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Survey of marine natural product structure revisions: A synergy of spectroscopy and chemical synthesis

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ABSTRACT

The structural assignment of new natural product molecules supports research in a multitude of disciplines that may lead to new therapeutic agents and or new understanding of disease biology. However, reports of numerous structural revisions, even of recently elucidated natural products, inspired the present survey of techniques used in structural misassignments and subsequent revisions in the context of constitutional or configurational errors. Given the comparatively recent development of marine natural products chemistry, coincident with modern spectroscopy, it is of interest to consider the relative roles of spectroscopy and chemical synthesis in the structure elucidation and revision of those marine natural products that were initially misassigned. Thus, a tabulated review of all marine natural product structural revisions from 2005 to 2010 is organized according to structural motif revised. Misassignments of constitution are more frequent than perhaps anticipated by reliance on HMBC and other advanced NMR experiments, especially when considering the full complement of all natural products. However, these techniques also feature prominently in structural revisions, specifically of marine natural products. Nevertheless, as is the case for revision of relative and absolute configuration, total synthesis is a proven partner for marine, as well as terrestrial, natural products structure elucidation. It also becomes apparent that considerable 'detective work' remains in structure elucidation, in spite of the spectacular advances in spectroscopic techniques.

1. Introduction

Natural products research has evolved into a multifaceted discipline at the interface of organic and analytical chemistry, biochemistry, biology, ecology and pharmaceutical sciences. As small molecules, which facilitate dynamic biological processes, natural products are also pivotal to the more recently designated fields of chemical and systems biology.[1] Therefore, the structural assignment of a new natural product molecule potentially provides the foundation for research in a multitude of disciplines, ultimately generating new therapeutic agents and/or new understanding of disease biology. The development of modern spectroscopic techniques has transformed the often painstaking structure assignment process, which previously relied on chemical degradation or derivatization followed by partial or total synthesis prior to the 1960's.[2] Subsequently, specialization in the spectroscopic structural assignment of natural products enabled the field of natural products chemistry to mature. Notably, it was only in this spectroscopic era that the field of marine natural products chemistry took shape, with the advent of SCUBA allowing exploration of shallow reef systems. One might then presume that the age-old partner of natural products chemistry, chemical synthesis, has had little application to the structural assignment of marine natural products. Indeed, today the processes of terrestrial and marine natural product isolation and structural determination are frequently streamlined and expeditious due to the evolving state-of-the-art in chromatographic[3] and spectroscopic[4,5] technologies. Consequently, the focus of natural products chemists has shifted from merely describing the chemical properties of newly isolated metabolites to investigate their biological properties, and also harnessing the biosynthetic capacity of the producing organisms for combinatorial biosyntheses of new analogues. Further opportunities of where and how to find new natural products, or their cryptic biosynthesis genes, are being addressed most recently by mining of microbial genomic data.[6] While the role of chemical synthesis in the pharmaceutical application and biosynthetic studies of marine natural products is easily recognized, the contribution of chemical synthesis to structure elucidation may be less apparent. Furthermore, the enduring fallibility of all structural assignment tools may be forgotten in view of the spectacular advances in analytical

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chromatographic and spectroscopic techniques, as well as chemical synthesis.

In 2005, Nicolaou and Snyder[2] published an inspiring and fairly comprehensive review of natural product structural revisions that were made possible by total synthesis over the period of 1990–2004. As the authors follow the evolution of natural products chemistry intertwined with techniques in chemical degradation, derivatization and total synthesis, they articulate amazement at the unexpectedly large number (over 300) and profoundness of structural misassignments made in relatively recent years. Structural misassignments were noted in virtually every compound class and included both constitutional and configurational errors in molecules of all sizes and degrees of complexity. Nicolaou and Snyder also discuss the ramifications of structural misassignments using high profile historical examples to highlight the potential to propose erroneous biosynthetic pathways for entire classes of compounds, and the costs associated with extensive detective work to revise a misassigned structure. Finally, the syntheses and collaborative reassignments of the complex natural products azaspiracid-1 and diazonamide A are discussed. The latter example in particular illustrates the development of new synthetic methodologies in the pursuit of molecular structures. A detailed and comprehensive 2009 review by Maier[7] extends this discussion of the role of total synthesis in the structural revision of natural products, highlighting a sustained rate of structural reassignments from 2005 to 2009. Maier also breaks down the types or sources of misassignments into subcategories of incorrect formula, constitution (planar connectivity), double bond configuration, absolute configuration, and one or several stereocenters assigned incorrectly, providing comprehensive treatment of numerous case studies.

These two reviews on the application of chemical (particularly total) synthesis to natural product structure elucidation, which are inclusive of both terrestrial and marine-derived metabolites, prompted our broad analysis and comparison between terrestrial and marine products, of the spectroscopic or chemical methods used in initial structural misassignments, detection of those misassignments and structural revisions. As has been highlighted in previous reviews, detection and revision of misassignments often constitute distinct and challenging steps, although they may be part of an iterative process. Given the comparative 'youth' of marine natural products chemistry, contemporary with the development of powerful spectroscopic methodologies, the role of total synthesis in the assignment of marine-derived structures was of specific interest. In addition, tabulation of revised marine natural product structures according to structural motif misassigned (within the two broad categories of constitution and configuration) draws attention to the limitations of particular techniques in certain structural contexts. The actual rate of structural misassignments remains elusive given the difficulty of estimating the total number of new natural products reported each year. However, Figure 1A shows that the number of all reported structural misassignments climaxed in the period 2001–2005, while the number of marine natural product misassignments was highest in the period 1996–2000 (Fig. 1B).

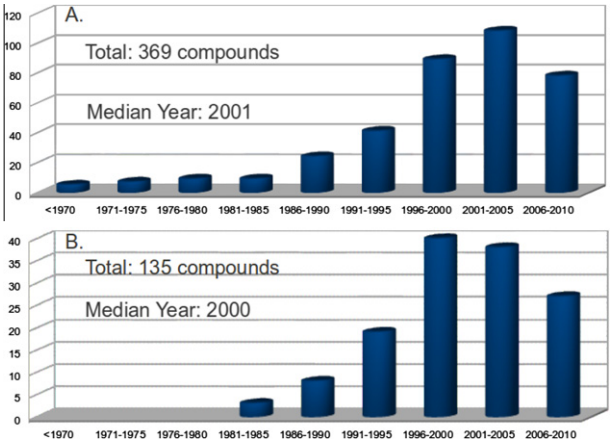


Figure 1. (A) Numbers of all natural products misassigned per 5-year period; (B) Numbers of marine natural products misassigned per 5-year period.

2. Sources of natural product structural misassignments

The considerable number of natural product structural misassignments reported each year elicits numerous questions within the two broad contexts of structure and corresponding assignment method. Consideration of structural elements most prone to misassignment and the techniques associated with these misassignments is undoubtedly an informative and educational pursuit. However, it may also provide deeper insight into the analytical process of structure elucidation to benefit the evolution of computer-assisted structure elucidation (CASE).[8] CASE mimics the human expert in making a logical inference of the most probable structure based on well-established correlations between spectral and structural features.

Given the relative ease of compiling data on the techniques used in structural assignments, Figure 2 presents the original techniques used for all misassigned natural products that were subsequently revised successfully (Fig. 2A), as well as the subset that were of marine origin (Fig. 2B).[9] The proportion of errors attributable to different techniques seems likely to reflect the frequency of use of those techniques. Thus, NOE data is the basis for the majority of structural misassignments (22% of total, 26% of marine), followed closely by NMR comparisons, and HMBC and other NMR-derived data, for both marine and terrestrial natural products. The high frequency of NOE-associated errors implies that configurational misassignments predominate over constitutional errors. Similarly, NMR comparisons (of ^{1}H and ^{13}C data) are used to infer configuration, as well as constitution, and may also propagate errors disproportionately when one considers that a majority of natural products occur in structural series, often based on detailed spectral analysis and assignment of only the major congener. However, a significant portion of all structural misassignments (11%) stem specifically from interpretation of HMBC data. This implies errors in bond connectivity of the planar structure (constitutional errors). Indeed, considering all natural products, constitutional errors (45%) rival configurational errors (55%), although to a lesser extent in the subset of marine natural products (33% and 67%, respectively). The logical follow-up questions elicited by these over-view analyses concern the nature of the constitutional or configurational errors and the associated techniques that were used. For the following discussion we focus on structural revisions of marine natural products in the period from 2005 to 2010, according to type of structural misassignment, as summarized in Tables 1–9. Remarkably, a large number (78) of the revised structures presented in these tables were first elucidated (misassigned) within the last decade.

2.1. Misassignments of constitution of marine natural products

The constitutional misassignments of marine natural products may be arranged into categories following the recurring themes of errors in cyclization (Table 1), regioisomerism (Table 2), substituent identity (Table 3), hydrocarbon chains (Table 4), and symmetry of dimerization (based on incorrect formula, Table 5).

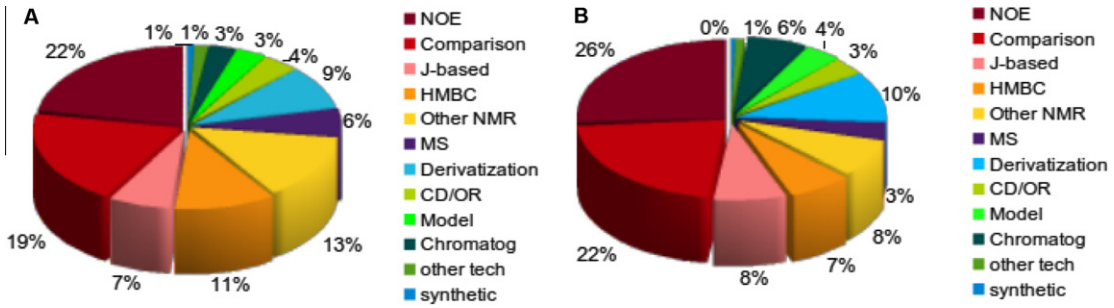
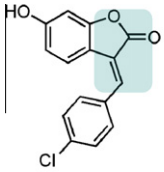
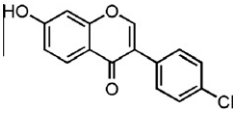
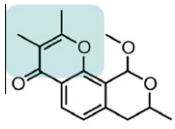
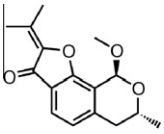
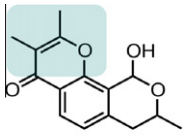
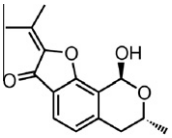
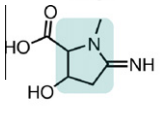
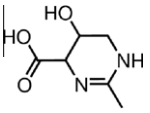
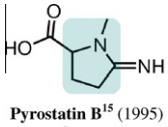
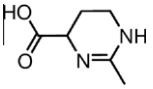
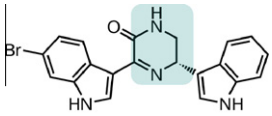
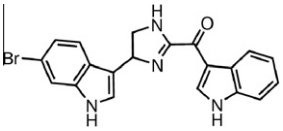


Figure 2. (A) Techniques used in the misassignment of all natural product structures revised during 2005–2010; (B) Techniques used in the misassignment of marine natural product structures revised during 2005–2010. Piechart key: NOE—NOE, NOESY, ROESY; Comparison—NMR comparison; *J*-based—coupling constant analysis; Other NMR—mostly 1D NMR, but includes COSY, HSQC, etc; MS—any MS technique except LC–MS; Derivatization—Marfey's, Mosher's, peptide hydrolysis, chemical correlation; CD/OR—circular dichroism or optical rotation; Model—any computational modeling; Chromatog—any TLC identification to HPLC (often in combination with 'Derivatization'); Other tech—IR, UV, biosynthetic considerations, etc; Synthesis—any of partial synthesis, model synthesis, semi-synthesis.

