A SCHOOL FOR SYNTHESIS: R. B. WOODWARD AND THE WOODWARD RESEARCH INSTITUTE REMEMBERED

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Supplemental material

Introduction

Almost 40 years ago the R. B. Woodward (RBW) Research Institute (WRI) closed its doors in Basel, responding to RBW's untimely death. Little is now known about the Institute and less published. No accurate, contemporary history of the WRI exists in any chemistry journal. Insiders' publications include Heusler's "The Woodward Institute" (1) and Vorbrüggen's *Working with R. B. Woodward* (2). Prelog mentions the WRI founding in his autobiography *My 132 Semesters of Chemistry Studies* (3), while Bowden and Benfey discuss the Institute in *Robert Burns Woodward and the Art of Organic Synthesis* (4). Other writings are a subentry in a popular online encyclopedia (5). Yet the WRI, because its operations and accomplishments informed Woodward's stellar career, continues to arouse interest within the international chemical community. It merits better treatment.

This essay narrows a gap in the history of organic chemistry and improves upon an inadequate (5) treatment of the Institute. With eye-witness testimony, it quashes doubt that RBW led his postdoctoral researchers, a calumny expressed by outsiders on both sides of the Atlantic. One of them wrote, "… did Woodward actually direct the research" (6)?

Scope and Limitations

Vignettes present our personal recollections of working at the WRI as postdoctoral researchers. A book chapter and the authorship of two articles testify to our having been among RBW's coworkers (7-9).

We indicate the scope and limitations of this essay lest our resources or viewpoint be misunderstood. Our recollections of the WRI restrict the subject matter, although we exploit information scattered through the chemical literature. No complete, authoritative history appears in these pages, dependent as it would be on interviews with far-flung WRI veterans. Some of these veterans are deceased, we lack contact information for most of those whom we knew long ago, and neither of us ever met eight of the WRI postdocs. Moreover, we cannot draw on any rich archive of personal or scientific information concerning the WRI, for none exists. We make no claim to recalling everything about the WRI. It began operations five years before either of us worked there and closed six and one half years after the last of us left. Moreover, as young researchers who were not RBW's peers we were not privy to his deliberations except as they concerned our day-to-day research. Nor were we consulted or advised by CIBA's executives with whom we had few interactions. All these constraints direct us to write a personal account of our years at the WRI, akin more to a postcard than to an epic film.

Topics

We do illuminate the founding, funding, leadership, benefits, operations, social interactions and achievements of the WRI. We also record some chemical research carried out there, unpublished except for certain patents and a book chapter, but instructive, interesting, and undimmed by time. These results invite contemporaneous development by other chemists. The essay concludes recounting the international influence of the WRI. A more authoritative history than ours awaits a professional historian with a journalist's skills and a generous grant.

Founding, Funding and Functioning of the Woodward Research Institute

Leopold Ruzicka and Vladimir Prelog, professors at the Swiss Federal Institute of Technology, Zürich (also known as the ETH or ETHZ), sought to attract RBW to Switzerland in the early 1960s (3). No research professorship could be offered him because none existed. Albert Wettstein (10), then director of pharmaceutical research at CIBA AG (11) filled the lacuna. He suggested that CIBA create and fund a research institute functioning as a school for synthesis. RBW's mandate was to direct and pursue whatever chemical research he chose as long as it lay "in the field of chemical compounds or processes associated in some way with living organisms" (4). He was to assign any valuable inventions to the company. Drug sales, based on RBW's assignments of his patent rights to CIBA, were to furnish the sponsor with a return on its investments in the WRI. Approved by regulators, the marketed drug Cefroxadine (**1**), an analog of Cephalosporin C (**2**), did emerge from the research.

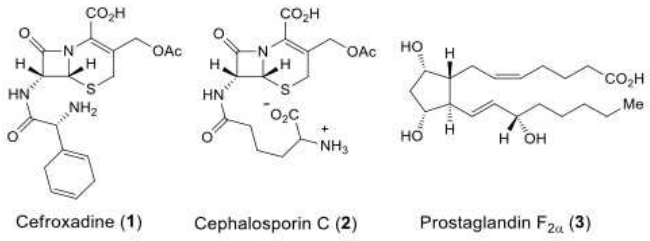


Figure 1. Two topics, b-lactam antibiotics such as 1 and 2 and the synthesis of Prostaglandin F_{2a} (3), dominated the papers published from the WRI.

CIBA complied with Wettstein's suggestion and on June 1, 1963, opened the doors of Klybeckstrasse 200 to the new research institute. It occupied one-half of one floor in a multistory CIBA building located on the Kleinbasel campus. Interior windows lined a corridor bisecting the WRI, and a single laboratory ran its length, housing most of the researchers. Opposite lay an instrument room, a two-person laboratory, a secretarial office, a conference room containing RBW's office, and another small laboratory. Tall exterior windows admitted ample light. At one end of the corridor stood a desk occupied by the senior chemical technician, while at the other two glass doors reading "Woodward Forschungsinstitut" marked the entryway.

Success came early and, 27 months after the WRI opened, the Swiss patent office assigned priority dates of September 10, 1965 to two process patents covering certain intermediate substances in RBW's Cephalosporin C synthesis (12, 13). By the 1970s, the Institute employed about 20 people, and produced streams of patents, papers, natural products, and β-lactam drug candidates. Patents and papers issued from the WRI at a rate of about seven per year.

