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Using a Combination of Magnetic Anisotropic Effects for the Configurational Assignment of Amino Alcohols

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In memory of José Manuel Concellón

Abstract: The combined magnetic anisotropic effects generated by two auxiliary moieties of 2-methoxy-2-phenylacetic acid (MPA), introduced on two families of terminal 1,2-amino alcohols (*prim*/*sec* and *sec*/*prim*), determine the signs of the $\Delta\delta^{RS}$ parameters—the differences in chemical shifts between the bis-(*R*)-MPA and the bis-(*S*)-MPA esters—of the hydrogen atoms placed at both sides of the stereogenic carbon atoms, thereby allowing the determination of the absolute configuration of those heterobifunctional compounds. Theoretical (AM1, B3LYP) and experimental (CD, ^3J, low-temperature NMR spectroscopy, isotopic labeling) studies, together with testing with a number of representative compounds, permit one to establish the foundations of this methodology.

Keywords: amino alcohols · absolute configuration · chirality · magnetic anisotropic effects · NMR spectroscopy

Introduction

Ever since it was first described as a physical phenomenon in the late 1930s,[1] NMR spectroscopy has become a scientific panacea that gives answers and solutions to a large number of questions and difficulties that researchers have to face in day-to-day work. Among the problems resolved by NMR spectroscopy, the establishment of absolute configurations—which Mosher and Trost pioneered[2]—stands out as one of the recent successes of this spectroscopic tool and has been applied to a wide range of chiral substrates, mainly to monofunctional compounds.[3]

Most of the methods that have been developed are based on the transformation of the substrate of unknown configuration in a pair of diastereomeric derivatives ("double derivatization") by means of the two enantiomers of an adequate chiral derivatizing agent (CDA). The signs of the $\Delta\delta^{RS}$ parameters—the differences in chemical shifts between the bis-(*R*)-MPA (MPA = 2-methoxy-2-phenylacetic acid) and the bis-(*S*)-MPA derivatives—obtained by comparison of the resulting ^{1}H NMR spectra allow one to determine the spatial position of the substituents around the stereogenic center. Nevertheless, approaches that require just the use of one enantiomer of the CDA ("single derivatization") are also available based on the controlled manipulation of the conformational equilibria in solution.[4]

The applications toward polyfunctional compounds have been developed more recently, and they include molecules bearing the same (diols,[5] triols[6]) or different (some types of amino alcohols[7]) groups acting as "handles" to link the CDAs. In these cases, a profound knowledge of the effects caused by the combined action of different anisotropic groups is necessary.

We now present a general methodology for both families of terminal 1,2-amino alcohols[8] (*sec*/*prim* and *prim*/*sec*; Figure 1) based on the formation of their bis-MPA derivatives (amide and ester) and interpretation of the signs of the

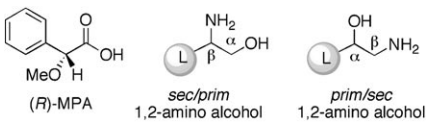

Figure 1. (*R*)-MPA and general structures of *sec*/*prim* and *prim*/*sec* 1,2-amino alcohols.

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$\Delta\delta^{RS}$ parameters obtained from the hydrogen atoms around the stereogenic center: $CH_2(\alpha,\beta)$ and the **L** group.[9] The challenge presented by these substrates to establish a general method for configurational assignment is more complex than in the case of terminal 1,2-diols[5h,i] owing to the presence of both amide and ester linkages in their bis-derivatives and to the known different conformational behavior of MPA esters versus MPA amides.[3d,e]

Results and Discussion

$\Delta\delta^{RS}$ Signs and Values

Two simple *sec*/*prim* and *prim*/*sec* 1,2-amino alcohols ((*S*)-2-aminopropan-1-ol (**1**) and (*S*)-1-aminopropan-2-ol (**11**), respectively) were chosen as model compounds and each one was bis-derivatized with (*R*)- and (*S*)-MPA to study their NMR spectroscopic behavior. In each case, the two MPA units were introduced simultaneously in single reactions.[10] Then $\Delta\delta^{RS}$ parameters for the methyl and methylene groups were calculated and, in each case, a coherent set of signs was obtained: opposite at both sides of the stereogenic center (+0.14 and −0.12/−0.09 for CH_3 and CH_2 in **1**; −0.18 and +0.10/+0.10 for CH_3 and CH_2 in **11**; Figure 2).