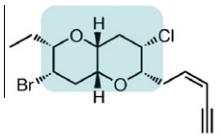
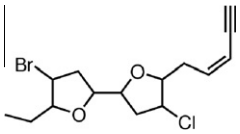
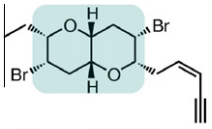
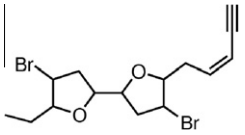
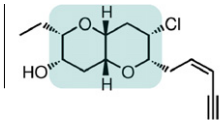
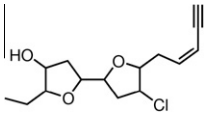
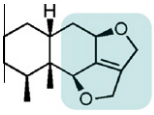
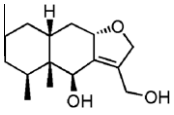
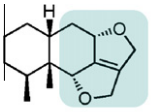
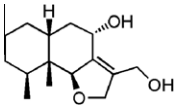
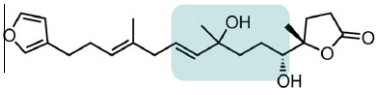
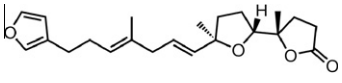
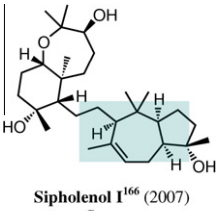
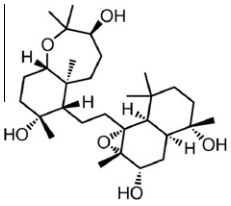
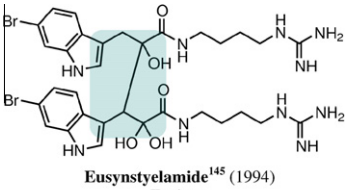
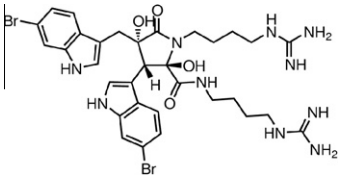
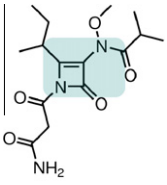
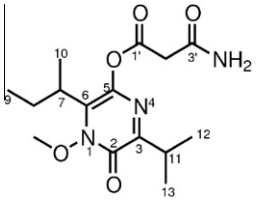
Constitutions of cycles (Table 1). The assignment of small cycles is challenging since direction of coherence around a ring is not necessarily discernible. A common constitutional error is differentiation of five- versus six-membered cycles by analysis of HMBC data. Several cases of an exocyclic olefin on a five-membered ring as opposed to a six-membered ring with endocyclic bond are evident in Table 1, for example, chloroaurone,[10,11] aspergiones A and B,[12–14] pyrostatins A and B,[15,16] and spongotine B.[17,18] Another problematic theme is differentiation of fused six-membered rings from two five-membered rings linked by a

Table 1
Marine natural product structural revisions of *cyclization* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Chloroaurone**[10] (2001) Brown alga	^{1}H & ^{13}C NMR HMQC HMBC		Total synthesis[11]
 **Aspergione A**[12] (2003) Fungus	HMBC ROESY *J*-based	 **Ustusorane C**	HMBC ROESY *J*-based[14]
 **Aspergione B**[12] (2003) Fungus	HMBC ROESY *J*-based	 **Pseudodeflectusin**	HMBC ROESY *J*-based[13]
 **Pyrostatin A**[15] (1995) Sponge	HMBC		Total synthesis[16]
 **Pyrostatin B**[15] (1995) Sponge	HMBC		Total synthesis[16]
 **Spongotine B**[17] (2005) Sponge	COSY		MS NMR[18]

(*continued on next page*)

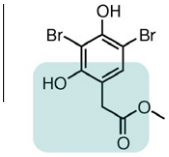
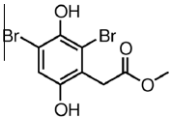
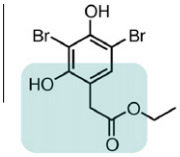
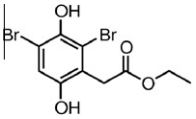
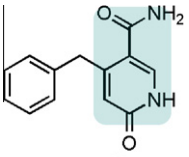
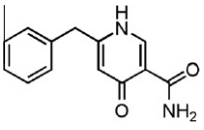
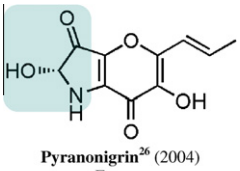
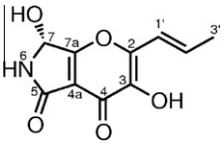
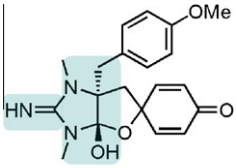
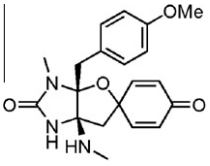
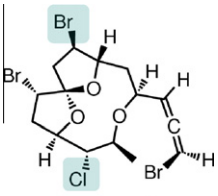
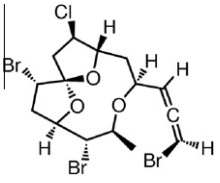
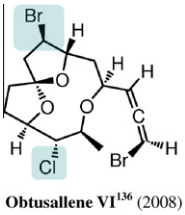
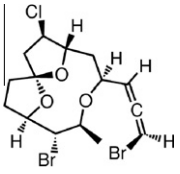
Table 1 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Laurendecumenyne B**[19] (2007) Red alga	Comparison		Comparison[20]
 **Elatenyne**[21] (1986) Red alga	NMR		Total synthesis[22]
 **"Enyne from Lyngbya"**[23] (1993) Cyanobacteria	Comparison		Total synthesis[22]
 **Peribysin C**[162] (2004) Fungus	HMBC NOE		EI-MS ^{13}C Prediction NMR comparison[163]
 **Peribysin D**[162] (2004) Fungus	HMBC NOE		EI-MS ^{13}C Prediction NMR comparison[163]
 **Irciformonin A**[164] (2006) Sponge	Artifact		Deriv.[165]
 **Sipholenol I**[166] (2007) Sponge	NMR		X-ray NMR[167]
 **Eusynstyelamide**[145] (1994) Tunicate	NMR		NMR Comparison[146]
 **Kasarin**[147] (2000) Bacteria	HMBC		Synthetic model NMR[148]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. Deriv. = derivatization.

single bond, as seen in the examples of the red algal metabolites laurendecumenyne B,[19,20] elatenyne[21,22] and *Laurencia* enyne.[22,23] In these three compounds, the observed ^{13}C NMR shifts of the oxygen-bearing carbons were more consistent with a 2,2′-bifuranyl moiety (>76 ppm) than the proposed pyrano[3,2-*b*]pyran (<76 ppm).[7] Consideration of these structures elicits the question of whether these errors may be attributed to the assignment of observed HMBC correlations as 4-bond connections. An alternative scenario is that key 3-bond HMBC correlations were absent, presumably because they were outside the coupling constant range detectable in a standard HMBC experiment optimized for $^{3}J_{CH}$ = 8 Hz.

Table 2
Marine natural product structural revisions of *regioisomers* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Subereaphenol B**[24] (2008) Sponge	HSQC HMBC		HSQC HMBC[25]
 **Subereaphenol C**[24] (2008) Sponge	HSQC HMBC		HSQC HMBC[25]
 **Aspernigrin A**[26] (2004) Fungus	HMBC		X-ray NOE[27]
 **Pyranonigrin**[26] (2004) Fungus	ROESY		Chemical reactivity CD predict.[28]
 **Spiroleucettadine**[29] (2004) Sponge	HMBC ROESY		^{13}C Predict. X-ray[30]
 **Obtusallene V**[136] (2008) Red alga	^{13}C Predict.		X-ray[137]
 **Obtusallene VI**[136] (2008) Red alga	^{13}C Predict.		Model synthesis Comparison[137]

(*continued on next page*)

Table 2 (*continued*)

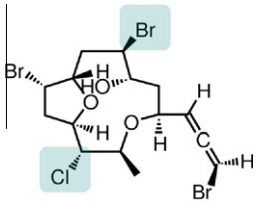
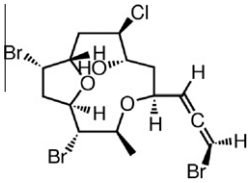
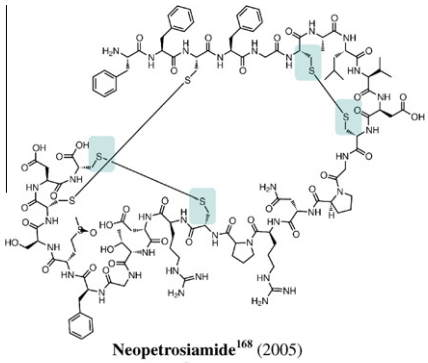
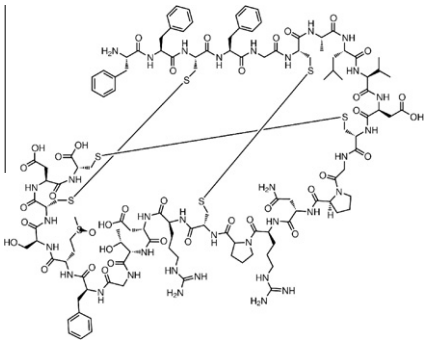
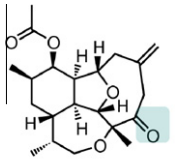
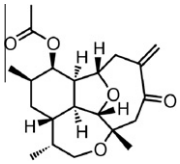
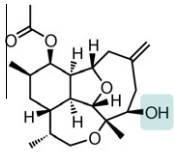
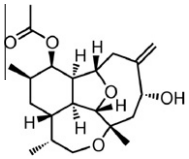
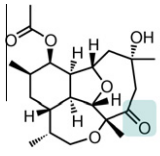
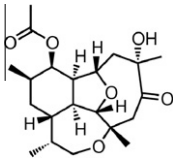
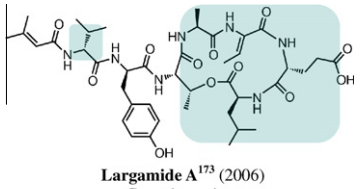
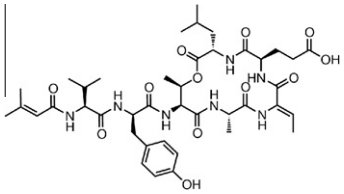
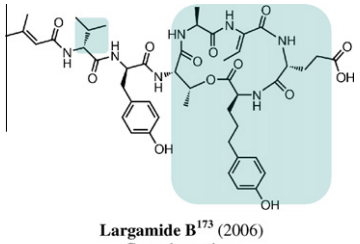
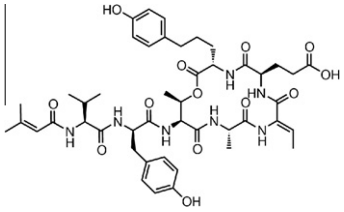
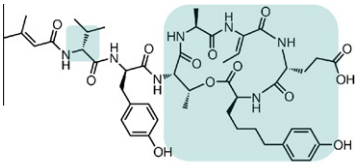
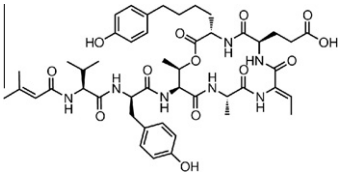
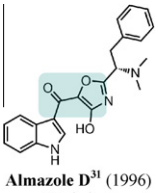
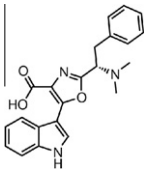
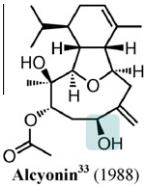
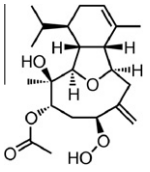
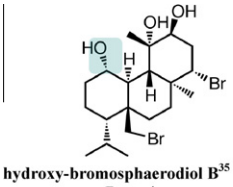
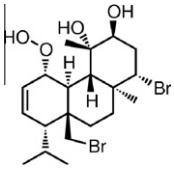
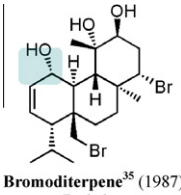
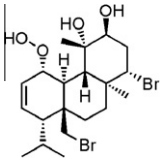
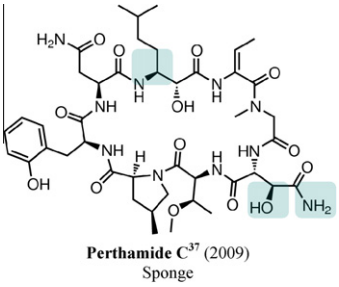
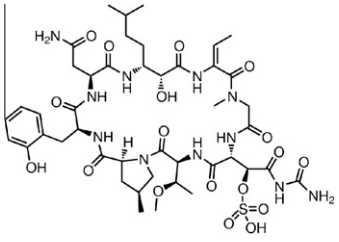
Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Obtusallene VII**[136] (2008) Red alga	^{13}C Predict.		Model synthesis Comparison[137]
 **Neopetrosiamide**[168] (2005) Sponge	NOE		Total synthesis[169]
 **Asbestinin 10**[170] (1993) Coral	Comparison		Deriv. NMR[171]
 **Asbestinin 20**[172] (1994) Coral	Deriv. NMR		Deriv. NMR[171]
 **Asbestinin 21**[172] (1994) Coral	Comparison		Deriv. NMR[171]
 **Largamide A**[173] (2006) Cyanobacterium	HMBC Marfey's		HMBC NOE Deriv. Chromatog.[174]
 **Largamide B**[173] (2006) Cyanobacterium	HMBC Marfey's		HMBC NOE Deriv. chromatog.[174]

