

Creating complexity – the beauty and logic of synthesis

The past decade has been a golden age for the total synthesis of natural products, marked by the conquest of some extraordinarily challenging target compounds – many of which are of significant pharmacological value. **K. C. Nicolaou** of The Scripps Research Institute and the University of California, San Diego, has led the field.^{1–4} He is driven by the passion to design elegant and efficient synthetic strategies that capture Nature at her most complex and diverse.



K. C. Nicolaou (right) with his early mentor E. J. Corey

BIOLOGICAL MOLECULES represent the most complicated forms of matter that we know of in the Universe. The structural variety and often downright strangeness of many natural compounds (especially those deployed as chemical weapons in inter-microbial warfare) cannot fail to astonish. Synthesising such materials from simple chemical building blocks represents an irresistible and profound intellectual challenge, that encapsulates the cultural core of chemistry. Total syntheses also have immense practical value: they generate new synthetic reactions and methodologies; and, most importantly, provide templates for novel therapeutic agents. Increasingly, assembling biological molecules in the lab offers insights into how Nature creates architectural diversity so effortlessly within the fragile medium of life.

At the heart of synthesis is, of course, the ultimate forging of new bonds in a variety of stereo and electronic environments to create linked rings, bridges, or chain-like structures with precisely determined geometries. This requires not only an encyclopaedic knowledge and understanding of chemical behaviour, but more importantly the ability to see in three dimensions a synthetic pathway that will efficiently stitch together the fragile molecular framework in the fewest steps. Modern synthesis combines a systematic analysis of a target molecule – breaking it

down into simple components from which it can then be built up (retrosynthesis) – and creative leaps of imagination in planning how to bring them together.

It was this combination of logic and artistry that first attracted K. C. Nicolaou to synthetic chemistry. Born on the island of Cyprus, surrounded by great natural beauty, he says his hellenic cultural heritage has deeply influenced his approach to chemistry. Synthetic design is an art as well as a science, says Nicolaou: “It’s almost like a ballet where you move from one step to another – a cyclisation, a ring-opening or a cascade reaction – to give an aesthetically pleasing sequence.” The intellectual satisfaction of total synthesis came into focus through exposure to the inspirational retrosynthetic methodology of the celebrated E. J. Corey. After a first degree and PhD in London and a postdoc at Columbia, Nicolaou joined Corey’s group at Harvard in the mid-1970s. “That’s where I learnt about natural products and found my passion for the field,” he says.

Nicolaou went on to found his own group at the University of Pennsylvania, and, during the late 1970s and 1980s, synthesised a long series of natural products, including various biologically active eicosanoids, the antibiotic efrotomycin,⁵ and the clinically used antifungal agent amphotericin B.⁶ This period was formative for Nicolaou:

he developed an approach that was to provide the future model for his group’s programmes – that of combining the total synthesis with research into new synthetic methods and investigations into the associated biological activity. His group’s work expanded considerably when they moved to California at the end of the 1980s, and the next decade saw the many remarkable synthetic firsts with which the Nicolaou team is now associated.

Impossible molecules

Nicolaou is well known for tackling alarmingly difficult structures with Greek heroic spirit. He admits that he enjoys the challenge: “The most important ingredient is courage, supplemented with flashes of ingenuity and a little serendipity,” he says – adding that the physical attraction of a molecule is important in choosing a target: “like falling in love.”

Calicheamicin, an anticancer antibiotic of bacterial origin, provided one of the first such challenges. Nicolaou recalls how, some 15 years ago, he was first secretly introduced to its bizarre structure (Fig. 1) by researchers at the Lederle Laboratories: “At first, I was completely speechless. This cannot be right, I thought; it does not look stable.” Indeed calicheamicin’s structure looks almost as though Nature is having a laugh. Attached to a pentacyclic oligosaccharide is a strained bicyclic ring system containing double and triple bonds (an enediyne), and to make the joke go further there’s a cheeky trisulfide tail tacked on. But this

aglycone fragment is lethal – binding and cleaving the DNA of a microbial adversary *via* an enediyne cyclisation reaction to form aggressive 1,4-benzenoid diradicals. Amazingly, this fascinating organic reaction had already been independently anticipated by Robert Bergman (then at the California Institute of Technology) in 1972.

