REVIEW

The *Woodward* Research Institute, *Robert Burns Woodward* (1917–1979) and Chemistry behind the Glass Door

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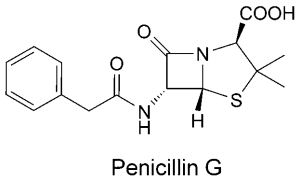
To commemorate the International Year of Chemistry, 2011, this article is dedicated to the memory of my research colleagues from the *Novartis* legacy family: *Zoecon Ltd.*: *David L. Grant* (1933–1994), *Robert J. Lamoreaux* (1947–1997), *F. Dan Hess* (1947–2000); *Jorge Pengman Li* (1934–2002). *Sandoz AG: Andreas Weiss* (1930–1990), *Rupert Schneider* (1926–1996), *Wolf-Dieter Hatzfeld* (1957–1996), *Fritz Irminger* (1929–2000), *Egon Moesinger* (1950–2002), *Karl Lutz* (1915–2007), *James Karapally* (1942–2008), *Charles Timbers* (1943–2008); *Alfred (Fredy) Schaub* (1940–2009), *Ciba-Geigy AG: John Grey Dingwall* (1943–2000), *Manfred Böger* (1940–1999), *Hardy Kühne* (1948–2009), and *Heinz Kienast* (1948–2010).

Certainly a highlight in the career of *Nobel* Laureate Professor *Robert Burns Woodward* (1917–1979) was the foundation of the *Woodward Research Institute* (*WRI*) at *Ciba AG* in Basel, Switzerland, in 1963. *Woodward*'s remarkable accomplishments in the development of organic chemistry altered not only our concepts of molecular structure, but also our comprehension of physico-chemical properties. In his legacy, *Woodward* devised innovative strategies for natural product syntheses based on brilliant rationale of their properties and an uncanny sense of *Nature*. The chemistry community benefited not only at Harvard but especially in Basel and Zürich from *Woodward*'s inspiring lectures and the opportunity to learn from the chemistry *Meister*. This article highlights parts of the chemistry and some personalities that contributed to forefront investigations at the *Woodward Research Institute* which began at the former *Novartis* legacy company, *Ciba AG*, Basel.

Introduction. – Professor *Robert Burns Woodward* (*Fig. 1*) has been elegantly described as one of the preeminent organic chemists of the 20th century [1][2]. The beginning of the *Woodward* era was an exciting time which challenged chemists to solve chemical problems by using what little was understood of structure, not to mention their chemical properties. *Woodward*'s mastery to deduce the structural features from the reactivity profile of a unique molecule such as penicillin (*Fig. 2*), often using a diverse range of reactions, to understand the molecule's chemical and physical properties based on rudimentary instrumental analyses, and then to combine all of the significant data into a consistent clear picture of its molecular structure was unquestionable artistry in chemistry. But *Woodward*'s achievement to orchestrate these facets together into a number of monumental syntheses was, to paraphrase Swedish Professor *Arne Fredga*'s (1902–1992) 1965 *Nobel Prize* introduction, '*a good second only to Nature*' [3].

Fig. 1. Robert B. Woodward *(1917–1979), recipient of the 1965* Nobel Prize *in Chemistry, smoking his* Benson & Hedges *in his office at* WRI. Courtesy of *Novartis Archive.*



Penicillin G

Fig. 2. *Penicillin G was proposed by* Woodward *in 1944 to contain a novel β-lactam in its structure based on degradation products, reaction profiles, and UV studies.*

Woodward's mentorship, his ability to educate and inspire his students, and then to eloquently mesmerize his peers, made him an undisputable legend!

Pre-*Woodward* Era. – We must reflect back to how synthetic chemistry was applied to natural products before *Woodward* received his in Ph.D. 1937 at twenty years of age in MIT (Massachusetts Institute of Technology). Painstaking breakthroughs in the determination of structure were achieved, not by single chemists but by large research groups. The *Nobel Prize* recipients, *Heinrich Wieland* (1877–1957; *Fig. 3*) and *Adolf Windaus* (1876–1959; *Fig. 4*) owed their reputations to prodigious chemical degradation of the steroids and related bile acids to simpler fragments for derivation and identification by using only elemental analysis and melting-point measurements. Cross-confirmation of structural informations accumulated in this way, led to a *reliable*

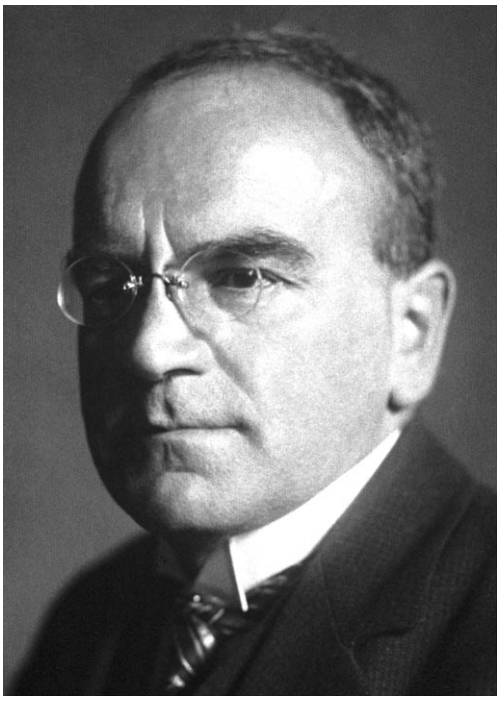


Fig. 3. Heinrich Wieland *(1877–1957), recipient of the 1927* Nobel Prize *in Chemistry.* Photo from http://en.wikipedia.org.

inference of the molecular structure. In those days, '*synthesis*' (from the Greek word, '*the process of putting together*') was more destructive than constructive! Consequently, the back-breaking endeavors of these large research groups led to a rapid advancement in deciphering the complex structure of steroids (*Fig. 5*). However, even the precise structure of the steroid nucleus was to remain questionable when *Wieland* gave his *Nobel Prize* speech in 1928 [4][5][1]). The deadlock between probable steroid skeletons was overcome in 1932, when a key part of the puzzle was supplied by *Otto Diels* (1876–1954), namely that dehydrogenation of cholesterol led to chrysene, a known fused tetrabenzene [5] (*Fig. 5*). The steroid nucleus was ultimately confirmed later the same year by X-ray crystallography [6].

Thus, synthesis of a natural product (or a key intermediate that can be converted to the natural product) by a sequence of well-established reactions was at that time the only reliable evidence for the molecular structure. However, the '*final experimental proof of structure*', then, relied amusingly on a simple melting point of the synthetic material mixed with the natural material, which then showed no melting-point depression when compared to that of the two separate samples [7]. The race to verify the structure of the notoriously complex alkaloid strychnine (*Fig. 6*) compelled

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[1]) The 1927 *Nobel Prize* was actually awarded *retroactively* to *Heinrich Wieland* at the *Nobel* ceremony in Stockholm when the 1928 *Nobel Prize* was awarded to *Adolf Windaus* [4].

Fig. 4. Adolf Windaus *(1876–1959), recipient of the 1928* Nobel Prize *in Chemistry.* Photo from http://en.wikipedia.org.