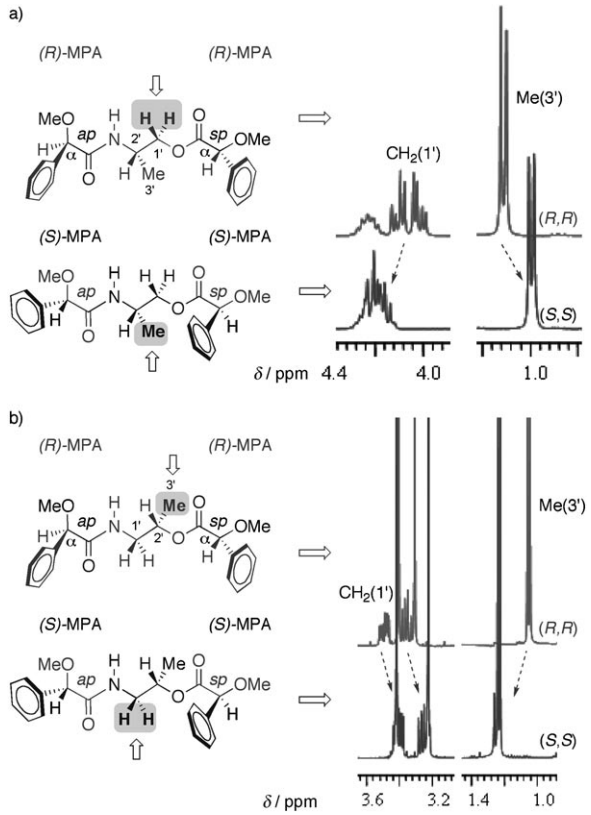

Figure 2. Partial ^{1}H NMR spectra of the bis-MPA derivatives of a) (*S*)-2-aminopropan-1-ol (**1**) and b) (*S*)-1-aminopropan-2-ol (**11**). The shielded protons and the main *sp*/*ap* conformers at the auxiliary sections are highlighted in each case.

To see if these results could be generalized to a broader set of *sec*/*prim* and *prim*/*sec* 1,2-amino alcohols, experiments were carried out with compounds **1**–**10** and **11**–**18** of known absolute configuration. The results are shown in Figure 3a and Figure 4a.

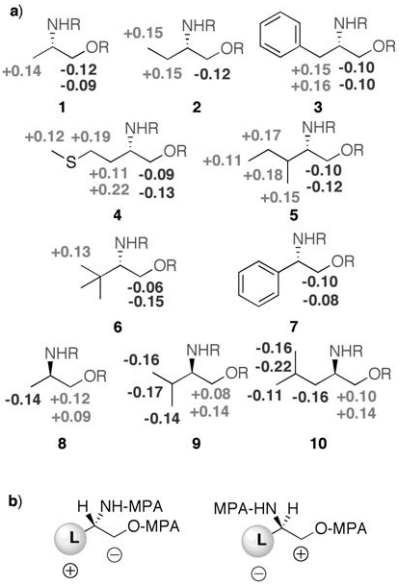

Figure 3. a) $\Delta\delta^{RS}$ signs and values for bis-MPA derivatives of *sec*/*prim* 1,2-amino alcohols **1**–**10** (R = MPA). b) $\Delta\delta^{RS}$ signs and 3D models for assignment.

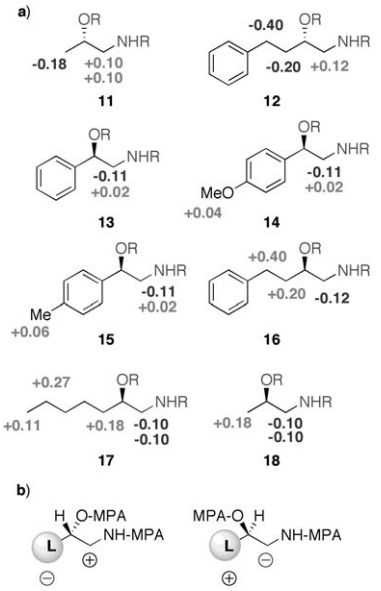

Figure 4. a) $\Delta\delta^{RS}$ signs and values for bis-MPA derivatives of *prim*/*sec* 1,2-amino alcohols **11**–**18** (R = MPA). b) $\Delta\delta^{RS}$ signs and 3D models for assignment.

In all cases, the pattern of the signs for the CH_2 and **L** groups suggested that there was a correlation between the $\Delta\delta^{RS}$ signs and the absolute configuration in both families of compounds. Even the presence of bulky groups (i.e., **6**) did

not disrupt the pattern. In the case of benzylic amino alcohols (**7**, **13**–**15**), despite the presence of the nearby phenyl rings that could be expected to disturb the influence of the two MPA units, the method can also be applied: in **7**, the signs are the expected ones, whereas in the *prim*/*sec* compounds **13**–**15**, the diastereotopic methylene protons show opposite signs but the assignment still can be carried out with total confidence because the proton experiencing the largest shift of the pair does behave according to the expected pattern and is the one that must be taken into account.[11] Three-dimensional models to place in space the amino alcohols according to the $\Delta\delta^{RS}$ signs are shown in Figure 3b and Figure 4b.

