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Natural Product Synthesis

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Natural Product Synthesis: Changes over Time

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history of science · natural product synthesis · synthetic methods

1. Introduction

The chemical synthesis of natural products, that is, of substances produced by living organisms, marked the beginning of organic chemistry. The synthesis of urea from inorganic ammonium cyanate by Woehler[1] in 1828 demonstrated that natural products, despite being derived from living organisms, are amenable to in vitro synthesis in the laboratory. With this mental barrier being removed, the path was clear for the first targeted synthesis of a natural product, that of acetic acid.[2] Targeted synthesis of a compound requires unambiguous knowledge of its constitution: at the time, this knowledge had to be based on the structural theories of Kekulé[3] (1858) and Butlerov[4] (1861). However, such a structural formula, postulated by degradation of a natural product, was little more than a simple working hypothesis. Only by synthesizing this compound from small, structurally defined building blocks, using reactions with a clearly defined scope, did a proposed structure reach the state of being securely determined. Hence, in the early times of natural product synthesis, the underlying incentive was to confirm the structures of natural products.

The motivation behind and the standards for natural product synthesis have been in a state of constant change for the past 180 years. These years can be roughly divided into the periods of before 1960, from 1960 to 1980, from 1980 to 2000, and after 2000. This essay addresses the changes in the targets and standards of natural product synthesis, focusing mainly on science-driven synthesis on a laboratory scale.

2. The Early Period of Natural Product Synthesis: Before 1960

In the early phase of natural product synthesis, a successful synthesis was the method of choice to confirm the proposed structure of a natural product. Such a structural proposal was, as a rule, the result of time- and material-intensive studies of the degradation of the natural product to the point that constituents of known constitution had been obtained. This was obviously only attained for such natural products that were accessible in copious amounts from their natural sources. This restriction is mirrored in the targets of natural product synthesis in this period.

The preceding degradation studies had generated a wide body of knowledge on the reactivity pattern of this class of compounds that could serve as a basis for the intended synthesis. Frequently, a degradation product was chosen as a primary target: a degradation product that was less complex than the complete natural product, yet retained its characteristic structural elements. Obtaining such a degradation product by synthesis opened the possibility of a relay synthesis of the natural product, that is, one in which the steps from the degradation product to the complete natural product could be explored and realized by using material obtained by degradation.

Before the advent of sophisticated methods for product separation and purification, crude products of a reaction had to be purified by crystallization or distillation. In consequence, individual experiments had to be run on a scale of 1 to 20 g, as can be seen from the experimental sections of the published syntheses. Proceeding with a relay synthesis was deemed favourable because this decreased the burden of the logistics of a synthesis, simply by having a less complex target that would require fewer steps, less time, and less starting material.

A typical example of a synthesis from this early period is that of the steroidal hormone oestrone (Scheme 1). Shown below is a merger of the studies of Robinson,[5] Bachmann,[6] and CIBA researchers Anner and Miescher.[7] This is a relay synthesis, because compound **1** had been previously synthesized by degradation of oestrone, and the reconstitution of oestrone had already been realized from **1**.[5] Many aspects of this synthesis are typical for the early phase of natural product synthesis: the molecular skeleton is created by using steps that individually induce only small changes to the overall structure. These steps are chosen such as to maximize the likelihood that the product of each step is the desired one. This concept means that these skeleton-building reactions are reliable, chiefly being confined to malonic ester synthesis, Dieckmann cyclization, and Reformatsky reactions. In this context, the use of Arndt–Eistert homologation,[8] which was considered very recent at the time, appears to be quite revolutionary. It is quite instructive to realize how few reactions natural product synthesis had at its disposal. Just looking into a copy of the "Gattermann" of that period[9] demonstrates how restricted the arsenal of synthetic methods was in those days.

