Critical Assessment of Pharmaceutical Processes—A Rationale for Changing the Synthetic Route

Mike Butters,*,† David Catterick,*,‡ Andrew Craig,‡ Alan Curzons,‡ David Dale,§ Adam Gillmore,*,§ Stuart P. Green,§ Ivan Marziano,§ Jon-Paul Sherlock,† and Wesley White†

AstraZeneca, Process R&D, Avlon/Charnwood, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, U.K., GlaxoSmithKline, Synthetic Chemistry, Old Powder Mills, Tonbridge, Kent TN11 9AN, U.K., and Pfizer, Chemical R&D, PGR&D, Ramsgate Road, Sandwich, Kent CT13 9NJ, U.K.

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* Corresponding authors. E-mail: M.B., Mike.Butters@astrazeneca.com; D.C., David.2.Catterick@gsk.com; A.G., Adam.Gillmore@Pfizer.com.
† AstraZeneca.
‡ GlaxoSmithKline.
§ Pfizer.

1. Introduction

The focus of this review is to identify and characterize criteria for rejecting a synthetic route and thus trigger the search for a viable alternative. Given the current pressures on the pharmaceutical industry,[1] process chemists are facing increasingly tough economic[2] and regulatory hurdles[3] and have less time with which to develop the commercial process for a drug candidate. In an attempt to shorten the development time scales, a "right-first-time" approach to route selection and scale-up is often sought by the process chemist.[4]

Chemists working in the field of pharmaceutical process research and development are responsible for preparing multi-kilogram quantities of active pharmaceutical ingredient (API) to support clinical and toxicology evaluation studies. Until the first few kilograms of API are made available, little can be done to progress these clinical and toxicology studies. Drug candidates range from relatively simple structures, such as fluconazole (**1**) (Figure 1), to highly complex ones, such as paclitaxel (**2**), but nearly all drug candidates present significant challenges to the process chemist.

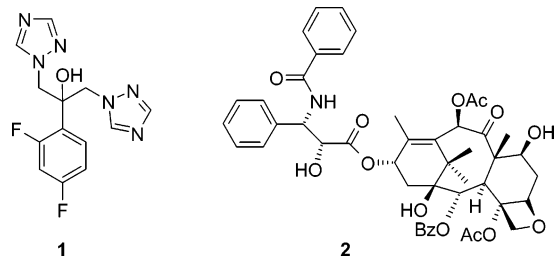

Figure 1. Structures of fluconazole (**1**) and paclitaxel (**2**).

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Mike Butters, born 1961 in Lancaster (U.K.), received his B.Sc. degree in 1982 with a major in Chemistry. In 1985 he obtained his Ph.D. in Organic Chemistry from University College Swansea under the mentorship of Professor Keith Smith. In 1985 he worked in the Synthesis Project Team at BP Research Centre, Sunbury on Thames. Then in 1988, he moved to the Process R&D group in Pfizer Global Research & Development (Sandwich U.K.), where his research focused on the design and scale-up of processes for numerous drug substances at various stages of development, regulatory submission, and commercial manufacture. In 1995 he was seconded to the Process R&D group in Pfizer Groton, USA, where he worked on a new synthesis of trovafloxacin. In 2001, he joined AstraZeneca Avlon/Charnwood Process R&D, and he is currently manager of the Avlon Process R&D Section in Bristol. His interests lie in the design of shorter synthetic sequences and the application of transition metal catalysis in the manufacture of pharmaceuticals.

David Catterick graduated with 1st class honors from Durham University in 1995 with a B.Sc. in Pure Chemistry. He subsequently moved to Oxford University to work with Professor Sir Jack E. Baldwin FRS, where he carried out the parallel syntheses of natural product families as part of his D.Phil. studies. Upon completion of his D.Phil. in 1998, he joined the group of Professor A. G. M. Barrett FRS at Imperial College, London, where his postdoctoral research involved the investigation of fluorous biphasic catalyst systems. From there he moved in 2000 to the GlaxoSmithKline Synthetic Chemistry Department at Tonbridge. Currently David is on a one year secondment to the GlaxoSmithKline Drug Discovery Department at Tres Cantos, Madrid, Spain, where he is working in the Diseases of the Developing World Unit.

Adam Gillmore completed his B.Sc. in Applied Chemistry in 1996 at Aston University in the U.K. He then went on to work with Prof. Stan Roberts at the University of Liverpool, studying the asymmetric epoxidation of enones catalyzed by poly-L-leucine. During this time, he spent 3 months working at GSK in Stevenage before completing his Ph.D. studies in 1999. From Liverpool he moved to Sandwich to join the Process R&D department at Pfizer, where he is currently based.

The start point for most process development programs is the medicinal chemistry route, which is typically designed to be divergent and allow access to a variety of targets. This route is not usually designed for further scale-up into a commercial process, and it is likely, therefore, that the process chemist will need to change the synthetic route at least once during the course of the development program. The performance of a process on a large scale can be hard to predict, and serious issues may not be uncovered until the process is taken to pilot plant scale. This review is designed to illustrate the most common types of issues in a process and provide representative examples. Numerous process development case histories have been described[5] in the literature, and the reasons for introducing new routes are many and varied. This review provides a uniform set of criteria (SELECT), which represent the different drivers for changing a synthetic route. The acronym SELECT stands for safety, environmental, legal, economics, control, and throughput. Each criterion has been illustrated in Table 1 by reference to examples that have been carefully selected to highlight important features of each issue and to illustrate the positive benefits associated with a new route. This SELECT approach should therefore facilitate early decision-making and avoid wasted investment in a route that will not support the target quantity of API.

2. Criteria for Process Assessment

As the life cycle of drug development unfolds, the demands on the synthetic process will change. In early development, the emphasis is very much on timely delivery of bulk supplies using a safe process. Thus, most of the SELECT criteria can usually be satisfied when preparing the first few kilograms of bulk, and the most frequent issue encountered involves lack of safety. By the time that a drug candidate reaches Phase III clinical trials, the process chemist will probably need to manufacture hundreds of kilograms of API and the demands on the process become more acute across the full range of SELECT criteria. Nevertheless, the chemist should be vigilant at all stages of development, and the case histories (below) illustrate this point.

2.1. Safety Issues

2.1.1. Potential Safety Issues and Their Significance

Safety is the most important of the SELECT criteria. If a route cannot be scaled up safely, then it should not be scaled up at all. The criterion of safety can be subdivided further into two main areas—(i) thermal and reactive hazards and (ii) toxic hazards—with the former being of most concern. A toxic chemical can be handled with the correct containment and engineering solutions, but a thermal or reactive hazard must be rendered intrinsically safe before it is scaled

Table 1.

criteria	subcriteria	examples of potential issues
safety	process safety exposure to substances harmful to health	explosions or exotherms; threat to workers or plant carcinogens or sensitizers; threat to workers
environmental	volume of wasted natural resources substances harmful to the environment	quantity and variety of solvents aquatic toxins and ozone depleting chemicals
legal	infringement of intellectual property rights regulations that control use of reagents and intermediates	key intermediate patented by competitor NONS (notification of new substances, EU legislation)
economics	meeting cost of goods target for future market investment costs to support development quantities	long synthesis using expensive materials high cost of process cannot be changed in near term
control	control of quality parameters control of chemistry and physical parameters	meeting specification and GMP requirements nonselective reactions, unstable intermediates
throughput	time scale of manufacture in available plant availability of raw materials	long route with dilute stages rare natural products

Figure 2. Site of Flixborough explosion (1974).

up; otherwise, the consequences can be very serious indeed. Figure 2 displays a picture of a plant explosion at Flixborough in 1974.

An understanding of the toxicity of chemical reagents must be obtained in order to maintain a safe environment for operators. Similarly, an understanding of the thermal and reactive hazards posed by reagents is essential to avoid damage to equipment, buildings, people, and the environment. Perhaps more important than consideration of the risks of individual chemicals is the need to understand the hazards associated with mixtures and combinations of chemicals, since the reactive hazards may not be easily deduced from a knowledge of the two individual chemicals.

The main types of issues associated with process and worker safety are as follows: (1) thermal runaway, (2) gas evolution, (3) potentially explosive, shock sensitive materials, (4) highly corrosive materials, (5) acute toxicity, (6) chronic toxicity, (7) genotoxicity, (8) pyrophoric and highly flammable materials. During a chemical reaction, heat can be absorbed (endothermic), or more frequently, heat is released (exothermic). In an exothermic reaction, thermal runaway occurs when the rate at which heat is produced increases exponentially but the rate at which it can be removed is a linear function. Once control for the reaction has been lost, then overpressurization of the reaction vessel may occur due to uncontrolled boiling or rapid gas generation. The increased temperatures may also initiate more dangerous secondary reactions or decompositions. These problems are further exacerbated on scale-up from laboratory to plant because the heat produced in a reaction mass is a function of volume, i.e., proportional to the cube of the reaction vessel diameter, whereas heat removal depends on the surface area available for heat transfer, i.e., only proportional to the square of the diameter.

2.1.2. Prediction and Assessment of Safety Issues

The preferred philosophy in process safety is to eliminate a hazard completely or reduce its magnitude to avoid the need for elaborate safety systems and procedures. This approach builds inherent safety[6] into the process. In order for this approach to be effective, it is important that the hazard assessment of the process commences at an early stage of development where route changes are easier to make.

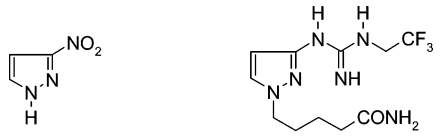
The assessment of toxic hazards presented by a medicinal chemistry route is often straightforward and can be done as a paper exercise since it is likely that the chemicals used are commercially available and safety data will be obtainable from the material safety data sheet (MSDS) or other sources such as *Sax's Hazardous Properties of Industrial Chemicals*.[7] After identification of the hazards, COSHH procedures (control of substances hazardous to health) can be applied to minimize the risks associated with the chemicals in question. Typically, a three-tier system is applied until the risk is considered to be under control. The tiers are as follows: (1) Where possible, the chemical should be substituted for a less hazardous one (e.g., substitution of benzene by toluene or of hexane by heptane). (2) If this is not possible, then the quantity of the chemical should be reduced (e.g., can a stoichiometric or catalytic quantity be used instead of an excess?). (3) The final line of protection against chemical hazards involves the use of engineering controls and PPE (personal protective equipment).

For novel intermediates (and some reagents), no adequate safety data are available to allow an assessment of the risks posed by a particular synthetic step. In these cases, predictive screening is often carried out to give an indication of the likely risks based on analogies drawn with chemicals of similar structural classes. One such database used in the pharmaceutical industry for this purpose is DEREK (deductive estimation of risk from existing knowledge).[8] This is an adaptive system capable of estimating the potential for carcinogenicity and mutagencity of a compound by comparison with known "structural alerts".

Any approach to reaction hazard assessment should address the three major chemical reaction hazards below: (1) The thermal instability of reactants, reaction mixtures,

waste streams, and products (including intermediates). (2) Exothermic reactions that raise the reaction temperature to produce decomposition reactions or uncontrolled boiling. (3) Gas evolution (either from the desired chemistry or via a decomposition pathway), which can cause reactor overpressurization and possible explosion.

The potential for explosion is a threat that should be eliminated as soon as possible. Nitropyrazole (**3**) (Figure 3)



3 4

Figure 3. Nitropyrazole (**3**) intermediate in the synthesis of ICI-162,846 (**4**).

was a starting material in the medicinal chemistry synthesis of ICI-162,846 (**4**). The heat of decomposition for **3** was found to be >2800 J/g (a potential explosive), and therefore, an alternative starting material was required.[9] A general strategy for chemical reaction hazard assessment is outlined in Table 2.

2.1.3. Options To Manage Safety Issues

An understanding of the thermal and reactive chemistry of a process can allow the process chemist to engineer the reaction so that it is as intrinsically safe as possible. Early thermal decomposition data such as DSC can give an indication of the operating limits for a particular process. A limit of 100 °C below the first exothermic event is commonly regarded[27] as a safe upper operating limit for chemical reactions due to the limitation of these tests to mimic process operations. Probably the most important information to obtain from reaction calorimetry is the potential adiabatic temperature rise—that is the maximum temperature rise achievable if no heat is lost to the environment—and represents a worst-case scenario. Using this information in conjunction with thermal stability data allows calculations to be made to see whether this temperature is enough to cause either the decomposition of the reaction mixture or boiling of the solvent. One way to use this information is to assign the reaction to a "reaction criticality class" and then modify the reaction to make it more intrinsically safe (e.g. dilute the reaction to reduce the temperature rise). Figure 4 (a Stoessel Diagram)[27] shows the five classes of reactions as defined by their normal operating temperature (T_p), relative maximum

Table 2.

DESK SCREENING ↓	Literature searches – *i.e.* Bretherick's handbook of reactive chemical hazards,[10] National Fire Protection Association's Manual of Hazardous Chemical Reactions.[11] Desktop calculations[12] such as oxygen balance and CHETAH[13] calculations. Molecules containing hazardous functional groups should also be avoided.
THERMAL SCREENING ↓	Used primarily at the laboratory scale development stage and equipment includes Differential Scanning Calorimetry (DSC),[14] Carius tube,[15] TSU, RSD, Radex and Differential Thermal Analysis (DTA). These techniques can be used to examine the thermal stability of an individual reaction component or a reaction mixture. Other tests such as shock sensitivity may also be considered at this stage. Techniques such as Carius Tube, TSU, RSD, and Radex[16] importantly have the ability to measure pressure as well as temperature excursions.
CHARACTERIZE DESIRED REACTION ↓	Usually isothermal calorimetry to give data on reaction heats, reaction kinetics, thermodynamics and heat transfer. Equipment includes the commercially available calorimeters from Mettler-Toledo (RC-1),[17] Hazard Evaluation Laboratories (SIMULAR),[18] Setaram (DRC),[19] and Chemisens.[20] Instruments to quantify the gas evolution rate during the reaction include thermal mass flow meters; Ritter gas meters, and U-tube devices. For all gas measurement the material of construction of the device and the solubility of the evolved gas in the instrument fluid should be considered.
CHARACTERIZE UNDESIRED REACTION	Usually performed using adiabatic calorimetry to gain runaway data on reactions and individual materials. This also then leads to data for reaction pressure relief sizing and other protective measures. Commercial equipment includes ARC,[21] PHI-TEC,[22] APTAC,[23] ARSST,[24] VSP[25] and adiabatic Dewar.[26]
↻ **BASIS OF SAFETY CAN BE DEFINED** ↺	

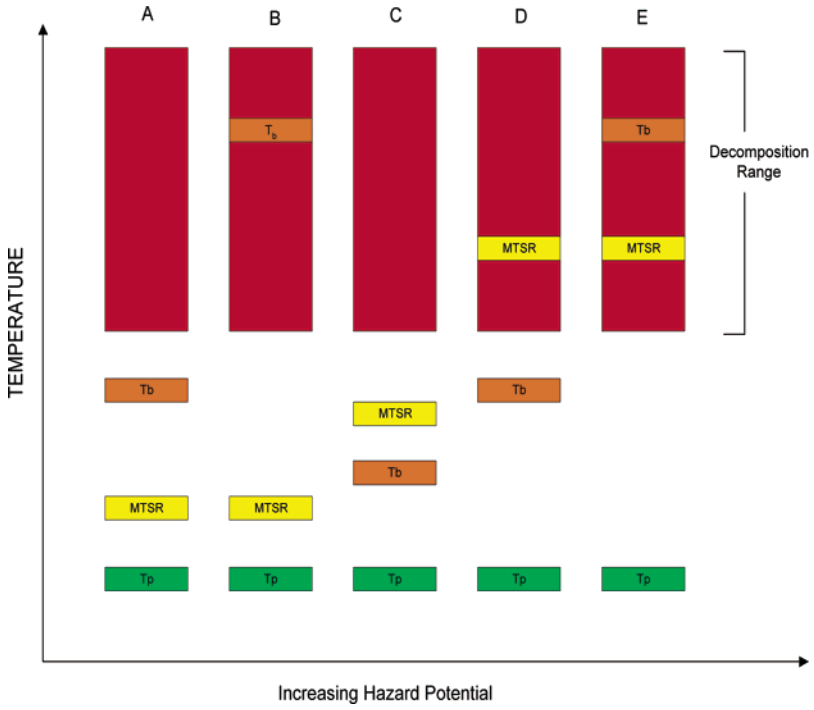


Figure 4. Stoessel diagram of reaction criticality class.

temperature of synthetic reaction (MTSR), boiling point of solvent (T_b), and decomposition range (red box).

(A) The MTSR is below the boiling point that is itself below the decomposition onset (including the 100 °C safety factor). This is a thermally safe process.

(B) Although the adiabatic peak temperature (MSTR) is below the onset of decomposition and boiling, the decomposition onset is also below the boiling point. In a class A reaction, the latent heat of evaporation acts as a safety barrier against reaching the decomposition temperature. This safety barrier is not present in a class B reaction. Measures to prevent overheating should be applied or protected against.

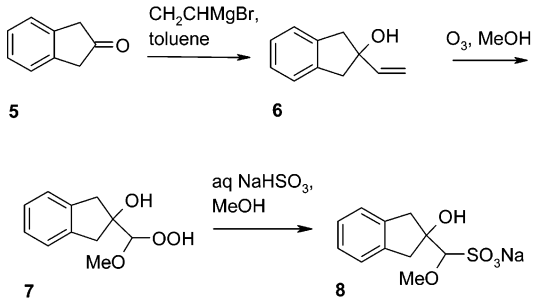
(C) The adiabatic peak temperature is above the boiling point, although the onset of decomposition is above both. Potential exists for vapor pressure effects in the reactor leading to potential overpressurization. Reaction control and/or protection must be applied.

(D) The peak adiabatic temperature rise exceeds the boiling point and will initiate decomposition if uncontrolled. Reaction control and/or protection must be applied. Emergency relief venting may prevent initiation of the decomposition, as vapor loss will remove heat.

(E) The peak adiabatic temperature rise exceeds the onset of decomposition but not the boiling point. Loss of reaction control will initiate decomposition, which may then lead to hybrid pressure effects (i.e. gases formed from decomposition will contribute to the pressure generation inside the reactor as well as vapor pressure effects associated with the solvent). Reaction control should be applied and/or protection should be designed to mitigate the consequences of the decomposition.

For reactions other than intrinsically safe ones (i.e. a class A reaction), safeguards must be put into place if the reaction is to be scaled up into the plant. These safeguards fall into two classes—preventative and protective measures. Preventative measures relate to defining a safe operating envelope by which the desired chemical reaction can be controlled. Application of preventative measures was demonstrated by

Scheme 1



Ragan and co-workers during the scale-up of an ozonolysis reaction (Scheme 1).[28] Protective measures aim to mitigate the consequences of a hazard.

