LIBERATING R. B. WOODWARD AND THE WOODWARD RESEARCH INSTITUTE FROM ERROR

Kaspar F. Burri, Höhenweg 47, CH-4102 Binningen, Switzerland, kaspar.burri@breitband.ch; and Richard J. Friary, 391 Aspen Way, Florence, Montana 59833, USA, skatesailor1@gmail.com

Abstract

Insiders' eyewitness accounts correct 14 factual errors and one misleading suggestion in an outsider's history of the Woodward Research Institute. Misrepresented are the recruiting, operations, and accomplishments of the WRI, especially in the syntheses of Cephalosporin C and Prostaglandin $F_{2\alpha}$.

Introduction

The year 2011 saw publication of a review concerning the late R. B. Woodward (RBW) and the erstwhile Woodward Research Institute (WRI) (1). The review, which came belatedly to our notice, proved to contain historical and chemical mistakes that eventually goaded us to write this essay. To the task of correcting the errors (2), we bring eyewitness testimony and firsthand chemical knowledge. Counted among RBW's researchers for several years (3-5), and among his admirers for decades (6), here we seek to liberate the man and his Institute from these errors.

Despite the passage of more than 40 years since the Institute closed, it still rouses international interest, so corrections will serve interested parties, chemical historians among them. Identifying scientific errors needs a chemist, but not necessarily a former WRI postdoctoral researcher. Correcting historical mistakes having to do

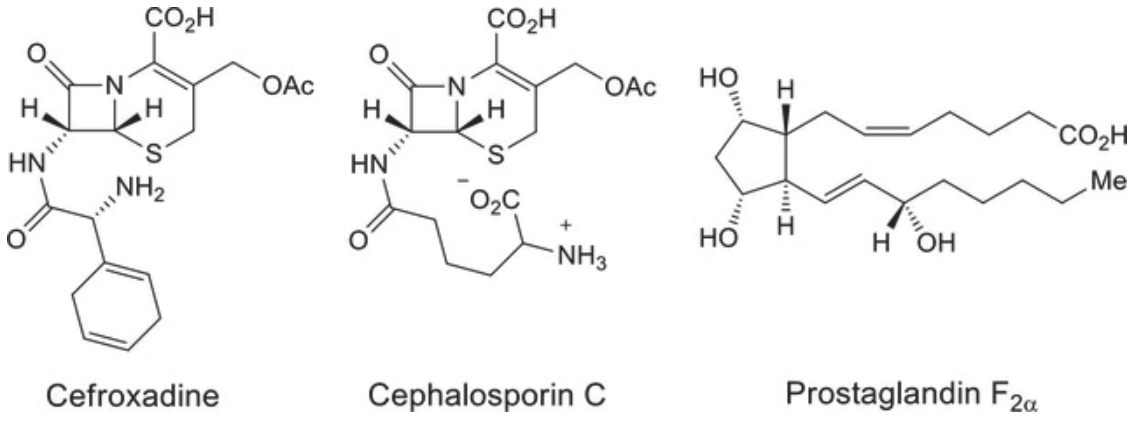

Figure 1. *Structures of a human drug, the antibiotic cefroxadine, and two natural products*

with Institute recruiting, operations, and attributions calls for an insider's familiarity with the WRI. We think it important to attack these last mistakes now because correcting them remains possible only as long as insiders abound (7). Otherwise the errors may stand forever to misinform and mislead chemists and historians alike.

Failing to correct the mistakes or publish the corrections may signify indifference, would perpetuate the errors, and might offend our science perhaps more than does erring initially. Such failures would tender miserable tribute to the man whom we think the greatest organic chemist of the 20th century.

The $PGF_{2\alpha}$ Synthesis: Misconstrued Accomplishments

From September of 1971 to April of 1972, WRI chemists began and completed Woodward's novel synthesis of Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Figure 1). A crucial intermediate was protoprostaglandinal **1** (Figure 2), so named by RBW himself, and embodying the 2-oxabicyclo[3.3.0]octane ring system (4). Ref. 1 incorrectly states, "[Woodward] developed an innovative synthesis of the pivotal bicyclic aldehyde **1** (Fig. 17) in Corey's early syntheses of PGE_2 and $PGF_{2\alpha}$ (Ref. [37] in 1)." What is incorrect here is the supposition that the bicyclic aldehyde **1** played any role in either of Corey's two prostaglandin syntheses; it did not.

