JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

General Quantum-Based NMR Method for the Assignment of Absolute Configuration by Single or Double Derivatization: Scope and Limitations

María M. Zanardi,[†,‡] Franco A. Biglione,[‡] Maximiliano A. Sortino,[†] and Ariel M. Sarotti*[,§]

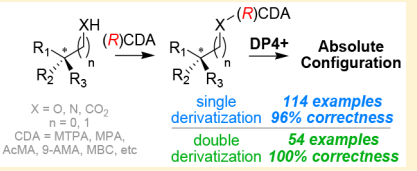
[†]Área Farmacognosia, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, Rosario 2000, Argentina

[‡]Facultad de Química e Ingeniería del Rosario, Pontificia Universidad Católica Argentina, Av. Pellegrini 3314, Rosario 2000, Argentina

[§]Instituto de Química Rosario (CONICET), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, Rosario 2000, Argentina

Supporting Information

ABSTRACT: The determination of the absolute configuration of chiral alcohols and amines is typically carried out with modified Mosher methods involving a double-derivatization strategy. On the other hand, the number of robust and reliable methods to accomplish that goal using a single derivatization approach is much less abundant and mainly limited to secondary alcohols or primary amines. Herein, we report a conceptually novel strategy to settle the most likely absolute configuration of a wide variety of substrates and chiral derivatizing agents following a single-derivatization experiment coupled with quantum calculations of NMR shifts and DP4+ analysis. Using an ambitious set of 114 examples, our methodology succeeded in setting the correct absolute configuration of the substrates in 96% of the cases. The classification achieved with secondary alcohols, secondary amines, and primary amines herein studied was excellent (100%), whereas more modest results (89%) were observed for primary and tertiary alcohols. Moreover, a new DP4+ integrated probability was built to strengthen the analysis when the NMR data of the two possible diastereoisomers are available. The suitability of these methods in solving the absolute configuration of two relevant cases of stereochemical misassignment ((+)-*erythro*-mefloquine and angiopterlactone B) is also provided.



INTRODUCTION

The determination of the absolute configuration (AC) is one of the most important and challenging stages during the structural elucidation of chiral molecules. To date, several methods are available, including X-ray crystallography analysis,[1] chiroptical spectroscopy,[2] chemical synthesis,[3] and NMR analysis.[4] Interestingly, all these methods might suffer from inaccuracies potentially leading to a wrong assignment,[5] making AC determination a fervent area of research.

Among the different approaches that rely on the basis of NMR spectroscopy, those involving chiral derivatizing agents (CDA) are perhaps the most popular ones.[4] A wide variety of CDAs have been described, and in all cases, the strategy involves the formation of a covalent linkage between the CDA and the substrate. Commonly, the experiment requires two derivatizations with both the (*R*)- and (*S*)-enantiomers of the chiral reagent (CDA), in order to determine the difference in chemical shifts of the nuclei of the substrate surrounding the derivatized center ($\Delta\delta^{RS}$ values). Depending on the magnitude and sign of the $\Delta\delta^{RS}$ values for the different substituent groups of the substrate, the AC can be determined following a given conformational model, which depends on the nature of the substrate and CDA (Figure 1).

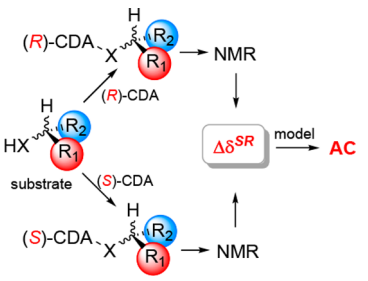


Figure 1. Schematic representation of the AC determination by NMR following a double-derivatization approach.

Since the pioneering work of Mosher in 1973 (introducing the so-called Mosher reagent, methoxytrifluoromethylphenylacetic acid, MTPA),[6] the number of CDAs and methodologies has increased significantly.[4] Nowadays, robust and reliable methods are available for primary, secondary, and tertiary alcohols, diols, thiols, primary and secondary amines, carboxylic acids, and sulfoxides, among others.[4]

Received: July 10, 2018
Published: September 4, 2018

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

One straightforward simplification to the process is to restrict the experimental procedure to the synthesis of only one of the two possible isomers resulting from either the (*R*)- or the (*S*)-CDA. However, in such a single derivatization alternative, the conclusion must be drawn with half of the experimental information available in a double-derivatization procedure. Therefore, the scenarios in which the former offers confident results are narrow.[4] One common approach limited to secondary alcohols requires the use of 9-AMA (vide infra), as the high anisotropy generated by the anthracene group often generates $\Delta\delta$ values large enough to allow a safe assignment.[7] Another strategy was developed for α-chiral secondary alcohols or primary amines with MPA as CDA and involves recording the NMR spectra before and after modification of the conformational equilibrium by lowering the temperature of the probe or by complexation with barium salts (Figure 2).[4,8]

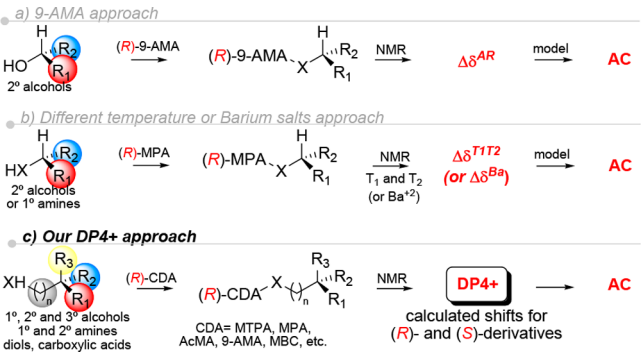


Figure 2. Schematic representation of the different approaches to determine AC following a single derivatization.

In any case, the need for an accurate and robust conformational model is required to understand the selective shielding/deshielding induced by the aromatic group typically present in most CDAs. In this regard, it is important to point out that each conformation plays a different role in terms of the strength and direction of the anisotropic effect of the aromatic moiety on the neighboring groups. Hence, whenever the real conformational equilibrium differs from the conformational model developed to predict the AC, the analysis might lead to a mistaken conclusion. This, coupled with small $\Delta\delta$ values and sign inconsistencies, is one of the most common sources of error in AC determination by CDAs.[4] Another typical mistake arises when using MTPA as CDA, since the Mosher esters change their Cahn–Ingold–Prelog label when obtained from the corresponding acid chlorides.[9]

Herein, we propose a new and more general alternative for a wide variety of substrates and CDAs based on the outstanding ability of quantum methods to predict the NMR properties of molecules (Figure 2c).

Recent years have witnessed an exponential growth in the field of structural or stereochemical assignment through quantum chemical calculations of NMR shifts and coupling constants.[10−12] The need for accurate and reliable predictions has motivated the development of new and sophisticated methodologies (including CP3,[13a] DP4,[13b] DP4.2,[13c] ANN-PRA,[13d,e] Case 3D,[13f,g] DU8+,[13h] and DiCE[13i]).[10a] Among them, we have recently introduced the DP4+ probability as a promising and effective elucidation tool to determine the most probable 3D structure of complex organic molecules.[14] We showed that the inclusion of unscaled data and the use of higher levels of theory for the GIAO NMR calculation procedure considerably improved the performance of the method.[14,15]

The ability of all of the current computational methodologies to differentiate among candidates bearing rigid structures and contiguous or near-by stereocenters tends to be excellent.[13−15] Nevertheless, when two stereoclusters are separated through flexible systems (such as methylenes, nonstereogenic quaternary carbons, alkenes, heteroatoms, etc.), the challenge of assessing the relative configuration becomes much more complicated.[16] In this regard, it is important to point out that in all the CDA derivatives, the stereocenters present in the substrate and CDA are separated by a flexible system composed by at least two atoms. Despite few isolated studies,[16a−c] the effectiveness of quantum-based NMR methods to tackle separated stereoclusters has not been thoroughly covered yet. In addition, the lack of systematic studies to fully explore the possibility of absolute configurational assignment by NMR calculations motivated us to evaluate the scope and limitations of DP4+ in this complex and useful task.

