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Perspective

Architectural Self-Construction in Nature and Chemical Synthesis

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Abstract—The chemistry of squalene oxide (**1**) exemplifies that architectural complexity can be encoded in the structures of relatively simple, polyunsaturated molecules. When the concept of architectural self-construction is an integral part of the design of a chemical synthesis, powerful strategies can be uncovered. this article addresses studies which showed that polyunsaturated, 19-membered ring carbocycle contains all of the molecular information that is required to give the stereochemically complex polycyclic architecture of the cytotoxic natural product FR182877.

Introduction

Molecular self-assembly implies the formation of higher-ordered structures or aggregates by the spontaneous union of two or more components through bonding that is either covalent or noncovalent.[1] The self-organization of the ribosome from its protein and RNA components and the formation of Buckminsterfullerene via the condensation of vaporized carbon are grand examples of noncovalent and covalent self-assemblies in Nature, respectively. But what are we to think of the stereospecific polycyclization of squalene oxide (**1**), the central step in the biogeneses of steroids such as dammaradienol (**2**), lanosterol (**3**), and cholesterol (**4**) (Scheme 1)?[2] This process starts with an acyclic chain of alkenes that is assembled, albeit not 'self-assembled', from acetyl CoA; in one fell swoop, squalene oxide transmutes to complex structures such as **2** under the direction of an enzyme that ensures the formation of only one enantiomer of the steroidal product. Remarkably, all of the molecular information necessary to accomplish this transformation is pre-programmed, so to say, in the polyunsaturated skeleton of squalene. The conformational diversity of the transition states of squalene polycyclizations translates into the constitutional and configurational diversity of the polycyclic triterpenes.[2c,2d,3] This stereospecific process has a strong component of 'self-assembly' or, better, 'self-construction', and efforts to simulate it in the context of organic natural product syntheses have been remarkably successful.[4] The cascade cyclization of squalene oxide is the prototype for architectural self-constructions that are encoded in the structures of polyolefinic molecules. The chemistry of squalene is deeply inspirational to synthetic organic chemists who attempt to harness the intrinsic capacity of certain complex, polycyclic molecules to self-construct. Nicolaou's striking biomimetic syntheses of the endiandric acids[5] and Heathcock's brilliant conversion of dihydrosqualene dialdehyde to dihydro-protodaphniphylline[6] are two achievements that exemplify the benefit to organic synthesis that can occur when the concept of architectural self-construction is an integral part of the design of a synthesis.

Emulating nature's efficiency in the synthesis of architecturally unique, bioactive natural products

The forerunner of the modern era of organic natural product synthesis, Sir Robert Robinson's influential synthesis of the alkaloid tropinone, is also an early example of a covalent self-assembly process.[7] This achievement brimmed with modern ideas about synthesis design, featured a splendid union of succindialdehyde, methylamine, and acetone dicarboxylic acid, and clearly showed that efforts to 'find nature's own way of working'[8] can lead to concise syntheses of novel and complex molecular architectures. Ideas about the structural origins of natural products are at the heart of biomimetic or biogenetic-type syntheses.[9] While some biomimetic syntheses simulated known biosynthetic transformations, others,

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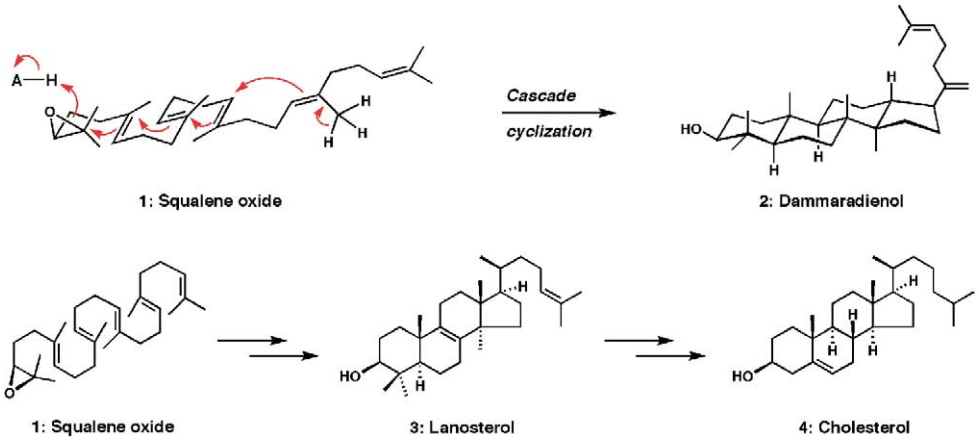


Scheme 1. The cascade cyclization of squalene oxide (**1**) is the prototype for architectural self-constructions.