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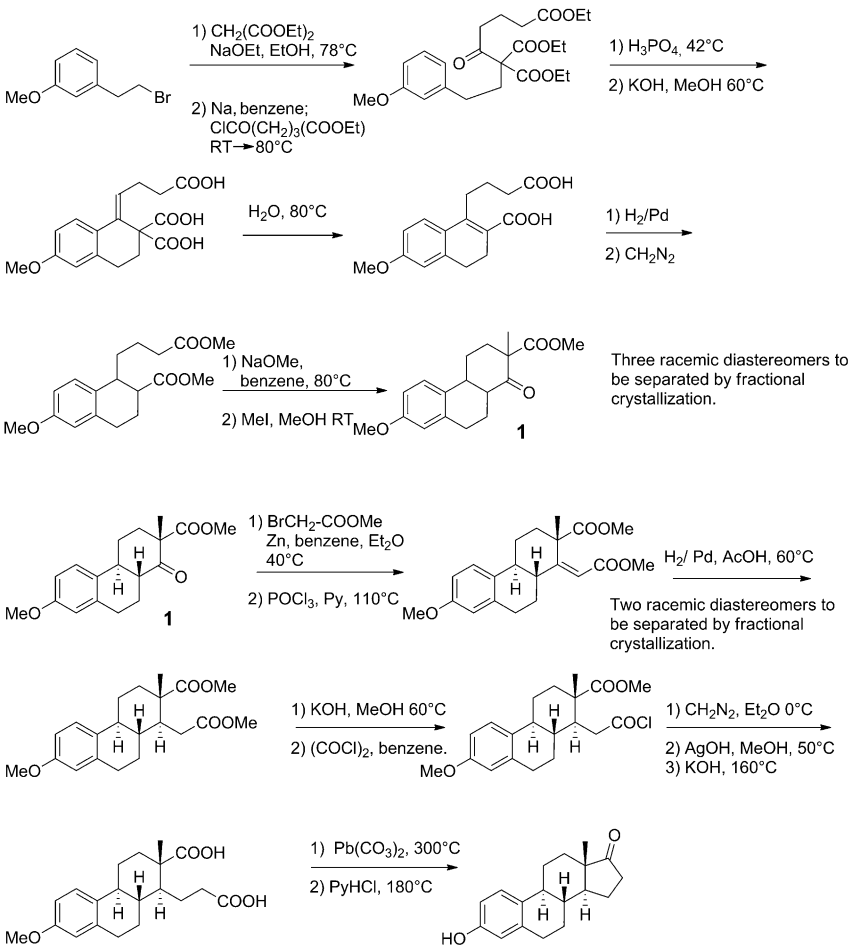


Scheme 1. Early synthesis of oestrone by Robinson, Bachmann, Anner, and Miescher. Py = pyridine.

In a similar vein, the helplessness is obvious when one analyzes the manner in which stereogenic centers were generated. Every stereogenic reaction led to mixtures of diastereomers that had to be separated by fractional crystallization. The importance of crystallization and the related capabilities of the chemists in those days are hard to imagine for present-day chemists. With almost every crude product, it was the "boss" who carried out the initial attempts at crystallization. It remained to the graduate student to provide a set of watch glasses and glass rods, as well as an arsenal of solvents in dispensing flasks. As a rule, the "maestro" succeeded in a miraculous manner to generate small crystals from a refractory oil. In hindsight, the beard of the old man probably served as a library of seeding crystals. If the oestrone synthesis had to be repeated today, students would probably fail with the separation of the diastereomers of **1** and would have to resort to chromatographic separation.

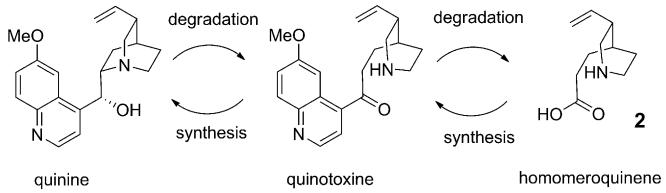
This early phase of natural product synthesis had been characterized by Kaufmann and Rúveda[10] with the following words: "*Although the syntheses were planned in advance, before the birth of what we now call retrosynthetic analysis, there was no rational and systematic approach to the design of synthetic strategies… The old masters in chemistry treated each synthetic target individually and obscurely related the final product to an appropriate starting material; therefore, success or failure was greatly influenced by their initial guesses.*"

This intuition became manifest in the total synthesis of quinine[11] by Woodward and Doering, an achievement that struck a major response in the scientific community and in the media.[12] This was also a relay synthesis, as Woodward and Doering obtained homomeroquinene (**2**) and quinotoxine, compounds that had been obtained before by degradation of quinine by Rabe[13] and Prelog,[14] and from which quinine could be reconstituted (Scheme 2).