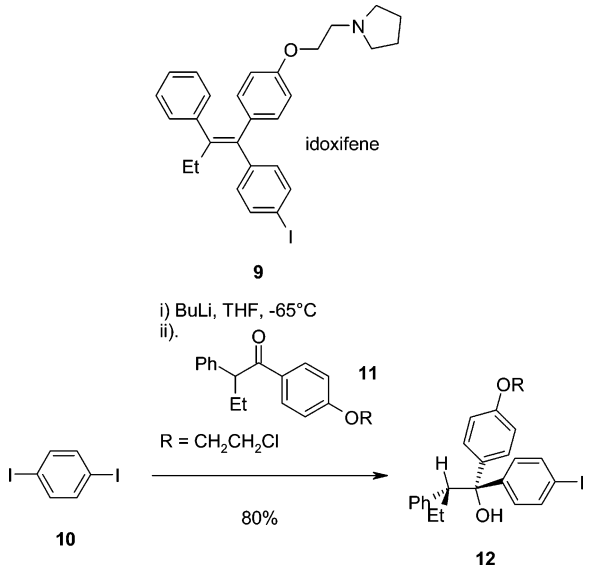
2.1.3.1. Process Engineering and Safe Scale-up of an Ozonolysis Reaction. Scale-up of the ozonolysis of alkene **6** (Scheme 1) was required for the preparation of an intermediate at Pfizer.[28] The alkene was treated with ozone in methanol at −65 °C before quenching the homogeneous reaction mixture into a slurry of $NaHSO_3$, giving the bisulfite adduct **8** as the isolated product.

Analysis of the reaction by calorimetry showed a ΔH_{obs} of −535 kJ/mol, which corresponded to an adiabatic temperature rise of 170 °C (in 10 L/kg of methanol). The reaction temperature of −65 °C resulted in a MSTR of 105 °C, which was well above the T_b, giving it a reaction criticality class of C. In this case, preventative measures are fairly easy to apply since the reaction is dose-controlled and stopping the flow of ozone into the reactor will stop the heat generation. DSC indicated that there was a moderate exothermic event (404 J/g) occurring near 45 °C. The operating temperature of the reaction was well below the 100 °C safety limit and was deemed acceptable for the quench at 0 °C. In addition to these safety controls, the composition of the headspace was carefully controlled to ensure that an explosive mixture of oxygen, ozone, and methanol vapor was not generated at any point. By generating the ozone from air (instead of

oxygen) and then diluting the reactor headspace with nitrogen, both the fuel (methanol) and oxygen/ozone were kept below the lower flammability limit and maximum oxygen concentration limit, respectively, and the process was scaled up to 3 kg without incident.

2.1.3.2. Example of Engineering a Safer Process. As part of the development program toward idoxifene (**9**), a selective estrogen receptor modulator, an efficient preparation of alcohol **12** was sought.[29] This was initially achieved by a low-temperature halogen−metal exchange reaction between 1,4-diiodobenzene (**10**) and *n*-BuLi. The resulting lithio species was quenched with the ketone **11** to form **12** as a single diastereoisomer in 80% yield (Scheme 2).

Scheme 2



The exothermic nature of both the iodine−lithium exchange (thermodynamic heat of reaction = −53 kJ/mol) and the subsequent carbon−carbon bond formation (thermodynamic heat of reaction = −126 kJ/mol) precluded effective temperature control on a larger scale. Assuming a reaction in a 115 L hastelloy reactor with a cooling capability of −60 °C, the *n*-BuLi would have to be added over 50 min in order to maintain the pot temperature below −50 °C. For the subsequent reaction with ketone **11**, a minimum addition time of 110 min would be required. At temperatures above −50 °C and addition times in excess of 60 min, it was found that yields of **12** dropped significantly due to the competing side reactions. These included formation of 1-butyl-4-iodobenzene together with a dimer of **12** resulting from lithium exchange of the second iodine group. In summary, this procedure could not be run at scales >16 molar and this would severely limit the potential batch sizes of this reaction.

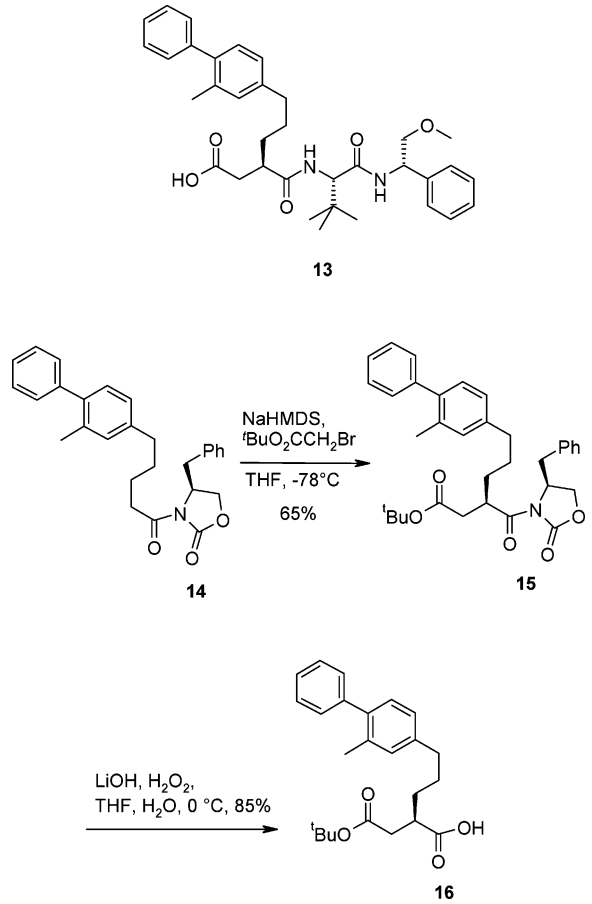
In a variation of this process, a Barbier-type reaction was investigated. Addition of *n*-BuLi to a mixture of 1,4-diiodobenzene and ketone **11** in a nonpolar solvent such as toluene gave an 83% yield of **12** at −65 °C. At elevated temperatures (−40 to −10 °C), reproducibly good yields (77%) of high purity **12** were obtained even when interrupting the reaction and restarting after several hours.

2.1.4. Designing a Safer New Route

If the information gathered about a process indicates that a basis of safety cannot be defined within the capabilities of laboratory or plant equipment, then a change of route should be made.

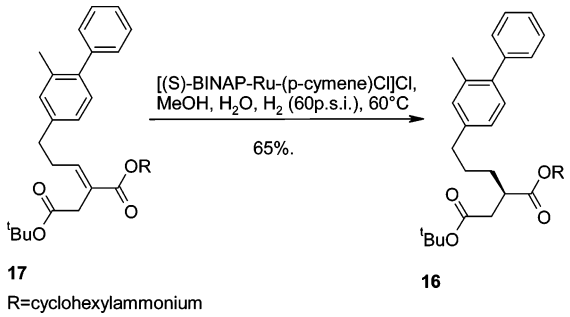
2.1.4.1. Removal of a Potential Explosion Hazard. The medicinal chemistry route[30] to the MMP3 inhibitor UK-370,106 (**13**) required the use of hydrogen peroxide and lithium hydroxide in THF to cleave the chiral auxiliary in intermediate **15** (Scheme 3). The handling of hydrogen peroxide in an ethereal solvent such as THF carries a risk of explosion due to the formation of thermally unstable organoperoxide derivatives.[31]

Scheme 3



This safety concern was one of several reasons that led the process team to explore an alternative route involving asymmetric hydrogenation. To this end, the *β*-substituted itaconate salt **17** was prepared via a Horner−Wadsworth−Emmons olefination, and it was found that this substrate could be hydrogenated (Scheme 4) using [(*S*)-BINAP−Ru−(*p*-cymene)Cl]Cl to give the product **16** in 88% ee Crystallization as the cyclohexylamine salt gave a purity of >98% ee and a 65% overall yield from itaconate **17**. This olefination/hydrogenation approach therefore obviates the need for

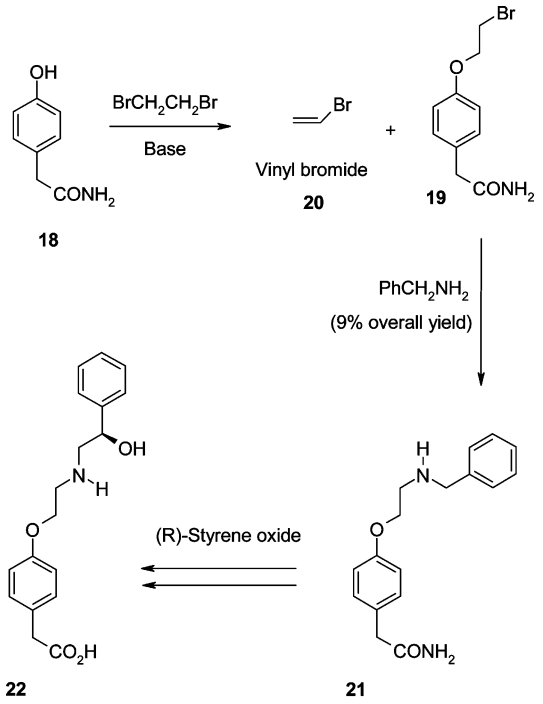
Scheme 4



the hazardous reagents required to remove the benzyl oxazolidinone auxiliary. In addition to having improved safety, it is also a more economical route.

2.1.4.2. Removal of a Genotoxic Hazard. The Zeneca Pharmaceuticals drug candidate ZD-2079 (**22**) (a beta-3 agonist)[32] entered development in 1991, intended for the treatment of noninsulin dependent diabetes. The medicinal chemistry route to **22** (Scheme 5) presented a number of

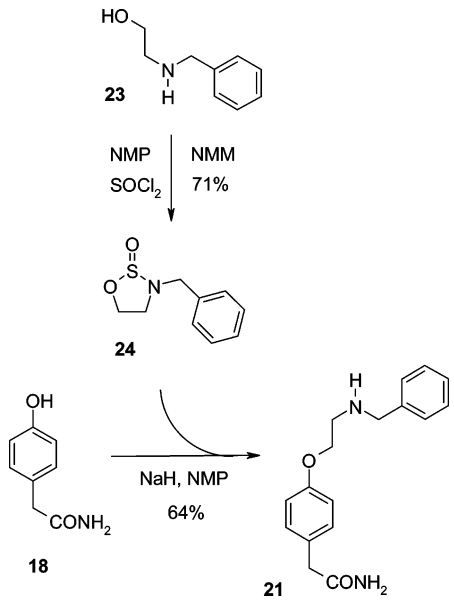
Scheme 5



challenges for scale-up. The generation of toxic vinyl bromide[33] gas **20** in step 1 (due to base promoted dehydrobromination) was unavoidable given that the reaction of dibromoethane with phenolic starting material **18** required base. Vinyl bromide **20** is known to have genotoxic properties and cannot be readily removed by scrubbing on a plant scale. A risk assessment concluded that the threat to worker safety was unacceptable, and a research program was initiated with the objective of finding a safe alternative route.

An alternative strategy for providing the two-carbon unit in step 1 involved ethanolamine derivatives (Scheme 6). *N*-Benzyl oxathiazolidine-*S*-oxide (**24**) was prepared by reaction of *N*-benzylethanolamine (**23**) with thionyl chloride. This cyclic derivative of ethanolamine provided activation of the oxygen toward nucleophilic attack while preventing intramolecular attack by nitrogen. This approach also circumvented the issue of controlling mono- versus disubstitution (e.g. dibromoethane can form a diether with phenol **18**). Reaction of **24** with the sodium salt of 4-hydroxylphenylacetamide (**18**) provided amine **21** in 64% yield (cf. route in Scheme 5 gave a 9% overall yield). Hydrolytic instability of the oxathiazolidine ring precluded isolation of **24** on large scale; therefore, *in situ* formation and purification was required. Thus, cyclization of **23** with *N*-methylmorpholine (NMM) base in NMP generated the insoluble hydrochloride salt of NMM that was removed by filtration.

Scheme 6



2.2. Environmental Issues

Global environmental legislation is becoming more stringent; therefore, consideration of these issues must be introduced during early stages of process development to achieve sustainable processes and products. Project cost reductions of 50% or more have been achieved when environmental issues are addressed concurrently in early stages of the project, and wider benefits to companies will come from using more sustainable processes and technologies that deliver significantly improved process efficiencies.

In the USA, the Environmental Protection Agency has developed a series of regulations and policies to protect the environment from chemical pollutants.[34] Within Europe, the major regulation relating to chemical manufacture is Integrated Pollution Prevention and Control (IPPC).[35] This regulation is founded on the hierarchy of prevent, minimize, and render harmless. Treatment of effluent streams, or rendering harmless, should only be used after prevention and minimization have been considered. Figure 5 illustrates that the earlier environmental impact is considered during development, the higher the chance of adopting prevention and minimization principles.

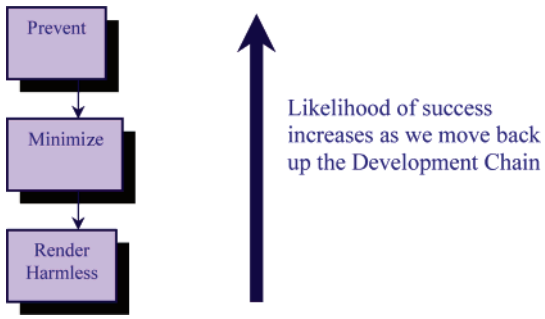


Figure 5. Integration of environmental controls with development time scales.

The BAT concept (best available technology)[35] embraces the prevent/minimize/render harmless hierarchy and translates this into specific expectations for how route development should proceed. It is not binding but is a UK-Environmental Agency expectation of what companies are able to achieve. Examples include (1) using substances that possess little or no hazard/risk to human health and the environment, and

(2) avoiding unnecessary derivatization (e.g. blocking or protecting groups).

2.2.1. Potential Environmental Issues and Their Significance

The manufacture of an API normally involves the use of multistage batch processes to prepare relatively small quantities of complex chemical compounds. However, relatively high levels of waste are produced per kilogram of product by chemical industry standards.

There are two key environmental issues, although they are somewhat interlinked: (1) environmental impact [(a) toxicity (human, plant, and animal); (b) ozone depletion; (c) climate change] and (2) sustainability [(a) depletion of natural resources; (b) high mass of materials used and waste generated; (c) energy-inefficient processes]. Materials that have significant environmental impact are often strictly controlled by regulations, and some may be subject to very demanding emission limits, either currently or at a planned future date. One such example is mercury and its compounds that are included on the Water Framework Directive "priority hazardous substances list". Under this regulation, within Europe, emissions of mercury to the aquatic environment will have to be "zero" by 2015. In the USA, the total maximum daily load (TMDL) for mercury is defined by section 303(d) of the Clean Water Act.[34] Assuming it takes 8 years to progress a candidate from drug discovery to market, a route using mercury today in early development may not be acceptable soon after launch.

2.2.2. Prediction and Assessment of Environmental Issues

The assessment of environmental improvements during process development is best achieved using a set of metrics.[36] However; there can often be a poor understanding around the definition and the value of these metrics. For example, pursuing a simple metric such as yield will not by itself drive a business toward sustainable practices despite the fact that, from an economic standpoint, yield remains a very good metric for high value added materials such as pharmaceuticals.

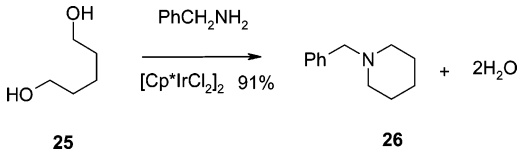
A variety of green chemistry metrics[37] are available: (1) solvent usage (includes mass used, solvent acceptability from an environmental and life cycle perspective, number of different solvents), (2) reaction mass efficiency (RME) (the proportion of the key reactants that end up in the product), (3) atom economy (the proportion of atomic mass in the reactants that ends up in the final molecule), (4) mass productivity [the "mass of product"/"mass of all materials used (reactants, solvents, reagents—but excluding water)" expressed as a percentage], and (5) environmental factor (E-factor; defined as "kg of total waste"/"kg of product").

A number of "tools" can also be utilized in order to carry out a so-called "design for the environment". These include AIChE CWRT metrics (Centre for Waste Reduction Technologies, of the American Institute of Chemical Engineers), life cycle inventory/assessment, total cost assessment (TCA), and the Green Technology Guide (GTG).[38,39]

2.2.3. Options To Manage Environmental Issues

Development of a process that is totally sustainable and has a low environmental impact is not always possible due to the current limits of science and technology; however, significant process improvements can often be achieved. Once the route is fixed, there may be significant opportunities to improve the process; for example, telescoping stages together can reduce energy usage (by avoiding energy intensive operations such as drying) and avoid the need to isolate toxic intermediates. Developing processes with high catalyst turnovers and removing stoichiometric reagents is another important area for improving environmental impact. For example, some iridium complexes are able to catalyze the alkylation of amines by alcohols using an internal redox cycle producing water as the only byproduct (Scheme 7).[40]

Scheme 7



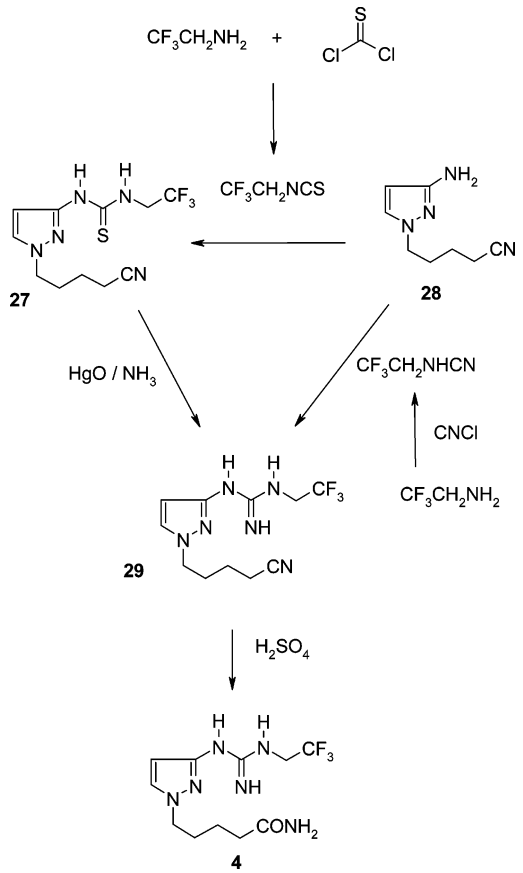
Solvent use is responsible for 60% of the overall energy used in a pharmaceutical process and accounts for 50% of the post-treatment green house gas emissions.[38] Given these figures, careful solvent selection to maximize efficiency and potential recovery can have a huge positive environmental impact. Processes that use single solvents and avoid complex mixtures greatly improve recycling potential within a process.