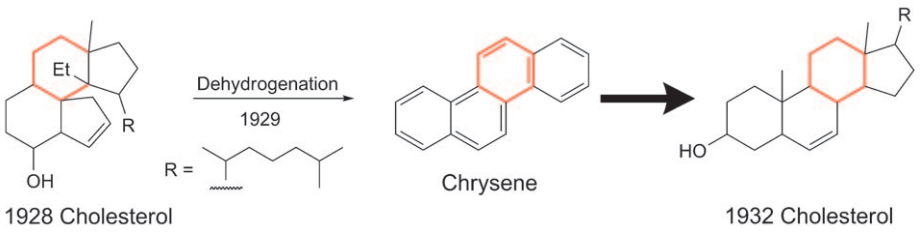

Fig. 5. *The skeletal structure of the steroid cholesterol, inferred in 1928, was reformulated due to dehydrogenation results of cholesterol to chrysene in 1929 which was later verified by X-ray crystallography.*

development of the ultimate structure-determination tool at the time, X-ray crystallography. Between 1951 and 1956 [8–10], it confirmed *Robinson*'s once-abandoned structural proposal from 1946 [11] and *Woodward*'s structure of strychnine proposed in 1947 [11][12], based on degradation *and* spectroscopic studies. Interestingly, the absolute configuration was established by X-ray crystallography, two years *after* the total synthesis of strychnine [2][13]. In time, this distinct order of synthesis before structure analysis reversed, as X-ray crystallography became the work-horse for even more audacious complex structures. Foremost was the practical desire to avoid

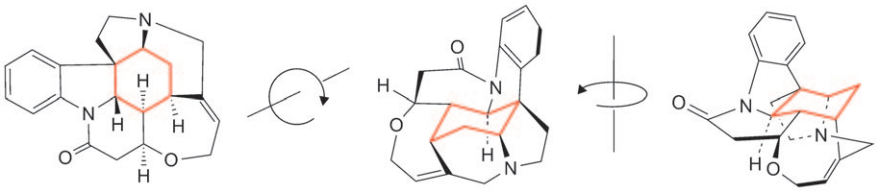

Fig. 6. *Strychnine's complex and controversial structure was correctly proposed by* Woodward *and* Robinson *in 1947 and 1946, respectively.*

labor-intensive years of total synthesis to obtain the wrong structure! Thus, the *Nobel Prize* was awarded to *Dorothy C. Hodgkin* (1910–1994) in 1964 '*for her advancement of X-ray crystallographic technique and the structural determinations of biological molecules, including penicillin and vitamin* B_{12}' [14]. Her exquisite structural determination of vitamin B_{12} in 1956 permitted *Woodward* and ETH Professor *Albert Eschenmoser* (b. 1925) to formulate their strategic plans to synthesize cobyric acid in 1972 and vitamin B_{12}, both ultimately achieved in 1976 as a masterpiece of a Harvard–ETH collaboration [15].

The Early *Woodward* Years. – In this setting, *Woodward* arrived at the chemistry scene and began to reshape the synthetic paradigm. He established a systematic set of ultraviolet (UV) spectroscopy rules in 1941 for identification of a detailed chromophore structure in the molecule [16]. Later, *Woodward* also made contributions to the optical rotatory dispersion (ORD) research pioneered by then Wayne State University Professor *Carl Djerassi* (b. 1923). *Woodward*, *Djerassi*, young Harvard Professor *William Moffitt* (1925–1958), and *Moffitt*'s then graduate student *Albert Moscowitz* (1929–1996) formulated the octant rule. Published in 1961, the octant rule correlated the dissymmetry of substituted ketones, often found embedded within the steroid skeleton, and the *Cotton* effect or absorption minimum of circularly polarized light [17]. Application of these new instrumental techniques invariably led to controversy about the structures of novel natural products. Despite his confrontations regarding structural interpretations with the great alkaloid chemist *Sir Robert Robinson* (1886–1975) (*Fig. 7*), young *Woodward,* barely twenty-eight years of age, determined quite precisely the unprecedented structures of penicillin [18] (*Fig. 2*) in 1944 and strychnine in 1947 [12] (*Fig. 6*).

Already in 1944, *Woodward* and *William von Eggers Doering* (1917–2011) had successfully completed the first total synthesis of quinine [2][19] (*Fig. 8*). Their announcement put *Woodward* and *Doering* under the spotlight of synthetic chemistry, partly because of the world's urgent need for an antimalarial medicine following World War II. More than 60 years later, *Williams* and *Smith* [20] have validated the original *Woodward* and *Doering* quinine synthesis by repetition of the *Rabe–Kindler* partial synthesis of quinine from *d*-quinotoxine [21] (*Fig. 8*). Their succint study has re-emphasized the '*formal nature*' of the *Woodward–Doering* total synthesis (*framed box* in *Fig. 8*), and it has reaffirmed the reputations of these outstanding personalities in the history of chemistry [22].

Fig. 7. Sir Robert Robinson *(1886–1975), recipient of the 1947* Nobel Prize *in Chemistry.* © Keystone/ Hulton Archive/Getty Images.

Woodward's growing reputation attracted postdoctoral students from nearly all continents. Among them was a young Swiss, *Karl Heusler* (b. 1923), who had just completed his Ph.D. thesis, *summa cum laude* at the Universität Basel under *Emil Schlittler* (1906–1979; *Fig. 9*), an expert in alkaloid chemistry. Prolific work carried out, later by *Schlittler*, resulted in the isolation of the complex alkaloid that he named reserpine [23]. Its total synthesis became yet another classic achievement by *Woodward* in 1958 [24][25].

Nevertheless, *Heusler*, having completed his chemistry studies in the isolation and identification of natural products from the *Buchsbaum (Buxus sempervirens*) [26], it was unclear how he might contribute to *Woodward*'s synthetic campaigns at Harvard. But these doubts were laid to rest in 1949, after he arrived in Boston. *Heusler* quickly acquired all of his on-the-job synthetic expertise! He and three other postdoctoral students, *William McLamore* (1921–2010), *David Taub* (b. 1925), and *Franz Sondheimer* (1926–1981) (*Fig. 10*), were assigned a novel and daring synthetic approach that was broadly connected to *Woodward*'s doctoral thesis [27][28]. Although *McLamore* soon left, the synthetic successes of this group [29] (*Fig. 11*) led to a rapid achievement of the first total syntheses of cholesterol [30] and cortisone in 1951 [31][32] (*Fig. 12*).

The young Harvard group learned quickly to work as a team, sharing work loads in 8–10-hour shifts. *Heusler* always began early and had the morning shift. He transferred

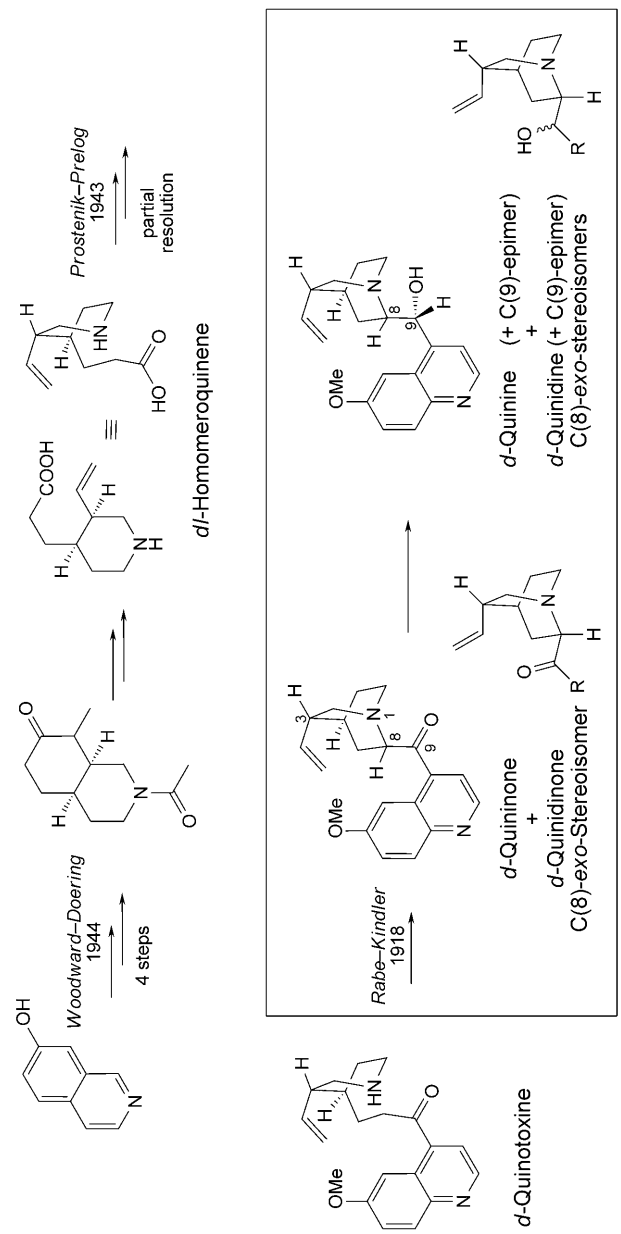

Fig. 8. Woodward *and* Doering*'s total synthesis of quinine in 1944 formally ended with the synthesis of* d*-quinotoxine which* Rabe *and* Kindler *had transformed earlier to* d*-quinine in their partial synthesis in 1918.*