Throughout much of its existence the WRI operated like a group of pharmaceutical-industry medicinal chemists. Its postdocs used intermediate substances from the Cephalosporin C synthesis to make new compounds for pharmacological testing as antibiotics. They sought to improve potency and suppress side effects by making structural changes (7, 9). However, to devise and carry out complete total syntheses represents a rare and daring beginning to the medicinal chemists' task is of making new compounds that improve the potency or safety of structurally complex and biologically active natural products. The task ordinarily begins with screening of file compounds for substances that are structurally unrelated to the natural product yet exhibit the desired pharmacology. To forgo initial screening and search for a specified pharmacological activity using a multi-step synthesis therefore commits resources of personnel, money, and time. Yet the commitment brings no certain prospect of a favorable conclusion. In this context, it seems appropriate to recall an anonymous accolade to Woodward. "He showed … that one could attack difficult problems without a clear idea of their outcome, but with confidence that intelligence and effort would solve them" (14).

Lacking during 1968-1973 at the WRI were interactions with experienced scientists permanently employed at CIBA-Geigy. WRI members did not attend (any) in-house lectures by invited external speakers, seminars by group leaders or talks by job seekers. Nor did the WRI chemists interact with the microbiologists who tested for antibiotic activity the Cephalosporin C analogs that the former prepared. Preserving the confi-

dentiality of sensitive, proprietary information explains these arrangements. However, the WRI's postdoctoral researchers were privileged to work with CIBA-Geigy's nuclear magnetic resonance experts, Hermann Fuhrer and Günther Rist.

Leadership

Fulfilling his mandate, RBW directed the research at the WRI, from Basel when he visited and from Cambridge when he occupied his Harvard office. He visited with a frequency ranging from one week in about four to one week in about seven or eight, and his working visits lasted about a week. They always included afternoon meetings in which he minutely studied experimental data and intently listened to the postdocs' reports of progress and regress. The meetings included situation reviews in which RBW noted progress, analyzed the work, and offered suggestions to advance it. In considering what compounds to make as antibiotics or synthetic intermediates, Woodward was always receptive to structural and procedural suggestions advanced by his postdocs. Nonetheless, the compounds they made were often—but not always—of his inventing, not theirs.

In residence at Harvard, he received weekly progress reports concerning WRI research and took part in long transatlantic telephone conferences with his Basel researchers. In his absence from the WRI, the postdocs reported to his successive administrative directors, Karl Heusler, Ivan Ernest, or Jacques Gosteli.

Recruitment

Both in Cambridge and Basel RBW participated in recruiting postdoctoral fellows. One (RJF) received his offer of WRI employment during a Harvard interview, thanks partly to a grapevine running from Basel to New York City. It alerted students to the existence of the WRI and brought news of an opening at the Institute. Today the interview seems to have been less harrowing than did its prospect in 1969. Having learned of the WRI from publicity associated with its founding and with a lecture that RBW gave in Basel, another of us (KFB) wrote Woodward. He sought a postdoctoral appointment without knowing of any opening. RBW interviewed him in Basel and offered him the job.

Nearly half of the Institute researchers were Swiss or American, with the Swiss outnumbering the latter by ten to six. Eight other countries—five of them European—contributed another 18 postdocs (15). The only woman Ph.D. to work at the WRI was Fortuna Haviv. During her tenure, female membership of the postdoctoral workforce reached 14% (1/7). Other female scientists to work in the WRI were chemical technicians.

RBW's early practice (16) of recruiting to Basel his postdoctoral researchers from Harvard did not persist. For examples, none of Fortuna Haviv, KFB, and RJF was ever a graduate student or postdoc at Harvard before their appointments to the WRI. Far from being one of RBW's Harvard postdocs or graduate students, the late Karel Syhora was an established Czech academic when the Soviets ended the Prague Spring in 1968. After fleeing Czechoslovakia, he and his family of three made their way from a Swedish refugee camp to Basel, where our friend Karel found employment in the WRI. Only six researchers (of 34) were RBW's postdocs at Harvard before taking up appointments to the WRI, while just two of his graduate students became members of the WRI. Seventy-six per cent of the WRI postdocs were neither his students nor his postdocs before joining the Institute (15).

Benefits

Postdoctoral appointments generally lasted two years (15), and the duration could be prolonged or curtailed by arrangement with RBW. The longest serving chemists were J. Gosteli (13.2 years), I. Ernest (10.5 years), and H.-R. Pfaendler (6.5 years) (15). For many of the WRI postdocs, their appointments represented their first full-time jobs. So, they were fortunate that these postdoctoral positions brought health insurance covering themselves and their spouses. The Institute assisted foreign postdocs in finding furnished housing and in securing work permits and residencies. The researchers paid Swiss Federal taxes and necessarily partook in the national social insurance scheme. The WRI judiciously secured for those postdocs who did not speak Basel Deutsch a waiver of limited but obligatory service in the municipal fire brigades.

The WRI sent each postdoc to one scientific meeting every year, including conferences in Moscow or Cambridge, UK. The Institute assumed the costs of meeting registration, travel, and lodging. It regularly released its postdoctoral fellows from work to attend lectures in Basel and Freiburg im Breisgau. On one occasion, RBW spoke in Freiburg on the synthesis of Vitamin B_{12}. His lecture was a *tour de force* voluntarily attended by all the WRI postdocs, meticulously illustrated in colored chalks, and painstakingly planned to the last of many blackboards.

Many postdocs were grateful—and not a little surprised given his demanding schedule—that RBW promptly wrote letters of recommendation on their behalves. He made time to offer career advice in one-on-one conversations. All in all, the WRI postdoctoral researchers were treated handsomely.