Anisotropic Contributions of the CDAs

When NMR spectroscopic methodologies for configurational assignment are employed with polyfunctional compounds, the anisotropic effects caused by the attached CDAs have to be considered in a combined manner. Therefore, a deep understanding of the anisotropic contributions of each CDA unit and the main conformational species present in solution is a must to envision how the "shielding" and "deshielding" cones—mainly generated by the aryl systems at the CDAs—influence the protons around the stereogenic centers.

The ^{1}H NMR spectra of appropriate MPA and acetyl derivatives of *sec*/*prim* and *prim*/*sec* model amino alcohols (**1** and **11**) illustrate the influence of each MPA on the different protons present in the substrate (diacetyl derivatives taken as standards, Figures 5 and 6). In both types of amino alcohols, the MPAs at the amino and hydroxy groups modulate each other's anisotropic effect, so the overall result on the substrate is a combination of both influences.

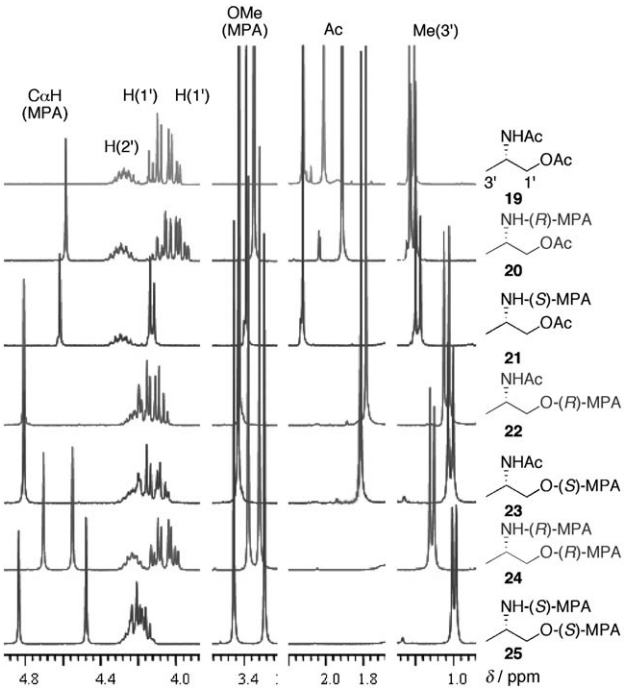

Figure 5. Study of the anisotropic effects caused by the CDAs on model *sec*/*prim* 1,2-amino alcohol **1**.

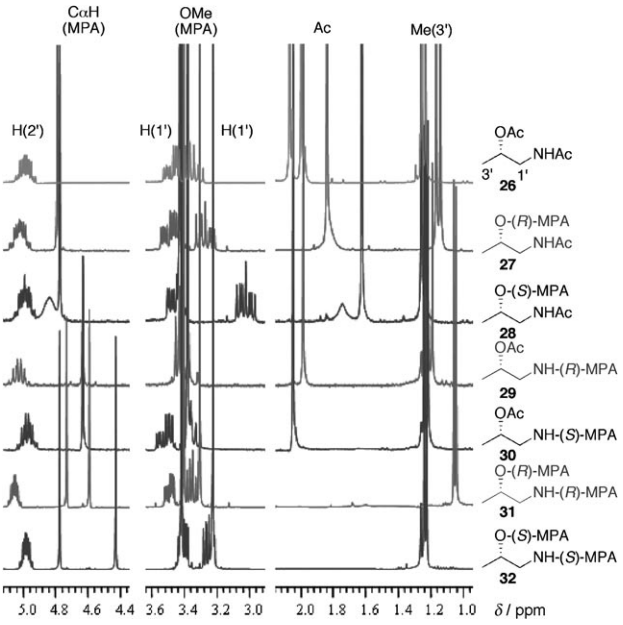

Figure 6. Study of the anisotropic effects caused by the CDAs on model *prim*/*sec* 1,2-amino alcohol **11**.

The experiments show that the anisotropic contributions of the two MPA moieties on the substrate are unique to each particular situation owing to the different conformational combinations present in the two auxiliaries and the amino alcohol part. As a result, the overall anisotropic contributions are not linear.

