Are Both the (*R*)- and the (*S*)-MPA Esters Really Needed for the Assignment of the Absolute Configuration of Secondary Alcohols by NMR? The Use of a Single Derivative

Shamil K. Latypov,† José M. Seco, Emilio Quiñoá, and Ricardo Riguera*

Contribution from the Departamento de Química Orgánica, Facultad de Química and Instituto de Acuicultura, Universidad de Santiago, E-15706, Santiago de Compostela, Spain

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Abstract: The absolute configuration of a secondary alcohol can be deduced from the ^{1}H NMR spectra of a single methoxyphenylacetic ester derivative [MPA, either the (*R*) or the (*S*)] recorded at two different temperatures. This new approach simplifies the current NMR-based methodologies, requiring just one derivatizing reaction, instead of two, and, correspondingly, half of the usual amount of sample. At low temperature, the relative population of the most stable *sp* conformer is increased and the resonances of the substituents of the alcohol (L_1/L_2), located under the shielding cone of the phenyl ring, are shifted upfield. At the same time, those protons under the shielding cone in the less populated *ap* conformer are shifted downfield. In this way, the spatial location of L_1/L_2 around the asymmetric center of the alcohol can be established comparing the ^{1}H NMR spectra both at room and low temperatures. Application of this finding to alcohols of known absolute configuration, including complex structures such as *cis*-androsterone, is presented.

Introduction

With increasing frequency, chemists worldwide face the need to work with very small amounts of compounds. Microscale methodologies are strongly welcomed in many research fields, particularly those where the amount of sample available is very limited. So, the search for new accurate elucidation techniques to be applied to minute amounts of a substrate is a continuous need in chemistry.

One of the most popular procedures to establish the absolute configuration of a chiral secondary alcohol or a primary α-substituted amine is the NMR approach, introduced by Raban and Mislow[1] and further developed by Mosher,[2a] Trost,[2b] and other researchers.[2c−f]

In this method, the substrate (i.e., alcohol or amine) of unknown absolute stereochemistry, (?)-A, is separately coupled with the (*R*) and (*S*) enantiomers of an auxiliary reagent B. Comparison of the ^{1}H NMR spectra of the two resulting diastereomers (?)-A-(*R*)-B and (?)-A-(*S*)-B, allows the establishment of the spatial location of the A substituents with regard to those of reagent B, that is to say, the absolute configuration at the asymmetric center of the substrate A is deduced.[2] Typical auxiliary reagents for the determination of the absolute configuration of secondary alcohols and amines are chiral arylmethoxyacetic acids such as methoxyphenylacetic acid (MPA), where their aromatic rings are able to produce selective shielding on the protons of the substrate moiety.

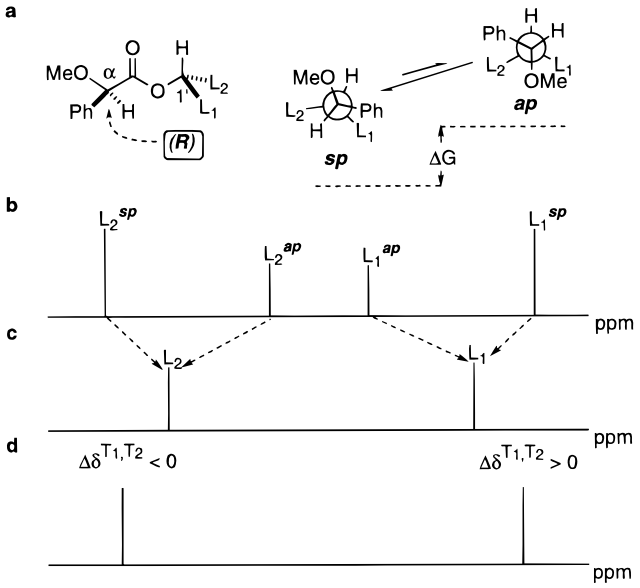

Figure 1. (a) Structure of the *sp* and *ap* conformers of a (*R*)-MPA ester; (b) chemical shifts of L_1 and L_2 in the *sp* and *ap* conformers; (c) average chemical shifts of L_1 and L_2 at room temperature (T_1); and (d) average chemical shifts of L_1 and L_2 at low temperature (T_2).

In this paper we disclose evidence demonstrating that derivatization of the alcohol with both (*R*)- and (*S*)-MPA is not necessary. A simpler NMR procedure that requires the use of only one enantiomer of the auxiliary reagent (either the (*R*)- or

* Fax: 34 81 59109.
† Present address: The Institute of Organic & Physical Chemistry of Russian Academy of Sciences, Kazan, 420083, Tatarstan, the Russian Federation.