2.2.4. Designing a New "Greener" Route

Understanding environmental issues and identifying opportunities in early development will maximize the chemist's ability to design "greener" synthetic approaches. This is exemplified by the following examples.

2.2.4.1. Avoiding the Use of a Mercury Reagent. ICI-162,846 (**4**) (Scheme 8) is a histamine H2 blocker that was under development[9] for the treatment of ulcers and gastric

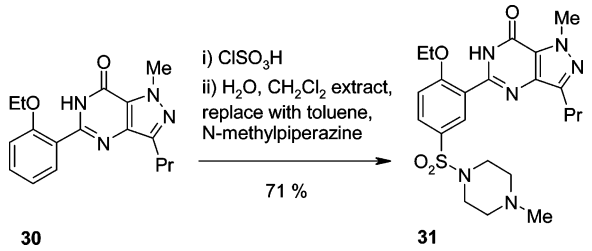
Scheme 8



disorders. The medicinal chemistry route to **4** involved mercury oxide desulfurization of a thiourea fragment **27** to give the key guanidine functionality. Although it may be possible to purify the API to remove low levels of mercury, the environmental consequences of mercury-containing waste are serious.[41] A number of mercury compounds are known to accumulate in aquatic ecosystems, and high levels can be found in certain fish. Even at low levels, mercury compounds act as neurotoxins and cause defects to the unborn child. It was very clear, therefore, that development quantities of **4** could not be manufactured using the mercury methodology, and the search for a new route (Scheme 8) was initiated. Treatment of the aminopyrazole intermediate **28** with a cyanamide reagent provided a more convergent synthesis of **29** and was used for the preparation of 100 kg quantities of **4**.

2.2.4.2. Change of Route To Avoid Large Volumes of Solvent Containing a Toxic Reagent. The medicinal chemistry route to sildenafil (**31**) (Scheme 9) employed a late stage chlorosulfonation of pyrazolopyrimidinone (**30**) which allowed the construction of the sulfonamide functionality in the final bond-forming step.

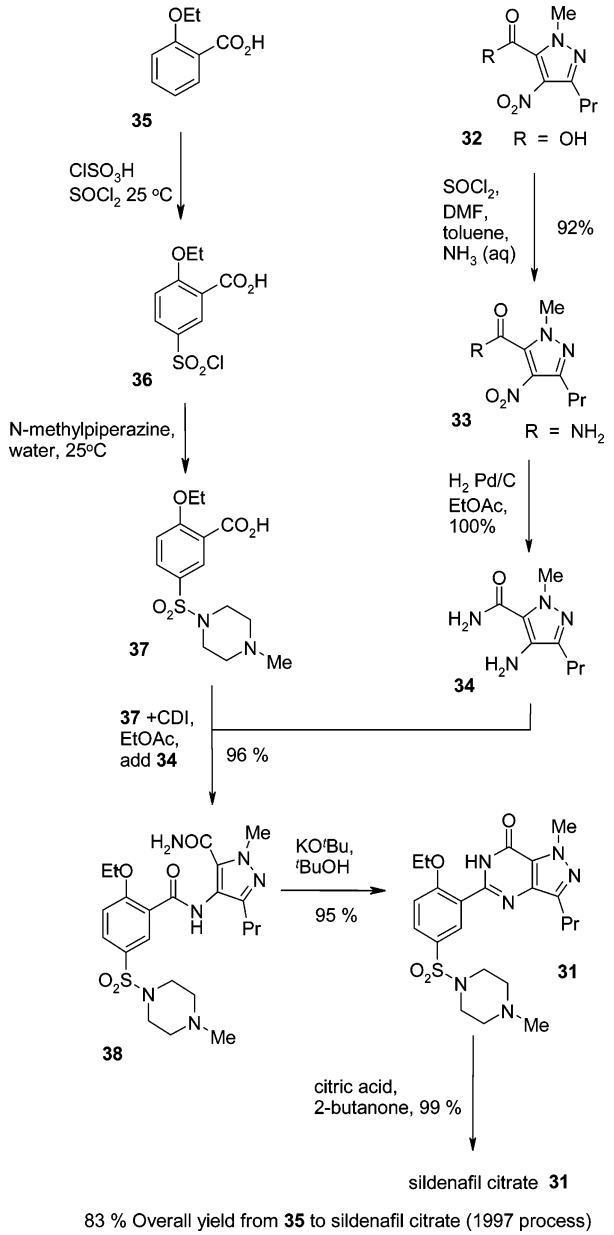
Scheme 9



Since the reaction was carried out using chlorosulfonic acid as both a reagent and solvent, considerable quantities of hazardous waste were generated from this step. A commercial route[42] was designed to incorporate the chlorosulfonation step earlier in the synthesis (Scheme 10). By carrying out this transformation on a lower molecular weight compound (namely, 2-ethoxybenzoic acid (**35**)), less chlorosulfonic acid was required and the quantity of acidic waste was much reduced. In addition to this, the starting material is a low-melting solid and could be used as a melt, allowing further reduction in the quantity of chlorosulfonic acid required as solvent.

After aqueous quench, the product was isolated as a water wet sulfonyl chloride **36**. This material was then resuspended in water and reacted with *N*-methylpiperazine, giving the sulfonamide **37**, which was collected by filtration following pH adjustment. In this way, the sulfonamide **37** could be prepared from 2-ethoxybenzoic acid (**35**) without using any organic solvents. Once the sildenafil process had been transferred to production, solvent recovery was introduced to minimize the environmental impact of the process. Toluene, ethyl acetate, and 2-butanone are all recovered and recycled. A comparison of solvent usage at different stages of development is shown in Figure 6. Comparison of the medicinal chemistry route with the commercial route shows that not only has the quantity of solvent per kilogram of API been reduced, but also the number of solvents used has been reduced, maximizing the potential for solvent recycling. Chlorinated solvents have been eliminated from the route, and highly volatile solvents such as diethyl ether have also been removed.

Scheme 10



83 % Overall yield from **35** to sildenafil citrate (1997 process)

2.2.4.3. Series of Route Changes That Reduce Environmental Impact. The medicinal chemistry synthesis (route A) of the glycoprotein IIb/IIIa antagonist lotrafiban (**42**), started from the Grignard reagent **39** and the chiral center, was introduced using L-aspartic acid. This synthesis involved 11 linear steps in an overall yield of 9% (Scheme 11).[43,44]

Route B (Scheme 12) was quickly developed to support early clinical requirements and involved a one-pot procedure converting 2-nitrobenzyl alcohol **43** to intermediate **44**. Enzymatic resolution of **45** using an immobilized form of *Candida Antarctica* lipase B gave the desired (*S*) stereochemistry. While this route was successfully scaled up to give kilogram quantities of **42**, it involved a wasteful late stage resolution and low-yielding preparation of mono *N*-Cbz-4,4′-bipiperidine.

Later in development, these issues were addressed through the introduction of route C (Scheme 13). Thus, enzymatic resolution of the simple benzodiazepine **44** proved advantageous in that the unwanted *R*-enantiomer **46** could be recycled. Furthermore, aminocarbonylation of **48** using 4,4′-

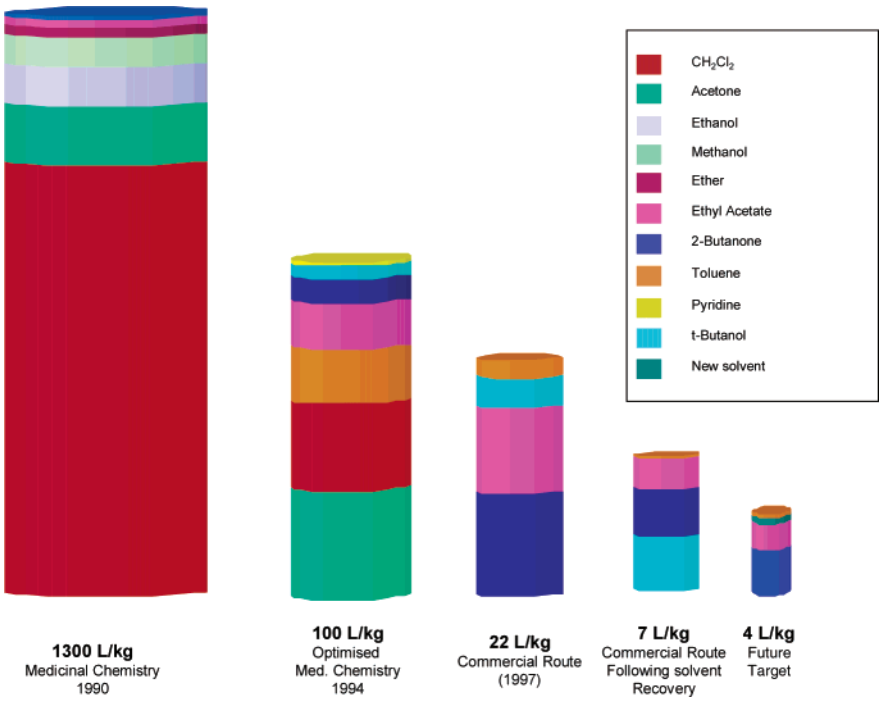
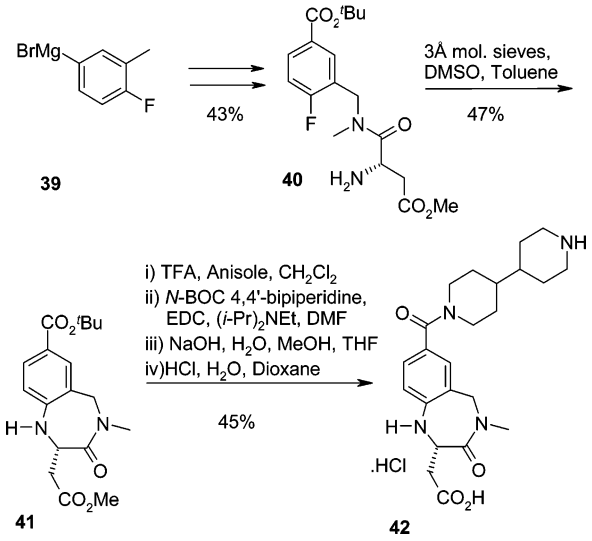
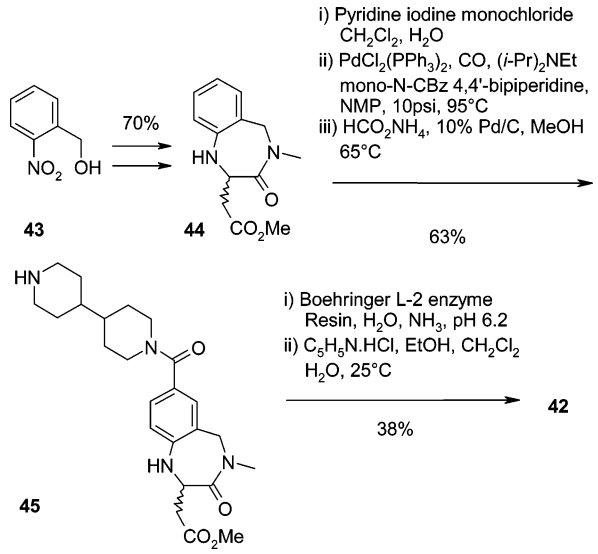


Figure 6. Solvent usage in the development of sildenafil. (Reproduced with permission from ref 42. Copyright 2004 Royal Society of Chemistry.)

Scheme 11



Scheme 12



pyridylpiperidine gave a more efficient introduction of the bipiperidine unit. Including the recycle of the *R*-enantiomer **46**, this route provided lotrafiban **42** in a 29% overall yield (cf. 17% for route B).

As mentioned above, E-factors and reaction mass efficiency (RME) are useful metrics that can be utilized to measure the environmental impact of a process. A summary of these data for routes A, B, and C is provided in Table 3.

Manufacture using route A would generate a significant amount of waste (>1.4 tons of waste per kg of API). The introduction of route C, however, provides a 5.4-fold improvement in waste reduction (reducing waste by >1.1 tons per kg of API). Figure 7 provides a breakdown of E-factors for aqueous, organic, and input materials (note: for details on route D, refer to the section on throughput (section 2.6.4.2)).

2.3. Legal Issues

It is important that the development and commercialization of a pharmaceutical product can be performed without either breaking laws or infringing valid intellectual property (IP). Failure to do so can result in a variety of possible actions depending on the circumstances. These include a court injunction, destruction of goods, payment of damages, confiscation of profits, and suspension of license to operate. Legal issues can arise at any point in development and can justify a change in synthetic route or process irrespective of other potential issues.

2.3.1. Potential Legal Issues and Their Significance

Types of legal issues fall into two major categories: (1) regulated substances [(a) use of controlled or banned substances; (b) using unacceptable quantities of COMAH

Scheme 13

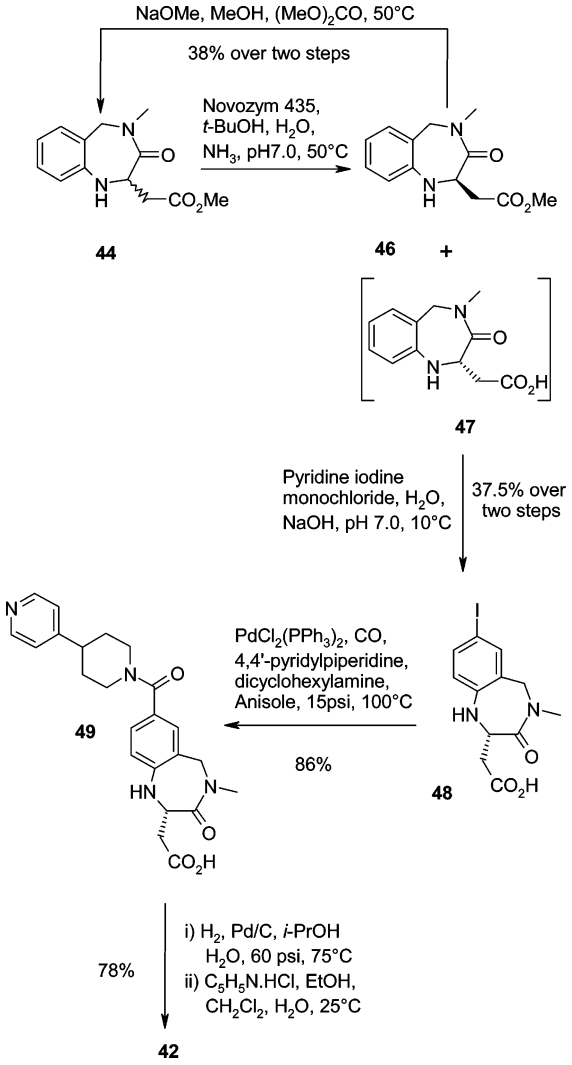


Table 3.

route	yield	E-factor	RME
A	9%	1429	1.3%
B	17%	1173	2.6%
C	29%	262	7.6%

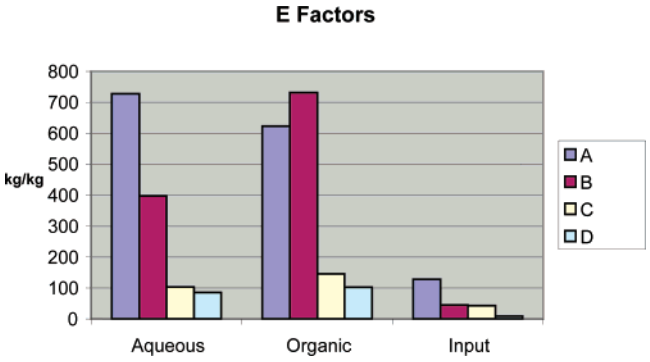


Figure 7. Comparison of E-factors for different routes to lotrafiban.

(Control of Major Accidents and Hazards, EU legislation) listed chemicals; (c) transportation of certain hazardous materials; (d) use of materials with third party restriction (e.g. NONS data)] and (2) patent infringement [(a) use of materials, technology, or processes that potentially infringe current and valid third party intellectual property].

2.3.2. Prediction and Assessment of Legal Issues Associated with Regulated Substances

2.3.2.1. Controlled or Banned Substances. The International Narcotics Control Board (INCB) monitors government control over chemicals that may be used in the illicit manufacture of drugs.[45−47] Licenses are often required for the possession, supply, and manufacture of any chemical that can also be used for illicit drug refinement.[48] For example, (+)-pseudoephedrine (**50**) (Figure 8) is a regulated chemical in the U.K. and the U.S., and yet it has many applications as a resolving agent (see also section 2.4.4 and Scheme 20), ligand, starting material, and chiral base in the development of chemical processes.[49] Awareness of regulated chemicals can be acquired through databases such as CHEMLIST (regulated chemicals listing).[50]

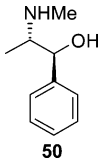


Figure 8. Structure of (+)-pseudoephedrine (**50**).

International governments also tightly control chemicals used in the production of chemical weapons.[51] Notable examples include phosgene and cyanogen chloride, both of which are used in the manufacture of pharmaceuticals.

2.3.2.2. COMAH Listed Chemicals. Most countries in the world enforce regulations to prevent and mitigate the effects of those major accidents involving dangerous substances (e.g. chlorine, liquefied petroleum gas, explosives, and arsenic pentoxide), which can cause serious damage and harm to people and/or the environment. In the U.K., these regulations are called COMAH (Control of Major Accidents and Hazards),[52] and in the U.S., the OSHA (Occupational Safety and Health Administration) Process Safety Management Standard targets highly hazardous chemicals that have the potential to cause a catastrophic incident.[53] There are also standards set by the U.S. Environmental Protection Agency's Risk Management Program.[54]

2.3.2.3. Shipping Regulations. Material hazards can often restrict method of transportation; for example, borane−THF complex[55] can only be transported by sea. In the EU, transportation is enforced through the Notification of New Substance Regulations 1993 (NONS).[56,57] Any material that is being shipped within or into Europe between two legal entities at >100 kg per supplier must be reported (Figure 9) unless it is listed in either the European Inventory of Existing Commercial Substances (EINECS) or the European List of Notified Chemical Substances (ELINCS).[58] API is exempt

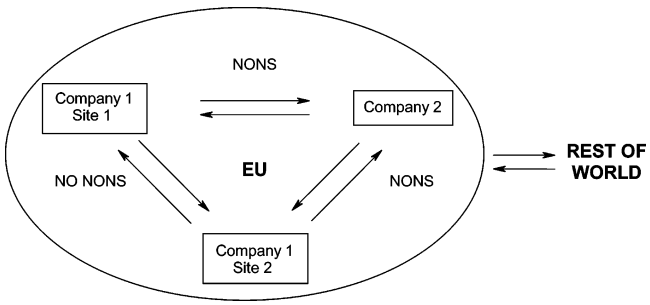


Figure 9. NONS regulations for shipment of substances in Europe. (Reproduced with permission from ref 61. Copyright 2000 Oxford University Press.)

from NONS, but it is important to realize that this is only for the specific API isomer and salt form. Data from any animal toxicity study that is carried out in support of a NONS dossier is the property of the first company for a period of 10 years. Other companies seeking notification for the same substance can only access the previously collected toxicity data through commercial agreements with the first company.