RESULT AND DISCUSSION

To achieve our goals, we selected an ambitious set of 114 examples of CDA derivatives of secondary alcohols (**1**−**56**), primary alcohols (**57**−**80**), primary amines (**81**−**94**), secondary amines (**95**−**98**), carboxylic acids (**99**−**102**), and tertiary cyanohydrins (**103**−**114**) featuring a wide variety of structural complexity and conformational freedom (Figure 3). Regarding the nature of the CDA, our selection covered the most popular ones, including MTPA, methoxyphenylacetic acid (MPA), mandelic acid (MA), acethylmandelic acid (Ac-MA), 9-anthrylmethoxyacetic acid (9-AMA), and 2′-methoxy-1,1′-binaphthalene-8-carbaldehyde (MBC). The absolute configurations of these compounds, many of them reported in earlier publications on the study of AC determination by NMR, were originally determined by well-known procedures (either the chiral substrates were purchased in enantiomerically pure forms, obtained from the chiral pool, or prepared using standard asymmetric transformations). In most examples, the key resonances were directly or indirectly (through the $\Delta\delta^{RS}$ values) assigned in the original publications. In cases where the experimental shifts of the least influential NMR data were incompletely assigned to any specific nuclei (common practice with carbon shifts), any remaining assignment was done by us after detailed analysis of the experimental and calculated chemical shifts and the experimental coupling constants and $\Delta\delta$ values as well. Following the DP4+ general and recommended procedure, the chemical shifts were computed at the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level of theory using the GIAO method implemented in Gaussian 09.[14,15] This level of theory was selected to afford good results at relatively low computational cost.[14] It is well-known that flexible molecules impose an additional difficulty to the NMR calculation process given the challenging conformational sampling. For that reason, in order to minimize the possibility of loosing significant rotamers, exhaustive conformational searches were done prior to the DFT calculation stage (see Computational Methods). With the shielding tensors in hand, we evaluated the DP4+ performance in establishing the correct absolute configuration of the studied compounds using the Excel spreadsheet provided free of charge at sarotti-NMR.weebly.com or as part of the Supporting Information of the

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

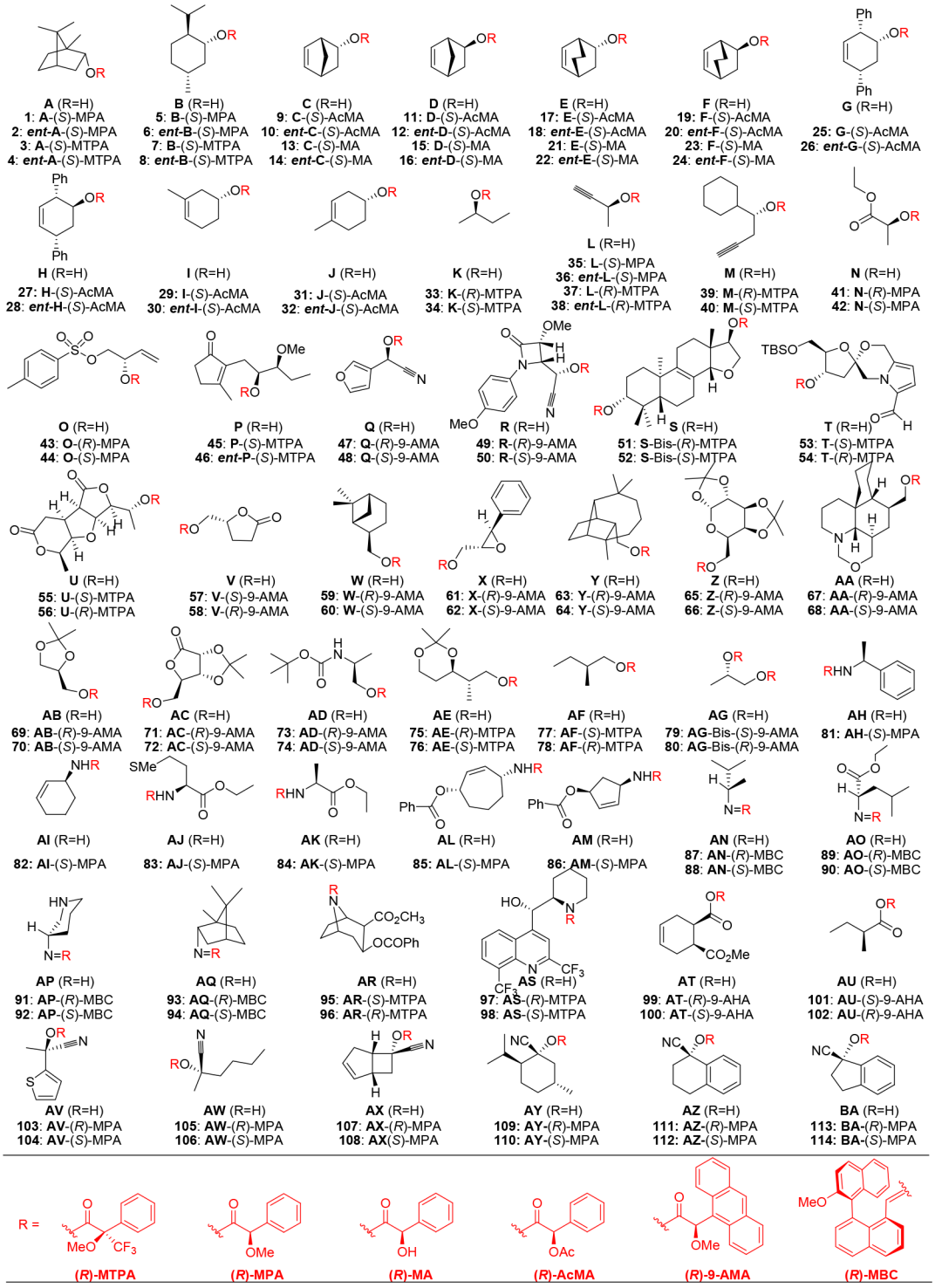


Figure 3. Test set of 114 CDA derivatives evaluated in this study.

original reference.[14] In all cases, we correlated the experimental NMR shifts of a given isomer with the calculated NMR values of both the correct isomer and the corresponding diastereoisomer with the opposite configuration at the CDA or substrate moiety. In this regard, it is important to point out that the experimental (and calculated) shifts of **x**-(*S*)-CDA must be identical than those of ***ent*-x**-(*R*)-CDA, as they are enantiomers.

We started our study by evaluating the performance of DP4+ in the determination of the absolute configuration *α*-chiral secondary alcohols (compounds **1**−**56**), among the most deeply studied and evaluated substrates using Mosher-type methods.[4] As depicted in Figure 4, upon correlating the computed NMR shifts of the two possible candidates of each compound with the corresponding experimental values, excellent levels of correct classification by DP4+ were achieved. In all cases, the correct isomer was identified as the most likely candidate, with DP4+ values ranging from 54% to >99.9%. In 86% of the cases, the right assignment was done in high overall confidence (DP4+ > 80%), which represents a noteworthy

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

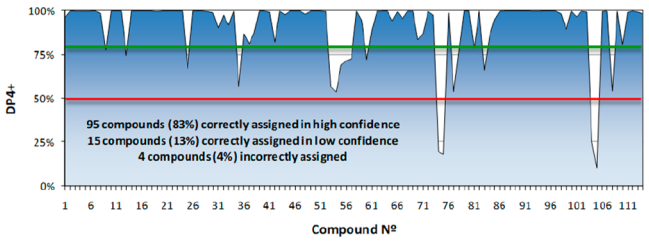
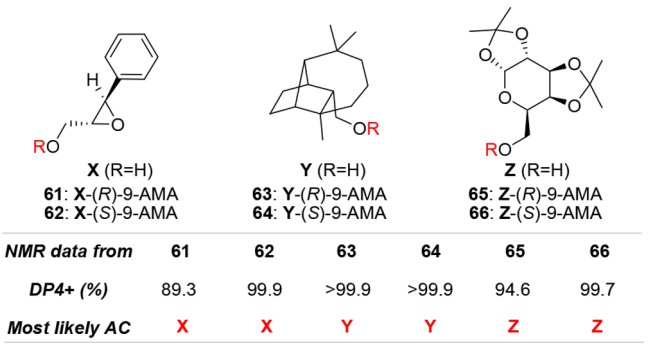


Figure 4. Overall performance of DP4+ computed for compounds **1**−**114**. Any value above the red line indicates that the correct isomer was identified as the most likely candidate (DP4+ >50%) and above the green line designates that the assignment was done in high confidence (DP4+ >80%).



NMR data from	61	62	63	64	65	66
DP4+ (%)	89.3	99.9	>99.9	>99.9	94.6	99.7
Most likely AC	X	X	Y	Y	Z	Z

Figure 5. Determination of the absolute configuration of alcohols **X**, **Y**, and **Z** following a single-derivatization strategy and DP4+ analysis.

result given the separation of the stereoclusters and the fact that only one set of experimental data was employed.

