HISTORY

Ming-Long Huang (1898–1979), A Chinese Chemist in Europe

by **Shanheng Ma**

Hefei No. 6, Middle School, Heifei, Anhui Province, P. R. China

and

G. Wayne Craig*

Lead Finding Research, Neumattstrasse 5, CH-4144 Arlesheim
(cralion@sunrise.ch)

Dedicated to our former mentors and professors of chemistry: *Yanlin Xiang*, *Hans Brunner*, *Richard J. Anderson*, *Ian S. Cloudsdale*, *Joel Kirkpatrick*, *Jonas Grina*, *Alfred Lui*, *Fritz Schaub*, *Hanspeter Keller*, *Mark Vasser*, *Parkash Jhurani*, *Peter Ng, John G. Moffatt*, *Thomas Gadek*, *Dan P. C. McGee*, *Rick Roman*, *Kevin M. Smith*, *Raymond J. Abraham*, *Rolf Huisgen*, *George S. Zweifel*, *Neil Schore*, *Philip P. Power*, *Clayton Heathcock*, *K. Peter C. Vollhardt*, *Ronald Marhenke*, *Howard K. Ono*, *Stephen Rodemeyer*, *Joe D. Toney*, *George B. Kauffman*, *David L. Frank*, *David Bird*, *David Kawano*, and *Larry Kirk.*

'*The reason why the universe is eternal is that it does not live for itself;*
it gives life to others as it transforms.'
Lao Tzu, Tao Te Ching

In the study of organic chemistry, the student has the daunting challenge, if not to memorize but to study many classic name reactions before mastery of reaction mechanism. But who is the named person behind this reaction? The name reaction trains the fledgling chemist to recognize the diverse reaction types and to associate with each a personage. However, this named pathfinder or explorer has been likely long forgotten! Comforting perhaps, the name humanizes the chemical reaction, and may inspire thought about its discovery and actual mechanism. One such pathfinder was *Ming-Long Huang* (1898–1979), a rare Chinese chemist who studied in Europe in the first quarter of the 20th century. In this article, we highlight *Ming-Long Huang*'s (Chinese spelling) life, his chemistry, and the well-known modification associated with the *Wolff–Kishner* reduction. The Chinese tradition of last name first referred to this reduction as the *Huang-Minlon* (Latin spelling in his publications) modification. We will refer to the name reaction in its original format, but to his first name in the Chinese tradition as *Ming-Long.*

Introduction. – *Ming-Long Huang* (1898–1979; *Fig. 1*) was born in Yangzhou City in the Jiangsu Province, China, in 1898. His father, *Yunzhang Huang*, was a scholar at the end of the *Qing Dynasty* (1636–1911) who had worked for a wealthy salt steward. In his youth, *Ming-Long* had to interrupt school several times because of relocation of his family. He spent only four years in primary school, two years in middle school, and

left high school before graduating. Although still a youth, he continued to educate himself further. Inspired to learn German, he sought the guidance of his oldest brother, *Shengbai Huang* (1888–1982). *Ming-Long*'s middle school in Yangzhou, Jiangsu Province, has since acquired notable fame. China's former President *Jiang Zemin* (b. 1926) graduated from this school, Yangzhou Middle School, and more than forty former graduates had been elected to the Chinese Academy. Among them, *Jilong Bi* (1914–2007), and *Qimei Xie* (b. 1922) both served in the United Nations as Under-Secretary-General [1].

Fig. 1. Ming-Long Huang (1898–1979). Courtesy of Prof. *Carl Djerassi*.

Ming-Long's ten-year older brother and mentor, *Shengbai*, specialized in herbal medicines and was appointed chief editor of *Chinese Medicine*, the first medicinal magazine of its kind in China. Throughout *Shengbai*'s successful career, he upheld the wishes of their father to encourage both *Ming-Long* and their sister to begin an education directed for the medical industry. In *Shengbai*'s opinion, science and technology were on the *Path* to best serve humanity. In 1919, *Shengbai* dispatched *Ming-Long* to Europe as pharmacist of the Medical Board, responsible for repatriation of German soldiers back to their homeland at the conclusion of World War I. Initially, *Ming-Long* traveled to the Netherlands and afterwards to Zürich, Switzerland, where he had the opportunity to begin studies in chemistry. He eventually relocated to complete research at the *Universität* Berlin, Germany, where he was awarded a Ph.D. in chemistry in 1924.

Following his return to China in 1925, *Ming-Long* accepted an appointment as Health Director of the Zhejiang Research Institute and Professor of Chemistry in the Zhejiang Pharmaceutical College of Medicine. He soon thereafter married *Qi Wang* (1901–1930) but she unexpectedly died at the young age of 29. He later married *Xiaolin Wang* (1911–1981; *Fig. 2*).

Fig. 2. Ming-Long Huang *with his second wife,* Xiaolin Wang (1911–1981). Courtesy of *Bin Huang.*

In 1934, *Shengbai* again summoned *Ming-Long,* accompanied with their brother *Mingju Huang* (1895–1990), Professor of Medicine at the Shanghai Second Military Medical University, and sent them both for advanced studies to Germany. In the Pharmaceutical Institute at the Universität Würzburg, *Ming-Long* undertook investigations of the complex alkaloids isolated from *Corydalis ambigua*, also known as *Yen-Hu-So* [2] and *Hsi-Hsin*, a Chinese medicinal extract used as a cough suppressant [3].

As a visiting professor, *Ming-Long* acquired a research position, 1937–1940, in the laboratory of *Hans Herloff Inhoffen* (1906–1992), research director at *Schering AG*, Berlin (*Fig. 3*). *Inhoffen* had received his doctorate in Berlin under the supervision of *Hermann O. L. Fischer* (1888–1960), son of eminent carbohydrate chemist, *Emil Fischer* (1852–1919). After an invited habilitation by *Nobel Prize* recipient *Adolf Windaus* (1876–1959; *Fig. 4*), *Inhoffen* had undertaken *Windaus*' quest to find a *Me(19)*-demethylation route to *A*-ring-aromatic steroids at *Schering Research Institute* [4]. Using their strategy, *Inhoffen*, *Ming-Long*, and *Zühlsdorff* achieved a partial synthesis of the aromatic steroid estradiol (**4**; see *Path A*, *Scheme 1*) from androsterone-17-acetate (**1**) [5–9]. In this connection, *Alfred L. Wilds* (1915–2002) and then

Fig. 3. Hans Herloff Inhoffen (1906–1992) *at* Schering AG, *Berlin, in the early 1940s.* Courtesy of Professor *Carl Djerassi.*

