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Lecture Transcripts

Development of a Process for a Chiral Aminochroman Antidepressant: A Case Story†

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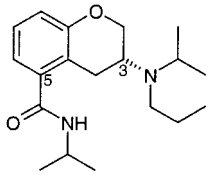
Abstract:

The authentic development aiming at a full-scale method for the new chemical entity ebalzotan (code name NAE-086), a selective $5HT_{1A}$-agonist chosen as an Astra candidate drug primarily for the treatment of depression and anxiety is described. As it turned out, largely due to severe time constraints the original Medicinal Chemistry route of synthesis comprising 13 steps arranged in linear fashion (starting from 3-methoxyphenol) and including a "classical" diastereomer resolution to generate the desired (*R*)-enantiomer had to be scaled up without sufficiently developed methods at hand. This resulted in an extended batch cycle time of 5 months after which time a very poor overall yield of 0.25% (!) could be isolated, albeit the product showed excellent stereochemical purity of 99.9% (*R*). Starting from this deploring position a process was designed which proved to operate well in a 400−600 L pilot scale affording ∼27 kg of high quality material.

Introduction: Defining the Target

The theme of this account is taken from the therapeutic area dealing with central nervous system (CNS) diseases, from the medical indications depression and anxiety to be more precise, both being clinically significant and acknowledged as indeed rather difficult to treat successfully. From the class of aminochromans, the new chemical entity ebalzotan (in-house code name: NAE-086) was selected as



a candidate drug by Astra in the early 1990s with the aim of documenting this compound as a selective $5HT_{1A}$-agonist (i.e., operating as a serotonin-mediated signal transduction mimic) for eliminating or reducing the symptoms caused by the mental illnesses indicated above.[1]

The structural features of this disubstituted chroman (or 3,4-dihydro-2*H*-1-benzopyran) besides its chirality are (i) the unsymmetrically substituted tertiary amine functionality in position 3 and (ii) the secondary carboxamide group attached to C-5. As is frequently observed[2] also the stereoisomers in this case exhibited a pronounced difference in pharmacological properties which eventually led to choosing the (*R*)-enantiomer as the desired form.[3]

The Medicinal Chemistry Route. The starting point for process development can in most cases be traced back to a synthetic sequence designed by medicinal chemists to serve their purpose of allowing the preparation of a maximum number of analogues. In the case of ebalzotan the linear "Med Chem" synthesis[4] outlined in Scheme 1 was the actual onset of activities in process R&D.

Chemically speaking, the sequence of steps displayed in Scheme 1 can be described in the following manner:

1. Introduction of the formyl group in a two-stage event consisting of an ethyl vinyl ether protection of the phenolic functionality, a subsequent BuLi-mediated electrophilic substitution where DMF (*N*,*N*-dimethylformamide) is utilized as CHO-equivalent, and finally an in situ deprotection effected by HCl.

2. Ring-closure forming the pyran moiety in a consecutive two-step domino fashion by an initial Michael-addition of the formylated phenol with acrylonitrile as the acceptor and DABCO (1,4-diazabicyclo[2.2.2]octane) as non-nucleophilic base. Capturing of the non-isolated intermediary anion by the CHO-group closes the ring by concomitantly forming a pair of 1,2-cyanoalcohols (in diastereomeric relationship). A final acidic treatment under reflux conditions causes dehydration to the unsaturated cyanochromene.

3. Straightforward hydrolysis of the nitrile to the unsaturated acid and a subsequent catalytic reduction offers the chroman carboxylic acid.

4. Applying Curtius rearrangement methodology using diphenyl phosphoryl azide (avoids the need for activation

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(1) Unfortunately, due to the observation of side effects during phase I clinical studies in humans, this project had to be discontinued before completion.

(2) For a recent review on this subject, see: Szelenyi, I.; Geisslinger, G.; Polymeropoulos, E.; Paul, W.; Herbst, M.; Brune, K. *Drug News Perspect.* **1998**, *11*, 139−160.

(3) Hammarberg, E.; Nordvall, G.; Leideborg, R.; Nylöf, M.; Hanson, S.; Johansson, L.; Thorberg, S.-O.; Tolf, B.-R.; Jerning, E.; Torell Svantesson, G.; Mohell, N.; Ahlgren, C.; Westlind-Danielsson, A.; Csöregh, I.; Johansson, R. *J. Med. Chem* **2000**, *43*, 2837−2850.

(4) Johansson, L.; Thorberg, S.-O.; Hammarberg, E.; Ross, S. Patent Appl. WO 93/07/135, 1992. For a detailed description on the current synthesis approach to aminochromans see: Thorberg, S.-O.; Hall, H.; Åkesson, C.; Svensson, K.; Nilsson, J. L. G. *Acta Pharm. Suec.* **1987**, *24*, 169−182.