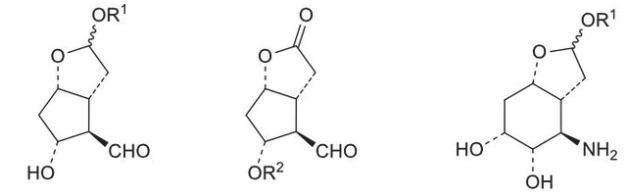

Figure 2. *Selected intermediates in prostaglandin syntheses*

Ref. 1 erroneously indicates that p. 278 of "The Logic of Chemical Synthesis" depicts the intermediacy of protoprostaglandinal **1** in Corey's work (8). However, that page (Figure 3) does not show this precursor, nor does any other page in the book do so. The failure of Figure 3 to depict this structure is akin to the dog's curious failure to bark in the night (9). It is the absence of the barking and the structure that is significant. Protoprostaglandinal **1** plays *no* role in Corey's work, but is unique to Woodward's. So, RBW's achievement does not entail an "… alternative synthesis of Corey's bicyclic aldehyde," as Ref. 1 inaccurately states.

Mediating Corey's prostaglandin syntheses (10-13) but not RBW's are other 2-oxabicyclo[3.3.0]octane-6-als (**3**-**5** (Figure 2)). None of these intermediates is a methyl acetal like protoprostaglandinal **1** but all except one (**2**) are C-3 lactones.

Attributions matter; and mistakenly to assert that the WRI made one of Corey's intermediate lactones diminishes Woodward's originality. In part, it lay in appreciating that any two hydroxyl groups of *cis*,*cis*-1,3,5-cyclohexanetriol contained the relative stereochemistry of the cyclopentane hydroxyls in $PGF_{2\alpha}$. At the same time, the remaining carbinol carbon of the triol pledged functionality enough ultimately to contract the cyclohexane of **6** to the cyclopentane of **1** (Figure 2). Compound **1** contains in the correct relative stereochemistry four of the five stereogenic centers of $PGF_{2\alpha}$.

Ref. 1 erroneously suggests that RBW borrowed his key intermediate **1** from one of Corey's prostaglandin syntheses. However, the opposite—that Corey took advantage of RBW's protoprostaglandinal synthesis—is true, as we show below.

Another 2-oxabicyclo[3.3.0]octane-6-al, compound **2** (13), arises from an alternative synthesis Like protoprostaglandinal **1**, compound **2** is an acetal, but one derived from cyclohexanol rather than methanol. Also like intermediate **1**, which arises from the acetal-amine **6** (Figure 2), precursor **2** comes from a Tiffenau-Demjanov ring contraction following diazotization of the derivative acetal-amine **7** (Figure 2).

Corey and Snider acknowledge that "T[heir] procedure [for making compound **2**] follows one applied by Professor R. B. Woodward and coworkers to an analogous prostaglandin intermediate [compound **1**] prepared by a different route (13)." By April of 1972, the WRI had made the first sample of racemic $PGF_{2\alpha}$. RBW's synthesis of it and the intermediates **6** and **1** were disclosed some weeks later to Professor Corey (14), after CIBA-Geigy applied to patent these compounds in Switzerland, naming Woodward as the inventor (15, 16). The dates of disclosure and application came a year before Corey and Snider submitted their article concerning compounds **7** and **2** to *Tetrahedron Letters* (13). The disclosure, application, and dates together show that RBW did not emulate Corey. They suggest that Corey's preparation of **2** took advantage of Woodward's synthesis of **1** (17), and it is this suggestion that Ref. 1 inverts.

