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Biogenesis and Biomimetic Chemistry: Can Complex Natural Products Be Assembled Spontaneously?

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With selected examples, we try to demonstrate that complex structures of natural products can be generated with surprising spontaneity. In such cases it appears that molecular complexity might emerge with minimal (if any) enzymatic assistance, through self-construction mechanisms. Rearrangements of linear molecules, light-induced reactions, dimerizations and multi-component reactions could explain the formation of secondary metabolites through the intrinsic reactivity of their precursors. A few examples, amongst the most significant, are presented, along with efficient biomimetic syntheses that strengthen the hypotheses.

Introduction

Defenders of a globalist vision of biological phenomena in general try to understand what directly depends on genes and their activity, but also try to demonstrate that spontaneity is important as well. Can this response to the "all genetics" point of view apply to secondary metabolites, natural products that have proven very useful in fields such as therapeutics?

When considering the problem of the biogenesis of natural products, one usually justifies the complexity and diversity by putting forward enzyme participation. Starting from a limited library of simple precursors (twenty at most) derived from primary metabolism, secondary metabolites (natural products) seem to be formed with intriguing ease.

Genetic Information or Self-Construction?

In some cases, complex natural products can be generated with surprising spontaneity, and it appears that molecular complexity might emerge with minimal (if any) enzymatic assistance through self-construction mechanisms. Rearrangements of linear molecules, light-induced reactions, dimerizations and multi-component reactions could explain the formation of secondary metabolites through the intrinsic reactivity of their precursors.

We have selected several examples of natural products that seem to be the result of self-assembly or self-construction, a fundamental property of supramolecular chemistry that is applied here to molecular chemistry. For these examples, biomimetic syntheses have been proposed to strengthen the corresponding biogenetic hypotheses. In such situations, biomimetic chemistry, in its attempts to reproduce biogenetic key steps in the laboratory, shows its purpose and allows the confirmation (to some extent at least) of biogenetic pathways. If enzymatic control is not crucial, the reaction should be easily carried out in the laboratory. Furthermore, if a single reaction can lead to the formation of a complex molecular framework, it can reasonably be assumed that a similar reaction can take place in nature, possibly spontaneously without any genetic intervention.

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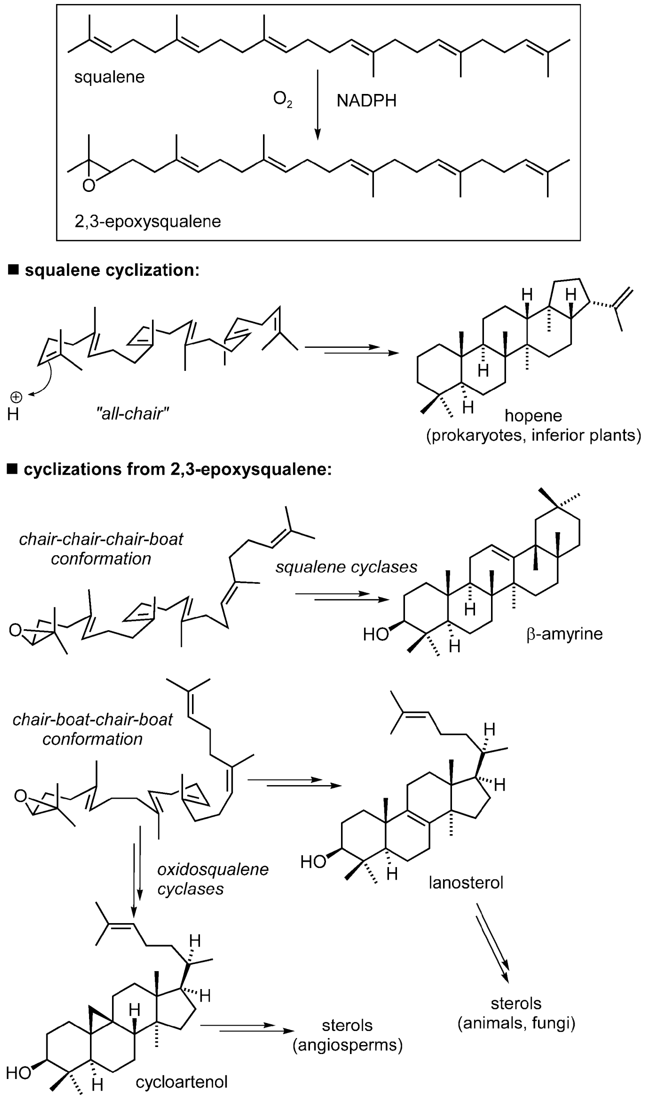
1. Intramolecular Cyclizations of Linear Precursors

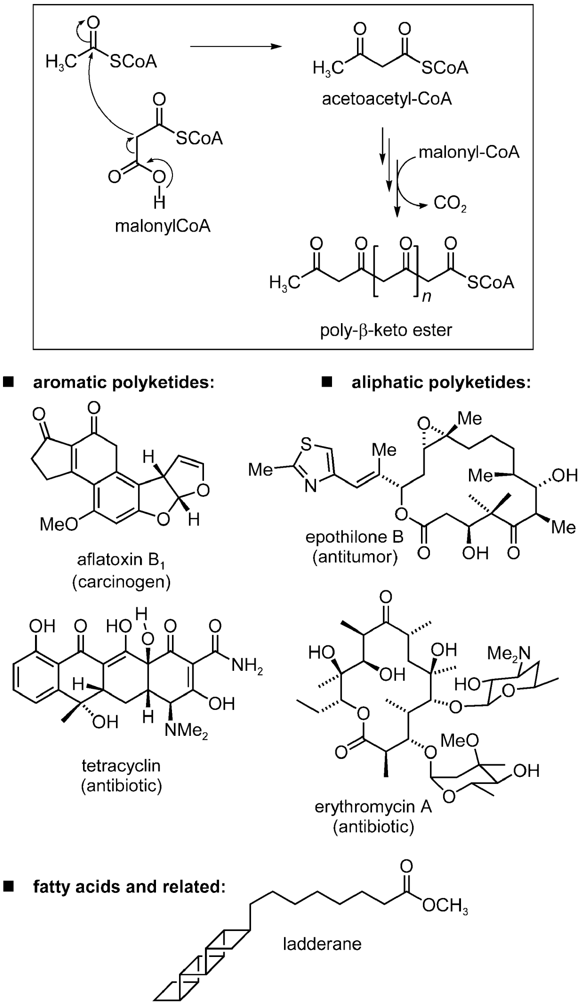
One typical example, beautifully demonstrating this process, can be found in the cyclization, or multiple cyclizations, that may occur with precursors derived from squalenes (squalene) and lead to triterpenes and steroids (Scheme 1).[1] In this case, enzymatic control is essential.



Scheme 1. The conformation of squalene in the enzyme's active site leads to the formation of different steroids and triterpenes.

The great structural diversity of the resulting molecules is a reflection of the precursors' conformations within the active sites of the enzymes (which should be regarded as matrixes or templates). Trying to mimic these reactions in the laboratory is still a challenge for organic chemists. In such cases, the role of enzymes is obviously preponderant, but are there cases in which linear precursors undergo cyclizations that lead to natural products in an apparently spontaneous manner?

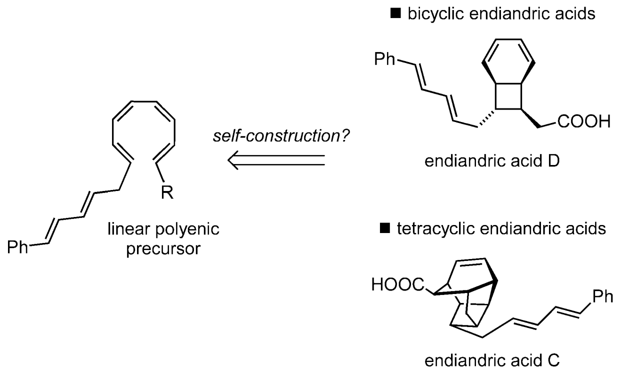
We find a few interesting examples in the family of polyketides. These molecules constitute a vast class of natural products, from the points of view both of biological activity and of the chemical diversity of the encountered structures. They are fundamentally the result of an assembly of acetate units (Scheme 2).



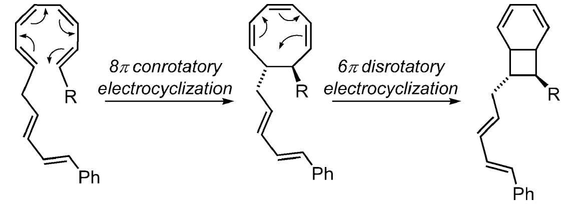
Scheme 2. Basic reactions for the formation of polyketo esters and examples representative of the diversity found within the family of polyketides.

Endiandric Acids and Electrocyclization Reactions

Endiandric acids are polyketides (Scheme 3) that were isolated from *Endiandra introrsa*, an Australian tree of the Lauraceae family.[2] These complex polycyclic compounds display a peculiar spatial organization and can bear as many as eight contiguous stereogenic centres. In 1980, Black's group suggested the first biogenetic hypothesis (Scheme 4) for these molecules.[3] They suggested that endiandric acids might originate in the organization of linear polyunsaturated precursors with a benzene ring at one end and a carboxylic acid at the other. It appears that endiandric acids A, D and E derive from precursor **8** (C_{21}), whereas endiandric acids B, C, G and F derive from precursor **9** (C_{23}).



Scheme 3. Examples of endiandric acids and their linear precursor.



