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REFLECTIONS ON PROCESS RESEARCH II[1]

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Among the various groups that are responsible for early drug development in the pharmaceutical industry, the Process Research Groups are among the most important because the drug development process cannot begin until sufficient bulk drug has been prepared. Those who are most removed from organic chemistry and process research typically associate bulk drug needs with the illusive term ''scale-up.'' They generally believe that because the medicinal chemists have devised a synthesis that can produce 2–20 grams of the candidate, straightforward ''scale-up'' by the process chemists will readily produce hundreds, if not thousands, of grams of product. Indeed, many in this group believe that process research and ''scale-up'' are synonymous. For some drug candidates, where the medicinal chemistry is relatively simple, this is indeed true, and today these candidates are most likely targets for outsourcing. However, this has not generally been the case in my 39-year career in the industry. Numerous candidates on which my groups have worked have required high levels of scientific creativity, novel synthetic methods, complex organic chemical development, and a bit of serendipity, all against tight timelines, to rapidly bring forward practical syntheses and large quantities of bulk drug for early clinical development. Given the explosive growth and development of novel synthetic organic methods in the past generation, medicinal chemists are now able to devise drug candidates of unprecedented complexity, and the role of organic synthesis in early drug development is more important than ever before.

In thinking about how to illustrate the importance of organic synthesis in early drug development, I thought to once again look back on some of the more

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interesting programs during my Merck career[1] and then choose a number of examples where organic synthesis proved to be the key element in being able to rapidly bring a program forward. Each of the examples selected explores the general thesis from different points of view. Most of the candidates discussed did not make it to product status (what's new?). Often getting a program going requires novel chemistry or complex chemical development or both. Although higher management would prefer that we quickly devise the ultimate process, this is most often not the case, and we must crawl before we walk, and walk before we run.

PROCESS RESEARCH AND PHYSICAL ORGANIC CHEMISTRY

In beginning this tale, I thought that I might highlight the importance of physical organic chemistry in process research, as well as emphasize its impact on early synthetic development. During my graduate training at the University of Rochester, the labs were not arranged by research groups; instead, the new students simply occupied available lab spaces. Thus, while I was trained as a synthetic organic chemist, I quickly came under the influence of the physical organic chemistry of Bill Saunders and the physical photochemistry of Jack Kampmeier via their students with whom I shared a lab. My quiet transition to a closet physical organic chemist with a desire to understand synthetically important reactions from the mechanistic perspective began from these simple roots. I think this has been frequently reflected in my programs. In fact, were I now considering a career in teaching, I would formulate a research program around studying the mechanisms of synthetically important reactions, along with their applications in the development of practical processes. Each time we have turned to physical organic chemistry during my Merck career, the results have always justified the effort we have put in. We have thus brought the chemistry to new levels and some excellent publications have resulted. It was also to my great joy to have worked with Dave Hughes during the early part of his Merck career. I consider him to be one of the Industrial Deans of physical organic chemistry. He continued to be a regular consultant to all of our chemists when reaction mechanisms and kinetics came to the table.

While I could cite many of our programs that have relied on physical organic chemistry and mechanistic considerations for solutions, I have been particularly fond of some of Dave's work from the early 1980s in which he proposed a simple yet elegant solution to a long-standing problem and then subsequently developed the most straightforward method for the selective *O*-alkylation of amino acids without protection. We were developing a prodrug of methyldopa, Merck's first major antihypertensive agent. The medicinal chemists chose to make the pivaloyloxyethyl (POE) ester (note that many said this stood for Poor Old Ed because the problem ended up in my group) via the synthesis shown in Figure 1.1. It was satisfactory for making tens of grams of product to initiate the program, but it was not serviceable beyond that scale. With a double protection (classical Cbz protection on nitrogen and diphenylmethyl protection on oxygen via an unscalable fusion reaction with dichlorodiphenylmethane), followed by the alkylation and double deprotection,

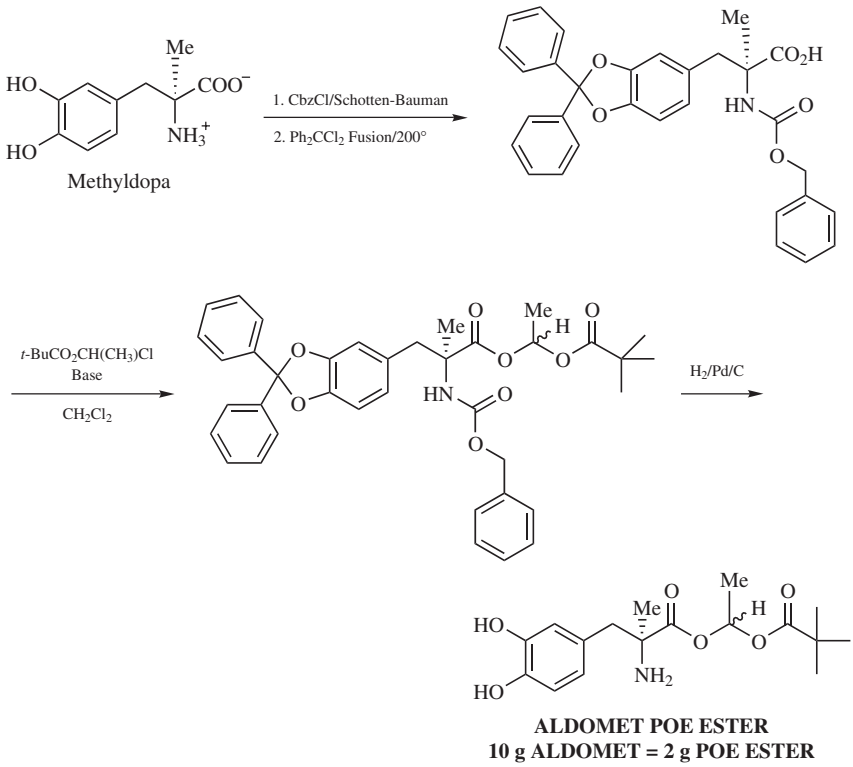

Figure 1.1. The medicinal chemistry synthesis of methyldopa POE ester.

the overall yield of the POE ester was poor. In addition, there were significant isolation problems since the product was a mixture of diastereoisomers.

