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Patent Review of Manufacturing Routes to Oncology Drugs: Carfilzomib, Osimertinib, and Venetoclax

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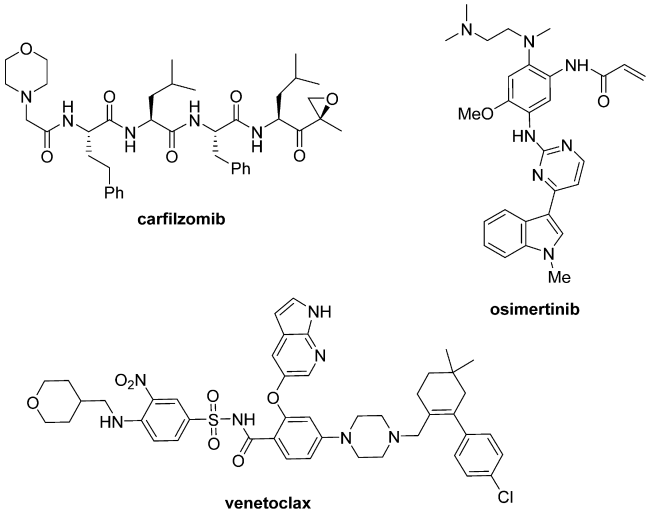
ABSTRACT: Synthetic routes and final forms for three recently approved oncology drugs are reviewed: carfilzomib (Kyprolis), osimertinib (Tagrisso), and venetoclax (Venclexta). Several patent applications have been filed for the major synthetic challenge for carfilzomib, installation of the chiral epoxide. The apparent manufacturing route to osimertinib involves seven steps and a longest linear sequence of six steps with a yield of 56%. The apparent manufacturing route to venetoclax is a ten-step convergent synthesis with a seven-step longest linear sequence that proceeds in 52% yield.

The current article continues the series of reviews[1] of the patent literature of recently approved drugs, focusing on manufacturing routes and final forms of three oncology drugs: carfilzomib (Kyprolis), osimertinib (Tagrisso), and venetoclax (Venclexta).



1. CARFILZOMIB (KYPROLIS)

Carfilzomib (marketed under the brand name Kyprolis) is a proteasome inhibitor for the treatment of multiple myeloma. The U.S. approved Kyprolis in July 2012 followed by Europe in November 2015 and Japan in July 2016.

Carfilzomib is derived from epoxomicin, a natural product discovered by Bristol Myers Squibb Research Institute (Tokyo) in 1992 as an antitumor agent. Epoxomicin was never advanced into development since its mode of action was unclear. The Crews laboratory at Yale determined the antitumor activity of epoxomicin was due to irreversible inhibition of protein complexes known as the proteasome.[2,3] These proteins function as waste managers in cells to hydrolyze and eliminate unneeded or damaged proteins. Inhibition of the proteasome causes cancer cell apoptosis (death) due to the buildup of the waste proteins.

The Crews laboratory undertook to optimize the potency and therapeutic window of epoxomicin, focusing on improving selectivity in cancer cells versus healthy cells. This effort culminated in selection of YU101 as a drug development candidate (Figure 1). Crews and Caltech professor Deshaies

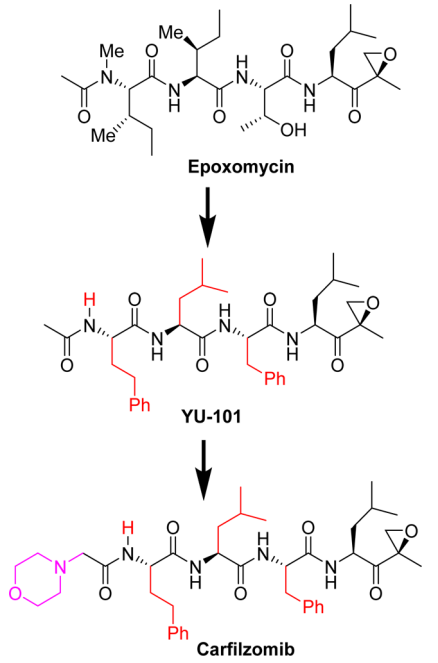


Figure 1. Medicinal chemistry from natural product epoxomycin to carfilzomib.

founded Proteolix in 2003 to initiate preclinical and clinical development of proteasome inhibitors based on their lead candidate. The team at Proteolix ultimately made only one structural change in YU101, the addition of a morpholine group to improve solubility (Figure 1), and progressed PR-171 (carfilzomib) into clinical development in 2005.[4−6]

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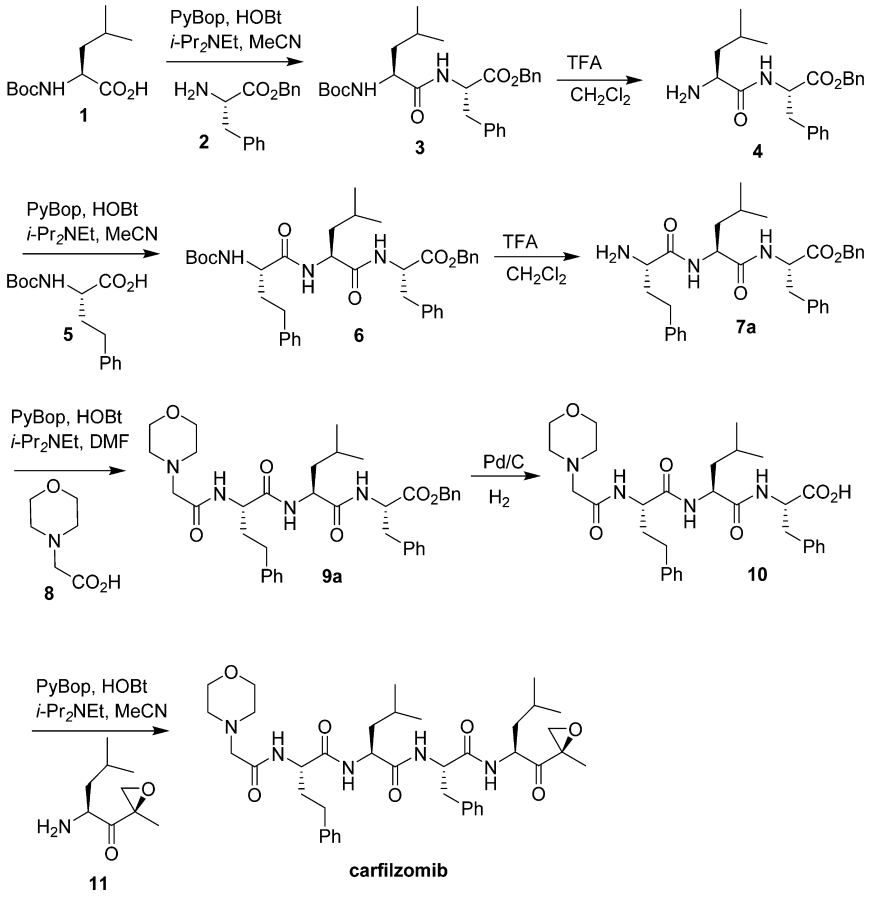
Scheme 1. Original Route to Carfilzomib

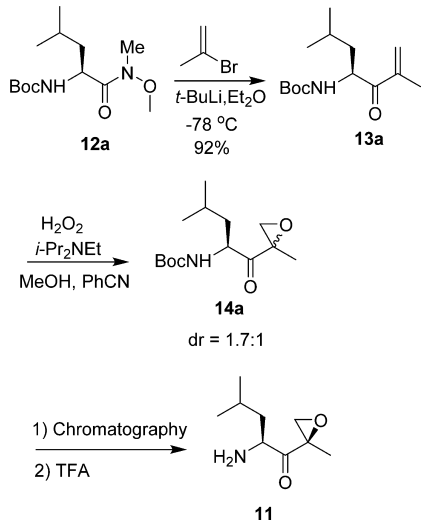


1.1. Medicinal Chemistry Route to Carfilzomib.[7] The medicinal chemistry effort of the Crews laboratory and Proteolix that culminated in the identification of carfilzomib not only improved the therapeutic window of epoxomicin but also greatly simplified the synthesis by eliminating three chiral centers, two of which would have been challenging to synthesize (Figure 1). Carfilzomib consists of a tetrapeptide comprising two leucines, phenylalanine and homophenylalanine. The chiral keto-epoxide warhead remained unchanged relative to the natural product and presents the primary synthetic challenge.

The Medicinal Chemistry route to carfilzomib is outlined in Scheme 1.[8−11] The tripeptide hPhe-Leu-Phe **7a** is assembled using standard solution phase peptide coupling conditions from the three amino acids *N*-Boc-leucine (**1**), *O*-Bn-phenylalanine (**2**), and *N*-Boc-homophenylalanine (**5**), with appropriate protection/deprotection sequences. The morpholine fragment **8** is then appended via amide coupling chemistry to afford **9a**. After deprotection of the benzyl group to generate tripeptide free acid **10**, the keto-epoxide fragment **11** is coupled via standard amide coupling reagents to furnish carfilzomib.

