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Review

Epoxide Syntheses and Ring-Opening Reactions in Drug Development

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Abstract: This review concentrates on success stories from the synthesis of approved medicines and drug candidates using epoxide chemistry in the development of robust and efficient syntheses at large scale. The focus is on those parts of each synthesis related to the substrate-controlled/diastereoselective and catalytic asymmetric synthesis of epoxide intermediates and their subsequent ring-opening reactions with various nucleophiles. These are described in the form of case studies of high profile pharmaceuticals spanning a diverse range of indications and molecular scaffolds such as heterocycles, terpenes, steroids, peptidomimetics, alkaloids and main stream small molecules. Representative examples include, but are not limited to the antihypertensive diltiazem, the antidepressant reboxetine, the HIV protease inhibitors atazanavir and indinavir, efinaconazole and related triazole antifungals, tasimelteon for sleep disorders, the anticancer agent carfilzomib, the anticoagulant rivaroxaban the antibiotic linezolid and the antiviral oseltamivir. Emphasis is given on aspects of catalytic asymmetric epoxidation employing metals with chiral ligands particularly with the Sharpless and Jacobsen–Katsuki methods as well as organocatalysts such as the chiral ketones of Shi and Yang, Pages's chiral iminium salts and typical chiral phase transfer agents.

Keywords: epoxides; drug development; catalytic asymmetric epoxidation; organocatalysis; process development and manufacturing routes; Sharpless and Jacobsen–Katsuki asymmetric epoxidation; chiral ketones/dioxiranes; iminium/oxaziridinium salts; epoxide ring opening

1. Introduction

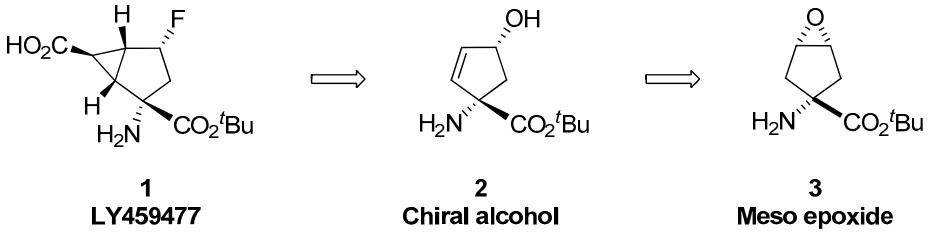
Epoxides are versatile electrophiles that support the stereospecific formation of ring-opened products with a wide array of nucleophiles. The implications of this reactivity in the context of drug design and desired biologic action as well as manifestation of adverse effects has been reviewed previously [1–4] although these are best exemplified by the plethora of natural products and the 14 approved drugs containing the epoxide functionality [5,6]. In the context of organic synthesis, the ring strain-induced electrophilicity of epoxides renders them excellent reactive intermediates for constructing in stereoselective/specific manner key bonds in larger and more complex molecules. From an academic perspective, general aspects of epoxide synthesis and ring-opening reactions spanning various levels of organic chemistry research have been reviewed extensively [7–9]. What is lesser known is how pivotal has been the successful management of epoxide chemistry on scale leading to robust, cost-effective and safe manufacturing processes. Emphasis is also given in the way certain intermediates are handled due to safety, reactivity, inappropriate state (oils, low melting point solids) or physical properties (hygroscopicity, poor filtration characteristics) or even time constraints. For example, in several cases a "telescoped" process is implemented which is a process term to describe a reaction that despite work up, washes, filtration of unwanted materials (inorganics, charcoal),

etc., avoids any isolation and a solution of the intermediate is carried forward in the next step, not necessarily in the same reactor. The more common term "one-pot" implies no processing/work up and the reagents for the next step are added sequentially in the same vessel. The focus of this review is the implementation of epoxide chemistry from a process development perspective and is presented through dedicated discussions to high profile approved drugs and clinical candidates.

1.1. LY459477—Development of a Selective Route via a Desymmetrization Process of a Meso-Epoxide

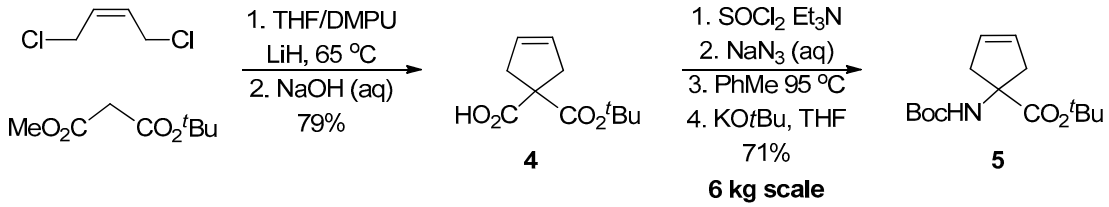
LY459477 (**1**) is a potent (EC_{50} 1 nm) orthosteric agonist for rodent and human mGlu2 and mGlu3 receptors. Development of an appropriate large-scale synthesis of LY459477 was required to support clinical trials for schizophrenia, generalized anxiety disorder and bipolar disorders [10]. Moreover, the supply route for LY459477 served as an excellent platform for the development of subsequent structurally related mGlu2/3 agonists as drug candidates for neuropsychiatric disorders [11].

The chemotype of LY459477 was based on a cyclopentene scaffold first introduced by Hodgson and scientists at GlaxoSmithKline (then Glaxo Wellcome) [12] where the key intermediate, chiral alcohol **2**, was obtained from desymmetrization of the meso epoxide **3** (Scheme 1).



Scheme 1. Retrosynthesis of LY459477 into the key alcohol and epoxide intermediates.

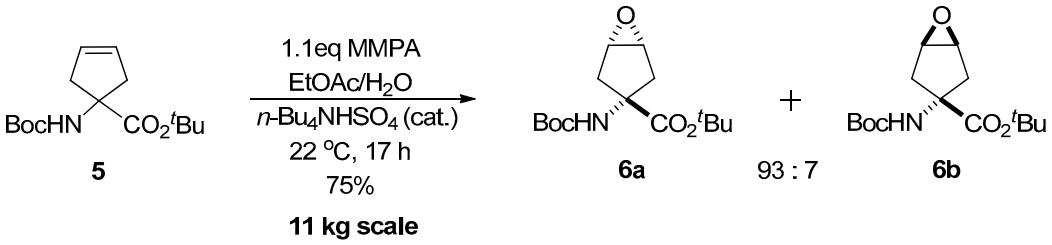
A team of process chemists from Eli Lilly developed the original synthesis further in order to deliver cyclopentene precursor **5** on a multikilogram scale (Scheme 2). The synthesis comprises of six discreet steps but proceeds through several telescoped stages with only two isolable intermediates; monoacid **4** and cyclopentene **5**. Peracid-mediated epoxidation of **5** delivers the oxygen atom preferentially on the same face of the cyclopentene as the NHBoc substituent as result of a hydrogen bonding interaction between the oxidant and the latter functionality. A variety of conditions were examined for optimum diastereoselectivity in the epoxidation of **5** towards the desirable diastereomer **6a**, concluding to magnesium monoperoxyphthalate in a biphasic water/ethyl acetate mixture with *n*-Bu_4NHSO_4 as a phase transfer catalyst (Scheme 3). This method was successfully scaled up to 11 kg and the final product was recrystallized from EtOAc/heptane giving **6a** at 75% yield with 3% of the diastereomer **6b**.



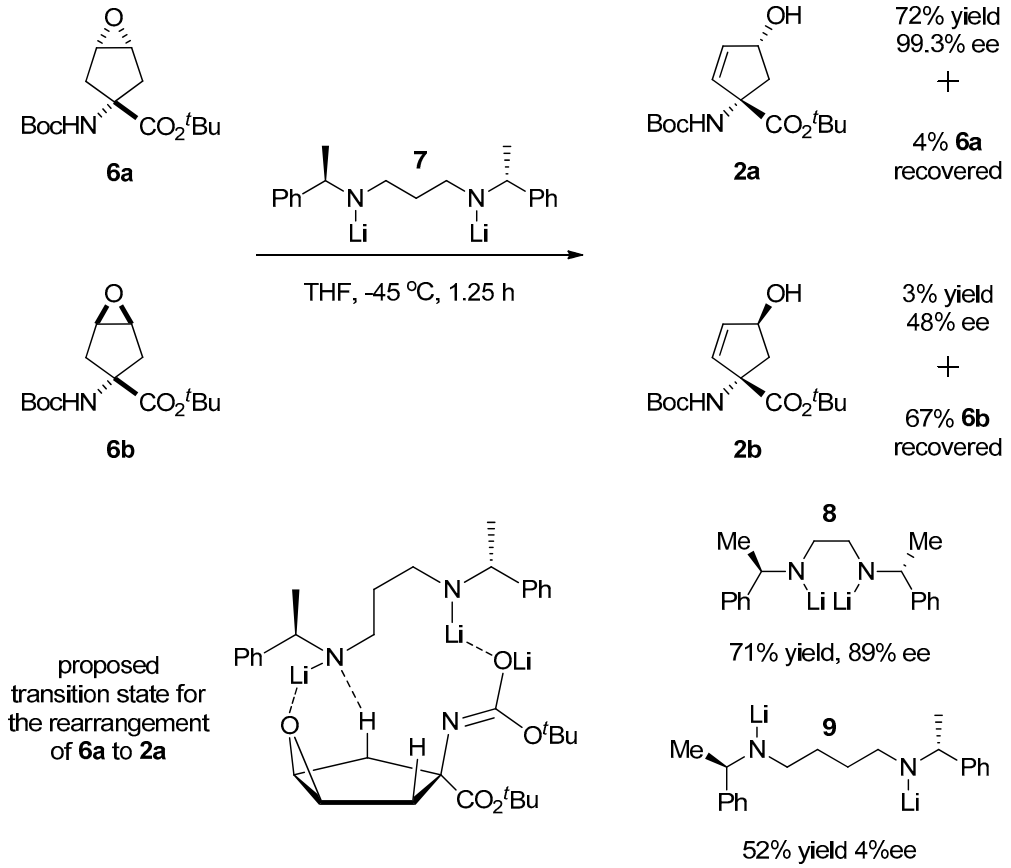
Scheme 2. Synthesis of meso-epoxide precursor **5**.

The desymmetrization of epoxide **6a** into chiral allylic alcohol **2** demanded a wide screen of chiral lithiated mono- and diamines as well as amino alcohols, temperatures, additives, reaction times and stoichiometry in order to achieve maximum yield and enantioselectivity. Best results were obtained with diamine **7** (Scheme 4) affording the desired chiral allylic alcohol in 72% yield and >99% ee, followed closely by the corresponding diamine with an ethylene linker between the nitrogen atoms (71% yield and 89% ee) whereas the analog with the butylene spacer proved non selective. Interestingly, under the same conditions diastereomeric epoxide **6b** essentially does not rearrange.

The rearrangement of epoxides to allylic alcohols has been demonstrated to proceed via abstraction of either the *syn*-β H or the *anti*-β H, with cyclopentane skeletons favoring the former mode. This was also shown to be the case for **6a** through deuterium labeling studies.



Scheme 3. Substrate-controlled diastereoselective epoxidation of **5**.



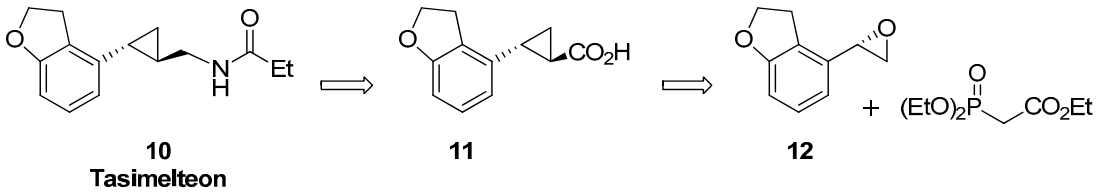
Scheme 4. Desymmetrization of meso epoxide **6a** with chiral bases.

A transition state consistent with above findings was proposed and involves the complexation of the lithiated diamine with both the (deprotonated under the reaction conditions) Boc group and the epoxide. In the latter case the lithium cation serves as a Lewis acid activating the epoxide towards ring opening with concomitant abstraction of the adjacent enantiotopic epoxide-*syn*-β H. This epoxide activation would be absent in the analogous complex of the lithiated diamine and the Boc group of diastereoisomer **6b** (being in opposite sides) thus consistent with the inertness of the latter. The proposed transition state also exemplifies the importance of the distance between the two lithiated amino groups as this must match the distance between the epoxide and Boc oxygen atoms so that a stable complex is formed. This in turn supports the alignment of one of the basic nitrogen atoms with one of the two enantiotopic *syn*-β H atoms, abstraction of which leads to high enantioselectivities.

The cost-effectiveness and of this competitive synthesis stems from the inexpensive starting materials including chiral diamine **7** which can be easily prepared from (*R*)-α-methyl benzylamine and is recovered up to 80% from the pilot-plant operations. Overall, an important chiral and pharmaceutically privileged scaffold is accessed in multikilogram quantities through the desymmetrization of a meso epoxide.

1.2. Tasimelteon—Comparison of Large-Scale Catalytic Asymmetric Epoxidation Processes Towards a Chiral Dihydrobenzofuran Epoxide

Agonism at the melatonin receptors 1 and 2 has produced drug molecules that have been approved for the treatment of insomnia and circadian rhythms sleep–wake disorders (ramelteon, tasimelteon) as well as for depression (agomelatine) [13]. During the development of tasimelteon, **10** (Scheme 5) by Bristol-Myers Squibb, provision of large quantities of **11**, required the development of a supply route. One of the first syntheses examined by process chemists at BMS involved chiral epoxide **12** as the key intermediate as this could be transformed to acid **11** by reaction with triethyl phosphonoacetate followed by ester hydrolysis [14].



10
Tasimelteon

11

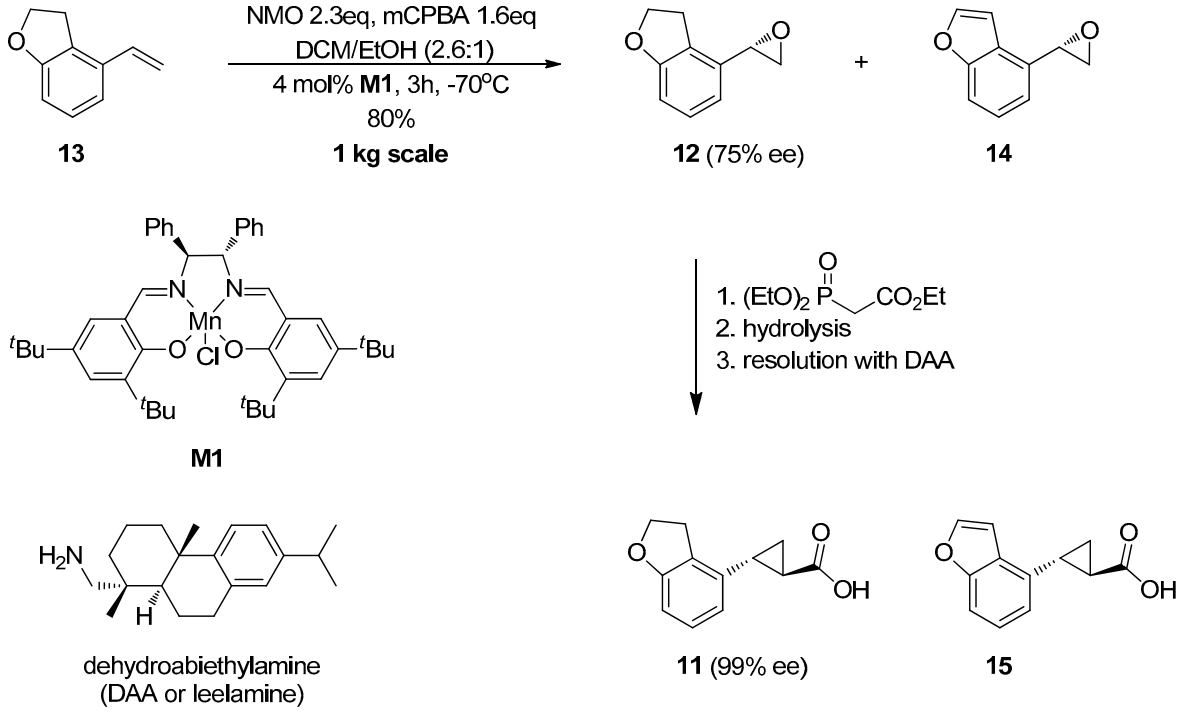
12

Scheme 5. Retrosynthetic analysis of tasimelteon into key epoxide intermediate **12**.

Initially the Jacobsen–Katsuki asymmetric epoxidation (AE) [15–17] was attempted and its optimization involved extensive screening of catalysts, solvents, oxidants, additives, reaction temperature and time. It quickly became evident that the reaction needed to be carried out at very low temperature in order to achieve significant enantioselectivity which never actually exceeded 76% ee. mCPBA (*meta*-chloroperoxybenzoic acid) provided higher enantioselectivities than MMPP (magnesium monoperoxyphthalate) or bleach and addition of NMO (N-methylmorpholine N-oxide) was also beneficial. DCM proved the best solvent both in terms of conversion and enantioselectivities, yet this also proved the Achilles heel of the process since it caused significant safety and operational issues. Specifically, the moderate solubility of mCPBA in DCM exacerbated by the low reaction temperature at −75 to −65 °C, caused precipitation of the reagent leading to inconsistent reaction mixtures. More frequently than not, large exotherms and abrupt gas evolution were observed upon addition of the mCPBA solution in the reaction mixture which caused serious safety concerns. Adjusting for concentration, time and order of reagent addition did not solve these issues. Solvents in which mCPBA dissolves better, like EtOAc or ethanol were attempted as DCM replacements, but the reaction did not proceed. Finally, by keeping DCM as the reaction and using the minimum amount of ethanol to dissolve and transfer the mCPBA into the reaction mixture solved these issues and provided a fast reaction reaching 95% conversion within the three hours employed for addition of the mCPBA at −70 °C. The optimized process involving catalyst **M1** (Scheme 6) was successfully scaled up to 1 kg scale and delivered chiral epoxide **12** in 80% yield and 74% ee. This was deemed acceptable at this point since a resolution step, using dehydroabietylamine (leelamine), was to be implemented later in the synthesis at the amine intermediate which upgraded the optical purity to 99% ee.

Despite the temporary success in supplying the initially required quantities of drug substance, the necessity for a resolution step, the varying levels of manganese salts in the isolated intermediates and the apparently unavoidable formation of benzofuran impurity **14** (>3%), undermined the potential of this route in developing into a manufacturing process. Overoxidized impurity **14** in particular, presumably formed by mCPBA or catalyst-induced hydroxylation at the benzylic position followed by dehydration [18,19], posed significant quality issues as it transformed through the synthesis to

species that were difficult to purge, such as the acid **15**, due to the high similarity with the desired intermediates and ultimately with the final product.



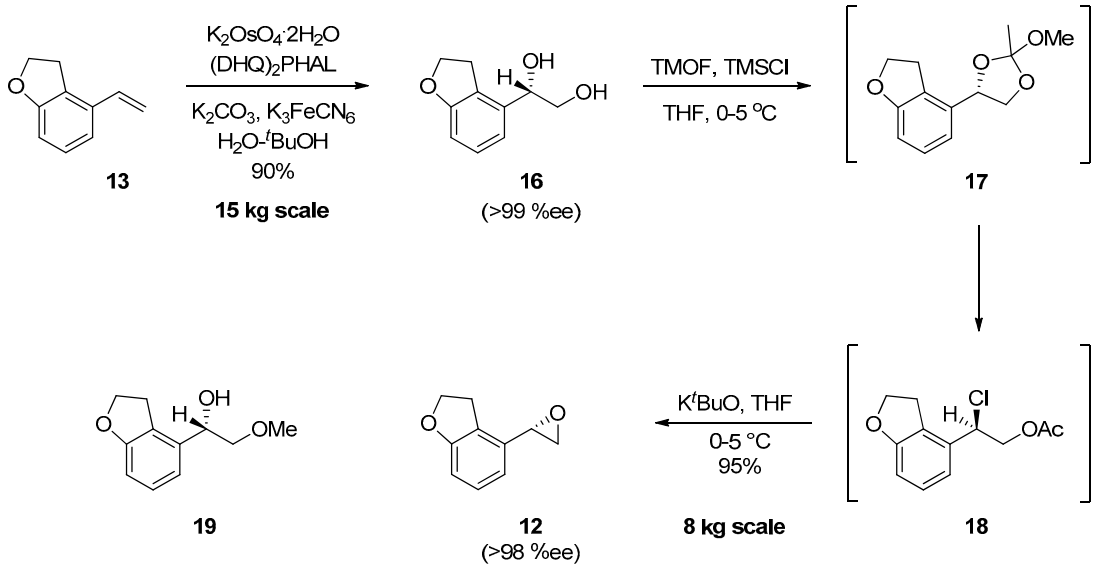
Scheme 6. Catalytic asymmetric epoxidation of **13** and conversion to cyclopropane intermediate **11**.

This prompted the investigation of an alternative route to epoxide **12**. Towards this end, Sharpless Asymmetric Dihydroxylation on alkene **13** followed by transformation of the chiral diol **16** (Scheme 7) to the epoxide was considered next [20]. Encouraging results were obtained from preliminary experiments as diol **16** was isolated with high ee as a crystalline and easy to handle solid. Significant work was dedicated before selecting potassium ferricyanide as the osmium reoxidant over the less expensive NMO. Potassium ferricyanide requires larger solvent quantities to be suspended adequately, produces a significant solid waste that must be removed during isolation and constitutes an additional burden in terms of toxic materials in the process. Nevertheless, it provided consistently high enantioselectivities (98–99% ee) thus eliminating the necessity for a resolution step and robust reactions whereas the process with NMO proved sensitive to the rate of addition of alkene **13**. The next issue that had to be dealt with was the poor solubility of **13** in *tert*-butanol/water mixtures which was eventually solved by replacing *tert*-butanol with isopropanol. Interestingly the reaction failed to proceed with commercially available AD-Mix-α, and potassium persulfate was used and required the in situ preparation of the catalyst. The final problem intrinsically linked to the Asymmetric Dihydroxylation reaction was the reduction of the toxic osmium species to pharmaceutically acceptable levels which for the isolated diol intermediate was set at <10 ppm. Following a screening of resins, filter aids and reagents as well as the development of an appropriate analytical method, the use of a sodium sulfite wash in the work up reduced the osmium levels to less than 6 ppm as determined by inductively coupled plasma atomic emission spectroscopy (ICP-ES).

The optimized process (Scheme 7) was gradually scaled up to 1, 8 and 15 kg scale furnishing diol **16** in 90% yield, HPLC purity of 98% and >99% ee and as a crystalline solid, provided the water content of the organic solution after work up was <1% *w/w*.

Finally, diol **16** was transformed to the desired epoxide **12** through the Kolb -Sharpless method [21], by treatment with trimethyl orthoacetate and trimethylsilyl chloride followed by base. In this process, the initially formed orthester **17** is converted in situ to chloroacetate intermediate **18** with inversion of configuration and after hydrolysis of the ester and ring closure, also with inversion of configuration,

provides the desired chiral epoxide **12**. When the traditional conditions of K_2CO_3/MeOH were used for the latter part of the process, significant amounts of impurity **19** were observed (up to 10%) presumably via opening of the epoxide by methoxide anion. The epoxide stability issue surfaced required investigation of appropriate solvents, bases, reaction temperature and times temperatures as well as work up procedures in order to inhibit the formation of impurity **19**. The optimum conditions found involved confirming by HPLC the completion of chloroacetate formation, followed by charging a solution of KO^{t}Bu in THF at 0–5 °C and maintaining at the same temperature until conversion to the epoxide was complete (~1 h) (Scheme 7). No deterioration of the epoxide quality is observed under these conditions even after prolonged reaction times. The optimized process was successfully scaled up to 8 kg batches delivering the epoxide 90–95% yield and >98% ee.



Scheme 7. Synthesis of chiral epoxide **12** via Sharpless asymmetric dihydroxylation of **13**.

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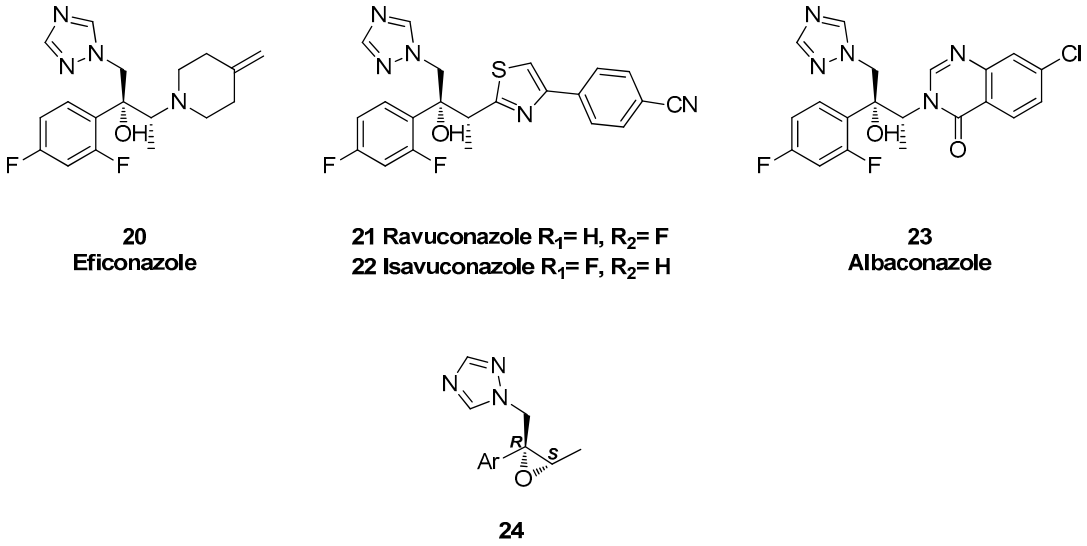
Overall, the efforts to develop a large-scale route to tasimelteon culminated in interrogating the performance and viability of two of the most popular asymmetric transformations, namely the Jacobsen–Katsuki Asymmetric Epoxidation and the Sharpless Asymmetric Dihydroxylation. Both processes required careful navigation through safety and product quality issues arising from reagents, catalysts and associated process impurities as well as technical difficulties in several unit operations. Despite the shorter route offered by the Asymmetric epoxidation process, the lower enantioselectivity achieved renders imperative the implementation of a resolution step and in addition, suffers from a persistent impurity. The Asymmetric Dihydroxylation route although more process

intensive, provides excellent enantioselectivity, superior purity profile and higher overall yield of the final drug substance (43% vs 22%).

1.3. Efinaconazole, Ravuconazole, Isavuconazole, Albaconazole—Synthesis via Two Successive Chiral Epoxide Intermediates and Ring Opening Reactions

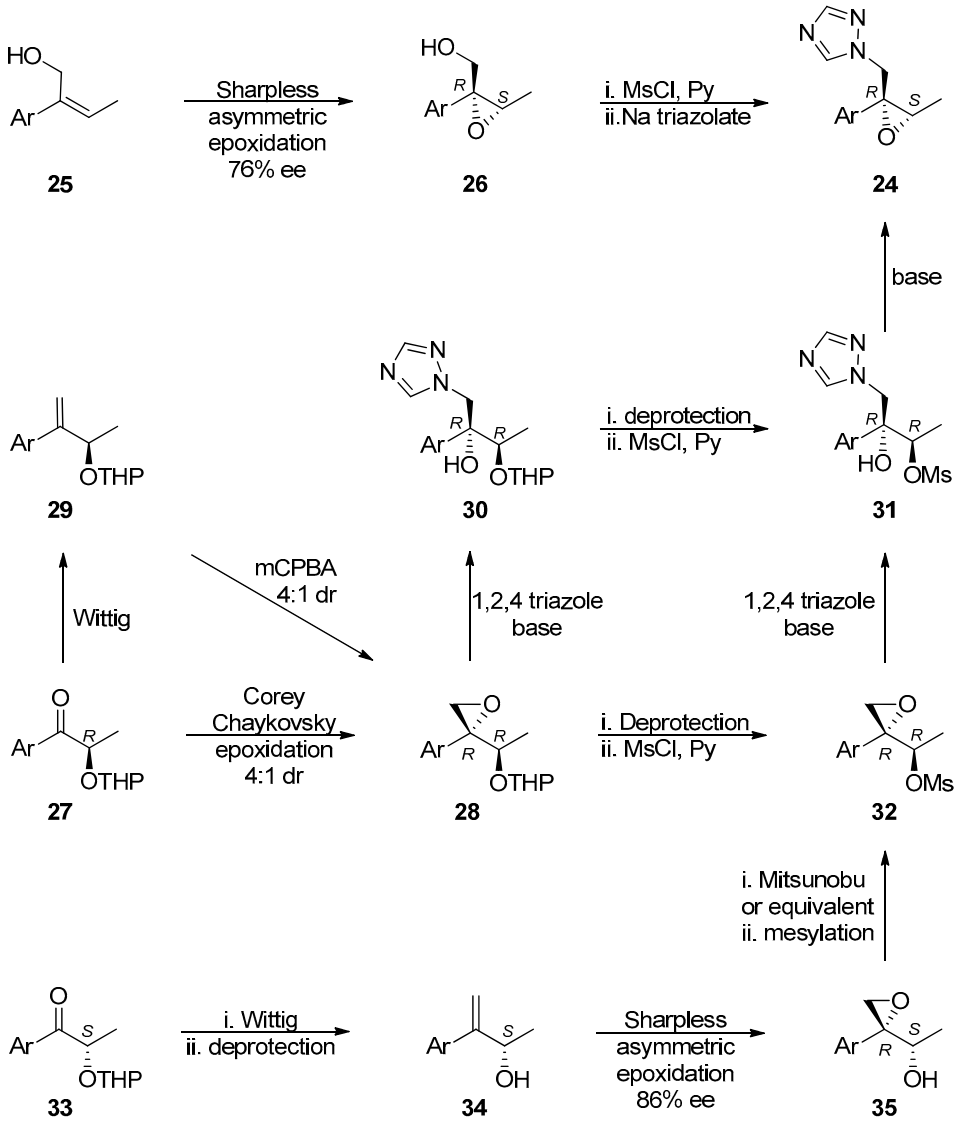
The introduction of fluconazole in 1988 was a major breakthrough in the treatment of fungal infections harming humans, animals and plants [22,23]. Fungal infections vary in severity from mild to fatal particularly when the people infected receive chemotherapy, immunosuppressant treatment or are immunocompromised such as HIV patients. Azole antifungals work by inhibiting primarily the cytochrome P450-dependent lanosterol 14α-demethylase (Erg11p, CYP51) involved in the biosynthesis of ergosterol which is essential for fungi membrane integrity. Over the years, issues related to bioavailability, toxicity, resistance, limited spectrum activity and cost has prompted intense research in antifungal research including analogs of the triazole class. This effort has produced approved drugs such as efinaconazole [24], isavuconazole (in its prodrug form isavuconazonium sulfate) [25] and clinical candidates like ravuconazole [26] and albaconazole [27] (Scheme 8). In the triazole and imidazole classes of antifungals optimum biologic activity requires the *R,R* stereochemistry at both the benzylic and adjacent stereocenter. In this context, epoxide 24 presents a key intermediate for the synthesis of these molecules, but also an attractive diversification point for the preparation of related analogs. The *R,S* stereochemistry of **24** ensures that regardless of the nucleophile used, the subsequent ring opening of the epoxide which proceeds with inversion of configuration, will deliver the correct stereochemistry hence active analogs.



Scheme 8. Approved triazole antifungals and their common synthetic precursor epoxide **24**.

