ORGANIC LETTERS

2000
Vol. 2, No. 21
3261−3264

Absolute Configuration of 1,*n*-Diols by NMR: The Importance of the Combined Anisotropic Effects in Bis-Arylmethoxyacetates

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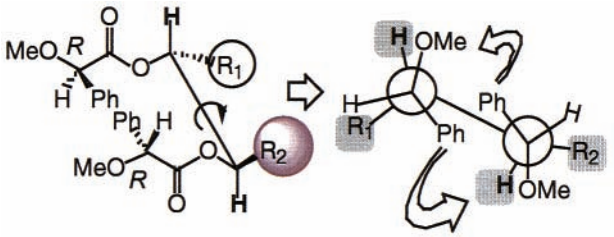
Received June 30, 2000

ABSTRACT



The absolute configuration of a 1,*n*-diol can be assigned from the ^{1}H NMR spectra of its (*R*)- and (*S*)-AMAA diesters if the chemical shifts are interpreted as the result of the joint action of the two chiral auxiliaries.

The reliability of NMR spectroscopy for the determination of the absolute configuration of chiral secondary alcohols and other monofunctional compounds using arylmethoxyacetic acids [AMAAs, e.g., methoxyphenylacetic acid, MPA (**1**); 9-anthrylmethoxyacetic acid, 9-AMA (**2**)] as auxiliaries has been amply demonstrated theoretically and experimentally with a wide variety of compounds of known configuration.[1] Attempts to assign the absolute stereochemistry of some polyalcohols of natural origin by comparison of the NMR data of their MTPA (methoxytrifluormethylphenylacetic acid) peresters have been described.[2a] However, this procedure is far from being well established basically because no systematic studies with compounds of known absolute configuration have been carried out to confirm the reliability of the assignments.

Indeed, identical signs of $\Delta\delta^{SR}$ for the two substituents (L_1/L_2) directly bonded to the asymmetric carbon have been obtained in certain cases, a situation that does not allow a safe assignment.[2b]

Apart from that, the main problem with those reports[2a] resides in the assumption made by the authors that in a polyalcohol the configuration of a given hydroxylic carbon can be deduced by considering that only the MTPA directly bonded to that -OH contributes to the $\Delta\delta^{SR}$ values[3] used for its assignment and therefore that the model developed for monoalcohols can be directly applied to every hydroxylated carbon of the polyol.

(1) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Trost, B. M.; Belletire, J. L.; Goldleski, P. G.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (d) Seco, J. M.; Latypov, Sh. K.; Quiñoá E.; Riguera R. *Tetrahedron Lett.* **1994**. *35*, 2921−2924. (e) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1997**, *53*, 8541−8567. (f) Seco, J. M.; Latypov, Sh. K.; Quiñoá E.; Riguera R. *J. Org. Chem.* **1997**, *62*, 7569−7574. (g) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877−882. (h) Latypov, Sh. K.; Ferreiro, M. J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 4741−4751. (i) Ferreiro, M. J.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2000**, *65*, 2658−2666. (j) López, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9724−9725. (k) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1999**, *55*, 569−584. (l) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669−4675.

(2) (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781−2791 and references therein. (b) The conformational composition of MTPA esters is more complex than that of AMAAs (MPA, 9-AMA), which makes that reagent less recommended. See refs 2a and 4b.