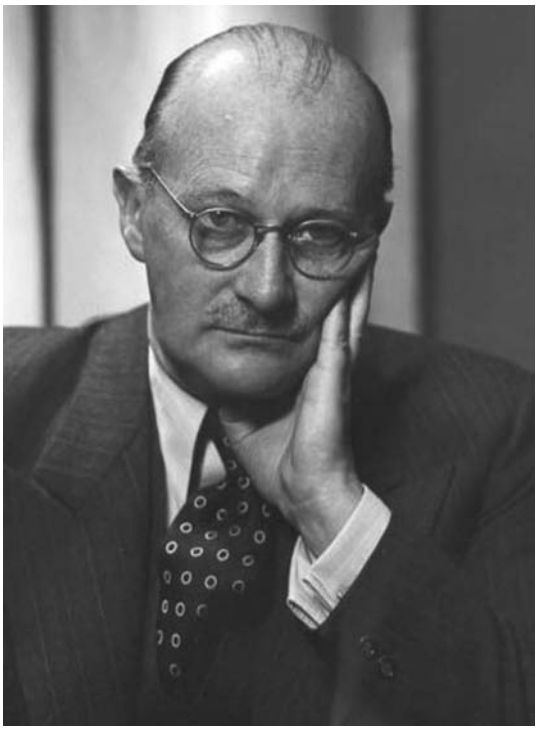
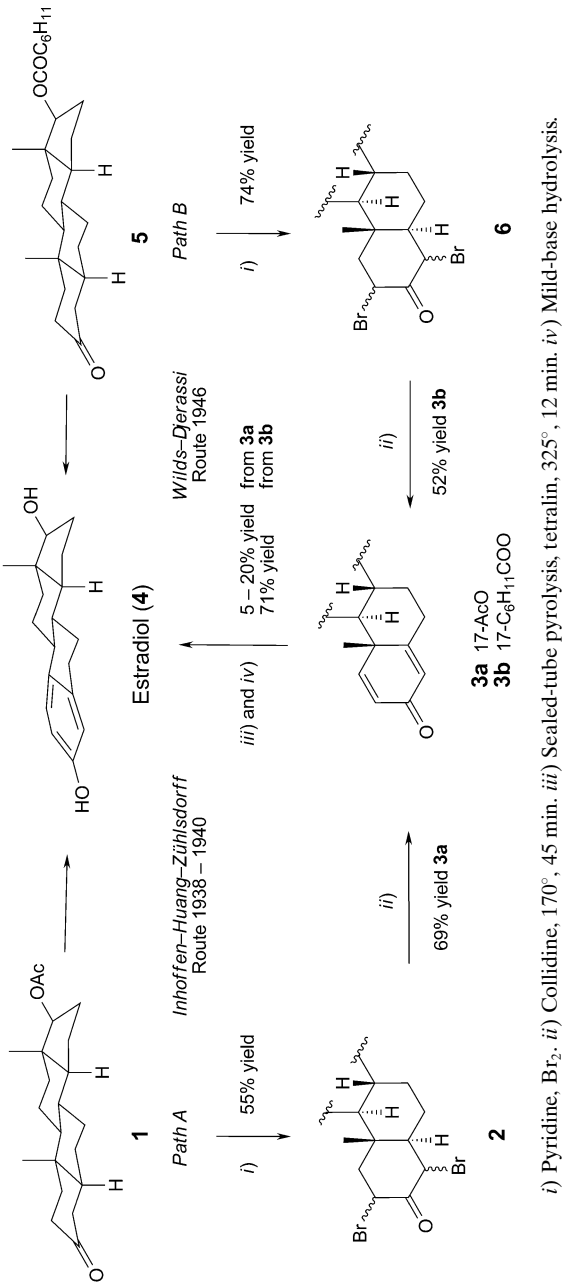


Fig. 4. Adolf Windaus (1876–1959). Photograph from http://en.wikipedia.org.

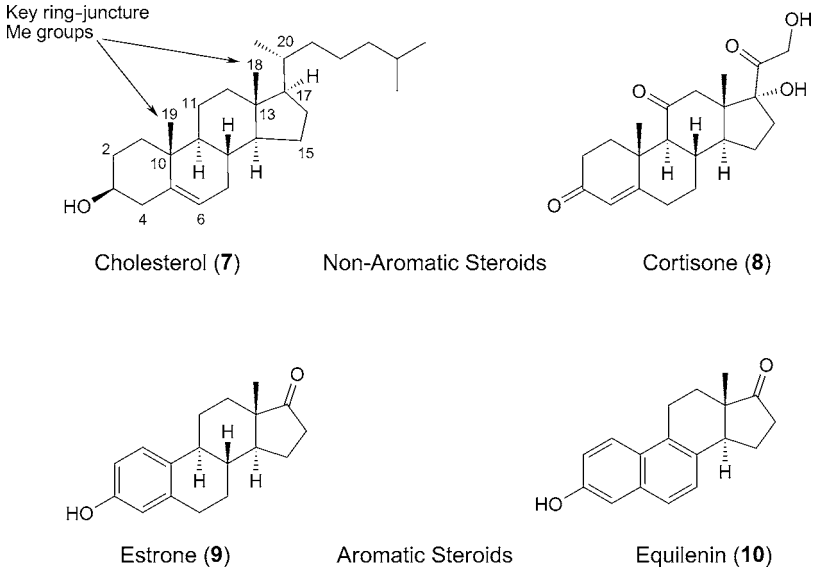
Scheme 1. *Partial Syntheses of Estradiol* (**4**)



i) Pyridine, Br_2. *ii*) Collidine, 170°, 45 min. *iii*) Sealed-tube pyrolysis, tetralin, 325°, 12 min. *iv*) Mild-base hydrolysis.

graduate student, *Carl Djerassi* (b. 1926) synthesized estradiol (**4**) similarly but starting instead from androsterone-17-hexahydrobenzoate (**5**; see *Path B*, *Scheme 1*) [10]. These were important exploratory steps in the foremost goal to achieve the first total synthesis of the aromatic steroid estrone (**9**; *Scheme 2*), first realized in 1948 by the Swiss chemists *Georg Anner* (b. 1917) and *Karl Miescher* (1892–1974) [11].

Scheme 2. *Non-Aromatic and Aromatic Steroids*



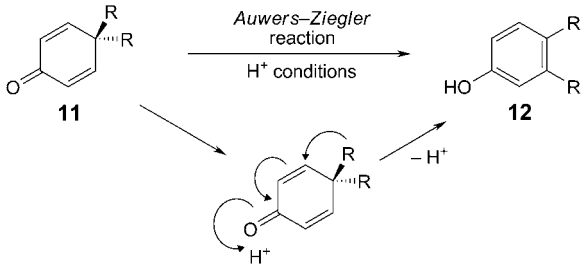
Later, *Woodward*'s brilliant total syntheses of the non-aromatic steroids cholesterol (**7**) and cortisone (**8**; *Scheme 2*) vaulted almost all competitors, exploiting not only *Robinson*'s own annulation strategy but also the *Diels–Alder* reaction to incorporate the key ring-juncture Me groups (arrows in *Scheme 2*) [12]. Ten years earlier, *Werner E. Bachmann* (1901–1951), *J. Wayne Cole* (1913–2002), and *Wilds*, then a doctoral student at Michigan, had elegantly achieved the first total synthesis of the *A–B*-ring-aromatic steroid equilinen (**10**; *Scheme 2*) which contained a mixture of three of the four possible racemates [13].

The innovative approach by *Inhoffen* and *Ming-Long* at *Schering AG* caught the attention of a talented then unknown thirty-three-year-old Harvard professor. It was their usage of another strategy, the dienone–phenol rearrangement, which triggered a turning point that coincided with the meteoric rise of modern chemistry's indisputable legend, *Robert Burns Woodward* (1917–1979; *Fig. 5*). *Woodward*'s career focused on the understanding of chemical mechanism to achieve rational syntheses of complex natural products. His eccentric personality as Professor of Chemistry at Harvard University and later at the *Woodward Research Institute* in Basel, captivated generations of new chemists to follow in his footsteps [12]. *Woodward*'s '*art-in-chemistry*' inspired future generations each year to take up the challenge of synthesis of complex natural products.