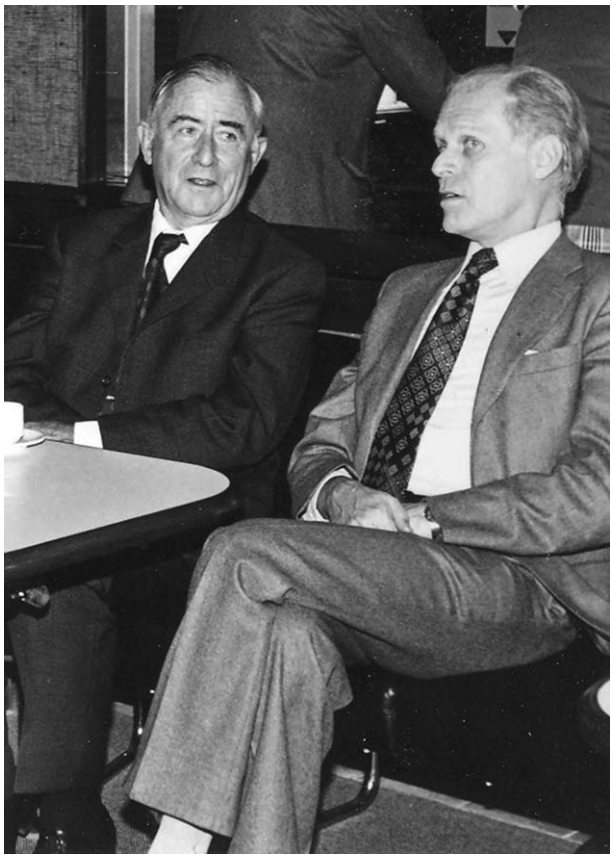

Fig. 9. Emil Schlittler *(1906–1979), Universität Basel* (left), *and* Karl Heusler *(b. 1923)* (right). Courtesy of *Novartis Archive.*

his products after reaction workup and purification to the next team member. *Taub* or *Sondheimer* took *Heusler*'s reaction products for the evening shift, performed the next reactions, and completed the workup and purification. When *Heusler* returned the next morning, the synthetic material was already well-advanced toward the final target! They formed an elite team of chemists that had access to *Woodward* and even his office, when *Woodward* was unavailable. *Woodward*'s younger doctoral students were not so privileged, and they often asked for an appointment. *McLamore* and *Taub* later went on to successful careers at *Pfizer Ltd.* and *Merck Sharp & Dohme*, respectively [27]. *Sondheimer* discovered the annulenes, *i.e.*, cyclic polyenes, that challenged the limits of the *Hückel* rule ($4n+2$ electrons) for aromaticity and furthered steroid research culminating in his appointment as Director of *Syntex SA*, Mexico. *Heusler*, the first in a long line of Swiss postdoctoral co-workers of *Woodward* at Harvard, returned to Basel to accept a research position in the Pharma Research Division at *Ciba AG.* In 1963, he was appointed Senior Scientist and Administrative Head of the newly established

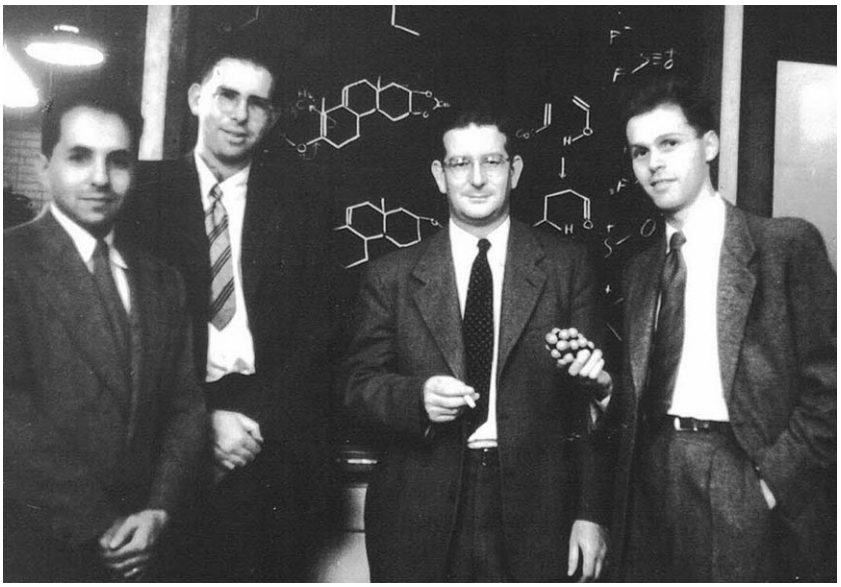

Fig. 10. *The 1949 Harvard group* (left to right)*:* David Taub *(b. 1925)*, Franz Sondheimer *(1926–1981)*, Robert B. Woodward*, and* Karl Heusler. Courtesy of *K. Heusler*.

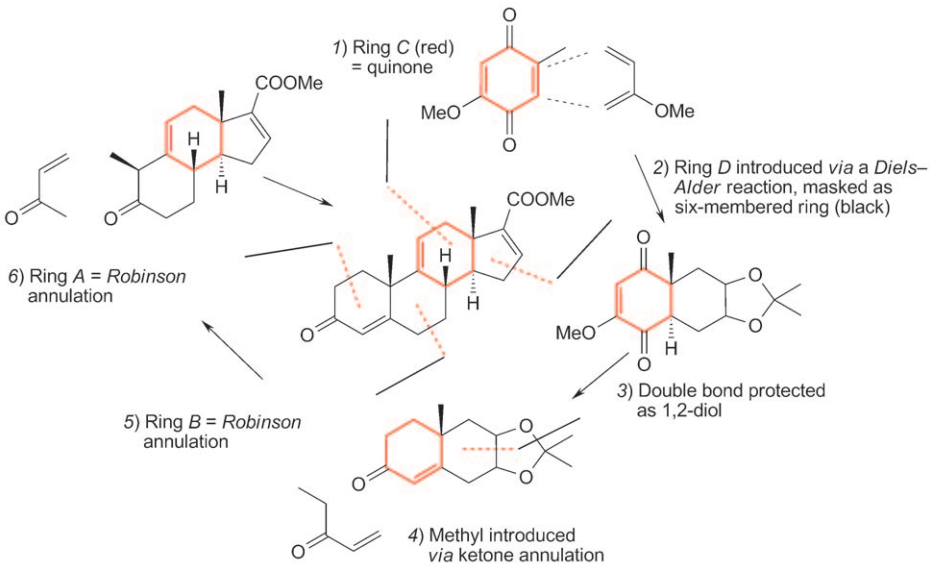

Fig. 11. *Retrosynthetic analysis of the first total synthesis of a non-aromatic steroid,* 'dl-*3-keto-delta-[4,9,(11)16]-etiocholatrienate', published by* Woodward *and the Harvard group in 1951*

Woodward Research Institute (*WRI*) that brought his former Harvard mentor regularly to Switzerland (*Fig. 13*).

