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Review

Process R&D under the magnifying glass: Organization, business model, challenges, and scientific context ☆

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ABSTRACT

Initially, the aim is to provide the big picture illustrating the as is situation in the pharmaceutical industry: a lack of productivity resulting in too few products reaching the market; a loss of billions in revenue over the next few years as some of the major megabrands go off patent; a spiraling cost for developing new drugs and taking them through clinical and safety studies. Following on, a look deeper into the organization will offer an insight into the state-of-the-art in a technical function accountable for chemical Process R&D (with a remit to develop scalable, robust, and cost efficient processes for small molecules). The vast majority of compounds already launched in the form of drug products on the market or still being pursued through the phases of discovery and development, fall within the category of small molecules (as opposed to biopharmaceuticals, e.g., proteins, monoclonal antibodies). This typically means molecular weights of <1000 Da and puts organic synthesis in the widest sense of the word at the forefront of technologies needed to support R&D programs in the pharma industry.

Understandably, the demands on Medicinal Chemistry are quite different to what applies in a Process R&D (PR&D) organization. In the former, making large numbers of potentially interesting molecules, many of which are discarded after testing, is a key driver and for this virtually any synthetic methodology will suffice. For PR&D, however, homing in on selected compounds there is an expectation that the best synthetic routes will be delivered that meet a number of tough criteria, for instance from an environmental and safety point of view, allowing operation on large scale, offering cost competitiveness, avoiding patent infringements, showing sustainability for long-term production, etc. The intention is to focus on issues to be addressed during this transition by providing examples of changes that had to be put in place in order to make the supply of larger amounts of material feasible. At the end some forward looking conclusions will be shared.

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☆ This paper is based on a lecture presented at the Department of Chemical Biology, Max-Planck Institut für Molekulare Physiologie, Dortmund, Germany on 27th March 2008.

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1. Introduction: setting the scene

A short and simple way of describing how to make a drug could be: take your active compound and turn it into a formulated product (e.g., a tablet) by adding the appropriate excipients. The former requires chemists and chemical engineers to define the molecular structure and ways of making it; the latter formulators who know what components to add in order to arrive at a medicine that is suitable for patients to use. This two-stage process might, at least formally speaking, look rather straightforward, but does as a matter of fact represent just a small portion of the field of pharmaceutical R&D. As the core purpose of this review is to scrutinize the principles and methods applied in defining manufacturing procedures for the bulk active (the ingredient that is responsible for the pharmacological effect), the deeper understanding of the context requires a broader picture to be painted where the current situation is highlighted together with some of the associated challenges.

The development of novel medicines, an endeavor ultimately aimed at providing benefit to patients, is a complex, risky, and very expensive franchise that only rarely succeeds in bringing new products onto the market. There are obviously many reasons for the high failure rates, but one that stands out is intrinsic to the whole concept of creating drugs; the difficulty in achieving non-harmful interactions of chemical compounds, whether these are small sized (low molecular weight) or large moieties (proteins, antibodies), with the plethora of exquisitely operating, fine-tuned biological receptors and processes present in the human body. It is this chemistry-based interplay of structure and activity, characterized by the influence of molecules on a wide variety of targets that, in essence, holds the explanation to why an average of >9 out of 10 candidate drug (CD) projects entering pre-clinical development have to be discontinued before reaching the registration phase several years later. Among the range of reasons for failure, toxicological properties in animal species and lack of efficacy in man stand out as being the most common, with both having direct links to chemical and physical properties expressed by the compounds chosen to be investigated and developed.[1]

With the unprecedented situation that a number of high profile, branded products marketed by the originating innovator company (notably big and mid-sized pharma) and currently selling at a value of multi-billion dollars per annum will lose their patent protection over the 10-year period from 2006 to 2015 poses a major threat. In absolute terms, in 2008 drugs responsible for revenues of $17Bn lost patent coverage in the USA alone and for the entire period alluded to, the potential loss of sales sums up to the stunning overall figure of more than $120Bn. It can easily be understood that in light of these facts, many experts predict that the generics business will see a formidable boom over the next few years. Extending the analysis up to the year 2015 by comparing the performance in revenue terms with a benchmark of 5% CAGR (compound annual growth rate), it turns out that only a small fraction of large-cap pharmaceutical enterprises will show a positive gap pointing towards a very unhealthy future for many companies.[2] As expected, the traditional pharmaceutical industry is not sitting idle watching the 'catastrophe' approaching. On the contrary and there are many initiatives underway to address the underlying weakness of low productivity measured as number of annual approvals of new chemical entities, NCEs (in the recent past the output per company, defined as the top 15 pharma, has been an appalling 0.5 to be compared with the aspirational target of at least 2 if not more).[3] One strategy that has emerged which is bound to have a clear impact on the future performance is the sharp increase in number of licensed and acquired products at the expense of a shrinking share of drugs emanating entirely from in-house efforts. Thus, the latter category is forecasted to be reduced from above 45% in 2008 to just under 40% 5 years later (2013), whereas the combined portfolio of products generated via licensing and acquisition will increase by 5%.[4] Another approach to tackle the problem is taking the current estimated level of internal rate of return (~7.5%) as its starting point; a figure seen as entirely unsatisfactory as it in fact is less than the cost of capital faced by the industry. Reaching the historical levels of >~12% (achieved, e.g., in the period 1997–2001), the focus for companies should be cost, speed and decision-making. Their respective contribution would be expressed as reduction in overall cost for each molecule in development by 15%, an increase in speed enabling the time-to-launch to be conducted 1½ years faster, and acceptance of higher phase II attrition leading to an increase in the probability of success at the crucial phase III stage by 10%.[5]

Given this rather frightening background the question to address is how a technical function such as Process R&D should approach the challenges and what improvements have to be put in place to better deliver to the needs of the business? With the key accountabilities being (i) the development of safe, environmentally considerate, and cost-effective processes for the active pharmaceutical ingredients (APIs) allowing sustainable commercial production; (ii) scale up and manufacture of APIs in support of drug development projects from pre-clinical studies through clinical phases and registration; (iii) contribution with significant processing and quality control documentation for regulatory filings and (iv) maintenance of responsibility for registered API processes throughout their entire life-cycle as marketed products, there are numerous ways in which the current continuous improvement paradigm can be approached.[6,7] Admittedly, the areas of responsibility just described will hardly put a drug project in a situation of major risk and this is confirmed by looking at reasons for termination. The picture that emerges based on aggregated company statistics does not even show chemistry or process scale up problems to be a factor in its own right. If at all detectable, it might be found grouped together as other or unknown which combined represent about 7% of the total causes for stopping projects.[1] Another way of expressing this fact is to say that PR&D has its house in order, whereas other parts in pharmaceutical R&D will have to improve on their capability to reduce the failure rate. Analyzing the roots behind the weakening pharma franchise and discussing measures to be implemented that will enable the return to a position of strength once held will be addressed in the following section.

2. Declining performance—where are the issues?

How to define the problems and where are the areas of weakness? A good start is to take a look right into the current as is situation that one is most likely to be exposed to, virtually wherever you tend to cast your eyes across the major pharma companies. From a purely financial point of view, the years since turning into the new millennium have delivered a more or less constantly downwards-directed outcome when analyzing some key indicators. Shareholder value is one such measure that, however debatable with regard to indicative power and reliability, sends a clear message saying that over the slightly more than 7-year period (December 2000–February 2008) the top 15 companies have lost in the order of $850Bn.[8] This enormous decay is, furthermore, expressed by the dramatic reduction in the ratio of share price over earnings that during this relatively short time span has plummeted from 32 to 13—a fall by roughly 60%.

The question to ask is whether these stock-based performance indicators are justifiable or if they are built on misconceptions held by less well informed outside 'spectators' or self-appointed

experts. Looking at recorded authentic data accumulated over the past decade (1998–2008) shows that the latter does not apply, but rather strengthens the perception that the industry is not doing so well—now and in the recent past. Perhaps the most indicative parameters to take into account that signify the criticality of the situation are the cost for running the R&D machinery and the output of New Chemical Entities (NCEs) on the market; the former has increased by a hefty 80% (non-inflation adjusted) and the latter has seen a reduction by a stunning 43% (see Fig. 1). Some basic facts describing the reasons behind this state-of-the-art will help in understanding how the current situation has arisen. With the focus being on more and more complex deceases—Alzheimer's, stroke, obesity, diabetes, arteriosclerosis to mention but a few—where society is facing a high degree of unmet medical need, the challenge to find efficient treatment paradigms is enormous. As a consequence, this has led to the design of highly sophisticated clinical study protocols to show not only efficacy in man, but also safety. Coupled with the more and more stringent regulatory requirements in these regards, the prerequisite to demonstrate at least similarity if not superiority in cases where existing drugs on the market have established a baseline (frequently leading to hugely populated outcomes studies), this altogether has made the cost of developing novel drugs sky-rocketing. In plain terms, the renowned and widespread figure of USD802M that was launched in the early years of the new century[9,10] has now been surpassed by a wide margin. Thus, an update presented some time later quoted USD1.3Bn as a more likely figure when it comes to estimating what it really costs to take an NCE from start of discovery through the various stages of development to registration. Even more freshly publicized figures make this aforementioned cost obsolete, in that they point toward >USD2Bn in inflation adjusted terms as a more realistic level; to a large extent driven by the continuously downwards pointing success rates (in constant decline since 1995). In a very enlightening and ambitious hot-off-the-press study covering the track record of the pharmaceutical industry over the past 60 years (1950–2008), a wealth of highly interesting (and perhaps surprising) facts is presented.[11] Among these, an updated cost per NCE stands out in particular as the figure calculated mounts to the breathtaking level of USD3.9Bn which brings the earlier estimate (USD802M) up to its current level after adjustment for the average annual inflation and various other cost increasing factors such as toughening regulatory demands, and decline in success rates. Furthermore, it is important to emphasize that this by no means relates to the entire cost to be carried, as the expenditures for marketing support have to be added on top. As a matter of fact, data from multiple sources indicate, that this investment in all likelihood surmounts the economic burden seen in R&D. Claims have even been made that blame the hardships being faced with today by a gradual movement away from the situation where research was supervised and controlled by scientists in favor of marketers.[12]

3. Close-up of Process R&D

The core purpose for a Process R&D (PR&D) organization in any pharmaceutical company is to ensure that desired target molecules (notably the APIs but also the intermediates included in the overall synthetic pathway) can be made at whatever scale is required and that the methods used to achieve this are safe, environmentally considerate, and economically viable. Looking at the entire work space in a flow chart mode, the stream starts with a chemical structure that has been defined by medicinal chemists in a set of screening studies where the best compound is chosen (and given the status of a CD) based on a series of criteria (i.e., toxicity, pharmacological properties, receptor affinity, and physical characteristics). At this point, the main remit for PR&D is to ensure a speedy delivery of larger quantities of material; normally in the range of a few kg. Further progression puts the focus on defining and developing the best synthetic route alongside scale up investigations and manufacture of bulk amounts as requested (10s to 100s kg). Ultimately the optimized process, fully validated and documented, will be transferred into commercial production, where the responsibility lies to secure supply of amounts responding to the needs from the market (see Fig. 2).[1,6,13,14]. The handover to the manufacturing organization accountable for producing the bulk drug does by no means imply that the ownership of the method defining the way in which the production process should be operated is also passed on. Quite the opposite; it stays with PR&D and as such is maintained part of the life-cycle management (LCM) of any given product. This accountability is general in the sense that all launched drugs are covered, but might, in practice, mean different things for different APIs. Thus, if one process is regarded state-of-the-art right from launch, expressed, for example, in terms such as high yield, environmentally considerate, safe, and cost efficient, then the need for further improvements could be seen as low based on factors like annual volume, the competitive situation, life span, etc. On the other hand, in a situation where the process is quite mediocre (maybe depending on lack of appropriate technol-

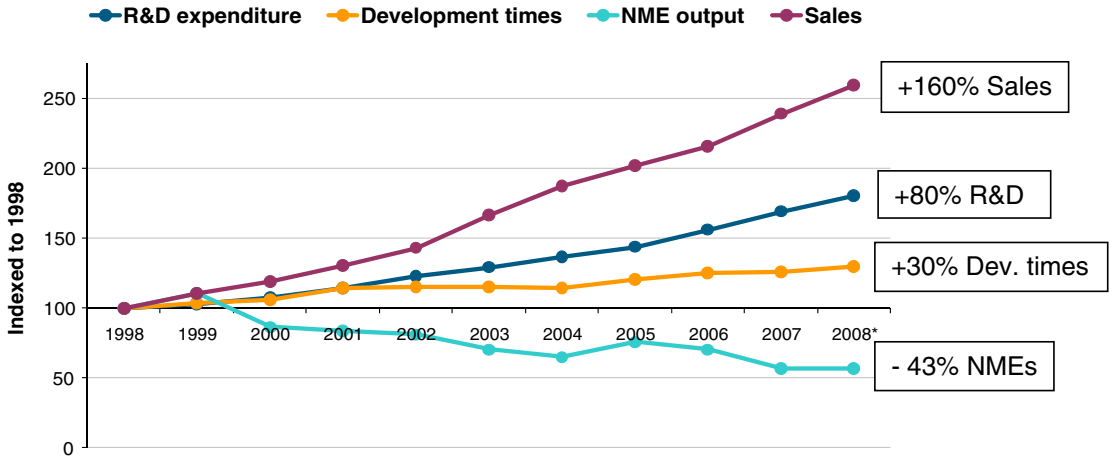


Figure 1. An industrial overview showing global R&D expenditure, development times, global sales, and NME (New Molecular Entity) output (financial data not inflation adjusted). Source: CMR International (2009 FactBook) & IMS Health.