(1) (a) Raban, M.; Mislow, K. *Tetrahedron Lett.* **1965**, *48*, 4249−4253. (b) Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, *2*, 199−230. (c) Lewis, R. A.; Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4847−4853.- (d) For a review, see: Uray, G. In *Houben-Weyl Methods in Organic Chemistry*; Helchen G., Hoffmann R. W., Mulzer J., Schaumann E., Eds.; Thieme: Stuttgart, 1996; Vol. 1, p. 253.

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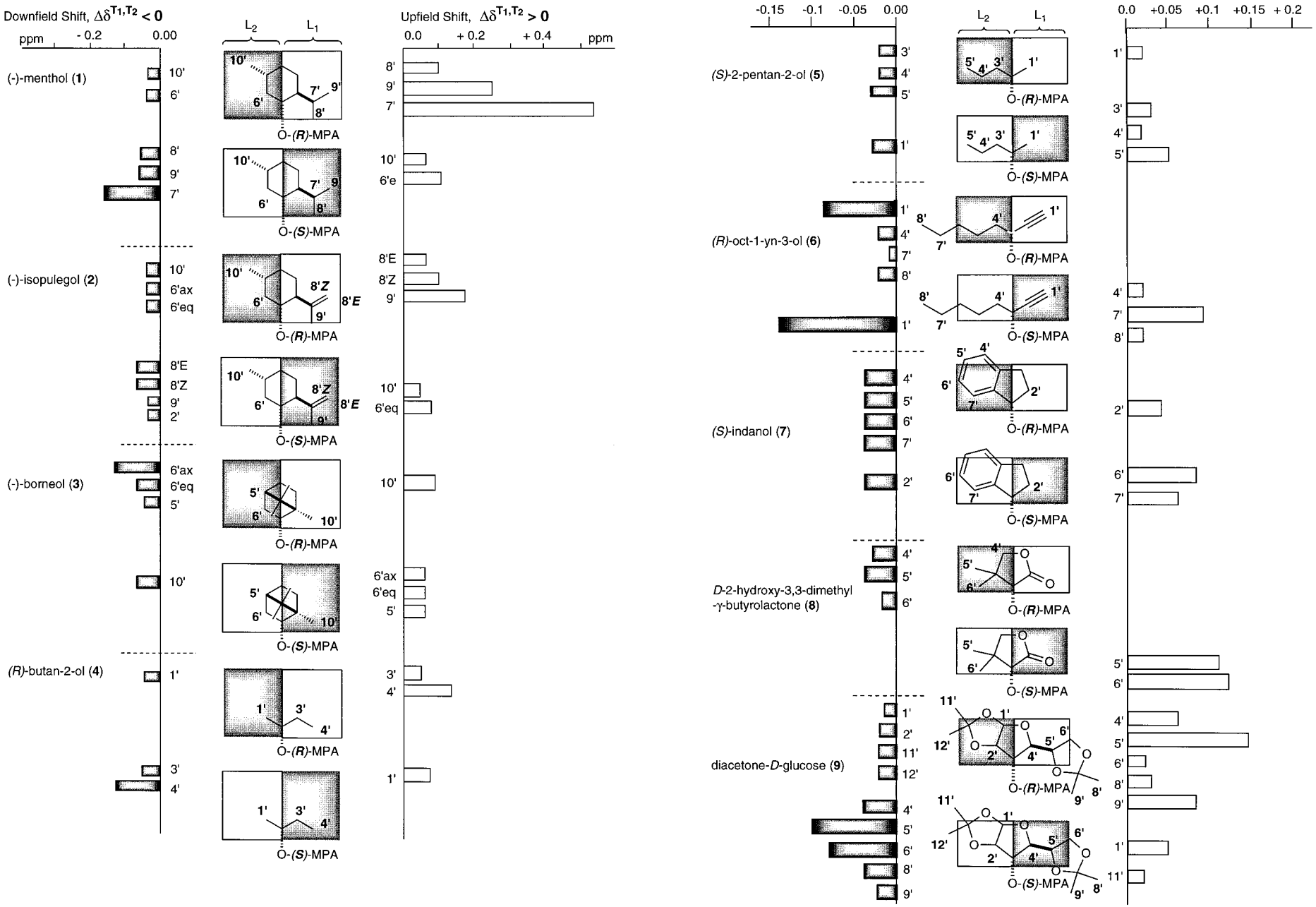

Figure 2. Distribution of shielded and deshielded areas in the (*R*)- and (*S*)-MPA esters of (−)-menthol (**1**), (−)-isopulegol (**2**), (−)-borneol (**3**), (*R*)-(−)-butan-2-ol (**4**), (*S*)-(+)-pentan-2-ol (**5**), (*R*)-oct-1-yn-3-ol (**6**),[8] (*S*)−(+)-indanol (**7**), D-(−)-2-hydroxy-3,3-dimethyl-γ-butyrolactone (**8**), and diacetone D-glucose (**9**) with indication of the $\Delta\delta^{T_1,T_2}$ values and signs for selected protons.

