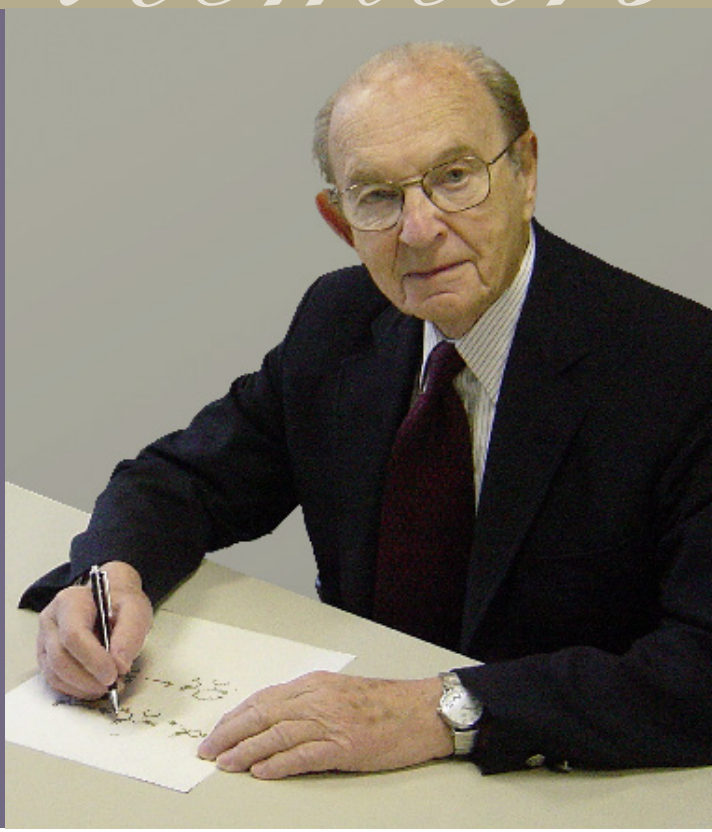
Gilbert Stork

1921-2017

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by Jeffrey D. Winkler, Paul A. Wender, and Daniel Kahne

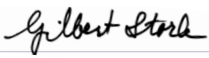


NATIONAL ACADEMY OF SCIENCES

GILBERT **STORK**

December 31, 1921–October 21, 2017

Elected to the NAS, 1960



By Jeffrey D. Winkler, Paul A. Wender, and Daniel Kahne

Gilbert Stork was one of the giants of organic chemistry. In a career that began in the 1940s, and spanned eight decades, Stork expanded what could be achieved in organic chemistry and changed the way people think about how to synthesize organic compounds. His pioneering achievements were recognized by numerous honors, including election to the National Academy of Sciences at the age of 39 and induction as a foreign member into two of the oldest and most prestigious science academies in the world: the Institut de French Académie des Sciences (1989) and the Royal Society of the United Kingdom (1999). In 1983, Stork also received this country's highest award in science, the National Medal of Science, presented by Pres. Ronald Reagan. He also won the Roussel Prize (1978), the Arthur C. Cope Award (1980), the National Academy of Sciences Award (1982), the Roger Adams Award (1991), the Robert A. Welch Award (1993), and the Wolf Prize (1996), among others.

One of his most enduring legacies is the training of more than 400 students and postdoctoral associates, each of whom considered themselves proud members of the Stork Group. Among them, Ronald Breslow, Eugene van Tamelen, Clayton Heathcock, Samuel Danishefsky, Paul Wender, Stephen Buchwald, and Daniel Kahne were themselves elected to the National Academy of Sciences. Members of the Stork Group have gone on to become leaders at universities and industries in the United States and abroad, the ultimate tribute to Gilbert Stork's mentorship. No one was more universally loved and respected by his associates, friends, and colleagues than Gilbert Stork, whose unbridled enthusiasm and passion for chemistry made an indelible impression on his co-workers and on the larger synthetic community. In the highly competitive world of modern science, he was truly an anomaly. Stork used to say, "Make friends, because without them science is just a competition." He lived his entire life at an unsurpassably high standard of integrity, dignity, and discipline.

