 136.4, 170.2, 170.9 ppm; MS (EI): m/z: 534 [M^+].

Bis-(*S*)-MPA ester of (*R*)-1-(9-anthryl)ethane-1,2-diol ((*S*)-10): $[\alpha]_D$=+98.78 (c=0.008 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=3.27 (s, 3H), 3.32 (s, 3H), 4.47 (s, 1H), 4.63 (dd, J=5.0 Hz, 12.2 Hz, 1H), 4.68 (dd, J=8.8 Hz, 12.2 Hz, 1H), 4.78 (s, 1H), 7.65 (dd, J=5.0, 8.8 Hz, 1H), 7.26–7.56 (m, 1H), 7.26–7.56 (m, 13H), 7.98–8.01 (m, 2H), 8.46–8.51 ppm (m, 3H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=57.8, 57.9, 65.9, 71.3, 82.4, 82.9, 125.4, 126.0, 127.6, 127.8, 129.0, 129.1, 129.2, 129.8, 130.2, 130.4, 136.4, 136.7, 170.5, 170.9 ppm; MS (EI): m/z: 534 [M^+].

Bis-(*R*)-MPA ester of (*R*)-3,3-difluoroheptane-1,2-diol ((*R*)-11): $[\alpha]_D$=−88.85 (c=1.22 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=0.73 (t, J=7.1 Hz, 3H), 0.94–1.08 (m, 2H), 1.10–1.22 (m, 2H), 1.23–1.25 (m, 2H), 3.39 (s, 3H), 3.40 (s, 3H), 4.35 (dd, J=7.3 Hz, 12.4 Hz, 1H), 4.48 (ddd, J=1.2, 3.1 Hz, 12.2 Hz, 1H), 4.68 (s, 1H), 4.70 (s, 1H), 5.25 (dddd, J=1.6, 4.4, 7.5 Hz, 13.5 Hz, 1H), 7.33–7.42 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=14.1, 22.6, 23.5, 33.1, 33.5, 33.8, 57.8, 57.9, 61.8, 70.8, 71.2, 71.6, 82.4, 82.8, 127.4, 127.6, 129.0, 129.1, 129.2, 129.3, 136.1, 136.2, 170.0, 170.5 ppm; MS (EI): m/z: 464 [M^+].

Bis-(*R*)-MPA ester of (*R*)-3,3-difluoroheptane-1,2-diol ((*S*)-11): $[\alpha]_D$=+126.74 (c=1.04 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=0.84 (t, J=7.1 Hz, 3H), 1.19–1.28 (m, 2H), 1.30–1.43 (m, 2H), 1.55–1.76 (m, 2H), 3.33 (s, 6H), 3.98 (dd, J=8.2 Hz, 12.1 Hz, 1H), 4.60 (dd, J=2.4 Hz, 11.9 Hz, 1H), 4.42 (s, 1H), 4.63 (ddd, J=0.9, 2.8 Hz, 11.9 Hz, 1H), 4.81 (s, 1H), 5.33–5.46 (m, 1H), 7.24–7.48 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=14.0, 22.4, 23.3, 32.6, 32.9, 57.7, 61.7, 70.1, 71.5, 82.4, 82.6, 127.6, 127.7, 129.1, 129.3, 129.5, 135.9, 136.2, 169.6, 170.7 ppm; MS (EI): m/z: 464 [M^+].

Bis-(*R*)-MPA ester of (*S*)-3-chloropropane-1,2-diol ((*R*)-12): $[\alpha]_D$=+66.55 (c=2.92 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=3.25 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.32 (dd, J=6.0 Hz, 11.5 Hz, 1H), 3.39 (s, 3H), 3.40 (s, 3H), 4.24 (dd, J=5.6 Hz, 11.9 Hz, 1H), 4.48 (dd, J=4.1 Hz, 12.2 Hz, 1H), 4.64 (s, 1H), 4.74 (s, 1H), 5.09–5.18 (m, 1H), 7.31–7.44 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=42.1, 57.7, 57.7, 62.9, 71.4, 78.0, 82.4, 82.6, 127.5, 127.6, 127.8, 129.1, 129.1, 129.2, 129.3, 136.2, 136.3, 170.2, 170.4 ppm; MS (EI): m/z: 406 [M^+].