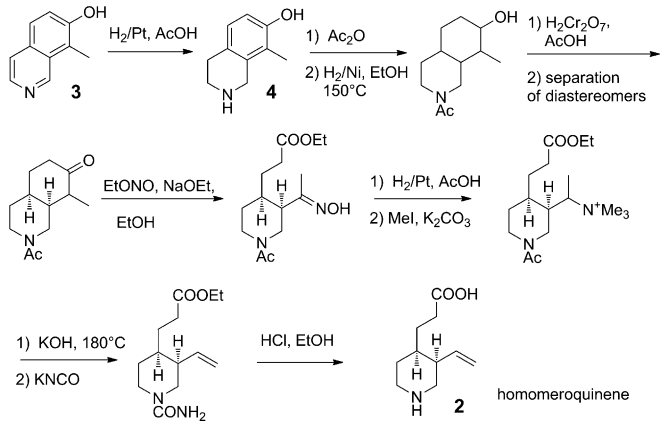
This natural product synthesis, which was Woodward's first total synthesis, gives testimony to the brilliance of this scientist in his choice of the starting material, hydroxyquinoline **3**, as it contains all the skeletal atoms of the targeted intermediate **2** (Scheme 3). However, on hydrogenation of **4**, the desired *cis* arrangement of the hydrogen atoms at the ring juncture could not be realized. Hence, here as well, a separation of diastereomers could not be avoided.

The synthesis of homomeroquinene (**2**) had been further extended by Woodward to that of quinotoxine. Yet, the claim of a total synthesis of quinine remained under dispute[12] until the conversion of quinotoxine to quinine, originally reported by Rabe,[13] had been successfully repeated.[15]

These impressive syntheses in the early phase of natural product synthesis remain as benchmarks today. Nevertheless,

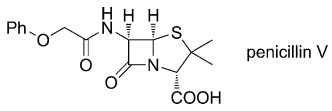


Scheme 2. Structural relationship between quinine, quinotoxine and homomeroquinene.



Scheme 3. Woodward's synthesis of homomeroquinene.

this synthetic approach had its deficiencies, which became obvious in the synthesis of penicillin (Scheme 4),[16] when



Scheme 4. Structure of penicillin V.

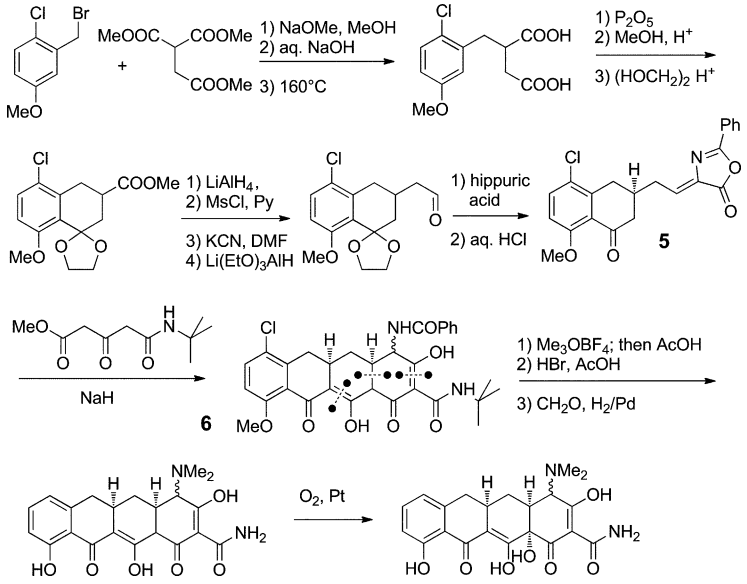
a global armada of more than a thousand chemists in thirty-nine laboratories did not result in a breakthrough.