These encouraging results motivated us to turn our attention to primary alcohols bearing stereogenic centers at the β-position. The main difficulty surrounding AC determination of primary alcohols is linked to the higher conformational flexibility of the resulting CDA derivative and the larger separation between the groups neighboring the β-carbon and the aromatic fragment in the auxiliary reagent.[4] For that reason, there are few methods to determine AC of primary alcohols, and all of them involve a double-derivatization approach.[17] In addition, some substrates cannot be safely assigned as their conformational behavior does not follow the model developed to rationalize the $\Delta\delta^{RS}$ values (for example, alcohols **X**, **Y** and **Z**, Figure 3).[17a] In order to explore the classification ability of DP4+ in the case of singly derivatized primary alcohols, we selected 20 examples of 9-AMA derivatives (compounds **57**−**74** and **79**−**80**, Figure 2), including those three examples that could not be experimentally solved (compounds **61**−**66**). We also tested four derivatives of MTPA (compounds **75**−**78**, Figure 3), a nonrecommended reagent for these types of substrates. Interestingly, DP4+ performed nicely in this challenging test set, with 22 cases correctly assigned (Figure 4) and 82% of them being made in high confidence (DP4+ > 80%, Figure 4). On the other hand, in only two examples was the incorrect isomer selected in higher probability (compounds **74** and **75**). Notably, using our DP4+ formalism, the most likely configuration of the six diastereoisomers **61**−**66** could be successfully predicted in high confidence when the corresponding experimental NMR shifts collected for **61**−**66** were used. Hence, the absolute configuration of challenging alcohols **X**, **Y**, and **Z** could be correctly assessed even using a single-derivatization procedure (Figure 5).

We also tested DP4+ in other derivatives, including primary amines (compounds **81**−**94**), secondary amines (compounds **95**−**98**), carboxylic acids (compounds **99**−**102**), and tertiary cyanohydrins (compounds **103**−**114**). In the case of primary amines, we also covered MBC derivatives (compounds **87**−**94**). This last CDA is different to the others under study, which share a similar structural motif of α-branched carboxylic acid. In contrast, MBC is a chiral binaphthalene aldehyde that reacts with a primary amine to afford a chiral imine yielding often higher $\Delta\delta^{RS}$ values than those observed for other CDA reagents (such as MTPA or MPA).[18] The results afforded by DP4+ were excellent, with 32 out of 34 examples being successfully classified (Figure 4). This is a noteworthy outcome, as it is known that these motifs might be difficult substrates for AC determination, even from a double-derivatization perpective.[4]

To sumarize, using a test set of 114 examples, DP4+ succeeded in assessing the right absolute configuration in 96% of the cases (Figure 4), which is a noteworthy score given the flexibility of the systems under study and the separation of the two stereoclusters in the molecule. Moreover, in 83% of the cases the assignment was done in high confidence (DP4+ > 80%, Figure 4).

Scaled vs Unscaled Shifts. Apart from the level of theory employed during the NMR calculation procedure, the main feature of our DP4+ probability is the use of both scaled and unscaled shifts to correlate with the experimental values. Briefly, the scaling is a common procedure to remove systematic errors according to $\delta_s = (\delta_{calc} - b)/m$, where b and m are the intercept and slope, respectively, obtained from the plot of δ_{calc} against δ_{exp}. Such scaling factors (b and m) can be determined in two different ways, namely[10b] (a) using the NMR data from large databases (for example, see: http://cheshirenmr.info), in which the scaling factors b and m depend exclusively on the level of theory, or (b) from a plot of δ_{calc} against δ_{exp} for each particular compound under study. In this approach, the factors b and m vary not only with the level of theory but also with the experimental NMR values. Both DP4 and DP4+ were built using this last option,[13a,14] which was the method of choice in this study. Naturally, upon scaling, the computed shifts (δ_s) are closer to the experimental values (δ_{exp}) than the corresponding unscaled shifts (δ_{calc}). However, we have shown that there are two potential drawbacks related to this practice. On one side, the magnitude of the individual errors (differences between experimental and calculated shifts) becomes independent from the chemical environment of the molecule, which in general should not be the case. On the other hand, scaling might lead to false positives when an incorrect isomer affords an unforeseen better fit with the experimental data. Hence, DP4+ was built as a function of two contributions, sDP4+ and uDP4+, which reflect the probability distributions when using exclusively scaled and unscaled shifts, respectively. We demonstrated that the inclusion of unscaled shifts significantly improved the classification performance of DP4+, correcting in many cases a wrong assignment made by sDP4+.[14] This interesting compensation was also found in a recent benchmark study of the use of DP4+ in the stereoassignment of spiroepoxides or related quaternary carbon-containing oxiranes.[15] In an attempt to rationalize the role of scaled and unscaled shifts when dealing with Mosher-type derivatives, we next analyzed the contributions of sDP4+ and uDP4+ in the 114 examples herein discussed. As shown in

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

Figures S2 and S3, the classification performance dropped when using the scaled or unscaled data alone. For instance, sDP4+ and uDP4+ reproduced the correct absolute configuration in 103 and 99 cases, respectively, representing 90% and 87% of correct classification, respectively. These values were lower than the 96% observed with the full DP4+ formalism, clearly indicating a virtuous compensation between sDP4+ and uDP4+. In fact, the failure of sDP4+ in assigning the correct isomer was corrected by uDP4+ leading to a correct result (for example, in compounds **9**, **44**, **53**, **57**, **59**, **65**, **74**, **78**, **98**, and **104**) or vice versa (for example, in compounds **13**, **25**, **33**, **35**, **54**, **60**, **71**, **73**, **75**, **82**, **83**, **84**, **99**, and **108**). In contrast, when dealing with isomers showing similar ^{1}H NMR shifts (vide infra), this error compensation might not be achieved, potentially leading to a wrong assignment. In fact, this was the source of error in the case of compounds **74** and **75** (two of the four incorrectly assigned by DP4+ in this study). When correlating the experimental NMR data of **74** with the computational data of **73** and **74**, the incorrect isomer **73** showed higher sDP4+ values (94.79% vs 5.21%), whereas the uDP4+ values was higher for **74** (81.76% vs 18.24%). Unfortunately, the correction introduced by uDP4+ was no enough to turn back the bad assignment made by sDP4+, leading to an overall DP4+ of 19.77% for **74** and 80.23% for **73**. The exact opposite situation was observed for the pair **75** (DP4+ = 18.34%) and **76** (DP4+ = 81.66%) when using the experimental NMR data of **75**, as sDP4+ (65.24% in favor of **75**) was unable to revert the incorrect trend exerted by uDP4+ (89.31% in favor of **76**). It is important to point out that in the two last cases (**73** vs **74** and **75** vs **76**), minor differences were noticed in the calculated shifts for each isomer (with mean absolute error differences, ΔMAE, defined as the difference in the mean absolute error between the two candidate structures of only 0.02 ppm, and corrected mean absolute error differences, ΔCMAE, of 0.03 ppm (pair **73**−**74**) and 0.01 ppm (pair **75**−**76**).

Proton Data vs Carbon Data. Apart from the type of data (scaled or unscaled), we also aimed to understand the effect of the nucleus type (proton or carbon) in terms of the classification ability of DP4+. Although proton data was suggested to be more discriminating than carbon data for the stereochemical assignment of organic molecules,[19] we showed that both types of data were equally important from a DP4+ perspective using a broad set of diastereoisomers.[14,15] However, as expected when dealing with Mosher-type derivatives, we found that proton data are, by far, the most relevant for AC determination. As shown in Figures S4 and S5, whereas 92% of the examples were correctly reproduced by H-DP4+ (that is, the DP4+ probability computed using only proton data), the outcomes drastically worsened upon computing DP4+ with only carbon data (C-DP4+), showing only a 59% of right assignment. Nevertheless, a constructive compensation of errors was noticed in some cases in which a bad assignment made by H-DP4+ was corrected by C-DP4+ (for example, compounds **4**, **25**, **35**, **60**, **71**, and **108**), suggesting that whenever possible both types of NMR shifts should be employed. The fact that proton data were more relevant in the stereoassignment of Mosher-type diastereoisomers was fully consistent with the differences in the experimental NMR shifts exhibited in the diastereoisomeric pairs. In general, whereas the proton shifts can be significantly affected by the anisotropy exerted by the aromatic group at the CDA moiety, the effect on the carbon shifts is often much lower.[20] Hence, whenever the ^{1}H NMR shifts of the two possible diastereoisomers show high similarity, a slight random error in the computed ^{13}C shifts might lead to a wrong conclusion. This was the case of the failure of DP4+ when correlating the calculated NMR data of **103** and **104** with the experimental shifts of **104**. Here, the proton data computed for **104** showed a closer fit with the experimental values than **103** (CMAE 0.04 ppm vs 0.05 ppm, respectively), whereas the opposite trend was found with carbon data (CMAE 1.89 ppm vs 1.77 ppm, respectively). Accordingly, the H-DP4+ values were higher for **103** (95.2%), whereas the C-DP4+ values were higher for **104** (98.3%), shifting the overall DP4+ toward **104** (74.07%).