Early Life and Education

Stork was born in Belgium in the Brussels suburb of Ixelles on December 31, 1921. Shortly after his birth, his parents moved to Paris. He was the oldest of three children. His younger brother, Michel, died at age three of an ear infection in the era before the advent of antibiotics, and Stork is survived by his younger sister, Monique, who lives in France and was an integral part of his family throughout his life.

Stork attended school in Paris until he was fourteen, when the family moved to Nice, where he attended the Lycée de Garcons and completed his baccalaureate. From that time, his passion for chemistry was clear. His family, which was of Jewish origin but not religious, decided at the onset of World War II to leave Europe and traveled by boat from Bordeaux to New York. Stork intended to pursue his undergraduate degree in chemistry at the University of North Carolina, but when he arrived there by bus from New York he discovered that one had to apply for admission. In his often comically understated assessments, he noted, "the weather was not so great (this was December)." He therefore continued on to St. Petersburg, Florida, with the intention of enrolling at the University of Florida in Gainesville. With a gap between his arrival and the start of the spring semester, he audited classes at St. Petersburg Junior College to improve his English. It was there that he met Winifred Stewart, whom he impressed with his gallantry, his accent, and his strange clothes! They married in 1944 in Madison, Wisconsin.

At the University of Florida, Stork began his lifelong love affair with natural products, where he happened upon the work of Paul Rabe on the synthesis of quinine while perusing Chemical Abstracts. He described this as a revelation, that natural products, once their structures were known, could be synthesized in the laboratory. As he described it, "I found this fantastic, and quinine remained a goal for the rest of my life."

In an oral history stored at the Chemical Heritage Foundation (now the Science History Institute in Philadelphia), Stork described his fascination with organic 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's kind of a sculpture. It's a challenge." It is no surprise that this keen aesthetic sense was coupled to a deep appreciation of the fine arts, as well.

Even more remarkable was that the Chemistry Department at Florida gave this precocious undergraduate student laboratory facilities to begin his independent studies on the synthesis of quinine. His initial attempts included the use of β, β'-dichloroethyl N-me-

thylamine, or nitrogen mustard, which caused edema in his hand such that his fingers "could hardly be seen." Fortunately, that situation resolved, and Stork continued his fascination with piperidine-based natural products, intending to pursue his doctoral studies with Roger Adams at the University of Illinois. When he visited the university and found out that he couldn't see Adams without an appointment, he moved on to the University of Wisconsin, where he pursued his doctoral studies with Samuel McElvain. McElvain, a former student of Adams, was involved with pyridine chemistry, which Stork reasoned was close enough to the piperidines central to the structure of quinine.

At Wisconsin, Stork digressed from quinine to pursue a synthesis of biotin, which resulted in his first (and sole-author) publication in the *Journal of the American Chemical Society* in 1945 entitled, "The Synthesis of 3,4-Diaminocarbethoxyfuran."[1] Stork recounted that he

> *did not know you were supposed to put your professor's name on your papers. It shows how tolerant McElvain was. Most people would have been very upset. He flipped slightly, but not too much, when he picked up an issue of JACS [in 1945] and saw there was this communication, my first paper [that he knew nothing about]…McElvain said, "You cut this fooling around out," and moved me next to his office [laughter]. Then I started working more seriously on [our joint projects].*

During this time, Stork developed two lifelong friendships. The first was with fellow graduate student Carl Djerassi, who worked with Alfred Wilds and whom Stork enlisted to work on an approach Stork had designed for the synthesis of morphine, effectively making Djerassi Stork's first (unofficial) graduate student. This arrangement was short-lived, however, as it was terminated when Wilds became aware of it! The second was with W. S. Johnson, who at the time was an assistant professor in the Chemistry Department at the University of Wisconsin and who would later play a critical role in the validation of the Stork-Eschenmoser hypothesis for the synthesis of sterols.