2.3.3. Prediction and Assessment of Legal Issues Associated with Patent Infringement

It is vital when developing new processes to existing substances and new processes to new substances that an extensive patent search is conducted.[59,60] This search should establish what processes have been used in the past, what intermediates have been patented (by whom and in which countries), whether the patents have expired, and the validity of the claims. If there are valid patents that overlap with the intended route of manufacture, it is usual to seek a license agreement or find an alternative noninfringing route of synthesis. A description of some of the databases that are commonly used to facilitate prior art searches can be found below.

2.3.3.1. Exemplified Compound Sources. (1) Beilstein Xfire V 6.0—*Beilstein Handbook of Organic Chemistry* provides data from 176 journals in chemistry covering the period 1779 to the present. (2) CAS Registry—The Registry File is a chemical structure and dictionary database (includes CAplus, CA, and CAOLD) with over 24 million substances (http://www.stn-international.de/stndatabases/databases/registry.htm).

2.3.3.2. Markush Sources. In general, a Markush structure is a chemical structure with multiple "functionally equivalent" chemical entities allowed in one or more parts of the compound. They are therefore a way of representing a number of compounds by identifying a core structure, which remains the same, and listing all the possible variants or substitutes. A number of tools are available which search patent databases based on Markush or related graphical representations of structures. These include Marpat (http://www.stn-international.de/stndatabases/databases/marpat.html), Merged Markush Service (http://mms.inpi.fr/what_is_mms.htm), and World Patent Index (http://www.stn-international.de/stndatabases/databases/wpidswpx.html). Another useful tool is CASREACT, which is a chemical reaction database containing reaction information derived from journal and patent documents from 1840 to date (http://www.stn-international.de/stndatabases/databases/casreact.html).

2.3.4. Options To Manage Patent Issues

In developing a commercially viable route to an API, there is a basic "freedom to operate" consideration. There may be little point developing a route to an API that uses an intermediate or process that is claimed in a valid third party patent. Such a patent might exclude the process chemist from using the process or intermediate for commercial manufacture. These situations are generally dealt with on a case-by-case basis, and it is best to seek advice from a patent attorney. A typical assessment and decision process is outlined in Figure 10.

Third party patents that have been granted and maintained by the innovator may pose a potential barrier around freedom to operate the route. In this event, the patent agent would consider the strength and potential validity of the patent(s) in question and the countries in which it is active. Although

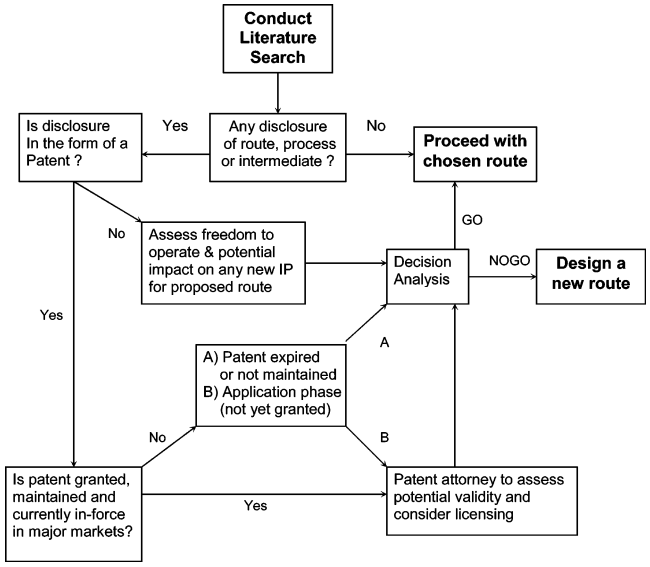


Figure 10. Decision process in response to prior-art disclosures.

it may be possible to obtain a licensing agreement, the associated costs and complications may be less attractive than developing a new route. Ultimately, a decision is then made whether to proceed with the proposed route or to design and develop a new route.

2.3.4.1. Modifying a Synthetic Route outside of Patent Claims. Acyclovir (**51**) (Figure 11) is a deoxyguanosine that was discovered, developed, and marketed by GSK as an antiviral under the trademarks Zovirax, Zyclir, and Acyclo. In 1996, acyclovir **(51)** accounted for 40% (ca. $1.25B) of the total antiviral agents market. Not surprisingly, therefore, this product engendered intensive competition among industrial research groups, which led to many challenges by generic companies to the patented Burroughs-Wellcome processes.

An important example[61] is that of the Recordati Company, who successfully identified an arguably patent-free synthetic route to acyclovir (**51**) by noting a small omission in the Wellcome process patent. Wellcome did not claim R = H (on a literal interpretation of the claims) in the definition of a key intermediate **52**, and the Recordati Company subsequently exploited this.

In the U.S. version, it can be noted in the compound claims that R can indeed be H, therefore more clearly covering the N-formyl derivative. However, in the Italian/English version there is no explicit claim for a compound where R = H, which on a literal interpretation of the claims arguably allowed the Recordati Company to define an industrial process using the formyl as a 2-amino protecting group.

This highlights the care and attention that must be made when filing patent applications. An incorrect or missed word in a claim can create arguable legal opportunities for competitors which could have a significant impact on the exclusivity rights a company may have on a product they have discovered and developed. However, the possibility in

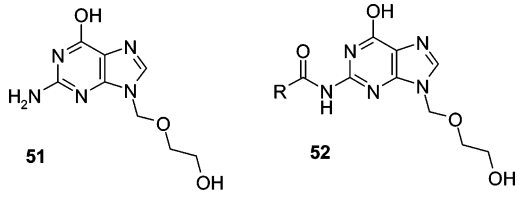
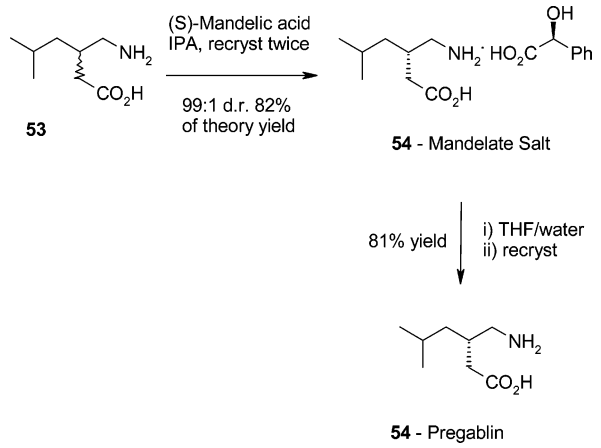


Figure 11. Structure of acyclovir (**51**) and its precursor **52**.

the U.S. and certain European countries of asserting patent infringement in respect of a technically-"equivalent" process falling just outside the literal scope of the claims should be noted.

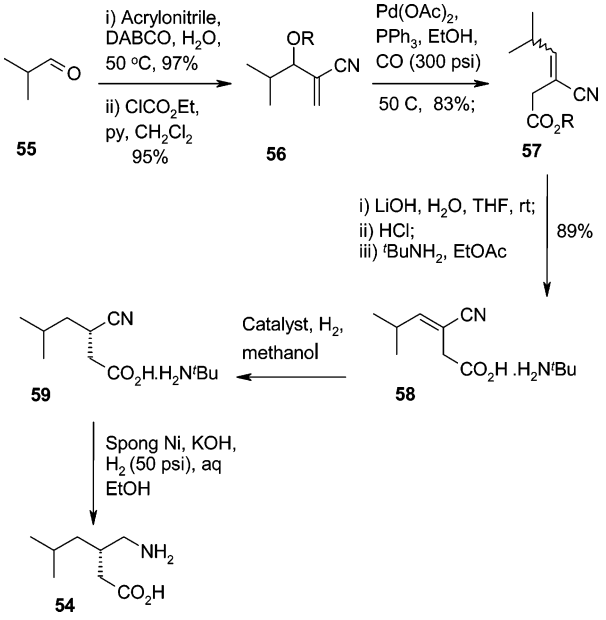
2.3.4.2. Use of a Royalty-Free Ligand in a Catalytic Process. Pregabalin (**54**) is a potent anticonvulsant for the treatment of epilepsy and pain marketed by Pfizer. The initial route to the biologically active (*S*) enantiomer involved a classical resolution of **53** with (*S*)-(+)-mandelic acid (Scheme 14).[62] Since the resolution occurred in the final stage and the opposite enantiomer could not be readily recycled, a more efficient route was required.

Scheme 14

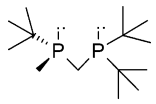


A route based on asymmetric hydrogenation was developed[62] that initially employed Chirotech's commercially available Rh Me-DuPHOS catalyst, delivering the chiral product in 97% ee at a substrate to catalyst loading of 2700:1 (Scheme 15).

Scheme 15



As part of an investigation into the utility of hindered three quadrant asymmetric hydrogenation catalysts, the TriChickenfootPhos (TCP) ligand (**60**) (Figure 12) was prepared and shown to provide rhodium complexes that are effective catalysts for the asymmetric hydrogenation of α-acetamido dehydroamino acids.[62]



60

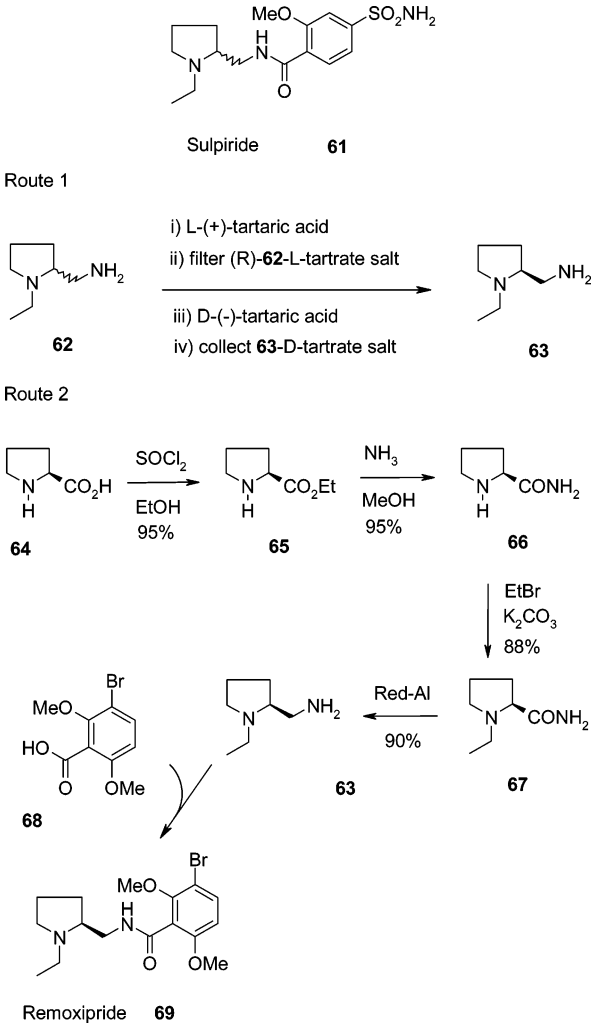
Figure 12. TriChickenfootPhos (TCP) ligand **60**.

Catalysts based on **60** were found to be effective in the asymmetric hydrogenation of the pregabalin intermediate **58**, giving the desired product **59** in 98% ee using half the amount of solvent and one tenth of the previously reported catalyst loading (Scheme 15). Not only does this provide a more economical process in itself, but it must also be noted that the TCP catalyst is owned by Pfizer and would therefore not incur any royalty payments if used on large scale.

2.3.5. Designing a New Route with Freedom To Operate

After safety considerations, the most important aspect of developing a new route is to ensure that the company has freedom to operate the process. New patents covering aspects of a new process serve to (i) capture competitive advantage in obtaining exclusivity to use the route and (ii) maintain freedom to operate in the future, i.e. avoid the prospect of a third party patenting aspects of the route, which would impinge on the company's ability to operate that route in the future.

Scheme 16. (Reproduced with permission from ref 63. Copyright 1997 John Wiley and Sons.)



2.3.5.1. Route Change To Avoid Third Party Patent Infringement. In the late 1960s, it was found that the racemic compound sulpiride (**61**) (Scheme 16) exhibited pronounced antipsychotic activity. Astra became interested in this benzamide group of compounds and developed remoxipride[63] (**69**) (a dopamine D2 receptor antagonist) for the treatment of schizophrenia (launched as Roxiam in the beginning of the 1990s). The medicinal chemistry route to remoxipride (**69**) involved a classical resolution of racemic pyrrolidinamine (**62**). This racemate was used in the commercial synthesis of sulpiride and readily available in bulk quantities. The resolution of **62** (route 1, Scheme 16) was patented[64] by a third party, and various claims in the patent blocked commercialization of this method. For example, a "composition of matter" type claim for the tartrate salt of enantiomerically pure pyrrolidinamine (**63**) was covered in the scope of this patent. It was therefore necessary to identify an alternative noninfringing route for long-term manufacture of remoxipride **69**. A commercial process was established in which (*S*)-proline (**64**) (natural enantiomer) was converted to the amide **66**, alkylated with ethylbromide to give **67**, and reduced with Red-Al to provide **63** as the free base (route 2, Scheme 16). This route has the advantage that the starting material proline (**64**) is available as a single enantiomer compared with the resolution process, which has a 50% maximum theoretical yield.

2.4. Economic Issues

The economic viability of a new drug product (e.g. tablet, capsule) is determined by several key variables. These include (1) cost of goods, (2) selling price for the product, (3) marketing costs for the product, and, (4) in some cases, product and/or technology licensing costs (see above section on legal issues).

The term "cost of goods" (CoG) is used to describe the total costs involved in manufacture of a drug product (this includes API manufacture, formulation, and packaging) expressed as a percentage of the selling price of the drug. API manufacturing costs are therefore a subset of cost of goods.

2.4.1. Potential Economic Issues and Their Significance

The main types of economic issues associated with manufacture of API are as follows: (1) failing to meet the CoG target, (2) unacceptable investment costs during development, and (3) licensing costs for third party intellectual property.

2.4.2. Prediction and Assessment of Economic Issues

Predicting the capability of a process to meet the cost of goods target for the future market is a critical activity. An analysis[65] published by the Office of Technology Assessment (using data from six U.S. pharmaceutical firms) suggests that cost of goods as a proportion of total product sales is, on average, 25% (see eq 1). Thus, on average, 75% of product sales contribute to marketing costs, research and development, operating costs, and profit margin. It must be stressed that this is an average picture across a variety of product types. There will be some products that individually are not profitable but satisfy an important role such as treating diseases in the developing world (some products may be provided free of charge). Assuming that the target CoG is going to be 25%, the next step is to predict likely ranges for each variable in eq 1 and assess the probability of meeting the target.

$$\frac{[(\text{daily dose} \times \text{cost of bulk}) + \text{cost of formulation}]}{\text{selling price}} \times 100 = \%\ \text{cost of goods} \quad (1)$$

Illustrative example:

daily selling price = £2/day

daily dose = 0.2 g/day

API cost = £1,500/kg

formulation cost = £0.1/daily dose

Calculation:

$$\frac{(0.2 \times 2) + 0.1}{2} \times 100 = 25\%\ \text{cost of goods}$$

In predicting selling price,[66] it is necessary to consider: (1) duration of use (acute use products are likely to be more expensive), (2) price and features of competitor products, (3) patient and disease characteristics, (4) economic and social value of the therapy, (5) decision making criteria of prescribers, (6) desired market position, (7) public policy and insurance policy. (This list is reproduced with permission from Haworth Press Inc.)

During Phase I and II clinical trials, pricing (and marketing) research should be based on key decision criteria for product use.

In early drug development, the prediction of API cost is not easy. A reasonable approach is to compare the complexity of the drug candidate with existing commercial drugs. For example, commercial products could be grouped into three cost ranges: low (e.g. less than £500/kg), medium, and high. Similar approximations can be made to estimate formulation costs, especially for simple immediate release formulations based on tablets or capsules. Controlled release tablet profiles and formulations for other routes of administration (e.g. intravenous, intramuscular, intranasal, inhalation) are often more expensive and may involve licensing costs for proprietary technology.

Accurate prediction of dose is not usually possible until clinical Proof of Concept or even Phase III clinical trials. In early drug development, however, it is helpful to model the economic viability by considering pricing scenarios and using expected ranges for daily dose and for API costs. The chart in Figure 13 can be constructed using eq 1 and assuming a fixed selling price and a fixed formulation cost.

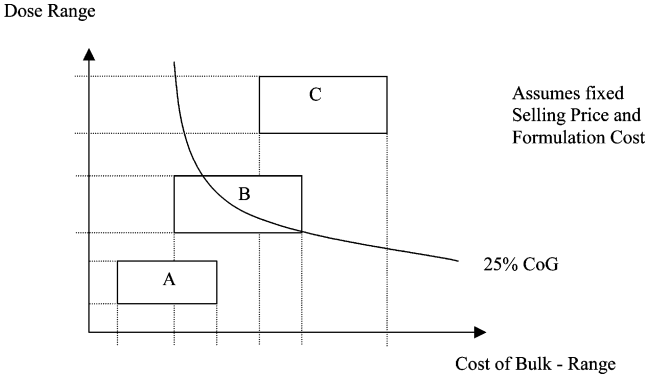


Figure 13. Probability of meeting CoG target (25%) as a function of dose and API cost.

In Figure 13, the box labeled A represents a low-risk cost analysis; the expected dose range and API cost range place the box underneath the target cost of goods curve (25%) and suggest it should be easy to devise an economic process. Box C, on the other hand, illustrates a high-risk position where confidence in reaching an acceptable combination of dose and API cost is very low. The majority of early development projects fall into category A or B, where there is a low to medium risk of economic failure. It is expected, therefore, that the development chemist will be successful in establishing a cost-effective process.