Scope and Limitations of DP4+ in Single-Derivatization Methods. The high classification performance offered by DP4+ offers an entry to a new single-derivatization strategy (Figure 2). In this way, the experimental shifts collected for a single diastereoisomer could be correlated with the theoretical shifts computed for the two possible candidates using DP4+ to determine the most likely relative configuration. Finally, with the knowledge of the absolute configuration of the CDA employed, the absolute configuration of the substrate can be easily guessed.

This approach can be illustrated with the results obtained with the (*S*)-MPA derivative of *endo*-borneol (**A**, Figure 6). By

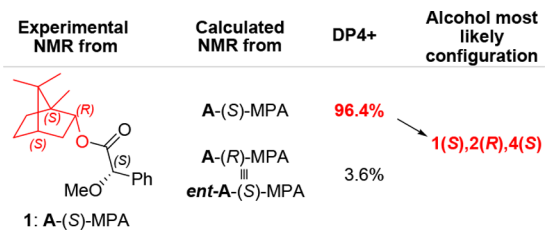


Figure 6. Schematic representation of the use of DP4+ in determining absolute configuration through a single-derivatization approach.

correlating the experimental NMR data of **A**-(*S*)-MPA (compound **1**) with the calculated values of the two possible diastereoisomers (**A**-(*S*)-MPA and ***ent*-A**-(*S*)-MPA, or equivalently, **A**-(*R*)-MPA), DP4+ identifies **A**-(*S*)-MPA as the most likely structure. As a result, since the configuration of the CDA is known, the absolute configuration of **A** can be correctly defined as 1(*S*),2(*R*),4(*S*). It should be important to highlight that the conclusion can be drawn with only the experimental NMR information on one isomer.

Apart from the apparent operational benefits associated with the preparation of only one isomer, particularly when the amount of sample is low, the present alternative does not require acquiring NMR spectra under special conditions. Moreover, it can be used for a broader range of substrates and CDAs, including systems that can only be solved by double derivatizations (for instance, primary alcohols, MTPA derivatives of secondary alcohols and primary amines, etc.).[4] In addition, since the procedure involves a free conformational sampling, it is not needed to follow a predetermined and fixed conformational model, which could not reflect the real equilibrium in certain systems.

As in the experimental determination of AC by NMR, the main limitation of the present methodology arises when the two CDA derivatives show very similar NMR spectra (that is, small $\Delta\delta^{RS}$ values). Hence, fortuitous errors in the calculations of the ^{1}H or ^{13}C shifts might lead to a wrong assignment

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

(which was the situation in the four cases incorrectly assigned by DP4+). For that reason, and despite the fact that the overall confidence in the assignments cannot be higher than 96% (which is the general classification capacity observed in this study), the present methodology affords more robust results when dealing with α-chiral secondary alcohols, secondary amines, and primary amines, which are expected to yield higher $\Delta\delta^{RS}$ values. In fact, according to our results, these types of substrates were correctly classified in all cases. On the other hand, the assignment made for primary and tertiary alcohols (known to afford lower $\Delta\delta^{RS}$ values, mainly in their MTPA or MPA derivatives) must be taken more cautiously. In this study, we tested 36 primary and tertiary alcohols, observing a 89% of correctness in the AC determination. Still, given the simplicity in the overall procedure, DP4+ can be an excellent alternative to suggest the most likely absolute configuration when the NMR data of only one CDA derivative is known.

DP4+ in Double-Derivatization Methods. DIP probability. Our present methodology can be also useful in the most popular double-derivatization approach. Since two different and independent DP4+ results are obtained in that case, two possible scenarios could be drawn depending on the values provided by each result: either the most likely candidate in both cases has the same absolute configuration at the target substrate (matched) or not (mismatched) (Figure 7).

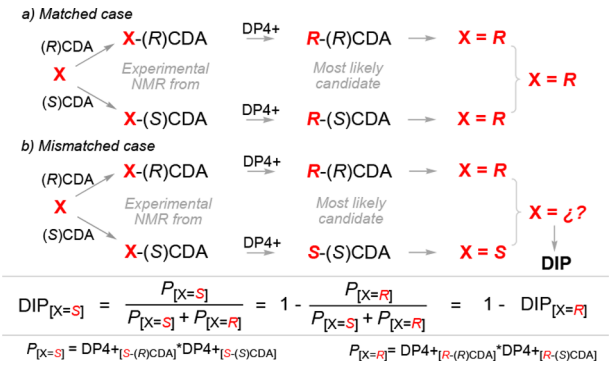


Figure 7. DP4+-integrated probability (DIP).

In the matched case, in turn, there are two possibilities: either DP4+ succeeds in assessing the correct configuration in both cases or it fails badly by simultaneously pointing toward the wrong candidate. However, according to the results presented herein, this latter case is highly unlikely. Setting the probability of DP4+ to afford a correct assignment to 96% (as we showed in this study), the probability associated with two consecutive wrong assignments could be guessed as 0.04 × 0.04 = 0.16%. In fact, such a situation did not take place in any of the 54 diastereoisomeric pairs under study (Figure 3). Hence, it should be postulated that, whenever the two DP4+ results point toward the same direction, both assignments are likely to be correct. On the other hand, in a mismatched case a more subtle analysis arises because one of the DP4+ results must be right and the other, inevitabl wrong. To unravel this issue, we developed a new probability distribution by merging the two individual DP4+ results. This DP4+ integrated probability (DIP) can be computed as shown in Figure 7, where $P_{[X=S]}$ and $P_{[X=R]}$ accounts for the combined probability that the correct configuration of the target molecule is *S* or *R*, respectively, which in turn can be computed as the product of the two individual DP4+ values corresponding for that specific configuration (X = *S* or *R*, respectively).

To understand the correction introduced by DIP in the few mismatched cases located, a detailed discussion regarding the assignment of **AV** will be given (Figure 8). After correlating the

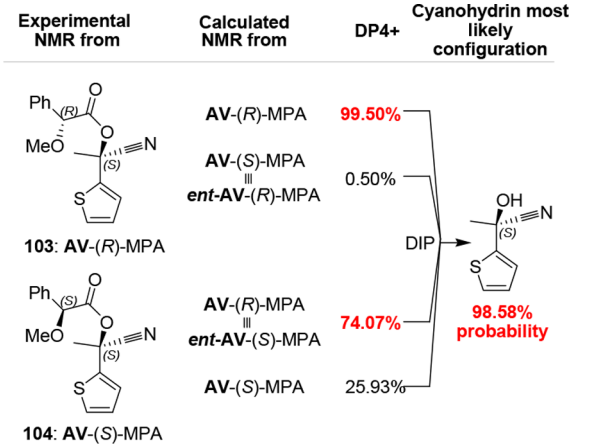


Figure 8. Schematic representation of the use of DP4+ in determining absolute configuration through a double-derivatization approach.

NMR data of **103** (the (*R*)-MPA derivative of **AV**) with the calculated shifts of (*S*)-**AV**-(*R*)-MPA and (*R*)-**AV**-(*R*)-MPA (equivalent to (*S*)-**AV**-(*S*)-MPA), DP4+ correctly identified the former as the most likely candidate. According to this result, the absolute configuration of cyanohydrin **AV** should be set as *S*. However, when the experimental NMR data of the (*S*)-MPA derivative (compound **104**) were used, isomer [(*R*)-**AV**-(*S*)-MPA] was the most probable one, suggesting that the absolute configuration of **AV** should be *R*. Taking collectively the two results, the DIP calculation correctly predicted the absolute configuration of (*S*)-**AV** in 98.6% probability ($DIP_{[X=S]}$ = 0.9950 × 0.2593/(0.9950 × 0.2393 + 0.0050 × 0.7407) = 0.9858). In this regard, it is important to emphasize that [(*R*)-**AV**-(*S*)-MPA] and [(*S*)-**AV**-(*R*)-MPA] are enantiomers (the same accounts for [(*R*)-**AV**-(*R*)-MPA] and [(*S*)-**AV**-(*S*)-MPA]), and for that reason, there is no need to compute the four possibilities, just one isomer of each pair.

Naturally, DIP calculations can be also performed to reinforce the analysis in matched situations. In this case, the result of integrating the two DP4+ values is to increase the certainty in the given assignment (Table S2 and Figure S6).

