FROM PATENT TO PRESCRIPTION: PAVING THE PERILOUS PATH TO PROFIT

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1.1 INTRODUCTION

A research director at a major pharmaceutical firm used to tell the new scientists in his company that there was no nobler career than to discover and develop a drug that would help alleviate human suffering or cure a deadly disease without causing serious side effects. Many others have doubtless said the same, and added that the complexity of this adventure can be compared to landing people on the moon and getting them home safely to Earth. Notice that safety is paramount in both endeavors. Although we must at first do no harm, our drugs must also do some good. Ethical drug companies spend millions of dollars studying new drugs over many years to determine both safety and efficacy, in order to legitimately promote new chemical entities and formulations to physicians, and more recently directly to the public. Even with enormous research expenditures and careful regulatory scrutiny, safety issues with blockbuster drugs are frequently in the news. Patients do not all respond adequately to existing drugs or even drug classes, and new agents are regularly needed to fight infections caused by microorganisms that become resistant to available antibiotics. So how do we get started along this path to better and safer drugs?

First, a target must be identified. This is a medical and marketing exercise, where a problem is recognized that could be treated with a pharmaceutical drug that fits into a company’s portfolio. It is necessary to assure that adequate financial and human resources will be available for this daunting task. Once the commitment is established, teams of scientists must determine how a chemical could possibly be used to help patients. After all, pharmaceuticals are chemicals, and pharmaceutical companies sell chemicals.
Biochemists, molecular biologists, physicians, pharmacologists, and others team up with synthetic chemists to determine a strategy to attack a disease. Often, these scientists are in what might be considered a virtual team: not in the same company, not on the same continent, nor even working in the same decade. By following the medicinal literature carefully over many years, often in fields seemingly unrelated to their own, scientists can gain insight into possible treatments and apply their own unique talents to come up with a new drug. There is an enormous amount of information available online, on the World Wide Web and various scientific databases, and modern search engines make it easy to find both obvious and obscure relationships. A small well-equipped startup company with the right mix of desire and talent can make breathtaking strides only dreamed of a few decades ago. They need to understand biology and chemistry, law and economics. To do so, they must seek the wisdom from the past that often made success achievable even without these modern tools. Wisdom translates knowledge into understanding.

Very sophisticated approaches are often envisaged that involve inhibiting complex enzyme pathways, preventing invading microorganisms or invasive cancer cells from multiplying, replacing natural hormones that are lacking in the body, or a host of other possible ways to treat medical conditions. Chemists are involved in every phase, from planning to execution of the research, from the laboratory to the clinic. The resulting product sold will be a chemical, a pure chemical, or a well-defined mixture, often a single enantiomer. It must be stable enough to ship to pharmacies and consumers, who will store it, dispense it, and use it. It must be safe to handle and have unambiguous safety and a predictable side-effect profile once administered. These days especially, it must be cost-effective, offering worthy advantages over cheaper generic drugs, often helping a patient avoid an expensive hospital stay and getting him or her back to work sooner. There is always competition to deal with, so the patent literature must be studied carefully, and risks must sometimes be taken when working in areas where other companies may have also begun research, because earlier priority dates may already have been secured. As you will see below, you may be sowing the seeds for a future partnership by doing research in a crowded field.

The chemical that will become the drug substance or API (active pharmaceutical ingredient) will often be chosen by a process of screening thousands of contending structures, with various attributes evaluated at each stage. Any structural insights that scientists have in the early stages can help enormously to abbreviate this development. Rules of thumb regarding stability, solubility, and toxicity are ubiquitous, and the successful team will know these well. ADME (adsorption, distribution, metabolism, and excretion) concepts must be studied and applied to the drug candidates and their biochemical targets.

Modern approaches that can gain real advantages often involve computer-assisted modeling of potential drug molecules and the sites of their activity. If an x-ray structure of a target enzyme is known, especially with an inhibitor molecule firmly docked, computer modeling can be used to determine what other drug candidates may also bind strongly with that site. NMR techniques are also used to screen and assess the interactions of hosts and potential drugs. With this flood of new technologies only now becoming available to medicinal chemists, it is amazing indeed that so many powerful wonder drugs were discovered and developed in the antediluvian days of the recent past.

