The Synthetic Route to a Target Molecule

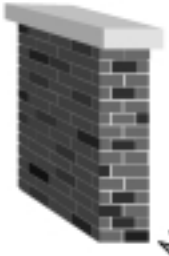
The Planning

Starting Materials ← **Target Molecule**

The Reality

Dead End

Starting Materials ↷ Advanced Intermediate ↷



~~**Target Molecule**~~

A failed key step

Starting Materials ↷ Advanced Intermediate ↷

Needful Knowledge

↷ More and More Steps ↷

Bulls-Eye! (Finally...)

Dead Ends and Detours En Route to Total Syntheses of the 1990s**

Miguel A. Sierra* and Maria C. de la Torre

From the very beginning organic chemistry and total synthesis have been intimately joined. In fact, one of the first things that freshmen in organic chemistry learn is how to join two molecules together to obtain a more complex one. Of course they still have a long way to go to become fully mature synthetic chemists, but they must have the primary instinct to build molecules, as synthesis is the essence of organic chemistry. With the different points of view that actually coexist in the chemical community about the maturity of the science (art, or both) of organic synthesis, it is clear that nowadays we know how to make almost all of the most complex molecules ever isolated. The primary question is how easy is it to accomplish? For the readers of papers describing the total synthesis of either simple or complex molecules, it appears that the routes followed are, most of the time, smooth and free of troubles. The synthetic scheme written on paper is, apparently, done in the laboratory with few, if any, modifications and these, essentially, seem to be based on finding the optimal experimental conditions to effect the desired reaction. Failures in the planned synthetic scheme to achieve the goal, detours imposed by unexpected reactivity, or the absence of reactivity are almost never discussed, since they may diminish the value of the work reported. This review attempts to look at total synthesis from a different side; it will focus on troubles found during the synthetic work that cause detours from the original synthetic plan, or on the dead ends that eventually may force redesign. From there, the evolution from the original route to the final successful one that achieves the synthetic target will be presented. The syntheses discussed in this paper have been selected because they contain explicit information about the failures of the original synthetic plan, together with the evolution of the final route to the target molecule. Therefore, they contain a lot of useful negative information that may otherwise be lost.

Keywords: natural products · protecting groups · synthesis design · synthetic methods · total synthesis

1. Introduction

Much of the current chemical literature deals with the synthesis of organic molecules or describes the development of methodology for organic synthesis. The achievements in synthetic methodology are impressive and the most complex molecules are, in principle, accessible.[1] From the beginning of the 1990s a feeling has spread throughout the chemical community about the maturity of this branch of chemistry,[2] and today terms such as atom economy,[3] highly efficient homogeneous[4] and heterogeneous catalytic transformations,[5] combinatorial chemistry,[6] and so on, are frequently used when talking about organic synthesis.

Great optimism transpires from the chemical literature when describing how the molecules are synthesized. It seems that our ability to devise synthetic routes has become infallible, and that even the most complex target molecules are prepared without apparent effort. Is this always true? Or is a lot of effort still necessary to make every step in a multistep synthesis possible? The readers of papers that describe the preparation of organic molecules are very familiar with sentences such as "after extensive experimentation it was found, to our delight the reaction worked nicely", and other synonyms thereof. Apparently, to go into details about the failures or to discuss all the unfruitful approaches decreases the beauty of the synthetic route reported.[7] Therefore, it is not often easy to recognize when the synthesis developed as planned. In the meantime a lot of useful information may be lost.[8] The aim of this work is to look at total synthesis from a different point of view. We will focus on the detours from the original synthetic plan, the dead ends that may have arisen at

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[**] A list of abbreviations can be found at the end of the article.

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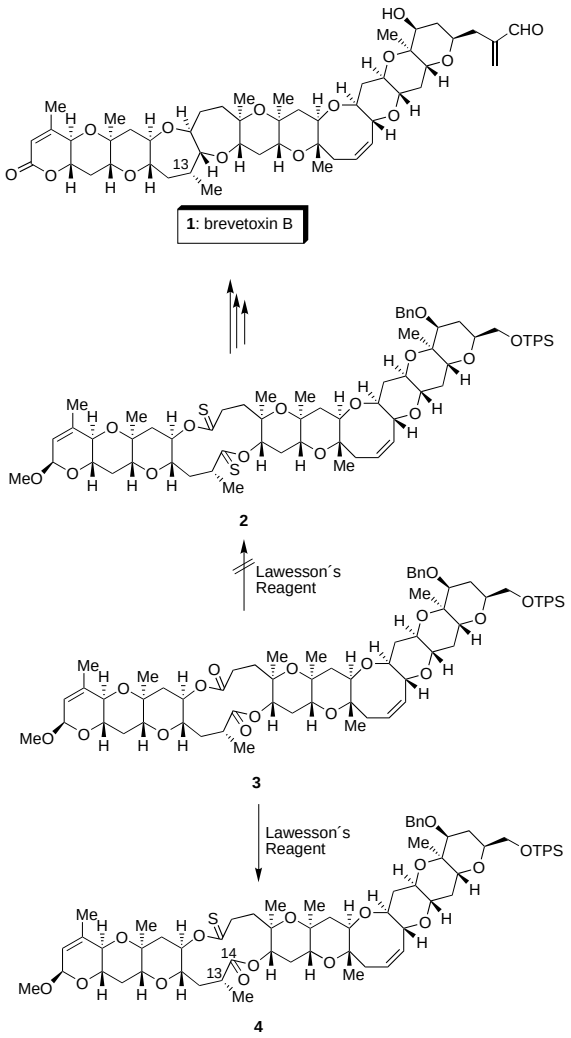
specific steps of a total synthesis, as well as the thinking involved to solve the problems en route to the synthetic goal. The final route is often at least of equal beauty to that originally planned. The selection of problems discussed below has been extracted from papers that explicitly expressed the failure of the original planning, and the evolution of the final—mainly—successful solution to the problem.

The following example displaying how the failure of a well-tested transformation can truncate a total synthesis in an advanced step, may serve to focus the aim of this review. The transannular bridging of the 12-membered bis(thiolactone) **2** was designed by Nicolaou et al. to build the remaining two rings of brevetoxin B (**1**, Scheme 1).[9] The process had been thoroughly tested[10] in model systems such as **6** (Scheme 2) and seemed to be a very attractive strategy to prepare the desired final product. However, all attempts to prepare compound **2** by reaction of the macrodilactone precursor **3** with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,2,3,4-dithiadiphosphetan-2,4-dithione)[11] produced very low yields of the desired di(thiolactone) **2**.[9] The lactone carbonyl group at C(14) remained unaltered, and the reaction product was monothiolactone **4**. Other Lawesson-like reagents were also unable to effect the transformation, and this route was eventually abandoned.[12] In spite of this apparent failure a full body of methodology to build fused seven-membered rings was developed in the process.[10] The successful synthesis of brevetoxin B by Nicolaou and co-workers is now a landmark in organic synthesis.[13]

This example shows how the failure of a single transformation can thwart a beautiful idea. In most of the cases, the nature of the trouble found in a specific synthesis may be attributable to more than one cause. The selected syntheses that follow are classified into seven different groups pertaining to the nature of the main problem found in each case.



Scheme 1. The steric hindrance of the C(13) methyl group provokes the failure of the transformation of dilactone **3** to di(thiolactone) **2**, and, hence, truncates the synthesis of brevetoxin B at an advanced stage.

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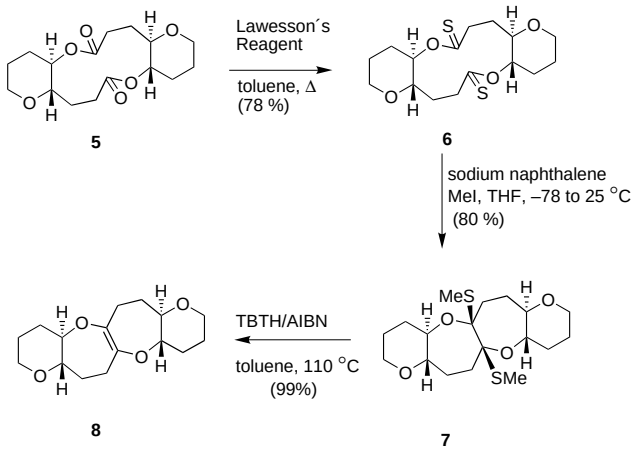


Scheme 2. Models for brevetoxin B synthesis: the efficient bridging of macro di(thiolactones) to obtain fused seven membered rings.

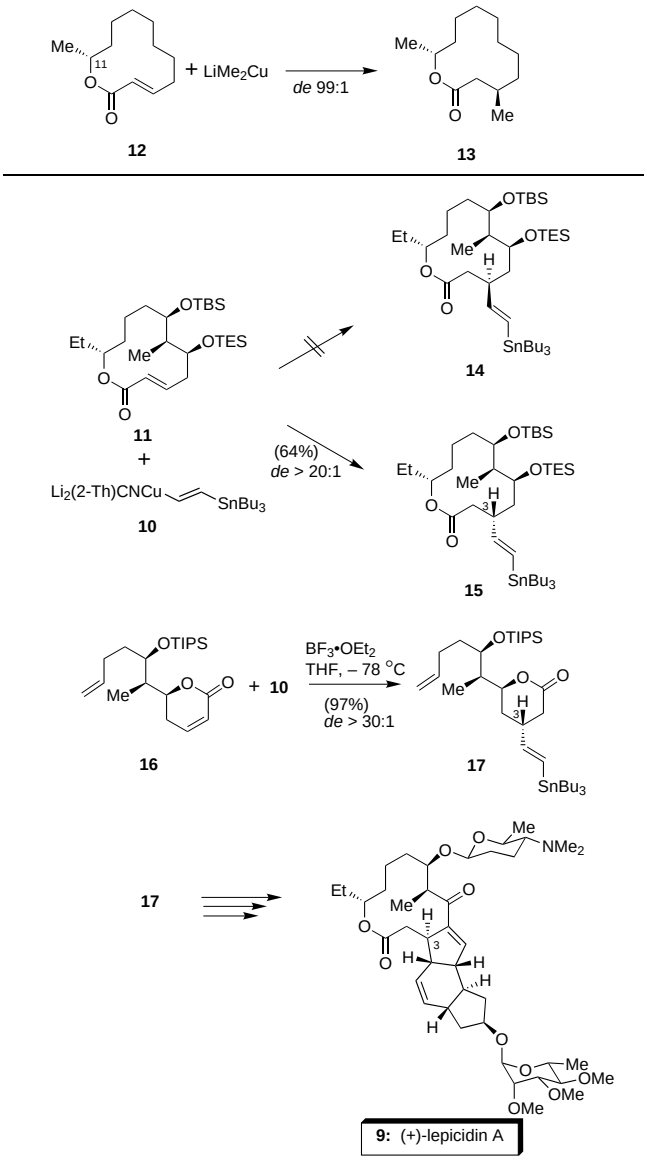
2. Working Models that do not Work

Let's consider first the use of model reactions. Their usefulness in synthetic chemistry is undoubted as demonstrated by the huge amount of work published detailing the construction of model compounds of specific molecules. Nevertheless, how applicable to the real targets are the results obtained when working with models? Thankfully for us, most of the time they are, but sometimes they are not. The synthetic plan resting on reactions that have been developed for the model compound then needs to be changed, or at least thoroughly modified, to achieve the desired result.

One troublesome situation arises when the configuration of a newly formed stereogenic center obtained in a synthetic reaction is opposite to that predicted by the results obtained previously in a suitable model system. One of these cases arose in Evans' synthesis of (+)-lepicidin A (**9**, Scheme 3).[14] An early planned route to obtain lepicidin A rested on the conjugate addition of cuprate **10** to the α,β-unsaturated lactone **11**. Previous studies carried out on macrolactone **12** as a model (which formed the Michael adduct **13** by reaction with Me_2CuLi),[15, 16] as well as computer calculations,[17] pointed to the nearly exclusive production of the desired Michael adduct **14**. However, the addition of cuprate **10** to compound **11** yielded lactone **15** with the wrong stereochemistry at C(3). Therefore, the original idea of delaying the introduction of the labile vinylstannane moiety until the later stages of the synthesis was abandoned.

In the successful approach to lepicidin A, the vinylstannane moiety was placed in the precursor **16**. Michael addition of cuprate **10** to **16** gave this time compound **17** with the desired α stereochemistry. The sensitive tin moiety had to be carried through the whole synthetic route and finally intermediate **17** was successfully converted into **9** (Scheme 3).

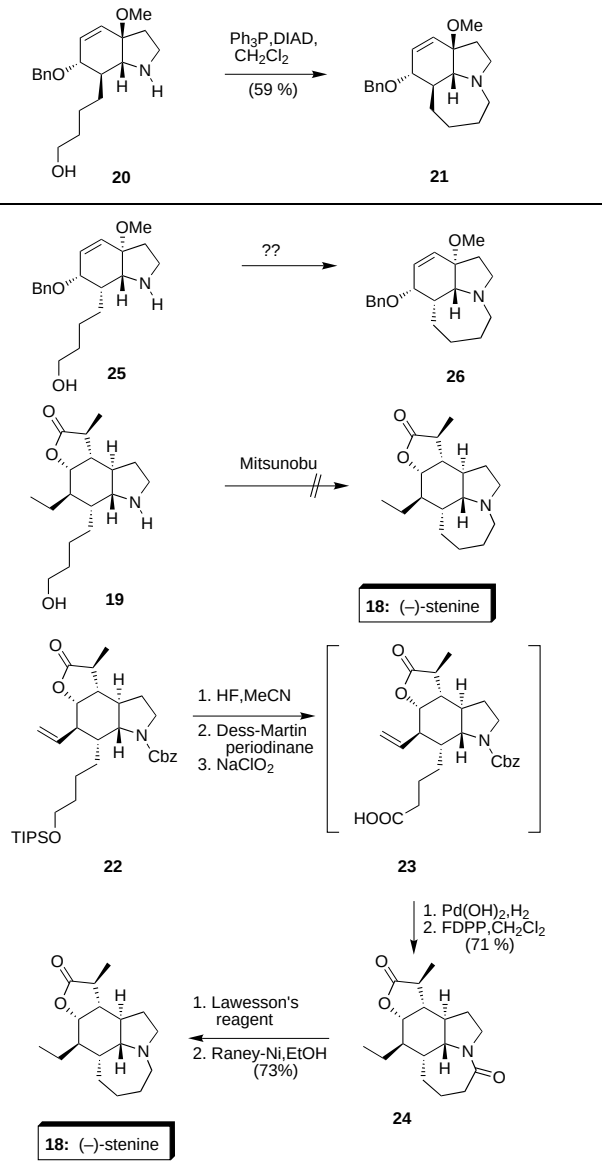
Sometimes a cyclization step works well on a compound having a structure that is reminiscent of the compound being used to access the target molecule. However, sometimes the same reaction stubbornly refuses to occur with the desired intermediate. One of these cases is found in Wipf's synthesis of (−)-stenine (**18**, Scheme 4).[18] The key step to complete the



Scheme 3. Obtaining the wrong stereochemistry with respect to the model reaction necessitates carrying a labile group from the early stages of the synthesis.

synthesis of (−)-stenine was the Mitsunobu cyclization of **19** to **18**.[19] The cyclization step worked nicely on the related model **20**. In fact, bicycle **20** yielded the tricycle **21** when submitted to the Mitsunobu reaction conditions. However, when intermediate **19** was subjected to these reaction conditions the cyclization failed. This failure was claimed to be due to the fact that formation of a medium ring by a Mitsunobu reaction strongly depends on the rate of cyclization versus side reactions of the activated alcohol. According to the authors, compound **20** is more preorganized towards the formation of the seven-membered ring than **19**. Therefore access to (−)-stenine (**18**) through a Mitsunobu cyclization was abandoned.