Fig. 5. Robert Burns Woodward (1917–1979). Courtesy of the *Novartis Archive*.

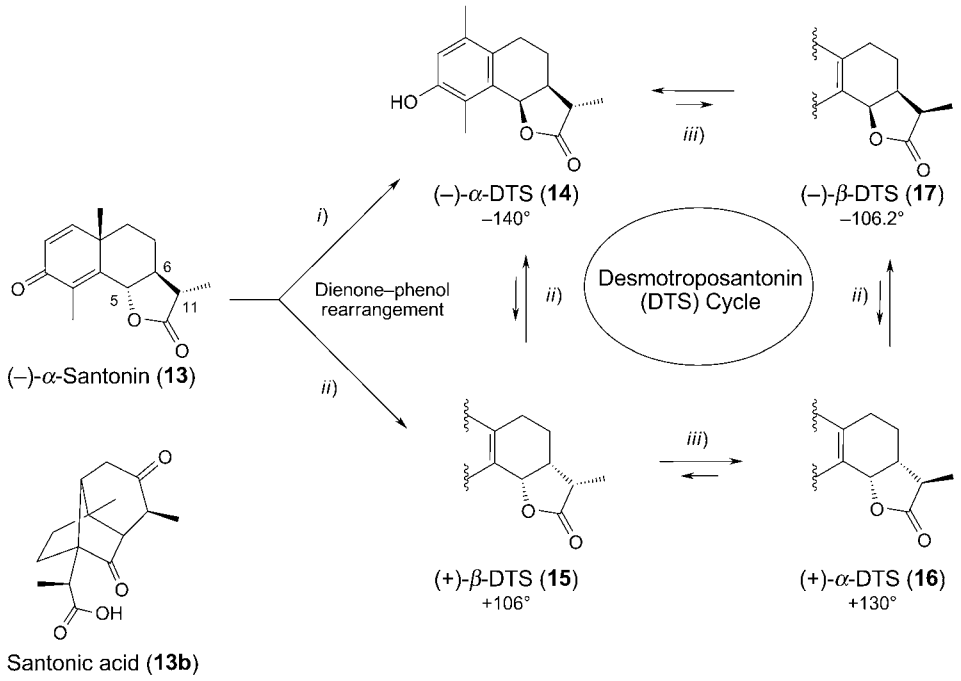
In the search for new hormone-active steroids, *Inhoffen* and *Ming-Long* intended to exploit the dienone–phenol rearrangement (*Scheme 3*)[1]), known to occur with the

Scheme 3. *The* Auwers–Ziegler *Reaction Better Known as the Dienone–Phenol Rearrangement* [14]



[1]) In this type of 1,2-alkyl migration reaction, the names of its original discoverers *Karl von Auwers* (1863–1939) and *Karl Ziegler* (1898–1973) were even more difficult to remember! *Wilds* and *Djerassi* had proposed the chemically descriptive alternative, dienone–phenol rearrangement, in *Djerassi*'s seminal dissertation work at Madison, Wisconsin [15].

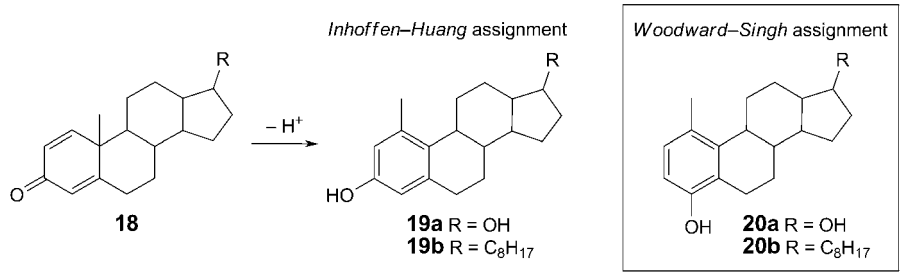
Scheme 4. *Relative Configurations of Desmotroposantonin* (DTS) *Products* **14**–**17** *Based on Optical-Rotation Measurements after Rearrangement from (–)-α-Santonin* (**13a**)



i) Ac_2O, H^+. *ii*) 40% H_2SO_4, H_2O. *iii*) KOH, EtOH.

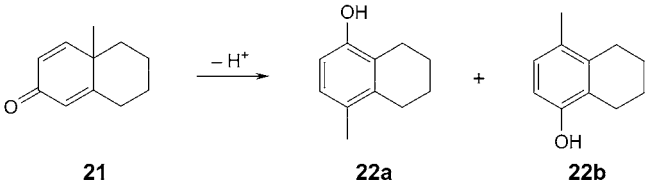
sesquiterpene (–)-α-santonin (see **13a**; *Scheme 4*) [16], to procure novel Me-substituted estradiol analogs (see **19a**/**19b**; *Scheme 5*) for biological testing. Under the conditions of the *apparent* 1,2-Me rearrangement, the reaction products were isolated as crystalline materials and assigned according to this mechanism. Disappoint-

Scheme 5. *Misassigned Structures* **19a**/**19b** *of Hormone-Inactive Analogs. Inhoffen* and *Huang* assigned the structures **19a** and **19b** for the isolated reaction product from two different reactions in analogy to the dienone–phenol rearrangement known with santonin.

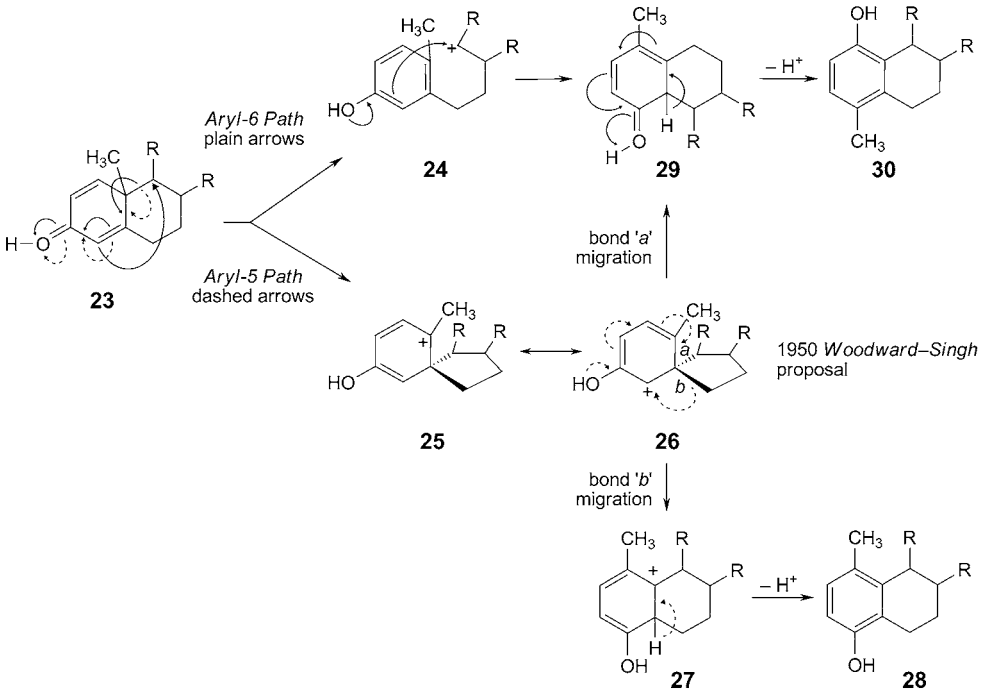


ingly, their expected steroidal derivatives were devoid of the expected hormonal activity as evaluated by their relative potency in the *Doisy–Allen* assay [17]. It took the unconventional reason and the audacity of a young *Woodward* to propose, based on their model studies (*Scheme 6*), that the actual structures were not those assigned by the more experienced German research group but instead isomeric products (see **20a**/**20b**; *Scheme 5*). More importantly, overall results had uncovered the merits of an alternative reaction mechanism in which a spiro-carbocation (**25**/**26**; *Scheme 7*), not previously considered, explained the resulting products [18]. One must remember, today's structure determination tool, NMR spectroscopy, had not yet been developed, and structure verification relied heavily on time-consuming derivatization or degradation to a molecule of known structure. Further research showed later that the

