ORGANIC LETTERS

2006
Vol. 8, No. 20
4449−4452

The ^{1}H NMR Method for the Determination of the Absolute Configuration of 1,2,3-*prim*,*sec*,*sec*-Triols‡

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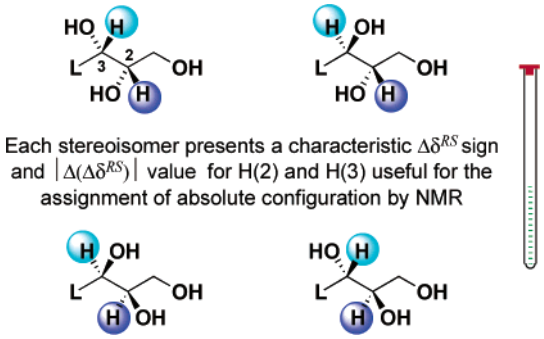
Received June 30, 2006

ABSTRACT



The absolute configuration of 1,2,3-*prim*,*sec*,*sec*-triols can be assigned by comparison of the ^{1}H NMR spectra of the tris-(*R*)- and the tris-(*S*)-MPA ester derivatives. An experimental demonstration of this correlation with 24 triols of known absolute configuration and a protocol using two parameters—$\Delta\delta^{RS}$(H3) and the difference between $\Delta\delta^{RS}$(H2) and $\Delta\delta^{RS}$(H3) = $|\Delta(\Delta\delta^{RS})|$—for its application to the determination of the absolute configuration of other triols are presented.

^{1}H NMR has been amply used for the determination of the absolute configuration of monofunctional compounds by derivatization with the enantiomers of appropriate auxiliary reagents and use of the $\Delta\delta^{RS}$ parameter,[1] but extension of the methodology to difunctional compounds is a recent development due to its complexity.[2]

The structural fragment represented by 1,2,3-triols with two secondary [C(2)/C(3)] and one primary [C(1)] alcohol groups (four possible stereoisomers, Figure 1a) is very frequent in nature,[3] can be prepared by several synthetic methods, and is a good substrate to test the application of this methodology to trifunctional compounds. We now present experimental evidence showing that the absolute configuration of 1,2,3-triols with two secondary chiral centers can be determined in a very simple way by comparison of

‡ Dedicated to the memory of Prof. Marcial Moreno.

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10.1021/ol0616135 CCC: $33.50
Published on Web 08/29/2006

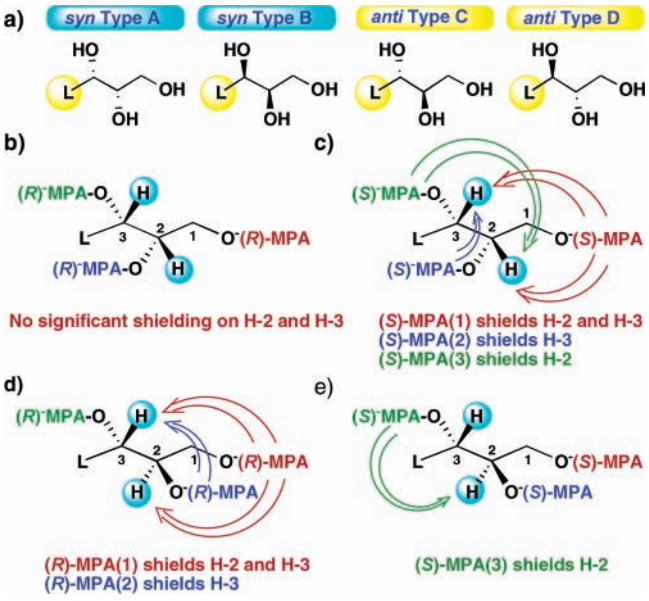

Figure 1. (a) Four stereoisomers of 1,2,3-*prim*,*sec*,*sec*-triols. (b) Main shielding effects in the tris-(*R*)-MPA ester of a syn type A triol and (d) an anti type C triol. (c) Main shielding effects in the tris-(*S*)-MPA ester of a syn type A triol and (e) an anti type C triol.

the ^{1}H NMR spectra of the corresponding tris-(*R*)- and tris-(*S*)-MPA ester derivatives, easily prepared in one pot by reaction of the auxiliary and the triol.[4]