The epoxy-ketone fragment (Scheme 2) is prepared via the route published by Crews in 1999.[8] 2-Bromopropene is lithiated at −78 °C with *t*-BuLi, then added to the Weinreb amide **12** to afford vinyl ketone **13a** in 92% yield. Epoxidation with hydrogen peroxide leads to a 1.7:1 ratio of diastereomers **14a** which are separated by column chromatography. The desired isomer is then deprotected to afford chiral keto-epoxide **11**.

Scheme 2. Original Synthesis of Keto-Epoxide 11



1.2. Potential Manufacturing Route to Carfilzomib. The manufacturing route to carfilzomib appears to follow the same bond disconnections as the original route, based on descriptions provided in several Onyx process patents.[12−16] In particular, the route to the tripeptide **10** appears to be largely the same, with minor variations in peptide coupling reagents and protecting groups. The process from compound **7a** to carfilzomib was claimed, but none of the intermediates were claimed.[14]

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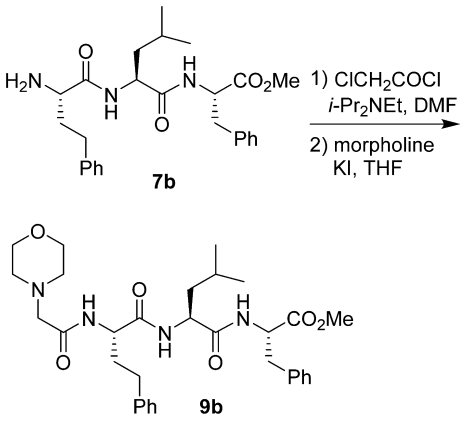
Two variations to tripeptide **10** are described by Onyx: (1) the morpholine group may be appended in two steps via acylation and displacement (Scheme 3); and (2) a methyl protecting group is used instead of benzyl, allowing for deprotection with LiOH.[12]

Scheme 3. Alternate Introduction of Morpholine Moiety

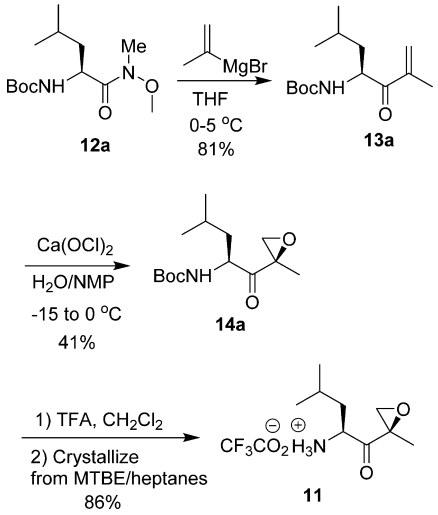


The major synthetic challenge for carfilzomib is the asymmetric synthesis of the keto-epoxide **11**.

The original route to the keto-epoxide (Scheme 2)[8] is not suitable as a manufacturing route for two major reasons: (1) the use of pyrophoric *t*-BuLi in diethyl ether, and (2) the diasteroselectivity of only 63:37 in the epoxidation, requiring chromatography to purify the desired isomer.

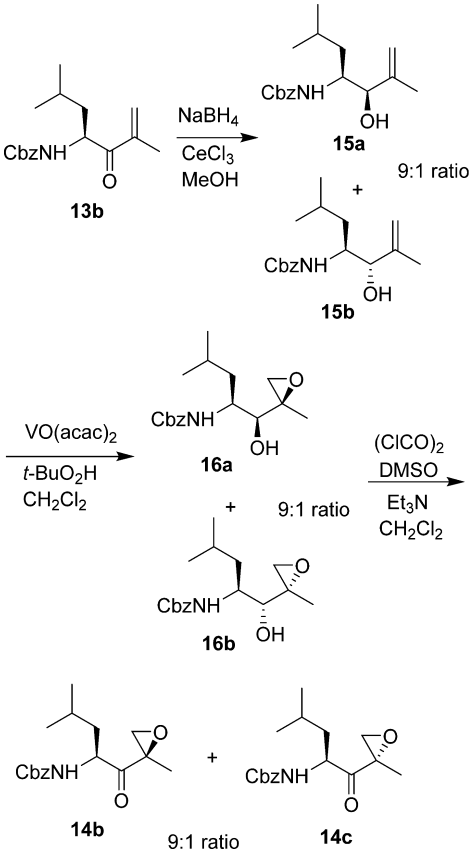
The first concern has been adequately addressed. Process patents granted to Onyx describe the replacement of *t*-BuLi with isopropenylmagnesium bromide in a reaction that proceeds at 0−5 °C in THF and furnishes **13a** in 80% yield (Scheme 4).[12−15]

Scheme 4. Onyx Alternate Route to Keto-Epoxide 11



The second concern, an improved epoxidation, has not been fully addressed in Proteolix and Onyx patents. Two routes are described. In the most direct route described on a 50 g scale, epoxidation of **13a** is carried out using calcium hypochlorite in aq. NMP at 0−15 °C, affording epoxide **14a** in 41% yield (Scheme 4).[15] No dr is provided, but the same conditions reported in a Chinese patent application, as discussed further below,[17] afford a dr of only 2:1 (Scheme 5). In the specification section of U.S. Patent 8,367,617, pyridine as a cosolvent with

Scheme 5. Proteolix Diastereoselective Route to Keto-Epoxide



water is identified as the preferred solvent for the epoxidation, but these conditions are not exemplified nor claimed.[12] Pyridine was shown to be an excellent cosolvent for epoxidation of enones, although not studied for diastereoselective reactions.[18]

Epoxide **14a** is isolated as an oil after purification by filtration through a plug of silica gel and concentration.[15] Deprotection of **14a** is carried out with TFA in CH_2Cl_2, and the resulting TFA salt of compound **11** is crystallized from MTBE/heptanes in 86% overall yield. Since no dr is provided, it is unknown if the crystallization upgrades the stereochemical purity, although a recovery of 86% suggests that a significant amount of the undesired isomer must remain.[15]

Compound **11** is claimed in granted U.S. Patent 8,921,583 along with the deprotection process and the crystalline TFA salt.[15] An epoxidation process is not claimed. A claim for compound **11** and its crystalline salt is valuable since it will preclude competitors from using any route that makes or uses this compound or the TFA salt until the patent expires. While the expiration date is uncertain, if the filing date of Feb 2013 becomes the priority date, then the patent would expire in 2033, about 8 years after the carfilzomib composition of matter patent.

In an alternate epoxidation route reported by Proteolix,[16] the desired diastereomer is prepared with 9:1 selectivity but requires an additional reduction/oxidation sequence (Scheme 5). In the first step the ketone **13b** is selectively reduced with

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$NaBH_4$ to afford a 9:1 mixture of diastereomers (**15a**/**15b**). Vanadium-catalyzed epoxidation with *t*-butyl hydroperoxide leads to a 9:1 diastereomeric mixture (**16a**/**16b**). Swern oxidation back to the ketone oxidation state affords a 9:1 ratio of diastereomers (**14b**/**14c**). Combining this route with the crystallization of the TFA salt of **11** described above[15] could provide a viable route to **11** with high diastereoselectivity. While this route is claimed in a patent application,[16] the patent has never been issued in the U.S. Nonetheless, publication of the patent application ensures freedom to operate.

When a Boc protecting group is used instead of Cbz for the chemistry described in Scheme 5, the initial reduction affords a 4.5:1 ratio of diastereomers, but the ensuing oxidation results in only a 1:1 mixture of epoxide isomers from each alcohol diastereomer.[12,15] This profound impact of the protecting group on the diastereoselectivity of the epoxidation is discussed further below.

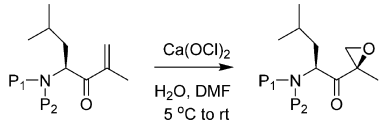
The final coupling of **10** with **11** is described and claimed in Onyx process patent 8,207,297 on a 242 g scale using HBTU, HOBt, and *i*-Pr_2NEt in DMF at 0 °C.[14] A number of work-up and purification procedures are provided. The most efficient involves quenching into cold 5% $NaHCO_3$, extraction with EtOAc, then solvent turnover to MeOH, and crystallization of the free base from MeOH/water. Crystallization from methyl ethyl ketone is also described as are recrystallizations from MeOH and EtOH. No diastereomer ratios are provided so it remains unclear if crystallization provides an upgrade in the stereochemical purity if keto-epoxide **11** of lower dr is used in the process.