There have been several approaches in accessing key epoxide **24** over the years by various academic groups and pharma companies. Almost invariably the key feature of these efforts concentrated in establishing the *S* stereochemistry at the stereocenter bearing the methyl group so that it is inverted to the correct *R* configuration in the subsequent reaction with the choice nucleophile, namely CN^- for ravu/isavuconazole, methylene piperidine for efinaconazole and 7-chloroquinazolin-4(3H)-one for albaconazole. A summary of these routes outlined in Scheme 9 below. One of the early attempts to install the *S* stereochemistry in **24**, involved the use of the Sharpless asymmetric epoxidation reaction on allylic alcohol **25** to provide epoxy alcohol **26** in 95% yield and 76% ee [28]. Mesylation of the primary alcohol followed by triazole displacement furnished the key epoxide **24**. A variation of this approach was reported in a recent synthesis of efinaconazole where the triazole analog rather than hydroxy-substituted alkene **25** was subjected to the Sharpless asymmetric dihydroxylation [29].

Despite the ability to upgrade the optical purity downstream the synthesis, the issue with these routes is the preparation of the *cis* double bond in the alkene substrate. In the case of **25** extensive manipulation was required to isomerize the predominant *trans* isomer (formed by Wittig reaction on the corresponding acetoxy-acetophenone) which negated further development work.



Scheme 9. Summary of approaches towards an asymmetric synthesis of **24**.

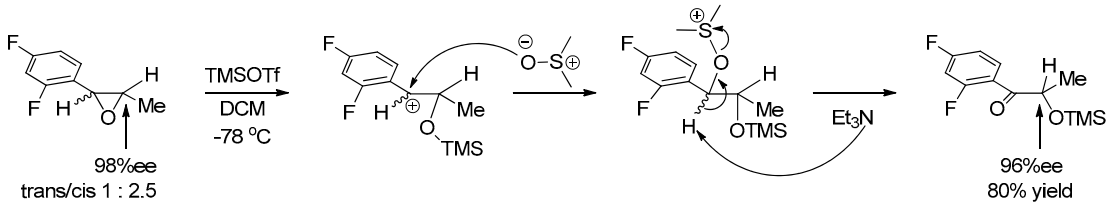
Earlier than that, chemists at Sankyo (legacy company of Daichi Sankyo) after proving the viability of a synthesis with racemic lactic acid derivatives, switched to the chiral pool and used D-(−)-lactic acid [30–33]. This was converted to the THP-protected morpholine amide and reacted with the 2,4-difluorophenyl Grignard reagent producing ketone **27**. Corey–Chaykovsky epoxidation reaction with trimethyl sulfoxonium ylide yielded THP-protected epoxy alcohol **28** in 4:1 diastereomeric ratio favoring the desired *R,R* stereochemistry. The same result was obtained from the mCPBA epoxidation of terminal alkene **29** (produced via a Wittig reaction from **27**), thus no advantage was gained by adding the extra step in the synthesis. Ring opening of the epoxide by triazole to form **30** followed by THP deprotection and mesylation affords hydroxy mesylate **31** which upon base treatment ring closes to the second epoxide of the synthesis and key intermediate **24**. These and subsequent steps rectify the optical purity. The steps of triazole installation and mesylation could be reversed providing

actually a cleaner profile overall, as the 1,2,4-triazole was shown to react chemoselectively with **32** by ring opening the epoxide.

Interestingly, the corresponding triflate reacts with inversed chemoselectivity, giving the S_N2 triflate substitution product when treated with the triazole. This aspect was investigated in the context of inversing the configuration of that center if the L-(+)-lactic acid was initially employed. Both enantiomers of lactic acid occur naturally, but the *S* enantiomer is much more abundant, and its utilization would reduce the cost of the triazole antifungals.

In analogy to **27**, its enantiomer, **33**, would give the opposite and undesired stereochemistry at the stereogenic epoxide carbon in the Corey–Chaykovsky epoxidation reaction. For this reason, ketone **33** was converted to allylic alcohol **34** and subjected to vanadium catalyzed epoxidation to provide epoxy alcohol **35** [34]. The same transformation has also been reported with the use of the Sharpless asymmetric epoxidation reaction which gives **35** with 86% ee [35,36]. Inversion of the *S* stereochemistry at the hydroxyl-bearing carbon has been reported via both Mitsunobu conditions on the alcohol and displacement its triflate by nitrite or hydroxide anions. Some degree of retention of configuration is also observed during these extended manipulations rendering the routes from the less costly L-(+)-Lactic acid less efficient overall. It is worth noting that reducing the cost contribution of D-(−)-Lactic acid, particularly in the case of efinaconazole (a full course of efinaconazole, 10%, therapy for one-nail costs $2,307) [37] has prompted intensive investigations for alternative preparations of **27** and related derivatives. These include utilization of Evans' auxiliary [38], asymmetric hydroxylation of 2,4-difluoro propiophenone [39], enzymatic resolution [40], asymmetric cyanohydrin formation [41], asymmetric Henry reaction [42] and the oxidative ring opening of β-methyl-2,4-difluorostyrene oxide [43]. The latter is a particularly resourceful and rarely encountered transformation that deserves a special mention.

In a styrene oxide substrate (Scheme 10), activation of the epoxide oxygen atom with TMS (trimethylsilyl) or TBDMS triflate (tert-butyldimethylsilyl trifluoromethanesulfonate) causes ring opening with concomitant generation of the benzylic cation (probably an equilibrium) thanks to the resonance stabilization provided by the aryl substituent. In the absence or more potent nucleophiles, dimethyl sulfoxide may engage the cation and form a sulfoxonium intermediate akin to that encountered in Swern-type oxidations of alcohols. Introduction of triethylamine at this advanced stage of the reaction eliminates triethylammonium triflate and dimethyl sulfide to generate the ketone. The starting cis/trans geometry of the epoxide substituents is inconsequential as this information is lost in the product. More important, the stereochemistry at the carbon preserving the original bond to the epoxide oxygen is retained in the alcohol product. The generality of this reaction has been demonstrated with several stilbene and styrene oxides.



Scheme 10. Innovative oxidative ring opening of epoxides with electron donating substituents.

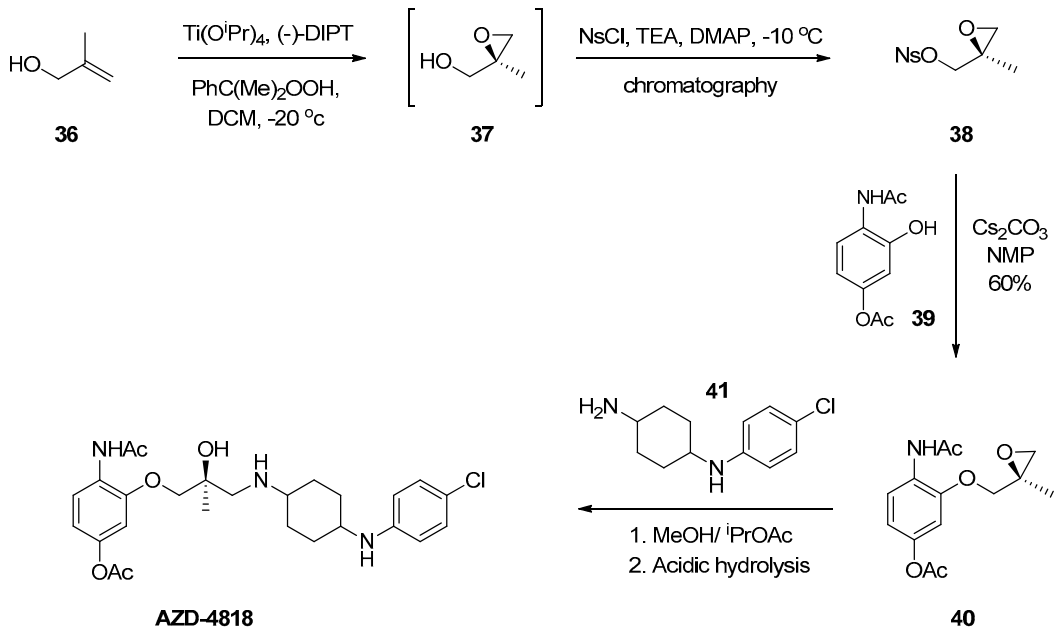
The ring opening of epoxide **24** with various nucleophiles has also been investigated extensively. Almost invariably, alkali and alkaline earth metal salts are reported as the optimum additives to aid the nucleophile in the ring opening of **24** [44–47]. In a recent iteration $(t\text{-BuO})_2Mg$ was found to facilitate the reaction of **24** with a secondary amine used directly in its hydrochloride form [48]. The first event is the neutralization of the salt to form the amine-free base, *t*-BuOH and *t*-BuOMgCl which in turn acts as Lewis acid to activate the epoxide. This was demonstrated on 700 g scale in the synthesis of efinaconazole which was isolated in 96% yield.

From all interconnected routes discussed above (Scheme 9) and variations thereof, process chemists at Bristol-Myers Squibb selected to develop further the process from **27**, that leads to the key epoxide **24** via intermediates **28, 32, 34** as the manufacturing route of choice for ravuconazole [49]. This process that proceeds through the synthesis and ring opening of two epoxide intermediates has its roots in Sankyo's original approach towards triazole antifungals and ever since has been regarded as the standard method to prepare these and related scaffolds [50–54].

1.4. AZD-4818—Development of a Multikilogram Synthesis of a Chiral Epoxide Precursor to A CCR1 Antagonist

The CCR1 (chemokine receptor 1) is a G protein-coupled receptor expressed on a wide range of cell types including monocytes, NK cells, basophils, eosinophils, mast cells, osteoclasts and predominantly in neutrophils, dendritic cells and T lymphocytes. Based on animal models, pharmacological blockade of CCR1 has been proposed to combat inflammatory and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and more recently cancer thus CCR1 antagonists have attracted significant interest [55–57].

Astra Zeneca's compound AZD-4818 (Scheme 11) is a CCR1 antagonist and a clinical candidate for the treatment of immune and inflammation disorders [56,58].

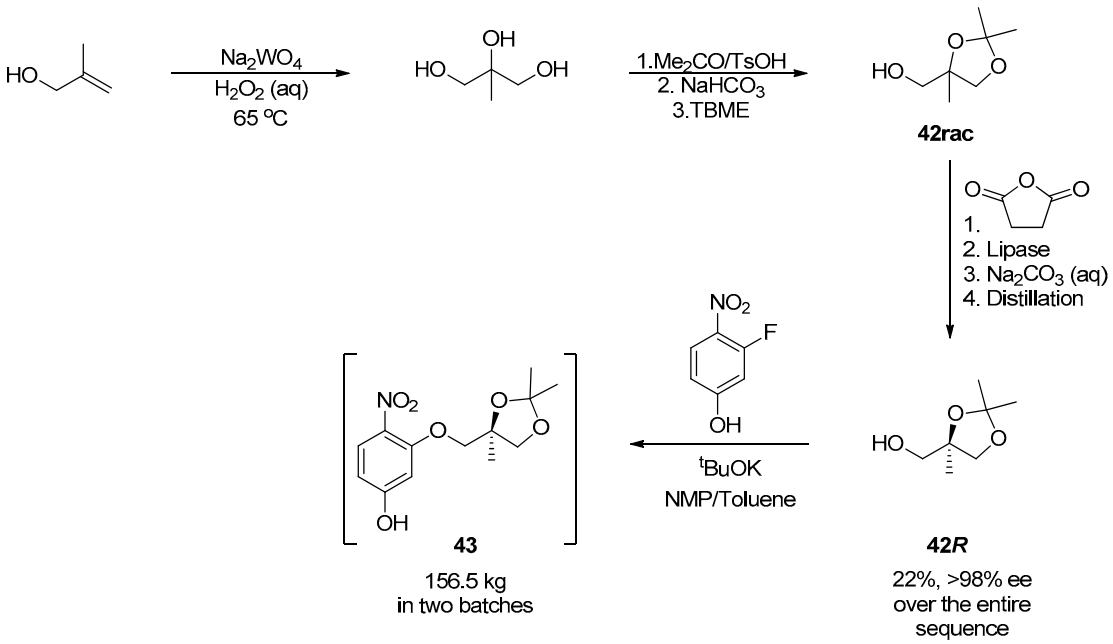


Scheme 11. Early medicinal chemistry route to **AZD-4818**.

Initial modifications of the original medicinal chemistry route to CCR1 (Scheme 11), identified the formation of the intermediate **40** from 4-(acetylamino)-3-hydroxyphenyl acetate (**39**) and ((2*S*)-2-methyloxiranyl)-methyl 3-nitrobenzenesulfonate (**38**) as the critical step of the synthesis [59]. Epoxy nosylate **38** turned out to be a highly energetic material that decomposed in an autocatalytic manner even at low temperatures. In addition, during the first 43 and 120 kg campaigns, robustness issues in the asymmetric Sharpless epoxidation of 2-methyl-2-propen-1-ol (**36**) became a concern which prompted the investigation of alternative routes towards **40**.

AstraZeneca process chemists considered connecting the aromatic moiety to an appropriate glycerol fragment that would bear a latent epoxide functionality to be revealed later in the synthesis. An acetonide-protected diol serves well this purpose [60] thus a chiral glycerol intermediate **42*R*** was prepared initially in the racemic form **42rac** followed by enzymatic resolution of its succinate derivative (Scheme 12). Extensive optimization of this sequence enabled isolation of **42*R*** in 22% overall yield at >98% ee. Its subsequent nucleophilic aromatic substitution with 3-fluoro-4-nitrophenol was also carefully optimized and demonstrated successfully in multikilogram batches (156 kg in two batches).

Intermediate **43** however could not be isolated as a solid hence its solution was used directly in the next reaction.



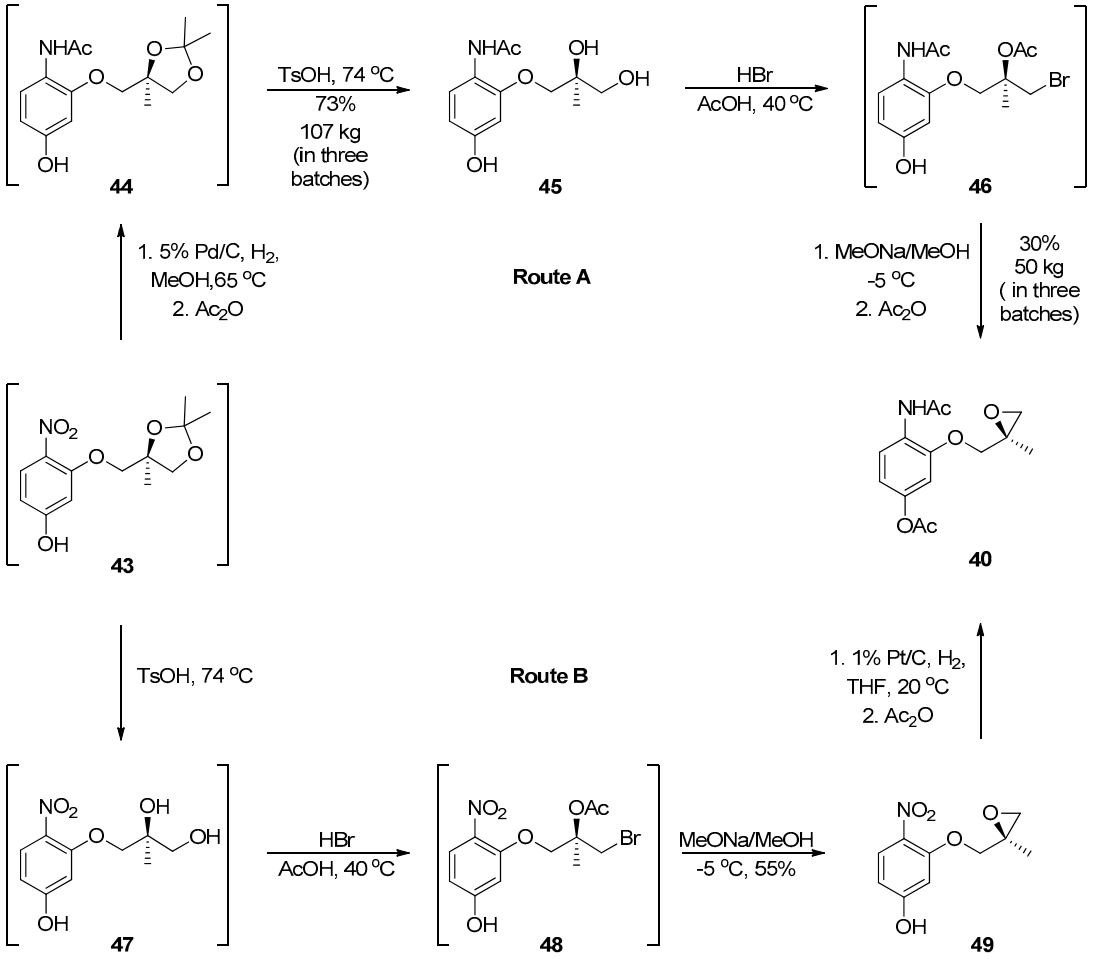
Scheme 12. Process route to key intermediate **43**; carried forward as a solution thereof.

At this point two options were considered with respect to the sequence of the following steps involving the reduction of the nitro group and acetonide hydrolysis/epoxide formation (Scheme 13).

In Route A the solution of intermediate **43** was carried forward in a telescoped process to hydrogenate the nitro group followed by N-acetylation. Inclusion of acetic anhydride at the onset of the hydrogenation to trap the toxic aminophenol intermediate as it forms negatively affected the performance of the hydrogenation reaction and led to mixtures of N-, O- and diacetylated products. Attempts to isolate anilide **44** thus produced were not successful although TsOH (p-Toluenesulfonic acid) catalyzed deprotection to the diol **45** allowed for isolation of a crystalline intermediate. Three batches totaling 107 kg of the diol intermediate **45** were produced in this way. The subsequent formation of bromide **46** proceeded smoothly although this intermediate too proved unstable to store or handle for long times; best case scenario without degradation was 24 h at −5 °C. Inevitably this was carried over as a solution into the deacetylation of the hydroxyl group followed by the ring closure to form epoxide **40**. An additional problem appeared in the consistent crystallization and purification of the epoxide due to the nature of the reaction medium built over the telescoped process.

This aspect combined with the limited stability of bromide **46** led the Astra Zeneca process team to examine Route B (Scheme 13), namely the reverse sequence of events where epoxide generation from **43** precedes the reduction of the nitro group. The TsOH deprotection step to **47** and subsequent conversion to the acetoxy bromide **48** followed by formation of epoxide **49** were accomplished using the same conditions as in Route A for the anilide intermediates. In this sequence both bromide **48** and nitrophenol epoxide **49** were much more stable than their anilide counterparts **46** and **44** from Route A. Nitrophenol epoxide **49** could actually be isolated in good yield and quality. Initial attempts to hydrogenate the nitro group produced significant amounts of reductive ring opening of the epoxide hence a wide range of catalysts and conditions were screened for the selective hydrogenation to the aniline. This was achieved with a Pt/C catalyst in THF (4 bar H_2) which was telescoped with the acetylation of both the aniline and phenol groups by addition of acetic anhydride. Despite the better behaving intermediates of Route B, a number of impurities (Scheme 14) found in the key epoxide intermediate **40** isolated from this process casted serious doubts over its potential as a manufacturing route. One set of impurities (**50–52**) was shown to form by water attack on the terminal epoxide under

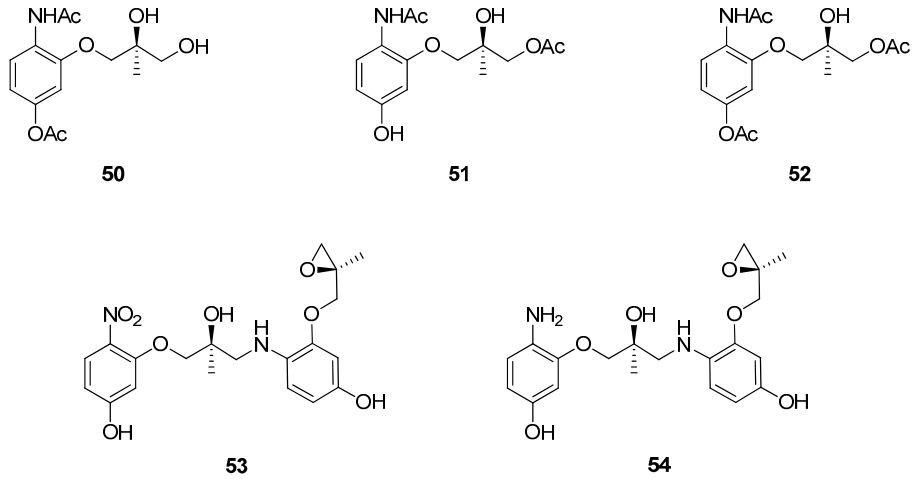
the processing conditions generating initially impurity **50**. The generated primary alcohol participated in a transesterification process producing deacetylated phenol impurity **51** which in turn is acetylated again by acetic anhydride giving rise to impurity **52**. These impurities were ultimately managed by control of the water content and processing conditions. This was not however the case with a second set of impurities (**53, 54**). These arise from the aniline reacting with the epoxide moiety of its nitro precursor thus generating dimer **53** which in turn gets reduced to **54** and associated acetylated derivatives.



Scheme 13. Scaled-up routes to intermediate **40** from **43**; route A was finally selected.

These side reactions became more pronounced in conditions simulating large-scale processing and the dimeric impurities could not be purged in the already challenging crystallization of intermediate **40**. This issue rendered Route B inappropriate for future deliveries and exemplified Route A as the process of choice which was subsequently optimized further. The final coupling of **40** and **41** (Scheme 11) had been optimized in earlier campaigns and posed no issues in subsequent large-scale deliveries. The successful preparation of AZD-4818, at the required specifications depends heavily on the purity of the key epoxide intermediate **40** that the new process achieved in supplying at an appropriate quality.

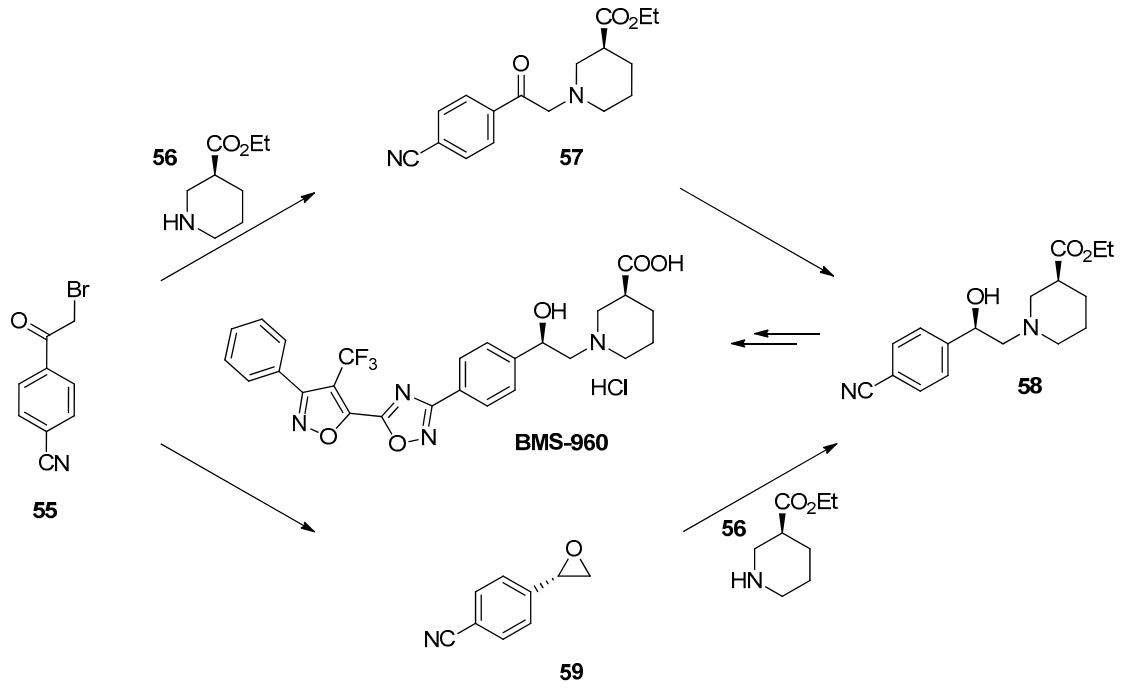
The synthetic efforts towards Astra Zeneca's CCR1 antagonist, highlights the quality of skills, expertise and perseverance of process chemists in managing sensitive, non-crystalline intermediates and multiple telescoped stages on scale.



Scheme 14. Impurities in Route B; **53** and **54** were difficult to purge hence Route A was selected.

1.5. BMS-960—Development and Scale up of a Chiral Epoxide Route through an Enzymatic Reduction

Sphingosine 1-phosphate (S1P) regulates through five high-affinity G protein-coupled S1P receptors multiple physiological and pathophysiological processes including cell proliferation and survival, cell migration, inflammatory mediator synthesis and tissue remodeling [61–63]. The S1P1 receptor in particular has received intensive investigation for the modulation of various autoimmune and inflammatory diseases with the products of this effort being two approved drugs for multiple sclerosis: fingolimod and ozanimod [64–66]. Research on S1P1 agonists continues to unfold both in terms of novel molecules and additional indications. In this context Bristol-Myers Squibb developed BMS-960 (Scheme 15, a potent agonist of the S1P1 receptor. For the ongoing biologic and toxicological investigations, a reasonable supply route was required that would address the issues of the original medicinal chemistry synthesis. These included the low yielding (36%) alkylation of amine **56** with bromoketone **55** and the inefficient separation of diastereomers of **58** generated from $NaBH_4$ reduction of **57**.



Scheme 15. Alternative syntheses of key intermediate **58**, precursor of **BMS-960**.

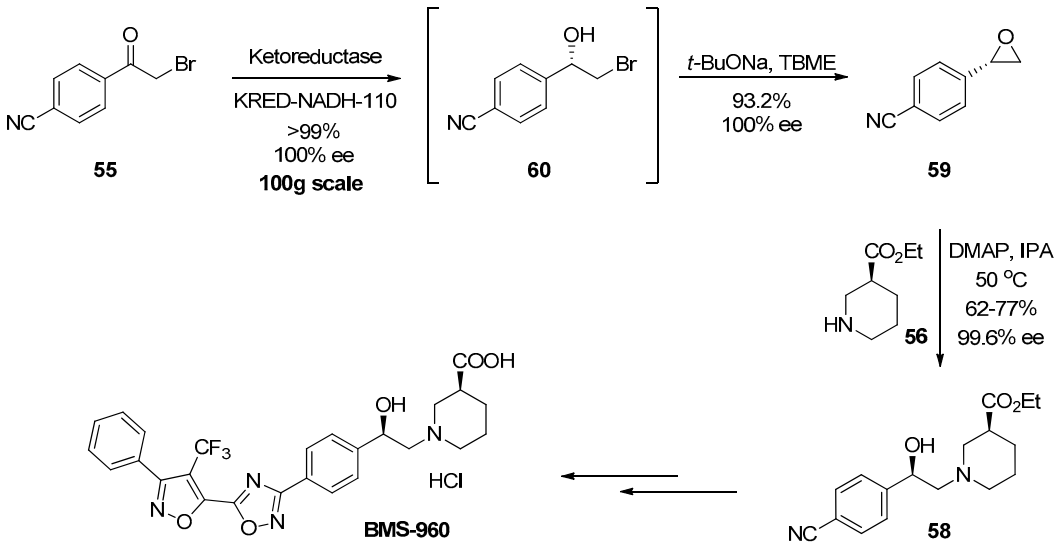
Bristol-Myers Squibb chemists examined the potential of an alternative route that could deliver enantiopure **58** via optically pure epoxide **59** [67].

Initial efforts focused on the preparation of racemic **59** with a view to subject it to chiral separation. The Corey–Chaykovsky reaction from the *p*-cyanobenzaldehyde and trimethyl sulfonium iodide [68] met with low yields. In contrast, $NaBH_4$ reduction of the commercially available bromoketone **55** gave initially racemic bromohydrin **60** which was transformed to racemic **59** in high yield when subjected to mild base. The chiral separation of racemic **59** however proved unviable hence a two-step asymmetric synthesis was considered next. After careful consideration of asymmetric reduction methods, B-chlorodiisopinocampheylborane (DIP-chloride) was initially tested and provided good yields (85%) and enantiomeric excess (90% ee) of chiral bromohydrin **60**. Despite these encouraging results, upgrade of the optical purity through chiral separation was still required hence an enzymatic reduction was pursued.

Towards this end, a large array of both NADH- and NADPH-dependent ketoreductases was screened for the reduction of **55** and several enzymes were identified that could produce either enantiomer of bromohydrin **60** in >99% yield and enantiomeric excesses of >99%.

In the end, based on its activity, selectivity and substrate-to-enzyme ratio, ketoreductase enzyme KREDNADH-110 (Codexis) was selected for the synthesis of the (*S*)-enantiomer of **60**. Though both NADH and NADPH cofactors must be regenerated for cost reduction, KREDNADH-110 also has the additional advantage of requiring the lower cost NADH cofactor.

The conversion of (*S*)-**60** to the epoxide was optimized with sodium *tert*-butoxide giving the best results (>93% and 100% ee) and eventually this was bolted on the enzymatic reduction thus developing a telescoped process (Scheme 16). The next step in this synthesis was the epoxide ring-opening reaction of the chiral (*S*)-**60** with amino-ester **56** to give the desired key intermediate **58**. This reaction took place in a regiospecific manner at 50 °C with a catalytic amount of DMAP (4-dimethylaminopyridine) in 77% yield.

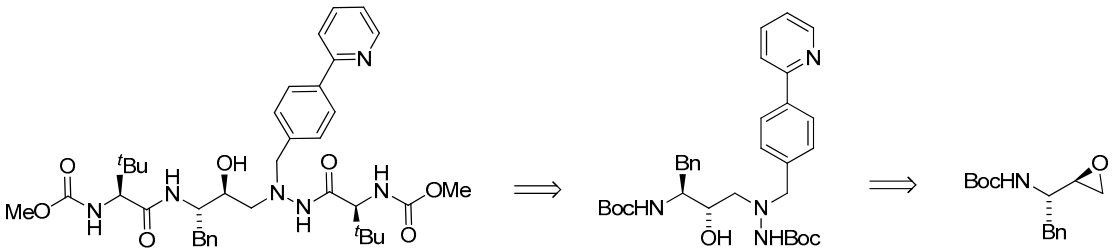


Scheme 16. Scale up of enzymatic reduction to halohydrin and epoxide formation en route to **58**.

As will be further discussed below, halohydrins (and equivalent species) provide a powerful route to epoxide synthesis. In this case a chiral halohydrin produced via an enzymatic reduction of an appropriate bromoketone at 100 g scale gave access to the key epoxide and its ring opened product. This approach was pivotal for the development of a cost effect and efficient route towards BM-960.

1.6. Atazanavir (BMS-232632)—Process Research and Development towards an Efficient Synthesis of an HIV Protease Inhibitor

Atazanavir (BMS-232632) (Scheme 17) is a potent HIV-1 protease inhibitor and an FDA approved drug for HIV/AIDS both as monotherapy and in combination with other anti-HIV agents [69–72]. Atazanavir (BMS-232632) is an aza-peptidomimetic transition state inhibitor for the HIV-1 protease that was discovered by Novartis [73], but after a preliminary investigation it was licensed to Bristol Myers Squibb who developed it fully to the point of FDA approval.



Scheme 17. Retrosynthetic analysis of atazanavir leading to key epoxide intermediate **62**.