Operations and Social Interactions

The WRI chemists labored in the prosaic, transatlantic style of industrial postdoctoral researchers. Beginning each day at about 8 AM and quitting at 5-6 PM, the postdocs worked five-day weeks. On Fridays they gathered in RBW's conference room to compose a weekly progress report, which the Institute secretary Katerina Lüthi typed and mailed to Cambridge on Mondays. Sometimes one of the researchers telephoned RBW, because a result was too interesting or important to await the next progress report. Woodward listened carefully, thought deeply, and spoke deliberately; he said little if anything that was not definitive. Fewer words than silences passed East and West over the transatlantic line, suggesting that telephony was only little more effective than telepathy. Nevertheless, to be encouraged to call Harvard was a heady preliminary to the thrill of disclosing a result to RBW.

When he visited, his chemists devoted their mornings to benchwork as usual. Afternoons and evenings, however, were often informed and enlivened, respectively by group meetings in his office and dinners in his Basel hotel, Die Drei Könige. At meetings, RBW usually reviewed progress and once presented a foretaste of dazzling new work from the ETH laboratories of Albert Eschenmoser. At dinners taking place during the successful Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, **3**) synthesis, the chemists celebrated each intermediate step with a bottle that RBW presented and that all of them—especially including RBW—signed after drinking the champagne it held. RBW conferred the autographed bottle on the chemist responsible for the step. The signatures faded to invisibility during the next 40 years. What remained was reluctance ever to spurn an opportunity to celebrate.

Not only did RBW and his researchers celebrate successes with champagne, but he also used bubbly to challenge them. At the beginning of the $PGF_{2\alpha}$ work, he called on them to bring about an intramolecular cycloaddition of *cis*,*cis*-epoxyoctadienal (**14b**, Scheme 3). Among the incentives was a bottle he promised to the chemist who accomplished the change. In his enthusiasm for a WRI synthesis of the natural product, the late Albert Wettstein topped Woodward's offer by pledging another two bottles to any chemist who succeeded (10). Wettstein then outdid himself by promising champers to all the nearly 20 employees in the Institute, who comprised three housekeepers, six to eight chemical technicians, a secretary, an administrative director, and seven postdoctoral researchers. "Try a thermal cyclization," said Woodward, "but stand well back!"

RBW's postdocs lingered at the Three Kings hotel one night while J. Gosteli drew a stereoptical pair of wine glasses and Woodward used the drawing to teach the postdocs to achieve naked-eye stereopsis. This feat lets a researcher merge two two-dimensional images into one three-dimensional image without a stereoscope; it is useful in studying X-ray crystallographic structural drawings. The lesson retarded progress at the bench on the morning after; the chemists consolidated their gains by rehearsing what they learned on the night before.

***Figure 2**. R. B. Woodward signing a structural drawing of $PGF_{2\alpha}$ to mark completion of his synthesis on Saturday, April 22, 1972. The drawing appeared on an interior laboratory window of the WRI in Basel, with I. Ernest in the background. RJF's artwork remained for months. Photo by T. Rogger.*

On rare occasions, the postdocs reconvened at RBW's conference table for post-prandial discussions in the WRI. Arriving at the table one evening, finding RBW seated but alone, and making small talk, one of his postdoctoral researchers questioned him. Why did he draw β-lactam antibiotics with the lactam oxygen and nitrogen respectively occupying the Northwest and Northeast corners of the azetidine ring? Everyone else places them in the Southwest and Southeast, effectively rotating the enchanted ring through 180°. "Because," he said, "Dorothy Hodgkin tells me that's how they lie in the crystal."

Only on one Saturday did the postdocs attend the Institute, which happened when the (±)-$PGF_{2\alpha}$ synthesis

reached completion. To make, purify, characterize, and identify the WRI's first synthetic sample of **3**, C. Suter worked all night. On the following day, April 22, 1972, his spectacles raised to his forehead, RBW closely examined thin-layer chromatograms and spectra of synthetic prostaglandin $F_{2\alpha}$. He compared them to chromatograms and spectra of the natural material and, satisfied, commemorated a successful synthesis by signing and dating one-meter-long, blue drawings of the $PGF_{2\alpha}$ structure (Figure 2). The utmost gravity attended the signings. For many months, the drawings ornamented all the interior windows and glass doors of the WRI.

Closure of the WRI (15)

The WRI closed its doors on December 31, 1979, almost six months after the death of RBW on July 8, 1979. One of the postdocs left as early as September of 1979. However, three of the remaining postdoctoral researchers continued until December of 1979, as did the administrative director J. Gosteli and I. Ernest. Permanently appointed to the Institute, I. Ernest worked there from May 1, 1968, until December 31, 1979. The Institute secretary, K. Lüthi, also served until late December of 1979, having begun her employment in early June of 1963.

Achievements of the Woodward Research Institute

An exceptional and fruitful collaboration linked RBW and Hans Bickel, a CIBA-Geigy group leader in Basel but not a WRI veteran. It led to 34 patents (Supplement II) of which they were co-inventors and CIBA-Geigy the assignee. These patents represented a little more than one third of the Institute's entire output of patents. A β-lactam antibiotic marketed for oral human use, Cefroxadine **1**, resulted from the cooperation. Compound **1** was still on the Italian market late in 2017. Such a success elevated RBW and Bickel to the coterie of academic and industrial chemists who contributed to the discovery of a marketed human drug.

In the sixteen years that the Institute existed, thirty-four postdoctoral researchers worked and received training at the school for synthesis, including the three administrative directors (Table 1). Two of them, Gosteli and Heusler, were among the WRI's first intake of postdocs, becoming co-authors of the Cephalosporin C synthesis. Five WRI veterans became professors of chemistry, while many of the others enjoyed rewarding careers in the international pharmaceutical industry. Heusler ultimately came to lead the Pharma Research Division of CIBA-Geigy.

Twenty-five published papers, a book chapter, and 90 patents or patent families originate in the WRI. (See Supplemental Material.) The patents date from 1965, and the papers from 1966. (Some of these will be discussed in more detail below.) Some citations unsurprisingly post-date the unexpected closing of the Institute. The latest of these—a paper—bears a date as recent as 1981 while the last patent was granted in 1986. Because patent terms ranged from 17-20 years, all the original patents have now expired and their inventions have entered the public domain.

