Gilbert Stork: Organic Chemist and Teacher

(1921–2017)

Vijay Nair

Professor Gilbert Stork, the organic chemist and teacher par excellence, passed away on 21 October 2017. His departure marked the end of a hallowed era of classical organic synthesis. His extraordinary scholarship in organic chemistry, originality, and human qualities such as humility, kindness, warmth and concern for students, and humanity in general, sets him a class apart.

Gilbert Stork was born in Brussels, Belgium, on 31 December 1921. Shortly thereafter, his family moved to Paris, where he had his early education. In 1939, in the nick of time, they moved to the United States. He obtained his BS from the University of Florida in 1942 and PhD from the University of Wisconsin in 1945. In 1946, he accepted a position at Harvard University. In 1953, he moved to Columbia University; became a Professor in 1955; and occupied the Eugene Higgins Chair during 1967–1993. Within a short span of joining Columbia, with his vision and persuasion, he accomplished the mission of building up a top of the line, student and faculty-friendly organic chemistry division.

Gilbert Stork is well-known for his numerous path-breaking contributions to organic synthesis, synthetic methodologies and mechanistic insights into reactions. It will be a gigantic task to cover the breadth and depth of his original contributions. Nevertheless, I will deal with a few of his selected publications with the hope of exposing the quintessence of his work. We will start with the most cited Stork enamine reaction – a general protocol for carbonyl-activation for carbon–carbon (C–C) bond construction. Parenthetically it may be added that much of the modern organocatalysis is centered on enamine activation of carbonyl compounds invented by Stork. It is evident from the literature that the advent

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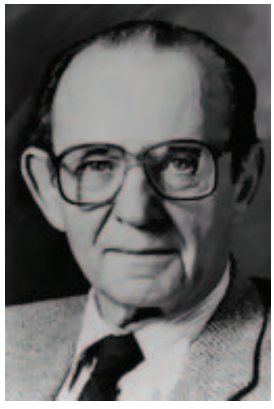
Keywords

Stork enamine reaction, organocatalysis, vinyl radical cyclization, triterpes, steroids, alkaloids, reserpine, quinine, germine, chirality transfer.

Box 1. Why I Like Synthesis

"The origin (of my passion for synthesis) is the structure, and the structure needs methods. Not the method first and then the structure. Structure, problem, method, back to structure. It is kind of a sculpture. It is a challenge. Everybody gets interested; as soon as you can make a problem of something, it gets interesting. Whether you are a chess player, or whether you try to find a way of preventing paper bags from falling apart when they are wet. If you can make it into a problem, it becomes interesting."

– G Stork, *Chemical Research Foundation Oral History*, given to J J Bohning and L Fine. New York, NY, 6 August 1991 (cited by J I Seeman in his article in *Angew Chem*).



Prof. Gilbert Stork
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of enamines, as well as metalloenamines, heralded a revolutionary change in the C–C bond construction arena. Stork himself made elegant use of the methodology in the synthesis of complex alkaloids such as aspidospermin lycopodine, yohimbine, etc. Equally exciting is Stork's work on the regio-selective generation of enolates and their trapping, culminating in the synthesis of the pentacyclic triterpene – lupeol – and other natural and unnatural molecules.

Especially noteworthy is the brilliant postulate of the stereochemistry of cationic cascade cyclization of polyenes (Stork–Eschenmoser hypothesis), applicable to the synthesis of natural products such as steroids and triterpenes. In some ways, this parallels nature's own way of making such molecules. In the early days of synthesis, the idea of stereospecificity did not exist. Gilbert Stork's synthesis of cantharidin is the first stereospecific synthesis of a natural product of some complexity.

Stork's brilliant postulate of the stereochemistry of cationic cascade cyclization of polyenes applicable to the synthesis of natural products such as steroids and triterpenes is noteworthy.