Bis-(*S*)-MPA ester of (*S*)-3-chloropropane-1,2-diol ((*S*)-12): $[\alpha]_D$=−73.96 (c=8.24, $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=3.33 (s, 3H), 3.36 (s, 3H), 3.44 (dd, J=5.4 Hz, 11.9 Hz, 1H), 3.52 (dd, J=5.4 Hz, 11.9 Hz, 1H), 4.09 (dd, J=6 Hz, 11.9 Hz, 1H), 4.29 (dd, J=4.1 Hz, 12.1 Hz, 1H), 4.55 (s, 1H), 4.78 (s, 1H), 5.17–5.25 ppm (m, 10H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=41.6, 57.7, 57.8, 62.7, 71.4, 82.5, 82.6, 127.5, 127.6, 127.8, 129.1, 129.1, 129.2, 129.3, 136.1, 136.3, 170.1, 170.5 ppm; MS (EI): m/z: 406 [M^+].

Bis-(*R*)-MPA ester of (*Z*)-3-benzyloxyimine-3-deoxy-1,2-*O*-isopropyliden-α-D-glucofuranose ((*R*)-13): $[\alpha]_D$=+52.85 (c=0.28 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.21 (s, 3H), 1.27 (s, 3H), 3.34 (s, 3H), 3.36 (s, 3H), 4.08 (dd, J=5.2 Hz, 11.7 Hz, 1H), 4.19 (dd, J=7.0 Hz, 11.7 Hz, 1H), 4.21 (d, J=4.7 Hz, 1H), 4.57 (s, 1H), 4.63 (s, 1H), 4.90 (d, J=4.1 Hz, 1H), 4.94 (d, J=3.5 Hz, 1H), 5.04 (br s, 2H), 5.47–5.52 (m, 1H), 7.29–7.38 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=27.5, 27.6, 57.5, 62.7, 73.0, 76.6, 77.7, 78.2, 82.3, 82.5, 104.4, 113.9, 127.5, 127.8, 128.7, 128.9, 129.1, 129.5, 136.0, 136.9, 151.8, 169.5, 170.2 ppm; MS (EI): m/z: 620 [M^+].

Bis-(*S*)-MPA ester of (*Z*)-3-benzyloxyimine-3-deoxy-1,2-*O*-isopropyliden-α-D-glucofuranose ((*S*)-13): $[\alpha]_D$=+245.30 (c=0.075 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.32 (s, 3H), 1.37 (s, 3H), 3.29 (s, 3H), 3.31 (s, 3H), 3.83 (dd, J=8.2 Hz, 11.7 Hz, 1H), 4.21 (dd, J=5.7 Hz, 11.7 Hz, 1H), 4.44 (s, 1H), 4.73 (s, 1H), 4.85 (d, 3.5 Hz, 1H), 5.15 (br s, 2H), 5.15–5.19 (m, 1H), 5.54 (d, J=4.7 Hz, 1H), 5.60–5.65 (m, 1H), 7.28–7.42 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=27.4, 57.4, 62.7, 71.6, 76.3, 78.1, 82.0, 82.2, 104.5, 113.9, 126.9, 127.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 135.7, 136.6, 156.6, 157.6, 169.6 ppm; MS (EI): m/z: 620 [M^+].

