CHIRALITY 17:S249–S259 (2005)

Enantiopure Drug Synthesis: From Methyldopa to Imipenem to Efavirenz

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ABSTRACT An historical retrospective is presented relative to the development of practical processes for the syntheses of three major drugs: methyldopa, imipenem, and efavirenz. Each highlights a major method for asymmetric synthesis. This work was initially presented as a lecture at the BLOCKBUSTER CHIRALITY section of the CHIRALITY 2004 meeting in New York City, and this paper is simply a written account of that presentation. The original literature that details the chemistry discussed herein is noted in the reference section. *Chirality 17:S249–S259, 2005.*

KEY WORDS: continuous resolution; asymmetric synthesis; acetoxyazetidinone; diazoinsertion; silyl enol ether alkylation; enantioselective acetylide addition; cubic tetramer

Methyldopa was prepared via a continuous fluidized-bed crystallization resolution–racemization process, which, although more than 30 years old, still represents a remarkable achievement in science and technology. Imipenem, a broad-spectrum antibiotic which has three stereocenters, was initially prepared on a preparative scale via a phenethylamine chiral auxiliary. This method was subsequently improved by a new synthesis based on aspartic acid, a substance from the chiral pool. The key acetoxyazetidinone intermediate developed for this synthesis is now commercially available and forms the basis for the imipenem process. Efavirenz, a novel reverse transcriptase inhibitor for the treatment of AIDS, was originally manufactured via a very unusual lithium cubic tetramer derived form cyclopropyl acetylene and an ephedrine analogue, and this method for enantioselective acetylide addition was superseded by a novel synthesis employing a zinc complex of the ephedrine and acetylide in the presence of magnesium ion.

The development of asymmetric syntheses for drug candidates and products has been a major endeavor in the pharmaceutical industry for more than forty years. Although many drugs have been developed and marketed as racemates during this period, it has generally been the case that the desired activity resides in one of the enantiomers of the racemate, and the other isomer simply represents debris. This manuscript represents the written version of a lecture presented in the BLOCKBUSTER CHIRALITY section of the CHIRALITY 2004 meeting held in New York City during July 2004. The development of asymmetric processes for three major drug candidates are highlighted.

METHYLDOPA

The Merck Research Laboratories have a long history in the areas of enantioselective and asymmetric syntheses that dates back to the Max Tishler days of the 1960s and methyldopa. Max was a legend at Merck, and the company prospered under his administration. Part of the lore of Merck suggests that when Max was asked whether we should develop methyldopa as the D,L-racemate or the L-single enantiomer, he responded, "Give 'em L, boys!" Though this may be more legend than fact, it does reflect long-standing traditions within the laboratories, and these, in turn, are reflected in the process work that defined manufacturing processes for methyldopa, imipenem, and, most recently, efavirenz.

Despite its age, the methyldopa process reflects the very best in process and chemical engineering research, and it is unlikely that it could be bettered even today, with all of the modern methods now available.[1] Beginning with readily available vanillin (Fig. 1), a simple nitroethane condensation and partial reductive hydrolysis afforded methyl vanillyl ketone. This was subjected to a traditional Strecker reaction, which afforded the racemic amino nitrile. Although earlier work focused on a classical resolution from this point, it was recognized that an ultimate process would only result when both enantiomers of the amino nitrile were incorporated into the synthesis. To achieve this goal, the nitrile was acetylated, and it was established that this intermediate possessed the properties of a conglomerate—i.e., the racemate was a physical mixture of D and L forms. Were one to remove a single crystal from the mixture, it would be enantiomerically pure. One of the

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Received for publication 13 October 2004; Accepted 4 January 2005
DOI: 10.1002/chir.20143
Published online 20 June 2005 in Wiley InterScience (www.interscience.wiley.com).

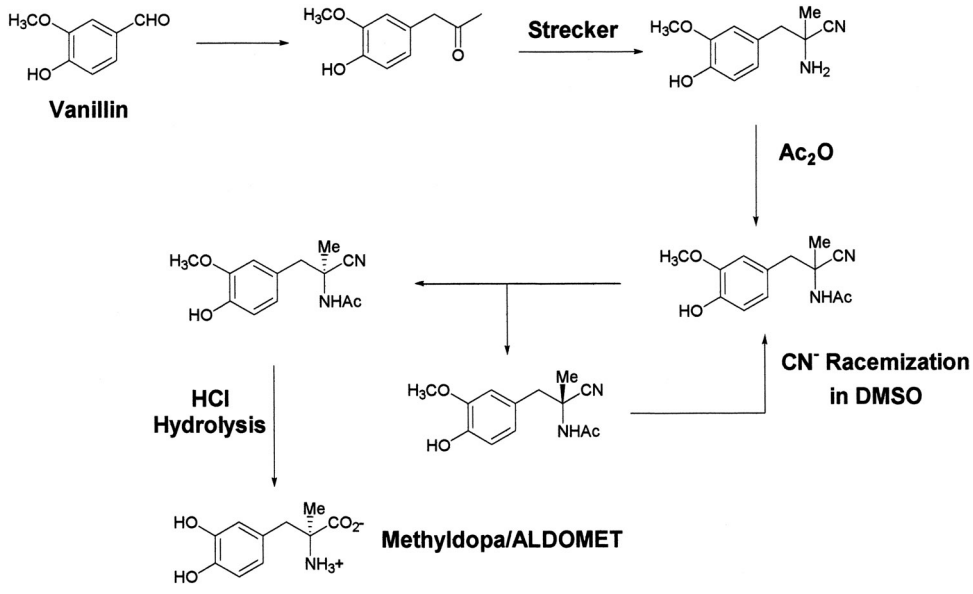


Fig. 1. Methyldopa manufacturing process with the continuous resolution of the acetamidonitrile.

properties of a conglomerate is that the enantiomers are equally and independently soluble, and if one were to prepare a supersaturated solution with regard to both isomers and seed with one, that one could be selectively grown. This seemingly simple principal became the heart of the methyldopa manufacturing process,[2] wherein a continuous resolution was developed by Merck's Chemical Engineering group which employed a dissolver at T_1 and two fluidized-bed crystallizers at T_2. With seeds of the D-isomer in one column and the L-isomer in the other, the isomers were individually grown. When the columns became full, the products in them were separately isolated, the residual crystals within the columns were sonicated to reduce their particle size, and the resolution was restarted. A laboratory version of this system is shown in the next section of this paper. The desired L-isomer was hydrolyzed to methyldopa with concentrated HCl (note that this reaction hydrolyzed the nitrile to the acid, removed the acetyl group, and demethylated the ether in one reaction). The undesired D-isomer was racemized with NaCN in DMSO (HCN elimination and readdition to effect racemization), and it was returned to the resolution.[1] The factory resolution columns were more than a meter in diameter and many meters high. Using this process, Merck produced millions of kilograms of methyldopa over the lifetime of the product. Economically, this proved to be an extremely powerful process, reflecting the very best in what we refer to today as "atom economy." When we subsequently successfully demonstrated the first practical enantioselective phase-transfer reaction in the mid-1980s on another project,[3] we were naive enough to propose a phase-transfer process for methyldopa employing 3,4-dimethoxybenzyl halide as an alkylating agent. It was pointed out to us at the time that the cost of producing this complex alkylating agent (most likely from the O-methylation of vanillin, reduction of the aldehyde and activation of the alcohol) could well be comparable to the manufacturing cost of methyldopa itself!