The desired target was reached from the doubly protected intermediate **22**. Removal of the silyl protecting group followed by sequential oxidation of the free alcohol to carboxylic acid **23**, hydrogenation of the double bond, and



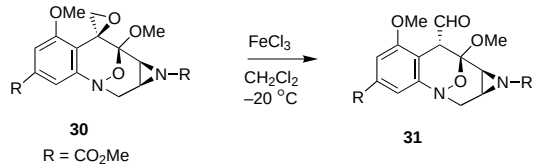
Scheme 4. Unsuccessful and successful synthesis of (−)-stenine.

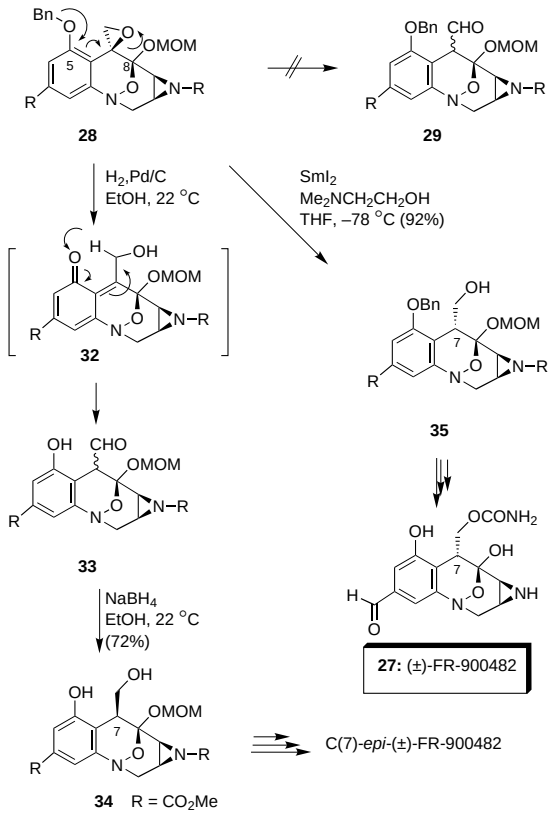
ring closure formed **24**. Finally, the two-step reduction of the amide group of **24** furnished (−)-stenine.

What have **19** and **20** in common, since they are significantly different compounds? The failure of intermediate **19** to cyclize may be attributable to reasons other than the absence of a hypothetical preorganization present in **20**. In fact, molecular mechanics analysis showed no appreciable differences between the two compounds regarding a preorganization towards cyclization.[20] The *cis-anti*-tricyclic system **21** is 7.8 kcal mol^{-1} more stable than **26**, which harbors the ring stereochemistry present in compound **18.** Perhaps the energetically more-demanding cyclization to yield the *trans-syn*-fused system present in stenine is responsible for the failure of compound **19** to cyclize under Mitsunobu conditions.

Other troublesome situations may arise when protecting groups that work well in a model can not be applied to an intermediate used in the synthesis. For example, Danishefsky's approach to (±)-FR-900482 (**27**) was designed to include the rearrangement of epoxide **28** to aldehyde **29** as a key step (Scheme 5).[21] This reaction worked efficiently in the model epoxide **30**, which smoothly rearranged to **31** in the presence of $FeCl_3$.[22] Unfortunately, all attempts to realize the analogous reaction with **28** failed to yield aldehyde **29**, and only highly complex mixtures resulted from the use of $FeCl_3$ or other mild Lewis acid catalysts. These results were explained by considering the lability of the ether functions at C(5) and C(8) on intermediate **28**. In the words of the authors "the seemingly innocuous alterations of two protecting groups resulted in a breakdown of some of the model system chemistry".

Interestingly, the lability of the benzyl ether group on **28** was actually exploited in the synthesis of (±)-FR-900482 (**27**). Hydrogenolysis of the benzyl ether group of compound **28** formed aldehyde **33** via **32**. Reduction of **33** with $NaBH_4$ afforded product **34** with a configuration of C(7)-*epi*(±)-FR-900482. Formation of compound **34** was explained by the initial formation of aldehyde **33** in the natural α-configuration

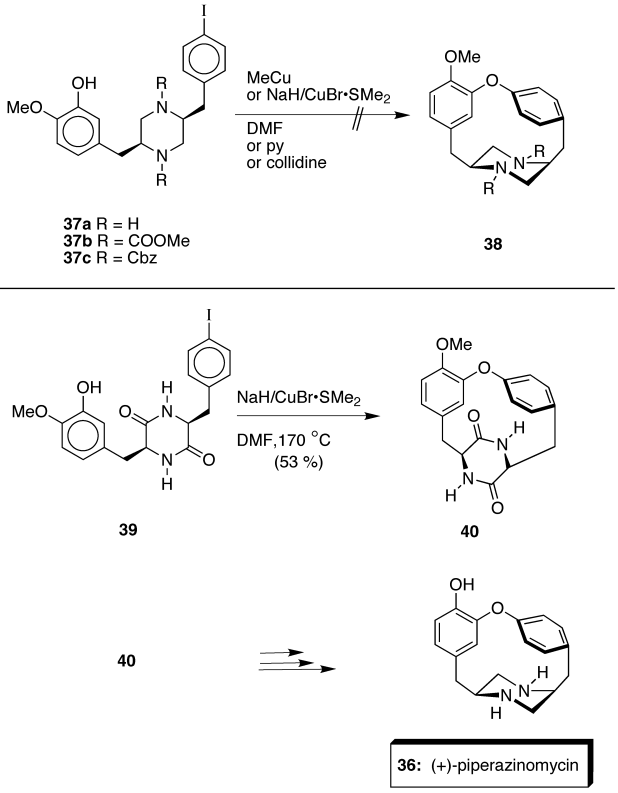




Scheme 5. The seemingly innocuous alteration of two protecting groups resulted in a breakdown of some of the chemistry used successfully in the model system. However, the chemistry learned was successfully applied to the synthesis of (±)-FR-900482 (**27**).

and its rapid epimerization to the more stable C(7)-β-series. Hence, reaction conditions were fine-tuned to effect protonation at C(7), after the opening of the epoxide from the less-hindered β-face, which led to a nonepimerizable product with the correct configuration at C(7). Treatment of compound **28** with SmI_2 afforded compound **35** in excellent yield, which fulfilled all of these stereochemical requirements, and was then transformed to **27**. This example shows how the chemistry learned from a failure can be successfully applied to a new approach to the desired target. Could the reader have known if that happened if only the final route would have been reported?

Other times the structurally closest compound to the planned intermediate does not produce satisfactory results with the desired transformation, but the desired results are obtained with a structurally distant, yet synthetically equivalent product. This situation arises quite often and may be exemplified by Boger's synthesis of (+)-piperazinomycin (**36**, Scheme 6).[23]

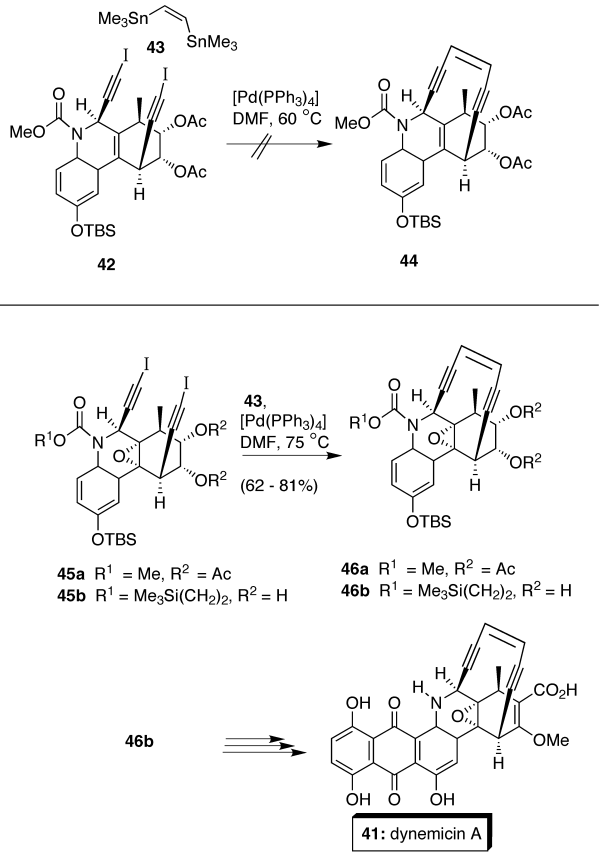


Scheme 6. How close should the model molecule be to the intermediate? For the total synthesis of (+)-piperazinomycin **36** not so close. The flattening of the six membered ring of **39** may be the key for a successful Ulmann cyclization.

Prior to the implementation of the successful cyclization reaction that ultimately leads to (+)-piperazinomycin (**36**), the cyclization of a number of compounds **37**, closely related to the natural product, were studied. The common feature of these models was the piperazine nucleus that is present in the natural product. While other molecules related to **37** but lacking the six-membered ring were cyclized with different degrees of success, compounds **37** systematically failed to produce the desired macrocycles **38**. Nevertheless, compounds **37** were potentially excellent substrates for the cyclization, as there exists no possibility for their racemization during the conditions employed to close the ring. Access to (+)-piperazinomycin (**36**) was finally gained by utilizing the diketopiperazine **39** to effect the Ullmann ring closure to give macrocycle **40**.[24] These reaction conditions were carefully optimized to minimize the racemization of substrate **39**. Reduction of the amide carbonyl groups of **39** and deprotection of the phenolic group finally afforded (+)-piperazinomycin (**36**).

The observed differences found during the cyclization step could clearly be explained by modeling compounds **37** and **39**. Both compounds must adopt a boat conformation to cyclize. This conformational switch is energetically more demanding for piperazines **37** ($E_{boat} - E_{chair} = 6.6$ kcal mol^{-1}) than for the flatter diketopiperazine **39**, for which the preferred conformation is already boatlike ($E_{boat} - E_{chair} = -0.4$ kcal mol^{-1}).

An interesting situation emerges when a reaction tested in a model system (or in an earlier precursor in a synthetic route) does not work at all, but is thereafter successfully applied to the final synthetic route. Unfortunately, it is not easy to ascertain how often this situation arises because of the lack of reported instances. Nevertheless, even against the odds and coupled with negative results from models in hand, to try a nice idea on a few milligrams of an advanced intermediate may be appealing. One of these examples is found in Danishefsky's synthesis of dynemicin A (**41**, Scheme 7).[25]



Scheme 7. When a sensitive transformation fails in an early intermediate, it may be worthwhile to try it in a more elaborate compound. The chemistry learned from the failure of the building of dienemycin A was applied to reach the target molecule.

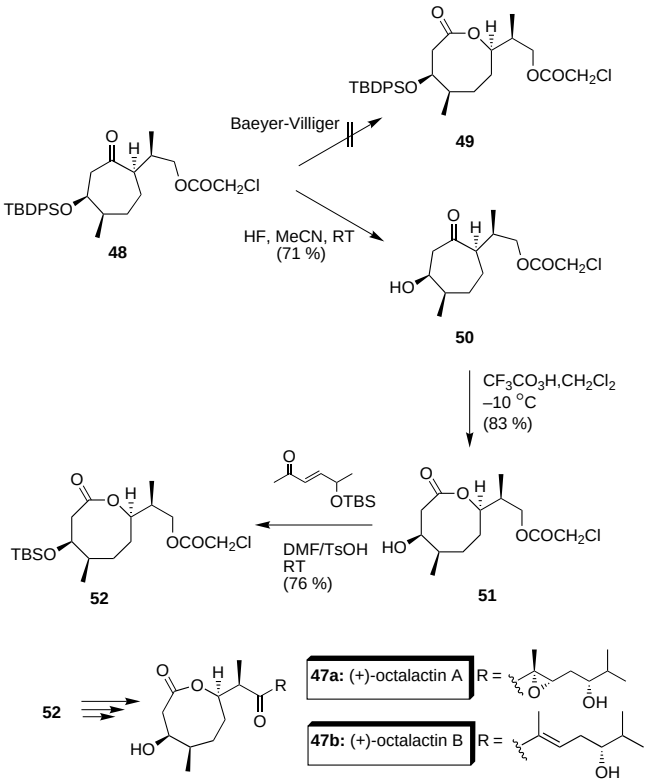
One of the most sensitive steps in the building of dynemicin A was the incorporation of the enediyne moiety characteristic of this class of compounds. This transformation was first tested on the intermediate **42**. Reaction of tricycle **42** with distannane **43** in the presence of $[Pd(PPh_3)_4]$ resulted in a detrimental and rapid cross-coupling, to give the product of two intermolecular couplings without any of the desired enediyne **44**. The reaction was tested next on compound **45a**, which had the epoxide ring of the final product in place. Reaction of **45a** with **43** in the presence of $[Pd(PPh_3)_4]$ under medium dilution conditions yielded 62 % of the enediyne **46a**. The explanation for this success was that the presence of the epoxide shortens the approach of the two ethynyl groups, while providing some relief from the projected strain in the cyclization product. The introduction of this strain may be what forces the Bergman cyclization upon epoxide opening.[26] Success of the bis-Stille cyclization step ultimately led to the total synthesis of dynemicin A from **46b.**

Evidently, the extensive use of model compounds to predict the reactivity of a complex synthetic intermediate, or the outcome of a reaction to be carried out on a densely functionalized molecule, has many other drawbacks. The few examples we have presented so far are also a brief introduction to the specific troublesome situations discussed below. The overbearing question pertaining to the huge amount of work done to synthesize models of a plethora of different kinds of molecules, often barely resembling the real target, could be: is the effort really worth it? We have selected four examples of the many possible. From the lepicidin A (**9**) and stenine (**18**) cases, it may be learned that the model and the real system have to be as similar as possible in the region of the reactive center. However, this is not the case for piperazinomycin (**36**) where the closest models (or precursors) to the target refuse to cyclize. For dynemicin A (**41**), the reaction carried out on an early intermediate in the synthetic route fails, while stepping ahead and introducing a new element of structural constraint results in success. The final conclusion is that models are useful training grounds that provide critical information before entering the real battlefield, and even when a model fails there is a lot of chemistry already done that will help to smooth the rough road ahead that leads to the target. Nevertheless, the answer to the question: What makes a model good? is, probably, to sculpt the model as similar to the real system as possible. From here the conclusion is clear, after exploring all facets of the upcoming chemistry on a model substrate, why not do the real thing?

