Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

Synthetic Approaches to the New Drugs Approved During 2015

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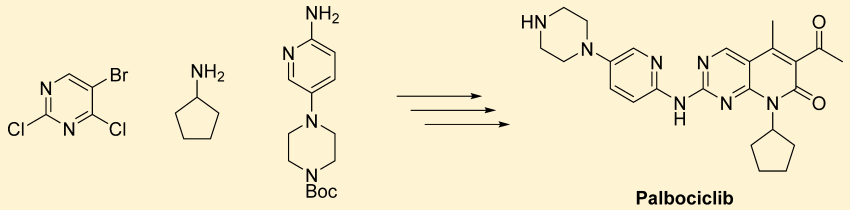


Plus the 28 other New Drugs marketed in 2015

ABSTRACT: New drugs introduced to the market every year represent privileged structures for particular biological targets. These new chemical entities (NCEs) provide insight into molecular recognition while serving as leads for designing future new drugs. This annual review describes the most likely process-scale synthetic approaches to 29 new chemical entities (NCEs) that were approved for the first time in 2015.

1. INTRODUCTION

The most fruitful basis for the discovery of a new drug is to start with an old drug.

Sir James Whyte Black, winner of the 1988 Nobel Prize in medicine[1]

Inaugurated 14 years ago,[2] this annual review presents synthetic methods for molecular entities that were approved for the first time by governing bodies within various countries during the past year. Because drugs tend to have structural homology across similar biological targets, it is widely believed that the knowledge of new chemical entities and approaches to their construction will greatly enhance the ability to discover new drugs more efficiently. The pharmaceutical industry enjoyed a productive year during 2015: 50 new drugs consisting of new molecular entities (NMEs) and biologics were approved which spanned a variety of indications including the first treatment for female hypoactive sexual desire disorder, binge eating disorder, the first vaccine for dengue, as well as the first pharmacotherapies for three rare metabolic disorders.[3] The field of oncology was the most active therapeutic area in terms of numbers of drug approvals in 2015, with 14 new drugs and biologics within this class reaching the market, including four new drugs for the treatment of multiple myeloma. Furthermore, six hematologic therapies and six metabolic treatments were brought to the market. In contrast to the productivity realized industrywide during 2014 and 2015, the number of medicines approved decreased in 2016. Nonetheless, an additional 21 new drugs were in the process of approval from various governing bodies during 2015 but were not launched before the end of the year.[3]

This review describes the syntheses of the 29 small-molecule NCEs that were approved for the first time in 2015 around the world (Figure 1). New indications for previously launched medications, new combinations, new formulations of existing drugs, and drugs synthesized purely via bioprocesses or peptide synthesizers have been excluded from this review.

Drugs presented in this review are divided into eight therapeutic categories: anti-infective, cardiovascular, neuroscience, gastrointestinal, hematologic, metabolic, musculoskeletal, and oncology. Within the therapeutic areas, drugs are ordered alphabetically by generic name. Although the scale of the synthetic routes were not explicitly disclosed in most cases, this review presents the most likely scalable routes that have been disclosed within published or patent literature beginning from commercially available starting materials.

2. ANTI-INFECTIVE DRUGS

2.1. Isavuconazonium Sulfate (Cresemba). Isavuconazonium sulfate is a broad spectrum antifungal agent that was codeveloped by Basilea Pharmaceutica (a subsidiary of Hoffmann−La Roche acquired in 2000) and Astellas Pharma, which obtained its first approval by the United States Food and

Received: January 3, 2017
Published: April 19, 2017

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

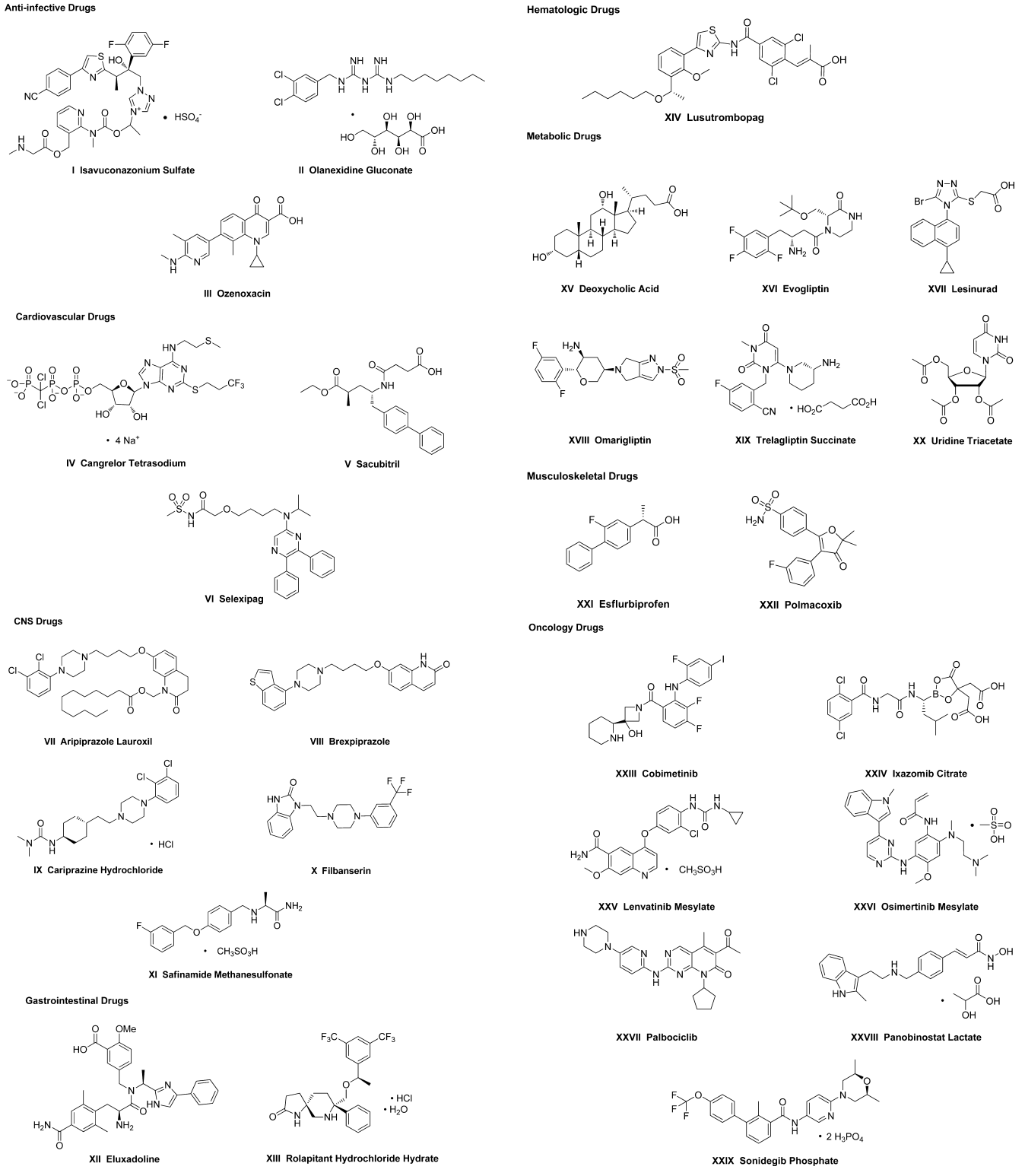
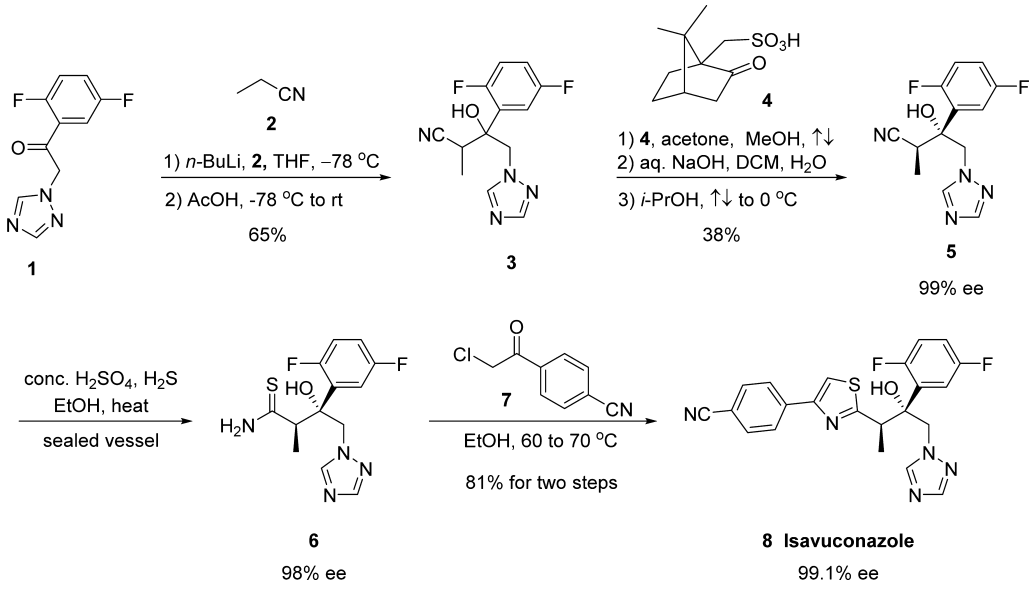


Figure 1. Structures of 29 NCEs approved in 2015.

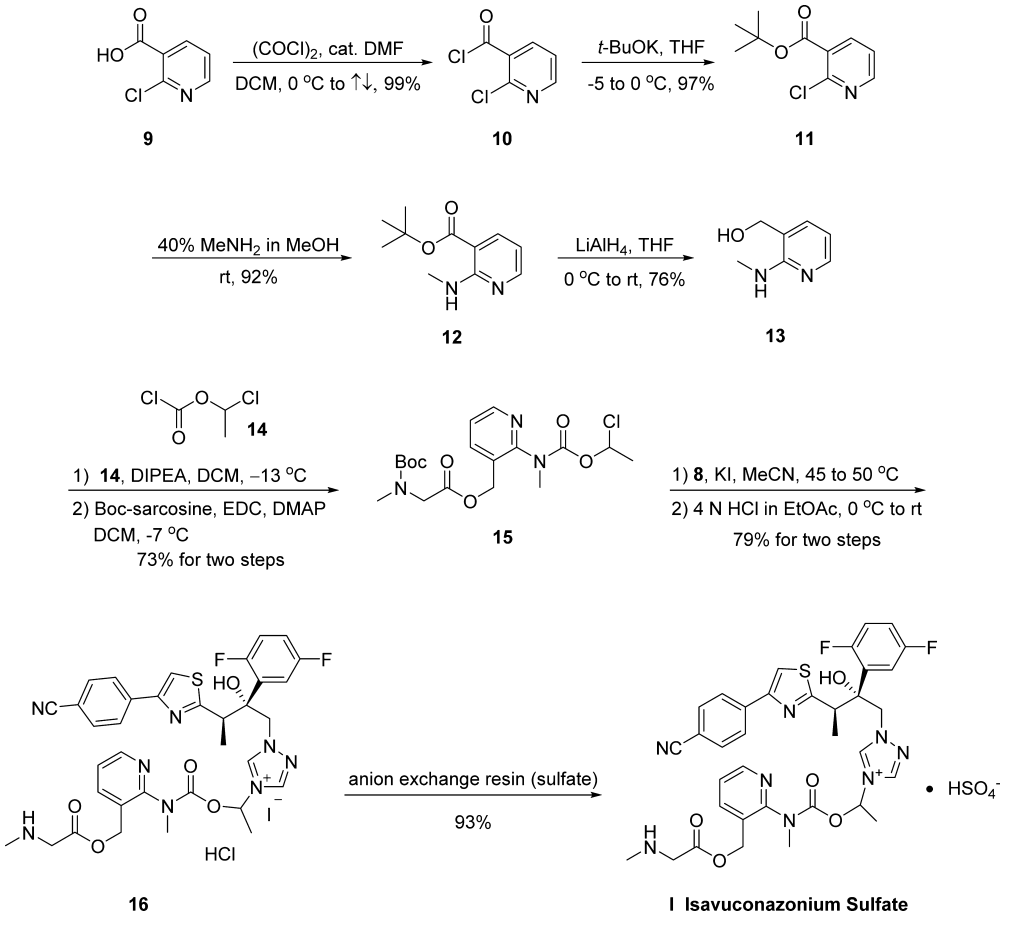
Drug Administration (FDA) for the treatment of invasive aspergillosis and invasive mucormycosis, available as both oral and intravenous formulations.[4] Isavuconazonium sulfate is a water-soluble prodrug, which is rapidly hydrolyzed by esterases (mainly butylcholinesterase) in plasma into the active moiety isavuconazole (BAL-4815) and an inactive cleavage product (BAL-8728).[4] Isavuconazole inhibits cytochrome P450 (CYP)-dependent enzyme lanosterol 14-ademethylase (CYP51) and thereby inhibits the synthesis of ergosterol, a key component of the fungal cell membrane.[4] Isavuconazole displayed potent fungistatic or fungicidal activity in vitro against a broad range of clinically important yeasts and molds, namely *Candida* spp., *Cryptococcus* spp., *Trichosporon* spp., *Geotrichum capitatum*, *Pichia* spp., *Rhodotorula* spp., *Saccharomyces cerevisiae*, *Aspergillus* spp., and most species known to cause mucormycosis (*Mucorales* mucorales). This broad range of antifungal activity

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

Scheme 1. Synthesis of Fragment 8 of Isavuconazonium Sulfate (I)



Scheme 2. Synthesis of Isavuconazonium Sulfate (I)

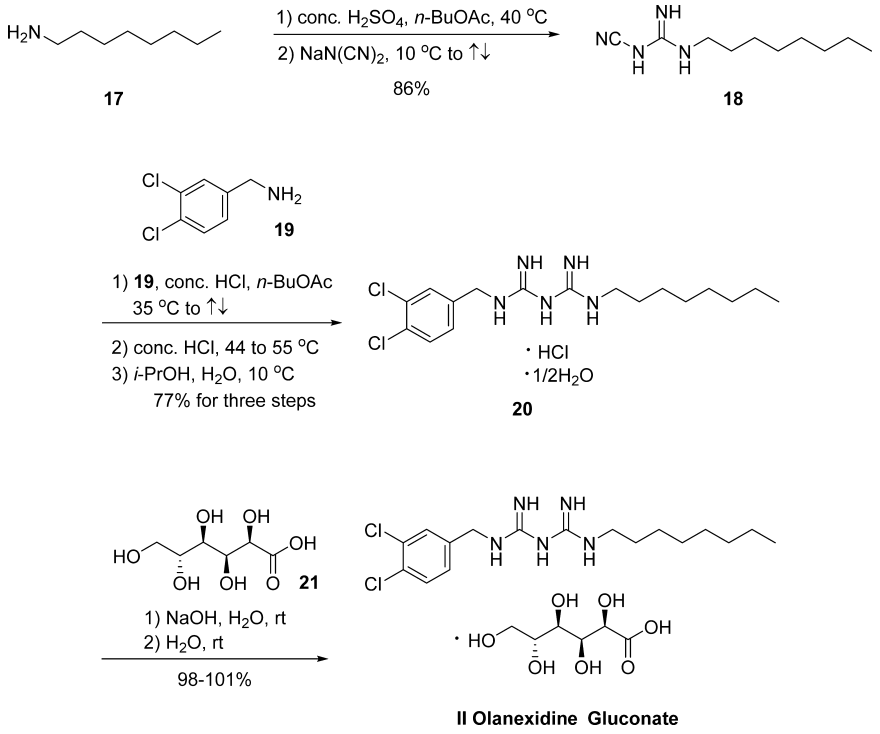


renders this drug more clinically appealing compared to other azoles with narrower indications.[5] Furthermore, isavuconazole does not require a cyclodextrin vehicle due to its water solubility, and currently does not require therapeutic drug monitoring. Moreover, isavuconazole has displayed improved safety and tolerability compared to voriconazole.[5b]

As a prodrug, the structure of isavuconazonium sulfate **I** consist of two parts: the active moiety isavuconazole **8** and a water-soluble, prodrug side chain **15**. Several papers have been published on the synthesis of isavuconazonium sulfate **I**,[6] and the approach to enantiomerically pure isavuconazole **8** has been reported through three different synthetic strategies.[6a,c,e] The following Scheme 1 and Scheme 2 describe the most likely

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480–6515

Scheme 3. Synthesis of Olanexidine Gluconate (II)



process route to both **8** and **15**, including the union of both fragments, as described by researchers at Carbo-Design LLC and Wockhardt Ltd., respectively.[6]

The synthesis of active moiety isavuconazole **8** was started with commercial 1-(2,5-difluorophenyl)-2-(1*H*-l,2,4-triazol-l-yl)ethanone (**1**) as depicted in Scheme 1. Triazole **1** was treated with *n*-BuLi followed by exposure to propionitrile (**2**) and acidic quench to give racemic alcohol **3** in 65% yield. Next, resolution of this racemic alcohol was facilitated through the use of camphor derivative **4** to provide alcohol **5** in 38% yield and 99% ee.[6c] Nitrile **5** was then treated with concentrated H_2SO_4 and H_2S to furnish thioamide **6**, and this was followed by a cyclization reaction involving 4-(2-chloroacetyl)-benzonitrile (**7**) which gave rise to isavuconazole **8** in 81% yield across the two-step sequence.[6c]

The preparation of water-soluble side chain **15** (Scheme 2) was initiated from commercially available 2-chloronicotinic acid (**9**), which was converted to the corresponding *tert*-butyl ester **11** via acid halide **10** in excellent yield for the two-step protocol. Subjection of pyridyl chloride **11** to methanolic methylamine furnished aminopyridine **12** in 92% yield, and this compound was subsequently reduced with lithium aluminum hydride to give aminoalcohol **13** in 76% yield. Next, *N*-acylation of **13** with 1-chloroethyl chloroformate (**14**) followed by treatment with *N*-Boc-sarcosine under esterification conditions delivered chloroethyl ester **15** in 73% yield.[6b] The union of the aminopyridyl side chain **15** with thiazoloalcohol **8** was facilitated by reacting the two compounds in the presence of KI in acetonitrile, and this alkylation was followed by removal of the Boc group with hydrochloric acid to give rise to isavuconazonium iodide hydrochloride (**16**) in 79% yield. Finally, isavuconazonium sulfate (**I**) was prepared from **16** using an anion exchange resin in 93% yield to finish the construction of the API.