Two research topics dominate the papers, the preparation of β-lactam antibiotics and a synthesis of prostaglandin $F_{2\alpha}$ (Figure 1). The earliest articles relate the syntheses of Cephalosporin C and of analogs of that natural product. Later papers present Institute work on penems.

Woodward's Nobel Prize Lecture (17) recounts the Cephalosporin C synthesis. A concise communication (18) gives the main story. It is also a tale told by RBW himself in a video-taped lecture dating to 1966 (19). In keeping with his reputation for lecturing punctiliously, he speaks for 469 milliwoodwards on this occasion (20). This lecture gave occasion for one of his remarkable observations. Speaking of synthesis he says, "It is perhaps worthwhile sometimes to make compounds that an examiner of an elementary student would regard as ridiculous suggestions." RBW's remark is unique to the lecture, failing to appear in any of the Cephalosporin C papers.

A book chapter and a paper relate the work of making analogs of Cephalosporin C (7, 9). Woodward reviewed the Institute's penem labors (21-23), but never the $PGF_{2\alpha}$ work.

Only two papers from the *oeuvre* deal with prostaglandins, one of them a communication concisely presenting the course of the completed synthesis (8). That work began no earlier than September 6, 1971, and ended on May 2, 1972, with a sample of racemic $PGF_{2\alpha}$. By mid 1973, an effort to make the optically active natural product was well underway. The other paper offers an account of the tactics and strategy, and of the failures and successes, that underlie the synthesis (24).

Neither the WRI nor CIBA-Geigy capitalized on Woodward's $PGF_{2\alpha}$ synthesis by making prostaglandin

analogs as drugs. A 1993 review (25), published 21 years after the synthesis was completed, cites 24 pharmaceutical companies that won 14 regulatory approvals for prostaglandin-related drugs. CIBA-Geigy was not among them. However, the number of approvals vindicated A. Wettstein's conviction (26) that a prostaglandin synthesis was a worthy venture.

Other published work from the WRI included two brief excursions. They comprise Heusler's preparation of 1-azatwistane (27), and Ernest's "A Novel Heterocycle of Unusual Properties" (28). Unusually, the atoms composing the heterocycle comprised only sulfur and nitrogen. Ernest's work represented a sortie into organic superconductors, which preoccupied RBW's thinking late in his life (29). Decades after the WRI closed, Helmut Vorbrüggen described researches inspired by the Cephalosporin synthesis. One explored the preparation of β-lactams from aminoacid esters and alkylaluminum bases (30), while the other dealt with uses of *tert*-butoxycarbonyl chloride (31).

Granted patents coming from work at the WRI fell into two categories, β-lactam antibiotics and precursors, and prostaglandin intermediates (Supplement II). The β-lactam patents claimed methods of treating infectious diseases, pharmaceutical compositions, compositions of matter and processes for making them. The prostaglandin patents protected from competition intermediate compounds in the synthesis. They claimed compositions of matter and methods of making them, but not methods of treating diseases or pharmaceutical compositions.

In all the patents, the assignee was CIBA-Geigy AG or a subsidiary. Woodward was an inventor of each patent, and in 16 of the patent cases, he was the sole inventor. The only other inventors named by WRI patents were his administrative directors or collaborators, the latter employed at CIBA-Geigy but not in the WRI. His ordinary postdoctoral researchers at the WRI worked under contracts to him. They agreed as a condition of their employment to assign to him any rights they owned in inventions they made at the Institute. RBW's death left a backlog of patentable inventions, and 17 patents were granted posthumously.

In the two subsequent sections, we present vignettes from each of the two dominant research topics at the Institute. Concerning the β-lactam antibiotics, we give an account not of relatively routine syntheses of Cephalosporin C analogs (9), but of more subtle and demanding work for which no in-house precedents existed, and which yielded the disulfide **4** (X = S, Scheme 2). Concerning the attempted $PGF_{2\alpha}$ synthesis, we recount an unpublished tale, which Ernest's paper omits (24, 32). The tale concerns a stoichiometric enamine reaction inducing asymmetry at the six chiral centers of **16** (Scheme 3) and an opportunity that remains largely unexplored.

2-Thiacephems

Fifty years ago, the 2-thiacephems **4** (X=S) were an unknown class of heterocycles. To this day, the following effort remains to our knowledge the only synthetic entry to this novel class of compounds. We describe this work because the cascade of reactions changing *Z,Z*-**9** to **4** (X = S, Scheme 2) illustrates medicinal chemists' thinking late in the last century. It was biased. It presumed that innovative synthetic approaches would ultimately lead to pharmaceutically useful compounds, a strategy long since proven wrong. The synthesis below is a good example of this kind of reasoning. Furthermore, it demonstrates the great length to which big pharma was then ready to go, supporting what RBW termed "art in organic synthesis" (33). Indeed, one of us (KFB) was almost exclusively engaged with the work for nearly 3 years (1968-1970), and one of our WRI colleagues, Romeo Paioni, also made 2-thiacephems during 1971. Another colleague, Wolfgang Oppolzer, prepared saturated 2-thiacephams during the last year (1967) of his WRI appointment.

Synthesis

The building block **5**, having served the WRI team as an intermediate for the synthesis of a large number of Cephem derivatives (7, 9), was abundantly available, and was thus an obvious point of origin for an approach to 2-thiacephems **4** (X = S).

