The Art of Total Synthesis
István E. Markó
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binds to a structured region of RNA within an HIV intron and thereby facilitates export of HIV pre-mRNA. However, CRM1 appears not to be the major export receptor for cellular mRNAs, because bulk mRNA export is largely unaffected by leptomycin B, a small-molecule inhibitor of CRM1 activity. In contrast, NES-mediated protein export, Rev-mediated RNA export, and small nuclear RNA (snRNA) export are all completely inhibited by leptomycin B. This suggests that redundancy (that is, the presence of another protein with activity identical to that of CRM1) does not explain the lack of an effect of leptomycin B on bulk mRNA export.

Leptomycin B binds tightly, and probably covalently, to CRM1 and is a rapid and potent inhibitor with minimal known side-effects—a dream for cell biologists. However, because no other effective small-molecule inhibitors have been identified, and an excellent in vitro system for export has yet to be developed, RNA export has remained a largely "in vivo" field. It is from this perspective that the paper by Gallouzi and Steitz (*1*) is so valuable. In addition to defining the tasks of new receptors and adaptors for the export of specific mRNAs and raising the profile of CRM1, the authors describe a strategy that should permit the design of many more small-molecule inhibitors. As a demonstration of the power of their approach, they show that there are two pathways for the export of c-*fos* mRNA (see the figure). In one pathway, the HuR adaptor protein interacts with the transportin export receptor, and in the other, HuR interacts with its ligands (pp32 and APRIL) and the CRM1 export receptor.

In principle, because cell-penetrating peptide inhibitors should inhibit their target proteins rapidly, they are superior to other "functional knockout" approaches such as RNA interference (RNAi). RNAi prevents translation of a protein by destroying its mRNA; however, a long-lived protein will continue to be active long after its synthesis has stopped. The more rapidly a peptide affects RNA export, the more likely it is that the peptide directly (rather than indirectly) inhibits export of the target RNA. This logic has been applied to the interpretation of yeast temperature-sensitive export mutants: In some cases, mRNA retention is detectable within 5 minutes of a shift to the nonpermissive temperature, suggesting that the wild-type proteins contribute directly to mRNA export. From this perspective, it is conceivable that these designer inhibitory peptides will generate a mammalian cell tool kit that will parallel the temperature-sensitive mutant collection available to yeast geneticists.

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PERSPECTIVES: NATURAL PRODUCT SYNTHESIS

The Art of Total Synthesis

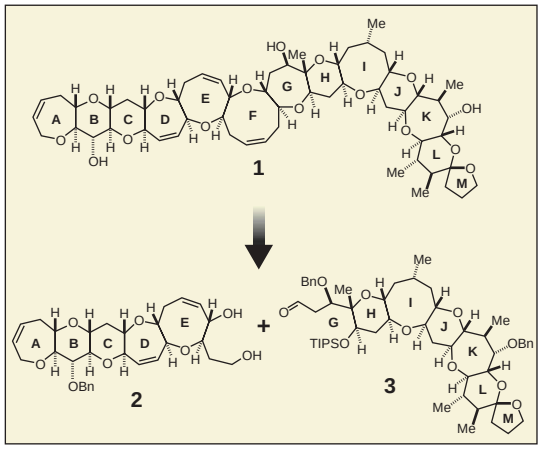
István E. Markó

The total synthesis of complex natural products remains the most difficult, daunting, and challenging endeavor in organic chemistry. It is also the most humbling, exhilarating, and formative entreprise in our science. The sizes and complexities of the natural products synthesized today bear no resemblance to the substrates that were targeted in the beginning (*1*). The assembly of complex natural products has stimulated the development of powerful synthetic methodologies that enable organic chemists to build, in a shorter time and more efficient manner, structures of previously undreamed complexity. The desire to imitate nature has led to the discovery and establishment of powerful biomimetic approaches, as exemplified by the Johnson synthesis of steroids (*2*).