Bis-(*R*)-MPA ester of (*E*)-3-benzyloxyimine-3-deoxy-1,2-*O*-isopropyliden-α-D-glucofuranose [(*R*)-14]: $[\alpha]_D$=+107.09 (c=0.31 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.28 (s, 3H), 1.31 (s, 3H), 3.35 (s, 3H), 3.38 (s, 3H), 4.17 (dd, J=4.7 Hz, 11.7 Hz, 1H), 4.34 (dd, J=7.0 Hz, 11.7 Hz, 1H), 4.45 (d, J=4.1 Hz, 1H), 4.48 (s, 1H), 4.55 (br s, 1H), 4.68 (s, 1H), 4.77 (d, J=4.6 Hz, 1H), 5.06 (d, J=12 Hz, 1H), 5.12 (d, J=12 Hz, 1H), 5.30–5.37 (m, 1H), 7.19–7.38 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=27.4, 57.5, 62.0, 72.0, 74.2, 76.1, 82.2, 82.3, 82.4, 104.6, 113.4, 127.4, 127.5, 127.7, 127.8, 128.3, 128.6, 128.9, 129.0, 129.1, 136.0, 136.3, 137.7, 155.9, 169.3, 170.2 ppm; MS (EI): m/z: 620 [M^+].

Bis-(*S*)-MPA ester of (*E*)-3-benzyloxyimine-3-deoxy-1,2-*O*-isopropyliden-α-D-glucofuranose ((*S*)-14): $[\alpha]_D$=+188.40 (c=0.26 in $CHCl_3$); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.36 (s, 3H), 1.42 (s, 3H), 3.29 (s, 3H), 3.33 (s, 3H), 3.97 (dd, J=8.2 Hz, 12.3 Hz, 1H), 4.25 (dd, J=3.5 Hz, 12.3 Hz, 1H), 4.48 (s, 1H), 4.72 (s, 1H), 4.81 (d, J=2.3 Hz, 1H), 5.01 (d, J=3.5 Hz, 1H), 5.13 (d, J=12.3 Hz, 1H), 5.17 (d, J=12.3 Hz, 1H), 5.38–5.43 (m, 1H), 5.47 (d, J=4.1 Hz, 1H), 7.23–7.41 ppm (m, 15H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=27.4, 57.5, 62.2, 72.1, 74.1, 76.1, 82.2, 82.6, 104.7, 104.8, 109.3, 113.7, 127.1, 127.2, 127.3, 127.4, 127.5, 127.8, 128.2, 128.4, 128.6, 128.8, 128.9, 129.0, 129.1, 137.5, 155.9, 169.9, 170.2 ppm; MS (EI): m/z: 620 [M^+].

Bis-acetate ester of (*S*)-propanediol (15): $[\alpha]_D$=−14.7 (c=0.15 in CH_3OH); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.25 (d, J=6.6 Hz, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 4.05 (dd, J=6.7 Hz, 11.9 Hz, 1H), 4.17 (dd, J=3.6 Hz, 11.9 Hz, 1H), 5.07–5.19 ppm (m, 1H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=16.4, 20.8, 21.2, 66.1, 68.2, 170.5, 170.8 ppm; MS (EI): m/z: 160 [M^+].

(*R*)-MPA ester of (*S*)-1-acetoxy-2-propanol ((*R*)-16): $[\alpha]_D$=−36.92 (c=0.26 in CH_3OH); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.33 (d, J=6.7 Hz, 3H), 1.99 (S, 3H), 3.42 (s, 3H), 4.03 (dd, J=7.3 Hz, 11.9 Hz, 1H), 4.18 (dd, J=3.3 Hz, 11.8 Hz, 1H), 4.77 (S, 1H), 5.14–5.25 (m, 1H), 7.33–7.46 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=16.0, 20.6, 57.3, 65.8, 66.2, 69.1, 82.6, 127.1, 127.2, 128.5, 128.6, 128.7, 136.1, 170.1, 170.6 ppm; MS (EI): m/z: 266 [M^+].