Theoretical and experimental studies (calculations,[5] dynamic and low-temperature NMR, CD) of the tris-(*R*)- and tris-(*S*)-2-methoxy-2-phenylacetic acid (MPA) esters of syn and anti triols showed us the way the chemical shifts of H(2) and H(3) result from the combined action of the shielding due to the three auxiliaries. This is graphically illustrated in Figure 1 and can be summarized as follows: (a) In the (*R*)-derivative of a syn type A isomer (Figure 1b), H(2) and H(3) are subjected to neither the shielding from the primary MPA nor that from the secondary MPAs.[6a] (b) In the (*S*)-MPA derivative of a syn type A isomer (Figure 1c), the shielding generated by the primary MPA reinforces those produced by the two secondary MPAs.[6b] (c) In the (*R*)-MPA derivative of an anti type C isomer (Figure 1d), the primary MPA shields H(3), adding its effect to that caused by the MPA at C(2), and also shields H(2).[6c] (d) In the (*S*)-MPA derivative of an anti type C triol (Figure 1e), the major shielding contribution is the one generated on H(2) by the MPA unit at C(3).[6d]

The above studies introduce four clearly distinct anisotropic scenarios, one for each stereochemical situation. This allows us to propose an unambiguous strategy to distinguish them by means of two different NMR parameters related to H(2) and H(3). This is summarized in the following points:

(A) The sign of the $\Delta\delta^{RS}$ parameter for H(3) becomes highly diagnostic[7] and reduces the configurational possibilities of a triol to just two out of four possible stereoisomers: (1) If the $\Delta\delta^{RS}$ of H(3) is positive, the stereochemistry of the triol is either syn type A or anti type D. (2) If the $\Delta\delta^{RS}$ of H(3) is negative, the triol is either syn type B or anti type C.

The validity of these predictions was experimentally demonstrated from the ^{1}H NMR spectra of the tris-(*R*)- and the tris-(*S*)-MPA ester derivatives of triols **1**−**24** of known absolute configuration (Figure 2). All the syn type A (**1**−**5**, **24**) and the anti type D triols (**21**−**23**) present positive $\Delta\delta^{RS}$ for H(3), while those belonging to syn B (**6**−**12**) and anti C (**13**−**20**, **24**) present negative $\Delta\delta^{RS}$ for H(3). Figure 3 shows a bar diagram with those values and signs.

(B) A new NMR parameter $|\Delta(\Delta\delta^{RS})|$, which compares the shielding supported by H(2) and H(3), makes it possible to carry out an effective discrimination between the syn A/anti D and syn B/anti C pairs and therefore to attain an unambiguous correlation between NMR and absolute stereochemistry.

This parameter arises from detailed analysis of the effects caused by the three MPA units in the syn and anti series. It shows two clearly different situations, summarized as follows:

(1) In the syn series, protons H(2) and H(3) are either unaffected or similarly affected by the shielding caused by the Ph groups (in tris-(*R*)- and tris-(*S*)-derivatives; Figures 1b,c and 2Sf,g) and accordingly the difference between the $\Delta\delta^{RS}$ values for H(3) and for H(2) is expected to be small.

(2) In the anti series, there is a significant difference between the overall shielding experienced by H(2) and by H(3) (in tris-(*R*)- and tris-(*S*)-derivatives; Figures 1d,e and 2Sh,i): H(2) is heavily shielded in one derivative and H(3) is heavily shielded in the other. Consequently, the difference between the $\Delta\delta^{RS}$ values for H(3) and for H(2) is expected to be high.

Experimental corroboration of that reasoning is presented in Figure 3. A bar diagram shows the magnitude of the difference (as absolute value) between the $\Delta\delta^{RS}$ of H(2) (with its sign) minus the $\Delta\delta^{RS}$ of H(3) (with its sign), expressed as $|\Delta\delta^{RS}_{H(2)} - \Delta\delta^{RS}_{H(3)}| = |\Delta(\Delta\delta^{RS})|$, for triols **1**−**23**.

As predicted, the differences $|\Delta(\Delta\delta^{RS})|$ are clearly smaller for the syn than for the anti series. The values experimentally obtained for the syn A and syn B triols tested (**1**−**12**) range from 0.00 to a maximum of 0.05 ppm, while in the anti series, the $|\Delta(\Delta\delta^{RS})|$ values are larger and range from 0.16 up to 0.60 ppm for the triols tested (**13**−**23**). These $|\Delta(\Delta\delta^{RS})|$ values are so different they allow the discrimination between

(3) It is present in sugars, itols, and many compounds of pharmaceutical and biological interest such as Zanamavir (Relenza), sialic acid derivatives, polyoxamic acid (component of polyoximes), and sphingofungin components (see Figure 1S and references in the Supporting Information).

(4) See the Supporting Information for the complete experimental procedure.