For example, let us look at the behavior of Me(3′) (amino alcohol **1**) with different auxiliaries (Figure 5). Diacetyl **19** presents just the effects of inserting amide and ester linkages on the substrate ($\delta = 1.18$ ppm, Me(3′)). In **20**, the (*R*)-MPA amide practically does not affect Me(3′) (slight deshielding, $\delta = 1.22$ ppm), whereas the same auxiliary as ester (in **22**) shifts its signal upfield dramatically ($\delta = 1.03$ ppm). When two (*R*)-MPA auxiliaries are introduced (**24**), the shift for the methyl seems to represent a compromise between both values ($\delta = 1.11$ ppm) and not only the effect of the ester. At first glance, and to explain these results, the known predominant antiperiplanar (*ap*, see below) form for MPA amides in **20** justifies the lack of shielding at Me(3′) (as expected, the shielding does affect the other side of the molecule; see Figure 7a), whereas the large degree of rotational freedom experienced by the ester moiety in **22** projects the shielding in a less selective but more intense way over all the groups, including Me(3′) (see Figure 7b). When both MPAs are present, the one placed on the amine modulates the strong shielding projected by the other unit (on the alcohol), thus making the overall distribution of the anisotropic effects more selective (Figure 7c).

On the other hand, the introduction of (*S*)-MPA shields the Me(3′) signal to some extent ($\delta = 1.17$ ppm) as amide (**21**) and considerably ($\delta = 1.01$ ppm) as ester (**23**). However,

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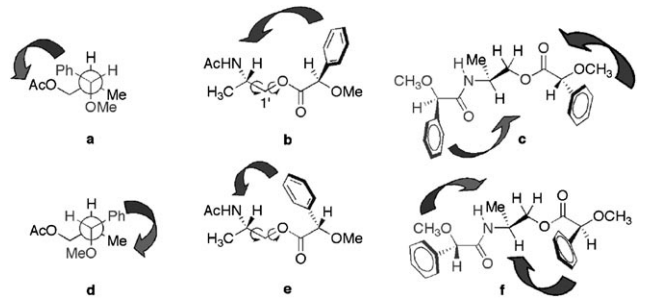

Figure 7. Shielding effects transmitted by the phenyl groups of the a–c) (*R*)-MPA and d–f) (*S*)-MPA (*S*)-2-aminopropan-1-ol (**1**) derivatives.

this time in the bis-derivative **25** the signal ($\delta = 0.97$ ppm) does not correspond to the middle ground, but rather to the predominant ester influence. Again, the *ap* form of the amide (Figure 7 d) and the rotational freedom of the ester (Figure 7 e) help to explain the experimental outcome, although in this case the combination of both effects (Figure 7 f) does not result in a modulation as effective as in the case of the (*R*)-MPAs.

A parallel analysis can be performed for the *prim*/*sec* 1,2-amino alcohols (spectra in Figure 6). In these compounds, the predominant synperiplanar (*sp*) form for the secondary ester modulates the terminal amide (Figure 8), the effect of

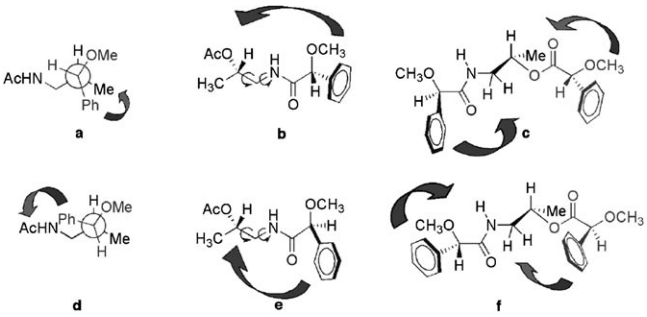

Figure 8. Shielding effects transmitted by the phenyl groups of a–c) the (*R*)-MPA and d–f) (*S*)-MPA (*S*)-1-aminopropan-2-ol (**11**) derivatives.

which is less intense than those caused by the terminal esters in the *sec*/*prim* family. Once more, the final result is not a linear combination of the individual effects.

Consequently, this complexity found in the combined anisotropic effects of the MPA auxiliaries made it necessary to reach for a deeper understanding of the conformational scenario through additional conformational studies.

Conformational Analysis

As stated above, a good knowledge of the main conformational species present in solution is necessary to justify the empirical data. The studies performed to reach this goal include CD experiments; constant coupling (^3J) analysis; selective deuteration; mono- and bidimensional, and room- and low-temperature NMR spectroscopic experiments; and theoretical calculations (AM1, B3LYP). (*S*)-2-Aminopropan-1-ol (**1**) and (*S*)-1-aminopropan-2-ol (**11**) were chosen as model compounds together with their MPA, benzoyl, and acetyl derivatives. A summary of the main results follows.

