Synthetic Approaches to the 2008 New Drugs

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Abstract: New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biological target. These new chemical entities (NCEs) provide insights into molecular recognition and also serve as leads for designing future new drugs. This review covers the syntheses of 18 NCEs marketed in 2008.

Keywords: Synthesis, New Drug, New Chemical Entities, Medicine, Therapeutic Agents.

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 physiology and medicine [1].

Inaugurated seven years ago, this annual review presents synthetic methods for molecular entities that were launched in various countries for the first time during the past year [2-7]. Given that drugs tend to have structural homology across similar biological targets, it is widely believed that the knowledge of new chemical entities and their syntheses will greatly enhance the ability to design new drugs in shorter periods of time. In 2008, 31 new products which include new chemical entities, biological drugs, and diagnostic agents reached the market [8]. Eleven additional products were approved for the first time in 2008; however, they were not launched before year's end and thus the syntheses of those drugs will be covered in 2009's review. This review focuses on the syntheses of 18 new drugs marketed in 2008 (Fig. **1**) and excludes new indications for known drugs, new combinations, new formulations and drugs synthesized *via* bioprocesses or peptide synthesizers. The synthetic routes cited herein represent the most scalable methods reported and appear in alphabetical order by generic name.

Alvimopan Hydrate (*Entereg*®)

Alvimopan is a μ-opioid receptor antagonist approved in the U.S. in May 2008 for the treatment of post-operative ileus (POI) – a temporary dysfunction of the gastrointestines. Alvimopan does not penetrate the central nervous system (CNS) and acts as a peripheral antagonist. The molecule inhibits the negative effects of opioids on the gastrointestinal (GI) system without inhibiting the desired analgesic effects of CNS penetrant opioids [8, 9]. Alvimopan was originally developed by Lilly and later licensed to GlaxoSmithKline, which co-markets the drug with Adolor Pharmaceuticals. Several synthetic routes have been disclosed [10-12], and the process route is described in Scheme **1** [13]. This route was performed on kilogram scale and no yields were reported beyond the generation of compound **8**. 3-Bromophenol **1** was treated with isopropyl bromide and potassium carbonate at 60-65 °C for 16 h to give 3-isopropyoxy bromobenzene **2**. Bromide **2** was added to a suspension of Mg turnings in THF at 40-60 °C generating the corresponding Grignard reagent to which a solution of 1,3-dimethylpiperidone **3** in THF was added as four separate fractions over a period of 2 h. Upon completion, the reaction mixture was quenched with aqueous ammonium chloride, the product was extracted into heptane and crystallized out of solution and was isolated by filtration to provide a *cis*-(±) enriched mixture of piperidone alcohol **4** in 97% purity. This mixture was recrystallized from heptane to afford exclusively the *cis*-(±) piperidone **4** in 97% purity and 66% yield. Piperidone alcohol **4** was treated with ethylchloroformate and triethyl amine at 0 °C and warmed to room temperature over 3 h. The resulting ethylcarbonate was resolved via classical resolution with (+)-di-*p*-toluyl-D-tartaric acid and then recrystallized from ethanol to give **5** in 99% purity and 99.5% ee. The conversion of **5** to 3,4-*trans* dimethyl piperidine **8** followed the sequence described by Werner, *et. al.* as no experimental was disclosed in the process patent for this sequence [11, 13]. The (+)-DTTA salt **5** was treated with sodium hydroxide to liberate the free base which then underwent thermal elimination of the carbonate at 190 ºC in decalin to give the desired trisubstituted olefin **6** in 92% yield. Treatment of piperidine **6** with *n*-BuLi followed by addition of dimethyl sulfate at -50 ºC gave the desired 3,4-*trans*-dimethyl enamine **7**. Due to the reactivity of the dimethyl sulfate, only one equivalent was used and the reaction had to be quenched into aqueous ammonium hydroxide to avoid *N*-methylation. The crude enamine **7** was reduced with sodium borohydride and purified by crystallization with (+)-DTTA, giving (+)-DTTA salt **8** in 65% overall yield from **5**. Additionally, the crystallization provided **8** with less than 1% impurities and 98.8% ee. The free base of **8** was liberated upon treatment with sodium hydroxide and reacted with phenyl chloroformate at 80-85 °C, to effectively demethylate the nitrogen. The resulting crude phenylcarbamate **9** was refluxed in HBr/acetic acid for 18 h to simultaneously cleave the isopropyl ether and carbamate protecting groups to give the aminophenol **10**, which was precipitated out of solution and collected by filtration. Amine **10** was

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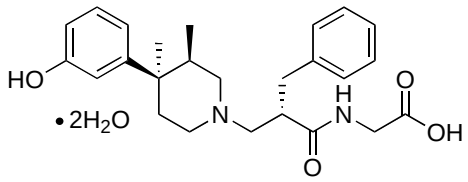
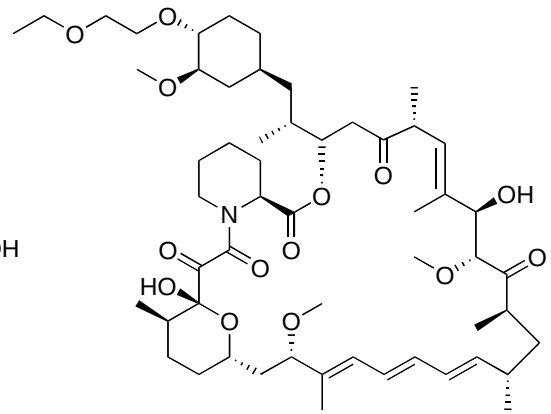
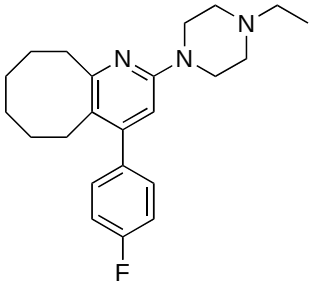


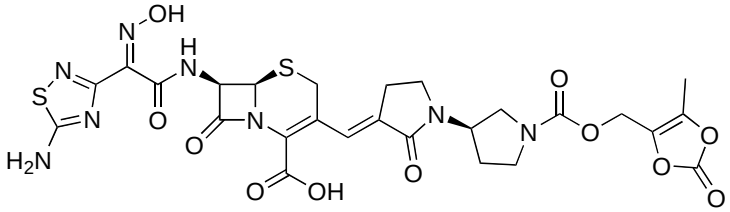
I Alvimopan hydrate



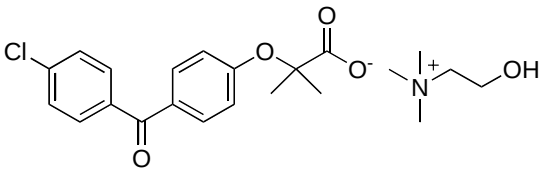
II Biolimus A9



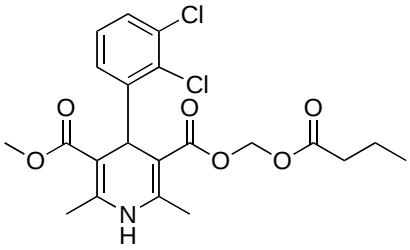
III Blonanserin



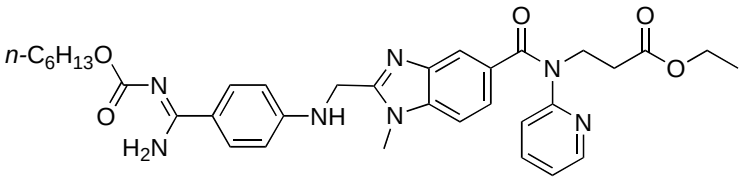
IV Ceftobiprole medocaril



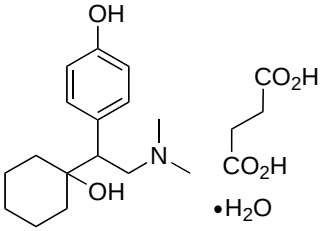
V Choline Fenofibrate



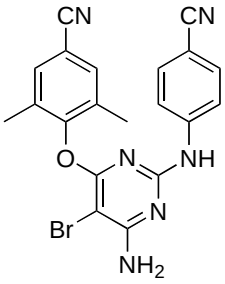
VI Clevidipine butyrate



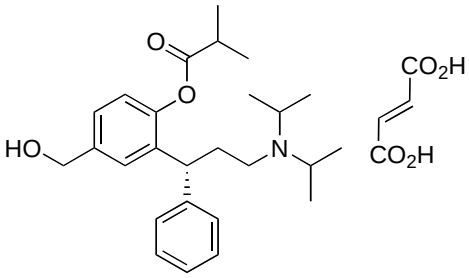
VII Dabigatran etexilate



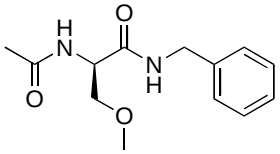
VIII Desvenlafaxine succinate



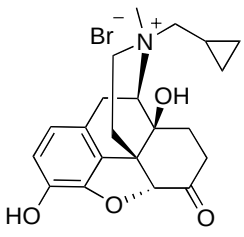
IX Etravirine



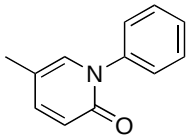
X Fesoterodine fumarate



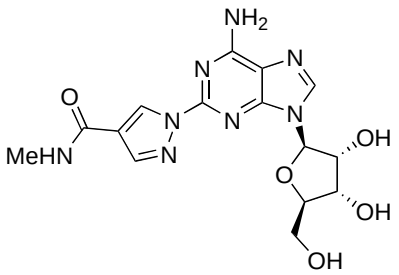
XI Lacosamide



XII Methylnaltrexone bromide



XIII Pirfenidone



XIV Regadenoson

Fig. (1). Contd….

