Absolute Configuration Reassignment of Natural Products: An Overview of the Last Decade

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The assignment of absolute configuration (AC) is a crucial step in the structural characterization of natural products, especially for those subjected to biological assays. Methods such as X-ray crystallography, stereocontrolled organic synthesis, nuclear magnetic resonance (NMR), and chiroptical spectroscopies are commonly used to determine the AC of chiral natural compounds. Even with these well-established techniques, however, unambiguous stereochemical assignments of natural products remain a challenge, resulting in an increasing number of structural misassignments being reported every year. Herein, we will present the main techniques that have been used in AC reassignments of natural products over the last 10 years, along with some selected examples. Special attention will be paid to the strengths and weaknesses of each approach. With this, we expect to provide the readers with critical information to help them to choose the appropriate methods for correct AC determinations.

Keywords: secondary metabolites, stereochemical reassignment, structure revision, misassignment

1. Introduction

Natural products and/or natural product structural scaffolds have played a significant role in the drug discovery and development processes over the years due to their wide range of biological activities. Even today, a large number of new chemical entities of pharmaceutical interest are developed with the help of natural products, since they offer complementary features to synthetic compounds in terms of composition, weight, size, functional groups, and architectural and stereochemical complexity. Lovering et al. reported that both intricacy and the presence of chiral centers are correlated with the successful passage of compounds from discovery, through clinical testing, to drugs. Thus, such success of natural products in the drug discovery pipeline has been attributed to the structural complexity of molecules found in living organisms, which have an average of 6.2 chiral centers per molecule when compared to an average of 0.4 chiral centers in molecules found in synthetic combinatorial libraries. Although several chiral drugs currently in the market are racemates (equimolar mixture of two enantiomers), many stereoisomers of chiral drugs exhibit marked differences in their pharmacological, toxicological, pharmacokinetics, and metabolism properties. This is observed because the interaction between a drug molecule and its target is mostly dependent on the three-dimensional environment around them. Plenty of examples of chiral drugs whose enantiomers vary drastically in their properties are reported for commercially available drugs, such as the antidepressant citalopram and the antitubercular agent ethambutol. In the former, the (+)-(S)-enantiomer is 100 times more potent than the (−)-(R)-stereoisomer; in the latter, the (S,S)-enantiomer is active while the (R,R)-enantiomer causes optical neuritis that can lead to blindness. As a result, there currently is a tendency in the pharmaceutical industry to switch from racemates to single enantiomers.

In this context, the structural characterization of chiral compounds, especially those that will have their biological activities evaluated, must include the unambiguous assignment of their absolute configurations (AC). However,
even today, the configurational assignment of natural products remains a challenge.8

The main techniques available to determine AC are X-ray crystallography, nuclear magnetic resonance (NMR) methods, stereocontrolled organic synthesis, and chiroptical spectroscopy. Each of these methods, however, presents some limitations for natural product molecules. X-ray crystallography, despite providing resolution at atomic level, requires a single well-defined crystal,9 which can be difficult to achieve in the case of natural products, especially for terpenes and related molecules. NMR spectroscopy is the main technique used for small molecule structural elucidation, however, as it is normally used in isotropic media, it is intrinsically insensitive to chirality. To that end, it requires the use of chiral auxiliaries, chiral solvents and related methods.10 Stereocontrolled organic synthesis is dependent on the correct AC of both starting materials and products, besides being expensive, laborious, and time-consuming.11 Chiroptical methods, which include OR (optical rotation), ORD (optical rotatory dispersion), ECD (electronic circular dichroism), VCD (vibrational circular dichroism), and ROA (Raman optical activity), are naturally sensitive to chirality, yet also have limitations. Flexible molecules can be particularly difficult to analyze due to the presence of multiple conformers in solution which may present opposite optical contributions.12 Moreover, for ECD analyses, proper UV/Vis chromophores are required within the molecule. In the case of VCD and ROA, the determination of AC depends mainly on a good correspondence between experimental and theoretical spectra, that results in high computational demands.8

As a result, even with the use of these well-established methods, a significant number of errors in the AC determination of natural products still occur. A common practice within the natural product community involves the determination of the AC of natural products based on comparisons of the OR and/or ECD experimental data with those described for analogous molecules. In some cases, spectral analyses based on empirical rules are also carried out. Such approaches, however, are not always applicable since similar molecules, containing the same absolute stereochemistry, have been reported with oppositely-signed OR values, and empirical rules constantly present exceptions.13-15