At first the cost of producing samples for early testing may not be a major factor, but it will become more and more important as larger quantities are needed for testing and progress is made toward clinical trials and commercialization. It is also essential that chemists and engineers use the most cost-effective syntheses and modern approaches as early as possible along the drug development timeline so that when scale-up issues arise, as they
always do, the best options are available to solve problems quickly. In 2001, the top 16 pharmaceutical companies spent $90 billion to manufacture their products. Manufacturing costs have become more than twice the cost of R&D and nearly as much as marketing and administrative costs. This is due partially to the enormous regulatory and quality issues, which can lock inefficiencies into a manufacturing process very early in the filing strategy. Detailed process information, equipment specifications, testing protocols, and storage and stability programs must all be put in place long before clinical studies on a new drug are completed and reviewed by the Food and Drug Administration (FDA). This is caused by concerns that any process changes may lead to new impurities or higher levels of extant impurities, or may make a product that will decompose more quickly and lose potency or develop harmful by-products. Companies must choose between delaying a filing, which could allow competitors to move ahead or could lose precious patent life, or must submit a filing with a less than ideal manufacturing process. Because of the enormous profit incentives to get a drug onto the market quickly, the latter is often the course chosen. The drugs discussed in this chapter each sell at least $1 million to $3 million per day, so any delays requested to investigate new chemical processes, even for a few weeks, may be considered too costly. This often plays into the hands of the generic companies, which can start refining the manufacturing processes years before the innovator’s patents expire. Chemistry is always on the critical path.

A glance into the past may convince the reader that human ingenuity, recognizing the essential features of a problem, and applying Occam’s razor can often lead to success. Such cleverness may sometimes be rewarded with a dash of serendipity as well. Genius transforms understanding into beauty.

1.2 A SIMPLE SOLUTION TO A COMPLEX PROBLEM

Erythromycin was introduced into the clinic in 1952, and although it was a useful antibiotic with an excellent safety profile, allowing its use even in children and pregnant women, blood levels were erratic and there were often annoying side effects, such as nausea, upset stomach, and diarrhea. In fact, in 1984, the director of antibiotic sales for Abbott Laboratories announced in a meeting with scientists that if they could come up with “[a compound identical to] erythromycin, but without the belly ache,” he could triple the sales. Newer formulations of erythromycin were tried but had only limited success in reducing this relatively benign but market-limiting side effect.

It was recognized very early on that acid instability in the digestive track could be a major cause of these problems. Although the mechanism of the acid-catalyzed degradation was explored in a one-page publication by Abbott chemists in 1971, the acid degradation of erythromycin is not as simple as first envisaged. It was known that erythromycin A (IA) formed enol ether (IIA), as did erythromycin B (IB). Due to the –OH group on C-12 of IIA, a further reaction can take place to form anhydroerythromycin A (III), a spiroketal that is nearly devoid of antimicrobial activity. A paper published in 1986 corroborated this idea, and a more detailed kinetic study in 1989 suggested that there is equilibrium between IA and IIA. This equilibrium was confirmed by the very simple deuterium labeling study shown in Scheme 1.1. Work continues on this intriguing system.

Erythromycins A and B (IA and IB) were treated with anhydrous CH$_3$CO$_2$D to form IIA and IIB, with the –OH’s exchanged for –OD’s. When IIB was treated further with CH$_3$CO$_2$D in D$_2$O, a more acidic medium, erythromycin B was recovered, with deuterium
incorporation and some epimerization\(^8\) at C-8. It was known that under similar protic conditions, II\(_A\) would convert to a single epimer of III.\(^3\) However, when, after exchanging the −OH’s for −OD’s, IA was treated directly with CH\(_3\)CO\(_2\)D in D\(_2\)O, within a few minutes the anhydroerythromycin A (III) that was formed contained about 50% deuterium at C-8, as analyzed by \(^{13}\)C-NMR. No deuterium was detected at C-10. Furthermore, when naturally labeled (III) was treated similarly with CH\(_3\)CO\(_2\)D in D\(_2\)O, deuterium was slowly incorporated at C-8.

Physiologically active compounds often have emergent properties that are due to the unique spatial arrangement and interactions of their functional groups. For example, the macrolactone (macrolide) ring appears to have a hydrophobic and a hydrophilic side in its low-energy conformations, perhaps accounting for the amphiphilic nature of the molecule, with the OH at C-6 sticking out on the hydrophilic side. IR spectra of erythromycin A indicate that there is one OH that is not involved in a hydrogen bond. The x-ray structures as well as molecular modeling show that the OH on carbon 6 is the only one in the molecule not involved in an internal hydrogen bond with a neighboring polar functionality (see Scheme 1.2).