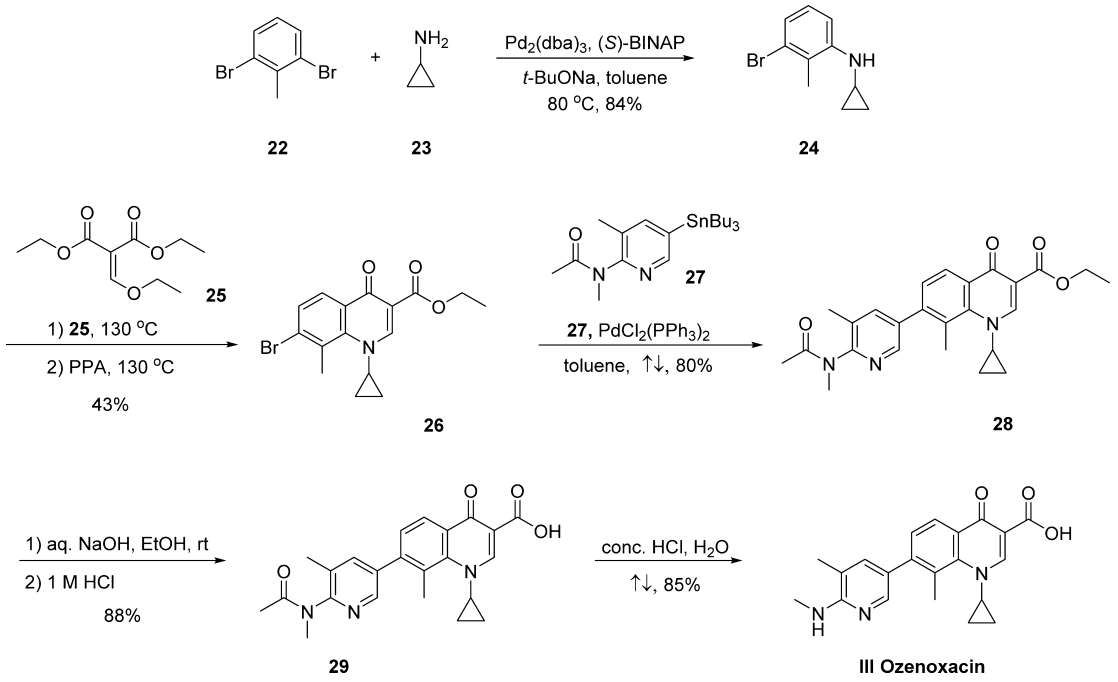
2.2. Olanexidine Gluconate (Olanedine). In July 2015, olanexidine gluconate, a biguanide compound with remarkable antibacterial activity, was approved by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan for skin antisepsis at surgical sites.[7] The drug was developed and marketed by Otsuka Pharmaceutical in Japan and is available as topical solution (1.5%). Olanexidine gluconate exhibited efficacy against a wide range of bacterial strains, especially Gram-positive bacteria. In vitro experiments exploring its mechanism of action indicated that olanexidine interacts with bacterial surface molecules (such as lipopolysaccharides and lipoteichoic acid), disrupting the cell membranes of liposomes.[8] These models suggest that the drug permeates the membranes of both *Escherichia coli* and *Staphylococcus aureus* and denatures proteins at relatively high concentrations (>160 g/mL).[8]

The synthesis of olanexidine gluconate is relatively straightforward, involving the linkage of an *n*-octyl side chain and a dichlorobenzylamine through a bis-guanidyl lynchpin. The synthesis began with the reaction of commercial *n*-octylamine (**17**) with sodium dicyanamide in the presence of concentrated sulfuric acid in refluxing *n*-butyl acetate to give rise to 1-cyano-3-octylguanidine (**18**) in 86% yield (Scheme 3). Conditions employed to subsequently secure biguanidine **20** as the HCl salt hemihydrate in 77% yield were nearly identical to those used for the conversion of **17** to **18**.[9] Finally, treatment of **20** with sodium hydroxide in the presence of gluconic acid (**21**) gave rise to olanexidin gluconate (**II**) in almost quantitative yield.[10]

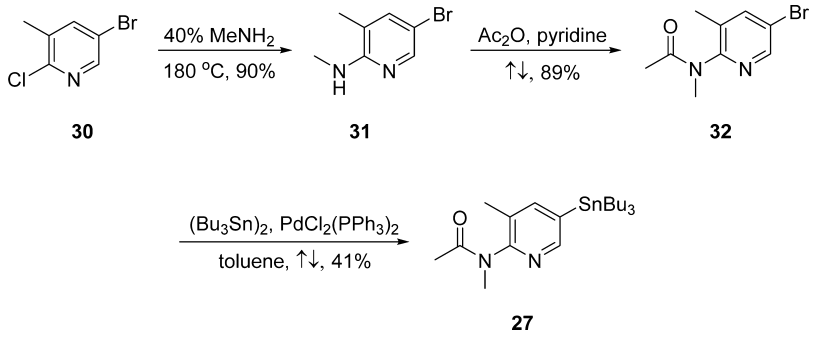
2.3. Ozenoxacin (Zebiax). Ozenoxacin is a novel, nonfluorinated quinolone antibiotic discovered by Toyama Chemical Co. Ltd. and developed by Maruho Co. Ltd. Ozenoxacin was approved by the PMDA of Japan in September 2015 for the treatment of acne and skin infections.[3] Ozenoxacin shows potent antibacterial activity against anaerobic and aerobic, gram-positive and -negative bacteria, especially those

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

Scheme 4. Synthesis of Ozenoxacin (III)



Scheme 5. Synthesis of Fragment 27 of Ozenoxacin (III)



implicated in superficial skin infections such as *S. aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acnes*.[3,11] The mechanism of action of ozenoxacin involves the drug's affinity for DNA gyrase and DNA topoisomerase IV and upon binding triggers bacterial apoptosis.[3]

A U.S. patent filed by co-workers at Toyama describes the only publicly disclosed synthetic approach to this drug.[12] The drug's assembly hinges upon a key Stille coupling between a quinolonyl bromide and a stannylpyridine (Schemes 4 and 5). Buchwald−Hartwig coupling of commercially available 2,6-dibromotoluene (**22**) and cyclopropylamine (**23**) gave *N*-cyclopropyl-3-bromo-2-methylaniline **24** in 84% yield (Scheme 4), and this step was followed by reaction with diethyl ethoxymethylenemalonate (**25**) and subsequent cyclization under acidic conditions to secure bromoquinoline **26** in 43% yield over the two-step sequence. Stille coupling of **27** with bromoquinoline **26** resulted in pyridyl quinoline adduct **28** in 80% yield. Saponification of ester **28** followed by acidic removal of the *N*-acetyl group delivered the active pharmaceutical ingredient ozenoxacin (**III**) in 75% yield.

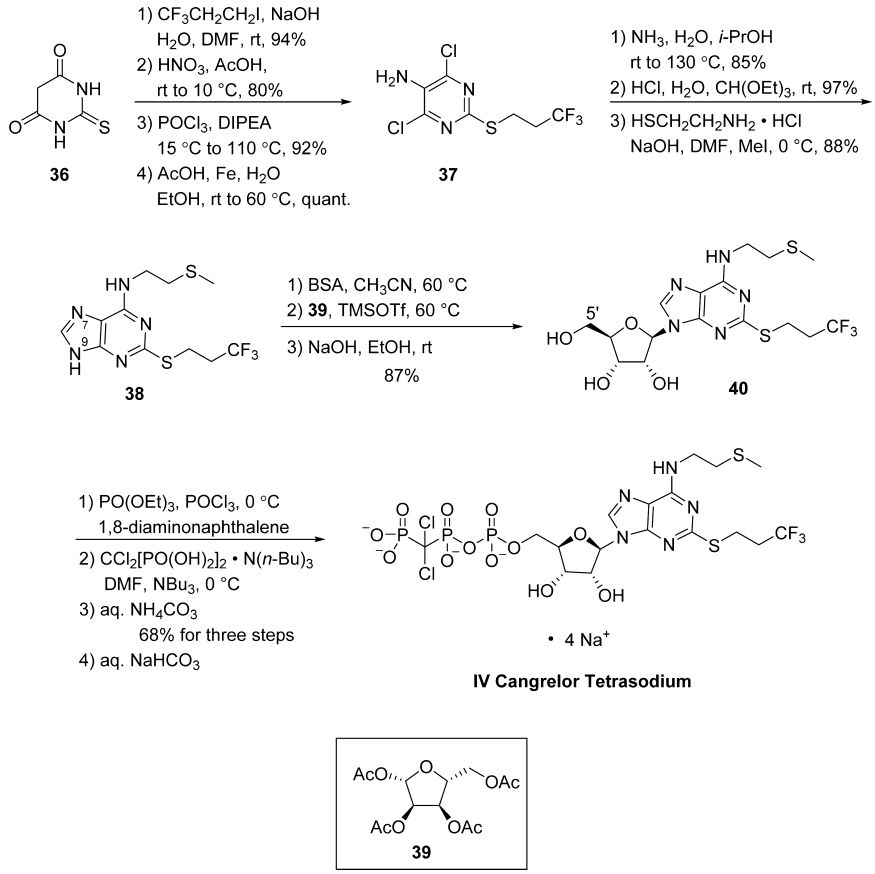
The preparation of key stannane **27**, which is not commercially available, is depicted in Scheme 5 and began with the conversion of commercially available 5-bromo-2-chloro-3-methylpyridine (**30**) to aminopyridine derivative **31** upon treatment with aqueous methylamine at elevated temperature in a sealed vessel. The resulting aminopyridine was subjected to acetic anhydride in pyridine, resulting in acetamide **32** in good yield, and this coupling was followed by a modest-yielding palladium-catalyzed installation of the stannyl group to deliver subunit **27**.

3. CARDIOVASCULAR DRUGS

3.1. Cangrelor Tetrasodium (Kengrexal). Cangrelor tetrasodium is a direct purinergic platelet receptor (P2Y12) inhibitor that blocks ADP-induced platelet activation and aggregation.[13] The drug, which was developed by The Medicine Company, binds reversibly to the P2Y12 receptor, preventing further signaling and platelet activation.[13] Cangrelor, which was approved in June 2015 by the FDA, is indicated as an adjunct to percutaneous coronary intervention for reducing the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.[13] The most common side effect observed with the drug was bleeding.[13]

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

Scheme 6. Synthesis of Cangrelor Tetrasodium (IV)

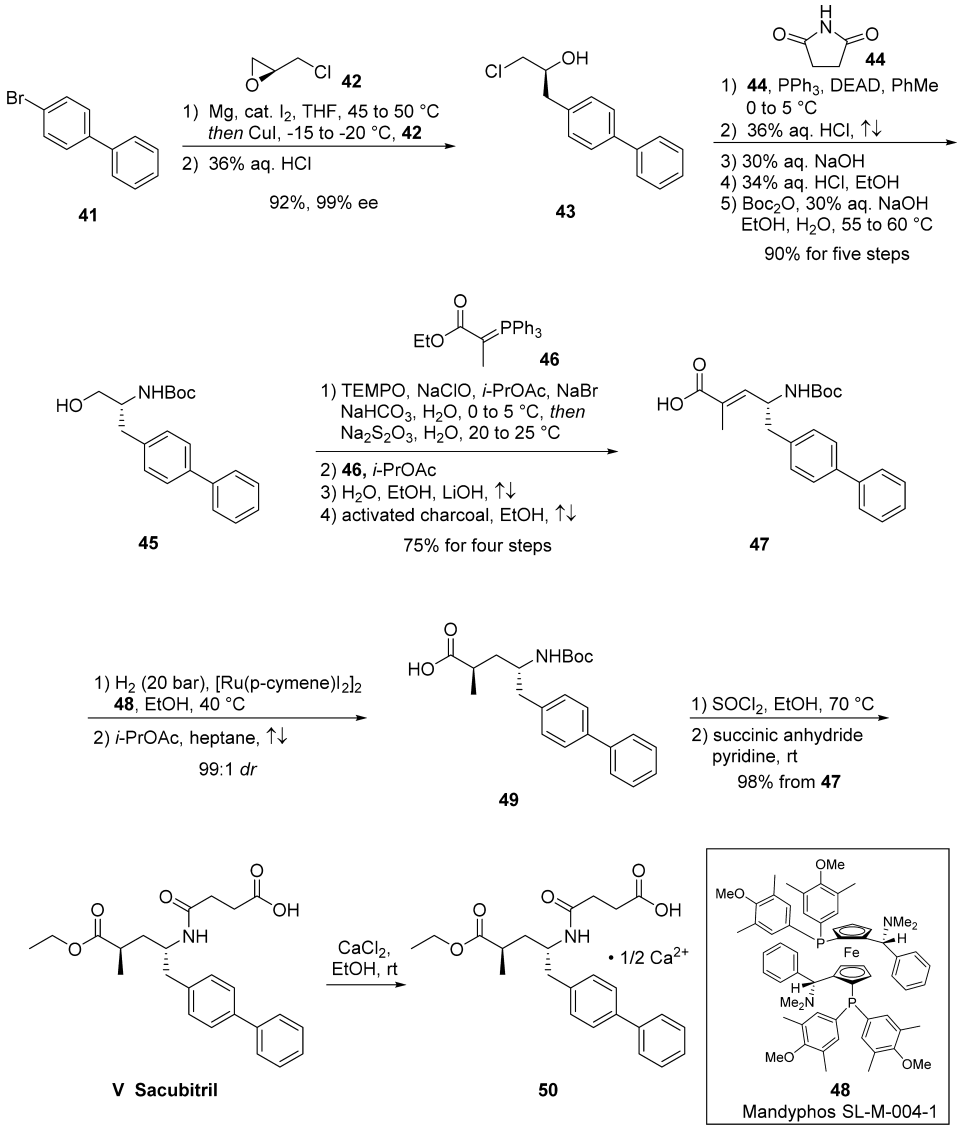


While several discovery-scale routes to cangrelor tetrasodium were previously reported,[14] an improved procedure developed with the goal of providing a manufacturing scale route to cangrelor tetrasodium has recently been reported by Jinan Bestcomm Pharmaceutical R&D. Starting from commercially available 2-thiobarbituric acid (**36**, Scheme 6),[15] *S*-alkylation with 3,3,3-trifluoropropyl iodide proceeded in high yield (94%) under basic conditions. Nitration of this intermediate with HNO_3/AcOH generated a nitro-pyrimidine diol in 80% yield. Bis-chlorination via treatment with $POCl_3$ provided the corresponding dichloro pyrimidine (92%), and subsequent nitro reduction with AcOH/Fe under aqueous conditions yielded intermediate **37** (quantitative yield), which readily provided the bis-aniline analogue by reaction with ammonia in EtOH/H_2O at 80 °C. Condensation with triethyl orthoformate/HCl at room temperature provided access to the desired purine in high yield (97%). A one-pot alkylation/amination strategy was then employed, first relying on *S*-alkylation of 2-aminoethanethiol hydrochloride with MeI/NaOH and reaction of the resulting amine with the purine chloride generated **38** in 88% across the sequence. Alkylation of **38** with commercial furanose **39** proceeded in a regioselective manner favoring *N*-9 functionalization, employing conditions similar to those previously described by Almond and co-workers.[16] Toward this end, silylation of **38** with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) followed by subjection to TMSOTf and **39**, resulted in the desired *N*-9 alkylated product, which was carried crude to global deacetylation with NaOH/EtOH at room temperature, making way for smooth conversion to alcohol **40** (87% from **38**). Although phosphorylation of **40** has been performed using a variety of related methods,[14] the largest scale conditions reported to date consist of initial 5′ alcohol activation with $POCl_3$ and $PO(OEt)_3$[17] in the presence of 1,8-diaminonaphthalene, furnishing the 5′ monophosphonate intermediate. This intermediate was not isolated but further treated with a solution of dichloromethylenebis(phosphonic acid) tributylammonium salt and tributylamine in DMF at 0 °C, yielding cangrelor as a crude ammonium salt following quench with NH_4HCO_3.[15] Purification via ion exchange chromatography provided cangrelor as its ammonium salt in 68% yield over the three-step sequence, which was subjected to aqueous $NaHCO_3$ solution and lyophilization and provided cangrelor tetrasodium salt (**IV**). This synthesis was performed starting on >100 g scale of **36** and required only one chromatography step which involved ion exchange chromatography of the cangrelor ammonium salt.[15] More recently, while beyond the scope of this article, additional reports have been disclosed describing the development of specific pharmaceutical formulations for delivery of cangrelor in high purity.[18]

3.2. Sacubitril (Entresto). Sacubitril is a neprilysin inhibitor prodrug developed by Novartis that was approved as part of an orally administered supramolecular sodium salt complex with the angiotensin receptor blocker (ARB) valsartan in the U.S. and EU in 2015.[19] Sacubitril/valsartan (also known as LCZ-696) is a first-in-class dual angiotensin receptor blocker−neprilysin inhibitor (ARNI) marketed for the treatment of chronic heart failure with reduced ejection fraction (HFrEF).[19] It represents a novel mechanistic approach to targeting HFrEF and is the first pharmacologic agent approved for HFrEF since 2004.[20] Sacubitril is metabolized by enzymatic conversion of the ethyl ester to the active diacid (LBQ-657, structure not disclosed), which inhibits neprilysin and prevents

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

Scheme 7. Synthesis of Sacubitril (V)



endogenous natriuretic peptide degradation.[21] Neprilysin inhibitors like sacubitril are not effective as monotherapy and need to be combined with a renin−angiotensin−aldosterone system (RAAS) inhibitor such as valsartan. Notably, dual neprilysin and angiotensin-converting enzyme (ACE) inhibition, as in omapatrilat, was found to be associated with an increased risk of life-threatening angioedema due to increased bradykinin levels.[21] In phase III clinical trials, sacubitril/valsartan displayed a superior safety profile to enalapril, with a 20% decrease in heart failure hospitalizations or cardiovascular death and a 16% reduction in the risk of death from any cause. Sacubitril/valsartan is now recommended as the standard of care for HFrEF as an alternative to ACEs and ARBs.[22]

Several routes to sacubitril, particularly to advanced intermediates, have been published in the primary and patent literature.[23] They differ generally in their choice of chiral pool starting material and their approach to introduction of the second stereocenter. The industrial scale synthesis of intermediate **47** has been reported, and this route is described in Scheme 7.[23e] Accordingly, addition of the cuprate of biaryl bromide **41** to (*S*)-epichlorohydrin **42** followed by subjection to HCl provided chloropropanol **43** in 92% yield and 99% ee. Next, a Mitsunobu reaction involving succinimide **44** followed by treatment with refluxing HCl and NaOH generated the corresponding aminoalcohol, which was isolated via crystallization as the HCl salt prior to Boc protection to give *N*-Boc aminoalcohol **45** in >99% ee. Alcohol **45** was then carried through a four-step process to give acid **47** in 75% yield, starting with oxidation of the alcohol to the corresponding aldehyde with TEMPO/NaOCl. The organic phase was carried forward directly into a Wittig reaction with ylide **46**, generating an α,β-unsaturated ester which was hydrolyzed to acid **47** with LiOH in an ethanol/water mixture. Interestingly, a separate patent disclosed the stereoselective hydrogenation of the trisubstituted olefin **47**, in which subjection of **47** to catalytic $[Ru(p\text{-cymene})I_2]_2$ and chiral phosphine ligand Mandyphos SL-M004-1 (**48**) under 40 bar of hydrogen gas in warm ethanol delivered **49** in 99:1 dr before recrystallization.[23b,f−h] Subsequently, activation of the acid as the acid halide through the use of thionyl chloride and ethanol not only reestablished the ethyl ester but removed the Boc group, revealing a primary amine which then reacted with succinic anhydride to ultimately deliver sacubitril (**V**). The freebase form of sacubitril does not readily crystallize; the isolation of a number of pharmaceutically

DOI: 10.1021/acs.jmedchem.7b00010
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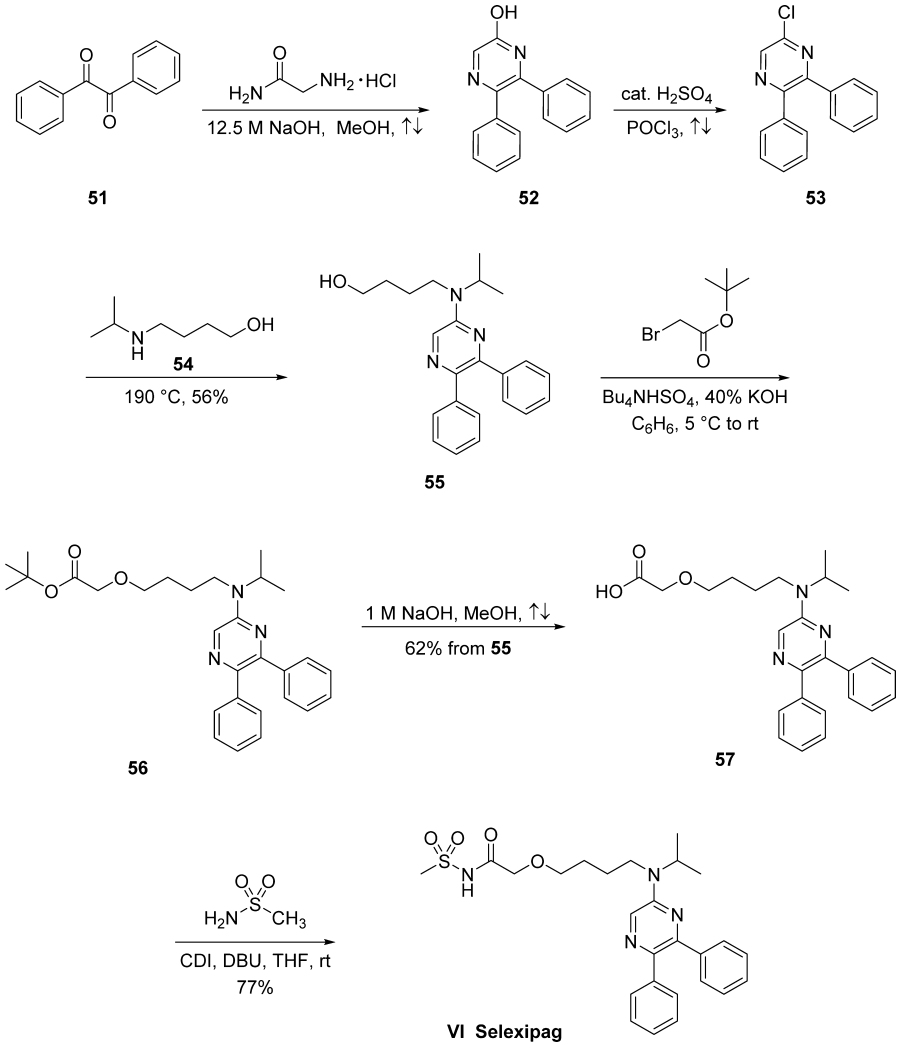
Scheme 8. Synthesis of Selexipag (VI)



acceptable salts of sacubitril via crystallization, most preferably the calcium salt **50** or sodium salts, have been reported.[23c,d,i,j] Preparation of the sacubitril/valsartan supramolecular complex (trisodium salt, hemihydrate) has been described on a kilo-scale from sacubitril calcium salt via neutralization to the freebase and subsequent complexation with valsartan in *i*PrOAc/acetone.[23j] Addition of NaOH and crystallization then provided the desired trisodium salt hemihydrate.