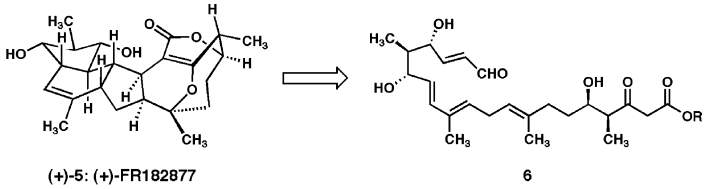
such as Woodward's synthesis of chlorophyll[10] and Eschenmoser's A–D variant for the synthesis of vitamin B_{12},[11] may have provided glimpses into the evolutionary past of a natural product's molecular structure.

The research of our laboratory is often guided by questions about how architecturally unique, biologically active natural products are formed in nature, and we recently synthesized both enantiomers of the cytotoxic natural product FR182877 (**5**) by an approach that provided a chemical rationalization of its molecular structure.[12] Scientists from the Fujisawa Pharmaceutical Company elucidated the novel structure of this cytotoxic, bacterial-derived natural product and discovered that this compound is capable of stabilizing microtubules in a Taxol-like fashion.[13] FR182877 possesses several elements that are hallmarks of molecular complexity, and yet it seemed to be the type of structure that could potentially form itself from the much less complex, polyketide-like compound **6** (Scheme 2). Our goal was to evaluate the chemical basis of this hypothesis and the feasibility of the ring-forming reactions shown in Scheme 3.

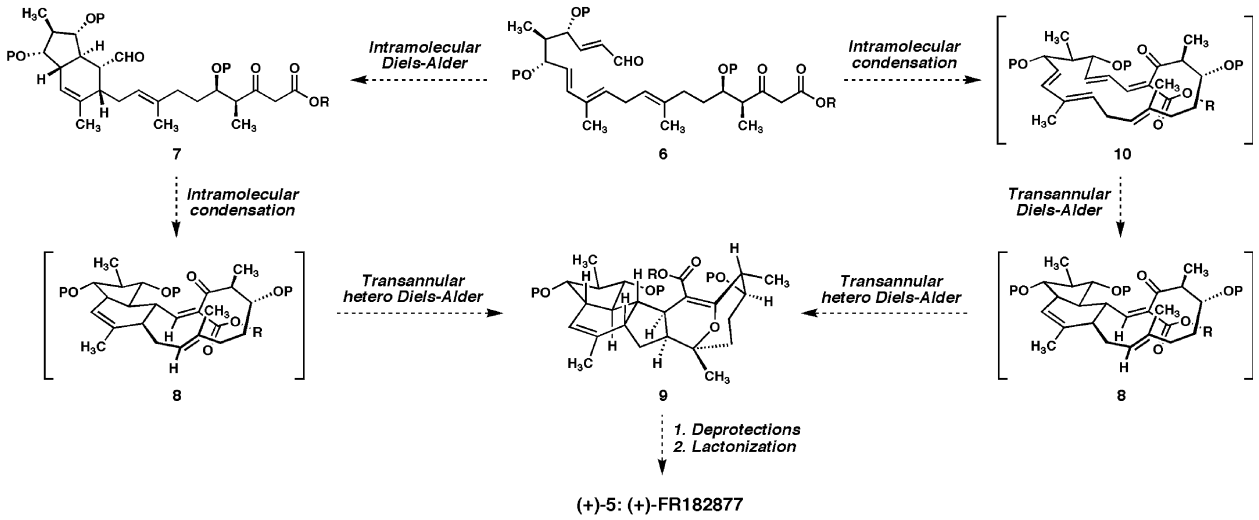
At an early stage in our work, we observed that compounds of type **6** with acyclic protecting groups on the 1,3-diol grouping were efficiently converted to both *endo* cycloadducts of a type-I intramolecular Diels–Alder reaction in aqueous and organic solvents (for clarity, only *endo* cycloadduct **7** is shown). However, it was not possible to advance **7** (in protected or unprotected form) to compound **8** via a Knoevenagel condensation, nor was it possible to form polyunsaturated, 19-membered ring carbocycles of type **10** through cyclocondensations of long-chain compounds such as **6**. The intriguing possibility that macrocycle **10** might undergo tandem transannular Diels–Alder reactions to give pentacycle **9** and that the outcome of such a complexity-generating process would be encoded in the structure and conformational preferences of **10** was of much interest to our laboratory. The pioneering studies of transannular Diels–Alder reactions by the Deslongchamps laboratory[14–16] fostered confidence in this idea for synthesis.