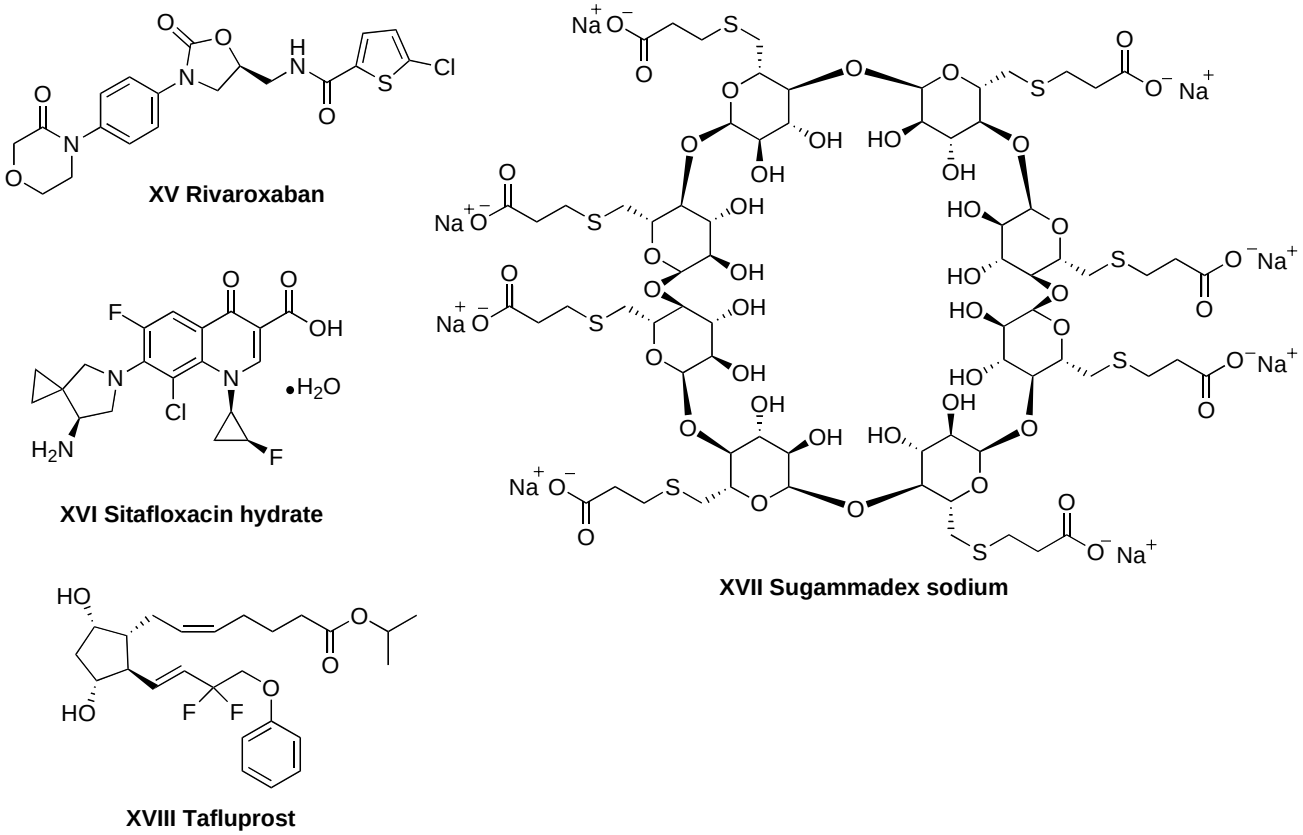


Fig. (1). Structures of 18 new drugs marketed in 2008.

then treated with methylacrylate (**11**) in THF at 40-45 °C for 18-19 h to give the intermediate **12**, which was transferred directly into a solution of LDA. A solution of benzyl bromide in THF was added to the enolate of **12** at -20 °C and upon complete benzylation, **13** was isolated as its HCl salt. Ester **13** was hydrolyzed with sodium hydroxide to give **14**, which was coupled to glycine ethyl ester hydrochloride **15** in the presence of DCC, HOBT and triethylamine in THF providing crude ethyl ester **16**. Finally, ester **16** was hydrolyzed with sodium hydroxide to give alvimopan (**I**), which was purified by crystallization from the reaction mixture in 99.2% purity and 99% ee.

Biolimus A9

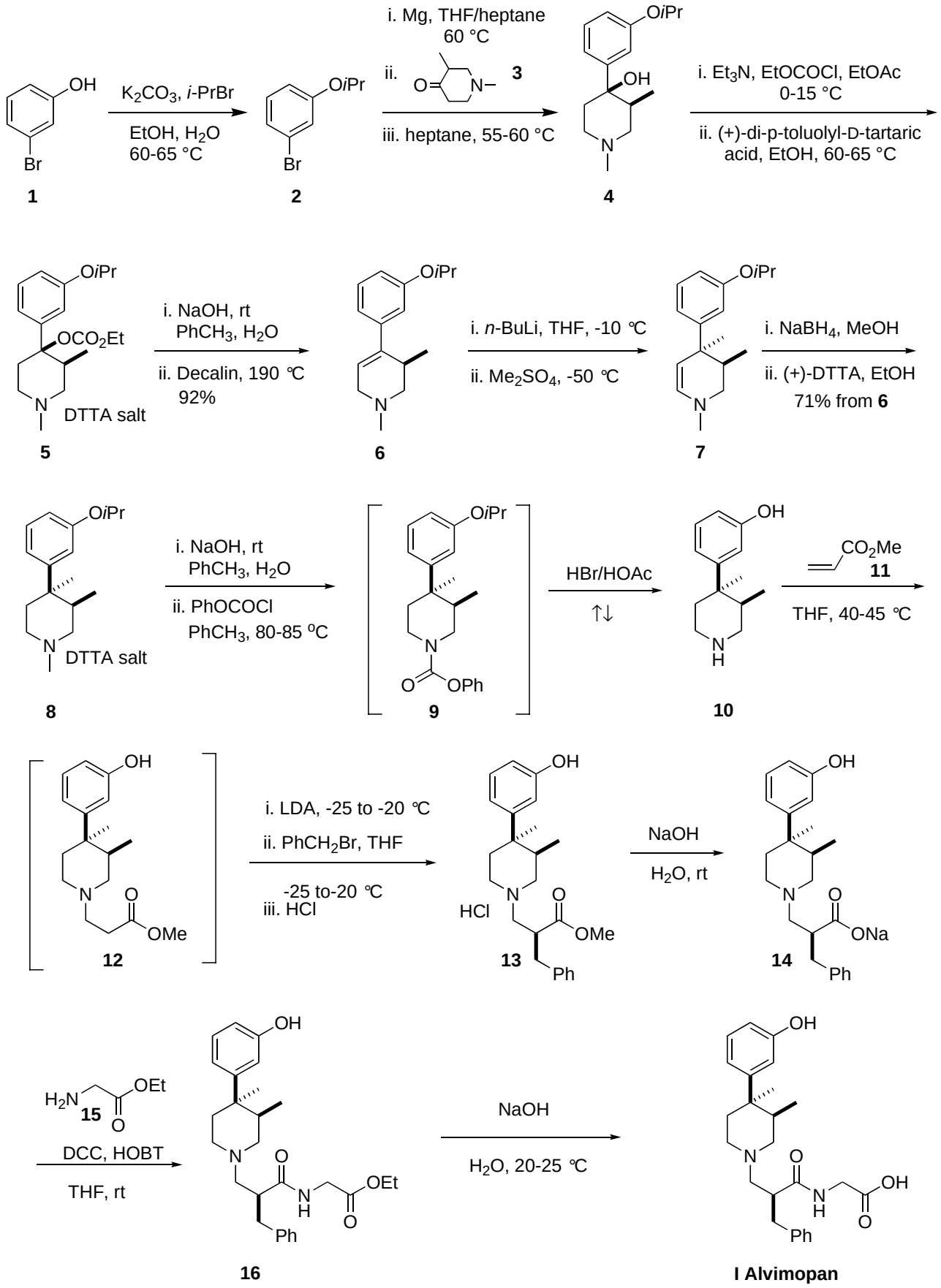
Biolimus A9 is a new rapamycin analog for the treatment of inflammation, late thrombosis and restenosis. The drug is coated with a biodegradable polylactic acid polymer and is delivered on a Biomatrix stent developed by Biosensors [14a, b]. Biolimus A9 was designed for this stent system specifically with high lipophilicity to allow rapid absorption of the drug by the target tissue which reduces systemic exposure. The new stent with the biodegradable polymer is designed to improve safety when compared to other earlier stents with durable polymer coatings. The synthesis involves the preparation of the ethoxyethyl triflate **18** which was obtained by reacting ethoxyethanol **17** with triflic anhydride in dichloromethane in the presence of 2,6-lutidine at 0 °C (Scheme **2**) [14b]. Selective alkylation of rapamycin **19** alcohol at C-42 with crude triflate **18** in a mixture of toluene and 2,6-lutidine at 60 °C gave biolimus A9 **II** in 25% isolated yield.