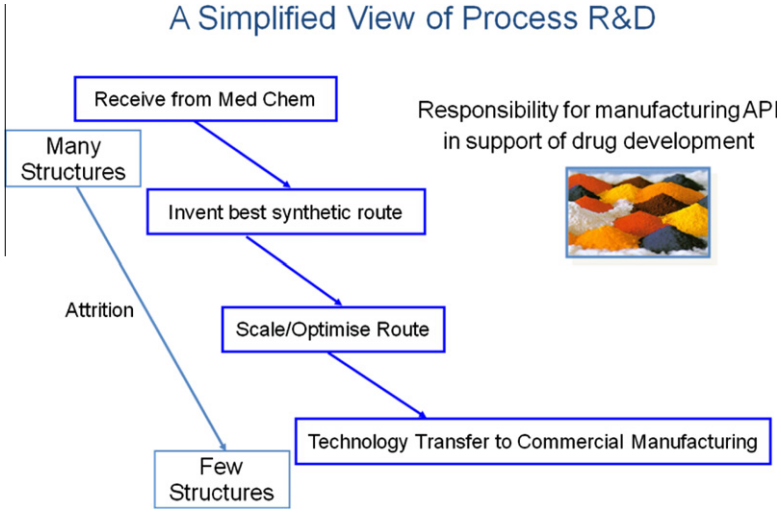


Figure 2. The concept of Process R&D at a glance. A simplified flow chart illustrating the various core activities over time alongside the concurrent effect exerted by the attrition; the mechanism by which the number of drug projects is gradually declining.

ogies) when going into large scale manufacturing, then there are most certainly a multitude of drivers, who will demand continued efforts being spent on changing and optimizing the current route or even find an entirely new one.

This neatly describes the string of activities forming the fundament of most PR&D departments, even if variations (e.g., in LCM responsibilities or accountabilities for the earliest API deliveries) might occur. It is, however, essential to include the aspects of documentation and the role this plays for PR&D. As the quality attributes of the API is a key deliverable, which is defined by the synthetic route selected and the process designed for its manufacture, explaining the rationale behind the production method and what controls have been put in place to secure the desired outcome is a cornerstone in the regulatory file. More specifically, the necessary data describing the details of the process—raw materials, synthetic steps, batch size, in-process-analyses, isolation and purification of final drug compound—form a central part in the CMC (Chemistry, Manufacturing, and Control) section of what will end up being the NDA (New Drug Application) file to be submitted to the appropriate regulatory bodies for evaluation and (hopefully) approval.

The science and technology that builds up PR&D as a function to support the various phases along the drug discovery and development pipeline is primarily a variety of chemistry based disciplines.[13] These can be structured according to the shape and form in which they impact the design and optimization of a scalable manufacturing process:

- Process chemistry
  - This field constitutes organic synthesis in the widest meaning of the word, as virtually every aspect of making the molecules at stake need to be covered—either using in-house knowledge or finding suitable skills outside. Core capabilities are route discovery and design with the expectation that the result is the best to be achieved under current circumstances; that is, a synthetic challenge that is still suffering from being poorly understood will not see the same demands on excellence and performance than one where there is ample precedence available of a high-yielding outcome.
- Analytical chemistry
  - Application of the broad range of techniques available—spectroscopic, chromatographic, titrimetric and other wet-based procedures, single crystal and powder X-ray, elemental, etc.—to firmly establish the structural integrity of a starting material, an intermediate or a final product and their respective impurity patterns. Trends defining current areas in focus are the ability to achieve low levels of detection (e.g., to identify potential genotoxic impurities [PGIs[15]] in the ppm range or below), improving the capability to successfully spotting molecules difficult to analyze (e.g., lacking UV-responsive groups or substituents), monitoring challenging reactions (e.g., constituted by complex matrices), establishing structures of complicated molecules (substitution pattern, stereochemistry), and enabling faster development of novel analytical methods and driving down the times required for analyses (genericized procedures allowing swift throughput).
- Process engineering
  - The ultimate aim is to improve on the quality and understanding of processes leading to the active drug substance. Areas to focus on in this regard are manufacturability, capacity, safety-health-environment regulations (SHE), and freedom to operate issues (avoiding IP restrictions). Core components of this broad discipline can be exemplified by the design and scale up of unit operations (mixing, crystallization/solid state engineering, separation, isolation, and drying being among the most important), reaction engineering, risk assessments, selection and design of equipment and technologies. A further core capability is the identification of bottlenecks in the scaled process and devising means for how to circumvent intrinsic capacity restrictions, by for instance applying modeling and simulations. Selection of suitable construction materials for equipment to be used in production—for example, by performing material compatibility studies such as corrosion tests—constitutes a significant activity aimed at protecting both reactors and other kit from unnecessary ware/damage but also avoid leakage of unwanted impurities into the process stream risking the quality of the product.
- Production technology and associated areas
  - In order to produce materials on large scale, an activity that is normally done in pilot plants during the R&D phases of a project, the translation of laboratory procedures making them suitable for being operated in a factory like environment is a key step. This is achieved in close collaboration between the chemists being responsible for the construction of the

methods and the receiving operators, who will ensure that the transfer is as smooth as ever possible. Needless to say, the equipment used to run chemical processes on pilot scale differs vastly from what is normally used in a laboratory and, hence, knowledge and expertise on how to handle, for example, centrifuges, filter nutches, pumps, valves, mechanical stirrers, driers, etc. is a prerequisite. Hand in hand with the up scaling of reactions goes the uncompromising demand for a strict coverage on safety issues. Thus, by the use of mainly calorimetric techniques of various types, each transformation has to be documented from an energy content point of view. This means for instance the unraveling of exothermic events that threaten to come into play above a certain temperature threshold. Once this critical value has been established, it is of the essence that a high enough safety margin is included in the final batch record in order to avoid a potential runaway scenario that might result in great danger for staff and equipment alike and eventually could lead to a major disaster.

- Chemometrics
  - In order to ensure that processes operate at optimum conditions—both from yield and quality points of view—it is important to have access to a toolbox of mathematical methods supported by various software systems. Examples of what is regularly applied are experimental factorial design protocols, multivariate techniques, Monte-Carlo simulations, and process analytical technology (PAT).[16] The latter of these provides a live insight into the intricacies of chemical reactions or unit operations (e.g., crystallization processes[17]) by virtue of inserted probes—for example, operating in the Raman or near infra-red (NIR) domains. This allows the observation on a time resolved course of how a starting material is gradually shifting to a product either directly or via an intermediate and by so doing offering invaluable data and understanding of the process under scrutiny.
- Quality assurance
  - In the context of drugs to be used in humans (and animals for that matter) the quality of the product assumes a central position. Therefore, very stringent criteria have been put in place to guarantee that there is virtually no chance that inferior materials are used in the process of making the final medicine. Quality professionals will, thus, carefully review and approve all stages of manufacturing—irrespective if it is in pilot scale or commercially as long as the intended use of the product is in areas under strict regulatory control, for example, for clinical trials—by scrutinizing batch protocols, deviations, signing procedures, analytical data, etc. The detailed rules applying to all pharmaceutical manufacturing is included under the concept of current Good Manufacturing Practice (cGMP)[18] and this provides dos and don'ts aimed at maintaining the highest standards across the supply chain in the drug industry.

Homing in on the workflow as projects proceed through the various R&D phases (see Fig. 3), it is evident that PR&D has an involvement from rather early on and it stays that way not only up to the point of launch, but even beyond. Thus, when entering the commercial stage, a life-cycle management (LCM) era starts which in practice means either keeping a watching brief on process performance from a yield and quality aspect on one hand to a scenario where an entirely novel production method is introduced (which most likely requires regulatory filing and acceptance by relevant authorities, e.g., FDA). At the front end of the pipeline the aforementioned interactions with medicinal chemists to pick up on the new drug projects coming forward constitutes a key activity that commences during lead optimization. This business model provides an alerting signal to PR&D and allows transfer, from chemist to chemist, of crucial information that eventually will enable an early start of route work and scale up. The frontloading of resource achieved by this approach will ensure a speedy delivery of the first batch of material eagerly needed to support more in depth formulation and toxicological studies as well as initial clinical trials, in a timely manner. With a relatively small effort and risk taking, this way of working has brought about a virtually 100% guarantee, that this decisive contribution by PR&D is no longer on the critical time path.

4. How molecules are assembled—some illustrative case stories

Having just pointed out the interdisciplinary character of PR&D it must be emphasized that the very core area resides in organic chemistry at large and synthetic methodology in particular. This said, the other topics contribute in enormously valuable ways and without their close involvement a fully operational chemical manufacturing process would not be possible. However, the art of making molecules from available starting materials or building blocks and applying either known or entirely novel reactions to obtain desired products at high yield and quality in a controlled manner is the main purpose and will form the basis of the following account in which a number of authentic in-house cases are presented.

4.1. Zimelidine

This API (Fig. 4) was developed quite some time ago—mainly during the 1970s (by Astra)—with the main indication being as an antidepressant (mechanism of action: serotonin re-uptake inhibitor).[19,20] The outcome was actually successful in the sense that a drug named Zelmid® was launched in the early 1980s (prior to world bestseller fluoxetine/Prozac® with which it shared a common pharmacological principle), but where unforeseen side effects forced the product to be withdrawn from the market after only 1 or 2 years in clinical practice. The route designed by the medicinal chemists was short and straightforward as is evident in Scheme 1.[21] The main features that are apparent from a scale up perspective are the low temperature lithiation and coupling reaction (−70 °C) and the poor selectivity in the dehydration constituting the final step. While the former could be handled in the pilot plant after optimization once the importance of effective stirring had been addressed in order to avoid excessive by-product formation, the latter did not seem amenable to further improvement beyond achieving a *Z*/*E* ration of 3:1. This outcome was unsatisfactory as the method suffered from a significant yield penalty, which was seen as particularly troublesome being generated at the very final stage. The resulting process was, therefore, not considered fit for purpose as the overall capacity was deemed too low, which also impacted on the cost in a negative fashion.

A novel synthetic approach had to be developed and this led to an equally short route of only three steps (Scheme 2).[22] Instead of bringing the heteroaryl-group onboard via its Li-congener, the molecular framework was created by connecting the two aromatic moieties using a conventional Friedel–Crafts acylation followed by an addition of a commercially available and easy-to-handle organomagnesium reagent at a somewhat more production friendly temperature (−40 °C) compared to previously. This led to a *tert*-alcohol that in a one pot dehydrative allylic rearrangement step gave the desired olefinic architecture, albeit with a *Z*/*E* ratio that at 10:1 was far better than in the previous route. The tremendous benefit that this created is easily imaginable and offered a significant improvement in the materials throughput of the manufacturing pro-

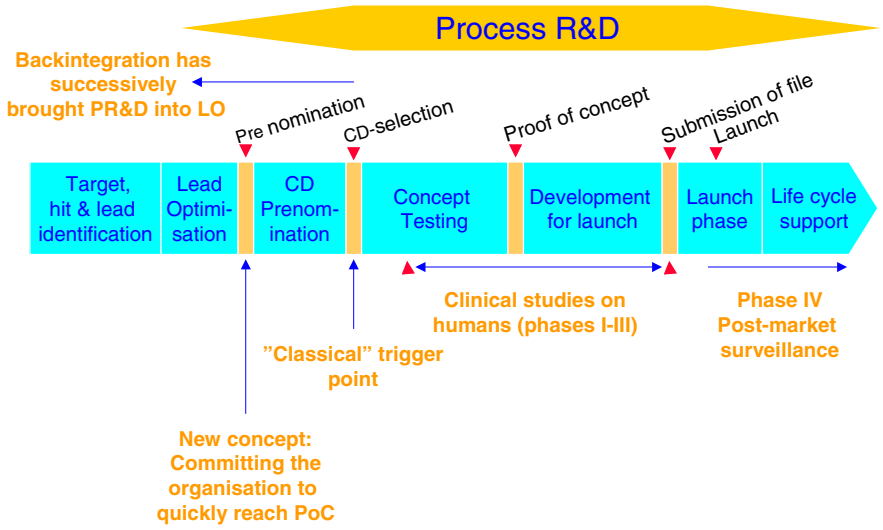


Figure 3. A schematic showing activities along the time axis in pharmaceutical R&D. Key events with special relevance to Process R&D have been highlighted.