Table 2 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Largamide C**[173] (2006) Cyanobacterium	HMBC Marfey's		HMBC NOE Deriv. Chromatog.[174]

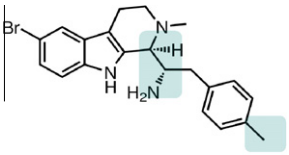
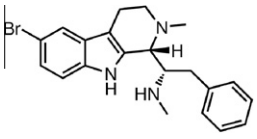
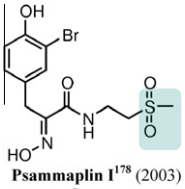
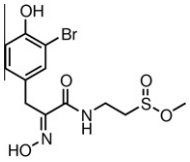
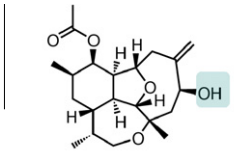
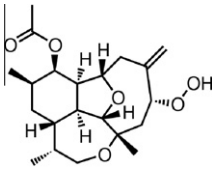
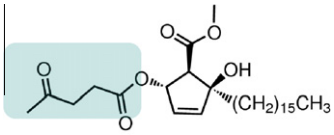
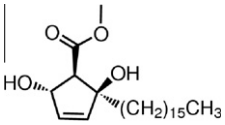
[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. Predict. = predictions based on molecular modeling. Mol. Mod. = use of geometry optimized structure. Deriv. = derivatization. Chromatog. = chiral HPLC or GC with or without derivatization.

Table 3
Marine natural product structural revisions of *substituents* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Almazole D**[31] (1996) Red alga	Comparison		Total synthesis[32]
 **Alcyonin**[33] (1988)	MS NMR		Total synthesis[34]
 **hydroxy-bromosphaerodiol B**[35] (1987) Bacterium	MS		X-ray[36]
 **Bromoditerpene**[35] (1987) Red alga	HR-MS ^{1}H NMR		X-ray[36]
 **Perthamide C**[37] (2009) Sponge	*J*-based Deriv.		Partial synthesis Comparison[38]

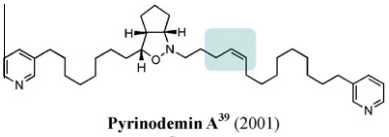
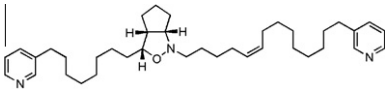
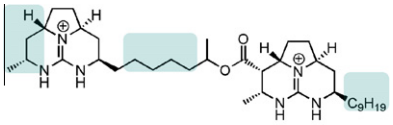
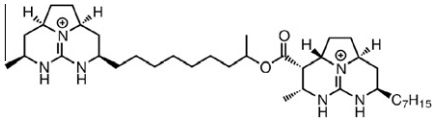
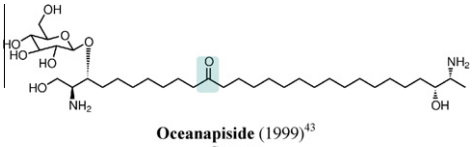
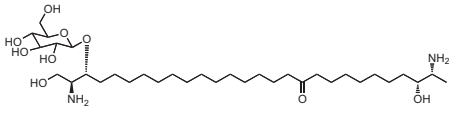
(*continued on next page*)

Table 3 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Eudistomidin B**[175] (1990) Tunicate	NOE CD		Total synthesis[176,177]
 **Psammaplin I**[178] (2003) Sponge	IR ^{13}C NMR		MS Mol. Mod.[179]
 **11-acetoxy-4-deacetoxyasbestinin F**[172] (1994) Coral	MS		Deriv. NMR[171]
 **Plakevulin A**[180] (2003) Sponge	Contamination		Total synthesis[181]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. Mol. Mod. = use of geometry optimized structure. Deriv. = derivatization.

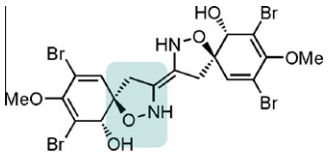
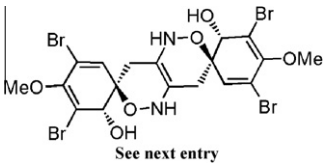
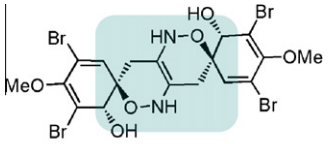
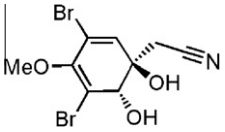
Table 4
Marine natural product structural revisions of *hydrocarbon chains* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Pyrinodemin A**[39] (2001) Sponge	EIMS		Total synthesis[40]
 **Batzelladine F**[41] (1997) Sponge	Comparison NOE DCI-MS		Total synthesis[42]
 **Oceanapiside** (1999)[43] Sponge	MS		Deriv. MS[44]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. DCI = Desorption Chemical Ionization.

Regioisomers (Table 2). As noted above, the assignment of small cycle connectivity can be ambiguous, and this issue extends to the placement of substituents on cycles. The difficulty of assigning substitution patterns on cycles is exacerbated especially by a paucity of ^{1}H to provide HMBC correlations, as in highly substituted phenolic compounds (e.g., subereaphenols B and C[24,25]), in tandem with possible signal overlap. In some instances, such as aspernigrin A,[26,27] a single HMBC correlation may theoretically differentiate

Table 5
Marine natural product structural revisions of *dimerization* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Zamamistatin**[45] (2001) Sponge	NOESY ESI HR-MS	 **See next entry**	Synthetic model compounds[46]
 **Zamamistatin**[46] (2001) Sponge	Synthetic model compounds		IR NMR and OR[47]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table.

two isomers. However, in cases such as pyranonigrin,[26,28] spiroleucettadine[29,30] and almazole D (Table 3),[31,32] careful consideration of the chemical shift values in the assigned structure may have provided the only clue to the structural misassignment.

Substituent identity (Table 3). The identity of heteronuclear substituents may only be inferred indirectly from NMR data. Thus, the assignment of these substituents is often reliant on mass spectrometry (MS), and is subject to error depending on the stability of the substituent and the ionization technique used. For example, alcyonin,[33,34] 12*S*-hydroxy-bromosphaerodiol B[35,36] and the red algal bromoditerpene[35,36] were misassigned with hydroxy rather than hydroperoxy subsituents, despite the acquisition of high resolution (HR) MS data. In the case of perthamide C,[37,38] sulfone and amide substituents went undetected until negative mode HR electrospray ionization (ESI) MS was employed.

Hydrocarbon chains (Table 4). MS is again the traditional tool of choice in assigning saturated and unsaturated alkyl chains, based on the observed molecular ion and fragmentation patterns. However, these assignments remain a considerable challenge. Initial interpretation of the MS fragmentation data obtained for sponge metabolites pyrinodemin A[39,40] (electron ionization MS) and batzelladine F[41,42] (desorption chemical ionization MS) did not locate the olefin, or provide the correct chain lengths, respectively. Pyrinodemin A yielded an MS fragmentation pattern that was not exclusive to the proposed structure,[40] while batzelladine F assignment was complicated by the presence of both an alkyl tether (between the two guanidine moieties) and a side chain.[42] Misplacement of the keto group on C-11 in the hydrocarbon chain of oceanapiside resulted from charge-localized fragmentation of the Li^+ adduct by MALDI (matrix-assisted laser desorption ionization) MS/MS.[43] Finally, MS analysis of the Baeyer–Villiger oxidation products obtained from the oceanapiside ketone relocated the keto group to C-18, consistent with the related rhizocalins.[44]

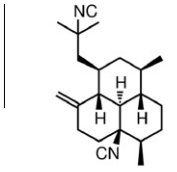
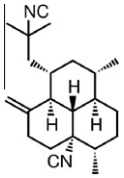
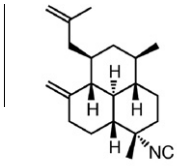
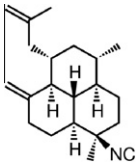
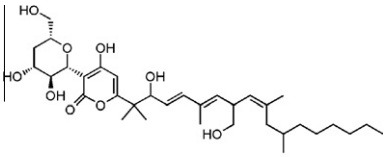
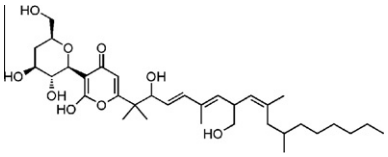
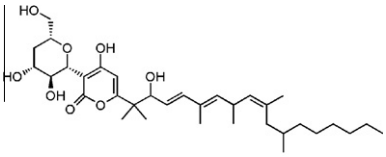
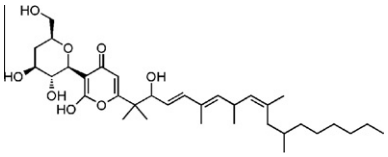
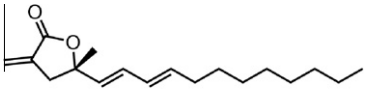
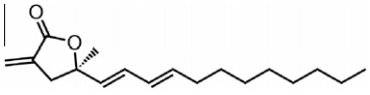
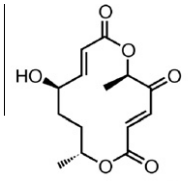
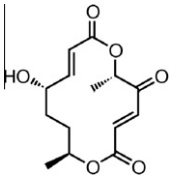
Dimerization (Table 5). The unusual structure of the sponge metabolite zamamistatin required repeated revision to arrive at the correct assignment.[45–47] The more common scenario is that an NMR-derived monomeric structure is proven to exist as a dimer by MS. However, in this case, the tentative molecular ion peak at *m/z* 700.8 was attributable to the tendency for the isonitrile to dimerize under the conditions of MS analysis, and was finally shown to disappear upon dilution, leaving a peak at *m/z* 361.9.[47] Thus, structural revision finally assigned zamamistatin as the known compound aeroplysinin-1, exemplifying the extensive effort that may be required to revise even misassigned known structures.

2.2. Misassignments of configuration of marine natural products

Configurational errors may be readily classified as misassignments of either absolute (Table 6) or relative configuration, the latter comprising the majority of misassigned marine natural products tabulated here (Tables 7–9). Misassignments of relative configuration have been sorted according to whether one or multiple stereocenters, or double bond geometries were misassigned. Structural themes emerging in the misassignment of multiple stereocenters then become evident.

