PHARMACEUTICAL PROCESS CHEMISTRY FOR SYNTHESIS

Rethinking the Routes to Scale-Up

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Better Pharma Processes, LLC
Louisville, Colorado

A JOHN WILEY & SONS, INC., PUBLICATION

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INTRODUCTION

1.1 INSPIRATION

This project was first conceptualized at a most unlikely place: at a visit to an *Inspiring Impressionism* exposition at the Denver Art Museum in 2008. The exhibition focused on the impressionists as students of earlier masters. They immersed themselves in these earlier masterpieces and then incorporated the insights they had gained and added their own techniques to convey the same subject matter in profound new ways. My 20 years as a process chemist at Syntex and Roche are much like the years the impressionists spent camped out in front of the works of the masters. The insights gained could be conveyed by presenting the theory and concepts of process research and development, but there are many well-worn reference books that collectively accomplish that objective. My experience has been that process chemistry is a roller-coaster ride, with tremendous highs and lows, where you learn theory and concepts, as needed, on the fly, from your colleagues and from those reference books (while meeting seemingly unattainable milestones and timelines). The aim of this book is to convey some of this experience by immersing the reader in the process chemistry of some of the most valuable pharmaceuticals we are fortunate to have available today. The masterpieces in this book are the top-selling drugs in the United States in 2007–2008. These are Lipitor®, Nexium®, Advair Diskus®, Prevacid®, Plavix®, Singulair®, Seroquel®, Effexor XR®, Lexapro®, and Actos®, all "blockbuster" drugs, generating more than $1 billion in revenue for their owners each year (Figure 1.1).[1]

I have no previous detailed knowledge of the process chemistry of most of these drugs. Why choose these as the subject matter? First, there is currently intense interest in the process chemistry of these drugs. Second, if I had detailed unpublished knowledge about these drugs, I would be bound by a secrecy agreement to discuss only information already in the public domain. Third, having no financial stake in any of these drugs or their process technology, I can be completely (and refreshingly) objective. I am not "selling" the value of any target or proprietary technology to a patent agency or a pharmaceutical manufacturer.

After a detailed review of the process chemistry for Plavix® and Nexium®, these will not be included. The process chemistry for Plavix® is omitted because I have published and patented process work and have detailed knowledge of the manufacturing process for Ticlid®. The antiplatelet drug Ticlid® is an adenosine diphosphate (ADP) receptor inhibitor with the same thienopyridine core as Plavix® (Figure 1.2).[2] The process chemistry for Nexium® is omitted because Prevacid® and Nexium® have the same core and there is considerable overlap in their process chemistry. Advair Diskus® has two active ingredients: salmeterol and fluticasone. The process chemistry of salmeterol is included. The process chemistry of fluticasone would be better presented "in context" with the process chemistry of other valuable steroids.

With this format, will this book touch on every important aspect of process chemistry in the pharmaceutical industry? If you carefully studied the techniques used to create 10 masterpieces at the art museum would you become an art

Pharmaceutical Process Chemistry for Synthesis: Rethinking the Routes to Scale-Up, By Peter J. Harrington

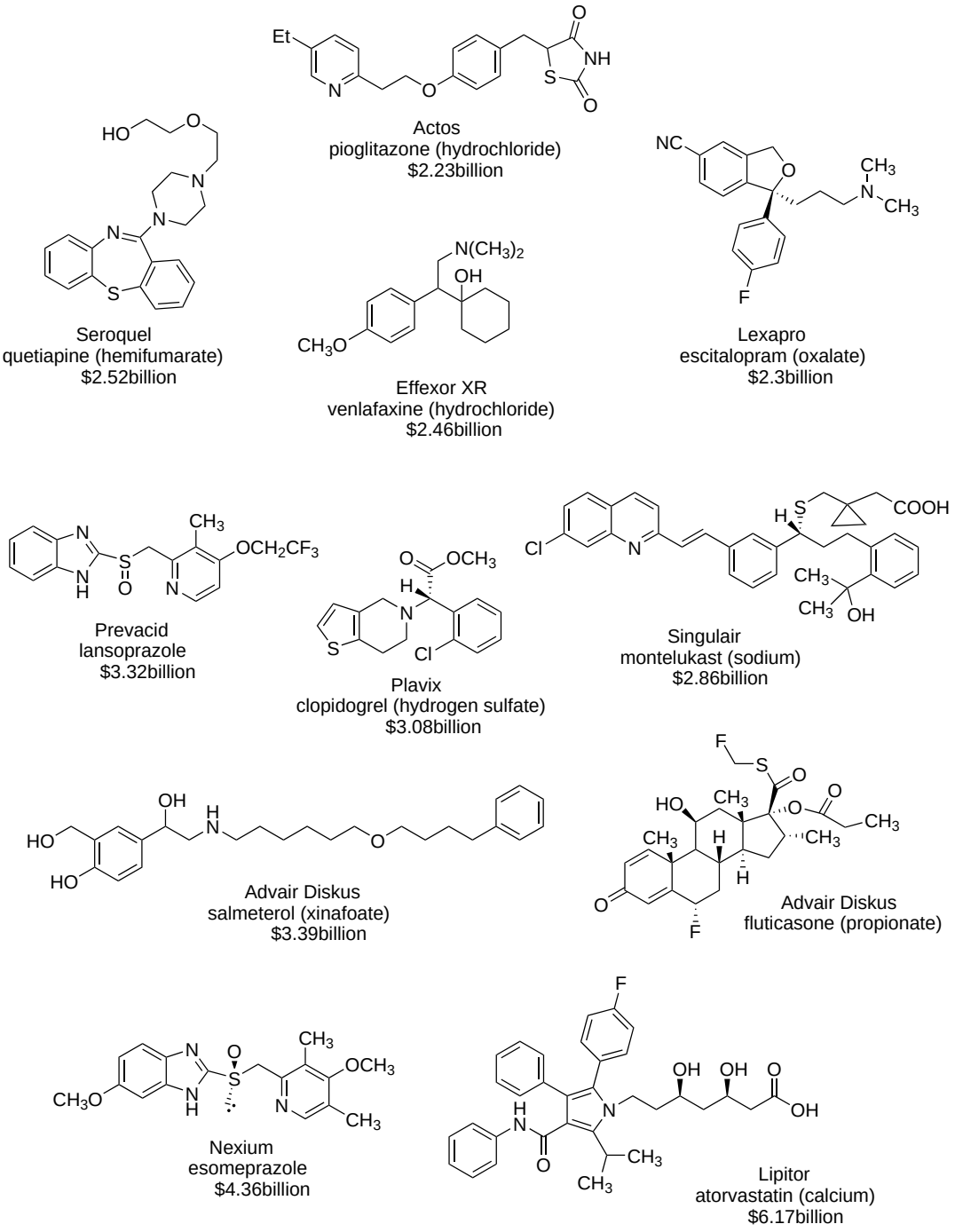


FIGURE 1.1 The top-selling drugs in the United States in 2007.

expert? Most people would say no. Would you be better able to utilize the techniques in your own paintings? Most people would say yes. The scientific objective of this book is then twofold: to identify one "best" process for manufacturing these blockbuster drugs and to highlight the strategies and methodology that might be useful for expediting the process research and development of the blockbusters of the future.

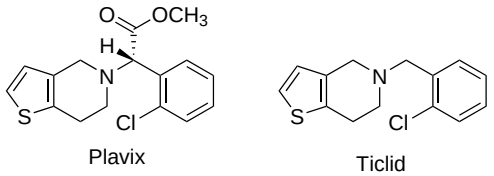


FIGURE 1.2 The close structure similarity between the antiplatelet drugs Plavix® and Ticlid®.

1.2 INFORMATION SOURCES

This project must begin with meaningful and realistic objectives. A consistent strategy will be used to define, retrieve, and review the relevant literature. The process chemistry presented is based on published experimental data harvested from patents and journal publications. The majority of the information is taken from U.S., European (EP), and World (WO) patents. Other country-specific patents are included if they are cross-referenced several times, do not have a U.S./EP/WO equivalent, and are available in English, French, or German. Working with a finite production budget, information from Chinese (CN) and Japanese (JP) patents is taken from *Chemical Abstracts.* Journal articles are often published in tandem with patents and offer the same experimental procedures and data. Key journal articles offering information not found in the patent literature are included. The presentation is weighted to emphasize the process patents and publications and the marketplace information published in the past decade.

It is likely that at least a few details of the process chemistry of a valuable pharmaceutical may be carefully guarded as a trade secret. Speculation about unavailable data will be clearly marked as such. Legal questions such as who owns a particular patented process, how long they will own it, or how valid are their patent claims are important questions that should be directed to a legal expert. The answers to these questions are outside the scope of this book.

A quick SciFinder® search (January 1, 2009) for the Prevacid® structure, for example, revealed approximately 1700 references. A review using this number of references for each target cannot be accomplished in a realistic time frame. A solution to this is to structure search for the building blocks unique to each target. The building blocks selected for Prevacid® are shown in Figure 1.3. The building block structure searches provide the first generation of references. The cross-references from the first generation are then used and the process repeated until the cross-reference loop is completed. For Prevacid®, this structure search approach reduced 1700 references to a manageable 200 references. The structures searched are provided at the end of each chapter. No effort was made to update the chapters completed first.

Process chemistry is so multidimensional that there will inevitably be important points overlooked. I welcome your comments and suggestions for improving the content and format of future publications.

1.3 CONTENT AND FORMAT FOR PRESENTATION

The content of each chapter will vary according to the information harvested from the references. For example, one chapter emphasizes the manufacturing route selection while another focuses on conversion of the penultimate intermediate to the final target. This variable content accurately reflects the range of tasks assigned to process chemists. Your role in a process research and development team may be early route selection in one project. Your role may be late troubleshooting of a difficult crystallization to produce a target that filters well and meets crystal size and purity specifications in another. Your role might involve working closely with procurement specialists or engineers in the early route selection or with analytical and regulatory specialists on the difficult crystallization.

Just as the chemical transformations are central to the manufacturing process, the process chemist is the hub of manufacturing process research and development. The process chemist does not have to be an expert in the related specialties of marketing strategy, patent law, procurement, environmental health and safety, analytical chemistry, formulation, regulatory affairs, and engineering and facilities but he must be knowledgeable enough to identify questions best answered working in close collaboration with these experts. Answers will sometimes be offered to questions best answered by these experts with the understanding that the answer is meant to trigger a discussion with the expert.

Each chapter is written to stand alone. Chapters 2–9 can be read in any order. While the content for each chapter will vary, the same format will be used to present the available information. Each chapter begins with an *overview of current and past marketplace information* for the target. This discussion is included to emphasize that the process research and development team cannot work in a vacuum. The team should receive detailed updates at regular intervals on the market potential of the target, the timing of the delivery, and new clinical and post-launch data that may impact the market potential and timing of the delivery. This

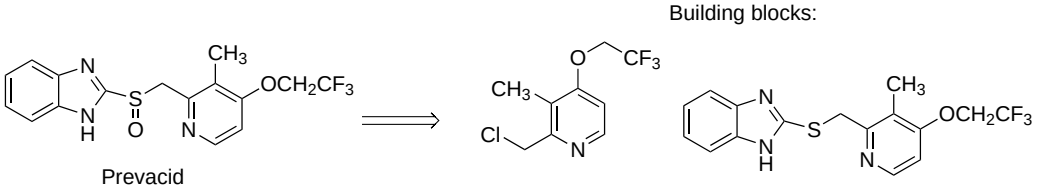


FIGURE 1.3 Building blocks searched to provide references to process chemistry for Prevacid®.

information might come from a marketing or business development expert.

To minimize repetition, retrosynthetic analysis will not be used to stage the synthesis discussion. To emphasize the modularity of pharmaceutical manufacturing, the synthesis discussion in each chapter starts with identification of raw materials. These *raw materials* are usually commercially available or can be produced in a few steps from commercial materials.

Every process begins with *commercially available raw materials*. A price is provided for each raw material *that contributes at least one atom to the target* when that raw material first appears in the discussion. Since suppliers and prices for raw materials are in constant flux, all prices quoted are taken from the 2007–2008 Aldrich catalog. It is my intention that these prices will give a "snapshot" of a relative price and availability at this point in time. Quoting an Aldrich catalog price should suggest scheduling a preliminary communication with a procurement group. This communication would include estimates of the quantity and purity specifications, a preferred delivery date, and any special shipping and handling requirements. Other raw materials, for example, acids, bases, reagents used to create protecting groups or leaving groups, drying agents, filter aids, and decolorizing carbon are not priced since expensive materials might be replaced by less expensive alternatives.