Blonanaserin (*Lonasen*®)

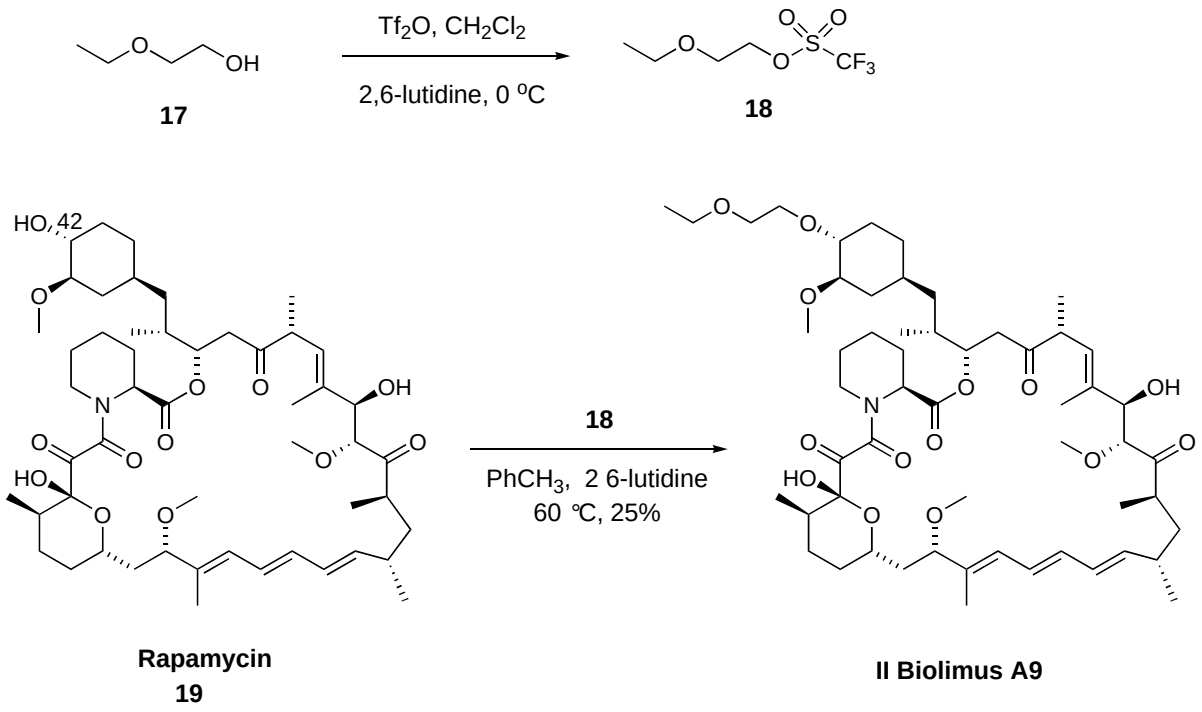
Blonanserin is an atypical antipsychotic agent approved last year in Japan and is promoted jointly by Dainippon Sumitomo and Almirall. Blonanserin is a D_2 preferring dual D_2/5-HT_{2A} antagonist for the treatment of schizophrenia [8, 15-16]. The synthesis of blonanserin **III** has been described in both the primary and patent literature (Scheme **3**) [17,18]. Condensation of cyclooctanone (**21**) with 4-fluorobenzoyl acetonitrile (**20**) in 75% polyphosphoric acid at 110 °C provided the fused cyclooctapyridone **22** in 64% yield. Reaction of **22** with phenyldichlorophosphinic acid (**23**) at 170 °C gave chloride **24** in 76% yield, which was then reacted with potassium idodide and 4-ethyl piperidine (**25**) at 170 °C to give blonanserin (**III**) in 47% yield after crystallization from acetonitrile.

Ceftobiprole Medocaril (*Zeftera*™)

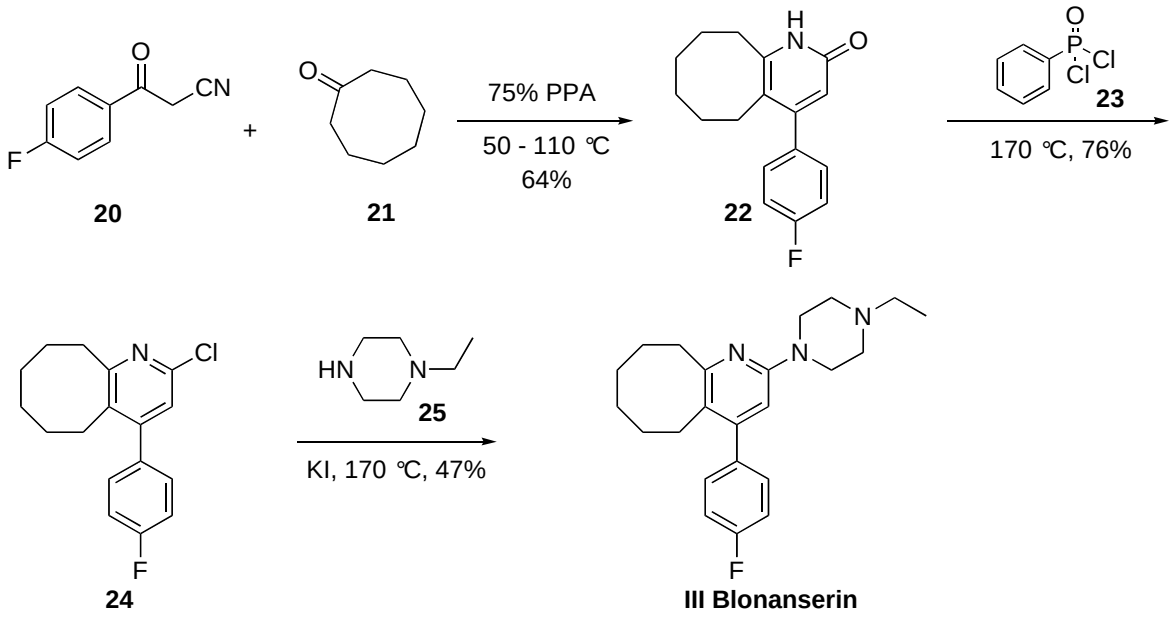
Ceftibiprole medocaril is a broad-spectrum anti-methicillin-resistant *Staphylococcus aureus* (MSRA) cephlasporin antibiotic first launched by Basilea Pharmaceutiacals in Canada for the treatment of skin related infections in 2008 [8, 19, 20]. Basilea is co-developing ceftibiprole with Johnson & Johnson (Phase III clinical trials) for the treatment of both community- and hospital-acquired pneumonia. Ceftobiprole is administered as the water soluble prodrug



Scheme 1. Synthesis of Alvimopan (I).