Due to the points raised above and recent advancements in structural characterization techniques, a series of stereochemical reassignments of chiral molecules have been described in the literature.16 The present review has surveyed examples of natural products that have had their ACs reassigned over the 2010-2020 period. “Absolute configuration reassignment” or “stereochemical reassignment” associated with “natural products” were used as keywords to perform a search in the available databases (ACS, PubMed, RSC, Science Direct, SciFinder, Scopus, Web of Science, and Wiley databases). In the cases of compounds with multiple chiral centers, the reassignment of the AC commonly leads to (or derives from) revisions of the relative configuration. In this review, we considered as examples only the cases where the cited article mentions stereochemical corrections in absolute sense. Despite trying to address as many cases as possible within the chosen search criteria, this review does not aim to exhaust the literature. Its main goals are to evidence the gradual increase in the number of articles dealing with stereochemical reassignments of natural products over the last decade (Figure 1), describe the main techniques employed in the original incorrect assignments as well as those used for the stereochemical corrections. As computational methods have become a common tool in the structural elucidation process, some general guidelines for the correct prediction of spectral properties will also be provided. By doing this, we want to highlight the importance of the proper choice of either individual or combined methods to determine unequivocally the AC of natural products.

Figure 1. Number of articles dealing with absolute configuration reassignments of natural products over the last decade, according to the search criteria used.

2. Misassignments of the Absolute Configuration of Natural Products

In this section, we present a list of natural compounds subjected to the revision of AC over the last decade. The results will be presented based on the main method used in the reassignment.

2.1. Synthesis

Organic synthesis associated with NMR, X-ray crystallography and/or chiroptical methods has been by far the most widely used approach for the stereochemical reassignment of natural products (Table 1). About 70 percent of the articles surveyed in this review used this methodology.
Table 1. Absolute configuration reassignment of natural products using synthesis as the main approach (2010-2020)

| Initial structure | Initial structure determination methods | Revised structure | Methods used in the reassignment |
|-------------------|----------------------------------------|-------------------|----------------------------------|
| ![bisebromoamide](image) | chemical degradation and chiral HPLC[17] | ![(+)-bisebromoamide](image) | synthesis and comparison of OR and NMR data[18] |
| ![exciton chirality CD](image) | | ![(+)-fusarisetin A](image) | synthesis and comparison of OR and NMR data[20] |
| ![NMR and ECD analysis](image) | (+)-(6R,8S*,10S*,12S*,14S*,16R*)-cryptocaryol A (R = H) (+)-(6R,8S*,10S*,12S*,14S*,16R*)-cryptocaryol B (R = Ac) | ![(+)-cryptocaryol A (R = H)](image) ![(+)-cryptocaryol B (R = Ac)](image) | computation, total synthesis, and comparison of OR and NMR data[22] |
| ![2D NMR](image) | (-)-laurefurenyne A (3Z) (-)-laurefurenyne B (3E) | ![(-)-laurefurenyne A (3Z)](image) laurefurenyne B (3E) | synthesis, comparison of OR and NMR data and X-ray crystal data[24] |
| ![NMR](image) | (-)-Q-1047H-A-A (-)-Q-1047H-R-A | (-)-Q-1047H-A-A (-)-Q-1047H-R-A | synthesis, X-ray crystal data and comparison of OR and NMR data[26] |
| ![NMR, HRESIMS, and calculated ECD data](image) | (+)-(2R,10R,11S,19R*)-azonazine | (+)-(2S,10R,11S,19S*)-azonazine | synthesis, NMR data, modified Mosher and PGME analyses[28] |
| ![degradation/derivatization experiments, modified Mosher and PGME analysis](image) | didemnaketal B | didemnaketal B | synthesis, NMR data, modified Mosher and PGME analyses[30] |
Table 1. Absolute configuration reassignment of natural products using synthesis as the main approach (2010-2020) (cont.)