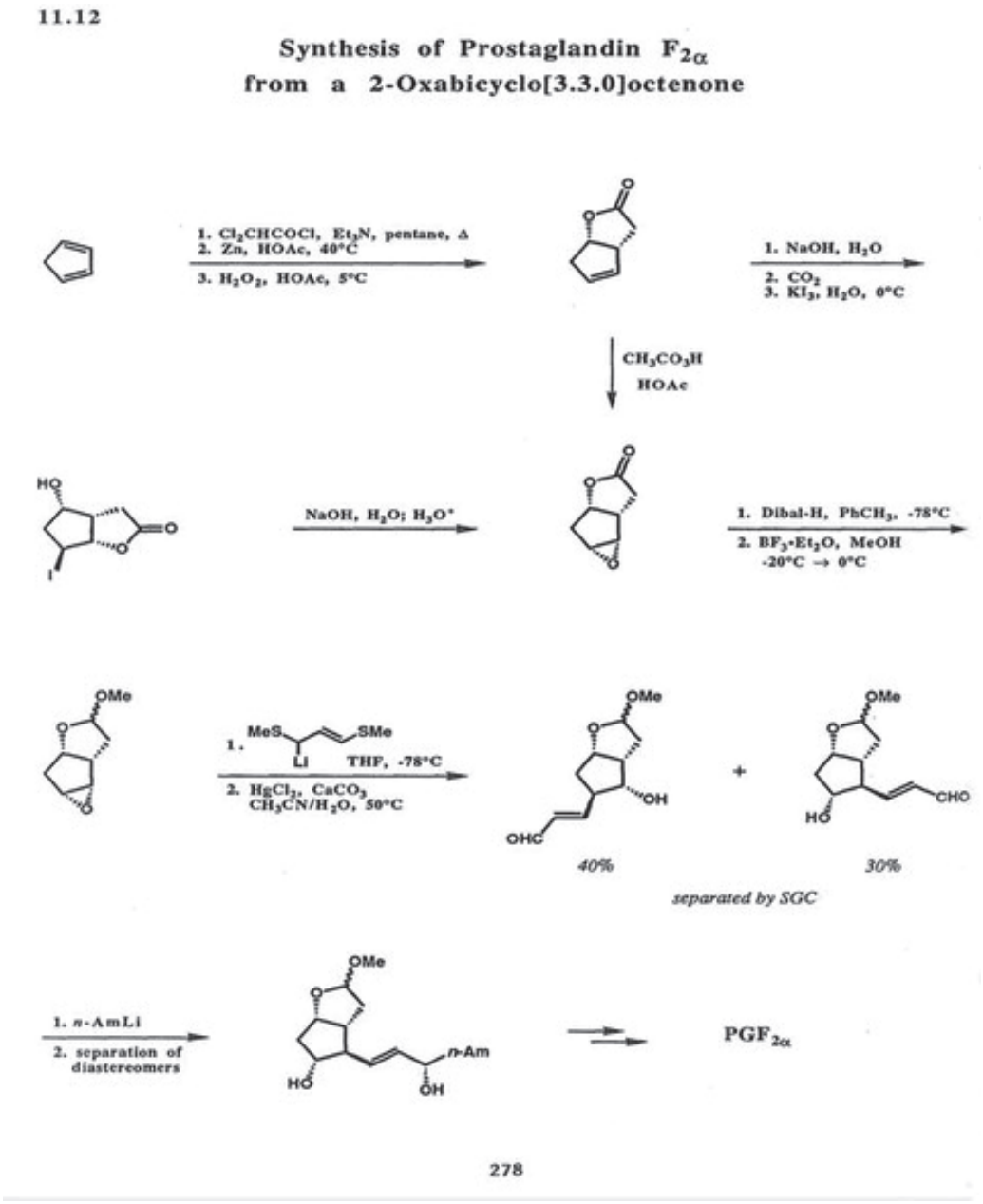

Figure 3. *Page 278 of Corey and Cheng's* The Logic of Chemical Synthesis *(8), in which protoprostaglandinal* ***1*** *does not appear. Reprinted with permission of J. Wiley & Sons.*

Ivan Ernest's Insight

The insight of Ivan Ernest (Figure 4), which Ref. 1 neglects, solved the synthetic problem preoccupying the WRI chemists in 1971-1972. Their challenge was to contract the six-membered ring of **6**, **8,** or some other tricyclic acetal to a 5-membered carbocycle bearing an aldehyde group. An examination of molecular models showed that the vicinal, axial amino and hydroxyl groups in the tricyclic **8** would become equatorial in the bicyclic **6**, adopting an antiperiplanar arrangement (Figure 5). Ernest then supplemented analysis with experiment, subjecting the tricyclic **8** to methanolysis and the bicyclic product **6** to diazotization. The diazonium salt **[6a]** formed (Figure 5) and ruptured, and protoprostaglandinal **1** resulted.

Figure 4. *Ivan Ernest (1922-2003). Photo by K. F. Burri.*

Ernest's other contributions to the WRI were numerous but overlooked by Ref. 1. In the 11½ years he worked at the Institute, he became a co-inventor of 17 patents, a co-author of 12 papers, and the sole author of a book chapter, four papers (6), and a textbook. The chapter (18) and one of those four papers dealt with the chemistry of penicillin-derived diazoketones (19) while two of the others concerned the synthesis and antibacterial properties of 2-oxocephems (20, 21). The textbook set forth bonding, structure, and reaction mechanisms in organic chemistry (22). In terms of authorship and inventorship, Ernest was the more productive of the two full-time administrative directors of the WRI during their appointments, which were unequal in duration.

However, the notion that Ernest "…followed up research ideas in search of novel PGs…." was mistaken by Ref. 1. On the contrary, he never reported attempts to make prostaglandins other than $PGF_{2\alpha}$ (23).