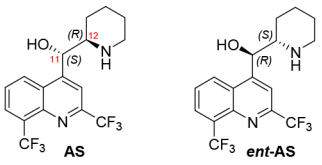
When computing the DIP probabilities for the 54 diastereoisomeric pairs under study, we were delighted to observe that the absolute configuration of the substrate was correctly reproduced in all cases, with DIP values ranging from 61% to >99.9% (Figure S6). In addition, in 96% of the cases the assignment was made in high certainty (DIP > 80%), indicating the power of the method when following a double-derivatization approach.

Finally, to demonstrate the usefulness of our methodology in the determination of the absolute configuration of natural and synthetic products using quantum calculations of NMR shifts, two recent and controversial case studies will be given and discussed.

Case Study 1. (+)-*erythro*-Mefloquine. The asymmetric total synthesis of a natural product is usually taken as a proof of structural and configurational identify. However, in some cases, the determination of the absolute configuration can be further

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

evasive, as in the case of (+)-*erythro*-mefloquine (compound **AS**, Figure 9). Briefly, *rac-erythro*-mefloquine (commercially



(+)-*erythro*-mefloquine

Authors	Configuration	Method
Carrol and co-workers (1974)	***ent*-AS**	CD
Karle and co-worker (2002)	**AS**	X-ray
Xie and co-workers (2008)	***ent*-AS**	total synthesis
Coltart and co-workers (2011)	***ent*-AS**	total synthesis
Reinscheid and co-workers (2012)	**AS**	NMR, ORD, CD, DFT
Bryant and co-workers (2012)	***ent*-AS**	total synthesis
Reinscheid and co-workers (2013)	**AS**	X-ray MTPA amides
Sonnet and co-workers (2013)	**AS**	X-ray and CD
Leonov and co-workers (2013)	**AS**	total synthesis
Chen and co-workers (2013)	**AS**	total synthesis
Hall and co-workers (2013)	**AS**	total synthesis

Figure 9. Temporal evolution in the assignment of the absolute configuration of (+)-*erythro*-mefloquine.

known as Lariam) was developed by Roche in the 1970s as an antimalarial agent. One of the major problems associated with this drug is the neuropsychiatric adverse effect generated by the levorotatory enantiomer.[21] Given the sharp differences exhibited by the two enantiomers in terms of pharmaceutical activities, several researchers attempted to determine the absolute configuration (+)-*erythro*-mefloquine. The results were, however, ambiguous and controversial. Carroll and co-workers first suggested the (11*R*,12*S*) configuration for the dextrorotatory isomer based on circular dichroism (CD) and empirical rules (***ent*-AS**, Figure 9),[22a] whereas Karle settled the same configuration for the levorotatory isomer using the anomalous signal from single-crystal X-ray diffraction.[22b] The first total synthesis of (+)-*erythro*-mefloquine by Xie et al. in 2008 supported the assignment of Carroll,[22c] but a more recent study by Griesinger, Reinscheid and co-workers combining NMR, ORD, CD and DFT techniques suggested that Karle was right.[22d] However, two additional total syntheses reignited the dispute by claiming the (11*R*,12*S*) configuration for (+)-*erythro*-mefloquine.[22e,f] To terminate this puzzling situation, Reinscheid, Dittrich, Griesinger, and co-workers determined the (11*S*,12*R*) configuration for the (+)-isomer by X-ray analysis of the resulting MTPA amides of the two enantiomers of *erythro*-mefloquine.[23] A few months later, Sonnet and co-workers arrived at the same conclusion by X-ray crystallography, CD spectroscopy, and molecular modeling,[22g] and their results were further validated by three total syntheses published the same year.[22h−j]

To understand how our methodology could have been useful to settle this 40-year controversy, we computed the NMR shifts of the two (*R*)- and (*S*)-MTPA amides of (11*S*,12*R*)-*erythro*-mefloquine (compounds **97** and **98**, Figure 3). Upon correlating with the experimental NMR data collected for the (*R*)-MTPA derivative of (+)-*erythro*-mefloquine, isomer **97** (**AS**-(*R*)-MPTA) was identified as the most likely one by our DP4+ calculations (>99.9%, Figure 10), allowing us to set the 11*S*,12*R* configuration for the dextrorotatory isomer. The same conclusion was achieved when the experimental shifts of the (+)-*erythro*-mefloquine-

Experimental NMR from	Calculated NMR from	DP4+	Most likely configuration
(+)-*erythro*-mefloquine (*R*)-MTPA	**AS**-(*R*)-MTPA	>99.9%	**AS** (11*S*,12*R*)
	AS-(*S*)-MTPA ‖ ***ent*-AS**-(*R*)-MTPA	<0.1%	
(+)-*erythro*-mefloquine (*S*)-MTPA	**AS**-(*R*)-MTPA ‖ ***ent*-AS**-(*S*)-MTPA	1.5%	**AS** (11*S*,12*R*)
	AS-(*S*)-MTPA	98.5%	

Figure 10. DP4+ in the assignment of the absolute configuration of (+)-*erythro*-mefloquine.

(*S*)-MTPA amide were used, with isomer **98** being correctly classified in high confidence (98.5%). Hence, DP4+ could predict the correct configuration of *erythro*-mefloquine using a single-derivatization approach by preparing either of the two MTPA diastereoisomers. Naturally, using the NMR shifts of the two derivatives (double derivatization), the DIP calculations correctly predict the 11*S*,12*R* configuration in high probability (>99.9%).

Case Study 2: (+)-Angiopterlactone B. This complex bis-lactone metabolite was isolated from the rhizome of *Angiopteris caudatiformis* by Zou and co-workers in 2009.[24] The plane structure and relative configuration were determined by extensive NMR and MS studies, further verified by X-ray crystallography analysis. Using the CD excitation chirality method, the authors suggested the 4*R* and 3′*R* configurations, whereas the configuration at C-6′ was settled as *S* by the modified Mosher method. Hence, the absolute configuration of (+)-angioperlactone B was assigned as 4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S* (compound ***ent*-U**, Figure 11).[24]

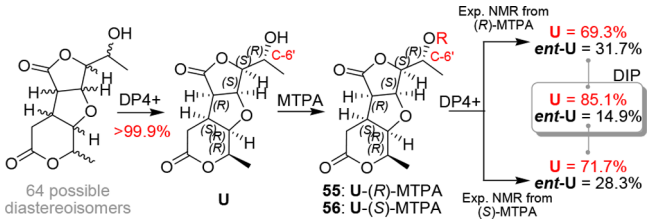


Figure 11. DP4+ in the assignment of the relative and absolute configuration of (+)-angiopterlactone B.

However, in 2017, Lawrence and co-workers accomplished the first total synthesis of the proposed structure of (+)-angiopterlactone B and observed that the synthetic sample displayed opposite sign in the optical rotation ($[\alpha]_D = -25$) compared to that reported for the natural product ($[\alpha]_D = +22$), suggesting the need for revision of the original structure.[25a] Few months later, Bhattacharya and co-workers independently arrived the same conclusion through the synthesis of the two enantiomers of angiopterlactone B, showing that the natural dextrorotatory isomer has the 4*S*,5*R*,6*R*,2′*S*,3′*S*,4′*R*,6′*R* configuration (compound **U**, Figure 11).[25b]

To show the power of our computational tools in establishing both the relative and absolute configurations of natural products, we carried out an in silico reassignment of (+)-angiopterlactone B. According to our computational work, when the NMR data of the natural product were correlated with the calculated shifts of all possible 64 diastereoisomers, DP4+ identified the correct relative configuration in high

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

probability (Figure 11). Next, to determine which enantiomer should be the correct (+)-angiopterlactone B, we computed the NMR shifts of the two possible MPTA esters for further comparison with the experimental data of the corresponding derivatives. However, after detailed analysis of the information provided by the isolation team, we concluded that the authors did not consider the change in the Cahn−Ingold−Prelog label when preparing the MTPA esters from the corresponding acid chlorides.[26] In fact, when correlating the NMR shifts computed for **55** (**U**-(*S*)-MTPA, equivalent to ***ent*-U**-(*R*)-MTPA) and **56** (**U**-(*R*)-MTPA, equivalent to ***ent*-U**-(*S*)-MTPA) with the experimental shifts of the (*R*)-MTPA ester of (+)-angiopterlactone B (which according to our hypothesis were originally reported for the (*S*)-MTPA derivative),[26] DP4+ suggests that **56** is the most likely one (69%, Figure 11). Since the configuration of the MTPA is *R*, the absolute of the natural product should be **U**. Following a similar reasoning, when using the experimental NMR shifts of the (*S*)-MTPA ester (originally reported for the (*R*)-MTPA ester), structure **55** was now the most likely candidate by DP4+ (72%), reinforcing the previous assignment. Combining the two DP4+ results using our DIP probability, the absolute configuration of natural (+)-angiopterlactone B can be defined as 4*S*,5*R*,6*R*,2′*S*,3′*S*,4′*R*,6′*R*, in excellent accordance with the synthetic evidence.[25] Admittedly, without having access to authentic sample of the natural product the previous analysis only represents a sound explanation for the origins of the misassignment.