Although technically not a part of this symposium on BLOCKBUSTER CHIRALITY, as it never exceeded drug-candidate status, our work on 3-fluoro-D-alanine-2-*d* illustrates the power of a continuous resolution as applied to the first preparative scale delivery of a drug candidate. This may well be the first and only time such has been done.[4] The compound, which was being developed as a broad-spectrum antibiotic wherein the deuterium was added to effect an in-vivo kinetic isotope effect to minimize formation of fluoropyruvate, was originally prepared by photofluorination of D-alanine-2-*d* with CF_3OF in HF (Fig. 2).[5] We deemed this not to be a viable method for preparative scale use. Lithium fluoropyruvate hydrate was prepared by a classical condensation–decarboxylation sequence, and its equilibration in conc. ammonium hydroxide at 37°C for 1.5 h produced a 95:5 equilibrium mixture of the gemdiamine and the aminal (Fig. 3). Cooling the solution to 0–5°C to freeze the equilibrium, followed by addition of

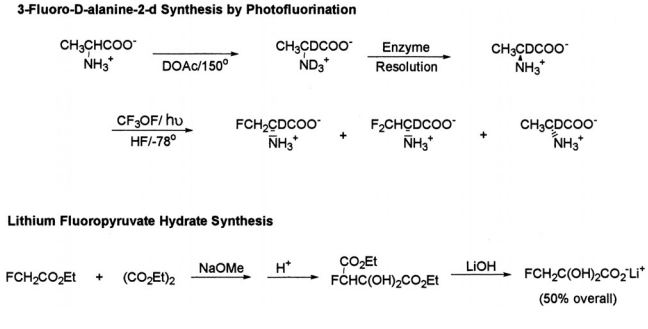
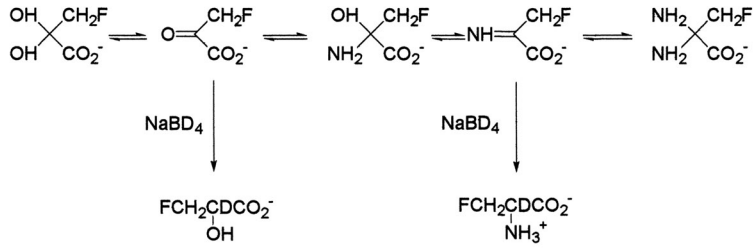


Fig. 2. Preparation of 3-fluoro-D-alanine-2-*d* by photofluorination and preparation of lithium fluoropyruvate hydrate.

Equilibration and Reduction of Lithium Fluoropyruvate in Aqueous Ammonia



The racemate is a racemic compound, but the benzenesulfonate salt is a conglomerate (racemic mixture) and resolvable by continuous resolution

This technique was applied to the FIRST kilogram-scale synthesis of this drug

Fig. 3. Synthesis of racemic 3-fluoroalanine-2-*d* by reductive amination of lithium fluoropyruvate hydrate in concentrated ammonia.

sodium borodeuteride (prepared at kilogram-scale by the Merck Isotopes Division at the time) and removing the ammonia by vacuum and a nitrogen purge to drop the pH and effect reduction of the imine afforded a ~70% isolated yield of racemic 3-fluoroalanine-2-*d* based on the equivalents of deuterium in the borodeuteride used as the limiting reagent in the reaction.[6]

Faced with the need resolve the racemate, we contacted Dr. Mike Midler for consultation on how to do a continuous resolution comparable to the one that he pioneered for methyldopa. The amino acid was not a conglomerate, but its benzenesulfonate salt was.[7] Employing *n*-propanol as the solvent, with a dissolver temperature of 28°C and a crystallizer temperature of 23°C, we were able to effect a preparative-scale resolution with the apparatus shown in Figure 4. The dissolver, crystallizers, sonicator (one, but another is present), and heat exchangers are clearly visible, and I take great pride in noting that this was the first resolution on which I had ever worked.

The details of the continuous resolution are recorded in Figure 5. A temperature difference of only −5°C provided a supersaturation of 16.8% to drive the crystallization, and we were able to produce 320–330 g of each isomer in a day of production. Overall, we resolved 13.5 kg of racemate with an initial optical purity of 99.8–99.9% and no loss of deuterium. One wonderful property of a conglomerate is that it can be readily upgraded by slurry in the resolution solvent. If one had material of 90% optical purity (95:5 ER), slurry in enough *n*-propanol to dissolve 5% of each enantiomer and that would leave material that was essentially 100% optically pure. For the final delivery of drug, we had an enzyme assay that demonstrated that our optical purity for this compound was

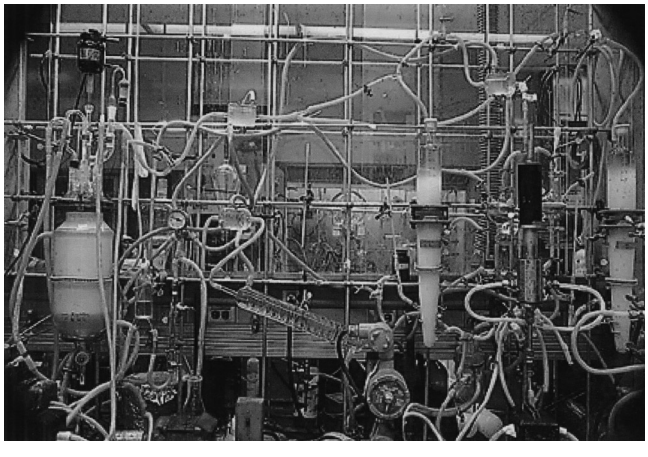


Fig. 4. Continuous resolution of racemic 3-fluoroalanine-2-*d* benzenesulfonate salt. The dissolver is to the left, and the two crystallization columns and one sonicator are seen.