Other Misrepresentations of the $PGF_{2\alpha}$ Synthesis

Ref. 1 misrepresents RBW's $PGF_{2\alpha}$ synthesis in another respect. Fig. 17 in Ref. 1 erroneously shows direct conversion of the ***tricyclic*** aminoalcohol **8** (Figure 5) to protoprostaglandinal **1** by a Tiffenau-Demjanov ring contraction. Such a contraction was never realized or tried (24), so the claim is erroneous; the effective ring contraction of **6** to **1** is published (4). Indeed, successful diazotization of the tricyclic aminoalcohol **8** followed by loss of nitrogen would have yielded the tricyclic α-epoxide **9** (Figure 5), from which **8** was prepared.

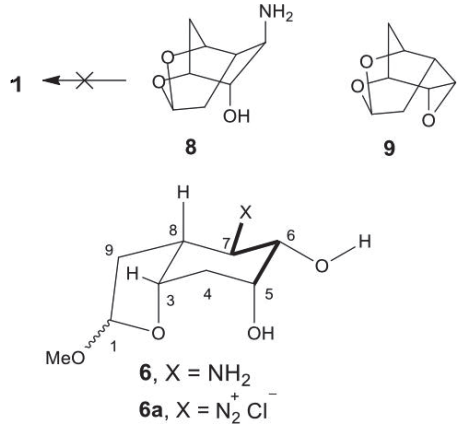

Figure 5*. The antiperiplanar disposition of bonds (emboldened) in a key intermediate (**6a**)*

In Ref. 1 the text below Fig. 17 contradictorily reads, "The crucial step, Tiffenau-Demjanov rearrangement (step 6, Fig. 17) involved a stereospecific ring contraction from the ***bicyclic*** amino alcohol with ***four*** contiguous stereogenic centers … [emphasis added]." However, Fig. 17 does not show ***any*** bicyclic amino alcohol, and certainly ***not*** the bicyclic aminoalcohol **6**, that possesses ***five*** contiguous chiral centers and does form protoprostaglandinal **1**. What step 6 of Fig. 17 depicts is the ***tricyclic*** aminoalcohol **8** (not a bicyclic aminoalcohol) undergoing a ring contraction that was not in fact part of the synthesis.

The Cephalosporin C Synthesis: Miscellaneous Chemical Errors

Fig. 19 of Ref. 1 portrays RBW's Cephalosporin C synthesis, carried out at the WRI during 1963-1966 (25) and becoming the subject of his Nobel Prize address (26). Four mistakes flaw Fig. 19 of Ref. 1. (+)-L-Cysteine is a carboxylic acid, not a methyl ester as Ref. 1 mistakenly shows in Fig. 19. In the synthesis, methyl N-t-butyloxycarbonyl-2,2-dimethyl-thiazolidine-4-carboxylate **11** (Figure 6) reacts with dimethylazodicarboxylate (DMAD) (25). Fig. 19 of Ref. 1 says that cysteine does so and shows its methyl ester doing so, but neither undergoes such a reaction as part of the synthesis. This startling, crucial reaction with DMAD yields the hydrazo compound **12** bearing three carbomethoxy groups, not the azo compound with two carbomethoxy groups mistakenly shown in Ref. 1 (25). Ref. 1 mistakes

the product of this reaction with DMAD as well as one of the reactants, which became an early intermediate compound in the synthesis.

Ref. 1 not only mistakes this intermediate but the structure of the final product as well. Fig. 19 in Ref. 1 shows a glutamic acid sidechain in the final product, but the natural substance (Figure 1) derives from α-aminoadipic acid, not glutamic acid (25). The mistaken Cephalosporin C drawing (1) is shy one methylene group. In Fig. 18, however, Ref. 1 does show the full complement of six methylene groups.

Recruiting

After listing the first WRI postdocs Ref. 1 reads, "Almost all of the later members of WRI were previous postdoctoral students [*sic*] of Woodward at Harvard." However, only seven researchers (20%) worked for RBW at Harvard as postdocs or graduate students before joining the WRI (6). The postdocs were Ernest, Jacques Gosteli, Karl Heusler, Robert Ramage, and Subramania Ranganathan while the graduate students were Robert Sitrin, and James Whitesell.