3.3. Selexipag (Uptravi). Selexipag and its active metabolite, the corresponding carboxylic acid, are non-prostanoid prostaglandin I2 (PGI-2) receptor agonists (Scheme 8).[24] The *N*-methylsulfonamide within selexipag is hydrolyzed to the corresponding carboxylic acid in vivo by hepatic microsomes at a rate which provides a slow-release pharmacological effect.[24] The compound was originally discovered by Nippon Shinyaki and later licensed to Actelion for development. The drug was approved in 2015 and first launched for the oral treatment of pulmonary arterial hypertension (PAH) in the U.S. in 2016 to delay disease progression and reduce the risk of hospitalization.[25]

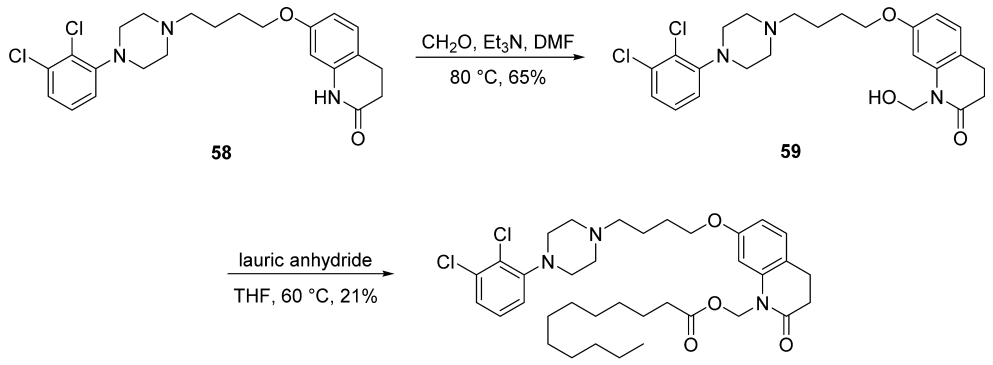
The synthesis of selexipag began with condensation of commercially available benzil (**51**) and glycinamide hydrochloride in the presence of concentrated sodium hydroxide in refluxing MeOH to yield hydroxypyrazine **52**. This compound was subsequently converted to 5-chloro-2,3-diphenylpyrazine (**53**) upon treatment with refluxing $POCl_3$ in the presence of a catalytic amount of H_2SO_4.[26] Chloride **53** was then subjected to neat 4-(isopropylamino)-1-butanol (**54**, prepared by the reductive alkylation of 4-amino-1-butanol and acetone with hydrogen over PtO_2 in EtOH) at 190 °C to give amino-pyrazinyl alcohol **55** in 56% yield as colorless crystals. Alcohol **55** was alkylated with *tert*-butyl bromoacetate using Bu_4NHSO_4 as a phase-transfer catalyst and 40% aqueous KOH in benzene to give ester **56**. Although it is particularly unusual to employ benzene on a production scale, these are the only reported conditions for this transformation. The crude ester **56** was then saponified using methanolic sodium hydroxide to yield the corresponding carboxylic acid **57** in 62% as pale-yellow crystals in two steps from compound **55**. Finally, the carboxylic acid **57** was coupled with methanesulfonamide in the presence of CDI and DBU in THF to give selexipag (**VI**) in 77% yield.[27]

4. CNS DRUGS

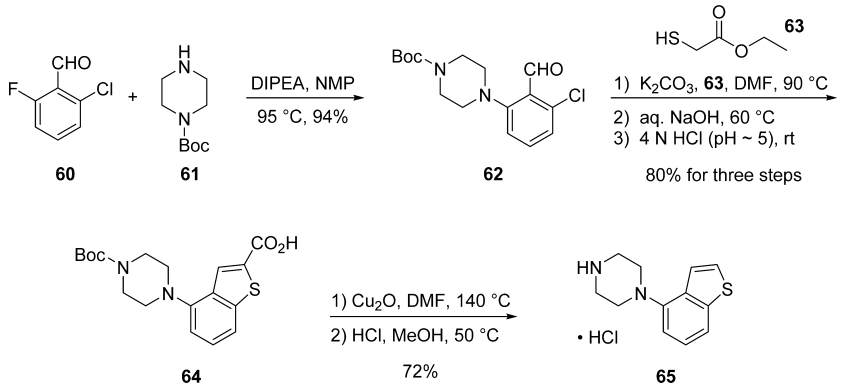
4.1. Aripiprazole Lauroxil (Aristada). Aripiprazole lauroxil is a long acting injectable (LAI) pro-drug formulation of aripiprazole approved in the U.S. for the treatment of schizophrenia.[28] Aripiprazole lauroxil is a dopamine D2 receptor partial antagonist, a 5-HT_{2A} antagonist, and a 5-HT_{1A} partial agonist that was developed by Alkermes. It was

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

Scheme 9. Synthesis of Aripiprazole Lauroxil (VII)



Scheme 10. Synthesis of Piperazinyl Fragment 65 of Brexpiprazole (VIII)



approved for once monthly and once every six weeks injection and is the second LAI of aripiprazole (with Abilify Maintena being the first).

The synthesis of aripiprazole lauroxil has only been described on gram scale in the patent literature and is highlighted in Scheme 9.[29] Commercially available aripiprazole (**58**) was treated with formaldehyde to give hemiaminal **59** in 65% crude yield and was then heated with lauric anhydride to give aripiprazole lauroxil (**VII**) in 21% overall yield.

4.2. Brexpiprazole (Rexulti). Brexpiprazole is a novel antipsychotic drug which serves as a serotonin−dopamine activity modulator and has demonstrated efficacy as an adjunctive treatment in patients with major depressive disorder (MDD).[30] The drug exhibits a unique pharmacological profile, acting as a partial agonist of serotonin 5-HT_{1A} and dopamine D2 receptors and as a full antagonist of 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, with similar subnanomolar binding affinity.[31] The drug, which was developed by Otsuka and Lundbeck, was approved in 2015 by the FDA for the treatment of schizophrenia and as an adjunctive treatment for depression.[30] Brexpiprazole is widely considered to be a successor to Otsuka's antipsychotic drug aripiprazole (trade name Abilify) whose patent expired in August 2014.[32]

The structure of brexpiprazole affords a retrosynthetic disconnection that divides the molecule into two key subunits joined by a *n*-butyl linker. The most likely process-scale synthetic approach to brexpiprazole follows a 2013 Otsuka patent which describes the kilogram scale of the final API and a key intermediate en route to the final API.[33] Interestingly, an improved process-scale synthesis of piperazinyl benzothiophene subunit **65** (Scheme 10) was disclosed by a group at the Chinese Academy of Sciences in 2015.[34]

Commercially available fluorobenzaldehyde (**60**) underwent a substitution reaction with commercial *tert*-butyl piperazine-1-carboxylate (**61**) under basic conditions to afford the piperazinyl benzaldehyde **62** in excellent yield. Next, the construction of the benzothiophene was affected by initial condensation of thioglycolic acid ethyl ester **63** with *o*-chlorobenzaldehyde **62** under mildly basic conditions at elevated temperatures. Treatment with aqueous base and adjustment of pH to roughly 5 through the use of 4 N HCl furnished the 2-carboxylic acid benzothiophene **64** in 80% yield across the three-step operation. Next, decarboxylation through the use of cuprous oxide using conditions slightly modified from those originally described by Goosen[35] followed by acidic removal of the Boc protecting group on the terminal piperazine nitrogen secured the key piperazinyl benzothiophene subunit **65** as the corresponding hydrochloride salt.[34]

The hydroxyquinolone and linker component synthesis began with alkylation of commercially available quinolone **66** with 1,4-bromochlorobutane (**67**) under basic conditions to furnish chloroalkoxyquinolone **68**. A subsequent alkylation with hydrochloride salt **65** using potassium carbonate and warm aqueous ethanol followed by recrystallizative workup resulted in clean conversion to brexpiprazole (**VIII**) in 78% yield from **68** (Scheme 11).

4.3. Cariprazine Hydrochloride (Vraylar). Cariprazine hydrochloride (**IX**) is an oral, brain-penetrant, atypical antipsychotic developed by the Hungarian pharmaceutical firm Gedeon Richter. It was approved by the FDA in

DOI: 10.1021/acs.jmedchem.7b00010
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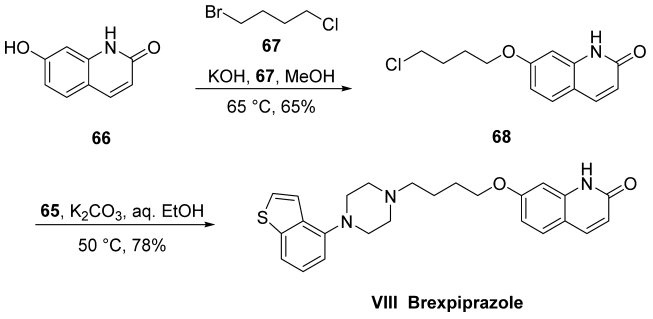
Scheme 11. Synthesis of Brexpiprazole (VIII)

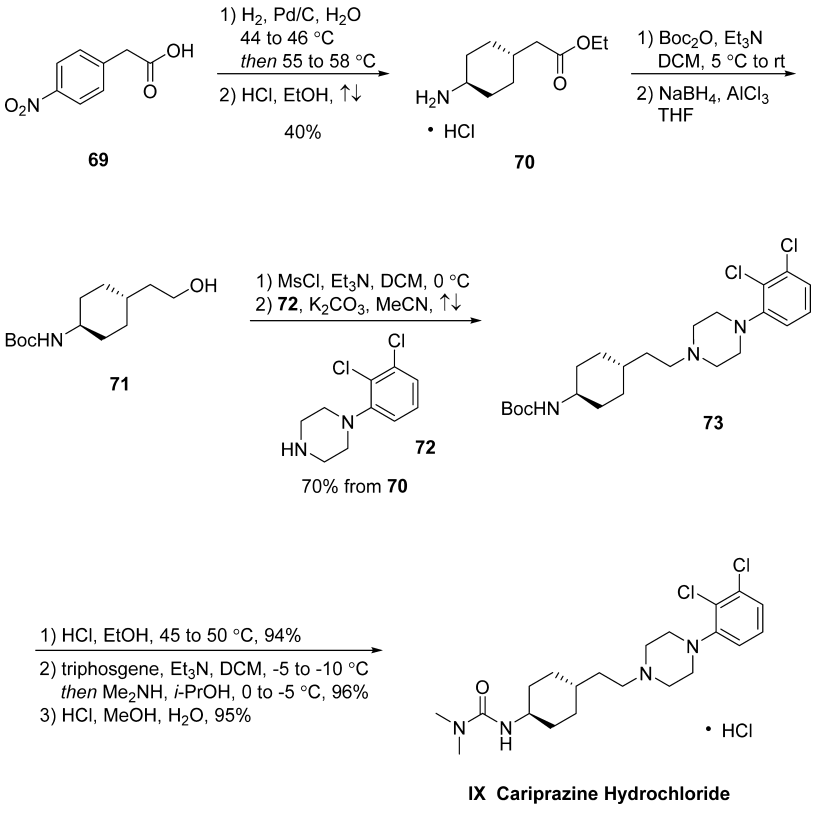


September 2015 for treatment of schizophrenia and for the acute treatment of manic or mixed episodes of bipolar I disorder.[36] While the precise mechanism of action of cariprazine is unknown, its antipsychotic and procognitive effects may be mediated through partial agonism at dopamine D2/D3 and serotonin 5-HT_{1A} receptors as well as antagonism at serotonin 5-HT_{2A} receptors.[37] Unlike many antipsychotics, cariprazine displays particular selectivity for the D3 receptor (D3, K_i = 0.085 nM; D2L, K_i = 0.49 nM; D2S, K_i = 0.69 nM).[38] Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, CYP2D6; desmethyl and didesmethyl cariprazine, the primary metabolites, are pharmacologically equipotent to the parent drug.[38b,39,40] In clinical trials, cariprazine demonstrated improvement compared to placebo as measured by Young Mania Rating Scale (YMRS) total scores in patients with bipolar mania and by Positive and Negative Syndrome Scale (PANSS) total scores in patients with schizophrenia.[41] Forest Laboratories (now Allergan) has exclusive rights to cariprazine in the U.S. and Canada, while Mitsubishi Pharma Corporation has exclusive rights to the sale of the drug in Japan and Asia.[36a]

While the synthesis of cariprazine hydrochloride has been reported in a number of patents as well as its discovery synthesis in the publicly disclosed literature, the process route has not yet been disseminated.[42] The route detailed in Scheme 12 represents the most probable large scale route reported to date.[43] Starting with the reduction of commercial 2-(4-nitrophenyl)acetic acid (**69**) via hydrogenation in water in the presence of Pd/C,[44] this reaction proceeds a one-pot, stepwise reduction of the nitro group. A separate reduction event converting the phenyl ring to the corresponding cyclohexane provides 4-aminocyclohexylacetic acid with 60–70% selectivity for the desired *trans* isomer. Following filtration and distillation, the crude aqueous solution was treated with HCl in refluxing ethanol to generate the corresponding ethyl ester **70**. Crystallization from acetonitrile gave the HCl salt in high purity and 40% yield over two steps (a reaction sequence that was reported on 200 kg scale). Amine **70** was transformed into intermediate **73** via Boc protection followed by ester reduction to the primary alcohol **71**, which was obtained as a solution in toluene following extraction. Next, mesylation of the alcohol followed by alkylation with commercially available piperazine **72** provided piperazinyl cyclohexane **73** in 70% over the four-step sequence. The carbamate protecting group within **73** was removed via acidic ethanolysis, and the resulting product was treated with triphosgene and dimethylamine to generate cariprazine as the freebase. Salt formation by means of methanolic HCl ultimately furnished cariprazine hydrochloride **IX** in 85% yield from **73**.[45]

4.4. Flibanserin (Addyi). Flibanserin is a drug originally developed by Boehringer-Ingelheim and later Sprout Pharma-

Scheme 12. Synthesis of Cariprazine Hydrochloride (IX)



DOI: 10.1021/acs.jmedchem.7b00010
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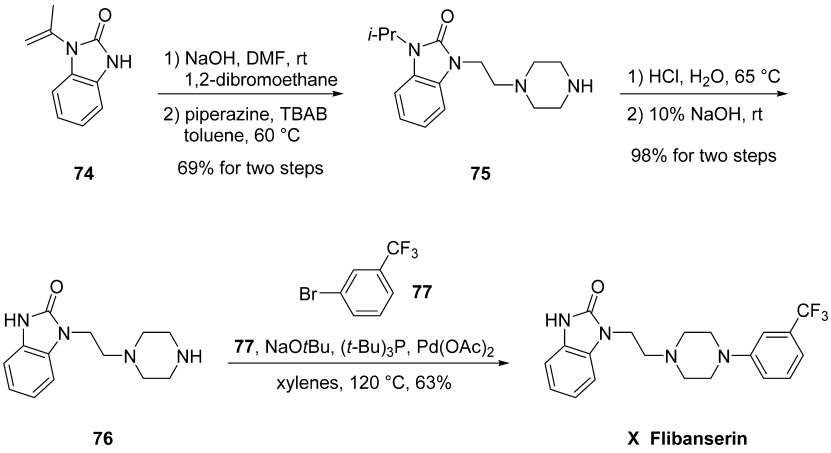
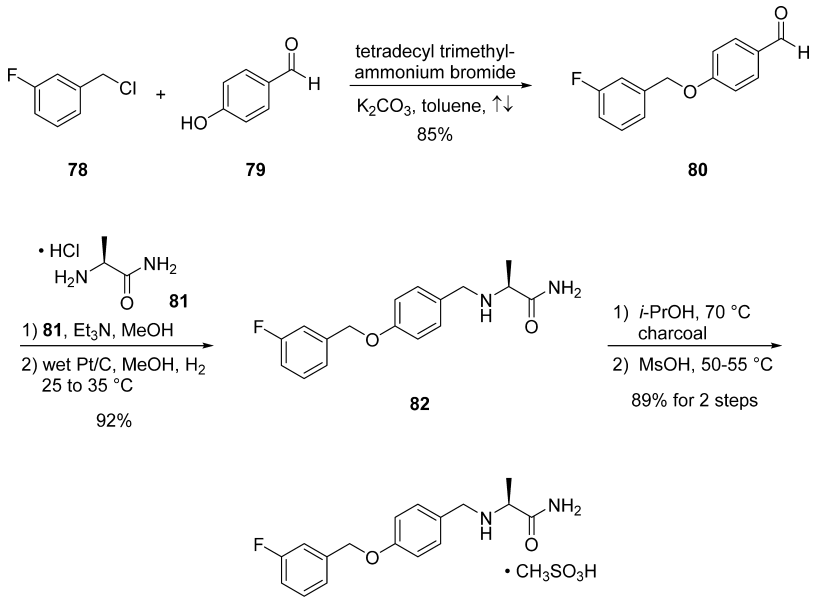
Scheme 13. Synthesis of Flibanserin (X)



Scheme 14. Synthesis of Safinamide Methanesulfonate (XI)



ceuticals, which was approved in 2015 by the FDA for the treatment of premenopausal women with hypoactive sexual desire disorder (HSDD).[46] The drug, which was originally developed for the treatment of depression by Boehringer-Ingelheim, is a full agonist of the 5-HT_{1A} receptor, an antagonist of the 5-HT_{2A} receptor, and a partial agonist of the dopamine-4 (D4) receptor, which triggers increased dopamine and norepinephrine levels along with decreased serotonin levels.[46] However, the exact mechanism of action against HSDD is unknown.[47] In three randomized trials involving 2400 premenopausal women, the drug was found to increase the number of satisfying sexual events by 0.5−1.0 events per month and increased sexual desire on average by 10−12% over placebo. Side effects include decreased blood pressure and loss of consciousness, especially in subjects who consumed alcohol.[47]

Interestingly, the original submission of flibanserin to the FDA from Boehringer-Ingelheim was rejected on the basis of results from two pivotal trials in 2010, which unanimously found that the drug's side effects were unacceptable and that the drug did not demonstrate efficacy.[47] Boehringer discontinued development of the drug after the rejection and sold the rights of the compound to Sprout Pharmaceuticals in 2011, which launched redevelopment and resubmission of the drug to the FDA in 2013 with data from a third pivotal trial, only to have it rejected again that year. Sprout resubmitted the drug in 2015 with additional safety data, and at the FDA advisory meeting in June, independent experts voted 18 to 6 to approve the drug with a risk evaluation and mitigation strategy (REMS).[47]

The large-scale synthesis of flibanserin (**X**) mostly follows a patent from Symed Laboratories Limited which demonstrated hundred-gram-scale preparation of the drug as described in Scheme 13.[48] Starting from commercially available 1-(prop-1-en-2-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (**74**), installation of an ethylene side chain was accomplished under conventional alkylation conditions with 1,2-dibromoethane and base, and this event was immediately followed by a second alkylation reaction involving piperazine to secure piperazinyl benzimidazolone **75**. Interestingly, the enamine double bond

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

within **74** was apparently reduced to the corresponding isopropyl group under these conditions. Although the authors do not comment about this reduction directly, similar examples of olefin reduction under non-hydrogenative alkylation conditions have been reported in the literature separately by both Pai[49] and Ryu.[50] Removal of the isopropyl group was facilitated by means of aqueous sodium hydroxide to afford **76**, which underwent *N*-arylation under Buchwald conditions with 1-bromo-3-(trifluoromethyl)benzene **77** to furnish flibanserin (**X**) in 63% yield.