Temperature difference: –5°C
Solvent: 1-propanol
Flow rate: 400–600 ml/min
Growth period: 8.4 h
Seed: 100 g of each isomer, 80/140 mesh
D-Isomer (net): 323 g at 99.9% ee
L-Isomer (net): 330 g at 99.8% ee
Growth rate: initial, 22%/h; final, 14%/h
Depletion: initial, 15%/h; final, 40%/h
Supersaturation: 16.8%
Total resolution: 13.5 kg of D,L; 5.7 kg of D net
Optical purity: 99.995% (enzyme assay)
Deuterium content: 98.5% (complete retention)

Fig. 5. Data from the preparative-scale continuous resolution of 3-fluoroalanine-2-*d* benzene sulfonic acid salt.

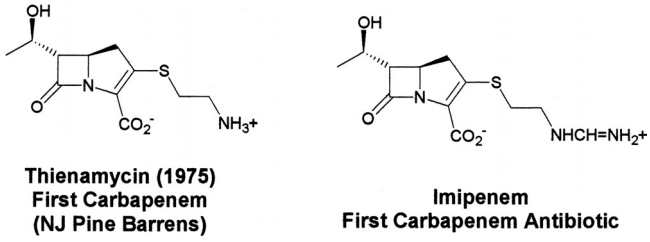


Fig. 6. Structures of thienamycin, the world's first carbapenem, and imipenem, the world's first carbapanem antibiotic.

99.995% or better, possibly a record for a synthetically produced sample.[6]

IMIPENEM

The Merck thienamycin–imipenem story illustrates the power of asymmetric synthesis. Thienamycin, the world's first carbapenem, was discovered in a soil sample from the New Jersey Pine Barrens. After an extensive structure–activity study by our Medicinal Chemists, simple formimidoylation produced imipenem, the world's first carbapemen antibiotic (Fig. 6). Initially, the Research laboratories supported the early safety and clinical work with material prepared by fermentation, but the fermenataion had a serious limitation. Because of a second-order reaction of thienamycin with itself (the β-lactam of one molecule reacting with the amine of a second), the titer of the fermentation could never be brought above ~100 mg/liter. Ed Paul, who headed the Chemical Engineering effort on this program at the time, commented, "To produce 40,000 kg of imipenem per year, we would have to run the thienamycin fermentation in Lake Erie and pump to Lake Ontario for the workup!" Faced with this dilemma, we began an odyssey in total synthesis wherein Merck chemists produced six total syntheses which included two manufacturing processes for this product. The basic research scientists devised the first total synthesis with a remarkable diazoinsertion reaction (described later) to effect formation of the 4–5 ring system.[8] This was followed by the first total synthesis from Process Research based on acetone dicarboxylate, which incorporated resolution and the diazoinsertion reaction.[9] Although this was not satisfactory for the manufacturing scale, it did support the early safety and clinical studies. Thereafter, this was converted to an asymmetric synthesis employing a chiral phenethylenamine enamine for the reduction step, and this became the first manufacturing process for this antibiotic.[10] Subsequently, another total synthesis was achieved in Medicinal Chemistry starting with aspartic acid,[11] and the Process Chemists responded with one from penicillin.[12] Within my own group, we borrowed ideas from most of these synthesis, and with a bit of new chemistry, we designed the second and still-current manufacturing process based on a 4-acetoxy-2-azetidinone.[13]

The acetone dicarboxylate (ADC) manufacturing process was remarkable for its time (Fig. 7). ADC was converted to its chiral phenethylenamine and acetylated with ketene to provide the enamine. Diastereoselective reduction and hydrolysis provided the lactone, which on solvolysis in methanol and β-lactam cyclization provided the methyl ester. Subsequent hydrolysis and Mukiyama chain extension provided the hydroxyethyl-β-lactam *p*-nitrobenzyl ester. The chirality at the alcohol center was incorrect and was inverted with a Mitsunobu reaction. Thereafter, diazotransfer and diazoinsertion provided the ketone, which upon activation with diphenylphosphoryl chloride and side-chain insertion afforded imipenem. Despite its length, this synthesis served Merck well for many years. Its drawbacks included the Mitsunobu reaction and the extensive use of methylene chloride, which was employed

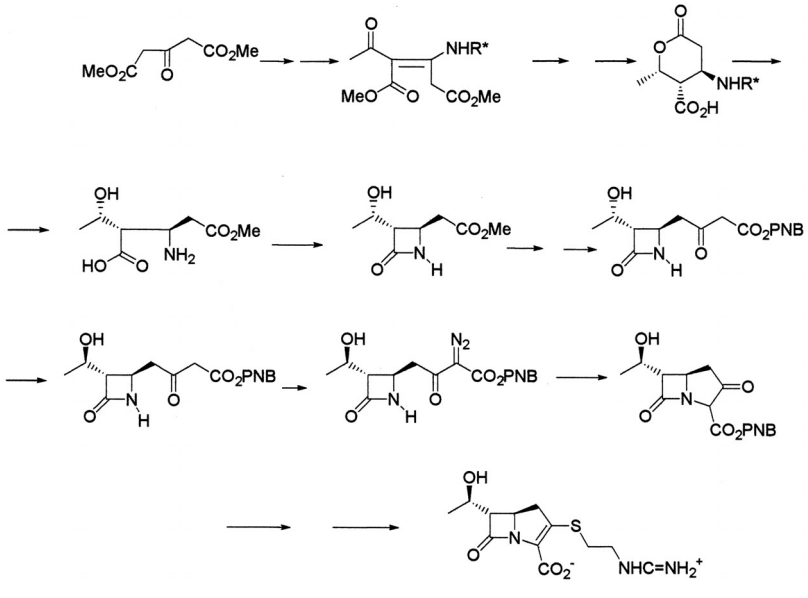


Fig. 7. Outline of the acetone dicarboxylate manufacturing process for imipenem.

in the Mitsunobu reaction, the chain extension, and the diazoinsertion reaction. The Mitsunobu reaction, despite its elegance and widespread use, is the antithesis of atom economy and green chemistry.[14] To drive it kinetically required the phosphine/azodicarboxylate/formic acid ratio to be 2.5:2.5:5, and it produced huge quantities of byproducts with no growth in molecular weight. The use of a double charge of formic acid was required to stabilize the Mitsunobu reagent and prevent formylation of an azodicarboxylate intermediate.[15] The product was separated from the Mitsunobu debris via a complex Podbielniack extraction, making the process even more technically complex. The diazoinsertion reaction, which was discovered by our Medicinal Chemists, was a major breakthrough in carbapenem chemistry, and has withstood the test of time as one of the very best methods for constructing the 4–5 carbapenem ring system. However, methylene chloride was the solvent of choice for this reaction, and even in the 1980s there were serious concerns about its impact on the environment. These issues set the stage for even further studies in imipenem total synthesis.

