Natural Products Synthesis

Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation

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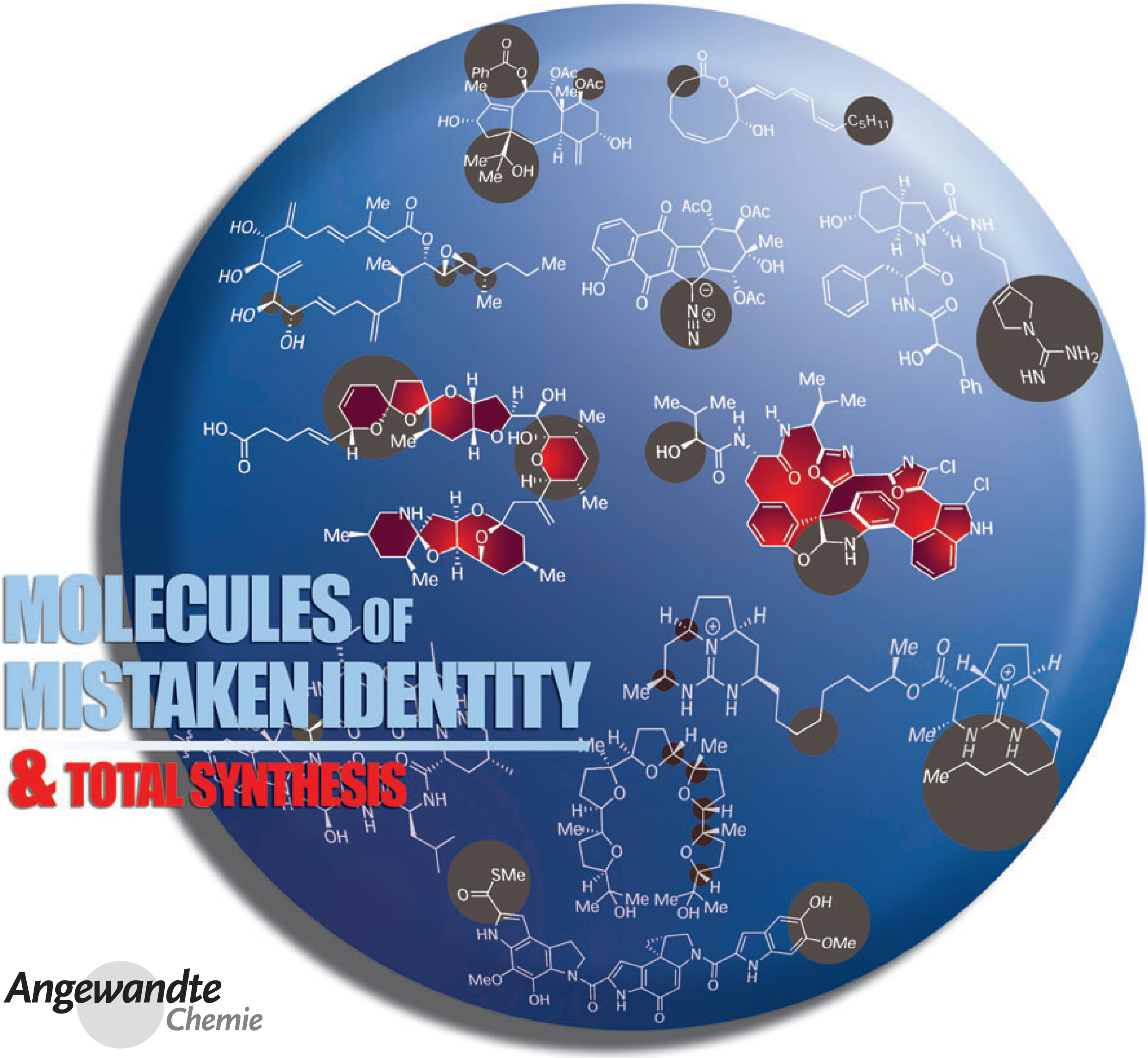
Keywords:
azaspiracid-1 · diazonamide A · natural products · revised structures · total synthesis



Angewandte Chemie

DOI: 10.1002/anie.200460864

Over the course of the past half century, the structural elucidation of unknown natural products has undergone a tremendous revolution. Before World War II, a chemist would have relied almost exclusively on the art of chemical synthesis, primarily in the form of degradation and derivatization reactions, to develop and test structural hypotheses in a process that often took years to complete when grams of material were available. Today, a battery of advanced spectroscopic methods, such as multidimensional NMR spectroscopy and high-resolution mass spectrometry, not to mention X-ray crystallography, exist for the expeditious assignment of structures to highly complex molecules isolated from nature in milligram or sub-milligram quantities. In fact, it could be argued that the characterization of natural products has become a routine task, one which no longer even requires a reaction flask! This Review makes the case that imaginative detective work and chemical synthesis still have important roles to play in the process of solving nature's most intriguing molecular puzzles.

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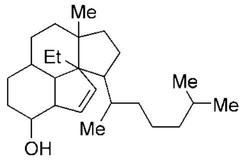
1. Introduction

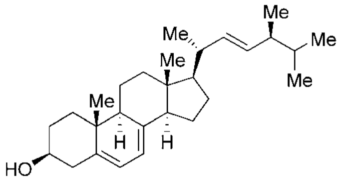
During all of the 19th century and most of the early half of the 20th century, natural product structure elucidation was an art that depended almost entirely on the power of chemical synthesis, or, more specifically, on the effectiveness of degradation or derivatization processes, to reveal the architectural design of a molecule. Assuming both that gram quantities of the substance under investigation were available and that the chemical transformations employed proceeded along expected lines, researchers of that era might have expected to solve their molecular puzzles after a few years of painstaking effort. The assignment of absolute or relative configuration was, of course, essentially out of the question in most cases.

Needless to say, this intellectually difficult and physically tedious approach had its limitations, and was often attended with errors. For example, during the 1920s there was tremendous interest in establishing the structures of a number of steroids. Although a formidable task that stymied many, two researchers in Germany, Wieland and Windaus, rose to the challenge and unraveled several of the key structural motifs of these molecules, leading them to propose a number of architectures, such as structure **1** for cholesterol (Figure 1).[1] So impressed was the chemical community with this work that it ultimately served as part of the basis for their separate receipt of the Nobel Prize in Chemistry in 1927 and 1928, respectively. Unfortunately, as anyone today can instantly recognize, their proposals had a number of inaccuracies in terms of the core structure—mistakes that were revealed in 1932 when Bernal obtained the first X-ray crystal structure of a steroid (ergosterol (**2**), Figure 1).[2]

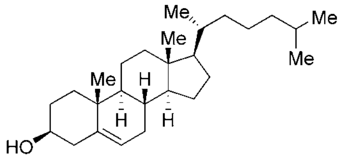
Nevertheless, the near-exclusive use of chemical synthesis for structural elucidation did score a number of remarkable successes, such as correct assignments for the natural products quinine (**4**)[3] and haemin (**5**)[4] prior to the start of World War II, and strychnine (**6**) in 1946 (Figure 2).[5] Equally



1: Wieland/Windaus structure for cholesterol (1927)



2: structure of ergosterol (1932)
(verified by X-ray crystal-structure analysis)



3: correct structure of cholesterol (1932)

Figure 1. A classical misassignment: Wieland and Windaus were awarded the Nobel Prize in Chemistry in 1927 and 1928, respectively, for deriving structures of natural products, such as their proposed structure **1** for cholesterol.

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DOI: 10.1002/anie.200460864

important, if not more so, these efforts also served as the principle driving force for the discovery of new chemical reactivity. Indeed, much of our present knowledge regarding heterocyclic chemistry was established through structural work directed towards the targets shown in Figure 2, among others, just as work focused on confirming the connectivities of the steroids afforded insight into how carbon–carbon bonds could be forged and cleaved. Phrased differently, as recently formulated by Doering: "In the beginning, the isolation of chemicals from natural sources provided an unceasing stimulus to the creation and development of science."[6]

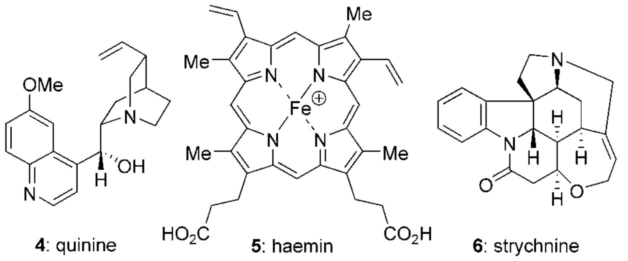
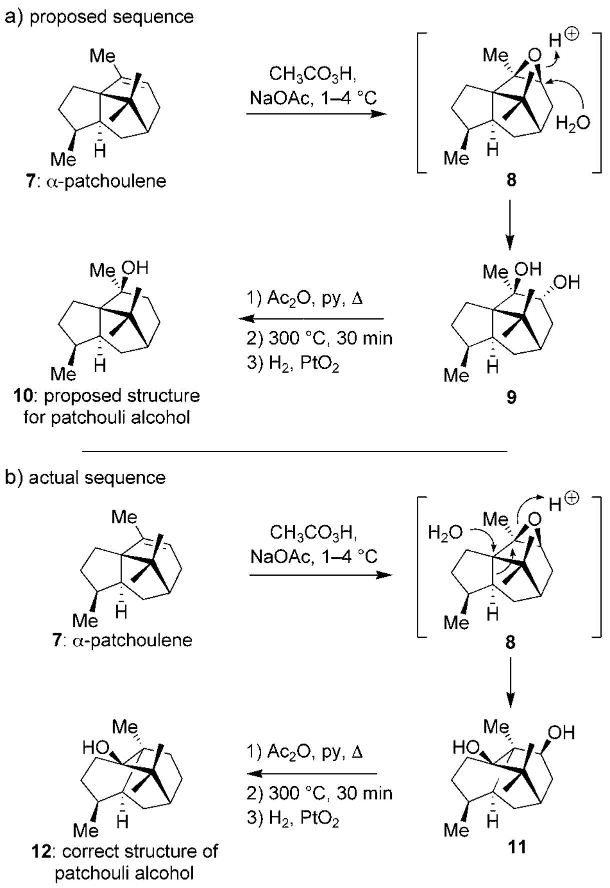


Figure 2. Quinine (**4**), haemin (**5**), and strychnine (**6**): The elucidation of the structures of these natural products inspired a great deal of new chemistry.

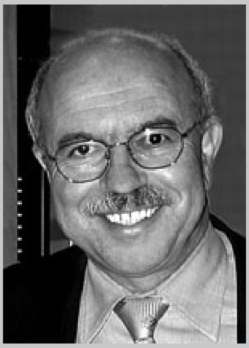
By contrast, total synthesis played almost no role as a vehicle for chemical discovery during these early days. Instead, it served as the means to obtain a final proof of structure once degradative work had been completed, under the belief that if synthetically derived material matched its natural counterpart in all respects, then the proposed structure must be correct. This assumption was an accurate one for the most part, though it, too, could lead to misassignments. A classic example resides in work directed towards patchouli alcohol, a natural product that had been assigned structure **10** (Scheme 1) in 1961 by Büchi and his colleagues at the Massachusetts Institute of Technology (MIT) after several years of careful study.[7] In 1962, the Büchi group felt that they had confirmed their structural proposal by obtaining synthetic material that corresponded fully to authentic patchouli alcohol in just four steps from another natural product, α-patchoulene (**7**).[8] As shown in Scheme 1 a, those operations were: 1) epoxidation of the double bond in **7** followed by nucleophilic ring opening to generate diol **9**; 2) acetylation of the resulting secondary alcohol; 3) thermally induced elimination of the newly formed acetate; and 4) hydrogenation of the resulting olefin.


a) proposed sequence

b) actual sequence

Scheme 1. The total synthesis of patchouli alcohol by Buchi et al. caused faith to be placed in the wrong structure for the natural product (they postulated **10** instead of **12**). The error occurred as a result of an unexpected skeletal rearrangement.

Although this synthesis should have provided the final verdict on the structure of patchouli alcohol, the case was reopened a year later when Dunitz and his colleagues at the Eidgenössische Technische Hochschule Zürich obtained an X-ray crystal structure of a diester derivative that suggested that **12**, rather than **10**, was the structure of patchouli alcohol.[9] What had happened? Well, the problem did not



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Scott A. Snyder, born in Palo Alto, California, received his BA in chemistry from Wiliams College in 1999. He completed his PhD in May 2004 at The Scripps Research Institute with K. C. Nicolaou on the total synthesis of diazonamide A and is currently an NIH postdoctoral fellow with E. J. Corey at Harvard University. He is co-author of Classics in Total Synthesis II and has contributed to over 30 publications, review articles, book chapters, and patents. He received predoctoral fellowships from the National Science Foundation, Pfizer, and Bristol-Myers Squibb.

lie with the crystal structure or with the sequence employed by the MIT team. Instead, the discrepancy resulted from an unanticipated skeletal rearrangement that had occurred in the Büchi synthesis when **7** was treated with peracid, an operation that fortuitously generated the correct architecture of the natural product as represented by **11**.[10] A lucky coincidence, indeed!

By the late 1960s, the chances of encountering such an unanticipated outcome during efforts towards structure elucidation dropped precipitously as the "classical" chemical approach was gradually replaced by a far more accurate battery of nondestructive methods, such as nuclear magnetic resonance (NMR), ultraviolet (UV), and infrared (IR) spectroscopy, circular dichroism (CD), and mass spectrometry (MS).[11] Today, these methods have grown both in number and power to the extent that a researcher seeking to characterize a few milligrams of an unknown natural product would probably rely entirely on spectroscopic techniques to obtain a complete structural assignment. The benefits, at least based on some recently assigned natural product structures, are clear: Far more complex molecules can be tackled in far less time, even when the compounds are isolated in miniscule amounts. Furthermore, for synthetic chemists, discovery has become intricately linked to processes other than degradation, such as total synthesis. Even as early as 1963, the chemical community keenly perceived the power of these changes, as evidenced by the following remarks:

> If penicillin were discovered today … the scientific problems of studying a pure crystalline compound with a molecular weight of about 350 would not have been nearly so difficult. The conclusion is that a good graduate student would probably work out the structure of penicillin in a day or so. Just a generation ago, that same scientific feat took the best of us years of intensive work.
>
> John C. Sheehan (1982)[12]

> We have now reached the stage where often we have insufficient material for a retention sample; where crystallization is not worth attempting; where determination of a melting point may be a prohibitive waste of material; and yet, where we have learned more about the structure of that molecule than we did years ago with grams of substance.
>
> Carl Djerassi (1980)[13]

> While it is undeniable that organic chemistry will be deprived of one special and highly satisfying kind of opportunity for the exercise of intellectual *élan* and experimental skill when the tradition of purely chemical structure elucidation declines, it is true too that the not infrequent dross of such investigations will also be shed; nor is there any reason to suppose that the challenge for the hand and the intellect must be less, or the fruits less tantalizing, when chemistry *begins* at the advanced vantage point of an established structure.
>
> R. B. Woodward (1963)[5d]

At the same time, these advances have also left some (especially those who "grew up" during the classical era) with a lingering sense that something important and valuable has been lost, that the practice of structure elucidation can never again provide the drama it once did:

> Today … spectroscopic methods have almost entirely supplanted this classical approach, and therewith deprived the science of a nigh inexhaustible source of unpremeditated discoveries.
>
> W. von E. Doering (1999)[6]

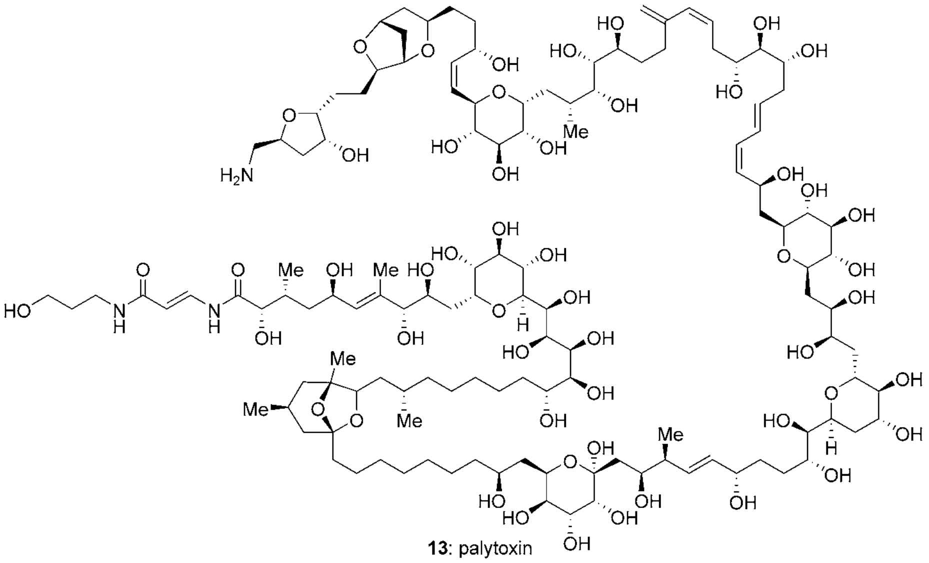
> Until the mid-1960s, structure determination was an art that could be likened to solving a complicated detective case, but with the spectacular advancement in spectroscopy it has become less inspiring, and since the mid-1980s, in most cases, structure determination has become rather "routine".
>
> Koji Nakanishi (1991)[14]

In any event, progress can not be reversed, and, at present, our spectroscopic abilities have converted chemical synthesis into its own highly specialized and rewarding discipline, one that has little to do with structure elucidation apart from the assignment of absolute or relative stereochemistry in those cases where spectroscopy or X-ray crystallography can not provide the answer. We might be able to gauge the current state of the field of structural elucidation by considering molecules such as palytoxin (**13**, Figure 3), a compound whose highly ornate architecture was established almost completely by spectroscopic means with synthesis filling in the missing stereochemical information.[15] A number of other examples could also be used as a barometer. To mention just one, synthesis has not yet made its final mark on amphidinolide N (**14**). With nine unassigned stereocenters, the correct structure is one of 512 possible isomers![16]

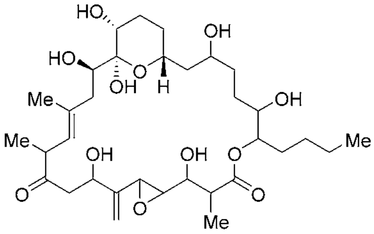
Certainly a rosy picture, but is it completely accurate? Are structural elucidations mostly uneventful endeavors? Have spectroscopic techniques made the process of characterization one almost devoid of errors? Is there no role for total synthesis beyond stereochemical assignment? Herein we address these issues and hope to succeed in convincing you not only that chemical synthesis still has much to offer, but also that there is a long way to go before natural product characterization can be considered a process devoid of adventure, discovery, and, yes, even unavoidable pitfalls.

2. The State of Modern Structure Elucidation

As a starting point for tackling some of the questions listed above, we searched a variety of scientific databases for a series of keyword terms, such as "structural misassignment" and "revised structure", to ascertain just how frequently natural products have been incorrectly assigned during the past few years.[17] We expected to find only a few errors, with most of these arising from a misassigned stereocenter or two, and those in only the most complex or unique of structures. The actual output proved to be very different. Limiting our search to literature published from January 1990 to April 2004, we uncovered the existence of well over 300 structural revisions, many of which extended far beyond simple stereo-



13: palytoxin



14: amphidinolide N

Figure 3. Determination of absolute/relative configuration: the last frontier of chemical-stucture elucidation? The structure of palytoxin (**13**) was ultimately determined by chemical synthesis. In the proposed structure of amphidinolide N (**14**) the configurations of nine stereocenters remain unassigned.

chemical problems into the realm of profound, and sometimes complete, constitutional changes. Tables 1 to 8 present 50 members of this collection in no particular order. Amazingly, the examples cover virtually every compound class, including steroids, terpenes, indole alkaloids, and peptides, and encompass molecules of all sizes and levels of stereochemical complexity.

Clearly, this diverse array of structures reveals that mistakes are still a common occurrence despite our present advantages. But why do so many errors occur? The answer certainly does not place into question the skills of the scientists who made the original structural determination. On the contrary, it is amazing just how many complicated natural products have been assigned correctly, especially when only limited material was available or the natural substance in question was unlike any other ever observed. Instead, the number of errors simply reflects the fact that *every* method for assignment has its weaknesses, some of which can not be resolved even if every other tool for structural elucidation is also applied.

For example, although X-ray crystallography is traditionally viewed as an infallible technique, it can occasionally lead to misassignments because it does not reveal the positions of hydrogen atoms (those shown in any crystal structure have always been drawn in). Consequently, it is sometimes difficult to discern between O atoms and NH groups, as discussed at some length with an example in Section 4. X-ray crystallography can also confuse the identity of atoms within certain functional groups devoid of hydrogen atoms. Table 4 shows an example in which the assignment of a C atom instead of an N atom (a cyano rather than a diazo group) led to a long-standing incorrect structure for the kinamycins.[70–72]

NMR spectroscopy, too, can only provide so much of the overall picture, especially in the case of molecules with insufficient hydrogen atoms to obtain the ^{1}H,^{13}C correlations needed to assign their deeper domains properly. Many of the structural revisions in the tables fall into this category, even though a number of powerful two-dimensional techniques, such as INEPT, HMBC, HMQC, and TOCSY, were applied. In some cases, even NMR spectroscopy is of little use as a tool despite its awesome power, and more basic methods, such as IR spectroscopy, become the principal source of structural information. Such was the case with the unnamed coumarin shown in Table 2, a compound whose structure proved exceedingly difficult to ascertain considering its relatively small size.[39,40]

Of course, structural assignments are rarely based on just one method and are typically the culmination of a careful refinement process that considers a variety of architectural possibilities, pruned only when new information is added to the overall picture. Consequently, assignment errors are often the result of faith placed in spectroscopic data that is actually spurious, as incorrect structures that should have been excluded early in the process can then survive. For example, in their effort to assign a structure to halipeptin A (see Table 1), the research group of Gomez-Paloma used high-resolution mass spectrometric data obtained by the fast-atom bombardment (FAB) technique to identify its molecular formula. Their finding ($C_{31}H_{54}N_4O_8$) was then combined with information from other sources (primarily NMR spectroscopy) to generate a proposed structure that included a unique four-membered ring linked to a carbonyl group at the core of the molecule.[27] However, upon reinvestigation of the molecular formula a year later by using a different high-resolution mass spectrometric technique (electron-spray ionization, ESI), the data now suggested that the molecular formula $C_{31}H_{54}N_4O_6S$ was a far better match for halipeptin A (i.e., the exchange of two oxygen atoms for a sulfur atom). Consequently, a very different structural assignment for the central portion of the molecule resulted.[28] A similar type of mass spectrometric error was responsible the misassignment of a portion of didemniser-

Table 1: Selected structures of misassigned natural products and proposed structural revisions.