| Initial structure | Initial structure determination methods | Revised structure | Methods used in the reassignment |
|-------------------|-----------------------------------------|-------------------|----------------------------------|
| (+)-fortuine      |                                         | (+)-fortuine      | synthesis, X-ray crystal data and comparison of NMR, OR and ECD data$^{32}$ |
| (−)-lyngbyaloside B |                                         | (−)-lyngbyaloside B | synthesis and comparison of OR and NMR data$^{34}$ |
| (−)-(2R,3S,4S)-ribisin C | comparison of OR with analogues$^{37}$ | (−)-ribisin C | synthesis and comparison of OR and NMR data$^{36}$ |
| (+)-(15S,3R,5S)-diosniponol A |                                         | (+)-diosniponol A | synthesis and comparison of OR and NMR data$^{38}$ |
| (−)-(2E,5S,7S,9R,11R,12E,14Z,17R,18R,20R,21R,23R)-mandelalide A | hydrolysis and chiral GC-MS analysis and ROESY data$^{40}$ | (−)-mandelalide A | synthesis and comparison of OR and NMR data$^{40}$ |
| (−)-(1R,2E,4S,5R)-1-[(2R)-5-oxotetrahydrofuran-2-yl]-4,5-dihydroxy-hex-2-en-1-yl(2E)-2-methylbut-2-enoate | comparison with analogous compound$^{41}$ | (−)-(E)-{(1R,4S,5S,E)-4,5-dihydroxy-1-[(R)-5-oxotetrahydrofuran-2-yl]hex-2- enyl}-2-methylbut-2-enoate | synthesis and comparison of OR and NMR data$^{45}$ |
Table 1. Absolute configuration reassignment of natural products using synthesis as the main approach (2010-2020) (cont.)

| Initial structure | Initial structure determination methods | Revised structure | Methods used in the reassignment |
|------------------|----------------------------------------|-------------------|----------------------------------|
| (-)-lyngbyaloside C |                                         | NMR<sup>43</sup> | synthesis and comparison of NMR data<sup>44</sup> |
| (<-)-lyngbyaloside C |                                         | (->)-lyngbyaloside C |                                     |
| Yaku'amide A (R = H) Yaku'amide B(R = Me) | Marfey's and dansylation analyses<sup>45</sup> | Yaku'amide A (R = H) Yaku'amide B (R = Me) | synthesis and comparison of Marfey's analyses<sup>46</sup> |
| Maedamide | hydrolysis, chiral HPLC analysis, and modified Mosher analysis<sup>47</sup> | (+)-maedamide | synthesis and comparison of NMR data<sup>48</sup> |
| (-)-isosarcophytolide D | NMR<sup>49</sup> | (-)-isosarcophytolide D | synthesis and comparison of OR and NMR data<sup>50</sup> |
| (-)-isosarcophytolide D | degradation studies<sup>51</sup> | (-)-isosarcophytolide D | synthesis and comparison of OR and NMR data<sup>52</sup> |
| (-)-(2'R,2'R,2'S)-aspergillomarasmine A | biosynthetic considerations, hydrolysis and chiral HPLC analysis<sup>53</sup> | (-)-(2'S,2'S,2'S)-aspergillomarasmine A | synthesis and comparison of NMR data<sup>54</sup> |
| (-)-(30'R)-apratoxin E | modified Mosher analysis and ECD calculations<sup>55</sup> | (-)-(30'R)-apratoxin E | synthesis and comparison of NMR and OR data<sup>56</sup> |
| (+)(2'R,7'R,15'S,19'R,20'R)-alsmaphorazine E |                                         | (+)-alsmaphorazine E |                                     |
Table 1. Absolute configuration reassignment of natural products using synthesis as the main approach (2010-2020) (cont.)

| Initial structure | Initial structure determination methods | Revised structure | Methods used in the reassignment |
|-------------------|-----------------------------------------|-------------------|----------------------------------|
| (+)-chaetoviridin A | ECD and chemical reactions<sup>57</sup> | (+)-(75,4'R,5'R,11S)-chaetoviridin-A | synthesis and comparison of ECD and NMR data<sup>68</sup> |
| (-)-(3S,3'S,12R,12'S)-pestalospirane B | ECD calculations<sup>59</sup> | (-)-(3R,3'S,12S,12'S)-pestalospirane B | synthesis, comparison of ECD, and X-ray crystal data<sup>60</sup> |
| (-)-(9R)-mukanadin F | Mosher analysis<sup>61</sup> | (-)-(9S)-mukanadin F | synthesis, comparison of OR and NMR data<sup>62</sup> |
| (+)-sarcophytin | NMR and X-ray crystal data<sup>63</sup> | (+)-sarcophytin | synthesis, analysis of NMR data and ECD calculations<sup>65</sup> |
| (-)-mollenine A (R = H) | OR<sup>64</sup> | (-)-(3S,6S,14S,16S)-mollenine A (R = H) | synthesis and comparison of OR and NMR data<sup>66</sup> |
| (-)-mollenine B (R = CHO) | 2D NMR and comparison with analogues<sup>67</sup> | (-)-(3S,6S,14S,16S)-mollenine B (R = CHO) | synthesis and comparison of NMR and OR data<sup>68</sup> |
| (+)-repraesentin F | | (+)-repraesentin F | |
| (+)-2,18-seco-lankacidin B | NMR<sup>69</sup> | (45,5R)-2,18-seco-lankacidin B | synthesis and comparison of NMR data<sup>70</sup> |
| (-)-dragomabin | Hydrolysis and chiral HPLC analysis and comparison of OR and NMR data<sup>71</sup> | (-)-dragomabin | synthesis and comparison of OR and NMR data<sup>72</sup> |
Table 1. Absolute configuration reassignment of natural products using synthesis as the main approach (2010-2020) (cont.)