3. Troublesome Protecting Groups

A primary necessity when planning the synthesis of any molecule is the use of protecting groups. Every freshman of organic chemistry learns that the selectivity of an organic transformation can be controlled in a molecule harboring a multitude of functional groups by selecting an appropriate protecting group. There exists a huge arsenal of protecting groups available to the synthetic chemist for almost every situation and necessity imaginable.[27] Sometimes, however, a protecting group can serve dual roles, not only does it have a protective role but it becomes a nuisance to the synthesis by either inhibiting a crucial step or refusing to be displaced when its protecting role has finished. The presence of troublesome protecting groups, even with the multitude of known alternatives, is much more habitual than would be desired.

Let us consider first the inhibition of a crucial step by the presence of a protecting group. This problem is solved by removing the protecting group and effecting the desired transformation, either with a new protecting group or with the free functional group, without significant deviations from the original planning but with additional deprotection–protection steps. Clardy's synthesis of (+)-octalactins A and B **47a–b** illustrates this point succinctly (Scheme 8).[28] The Baeyer–Villiger reaction carried on the seven-membered ring ketone **48** to form the eight-member ring lactone **49** characteristic of octalactins A and B, resulted in low conversions and substantial decomposition of the substrate.



Scheme 8. During the synthesis of octalactins A (**47a**) and B (**47b**) the TBDPS group protected not only the alcohol but the carbonyl group, thus inhibiting the Baeyer–Villiger oxidation needed to access the eight-membered ring of octalactins.

After removal of the TBDPS protecting group and treatment of the free hydroxyketone **50** with CF_3CO_3H the desired lactone **51** was obtained in 83 % yield. The free alcohol **51** was reprotected and the intermediate **52** was used to prepare octalactins A and B. Examination of the molecular models of ketone **48** clearly shows that the bulky silicon protecting group is not only protecting the hydroxyl group, but also shielding the carbonyl group by its immense steric bulk. In

fact, both faces of the carbonyl group are blocked, one by the ring and the other by both the TBDPS and the methyl groups on the side chain.

The troublesome transformation in the previous example resulted in only a minor deviation from the original planning, since it was resolved by removing the source of the problem. Nevertheless, such failed reactions consume precious material that could be further allocated to complete the synthesis. Other times it is not so simple to pass through the bottleneck caused by the presence of a stubborn protecting group that either inhibits a crucial step or switches the reaction to a different and undesired end. Now a new protecting group must be carefully selected and placed in an early intermediate and the synthesis has to be repeated in order to avoid the problematic step. Overman's synthesis of (±)-akuammicine (**53**, Scheme 9) serves as an example for both situations.[29]

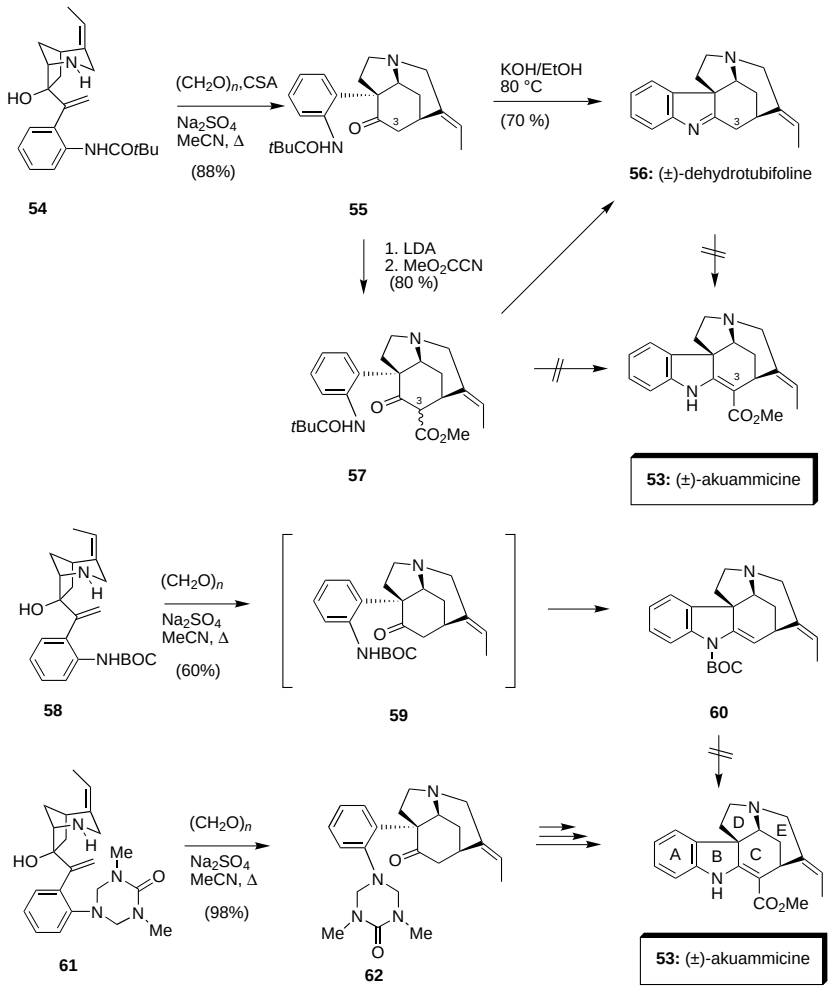
The aza-Cope-Mannich rearrangement[30] of compound **54** worked splendidly to form **55**, which was transformed to (±)-dehydrotubifoline (**56**) by base-mediated hydrolysis of the amide pivaloyl group. The transformation of **56** into (±)-akuammicine by direct acylation at C(3) was then attempted. After the diverse reaction conditions employed met with no success, the carbomethoxy group was introduced at C(3) of ketone **55** prior to ring closure. Thus, ketone **55** was acylated to yield β-keto-ester **57**. All attempts to remove the pivaloyl group from **57**, either returned **57** or led to the formation of dehydrotubifoline (**56**).

The robustness of the pivaloyl group was certainly responsible for the inability to convert **57** into akuammicine (strikingly the hydrolysis of the same group in compound **55** gave dehydrotubifoline (**56**) in 70% yield). Hence, the BOC group was chosen to protect the aromatic amine nitrogen atom, as it could be removed by mild acid treatment. Compound **58** was procured after a good number of difficulties caused by the seemingly innocuous change of a protecting group were encountered. The reaction of **58** under standard aza-Cope-Mannich conditions led not to the expected ketone **59** but instead gave the tetracyclic compound **60**. All attempts to isolate the intermediate ketone **59** were fruitless. Presumably, the formation of **60** arises from the greater nucleophilicity of the carbamate nitrogen atom on **59**, relative to the pivaloyl-protected nitrogen atom of **54** that successfully rearranged to ketone **55**.

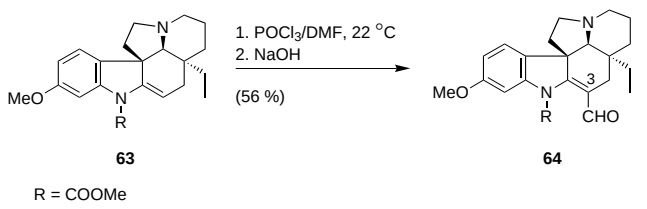
Tetracycle **60** could not be transformed to (±)-akuammicine either. In the author's words the striking difference in reactivity of BOC- and pivaloyl-protected anilines in these series "underscores the profound effects on reaction outcome that can arise from small changes in electron density". The solution (once all the chemistry above was learned) was to use a protecting group that was able to shield both amine protons. The selected group should have the considerable stability required to survive the aza-Cope-Mannich rearrangement but should also be easily removed at the end of the synthesis. The chosen group was a triazone (1,3-dimethylhexahydro-2-oxo-1,3,5-triazine), which was incorporated at the very beginning of the synthesis and carried through the complete synthetic route to the aza-Cope-Mannich precursor **61**. Intermediate **61** rearranged uneventfully to ketone **62**, which was further converted into (±)-akuammicine **53**.

The reactions shown in Scheme 9 illicit one additional intriguing question: Why couldn't enamine **56** be transformed to (±)-akuammicine? Apparently, the C(3) position is fully shielded by the adjacent bridged E ring, thus precluding any transformation at this carbon atom. In agreement with this is the fact that acylation of compound **63** to yield **64** occurred in the Aspidosperma alkaloid series which lacks the bridged E ring (Scheme 10).[31]

The occurrence of an overprotective protecting group is more frequent than one could imagine. Once the protecting group has fulfilled its role in the synthesis it has to be removed. Usually, before chosing a blocking group to protect a certain functional group, the reaction conditions to remove it

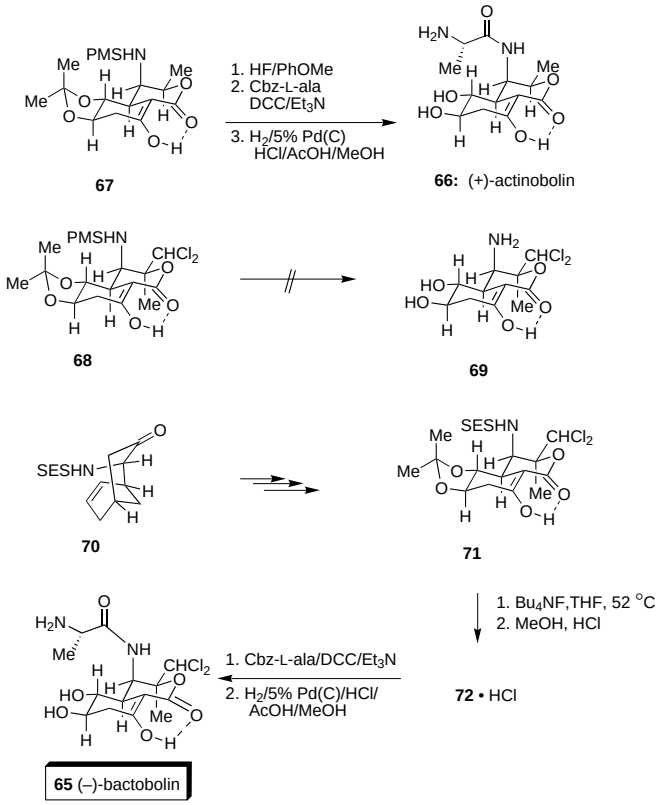


Scheme 9. The profound effects on reaction outcome that can arise from small changes in electron density, in this case changing an amide for a carbamate group, thwarted the synthesis of (±)-akuammicine in its final stages. Placing a new protecting group at the aniline nitrogen atom obliged the authors to repeat the synthetic scheme almost from the beginning.



Scheme 10. Successful formylation of **63**.

are carefully evaluated. Nevertheless, sometimes the removal of a protecting group becomes the problem step of a synthesis, which if not totally frustrating the original plan, at least forces the synthesis to be restarted from the very beginning with a new protecting strategy. Weinreb's synthesis of (−)-bactobolin (**65**) is one of such cases (Scheme 11).[32]



Scheme 11. The presence of an overprotective protecting group truncated the synthesis of (−)-bactobolin in its final stages. Once again, a new protecting group has to be placed at the very beginning of the synthesis.

The late stages of the synthesis of the closely related actinobolin **66** involved the deprotection of amide **67**. The removal of the PMS group from **67** was effected by treatment with liquid HF, which concomitantly removed the acetonide group. An analogous treatment on **68**, the immediate precursor of (−)-bactobolin, resulted in the exclusive removal of the acetonide moiety and failed to remove the PMS group. Decomposition was noted under forcing conditions. Other reaction conditions, including a variety of reductive (H_2, Pd/C, HF) or oxidative methods (LHDMS/O_2 or MoOPH) did not afford any of the desired amine. It was therefore necessary to mask the nitrogen atom in a different way and at the very beginning of the synthetic route, in this case in precursor **70**. The [β-(trimethylsilyl)ethyl]sulfonyl (SES) group was chosen this time and it was carried through the complete synthetic scheme to be finally removed from intermediate **71** by treatment with fluoride. The amino derivative **72** thus obtained was transformed into (−)-bactobolin in two steps.

The steric hindrance caused by the bulky substituents at the carbon atom contiguous to the reactive nitrogen atom, coupled with the stability of the sulfonyl protecting group may be responsible for this failure. The over-stability of the sulfonyl-protecting group was eventually overcome by the use of a β-silylethyl group.