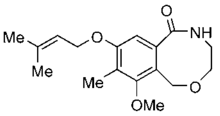
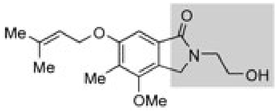
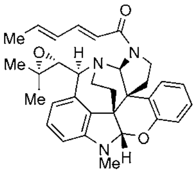
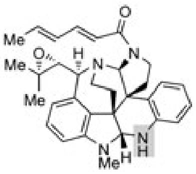
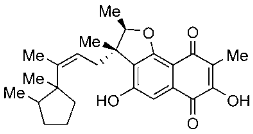
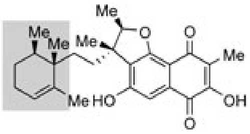
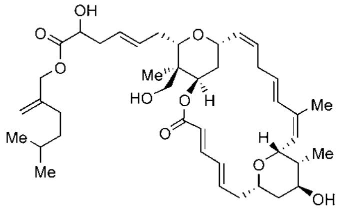
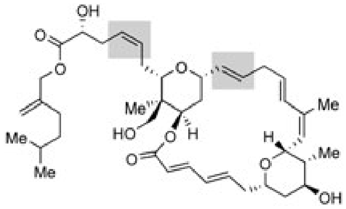
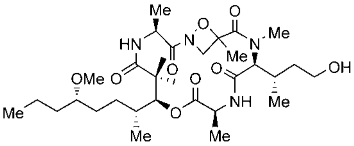
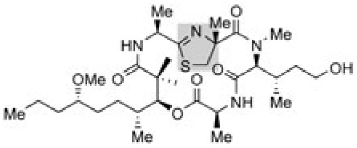
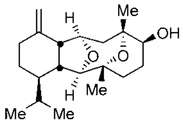
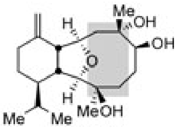
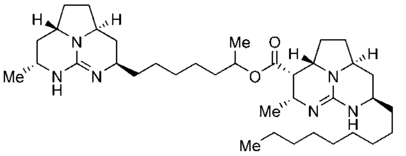
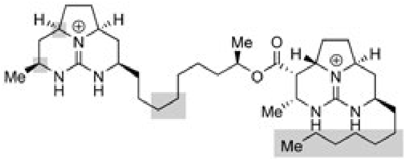
Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **porritoxin** Suemitsu et al. (1992)[18]	NMR UV IR MS	 2D NMR experiments Horiuchi et al. (2002)[19]	Cornella and Kelly (2004)[20]
 **nomofungin** Hemscheidt et al. (2001)[21]	NMR UV IR CD MS	 comparison with literature data for another natural product Stoltz et al. (2003)[22]	no
 **neomarinone** Fenical et al. (2000)[23]	NMR UV IR MS	 2D NMR spectroscopy and feeding experiments Moore et al. (2003)[24]	no
 **lasonolide A** McConnell et al. (1994)[25]	NMR IR MS	 chemical synthesis Lee et al. (2002)[26]	Lee et al. (2002)[26]
 **halipeptin A** Gomez-Paloma et al. (2001)[27]	NMR UV IR MS derivatization	 reevaluation of MS data and chemical synthesis Gomez-Paloma et al. (2002)[28]	no
 **sclerophytin A** Sharma and Alam (1988)[29]	NMR IR MS	 2D NMR spectroscopy and chemical synthesis Paquette et al. (2000)[30]	Overman, Paquette, et al. (2001)[31]
 **batzelladine F** Faulkner et al. (1997)[32]	NMR UV IR MS	 reevaluation of MS data and chemical synthesis Cohen and Overman (2001)[33]	Cohen and Overman (2001)[33]

Table 2: Selected structures of misassigned natural products and proposed structural revisions.

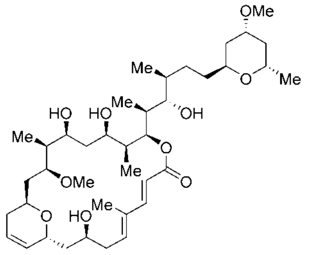
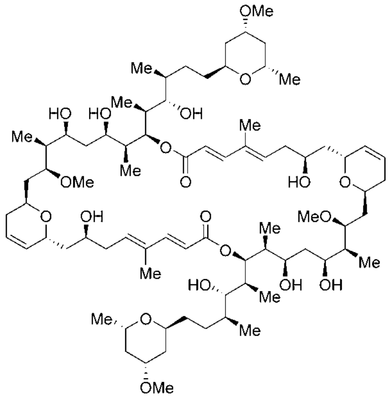
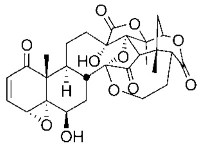
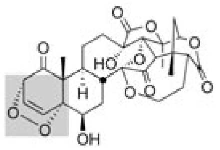
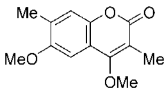
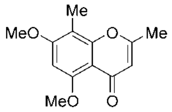
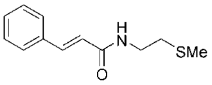
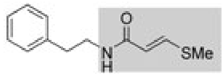
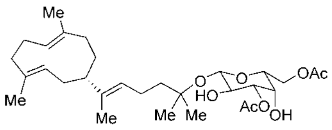
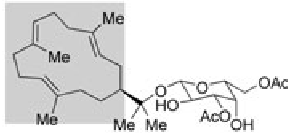
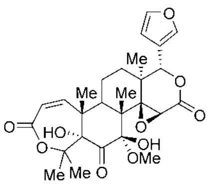
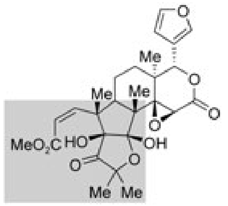
Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **swinholide A** Carmely and Kashman (1985)[34]	NMR UV IR MS	 reisolation and reexamination Kitagawa et al. (1990)[35]	Paterson et al. (1994)[36]
 **physalin K** Ramachandra Row et al. (1980)[37]	NMR EA UV IR CD MS derivatization	 isolation of related compounds and more detailed spectroscopic investigations Kawai et al. (1995)[38]	no
 **unnamed coumarin** Atta-Ur-Rahman et al. (1991)[39]	NMR UV IR MS	 chemical synthesis Kalinin and Snieckus (1998)[40]	Kalinin and Snieckus (1998)[40]
 **sinharine** Hofer et al. (1992)[41]	NMR UV IR MS	 chemical synthesis Johnson et al. (1994)[42]	Johnson et al. (1994)[42]
 **calyculaglycoside A** Rodríguez et al. (1997)[43]	NMR UV IR MS degradation	 isolation of related compounds, biogenetic considerations, and degradation Rodríguez et al. (2001)[44]	no
 **harrisonin** Nakanishi et al. (1976)[45]	NMR UV IR CD MS	 X-ray crystallography and 2D NMR spectroscopy Fischer et al. (1997)[46]	no

Table 3: Selected structures of misassigned natural products and proposed structural revisions.

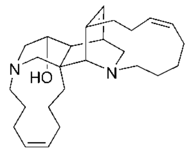
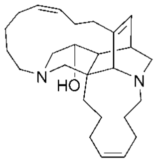
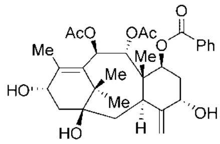
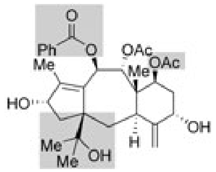
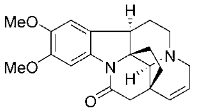
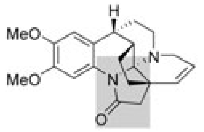
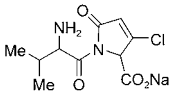
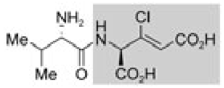
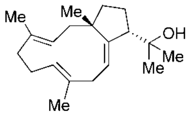
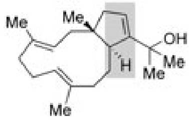
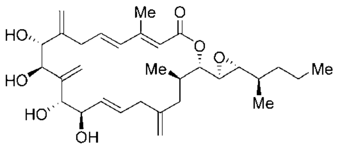
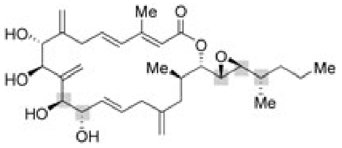
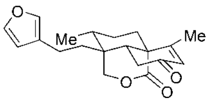
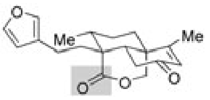
Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **xestocyclamine A** Crews et al. (1993)[47]	NMR IR MS	 isolation of related compounds and reevaluation Rodríguez and Crews (1994)[48]	no
 **brevifoliol** Tachibana et al. (1991)[49]	NMR IR MS	 reisolation and reexamination Georg et al. (1993)[50]	no
 **isoschizogamine** Renner and Fritz (1965)[51]	NMR EA UV IR derivatization	 reisolation and 2D NMR spectroscopy Hájícek et al. (1998)[52]	Hubbs and Heathcock (1999)[53]
 **FR900148** Kuroda et al. (1980)[54]	NMR EA IR derivatization	 reisolation and reexamination Yasuda and Sakane (1991)[55]	no
 **palominol** Rodríguez et al. (1990)[56]	NMR IR MS derivatization	 isolation of related compounds and comparison of spectra Shin and Fenical (1991)[57]	Corey and Kania (1998)[58]
 **(+)-amphidinolide A** Kobayashi et al. (1991)[59]	NMR UV IR CD MS derivatization	 chemical synthesis Trost and Harrington (2004)[60]	Trost and Harrington (2004)[60]
 **sacacarin** Maciel et al. (1998)[61]	NMR UV IR MS	 chemical synthesis Grossman and Rasne (2001)[62]	Grossman and Rasne (2001)[62]

Table 4: Selected structures of misassigned natural products and proposed structural revisions.

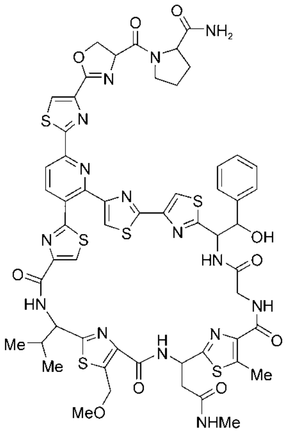
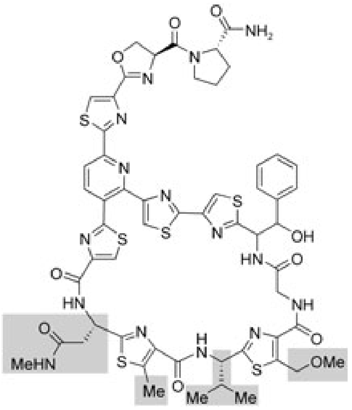
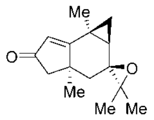
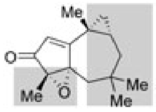
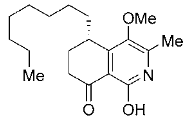
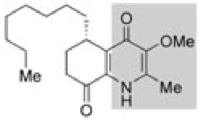
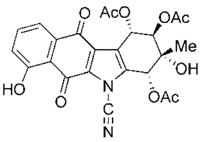
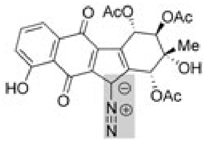
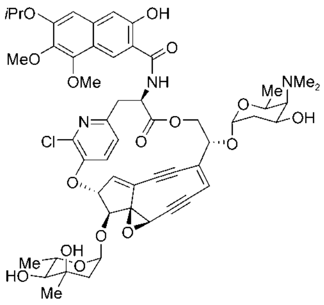
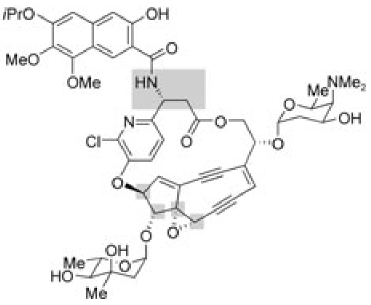
Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **GE2270A** Ferrari et al. (1991)[63]	NMR EA UV IR MS degradation	 degradation and chemical synthesis Tavecchia et al. (1995)[64]	no[65]
 **caespitenone** Asakawa et al. (1980)[66]	NMR UV IR MS derivatization	 2D NMR spectroscopy Asakawa et al. (1993)[67]	no
 **antidesmone** Bringmann et al. (1999)[68]	NMR UV CD IR MS derivatization	 feeding experiments Bringmann et al. (2000)[69]	no
 **kinamycin C** Ômura et al. (1973)[70]	X-ray crystallography NMR UV IR MS degradation derivatization	 2D NMR spectroscopy and chemical synthesis Gould et al. (1994)[71] and Dmitrienko et al. (1994)[72]	no
 **kedarcidin chromophore** Leet et al. (1992)[73]	NMR UV IR MS degradation derivatization	 chemical synthesis Hirama et al. (1997)[74]	no[75]

Table 5: Selected structures of misassigned natural products and proposed structural revisions.

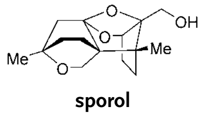
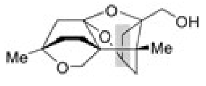
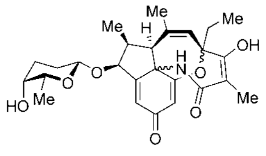
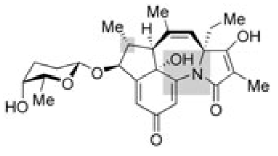
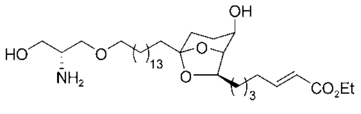
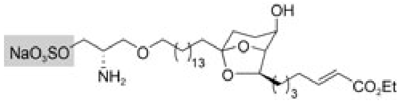
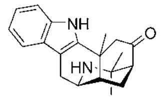
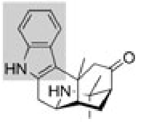
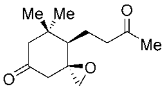
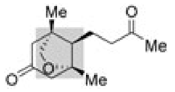
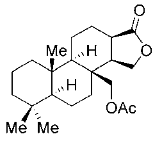
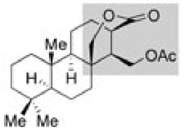
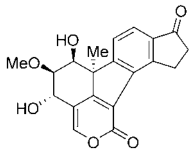
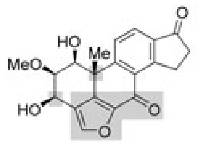
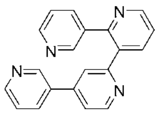
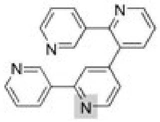
Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **sporol** Tempesta et al. (1986)[76]	NMR IR MS	 NMR spectroscopy and chemical synthesis Ziegler et al. (1988)[77]	Ziegler et al. (1992)[78]
 **tetrapetalone A** Hirota et al. (2003)[79]	NMR UV IR MS derivatization	 ^{1}H-^{15}N HMBC spectroscopy Hirota et al. (2003)[80]	no
 **(+)-didemniserinolipid B** Jiménez et al. (1999)[81]	NMR UV IR MS	 MS and chemical synthesis Ley et al. (2002)[82]	Ley et al. (2002)[82]
 **(+)-aristolasicone** Husson et al. (1988)[83]	NMR UV IR CD MS derivatization	 X-ray crystallography and chemical synthesis Borschberg et al. (1991)[84]	Borschberg et al. (1991)[84]
 **annuionone A** Macías et al. (1998)[85]	NMR IR MS	 reevaluation of NMR spectroscopic data Takikawa et al. (2003)[86]	Takikawa et al. (2003)[86]
 **aplyroseol-14** Taylor and Toth (1997)[87]	NMR MS	 chemical synthesis Arnó et al. (2003)[88]	Arnó et al. (2003)[88]
 **TAEMC161** Nakajima et al. (2000)[89]	NMR UV IR MS	 comparison with literature data for another natural product Wipf and Kerekes (2003)[90]	no
 **nemertelline** Kem et al. (1976)[91]	NMR MS	 X-ray crystallography and chemical synthesis Zoltewicz and Cruskie (1995)[92]	Zoltewicz et al. (1995)[93]

Table 6: Selected structures of misassigned natural products and proposed structural revisions.

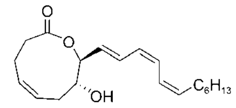
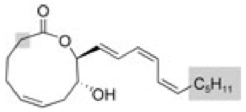
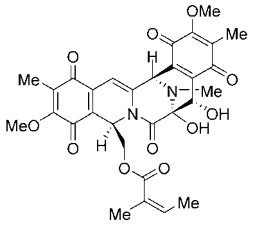
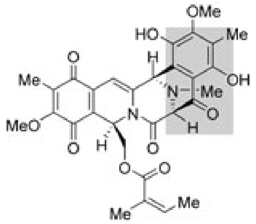
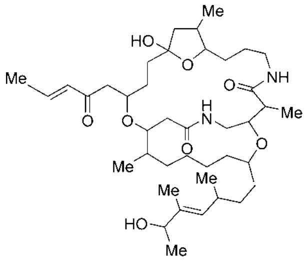
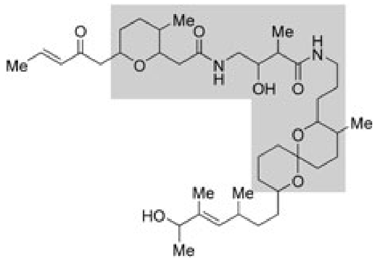
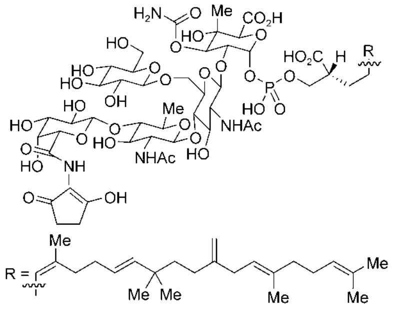
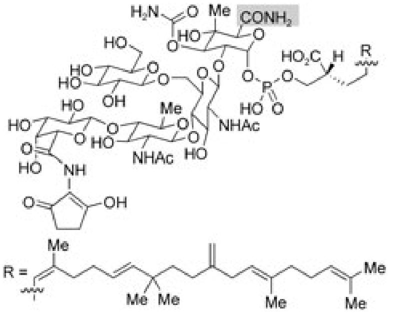
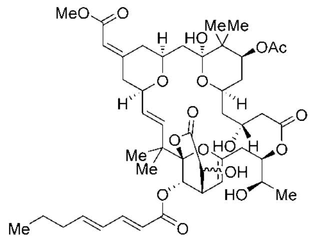
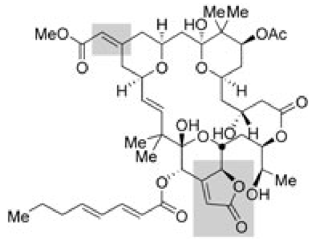
Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **ascidiatrienolide A** Lindquist and Fenical (1989)[94]	NMR UV IR MS	 chemical synthesis Holmes et al. (1993)[95]	Holmes et al. (1993)[95]
 **renieramycin H** Parameswaran et al. (1998)[96]	NMR UV IR MS	 2D NMR spectroscopy and X-ray crystallography Saito et al (2001)[97]	no
 **bistramide A** Hawkins et al. (1989)[98]	NMR MS	 reisolation and reevalution Ireland et al. (1992)[99]	no
 **moenomycin A** Riemer et al. (1981)[100]	NMR MS degradation derivatization	 MS and 2D NMR spectroscopy Fehlhaber et al. (1990)[101]	no
 **bryostatin 3** Pettit et al. (1983)[102]	NMR UV MS	 2D NMR spectroscopy Schaufelberger et al. (1991)[103]	Yamamura et al. (2000)[104]

Table 7: Selected structures of misassigned natural products and proposed structural revisions.

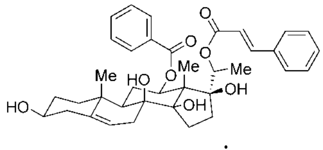
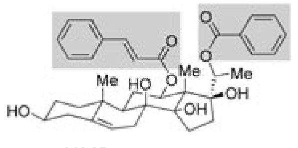
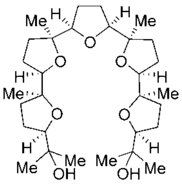
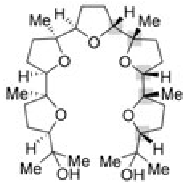
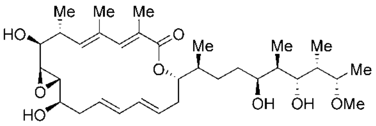
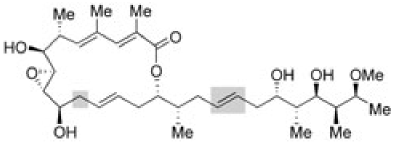
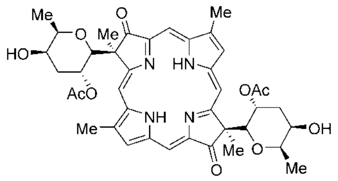
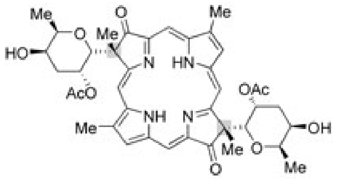
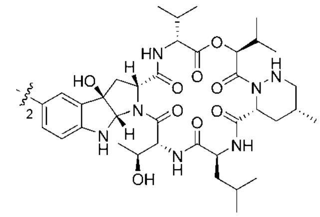
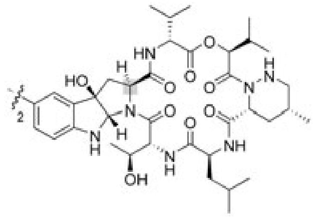
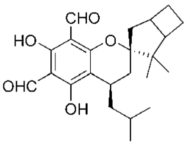
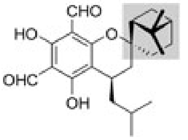
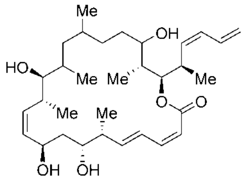
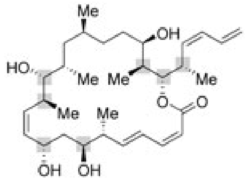
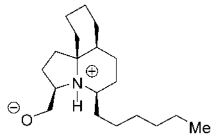
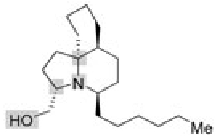
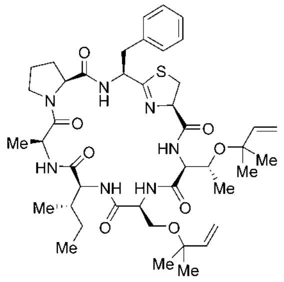
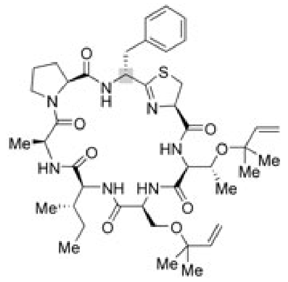
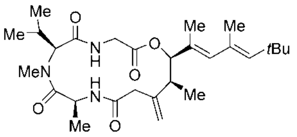
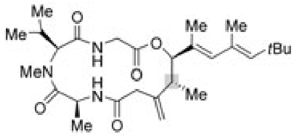
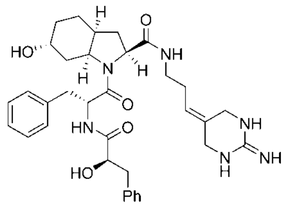
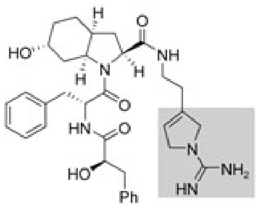
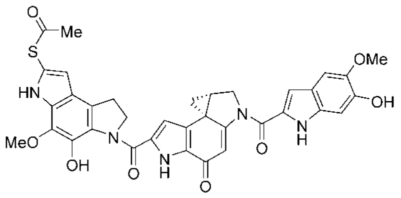
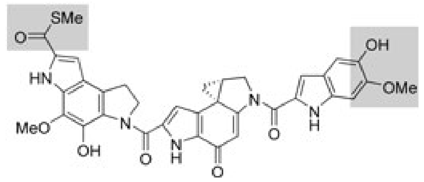
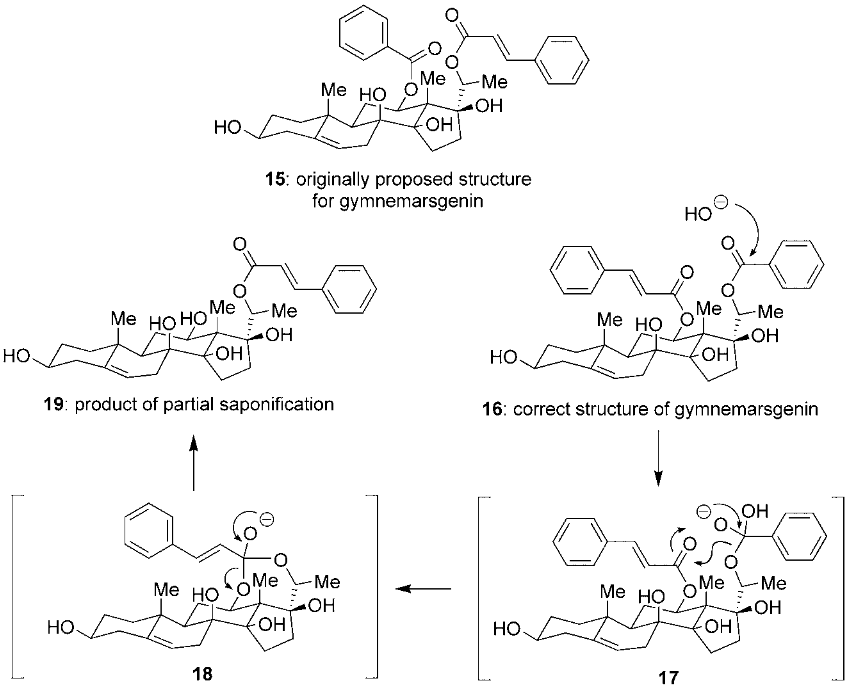
Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **gymnemarsgenin** Zhou et al. (1989)[105]	NMR UV IR MS degradation	 NMR spectroscopy Cordell et al. (1995)[106]	no
 **glabrescol** Reynolds et al. (1995)[107]	NMR IR MS	 chemical synthesis Morimoto et al. (2000)[108b]	Morimoto et al., Xiong and Corey (2000)[108b,c]
 **FD-891** Eguchi, Kakinuma, et al. (2002)[109c]	NMR UV IR MS degradation	 chemical synthesis and comparison with literature data for another natural product Eguchi, Kakinuma, et al. (2004)[110]	no
 (+)-**tolyporphin A** Moore et al. (1992)[111]	NMR UV MS derivatization	 chemical synthesis and NMR spectroscopy Kishi et al. (1999)[112]	Wang and Kishi (1999)[113]
 **himastatin** Leet et al. (1996)[114]	NMR UV IR MS degradation derivatization	 chemical synthesis Kamenecka and Danishefsky (1998)[115]	Kamenecka and Danishefsky (1998)[115]
 **robustadial A** Nakanishi et al. (1984)[116]	NMR UV IR CD MS degradation derivatization	 chemical synthesis Cheng and Snyder (1988)[117]	Salomon et al. (1988)[118]

Table 8: Selected structures of misassigned natural products and proposed structural revisions.