(*S*)-MPA ester of (*S*)-1-acetoxy-2-propanol ((*S*)-16): $[\alpha]_D$=+52 (c=0.32 in CH_3OH); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.27 (d, J=6.4 Hz, 3H), 1.79 (s, 3H), 3.42 (s, 3H), 3.97 (dd, J=7.3 Hz, 11.9 Hz, 1H), 4.02 (dd, J=3.9 Hz, 11.9 Hz, 1H), 4.76 (s, 1H), 5.13–5.26 (m, 1H), 7.32–7.46 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=16.3, 20.3, 57.2, 65.7, 66.4, 67.8, 68.9, 82.3, 82.4, 127.1, 127.2, 128.5, 128.6, 128.7, 136.2, 170.1, 170.5 ppm; MS (EI): m/z: 266 [M^+].

(*R*)-MPA ester of (*S*)-2-acetoxypropanol ((*R*)-17): $[\alpha]_D$=+21.5 (c=1.19 in CH_3OH); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.13 (d, J=6.6 Hz, 3H), 1.92 (s, 3H), 3.41 (s, 3H), 4.12 (dd, J=6.3 Hz, 11.7 Hz, 1H), 4.20 (dd, J=3.8 Hz, 11.6 Hz, 1H), 4.78 (s, 1H), 4.97–5.09 (m, 1H), 7.26–7.46 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ 16.2, 20.9, 29.7, 57.3, 66.2, 66.4, 67.8, 67.9, 82.3, 82.4, 127.0, 128.5, 128.6, 135.9, 170.0, 170.1 ppm; MS (EI): m/z: 266 [M^+].

(*S*)-MPA ester of (*S*)-2-acetoxypropanol ((*S*)-17): $[\alpha]_D$=−9.5 (c=0.86 in CH_3OH); ^{1}H NMR (250.17 MHz, $CDCl_3$): δ=1.14 (d, J=6.6 Hz, 3H), 1.88 (s, 3H), 3.42 (s, 3H), 4.11 (dd, J=6.6 Hz, 11.6 Hz, 1H), 4.18 (dd, J=3.8 Hz, 11.9 Hz, 1H), 5.03–5.16 (m, 1H), 7.30–7.46 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): δ=16.2, 20.9, 29.4, 57.3, 66.2, 66.4, 67.8,

67.9, 82.3, 82.4, 127.2, 128.6, 128.7, 136.0, 170.2, 170.3 ppm; MS (EI): *m/z*: 266 [M^+].

(2*S*)-1{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-propanol (18): $[\alpha]_D = +7.1$ ($c = 8.81$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 0.02$ (s, 6H), 0.86 (s, 9H), 1.04 (d, $J = 6.4$ Hz, 3H), 2.58 (d, $J = 2.9$ Hz, 1H), 3.31 (dd, $J = 7.6$, 9.3 Hz, 1H), 3.53 (dd, $J = 3.5$, 9.9 Hz, 1H), 3.70–3.82 ppm (m, 1H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = -5.5$, 18.2, 25.8, 67.8, 68.5 ppm; MS (EI): *m/z*: 190 [M^+].

(*R*)-MPA ester of (2*S*)-1{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-propanol ((*R*)-19): $[\alpha]_D = -33.4$ ($c = 3.48$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = -0.02$ (s, 6H), 0.82 (s, 9H), 1.01 (d, $J = 6.4$ Hz, 3H), 3.35 (s, 3H), 3.53 (dd, $J = 4.7$ Hz, 10.7 Hz, 1H), 3.57 (dd, $J = 5.2$ Hz, 10.6 Hz, 1H), 4.67 (s, 1H), 4.88–5.00 (m, 1H), 7.20–7.40 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$) $\delta = -5.5$, 15.8, 25.7, 57.3, 65.3, 72.2, 82.5, 127.1, 128.4, 136.2, 170.2 ppm; MS (EI): *m/z*: 338 [M^+].

(*S*)-MPA ester of (*S*)-1{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-propanol [(*S*)-19]: $[\alpha]_D = +24.7$ ($c = 3.88$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = -0.14$ (s, 3H), -0.13 (s, 3H), 0.74 (s, 9H), 1.14 (d, $J = 6.4$ Hz, 3H), 3.33 (s, 3H), 3.40 (dd, $J = 4.7$ Hz, 10.5 Hz, 1H), 3.47 (dd, $J = 5.8$ Hz, 10.5 Hz, 1H), 4.66 (s, 1H), 4.86–4.97 (m, 1H), 7.20–7.38 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = -5.7$, 16.1, 25.7, 57.2, 65.1, 72.2, 82.7, 127.1, 128.4, 136.2, 170.2 ppm; MS (EI): *m/z*: 338 [M^+].