4.5. Safinamide Methanesulfonate (Xadago). Safinamide methanesulfonate was approved in February 2015 by the EMA for the treatment of mid- to late-stage fluctuating Parkinson's disease. This approval included use of the drug as an add-on therapy for use with levodopa, either alone or in combination with other existing therapies for Parkinson's disease.[51] Safinamide methanesulfonate, an oral α-aminoamide originally discovered by Farmitalia Carlo Erba and later developed by Newron/Zambon, functions as a highly selective and reversible inhibitor of MAO-B,[52] leading to increased levels of dopamine and subsequent improvement in the motor symptoms of Parkinson's disease,[53] side effects that often result from use of other traditional treatments relying on dopamine replacement therapy.[51,54] Furthermore, unlike other therapies, safinamide employs several mechanisms of action, functioning as both a dopaminergic agent through inhibition of MAO-B as well as a nondopaminergic agent via selective calcium and sodium channel modulation, leading to inhibition of glutamate release.[54,55] At least one of several clinical studies of patients with mid- to late-stage Parkinson's disease showed increased daily ON time (periods of symptom control) without accompanying motor complications (dyskinesias) upon treatment with safinamide,[56] while studies of early stage Parkinson's disease patients treated with this drug showed significantly improved motor symptoms during the 18-month study.[57] Additionally, safinamide is chemically and metabolically stable,[54] is well tolerated in patients, and has not exhibited serious adverse effects even upon treatment at higher dosage ranges.[54,57]

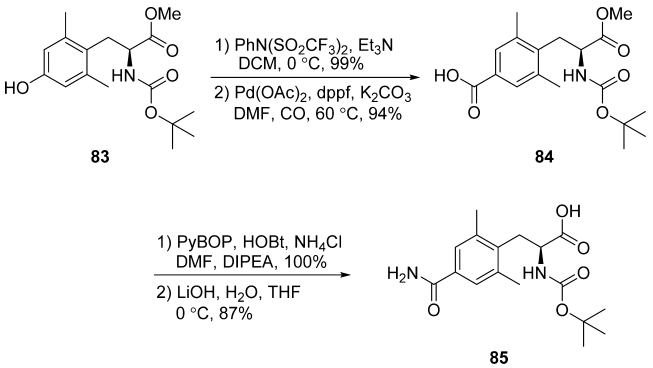
While the reported discovery-scale synthetic approaches to safinamide methanesulfonate were similar to the process-scale approach,[58] the identification of optimized and improved reaction conditions were essential for isolation of the target in high purity and without the presence of highly toxic byproducts.[59] For example, initial attempts to prepare aryl benzyl ether **80** (Scheme 14) from benzyl chloride (**78**) and phenol (**79**) employed conditions which led to the desired *O*-alkyl product **80** in addition to the undesired C3-aryl alkylation product, necessitating laborious and inefficient final-stage purifications. Alternatively, employing phase transfer catalysis conditions, specifically the use of tetradecyl trimethylammonium bromide with K_2CO_3 in refluxing toluene as shown in Scheme 14, have become the conditions of choice, enabling high selectivity of *O*-alkylation product **80** in 85% yield and 99.9% purity with minimal amounts of impurities arising from competitive *C*- and *O*-alkylation arising after recrystallization from diisopropyl ether.[59a] From **80**, a one-pot reductive alkylation with L-alaninamide hydrochloride **81** was effected under standard reductive amination conditions ($NaBH_3CN$/MeOH). However, poor yields were observed as well as formation of undesired byproducts. Interestingly, while not a generally accepted method, an alternate one-pot route for synthesis of **82** could be realized using heterogeneous reduction conditions. Toward this end, condensation of **81** with the aldehyde **80** was followed by immediate reduction with H_2 on wet Pt/C in MeOH, affording safinamide **82** in 92% yield (98.4% purity). Treatment of **82** with charcoal filtration followed by salt formation with methanesulfonic acid provided safinamide methanesulfonate (**XI**) in 97% yield. In this improved synthesis, all reactions could be performed on multikg scale, yielding the final drug target in >99.9% purity and containing <0.005% of the undesired *C*,*O*-bis-alkylated derivative.

5. GASTROINTESTINAL DRUGS

5.1. Eluxadoline (Viberzi). Eluxadoline, originally developed by Janssen and currently marketed by Allergan (formerly Actavis), was approved in May 2015 by the FDA for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D).[60] Eluxadoline, an orally dosed agent, employs a unique mechanism for IBS-D treatment, as it functions simultaneously as a μ- and κ-opioid receptor agonist and a δ-opioid receptor antagonist,[61] leading to a first-in-class therapy for treatment of IBS-D. Specifically, in animal studies, eluxadoline was found to interact with opioid receptors in the gut, inhibiting neurogenically mediated secretion and reducing intestinal contractility.[62] Additionally, the treatment led to a decrease in stress-induced acceleration of upper GI transit without causing rebound constipation,[60−62] earning its mark as a first-line therapeutic treatment for IBS-D. In two phase III clinical trials of over 2400 patients with IBS-D, patients taking eluxadoline showed a greater improvement toward the end point (≥30% improvement from their baseline IBS-D score on at least 50% of days treated with eluxadoline) compared to patients treated with placebo.[63]

The synthesis of eluxadoline begins with preparation of advanced coupling component **85**, which could be completed via a four-step route from commercially available *N*-Boc-protected aminoester **83** (Scheme 15).[64] Triflate formation

Scheme 15. Synthesis of Eluxadoline Intermediate 85



using *N*-phenyltrifluoromethanesulfinimide in DCM under basic conditions led to nearly quantitative yield of the desired triflate, which was subjected to a carbonylation reaction to yield aryl acid **84** in 94% yield. Employing NH_4Cl as a source of ammonia, amidation of **84** took place in the presence of PyBOP/HOBt and DIPEA in DMF. Finally, acid **85** was revealed upon methyl ester saponification with aqueous LiOH in THF. This sequence provided **85** without purification ,and this acid could be used directly as applied in Scheme 16.[64]

With coupling component **85** in hand, the synthesis of eluxadoline proceeds as described in Scheme 16 and initiated

DOI: 10.1021/acs.jmedchem.7b00010
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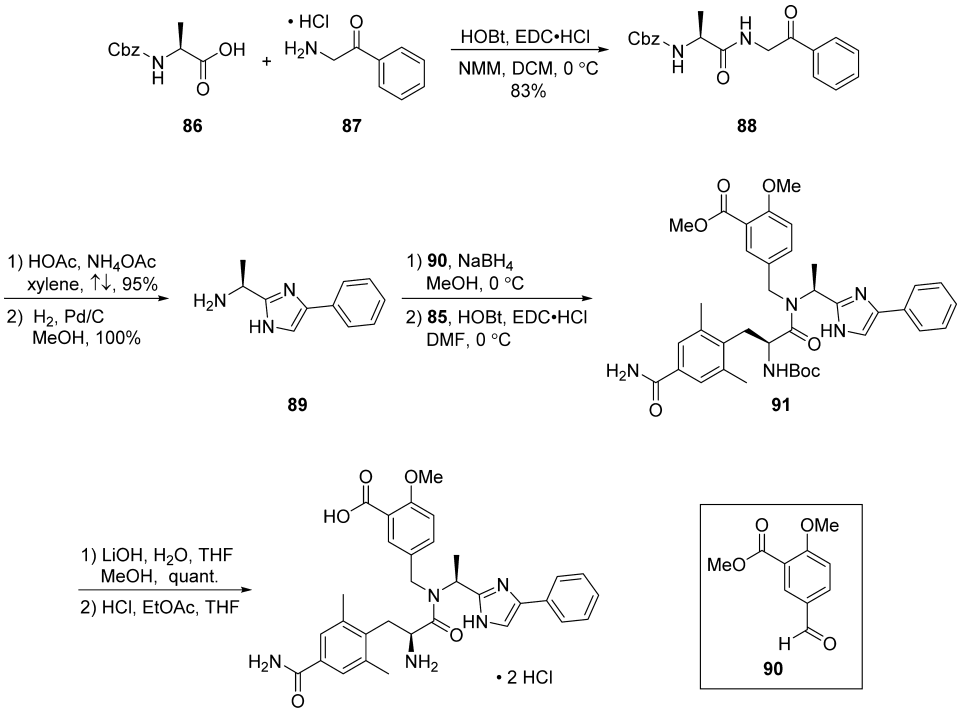
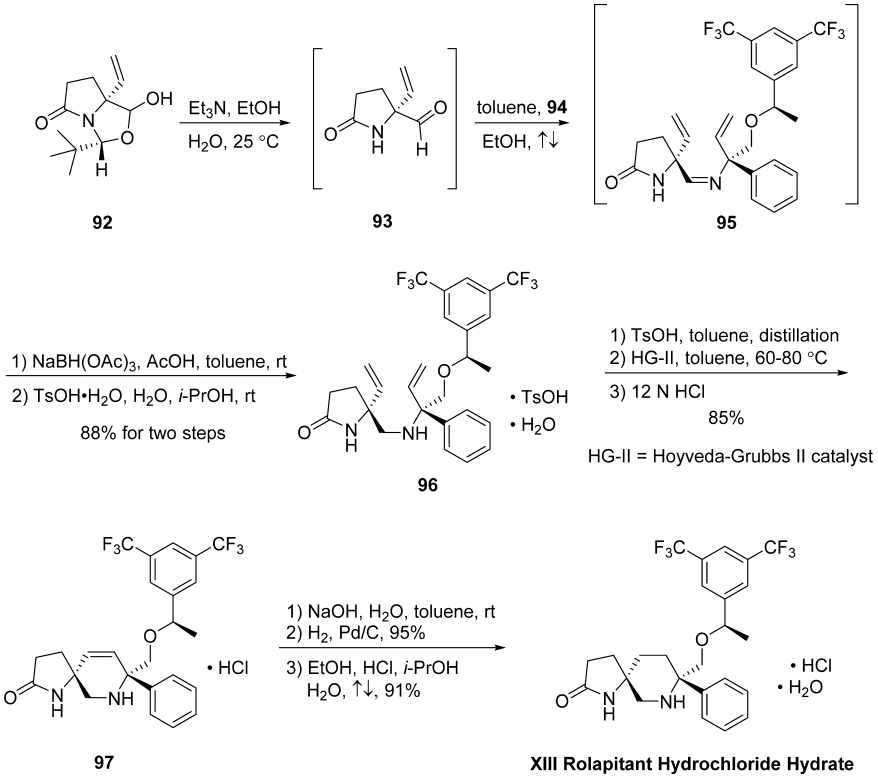
Scheme 16. Synthesis of Eluxadoline (XII)



Scheme 17. Synthesis of Rolapitant Hydrochloride Hydrate (XIII)



from a HOBt and EDC·HCl-mediated coupling of commercial *N*-Cbz-L-alanine (**86**) with commercial 2-amino acetophenone hydrochloride (**87**) to provide intermediate **88** in 83% yield.[64,65] Addition of NH_4OAc and AcOH to a suspension of **88** in refluxing xylenes furnished the desired imidazole in excellent yield (95%). Submission of this *N*-Cbz-imidazole to hydrogenation conditions (H_2, Pd/C, MeOH) enabled liberation of the free amine to access **89** in quantitative yield following filtration and concentration. From intermediate **89**, reductive amination with commercially available aryl aldehyde **90** under standard conditions ($NaBH_4$, MeOH) followed by subsequent coupling of the corresponding crude amine with

DOI: 10.1021/acs.jmedchem.7b00010
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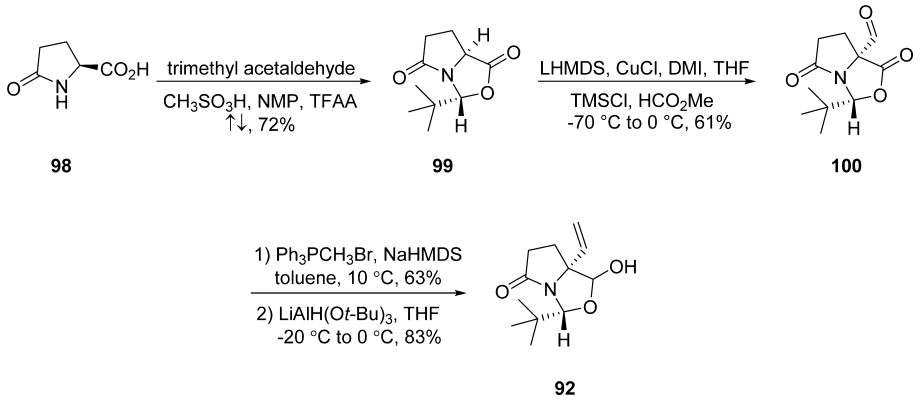
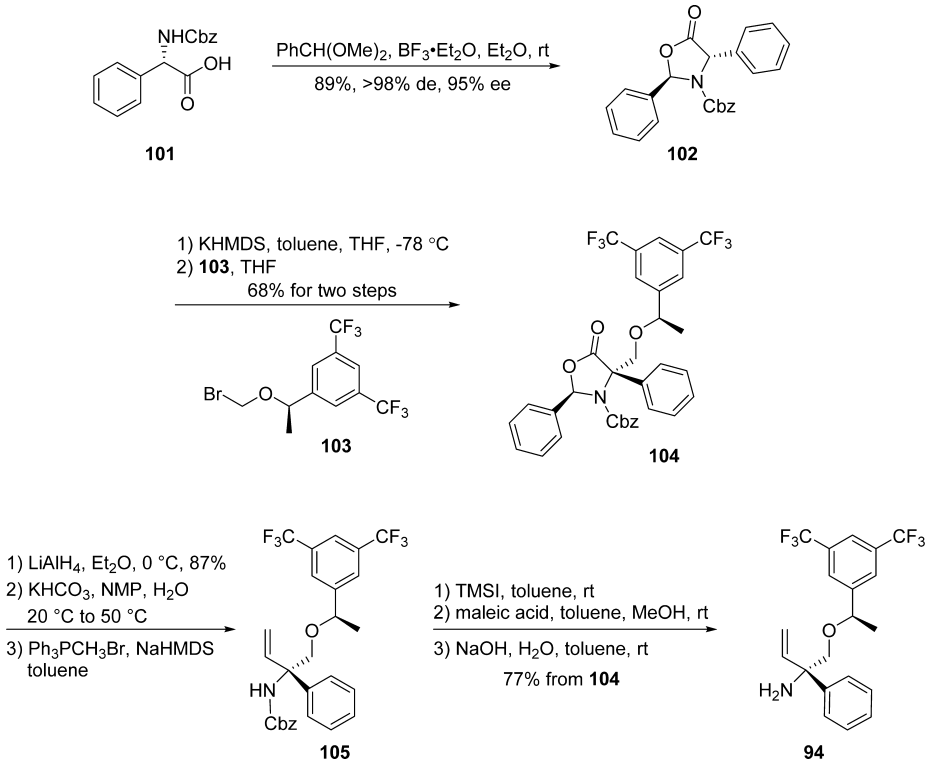
Scheme 18. Synthesis of Fragment 92 of Rolapitant Hydrochloride Hydrate (XIII)



Scheme 19. Synthesis of Fragment 94 of Rolapitant Hydrochloride Hydrate (XIII)



acid **85** using HOBt/EDC·HCl enabled formation of the carbon framework of eluxadoline (**91**). Saponification of the ester within **91** with LiOH in MeOH/THF yielded the corresponding acid in quantitative yield. Immediate subjection of this intermediate to acidic conditions (HCl in EtOAc/THF) led to *N*-Boc cleavage and isolation of eluxadoline (**XII**) as the bis-HCl salt in 71% yield, requiring no further purification.[64,65] It should be noted that since this initial report, additional details for the isolation of eluxadoline in high purity in various crystal forms and as a zwitterion have been reported,[66] although most reported routes described isolation of this drug in its HCl salt form.[64,65]

5.2. Rolapitant Hydrochloride Hydrate (Varubi). Rolapitant hydrochloride hydrate, originally discovered by Schering-Plough and later developed by TESARO, Inc., was approved by the FDA in September 2015 for the prevention of delayed chemotherapy-induced nausea and vomiting (CINV) in combination with other antiemetic agents.[67] Rolapitant is a highly selective NK-1 receptor antagonist, exhibiting >1000-fold selectivity for NK-1 over human NK-2 and NK-3 receptors in vitro.[68] In contrast to other NK-1 inhibitors that play an essential role in delayed CINV therapy,[69] rolapitant shows no inhibition of CYP3A4,[68] eliminating the need for concern when coadministering with CYP34A substrates. Additionally, rolapitant is an orally active agent with a relatively long half-life (180 h),[68,70] providing potential opportunities for single- and prechemotherapy-based treatments.[71] In three large clinical trials involving patients receiving moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC), subjects using rolapitant as a cotherapy with granisetron and dexamethasone showed a significant improvement in complete response compared to those receiving treatments of granisetron and dexamethasone.[70,72]

Rolapitant features a fascinating molecular architecture consisting of two tetrasubstituted stereogenic carbon centers situated at the 2- and 5-carbons within a central piperidine ring

DOI: 10.1021/acs.jmedchem.7b00010
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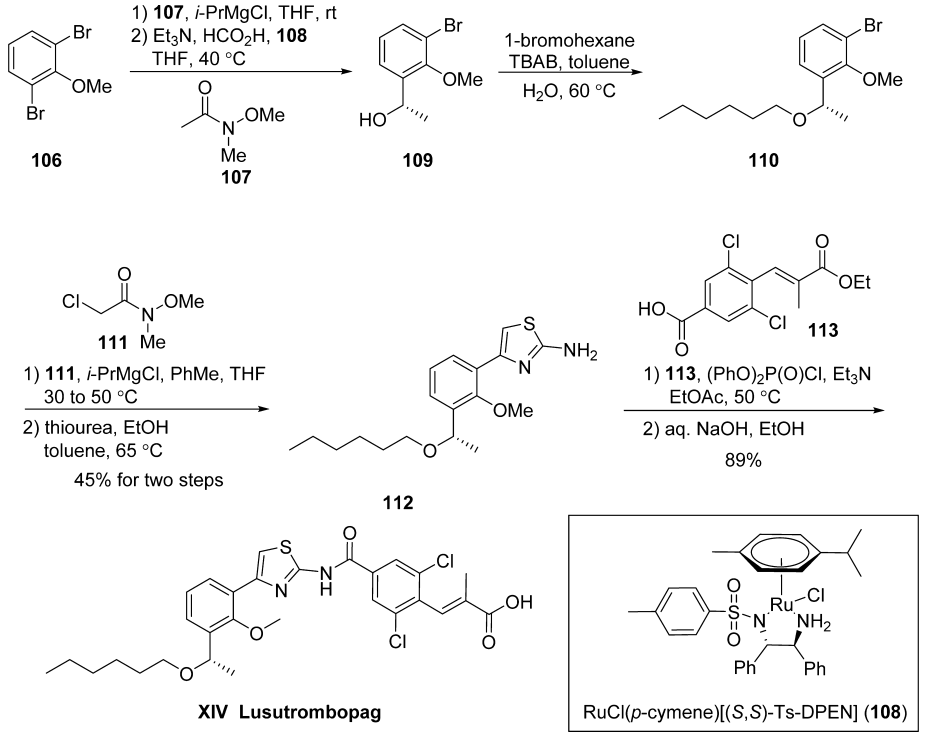
Scheme 20. Synthesis of Lusutrombopag (XIV)



and a spirocyclic array residing at the 5-position and a phenyl ring and ethereal linkage branching from the 2-position (Scheme 17). The overall synthetic strategy to secure rolapitant hydrochloride hydrate relies upon the union of two advanced chiral building blocks that contain functional groups capable of securing the central piperidine ring. These two key intermediates, pyroglutamate derivative **93** and allylic amine **94**, each bear one of the essential stereocenters embedded within the structure of the active pharmaceutical ingredient.[73] The first of these advanced intermediates, amidoaldehyde **93**, is generated directly by base-mediated decomposition of pyroglutamic aminal **92**, which was prepared according to the route shown in Scheme 18. Subjection of **92** to triethylamine in $EtOH/H_2O$ at ambient temperatures led to generation of chiral allyl aldehyde **93**, which was not isolated but condensed immediately with amine **94** (Scheme 19) in the presence of refluxing toluene to provide divinyl imine **95**, which underwent immediate reduction using $NaBH(OAc)_3$ in AcOH/toluene to furnish the free amine. The free amine was converted to the corresponding tosylate monohydrate salt and triturated, providing **96** as a white crystalline powder after subjection to $TsOH{\cdot}H_2O$ in i-$PrOH/H_2O$. Divinyl amine **96** could then be reacted with a solution of TsOH in toluene, distilled, and directly combined with a toluene solution of Hoveyda−Grubbs second-generation catalyst (HG-II) under heating conditions, leading to the desired ring-closing metathesis product **97** as the HCl salt (85% yield over two steps) after filtration, distillation, and workup with 12N HCl. Washing of a toluene solution of **97** with aqueous NaOH and subsequent treatment of the resulting organic solution with H_2, wet Pd/C, and additional granular activated carbon (Nuchar Aquaguard) led to the fully reduced piperidine product in high yield (95%). Rolapitant hydrochloride hydrate **XIII** was accessed thereafter by precipitation from a solution of $EtOH/i$-$PrOH/H_2O$/HCl, providing the product as a white solid (91% yield).[73]

Aldehyde precursor **92** was accessed in a four-step sequence starting from commercially available L-pyroglutamic acid **98** (Scheme 18).[73,74] Condensation of **98** with trimethylacetaldehyde at elevated temperatures in the presence of methanesulfonic acid and NMP prior to careful addition of TFAA led to formation of pyrrolo-oxazolidone **99** in 72% yield. Deprotonation (LHMDS) and stereoselective alkylation of **99** with methyl formate, assisted by addition of copper chloride as a Lewis acid, provided access to carbaldehyde **100** in moderate yield (61%) as a single diastereomer[74] after aqueous workup and crystallization from MTBE. Wittig olefination of aldehyde **100** (Ph_3PCH_3Br/LHMDS) followed by aqueous workup and precipitation of triphenylphosphine oxide via addition of $MgCl_2$ constructed an allyl lactone intermediate in 63% yield as an off-white solid, which then immediately underwent partial reduction with $LiAlH(Ot\text{-}Bu)_3$ to smoothly deliver the key aldehyde precursor **92** in 83% yield as an inconsequential mixture of diastereomers (the stereocenter of consequence arose from the naturally occurring L-pyroglutamic acid **98**), which could be employed directly in Scheme 17.[73]