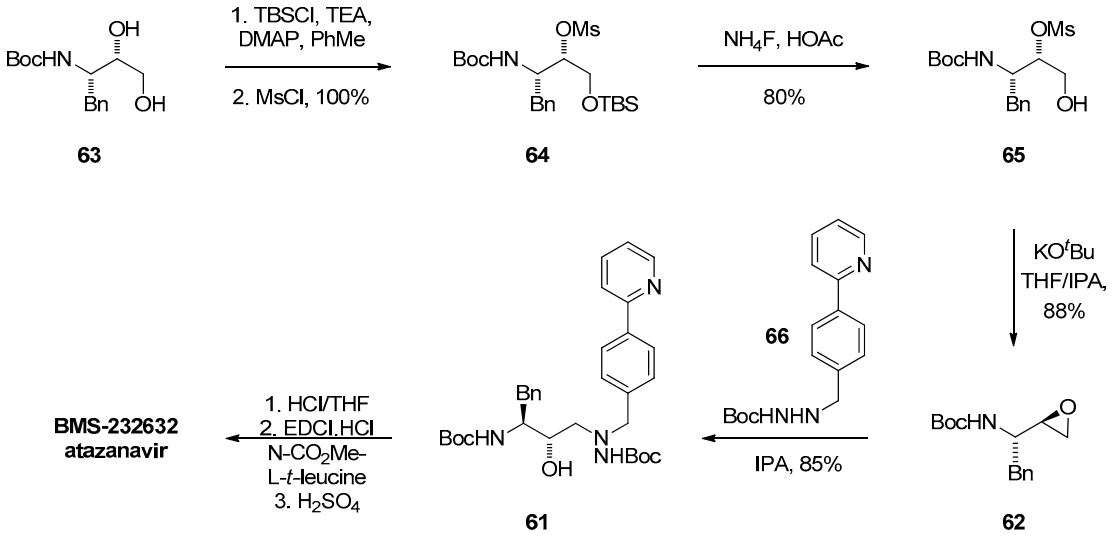
In order to do so, a reliable cost-effective and robust process had to be developed by the Bristol Myers Squibb process department. The original medicinal chemistry route was unsuitable for large-scale deliveries due to a number of issues including hazardous reagents and solvents, several protection/deprotection steps, expensive amide coupling reagents and elaborate chromatographic purifications.

In order to develop a viable manufacturing route to atazanavir it was imperative that both *N,N′-bis*-Boc-protected hydrazino–amino alcohol **61** and the chiral epoxide **62** intermediates were accessed in a scalable and robust manner.

The synthesis of optically pure epoxide **62** in particular was of great concern as its quality influences heavily the performance of the downstream chemistry and isolation/purification of subsequent intermediates. In the original route **62** was made in 80% ee by mCPBA epoxidation of the corresponding allylic Boc-protected amine. The main reason for the enantiomeric leakage was the aldehyde precursor Boc-Phe-H which racemized to a significant extend even when the Wittig reaction was performed at −78 °C. Additionally, the need for chromatographic purification for both the aldehyde and epoxide intermediates combined with the low yield of the two-step sequence, forced the development of a new, more robust and suitable for scale-up synthesis of **62**.

The Bristol Myers Squibb process group responded to this challenge [74] by exploiting the readily synthesized and also commercially available vicinal diol **63** (Scheme 18). Based on the work of Moyano and Pericàs [75], they developed further the three step process to access the key epoxide.

Initial selective silylation of the primary alcohol followed by mesylation of the secondary alcohol proceeded cleanly although the silyloxy mesylate **64** was not a crystalline intermediate. Using this oil directly in the silyl deprotection step provided the crystalline and easy to purify hydroxy mesylate **64**. For this step they introduced the inexpensive and easier to handle ammonium fluoride in place of TBAF (tetra-n-butylammonium fluoride) and isolated the mesylate intermediate **65** in 80% yield and excellent quality. After extensive screening of bases and reaction conditions, KO^{t}Bu in THF/IPA turned out to be the most successful combination for the ring closure of hydroxy mesylate **65** to epoxide **62**. The latter was isolated directly in 90% yield and in 100% ee without need for chromatography. The regiospecific ring opening of the epoxide with protected hydrazine **66** was accomplished in refluxing isopropanol and provided key intermediate **61** in >85% yield. Finally, deprotection of the Boc groups telescoped into an EDCI-promoted (1-ethyl-3-(3- dimethylaminopropyl)carbodiimide) coupling with N-methoxycarbonyl-L-tert-leucine at both the amino and hydrazino termini, gave atazanavir-free base which was ultimately converted to its bisulfate salt.



Scheme 18. Process route to atazanavir via asymmetric synthesis of epoxide **62**.

This process (Scheme 18) was scaled-up successfully and delivered 3.5 kg of atazanavir bisulfate thus demonstrating reproducibility and robustness in this epoxide-enabling manufacturing route to an approved drug.

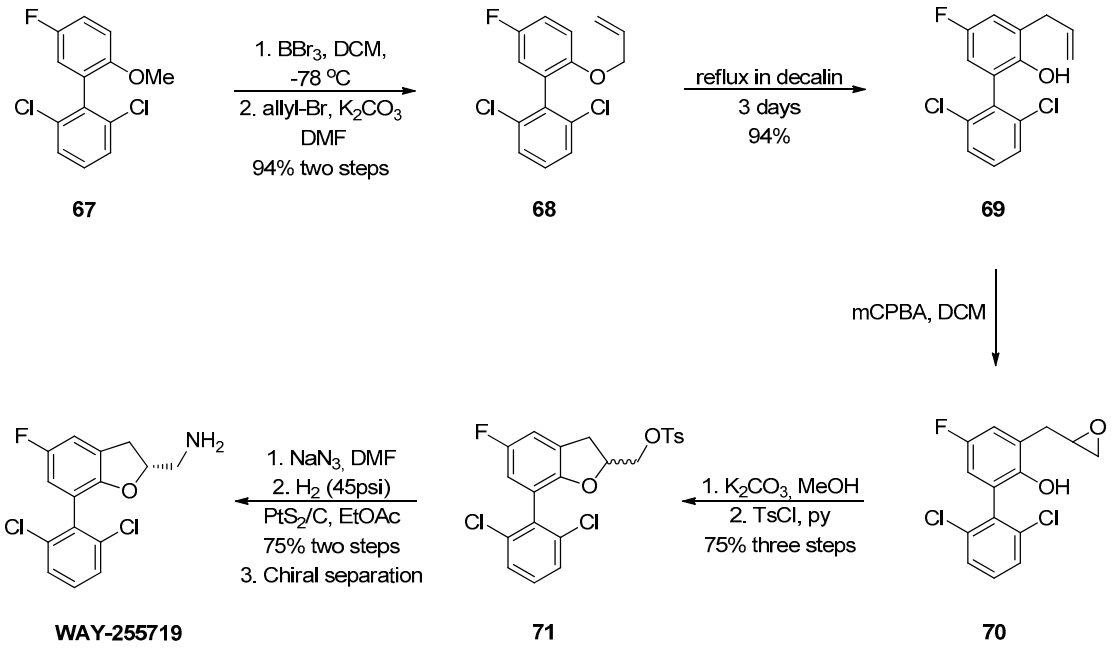
1.7. WAY-255719—Ring Opening of a Chiral Epoxide with Grignard Reagents

The 5-HT_{2c} receptor is one of the 14 serotonin receptors and is located in several regions of the brain. Activation of this G protein-coupled receptor by serotonin inhibits dopamine and norepinephrine release in certain areas of the brain therefore 5-HT_{2c} receptor agonism has demonstrated benefits in the treatment of obesity (lorcaserin), substance use disorders (SUD) and impulse control disorders while antagonism augments treatment of anxiety, depression and schizophrenia [76]. In this context Wyeth (legacy company of Pfizer) discovered WAY-255719 [77] a potent 5-HT2C full agonist with greater than 100-fold selectivity over the related 5-HT2A and 5-HT2B receptors. WAY-255719 demonstrated anti-psychotic activity in several animal models thus was selected among several other analog compounds to advance into development as a drug candidate.

The medicinal chemistry route to WAY-255719 (Scheme 19) had a number of issues including a low yielding (<45%) Suzuki reaction to biaryl **67**, extremely low temperature for phenol demethylation, a thermally intensive and protracted Claisen rearrangement, racemic epoxide formation, hazardous azide chemistry and a special hydrogenation to ensure chemoselectivity over the aromatic chlorides. In addition to the nine steps, the racemic amine product had to be converted to its Cbz derivative in order achieve chiral resolution and finally be subjected to hydrogenolysis to afford enantiopure WAY-255719.

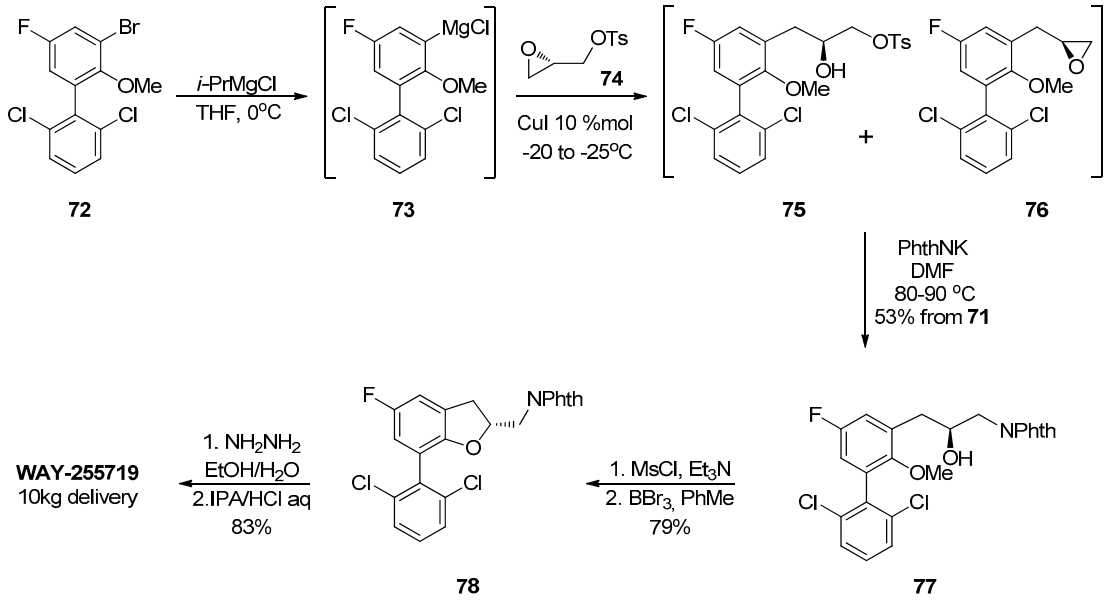
Initial improvements, including chiral separation on the amine without Cbz derivatization (on 100 g scale took one week to complete using a 25 cm × 3 cm column) succeeded in delivering up to 100 g of the desired product, but clearly a much better synthesis was needed for larger scale deliveries and commercial manufacturing. An asymmetric route that would negate the need for chiral chromatography therefore became a critical objective for the viability of the project.

One of the ideas that prioritized high for the asymmetric synthesis of the chiral 2-substituted dihydrobenzofuran domain involved the introduction of an appropriately functionalized enantiopure three-carbon fragment directly at the position *ortho* to the methoxy group of **67**. Reaction of the corresponding aryl Grignard with glycidol surrogates presented an attractive option to access **70** directly because many of the latter are commercially available in enantiopure form and there is literature precedence for their reaction with organometallic reagents, at least on small scales.



Scheme 19. Initial improvements made on the medicinal chemistry route to WAY-255719.

Having first developed a much higher yielding Suzuki–cross coupling reaction for generating **67** and resolved HBr-induced demethylation issues in the subsequent bromination to **72** (Scheme 20) attention was turned into the formation of the Grignard reagent **73** and reaction with glycerol tosylate **74** [78].



Scheme 20. Development of a telescoped process for multi-kilogram delivery of **WY-255719**.

Generation of the Grignard reagent **73** from the aryl bromide under standard conditions with magnesium metal was accompanied by magnesium oxidatively inserting into the aryl-chloride bonds. Chemoselective formation of the desired organometallic reagent **73** was accomplished by a Grignard exchange reaction with isopropyl magnesium bromide.

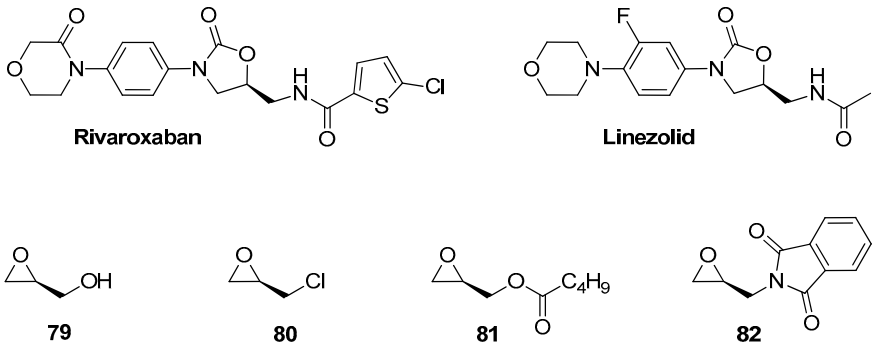
In the absence of Lewis acid catalysts, reactions between epoxides and organometallic reagents are known to proceed slowly and with formation of side products. In this case copper(I) salts provided optimum results with little difference among CuCN, Li_2CuCl_4 and CuI at 5–10 mol%. Without the copper catalyst the reaction did not proceed at all. Initially CuCN was selected due to its stability,

nonhygroscopic nature and availability in small particle size although it was later replaced with CuI to avoid issues associated with cyanide toxicity. Another critical process parameter was the reaction temperature leading to either incomplete reactions below −25 °C or significant formation of impurities above −20 °C. Within the −25 to −20 °C window, the reaction is complete after 4–5 h giving an oil consisting predominantly the hydroxy tosylate **75** with an approximately 10% (HPLC) of the terminal epoxide **76**. This was not an issue because subsequent treatment of the crude product with NaOH-induced ring closure of **75** to epoxide **76** quantitatively. Theoretically, the enantiomer of epoxide **76** can form by direct displacement of the tosylate in **74** without epoxide opening. This however does not happen in practice and indeed **76** forms via epoxide opening of **74** to **75** and subsequent closure on the other side by chloride displacement. This was confirmed as the Wyeth team established that no loss of enantiomeric purity occurred, whereas direct tosylate displacement would lead to the terminal epoxide of opposite stereo configuration and **76** with reduced ee. The process was further streamlined by eliminating the separate step for the conversion of **75** to **76** since this transformation could be accomplished quantitatively during alkaline washes in the work up of the Grignard reaction with **74**. Thus, after solvent swapping to DMF the resulting solution of **76** was telescoped in the second epoxide ring-opening reaction with potassium phthalimide to give intermediate **77** in 53% yield with respect to **74**, 98.7% purity by HPLC and 99% ee. Activation of the alcohol as its mesylate ester followed by treatment with BBr_3 gave directly the cyclized dihydrobenzofuran intermediate **78**. Apparently, once the phenol is demethylated, it cyclizes spontaneously via the intramolecular S_N2 reaction on the mesylate; the uncyclized phenol/mesylate intermediate was never detected in this process. Deprotection and hydrochloride salt formation/crystallization of the right polymorph gives WAY-255719 with purity >99.5% and 98.6% ee.

After a tremendous amount of work (including with model substrates) the Wyeth process team managed to develop a robust manufacturing route for WAY-255719 without the pitfalls of the original synthesis The new route proceeds through a telescoped process encompassing four chemical transformations, namely two consecutive epoxide ring-opening/ring-closing reaction sequences and has delivered 10 kg batches of the API at specification.

1.8. Linezolid and Rivaroxaban—Exploiting Glycerol Surrogates in Chiral Oxazolidinone Syntheses

Linezolid and rivaroxaban (Scheme 21) share striking structural similarity therefore common synthetic strategies have been described for their syntheses. The chiral oxazolidine moiety is accessed conveniently from the chiral pool, perhaps almost invariantly with the use of glycerol (**79**), epichlorohydrin (**80**) and conveniently functionalized glycerol derivatives (**81**, **82** Scheme 21).

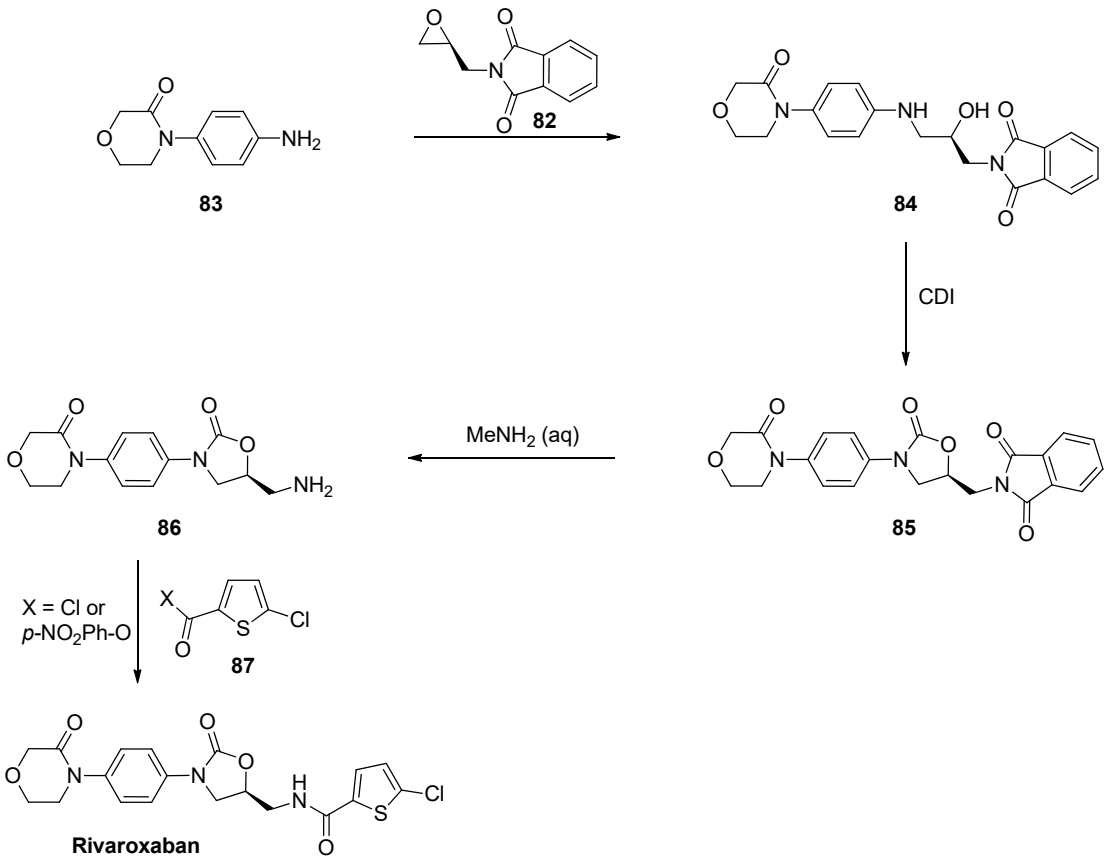


Scheme 21. Structures of rivaroxaban, linezolid and glycerol equivalents from the chiral pool.

In contrast to the high similarity of their chemical structure and syntheses, the biologic and pharmaceutical profiles of linezolid and rivaroxaban could not be more different. Linezolid (trade name Zyvox) discovered and developed by Pharmacia UpJohn (legacy company of Pfizer) is a protein synthesis inhibitor and member of the oxazolidinone class of antibiotics [79]. It shows excellent activity against major Gram-positive bacteria and is very effective in the treatment of infections of the

respiratory tract and skin disorders. The rare, if any, cases of cross resistance with other antibiotics is attributed to its unique mechanism of action. In contrast to common protein synthesis inhibitors which halt protein synthesis at the elongation phase, linezolid inhibits protein synthesis at the initiation phase. It does so by binding at the 23S component of the 50S ribosome subunit which is responsible for the peptidyl transferase activity thus preventing formation of a functional 70S initiation complex [80]. Because of its action on ribozymes, linezolid has been designated as a riboswitch [81,82]. Despite the high degree of structural resemblance, rivaroxaban possesses no antibiotic activity whatsoever and does not bind to RNA molecules. Rivaroxaban (trade name Xarelto) was discovered and developed by Bayer and Ortho-McNeil Pharmaceutical, Inc. (legacy company of *Johnson* and *Johnson*). It was approved in Germany, Canada and by the FDA in 2008 for the treatment, prevention and reduction in the risk of recurrent deep vein thrombosis, stroke, systemic and pulmonary embolism. More recently it also obtained approval for reducing the risk of major cardiovascular events, such as death, myocardial infarction and stroke. Rivaroxaban inhibits both free and prothrombinase complex bound Factor Xa and prevents thrombin formation, but not its action [83]. It has a rapid onset of action and was the first approved oral Factor Xa inhibitor.

As a consequence of the structural similarity between linezolid and rivaroxaban there is great deal of overlap in the respective reported syntheses. In fact, most of the known syntheses for one molecule have been tested in the preparation of the other with modifications on the terminal aniline and amide as appropriate. The original Bayer synthesis of rivaroxaban is described in Scheme 22 [84].

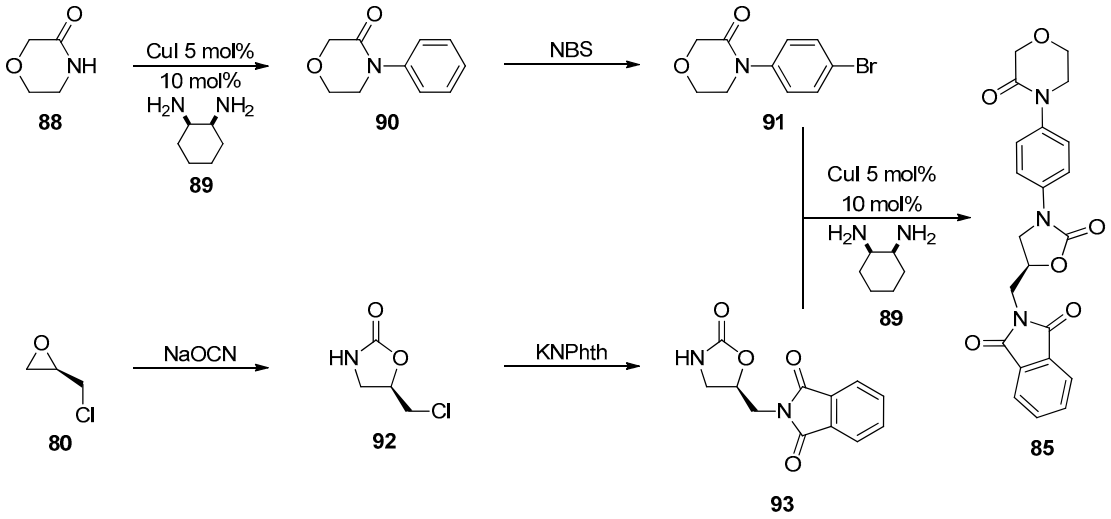


Scheme 22. Original Bayer synthesis of rivaroxaban.

Bayer and others have since patented several other syntheses [85–87] yet over the years it was the first route that attracted numerous suitors who put much effort in developing it further into a viable large-scale process. In this context, all modifications reported concern reaction conditions, solvents and reagents in each of the steps without changing any of the intermediates/transformations of the Bayer route [88–90]. The reported syntheses for rivaroxaban and linezolid have been reviewed

extensively [91] and repetition of this is beyond the scope of the present work. The following cases were selected simply because they exemplify the synthetic creativity and versatility that may be expressed through the chemistry of the epoxide functionality.

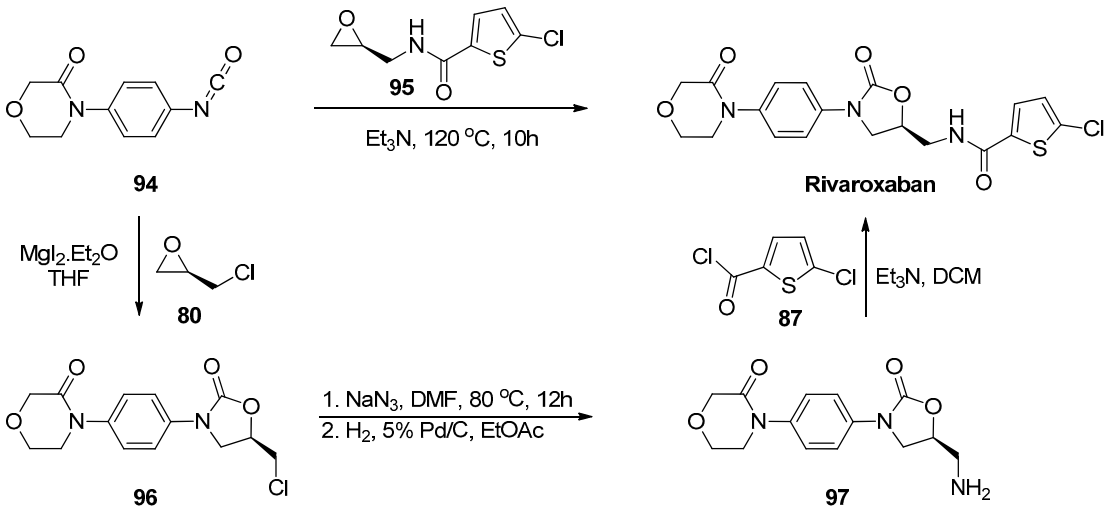
For example in the synthesis of Yuan et al. [92] (Scheme 23), the penultimate intermediate **85** of the Bayer synthesis is targeted via a completely different strategy where the oxazolidinone ring is constructed first (**92**) followed by installment of the phthalimido group (**93**) and attachment of the oxazolidinone **93** on the morpholinone-substituted aromatic ring **91** via a Goldberg coupling reaction. The same reaction was used to install the morpholinone **88** on the aromatic ring. This and other efforts attempt to address the synthesis of the morpholinone aryl moiety as this is a significant cost contributor for rivaroxaban.



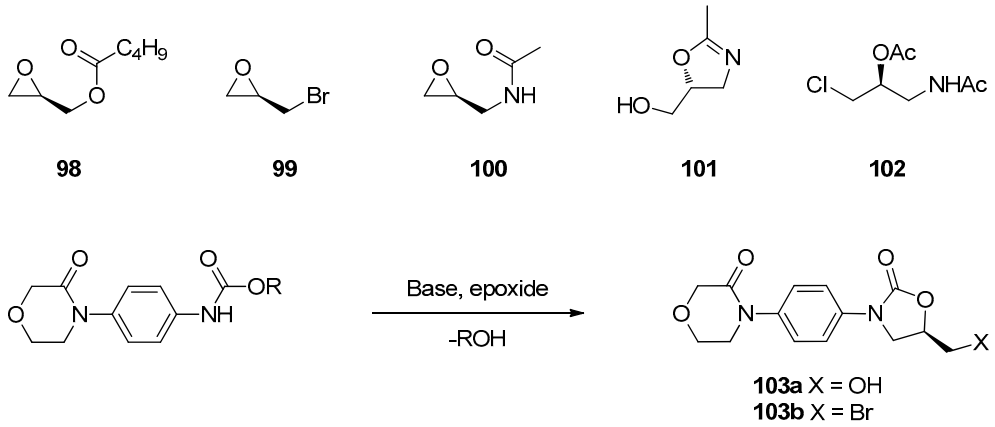
Scheme 23. The Yuan et al. synthesis of the rivaroxaban N-Phth-intermediate via a Goldberg reaction.

Similar to the reaction of epichlorohydrin with sodium cyanate, the Lewis acid or base catalyzed cycloaddition of epoxides with isocyanates gives N-substituted rather than the N–H oxazolidinones (Scheme 24 upper portion). This transformation has been used by Bayer as the last step in a convergent synthesis of rivaroxaban where the 4-morpholinone-benzene isocyanate (**94**) is reacted with an epoxide (**95**) bearing the domain of the target molecule with the thiophene carboxamide already formed [86]. In a variation of this strategy (Scheme 24 lower portion), the epoxide/isocyanate cycloaddition was used in the beginning thus building the rivaroxaban skeleton in a linear fashion [93].

One of the earlier Bayer attempts involved the use of the anion of Cbz-(4-morpholino)-aniline to ring open glycerol butyrate (**98**). The resulting secondary alkoxide bites back on the carbamate and displaces benzyl alcohol (Scheme 25) [94]. In this way the hydroxymethyl oxazolidinone **103a** is generated in a single step and with the butyrate is lost in the work up, two steps are eliminated from the synthesis. In an improvement of this, the cryogenic BuLi deprotonation of the carbamate was replaced Li^{t}BuO at room temperature and **103a** was isolated in 80% [95]. Further improvement that saves the subsequent mesylation step of alcohol **103a** was reported recently where glycerol butyrate/Li^{t}BuO is replaced with epibromohydrin (**99**)/Cs_2CO_3 [96].



Scheme 24. Direct synthesis of chiral oxazolidinones via epoxide/isocyanate cycloadditions.



Scheme 25. Synthesis of oxazolidinone intermediates via condensation of carbamates with epoxides.

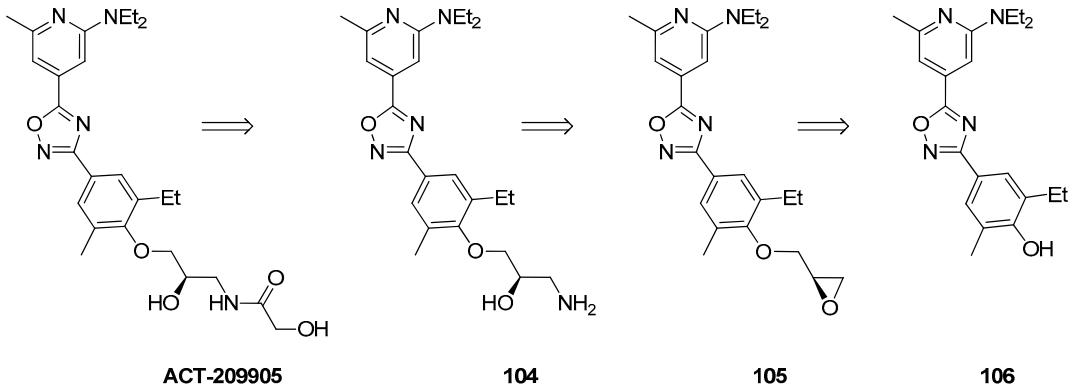
Pharmacia Upjohn also tried this approach in the early days of linezolid development where several carbamates of the linezolid aniline were screened in the-in-the reaction with epoxide **100** with the view of accessing the drug substance directly [97] In this case however the deprotonation of the acetamide side chain competed resulting in an intramolecular ring opening of the epoxide and formation of **101**. This issue was bypassed with the use of electrophile **102** which also loses the acetate group after displacement and the secondary alcohol cyclizes onto the carbamate to produce the oxazolidine thus linezolid.

Arguably, either enantiomer [98] of any glycerol derivative available in bulk has been tested at some point in the synthesis of the chiral oxazolidinone domains in these two important medicines. Despite the entirely different pharmacology and mode of action, the significant structural similarity between linezolid and rivaroxaban has benefited the development of viable large-scale processes for each since in most cases the respective synthetic approaches have been equally applicable to both molecules.

1.9. ACT-209905—Ring Opening of an Epoxide with Ammonia Surrogates

ACT-209905 is an immunomodulating S1P1 agonist under development by Actelion for the treatment of autoimmune disorders. The scope and potential of S1P1 agonism was discussed earlier under BMS-960. One of the key features in ACT-209905 (Scheme 26) is the chiral alcohol present in the pendant aliphatic chain attached to the phenol. The approach was to form the amide last from amine

104 resulting from ammonia-induced opening of epoxide **105** which in turn should be accessed using phenol **106** and the inexpensive glycidol as the chiral building block.



Scheme 26. Retrosynthesis of the S1P1 agonist ACT-209905.

This approach was adopted by the medicinal chemistry team who used the Mitsunobu reaction to condense phenol **106** with glycidol into ether **105** and then excess ammonia in methanol to generate **104**.