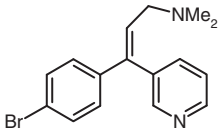


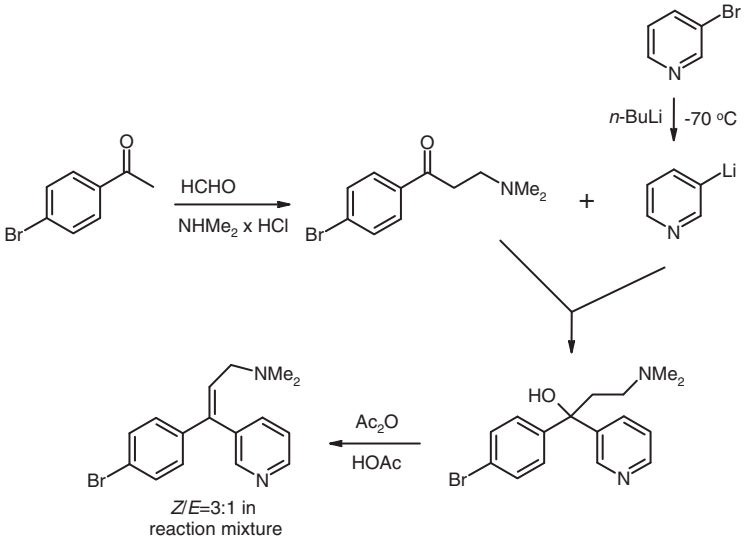
Figure 4. Zimelidine (*Z*-isomer); a serotonin re-uptake inhibitor with antidepressant activity profile.

cess. In the very final transformation, the allylic chloride thus generated was smoothly transformed to the desired zimelidine product by virtue of a displacement reaction using dimethylamine. On scale up the method developed proved to be robust and reliable and was successfully applied for production of the multi-ton amounts up to the point when the drug had to be taken off the market.

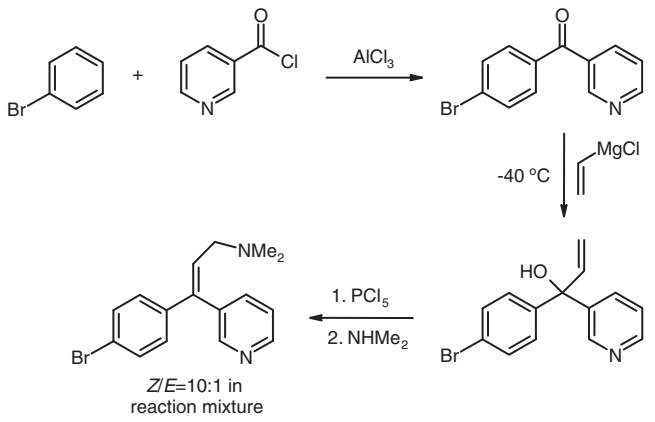
4.2. Ropivacaine

This molecule (Fig. 5), successfully developed as a local anesthetic in the late 1980s and early 1990s, represents a unique feature by virtue of being marketed (Naropin®) in an enantiomerically pure form (*S*-isomer). The rationale for choosing a single enantiomer in this case, rather than the more common therapeutic use of racemic mixtures in the field of local anesthesia, was the considerably improved pharmacological profile. Especially noteworthy is the lack of any heart toxicity that was clearly demonstrated to reside solely in the (*R*)-form.[23]

The synthesis of ropivacaine is achieved in only three steps, as in the previous example, comprised of a resolution of a racemic, commercially available starting material (pipecoloxylidide) followed by an N-alkylation and the final precipitation of the product as its HCl salt.[14,24] Focusing on the middle step—the attachment of a propyl moiety onto the piperidine nitrogen—this reaction when developed in the laboratory and scaled up to maximum pilot plant volume (1000 L) behaved very well (Scheme 3). Thus, boiling the reaction mixture (reactants in a H_2O/organic solvent mixture in the presence of a solid inorganic base) for an extended period of time (6 h) at high temperature (100 °C), the transformation was considered complete once a sample of the process solution showed <1% of remaining starting material. In preparation for launch, the method that had been thoroughly investigated and tested over a



Scheme 1. The first route to zimelidine used for scale up to pilot plant.



Scheme 2. The final synthesis of zimelidine, ultimately taken to commercial production.

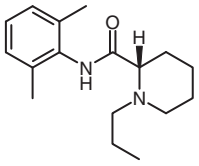
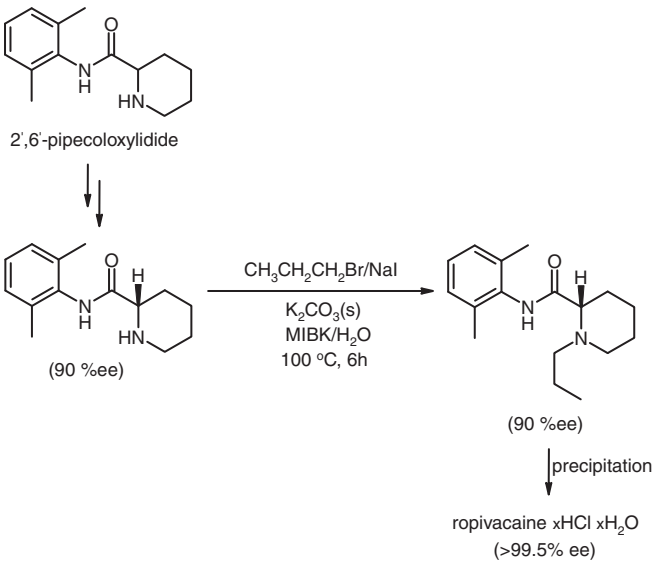


Figure 5. The local anesthetic ropivacaine/Naropin®, a chiral molecule in therapeutic use as the (*S*)-enantiomer.



Scheme 3. A troublesome stage in the synthesis of ropivacaine; the heterogeneous N-alkylation did not proceed as expected when scaled up to commercial reactor volume.

number of years and proven reliable on scale up had to be validated in the authentic 4000 L production equipment. Much to our surprise (and shock) we, however, found that the reaction came to a complete stand still long before reaching the expected end point. With a large amount of un-reacted starting material (30–40%) we were facing a situation that had never occurred during the lengthy development phase and this put the whole project in a very critical state as we were not able to reproduce the manufacturing method.

As it turned out the material that precipitated out of the reaction was identified as the starting material in the form of the HBr salt. In an unprecedented way, the HBr released as a by-product in the reaction was not neutralized by the added base (K_2CO_3) but was instead captured by another basic component, namely the starting material which being an amine (piperidine nitrogen) shows basic properties (Fig. 6). By some mysterious mechanism the neutralization as experienced previously failed and this was explained (and later on proven in down scaled laboratory experiments) to be caused by insufficient contact between the inorganic base and the HBr released in the bulk of the reaction solution. K_2CO_3 being a very heavy material combined by the geometry of the reaction vessel (cylindrical shape) created an unfavorable combination where the phase contact (solid–liquid) was insufficient, resulting in excessive precipitation of the HBr salt of the compound most abundantly available, the starting material. Could the critical situation be salvaged? Yes, by modifying the H_2O content in the solvent and by optimizing the stirring (without going beyond the regulatory limits of the filed process), the problem disappeared and has never occurred again.

4.3. Esomeprazole

A world leading product (marketed as Nexium®) in the field of gastrointestinal illnesses, notably as an inhibitor of gastric acid secretion. This chiral sulfoxide compound, therapeutically applied as the pure (*S*)-enantiomer, has surpassed its racemic congener omeprazole (Losec®/Prilosec®) as a first in line treatment for peptic ulcers and gastroesophageal reflux disease (GERD) by virtue of an increased bioavailability.[25,26] Achieving a commercially viable synthesis of esomeprazole posed a tremendous technical challenge at the time (early 1990s) when it was decided to progress this project at the highest priority. Thus, the first approach was based entirely on the abundant availability of the racemic material (omeprazole) that obviously contained the (*S*)-isomer at 50% (Scheme 4). However, instead of being amenable to a 'classical' diastereomer resolution (because of the sensitivity of the sulfoxide molecule) a much more elaborated chromatographic separation had to be applied. This methodology required chemical derivatization before attaching a chiral handle (L-mandelic acid) leading to a mixture of diastereomers, which then was subjected to large scale chromatography (C_{18}-silica stationary phase in a ∅15 cm/1 m long column consuming >10 m^3 of eluant) at a 5 kg scale.[27] A tedious and expensive procedure sufficient to deliver the urgently required amounts to move into more comprehensive in depth studies of esomeprazole, but certainly not a viable process for manufacture on the multi-ton scale.

Identifying an alternative method proved to be a very challenging task and the most tempting, if not brave, approach that could be envisaged was to operate in an asymmetric mode. The likelihood of succeeding in finding such an enantioselective transformation somewhere along the synthetic pathway now turned out to be the key question. Right from the outset all attention was focused on pyrmetazole, the pro-chiral sulfide constituting the penultimate intermediate in the omeprazole process (Scheme 4). Thus, if an oxidative procedure could be developed that would selectively result in the (*S*)-sulfoxide, this would make the separation of stereoisomers redundant and probably represent the ultimate method to achieve the desired product. The prospects for succeeding were, however, rather low as the known technology, albeit capable of obtaining sulfoxides in relatively good yields and isomeric purities (~90% ee), was severely limited to relatively simple substrates (e.g., benzyl methyl sulfide).[28] In line with this, applying the state-of-the-art literature protocol[29] to the current sulfide (pyrmetazole) with its considerably higher structural complexity, the outcome was, as predicted, very poor and the purity of the isolated product was only ~5% ee; a value far from being of any practical use in the present case.

Instead of giving up after this initial set-back, a wide-reaching investigation was launched with the aim to screen various reaction

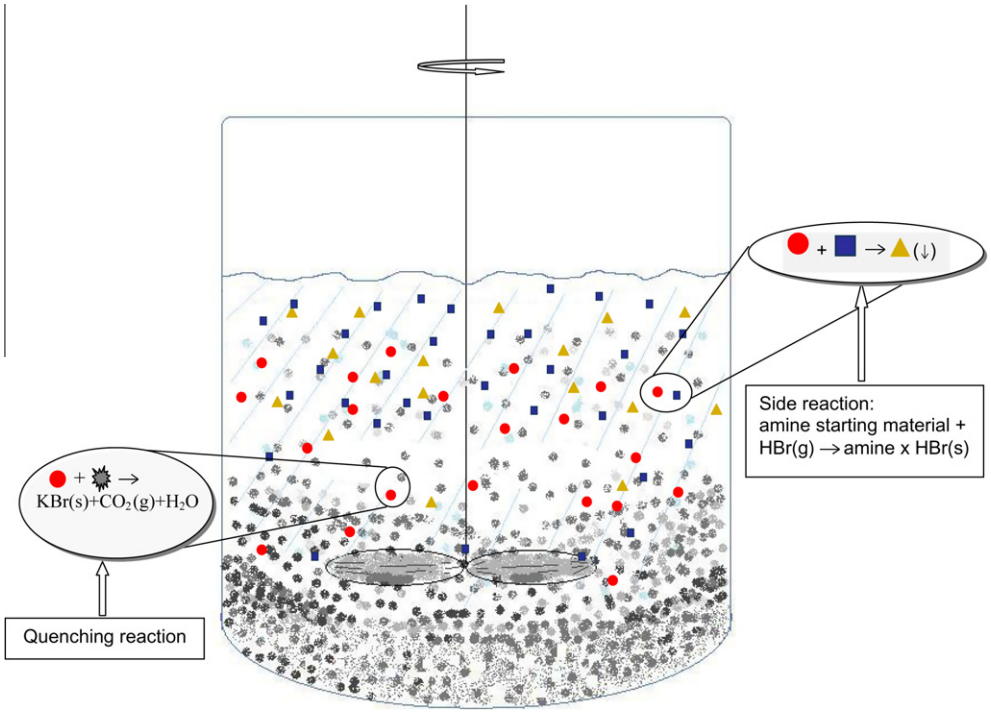
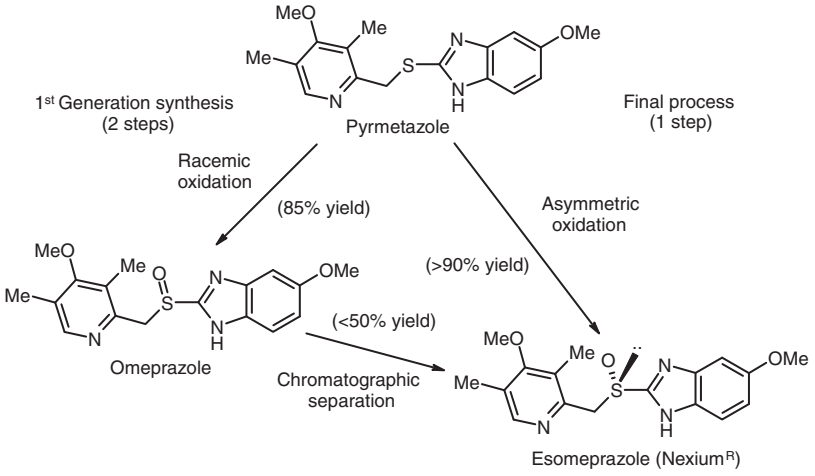


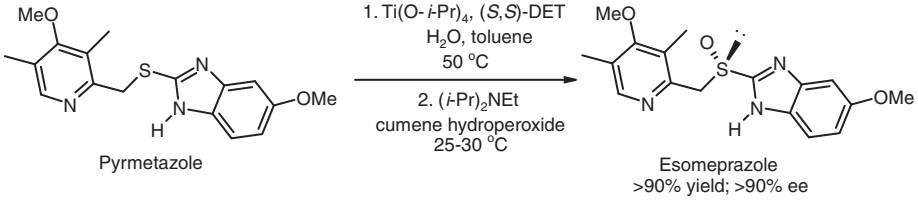
Figure 6. Qualitative model explaining the failure of an N-alkylation reaction on scale up to commercial reactor volume (4000 L). Legend: , K_2CO_3(s); , pipecoloxylidide starting material (amine SM); , HBr; , HBr salt of pipecoloxylidide (amine × HBr by-product).