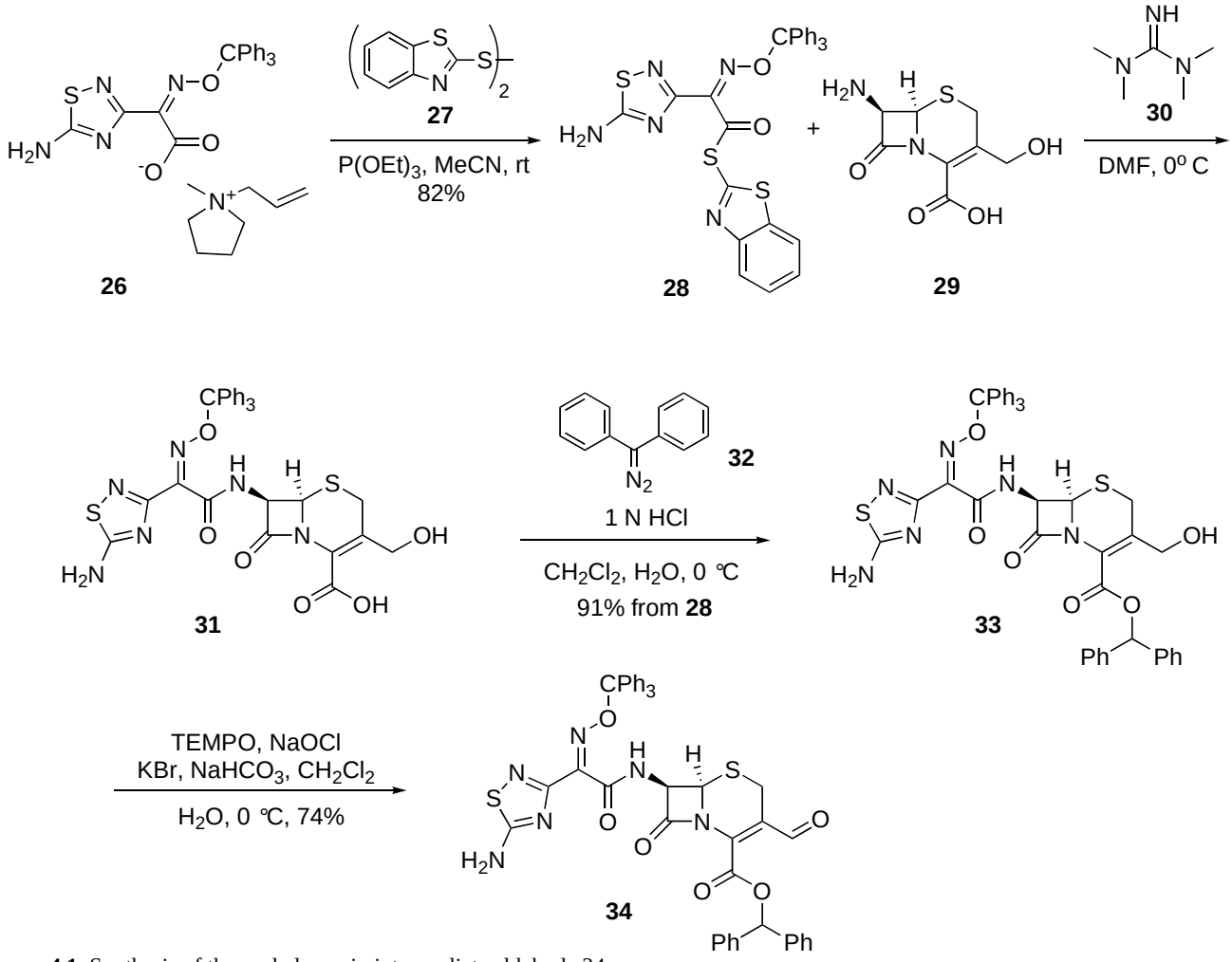
Scheme 2. Synthesis of Biolimus A9 (II).



Scheme 3. Synthesis of Blonanserin (III).

ceftobiprole medocaril, which is readily hydrolyzed to ceftobiprole in the plasma. The synthesis of ceftobiprole and ceftobiprole medocaril have been reported in several patents and the synthesis of the prodrug will be highlighted as shown in Schemes **4.1**-**4.3** [21-25]. Activation of the amino dithiazole acid salt **26** [26] with benzothiazole disulfide **27** via diethyl phosphite gave thioester **28** in 82% yield. Condensation of **28** with aminocephalosporin **29** using tetramethyl guanidine (**30**) as the base in DMF at 0 °C provided intermediate acid **31** (Scheme **4.1**), which was then immediately esterified by reaction with diphenyl diazomethane at 0 °C to give diphenylemethyl ester **33** in 91% yield. Alcohol **33** was then oxidized with sodium hypochlorite in the presence of TEMPO to give the desired aldehyde **34** in 74% yield, which was ready to be coupled to the phosphonium salt **41**.

The preparation of phosphonate **41** is described in Scheme 4.2 and was initiated by the reaction of amino pyrrolidine **35** with acid chloride **36** with 50% sodium hydroxide in DCM to provide the amidopyrrolidine **37** in quantitative yield. Bromide **37** was then treated with triphenylphosphine to give phosphonate **38** in 78% yield. Removal of the allyl carbonate protecting group was accomplished



Scheme 4.1. Synthesis of the cephalosporin intermediate aldehyde 34.

through reaction with tributyltin hydride with palladium catalysis to afford bipyrrolidine **39**, which was then treated with the carbonate **40** to give phosphonium salt **41** in 26% yield, which was now activated for Wittig condensation with aldehyde **34**.

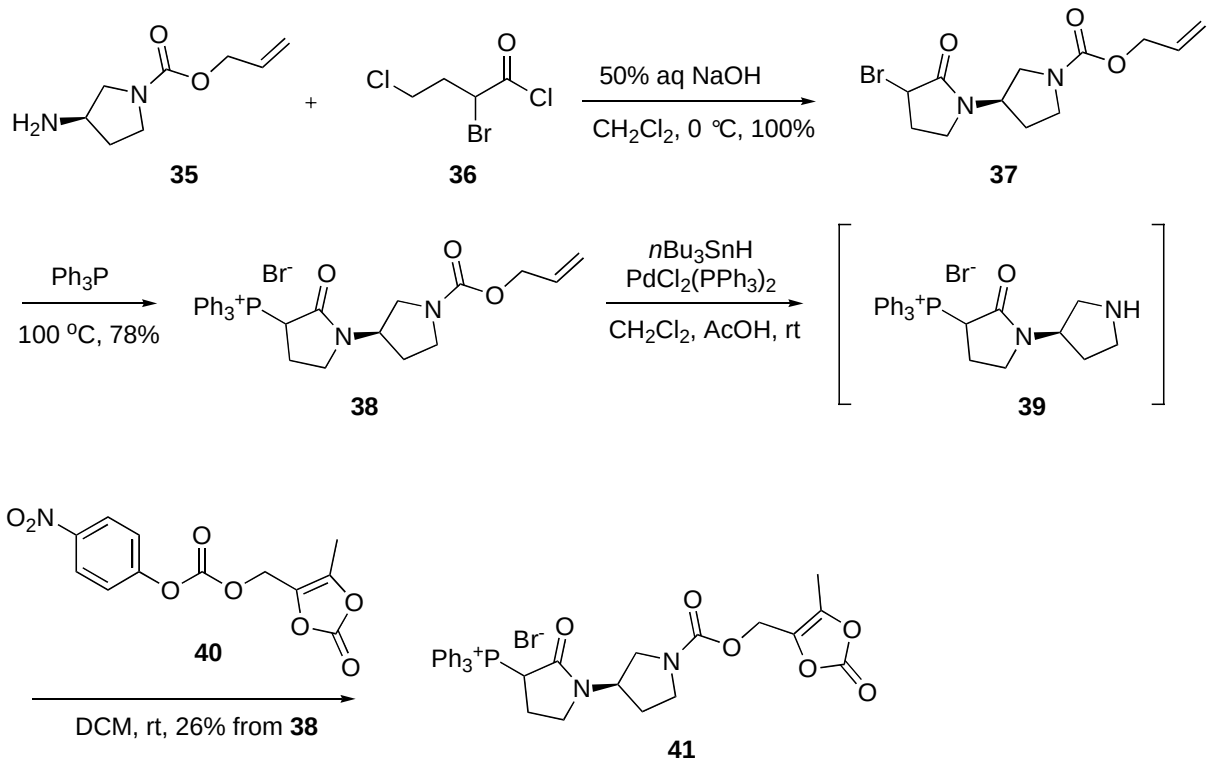
The completion of the preparation of ceftobiprole medocaril is described in Scheme **4.3**. Phosphonate **41** was deprotonated with potassium *t*-butoxide to generate the corresponding ylide that was subsequently reacted with the cephalosporin aldehyde **34** to produce the olefinic betalactam ester **42** in 29% yield. Removal of the diphenylmethyl ester and trityl groups were accomplished by reaction with triethylsilane in the presence of TFA completing the synthesis of ceftobiprole medocaril (**IV**) in 92% yield.