The raw material prices are only intended for "back-of-the-envelope" calculations. Detailed cost calculations should include vendor-guaranteed raw material prices and labor and overhead (LOH) costs for the manufacturing site and are beyond the scope of this book.

Aldrich catalog names are used for all starting materials and *ChemDraw 11.0*® is used to generate names for all process intermediates. With the intention that each sentence can stand alone, full chemical names are used in the text in many cases. Process intermediates and products are each assigned a number to facilitate correlation of the names with the structures in schemes and figures. An example of a stand-alone sentence is taken from the Seroquel® discussion.

> The reaction of 11-chlorodibenzo[*b*,*f*][1,4]thiazepine **(25)** with 2-(2-(piperazin-1-yl)ethoxy)ethanol **(26)** (2.0 equivalents) in refluxing toluene is complete in 8 h.

Patent procedures often contain *data gaps*. These can be separated into two categories. A major data gap is missing information that would certainly have been generated but was not included in the process description. Examples of major data gaps are a missing quantity for one reagent of several or a missing volume for the reaction solvent. Major data gaps are clearly identified in the discussion, and where possible, an attempt is made to fill the gaps with information gleaned from another source. A minor data gap is information presented in a format that requires a translation. For example, reagent quantities might be quoted only in weights or volumes. This gap is filled by converting reagent quantities into *equivalents*. In process chemistry, an equivalent simply refers to the number of moles of reagent per mole of limiting reagent. Equivalents in this book are calculated to the nearest 0.1.

Solvents and *reaction temperatures* are critically important process characteristics. These are included in each reaction description. After selecting a best process, the process solvents used are revisited to emphasize the importance of minimizing the number of process solvents and to highlight the solvents commonly used in a pharmaceutical manufacturing plant. Temperatures in the range of 20–30°C, or "ambient," are standardized as 25°C in the reaction descriptions. Very low temperatures (<-70°C) require that expensive liquid nitrogen be available locally and that liquid nitrogen storage facilities be available on site. Expensive circulating fluid and energy are required to achieve and maintain very high reaction temperatures (>160°C). Examples of a reaction description and a process solvent review are taken from the Actos® discussion.

> The condensation of 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde **(19)** with thiazolidine-2,4-dione (1.2 equivalents) and pyrrolidine (1.0 equivalent) in methanol at 45°C is very efficient even after multiple precipitations and isolations for purity upgrade (95% yield). The process solvents are toluene, THF, ethanol, isopropanol, and water, all solvents commonly used in a pharmaceutical manufacturing plant.

It is assumed that all operations involving combustible organic materials are performed *under nitrogen* and that all chemical mixtures are *stirred*. This is not specifically stated in the procedures described.

When there are many similar procedures, they will be presented in a *parallel format* to facilitate comparison and highlight the differences. Material presented in parallel format is usually preceded by a summary of the trends and results. An example of parallel formatting is taken from the Effexor XR® discussion.

> A mixture of 1-(2-amino-1-(4-methoxyphenyl)ethyl)cyclohexanol **(34)**, 88% formic acid (5.0 equivalents), and 36% aqueous formaldehyde (3.1 equivalents) in water (96 L per kg **34**) is refluxed for 21 h.
>
> A mixture of 1-(2-amino-1-(4-methoxyphenyl)ethyl)cyclohexanol **(34)**, formic acid (6.3 equivalents), and paraformaldehyde (2.9 equivalents) in water (7.9 L per kg theoretical **34**) is refluxed for 24–48 h.

When the discussion leads to a choice between two very similar processes, the analysis may be taken to an even greater level of detail. An example of information on this next level is *volume throughput*. The discussion at this next

level should be prefaced with the understanding that throughputs are rarely the focus of patent procedures, that some assumptions must be made, and that some questions (e.g., solubility and viscosity) can only be answered in the laboratory.

Nowhere is the phrase "time is money" more apt than in a manufacturing plant. Patent procedures typically quote reaction times in the range of 30 min to 24 h. I would suggest that a *reaction time* of 2 h is close to ideal, slow enough to allow for efficient heat transfer to or from the reaction vessel and to allow for sampling and an offline completion check. Any unusually long reaction times in key procedures will be identified and the potential for reducing these times may be addressed.

A great deal of process research and development effort is spent streamlining the transitions from one reaction to the next. For this reason, *workup procedures* are presented in detail to highlight potential scale-up problems. There may be product stability issues that will only become apparent during a scale-up or there may be a concentration at reduced pressure to a solid residue. When the workup description does not add to the discussion, it may be omitted or abbreviated to a "routine workup." In a routine workup, the reaction is quenched with water, dilute bicarbonate, or dilute brine and then extracted into an organic solvent (toluene, ethyl acetate, or dichloromethane). There may be several extractions. The combined organic layers are optionally dried ($MgSO_4$ or Na_2SO_4) and the solvent removed at reduced pressure to produce an oil or solid residue.

Drying agents such as sodium sulfate or magnesium sulfate are routinely used in the laboratory but rarely used at pilot plant scale. Drying agents used in the experimental procedure are omitted from the process descriptions in this book. The process chemist must use the water-wet solution or rely on (design in) an azeotropic distillation to remove water from the solution.

Purity analysis is critically important in process chemistry, yet often is not included in patent experimental procedures. The centrifuge may be filled to capacity with product but remember: *If the material does not meet specifications, the yield is zero.* To be consistent with this important tenet, yield and purity data are quoted when available. In the absence of purity data, the yield is quoted if the product is precipitated, chromatographed, crystallized, or distilled. Crude yields of early intermediates are included when other data suggest that the yield is an accurate reflection of efficiency of the reaction. HPLC area% data will be used for completion checks but not for purity analysis. Purity data for process intermediates are rounded to 0.1%. Purity data for the final drug substance, if available, are rounded to 0.01%.

Physical data such as boiling point or melting point are provided for process intermediates if those data are critical for determining the suitability of the process. For example, the crystallization and isolation of a solid with a low melting point ($<50^{\circ}C$) may be more challenging. The distillation of an oil at high temperature and low pressure ($>150^{\circ}C$ at <1 mmHg) may not be a viable option.

Every effort will be made to identify undesirable reagents and intermediates. These include *carcinogens*, *lachrymators*, *sensitizers*, and *malodorous chemicals*. Information on these chemicals will be quoted from *material safety data sheets* (MSDS) to substantiate the objection to use of the chemical. The date accessed and online reference to the MSDS are not included in the references. *The most current version of the MSDS should be reviewed before working with any chemical*. An example of an MSDS review is taken from the Prevacid® discussion.

> Vanadium(V) oxide is considered to be a carcinogen.[82] All vanadium compounds should be considered toxic.[83] The toxicity depends on the valence state and the solubility of the compound. For example, vanadium(V) oxide (V_2O_5) is considered to be five times as toxic as vanadium(II) oxide (V_2O_3). The first concern in handling these vanadium catalysts is exposure to dust. For vanadium(V) oxide, the OSHA permissible exposure limit (PEL) for vanadium respirable dust is 0.5 mg/m^3 (ceiling) and for vanadium fume is 0.1 mg/m^3 (ceiling), and the ACGIH threshold limit value (TLV) is 0.05 mg/m^3.

The "no stone left unturned" level of detail is chosen to accurately reflect the day-to-day concerns and activities of a process chemist. It is also intended that the level of detail is sufficient to allow the reader to make an informed process decision without revisiting the original experimental description for additional details.

Text boxes are used to elaborate on the logic behind a process decision. They are largely the author's personal preferences honed by trial and error in the laboratory and pilot plant over 20 years. Text box topics include setting starting material specifications, solid addition to a reaction mixture, stability of intermediate mixtures produced during sequential reagent charges, compatibility of materials of construction with reaction conditions, concentration at reduced pressure, acceptable volume throughputs, estimating volume throughputs from gram-scale procedures and kilogram-scale procedures, identifying first/second-generation side products for workup design, distillation of high-boiling polar aprotic solvents, routine safety testing of lab distillation bottoms, self-accelerating decomposition temperature (SADT), alternatives to dichloromethane, "one-pot" procedures, the importance of hold points, mixtures of sulfonic acids and methanol, alignment of economic and environmental incentives, selecting reaction variables for design space studies, analysis of suspensions, why polymorphs are important, and deconvoluting polymorph literature. While the same text box topic could be inserted at many points in the book, each topic appears only once and where it is most

relevant. An example of a text box is taken from the Singulair® discussion.

> Now that the challenges of producing 7-chloroquinaldine (**3**) are understood, a specification for 5-chloroquinaldine (**4**) in the starting material must be set and the fate of the side products from 5-chloroquinaldine (**4**) produced in the following step(s) must be determined. Our first inclination, as synthetic chemists, is to demand high-purity starting material. However, it would be prudent to invest some time up front to demonstrate efficient rejection of the side product from 5-chloroquinaldine (**4**). These data will empower us to use a lower grade of 7-chloroquinaldine (**3**) that will be available at a better price.

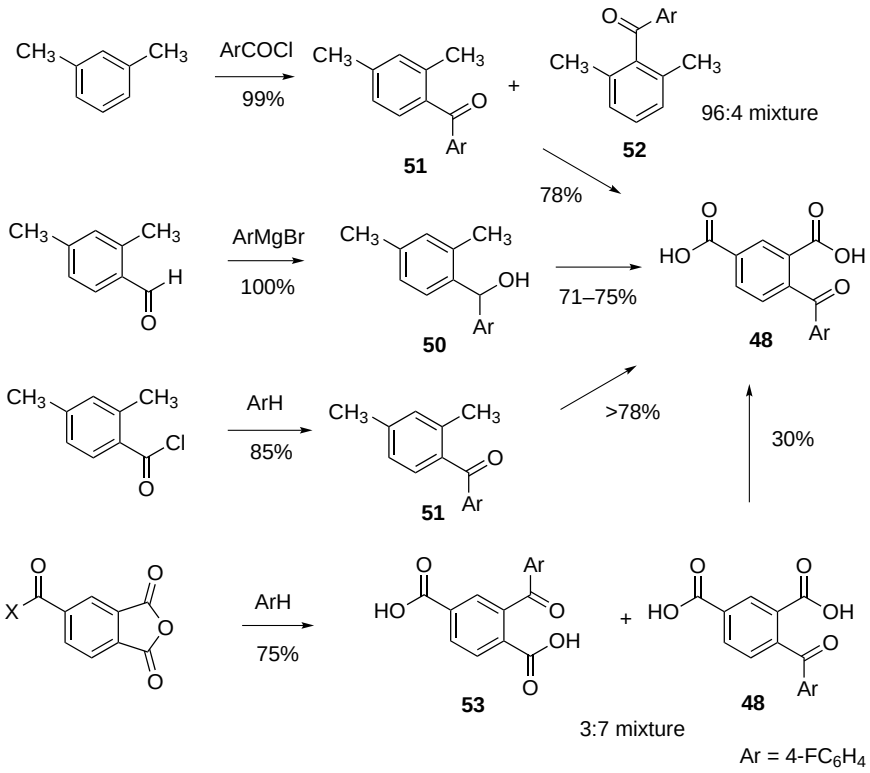
Schemes immediately follow the chemistry discussion. Since reagents and conditions are provided in the text and since many of the transformations can be performed using more than one combination of reagents and conditions, these are not included in the schemes. The highest yield or an appropriate yield for each transformation is provided under the reaction arrow. For example, see the scheme from the Lexapro® presentation (Scheme 1.1).

A section on *trade secrets, impurities, and analytical methods* is sometimes used to capture valuable process information that does not appear in the earlier chemistry review sections but might prompt valuable additional discussion.

Finally, the *best process available* offers criteria for selecting the process and uses the criteria to arrive at a single route as the standard for comparison. This best process is an amalgamation of the best available process steps and is intended to serve as a basis for further discussion rather than to end it.

For most of the targets, the method developed for generating the limited reference set intentionally minimizes the publications in other important areas, including *crystallization*, *polymorphism*, *particle size*, *storage stability*, and *formulation* of the final drug product. The Lexapro® presentation is expanded to include a detailed discussion on crystallization and polymorphism. The Lipitor® discussion includes a discussion of amorphous and crystalline polymorphs and the drying and storage stability of the final drug product.

A suitable formulation is most efficiently attained by the process chemist working in close collaboration with a formulation group. The involvement of the process chemist might end with developing crystallization, drying, and milling procedures to deliver the desired polymorph of the target to the formulation group with acceptable storage stability



SCHEME 1.1 A scheme from the Lexapro® presentation.

and a well-defined particle size range. Formulation is outside the scope of this book.

How reproducible are the patent experimental procedures at the heart of this project? Comparing similar procedures side by side certainly makes it easier to find inconsistencies. The inconsistencies are pointed out and corrections for typographical errors may be suggested. An example is taken from the Effexor XR® discussion.