**Scheme 1.1**

IA = erythromycin A, R = OH
IB = erythromycin B, R = H

II\(_A\) = ery A enol ether, R = OH
II\(_B\) = ery B enol ether, R = H

III = anhydroerythromycin (spiroketal)

\(X = 52\% \text{ H}, 48\% \text{ D}\)
Scheme 1.3 shows that the three secondary hydroxyl groups in erythromycin A (2′, 4′, and 11) can readily be differentiated chemically. The most reactive \(-\text{OH}\) group is on the desosamine sugar moiety by virtue of the 3′-dimethylamino group acting as an intramolecular catalyst. Thus, erythromycin A can easily be converted to its 2′-acetate (IV) in dichloromethane by reacting with acetyl chloride and sodium bicarbonate as base, or acetic anhydride and triethylamine, rendering the amino group nearly two pK units less basic, due to the neighboring group interaction.\(^9\) Further reaction when DMAP is present leads to acetylation on the cladinose sugar at the 4′′-hydroxyl group, and the hydroxyl group at C-11 can be acetylated only after heating. The lone pairs of electrons on the oxygen at C-4′′ are more readily accessible to the reagents than those at C-11, which is involved in a hydrogen bond. However, if IV is treated with strongly basic conditions capable of fully deprotonating an \(-\text{OH}\) on the molecule, such as sodium hexamethyldisilazide in THF at \(-78^\circ\text{C}\), and acetic anhydride is added, the \(-\text{OH}\) at C-11 is preferentially acetylated over the \(-\text{OH}\) at C-4′′. This can be understood by stabilization of the C-11 alkoxide by the neighboring proton on the C-12 hydroxyl, while an alkoxide at 4′′ is relatively less stable. Interestingly, compound V was shown to be a 12,9-hemiacetal by NMR, and in the presence of water–deuterium oxide mixtures undergoes slow hydrogen–deuterium exchange of the proton at the hydroxyl at C-6 on the NMR time scale. A similar 12,9-hemiacetal was reported to be a major contributor to the equilibrium structures of erythromycin A (IA) itself.\(^{10}\)

Although many scientists were studying these issues, a small group of scientists working at Taisho Pharmaceuticals in Japan read Abbott’s brief 1971 publication in *Experientia*\(^3\) and thought of a very simple solution to the acid instability of erythromycin. In a meeting with Abbott executives in the 1985, the lead Taisho chemist, Dr. Yoshiaki Watanabe, in somewhat broken English, thanked Abbott for this one-page revelation. The head of the Abbott delegation then mumbled to his scientists, on his side of the table, something to the effect that they were never going to publish another (expletive deleted) paper. Thank
goodness he was joking! A partnership was soon born, bridging time and space, and has flourished. Both clarithromycin and azithromycin, discussed below, have achieved annual sales around $1 billion.

By the amazingly simple idea of blocking the hydroxyl group on carbon 6 with a methyl group, these Japanese chemists were able to prevent formation of the enol ether (II\textsubscript{A}) or anhydroerythromycin A (III). The compound they first made in 1980,\textsuperscript{11} now sold as clarithromycin VII (Scheme 1.4), not only has superior acid stability, but produces less stomach irritation, a major drawback to the widespread use of erythromycin itself. This serendipitous result may be due at least in part to the inability of clarithromycin to form the enol ether (II), which was later shown in animal studies to increase gastrointestinal motility to a much greater extent than the parent structure. This effect was seen even after intravenous administration, so it is not simply the result of contact of the drug with the stomach. Abbott had developed a gastrointestinal motility assay to screen new drug candidates. Pressure transducers were attached along the outside of the GI tract in an anesthetized beagle dog, and peristaltic contractions were recorded after administering an erythromycin analog. Clarithromycin not only demonstrated a

Scheme 1.3
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reduction in the recorded contractions relative to erythromycin, but fewer belly aches were reported in the clinic. Clarithromycin has also improved absorption from the GI tract and enhanced blood levels, coupled with lower intrinsic minimum inhibitory concentrations (MICs) against important pathogens. Thus, this second-generation semi-synthetic macrolide is a better antibiotic overall than the direct fermentation product from which it is made.