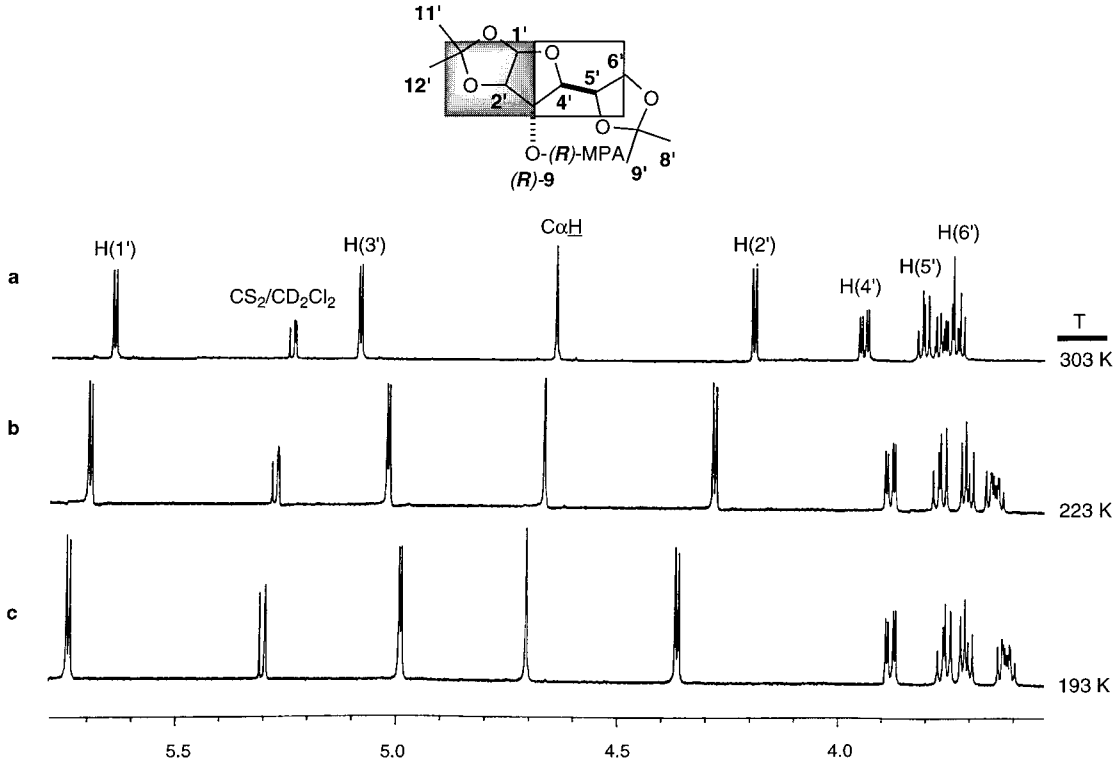

Figure 3. Partial NMR spectra of the (*R*)-MPA ester of diacetone D-glucose (**9**) at (a) 303 K, (b) 223 K, and (c) 193 K.

the (*S*)-MPA), and, as a consequence, half the amount of substrate and fewer manipulating operations, is presented.

Results and Discussion

It is now well-documented that (*R*)- and (*S*)-methoxyphenylacetic acid (MPA) esters of chiral secondary alcohols are composed by two main conformers (*sp* and *ap*) in equilibrium around the $C_\alpha-CO$ bond, with the $CO-O-C_1'HL_1L_2$ fragment virtually rigid (Figure 1a).[3] The orientation of the aromatic ring produces different shieldings in the two forms,[4] and consequently, different chemical shifts for L_1 and L_2 in each of both conformers. This is illustrated in Figure 1b, where in a (*R*)-MPA ester, L_1 is shielded by the phenyl ring in the *sp* conformer but it is not affected in the *ap* form, while L_2 is shielded in *ap* but not in *sp*. The opposite situation is observed in the (*S*)-MPA ester or when the configuration of the alcohol is inverted.

Of course, due to conformational exchange, the shielding and chemical shifts observed for L_1 and L_2 are average values and their magnitudes depend on the relative population of the *sp* and *ap* conformers (Figure 1c).[5]

Experimental and theoretical data[3] indicate that the *sp* conformer is the most stable one in both the (*R*)- and the (*S*)-MPA esters. In addition, the relative population of the *sp* conformer is practically unaffected by the nature of the alcohol. The relationship between the *sp/ap* relative populations and the shielding associated with the *sp* form, led us to think about the possibility of using only one ester derivative (either with the (*S*)- or the (*R*)-MPA). We deduced that if a controlled modification of the *sp/ap* populations were feasible, the position of substituents L_1 and L_2 relative to the aryl ring could be decided by the changes observed on their chemical shifts. So, the spatial location of the substituents around the alcohol asymmetric carbon can be determined through their connection to the absolute configuration of the chiral auxiliary reagent.