(5) Theoretical calculations [energy minimization by semiempirical (AM1), and DFT (B3LYP)] were performed with Gaussian 98.

(6) (a) Exactly the same pattern of shielding is expected in the (*S*)-derivative of a syn type B isomer (Figure 2S(g), Supporting Information), (b) for the (*R*)-MPA derivative of a syn type B isomer (Figure 2S(f), Supporting Information), (c) for the (*S*)-MPA derivative of an anti type D isomer (Figure 2S(i), Supporting Information), and (d) for the (*R*)-MPA derivative of the anti type D isomer (Figure 2S(h), Supporting Information).

(7) The studies show that the diagnostic value of H(2) for this purpose presents limitations.

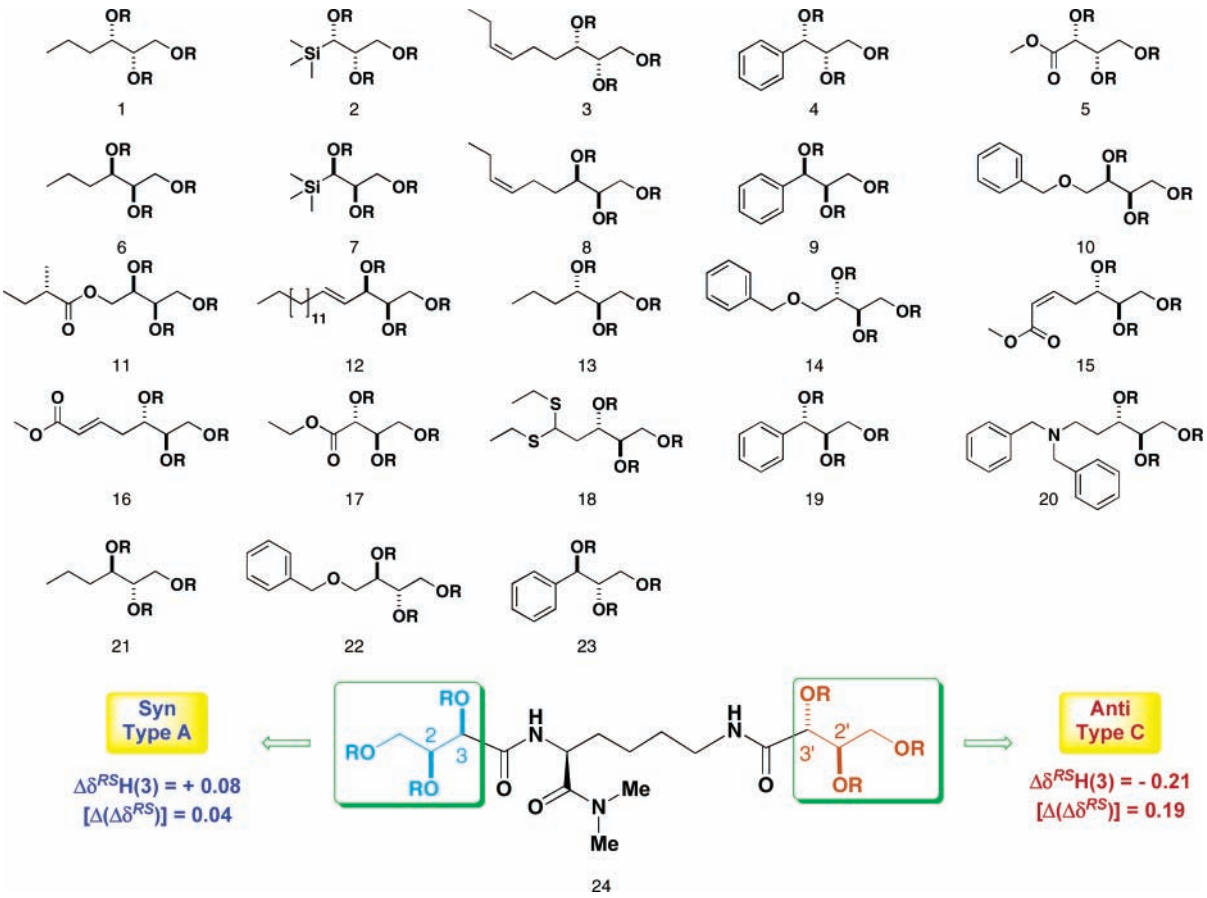

Figure 2. Triols series employed in this study: syn type A, **1**−**5** and **24**; syn type B, **6**−**12**; anti type C, **13**−**20** and **24**; anti type D, **21**−**23**. $\Delta\delta^{RS}$ and $|\Delta(\Delta\delta^{RS})|$ parameters are highlighted for bis-triol **24**.