As a graduate student at Wisconsin, Stork developed a stereoselective approach (based on Rabe's work) to the construction of cis-3-ethyl-4-piperidine acetic acid, or "cincholoipon," as a model for the cis-3-vinyl-4-piperidine acetic acid or "meroquinene," a critical component for the synthesis of quinine. As Stork recounted,

the synthesis (of the cis-3-ethyl-4-piperidine acetic acid) also had an important feature: it was designed to give only the cis compound, and thus represented the first synthesis of a compound, related to a natural product, which was designed to give the correct stereochemistry. This was very significant and contrasted with the work of Woodward and Doering, which produced the key disubstituted piperidine intermediate (for their landmark synthesis of quinine in 1945) as a 1:1 mixture of cis and trans stereoisomers.

The concept of stereocontrol in organic synthesis, and the selective preparation of relative stereochemical relationships in the synthesis of natural products, can be traced to these studies by Stork from the 1940s.

Career

After Stork completed his dissertation studies, McElvain helped him to secure a position as a senior research chemist at Lakeside Laboratories in Milwaukee, where he worked, technically as an illegal alien given his visa status, on the preparation of thiophene derivatives of benzene-containing compounds with useful pharmacological properties. With the encouragement of Johnson, Stork applied for an independent research fellowship at Harvard University, and as part of that application proposed a stereospecific synthesis of estrone. This led to his being appointed, in 1946 (at the age of twenty-four), not as a research fellow, but instead as an instructor in the Chemistry Department at Harvard, a position that would not allow him to independently mentor graduate students. When Stork presented his proposed synthesis of estrone to the Chemistry Department, R. B. Woodward offered to share three of his graduate students if Stork would merge his plan for the synthesis of estrone with the Woodward approach to the synthesis of the steroidal C/D ring system, an irresistible offer.

Stork was promoted to assistant professor in 1948, which allowed him to take on graduate students for the first time, and these students included Albert Burgstahler, Eugene van Tamelen, Harold Conroy, and Richard Hill. With Burghstahler, Stork completed the synthesis of cantharidin, the first example of a rationally designed stereospecific synthesis of a natural product.[2] The Stork synthesis elegantly exploited the venerable Diels-Alder cycloaddition to prepare both **1** and **2**, which was then transformed into cantharidin, **3**, as shown in the diagram.

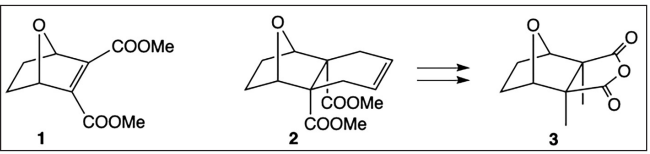


Figure 1:The Stork synthesis elegantly exploited the venerable Diels-Alder cycloaddition to prepare both 1 and 2, the latter of which was then transformed into cantharidin, 3, as shown here.

From the beginning of his career, Stork not only demonstrated singular and transformational insights into organic chemistry but did so with a unique sense of humility and humor. As his then-colleague Louis Fieser stated at the time, "Stork is as nice as they come. Few people of his brilliance are so completely free from any conceit."

In 1950, Stork presented a colloquium to the Harvard Chemistry Department in the presence of luminaries like Woodward, Fieser, Paul D. Bartlett, and George Buchi from the Massachusetts Institute of Technology, in which he outlined a proposal for the stereoselective cyclization of acyclic 1,5,9-polyenes to generate the trans-anti-trans six-membered ring systems that were found in steroids and triterpenes. As outlined in the Burgstahler Ph.D. thesis in 1952, Stork posited that a chair-like folding of the polyene as outlined in **4** would lead to the trans-fused bicyclic ring system shown in **6**. This was in contrast to the known proclivity of cation-olefin cyclization onto pre-existing rings to generate cis-fused products and was used to support the proposed concerted mechanism.