> Palladium on carbon (10% w/w, 50% water-wet) (50 g Pd per kg **17**) is added to a mixture of 2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)acetonitrile **(17)** and hydrochloric acid in methanol (8 L per kg **17**), presumably at 25°C. (*Note*: The amount of hydrochloric acid charged is quoted as "1–3 moles" or 10–29 equivalents. This is presumably a typographical error.)

If a quoted yield can't be reproduced is the best process still viable? *The underlying principle for selecting the process is still valid*. An optimistic process chemist would respond: if you can get 50%, you can get 80%. If you can get 80%, you can get 90%. All that is required is motivation and development time.

1.4 SPECIALIZATIONS: BIOTRANSFORMATIONS AND GREEN CHEMISTRY

Some readers will be disappointed that a particular specialization in process chemistry does not receive more attention. The presentation is weighted based solely on how many of the patents and publications deal with that specialization. For example, a chiral alcohol intermediate in the Singulair® discussion can be produced by a microbial reduction.

> There are five options for the asymmetric reduction: microbial reduction to (*R*)-alcohol **31** with the novel microorganism *Microbacterium* MB5614 (ATCC 55557) and a Mitsunobu inversion,[50,32] microbial reduction to (*S*)-alcohol **32** with *Mucor hiemalis* IFO 5834,[51] reduction to (*S*)-alcohol **32** with borane–THF catalyzed by an oxazaborolidine,[32] reduction to (*S*)-alcohol **32** with diisopinocampheylchloroborane,[43] and ruthenium-catalyzed transfer hydrogenation to produce (*S*)-alcohol **32**.[52] Since the microbial reduction patents provide only milligram-scale procedures and are more than 10 years old, we will focus on the chemical methods.

While the process chemist is not an expert in green chemistry, the process chemist plays a pivotal role in the *implementation* of green chemistry on a plant scale. The terms *green or greener* may be used to denote a process that is superior in its qualitative or quantitative adherence to one or more of the *Twelve Principles of Green Chemistry*.[3]

1.5 IMPACT ON PROCESS CHEMISTRY IN THE FUTURE

Rethinking the step-by-step *manufacturing process* is the overriding theme of this book. A secondary objective of this book is to increase awareness about the *process by which we transition from one supplier to multiple generic suppliers*. A long-standing interest in this transition dates back to the 1980's second-generation process research and development for (*S*)-naproxen, now sold as Aleve®.[4] After reading this book, it will be clear that there may be an incentive to regress to inferior process technology and that the regression is often accompanied by an increase in the environmental impact of manufacturing the drug. This regression is the inevitable consequence of the normal progression of patent protection for a new drug: the patents for the drug itself and the medicinal chemistry route(s) to the drug are followed, often over the course of many years, by a series of process patents from the manufacturing group. These process patents protect key steps in one or more finely honed manufacturing processes for many years beyond expiration of the drug patent. Unless groundbreaking new and directly applicable synthetic methodology is discovered in the 10 years after the drug manufacturing process was first put online, new manufacturing processes may offer little that is new and improved. Process regression is science in reverse, a step back for a society that celebrates and rewards innovation.

1.6 AUDIENCE

Synthetic chemists interested in manufacturing these top-selling drugs are the primary audience for this book. Another audience is graduate students with a specialization in organic synthesis. In many university interview trips in search of the next generation of process chemists, it became clear that most graduate students have no idea what a process chemist does. With instructor-added emphasis on synthetic strategy and control, this book could provide the core information for an interactive one-semester graduate course in process chemistry. Where is the academic value of learning process chemistry? Process research is mechanism based, it requires an in-depth analysis and understanding of reaction kinetics and thermodynamics, and it pushes the limits of established synthetic technology. Process research generates unexpected results, results considered improbable during the project planning phase, and results that are often the basis of valuable process patents.

Another intended audience for this book is process chemists always in search of *methods proven on scale-up*. Looking for a method for nitrile reduction to a primary amine? What better place to look than in the chapter on Effexor XR®. Methods are compared and contrasted for creating a chiral secondary alcohol from a ketone

(Singulair®), oxidation of a sulfide to sulfoxide (Prevacid®), and introducing an amino group using an ammonia surrogate (salmeterol of Advair Diskus®).

Discovery chemists seeking a strategy to protect their investment in a new drug might review the strategies generic manufacturers used to develop noninfringing processes. Generic drug manufacturers eager to design and implement new manufacturing processes can map out the company-specific patent strategies used to protect new drugs. The environmental chemist will find useful information on the environmental impact of drug manufacturing for these specific targets and for small-molecule drugs in general. Finally, the consumer activist will find useful information on the cost to produce these blockbuster drugs.

ACKNOWLEDGMENTS

Thanks to Chemical Abstracts® for a grant of 115 tasks/1 year used for the structure searches. Journal articles were obtained through the interlibrary loan (ILL) program. Thanks to the ILL program coordinator, Sandra Richmond, at the Louisville Public Library for her time and support. Current and past marketplace information for each target was developed working in collaboration with Karen Ingish, reference librarian at the Louisville Public Library. A special thanks to Karen for her enthusiasm and her invaluable contribution. Thanks to Dr. Dave Johnston and Dr. Neal Anderson for their sage advice and support for this project. Finally, Rosemarie and Jack, my home team, there are no words of thanks I can offer to tell you how much I appreciate all that you did. This book is dedicated to you, Jack. No man could ask for a finer son.

At the beginning of this project, it was clear that this would be a journey of a thousand miles. You will be gratified with expectations met in some cases and surprised by unexpected selectivity in others. You will delight in the victory of efficiency of some manufacturing processes and be left dissatisfied with the state of affairs of others.

> A journey of a thousand miles begins with a single step.
>
> Lao-tsu (604–531 B.C.)

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2

ACTOS® (PIOGLITAZONE HYDROCHLORIDE)

2.1 ACTOS® IN THE DIABETES MARKET

Pioglitazone hydrochloride (Actos®) and rosiglitazone maleate (Avandia®) are two thiazolidinedione (TZD) drugs used to treat patients with type II diabetes. Both are also marketed in combination with metformin or glimepiride, pioglitazone as Actoplus Met® and Duetact® and rosiglitazone as Avandamet® and Avandaryl®. Pioglitazone and rosiglitazone are agonists of peroxisome proliferation-activated receptors (PPAR), specifically PPAR-γ (Figure 2.1). These agonists improve glucose utilization and reduce glucose production in the liver by increasing insulin sensitivity in adipose and muscle tissue.

The statistics for the global diabetes epidemic are compelling. The global prevalence of diabetes for all age groups is estimated to rise from 2.8% (171 million people) in 2000 to 4.4% (366 million people) by the year 2030.[1] Another analysis estimated that 23.6 million people had diabetes in the United States in 2007.[2] The biggest increase in diabetes prevalence will be in the adult population and the vast majority (90–95%) of the adults diagnosed with diabetes are diagnosed as type II.

Global 2006 sales figures for pioglitazone were $2.8 billion. Pioglitazone was Takeda's best seller and accounted for 25% of their revenues. Global 2006 sales figures for rosiglitazone were $3.3 billion. Rosiglitazone was GSK's third best-selling drug that year. The U.S. figures for pioglitazone and rosiglitazone for 2006 were $1.9 billion and $1.7 billion, respectively, each up 20% from the 2005 figures. Both drugs had a promising future. But a lot has happened since then. Two meta-analyses were published back to back in the *Journal of the American Medical Association* on September 12, 2007. One reported that rosiglitazone increased the risk of heart attack by 42% while the other found that pioglitazone actually lowered the combined risks of heart attack, stroke, and death by 18%.[3,4] This was the first time a diabetes drug has been shown to reduce the risk of heart attacks. The U.S. figures for pioglitazone and rosiglitazone for 2007 showed a quick response to these meta-analyses: pioglitazone sales increased to $2.2 billion and rosiglitazone sales dropped to $1.1 billion.[5] Of course, this is just a snapshot in time and more studies are underway but, in 2008, pioglitazone was a very important target.

2.2 SYNTHESIS LEFT TO RIGHT

2.2.1 2-(5-Ethylpyridin-2-yl)ethanol (2)

Pioglitazone (**1**) has three distinct regions: the 2,5-dialkylpyridine, the *para*-substituted aryl ether, and the thiazolidine-2,4-dione (Figure 2.2). There is a chiral center at the 5-position of the thiazolidine-2,4-dione but this center is easily epimerized, so the synthetic challenge is to produce the racemate. Disconnection near the center, on either side of the ether oxygen, leads back to 2-(5-ethylpyridin-2-yl)ethanol (**2**). While many simple mono-, di-, and trimethylpyridines (picolines, lutidines, and collidines), and some ethylpyridines are obtained from coal tar, 2-(5-ethylpyridin-2-yl) ethanol (**2**) is not directly obtained from a natural source. It is a specialty chemical. A *Chemical Abstracts* structure search [5223-06-3] reveals less than 100 references, with

Pharmaceutical Process Chemistry for Synthesis: Rethinking the Routes to Scale-Up, By Peter J. Harrington

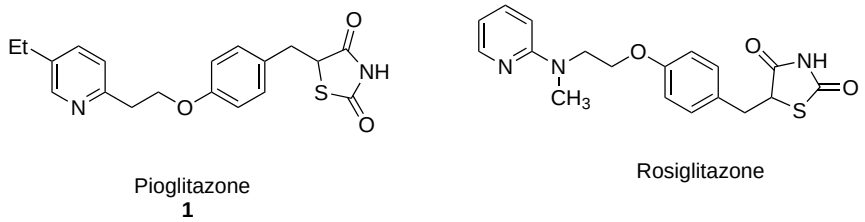


FIGURE 2.1 Pioglitazone (**1**) and rosiglitazone.

the majority directly associated with pioglitazone process chemistry.

Since the alcohol **2** is a key component of pioglitazone, it is critically important to know who produces it, how and on what scale they produce it, and what is it produced from. The same questions should then be asked and answered for the material(s) used to produce **2**. At least two suppliers for **2** should be online. Taking this a step further, it would be preferable to have suppliers who have a long track record for reliability, perhaps suppliers in several continents. A search of *Chemical Abstracts* and a Google search "suppliers for 5223-06-3" provide lists of suppliers. The goal is not to identify the lowest price or the specific suppliers at this point but to make a case for the material as "readily available and inexpensive."

How is 2-(5-ethylpyridin-2-yl)ethanol (**2**) produced? Does the process involve operations that may raise safety concerns? Does it require special processing equipment? Conditions for the condensation of 5-ethyl-2-methylpyridine (**3**) with formaldehyde to produce 2-(5-ethylpyridin-2-yl) ethanol (**2**) were first described more than 60 years ago (**3**, trioxane, potassium persulfate, and *tert*-butylcatechol in ethanol at 220°C).[6] Perhaps it is produced today by an amine-catalyzed condensation of 5-ethyl-2-methylpyridine (**3**) with paraformaldehyde in water at 170°C.[7] The high temperatures and pressures and handling of aqueous formaldehyde waste (from paraformaldehyde or trioxane) are cost drivers.

High temperatures and pressures and aqueous formaldehyde waste are also associated with the manufacture of 5-ethyl-2-methylpyridine (**3**) (also known as "aldehyde-collidine") from paraformaldehyde, ammonium hydroxide, and ammonium acetate.[8] This ultimate starting material is readily available and amazingly inexpensive.[9] The similarities in materials and process conditions suggest that significant cost savings might be realized by producing both **2** and **3** at the same manufacturing site.

2.2.2 Construction of the Ether C–O Bond

There are two well-established approaches to construction of the ether C–O bond: S_NAr displacement by alkoxide of a good leaving group on an aromatic activated by an electron-withdrawing group and Williamson ether synthesis using a primary alkyl toluenesulfonate or methanesulfonate and a phenoxide (Scheme 2.1).