syn and anti triols.[8] Thus, combination of the sign of $\Delta\delta^{RS}$ for H(3), with the value of $|\Delta(\Delta\delta^{RS})|$ allows the unambiguous distinction and identification of each one of the four possible stereoisomers of a 1,2,3-*prim*,*sec*,*sec*-triol. Lysine derivative **24** (a bis-triol), bearing two syn/anti moieties (six MPA units introduced in a one-pot reaction to yield the hexakis-ester),

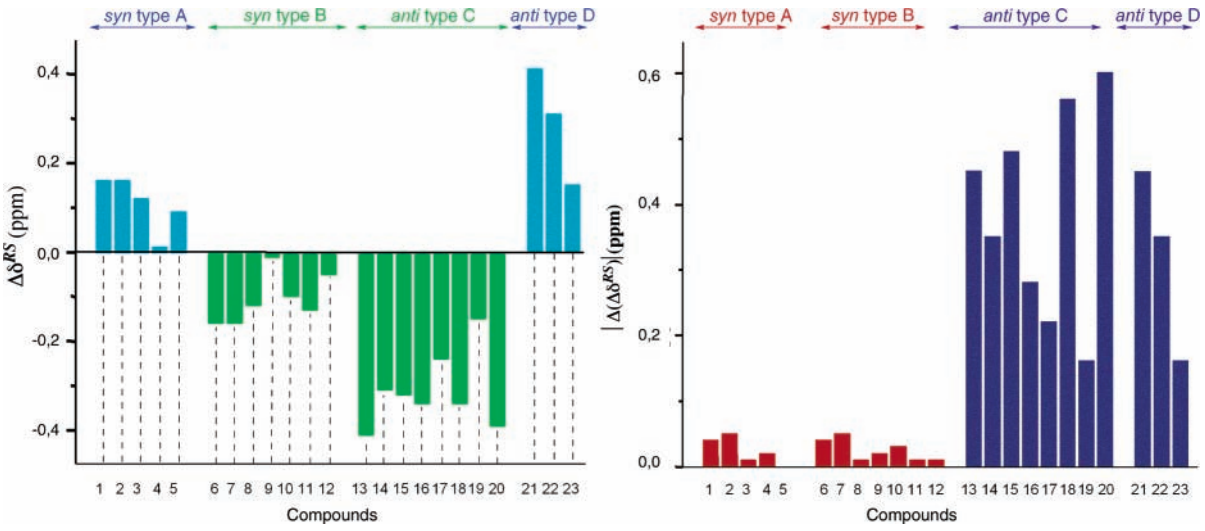

Figure 3. $\Delta\delta^{RS}$ for H(3) (left) and $|\Delta(\Delta\delta^{RS})|$ values (right) observed for triols **1**−**23** classified according to the four stereochemical types.

shows the effectiveness of the method to infer the chirality of four centers.

In conclusion, the ^{1}H NMR spectra of the tris-(*R*)- and tris-(*S*)-MPA ester derivatives of a series of 24 1,2,3-*prim*,*sec*,*sec*-triols of known absolute configuration show that each one of the four possible stereoisomers presents a specific pattern of NMR parameters ($\Delta\delta^{RS}$ and $|\Delta(\Delta\delta^{RS})|$) for H(2) and H(3). This constitutes a very convenient method for the simultaneous and reliable assignment of the two asymmetric carbons of a triol with the minimum of experimental effort and economic cost. This work demonstrates that the NMR methodology for configurational assignment can be successfully expanded to complex polyfuntional molecules if a careful examination of the shielding effects due to the auxiliaries is carried out.

(8) A protocol for the assignment of the absolute configuration of a 1,2,3-*prim*,*sec*,*sec*-triol and a graphical summary to facilitate the use of this method by interested researchers are shown in the Supporting Information.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (MEC) and the Xunta de Galicia for financial support (CTQ2005-05296/BQU; SAF2003-08765-C03-01; PGIDT 03PXIC20908PN; PGIDIT 04PXIC20903PN), the Centro de Supercomputación de Galicia (CESGA) for their assistance with the computational work, and Yamakawa Chemical Industry Co. Ltd. for their gift of MPA.

Supporting Information Available: Figures 1S and 2S showing the main shielding effects in a model triol (full drawing, Figure 3S), protocol and graphical summary for assignment, experimental details, and NMR spectra of MPA esters **1**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0616135