The original synthesis of VII involved protecting both the 2'-OH and the 3'-dimethylamino functions on the desosamine sugar with benzyloxy carbonyl groups (Z-groups). This was a method that had been used by many others and results in the loss of one of the methyl groups on the nitrogen. This step was then followed by simple and somewhat selective methylation of the 6-OH with methyl iodide. The Z-groups were then removed by hydrogenolysis, and a methyl group was put back on the nitrogen by reductive amination with formaldehyde. However, as mentioned above, the mere presence of an ester functionality on the 2'-OH, such as an acetate, renders the neighboring nitrogen group much less basic and much less nucleophilic. Therefore, the first process used to prepare larger quantities of VII was simply to methylate IV, erythromycin 2'-acetate, a compound that is much more easily prepared and subsequently deprotected. This chemistry is shown in Scheme 1.5, where each structure is purposely drawn with a different convention taken from contemporaneous literature, to illustrate how information, even accurate information, does not always lead to clarity! A highly crystalline product resulted from the methylation of IV, albeit in low yield, which could be purified sufficiently for early studies. In these early studies large supplies of drug were more important than the efficiency of the manufacturing process. The only significant impurity was the 6,11-dimethylated compound, similar to what was seen with the more onerous Z-group protection–deprotection scheme. Dissolving IV in methanol, and allowing the methanolysis to take place at room temperature overnight, quantitatively removed the acetyl group. It is interesting to realize

![Scheme 1.4 Clarithromycin (VII).](image)
how close many scientists were to this novel second-generation macrolide when they were working with the simple 2'-esters of erythromycin many years earlier. This is something to keep in mind when working with a readily available derivative of an active compound: What new chemistry can you do with it?

1.3 AN INTRIGUING PATENT PROBLEM

A different solution to the acid instability and erratic blood-level problems of erythromycin was found with another analog. Ironically, this new compound has such low blood levels that at first it seemed to some researchers that infectious disease physicians would not trust it. The old paradigm was that an antibiotic had to exhibit blood concentrations above the MIC for the particular strain of bacteria causing the illness. In fact, the
infectious organism is often compartmentalized in particular tissues such as the tonsils and the prostate gland. An antibiotic that can penetrate and sustain therapeutic levels in those diseased tissues would actually be more useful than one that was largely in the blood serum. This concept is also true of cancer chemotherapy agents, which need to accumulate in the tumor cells rather than in the bloodstream or healthy tissue. Scientists at Sour Pliva in Zagreb, in what was then Yugoslavia,14 and at Pfizer in Groton, Connecticut,15 were able, almost simultaneously and concurrently to solve the tissue penetration problems and acid instability issues by cleverly adding an additional basic nitrogen atom in a Beckman rearrangement process followed by reduction. Almost simultaneously—and the resulting blockbuster drug, azithromycin (VIII), is the subject of two U.S. composition of matter patents! Although Pliva filed their patent more than a year earlier, Pfizer’s patent was issued seven months sooner. It turns out that the two companies drew their new structures and named their compounds using quite different conventions. They even numbered the macrocyclic ring differently than the classical structures shown in Schemes 1.1, 1.3, and 1.4. Due to this confusion, the U.S. Patent and Trademark Office thought the groups were claiming two distinctly different compounds. Pliva had pioneered work with the ring-expanded macrolides,16 and since they filed their patent first, Pfizer had to negotiate the rights to a compound that it had discovered and patented independently (Scheme 1.6 and Table I.1). In today’s competitive world, the Patent Cooperation Treaty requires publication of patents 18 months after filing, or earlier claimed priority date: for example, from a provisional patent application. Had this process been in place in the early 1980s, it would have allowed Pfizer scientists to see the Pliva application much sooner (the Pliva application would have been published four months after the Pfizer filing), and the Pfizer experts would doubtless have realized that the compounds they both claimed were identical.

Scheme 1.6  (a) U.S. patent 4,517,359, May 14, 1985; (b) U.S. patent 4,474,768, October 2, 1984.
The first generic formulations of azithromycin were approved by the FDA on November 14, 2005 for two companies, Teva Pharmaceuticals and Sandoz, to sell this blockbuster drug for a wide variety of indications, permitting Pfizer and Pliva almost exactly a 20.5-year head start, due to the extension of 3.5 years granted May 20, 1993 for the Pliva patent. At that time, patents expired 17 years after issuing rather than 20 years from the date of filing, as is now the case (unless extensions are granted).