Generation of **94** began with commercially available *N*-Cbz-(*S*)-phenylglycine **101** based on reports by O'Donnell and coworkers (Scheme 19).[75] Reaction of **101** with benzaldehyde dimethylacetal under Lewis acid conditions ($BF_3{\cdot}Et_2O$) in diethyl ether led to high yield, diastereoselectivity, and enantioselectivity of *trans*-disubstituted oxazolidinone **102**. In this case, selection of diethyl ether as a solvent was essential, as the use of DCM under similar reaction conditions favored formation of the undesired *cis*-product. Removal of the most acidic proton within **102** by means of KHMDS in toluene/THF, followed by alkylation with commercially available bromomethyl ether (**103**) in THF, led to 68% yield of **104** as a single diastereomer.[73,76] Reduction of **104** to the corresponding lactol ($LiAlH_4/Et_2O$) and subsequent ring opening with $KHCO_3/H_2O$ in NMP yielded the intermediate

DOI: 10.1021/acs.jmedchem.7b00010
J. Med. Chem. 2017, 60, 6480−6515

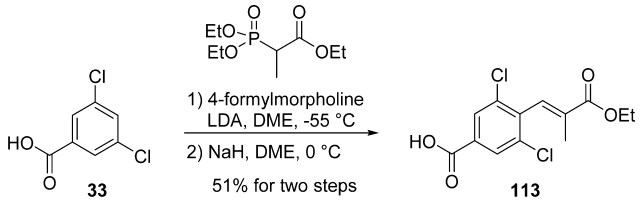
aldehyde, which was readily converted to **105** via addition of the crude aldehyde solution to a mixture of Ph_3PCH_3Br and NaHMDS in toluene. As described in Scheme 15, triphenylphosphine oxide scavenge by way of $MgCl_2$ enabled generation of crude product in good purity after a simple filtration. TMSI-mediated Cbz removal converted **105** to the resulting free amine. Formation of the maleic acid salt enabled the product to be isolated as a crystalline solid in high purity without chromatography. Treatment of the maleate salt with NaOH in toluene provided the free base **94**, which was incorporated as previously described in Scheme 17 without the need for additional purification.[73]

6. HEMATOLOGIC DRUGS

6.1. Lusutrombopag (Mulpleta). Lusutrombopag is an orally bioavailable thrombopoietin (TPO) receptor agonist developed by Shionogi for improvement of thrombocytopenia associated with chronic liver disease in patients undergoing an elective invasive procedure (e.g., liver biopsy, liver transplantation) (Scheme 20).[77] Thrombocytopenia, which is common among patients with chronic liver disease, increases the risk of bleeding when undergoing invasive procedures, which in turn complicates therapy and increases the risk of mortality.[78,79] Lusutrombopag, which was approved in Japan in September 2015, promotes platelet production by stimulating the proliferation and differentiation of human bone marrow progenitor cells into megakaryocytes via the thrombopoietic pathway. The consequent increase in platelet levels avoids postponement of invasive procedures or transfusion of platelets and administration of platelet products, the current standard of care for thrombocytopenia in these patients.[77]

To date, only two synthetic routes to lusutrombopag have been reported: one in the Japanese patent literature which has been exemplified on kilogram scale[80] and the other a closely related discovery route which has been reported in the United States patent literature.[81,82] Commercial 2,6-dibromoanisole (**106**) was treated with isopropylmagnesium chloride to form the corresponding Grignard reagent prior to reaction with Weinreb amide **107**, furnishing a ketone which underwent immediate reduction with formic acid in the presence of chiral catalyst RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (**108**) and generate the desired (*S*)-stereogenic alcohol **109**. Unfortunately, neither the yield nor the stereoselectivity of this reduction was reported in any of the disclosures. Benzyl alcohol **109** was subjected to Williamson etherification conditions with *n*-hexyl bromide to furnish ether **110**. The aryl bromide within **110** was then converted to the corresponding Grignard reagent, which was reacted with *N*-methyloxy-*N*-methyl-2-chloroacetamide (**111**), followed by subsequent treatment with thiourea in toluene/ethanol at elevated temperatures to give aminothiazole intermediate **112** in 45% yield across the two-step sequence. Next, activation of acid **113** prior to exposure to **112** facilitated amide bond formation. Saponification of the pendant ester with sodium hydroxide furnished luxutrombopag (**XIV**) in 89% yield. Although acid **113** is not commercial, it could be prepared from 3,5-dichlorobenzoic acid (**33**) via formylation with 4-formylmorpholine, followed by a Horner–Wadsworth–Emmons reaction with triethylphosphonopropionate (Scheme 21).

Scheme 21. Preparation of Lusutrombopag Intermediate 113



7. METABOLIC DRUGS

7.1. Deoxycholic Acid (Kybella). Deoxycholic acid sodium salt, which is a secondary bile acid and the metabolite of intestinal bacteria, provides a nonsurgical treatment to significantly reduce submental fat in adults via injection directly into moderate-to-severe fatty tissue below the neck.[83] When injected into fatty tissue, deoxycholic acid helps destroy fat cells.[83] Although deoxycholic acid has many applications beyond human health, the application as a dyslipidemia drug was licensed to Kythera from Los Angeles Biomedical Institute at Harbor–UCLA Medical Center in 2007. Allergan acquired Kythera recently in 2015.[84]

The synthesis started from the commercially available 9-hydroxyandrost-4-ene-3,17-dione (**114**, Scheme 22).[85] Hydrogenation of **114** gave the saturated 5β-dione **115** in 85% yield. Alcohol **115** was then dehydrated with H_2SO_4 in CH_2Cl_2 to provide 5β-androst-9(11)-ene-3,17-dione **116** in 95% yield as off-white solid, and this was followed by selective reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ to afford (3α,5β)-3-hydroxyandrost-9(11)-en-17-one (**117**). The crude ketone **117** was submitted to a Wittig reaction with triphenylethylphosphonium bromide in the presence of potassium *t*-butoxide in THF to yield (3α,5β,17*E*)-pregna-9(11),17-dien-3-ol (**118**). The crude alcohol **118** was acetylated with Ac_2O in the presence of DMAP and Et_3N to yield prenyl acetate **119** in 64% across the three-step sequence. Compound **119** was reacted with methyl acrylate in the presence of $EtAlCl_2$ to facilitate conjugate addition and subsequent tertiary carbocation elimination to afford adduct **120**, and this resulting olefin was hydrogenated to selectively saturate the cyclopentenyl double bond, resulting in steroid **121** in 85% yield from **119**. The remaining alkene **121** then underwent allylic oxidation with *tert*-butyl hydrogen peroxide and 10% NaOCl aqueous solution in EtOAc to give enone **122**, and this material was then hydrogenated over 10% Pd/C in EtOAc to afford the saturated ketone **123**. Next, the ketone within **123** was selectively reduced with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF to give the 12α-hydroxy precursor **124** in excellent yield. Finally the remaining methyl ester **124** was hydrolyzed with 20% NaOH aqueous solution in THF/MeOH and acidified with 4 M HCl to give deoxycholic acid (**XV**) in 99% yield as a white solid.

7.2. Evogliptin (Suganon). Developed by Dong-A ST, evogliptin was approved in 2015 in the Republic of Korea for blood glucose control in patients with diabetes mellitus type 2 (type 2 DM). Evogliptin is an orally bioavailable dipeptidyl peptidase IV (DPP-4) inhibitor, which acts to prevent insulin secretion following meals. Dong-A ST arranged licensing agreements with Geropharm and Eurofarma Laboratórios for the sale of evogliptin in various countries in eastern Europe and Brazil, respectively, pending future approvals.[86] While a manufacturing route has not been disclosed to date, the most scalable published route is described below.[87] Strategically, evolgliptin is prepared from the union of two key fragments

DOI: 10.1021/acs.jmedchem.7b00010
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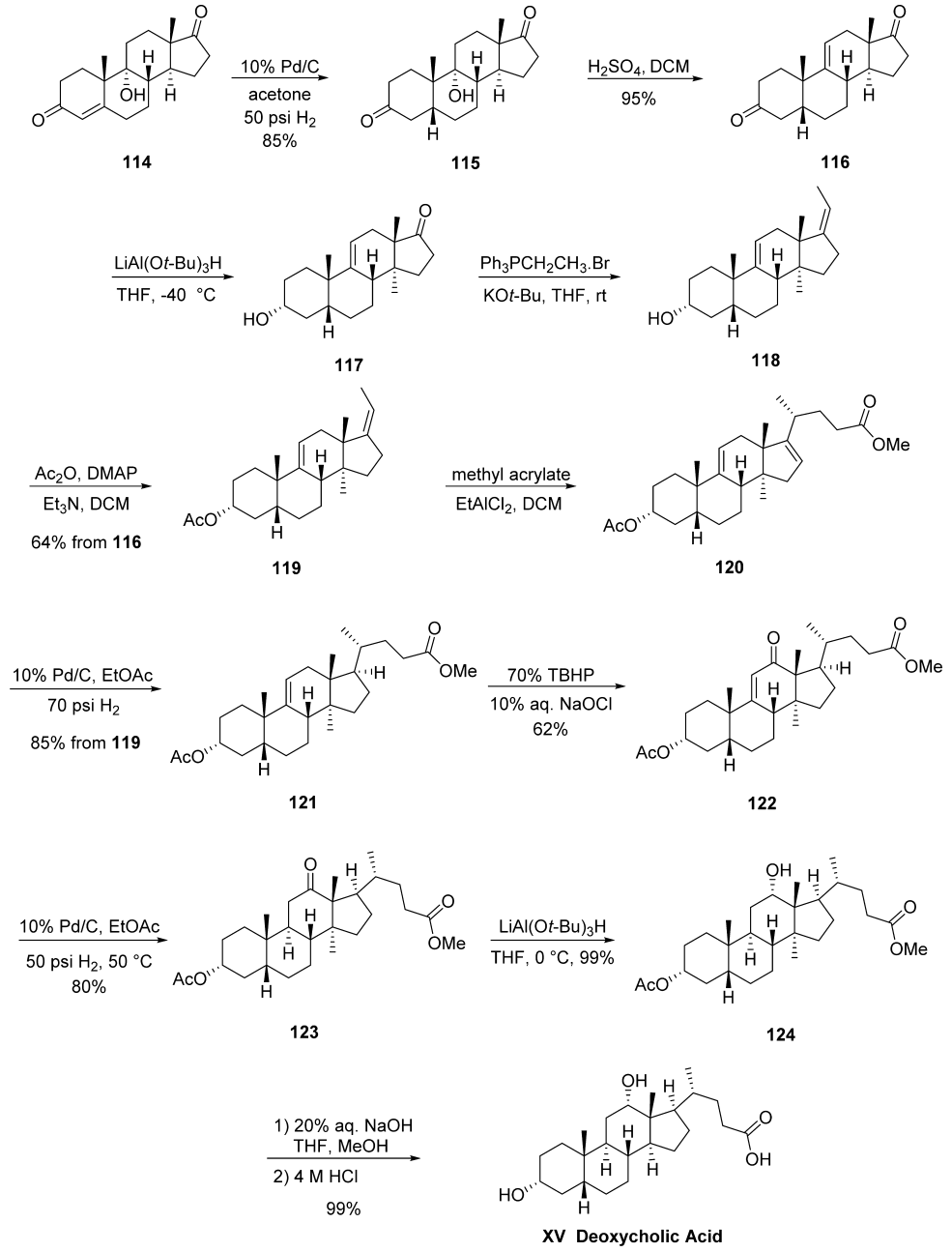
Scheme 22. Synthesis of Deoxycholic Acid (XV)



which consist of a piperizone **125** and a β-amino acid fragment **136**.[87]

The synthesis of piperizone **125** began from commercially available amino acid derivative **127** (Scheme 23). The alcohol within **125** was then quantitatively converted to *tert*-butyl ether **128** by treatment with isobutylene gas in the presence of acid. Subsequent hydrogenation to remove the Cbz protecting group resulted in amine **129**, and this was followed by reductive amination to provide ethylene diamine intermediate **130**. Hydrogenative carbamate removal facilitated a cyclization reaction, giving rise to piperizone **131** as the free base. Finally, treatment with a tartaric acid derivative delivered the stable piperizone salt **125**.[88]

The second key synthon of evogliptin is the β-amino acid fragment **136**, the synthesis of which is described in Scheme 24. Commercially available acid **132** was treated with CDI prior to subjection to Meldrum's acid to afford ketodiester **133**. Subjection of **133** to warm EtOH triggered a decarboxylation event, and this was followed by reductive amination reaction involving ammonium acetate and the remaining ketone functionality to afford racemic amine **134** in 91% over the three steps. Resolution with a tartaric acid derivative followed by free base formation with sodium carbonate gave the enantiopure aminoester **135** in good yield. Finally, a two-step Boc protection followed by ester saponification furnished aminoester **136** in 89% yield over the final two-step sequence, setting the stage for the final assembly of evogliptin.[89]

The final API was assembled in a straightforward manner from intermediates **125** and **136** (Scheme 25). Acid **136** was first activated as the mixed anhydride, followed by the addition of **125** in the presence of Hünig's base to give penultimate product **137** in 71% over two steps. Hydrogenolytic removal of

DOI: 10.1021/acs.jmedchem.7b00010
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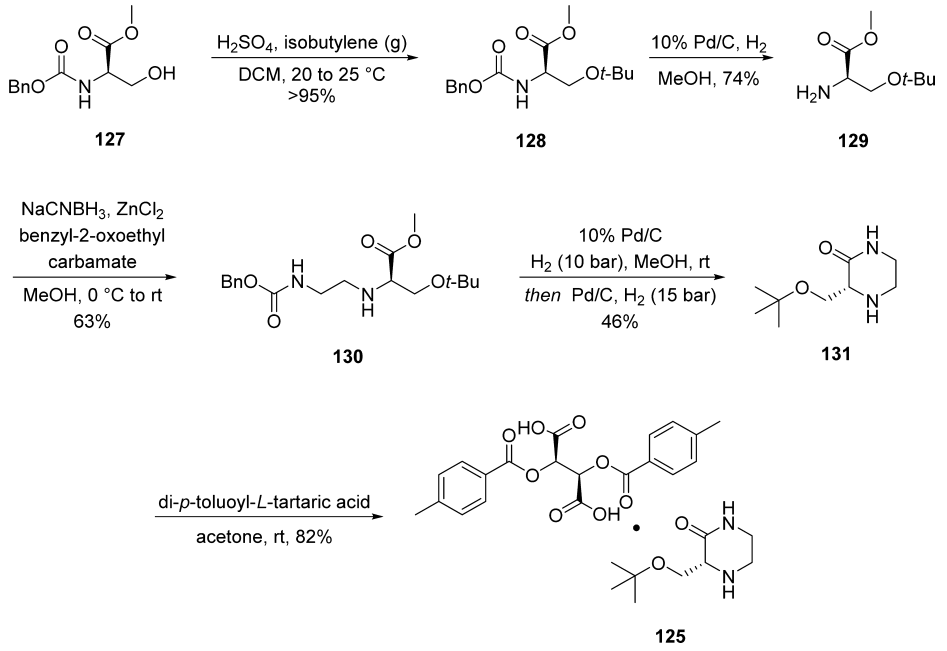
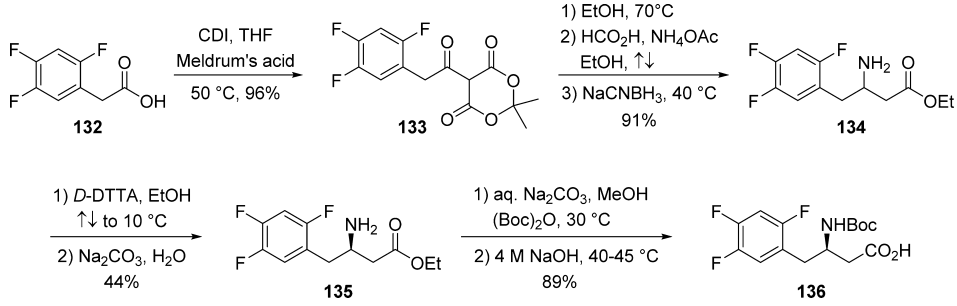
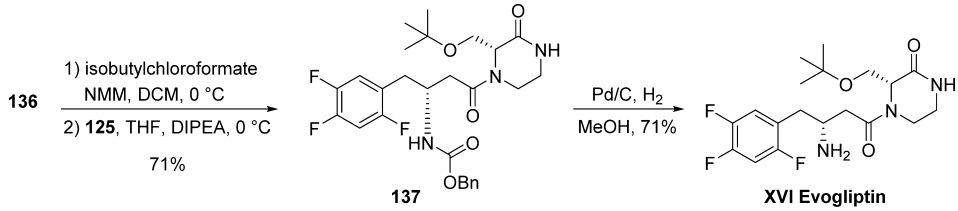
Scheme 23. Synthesis of Evogliptin Piperazone 125



Scheme 24. Synthesis of Evogliptin Fragment 136



Scheme 25. Synthesis of Evogliptin (XVI)



the benzyl carbamate afforded evogliptin (**XVI**), with a longest linear sequence of eight steps from simple amino acid building blocks.[87]

7.3. Lesinurad (Zurampic). Approved by the FDA late in 2015, lesinurad is an urate anion exchange transporter 1 (URAT1) inhibitor for use in the treatment of gout. Ardea Biosciences, which is a subsidiary of AstraZeneca, developed lesinurad to be used in a combination therapy with xanthine oxidase inhibitors for the treatment of hyperuricaemia associated with gout. The approval process is ongoing in several other countries across the globe, with the EMA Committee for Medicinal Products for Human Use giving lesinurad a positive opinion for use as an adjunctive therapy in combination with xanthine oxidase inhibitors to treat hyperuricaemia.[90] While several syntheses of lesinurad have been disclosed to date,[91] a patent describing hundreds of kilograms of material describes the likely process route, which is depicted in Scheme 26 (note: for some reactions within this route, no yields were provided).[92]

The synthesis of lesinurad began with commercial 1-bromonaphthalene (**138**, Scheme 26). A Kumada coupling between this bromide and cyclopropyl Grignard delivered **139**, which after selective nitration to give **140**, delivered the oxylate salt **141** (which now is commercially available). Treatment of **141** with KOH followed by thiophosgene at 5 °C delivered isothiocyanate **142** in 63% yield. Reaction of **142** with formyl hydrazine followed by addition of potassium bicarbonate and mild heating resulted in thio-1,2,4-triazole **144** by the intermediacy of **143**. Quantitative alkylation of triazolothiol **144** resulted in α-mercaptan **145**, and this was followed by NBS bromination to afford bromotriazole **146**. Ester