2-(*R*)-MPA ester of (*S*)-propane-1,2-diol ((*R*)-20): $[\alpha]_D = -44.8$ ($c = 2.06$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.11$ (d, $J = 6.4$ Hz, 3H), 3.40 (s, 3H), 3.58–3.68 (m, 2H), 4.79 (s, 1H), 4.97–5.07 (m, 1H), 7.30–7.45 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 15.6$, 57.2, 65.3, 72.8, 82.5, 127.0, 128.5, 128.6, 136.0, 170.6 ppm; MS (EI): *m/z*: 224 [M^+].

2-(*S*)-MPA ester of (*S*)-propane-1,2-diol ((*S*)-20): $[\alpha]_D = +56.1$ ($c = 2.08$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.23$ (d, $J = 6.4$ Hz, 3H), 3.41 (s, 3H), 3.46–3.55 (m, 2H), 4.78 (s, 1H), 4.96–5.05 (m, 1H), 7.36–7.46 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 15.9$, 57.2, 65.3, 72.8, 82.6, 127.0, 128.7, 128.8, 136.3, 170.4 ppm; MS (EI): *m/z*: 224 [M^+].

(*R*)-MPA ester of (*S*)-2-hydroxypropanal ((*R*)-21): $[\alpha]_D = -28.0$ ($c = 1.49$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.32$ (d, $J = 7.1$ Hz, 3H), 3.45 (s, 3H), 4.85 (s, 1H), 5.10 (q, $J = 7.1$ Hz, 1H), 7.34–7.49 (m, 5H), 9.52 ppm (s, 1H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 13.8$, 57.4, 68.6, 75.1, 82.2, 127.3, 128.7, 128.9, 135.6, 170.0, 197.5 ppm; MS (EI): *m/z*: 222 [M^+].

(*S*)-MPA ester of (*S*)-2-hydroxypropanal [(*S*)-21]: $[\alpha]_D = +15.0$ ($c = 1.32$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.40$ (d, $J = 7.1$ Hz, 3H), 3.45 (s, 3H), 4.86 (s, 1H), 5.11 (q, $J = 7.1$ Hz, 1H), 7.32–7.50 (m, 5H), 9.35 ppm (s, 1H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 14.1$, 57.4, 68.6, 75.1, 82.3, 127.1, 128.6, 128.9, 135.7, 169.9, 197.8 ppm; MS (EI): *m/z*: 222 [M^+].

2-(*R*)-MPA ester of (*S*,*S*)-1,*d*-propane-1,2-diol ((*R*)-22): $[\alpha]_D = -24.6$ ($c = 1.14$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.11$ (d, $J = 6.4$ Hz, 3H), 3.40 (s, 3H), 3.62 (d, $J = 6.1$ Hz, 1H), 4.79 (s, 1H), 4.97–5.07 (m, 1H), 7.30–7.45 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 15.6$, 57.2, 65.3, 72.8, 82.5, 127.0, 128.5, 128.6, 136.0, 170.6 ppm; MS (EI): *m/z*: 225 [M^+].

2-(*S*)-MPA ester of (*S*,*S*)-1,*d*-propane-1,2-diol ((*S*)-22): $[\alpha]_D = +30.1$ ($c = 1.08$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.23$ (d, $J = 6.4$ Hz, 3H), 3.41 (s, 3H), 3.50 (d, $J = 7.4$ Hz, 1H), 4.78 (s, 1H), 4.96–5.05 (m, 1H), 7.36–7.46 ppm (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$): $\delta = 15.9$, 57.2, 65.3, 72.8, 82.6, 127.0, 128.7, 128.8, 136.3, 170.4 ppm; MS (EI): *m/z*: 225 [M^+].