Proposed structure	Methods used in original assignment	Revised structure and basis for revision	Verified by total synthesis
 **dictyostatin 1** Pettit et al. (1995)[119]	NMR UV IR MS	 reisolation and reexamination Paterson et al. (2004)[120]	no
 **lepadiformine** Biard et al. (1994)[121]	NMR IR MS derivatization	 chemical synthesis Kibayashi et al. (2000)[122]	Kibayashi et al. (2000)[122]
 **trunkamide A** Ireland, Bowden, et al. (1996)[123]	NMR UV IR MS degradation derivatization	 chemical synthesis Wipf and Uto (2000)[124]	Wipf and Uto (2000)[124]
 **antillatoxin** Gerwick et al. (1995)[125]	NMR CD UV IR MS	 chemical synthesis Shioiri et al. (1999)[126]	Shioiri et al. (1999)[126]
 **oscillarin** Martin et al. (1996)[127]	NMR MS	 chemical synthesis Hanessian et al. (2004)[128]	Hanessian et al. (2004)[128]
 **yatakemycin** Igarashi et al. (2003)[129]	NMR UV IR MS	 chemical synthesis Boger et al. (2004)[130]	Boger et al. (2004)[130]



Scheme 2. Potential characterization pitfalls: A degradation reaction leads to an internal migration, and the structure **15** is therefore assigned (erroneously) to the steroid natural product gymnemarsgenin (**16**).

inolipid B (Table 5), although the revision in this case involved a much smaller constitutional change.[81,82]

In other instances, the collected spectroscopic data might have led to the right assignment, if a chemical method had not led to a mistake. Such was the case in the attempt to assign a structure to the steroid natural product gymnemarsgenin (Table 7), whereby a final degradative reaction seeking to cleave only one of the two ester groups was employed to assist in confirming the positions of these functionalities within the molecule. Unfortunately, this experiment led the original research team to propose an incorrect structure (**15**, see Scheme 2), as an internal migration reaction occurred under the conditions used, an outcome that was not recognized until well after publication.[105,106]

We could fill pages with the stories behind some of these reassignments. Rather than doing this, we encourage you to explore independently those examples that interest you most, as they provide a rich source of potential research projects and a wealth of interesting problems as to how one might attempt to discern between the original and revised structures. Instead, we use the examples in Tables 1 to 8 to make the case that chemical synthesis still has a major role to play in structural assignments, especially structural revisions. Indeed, for over half of the reassignments in this sample (27), chemical synthesis was required to reach a revised architecture, and in 22 cases it was total synthesis that indicated that there was a problem in the first place. Many of these examples involved the process of establishing/revising the configuration of stereocenters, as hinted above, but that should not give the false impression that such a correction involved little work. For example, the research group of Lee had to prepare a number of structural isomers of lasonolide A (Table 1) before they realized its true constitution.[25,26] Similarly, Trost and Harrington synthesized ten different diastereomers of amphidinolide A (see Table 3) to assure themselves of its identity, as differences in the chemical-shift values in the NMR spectra were only slight, and no natural sample was available to enable a direct comparison.[59,60]

In other cases, chemical synthesis served to confirm a given motif. For example, apart from using a different mass spectrometric experiment to reassign the structure of halipeptin A, the Gomez-Paloma team also synthesized a model compound bearing the newly proposed thiazoline motif so that they could compare its spectroscopic properties to those of the natural product.[28] Similarly, Hirama and co-workers prepared a substantial portion of the kedarcidin chromophore (Table 4) to convince themselves of

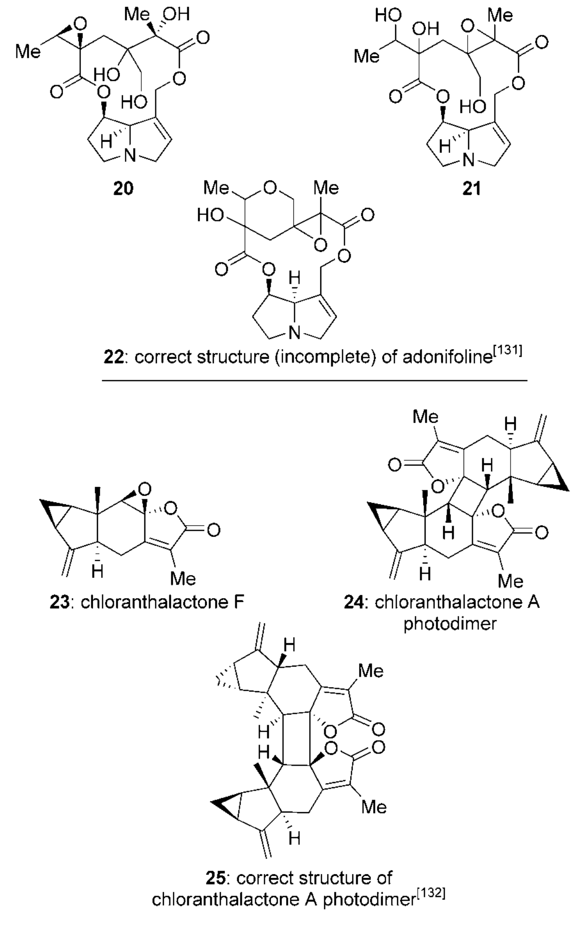


Figure 4. Selected examples of natural products isolated independently by two different research groups, each of whom proposed a structure. In each case it was ultimately shown that neither proposal was correct.

the altered connectivity and configuration that they intended to propose in its revised architecture.[74] It is inconceivable, of course, that all these corrections could have been made without chemical synthesis.

Thus, given our present state, the question becomes: Can anything be done to limit the number of mistakes made in structural assignments? In our opinion, apart from perhaps the isolation of more sample, there is only modest room for improvement without the introduction of more powerful spectroscopic techniques. However, one type of unfortunate error could potentially be avoided if chemists were to deposit all their spectral data into a universal database similar to that used for X-ray crystal structures: namely, the proposal of an incorrect structure for a natural product that has already been isolated and characterized. There are five examples in the tables in which this situation occurred: nomofungin, TAEMC151, FD-891, renieramycin H, and the unnamed coumarin. Figure 4 shows two additional examples, whereby different research teams isolated the same natural product independently and proposed different structures (and names) for that compound, only for it to be recognized later that they were both in error.[131,132] Perhaps all these mistakes (and much work) could have been avoided if it was easier to determine through a computer search engine whether a given natural product had already been isolated and/or independently characterized. Access to spectra (not just tables of data) could certainly assist in the assignment of newly isolated members of a given class of natural products and should facilitate the structural reassignment process in those instances in which an error has occurred.

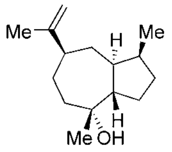
Finally, for a considerable number of natural products whose originally proposed structures have been called into question through total synthesis, a revised assignment has yet to be made. Figure 5 shows just a few of these unsolved mysteries, some of which have been lingering without an alternative structure for a number of years.

3. The Ramifications of Structural Misassignments

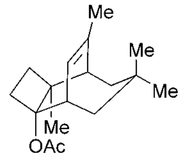
While the story behind any individual reassignment of the structure of a natural product can afford insight into the weaknesses of a particular method used for its initial assignment, it is rare that such a misassignment does not also incur a number of palpable and sometimes far-reaching consequences. Of these, the most serious might be the temptation to develop inaccurate biosynthetic proposals for entire classes of compounds.

For example, in 1925 Pummerer et al. showed that the one-electron oxidation of *p*-cresol with $K_3[Fe(CN)_6]$ afforded the dimeric product **28** (Scheme 3), whose formation was rationalized as the coupling of two radicals (**26a** and **26b**) followed by a spontaneous cyclization. This structural assignment was further supported by the subsequent reaction of the compound with acid and acetic anhydride to generate the biaryl system **29**.[147] Although the Pummerer ketone (**28**) is not a natural product, the assignment of its structure was important because its identity and mode of formation served as the basis for a number of biosynthetic pathways proposed over the next 30 years, such as that proposed by Robinson for morphine (**34**).[148]

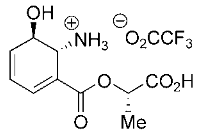
These ideas would all be turned upside down in 1955. Unable to formulate a mechanism by which compound **28** could be converted into **29** and uncertain of why the cyclization step required for the formation of **28** from **27** would occur at ambient temperature, Barton[148] proposed an alternative pathway for the reaction (Scheme 3). He suggested that the true structure of the Pummerer ketone was the product **31** derived from the union of the two carbon-centered radicals **26b** and **26c**. Compound **29** could then be formed from **31** simply by an acid-induced dienone–phenol



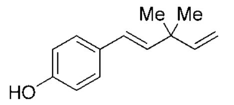
pogostol
Isolation: Waterman et al. (1997)[133]
Synthesis: Booker-Milburn et al. (2003)[134]
Likely problem: unknown, but not simply stereochemical



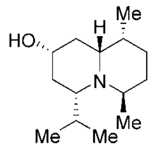
paesslerin A
Isolation: Palermo et al. (2001)[135]
Synthesis: Ihara et al. (2003)[136]
Likely problem: unknown



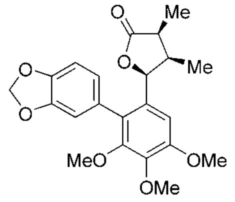
oryzoxymycin
Isolation: Hashimoto et al. (1968)[137]
Synthesis: Steel et al. (2003)[138]
Likely problem: sidechain placement and composition



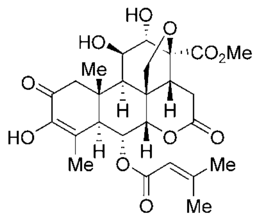
corylifolin
Isolation: Snapka et al. (1998)[139]
Synthesis: Van Vranken et al. (2002)[140]
Likely problem: unknown



plumerinine
Isolation: Malik et al. (1989)[141]
Synthesis: Comins et al. (2002)[142]
Likely problem: unknown

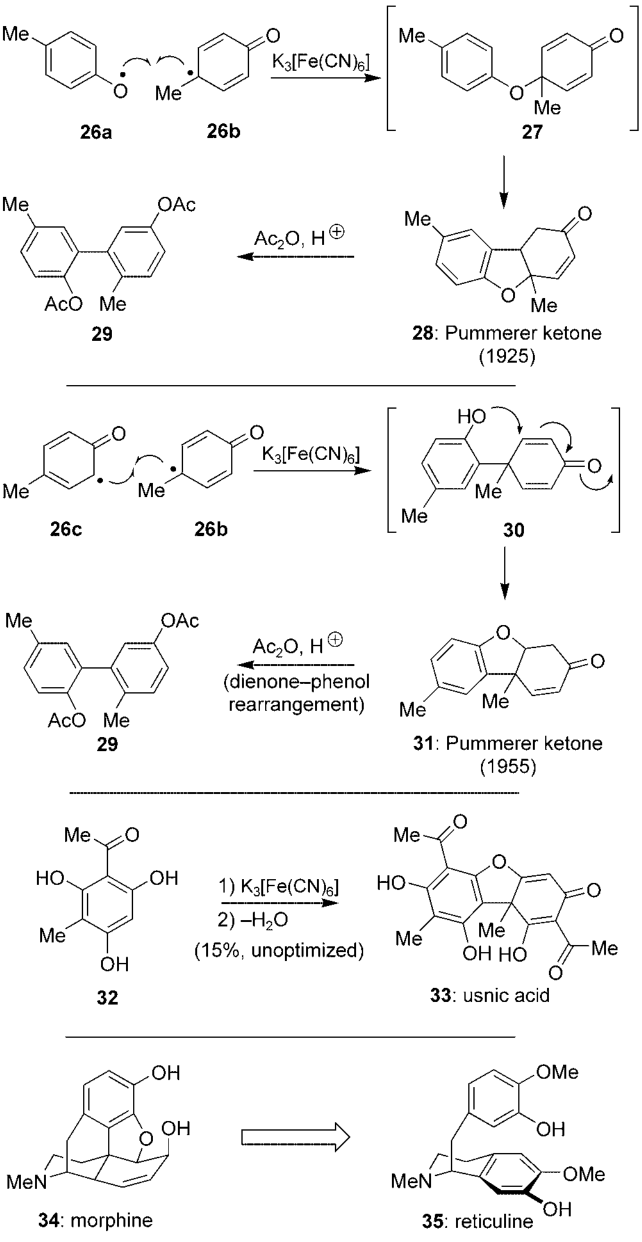


eupomatilone-6
Isolation: Carroll and Taylor (1991)[143]
Synthesis: Gurjar et al. (2004)[144]
Likely problem: stereochemical



bruceoside A aglycon
Isolation: Okano et al. (1992)[145]
Synthesis: VanderRoest and Grieco (1996)[146]
Likely problem: unknown

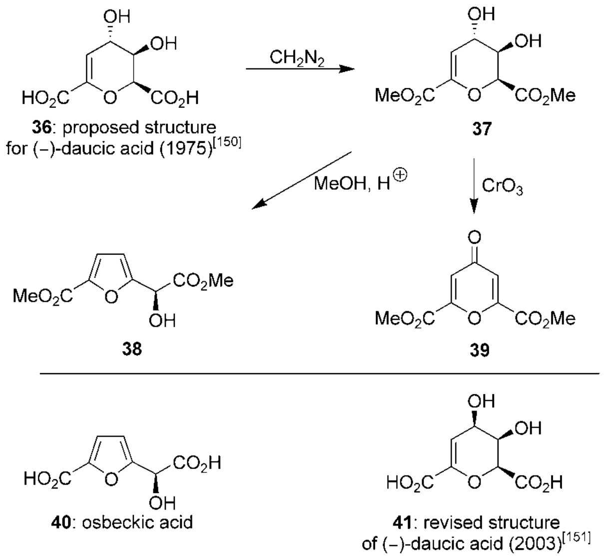
Figure 5. Unsolved mysteries: natural products whose proposed structures have been disproved by synthesis, but are awaiting a revised proposal.



Scheme 3. A structural misassignment for the Pummerer ketone served as the basis for numerous errors regarding the biosynthesis of natural products such as morphine (**34**). Barton's reexamination of this problem led to a structural revision with important ramifications, including a two-step total synthesis of usnic acid (**33**).

rearrangement. Within a few weeks, laboratory experiments proved him right, and he was able to extend the validity of his alternate mechanism and the new structure for the Pummerer ketone to a number of other areas, such as the synthesis of the lichen-derived natural product usnic acid (**33**) in just two steps from **32**. Barton also used his mechanism to formulate a biosynthetic pathway for morphine that was entirely different from those previously proposed, with benzylisoquinoline alkaloid **35** as a likely starting substrate. Although unknown at the time, compound **35** was isolated as a natural product a few years later (named reticuline)[149] and shown through feeding experiments to be intimately involved in the biosynthesis of morphine.

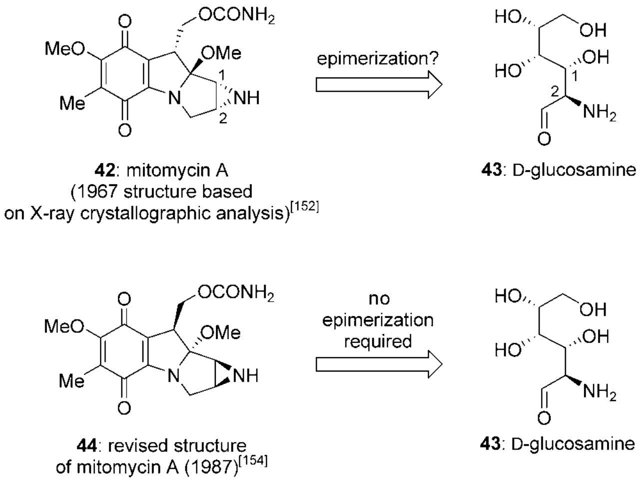
Such major revisions to biosynthetic pathways occur with some frequency today. Although there are several elegant examples we could cite, perhaps one of the most interesting comes from recent work by the research group of Lichtenthaler that disproved a structure established by Barton himself! The natural product in question is daucic acid, which was first assigned structure **36** (Scheme 4) based primarily on



Scheme 4. Although many aspects of Barton's original proposed structure for daucic acid (**36**) were accurate, the structure was ultimately proven to be incorrect in 2003 through chemical synthesis.

its conversion into compounds such as **37**, **38**, and **39**, the second of which fully matched a diester of another natural product, osbeckic acid (**40**).[150] In 2003, the Lichtenthaler team was not entirely convinced that the configurations of the C2 and C3 stereocenters proposed earlier by Barton were correct, so they synthesized all possible stereoisomers of daucic acid and proved that **41** was the actual structure.[151] The fact that daucic acid has a D-lyxo configuration, rather than the D-xylo configuration originally proposed, has a number of implications for the biosynthetic pathways through which plants generate such dicarboxylic acids, a line of study that is still being investigated today.

Sometimes, though, it need not be an entire pathway that is wrong. Confusion can also arise when a proposed structure appears incongruent with known biosynthetic data. A good example of such a phenomenon comes from the story of the mitomycins, an especially important group of natural products, one of which (mitomycin C) is employed clinically as an anticancer agent. In 1967, their structures were fully assigned (including their absolute configurations) based on a battery of spectroscopic methods and X-ray crystallography.[152] The structure of one of these agents, mitomycin A (**42**), is shown in Scheme 5. A few years later this assignment seemed questionable in light of some feeding experiments that revealed D-glucosamine (**43**) as the source of most of the "right-hand"



42: mitomycin A (1967 structure based on X-ray crystallographic analysis)[152]

43: D-glucosamine

44: revised structure of mitomycin A (1987)[154]

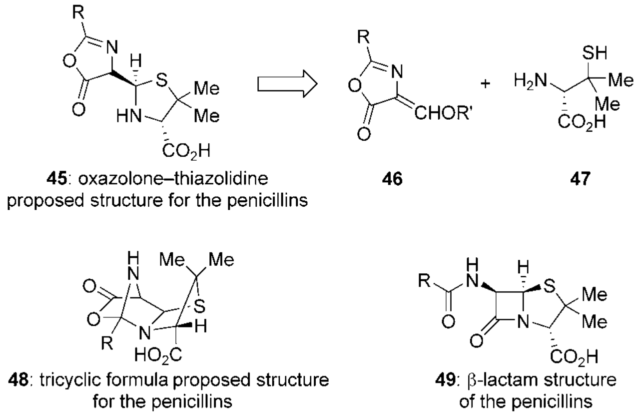
43: D-glucosamine

Scheme 5. Although established by X-ray crystallography, the absolute configuration of the structure assigned to mitomycin A (**42**) in 1967 did not make sense in light of biosynthetic feeding experiments. This discrepancy would not be reconciled for 20 years.

domain of the molecule. If this were true, a number of the stereocenters of this building block would have to be epimerized to produce a mitomycin architecture with the absolute configuration corresponding to **42**.[153] Why was there this discrepancy? As it turns out, the original X-ray crystal structure of mitomycin A provided the wrong absolute configuration (as determined by the R-factor-ratio test). In 1987, a crystal of better quality was obtained, and the structural and biosynthetic data were finally reconciled with the revised structure **44**.[154]

Incorrectly assigned natural products not only complicate the determination of biosynthetic schemes, but can have additional costs in terms of time and money if effort is devoted toward their synthesis. Perhaps one of the earliest and best illustrations of this point is the truly profound body of resources brought to bear by the American and British governments on the problem of synthesizing penicillin during World War II in the hopes of increasing its supply. Since these were the days before the β-lactam structure **49** (Scheme 6) of this agent was verified by Crawfoot-Hodgkin by X-ray crystallography,[155] the lack of certainty regarding its actual constitution led synthetic chemists of the period to pursue a number of potential penicillin structures in the laboratory. Famous examples include the oxazolone–thiazolidine architecture **45** favored principally by Robinson and a tricyclic alternative **48** that was advocated at one point by Woodward.[12] Each of these structures calls for a unique synthetic approach (such as the connection of **46** and **47** to generate **45**). However, since neither comes even close to matching the true architecture of the target molecule, it is not surprising that the millions of dollars and hundreds of years' worth of human effort invested in their synthesis during the war afforded few dividends on the penicillin-supply front.[156] Indeed, fermentation remained the only viable source of these powerful antibiotics until the late 1950s, when Sheehan and his colleagues at MIT finally completed a total synthesis after developing a number of novel synthetic methods for the purpose.[12]

Similar chances exist today for a synthetic chemist to devote effort to the synthesis of a proposed structure that bears little relationship to the actual architecture of the natural product, even though it has been assigned based on a number of advanced spectroscopic techniques unavailable during the 1940s and 1950s. Several of the natural products listed in the eight tables in Section 2 would certainly fit this bill. As a further example, consider the series of structures **50**–**52** proposed between 1982 and 1992 for the relatively complex and stereochemically rich natural product carzinophilin (Figure 6).[157–159] These proposals are certainly quite



45: oxazolone–thiazolidine proposed structure for the penicillins

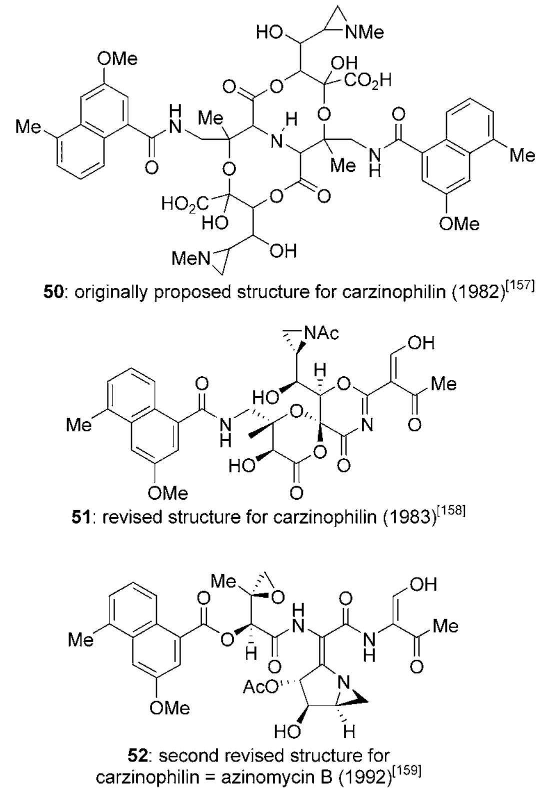
46

47

48: tricyclic formula proposed structure for the penicillins

49: β-lactam structure of the penicillins

Scheme 6. Debate surrounding the structure of the penicillins had a profound effect on synthetic approaches to their total synthesis both during and after World War II.