CONCLUSION

In summary, the classification ability of DP4+ has been thoroughly evaluated in 114 examples of CDA derivatives featuring a wide diversity of structural and stereochemical motifs. The performance of the method varied from very good to excellent, depending upon the nature of the CDA and the substrate, allowing the assignment of the most likely absolute configuration of alcohols and amines following a single derivatization approach. The classification level observed with secondary alcohols, secondary amines, and primary amines was high (100%), whereas in the case of primary and tertiary alcohols the results were more modest (89%). Moreover, in the most typical scenario of a double derivatization, the two independent DP4+ results can be combined into a single DIP probability, which correctly identified the AC of all the 54 diastereoisomeric pairs under study.

On the basis of these results, we suggest that DP4+ emerges as a powerful and simple tool to suggest the absolute configuration of organic molecules, which could be used in combination with other techniques to reinforce or challenge a certain assignment.

EXPERIMENTAL SECTION

Computational Methods. All of the DFT calculations were performed using Gaussian 09.[27] For all compounds depicted in Figure 3 and the corresponding diastereoisomer with the opposite configuration at the CDA or substrate moiety, the conformational searches were done in the gas phase using the MMFF force field (implemented in Spartan '08).[28] The rotatable bonds were analyzed typically following a 6-fold sampling without constraints. All ring-flip conformations of compounds containing flexible ring systems were also considered. It is well-known that the NMR calculations of flexible systems offer additional challenges given the possibility of losing relevant conformations during the conformational search stage. For that reason, we carried out systematic conformational searches, and all conformers within a 10 kcal/mol window from the global minima were kept for further geometry optimization at the DFT level. The choice for the 10 kcal/mol of cutoff was set as a balance between reducing the overall CPU calculation time and minimizing the possibility of losing further contributing conformers. The number of conformations obtained in each case varied significantly with the overall flexibility of the system, ranging from few dozens to >500. Final geometry optimization was carried out at the B3LYP/6-31G* level of theory in the gas phase (including frequency calculations to identify the nature of the stationary points found). The conformations within 2 kcal/mol from the B3LYP/6-31G* global minima were subjected to NMR calculations. Moreover, we randomly replicated the conformational searches of some compounds at the MM+ level using Hyperchem[29] (including the four compounds incorrectly assigned by DP4+) and did not find any additional significantly populated rotamer after B3LYP/6-31G* optimization stage. The magnetic shielding constants (σ) were computed using the gauge including atomic orbitals (GIAO) method,[30] the method of choice to solve the gauge origin problem,[10] at the PCM/mPW1PW91/6-31+G** level of theory. The calculations in solution were carried out using the polarizable continuum model, PCM,[31] with chloroform as the solvent. The unscaled chemical shifts (δ_u) were computed using TMS as reference standard according to $\delta_u = \sigma_0 - \sigma_x$, where σ_x is the Boltzmann averaged shielding tensor (over all significantly populated conformations) and σ_0 is the shielding tensor of TMS computed at the same level of theory employed for σ_x. The Boltzmann averaging was done according to eq 1

$$\sigma^x = \frac{\sum_i \sigma_i^x e^{(-E_i/RT)}}{\sum_i e^{(-E_i/RT)}} \quad (1)$$

where σ_i^x is the shielding constant for nucleus x in conformer i, R is the molar gas constant (8.3145 J K^{-1} mol^{-1}), T is the temperature (298 K), and E_i is the energy of conformer i (relative to the lowest energy conformer), obtained from the single-point NMR calculations at the corresponding level of theory. The scaled chemical shifts (δ_s) were computed as $\delta_s = (\delta_u - b)/m$, where m and b are the slope and intercept, respectively, resulting from a linear regression calculation on a plot of δ_u against δ_{exp}. The DP4 calculations were carried out using the Applet from the Goodman group (at www-jmg.ch.cam.ac.uk/tools/nmr/DP4/). The DP4+ calculations were carried out using the Excel spreadsheet available for free at sarotti-NMR.weebly.com, or as part of the Supporting Information of the original paper.[14]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01749.

Detailed DP4+ probabilities computed for all compounds, detailed DIP probabilities computed for all diastereoisomeric pairs, full list of experimental chemical shifts (with references), GIAO isotropic shielding tensors, and B3LYP/6-31G* Cartesian coordinates (with energies) of all compounds evaluated in this study (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: sarotti@iquir-conicet.gov.ar.

ORCID

Ariel M. Sarotti: 0000-0002-8151-0306

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

This research was supported by UNR (BIO 316), ANPCyT (PICT-2016-0116), and PhosAgro/UNESCO/IUPAC (Green Chemistry for Life Program, project 121).

■ REFERENCES

(1) Flack, H. D.; Bernardinelli, G. The use of X-ray crystallography to determine absolute configuration. *Chirality* **2008**, *20*, 681−690.

(2) Freedman, T. B.; Cao, X.; Dukor, R. K.; Nafie, L. A. Absolute configuration determination of chiral molecules in the solution state using vibrational circular dichroism. *Chirality* **2003**, *15*, 743−758.

(3) For recent examples, see: (a) Odagi, M.; Yamamoto, Y.; Nagasawa, K. Total Synthesis of (+)-Gracilamine Based on an Oxidative Phenolic Coupling Reaction and Determination of Its Absolute Configuration. *Angew. Chem., Int. Ed.* **2018**, *57*, 2229−2232. (b) Nicolaou, K. C.; Liu, G.; Beabout, K.; McCurry, M. D.; Shamoo, Y. Asymmetric alkylation of anthrones, enantioselective total synthesis of (−)-and (+)-viridicatumtoxins B and analogues thereof: absolute configuration and potent antibacterial agents. *J. Am. Chem. Soc.* **2017**, *139*, 3736−3746. (c) Chen, R.; Li, L.; Lin, N.; Zhou, R.; Hua, Y.; Deng, H.; Zhang, Y. Asymmetric Total Synthesis of (+)-Majusculoic Acid via a Dimerization−Dedimerization Strategy and Absolute Configuration Assignment. *Org. Lett.* **2018**, *20*, 1477−1480.

(4) For leading reviews, see: (a) Seco, J. M.; Quinoá, E.; Riguera, R. The assignment of absolute configuration by NMR. *Chem. Rev.* **2004**, *104*, 17−118. (b) Seco, J. M.; Quinoá, E.; Riguera, R. Assignment of the absolute configuration of polyfunctional compounds by NMR using chiral derivatizing agents. *Chem. Rev.* **2012**, *112*, 4603−4641. (c) Seco, J. M.; Quinoá, E.; Riguera, R. A practical guide for the assignment of the absolute configuration of alcohols, amines and carboxylic acids by NMR. *Tetrahedron: Asymmetry* **2001**, *12*, 2915−2925. (d) Seco, J. M.; Riguera, R. NMR Methods for the Assignment of Absolute Stereochemistry of Bioactive Compounds. *eMagRes.* **2015**, *4*, 1−30.

(5) (a) Suyama, T. L.; Gerwick, W. H.; McPhail, K. L. Survey of marine natural product structure revisions: A synergy of spectroscopy and chemical synthesis. *Bioorg. Med. Chem.* **2011**, *19*, 6675−6701. (b) Nicolaou, K. C.; Snyder, S. A. Chasing molecules that were never there: misassigned natural products and the role of chemical synthesis in modern structure elucidation. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.

(6) (a) Dale, J. A.; Mosher, H. S. Nuclear magnetic resonance enantiomer regents. Configurational correlations via nuclear magnetic resonance chemical shifts of diastereomeric mandelate, O-methyl-mandelate, and. alpha-methoxy-alpha-trifluoromethylphenylacetate (MTPA) esters. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. Correlation of configuration and fluorine-19 chemical shifts of alpha-methoxy-alpha-trifluoromethyl-phenyl acetate derivatives. *J. Org. Chem.* **1973**, *38*, 2143−2147.

(7) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. 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. *J. Am. Chem. Soc.* **1998**, *120*, 877−882.