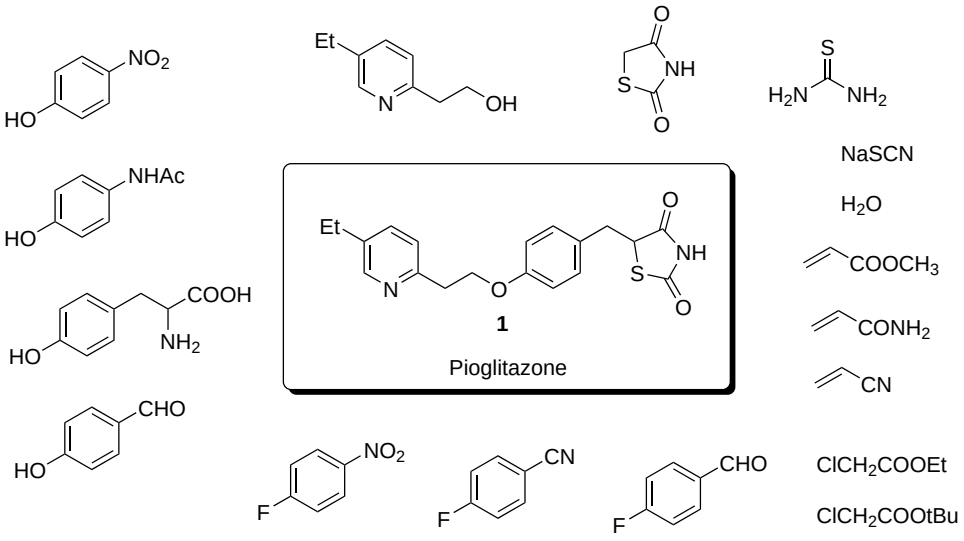
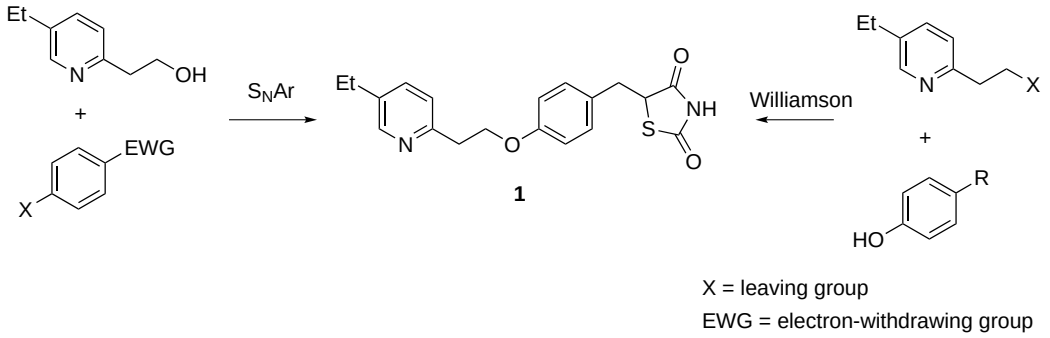


FIGURE 2.2 Pioglitazone building blocks.



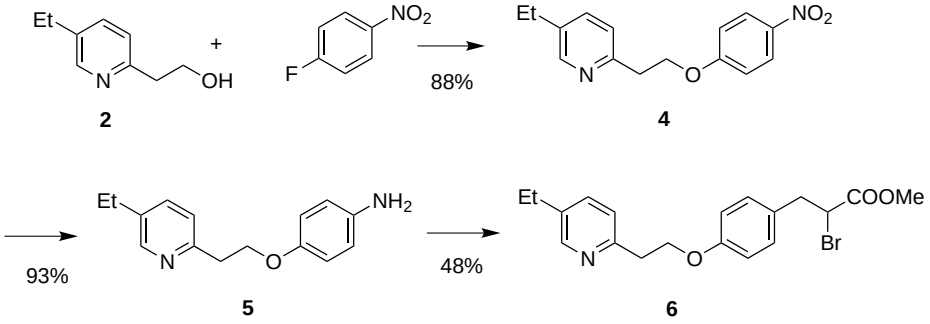
SCHEME 2.1 Options for construction of an ether C–O bond in pioglitazone (**1**).

2.2.2.1 S_NAr Using 4-Fluoronitrobenzene The S_NAr approach on a nitro-activated aromatic is well documented. Reaction of 2-(5-ethylpyridin-2-yl)ethanol (**2**) with 4-fluoronitrobenzene and sodium hydride in DMF at 25°C affords 5-ethyl-2-(2-(4-nitrophenoxy)ethyl)pyridine (**4**) (63%).[10,11] Other base and solvent combinations (powdered NaOH in DMSO, KOH in dichloromethane, NaOH in DMSO–water, and simply NaOH in water) eliminate the hazard associated with handling and quenching sodium hydride and avoid the formation of 4-dimethylaminonitrobenzene from DMF.[12–14] For example, the reaction of 2-(5-ethylpyridin-2-yl)ethanol (**2**) with 4-fluoronitrobenzene (1.06 equivalents) and aqueous sodium hydroxide (2.7 equivalents) in water at 30–35°C affords 5-ethyl-2-(2-(4-nitrophenoxy)ethyl)pyridine (**4**) (88%).[14]

This S_NAr methodology is coupled with a Meerwein arylation via nitro group reduction and diazonium salt formation.[10,11] Reduction using 10% Pd on carbon (50% water wet) in methanol at 25°C and 1 atm hydrogen affords 4-(2-(5-ethylpyridin-2-yl)ethoxy)aniline (**5**), which requires no purification (93%). The nitro group is also reduced using Raney nickel and hydrogen or Raney nickel and hydrazine to eliminate the fire hazard associated with handling of the palladium catalyst after reduction. Aniline **5** is a low-melting solid that turns dark over time.[14]

The Meerwein arylation, first described in 1939, is the copper-catalyzed replacement of a diazonio group of an arenediazonium salt by an alkene or alkyne.[15–17] The Meerwein arylation is suggested to proceed via a free radical chain mechanism. The addition of the aryl radical to an alkene affords the more stable alkyl radical. This radical is then converted to an alkene by hydrogen atom abstraction or to a 1-aryl-2-haloalkane by halogen abstraction from copper (II) halide. Meerwein arylations of acrylic acids, acrylate esters, acrylonitriles, acrylamides, vinyl ketones, vinyl halides, and styrenes are all known with yields typically in the 40–70% range.

What can be described as typical Meerwein arylation conditions are used in one pioglitazone process. The arenediazonium salt is prepared by addition of sodium nitrite to the aniline in methanol–acetone–aqueous hydrobromic acid at <5°C. Methyl acrylate (5.9 equivalents) is added. Cuprous oxide is then added in small portions at 38°C. Aging the reaction at 38°C until complete, neutralization, concentration at reduced pressure, and an extractive workup affords methyl 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoate (**6**) as an oil (86% crude).[10,11] A similar procedure suggests that the yield after correction for purity could be much lower (47–48%) (Scheme 2.2).[14]



SCHEME 2.2 Pioglitazone intermediate methyl 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoate (**6**) from 1-fluoro-4-nitrobenzene via S_NAr and Meerwein arylation.

This procedure raises many scale-up concerns. The diazonium salt solution must be prepared and held at 5°C. If cooling is lost during or after the diazonium salt preparation due to an unplanned power outage, the diazonium salt will decompose. Solid copper(I) oxide is charged in small portions, potentially exposing the operators to the corrosive reaction vapors during the vigorous nitrogen gas evolution that accompanies each charge. Careful planning could mitigate these concerns: have a backup power supply ready and charge the copper catalyst as an aqueous suspension. There are still other concerns. Malodorous methyl acrylate is both toxic and irritating. There will be copper in the aqueous waste stream. The low purity of the crude oil **6** suggests that chromatography or at least a carbon treatment will be necessary before moving on to construction of the thiazolidinedione.

There is one phrase in the above procedure that at first appears innocuous: *concentrate at reduced pressure*. We concentrate at reduced pressure on a rotary evaporator in the lab every day. We have the option of using a water-cooled coil condenser or cold finger condenser. We have a trap in the vacuum line to collect any volatiles not condensed in the rotary evaporator. We have a pump that can be set to deliver vacuum down as low as 5 mmHg, allowing us to evaporate at or near ambient temperature. All the wetted surfaces are glass or Teflon. The condensate is transferred to a waste can for appropriate disposal. The entire process from setup to waste disposal can be completed in less than an hour. The situation changes dramatically when you consider scale-up of a concentration at reduced pressure. First, there will likely be no option for chilling the condenser below −10 to −20°C. The condensate will be sent to a second reactor cooled to −10°C. The trap in the vacuum line, if there is one, will likely be a third reactor also cooled to −10°C. The vacuum pump will maintain, at best, 50–100 mmHg. We should certainly know the composition of the condensate and have a plan in place to recycle the expensive components. The scaled-up concentration at reduced pressure may take anywhere from 2 to12 h.

The composition of the condensate in the Meerwein arylation workup is a witch's brew of hydrobromic acid, methanol, acetone, water, methyl acrylate, and the by-product bromoacetone. Bromoacetone is a potent lachrymator and is a "show-stopper" for this process.[18] While an alternative acetone-free procedure starting with the isolated arenediazonium tetrafluoroborate[19] could eliminate this "show-stopper," the combined weight of all these concerns would certainly motivate a process research group to find an alternative route.

2.2.2.2 Williamson Ether Synthesis

Preparation of a Sulfonate Ester A Williamson ether synthesis will provide many more options for introducing and elaborating a *para*-substituent. The Williamson ether synthesis invariably begins with the conversion of the hydroxyl group of 2-(5-ethylpyridin-2-yl)ethanol (**2**) to a halide, methanesulfonate, or toluenesulfonate leaving group. These intermediates will not be "campaignable." They possess both a leaving group and a basic pyridine ring nitrogen and will be prone to elimination. The chloride, bromide, or iodide could be prepared by many well-established methods using, for example, thionyl chloride, phosphorus oxychloride, phosphorus tribromide, or triphenylphosphine–iodine. The methanesulfonate or toluenesulfonate esters are the preferred intermediates, since they can be prepared at or below ambient temperature. For example, the methanesulfonate ester **7** is prepared by slow addition of methanesulfonyl chloride to solution of 2-(5-ethylpyridin-2-yl)ethanol (**2**) and triethylamine in dichloromethane or toluene at 0–10°C. The reaction is complete in 1–4 h at 25°C. A water wash to separate triethylamine hydrochloride follows. At this point, the lab-scale and large-scale procedures diverge. In the lab, the solution is dried over sodium sulfate and concentrated at ambient temperature and reduced pressure. On large scale, it would be desirable to use the water-wet solution in toluene in the Williamson ether synthesis. A nearly quantitative yield of the methanesulfonate **7** is expected both in the lab and on large scale.

How dry does the toluene solution of the methanesulfonate **7** have to be after the water wash? Assume that the toluene solution would at least be saturated with water (0.05 wt%) after a perfect layer separation. And a near-perfect layer separation is far easier to achieve when draining a separatory funnel in the lab than when draining a large reactor using a sight glass. What is the best answer we can hope for? The answer is that we do not need to do anything to remove the water, as low levels of water are acceptable in the next step. Is this the case? Isolate some methanesulfonate **7** by a standard lab workup procedure: dry the toluene solution over sodium sulfate and concentrate it at 25°C and reduced pressure. Prepare a toluene stock solution of methanesulfonate **7** (store cold) and use this solution to screen the Williamson ether synthesis with different concentrations of water present. Even after the screen confirms that water is tolerated in the next step, it would be wise to be present during the phase split in the pilot plant to see just how easy it is to detect the interface as it enters the sight glass. The phase split will be easier to see (more precise and reproducible) if there is little or no interface emulsion, if the layers are of different colors, and/or if there is a trace of interface "rag."

If water cannot be tolerated in the next step, the options are quite limited. Removing the water by azeotropic distillation at atmospheric pressure will likely cause

decomposition of thermally labile methanesulfonate **7**. Removing the water by azeotropic distillation at a reduced temperature and pressure is far less efficient because the vapor phase contains less water.[20]

There are several examples using dichloromethane as solvent in lab preparation of the methanesulfonate **7** or toluenesulfonate ester **8**. Since the lab yields are comparable in either solvent, preparation on large scale in dichloromethane offers no advantages over preparation in toluene.[21] Dichloromethane retains more water after a water wash (0.2 wt%) than toluene (0.05 wt%) and an azeotropic removal of water is less efficient (1.5 wt% H_2O removed by azeotrope versus 13.5 wt% for toluene). Of course, both these points are moot if the wet dichloromethane solution of **7** is carried into the Williamson ether synthesis. The decision point then comes after the Williamson ether synthesis. Whether distilling at atmospheric or at reduced pressure, the recovery of dichloromethane (bp 40°C) will be less efficient than the recovery of toluene (bp 111°C). Keep in mind the high odor threshold (205–307 ppm) and the low permissible exposure limit (25 ppm time-weighted average (TWA) with 12.5 ppm 8-hour TWA action level) for dichloromethane when considering the amount of dichloromethane that will not be recovered.