Bis-(*R*)-MPA ester of (*S*,*S*)-1,*d*-propane-1,2-diol ((*R*)-23): $[\alpha]_D = -171.9$ ($c = 1.6$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.00$ (d, $J = 5.9$ Hz, 3H), 3.37 (s, 3H), 3.38 (s, 3H), 4.09 (d, $J = 5.9$ Hz, 1H), 6.61 (s, 1H), 4.69 (s, 1H), 5.03–5.12 (m, 1H), 7.28–7.40 ppm (m, 10H); MS (EI): *m/z*: 373 [M^+].

Bis-(*S*)-MPA ester of (*S*,*S*)-1,*d*-propane-1,2-diol ((*S*)-23): $[\alpha]_D = +168.9$ ($c = 1.4$ in CH_3Cl); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.15$ (d, $J = 6.6$ Hz, 3H), 3.33 (s, 3H), 3.35 (s, 3H), 3.88 (d, 7.3 Hz, 1H), 4.51 (s, 1H), 4.71 (s, 1H), 5.11–5.19 (m, 1H), 7.27–7.43 ppm (m, 10H); MS (EI): *m/z*: 373 [M^+].

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[1] a) B. M. Trost, J. L. Belletire, P. G. Goldleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S. Ponticello, S. L. Varga, J. P. Springer, *J. Org. Chem.* **1986**, *51*, 2370–2374; b) J. M. Seco, Sh. K. Latypov, E. Quiñoá, R. Riguera, *Tetrahedron* **1997**, *53*, 8541–8564; c) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519; d) G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143–2147; e) J. M. Seco, Sh. K. Latypov, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1997**, *62*, 7569–7574; f) Sh. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1996**, *61*, 8569–8577; g) "Determination of the Absolute Configuration of Biologically Active Compounds by the Modified Mosher's Method": T. Kusumi, I. Ohtani in *The Biology-Chemistry Interface* (Eds.: R. Cooper, J. K. Snyder), Dekker, New York, **1999**, pp. 103–137; h) T. Kusumi, T. Hamada, M. O. Ishitsuka, I. Othani, H. J. Kakisawa, *Org. Chem.* **1992**, *57*, 1033–1035; i) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096; j) I. Ohtani, T. Kusumi, M. O. Ishitsuka, H. Kakisawa, *Tetrahedron Lett.* **1989**, *30*, 3147–3150.

[2] $\Delta\delta^{RS}$ values are defined as the difference between the chemical shift for a given proton in the (*R*)-AMAA derivative (MPA and 9-AMA) and its chemical shift in the (*S*)-AMAA derivative (i.e., $\Delta\delta^{RS}L_1 = \delta L_1(R) - \delta L_1(S)$). For the MTPA derivatives, $\Delta\delta^{SR}$ is used instead of $\Delta\delta^{RS}$ values and calculated as the difference between the chemical shift in the (*S*)- and (*R*)-MTPA derivatives.

[3] a) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17–117; b) J. M. Seco, E. Quiñoá, R. Riguera, *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925; c) J. M. Seco, E. Quiñoá, R. Riguera, *Tetrahedron: Asymmetry* **2000**, *11*, 2781–2791.

[4] a) Y. Takeuchi, H. Fujisawa, R. Noyori, *Org. Lett.* **2004**, *6*, 4607–4610; b) P. L. Rinaldi, *Prog. Nucl. Magn. Spectrosc.* **1982**, *15*, 291–352; c) "Nuclear Magnetic Resonance Analysis Using Chiral Derivatives": S. Yamaguchi in *Asymmetric Synthesis*, *Vol. 1* (Ed.: J. D. Morrison), Academic Press, New York, **1983**, pp. 125–152; d) G. Uray in *Houben-Weyl Methods in Organic Chemistry*, *Vol. 1* (Eds.: G. Helchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, New York, **1996**, p. 253; e) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**, p. 221; f) D. Parker, *Chem. Rev.* **1991**, *91*, 1441–1457.