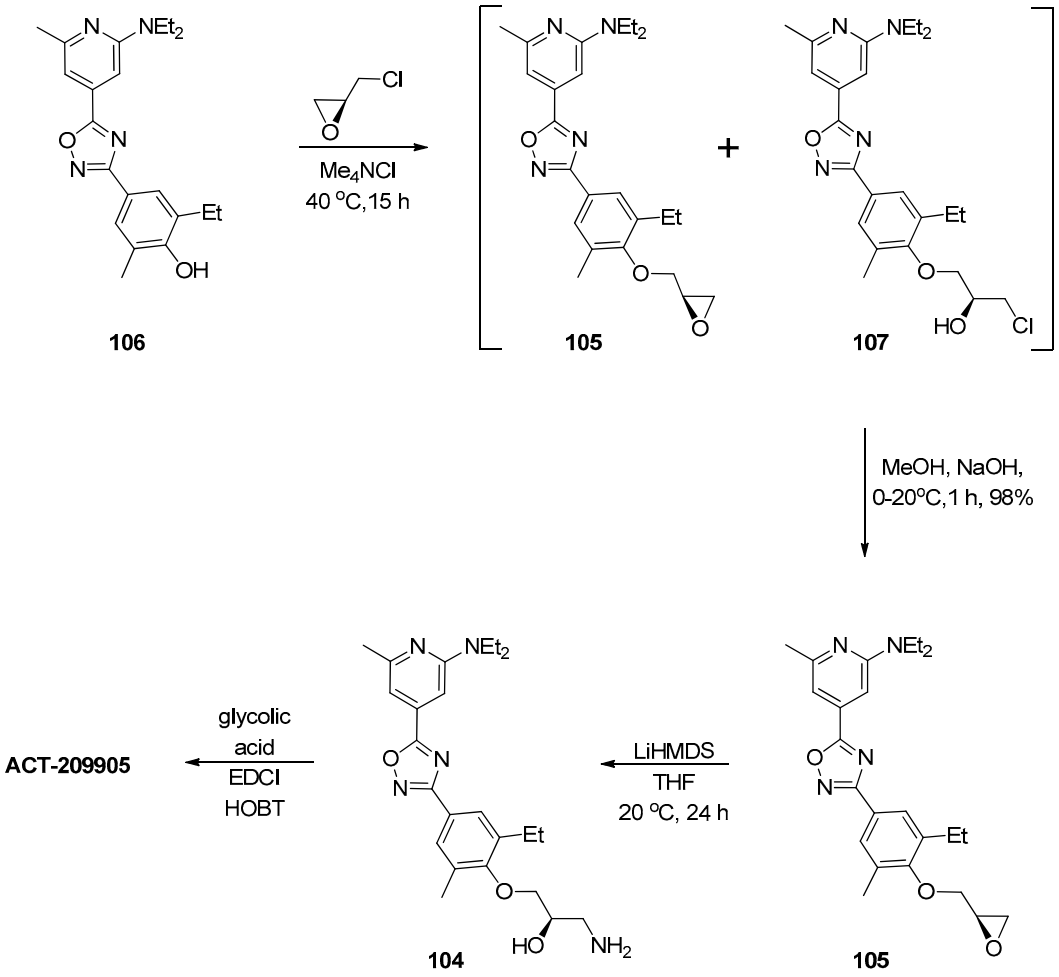
Overall, this constituted a 12-step synthesis that served the project team well for up to half a kilo drug substance deliveries. For larger scale demands this route presented several issues particularly around the cost-effective synthesis of phenol **106**, the workup difficulties and chromatographic purification of the Mitsunobu reaction as well as amine dimers generated by the reaction of amine **104** with epoxide **105**.

The Actelion process team had to respond with a reasonable supply route amid tight project deadlines which precluded extensive development and raw materials with long lead-times [99]. Having resolved the synthesis of the challenging phenol **106** focus was turned on an alternative to Mitsunobu reaction for securing the epoxy intermediate **105**.

Economics and literature precedence and suggested alkylation of the phenol with (*R*)-epichlorohydrin may provide a viable option. Cognizant of the fact that reaction of the phenoxide anion at the carbon bearing the chlorine atom in epichlorohydrin would produce the undesired enantiomer of **105**, careful reaction conditions were employed to safeguard that only epoxide ring opening ensues.

In neat (10 equivalents) epichlorohydrin and Me_4NCl as phase transfer catalyst, in the absence of base, it took two days for the phenol to be fully consumed at 25 °C. From the onset, a product mixture of epoxide **105** and chlorohydrin **107** is observed whose composition shifted from 30:70 to 60:40 (**105**:**107**) as the reaction progressed. Increasing the temperature from 25 to 30 and 40 °C the reaction completed in 1.5 days and 15 h, respectively although a slight erosion of ee was observed from 96 to 94%. Addition of methanol and aqueous NaOH led to full conversion of the halohydrin **107** to epoxide **105** (Scheme 27). These conditions were successfully scaled up and delivered 17 kg of epoxide **105**.

The use of glycerol derivatives bearing a latent amine group such as **81** in place of epichlorohydrin may potentially eliminate the need for reaction of the epoxide with ammonia, but time constraints did not allow this option to be explored or source this or equivalent reagent. The reaction of the epoxide with ammonia typically produced up to 20% of the bis-alkylated amine impurity which could be removed only by chromatography. An enormous excess of ammonia was required to suppress the second alkylation and drive the reaction to amine **104**.



Scheme 27. The ACT-209905 process including rectification of an undesired epoxide ring-opening.

Clearly a protected ammonia equivalent was required. The potassium salt of phthalimide reacted very slowly with **105** in DMF even at elevated temperatures. Sodium azide gave a fast and complete reaction however its subsequent Pd-catalyzed hydrogenation was incompatible with oxadiazole ring. No reaction occurred with hexamethyldisilazane (HMDS), but its lithium salt (LiHMDS) proved an excellent nucleophile in the opening of the epoxide ring and gave none of the dimeric impurity. After solvent swapping to TBME and aqueous wok up the amine was isolated in 55% yield

Further purification of amine **104** was not required and was treated directly with a mixture of glycolic acid, EDCI and HOBt in THF followed by crystallization from EtOAc afforded ACT-209905 in 49% yield with 98.6% purity and er 98.4:1. (Scheme 27) This chemistry was scaled up and delivered the desired active pharmaceutical ingredient at 12 kg scale.

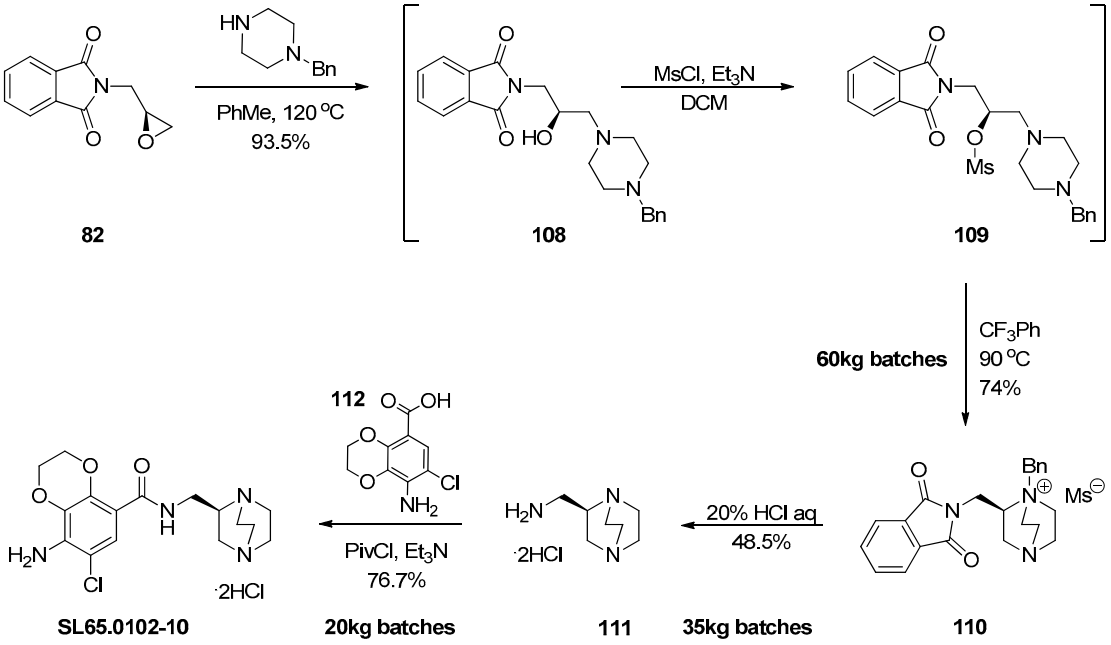
Undeterred by project constraints the Actelion process team delivered a scalable and efficient route to ACT-209905 that apparently encompasses the first example of a large-scale epoxide ring opening with LiHMDS as ammonia surrogate.

1.10. SL65.0102–10—Refocusing Attention from the Active Pharmaceutical Ingredient to the Chiral Epoxide Starting Material

The 5-HT4 receptor is widely expressed in the periphery and development of 5-HT4R agonists has led to approved drugs for gastrointestinal disorders. The 5-HT4 receptor is also highly expressed in the CNS in areas which are involved in cognitive functions (learning, memory) and their stimulation leads to production of acetylcholine and regulation of the neurotrophic soluble amyloid-protein precursor alpha (sAPP) [100–103]. Consequently, 5HT4 receptor agonists have attracted attention for their

therapeutic potential in the treatment of Alzheimer's Disease and cognitive impairment [104,105]. SL65.0102–10 is a selective 5-HT4 partial agonist that was discovered and developed by Sanofi as promising agent for the treatment of cognitive impairment.

The Sanofi process team developed the original medicinal chemistry route by optimizing and streamlining the first three steps involving epoxide **82** ring opening, mesylation of the resulting alcohol **108** and intramolecular displacement of the mesylate **109** by the N-benzyl end of the piperazine (Scheme 28). This process was successfully scaled up to 60 kg batches affording intermediate **110** directly in 74% yield.

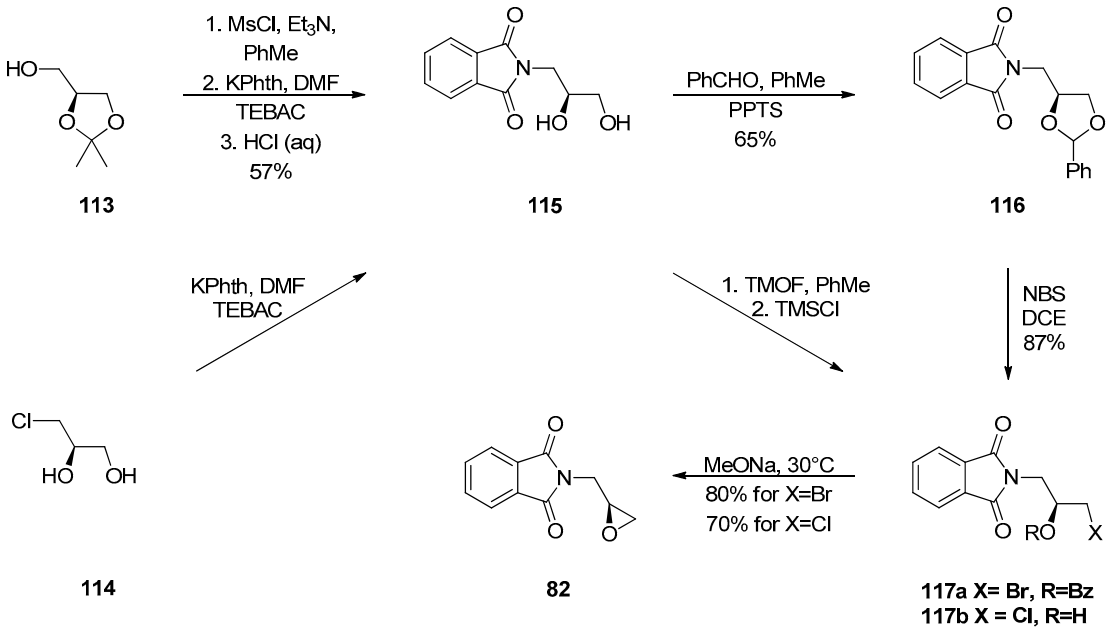


Scheme 28. Initial improvements to the medicinal chemistry route towards **SL65.0102–10**.

The medicinal chemistry 2-step deprotection of **110** by hydrogenolysis of the benzyl ammonium moiety followed by hydrazine treatment was replaced by a single step double deprotection in 20% aqueous HCl. Despite the slow rate and technical difficulties in removing the generated benzyl chloride and benzyl alcohol this step performed well on scale and delivered the key amino methyl piperazine **111** in 48.5% yield in 35 kg batches. The final step coupling of **111** with acid **112** was also optimized and provided SL65.0102–10 in 76.7% yield and excellent quality even at 20 kg batches [106].

Nevertheless, the lack of a reliable supplier of **82** at the quantities jeopardized the agreed project deliveries hence the Sanofi process chemists were forced to develop a quickly a large-scale synthesis for this starting material. The available conventional reactors however were inappropriate to host safely the epichlorohydrin involved in the standard synthesis of **82**. (*S*)-(+)-solketal [(*S*)-(+)-1,2-isopropylideneglycerol] **113** and (*R*)-(-)-3-chloro-1,2-propanediol **114** were identified as suitable (*S*)-epichlorohydrin surrogates which are cheap and available in bulk. Respectively, two alternative syntheses of **82** were investigated and evaluated at pilot plant scale (Scheme 29).

The (*S*)-(+)-solketal (**10**) route to **82** through intermediates **115, 116** and **117a** comprises 6 steps and was scaled up to 50 kg batches in the pilot plant thus enabling imminent deliveries of SL65.0102–10. In parallel optimization of the (*R*)-(-)-3-chloro-1,2-propanediol route through the orthoformate derivative of **115** [21,107] demonstrated significant benefits over the (*S*)-(+)-solketal route both in terms of number of steps and required isolations of intermediates. The (*R*)-(-)-3-chloro-1,2-propanediol became the method of choice and generated over 180 kg of **82** in excellent quality (98% purity and >99% ee) for subsequent campaigns towards SL65.0102–10.



Scheme 29. Process development towards chiral epoxide **81** enabling a convergent API route.

Overall, project deadlines combined with difficulties in sourcing convenient raw materials drove the project team focus both on the API and the chiral epoxide starting material and succeeded at both fronts. The Sanofi process team developed a second-generation route to SL65.0102–10 by improving the 12 steps/8 isolations in the first route to 10 steps/5 isolations capable of performing at multikilogram scale.

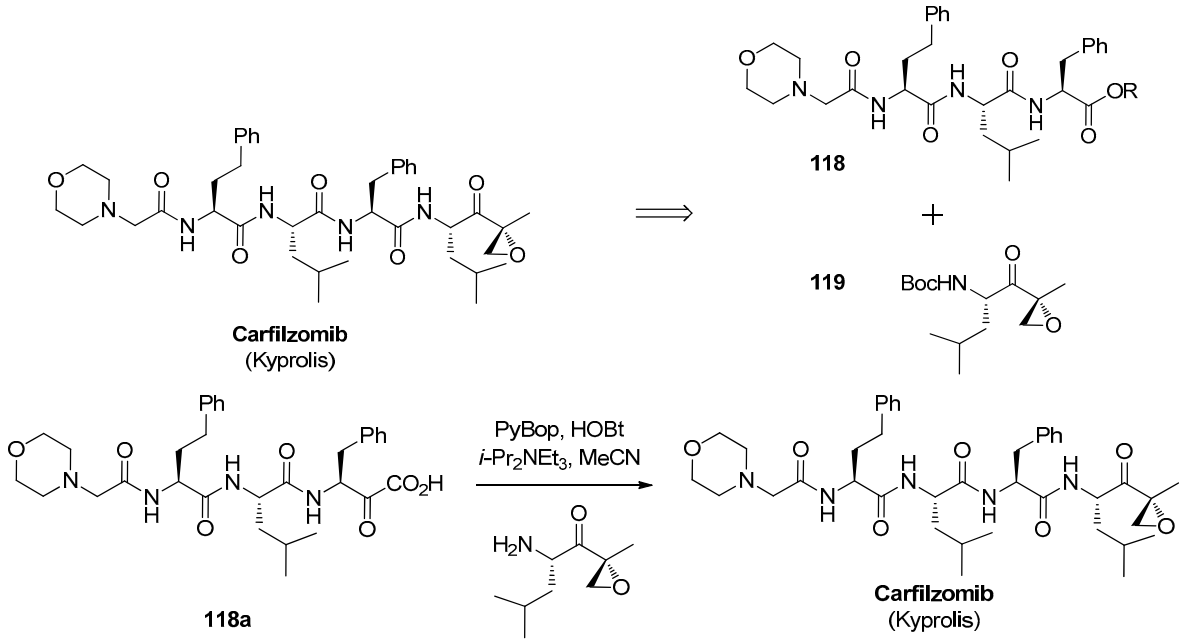
1.11. Carfilzomib—A Natural Epoxide Product Turned into a Drug and the Challenge of Its Diastereoselective Epoxidation

Carfilzomib (trade name Kyprolis) is a highly selective irreversible inhibitor of the chymotrypsin-like activity of both the constitutive (β5c subunit) and the immuno-isoform (β5i or LMP7 subunit) of the 20S proteasome [108,109]. It was approved by the FDA for multiple myeloma in 2012 and by the European Medicines Agency in 2015. Carfilzomib is a great example of an anticancer drug that was developed through a series of systematic modifications of a natural product, in this case epoxomicin. Epoxomicin was discovered by Bristol Myers Squibb Research Institute (Tokyo) in 1992 and demonstrated significant antitumor activity, but its development was abandoned because its mode of action was unclear and being a peptide did not have the appropriate pharmacokinetic profile. Prof. CM Crews (Yale University) and Prof. R Deshaies (California Institute of Technology) among others, founded Proteolix (later acquired by Onyx Pharmaceuticals; legacy company of Amgen) and decided to develop epoxomicin derivatives with desirable drug-like properties, particularly improved potency and solubility. This effort born carfilzomib whose mechanism of action was also elucidated [110].

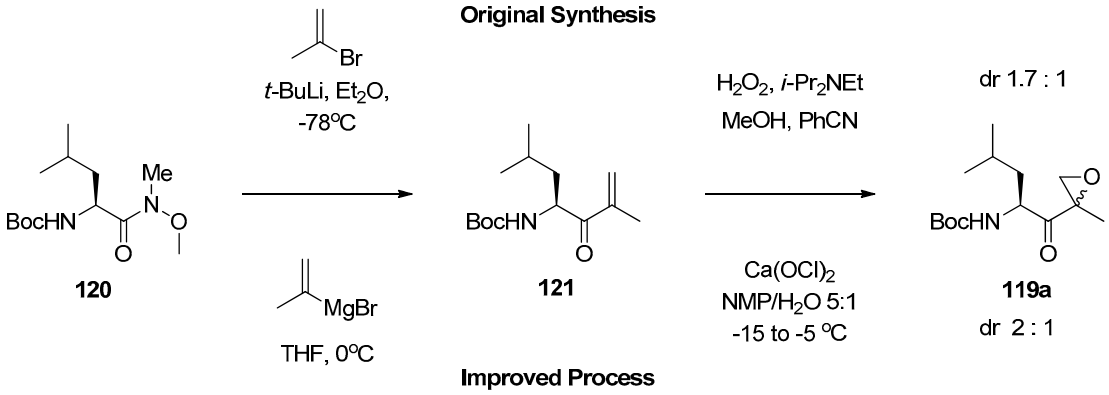
Carfilzomib (Scheme 30) is a tetrapeptide comprising two leucines, phenylalanine and a homo-phenylalanine with a the terminal morpholino cap benefiting the PK profile. Critical for biologic activity however is the chiral keto-epoxide warhead which was maintained throughout the SAR work and constitutes the principle synthetic challenge. The synthesis of the methyl or benzyl ester of the tripeptide core hPheLeu-Phe **118** is achieved using standard solution phase peptide coupling conditions and only minor improvements have been made over the years [111–116].

In the original synthesis of carfilzomib [117] the keto-epoxide was prepared by lithium/halogen exchange between *t*-BuLi (*tert*-Butyllithium) and 2-bomopropene and addition of the resulting vinyl anion on the Weinreb amide **120** at −78 °C thus affording vinyl ketone **121** (Scheme 31). Hydrogen

peroxide oxidation of the latter produces the Boc-protected amino keto-epoxide **119a** in a 63:37 mixture of diastereomers the desired isomer of which is obtained by column chromatography.



Scheme 30. Retrosynthesis of carfilzomib into epoxyketone **119** and final coupling step.



Scheme 31. Original and improved syntheses of the key chiral epoxyketone **119**.

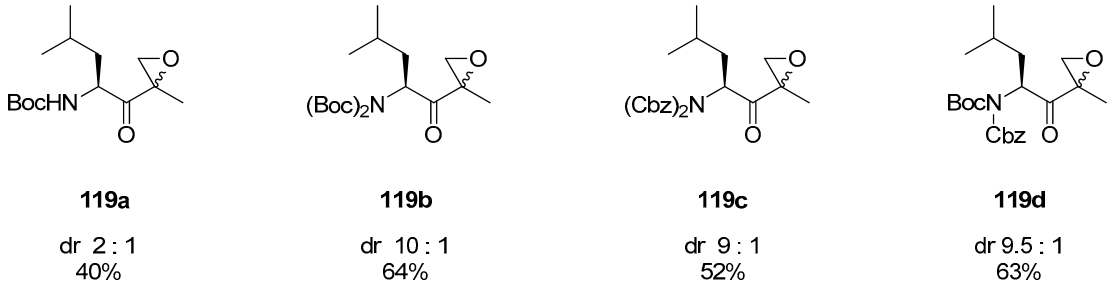
Obviously, the cryogenic temperatures, the pyrophoric *t*-BuLi and the chromatographic purification render this synthesis unsuitable for manufacturing. The issue with *t*-BuLi was successfully addressed later by Onyx Pharmaceuticals, as they replaced it with the isopropenylmagnesium bromide thus enabling the formation of vinyl ketone **121** to proceed in THF at 0–5 °C [111].

In the same work, marginal improvement (dr 2:1) was achieved in the epoxidation of **121** with calcium hypochlorite in aqueous NMP at −15 °C or with bleach in aqueous pyridine at −5 °C.

As carfilzomib had grown as an Amgen asset and established marketed product, Amgen process chemists made further improvements to the process upstream and downstream of the pyridine/bleach epoxidation reaction and resolved issues related to a) the epimerization of **121** due to the interaction of the enone/residual inorganics/silica during its purification, b) quality, yield and robustness issues of the oxidation step due to pH-dependent decomposition of bleach, c) impurity built-up derived by the solvent stabilizer [118].

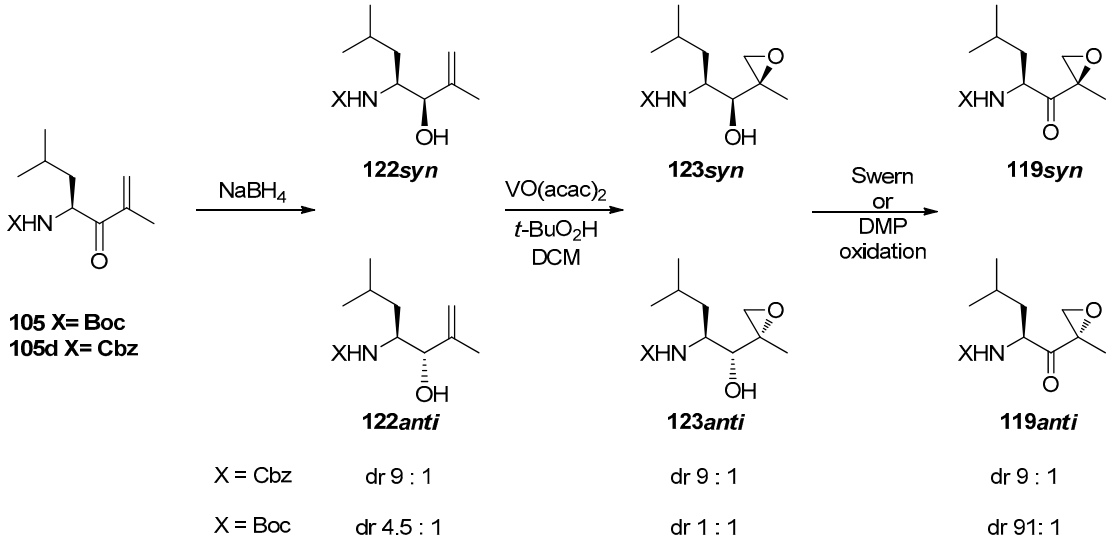
Other parties interested in improving the synthesis and optical purity of the key carfilzomib intermediate **119**, interrogated the influence of the **121** N-protecting group(s) in the $Ca(OCl)_2$ epoxidation

reaction [119]. Apparently, the nature and number of protecting groups has a great impact on the yield and diastereoselectivity of the epoxidation since this improved from 40% and dr 2:1 with the mono-Boc derivative **119a** to 64% and dr 10:1 with the bis-Boc analog **119b**. The latter was marginally better than the bis-Cbz and mixed Boc/Cbz analog structures **119c** and **119d**, respectively (Scheme 32).



Scheme 32. Effect of nitrogen atom protection on the diastereoselectivity of the enone epoxidation

Another approach was to enhance the substrate control in the epoxidation reaction by using the allylic alcohol(s) **122** as the substrate (Scheme 33). The Cbz substrate generated the *syn* and *anti* alcohols **122** in dr 9:1 which were in turn epoxidized using vanadium catalysis. The *syn* and *anti* epoxides **123** were obtained in the same ratio which was also maintained in the subsequent oxidation of the hydroxyl groups back to the ketone state. Interestingly the Boc-protected ketone **121** gave a 4:1 mixture of the *syn* and *anti* alcohols **122**, but this did not transcend to the *syn* and *anti* epoxides **123**. These were obtained in a 1:1 ratio suggesting a mismatched conformation of the major Boc diastereoisomer **122*syn*** exemplifying once more the influence exerted by the protecting group in the stereochemical course of the epoxidation [111,115,116].



Scheme 33. Effect of nitrogen atom protection on the diastereoselectivity of the allylic-OH epoxidation.

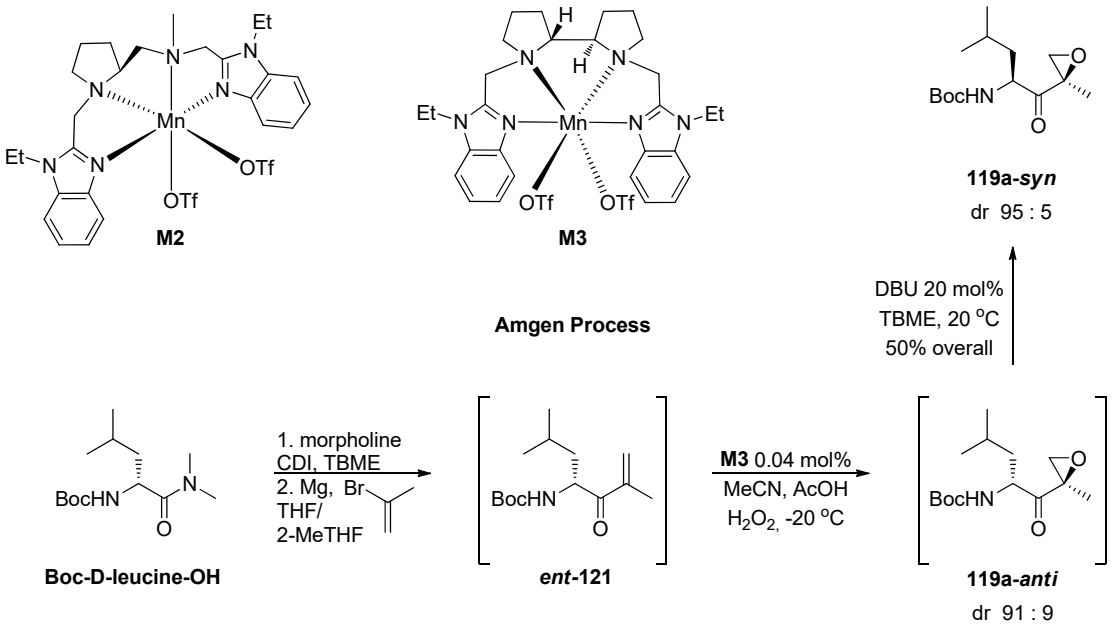
In another attempt, the Sharpless asymmetric hydroxylation was applied on **121** although the diastereoselectivity of this was not reported. In this case the synthesis of carfilzomib required additional steps associated with transforming the diol to the epoxide through protection as the diacetate prior to Boc removal and coupling with the tripeptide, deprotection of the diol, activation of the primary alcohol as mesylate followed by ring closure to the epoxide. The additional process intensity and length render this approach unattractive for further development.

Other efforts involved the oxidation of the epoxyketone moiety at the dipeptide or tripeptide stages post deprotection and coupling of **121** to the adjacent amino acids in carfilzomib or even

at des-oxy carfilzomib itself. The diastereoselectivities (where reported) were no better than those obtained with **121** [120–123]. This and other approaches are discussed in more detail in an excellent patent review by D.L. Hughes [124].

The cause of carfilzomib had attracted the application of alternative catalytic epoxidation methods. In one of them, epoxidation of **121** has been reported to occur with 93% de and 85% yield with the lanthanum(III) BINOL complex, in toluene at ambient temperature with TBHP (*tert*-Butyl hydroperoxide) in the presence of triphenyl phosphine [125] (the real additive being the triphenyl phosphine oxide generated in situ by the oxidant) [126]. This reaction was demonstrated at 100 g scale nevertheless it requires a catalyst-loading of at least 20 mol% for best results.

In contrast to this requirement, a chiral manganese complex (M2, Scheme 34) developed specifically for the epoxidation of enones with H_2O_2, sufficed at 0.2 mol% to epoxidize (*S*)-ketone **121** in 96% yield, but at dr 1:7 favoring the undesired diastereoisomer of **119a-*syn*** (*S* at the ketone, *R* at the epoxide) [127].



Scheme 34. Catalytic asymmetric (substrate-controlled) epoxidation followed by epimerization.

The Amgen process chemists took notice of this and decided to investigate if the diastereoselectivity of this excellent performing catalytic epoxidation could be reversed. A thorough optimization led to a more efficient Mn ligand/active catalyst **M3** nevertheless the diastereoselectivity of this process remained overwhelmingly substrate-controlled producing the undesired diastereoisomer of **119a-*anti*** in 91:9 ratio. This was ingeniously exploited by employing the enantiomer of enone **121** (i.e., the *R* enantiomer) to generate the correct epoxide stereochemistry (*S*) followed by epimerization of the α-carbon into the *S* stereochemistry for which DBU (1,8-Diazabicyclo[5.4.0] undec-7-ene) emerged as the optimum base (79% yield, dr 95:5).

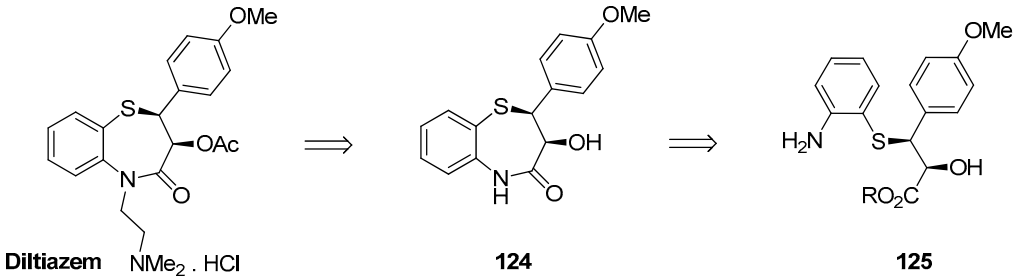
The higher crystallinity of the *R,S* diastereoisomer allowed also for the development of a crystallization process which obviated the need for chromatography. The Amgen process group transformed entirely the synthesis of **119a** by developing a continuous process for the Grignard addition of 2-propenyl to the Boc-D-leucine morpholine amide instead of the Weinreb amide **120** and telescoping this into the catalytic epoxidation reaction. This remarkably innovative process was demonstrated at 2 kg scale and delivered enantiopure **119a-*syn*** in 50% yield in a much greener, safer and efficient manner [128].