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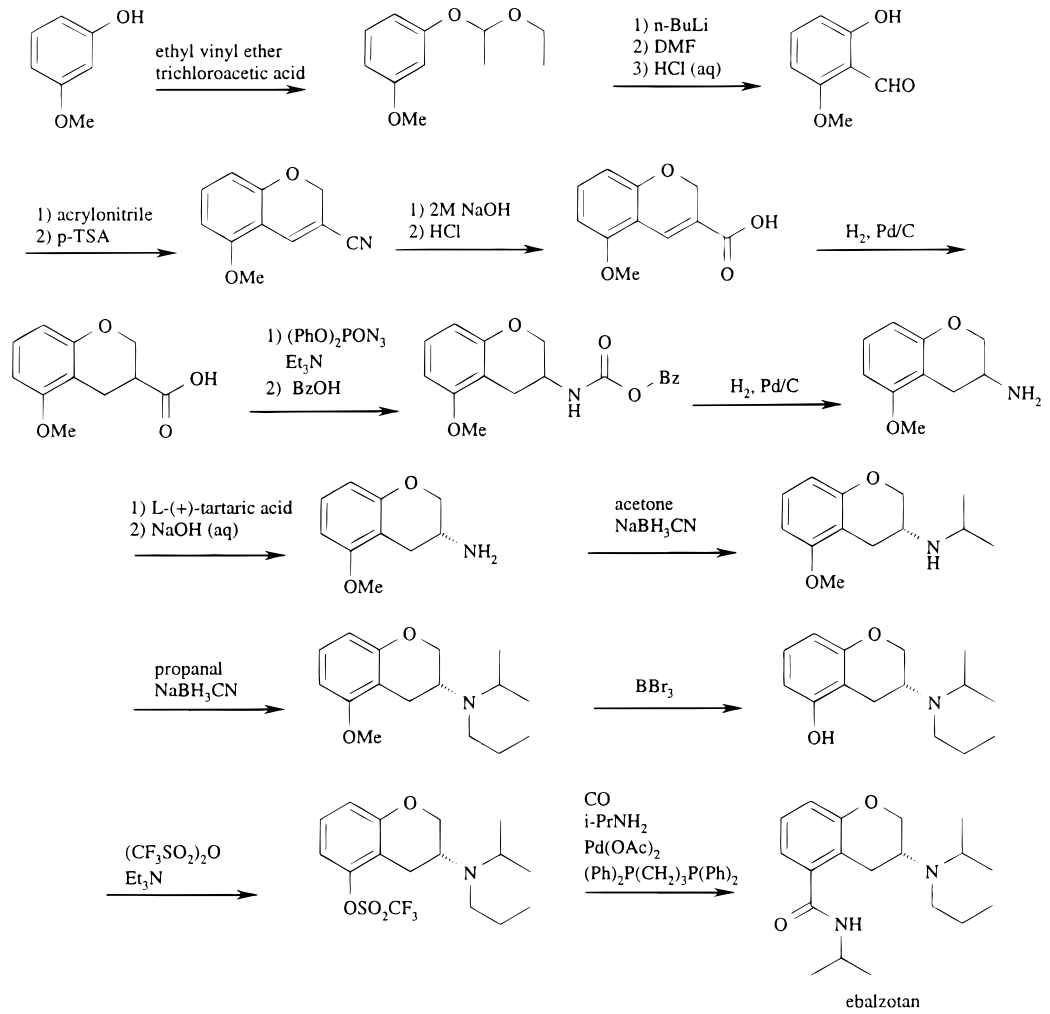
Scheme 1



to acid chloride when for example NaN_3 is used as azide transfer reagent) generates the isocyanate, which is immediately transformed to the carbamate by reaction with benzyl alcohol. Reductive conditions (H_2/Pd) smoothly afford the racemic aminochroman key intermediate.

5. "Classical" diastereomer resolution by crystallising the L-tartrate salt (natural enantiomer) followed by alcaline work-up generates the desired (*R*)-enantiomer in high stereochemical purity (i.e. > 98% ee).

6. Sequential two-step attachment of alkyl side-chains on the nitrogen atom either by a reductive procedure using the appropriate carbonyl precursor (i.e. acetone or propanal) and a borohydrate reducing agent or (as in the very original Med Chem procedure) the corresponding alkyl halides.

7. Standard type BBr_3-mediated demethylation and subsequent activation with triflic anhydride renders the oily phenolic triflate.

8. A formal Pd(II)-catalysed in situ carboxamidation (in reality consisting of a CO-insertion followed by a displacement with *iso*-propylamine)[5] concludes the series of steps leading to the desired product, which is isolated as the free base and used as such in the subsequent pharmaceutical formulation.

A further few outstanding characteristics of this synthesis are evident by mere visual inspection and require to be pointed out.

- There are a total of 13 steps laid out in a linear fashion (due to the fairly back-integrated synthesis starting as early as from 3-methoxyphenol).
- Structural complexity necessitates several carbon−carbon bond formations (again due to the use of a simple starting material).
- There is "loss" of valuable carbon in the Curtius rearrangement step (atom economy drawback).
- The first half of the synthesis forms racemic amine, at which point a "classical" diastereomer resolution can be performed (waste of unwanted antipode if not prone to "facile" racemization).
- The final step is organometallic, using palladium as catalyst, which demands a highly efficient separation of residual amounts of heavy metal contamination (down to low ppm levels).

Our initial involvement in this project aimed at "getting the chemistry to work" and establishing necessary analytical procedures as quickly as ever possible. In reality, after initial

(5) Selected literature on carbonylation chemistry: (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991. (b) Herbert, J. M.; McNeill, A. H. *Tetrahedron Lett*. **1998**, *39*, 2421−2424.

elimination of mainly synthetically oriented problems and methodological shortcomings in some steps it was actually possible to reach (and occasionally even surpass) previously[4] reported yields. Not neglecting the high risk of various degrees of failure due to too rapid an upscaling it was anyhow decided that despite some major uncertainties the start of a first pilot batch should be initiated, largely driven be the extremely urgent need to deliver material to allow the research programme in other key areas, for example, toxicology, galenic pharmacy, and pharmaceutical analysis, to be commenced.