50: originally proposed structure for carzinophilin (1982)[157]

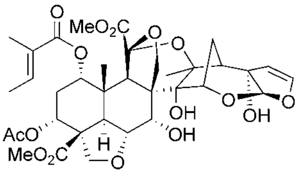
51: revised structure for carzinophilin (1983)[158]

52: second revised structure for carzinophilin = azinomycin B (1992)[159]

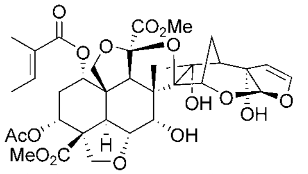
Figure 6. Progression of structural assignments for carzinophilin.

disparate, as no structural element apart from the terminal aromatic motif is shared by all.[160]

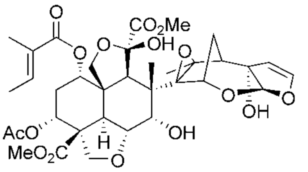
However, a structural reassignment that involves a much smaller alteration to the molecular architecture can throw a synthetic approach into a similar degree of disarray. A good illustration resides in the elucidation of the structure of the liminoid insect antifeedant azadirachtin. In 1975, the research group of Nakanishi correctly determined most of its architecture based exclusively on spectroscopic methods and proposed structure **53** (Figure 7).[161] By the mid-1980s, however, the isolation of some structurally related compounds began to suggest that some elements of the central core were inaccurate. These findings led ultimately to a series of reassignments, first by Ley and co-workers in 1985, who proposed structure **54**,[162] and then by teams led by Ley and Kraus a few months later, who finally proposed structure **55** based on X-ray crystallography in the former case and NMR spectroscopy in the latter.[163] Although apparently subtle, these changes are profound in terms of the strategies that one would probably employ for the synthesis of the different structures, especially considering that most published strategies at the time these revisions were made sought to build the azadirachtin structure by connecting fragments corresponding to its "left-" and "right-hand" domains.[164]



53: originally proposed structure for azadirachtin (1975)[161]



54: first revised structure for azadirachtin (1985)[162]



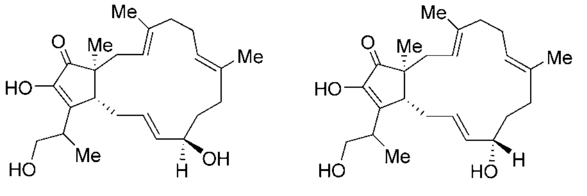
55: final revised structure for azadirachtin (1985/1986)[163]

Figure 7. Progression of structural assignments for the limonoid insect-antifeedant azadirachtin.

Arguably, the misassignment of the configuration of a single stereocenter can have similar ramifications. For example, if a stereocenter at a ring junction is incorrectly assigned, as happened with the natural product dictamnol (**57**, Scheme 7), then a completely new synthetic approach might be required.[165–167] Similarly, in an age driven by the use of asymmetric reactions to establish stereocenters, a stereochemical error in another part of the molecule could have an impact on the strategy/catalyst design. A recent example is a total synthesis reported by Chan and Jamison at MIT[168] that showed that the proposed structure **58** of siccanol[169] was incorrect and that the natural product is identical to (−)-terpestacin (**59**).[170]

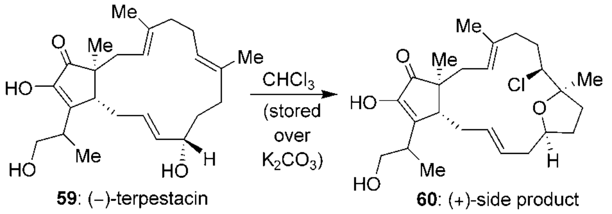
56: proposed structure for dictamnol (1993)[165]

57: revised structure for dictamnol (1996)[166]



58: proposed structure for siccanol (2002)[169]

59: revised structure for siccanol = (−)-terpestacin (2003)[168]



59: (−)-terpestacin

60: (+)-side product

Scheme 7. When misassigned stereocenters occur at critical positions, such as ring junctions, profound alterations in the synthetic strategies are typically required to access the revised structure.

As a final note, the process by which the structure of (−)-terpestacin (**59**) was assigned is also worth mentioning, since a number of problems were caused by what is normally a routine step in the characterization process: determination of the sign of its optical rotation. Terpestacin (**59**) was originally reported to have a positive optical-rotation value in chloroform. In 2002, the research group of Myers at Harvard University synthesized the same enantiomer, only to obtain a negative value when they measured its optical rotation in the same solvent.[171] What was the problem? The chemists who had isolated **59** stored their chloroform over K_2CO_3, a practice which generated enough elemental chlorine to convert terpestacin (**59**) into **60**, a product whose optical-rotation value is positive!

4. Misassignment Case Studies

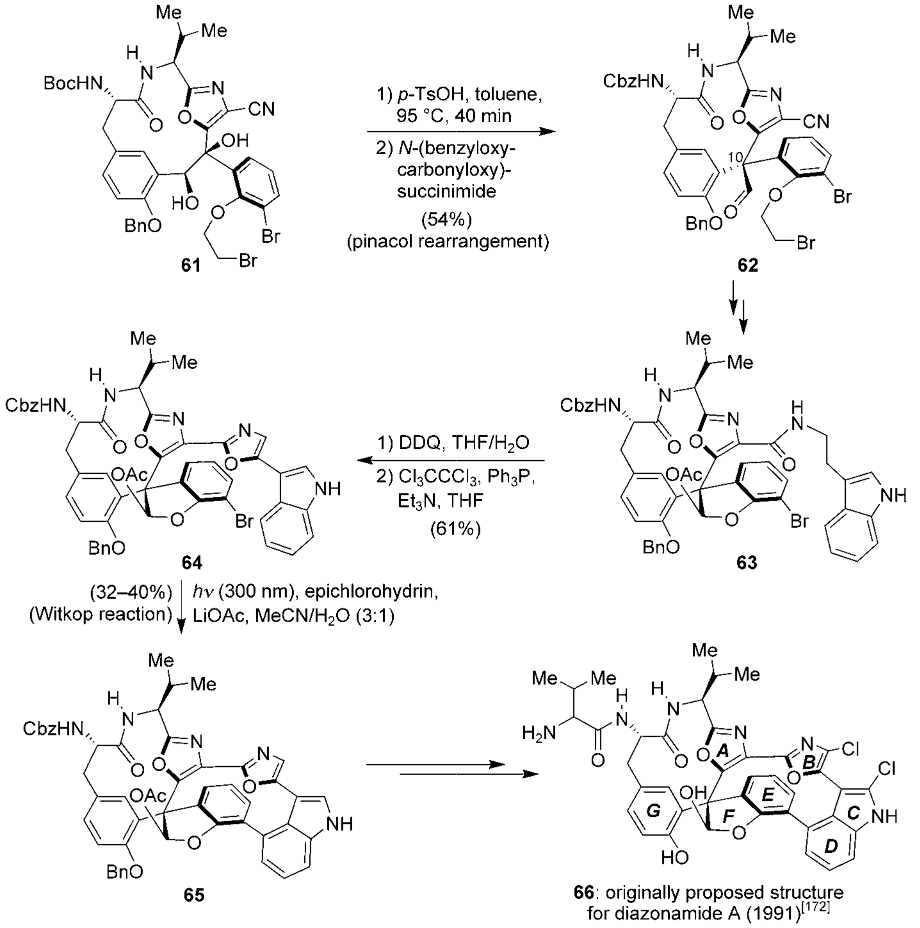
Structural misassignments, as with all errors in science, also have an emotional component. Certainly a researcher would be disturbed to discover that an assignment he or she had made was incorrect, just as he or she would probably be pleased to find out that his or her proposal had been verified. Since our research group is not directly engaged in the process of isolation and/or characterization, we can not comment on how a scientist feels in such a position from a first-hand perspective. We know, however, what it is like as a synthetic chemist to be in the midst of a total synthesis or at its “end”, only to find out that the molecule we were chasing was never there! In this section, we present two personal accounts that hopefully convey a sense of these emotions, and we hope to show how misassignments can lead to some benefits as well. We want to reiterate, however, that these case studies are not meant to point any blame at structural chemists or indicate frustration with their efforts. Quite on the contrary, these pioneers work wonders with often incredibly complex puzzles, frequently under severe constraints of material and time (present cases included).

4.1. Case Study 1: Diazonamide A

The tale of the marine natural product diazonamide A began in 1991 when the research groups of Fenical and Clardy first communicated its structure (i.e. **66**, Scheme 8) in the *Journal of the American Chemical Society*.[172] From that moment forward, this molecule enraptured the synthetic community in a way that few others ever match, primarily by virtue of its highly intricate and structurally novel architecture and its potential as a new weapon in the fight against cancer. Over the course of the next decade, nearly a dozen research groups initiated campaigns to synthesize its diabolically complex structural elements and explore its chemical biology more fully.[173]

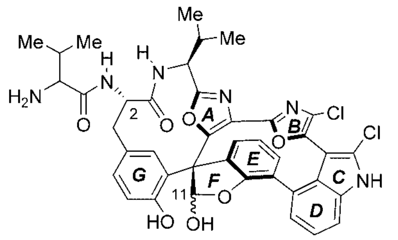
Our own journey of discovery began in June of 1999, when we embarked on the total synthesis of diazonamide A, armed with what we thought was a carefully designed synthetic strategy. Unfortunately, the next few months would teach us what a number of teams before us had already learned: the synthesis of the individual domains, such the indole ring or an oxazole subunit, was relatively simple, but joining these fragments together to form even one of the two 12-membered rings was astonishingly difficult.[174]

When the synthetic community at large is fully mobilized, however, few challenges in total synthesis remain unanswered for long. At the end of 2001, a team led by Harran at the Southwestern Medical Center in Dallas was finally able to assemble all the disparate subunits of diazonamide A,[175] by using a creative strategy featuring two powerful reactions to forge the formidable macrocyclic domains of the molecule (Scheme 8). The first was an acid-induced pinacol rearrangement of chiral diol **61**. In this step, contraction of the 13-membered ring in **61** led to the formation of the 12-membered AG macrocycle and the daunting C10 quaternary center at the heart of the molecule. The second key reaction was an inventive use of the Witkop photocyclization. This operation converted **64** into **65** with complete atropselectivity as a result of π stacking between the B and E rings in the starting material. With these domains in place, a few finishing touches then converted **65** into diazonamide A; or at least into what was supposed to be diazonamide A (**66**). Instead, chemical synthesis had uncovered yet another example of a structural misassignment!

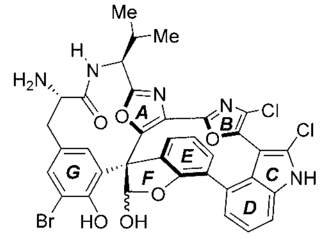


Scheme 8. The creative synthetic route of Harran and co-workers led to the proposed structure of diazonamide A (**66**), but the spectral data did not match those of the natural product.

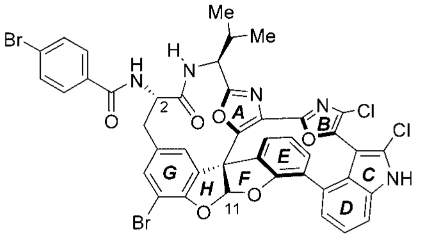
What had gone wrong? The story is certainly an interesting one. During the early stages of their structural-elucidation efforts, the Fenical and Clardy groups worked exceedingly hard to obtain a crystal structure for diazonamide A to support their assignment of a structure that was unlike that of any other natural product ever isolated. Although that task would ultimately prove impossible with diazonamide A, the conversion of diazonamide B (**67**, Figure 8), a structural relative with similar NMR, UV, and IR spectroscopic data, into a *p*-bromobenzamide derivative provided a beautifully crystalline solid. The structure of this derivative (**68**) verified much of the anticipated general diazonamide skeleton with only one exception: the presence of an acetal moiety bridging the F and G rings. This outcome was surprising, as NMR spectroscopic data seemed to indicate the existence of an open hemiacetal instead (as drawn for structure **67**) based on a small coupling constant between what was assigned as the hydrogen atom at C11 and a hydrogen atom that underwent isotope



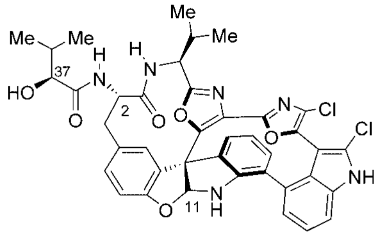
66: originally proposed structure for diazonamide A



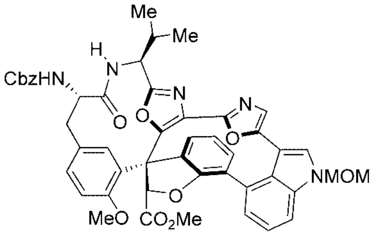
67: putative structure of diazonamide B



68: structure assigned by X-ray crystallographic analysis a diazonamide B derivative



69: revised structure of diazonamide A



70

Figure 8. Basis for the structural misassignment and reassignment of diazonamide A.

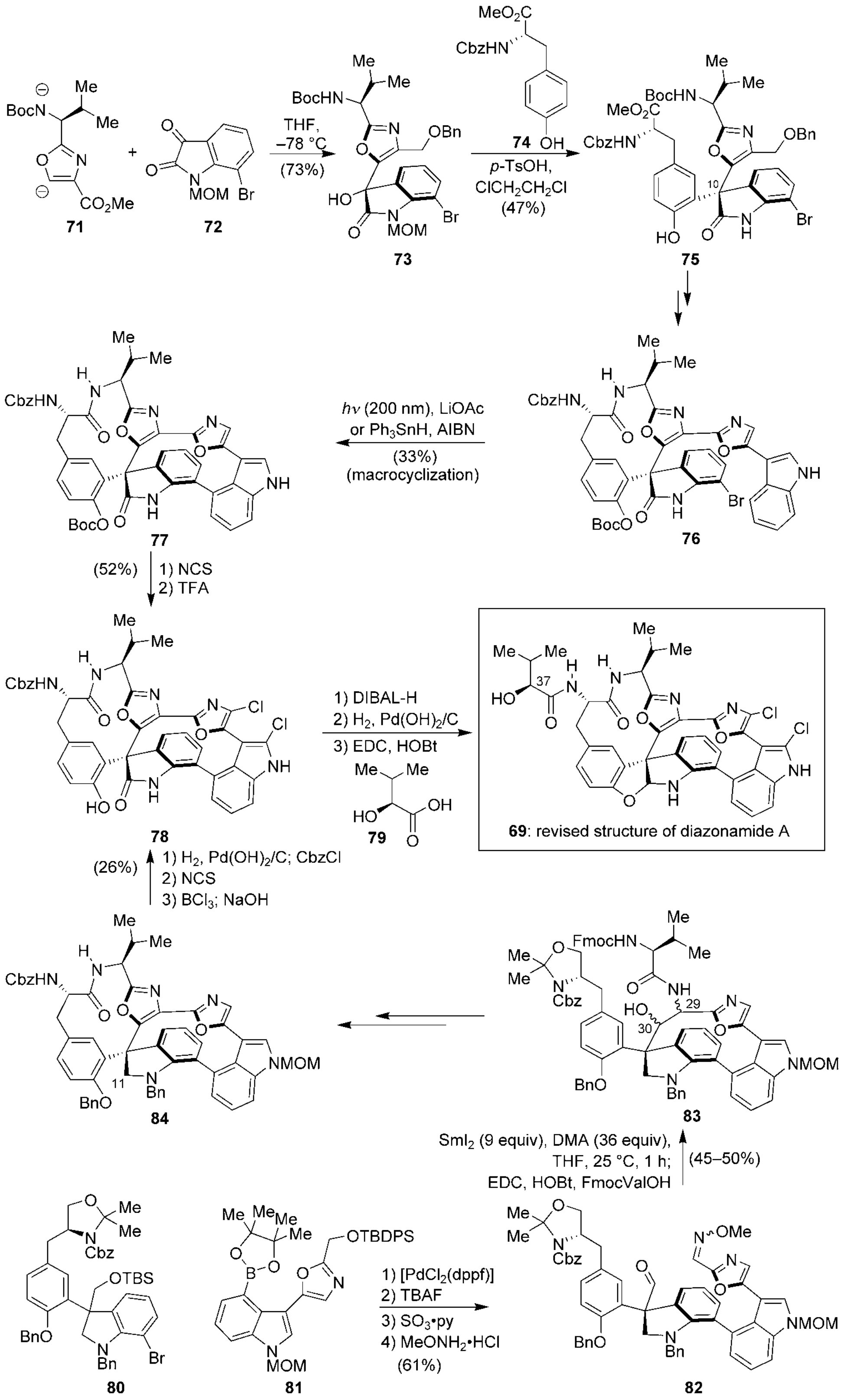
exchange with D_2O. Needing to reconcile this incongruity, the Fenical and Clardy groups proposed that the closed acetal observed in crystal structure **68** was an artifact resulting from the conditions employed to attach the *p*-bromobenzamide group to **67**. Thus, if a hemiacetal was accepted for the F ring of diazonamide A, then the one element of diazonamide A which the X-ray crystal-structure analysis of **68** could not reveal, namely, the amino acid tethered at the C2 position, must be a valine residue. This hypothesis would agree with a signal observed by mass spectrometry corresponding to $[M+H-H_2O]^+$. As a result of these observations, diazonamide A was assigned structure **66**.[172]

Armed with the knowledge that both the X-ray crystal structure of **68** and the formula derived from the mass spectrometric data of diazonamide A corresponded to the loss of a molecule of water, the research group of Harran speculated that perhaps the correct structure for the natural product differed from **66** simply through the presence of a closed acetal. This alternate compound would contain all the critical elements of the crystal structure **68** and would thus have a signal in the mass spectrum corresponding directly to $[M+H]^+$. Admirably, this compound was immediately synthesized by the Harran team, but, once again, the physical data of the synthetic material failed to correlate with data obtained from the natural sample of diazonamide A.[175] Where was the problem?

The answer resided in the assignment of the crystal structure that gave **68**. By computational analysis, the Harran group subsequently determined that the oxygen atom in the F ring of **68** (and thus in **66**) should really be an NH group within an aminal system, as in the revised structure **69**. Consequently, a second modification somewhere else in the molecule was required to account for the mass spectrometric profile of diazonamide A. The obvious site for a change was that occupied by the terminal group attached to the amine functionality at C2. If this fragment was 2-hydroxyisovaleric acid, as shown in **69**, then all of the previously incongruent data would appear to be reconciled. Thus, the misassignment was the result of a series of logical deductions stemming from a single piece of bad evidence; now it was up to synthesis to prove whether or not the new proposal was correct.

With little question, this structural reassignment sent shockwaves to all the research groups that had been attempting to synthesize this molecule when it was first published in the last December issue of *Angewandte Chemie* in 2001.[175] Although we certainly admired the beautiful synthesis of Harran and his team as well as the logic behind the proposed structural revision, our initial reaction could only be described as intense disappointment and frustration. Not only did the molecule that we had been pursuing for over two years not exist, but we were uncertain whether we could even apply any part of our developed sequence in a new drive to access **69**, since this new structure was constitutionally different from **66** at a key position. These feelings were magnified by a certain sense of irony in that we had just overcome a major synthetic hurdle which had held us back for a couple of months, finally reaching the advanced and critical intermediate **70** (Figure 8) that we thought was only a few steps away from the final target.

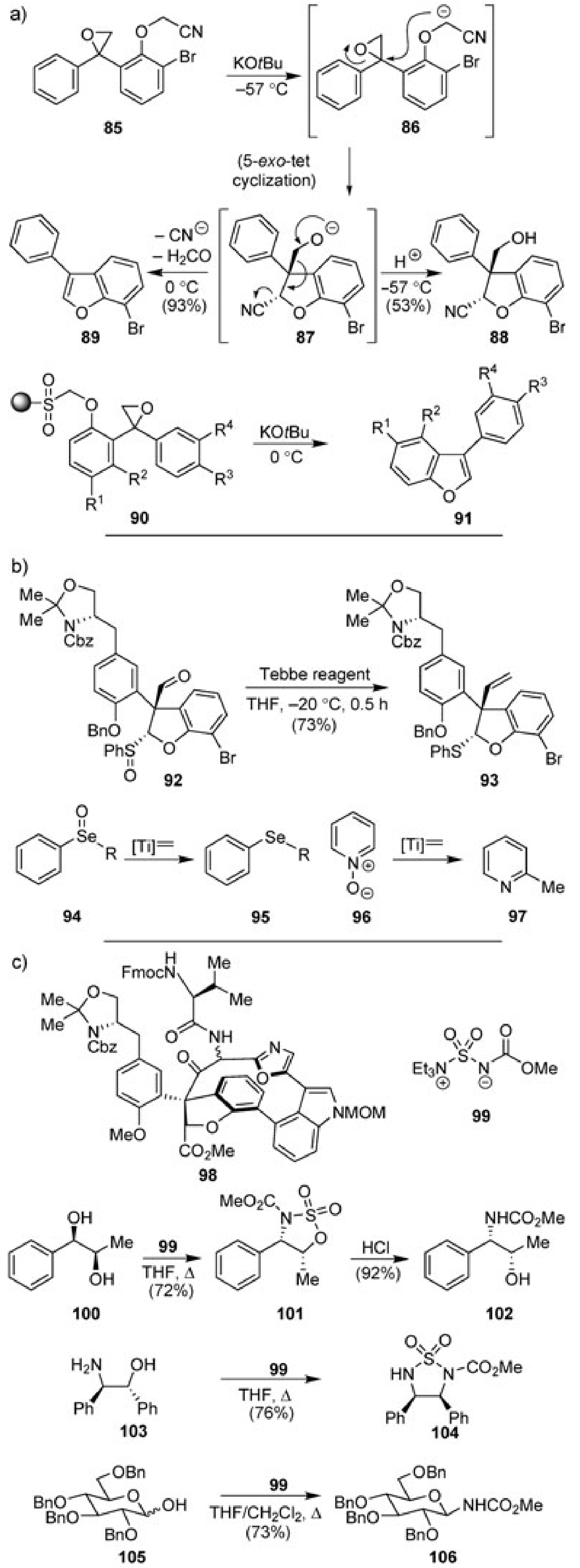
For a few days, we were unsure of just how to proceed. Questions running through our minds included whether or not we should go ahead and complete the originally proposed structure even though it did not represent the natural substance, and just how we should attempt to tackle the "new" diazonamide A. The team took advantage of the convenient timing of the Christmas holiday and came back together in January of 2002 with a clear battle plan. We would



Scheme 9. The two synthetic routes developed by the Nicolaou group to verify **69** as the correct structure of diazonamide A and ultimately establish the configuration at C37.

tackle the new molecule from two different angles: one based on the order of macrocycle construction that the Harran team had employed to great success, and the other based on key elements of the strategy we had already developed to access the original structure **66**. It would take a year for both of these plans to reach fruition following the development of some novel synthetic strategies and tactics. Finally the correct structure of diazonamide A was proved to be **69** and the absolute configuration of its C37 stereocenter was established.[176,177] The key elements of these two total syntheses are summarized in Scheme 9. Of particular note are the construction of the quaternary carbon center with its adjoining aromatic systems in the first synthesis of diazonamide A, and the application of a novel SmI_2-promoted hetero-pinacol cyclization sequence to create the heteroaromatic core in the second.[178,179]

Reflecting on our project as a whole, we realize now that the frustration we felt at the end of 2001, although understandable, was misplaced. The misassignment of diazonamide A turned out to be more of a reward than a punishment, even though it extended the duration of the project by several months. Indeed, had the correct structure **69** been known from the outset, we would probably have learned much less. For example, our work towards the "incorrect" F ring led us to design a novel 5-*exo*-tet cyclization reaction to form the quaternary stereocenter of the target molecule (namely, to synthesize **88**). When tweaked properly, this reaction can also deliver 3-aryl benzofurans, such as **89**, in a controlled manner (Scheme 10a).[180] Furthermore, during work on manipulating this ring system we found that titanocene methylidene compounds can deoxygenate sulfoxides and selenoxides, and can convert pyridine *N*-oxides into 2-methylpyridines (Scheme 10b).[181] None of these discoveries would have been made if we had been working with indoles or oxindoles instead. Similarly, had we not encountered difficulties in our efforts to form the A ring of **66** from intermediate **98** with the Burgess reagent (**99**; Scheme 10c), we might never have been inspired to explore the chemistry of this reagent further. These explorations recently led to the discovery that the Burgess reagent is remarkably effective at mediating a number of nondehydrative transformations, such as the formation of

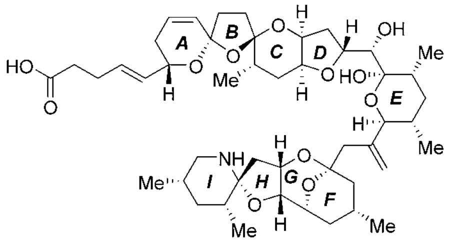


Scheme 10. a)–c) During the synthesis of the originally proposed structure of diazonamide A, a number of new synthetic methodologies were discovered.