Syntheses of imipenem from aspartic acid[11] and penicillin[12] followed, but neither was considered suitable for a replacement for the asymmetric ADC route. We then joined the effort and were able to assemble some of the best ideas from existing synthesis with a bit of novel chemistry and came up with the basis for the next manufacturing process.[13] Starting with the azetidinone carboxylic acid from the aspartic acid synthesis, we developed an acylation–reduction protocol to produce the hydroxyethyl analogue (Fig. 8). Oxidative decarboxylation with lead tetraacetate in acetic acid/DMF afforded the acetoxy compound. When treated with the diazosynthon, developed for the penicillin synthesis, under Lewis acid catalysis, we produced the diazointermediate that was part of the ADC process and the original Medicinal Chemistry synthesis. Many noted the similarity of our synthesis to the work of the famous Dr. Frankenstein, who assembled his creature from various pieces stolen from the morgues of eastern Europe, and they have referred to our synthesis as the Frankenstein Synthesis. We freely admit our indebtedness to those who came before us, but take great pride in that we showed that acetoxyazetidinones react simply, readily, and in high yield with silyl enol ethers, and this became the basis for the new process which we prefer to call the acetoxyazeditinone process.[13]

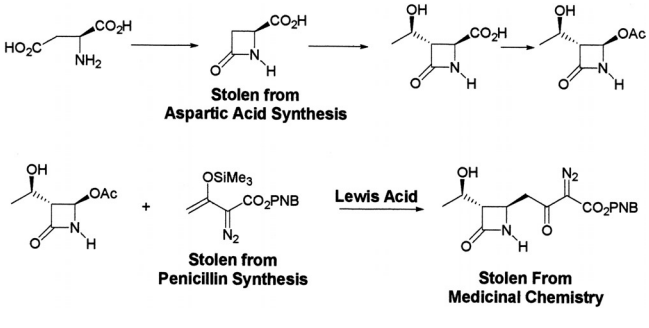


Fig. 8. Origins of the acetoxyazetidinone process (a.k.a. the Frankenstein Synthesis) and definition of the key silylenol ether reaction which defined the process.

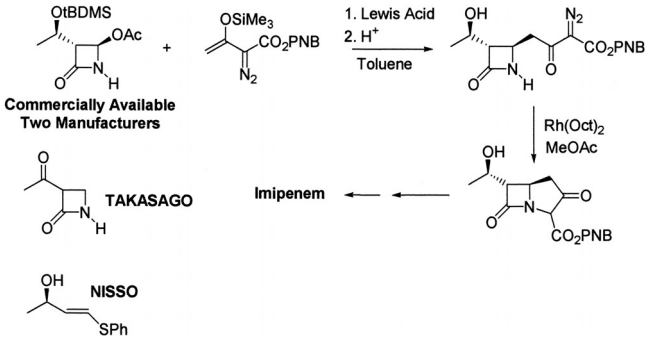


Fig. 9. Acetoxyazetidinone manufacturing process for imipenem showing the starting materials for the Takasago and Nisso processes for the manufacture of the acetoxy intermediate, and the diazoinsertion reaction pioneered by MRL Medicinal Chemistry.

Our paper describing this work was well received, with more than one hundred citations during its first year. Subsequently, Tagasako and Nisso developed independent manufacturing processes for the TBDMS-acetoxyazetidinone (Fig. 9), and combining this now readily available intermediate with our chemistry, after a bit of further development, afforded an excellent manufacturing route. This route addressed all of the major issues of atom economy and green chemistry that were noted with the ADC route.

EFARIRENZ

More recently our Medicinal Chemistry associates developed two candidates as reverse transcriptase inhibitors for the treatment of AIDS (Fig. 10). While we were defining a practical synthesis of the first, they developed the second which was more potent and less prone to the development of resistance by the AIDS virus. The latter has become the marketed entity efavirenz, which is now used worldwide for the treatment of AIDS. But the story

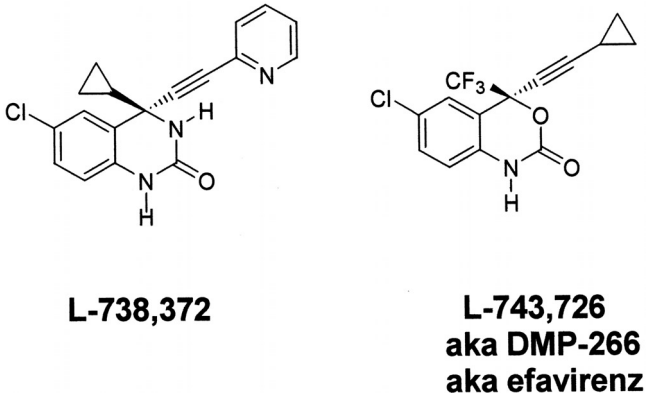


Fig. 10. The reverse transcriptase inhibitors developed by the Merck Research Laboratories for the treatment of AIDS.

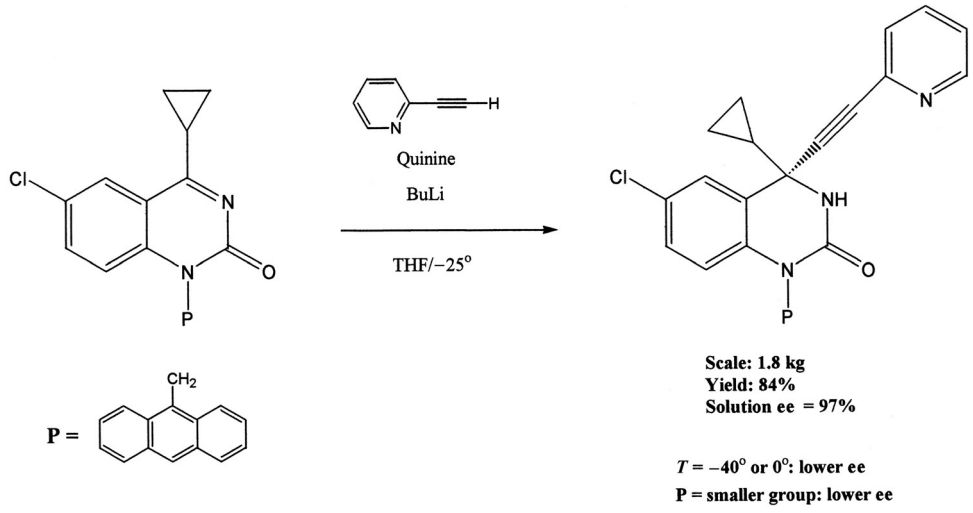


Fig. 11. The first enantioselective acetylide addition to an imine mediated by quinine lithium alkoxide.