The development of carfilzomib has been established as a point of reference in anticancer drug research and has inspired the development of several other related and unrelated natural products for various indications most notably cancers. After years of research and development by various

groups, Amgen process chemists achieved a highly diastereoselective and viable in large-scale catalytic epoxidation process for the terminal vinyl ketone moiety.

1.12. Diltiazem—A Rare Example of Chiral Epoxide Industrial Synthesis via Asymmetric Organocatalysis Followed by Ring Opening with Retention of Configuration

Diltiazem (Cardizem) is a calcium channel blocker and is FDA approved for atrial arrhythmia, hypertension, paroxysmal supraventricular tachycardia and chronic stable angina. Diltiazem is a chiral 1,5-benzothiazepine with the *threo* (2*S*,3*S*)-isomer demonstrating superior vasodilating properties. The end game in the various syntheses of diltiazem almost invariably involves the attachment of the dimethylamino-ethyl side chain on the amide nitrogen of intermediate **124** (Scheme 35) followed by O-acetylation. Lactam **124** is obtained by cyclisation of an appropriate carboxyl derivative **125** such as an ester or amide.

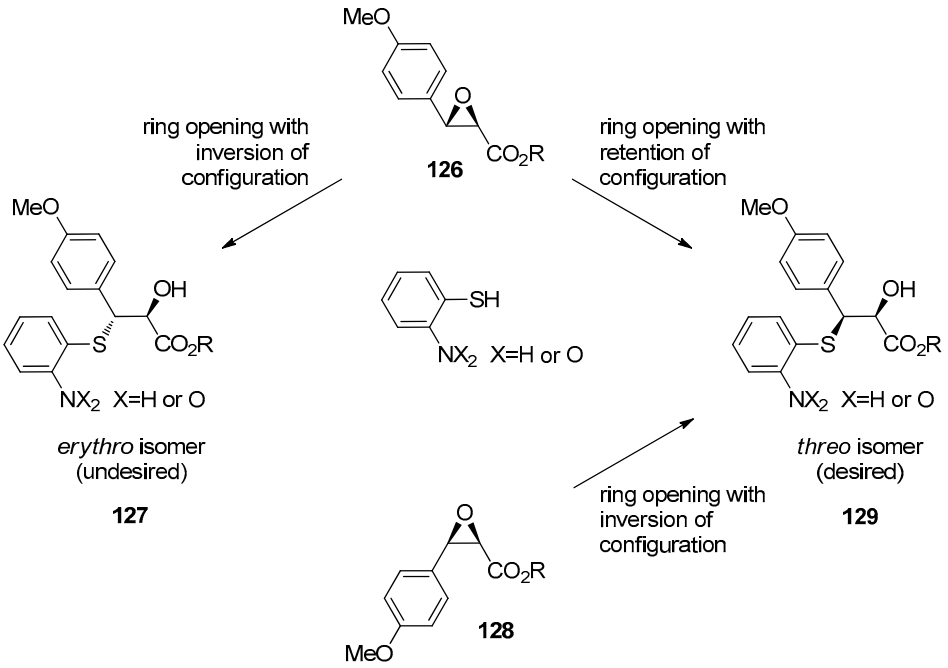


Scheme 35. Retrosynthesis of diltiazem to chiral precursor **125**.

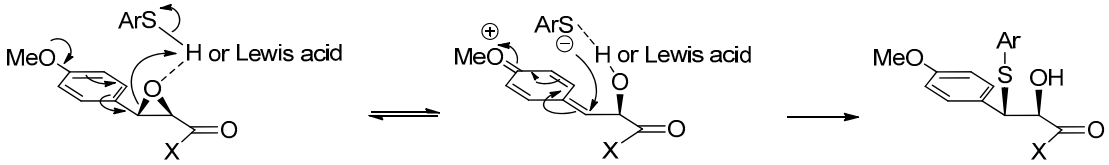
Initially, development of manufacturing routes to diltiazem were based on both chemical [129] and enzymatic [130] resolutions of appropriate intermediates. The route based on resolution of (2*S*,3*S*)-3-(4-methoxyphenyl) glycidic acid methyl ester, (**126** Scheme 36) in particular, provided significant cost benefits [131]. In the context of asymmetric synthesis, setting up the correct stereochemistry of the thio- and acetoxy- substituents precipitates a major challenge in the synthesis of diltiazem. Standard ring opening of the *trans*-epoxide **126** by nucleophilic attack of 2-amino-(or 2-nitro) thiophenol with inversion of configuration at the benzylic carbon would generate the undesired *erythro* isomer **127**. One strategy to overcome this issue was demonstrated by Jacobsen who used the corresponding *cis*-epoxide **128** thus starting with inverted stereochemistry at the benzylic carbon [132]. Indeed, ring opening of the *cis*-epoxide **128** (R = ^{i}Pr) with 2-nitrothiophenol provided intermediate **129** (X = O, R = ^{i}Pr, Scheme 36). Reduction of the nitro group followed by the standard end game steps yielded diltiazem. The synthesis of *cis*-epoxide **128** was realized in 96% ee (10:1 *cis*/*trans* ratio) by applying the Jacobsen–Katsuki epoxidation protocol with a chiral salen complex on the corresponding *cis*-cinnamate ester. The availability of the latter alkene constitutes the Achilles' heel of this route as it is obtained by photoisomerization of the *trans* isomer.

An alternative strategy had been developed a decade earlier by chemists at Tanabe Seiyaku (legacy company of Mitsubishi Tanabe Pharma), the inventors of diltiazem, who recognized that the easy-to-access *trans* epoxide **126** could be exploited in a ring-opening reaction with retention of configuration at the benzylic carbon [133].

This transformation is largely facilitated by the *p*-methoxy phenyl substituent supporting the opening of the ring by virtue of its electron donating capacity (Scheme 37) and ability to stabilize the resulting benzylic cation (other less electron donating substituents do not work as well, if at all). This reaction is further assisted by Lewis acid activation of the epoxide, presumably in a form involving prior complexation with the nucleophile, thus allowing the reaction to proceed in a pseudo-intramolecular fashion. A similar case culminating the reduction of a chiral epoxide with retention of configuration has been described by Merck chemists in the synthesis of the PDE IV inhibitor CDP840 [134].



Scheme 36. Ring opening of epoxides **126** and **128** with retention and inversion of configuration.

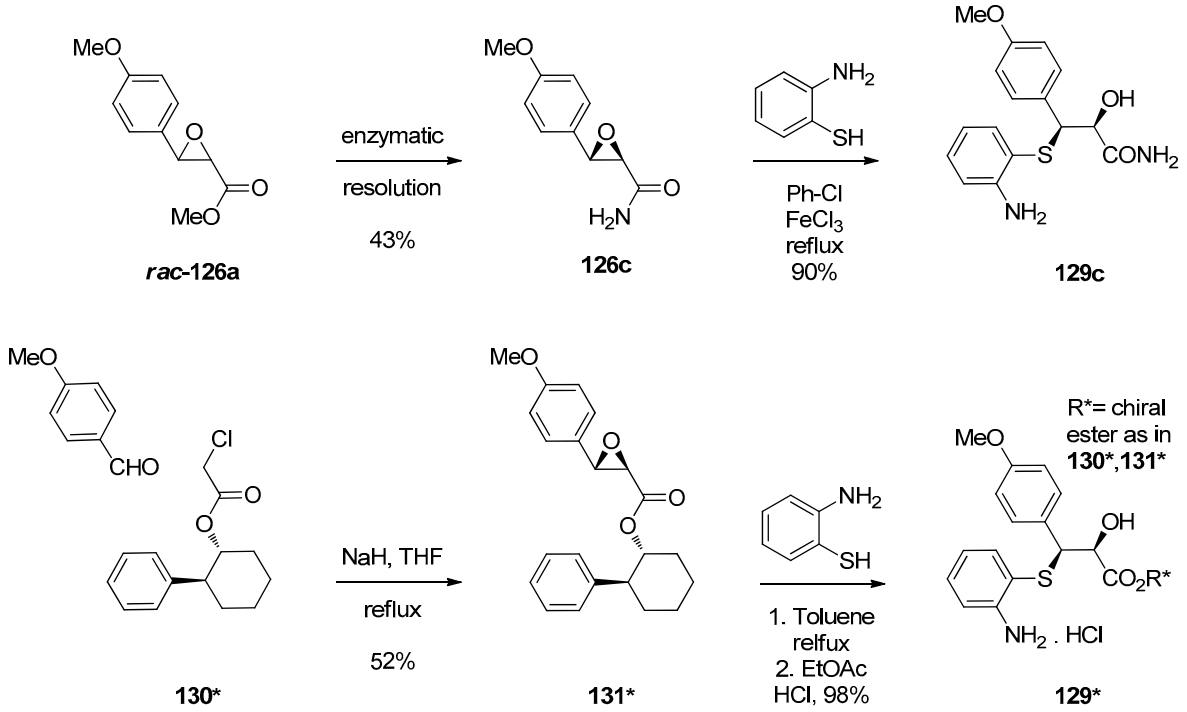


Scheme 37. Mechanism of epoxide ring opening with retention of configuration.

The Tanabe chemists later expanded their original work and screened a wide array of catalysts and solvents for this transformation [135]. Best results (90% yield **129c**, 92:8 *threo/erythro* ratio) were obtained with iron (III) salts, particularly with the chloride and the sulfate, at 10^{-4} mol% catalyst-loading in refluxing xylene (Scheme 38, upper).

Chemists at Roche, in their effort to develop diltiazem analogs such as naltiazem, accomplished this thermally (Scheme 38, lower) in the presence of 2-aminothiophenol alone which is acidic enough to support protonation of the epoxide and self-ring opening to the stabilized benzylic cation thus inviting the attack by the thiolate anion [136]. This process was demonstrated on kg scale affording intermediate **129*** in 98% yield. In this case, the prerequisite chiral epoxide was synthesized via employing a chiral auxiliary in a diastereoselective Darzens reaction between p-anisaldehyde and the chloroacetate ester of (1*R*,2*S*)-2-phenylcyclohexanol **130***. This reaction produces a 62:38 mixture of the two diastereomeric epoxides **131*** from which the desired diastereoisomer is isolated by simple crystallization in 54% yield (400 g scale).

In terms of preparation of the appropriate chiral epoxy cinnamate ester **129a**, the Tanabe chemists addressed an occupational health issue in their original enzymatic resolution process [131]. Because the epoxy ester intermediate was shown to be a severe irritant, the enzymatic resolution was modified to produce optically pure and safe to handle epoxy amide **129c** either directly using ammonia or by converting resolved methyl ester **129a** to the primary amide. The epoxy amide **129c** performed well in the ring opening and the subsequent acid-catalyzed lactamization, eventually allowing for successful preparation of diltiazem in multigram scale.



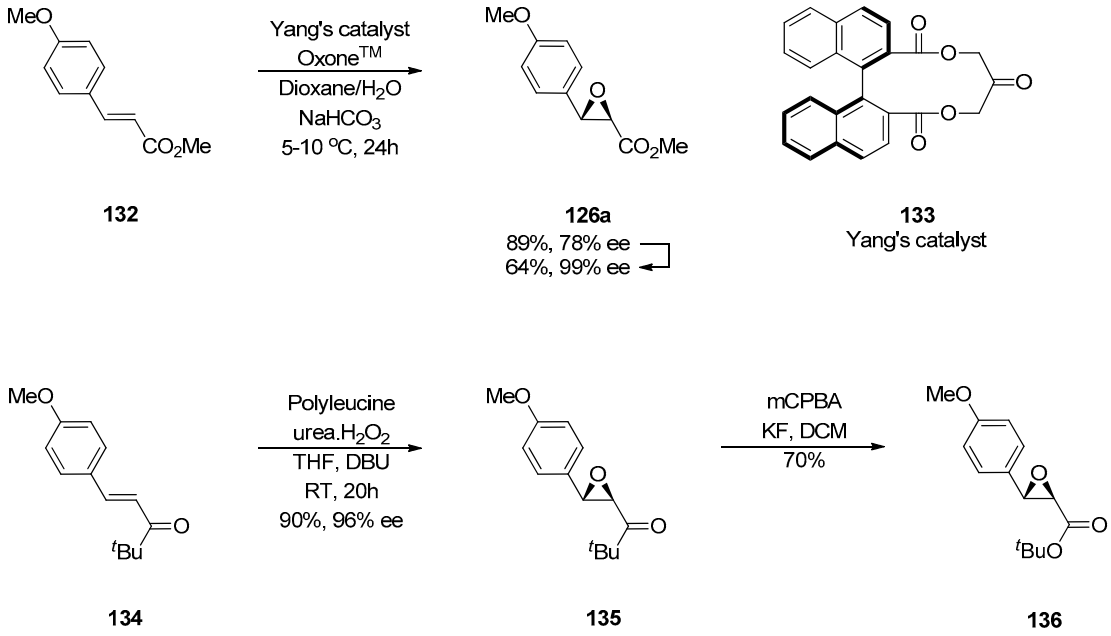
Scheme 38. Alternative synthesis of diltiazem intermediate **129** via asymmetric Darzen reaction.

In order to improve further on the efficiency of the synthesis of the chiral epoxide the Tanabe chemists investigated alternative routes that would preclude the >50% yield loss associated with resolution methods (either chemical or enzymatic). Thus, a catalytic asymmetric epoxidation of *p*-methoxy cinnamate esters (**132**) became the next objective of the Tanabe investigation. Given the electron deficient nature of the alkene potion in the cinnamic substrate, a powerful electrophilic oxidant must be used in order for the epoxidation to take place. For this reason, chiral dioxiranes generated in situ from appropriate chiral ketones were considered for this task [137,138].

Yang's chiral ketone **133** (Scheme 39) emerged as the optimum organocatalyst for this transformation in terms of ease of preparation, catalyst-loading and stability [139]. The process was gradually scaled up to 100 g with 5 mol% of the ketone catalyst in the presence of Oxone^{TM} as the terminal oxidant and delivered the crude chiral epoxy cinnamate in 89% yield and 78% ee [139]. A special recrystallization process was developed for isolating the product without contamination from the catalyst which not only upgraded the quality of the intermediate to 99% ee (64% yield), but also allowed for the recovery of the catalyst. In a subsequent effort, the crystallization process was coupled to a lipase-catalyzed transesterification step that also allowed for recycling of the unwanted epoxide enantiomer [140].

The asymmetric epoxidation of α,β-unsaturated ketones may be accomplished by the Julia Colona protocol with nucleophilic oxidants such as hydrogen peroxide. In this, the substrate associates with polyleucine catalyst via hydrogen bonding and becomes activated towards a conjugate addition by the oxidant within the chiral environment of the catalyst. This approach was demonstrated in the synthesis of diltiazem via the catalytic asymmetric epoxidation of ketone **134** (Scheme 39) followed by a Bayer Villiger reaction on epoxide **135** to generate the *t*-butyl cinnamate ester **136** [**141**]. Using the conditions developed by Roche and the established endgame reactions, a second alternative synthesis of diltiazem based on an organocatalyst was achieved. It is worth noting that this synthesis was performed three consecutive times at 4 g scale with reuse of the immobilized polyleucine catalyst each time, without deterioration of the yield or ee.

Overall, the process development efforts towards diltiazem encompass two rare aspects of epoxide chemistry performed on scale, namely the asymmetric synthesis of an epoxide using an organocatalyst and its subsequent ring opening with retention of configuration.



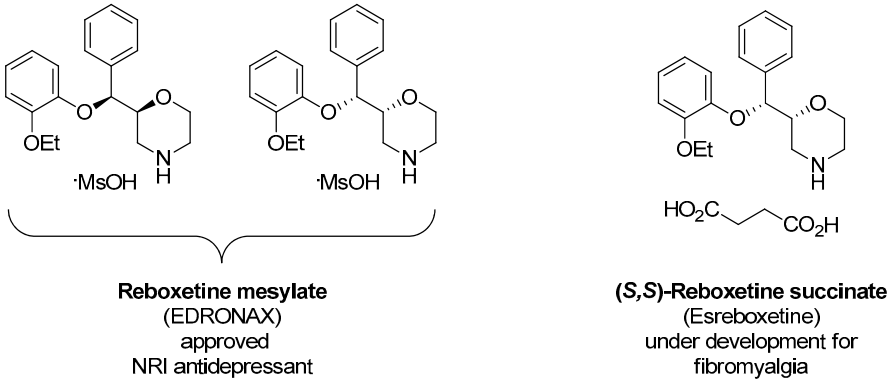
Scheme 39. Synthesis of chiral epoxy cinnamate intermediates using asymmetric organocatalysis.

1.13. Reboxetine—Epoxide Intermediates Transcending from a Racemic to an Asymmetric Synthesis

CNS disorders are largely associated with deregulation of neurotransmitter and neurohormone signaling. Prominent members of the former category include the biogenic amines serotonin, norepinephrine (noradrenaline) and dopamine. Depression encompasses several disorders with various symptoms, ailments and disabilities that may affect our emotions, thoughts, actions and physical condition of the entire human body. Intervention at the serotoninergic and noradrenergic signaling has produced the state of the art of antidepressants (SSRIs, NRIs and SNRIs) [142,143] primarily through inhibition of the reuptake of the respective neurotransmitters in the synaptic cleft. Reboxetine is a highly potent and selective norepinephrine reuptake inhibitor that is approved in many countries, but not the FDA, for the acute treatment of depressive illness/major depression. Its efficacy for these indications has been a matter of controversy instead clearer benefit is observed in cases with symptoms of anhedonia and somatic pain. Furthermore, reboxetine appears to be widely endorsed (off label) for SSRI-resistant panic disorder and attention deficit hyperactivity disorder (ADHD). Reboxetine was discovered by Farmitalia which was acquired by Pharmacia in 1993 and succeeded in obtaining regulatory approvals. Pharmacia merged with Upjohn in 1995 forming Pharmacia-Upjohn which in turn was acquired by Pfizer in 2003.

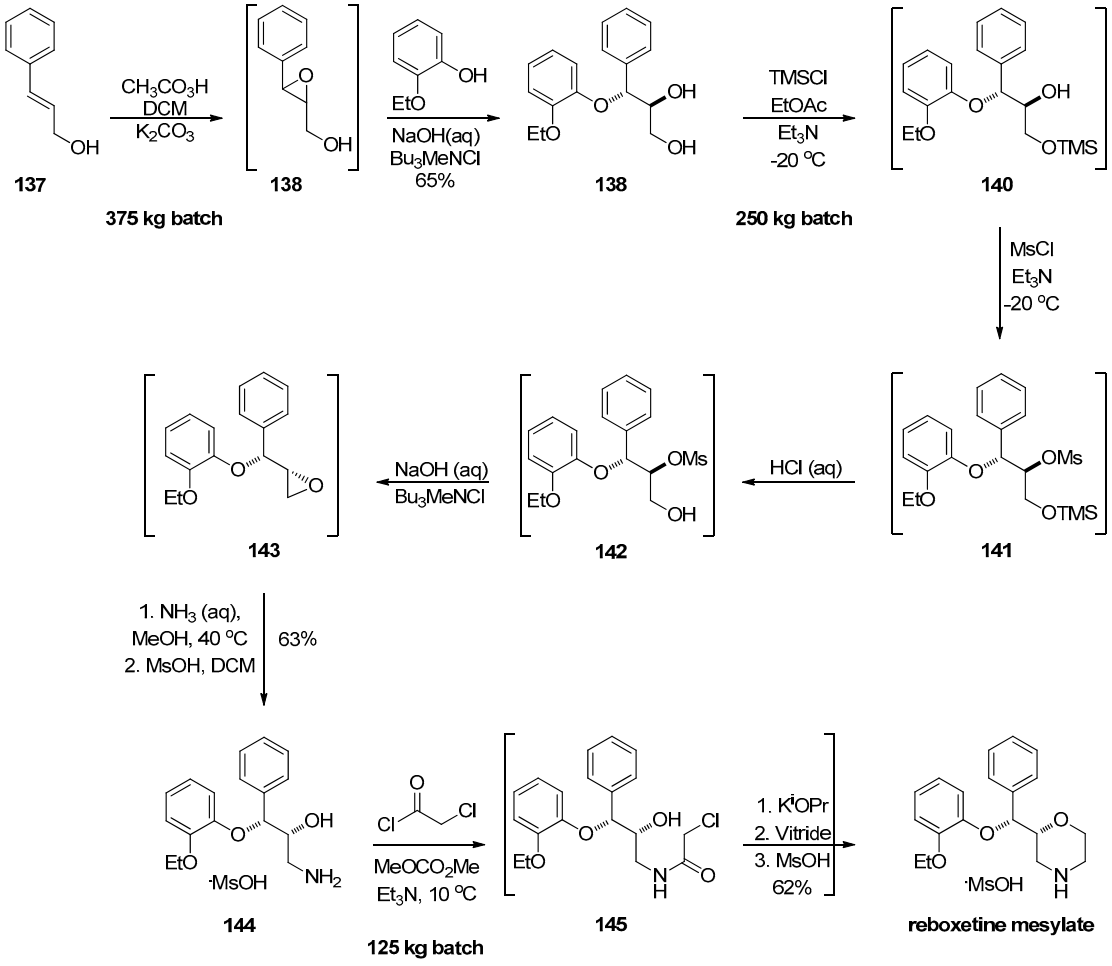
Reboxetine has two stereogenic centers and consequently there are four diastereoisomers, two sets of enantiomers, associated with its structure. The registered NRI antidepressant, reboxetine mesylate (trade name Edronax, Scheme 40), comprises actually one set enantiomers the (*S*,*S* and the *R*,*R*), namely the set of *syn* diastereomers and is therefore marketed in a diastereomerically pure yet racemic form.

For this reason, the initial synthesis of reboxetine were racemic. More recent studies have shown that the (*S*,*S*)-enantiomer (esreboxetine, Scheme 40) is more active than its enantiomer in certain biologic assays [144] and (*S*,*S*)-reboxetine succinate is under development at Pfizer for the treatment of fibromyalgia. A number of reboxetine syntheses have been described over the years and these have been recently reviewed [145]. The discussion that follows focuses on the relevant epoxide-involving routes particularly those of large scale/manufacturing potential.



Scheme 40. Stereochemistry of reboxetine (approved drug) and esreboxetine (clinical candidate).

The first synthesis for reboxetine mesylate (the racemic approved drug) was reported by its inventors Farmitalia-Carlo Erba. By the time the drug became a Pfizer asset it had grown in demand and a more efficient route was needed, but there was limited freedom for changes due the restrictions that apply to registered processes with regulatory bodies. Pfizer process chemists made several modifications (Scheme 41) to the Farmitalia route and developed a process which involves 12 chemical transformations yet only three isolations improving the yield of the drug substance from 11 to about 25% [146].



Scheme 41. Pfizer's manufacturing route for reboxetine.

In particular, due to work up difficulties, long processing times and size of waste, the reagent for the epoxidation of cinnamyl alcohol **137** was switched from monoperoxyphthalic acid (prepared from H_2O_2 and phthalic anhydride) to peracetic acid (Scheme 41). The epoxide **138** was telescoped into the ring-opening reaction with 2-ethoxyphenol which was now run in water in the presence of a phase transfer catalyst instead of dioxane. Diol **139** was isolated after the telescoped epoxidation and ring-opening process in 65% yield at > 0.3 ton scale. The protecting group for the primary alcohol in the next step was changed from *p*-nitrobenzoyl to TMS in order to limit the extensive migration of the acyl group (>20%) to the secondary alcohol which would ultimately lead to the wrong API diastereomer. The regioselectivity of the TMS protection towards exclusive formation of **140** was carefully controlled before addition of mesyl chloride to generate mesylate **141**. Acid treatment removes the silyl group revealing hydroxy mesylate **142** followed by base-induced epoxide formation. Ring opening of epoxide **143** with ammonia required large excess of the latter to suppress further reaction of the generated amine **144** with a second molecule of epoxide. The dimeric amine generated in this way was difficult to purge down downstream if formed at >8% at this stage. After careful optimization of these steps the telescoped process from diol **139** spanning 5 steps was run at 275 kg batches and delivered key intermediate amine **144** as its mesylate salt in 63% yield and excellent quality.

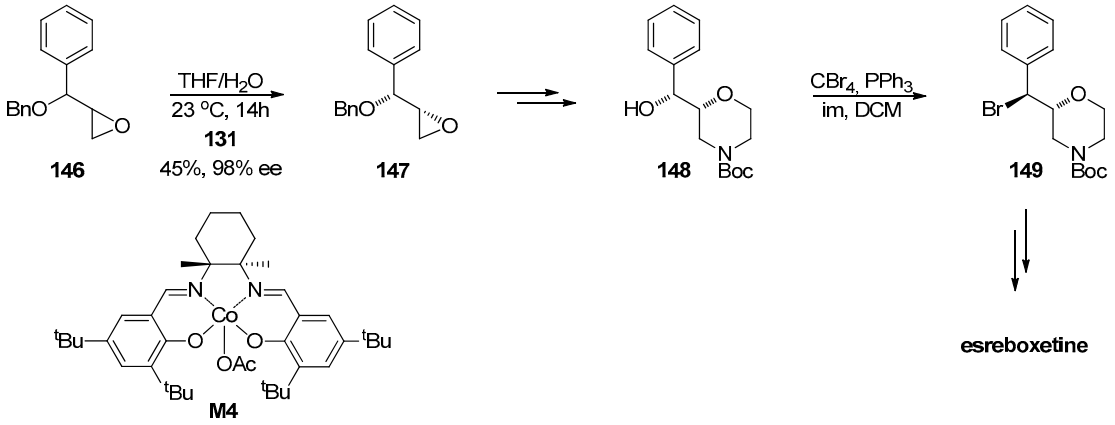
The construction of the morpholine ring was realized via a telescoped three step sequence involving amidation of **144** with chloroacetyl chloride, cyclisation of **145** and reduction of the resulting morpholinone. Features of this process such as the dimethyl carbonate solvent in the amidation step and the final Vitride reduction were maintained in order to avoid major deviations from the registered process. Modifications in the reduction step nevertheless led to significant minimization of certain impurities and improved the work up. These were implemented in 125 kg batch processes delivering reboxetine mesylate at specification in 62% yield over the three steps.

The progression of esreboxetine succinate to clinical candidate status precipitated the need for kilogram scale deliveries of enantiopure reboxetine. Initially this was achieved by resolution of reboxetine mesylate itself involving conversion to the free base, resolution with (*S*)-mandelic acid, conversion to the free base and succinate salt formation [147]. Despite delivering 100 kg this process was deemed highly inefficient as 3 kg of reboxetine mesylate were required to produce 1 kg of esreboxetine succinate. In addition, using an established drug substance as a starting material carried several supply and regulatory issues. For these reasons, resolution at the stage of amino alcohol **144** was considered next.

A wide range of resolving agents and solvent systems were screened with (*R*)-camphanic acid providing the most robust, scalable and efficient resolution. Unfortunately, it is the (*S*)-camphanic acid that is cheaper and more widely available which conversely induces crystallization of the undesired enantiomer of reboxetine as its (*S*)-camphanate salt. A process was thus developed that removed the unwanted diastereomeric salt by filtration and the synthesis progressed with the desired enantiomer retained in the liquors as free base in 88% ee; this was upgraded to 99% ee to upon its isolation as the benzoate salt. This process was scaled up to 150 kg batches and delivered close to perfect yields for a resolution step (47% on average) rendering the overall route to esreboxetine three times more efficient and cost-effective than the process implementing the resolution at the reboxetine mesylate stage [147].

Following this logic, a resolution further upstream in the synthesis could increase the efficiency of the synthesis and such an attempt has been described by Reddy et al. the resolution of epoxide **146** catalyzed by Jacobsen cobalt salen complex **M4** (Scheme 42) [148].

Resolved epoxide **147**, following ring opening with ammonia, was converted to the morpholine derivative **148** via the standard 3-step procedure and protected with Boc. In this approach whatever advantage was gained by conducting the resolution early, is lost in the manipulation of the Bn and Boc protecting groups and necessity to invert the stereochemistry of the benzylic alcohol **148** and then again of the benzylic bromide **149** with 2-ethoxyphenol.

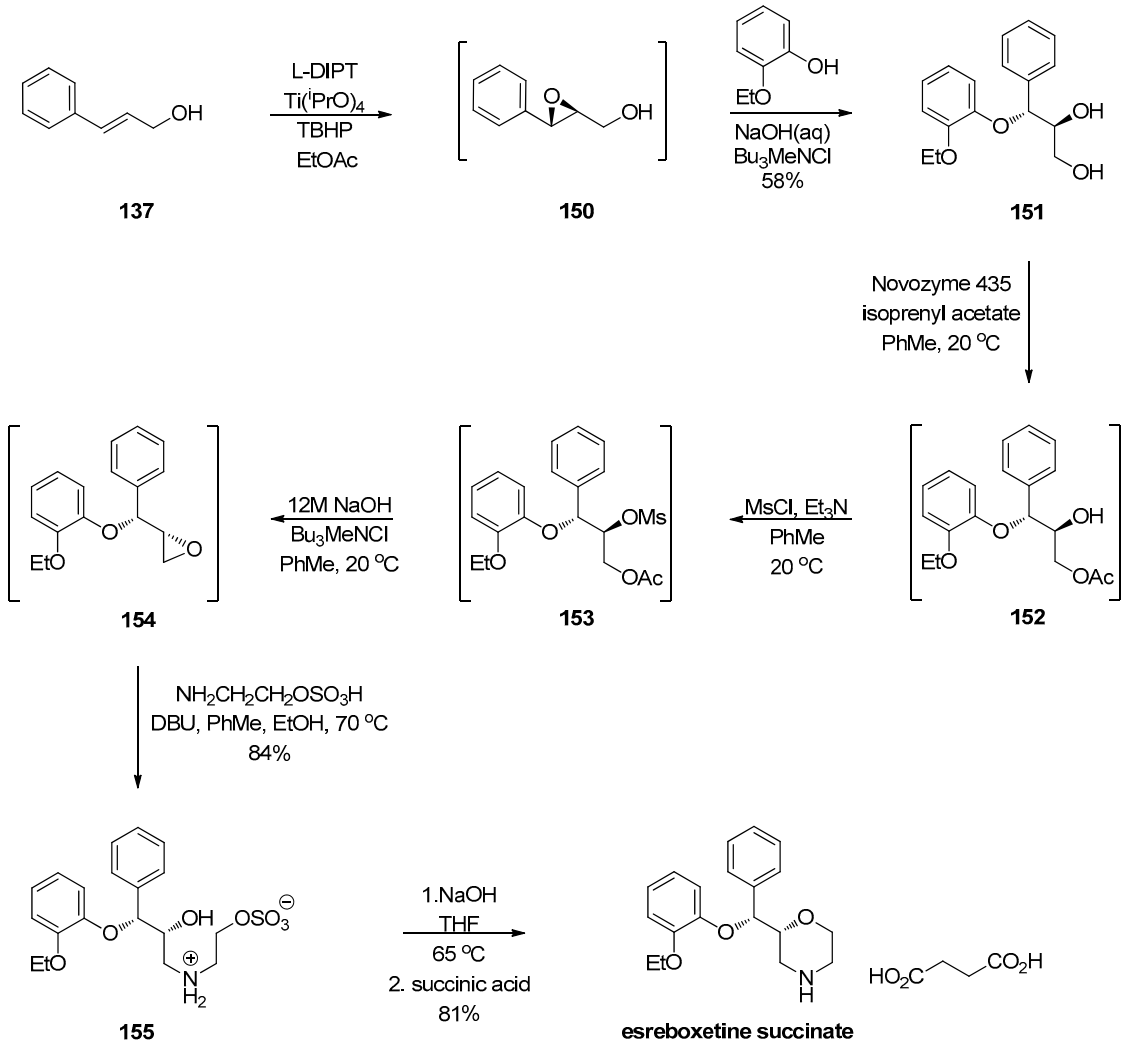


Scheme 42. Reddy's kinetic resolution of an early epoxide intermediate using Jacobsen's catalyst **M4**.