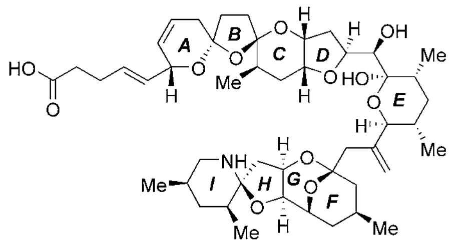
sulfamidates from 1,2-diols, α- and β-glycosylamines from carbohydrates, and cyclic sulfamides from 1,2-aminoalcohols.[182] We also may never have been inspired to devise two distinct strategies to reach diazonamide A (**69**) in such a short period of time. That alone was a unique and highly rewarding experience.

4.2. Case Study 2: Azaspiracid-1

Our second adventure in the area of structural revision through chemical synthesis concerns the natural product azaspiracid-1, the flagship member of a family of marine toxins identified as the causative agents of several incidents of rather severe shellfish poisoning (termed the azaspiracid syndrome). First isolated in 1996 as a 2-mg sample from 20 kg of mussel meat by the research group of Yasumoto, the structure of azaspiracid-1 was elucidated within a relatively short period of time through the careful application of sophisticated spectroscopic techniques. Azaspiracid-1 was assigned the structure **119** in 1998 (Figure 9).[183] These pioneering studies, however, failed to unveil the absolute configuration of the molecule and the relative stereochemistry between its ABCDE and FGHI domains.



119: originally proposed structure for azaspiracid-1



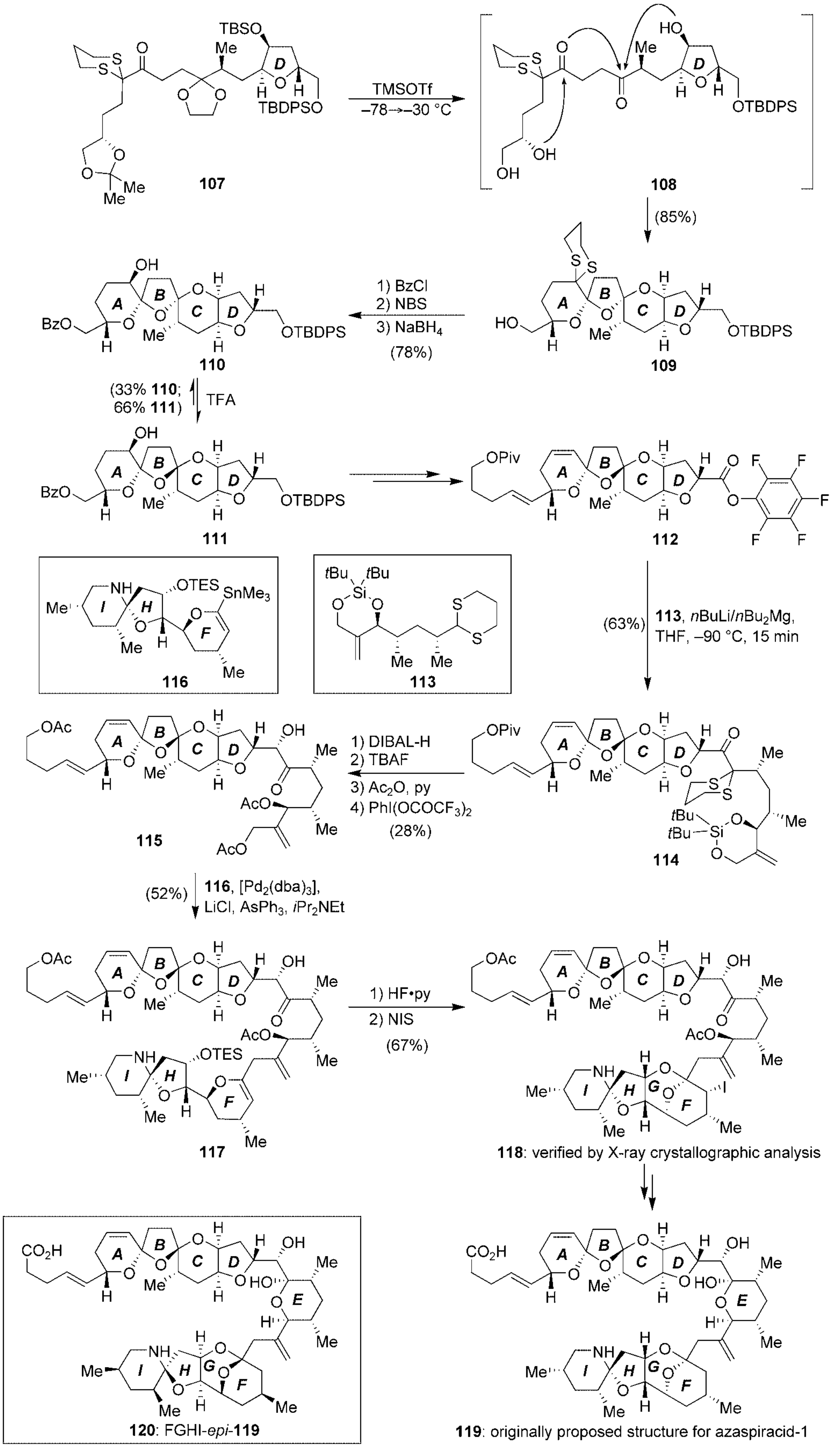
121: revised structure of azaspiracid-1

Figure 9. The revised structure of azaspiracid-1 (**121**): far more than just a simple change.

Just like diazonamide A, this molecule quickly caught the attention of the synthetic community because of its structural uniqueness. Of particular interest are an unusual azaoxaspiro ring fused to a 2,9-dioxabicyclo[3.3.1]nonane system, and a trioxadispiroketal framework attached to a tetrahydrofuran ring. Indeed, the first reports on synthetic studies towards structural subunits of this formidable synthetic target already began to appear within months of its structure being disclosed.[184] A team in our research group also began exploring means by which to construct this molecule, with a full assault beginning in 2001 after some other projects had been completed.[185]

By the end of 2002 we were able to construct the 9 rings and 20 stereogenic centers of structure **119** through the route summarized in Scheme 11.[186] Key features of the chemistry developed included a TMSOTf-induced cascade spirocyclization to form the tetracyclic ABCD system **109** from the linear precursor **107**, a subsequent directed epimerization step to generate the correct ABCD stereostructure (**110**→**111**), and fragment coupling steps that made use of a dithiane subunit (**112**+**113**→**114**) and a Stille reaction (**115**+**116**→**117**). Nevertheless, as you might have already guessed, when we finally reached the coveted structure **119**, the properties of the synthesized material did not match those of the natural product. The same news awaited us when we arrived at the FGHI epimer of **119** (i.e. **120**) through an identical route by using the enantiomer of **116**.

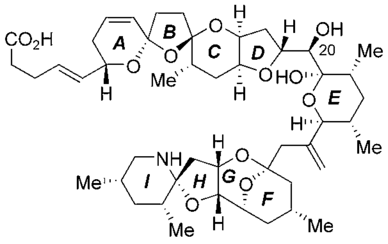
At first, we thought this unexpected outcome reflected the fact that something had gone wrong in our reaction sequence: that a stereocenter had been inverted by accident or that an unintended rearrangement had taken place. These fears were quickly allayed when we obtained an X-ray crystal structure for compound **118**, an intermediate six steps from the end of the sequence. This result verified that all the preceding steps had gone according to plan. Thus, barring an unknown problem during the final operations, our synthesis had revealed that the proposed



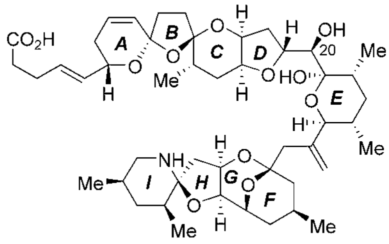
Scheme 11. Selected highlights of the synthesis by Nicolaou and co-workers of the originally proposed structure **119** of azaspiracid-1.

structure for azaspiracid-1 was incorrect. Where the problem(s) lay, however, was far from obvious. It would take us another year of intensive investigations involving synthetic and degradative work (the latter in collaboration with the research group of Satake of Tohoku University), a series of frustrating close calls, and the unearthing of some subtle clues before we were finally able to determine that the solution was structure **121** (Figure 9). This assignment was ultimately verified by total synthesis.[187]

Our first foray into the identificaiton of the correct structure of azaspiracid-1, as guided by discussions with Professor Satake (a member of the team that isolated the compound), sought to evaluate the orientation of the hydroxy group at C20, since a cloud of doubt surrounded its original assignment. This task proved quite easy to accomplish by using advanced intermediates from our developed sequence, and within a few days we were able to generate both **122** and **123** (Figure 10), the C20 epimers of our originally synthesized compounds **119** and **120**. Despite their ready accessibility, however, compounds **122** and **123** brought us no closer to the ultimate goal, for their spectroscopic data bore as many differences to those of the natural sample as the data of the substances we had made before. Clearly, we needed to adopt a much more systematic and rational strategy to pinpoint the location and nature of the errors; guesswork would only waste time and material resources.



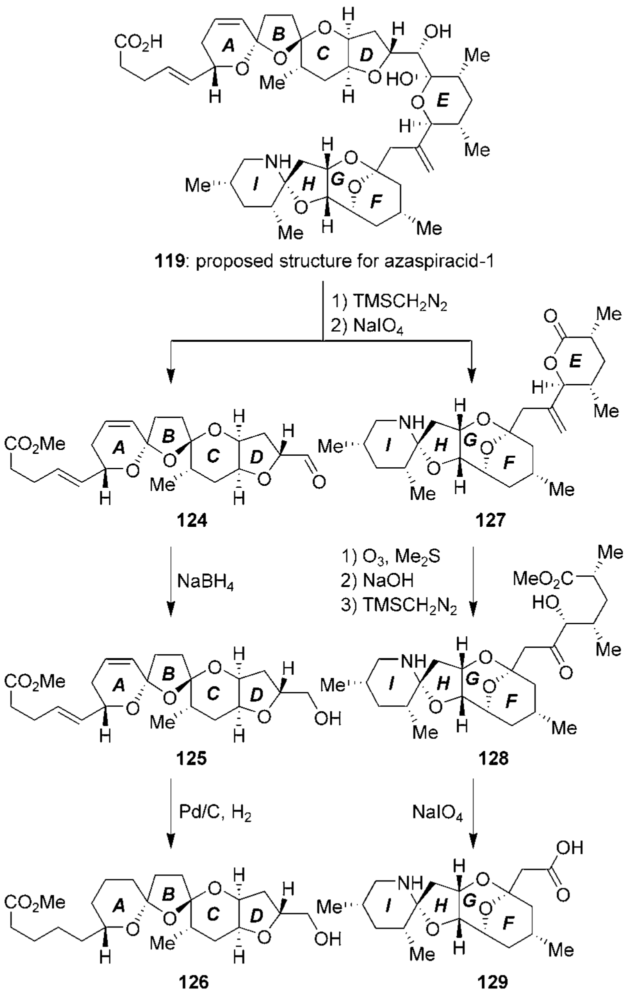
122: C20 epimer of **119**



123: C20 epimer of **120**

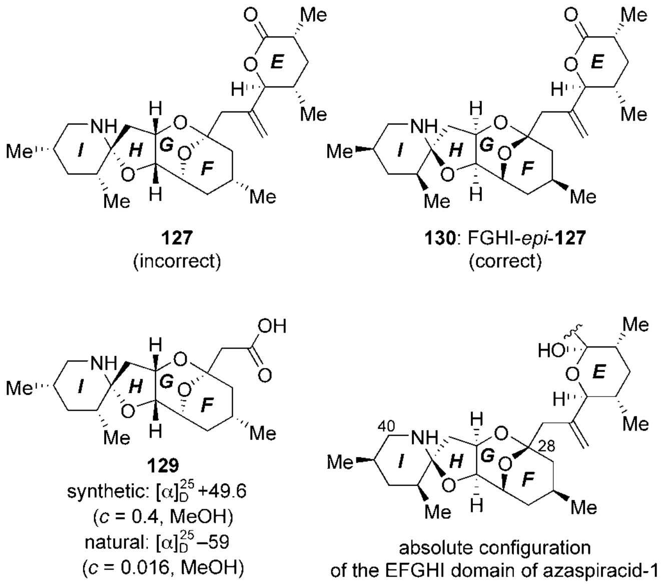
Figure 10. The search for the correct structure of azaspiracid-1: The problem does not lie with the configuration at C20.

Fortunately, a classical approach to structure elucidation made a crucial contribution to this analysis. The Satake group provided the information needed by degrading and derivatizing natural azaspiracid-1 (the originally miniscule supplies of which had been somewhat enriched by a series of additional isolations) into an array of fragments corresponding to both the "upper" (**124**, **125**, and **126**) and "lower" domains (**127**, **128**, and **129**) of the molecule (Scheme 12). Consequently, our next goal became the preparation of synthetic material that corresponded to these products for comparison purposes. We expected that we could then immediately locate the site (or sites) of the structural errors. We also hoped that these endeavors would help define the relative configuration of the ABCDE and FGHI domains as well as reveal the absolute configuration of each fragment and thus of the entire structure.



Scheme 12. Chemical degradation and derivatization of azaspiracid-1: The structures of all compounds are based on the originally assigned structure **119** of azaspiracid-1. (Only one of the four possible absolute configurations based on the original drawings of Satake et al. is shown.)

We began our studies by focusing on the "lower" half of the structure. Within a few weeks we had synthesized two compounds which corresponded to the degradation product represented in Scheme 12 as **127**: the compound with the configuration shown in Scheme 12 and its FGHI epimer **130** (Figure 11). Of these two diastereomers, only **130** was a perfect match with the degradation product. Thus, we now knew that there were no structural misassignments in this region of the molecule, and we knew what the relative configuration was within the EFGHI domain. To ascertain the absolute configuration, we then generated **129** through total synthesis. Since the optical rotation of **129** proved to be equal in value but opposite in sign to that of the degradation



127
(incorrect)

130: FGHI-*epi*-**127**
(correct)

129
synthetic: $[\alpha]_D^{25}$ +49.6
(c = 0.4, MeOH)
natural: $[\alpha]_D^{25}$ −59
(c = 0.016, MeOH)

absolute configuration
of the EFGHI domain of azaspiracid-1

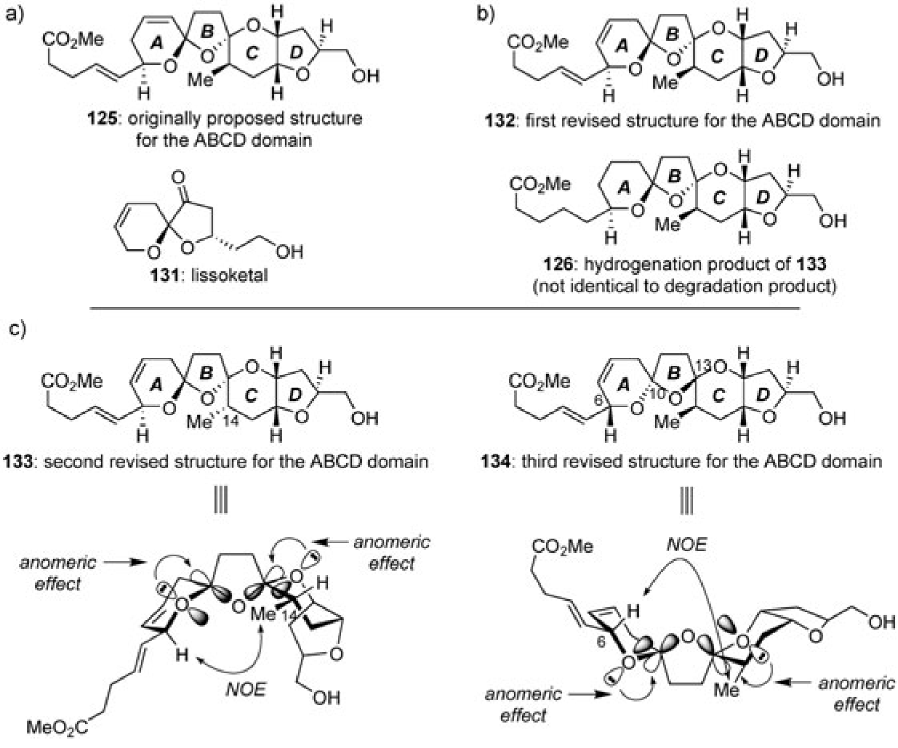
Figure 11. Determination of the relative configuration within the EFGHI domain and the absolute configuration of the FGHI domain of azaspiracid-1.

product, we could then assign with confidence structure **130** to the EFGHI fragment (Figure 11).

With the "bottom" half of the molecule secured, we then focused our attention on the "upper" framework. Now the true adventure would begin. Aware that the structural error(s) must lie within this domain, we began our detective work with an analysis of synthetic materials corresponding to the degradation fragment **125** (Scheme 12). That precise structure had already been synthesized, and, as expected, it did not match the sample derived from the natural product. Interestingly, however, most of the spectroscopic discrepancies seemed to reside within a single domain of this fragment: the A ring. Yet, despite careful investigations of this structural region, the required correction remained a mystery, since the use of 2D NMR spectroscopic techniques failed to provide any conclusive hints.

As is often the case, nature had already solved the problem for us: Hopmann and Faulkner had isolated and characterized a natural product, lissoketal (**131**, Figure 12), whose NMR spectroscopic data were beautifully reminiscent of those of the A-ring region of compound **125** derived from natural azaspiracid-1.[188] Therefore, we expected that the structural problem with azaspiracid-1 might reside simply in the positioning of the A-ring double bond, with **132** being the correct target structure! Filled with excitement that synthetic azaspiracid-1 would soon be in our grasp, we prepared **132** as quickly as we could. Its NMR spectrum would, unfortunately, knock the wind out of our sails, as although the A-ring signals now appeared to be mostly correct, the chemical shifts of a number of other resonances were still incorrect. The fact that we were still dealing with the wrong structure was further confirmed when the double bonds in **132** were hydrogenated to give the fully saturated compound **126**, whose ^{1}H NMR spectrum also differed from that of the hydrogenated derivative of the degradation product.

We now had to go back to the drawing board. Although we had conclusively established the positioning of both double bonds within the azaspiracid-1 framework, we were now left with 128 possible structures for the ABCD domain, since we could not be confident in the assignment of any of the seven stereogenic centers. Not even an army of chemists could hope to prepare such an array of compounds in a timely manner, even with unlimited funding (which we certainly did not have)! The problem seemed insurmountable, but again we were helped by a clue from nature. That piece of information related to thermodynamic stability. During the handling of both azaspiracid-1 itself and the ABCD fragments derived through degradation we noted that the ABC double-spiroketal unit was stable under acidic conditions. By contrast, our synthetic compounds that should correspond to this portion of the molecule had only fleeting lifetimes when exposed to a pH value less than 5, because of epimerization at the C13



125: originally proposed structure for the ABCD domain

132: first revised structure for the ABCD domain

131: lissoketal

126: hydrogenation product of **133** (not identical to degradation product)

133: second revised structure for the ABCD domain

134: third revised structure for the ABCD domain

Figure 12. Final steps a)–c) in the assignment of the structure **134** to the ABCD domain of azaspiracid-1. The differences in all of the proposed structures versus the original assignment have been highlighted.

center. This tidbit of information suggested that the problem might lie in this region. Indeed, molecular models pointed to structure **133** as a possible candidate for the degradation product, since it would be favored by a double anomeric effect (an advantage that our original targets did not have) and would be likely to exhibit the obligatory NOE reported for the natural product (see Figure 12c). However, once again chemical synthesis would prove this intuition to be false, as synthetic intermediates encountered en route to **133** were not stable.