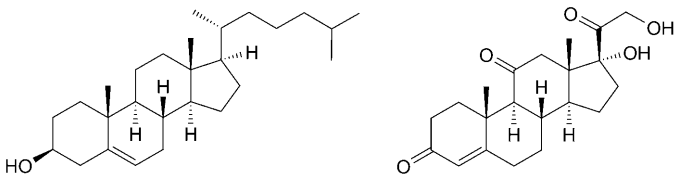

Fig. 12. Woodward *achieved the total syntheses of both cholesterol* (left) *and cortisone* (right) *in 1951.*

Fig. 13. Robert B. Woodward *serving champagne to* Subramania Ranganathan (b. 1934) *at* WRI *Second-Year Jubilee in 1965 at* Ciba AG. Courtesy of *Novartis Archive.*

The *Woodward* Research Institute. – The *Woodward Research Institute* (*WRI*) in Basel was located at the Klybeck site in Building 401, previously occupied by the sweetner research section [33]. Officially, the *WRI* was separated from the rest of the research floor by a glass door which was a reminder that *WRI* had extra-territorial status within *Ciba*. However, in *Heusler*'s words, '*the Ciba chemist behind the glass door was considered the guest, but of course an often and gladly seen guest, the glass door was more symbolic than real. Chemists from five different nations, from Switzerland, Germany, Austria, Scotland, and India, worked in the Institute with the official language behind the glass door designated as English*' [33].

From these countries mentioned arrived the first experienced chemists, *Jacques Gosteli* (b. 1933), *Helmut Vorbrüggen* (b. 1930), *Wolfgang Oppolzer* (1937–1996), *Pietro Bollinger* (b. 1935), and *Subramania Ranganathan* (b. 1934) (*Fig. 14*), respectively. *Robert Ramage* (b. 1934) and *Peter Naegeli* (b. 1934) were also soon welcomed *Ciba guests* at the Institute. Almost all of the later members of *WRI* were

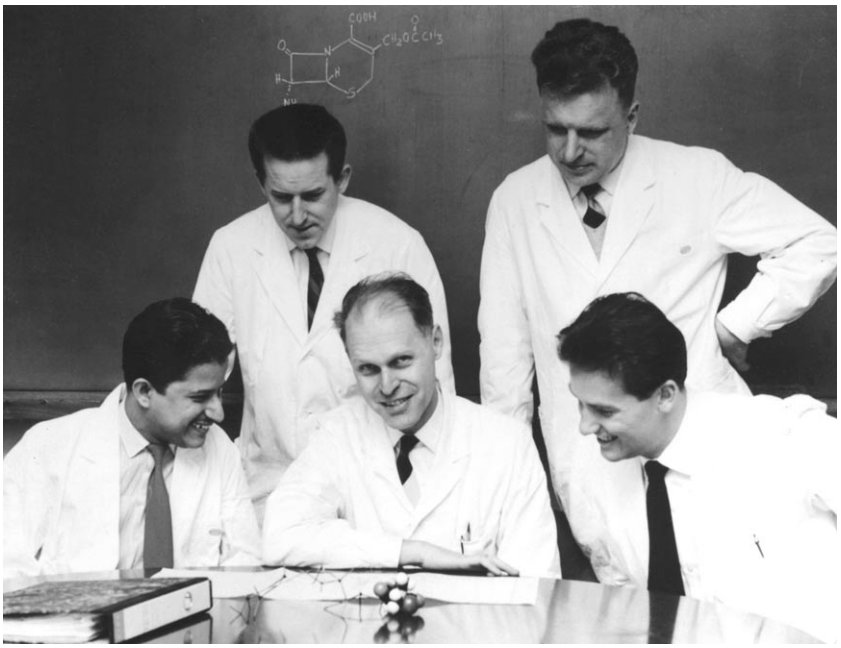

Fig. 14. *The WRI Group in 1965* (clockwise from left)*:* Subramania Ranganathan*,* Jacques Gosteli *(b. 1933),* Helmut Vorbrüggen *(b. 1930), and* Wolfgang Oppolzer *(1937–1996) with* Karl Heusler *in the center.* Courtesy of *Novartis Archive.*

previous postdoctoral students of *Woodward* at Harvard. A notable exception was the young *Wolfgang Oppolzer* (1937–1996) (*Fig. 15*), former doctoral student of *Vladimir Prelog* (1906–1998) at the ETH. He had completed postdoctoral studies with *Elias J. Corey* (b. 1928) at Harvard before joining *WRI*. Later, at the Université Genève, *Oppolzer* developed elegant stereoselective applications of pericyclic reactions for the synthesis of natural products [34].

At *WRI*, the chemists worked in the American style of postdoctoral research, accompanied by long hours with usual discussions late into the night. When *Woodward* visited, five to six times each year, he was often found with his group discussing their research progress and sketching his synthetic ideas, often on his famous *yellow sheets* [35].

Woodward was attracted certainly by the wealth of modern instruments, technical support, analytical services, not to mention the diversity of scientists to discuss research problems at *Ciba AG*. In addition, *Woodward* had neither administrative nor teaching duties and was '*free to investigate any chemistry as long as it was related to living organisms*' [33]. To optimize communications between *Woodward* and *Ciba AG*, all spectra and reports were duplicated and sent regularly to Harvard. Of course, *Ciba AG* retained legal rights of any inventions or discoveries involving chemistry projects at *WRI*.

One of *Woodward*'s many research projects involved the prostaglandins (PGs), an important class of hormones that regulate hypertension, asthma, pregnancy, and pain

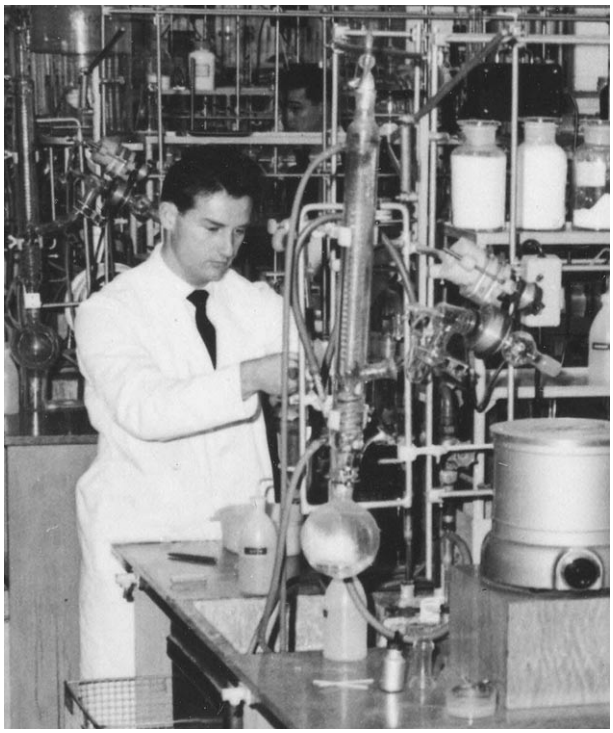

Fig. 15. *Postdoctoral co-worker,* Wolfgang Oppolzer *(1937–1996), former ETH doctoral student of* Vladimir Prelog *(1906–1998), in the laboratory at* WRI. Courtesy of *Novartis Archive.*

[36] (*Fig. 16*). He developed an innovative synthesis of the pivotal bicyclic aldehyde **1** (*Fig. 17*) in *Corey*'s early syntheses of PGE_2 and $PGF_{2\alpha}$ [37]. Granted, *Woodward*'s synthesis involved several steps, but the simplified transformations involved *meso-*