3. The Adolescence of Natural Product Synthesis: 1960 to 1980

During the twentieth century, spectroscopic methods developed into important tools of analytical chemistry. In the 1930s, it was UV/vis spectroscopy, from the 1940s IR spectroscopy, and from the 1950s onwards mass spectroscopy was added to this collection, which provided additional information in the structure elucidation of natural products. A major advance was reached after 1960 by the advent of NMR spectroscopy. Since then, spectroscopic methods alongside with crystal structure analysis became the workhorses of structure elucidation, rendering a novel setting for natural product synthesis. This setting was described by Eschenmoser as follows:[17]

"*Elimination of the classical function of providing structural proof for natural products implied (for natural product synthesis) liberation from the restriction that only very well established reactions may be applied in a synthesis. Natural product synthesis henceforth provides a challenge to invent and to develop novel reactions and to discover novel reactivity patterns.*" This challenge attracted the best young organic chemists, and after 1970, this led to a boom in natural product synthesis and in the development of preparative methods. In the preceding years, the investigation of reactivity patterns of certain classes of compounds and of certain functional groups was the main theme of research in organic chemistry. Now, the development of synthetic methods became a clearly stated objective. Synthesis itself became an object of research: The way is the goal.

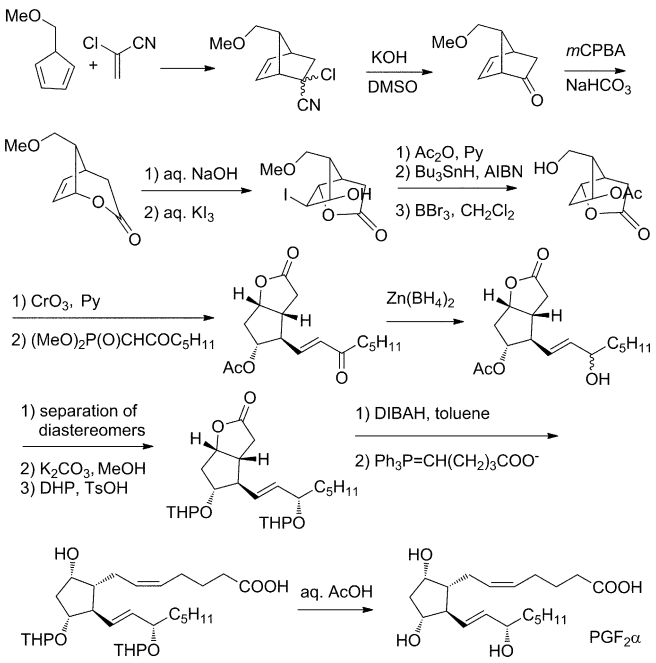
The first modern synthesis of this period is arguably that of tetracycline by Muxfeldt (Scheme 5).[18] Up to intermediate **5**, this synthesis proceeded in a classical manner. Then,



Scheme 5. Muxfeldt's tetracycline synthesis.

however, followed the one-step conversion into **6**, a reaction cascade that formed two rings and three skeletal bonds in one stroke. This showed the new liberty in designing a synthesis.

Focal points of synthesis in this period revolved around the prostaglandins.[19] An initial synthesis by Corey's group (Scheme 6)[20] featured aspects of the newly won liberty in



Scheme 6. Corey's prostaglandin synthesis. AIBN = 2,2′-azobisisobutyronitrile, DHP = 3,4-dihydro-2H-pyran, DIBAH = diisobutylaluminiumhydride, *m*CPBA = *meta*-chloroperbenzoic acid, THP = tetrahydropyranyl.

natural product synthesis, for example, the use of new methods, such as the "ketene synthetic equivalents" that had been developed in parallel to the synthesis efforts.[21] This synthesis was planned with clearly defined goals, such as the control of stereogenic centers and the creation of intermediates that can serve in the synthesis of all prostaglandins of interest. Overall, it was this particular focus on the prostaglandins that triggered a boom in method development for synthesis.[22]

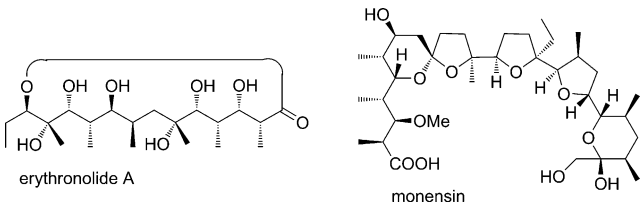
More importantly, natural product synthesis and synthesis planning were recognized as intellectual challenges and turned into objects of systematic study. In a programmatic publication, E. J. Corey wrote:[23] "*Such an effort is surely more than an intriguing theoretical exercise; it is a prerequisite to a deeper comprehension of Synthesis and the methodologies which are fundamental to it, and it is likely to be a keystone in the rational development of Synthesis to still higher forms.*" Forward-oriented strategies to transform an intuitively chosen starting material into the target structure were overtaken by retrosynthetic considerations,[24] in which a target structure could be related to a starting material in the most efficient manner. This was practiced for the first time by Corey in the synthesis of longifolene[25] and soon became common knowledge among synthetic chemists.[26] In a lecture, Corey stated:[27] "*During the past twenty years retrosynthetic thinking has permeated all areas of organic synthesis and, together with new methods and processes for molecular construction, has significantly enhanced the field.*"