This route was untenable at a preparative level, and the development program could not begin until we defined a new route. In thinking about how to approach this problem, we were guided by a comment from John Chemerda, who headed Merck Process Research until the late 1970s: ''The best protecting group is NO protecting group!'' Indeed we found that the direct alkylation of methyldopa in HMPA, TMU (tetramethylurea), or other polar aprotic solvents with 1-chloroethyl pivalate (pivaloyloxyethyl chloride: POECl) afforded a 65:35 ratio of isomeric *O*- versus *N*-alkylation adducts. The *O*-adducts could be separated from the product mixture by acid extraction. We conducted a formidable amount of phenomenological work on trying to improve this ratio, all to no avail. However, even at a modest yield we were able to prepare sufficient quantities of material to begin safety studies via a co-crystallization of the diastereomeric salts.[2] While the direct alkylation of the unprotected amino acid was a good idea, we were not able to improve the selectivity of the *O*- versus *N*-alkylation. This illustrates a point often seen in process research: A great idea is brought to the table, but the team is not able to bring it completely home. At this point Dave Hughes joined the program, and he brought

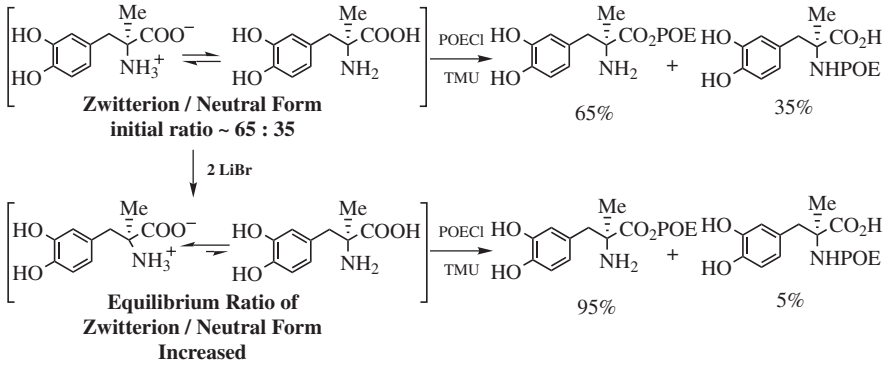

Figure 1.2. Direct alkylation of methyldopa in TMU employing Li Br addition.

his formidable background in physical organic chemistry to bear on the issue. He quickly recognized that the alkylation results represented a snapshot of the equilibrium between the neutral and zwitterionic forms of methyldopa present in polar aprotic solvents.

Alkylation of the neutral form occurred on nitrogen, while alkylation of the zwitterion occurred on oxygen affording the desired product. After a detailed comparison of the pK_a's of a variety of amino acids in water and DMSO, Dave established that the equilibrium could be favorably influenced toward the zwitterionic form by adding salts to solutions of the amino acids in polar aprotic solvents. With these results in hand, Dave redesigned the ester synthesis employing two equivalents of LiBr in TMU. In this strongly polar environment the equilibrium strongly favored the zwitterionic form of methyldopa, and a >90% yield of the desired ester resulted (Figure 1.2). Dave then developed the procedure into a general method for direct and simple amino acid ester synthesis.[3] This was a prelude to Dave's work and publications on the Mitsunobu reaction, which received worldwide recognition in its day.[4]

FLUDALANINE: ONE WE NEVER SOLVED—AT LEAST I THINK SO

The 1970's brought a remarkable, orally active, broad-spectrum antibiotic to Merck development: 2-deutero-3-fluoro-D-alanine (fludalanine). The deuterium was added to slow *in vivo* metabolic oxidation to the imine, which after hydrolysis and reduction would produce fluorolactate, a possibly toxic metabolite. This was a remarkable target—all functionality, no fat, and an isotope to boot! Immediately there were concerns about cost, but we chose to proceed forward with development. This view—that is, not letting product potential cost (or synthesis complexity for that matter) be a serious impediment at the beginning of a program—has proven to be a hallmark of the Merck Process Group. While some process groups place significant weight on synthesis complexity and possible product cost very early in a

program, and often refuse to accept candidates for development based on these considerations, this has never been the case at Merck. Had it been, we probably would have never developed products such as cefoxitin, imipenem, or crixivan.

This was a case with fludalanine wherein the medicinal chemistry synthesis was simply not applicable to the preparative scale. Over the years, Janos Kollonitsch, who began his Merck career in Process Research but then moved into Medicinal Chemistry, had developed a program of photohalogenation of medicinally important substrates in strong acid media to provide unusual and new halogenated analogs of the substrates.[5] Initially, the focus was on chlorination, but even 30 years ago the potential of fluorine in bioactive molecules was recognized. Janos and his co-workers developed a photofluorination protocol wherein substrates were dissolved in liquid HF at −78°C and photofluorinated employing trifluoromethylhypofluorite (CF_3OF) and unfiltered UV light from a 1000-W high-pressure Hg/Xe lamp.[6] The fluorination was radical in nature and tended to produce mixtures of products which required separation.

Photofluorination of alanine produced a mixture of 3-fluoroalanine and 3,3-difluoroalanine and left residual alanine, but reasonable yields of 3-fluoroalanine could be obtained after careful workup and chromatographic purification. The chirality and the isotope made complex matters even more complex. At that time the Merck–Frosst Isotopes Division produced 2-deutero-D-alanine for Janos' work by labeling racemic alanine with deuteroacetic acid (AcOD) at 150°C. Not only was the proton at the chiral center exchanged under these conditions, but also all of the exchangeable hydrogens had to be exchanged to ensure ∼99% deuterium incorporation at carbon. Thus, 400 moles of AcOD per mole of alanine was required in the exchange process. Thereafter, an enzymic resolution produced the 2-deutero-D-alanine for the photofluorination. In terms of deuterium efficiency, this was a terrible method, yet it sufficed to make the initial quantities of material necessary to bring the compound into development (Figure 1.3). I was asked to do the initial projections for this program, and I concluded that we would need numerous photoreactors running for weeks at a time to produce the first kilogram of drug needed to initiate safety, formulation, and Phase I studies. Given that this needed to be done in liquid HF with an explosive fluorinating agent at low temperature, we were between a rock and a hard place, as they say. We desperately needed a new approach, and having no idea what it might be, I projected that we could have the first kilogram in nine months. Clearly, we were relying on organic synthesis and its impact to get this program into development.

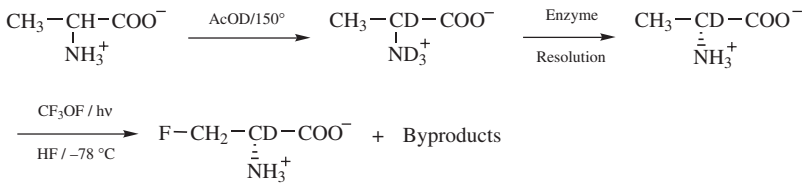

Figure 1.3. Synthesis of fludalanine by photofluorination.