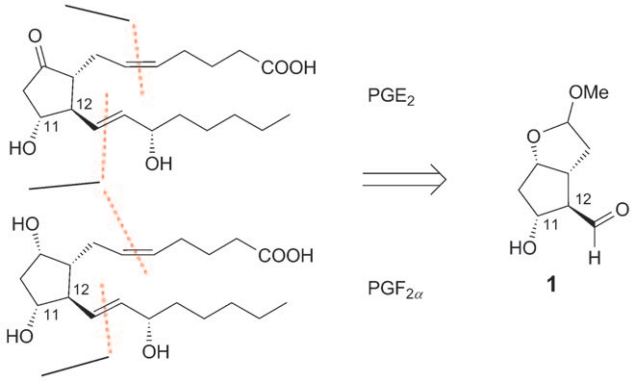

Fig. 16. *Retrosynthetic analysis of* E. J. Corey*'s synthesis of prostaglandins* PGE_2 *and* $PGF_{2\alpha}$ *from the versatile bicyclic aldehyde* **1**

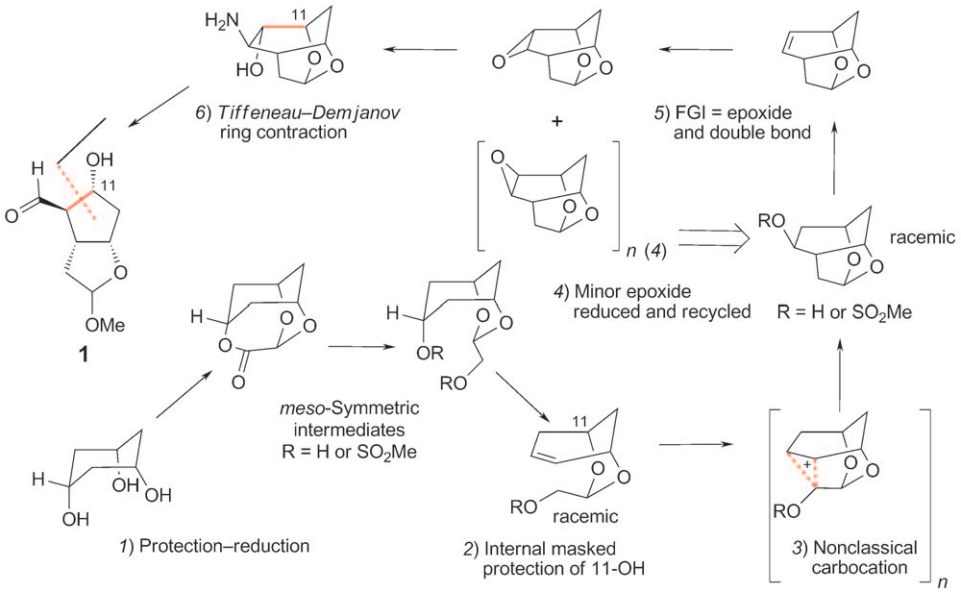

Fig. 17. *Synthetic analysis of* Woodward*'s alternative synthesis of* Corey*'s bicyclic aldehyde* (**1**) *used in the syntheses of prostaglandins,* PGE_2 *and* $PGF_{2\alpha}$

symmetric intermediates, were highly efficient, utilized common reagents, were amenable to recycling minor products, and were remarkably reproducible on a large scale. The crucial step, *Tiffeneau–Demjanov* rearrangement (*Step 6*, *Fig. 17*) involved a stereospecific ring contraction from the bicyclic amino alcohol (*Fig. 17*) with four contiguous stereogenic centers to the final product **1**.

Another major area of research at *WRI* was the development of novel antibiotic β-lactam analogs (*Fig. 18*). Despite, the sensitive reactivity of the penicillin β-lactam C=O group, attributed to the ring-strained pyramidal N-atom, *Woodward* devised brilliant usage of mild protecting groups and intramolecular reactions to attain the

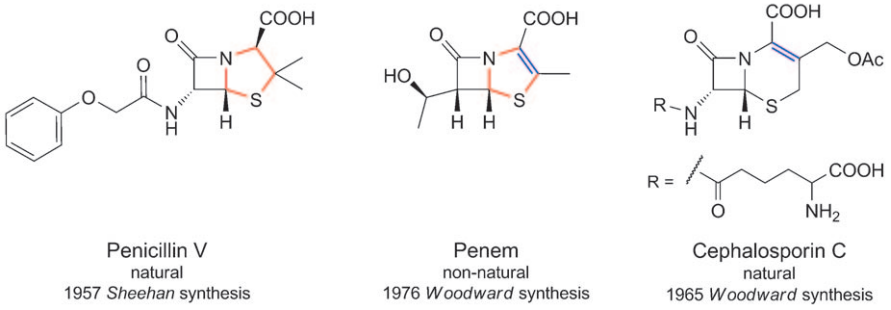

Fig. 18. Woodward *combined the β-lactam features of natural cephalosporin* (double bond) *and penicillin* (thiazole ring) *in the novel unnatural penem class which proved to be exceedingly bioactive.*

cephalosporin target (*Fig. 19*). Two different routes were developed beginning with the natural chiral building blocks, penicillin and (+)-L-cysteine (*Fig. 19*). Moreover, a little-known *Pummerer*-like rearrangement reaction with dimethyl azodicarboxylate (*Step 1*) was carefully exploited to modify the N- and S-containing segments of the cysteine sulfur-carbon (Steps 2–5, *Fig. 19*) [2][38]. Space limitation here precludes a detailed analysis, but the reader is referred to *Woodward*'s *Nobel Prize* address [2][38]. '*For his meritorious contributions to the art of organic synthesis*,' *Woodward* received the 1965 *Nobel Prize* [3]. It was hardly surprising that *Woodward* invited his entire synthesis team from *WRI* to accompany him to the *Nobel Prize* ceremony in Stockholm. Moreover, it was typical that the chemistry which *Woodward* described at the ceremony was successfully completed and confirmed by mixed-melting point, literally the evening before his presentation [35]!

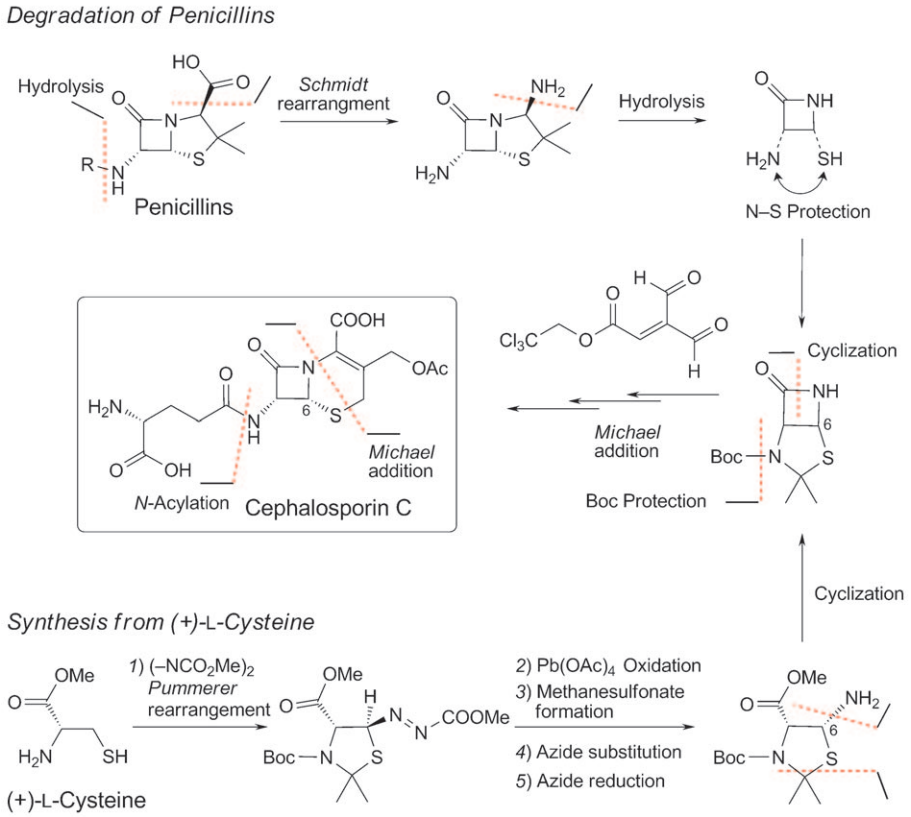

Fig. 19. *Retrosynthetic analysis of* Woodward*'s synthesis of cephalosporin C from (+)-*L*-cysteine and from degradation of natural penicillins*