(8) (a) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. Absolute configuration of secondary alcohols by ^{1}H NMR: in situ complexation of α-methoxyphenylacetic acid esters with barium (II). *J. Org. Chem.* **2002**, *67*, 4579−4589. (b) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. Role of barium (II) in the determination of the absolute configuration of chiral amines by ^{1}H NMR spectroscopy. *J. Org. Chem.* **2006**, *71*, 1119−1130.

(9) Maier, M. E. Structural revisions of natural products by total synthesis. *Nat. Prod. Rep.* **2009**, *26*, 1105−1124.

(10) For leading reviews, see: (a) Grimblat, N.; Sarotti, A. M. Computational chemistry to the rescue: Modern toolboxes for the assignment of complex molecules by GIAO NMR calculations. *Chem. - Eur. J.* **2016**, *22*, 12246−12261. (b) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. Computational prediction of ^{1}H and ^{13}C chemical shifts: A useful tool for natural product, mechanistic, and synthetic organic chemistry. *Chem. Rev.* **2012**, *112*, 1839−1862. (c) Bagno, A.; Saielli, G. Addressing the stereochemistry of complex organic molecules by density functional theory-NMR. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2015**, *5*, 228−240. (d) Tantillo, D. J. Walking in the woods with quantum chemistry−applications of quantum chemical calculations in natural products research. *Nat. Prod. Rep.* **2013**, *30*, 1079−1086. (e) Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. Determination of relative configuration in organic compounds by NMR spectroscopy and computational methods. *Chem. Rev.* **2007**, *107*, 3744−3779. (f) Navarro-Vázquez, A. State of the art and perspectives in the application of quantum chemical prediction of ^{1}H and ^{13}C chemical shifts and scalar couplings for structural elucidation of organic compounds. *Magn. Reson. Chem.* **2017**, *55*, 29−32.

(11) For seminal references, see: (a) Bagno, A.; Rastrelli, F.; Saielli, G. Toward the complete prediction of the ^{1}H and ^{13}C NMR spectra of complex organic molecules by DFT methods: application to natural substances. *Chem. - Eur. J.* **2006**, *12*, 5514−5525. (b) Bagno, A. Complete Prediction of the ^{1}H NMR Spectrum of Organic Molecules by DFT Calculations of Chemical Shifts and Spin−Spin Coupling Constants. *Chem. - Eur. J.* **2001**, *7*, 1652−1661. (c) Barone, G.; Gomez-Paloma, L.; Duca, D.; Silvestri, A.; Riccio, R.; Bifulco, G. Structure validation of natural products by quantum-mechanical GIAO calculations of ^{13}C NMR chemical shifts. *Chem. - Eur. J.* **2002**, *8*, 3233−3239. (d) Barone, G.; Duca, D.; Silvestri, A.; Gomez-Paloma, L.; Riccio, R.; Bifulco, G. Determination of the relative stereo-chemistry of flexible organic compounds by *ab initio* methods: conformational analysis and Boltzmann-averaged GIAO ^{13}C NMR chemical shifts. *Chem. - Eur. J.* **2002**, *8*, 3240−3245.

(12) For leading references, see: (a) Lodewyk, M. W.; Soldi, C.; Jones, P. B.; Olmstead, M. M.; Rita, J.; Shaw, J. T.; Tantillo, D. J. The Correct Structure of Aquatolide- Experimental Validation of a Theoretically-Predicted Structural Revision. *J. Am. Chem. Soc.* **2012**, *134*, 18550−18553. (b) Saielli, G.; Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Bagno, A. Addressing the stereochemistry of complex organic molecules by density functional theory-NMR: Vannusal B in retrospective. *J. Am. Chem. Soc.* **2011**, *133*, 6072−6077. (c) Jain, R.; Bally, T.; Rablen, P. R. Calculating accurate proton chemical shifts of organic molecules with density functional methods and modest basis sets. *J. Org. Chem.* **2009**, *74*, 4017−4023. (d) Kutateladze, A. G.; Mukhina, O. A. Relativistic Force Field: Parametric Computations of Proton−Proton Coupling Constants in ^{1}H NMR Spectra. *J. Org. Chem.* **2014**, *79*, 8397−8406. (e) Della-Felice, F.; Sarotti, A. M.; Pilli, R. A. Catalytic Asymmetric Synthesis and Stereochemical Revision of (+)-Cryptoconcatone H. *J. Org. Chem.* **2017**, *82*, 9191−9197. (f) Rychnovsky, S. D. Predicting NMR spectra by computational methods: Structure revision of hexacyclinol. *Org. Lett.* **2006**, *8*, 2895−2898. (g) Grimblat, N.; Kaufman, T. S.; Sarotti, A. M. Computational chemistry driven solution to rubriflordilactone B. *Org. Lett.* **2016**, *18*, 6420−6523.

(13) (a) Smith, S. G.; Goodman, J. M. Assigning the stereochemistry of pairs of diastereoisomers using GIAO NMR shift calculation. *J. Org. Chem.* **2009**, *74*, 4597−4607. (b) Smith, S. G.; Goodman, J. M. Assigning stereochemistry to single diastereoisomers by GIAO NMR calculation: The DP4 probability. *J. Am. Chem. Soc.* **2010**, *132*, 12946−12959. (c) Ermanis, K.; Parkes, K. E. B.; Agback, T.; Goodman, J. M. Doubling the power of DP4 for computational structure elucidation. *Org. Biomol. Chem.* **2017**, *15*, 8998−9007. (d) Sarotti, A. M. Successful combination of computationally inexpensive GIAO ^{13}C NMR calculations and artificial neural network pattern recognition: a new strategy for simple and rapid detection of structural misassignments. *Org. Biomol. Chem.* **2013**, *11*, 4847−4859. (e) Zanardi, M. M.; Sarotti, A. M. GIAO C−H COSY simulations merged with artificial neural networks pattern recognition analysis. Pushing the structural validation a step forward. *J. Org. Chem.* **2015**, *80*, 9371−9378. (f) Troche-Pesqueira, E.; Anklin, C.; Gil, R. R.; Navarro-Vázquez, A. Computer-Assisted 3D Structure Elucidation of Natural Products using Residual Dipolar Couplings. *Angew. Chem., Int. Ed.* **2017**, *56*, 3660−3664. (g) Navarro-Vázquez, A.; Gil, R. R.;

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

Blinov, K. Computer-Assisted 3D Structure Elucidation (CASE-3D) of Natural Products Combining Isotropic and Anisotropic NMR Parameters. *J. Nat. Prod.* **2018**, *81*, 203−210. (h) Kutateladze, A. G.; Reddy, D. S. High-Throughput in Silico Structure Validation and Revision of Halogenated Natural Products Is Enabled by Parametric Corrections to DFT-Computed ^{13}C NMR Chemical Shifts and Spin−Spin Coupling Constants. *J. Org. Chem.* **2017**, *82*, 3368−3381. (i) Xin, D.; Jones, P. J.; Gonnella, N. C. DiCE: Diastereomeric in Silico Chiral Elucidation, Expanded DP4 Probability Theory Method for Diastereomer and Structural Assignment. *J. Org. Chem.* **2018**, *83*, 5035−5043.

(14) Grimblat, N.; Zanardi, M. M.; Sarotti, A. M. Beyond DP4: An improved probability for the stereochemical assignment of isomeric compounds using quantum chemical calculations of NMR shifts. *J. Org. Chem.* **2015**, *80*, 12526−12534.

(15) Zanardi, M. M.; Suárez, A. G.; Sarotti, A. M. Determination of the relative configuration of terminal and spiroepoxides by computational methods. Advantages of the inclusion of unscaled data. *J. Org. Chem.* **2017**, *82*, 1873−1879.

(16) (a) Cen-Pacheco, F.; Rodríguez, J.; Norte, M.; Fernández, J. J.; Hernández Daranas, A. Connecting discrete stereoclusters by using DFT and NMR spectroscopy: The case of nivariol. *Chem. - Eur. J.* **2013**, *19*, 8525−8532. (b) Tarazona, G.; Benedit, G.; Fernández, R.; Pérez, M.; Rodríguez, J.; Jiménez, C.; Cuevas, C. Can Stereoclusters Separated by Two Methylene Groups Be Related by DFT Studies? The Case of the Cytotoxic Meroditerpenes Halioxepines. *J. Nat. Prod.* **2018**, *81*, 343−348. (c) Zuber, G.; Goldsmith, M. R.; Hopkins, T. D.; Beratan, D. N.; Wipf, P. Systematic Assignment of the Configuration of Flexible Natural Products by Spectroscopic and Computational Methods: The Bistramide C Analysis. *Org. Lett.* **2005**, *7*, 5269−5272. (d) Wang, C.-X.; Chen, G.-D.; Feng, C.-C.; He, R.-R.; Qin, S.-Y.; Hu, D.; Chen, H.-R.; Liu, X.-Z.; Yao, X. S.; Gao, H. Same data, different structures: diastereoisomers with substantially identical NMR data from nature. *Chem. Commun.* **2016**, *52*, 1250−1253.