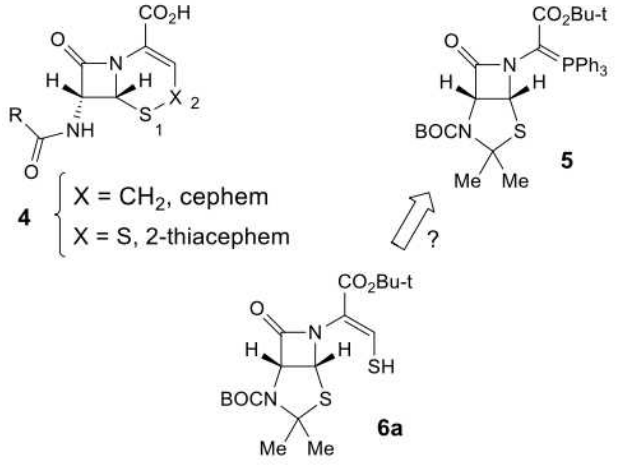
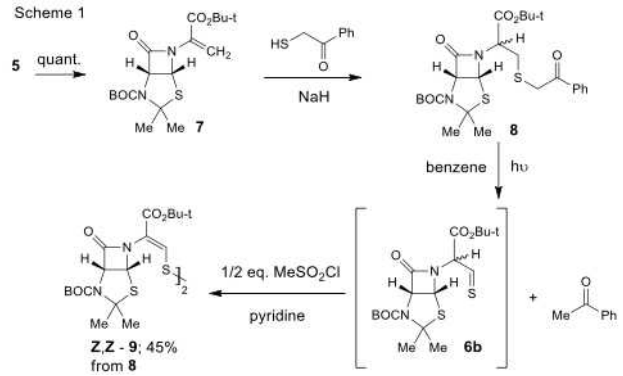


***Figure 3**. Key intermediates in the synthesis of thiacephems.*

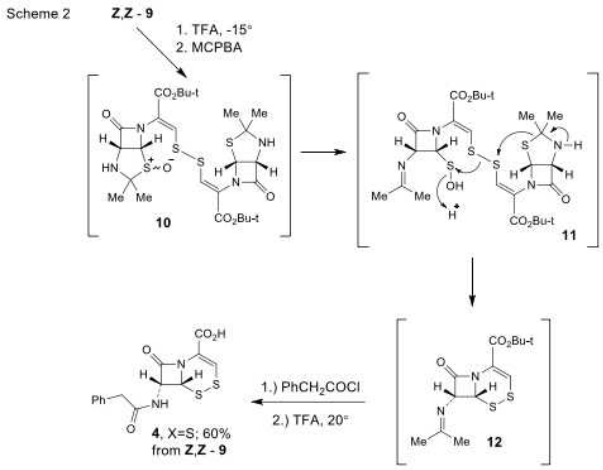
Wittig reaction of **5** with formaldehyde afforded **7** (Scheme 1), which in turn underwent a Michael reaction with phenacyl mercaptan to produce the phenacyl sulfide **8** (34, 35).



Phenacyl sulfides have occasionally been investigated as candidates for Norrish photocleavage reactions (36, 37). The presence of sulfur seems to promote the Norrish Type II cleavage, producing acetophenone and a thiocarbonyl component. If applicable to the phenacyl sulfide **8**, such a photofragmentation should yield **6b**, the thiocarbonyl tautomer of the desired thioenol **6a**.

Irradiating **8** in benzene with a Pyrex-filtered, high-pressure mercury lamp encouragingly formed acetophenone but also gave polymeric material. However, when the photolysis occurred in the presence of diphenyl diazomethane, the desired product (**6b**) of the cleavage could be trapped as the diphenyl carbene adduct. The isomeric mixture of thiirans that resulted established that **6b** had been formed. Omitting the diphenyl diazomethane and adding one equivalent of pyridine instead to the benzene solution induced tautomerization of **6b** to the less fugacious thioenol **6a**. After oxidation, compound **6a** could be isolated as the dimeric disulfide **9** (**38**). The yield from **8** of the pure *Z,Z*-isomer **9** was 45% after crystallization.

Exposure of **9** to trifluoroacetic acid at –15°C (Scheme 2) selectively removes the BOC-groups, leaving the *tert*.-butyl ester groups intact. Subsequent oxidation with *meta*-chloroperbenzoic acid (mCPBA) takes place at the thiazolidine sulfur, rather than at the disulfide bridge, yielding the sulfoxide **10**; some bis-sulfoxide is inevitably formed.



On treating **10** with trifluoroacetic acid at –15°C, the remarkable unraveling outlined in formula **11** took place, affording *two* equivalents of the cyclic disulfide **12**. Without isolation, the Schiff base of **12** can directly be acylated and the *tert*-butyl ester cleaved to the desired final product **4** (X = S). *Z,Z*-**9** furnished 60% of thiacephem **4**.

To improve efficiency and to avoid the prodigal formation of the bis-sulfoxide, the mCPBA oxidation was carried out directly in the medium known to promote the fragmentation. To this end, **9** is kept at –15° for 30 minutes to cleave the BOC groups, and mCPBA in THF is then slowly added at –15°. Apparently, whatever sulfoxide **10** is generated under these conditions undergoes instant fragmentation to **12**, which in turn appears to resist further oxidation to a disulfide oxide.

This synthetic strategy also proved to be generally applicable to thiacephems substituted at position 3, as well as to other N-acylated thiacephems (7, 39).