Main Conformations in the Amino Alcohol Substructures

a) The $C_{1'}$–$C_{2'}$ bond was studied by CD analysis of the corresponding dibenzoyl derivatives **33** and **34** (Figure 9). Two Cotton effects (237 ($\Delta\varepsilon = 22.57$ cm^{2}mol^{-1}) and 215 nm ($\Delta\varepsilon = -11.17$ cm^{2}mol^{-1}); 238 ($\Delta\varepsilon = 20.40$ cm^{2}mol^{-1}) and 226 nm ($\Delta\varepsilon = -8.41$ cm^{2}mol^{-1}); for **33** and **34**, respectively) indicated a positive angle between the benzoyl groups in the predominant conformer (*gt*, angle $\approx 60°$)[12] in each case and ruling out other possibilities (*tg*, *gg*; Figure 9).

The ^3J values found in the dibenzoyl compounds agree with a prevalence of the *gt* conformers (Figure 9), and similar ^3J values were found in most of the MPA derivatives of the amino alcohols studied, thus suggesting a prevalence of the *gt* conformation in the majority of the cases (Table 1). Semiempirical calculations (AM1) also proposed the *gt* conformer as the most stable one.

The constant coupling studies also allowed the assignment of the diastereotopic methylene hydrogen atoms in the spectra. According to the CD and AM1 results, in each pair of derivatives the pro-*R* must be the one with larger ^3J value (angle $\approx 180°$) and the pro-*S* the one with smaller value

Table 1. Vicinal ^3J of dibenzoyl and MPA derivatives of amino alcohols **1**–**18**.

Derivative	No.[a]	^3J [Hz]		No.[d]	^3J [Hz]	
		H(1′)[b]	H(1′)[c]		H(1′)[b]	H(1′)[c]
dibenzoyl	**1** (**33**)	6.1	4.3	**11** (**34**)	3.4	7.9
R[f]	**1** (**24**)	5.2	4.6	**11** (**31**)	3.5	7.2
S[g]	**1** (**25**)	_[e]	_[e]	**11** (**32**)	3.5	7.5
R[f]	**2**	6.9	_[e]	**12**	_[e]	_[e]
S[g]	**2**	5.6	3.8	**12**	_[e]	_[e]
R[f]	**3**	4.8	4.7	**13**	3.9	8.7
S[g]	**3**	4.6	4.0	**13**	4.3	7.8
R[f]	**4**	4.9	4.4	**14**	4.4	8.9
S[g]	**4**	4.9	3.4	**14**	4.6	7.8
R[f]	**5**	5.8	3.8	**15**	4.0	8.8
S[g]	**5**	6.2	3.6	**15**	4.3	7.8
R[f]	**6**	7.6	3.9	**16**	_[e]	_[e]
S[g]	**6**	3.5	8.4	**16**	_[e]	_[e]
R[f]	**7**	6.4	4.9	**17**	3.4	7.1
S[g]	**7**	6.9	4.7	**17**	3.5	7.2
R[f]	**8**	_[e]	_[e]	**18**	3.5	7.5
S[g]	**8**	5.2	4.6	**18**	3.5	7.2
R[f]	**9**	6.2	3.8	–	–	–
S[g]	**9**	5.9	4.1	–	–	–
R[f]	**10**	4.1	_[e]	–	–	–
S[g]	**10**	4.7	4.5	–	–	–

[a] *sec*/*prim* 1,2-Amino alcohols. The numbers refer to general structures in Figure 3. Specific numbering given in some cases is shown in parentheses. [b] Low-field proton. [c] High-field proton. [d] *prim*/*sec* 1,2-Amino alcohols. The numbers refer to general structures in Figure 4. Specific numbering given in some cases is shown in parentheses. [e] Not measured owing to overlapping. [f] Bis-(*R*)-MPA derivative. [g] Bis-(*S*)-MPA derivative.