Scheme 4. Two routes leading to esomeprazole: one 2-stage resolution-based; one direct asymmetric pathway.

parameters (solvents, catalyst composition, additives, and experimental procedures) in the hope that a breakthrough would be achieved. And indeed, the efforts invested paid-off as it was unexpectedly found that the presence of a base was crucial to the performance in terms of stereoisomeric purity. Testing of a wide variety of compounds displaying basic properties—organic and inorganic—showed that a simple aliphatic amine, Hünig's base, was the ideal component ensuring that the oxidation process operated at an unprecedented efficiency. Fine tuning and optimization of the experimental details such as running conditions, catalyst loading, amount of oxidant, pre-catalyst formation, reaction time, and work-up resulted in a sulfoxidation step that consistently delivered yields >90% at a product quality >90% ee (Scheme 5).[14,27,30,31] The mechanistic implications explaining the reasons behind this phenomenal sulfide to sulfoxide transformation have only recently been elucidated. Thus, in the DFT (density functional theory) modeling, the critical role of the amine base becomes clear by virtue of its ability to impose a steric bias in the transition state that eventually impacts the outcome of the reaction in a stereochemical sense (stereoelectronic effects require a linear arrangement of peroxide and the *S*-atom of the substrate, which in the transition state directs the *O*-transfer to occur from predominantly one face of the sulfide molecule).[32,33]

Since the launch of Nexium® in 2000, the active ingredient esomeprazole has been produced commercially on a multi-ton scale per annum by a process which uses the landmark sulfoxidation method as the final chemical step. A particularly elegant feature is the incorporation of this novel asymmetric transformation in the already existing manufacturing procedure for omeprazole, by just tacking it onto the process stream containing the sulfide



Scheme 5. At the core of the esomeprazole process: an asymmetric sulfide oxidation with unsurpassed performance.

in a toluene solution. The resulting batch process and the associated unit operations are shown in a schematic flow chart form (Chart 1).

4.4. Ebalzotan and robalzotan

The reason for combining these two compounds is that they share a common structural element in that both belong to the family of 3-aminochromans (Fig. 7). Besides their apparent chemical similarity they also represent the same therapeutic area, neuroscience, with the original intention to develop them as novel antidepressant drugs (selective on the $5HT_{1A}$-receptor). While they were progressed into the clinic, ebalzotan[34] was stopped in phase I (healthy volunteers) whereas robalzotan[35] continued to the next stage, phase II (small number of patients), only to meet the same destiny. In the first instance the reason was the observation of side effects and in the last due to lack of efficacy.

Focusing on the synthesis of these molecules and starting in a chronological order with ebalzotan, it was an interesting observation when planning for the first batch on pilot scale that there were very few compounds commercially available in bulk quantities containing the chroman motif. As unfortunately none of them was considered to be useful as a starting material for our product, the task was instead to design a viable synthesis that at least would suffice to deliver low kg amounts. The natural entry point was, not surprisingly, to review the synthetic route that the medicinal chemists had used to make small amounts in the laboratory (Scheme 6).[36] There are a number of interesting aspects to this route constituting a de novo strategy for the assembly of the chroman core that deserve to be mentioned; foremost the linear layout of the synthesis (13 consecutive steps), back-integration to a rather trivial starting material (resorcinol mono-methyl ether), the diastereomer resolution to obtain the desired (*R*)-isomer taking place about mid-way into the process, and the final stage that consists of an organometallic transformation (Pd catalyzed) using carbon monoxide and *i*-$PrNH_2$ as reactants. It was easily realized that staying with this synthetic approach would present us with some major technical challenges, but not only that as a simple calculation of a projected cost for the final compound clearly indicated that the figure would come out at a very high level. Taking these considerations together, it was decided to allocate a fair amount of resource in an attempt to identify a better route option. However, as the demand for larger quantities of ebalzotan was on the critical time line, the development of the existing method to ensure robustness and scalability of the various steps had to be prioritized, inasmuch as a feasible alternative did not seem to be quickly accessible. Putting the route devised by the medicinal chemists into pilot plant operation turned out in a very unfavorable way, not to say close to catastrophic. Thus, after 5 months of virtually continuous work on the plant not more than 80 g, corresponding to a total yield of 0.25%, was managed to be isolated as an approved product (the target set out from start was about 1 kg).[14,37] To mention but a few of the problems being faced during this tour de force, the 2nd step forming the benzaldehyde derivative underperformed severely (38% yield compared to the expected >70%), with just 25% yield in the Pd-catalyzed carbonylation including the subsequent work-up a huge loss of material was suffered (to a high degree dependent on an impure process stream from the previous stage), and a poor outcome (low ee led to the need for extra purification) in the separation of the antipodes which resulted from instability in the diastereomer crystallization.

The drug project requesting the API material to support further formulations development and toxicity studies were far from satisfied with the small amount provided and this threatened to severely slow down the progress. But instead of immediately starting a new batch with the obvious risk of repeating many of the committed mistakes, the decision was to focus on the weakest parts of the process (alluded to above) in an endeavor to improve the outcome. Thus, the failure of the formylation step in the very beginning was found to be reliant to a large extent on inadequate mixing when introducing the BuLi-solution to the process stream. An indirect proof of this being the main cause of the problem was that merely changing the configuration of the inlet pipe from releasing the BuLi-flow above the surface of the reaction mixture to one where the release took place some distance beneath. The interpretation of this phenomenon was that the latter procedure ensured a swift dispersion of BuLi in the bulk of the solution, guaranteeing that the desired lithiation on the aromatic nucleus would proceed at high efficiency, whereas in the previous scenario side reactions would take command generating a considerably lower content of the Li-intermediate. A critical step to improve on was the resolution, where a careful definition of the conditions during the precipitation of the diastereomer salt raised the stereochemical yield from 65% to 80%. Further downstream, the somewhat safety concerned reagent $NaBH_3CN$ (at least on large scale) in the sequential reductive alkylations was replaced by more robust H_2/Pd on charcoal and the use of the extremely nasty BBr_3 in the demethylation (at −10 °C) was changed to HBr (aq) at reflux in an elegant move. Addressing the heavy yield penalty experienced in the final chemical transformation, which was ascribed to improper purity of the penultimate intermediate (the triflate), a meticulous chromatography based purification procedure was applied. Finally, to meet the regulatory requirements on maximum tolerable level of residual heavy metals in the drug substance a refined work-up process was designed (charcoal treatment of an acidic H_2O solution) which brought the Pd content down below the limit of 10 ppm by a good margin.

The second run in the pilot plant turned out considerably more successful than the first. Thus with an overall yield of 1%, the increase was fourfold which meant that starting from 226 kg of 3-methoxyphenol generated 5.8 kg product meeting the quality criteria (e.g., 99.6% ee). An embryo for a process had been created, that would seem to hold some promise for further development and improvement unless a better route would be identified that could be considered as replacement. Unfortunately, in spite of continuing efforts to find such a 2nd generation synthesis, none of those tested demonstrated enough advantages to be seen as serious competitors.[37] Instead the optimization finally led to a method that allowed the safe and reliable production of batch sizes of ~27 kg which represents a total yield of 3.7%, in itself a

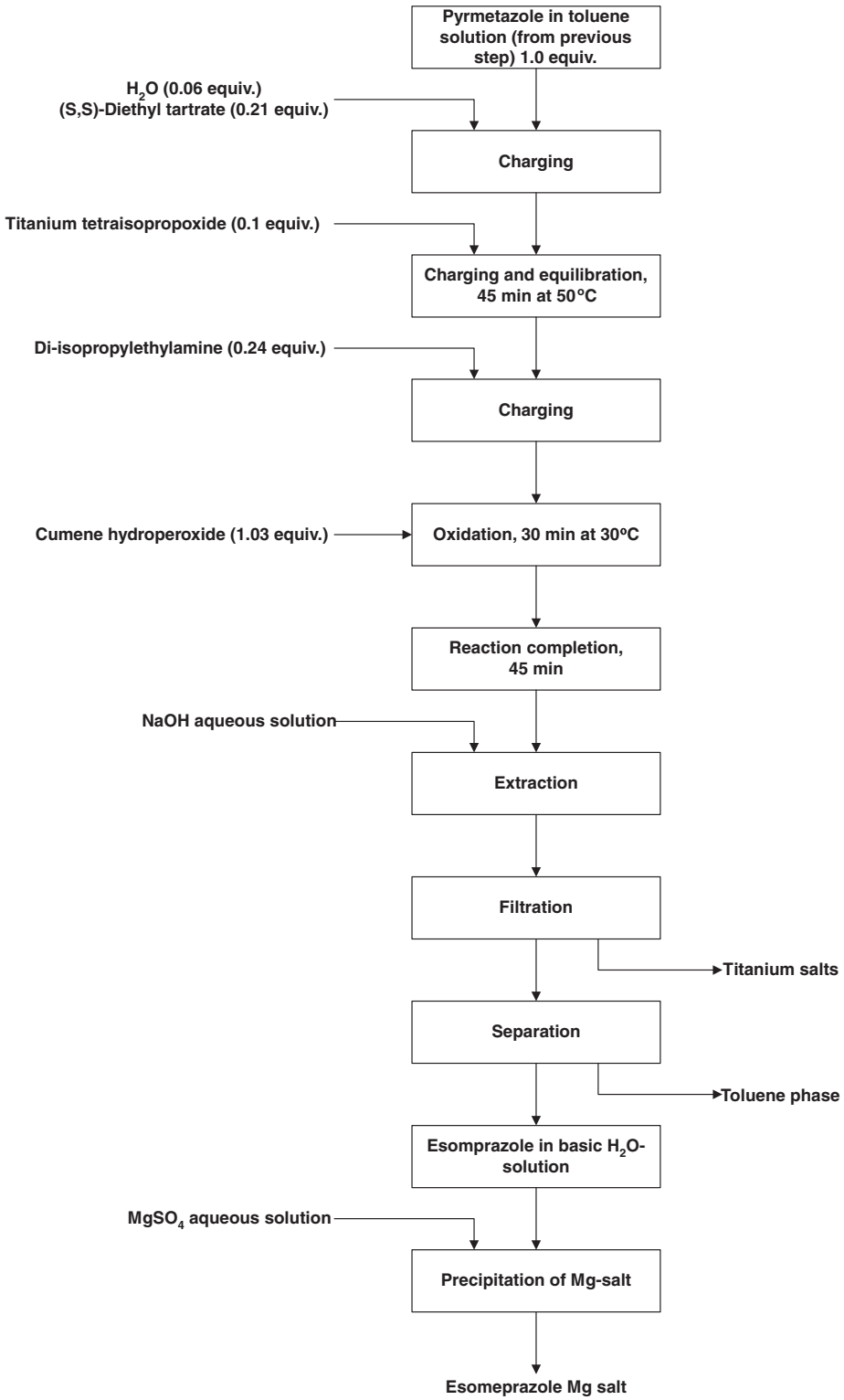


Chart 1. Manufacturing esomeprazole: the flow scheme of the final stage including the Ti-catalyzed sulfide oxidation, the work-up, and the formation of the final product (Mg-salt of esomeprazole).

tremendous achievement from the starting point of 0.25%. One critical factor that heavily contributed to the still annoyingly high cost of the API was the fact that the 'wrong' antipode was lost in the waste stream after the resolution, as attempts to find a racemisation procedure ended in total failure. Just before discontinuing the project, we managed to prove the viability of conducting the resolution two steps earlier, namely at the stage of the carboxylic acid intermediate; the first chiral compound in the sequence and, therefore, the best place to perform the separation of enantiomers, economically speaking. As this approach opened up for an easy racemisation of the recycled (*S*)-isomer, the yield of the entire diastereomer separation increased to 80% (which required two recycling loops) as compared to the theoretical 50% on just a straightforward resolution without recovery of the (*R*)-form (Scheme 7).[38] Another