1.3. Regulatory Starting Materials. According to the European Public Assessment Report (EPAR),[19] carfilzomib is manufactured in an 11-step convergent synthesis from four regulatory starting materials (RSMs). The likely RSMs are the protected amino acids **1**, **2**, **5**, and morpholine acetic acid **8**. *N*-Boc-Leucine (**1**) serves as a starting material for each fragment (Schemes 1 and 4). The EPAR notes that the applicant's original designation of RSMs was not acceptable and were redefined to include all steps in which stereochemistry is defined. This suggests epoxide **11** or **14** may have been the applicant's suggested RSM that was not accepted by the EMA. The change in RSMs required additional analytical work be conducted since the initially defined RSM's were redefined as intermediates, which require validated assays. The EMA allowed the analytical validation to be completed and submitted postapproval (1Q2016).[19]

Although the guidance on genotoxic impurities (ICH M7) does not apply to many anticancer compounds,[19,20] to minimize regulatory risk sponsors often still carry out an analysis on potential genotoxic impurities, especially if the compound has a noncytotoxic mechanism. The EPAR reports that the applicant conducted an evaluation of genotoxic impurities.[19] Although the epoxide is a structural alert for genotoxicity, carfilzomib was nonmutagenic in experimental studies. Therefore, epoxide impurities related to carfilzomib are considered nonmutagenic. This is important from a manufacturing perspective since it would allow handling of epoxide intermediates **11** and **14**, and carfilzomib, as nonpotent compounds.

1.4. Alternate Routes to Carfilzomib. *1.4.1. Epoxidation of Bis-Protected Vinyl Ketone.* Scientists from Shanghai Hao Yuan Biomedical Technology Co., Ltd., and Shanghai Hao Yuan Chemical Technology Co., report that epoxidation of bis-protected vinyl amines affords much improved diastereoselectivity versus the monoprotected counterparts.[17] As a control experiment, following the conditions reported by Onyx,[15] the epoxidation of Boc-amine **13a** produced epoxide **14a** with only 2:1 selectivity in 40% yield. By contrast, the bis-protected substrates generated selectivities of 9:1 to 10:1, although yields remained modest (52−64%) (Scheme 6). The bis-protected substrates are prepared from bis-protected leucine via preparation of the Weinreb amide followed by displacement with isopropenyl magnesium bromide (using route in Scheme 4). Epoxidation via the bis-protected vinyl ketones appears to be a straightforward method to improve selectivity for the preparation of fragment **11** and should be amenable to development as a manufacturing process.

Scheme 6. Epoxidation of Bis-Protected Vinyl Ketones



Vinyl ketone	Keto-Epoxide	P_1	P_2	dr	Yield (%)
13a	**14a**	H	Boc	2:1	40
13d	**14d**	Boc	Boc	10:1	64
13e	**14e**	Cbz	Cbz	9:1	52
13f	**14f**	Cbz	Boc	9.5:1	63

1.4.2. Epoxidation of Late Stage Intermediates. The current route to carfilzomib builds the tetrapeptide in a "3 + 1" fashion via the tripeptide **10** and a single amino acid (leucine) that incorporates the keto-epoxide **11**. Other bond disconnections reported in recent patent applications include "2 + 2" and "4 + 0" approaches where the epoxidation is conducted on either a dipeptide or the entire tetrapeptide.

A Sandoz patent application describes epoxidation of vinyl dipeptide **17** (Table 1), vinyl tetrapeptide **18**, and the vinyl morpholino tetrapeptide **19**, although experimental data are only provided for **17** and **19**.[21] Several vinyl precursor compounds are broadly claimed along with a specific claim for penultimate intermediate **19**.[22] For dipeptide **17**, the calcium hypochlorite conditions in aq. NMP provide only a slightly improved diastereoselectivity (3:1) versus the vinyl amino acid **13a**, but using hydrogen peroxide in MeOH, a much improved 9:1 selectivity is realized. This results prompts the question of whether these conditions also provide improved selectivity for **13a** but have not been disclosed.

Epoxidation of penultimate intermediate affords 5:1 diasteroselectivity at 60% conversion in the only experimental procedure provided for this substrate.[21]

A Chinese patent application from Suzhou Pengxu Pharmatech also describes epoxidation of dipeptide **17** using H_2O_2, K_2CO_3, and PhCN in MeOH, but no dr for the reaction is provided.[23] After chromatography, the epoxide **20** is isolated in 62% yield with none of the undesired diastereomer detected (Scheme 7).

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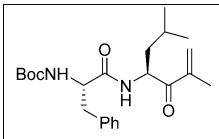
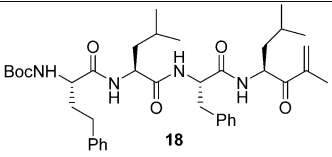
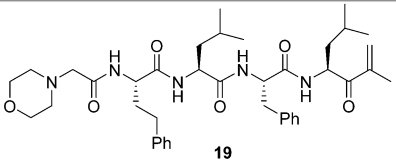
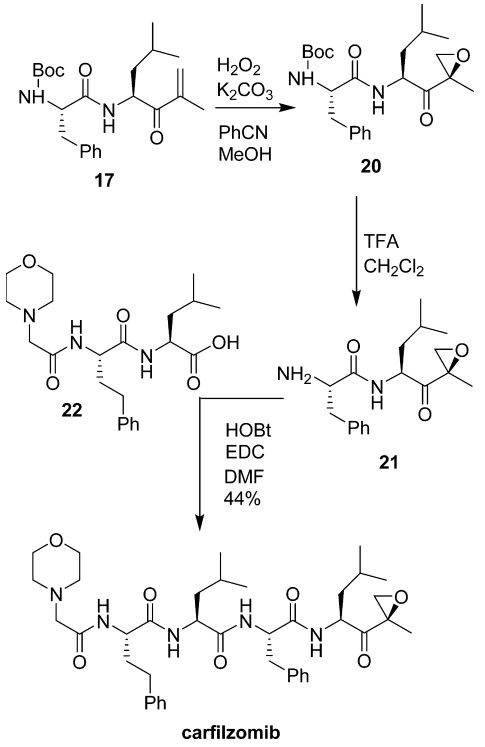
Table 1. Epoxidation of Vinyl Peptides 17, 18, and 19[21]

	Yield (%)	dr
 **17**		
H_2O_2, KOH, MeOH	97	9:1
$Ca(OCl)_2$, aq. NMP	51	3:1
mCPBA, CH_2Cl_2	23	1:1
 **18**	No data	No data
 **19**		
H_2O_2, KOH, MeOH	60%	5:1

Scheme 7. Carfilzomib via Dipeptide Epoxidation



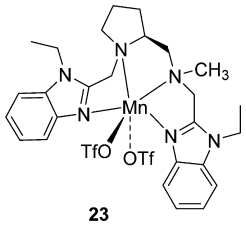
This patent application also describes the deprotection of epoxide **20** and coupling with dipeptide **22** to afford carfilzomib in 44% yield after chromatography (Scheme 7).[23]

Coupling of **21** and **22** is also exemplified in an Apicore patent although no yields are provided.[24]

A Chinese patent application from Chongqing Taihao Pharmaceutical Company describes epoxidation of **19** using $NaHCO_3$, oxone, and trifluoroacetone in dichloromethane at −10 °C.[25] After chromatography, carfilzomib is isolated in 46% yield and a purity of >99%. The dr in the reaction is not provided.

The route in Scheme 7 is somewhat more convergent than the original route but requires the same number of steps overall. This route appears feasible as a manufacturing route if compounds **20** or **21** can be crystallized to upgrade dr and overall chemical purity.

1.4.3. Epoxidation via Asymmetric Synthesis. Sun and co-workers report an asymmetric epoxidation of **13a** using a chiral manganese complex **23** with H_2O_2/AcOH in MeCN at −20 °C to afford epoxide **14a** in a 7:1 ratio (96% isolated yield of combined diastereomers).[26] Only 0.2 mol % catalyst **23** is required. The ligand is prepared in 5 steps from proline.



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A patent application from Zhejiang Yongning Pharma describes epoxidation of vinyl ketone **13a** with a chiral lanthanum (*R*)-BINOL catalyst (2%), triphenylphosphine (20%), and using *t*-BuOOH as the terminal oxidant in toluene as solvent.[27] The epoxide **14a** is isolated in 85% yield. The stereochemical outcome is noted as "93% ee." Assuming the authors meant "de," the ratio of diastereomers would be 96.5:3.5. The asymmetric epoxidation of enones with lanthanide BINOL complexes was originally described by Shibasaki et al.[28] Daikai et al. then reported an increase in stereoselectivity could be achieved with enone substrates by use of triphenylphosphine oxide as cocatalyst.[29]

A patent application from Biophore describes an asymmetric dihydroxylation of vinyl ketone **13** using AD-mix β (Scheme 8).[30] No dr of product diol **24** is provided. Completion of the synthesis of carfilzomib requires six steps: protection of the diol as the diacetate **25**, deprotection of the Boc group, coupling with tripeptide **10** to generate **26**, deprotection of the diol, conversion of the primary alcohol to the mesylate, then cyclization to generate the epoxide. Dihydroxylation of tetrapeptide **19** is described in the specification but is not exemplified.