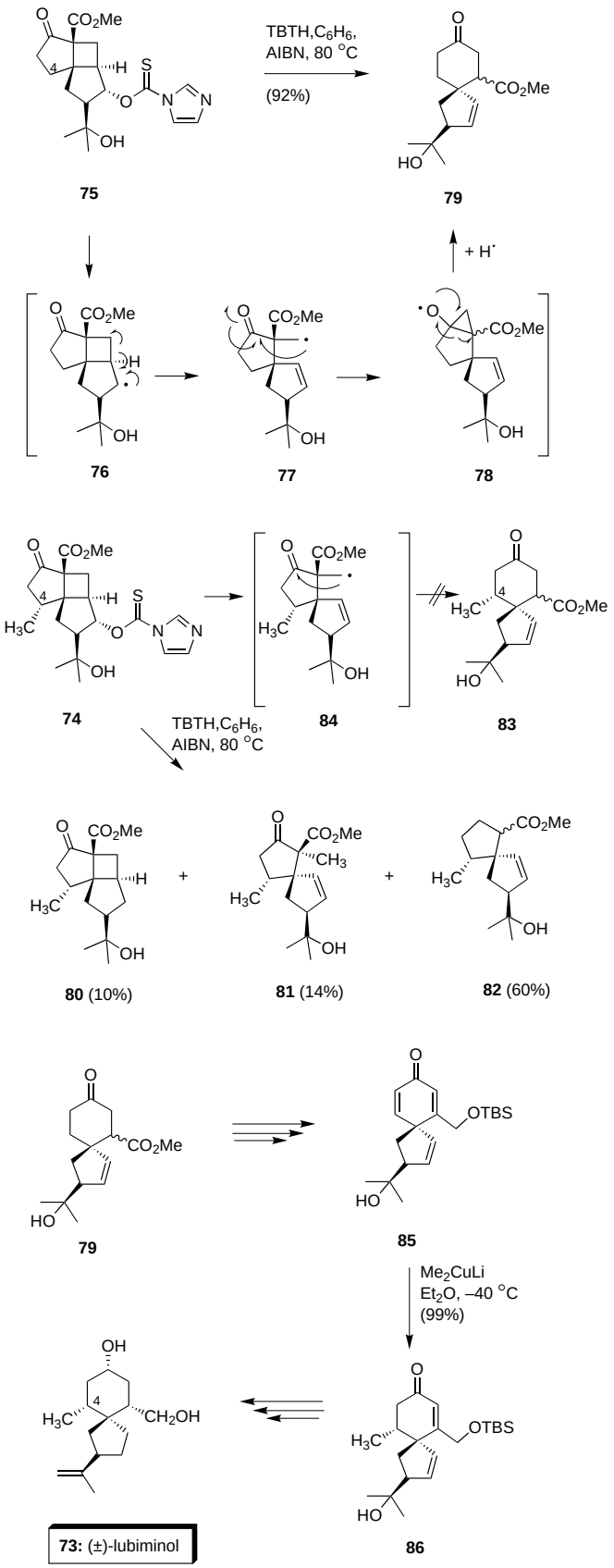
These few examples show that, even with an impressive array of very specific protecting groups in hand, things can go wrong just because a troublesome protecting group appears. Most of the time the source of the problem is easily explained, but the explanation is generally found after the trouble has truncated the designed route. Unless we understand why structurally similar compounds such as **55** and **57**, or **67** and **68** behave so differently, it will be extremely difficult to foresee troubles such as those found in the examples presented.

4. The Unexpected Influence of Remote Substituents

During the designing stages of the synthesis of a target molecule (not necessarily a complex one) the chemist studies the transformations needed to reach the desired target. Retrosynthetic analysis often gives more than one alternative to achieve an specific transformation.[33] The individual steps are studied and a sketch of the work to be done is produced. The crucial steps are carefully and critically evaluated, in many cases thoroughly tested in models and, except for those syntheses done to probe the efficiency of a new synthetic procedure, well established synthetic transformations are generally chosen. Sometimes, however, an extensively tested transformation fails in an advanced intermediate because of the presence of an offending remote substituent. Crimmins' synthesis of (±)-lubiminol (**73**) is one of these cases (Scheme 12).[34]

Compound **74** has all the carbon atoms required for the target molecule and the synthesis of lubiminol seemed to be in hand. The projected radical rearrangement to access lubiminol (**73**) worked very efficiently on compound **75**, wich lacked the C(4) methyl group. Thus, heating **75** in the presence of TBTH/AIBN induces the formation of radical **76**, which evolves by regioselective fragmentation of the cyclobutane ring to give the new radical **77**. Intermediate **77** undergoes a Dowd–Beckwith-type ring expansion[35] to produce the spirofused intermediate **78**. Compound **79** is obtained by fragmentation of the cyclopropyl ring and hydrogen abstraction. However, heating alcohol **74** resulted in the isolation of a mixture of three products **80**–**82**, none of them being the desired rearranged product **83**.

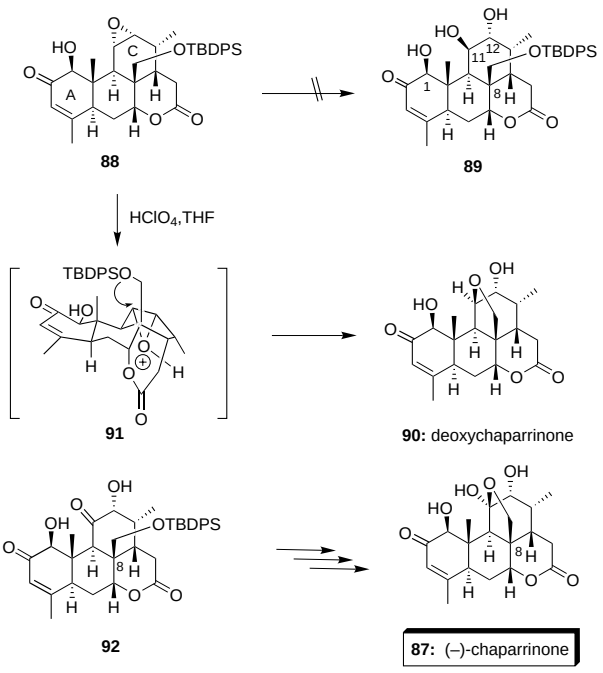
The failure of radical intermediate **84** to undergo the rearrangement to **83** is apparently because of the highly congested transition state necessary for the addition of the



Scheme 12. The dramatic effect of a remote, and in principle innocuous, methyl group inhibits the key Dowd–Beckwith rearrangement designed to access the spirocyclic structure of (±)-lubiminol (**73**). A longer route to introduce the problematic methyl group once the key rearrangement had occurred was used.

primary radical in intermediate **84** to the adjacent carbonyl group in the Dowd–Beckwith rearrangement.[35] The 1,3-relationship of the primary radical with the α-C(4) methyl group on intermediate **84** may either sterically prohibit the addition to the carbonyl group or promote a hydrogen-atom transfer from the α-methyl group. Compound **80** would be formed by hydrogen capture by the radical derived from **74** prior to fragmentation of the cyclobutane ring, while radical **84** would lead to **81** by hydrogen capture and to **82** by decarbonylation. This failure forced the incorporation of a methyl group on trienone **85** once the rearrangement had occurred, and resulted in a considerable lengthening of the synthesis.

The syntheses of (±)-lubiminol (**73**) is an example in which a group inhibits the desired transformation by imposing several restrictions to the transition states involved, mainly by steric means which may or may not be predicted a priori. A different situation is encountered when the desired transformation is inhibited by the presence of a chemically active group. This problem is found in Grieco's synthesis of (−)-chaparrinone (**87**, Scheme 13).[36]

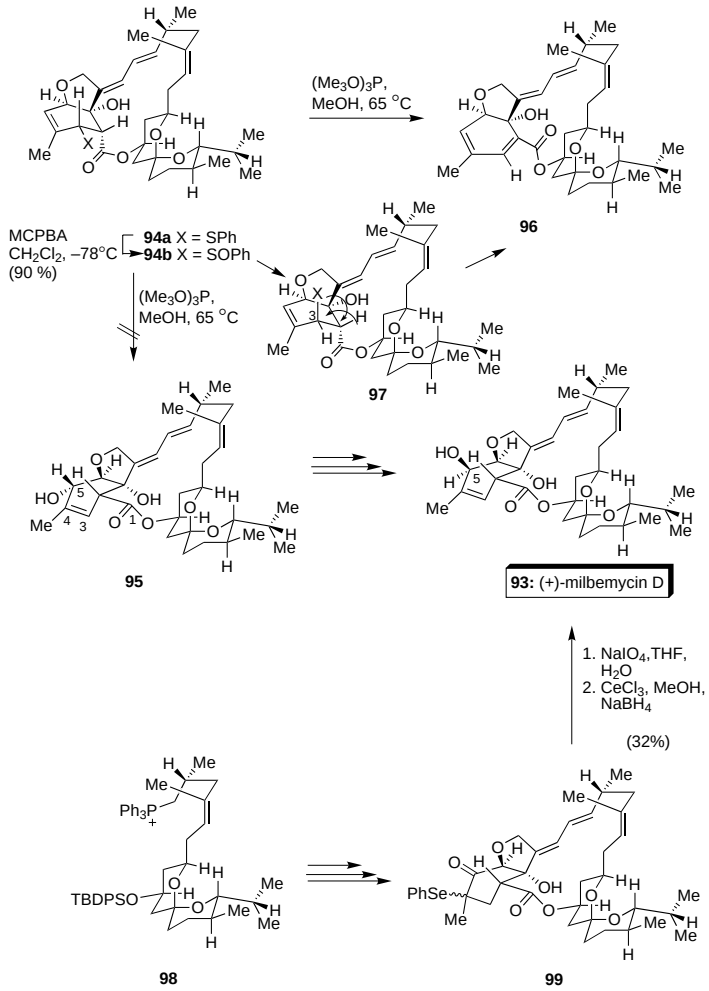


Scheme 13. The straightforward transformation of epoxide **88** to triol **89** was truncated because the protected hydroxymethyl group and the oxirane ring are nicely set up to react intramolecularly and yield deoxychaparrinone (**90**). Changes in the alcohol protecting group were useless. A completely different strategy was needed to reach (−)-chaparrinone (**87**).

The transformation of epoxide **88** to (−)-chaparrinone by replacing the ring C hemiketal array appeared to be a straightforward exercise. It was anticipated that an acid-catalyzed opening of the epoxide ring would generate triol **89**. The functionality present in ring A was expected to withstand the strongly acidic conditions required to effect an opening of the epoxide ring, because of the results obtained during the synthesis of the related compound klaineanone.[37] Selective protection of the C(1) and C(12) hydroxyl groups in **89**,

followed by oxidation of the remaining C(11) hydroxyl and subsequent global deprotection would provide access to (−)-chaparrinone. However, treatment of **88** with $HClO_4$ yielded exclusively deoxychaparrinone **90**. This compound arose from the acid-catalyzed intramolecular epoxide opening by the alcohol group on C(8), since the structure of the plausible intermediate **91** is nicely set up for this transformation. Neither changing the protecting group on the hydroxymethyl group at C(8), nor the preparation of the β-epoxide analogous to **88** proved to be successful. An alternative access to (−)-chaparrinone was developed by attaching the ring A 1β-hydroxy-2-oxo-Δ^3 olefin unit onto a substrate having a fully functionalized, protected ring C. This task was achieved from tetracycle **92**, obtained through a sequence of steps conceptually different from those first attempted.

One final example for this chapter is found in Crimmins' synthesis of (+)-milbemycin D (**93**).[38] This time the problem appeared at the very final stages of the synthesis with the full carbon skeleton of the target molecule prepared, and resulted in a regrouping to an early precursor. The completion of the synthesis from intermediate **94** to **93** seemed imminent (Scheme 14). Only rearrangement of the allylic sulfide **94a** via the sulfoxide **94b** and inversion of the resultant C(5) hydroxyl group in **95** remained to be done. Selective oxidation of sulfide **94a** to sulfoxide **94b** was uneventful. However, treatment of **94b** by heating with $(MeO)_3P$ produced elimination leading to diene **96** rather than the desired [2,3] sigmatropic rearrangement product **95**. The explanation for this behavior was that the equatorial disposition of the phenylsulfinyl group in **94b** and the fact that the macrolactone ring was closed, apparently slowed down the allylic rearrangement to the point where competitive epimerization of either the C(2) or C(3) stereocenters was faster than the [2,3] sigmatropic rearrangement. Epimerization of C(2) or C(3) results in an intermediate having a *syn* relationship between the phenylsulfinyl group and the C(2) hydrogen atom, thereby allowing thermal elimination to occur.



Scheme 14. The approach to (+)-milbemycin D was in hand. However, sulfoxide **94b** undergoes elimination to yield **96** rather than the desired [2,3] sigmatropic rearrangement to **95**. This causes a dead end and the synthesis was redesigned to avoid the formation of the cyclic diene moieties as in compound **96**.

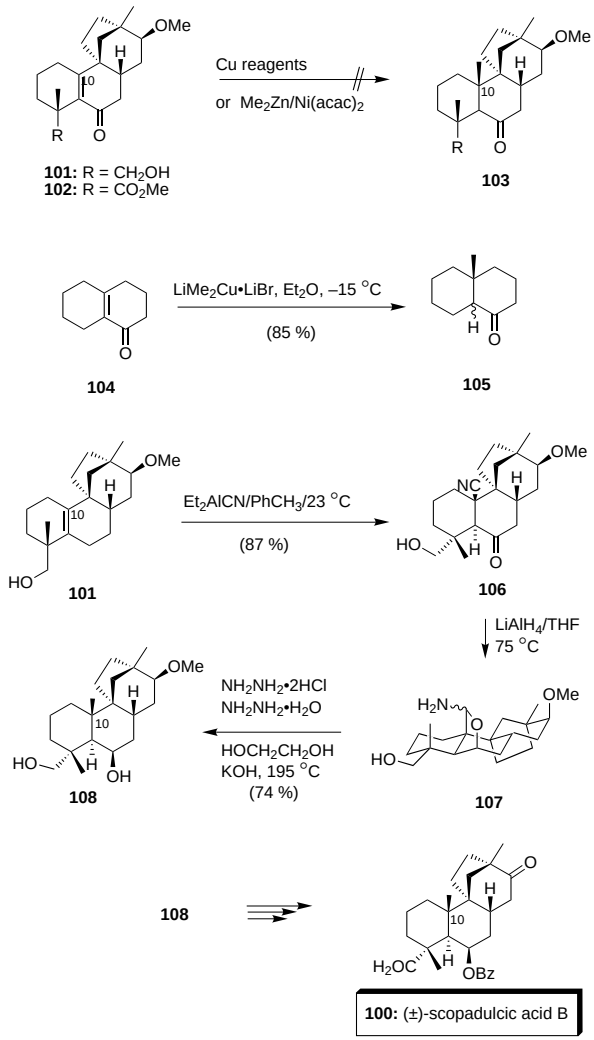
The alternative, and finally successful route to (+)-milbemycin D (**93**) involved the removal of the alkene present in the six-membered ring of **94** to avoid the elimination problems. The C(3)-C(4) olefin was then introduced at the end of the synthesis through selenylation and elimination on the α-position of ketone **99**. The early intermediate **98** was sequentially converted into product **99**, which lacked the troublesome double bond. The olefin functionality and the hydroxyl-bearing stereocenter at C(5) were appended onto **99** to accomplish the total synthesis of **93**.