Absolute configuration (Table 6). In the majority of cases, the assignment of absolute configuration necessitates chemical degradation and/or derivatization, which may be followed by comparison of chromatographic retention and/or spectroscopic properties with standards or model compounds. Various Mosher's ester and Marfey's chiral derivatization methods are widely used examples of this general empirical approach. The destructive and/or laborious procedures necessary for most assignments of absolute configuration mean that spectroscopic comparisons of new metabolites with known assigned compounds to extrapolate absolute configuration is common and may lead to extensive propagation of errors. Given the frequently limited quantities of marine natural products isolated, errors resulting from these approaches almost exclusively await detection and revision by total synthesis. Thus, they may be more common than is evident from the structural revisions reported to date. Chiroptical spectroscopy in the form of circular dichroism (CD) or optical rotatory dispersion (ORD) is an attractive alternative for the analysis of configuration that may not require modification of the isolated natural product. However, similar to Mosher and Marfey's analyses, interpretation of these data relies largely on application of empirically derived principles, such as the octant rules, or comparison with data for analogous compounds of known conformation and configuration.[48] In either of these indirect approaches, errors can be sustained and propagated. The use of CD has traditionally been confined to consideration of the sign (but not magnitude) of the Cotton effects, which provides information only about the sign of a torsion angle around a bond, in other words the *absolute conformation* of a molecule. The determined absolute conformation needs to be correlated to the

Table 6
Marine natural product structural revisions of *absolute configuration* (2005–2010)[a]

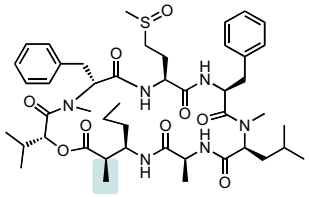
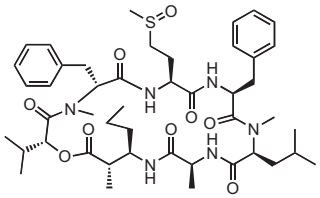
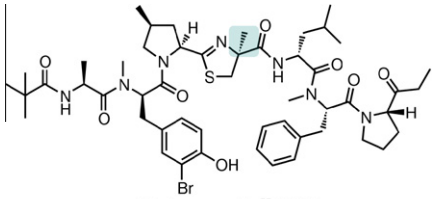
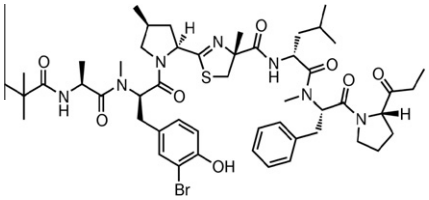
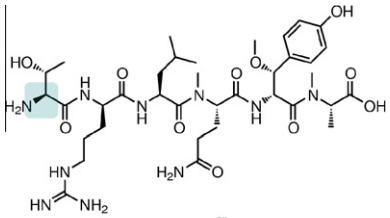
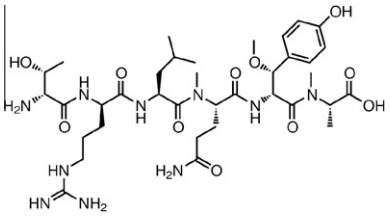
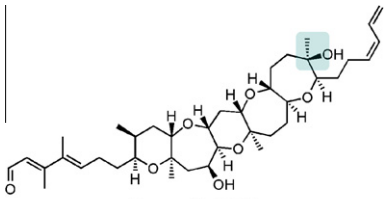
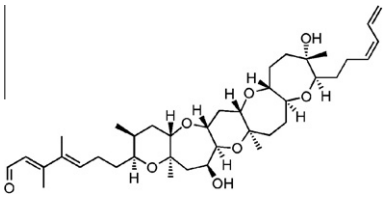
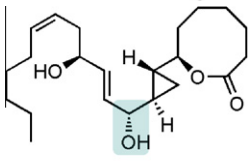
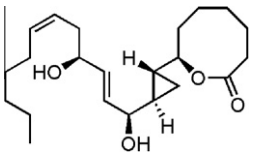
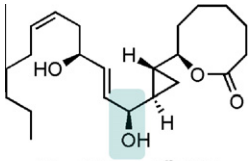
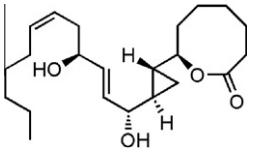
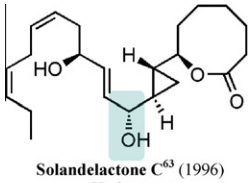
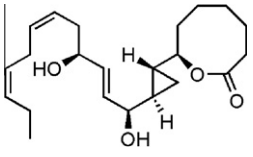
Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Amphilactene derivative**[50] (1999) Sponge	Mosher's		Mosher's[51]
 **Amphilactene derivative**[50] (1999) Sponge	Comparison		X-ray[51]
 **Fusapyrone**[128] (1994) Fungus	1D & 2D NMR		HMBC NMR Comparison[129]
 **Deoxyfusapyrone**[128] (1994) Fungus	1D & 2D NMR		HMBC NMR Comparison[129]
 **Plakolide A**[182] (2004) Sponge	CD		Total synthesis[183]
 **4-keto-clonostachydiol**[184] (2006) Fungus	Deriv. OR		Total synthesis[185]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. Predict. = predictions based on molecular modeling. Mol. Mod. = use of geometry optimized structure. Deriv. = derivatization. Chromatog. = chiral HPLC or GC with or without derivatization.

predicted absolute configuration by a second CD argument (e.g., magnitude and position of bands) or an alternative analytical method, such as conformational analysis, NMR, or X-ray, to avoid erroneous assumptions of quasi–axial or quasi–equatorial conformations of ring substituents, for example.[48] In other words, one must be certain of the molecular conformation in order to derive the absolute configuration by chiroptical spectroscopy. Notably, an additional achiral substituent on an aromatic moiety may even lead to inversion of the sign of a Cotton effect.[48] Mosher's method[49] is an empirically derived correlation of configuration and NMR chemical shifts for diastereomeric phenylacetate ester derivatives (commonly α-methoxy-α-trifluoromethyl phenylacetate, MTPA) that is widely used for small-scale analyses of secondary alcohols, amines and chiral α-substituted carboxylic acids. In this method, it is important to carefully examine models of the expected diastereomeric esters to ensure that the experimentally observed chemical shift changes are consistent with the predicted orientation and thus shielding effect of the phenyl ring. However, the sponge-derived amphilectenes[50,51] were misassigned simply due to overlapping ^{1}H NMR chemical shifts in the $CDCl_3$ spectrum of the Mosher ester of an alcohol-containing congener. Subsequent analysis of the more dispersed spectrum obtained in pyridine-d_5 for this compound, and also crystallization of the isobutene-containing amphilectene, permitted structural revision of this series.[51]

Marfey's method, using the chiral derivatizing agent 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (FDAA, Marfey's reagent) or 1-fluoro-2,4-dinitrophenyl-5-L-leucinamide (modified Marfey's reagent), also requires little material and is particularly effective

Table 7
Marine natural product structural revisions of *single stereocenters* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Carriebowmide**[53] (2008) Cyanobacterium	Marfey's		Marfey's[54]
 **Bisebromoamide**[55] (2009) Cyanobacterium	Marfey's		Total synthesis[56]
 **Callipeltin E**[57] (2002) Sponge	Marfey's		Total synthesis[58]
 **Brevenal**[61] (2005) Dinoflagellate	NOE		Total synthesis[62]
 **Solandelactone A**[63] (1996) Hydrozoan	HMQC COSY Comparison NOE		Total synthesis[64]
 **Solandelactone B**[63] (1996)	Comparison NOE		Total synthesis[64]
 **Solandelactone C**[63] (1996) Hydrozoan	Comparison NOE		Total synthesis[64]

(*continued on next page*)

Table 7 (*continued*)

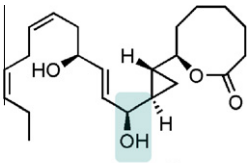
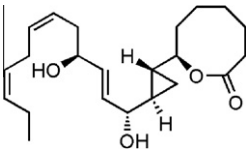
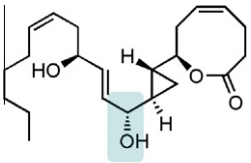
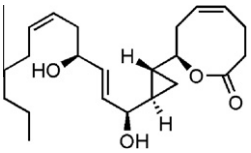
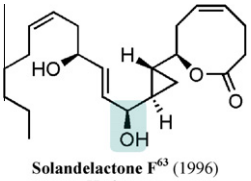
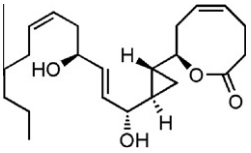
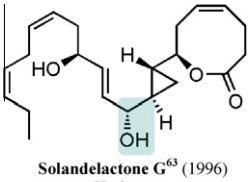
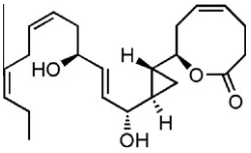
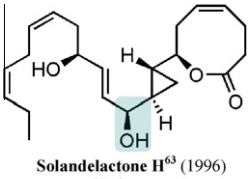
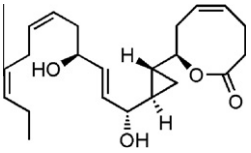
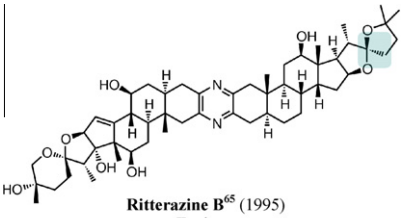
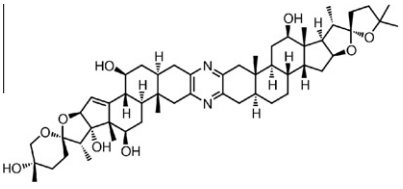
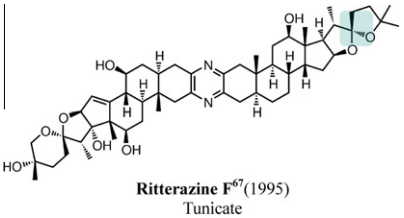
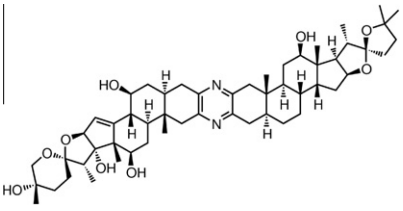
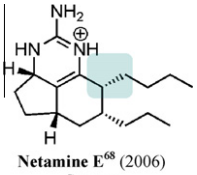
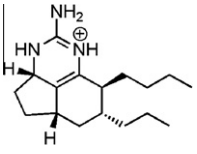
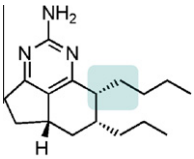
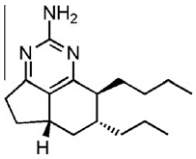
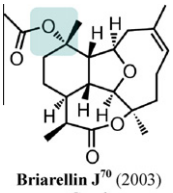
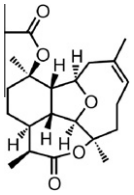
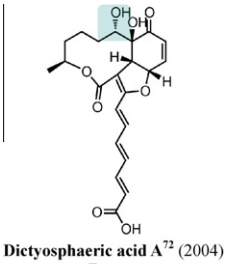
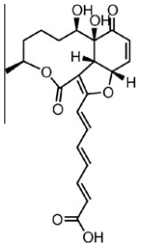
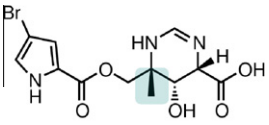
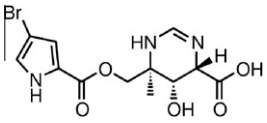
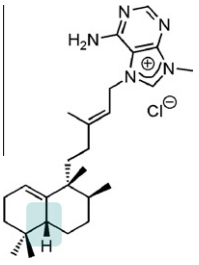
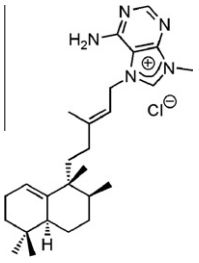
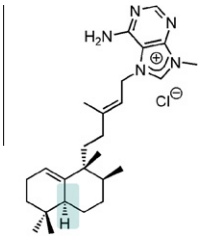
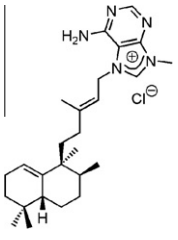
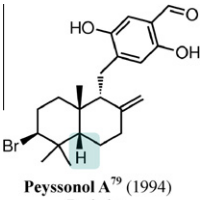
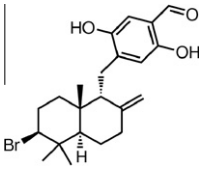
Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Solandelactone D**[63] (1996) Hydrozoan	Comparison NOE		Total synthesis[64]
 **Solandelactone E**[63] (1996) Hydrozoan	Comparison NOE		Total synthesis[64]
 **Solandelactone F**[63] (1996) Hydrozoan	Comparison NOE		Total synthesis[64]
 **Solandelactone G**[63] (1996) Hydrozoan	Comparison NOE		Total synthesis[64]
 **Solandelactone H**[63] (1996) Hydrozoan	Comparison NOE		Total synthesis[64]
 **Ritterazine B**[65] (1995) Tunicate	NOE Comparison		Partial synthesis[66]
 **Ritterazine F**[67](1995) Tunicate	NOE Comparison		Partial synthesis[66]
 **Netamine E**[68] (2006) Sponge	NOE		Total synthesis[69]