8 (R = CH_2CO_2H)
9 (R = $CH_2CH{=}CHCO_2H$)

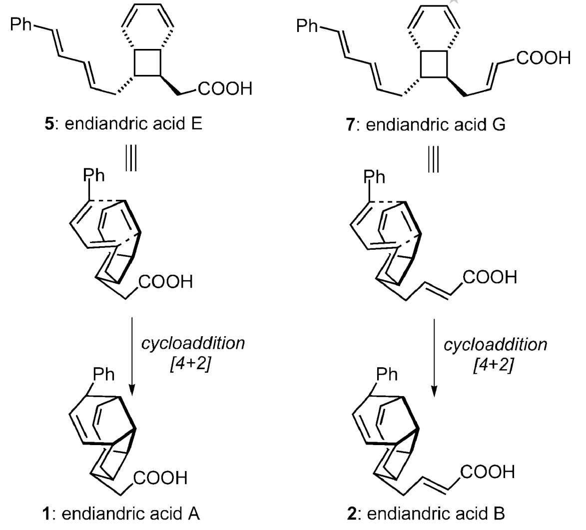
4, **5** (R = CH_2CO_2H)
6, **7** (R = $CH_2CH{=}CHCO_2H$)

Scheme 4. Biogenetic hypothesis for endiandric acids D, E, F and G.

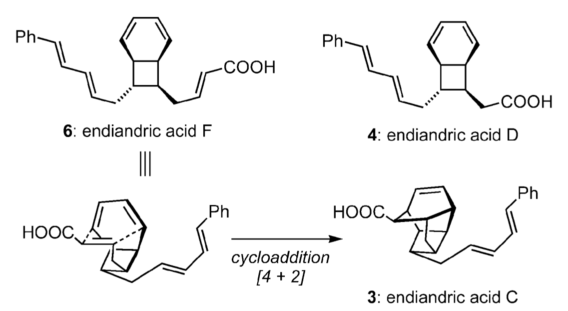
Both precursors feature the same tetraenic system, with two central olefins in *Z* configuration. This system must first undergo a conrotatory electrocyclization to give rise to a cyclooctatrienic ring, which itself undergoes a disrotatory electrocyclization. The bicycle thus obtained can have two different configurations that will allow the formation of various endiandric acids through a Diels–Alder cycloaddition process.

The spatial organizations of compounds **5** and **7** (endiandric acids E and G, respectively) allow the aromatic ends of the molecules to be near the bicycles. In these cases, the cyclohexadienes of the central cores play the role of the dienophile and the linear regions that of the diene. It is therefore possible to understand how endiandric acid A (**1**) can be obtained from **5** and endiandric acid B (**2**) from **7** (Scheme 5).

The configurations of compounds **4** and **6** (endiandric acids D and F, respectively) allow the carboxylic acid ends to come near the central bicycles. In the case of endiandric acid F (**6**), the cyclohexadienic ring plays the role of the diene and the linear chain plays the role of the dienophile to allow the formation of endiandric acid C (**3**). Endiandric acid D (**4**) bears no olefin on its carboxylic-terminated linear region and thus cannot undergo any further cycloaddition (Scheme 6).



Scheme 5. Formation of endiandric acids A and B.

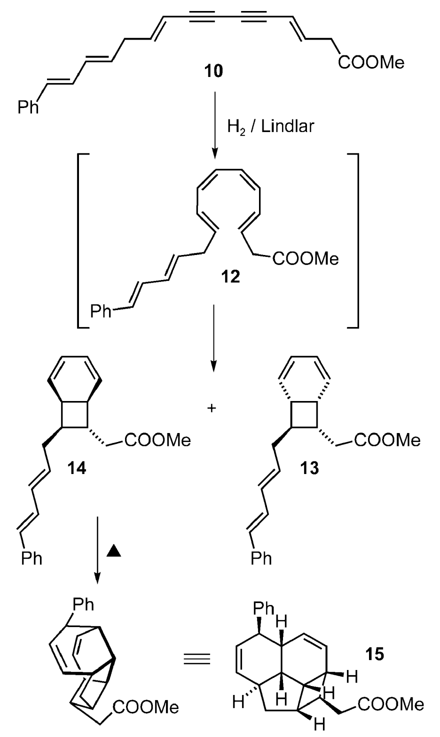


Scheme 6. Conversion of endiandric acid F into endiandric acid C.

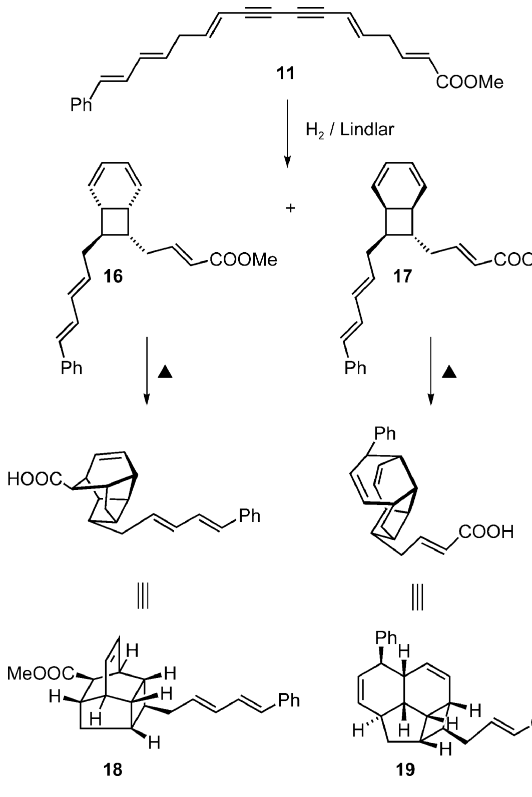
Black's hypothesis was confirmed by the biomimetic synthesis work carried out by Nicolaou's team in the early 1980s.[4] They began with the synthesis of two linear compounds similar to **8** and **9**, but with methyl esters instead of carboxylic acids and bearing two triple bonds where Black's intermediates had two olefins in *Z* configurations. The reduction of compound **10** (Scheme 7) in the presence of Lindlar catalyst led to in situ formation of a tetraenic intermediate **12** (with two central olefins in *Z* configurations). Compound **12** could not be isolated, as it spontaneously undergoes the two expected electrocyclizations described by Black in his biogenetic hypothesis to give rise to the methyl esters of endiandric acids D and E (**13** and **14**). The latter compound, when heated to 100 °C in toluene, was transformed into the methyl ester of endiandric acid A (**15**).

Hydrogenation of compound **11** in the presence of Lindlar catalyst logically afforded the methyl esters of endiandric acids F and G (**16** and **17**), which, when heated to 100 °C, produced the methyl esters of endiandric acids C and B (**18** and **19**; Scheme 8).

It is interesting to note that when this work was published, endiandric acid D had not been isolated, so this compound was described by Nicolaou's team even before its presence was actually detected in the plant. This example illustrates the power of biomimetic synthesis when it comes to the spontaneous assembly of "biocompatible" products, which might even lead to the formation of natural products that have not yet been described as such. It is also noteworthy that the endiandric acids were isolated as racemates,



Scheme 7. Biomimetic synthesis of endiandric acids D, E and A.

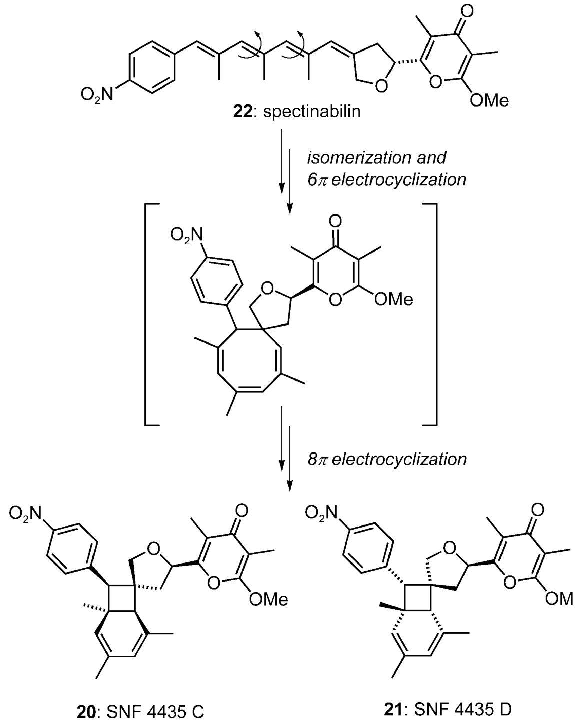


Scheme 8. Biomimetic synthesis of endiandric acids F, G, C and B.

strengthening the probability that their formation is spontaneous and occurs without any chiral induction, which is usually due to the influence of enzymes.

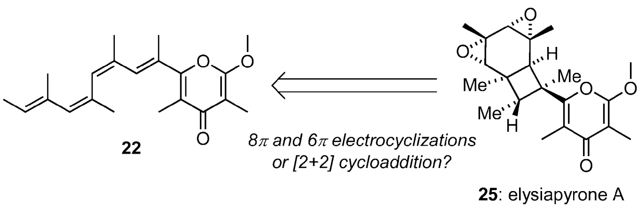
Electrocyclizations for the Generation of Molecular Complexity

A large number of secondary metabolites that might be the result of electrocyclizations have been isolated from different organisms. These molecules have recently been listed in a review article to which the reader should refer with great interest.[5] Compounds SNF 4435 C and D (**20** and **21**, respectively; Scheme 9) can serve as good examples to illustrate the role of electrocyclizations. These two molecules have been isolated from *Streptomyces spectabilis* and are the result of an 8π–6π cascade following the *E*/*Z* isomerization of spectinabilin, their common linear precursor. The biomimetic synthesis of these compounds has recently been studied by different groups.[6]



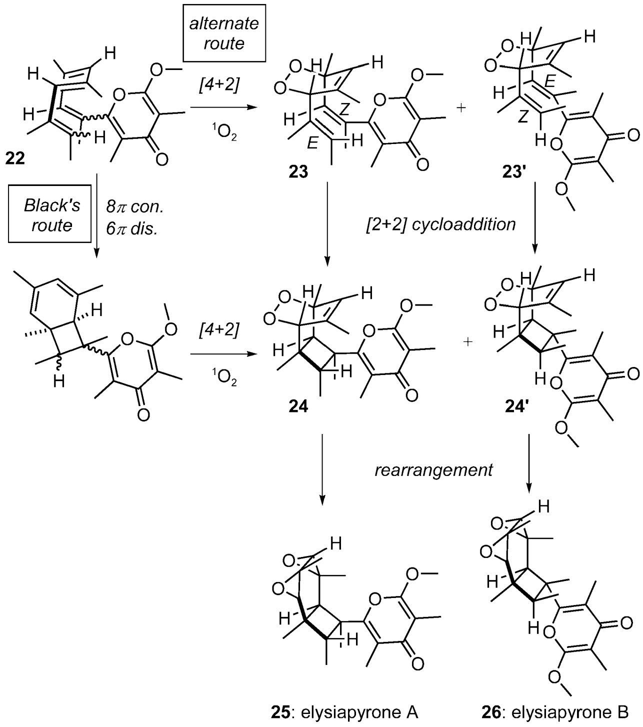
Scheme 9. Biogenetic hypothesis for SNF 4435 C and D.[5]

The biogenesis of elysiapyrones could involve either an enzymatically assisted electrocyclization process or an intramolecular [2 + 2] cycloaddition (Scheme 10).