10.1021/ol0062852 CCC: $19.00
Published on Web 09/29/2000

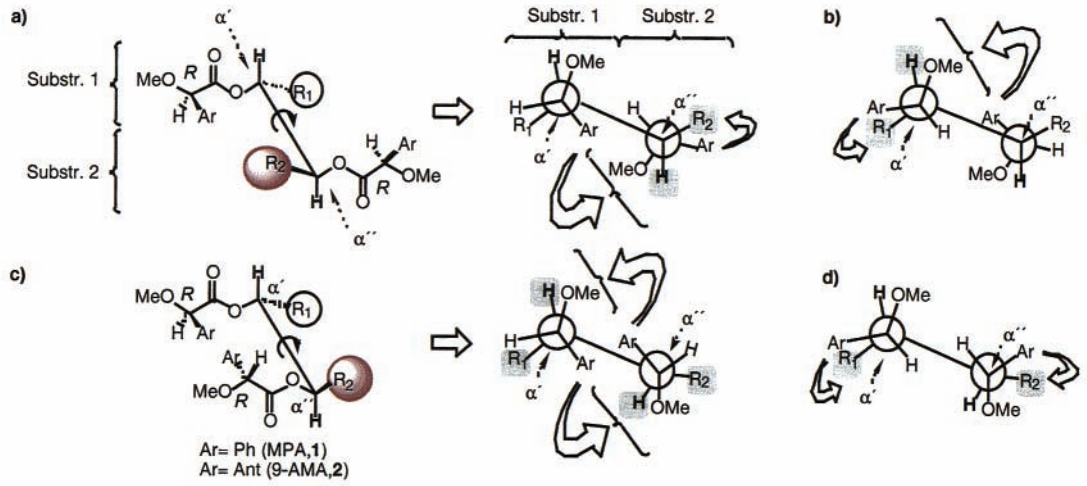


Figure 1. (a) (*R*)-MPA diester of an *anti*-1,2-diol. The groups shielded by the aryl rings are shaded. Only the NMR significant *sp* conformers are shown. (b) (*S*)-MPA diester of an *anti*-1,2-diol. (c and d) (*R*)-MPA and (*S*)-MPA diesters of a *syn*-1,2-diol, respectively.

Magnetic anisotropy is a through-space phenomenon, and accordingly, the chemical shift (and $\Delta\delta^{SR}$) observed for a certain proton is the result of the additivity of the shielding/deshielding effects produced by all the MTPAs present in the perester and not only due to the influence of the closer one. Each reagent unit contributes to the chemical shift in a different way (shielding or deshielding) and strength, depending on the actual structure of the polyol, and therefore the resulting $\Delta\delta^{SR}$ may obviously present signs and values different than those predicted if only the effect of one auxiliary were considered.

In this Letter, we wish to show that the absolute configuration of the two secondary hydroxylated asymmetric carbons of an acyclic 1,*n*-diol can be safely assigned by comparison of the NMR spectra of its (*R*)- and (*S*)-AMAA diesters, provided the experimental $\Delta\delta^{RS}$ data is interpreted as the result of the combined anisotropic effects (shielding/deshielding) produced by the two AMAA units present in the molecule.

The first point that should be addressed is the evaluation of the contribution of each AMAA unit in the diester. For secondary alcohols, the conformational composition of their (*R*)- and (*S*)-AMAA esters is well-known.[4] So is the spatial relationship that selectively places one of the substituents at the asymmetric center (L_1 or L_2) under the shielding cone of the aryl ring.[5]

Application of those concepts to an *anti*-1,2-diol, derivatized as the (*R*)-AMAA diester (Figure 1a), shows that the two substituents around the Cα′ chiral center are R_1 and substructure 2 (including Cα″H). R_1 is away from the aryl ring of the auxiliary reagent while substructure 2 is located under its shielding cone.

In a similar way, when the two substituents of the second chiral center (Cα″) are considered, one of them (R_2) is under