Evidently a larger number of examples focusing on different drawbacks of the synthetic plans caused by remote substituents may be recorded. The point is that the problems associated with the interference of a remote substituent on a desired transformation still occur. As the complexity of intermediates increases, the number of variables involved in a simple transformation grows exponentially making predictions complicated. The fact that such variables can be minimized demonstrates how predictable modern organic synthesis can be nowadays. It is clear that the ability to devise alternative routes to circumvent the failed transformation and to resolve the specific problem found in the synthetic plan are symptomatic of the maturity of the synthetic science. On the other hand, the lack of predictability in so many cases and the very empirical nature of synthetic chemistry implies that the science is not fully developed.

5. The Elusive Side Chain

Many synthetic routes are designed to build the fully functionalized, fully protected main carbon skeleton of a target product. To complete the synthesis a side chain of a few carbon atoms (as few as one) may remain to be included at a late stage. How easy it is to join these "harmless" side chains to the main body of the target molecule? Apparently it should be pretty easy, as very few comments about this question are found in the papers that deal with total synthesis. However, when the matter is considered in depth, it seems that this is not always the case. The three following examples are cases in which the formidable task of building the more complicated features of the target molecule have already been achieved, but gaining access to the final product is lengthened by the incorporation of a side chain.

The preparation of (±)-scopadulcic acid B (**100**) by Overman is a good example of how difficult the joining of a methyl group to a preformed skeleton can be.[39] The intermediate **101** required just the development of the remaining quaternary center at C(10), to access to the full carbon skeleton of scopadulcic acid B (Scheme 15). This functionalization was

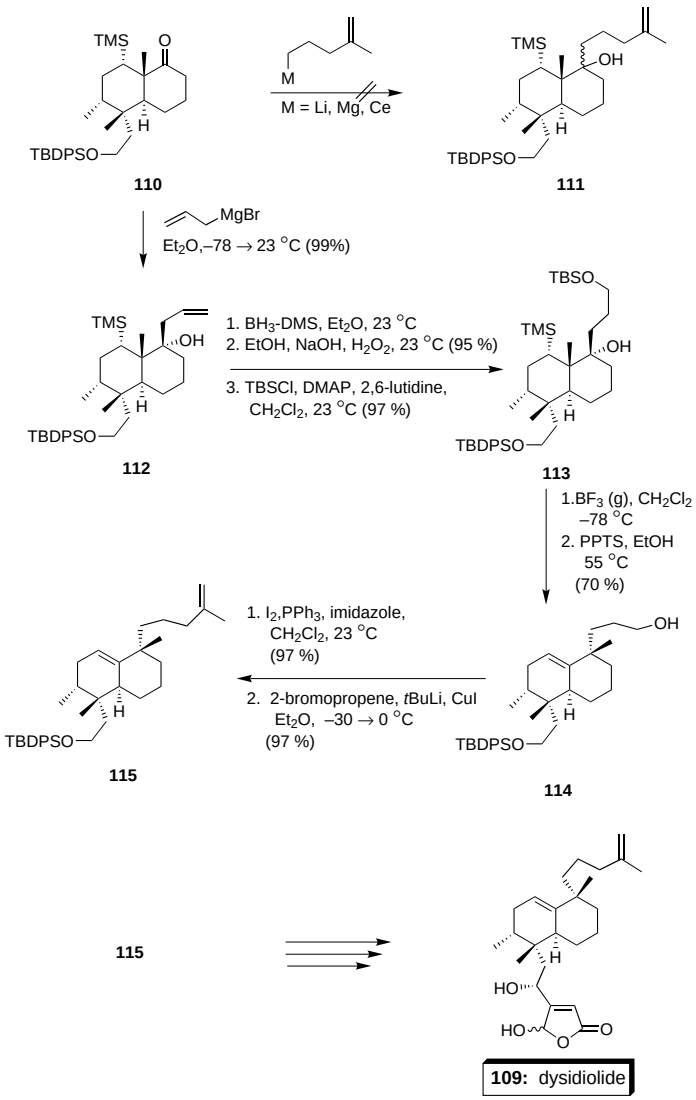


Scheme 15. The joining of the last carbon atom at C(10) to obtain the full carbon skeleton of scopadulcic acid B required a number of steps, as the straight introduction of the methyl group on **101** or **102** was not achieved.

anticipated to be difficult, since C(10) was flanked by a quaternary center of the bicyclo[3.2.1]octane unit. All attempts to introduce the angular methyl group on intermediates **101** or **102** directly were met with failure. These included $Me_2CuLi/TMSCl$; $MeCu \cdot nBu_3P$; "higher order" cyanocuprates, $BF_3 \cdot OEt_2$-catalyzed cuprate addition, and the [Ni(acac)$_2$]-catalyzed addition of Me_2Zn. The starting enone and/or the 1,2 adduct were obtained in these reactions. As a matter of fact, $\beta\beta$-disubstitued enones are known to be poor Michael acceptors.[40] However, the authors found that 1,4 adduct **105** could be obtained in good yields (86 %) when model enone **104** was treated with five equivalents of Me_2CuLi in diethyl ether.

According to the authors, this last obstacle (the introduction of the methyl group at C(10)) was "finally surmounted in an efficient, albeit classical, fashion". The problem of the quaternary center was solved by hydrocyanating **101** to **106**. An attractive transformation of **106** to the immediate precursor of scopadulcic acid B, was discovered when **106** was reduced with $LiAlH_4$ in THF. These reaction conditions formed pentacycle **107** in essentially quantitative yield. Reduction of this stable cyclic aminal was accomplished in 74 % yield under forced Wolff–Kishner conditions, to afford the tetracyclic diol **108**. Compound **108** was thereafter transformed to **100**.

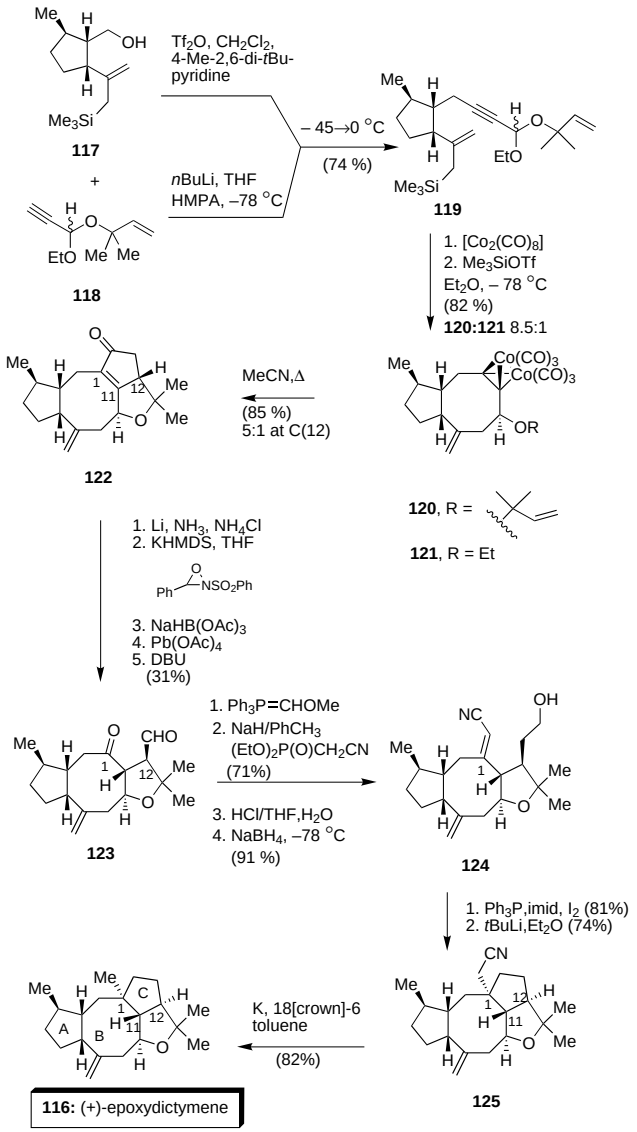
Corey's synthesis of dysidiolide (**109**) exemplifies a detour caused by the refusal of a side chain to join the preformed bicyclic skeleton of the starting material (Scheme 16).[41] Compound **110** was treated with 4-methyl-4-pentenyl-lithium, magnesium, and cerium reagents, but only recovered starting material instead of the desired bicycle **111** was obtained. The required side chain was built by the addition of allylmagne-



Scheme 16. The refusal of the carbon side chain present in dysidiolide to join ketone **110**, forced the authors to build this chain sequentially, considerably lengthening the synthesis.

sium bromide to **110** to obtain **112**, which was further elaborated to yield **113**. The 4-methyl-4-pentenyl moiety characteristic of **109** was formed on the three carbon side chain of **114** by sequential halogenation and cuprate nucleophilic substitution. Evidently, things would have been easier if the full side chain had been joined to the bicyclic skeleton of **110**.

A final example for this section is Schreiber's synthesis of (+)-epoxydictymene (**116**, Scheme 17).[42] The building of the fully functionalized tetracyclic skeleton of the target molecule from cyclopentane **117** and acyclic enyne **118**, through a sequential Pauson-Khand-Nicholas reaction, is a superb example of how to increase molecular complexity in only a few synthetic steps.[43, 44] With enone **122** in hand, completion of the synthesis required elaboration of the enone ring to the ring C of **116**, with incorporation of the last carbon atom at C(1). This example is more complex than the two precedents



Scheme 17. Epoxydictymene is a superb example of increasing molecular complexity in a few synthetic steps. After the formidable task of building the tetracyclic skeleton of the natural product in a few steps, the synthesis became more complicated because of problems found during the incorporation of the last methyl group.

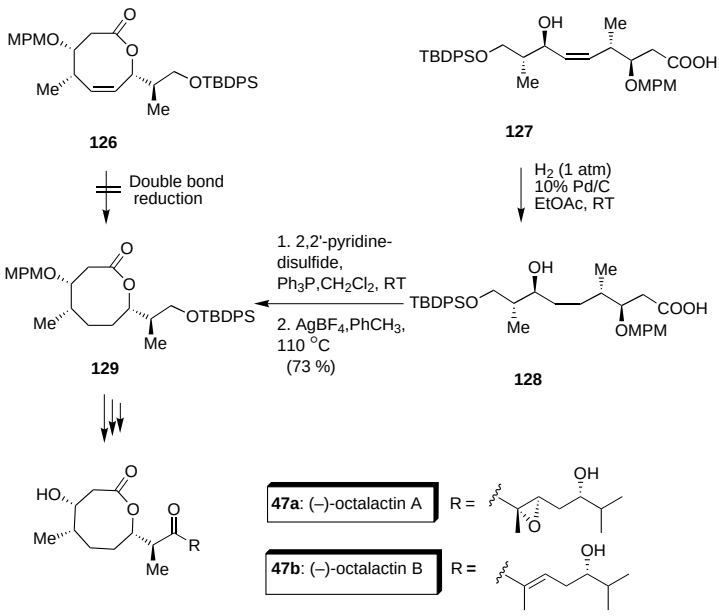
in the sense that there are problems other than attaching the methyl group at C(1), for example, epimerization at C(12) has to be achieved. Neither reductive nor deconjugative alkylation procedures proved successful in effecting the incorporation of the last methyl group at C(1). Complex reaction mixtures or products with the incorrect stereochemistry at the quaternary C(1) center were consistently obtained. Extensive experimentation suggested that alkylation at C(1) with the desired stereochemistry could be achieved only after inversion of the C(12) stereocenter in **122**. This hypothesis was also supported by molecular modeling calculations, which revealed that a two-atom bridge between C(1) and C(12) is more easily accommodated in a *syn* rather than in an *anti* fashion. Thus, the stereochemistry at C(12) was corrected in a five-step sequence from **122**, with ring C being opened. Ring C was reclosed after the methyl group precursor had been incorporated on **123** as a C2 fragment, and the resulting product was refunctionalized to form **124**. The anionic cyclization of **124** yielded **125** with the complete skeletal and stereochemical arrangement of the natural product. Reductive decyanation of **125** completed the synthesis of (+)-epoxydictymene (**116**).

These few examples demonstrate how unexpected hurdles can arise and complicate matters when an advanced intermediate only lacks a few carbon atoms. Perhaps the incorporation of a side chain is not a dead end that forces the researchers to quit the synthetic route, but clearly causes a nearly intractable problem that lengthens the number of steps and, in some cases, causes significant detours before reaching the final target.

6. The Trivial Functional Group Transformation

At this point it may be convenient to ask: How predictable is the reactivity of a certain functional group in a densely functionalized molecule? Taken at face value, this seems to be a silly question since, for instance, a carbonyl group is still a carbonyl group even in the more complex molecular environment. Nevertheless, even the simplest transformation of a functional group can be a nightmare when the reaction outcome is different to the expected, or when the functional group does not react at all. In the introduction of this article we showed one example in which some critical functional group transformations forced abandonment of a synthetic sequence at the final events of the synthesis (Schemes 1 and 2). The additional examples discussed below demonstrate the necessity of gathering more information concerning the reactivity of densely functionalized molecules, and of learning more about the behavior of commonly used reagents in these systems.