The remarkable synthesis of vitamin B12 by Eschenmoser (*3*) and Woodward (*4*) marks the start of the modern natural product synthesis. Before this work, organic synthesis was performed primarily to nail down the structure of particular molecules. But the structure of vitamin B12 was known through the pioneering crystallographic work of Dorothy Crowford Hodgin. The emphasis thus shifted to exploring new synthetic routes to make this complex material from simple starting materials.

The synthesis took 11 years and involved more than 90 separate reactions performed by over 100 co-workers. The stereochemical puzzles involved in the synthesis led to the Woodward-Hoffman rules, which spell out how the electronic structures of molecules reorganize during reactions. The vitamin B12 synthesis revolutionized theoretical chemistry, and the Woodward-Hoffman rules paved the way to the use of orbital theory by the chemical community (*5*).

The next milestone in organic chemistry was the discovery by Barton that organic molecules could be assigned a preferred conformation and that the chemical and physical properties of a molecule could be interpreted in terms of that preferred conformation (*6*). This discovery helped to guide synthetic pathways. Retrosynthetic analysis, which entails going backward from a target molecule to starting materials, was introduced by Corey and Cheng (*7*) and its relevance demonstrated by a number of exquisite total syntheses. The advent of organometallic chemistry and the realization that metal complexes could perform unique transformations resulted in a major leap forward in the complexity and size of the molecules that could be prepared (*8*). Analytical tools have evolved in parallel. For example, powerful nuclear magnetic resonance spectrometers can now routinely detect



The key strategic disconnection.

The author is at the Université Catholique de Louvain, Unité de Chimie Organique et Médicinale, Batîment Lavoisier, Place Louis Pasteur 1, B-1348 louvain-la-Neuve, Belgium. E-mail: marko@chim.ucl.ac.be

microgram quantities of substances. But the challenges awaiting organic synthesis are unlimited as ever more complex biological structures are discovered.

In this context, Hirama *et al.*'s synthesis of ciguatoxin CTX3C **1** (see the figure), which is reported on page 1904, is a formidable achievement (*9*). Ciguatoxin CTX3C, a highly potent marine toxin produced by the dinoflagellate *Gambierdiscus toxicus*, belongs to the ciguatera family of neurotoxins, which are causative agents of seafood poisoning in subtropical and tropical regions. These neurotoxins, which are far more dangerous than the related red-tide toxins, the brevetoxins (*10*), can be carried by more than 400 species of fish and are responsible for poisoning more than 20,000 people annually. The content of ciguatoxins in fish is so low that it has hampered their isolation, studies of their biological activity, and, most importantly, the preparation of antibodies to ciguatoxin that would be of enormous help in detecting their presence in contaminated seafood.

The synthetic challenge in building up ciguatoxin CTX3C **1** is reflected in its uniquely complex, ladderlike structure, which contains 13 rings with 5 to 9 members. Twelve of the rings are trans-fused and one belongs to a spiroketal function. In addition, 30 stereogenic centers are disseminated throughout the backbone of the molecule, which does not contain any other elements than carbon, hydrogen, and oxygen.

Hirama's synthesis of **1** hinges upon the union of the two halves **2** and **3** by a remarkably selective acetalization reaction, followed by a challenging metathesis reaction to install the final C–C double bond and, at the same time, complete the construction of the whole skeleton of ciguatoxin CTX3C. It is a clear testimony to the power and selectivity of modern synthetic reagents that this metathesis proceeds, on such a complex structure, with a yield of 77%.

The beauty of Hirama's approach lies not only in the ultimate preparation of the natural product itself and in the demonstration of the ability of organic chemists to assemble such fascinating and complex structures but also in his elegant and highly convergent strategy. The latter should eventually lead to the synthesis of congeners of **1** and to the establishment of antibodies to ciguatoxin for the detection of contaminated seafood.