Scheme 6. *Rearrangement Model Study*



Scheme 7. *A Novel Alternative Mechanism in Which a Ring C-Atom May Preferentially Migrate Rather Than the Ring-Juncture Me Group to Form the Spiro-Carbocation Intermediate* **25**/**26**



mechanistic pathway was even more complex [16]. The reaction pathway was dependent on the reaction conditions and the nature of the substitutents on the dienone periphery. This fact exemplified *Woodward*'s often quoted laconic remark, '*there are no general reactions*'. However, *Woodward*'s fearless approach to synthesis and his persuasive eloquence stimulated a renewed wave of carbocation investigations, which nurtured the later verification of *Aryl-5* and *Aryl-6* anchimeric assistance pathways (*Scheme 7*) using isotopic labeling [19]. However, that is another story encompassed in the discovery and elucidation of the *Wagner–Meerwein* rearrangement, brilliantly described by *Woodward*'s former postdoctorant, *Jerome A. Berson* (b. 1924) [20]!

In 1939, during his brief stay at the Biochemistry Institute of Medicine, Britain Middlesex Hospital, *Ming-Long* initiated a biological study of hormone production in women. But the looming outbreak of World War II with Germany required that he be immediately recalled to China to serve as part-time Professor of Chemistry at Southwest Associated University and researcher in the Institute of Chemistry, Academia Sinica, Kunming. The war-time-occupation conditions not only delayed publications of his scientific research (see footnote remarks indicated in [21–23]) but made laboratory equipment and chemical reagents very scarce. However, with *Shengbai*'s support, *Ming-Long* acquired discarded equipment to carry out rudimentary chemical analyses. At a local drugstore, *Ming-Long* acquired amounts of a medicinal extracted from the plant *Artemisia santonica* used for anthelmintic treatment against flute roundworm. Not surprisingly, this remedy extract was composed of *Ming-Long*'s *earlier nemesis*, (−)-α-santonin (**13a**) which had spurred his successful steroid syntheses at *Schering AG*. Despite the frequent disturbance from air-raid sirens, *Ming-Long*'s research group deduced the relative configurations in (−)-α-santonin's (**13a**) rearrangement–epimerization cycle (see **13**–**17**; *Scheme 4*) based on optical-rotation measurements (specific optical-rotation values are indicated in *Scheme 4*) [23]. *Ming-Long*'s classic research demonstrated the power of instrumental measurement in elucidating the configuration of a molecule![2])

Today, the absolute configuration of natural (−)-*α-santonin* (**13a**) and the subtle solubility effects to produce the DTS products (see **14**–**17**; *Scheme 4*) by rearrangement have been additionally clarifed by *Huffman et. al.* with the aid of X-ray crystallography, ^{1}H- and ^{13}C-NMR spectroscopy, and conformation calculations [28], almost 30 years after the skeletal structure of (−)-α-santonin (**13a**) had been determined!

---

[2]) It should be mentioned that the complete determination of the constitution of (−)-α-santonin (**13a**) was an incredible feat that spanned over 100 years predating modern analytical methods used today. During that time, chemical investigation of (−)-α-santonin (**13a**), desmotroposantonin (DTS) products **14**–**17**, and related santonic acid (**13b**) led to erroneous and seemingly contradictory conclusions [24]. In retrospect, the migration of the Me group at C(9) and the often simultaneous isomerization of the strained 5/6-*trans*-bicyclic ring system to the 5/6-*cis*-ring junction of (−)-α-santonin (**13a**) under acidic conditions were recognized, but whose magnitudes were not easily assessed in (−)-α-santonin (**13a**) and its DTS products, **14**–**17**, [25]. Eventual crystallographic X-ray data of santonic acid (**13b**) [26] reaffirmed the proposed configuration revision of (−)-α-santonin (**13a**) to that shown in *Scheme 4* [27].

Following World War II, *Ming-Long* visited America to spend a sabbatical with Professor *Louis F. Fieser* (1899–1977; *Fig. 6*) at Harvard University [29]. Although, *Ming-Long* was an experienced chemist, *accident* was to play a key factor in the discovery and improvement of novel chemistry. The following excerpt from *Fieser*'s textbook on organic chemistry described the circumstances of how *Ming-Long*'s modification came to light [30],

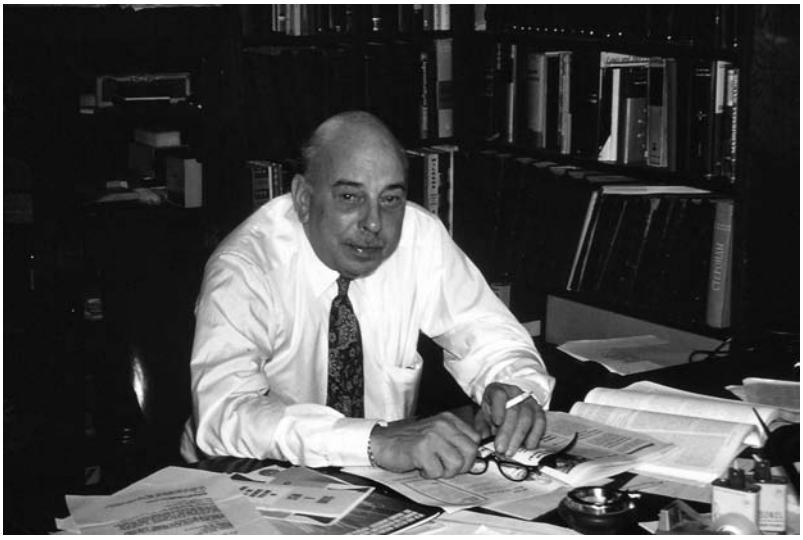


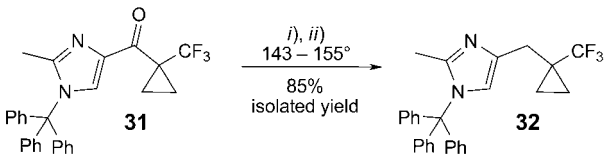
Fig. 6. Louis Frederick Fieser (1899–1977). Photograph from http ://en.wikipedia.org.