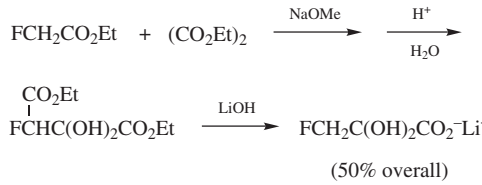

Figure 1.4. Lithium fluoropyruvate hydrate synthesis.

Working with a newly hired chemist named Ulf Dolling, who would become famous for his work on chiral, catalytic phase transfer reactions in the next decade, we decided to study the reductive amination of 3-fluoropyruvate which could be made by an ethyl fluoroacetate-ethyl oxalate condensation. For a possible source of deuterium, we asked the Frosst division if they could come up with a practical synthesis of sodium borodeuteride. They quickly showed that sodium borohydride could be exchanged with deuterium gas at 340°C, and they developed the equipment and a practical process to carry out this transformation on a kilogram scale! In approaching the fluoropyruvate reductive amination, we had three substrates to consider: esters, the acid, and salts. Of the three possibilities, we settled on the lithium fluoropyruvate hydrate, because of its relative aqueous insolubility, facile isolation, and overall stability. It was prepared by a classical condensation–decarboxylation sequence (Figure 1.4).

The reductive amination sequence on lithium fluoropyruvate hydrate proved most interesting. The amination of lithium fluoropyruvate hydrate in 13 M aqueous ammonium hydroxide at 37°C showed two FCH_2 doublets in a 95:5 ratio by proton NMR immediately after dissolution. After 1.5 hr the ratio had reversed to 5:95. Extensive NMR studies, including equilibration in $^{15}NH_4OH$, confirmed that the hydrate was immediately converted to the aminal (initial major species) upon dissolution in aqueous ammonia, and this species subsequently equilibrated to the diamine. The ketone and imine were not observed under these conditions, but the ketone and imine must be present in low concentrations to effect the observed equilibrium. The goal became to effectively reduce the imine to racemic deuterofluoroalanine and minimize back equilibrium to the ketone, which would afford deuterofluorolactate as a byproduct, keeping in mind that the borodeuteride was the cost-controlling reagent in the process. Extensive studies of the reaction kinetics, varying borodeuteride concentration, ammonia concentration, and temperature, were carried out to establish the appropriate reaction conditions. In a typical experiment, 0.2 mole of lithium fluoropyruvate hydrate was equilibrated in 300 ml of 13 M aqueous ammonia for 1.5 hr at 37°C to establish the 95:5 ratio of diamine to aminal. At this point the solution was cooled to 10°C to freeze the equilibrium ratio and then 0.085 mole (1.7 eq) of sodium borodeuteride was added (Figure 1.5). Little reduction occurred at this point because the pH of the system was too high. With the equilibrium ratio essentially frozen, the pH of the system was rapidly lowered with vacuum and nitrogen sparging to remove the excess ammonia and effect the desired reduction as the system back-equilibrated through

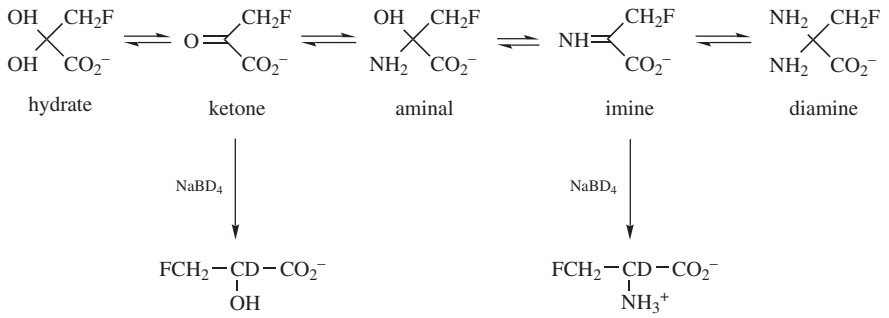

Figure 1.5. Equilibration and reduction of lithium fluoropyruvate in aqueous ammonia.

the imine. Subsequent workup employing a Dowex resin afforded a 70% crude yield (based on borodeuteride) of racemic product, which contained 99% deuterium at C-2. Using these conditions, we were able to make more than 60 kg of the racemate in the Pilot Plant over the course of the program.

I have always taken great pride in this synthesis. It illustrates the importance of understanding and controlling fundamental equilibria in a chemical process—all that stuff they taught us in freshman chemistry is actually true! At first glance it appears that this synthesis will never work, because the high pH necessary to convert the ketone hydrate to the diamine is contrary to the requirements of an efficient borodeuteride reduction. Yet the diamine:aminal ratio in the equilibrium mixture can be preserved by lowering the temperature, and the desired pH for the reduction was achieved by removing the excess ammonia. When we did the equilibration with fluoropyruvic acid hydrate, two changes to the process were noted. The equilibrium was achieved in less than 5 minutes because it was catalyzed by the protons brought into the system with the acid. But in attempting to do the reduction, the presence of these protons caused exchange of the borodeuteride under the reduction conditions, and the level of deuterium label dropped to about 90%.

Of course this process produced the racemate, and we had to face the question of resolving the product to afford the D-isomer. Given the Merck experience with the continuous resolution in the methyldopa process,[7] we opted for a continuous resolution of a conglomerate. The benzenesulfonic acid salt of 3-fluoro-2-deuteroalanine had all of the desired properties for an effective continuous resolution in *n*-propanol employing a dissolution temperature of 28°C and a crystallization temperature of 23°C which afforded a 16.8% supersaturation. It is noteworthy to mention the contributions of Dr. Mike Middler of our Chemical Engineering Department. He was one of the principals in designing the methyldopa continuous resolution, and we traded on his expertise almost daily when we were designing the conditions and system for our resolution. A summary of the details of this resolution, including a picture of the equipment necessary to perform this resolution on a laboratory scale, is included in a recently published paper.[8] With the chemistry and resolution established, we were able to make the first kilogram of drug substance in 10 months, one month more than the initial projection.[9] Employing this overall