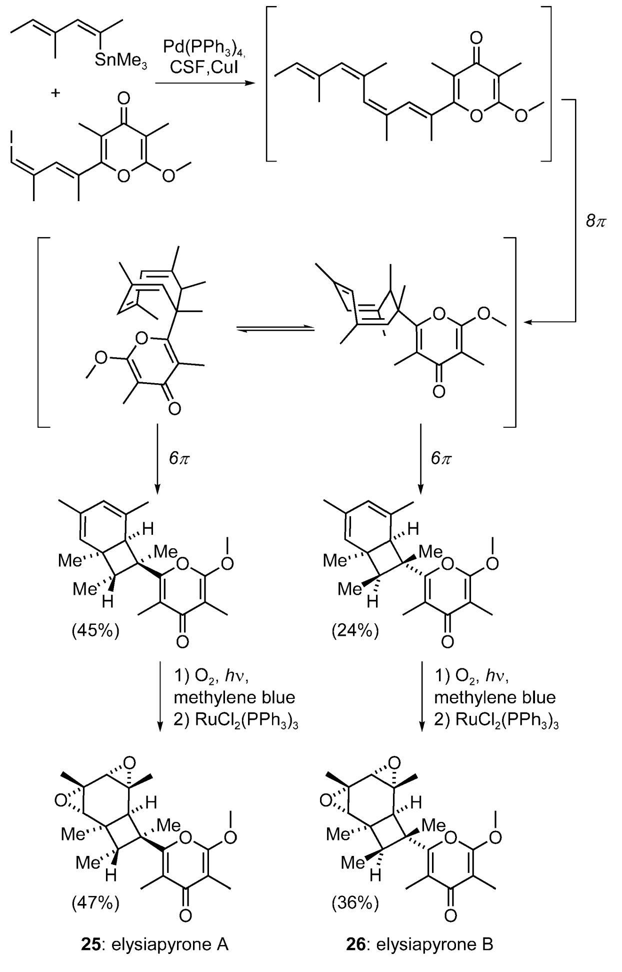


Scheme 10. Elysiapyrone A and its probable precursor.

Elysiapyrones, isolated from *Elysia diomedea* in 2004,[7] are another group of natural products featuring the bicyclo[4.2.0]octane network. In nature, they are not found in



Scheme 11. Biogenetic hypotheses for elysiapyrones.



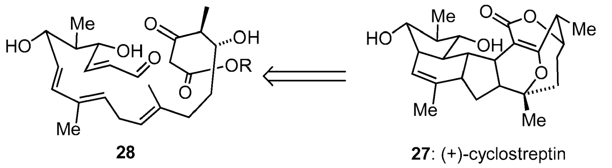
Scheme 12. Biomimetic synthesis of elysiapyrones.

racemic form but are optically active (as are SNF4435 C and D), and Cueto et al. have proposed a biogenetic hypothesis for the bicyclic core that differs from Black's. Instead of an enzymatically controlled electrocyclization cascade, the authors suggest that the alkenyl open chain of precursor **22** might be a chemical quencher of singlet oxygen and could give rise to chiral endoperoxides **23** and **23′**, which could then undergo intramolecular [2+2] cycloaddition and rearrangement into vicinal *syn*-epoxides **24** and **24′** to yield elysiapyrones A (**25**) and B (**26**) in optically active form (Scheme 11).

This alternate biogenetic route has not yet been followed by any synthetic experiments, whereas Black's hypothesis has been strengthened by the racemic total synthesis of elysiapyrones published by Trauner's group in 2005 (see Scheme 12).[8]

Cyclostreptin (FR 182877): A Bacterial Polyketide

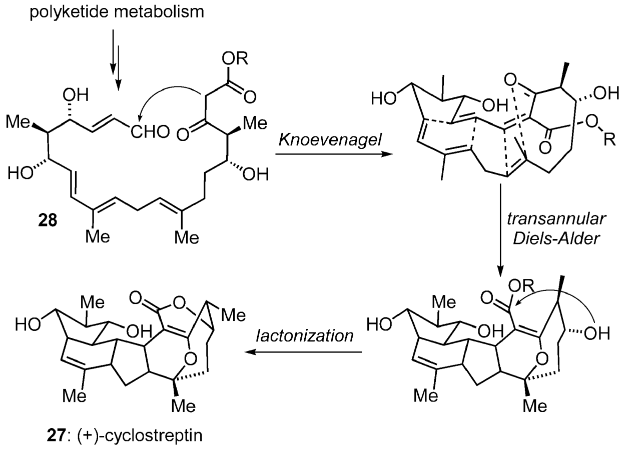
Also with regard to the metabolism of polyketides, the case of cyclostreptin (**27**), known as FR 182877 (Scheme 13), is quite instructive. Isolated from cultures of *Streptomyces*, this polycyclic compound has shown promising antitumor activity involving interaction with the "taxoid" site of tubulin and is a selective inhibitor of carboxylesterase-1.[9]



Scheme 13. Cyclostreptin and its linear precursor.

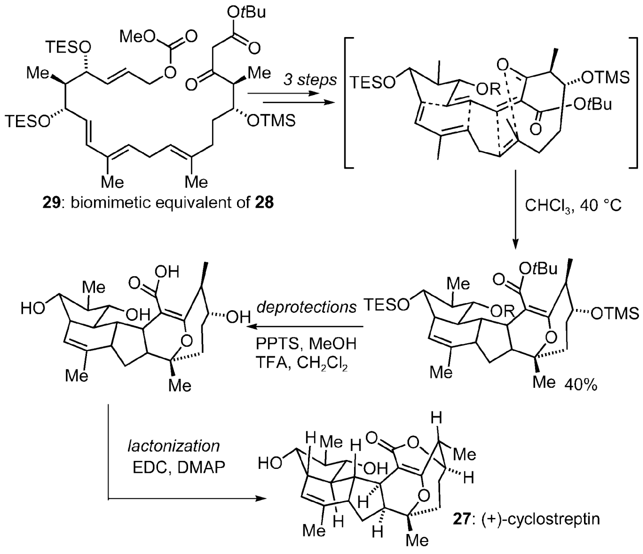
The boundary between what is genetically determined and what is spontaneous is obvious here. On the one hand, the assembly of the linear precursor **28** is clearly carried out under strict enzymatic control. On the other hand, the cyclization steps, which are responsible for most of the molecular complexity, can be explained by a spontaneous cascade of intramolecular reactions (Scheme 14). After a macrocyclization process through a Knovenagel-like reaction, two transannular Diels–Alder reactions and a final macrolactonization are needed to complete the biosynthesis of the natural product. It is worth noting that six cycles and seven asymmetric centres are formed during this three-reaction cascade.

The biomimetic synthesis proposed by Sorensen et al. confirms the biogenetic hypothesis and is, in our opinion, one of the most elegant achievements in biomimetic chemistry.[10,11] Compound **29** was synthesized as a strict biomimetic equivalent of precursor **28**. While the first macrocycliza-



Scheme 14. Biogenetic hypothesis for (+)-cyclostreptin.

tion was quite difficult to carry out, the following step to complete the synthesis of **27** proved to be of stunning efficacy (Scheme 15).

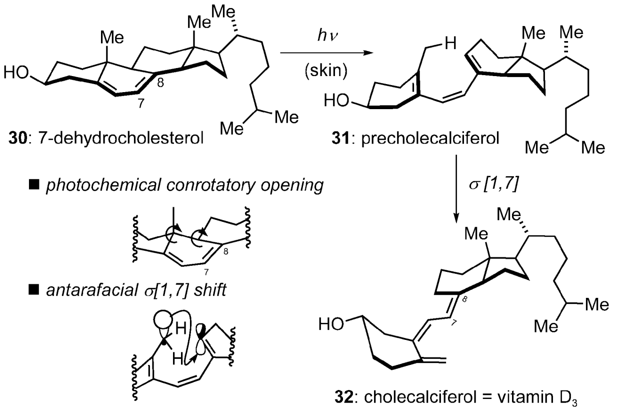


Scheme 15. Biomimetic synthesis of (+)-cyclostreptin.

2. Light-Induced Reactions

Vitamins D Are Formed by Light-Induced Rearrangements

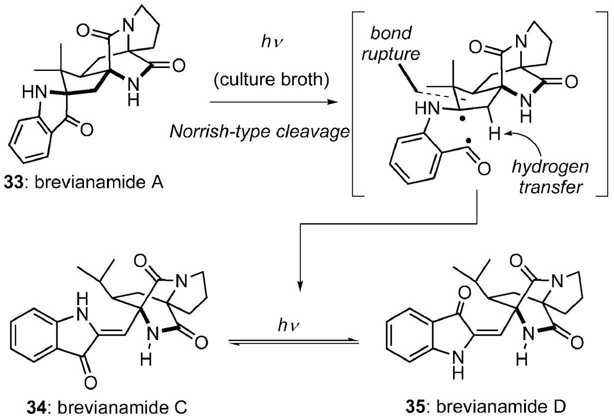
The best examples of light-induced natural products are probably the vitamins D. Vitamin D3 is the main form in animals; it is formed through the action of UVB light on the skin. The direct precursor is 7-dehydrocholesterol (**30**), a ring opening of which is the consequence of the first photochemical reaction and leads to precholecalciferol (**31**; Scheme 16). The second reaction is a spontaneous antarafacial [1,7] sigmatropic transposition that gives rise to cholecalciferol or vitamin D3 (**32**).