Although free radicals have been reported in the literature for a long time, their utility in synthesis remained practically unaddressed. Stork's conceptualization of controlled generation of vinyl radicals as well as their addition to alkenes opened a versatile route for C–C bond construction, readily applicable to the synthesis of polycyclic natural products. Explorations in the Stork

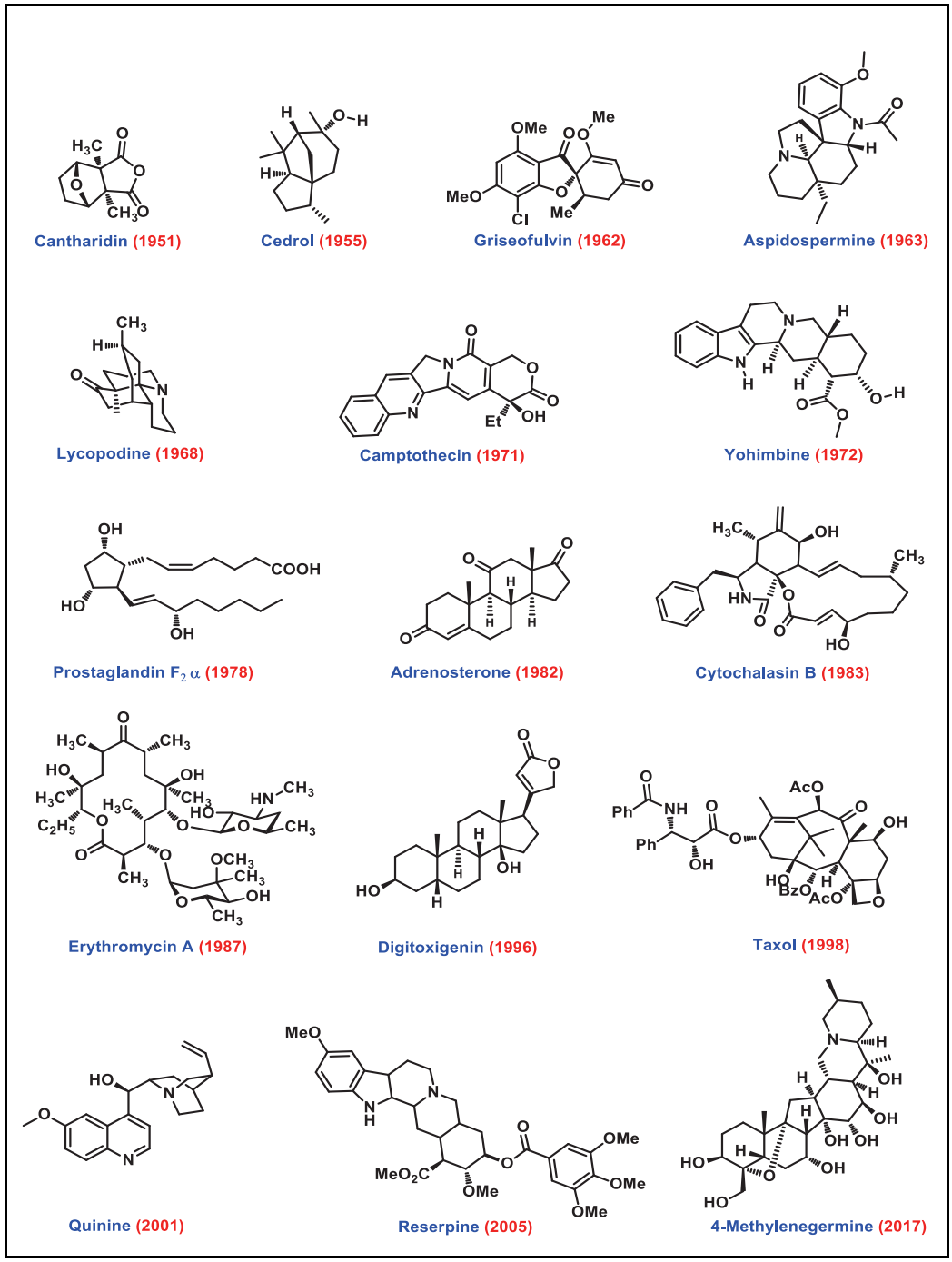

Figure 1. Evolution of total synthesis in the 'Stork Club' (1951–2017).

Box 2. On the Relevance of Organic Synthesis

"I truly believe that synthesis is tremendously important for the progress of organic chemistry. One cannot be interested in a method, merely in an abstract way; the scope and limitations of a method can be best explored by applying it under difficult and preset requirements and that is synthesis."