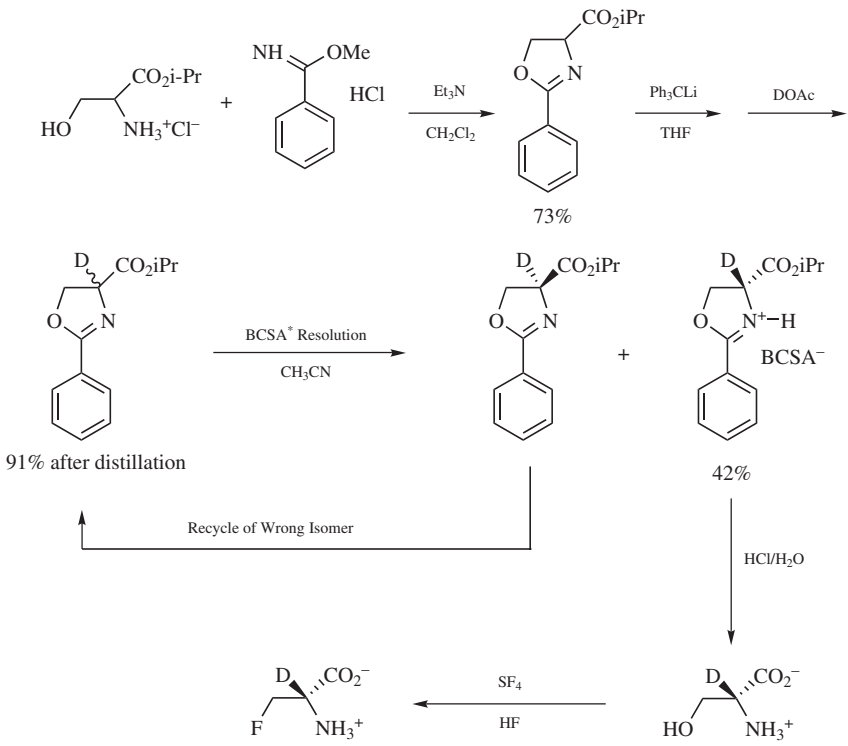

Figure 1.6. The oxazoline approach to fludalanine.

process, our engineers were able to make more than 20 kg of product to support the overall program.

In spite of the advances of this synthesis over photofluorination, it would be an inherently expensive process, relying on sodium borodeuteride for the deuterium source, making the racemate instead of the single enantiomer and employing a continuous resolution process, which would have required extensive capital investment for the program. Racemization of the free amino acid or its derivatives is not possible because of HF elimination. As we moved further into the program and began thinking of a synthesis that could produce hundreds of kilograms instead of tens of kilograms, Paul Reider, who had completed studies with Al Meyers at CSU, joined the Merck Process Group and was assigned to work on this program. Paul applied his expertise in oxazoline chemistry to propose and develope a new process for fludalanine.[10] The key in this approach was the conversion of isopropyl serinate to the 2-phenyloxazoline (Figure 1.6), followed by anion formation and deuteration. Because of concerns with exchange of the deuterium in the oxazoline, trityl lithium was used as a selective base for deprotonation and AcOD was used as the source for deuterium. This approach resulted in a dramatic improvement over the borodeuteride route because the AcOD could be readily made from acetic anhydride and D_2O, and the deuteration was essentially pinpoint, though racemic. The resulting

deutero-oxazoline was resolved with D-α-bromocamphorsulfonic acid (BCSA) in acetonitrile to give the desired isomer in 42% yield and >99.8% e.e. (84% corrected for 50% availability of the desired isomer). The wrong isomer was racemized with potassium carbonate in acetonitrile. The use of the same solvent for the resolution and racemization was a bonus for the procedure. Acid hydrolysis of the freed deutero-oxazoline afforded (*R*)-2-D-serine in 92% yield. Subsequent fluorination in HF with SF_4 afforded an excellent yield of fludalanine when run at concentrations of <0.05 M. At higher concentrations, serine regeneration became a problem because of a termolecular reaction among two serines and one SF_4 which formed an $(RO)_2SF^+$ species. This subsequently afforded fludalanine and an ROS(O)F intermediate that hydrolyzed back to serine.[11]

While this procedure represented a great improvement over the borohydride route in terms of addressing the cost of the introduction of the deuterium, it was not without its liabilities. Atom economy was poor, particularly with the need for the use of trityl lithium. Resolution–racemization was required, rather than a pinpoint, enantiospecific deuteration. Finally, the use of SF_4 in HF, particularly at dilute concentrations, is inherently dangerous and expensive.

This prompted a yet another approach to fludalanine. Racemic proteo-fludalanine could be readily made via reductive amination of lithium fluoropyruvate employing sodium borohydride. The plan was to protect the amino group in the racemate as its phthalimide derivative and convert the acid to the acid chloride. Reaction with base could afford the ketene (Figure 1.7), which upon subsequent reaction with a chiral, deuterated alcohol could afford the *N*-protected deuterofludalanine ester. At this time there were the emerging reports in the literature on the diastereoselective addition of enantiopure alcohols to ketenes. The phthalimidoacid

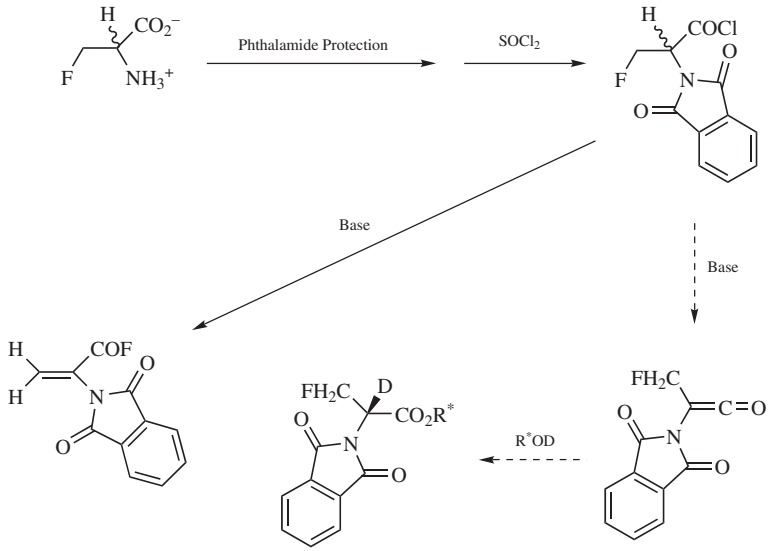

Figure 1.7. Projected ketene route to fludalanine.