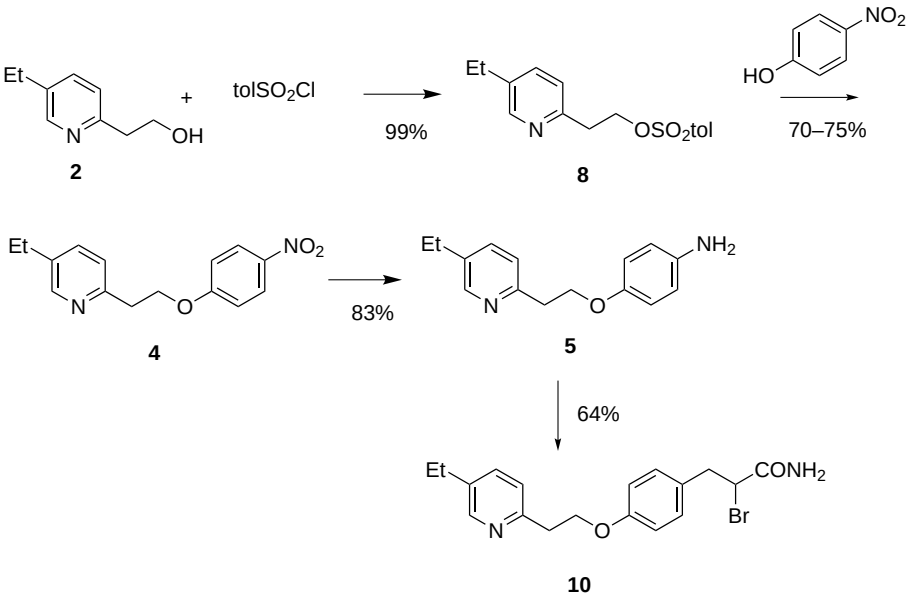
4-Nitrophenol The first of many ethers accessed from **2** by Williamson ether synthesis is 5-ethyl-2-(2-(4-nitrophenoxy) ethyl)pyridine (**4**).[22] The sodium salt of 4-nitrophenol is first prepared using sodium hydroxide in methanol–toluene. After removal of the solvent by distillation and drying at 100–110°C under vacuum, the isolated sodium salt is reacted with isolated toluenesulfonate **8** in DMSO at 40°C. The procedure is not detailed enough to say the conditions are anhydrous. The yield is 70–75% from 2-(5-ethylpyridin-2-yl)ethanol (**2**). The same mixture of the salt of 4-nitrophenol and the toluenesulfonate **8** might also be produced under Williamson ether synthesis conditions by a toluenesulfonate exchange. The reaction of 4-nitrophenyl toluenesulfonate (**9**) with 2-(5-ethylpyridin-2-yl)ethanol (**2**) also affords 5-ethyl-2-(2-(4-nitrophenoxy)ethyl)pyridine (**4**).[23]

Reduction of the nitro group is accomplished with sodium sulfide in methanol–water (83%). Again Meerwein arylation conditions are used, this time with acrylamide in place of methyl acrylate. The arenediazonium salt is prepared by addition of sodium nitrite to the aniline **5** in methanol–acetone–aqueous hydrobromic acid at <5°C. Acrylamide (5.6 equivalents) is added. Freshly prepared cuprous bromide catalyst is then added at 30–35°C. Aging the reaction at 30–35°C until complete, concentration, aqueous bicarbonate–hexanes digestion, isolation, and purity upgrade by water and hexanes resuspension affords 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanamide (**10**) as an oil in 64% crude yield (Scheme 2.3).[22]

The acrylamide process highlights a logic trap:

> Acrylamide is *not as bad as* ethyl acrylate.
>
> Therefore, the acrylamide process is better than the ethyl acrylate process.

But, why is acrylamide *not as bad as* ethyl acrylate? The response would be: because ethyl acrylate is a volatile liquid (bp 99.4°C at 760 mmHg) with a sharp, acrid odor and



SCHEME 2.3 Pioglitazone intermediate 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanamide (**10**) from 4-nitrophenol via Williamson ether synthesis and Meerwein arylation.

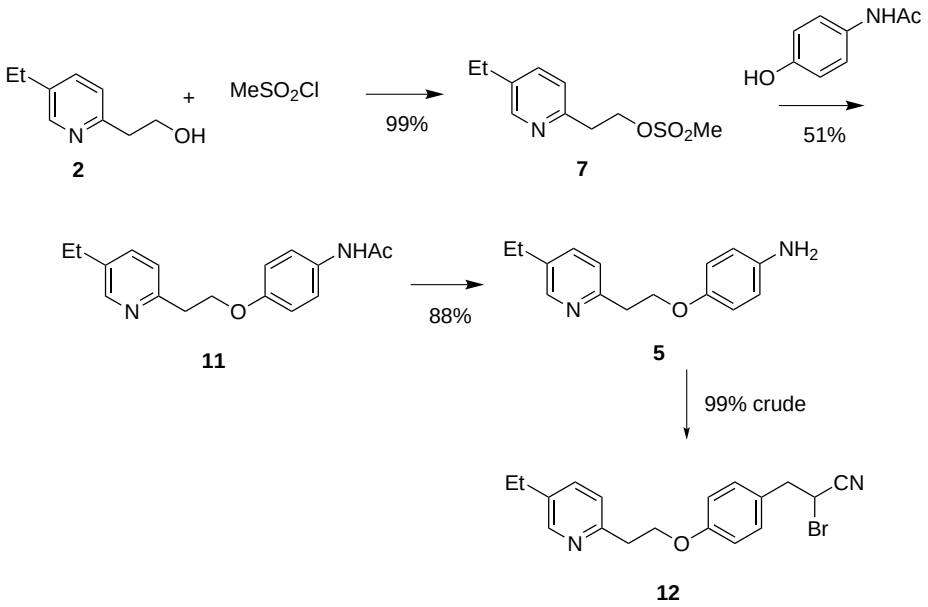
acrylamide is a solid. This response focuses only on how the reagents' physical properties complicate the concentration after the Meerwein arylation. From the perspective of charging the vessel before the Meerwein arylation, there is less potential for operator exposure while charging the liquid ethyl acrylate than when charging the solid acrylamide. From an environmental health and safety perspective, the permissible exposure limit (PEL) for ethyl acrylate is 100 mg/m^3 as an 8-hour TWA while the PEL for acrylamide is just 0.3 mg/m^3. The process operations and the safety data sheets could be reviewed line by line and the debate continued but the bottom line is this: *ethyl acrylate and acrylamide are both unacceptable*.

Acetaminophen 4-(2-(5-Ethylpyridin-2-yl)ethoxy)aniline (**5**) can be produced from acetaminophen. Williamson ether synthesis of the isolated methanesulfonate **7** with the potassium salt of acetaminophen[24] in ethanol at 60°C affords the crystalline *N*-(4-(2-(5-ethylpyridin-2-yl)ethoxy) phenyl)acetamide (**11**) (51%).[25] Comparable yields are achieved with acetaminophen, benzyltributylammonium chloride, and potassium carbonate in dichloromethane–water at 25°C. The acetanilide **11** can be converted to the aniline **5** by acid hydrolysis (HCl in ethanol at reflux) (88%) or basic hydrolysis (KOH in ethanol at reflux) (80%). A toluenesulfonate exchange approach is possible in this context as well. 4-Aminophenol is N-protected and converted to the toluenesulfonate. The reaction of this toluenesulfonate with 2-(5-ethylpyridin-2-yl)ethanol (**2**) and sodium hydride in DMF followed by N-deprotection (KOH in THF) also affords 4-(2-(5-ethylpyridin-2-yl) ethoxy)aniline (**5**).[26]

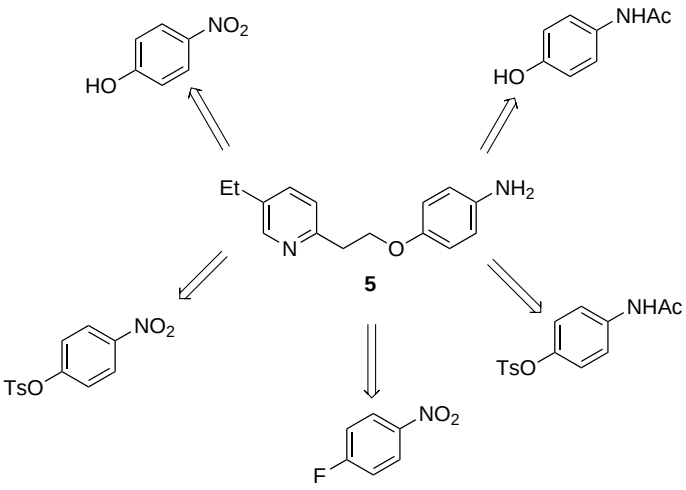
It is preferable to hydrolyze the acetamide with hydrobromic acid and carry the aniline hydrobromide salt solution directly into the next step. Again, typical Meerwein arylation conditions are used, this time with acrylonitrile. The arenediazonium salt is prepared by addition of sodium nitrite to the aniline **5** in methanol–acetone–aqueous hydrobromic acid at <5°C. Acrylonitrile (4.8 equivalents) (recall the *not as bad as* logic trap) is added. The cuprous oxide catalyst is then added in small portions at 38°C. Aging the reaction at 38°C, concentration at reduced pressure, neutralization, and an extractive workup affords 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanenitrile (**12**) as an oil in a remarkable 99% crude yield (Scheme 2.4). Since this oil has seen neither chromatography nor a carbon treatment, purity is difficult to assess.

The Williamson ether syntheses with acetaminophen (50–55%) and 4-nitrophenol (70–75%) were not run under identical conditions, nor were they run under conditions suitable for scale-up. While we cannot make an apples-to-apples comparison, these two approaches are, at best, comparable. Both the amide hydrolysis and the nitro group reduction are high yielding and do not require an isolation of 4-(2-(5-ethylpyridin-2-yl)ethoxy)aniline (**5**).

Taking a still broader perspective, there are five routes to 4-(2-(5-ethylpyridin-2-yl)ethoxy)aniline (**5**): S_NAr with 1-fluoro-4-nitrobenzene and Williamson ether synthesis with 4-nitrophenol or acetaminophen and their toluenesulfonate exchange cousins (Scheme 2.5). How do you choose which is



SCHEME 2.4 Pioglitazone intermediate 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanenitrile (**12**) from acetaminophen via Williamson ether synthesis and Meerwein arylation.



SCHEME 2.5 Routes to pioglitazone intermediate 4-(2-(5-ethylpyridin-2-yl)ethoxy)aniline (**5**).

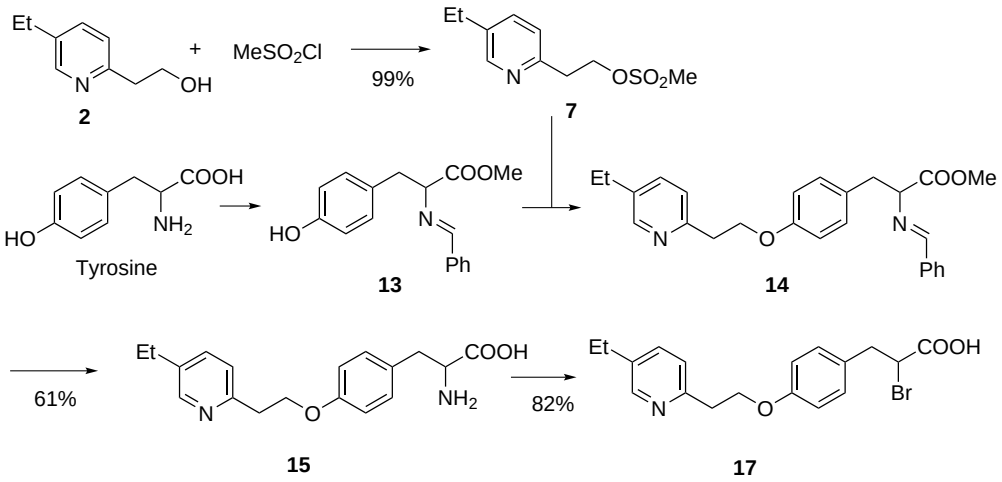
best? The question is not relevant to the final objective. They all lead to the Meerwein arylation and its associated negatives: excess methyl acrylate (acrylamide, acrylonitrile) in the distillate and aqueous waste, bromoacetone in the distillate and aqueous waste, a necessary carbon treatment or chromatography of the product, and a low overall yield.

Tyrosine An efficient Williamson ether synthesis with the hydroxyl group of tyrosine[27] starts with protection of the amino acid carboxyl and amino groups as the methyl ester and the benzaldehyde imine, respectively, to produce **13**. Ether formation is then accomplished using a dry toluene solution of the methanesulfonate **7**, potassium carbonate, and tetrabutylammonium bromide in toluene at 70°C. After deprotection of the imine and ester, 2-amino-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoic acid (**15**) is isolated in 63% yield based on tyrosine and 61% yield based on 2-(5-ethylpyridin-2-yl)ethanol (**2**). The yields are lower using other amino protecting groups (*t*-BuOC(O), 24%; BnOC(O), 21%; CH_3CO, 12%).