According to Boltzman's law, a selective increase of the *sp* conformer population over the *ap* is expected at lower temperature. Thus, decreasing the temperature, an upfield shift should be observed for the L_1 group of a (*R*)-MPA ester (positive $\Delta\delta^{T_1,T_2}$),[6] because the fraction of molecules having L_1 under the shielding cone of the phenyl ring is being increased. Analogously, a downfield shift for L_2 should be expected (negative $\Delta\delta^{T_1,T_2}$, Figure 1d). Similar analysis of the (*S*)-MPA ester leads to opposite shifts which are equally useful: at decreasing temperatures, L_1 should be shifted downfield (negative $\Delta\delta^{T_1,T_2}$), while L_2 should be moved upfield and so the corresponding $\Delta\delta^{T_1,T_2}$ values must become positive.

As a result, the relative position of L_1 or L_2 in relation to the aromatic ring in the *sp* conformation can be established from the signs of the variations of the chemical shifts of substituents L_1 and L_2 with the temperature (positive or negative $\Delta\delta^{T_1,T_2}$), being the assignment of the configuration of the chiral center straightforward. Furthermore, as the conformational equilibrium reported is equally operative in the esters of the (*R*)- and the (*S*)-MPA acid, only one of those derivatives (either the (*R*) or the (*S*)) has to be prepared to determine the absolute configuration of the secondary alcohol.

Experimental demonstration of this proposition has been obtained by comparing at two different temperatures the ^1H NMR spectra of either the (*R*)- or the (*S*)-MPA esters of a series of 15 secondary alcohols of known absolute configuration. These spectra were recorded at room (297−302 K) and low

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(6) The evolution of the chemical shifts of L_1 and L_2 with the temperature is quantitatively indicated by $\Delta\delta^{T_1,T_2}$. This value for each nuclei is the difference between the chemical shift at high temperature (T_1) and low temperature (T_2). A positive $\Delta\delta^{T_1,T_2}$ value means that the resonance of the specified group (L_1 or L_2) moves upfield when the temperature is decreased. A negative value means that the resonance for that group shifts downfield.

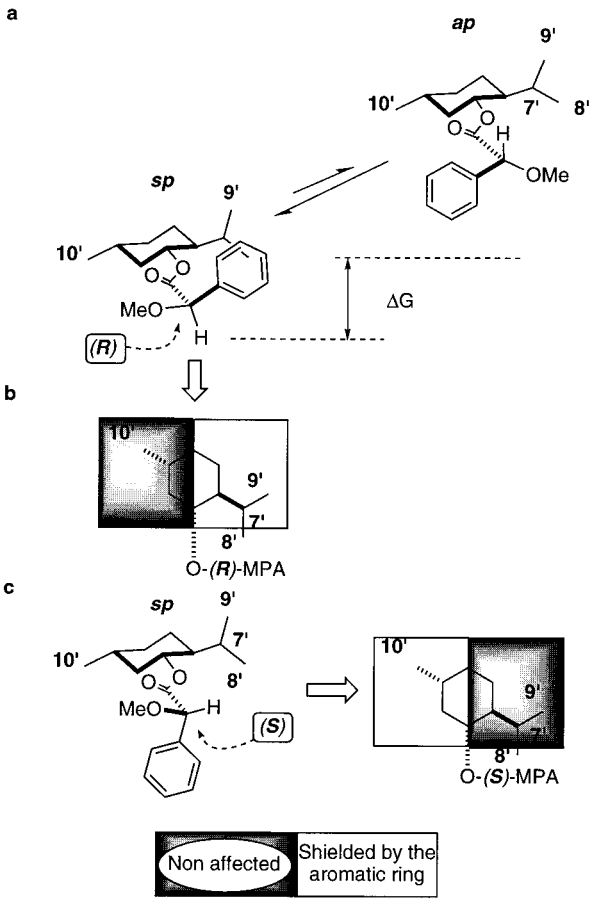

Figure 4. (a) Conformational equilibrium in the (*R*)-MPA ester of (−)-menthol (**1**) and structure of the *ap* and *sp* conformers; (b) projection of the main *sp* conformer showing the shielded and deshielded areas by the aromatic ring upon decreasing the probe temperature; and (c) the same for the (*S*)-MPA ester.

temperatures (193−203 K) in CS_2/CD_2Cl_2 (4:1) and were found to produce results perfectly coherent with the above predictions.[7]

Experimental $\Delta\delta^{T_1,T_2}$ values for the (*R*)- and (*S*)-MPA esters of (−)-menthol (**1**), (−)-isopulegol (**2**), (−)-borneol (**3**), (*R*)-(−)-butan-2-ol (**4**), (*S*)-(+)-pentan-2-ol (**5**), (*R*)-oct-1-yn-3-ol (**6**),[8] (*S*)-(+)-indanol (**7**), D-(−)-2-hydroxy-3,3-dimethyl-γ-butyrolactone (**8**), and diacetone-D-glucose (**9**) are shown in Figure 2. Figure 3 shows actual spectra of the (*R*)-MPA ester of diacetone-D-glucose (**9**) taken at 303, 223, and 193 K.