chloride was readily made by standard methods. Reaction with bases ranging in strength from 4-cyanopyridine to diisopropyl ethylamine (DIPEA) afforded the same crystalline, stable product. It had IR carbonyl absorptions at 1825 cm^{-1} and 1795 cm.$^{-1}$ In addition to the phthalimido group in the proton NMR spectrum, a doublet and a quartet (2*H*) were present in the 6- to 7-ppm region, with small (1 Hz) couplings. The IR should have given the structure away, but we were fascinated by the possibility of formation of cyclobutanones arising from 2 + 2 cycloaddition of the ketene, and wandered on a misadventure. Subsequently, we recognized that we had an acid fluoride, and the solution to the structural problem was obvious. Given the choice of eliminating HCl to form a ketene (high-energy path) or HF to form an acryolyl chloride (low-energy pathway), the latter occurred. With free fluoride ion in the system, the acid chloride is converted to the acid fluoride, which is remarkably stable.[12] I have presented this problem (IR and NMR data) to many chemists over the years, and they either have failed to get the correct answer or have taken days to do so. The exception was Glen Berchtold, my MIT senior thesis advisor, who looked at the problem for less than a minute and had the correct answer. He recognized the acid fluoride carbonyl and the need for a second coupling to one of the vinyl hydrogens in the product—a W arrangement with the F atom. When I asked him how was he able to get the answer so quickly, he noted that he had been teaching the spectroscopy course for organic chemists for the prior 15 years!

The program ended due to non-chemistry issues, and our adventures on fludalanine were terminated. I do not think we came up with the ultimate process, though Paul Reider might disagree. In our ratings for that year, the lack of an enantiospecific synthesis was noted. My memory indicates that an asymmetric diastereospecific reduction of the acetamidofluoroacrylate has been reported in the literature, but that does not produce the desired target, because a new FHDC chiral center is created at C-3. Regarding the ketene approach, Rob Larsen and Ed Corely revisited that in the context of a synthesis of (*S*)-ibuprofen a few years later, and they actually solved that problem in a most elegant way which will be described later in this chapter.[13]

FINASTERIDE: CAN THE ENGINEERS ACTUALLY BE RIGHT?

In the first "Reflections..." chapter[1] I noted the unusual silylation-mediated [bistrimethylsilyltrifluoroacetamide (BSTFA)] DDQ oxidation of a lactam to form its unsaturated analog proceeding via a substrate–DDQ adduct followed by a thermal loss of the hydroquinone (Figure 1.8). This chemistry forms the nucleus of the finasteride manufacturing process,[14] but the story from the bench to the pilot plant during the early development of this product is much more complex than the scheme indicates. We have all delighted in telling this episode over the years in our finasteride presentations. It highlights the unexpected difficulties that one can encounter when trying to put a new process in place early in the drug development process, and it highlights the misplaced bravado that we process chemists are sometimes guilty of in our interactions with the chemical engineers.

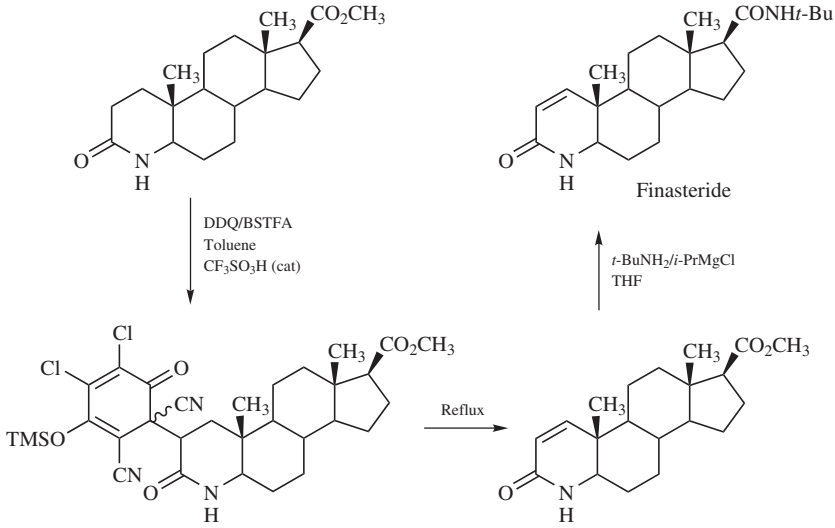

Figure 1.8. Outline of the finasteride manufacturing process.

The first indication of unexpected complexity in this chemistry occurred when we noted that the optical rotation of finasteride prepared by the silylation/quinone method was a few degrees higher than material prepared by the medicinal chemists' phenylselenic anhydride method. (We chose not to proceed with this method because of the toxicity issues associated with the handling of selenium reagents.) Of course, our first response to this situation was to simply claim that our product was purer than theirs, and the resulting rotations were the first reflection of purer final product. However, the analytical chemists would have none of this explanation, because materials prepared by both methods were >99% pure by area and weight percent. They did note, however, that we had three low-level impurities (0.1–0.3 area %) that were not produced during the selenium oxidation. Isolation and analyses of these impurities indicated that they were further oxidation products wherein one, two, and three (!!!) additional double bonds (Figure 1.9) are present in the B rings.[15] The standard optical rotations of these materials were of the order of 1000°, approximately 10 times that of finasteride. Thus, low levels of these compounds would easily increase the observed product optical rotation.

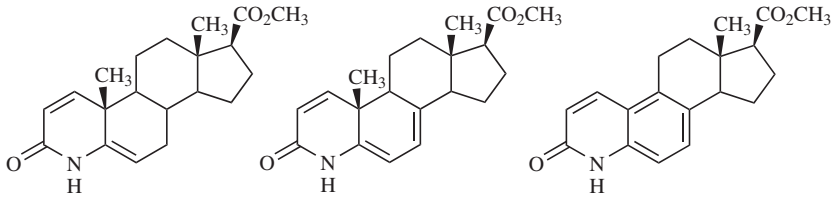

Figure 1.9. Finasteride overoxidation products produced during the silylation-mediated quinone oxidation.