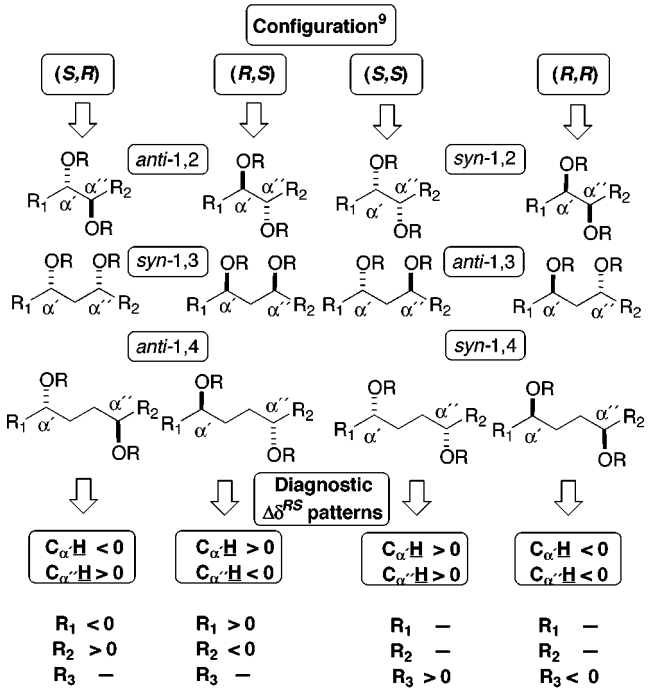


Figure 2. Diagnostic $\Delta\delta^{RS}$ signs for the four steroisomers of 1,*n*-diols. For simplicity, only 1,2-, 1,3-, and 1,4-diols are shown. R = AMAA. $R_3 = -(CH_2)_m-$ for 1,3-diols or higher. A dash means that the experimental $\Delta\delta^{RS}$ sign is unreliable for assignment purposes. For *meso* forms, where $R_1 = R_2$, either the (*S*,*R*) or (*R*,*S*) series applies.

(3) $\Delta\delta^{SR}$ for L_1 (or L_2) represents the difference between the chemical shift of the substituent L_1 (or L_2) of the chiral substrate when it is derivatized with (*S*)-MTPA and the shift when the substrate is derivatized with (*R*)-MTPA. With MPA (**1**) or other AMAA reagents, such as 9-AMA (**2**), $\Delta\delta^{RS}$ is usually employed.

(4) (a) Latypov, Sh. K.; Seco, J. M.; Quiñoá E.; Riguera R. *J. Org. Chem.* **1995**, *60*, 504−515. (b) Latypov, Sh. K.; Seco, J. M.; Quiñoá E.; Riguera R. *J. Org. Chem.* **1996**, *61*, 8569−8577.

(5) See Figure 1S in Supporting Information.