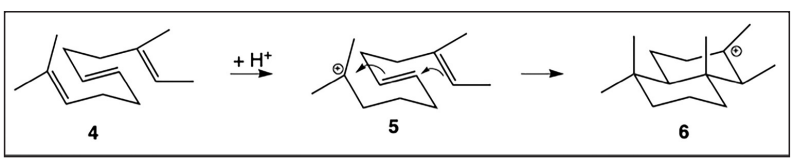


Figure 2. As outlined in the Burgstahler Ph. D. thesis in 1952, Stork posited that a chair-like folding of the polyene as outlined in 4 would lead to the trans-fused bicyclic ring system shown in 6. This was in contrast to the known proclivity of cation-olefin cyclization onto pre-existing rings to generate cis-fused products, and was used to support the proposed concerted mechanism.

This concerted cyclization mechanism, which became known as the Stork-Eschenmoser hypothesis because it was independently developed by Albert Eschenmoser and colleagues at the Eidgenössische Technische Hochschule Zürich, was ultimately brought to fruition in a series of publications by W. S. Johnson and others on the synthesis of steroids and other terpenoids by polyene cyclization. This convergence of theory and experiment by thought leaders of the time proved to be one

of the seminal contributions to the then-emerging field of biomimetic synthesis, which combined the power of biological and abiological synthesis to produce molecules of extraordinary complexity in a single multi-bond forming step. This science subsequently enabled access to many human hormones and therapeutic leads.

When it became clear that Stork would not be promoted with tenure at Harvard, J. D. Roberts of the California Institute of Technology (Caltech), who had overlapped with Stork at Harvard when Roberts was an independent postdoctoral fellow there, recommended Stork to Louis Hammett at Columbia University. In 1953, Columbia offered Stork a position as a tenured associate professor, and he moved with Winifred and their two older children, Diana and Linda, to Leonia, New Jersey.

Stork spent the next sixty-four years as a member of Columbia's Department of Chemistry. By the time he joined the department, Robert Elderfield, William Doering, and David Curtin, the leaders of the organic group, had all left, leaving only Cheves Walling. Stork played a central role in the rebuilding of the department, first adding Ronald Breslow, who had worked in the Stork laboratory as an undergraduate at Harvard and published with Stork on the structure of cedrene. Koji Nakanishi, who was a Fieser postdoc during Stork's Harvard years and also served as a Stork tennis partner; Tom Katz, a Woodward Ph.D.; and Nick Turro, who had been recommended to Stork by J. D. Roberts at Caltech, formed the remainder of the core of the organic group at Columbia during the 1960s and 1970s. To that august group was subsequently added two former Stork postdoctoral fellows, W. Clark Still and Samuel Danishefsky. One of the greatest sources of pride in Stork's career was that no tenured organic faculty who joined the department after 1954 left during this Golden Age, often referred to as the Stork Era. This era was marked not only by scholarly excellence across a broad range of chemical disciplines, but also by a faculty who inspired cooperation, collaboration, and camaraderie rather than competition. For many students, it provided the best educational and research experiences of the time.

On a personal level, his family in New Jersey, expanded to include a third daughter, Janet, and a son, Philip. Stork commuted from his home to the labs at Columbia, which led to a series of iconic stories of his cars and daily commuting to New York over the George Washington Bridge, featuring a Fiat 600, a green Austin, a white Simca, and in later years a treasured T-Bird, among others. Several of these experiences ended up with broken-down cars being sold to various people, including a gas station attendant for $10 and a Connecticut policeman for $25. In Mexico, creatively dealing with a failed car

engine cooling system, he and his friend Carl Djerassi popped open the front hood of the car to force air over the engine as they proceeded to drive while hanging out the side windows. Another time, his left front wheel separated from his car on the George Washington Bridge, causing damage to multiple cars, but no serious personal injury to him or anyone else!