An innovative asymmetric organocatalytic Mannich approach to the epoxide **14g** is reported in a Sandoz patent application (Scheme 9).[31] In the first step, a Mannich reaction with *p*-anisidine, isovaleronitrile, and ketone **27**, catalyzed by *L*-alanine, sets two stereocenters in Mannich product **28** with 99% ee.[32] Methylmagnesium bromide is then added to the ketone to form tertiary alcohol **29**. While an ee of 99% is reported for this step, this should be a "de" since only one new stereocenter is being formed. Benzylation of the nitrogen affords tertiary amine **30**. The formation of the tertiary amine is likely required to ensure the nitrogen is not involved in the downstream displacement reaction to avoid formation of a five-membered pyrrolidine, which could be enhanced by a Thorpe–Ingold effect. Acidic deprotection of the acetal generates triol

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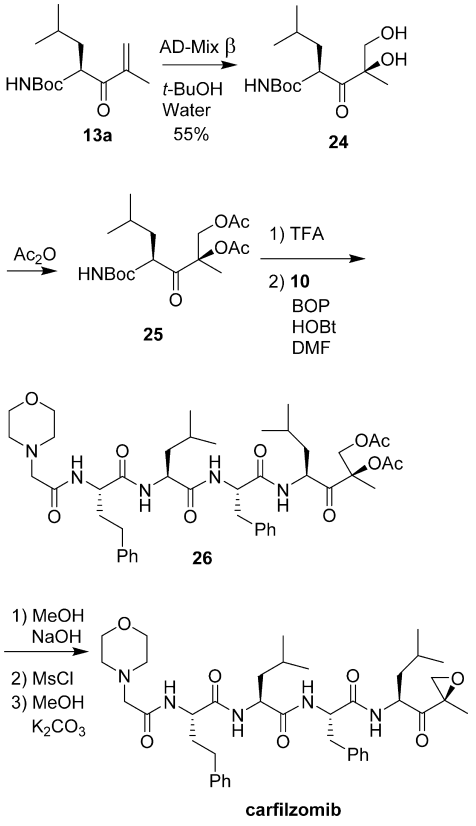
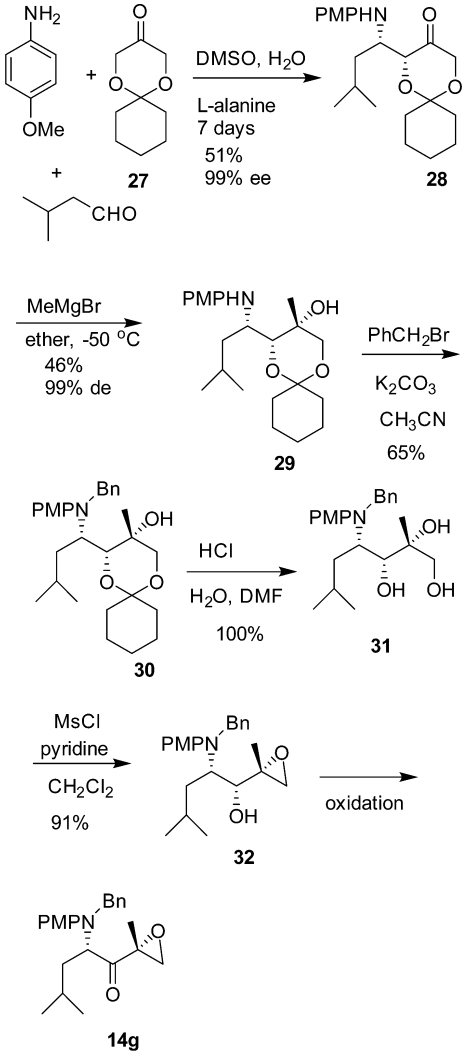
Scheme 8. Asymmetric Dihydroxylation Approach to Carfilzomib



Scheme 9. Epoxide Formation via Asymmetric Mannich Reaction



31. According to the experimental procedure provided, the triol is cyclized to epoxide **32** upon treatment with MsCl. Conditions for the oxidation of the alcohol to ketone **14g** and deprotection to **11** are not provided. In the specification, the sequence is described as mesylation of the primary alcohol, oxidation to the ketone, then ring closure.

Given the length of the synthesis, this route is likely not viable as a manufacturing route.

Two Chinese patent applications describe solid phase synthesis of the tripeptide **10** (Scheme 10).[33,34] Interestingly, solid phase synthesis of a *p*-CF_3 analogue of carfilzomib was exemplified but not claimed in an early patent from Proteolix, which may be considered prior art.[10]

The solid phase sequence (Scheme 10) starts with the reaction of the carboxylic acid of Fmoc-phenylalanine with the trityl resin to produce **33**. The Fmoc group is cleaved with piperidine; then Fmoc-leucine is coupled using typical amide bond forming conditions to produce **35**. This is followed with similar coupling/deprotection with Fmoc-homophenylalanine and morpholine acetic acid to afford tripeptide **10**. Cleavage from the resin is accomplished with TFE in CH_2Cl_2. Reported yields for the sequence range from 48 to 95%.[33]

The advantage of synthesis on a resin is that it minimizes protection−deprotections and isolations of intermediates and can thereby shorten the synthesis of peptides with improved yield and productivity. The downside is expense of resin and scalability.[35] In addition, significant waste is generated from use are large amounts of solvents, typically dichloromethane and DMF, for resin swelling and washing steps.

1.5. Carfilzomib Final Form. According to the Kyprolis EPAR,[19] the final form of carfilzomib is a crystalline free base which is described and claimed in two patents.[12,36] A single polymorph is generated from several solvent systems including MeOH, EtOH, MeOH/water, methyl ethyl ketone, MeCN/water, and EtOAc/water.[12,36]

As regards other forms, a toluene solvate can be prepared from neat toluene or a toluene/MTBE mixture.[37] In addition, a crystalline citrate salt, crystallized from THF/acetonitrile, has been described and claimed by Onyx.[13]

Crystalline oxalate, maleate, succinate, and citrate salts of carfilzomib are described in the specification from a Fresenius Kabi Oncology patent application, but only the oxalate salt is exemplified and claimed.[38] The oxalate salt is crystallized from THF/MeCN. Crystallization of the free base from EtOAc/MTBE is also exemplified.

A patent application from Dr. Reddy's Laboratories describes a cocrystal of carfilzomib with maleic acid that is formed in THF/acetonitrile.[39] Finally, an amorphous carfilzomib free base is produced by precipitation from 2-PrOH/water or MeOH/water.[36,39]

Carfilzomib is an intravenous drug. Due to its poor aqueous solubility, carfilzomib is formulated with sulfobutylether *β*-cyclodextrin.[40]

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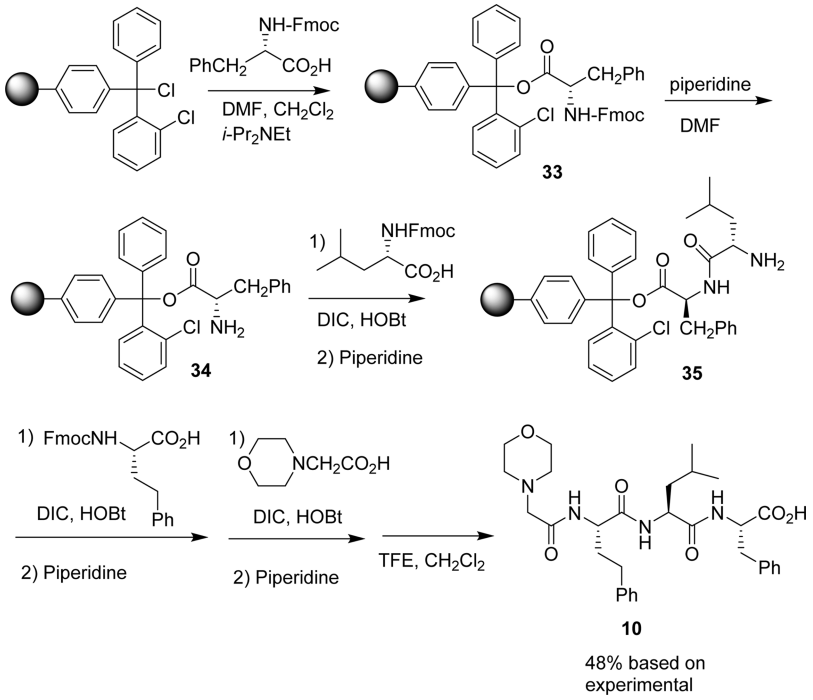
Scheme 10. Solid Phase Synthesis of 10 Using 2-Chlorotrityl Chloride Resin