Note that in Scheme 1.7 azithromycin is drawn in two additional ways, as shown currently in SciFinder17 (clockwise numbering) and the Merck Index18 (counterclockwise numbering), reversing the order of the sugars. The Physicians’ Desk Reference19 draws azithromycin in a fashion related, but not identical, to the Pfizer patent (Scheme 1.6b), which depicts the stereochemistry of C-6 as S when in fact it is R. Clarithromycin and erythromycin are drawn in a format similar to that used in SciFinder, except inverted (so the numbering runs traditionally counterclockwise); there are some ridiculously long bonds, so the drawings don’t overlap; and all the necessary centers are reversed to maintain the correct stereochemistry. It is highly unlikely that anyone has ever looked at structures presented in that fashion and gained any useful insights. How could anyone be expected to see the crucial interaction of the C-6 OH group with the carbonyl at C-9 in such a rendition? [Compare erythromycin (R = H) in Scheme 1.8b with Scheme 1.1 and 1.2.] The enormous confusion caused by following such diverse conventions when drawing and naming significant compounds has restricted an understanding of the literature to the few experts who take the time to become familiar with the structures and conventions. It is fortunate that modern desktop computer programs can recognize instantly that these structures are equivalent, calculate empirical formulas, assign stereochemistry, and even predict NMR spectra.20 The use of such powerful computer routines, CAS Registry numbers, and other modern library tools can save time for the expert and be invaluable to the uninitiated. It is hoped that the confusion over structures such as these will become a relic of the past.

1.4 ANOTHER STRUCTURAL INSIGHT

Recently, it has been widely reported that the new class of wonder drugs called COX-2 inhibitors exhibit serious cardiovascular side effects, and several of these drugs have been withdrawn from the marketplace. Meanwhile, another class of blockbuster drugs, the statins, may not only be safe and effective in their intended role of lowering cholesterol, but may have a plethora of other potentially valuable properties. Cancer, Alzheimer’s disease, diabetes, osteoporosis, high blood pressure, multiple sclerosis, and macular degeneration are
Scheme 1.7  Azithromycin: (a) SciFinder, registry number 83905-01-5; (b) from the Merck Index.
Scheme 1.8  Structures similar to those in the 2002 Physicians' Desk References: (a) azithromycin, pp. 2739, 2743, 2748; (b) clarithromycin, R = CH₃, pp. 403, and erythromycin, R = H, pp. 454, 456.
among the diseases that the statins may ameliorate. It has often been said that drugs are discovered in the clinic. In this sense the clinic consists of the patients using these drugs in the general population. Observational studies on the millions of people taking these drugs revealed the problems of COX-2 inhibitors and the additional potential indications for the statins. Another example of this in a much smaller population can serve as an illustration.

In the late 1960s, Pfizer filed patents on an α₁-adrenergic blocker that came to be known as prazosin. The structure is shown in Scheme 1.9, next to a very similar compound, terazosin, patented in 1977 by Abbott. Both of these compounds are effective in lowering blood pressure and have beneficial effects on the plasma lipid profile. Dr. Marty Winn, a chemist at Abbott, looked at a drawing of the structure of prazosin, and realizing that its failings included problematic intravenous formulation and short duration of action, thought that a similar molecule with higher water solubility might be more effective. He knew that furan is only sparingly soluble in water, whereas tetrahydrofuran (THF) is completely miscible with water. He concluded correctly that simply saturating the furan ring in prazosin might lead to a much more soluble compound. In fact, his first samples were made by direct hydrogenation of prazosin, leading, of course, to a racemate. This was not a problem since in those days the FDA did not require compounds to be pure single enantiomers. In the 1990s, Abbott considered making a new compound as the single enantiomer, a chiral switch, but did not pursue the issue. It turns out that the base form of terazosin is 25 times more water soluble than prazosin, and its elimination half-life is about three times greater, permitting once-daily administration of the new drug. The difference for the corresponding hydrochloride salts is even more dramatic. The terazosin salt is over 500 times more soluble than the corresponding prazosin salt!

Since terazosin was projected to be a relatively low volume (about a ton per year) high-potency (10 mg/day) drug, the cost of manufacturing was not deemed a big issue. Note that one patient would take 3.65 g per year, so 1 metric ton of API is enough to treat 274,000 patients per year. At a price of $1.00 per day, the annual sales would be $100 million. In the late 1980s a clever process chemist in the pharmaceutical division suggested ways to streamline the process and save as much as $500,000 per year. Management decided not to pursue the new chemistry because it was estimated that it would cost over $2 million to run several successful manufacturing scale batches, place the API on stability studies, manufacture tablets, put the tablets on stability for a year, file all the data with the FDA, and wait for approval, before being able to switch over to the new process. The FDA would have to be convinced that the new API made tablets that were identical to those made by the old process, and the review process could take many months. Little did Abbott realize that the market for terazosin was about to increase dramatically, so the new process, despite the costs of implementing it, could have saved them many millions of dollars in manufacturing the drug over the long term.