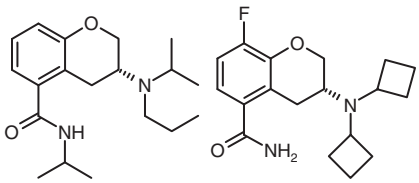
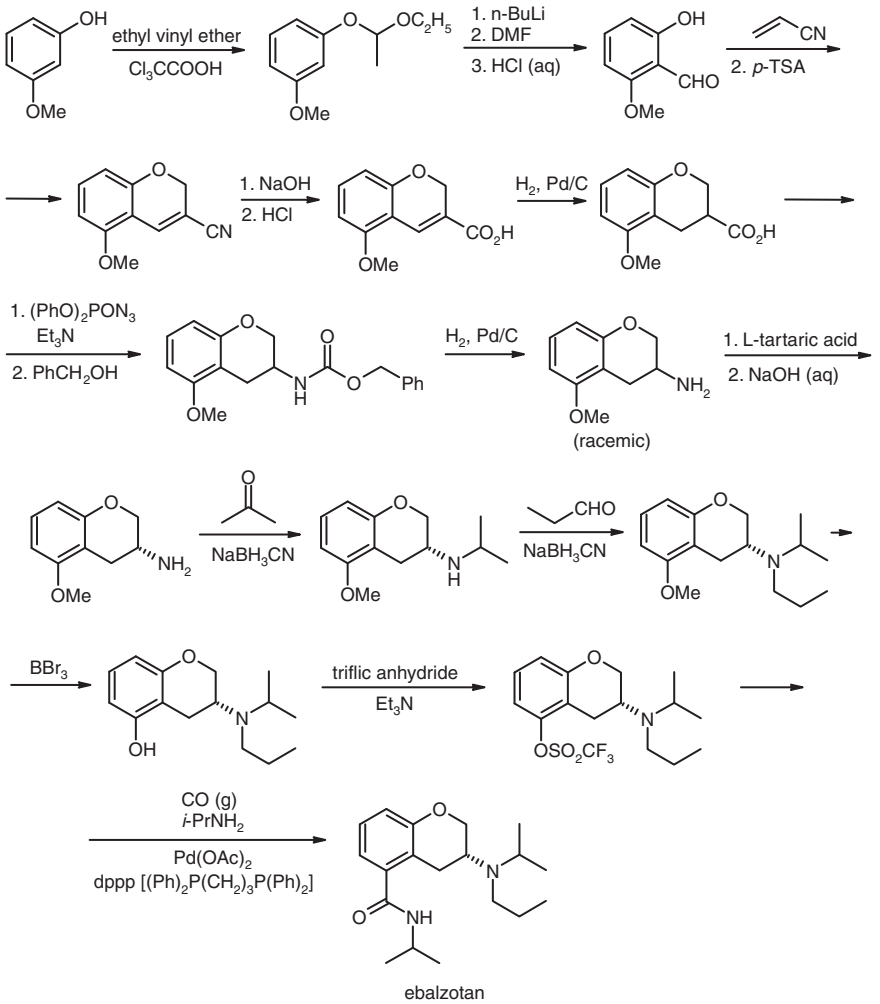


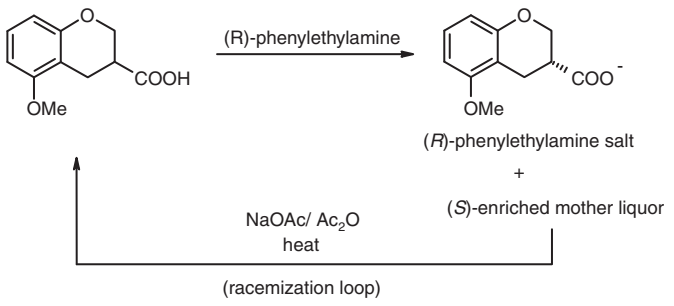
Figure 7. Two molecules with antidepressant activity operating on the $5HT_{1A}$-receptor: ebalzotan (left); robalzotan (right).

critical step that requested meticulous investigation and fine-tuning was the carboxamidation constituting the final transformation, as this involved the application of a poisonous heavy metal (Pd) and highly toxic carbon monoxide gas. Furthermore, the disadvantage of not being able to convert the end product into a workable and stable salt with a concomitant purification benefit to be achieved provided a methodological challenge in terms of the required efficiency in the work-up procedure. As in most catalytic reactions, a refined balancing of substrate over catalyst ratio is essential in order to maximize the output of product. By careful selection of conditions, for example, the definition of pre-catalyst and ligand, solvent composition, temperature, and partial pressure of CO, it was possible to drive down the Pd-loading to 1 mol %. Furthermore, we found that pre-forming of the catalytic species before adding the triflate substrate was crucial as was the careful dosing of CO gas not to exceed a relative pressure of 1.3–1.5 bar as there otherwise was a high risk of a second insertion of a carbonyl moiety creating a bis-carbonylated product. By putting all pieces of the puzzle together, in combination with a sophisticated charcoal–H_2O–toluene–*iso*-octane–EtOH extractive work-up and crystallization yielded ebalzotan of impeccable quality as demonstrated at maximum batch sizes of roughly 40 kg (Scheme 8).

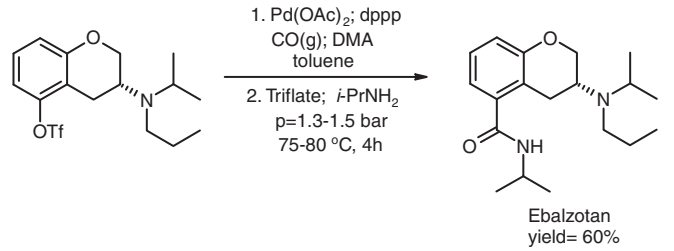
The initial synthetic approach to the follow-up compound robalzotan was to build on the experience gathered during the work on the forerunner. Thus, with the chroman motif as the core element shared between both targets, the racemic 3-aminochroman (Scheme 6) was seen as an ideal entry point. After conducting the 'standard' resolution of this by now amply available starting material, a series of linear steps comprised of, for example, a bromination, reductive alkylation, electrophilic fluorination, and the multi-stage transformation of a methoxy substituent to eventually become an amide moiety via a Pd-catalyzed CO insertion (in analogy to the method previously described in Scheme 6) yielded the product as a free base before the final precipitation as the tartrate salt (Scheme 9).[39] In spite of the acquired expertise in chroman related chemistry, the overall yield achieved in the first scale up run was merely 1%, which translated into the isolation of 0.5 kg product (of excellent purity at >99% ee) starting from 17 kg of the racemate. Evaluating the performance in the pilot plant clearly showed that this first generation route would not suffice to meet the requirements of being commercially viable. The main reasons for this, besides the large



Scheme 6. The 13-step linear sequence leading to ebalzotan as designed by medicinal chemistry.

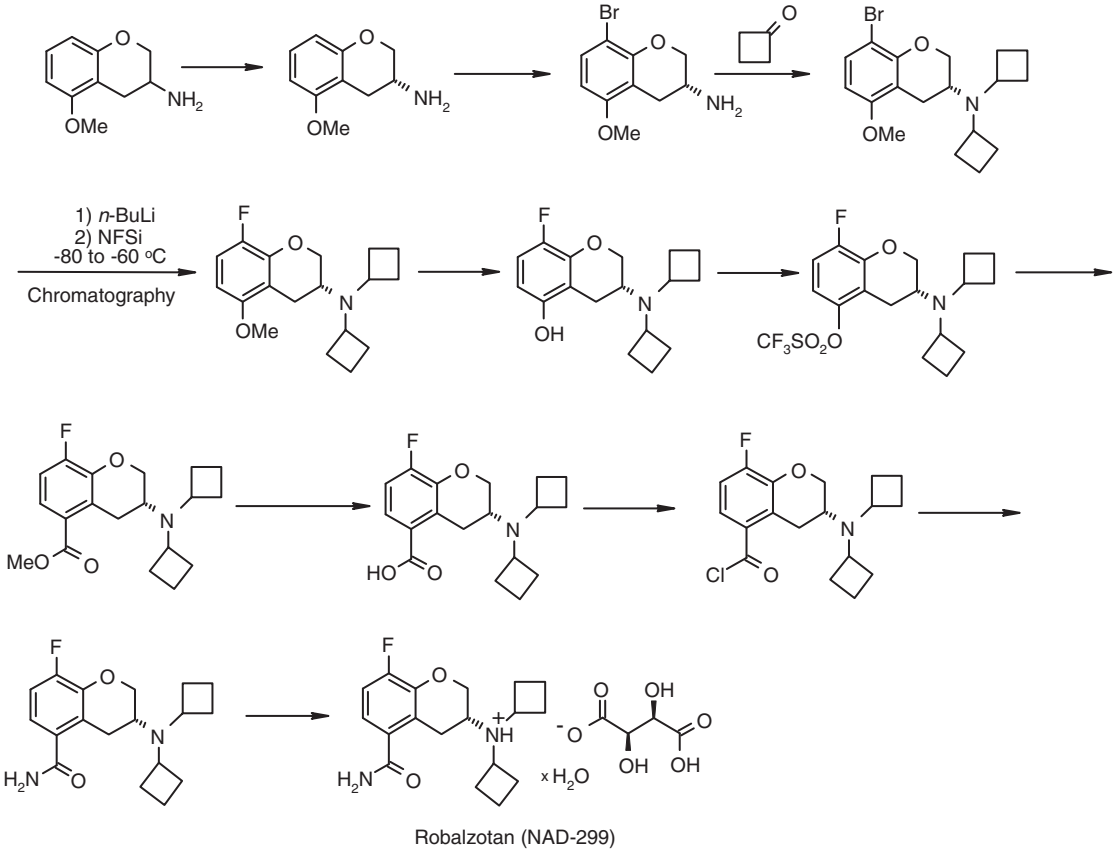


Scheme 7. Applying a racemization/resolution loop in the ebalzotan process offers considerably improved overall yields.



Scheme 8. The final transformation in the ebalzotan process is constituted by a one pot organometallic carboxamidation using a Pd/dppp [1,3-bis(diphenylphosphino)propane] catalyst.

number of sequential stages (11), were twofold: (i) the introduction very early on of the, by far, most expensive chemical/building block, cyclobutanone, in the entire synthesis and (ii) the attachment of the aromatic fluorine substituent. Especially the latter was seen as a major technical weakness due to the large amount of highly undesirable *H*-analog that was concomitantly generated in this low temperature reaction (<−60 °C). Poor process control was seen as the major reason for this failure and the root cause was most likely related to the presence of proton-releasing impurities with H_2O being an obvious candidate. The sensitivity to interference from protic moieties (notably solvents but also by the fluorinating agent itself!) presented a serious shortcoming to the whole procedure in particular on scale up, as achieving the same rigor with regard to meticulous control of conditions will become increasingly complicated. Moreover, the handling of the expensive and extremely atom inefficient fluorination reagent NFSi[40] (merely ∼6% of the atomic mass is utilized) turned out to be very challenging on large scale because of its nasty properties. In order to separate the *H*-substituted by-product from the desired *F*-compound, recourse had to be taken to a tedious preparative chromatography procedure that required the input of 6000 L CH_2Cl_2 as eluant in order to obtain 1 kg of the pure material. Failing to achieve a better *F*/*H*-ratio in this step, thus, rendered an isolated yield of merely 35%, which resulted in an extremely unfavorable cost pattern that was judged as being entirely unsustainable going forward. Furthermore, an extremely challenging limit (⩽0.1%) had been set for tolerable residual amounts of the *H*-impurity at this stage of the process due to the obvious risk of carry-over to the final stage creating the *H*-analog of robalzotan after undergoing the remaining transformations in the synthetic pathway. The reason for this tough demand on quality was that this by-product showed highly potent agonistic properties, counter-indicative to robalzotan itself, which could have severely blurred the wanted pharmacolog-



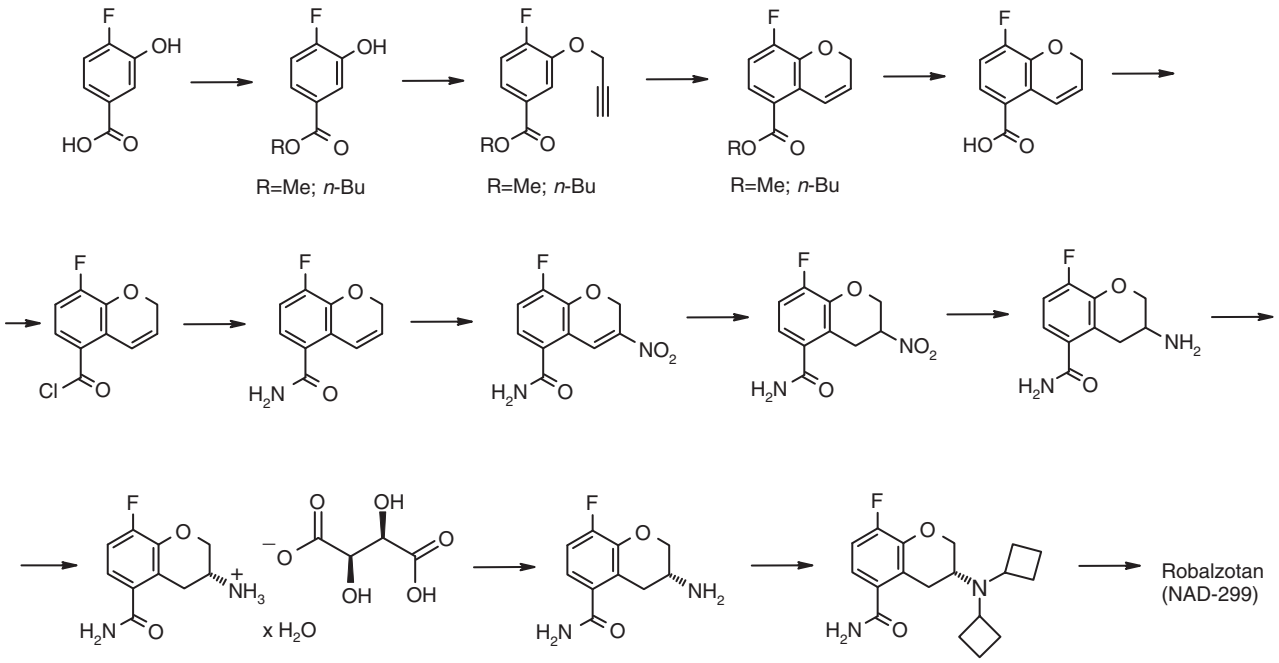
Scheme 9. The 11 stage original synthesis of robalzotan as devised by medicinal chemistry. NFSi, *N*-fluorobenzenesulfonimide.

ical effects on the target receptor. Therefore, even with the potential to considerably improve on the fluorination step, it was judged as being a close to un-surmountable task to design a process robust enough to guarantee the pre-defined limit of 0.1%, without having to revert to costly and tedious purification procedures. This became even clearer when, as a next stage, starting the planning for production of 15 kg robalzotan revealed that a linear scale up of the chromatographic method outlined above would have consumed 100,000 L (!) eluant (CH_2Cl_2) on the assumption that the ratio between *F*- and *H*-congeners did not undergo considerable improvement. The final conclusion was easy: this process was not fit for purpose.