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PERSPECTIVES: PLANETARY SCIENCE

Clues to the Martian Atmosphere

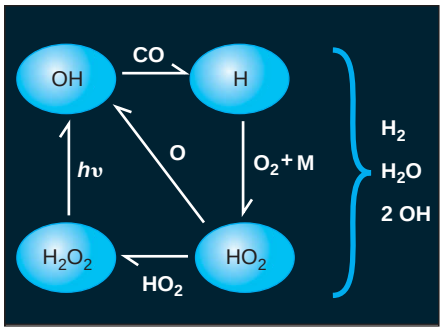
Donald M. Hunten

On page 1914 of this issue, Krasnopolsky and Feldman (*1*) report the detection of molecular hydrogen in the upper atmosphere of Mars. Its presence was predicted almost 30 years ago, but detection proved difficult. The new results furnish strong support for the photochemical models developed (*2*, *3*) to explain the scarcity of CO and O_2 in the martian lower atmosphere. These gases are the photodissociation products of the principal gas, CO_2, in the martian atmosphere and would therefore be expected to be abundant. It took several years to work out why they are not.

The fact that the main constituent (95%) of the martian atmosphere is CO_2 was established almost simultaneously in 1965 by the radio occultation experiment on Mariner 5 (*4*) and by ground-based spectroscopy (*5*). Further ground-based observations detected trace amounts (~0.1%) of CO (*6*) and O_2 (*7*). Earlier work had already established that O_2 was rare. An early attempt to explain this observation (*8*) postulated the formation of a CO_3 molecule that could rapidly react with CO, but this idea was soon refuted by laboratory measurements. A more successful suggestion was that species such as OH and HO_2, produced from water vapor, could be responsible. Water vapor was detected in 1970 (*9*) and has been extensively studied by further ground-based spectroscopy and from the Viking orbiters (*10*, *11*). It shows strong seasonal variations at high latitudes, with maxima in summer and minima in winter.

Attempts to rationalize these observations are based on the concept of "odd hydrogen" (*2*, *3*). Photolysis of H_2O yields H and OH, which engage in catalytic oxidation of CO. Odd hydrogen consists of H, OH, and HO_2. These species rapidly interconvert but only slowly recombine back to "even hydrogen" (H_2O and H_2) (see the figure). The catalytic cycle OH–H–HO_2 is traversed several times per minute under typical daytime conditions near the surface. Each traversal combines one CO molecule and one O atom into a CO_2 molecule, thereby preventing the buildup of CO and O.

However, there is considerable production of O_2 by reactions not shown. Furthermore, the cycle just mentioned requires atomic O. Two solutions for this problem have been offered. Parkinson and Hunten (*2*) invoke the production and photolysis of H_2O_2, whereas McElroy and Donahue (*3*) inhibit the production of O_2 by mixing O atoms down from the upper atmosphere so rapidly that they do not have enough time to react. A number of models published in recent years use better measurements of reaction rates and of the vertical distribution of water vapor in the Mars atmosphere, but the underlying ideas are the same.



Flow chart for the odd-hydrogen system. M is a third body and $h\nu$ represents a solar ultraviolet photon. H_2O_2 appears in the odd-hydrogen box because photolysis rapidly converts it to a pair of OH radicals.

In the present context, the interesting issue is the production of H_2. The reaction of H and HO_2 produces H_2, H_2O, and OH (see the figure). H_2 is nearly inert until it is mixed up to the ionosphere, where reactions with positive ions convert part of it to H atoms. H atoms were first observed by the ultraviolet spectrometers aboard Mariners 6 and 7 (*12*). The detection of H_2 requires much better spectral resolution and has only just been achieved (*1*). It confirms the body of theory that was first worked out to explain the stability of CO_2.

The author is at the Lunar and Planetary Laboratory, University of Arizona, Tucson, AZ 85721, USA. E-mail: dhunten@lpl.arizona.edu