begins with the first, and the need to effect an enantioselective addition of an acetylide anion to a cyclic imine. The Medicinal Chemists originally did such in the racemic mode and separated the isomers by diastereomeric derivatization. We were able to define a most remarkable enantioselective addition (Fig. 11) by first protecting the imine with the largest N-protecting group we could find in the chemical catalogs (anthranylmethyl). We then prepared a solution of the pyridylacetyline and quinine in THF, deprotonated both with butyl lithium, and added the protected imine to mixture of acetylide and alkoxide anions at −25°C. This produced a 97% ee for the addition at a 1.8-kg scale, and we began to smell some very exciting chemistry.[16] At this point, the Medicinal Chemists asked us to focus our attention on what became efavirenz, and we had to let the projected studies fall by the wayside.

Keeping our already-demonstrated concept of complexing a lithium acetylide with a lithium aminoalkoxide (we had yet to develop a working hypothesis for the observations), we treated the unprotected aminoketone in Figure 12 with mixtures of alkoxides generated from cyclopropylacetylene and various aminoalcohols. In retrospect, this was a bold move, as the amine in the

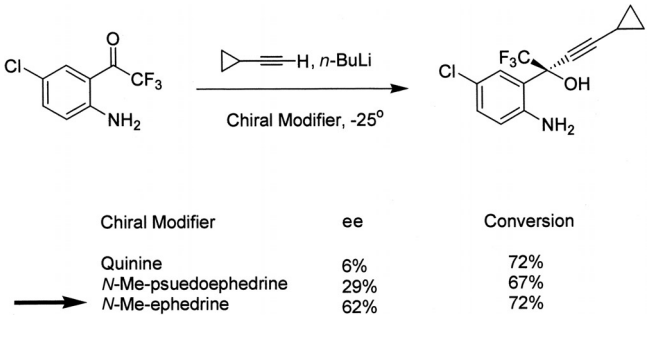


Fig. 12. Additions of lithium cyclopropylacetylide to the unprotected ketone in THF.

aminoketone is quite acidic. Despite this, we were able to achieve about 60% ee at 70% yield for the conversion employing one of the ephedrines but could go no higher. We subsequently decided to protect the amine, and an experimental survey of protecting groups revealed that the *p*-methoxybenzyl would prove best. We next found that with the PMB protecting group, we needed 2 mol of the acetylide and 2 mol of the amino alkoxide to achieve complete conversion of the ketone (Fig. 13). Additionally, the best amino alcohol for the addition proved to be the pyrrolidino ephedrine analogue shown in Figure 13, which produced an ee in the 80–85% range at full conversion, with reaction temperatures at or below −40°C.[17]

At this point in the program, Ed Corley, who was working with Andy Thompson, remembered that the nature of lithium aggregates changes with temperature and decided to warm the acetylide–alkoxide solution to 0°C and then cool it down to −40°C or below for the ketone addition. This proved to be a key experiment for the program, as the ee for the addition was now >98% at full ketone conversion (Fig. 14). Subsequent experiments showed that the reaction exhibited a nonlinear effect, suggesting that more than 1 mol of the ephedrine was involved in the chirality-transferring event. Capping of the ephedrine destroyed the chirality.[17]

Clearly, we had something exciting going on, and decided to seek the help of one of the world's experts in lithium aggregation, Dave Collum at Cornell. Dave was pleased to join the team, and he began a series of studies to define the nature of the aggregation states that were relevant to our system. His first set of experiments (Fig. 15) represent one of the most exciting times in my chemical career. Doing the deprotonation at low temperature (>−70°C) afforded a complex ^{6}Li-NMR spectrum. Doing the same experiment at higher temperatures to allow equilibration converted the first complex spectrum in to a simple two-line ^{6}Li-NMR spectrum, suggesting that we were producing a dimer or a tetramer of the acetylide and alkoxide.[18] We made ^{13}C-labeled acetylene

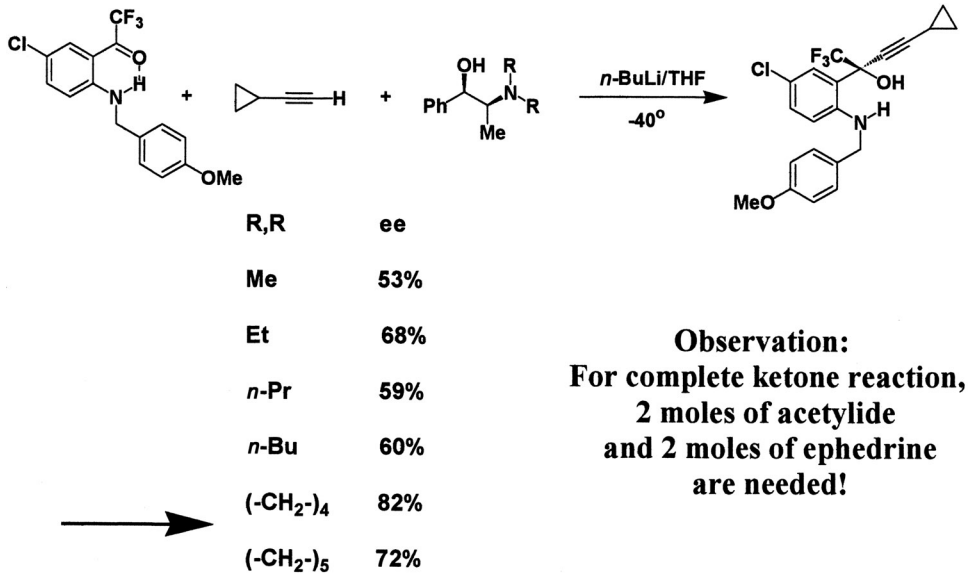


Fig. 13. Acetylide additions in the presence of various norephedrines wherein 2 mol of acetylide and 2 mol of ephedrine alkoxide are required to achieve complete conversion. For complete ketone reaction, 2 mol of acetylide, 2 mol of ephedrine, and 4 mol are needed of butyl lithium are needed.

and ^{15}N-labeled ephedrine in Rahway and shipped them to Dave. With ^{13}C-acetylide, the spectrum became a triplet and a doublet, suggesting that we formed a cubic tetramer during the high-temperature equilibration. The spectrum of the complex with the ^{15}*N*-ephedrine clearly showed that the ^{6}Li that was split into a triplet in the ^{13}C-NMR study was chelated to the nitrogen of the ephedrine, completing the assignment of the structure of the cubic tetramer complex[18] (Fig. 16).