Luckily, the search for an alternative synthesis paid-off fairly rapidly as a route was identified that addressed many of the shortcomings of the previous one. Thus, finding a starting material in the form of commercially available 4-fluoro-3-hydroxybenzoic acid elegantly eliminated the need for conducting the technically demanding fluorine attachment. Also the introduction of the two cyclobutyl groups in the very last step (just prior to the salt formation) immediately exerted a dramatic improvement on the economics of the process. With these options at hand, the main criteria set up for a 2nd generation synthesis were fulfilled, albeit this meant accepting that the resolution establishing the (*R*)-stereochemistry was not conducted until towards the very end (Scheme 10).[39] In contrast to the previous approach, this synthetic strategy reverted the starting point back to a level where the pyran-ring had to be installed in a de novo fashion. Nevertheless, the gains that were obtained through this switch easily outweighed the apparent downside that the back-integration would lead to. Fortunately the instalment of the chroman motif was rather straightforward, inasmuch as it could be achieved in just three steps: (i) acid to ester transformation; (ii) phenolic O-propargylation; (iii) Claisen rearrangement. Thus, having access to a properly substituted chromene moiety required a number of sequential transformations in order to put the NH_2-functionality in place, before finishing off with the resolution and reductive alkylation stages. All in all a 13 stage synthesis up to the final tartrate salt of robalzotan, admittedly in a linear layout.

As had already been experienced in the ebalzotan case, when first testing this route on pilot plant scale the overall yield was far below the expected. This translates to 0.3% on a 2 kg batch size compared to the 5% that was anticipated, albeit at an excellent stereochemical purity of >99% ee. A closer analysis of the campaign revealed that the bottlenecks were concentrated to just a few of the reactions—Claisen rearrangement, nitration, nitro reduction, and di-alkylation—but also that the whole procedure suffered from general weaknesses with regard to volume efficiency and complex work-up methods. Hence, many opportunities could be seen for considerable improvements both yield-wise and from a processing point of view.

Starting with the Claisen step, this rearrangement constitutes a [3,3]-sigmatropic shift and requires high temperature—around 200 °C—to be operable. Consequently, there is a demand to use a high boiling solvent as reaction medium and the first choice was *N*,*N*-diethylaniline, which however has some obvious limitations dictated by an unfavorable toxicity profile (general property of aromatic amines) and the high volume extractive work-up needed to ensure complete removal. There is also an obvious equipment related complication to be mindful of, namely the demand that the elevated temperature places on the quality and performance of the jacketed vessel, the heating system, and other ancillary components as the range of operation normally stops around 150 °C. Screening for a replacement of the aniline solvent identified diphenyl ether as a rather attractive alternative, mainly due to good stability (no or only minor chemical degradation at intended reaction temperature) and virtually complete lack of toxic effects. In a first test run at scale a yield as high as 80–82% was obtained of the chromene product and, therefore, this process step was seen as a promising embryo for future sustainable production. However, there was one caveat to this in the unexpected finding of corrosion attacks on the walls of the reactor vessel observed after the cleaning procedure had been conducted. Suspecting the release of HF, an extremely corrosive moiety, from the *F*-containing compounds involved in the reaction, an extensive study was designed that eventually confirmed the hypothesis. In spite of identifying levels of only a few ppm HF in the process solution, due to the severity of

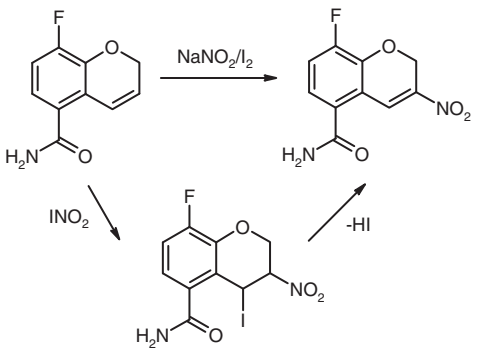


Scheme 10. The totally re-designed synthetic route to robalzotan which, as a key feature, eliminates the need for conducting a fluorination.

the corrosion a countermeasure had to be found to preserve the integrity of the reactor. The obvious choice was to add a base in order to neutralize the acidic component and for this purpose *N*-methylmorpholine (NMM) was identified as ideally suitable. Unfortunately, this was not the end of our problems as it was found that NMM did not function very well in the current reaction system, which as a knock-on effect led to yet another search for a better solvent; an exercise that ultimately showed that xylene was optimal. There was, though, one more issue to address: with a boiling point of just around 140 °C this was far from the set temperature required to get the rearrangement reaction to work properly. The elegant way to eliminate this obstacle was to conduct this step under pressure and so allowing 3 bar of overpressure the required operating conditions were secured allowing the product to be consistently produced at or above 80% yield in high quality.

Moving on to the olefinic nitration, this step was probably the most critical of all for the survival of the whole synthetic pathway. Not only because of the intrinsic safety issues, that always need to be properly addressed when handling highly energetic reactions of this sort, but also the mere conditions outlined in the medicinal chemistry method based on a literature precedent.[41] In a formal sense, the reaction proceeds via an in situ formation of nitryl iodide (INO_2) by mixing $NaNO_2$ and I_2 followed by the addition of this species to the olefinic bond and a subsequent elimination of HI to create the mono-nitro product (see Scheme 11). The major problem is that the experimental protocol requires a w/w-ratio of 4:1 of I_2 over olefin substrate (equals a threefold molar excess of I_2) and this coupled with the nitrite salt (large excess) makes this procedure very unsuitable for scale up by virtue of the vast amounts of inorganic salts in the system which renders a poor volume efficiency (product shows low solubility in the process solution) and leads to a complex work-up. Given the time pressure in the project, this far from ideal synthesis was scaled up to pilot plant operation (1000 L reactor volume) and found to offer 45% isolated yield, equaling just 5% below the best results from laboratory trials.

As the sustainability of the current process was strongly questioned, the way forward presented two options; to either succeed in drastically improving the method at hand or to design an entirely novel synthetic strategy. As a matter of fact, both alternatives were pursued. What turned the coin in favor of the I_2-route was the realization that the overall synthesis in actual fact was catalytic in iodine. Thus, the prime question to address was whether catalysis would be feasible for our transformation, which would require reduced iodide (I^-) to be re-oxidized to elemental iodine? As it turned out, this was indeed possible by designing a separate oxidation cycle where spent I^- was brought back to I_2, which closed the reaction loop. Comprehensive testing of various oxidizing agents showed that a mixture of per acetic acid (15%) and hydrogen peroxide (24%) in HOAc and H_2O was ideal and allowed the nitration



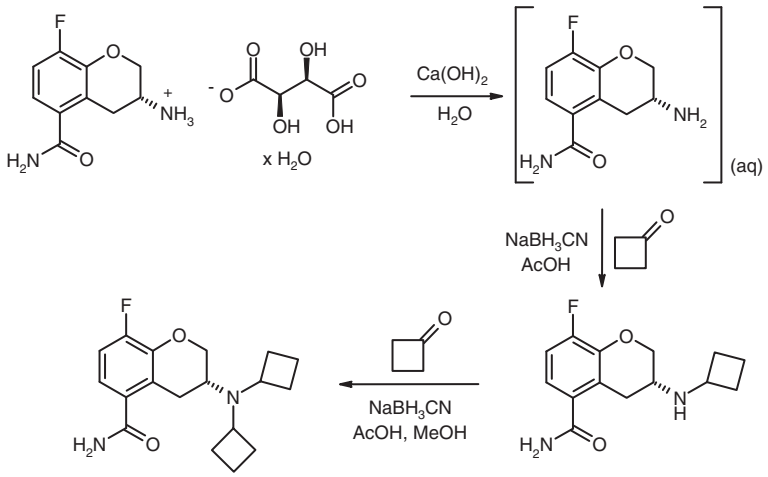
Scheme 11. Olefinic nitration using sodium nitrite/iodine in super-stoichiometric amounts.

to be performed in a one pot scenario with a yield of 70–75% using only 0.2 mol equiv of I_2 (a 15-fold decrease in catalyst loading compared to the original experimental procedure).[42] An enormous step change had been achieved that in itself increased the competitiveness of the whole synthetic sequence.

The final step to home in on in the sequence is the reductive dialkylation, a seemingly trivial step that nonetheless poses some noticeable challenges. One of these is of course the cost implications presented by the ketone building block (cyclobutanone) which, as already mentioned, is the most expensive component in the entire synthesis. Another complication is the low solubility of the resolved primary amine as the free base in a range of organic solvents, which necessitates running the reaction as two separate stages; first in aqueous medium to obtain the mono-alkylated intermediate, then switching to methanol in order to conduct the second alkylation. All in all, this protocol made use of 5.5 equiv cyclobutanone (2.75-fold relative excess per alkyl-group to become attached) and 5.5 equiv of reducing agent ($NaBH_3CN$) in a reaction that lasted over 7 days to offer a yield of 60% (see Scheme 12)—a not very production-friendly process to say the least.

Investigating the reasons behind this extended reaction time revealed that attaching the second cyclobutyl moiety was extremely sluggish due to the considerable steric hindrance featured by the mono-alkyl adduct. Another factor to take into account is the side reaction where the keto-functionality of cyclobutanone is reduced to the alcohol by virtue of the excess reductant ($NaBH_3CN$). The normal mode of conducting this one pot amine → imine → alkylamine transformation is to maintain a pH > 5, where the reduction of the ketone (or aldehyde) moiety is negligible. In the present case, however, there is a considerable amount of the corresponding alcohol formed as revealed in a directed study. Thus, applying the conditions set in our method (no amine present; only cyclobutanone) it was found that sampling after ½ h at 50 °C 62% cyclobutanol was present at pH 5, 28% at pH 6, and 21% at pH 7. The reason behind this extremely high level of ketone reduction was attributed to the strain of the four-membered ring that forces the sp^2-hybridized carbonyl group away from its normal 120° conformation into a state of much higher energy; the release of which will be effected by the transformation to the alcohol that creates a sp^3-arrangement of improved stability. It was subsequently found that the best compromise for the authentic reaction—amine → dialkylamine—was to maintain pH 6 (via addition of HOAc) and accept some waste of the expensive ketone, as going higher would considerably slow down the process with only little gain in avoiding cyclobutanone reduction.