Although excited and intrigued by the structure, Nicolaou was at first dubious that the molecule could be synthesised. Nevertheless, in 1987 he and his colleagues started planning the assault, retrosynthetically constructing the oligosaccharide and enediyne sections and then designing a method of coupling them together. As well as generating some bold new synthetic steps, the resulting project led to a detailed study of the chemistry of enediyne analogues, and their potential therapeutic action. By 1992, Nicolaou's group had achieved their goal,⁷ ahead of stiff competition from other groups.

Total synthesis is indeed a notoriously competitive field – though attracting only the very best organic chemists – and the synthesis of the compound taxol (Fig. 2), found in the bark of the Pacific yew tree, was perhaps the mostly hotly contested race in the 1990s. Not only did its structure represent a formidable synthetic challenge, but it was, of course, also recognised as an important anticancer agent. By 1992, some 30 groups were working on its total synthesis. At first unsure whether to enter the race at this late stage, the Nicolaou group was nevertheless inspired to try an ingenious strategy typical of its leader, which is to put the molecule together in a non-obvious, but elegant way. Taxol's core consists of four fused rings: A, B, C and D. Ring B is a frightening, strained eight-membered entity with some tricky stereochemistry and regiochemistry to get right. Nicolaou took a convergent approach in which the conformationally and chemically pre-organised flanking rings A and C were first

made using clever versions of the Diels–Alder reaction, and then coupled *via* two unusual steps – the Shapiro and McMurray reactions – to give the correct form of ring B. The synthesis of taxol was completed in just two years and was the first to be published⁸ – though publication was a photofinish with Robert Holton's group at Florida State University.

Although achieved with incredible speed, the taxol synthesis inevitably encountered obstacles along the way: reactions that didn't go because of unanticipated steric hindrance, or unexpected side-reactions that took precedence. Enormous persistence and fortitude are needed in turning a synthetic plan into reality. Nowhere is this better illustrated than in the tortuous path to the synthesis of the molecule for which Nicolaou is famed – brevetoxin B. The brevetoxins are a group of neurotoxic chemicals released by pigmented marine algae known for causing algal blooms. These 'red tides' can cause massive fish kills and even human food poisoning through eating affected seafood.

The molecule is a hugely complex entity consisting of 11 ether rings (including two seven-membered rings and one eight-membered ring, and labelled A to K), with 23 stereocentres, *trans*-fused in a ladder-like structure (Fig. 3). When Nicolaou first saw brevetoxin B in 1981, he admits being transfixed by its satisfying geometric regularity. "It was love at first sight," he says. However, he realised that starting on such a difficult synthesis was a gamble. Indeed, initial attempts based on convergent planning led to frustrating dead

ends and the overall strategy had to be redesigned several times before achieving success. Nevertheless, various new methods of making the constituent cyclic ethers and stitching them together were developed, and a stripped-down model version of the structure, constructed *en route*, proved useful for chemical biological studies. The final plan involved pre-assembling the ABCDEFG ring system and combining it with the IJK section to forge the interconnecting eight-membered H ring. The synthesis was finally published in 1995⁹ – the end of a truly Homeric journey which had taken the team 12 years to complete. The synthesis was an awe-inspiring achievement, involving 82 steps, each achieved with an average yield of 92 per cent.