Chemistry Spin-Offs. – *Heusler* remarked, '*whenever a chemist had an idea, Bob* [Woodward] *never discouraged him* [*or her*] *to follow up their ideas*'. In this respect, *Heusler*, *Gosteli*, and *Ernest* from the former Czechoslovakia, who each in turn served

as Administrative Head at the *Woodward* Research Institute, were at liberty to work on their personal ideas, but they were always expected to make active contributions to the *WRI* Projects directed by *Woodward* [35]. *Gosteli* investigated alternatives for the synthesis of indigo [39], the dyestuff which had previously shaped the chemistry development of dyestuffs at *Ciba AG* [40]. *Ernest* followed up research ideas in search of novel PGs [41], while *Heusler* continued his early developed interests in free-radical reaction applications to steroids [42].

At *Ciba AG*, the early years of steroid research were already well-established in the 1930s due to collaborations with *Nobel Prize* recipients, *Leopold Ružička* (1887–1976) at the ETH, Zürich, and *Tadeus Reichstein* (1897–1996) at the Universität Basel [43][44]. During the years 1950–1969, *Ciba AG*, *Merck Sharp & Dohme*, *Pfizer Ltd.*, *Schering AG*, *Syntex Ltd.*, and *Upjohn* competed vigorously to synthesize cheaply the then new anti-inflammatory, cortisone (*Fig. 12*). After his return from Harvard, *Heusler* began steroid research at *Ciba AG* where he made crucial contributions to the area [42], later referred to as '*through-space*' oxidation investigated at both the ETH and Harvard. The ETH Professors *Oskar Jeger* (1917–2002) and *Duilio Arigoni* (b. 1928) had discovered this effect using chloramine [45], while *Corey* had reported this simultaneously in the partial synthesis of dihydroconessine [46]. *Heusler* at *Ciba AG* found that steroidal C-atoms, particularly Me groups, 1,3-diaxially disposed to a proximal OH group, underwent selective free-radical oxidation with hypoiodite reagents [42] (*Fig. 20*). These critical studies opened the way for '*transannular*' functionalization of the steroidal Me(18) group in the partial syntheses of aldosterone, an important steroid responsible for ion absorption in the kidneys [47][48] (*Fig. 21*), and the Me(19) group for obtaining 19-norsteroids [49]. *Sir Derek H. R. Barton* (1918–1998) developed his splendid partial synthesis of aldosterone alternatively by mild photodecomposition of nitrite esters [31][50]. For his exceptional research, the determination of the key factors for selective intramolecular and free-radical reactions and their subsequent application to the modification of steroids, *Heusler* was awarded the prestigious *Ružička Prize* in 1965 by the *Swiss Chemical Society* [51].

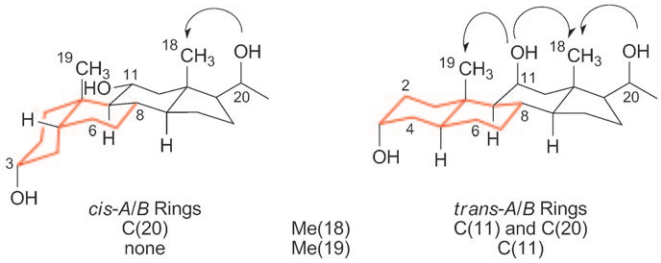

Fig. 20. *Selective free-radical oxidation of Me(18) or Me(19) in steroids with* cis- *and* trans-A/B-*fused ring systems depend on the proximal positions of the 1,3-diaxial OH groups* (note arrows).

This vibrant atmosphere created productive and exciting chemistry during the *WRI* years. In connection with another synthesis of quinine, azatwistane, a novel tricyclic amine, was discussed at *WRI* in 1969 (*Fig. 22*) [35]. The parent all-C-twistane had been synthesized by *Whitlock Jr.* (b. 1936) and *Siefken* in 1962 [52]. *Woodward*

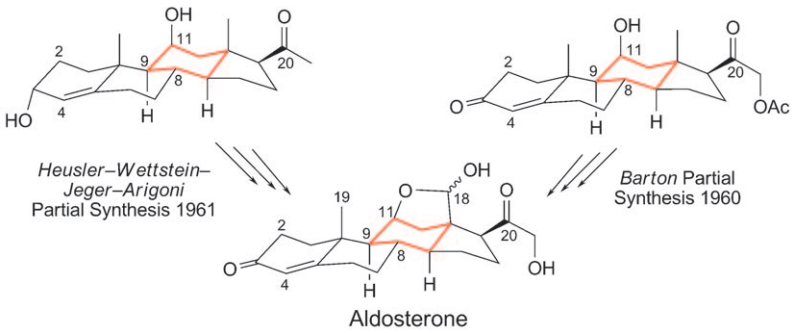

Fig. 21. *Partial syntheses of aldosterone, developed between 1955–1961, exploited free-radical through-space* (remote) *oxidation of Me(18) in steroidal intermediates.*

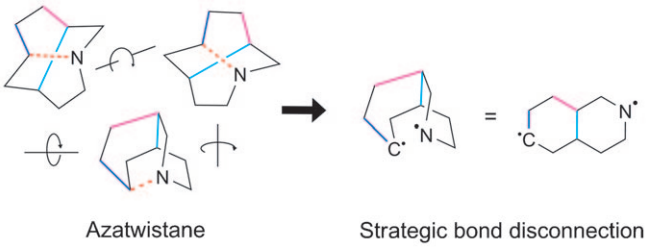

Fig. 22. *Retrosynthetic analysis and bond disconnection based on the planned synthetic strategy to azatwistane*

approached *Heusler* at *WRI* and proposed synthesis of quinine *via* an alternative path to that which he and *Doering* had published in 1944. To paraphrase *Woodward*'s words, azatwistanone (**6a**) had potentially all the necessary atoms for a masked quinuclidine [35] (*Figs. 23* and *24*).

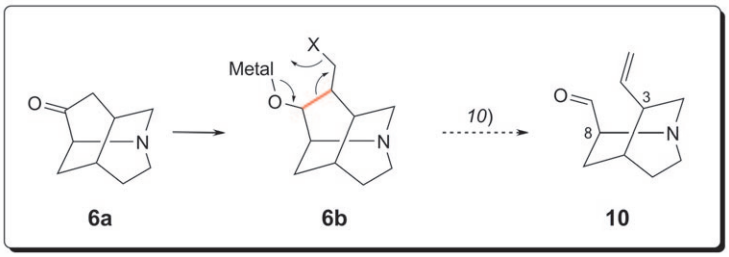

Fig. 23. Path B: *In 1969,* Woodward *proposed the key azatwistanone* (**6a**) *for the synthetic achievement of quinine* [53].