The proposed mechanism for reaction of the PMB-ketone is shown in Figure 17. In forming a C–C bond between the acetylide and ketone carbons two paths are available: in the higher energy one, the aryl of the ketone must share the same space as the phenyl and methyl groups of the ephedrine in a sterically very crowded environment, whereas in the lower energy one the aryl group of the ketone is in a relative void in the tetramer, and the CF_3 group of the ketone is in the same space as the phenyl and methyl of the ephedrine. This simple construct predicts the observed enantioselectivity for the reaction.[18] In fact, during the course of the proposed reaction, the product alkoxide is now present in the new cubic tetramer that is formed. At this point in the program, we began to do our own ^{6}Li-NMR work and decided to try and establish the structure of the product tetramer. The mechanism predicts a tetramer that has no symmetry and should therefore show a four-line ^{6}Li-NMR spectrum. We were able to do an NMR experiment at −100°C and make this expected observation (Fig. 18). Employing ^{13}C-ephedrine, one predicts that three of the ^{6}Li signals should become doublets, as we indeed observed (Fig. 18). With ^{15}*N*-ephedrine the two downfield ^{6}Li signals of the product become doublets, and when we placed an ^{15}N at the nitrogen of the ketone, no changes in the product spectrum were noted. All of these observations are detailed in the our second paper dealing with these aggregation phenomena.[19] We also noted experiments in that paper that clearly show that the

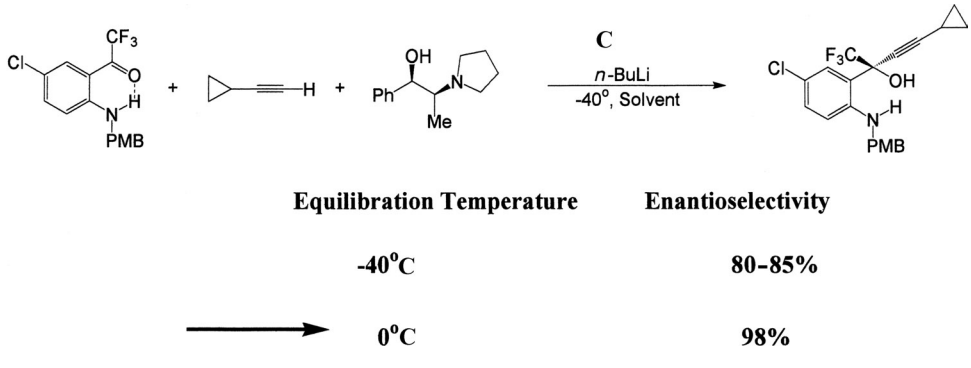


Fig. 14. Effect of equilibration of the acetylide/alkoxide solution on the final ee.

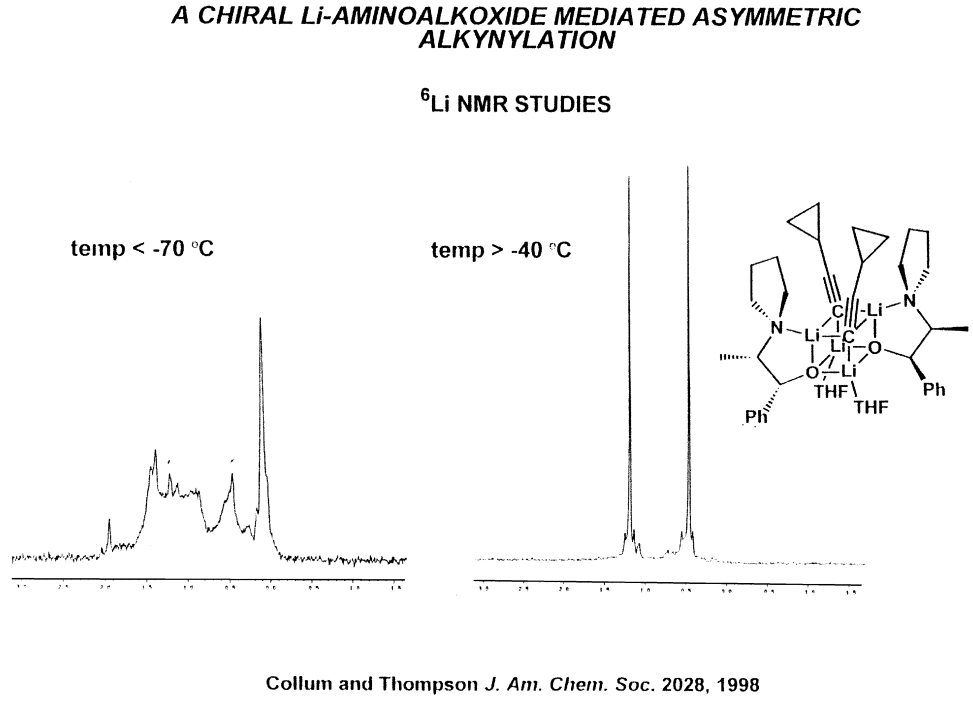


Fig. 15. Impact of equilibration on ^{6}Li-NMR spectrum of the acetylide–alkoxide mixture.

acetylide–alkoxide complexes do not equilibrate below 0°C, indicating that the mechanism from starting tetramer to product tetramer is indeed correct. These experiments ruled out a mechanism involving equilibration from tetramer to dimer and reaction via the dimer, which we had long considered.