Two groups of signals are distinguishable in all the (*R*) esters. The first group is formed by signals that move upfield in the low-temperature spectrum (positive $\Delta\delta^{T_1,T_2}$). This group is represented by L_1 in the model shown in Figure 1 and all the protons originating these signals are located on the same side

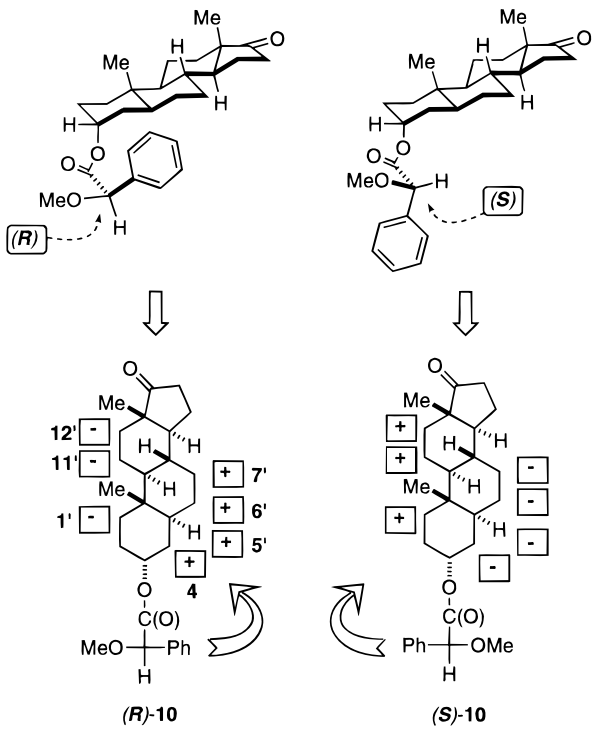

Figure 5. The *sp* conformers of the (*R*)- and (*S*)-MPA esters of *cis*-androsterone and their projections showing the distribution of the $\Delta\delta^{T_1,T_2}$ signs.

of the plane that cuts the molecule through the asymmetric carbon. The second group is formed by signals that shift downfield in the spectrum recorded at low temperature (negative $\Delta\delta^{T_1,T_2}$). It is represented by L_2 in the model of Figure 1 and the corresponding protons occupy the other side of the plane in the projection of the molecule. The signs of $\Delta\delta^{T_1,T_2}$ are the opposite when the (*S*) esters are used, or when the configuration of the alcohol is reversed.

These results are easily explained if one considers the structure and stability of the conformers in equilibrium and the relative position of the protons taken into account in relation to the phenyl group (Figure 4). For instance, in the (*R*)-MPA ester of (−)-menthol (**1**), protons H(7′), H(8′), and H(9′) are located under the influence of the phenyl ring in the *sp* conformer. Accordingly, those protons are more shielded at low temperature than at room temperature due to the increment of the *sp* population. Proton H(10′) occupies a similar position in the *ap* conformer. As the *ap* population decreases at low temperature, H(10′) gets deshielded in relation to its chemical shift at room temperature. The projection shown in Figure 4b is useful to identify which protons in (−)-menthol get shielded or deshielded at low-temperature according to their relative position with the phenyl ring in the *sp* conformer. Figure 4c shows the structure of the most stable *sp* conformer of the (*S*)-MPA ester and its projection illustrates the shielding observed at low temperature for H(10′). Similar coherent results have been obtained with the (*R*)- and the (*S*)-MPA esters of the enantiomers of **1** and **3**−**6**.

To ensure that the above conclusions are not due to—or heavily influenced by—associations in solution or solvent effects, we tested the (*S*)-MPA esters of (+)- and (−)-menthol and found that they have identical temperature-dependent NMR spectra than those of the (*R*)-MPA esters of (−)- and (+)-menthol, respectively. Besides, concentration and solvent polarity effects were ruled out as causes of concern, because NMR spectra recorded at room and low temperatures at concentrations ranging

(7) All the shifts reported in this paper are referred to TMS. The election of a temperature-independent NMR reference is particularly important in these NMR experiments and we have found TMS (internal reference) as the most suitable choice.