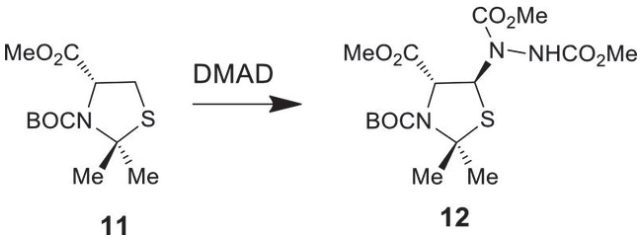

Figure 6*. A crucial stage in the synthesis of Cephalosporin C: stereoselective introduction of nitrogen. (DMAD abbreviates dimethylazodicarboxylate.)*

Postdoctoral researchers at the WRI represented ten nations including the five mentioned by Ref. 1 in an obsolete listing (27). These nations were Austria, Canada, Czechoslovakia, France, Germany, India, Israel, Switzerland, the United Kingdom, and the United States. In 1980, Ernest noted all the postdocs' national origins in his final report from the WRI (6, 28). The five countries listed by Ref. 1 were those of the first seven postdoctoral workers, all of whom joined the WRI before 1966. Heusler's article "The Woodward Institute" from which Ref. 1 drew, appeared in that year (27).

Operations

"At WRI, the chemists worked in the American style of postdoctoral research accompanied by long hours with [the] usual discussions late into the night" (1). This claim misrepresents history in two respects. First, Ref. 1 invokes what we think a non-existent but colorful style of American industrial postdoctoral research; and second, it mistakenly claims the fanciful style governed operations at the WRI.

In general, the WRI chemists labored in the colorless, international style of industrial postdoctoral researchers in North America and Europe. They began each day at about 8 AM and ended it at 5-6 PM. Neither long hours nor late nights were customary during our tenures at the WRI. Working hours did include some evenings when RBW visited Basel (29). The postdocs' practice had changed by 1968 or earlier. In contrast, before 1966, "Oft und besonders während der Besuche von Professor Woodward… Brennen die Lichter im Institute bis spät in die Nacht hinein" (27, 30).

Chemistry Spinoffs?

In a section entitled Chemistry Spinoffs, Ref. 1 misattributes J. Gosteli's indigo syntheses (31) to the WRI. They were carried out on the premises of what had been Geigy AG before the 1970 merger with CIBA AG. Gosteli writes, "My work on indigo was entirely done there [Geigy] and had not the least to do with the WRI (32)." The syntheses were completed before Gosteli became the administrative director of the Institute, but not published until he after had taken up the new post. Each of the three papers gives his WRI address. Ref. 1 cites the WRI not Geigy, because determining the correct attribution was impossible without interviewing a knowledgeable WRI veteran.

A previous section of this essay, namely Ivan Ernest's Insights, summarizes some of his accomplishments in the WRI and refutes a mistaken notion concerning his contribution to the $PGF_{2\alpha}$ synthesis. His search for novel prostaglandins appears as a topic in Ref. 1's Chemistry Spinoffs, but he undertook no such search.

In Chemistry Spinoffs Ref. 1 also cites through-space oxidations and devotes to them ca. 275 words and drawings of two steroid structures. These were reactions studied by Barton (1960), Arigoni (1958), Jeger (1958), Corey (1958), and Heusler and Kalvoda (1964). However, this work had no influence on the WRI according to an alumnus (32) whose appointment ran from June of 1963 when the Institute began until May of 1967.

What the present essay reveals about these oxidations, Gosteli's indigo syntheses, and Ernest's contribu-

tions to WRI projects implies that Ref. 1's Chemistry Spinoffs discloses no spinoffs whatsoever. By contrast, genuine influences exerted by RBW and the WRI on organic and medicinal chemistry inform a published history (6). For example, the WRI did spin off an extensive, international effort devoted to making pharmacologically active analogs of the penems, a Woodward invention. In 1988 the work culminated in a review of nearly 100 references, detailing the *in vitro* activity of the new class of antibiotics (33). Ref. 1, published in 2011, does illustrate a penem (Fig. 18).

A Misleading Suggestion

In Ref. 1, Fig. 29 and its legend are misleading. The photograph in the figure shows the multi-story Building 401 at Klybeckstrasse 200 in Basel. The legend claims that the photograph depicts the WRI. While the WRI was housed in this building, the Institute occupied only one-half of one floor, in contrast to what Ref. 1 suggests in the legend accompanying Fig. 29. In defense of Ref. 1, we note it states obliquely that "…the WRI was separated from the rest of the research floor by a glass door…."

Summary

Fourteen errors and a misleading suggestion, which we recount below, inform a review concerned with R. B. Woodward and the Woodward Research Institute (1). In what follows here, these errors are assigned lower-case Roman numerals; parenthetical page and figure numbers refer to Ref. 1.