[5] a) Sh. K. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Am. Chem. Soc.* **1998**, *120*, 877–882; b) J. M. Seco, E. Quiñoá, R. Riguera, *Tetrahedron* **1999**, *55*, 569–584; c) R. T. Williamson, A. Boulanger, A. Vulpanovici, M. A. Roberts, W. H. Gerwick, *J. Org. Chem.* **2002**, *67*, 7927–7936; d) H. Yamase, T. Ooi, T. Kusumi, *Tetrahedron Lett.* **1998**, *39*, 8113–8116; e) B. López, E. Quiñoá, R. Riguera, *J. Am. Chem. Soc.* **1999**, *121*, 9724–9725; f) R. García, J. M. Seco, S. A. Vázquez, E. Quiñoá, R. Riguera, *J. Org. Chem.* **2002**, *67*, 4579–4589; g) M. Trujillo, E. Q. Morales, J. Vázquez, *J. Org. Chem.* **1994**, *59*, 6637–6642; h) S. Porto, J. Durán, J. M. Seco, E. Quiñoá, R. Riguera, *Org. Lett.* **2003**, *5*, 2979–2982; i) J. M. Seco, L. H. Tseng, M. Godejohann, E. Quiñoá, R. Riguera, *Tetrahedron: Asymmetry* **2002**, *13*, 2149–2153.

[6] a) M. C. González, C. Lavaud, T. Gallardo, M. C. Zafra-Polo, D. Cortes, *Tetrahedron* **1998**, *54*, 6079–6088; b) Z. Gu, J. Zeng, X. P. Fang, T. Colman, M. Huo, J. L. McLaughlin, *J. Org. Chem.* **1994**, *59*, 5162–5172.

[7] J. M. Seco, M. Martino, E. Quiñoá, R. Riguera, *Org. Lett.* **2000**, *2*, 3261–3264.

[8] N. Harada, A. Saito, H. Ono, S. Murai, H. Y. Li, J. Gawronski, K. Gaworonska, T. Sugioka, H. Uda, *Enantiomer* **1996**, *1*, 119–138.
[9] H. Uzawa, Y. Nishida, H. Ohrui, H. Meguro, *J. Org. Chem.* **1990**, *55*, 116–122.
[10] a) J(H(1′),H(2′)) and δ of methylene protons for bis-(*R*)-MPA ester of (*S*)-1,2-propanediol: 3.2 Hz and 4.2 ppm for *pro-S*-H(1′) and 6.9 Hz and 3.9 ppm for *pro-R*-H(1′), respectively; b) J(H(1′),H(2′)) and δ of methylene protons for bis-(*S*)-MPA ester of (*S*)-propane-1,2-diol: 3.5 Hz and 4.2 ppm for *pro-S*-H(1′) and 6.5 Hz and 4.1 ppm for *pro-R*-H(1′)-*pro-R*, respectively.
[11] D. Leigh, R. P. Martin, J. P. Smart, A. M. Truscello, *J. Chem. Soc. Chem. Commun.* **1994**, *11*, 1373–1374.
[12] A. T. Khan, E. Mondal, *Synlett* **2003**, 694–698.
[13] J. Lindberg, S. C. Svensson, P. Phalsson, P. Konradsson, *Tetrahedron* **2002**, *58*, 5109–5117.
[14] G. Keck, D. Krishnamurthy, *J. Org. Chem.* **1996**, *61*, 7638–7639.
[15] Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.
[16] From the NMR point of view in the bis-(*R*)-MPA esters conformers *sp*-I and *sp*-II are practically identical, the only difference is the slightly different orientation in the carbonyl group ($\pm 30°$).
[17] S. Jonsson, H. Adolfsson, J.-E. Bäckvall, *Chem. Eur. J.* **2003**, *9*, 2783–2788.
[18] Sh. K. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1995**, *60*, 504–515.

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