His wife, Winifred, passed away in May 1992 at Memorial Sloan Cancer Center, and Gilbert and the four children were all able to spend time with her before her death. During their forty-eight years of marriage, Winifred was a core of Stork's life, with her unyielding support to him and to his career. Subject to mandatory retirement at the age of seventy, Stork was granted emeritus status in 1992 and spent the subsequent twenty-five years as an emeritus professor at Columbia. In 2015, Stork married Ayako Yamashita, a Ph.D. chemist and his longtime companion.

Stork was a remarkable scientist, educator, and person. He was satirical, self-critical, and rigorously insightful. He inspired by example and by his passionate engagement in science and education. Unlike many carefully choreographed lectures of the time, Stork lectures were often seemingly extemporaneous but remarkably coherent, insightful, and inspirational, as would be expected from his deep personal and professional immersion in his subject matter. He spoke from experience, not from his notes. His recollection of science and scientists was encyclopedic. Prompted by a topic of one's interest, he would deliver, often without notes, a lecture blending methods, mechanisms, and applications, infused with commentary on the scientists behind them all. He brought science and scientists to life in amazing and inspiring ways. In the words of one of his students, "His teaching was like everything else that he did—magical."

Research Career

Stork's scientific contributions during the Columbia years focused in large measure on issues of both stereochemical control and regiochemical control of carbon-carbon bond formation, as exemplified by the development of the enamine alkylation and acylation, which were invented to solve the problem of selective monoalkylation of β-tetralone **7** to give **10**. This landmark reaction with pyrrolidine was developed before the role of enamines in aldolases had been discovered! This strategy proved to be a general and remarkably effective method for the alkylation of aldehydes with reactive electrophiles. This procedure was also applied to less reactive electrophiles using the more reactive metalloenamines. Stork was also the first to use metallohydrazones in this context as well. These reactions were the first of many examples of Stork's role in changing the way that

chemists approached the control of regiochemistry, reactivity, and stereochemistry in organic synthesis.

The use of pyrrolidine enamines was showcased in the Stork synthesis of yohimbine, a prototypical example of the application of a method developed by Stork, in this case the enamine alkylation, to the synthesis of a natural product, yohimbine. The enamine approach was also applied to syntheses of byssochlamic acid (1972)[3] and aspidospermine (1963).[4] The subsequent use of proline, a chiral pyrrolidine, in asymmetric organocatalysis, attests to the transformative power of this foundational methodology in organic synthesis.

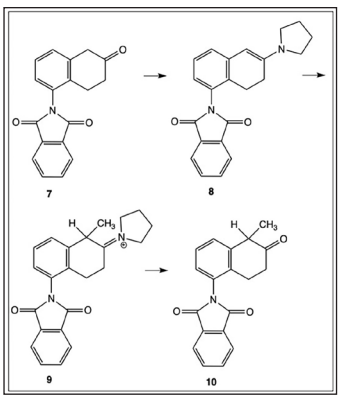


Figure 3: The selective monoalkylation of β-tetralone 7 via enamine alkylation.

Stork also made seminal contributions to the regiochemically controlled formation and reaction of ketone enolates, which had heretofore relied on the judicious introduction of "blocking groups." Stork circumvented this tactic through the dissolving metal reduction of enones **11** with lithium metal in liquid ammonia to give the corresponding alkylated products, **13**, via ketone enolate **12**. Stork and co-workers demonstrated that these enolates could undergo alkylation in the liquid ammonia or could be isolated as their enol silyl ethers **14**, from which the enolates could be regenerated by treatment with fluoride ion. This new method was then showcased in the synthesis of lupeol, **15**, a complex pentacyclic diterpene in which both regio- and stereochemical control was effected using this new method. Stork also applied this strategy to ingenious approaches to the synthesis of prostaglandin F_{2a},[5] progesterone,[6] adrenosterone,[7] 11-ketosteroids (from enediones),[8] and lycopodine,[9] via conjugate addition of Grignard reagents to enones.