First Pilot Plant Production: A Hard Lesson to Be Learned. The hardships perceived during our lengthy "battle" in the pilot plant can neatly be summarised in the following conclusions:

- A total overall yield of only 0.25% (!) was obtained which, expressed in another way, means that starting from 12.3 kg (99.2 mol) of 3-methoxyphenol afforded a meagre 80 g (0.25 mol) of ebalzotan.
- The enantiomeric purity of the final product was superb, 99.9% (*R*).
- From a yield point of view two main bottlenecks were detected, (a) the formylation step, that is, step 2 in Scheme 1, only gave 38% and (b) the carbonylation (via CO-insertion and *iso*-propylamine displacement) constituting the last chemical transformation including a final purification step, ended in 25%.
- In the resolution of racemic primary amine it was found that the diastereomer crystallisation was *non*-robust in the sense that laboratory scale results could not be reproduced in the pilot plant, leading to substantial yield penalties and poor stereochemical purity.
- The oily penultimate triflate intermediate required purification using both SiO_2-short-path filtration and regular chromatography.
- In total the batch cycle time was extended over 5 months using regularly three to five chemists and technicians on a continuous basis.

Given this rather disappointing result when it comes to amount of material produced combined with the just presented listing of major conclusions the following factors were identified as characteristic of the process in its current state.

Weaknesses:

1. Due to the lack of any commercially available *late*-stage building blocks the process needed to be very much back-integrated.

2. Even after putting in some considerable efforts in trying to theoretically convert the synthesis approach from a linear into a convergent mode no such obvious possibilities could be discerned.

3. The formylation step (second in sequence) is strongly exothermic and therefore requires efficient cooling. Metalation effectiveness is crucial to outcome and capacity is a bottleneck.

4. The undesired amine enantiomer is not prone to any facile racemization which has a severe negative impact on the overall economy in the process.

5. The need for triflate activation of penultimate phenol intermediate (using expensive triflic anhydride) prior to CO-insertion has a pronounced economical influence due to bad atom economy (i.e., triflate group is not retained in final product).

Superficially there did not seem to be anything really positive to highlight but a few **strengths** could at least be mentioned:

1. An infringement search revealed that the synthetic sequence described was indeed patentable.

2. From a process perspective the one-step in situ attachment of the carboxamide functionality in the final chemical transformation was quite appealing.

3. Given the rather miserable outcome of the first pilot batch, this brought about the identification of a multitude of opportunities for improvements. To conclude, a major challenging question could be formulated:

How to design a process capable of supplying multi-tonne quantities of the drug substance per annum?????

Pilot Batch No. 2: A Glimpse of Hope. This post-first-pilot-batch analysis was followed by some directed efforts to improve the chemistry and operability of at least the weakest parts of the process. Unfortunately, however, the small amounts of product delivered until now being far below what was required severely reduced the available time slot to conduct the necessary development work, and instead the planning for a new pilot run was initiated. Of course this time the awareness of risks and problems was much greater, and with the experience already gained we felt much more comfortable when restarting on this new adventurous journey the final outcome of which is summarised as follows:

- Total overall yield was 1.0% which, albeit being low, actually equals a 4-fold increase compared to batch no. 1.
- Starting with 226 kg (1821 mol) of 3-methoxyphenol gave at the end 5.8 kg (18.3 mol) of ebalzotan product.
- Again, the enantiomeric purity was outstanding, 99.8% (*R*).
- The total occupancy of the pilot plant was 13 weeks.

In total not that impressive a yield figure as such but in retrospect quite a remarkable improvement of some key steps in the synthesis:

1. By merely changing the procedure from introducing the butyl lithium solution in the formylation step sub-surface instead of above the reaction mixture a spectacular yield increase from 38 to 70% was noted! A most likely explanation for this is that the former methodology guarantees a far better dispersion and mixing efficiency, hence avoiding the creation of so-called local hot spots which cause various types of chemical degradation in its vicinity.

2. Applying better and more rigorous control of the conditions (mainly temperature profile and seeding procedure) during the diastereomer crystallization (resolution step) ended in an increased optical yield of 80 vs 65% previously (equals 40 and 32.5%, respectively, if the content of unwanted isomer is not compensated for).

3. The reducing agent sodium cyanoborohydride ($NaBH_3$-CN) in the two consecutive *N*-alkylations which is burdened by handling problems (toxicity due to e.g., the risk of

Table 1. **Generalised characteristics of chemical resolutions**

strengths	weaknesses
simple technology (crystallization)	trial-and-error approach in process optimization
"standard" type conditions	recycling of resolving agent and unwanted stereoisomer
high productivity	patent constraints
easy product separation	

releasing HCN and flammability), at least in the large scale, together with cost (expensive material even in bulk) and sourcing constraints is replaced by H_2/Pd frequently used in production to effect catalytic hydrogenations.

4. The corrosive, toxic, and expensive boron tribromide (BBr_3) was changed to somewhat more user-friendly HBr (aq) in the demethylation of the aromatic methoxy group. This switch also calls for a drastic increase in reaction temperature by going from −10 °C to reflux conditions, that is, >120 °C!