'A member of Fieser*'s research group was investigating the antimalarial medicinals, which required preparation of a large amount of active compound for clinical studies. Specifically needed was the starting material γ-[*p*-phenoxyphenyl]butryric acid.* E. Berliner *had tried the* Clemmensen *reduction several times on β-[*p*-phenoxybenzoyl]-propionic acid, but never obtained more than a 54% yield. It was at this time that* Minlon*, from the Academia of Sinica in Shanghai arrived at Harvard. He had already acquired experience in solving chemistry problems and was supported from* Fieser*'s research grants. Consequently,* Minlon *was commissioned to investigate synthetic variations of the* Wolff–Kishner *reduction, suggested from* M. D. Soffer *who had worked on the problem one year earlier. In one variation, the reaction was carried out in triethylene glycol with one to ten equivalents of sodium metal, anhydrous hydrazine and then heated to reflux for one hundred hours. During one such trial run,* Minlon *decided to drive to New York over the weekend. As he was leaving,* Minlon *asked* George Fawaz*, a Libanese colleague, to check the reaction during his absence. The reaction flask was connected to the water condenser with an ordinary cork. Later, while* George *was inspecting the reaction flask with noticeable displeasure, the cork flew off. Unfortunately,* George *had only instructions to observe the reaction and not to alter anything, hence* Minlon *found the reaction upon his return in a completely overheated state. As required, he went to* [Professor] Fieser *and reported, – 'yield excellent, experiment bad.' When the experiment*

was repeated however using ground-glass connections, the meager 48% yield was obtained once again. Huang Minlon *concluded that in the first experiment, the unintentional removal of water and hydrazine by distillation had led to an increase in temperature to completely consume the hydrazone* [intermediate] *producing the high yield. Such was the development of the currently used procedure. By this method, the desired product was synthesized on a 500-gram scale in over 90% yield*.'

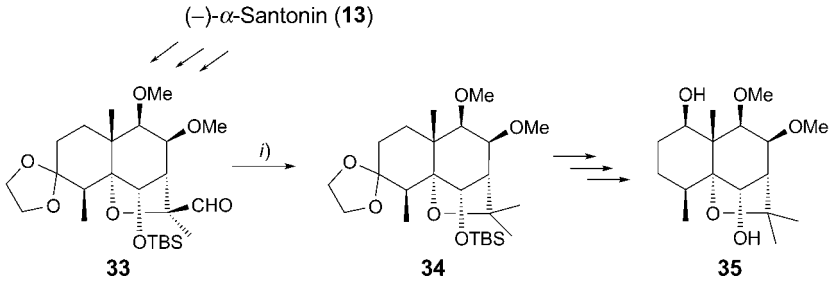
In retrospect, these optimal reaction conditions for the efficient reduction of the C=O to a CH_2 group have not significantly changed [31], exemplified by the large-scale transformation of imidazolyl ketone **31** to the reduction product **32** (*Scheme 8*) [32]. Ironically, the *Huang-Minlon* (*HM*) modification returned to play a key role in the semisynthesis of dihydroagarofuran (**35**) from (–)-α-santonin (**13a**; *Scheme 9*) [33]. Despite the development of metal hydrides for the reduction of the C=O group in the presence of base-sensitive functional groups [34], the *HM*-modification continues to impact the progress of chemical synthesis today.

Scheme 8. *Large-Scale* Huang-Minlon *Modification of the* Wolff–Kishner *Reduction of Imidazolyl Ketone* **31**



i) $NH_2NH_2 \cdot H_2O$, 4 equiv. powdered KOH, diethylene glycol/H_2O. *ii*) MeCN/H_2O.

Scheme 9. *The* Huang-Minlon *Modification of the* Wolff–Kishner *Reduction Used in the Semisynthesis of Dihydroagarofuran* **35**

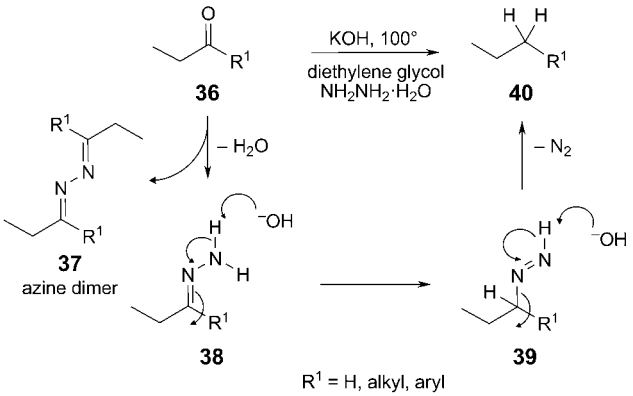


i) $NH_2NH_2 \cdot H_2O$, K_2CO_3, diethylene glycol, 150 – 220°; 72% yield of **34**.

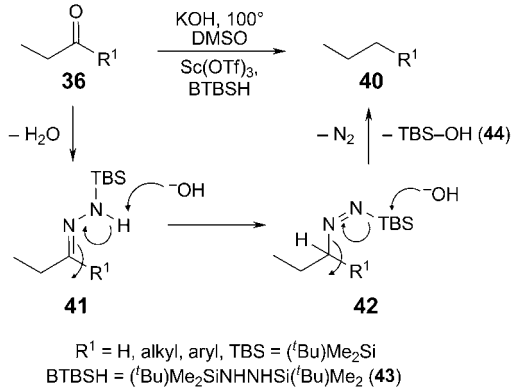
The original *Wolff–Kishner* reaction developed for the reduction of ketones and aldehydes was initially investigated in 1911 by the Russian chemist *Nikolai Mateyevich Kishner* (1867 – 1935), who received his Ph.D. in 1901 at Moscow University with the great *Vladimir Vasilevich Markovnikov* (1838 – 1904). In 1912, *Johannes Ludwig Wolff* (1857 – 1919) undertook independent research. He had already developed another name reaction, the *Wolff* rearrangement during his doctoral research with *Wilhelm*

Rudolf Fittig (1835–1910) at Strasburg in 1882. Technically, the *Wolff–Kishner* reduction was cumbersome, since it originally required anhydrous conditions in a sealed ampule to achieve the desired reaction. Furthermore, the closed system did not allow for a convenient way to analyze the reaction progress. In the reaction with aldehydes, azine-dimer formation effectively competed to form a major side-product (see **37**, *Scheme 10*). However, *Ming-Long*'s improved procedure made use of high-boiling di- or triethylene glycol as solvent which permitted distillation removal of water, shifting the equilibrium to a high-yield conversion of the hydrazone intermediate. Subsequent base-catalyzed tautomerization and elimination of a N_2 molecule afforded the reduced product, **40**. The ability to perform the reactions under atmospheric conditions was a giant leap forward for the ordinary bench chemist, particularly in its application to steroid research between 1949 and 1969. The later development of 1,2-bis[(*tert*-butyl)dimethylsilyl]hydrazine (BTBSH, **43**; *Scheme 11*) provided fine-tuning to hinder azine-dimer formation [35]. Today, catalytic formation of the hydrazone with

Scheme 10. *Azine Dimer Side-Product* **37**



Scheme 11. *Reduction with* N,N′*-bis[(*tert*-Butyl)dimethylsilyl]hydrazine* (**43**)



scandium(III) triflate permits efficient reduction at lower temperatures and subsequent cleavage of the by-product, (*tert*-butyl)dimethylsilanol (**44**; *Scheme 11*) [36].