The synthesis of β-vetivone[10] **16** by Stork provides another example of the regiochemical control of both ketone enolization and alkylation starting from a β-alkoxyenones. Other notable synthetic methods that emerged from the Stork group during that period d to a synthesis of (-)-histrionicotoxin; the acylcyclopropane cyclization via diazoketones; the keto-alkyne cyclization; the epoxynitrile cyclization; the use of vinylsilanes as carbonyl precursors; the use of temporary silicon connection for the control of regio- and stereochemistry in the synthesis of C-glycosides; and the use of protected cyanohydrins as acyl-carbanion equivalents and their application to the synthesis of prostaglandins.

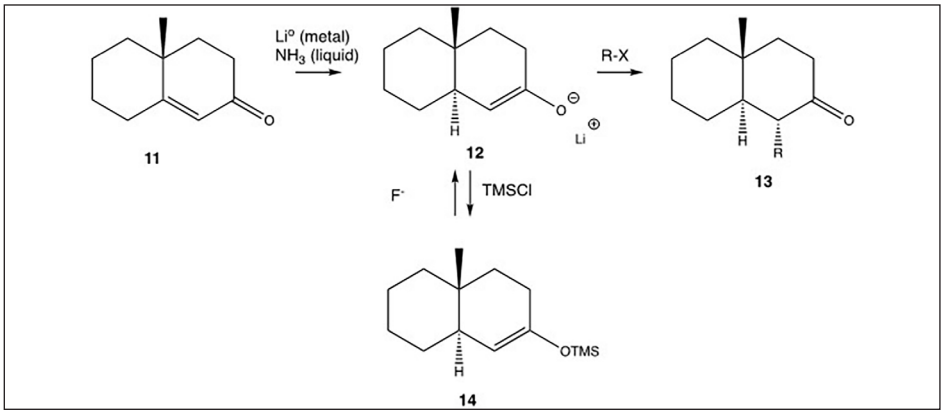


Figure 4:The reductive alkylation of conjugated enones with enolate trapping as the trimethylsilyl ether.

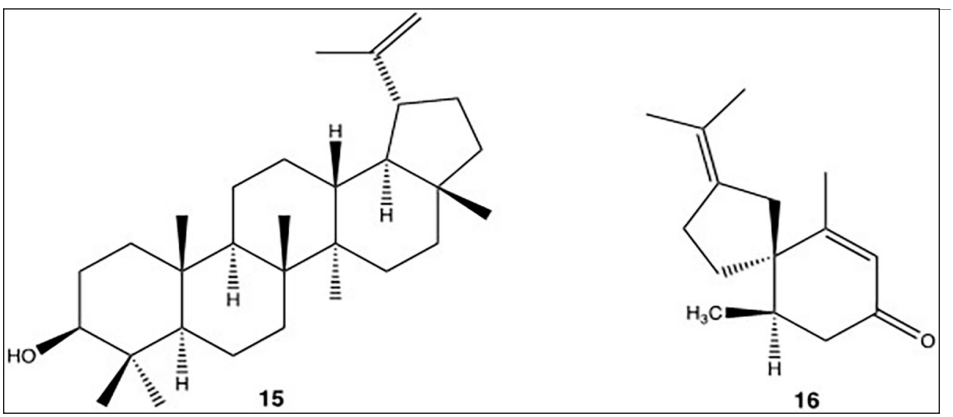


Figure 5: The structures of two of the many naturally occurring compounds synthesized in the Stork Laboratories: lupeol 15 and β-vetivone 16.