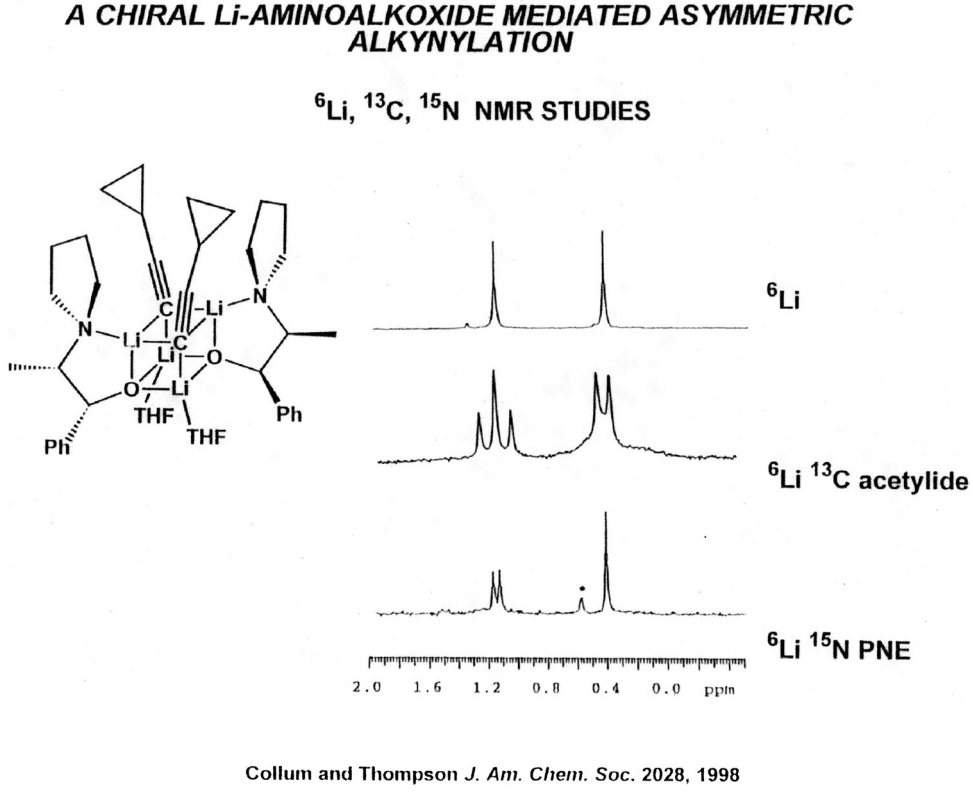


Fig. 16. Confirmation of the cubic tetramer structure based on NMR coupling studies.

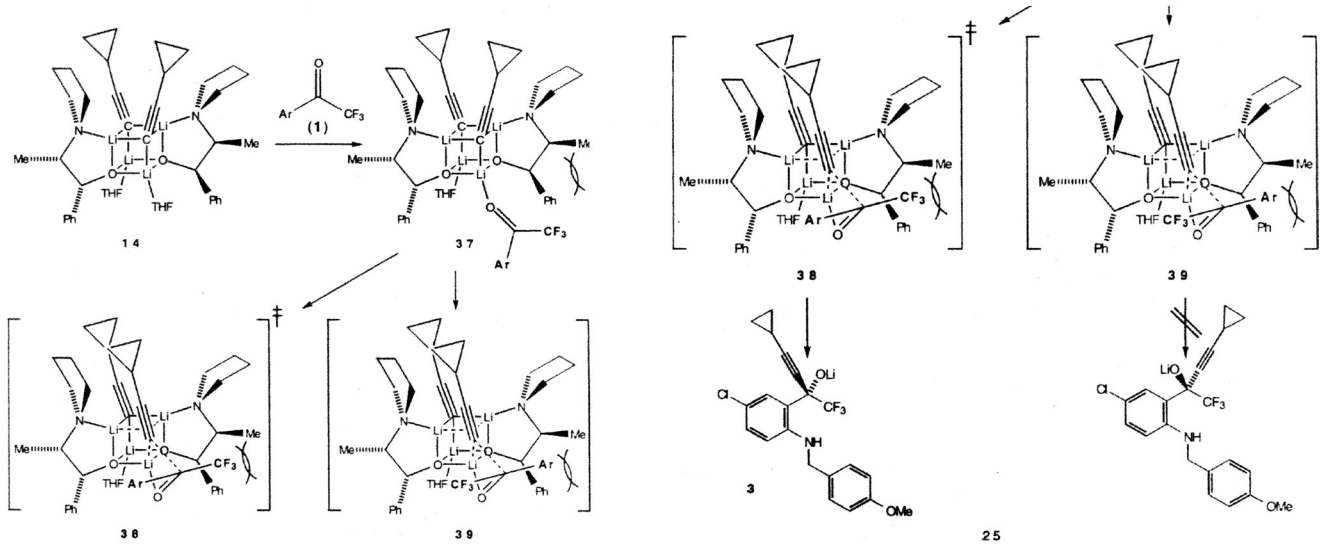


Fig. 17. Mechanism of the reaction of the protected ketone with the acetylide–alkoxide 2-2 complex illustrating the steric interactions in the higher-energy transition state.

On the preparative side, we joined with our associates in Chemical Engineering to demonstrate this reaction on the 30-kg scale at 98% assay yield and 98.4% ee, which on crystallization produced material at 93% yield and 100% ee. Two additional 125-kg runs were run to provide material for development studies and demonstrate the viability of this process. With additional development of this process,[20] it was then used to prepare the clinical, launch, and early sales quantities of this now-marketed product, efavirenz (Fig. 19).

With this chemistry well in hand, we asked if it would be possible to prepare efavirenz without the *p*-methoxy-