5. A considerably simplified, more effective, and capacity enhancing workup procedure was applied to the triflate intermediate by using a short-path flash-type chromatography, allowing elution of purified material from a silica/crude product slurry directly out of the centrifuge.

6. The indeed crucial reduction (down to low ppm levels!) of the palladium content in the reaction stream after the final chemical transformation was changed from a yield-consuming multistep method involving chromatography into an extractive procedure where the metal is efficiently eliminated (to ∼10−20 ppm) from a weakly acidic aqueous solution in the presence of charcoal.

Focusing on the Resolution Step: Creating the Right Stereoisomer. As mentioned earlier, our route of synthesis originated from Med Chem with their essentially divergent approach aiming at generating a set of compounds (i.e., a small library) from a common building block, which in this case for reasons of synthetic convenience turned out to be the (*R*)-aminochroman seen as easily accessible via a "classical" diastereomer crystallization. This technique may appear to be at a low scientific level with its, at least until now,[6] largely trial-and-error driven developmental procedure starting from the very search for a suitable resolving agent until the state of large-scale refinement. The fact is, however, that despite the tremendous growth in well-documented scalable alternatives (i.e., in the field of asymmetric reactions) resolutions still retain a strong, not to say dominant, position in industry, a fact that is clearly underpinned by the patent applications in this area which actually still in the mid 1990s outnumber those in the field of asymmetric processes.[7] Table 1shows a compilation of some selected characteristics briefly describing in a generalised sense the strengths and weaknesses frequently ascribed to this well-known methodology.

As mentioned previously, our first experience from the upscaled resolution was rather disappointing with both low yield (only 65% of desired stereoisomer, meaning a lot of valuable material was being wasted) and relatively poor stereochemical purity (70% ee) which necessitated an extra recrystallisation. In-depth study of the interplay between physical and chemical reaction parameters (e.g., type of resolving agent, water content, concentration, cooling rate, seeding, product isolation procedure) in this key step, from the points of view of yield and quality, showed that the outcome could be strongly influenced and, hence, allowed further optimization. A side-by-side comparison, as shown in Table 2, clearly reveals that what at least superficially (or better macroscopically) seem to be subtle changes can have a tremendous impact on the output of the desired material.

With this resolution method being proven as robust on scale-up we now turned our attention towards the identification of optional procedures which would allow the "wrong" enantiomer (i.e., the (*S*)-amine) to be inverted, eventually enabling a considerable increase in yield of the desired (*R*)-product to be achieved. Literature reports on the inversion of unactivated aliphatic (or alicyclic) primary amines are very scarce, but one procedure[8] where the amine is first transformed into the *N,N*-ditosylimide (to greatly enhance its leaving-group capabilitiy) followed by a nucleophilic displacement using azide as an NH_2-equivalent seemed rather attractive. Applied to our system, however, disappointing results were obtained, and the reaction delivered only the corresponding monotosylate, albeit isolated in good yield; see Scheme 2. The interpretation of this failure was that our aminochroman substrate offered a substantial steric hindrance at the intended reaction site (position C-3), leading instead to an N_3-attack at one of the considerably more accessible tosyl groups.

In Search of Alternative Syntheses. Four main streams were pursued in a retrosynthetic analysis of the target molecule:

1. An asymmetric approach where the desired stereochemistry would be introduced on a prochiral intermediate, for example, a ketone or an olefin, applying suitable methodologies (preferably operating in a catalytic mode) selected from the vast numbers reported in the literature in recent years.

2. The use of a chiral building block (preferentially available from a commercial source) which incorporates necessary functionality and other substituents to allow expedient assembly of a molecular scaffold with correct configuration that is ultimately transformed to the end product.

3. Achiral routes based on either the condensation of various (relatively simple) aromatic building blocks, eventually leading to intermediates (similar to the ones found in the current process) that should be prone to chemical

(6) For a recent example of a procedure allowing a more directed effort (and hence an increased success rate) in finding the most suitable resolving agent, see: (a) Vries, T. R.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A. J.; Kaptein, B.; van der Sluis, S.; Hulshof, L. A.; Kooistra, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2349−2354. (b) Broxterman, Q. B.; van Echten, E.; Hulshof, L. A.; Kaptein, B.; Kellogg, R. M.; Minnaard, A. J.; Vries, T. R.; Wynberg, H. *Chim. Oggi/Chem. Today* **1998**, *16*(9), 34−37.

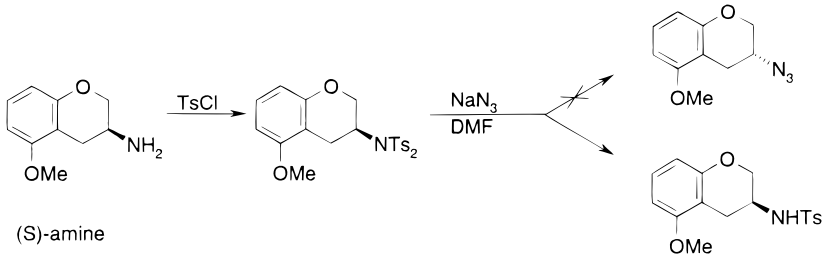
(7) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 388 and references therein.