2.4.3. Options To Manage Economic Issues

The components that affect commercial manufacturing costs of an API are (i) product volume, (ii) asset costs and depreciation, (iii) manpower, (iv) maintenance, (v) waste and utilities, (vi) cost of raw materials and reagents, (vii) licensing costs for intellectual property, (viii) supplier profit margin, and (ix) throughput (as detailed later). The balance of these components will be greatly influenced by the structure of the supply chain and the loading of other products in the plant. It is not possible, therefore, to generalize percentage contributions from each component for the industry. Various software products[67] are currently available to model the performance of a process in a plant and highlight key cost elements as well as allowing the chemist and engineer to test the cost benefit of different process scenarios in the model before investing in laboratory and plant trials.

Other options available to manage economic issues include (1) relaxing the percentage cost of goods target, (2) replacing the drug candidate with a more potent and more bioavailable alternative, and (3) researching more cost-effective synthetic routes.

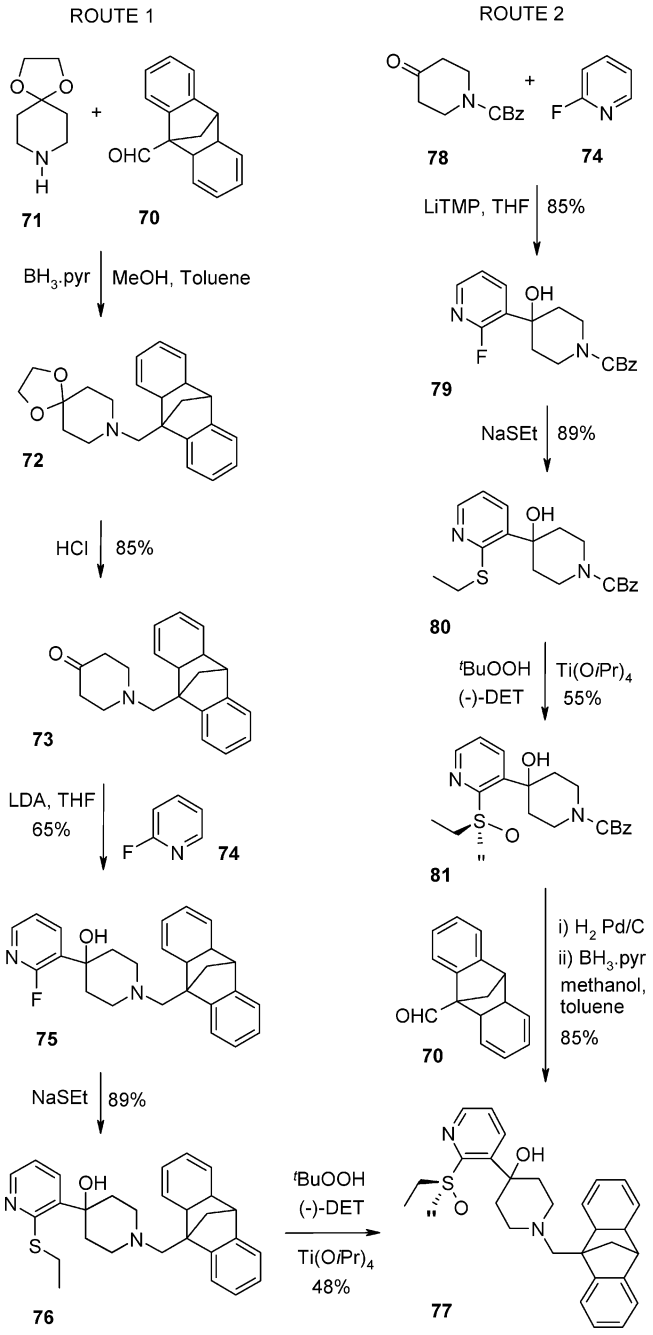
2.4.4. Designing a Cost-Effective New Route

In general, more cost-effective routes involve fewer steps, are more convergent, use cheaper raw materials, and have higher throughput (see section on throughput below).

2.4.4.1. Change of Route To Introduce an Expensive Raw Material at a Later Stage. ZD-3638 (**77**) (Scheme 17) is an atypical antipsychotic agent for the treatment of schizophrenia and was developed[68] by Zeneca from 1993 to 1997. Early clinical evaluation predicted that the daily dose requirement was likely to be somewhere in the range 10−50 mg. An economic assessment of the drug candidate indicated that there was only a medium probability of meeting a 25% CoG target when using the early development route (route 1, Scheme 17) with raw material costs of £1475/kg.

The most significant contributor to raw material costs was aldehyde **70** (£910/kg of **77**), which was processed through five chemical steps to make sulfoxide **77**. In an addition reaction, lithio fluoropyridine **74** (from LDA) was reacted with **73** in a modest 65% yield. A series of alternative routes were evaluated which introduced the expensive aldehyde **70** at a later point in the sequence. In route 2 (Scheme 17), aldehyde **70** was introduced in the final step. In addition, improved yields of the addition reaction between **74** and **78** (85%) were achieved using LiTMP. Raw material costs for route 2 were much lower (£789/kg), and the contribution from aldehyde **70** was only £294/kg of **77**. This change of synthetic route significantly improved the probability of meeting the cost of goods target.

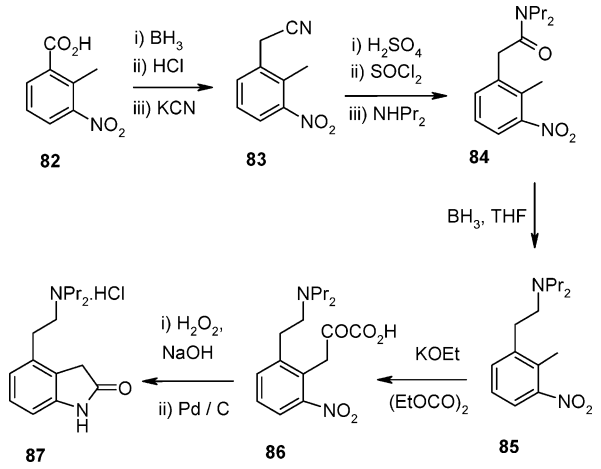
Scheme 17



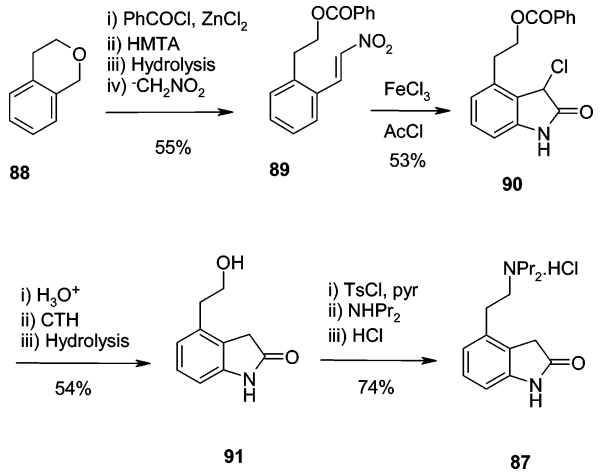
2.4.4.2. Change of Route To Reduce Starting Material Costs. Ropinirole (Scheme 18) (**87**) is a potent non-ergot dopamine receptor agonist and is marketed by GSK as ReQuip for the treatment of Parkinson's disease. It has also been approved in the U.S. for the treatment of primary restless legs syndrome (RLS).

Although the originally reported synthesis[69] (Scheme 18) was suitable for the preparation of small quantities of compound, the chemistry was expensive due to its length (nine stages) and the high material costs. Therefore, a more cost-effective synthesis was required. A commercial route was designed using Royer's ferric chloride−acetyl chloride mediated cyclization of β-nitrostyrenes to 3-chlorooxindoles. Thus, isochroman (**88**) was modified[70] to generate the required β-nitrostyrene (**89**) via a catalytic $ZnCl_2$/benzoyl chloride ring opening, Sommelet oxidation, and, finally,

Scheme 18



Scheme 19



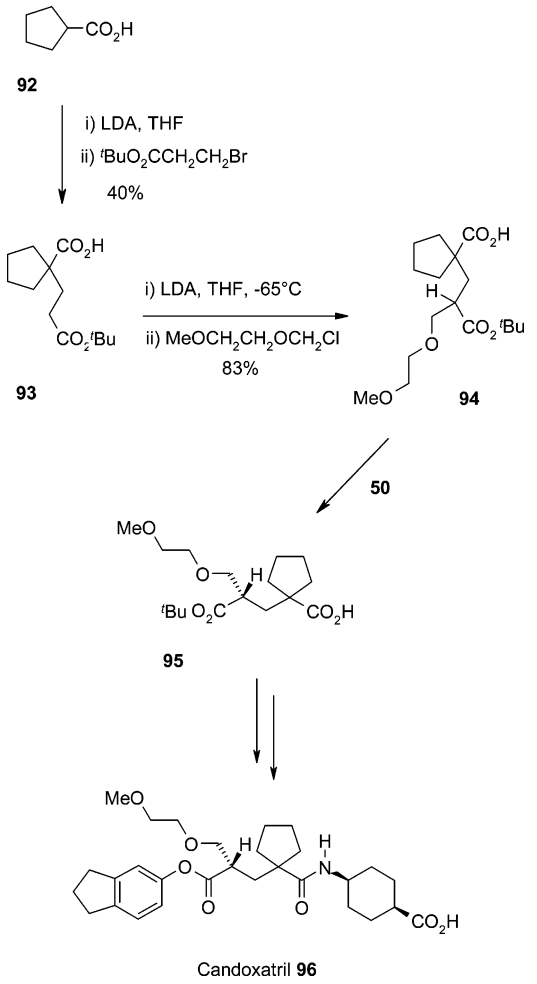
treatment with nitromethane anion using a variant of the MacDonald procedure (Scheme 19).

The required 3-chlorooxindole **90** was successfully prepared from **89** by the ferric chloride mediated cyclization, and this was converted to ropinirole (**87**) by catalytic transfer hydrogenation (CTH), hydrolysis, tosylation, nucleophilic substitution with dipropylamine, and HCl salt formation.

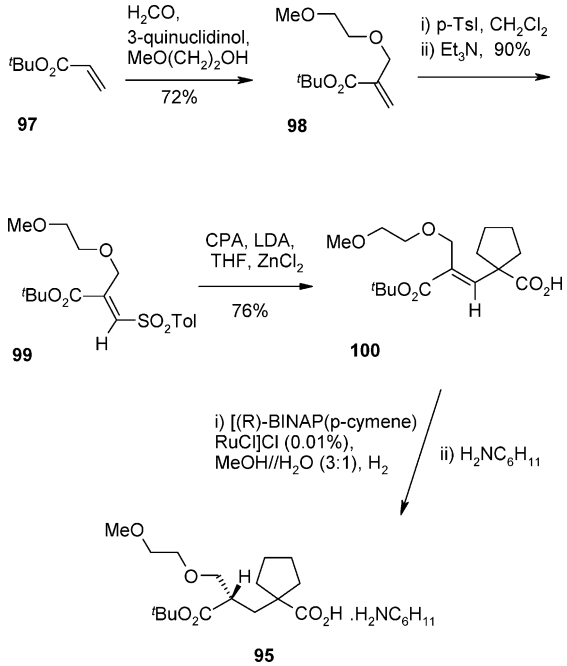
It was demonstrated that a robust conversion of isochroman (**88**) to the nitrostyrene (**89**) could be performed without isolation of any intermediates, and this, along with modification of the final substitution chemistry, allowed the synthesis of ropinirole (**87**) in only five stages and 22% overall yield. This route resulted in a 75% cost saving over the original synthesis and was selected for the commercial manufacture of ropinirole (**87**).

2.4.4.3. Change of Route from Classical Resolution to a Catalytic Asymmetric Induction. Candoxatril (**96**) (Scheme 20) is an orally active prodrug of candoxatrilat, a potent atrial natriuretic factor (ANF) potentiator indicated in the treatment of hypertension and congestive heart failure that was developed by Pfizer. While any new drug needs to demonstrate significant advantages over existing therapies, in the hypertension market, it is also important that new treatments are economically viable due to the number of cheap, effective remedies already available. Candoxatril (**96**) contains a chiral center, and therefore, an efficient synthesis of the single enantiomer was required. The first development route employed a classical resolution[71] of racemic glutarate **94** with

Scheme 20



Scheme 21



(+)-pseudoephedrine (**50**) to furnish the chiral glutarate **95** in 13% yield over four steps (Scheme 20).

The new route (Scheme 21) used the inexpensive starting material *tert*-butyl acrylate (**97**) in a Baylis−Hillman reaction to install the methoxyethyl side chain and give acrylate **98**

in a single step. An iodosulfonation−dehydroiodination sequence gave the tosyl acrylate **99**, which then underwent an addition−elimination step to give the geometrically pure alkene **100** ready for hydrogenation investigations.

A ruthenium BINAP based catalyst was employed[72] in the hydrogenation to complete the new route to chiral glutarate **95** in 33% overall yield, an increase of 2.5-fold over the medicinal chemistry route. An analysis of the relative costs of the two routes showed that the asymmetric hydrogenation route was approximately three times cheaper than the resolution route. This brought the cost of API below the percentage CoG target.

2.5. Control Issues

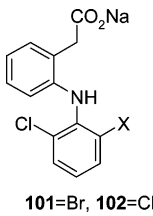
To conduct clinical trials in the USA, it is necessary to manufacture API according to FDA published guidelines[73] and in compliance with ICH guidelines[74] (Q3, Q6, and Q7). Equivalent guidelines are in place for the EU[75] and the rest of the world. These guidelines serve to protect patient safety during the clinical trials, and this is achieved through setting appropriate quality criteria[76] in the API specification and through working to cGMP (current Good Manufacturing Practice). A key challenge for the process chemist is to scale-up the process reproducibly and without adversely affecting the quality of the API. Control of API quality is achieved through control of chemical and physical parameters in the process.

2.5.1. Potential Control Issues and Their Significance

When assessing a synthetic route for control issues, the process chemist should identify the following: (1) nonselective reactions (chemo-, regio-, and stereo-) and other side reactions that are likely to generate process related impurities, (2) the chemical stability and physical properties of each intermediate and reagent (in particular, labile functional groups and chiral centers, stability toward heat, moisture, and oxygen, hygroscopicity, viscosity and crystallinity), and (3) the number and efficiency of potential purification points in the route.

Quality control points are usually isolated intermediates that have specification requirements to limit the level of the impurities that may be present. Effective purification at these points helps to ensure the quality of the final API. Perhaps the most important control point in any route is the isolation of the API, where the physical properties of the compound have a significant influence on chemical purity and ease of formulation. However, this specific area is beyond the scope of this article.

During registration of a new drug with a regulatory authority, a specification must be set for the API that defines what the "acceptable quality" is. Included in the specification are the acceptable levels for each impurity. Impurity **101** (Figure 14) for example, is specified in generic dichlofenac sodium[77] (**102**) and is controlled by U.K. and U.S. pharmacopoeia to a limit of <0.1%. The acceptance criterion for each impurity will depend on several factors, including the nature of the impurity (e.g. solvent, inorganic, process related), its toxicological qualification status, the dose of the drug, and whether the medicine is destined for human or animal use. Guidance on setting acceptable limits for impurities in the API specification can be found in ICH (human health) and VICH (animal health) guidelines, which are available on the ICH and VICH Web sites, respectively. As an example, the following guidelines[73−76] currently apply to impurity levels for a human medicine dosed at <2 g/day: (1) Impurities below 0.05% do not need to be reported (reporting threshold). (2) Impurities above 0.05% but below 0.10% must be reported but do not need to be identified. (3) If an impurity exceeds 0.10%, then it must be structurally identified (identification threshold). This is typically the unspecified limit for impurities. (4) If an impurity is present between 0.10 and 0.15%, no toxicological qualification is required, provided that the impurity does not contain structural alerts for high toxicity (e.g. an alkylating agent). (5) If an impurity is present above 0.15%, then toxicological qualification is required (qualification threshold).



101=Br, **102**=Cl

Figure 14. Structure of dichlofenac sodium (**102**) and its impurity **101**.

When process related impurities have the same structure as an API metabolite, qualified levels can be justified on the basis of human exposure data. Heavy metals are typically limited[73−75] to below 10 ppm in API. In the case of a known genotoxic compound, the chemist is challenged to find alternative chemistry that avoids generation of this impurity or, if this is not possible, designs the process so that the genotoxic compound is introduced at the earliest possible step and is stringently controlled. If any of the raw materials or reagents in a synthetic route are derived from animal sources (e.g. amino acids, enzymes, proteins), then consideration must be given to the likely presence of transmissible spongiform encephalopathy (TSE) agents. Typically, certification is sought from the suppliers to either state that the source of the material is nonmammalian or that the manufacturing safeguards put in place minimize the risk of TSE agents being present.

2.5.2. Prediction and Assessment of Control Issues

In reality, a manufacturing process consisting of completely selective reactions is not always possible when preparing complex drug molecules. In addition, the time scales involved in conducting pilot scale reactions often reveal vulnerabilities in a laboratory scale process. This is particularly evident when a key intermediate has limited solution stability.

After conducting a desk screening exercise to identify potentially labile functionalities, stability screening of isolated intermediates and components of the process should be carried out. Subjecting parts of the process to extended reaction times and stressing other parameters (e.g. excess acid, heat, or moisture) can expose potential control issues. A similar exercise needs to be undertaken for solid-state stability of intermediates and, particularly, the API. This can be done using a number of techniques (e.g., dynamic vapor sorption, thermogravimetric analysis, and ICH stability tests).

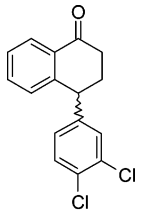
2.5.3. Options To Manage Control Issues

Nonselective reactions (chemo-, regio-, and stereo-) can be managed in a number of ways, and the most helpful approach is to gain a detailed understanding of the reaction mechanism and to screen alternative catalysts and conditions

from the literature. In addition, it can be attractive to use engineering technologies such as continuous flow reactors to improve selectivity.[79] First principles modeling can also be helpful where the key process factors are known and a screening exercise is not necessary.[78] In addition, statistical design of experiments (DoE) can be used to map process output as a function of the parameter range and to identify a robust area away from the edge of process failure.[80,81] A number of analytical tools are available that allow the process development chemist to gain the understanding that underpins process control. Process analytical technology (PAT) is used for real-time monitoring of reactions and reactive intermediates. A typical PAT toolbox for a process development chemist may include on-line mid-IR, NIR, and/or Raman spectroscopy; a Lasentec focused beam reflectance measurement (FBRM) instrument; and at line HPLC or GC(-MS). These techniques[82−84] can also provide, on a laboratory or plant scale, information about reaction mechanisms, including competing mechanisms giving rise to unwanted products.