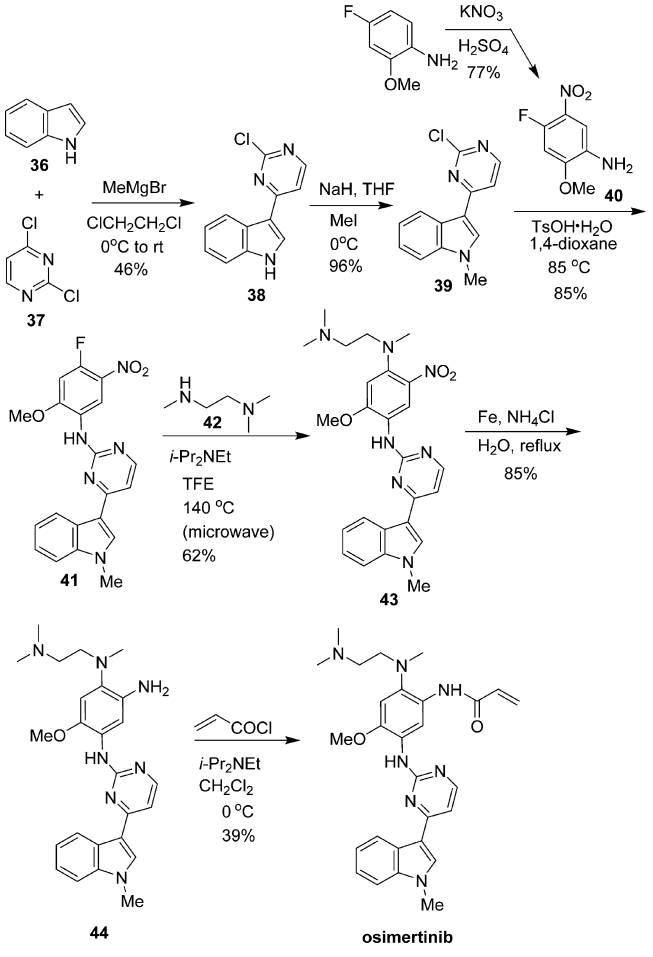
Summary. Carfilzomib is a tetrapeptide with an asymmetric epoxide that covalently reacts with N-terminal threonines in the active site of the 20S proteasome, resulting in irreversible inhibition of the proteasome and death of cancer cells. The primary synthetic challenge for carfilzomib is creation of the asymmetric epoxide. In the granted patents and filed patent applications from the originator companies (Proteolix and Onyx), the routes to the epoxide either afford product with low diastereoselectivity (Scheme 4) or require a lengthy synthesis (Scheme 5). Therefore, the manufacturing process for the epoxide remains uncertain based on publically disclosed information. A number of alternate approaches have been published in journal publications and patent applications. Of these, an attractive route is use of bis-protected vinyl ketones (Scheme 6), which afford much improved diastereoselectivities (9−10:1) in the direct epoxidation.

2. OSIMERTINIB (TAGRISSO)

Osimertinib, sold under the brand name Tagrisso, is an orally active irreversible inhibitor of epidermal growth factor receptor (EGRF), discovered and developed by AstraZeneca. Tagrisso was approved for the treatment of nonsmall cell lung cancer in the U.S. in November 2015, Europe in February, 2016, and Japan in March, 2016, The recommended dose in the U.S. is one 80 mg tablet taken once daily with or without food until disease progression or unacceptable toxicity. Both 40 mg and 80 mg dose strength tablets are available.[41]

2.1. Medicinal Chemistry Route. The original 7-step route to osimertinib (Scheme 11)[42,43] starts with the deprotonation of indole (**36**) with MeMgBr followed addition of the anion to 2,4-dichloropyrimidine (**37**), affording **38** in 46% yield. Methylation with NaH/MeI furnishes indole **39** in 96% yield. The displacement of the other chloride of the pyrimidine is carried out under acidic conditions at 85 °C in dioxane with aniline **40**, generating **41** in 85% yield after isolation by crystallization. S_NAr reaction with the diamine **42** under microwave conditions affords **43** in 62% yield. Reduction with iron in aq. ammonium chloride provides penultimate

Scheme 11. Medicinal Chemistry Route to Osimertinib



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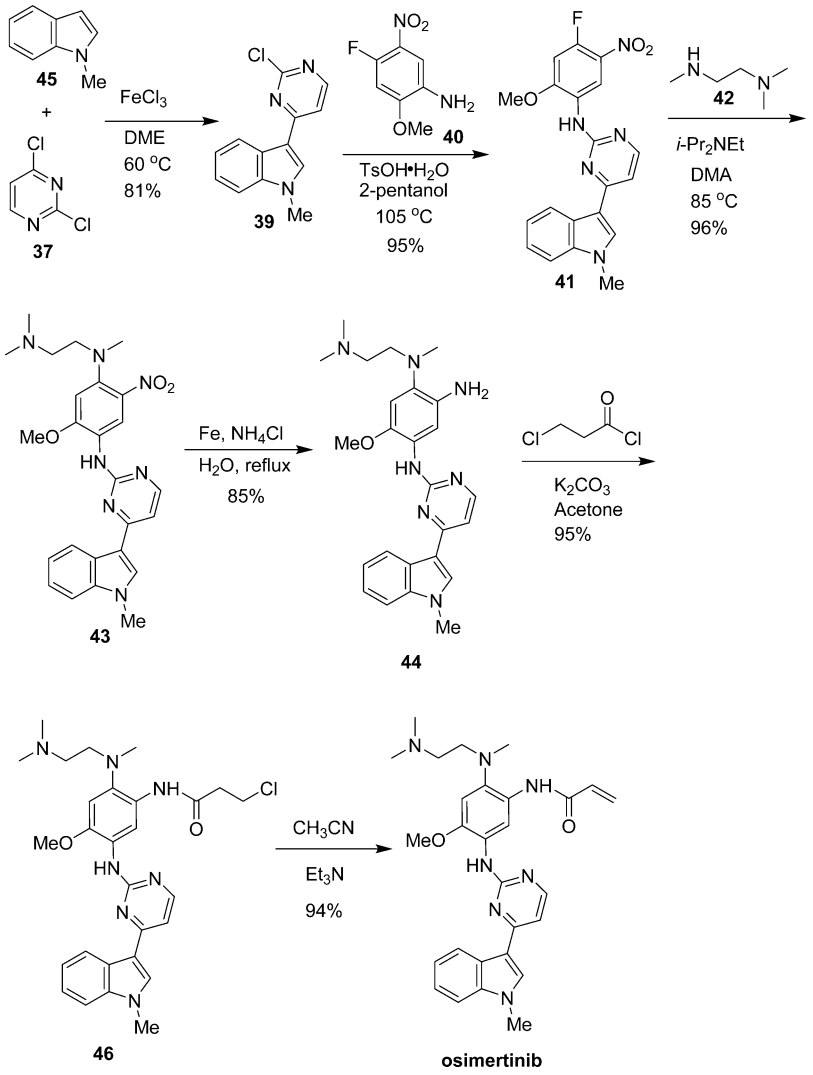
Scheme 12. Apparent Manufacturing Route to Osimertinib



intermediate **44** in 85% yield. Acylation with acryloyl chloride affords osimertinib in 39% yield.

2.2. Apparent Manufacturing Route. No process patents have been filed by AstraZeneca for osimertinib. The final route appears to be included in the Medicinal Chemistry patent[43] with a focus on process development of the original route, including removing chromatographies, transitioning to environmentally acceptable solvents, and eliminating microwave heating conditions. The final route is seven steps with a longest linear sequence of six steps with a 56% yield. A summary of the process improvements is outlined in Scheme 12 and summarized below.

- Intermediate **39** is prepared in a single step from *N*-methylindole and 2,4-dichloropyrimidine using $FeCl_3$ in DME at 60 °C (81% yield, crystallized from the reaction mixture with MeOH/water) or $AlCl_3$ in DME at 80 °C (67% recrystallized yield).
- In the reaction of **39** with **40**, the reaction at 85 °C in 1,4-dioxane[44] is replaced with reaction at 105 °C in 2-pentanol, resulting in a yield of 95% of product that crystallizes from the reaction mixture.
- Microwave heating for the conversion of **41** to **43** can be avoided by use of *i*-Pr_2NEt in DMA at 85 °C. The product **43** is isolated in 96% yield by addition of water to induce crystallization directly from the reaction mixture.
- The one-step acylation of **44** with acryloyl chloride (yield reported as 39% after chromatography) is replaced in the final route with an amidation with 2-chloropropanoyl chloride using K_2CO_3 in acetone (95%) to form **46** followed by elimination with trimethylamine in MeCN (94% yield). The free base of osimertinib is crystallized by addition of water and isolated as polymorph D.

According to the European Public Assessment Report (EPAR) for Tagrisso, osimertinib is manufactured in four steps.[45] No information is provided on the regulatory starting materials.