(8) Seljestokken, B.; Fiksdahl, A. *Acta Chem. Scand.* **1993**, *47*, 1050−1052. For more recent results concerning this topic, see: Said, A. A.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2627−2633 and references therein.

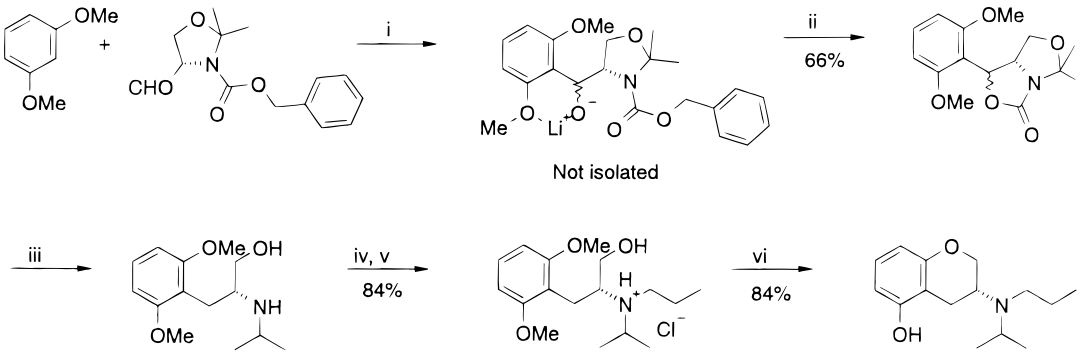
Table 2. **Early results from development of method for creation of desired enantiomer**

first pilot batch	second pilot batch
racemic amine (1 equiv) and (L)-tartaric acid (1 equiv) were dissolved in H_2O at 100 °C; ***slow cooling*** (to 10 °C in 7 h) gave crystals with 85:15 (*R*)/(*S*)-ratio; recrystallization from H_2O increased purity to 99:1.	same conditions as in batch no. 1 (conc = 30 mL H_2O/g tartaric acid) during resolution, then ***rapid cooling*** to 43 °C (in ~1 h 45 min) and seeding; crystallization onset at 37 °C; at 6 °C, immediate isolation ⟹ purity of 98% ee!

Scheme 2



Scheme 3[a]



[a] i. n-BuLi/monoglyme/−20 °C, ii. +30 °C, iii. acetone/H_2/Pd/C/MeOH/+50 °C, iv. propanal/H_2/Pd/C/MeOH/+50 °C, v. HCl (2-propanol), vi. HBr(47% aq)/+120 °C.

resolution, however with a pronounced possibility to racemise the "wrong" enantiomer as an add-on feature.

4. Or as a very final option implementing more subtle changes in the existing route notably in the sense of substituent modifications, for example, the methoxy group in the ultimate starting material is replaced by one (e.g., a cyano group) which allows more expeditious and hence a less effort-consuming transfer into the C-5 carboxamide functionality in the product. Following this track, however, only led to the formation of undesired by-products due to the incompatibility of the newly incorporated substituents with the reaction conditions in the BuLi-mediated formylation and hence had to be added to the ever growing list of dead ends.

The seriousness put into this matter is strongly emphasized by the fact that in the range of almost 30 (!) discrete cases were assessed from a theoretical point of view with a majority of them actually being investigated experimentally as well. Much to our deep disappointment and despair none was identified as worthwhile to progress into a developmental phase after having confronted each of them with our indeed very tough selection critera. Actually, only two of the alternatives deserve more attention in this context emerging as at least potentially promising on the basis of initial experimental results.

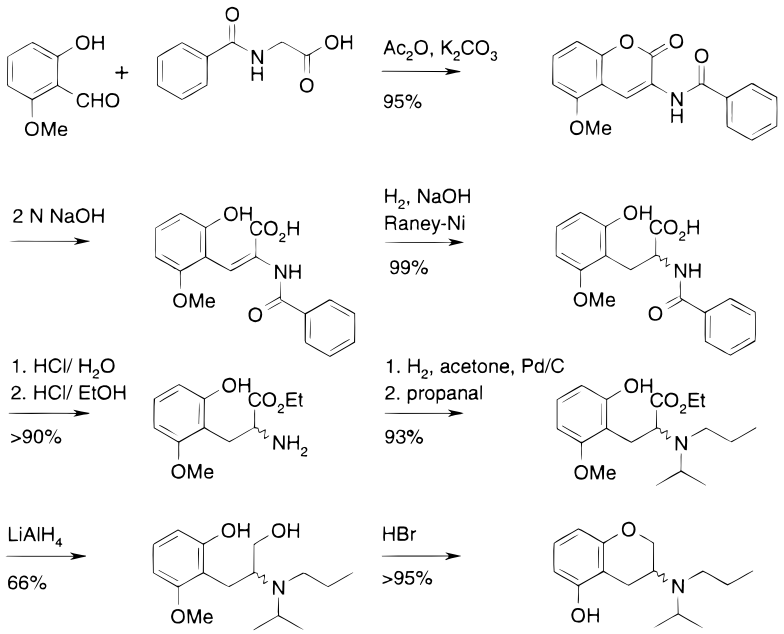
A. Out of group 2 above an ortho-lithiation strategy starting from resorcinol dimethyl ether was examined in some detail. After transformation to the lithiated species (using n-BuLi) a condensation with an *N*-Cbz derivative of (*S*)-serinaldehyde acetonide (also known under the name of Garner aldehyde[9]) led to a diastereomeric adduct, which on submission to reductive conditions (H_2, Pd/C) led to a 1,2-aminoalcohol as a single enantiomer (with retention of configuration compared to the chiral building block used); see Scheme 3.