| Initial structure | Initial structure determination methods                    | Revised structure | Methods used in the reassignment |
|-------------------|-------------------------------------------------------------|-------------------|----------------------------------|
| ![Image](link)    | X-ray crystal data and modified Mosher analysis<sup>73</sup> | ![Image](link)   | synthesis and comparison of OR and NMR data<sup>74</sup> |
| ![Image](link)    | modified Mosher analysis and Murata’s J-based configurational analysis<sup>76</sup> | ![Image](link)   | synthesis and NMR analysis<sup>76</sup> |
| ![Image](link)    | ECD<sup>77</sup>                                             | ![Image](link)   | synthesis and comparison of OR and NMR data<sup>78</sup> |
| ![Image](link)    | biosynthetic considerations<sup>75</sup>                   | ![Image](link)   | synthesis and comparison of OR and NMR data<sup>75</sup> |
| ![Image](link)    | ECD calculations<sup>80</sup>                               | ![Image](link)   | synthesis and comparison of OR and NMR data<sup>81</sup> |
| ![Image](link)    | variable temperature Mosher analysis<sup>82</sup>           | ![Image](link)   | synthesis and comparison of NMR data<sup>83</sup> |
| ![Image](link)    | ECD calculations<sup>84</sup>                               | ![Image](link)   | synthesis and comparison of OR and NMR data<sup>85</sup> |
| ![Image](link)    | hydrolysis and Mosher analysis<sup>86</sup>                 | ![Image](link)   | synthesis and comparison of OR and NMR data<sup>87</sup> |
| ![Image](link)    | chaunopyran A s<sup>88</sup>                                | ![Image](link)   | synthesis and comparison of OR data, ECD calculations and X-ray crystal data<sup>89</sup> |
Table 1. Absolute configuration reassignment of natural products using synthesis as the main approach (2010-2020) (cont.)

| Initial structure | Initial structure determination methods | Revised structure | Methods used in the reassignment |
|-------------------|-----------------------------------------|-------------------|----------------------------------|
| (2'R,4'R)-caesalpinflavan B | ECD<sup>40</sup> | (+)-(2'S,4'R)-caesalpinflavan B | synthesis and biosynthetic considerations<sup>41</sup> |
| (−)-harziane | NMR and X-ray crystal data<sup>32</sup> | harziane | synthesis, comparison of NMR data, and X-ray crystal data<sup>33</sup> |
| asperipin-2a | hydrolysis and chiral HPLC analysis and NMR data<sup>34</sup> | asperipin-2a | synthesis and comparison of NMR data<sup>35</sup> |
| (−)(2R,3S,4R)-chaunopyran A | comparison of OR with analogue<sup>36</sup> | (−)(2S,3R,4S)-chaunopyran A | synthesis and comparison of OR and NMR data<sup>37</sup> |
| kasumigamide | NMR, hydrolysis, HPLC analysis and chemical derivatization experiments<sup>38</sup> | kasumigamide | synthesis, hydrolysis and Marfey’s analysis<sup>39</sup> |
| (−)(3R,6R,10S,11R,14R)-spiroviolene | enzymatic transformation and NMR<sup>40</sup> | (−)-spiroviolene | synthesis, computational investigations and NMR data<sup>30</sup> |

<sup>1</sup>Authors mention only the determination of the relative configuration. HPLC: high-performance liquid chromatography; OR: optical rotation; NMR: nuclear magnetic resonance; CD: circular dichroism; ECD: electronic circular dichroism; HRESIMS: high resolution electrospray ionization mass spectrometry; PGME: phenylglycine methyl ester; GC-MS: gas chromatography mass spectrometry; ROESY: rotating frame Overhause effect spectroscopy.