The period between 1960 to 1980 witnessed further important contributions to the concepts of synthesis, for example, polarity inversion on bond formation[28] (leading to a more elaborated principle of umpolung),[29] the importance of convergency when joining building blocks in synthesis,[30] and the definition of the "ideal synthesis", one that should only consist of skeleton-forming reactions.[31]

4. Maturation of Natural Product Synthesis: 1980 to 2000

Is there any reason to set a break around 1980? This point in time coincides only accidentally with the premature death of R. B. Woodward in 1979. Rather, this turning point became apparent at the 6th International Symposium: "Synthesis in Organic Chemistry" in Cambridge, 1979. As a highlight of this symposium, R. B. Woodward was scheduled to lecture on his synthesis of erythronolide A, to the completion of which nearly 50 scientists contributed.[32]

In his stead, W. C. Still presented his synthesis of monensin,[33] a compound, which exceeds erythronolide in complexity (Scheme 7). Nonetheless, this synthesis had been

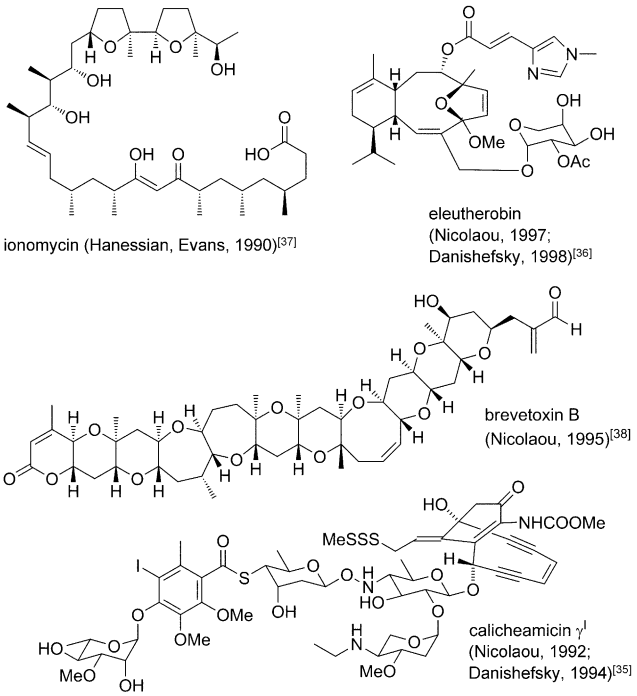


Scheme 7. Structures of erythronolide A and monensin.

realized by only two co-workers! In the attentive silence during this lecture, everybody in the audience realized that the clock of natural product synthesis had advanced by one notch. From then onward, only highly focused syntheses of complex natural products would make an impact on the organic chemistry community.

The following two decennia witnessed the completion of natural product syntheses with a high success rate. As soon as a new class of natural products had been described (e.g., the polyether antibiotics, the ene-diyne antibiotics,[34] the epothilones, and so forth), their synthesis followed right away. The most highly visible efforts were commanded by the groups of S. J. Danishefsky (Yale and New York), D. A. Evans (Harvard), and K. C. Nicolaou (Scripps, La Jolla). Their success was complemented by numerous other research groups that completed the synthesis of complex natural products in impressive style. The following examples serve to illustrate the complexity of the target molecules of this period (Scheme 8).