It must be noted that all reported syntheses that involve the formation of the O-aryl bond from the benzylic alcohol do so with the use Mitsunobu or equivalent reactions or chromium tricarbonyl arene complexes depending on the stereochemistry at the benzylic alcohol. Such methods may be acceptable for the preparation of analog structures in small scale but are render the synthesis uncompetitive and practically invalid in a large scale/manufacturing set up due to waste and toxicity issues of the reagents involved (Cr, azodicarboxylates) [149–155].

From a process chemist's perspective, the best approach for constructing the aryl-benzylic ether fragment in reboxetine is to install this by using the phenol in a nucleophilic substitution reaction at the benzylic center preferably early on. It is therefore not a coincidence that both racemic and asymmetric syntheses of reboxetine by the process team of Pfizer employ this very strategy. The Pfizer team considered that an asymmetric synthesis that could offset the 50% yield reduction associated with their nearly perfect resolution processes would be ever more efficient and cost saving. With more freedom to operate now in the context of esreboxetine development, the racemic route was modified into an asymmetric one simply by replacing the racemic epoxidation of cinnamyl alcohol in the first step by a Sharpless asymmetric epoxidation of the very same allylic alcohol in 92% ee (Scheme 43) [156]. Without isolation, chiral epoxide **150** was subjected to the ring-opening reaction by the phenol as in the previous process and recrystallization of the diol **151** allowed the upgrade of optical purity to >98%. In this first iteration, only minor modifications were made to the rest of the stages (Scheme 41) in order to accommodate the differences in solubility and behavior of the enantiopure intermediates from those of the racemic ones. Still, it was possible to improve the asymmetric process further in the next iteration [147]. In particular, the −20 °C TMS protection of the primary alcohol in **151** suffered from moderate yields and incomplete regiocontrol (either by direct silylation of the secondary alcohol or via TMS migration) and lacked robustness in larger scale processing.

An innovative protection step was introduced using an enzyme-catalyzed acetylation to form **152** which occurred consistently with almost complete regiocontrol even at 20 °C. This was telescoped into the mesylation step and mesylate **153** was subjected directly in the base-induced acetate ester hydrolysis and ring-closure to epoxide **154**. This sequence saved one step/operation from the synthesis since the corresponding TMS intermediate **141** required acidic deprotection prior to epoxide formation. Another step was eliminated from the synthesis by ring opening of epoxide **154** to intermediate **155** by using 2-aminoethyl hydrogen sulfate instead of ammonia. This reagent bears the ethylene portion of the morpholine already preinstalled at the nitrogen atom and more important, at the correct oxidation state, obviating the need for a reduction step. The ring opening of epoxide **154** had to be optimized against formation dimeric impurities (amine **155** reacting with a second epoxide molecule) by careful control of reagent stoichiometry, reaction temperature, order and duration of additions. Morpholine ring closure under basic conditions was telescoped into the succinate salt generation thus providing esreboxetine succinate in 81% yield at specification.

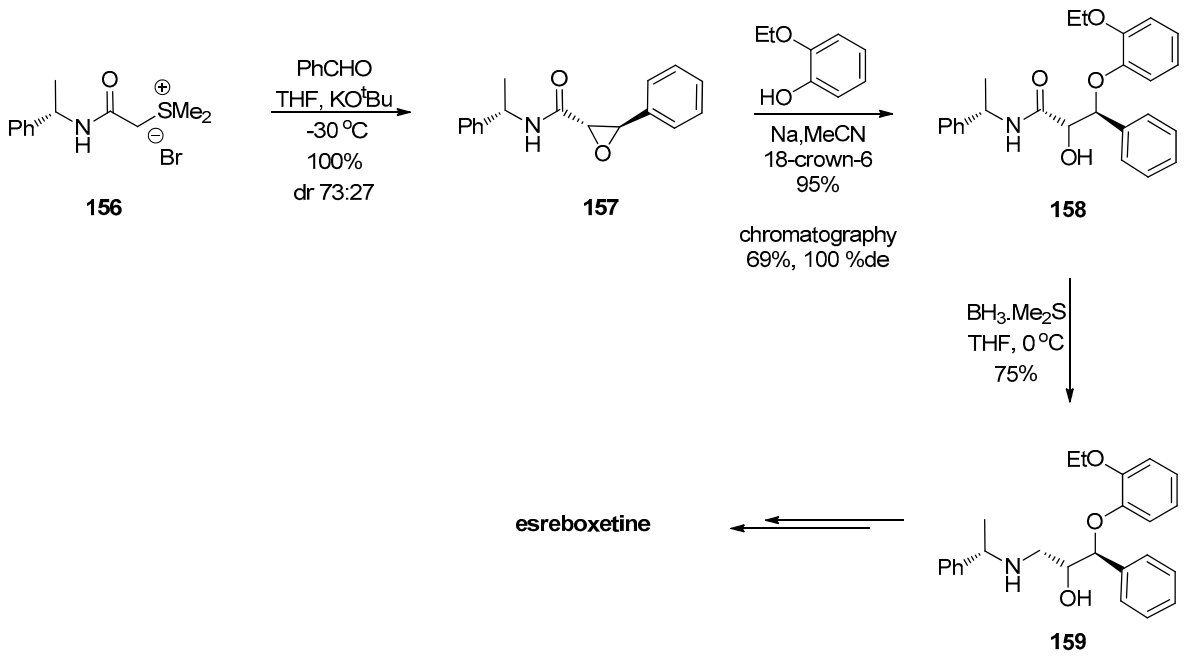


Scheme 43. Pfizer's final process for the asymmetric synthesis of esreboxetine.

The new asymmetric process for reboxetine succinate afforded a 58% improvement in overall yield, reduced processing times, significant cost savings and waste reduction by 90% hence it received a Green Chemistry Award [157].

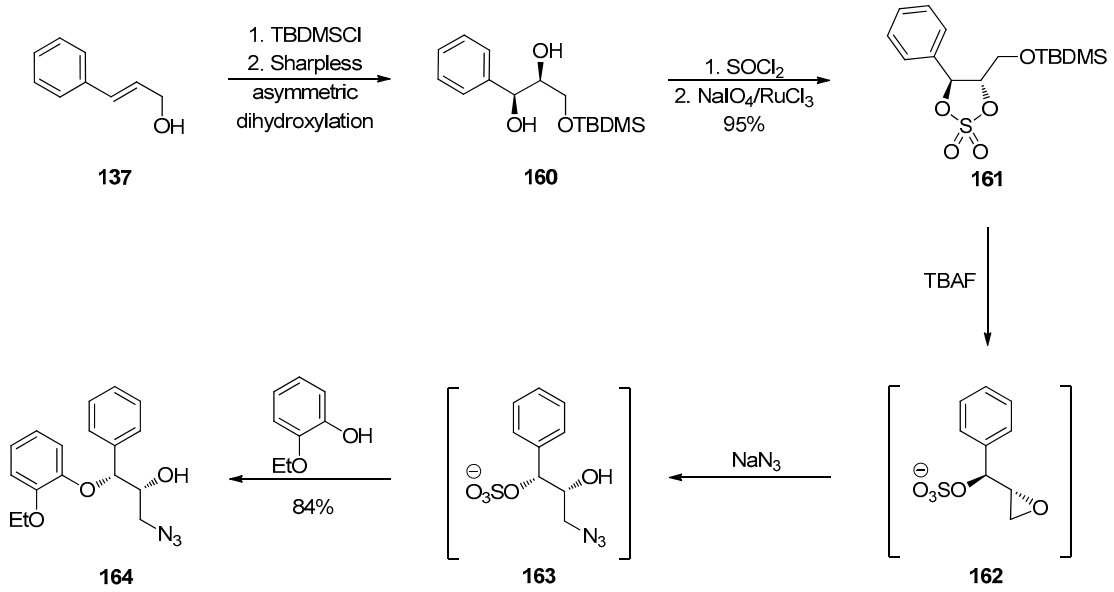
Although a number of syntheses have been reported for racemic and enantiopure reboxetine and derivatives, including several of questionable merit [130], there are two efforts that also employ the early installation of the phenol and proceed through epoxide intermediates and deserve to be mentioned.

Aparicio et al. reported an asymmetric synthesis of reboxetine based on a chiral auxiliary approach to facilitate a diastereoselective Darzens/Corey−Chaykovsky reaction (Scheme 44) using chiral amido sulfonium salt **156** [158]. The corresponding ylide was reacted with benzaldehyde and generated the two diastereomeric epoxides (only the desired one is shown, **157**) in dr 73:27. These were inseparable, so they were progressed into the epoxide ring-opening reaction with 2-ethoxyphenol which, as expected occurred at the benzylic position with inversion of configuration. This time the diastereomeric hydroxy amides were separable by chromatography and the desired one **158** was isolated as a crystalline solid. Optimization of the amide reduction step followed by the three-step process (via the morpholinone) for morpholine formation and hydrogenolysis of the chiral auxiliary provided enantiopure reboxetine.



Scheme 44. Aparicio's approach to esreboxetine using a diastereoselective Darzens reaction.

Another innovative and efficient approach has been reported by Yu and Ko who applied the Sharpless' asymmetric dihydroxylation reaction on protected cinnamyl alcohol **137** generating the *cis*-diol **160** (Scheme 45). Formation of the cyclic sulfate **161** followed by TBAF treatment reveals the terminal alkoxide which ring opens intramolecularly the cyclic sulfate with inversion of configuration at the adjacent carbon forming epoxy sulfate **162**. Azide addition at this point ring opens the newly formed epoxide generating intermediate **163** in which the benzylic alcohol is in an activated form ready for displacement. The latter is realized by the addition of 2-ethoxyphenol which affords key intermediate **164** whose conversion to esreboxetine is straight forward. Optimization of these steps led to an impressive one-pot telescoped process from **161** to **164** in 84% yield.



Scheme 45. Yu and Ko's approach to esreboxetine using Sharpless' asymmetric dihydroxylation.

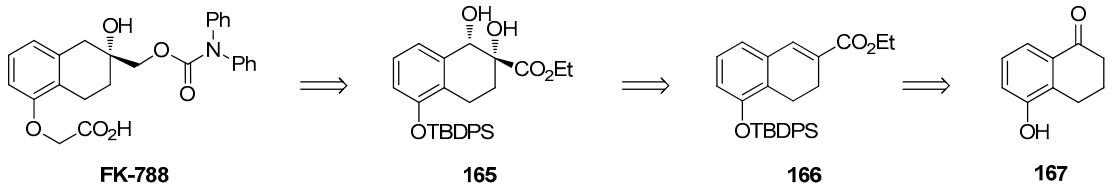
Both of the syntheses described above required chromatographic purifications nevertheless, they were conducted in gram scale and represent inspiring epoxide-mediated synthesis of reboxetine who are novel and aligned with the Pfizer strategy therefore rank highest among academic routes.

1.14. FK-788—Replacement of an Asymmetric Synthesis by a Resolution Process with Recycling of the Undesired Enantiomer; the Meinwald Rearrangement on Scale

Prostaglandin I_2 (PGI_2 p), commonly known as prostacyclin, is a lipid product of arachidonic acid metabolism and is generated in greatest abundance by vascular tissues primarily by COX1 [159,160]. It is arguably the most potent endogenous vasodilator and exerts its signaling through the IP receptor, a GPCR. Although primarily recognized for protection against vascular remodeling and platelet formation, PGI_2 has been found to regulate both the innate and adaptive immune systems and this has been aimed mainly at anti-inflammatory or immunosuppressive applications [161]. More recently, prostacyclin was directly linked with obesity treatment [162] and inhibition of lung tumor progression [163].

Prostaglandin I_2 (PGI_2) has been approved as a medicine under the name of epoprostenol, but its short half-life (42 s) has prompted intense research for more appropriate alternatives which has produced the synthetic analogs iloprost and treprostinil [164]. Improved selectivity among prostaglandin receptors and desirable pharmacokinetic profile continue to be at the heart of research for novel IP agonists.

FK-788 (Scheme 46) is a prostacyclin structurally unrelated IP agonist with significant potency, selectivity, solubility and bioavailability that was discovered by Fujisawa (legacy company of Astellas Pharma) [165]. In the medicinal chemistry route (Scheme 46), the chiral center was introduced at intermediate **165** by an asymmetric dihydroxylation at the unsaturated ester **166**. Besides the toxicity of osmium and cyanide reagents involved in this step, persistent impurities formed both in the downstream chemistry and in the reactions leading to **166** from **167**, forced Astellas chemists to develop an alternative route to FK-788 that could be used for large-scale deliveries.

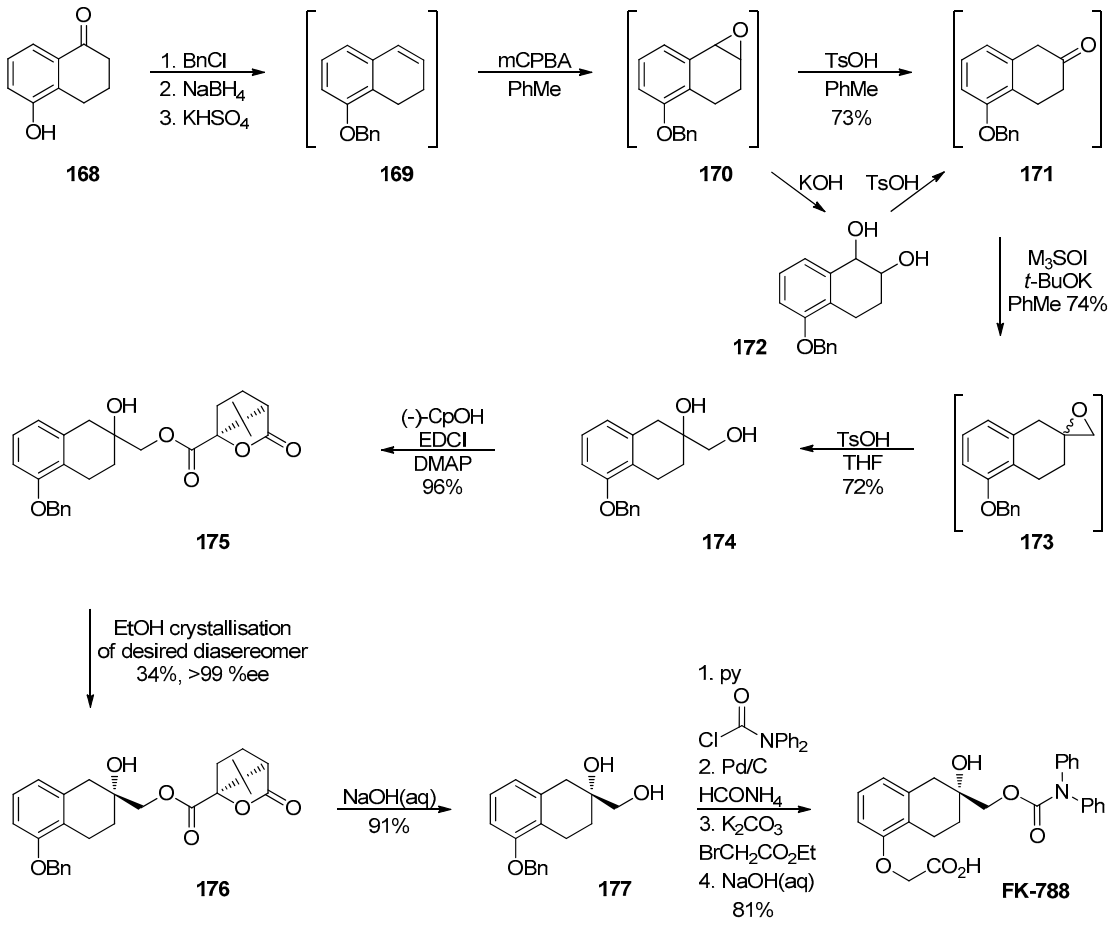


Scheme 46. Retrosynthetic analysis of **FK-788**.

Initial attempts aimed at alternative asymmetric syntheses, for example using the Jacobsen–Katsuki asymmetric epoxidation on appropriate substrates, had limited success. In the end it was envisaged that the racemic key intermediate, diol **174**, could be accessed relatively easily and that a diastereomeric resolution of this would enable the provision of FK-788 in enantiomerically pure form [166]. Astellas' process team initially developed and scaled up a process capable of converting 1-tetralone **168** to 2-tetralone **169**.

Accordingly, **168** was protected, reduced and dehydrated to furnish intermediate **153** (Scheme 47). Epoxidation of this to **170** followed by TsOH-catalyzed Meinwald rearrangement gave 2-tetralone **171**. It must be noted that the latter transformation was attempted by hydroxide-ring opening of the epoxide **170** to diol **171** followed by dehydration of the benzylic alcohol towards the enol tautomer of **172** (Scheme 47). The yield of **171** by this sequence however did not exceed 48% even after stringent optimization. In contrast screening of several acids for the Meinwald rearrangement produced several good yielding hits with TsOH being the best (73%). Interestingly, the Corey−Chaykovsky epoxidation of **171** with trimethyl sulfonium iodide did not work, but did so, with the sulfoxonium analog which provided epoxide **173** in 74% yield. Acid-catalyzed ring opening of epoxide **173** in aqueous THF furnished racemic diol **174**. This ring opening was also attempted under alkaline conditions which

needed to be harsh and gave **174** in reduced yield (58%). Again, among several acids TsOH proved the best in catalyzing the ring opening of **173** to **174**. Several chiral acids were screened for the derivatization of **174** into diastereomeric esters yet only (-)-camphanate esters **175** proved crystalline. Double recrystallization of diastereomeric esters **175** from ethanol provided enantiopure camphanate ester **176** in 34% yield and in >99% ee. Hydrolysis of the chiral auxiliary (and recycling thereof) generated the key intermediate, chiral diol **176** which was converted to FK-788 using established conditions (Scheme 47). It is worth noting that the Astellas team managed to develop an impressive telescoped process for converting **168** to **174**, spanning 7 chemical steps which was run at 25 kg scale producing 11 kg (25%) of **174** as the only isolable intermediate in the entire sequence. The resolution and subsequent steps towards FK-788 were performed successfully at 10–15 kg scale.

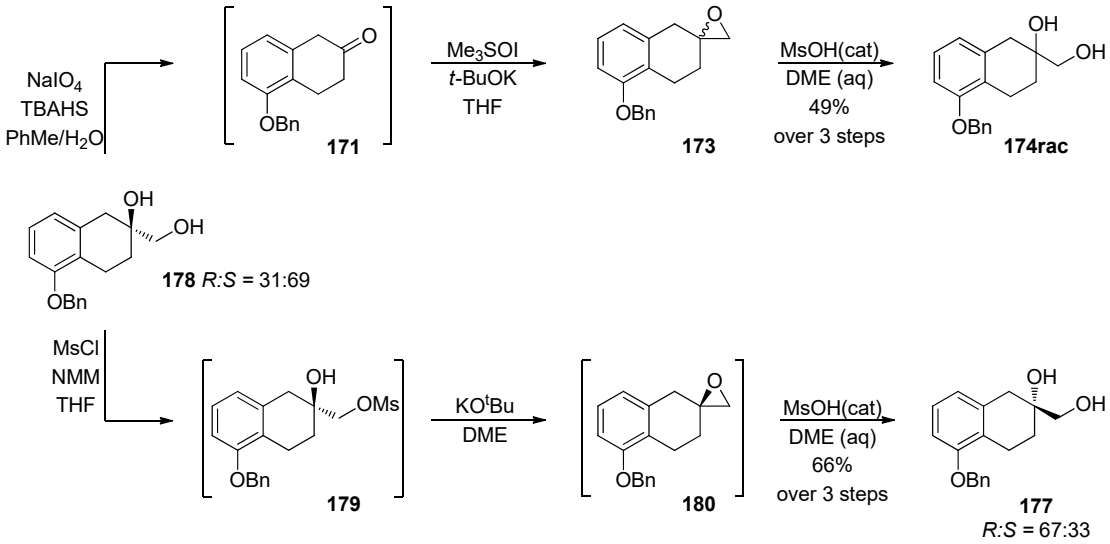


Scheme 47. Astellas' process route to **FK-788** via resolution of diol **174**.

Obviously, the maximum achievable yield for standard resolution processes cannot exceed 50% unless the undesired isomer could be somehow transformed in the desire one. The Astellas team decided to explore this scenario by isolating the remaining **175** present in the liquors of **176** and recovered 52% of this that was found to be enriched in the unwanted diastereomer in dr 31:69. Hydrolysis of this gave **178** in er 31:69 (Scheme 48, only major isomer is shown). Two strategies were investigated in recycling the *S*-enantiomer of the diol into the desired *R*.

The first (Scheme 48 upper) involved periodate cleavage of the diol back into the 2-tetralone **155** which was subjected to the same Corey–Chaykovsky epoxidation and acid catalyzed ring opening of **173** to furnish the same racemic diol **174** as in the mainstream synthesis. The overall yield for this three-step sequence was 49%, namely 25% from the recovered esters, which meant that applying the same resolution with camphanic acid (34%) would give an additional 8.5% of the desired *R*-diol **177**. Alternatively (Scheme 48 lower) mesylation of the primary alcohol in **178** followed by based-induced

ring closure of **179** to epoxide **180** and acid-catalyzed ring opening gave diol **177** enriched in the desired *R*-enantiomer (er 2:1) in 66% yield (33% from the recovered esters). Resolution of the scalemic diol mixture via the camphanate esters furnished the enantiopure diol **177** in 11.2% from the recycling process thus in 44% overall.



Scheme 48. Recycling of unwanted diol enantiomer **178** into scalemic diol **177**.

It is worth noticing that the acid-catalyzed ring opening of **180** to **177** (Scheme 48 lower) proceeds with water attack on tertiary carbon on which more positive charge is built when the epoxide oxygen is protonated and the tertiary C–O bond is weekend thus facilitating the ring opening with inversion of configuration at that stereogenic center. This stereochemical/ mechanistic information is lost in the reaction with the racemic counterpart (**172** to **174** in Schemes 47 and 48 upper) since the racemic epoxide gives racemic diol irrespective of which epoxide end is attacked.

1.15. A Lead Candidate for Asthma—Improved Synthesis via a Decarboxylative Rearrangement of an α-Carboxyl Epoxide

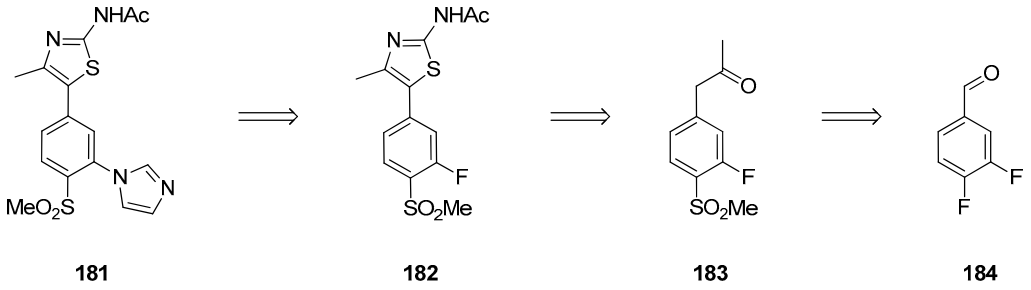
Asthma is a lifelong respiratory disease which is characterized by a huge variety of symptoms, especially concerning the lungs. As there is no treatment for asthma, it is a great challenge for the pharmaceutical companies to find APIs capable of lifelong management of the disease.

One of Novartis' recent entries in this area was the lead compound **181**, a triaryl thiazole [167]. The original medicinal chemistry route followed the retrosynthetic analysis shown in Scheme 49 where the imidazole ring was introduced last by S_NAr on thiazole intermediate **182** which in turn was constructed after α-bromination of the ketone **183** and condensation with N-acetyl thiourea. Ketone **183** was synthesized from nitroethane condensation on aldehyde **184** followed by reduction of the nitro group. In addition to chromatographic purifications and low yields, these steps were hampered by serious process safety concerns that ultimately rendered this reaction sequence unsuitable for large-scale preparations of **181**.

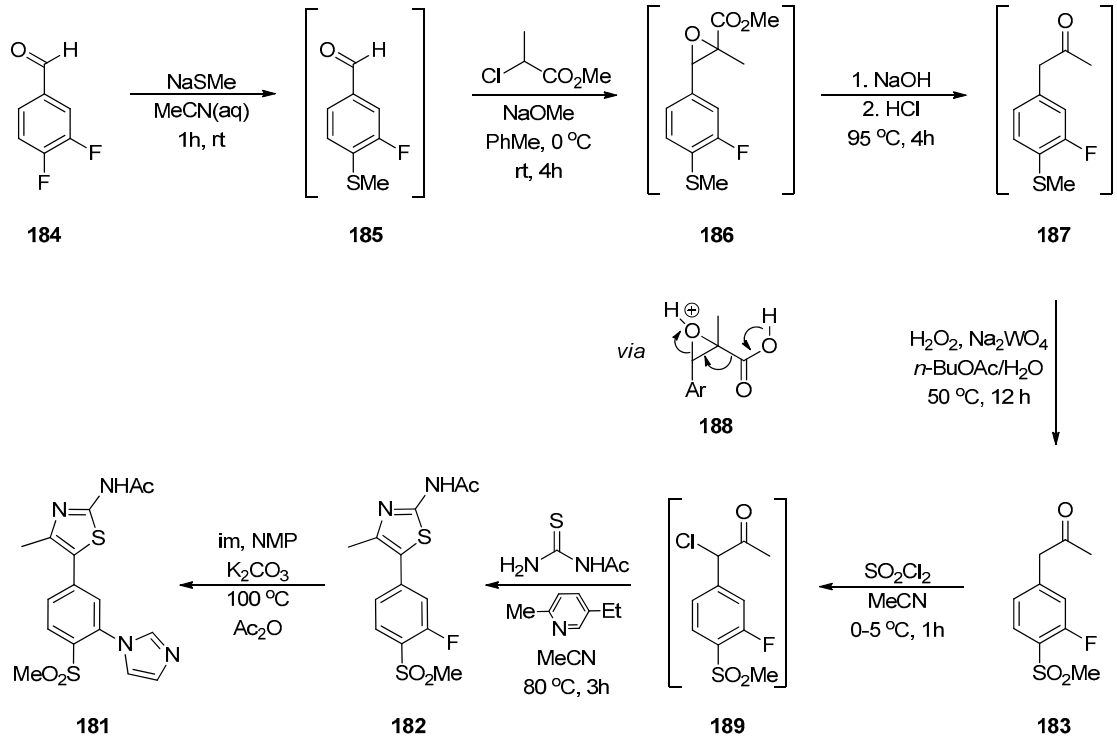
The process group at Novartis decided to develop a synthesis that would involve the same starting materials (registered and raw) and the same end game transformations. This shifted the focus on an alternative synthesis of **183** from **184** that would not succumb to safety and purification issues.

Reaction of aldehyde **184** with sodium thiomethoxide generated substituted aldehyde **185** which was subjected to a Darzens condensation with α-chloro methyl propionate to generate initially epoxide **186** (Scheme 50). Hydrolysis of the ester followed by heating in acidic conditions drove the decarboxylative rearrangement to ketone **187** presumably via transition state **188**. Oxidation of the thiomethyl substituent to the corresponding sulfone was achieved by tungstate catalysis as reported

by Noyori [168]. Impressively, the conversion of **184** to **183** was developed as telescoped process encompassing five chemical steps performed on 100 g scale delivering 73% of **183** 99.5% pure.



Scheme 49. Retrosynthesis of clinical candidate **181** into pivotal ketone **183** and its precursor **184**.



Scheme 50. Large-scale synthesis of clinical candidate **181** via a decarboxylative Darzens reaction.

It is worth pointing out that this two-step construction of the sulfone was much more efficient and cost-effective than introducing it in one step by means of S_NAr on **185** with sodium methanesulfinate. Furthermore, the Noyori oxidation could be performed on aldehyde **185**, but for reasons yet unclear the corresponding 3-fluoro-4-methylsulfone benzaldehyde failed to give the Darzens reaction.

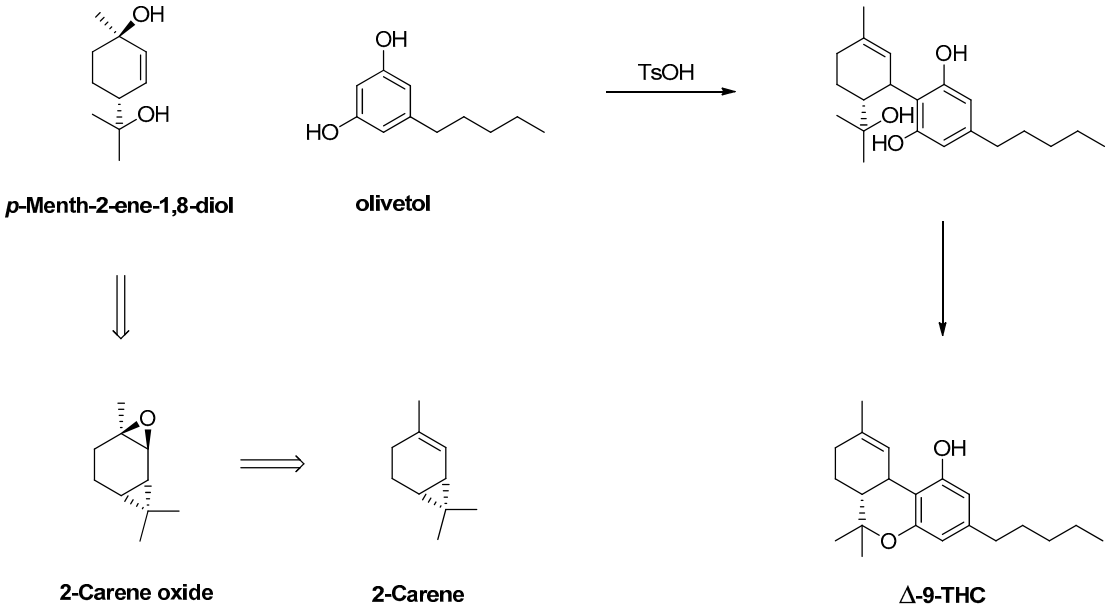
Development and of the α-chlorination of ketone **183** proved a much better choice than its bromination due to significant side product formation with the latter. Formation of chloroketone **189** was telescoped in the thiazole forming step (Scheme 50) where some degree of N-deacetylation proved unavoidable hence the treatment with acetic anhydride after the installation of the imidazole substituent in the last step.

Overall, an innovative solution to the safety, efficiency and purity issues in accessing key intermediate **183** was developed by a decarboxylative rearrangement of an epoxide generated by a Darzens reaction. This further demonstrates the versatility and rich chemistry of epoxides in robust, large-scale synthesis of pharmaceuticals.

1.16. Δ-9-Tetrahydrocannabinol—From 3-Carene to 2-Carene Oxide and Δ-9-THC in Large Scale

(-)-*trans*-Δ-9-tetrahydrocannabinol (Δ-9-THC) is the primary psychoactive compound among the 113 cannabinoids found in the female marijuana plant and is a partial agonist of the CB1 receptor. In its medicinal form is known as dronabinol and is FDA approved under the trade names of Marinol (gelatin capsules) and Syndros (oral solution) for the treatment of HIV/AIDS-induced anorexia and chemotherapy-induced nausea and vomiting. Its 1:1 mixture with cannabidiol, known as nabiximols (trade name Sativex), is approved in Europe for treating spasticity associated with multiple sclerosis [169]. United States federal law currently registers dronabinol as a Schedule III controlled substance, but all other cannabinoids remain Schedule I under the Single Convention on Narcotic Drugs., except synthetics like nabilone. Current research is focusing on expanding the medicinal applications of (-)-*trans*-Δ-9-THC and synthetic analogs to treating body weight disorders, neuropathic and cancer associated pain, but negating potential psychotropic and tolerance effects [170–172].

Current and projected requirements for (-)-*trans*-Δ-9-THC warrant a robust scalable process for its production which is primarily based on the Friedel–Crafts alkylation/cyclisation between olivetol and *p*-menth-2-ene-1,8-diol which in turn is accessed from 2-carene oxide (Scheme 51) [173–175].