Clearly the DDQ/BSTFA oxidizing system had components that we did not understand, and some sort of remedy was needed. We had already established that silylenol ethers and DDQ form substrate–quinone adducts analogous to those formed by the silyl imidates,[16] so we began to envision a stepwise protocol for conducting the finasteride oxidation. The first step would be formation of the silylimidate followed by its reaction with the quinone to form the substrate–quinone adduct. Both of these readily occurred at room temperature via what we have presumed to be an electron transfer reaction between the silylimidate and the DDQ with concurrent silyl transfer. Excess DDQ was used in the reaction to ensure complete conversion to the adduct (<0.1% starting material), because unreacted starting material could not be removed from the product mixture by crystallization. Yet, it was the excess DDQ that was the source of our overoxidation byproducts. Thus, we reasoned that addition of a ketone to the mixture that would form a silylenol ether which would subsequently react with the excess DDQ to form a new adduct and remove the DDQ from the picture.[16] Thermolysis at this point should provide product free of over oxidation products. For the ketone we selected cyclohexane-1,3-dione, which readily formed the disilylenolether under the reaction conditions. Reaction with DDQ would produce an adduct, and thermolysis would afford monosilylated 1,3-dihydroxyphenol and the hydroquinone, both of which would be subsequently silylated by the BSTFA. This would render the excess DDQ benign, and we would not create these low-level impurities (Figure 1.10).

This chemistry progressed well in laboratory runs, and we proceeded to our first Pilot Plant campaign. Appropriate charges of the azasteroid ester (1 part), BSTFA (four parts to ensure silylation of all hydroxyls to prevent them from undergoing Michael reactions with the unsaturated lactam product), and DDQ (1.2 parts) at 25°C produced the desired silylated steroid–quinone adduct with <0.1% residual starting material as expected. The cyclohexane-1,3-dione (~0.2 parts) was added and the reaction aged an hour to produce its dienol ether and subsequent adduct, and then the reaction was heated at reflux to complete the overall transformations. To our dismay, the resulting product contained ~1% starting azasteroid, despite the fact that we had consumed >99.9% of it in the DDQ adduct formation. Faced with this conundrum, we did what all process chemists do: We blamed the engineers! Obviously we assumed that the reactor and/or its lines were contaminated with

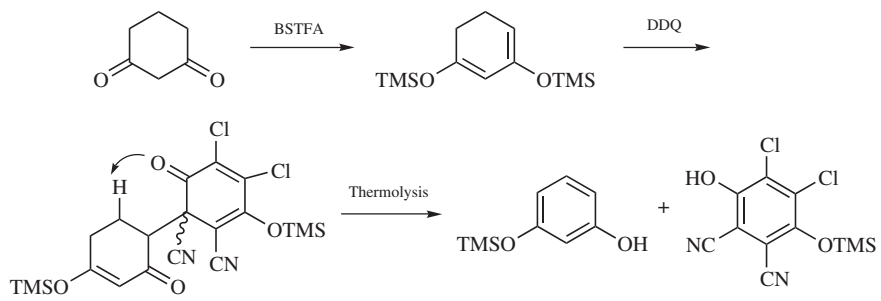

Figure 1.10. Reaction of DDQ with cyclohexane-1,3-dione and thermolysis of the adduct.

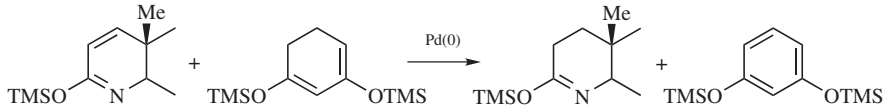

Figure 1.11. Inadvertant reduction of the oxidation product under transfer hydrogenation conditions brought about by the wrong choice of a ketone to consume the excess DDQ and the presence of trace levels of palladium in the starting lactam.

starting material, which was reintroduced into the reaction during its later stages. What we had was *not* some bizarre chemistry, but a simple contamination issue. We were steadfast in our explanation and would consider no others. Our engineering team was equally committed to the opposite thought—that is, that the reactors and their lines were *not* contaminated with starting material. To their credit, they absolutely refused to accept our explanation of the events. No matter how hard we pushed, they refused to budge—the system was clean, and something was wrong with the chemistry.

Desperate for an answer, we began to consider the engineer's views. When we ran a control experiment wherein we took the desired unsaturated product (namely, cyclohexane-1,3-dione) and BSTFA and heated the solution at reflux in toluene we saw, much to our dismay, the slow formation of *saturated* starting material. The engineers were right: There was a fatal flaw in our chemistry that we had missed. At this point we recognized that the dione forms the 1,3-disilyloxycyclohexadiene under our reaction conditions—in fact it acts as a transfer hydrogenation reagent! Could we be reducing the product back to starting material during the thermolysis reaction? As soon as we asked this question, the answer became obvious. During the preparation of the saturated azasteroid ester starting material, a double bond in the B ring of the azasteroid is reduced over Pd/C. A quick assay showed that this starting material contained $\sim$5 ppm residual Pd from the reduction, and this Pd along with the inadvertent addition of a transfer hydrogenation reagent created the reductive environment and produced starting material from the desired product (Figure 1.11). The engineers were correct: The equipment was clean. Once the problem was understood, the solution was simple. The dione was replaced with methyl acetoacetate, which forms a silylenol ether in the reaction that reacts with DDQ to form a benign adduct under the reaction conditions.

I have delighted in telling this story in lectures over the years—it clearly shows the fallibility of process chemists, as we often think we know more than we really do. It is also an excellent example of how things can go wrong despite the best of intentions and the projections of excellent science.

KETENE ADDITIONS REVISITED

As noted during the previous discussion on fludalanine, we did not succeed in doing a diastereoselective addition of a chirally pure alcohol to a ketene. Many years after these efforts, we, along with many in the pharmaceutical industry, became

interested in the single enantiomers of the common 2-arylpropionic acid nonsteroidal anti-inflammatory drugs (NSAIDs). At that time, additions of ketenes to chirally pure alcohols with d.e.'s as high as 80% had been reported, but the alcohols needed were of limited availability and expensive. Rob Larsen and Ed Corley, who were not aware of the previous work on fludalanine, rose to the challenge and defined a simple protocol based on naturally and/or commercially available chirally pure α-hydroxy esters and lactones.[13]

The plan was straightforward: generate the ketene from an NSAID such as racemic ibuprofen and define conditions for a diastereoselective addition to a chirally pure simple alcohol. (*S*)-Ethyl lactate proved to be one of the best-performing alcohols, and the reaction conditions that emerged proved to be highly specific. Nonpolar solvents such as hexane or heptane provided the best d.e.'s. Phenomenological studies indicated that the addition proceeded best in the presence of small tertiary amines (i.e., trimethylamine, dimethylethylamine, and *N*-methylpyrrolidine, for example), which were already in play to generate the ketene from the acid via the acid chloride. Without an added amine, d.e.'s were in the 60% range. Both low reaction temperatures and lower concentrations provided the maximum d.e.'s. Optimum conditions with (*S*)-ethyl lactate were as follows: −78°C; 0.02 M concentration; in heptane with trimethylamine as the base. A 98.6:1.4 SS/SR ratio of diastereomers resulted under these conditions. The d.e. dropped to 95:5 when the reaction concentration was raised to a more practical 1.0 M. A study of the structure versus d.e. for various alcohols revealed that (*R*)-pantolactone [(*R*)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone] was by far the best affording a d.e. ratio of 0.5:99.5 for the RS/RR isomers at preparatively useful reaction conditions. The results are summarized in Figure 1.12.