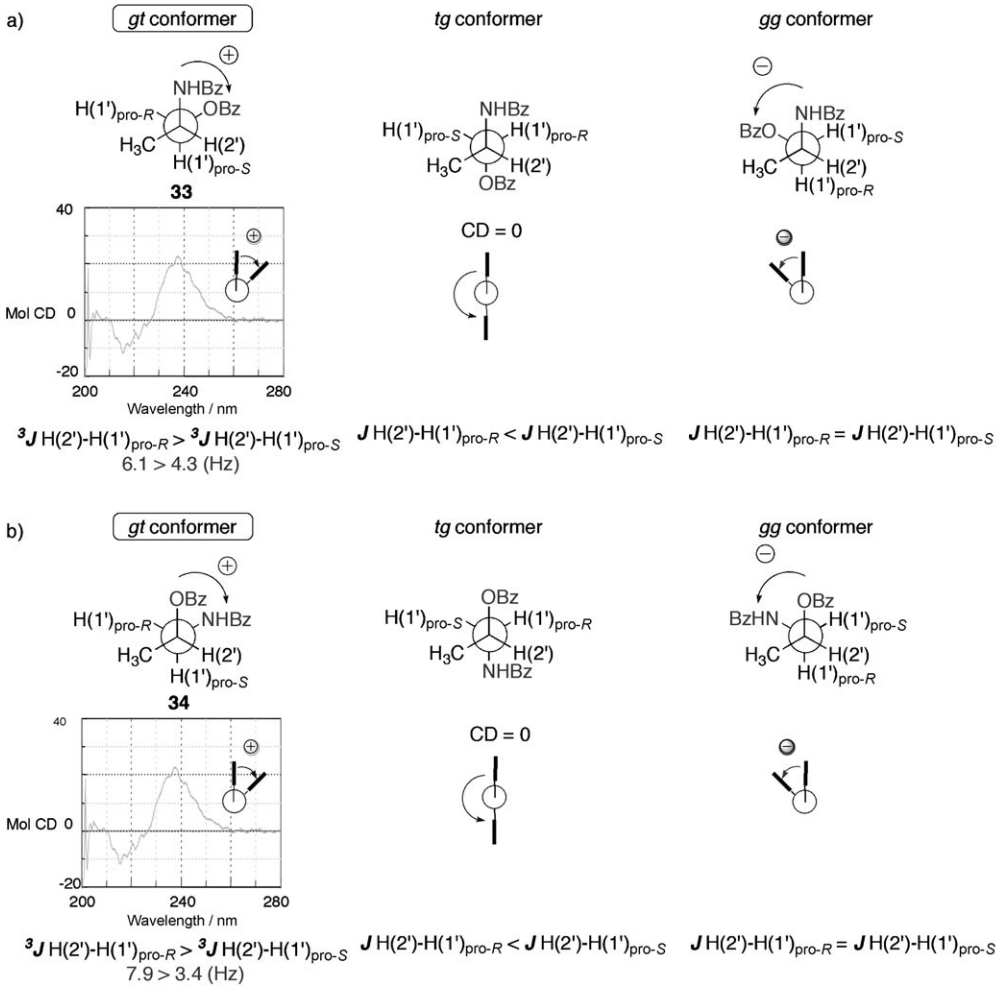

Figure 9. Main conformations, CD spectra, and ^3J values for dibenzoyl amino alcohols a) **33** and b) **34**.

(angle ≈ 60°). To confirm this assignment, the bis-MPA derivatives of (1*S*,2*S*)-1-[^{2}H]-2-aminopropan-1-ol (**41** and **42**, Scheme 1) were prepared by selective deuteration from (*S*)-2-aminopropan-1-ol (**1**). Their ^{1}H NMR spectra show the disappearance of the high-field double doublets (smaller ^3J) that correspond, consequently, to the "pro-*S*" hydrogen. b) The $C_{1'}$–O, $C_{1'}$–N bonds (in *sec*/*prim* and *prim*/*sec*, respectively) were studied by theoretical calculations (AM1 and DFT (B3LYP))[15] on model compounds (bis-MPA derivatives of **1** and **11**). In both cases, three main conformations arise (Figure 10), in which the nearby carbonyl group—in combination with the phenyl groups of the MPAs—plays a key role in the generation of different chemical environments for each of the methylene protons at $C_{1'}$, as was also observed in *prim*/*sec* 1,2-diols.[5i]

In both bis-(*R*) and bis-(*S*)-MPA derivatives of *sec*/*prim* amino alcohols ($C_{1'}$–O bond), conformation I is lower in energy (Figure 10). In any case, the differences in energy among conformers I–III are small (differences not larger than 1.69 Kcal mol^{-1} (B3LYP)) owing to the larger conformational flexibility of these systems. For its part, in the bis-(*R*)- and bis-(*S*)-MPA derivatives of *prim*/*sec* amino alcohols ($C_{1'}$–N bond), conformation II is lower in energy in the bis-(*R*) and I is lower in the bis-(*S*) derivative.[16] Again, the differences in energy among conformers I–III are small (not larger than 0.91 Kcal mol^{-1} (B3LYP)).

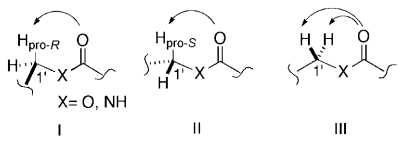

Figure 10. Main conformations on $C_{1'}$–O and $C_{1'}$–N bonds.