Table 7 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Netamine G**[68] (2006) Sponge	NOE		Total synthesis[69]
 **Briarellin J**[70] (2003) Coral	NOESY		Total synthesis[71]
 **Dictyosphaeric acid A**[72] (2004) Fungus	NOE		Total synthesis[73]
 **Manzacidin B**[74] (1991) Sponge	*J*-based Comparison		Total synthesis[75]
 **Agelasine C**[76] (1984) Sponge	CD Comparison NMR		Total synthesis[77]
 **Epi-agelasine C**[78] (1984) Sponge	CD Comparison NMR		Total synthesis[77]
 **Peyssonol A**[79] (1994) Red alga	^{13}C NMR		Total synthesis[80]

(*continued on next page*)

Table 7 (*continued*)

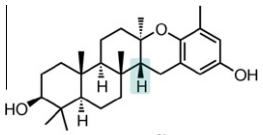
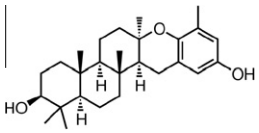
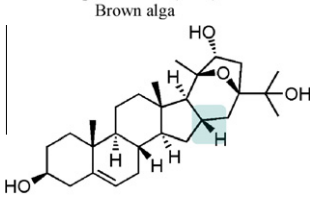
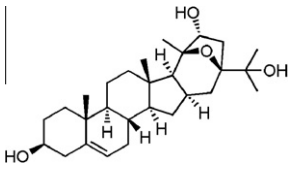
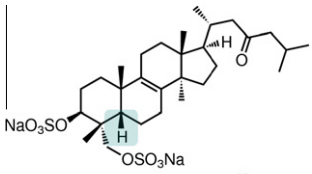
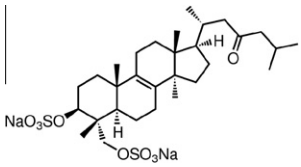
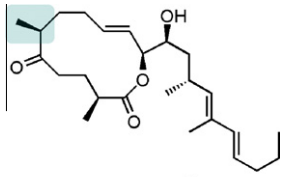
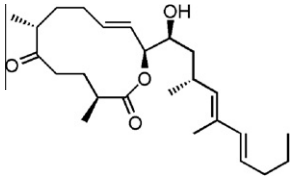
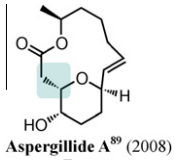
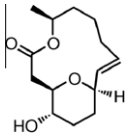
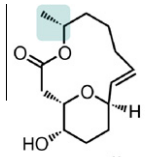
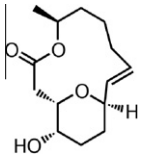
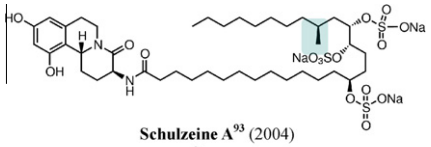
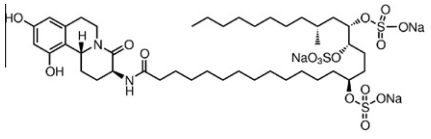
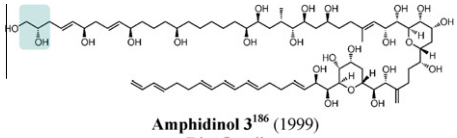
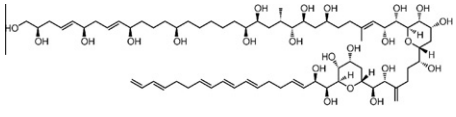
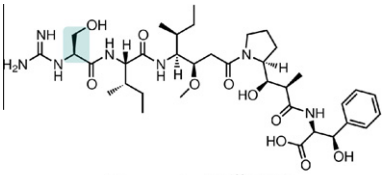
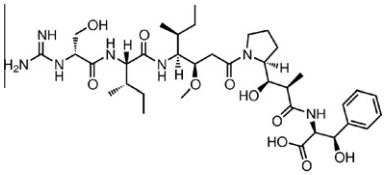
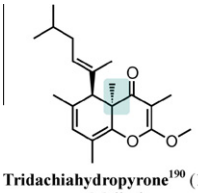
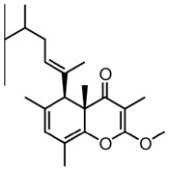
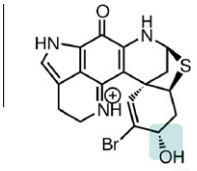
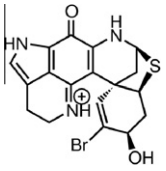
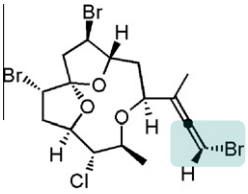
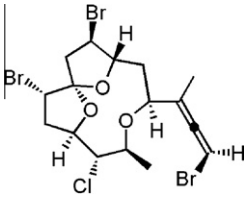
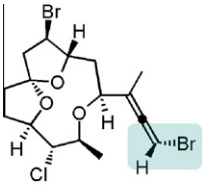
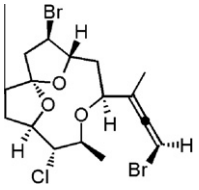
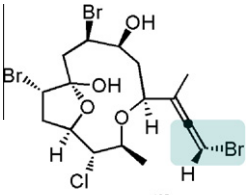
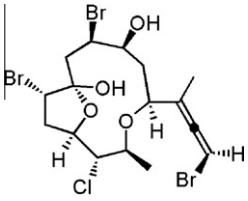
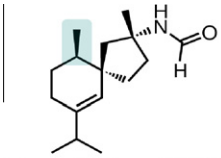
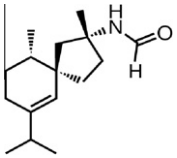
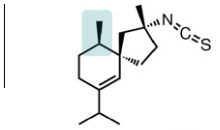
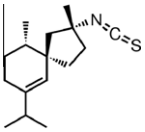
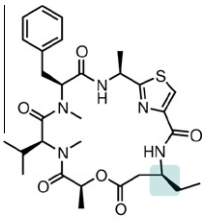
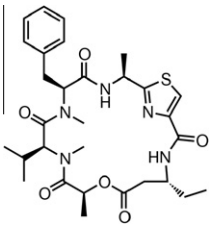
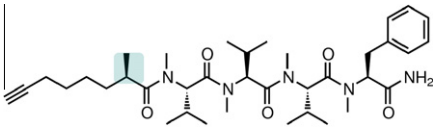
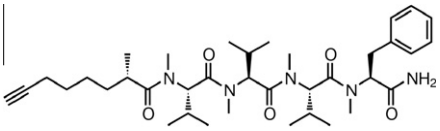
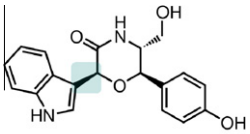
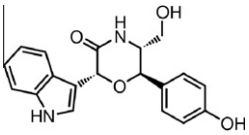
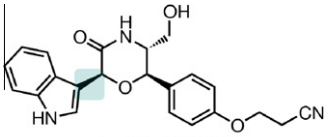
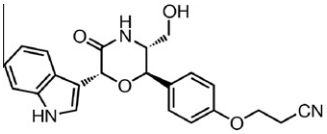
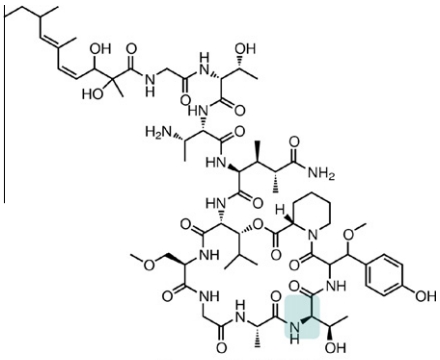
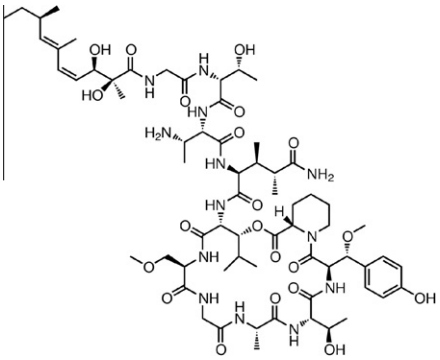
Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Isoepitaondiol**[81] (1992) Brown alga	Comparison		X-ray[82]
 **Suberoretisteroid B**[83] (2000) Gorgonian	^{1}H NMR		NMR Comparison[84]
 **Lanostane-type triterpenoid**[85] (1994) Green alga	Comparison		X-ray NMR[86]
 **Amphidinolide W**[87] (2002) Dinoflagellate	Derivatization *J*-based Mosher		Total synthesis[88]
 **Aspergillide A**[89] (2008) Fungus	Mosher's NOE		X-ray[90]
 **Aspergillide B**[89] (2008) Fungus	Mosher's NOE		Total Synthesis[91,92] X-ray[90]
 **Schulzeine A**[93] (2004) Sponge	Deriv. Comparison		Total synthesis[94]
 **Amphidinol 3**[186] (1999) Dinoflagellate	Ozonolysis Derivatization Chiral HPLC		Combinatorial synthesis of fragments[187]

Table 7 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Gymnangiamide**[188] (2004) Hydrozoan	Degradation Deriv. Marfey's		Total synthesis[189]
 **Tridachiahydropyrone**[190] (1996) Mollusk	NOE		Total synthesis[191]
 **dihydrodiscorhabdin A**[192] (2009) Sponge	*J*-based Mol. Mod.		CD Semi-synthesis[193]
 **Obtusallene V**[135] (2000) Red alga	Mol. Mod. NMR Comparison		^{13}C Predict.[136]
 **Obtusallene VI**[135] (2000) Red alga	Mol. Mod. NMR Comparison		^{13}C Predict.[136]
 **Obtusallene VII**[135] (2000) Red alga	Mol. Mod. NMR Comparison		^{13}C Predict.[136]
 **2-formamido-6-axene**[194] (1989) Sponge	NOE		NOE Comparison[195]

(*continued on next page*)

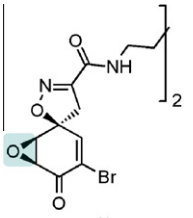
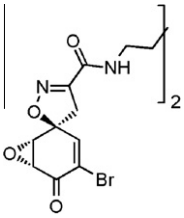
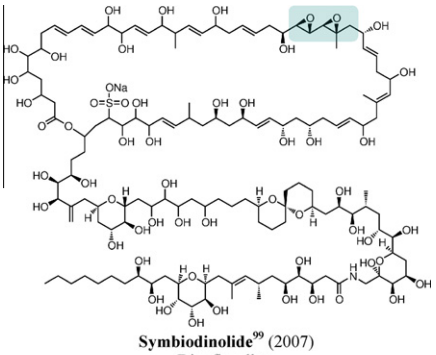
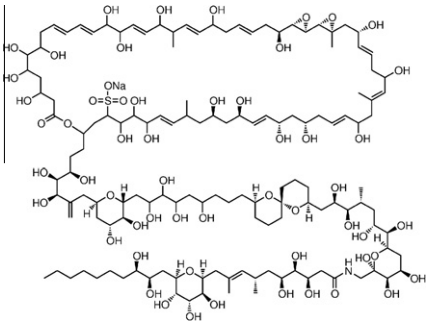
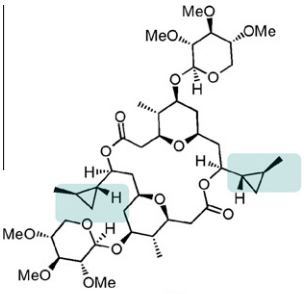
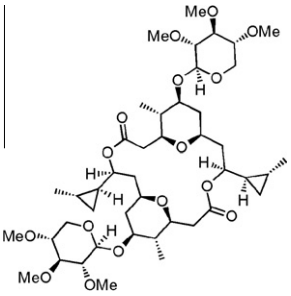
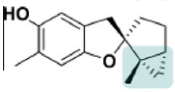
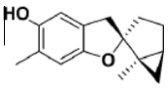
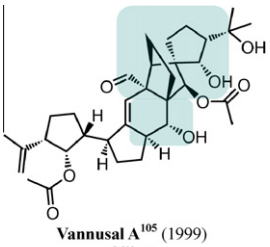
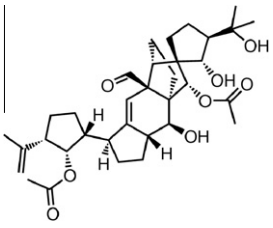
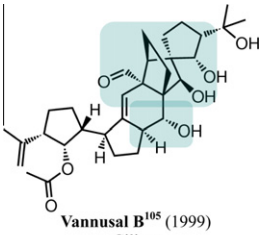
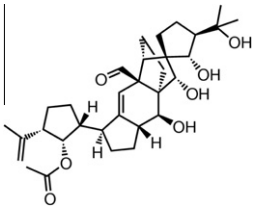
Table 7 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Isothiocyanato-6-axene**[194] (1989) Sponge	NOE		NOE Deriv.[195]
 **Obyanamide**[196] (2002) Cyanobacterium	Degradation Chromatog.		Total synthesis[197]
 **Dragonamide**[198] (2001) Cyanobacterium	Degradation OR		Total synthesis[199]
 **Oxazinin-2**[200] (2001) Mussel	ROESY		Total synthesis[201]
 **Oxazinin-1**[200] (2001) Mussel	ROESY		Comparison[201]
 **Papuamide B**[202] (1999) Sponge	Degradation Chromatog.		Total synthesis[203]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. Predict. = predictions based on molecular modeling. Mol. Mod. = use of geometry optimized structure. Deriv. = derivatization. Chromatog. = chiral HPLC or GC with or without derivatization.