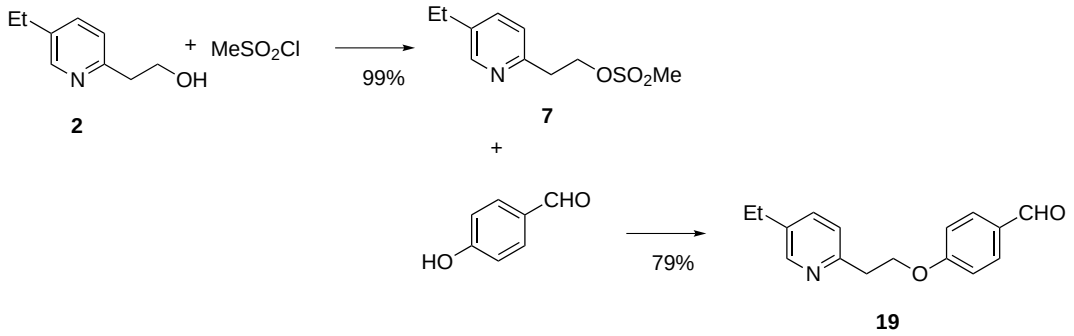
The Williamson ether synthesis can also be accomplished using *N*-acetyltyrosine isopropyl ester (**16**). The ether formation is accomplished with a dry toluene solution of the methanesulfonate **7** and *N*,*N*-diisopropylethylamine (Hunig's base) in isopropanol at reflux. After hydrolyzing the ester and amide, 2-amino-3-(4-(2-(5-ethylpyridin-2-yl) ethoxy)phenyl)propanoic acid (**15**) is isolated in 49% yield based on 2-(5-ethylpyridin-2-yl)ethanol (**2**). As is typically the case, the phenol **16** is used in excess (1.22 equivalents).[28]

The amino group is next converted to the bromide **17** via the diazonium salt. No yield is reported for this conversion. The yield from 2-amino-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoic acid (**15**) to pioglitazone (**1**) is 41%. The yield from ethyl 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoic acid (**18**) to pioglitazone (**1**) is 50%.[14] Assuming a 50% yield from 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoic acid (**17**) to pioglitazone (**1**), the yield for the amine-to-bromide transformation is 82% (Scheme 2.6). Thus, the yield and stability issues associated with the diazonium salt step in this process are comparable to the yield and stability issues associated with the earlier Meerwein arylation. Disadvantages of this route are the high cost of tyrosine,[29] the long linear sequence including two protection and deprotection steps, the challenges of scaling up the diazonium salt chemistry, and the low overall yield.

4-Hydroxybenzaldehyde The Williamson ether synthesis with 4-hydroxybenzaldehyde has been extensively studied



SCHEME 2.6 Pioglitazone intermediate 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoic acid (**17**) from tyrosine via Williamson ether synthesis.



SCHEME 2.7 Pioglitazone intermediate 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**) via Williamson ether synthesis.

and conditions ranging from phase transfer catalysis in water–organic solvent (1:1) to carefully anhydrous all afford the desired 4-(2-(5-ethylpyridin-2-yl)ethoxy) benzaldehyde (**19**). The reaction of the toluenesulfonate **8** with 4-hydroxybenzaldehyde can be run under phase transfer conditions using sodium hydroxide and benzyltributylammonium chloride in dichloromethane–water at 25°C.[30] The toluenesulfonate **8** is preferred in this case because it can be produced under the same phase transfer conditions. Thus, both the preparation of toluenesufonate **8** and the Williamson ether synthesis can be run in one pot. Unfortunately, the lab results for this two-phase, one-pot process are difficult to reproduce on scale. The reaction of the methanesulfonate **7** with 4-hydroxybenzaldehyde in toluene under phase transfer conditions using potassium carbonate and PEG 200 is very efficient at 80°C.[31]

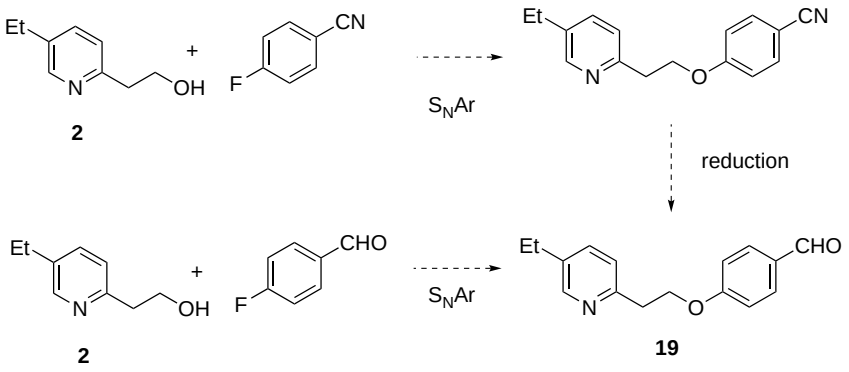
When the Williamson ether synthesis is not run under phase transfer conditions, hydrophilic solvents such as ethanol and isopropanol are preferred. The phenoxide is generated using potassium hydroxide,[32] potassium *tert*-butoxide,[33] or potassium carbonate. In what are perhaps the best procedures for scale-up, reaction of the methanesulfonate **7** with 4-hydroxybenzaldehyde and potassium carbonate in ethanol–toluene or isopropanol–toluene–water at 77–80°C affords 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**).[34,35] Lower yields are reported using other solvents (toluene, 1,2-dichloroethane, THF, and acetonitrile). The crude aldehyde **19** produced using any of these protocols is typically of unacceptable quality, due to the competitive elimination of the sulfonate ester to 5-ethyl-2-vinylpyridine (**20**) and polymerization of the vinylpyridine. The crude 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**) generated from the toluenesulfonate **8** under phase transfer conditions is upgraded by silica gel chromatography (62% yield from **2**).[30] The crude 4-(2-(5-ethylpyridin-2-yl) ethoxy)benzaldehyde (**19**) generated from the methanesulfonate **7** is upgraded by carbon treatment[34] or by salt formation with hydrochloric, trifluoroacetic, maleic, or oxalic acid.[35] The yield of the free base from **2** after carbon treatment is 79% (79% purity by HPLC assay) and the yield of oxalate salt from **2** is 74% (99.7% purity by HPLC assay) (Scheme 2.7).

An exchange of the methanesulfonate ester to the phenol to give 4-formylphenyl methanesulfonate may compete with the desired methanesulfonate ester displacement. Addition of sodium or potassium iodide minimizes this transfer by converting the methanesulfonate to the iodide, which is then displaced. The reaction of isolated methanesulfonate **7** with 4-hydroxybenzaldehyde, potassium hydroxide, and 6.3 mol % potassium iodide in isopropanol at reflux affords 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**) (74%). Thus, short-circuiting the transfer does not increase the yield.[36]

2.2.2.3 S_NAr Using 4-Fluorobenzonitrile and 4-Fluorobenzaldehyde Does a nitrile or aldehyde activate a halogen at the 4-position of an aromatic toward S_NAr? If so, 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**) could be produced in a single step from 2-(5-ethylpyridin-2-yl)ethanol (**2**) (Scheme 2.8). This would lead to a more robust process by avoiding the methanesulfonate intermediate **7** and its propensity to eliminate.

A nitrile does activate the fluorine of 4-fluorobenzonitrile toward S_NAr by alkoxide. The reaction of 4-fluorobenzonitrile with 2-(6-methylpyridin-2-yl)ethanol (**21**) and sodium hydride in THF at 25°C affords 4-(2-(6-methylpyridin-2-yl) ethoxy)benzonitrile (**22**) (50%). Nitrile **22** is reduced using Raney nickel in refluxing 75% formic acid to give 4-(2-(6-methylpyridin-2-yl)ethoxy)benzaldehyde (**23**) (64%).[30,37] The reaction of 4-fluorobenzonitrile with 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol (**24**) and sodium hydride in THF at 25°C is even more efficient (91%).[38] The same conditions are used for nitrile reduction (65%). So, the fluoride is activated and the nitrile can be reduced. But, is 4-fluorobenzonitrile readily available and inexpensive?[39]

An aldehyde also activates fluorine at the 4-position of an aromatic ring toward S_NAr by alkoxide. The reaction conditions are usually more vigorous than those for the reaction with the nitrile. The reaction of 4-fluorobenzaldehyde with 2-(methyl(pyridine-2-yl)amino)ethanol (**25**) and sodium



SCHEME 2.8 Proposed routes to pioglitazone intermediate 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**) from 4-fluorobenzonitrile and 4-fluorobenzaldehyde.

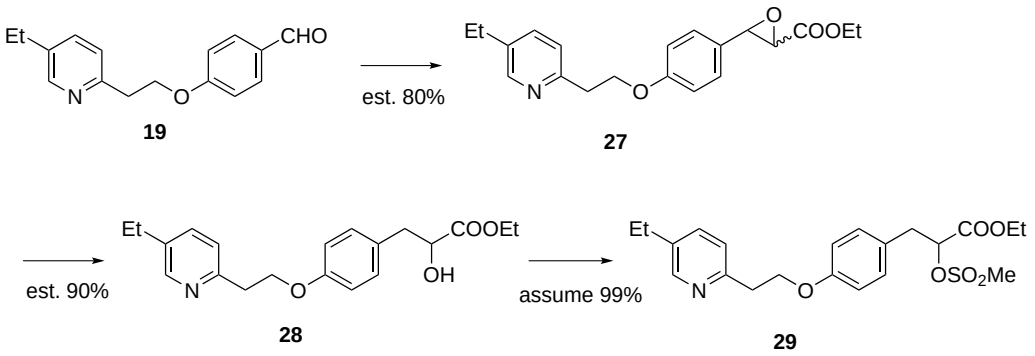
hydride in DMF at 80°C affords 4-(2-(methyl(pyridin-2-yl) amino)ethoxy)benzaldehyde (**26**). The yield is not provided. The S_NAr with this and many other *N*-methyl-*N*-heteroaryl aminoethanols can also be carried out using potassium carbonate as the base in DMSO at 100–120°C.[40] But is 4-fluorobenzaldehyde readily available and inexpensive?[41] 4-Fluorobenzaldehyde is certainly less expensive than 4-fluorobenzonitrile.

2.2.3 4-(2-(5-Ethylpyridin-2-yl)ethoxy)benzaldehyde (19) to Pioglitazone (1)

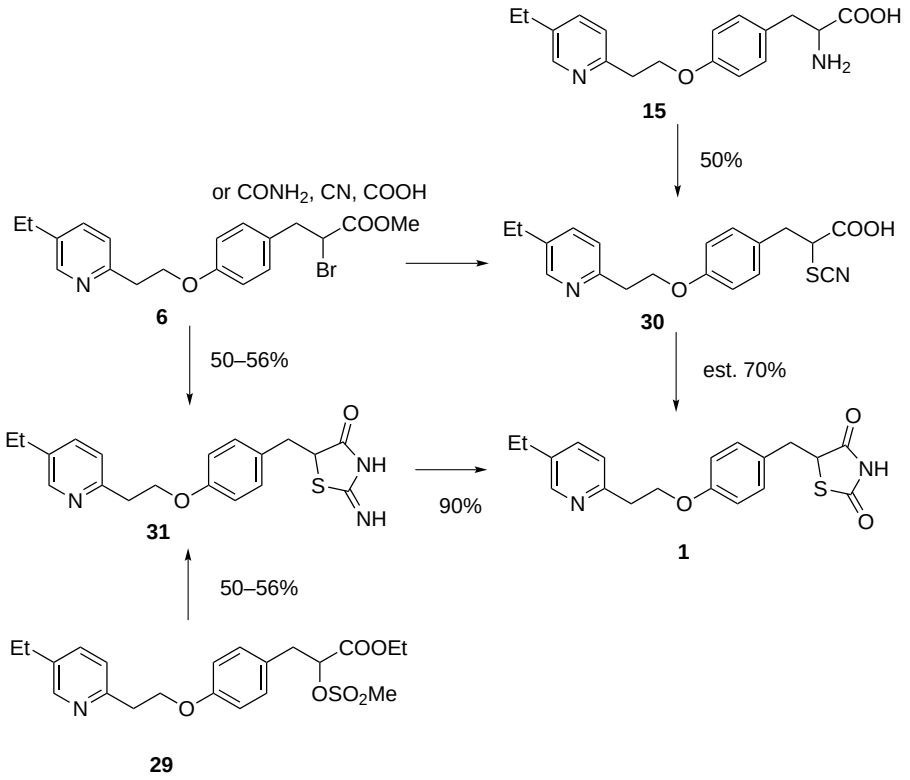
2.2.3.1 Darzens Condensation and Tcherniac's Synthesis

There are several options for elaborating the thiazolidinedione-containing side chain from the aldehyde **19**. A Darzens condensation with ethyl chloroacetate and sodium ethoxide in ethanol at 25°C yields the *cis*- and *trans*-glycidic esters (**27**).[42] Hydrogenolysis of the mixture using 10% Pd on C in methanol at 25°C and 1 atm hydrogen and methanesulfonylation of the resulting alcohol **28** affords the α-methanesulfonyloxy ester **29** (Scheme 2.9).