In two consecutive steps (a double reductive alkylation and an acid-mediated demethylation of the aromatic methoxy groups with a concomitant ring-closure under elimination of H_2O) this intermediate is smoothly converted to an aminochroman which nicely intercepts the original route at a late-stage position. The overall stereochemical outcome of the synthesis was excellent with an enantiomeric purity >99.7%, albeit with only moderate yield in several of the steps.

B. From group 3 a Perkin condensation-based sequence was scrutinized where in the first step the previously available hydroxy-methoxy-benzaldehyde from the "old" route was reacted with *N*-benzoylglycine (hippuric acid) under mildly

(9) (a) Garner, P.; Park, J. M. *J. Org. Chem*. **1987**, *52*, 2361−2364. (b) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31−33.

Scheme 4



basic conditions. The chromen-2-one thus formed was then ring-opened to an α,*β*-unsaturated amino acid derivative which underwent facile reduction to the saturated analogue; see Scheme 4.

This latter transformation offered a clear possibility to be conducted in an asymmetric fashion which then would more or less selectively lead to the desired stereoisomer instead of the racemate, an approach which, however, was never tested in practice. Before the chroman ring was reconstructed again, a series of straightforward reactions (hydrolysis of benzoyl group, double alkylations, and reduction of ester functionality) led to a properly dressed-up penultimate intermediate which underwent almost quantitative ring-closure using concentrated HBr (aq) as reaction medium. Obviously, this tertiary amine product could be subject to resolution, but more importantly, some of the earlier carboxylic acid derivatives possessing a labile α-hydrogen atom would in addition to being prone to diastereomer separation (e.g., by conventional precipitation with an optically pure amine) also allow inversion of undesired enantiomer.

Final Methods Optimizations and an Innovative Resolution

Now that the likelihood of finding a feasible alternative on short term was low, a suitable external partner was identified to contract out at least a part of the synthesis mainly for in-house capacity reasons. An agreement to produce stage one benzaldehyde product was installed which subsequently was expanded to include all steps up to the racemic amine. Hereafter our own attention was targeted entirely towards the second half where some significant improvements were achieved:

- To prevent formation of Friedel-Craft type by-products (alkylated aryl moiety of the chroman skeleton) a meticulous removal of the alkyl donors acetone and propanal (both present in large excess in the reaction mixture) from the consecutive reductive alkylations was ensured by a careful evaporation procedure (and subsequent monitoring of residual amounts down to levels of ∼0.1%).
- For technical reasons (avoidance of extensive splattering) the procedure described in the previous bullet also required the Pd/C catalyst to be separated off. Instead of being subsequently reused in the second alkylation it was replaced with a fresh one which as a spin-off brought the advantage of shorter and more consistent reaction times for this step (from at best 14 h, but with occasional highs in the range of 5−6 days (!), down to only 7 h). Whether this was achieved merely by virtue of catalyst replenishment or driven by the careful elimination of acetone/H_2O mixture from the first alkylation (or a combination of both) has not been elucidated in detail.
- A loop-type reactor technology (pumping of the reactant stream in a circular fashion through a short-path tubular reaction zone equipped with catalyst) was evaluated as a means of increasing the capacity in the reductive alkylations, however, without obtaining any immediate advantages compared to the original methodology (the transformations in question still required extended reaction times of 12 and 50 h, respectively).
- Quality improvement of the penultimate triflate intermediate was achieved by applying a high-vacuum short-path distillation procedure to increase performance (i.e., yield) in the final step.
- Change of solvent in the precipitation of crude ebalzotan to *iso*-octane offered a noticeable improvement in yield and purity.

As one of the very final measures to be pursued the possibility to conduct a successful resolution at some other stage in the synthetic sequence was investigated. The obvious target for this approach was the saturated carboxylic acid intermediate two steps backwards from the racemic amine.

Our search for a suitable resolving agent was quickly rewarded when finding that the commonly used (*R*)-

Scheme 5

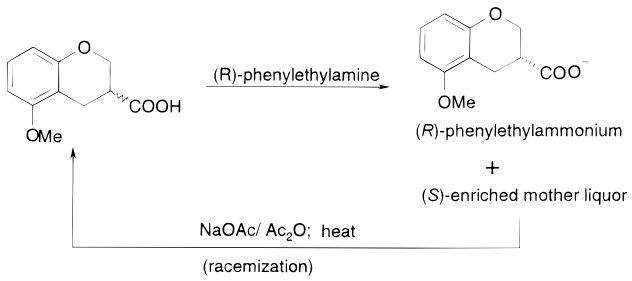
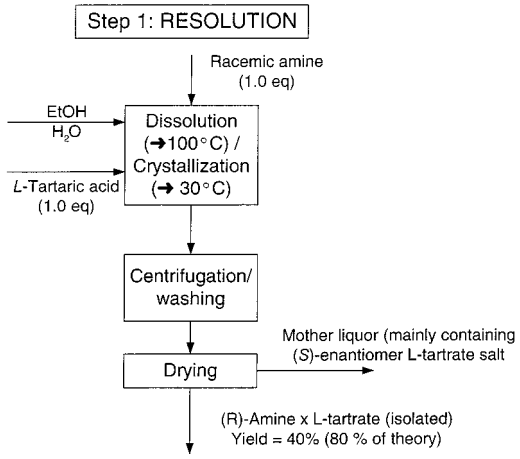