for the configurational assignment of peptidic natural products. Regular C_{18} HPLC is used to compare retention times of the diastereomeric Marfey's derivatized standards and the unknown. Importantly, neutral Marfey's reagent reacts rapidly (within 1 h), stoichiometrically, and without significant racemization, with the α-amino group of amino acids.[52] The predominant source of errors arising from Marfey's analyses appears to be misassignment or close overlap of HPLC peaks (representing different amino acids) for the natural product hydrolysates and/or the Marfey's derivatized standards (e.g., carriebowmide,[53,54] bisebromide[55,56] and callipeltin E,[57,58] Table 7). It is often impossible to gain resolution of all residues in the hydrolysate, as well as the stereochemical standards, under one set of HPLC conditions. Changes in retention time for all residues must then be tracked under several different solvent conditions. These challenges warrant the consistent use of LC–MS for Marfey's analyses of peptide

Table 8
Marine natural product structural revisions of *multiple stereocenters* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Calafianin**[96] (2000) Sponge	NOE		Total synthesis[97,98]
 **Symbiodinolide**[99] (2007) Dinoflagellate	Degradation NOE *J*-based		Degradation Partial synthesis Comparison[100]
 **Clavosolide A**[101] (2002) Sponge	*J*-based ROESY		Total synthesis[102]
 **Laurentristich-4-ol**[103] (2005) Red alga	NOE		Total synthesis[104]
 **Vannusal A**[105] (1999) Ciliate	NOE *J*-based		Total synthesis[106,107]
 **Vannusal B**[105] (1999) Ciliate	NOE *J*-based Comparison		Total synthesis[106,107]

(*continued on next page*)

Table 8 (*continued*)

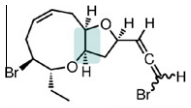
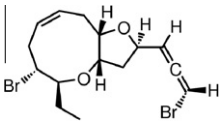
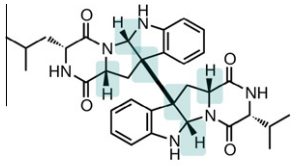
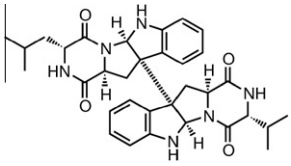
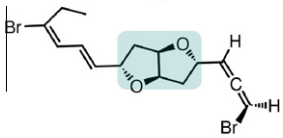
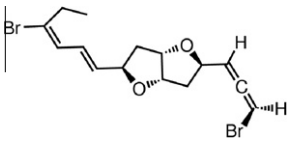
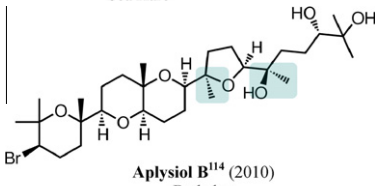
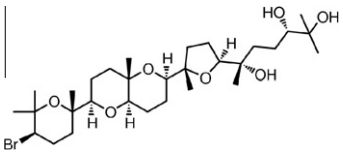
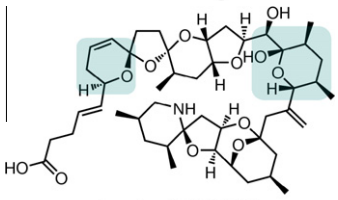
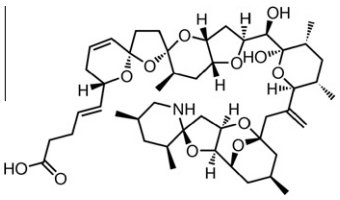
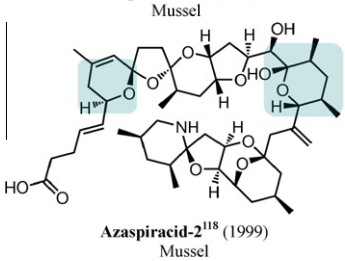
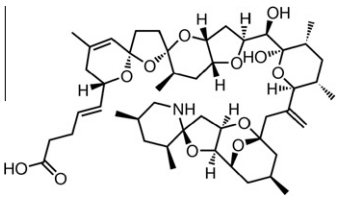
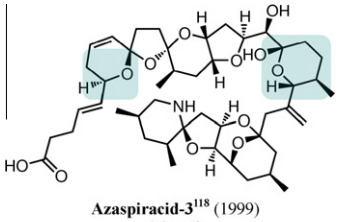
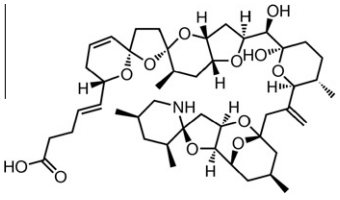
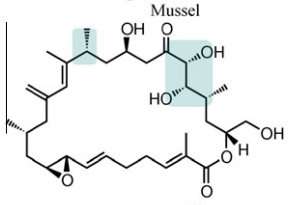
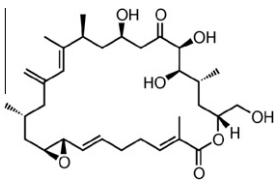
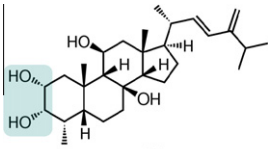
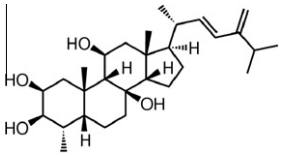
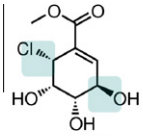
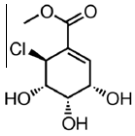
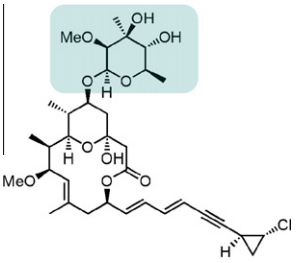
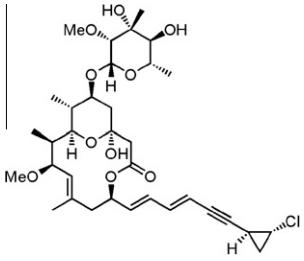
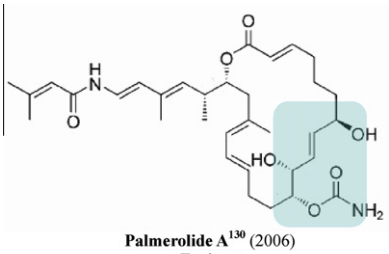
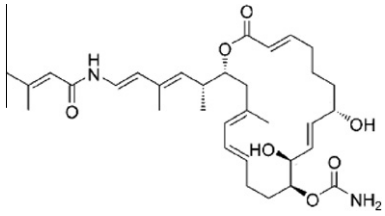
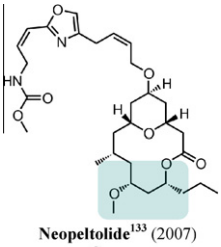
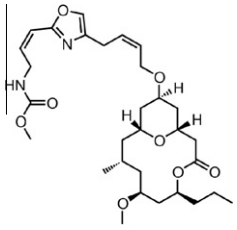
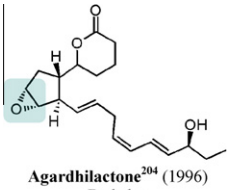
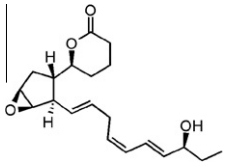
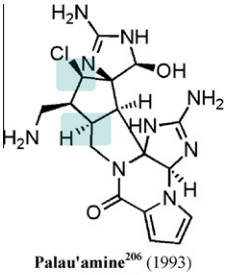
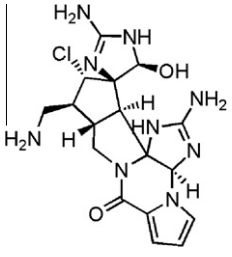
Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Itomanallene A**[108] (2002) Red alga	NOE		Total synthesis[109]
 **Asperdimin**[110] (2004) Fungus	Comparison		Total synthesis[111]
 **Aplysiallene**[112] (1985) Sea Hare	OR NOE Comparison		Total synthesis[113]
 **Aplysiol B**[114] (2010) Red alga	NOE *J*-based Mol. Mod.		Biogenesis NOE[115]
 **Azaspiracid-1**[116] (1998) Mussel	NOE *J*-based		Total synthesis[117]
 **Azaspiracid-2**[118] (1999) Mussel	NOE Comparison		Total synthesis[119]
 **Azaspiracid-3**[118] (1999) Mussel	NOE Comparison		Total synthesis[119]
 **Amphidinolide H2**[120] (2002) Dinoflagellate	NOE		Total synthesis[121]

Table 8 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Hyrtiosterol**[122] (2004) Coral	NOE		NOE[123]
 **Pericosine A**[124] (1997) Fungus	NOE *J*-based		Total synthesis[125]
 **Callipeltoside C**[126] (1996) Sponge	ROESY NOE		Total synthesis[127]
 **Palmerolide A**[130] (2006) Tunicate	Mosher *J*-based NOE		Total synthesis[131,132]
 **Neopeltolide**[133] (2007) Sponge	NOE		Total synthesis[134]
 **Agardhilactone**[204] (1996) Red alga	Derivatization NMR		Total synthesis[205]
 **Palau'amine**[206] (1993) Sponge	ROESY *J*-based		ROESY Mol. Mod. *J*-based[207]

(*continued on next page*)

Table 8 (*continued*)