(8) NH, OH, and methine protons involved in intramolecular exchange processes present intrinsic temperature and solvent dependence that precludes their use in this method. Furthermore it is reasonable to expect that the presence in L_1/L_2 of other magnetically anisotropic groups could complicate the spectra and make difficult their analysis. For example, the methine proton of (*R*)-oct-1-yn-3-yl acetate shows dramatic solvent and temperature dependence: $\delta = 2.321$ ppm at 298 K, vs $\delta = 2.465$ ppm at 194 K in CS_2 and $\delta = 2.933$ ppm at 298 K vs $\delta = 3.877$ ppm at 194 K in $(CD_3)_2CO$. Therefore, the downfield shift observed in the methine proton of the (*R*)- and (*S*)-MPA esters of (*R*)-oct-1-yn-3-ol (**6**) at decreasing temperatures can well be due to interactions with solvent and not necessarily due to aromatic shielding.

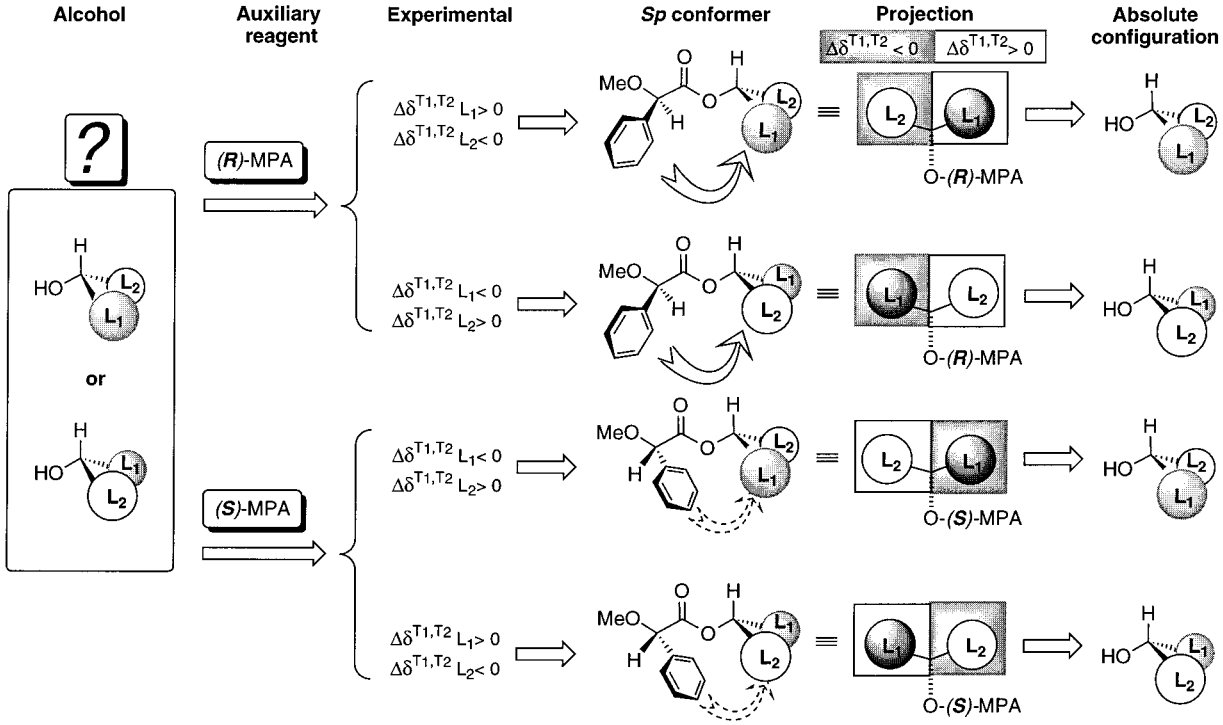

Figure 6. Diagram to deduce the absolute configuration of an alcohol from the experimental $\Delta\delta^{T_1,T_2}$ signs of either its (*R*)- or (*S*)-MPA ester.

from 1 to 8 mg/mL and in solvents of low to high polarity [$CDCl_3$, CS_2/CD_2Cl_2, $(CD_3)_2CO$] showed no relevant changes.

A particularly interesting example for testing the application of this methodology is *cis*-androsterone (**10**), a large molecule that shows a very complex and overcrowded spectrum. The experimental $\Delta\delta^{T_1,T_2}$ values observed for a number of protons in the (*R*)-MPA and the (*S*)-MPA esters are in the range 0.03−0.35 ppm, and the shielding/deshielding distribution (positive/negative $\Delta\delta^{T_1,T_2}$) is in perfect agreement with the predictions and the absolute configuration of the compound (Figure 5).