Scheme 16. Light-induced rearrangement of 7-dehydrocholesterol into cholecalciferol.

When Exposed to Light, Brevianamide A Converts into Brevianamides C and D

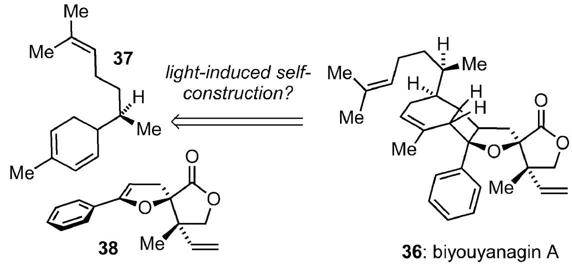
A. J. Birch clearly demonstrated this phenomenon in the early seventies.[12] Brevianamide A (**33**; Scheme 17) was isolated from a *Penicillium brevicompactum* culture. It belongs to a small family of indole alkaloids possessing an interesting bicyclo[2.2.2]diazaoctane core ring.[13] Brevianamides C and D (**34**, **35**) were isolated later from the same fungus, and it was postulated and verified that they were in fact derived from light exposure of **33**. In fact, when the fungus was grown in the dark and workup was executed under low light intensity, no formation of **34** and **35** was observed. The mechanism of this transformation probably begins with a Norrish-type photochemical cleavage of the light-activated ketone, followed by a series of rearrangements.



Scheme 17. Light-induced rearrangement of brevianamide A into brevianamides C and D.

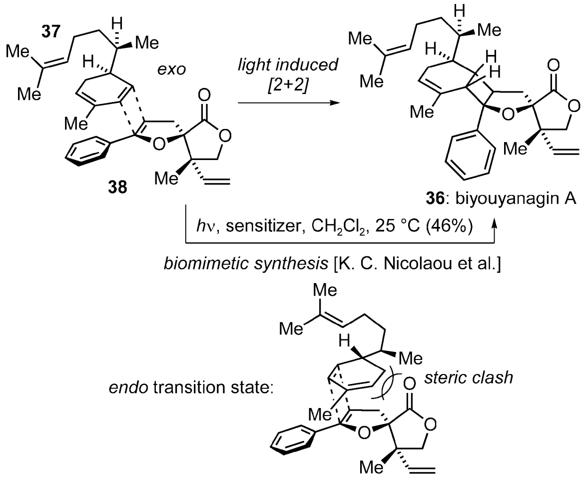
Is Biyouyanagin A Formed by a Light-Induced [2+2] Cycloaddition in the Leaves of *Hypericum* sp.?

Biyouyanagin A (**36**; Scheme 18) was isolated in 2005[14] from the leaves of *Hypericum chinense* var. *salicifolium* (a folk remedy in Japan against women's disorders) by Takaishi et al. This structurally unique natural compound displayed interesting anti-HIV activities. The authors postulated a biosynthetic pathway involving an unprecedented [2+2] cycloaddition between a zingiberene-like terpene (**37**) and a hyperolactone (**38**).



Scheme 18. Biyouyanagin A and its biogenetic precursors.

In 2007, Nicolaou et al.[15] made their own contribution to the topic by verifying the biosynthetic proposals and in the process revising the initial stereochemistry of biyouyanagin A (Scheme 19). Under classical photochemistry conditions, the two partners reacted in an efficient chemo-, regio- and stereoselective manner to give **36** in good yields.



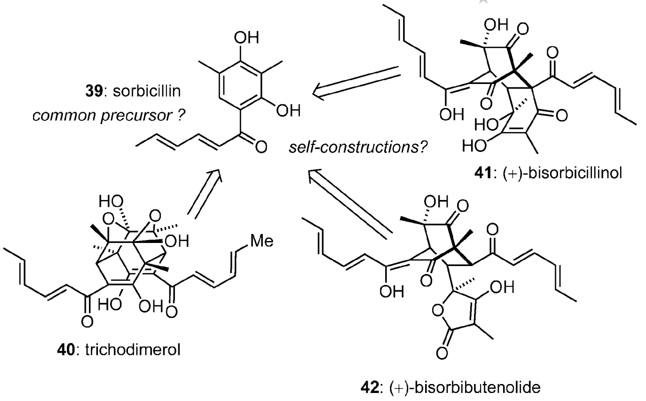
Scheme 19. Biomimetic synthesis of biyouyanagin A.

3. Dimerization as a Source of Complexity

Some natural products appear to have gained complexity from dimerization processes. To illustrate such phenomena, we have chosen some significant examples for which dimerization and further rearrangements can take place with a high degree of spontaneity. The following examples probably count among the most representative of the concepts discussed in this article.

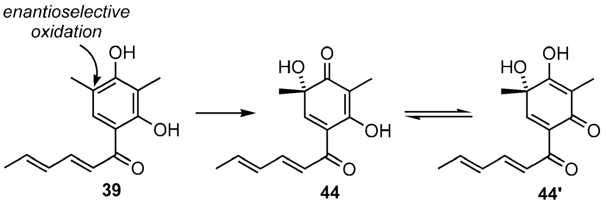
Divergent Cascades from a Common Precursor Give Rise to Bisorbicillinoids

Several compounds of a new family, isolated from different fungi such as *Trichoderma* sp., that display incredibly intricate structural features are known as bisorbicillinoids (Scheme 20).[16]



Scheme 20. Examples of different bisorbicillinoids and their common precursor.

All these molecules, despite their apparent chemical diversity, seem to be derived from the same simple polyketide precursor: sorbicillin (**39**). According to the proposed biogenetic hypothesis, sorbicillin (**39**) is first activated by oxidation (Scheme 21).

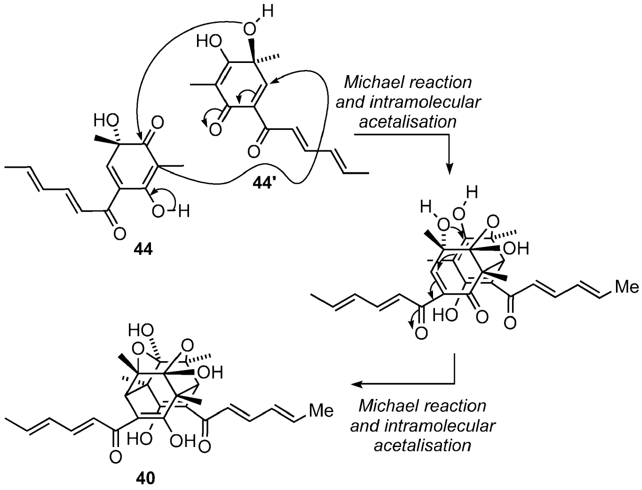


Scheme 21. Activation of sorbicillin.

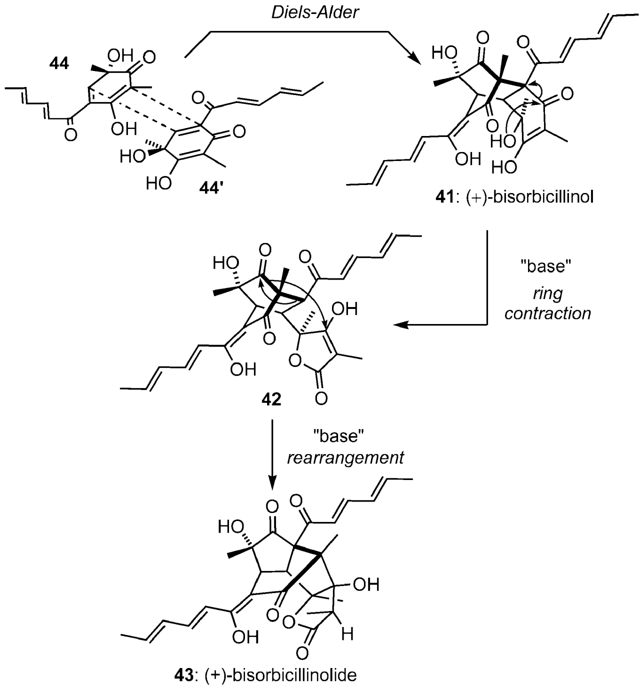
It is likely that all enzymatic participation ends here and that the remaining transformations occur through a spontaneous dimerization event followed by intramolecular reactions. Closer investigations show that two major dimerization pathways, reflecting two types of reactivity, deserve to be taken into consideration. A Michael reaction leads to the formation of trichodimerol (**40**; Scheme 22), whereas a cycloaddition process leads to bisorbicillinol (**41**; Scheme 23).

The two chemical routes probably operate in competition within the living organisms from which both molecules have been extracted. Further rearrangements of bisorbicillinol (**41**) might give rise to compounds such as bisorbutenolide (**42**) or bisorbicillinolide (**43**).