Most of the structural revisions using synthesis as the principal approach determine the AC of the natural product mainly by comparison of the OR data obtained for the synthetic compounds with those of the natural counterparts. An interesting example is the case of the sesquiterpene lineariifolianone. The AC of this compound, isolated from the plant *Inula lineariifolia*, was initially determined based on a combination of the modified Mosher method and X-ray crystal data as (−)-(1S,4R,5S,7S,10S)-lineariifolianone. However, in a recent work, Reber *et al.* have reported the total synthesis of lineariifolianone and, based on a comparison of OR and NMR data of the synthetic and the isolated compounds, they suggested that the AC of the natural product had been misassigned. To explain the
original misassignment, this later work points out that “Mosher ester analysis often gives erroneous results when applied to sterically hindered secondary alcohols”.74

Although the comparison of OR values between synthetic and natural compounds is widely used, a recent example highlights the risk of AC assignments based on this approach.102 The natural product (+)-frondosin B had its AC originally assigned by total synthesis by different groups,103 however conflicting results were observed. In 2018, Joyce et al.102 unambiguously confirmed the AC of this compound as (+)-(R)-frondosin B using chiroptical methods associated with quantum-mechanical calculations. The authors also discovered that a minor impurity resulting from different synthetic routes was responsible for the conflicting OR values of the synthetic products with the same AC.102 Therefore, we strongly discourage the comparison of OR values at single wavelengths as the main method to assign AC of chiral compounds in general.

The careful reading of the articles reported in this review also indicated that the need for stereochemical reassignment was, in many cases, due to previous errors in the relative configuration of the target compound. Two dioxomorpholines, named mollenines A and B, isolated from the ascostromata of *Eupenicillium molle* (NRRL 130062), had their relative stereochemistry deduced from nuclear overhauser effect spectroscopy (NOESY) analysis.65 Then, the AC of (−)-mollenine A was assigned by comparing the OR data of its hydrolysis product with that of a standard.65 The AC of (−)-mollenine B was assumed to be analogous to that of (−)-mollenine A. Years later, the total synthesis of these compounds led to the revision of their AC.66 As the NMR data of the synthetic and natural (−)-mollenine A were not compatible, an epimer of (−)-mollenine A was synthesized. The NMR and OR data of this epimer showed complete agreement with those reported for the natural compound. Furthermore, a comparison of experimental and calculated ECD spectra for both synthesized compounds supported the AC reassignment of natural (−)-mollenine A as 3S,6S,14S,16S.66

2.2. Chiroptical methods

Chiroptical methods, mainly associated with quantum-mechanical calculations, have been proved to be a powerful and reliable tool for the determination of AC of chiral compounds104 and, consequently, this methodology has also been used in several stereochemical revisions of natural products (Table 2).

### Table 2. Absolute configuration reassignment of natural products using chiroptical methods as the main approach (2010-2020)