Choline Fenofibrate (*Trilipix*™)

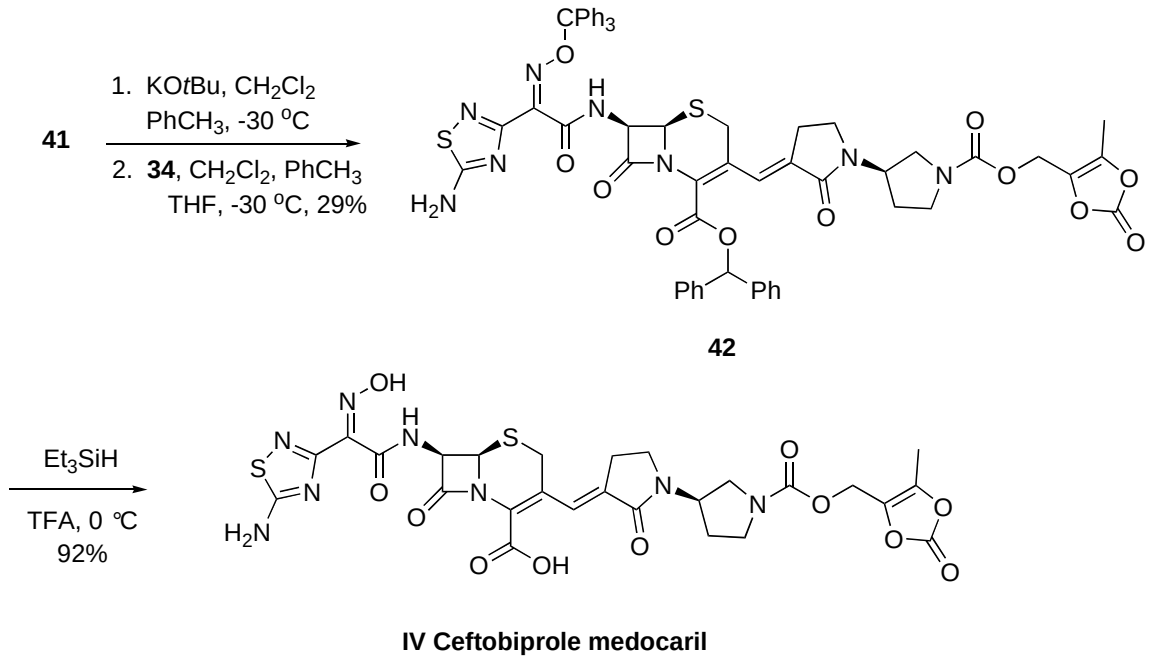
Choline fenofibrate is the choline salt of fenofibric acid and is used for the treatment of hypercholesterolemia and hyperglyceridemia by activating peroxisome proliferator-activated receptor (PPARalpha). Additionally, choline fenofibrate is the active metabolite of fenofibrate and it displays improved bioavailability compared to fenofibrate. Choline fenofibrate was developed by Abbott Laboratories as the next generation drug for the treatment of dyslipidemia, both as a single agent and in combination with statins [8, 27]. Many syntheses of fenofibrate have been described in the literature which involve hydrolysis and conversion to the appropriate salts [28-29]. The most recent telescope approach to make the choline salt in a single step is highlighted in Scheme **5** [30]. (4-Chlorophenyl)(4-hydroxyphenyl)-methanone (**43**), isopropyl 2-bromo-2-methylpropanoate (**44**), and potassium carbonate were heated to 155 °C for 4 h to give intermediate **45**. The temperature was lowered to 145 °C and excess bromide **44** was removed by distillation. The reaction mixture was cooled to 120 °C and *n*-propanol was added. Upon further cooling to 80-90 °C, the resulting solids were removed by filtration and washed with hot propanol. The filtrate was then treated with 45% aqueous choline hydroxide (**46**) and heated to reflux. Upon removal of the solvent by distillation, the reaction mixture was cooled to 10 °C and the resulting crystalline choline fenofibrate (**V**) was collected in 70% overall yield.

Clevidipine Butyrate (*Cleviprex*™)

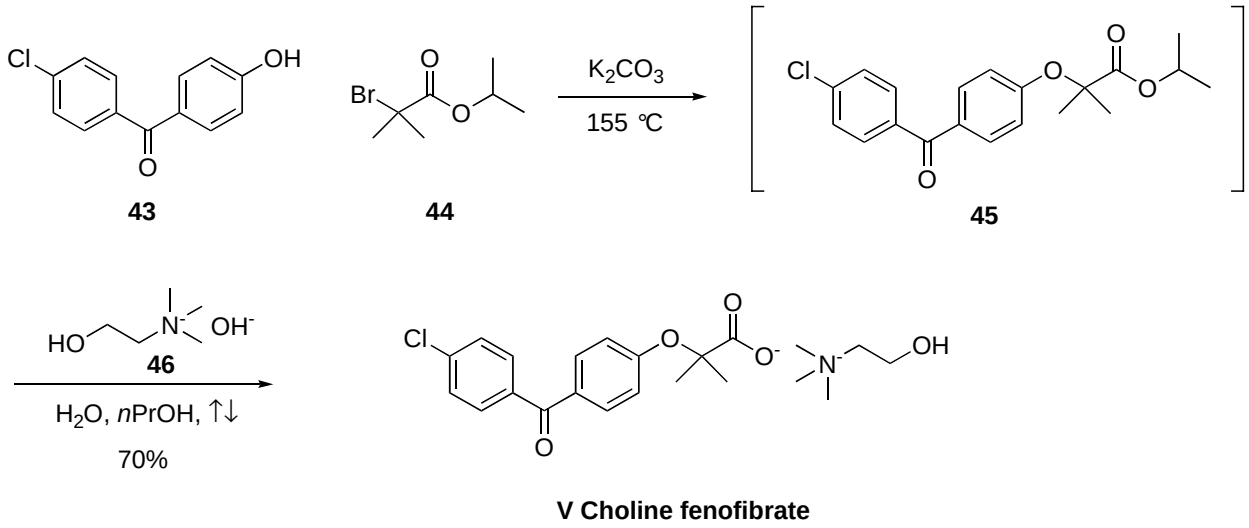
Clevidipine butyrate is a novel intravenous, short-acting calcium channel blocker that provides quick and accurate control of blood pressure in an emergency setting [31]. Unlike other intravenous hypertension drugs which are metabo



Scheme 4.2. Synthesis of intermediate phosphonate 41.



Scheme 4.3. Synthesis of Ceftobiprole medocaril (IV).

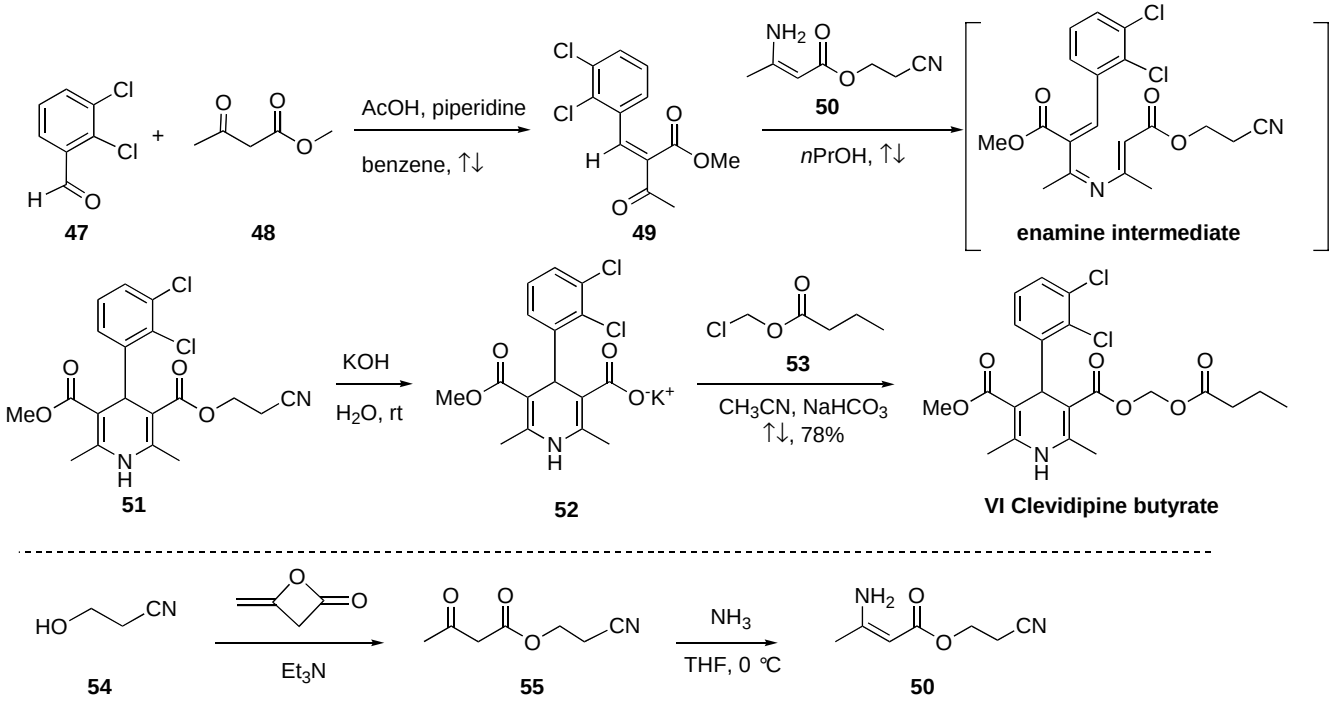


Scheme 5. Synthesis of Choline fenofibrate (V).

lized in kidney or liver and tend to accumulate in the body, clevidipine is metabolized in the blood and tissues and thus avoids accumulation. The drug was launched by Medicines Company which aquired the rights from AstraZeneca. The synthesis is described in Scheme 6 and was inititated with a Knoevenagel condensation between 2,3-dichlorobenzaldehyde (**47**) and methyl acetoacetate (**48**) in refluxing benzene and piperidine to give intermediate **49** [32]. Compound **49** was used without purification and reacted with 3-aminocrotonate (**50**) to give the 1,4-dihydropyridine **51**, presumably by generating the corresponding imine via the condensation of **49** with **50**, followed by a [3,3] sigmatropic rearrangement and tautomerization to give **51**. Compound **50** was prepared as follows: diketene was reacted with 2-cyanoethanol (**54**) in the presence of triethylamine to give ester **55** which was treated with ammonia gas in cold THF to give **50**. The synthesis was completed by selective hydrolysis of the cyanoethyl ester **51** by reaction with aqueous potassium hydroxide at room temperature to give **52**, followed by esterification with chloromethyl butyrate (**53**) to give clevidipine (**VI**) in 78% yield.