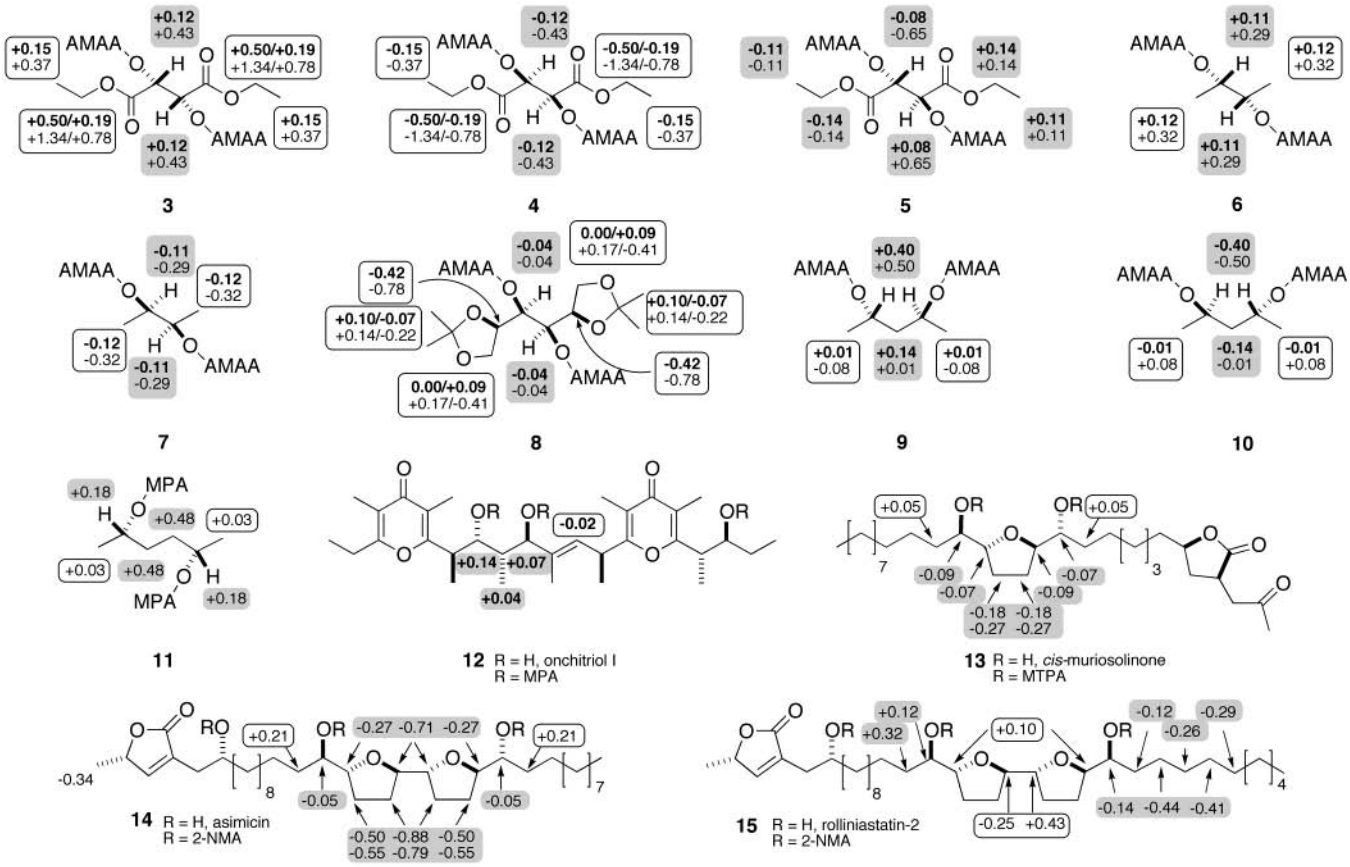


Figure 3. $\Delta\delta^{RS}$ values for diols **3**−**15**. Bold and plain numbers correspond to values from MPA and 9-AMA derivatives, respectively (**3**−**12**). Shaded and white squares refer to diagnostic and non-diagnostic values, respectively.

the shielding cone of the reagent at Cα″ and the other is constituted by substructure 1 (Cα′H included) that is not affected by that reagent. Clearly the two AMAA units transmit their effects through space to the whole diol framework, and the chemical shifts for the protons of R_1, R_2, Cα′H, and Cα″H have to reflect this combined action. Figure 1b shows the substituents shielded by each AMAA unit in the (*S*)-diester.

Comparison of the NMR spectra of the (*R*)- and (*S*)-AMAA diesters should reflect that R_2 and Cα″H are more heavily shielded in the (*R*)- than in the (*S*)-AMAA diester, therefore presenting negative $\Delta\delta^{RS}$ values. For their part, R_1 and Cα′H are more shielded in the (*S*)- than in the (*R*)-AMAA diester and should present positive $\Delta\delta^{RS}$ values.[6] Naturally, if the configuration of the diol were the enantiomeric configuration of the one shown in Figure 1, the resulting signs of $\Delta\delta^{RS}$ would be opposite.

When a *syn*-1,2-diol is studied (Figure 1c,d), a similar, but different, set of $\Delta\delta^{RS}$ signs is obtained for the AMAA diesters. In this case, however, there is an interesting difference: substituents R_1 and R_2 are now shielded in both the (*R*)- and (*S*)-AMAA diesters.[7] As the exact magnitude of the shielding in each derivative cannot be known, no prediction of $\Delta\delta^{RS}$ can be made for R_1 and R_2. Fortunately, Cα′*H* and Cα″*H* are afected by the shielding cone only in the (*R*)-diester and thus a reliable relationship between the $\Delta\delta^{RS}$ signs (both negative in this case) and stereochemistry can be established.

It should be mentioned at this point that rotation around the connecting Cα′−Cα″ bond does not change the spatial relationship of the aryl rings with respect to R_1, R_2, Cα′H, and Cα″H, and in consequence, characteristic $\Delta\delta^{RS}$ patterns that depend only on the absolute configuration of the chiral centers should be obtained for each one of the four possible stereoisomers of a 1,2-diol and by extension of this analysis to diols with the chiral centers separated by one or more methylene groups.[8]

Figure 2 shows the distinctive $\Delta\delta^{RS}$ patterns obtained by application of these ideas to the four stereoisomers of a set of 1,*n*-diols.[9]

(6) This is in contrast with the case of isolated secondary alcohols, where the chemical shifts of CαH have no diagnostic value.