After his successful stay at Harvard, *Ming-Long* returned to steroid research, but this time at the American corporation *Merck & Co. Inc.* in 1948. He investigated the chemical reactivity of novel cortisone derivatives and the structure identification of key steroid subclasses [37–40]. *Merck* eventually went on to manufacture and market its discovery of naturally occurring cortisone (**8**) industrially produced by semisynthesis [41]. In 1949, *Ming-Long* returned to the National Research Institute, Academia Sinica in Shanghai. In 1950, this national body merged with the Institute of Chemistry and Institute of Materia Medica of the Peking Academy of Science to become today's Shanghai Institute of Organic Chemistry (SIOC). Two years later, *Ming-Long* was appointed director and researcher in the Department of Chemistry, Academy of Military Medical Sciences of the People's Liberation Army, Shanghai, China.

In 1998, to commemorate *Ming-Long Huang*'s 100th birthday, SIOC published highlights of his chemical contributions (*Fig. 7*) and established the *Ming-Long Huang Scholarship* at the University of Science and Technology of China in June, 2006 [42].

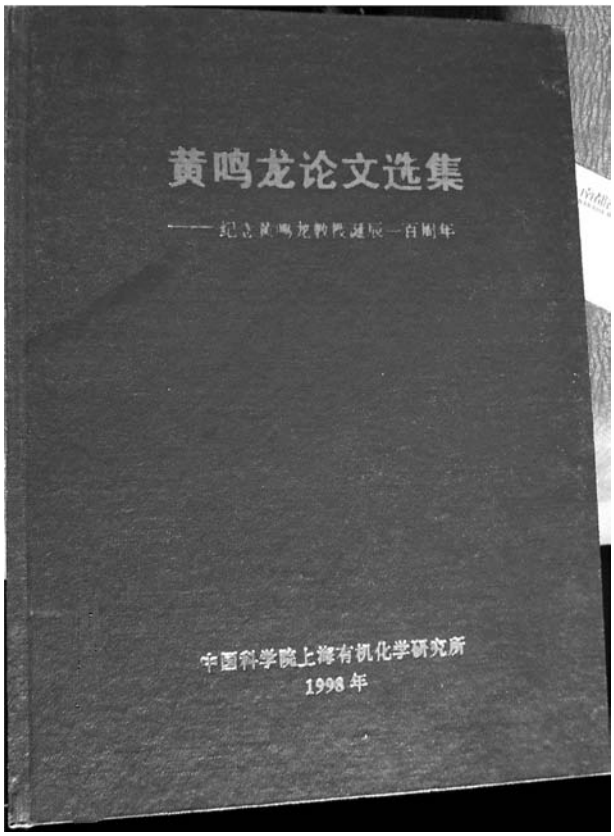


Fig. 7. *The 100th birthday commemoration of* Ming-Long Huang. Photograph from *S. Ma*.

Conclusions. – By the middle 19th century, Great Britain and America had already promoted sending their students to Germany for advanced chemistry training [43][44]. However, relatively few Asian countries encouraged their students to travel to Europe to study chemistry. Despite the obvious language barrier, Japan became proactive only following its Period of Isolation. This resulted in their students finding research positions in Great Britain [45], Switzerland [46], and Germany [47]. The European-born chemists, *Heinrich Wieland* (1877 – 1957) and *Bernhard Witkop* (1917 – 2010) often described their working experiences with Japanese chemists with particular appreciation and admiration [47][48].

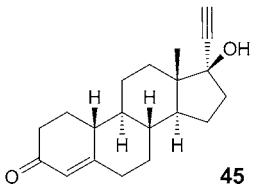
Although early alchemical developments in China had already produced the silicate pigment, Chinese blue, carbon-dated to *ca.* 800 B.C. [49], and despite China's production of gunpowder in the 7th century, further development in chemistry remained fully dormant until the 20th century. In his time, *Ming-Long* was a rare Chinese who ventured out of homeland China to obtain a chemistry education in Europe. *Ming-Long* represented the metaphorical young sheppard in '*The Alchemist*' [50], whom *Coelho* described '*He was an alchemist that does what alchemists do. They show that, when we strive to become better than we are, everything around us becomes better too*' [46]. *Ming-Long* opend the *Way* to Europe for a younger generation of Chinese chemists led by Professor *Wang You* (1910 – 1997) to seek and complete a 1937 doctorate with *Nobel* laureate *Heinrich Wieland* in Munich [51].

Although the earth has become small due to modern globalization, European or Western cultures still remain vastly separated from Asian and Middle Eastern cultures through a language gap. These differences, disparately caused by the lack of a single international alphabet, for example, usage for element symbols in the periodic chart, challenge us to find ways to bridge and cross-cultivate our cultural philosophies. It was indeed a testament to *Ming-Long*'s strong character that he successfully educated himself in Europe and served his homeland with remarkable distinction.

Ming-Long Huang produced a total of 73 research publications with his collaborators. He prepared volumes of teaching materials and four monographs, not including an unpublished manuscript. In addition, he wrote nearly 40 literary articles. His chemistry contributions were recognized as first-class quality both within China and internationally.

Ironically, *Ming-Long*'s chemistry may seem relegated to a single accidental chemical discovery rather than for his numerous other scientific contributions. However and justifiably, the *HM* modification attracted immediate attention and found wide application in the chemical arena to become the preferred variation of the *Wolff–Kishner* reduction of a C=O to a CH_2 group. Although, this discovery was a *small* breakthrough, it had an overwhelming impact in the aftermath age of the historical '*steroidal-molecule chase*' for the anti-inflammatory cortisone (**8**) [52][53], the *Syntex* contraceptive-active ingredient norethindrone (**45**) [54][55], and the progress of synthetic chemistry overall [56][57].

The historical achievement of these two particularly coveted pharmaceutical milestones had a global impact on the health and social welfare of the entire world population and the future perception of synthetic chemistry! Their subsequent medical and economic successes stimulated new syntheses and, whenever possible, employment of the *HM* modification as an efficient inexpensive method for C=O group reduction.



45

Fifty years after the publication of the *HM* modification, this article (*i.e.*, [24]) was still ranked among the top 120 cited publications [58]. Indeed, behind his name reaction, one discovers a personal story of chemistry *and* life! In a modest way, *Ming-Long* humanized the chemistry and chemical origin behind the *HM* modification of the *Wolff–Kishner* reduction. Like many chemists, passionate about discovery and excited to understand Nature, *Ming-Long* became *One* with his chemistry.

Spiritually, *Ming-Long* established China early in its pioneering status for natural-products research, but particularly for his contributions to the characterization and

Fig. 8. *Professor* Carl Djerassi (b. 1926; left) *and Professor* Ming-Long Huang (1898–1979) *in Shanghai, 1973*. Courtesy of Professor *Carl Djerassi*.

syntheses of steroids. For this reason perhaps, *Ming-Long Huang* has been aptly referred to as '*the father of steroid chemistry in China*' by Professor *Carl Djerassi* (*Fig. 8*) [55], whose autobiography in German is delightfully entitled, '*Carl Djerassi, Die Mutter der Pille*' [54][3]).

Ming-Long Huang was elected as an honorary editorial board member of *Tetrahedron*, an international journal of organic chemistry established by the eminent alkaloid chemist Sir *Robert Robinson* (1886 – 1975) which dedicated an inaugural issue in honor of *Ming-Long Huang* [60].