| Initial structure | Initial structure determination method | Revised structure | Method used in the reassignment |
|-------------------|---------------------------------------|-------------------|---------------------------------|
| ![Image](image1.png) | ECD and empirical rules65 | (+)-(R)-3,4-dihydro-5-hydroxy-2,7-dimethyl-8-(3'-methyl-2''-butenyl)-2-(4'-methyl-1'',3''-pentadienyl)-2H-1-benzopyran-6-carboxylic acid | VCD and ECD associated with quantum-mechanical calculations14 |
| ![Image](image2.png) | X-ray crystal data and hydrolysis experiments66 | (−)-(2S,13S)-brevianamide M | VCD, ECD and ORD associated with quantum-mechanical calculations107 |
| ![Image](image3.png) | NMR and ECD compared with analogues106 | (+)-(7S,8S)-schizandrin | VCD and ECD associated with quantum-mechanical calculations109 |
| ![Image](image4.png) | | (+)-(7S,8S)-schizandrin | |
| Initial structure | Initial structure determination method | Revised structure | Method used in the reassignment |
|------------------|----------------------------------------|-------------------|---------------------------------|
| (+)-(3R,4R,6S)-3,6-dihydroxy-1-menthene | biosynthetic considerations$^{110}$ | (+)-(3S,4S,6R)-3,6-dihydroxy-1-menthene | VCD associated with quantum-mechanical calculations of some analogues and X-ray crystal data$^{111}$ |
| (-)-1,6-dihydroxy-2-menthene | authors drew the structure but did not mention the AC$^{112}$ | (+)-(1R,4S,6R)-1,6-dihydroxy-2-menthene | VCD associated with quantum-mechanical calculations of some analogues$^{113}$ |
| (-)-(75S,1'S,7'S,8'R)-sibiricumin A | ECD calculations using simplified model$^{113}$ | (-)-(7R,8S,1'R,7'R,8'S)-sibiricumin A | OR and ECD associated with quantum-mechanical calculations$^{114}$ |
| (+)-(S)-frondosin B | synthesis and comparison of OR data$^{103}$ | (+)-(R)-frondosin B | VCD and ECD associated with quantum-mechanical calculations$^{102}$ |
| (-)-(R)-distaminolyne A | synthesis and comparison of OR data$^{115}$ | (-)-(S)-distaminolyne A | exciton coupling ECD of synthetic fragment$^{116}$ |
| (+)-(1R,1'S)-cepharanthine | degradation methods$^{117}$ | (+)-(1R,1'R)-cepharanthine | VCD, ECD and ORD associated with quantum-mechanical calculations$^{118}$ |
| (2S)-14-deoxy-13(14)-dehydroterrefuranone | ECD$^{119}$ | (2R)-14-deoxy-13(14)-dehydroterrefuranone | Snatzke’s sector rules, modified Mosher analysis of analogue and ECD calculation of analogue$^{120}$ |
| (-)-(3,7,4'A,R)-agropyrenol | modified Mosher analysis$^{121}$ | (-)-(3,5,4'S)-agropyrenol | ECD associated with quantum-mechanical calculations$^{122}$ |
Cepharanthine is a bioactive bisbenzylisoquinoline alkaloid. The AC of (+)-cepharanthine was originally determined as 1R,1'S using degradation methods.117 In 2019, Ren et al.118 reassigned the ACs of (+)-cepharanthine and other 13 analogues by comparing experimental and calculated ORD, ECD and VCD spectra. However, even theoretical calculations can lead to AC misassignments.125 In order to guarantee the correct determination of AC by means of quantum chemical calculations, some factors must be considered, such as the methodological approach and the correct prediction of the conformational ensemble of a given molecule. This includes the choice of adequate levels of theory, comprehensive conformational searches, proper optimization of geometry and accurate simulations of the relative energies of the conformers.125 Good practices for the correct computation and analysis of chiroptical spectra can be found elsewhere.8,104,125,126

Recently, the cathecol derivative hinduchelin A was isolated from Streptomyces hindustanus and its AC was established by interpretation of ECD spectra associated with quantum chemical calculations as (−)-(7'S).80 One year later, the total synthesis of this compound was achieved and, based on the comparison of NMR and OR data, the stereochemistry of the natural hinduchelin A was reassigned as (−)-(7'R).128 Another case, widely discussed by Grauso et al.,125 is the assignment of the AC of pestalospirane B that was determined based on ECD calculations as 3S,3'S,12R,12'R59 and revised to 3R,3'R,12S,12'S by total synthesis, ECD and X-ray analysis.60

2.3. NMR methods

Few reports used NMR methods as the main methodology to reassign the AC of natural products (Table 3) over the considered time span. The case of the polyketide macrolactams heronamides A-C is an interesting example. These compounds were isolated from a Streptomyces sp. and had their structures determined based on spectroscopic analysis, Mosher’s method and biosynthetic considerations.127 In 2013, the AC of heronamide A was reassigned by interpretation of the NOESY data and modified Mosher analysis, since the original NMR data were not in agreement with the proposed stereochemistry. However, in contrast to the former work where only the 17-OH was esterified, in the latter, heronamide A was converted to 9,17-bis-(S)- or 9,17-bis-(R)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) derivatives. Based on this, the AC of natural (−)-heronamide A was revised to 2S,7S,8S,9R,12R,15S,16R,17S,19R.128

Table 2. Absolute configuration reassignment of natural products using chiroptical methods as the main approach (2010-2020) (cont.)

| Initial structure | Initial structure determination method | Revised structure | Method used in the reassignment |
|-------------------|----------------------------------------|-------------------|--------------------------------|
| (+)-cottoquinazoline F | NMR data and comparison with analogues123 | (+)-(3S,14S,16S,17S,19S)-cottoquinazoline F | ECD and NMR and X-ray crystal data124 |

Table 3. Absolute configuration reassignments of natural products using NMR method as the main approach (2010-2020)

| Initial structure | Initial structure determination method | Revised structure | Method used in the reassignment |
|-------------------|----------------------------------------|-------------------|--------------------------------|
| (+)-(3R,4R,6S)-plakortolide I | OR and NMR data129 | (+)-(3R,4R,6R)-plakortolide E | Mosher analysis130 |
Table 3. Absolute configuration reassignments of natural products using NMR method as the main approach (2010-2020) (cont.)