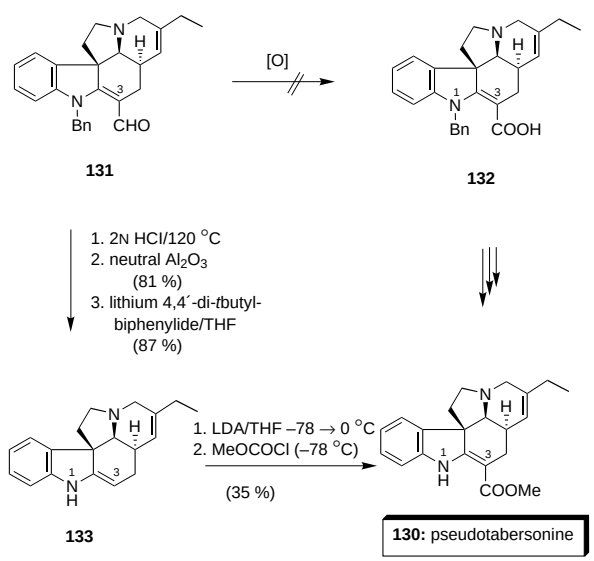
Let's start with one of the first reactions learned at the introductory level of organic chemistry: the standard olefin hydrogenation. Buszek's synthesis of octalactin A (**47a**) and B (**47b**) illustrates this point (Scheme 18).[45] Unsaturated eight-membered lactone **126** has the cyclic core of octalactin and it is properly functionalized to be transformed to the desired target. Unfortunately, in the words of the authors, "the seemingly prosaic task of reducing the double bond could



Scheme 18. The refusal of the double bond present in **126** to be hydrogenated forced the authors to face up to the risky ring closure of saturated intermediate **128**.

not be carried out under the many conditions tried, including heterogeneous and homogeneous catalytic hydrogenation, diimide reduction…". Thus, the olefinic bond had to be hydrogenated in the open-chain precursor of **127** prior to lactonization, although the literature offered little encouragement for the lactonization of a saturated intermediate such as **128**. In the event, the open-chain hydroxy acid **128** lactonized in high yield to the desired compound **129**.

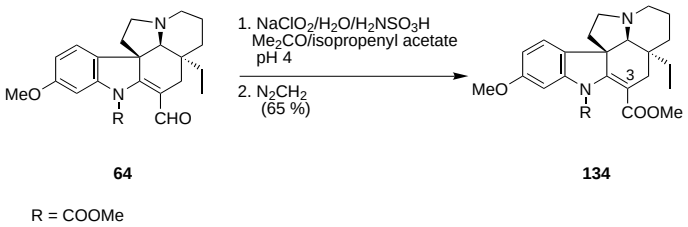
Another standard reaction (this time the oxidation of an aldehyde to a carboxylic acid) that did not occur at the final stages of the synthesis and led to a significant detour of the original plan, is found in Grieco's synthesis of pseudotabersonine (**130**, Scheme 19).[46] Transformation of the formyl



Scheme 19. The oxidation of aldehyde **131** to acid **132** could not be achived. Hence, a low yielding, long detour had to be undertaken to reach pseudotabersonine.

group at C(3) into a carbomethoxy unit and removal of the N(1) benzyl group were the sole transformations needed to arrive at pseudotabersonine from intermediate **131**. All attempts to oxidize **131** to **132** met with no success. Hydrolytic deformylation of **131**, followed by debenzylation yielded **133**, which lacked the carbon atom that was to become the carbomethoxy group. Installation of the C(3) carbometoxy group was realized—albeit in low yield—by lithiation of **133** followed by treatment with methyl chloroformate. This series of reactions finally produced pseudotabersonine (**130**).

It is intriguing that the formyl group of **131** could not be oxidized while the related compound **64** was oxidized uneventfully to **134** in the final stages of Magnus's synthesis of (+)-16-methoxytabersonine (Scheme 20).[31] The vinylogous amide nature of the formyl group in **131** may be responsible for the failure, while the carbamate group used to block the aniline nitrogen atom of **64** may attenuate this amide-like character, thus allowing its oxidation. This explanation goes back to similar observations made by Overman in his synthesis of (±)-akuammicine (see Scheme 9).[29]

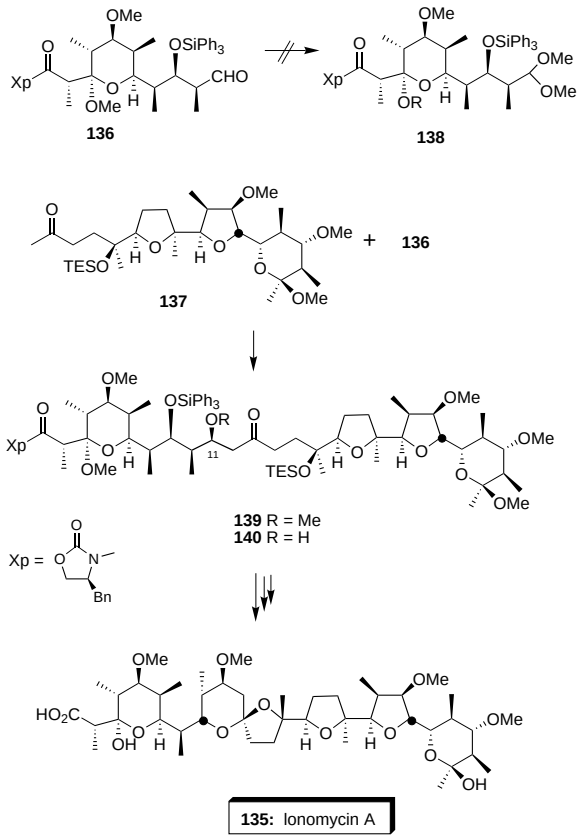


Scheme 20. The conversion of **64** into **134** was achieved by oxidation of the formyl group.

The last example of this section does not cause a deviation in the planned synthesis but it forced the researchers to confront an additional problematic transformation. Evans's synthesis of polyether antibiotic lonomycin A (**135**) involved the joining of fragments **136** and **137** in an advanced stage of the synthesis (Scheme 21).[47] Two different plans were evaluated for this transformation. The acid-catalyzed reaction of the dimethylacetal **138** and the enol silane derived from ketone **137** was considered more attractive than a conventional aldol union between **136** and **137**. Among the reasons for this, the possibility of obtaining the methylated aldol adduct **139** directly was especially appealing. The second option would involve an obligatory post-aldol methylation to convert aldol **140** into **139**, a step that the authors viewed as highly speculative because of the large number of oxygen-bearing functional groups present in intermediate **140**.

However, all attempts to transform aldehyde **136** into its dimethyl acetal **138** were condemned by the intrinsic acid lability of this intermediate. This failure forced the authors to use the second alternative. The preparation of lonomycin A was pursued and completed by condensation of the lithium enolate of ketone **137** and aldehyde **136**. The methoxy group at C(11) was incorporated at a latter stage in the synthesis as the aldol **140** could not be methylated, as expected.

The examples shown in this section are just a pale reflection of how matters can complicate when, at first glance, simple



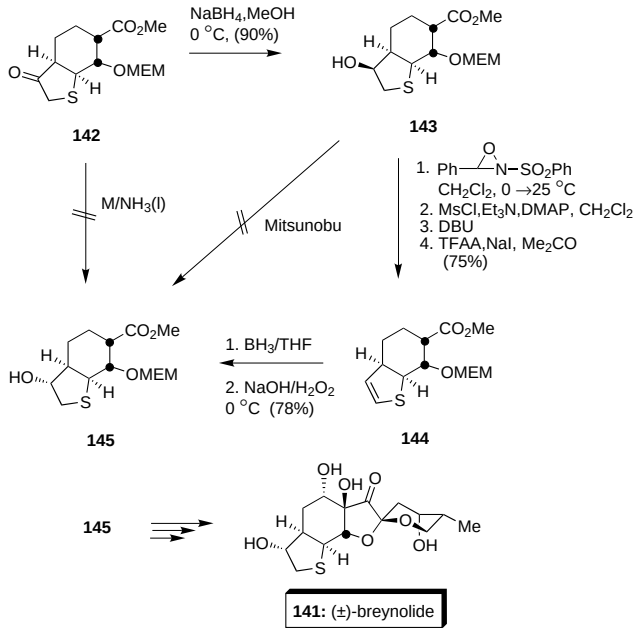
Scheme 21. To avoid the risky methylation of an alcohol in an advanced intermediate, the synthesis of Ionomycin A was designed to include the joining of acetal **138** and the enol silane derived from **137**. The impossibility of transforming aldehyde **136** into acetal **138** forced the authors to use the alternative aldol condensation between **136** and **137**, and to face up to the risky methylation after the aldol reaction.

transformations are done in complex molecules. Evidently, this does not mean that chemical reactions always have unpredictable outcomes. Perhaps this section header should be changed to "how trivial is a trivial synthetic transformation in real life?"

7. The Unpredictable Stereochemistry Problem

Talking about unpredictable stereochemistry in this time of highly stereoselective methods, exquisite stereocontrol, enantio-differentiating reactions, chiral discrimination, etc. may be quite dangerous. Superb achievements have been obtained in the development of methodologies to control the stereochemistry of many fundamental processes and today, asymmetric synthesis[48] is practically synonymous with organic synthesis. For people like us, who were at high school when modern asymmetric synthesis began and who willingly followed (and still follow) the amazing developments in the field, asymmetric synthesis has become almost a doctrine. But in agreement with the aim of this work, we present some examples in which stereocontrol led to the wrong outcome, again forcing undesirable detours or causing a lengthening of the synthetic path.

One of the simplest cases happens when the main carbon skeleton is in hand, the configuration of the stereocenters is correct, and a new stereocenter is to be placed by the reduction of a ketone to an alcohol. One of such cases is found in Smith's synthesis of (±)-breynolide (**141**, Scheme 22).[49] The key intermediate **142** was submitted to $NaBH_4$ reduction



Scheme 22. The intrinsic facial selectivity of ketone **142** thwarted all the efforts to obtain alcohol **145** by direct reduction of the carbonyl group. This facial selectivity was used to prepare **145** from **142** using a seven-step sequence.

to give the *endo* alcohol **143** as the exclusive product (>99:1). Since alcohol **143** has the wrong stereochemistry, standard tactics to invert the configuration were enlisted. Unfortunately, a variety of methods including the Mitsunobu inversion of **143**, or reduction of **142** by dissolving metal in liquid ammonia, gave only trace amounts of the desired *exo* isomer **145**. Therefore, a detour was taken to prepare the desired stereoisomer. Alcohol **143** was transformed into the dihydrothiophene derivative **144** in a four-step sequence, and the alcohol group was then reintroduced with the right configuration through hydroboration, by exploiting the convex bias of the bicyclic skeleton to set the *exo* configuration. This bias was, in fact, responsible for the detour as the fully shielded concave face of the molecule forced the hydride attack on **142** to furnish only **143**. The overall yield for this five-step transformation of **143** to **145** was 19%.

Another situation encountered is the coupling of two different enantiomerically pure intermediates, a step present in many convergent syntheses and, in regard to the stereochemical outcome of the process, still in need of refinement.[50] In the absence of external elements of stereocontrol, the resident chirality determines the stereochemical outcome, which may or may not be the desired one. That question has been nicely addressed in many articles and will not be dealt with here.[51] We will illustrate the problem using the coupling of two identical chiral compounds in a dimerization reaction

to form a new stereogenic element as in Coleman's synthesis of calphostin A (**146**, Scheme 23).[52]

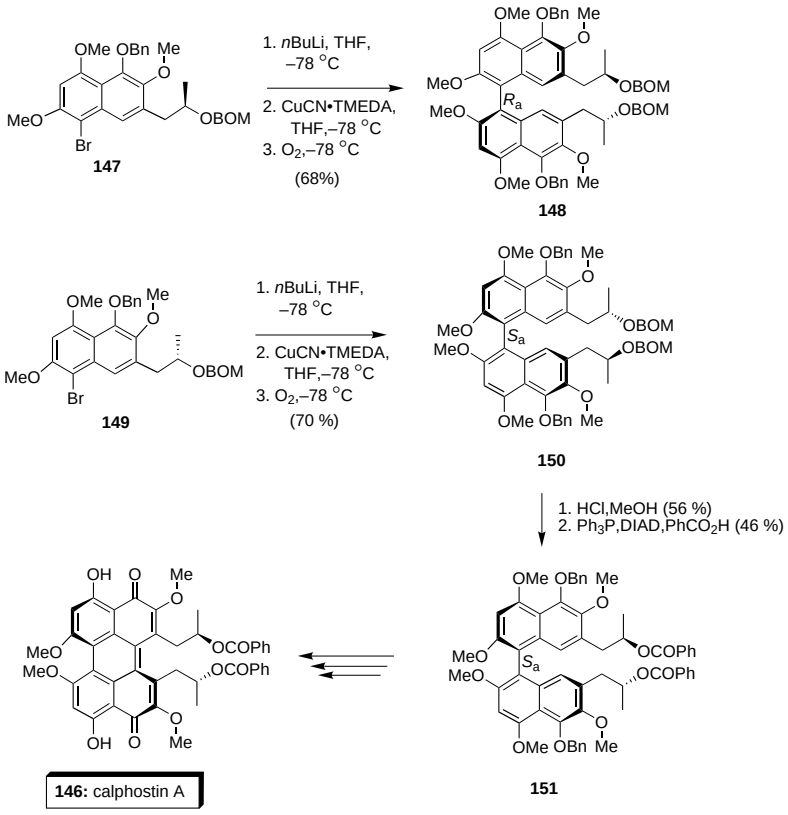
The preparation of calphostin A (**146**) was first attempted by the Cu^{I}-catalyzed coupling of the naphthalene derivative **147**. The reaction produced an 8:1 mixture of diastereomers about the axis of chirality, with the undesired R_a diasteromer **148** predominating. Once again this result contrasted with the sense of atropdiastereoselection previously observed for substrates related to **147** and having a protected (*R*)-2-hydroxypropyl side chain that induced S_a chirality about the binaphthalene axis.[53] Access to the desired diastereomer was gained from the enantiomer of **147**, naphthalene **149**, that formed the desired S_a atropisomer **150** as the major isomer. Introduction of the *2R* stereogenic center required for the natural product was accomplished by using a double Mitsunobu inversion on **150** with concomitant introduction of the acyl groups present in the natural product. The double acylated intermediate **151** was hence converted into calphostin A in three steps.