Intermediates with poor chemical and/or physical stability can be very problematic and are best avoided if possible. When an intermediate is not sufficiently stable for isolation, it can be attractive to telescope the process through to the next step.

Difficulties in controlling levels of impurities in an API can be overcome through a variety of approaches. To prepare API reproducibly to an acceptable high quality, it is often advantageous to establish a series of crystalline intermediates that can be readily purified. Derivatives such as salt forms or esters are a good way of achieving this. Alternative methods include distillation, polymer bound scavenging agents, and adsorbents. Recent advances in simulated moving bed (SMB) chromatography now mean that even chromatographic purification is possible on a production scale, as demonstrated with Pfizer's sertraline process with the separation of the racemic tetralone intermediate **103** (Figure 15).[85]



103

Figure 15. Tetralone intermediate**103** for setraline.

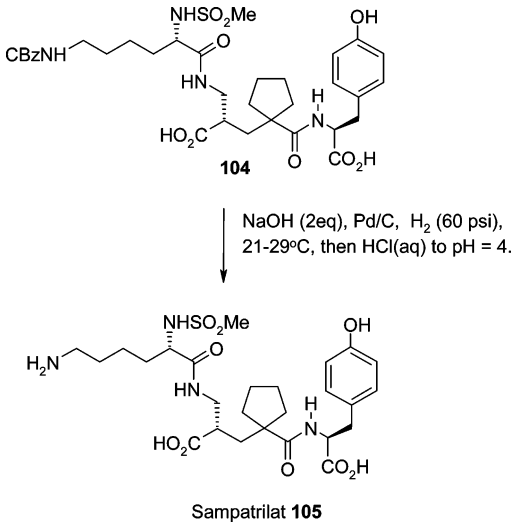
One strategy currently promoted by regulatory authorities, which addresses impurity control, is "quality by design". Rather than developing a process that wholly relies on removal of impurities by, for example, recrystallization, it is better to identify the cause of the impurity in the first place. The origin of each specified impurity should be identified, and if it is a process related impurity, the step in which it is generated is considered to be a key control point for this impurity. The next stage is to identify the parameter or parameters that lead to the generation of the impurity and set tight controls, thereby minimizing the level that is formed and, thus, reducing reliance on final step purification.

Crystallization is another area where process control issues can arise and use of PAT can be helpful,[86] especially in relation to downstream processing. Particles can be engineered to a desired size that allows acceptable separation, drying, and formulation properties (predictive techniques are available for filtration scale-up).[87] A particle size target for a crystallization process may be achieved by identifying the key parameter ranges based on a design of experiments (DoE) data set. Progress of the process is monitored using PAT to understand the prevailing crystallization mechanism and control phenomena such as polymorphism.[88,89]

PAT can be extended to incorporate feedback loops linking the on-line measurement of a critical quality factor to reactor control software, thus shifting the emphasis away from fixed processes to ensure the delivery of API that consistently meets specification. This was implemented, for example in a 1 L reactor, where a Lasentec FBRM[90] instrument and HEL[91] control software were linked during a cooling crystallization.[92] A lower limit for the mean chord size (a measure of particle size) was specified, and the control algorithm adjusted the cooling rate at regular intervals to ensure that the target was met.

2.5.3.1. Process Modification To Accommodate a New, More Stable Polymorph. Sampatrilat (**105**) is a dual ACE/NEP inhibitor developed by Pfizer to potentiate atrial natriuretic factor in animals and man. During the development of this candidate, an interesting example of introducing crystalline intermediates as control points was discovered.[93] The medicinal chemistry route included hydrogenolysis of the CBz group of **104** followed by isolation of the API as an amorphous freeze-dried solid (Scheme 22).

Scheme 22



It was discovered that the API could be isolated as a crystalline hydrate from aqueous methanol. This purified hydrate could then be dehydrated in acetone to give an anhydrous polymorph, which melted at 185 °C (designated P185). While this procedure was successful for the preparation of early toxicological and clinical supplies, a routine purification rework on a 25 L scale revealed a new polymorph, which set solid in the flask. The new form melted at 256 °C, which was over 70 °C higher than the melting point of the previous anhydrous form; this meant that the new form (P256) was significantly more stable. The interconversion diagrams before and after the discovery of P256 are shown in Figures 16 and 17.

Although it was still possible to make the P185 form via freeze-drying P256 and reslurrying in 1-propanol or acetonitrile, no method could be found to prepare the hydrate again. As a result of this, the old process could not be used to make sampatrilat (**105**) as the P256 form was so insoluble that it crystallized out onto the hydrogenation catalyst. The

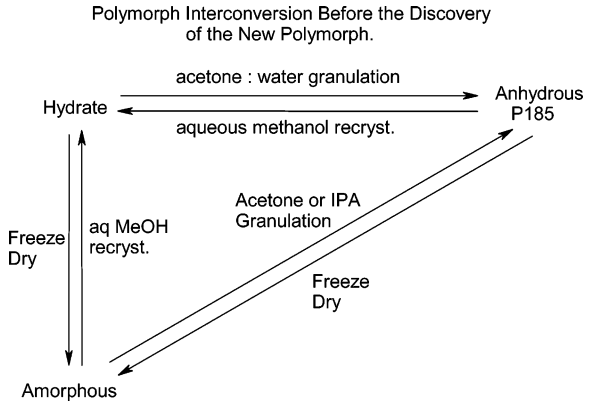


Figure 16. Polymorph interconversion prior to P256 discovery.

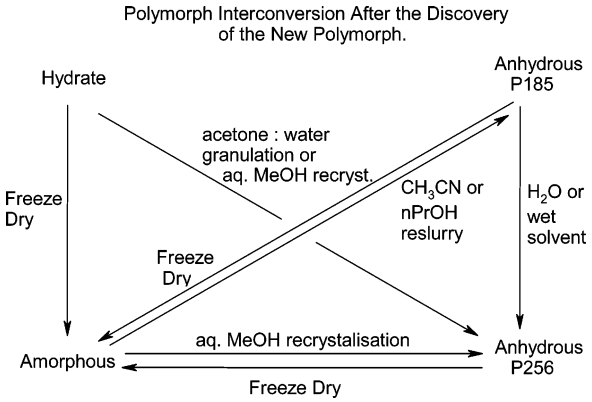


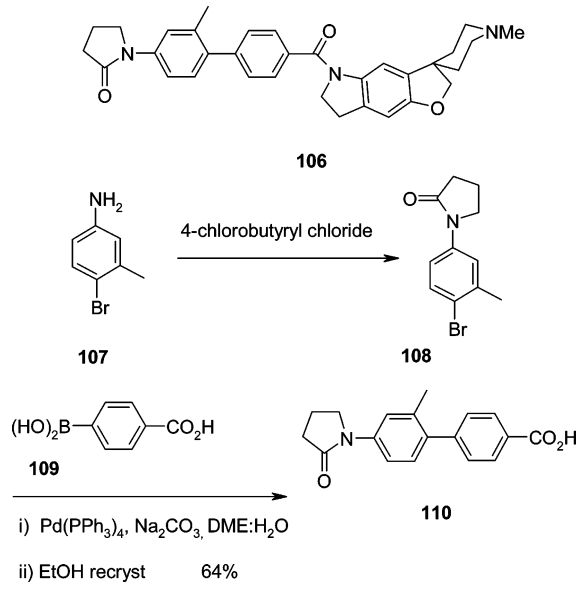
Figure 17. Polymorph interconversion after P256 discovery.

solution to this problem was to carry out the process in aqueous sodium hydroxide to hydrogenate the sodium salt of the starting material, which was soluble under these conditions. After removal of the catalyst by filtration, a pH adjustment resulted in precipitation of the P256 form, which could then be collected by filtration. The discovery of the new form had three advantages: (1) The new form was significantly less hygroscopic than P185, allowing more control over the process. (2) The new form was very insoluble and resulted in a 15% yield increase, thus improving the throughput of the process. (3) The biological performance of the new polymorph was unchanged and a new polymorph patent was granted, giving Pfizer a potential legal advantage over generic competitors.

2.5.3.2. Modification of a Route To Control Palladium Contamination and Crystalline Particle Size. SB-245570 (**106**) was developed by GSK for the treatment of depression.[94] A key intermediate in its preparation is biphenyl acid **110**, which was prepared by a Suzuki coupling between aryl bromide **108** (assembled from aniline **107**) and 4-carboxyphenylboronic acid (**109)** (Scheme 23). Unfortunately, material prepared using $Pd(PPh_3)_4$ catalyst was contaminated with residual palladium at levels of 40−80 ppm, so it was attractive to look for alternative catalysts that reduced the level of palladium contamination in **106**.

It was found that Pd/C could be employed to catalyze this Suzuki reaction using modified and optimized Buchecker conditions. The inexpensive and readily available Pd/C proved ideal for this process, providing a palladium source supported on charcoal and easily removed by filtration. Crude product was isolated by acidification to effect crystallization and further purified by slurrying at reflux in ethanol (or IMS), giving **110** in a yield of 90−93% with residual palladium

Scheme 23



levels of <4−6 ppm. This Pd/C mediated Suzuki coupling procedure was successfully carried out in the pilot plant to prepare two 6.3 kg batches of **110**.

During this plant campaign, a processing problem was encountered during the acidification and isolation of **110**. The acidification produced a thick suspension of very fine material that was extremely slow to filter, even using a centrifuge. Using a Lasentec crystallization monitor, a comparison of the particle size distributions under different crystallization conditions could be made. This showed that the mean chord length of particles obtained under standard conditions was 8.26 μm and the fines constituted 66% of the suspension. After investigating a range of conditions, it was shown that the temperature of acidification was crucial. Acidification at 80 °C led to particles with a much longer mean chord length of 26.3 μm, and the percentage of fines was significantly reduced to 34%. Subsequent filtrations proceeded rapidly, and recoveries were still maintained at 91−93%.

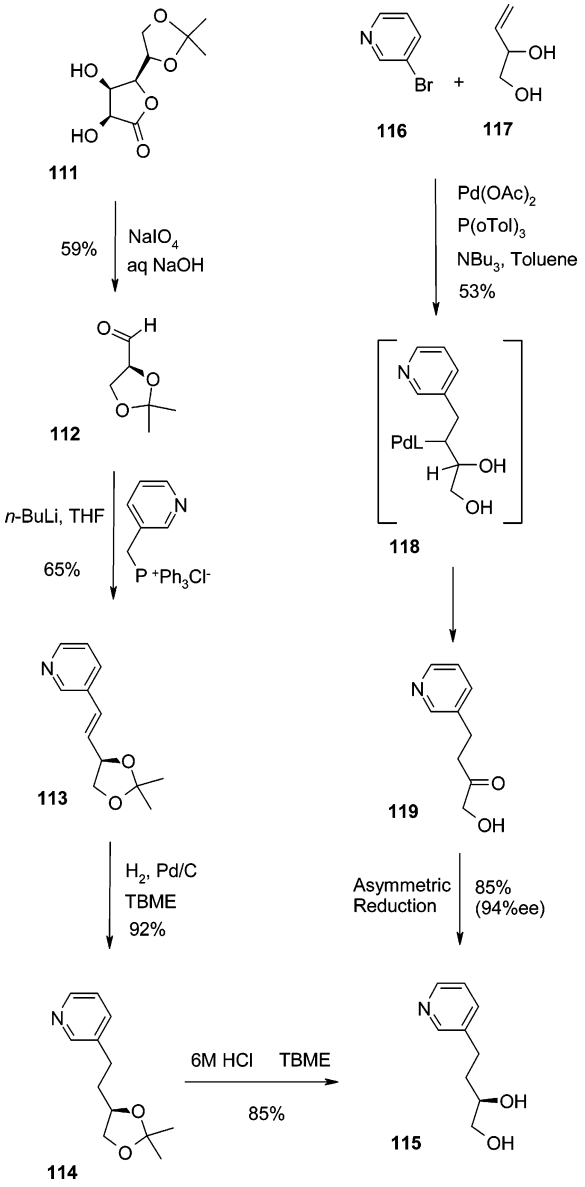
2.5.4. Designing a New Route with Adequate Control Measures

In changing the synthetic route, it is possible that the API will have a different impurity profile requiring repeat qualification in toxicology studies. This may be avoided if the new impurities are below 0.15% and there is no anticipated overt toxicology (e.g. genotoxic impurities). However, if the chemist can assess quality control at the start of development before selecting a synthetic route, this may be avoided. Careful choice of intermediates, process conditions, and solvents can significantly improve success in controlling impurities.

Other examples of changing the synthetic route to achieve control over residual impurities[95] and nonselective reactions[96] and to introduce crystalline control points[30] have been reported in the literature.

2.5.4.1. Change of Route To Avoid an Unstable Chiral Intermediate. Homochiral pyridine diol **115** is a key intermediate in the bulk manufacture of an AstraZeneca drug candidate.[97] The medicinal chemistry route (Scheme 24) to this intermediate involved acetonide protection and periodate oxidation of gluconolactone **111** to generate 2,3-*O*-isopro-

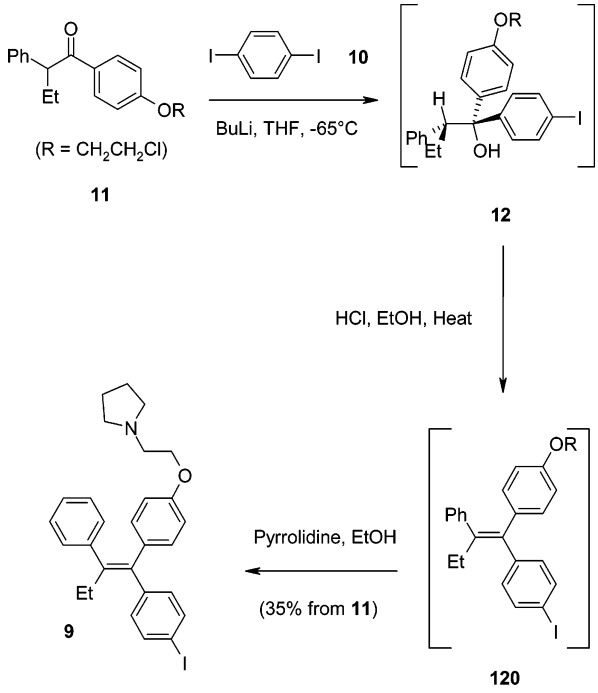
Scheme 24



pylidene-L-glyceraldehyde (**112**). While it might be possible to find more economic routes to aldehyde **112**, the stability of this aldehyde is variable and presents a significant concern for commercial manufacturing. Several reports in the literature site difficulties with epimerization, although work on the D-isomer suggests these reports may be erroneous.[98] Extensive polymerization of **112** occurs within a few days; exclusion of moisture and air retards this polymerization to a rate of 10% per week. The option of learning how to manage the stability issues with **112** was considered. However, given the high cost of gluconolactone, it would still be necessary to evaluate new routes at some point in development. It was therefore attractive to design an alternative route to **115** using a stable intermediate in which the chiral center could be controlled without loss of optical purity. Asymmetric reduction of ketone **119** gave diol **115** in high yield and enantiomeric excess. A Heck reaction of 3-bromopyridine (**116**) with 3-butene-1,2-diol (**117**) provided a simple route to **119** whereby the dehydropalladation of **118** favored the enol product.

2.5.4.2. Change of Route To Control Olefin Geometry. Idoxifene (**9**) (Scheme 25), a selective estrogen receptor

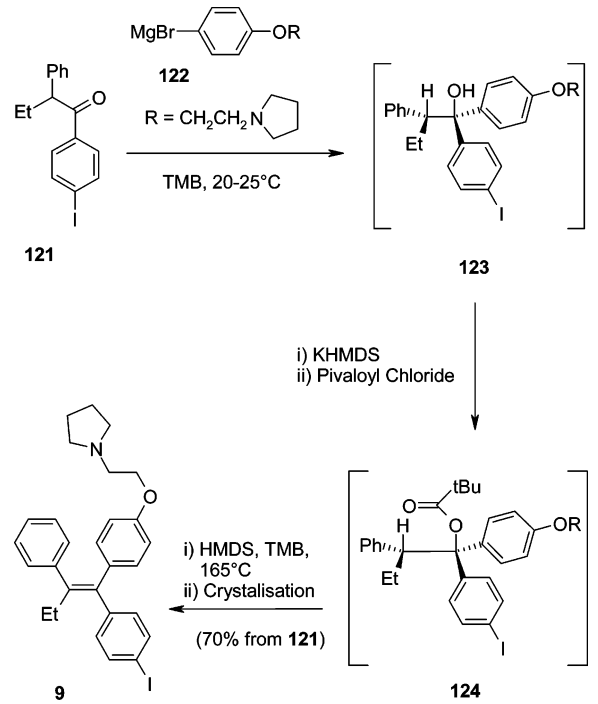
Scheme 25



modulator (see section 2.1.3) developed by GSK, contains a tetrasubstituted double bond.[99] The initial supply route to this compound involved preparation of the alcohol **12**, which was dehydrated under acidic conditions to give the desired *E*-olefin **120** as a mixture of *E*/*Z* isomers (70:30). The olefin mixture was then taken forward to idoxifene **9** by substitution with pyrrolidine and purification by crystallization. This gave a 35% yield from **11** (Scheme 25) and a 24% overall yield.

The lack of selectivity with respect to the alkene geometry meant that a new long-term route was required. It was noted that much of the stereochemical information was lost in the acid-catalyzed dehydration reaction, and it was believed that an improved *E*/*Z* ratio could be obtained using a concerted

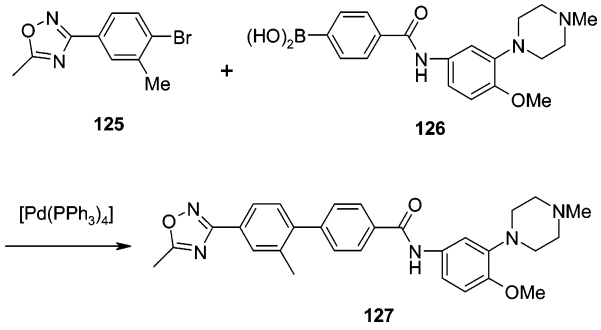
Scheme 26



syn-elimination of a diastereomerically enriched substrate. The preparation of alcohol **123** was therefore developed via a Felkin−Anh controlled Grignard addition to **121** (Scheme 26). This alcohol was converted to the pivalate ester **124**, which was in turn converted to idoxifene (**9**), via a selective *syn*-elimination by refluxing with HMDS in 1,2,4-trimethylbenzene. This methodology gave excellent control and a considerably improved *E*/*Z* olefin ratio of 93:7. It also overcame the safety issues described in section 2.1.3. This allowed formation of **9** in a 70% yield from **121** and an overall 66% yield and was subsequently selected as the route of manufacture.