DOI: 10.1021/acs.jmedchem.7b00010
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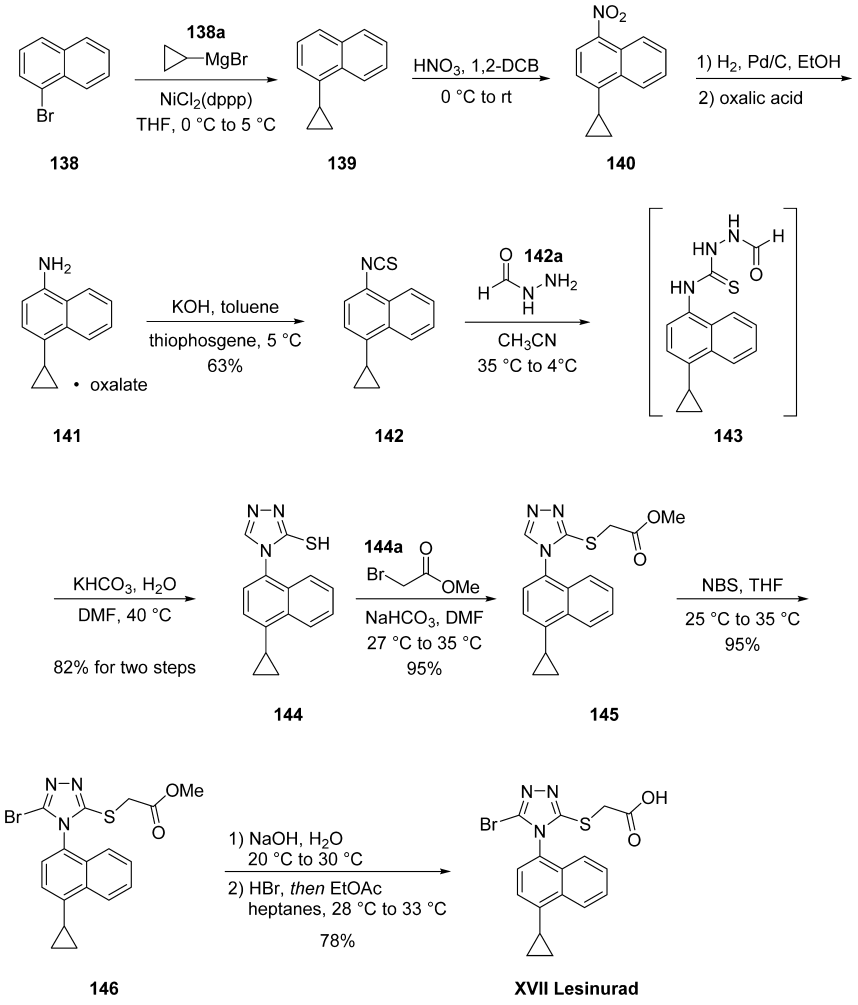
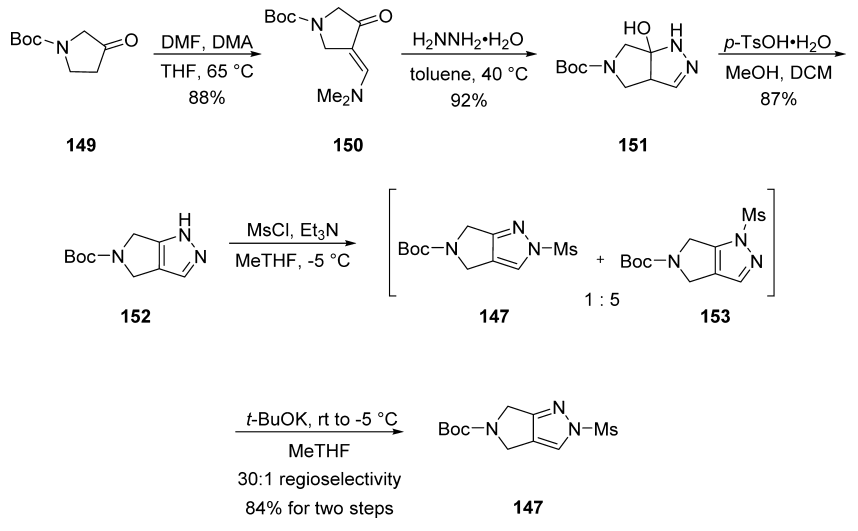
Scheme 26. Synthesis of Lesinurad (XVII)



Scheme 27. Synthesis of Fragment 147 of Omarigliptin (XVIII)



saponification followed by acidification secured lesinurad (**XVII**) in a good yield over the final three steps.[92]

7.4. Omarigliptin (Marizev). Merck earned its first global approval for omarigliptin in Japan in 2015, and phase III development is ongoing in other countries around the globe for this interesting small molecule DPP-4 inhibitor.[93] Interestingly, while most DPP-4 inhibitors used to treat type 2 DM require daily administration, omarigliptin is a weekly treatment. The process-scale synthesis of omarigliptin has been nicely described in an October 2015 paper from the Merck process group.[94,95] Retrosynthetically, omarigliptin can be subdivided into two key fragments **147** and **148**, and the synthesis of each

DOI: 10.1021/acs.jmedchem.7b00010
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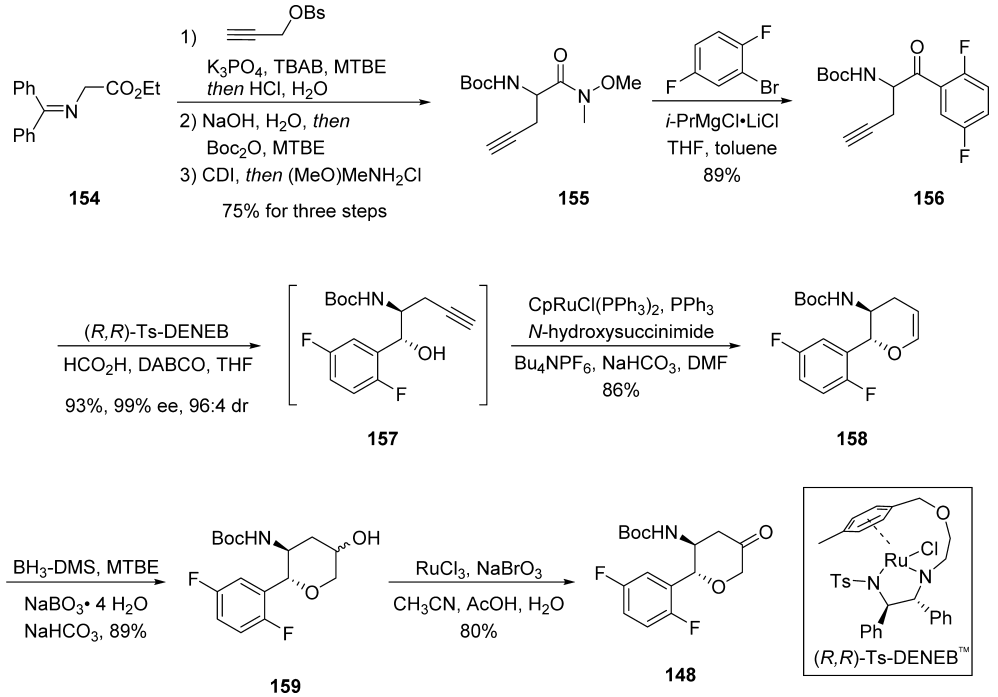
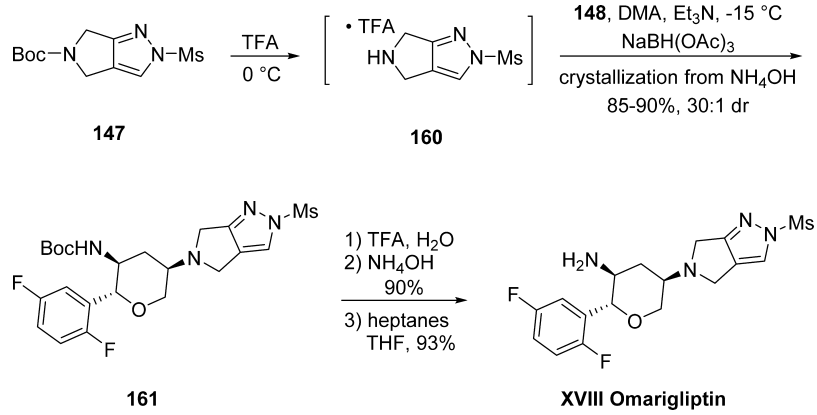
Scheme 28. Synthesis of Fragment 148 of Omarigliptin (XVIII)



Scheme 29. Synthesis of Omarigliptin (XVIII)



fragment, along with their union, is described in Schemes 27–29.

The synthesis began with the efficient condensation of pyrrolidinone **149** with dimethylformamide-dimethylacetal (DMF-DMA) to afford enaminoketone **150** in 88% yield (Scheme 27). Subsequent condensation with hydrazine monohydrate gave tertiary alcohol **151** in 92% yield, and this step was followed by acid-promoted dehydration to afford fused pyrazole **152**. An initial kinetic mesylation delivered a 1:5 ratio of **147**:**153**, in favor of the undesired regioisomer. However, when the crude mixture was warmed to ambient temperature and treated with potassium *tert*-butoxide, thermodynamic equilibration provided the more stable *N*1-mesylate **147**. This process furnished the desired regioisomer **147** in a 30:1 ratio and 84% yield over the two steps (Scheme 27). Reaction monitoring by HPLC suggests that cleavage of the mesyl group of **153** results in anion formation on the adjacent nitrogen, which then allows for mesylation at the desired position.[95]

The innovative synthesis of the omarigliptin lactone fragment **148** is shown in Scheme 28.[95] Ester **154** was subjected to a three-step sequence whereby alkylation with propargyl besylate followed by saponification with sodium hydroxide and Boc protection resulted in amide **155** in 75% yield over three steps. The Weinreb amide was then subjected to the Knochel "turbo Grignard" reagent derived from 1-bromo-2,4-difluorobenzene to provide ketone **156** in 89% yield. An enantioselective transfer hydrogenation was carried out utilizing (*R*,*R*)-Ts-DENEB as the chiral induction reagent to afford intermediate **157** in excellent yield and enantio- and diastereoselectivity, which underwent ruthenium-mediated cyclization with the pendant alkyne to afford dihydropyran **158** in 86% yield. A two-step hydroboration/oxidation involving the endocyclic vinyl ether furnished **159** as a mixture of diastereomers in 89% yield, and this was followed by $RuCl_3/NaBO_3$-mediated oxidation to provide the lactone fragment **148** in 80% yield.

The endgame assembly of omarigliptin is described in Scheme 29.[95] Removal of the Boc group within **147** was effected upon treatment with TFA, affording intermediate **160**, which was not isolated but instead exposed to ketone **148** under reductive amination conditions to afford diaminopyran

DOI: 10.1021/acs.jmedchem.7b00010
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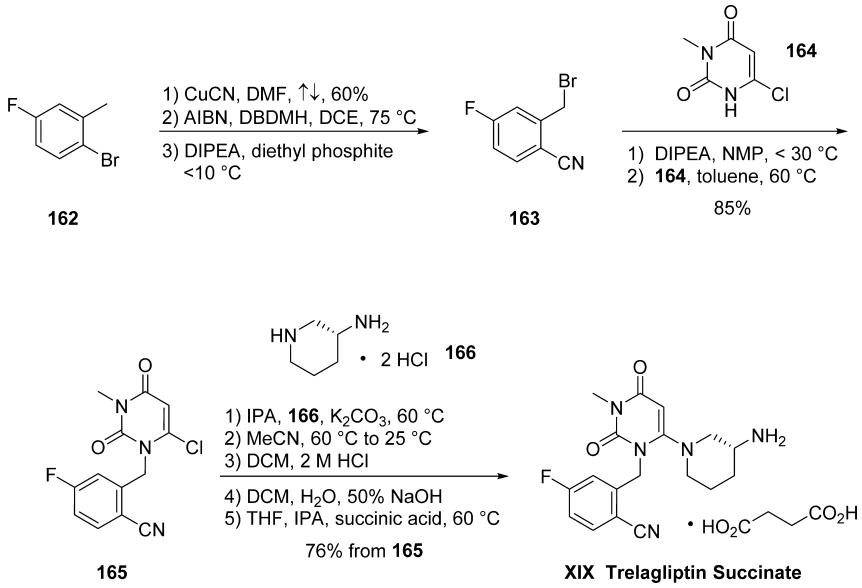
Scheme 30. Synthesis of Trelagliptin Succinate (XIX)



161 in excellent yield and diastereoselectivity (30:1 dr). Finally, Boc deprotection and crystallization from THF/heptanes furnished omarigliptin in an impressive 45% yield over its nine-step longest linear sequence.

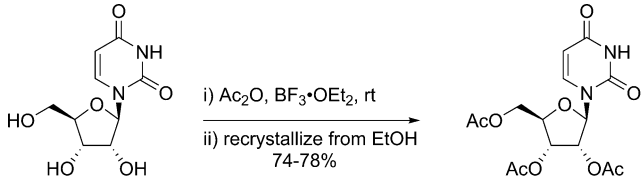
7.5. Trelagliptin Succinate (Zafatek). Similar to omarigliptin, trelagliptin succinate (**XIX**) is a highly selective, orally delivered inhibitor of DPP-4 developed by Takeda Pharmaceuticals and approved in Japan in March 2015 for the treatment of type 2 DM.[96] Interestingly, trelagliptin is structurally similar to alogliptin, a DPP-4 inhibitor also marketed by Takeda and described in our 2010 review,[2i] differing only in the presence of a fluorine in the 5-position of the cyanobenzyl moiety. Both trelagliptin and alogliptin are potent inhibitors of DPP-4, with IC_{50}s of 1.3 and 5.3 nM, respectively.[97] Notably, while similar drugs are dosed once daily, trelagliptin is the first DPP-4 inhibitor approved for once-weekly dosing. Kinetic analysis has revealed that trelagliptin is a substrate-competitive, reversible, slow-binding inhibitor ($t_{1/2}$ for dissociation = ca. 30 min) of DPP-4, although the dissociation time is insufficient to explain its long-acting effects.[97] In a phase III trial, once-weekly trelagliptin (100 mg) showed similar efficacy and safety to once-daily alogliptin (25 mg) in patients with type 2 DM inadequately controlled by diet and exercise.[98] The medicinal chemistry discovery of trelagliptin and alogliptin[99] as well as reviews of this class of compounds have been published.[100,101]

The kilogram-scale synthesis of trelagliptin succinate has been reported in five steps from commercial starting material, and this is depicted in Scheme 30.[102] Commercial 2-bromo-5-fluorotoluene (**162**) was reacted with copper cyanide in refluxing DMF to provide the corresponding nitrile in 60% yield. Benzylic bromination with AIBN and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in DCE followed by treatment with diethyl phosphite and DIPEA gave crude benzyl bromide **163**, which was substituted directly with 6-chloro-3-methyluracil (**164**) in the presence of DIPEA in NMP to provide chloride **165** in 86% yield. Reaction with commercial (*R*)-3-aminopiperidine dihydrochloride **166**[103] in the presence of K_2CO_3 and *i*-PrOH furnished trelagliptin as the freebase. Conversion to the HCl salt and purification by crystallization from dichloromethane, followed by a freebasing via 50% NaOH, and treatment with succinic acid in THF/*i*-PrOH at 60 °C, and final recrystallization, generated trelagliptin succinate **XIX**.[104]

7.6. Uridine Triacetate (Xuriden, Vistogard). Uridine triacetate is an orally available pro-drug of uridine approved by the FDA for the treatment of the rare autosomal recessive disorder called hereditary orotic aciduria.[105] The drug was also approved for treating overdose of two chemotherapies (fluorouracil and capecitabine).[106] Uridine triacetate was developed by Wellstat Therapeutics and licensed to BTG.

The synthesis of uridine triacetate is described in Scheme 31. Commercially available uridine (**167**) was treated with acetic anhydride in the presence of catalytic boron trifluoride-etherate, and the crude product was recrystallized from ethanol to give uridine triacetate (**XX**) in 74−78% yield.[107]

Scheme 31. Synthesis of Uridine Triacetate (XX)



8. MUSCULOSKELETAL DRUGS

8.1. Esflurbiprofen (Loqoa Tape). Marketed by Taisho Pharmaceutical Holdings Co., Ltd., and Teijin Pharma Ltd.,[108] the (*S*)-enantiomer of flurbiprofen (named Esflurbiprofen) was approved as a new drug by the PMDA of Japan in 2015. (*S*)-Flurbiprofen, a cyclooxygenase (COX)-inhibiting nonsteroidal anti-inflammatory (NSAID) drug, is formulated with mentha oil and administered by way of a patch as a treatment for osteoarthritis in the current invention. Interestingly, the (*R*)-enantiomer is responsible for minimal COX inhibition but has been implicated as a possible treatment for a variety of other diseases.[109] Synthetic approaches to racemic flurbiprofen have

DOI: 10.1021/acs.jmedchem.7b00010
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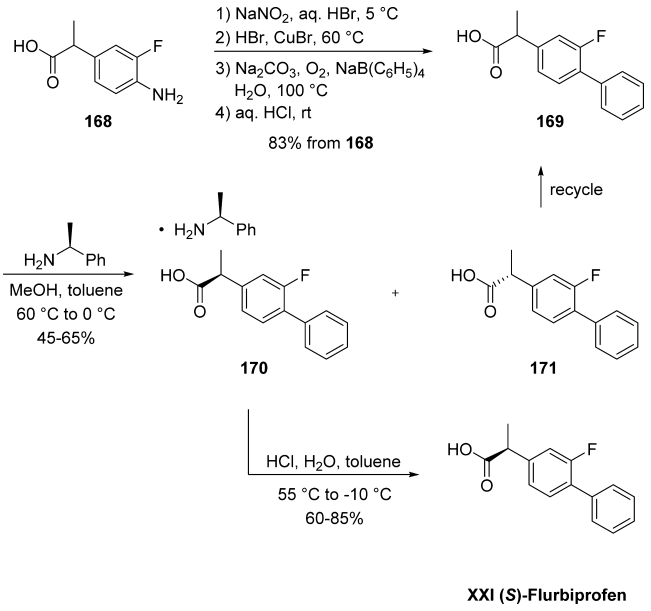
been reported in the chemical literature as early as the 1960s,[110] and the mixture was approved as a drug in the United States by the FDA in 1988, marketed by Pharmacia and Upjohn.[111] Toward this end, the current patent estate defines the utility of the active *S*-enantiomer, and synthetic approaches therein apply to this enantiomer only.

The synthesis began with conversion of commercially available aniline **168** to racemic flurbiprofen (**169**, Scheme 32) through a Sandmeyer reaction and subsequent phenyl group introduction through the use of sodium tetraphenylborate.[110] A chiral resolution was then performed on the resulting stereogenic acid on multikilogram scale by treatment with (*S*)-1-phenylethylamine in MeOH/toluene, which gave various yields of salt **170** as reported by the authors.[110] Acidification with aqueous HCl delivered (*S*)-flurbiprofen (**XXI**). Importantly, with respect to green chemistry considerations, the (*R*)-enantiomer could be recycled by racemizing the undesired (*R*)-enantiomer **171** in refluxing methanolic sulfuric acid, improving the overall atom economy of the process and significantly reducing waste.[112]

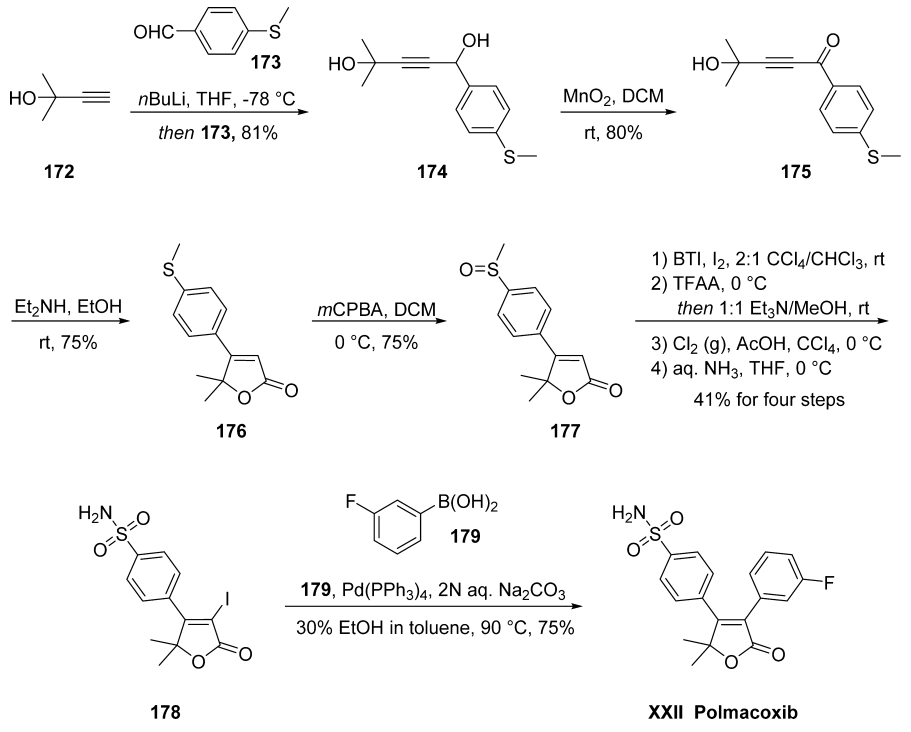
Scheme 32. Synthesis of Esflurbiprofen (XXI)



8.2. Polmacoxib (Acelex). Polmacoxib, also known as (CG-100649), is a first-in-class NSAID which is a dual inhibitor of COX-2 and carbonic anhydrase (CA).[113] The drug, which was approved in South Korea for the treatment of colorectal cancer (CRC) in 2015 and whose discovery has been described by workers at AmorePacific R&D,[114] interacts with CA in red blood cells, providing a novel "tissue-specific" transport mechanism that is designed to deliver sustained levels of drug to inflamed tissues while maintaining low systemic exposure.[115] Although the unique dual COX-2/CA inhibition is designed to provide potentially superior safety to cardiovascular, renal, and gastrointestinal tissues compared to traditional NSAIDs or COX-2 inhibitor drugs, the long-term safety profile of the drug, particularly cardiovascular risks notoriously associated with inhibition of COX-2,[116] has yet to be determined, and the drug is currently not approved for use in any other country outside of South Korea.[115]

The molecular structure of polmacoxib closely resembles that of several marketed COX-2 inhibitors such that it features a classic 1,2-diaryl motif arranged about a 5-[117] or 6-membered[118] hetereocyclic linker. Although no process-scale synthesis has been reported to date, preparation of polmacoxib and several structural derivatives were described in a 2004 medicinal chemistry communication by authors at AmorePacific R&D.[114] It is possible that an adaptation of this sequence, which is described in Scheme 33, could have been (or is) used