There are two methods for converting the α-bromo esters **6** and **18** (acid **17**, amide **10**, or nitrile **12**) and α-methanesulfonyloxy ester **29** to pioglitazone (**1**) (Scheme 2.10). In the first process, bromide displacement with thiocyanate (Tcherniac's synthesis) followed by hydrolysis of the thiocyanate **30** and cyclization affords pioglitazone (**1**) in low yield. The 2-thiocyanatopropanoic acid **30** can also be produced directly from the 2-aminopropanoic acid **15** and lithium thiocyanate by diazotization with isopentylnitrite in THF–acetic acid at 25°C (50%).[28] No yield is provided for the thiocyanate hydrolysis/cyclization to pioglitazone (**1**) but we can anticipate a yield of 70% based on earlier work preparing other 5-(4-oxobenzyl)thiazolidine-2,4-diones.[43] In the second and preferred process, reaction of **6** or **29** with thiourea and sodium acetate (Hantzsch's synthesis) generates a 2-imino-4-thiazolidinone **31** in ethanol or isopropanol at reflux, which is then hydrolyzed with dilute hydrochloric acid. The yield for the 2-imino-4-thiazolidinone formation from the crude α-bromo esters **6** and **18** (acid **17**, amide **10**, or nitrile **12**) is 50–56% and yield for the imine hydrolysis is high (90%).[14,22]



SCHEME 2.9 Pioglitazone intermediate ethyl 3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)-2-methanesulfonyloxy)propanoate (**29**) via Darzens condensation.



SCHEME 2.10 Pioglitazone (**1**) via Hantzsch and Tcherniac methods of thiazolidine-2,4-dione synthesis.

The yield for the 2-imino-4-thiazolidinone formation from the α-methanesulfonyloxy ester **29** in the linear sequence of five steps converting 4-(2-(5-ethylpyridin-2-yl) ethoxy)benzaldehyde (**19**) to pioglitazone (**1**) is not available, since the purities of the crude oils obtained in each step are not reported. The overall yield for the five-step sequence is 33%. Assuming an 80% yield for the Darzens condensation and a 90% yield for the hydrogenolysis, the yield for the imine hydrolysis is 90%.[14,42] Assuming a 99% yield for the methanesulfonylation leaves a 51% yield for the 2-imino-4-thiazolidinone formation. This nicely fits the yield data for the α-bromo esters **6** and **18** (acid **17**, amide **10**, or nitrile **12**). While the Darzens route does circumvent the Meerwein arylation and its issues, this route has a long linear sequence and a low overall yield.

2.2.3.2 Knoevenagel Condensation and Catalytic Reduction

The same conversion of 4-(2-(5-ethylpyridin-2-yl)ethoxy) benzaldehyde (**19**) to pioglitazone (**1**) can also be accomplished in just two steps: Knoevenagel condensation with thiazolidine-2,4-dione and reduction of the double bond. The Knoevenagel condensation partner, thiazolidine-2,4-dione, is commercially available but expensive.[44] The condensation product, 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene) thiazolidine-2,4-dione (**32**), conveniently precipitates as the (*Z*)-isomer when the condensation solvent is methanol or ethanol. The configuration is determined by irradiation of the single isomer to produce an equilibrium mixture, separation of the other isomer by silica gel chromatography, and assignment of the methine proton of each isomer by ^{1}H NMR. The (*Z*)-isomer methine hydrogen is further downfield (δ 7.74 for *Z*-isomer and δ 7.30 for *E*-isomer), suggesting that it is on the same side as the carbonyl group at the 4-position of the thiazolidinedione (Figure 2.3).[37] ChemNMR ^{1}H estimates these methine protons at δ 7.95 for the *Z*-isomer and δ 7.76 for the *E*-isomer.

The condensation of 4-(2-(5-ethylpyridin-2-yl)ethoxy) benzaldehyde (**19**) with thiazolidine-2,4-dione (1.2 equivalents) and pyrrolidine (1.0 equivalent) in methanol at 45°C is very efficient even after multiple precipitations and isolations for purity upgrade (95% yield) (Scheme 2.11).[34] Just one isolation is required to obtain the condensation product using thiazolidine-2,4-dione (2.7 equivalents) and piperidine (0.78 equivalents) in ethanol at reflux (73%, 99.5% pure).[32] 5-(4-(2-(5-Ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) can also be isolated from ethanol as the hydrochloride salt (81%, 99.6% pure by HPLC).[35] One key feature of almost every robust pharmaceutical manufacturing process is a highly reproducible purification of the penultimate intermediate. With these three detailed procedures, this process feature is certainly demonstrated for the Knoevenagel process.

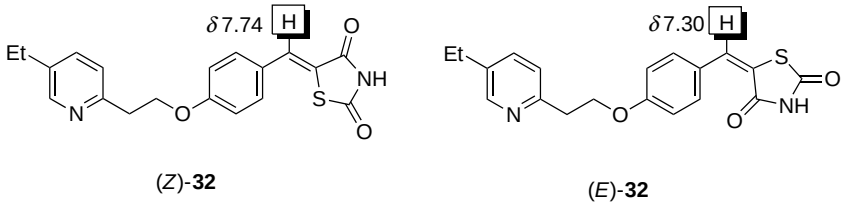
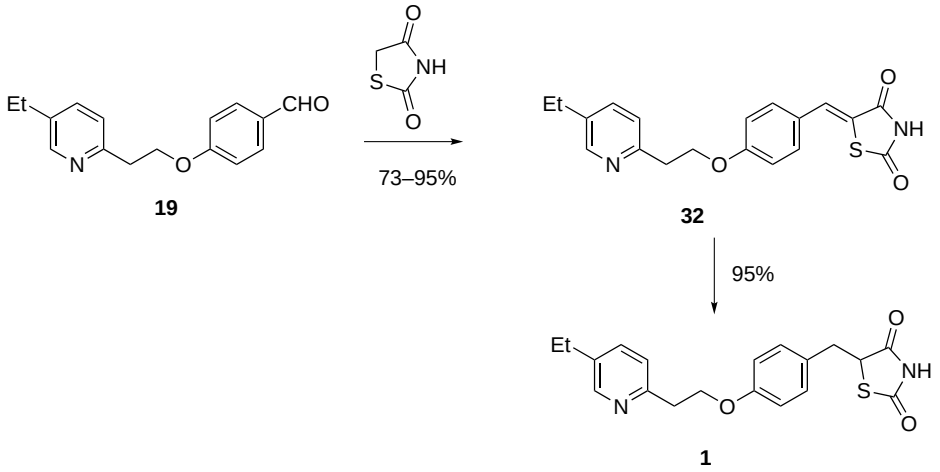


FIGURE 2.3 Assignment of the configuration of 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) by ^{1}H NMR.

> Piperidine and morpholine are often used almost interchangeably in Knoevenagel condensations. When the condensation yields are comparable, exposure limits suggest that morpholine is a better choice. The OSHA permissible exposure limit for morpholine is 20 ppm or 70 mg/m^3 TWA with skin absorption designation. Although OSHA does not have a permissible exposure limit for piperidine, in the 1980s the American Industrial Hygiene Association recommended a level of 1 ppm TWA with skin absorption designation.[45]

While the low solubility of 5-(4-(2-(5-ethylpyridin-2-yl) ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) in methanol and ethanol greatly simplifies the workup of the Knoevenagel condensation, it certainly makes the final reduction more challenging. Reductions run in DMF, tetrahydrofuran, or dioxane (a carcinogen[46]) require a high catalyst loading, high temperatures and pressures, and a hot filtration of the catalyst. Reduction of 30 g in dioxane (580 mL) at 110°C and 711 psi required 0.75 g of palladium (30 g of 5% palladium on carbon, 50% water wet).[34] With a reduction yield of 70%, the cost of palladium[47] metal to produce 1 kg of pioglitazone (**1**) crude by this process will be roughly $340. The cost for palladium on support will be still higher. Of course, the spent catalyst can be returned to the catalyst manufacturer for recovery of the metal and some cost savings. While the first inclination might be to focus on reducing the cost of the precious metal, another difficult hurdle for this reduction process will be to reduce palladium to an acceptable level in the final product. The oral PDE (permitted daily exposure) for palladium has been set by the EMEA at 100 μg/day (2 μg/kg/day in a 50 kg person).[48]

The 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene) thiazolidine-2,4-dione (**32**) hydrogen chloride salt has higher solubility than the free base in methanol–water. Reductions of the hydrogen chloride salt in methanol–water give better yields (80–85%) but still require a high catalyst loading and high temperatures and pressures. Reduction of 22.5 g of the free base in methanol and 36% hydrochloric acid at 100°C and 121 psi hydrogen requires 1.125 g of palladium (11.25 g of 20% palladium on carbon, 50% water wet).[34] Reduction of 9.77 g of the isolated hydrochloride salt can be accomplished in methanol–water in 15 h at 60°C at 73–87 psi hydrogen using just 0.15 g of palladium (1.5 g of 10% palladium on carbon).[35] Either the first example did not require such vigorous conditions or the second example illustrates the value of isolating and upgrading the purity of the hydrogenation substrate!



SCHEME 2.11 Pioglitazone (**1**) from the Knoevenagel condensation of 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**) and thiazolidine-2,4-dione.

5-(4-(2-(5-Ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) has good solubility in formic acid. Reduction in formic acid can have a higher throughput in the hydrogenation reactor and yields are as high as 84%. Hydrogen pressures are 30–90 psi but reaction temperatures and catalyst loadings are still high.[49] Reduction of 50 kg of **32** in formic acid at 80°C and 29 psi hydrogen required 2 kg of palladium (40 kg of 10% palladium on carbon, 50% water wet). Under these conditions, formic acid is both solvent and reducing agent.[50] The by-product of reduction by formic acid is carbon dioxide. The reactor is vented every 30 min to purge the carbon dioxide and then refilled with hydrogen. The reduction described above required 20 h, *and 40 purges*, to go to completion! This is not a "green" option. Even the higher throughput in the hydrogenation reactor is questionable since the frequency of purges and the percentage of the volume in the hydrogenation reactor that must be used for headspace will be linked.

If formic acid is an effective reducing agent, is hydrogen gas required? A positive pressure of hydrogen is necessary to maintain palladium catalyst activity. Incomplete conversion (66%) is observed in the reduction of 2.5 g in 99% formic acid at reflux under nitrogen using 0.064 g of palladium (as 1.37 g of 10% palladium on carbon, 53% water wet).[49] The positive pressure of hydrogen is not necessary using a platinum catalyst. Reduction of 20 g of **32** in 99% formic acid at 84°C under nitrogen required 0.5 g of platinum (as 0.6 g of platinum oxide).[50] Unfortunately, even with a reduction yield of 97%, the cost of platinum[51] metal to produce 1 kg of pioglitazone (**1**) crude by this process will be roughly $1060. Other heterogeneous and homogeneous iridium, rhodium, ruthenium, and nickel catalysts apparently give inferior results.

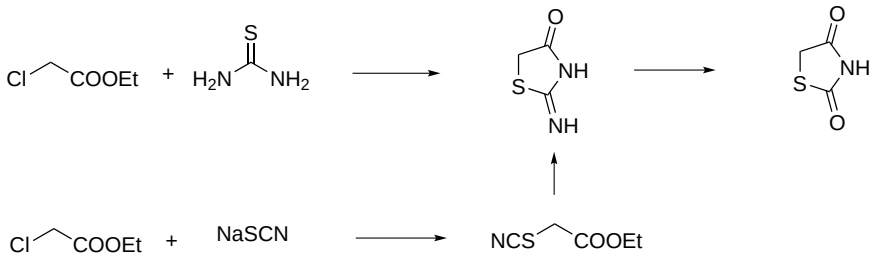
Hydrogenations at elevated pressures are typically run in 316 stainless steel reactors. The materials of construction were not specified for the lab autoclaves used in the hydrogenations of 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy) benzylidene)thiazolidine-2,4-dione (**32**) as the hydrogen chloride salt in methanol–water or 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) in formic acid. Material compatibility tables[20] indicate that a 316 stainless steel reactor should not be used. A Hastelloy C reactor is a better choice (good for ammonium chloride, excellent for dilute hydrochloric acid, and excellent for formic acid). When considering scale-up of any process always identify special equipment needs and verify that the equipment is available at the manufacturing site.