2.5.4.3. Route Change To Reduce Palladium Contamination by Step Reordering. The initial medicinal chemistry synthesis of GR127935 (**127**) a $5HT_{1D}$ antagonist in development with GSK, involved a $Pd(PPh_3)_4$ mediated cross-coupling reaction between the boronic acid **126** and bromooxadiazole **125** in the final step. This led to unacceptable palladium contamination of the product **127** (Scheme 27). Unlike the example in section 2.5.3.2, changing the source of palladium or recrystallization of **127** was not effective in reducing the level of contamination.

Scheme 27



To minimize palladium contamination, a new route was developed in which the cross-coupling reaction was moved to an earlier point in the sequence. This not only avoided the preparation of complex boronic acid **126** in favor of commercially available **109**, but it also allowed the final stage to be changed to a simple amide formation. Thus, introduction of an additional isolation and purification point after the palladium cross-coupling reaction led to the desired reduction of palladium levels in the final product **127** (Scheme 28).

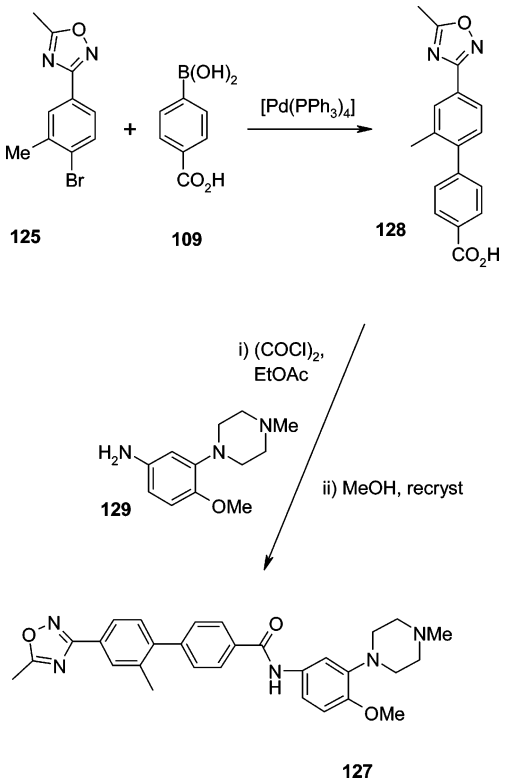
2.6. Throughput Issues

The throughput of a process defines the amount of material (in grams, kilograms, or tons) that can be manufactured in unit time. Throughput issues may not be identified until late in development, potentially only upon transfer to manufacturing. However, consideration of throughput issues earlier than transfer to manufacturing can benefit process chemists in several ways, including delivery time and plant availability.

2.6.1. Potential Throughput Issues and Their Significance

Much of the literature on batch process design and operation[100−102] focuses on plant related aspects of throughput; rarely are the process constraints considered. Key variables that influence the throughput of a process include (1) chemical yield, (2) the capacity, number, and types of processing vessels as well as their availability, (3) cycle time—linked to reaction time, number of solvent replacements, extraction time, crystallization, filtration and drying time, and cleaning difficulties, (4) limiting concentrations of the various stages, (5) number of unit operations—linked to the number of chemical steps and convergency, (6) use of specialist equipment and techniques (e.g., chromatography or microwave reactors), (7) use of high molecular weight protecting groups or salt forms that unnecessarily increase the size of the campaign, and (8) poor availability of raw materials (e.g. natural products).[103]

Scheme 28



2.6.2. Prediction and Assessment of Throughput Issues

Throughput is likely to be an issue when the estimated time of manufacture and delivery date is unacceptable. The principal technical factors affecting throughput for batch manufacture on a commercial scale are the volume limiting operation and the time limiting operation (or cycle time). The chemical process defines the solubility of a species in the process solvent and, therefore, the mass of material that can be generated per liter of plant volume. The chemical process also defines the minimum time required for a unit operation to achieve specification (i.e. reaction conversion, impurity level, particle size distribution). The cycle time for a batch chemical manufacture or the elapsed time between consecutive batches being discharged may be equivalent to or greater than the process time and defines the mass produced per hour of plant time.

A recent survey of processes (using first cGMP batches) in AstraZeneca established a clear relationship between number of synthetic steps and the amount of API that can be manufactured in a unit time. A simple model has been devised (eq 2) which supports these data. The model is based upon calculating the number of batches required to meet the demands of the project and makes use of process and plant information. The variables considered are as follows: (1) chemical yield, Y (%); (2) molecular weight, M_{wt} (g/mol);

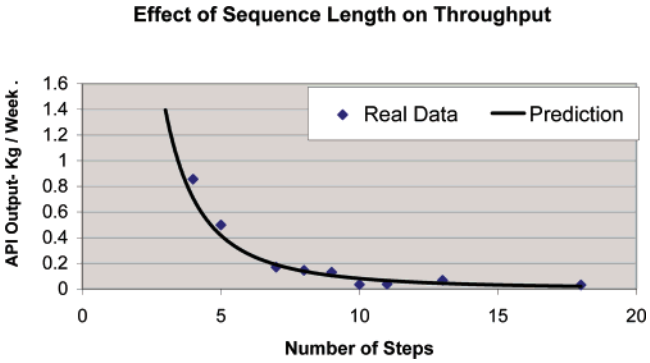


Figure 18. Effect of sequence length on throughput.

(3) bottleneck operational volume, V (L); (4) plant volume, V_P (L); (5) plant availability, A_P; (6) process cycle time, T_c (wks); (7) productivity, P (equivalent to A_P/T_c) (batches per week).

These variables can be used via eq 2, where n equals the number of isolated steps, to calculate the number of batches, N_B, required for a defined material requirement, R (i.e. R at $n = n$ is the amount of API required, and R at $n = 1$ is the amount of the first stage isolated intermediate).

$$N_B = \sum_1^n \left(\frac{R_n M_{wt,n-1}}{M_{wt,n} Y_n}\right)\frac{V_n}{V_{P,n}} \quad (2)$$

The length of the manufacturing campaign, T_m, is then calculated using eq 3

$$T_m = \frac{N_B}{P} + \text{misc} \quad (3)$$

where"misc"refers to any time required for additional activities such as interstage cleaning. The model can be configured to allow appropriate selection of plant capacity depending on the amount of material required. Figure 18 shows the model predictions for how the amount of API produced divided by the total time required to manufacture varies with the number of steps in a linear synthesis. Note that API is not usually manufactured using a continuous process and the use of "API Output − kg per week" should not be confused with the ability to make API on a weekly basis. These units are employed to reflect the overall rate of manufacture for a multistep process making several kilograms of API taking a number of weeks to reach completion. For the example in Figure 18, a constant yield, bottleneck operational volume, and productivity have been assumed.

While there are obvious limitations to this simple model, the time saving benefit of using shorter or more convergent routes is evident. The graph shows that while the number of steps decreases in a linear fashion, the throughput increases exponentially; that is, a new route with half the number of steps takes less than half the time to complete. By referring to this model, it is possible to generate a crude prediction of manufacturing times for a paper route and an established route, and in many cases, it will be quicker to discover, develop, *and* scale-up a new route if it is significantly shorter than the existing route. This type of analysis can be helpful in planning the strategy for process research and development ahead of candidate nomination.

2.6.3. Options To Manage Throughput Issues

Options to improve the various elements of throughput are summarized as follows:

1. Chemical yield can often be improved through a deeper understanding of kinetics and mechanism. Screening of alternative solvents, reagents, and catalysts is also an important approach to yield improvement.

2. The capacity, number, and types of processing vessels as well as their availability is a limiting factor, and sometimes it might be attractive to transfer the campaign to an alternative plant.

3. In general, reducing the number or the length of the most time-consuming unit operations will improve throughput (e.g. reaction time, number of solvent replacements, extraction time, crystallization, filtration and drying time, and cleaning activities). A popular approach is to "telescope" two or more reactions and thereby avoid extended isolation and drying operations.

4. Poor solubility (limiting concentration) is a common issue that impacts throughput. This can be difficult to overcome, and it may be necessary to change solvent systems or make soluble derivatives of either the starting material or product.

5. Some specialist techniques can be very time-consuming or limiting on throughput due to equipment availability (e.g. chromatography). Often this is difficult to avoid, although it can be improved by using continuous processing techniques.

6. High molecular weight protecting groups or salt forms can unnecessarily increase the size of a campaign, so lower molecular weight alternatives should be considered.

7. Thorough investigation of raw material suppliers and lead times allows the development of an efficient sourcing strategy.

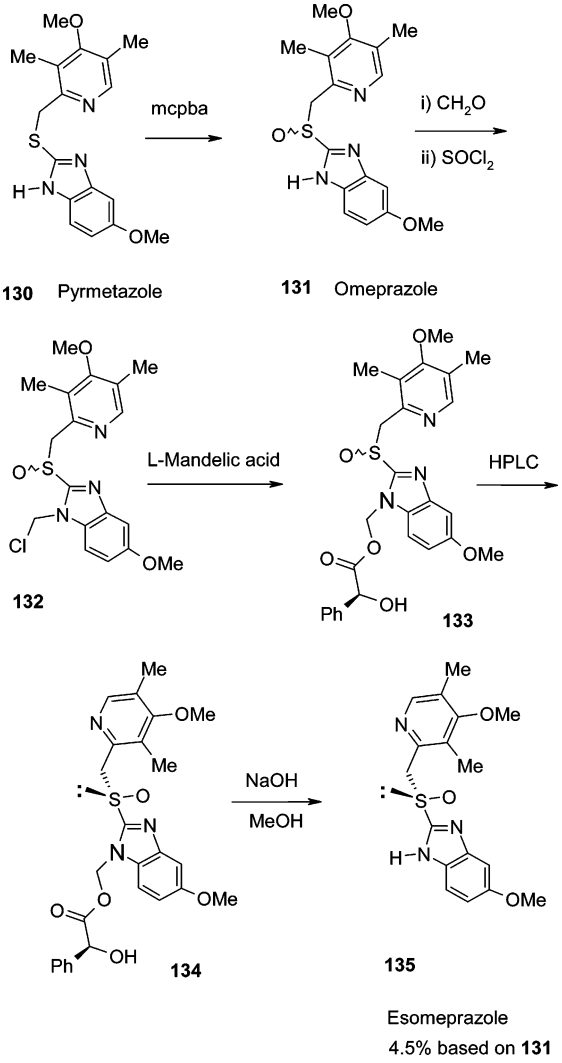
2.6.4. Designing a New Route with High Throughput

2.6.4.1. Route Change To Avoid Preparative HPLC. Omeprazole[104] (**131**) (a racemic mixture, Scheme 29) is a proton pump inhibitor (PPI) used in the treatment of gastric reflux disease. In 1999, omeprazole (Losec) was the largest selling drug in the pharmaceutical industry with annual sales of approximately 6 billion USD. Esomeprazole (**135**) is the *S*-enantiomer of omeprazole (**131**) and is marketed under the name Nexium. Esomeprazole[105] entered development in 1993, and the chemical synthesis involved separation of diastereoisomers **133** by HPLC (Scheme 29).

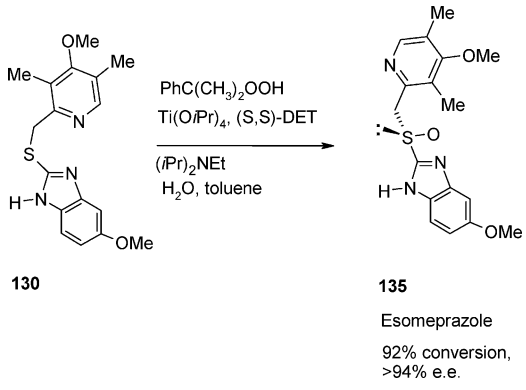
The first development campaign for esomeprazole converted 40 kg of omeprazole (**131**) to supply only 500 g of pure enantiomer **135**. It took 6 weeks to perform the first 3 steps on a 250−500 L pilot scale, providing 5.5 kg of unresolved mandeloyl-derivative **133**. Moreover, 430 injections on a 15 cm × 100 cm HPLC column were necessary to separate the diastereomers, taking at least 1 week with continuous operation. After processing the column fractions and cleaving the mandelate auxiliary of **134**, crystallization gave 500 g of esomeprazole (**135**) as the sodium salt. The next supply requirement was 5 kg of bulk esomeprazole. Extrapolation of the HPLC method would require 60 000 L of eluent to support such a campaign with an unacceptable campaign time. This serious throughput issue triggered a research program to identify an enantioselective synthesis to support development of the product.

In principle, the most attractive approach to the homochiral sulfoxide **135** would involve catalytic asymmetric oxidation of the sulfide precursor **130**. Applying Kagan conditions unfortunately gave a near racemic mixture of isomers. An enantioselective process (Scheme 30) was discovered[106] when

Scheme 29. (Reproduced with permission from ref 106. Copyright 2004 Wiley-VCH Verlag GmbH & Co. KG.)



Scheme 30



the catalyst system was modified using diisopropyl ethylamine (Hünig's base), giving esomeprazole (**135**) in 94% ee and 92% conversion. This new route to **135** offers a significant improvement in throughput, and application of the throughput model (see above) predicts the differences in campaign time shown in Table 4.

2.6.4.2. Avoiding a "Recycle" Bottleneck through Use of an Asymmetric Hydrogenation. The commercial route chosen for the primary manufacture of lotrafiban (**42**) (route C, see section 2.2.4.3) involved a cost-effective recycle/epimerization of unwanted *R*-enantiomer **46**.[43,44] As a product

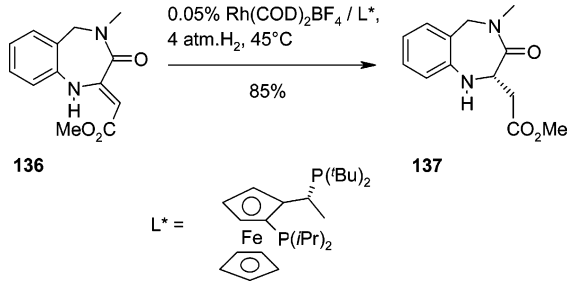
Table 4.

route	steps from **130**	manufacture of **135** (5 kg in plant)
medicinal route	6	14 weeks
new route	1	2 weeks

enters the growth phase of commercial sales, it becomes more likely that plant volume will limit the throughput of the process and threaten the supply chain. While recycling of the *R*-enantiomer **46** reduces the raw material costs, it also "ties up" additional plant volume and so improvements to throughput are limited.

In the final stage of development, an asymmetric hydrogenation of the unsaturated intermediate **136** was investigated. It was found that using 0.05 mol % of $Rh(COD)_2BF_4$ precatalyst and a Josiphos ligand, L*, affords the desired enantiomer **137** in an 85% yield with 99.7% *S* stereochemistry (Scheme 31).

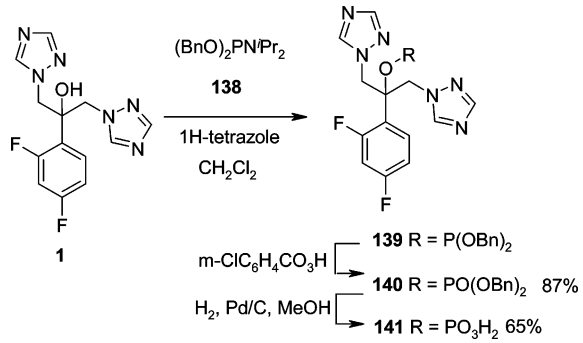
Scheme 31



This new route significantly improved throughput by dramatically reducing the required processing time to deliver the same amount of material. It also improved the overall yield (increasing it to 34%) and the CoG (removing resin bound enzyme Novozym 435 priced at £500/kg).

2.6.4.3. Route Change To Utilize Commercially Available Bulk Starting Materials. The availability of starting materials clearly has an impact on the potential throughput of a process and can be a major factor requiring the identification of a new route. This was the case in the development[107] of the water-soluble prodrug fosfluconazole (**141**). The first route to this compound (Scheme 32) involved

Scheme 32

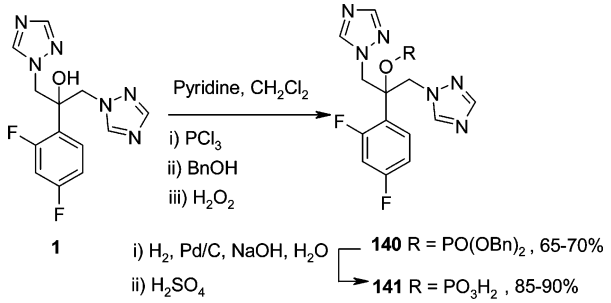


reaction of fluconazole (**1**) with phosphoramidite **138** to yield the corresponding phosphite **139**. Carrying out oxidation to the phosphate **140** and removal of the benzyl groups by hydrogenolysis then completed the synthesis of **141**.

While this route was acceptable for providing early bulk for the program, the dibenzyl diisopropylphosphoramidite **138** was only available in limited quantities from catalog

suppliers. Attempts to source this material from custom manufacturers were hampered by the instability of the material toward moisture and difficulties in purification of this high-boiling liquid on kilo scale. As a result, a new route was identified (Scheme 33) in which the dibenzyl phosphate moiety of **140** was installed by sequential reaction of fluconazole (**1**) with phosphorus trichloride, benzyl alcohol, and then hydrogen peroxide. All of these reagents are commercially available on large scale, and the dibenzyl phosphate ester **140** has now been produced on approximately 1 ton scale using this route.

Scheme 33



3. Interrelationships between Process Issues

Different process issues are often inter-related, and actions taken to address one issue may ultimately solve issues associated with a number of others. On the other hand, some actions may address the most significant issue at the expense of introducing problems in other areas. It is usually possible to identify one issue in particular that can be regarded as the most significant. By definition, the most significant issue is one that is most likely to prevent supply of the next manufacturing campaign and cannot be addressed without resorting to an alternative route. Most of the above case histories describe routes with not one but a combination of issues. For the sake of simplicity, descriptions of these case histories have been focused on the most significant issues.

4. Conclusions

The approval and launch of a new pharmaceutical product is the result of a huge collaborative effort between scientists from a variety of disciplines. The process chemist is responsible for supply of API to support clinical and toxicology studies. However, the most significant contribution that a process chemist can make is to design and develop the best process for commercialization and regulatory approval. To excel in this activity, the process chemist must be highly innovative, have a drive to gain a detailed scientific understanding of the chemistry, and have an ambition to discover and develop the shortest and most efficient synthesis. It is also important to pay attention to detail where interrelated issues may occur, as well as to keep a holistic view of the benefits of each route.