| Initial structure | Initial structure determination method | Revised structure | Method used in the reassignment |
|------------------|----------------------------------------|-------------------|---------------------------------|
| (-)-heronamide A | Mosher analysis\textsuperscript{127} | (-)(2S,7S,8S,9R,12R,15S,16R,17S,19R)-heronamide A | modified Mosher analysis\textsuperscript{128} |
| (+)-(6R,4'R,5'R,6'S)-synargentolide A | ECD and Mosher analysis\textsuperscript{111} | (+)-(6R,4'S,5'S,6'S)-synargentolide A | NMR coupling constant calculations and ECD\textsuperscript{132} |
| (+)-(3R,5S,10S,13R,17R)-xylogranatin F | ECD calculations and modified Mosher analysis\textsuperscript{133} | (3S,5S,10S,13R,17R)-xylogranatin F | GIAO NMR calculations\textsuperscript{134} |
| (+)-(7R,13S,15R,16R,17R,21R,23S,25R,26R,27S,29S)-phormidolide A | variable temperature Mosher analysis\textsuperscript{12} | phormidolide A | GIAO NMR calculations and anisotropic NMR\textsuperscript{135} |
| (21S,23R,25S,26R,27R,29R)-phormidolide A | synthesis and comparison of NMR data\textsuperscript{131} | | |
| (+)-(4aS,6R,8aS,9S)-diplopyrone | ECD and OR calculations\textsuperscript{136} | (+)-(4aS,6S,8aS,9R)-diplopyrone | NMR calculations and Mosher analysis\textsuperscript{137} |

OR: optical rotation; NMR: nuclear magnetic resonance; ECD: electronic circular dichroism; GIAO: gauge-including atomic orbitals.

2.4. X-ray crystallography

X-ray crystallography was employed as the main approach for the AC reassignment of natural products in three publications (Table 4) only. Despite being a powerful tool for AC determination, the difficulty in obtaining single crystals with suitable quality from natural products can explain the low number of reports using this methodology.
3. Quantum Chemical Calculations in Structure Elucidation of Natural Products

3.1. NMR calculations

A careful analysis of the articles dealing with the revision of the AC of chiral natural products covered by the present review revealed some approaches that can commonly lead to misassignments. One particularly critical aspect related to the AC determination is the correct assignment of the relative configuration.

The structural elucidation of natural products, including the relative configuration determination, is predominantly based on NMR experiments.\(^{143}\) Even with continuous advances in the field, misinterpretation of NMR data is still frequently observed in natural product chemistry.\(^{144}\) The presence of sample impurities, signal ambiguities and high molecular complexity can lead to an incorrect interpretation of the NMR data and consequent structural misassignments.\(^{145}\) One way to ensure the correct determination of relative configuration of molecules with more than one chiral center is the use of computational techniques. Quantum chemical calculations of NMR properties have become popular over the last years and nowadays such studies are routinely found in the literature. Such popularity can be ascribed to the possibility to discriminate closely related stereorecognitions for complex natural product molecules.\(^{144}\) This approach greatly

Table 4. Absolute configuration reassignments of natural products using X-ray crystallography data as the main approach (2010-2020)

| Initial structure | Initial structure determination method | Revised structure | Method used in the reassignment |
|------------------|----------------------------------------|-------------------|---------------------------------|
| ![(-)-haliclonadiamine](image) | synthesis and comparison of OR and NMR data\(^{138}\) | ![(-)-(1S,3R,8S,9R,14S,R,20R,22R)-haliclonadiamine](image) | X-ray crystal data and ECD associated with quantum-mechanical calculations\(^{139}\) |
| ![(-)-membranoid C](image) | NMR\(^{141}\) | ![(-)-(15S,16R)-membranoid C](image) | X-ray crystal and NMR data\(^{141}\) |
| ![(+)-membranoid D](image) | NMR data and comparison with analogues\(^{123,142}\) | ![+(+)-(3S,14S,16S,17S,19S)-cottoquinazoline E](image) | X-ray crystal data, NMR and ECD\(^{124}\) |
| ![(+)-cottoquinazoline E](image) | comparison of OR with analogues and biosynthesis considerations\(^{142}\) | ![+(+)-(3S,14S,16S,17S,19S)-cottoquinazoline E](image) | |
| ![(+)-cottoquinazoline G](image) | | ![+(+)-(3S,14S,16S,17S,19S)-cottoquinazoline G](image) | |

\(^{a}\)Authors mention only the determination of the relative configuration. OR: optical rotation; NMR: nuclear magnetic resonance; ECD: electronic circular dichroism.
improves the quality of structural clarification regarding relative stereochemistry and therefore helps to prevent errors in AC determinations.