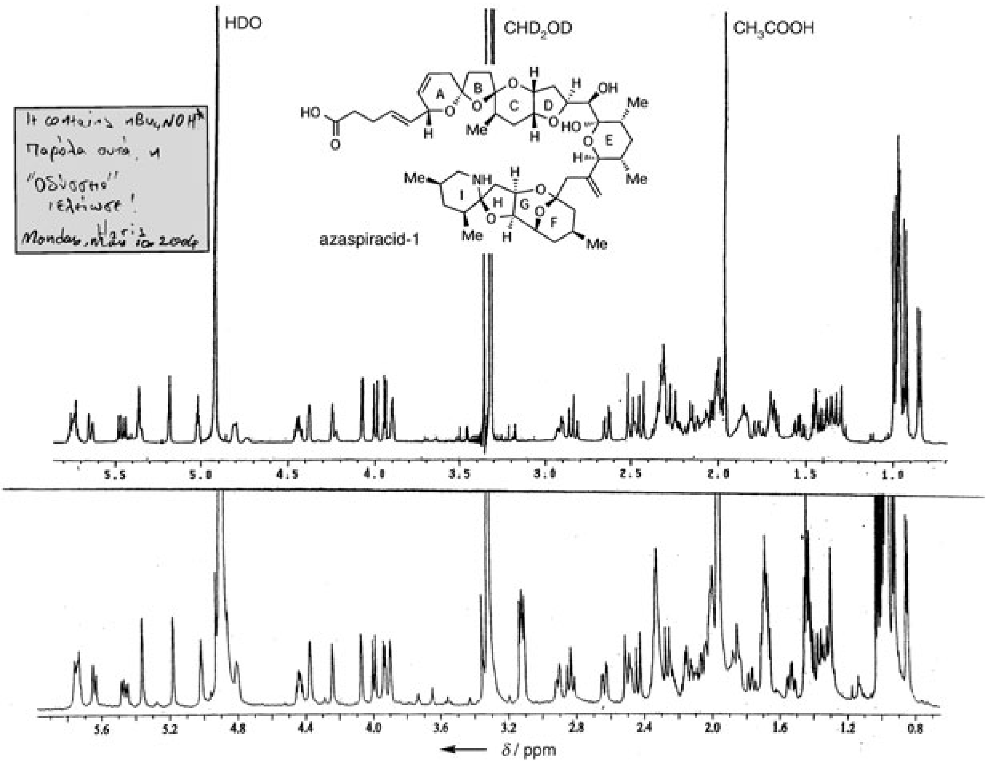


Figure 13. Correlation of NMR spectra of natural (top) and synthetic (bottom)azaspiracid-1 (not exactly to the same scale).

There was still one more chance for success. What if we inverted the C6 stereocenter in the A ring? Molecular modeling studies suggested that this variant, **134** (Figure 12c), would exhibit both a double anomeric effect and the required NOE, whereas alterions to any of the other potentially relevant stereocenters in this domain (i.e. C10, C13, and C14) appeared less promising. Our next move was, therefore, to synthesize compound **134** as quickly as possible, and this time the ^{1}H NMR spectrum fully matched that of the degradation product!

This outcome was certainly welcome after nearly a year of intense study, but one question remained: What was the absolute configuration of this domain? Only synthesis could answer this question, as the limited amount of material derived from degradation reactions corresponding to the ABCD region of the natural product did not permit the accurate measurement of its optical rotation. Which enantiomer to use was a gamble: a bet that we would ultimately lose, for the wrong stereoisomer was completed first! After a final retreat (and in the knowledge that we would soon prevail) we advanced on the alternate "upper-domain" fragment, and on Monday, May 10, 2004 at 9.00 a.m. one of us (K.C.N.) returned from a meeting in Moscow to discover a set of matching ^{1}H NMR spectra (Figure 13), which indicated that azaspiracid-1 had finally been synthesized and that its correct structure was **121** (Figure 9)! This data was accompanied by a note written half in Greek and half in English from Dr. Theocharis Koftis, one of the azaspiracid-1 team (Figure 14): "It contains some nBu$_4$NOH, but the odyssey is over!"

Figure 14. The "finalists" of the triumphant team proudly display the azaspiracid-1 structure and their flags. From left to right: Taotao Ling, Wenjun Tang, Goran Petrovic, Theocharis Koftis, Stepan Vyskocil, Michael Frederick.

In this long campaign, one which filled us at times with great excitement and at times with intense disappointment, the goal was finally reached through the power of chemical synthesis in a manner not too dissimilar from that used decades ago for structural elucidation.[187] Although spectroscopy revealed most features of the structure of azaspiracid-1 with an amazingly small amount of material, ultimately it could not do it all. Only when spectroscopy was combined with synthesis were all the details finally resolved.

5. Summary and Outlook

Although the past half century has witnessed a remarkable improvement in our ability to isolate and characterize complex natural products, mistakes are still a relatively common occurrence. However, as the stories in Section 4 relating to our own experiences hopefully indicate, this state of affairs is far from catastrophic. Indeed, structural misassignments clearly provide opportunities for synthetic chemists to make discoveries through total synthesis, and certainly show that there is still adventure to be had in the process of structure assignment. It will be interesting to see just what the next half century will bring in terms of the isolation and synthesis of natural products. Only time will tell, but we can be certain that as long as chemists continue to isolate new and diverse substances from nature, there will be plenty of challenges for our intellectual and physical skills. Moreover, much new science awaits discovery during the struggle to synthesize such new molecular puzzles.[189,190]

List of Abbreviations

AIBN	2,2′-azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
CD	circular dichroism
dba	*trans*,*trans*-dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DMA	*N*,*N*-dimethylacetamide
4-DMAP	4-dimethylaminopyridine
dppf	1,1′-(diphenylphosphanyl)ferrocene
EA	elemental analysis
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Fmoc	9-fluorenylmethoxycarbonyl
HOBt	1-hydroxybenzotriazole
INEPT	insensitive nuclei enhanced by polarization transfer
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NOE	nuclear Overhauser enhancement
py	pyridine
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THP	tetrahydropyranyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

It is with great pride and pleasure that we thank our collaborators, whose names appear in the references cited and whose contributions made the work described so rewarding and enjoyable. We gratefully acknowledge the National Institutes of Health (USA), the Skaggs Institute for Chemical Biology, American Bioscience, Amgen, Novartis, Bristol-Myers Squibb (fellowship to S.A.S.), CaPCURE, the George E. Hewitt Foundation, Pfizer (fellowship to S.A.S.), and the National Science Foundation (fellowship to S.A.S.) for supporting our research programs.

Received: June 3, 2004

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[1] To explore these assignments further, see the Nobel Prize website: http://www.nobel.se/chemistry.

[2] J. D. Bernal, *Nature* **1932**, *129*, 721.

[3] a) P. Rabe, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 62; b) P. Rabe, E. Ackerman, W. Schneider, *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3655; for the first total synthesis of quinine, see: c) R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1944**, *66*, 849; d) R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1945**, *67*, 860–874.

[4] H. Fischer, K. Zeile, *Justus Liebigs Ann. Chem.* **1929**, *468*, 98.

[5] a) L. H. Briggs, H. T. Openshaw, R. Robinson, *J. Chem. Soc.* **1946**, 903–908; b) R. Robinson, *Experientia* **1946**, *2*, 28; for the first total synthesis of strychnine, see: c) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751; d) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *Tetrahedron* **1963**, *19*, 247–288; see also: e) *Robert Burns Woodward: Artist and Architect in the World of Molecules* (Eds.: O. T. Benfey, P. J. T. Morris), Chemical Heritage Foundation, Philadelphia, **2001**, p. 470.

[6] W. von E. Doering in H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**, p. 547.

[7] G. Büchi, R. E. Erickson, N. Wakabayashi, *J. Am. Chem. Soc.* **1961**, *83*, 927–938.

[8] G. Büchi, W. D. MacLeod, *J. Am. Chem. Soc.* **1962**, *84*, 3205–3206.

[9] a) M. Dobler, J. D. Dunitz, B. Gubler, H. P. Weber, G. Büchi, O. J. Padilla, *Proc. Chem. Soc. London* **1963**, 383; b) G. Büchi, W. D. MacLeod, O. J. Padilla, *J. Am. Chem. Soc.* **1964**, *86*, 4438–4444.

[10] Interestingly, one could actually consider the birth of organic synthesis to be the product of a structural misassignment. In 1828, Friedrich Wöhler was attempting to synthesize ammonium isocyanate (NH_4OCN), which actually has the structure NH_4NCO. When he took a bottle of what he thought was silver isocyanate (actually silver cyanate), added ammonium chloride, and heated, urea resulted, an outcome that he did not intend, but one which was fortuitous nonetheless. For an interesting discussion on Wöhler's synthesis of urea, see: P. S. Cohen, S. M. Cohen, *J. Chem. Educ.* **1996**, *73*, 883–886.

[11] a) K. Nakanishi in *Comprehensive Natural Products Chemistry, Vol. 1* (Eds.: D. H. R. Barton, K. Nakanishi, O. Meth-Cohn), Elsevier, Amsterdam, **1999**, pp. xxiii–xl; b) C. Djerassi, *Pure Appl. Chem.* **1975**, *41*, 113–144; for an interesting recent account on two misassignments in inorganic chemistry, see: c) J. A. Labinger, S. J. Weininger, *Angew. Chem.* **2004**, *116*, 2664–2672; *Angew. Chem. Int. Ed.* **2004**, *43*, 2612–2619.

[12] J. C. Sheehan, *The Enchanted Ring: The Untold Story of Penicillin*, MIT Press, Cambridge, **1984**, p. 224.

[13] C. Djerassi, *Steroids Made It Possible* (Ed.: J. I. Seeman), American Chemical Society, Washington, DC, **1990**, p. 205 (Profiles, Pathways and Dreams Series).

[14] K. Nakanishi, *A Wandering Natural Products Chemist* (Ed.: J. I. Seeman), American Chemical Society, Washington, D.C., **1991**, p. 230 (Profiles, Pathways and Dreams Series). The quote is on page 87. For a further insightful analysis of the state of the art of

total synthesis in 1974, see: A. Eschenmoser, *Naturwissenschaften* **1974**, *61*, 513 – 525.

[15] a) L. L. Klein, W. W. McWhorter, S. S. Ko, K.-P. Pfaff, Y. Kishi, D. Uemura, Y. Hirata, *J. Am. Chem. Soc.* **1982**, *104*, 7362 – 7364; b) S. S. Ko, J. M. Finan, M. Yonaga, Y. Kishi, D. Uemura, Y. Hirata, *J. Am. Chem. Soc.* **1982**, *104*, 7364 – 7367; c) H. Fujioka, W. J. Christ, J. K. Cha, J. Leder, Y. Kishi, D. Uemura, Y. Hirata, *J. Am. Chem. Soc.* **1982**, *104*, 7367 – 7369; d) J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, Y. Kishi, L. L. Klein, S. S. Ko, J. Leder, W. W. McWhorter, K.-P. Pfaff, M. Yonaga, D. Uemura, Y. Hirata, *J. Am. Chem. Soc.* **1982**, *104*, 7369 – 7371; for a detailed account of this synthesis, see: K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis: Targets, Strategies, Methods*, VCH, Weinheim, **1996**, chap. 36, p. 798.

[16] M. Ishibashi, N. Yamaguchi, T. Sasaki, J. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1994**, 1455 – 1456.

[17] Our SciFinder search terms included: revised structure, structural reassignment, misassigned structure, incorrect structure, putative structure, tentative structure, and structural revision. Interestingly, each of these searches produced quite a different set of results, and well over 1000 hits were obtained overall for the period of January 1990 to March 2004.

[18] R. Suemitsu, K. Ohnishi, M. Horiuchi, A. Kitaguchi, K. Odamura, *Phytochemistry* **1992**, *31*, 2325 – 2326.

[19] M. Horiuchi, T. Maoka, N. Iwase, K. Ohnishi, *J. Nat. Prod.* **2002**, *65*, 1204 – 1205.

[20] I. Cornella, T. R. Kelly, *J. Org. Chem.* **2004**, *69*, 2191 – 2193.

[21] A. S. Ratnayake, W. Y. Yoshida, S. L. Mooberry, T. K. Hemscheidt, *J. Org. Chem.* **2001**, *66*, 8717 – 8721.

[22] J. A. May, R. K. Zeidan, B. M. Stoltz, *Tetrahedron Lett.* **2003**, *44*, 1203 – 1205. Nomofungin is identical to the natural product communesin B, which had been isolated and characterized almost a decade earlier: A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito, T. Hasegawa, *Tetrahedron Lett.* **1993**, *34*, 2355 – 2358.

[23] I. H. Hardt, P. R. Jensen, W. Fenical, *Tetrahedron Lett.* **2000**, *41*, 2073 – 2076.

[24] J. A. Kalaitzis, Y. Hamano, G. Nilsen, B. S. Moore, *Org. Lett.* **2003**, *5*, 4449 – 4452.

[25] P. A. Horton, F. E. Koehn, R. E. Longley, O. J. McConnell, *J. Am. Chem. Soc.* **1994**, *116*, 6015 – 6016.

[26] a) E. Lee, H. Y. Song, J. W. Kang, D.-S. Kim, C.-K. Jung, J. M. Joo, *J. Am. Chem. Soc.* **2002**, *124*, 384 – 385; b) E. Lee, H. Y. Song, J. M. Joo, J. W. Kang, D. S. Kim, C. K. Jung, C. Y. Hong, S. Jeong, K. Jeon, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3519 – 3520; c) H. Y. Song, J. M. Joo, J. W. Kang, D.-S. Kim, C.-K. Jung, H. S. Kwak, J. H. Park, E. Lee, C. Y. Hong, S. Jeong, K. Jeon, J. H. Park, *J. Org. Chem.* **2003**, *68*, 8080 – 8087. In this reassignment not only was an error found in the proposed structure, but the sign of the optical rotation reported for the natural product was also incorrect.

[27] A. Randazzo, G. Bifulco, C. Giannini, M. Bucci, C. Debitus, G. Cirino, L. Gomez-Paloma, *J. Am. Chem. Soc.* **2001**, *123*, 10 870 – 10 876.

[28] C. Della Monico, A. Randazzo, G. Bifulco, P. Cimino, M. Aquino, I. Izzo, F. De Riccardis, L. Gomez-Paloma, *Tetrahedron Lett.* **2002**, *43*, 5707 – 5710.

[29] P. Sharma, M. Alam, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2537 – 2540.

[30] a) L. A. Paquette, O. M. Moradei, P. Bernardelli, T. Lange, *Org. Lett.* **2000**, *2*, 1875 – 1878; b) D. Friedrich, R. W. Doskotch, L. A. Paquette, *Org. Lett.* **2000**, *2*, 1879 – 1882; for the full account of this reassignment, see: c) D. Friedrich, L. A. Paquette, *J. Nat. Prod.* **2002**, *65*, 126 – 130; for another synthesis of the originally assigned structure of sclerophytin A, see: d) L. E. Overman, L. D. Pennington, *Org. Lett.* **2000**, *2*, 2683 – 2686.

[31] a) F. Gallou, D. W. C. MacMillan, L. E. Overman, L. A. Paquette, L. D. Pennington, J. Yang, *Org. Lett.* **2001**, *3*, 135 – 137; for the full account of these total syntheses, see: b) P. Bernardelli, O. M. Moradei, D. Friedrich, J. Yang, F. Gallou, B. P. Dyck, R. W. Doskotch, T. Lange, L. A. Paquette, *J. Am. Chem. Soc.* **2001**, *123*, 9021 – 9032; c) D. W. C. MacMillan, L. E. Overman, L. D. Pennington, *J. Am. Chem. Soc.* **2001**, *123*, 9033 – 9044; for a personal account of one of these research programs, see: d) L. A. Paquette, *Chem. Rec.* **2001**, *1*, 311 – 320; e) L. A. Paquette, *Chemtracts* **2002**, *15*, 345 – 366.

[32] A. D. Patil, A. J. Freyer, P. B. Taylor, B. Carté, G. Zuber, R. K. Johnson, D. J. Faulkner, *J. Org. Chem.* **1997**, *62*, 1814 – 1819.

[33] a) F. Cohen, L. E. Overman, *J. Am. Chem. Soc.* **2001**, *123*, 10 782 – 10 783. Earlier work by other groups had revised the stereostructure of the left-hand guanidine portion of batzelladine F, but the carbon framework was not corrected: b) G. P. Black, P. J. Murphy, A. J. Thornhill, N. D. A. Walshe, C. Zanetti, *Tetrahedron* **1999**, *55*, 6547 – 6554; c) B. B. Snider, M. V. Busuyek, *J. Nat. Prod.* **1999**, *62*, 1707 – 1711; d) K. Nagasawa, H. Koshino, T. Nakata, *Tetrahedron Lett.* **2001**, *42*, 4155 – 4158.

[34] S. Carmely, Y. Kashman, *Tetrahedron Lett.* **1985**, *26*, 511 – 514.

[35] a) M. Kobayashi, J. Tanaka, T. Katori, M. Matsuura, I. Kitagawa, *Tetrahedron Lett.* **1989**, *30*, 2963 – 2966; b) I. Kitagawa, M. Kobayashi, T. Katori, M. Yamashita, J. Tanaka, M. Doi, T. Ishida, *J. Am. Chem. Soc.* **1990**, *112*, 3710 – 3712; c) M. Kobayashi, J. Tanaka, T. Katori, M. Matsuura, M. Yamashita, I. Kitagawa, *Chem. Pharm. Bull.* **1990**, *38*, 2409 – 2418; d) M. Kobayashi, J. Tanaka, T. Katori, I. Kitagawa, *Chem. Pharm. Bull.* **1990**, *38*, 2960 – 2966; e) M. Doi, T. Ishida, M. Kobayashi, I. Kitagawa, *J. Org. Chem.* **1991**, *56*, 3629 – 3632.

[36] a) I. Paterson, J. D. Smith, R. A. Ward, J. G. Cumming, *J. Am. Chem. Soc.* **1994**, *116*, 2615 – 2616; b) I. Paterson, K.-S. Yeung, R. A. Ward, J. G. Cumming, J. D. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 9391 – 9392; for the full account of this total synthesis, see: c) I. Paterson, J. G. Cumming, R. A. Ward, S. Lamboley, *Tetrahedron* **1995**, *51*, 9393 – 9412; d) I. Paterson, J. D. Smith, R. A. Ward, *Tetrahedron* **1995**, *51*, 9413 – 9436; e) I. Paterson, R. A. Ward, J. D. Smith, J. G. Cumming, K.-S. Yeung, *Tetrahedron* **1995**, *51*, 9437 – 9466; f) I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cumming, S. Lamboley, *Tetrahedron* **1995**, *51*, 9467 – 9486; for a later total synthesis of swinholide A, see: g) K. C. Nicolaou, K. Ajito, A. P. Patron, H. Khatuya, P. K. Richter, P. Bertinato, *J. Am. Chem. Soc.* **1996**, *118*, 3059 – 3060; h) K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewski, *Chem. Eur. J.* **1996**, *2*, 847 – 868; for a review of these two syntheses, see: K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II: More Targets, Strategies, Methods*, Wiley-VCH, Weinheim, **2003**, chap. 3, p. 639.

[37] L. Ramachandra Row, K. S. Reddy, N. S. Sarma, T. Matsuura, R. Nakashima, *Phytochemistry* **1980**, *19*, 1175 – 1181.

[38] a) B. Makino, M. Kawai, Y. Iwata, H. Yamamura, Y. Butsugan, K. Ogawa, M. Hayashi, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 219 – 226; for the structural revision of another member of this family, see: b) B. Makino, M. Kawai, T. Ogura, M. Nakanishi, H. Yamamura, Y. Butsugan, *J. Nat. Prod.* **1995**, *58*, 1668 – 1674; for the structural revision of another physalin, whose proposed structure was based on a misassigned degradation product, see: c) M. Kawai, T. Ogura, Y. Butsugan, T. Taga, M. Hayashi, *Tetrahedron* **1991**, *47*, 2103 – 2110.

[39] T. H. Al-Tel, M. H. A. Zarga, S. S. Sabri, M. Feroz, N. Fatima, Z. Shah, Atta-Ur-Rahman, *Phytochemistry* **1991**, *30*, 3081 – 3085.

[40] A. V. Kalinin, V. Snieckus, *Tetrahedron Lett.* **1998**, *39*, 4999 – 5002. This revised structure is that of isoeugenetin methyl ether, a derivative of the natural product isoeugenetin that had been

prepared nearly fifty years earlier: a) H. Schmid, A. Bolleter, *Helv. Chim. Acta* **1949**, *32*, 1358 – 1360; b) H. Schmid, A. Bolleter, *Helv. Chim. Acta* **1950**, *33*, 917 – 922.

[41] H. Greger, O. Hofer, H. Kählig, G. Wurz, *Tetrahedron* **1992**, *48*, 1209 – 1218.

[42] W. M. Johnson, S. W. Littler, C. R. Strauss, *Aust. J. Chem.* **1994**, *47*, 751 – 756; for a later total synthesis of sinharine and a discussion of the original misassignment, see: S. Hinterberger, O. Hofer, H. Greger, *Tetrahedron* **1994**, *50*, 6279 – 6286.

[43] O. M. Cóbar, A. D. Rodríguez, O. L. Padilla, J. A. Sánchez, *J. Org. Chem.* **1997**, *62*, 7183 – 7188.

[44] Y.-P. Shi, A. D. Rodríguez, O. L. Padilla, *J. Nat. Prod.* **2001**, *64*, 1439 – 1443.

[45] I. Kubo, S. P. Tanis, Y.-W. Lee, I. Miura, K. Nakanishi, A. Chapya, *Heterocycles* **1976**, *5*, 485 – 498.

[46] M. S. Rajab, J. K. Rugutt, F. R. Fronczek, N. H. Fischer, *J. Nat. Prod.* **1997**, *60*, 822 – 825.

[47] J. Rodríguez, B. M. Peters, L. Kurz, R. C. Schatzman, D. McCarley, L. Lou, P. Crews, *J. Am. Chem. Soc.* **1993**, *115*, 10436 – 10437.

[48] J. Rodríguez, P. Crews, *Tetrahedron Lett.* **1994**, *35*, 4719 – 4722.

[49] F. Balza, S. Tachibana, H. Barrios, G. H. N. Towers, *Phytochemistry* **1991**, *30*, 1613 – 1614.

[50] a) G. I. Georg, S. R. Gollapudi, G. L. Grunewald, C. W. Gunn, R. H. Himes, B. K. Rao, X.-Z. Liang, Y. W. Mirhom, L. A. Mitscher, D. G. Vander Velde, Q.-M. Ye, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1345 – 1348; b) G. I. Georg, Z. S. Cheruvallath, D. Vander Velde, Q.-M. Ye, L. A. Mitscher, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1349 – 1350; for a slightly later publication leading to the same structural revision based on X-ray crystallographic analysis of a related compound, see: c) G. Appendino, L. Barboni, P. Gariboldi, E. Bombardelli, B. Gabetta, D. Viterbo, *J. Chem. Soc. Chem. Commun.* **1993**, 1587 – 1589; in concurrent work, a group (which included some of the initial isolation chemists) identified the transpositon of the acetate and benzoate units originally at C7 and C10, respectively, but not the constitutional change: d) A. Chu, J. Zajicek, G. H. N. Towers, C. M. Soucy-Breau, N. G. Lewis, R. Croteau, *Phytochemistry* **1993**, *34*, 269 – 271.

[51] a) U. Renner, H. Fritz, *Helv. Chim. Acta* **1965**, *48*, 308 – 317; for the earlier report of the isolation of isoschizogamine, see: b) U. Renner, P. Kernweisz, *Experientia* **1963**, *19*, 244 – 246.

[52] J. Hájícek, J. Taimr, M. Budesínsky, *Tetrahedron Lett.* **1998**, *39*, 505 – 508.

[53] J. L. Hubbs, C. H. Heathcock, *Org. Lett.* **1999**, *1*, 1315 – 1317.

[54] a) Y. Kuroda, M. Okuhara, T. Goto, M. Yamashita, E. Iguchi, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1980**, *33*, 259 – 266; b) Y. Kuroda, M. Okuhara, T. Goto, M. Okamoto, M. Yamashita, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1980**, *33*, 267 – 271.

[55] a) N. Yasuda, K. Sakane, *J. Antibiot.* **1991**, *44*, 801 – 802. Interestingly, the structure of FR900148 was questioned earlier based on the isolation of a potential biosynthetic precursor, but was not revised: b) L. Chaiet, B. H. Arison, R. L. Monaghan, J. P. Springer, J. L. Smith, S. B. Zimmerman, *J. Antibiot.* **1984**, *37*, 207 – 210.

[56] J. Cáceres, M. E. Rivera, A. D. Rodríguez, *Tetrahedron* **1990**, *46*, 341 – 348.

[57] a) J. Shin, W. Fenical, *J. Org. Chem.* **1991**, *56*, 3392 – 3398; for a follow-up article by the original isolation chemists on the structural assignment, see: b) A. D. Rodríguez, A. L. Acosta, H. Dhasmana, *J. Nat. Prod.* **1993**, *56*, 1843 – 1849.