(7) Shielding originates from the aryl ring of one AMAA unit in one diester and from the aryl ring of the other AMAA unit in the other diester as shown in Figure 1c,d.

(8) The quantitative result of the combination of shielding effects clearly depends on the distances involved and the strength of the auxiliary reagent used. For instance, 9-AMA and 2-NMA project their shielding cone further and with more intensity than MPA.

Experimental support for these predictions has been obtained with diols **3**−**15**, of known absolute configuration, that have been derivatized with several AMAAs (Figure 3). These include the MPA (**1**) and 9-AMA (**2**) diesters of *syn*-1,2 (**3**/**4**; **6**/**7**), *anti*-1,3 (**9**/**10**), *syn*-1,4 (**11**), and *meso* [*anti*-1,2 (**5**)] forms and those of polyfunctionalized compounds **8** and **12** (*syn*-1,2 and *anti*-1,3, respectively). Data on compounds **14** and **15** are from the literature[10] and were obtained with 2-naphthylmethoxyacetic acid (2-NMA) as AMAA reagent.

The signs of the $\Delta\delta^{RS}$ experimentally obtained for protons considered of diagnostic value are in all cases coincident with those predicted and shown in Figure 2.[11]

The correlation between the predictions and the experimental data clearly indicate that the sign distributions shown in Figure 2 can be used as an effective tool to deduce the absolute configuration of any diol, directly from the NMR spectra of its AMAA diesters.[12]

In summary, in this preliminary account, we have shown that there is a correlation between the absolute configuration of a 1,*n*-diol and the chemical shifts of its diesters with (*R*)- and (*S*)-AMAA and that if the NMR spectra are adequately interpreted they allow the simultaneous assignment of the absolute configuration at the two asymmetric carbons of the diol.

From a practical point of view, to elucidate the stereochemistry of an unknown diol, the corresponding diesters with (*R*)- and (*S*)-MPA or 9-AMA should be prepared, their NMR spectra taken, and the $\Delta\delta^{RS}$ signs compared with those shown in Figure 2.

Examination of a larger set of diols is now underway in order to ensure the generality of this procedure and its scope and limitations.

Acknowledgment. This work was financially supported by grants from CICYT (PM98-0227, FEDER-CICYT 1FD97-2157) and from Xunta de Galicia (XUGA-20908B97, XUGA-PGIDT99PXI20906B, and XUGA-PGIDT99BIO-20901).

Supporting Information Available: Figure 1S: main conformers in equilibrium (*ap* and *sp*) for AMAA esters of chiral secondary alcohols and experimental $\Delta\delta^{RS}$ values for L_1/L_2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For the sake of simplicity, the configurations in Figure 2 are assigned on the assumption that the substituents at the chiral centers are ranked in the arbitrary order of decreasing precedence as follows: O-AMAA > substructure with the other chiral center > R_1 or R_2 > H. This point must be taken into account when the substituents have other priorities. However, the drawings always represent the real situation and can be used as such.

(10) Duret, P.; Waechter, A.; Figadere, B.; Hocquemiller, R.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 4717−4720.

(11) Contradictory signs are observed for some of the protons considered of no diagnostic value. For instance, compounds **8**, **9**, and **10** show contradictory signs for R_1/R_2 and, as predicted (see Figure 2), those values are useless for assignment purposes.

(12) When MTPA is used as auxiliary reagent instead of MPA or 9-AMA, the same reasoning applies but the distribution of shielding/deshielding areas around the diol framework and the resulting sign distributions are different because of the different conformational composition of MTPA esters. Although the use of MTPA as auxiliary reagent is discouraged (ref 2), when using it the same set of signs shown in Figure 2 for AMAA diesters can be applied by simply changing $\Delta\delta^{RS}$ for $\Delta\delta^{SR}$. The coherent set of $\Delta\delta^{SR}$ data obtained for compound **13** illustrates the application of this method to MTPA diesters. For experimental details on compound **13**, see: Woo, M. H.; Cho, K. Y.; Zhang, Y.; Zeng, L.; Gu, Z.-M.; McLaughlin, J. L. *J. Nat. Prod.* **1995**, *58*, 1533−1542.