The rapid progress in natural product synthesis during this period occurred in parallel to developments in synthetic methodology. Methods for acyclic stereocontrol were brought



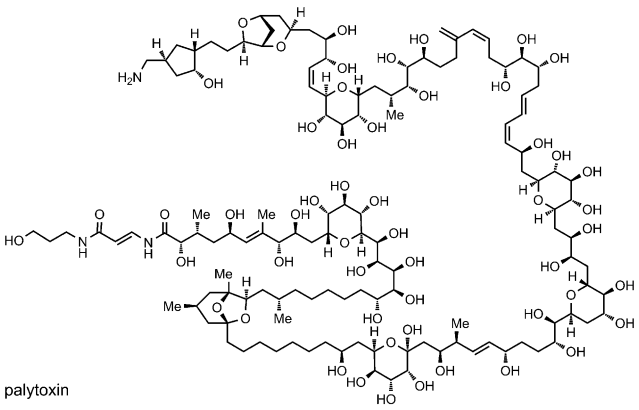
Scheme 8. Structures of ionomycin, eleutherobin, brevetoxin B, and calicheamicin γ^{I}.

to full maturation and found direct applications in natural product synthesis. Methods to create C–C and C–N bonds with the aid of organometallic reagents were developed in rapid sequence, such as olefin metathesis, Stille coupling, Suzuki coupling, Negishi coupling, the Heck reaction, and the multitude of ruthenium-catalyzed couplings of π-electron systems. Compared to 1950, the toolbox of organic synthesis in 1980 was a cornucopia of highly effective methods. Moreover, these new synthetic methods turned out to be superior to the classical ones regarding chemoselectivity, regioselectivity, and stereoselectivity.[39]

Even with a growing number of new natural products appearing as targets for synthesis, the original role of synthesis, to provide proof of structure, had surprisingly not become obsolete. With increasing frequency, the proposed structure of a natural product was synthesized but was found to not match the reported spectroscopic data.[40] Such syntheses necessitated that several accepted structural proposals for natural products had to be scrutinized again, and the reference compounds provided by synthesis turned out to be especially valuable in the structural reassignment.

It is impossible to rate all the notable syntheses of natural products published between 1980 and 2000, but the highlight is perhaps the esteemed synthesis of palytoxin by Kishi (Scheme 9).[41]

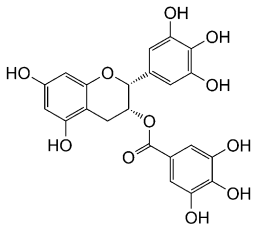
Inherent to any culmination point is that when passing through it, it results in a decline. Natural product synthesis is no exception, as the years 1980 to 2000 were its most prosperous years. Together with the development of synthetic methodology, natural product synthesis was the leading theme of organic chemistry; such a privileged position is fleeting.[42]



Scheme 9. Structure of palytoxin.

5. The Wider Horizon of Natural Product Synthesis? The Years After 2000

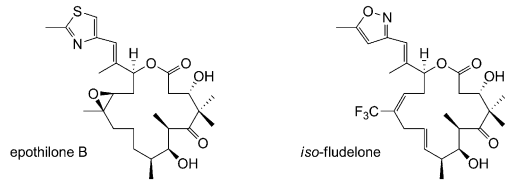
Even today, natural product synthesis is still the driving force behind the development of new synthetic methods, a development that is essential for chemistry. However, in the 21st century, this justification for natural product synthesis is much less accepted. Hence, the position of natural product synthesis needs to be redefined. In a fortunate coincidence, the field of "chemical biology" emerged—a research area that fuels interest in natural products because they interact with various proteins in biological systems and thereby enlighten the role of proteins in living organisms. Thus, natural products, such as FK506, forskolin, or brefeldin, acquired a special role as "chemical probes" in chemical biology.[43] Making these compounds accessible in sufficient amounts became an additional task of natural product synthesis. A simple example of a natural product serving as a chemical probe is given by *epi*-gallocatechol-3-gallate, which interacts in a manifold manner with proteins of biological or pharmaceutical relevance (Scheme 10).[44]



Scheme 10. Structure of *epi*-gallocatechol-3-gallate.