Main Conformations in the MPA Substructures

In *sec*/*prim* and *prim*/*sec* 1,2-amino alcohols bis-derivatized with (*R*)- and (*S*)-MPA, theoretical calculations show that the MPA amide substructures exhibit a conformational preference for the antiperiplanar (*ap*) conformers relative to the (O)C–C(OMe) bonds. With regards to the MPA ester substructures, the preference favors the synperiplanar (*sp*) con-

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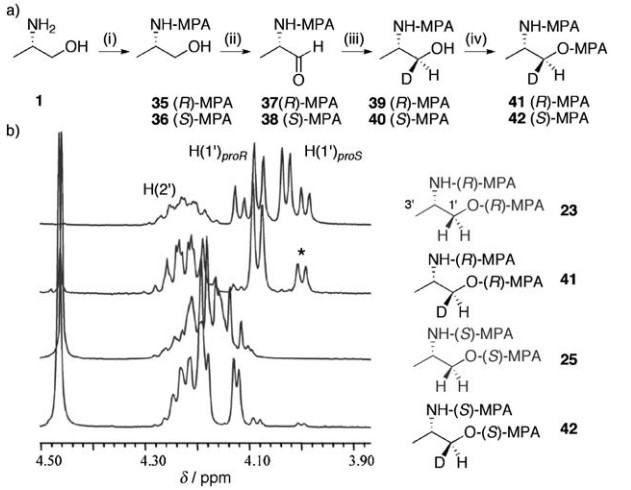

Scheme 1. a) Reagents and conditions: i) (*R*)- or (*S*)-MPA, *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC), dry CH_2Cl_2; ii) Dess–Martin oxidation;[13] iii) Bu_3SnD, (*S*)-BINOL (BINOL = 1,1′-bi-2-naphthol), $Ti(OiPr)_4$, trifluoroacetic acid (TFA), Et_2O, molecular sieves;[14] iv) (*R*)- or (*S*)-MPA, EDC, 4-dimethylaminopyridine (DMAP; cat.); dry CH_2Cl_2. b) Partial ^1H NMR spectra of the compounds shown. The asterisk points to the epimer at 2′ owing to partial racemization on (ii).

formers relative to the same bond (see a depiction of these forms in Figure 2).

These conformers that arise around the (O)C–C(OMe) bonds are a major cause of the overall anisotropic effects that affect the molecule.[9a] The conformations that emerge from the other bonds involved ($C_{1'}$–$C_{2'}$, $C_{1'}$–O, and $C_{1'}$–N), and mainly as a result of the larger rotational freedom and smaller conformational preference, are not so crucial for the final shielding/deshielding experienced by the substrate.

As a whole, the theoretical calculations mentioned lead us to propose low-energy conformers that, when taken as NMR spectroscopic representatives, match the experimental and selective shielding effects observed at both sides of the chiral centers of the amino alcohols, as those shown in Figure 2 for $CH_2(1')$ and Me(3′). The most significant low-energy conformations are shown in Figure 11. Low-temperature NMR spectroscopic experiments, recorded from 298 to 213 K, are in agreement with those conformational preferences.

Conclusion

The understanding of the magnetic influence on the substrate caused by the combination of the anisotropic effects originated by the aromatic rings of the chiral auxiliaries allows for the development of a methodology for the assignment of absolute configuration of two families of terminal 1,2-amino alcohols (*prim*/*sec* and *sec*/*prim*), based on double-derivatization procedures.

In the two cases, the chiral amino alcohol is bis-derivatized with the two enantiomers of MPA, followed by comparison of the ^1H NMR spectra of the amide/ester diastereomeric derivatives. The assignment can be easily performed by means of the $\Delta\delta^{RS}$ signs of the methylene and **L** groups placed at both sides of the chiral center, thus following the stereochemical models depicted in Figures 3b and 4b.