The addition reaction proved to be third order overall, being first order in ketene, alcohol, and tertiary amine. A k_H/k_D of ∼4 was noted for the ROH/ROD isotope effect. These results prompted many vigorous mechanistic discussions; however, without appropriate carbon and oxygen isotope effects, it was difficult to provide a convincing picture of the mechanism of the addition. At one of the Gordon Conferences, Rob and I were able to convince Ken Houck to consider the problem from

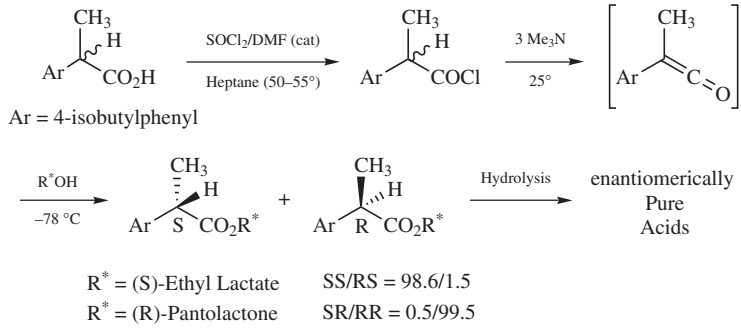

Figure 1.12. Preparation of chirally pure arylpropionic acids via ketene additions.

a theoretical view. The reader is referred to the resulting JACS papers for a discussion of the outcome of the calculations.[17]

Of course we were between a rock and a hard place on this problem. Despite publishing our results in JACS, we were far from a practical and economical process. Indeed, any process dependent on purchased racemic ibuprofen as a starting material was doomed to failure at the outset. Commercial suppliers were producing millions of kilograms of this material each year by well-established and highly efficient processes. Since the chiral center is between activating aryl and carboxyl groups, it is readily amenable to racemization, and single enantiomers can be prepared by simple resolution/racemization processes.

THE CONTINUOUS CONUNDRUM

A problem that besets all process chemists is how much effort to apply to a given program. When I began my Merck career, we took the long-range view on every compound entering development. Each was considered a likely product, and we strove to establish the best synthesis as quickly as possible. Safety Assessment typically did 14-week studies; Pharmaceutical Research began by immediately trying to develop a solid dosage form; and the early planned clinical studies were extensive. Materials requirements to initiate a program were generally high. In the final analysis, we had a lot of superb processes for candidates that died very early in the development cycle, and lots of left over material in the sample collection awaiting some unforeseen use. Obviously, we were not using our resources efficiently. Today, we recognize that of twenty compounds entering development only one is likely to reach product status. (These are my figures, and others may dispute them.) With the probability of success of a typical candidate being in the vicinity of 5%, what resources should we devote to each new candidate as it enters development? Unfortunately, the equation that determines such is not a simple one. The first consideration is where are the quick GO/NO GO points in a program? If a compound has a serious potential safety issue, the answer might be had in short safety studies. If there are questions about half-life or bioavailability of a given candidate, this information can be gotten with short safety studies and a simple Phase I study. Neither situation requires a lot of material or a synthesis resembling a manufacturing process. On the other hand, the key GO/NO GO point in a program might not come until the Phase III clinical studies, and the problem has to be approached differently. If you proceed conservatively, develop a solid process and make a large quantity of material, and the compound dies in the first few weeks of safety assessment, you have wasted a lot of effort. If, on the other hand, you prepare a small quantity of material by bulling through the medicinal chemistry synthesis to quickly answer a half-life or bioavailability question, and the results are strongly favorable and the project catches fire, you are left with a synthesis that can not support the program's needs, and drug supply becomes the program's rate-limiting issue. Companies have developed their own protocols for addressing these questions, and much more thought is now given up-front as to how to proceed on an individual program.

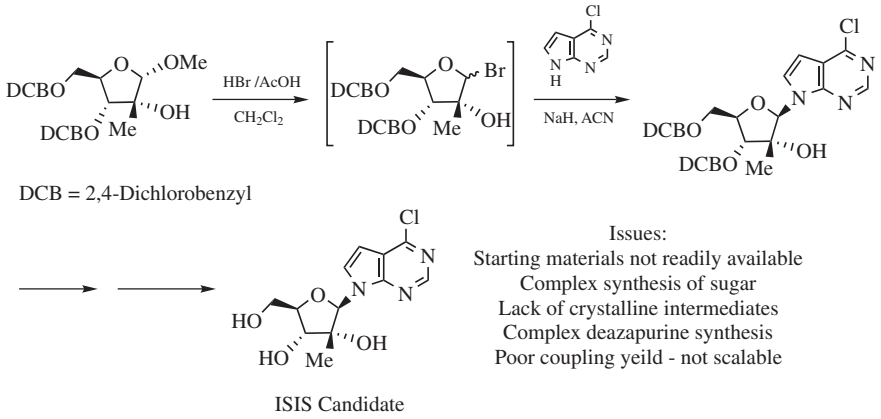

Figure 1.13. Original synthesis of ISIS candidate.

Today we might use outsourcing to prepare early material by the medicinal route to give the process chemists time to develop a preparatively viable route. Or, if the program does not have high priority, we might sequence all of the program activities in series, until we have a clear and definite GO indication. Despite all of the current planning, we still end up with imbalances. Some of our work illustrates the complexity of developing the path forward.