Chemical Errors — Errors in the discussion of RBW's $PGF_{2\alpha}$ work begin with a claim (p. 934) that (i) one of E. J. Corey's prostaglandin syntheses entailed use of protoprostaglandinal **1**. That (ii) the structure of **1** was illustrated in a book reviewing a published Corey synthesis of $PGF_{2\alpha}$ from 2-oxabicyclo[3.3.0]octenone (p. 934, Fig. 16) is untrue. The writer also mistakenly claimed (p. 935, Fig. 16) that (iii) RBW's preparation of **1** represented an alternative synthesis of an intermediate first made by Corey and his coworkers.

In presenting the ring-contraction that RBW's $PGF_{2\alpha}$ synthesis entails, the author mistakes the substrate undergoing the contraction (p. 935, Fig. 17). (iv) It is neither the tricyclic aminoalcohol **8**, nor (v) an unidentifiable bicyclic aminoalcohol with four contiguous stereogenic centers.

Discussing the Cephalosporin C synthesis, Ref. 1 (p. 936, Fig. 19) mistakenly depicts as part of the work (vi) cysteine or (vii) its methyl ester reacting with DMAD, and (viii) it depicts a different product of the DMAD reaction than was actually obtained in the synthesis. Containing a glutamic acid sidechain instead of an α-aminoadipic acid group (25), (ix) the structure of Cephalosporin C is erroneously drawn (compare Figure 1 in this work).

Historical Errors — WRI recruiting of postdoctoral researchers, operations, spinoffs, and an affiliation are all subject to errors.

Recruiting. Claiming (pp. 932-933) that (x) "Almost all of the later members of WRI were previous postdoctoral students [*sic*] of Woodward at Harvard" is false. That (xi) five nations only were represented by the postdoctoral researchers (34 in number) who passed through the WRI is a mistaken underestimate (p. 932).

Operations. The author of Ref. 1 invents (p. 933) a non-existent American style of postdoctoral research, and (xii) mistakenly claims (p. 933) it governed WRI operations. (xiii) He asserts (p. 937) that Ernest at the WRI sought to make novel prostaglandins.

Chemistry Spinoffs. The eponymous section in Ref. 1 fails to reveal any spinoffs.

Affiliation. (xiv) The remaining misattribution (p. 937) deals with J. Gosteli's affiliation, which appears in articles detailing new indigo syntheses.

Misleading Suggestion. The WRI did not occupy all of the Ciba building at Klybeckstrasse 200 (p. 943, Fig. 29), but only about half of one floor.

Readers interested in an accurate account of WRI research may wish to read "A School for Synthesis: R. B. Woodward and the Woodward Research Institute Remembered" (6).

Sources of Error — A concatenation of deficiencies explains why the errors in Ref. 1 were uttered and committed. We think editor, referee(s) if any, and author share responsibility, albeit unequally. Adequate editing and refereeing would have averted the publication that ensued. Thoughtlessness in writing, carelessness in researching, and negligence in verifying factual claims inform its flaws, as does a shortfall in interviewing WRI alumni. Failures to discover or confirm published or unpublished information, especially concerning RBW's prostaglandin $F_{2\alpha}$ synthesis and Ernest's insightful role in it, result from neglecting to interview more than one

WRI veteran. Indeed, more than two years before the attempts to make $PGF_{2\alpha}$ (Figure 1) began in 1971, the only veteran (K. Heusler) interviewed for Ref. 1 had left the Institute (6). Errors in presenting the first crucial step of the Cephalosporin synthesis and in discussing the $PGF_{2\alpha}$ synthesis we attribute to insufficient self-criticism of the manuscript or lack of a colleague's help in vetting it.

Lessons — Valuable but well known lessons may be drawn from Ref. 1. In a roundabout way, its errors testify to the importance of consulting the available literature, of attentive reading and note taking, of many interviews when the published literature is insufficient, and of colleagues' critical reading of drafts. They also demonstrate indirectly the importance of painstaking refereeing and editing. Editing would have prevented publication of mistakes, while refereeing would have encouraged the author to correct errors. An error that escaped a referee's notice might have been corrected by the editor or brought to the author's notice. Of course, an author's responsibility to submit for publication an error-free manuscript is paramount.

Consulting Ernest's final report from the WRI (Schlussbericht (28, 34) available through the Novartis Archive) would have prevented errors x-xi. Attentive reading of three articles presenting the $PGF_{2\alpha}$ and Cephalosporin C syntheses (4, 23, 25) and other sources (8, 10) would have prevented nine chemical errors. A reading of Ernest's "A Synthesis of Prostaglandins; Strategy and Reality" (23) would have avoided the mistake (xiii) of thinking he tried synthesizing prostaglandins other than $PGF_{2\alpha}$. Interviewing more WRI veterans than one would have averted five historical errors and a misleading suggestion, all associated with operations, recruiting, and affiliation.