Dabigatran Etexilate (*Pradaxa*®)

Boeringer Ingelheim's novel oral thrombin inhibitor dabigatran was approved by EMEA in March 2008 for the preventive treatment of venous thromboembolic events



Scheme 6. Synthesis of Clevidipine butyrate (VI).

(VTE) in adult patients who had undergone total hip or knee replacement. Clinical trials have shown this oral treatment to be as efficacious as the injectable standard enoxaparin and with a good safety profile [8, 33]. Several syntheses of dabigatran etexilate have been published [34-36] and the process route is described as shown in Scheme 7 [37]. The synthesis starts with reaction of 4-cyanoaniline (**56**) with hydroxylamine hydrochloride salt in the presence of sodium carbonate at 60 °C which provided *N*-hydroxyamidine **57** in 90% yield. Ring closure to form oxadiazolone **58** was accomplished in 88% yield by reaction of **57** with diethylcarbonate and sodium methoxide in ethanol at 70-75 °C. Aniline **58** was then treated with methylbromoacetate in the presence of sodium carbonate at room temperature to provide the ester intermediate **59**, which was then saponified with sodium hydroxide at 60 °C to provide the key acid intermediate **60**. The coupling partner **64** was prepared in two steps from readily available acid chloride **61**. Thus acylation of aminopyridine **62** with acid chloride **61** in THF at room temperature gave the nitro amide **63** in 61% yield, which was then reduced via hydrogenation in the presence of catalytic Pd/C giving intermediate **64** in 83% yield. Condensation of diamine **64** with acid **60** was accomplished with either 50% PPA in THF at 90 °C or via pivaloyl chloride in refluxing NMP/THF providing benzamidazole **65** in 76-80% yield. Hydrogenolysis of the oxadiazolone followed by trapping the resulting amidine as its toslyate salt provided **66** in 91% yield. This amidine salt **66** was reacted with *n*-hexylchloroformate and potassium carbonate to provide the prodrug dabigatran etexilate (**VII**) in 82% yield.

Desvenlafaxine Succinate (*Pristiq*®)

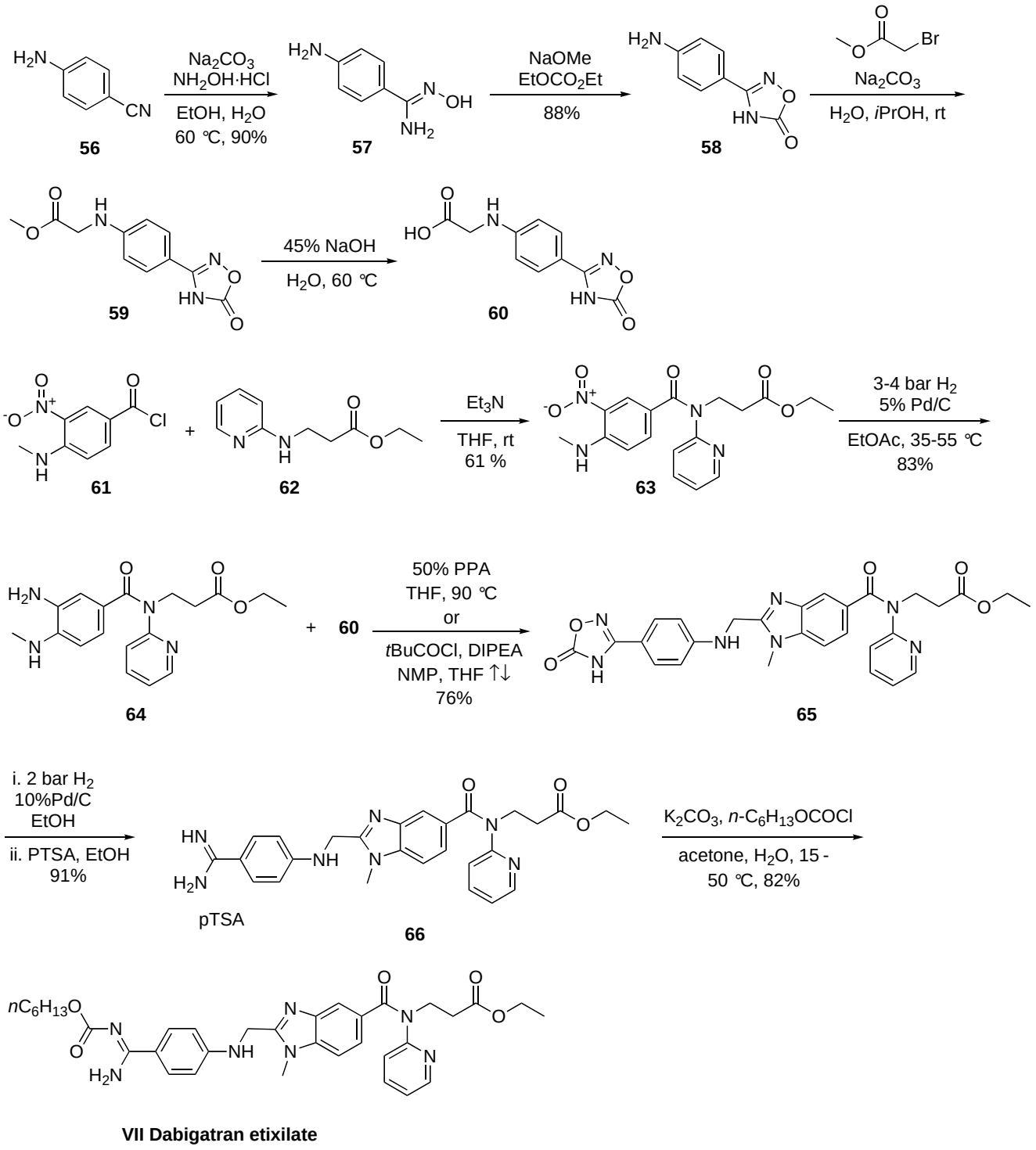
Desvenlafaxine Succinate is a dual serotonin and norepinephrine reuptake inhibitor (SNRI) that was approved for the treatment of major depressive disorder (MDD) in the United States in 2008 [38]. In order to improve the efficacy and safety profile of venlafaxine, Wyeth discovered and developed one of the major metabolites of venlafaxine, namely the *O*-desmethyl metabolite (desvenlafaxine). Desvenlafaxine is also being developed for the treatment of moderate to severe vasomotor symptoms associated with menopause (i.e., hot flashes and night sweats) and is also in phase III clinical trials to study it's effectiveness in treating fibromyalgia and neuropathic pain [39]. Desvenlafaxine has been prepared via two different routes, and both are described in Scheme **8**. The first route involved simple demethylation of venlafaxine [40] (**67**) using L-selectride in dimethoxyethane giving desvenlafaxine **68** as its free base in 91% yield [41]. Compound **68** was then recrystallized with succinic acid in acetone/water to give desvenlafaxine succinate (**VIII**) in 86% yield. An alternative method to prepare desvenlafaxine is described in the bottom portion of Scheme **8**. 4-Benzyloxyphenylacetic acid **69** was converted to its corresponding acid chloride upon treatment with thionyl chloride and catalytic DMF in refluxing methylene chloride [42]. The crude reaction mixture was added to a solution of dimethylamine hydrochloride and triethyl amine in methylene chloride at 5 °C to give dimethylacetamide **70** in 90% yield. Deprotonation of **70** with LHMDS in THF at -70 °C followed by addition of cyclohexanone gave alcohol **71** in 82% yield. Reduction of the acetamide with borane THF complex in refluxing THF produced dimethyl amine **72** in 66% yield. Catalytic hydrogenation in the presence of 20% Pd/C effected debenzylation of **72** to give desvenlafaxine free base **68** in 87% yield.