The *Huang* family in Yangzhou was a rich source of chemistry talent that made contributions to organic chemistry and the pharmaceutical industry. *Ming-Long*'s two senior brothers, *Shengbai Huang* (1888 – 1982) and *Mingju Huang* (1895 – 1990), and his nephews, *Lansun Huang* (1911 – 1997) and *Xian Huang* (1933 – 2010), also developed notable careers in biochemistry and medicinal chemistry [58].

We gratefully acknowledge *Bin Huang* from Hangzhou, China, son of *Minghao Huang*, *Ming-Long*'s youngest brother, and *Yuan Chen*, *Xian Huang*'s wife, who kindly provided detailed personal information about *Ming-Long Huang*. Moreover, we thank emeritus Professor of Chemistry of Stanford University and former president of the historical research centers, *Syntex Ltd.*, and *Zoecon Ltd.*, Palo Alto, California, *Carl Djerassi*, for permission to reproduce photographs from his private collection. Indeed, Professor *Djerassi*'s personal recollections about his previous meetings with Professor *Ming-Long Huang* are especially appreciated. We are also grateful for the kind assistance of Dr. *Walter Dettwiler* and Dr. *Carole Billod,* and permission to reproduce photographs from the *Novartis Archive*, Basel. Lastly, we thank *Syngenta* colleagues, Dr. *Andrew J. F. Edmunds* for reading a preliminary manuscript version, and to Ms. *Ines Friess* for her unrelenting assistance in the preparation of this manuscript for submission.

REFERENCES

[1] Yangzhou Middle School, Jiangsu Province, Dec. 23, 2009, http://61.155.62.52/yzzx/.
[2] H. Minlon, '*Über die Alkaloide der chinesischen Corydalisknollen (Corydalis ambigua, 'Yen-Hu-So')*', *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1737 – 1745.
[3] H. Minlon, '*Untersuchung von chinesisch Asarum, Asarum blumei Duch, 'Hsi-Hsin'. Die Konstitution eines neutralen Inhaltsstoffs*', *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 951 – 958.
[4] G. Quinkert, '*Hans Herloff Inhoffen in His Times (1892 – 1992)*', *Eur. J. Org. Chem.* **2007**, 3727 – 3748.
[5] H. H. Inhoffen, H. Minlon, '*Umwandlungsreaktionen von bromierten Derivaten des Cholesterins, V. Mitteil., Weitere Versuche mit Dibromcholestanon*', *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 7120.
[6] H. H. Inhoffen, H. Minlon, '*Übergang von Sterinin in aromatische Verbindungen, III. Mitteil., Aromatisierung des 1,2,4,5-Cholestadienon-3*', *Naturwissenschaften* **1938**, *26*, 756.
[7] H. H. Inhoffen, H. Minlon, '*Umwandlungsreaktionen von bromierten Derivaten des Cholesterins, VI. Mitteil., Zur Konstitution des 1,2,4,5-Cholestadienon-3*', *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 1686.
[8] H. H. Inhoffen, H. Minlon, '*Zur Photochemie des Cholestanons, III. Mitteil., Aromatisierung des 1,2,4,5-Cholestadienon-3*', *Naturwissenschaften* **1939**, *27*, 167.

---

[3]) Professor *Carl Djerassi*, chemistry legend and inventor of the contraceptive pill, norethindrone (**45**), kindly communicated the following comment with his photograph contributions: '*I met him* [Huang] *the last time in 1973, when I was one of the first American scientists to be invited to China after the famous Kissinger visit. I spent about three weeks lecturing about birth control and steroids and met Huang Minlon in Shanghai at his apartment where the attached picture was taken. He was charming and wide-awake and still recalled the meeting we had once in the States in the 1940s before he returned to China – probably one of the first Chinese scientists to return*' [59].

[9] H. H. Inhoffen, G. Zühlsdorff, H. Minlon, '*Umwandlungsreaktionen von bromierten Derivaten des Cholesterins, VII. Mitteil., Darstellung des 1,2,4,5-Androstadienol-17-ons-3*', *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 451.
[10] A. L. Wilds, C. Djerassi, '*The Synthesis of Estradiol and 1-Methylestradiol from Cholesterol*', *J. Am. Chem. Soc.* **1946**, *68*, 2123 – 2133.
[11] G. Anner, K. Miescher, '*Über Steroide. 81. Mitteilung. Die Synthese des natürlichen Oestrons III*', *Helv. Chim. Acta* **1948**, *31*, 2173 – 2183.
[12] G. W. Craig, '*The Woodward Research Institute, Robert Burns Woodward (1917 – 1979), and Chemistry Behind the Glass Door*', *Helv. Chim. Acta* **2011**, *94*, 923 – 946.
[13] W. E. Bachmann, W. Cole, A. L. Wilds, '*The Total Synthesis of the Sex Hormone Equilenin*', *J. Am. Chem. Soc.* **1939**, *61*, 974 – 975.
[14] K. F. v. Auwers, K. Ziegler, '*Über Kohlenwasserstoffe der Semibenzolgruppe*', *Liebigs Ann. Chem.* **1921**, *425*, 217 – 280.
[15] A. L. Wilds, C. Djerassi, '*The Preparation and Partial Aromatization of 1,4-Cholestadienone-3 by the Dienone-Phenol Rearrangement*', *J. Am. Chem. Soc.* **1946**, *68*, 1712 – 1715.
[16] J. A. Berson, 'Chemical Creativity, Ideas from the Work of Woodward, Hückel, Meerwein, and Others', Wiley-VCH, New York, 1999, p. 80 – 81.
[17] E. A. Doisy, C. D. Veler, S. Thayer, '*The Preparation of the Crystalline Ovarian Hormone from the Urine of Pregnant Women*', *J. Biol. Chem.* **1930**, *122*, 499 – 509.
[18] R. B. Woodward, T. Singh, '*Synthesis and Rearrangement of Cyclohexadienones*', *J. Am. Chem. Soc.* **1950**, *72*, 494 – 500.
[19] M. Gates, D. L. Frank, W. C. von Felten, '*Formolysis of 4-(p-Methoxphenyl)butyl-p-bromobenzenesulfonate*', *J. Am. Chem. Soc.* **1974**, *96*, 5138 – 5143.
[20] J. A. Berson, 'Chemical Discovery and the Logician's Program', John Wiley & Sons, New York, 1999, p. 174.
[21] H. Minlon, C.-P. Lo, L. J.-Y. Chu, '*Studies in the Santonin Series. II. The Bromination Products of Desmotropo-santonins and Desmotropo-santonous Acids*', *J. Am. Chem. Soc.* **1944**, *66*, 1954 – 1957.
[22] H. Minlon, S. Cheng, '*Studies in the Santonin Series. III. The Introduction of Nitrogen into the Desmotroposantonin Molecule*', *J. Am. Chem. Soc.* **1948**, *70*, 449 – 452.
[23] H. Minlon, C.-P. Lo, L. J.-Y. Chu, '*Studies in the Santonin Series. I. The Two New Desmotropo-santonins and the Two New Desmotropo-santonous Acids*', *J. Am. Chem. Soc.* **1943**, *65*, 1780 – 1781; see correction in *J. Am. Chem. Soc.* **1943**, *65*, 2483.
[24] L. Birladeanu, '*The Stories of Santonin and Santonic Acid*', *Angew. Chem., Int. Ed.* **2003**, *43*, 1202 – 1208.
[25] D. N. J. White, G. A. Sim, '*The Santonins, Quantitative Conformational Analysis*', *Tetrahedron* **1973**, *29*, 3933 – 3938.
[26] A. P. J. Brunskill, H. W. Thompson and R. A. Lalancette, '*Santonic Acid, Catemeric Hydrogen Bonding in γ,ξ-Diketocarboxylic Acid*', *Acta Crystallogr., Sect. C* **1999**, 55, 566 – 568.
[27] Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga, '*Santonin. II. The Synthesis of New Stereoisomers of Santonin*', *J. Am. Chem. Soc.* **1956**, *78*, 1416 – 1421.
[28] J. W. Huffman, W. T. Pennington, D. W. Bearden, '*Stereochemistry of the Desmotropsantonins*', *J. Nat. Prod.* **1992**, *55*, 1087 – 1092.
[29] D. Lenoir, T. T. Tidwell, '*Louis Fieser, An Organic Chemist in Peace and War*', *Eur. J. Org. Chem.* **2009**, 481 – 491.
[30] L. F. Fieser, M. Fieser, 'Fieser und Fieser, Organische Chemie', 2nd edn., Verlag Chemie, Weinheim, 1972, Chapt. 36 Steroide, Footnote 2, pp. 1634 – 1635; the original English book title, 'Advanced Organic Chemistry', Reinhold Publishing, New York, 1961 and 'Topics in Organic Chemistry', Reinhold Publishing, New York, 1963.
[31] H. Minlon, '*A Simple Modification of the Wolff-Kishner Reduction*', *J. Am. Chem. Soc.* **1946**, *68*, 2487 – 2488.
[32] J. T. Kuethe, K. G. Childers, Z. Peng, M. Journet, G. R. Humphrey, T. Vickery, T. Bachert, T. T. Lam, '*A Practical Kilogram Scale Implementation of the Wolff-Kishner Reduction*', *Org. Proc. Res. Dev.* **2009**, *13*, 576 – 580.