In typical *Woodwardian* fashion, this chemistry was also offered to anyone else at the *WRI* to take it up if he wanted. As noted by *Heusler*, '*I took up the suggestion and developed the synthesis of the azatwistane structure* [*myself*] *but could not prepare the azatwistanone* (**6a**). *The hydroxide displacement of chloride was too hindered to*

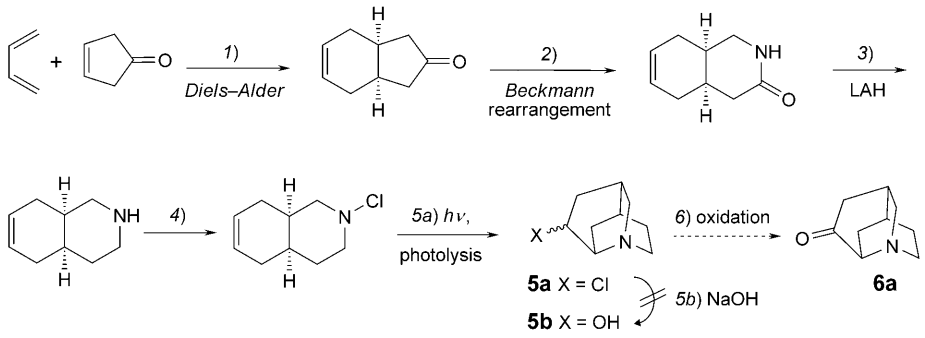

Fig. 24. Heusler*'s synthesis of chloro-azatwistane* (**5a**)

synthesize the desired alcohol, the azatwistanone precursor' (see **5b**; *Fig. 24*). *Heusler* proposed a synthesis of azatwistene (**7**), from the chloro-azatwistane (**5a**), which could then be ozonized to the *syn* bis-formyl quinuclidine **8a** (*Path A*, *Fig. 25*) [54]. It could be expected that *syn*/*anti* bis-formyl quinuclidines (*i.e.*, **8a**/**8b**) would equilibrate. Perhaps, intramolecular H-bonding from the enolate form of the *C(8)-endo*-formyl to the quinuclidine N-atom might be thermodynamically favored, additionally supported by the equilibration of first formed *exo*-quinidinone to the desired *endo*-quininone in basic media noted by *Williams* and *Smith* [20].

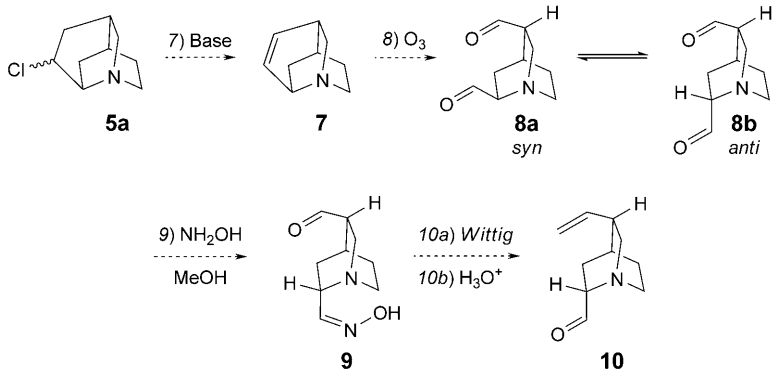

Fig. 25. Path A: Heusler *proposed the formation of the 3,8-diformylquinuclidine* (**8**) *by base elimination of* **5a** *to azatwistene* (**7**; *Step 7*) *and subsequent ozonation* (*Step 8*).

Woodward proposed a novel metal-catalyzed fragmentation of **6b**, available from azatwistanone (**6a**), leading directly to the formyl-vinyl-quinuclidine **10** (*Path B*, *Fig. 23*). The intended metal complex has since been forgotten [53], however, the nature of *Woodward*'s substituent X in *Fig. 23* can be left to the imagination of the reader, either in its historical context or for consideration from a modern synthetic perspective.

Woodward's knowledge of *Pasteur*'s mild acid degradation of quinine to quinotoxine would have led him to recognize the potential enolate pathway for epimerization of

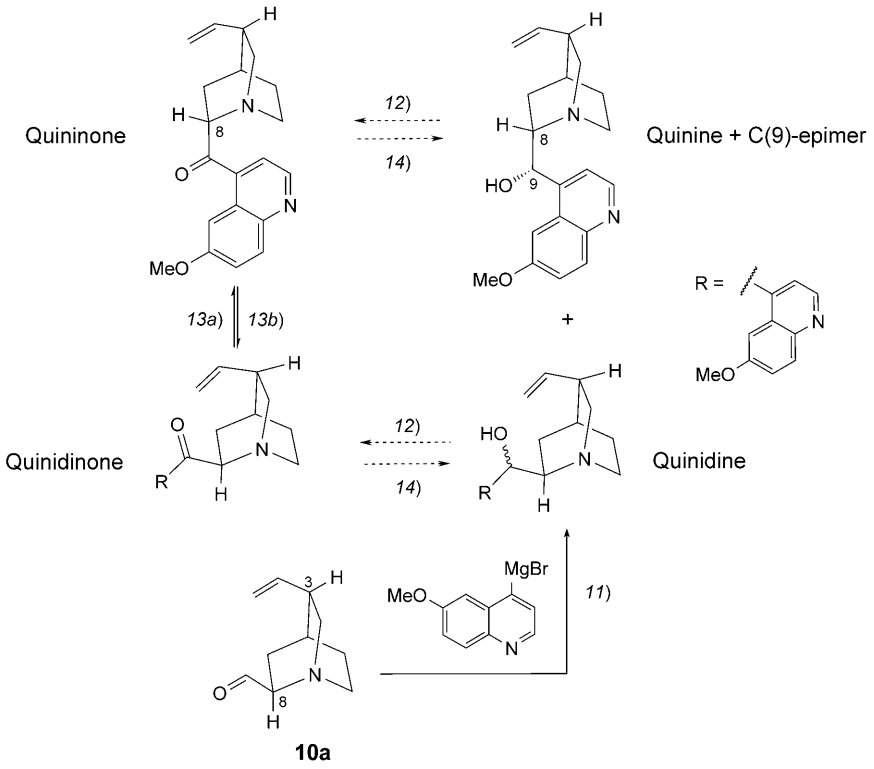

Fig. 26. *Resolution of quinine from its diastereoisomers*

exo/*endo*-stereoisomers after the oxidation of OH at C(9) (*Fig. 26*) [55][56]. Consequently, any mixture of quinidine/quinine (*C(9)* exo/endo) stereoisomers after *Grignard* addition (*Fig. 26*, *Step 11*) might be *1*) initially purified and the stereoisomers separated, *2*) the undesired quinidine (and *C(9)*-OH epimer) reoxidized (*Step 12*) to the C(8)-*exo*-stereoisomer, quinidinone, *3*) epimerized (*Step 13*) to the desired C(8)-*endo*-stereoisomer, quininone, *4*) and separate reduction (*Step 14*) to yield additional quinine. This strategy essentially achieves a partial resolution of C(8) *exo*/*endo* mixture. Perhaps, from the historical perspective, this second synthetic approach *via* azatwistanone (**6a**) was *Woodward*'s attempt to readdress any dissatisfaction in the first formal total synthesis of quinine.

Heusler says, '*Obviously, quinine could perhaps be prepared from the azatwistene via the quinuclidine intermediate envisaged by Bob* [Woodward], *but when I left the* [*Woodward* Research] Institute*, the chemistry was not pursued any further*' [53] (*Fig. 25*). In 1969, during the predawn merger of the chemical industrial giants, *Ciba AG* and *J. R. Geigy AG*, *Heusler* (*Fig. 27*) was promoted to Director of the Pharma Research Division. *Ivan Ernest* (1922–2003) was chosen as *Heusler*'s successor at *WRI*, and, after 37 years service, *Heusler* retired in 1988 from *Ciba-Geigy AG* (*Fig. 28*). Since then, there have appeared brilliant solutions, by *Milan R. Uskoković* (b. 1924) at *F.*

Fig. 27. Robert B. Woodward (right) *greeting* Karl Heulser (left) *in* Woodward*'s office at* WRI. Courtesy of *Novartis Archive*.

Hoffmann-La Roche AG [56], *Gilbert Stork* (b. 1923) at Columbia University [57], and *Eric N. Jacobsen* (b. 1961) at Harvard [56], for the stereocontrolled total synthesis of *d*-quinine such that *Woodward* would gladly have honored with a toast, and a glass or two of champagne!