Scheme 33. Synthesis of Polmacoxib (XXII)



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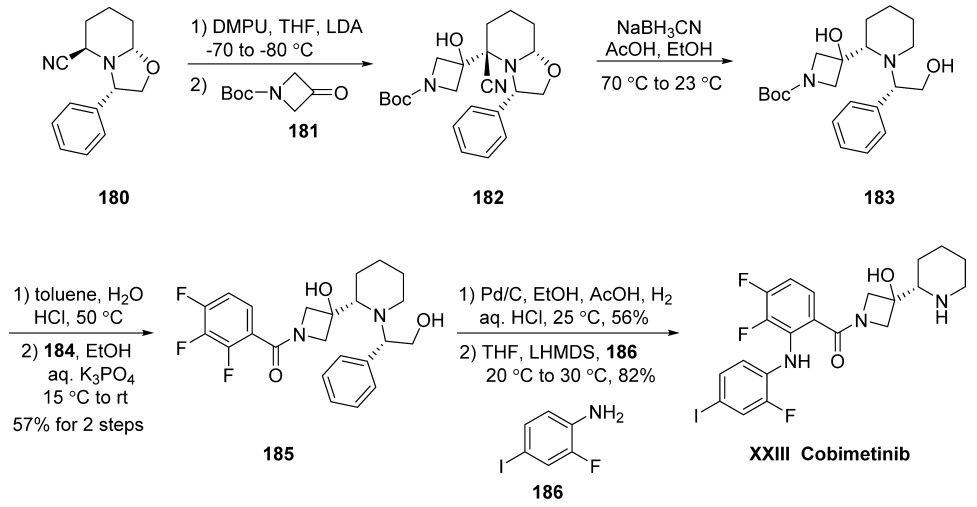
Scheme 34. Synthesis of Cobimetinib (XXIII)



for the scale preparation of the API. However, the authors from AmorePacific report that the synthetic approach depicted in Scheme 33 delivered an amount of polmacoxib totaling 200 mg.[115]

Subjection of commercial propargyl alcohol **172** to *n*-butyllithium at cryogenic temperatures followed by quenching with commercial benzaldehyde **173** resulted in the formation of benzyl alcohol **174** in 81% yield. This alcohol could be oxidized by three different means, but the authors report that the most suitable method on scale was through the use of manganese dioxide in methylene chloride, which furnished ketone **175** in 80%.[114] Next, an interesting cyclization reaction secured the key furanone residue **176**. Mechanistically, subjection of ynone **175** to dimethylamine likely resulted in a conjugate addition followed by tautomerization of the resulting allenol to the corresponding ketone. The resulting ketone then probably underwent intramolecular nucleophilic attack by the pendant tertiary alcohol and after ejection of a molecule of water through iminium-mediated lone pair assistance, hydrolysis of the iminium species to the corresponding ketone delivered **176**. Next, *m*CPBA was employed to oxidize sulfide **176** to the corresponding sulfoxide. Subsequently, iodination of the furanone through use of bis(trifluoroacetoxy)iodobenzene (BTI), followed by a three-step sequence to convert the methylsulfoxide to the corresponding primary sulfonamide **178** occurred in 41% overall from the four-step sequence. Finally, Suzuki installation of the fluorobenzene resulted in the completion of the synthesis of polmacoxib (**XXII**).[114]

9. ONCOLOGY DRUGS

9.1. Cobimetinib (Cotellic). Cobimetinib, codeveloped by Genentech and Exelixis, was approved in August 2015 in Switzerland and November 2015 in the U.S. and Europe for the treatment of unresectable or metastatic $BRAF^{V600}$ mutation-positive melanoma when used in combination with vemurafenib.[119] Cobimetinib is a potent, highly selective reversible inhibitor of mitogen-activated protein kinases (MEK) 1 and 2,[120] which serves to inhibit phosphorylation of ERK1/2,[121] disrupting the MAPK pathway which is responsible for cell proliferation, cell survival, and migration.[122] Combination of cobimetinib with vemurafenib, an important BRAF inhibitor,[123] enables targeting of multiple points on the MAPK pathway, leading to overall enhanced tumor cell apoptosis and response as compared to stand-alone treatment with vemurafenib.[124] Specifically, in a representative trial of previously untreated patients with $BRAF^{V600}$ mutation-positive, unresectable, stage IIIc or IV melanoma, combination of these two therapies led to a significantly improved progression-free survival and overall response rate versus patients treated only with vemurafenib.[124a,125]

Structurally, cobimetinib features an interesting azetidinol substructure appended to the 2-position of a piperidine, rendering the 2-carbon of the piperidine as a stereogenic center bearing the (*S*)-configuration. While the early discovery routes to cobimetinib relied on a piperidine resolution-based route[120a,126] for accessing the cobimetinib core, the scale route to this drug employs an impressive *N*-cyanomethyl oxazolidine chiral auxiliary-mediated sequence to induce strereocontrol,[127] generating the requisite stereocenter with excellent selectivity and requiring no chromatographic purification in the overall synthetic sequence.[128] Toward this end, the most likely scale synthetic approach was initiated with deprotonation of commercially available (3*S*,5*R*,8a*S*)-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-carbonitrile (**180**, Scheme 34), followed by addition of commercial 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester (**181**), yielded **182** in high purity (92%) after distillation and providing a rapid route to the core structure of cobimetinib.[129] One-pot ring opening and reduction of **182** was accomplished by exposing this hemiaminal to acetic acid and sodium cyanoborohydride, giving rise to intermediate **183**. This carbamate could be further reacted with aqueous HCl in toluene to liberate the azetidine amine salt in high purity (97.6%), which underwent immediate acylation with commercially available 2,3,4-trifluoro-benzoyl chloride (**184**) to enable formation of intermediate **185** in 85% purity after aqueous workup. Reductive cleavage of the chiral auxiliary of **185** with Pd/C and H_2 under aqueous acidic conditions (AcOH, aq HCl) yielded the desired piperidine amine, which could be isolated as a solid (99.6% pure) after trituration with aqueous HCl. Finally, aromatic fluoride substitution with commercially available aniline **186** under basic conditions provided cobimetinib in 99.7% purity after slow precipitation from toluene (it is important to note that the authors offer no comment as to the regioselectivity of this aromatic substitution reaction).[129] While the drug reportedly exists as a fumarate salt, no synthetic reports describing the conversion of cobimetinib

DOI: 10.1021/acs.jmedchem.7b00010
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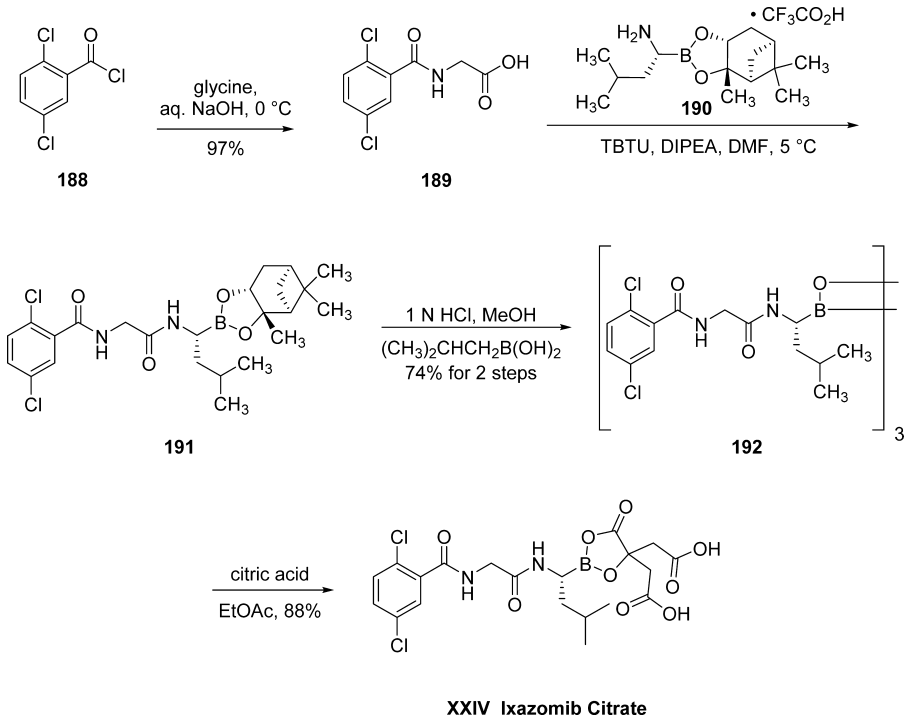
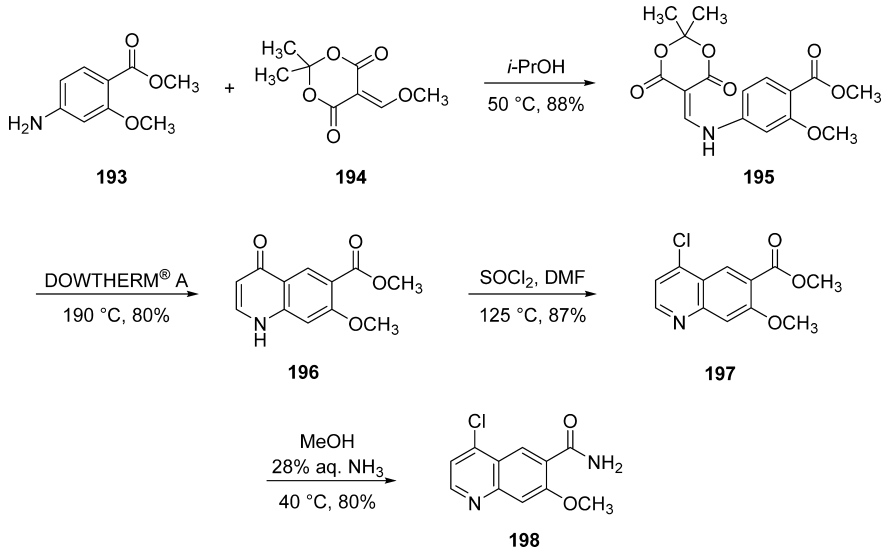
Scheme 35. Synthesis of Ixazomib Citrate (XXIV)



Scheme 36. Synthesis of Fragment 198 of Lenvatinib (XXV)



to the corresponding fumarate salt[130] were available in the chemical literature to our knowledge at the time of publication.

9.2. Ixazomib Citrate (Ninlaro). Ixazomib citrate is a proteasome inhibitor prodrug for the treatment of multiple myeloma in patients who have received at least one prior therapy in combination with lenalidomide and dexamethasone.[131] The drug was developed by Takeda and reversibly inhibits the protein proteasome subunit β type-5, which is part of the 20S proteasome complex.[132] Ixazomib citrate (**XXIV**) is hydrolyzed quickly in vivo to give the biologically active compound ixazomib, which presumably is the corresponding boronic acid variant of **XXIV**.[132]

The structure of ixazomib citrate is particularly interesting in that it is one of the relatively few marketed drugs which feature a boron atom within its structure (others of note being the oncology medication bortezomib[12] and the antifungal drug tavaborole[13]). The ostensible scale synthetic approach began with reaction of commercial 2,5-dichlorobenzoyl chloride (**188**, Scheme 35) with glycine in aqueous NaOH to furnish amide **189** in 97% yield as a white crystalline solid. Acid **189** was then coupled with commercially available 1,3,2-benzodioxaborolane **190**[133] in the presence of TBTU and DIPEA in DMF at low temperature to give diamide **191**, which was used without purification for the next step. Borane **191** was then deprotected with (2-methylpropyl)boronic acid in methanolic HCl to provide trimer **192** in 74% as a white solid. Finally, boroxin **192** was reacted with citric acid in EtOAc to dissociate the trimer, resulting in ixazomib citrate (**XXIV**) in 88% yield as a crystalline solid.[134]

DOI: 10.1021/acs.jmedchem.7b00010
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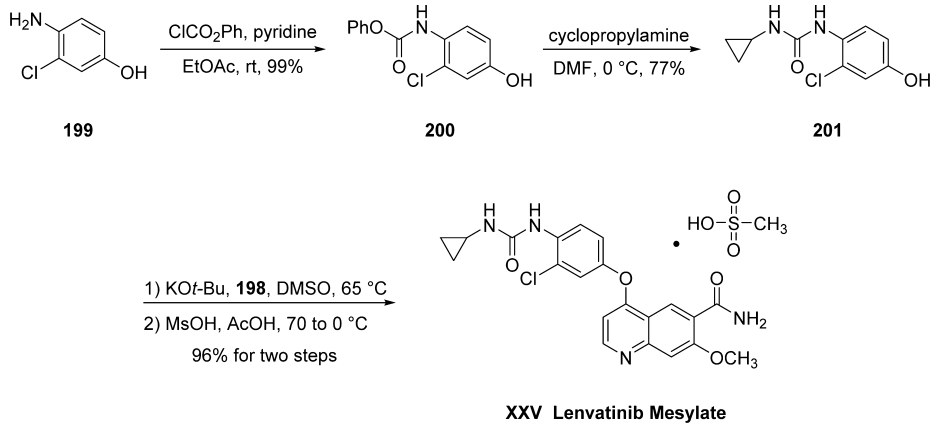
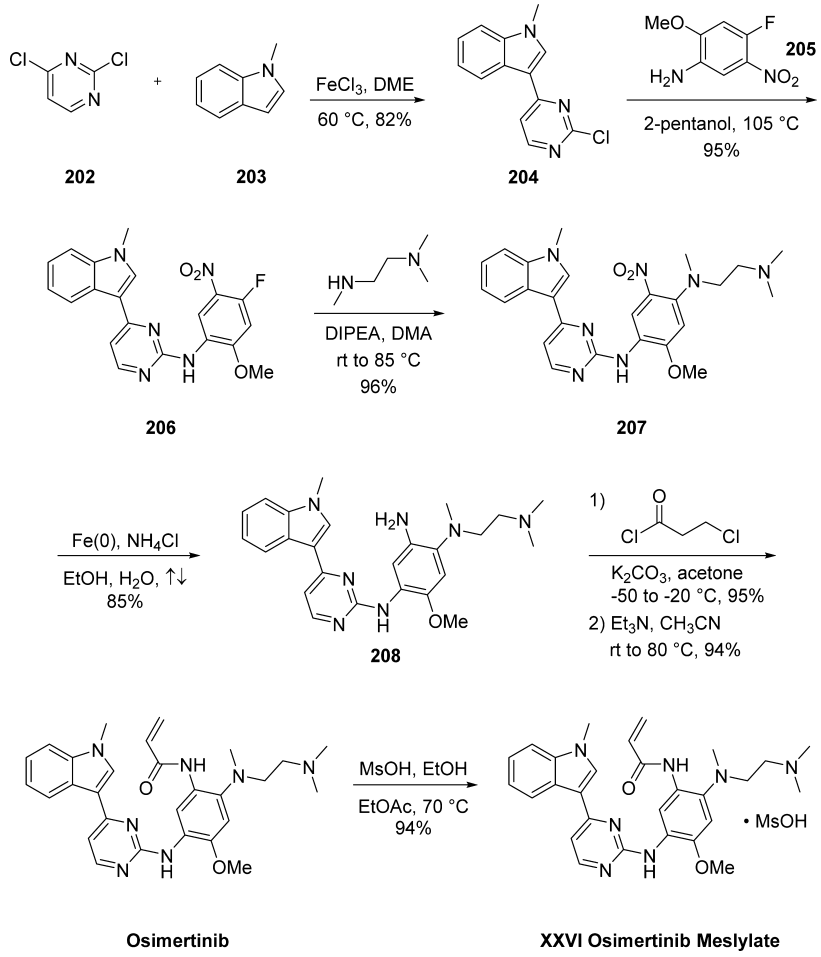
Scheme 37. Synthesis of Lenvatinib Mesylate (XXV)



Scheme 38. Synthesis of Osimertinib Mesylate (XXVI)



9.3. Lenvatinib Mesylate. Developed by Eisai Inc., lenvatinib mesylate is a vascular endothelial growth factor receptor (VEGF) inhibitor which has activity against VEGF subtypes 1, 2, and 3 and was approved by the FDA in 2015 for the treatment of differentiated thyroid cancer that is either locally recurrent, metastatic, or progressive and did not respond to radioactive iodine treatment.[135] In May 2016, the FDA approved the drug as a combination therapy with everolimus for the treatment of advanced renal cell carcinoma.[136] Because VEGF (and fibroblast growth factor receptors, known as FGFRs) are thought to play a role in cardiovascular signaling pathways, VEGF2R and FGFR inhibition are thought to be the mechanisms behind the primary side effect of lenvatinib mesylate, which is hypertension.[135]

The most likely process scale synthetic route to the drug probably follows a patent procedure which was published by Eisai R&D Management Company, Ltd.[137] In this 2007 U.S. patent application, the authors described the kilogram-scale preparation of lenvativnib.[137] A separate 2004 European patent filing from Eisai dealt with the formation of the mesylate as well as several different crystalline salts and the solubility rates of each of the solid forms of these complexes.[138] The structure of

DOI: 10.1021/acs.jmedchem.7b00010
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lenvatinib consists of a diarylethereal linkage between a substituted quinoline and a urea-containing aniline, which conveniently divides the compound into two subunits in the retrosynthetic sense.

The preparation of the lenvatinib quinoline subunit **198** is outlined in Scheme 36.[137] Starting from commercial aniline **193**, a substitution reaction under neutral conditions in warm isopropyl alcohol with a commercial vinyl methoxy derivative of Meldrum's acid (**194**) produced enamine **195** in good yield. Next, subjection of **195** to DOWTHERM A at 190 °C affected an intramolecular cyclizative substitution reaction, followed by loss of acetone, and a decarboxylation reaction to furnish quinolone **196**. This cyclization reaction, which is a variant of the Conrad–Limpach reaction,[139] is particularly noteworthy given the temperature and pH at which it takes place. Conrad–Limpach cyclizations typically proceed under basic conditions at temperatures well above 240 °C.[140] However, a process was developed by Zeneca in 2004 which involved subjecting **195** to the DOWTHERM heat transfer fluid (commercially available from Dow and Sigma-Aldrich, consisting of a eutectic mixture of biphenyl and diphenyl oxide)[141] allowed the team to lower the temperature required for the reaction, clearly observe bubbling of gas indicating the progress of the reaction, and simple cooling and treatment with ether to facilitated precipitate formation.[142] The resulting solid could be collected by filtration and required no additional purification on scale in 80% yield.[142] Quinoline **196** was then converted to the corresponding chloride using thionyl chloride in refluxing DMF, and the resulting ester **197** was converted to the corresponding amide through the use of 28% aqueous ammonia in warm ethanol, which ultimately produced the key chloroquinoline lenvatinib subunit **198** in 80% yield from **197**.[137]

The final approach to the synthesis of lenvatinib mesylate is described in Scheme 37. Commercial aminophenol **199** was converted to the corresponding carbamate through the use of phenyl chloroformate in essentially quantitative yield prior to subjection to cyclopropylamine in chilled DMF, which ultimately furnished urea **201** in 77% overall yield from **200**. Next, exposure of phenol **201** to chloroquinoline **198** (Scheme 36) in the presence of potassium *t*-butoxide followed by treatment with methanesulfonic acid and acetic acid resulted in clean formation of lenvatinib mesylate (**XXV**) in 96% yield across the two-step sequence.[137,138]

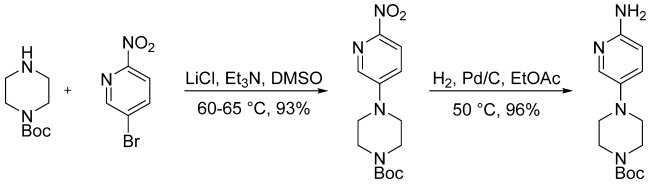
9.4. Osimertinib Mesylate (Tagrisso). Osimertinib is a third-generation EGFR inhibitor which received accelerated approval from the FDA in 2015 for the treatment of non-small cell lung carcinoma.[143] This drug, which reacts as a covalent inhibitor with its intended biological target, was designed by AstraZeneca to bind EGFR and target the T790 M mutation while sparing wild-type EGFR.[143] While a variety of synthetic approaches to this drug have been reported in the literature,[144] the most likely scale route is depicted in Scheme 38.