Learning from biology

Originally, Nicolaou had hoped to take advantage of brevetoxin B's qualities of symmetry to develop a biosynthetic approach that would 'zip up' the rings from a long-chain polyepoxide rather as enzymes often do in Nature. Such biomimetic cascade reactions, in which an initial reaction provides the substrate (with the correct geometry) for the next reaction, which then leads to further consecutive reactions until the final product is obtained, offer an extremely attractive synthetic approach. They are elegant and efficient, reducing the amounts of reagents and solvent needed. There is currently a great deal of interest in biomimetic strategies¹⁰ – although the approach goes back to one of the founding fathers of natural product synthesis, Sir Robert

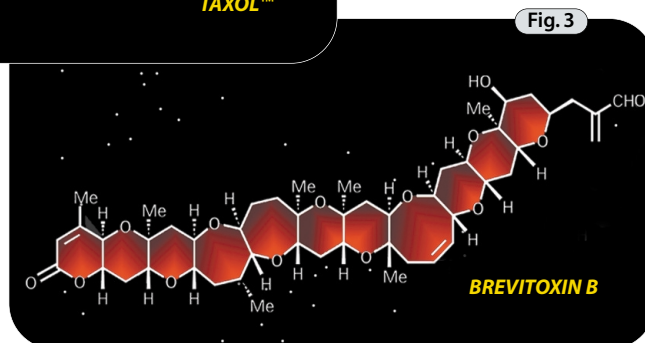
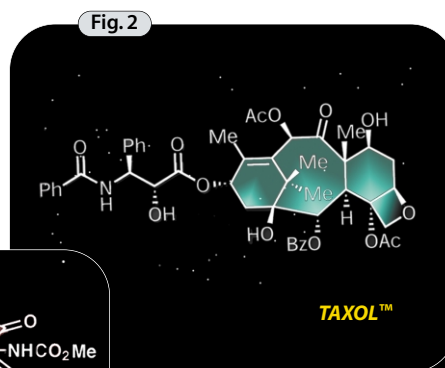
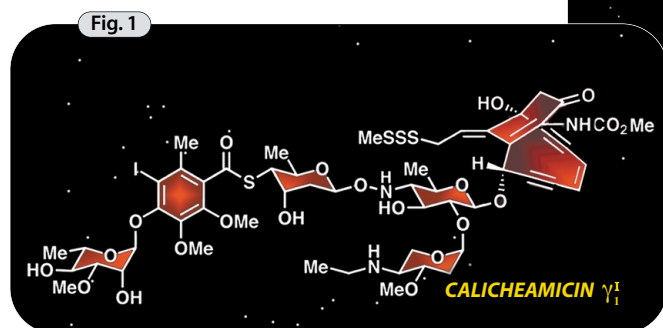


Fig. 1 Molecular structure of calicheamicin

Fig. 2 Molecular structure of taxol

Fig. 3 Molecular structure of brevetoxin B

Robinson, who developed a classic one-pot synthesis of tropinone as early as 1917.

The biomimetic approach didn't work for brevetoxin B, but Nicolaou has exploited such strategies to great advantage in synthesising other targets. One of his earliest conquests was the synthesis in 1982 of the endriandric acids¹¹ found in the Australian plant *Endiandra introrsa* (Fig. 4). Surprisingly for natural products, these compounds, which harbour eight stereocentres, actually exist as racemic mixtures. It had been suggested that their complex cyclic systems were assembled in Nature from achiral polyunsaturated precursors *via* a cascade of electrocyclisations. Nicolaou investigated these, then little-known transformations, demonstrating in the laboratory how the cascade generated the rings from the linear precursors in a satisfyingly stereocontrolled way.