A cobalt catalyst generated by reaction of cobalt(II) chloride, cobalt(II) acetate, or cobalt(III) chloride with sodium borohydride and dimethylglyoxime mediates the reduction of 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) by sodium borohydride.[52] Reduction of 5.0 g in tetrahydrofuran–water using a solution of sodium borohydride (1.25 equivalents) in water containing dilute HCl at 15°C required 42 mg of cobalt(II) chloride hydrate. With a reduction yield of 95%, the catalyst cost to produce 1 kg of pioglitazone (**1**) crude by this process is just $1.[53]

It is known that cobalt(II) chloride and sodium borohydride react rapidly to produce cobalt boride (Co_2B). It is also known that freshly prepared cobalt boride is an effective catalyst for the heterogeneous catalytic hydrogenation of alkenes. These facts together suggest that the reduction to pioglitazone (**1**) is a heterogeneous hydrogenation catalyzed by cobalt boride generated *in situ*. The required hydrogen is generated by decomposition of sodium borohydride in the aqueous reduction medium.[54] Why does this cobalt boride-catalyzed heterogeneous hydrogenation proceed at 15°C and ambient pressure when palladium-catalyzed variants require high catalyst loadings and high temperatures and pressures? Perhaps cobalt boride is less prone to catalyst poisoning by the divalent sulfur found in both the substrate and product.

Two issues associated with the use of a cobalt boride catalyst are the potential for operator exposure during handling of solid cobalt(II) chloride and the residual cobalt in the pioglitazone (**1**) isolated from the catalytic reduction. Cobalt (II) chloride is an animal carcinogen. The OSHA permissible exposure limit is 0.1 mg/m^3 (TWA) for cobalt metal dust and fume as cobalt. The ACGIH threshold limit value for inorganic cobalt compounds is 0.02 mg/m^3 (TWA) as cobalt. The cobalt solids charging procedure must be designed to meet these limits and air monitoring and analysis must confirm that the containment procedure is adequate. What would be an acceptable level of residual cobalt in a final drug substance has not been specifically addressed by the regulatory agencies. Cobalt is a naturally occurring element. As the core metal in vitamin B_{12}, it is an essential element in humans. The average daily intake of cobalt from food is 5–40 μg/day.[55]

A chemical reduction approach would eliminate the need for high-pressure equipment and avoid the safety issues associated with using hydrogen gas or hydride. For example, 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) is reduced by sodium hydrosulfite and potassium carbonate in water–DMF at 80°C (55%).[31] The isolated pioglitazone (**1**) (HPLC purity 99%) contains just 0.05 area% by HPLC of the starting material **32**. This is important since the starting material is difficult to separate from pioglitazone (**1**) downstream. Higher levels of starting material **32** are left using methanol (0.50–0.58%), ethanol (0.28–0.30%), tetrahydrofuran (0.38%), or dioxane (1.09%) as the cosolvent. The low yield and poor solubility of both 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)



SCHEME 2.12 Hantzsch and Tcherniac methods for synthesis of thiazolidine-2,4-dione.

thiazolidine-2,4-dione (**32**) and pioglitazone (**1**) result in an unacceptable volume throughput (just 9.7 g/L) for the hydrosulfite reduction.

> Always anticipating the need for maximum efficiency in a production train, a process chemist strives to achieve an acceptable volume throughput (here defined as g product/L reaction mixture) for each process step. A volume throughput of 100–250 g/L is typical in an efficient batch process.

5-(4-(2-(5-Ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) is reduced by free whole yeast cell culture or immobilized whole yeast cells from *Rhodotorula glutinis* CBS 4406 or *Rhodotorula rubra* CBS 6469. Yeast reductions show promise for producing enantiomerically enhanced glitazones, including pioglitazone (**1**).[56]

5-(4-(2-(5-Ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**32**) is certainly highly valued as the penultimate intermediate to pioglitazone (**1**). There are at least six methods for the final double bond reduction: hydrogenation with palladium on carbon, transfer hydrogenation with formic acid and palladium, transfer hydrogenation with formic acid and platinum, reduction with sodium borohydride and cobalt boride, reduction with sodium hydrosulfite, and reduction with yeast.

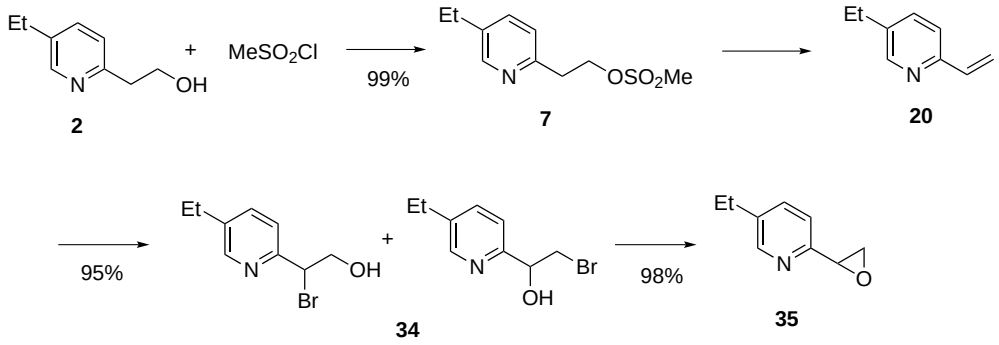
2.2.4 Preparation of Thiazolidin-2,4-dione

With a demonstrated two-step sequence from 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde (**19**) to pioglitazone (**1**), the next step is to identify the bulk suppliers of thiazolidine-2,4-dione and gain an understanding of how and from what starting materials it is manufactured. The methods for ring construction parallel the methods used to convert methyl 2-bromo-3-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)propanoate (**6**) to pioglitazone (**1**). A Hantzsch approach converts two inexpensive starting materials, ethyl chloroacetate and thiourea, to 2-imino-4-thiazolidinone (pseudothiohydantoin), which is then hydrolyzed to thiazolidine-2,4-dione. A Tcherniac approach also converts inexpensive starting materials, ethyl chloroacetate and sodium thiocyanate, to pseudothiohydantoin (Scheme 2.12).

2.3 SYNTHESIS LEFT TO RIGHT FROM 5-ETHYL-2-VINYLPYRIDINE (20)

The one constant in all the routes described so far is the starting material, 2-(5-ethylpyridin-2-yl)ethanol (**2**). It is used as the nucleophile in S_NAr displacements and is converted to the electrophile, the methanesulfonate **7**, for the Williamson ether syntheses. We have seen that the Williamson ether syntheses afford less than optimal yields and require chromatography or carbon treatment due to the competitive elimination of methanesulfonate **7**. The elimination product, 5-ethyl-2-vinylpyridine (**20**), is a novel starting material for a parallel approach.[57,58] The parallel approach uses methodology already discussed to produce 5-(4-(2-(5-ethylpyridin-2-yl)-2-hydroxyethoxy)benzyl)thiazolidine-2,4-dione (**33**). Pioglitazone (**1**) is then produced by conversion of the hydroxyl group to a chloride and reductive dechlorination (Schemes 2.13 and 2.14).

The reaction of 5-ethyl-2-vinylpyridine (**20**) with *N*-bromosuccinimide in 25% aqueous *tert*-butanol at 25–30°C affords a mixture of bromohydrins **34** (95%). The same conditions (25% aqueous *tert*-butanol at 25–30°C) are also suitable for converting the bromohydrins **34** to the oxirane **35** by reaction with potassium carbonate (98%). Both the bromohydrins **34** and the oxirane **35** should be reactive with 4-hydroxybenzaldehyde in a Williamson ether synthesis. Recall that Williamson ether syntheses with 4-hydroxybenzaldehyde and the methanesulfonate **7** are best run in alcohol solvents, especially in ethanol, ethanol–toluene, or isopropanol–toluene–water. The Williamson ether synthesis with the bromohydrins **34**, and/or with the oxirane **35** generated *in situ*, can be carried out using potassium carbonate in 25% aqueous *tert*-butanol. Thus, in a remarkably efficient and convenient one-pot process, sequential bromohydrin formation, conversion to the oxirane **35**, and ether formation with 4-hydroxybenzaldehyde affords 4-(2-(5-ethylpyridin-2-yl)-2-hydroxyethoxy)benzaldehyde **36** (79% from vinylpyridine

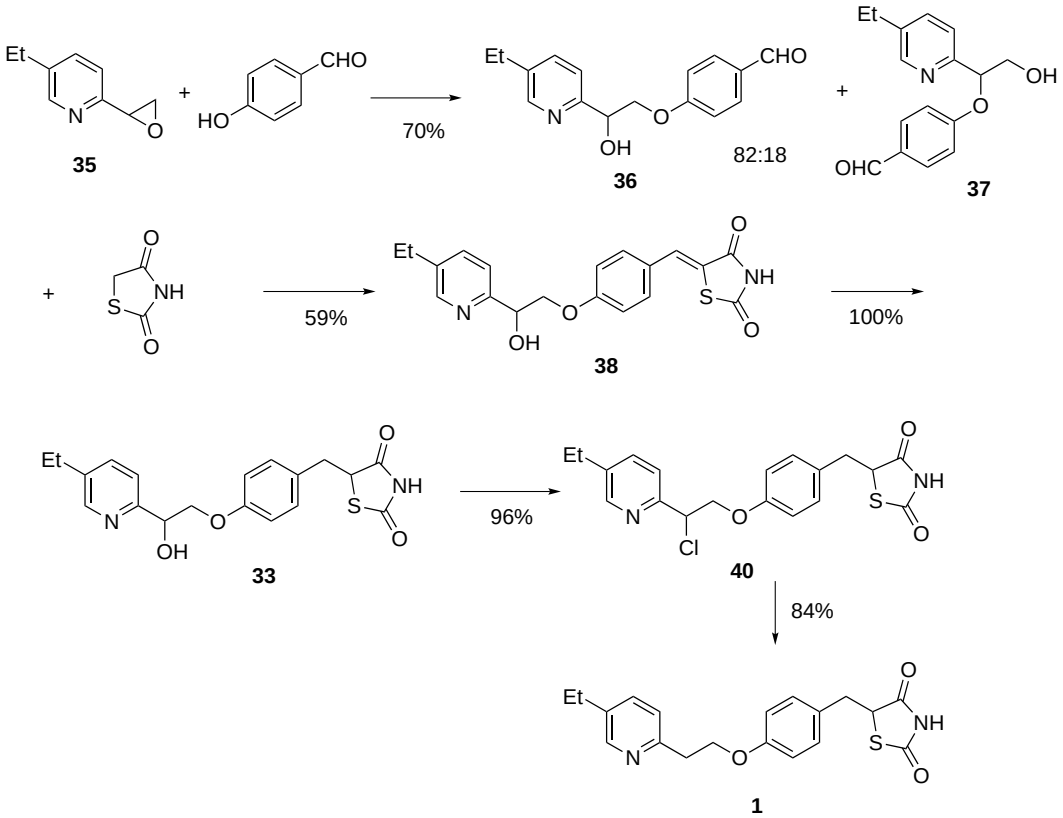


SCHEME 2.13 5-Ethyl-2-(oxiran-2-yl)pyridine (**35**) from 2-(5-ethylpyridin-2-yl)ethanol (**2**).

20). Aldehyde **36** requires a purity upgrade but the procedure is not specified.[58]

The process description to this point is encouraging but leaves us with many questions. What is the stability of the vinylpyridine **20** and of the oxirane **35**? What is the regioselectivity of the Williamson ether synthesis using the oxirane **35**? How stable is oxirane **35** under Williamson ether synthesis conditions? Reeder's *Organic Process Research & Development* publication[57] addresses these questions. 5-Ethyl-2-vinylpyridine (**20**), as a neat oil, is prone to polymerization even when stored cold. Oxirane **35** is more suitable for storage. It can be stored at ambient temperature in methyl *tert*-butyl ether solution for months without polymerization or decomposition. However, the onset temperature for decomposition of neat oxirane **35** is just 56°C.

The reaction of the potassium salt of 4-hydroxybenzaldehyde with oxirane **35** produces a mixture of regioisomers in DMF at 60–65°C (65%). Separation by chromatography on silica gel affords 43% of the desired 4-(2-(5-ethylpyridin-2-yl)-2-hydroxyethoxy)benzaldehyde (**36**) and 5% of the



SCHEME 2.14 Pioglitazone (**1**) from 5-ethyl-2-(oxiran-2-yl)pyridine (**35**).