Etravirine (*Intelence*®)

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) developed by Tibotec, a subsidiary of Johnson and Johnson, for the treatment of HIV-1 infection. Etravirine was approved and launched in January and August 2008 in the US and Europe, respectively. It is indicated for treatment-resistant HIV-1 patients [8, 43-44]. Only the discovery synthesis [45-47] and small scale syntheses [46-50] have been disclosed for this compound (Scheme **9**). The largest scale synthesis was initiated by the portionwise addition of cyanamide to a solution of the *p*-cyanoaniline hydrochloride salt **73**. The mixture was refluxed in diglyme to give guanidine salt **74** in 85% yield after concentration of the reaction mixture and recrystallization from acetone [48]. Reaction of guanidine **74** with diethylmalonate in the presence of sodium ethoxide in refluxing ethanol gave pyrimidine diol **75** in 57% yield, which upon refluxing in phosphorous oxychloride for 30 min gave dichloride **76** in 97% yield. Bromination of dichloride **76** with NBS in chloroform at room temperature provided bromide **77** in 55% yield. Heating a mixture of the dichlorobromide **77** with the sodium salt of 2,5-dimethyl-4-cyanophenol **78**, generated by reaction with sodium hydride *in situ*) in diglyme and NMP at 155 °C gave the coupled product **79** in 45% yield. Finally, reaction of the chloride **79** with ammonia in refluxing dioxane (or *i*PrOH) in a sealed tube gave etravirine (**IX**) in 41% yield after purification.

Fesoterodine (*Toviaz*®)

Fesoterodine, a selective muscarinic M_3 receptor antagonist, was approved in 2008 for the treatment of overactive bladder and urinary urge incontinence [51]. Fesoterodine was discovered and developed by Schwarz Pharma and purchased by Pfizer in 2006. Fesoterodine has been prepared by two different routes and the process scale synthesis developed by Pfizer is depicted in Scheme 10 [52, 53]. *trans*-Cinnamaldehyde **80** was added to a refluxing solution of 4-(hydroxymethyl)phenol **81** and *N*-methylpiperazine in toluene to give benzopyranol **82** in 53% yield. The product of this reaction is formed via 1,4-addition of the phenol into the imine generated from the condensation of *trans*-cinnamaldehyde with *N*-methylpiperazine and is followed by cyclization to generate a cyclic aminal intermediate which is hydrolyzed to lactol **82** upon acidic work up. The crude mixture of lactol **82** was condensed with diisopropyl amine in methanol and the resulting imine was subjected to catalyic hydrogenation using Pd/C as the catalyst to give amino phenol **83** in 93% crude yield. Classical resolution of **83** via crystallization with (*R*)-(-)-acetoxy(phenyl)acetic acid in *t*-amyl alcohol gave enantiopure (*R*)-aminophenol-(*R*)-acetoxy(phenyl)-acetate salt **84** in 38% yield with 99% ee. The free base was liberated in 67% yield with >99.6% ee upon treatment with aqueous potassium carbonate in toluene. The completion of the synthesis followed the route developed by Schwarz Pharma in that the phenol of the free base of **84** was reacted with isobutyric acid chloride to provide fesoterodine **85**

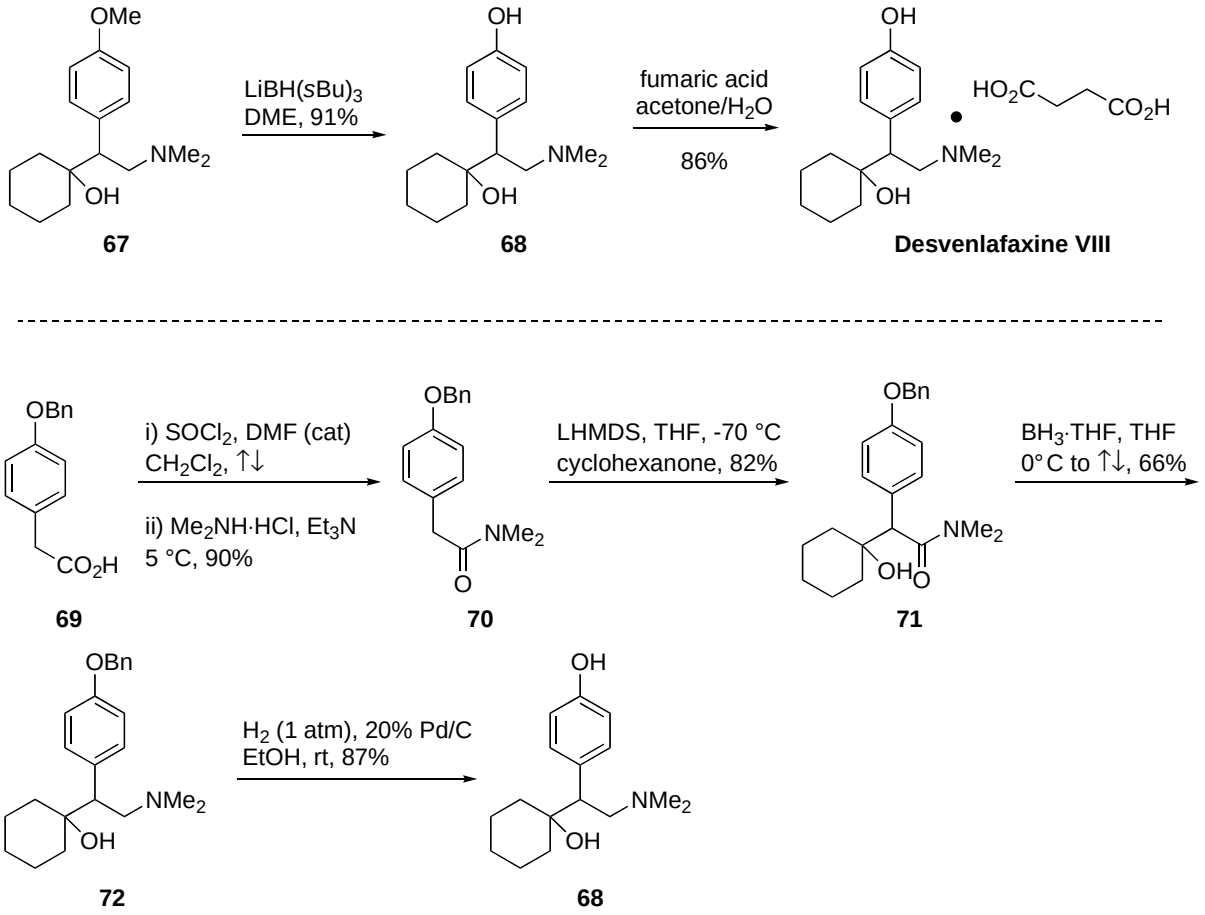


Scheme 7. Synthesis of Dabigatran etexilate (VII).

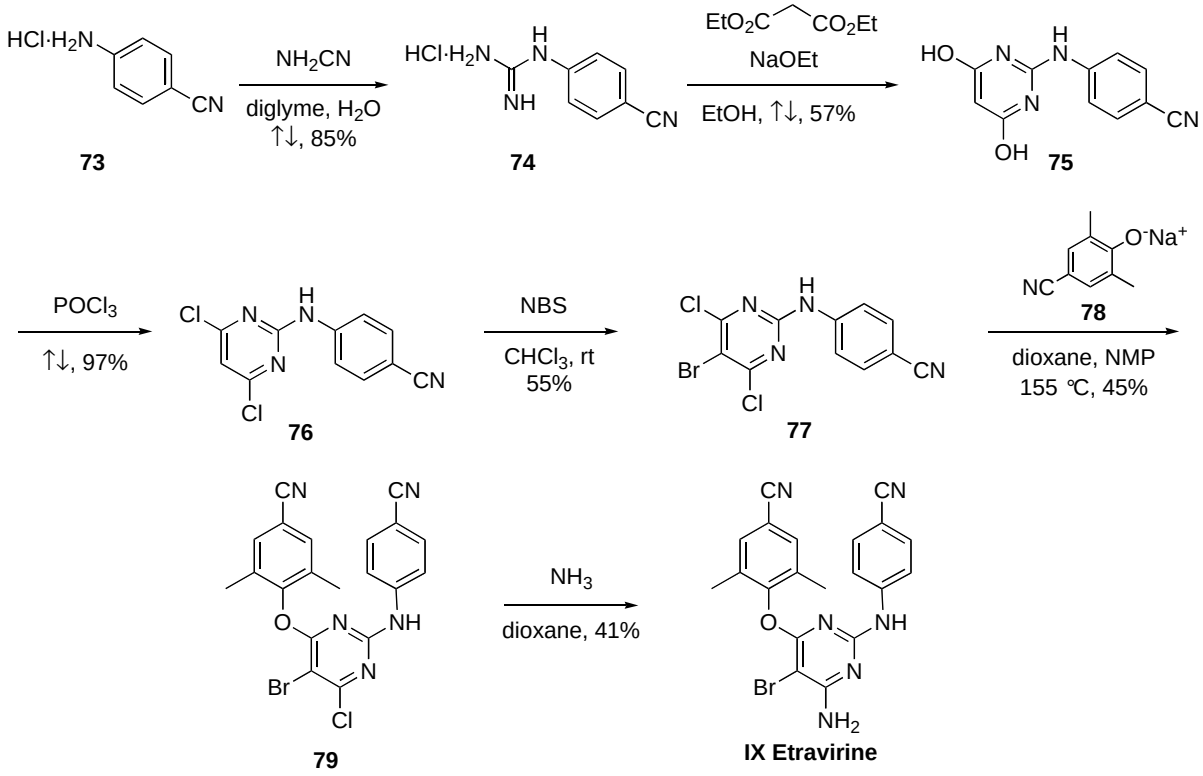
in 77% yield. Fesoterodine fumarate (**X**) was prepared upon crystallization of **85** with fumaric acid in 2-butanone/cyclohexane in 83% yield.