As matters transpired, we found that a ring forming method developed by the Trost laboratory[17] permitted a high-yielding synthesis of the desired 19-membered ring macrocycle. It proved to be impossible to isolate and characterize compound **10**, for this substance spontaneously undergoes the desired sequence of transannular pericyclic reactions even at room temperature! This transformation produced a complex ring system and seven new contiguous stereocenters in a highly diastereoselective fashion. Pentacycle **9** was isolated in yields ranging from 61-66%; the minor byproducts that were isolated and characterized all derived from the undesired α,β-alkene geometrical isomer of **10**. Interestingly the diastereoselectivity of the transannular cycloadditions that transformed **10** to **9** was a consequence of the geometries of the alkenes in **10** and a ring conformational preference and did not result from the directing effect of an external source of asymmetry.

By a straightforward reaction sequence featuring a lactone ring formation, pentacycle **9** was converted to (+)-FR182877 [(+)-**5**], the enantiomer of naturally occurring FR182877 [18]. We also synthesized (−)-FR182877 [(−)-**5**] and 5 grams of the immediate precursor to (−)-**5** by this chemistry. These chemical studies validated a hypothesis that evolved from thoughts about how



Scheme 2. Is FR182877 the product of an architectural self-construction?



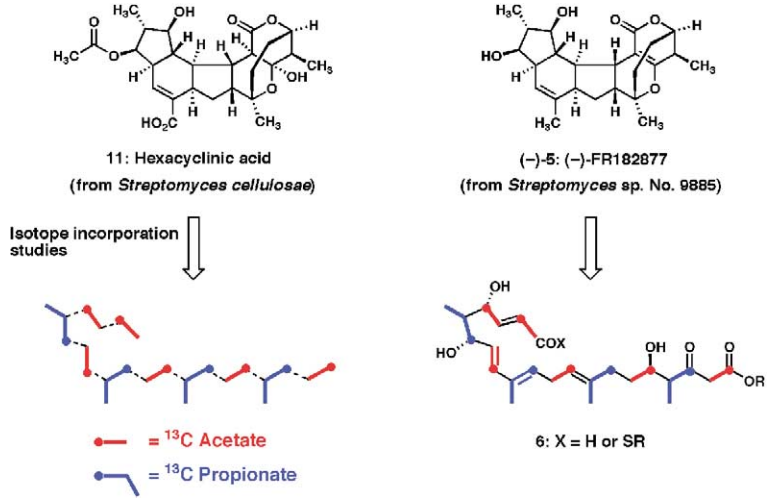
Scheme 3. Approaches to FR182877 featuring a cascade of cyclizations. P = protecting group.

nature may build the unique and complex structure of FR182877 (Scheme 2).

Future directions: A chemical approach to polyketide diversity

The facility and stereospecificity of the transannular cyclizations described above has induced our laboratory to ask the following question: Can architecturally diverse compounds possessing features of FR182877 be created by an analogous self-construction mechanism? Interestingly, the recently described natural product hexacyclinic acid (**11**) (Scheme 4) is closely related to (−)-FR182877 [(−)-**5**] with respect to constitution and absolute stereochemistry.[19] Through isotope incorporation studies, Zeeck and coworkers revealed the polyketide origin of hexacyclinic acid and an alternating sequence of six acetate and four propionate units that is reflected in **6**, a compound type that may have a counterpart in the biosynthesis of FR182877. It was of much interest to us that the complex architectures of hexacyclinic acid and FR182877 can be reduced to the same acyclic polyketide, and we regarded the findings of the Zeeck laboratory as support for the proposal that (−)-FR182877 is, like hexacyclinic acid (**11**), a polyketide natural product.

The discovery that the stereochemically complex, polycyclic structure of FR182877 is encoded in the constitution of a relatively simple macrocyclic precursor suggested that it might be feasible to synthesize manifold polyketide-like compounds by a strategy that would take full advantage of the power of transannular pericyclic reactions. Some of the most important pharmaceuticals and agrochemicals are naturally occurring polyketides, and there is a high current interest in the development of molecular genetic[20] and chemical[21] methods to expand the structural diversity within this class of compounds. An aim of our current research is to apply lessons that we learned in the course of our asymmetric synthesis of FR182877 to the problem of creating architecturally and stereochemically diverse polyketide-like compounds. We anticipate that this research in chemical synthesis will facilitate the discovery



Scheme 4. The polyketide hexacyclinic acid (**11**) and (−)-FR182877 [(−)-**5**] are closely related with respect to constitution and absolute stereochemistry and likely share a similar biosynthesis.

of molecules having novel bioactivities and offer an alternative to linear strategies based on genetic engineering.[20]

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