Discussion

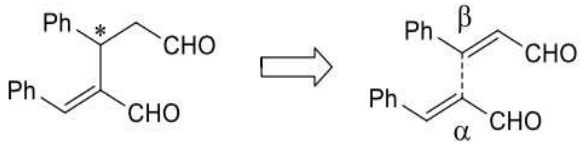
Compound **4**, as well as several analogs, were tested for antibacterial activity *in vitro*. Their antibiotic spectra resembled those of the respective cephem derivatives, i.e., they were mainly of the gram-positive type. This was then of sufficient interest to CIBA-Geigy to patent both the synthetic approach and the compounds (see Supplement II). But the project was eventually terminated when the CIBA-Geigy developers considered the synthetic methodologies involved to be unsuitable for production on a larger scale or on an industrial one. It was therefore gratifying to learn that this particular photocleavage of **8** to **6b** (Scheme 1) was later found by E. Vedejs to be more generally applicable (40, 41). During a discussion at the 1980 Gordon Research Conference on Natural Products one of us (KFB) provided him with experimen-

tal details, a contribution he gracefully acknowledged in his publications.

More than a decade after the WRI concluded its work, *unsaturated* 2-thiacephems like **4** became starting materials for now well-established syntheses of penems (42-44). The routes from 2-thiacephems to penems entail extrusion of sulfur as the dioxide (42) or as triphenylphosphine sulfide (43, 44), followed by ring contraction. In the late 1960s, RBW understood that an analogous extrusion and contraction of *saturated* 2-thiacephams would have led to a then-unknown class of β-lactams, namely the penams. Yet of many efforts to realize the transformation in the WRI, none succeeded. Not until 1982 did Ross and coworkers at Hoechst publish such a conversion, albeit one using an unsaturated 2-thiacephem (43).

Opportunity Arising

The published account of the attempted prostaglandin $F_{2\alpha}$ synthesis offers no sign of an opportunity to construct carbon-carbon bonds by an enamine reaction catalyzed by a secondary amine (24). Such a reaction would hypothetically join the α-position of cinnamaldehyde to the β-position of a second molecule, inducing formation of the asymmetric center of dialdehyde **13**. Unsaturated ketones might also participate in place of unsaturated aldehydes. Were the amine to be optically active, the reaction would be enantioselective or -specific. The utility of aldehyde and ketone reactions catalyzed by chiral enamines is evident, for example, in applications devised and reviewed by Barbas and coworkers (45). Earlier examples appear in a variant of the Robinson annulation, leading to an optically active product when the secondary amine is *S*-proline (46, 47). By 2007 asymmetric enamine catalysts were of sufficient international interest to merit a 98-page review of 477 references (48).



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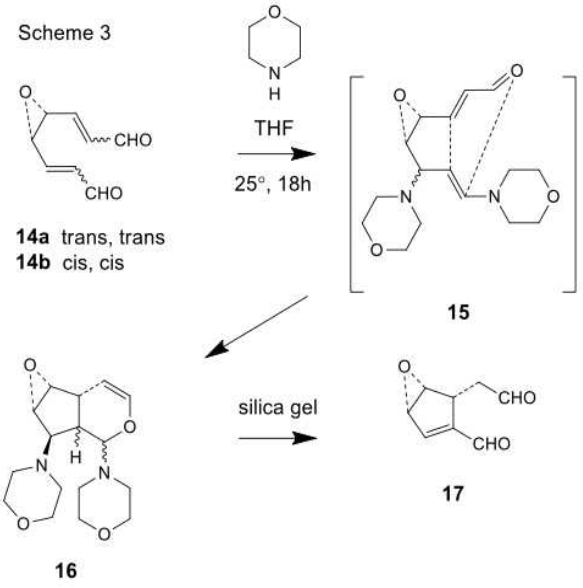
The opportunity follows from the discovery that a stoichiometric amount of the achiral morpholine converted **14ab** to (±)-**16** (Scheme 3). That discovery culminated treatments of the *cis*,*cis*-epoxyoctadiendial **14b** with diethyamine in the presence of silica gel (H. Raman) and with primary and tertiary amines (J. K. Whitesell). Treatment of the resulting *cis,cis*-epoxydialdehyde **14b** with triethylamine gave the *trans*,*trans*-isomer **14a**. The *cis*,*cis*-dialdehyde **14b**, which was to have undergone an internal $[_{\pi}4_{s} + _{\pi}2_{s}]$ cycloaddition (see Ref. 24), was the product of ozonolysis of cyclooctatetraene monoepoxide with one equivalent of ozone.



The source of **16** may be the γ-aminoenamine [**15**]. The enamine would arise from Michael addition of morpholine to one of the α,β-unsaturated aldehydes of **14**, yielding a saturated aldehyde group. Condensation of another molecule of morpholine with that saturated aldehyde group would then yield [**15**]. Mannich describes such reactions using cinnamaldehyde and secondary amines; they take place at temperatures at or below 0°C, and in the presence of powdered K_2CO_3 (49). Later workers use other starting materials to make γ-aminoenamines (50, 51). Concerted or stepwise attack of the enamine upon the remaining α,β-unsaturated aldehyde in [**15**] would form the new carbon-carbon bond that the five-membered ring of **16** embodies. It is this last reaction that constitutes the novel bond-forming step.

Neither primary nor tertiary amines changed the *cis*,*cis*-epoxyoctadiendial to **17**. This suggested that secondary amines were required, as they would be if an enamine mediated the cyclization. Although α,β-unsaturated aldehydes were known to form γ-aminoenamines, our crude products showed none of γ-aminoenamine [**15**]. Its absence was consistent with rapid cyclization to **16**, even in the presence of large amounts of secondary amine (52).

Ultimately, compound **16** came to represent the high-water mark of efforts to induce an intramolecular

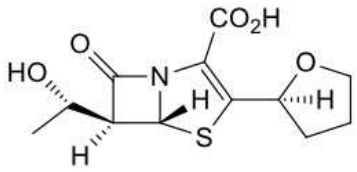
Diels-Alder reaction in service of a prostaglandin $F_{2\alpha}$ synthesis. Its structure corresponds to that expected from an intramolecular [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] cycloaddition of the γ-aminoenamine double bond to the unsaturated aldehyde of [**15**]. However, that correspondence implies no necessary mechanism for the creation of **16**, and not one that RBW formally endorsed or gainsaid, although in a progress review he referred to **16** as the Diels-Alder adduct (52). Still, it remains unknown whether a concerted cycloaddition is the mechanism by which **16** forms.