Chart 1



phenylethylamine was indeed serving this purpose, providing a nicely crystalline material of the stereochemically correct acid. After some optimisation we designed a process[10] that offered a total yield of about 80% which included one first cycle resolution completed with two further loops to follow consecutively after racemisation of the wrong antipode (requiring prolonged heating in the presence of NaOAc and Ac_2O). The resolved acid fractions thus isolated were of very good optical purity with ~97−99% (*R*), a situation which was maintained through the Curtius rearrangement (carboxylic acid → primary amine) proceeding virtually with full retention of configuration,[11] and a really promising economical potential was identified when noting that a substantial overall yield increase of 50−70% (!) for the steps from racemic acid to (*R*)-amine was within reach compared to the corresponding parts in the "old" process (Scheme 5).

The abrupt discontinuation of the project due to the previously mentioned clinical side-effects unfortunately prevented us from ever trying out this major improvement on a larger scale.

Process Flow Scheme

The way a process will be conducted in the plant is probably best captured in a flow scheme where the emphasis is put on equipment and unit operations as well as on product and waste streams. Thus, the layout of the remaining six in-house steps is presented in the following charts (Charts 1−5).

From these self-explanatory schemes it is evident that the yield in most of the steps has been optimized to quite

Chart 2

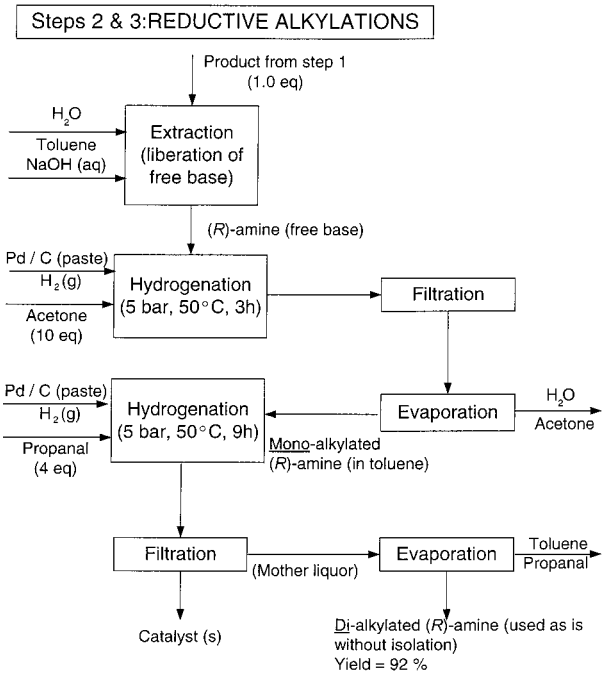
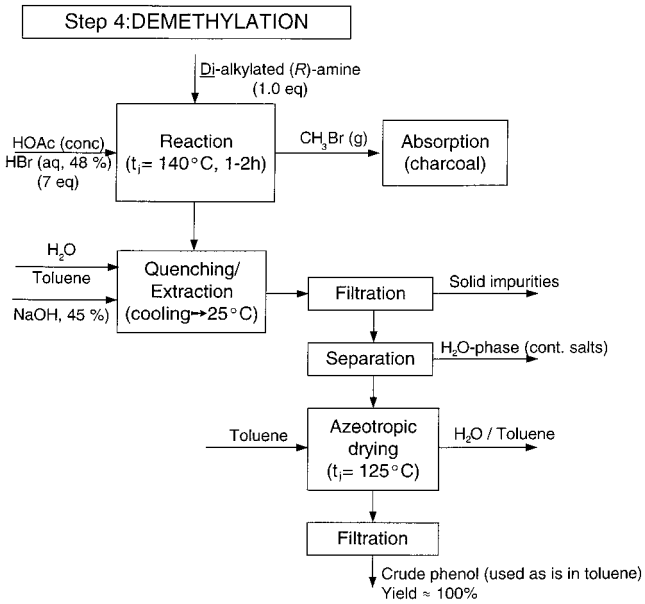


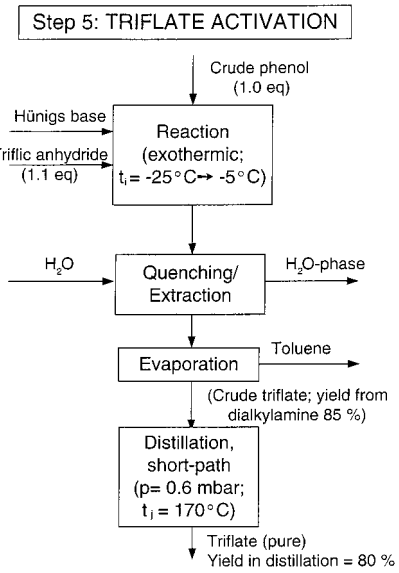
Chart 3



respectable levels, acknowledging that the 40% obtained in the resolution due to the loss of unwanted enantiomer is still a major weakness, as are the 60% in the combined carbonylation and final purification. Anyhow, at this stage the accumulated evidence (from laboratory and pilot plant) had provided us with a good understanding of critical parameters governing the latter reaction. Examples of these are the need for pre-formation of active catalytic species prior to adding triflate substrate, the highly significant adjustment of CO partial pressure (low values required) to avoid di-carbonylation, and rigorous control of triflate quality to reduce risk of forming by-products generated from nucleophilic impurities, for example, the phenolic precursor of the triflate, replacing *iso*-propylamine in the final displacement reaction. Nevertheless, the procedure described did well suffice to

(10) Eriksson, M. Patent Appl. WO 99/59988, 1999.
(11) *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Winterfeldt, E., Eds.; Pergamon: Oxford, 1991; Vol 6, p 798 and references therein.