Whether journalists writing an article embrace a standard for the minimum number of interviewees is arguable. Tom Rosenstiel, executive director of the American Press Institute and a co-author of "The Elements of Journalism," says there is no rule (35). Other journalists favor three interviewees (36, 37), while Rosenstiel also states that more verification is best given a static story, ample time, and available experts (35).

We suggest that finding WRI veterans to have interviewed for Ref. 1 was feasible. At least five of them lived and worked in and near Basel from the time they left the WRI until or after publication in 2011. The author of Ref. 1 was employed nearby at the time.

Epilog — In writing this article, we confined our efforts to relatively simple topics both chemical and historical. We restricted our criticism to subjects about which we had knowledge acquired during our WRI appointments, which began in 1968. Offering no comments on RBW's pre-WRI syntheses, beginning in 1944 and illustrated (Figs. 8, 11, and 12 in Ref. 1), was therefore appropriate. Nor do we remark on the unfinished synthesis of quinine from various azatwistanes, which Figs. 23-26 illustrate in Ref. 1. To chemical historians we leave opportunities to elucidate the choices of relevant figures and photographs that Ref. 1 presents.

Acknowledgments

RJF thanks the librarians of the University of Montana, Missoula; and owes debts of gratitude to Dr. P. J. T. Morris, Prof. Jeffrey Seeman, and Prof. Dr. Helmut Vorbrüggen for encouragement. We thank Dr. Jacques Gosteli, Prof. Stanley Roberts, and Emeritus Professor Richard W. Franck for helpful comments. We are grateful to Mr. Jeremy Alverson for structural drawings, and we thank Florence Wicker and Karin Grabs, Archivists at Novartis International AG, Basel. For correspondence and discussion, respectively, we thank Tom Rosenstiel and Tyler Christensen.

References and Notes

1. G. W. Craig, "The WRI, Robert Burns Woodward (1917-1979) and Chemistry behind the Glass Door*," Helv. Chim. Acta*, **2011**, *94*, 923-946.
2. We lack any reason to believe that these errors arose either from falsification or fabrication.
3. R. B. Woodward, K. Heusler, I. Ernest, K. Burri, R. J. Friary, F. Haviv, W Oppolzer, R. Paioni, K. Syhora, R. Wenger, and J. K. Whitesell, "Synthetic Analogs of β-Lactam Antibiotics. Biologically Active 2-Alklylidene-3-Deacetoxymethyl Cephalosporins," *Nouveau J. Chim.*, **1976**, *1*, 85-88.
4. R. B. Woodward, J. Gosteli, I. Ernest, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, Ch. Suter, and J. K. Whitesell, "A Novel Synthesis of Prostaglandin $F_{2\alpha}$," *J. Am. Chem. Soc.*, **1973**, *95*, 6853-6855.
5. K. Heusler, "Total Synthesis of Penicillins and Cephalosporins," in E. H. Flynn, Ed., *Cephalosporins and Penicillins*, Academic Press, New York, 1972, ch. 6, pp 255-279.
6. K. F. Burri and R. J. Friary, "A School for Synthesis: R. B. Woodward and the Woodward Institute Remembered," *Bull. Hist. Chem.*, **2019**, *44* (1), 37-50.