Biomimetic syntheses of bisorbicillinoids (Scheme 24) have, once again, confirmed biogenetic hypotheses. It is plausible that, from sorbicillin, the oxidation into sorbicillinol (**44**) takes place under enantioselective enzymatic control. Dimerization of this reactive precursor is then probably spontaneous and leads to the formation of bisorbicillinoids in a substrate-controlled enantioselective manner. K. C. Nicolaou et al.[17] on the one hand and E. J. Corey et al.[18] on the other have, in parallel, initiated studies to confirm Abe's hypotheses,[16] starting from compound **45** as

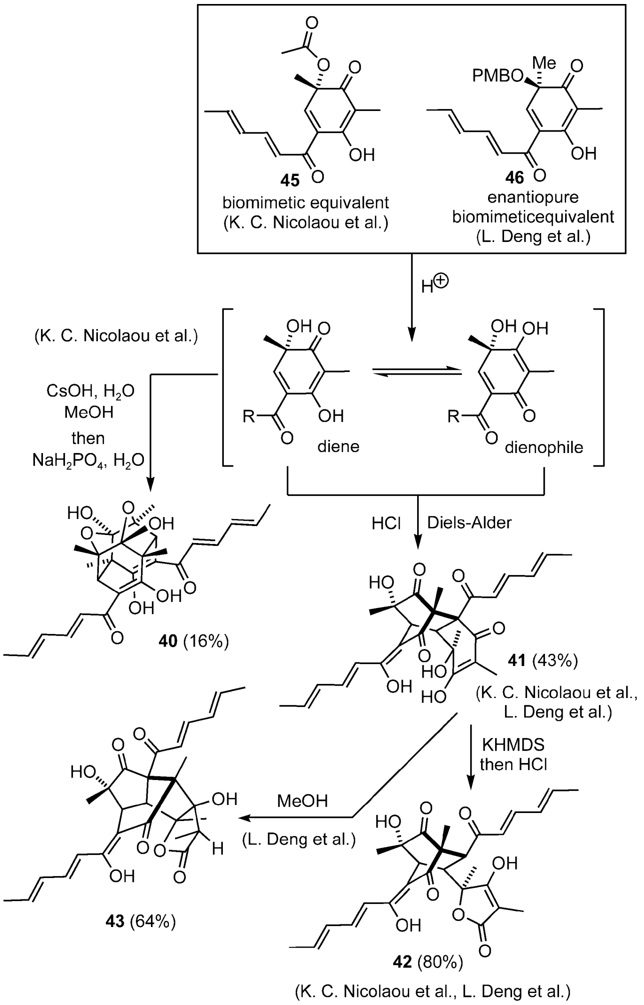


Scheme 22. Formation of trichodimerol (**40**) through Michael reactions.



Scheme 23. Formation of bisorbicillinol (**41**) through a cycloaddition process and further rearrangements to yield bisorbutenolide (**42**) and bisorbicillinolide (**43**).

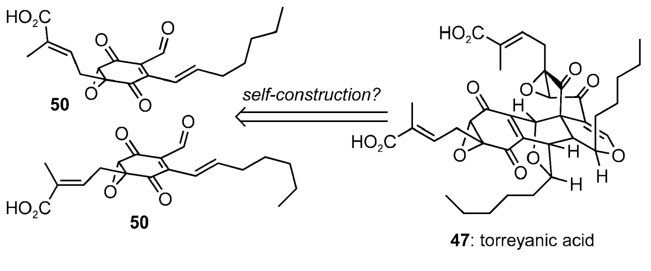
a biomimetic equivalent of **44**. By adjustment of the optimal experimental conditions, syntheses of **40**, **41** and **42** have been achieved with satisfying global yields considering the number of successive chemical reactions involved. Recently, Deng et al. have completed these studies with the synthesis of an enantiopure biomimetic equivalent **46**, which provided access to nonracemic bisorbicillinoids.[19]



Scheme 24. Biomimetic syntheses of different bisorbicillinoids.

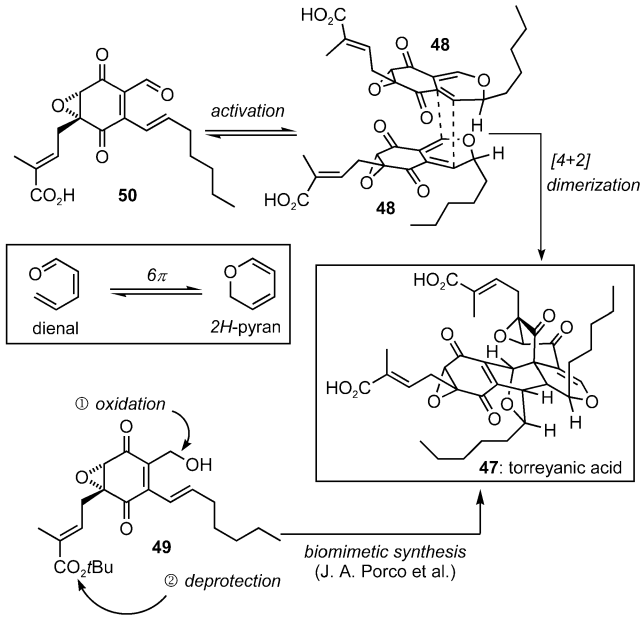
Torreyanic Acid Results from the Dimerization of an Electrocyclization-Activated Precursor

Torreyanic acid (**47**; Scheme 25) is a complex polycyclic molecule isolated from different species of the *Pestaliopsis* genus in the 1990s by Lee and co-workers.[20] These researchers then proposed a biogenetic hypothesis involving the dimerization of a tricyclic precursor **48** (the structure of which is closely related to that of ambuic acid, another natural product) through a Diels–Alder-like [4+2] cycloaddition process (Scheme 19).



Scheme 25. Torreyanic acid and its precursor.

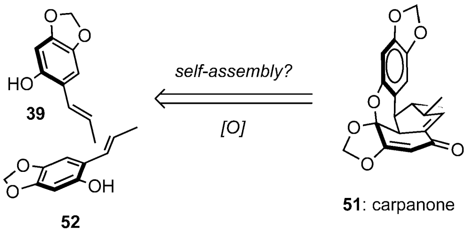
In 2003, J. A. Porco et al.[21] confirmed this hypothesis when they completed the total synthesis of **47** through the dimerization of a synthetic equivalent – compound **49** – of the compound that had been hypothesized by Lee a few years earlier (Scheme 26).[22] Oxidation of **49** (*tert*-butyl ester of **50**), followed by a 6π electrocyclization, resulted in the formation of the tricyclic compound **48**, which underwent dimerization through a [4+2] cycloaddition directly into the *tert*-butyl diester of torreyanic acid in 80% yield, demonstrating the high stereoselectivity of the reaction. It was then only necessary to carry out the hydrolysis of the two ester groups to complete the synthesis of torreyanic acid.



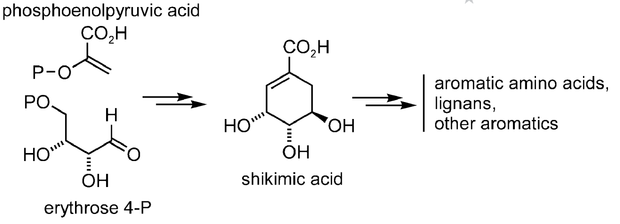
Scheme 26. Biogenetic hypothesis and biomimetic synthesis of torreyanic acid.

A Radical Coupling Followed by Spontaneous Reorganization Could Explain the Formation of Carpanone

Carpanone (**51**; Scheme 27) has been isolated from different species of the *Cinnamomum* genus. Its structure can be seen as the association of two units **52** derived from shikimic acid metabolism (Scheme 28).



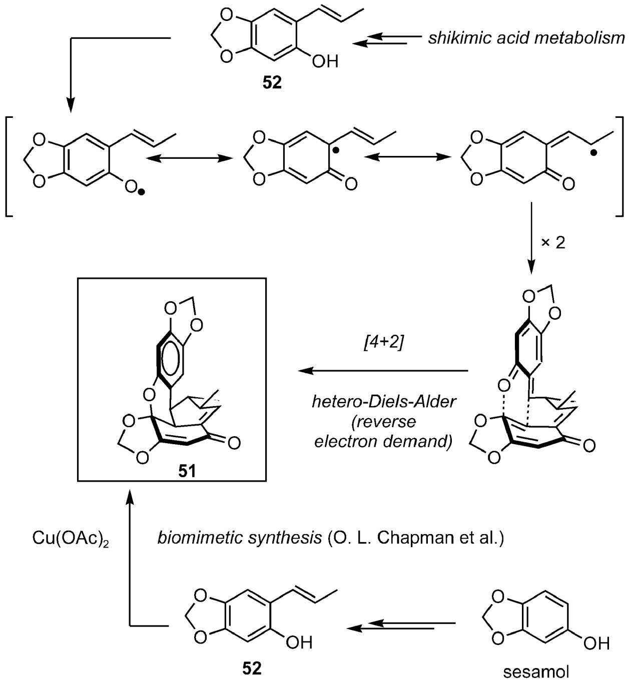
Scheme 27. Carpanone and its precursor.



Scheme 28. Overview of shikimic acid metabolism.

The key reaction here is a radical coupling. Oxidative couplings are common in nature; in the case of shikimate-derived secondary metabolites, for example, they are involved in the biosynthesis of lignans. As far as carpanone is concerned, only the formation of a free radical on the phenol of precursor **52** is needed (and enzymatic participation might come to an end at this point) to trigger a reaction cascade that easily explains the formation of the natural product. The coupling of two limit forms of the delocalized free radical and the organization of the molecular frame, through a reverse-electron-demand hetero-Diels–Alder-type reaction, can explain the formation of **51**, which, interestingly, was isolated as a mixture of enantiomers.

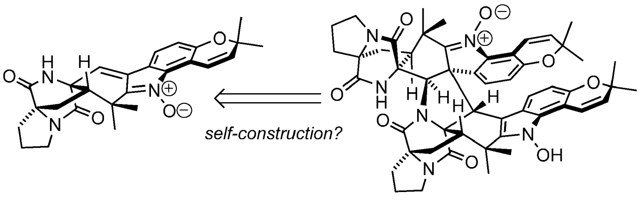
The one-step biomimetic synthesis (Scheme 29) described by Chapman et al. in 1971[23] can be seen as an elegant demonstration of the biogenetic hypothesis: under mild oxidative conditions, precursor **52** is directly transformed into carpanone.



Scheme 29. Biogenesis and biomimetic synthesis of carpanone.

Stephacidin B is Obtained Upon Spontaneous Dimerization of Avrainvillamide

Stephacidin B (**53**; Scheme 30), a member of the vast family of prenylated indoles, is probably one the most complex natural products known to this day, with its *N*-oxyindole core, fifteen cycles and nine stereogenic centres.