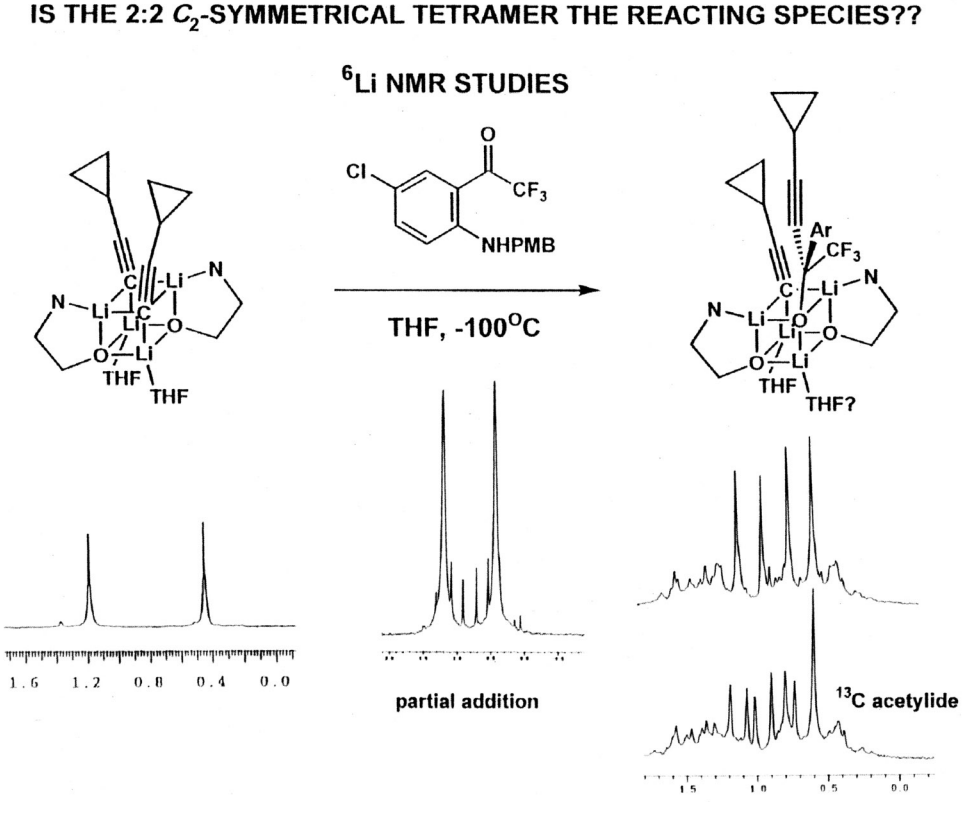


Fig. 18. Reaction of the cubic tetramer with the ketone produces a new cubic tetramer, containing two ephedrine alkoxides, one acetylide, and one product alkoxide.

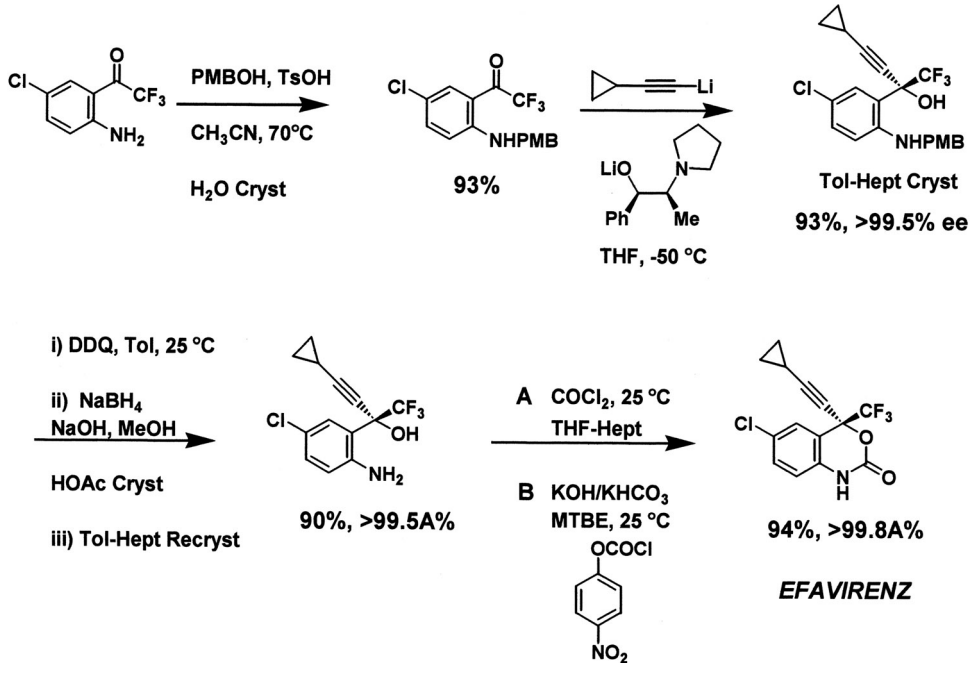


Fig. 19. The lithium acetylide manufacturing process.

benzyl group, saving two steps and the cost of the reagents for the protection and deprotection steps. We decided to turn to the zinc manifold, recognizing that zinc reagents are both mild bases and Lewis acids and might be able to support our desired chemistry. Two remarkable observations resulted for the new zinc synthesis highlighted in Figure 20. The same ephedrine that we used in the lithium acetylide chemistry was the best amino alcohol for the zinc chemistry, and 2 mol of alcohol was required per mole of zinc reagent to complete the reaction. Surprisingly, one could use a dummy alcohol in part for this purpose, and we chose trifluoroethanol. Employing the conditions given in Ref. 21, we were able to achieve a 95% isolated yield for the addition at >99% ee.[21] We published this chemistry in 1999, and it represents the most effective synthesis devised to date for this drug product.

For those interested in the details of these three programs, I refer them to the cited literature. Each program

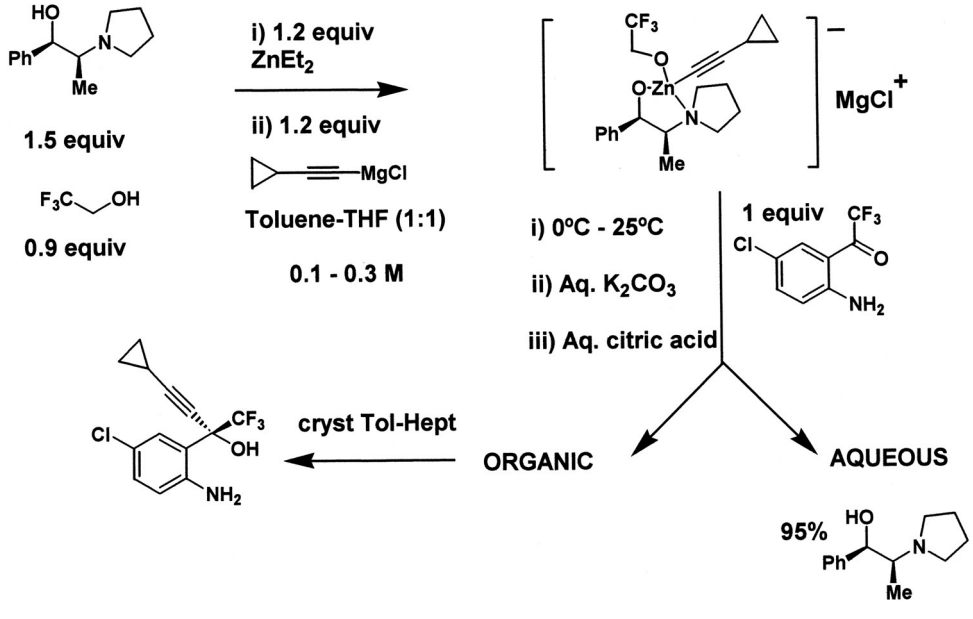


Fig. 20. The novel zinc synthesis of efavirenz at 95% isolated yield, 99.9 A% purity and 99.3% ee.

has been an adventure in both learning and total asymmetric synthesis, and I must acknowledge the excellent work of the various research teams that produced these results.

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