Furthermore, the ability of this procedure to induce selective shieldings is not only limited to nuclei located at nearby positions from the MPA reagent. Even protons at long distance from the hydroxy group used to link MPA are affected by the aromatic ring in a useful way and, in fact, $\Delta\delta^{T_1,T_2}$ values in the range 0.17−0.03 are observed at those positions [i.e., H(12′ax) and H(12′eq)] in the (*R*)- and the (*S*)-MPA esters. These results are comparable to the obtained $\Delta\delta^{RS}$ values[9] using the classical method, but in the latter case, both the (*R*)- and the (*S*)-MPA esters have to be prepared. This is one of the reasons why this new approach is particularly useful in natural product chemistry or other branches of chemistry, where one usually deals with compounds isolated in very small quantities.

Conclusions

To sum up, we propose a new simpler method to assign the absolute configuration of a chiral secondary alcohol by NMR. It requires only half the amount of the usual sample, only one auxiliary reagent and only one derivatization reaction. Absolute configuration elucidation by low-temperature NMR is based on the comparison of the ^{1}H NMR spectra of either the (*R*)- or the (*S*)-MPA ester derivative at two different temperatures. In one MPA ester, the signals of the alcohol moiety that are shifted upfield at lower temperature are located on the phenyl ring side in the *sp* conformer, while the protons that are shifted downfield in the low-temperature spectrum are close to the phenyl ring in the *ap* conformer. Figure 6 is a graphic summary that illustrates the steps to follow and how the configuration of the alcohol is deduced straightforward from the experimental values.

Experimental Section

NMR Spectroscopy. ^{1}H NMR spectra of samples in 4:1 CS_2/CD_2Cl_2 (4 mg in 0.5 mL) were recorded at 300 and 500 MHz (room- and low-temperature NMR experiments, respectively). Chemical shifts (ppm) are internally referenced to the TMS signal (0 ppm) in all cases.

For 1D ^{1}H NMR spectra, size 32 K, pulse length 2.8 ms (30°), 16 acquisitions were used.

For low-temperature NMR spectroscopy (193−203 K), the probe temperature was controlled by a standard unit calibrated with a methanol reference; samples were allowed to equilibrate for 15 min at each temperature before recording the spectra. To ensure that cooling−heating cycles are reversible, ^{1}H NMR spectra were repeated at room temperature (297−303 K) immediately after the low-temperature experiments.

General. Preparations of diastereomeric esters from the alcohol and *O*-methylmandelic acid were carried out by standard procedures with DCC-DMAP (see ref 3). The reaction mixtures were filtered to remove the dicyclohexylurea and the esters purified by flash chromatography on silica gel eluting with dichloromethane. Further purification was accomplished by HPLC (μ-Porasil, 3 mm × 250 mm or Spherisorb S5W, 10 mm × 250 mm, hexanes−ethyl acetate). MPA esters **1**,[3b] **2**−**4**,[2e] and **9**[10] were prepared according to literature procedures.

(*S*)-Pentan-2-yl (*R*)-α-methoxy-α-phenylacetate [(*R*)-5]: $[\alpha]_D = -39.1$ ($c = 0.027$; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.87 (t, $J = 7.34$ Hz, 3H), 1.07 (d, $J = 6.26$, 3H), 1.19−1.38 (m, 2H), 1.40−1.64 (m, 2H), 3.41 (s, 3H), 4.73 (s, 1H), 4.94−5.00 (m, 1H), 7.32−7.45 (m, 5H); MS (EI) *m*/*z* (%) 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; O, 20.31. Found: C, 71.16; H, 8.50.

(*S*)-Pentan-2-yl (*S*)-α-methoxy-α-phenylacetate [(*S*)-5]: $[\alpha]_D = +91.2$ ($c = 0.017$; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.73 (t, $J = 7.30$ Hz, 3H), 1.00−1.08 (m, 2H), 1.21 (d, $J = 6.26$, 3H), 1.25−1.49 (m, 2H), 3.41 (s, 3H), 4.72 (s, 1H), 4.91−4.97 (m, 1H), 7.32−

(9) For a given proton, $\Delta\delta^{RS}$ is the difference between the chemical shift in the (*R*) derivative and in the (*S*) derivative. See ref 3.

(10) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1997**, *53*, 8541−8564.

7.45 (m, 5H); MS (EI) *m*/*z* (%) 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; O, 20.31. Found: C, 71.12; H, 8.51.

(*R*)-Oct-1-yn-3-yl (*R*)-α-methoxy-α-phenylacetate [(*R*)-6]: $[\alpha]_D = +24.5$ ($c = 0.008$; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.87 (t, $J = 6.80$ Hz, 3H), 1.20−1.48 (m, 6H), 1.74−1.81 (m, 2H), 2.36 (d, $J = 2.26$ Hz, 1H), 3.43 (s, 3H), 4.79 (s, 1H), 5.39 (ddd, $J = J' = 6.71$, $J'' = 2.12$ Hz, 1H), 7.32−7.51 (m, 5H); MS (EI) *m*/*z* (%) 274 (M^+). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; O, 17.49. Found: C, 74.40; H, 8.06.