7. In 2020, the median age of 28 of the 29 living WRI veterans is 78 years (6).
8. E. J. Corey and Xue-Min Cheng, Ch. 11, "Prostanoids" in *The Logic of Chemical Synthesis*, Wiley, New York, 1989, pp 250-307.
9. A. Conan Doyle, "The Adventure of Silver Blaze," in *The Memoirs of Sherlock Holmes*, Oxford University Press, 1993 (originally 1892), p 274.
10. E. J. Corey, N. M. Weinshenker, T. K. Achaaf, and W. Huber, "Stereo-Controlled Synthesis of Prostaglandin $F_{2\alpha}$ and E_2 (*dl*)," *J. Am. Chem. Soc.*, **1969**, *91*, 5675-5677.
11. E. J. Corey, S. M Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, "New Reagents for Carbonyl Reductions. An Improved Synthetic Route to the Primary Prostaglandins," *J. Am. Chem. Soc.*, **1971**, *93*, 1491-1493.
12. E. J. Corey, Z. Arnold, and J. Hutton, "Total Synthesis of Prostaglandin E_2 and $F_{2\alpha}$ (*dl*) via a Tricarbocyclic Intermediate," *Tetrahedron Lett.*, **1970**, 307-310.
13. E. J. Corey and Barry B. Snider, "New Synthetic Route to Prostaglandins," *Tetrahedron Lett.*, **1973**, 3091-3094.
14. Personal communication from J. Gosteli to the postdoctoral researchers dated June 1973, in Basel at the WRI. At the time, Gosteli was the administrative director of the WRI.
15. R. B. Woodward, "Oxabicyclononanes," *Chem. Abstr.*, **1974**, *80*, 59850g; Swiss Appl. May 10, 1972.
16. R. B. Woodward, "Oxabicyclooctanes," *Chem. Abstr.*, **1974**, *80*, 598513k; Swiss. Appl. May 10, 1972.
17. The confluence of synthetic routes may have resulted from coincidence, and we thank a referee for pointing this out.
18. I. Ernest, "Penicillin-Derived Diazo Ketones: An Intramolecular Carbene Reaction," in J. Elks, Ed., *Recent Advances in the Chemistry of β-Lactam Antibiotics*, The Chemical Society, Burlington House, London, 1977, pp 252-259.
19. I. Ernest, "Penicillin-derived Diazoketones: Copper (II) Catalyzed Decomposition in Aprotic Media," *Tetrahedron*, **1977**, *33*(5), 547-552.
20. I. Ernest, "2-Oxocephems. Synthesis and Properties of 7-Acylamino-2-oxocephem-4-carboxylic Acids," *Helv. Chim. Acta*, **1979**, *62*(8), 2681-2694.
21. I. Ernest, "2-Oxocephems. II. Synthesis of 2-Oxocephalexin from Hetacillin," *Helv. Chim. Acta*, **1980**, *63*(1), 201-213.
22. I. Ernest, *Bindung, Struktur und Reaktionsmechanismen in der organischen Chemie*, Springer, Wien, 1972.
23. I. Ernest, "A Synthesis of Prostaglandins: Strategy and Reality," *Angew. Chem.*, *Int. Ed.*, **1976**, *15*, 207-214.
24. The 53 weekly issues of the *WRI Progress Reports* dated September 6, 1971, to July 1973, reveal no such experiment. These issues include the period when $PGF_{2\alpha}$ was made. A collection of *WRI Progress Reports* with call number HUGFP 68.45 resides in the Harvard University Archives, Pusey Library, Cambridge, MA.
25. R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, "The Total Synthesis of Cephalosporin C," *J. Am. Chem. Soc.*, **1966**, *88* (4), 852-853.
26. R. B. Woodward, "Recent Advances in the Chemistry of Natural Products" in *Nobel Lectures, Chemistry 1963-1970*, Elsevier, Amsterdam, 1972, pp 100-121.
27. K. Heusler, "The Woodward Institute," *CIBA Blätter,* **1966**, *202*, 1-6.
28. I. Ernest, "Woodward Research Institute. Schlussbericht. Liste der in den Jahren 1963-1979 im Woodward Forschungsinstitut arbeitenden Chemiker (in chronologischer Reihenfolge)," Basel, May, 1980, pp 17-25. This final report forms part of the Novartis Firmenarchiv, Bestand CIBA-Geigy, PH 3.03; Novartis Campus, WSJ-433.6.15, CH-4056 Basel, Switzerland.
29. The frequency of RBW's visits to the WRI ranged from about one week in four to about one week in seven or eight.
30. *Trans*.: Often, and especially when Professor Woodward visited, the Institute's lights burned late at night.
31. J. Gosteli, "New Indigo Syntheses," *Helv. Chim. Acta*, 1977, *60*, 1980-1983.
32. J. Gosteli, private communication, Dec. 31 2017.
33. S. W. McCombie and A. K. Ganguly, "Synthesis and *In Vitro* Activity of the Penem Antibiotics," *Medicinal Res. Rev.*, **1988**, *8*(3), 393-440.
34. Ernest's last report lay in the Novartis Archive in Basel from 1996 onward. Private communication from F. Wicker, Archivist, Nov. 27, 2019.
35. Tom Rosenstiehl, private communication, Mar. 6, 2020.
36. Tyler Christensen, opinion-page editor of the Missoulian, Missoula, MT, private communication, Feb. 25, 2020.
37. A. J. Coyne, The 18 Essential Rules of Journalism, https://writerswrite.co.za/the-18-essential-rules-of-journalism/ (accessed Mar. 21, 2020).

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-five patents name him as an inventor or co-inventor. Friary is the author or coauthor of 32 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.