Efforts to control the troublesome intrinsic selectivity of the substrates in reactions depicted in Schemes 22 and 23 were not made and instead were exploited to achieve the designed transformation. One different case is the use of enantiomerically pure reagents to overwhelm the presumed modest diastereofacial preferences of the chiral substrate and to control the sterochemical outcome. In these cases the configuration of the products are highly predictable and a lot of beautiful synthetic work on reagent-based control of stereochemistry has been made during the last twenty years.[54] However, surprises are still found sometimes. One such example is met in Evans's total synthesis of cytovaricin (**152**, Scheme 24).[55]

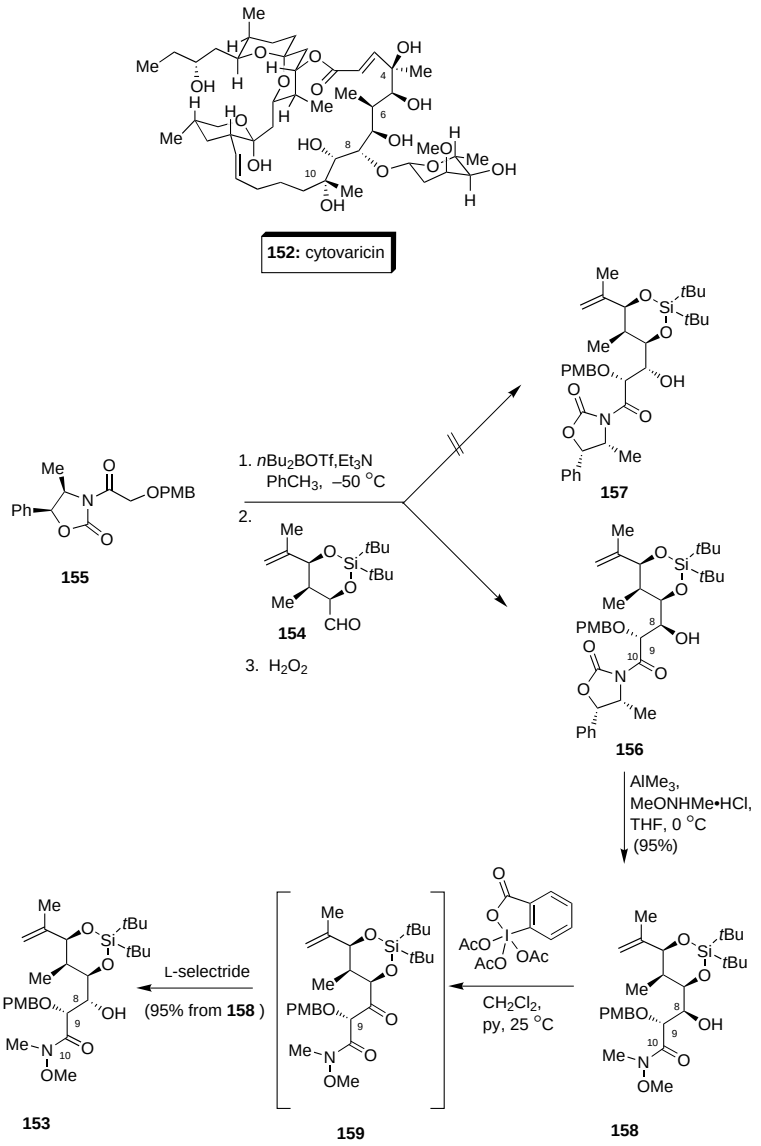
The synthesis of fragment **153** having the C(3)-C(10) carbon atoms of cytovaricin was made by the asymmetric aldol condensation between aldehyde **154** and the boron enolate derived from **155**. The extensive body of knowledge for this kind of reaction predicted complete control of the stereochemical outcome by the facial bias of the chiral enolate, its geometry, and the cyclic transition states for the aldol condensation, regardless of the configuration of the aldehyde.[56] Surprisingly, the *anti* aldol adduct **156** was obtained as a single diastereomer (the expected result was a single *syn*-aldol adduct **157**). The reversal of the stereochemistry was unprecedented in this condensation using this chiral enolate reagent. Apparently the configuration of C(9) is defined by the chiral enolate, while the inherent bias (predicted by the Felkin–Anh model)[57] of the chiral aldehyde determines the formation of the C(8) stereocenter. Other organometallic reagents such as MeLi and MeMgBr add to the same carbonyl diastereoface with selectivity greater than 20:1. All efforts to override the diastereofacial preference of aldehyde **154** were fruitless. In the words of the authors: "ironically all three of the undesired aldol diastereomers could be obtained as major products by variation of reaction conditions. A variety of metal enolates (B, Li, Ti, Zr, Mg) were surveyed. Stoichiometry, solvent, and auxiliary were also varied to no avail." Inversion of the stereochemistry of the C(8) center was undertaken on transaminated intermediate **158** by using the diastereofacial bias of a trigonal carbon atom at C(8). Oxidation of the alcohol at C(8) followed by immediate reduction of the β-ketoamide **159** with L-selectride gave a single diastereomer of the desired *syn*-alcohol **153**. In spite of the fact that β-ketoamide **159** is the intermediate in the transformation of **158** to **153**, no epimerization at C(9) was observed (an explanation of this fact is that allylic 1,3-strain forces the molecule into a conformation that sufficiently reduces the acidity of the C(9) methine hydrogen atom, to avoid the epimerization at this center).

A final example is found when, to prove its efficiency, the application of a new synthetic reaction at the key step of a synthesis leads to the wrong stereochemistry, either producing a diastereomeric mixture with the desired product being a very minor component or simply the wrong stereoisomer. For example McMurry's synthesis of (±)-crassin (**160**) was undertaken by using the intramolecular McMurry coupling of the *cis*-keto aldehyde **161** (Scheme 25).[58, 59]

Treatment of **161** in DME with a slurry of low-valent titanium reagent resulted in a mixture of cyclic diols **162**–**165** having all the possible configurations on the newly created stereocenters. The diol **165** with the configuration present in (±)-crassin (**160**) was the minor product (1%). To accomplish the synthesis of **160** a double



Scheme 23. In the absence of stereocontrol, the formation of a new chiral element with the desired configuration by joining together two fragments having pre-existent stereogenic centers is, in many cases, a matter of luck.



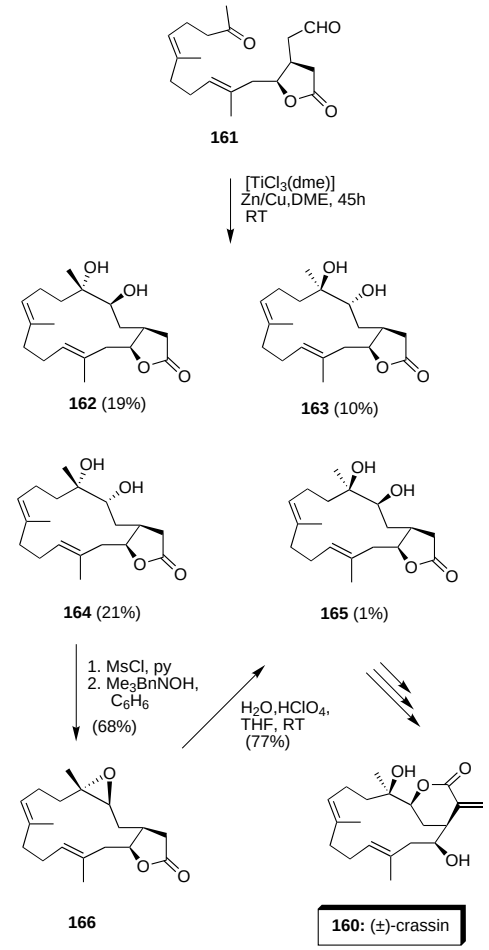
Scheme 24. In spite of all the powerful methodologies existing to achieve acyclic stereocontrol, and against the background existing for the stereocontrol in the aldol reaction, the unexpected configuration for aldol **156** was obtained this time. Steps to introduce the needed configuration had to be included in the synthetic scheme.

inversion of the hydroxyl groups in the major product (**164**) of this mixture was needed. This transformation was made possible by treatment of **164** with an excess of mesyl chloride, followed by reaction of the monomesylate with benzyltrimethylammonium hydroxide to give epoxide **166**. Rupture of epoxide **166** was accomplished by the action of 10 % aqueous $HClO_4$ to form diol **165** with the correct stereochemistry.

The few examples presented in this section are simple cases of how obtaining the wrong stereochemistry for a given transformation may interfere with a sucessful synthesis. Much has been learned about the elements involved in the control of the stereochemistry of synthetically relevant procedures, and the efficiency in terms of the stereocontrol obtained with many catalytic and stoichiometric reagents is breathtaking. The new catalytic asymmetric reactions, and the highly efficient chiral auxilaries developed during the last twenty years are amazing, but there is still much more to be done to control the generality and selectivity of these transformations. Among others, problems such as the stereocontrol in the joining of two chiral moieties having multiple (or just one as in calphostin A) preexistent stereocenters, and how to overcome the intrinsic facial selectivity of a cyclic substrate when this does not lead to the desired result (cyclic stereocontrol?) are issues yet to be completely resolved.[60]

8. Reluctant Ring Closures

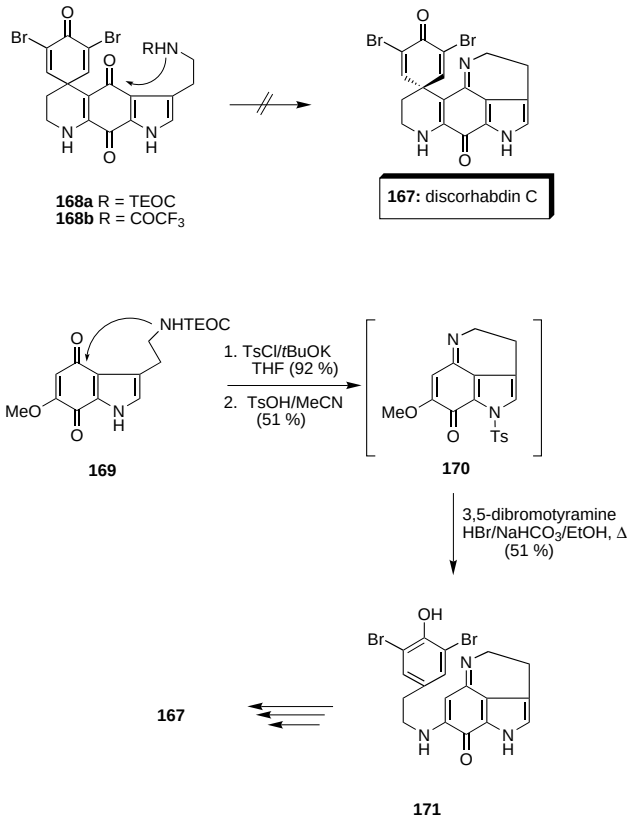
To complete this work we are going to discuss one of the most exciting topics in total synthesis: ring formation. Many synthetic routes devise a ring-closure reaction at some stage, since many synthetic targets bear at least one cycle in their core structure. Not surprisingly, the development of methodologies for ring formation has been (and still is) a priority in chemistry. It is beyond the scope of this article to review the many ways to access ring systems, or to evaluate their efficiency, but we have selected a few examples that show how cyclization processes are



Scheme 25. The building of the macrocyclic ring of crassin through a McMurry coupling produced a mixture of four possible diastereomers. The desired diastereomer was formed in less than 1 % yield.

not always totally under our control. On the other hand, it is also worth noting that failures in closing the desired ring may cause greater changes to the planned synthesis than any of the troubles discussed previously.

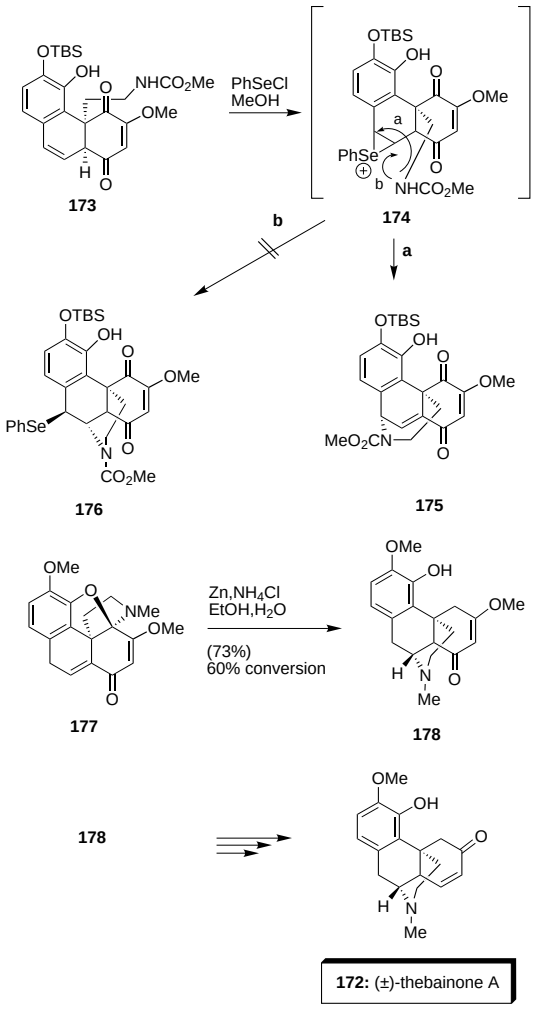
The final step of the original route to discorhabdin C (**167**) in Kita's synthesis (Scheme 26)[61] involved formation of an imine between the tryptamine nitrogen atom and the quinone carbonyl group in compounds **168a** or **168b**. All attempts to effect the imine formation in these intermediates were



Scheme 26. Failures during a key ring closure involve greater changes in the synthetic scheme than any other event in synthesis. The order of the ring building during the synthesis of discrohabdin had to be changed because of the refusal of the last ring to close.

unsuccessful. The failure of this ring closure was attributed to the weakly electrophilic nature of the carbonyl group of the quinone nucleus on **168**, which may be considered as a vinilogous urea and it is also very sterically hindered. The introduction of an electron-withdrawing group at the nitrogen atom also failed, because of the instability of **168b** under the basic conditions used. In the end, the alternative successful route to discorhabdin C used a phenolic coupling on the previously built aminoindoloquinone imine **171** as the final key step. This compound was obtained starting from the early intermediate **169**, which was previously used in the failed approach. This time the formation of imine **170** was ensured by the protection of the quinone nitrogen atom with the electron-withdrawing tosyl group, and by placing a 6-methoxy group on the quinone moiety.