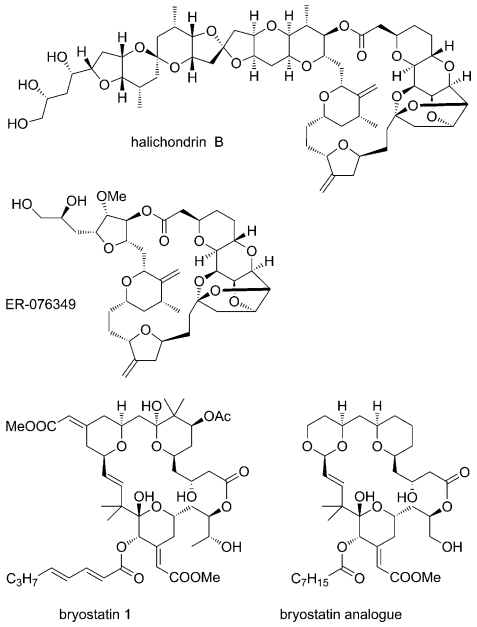
However, natural products are not necessarily optimal binding partners for a protein if it is not related to the original natural product. Fortunately, small modifications in the periphery of the natural product frequently suffice to improve binding properties in a significant manner. However, the possibilities of modifying a given natural product are in most cases rather restricted. Many more options are available when the synthesis of a natural product is designed in such a way that it allows access to a diversity of modified products. This approach of "diverted total synthesis" considerably broad-

ened the horizon in natural product synthesis. An example of an improvement in pharmaceutical profile generated in this manner is the redesign of epothilone B to iso-fludelone (Scheme 11).[45]



Scheme 11. Structures of epothilone B and iso-fludelone.

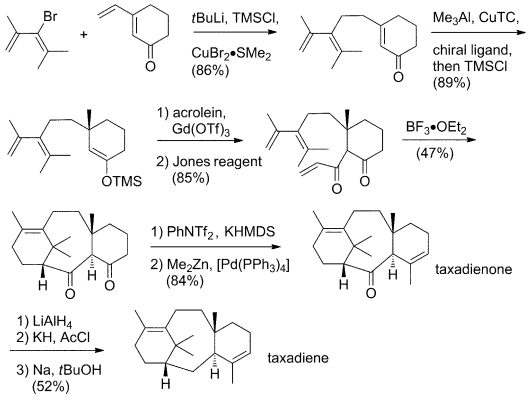
Some intermediates in a natural product synthesis represent the characteristic structural elements of the parent natural product without bearing its full complexity. Such intermediates help in defining the minimal pharmacophore of the active compound[46] and are valuable starting points for "diverted total synthesis".[47] The potential of this approach is illustrated by highly active analogues of halichondrin B,[48] and of bryostatin 1,[49] which resulted from diverted total synthesis (Scheme 12).



Scheme 12. Structures of halichondrin B and bryostatin 1, along with their respective analogues.

The tasks connected to diverted total synthesis or to probes for chemical biology highlight a deficiency of natural product synthesis of the past century: While it had been argued that only by synthesis can one generate enough amounts of naturally scarce material for biological studies, this promise has hardly been fulfilled, at least from academic laboratories.[50] Its fulfilment is now more and more emphatically in demand. Accordingly, natural product synthesis in the 21st century should provide the final compound at least in gram amounts. Yet synthesis at this level increases the problems associated with the logistics of providing sufficient amounts of reagents and disposing side products. In this context and with a view of transferring the synthesis to a commercial level, the formerly defined principles of green chemistry[51] and of atom economy[52] gain additional importance. Step economy[53] and redox economy[54] will have to be considered as well. In the end, however, the practicality of the individual steps will be of utmost importance.

A synthesis that meets most of these criteria is that of taxadiene, which has been obtained in gram amounts (Scheme 13).[56] The relevance of this synthesis is shown by the facts that taxadienone has been obtained in a few steps and in high yield. Taxadienone may serve as a starting point for a multitude of more highly oxidized taxane derivatives, hopefully including taxol itself.[57] Taxadienone thus constitutes a perfect basis for diverted total synthesis.



Scheme 13. Baran's synthesis of taxadiene. KHMDS = potassium hexamethyldisilazide, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

With the advent of the 21st century, the targets of natural product synthesis have become even more complex. While palytoxin,[41] polypeptides such as fuzeon,[58] or branched oligosaccharides[59] marked the frontiers of synthesis until recently, even more complex structures[60] such as glycoproteins have been conquered in the past decade. Thus, a glycoprotein with a molecular mass of 17868 has been obtained by Danishefsky through targeted synthesis,[61] setting a new benchmark for natural product synthesis.

Natural product synthesis is well focussed on the challenges of the 21st century. A branch of chemical science that mastered the changing demands over two centuries is set to meet these challenges, provided that scientists continue to fall in love and get deeply absorbed with a novel structure and to fight without reservation to provide a viable synthetic route to that target.

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