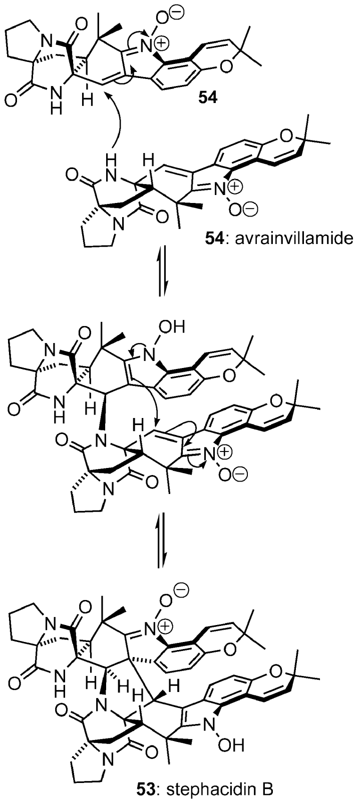


54: avrainvillamide **53**: stephacidin B

Scheme 30. Stephacidin B and its precursor, avrainvillamide.

It has been proposed that stephacidin B (**53**) might result from the dimerization of another natural product: avrainvillamide (**54**). Therefore, straightforward access to avrainvillamide (**54**) seemed rather interesting to many researchers in the community of organic chemists, in order to investigate the feasibility of the final dimerization.

Independently and almost at the same time, two total syntheses of **54** were published by Baran et al.[24] and Myers et al.,[25] and more recently Williams et al. also published their own approach.[26] Those three teams studied the biomimetic conversion (Scheme 31) of avrainvillamide into stephacidin B (**53**), which appears to be fairly efficient under diverse experimental conditions. It was shown that stephacidin B can also undergo a retrodimerization process during column chromatography purification steps. Two mutual Michael additions can be proposed to account for the mechanism of dimerization. The reversibility of such reactions is well known and explains the dynamic equilibrium observed between the two natural compounds.

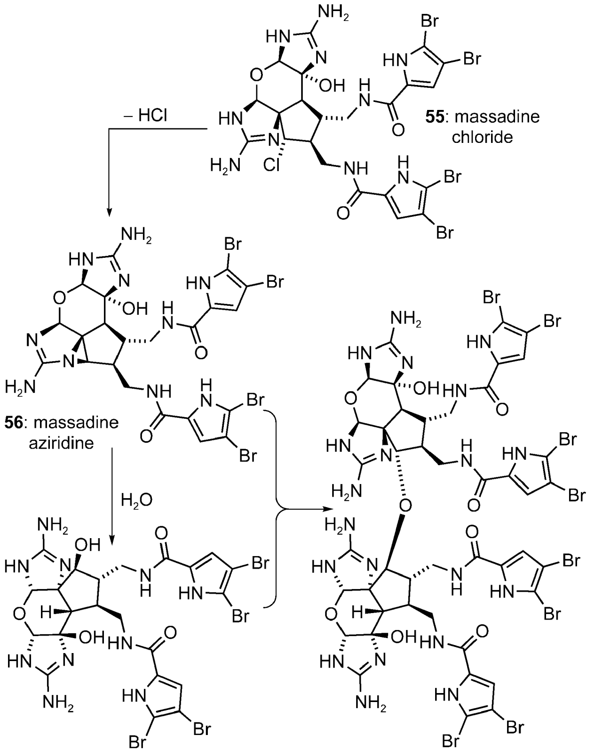


53: stephacidin B

Scheme 31. Conversion of avrainvillamide into stephacidin B.

Stylissadines Might Result from the Pseudo-Dimerization of Massadine Chloride via an Aziridine Intermediate

A recent article by Köck et al.[27] suggests that the complex polycyclic tetrameric pyrrole-imidazole alkaloids (PIAs)[28] known as stylissadines could arise from a spontaneous dimerization of massadine chloride[29] through an interesting solvolysis mechanism (Scheme 32). The authors propose that massadine chloride (**55**) might first undergo an intramolecular electrophilic substitution to form an aziridine ring (**56**), which could then be re-opened by the attack of various nucleophiles such as water (to yield massadine **57**)[30] or even by the attack of massadine itself to give rise to stylissadine A (**58**).[31] The authors are currently working on the conversion of massadine chloride into styllissadines.

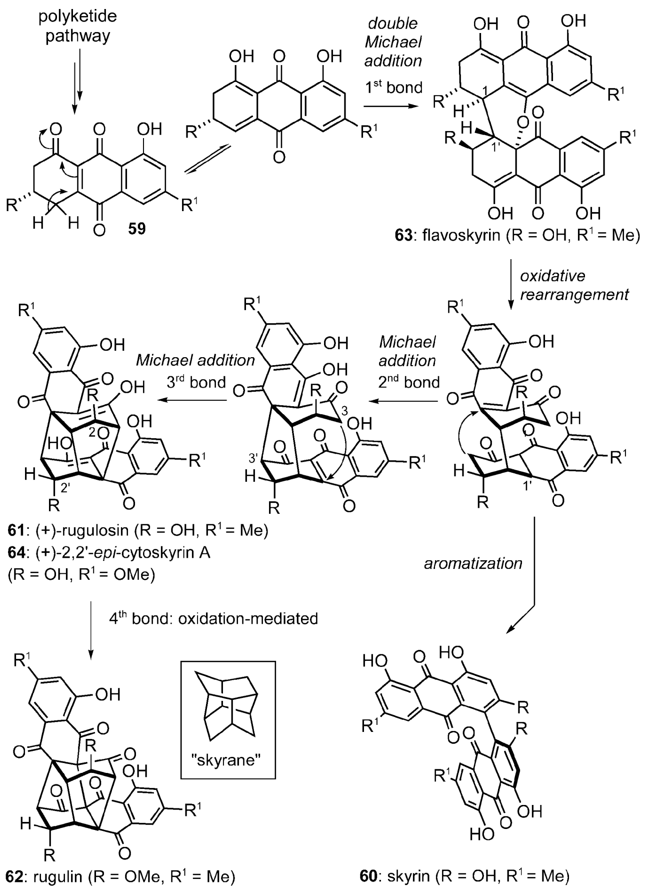


57: massadine **58**: stylissadine A

Scheme 32. Conversion of massadine chloride into massadine and stylissadine A.

The Rugulin Mystery – A "Skyrane" Core Tightly Unifies Two Anthraquinones in the Rugulin-Type Family

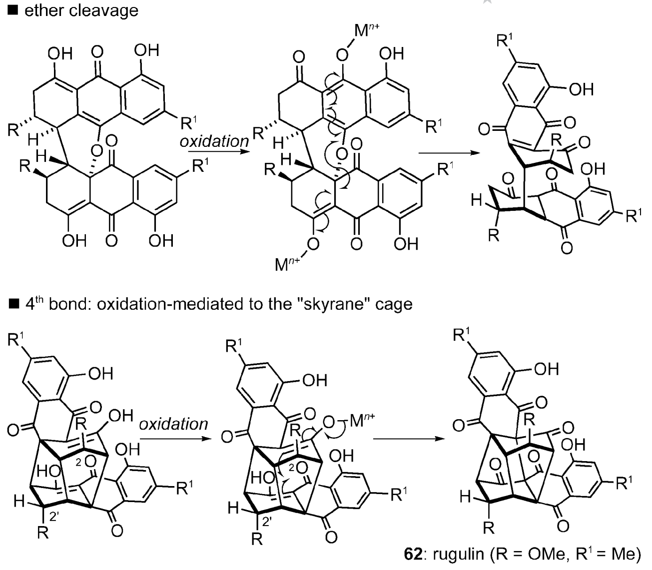
Finally, another stunning example was investigated recently. The modified bisanthraquinones isolated from endophytic fungal strains constitute an impressive example of generation of complexity starting from the dimerization of simple anthraquinones (such as **59**).[32] By way of validation, a series of molecules with increasing number of bonds between the two monomers have been isolated (Scheme 33), from one bond in the structure of skyrin (**60**) to three bonds in rugulosin (**61**) and even four bonds in the astonishing structure of rugulin (**62**). This last compound shows a unique cage system (12-carbon skeleton consisting of two six-membered rings and four five-membered rings), which has been named "skyrane".



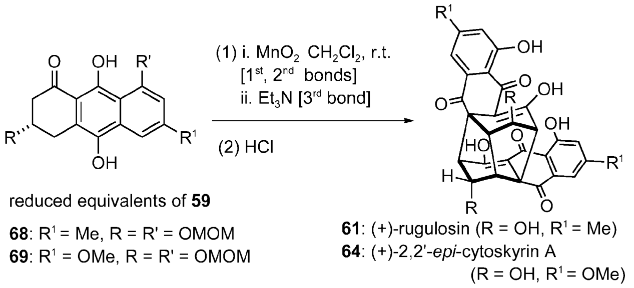
Scheme 33. The "skyrane" cascade.

From the precursors, the first step is probably the dimerization to structures such as flavoskyrin (**63**). Rearrangements then occur, explaining the formation of the diverse natural compounds: enolizations and oxidations are the driving forces for the cascades of reactions beginning with the cleavage of the ether bond (see Scheme 34 for mechanistic details).

Biomimetic investigations have been carried out and have provided answers to questions concerning the biosynthesis of these metabolites.[32,33] Simple reaction conditions permitted Nicolaou et al. the synthesis of representative members (**61**, **64**) from precursors **68** and **69** (Scheme 35). Questions arose when the route to the cytoskyrin A-type molecules[34] (**65**, **67** and precursor **66**) – which differ from the previous ones in their α-configurations at carbons 2 and 2′ – were considered. Stereochemical models have been proposed: the final absolute configuration can be explained by the stereochemistry of the starting monomers, and the 2 and 2′ configuration by the space arrangement during the dimerization step.