(*R*)-Oct-1-yn-3-yl (*S*)-α-methoxy-α-phenylacetate [(*S*)-6]: $[\alpha]_D = +77.4$ ($c = 0.042$; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.77 (t, $J = 6.53$ Hz, 3H), 1.05−1.24 (m, 6H), 1.52−1.57 (m, 2H), 2.39 (d, $J = 2.19$ Hz, 1H), 3.35 (s, 3H), 4.71 (s, 1H), 5.33 (ddd, $J = J' = 6.53$, $J'' = 2.16$ Hz, 1H), 7.24−7.39 (m, 5H); MS (EI) *m*/*z* (%) 274 (M^+). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; O, 17.49. Found: C, 74.44; H, 8.05.

(*S*)-(+)-Indan-1-yl (*R*)-α-methoxy-α-phenylacetate [(*R*)-7]: $[\alpha]_D = -56.9$ ($c = 0.036$; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.08−1.89 (m, 1H), 2.28−2.41 (m, 1H), 2.73−2.83 (m, 1H), 2.92−3.02 (m, 1H), 3.37 (s, 3H), 4.71 (s, 1H), 6.22 (dd, $J = 6.93$, $J' = 3.51$ Hz, 1H), 7.15−7.42 (m, 9H); MS (EI) *m*/*z* (%) 282 (M^+). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.50; H, 6.40.

(*S*)-(+)-Indan-1-yl (*S*)-α-methoxy-α-phenylacetate [(*S*)-7]: $[\alpha]_D = +3.0$ ($c = 0.036$; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.04−2.15 (m, 1H), 2.50−2.62 (m, 1H), 2.82−2.92 (m, 1H), 3.03−3.11 (m, 1H), 3.42 (s, 3H), 4.78 (s, 1H), 6.23 (dd, $J = 7.14$, $J' = 4.48$ Hz, 1H), 7.03−7.45 (m, 9H); MS (EI) *m*/*z* (%) 282 (M^+). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.54; H, 6.42.

D-(−)-2-*O*-((*R*)-α-methoxy-α-phenylacetyl)-3,3-dimethyl-γ-butyrolactone [(*R*)-8]: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.05 (s, 3H), 1.14 (s, 3H), 3.49 (s, 3H), 4.00 (dd, $J = 14.50$, $J' = 9.06$ Hz, 2H), 4.92 (s, 1H), 5.33 (s, 1H), 7.34−7.50 (m, 5H); $[\alpha]_D = -56.9$ ($c = 0.035$; $CHCl_3$); MS (EI) *m*/*z* (%) 278 (M^+). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.72; H, 6.52; O, 28.76. Found: C, 64.69; H, 6.54.

D-(−)-2-*O*-((*S*)-α-Methoxy-α-phenylacetyl)-3,3-dimethyl-γ-butyrolactone [(*S*)-8]: $[\alpha]_D = +3.0$ ($c = 0.039$; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.66 (s, 3H), 0.92 (s, 3H), 3.44 (s, 3H), 3.93 (s, 2H), 4.92 (s, 1H), 5.38 (s, 1H), 7.33−7.47 (m, 5H); MS (EI) *m*/*z* (%) 278 (M^+).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.72; H, 6.52; O, 28.76. Found: C, 64.73; H, 6.50.

Diacetone 3-*O*-((*R*)-α-Methoxy-α-phenylacetyl)-D-glucose [(*R*)-9]: $[\alpha]_D = -48.7$ ($c = 0.038$; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 3H), 1.27 (s, 3H), 1.31 (s, 3H), 1.48 (s, 3H), 3.41 (s, 3H), 3.74−3.79 (m, 1H), 3.85 (d, $J = 5.47$, 2H), 4.29 (dd, $J = 7.98$, $J' = 2.98$ Hz, 1H), 4.41 (d, $J = 3.66$ Hz, 1H), 4.76 (s, 1H), 5.31 (d, $J = 2.95$ Hz, 1H), 5.83 (d, $J = 3.66$, 1H), 7.33−7.69 (m, 5H); MS (EI) *m*/*z* 408 (M^+). Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91; O, 31.34. Found: C, 61.73; H, 6.89.

Diacetone 3-*O*-((*S*)-α-Methoxy-α-phenylacetyl)-D-glucose [(*S*)-9]: $[\alpha]_D = +10.6$ ($c = 0.025$; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21 (s, 3H), 1.28 (s, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 3.42 (s, 3H), 3.95−4.19 (m, 5H), 4.78 (s, 1H), 5.31 (d, $J = 1.96$ Hz, 1H), 5.59 (d, $J = 3.61$, 1H), 7.34−7.44 (m, 5H); MS (EI) *m*/*z* (%) 408 (M^+). Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91; O, 31.34. Found: C, 61.76; H, 6.93.

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