[58] a) E. J. Corey, R. S. Kania, *Tetrahedron Lett.* **1998**, *39*, 741 – 744; for a later total synthesis of palominol, see: b) H. Miyaoka, Y. Isaji, H. Mitome, Y. Yamada, *Tetrahedron* **2003**, *59*, 61 – 75.

[59] a) J. Kobayashi, M. Ishibashi, H. Hirota, *J. Nat. Prod.* **1991**, *54*, 1435 – 1439; for the original publication on the isolation, see: b) J. Kobayashi, M. Ishibashi, H. Nakamura, Y. Ohizumi, T. Yamasu, T. Sasaki, Y. Hirata, *Tetrahedron Lett.* **1986**, *27*, 5755 – 5758; for a review on this family of natural products, see: c) M. Ishibashi, J. Kobayashi, *Heterocycles* **1997**, *44*, 543 – 572.

[60] a) B. M. Trost, P. E. Harrington, *J. Am. Chem. Soc.* **2004**, *126*, 5028 – 5029; for earlier syntheses of the originally proposed structure, see: b) H. W. Lam, G. Pattenden, *Angew. Chem.* **2002**, *114*, 526 – 529; *Angew. Chem. Int. Ed.* **2002**, *41*, 508 – 511; c) R. E. Maleczka, L. R. Terrell, F. Geng, J. S. Ward, *Org. Lett.* **2002**, *4*, 2841 – 2844; d) B. M. Trost, J. D. Chisholm, S. T. Wrobleski, M. Jung, *J. Am. Chem. Soc.* **2002**, *124*, 12420 – 12421.

[61] M. A. M. Maciel, A. C. Pinto, S. N. Brabo, M. N. Da Silva, *Phytochemistry* **1998**, *49*, 823 – 828.

[62] R. B. Grossman, R. M. Rasne, *Org. Lett.* **2001**, *3*, 4027 – 4030.

[63] a) E. Selva, G. Beretta, N. Montanini, G. S. Saddler, L. Gastaldo, P. Ferrari, R. Lorenzetti, P. Landini, F. Ripamonti, B. P. Goldstein, M. Berti, L. Montanaro, M. Denaro, *J. Antibiot.* **1991**, *44*, 693 – 701; b) J. Kettenring, L. Colombo, P. Ferrari, P. Tavecchia, M. Nebuloni, K. Vékey, G. G. Gallo, E. Selva, *J. Antibiot.* **1991**, *44*, 702 – 715.

[64] a) P. Tavecchia, P. Gentili, M. Kurz, C. Sottani, R. Bonfichi, S. Lociuro, E. Selva, *J. Antibiot.* **1994**, *47*, 1564 – 1567; for the full account of this structural revision, see: b) P. Tavecchia, P. Gentili, M. Kurz, C. Sottani, R. Bonfichi, E. Selva, S. Lociuro, E. Restelli, R. Ciabatti, *Tetrahedron* **1995**, *51*, 4867 – 4890.

[65] For synthetic work which nearly reached this target molecule, see: T. Suzuki, K. Nagasaki, K. Okumura, C. Shin, *Heterocycles* **2001**, *55*, 835 – 840.

[66] Y. Asakawa, A. Yamamura, T. Waki, T. Takemoto, *Phytochemistry* **1980**, *19*, 603 – 607.

[67] M. Tori, K. Nakashima, M. Toyota, Y. Asakawa, *Tetrahedron Lett.* **1993**, *34*, 3751 – 3752.

[68] A. Buske, S. Busemann, J. Mühlbacher, J. Schmidt, A. Porzel, G. Bringmann, G. Adam, *Tetrahedron* **1999**, *55*, 1079 – 1086.

[69] G. Bringmann, J. Schlauer, H. Rischer, M. Wohlfarth, J. Mühlbacher, A. Buske, A. Porzel, J. Schmidt, G. Adam, *Tetrahedron* **2000**, *56*, 3691 – 3695.

[70] S. Ômura, A. Nakagawa, H. Yamada, T. Hata, A. Furusaki, T. Watanabe, *Chem. Pharm. Bull.* **1973**, *21*, 931 – 940.

[71] S. J. Gould, N. Tamayo, C. R. Melville, M. C. Cone, *J. Am. Chem. Soc.* **1994**, *116*, 2207 – 2208.

[72] S. Mithani, G. Weeratunga, N. J. Taylor, G. I. Dmitrienko, *J. Am. Chem. Soc.* **1994**, *116*, 2209 – 2210.

[73] a) J. E. Leet, D. R. Schroeder, S. J. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle, J. A. Matson, *J. Am. Chem. Soc.* **1992**, *114*, 7946 – 7948; b) J. E. Leet, D. R. Schroeder, D. R. Langley, K. L. Colson, S. Huang, S. E. Klohr, M. S. Lee, J. Golik, S. J. Hofstead, T. W. Doyle, J. A. Matson, *J. Am. Chem. Soc.* **1993**, *115*, 8432 – 8443.

[74] S. Kawata, S. Ashizawa, M. Hirama, *J. Am. Chem. Soc.* **1997**, *119*, 12012 – 12013.

[75] The Myers group has synthesized the complete kedarcidin chromophore aglycon enantioselectively in protected form, thus verifying its revised connectivities and stereostructure: A. G. Myers, P. C. Hogan, A. R. Hurd, S. D. Goldberg, *Angew. Chem.* **2002**, *114*, 1104 – 1109; *Angew. Chem. Int. Ed.* **2002**, *41*, 1062 – 1067.

[76] D. G. Corley, G. E. Rottinghaus, M. S. Tempesta, *Tetrahedron Lett.* **1986**, *27*, 427 – 430.

[77] F. E. Ziegler, A. Nangia, M. S. Tempesta, *Tetrahedron Lett.* **1988**, *29*, 1665 – 1668.

[78] a) F. E. Ziegler, C. A. Metcalf, G. Schulte, *Tetrahedron Lett.* **1992**, *33*, 3117 – 3120; for the full account of this total synthesis, see: b) F. E. Ziegler, C. A. Metcalf, A. Nangia, G. Schulte, *J. Am. Chem. Soc.* **1993**, *115*, 2581 – 2589.

[79] T. Komoda, Y. Sugiyama, N. Abe, M. Imachi, H. Hirota, A. Hirota, *Tetrahedron Lett.* **2003**, *44*, 1659 – 1661.

[80] T. Komoda, Y. Sugiyama, N. Abe, M. Imachi, H. Hirota, H. Koshino, A. Hirota, *Tetrahedron Lett.* **2003**, *44*, 7417 – 7419.

[81] N. González, J. Rodríguez, C. Jiménez, *J. Org. Chem.* **1999**, *64*, 5705 – 5707.

[82] H. Kiyota, D. J. Dixon, C. K. Luscombe, S. Hettstedt, S. V. Ley, *Org. Lett.* **2002**, *4*, 3223 – 3226.

[83] C. Kan-Fan, J.-C. Quirion, I. R. C. Bick, H.-P. Husson, *Tetrahedron* **1988**, *44*, 1651 – 1660.

[84] a) R. Güller, M. Dobler, H.-J. Borschberg, *Helv. Chim. Acta* **1991**, *74*, 1636 – 1642; for the full account of this total synthesis, see: b) J.-C. Quirion, H.-P. Husson, C. Kan, O. Laprévote, A. Chiaroni, C. Riche, S. Burkard, H.-J. Borschberg, I. R. C. Bick, *J. Org. Chem.* **1992**, *57*, 5848 – 5851; for total syntheses of related alkaloids whose structures were also revised, see: c) S. Burkard, H.-J. Borschberg, *Helv. Chim. Acta* **1991**, *74*, 275 – 289; d) R. Güller, H.-J. Borschberg, *Helv. Chim. Acta* **1991**, *74*, 1643 – 1653.

[85] F. A. Macías, R. M. Varela, A. Torres, R. M. Oliva, J. M. G. Molinillo, *Phytochemistry* **1998**, *48*, 631 – 636.

[86] H. Takikawa, K. Isono, M. Sasaki, F. A. Macías, *Tetrahedron Lett.* **2003**, *44*, 7023 – 7025.

[87] W. C. Taylor, S. Toth, *Aust. J. Chem.* **1997**, *50*, 895 – 902.

[88] M. Arnó, M. A. González, R. J. Zaragozá, *J. Org. Chem.* **2003**, *68*, 1242 – 1251.

[89] E. Sakuno, K. Yabe, T. Hamasaki, H. Nakajima, *J. Nat. Prod.* **2000**, *63*, 1677 – 1678.

[90] P. Wipf, A. D. Kerekes, *J. Nat. Prod.* **2003**, *66*, 716 – 718. TAEMC161 is actually the phytotoxin natural product viridiol, which had been isolated and characterized more than 30 years earlier: J. S. Moffatt, J. D. Bu'Lock, T. H. Yuen, *Chem. Commun.* **1969**, 839.

[91] W. R. Kem, K. N. Scott, J. H. Duncan, *Experientia* **1976**, *32*, 684 – 686.

[92] J. A. Zoltewicz, M. P. Cruskie, *Tetrahedron* **1995**, *51*, 11401 – 11410.

[93] a) M. P. Cruskie, J. A. Zoltewicz, K. A. Abboud, *J. Org. Chem.* **1995**, *60*, 7491 – 7495; for a later total synthesis of nemertelline, see: b) A. Bouillon, A. S. Voisin, A. Robic, J.-C. Lancelot, V. Collot, S. Rault, *J. Org. Chem.* **2003**, *68*, 10178 – 10180.

[94] N. Lindquist, W. Fenical, *Tetrahedron Lett.* **1989**, *30*, 2735 – 2738.

[95] a) M. S. Congreve, A. B. Holmes, A. B. Hughes, M. G. Looney, *J. Am. Chem. Soc.* **1993**, *115*, 5815 – 5816; for a later total synthesis of ascidiatrienolide A, see: b) A. Fürstner, M. Schlede, *Adv. Synth. Catal.* **2002**, *344*, 657 – 665.

[96] P. S. Parameswaran, C. G. Naik, S. Y. Kamat, B. N. Pramanik, *Indian J. Chem. Sect. B* **1998**, *37*, 1258 – 1263.

[97] N. Saito, H. Sakai, K. Suwanborirux, S. Pummangura, A. Kubo, *Heterocycles* **2001**, *55*, 21 – 28. These researchers were the first to note that renieramycin H is identical to cribrostatin 4, a compound isolated independently by Pettit et al. and characterized by using X-ray crystallographic analysis: G. R. Pettit, J. C. Knight, J. C. Collins, D. L. Herald, R. K. Pettit, M. R. Boyd, V. G. Young, *J. Nat. Prod.* **2000**, *63*, 793 – 798.

[98] a) B. M. Degnan, C. J. Hawkins, M. F. Lavin, E. J. McCaffrey, D. L. Parry, D. J. Watters, *J. Med. Chem.* **1989**, *32*, 1354 – 1359; for the original isolation, see: b) D. Gouiffès, S. Moreau, N. Helbecque, J. L. Bernier, J. P. Hénichart, Y. Barbin, D. Laurent, J. F. Verbist, *Tetrahedron* **1988**, *44*, 451 – 459. Bistramide A has also been named bistratene A; for a later isolation of other family members, see: c) J.-F. Biard, C. Roussakis, J.-M. Kornprobst, D. Gouiffes-Barbin, J.-F. Verbist, P. Cotelle, M. P. Foster, C. M. Ireland, C. Debitus, *J. Nat. Prod.* **1994**, *57*, 1336 – 1345.

[99] M. P. Foster, C. L. Mayne, R. Dunkel, R. J. Pugmire, D. M. Grant, J.-M. Kornprobst, J.-F. Verbist, J.-F. Biard, C. M. Ireland, *J. Am. Chem. Soc.* **1992**, *114*, 1110 – 1111.

[100] a) P. Welzel, F.-J. Witteler, D. Müller, W. Riemer, *Angew. Chem.* **1981**, *93*, 130 – 132; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 121 – 123; b) P. Welzel, B. Wietfeld, F. Kunisch, T. Schubert, K. Hobert, H. Duddeck, D. Müller, G. Huber, J. E. Maggio, D. H. Williams, *Tetrahedron* **1983**, *39*, 1583 – 1591.

[101] H.-W. Fehlhaber, M. Girg, G. Seibert, K. Hobert, P. Welzel, Y. Van Heijenoort, J. Van Heijenoort, *Tetrahedron* **1990**, *46*, 1557 – 1568.

[102] G. R. Pettit, C. L. Herald, Y. Kamano, *J. Org. Chem.* **1983**, *48*, 5354 – 5356.

[103] a) D. E. Schaufelberger, G. N. Chmurny, J. A. Beutler, M. P. Koleck, A. B. Alvarado, B. W. Schaufelberger, G. M. Muschik, *J. Org. Chem.* **1991**, *56*, 2895 – 2900; b) G. N. Chmurny, M. P. Koleck, B. D. Hilton, *J. Org. Chem.* **1992**, *57*, 5260 – 5264.

[104] K. Ohmori, Y. Ogawa, T. Obitsu, Y. Ishikawa, S. Nishiyama, S. Yamamura, *Angew. Chem.* **2000**, *112*, 2376 – 2379; *Angew. Chem. Int. Ed.* **2000**, *39*, 2290 – 2294.

[105] a) J.-J. Chen, S.-X. Qiu, Z.-X. Zhang, J. Zhou, *Acta Bot. Yunnanica* **1989**, *11*, 203 – 208; b) S.-X. Qiu, Z.-X. Zhang, J. Zhou, *Acta Bot. Sin.* **1990**, *32*, 936 – 942.

[106] S.-X. Qiu, L.-Z. Lin, Y. Nan. P. Lin, J.-J. Chen, Z.-X. Zhang, J. Zhou, G. A. Cordell, *Phytochemistry* **1995**, *40*, 917 – 921.

[107] W. W. Harding, P. A. Lewis, H. Jacobs, S. McLean, W. F. Reynolds, L.-L. Tay, J.-P. Yang, *Tetrahedron Lett.* **1995**, *36*, 9137 – 9140.

[108] Three groups synthesized the proposed structure of glabrescol independently at roughly the same time: a) H. Hioki, C. Kanehara, Y. Ohnishi, Y. Umemori, H. Sakai, S. Yoshio, M. Matsushita, M. Kodama, *Angew. Chem.* **2000**, *112*, 2652 – 2654; *Angew. Chem. Int. Ed.* **2000**, *39*, 2552 – 2554; b) Y. Morimoto, T. Iwai, T. Kinoshita, *J. Am. Chem. Soc.* **2000**, *122*, 7124 – 7125; c) Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 4831 – 4832. Reference [108b] included a revision of the structure and the first reported total synthesis of the true glabrescol. A few months later, a second and more efficient total synthesis of the revised structure was reported: d) Z. Zhong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9328 – 9329; for an attempt to use molecular modeling to predict the correct structure of glabrescol, see: e) B. R. Bellenie, J. M. Goodman, *Tetrahedron Lett.* **2001**, *42*, 7477 – 7479.

[109] For the original isolation and elucidation of parts of the structure, see: a) M. Seki-Asano, T. Okazaki, M. Yamagishi, N. Sakai, K. Hanada, K. Mizoue, *J. Antibiot.* **1994**, *47*, 1226 – 1233; b) M. Seki-Asano, Y. Tsuchida, K. Hanada, K. Mizoue, *J. Antibiot.* **1994**, *47*, 1234 – 1241; for the assignment of the stereostructure FD-891, see: c) T. Eguchi, K. Kobayashi, H. Uekusa, Y. Ohashi, K. Mizoue, Y. Matsushima, K. Kakinuma, *Org. Lett.* **2002**, *4*, 3383 – 3386.

[110] T. Eguchi, K. Yamamoto, K. Mizoue, K. Kakinuma, *J. Antibiot.* **2004**, *57*, 156 – 157. The revised structure is exactly the same as that of the natural product BE-45653: H. Ogawa, S. Nakajima, H. Suzuki, K. Ojiri, H. Suda, *Jpn. Kokai Tokkyo Koho*, **1997**, 0987285.

[111] a) M. R. Prinsep, F. R. Caplan, R. E. Moore, G. M. L. Patterson, C. D. Smith, *J. Am. Chem. Soc.* **1992**, *114*, 385 – 387; b) M. R. Prinsep, G. M. L. Patterson, L. K. Larsen, C. D. Smith, *Tetrahedron* **1995**, *51*, 10523 – 10530.

[112] a) T. G. Minehan, Y. Kishi, *Angew. Chem.* **1999**, *111*, 972 – 975; *Angew. Chem. Int. Ed.* **1999**, *38*, 923 – 925; b) T. G. Minehan, L. Cook-Blumberg, Y. Kishi, M. R. Prinsep, R. E. Moore, *Angew. Chem.* **1999**, *111*, 975 – 977; *Angew. Chem. Int. Ed.* **1999**, *38*, 926 – 928.

[113] W. Wang, Y. Kishi, *Org. Lett.* **1999**, *1*, 1129 – 1132.

[114] For the original isolation and elucidation of parts of the structure, see: a) K. S. Lam, G. A. Hesler, J. M. Mattei, S. W. Mamber, S. Forenza, K. Tomita, *J. Antibiot.* **1990**, *43*, 956 – 960; b) J. E. Leet, D. R. Schroeder, B. S. Krishnan, J. A. Matson, *J. Antibiot.* **1990**, *43*, 961 – 966; for the assignment of the stereostructure of himastatin, see: c) J. E. Leet, D. R. Schroeder, J. Golik, J. A. Matson, T. W. Doyle, K. S. Lam, S. E. Hill, M. S. Lee, J. L. Whitney, B. S. Krishnan, *J. Antibiot.* **1996**, *49*, 299 – 311.

[115] a) T. M. Kamenecka, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 3164 – 3166; *Angew. Chem. Int. Ed.* **1998**, *37*, 2993 – 2995; b) T. M. Kamenecka, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 3166 – 3168; *Angew. Chem. Int. Ed.* **1998**, *37*, 2995 – 2998; for the full account of this work, see: c) T. M. Kamenecka, S. J. Danishefsky, *Chem. Eur. J.* **2001**, *7*, 41 – 63.

[116] R.-s. Xu, J. K. Snyder, K. Nakanishi, *J. Am. Chem. Soc.* **1984**, *106*, 734 – 736.

[117] Q. Cheng, J. K. Snyder, *J. Org. Chem.* **1988**, *53*, 4562 – 4567; for an earlier total synthesis of the originally proposed structure of robustadial A, see: K. Lal, E. A. Zarate, W. J. Youngs, R. G. Salomon, *J. Am. Chem. Soc.* **1986**, *108*, 1311 – 1312.

[118] a) R. G. Salomon, K. Lal, S. M. Mazza, E. A. Zarate, W. J. Youngs, *J. Am. Chem. Soc.* **1988**, *110*, 5213 – 5214; for a full account of this synthesis, see: b) R. G. Salomon, S. M. Mazza, K. Lal, *J. Org. Chem.* **1989**, *54*, 1562 – 1570; for more recent total syntheses of the robustadials, see: c) S. Koser, H. M. R. Hoffmann, D. J. Williams, *J. Org. Chem.* **1993**, *58*, 6163 – 6165; d) S. Bissada, C. K. Lau, M. A. Bernstein, C. Dufresne, *Can. J. Chem.* **1994**, *72*, 1866 – 1869; e) I. R. Aukrust, L. Skatteboel, *Acta Chem. Scand.* **1996**, *50*, 132 – 140; for a synthesis of robustadial A dimethyl ether, see: f) M. Majewski, G. Bantle, *Tetrahedron Lett.* **1989**, *30*, 6653 – 6656; g) M. Majewski, N. M. Irvine, G. W. Bantle, *J. Org. Chem.* **1994**, *59*, 6697 – 6702.

[119] For the original isolation and elucidation of parts of the structure, see: a) G. R. Pettit, Z. A. Cichacz, F. Gao, M. R. Boyd, J. M. Schmidt, *J. Chem. Soc. Chem. Commun.* **1994**, 1111 – 1112; for the determination of parts of the stereostructure of dictyostatin 1, see: b) G. R. Pettit, Z. A. Cichacz, US Patent 5430053, **1995** [*Chem. Abst.* **1995**, *123*, 139562]; for some information on its biological activity, see: c) R. A. Isbrucker, J. Cummins, S. A. Pomponi, R. E. Longley, A. E. Wright, *Biochem. Pharmacol.* **2003**, *66*, 75 – 82.

[120] I. Paterson, R. Britton, O. Delgado, A. E. Wright, *Chem. Commun.* **2004**, 632 – 633.

[121] J. F. Biard, S. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber, K. Boukef, *Tetrahedron Lett.* **1994**, *35*, 2691 – 2694.

[122] a) H. Abe, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **2000**, *122*, 4583 – 4592; b) H. Abe, S. Aoyagi, C. Kibayashi, *Angew. Chem.* **2002**, *114*, 3143 – 3146; *Angew. Chem. Int. Ed.* **2002**, *41*, 3017 – 3020; for the full account of this total synthesis, see: c) C. Kibayashi, S. Aoyagi, H. Abe, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059 – 2074; for earlier total syntheses of the proposed structure of lepadiformine that did not point to a definitive structural alternative, see: d) W. H. Pearson, Y. Ren, *J. Org. Chem.* **1999**, *64*, 688 – 689; e) K. M. Werner, J. M. de los Santos, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1999**, *64*, 686 – 687; f) K. M. Werner, J. M. de los Santos, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1999**, *64*, 4865 – 4873; g) H. Abe, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **2000**, *41*, 1205 – 1208; for later total syntheses of the revised structure of lepadiformine, see: h) P. Sun, C. Sun, S. M. Weinreb, *Org. Lett.* **2001**, *3*, 3507 – 3510; i) T. J. Greshock, R. L. Funk, *Org. Lett.* **2001**, *3*, 3511 – 3514; j) P. Sun, C. Sun, S. M. Weinreb, *J. Org. Chem.* **2002**, *67*, 4337 – 4345; for a review of one of these research programs, see: k) S. M. Weinreb, *Acc. Chem. Res.* **2003**, *36*, 59 – 65.

[123] A. R. Carroll, J. C. Coll, D. J. Bourne, J. K. MacLeod, T. M. Zabriskie, C. M. Ireland, B. F. Bowden, *Aust. J. Chem.* **1996**, *49*, 659 – 667.

[124] a) P. Wipf, Y. Uto, *J. Org. Chem.* **2000**, *65*, 1037 – 1049; for their synthesis of the originally proposed structure, see: b) P. Wipf, Y. Uto, *Tetrahedron Lett.* **1999**, *40*, 5165 – 5169; for later total syntheses of the revised structure of trunkamide A, see: c) B. McKeever, G. Pattenden, *Tetrahedron Lett.* **2001**, *42*, 2573 – 2577; d) B. McKeever, G. Pattenden, *Tetrahedron* **2003**, *59*, 2713 – 2727; e) J. M. Caba, I. M. Rodriguez, I. Manzanares, E. Giralt, F. Albericio, *J. Org. Chem.* **2001**, *66*, 7568 – 7574.

[125] J. Orjala, D. G. Nagle, V. L. Hsu, W. H. Gerwick, *J. Am. Chem. Soc.* **1995**, *117*, 8281 – 8282.

[126] a) F. Yokokawa, H. Fujiwara, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 1915 – 1916; for the full account of this work, see: b) F. Yokokawa, H. Fujiwara, T. Shioiri, *Tetrahedron* **2000**, *56*, 1759 – 1775; for earlier syntheses of the proposed structure of antillatoxin that did not lead to the proposal of a definitive structural alternative, see: c) F. Yokokawa, T. Shioiri, *J. Org. Chem.* **1998**, *63*, 8638 – 8639; d) J. D. White, R. Hanselmann, D. J. Wardrop, *J. Am. Chem. Soc.* **1999**, *121*, 1106 – 1107.