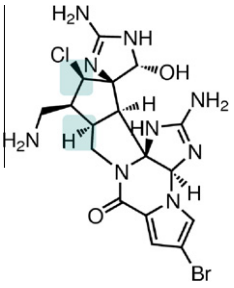
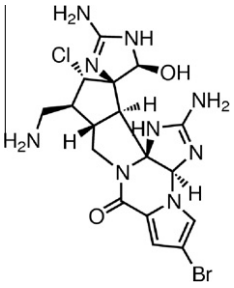
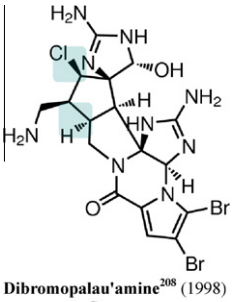
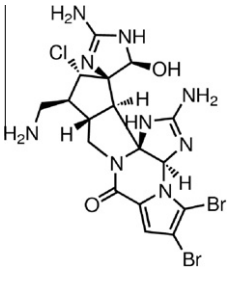
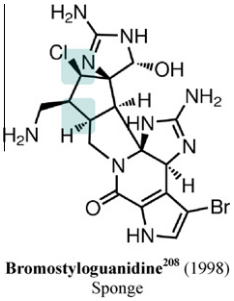
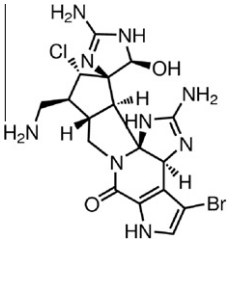
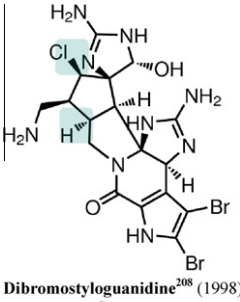
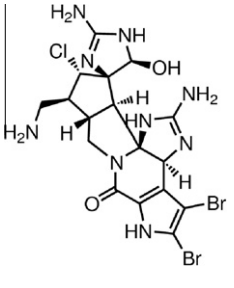
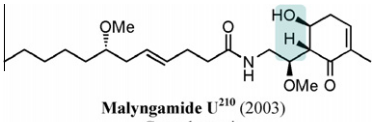
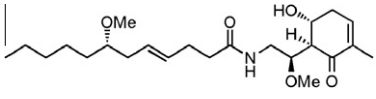
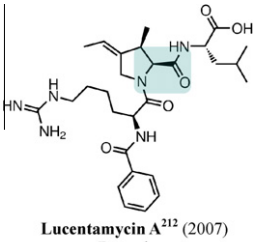
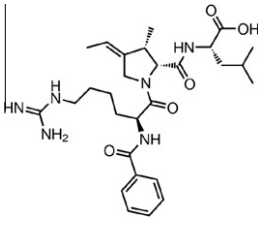
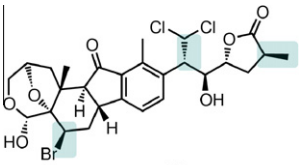
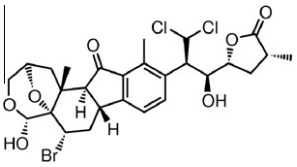
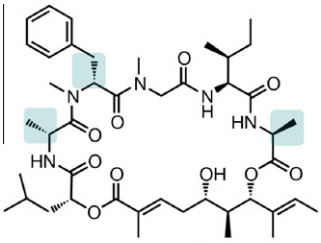
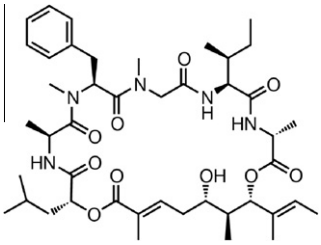
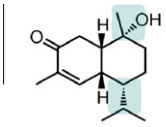
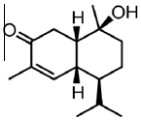
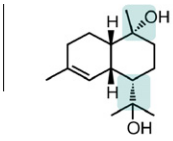
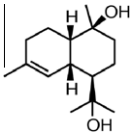
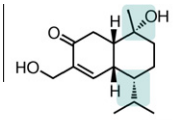
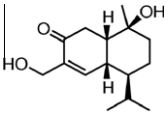
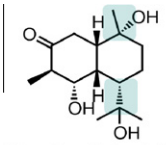
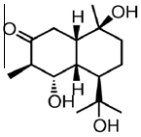
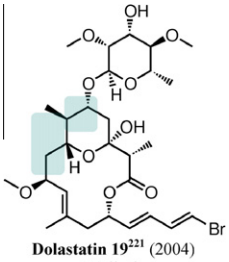
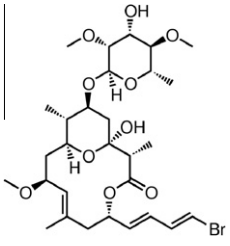
Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Bromopalau'amine**[208] (1998) Sponge	Comparison		Comparison[209]
 **Dibromopalau'amine**[208] (1998) Sponge	Comparison		ROESY[209]
 **Bromostyloguanidine**[208] (1998) Sponge	Comparison		Comparison[209]
 **Dibromostyloguanidine**[208] (1998) Sponge	Comparison		Comparison[209]
 **Malyngamide U**[210] (2003) Cyanobacteria	*J*-based NOESY		Total synthesis[211]
 **Lucentamycin A**[212] (2007) Bacterium	Marfey's		Total synthesis[213]

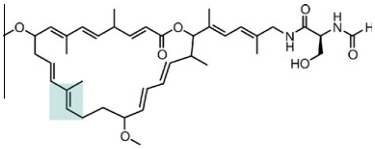
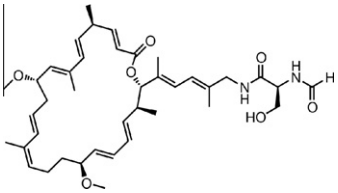
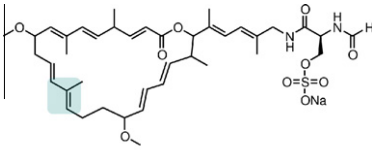
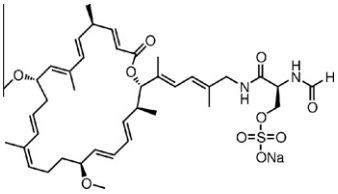
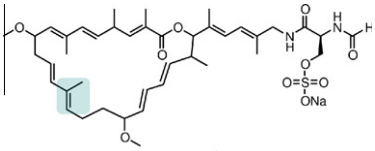
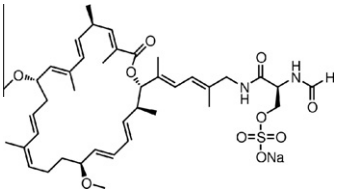
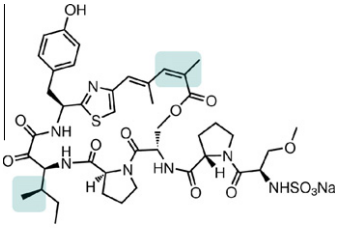
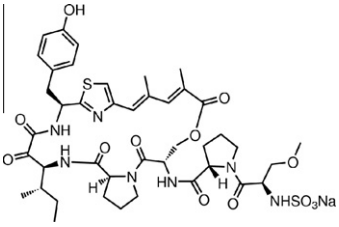
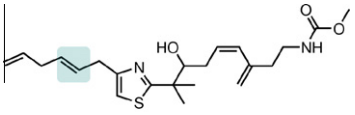
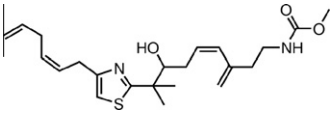
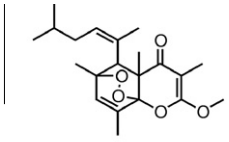
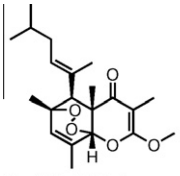
Table 8 (*continued*)

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Nakiterpiosin**[214] (2004) Sponge	NOE		Total synthesis[215]
 **Kulokekahilide-2**[216] (2004) Mollusk	Marfey's		Total synthesis[217]
 **Muurolane-derivative**[218] (1997) Bacterium	NOE *J*-based		X-ray[219]
 **Muurolane-derivative**[220] (2007) Bacterium	Comparison		Comparison NOE[219]
 **Muurolane-derivative**[220] (2007) Bacterium	Comparison		Comparison NOE
 **Muurolane-derivative**[220] (2007) Bacterium	Comparison		Comparison NOE[219]
 **Dolastatin 19**[221] (2004) Mollusk	NOE		Total synthesis[222]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. Predict. = predictions based on molecular modeling. Mol. Mod. = use of geometry optimized structure. Deriv. = derivatization. Chromatog. = chiral HPLC or GC with or without derivatization.

hydrolysates. Coinjection of standards with the natural product hydrolysate could also be performed more routinely, as well as standardization of the concentrations of injected derivatives. In addition, although the derivatization reaction with Marfey's reagent is mild, the potential for racemization under the harsh conditions of acid hydrolysis (reflux in 6 N HCl for 12–24 h) of the natural product should be recognized. For example, methionine, proline, arginine and lysine are more prone to racemization under these conditions than are threonine, serine, leucine, isoleucine and valine.[59] Thus, any configurational analysis that relies on initial hydrolysis of the natural product before derivatization is subject to potential errors.

Table 9
Marine natural product structural revisions of *double bond geometry* (2005–2010)[a]

Proposed structure	Initial structure determination method	Revised structure	Structure revision method
 **Iejimalide A**[138] (1988) Tunicate	NOE		NOE NMR[139]
 **Iejimalide C**[140] (1991) Tunicate	Comparison		Comparison[139]
 **Iejimalide D**[140] (1991) Tunicate	Comparison		Comparison[139]
 **Scleritodermin A**[141] (2004) Sponge	NOE Deriv. Chromatog.		Total synthesis[142]
 **Mycothiazole**[143] (1988) Sponge	*J*-based		Comparison[144]
 **Tridachiahydropyrone C**[223] (2000) a rotamer of B Mollusk	Comparison	 **Oxytridachiahydropyrone**	Total synthesis[191]

[a] The year in which the initial structure was published is in parentheses. Only the structure determination methods used for the portion of the structure that is erroneous are mentioned in this table. Deriv. = derivatization. Chromatog. = chiral HPLC or GC with or without derivatization.

With sufficient sample, X-ray crystallography is considered a gold standard for assignment of absolute configuration, when the sample is amenable to crystallization and contains either a sufficiently heavy atom for unequivocal determination or a known chiral center. However, an unlikely scenario is worth noting here. In the assignment of the terrestrial natural product platyphyllide,[60] total synthesis lead to a diastereomeric product that was derivatized for cystallization. Crystals of the minor ('unwanted') diastereomer were unwittingly selected for X-ray crystallography, and resulted in an incorrect revision of the absolute configuration for the natural product.

Relative configuration (Tables 7–9). Not unexpectedly, interpretation of NOE data and spectroscopic comparison contribute the majority of relative configurational misassignments of marine natural products. Misassignments of single stereocenters (Table 7) near to correctly assigned centers are associated with interpretation of NOE data for structurally diverse compounds. For example, this is the case for brevenal,[61,62] solandelactones A-H,[63,64] ritterazines B[65,66] and F,[67] netamines E and G,[68,69] briarellin J,[70,71] and dictyosphaeric acid A.[72,73] Consideration of the source of these errors highlights the need for careful evaluation of all possible alternative molecular models that adhere to NOE constraints. The starting conformation of the subject molecule is critical, as is a consideration of the predicted distances between atoms (NOE's may be observed between protons within 5 Å). These factors support the use of computational modeling for all applications of

NOE data to the assignment of configuration. Even use of physical models may readily result in overlooking possible free rotation about an atom in a linear chain or alternate conformations of a ring system, as well as over- or under-estimated interatomic distances. Once a putative configuration is assigned, it is clearly essential to examine molecular models closely for all potentially observable NOEs based on interatomic distances, and to match these to the NMR data. In this way, errors arising from assignments of configuration based on single NOE correlations may be avoided. Other common single stereocenter misassignments occur at ring junctions, as in the cases of manzacidin B,[74,75] agelasine C[76,77] and its epimer,[78] peyssonol A,[79,80] isoepitaondiol,[81,82] suberoretisteroid B[83,84] and the green algal lanostane-type triterpenoid[85,86] (Table 7), and are caused primarily by NMR spectral overlap. Assignment is also difficult for an isolated substituent on a macrocycle or extended chain, perhaps too far from the point of derivatization in a flexible system. Examples of this circumstance include amphidinolide W,[87,88] aspergillides A and B[89–92] and schulzeine A[93,94] (Table 7).

The presence of COSY-like peaks in ROESY and NOESY spectra necessitates careful attention to the phase of the cross peaks in these spectra. The long ROESY spin-lock pulse has the same effect as the last 90° pulse in a COSY experiment, causing coherence transfer between *J*-coupled spins to appear as weak antiphase cross peaks. Direct TOCSY effects are caused in a similar manner to COSY-like peaks in ROESY experiments since the TOCSY experiment relies on a similar spin-lock. While these TOCSY peaks are also antiphase to direct ROE cross peaks, multistep coherence transfers involving both ROESY and TOCSY (ROE–TOCSY or TOCSY–ROE) can lead to false ROEs that are in phase with direct (true) ROEs.[95]

Misassignments of multiple stereocenters in a broad range of marine natural products (Table 8) are also most frequently associated with NOE data. Structural motifs misassigned on the basis of NOEs include epoxides (calafianin,[96–98] symbiodinolide[99,100]), cyclopropyl rings (clavosolide A,[101,102] laurentristich-4-ol[103,104]), bridges (vannusals A and B[105–107]), fused ring junctions (itomanallene A,[108,109] asperdimin,[110,111] aplysiallene[112,113]), polyethers (aplysiol B,[114,115] azaspiracids[116–119]), vicinal polyols (amphidinolide H2,[120,121] hyrtiosterol,[122,123] pericosine A[124,125]), sugars (callipeltoside C;[126,127] fusapyrone and deoxyfusapyrone,[128,129] Table 6) and macrolides (palmerolide A,[130–132] neopeltolide[133,134]).