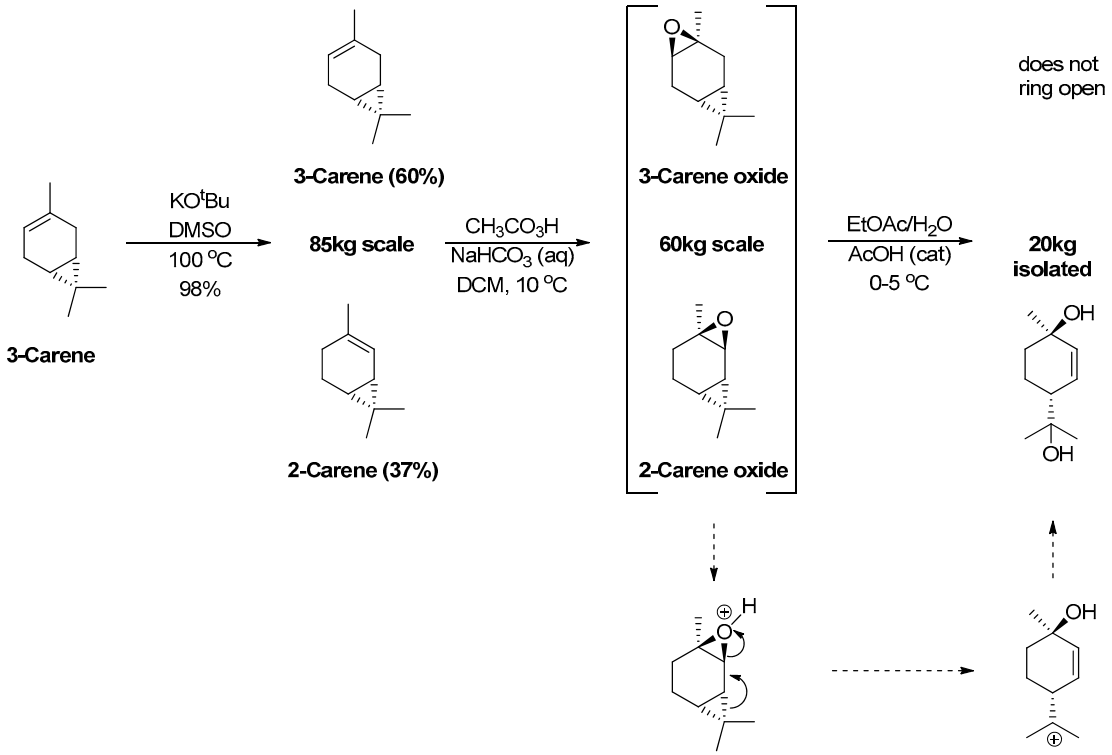


Scheme 51. Synthesis of Δ-9-THC from *p*-menth-2-ene-1,8-diol and its retrosynthesis to 2-carene.

As this process evolved over the years there have been two lingering issues that undermined its efficacy and cost-effectiveness. The first is associated with the starting material 2-carene (Scheme 51) which is relatively expensive. The second issue is related with the isolation and purification of *p*-menth-2-ene-1,8-diol from the other terpenoid products of the process often requiring chromatography and/or extensive extractions and evaporation of its solutions to dryness.

Process chemists from Cedarburg Pharmaceuticals (legacy company of Albany Molecular Research, Inc., AMRI) focused on solving these issues by assessing other starting materials and ways to crystallize *p*-menth-2-ene-1,8-diol directly as it was produced [176]. In contrast to 2-carene, 3-carene is relatively cheap and available in bulk. 3-Carene is equilibrated to 2-carene when heated with base at high temperature resulting in approximately a 60/40 mixture of the 3/2-carene isomers (Scheme 52). This was conducted at 85 kg scale and the mixture of isomers after separation from the aqueous phase was distilled thus providing quick access to technical grade 2-carene. Following a screening of reagents for the epoxidation of the 3/2-carene isomers, peracetic acid emerged as the optimum oxidant for this transformation. The epoxidation reaction was carried out in 60 kg scale and after work up, the solution of the carene oxides was subjected directly to acid-catalyzed ring opening. Under mildly

acidic conditions only 2-carene oxide ring opens via participation of the cyclopropane ring which also ring opens itself to support the built up of positive charge at the adjacent carbon of the protonated epoxide (Scheme 52). This neighboring group assistance by the cyclopropane moiety cannot take place with the remotely positioned epoxide in 3-carene oxide which survives intact under these conditions. Screening of antisolvents at this stage of the process identified heptane as the optimum choice enabling crystallization of *p*-menth-2-ene-1,8-diol directly from the reaction mixture while retaining the more soluble 3/2-carene oxides.



Scheme 52. Process route to *p*-menth-2-ene-1,8-diol from 2-carene via epoxidation/rearrangement.

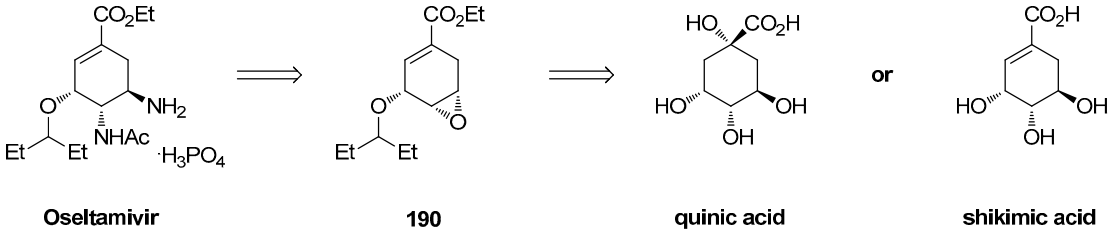
In this way a much-improved process for the large-scale synthesis of *p*-menth-2-ene-1,8-diol, a key intermediate in the synthesis of Δ-9-THC, was accomplished based on manipulation of inexpensive feedstock and a selective epoxide rearrangement.

1.17. Oseltamivir—Development of Three Manufacturing Routes via the Same Key Epoxide Intermediate

Oseltamivir phosphate (trade name Tamiflu) is an antiviral drug indicated for the treatment of influenza A and influenza B. It was discovered at Gilead Sciences, but was licensed to Roche for clinical development, approval and marketing. GlaxoSmithKline's zanamivir (Relenza) (discovered by the Australian company Biota) was the first neuraminidase inhibitor to be FDA approved (1999), followed by oseltamivir later in the same year. Oseltamivir however was the first orally active product (zanamivir is inhaled) hence it became more popular. Over the years, in addition to the Roche processes, there have been dozens of oseltamivir syntheses published by prominent academic research groups [177] that have expanded the synthetic creativity in organic chemistry and continue to inspire the next generation of chemists. Nevertheless, a comparison of all major syntheses published up to 2008 demonstrated that the Roche routes are superior with respect to length, complexity and across a number of green chemistry and efficiency parameters [178]; the most efficient academic route up to that point was the latest from the Fang group [179].

A number of other routes have been published since then [180–187] yet the Roche shikimic acid-based manufacturing process remains the most viable and proficient to date.

Consequently, the following discussion concentrates on the Roche manufacturing route to the key epoxide intermediate **190** (Scheme 53) and the subsequent ring-opening step by amine nucleophiles.



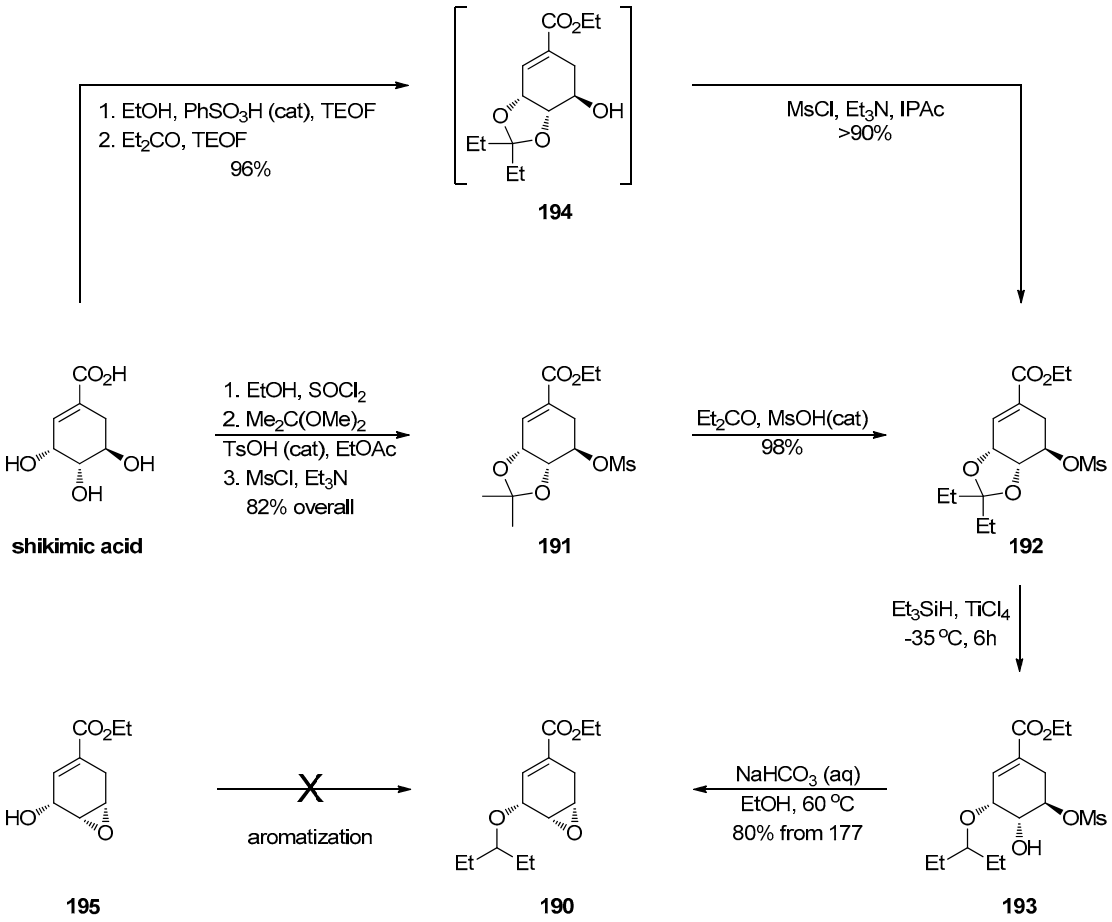
Scheme 53. Retrosynthesis of oseltamivir into quinic and shikimic acid.

Both quinic and shikimic acid provide an appropriately functionalized carbocyclic framework and were used to deliver oseltamivir on 100 kg scale. Quinic acid however requires an additional series of dehydration steps to generate the double bond which is already present in the shikimic acid. Despite intense optimization efforts, the dehydration-associated steps have not been particularly straight forward or high yielding hence shikimic acid emerged as the ideal starting material [188]. Gilead's original preference for the quinic acid route [189] was based on the limited supply of shikimic acid at that time. During Roche's development efforts shikimic acid became available in multi-hundred-ton quantities by extraction of star anis and by a fermentation process using a genetically engineered *E. coli* strain [190].

Shikimic acid esterification, acetonide protection and mesylation were telescoped to provide mesylate **191** in 82% yield after recrystallization (Scheme 54). Acid catalyzed transketalization with excess 3-pentanone gave new mesylate **192** almost quantitatively. The regioselective reductive ring opening of the ketal required extensive optimization since the original Gilead conditions involving $BH_3{\cdot}Me_2S$ and TMSOTf (trimethylsilyl trifluoromethanesulfonate) were not attractive for manufacturing (safety, cost and availability). A thorough screening was undertaken to identify suitable Lewis acids to facilitate the ring opening of the acetal to the corresponding oxenium cation and compatible reducing agents to reduce the latter to the desired hydroxy ether **193**. The combination of TES (triethyl silane) and $TiCl_4$ proved a viable option as it worked well provided the reaction temperature was kept between −32 to −36 °C (no reaction at lower temperatures and significant deprotection to the diol at higher temperatures). After work up of this stage the solution of **193** was treated directly with base which induced the ring closure of the hydroxy mesylate to the desired epoxide **190** in 80% for the latter two steps and 64% overall from shikimic acid. The direct ketal formation of shikimic acid ethyl ester with 2-pentanone would save one step from the synthesis (the transketalization of the acetonide intermediate) and naturally this was also investigated. In contrast to the hydroxy- and mesyl-acetonide intermediates which are crystalline and allow for upgrade of their purity by recrystallization, the pentylideneketal analog derivatives are oils and had to be progressed impure downstream with significant yield penalty in downstream purification. Nevertheless, an improvement of the direct pentylideneketal process was reported by Roche that enables pure **194** to be generated and progressed without isolation in the formation of **192** [191].

Interestingly the strategy to pursue the installation of the 2-pentyl ether in **190** via the reductive ring opening of the pentylideneketal ketal **192** was enforced by the failure of the corresponding epoxy alcohol **195** to undergo alkylation with 2-pentyl iodide. All attempts led to aromatized products presumably via base-induced epoxide isomerization/ring opening to the corresponding allylic alcohol followed by dehydration.

This undesired aromatization process was frequently encountered in subsequent reactions of **190** with various amines/nitrogenous nucleophiles and posed a significant issue in the progression of the synthesis via the ring opening of the epoxide.

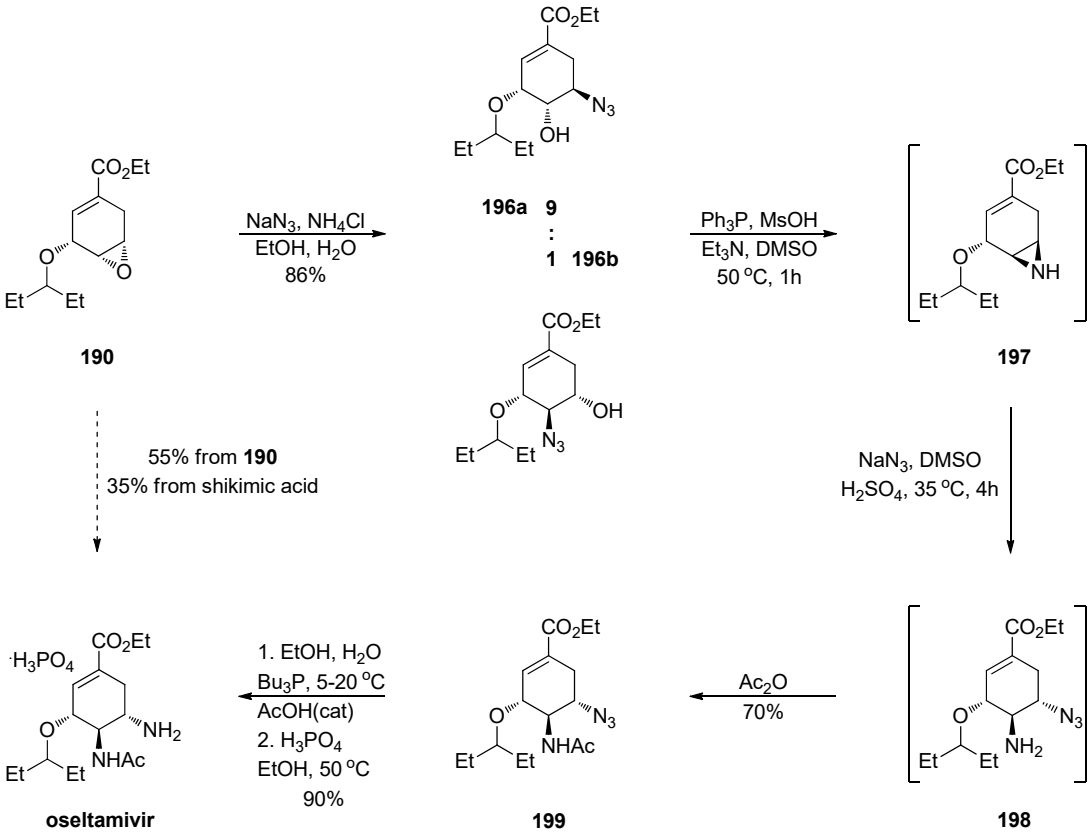


Scheme 54. Process development of an efficient route to key epoxide intermediate **190**.

In the original Gilead synthesis this was achieved with sodium azide producing a 9:1 mixture of the corresponding azido alcohols **195a/b** although this selectivity is inconsequential as both isomers, upon treatment with trimethyl phosphine, convert to the same aziridine **197** (Scheme 55). Aziridine ring opening again with azide attack, followed by acetylation, azide reduction with Raney Ni and addition of phosphoric acid, gave oseltamivir. This part of the process delivered successfully multiple kilograms of the drug substance, but the azide chemistry raised concerns for long term manufacturing. Pressed by competition from GlaxoSmithKline who at that time were slightly ahead with the development of zanamivir, a decision was made to render the azide route fit for manufacturing and registration rather than initiate the development of an azide-free route as this could take much longer and would be probably best to investigate it later. Working together with process safety and azide chemistry experts the Roche team quickly determined operating windows that ensured safety and precluded decomposition of the azide intermediates and consequently yield losses. This, combined with other improvements in this latter part of the synthesis, precipitated the manufacturing route to oseltamivir (Scheme 55) [192].

In particular, the ring opening of the epoxide **190** to **196a/b** required excess azide to drive the reaction to completion and avoid aromatization of the substrate; for safety reasons this was conducted at less than 70 °C. The hazardous trimethyl phosphine was replaced with the less reactive yet safer triphenyl analog which assisted by MsOH facilitated the Staudinger reduction of the azide and subsequent formation of aziridine **197**; for safety reasons this was conducted at less than 50 °C. Aziridine formation was coupled with aziridine ring opening by azide to generate **198** followed by acetylation of the amine. For safety reasons these steps were conducted at less than 50, 35 and 25 °C, respectively. Thus, acetamido azide **199** was isolated directly after a three-stage telescoped process in DMSO in 70% yield from **196a/b** (Scheme 55). The reduction of azide by hydrogenation and hydride

methods was found to generate several impurities related to double bond reduction and isomerization. Raney Ni was replaced with tributyl phosphine for an extremely selective Staudinger reduction/reaction which was coupled to the final salt forming step with phosphoric acid. This provided oseltamivir in 55% yield from epoxide **190** which translates to 35% overall yield from shikimic acid.

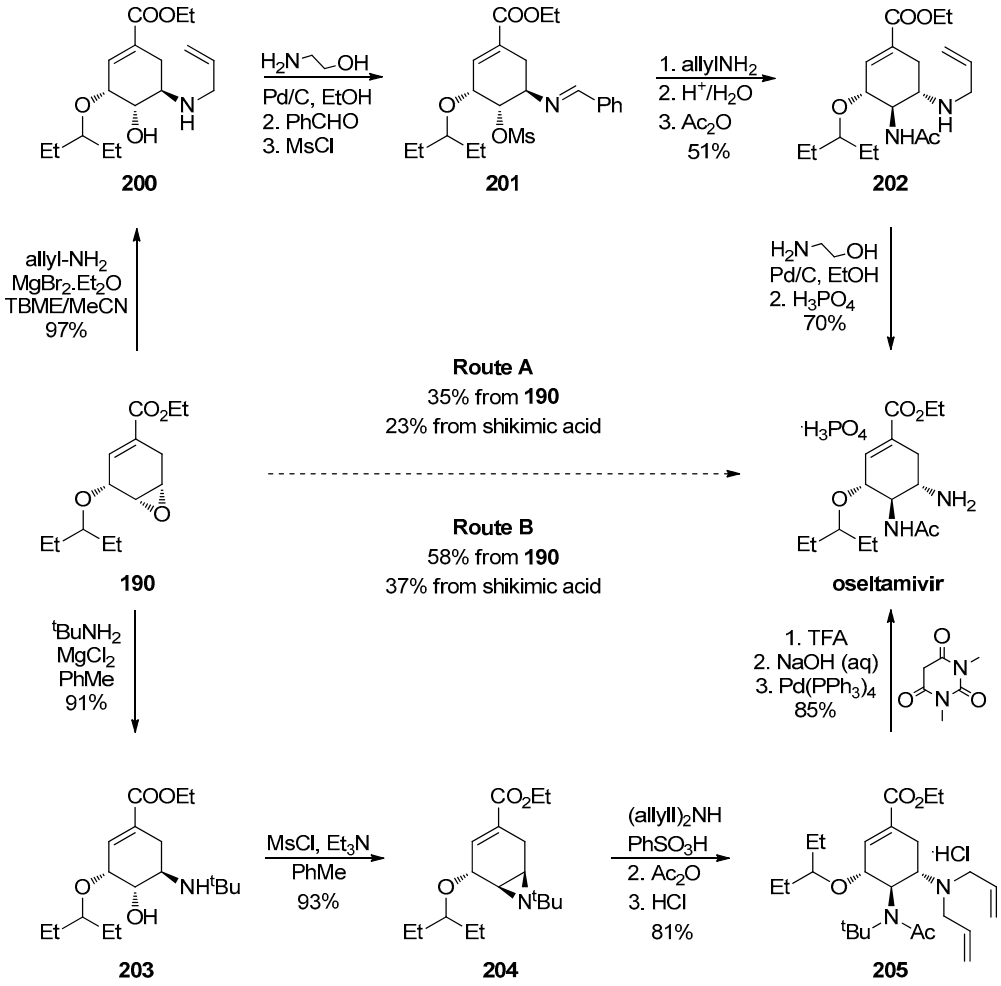


Scheme 55. Roche's manufacturing route to oseltamivir.

Roche followed this with two azide-free processes (Scheme 56). In the first one, a wide screen of appropriate amines/latent ammonia nucleophiles and Lewis acids were screened in order to identify conditions that led to efficient epoxide ring opening with minimum aromatization of **190** [193]. From this, allylamine in the presence of magnesium bromide etherate was demonstrated to provide the amino alcohol **200** in 97% yield (dr 9:1) with only traces aromatization products being formed. Pd-catalyzed de-allylation, followed by protection of the amine as its benzaldehyde imine allowed for clean formation of mesylate **201**. Further treatment with allylamine causes a transimination reaction to occur, freeing up the amino group next to the mesylate. The thus produced amino mesylate, cyclizes to the corresponding aziridine which is further attacked, and ring opened by allylamine with inversion of configuration. Careful adjustment of the apparent pH allows for selective acetylation of the primary amino group while the secondary is deactivated in its protonated form to give the *trans* vicinal diamine intermediate **202**. Despite the complexity of this domino process involving several equilibria, ring closing and opening events, **202** is the only intermediate isolated in relatively good yield. Pd-catalyzed de-allylation followed by phosphate salt formation afforded oseltamivir in 35% yield from **190** (23% from shikimic acid).

Based primarily on the discovery of the efficient Mg(II) promoted ring opening of **190** by amines, a second generation route was developed [194]. In this, allylamine was replaced with *t*-butylamine and the magnesium bromide etherate with the cheaper magnesium chloride. Interestingly the performance of the ring opening was highly dependent on the order of addition with pre-mixing the amine and the catalyst leading to superior yield of **203** whereas premixing the epoxide with magnesium chloride led

to significant amounts of the corresponding chlorohydrin. The bulky group on nitrogen allowed for clean activation of the alcohol as the mesylate which eventually cyclized to aziridine **204**. Ring opening of the latter with bis-allyl-amine followed by acetylation gave after HCl treatment the hydrochloride salt **205**. Pd-catalyzed de-allylation followed by phosphate salt formation afforded oseltamivir in 58% yield from **190** (37% from shikimic acid) which compares favorably with the azide route.



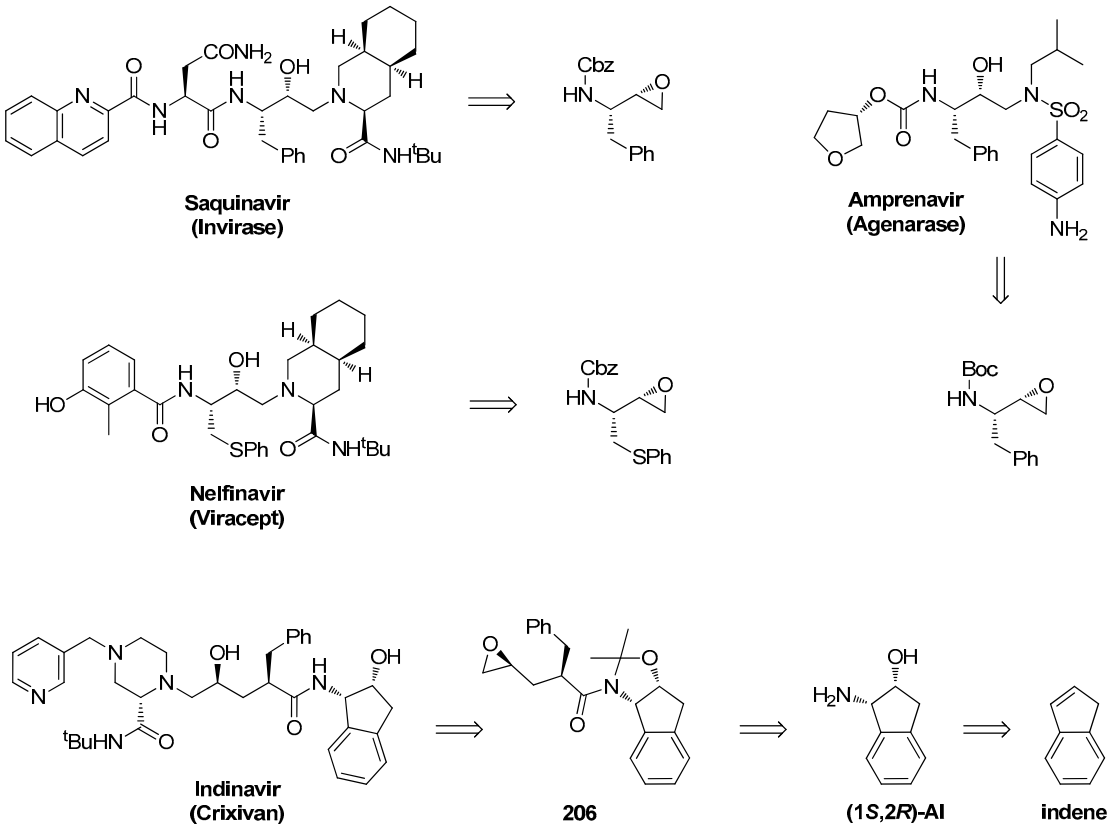
Scheme 56. Roche's second generation manufacturing routes to oseltamivir (azide-free).

Overall, under tremendous pressure for an expedited registration, a remarkable joined effort by process groups at Gilead, Roche and external contractors led to the development of a safe azide-based manufacturing process for the complex molecule of oseltamivir. Innovative navigation through epoxide and aziridine chemistry led to an azide-free, second generation route that also delivers the drug substance at specification and with improved efficiency.

1.18. Indinavir—A Member of Approved HIV Protease Inhibitors Synthesized by Chiral Epoxide Intermediates

Highly active antiretroviral therapy (HAART) is the current standard in HIV treatment and involves combination of drugs targeting different stages of viral infection such as entry, reverse transcription, integration and maturation/release [195]. HAART has revolutionized HIV treatment and increased considerably the life expectancy to the point that is now considered a manageable chronic disease. Key contribution to the combination treatment is provided in the form of a protease inhibitor which is represented in 10 of the approximately 30 approved drugs for HIV [196–198]. Merck's indinavir (trade name Crixivan, Scheme 57) was the third HIV protease inhibitor to be FDA-approved, one year after Roche's saquinavir and Abbott's (now AbbVie) ritonavir; these were followed in quick

succession by nelfinavir (Eli Lilly/Agouron), amprenavir (GlaxoSmithKline/Vertex) and lopinavir (also by Abbott).



Scheme 57. HIV protease inhibitors and their retrosynthesis into key epoxide intermediates.

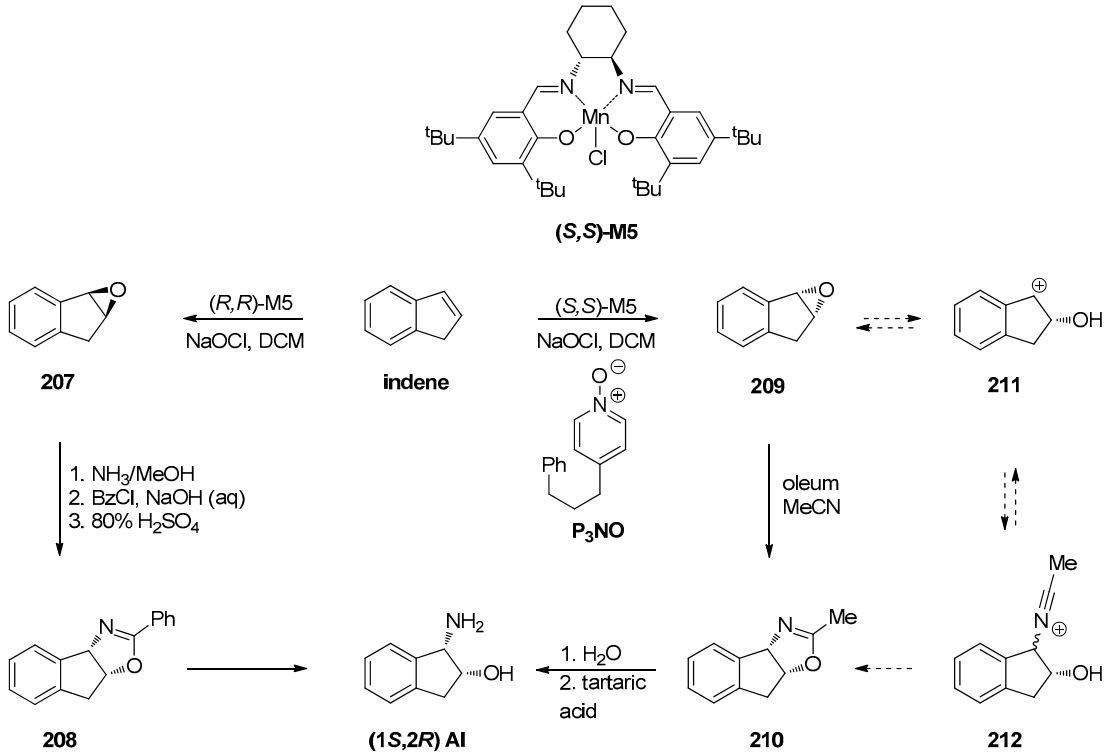
Protease inhibitors aim to halt maturation and release of viral particles by inhibiting certain cleaving events performed by the protease on the viral polyprotein, a process that releases mature, essential viral proteins (p7, 9, 17, 24) and active viral enzymes (protease, reverse-transcriptase and integrase among others).

HIV protease inhibitors have been designed primarily as transition state inhibitors equipped with a non-hydrolysable peptidomimetic isostere. Arguably, the 1,2-aminoalcohol motif has emerged the most successful consequently epoxide intermediates (Scheme 57) have been recruited extensively in the synthesis of this essential domain in HIV protease inhibitors [199].

Indinavir is synthesized via epoxide **206** (Scheme 57) the stereochemistry of which, including that at the amide α-carbon, are induced by the aminoindanol portion which therefore acts as a chiral auxiliary in their generation [200]. *Cis*-aminoindanol **(1*S*,2*R*)-AI** and its enantiomer are key components in several drug molecules, chiral auxiliaries and catalysts and are conveniently accessed by indene [201]. One of the earlier large-scale synthesis of **(1*S*,2*R*)-AI** by Sepracor (Scheme 58, left) involved the catalytic asymmetric epoxidation of indene using **(*R*,*R*)-M5** to give (1*S*,2*S*)-indene oxide **207**. Ring opening by ammonia followed by benzamide formation and exposure to strong acid generates oxazoline **206** which is hydrolyzed to **(1*S*,2*R*)-AI**. Both the ring opening, and the cyclisation step occur with inversion of configuration.