[127] S. Konetschny-Rapp, H.-W. Krell, U. Martin, World patent 96/11941, **1996** [*Chem. Abst.* **1996**, *124*, 315175].

[128] S. Hanessian, M. Tremblay, J. F. W. Petersen, *J. Am. Chem. Soc.* **2004**, *126*, 6064 – 6071.

[129] Y. Igarashi, K. Futamata, T. Fujita, A. Sekine, H. Senda, H. Naoki, T. Furumai, *J. Antibiot.* **2003**, *56*, 107 – 113.

[130] M. E. Tichenor, D. B. Kastrinsky, D. L. Boger, *J. Am. Chem. Soc.* **2004**, *126*, 8396 – 8398; for earlier studies relating to the chemical biology of this interesting natural product, see: J. P. Parrish, D. B. Kastrinsky, S. E. Wolkenberg, Y. Igarashi, D. L. Boger, *J. Am. Chem. Soc.* **2003**, *125*, 10971 – 10976.

[131] For the correction of the two incorrect structures, see: a) L. Witte, L. Ernst, V. Wray, T. Hartmann, *Phytochemistry* **1992**, *31*, 1027 – 1028; for the earlier misassignments, see: b) J. G. Urones, P. B. Barcala, I. S. Marcos, R. F. Moro, M. L. Esteban, A. F. Rodriguez, *Phytochemistry* **1988**, *27*, 1507; c) F. Bohlmann, C. Zdero, J. Jakupovic, M. Grenz, V. Castro, R. M. King, H. Robinson, L. P. D. Vincent, *Phytochemistry* **1986**, *25*, 1151 – 1159; see also: d) E. Roeder, *Phytochemistry* **1990**, *29*, 11 – 29.

[132] For the correction of the two incorrect structures, see: a) H. Okamura, T. Iwagawa, M. Nakatani, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3465 – 3467; for the earlier misassignments, see: b) Y. Takeda, H. Yamashita, T. Matsumoto, H. Terao, *Phytochemistry* **1993**, *33*, 713 – 715; c) M. Uchida, Y. Koike, G. Kusano, Y. Kondo, S. Nozoe, C. Kabuto, T. Takemoto, *Chem. Pharm. Bull.* **1990**, *28*, 92 – 102; d) M. Uchida, G. Kusano, Y. Kondo, S. Nozoe, T. Takemoto, *Heterocycles* **1978**, *9*, 139 – 144.

[133] T. C. Fleischer, R. D. Waigh, P. G. Waterman, *J. Nat. Prod.* **1997**, *60*, 1054 – 1056.

[134] K. I. Booker-Milburn, H. Jenkins, J. P. H. Charmant, P. Mohr, *Org. Lett.* **2003**, *5*, 3309 – 3312.

[135] M. F. Rodríguez Brasco, A. M. Seldes, J. A. Palermo, *Org. Lett.* **2001**, *3*, 1415 – 1417.

[136] K. Inanaga, K. Takasu, M. Ihara, *J. Am. Chem. Soc.* **2004**, *126*, 1352 – 1353.

[137] T. Hashimoto, S. Kondo, H. Naganawa, T. Takita, K. Maeda, H. Umezawa, *J. Antibiot.* **1974**, *27*, 86 – 87.

[138] M. E. Bunnage, T. Ganesh, I. B. Masesane, D. Orton, P. G. Steel, *Org. Lett.* **2003**, *5*, 239 – 242.

[139] N. J. Sun, S. H. Woo, J. M. Cassady, R. M. Snapka, *J. Nat. Prod.* **1998**, *61*, 362 – 366.

[140] J. B. Perales, N. F. Makino, D. L. Van Vranken, *J. Org. Chem.* **2002**, *67*, 6711 – 6717.

[141] S. N. Kazmi, Z. Ahmed, W. Ahmed, A. Malik, *Heterocycles* **1989**, *29*, 1901 – 1906.

[142] D. L. Comins, X. Zheng, R. R. Goehring, *Org. Lett.* **2002**, *4*, 1611–1613.

[143] A. R. Carroll, W. C. Taylor, *Aust. J. Chem.* **1991**, *44*, 1615–1626.

[144] M. K. Gurjar, J. Cherian, C. V. Ramana, *Org. Lett.* **2004**, *6*, 317–319.

[145] N. Fukamiya, M. Okano, M. Miyamoto, K. Tagahara, K.-H. Lee, *J. Nat. Prod.* **1992**, *55*, 468–475.

[146] J. M. VanderRoest, P. A. Grieco, *J. Org. Chem.* **1996**, *61*, 5316–5325.

[147] R. Pummerer, H. Puttfarcken, P. Schopflocher, *Ber. Dtsch. Chem. Ges. B* **1925**, *58*, 1808–1820.

[148] a) D. H. R. Barton, A. M. Deflorin, O. E. Edwards, *Chem. Ind.* **1955**, 1039; b) D. H. R. Barton, A. M. Deflorin, O. E. Edwards, *J. Chem. Soc.* **1956**, 530–532; for an engaging overview of this work, see: D. H. R. Barton, *Half a Century of Free Radical Chemistry*, Cambridge University Press, Cambridge, **1993**, p. 164.

[149] a) E. Brochmann-Hanssen, B. Nielsen, *Tetrahedron Lett.* **1965**, *7*, 1271–1274; b) A. R. Battersby, G. W. Evans, *Tetrahedron Lett.* **1965**, *7*, 1275–1278.

[150] D. H. R. Barton, B. D. Brown, D. D. Ridley, D. A. Widdowson, A. J. Keys, C. J. Leaver, *J. Chem. Soc. Perkin Trans. 1* **1975**, 2069–2076; see also: A. J. Keys, C. J. Leaver, D. H. R. Barton, B. D. Brown, D. A. Widdowson, *Nature* **1971**, *232*, 423–424.

[151] a) F. W. Lichtenthaler, K. Nakamura, J. Klotz, *Angew. Chem.* **2003**, *115*, 6019–6023; *Angew. Chem. Int. Ed.* **2003**, *42*, 5838–5843; b) F. W. Lichtenthaler, J. Klotz, K. Nakamura, *Tetrahedron: Asymmetry* **2003**, *14*, 3973–3986.

[152] For the initial assignment based on X-ray crystallography and other methods, see: a) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, J. E. Lancaster, *J. Am. Chem. Soc.* **1962**, *84*, 3185–3187; b) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, J. E. Lancaster, *J. Am. Chem. Soc.* **1962**, *84*, 3187–3188; c) A. Tulinsky, *J. Am. Chem. Soc.* **1962**, *84*, 3188–3190; d) A. Tulinsky, J. H. van - den Hende, *J. Am. Chem. Soc.* **1967**, *89*, 2905–2911.

[153] a) U. Hornemann, M. J. Aikman, *J. Chem. Soc. Chem. Commun.* **1973**, 88–89; b) U. Hornemann, J. P. Kehrer, C. S. Nunez, R. L. Ranieri, *J. Am. Chem. Soc.* **1974**, *96*, 320–322.

[154] N. Hirayama, K. Shirahata, *Acta. Crystallogr. Sect. B* **1987**, *43*, 555–559.

[155] For a detailed account of the British–American penicillin project, see: *The Chemistry of Penicillin* (Eds.: H. T. Clarke, J. R. Johnson, R. Robinson), Princeton University Press, Princeton, **1949**, p. 1094.

[156] Interestingly, two attempts to synthesize penicillin from compounds of type **46** and **47** did lead to miniscule amounts of the natural product through an unanticipated rearrangement. However, the yield was too low for this method to replace fermentation as the primary source of the penicillin during the war.

[157] J. W. Lown, C. C. Hanstock, *J. Am. Chem. Soc.* **1982**, *104*, 3213–3214.

[158] a) M. Onda, Y. Konda, A. Hatano, T. Hata, S. Ômura, *J. Am. Chem. Soc.* **1983**, *105*, 6311–6312; b) M. Onda, Y. Konda, A. Hatano, T. Hata, S. Ômura, *Chem. Pharm. Bull.* **1984**, *32*, 2995–3002.

[159] M. E. Salvati, E. J. Moran, R. W. Armstrong, *Tetrahedron Lett.* **1992**, *33*, 3711–3714. These researchers were also the first to recognize problems with the molecular formula proposed earlier for carzinophilin (see: P. England, K. H. Chun, E. J. Moran, R. W. Armstrong, *Tetrahedron Lett.* **1990**, *31*, 2669–2672; E. J. Moran, R. W. Armstrong, *Tetrahedron Lett.* **1991**, *32*, 3807–3810) and to recognize that carzinophilin is identical to azinomycin B, a compound isolated a few years earlier but thought, at the time, to have a different molecular formula: a) K. Nagaoka, M. Matsumoto, J. Oono, K. Yokoi, S. Ishizeki, T. Nakashima, *J. Antibiot.* **1986**, *39*, 1527–1532; b) K. Yokoi, K. Nagaoka, T. Nakashima, *Chem. Pharm. Bull.* **1986**, *34*, 4554–4561.

[160] For the total synthesis of azinomycin A, see: R. S. Coleman, J. Li, A. Navarro, *Angew. Chem.* **2001**, *113*, 1786–1789; *Angew. Chem. Int. Ed.* **2001**, *40*, 1736–1739; for the most advanced synthetic studies towards azinomycin B/carzinophilin, see: M. Hashimoto, M. Matsumoto, S. Terashima, *Tetrahedron* **2003**, *59*, 3019–3040 and ensuing publications in this series.

[161] P. R. Zanno, I. Miura, K. Nakanishi, D. L. Elder, *J. Am. Chem. Soc.* **1975**, *97*, 1975–1977.

[162] J. N. Hilton, H. B. Broughton, S. V. Ley, Z. Lidert, E. D. Morgan, H. S. Rzepa, R. N. Sheppard, *J. Chem. Soc. Chem. Commun.* **1985**, 968–971.

[163] a) H. B. Broughton, S. V. Ley, A. M. Z. Slawin, D. J. Williams, E. D. Morgan, *J. Chem. Soc. Chem. Commun.* **1986**, 46–47; b) W. Kraus, M. Bokel, A. Klenk, H. Pöhnl, *Tetrahedron Lett.* **1985**, *26*, 6435–6438; for the full account of these final structural investigations, see: c) D. A. H. Taylor, *Tetrahedron* **1987**, *43*, 2779–2787; d) C. J. Turner, M. S. Tempesta, R. B. Taylor, M. G. Zagorski, J. S. Termini, D. R. Schroeder, K. Nakanishi, *Tetrahedron* **1987**, *43*, 2789–2803; e) J. N. Bilton, H. B. Broughton, P. S. Jones, S. V. Ley, Z. Lidert, E. D. Morgan, H. S. Rzepa, R. N. Sheppard, A. M. Z. Slawin, D. J. Williams, *Tetrahedron* **1987**, *43*, 2805–2815; f) W. Kraus, M. Bokel, A. Bruhn, R. Cramer, I. Klaiber, A. Klenk, G. Nagl, H. Pöhnl, H. Sadlo, B. Vogler, *Tetrahedron* **1987**, *43*, 2817–2830.

[164] For reviews on synthetic work towards azadirachtin, see: a) S. V. Ley, A. A. Denholm, A. Wood, *Nat. Prod. Rep.* **1993**, *10*, 109–157; b) S. V. Ley, *Pure Appl. Chem.* **1994**, *66*, 2099–2102; for our own work towards this target, see: c) K. C. Nicolaou, M. Follmann, A. J. Roecker, K. W. Hunt, *Angew. Chem.* **2002**, *114*, 2207–2210; *Angew. Chem. Int. Ed.* **2002**, *41*, 2103–2106; d) K. C. Nicolaou, A. J. Roecker, M. Follmann, R. Baati, *Angew. Chem.* **2002**, *114*, 2211–2214; *Angew. Chem. Int. Ed.* **2002**, *41*, 2107–2110; e) K. C. Nicolaou, A. J. Roecker, H. Monenschein, P. Guntupalli, M. Follmann, *Angew. Chem.* **2003**, *115*, 3765–3770; *Angew. Chem. Int. Ed.* **2003**, *42*, 3637–3642.

[165] N. Takeuchi, T. Fujita, K. Goto, N. Morisaki, N. Osone, K. Tobinaga, *Chem. Pharm. Bull.* **1993**, *41*, 923–925.

[166] D. P. Piet, R. V. A. Orru, L. H. D. Jenniskens, C. van de Haar, T. A. van Beek, M. C. R. Franssen, J. B. P. A. Wijnberg, A. de Groot, *Chem. Pharm. Bull.* **1996**, *44*, 1400–1403. Prior to the publication of this article, the isolation group had reported a total synthesis of dictamnol that verified the originally proposed structure. Their synthesis had indeed provided synthetic dictamnol, but only because their use of the strongly acidic Jones reagent caused epimerization at one bridgehead carbon atom to produce the required *trans*-fused hydroazulene system of the revised structure: T. Koike, K. Yamazaki, N. Fukumoto, K. Yashiro, N. Takeuchi, S. Tobinaga, *Chem. Pharm. Bull.* **1996**, *44*, 646–652.

[167] For other total syntheses of dictamnol, see: a) G. L. Lange, A. Merica, M. Chimanikire, *Tetrahedron Lett.* **1997**, *38*, 6371–6374; b) G. L. Lange, C. Gottardo, A. Merica, *J. Org. Chem.* **1999**, *64*, 6738–6744; c) P. A. Wender, M. Fuji, C. O. Husfeld, J. A. Love, *Org. Lett.* **1999**, *1*, 137–139.

[168] J. Chan, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 11514–11515.

[169] Y. Nihashi, C.-H. Lim, C. Tanaka, H. Miyagawa, T. Ueno, *Biosci. Biotechnol. Biochem.* **2002**, *66*, 685–688.

[170] a) M. Oka, S. Iimura, Y. Narita, T. Furumai, M. Konishi, T. Oki, Q. Gao, H. Kakisawa, *J. Org. Chem.* **1993**, *58*, 1875–1881; b) S. Iimura, M. Oka, Y. Narita, M. Konishi, H. Kakisawa, Q. Gao, T. Oki, *Tetrahedron Lett.* **1993**, *34*, 493–496.

[171] a) A. G. Myers, M. Siu, F. Ren, *J. Am. Chem. Soc.* **2002**, *124*, 4230 – 4232; for other total syntheses of terpestacin, see: b) K. Tatsuta, N. Masuda, H. Nishida, *Tetrahedron Lett.* **1998**, *39*, 83 – 86; c) K. Tatsuta, N. Masuda, *J. Antibiot.* **1998**, *51*, 602 – 606; the latter synthesis suffered from the same problem with the optical-rotation measurement.

[172] N. Lindquist, W. Fenical, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 2303 – 2304.

[173] For highlights of previous synthetic studies towards the diazonamides, see: a) V. Wittmann, *Nachr. Chem.* **2002**, *50*, 477 – 482; b) T. Ritter, E. M. Carreira, *Angew. Chem.* **2002**, *114*, 2601 – 2606; *Angew. Chem. Int. Ed.* **2002**, *41*, 2489 – 2495.

[174] a) K. C. Nicolaou, S. A. Snyder, K. B. Simonsen, A. E. Koumbis, *Angew. Chem.* **2000**, *112*, 3615 – 3620; *Angew. Chem. Int. Ed.* **2000**, *39*, 3473 – 3478; b) K. C. Nicolaou, X. Huang, N. Giuseppone, P. Bheema Rao, M. Bella, M. V. Reddy, S. A. Snyder, *Angew. Chem.* **2001**, *113*, 4841 – 4845; *Angew. Chem. Int. Ed.* **2001**, *40*, 4705 – 4709.

[175] a) J. Li, S. Jeong, L. Esser, P. G. Harran, *Angew. Chem.* **2001**, *113*, 4901 – 4906; *Angew. Chem. Int. Ed.* **2001**, *40*, 4765 – 4770; b) J. Li, A. W. G. Burgett, L. Esser, C. Amezcua, P. G. Harran, *Angew. Chem.* **2001**, *113*, 4906 – 4909; *Angew. Chem. Int. Ed.* **2001**, *40*, 4770 – 4773.

[176] K. C. Nicolaou, M. Bella, D. Y.-K. Chen, X. Huang, T. Ling, S. A. Snyder, *Angew. Chem.* **2002**, *114*, 3645 – 3649; *Angew. Chem. Int. Ed.* **2002**, *41*, 3495 – 3499.

[177] K. C. Nicolaou, P. Bheema Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y.-K. Chen, S. A. Snyder, *Angew. Chem.* **2003**, *115*, 1795 – 1800; *Angew. Chem. Int. Ed.* **2003**, *42*, 1753 – 1758.

[178] For a review of these two syntheses, see: K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II: More Targets, Strategies, Methods*, Wiley-VCH, Weinheim, **2003**, chap. 20, p. 639; for the full account of our efforts towards diazonamide A, see: a) K. C. Nicolaou, S. A. Snyder, X. Huang, K. B. Simonsen, A. E. Koumbis, A. Bigot, *J. Am. Chem. Soc.* **2004**, *126*, 10162–10173; b) K. C. Nicolaou, S. A. Snyder, N. Giuseppone, X. Huang, M. Bella, M. V. Reddy, P. Bheema Rao, A. E. Koumbis, P. Giannakakou, A. O'Brate, *J. Am. Chem. Soc.* **2004**, *126*, 10174 – 10182; c) K. C. Nicolaou, D. Y.-K. Chen, X. Huang, T. Ling, M. Bella, S. A. Snyder, *J. Am. Chem. Soc.* **2004**, *126*, 12888 – 12896; d) K. C. Nicolaou, J. Hao, M. V. Reddy, P. Bheema Rao, G. Rassias, S. A. Snyder, X. Huang, D. Y.-K. Chen, W. E. Brenzovich, N. Giuseppone, P. Giannakakou, A. O'Brate, *J. Am. Chem. Soc.* **2004**, *126*, 12897 – 12906.

[179] A third total synthesis of diazonamide A was recently completed by the Harran group: A. W. G. Burgett, Q. Li, Q. Wei, P. G. Harran, *Angew. Chem.* **2003**, *115*, 5111 – 5116; *Angew. Chem. Int. Ed.* **2003**, *42*, 4961 – 4966.

[180] K. C. Nicolaou, S. A. Snyder, A. Bigot, J. A. Pfefferkorn, *Angew. Chem.* **2000**, *112*, 1135 – 1138; *Angew. Chem. Int. Ed.* **2000**, *39*, 1093 – 1096.

[181] K. C. Nicolaou, A. E. Koumbis, S. A. Snyder, K. B. Simonsen, *Angew. Chem.* **2000**, *112*, 2629 – 2633; *Angew. Chem. Int. Ed.* **2000**, *39*, 2529 – 2533.

[182] a) K. C. Nicolaou, X. Huang, S. A. Snyder, P. Bheema Rao, M. Bella, M. V. Reddy, *Angew. Chem.* **2002**, *114*, 862 – 866; *Angew. Chem. Int. Ed.* **2002**, *41*, 834 – 838; b) K. C. Nicolaou, D. A. Longbottom, S. A. Snyder, A. Z. Nalbandian, X. Huang, *Angew. Chem.* **2002**, *114*, 4022 – 4026; *Angew. Chem. Int. Ed.* **2002**, *41*, 3866 – 3870; c) K. C. Nicolaou, S. A. Snyder, A. Z. Nalbandian, D. A. Longbottom, *J. Am. Chem. Soc.* **2004**, *126*, 6234 – 6235; for the full account of this work, see: d) K. C. Nicolaou, S. A. Snyder, D. A. Longbottom, A. Z. Nalbandian, X. Huang, *Chem. Eur. J.* **2004**, *10*, 5581 – 5606.

[183] M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke, T. Yasumoto, *J. Am. Chem. Soc.* **1998**, *120*, 9967 – 9968; for the later isolation of some structurally related compounds, see: K. Ofuji, M. Satake, T. McMahon, K. J. James, H. Naoki, Y. Oshima, T. Yasumoto, *Biosci. Biotechnol. Biochem.* **2001**, *65*, 740 – 742.

[184] a) R. G. Carter, D. J. Weldon, *Org. Lett.* **2000**, *2*, 3913 – 3916; b) J. Aiguade, J. Hao, C. J. Forsyth, *Tetrahedron Lett.* **2001**, *42*, 817 – 820; c) J. Hao, J. Aiguade, C. J. Forsyth, *Tetrahedron Lett.* **2001**, *42*, 821 – 824; d) A. B. Dounay, C. J. Forsyth, *Org. Lett.* **2001**, *3*, 975 – 978; e) J. Aiguade, J. Hao, C. J. Forsyth, *Org. Lett.* **2001**, *3*, 979 – 982; f) C. J. Forsyth, J. Hao, J. Aiguade, *Angew. Chem.* **2001**, *113*, 3775 – 3779; *Angew. Chem. Int. Ed.* **2001**, *40*, 3663 – 3667.

[185] a) K. C. Nicolaou, P. M. Pihko, N. Diedrichs, N. Zou, F. Bernal, *Angew. Chem.* **2001**, *113*, 1302 – 1305; *Angew. Chem. Int. Ed.* **2001**, *40*, 1262 – 1265; b) K. C. Nicolaou, W. Qian, F. Bernal, N. Uesaka, P. M. Pihko, J. Hinrichs, *Angew. Chem.* **2001**, *113*, 3775 – 3779; *Angew. Chem. Int. Ed.* **2001**, *40*, 4068 – 4071.

[186] a) K. C. Nicolaou, Y. Li, N. Uesaka, T. V. Koftis, S. Vyskocil, T. Ling, M. Govindasamy, W. Qian, F. Bernal, D. Y.-K. Chen, *Angew. Chem.* **2003**, *115*, 3771 – 3776; *Angew. Chem. Int. Ed.* **2003**, *42*, 3643 – 3648; b) K. C. Nicolaou, D. Y.-K. Chen, Y. Li, W. Qian, T. Ling, S. Vyskocil, T. V. Koftis, M. Govindasamy, N. Uesaka, *Angew. Chem.* **2003**, *115*, 3777 – 3781; *Angew. Chem. Int. Ed.* **2003**, *42*, 3649 – 3653.

[187] a) K. C. Nicolaou, S. Vyskocil, T. V. Koftis, Y. M. A. Yamada, T. Ling, D. Y.-K. Chen, W. Tang, G. Petrovic, M. Frederick, Y. Li, M. Satake, *Angew. Chem.* **2004**, *116*, 4412 – 4418; *Angew. Chem. Int. Ed.* **2004**, *43*, 4312 – 4318; b) K. C. Nicolaou, T. V. Koftis, S. Vyskocil, G. Petrovic, T. Ling, Y. M. A. Yamada, T. Ling, W. Tang, M. Frederick, *Angew. Chem.* **2004**, *116*, 4418 – 4424; *Angew. Chem. Int. Ed.* **2004**, *43*, 4318 – 4324.

[188] C. Hopmann, D. J. Faulkner, *Tetrahedron Lett.* **1997**, *38*, 169 – 170.

[189] For a recent review on the types of discoveries that can emanate from programs in total synthesis, see: K. C. Nicolaou, S. A. Snyder, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 11929-11936.

[190] Note added in proof (17 January 2005): Since the submission of this Review, a number of additional structural revisions of natural products have been reported. Most involve stereochemical misassignments, but several are more profound. Rather than cite these works (as there are many), we suggest using a search engine such as SciFinder with terms such as "misassigned structure", "revised structure", and "structural revision" if you wish to explore this area further. Should a future review on this subject appear from other authors, hopefully these examples, as well as others not expounded upon here, will be presented in more detail.