Conclusions. – *Woodward*'s artistry was exquisitely reflected in the chemistry research at *WRI*, *Ciba AG*. He created an exciting environment for the synthesis of complex molecules using his brilliance and vast chemical knowledge. Each of his synthetic projects had the unmistakable, classic *Woodward* signature which challenged the chemist's imagination '*to become One with the molecule*'. *Woodward*'s favorite usage of rings to mask the predestined configuration in the target and exploitation of preferential intramolecular reactions have become common synthetic caveats today. In the design of intricate synthetic strategies for particularly difficult chemical problems, his legacy continues to inspire countless chemists to dream outside their limits. *Woodward*'s penchant to learn from *Nature* and the implementation of modern instrumental techniques had at least two defining effects. It guided the development of physical chemistry and instrumentation after 1940, and boldly altered synthetic chemistry's development. Ironically, this modern-day path has lured chemists away from learning first-hand about the properties of the molecule through chemical degradation. This expertise *extraordinaire* was *Woodward*'s foremost strength as the virtual *Magister Ludi,* the genius protagonist in *Hermann Hesse*'s novel, '*The Glass Bead Game*' [58]! Today, the majority of chemists seldom develop a keen sense of the molecule's *chemical* structure in terms of its inherent reactivity, if not to recognize only

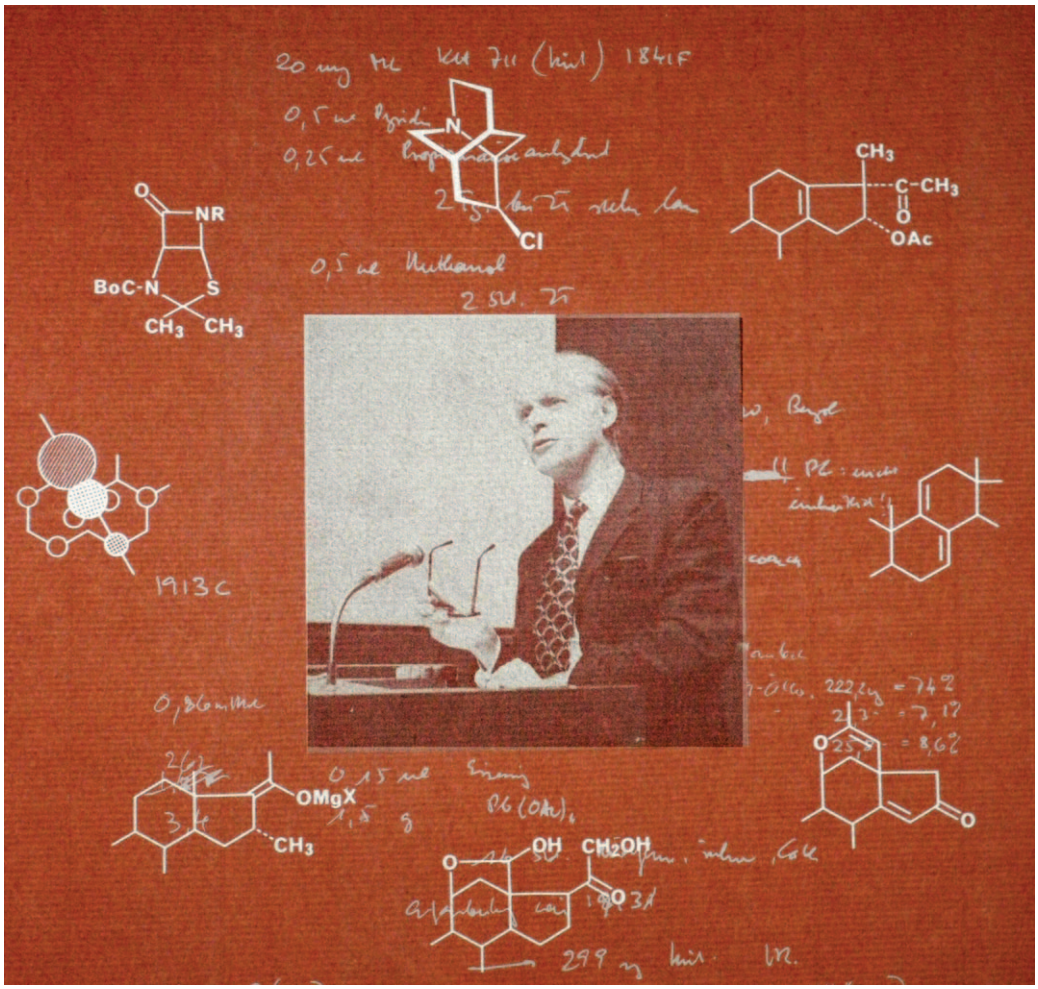

Fig. 28. *Photo depicting* Karl Heusler *and his chemistry, presented to him at his retirement at* Ciba-Geigy AG *in 1988.* Courtesy of *Novartis Archive.*

its *physical* structure in its more abstract representation in an NMR spectrum. As Yale Professor *Jerome A. Berson* (b. 1924), *former Woodward postdoctorate* concluded: '*When a field is new and undeveloped, someone must have the nerve to propose new and unprecedented ideas. Someone must have the self-confidence to risk eventually being shown wrong*' [59]. *Woodward* was one such person, but he was seldom wrong about his intuition and ideas in chemistry. He thrived in understanding physico-chemical properties and their relationship to molecular structure. But most of all, he enjoyed out-thinking the molecule. After his tragic death in 1979, the *Woodward Research Institute* closed its doors forever at *Ciba-Geigy AG* (*Fig. 29*).

Today, total synthesis is a journey in organic chemistry fully aided by a vast array of analytical instrumentation. Complex molecules are synthesized in fewer steps, and in

Fig. 29. *The former* Woodward *Research Institute, Building 401, Klybeckstrasse 200, Basel, currently home of* Huntsman GmbH. Photograph *G. W. Craig*, 2010.

higher yields than ever before. Development of synthetic methodology has expanded the chemist's '*synthetic toolbox*' to allow construction of almost any molecule imaginable. Even C–H bonds which were considered inert in former times can now be activated selectively for modification. Moreover, the physical structure of a molecule can be determined without involving a single reaction. Chemical synthesis is rarely required for structure determination nowadays; however, it remains *an absolute 'must'* for the discovery of new structural features that provide exciting insights into expression of chemical and biological properties of the molecule! *Woodward*'s legacy was epitomized by his courageous response to difficult, if not impossible, synthetic problems and the reward of discovery of chemistry insights that can never be planned in a designed synthesis. Organic chemistry has made glorious strides, but it was *Woodward*, the chemistry visionary, whose legacy, charisma, and extraordinary myth still guide the chemists' intellect today, in the *glass-bead game* called *synthesis.*

It gives me a special pleasure to acknowledge Dr. *Karl Heusler* who was especially generous and open to discuss his career in chemistry. I thank him for taking his valuable time to read rough versions of this manuscript and permission to reproduce his personal photographs during his history-making investigations with Professor *Robert B. Woodward*. His candid discussions about his personal experience at Harvard and *Ciba AG* will always be appreciated. I am also grateful for the assistance of Dr. *Carole Billod* and Dr. *Walter Dettwiler* at the *Novartis* Archive. Their professional experience and efficiency for cataloging the historical records was crucial to write about this chemistry landmark, the *Woodward* Research Institute, whose significance has almost vanished from the Chemical Industry in Basel. It also gives me pleasure to acknowledge the professional assistance of my former colleagues who began their careers in the *Novartis* legacy family, Dr. *Andrew J. F. Edmunds* (*Sandoz AG*), Dr. *Hans Tobler* (*Ciba-Geigy AG*), and Dr. Rolf Schurter (*Ciba-Geigy AG*). I thank them for the discussions of chemistry that was portrayed and described in this article. Finally, special thanks to Ms. *Ines Friess* (*Sandoz AG*), my devoted supporter who patiently and meticulously assembled and copied this manuscript for journal submission.

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