Recently, Merck licensed a hepatitis C candidate from ISIS (Figure 1.13), and it was brought into development. The candidate was nucleoside-like in structure, and in my entire career I had yet to work on a candidate of this structural type. I have never been able to predict which candidates will become products (we all want to have products listed on our cv's), and I have always made it a point, when possible, to choose candidates to work on based on potential chemical interest and complexity. The ISIS candidate looked like a good one from my point of view, and it was assigned to my group at my instigation. The medicinal synthesis was long and complex and was only suitable for making a few grams of product with a substantial effort. It is noted in detail in our paper on this program.[18]

Quickly, a number of issues with this synthesis were identified. The syntheses of the ribose and deazapurine portions were difficult and based on poorly available, expensive reagents. In proceeding forward with projected papyrochemical syntheses, we realized that much of the ISIS sugar and purine chemistry might not be useful for preparative work. The success of any sugar synthesis is highly dependent on selection and study of the appropriate protecting groups, which have to properly and successfully serve numerous functions during the course of the synthesis. One is to afford crystallinity and purification points, something that was lacking in the existing ribose synthesis. The synthesis of the deazapurine fragment was complex and not amenable to scale, and a more viable one was definitely needed. The most significant problem with this synthesis was the activation of the sugar and its coupling to the deazapurine anion. The intermediate bis-*O*-dichlorobenzyl-protected bromide was not stable to the conditions used to generate it. The net result was

that as you scaled the synthesis, the actual amount of product made remained essentially the same! With so many complex synthetic issues on the table, I became quite conservative in approaching this problem. Any process for this compound was going to be an *a priori* complex, and we wanted stability and control at each stage of the synthesis. Our goal became the development of a scaleable synthesis of a protected ribose that would serve all program needs, particularly with regard to crystallinity and points of purification. We also needed a new and efficient synthesis of the deazapurine. Preferably both the syntheses would be amenable to outsourcing. We also needed an efficient and stable method of activation, as well as a high-yielding coupling reaction to a penultimate protected intermediate that could be readily deprotected to final product. Part of my conservativism in approaching this program was that I wanted to be sure that we could continue to strongly support it if the early safety and clinical studies proved successful. Hepatitis C is a major threat to the world, and early successes in safety and the clinic would mean a fast-track program that could create the excitement of the protease inhibitors of the 1990s.

Recognizing that achieving these goals was going to be a difficult task, we assigned two teams to the program: The first was to develop the ribose synthesis and the coupling protocol, and the second was to develop the deazapurine synthesis. The latter was far more complex than anticipated because we were uncertain about how to introduce the primary amino group in this portion of the molecule. ISIS had used the chloro analog that was displaced with ammonia to complete the synthesis. In addition to ISIS's use of the chlorodeazapurine, we examined the azido group, simple amides, and imides and finally selected the phthalimido group. This meant that the team aiming for a practical deazapurine synthesis was shooting at a moving target and had to work very closely with those working on the ribose and coupling parts of the synthesis.

The process that resulted proved to be just about everything that we wanted. A synthesis of the ribose from readily available diacetone glucose was developed. Study of a variety of protecting groups revealed that the use of the *p*-methylbenzoyl protecting groups on the ribose portion afforded stable and crystalline intermediates throughout the synthesis. The epoxide group proved to be the coupling group of choice. It was readily generated from the diol, and it was stable to its generation conditions. It was also crystalline, but its isolation was not necessary. The deazapurine was readily prepared in phthalimido-protected form via a new synthesis from bromoacetaldehyde diethyl acetal, malonitrile, thiourea, and phthalic anhydride, all commercially available and inexpensive reagents. The coupling was catalytic in sodium hydride, and, most amazing, a global deprotection could be achieved at the end with butyl amine (Figure 1.14). The overall yield for this new process was excellent, and 3 kg of drug was initially prepared to demonstrate its viability and to provide material to begin development.[18] This could be a manufacturing process for this candidate. The only issue that I see is that of atom economy, because a large portion of the molecular weight is removed in the final deprotection step. But, in our defense, the sources of the protecting groups (*p*-methylbenzoyl chloride and phthalic anhydride) are materials of commerce.

Based on the chemistry that I have presented and the amount of drug that we made, the reader might consider this a very successful program. But, in the final

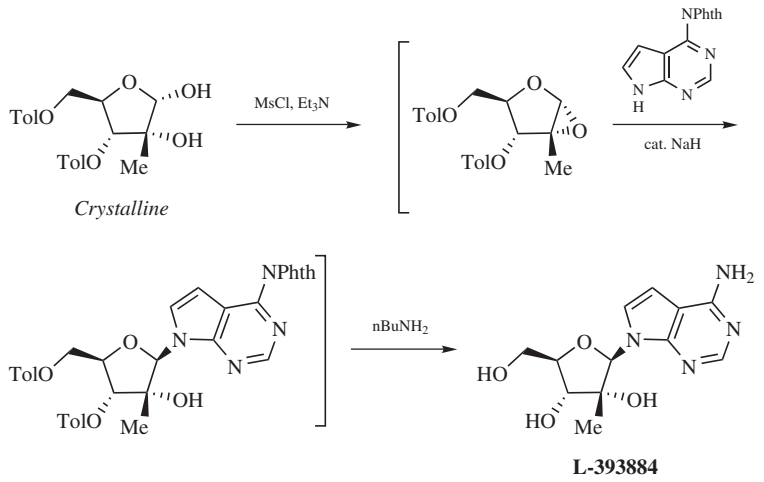

Figure 1.14. Practical synthesis of L-393884 from diacetone glucose.

analysis, the chemistry again ran well ahead of the rest of the development program. Issues arose during the safety studies. We could have achieved the same results with one-third of the material we actually made. Once we defined the outlines of the described synthesis, we could have proceeded forward without dotting most every i and crossing most every t. Generous use of preparative chromatography throughout the synthesis could have saved a lot of development time. But we did not know that issues would arise in the preclinical part of the program—all of the short-term studies done to bring the compound to development were on target. We chose to proceed conservatively and we need not have. This remains the continuous conundrum, and I do not know if anyone has a real answer. Some might suggest that we seek the help of the MBAs in planning our programs—my history indicates that this leads only to a lot of nonsense. We do the best planning that we can with the information available, and we take our kudos or lumps as they come. I could have chosen a program that illustrates success at every turn, but the readers would recognize that this is simply not a reflection of reality.

I hope that this very personal recounting of these process research wars has entertained and enlightened the reader and, hopefully, provided some useful chemistry and thoughts that will be of help to his/her future programs. Clearly, organic synthesis will continue to have a dominant role in early development. Contrary to current thinking, true process research is not just outsourcing and running lots of reactions. Serious opportunities for creative new chemistry are always present, and it is those who believe in their programs who are the ones who will really make things happen. The real question is whether process chemists will be able to continue to pull rabbits out of their hats on a timely basis to meet ever-demanding program timelines. As always, I must thank the members of the Merck Process Research Group for their superb efforts. From my position in retirement, I dearly miss them, their intellectual stimulation, and their innate drive for success.

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