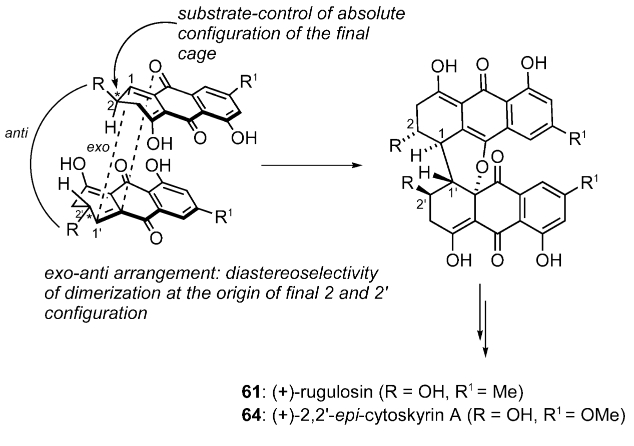


Scheme 34. Oxidative ether cleavage and fourth bond formation.

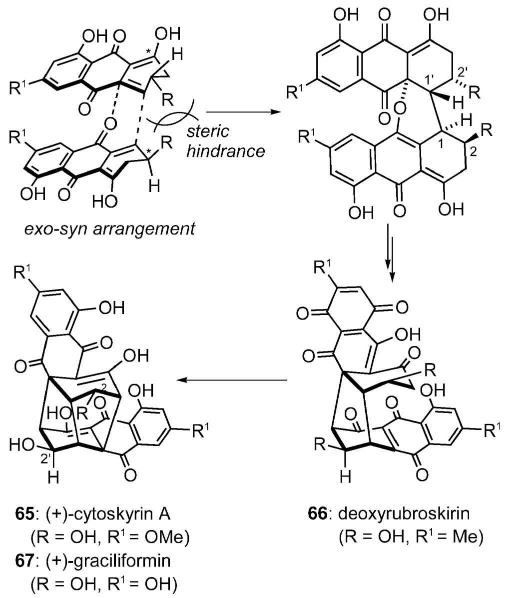


Scheme 35. The rugulosin cascade can be efficiently mimicked in the laboratory.

If this arrangement (*exo*-*anti*) is favourable in the rugulosin cascade (see Scheme 36), this is obviously not the case for the *endo*-*syn* transition state involved in the cytoskyrin A cascade (Scheme 37). In fact, whereas the rugulosin cascade was efficiently mimicked in the laboratory, no access to the cytoskyrin A-type members was possible.[32]

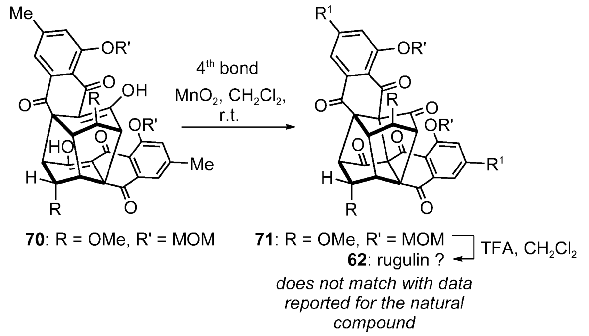


Scheme 36. Stereochemical outcome in the rugulosin series: a favourable transition state.



Scheme 37. The cytoskyrin A cascade suffers from unfavourable steric constraints.

Another issue was addressed when the total synthesis of rugulin was achieved with disconcerting ease from precursor **70**, via the formation of **71** (Scheme 38). The feasibility of accessing the skyran cage was clearly demonstrated, but the structure of the synthetic material did not match the data reported for the natural compound.[35,36]



Scheme 38. Skyrane formation and supposed structure of rugulin.

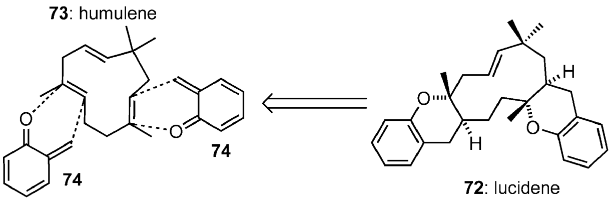
The structure of rugulin still needs to be clarified! This is a case study in which obvious spontaneous cascades are consequences of oxidation steps and where enzyme intervention is blurred. It is a typical case in which biomimetic chemistry brings answers but also opens the way to new problems.

4. Multicomponent Reactions

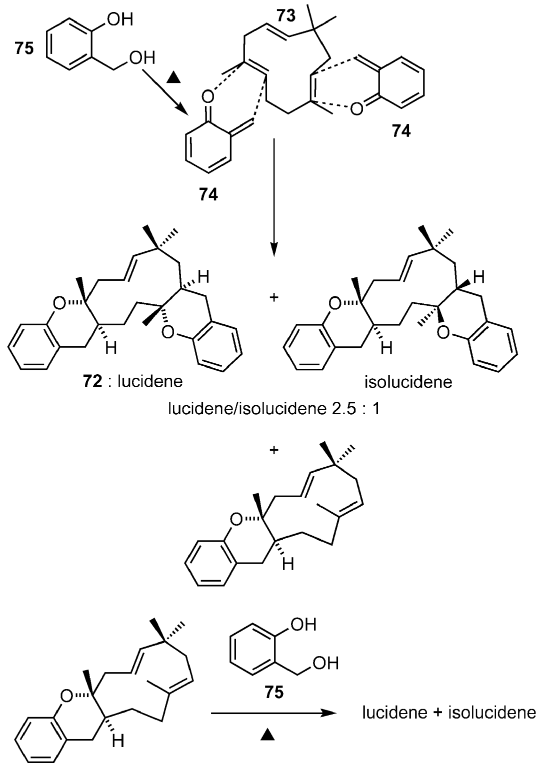
Multicomponent reactions (MCRs), which have gained popularity in organic synthesis in recent years, are in many cases extremely efficient when it comes to the preparation of complex molecules.

A Trimolecular Reaction Could Account for the Formation of Lucidene

Lucidene (**72**; Scheme 39) was isolated from the roots of *Ulvaria lucida* ssp *lucida* (Annonaceae) and is a bis(benzopyranyl) sesquiterpene found as a mixture of enantiomers in the plant.[37] From a biogenetic standpoint, humulene (**73**) could react with two molecules of methylenecyclohexadienone (**74**) to give rise to lucidene (**72**). In a biomimetic synthesis (Scheme 40) proposed by Baldwin,[38] compound **74** was generated in situ upon thermolysis of *o*-hydroxybenzyl alcohol (**75**) in the presence of humulene (**73**).



Scheme 39. Lucidene and its precursors.



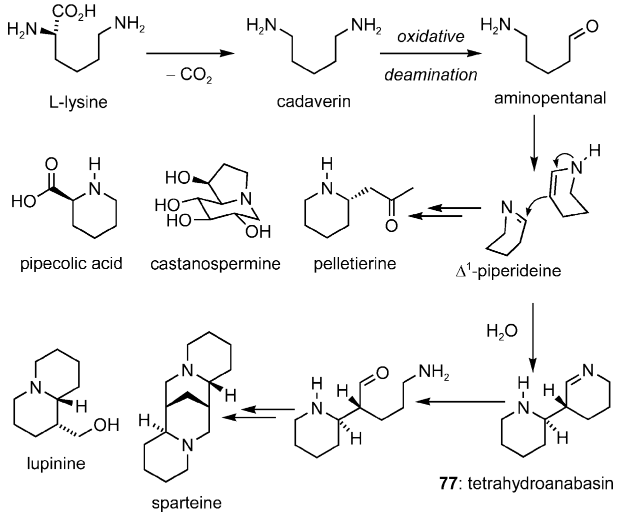
Scheme 40. Biomimetic synthesis of lucidene.

For this example, the following hypotheses can be proposed: in vivo, at a lower temperature, the formation of **74** could be achieved with enzymatic assistance, but the formation of lucidenes (lucidene and isolucidene) could be spontaneous, with the route leading to the natural diastereomer **72** being predominant.

Alkaloids of the *Nitraria* Genus Result from the Assembly of Lysine-Derived Precursors

Plants of the *Nitraria* genus, from the Zygophyllaceae family, are small bushes found in desert plains in different regions of the world (Middle-East, Australia, Northern Africa, South-Eastern Europe...).

There are many well known examples of alkaloids that originate in lysine metabolism (Scheme 41), such as lupinine, sparteine (*Lupinus* sp.) and pelletierine (vermifuge isolated from *Punica granatum*), castanospermine (glycosidase inhibitor from *Castanospermum australe*) or pipecolic acid (non-proteogenic amino acid found in bioactive peptides).

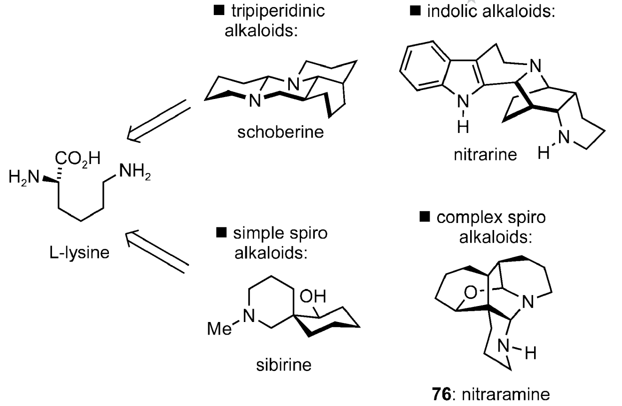


Scheme 41. Examples of alkaloids derived from the metabolism of L-lysine.

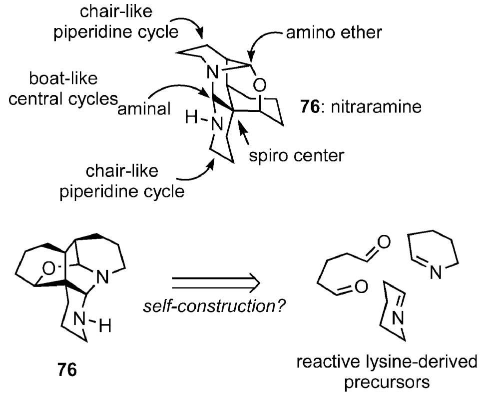
In the case of *Nitraria* alkaloids, the molecular mechanisms from lysine appear to be identical but the resulting natural products sometimes feature peculiar structures (Scheme 42), among which spiropiperidines (sibirine, nitramine), complex spiro-compounds (nitraramine) or indoles (nitrarine) are found. The fact that most of these alkaloids are isolated as mixtures of enantiomers bears witness to a rather primitive metabolism with very limited (if any) enzymatic assistance.