Double bond geometries are accessible through NOEs, and NMR comparisons of coupling constants and chemical shifts. The latter may be altered significantly by different heteroatom substituents, as for the bromo-substituted obtusallenes V–VII[135–137] (Tables 2 and 7). Similarly, NOE data analyses (iejimalides,[138–140] scleritodermin A,[141,142] Table 9) may be ambiguous for endocyclic double bonds if the structural constraints of the ring are not well defined. In the case of mycothiazole,[143,144] the side-chain double bond was misassigned based on an estimated $^{3}J_{H,H}$ coupling constant from the only resolved multiplet.[141]

3. Detection and revision of marine natural product misassignments

Consideration of the sources of structural misassignments leads to the question of how these errors are detected and what techniques are used in revisions of particular structural features. It is reasonable to assume that most errors are detected and revised by orthogonal, complementary approaches to those used in the original assignments. Initial detection of structural misassignments may be due to re-isolation of the same metabolite, or its close analogue, and identification of the error in the process of compound dereplication. Indeed, rigorous dereplication of assumed known compounds is an important exercise for its potential to either validate or question assigned structures. Moreover, a careful re-examination of structure in the compound dereplication process should also consider whether there are inconsistencies from a biosynthetic perspective, which is an important consideration in the de novo structure elucidation process. However, partial or total synthesis of complex and/or biologically active structures is most often the first indication of a structural misassignment. Subsequent revision of a configurationally complex structure may require the synthesis of numerous diastereomers.[2]

Total synthesis accounts for the overwhelming majority of natural product structural revisions (40%, Fig. 3A), but this is not mirrored for marine natural products (26%, Fig. 3B). Non-destructive and relatively sensitive NMR methods, although the greatest source of incorrect assignments, still provide a major contribution to marine structural revisions (38% for NOE and other NMR combined), exceeding that of total and partial syntheses (34% combined), which may require degradation of limited or unavailable natural products for comparisons.

As alluded to in Section 2.1, the significant number of misassignments associated with interpretation of HMBC data (Fig. 2) highlight a subtle problem. Unless all theoretically possible HMBC correlations are observed, some alternative structures are indistinguishable on the basis of HMBC experiments alone. In these circumstances, one needs to 'recognize' the alternative structure(s) and actively discredit these using another technique. It also becomes important to examine a designated structure for all possible 2- and 3-bond HMBC correlations. Those correlations expected but not observed experimentally indicate that further investigation may be necessary. Finally, the existence of 4-bond HMBC correlations needs to be taken into consideration in certain molecular classes (e.g., heteroaromatics).

Several marine natural product structure elucidations elicited our interest because of the use of NMR spectroscopy in the original

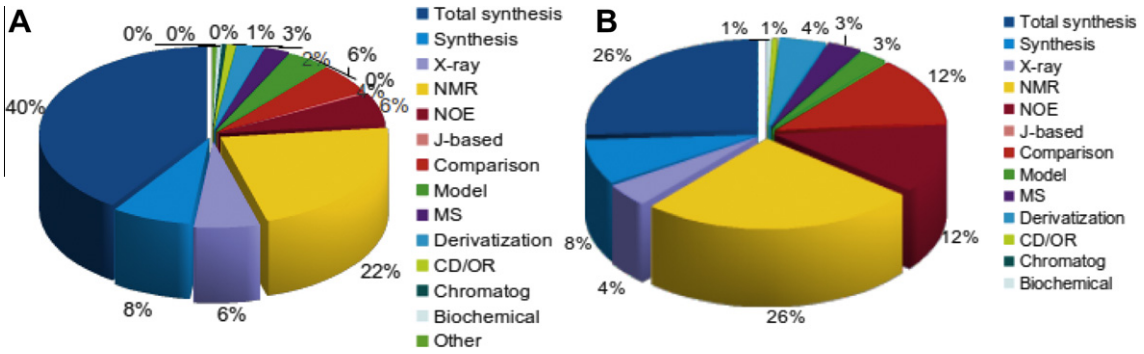


Figure 3. (A) Techniques used in the detection and revision of all natural product structures (2005–2010); (B) Techniques used in the detection and revision of marine natural product structures (2005–2010).

misassignment as well as in the detection of the misassignment and subsequent structural revision. For example, the structure proposed in 1994 for the ascidian metabolite eusynstyelamide (Table 1) was based on extensive 1D and 2D NMR analyses.[145] While, it was noted that dehydration of the proposed α-keto amide hydrate did not occur in aprotic solvents, this was presumed to occur during FABMS since the highest molecular weight ion observed was *m/z* 787, assigned as $[M+H-H_2O]^+$. In 2009, three metabolites named eusynstyelamides A–C were isolated from a different *Eusynstyela* species.[146] Comparison of the previously reported data sets for eusynstyelamide with those of the newly assigned compounds, revealed almost identical data for eusynstyelamide and eusynstyelamide A ($[M+H]^+$, *m/z* 787). A detailed analysis of the re-assessment of the NMR data for eusynstyelamide, and its reassignment as eusynstyelamide A, is presented in the report of eusynstyelamides A–C.[146] In particular, a small 3-bond HMBC correlation observed in the spectrum for eusynstyelamide A, one that was not likely observed in the 1994 spectrum for eusynstyelamide, would have represented a 6-bond connection for the original structure.

Kasarin (Table 1) is a fungal metabolite from the zoanthid coral symbiont *Hyphomycetes* sp. The β-lactam skeleton was originally assigned from ^{13}C and ^{15}N HMBC data, although it was noted that the connectivity between the lactam α-carbon and the methoxy-bearing nitrogen could not be established.[147] Re-isolation of kasarin by the same research group permitted the application of INADEQUATE, as well as ^{15}N and ^{13}C HMBC experiments. In this second analysis,[148] the methoxy substituent could be re-assigned to the original β-lactam nitrogen (N-1) on the basis of a ^{15}N HMBC correlation, and the isopropyl ^1H showed a 3-bond ^{13}C HMBC correlation to the lactam carbon, as well as a 2-bond correlation to the imino carbon on which it is located. To differentiate between the six-membered pyrazinone heterocycle and an alternative five-membered oxazolone, a model pyrazinone was synthesized. The spectral data (including IR and UV) for kasarin were much more consistent with the data for this pyrazinone derivative than with those of commercially available oxazolones which contain a significantly deshielded lactone carbon. Finally, ammonolysis of kasarin yielded a degradation product in which the malonyl substituent was eliminated. The total synthesis of kasarin is also in progress by the same research group.[148]

Interestingly, in the original assignment of pyranonigrin A, both regioisomers shown in Table 2 were considered, and their differentiation recognized as a challenge given the amino and oxymethine HMBC correlations permeating throughout the dihydropyrrole ring.[26] Finally, the incorrect 7-keto dihydropyrrole structure (numbering according to the revised structure) was assigned on the basis of a strong ROESY correlation between the amino and oxymethine protons. In the reassignment of pyranonigrin A,[28] initiated due to its re-isolation from the fermentation broth of the marine fungus *Aspergillus niger*, an ^{15}N HMBC permitted assessment of the pyrrole nitrogen chemical shift as more consistent with an amide N (δ 126.6 ppm) than the hemiaminal N (∼δ 80 ppm) of the original proposed structure. In addition, it was noted that the carbonyl ^{13}C NMR shift (δ 174 ppm) is more consistent with a lactam carbon than the isolated ketone of the original structure (predicted ∼190 ppm). Nevertheless, given the potential for keto-enol tautomerism in the molecule, three other possible regioisomers (around positions 5–7) had to be considered. Unequivocal assignment of the structure shown was enabled finally by acetylation of the two hydroxyl substituents, and subsequent methanolysis of the diacetate. Direct substitution of an acetate by a methoxy group can only have occurred in the regioisomer assigned (Table 2).[28]

4. Misassigned marine natural product structures not yet revised

Tables 1–9 present only those structures that have been revised successfully. In some cases, this multi-step process required repeated revisions (e.g., zamamistatin), or was substantially extended beyond the first report of structural misassignment. Misassigned natural products (Fig. 4) for which revised constitutions have yet to be presented include sponge-derived muzitone,[149] the anti-inflammatory gorgonian metabolites elisabethadione and elisabethamine,[150] iriomoteolides 1a–1c,[151–155] and likely marine actinomycete anthraquinone δ-indomycinone.[156] In all of these cases, total synthesis of the proposed structures revealed discrepancies between the spectroscopic data for the synthetic and natural products. Attempted total synthesis of elisabethamine revealed that this aminohydroquinone structure is unstable in air and is readily oxidized to the quinone.[150] In several of these cases, the lack of readily available authentic natural product sample precludes definitive structural revision, and therefore awaits re-isolation of the natural product or a close analogue. Total synthesis also revealed misassignment of the relative configurations for amphidinolide B2,[157] lituarines B and C from a sea pen,[158] marine fungal metabolite LL15G256γ,[159] and the molluscan depsipeptide onchidin[160] (Fig. 4). Thus, total synthesis has been instrumental in the detection of marine natural product structural misassignments.

5. Concluding remarks

Natural product structure elucidation has been described as routine and no longer the art that it once was.[161] However, while it may have evolved considerably since its origins, it is safe to

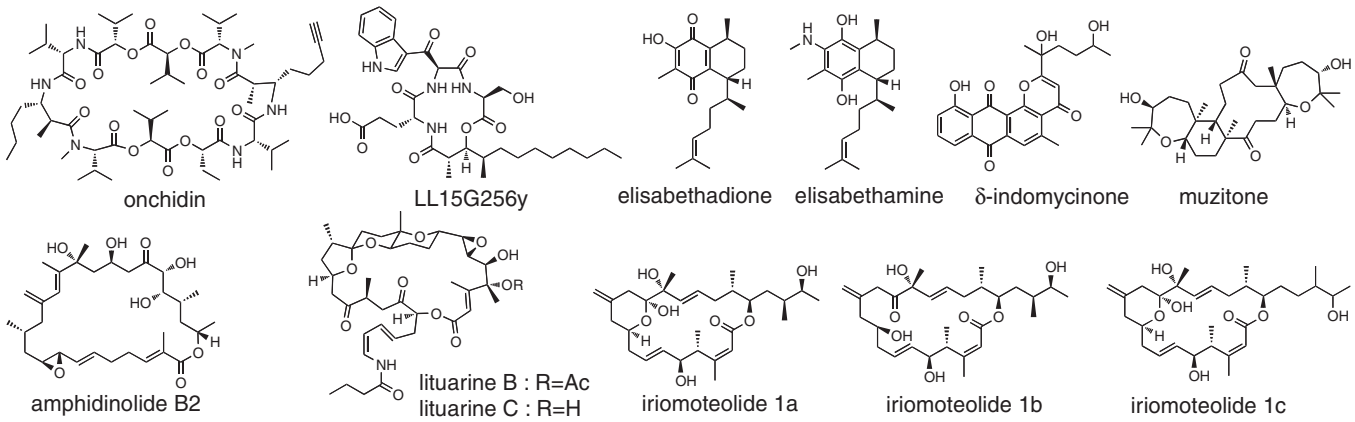


Figure 4. Misassigned marine natural product structures not yet revised (detected 2005–2010).

say that the art of structure elucidation has not yet achieved perfection, and that the partnership between natural products chemistry and synthetic organic chemistry is still very much in order. Although chemical degradation and derivatization may have been somewhat less involved in the constitutional assignment of marine-derived versus terrestrial natural products, total synthesis plays a critical role in marine natural product structure elucidation. Furthermore, it is clear that significant detective work using a variety of orthogonal techniques, while keeping in mind biosynthetic considerations, is still necessary for unequivocal assignment, not only of configuration, but also of constitution. The ramifications of structural misassignments in reallocation of resources become evident when almost simultaneous reports of a structural revision are published by different research groups, when sequential revisions of structure are necessary before the correct structure is achieved, or when total syntheses of multiple diastereomers for comparison with the natural product must be accomplished. It is also evident that all methodologies used for structure elucidation can generate errors, and thus structure elucidation of a new natural product should always be accomplished by the most rigorous methods available to the natural products chemist. Similarly, presumed known compounds re-isolated from new collections or cultures should be assigned unequivocally as such by orthogonal techniques and in light of current biosynthetic knowledge and understanding. Structural misassignments continue to be reported for even recently reported marine natural products, and thus, it seems that the increasingly high-field magnets and sensitive probes do not necessarily attenuate the rate of structural misassignments. Rather, they permit the attempted structure elucidation of increasingly limited quantities of minor components from natural products extracts, as well as larger molecules of greater structural complexity. Therefore, total synthesis of natural products will surely continue to be central to confirmation of natural product structure assignment, as well as providing material for biological testing towards pharmaceutical development, and investigations of biosynthetic pathways.

Acknowledgments

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