Sometimes the size of the ring to be formed is presumed to be the right one on the basis of the kinetic preference of the reaction to be used, but the presumption turns out to be wrong. An example is found in the preparation of (±)-thebainone A (**172**, Scheme 27) by Tius.[62] Initially, access to the tetracyclic core of thebainone A was attempted by the closure of the piperidine ring through activation of the C-C double bond in intermediate **173**, followed by intramolecular



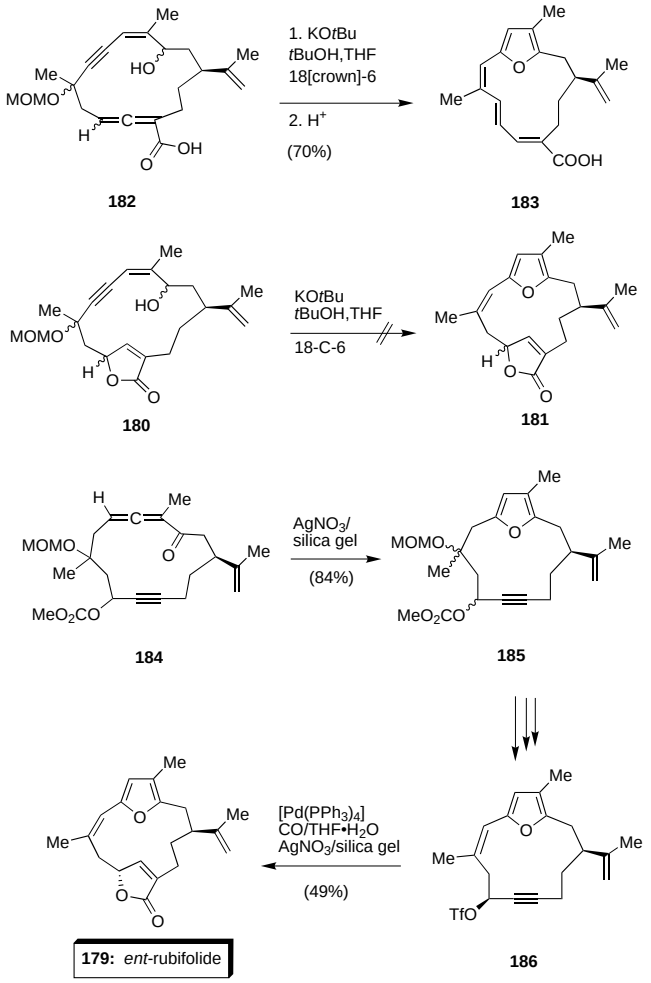
Scheme 27. The hope that a kinetic preference would be observed for the formation of the six-membered rather than the seven-membered ring unfortunately failed.

attack by the nitrogen atom. In the words of the authors "the hope that a kinetic preference would be observed for formation of the six-membered rather than the seven-membered ring from **19** [here **173**] was unfounded."

Exposure of **173** to PhSeCl in methanol produced the seven-membered nitrogen heterocycle **175** instead of the desired **176**. It was necessary to design a different sequence of steps relying on a conceptually different strategy. This time access to the tetracyclic core of thebainone A was gained from compound **177** by reductive cleavage of both the amine and the cyclic ether oxygen linkages by Zn dust and NH_4Cl. The subsequently released amino group underwent an intramolecular conjugate addition to furnish **178**, which was successfully converted into thebainone A. The origin of the failure of **173** to gave the desired compound **176** may reside in the

benzylic nature of the carbon atom attacked by the nitrogen center, which yields the observed product **175**. Selenacyclopropane **174** should be closest to an α-selenocarbocation with the majority of the positive charge centered on the benzylic position. Therefore, the attack of the carbamate nitrogen atom occurs exclusively at this position.

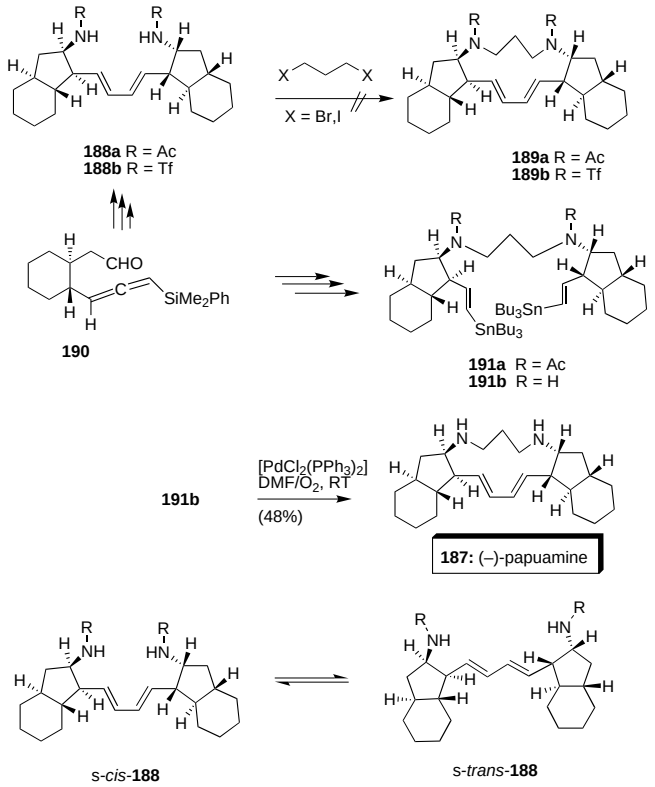
Another interesting situation is found in Marshall's synthesis of the furanocembrane *ent*-rubifolide (**179**, Scheme 28).[63] The macrocyclic skeleton of **179** was built in compound **180**, to leave just the introduction of the furan ring



Scheme 28. The building of *ent*-rubifolide by closing sequentially the furan and the butenolide rings failed. However, the inverse situation was successful.

to secure the final product. However, treatment of **180** with KO*t*Bu led to no identifiable products. The desired transformation actually occurred with a 70% yield with the model system **182**. An alternative entry to *ent*-rubifolide (**179**) involved first building the furan ring on the macrocyclic allenone **184** to form **185**. Sequential manipulation of **185** led to **186** on which the butenolide moiety was constructed to finally yield **179**.

Orchestration of the sequence, in which fragments are joined to effect a macrocyclization may become the cornerstone of the synthesis. A striking example is Weinreb's synthesis of (−)-papuamine (**187**, Scheme 29).[64] The first route to papuamine used intermediate **188** with the unsaturated chain of the molecule already closed. The 13-membered ring remained to be formed to access *N*,*N*-diacetylpapuamine (**189**). A number of attempts were made to close the ring by double N-alkylation of **188a** with 1,3-diiodo- and 1,3-dibromopropane. However, **187** was elusive in all attempted cases, even when the bistriflamide **188b** was used.



Scheme 29. There are no evident reasons to explain why the ring closure of diene **188** to give papuamine failed. Nevertheless, the successful approach to this marine natural product **187** had to use the closure of the olefin with the aliphatic chain already in place.

The synthetic route was reevaluated to close first the aliphatic chain of the molecule and then realize the final ring closure on the unsaturated bridge. Starting from the aldehyde **190**, the common intermediate for both approaches, the *bis*-stannane **191a** was prepared, initially with the two secondary amino groups protected as nonbasic acetate groups. All attempts of intramolecular coupling gave no trace of *N*,*N*-diacetylpapuamine (**189**). This result was explained by the difficulty of **191a** to adopt the conformation required for cyclization because of unfavorable amide rotamers. Finally, the cyclization was effected on **191b** with free amino nitrogen atoms by the action of $[PdCl_2(PPh_3)_2]$/DMF in the presence of oxygen. (−)-Papuamine was obtained in 48% yield.

It is not easy to rationalize the causes of the failure to access (−)-papuamine by closure of the aliphatic bridge of intermediate **189**. Compound **189** exists as its *s-trans* conformer. One can rationalize that a conformational change to the *s-cis*-conformer has to occur prior to closing the ring. The energy associated with this change is 6.5 kcal mol^{-1}. However, the

N-N distance on *s-trans*-**189** at 5.1 Å is shorter than the 6.3 Å in *s-cis*-**189**. Moreover, *s-trans*-papuamine is 1.6 kcal mol^{-1} more stable than *s-cis*-papuamine. The perplexing conclusion which is drawn is that cyclization should occur in theory, but it does not.

9. Conclusions (and Outlook?)

Many other examples dealing with problems found during the building of molecules are compiled in the literature.[65] The few discussed above represent particular cases of a general problem. Molecular complexity, additional electronic, steric, and conformational effects are often claimed as the ultimate cause for failures. The source of the trouble may rest in the still scarce knowledge of the behavior of densely functionalized, conformationally flexible molecules. The levels of predictability of computational calculations reach the edge in these cases, and much more has to be learned on how slight changes at the molecular level affect the final outcome of a given reaction. Highly selective reagents are often tested in simple transformations, yet they may be rendered useless when functional groups are present (the "methyl, ethyl, propyl, futile syndrome").[66] Without a doubt even the most complex molecules can be prepared by the present synthetic technologies, but the amount of effort devoted to simple transformations is still quite enormous. The simple conclusion is yes, we know how to do it but without doubt we will know how to do it simpler, better, and more efficient in the future.

Throughout this work we have tried not to be too enthusiastic about the beautiful examples presented; we have outlined the superb achievements and the impressive work contained in the syntheses. It is now the time to mention it. The overwhelming beauty of a total synthesis is only comparable with the feeling when looking at a work of art. And as with artworks, the modern techniques can make the work easier but still a veritable artistic heart is needed to construct a complex molecule. Moreover, although nobody cares if some parts of a painting or a symphony had to be erased or rewritten many times for the sake of the final work, in organic synthesis the detailed knowledge of the fruitless routes, the negative results, and those extensive and relentless efforts made during the total synthesis should also be written and discussed. In this way the value of the work performed will be heightened and the path for future developments in organic synthesis will be smoothed.

Abbreviations

Ac	acetyl
AIBN	2,2′-azobisisobutyronitrile
Bn	benzyl
BOC	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DIAD	diisopropylazodicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMS	dimethyl sulfide
FDPP	pentafluorphenyldiphenyl phosphinate
HMPA	hexamethylphosphoramide
imid	imidazole
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
MCPBA	*m*-chloroperbenzoic acid
MEM	(2-methoxyethoxy)methyl
MOM	methoxymethyl
MPM	methoxyphenylmethyl
Ms	methanesulfonyl (Mesyl)
PMB	*p*-methoxybenzyl
PMS	*p*-methylbenzylsulfonyl
PPTS	pyridinium *p*-toluenesulfonate
py	pyridine
SES	[β-(trimethylsilyl)ethyl]sulfonyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTH	tri-*n*-butyltin hydride
TEOC	trimethylsilylethylcarbonyl
TES	triethylsilyl
Tf	trifluormethansulfonyl
TFAA	trifluoroacetic anhydrid
Th	thienyl
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	toluene-4-sulfonyl

As with organic synthesis from the original idea to the final manuscript significant detours and some dead ends had to be overcome. We are indebted to Prof. Mar Gómez-Gallego and Dr. María J. Mancheño (UCM) for their valuable suggestions and their patience in correcting the manuscript. The assistance by Dr. Bernardo Herradon (CSIC) and his encyclopaedic knowledge of organic synthesis is gratefully acknowledged. We thank to Dr. Jesus Jiménez-Barbero (CSIC) for his invaluable help with molecular mechanics calculations. Finally, we thank the reviewers for their valuable comments, suggestions, criticisms, and different points of view that have contributed to considerably enrich this work. Support for this work under grants PB97-0323, 2FD97-0314-CO2-02 (MAS) and AGF98-0805-CO2-02 (MCT) from the Dirección General de Enseñanza Superiore Investigación Científica y Técnica (MEC-Spain), and the European Commission is acknowledged.

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[1] For a compendium of some of the most beautiful syntheses ever carried out, see a) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, Weinheim, **1996**; b) K. C. Nicolaou, D Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem.* **2000**, *112*, 46 – 126; *Angew. Chem. Int. Ed.* **2000**, *39*, 44 – 122.

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[7] One reviewer of this review pointed out two additional reasons not to go into details about failures: *first: "failed" reactions often lead to results that are not clean. These are usually described in papers as giving "decomposition of starting materials" or "complex mixtures of products". For those involved in Organic Synthesis such reactions seem to occur far too often! From such experiments conclusive and/or publishable information is difficult to glean. Reporting of results in this fashion, while being honest, does not provide much information from which the reader can learn and is often avoided. Second: often Organic Synthesis relies on luck! It doesn't matter how well planned a synthesis is, the route is nearly always going to have stages which are risky and predictably so in advance. Such risks are assessed in the planning stages before undertaking synthetic work. It may sometimes be judged that a very high-risk strategy may offer significant potential benefits which warrant investigation. Failures of high-risk work may go unreported as with the benefit of hindsight they may look to have strayed across the border between courageous and foolish!*

[8] There are, of course, other points of view for not reporting excessive details about failures. The words written by Danishefsky two years ago are fully illustrative: *Before relating a few of these episodes* [referring to the synthesis of some of the many molecules synthesized in his group], *some important cautionary notes and attributions are in order. For those schooled in the art (of Organic Synthesis), there will be little need for either. The experienced practitioner is well aware that the pathways of synthesis are circuitous, bumpy, and even treacherous. Seldom do straight lines suffice to connect points in a synthesis of real consequence. Hence, the seasoned chemist will appreciate that along with these "magic moments" of success, one could have reported a litany of setbacks and reversals. However, for younger and more optimistic enthusiasts, it is appropriate to underscore the uncertainties, the detours and, yes, the frustrations associated with Organic Synthesis. Success is often a prize reserved for those who temper noble ideas with appropriate measures of realism and skepticism. Given the episodic nature of our science, wisdom may well be more valuable than cleverness. The ability to plumb the implications of each experiment, positive and negative, is central to the process of learning as we go along. Our quest to reach the promised land should not render us insensitive to opportunities for discovery, even as we find our way through the desert*. See: S. J. Danishefsky, *Tetrahedron* **1997**, *53*, 8689 – 8730.

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[12] The description of this dead end by Nicolaou et al. in his paper telling the history of the total synthesis of brevetoxin B is specially dramatic: *The euphoria generated by the speed and efficiency of the sequences leading to* ***51*** [**3** in the present review] *was, however, soon to dwindle, as we shall see. First, it was the miserably low-yielding conversion of the dilactone functionality into the corresponding di(thiolactone) system using Lawessons's reagents. Then the bridging reaction, attempted on the meager amount of di(thiolactone)* [**2** in the present review] *obtained, proved equally problematic, leading to mixtures of products in low yields. In both instances, the steric hindrance of the C-13 methyl group adjacent to one of the reaction sites was to blame. That seemingly innocent methyl group, perfectly positioned to thwart our advance was almost certainly responsible for this failure*. See K. C. Nicolaou *Angew. Chem.* **1996**, *108*, 644 – 664; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 589 – 607.

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