With these changes put in place and exerting a stringent pH control (5.7–6.0) while allowing a continuous feed of cyclobutanone into the reaction vessel to further minimize risk of ketone → alcohol reduction a major step forward was achieved. The reaction time could be drastically reduced to 'only' 12 h in combination with a somewhat lower excess of ketone (4.5 equiv) and $NaBH_3CN$ (4.0 equiv) compared to the 1st generation method, resulting in a noticeable yield improvement to 70%. At this point there was still considered room for more development work in order to reach a final sustainable process. A key element to address, besides the desire to further reduce the level of excess of cyclobutanone and to raise the yield, was the type of reducing agent to be applied. While $NaBH_3CN$ is relatively user-friendly when working in laboratory scale it has definitive drawbacks when handled in bulk, such as an unfavorable toxicity profile (risk of HCN release!) and unattractive costing picture. Therefore, an ambitious screening effort was launched with the aim to identify a suitable replacement. Initially, this did not prove to be very successful as most of the reagents investigated did either not reduce the iminium ion intermediate or were too powerful which primarily led to ketone reduction. At the end, however, one alternative was found—pyridine–borane (a complex between pyridine and BH_3)—which met all criteria; readily available at a



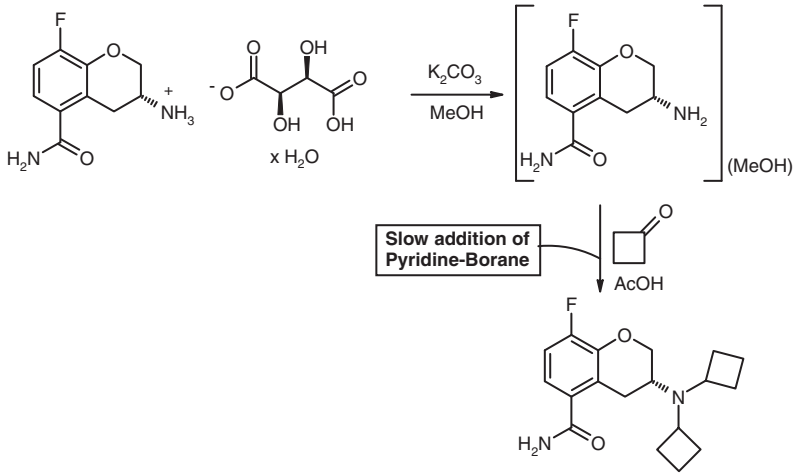
Scheme 12. Two consecutive reductive alkylations lead to the final molecule, albeit requiring large excess of expensive cyclobutanone and extended reaction times (7 days) according to the first generation method.

competitive price and a considerably easier handling by virtue of its physical character being a liquid (in contrast to $NaBH_3CN$ that is solid and requires dissolution before use). This reagent is not entirely devoid of safety issues as it also displays some toxic properties, but the main concern is due to the exothermic decomposition that comes into play >45 °C; a process that is both very rapid and autocatalytic. The potential 'show stopper' posed by this phenomenon could nonetheless be mitigated as it was possible to design a protocol where the borane reagent is added under a strictly controlled time regime, which even allowed operating at 65 °C—distinctly higher than the documented safety limit—without being exposed to severely hazardous risks. Implementing these changes in reaction conditions coupled with a novel procedure to bring the primary amine as the free base into a non-aqueous solvent (MeOH) gave a superb process step offering a yield of 80% in just 8 h with a cyclobutanone loading of only 4 equiv (Scheme 13). An interesting spin-off obtained by the use of pyridine–borane was that the need for a meticulous control of pH via continuous HOAc addition disappeared. Instead the HOAc was added in one portion and the pyridinium acetate generated on contact with the reducing agent provided the perfect pH level in what can be described as an 'auto-buffering' mode.

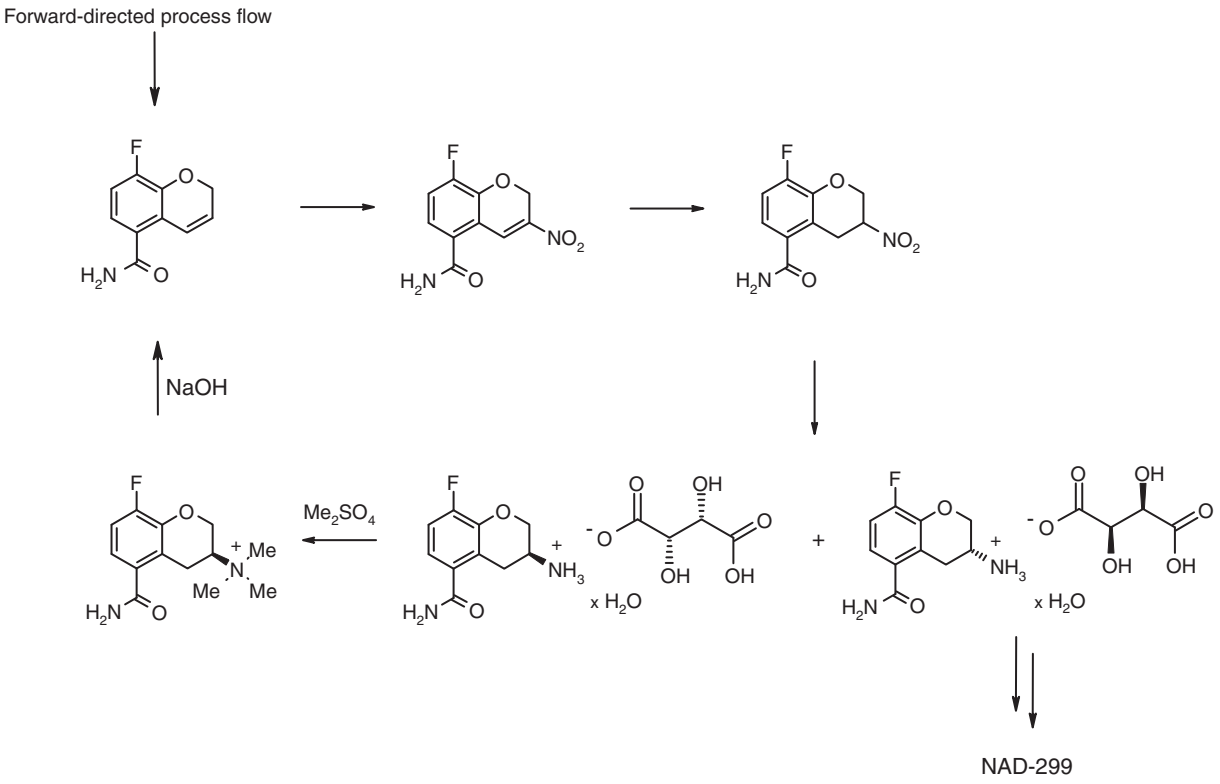
As a very final improvement it deserves to be mentioned that also in this case, comparably to what was described for ebalzotan, a method was identified that allowed the recycling of the unwanted stereoisomer. This meant exhaustively methylating the wrong antipode of the primary amine (using dimethyl sulfate) and then subjecting the quaternary ammonium salt thus obtained to treatment with strong base (NaOH at pH > 12). By this protocol a smooth elimination is achieved that forms a chromene intermediate that is intrinsically present in the forward-going synthesis, hence guaranteeing that no new impurities are inserted into the process (Scheme 14). As a matter of fact, the chromene formed via this recycling loop displayed a purity that was even higher than when running the normal production. Overall, when terminating the work on this process the batch size in the pilot plant had reached 25 kg (400 L reactor volume) and the yield was about 13% (over a total number of 13 chemical steps) or, if including 5–6 recirculation loops (two extra steps/loop) of the (*S*)-enantiomer, even mounted to somewhere around 19%.

4.5. AR-A2

In an effort to build on the vast experience gained over the years—both in-house and externally—from the comprehensive aminotetralin family, many of which have shown interesting and widely exploitable central nervous system (CNS) effects, the novel compound AR-A2 was designed (Fig. 8). The main indications were treatment of severe depression and anxiety and the pharmacolog-



Scheme 13. The final di-alkylation proceeds in one pot at considerably reduced excesses of ketone and shorter reaction times (8 h) with a much improved yield (80%).



Scheme 14. A multi-step recirculation loop that allows the undesired enantiomer (*S*) to be successfully converted to the desired (*R*).

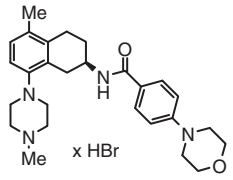
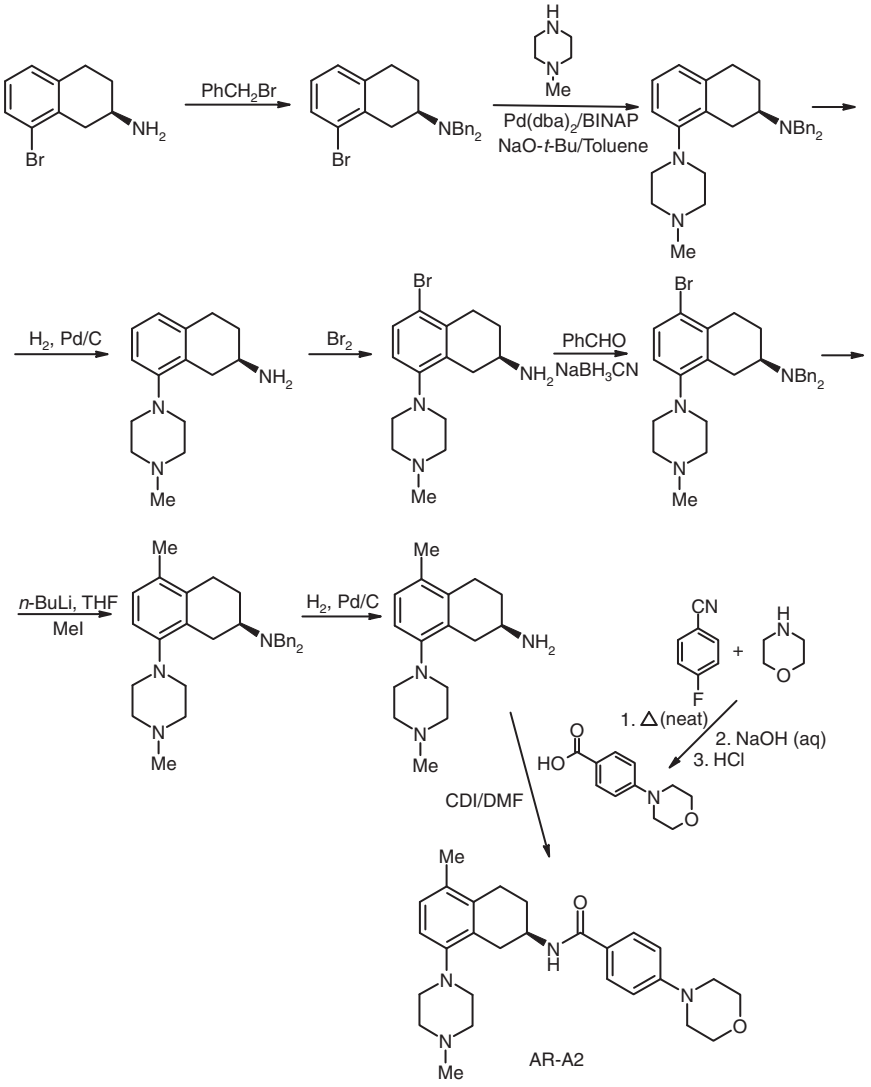


Figure 8. AR-A2, an antidepressant of the aminotetralin family with affinity for the $5HT_{1B}$-receptor.

ical mechanism of action was unraveled as a selective $5HT_{1B}$ antagonist.[43,44] Unfortunately, this promising molecule shared the destiny of the previously described CNS projects in that clinical studies in phase II (small number of patients) revealed a lack of efficacy, meaning that the pre-defined end point could not be reached which led to the termination of development work.

Within the medicinal chemistry unit a diversity-based synthetic strategy had been applied that was built on the commercial availability (on laboratory scale) of a small group of aminotetralins with defined stereochemistry on the C-2 position. However, the benefit of having the core part of the molecule in place right from the start was in this case clearly outweighed by the need to introduce a C-5 methyl substituent; a task that added a considerable burden to the synthetic complexity (Scheme 15). Besides this feature a piperazinyl moiety had to be attached at C-8 and this was very successfully conducted using a Buchwald–Hartwig protocol with a Pd/BINAP catalyst. At project initiation, time did not allow for exploring other route options and therefore this method was scaled up to deliver a few hundred gram of product, which somewhat surprisingly succeeded at a total yield of >20%, albeit at a high cost due to the expensive chiral starting material.[45,46]

With a prohibitive overall process economy at hand, largely due to the monopoly situation being faced with for the advanced (*R*)-tetralin building block, where the sole supplier offered small to medium pilot quantities at $50,000–100,000/kg, it was decided to abandon this route and instead focus on designing a novel one. Similar to what had been experienced in the previous robalzotan case this meant going back to a simpler starting material that required a de novo construction of the tetralin moiety (Scheme 16).[45,46] After a straightforward, albeit not very regioselective, bromination step offering about 30% yield (which, however, could be improved by recycling the mixture of wrong bromo isomers to be subjected to a catalytic hydrogenation/re-bromination sequence) the task was how to prepare the tetralone nucleus. This turned out to be elegantly achievable by using ethene as a cheap C_2-unit, which in a Friedel–Crafts manner could be attached to the in situ generated chloride of the phenylacetic acid derivative. A seemingly overlooked reaction which previously had been reported in the literature[47,48] that was found to be ideally suited for this transformation and provided an acceptable yield in the range of 60–70%. Following on, the reductive amination combined with a diastereomer resolution proved to be a real bottleneck in the synthesis. Thus, while the first stage operated smoothly at a high yield the overall outcome was a disappointing 25% (with 50% being the theoretical maximum as half of the material was destined to disappear as the wrong antipode). In the next step the piperazine substituent was attached using a similar Buchwald–Hartwig protocol that had already proven successful in the first route. A distinguishing factor to be noticed was, however, the use of the *N*-mono-benzyl derivative in the latter case compared to the *N*-di-benzyl analog previously; a gain in atom efficiency by reduction in atomic 'ballast' by 21% without suffering from loss in purity due to cross-coupling side reactions. As a matter of fact the isolated product was of high quality with only a small amount (<2%) of the 8*H*-analog present as major impurity. Finishing off with protective group removal, carbonyldiimidazole (CDI) mediated condensation with the benzoic acid side-chain, and precipitation of the mono-HBr salt this pathway managed to deliver batch sizes of up to 2 kg (1000 L pilot scale) at a total yield of 3–4%. A distinct step