One of the most sophisticated applications of the cascade philosophy was more recent – in the synthesis of the CP molecules. This pair of molecules, isolated from a fungus by researchers at Pfizer and known only by numbers CP-225,917 and CP-263,114, were shown to lower cholesterol as well as being active against cancer. Although their core structures are quite small – containing only 18 atoms – closer scrutiny reveals what a synthetic nightmare their superficially innocent-looking structures engender (Fig. 5). Indeed, Nicolaou frequently refers to the CP molecules as “diaboli- cal”. Each is a melange of highly reactive functional groups held closely *via* an unusually connected cage-like structure comprising five-, six-, seven- and nine-membered rings. They include a maleic anhydride ring, a γ -hydroxylactone, a tetrahydropyran system and a bridgehead double bond. Designing a synthetic plan

that takes account of all the possible reactions that these closely linked functionalities can undergo was an irresistible challenge for Nicolaou. In 1996, his team embarked on the CP-journey, which he likens to entering a labyrinth in which frequent dead-ends are encountered along the way. Nevertheless, starting from dimethyl malonate and passing through a series of inventive cascade reactions involving a total of 40 steps, the team arrived at their target three years later.¹² Nicolaou points out that many new synthetic technologies were discovered during this epic chemical adventure – an important feature of this kind of exploration.¹³

Combinatorial approaches

Another enabling methodology that has been exploited and extended by the Nicolaou camp is the burgeoning combinatorial approach allied with solid-phase chemistry (in which the substrate is attached to a resin). In this way, for the first time, the total synthesis of a natural product could be adapted to create analogues with enhanced pharmacological activity. In 1997, the Nicolaou group synthesised epothilones A and B (Fig. 6), macrocyclic molecules of microbial origin with cytotoxic properties similar to taxol.

They then went on to develop a solid-phase synthesis of epothilone A which could be applied to the creation of combinatorial libraries (using radiofrequency-encoded tags) which contained some highly potent analogues of potential pharmaceutical interest.¹⁴

This strategy reaped dividends in 1999 when further applied to ‘the antibiotic of last resort’ vancomycin. This molecule is of clear medicinal importance but synthesising its closely-packed, crosslinked glyco-polypeptide structure is not for the faint-hearted (Fig. 7). In 1998, the Nicolaou team, employing some novel methodology developed by the group, synthesised the aglycone version of vancomycin, later adding on the two missing sugars. They then extended the technology to build combinatorial libraries for biological screening. This led to the identification of new, highly potent vancomycin-based antibiotics that may offer a route to combatting emerging pathogens now resistant to conventional vancomycin.¹⁵

The future for synthesis

In the past 25 years, organic synthesis has developed dramatically. It has been particularly enhanced by the discovery of novel stereochemically selective reagents