Nitraramine (**76**) probably has the most original and intricate structure of the *Nitraria* alkaloids (Scheme 43). With several heterocycles (three peripheral cycles in a chair-like conformation and three central cycles in a boat-like conformation) and six contiguous stereogenic centres (one of which is a quaternary spiro centre), this molecule of rather modest molecular weight can be seen as a real challenge for organic synthesis.

Koomen's team proposed a biogenetic hypothesis[39] according to which nitraramine might result from the assembly of lysine-derived simple precursors, through a series of simple reactions. Starting from tetrahydroanabasine (**77**), compound **78** can be obtained through a retro-Michael reaction followed by an oxidative deamination step (Scheme 44). The attack of a piperideine molecule (**80**) on intermediate **78** could then lead to the formation of compound **79** (or **79′**), and an intramolecular spirocyclization reaction could then give rise to the spiro quaternary centre found in the natural product. At this point, a ring inversion (on the newly formed cyclohexane) is needed to permit the intramolecular ring-closing imine reduction that ends the reaction cascade and yields nitraramine **76**.



Scheme 42. Examples of *Nitraria* alkaloids.

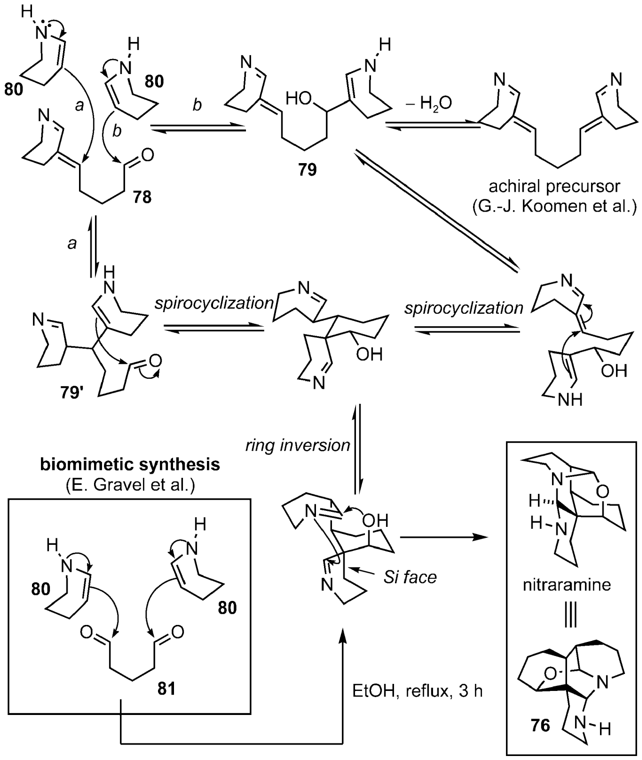


Scheme 43. Nitraramine and its possible precursors.

In view of the fact that compound **78** can be obtained from a simple reaction of piperideine (**80**) with an equivalent of glutaraldehyde (**81**), followed by dehydration, it was possible to set up a biomimetic total synthesis of nitraramine (**76**) by a one-pot process. As a matter of fact, from such simple starting materials (**80** and **81**), no oxidation or reduction step is needed and the reaction cascade quickly takes place. By treating **81** with two equivalents of **80** in ethanol under reflux for three hours, we were able to obtain nitraramine (**76**) with highly reproducible yields of 2–3% (Scheme 44). The obtained yields might seem low but are higher than those obtained in the only other published total synthesis[40] of this compound. Furthermore, the extraction of nitraramine from plants of the *Nitraria* genus (which are difficult to collect in large quantities, due to limited biomass) has proven to be of poor efficacy.

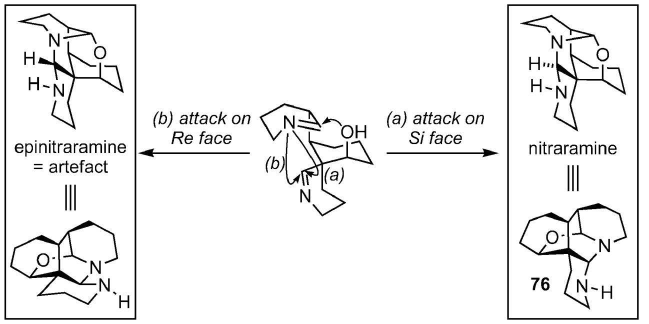
In a few hours, from very simple starting materials, we were able to synthesize enough **76** to enable the first biological studies on this compound.[41]

It should be noted that this total synthesis also highlighted the fact that the product described as epinitraram-



Scheme 44. Biogenesis and biomimetic synthesis of nitraramine.

ine, the isomer of **76** at position 1 (Scheme 45), was in fact an artefact, reflecting the variable state of protonation of nitraramine in the NMR solvent. The absence of epinitraramine in the reaction mixture shows the high "spontaneous" stereoselectivity of the cascade responsible for the formation of **76** without any enzymatic participation. Moreover, most of the reactions involved are potentially reversible, suggesting that in vivo, the biogenesis of *Nitraria* alkaloids might show dynamic behaviour.



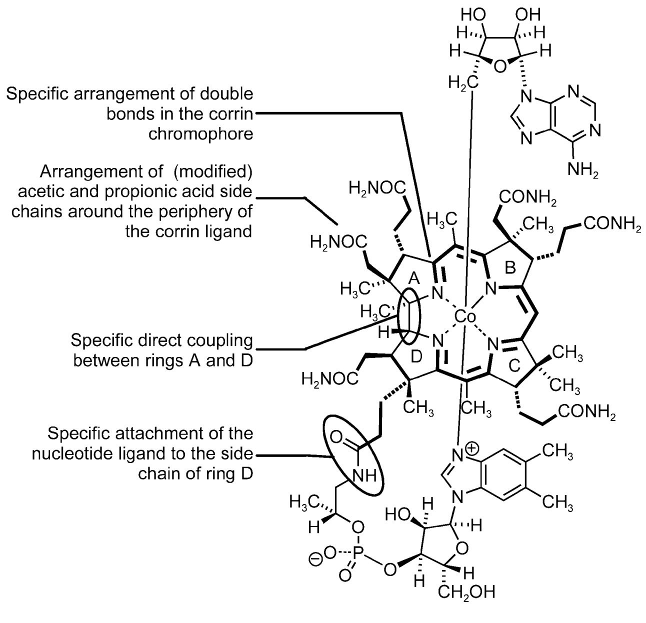
Scheme 45. Nitraramine and epinitraramine and their hypothetical common precursor.

Conclusions

Self-Construction of Natural Products, but to what Extent?

It appears that fundamental phenomena well known in the fields of biology and supramolecular chemistry (in these cases explained by noncovalent bonds) can, by analogy, be transposed to molecular levels and might account for the existence of natural substances that sometimes display puzzling degrees of structural complexity.[42] Chemical predisposition plays a key role in these cases: the reactions involved depend on the intrinsic reactivity of the precursors and the relative positions of functional groups.[43] In such circumstances, enzymatic assistance may be minimal.

With this in mind, one can explain, along with structural complexity, the impressive diversity of natural products in terms of chemical space occupation, with an optimization of the genes responsible for the biosynthesis of secondary metabolites (should all steps need a particular enzyme, the amount of DNA kilobases would be fatally incompatible with evolution's selection pressure). The work of Eschenmoser et al. on vitamin B12[44] has shown that many structural features of that complex biomolecule could indeed be formed spontaneously, or self-assembled (Scheme 46), as they are thermodynamically favoured, while their biosynthesis is known to involve many enzymatically assisted steps. These observations can also be seen as arguments in favour of some appealing theories on the origins of natural products. Molecules could be randomly and spontaneously synthesized in the beginning, in a manner close to what could be described as "natural combinatory chemistry" and, should they prove useful to the survival of the species, be selected by evolution. The organisms would then develop the enzymatic machineries needed to optimize their biosyntheses, perform a few modifications on the selected scaffolds or produce only the most beneficial of the two enantiomers.[45] Thus, when isolating compounds from an "archaic" organism (with very few specific enzymes), there will be a higher probability of finding secondary metabolites as mixtures of enantiomers.



Scheme 46. Potentially self-assembling structural elements of coenzyme B12 (5-deoxyadenosylcobalamin).

These hypotheses are part of a reasoning that is more globalist or holistic than reductionist. They tend to show that the emergence of complexity in the living world can sometimes only result from intrinsic properties of the precursors, from their reactivity or from "information" stored in matter. The genome, in such a situation, provides the proper environment, as the enzymes selected by evolution are the "useful" ones. In this spontaneous organic chemistry, one can see remnants of protometabolism[46] according to the principle of "congruence".

One should keep in mind that since the exploration of chemical space by natural products is highly effective (in terms of diversity and complexity), there is a globally higher probability of finding, for example, future medicines among these molecules than there is among compounds derived purely from chemical synthesis. Spontaneous formation of molecules could account for this exploration of chemical space, at least to some extent.

Complexity arises when the increase in self-organization exceeds the increase in entropy: supramolecular chemistry and biology demonstrate this in a baffling way. We have tried to highlight in a non-exhaustive way the fact that complexity can also appear spontaneously in the realm of natural products. To strengthen this hypothesis, strategies of biomimetic chemistry have in many cases proven to be of surprising efficacy. For instance, considering one aspect, biomimetic strategies are ideal for avoiding the overuse of protecting groups.[47] Chapters of the art of total synthesis have been beautifully written on the basis of biomimetic considerations, and it is probable that if other synthetic paths are investigated in the future, it will be difficult to have any gain in efficacy.

Acknowledgments

We wish to thank Prof. Reynald Hocquemiller for his constant interest in our work and Prof. Michel Lebœuf for his careful reading of the manuscript and his suggestions.

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