2.3. Flow Chemistry for Conversion of 44 to Osimertinib. A continuous process for the two-step conversion of **44** to osimertinib has been developed as a collaboration between AstraZeneca, Lancaster University, and the University of Leeds.[46] A self-optimizing flow reactor was designed, combining at-line HPLC analysis with evolutionary feedback algorithms to achieve optimized conditions for the two-step conversion of **44** to osimertinib in an automated fashion. The reactor setup involved three pumps, one each for the substrate **44** solution in MeCN/water, 2-chloropropanoyl chloride in MeCN, and triethylamine in MeCN/water, which

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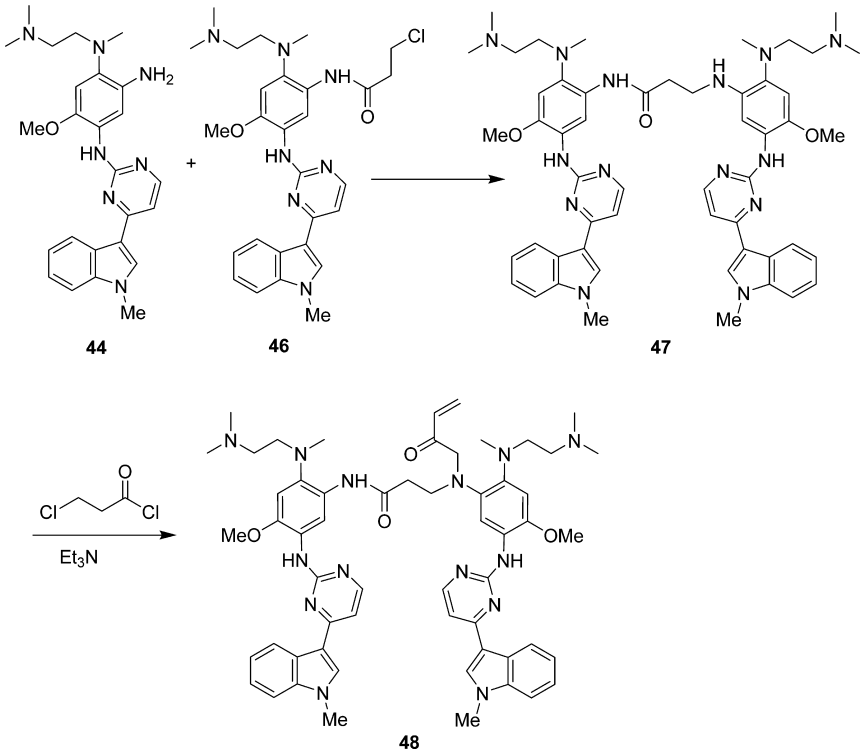
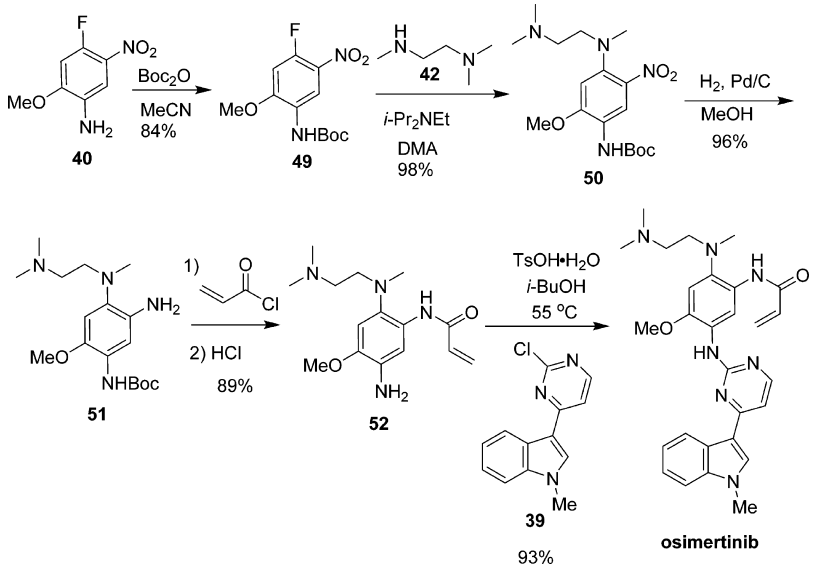
Scheme 13. Formation of Dimer 48



Scheme 14. Alternate Route to Osimertinib



were fed into a tubular reactor. The optimum conditions were 2.65 equiv of the acid chloride, 10.5 equiv of NEt_3, a reaction temperature of 123.9 °C, and a residence time of 9.36 min. The yield for the two steps was 89%. A buildup of intermediate **46** indicates the elimination is the likely rate-limiting step under the flow conditions. Excess acid chloride was required to compensate for hydrolysis. A major impurity **48** was identified, derived from reaction of **44** with **46** to form **47** followed by acylation (Scheme 13). The authors did not comment on whether minimization of this impurity was one of the optimization goals.

2.4. Alternate Routes to Osimertinib. *2.4.1. Resequencing of Steps.* A Chinese patent application and publication describe an alternate route to osimertinib (Scheme 14) having the same bond disconnections as the manufacturing route but in a different sequence.[47] Since the aniline **40** must be protected as a Boc group, and then later deprotected, the route is two steps longer than the current manufacturing route, although the deprotection is conducted in the same pot as the acylation with acryolyl chloride (**51** to **52**). The route is more convergent since two complex intermediates, **39** and **52**, are constructed and then coupled in the final step. The amine **52** is more nucleophilic than corresponding **40**, which contains the deactivating nitro group in the original route, which permits chloride displacement at at the relatively low temperature of 55 °C in 93% yield. This is important since the labile acrylamide

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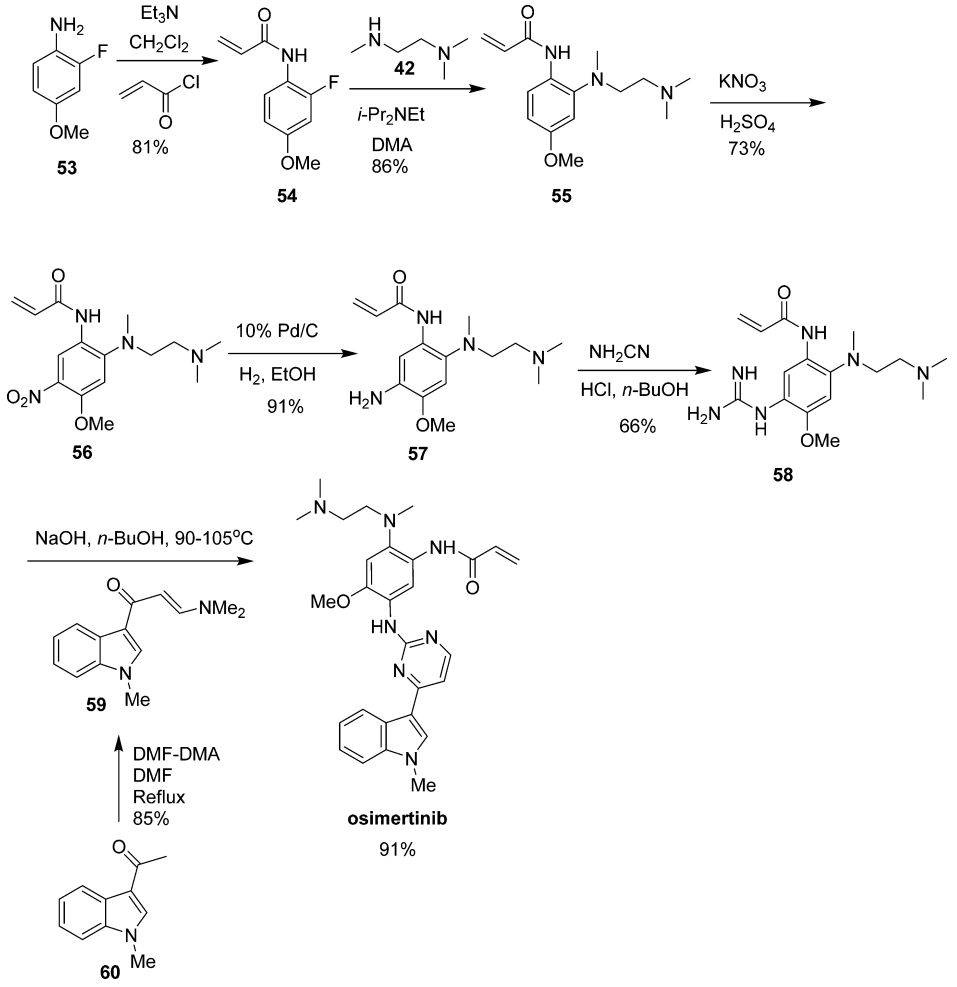
Scheme 15. Route to Osimertinib via Pyrimidine Formation as the Final Step



already installed in **52** might degrade or generate byproducts under more the more forcing conditions (105 °C) in the manufacturing route. The step yields are >90% except for the initial Boc protection (84%), with an overall yield of 65% for the six steps in the longest linear sequence. This route could be considered as a manufacturing route assuming development can provide an acceptable impurity profile.

2.4.2. Alternate Osimertinib Synthesis Via Construction of the Pyrimidine. A second alternate route to osimertinib has been recently published as a Chinese patent application, involving a late stage construction of the pyrimidine ring (Scheme 15).[48] The acrylamide is installed in step 1 via reaction of 2-fluoro-4-anisidine with acryloyl chloride to generate **54**. S_NAr reaction with diamine **42** in *N,N*-dimethylacetamide at 85−95 °C affords **55** in 86% yield, quite mild conditions for a substrate with no strong electron-withdrawing groups to activate the ring. The introduction of the amine at the 5-position is accomplished via nitration followed by hydrogenation to afford **57** in 66% over the two steps. Reaction with cyanamide furnishes guanidine **58** in 66% yield. The pyrimidine is then constructed by reaction with indole ene-amine **59** to afford osimertinib in 91% yield. The overall yield for the 6-step longest linear sequence is 28%.