(17) (a) Latypov, S. K.; Ferreiro, M. J.; Quiñoá, E.; Riguera, R. Assignment of the absolute configuration of β-chiral primary alcohols by NMR: scope and limitations. *J. Am. Chem. Soc.* **1998**, *120*, 4741−4751. (b) Fukui, H.; Fukushi, Y.; Tahara, S. NMR determination of the absolute configuration of β-chiral primary alcohols. *Tetrahedron Lett.* **2005**, *46*, 5089−5093. (c) Burns, A. S.; Wagner, A. J.; Fulton, J. L.; Young, K.; Zakarian, A.; Rychnovsky, S. D. Determination of the Absolute Configuration of β-Chiral Primary Alcohols Using the Competing Enantioselective Conversion Method. *Org. Lett.* **2017**, *19*, 2953−2956. (d) Ramon, D. J.; Guillena, G.; Seebach, D. Non-reductive Enantioselective Ring Opening of *N*-(Methylsulfonyl) dicarboximides with Diisopropoxytitanium $\alpha,\alpha,\alpha',\alpha'$-Tetraaryl-1,3-dioxolane-4,5-dimethanolate. *Helv. Chim. Acta* **1996**, *79*, 875−894.

(18) Fukui, H.; Fukushi, Y. NMR determinations of the absolute configuration of α-chiral primary amines. *Org. Lett.* **2010**, *12*, 2856−2859.

(19) (a) Chini, M. G.; Riccio, R.; Bifulco, G. Computational NMR Methods in the Stereochemical Analysis of Organic Compounds: Are Proton or Carbon NMR Chemical Shift Data More Discriminating? *Eur. J. Org. Chem.* **2015**, *2015*, 1320−1324. (b) Marell, D. J.; Emond, S. J.; Kulshrestha, A.; Hoye, T. R. Analysis of seven-membered lactones by computational NMR methods: proton NMR chemical shift data are more discriminating than carbon. *J. Org. Chem.* **2014**, *79*, 752−758.

(20) Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. ^{13}C NMR as a general tool for the assignment of absolute configuration. *Chem. Commun.* **2010**, *46*, 7903−7905.

(21) Schlagenhauf, P.; Adamcova, M.; Regep, L.; Schaerer, M. T.; Rhein, H. − G. The position of mefloquine as a 21st century malaria chemoprophylaxis. *Malar. J.* **2010**, *9*, 357−372.

(22) (a) Carroll, F. I.; Blackwell, J. T. Optical isomers of aryl-2-piperidylmethanol antimalarial agents. Preparation, optical purity, and absolute stereochemistry. *J. Med. Chem.* **1974**, *17*, 210−219. (b) Karle, J. M.; Karle, I. L. Crystal structure of (−)-mefloquine hydrochloride reveals consistency of configuration with biological activity. *Antimicrob. Agents Chemother.* **2002**, *46*, 1529−1534. (c) Xie, Z. − X.; Zhang, L. − Z.; Ren, X. − J.; Tang, S.-Y.; Li, Y. Asymmetric Synthesis of (+)-(11*R*, 12*S*)-Mefloquine Hydrochloride. *Chin. J. Chem.* **2008**, *26*, 1272−1276. (d) Schmidt, M.; Sun, H.; Rogne, P.; Scriba, G. K. E.; Griesinger, C.; Kuhn, L. T.; Reinscheid, U. M. Determining the absolute configuration of (+)-mefloquine HCl, the side-effect-reducing enantiomer of the antimalaria drug Lariam. *J. Am. Chem. Soc.* **2012**, *134*, 3080−3083. (e) Knight, J. D.; Sauer, S. J.; Coltart, D. M. Asymmetric total synthesis of the antimalarial drug (+)-mefloquine hydrochloride via chiral N-amino cyclic carbamate hydrazones. *Org. Lett.* **2011**, *13*, 3118−3121. (f) Hems, W. P.; Jackson, W. P.; Nightingale, P.; Bryant, R. Practical Asymmetric Synthesis of (+)-*erythro* Mefloquine Hydrochloride. *Org. Process Res. Dev.* **2012**, *16*, 461−463. (g) Dassonville-Klimpt, A.; Cézard, C.; Mullié, C.; Agnamey, P.; Jonet, A.; Da Nascimento, S.; Marchivie, M.; Guillon, J.; Sonnet, P. Absolute Configuration and Antimalarial Activity of *erythro*-Mefloquine Enantiomers. *ChemPlusChem* **2013**, *78*, 642−646. (h) Schützenmeister, N.; Müller, M.; Reinscheid, U. M.; Griesinger, C.; Leonov, A. Trapped in misbelief for almost 40 years: selective synthesis of the four stereoisomers of mefloquine. *Chem. - Eur. J.* **2013**, *19*, 17584−17588. (i) Zhou, G.; Liu, X.; Liu, X.; Nie, H.; Zhang, S.; Chen, W. A. Stereospecific Synthesis and Unambiguous Assignment of the Absolute Configuration of (−)-erythro-Mefloquine Hydrochloride. *Adv. Synth. Catal.* **2013**, *355*, 3575−3580. (j) Ding, J.; Hall, D. G. Concise synthesis and antimalarial activity of all four mefloquine stereoisomers using a highly enantioselective catalytic borylative alkene isomerization. *Angew. Chem.* **2013**, *125*, 8227−8231.

(23) Müller, M.; Orben, C. M.; Schützenmeister, N.; Schmidt, M.; Leonov, A.; Reinscheid, U. M.; Dittrich, B.; Griesinger, C. The Absolute Configuration of (+)-and (−)-*erythro*-Mefloquine. *Angew. Chem.* **2013**, *125*, 6163−6165.

(24) Yu, Y.-M.; Yang, J.-S.; Peng, C.-Z.; Caer, V.; Cong, P.-Z.; Zou, Z.-M.; Lu, Y.; Yang, S.-Y.; Gu, Y-Ch. Lactones from Angiopteris caudatiformis. *J. Nat. Prod.* **2009**, *72*, 921−924.

(25) (a) Thomson, M. I.; Nichol, G. S.; Lawrence, A. L. Total Synthesis of (−)-Angiopterlactone B. *Org. Lett.* **2017**, *19*, 2199−2201. (b) Kotammagari, T. K.; Gonnade, R. G.; Bhattacharya, A. K. Biomimetic Total Synthesis of Angiopterlactone B and Other Potential Natural Products. *Org. Lett.* **2017**, *19*, 3564−3567.

(26) According to the Experimental Section in ref 24, the (*S*)-MPTA and (*R*)-MPTA esters were prepared by reacting (+)-angiopterlactone with the (*S*)-MPTA and (*R*)-MPTA chlorides, respectively. However, it is well-known that the (*S*)-MPTA-Cl should yield the (*R*)-MTPA ester, and vice versa, since the Cahn−Ingold−Prelog labels change. For that reason, we believe that the experimental NMR shifts originally reported for the (*R*)-MPTA derivative should belong to the (*S*)-MTPA ester and vice versa.

(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.

(28) *Spartan'08*; Wavefunction: Irvine, CA.

(29) *Hyperchem Professional Release 7.52*; Hypercube, Inc., 2005.

(30) (a) Ditchfield, R. Molecular orbital theory of magnetic shielding and magnetic susceptibility. *J. Chem. Phys.* **1972**, *56*, 5688−5691. (b) Ditchfield, R. Self-consistent perturbation theory of diamagnetism: I. A gauge-invariant LCAO method for NMR chemical

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX

shifts. *Mol. Phys.* **1974**, *27*, 789−807. (c) McMichael Rohlfing, C.; Allen, L. C.; Ditchfield, R. Proton and carbon-13 chemical shifts: comparison between theory and experiment. *Chem. Phys.* **1984**, *87*, 9−15. (d) Wolinski, K.; Hinton, J. F.; Pulay, P. Efficient implementation of the gauge-independent atomic orbital method for NMR chemical shift calculations. *J. Am. Chem. Soc.* **1990**, *112*, 8251−8260.

(31) Tomasi, J.; Mennucci, B.; Cammi, R. Quantum mechanical continuum solvation models. *Chem. Rev.* **2005**, *105*, 2999−3094.

DOI: 10.1021/acs.joc.8b01749
J. Org. Chem. XXXX, XXX, XXX−XXX