One of the most common approaches to determine relative configuration of natural products from isotropic NMR calculations involves the simulation of 1H and/or 13C shielding constants (and thus chemical shifts) for all possible stereoisomers of a given molecule. Coupling constants can also be simulated. Routine methods involve gauge-including atomic orbitals (GIAOs) and model chemistries such as mPW1PW91/6-311+G(2d,p), PBE0/6-311+G(2d,p) or B3LYP/6-31+G(d,p) on B3LYP/6-31+G(d,p) or M062X/6-31+G(d,p) geometries. NMR calculation results can then be translated into structural information by assessing the goodness of fit between computed and experimental data. It can be done by means of artificial intelligence methods or by determining manually the most likely structure within a set of suitable candidates. Further analysis using the CP3 parameter or DP4 probability methods, which are the first of a series of useful tools, greatly help in the diastereoisomeric discrimination of complex molecules. Several comprehensive review articles are available in the literature that provide more in-depth information on the accurate simulation of NMR data.

### 3.2. Chiroptical properties calculations

As mentioned before, another important source of error in the AC determination of natural products is the comparison of the OR and/or ECD experimental data with those described for analogous molecules or even spectral analyses based on empirical rules. One way to prevent misassignments is the comparison of experimental data with density functional theory (DFT)-predicted spectra as well as the use non-empirical methods or quantum-chemically validated spectra-structure relationships. The comparison between calculated and experimental data greatly assists the unambiguous interpretation of experimental spectra by providing information on the origin of electronic or vibrational transitions as well as on the influence of conformational flexibility, solvation, and minor structural variations to the spectral shape. Notable developments in ab initio to predict theoretical spectra incorporated in commercially available software have contributed to a number of unambiguous AC determinations of natural products.

DFT-level calculations are generally the main computational method used in the quantum mechanical prediction of chiroptical spectroscopic properties. Despite a large number of DFT functionals available, B3LYP together with the 6-31G(d) basis set, either in gas phase or with implicit solvation, is still the most widely used. However, as B3LYP can provide inaccurate evaluations of conformer energy profiles, alternative functionals should be considered, such as B3PW91 or wB97XD. The choice of the most appropriate model chemistry will depend on the chiroptical property of interest. While B3LYP/6-31G(d) may suffice for some VCD spectral calculations, in the case of ECD for example, long-range correct functionals such as CAM-B3LYP and triple-zeta basis sets are recommended. A number of review articles can be found in the literature that provide detailed information and good practices for the accurate calculations of chiroptical properties.

### 4. Conclusions

The structural elucidation of natural products is a crucial part of the routine of research laboratories in this area. The complete structural characterization of natural compounds, however, including the exact spatial arrangement of their atoms, is still one of the most challenging steps. The methodologies used to assign the AC have evolved considerably and become more widely available, which has led to the AC reassignment of many natural products over the last decade, as demonstrated herein. The partnership between natural product chemistry and synthetic organic chemistry was the most used approach, followed by chiroptical methods, mainly associated with DFT calculations, and then NMR. It is worth mentioning that the unambiguous determination of the relative configuration of molecules with several stereogenic centers was a fundamental step for the correct (re)assignment of the AC. Incorrect relative configurations were responsible for many of the errors reported in the determination of the AC of natural compounds.

Thus, rigorous spectroscopic work using the available methods, either alone or in combination, is still the best approach for the unambiguous assignment of both relative and absolute configurations. These steps can be considered indispensable for the complete attribution of the structure of a natural product and provide further subsidies for biological tests and investigations of biosynthetic pathways. Finally, as already mentioned above, the assignments of AC based solely on comparison of OR values are strongly discouraged. Even in cases where the synthetic methodology affords the unambiguous AC of a given target molecule, the (re)assignment of the natural counterpart may not be reliable if only OR is considered. Despite of its simplicity and ease of use, OR values at single wavelengths may vary widely upon changes in solvent, sample concentration, and purity. As alternatives, methods
that provide information over a range of frequencies, such as ORD, ECD, VCD, ROA should be used instead.

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