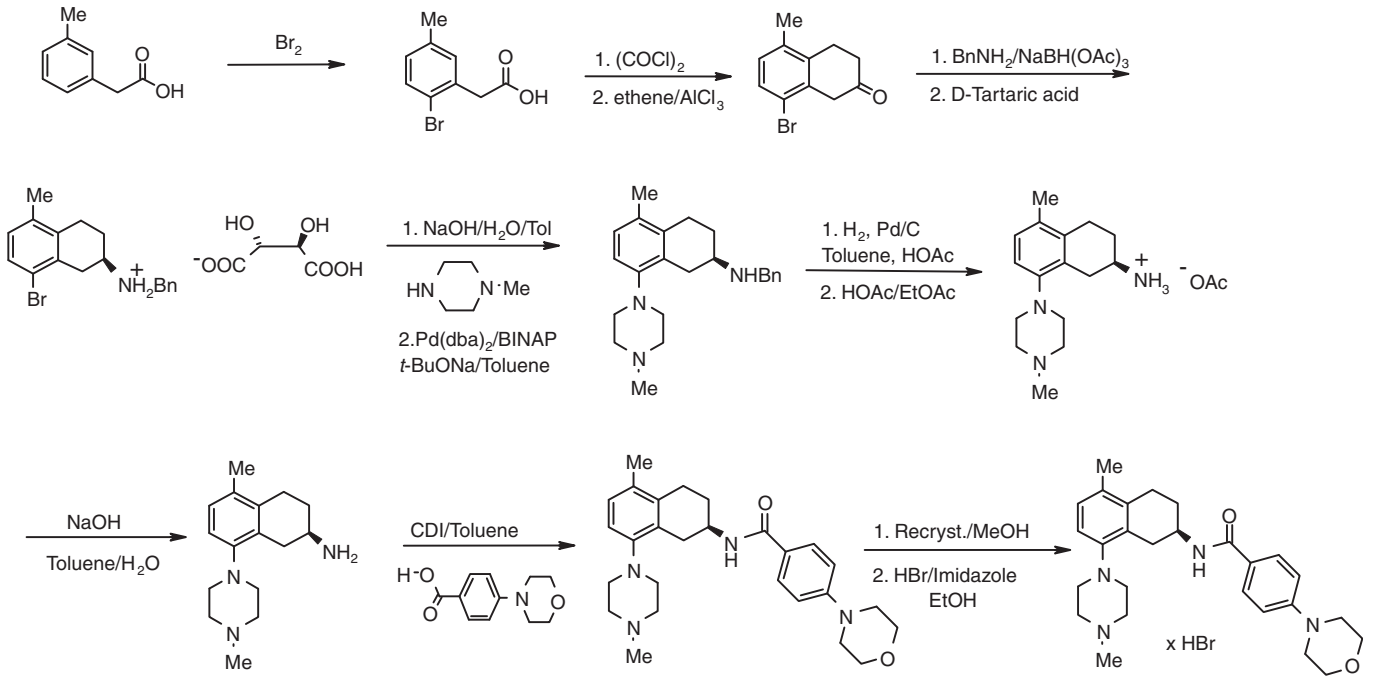


Scheme 15. The medicinal chemistry route to AR-A2 starting from a chiral aminotetralin obtained from an external supplier where it is produced via a biocatalytic method using a transaminase enzyme. CDI, *N*,*N*′-carbonyl-di-imidazole.

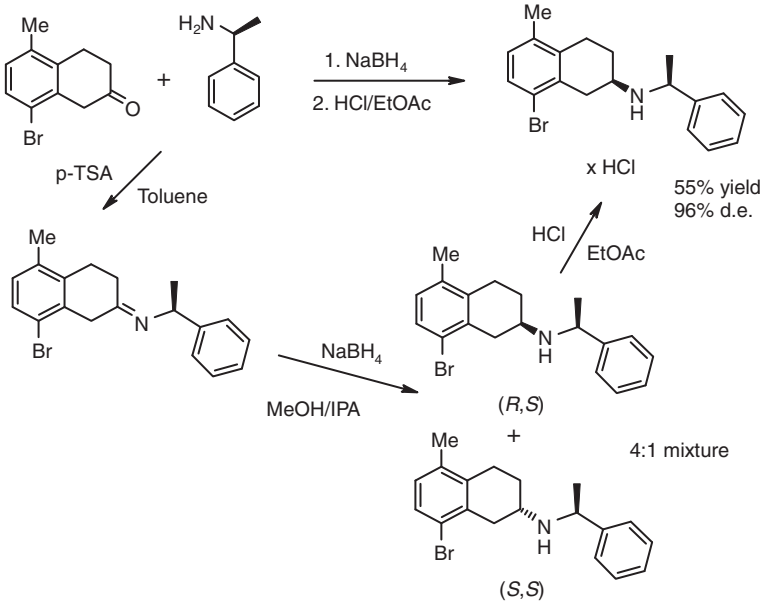
forward from a cost point of view, but considering the low yield still not qualified as the final commercial route.

Retaining the initial steps up to the tetralone intermediate seemed rather sensible, as the yields obtained were acceptable starting from an abundantly available phenylacetic acid building block. Furthermore, there were no alternative synthetic strategies in sight that might have presented any particular advantages. Thus, the main attention was paid to the instalment of the correct stereochemistry, especially as the resolution was the weak link in the previous route. One opportunity was to build on the literature precedent where pro-chiral enamides[49] or ene carbamates[50] have been transformed to the corresponding amines in enantomerically enriched form, albeit resulting in a widely varying range of enantiomeric purities. Testing this strategy in our case did, however, not offer any advantage as the product was composed of both isomers in a 1:1 ratio. Another idea that appeared to be even more attractive was to use a chiral α-alkylarylamine as the donor of the N-functionality, where it was hoped that a steric induction exerted by this appendage would direct the outcome of the imine reduction in stereochemical terms. And indeed using a prior art report from the patent literature[51] as a model, we managed to successfully obtain a workable excess of the desired diastereomer (*R*,*S*) over the undesired (*S*,*S*) of 4:1.[45] With this vastly improved two-stage procedure at hand we managed to consistently isolate a high quality product after purification through precipitation as the HCl salt at 96% de in 55% yield as compared to only 25% in the previous process (Scheme 17). Over the life-time of this project several hundred kg of the intermediate were manufactured following the methodology thus described.

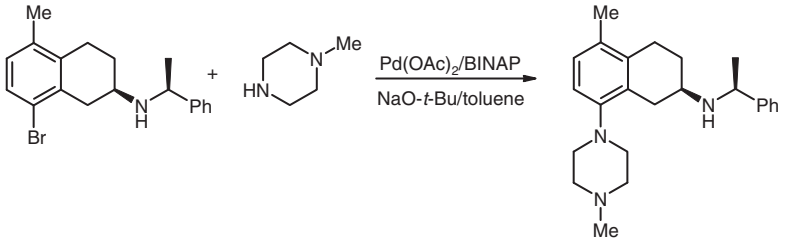
The subsequent Buchwald–Hartwig step (Scheme 18) was already in relatively good shape based on the development work conducted as part of the initial syntheses. Notwithstanding, it still remained to conduct final optimizations to ensure a robust performance on scale and to minimize the formation of unwanted *H*-analog (*H*-substituent at C-8 instead of piperazinyl moiety). Key areas to focus on were the catalyst loading and the exact definition of the catalytic system with issues such as finding the best ligand, type of base, solvent, reaction conditions, tolerable H_2O levels, etc. A crucial finding was the critical role of the ligand to metal (Pd) ratio in the generation of the *H*-by-product. Thus, with <2 mol equiv of ligand a level >10% of this contaminant was formed, whereas at $\geqslant$4 mol equiv this was sharply reduced to <0.5%. It was also noted that the amount of Pd catalyst (added as $Pd(OAc)_2$) was amenable to fine-tuning and would allow robust performance at a loading of



Scheme 16. An improved resolution-based synthesis of AR-A2, which eliminates the need for methyl group introduction but requires the construction of the tetralone nucleus. CDI, *N*,*N*′-carbonyl-di-imidazole.



Scheme 17. Operating the reductive amination in an induction mode by using a chiral NH_2-donor.



Scheme 18. The optimized and scaled up process for conducting the Buchwald–Hartwig step in the AR-A2 synthesis.

0.8 mol % in a production setting, as witnessed by the successful outcome on a batch size up to 125 kg in 2500 L reactor volume. From a yield point of view this reaction type that had just been reported in the literature[52,53] a few years earlier was demonstrated to deliver an outstanding result in our project. Conducting the reaction at 100 °C for 4 h managed to give a quantitative conversion of the substrate and after work-up (omitting product isolation) and catalytic debenzylation (H_2, Pd/C) the yield and quality of the penultimate intermediate (as the benzoate salt) was excellent at 88% and 96% ee, respectively. The final coupling (amide formation) was conducted as described before and it is worth pointing out that imidazole constituting a side-product from the use of CDI as condensing agent provides the ideal buffering conditions for providing solely the mono-HBr salt in spite of further two basic nitrogen atoms being present in the molecule. Summing up of the 3rd generation process for making AR-A2, an overall yield of ~7% was achieved and the purity in stereochemical terms was outstanding with ⩾99% >(*R*) produced in the pilot plant at a batch size of 72 kg. It was felt that in case the project had been successful and AR-A2 approved for marketing then the final synthetic route would have been sufficient to deliver the requested amounts at an entirely sustainable cost.

5. Conclusions and outlook

In this review, the ambition was set at painting a broad picture of the current state-of-the-art in the pharmaceutical industry in conjunction with providing a deeper insight in the flow of activities that characterizes work going on in a chemical Process R&D department. This account should leave no one uninformed of the demanding times virtually every company in the health care sector is facing and of the tremendous challenges that lie ahead. There is a productivity crisis and has been so for quite some time,[11] but maintaining the flow of new products to the market at today's level is not sustainable (as confirmed by fresh registration statistics from 2009[54,55]). Furthermore, the poor success rate of drug projects needs to be addressed and will hopefully enjoy a considerable improvement going forward. There is also a strong driver to bring down the still annoyingly long development timelines for new medicines as well as finding ways to counteract on the cost explosion experienced over the past years.

Looking specifically at the Process R&D environment, the design and optimization of synthetic routes for active molecules is at the very core of the business. With the ultimate goal of devising methods that allow a safe scale up and guaranteed product quality it is a question of bringing multi-disciplinary teams together that can successfully solve the many times challenging scientific and technical problems confronted with when setting out to make compounds of varying complexity. Outsourcing of ever increasing chunks of work from across the pharmaceutical business, exemplified by clinical and safety studies, product stability investigations, compound library synthesis, process design and development, commercial production, constitutes a trend that has been ongoing for quite some time. Suffice it to point out the current drive to establish stronger links into the growing Asian market (notably India and China) by creating both proprietary R&D centers as well as forging partnerships. From a Process R&D perspective, this will probably mean that more activities are shifted towards this part of the world and could eventually see integration with local large scale manufacture of the active ingredient. In other words this poses some serious challenges to the traditional European/US domination in the pharmaceutical arena, which in the coming years most likely is bound to redraw the industrial landscape.

From a capability point of view the toolbox of methodologies, which includes access to high performance computational software, has become increasingly rich allowing even some of the most demanding problems to be solved—now more than ever in a manner that can be described as sustainable. Being mindful of the massive scale and the speed with which new science is being explored and implemented it is an increasingly tough task to stay abreast of innovations taking place all across the world, even in a limited field. Notwithstanding, in order to stay competitive it is essential to remain updated on major achievements and present an open, yet critical, mind towards novelties potentially capable of having an impact now or in the future. In today's situation most, if not all, pharmaceutical companies realize that interactions with external partners is both necessary and fruitful and especially in non-competitive areas the model of multi-party collaborations has seen a real boost in the recent past. This change has also brought about a different view on intellectual properties (IP) that has resulted in a more differentiated approach. Thus, compared to the previous paradigm where ownership was the prime target for virtually all aspects of a drug the model applied now is more selective. For example, technology platforms or even very narrow technologies such as specific catalysts or pieces of equipment (e.g., reactor designs for continuous processing and sampling probes for accurate analysis of reaction progress) can be shared among a partnership with guarantee of freedom to operate for all. In this climate of more openness and watching out for externalization opportunities coupled with a firmly stated ambition to operate a lean and innovative organization at the highest possible efficiency in terms of cost, quality, and speed lies probably the solution to today's problems and the future of a successful pharmaceutical franchise.

Acknowledgments

Many colleagues and co-workers—past and present—have contributed to the in-house case studies presented in this paper. Unfortunately, far too many names to be individually mentioned one by one, albeit some have indeed been included as authors in the relevant references covering the projects on display. Nonetheless, my deepest gratitude goes to everyone for their highly valued and appreciated work—delivered in various shape and form—that has been instrumental in obtaining the excellent results reported herein.

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