Merck developed an alternative synthesis (Scheme 58, right) that uses (1*R*,2*R*)-indene oxide **209** and proceeds with retention of configuration through oxazoline **210** generated by a Ritter reaction (Scheme 58, right). This transformation probably proceeds through the benzylic cation **211** (formed by protonation of the epoxide or the associated diol) followed by attack of the most competent nucleophile present in the reaction, namely acetonitrile. This can take place at either diastereotopic side of the planar benzylic cation,

but only the *cis* adduct may cyclize to a bicyclic oxazoline with a *cis* ring junction. The instability of the nitrilium intermediate **212** renders its formation reversible and given the inability of the *trans* adduct to cyclize, all reaction is channeled through the cyclisation of the *cis* adduct. It is worth mentioning that in the Merck epoxidation process, P_3NO, 4-(phenylpropyl)pyridine N-oxide (Scheme 58) was found to be a superior external ligand to those employed regularly and at 4 mol%, it supported a robust reaction with reduced catalyst-loading (0.7 mol% (*R*,*R*)-M3, Scheme 58) capable of delivering (1*R*,2*R*)-indene oxide **209** in 90% yield and 88% ee at multikilogram scale. After hydrolysis of oxazoline **210** and recrystallization of **(1*S*,2*R*)-AI** as its tartrate salt, the optical purity is upgraded to >99%.



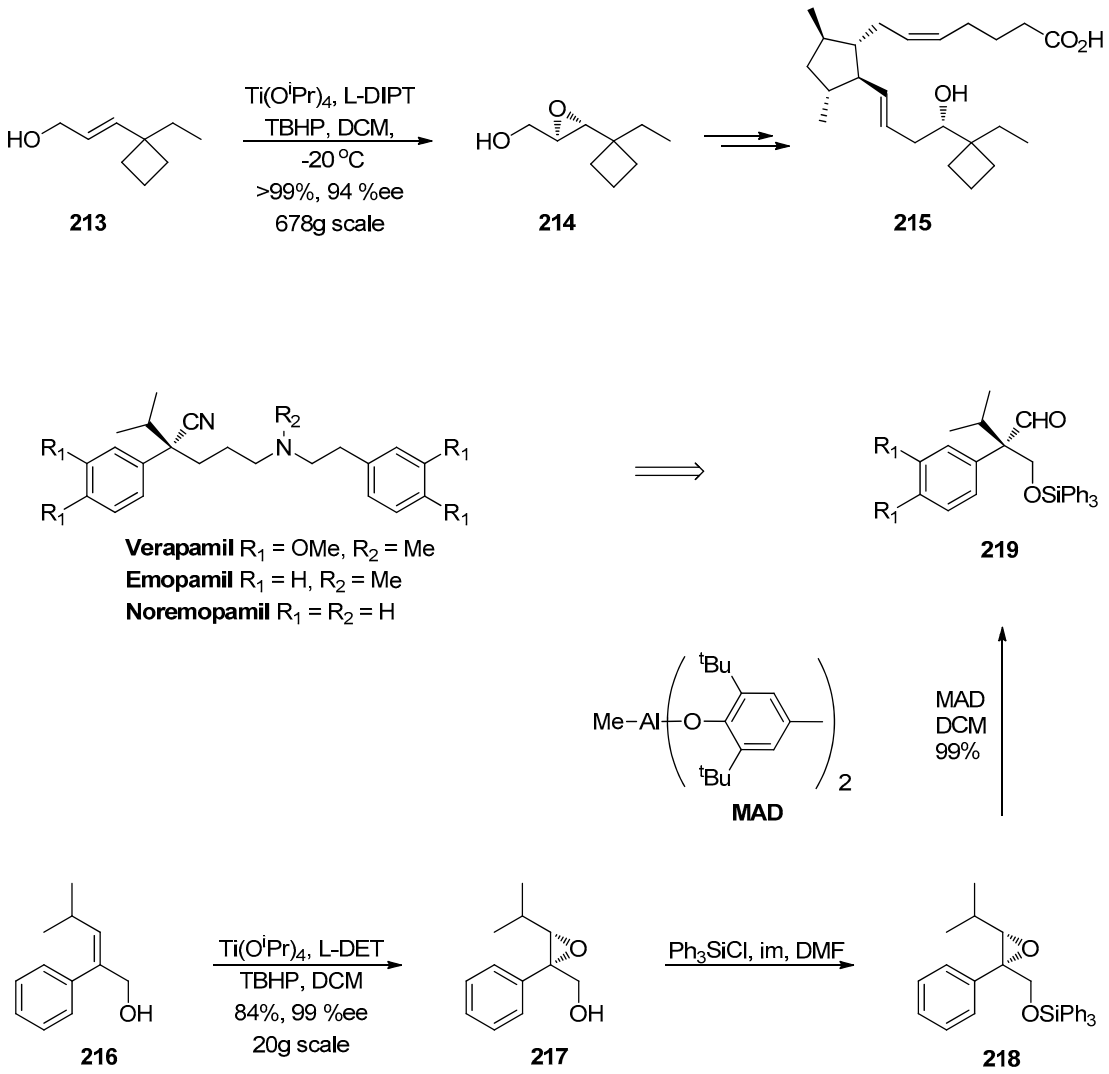
Scheme 58. Syntheses of (1*S*,2*R*)-aminoindanol via Jacobsen–Katsuki asymmetric epoxidation.

1.19. Metal-Catalyzed Asymmetric Epoxidations in Drug Development—Further Examples of the Sharpless and Jacobsen–Katsuki Methodologies

The Sharpless asymmetric epoxidation of allylic alcohols and the Jacobsen–Katsuki salen complexes-catalyzed epoxidation of cyclic and *cis* alkenes have dominated the field of metal catalyzed asymmetric epoxidations employed at various development stages of pharmaceuticals. Examples of these are highlighted below.

Ono Pharmaceutical developed and performed a Sharpless asymmetric epoxidation of allylic alcohol **213** on 678 g scale to access the key chiral epoxide **214** en route to the highly selective EP2 receptor agonist **215** (Scheme 59) [202].

Eisai used the Sharpless method to develop an innovative approach for the chiral tertiary-alkyl nitrile motif present in the calcium channel blockers enopamil, norenopamil and verapamil (Scheme 59) [203]. Accordingly, asymmetric epoxidation of **216** to **217** followed by protection of the alcohol provided the epoxide substrate **218** for the rearrangement to aldehyde **219**. This involved the MAD-catalyzed migration of the isopropyl group onto the benzylic carbon atom with concomitant epoxide ring opening and formation of the aldehyde.

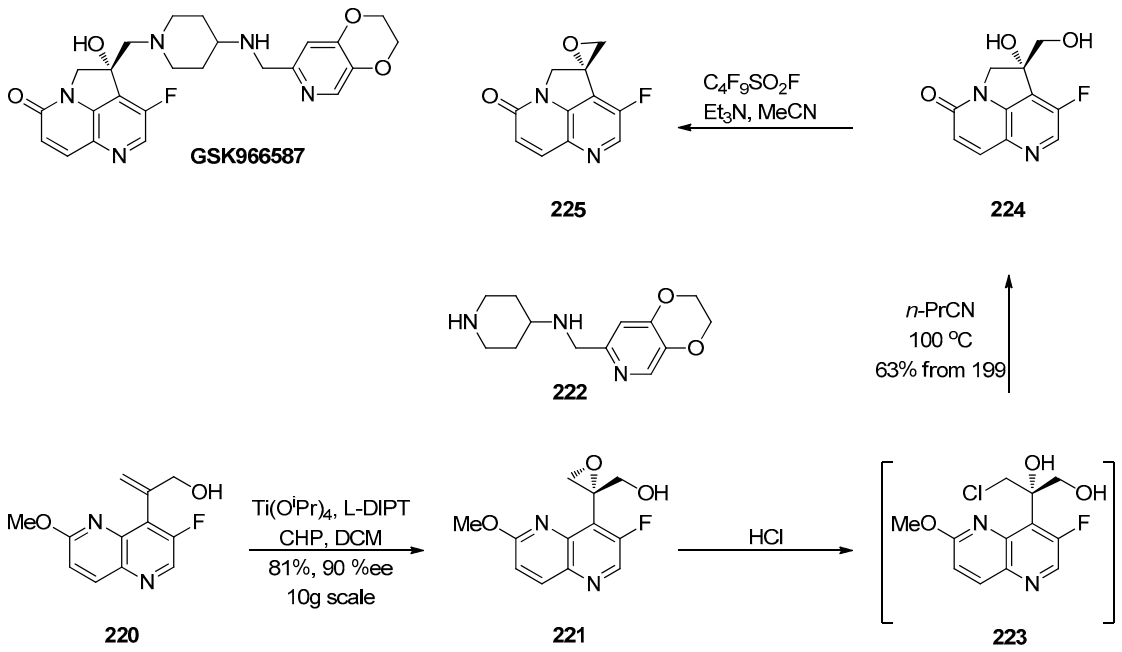


Scheme 59. Application of Sharpless' asymmetric epoxidation to the synthesis of drug candidates.

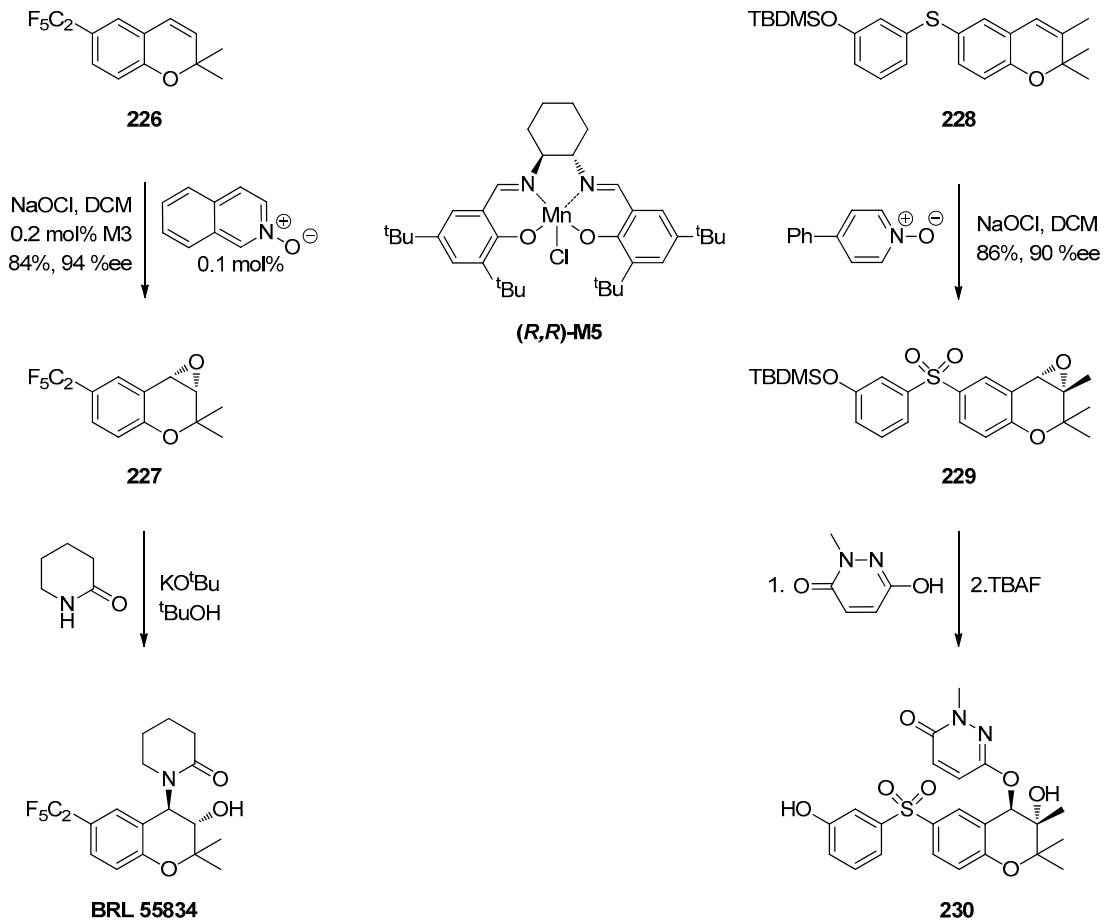
GlaxoSmithKline's effort for a scalable synthesis of GSK966587, an antimicrobial clinical candidate [204], pivoted on the asymmetric epoxidation of allylic alcohol **220** using the Sharpless method which delivered epoxide **221** in 81% yield and 90% ee in 10 g scale (Scheme 60). Under the basic ring-opening conditions of **221** with amine **222**, the undesired intramolecular S_NAr reaction between the primary alcohol and the adjacent aryl fluoride in the product was observed thus an alternative way was sought to install the amine portion. The ring opening of **221** with HCl gave initially chlorohydrin **223** which cyclized thermally under neutral conditions to **224** with concomitant O-demethylation.

Activation of the primary alcohol triggered cyclisation to epoxide **225** which was ultimately opened by amine **222** to furnish GSK966587.

GlaxoSmithKline process group optimized the Jacobsen–Katsuki method for epoxidizing **226** to **227** en route to the potassium channel opener BRL 55834 (Scheme 61, left) [205]. The reaction initially required at least 8 mol% of the Jacobsen salen complex/catalyst ***(R,R)*-M5** in order to complete and produce **227** with high enantioselectivity. Lower catalyst loadings led to erosion of ee and incomplete reaction even after 50 h. This was attributed to catalyst decomposition with active degradants potentially promoting racemic product formation. Examination of several additives known to benefit catalyst stability identified 4-Ph-pyridine N-oxide and isoquinoline N-oxide with the latter allowing the catalyst-loading to be lowered to 0.1 mol% and, in contrast to the former, could be removed by in the aqueous washes. This enabled the synthesis of BRL 55834 in multikilogram scale.



Scheme 60. Synthesis of GSK966587 via two chiral epoxide intermediates.



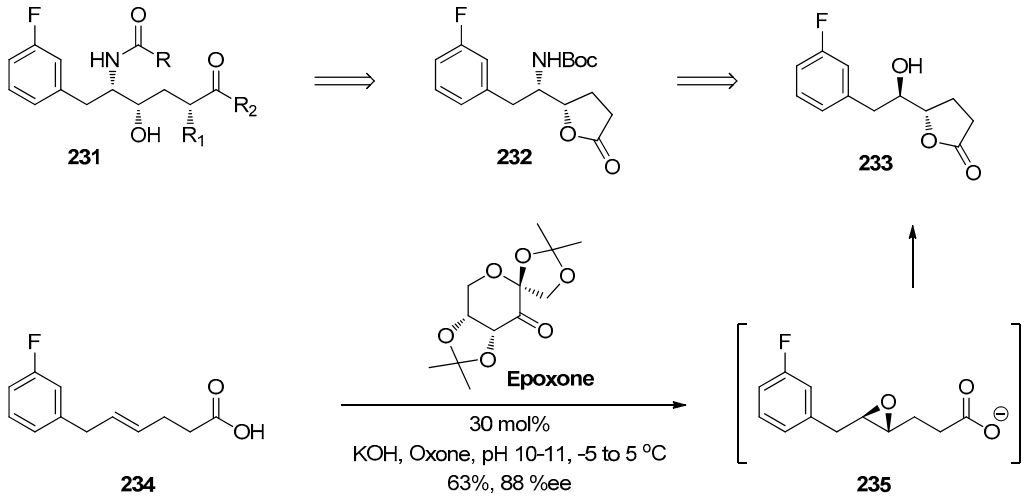
Scheme 61. Application of Jacobsen's asymmetric epoxidation to the synthesis of drug candidates.

Several years later, Pfizer reported the same approach to prepare **229** from **228** en route to a similar potassium channel opener, **230** (Scheme 61, right) [206]. In this case 4-phenyl pyridine N-oxide

proved the optimum external ligand for the epoxidation process which was demonstrated successfully at a scale of 225 g. Under the oxidative conditions the diaryl sulfide in **228** is also transformed to the sulfone.

1.20. Organocatalytic Asymmetric Epoxidation in Drug Development—Chiral Ketones, Iminium Salts and Phase Transfer Catalysts

The advent of organocatalysis has provided additional options in both normal and asymmetric epoxidation where a variety of organocatalytic systems have been developed including ketone/dioxirane, iminium/oxaziridinium salt, polyleucine/H_2O_2 and phase transfer catalysts/inorganic oxidants [137,138,207,208]. Two such systems were discussed in the diltiazem synthesis with Yang's chiral ketone/dioxirane selected as the system of choice for the large-scale process. Among academic efforts Shi's fructose-derived chiral ketone (commonly known as epoxone) has been established as the broadest scope organocatalytic system imparting high enantioselectivities in the epoxidation of various alkene substrates [137,138]. This prompted DSM process chemists to challenge its application in the large-scale synthesis of a key intermediate associated with a scaffold exhibiting significant antiviral activity (**231**, Scheme 62) [209].

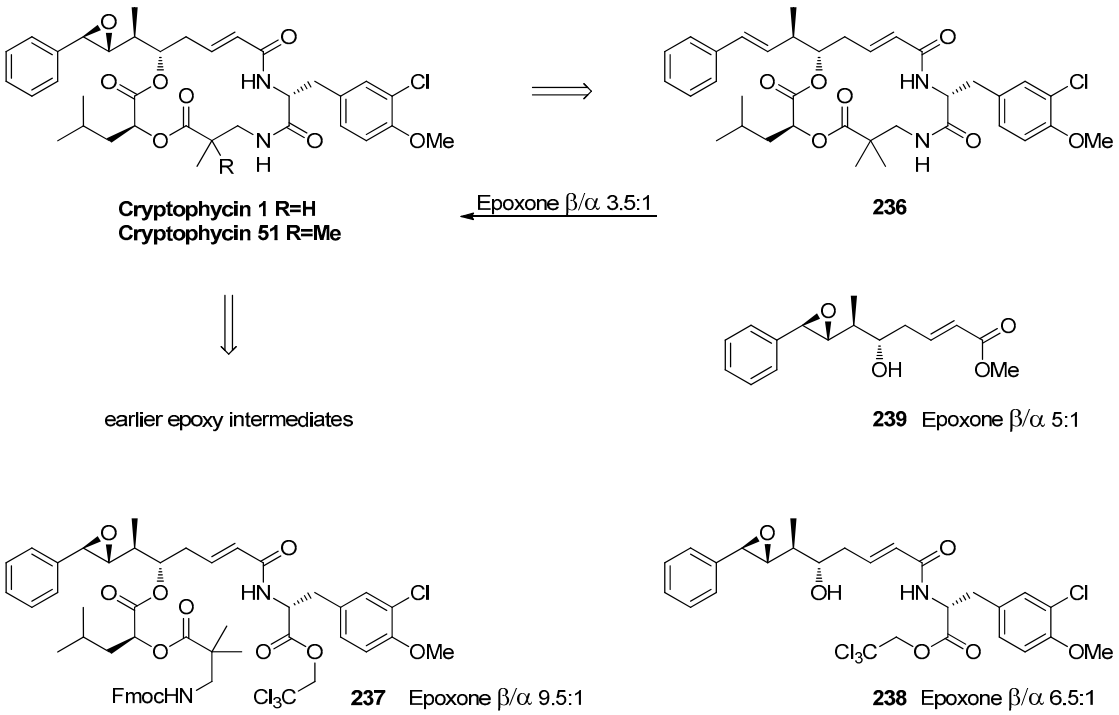


Scheme 62. Development of a large-scale organocatalytic asymmetric epoxidation/lactonization.

It was envisaged that **231** could be accessed from amino lactone **232** which in turn can be derived from hydroxy lactone **233**. The latter was shown to form spontaneously upon epoxidation of unsaturated acid **234** under basic conditions. Having earlier optimized the synthesis of the chiral ketone catalyst, DSM chemists looked into the tandem epoxidation/lactonization process. Oxirane formation from this ketone-catalyst requires a pH range of 10–11, at which the decomposition of catalyst, primarily via a Baeyer-Villiger reaction, becomes competitive hence the high catalyst loadings. The reaction also needs to be run under dilute conditions due to the low solubility of Oxone. After careful optimization of the reaction conditions and mode of reagent addition this process delivered more than 100 kg of **233** over several batches nevertheless issues related to process robustness and reproducibility persisted.

Substrate-controlled epoxidations may be subject to match/mismatched interactions with chiral catalysts/promoters therefore more efficient processes can be designed when a matched case is identified. Epoxone has also been used to install the epoxide functionality in cryptophycin 51, a synthetic analog of the natural product cryptophycin 1 (Scheme 63). Cryptophycin 51 was advanced to Phase I/II clinical studies by Eli Lilly but was terminated due to adverse effects; research on this scaffold continues with analog structures [210,211]. In the effort to support early supplies of the drug substance a battery of epoxidation protocols was tested with the ultimate intermediate **236** and epoxone emerged as the most diastereoselective agent giving a β/α ratio of 3.5:1 (mCPBA, Jacobsen methods 1.9:1) [212]. Eli Lilly

chemists considered investigating a better matched case in the substrate-controlled epoxidations of earlier non-macrocyclic intermediates such as **237**, **238** and **239** (Scheme 63). The former gave the most diastereoselective epoxidation, but low conversions made purification difficult and this option was abandoned. Optimization of **240** epoxidation increased the diastereoselectivity from 5:1 to 6.5:1 with >95% conversion and this was achieved with less epoxone (2 instead of 4 equivalents typically used in this work). Although not a true catalytic process, it enabled an improved synthesis for this complex drug candidate.



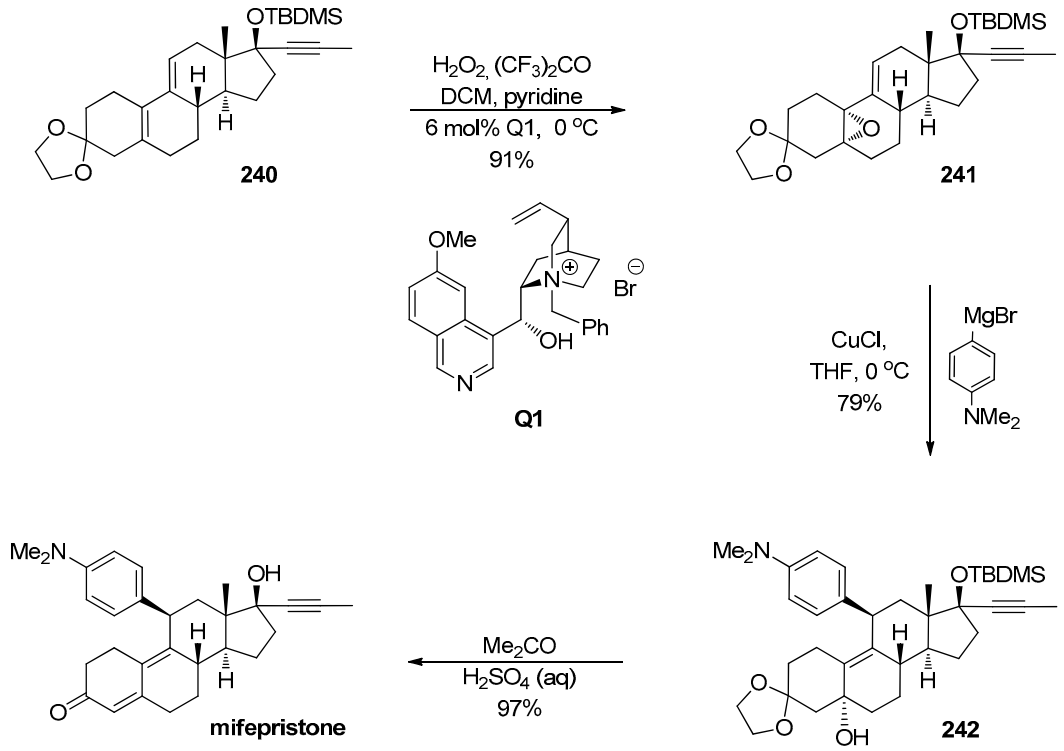
Scheme 63. Application of Shi's chiral ketone (epoxone) to the synthesis of cryptophycin 51.

A similar requirement for enhanced substrate control has been reported by Novartis in the synthesis of epothilone and analogs thereof where epoxone provided the highest diastereoselectivity in the epoxidation of the macrocyclic alkene (8–10:1) in the final step [213].

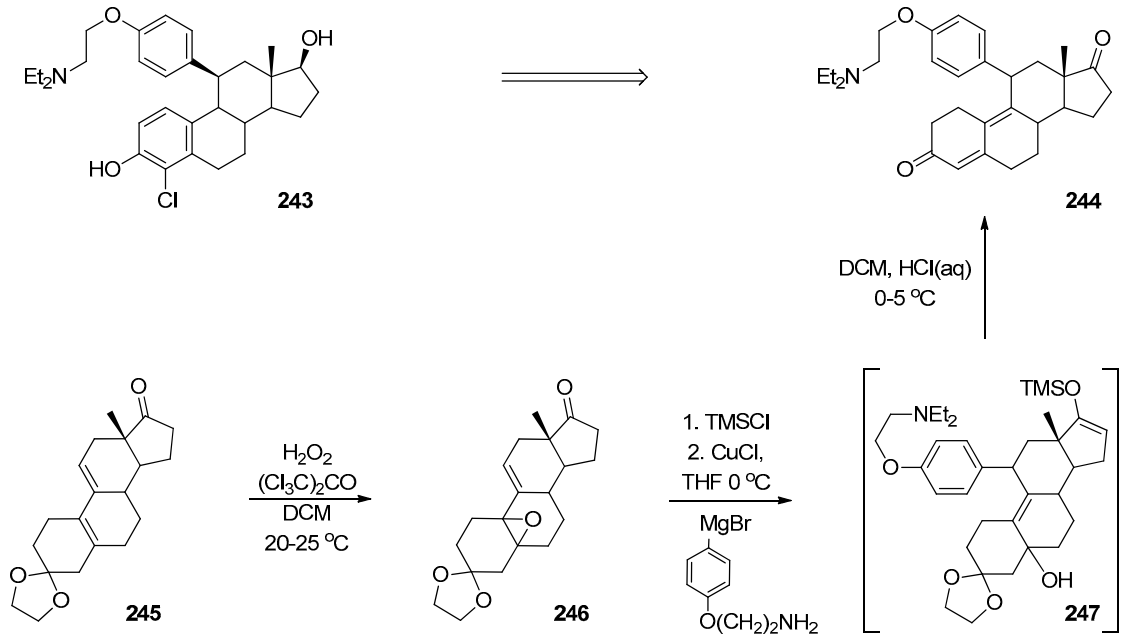
Another interesting case of matched substrate-controlled epoxidation was reported by Rusinov and Chertorizhskii in the synthesis of the contraceptive mifepristone who used a chiral phase transfer catalyst (**Q1**, Scheme 64) to enhance the desired diastereoselectivity in the epoxidation of **240** to 14:1 from 3.5:1 typically seen in the absence of the chiral species [214]. The diastereoselectivity was heavily dependent on the protecting group of the alcohol (7.75:1 with TMS in place of TBDMS). The stereochemistry of epoxide **241** is critical in installing the aryl group with the correct stereochemistry as this is dictated by the prerequisite antiperiplanar geometry in the S_N2' ring opening of the allylic epoxide. The resulting alcohol **242** is dehydrated removing thus the initial stereochemical information of the epoxide intermediate, but the stereochemistry at the carbon atom bearing aryl group constitutes chiral memory of this process.

In contrast, in the synthesis of the osteoporosis drug candidate **243** (Scheme 65) of Aventis (legacy company of Sanofi), process chemists found that this could form with the desired stereochemistry following isomerization of **244** and several unsaturated intermediates including those with the opposite stereochemistry, generated in previous steps. The initial focus from enhancing the substrate controlled epoxidation of **245** to **246** was shifted in the equilibration/isomerization process post the S_N2' Grignard addition (**247**) and culminated the development of a robust and more efficient process that avoided the losses associated with the rejection of the α-epoxide isomer. Consequently, the epoxidation

process mediated by hexachloroacetone and hydrogen peroxide (β/α 1.8:1) was retained (β/α 2.1:1 with hexafluoroacetone) [215].



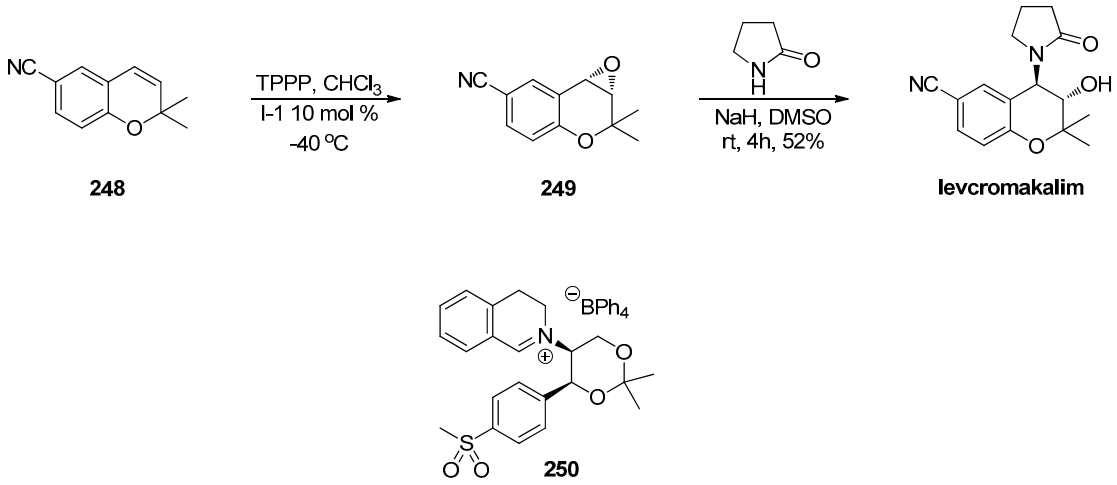
Scheme 64. Application of chiral phase transfer catalyst-mediated asymmetric epoxidation.



Scheme 65. Application of the catalytic ketone/dioxirane epoxidation system in drug development.

The iminium/oxaziridinium salt system is analogous to the ketone/dioxirane system and possesses significant reactivity as an electrophilic oxygen transfer agent by virtue of the positively charged nitrogen atom bonded to the oxygen in the oxaziridinium intermediate. The Page group was among the pioneers in developing this system in organocatalytic asymmetric epoxidations [216–219].

In the synthesis of GlaxoSmithKline's former drug candidate for hypertension (−)-cromakalim (or levcromakalim, the active enantiomer of cromakalim) the asymmetric catalytic epoxidation of **248** to **249** was achieved with Iminium salt **250** (Scheme 66) [220].



Scheme 66. Application of chiral iminium salt-catalyzed epoxidation system in drug synthesis.

Standard iminium salt-catalyzed epoxidations require aqueous solutions of the inorganic triple salt Oxone, the stoichiometric oxidant, thus limiting the temperature range at which the epoxidation reaction may be performed. In this work, the organic-solvent soluble TPPP (tetraphenylphosphonium peroxymonosulfate; the latter anion is the active component in Oxone) was used allowing the reaction to be conducted in pure organic solvent ($CHCl_3$) at lower temperatures. This afforded higher enantioselectivities in comparison with the typical conditions involving aqueous acetonitrile. With the modified protocol the desired epoxide **249** was obtained in 62% yield and 97% ee and its ring opening with pyrrolidin-2-one gave levcromakalim in 52% yield.

2. Conclusions

This work may be viewed as a tribute to process development chemists who respond to the challenge to transform seemingly impossible or problematic syntheses into robust, reproducible and safe manufacturing routes. Arguably, this could not be demonstrated better than by cases of successful management of epoxide synthesis and ring-opening reactions at the highest level which has enabled the manufacturing of drugs and clinical candidates at specification to support pivotal clinical trials and the availability of medicines to society. From an educational perspective, the chemistry discussed provides an insight on the synthetic options generated by epoxides and how these are affected by the ability to control reactant and product regio- and stereochemistry as well as side reactions and impurity formation. The established syntheses described in this review may potentially constitute a point of reference and inspiration for academic and industrial research in this and related fields.

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