– Gilbert Stork

group on vinyl radical cyclizations and radical mediated β-haloacetal cyclizations culminated in the efficient stereo-controlled synthesis of a wide variety of natural products ranging from butenolides and furans to prostaglandins and steroids. Importantly, the success of the radical reactions changed the mindset of chemists about these reactive intermediates.

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Another original and fascinating contribution of Stork is the design and application of a general method for the control of regio- and stereo- chemistry known as the 'temporary silicon connection'. This method is applicable in a wide range of reactions, viz., [4+2] cycloaddition, [3+2] dipolar cyclization, and [2+2] photo-addition. Inter alia, this game-changing invention has been availed in the construction of natural products, exemplified by the synthesis of 3-oxosilphinine, C-glycosides, aminosugars, prostaglandins and steroids. It is noteworthy that "the temporary silicon connection brings the advantages of the intra-molecularity of two initially unconnected moieties. This results not only in complete regio- and stereo-control", Stork has shown that "it sometimes also makes possible reactions, which would not take place intermolecularly." It is interesting to note that although one would not expect, magnesium and aluminum connections also work. A special mention should be made of Stork's enantio specific synthesis of prostaglandins utilizing chirality transfer from glucose, setting the trend for availing nature's chiral pool.

Gilbert Stork is noted for his penchant for unravelling the mechanistic underpinnings of organic reactions; this is evident throughout his work. Of special interest is the mechanistic interpretation

Box 3. On the Future of Organic Synthesis

"We have travelled far since 1828, and the interest attached to total synthesis has disappeared". Thus spoke the leading organic chemist of the time in his Pedler Lecture in 1936. "This statement was not really true in 1936. It will still not be true in a hundred years."

– Gilbert Stork, Roussel Prize Award Address, Institut Scientific, Paris, France 1978.

Box 4. Down the Memory Lane

I first saw Prof. Stork when I was a postgraduate student at BHU in 1964; shortly thereafter, there was an opportunity to give a seminar on the Stork enamine reaction. I was mesmerized by the chemistry and dreamt of working with him someday. Eventually, it materialized when he offered me a postdoctoral fellowship (1972–74). His mentorship was exceptional; I am eternally indebted to him for providing a very pleasant, intellectually charged atmosphere to pursue organic synthesis. Among many memorable events was his choice of me to teach his advanced organic chemistry class for BS students during his absence. Even after accepting an industrial job, for personal reasons, I stayed near the Columbia campus. Prof. Stork allowed me to keep my lab bench for use on the weekends and evenings, gave access to the lab and library, and he got me a Visiting Scientist card from the Department. This was a unique situation that I really enjoyed. Even after moving out of Manhattan, I used to go to Columbia for the Thursday afternoon and evening seminars and problem-solving sessions. Inter alia, a proud moment was his special/exclusive visit to Trivandrum in 1991, soon after I moved back to India. Except for the last few years, I used to visit Prof. Stork with some frequency. Indeed, it was a very special relationship that lasted for almost half a century.

he provided for the racemization of usnic acid. For a keen observer, Stork's proposal will appear to herald the dawn of pericyclic reactions.

Gilbert Stork became Professor Emeritus in 1993. Of course, his perpetual love affair with organic chemistry did not allow him to retire from research. Indeed, in his inimitable style, Stork continued to make stellar contributions to organic synthesis by publishing extraordinary papers revealing the stereoselective synthesis of 12α-deoxy tetracycline, digitoxigenin, morphine, quinine, reserpine, taxol, etc. Most fittingly, his last paper discloses a synthetic

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route to the formidable, heptacyclic steroidal alkaloid germine, just six weeks before the curtain fell for the Great Master.

Evidently, Gilbert Stork's original contributions to organic chemistry will immortalize him, but that is not all. Generations of his students will adore him for his personal charm, kindness, exemplary mentorship, and the exalted environment of learning he provided. He made each one of his students feel special. Not just students, anyone who came in contact with him instantly liked him. Such was his friendly demeanor, razor-sharp intellect, spontaneous humor, and readiness for interaction. Indeed, words are inadequate to express our feelings toward him. Truly, Gilbert Stork was one of a kind!

Suggested Reading

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