During the 1970s, Stork initiated a renaissance in free radical chemistry, with the demonstration that the reactions of vinyl radicals, which could be prepared from vinyl halides or alkynes, could be of significant synthetic utility. This sequence was showcased in applications to the synthesis of prostaglandin F_{2a}, 12α-deoxytetracycline, and the C/D ring system of calcitriol (Fig. 4).

Stork's contribution to the total synthesis of natural products impacted diverse structural classes. The synthesis of prostaglandins from glucose is a particularly elegant example of the use of the "chiral pool" as a source of absolute stereochemical control in total synthesis. Stork described it as "one of the landmarks of establishing that you can use the chiral sugar pool to make a complex chiral compound which is not obviously embedded within the glucose structure. There were others like this. They were just simply a thrill. Like solving a mathematical puzzle."

Over the course of his career, Stork synthesized many structurally complex naturally occurring compounds: cantharidin (1951), alloyohimbane (1954), cedrol (1955), cedrene (1955), a-onocerin (1959), conessine (1962), dehydroabietic acid (1956), griseofulvin (1962), aspidospermine (1963), quebrachamine (1963), Cephalosporins (1965), cis-jasmone (1964), lycopodine (1968), lupeol (1971), camptothecin (1971), yohimbine (1954), byssochlamic acid (1972), prostaglandin E1 and $F_{2\alpha}$ (1975, 1977), grandisol (1962), muscone (1975), cytochalasin B (1978), adrenosterone (1982), seychellene (1985), dihydroerythronolide A (1982 et al), reserpine (1989), (-)-histrionicotoxin (1990), calcitriol (1992), tetracyclines (1996), patchouli alcohol (1995), (+)-digitoxigenin (1996), morphine, codeine, and thebaine (1952), the structures of some of which are highlighted in Figure 6.

The philosophy in the Stork group echoed his early thinking: the synthetic target revealed key unsolved strategic problems in synthesis that then became the focus for creative solutions. In essence, a problem in search of a solution rather than a solution in search of a problem. Regardless of how daunting or complex a given chemical structure was, at any one time, there would often be only one graduate student or postdoctoral fellow working on a particular project. These projects could literally extend over the course of decades through a succession of coworkers. Some sixty years after his first foray into the chemistry of quinine as a graduate student at Wisconsin, he and his coworkers completed the first stereoselective total synthesis of quinine **17**.[11]