Soon after the introduction of terazosin into the marketplace as an antihypertensive, it was noticed anecdotally that men with symptomatic benign prostatic hyperplasia (BHP) who were given the drug to treat high blood pressure began reporting relief of their urethral pressure and bladder outlet problems. Sales of terazosin increased slowly as word got out of this promising new treatment for BPH, as it was evidently being prescribed for off-label use. Physicians have the authority to prescribe drugs for conditions other than those promoted by the pharmaceutical companies, so this is quite common: for example, with anticancer drugs. However, Abbott had to conduct costly clinical studies and get FDA approval to advertise and market the drug for this new use. Once the new indication was approved by
**Scheme 1.9** (a) Prazosin; solubility of the hydrochloride salt in water (pH ca. 3.5) at ambient temperature (mg/mL): 1.4. (b) terazosin; solubility in water at 25°C (mg/mL): 29.7-hydrochloride salt (mg/mL): 761.2 (544 times more soluble!).
the FDA for detailing, an unexciting drug that had been third or fourth tier for hypertension, selling much less than $100 million per year, became a major seller at about $500 million per year worldwide. Terazosin was becoming a very profitable drug just as its patents began to run out. It quickly became a very attractive target for generic drug manufacturers. Abbott was able to make deals with the generic competitors to keep them off the market temporarily, extending its very profitable franchise for about four years after the patent ran out. They paid several companies millions of dollars per month to keep them off the market with their cheaper generic version of terazosin. However, faced with an antitrust investigation in 1999, they canceled such arrangements with potential competitors. Abbott’s sales of terazosin fell 70% in the next year alone, to $141 million.

The insight of a chemist who looked at a structural drawing, and spotted the Achilles’ heel of the compound represented, and so elegantly corrected it is astounding. A clearly drawn chemical structure can reveal the beauty of subtle emergent properties of the functional groups to the astute imagination of a skilled scientist. The fact that this increase in solubility makes terazosin a superior drug for BPH makes a mark on the positive side of the ledger of unintended consequences. Serendipity can convert beauty into profits!

We should learn never to ignore the clues that any piece of the puzzle is revealing: by itself or as part of the emerging picture. Each fact that builds toward further understanding can be exploited, but since our fellow scientists, competitors, or future partners may be far from us in time and space, our discoveries must be published with clarity. Abbott’s brief paper in the 1970s paved the way for its future Japanese partner to solve a long-standing problem, and Pfizer wisely joined with Pliva when it found success in a research area that the Yugoslavians had pioneered. Despite the dazzling advances in the tools of modern science that you will see in the following chapters, there is no substitute for the wisdom of good common sense, along with painstaking attention to basic details and the occasional flashes of genius that reveal the true beauty of nature. If we only learn from mistakes, then, after we have made all the mistakes possible, we will finally do things right. Discovering wisdom from the past is a much more efficient process!

REFERENCES

2. The English philosopher William of Occam (1300–1349) propounded Occam’s razor: “Entities are not to be multiplied more than necessary.” This is especially appropriate when trying to keep microorganisms or cancer cells from dividing.
8. Under these conditions, erythromycin B epimerizes to about a 1:1 mixture of epimers at C-8 in a day or two.


12. Although it is imperative that animal models be validated in the clinic, demonstrating that the responses in the animal model translate to the human condition, the real proof is often found only after large populations have taken the drug.

13. During a plenary lecture on his monumental total synthesis of erythromycin at the 1977 ACS National Organic Symposium in Morgantown, West Virginia, R. B. Woodward had a cartoon on a slide depicting a tombstone with words to the effect: “Cahn–Ingold–Prelog R.I.P.” He was annoyed that each time he changed the protecting groups on his intermediates the $R$, $S$ nomenclature changed, so it appeared that stereogenic centers had been inverted when they had not. The problem of conveniently conveying data by use of various nomenclature conventions has plagued even Nobel laureates in this field! Thank goodness for computers.


19. 2002 *Physicians’ Desk Reference*, 56th ed. Medical Economics Company, Inc., Montvale, NJ. Since the data in the PDR are identical to the package inserts from the drug companies, it is surprising that Pfizer would approve an incorrect rendition of its own drug.

20. Programs such as *ChemDraw Ultra 9.0* from CambridgeSoft Corporation, Cambridge, MA.


24. Bruce W. Horrom, who started at Abbott in 1946 and became the longest-serving Abbott employee ever when he retired with more than 50 years of service. He came up with this new process idea after having been at Abbott for over 40 years.