Friedel–Crafts arylation of commercial *N*-methylindole (**203**) with commercial dichloropyrimidine **202** gave the 3-pyrazinyl indole **204** in good yield. Subsequent S_NAr with nitroaniline **205** (available from a one-step nitration from the commercially available *des*-nitroaniline) provided aminopyrazine **206**. Next, S_NAr reaction of **206** with *N,N,N′*-trimethylated ethylenediamine delivered **207** in near quantitative yield, and this was followed by nitro reduction with iron under acidic conditions to give rise to the triaminated arene **208** in 85% yield. Because acrylates are notoriously difficult to install directly due to their highly reactive nature and propensity to polymerize, a clever two-step acylation/elimination sequence was employed using 3-chloropropanoyl chloride, and this was immediately followed by mesylate salt formation, which furnished the osimertinib mesylate (**XXVI**) in excellent yield. This seven-step process which derives from readily available feedstock delivered the final product in nearly 57% overall yield from starting materials **202** and **203** (Scheme 38).[145]

9.5. Palbociclib (Ibrance). Palbociclib is a cyclin-dependent kinase (CDK) 4 and CDK6 inhibitor approved by the FDA to treat hormone receptor-positive (HR+) human epidural growth factor 2-negative (HER2−) metastatic breast cancer.[146] It is used in combination with letrazole as the first-line hormonal-based therapy in postmenopausal women,[147] or with fulvestrant in women with disease progression following hormonal therapy.[148] Palbociclib was discovered at Warner-Lambert[149] and developed by Pfizer after their merger. Pfizer is also studying the effectiveness of palbociclib in a variety of other cancers at various stages in the clinic.

Numerous syntheses of palbociclib have been reported,[149,150] and the commercial scale process published by scientists at Pfizer is described herein.[151] The amino-pyridylpiperazine fragment **212** was prepared in two steps. Commercial piperazine **209** was added to 5-bromo-2-nitropyridine (**210**) to give nitro-pyridine **211** in 93% yield (Scheme 39). Hydrogenation of the nitro group using catalytic palladium on carbon provided the amino-pyridylpiperazine **212** in 96% yield.

Scheme 39. Synthesis of Fragment 212 of Palbociclib (XXVII)



209 210 211 212

The completion of the synthesis of palbociclib is described in Scheme 40 and was initiated with the preparation of the pyridopyrimidinone fragment **217**. As such, cyclopentylamine (**214**) was added to 5-bromo-2,4-dichloropyrimidine (**213**) to give 5-bromo-2-chloro-6-cyclopentylaminopyrimidine (**215**) in 84% yield. Heck reaction with crotonic acid followed by treating the resulting product with acetic anhydride formed the mixed anhydride under elevated temperatures, and this resulted in cyclization to give pyrimidinone **214** in 81% yield. Bromination using *N*-bromosuccinimide (NBS) provided coupling partner **217** in 88% yield. Next, aminopyridine **212** was treated with cyclohexylmagnesium chloride and then reacted with **217** to give the S_NAr product **218** in 88% yield.[151c] A second Heck reaction between bromide **218** and butyl vinyl ether (**219**) using palladium acetate/bis(2-diphenylphosphinophenyl)ether (DPEPhos) as the catalyst provided enol ether **220** in 84% yield.[151d] Exposure of **220** to acidic conditions removed the Boc group from the piperazine while converting the enol ether to the corresponding ketone, providing palbociclib (**XXVII**) in 90% yield.[151a]

9.6. Panobinostat Lactate (Farydak). Panobinostat lactate is a histone deacetylase (HDAC) inhibitor that was

DOI: 10.1021/acs.jmedchem.7b00010
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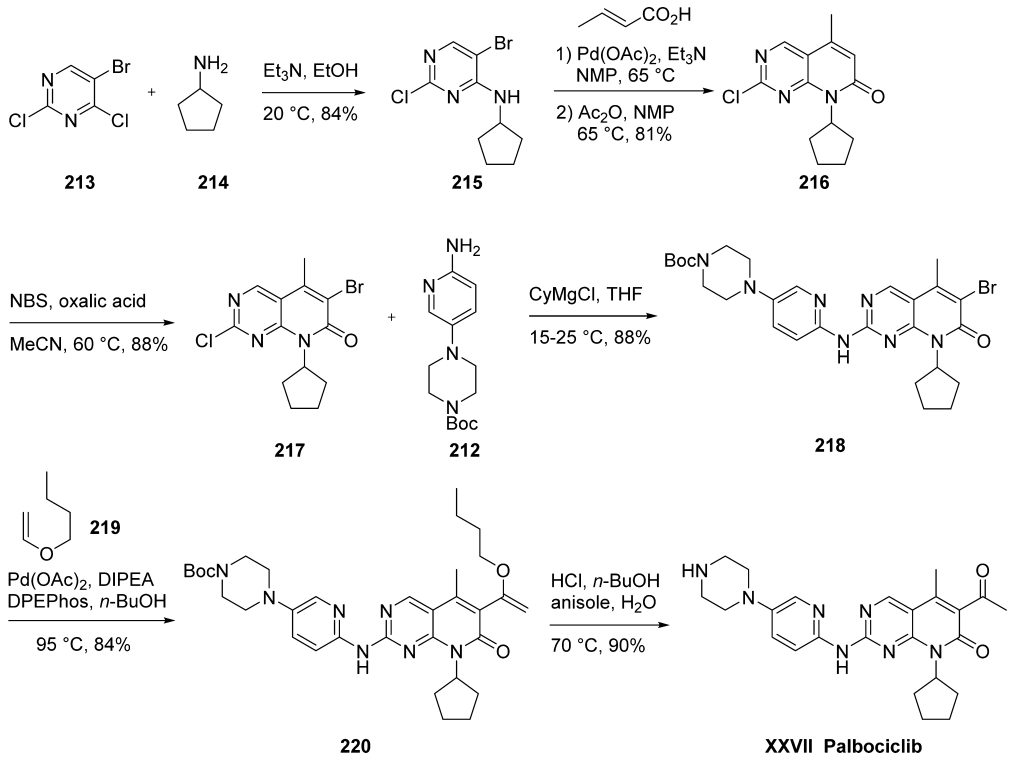
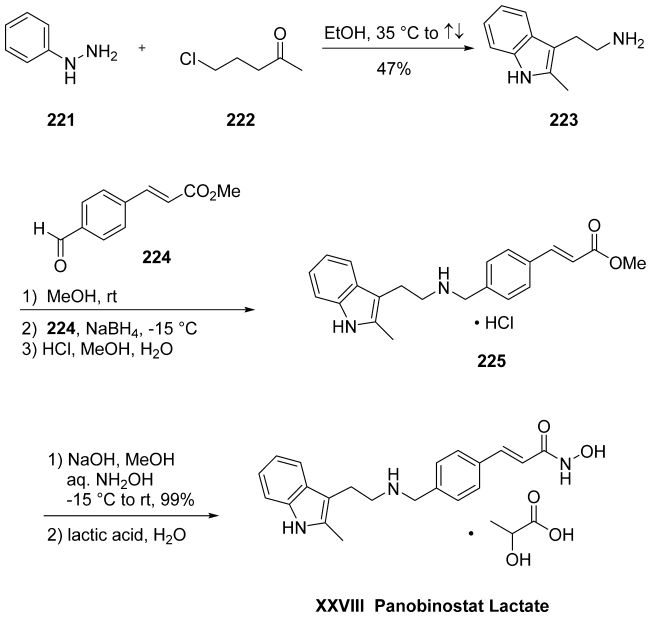
Scheme 40. Synthesis of Palbociclib (XXVII)



approved by the FDA for the treatment of multiple myeloma.[152] It was also approved for the same indication in Japan, and the EU approved its use in combination with bortezomib and dexamethasone for the treatment of adults with relapsed and/or refractory multiple myeloma.[153] Panobinostat was discovered and developed by Novartis and is currently being investigated for a number of hematological cancers as well as other indications.[153]

The synthesis of panobinostat lactate is described in Scheme 41.[154] Grandberg synthesis of 2-methyltryptamine (**223**) was accomplished in 47% yield by heating phenylhydrazine (**221**) with 5-chloro-2-pentanone (**222**).[155] Reductive amination of **223** with (*E*)-3-(4-formyl-phenyl)-acrylic acid methyl ester (**224**) and sodium borohydride followed by formation of the hydrochloride salt provided amine hydrochloride **225** in high purity. Saponification of the methyl ester followed by reaction with hydroxylamine provided panobinostat in high overall yield. The free base was treated with racemic lactic acid and recrystallized in water to give panobinostat lactate (**XXVIII**).[156]

Scheme 41. Synthesis of Panobinostat Lactate (XXVIII)



9.7. Sonidegib Phosphate. Sonidegib phosphate (**XXIX**), an orally bioavailable, small molecule smoothened (SMO) receptor antagonist developed by Novartis, was approved in 2015 in Switzerland, the U.S., and the EU for the treatment of adult patients with advanced or locally advanced basal cell carcinoma (BCC).[157] BCC is the most frequently diagnosed skin cancer, constituting 80% of all nonmelanoma skin cancers.[158] While most BCCs can be treated through surgery or radiation therapy, some patients (<10%) have more advanced tumors for which surgery may be contraindicated or impractical; treatment options for these patients are limited. SMO, a G-protein coupled receptor-like protein (GPCR), is a key regulator in the hedgehog (Hh) pathway, which is activated in a number of tumors including BCC.[159] In a multicenter clinical trial for sonidegib, an objective response rate of 43% was observed for patients with locally advanced BCC (dosing at 200 mg once daily), with sustained clinically meaningful responses based on an 18-month analysis.[160] Sonidegib joins vismodegib as marketable treatments of BCC. Vismodegib, which was approved in 2012 as a first-in-class SMO receptor antagonist, represented the first Hedgehog signaling pathway targeting agent to gain FDA approval.[161]

While an explicit process synthetic route to sonidegib phosphate has not been reported to date, the route described in Scheme 42 represents the most likely scalable synthesis that has been reported in the patent literature.[162] The synthesis was

DOI: 10.1021/acs.jmedchem.7b00010
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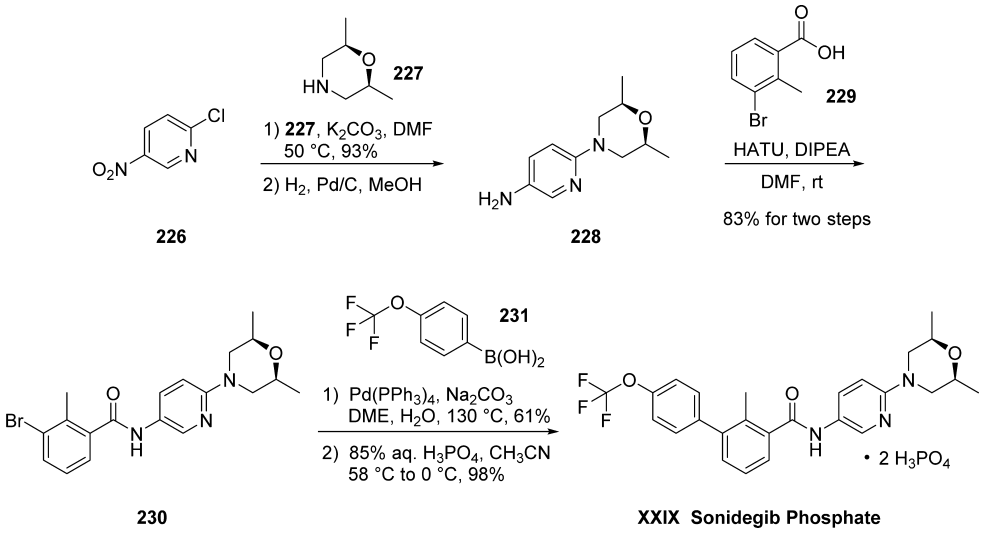
Scheme 42. Synthesis of Sonidegib Phosphate (XXIX)



initiated with an S_NAr reaction involving commercial 2-chloro-5-nitropyridine (**226**) and *cis*-dimethylmorpholine (**227**) followed by subsequent nitro reduction via hydrogenation to provide amine **228**. The crude amine was coupled directly to 3-bromo-2-methylbenzoic acid (**229**) in an amide bond-forming reaction to construct **230** in 77% yield over three steps. The resultant bromide was coupled to 4-(trifluoromethoxy)-phenylboronic acid (**231**) under Suzuki conditions to give rise to sonidegib as the freebase. Finally, treatment with 85% aqueous phosphoric acid in acetonitrile generated sonidegib phosphate (**XXIX**) in good yield.[163]

10. CONCLUSION

In summary, the pharmaceutical industry at large enjoyed another productive year in 2015, a year which saw the advance of these 29 new molecular entities to the marketplace. Innovative synthetic chemistry, particularly new methods for bond construction and the assembly of complex molecular architectures to be realized on scale, will continue to allow for new chemical space to be reached and play a critical role in the discovery and development of new medicines in the future. This review has highlighted the application of such technology toward the production of important therapies and hopefully will provide inspiration to researchers worldwide in the discovery of new drugs.

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Notes

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Hongxia X. Ding (Sheryl) obtained a B.S. in Pharmaceutics in 2001 and a Ph.D. in Medicinal Chemistry in 2006 from Zhejiang University in Hangzhou, China. Hongxia is the cofounder and Chief Executive Officer of PHARMACODIA, a company founded in 2013, which is an online platform (http://www.pharmacodia.com) providing big data and information service in the pharmaceutical R&D field. In 2010−2013, Hongxia joined Shenogen Pharma Group, a China-based Biotech company. As senior director of the R&D department, Hongxia is responsible for the CMC development of a novel ER-α36 targeted phase II candidates drug, named Icaritin (SNG162), and the discovery and development of second-generation small molecular based on the structure optimization of SNG162. Before Shenogen, Hongxia worked at BioDuro since 2006, as senior group leader and senior research scientist.

Carolyn A. Leverett began her career at Pfizer in 2012, focusing on the development of microtubule inhibitor-based payloads for use as antibody−drug conjugates. She currently works in the Applied Synthesis Technologies group, where she is involved in the discovery of biocatalytic routes to support various chemistry therapeutic areas. Carolyn is a native of North Carolina and obtained her B.S. in chemistry from North Carolina State University. She completed her doctoral studies with Professor Albert Padwa at Emory University in Atlanta, GA, working on total synthesis of several piperidine-based natural products and the alkaloid minfiensine. Prior to joining Pfizer, she was a postdoctoral fellow working with Professor Daniel Romo at Texas A&M University, exploring new applications of nucleophile-catalyzed aldol lactonization reactions.

Robert E. Kyne, Jr. is a Senior Scientist in the Chemical Biology group at Celgene Corp., located in Cambridge, MA. During his time at Celgene, Bob has contributed to the development of several target ID platforms and the expansion into new druggable modalities. Previously, Bob was a Senior Scientist in the BioTherapeutics medicinal chemistry group at Pfizer, Inc. There, in addition to working on several drug discovery programs, Bob contributed to the

DOI: 10.1021/acs.jmedchem.7b00010
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discovery of sulfonyl fluorides as selective tyrosine warheads, use of clickable photoaffinity labels for target ID/validation, and the use of CETSA as an orthogonal method for target confirmation. Bob received his Ph.D. from Boston College in 2012 after graduating with honors from Connecticut College in 2007.

Kevin K.-C. Liu is currently a Director at the Global Discovery Chemistry of Novartis Institute of BioMedical Research and he is located in Shanghai, China, since 2015. He received his B.S. in Chemistry from National Taiwan University, followed by his Ph.D. in Organic Chemistry, under the mentorship of Professor Chi-Huey Wong, at Texas A&M and The Scripps Research Institute. He did his postdoctoral fellowship with Professor Samuel Danishefsky at Yale University and Memorial Sloan Kettering Cancer Center in New York. He then joined Pfizer Research Center as a medicinal chemist and worked in different therapeutic areas. He joined Lilly China Research and Development Center in 2012 as a Senior Research Director. He has more than 80 peer-reviewed journal articles and patents that cover multiple therapeutic areas.

Sarah J. Fink is a Senior Manager for Integrated Programs at BioDuro and is based in the Boston area. She obtained a B.A. in Chemistry and English literature from Williams College, followed by a Ph.D. in Organic Chemistry from the University of Cambridge with Professor Ian Paterson. Her thesis work focused on the total synthesis of aplyronine C. After a fellowship for young international scientists at Shanghai Institute of Materia Medica, Sarah joined BioDuro in Shanghai in 2014, where she was a scientist and chemistry group leader for integrated drug discovery projects in multiple therapeutic areas. She relocated to Boston in early 2017; in her current role, she provides medicinal chemistry and scientific project management support for collaborations with pharma and biotech.

Christopher J. O'Donnell obtained a B.S. in Chemistry from the University of Illinois in Urbana/Champaign and a Ph.D. in Organic Chemistry from the University of Wisconsin, Madison. After postdoctoral research at the University of California—Irvine, he joined Pfizer in 1999 in the Neuroscience Medicinal Chemistry group. As a scientist, project leader, and manager, he has led project teams to the nomination of over 10 clinical candidates. In 2010, Chris moved to Oncology Medicinal Chemistry to build the Antibody Drug Conjugate chemistry group and his team has nominated 11 conjugates for clinical development. Currently Chris is the Executive Director of the newly created Applied Synthesis Technology group at Pfizer. Chris is an author/inventor of 70 peer-reviewed journal articles and patent applications.

■ ACKNOWLEDGMENTS

We would like to thank Dr. Dahui Zhou for assisting us with the translation of a few references.

■ ABBREVIATIONS USED

Ac, acetyl; AcOH, acetic acid; ADP, adenosine 5′-diphosphate; aq, aqueous; AIBN, azobis(isobutyronitrile); BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; Bn, benzyl; Boc, *N*-*tert*-butoxycarbonyl; Bs, benzenesulfonyl; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; BH_3-DMS, borane-dimethyl sulfide; BTI, bis(trifluoroacetoxy)iodobenzene; Bu, *n*-Bu, butyl, *n*-butyl; cat, catalytic; Cbz, benzyloxycarbonyl; CBzCl, benzyl carbonochloridate; CDI, *N*,*N*′-carbonyldiimidazole; CNS, central nervous system; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; dba, dibenzylideneacetone; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin; DBU, 1,8-diazobicyclo[5.4.0]undec-7-ene; DCB, dichlorobenzene; DCC, 1,3-dicyclohexylcarbodiimide; DCE, dichloroethane; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodiformate; 3,4-DHP, 3,4-dihydropyran; $(DHQ)_2PHAL$, hydroquinine 1,4-phthalazinediyl diether; DIAD, diisopropyl azodicarboxylate; DIBAL, diisobutylaluminum hydride; DIPEA, diisopropylethylamine; DM, diabetes mellitus; DMA, dimethylacetamide; DMAP, 4-dimethylaminopyridine; DME, dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMF-DMA, dimethylformamide−dimethylacetal; DMI, 1,3-dimethyl-2-imidazolidinone; DMPU, 1,3-dimethyl tetrahydropyrimidin-2(1*H*)-one; DMS, dimethylsulfide; DMSO, dimethyl sulfoxide; DPEN, (1*R*,2*R*)-2-amino-1,2-diphenylethyl; DPEPhos, bis[(2-diphenylphosphino)phenyl] ether; dppp, 1,3-bis(diphenylphosphino)propane; DTTA, di-*p*-toluyl-D-tartaric acid; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; Et, ethyl; EtOAc, ethyl acetate; HATU, *o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluronium hexafluorophosphate; HG-II, (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro(*o*-isopropylphenylmethylene)ruthenium; HOBt, 1-hydroxybenzotriazole hydrate; *i*-Pr, isopropyl; IPA, isopropyl alcohol; KHMDS, potassium hexamethyldisilazide; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazide; *m*CPBA, 3-chloroperoxybenzoic acid; Me, methyl; MeCN, acetonitrile; Ms, methanesulfonyl; MsCl, methanesulfonyl chloride; MsOH, methanesulfonic acid; MTBE, methyl *tert*-butyl ether; NaHMDS, sodium *bis*(trimethylsilyl)amide; *n*-BuLi, *n*-butyllithium; NBS, *N*-bromosuccinimide; NMM, *N*-methyl morpholine; NMP, *N*-methyl-2-pyrrolidone; $Pd_2(dba)_3$, *tris*(dibenzylideneacetone)dipalladium; $PdCl_2(PPh_3)_2$, bis(triphenylphosphine)palladium(II)chloride; $Pd(OAc)_2$, palladium acetate; Ph, phenyl; PhMe, toluene; PPA, polyposphoric acid; *p*-TsOH, *p*-toluenesulfonic acid; PTSA, *p*-toluenesulfonamide; Py, pyridine; PyBrop, bromotripyrrolidinophosphonium hexafluorophosphate; rt, room temperature; TBAB, *t*-butyl ammonium bromide; TBAF, tetrabutylammonium fluoride; TBHP, *t*-butyl hydroperoxide; TBME, *tert*-butylmethyl ether; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluronium tetrafluoroborate; *t*-Bu, *tert*-butyl; TCAA, trichloroacetic acid; TEA, triethylamine; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic acid anhydride; THF, tetrahydrofuran; THP, tetrahydropyranyl; TMDS, 1,1,3,3-tetramethyldisiloxane; TMS, trimethylsilyl; TNF, tumor necrosis factor; Tol, toluene; Ts, *p*-toluenesulfonyl

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■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was originally published ASAP on May 3, 2017. In Scheme 31, the ribose ring was missing the oxygen atoms in both structures. The corrected version was reposted on May 8, 2017.

DOI: 10.1021/acs.jmedchem.7b00010
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