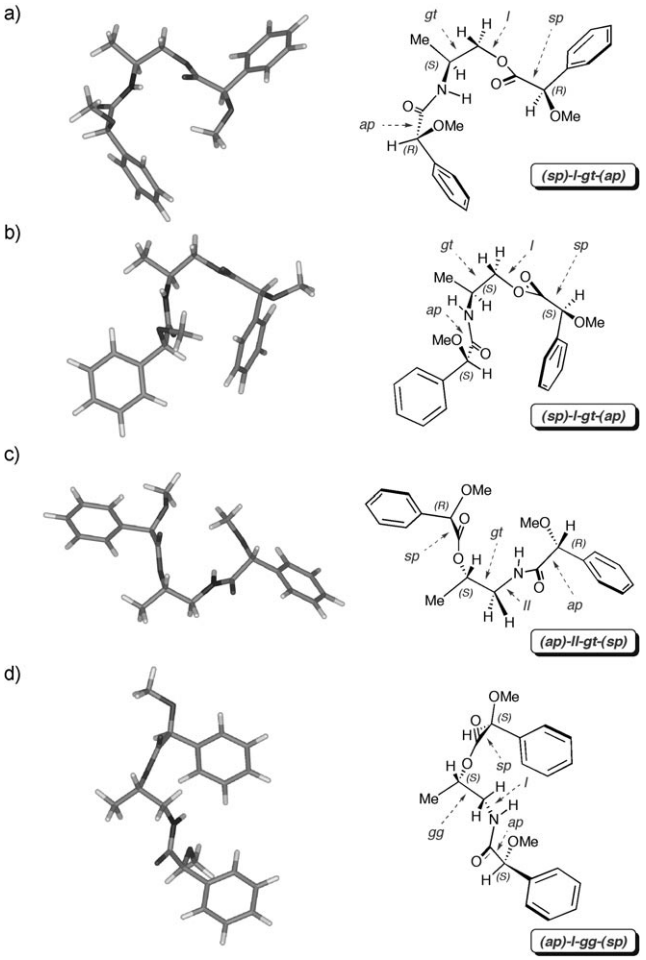

Figure 11. Low-energy conformer that is NMR spectroscopically representative of a) the bis-(*R*)-MPA derivative of (*S*)-2-aminopropan-1-ol (**1**) and b) its bis-(*S*)-MPA derivative. Low-energy conformer that is NMR spectroscopically representative of c) the bis-(*R*)-MPA derivative of (*S*)-1-aminopropan-2-ol (**11**) and d) its bis-(*S*)-MPA derivative.

The procedure has proven to be accurate with a number of amino alcohols of known configuration possessing diverse structures and is firmly supported by theoretical calculations and a variety of experimental evidences.

Experimental Section

General Derivatization Procedure

Bis-MPA derivatives of *prim*/*sec* and *sec*/*prim* 1,2-amino alcohols were prepared by treatment of the selected amino alcohol (1 equiv) with the corresponding (*R*)- and (*S*)-α-methoxy-α-phenylacetic acid (MPA; 2.2 equiv) in the presence of *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC; 2.2 equiv) and 4-dimethylaminopyridine (DMAP; catalytic amount) in dry CH_2Cl_2, under a nitrogen atmosphere. The reaction was stirred at room temperature for 3–8 h (TLC monitoring) until completion. Then the organic layer was sequentially washed with water, HCl

(1 M), water, saturated $NaHCO_3$, and water, then dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to obtain the bis-MPA derivative. Final purification was achieved by flash column chromatography on silica gel (230–400 mesh, elution with hexane/ethyl acetate mixtures, 90–95% yields after purification). All compounds were characterized by optical rotation, NMR (1D, 2D) spectroscopy, HRMS (EI), and elemental analysis.

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[8] *Secondary*/*primary* and *primary*/*secondary* (*sec*/*prim* and *prim*/*sec*) apply only to the carbon atoms to which the amino/hydroxy groups are linked. Sphingosines and epinephrines (adrenalines) are examples of compounds of biological interest that bear these substructures.

[9] Two approaches that do not make any use of $\Delta\delta^{RS}$ from the substrate and are based on the cross-interaction between auxiliaries—just $\Delta\delta^{RS}$ from the methoxy and methine groups of the MPAs—have been published recently. The method now described in this article is appropriate in cases in which the application of those previous approaches presents difficulties—that is, presence of extra methoxy groups in the substrate or overlapped methine signals—and is useful to double-check the configurational assignment. a) V. Leiro, J. M. Seco, E. Quiñoá, R. Riguera, *Org. Lett.* **2008**, *10*, 2729–2732; b) V. Leiro, J. M. Seco, E. Quiñoá, R. Riguera, *Org. Lett.* **2008**, *10*, 2733–2736.

[10] This approach avoids the use of protecting groups for the terminal primary group, thus making the experimental procedure much simpler.

[11] See the Supporting Information for a full explanation of the conformational equilibria that justifies the $\Delta\delta^{RS}$ signs in *prim*/*sec* benzylic amino alcohols.

[12] The *gt* conformer is defined as the one in which the benzoate is *gauche* to the benzamide and *trans* to the Me (*sec*/*prim*), or the benzamide is *gauche* to the benzoate and *trans* to the Me (*prim*/*sec*).

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[16] In this case, the lowest-energy conformer arises from a I conformation for the $C_{1'}$–N bond combined with a *gg* conformer for the $C_{1'}$–$C_{2'}$ bond.

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