Treatment of the symmetric all-*cis*-epoxyoctadiendial **14b** with morpholine in tetrahydrofuran at 25° for 18 hrs., followed by chromatography on deactivated alumina, led to (±)-**16**. It was a single racemic diastereoisomer, showing m. p. 161-163°, m/e 308, and microanalytical data in agreement with an empirical formula of $C_{16}H_{24}N_2O_4$. It formed in a yield of 36%, and contained six chiral centers thanks to induced asymmetry and the five degrees of freedom imposed by the *cis*-substituted epoxide ring. The yield rose to 55% when the corresponding *trans,trans*-epoxyoctadiendial **14a** was the starting material. Chromatography over alumina was crucial to obtaining **16**, as exposure of it to silica gel led to the unwanted dialdehyde (±)-**17** (53).

Except for the formation of **16**, the chemistry of γ-aminoenamines apparently remains unexplored eight decades after Mannich made them. It raises the prospect of an enantiospecific enamine reaction forming a carbon–carbon bond between the α-position of one α,β-unsaturated aldehyde or ketone and the β-position of another. The task of realizing such reactions catalyzed by optically active secondary amines may appeal to ambitious chemists.

Conclusion: External Influence

The Institute's most recent influence on outside chemical and microbiological research is the penem invention. RBW announced it in 1978 (54), expanded it at the WRI (55-62), and recounted progress in published lectures (21, 22). Veterans of the WRI, Riccardo Scartazzini and Marc Lang, subsequently employed by CIBA-Geigy, sought to make a drug based on the penem structure in efforts independent of the WRI (63-65). Within 10 years of the original invention, much work in many other laboratories developed the new class of antibiotics. The work merited a 1988 review of synthesis and *in vitro* activity of penem antibiotics, including almost 100 references (66). This number crudely measures the extent of international interest that Woodward's invention aroused. Development culminated in Japanese regulatory approval of the drug Faropenem 18 (67-69).



Faropenem **18**

About a decade after publication of RBW's Prostaglandin $F_{2\alpha}$ synthesis, it unpredictably aided a study in stereochemistry. Dutch workers, wanting to establish the conformation and stereochemistry of the two bicyclic acetals derived from acetaldehyde and *cis*-cyclohexane-1,3-diol, sought an authentic sample of one of the two achiral but C_3-prostereogenic acetal stereoisomers (70, 71). To make this compound the Delft chemists could select from RBW's $PGF_{2\alpha}$ synthesis an early intermediate to serve as their starting material. This compound was 3α-mesyloxymethyl-2,4-dioxabicyclo[3.3.1]non-6-ene (8). Catalytic hydrogenation of the double bond followed by hydride displacement of the mesylate group gave 3α-methyl-2,4-dioxabicyclo[3.3.1]nonane, its stereochemistry unequivocally determined by RBW's dramatic opening movement in his $PGF_{2\alpha}$ opus, namely the condensation of *cis*,*cis*-cyclohexa-1,3,5-triol with glyoxylic acid. Use of this synthesis and the tricvclic lactone that inaugurates it eased the successful Dutch efforts. Peters *et al.* say about the 2,4-dioxabicyclo[3.3.1]nonane ring system, "…it is [otherwise] rather difficult to obtain information on the geometry of the dioxane wing, due to the absence of vicinal H–H couplings in the $C_1OC_3OC_5$ part" (70).

Acknowledgments

RJF thanks the librarians of the University of Montana, Missoula, and University College, Cork; and owes a debt of gratitude to Prof. Jeffrey Seeman for encouragement, suggestions, and reprints. We thank Dr. Jacques Gosteli, Prof. Stanley Roberts, and Emeritus Professor Richard W. Franck for helpful comments on an earlier draft. We are grateful to Messrs. Tony Rogger and Jeremy Alverson respectively for the photograph and structural drawings, and to Dr. P. J. T. Morris for a reprint, literature searching, and advice. We thank Florence Wicker, Archivist at Novartis International AG, Basel, and Juliana Kuipers, Archivist at Harvard University, Cambridge

Table 1. Postdoctoral Researchers at the Woodward Research Institute (15).