While the number of steps for this route is similar to the manufacturing route, the overall yield is considerably lower. While further development could improve yields, the reduced yields may reflect the impact of carrying the reactive acrylamide throughout the entire sequence.

2.5. Osimertinib Final Form. The final form of osimertinib is the mesylate salt (EPAR) which is claimed in AstraZeneca U.S Patent 8,946,235.[43a] Given the good solubility of the salt and low permeability, osimertinib is classified as BCS III.[43a]

Although the EPAR[45] comments that "only one polymorphic form is known despite extensive polymorph screening," the AstraZeneca patent and patent applications describe forms A and B of the mesylate salt.[43] Form A is crystallized from acetonitrile, while form B is crystallized from either 1:1 EtOH/EtOAc or acetone/water (11:1).

Seven crystal forms of the free base were discovered and characterized. According to the Medicinal Chemistry publication,[42] the mesylate salt was selected for development not to enhance adsorption, but due to risks around controlling the physical form of the free base.

Summary. No process patents have been filed for osimertinib by the originator company, AstraZeneca. The apparent manufacturing process is incorporated into the compound patent[43] and appears to be an optimized Medicinal Chemistry route in which chromatographies and microwave heating have been eliminated and undesirable solvents have been replaced with environmentally acceptable solvents. The final route is seven steps with a longest linear sequence of six steps having a 56% yield. Since no process patents have been

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filed, the route for manufacturing osimertinib will expire at the same time as the compound patent (Aug2032).[43] The crystalline mesylate salt is also claimed in the compound patent,[43] meaning exclusivity for the current final form will also expire at the same time as the compound patent.

Two patent applications on alternate routes have been filed. Both could potentially be developed into manufacturing routes although they provide no compelling advantages over the AstraZeneca route. The patents on alternate routes, if granted, would provide the applicants with their own propriety routes to osimertinib.

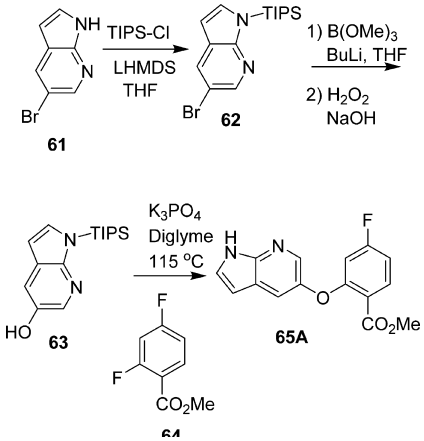
3. VENETOCLAX (VENCLEXTA)

Venetoclax, marketed under the trade name Venclexta in the U.S., is an orally active inhibitor of antiapoptotic protein B-cell lymphoma-2 (Bcl-2) developed and marketed by AbbVie and Genentech.[49] Venetoclax was approved in the U.S. in April 2016 for the treatment of chronic lymphocytic leukemia (CLL). Applications in Europe and Canada are pending.[49]

3.1. Medicinal Chemistry Route to Venetoclax. The Medicinal Chemistry route to venetoclax is concisely described in AbbVie patent 8,722,657,[51a] as well as in three other patents assigned to AbbVie.[50] The convergent route involves preparation of three main fragments, **65A**, **66**, and **67**, which are then assembled to construct venetoclax. The total step count is 14 with a longest linear sequence of eight steps (Scheme 18).

The preparation of aza-indole fragment **65A** (Scheme 16) starts with TIPS protection of 5-bromoindole followed by

Scheme 16. Medicinal Chemistry Synthesis of Aza-Indole 65A

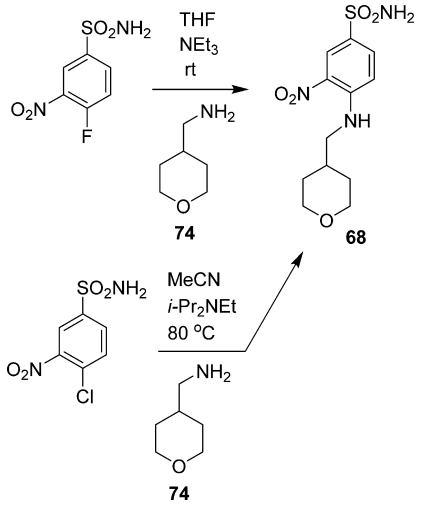


conversion of the bromo substituent to hydroxyl via the formation of the boronate ester and oxidation, affording **63**. S_NAr reaction with methyl 2,4-difluorobenzoate (**64**) affords indole **65A**. No yields are provided.

Sulfonamide **68** is synthesized in one step by S_NAr reaction of 4-fluoro-3-nitrobenzenesulfonamide with amine **74** (Scheme 17).

Preparation of intermediate **66** and subsequent conversion to venetoclax is presented in Scheme 18. Ketoester **69** is converted to enol triflate **70** and cross-coupled with 4-chlorobenezeboronic acid to afford **71**. Reduction of the ester is accomplished with $LiBH_4$; then the resulting primary alcohol **72** is activated as a mesylate and reacted with *N*-Boc-piperazine to furnish **73**. Acidic deprotection yields fragment **66**.

Scheme 17. Routes to Sulfonamide 68



Assembly of the fragments starts with S_NAr reaction of piperazine fragment **66** with aza-indole fragment **65A** in DMSO at 135 °C to afford **67** (Scheme 18). After hydrolysis of the ester, sulfonamide **68** is coupled using EDC to generate venetoclax.

3.2. Manufacturing Route to Venetoclax.[52] The main issues to address for the manufacturing route included length of the synthesis, availability of raw materials, and lack of regioselectivity in the S_NAr reaction of **63** with methyl 2,4-difluorobenzoate **64**.

To avoid lack of regioselectivity in the S_NAr reaction with **64**, the synthesis starts with 1-bromo-3-fluoro-4-iodobenzene **77** (Scheme 19).[52] Activation of the iodide with *i*-PrMgCl followed by reaction with Boc_2O affords ester **78**, which is reacted with aza-indole **79** to afford intermediate **65B**, which is crystallized as a crude solid by addition of water. Recyrstallization from EtOAc/heptane affords **65B** in overall 86% yield.

The manufacturing route to sulfonamide **68** involves S_NAr reaction with 4-chloro-3-nitrobenzenesulfonamide which is cheaper and more available than the 4-fluoro analogue used for the original route (Scheme 17).

The manufacturing route to intermediate **66** starts with 3,3-dimethylcyclohexanone and requires four steps (Scheme 20).[52] Reaction with $POCl_3$ and DMF affords vinyl chloride **75** in quantitative yield as an oil. Cross coupling with 4-chlorobenzene boronic acid furnishes aldehyde **76** in 87% assay yield, which is carried directly into the next step without isolation. Reductive alkylation with *N*-Boc-piperazine affords **73** in 85% yield after crystallization from toluene/acetonitrile. Acid deprotection with aq. HCl in 2-PrOH leads to fragment **66**, which crystallizes from the reaction mixture as the bis-HCl salt in 95% yield.

Palladium-catalyzed C−N coupling with **66** affords **67B** in 89% yield (Scheme 20) after work up with cysteine to remove Pd followed by crystallization from cyclohexane.[52] The final steps to venetoclax are similar to the route outlined in Scheme 18, with the hydrolysis of the ester followed by coupling with sulfonamide **68** to afford venetoclax in 71% isolated yield across the two steps, including after crystallization and drying of the final product. Overall yield for the 7-step longest linear sequence is 52%.