[33] W. J. Xia, D. R. Li, L. Shi, Y. Q. Tu, '*A Novel Approach for Construction of the Naturally Occurring Dihydroagarofuran Sesquiterpene Skeleton*', *Tetrahedron Lett.* **2002**, *43*, 627 – 630.
[34] J. March, '*Oxidations and Reductions*', in 'Advanced Organic Chemistry, Reactions, Mechanisms, and Structure', 3rd edn., John Wiley and Sons, New York, 1985, Chapt. 19.
[35] R. West, M. Ishikawa, R. E. Bailey, '*Anionic Rearrangement of Hydrazines. II. Isomers of Bis(organosilyl)hydrazines*', *J. Am. Chem. Soc.* **1966**, *88*, 4648 – 4653.
[36] U. Regnarsson, '*The Synthetic Methodology for Alkyl Substituted Hydrazines*', *Chem. Soc. Rev.* **2001**, *30*, 205 – 231.
[37] N. L. Wendler, H. Minlon, M. Tishler, '*Synthesis of 11-Hydroxylated Cortical Steroids, The Preferential Reduction of Carbonyl Systems in the Presence of Carbon-Nitrogen Multiple Bonds*', *J. Am. Chem. Soc.* **1951**, *73*, 3818 – 3820.
[38] H. Minlon, R. H. Pettebond, '*A Further Study on the Reduction of Steroid Semicarbazones*', *J. Am. Chem. Soc.* **1952**, *74*, 1562 – 1563.
[39] H. Minlon, E. Wilson, N. L. Wendler, M. Tishler, '*Steroid 17(α)-Acetates*', *J. Am. Chem. Soc.* **1952**, *74*, 5394 – 5396.
[40] H. Minlon, R. Tull, J. Babcock, '*Isomerization and Displacement Reactions in the Cyanopregnene Series. Synthesis of Cortisone 21-Methyl Ether*', *J. Am. Chem. Soc.* **1954**, *76*, 2396 – 2399.
[41] L. Gortler, '*Merck in America: The First 70 Years from Fine Chemicals to Pharmaceutical Giant*', *Bull. Hist. Chem*. **2000**, *20*, 1 – 9.
[42] Shanghai Institute of Organic Chemistry, Chinese Academy of Science, http://stuhome.ustc.edu.cn/content.php?id=1959.
[43] J. T. Stock, '*The American and British Students During the Leipzig Period of Johannes Wislicenus*', *Chem. Intell.* **1999**, 5, 35 – 38.
[44] D. S. Tarbell, A. T. Tarbell, 'The History of Organic Chemistry in the United States, 1875 – 1955', Folio Publishers, Nashville, 1986.
[45] Y. Kikuchi, '*Samurai Chemists, Charles Graham and Alexander William Williamson at University College London, 1863 – 1872*', *Ambix* **2009**, *36*, 115 – 137.
[46] J. S. Siegel, '*175 Years of Chemistry at the University of Zürich, Tradition, Dedication and Vision*', *Chimia* **2008**, *62*, 68 – 74.
[47] B. Witkop, '*Remembering Heinrich Wieland (1877 – 1957). Portrait of an Organic Chemist and Founder of Modern Biochemistry*', *Med. Res. Rev.* **1992**, *12*, 195 – 274.
[48] J. W. Daly, '*Bernhard Witkop, A Chemist in a Biomedical Institute*', *Heterocycles* **1998**, *49*, 1 – 8.
[49] H. Berke, '*Chemistry in Ancient Times: The Development of Blue and Purple Pigments*', *Angew. Chem., Int. Ed*. **2002**, *41*, 2483 – 2487.
[50] P. Coelho, 'The Alchemist', Caledonian International Book Manufacturing, Glasgow, 1995, p. 158.
[51] '*Milestones*', *Bull. Chin. Acad. Sci.* **2003**, *18(2)*, 9 – 18.
[52] H. Herzog, E. P. Olveto, '*A History of Significant Steroid Discoveries and Developments Originating at the Schering Corporation (USA) since 1948*', *Steroids* **1992**, *57*, 617 – 623.
[53] L. Cardenelli, '*Synthesizing a Life: An Interview with Carl Djerassi*', *J. Chem. Educ.* **2011**, *88*, 1366 – 1375.
[54] C. Djerassi, 'Die Mutter der Pille, Autobiographie', German edn., Diana Verlag, München, Zürich, 2001; the original English book title, 'The Pill, Pygmy Chimps, and Degas' Horse', Basic Books, New York, 1992.
[55] C. Djerassi, '*The Pill at 50 (in Germany): Thriving or Surviving?*', *J. Reproduktionsmed. Endokrinol.* **2011**, *8 (Special Issue 1)*, 14 – 31.
[56] H. O. House, 'Modern Synthetic Reactions', W. A. Benjamin, Menlo Park, 1972, pp. 228 – 229.
[57] L. F. Fieser, M. Fieser, 'Reagents for Organic Synthesis', John Wiley and Sons, 1967, Vol. 1, pp. 435 – 438.
[58] P. J. Stang, '*Editorial, 124 Years of Publishing Original and Primary Chemical Research: 135,149 Publications, 573,453 Pages and a Century of Excellence*', *J. Am. Chem. Soc.* **2003**, *125*, 1 – 8.
[59] Personal communication from Professor Carl Djerassi to G. W. Craig, Feb. 17, 2012.
[60] S. Ma, Interview with Yuan Chen, Shanghai, Dec. 23, 2009.

Received February 11, 2013