Name	**Citizenship**	**Birth Year**	**WRI Tenure**		**Ph.D. (University)**	**Mentor**
			from	**to**		
Karl Heusler	Swiss	1923	6/1/63	6/9/69	Basel	Schlittler
Jacques Gosteli	Swiss	1933	6/1/63	5/31/67	ETH Zürich	Martius
			9/20/71	12/31/79		
Peter Naegeli	Swiss	1934	6/1/63	10/31/65	ETH Zürich	Arigoni
Helmut Vorbrüggen	German	1930	6/1/63	3/31/65	Göttingen	Brockman
Robert Ramage	UK	1935	8/1/63	11/28/64	Glasgow	Raphael
Subramania Ranganathan	Indian	1934	10/1/64	7/31/66	Ohio State	
Wolfgang Oppolzer	Austrian	1937	1/15/65	4/15/67	ETH Zürich	Prelog
Pietro Bollinger	Swiss	1935	6/3/66	4/30/68	ETH Zürich	Arigoni
Roland Wenger	Swiss	1938	9/1/66	10/15/67	ETH Zürich	Schaffner
Johannes Hartenstein	German	1934	1/2/67	12/31/68	Freiburg i. Br.	Prinzbach
Jeffrey Nadelson	USA	1941	9/1/67	11/28/68	Rensselaer Poly. Tech.	
Riccardo Scartazzini	Swiss	1939	11/1/67	12/31/69	ETH Zürich	Arigoni
Kaspar Burri	Swiss	1941	4/1/68	12/31/70	Bern	Jenny
Ivan Ernest	Czechoslovakian	1922	5/1/68	12/31/79	TU Prague	Lukes
Fortuna Haviv	Israeli	1939	1/2/69	12/31/70	Indiana	Wenkert
Romeo Paioni	Swiss	1942	8/1/69	9/30/71	Bern	Jenny
Karel Syhora	Czechoslovakian	1925	12/10/69	4/15/71	TU Prague	Lukes
Richard J. Friary	USA	1942	1/15/70	7/6/73	Fordham	Franck
Christian Suter	Swiss	1942	1/4/71	8/3/73	Basel	Schiess
James K. Whitesell	USA	1944	1/10/71	6/14/73	Harvard	Woodward
Hariharan Raman	Indian	1942	6/15/71	6/14/73	Indian Inst. Tech.	Ranganthan
Gerhardt Nestler	Austrian	1943	11/1/71	10/31/73	Vienna	Zbiral
Robert Sitrin	USA	1945	1/19/72	4/30/73	Harvard	Woodward
Hans-Rudolf Pfaendler	Swiss	1945	7/1/73	12/31/79	Basel	Grob
Thomas C. Coburn	USA	1943	7/1/73	8/26/75	Florida	Jones
Phillip A. Rossy	Canada	1947	10/1/73	5/23/75	McGill	Just
Colin Greengrass	UK	1947	10/1/73	9/19/75	Liverpool	Ramage
Dennis E. Jackman	USA		3/3/75	2/28/77	Utah State	
Wolfgang Holick	German	1945	4/1/75	12/8/77	Freiburg i. Br.	Jenny
Marc Lang	French	1948	9/1/75	4/30/78	École Supérieure de Chimie de Mulhouse	Fleury
Kapa K. Prasad	Indian	1943	3/1/77	2/28/79	Vikram	Ujjain
Christian N. Hubschwerlen	French	1949	10/3/77	9/30/79	École Supérieure de Chimie de Mulhouse	Fleury
Michael R. Attwood	UK	1952	1/2/78	12/31/79	Oxford	Jones/Brown
Alan J. Main	UK	1953	10/10/78	12/31/79	Liverpool	Ramage

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69. The US Food and Drug Administration withheld approval of Faropenem because of preconditions informing human clinical trials for three indications and because of a result from a trial for another indication. In two trials, the sponsor omitted to test the drug against a placebo. In a trial for another indication, the sponsor did not establish to the FDA's satisfaction that the patients dosed were suffering from the disease treated. Finally, the FDA deemed a single trial for a fourth indication to have provided inadequate evidence of efficacy (68).

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About the Authors

Kaspar F. Burri was born in 1941, raised in Switzerland and received in 1968 his Ph.D. in Natural Sciences from the University of Bern, Switzerland. In 1968 he joined the Woodward Research Institute in Basel, Switzerland, as a postdoctoral fellow. He immigrated to the USA in 1971, where first he worked on the Vitamin B_{12} synthesis as a research fellow at Harvard University. Then, from 1973 to 1978 he served as a senior scientist at Hoffmann-La Roche Inc. in Nutley, N. J. From 1979 to 1995, back in Switzerland, he did research as a chemical project leader for F. Hoffmann-La Roche AG in Basel. From 1996 to 1999 he acted as chairman of the board for Lipomed AG in Arlesheim, Switzerland. From 1999 to 2007 he directed the chemical development of Iclaprim, a clinical candidate of the (now defunct) start-up company Arpida AG in Reinach, Switzerland.

Burri's research focused mostly on medicinal chemistry, especially in the fields of antibiotics and cardiovascular agents, where he is an inventor of many patents. He has published as the main author in *J. Am. Chem. Soc.* (1978) and in many issues of *Helv. Chim. Acta*, as well as in *Chimia*. He has co-authored in several international scientific journals, including *Nature*.

A native of Biddeford, Maine, born in 1942, Richard J. Friary became a synthetic organic and medicinal chemist. He earned bachelor's and master's degrees in chemistry and organic chemistry from Colby and Dartmouth Colleges, respectively. Fordham University conferred his doctor's degree in June of 1970. Richard W. Franck, now Emeritus Professor of Chemistry, supervised Friary's doctoral research. Friary joined the Woodward Research Institute in February of 1970, serving for 3 1/2 years. There he made Cephalosporin C analogs and worked on the $PGF_{2\alpha}$ synthesis. Leaving Basel for New Jersey, he worked 27 years at the Schering-Plough Pharmaceutical Research Institute, where he became one of that Institute's most prolific inventors. Twenty-one patents name him as an inventor or co-inventor. Friary is the author or coauthor of some 30 research publications in the chemical literature. He wrote two trade books, *Skate Sailing: A Complete Guide* (1996) and *Job$ in the Drug Industry: A Career Guide for Chemists* (2000). He retired in 2000 and writes about himself in the third person.

Selected Periodic Table Resources

- Periodic Table from Element Collection, Inc. (periodictable.com): photos of the elements on the main table. Click on an element for data. Much data available in plots and tables.
- Places of the Periodic Table (t.co/5rIi5ROMcl): interactive map of locations associated with the periodic table and its elements.
- PubChem Periodic Table (pubchem.ncbi.nlm.nih.gov/ptable/): interactive table. Click on an element for data from multiple cited sources.
- Royal Society of Chemistry Periodic Table (www.rsc.org/periodic-table): color-coded interactive table. Click on an element for data.