Chart 4



meet demands for quantities up to tens of kilograms.

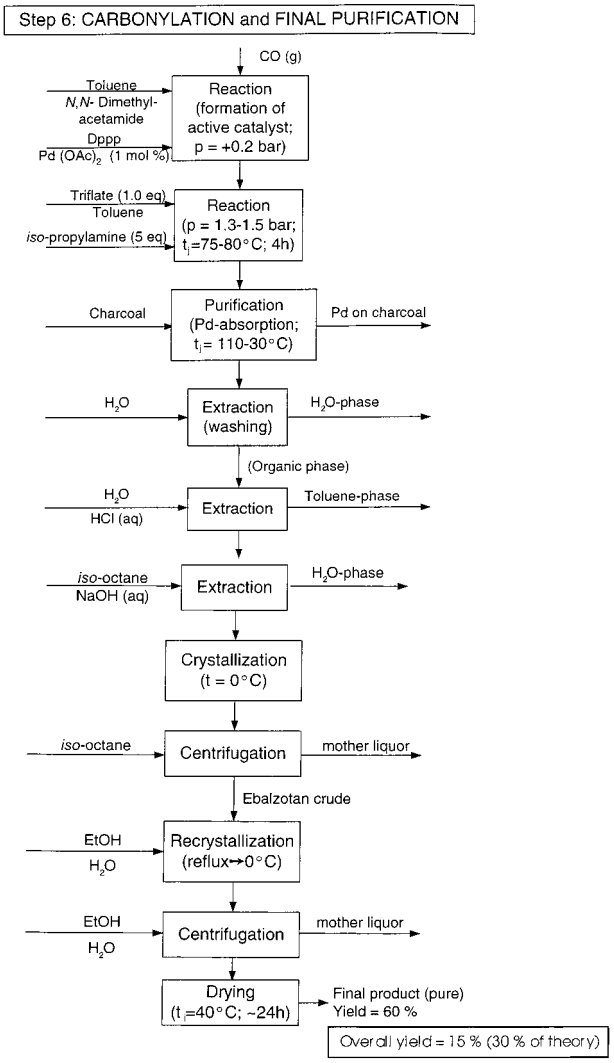
The technical operability was also quite acceptable even if a few of the steps were somewhat lengthy and laborious, hence requiring large inputs of resources, notably the consecutive reductive alkylations, the low-pressure triflate distillation, and the entire CO-insertion reaction followed by the streamlined work-up procedure to ensure effective elimination of Pd residues. In total, however, the process had reached a stage where it well-matched the requirements on quantities of high quality material to be delivered and also the overall developmental time schedule.

Final Stage: Major Conclusions and Messages To Remember

After six years dedicated to this challenging task the experience gathered and the conclusions drawn can be summarised in the following:

- Due to the established work procedure at the time between the Discovery organisation and Process R&D the project was initiated at too late a stage in the latter function which cemented the use of the Med Chem synthesis route. Time was merely not available to allow major changes in the synthetic sequence, partly of course depending on the complex nature of the final molecule.
- The Med Chem-based synthesis was modified, partly optimized, and streamlined, allowing a successful scale-up in the final developmental stage to a 400−600 L pilot plant reactor size. This enabled conversion of 100 kg of racemic amine produced at an external contractors to ∼27 kg of ebalzotan (free base), which translates into 15% overall yield (compared to 3.7% in the corresponding steps of batch no. 1).
- The isolated and delivered final product showed an excellent stereochemical purity with 99% (*R*), that is, 98% ee.
- In terms of cost of goods the compound was expensive due to a highly priced racemic amine starting material (requiring a number of sequential steps for its manufacture) and loss of unwanted enantiomer, which could not be utilized via racemization.

Chart 5



- Late-stage discovery of an alternative (and patentable) resolution of a carboxylic acid intermediate allowed the "wrong" antipode to be racemized and reused and led to a considerably higher turnover of racemic material to wanted stereoisomer.

Acknowledgment

The results reported herein and the really phenomenal progress made could not have been achieved without a team of experienced and skilful co-workers, who showed real commitment and dedication to the task even in difficult times when the future seemed far from bright. A number of them deserve to be explicitly mentioned: Mikael Eriksson, Jörgen Blixt, Björn Elman, Lars Lilljeqvist, Tibor Musil, Galina Bessidskaia, and Malin Gidlund, all in Process Chemistry; Helena Knutsson, Torsten Emanuelsson, Karl-Åke Berg, Stefan Lindholm, and Emilia Fulgencio-Bengtsson from Process Technology and the Pilot Plant; Britt-Marie Gawell and Egil Forsberg in Analytical Chemistry.

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