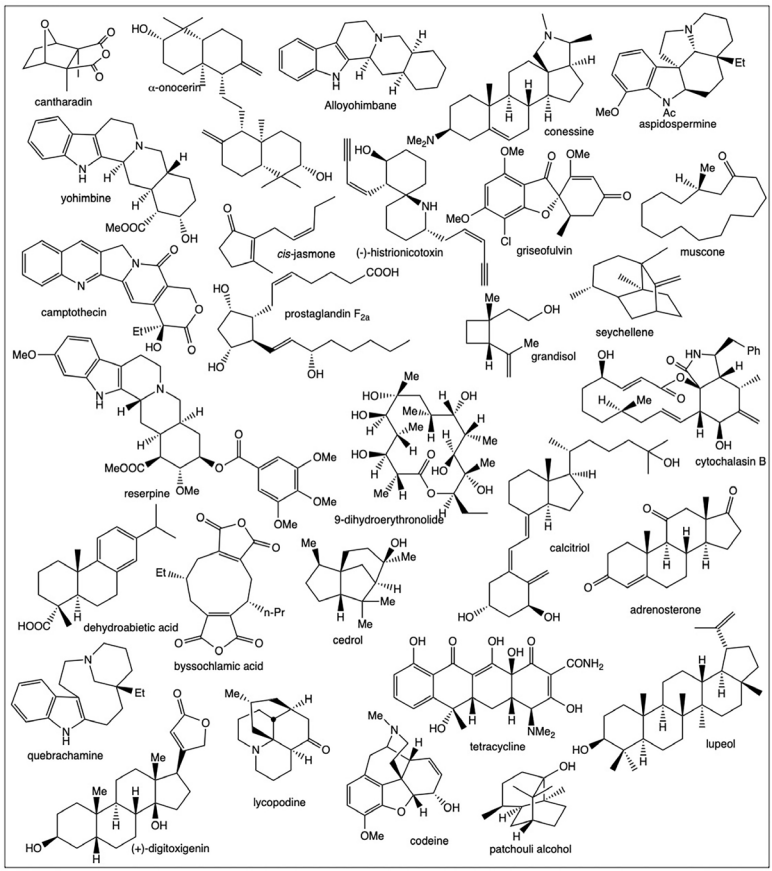


Figure 6: Selected natural products synthesized in the Stork Laboratories.

Over the course of six decades, Gilbert Stork led the development of an organic faculty at Columbia that was second to none. Stork transformed the field of organic synthesis. His penetrating and original insights into the control of regiochemistry, reactivity, and stereochemistry in carbon-carbon bond formation and into the creative generation and use of reactive intermediates that collectively enabled the remarkable total syntheses of dozens of natural products. His indefatigable enthusiasm for chemistry was such that he was still

actively engaged in the total synthesis of natural products until the age of ninety-five! Finally, and most significantly, Stork was a mentor whose kindness and support were instrumental to the success of all of his students. The hundreds of students who trained with him and have since gone on to make major contributions to science, education, and medicine represent a towering contribution. He made each of his students feel special. And not just students: anyone who came in contact with him instantly sensed his warmth and connection and appreciated his razor-sharp intellect.

The legacy that Stork has left in the Chemistry Department at Columbia is profound and was acknowledged by the posthumous naming of its famous main lecture hall the Gilbert Stork Lecture Hall. Annual lectureships were established in his honor at Columbia University, the University of Pennsylvania, and the University of Wisconsin.

When he reached the age of eighty, Stork decided that his main focus would not be to start new projects in either synthesis or methodology, but instead to finish two natural product syntheses that had served as inspirations throughout his career. Over the next fourteen years, Stork went to lab almost every day and worked side by side with his wife, Ayako Yamashita, to complete the synthesis of codeine **18**,[12] and, just three weeks before his passing in 2017, he published the synthesis of 4-methylenegermine **19**, with complete control of all sixteen stereocenters found in the natural product, germine.[13]

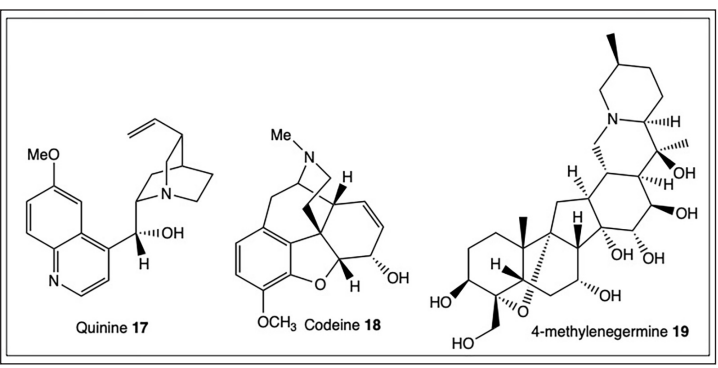


Figure 7: The chemical structures of quinine 17, codeine 18 and 4-methylenegermine 19, the last three published syntheses from the Stork Laboratories.

This extraordinary final synthesis was the culmination of work spanning thirty-eight years and sixteen coworkers! It was a labor of love that Stork and Yamashita carried out as a parting gift to the Stork group. Gilbert Stork's life is an inspiring model for how to combine devotion to work and a commitment to excellence with gentleness, humanity, and humor.

ACKNOWLEDGMENTS

All quotations in this memoir are excerpted from "Oral history interview with Gilbert J. Stork," August 6, 1991. Philadelphia, Penn.: Science History Institute. We thank the institute for permission to use the contents of the interview.

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