A variety of different process issues can hamper or prevent scale-up of a synthetic route. These issues have been grouped into six main categories, namely safety, environmental, legal, economics, control, and throughput (SELECT). This review provides guidance and case histories to help in the assessment of a synthetic route in terms of its viability for pharmaceutical development and manufacture. The possible options to address each type of issue need to be considered, in particular the design of an improved synthetic route. Early assessment of process issues will enable the process chemist to make a confident decision to embark on a search for alternative routes. Early implementation of the best route will improve delivery times and avoid wasting effort on a route with no long-term future.

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6. References

(1) Pressures on the Pharmaceutical Industry: Pharmaceutical Companies Overview 2003. www.bcc.ecnext.com (accessed Feb 2006).
(2) http://trade.gov/td/chemicals/drugpricingstudy.pdf (accessed Feb 2006).
(3) Neil Grubert, M. A. International Trends in Pharmaceutical Regulatory Affairs; Pharmaceutical Industry Dynamics 2003. www.dresources.com (accessed Feb 2006).
(4) Brummel, R. N. Creativity on large scale: Lesson from scale up. *Book of Abstracts*; 219th American Chemical Society National Meeting, San Francisco, CA, March 26−30, 2000.
(5) Gadamasetti, K. G.; Editor. *Process Chemistry in the Pharmaceutical Industry*; Marcel Dekker Inc.: 1999.
(6) Rogers, R.; Hallam, S. *Process Saf. Environ. Prot.* **1991**, *69*, 149.
(7) Lewis, R. J. *Sax's Dangerous Properties of Industrial Materials*, 10th ed.; Wiley: New York, 1999; 3-Volune Set.
(8) Sanderson, D. M.: Earnshaw, C. G. *Hum. Exp. Toxicol.* **1991**, *10* (4), 261.
(9) Lee, S. A. *J. Fluorine Chem.* **2001**, *109* (1), 55.
(10) Edited by Urben, P. G.; Compiled by Pitt, M. J. *Bretherick's Handbook of Reactive Chemicals*, 6th ed.; Butterworth-Heinemann Ltd: Oxford, 1999.
(11) *National Fire Protection Association's Manual of Hazardous Chemical Reactions*, 5th ed.; NFPA: Boston, 1975.
(12) (a) Craven, A. *Inst. Chem. Eng. Symp. Ser.* **1987**, *102*, 97. (b) Barton, J., Rogers, R., Eds. *Chemical Reaction Hazards*, 2nd ed.; Institution of Chemical Engineers: Rugby, U.K., 1997.
(13) Frurip, D. J.; Freedman, E.; Hertel, G. R. *International Symposium on Runaway Reactions*, Boston, 1989; CCPS/Institute of Chemical Engineers: New York, 1989; p 39.
(14) Lambert, P.; Amery, G. *Int. Symp. Runaway React.* AIChE: New York, 1989; p 525.
(15) Dale, D. J. *Org. Process Res. Dev.* **2002**, *6* (6), 933.
(16) Radex. www.systag.ch/e520rxco.htm (accessed Feb 2006).
(17) Mettler-Toledo (RC-1). mettler-toledo.mt.com/quickcal (accessed Feb 200).
(18) Hazard Evaluation Laboratories (SIMULAR). helgroup.co.uk/home/reactor-systems/process-scale-up/simular-en.html (accessed Feb 2006).
(19) Setaram (DRC). www.setaram.fr/fichiers/produit/drc_gb200392941710630.pdf (accessed Feb 2006).
(20) Chemisens. www.alliedchemicaltech.com/reaction (accessed Feb 2006).
(21) ARC. www.thermalhazardtechnology.com/products/urc.htm (accessd Feb 2006).
(22) PHI-TEC. www.helgroup.co.uk/home/consultancy/reaction-hazards-sp.html (accessed Feb 2006).
(23) APTAC. www.tiaxllc.com/technologies/tech_tiaxproducts.php (accessed Feb 2006).
(24) ARSST. www.arsst.com (accessed Feb 2006).
(25) VSP2. www.fauske.com/VSP2.asp (accessed Feb 2006).
(26) www.johnmorris.com.au/html/Hel/adiabatic_high_pressure_dewar.htm (accessed Feb 2006).
(27) (a) Hofelich, T. C.; Thomas, R. C. The Use/Misuse of the 100 °C Rule in the Interpretation of Thermal Hazard Tests. *International Symposium on Runaway Reactions*, Boston, 1989; CCPS/Institute of Chemical Engineers: New York, 1989; p 74. (b) Stoessel, F.; Fierz, H.; Lerena, P.; Kille, G. *Org. Process Res. Dev.* **1997**, *1* (6), 428.

(28) Ragan, J. A.; am Ende, D. J.; Brenek, S. J.; Eisenbeis, S. A.; Singer, R. A.; Tickner, D. L.; Teixeira, J. J., Jr.; Vanderplas, B. C.; Weston, N. *Org. Process Res. Dev.* **2003**, *7* (2), 155.

(29) Ennis, D. S.; Lathbury, D. C.; Wanders, A.; Watts, D. *Org. Process Res. Dev.* **1998**, *2*, 287.

(30) Ashcroft, C. P.; Challenger, S.; Derrick, A. M.; Storey, R.; Thomson, M. N. *Org. Process Res. Dev.* **2003**, *7*, 362.

(31) (a) Anon. *Org. Synth.* **1966**, *46*, 105. (b) Berthold, W. *Proc. 3rd Int. Symp. Loss Prev. Safety Prom. Chem. Ind.*, 1431, Basle, SSCI 1980.

(32) Barker, A. C.; Boardman, K. A.; Broady, S. D.; Moss, W. O.; Patel, B.; Senior, M. W.; Warren, K. E. H. *Org. Process. Res. Dev.* **1999**, *3* (4), 253.

(33) Anon. Vinyl bromide. *Dangerous Prop. Ind. Mater. Rep.* **1989**, *9* (1), 80; *Chem. Abstr.* **1989**, *110*, 198295 AN 1989:198295.

(34) http://oaspub.epa.gov/webi/meta_first_new2.try_these_first and www.epa.gov/srs/ (accessed Feb 2006).

(35) http://www.environment-agency.gov.uk/netregs/legislation/287972/652894/658261/?lang=_e (accessed Feb 2006).

(36) Constable, D. J. C.; Curzons, A. D.; Freitas dos Santos, L. M.; Geen, G. R.; Hannah, R. E.; Hayler, J. D.; Kitteringham, J.; McGuire, M. A.; Richardson, J. E.; Smith, P.; Webb, R. L.; Yu, M. *Green Chem.* **2001**, *3*, 7.

(37) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.

(38) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L.; Mortimer, D. N. *Green Chem.* **2001**, *3*, 1.

(39) Jimenez-Gonzalez, C.; Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Clean Technol. Environ. Policy* **2002**, *4*, 44.

(40) Fujita, K. *Org. Lett.* **2004**, *6* (20), 3525.

(41) Goldwater, L. J. *Sci. Am.* **1971**, *224* (5), 15.

(42) (a) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org Process Res. Dev.* **2000**, *4* (1), 17. (b) Dunn, P. J.; Galvin, S.; Hettenbach, K. *Green Chem.* **2004**, *6*, 43.

(43) Andrews, I. P.; Atkins, R. J.; Breen, G. F.; Carey, J. S.; Forth, M. A.; Morgan, D. O.; Shamji, A.; Share, A. C.; Smith, S. A. C.; Walsgrove, T. C.; Wells, A. S. *Org. Process Res. Dev.* **2003**, *7*, 655.

(44) Atkins, R. J.; Banks, A.; Bellingham, R. K.; Breen, G. F.; Carey, J. S.; Etridge, S. K.; Hayes, J. F.; Hussain, N.; Morgan, D. O.; Oxley, P.; Passey, S. C.; Walsgrove, T. C.; Wells, A. S. *Org. Process Res. Dev.* **2003**, *7*, 663.

(45) http://www.unodc.org/unodc/index.html (accessed Feb 2006).

(46) http://www.incb.org/incb/index.html (accessed Feb 2006).

(47) http://www.opsi.gov.uk/and http://www.usdoj.gov/dea/index.htm (accessed Feb 2006).

(48) (a) http://www.whitehousedrugpolicy.gov/index.html (accessed Feb 2006). (b) http://www.deadiversion.usdoj.gov/index.html (accessed Feb 2006).

(49) (a) Dack, K. N.; Maguire, R. J. (Pfizer Limited, U.K.; Pfizer Inc.). PCT Int. Appl. 2004, WO 2004056750; *Chem. Abstr.* **2004**, *141*, 106197. (b) Boswell, R. F.; Lo, Y. S. (Boehringer Ingelheim Chemicals, Inc., USA). 2002 US Pat. 6399828; *Chem. Abstr.* **2002**, *137*, 5982. (c) Song, Z. J.; Zhao, M.; Frey, L.; Li, J.; Tan, L.; Chen, C. Y.; Tschaen, D. M.; Tillyer, R.; Grabowski, E. J. J.; Volante, R.; Reider, P. J.; Kato, Y.; Okada, S.; Nemoto, T.; Sato, H.; Akao, A.; Mase, T. *Org. Lett.* **2001**, *3*(21), 3357. (d) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119* (28), 6496.

(50) http://www.cas.org/ (accessed Feb 2006).

(51) http://www.dti.gov.uk/index.html and http://www.state.gov/ (accessed Feb 2006).

(52) http://www.hse.gov.uk/comah (accessed Feb 2006).

(53) http://www.osha.gov/ (accessed Feb 2006).

(54) http://www.epa.gov/ (accessed Feb 2006).

(55) am Ende, D. J.; Vogt, P. F. *Org. Process Res. Dev.* **2003**, *7* (6), 1029.

(56) http://www.hse.gov.uk/index.htm (accessed Feb 2006).

(57) Details of EUSES can be found at the European Chemicals Bureau at http://ecb.jrc.it/ (accessed Feb 2006).

(58) European Chemical Substances Information System—ESIS. http://ecb.jrc.it/ (accessed Feb 2006).

(59) Jackson, H. Basic Intellectual Property Concepts. *Patent Strategy: For Researchers and Research Managers*, 2nd ed.; John Wiley & Sons Ltd: Chichester, 2001; Chapter 1.

(60) Simmons, E. S. *Drug Discovery Today* **1998**, *3* (2), 52.

(61) Cabri, W.; Di Fabio, R. *From Bench to Market: The Evolution of Chemical Synthesis*; Oxford University Press: Oxford, 2000; p 168.

(62) (a) Burk, M. J.; de Koning, P. D.; Grote, T. D.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Skissell, W.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003,** *68* (14), 5731. (b) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126* (19), 5966.

(63) Federsel, H.-J. *Chirality in Industry II*; Wiley: 1997; p 225.

(64) Bulteau, G. S. Afr. Pat. 6802593, 1968; *Chem. Abstr.* **1969**, *71*, 30354b.

(65) *Pharmaceutical R&D, Costs, Risks and Rewards*; Office of Technology Assessment, Congress of the U.S.: 1993; Appendix G, p 302.

(66) Kolassa, E. M. *Elements of Pharmaceutical Pricing*; The Pharmaceutical Products Press (Haworth Press Inc.): 1997.

(67) Batch Plus. www.aspentec.com (accessed Feb 2006).

(68) Moseley, J. D.; Moss, W. O.; Welham, M. J. *Org. Process. Res. Dev.* **2001**, *5* (5), 491.

(69) Dagger, R. E.; Fortunak, J. M.; Giles, R. G.; Halyer, J. D.; Howie, S. L. B.; Mastrocola, A.; Negus, A.; Oxley, P. W.; Walsgrove, T. C.; Walsh, S. E. *J. Heterocycl. Chem.* **1995**, *32*, 875.

(70) Giles, R. G.; Halyer, J. D.; Howie, S. L. B.; Negus, A.; Oxley, P. W.; Walsgrove, T. C.; Whiter, M. *Org. Process Res. Dev.* **1998**, *2*, 3.

(71) Challenger, S.; Derrick, A.; Mason, C. P.; Silk, T. V. *Tetrahedron. Lett.* **1999**, *40* (11), 2187.

(72) Burk, M. J.; Bienewald, F.; Challenger, S.; Derrick, A.; Ramsden, J. A. *J. Org. Chem.* **1999**, *64* (9), 3290.

(73) http://www.fda.gov/cder/OPS/default.htm (accessed Feb 2006).

(74) ICHQ3A(R): Impurities In New Drug Substances. http://www.ifpma.org/ich5q.html - Q3A(R) (accessed Feb 2006). ICHQ3C: Impurities: Guideline For Residual Solvents. http://www.ifpma.org/pdfifpma/q3c.pdf (accessed Feb 2006). ICHQ6A: Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances. http://www.ifpma.org/pdfifpma/q6a.pdf (accessed Feb 2006). ICH Q7A GMP for Active Pharmaceutical Ingredients. http://www.ifpma.org/ich5q.html#GMP (accessed Feb 2006).

(75) http://www.emea.eu.int/pdfs/human/qwp/013096en.pdf (accessed Feb 2006).

(76) http://www.pharmtech.com/pharmtech/data/articlestandard/pharmtech/062003/45872/article.pdf (accessed Feb 2006).

(77) (a) http://online.pheur.org/entry.html (accessed Feb 2006). (b) Ciba Geigy. Neth. Pat. Appl. 6,604,752, 1966; *Chem. Abstr.* **1967**, *67*, 81925.

(78) Braatz, R. D. *Lasentec User Forum*; New York, 2003.

(79) Paul, E. *Chem. Ind. (London, U.K.)* **1990,** *10*, 320.

(80) Hawkins, J. M.; Makowski, T. W. *Org. Process. Res. Dev.* **2001**, *5* (3), 328.

(81) Owen, M. R.; Luscombe, C.; Lai, L.-W.; Godbert, S.; Crookes, D. L.; Emiabata-Smith, D. *Org. Process Res. Dev.* **2001**, *5* (3), 308.

(82) Ward, H. W.; Sekulic, S. S.; Wheeler, M. J.; Taber, G.; Urbanski, F. J.; Sistare, F. E.; Norris, T.; Aldridge, P. K. *Appl. Spectrosc.* **1998,** *52*, 17.

(83) LeBlond, C.; Wang, J.; Larson, R.; Orella; Sun, Y.-K. *Top. Catal.* **1998,** *5*, 149.

(84) Marziano, I.; Sharp, D. C. A.; Dunn, P. J.; Hailey, P. A. *Org. Process Res. Dev.* **2000**, *4* (5), 357.

(85) Quallich, G. J. *Chirality* **2005**, *17* (Suppl.), S120−S126.

(86) Yu, L. X.; Lionberger, R. A.; Raw, A. S.; D'Costa, R.; Wu, H.; Hussain, A. S. *Adv. Drug Delivery Rev.* **2004**, *56* (3), 349.

(87) *Perry's Chemical Engineers' Handbook*, 7th ed.; Perry, R., Green, D., Eds.; McGraw-Hill: London, 1997.

(88) Jozwiakowski, M. J. *Water-Insoluble Drug Formulation. 2000*; Interpharm Press: Englewood, CO, 2000; p 525.

(89) (a) Marziano, I. *3rd International Workshop on Polymorphism and Crystallisation*, San Francisco, 12−14 Nov 2001, Scientific Update: Mayfield, U.K., 2001. (b) Chemburkar, S. R.; Bauer, J.; Deming, K.; Spiwek, H.; Patel, K.; Morris, J.; Henry, R.; Spenton, S.; Dziki, W.; Porter, W.; Quick, J.; Bauer, P.; Donaubauer, J.; Narayanon, B. A.; Soldani, M.; Riley, D.; McFarland, K. *Org. Process Res. Dev.* **2000**, *4* (5), 413.

(90) http://www.lasentec.com (accessed Feb 2006).

(91) http://www.helgroup.co.uk/home/software-sp.html (accessed Feb 2006).

(92) Birch, M.; Fussell, S.; Hardy, R.; Higginson, P. D.; Jupp, K.; Marziano, I. *Lasentec User Forum*; New York, 2003.

(93) Dunn, P. J.; Hughes, M. L.; Searle, P. S.; Wood, A. S. *Org. Process Res. Dev.* **2003**, *7*, 244.

(94) Ennis, D. S.; McManus, J.; Wladyslaw, W.-K.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248.

(95) Dale, D. J.; Draper, J.; Dunn, P. J.; Hughes, M. L.; Hussain, F.; Levett, P. C.; Ward, G. B.; Wood, A. S. *Org. Process Res. Dev.* **2002**, *6* (6), 767.

(96) Waite, D. C.; Mason, C. P. *Org. Process Res. Dev.* **1998**, *2* (2), 116.

(97) Ainge, D.; Vaz, L.-M. *Org. Process Res. Dev.* **2002**, *6*, 811.

(98) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem*. **1991**, *56*, 4056.
(99) Ace, K. W.; Armitage, M. A.; Bellingham, R. B.; Blackler, P. D.; Ennis, D. S.; Hussain, N.; Lathbury, D. C.; Morgan, D. O.; O'Conner, N.; Oakes, G. H.; Passey, S. C.; Powling, L. C. *Org. Process Res. Dev*. **2001**, *5*, 479.
(100) Sharratt, P. N., Ed. *Handbook of Batch Process Design*: Kluwer Academic: 1999.
(101) Ku, H.-m; et al. *Chem. Eng. Prog.* **1987,** *83* (8), 35.
(102) Manganaro, J. L. *Chem. Eng. Prog.* **2002,** *98* (8), 70.
(103) Cabri, W.; Di Fabio, R. *From Bench to Market: The Evolution of Chemical Synthesis*; Oxford University Press: 2000; p 214.
(104) Lindberg, P.; Brandstrom, A.; Wallmark, B.; Mattsson, B.; Rikner, L.; Hoffman, K. *J. Med. Res. Rev*. **1990,** *10*, 1.
(105) Olbe, L.; Carlsson, E.; Linberg, P. *Nat. Rev. Drug. Discov*. **2003,** *2*, 132.
(106) Federsel, H.-J.; Larsson, M. *Asymmetric Catalysis on Industrial Scale*; Wiley: 2004; p 413.
(107) Bentley, A.; Butters, M.; Green, S. P.; Learmonth, W. J.; MacRae, J. A.; Morland, M. C.; O'Connor, G.; Skuse, J. *Org. Process Res. Dev.* **2002**, *6* (2), 109.

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