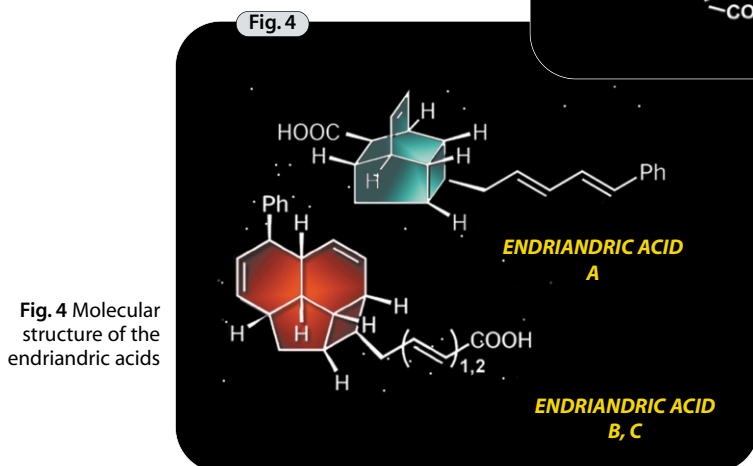


Fig. 4 Molecular structure of the endriandric acids

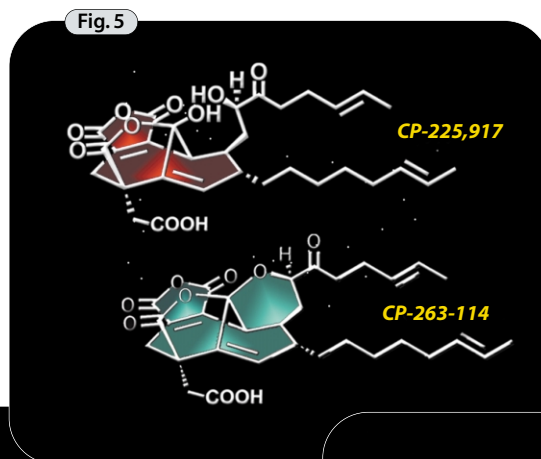


Fig. 5 Molecular structure of the CP molecules

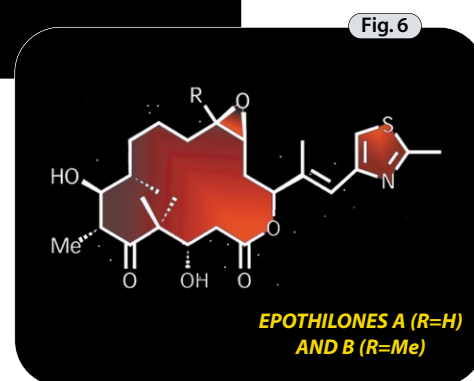


Fig. 6 Molecular structure of epothilones A and B

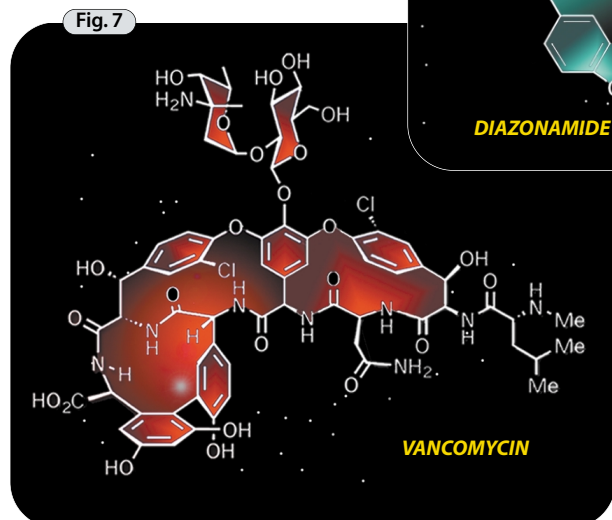


Fig. 7

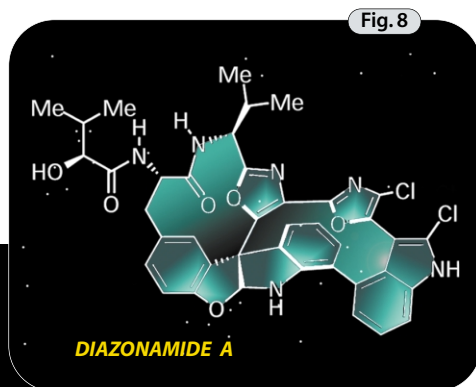


Fig. 8

Fig. 7 Molecular structure of vancomycin

Fig. 8 Molecular structure of diazonomide A

relying on sophisticated coordination chemistry or on enzyme action. Ingenious approaches based on biomimetic cascade or tandem sequences and solid-phase combinatorial technologies are also continuing to further the art and science of total synthesis. During this time, K. C. Nicolaou (known as 'K. C.' to the chemical community) and his teams of researchers have synthesised dozens of extraordinary natural molecules, designing and extending these new synthetic methodologies in the process.

Will the team run out of challenging targets? This is not likely; chemists have probably tapped into only a fraction of the molecular diversity created by Nature. New puzzling molecular architectures are bound to elicit ingenious responses from synthetic chemists, such as that recently formulated by Nicolaou's group against the marine-derived antitumour agent diazonomide A (Fig. 8).¹⁶ In the next decade, as genome and proteome research start to generate new pharmaceutical targets, chemical biological studies will become ever more important – and with it the development of efficient syntheses of new bioactive natural materials and their analogues. We can expect to see K. C. and his colleagues continuing to take up the challenge of what is perhaps the most creative of the chemical sciences and apply it for the benefit of humanity.

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