Intermediates **65B** and **67B** are claimed in U.S. Patent Application 2014/0275540.[52b]

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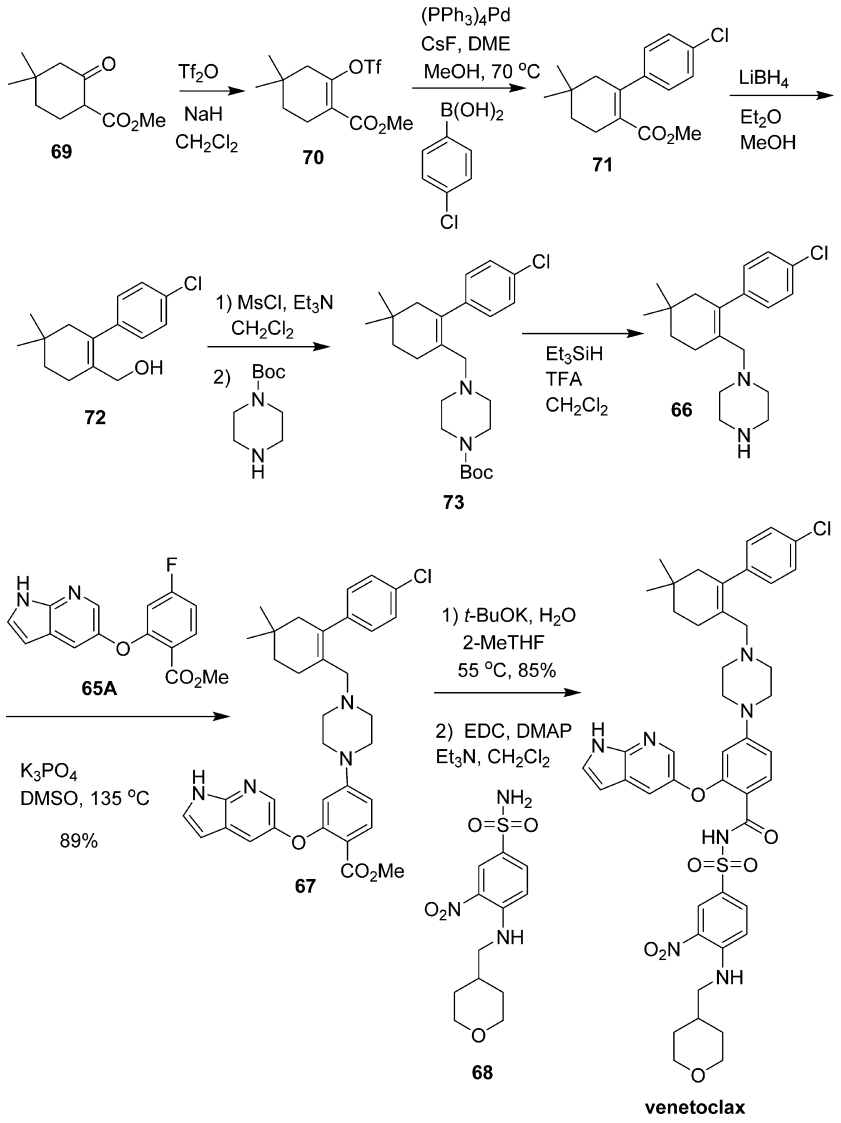
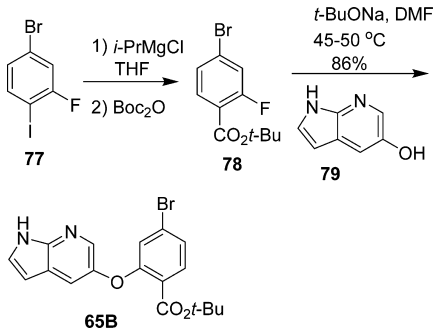
Scheme 18. Original Route to Venetoclax



Scheme 19. Manufacturing Route to 65B



3.3. Alternate Route to Venetoclax. An alternate route to venetoclax is described in a Chinese patent application (Scheme 21).[53] This route uses the same intermediate **72-Ms** as the Medicinal Chemistry route (Scheme 18) but builds the piperazine fragment as a part of the aza-indole intermediate prior to reaction with the mesylate.

Intermediate **84** is formed via three telescoped steps in 57% yield. This sequence starts with aza-indole **79**, which is reacted with methyl 2-fluoro-4-nitrobenzoate (**80**) to afford ester **81**, then directly hydrogenated to afford aniline intermediate **82**. Reaction with bis(2-chloroethyl)amine (**83**) under basic conditions affords fragment **84**. Coupling of **84** with **72-Ms** provides common intermediate **67** in 88% yield.

Overall, this route appears to be developable into a viable manufacturing route but offers no major advantage over the current route.

3.4. Final Form of Venetoclax. The final form of venetoclax is a crystalline anhydrous free base, form A, claimed in granted U.S. Patent 8,722,657.[51a] The only description provided in this patent for the preparation for form A is by drying dichloromethane and EtOAc crystalline solvates. Another anhydrous free base polymorph (form B) is described and is prepared by drying of the acetonitrile solvate.

The process patent[52] describes isolation of venetoclax free base by crystallization from a mixture of dichloromethane, MeOH, and EtOAc, but no details are provided on which crystal form is generated by this procedure. The patents do not claim any crystallization processes.

Other free base forms described and claimed include the free base hydrate (2 forms) and solvates of EtOAc, dichloro-

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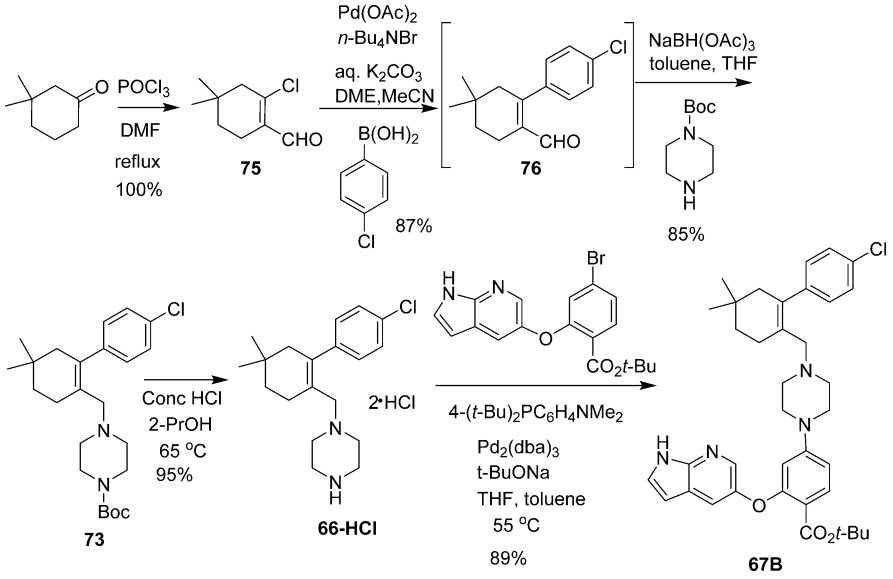
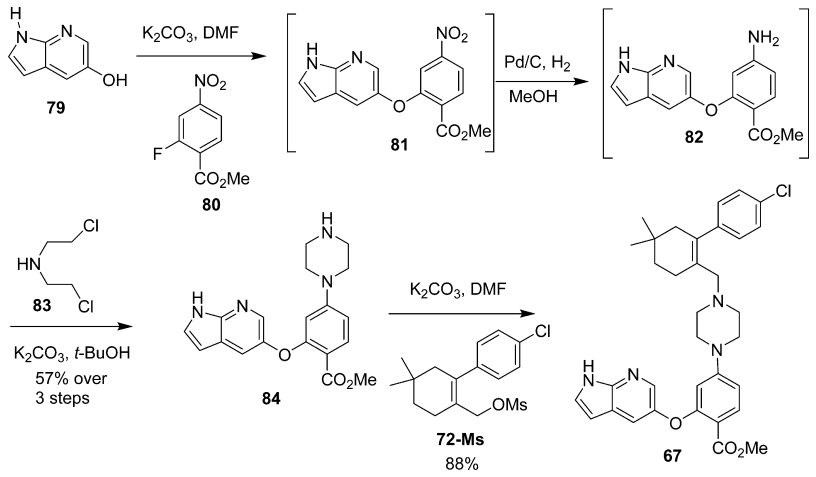
Scheme 20. Manufacturing Route to Intermediate 67B



Scheme 21. Alternate Route to Venetoclax



methane, MeCN, THF, and acetone.[51b−e] The hydrochloride and sulfate salts are described and claimed. Characterization of the forms is limited to X-ray diffraction patterns.

The solubility of the free base at pH 7.4 is <0.0042 mg/L. In Caco-2 permeability experiments, venetoclax had low recovery so its permeation could not be established. Therefore, venetoclax is considered either a BCS class II or IV compound.[54]

Summary. The manufacturing process to venetoclax described in AbbVie patents is an efficient 11-step route with a yield of 52% for the seven-step longest linear sequence.[52] An alternate route described in a Chinese patent application uses fragments **72-Ms** and **79** from the Abbvie routes but is unique in that it builds the piperidine fragment (Scheme 21).[53] If granted, this patent will provide the applicant with a proprietary route of its own, although the route offers limited advantages to the current manufacturing route.

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Notes

The author declares no competing financial interest.

ABBREVIATIONS

Boc, *t*-butyloxycarbonyl; Cbz, carboxybenzyl; DIC, *N*,*N*′-diisopropylcarbodiimide; DME, dimethoxyethane; DMF, *N*,*N*-dimethylformamide; dr, diastereomeric ratio; EMA, European Medicines Agency; EPAR, European Public Assessment Report; Fmoc, fluorenylmethyloxycarbonyl; cGMP, current good manufacturing practices; HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, hydroxybenzotriazole; mCPBA, *m*-chloroperoxybenzoic acid; MTBE, methyl *t*-butyl ether; NMP, *N*-methylpyrrolidinone; PMP, *p*-methoxyphenyl; RSM, regulatory starting materials, the point at which cGMP starts; TFE, trifluoroethanol; TFA, trifluoroacetic acid

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