Lacosamide (*Vimprat*®)

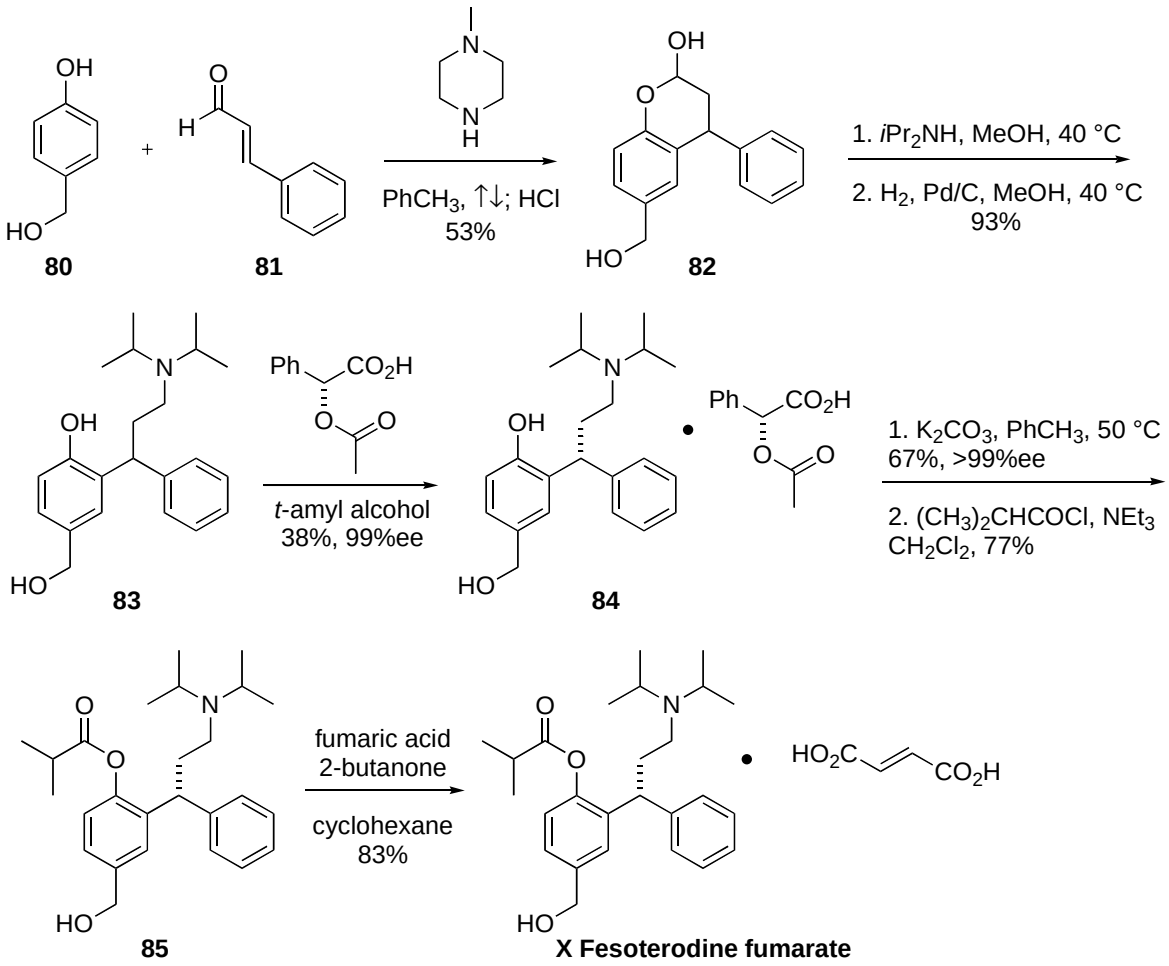
Lacosamide is a glycine-site NMDA receptor antagonist that was approved in Europe in 2008 for the treatment of partial-onset seizures in patients with epilepsy [54]. Lacosamide was discovered at the University of Houston and licensed to Research Corporation Technologies and later to Harris FRC for its early development. In 1999 Schwarz Pharma aquired the rights to lacosamide and completed its development. Five different synthetic routes to lacosamide have been reported [55]. The route described in Scheme 11 was reported on the largest scale and appears to be the most efficient with respect to overall yield, most amenable to scale up and avoids potential racemization of the chiral center



Scheme 8. Synthesis of Desvenlafaxine succinate (VIII).



Scheme 9. Synthesis of Etravirine (IX).



Scheme 10. Synthesis of Fesoterodine fumarate (X).

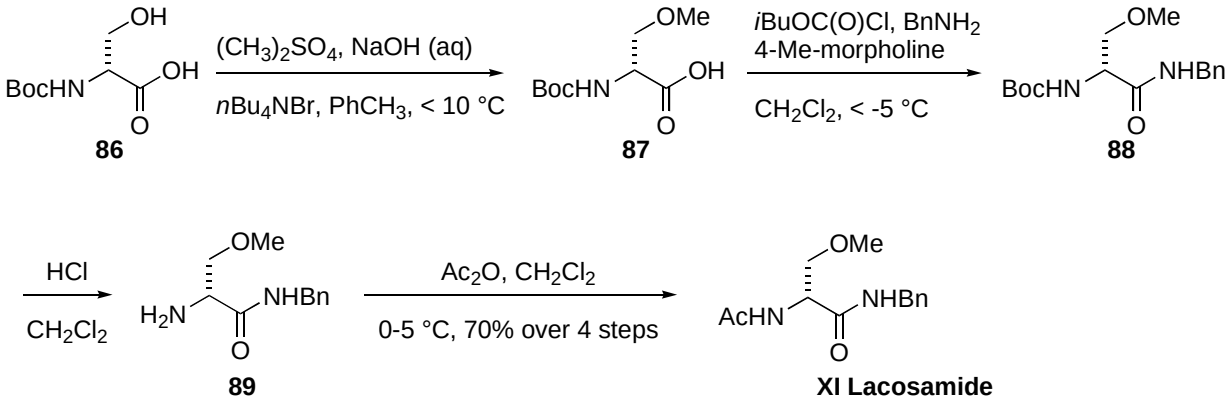
[56]. The synthesis was initiated with the methylation of *N*-Boc-D-Serine **86** with dimethylsulfate under phase transfer conditions (aqueous sodium hydroxide, toluene, tetrabutylammonium bromide) to give methyl ether **87** in quantitative yield. Activation of the carboxylic acid of **87** with isobutylchloroformate followed by reaction with benzylamine gave amide **88** which was carried to the next step without isolation. Liberation of the amine **89** was accomplished by reaction with HCl, and the resulting amine was treated with acetic anhydride to give lacosamide **XI** in 70% yield and 99.8% ee.

Methylnaltrexone Bromide (*Relistor*®)

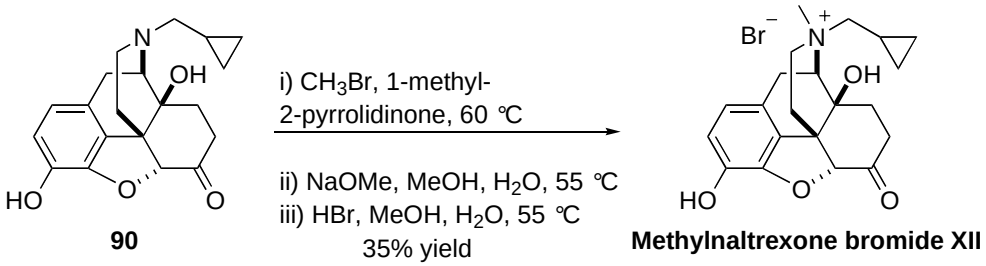
Methylnaltrexone bromide is an opioid antagonist developed for the treatment of opioid-induced bowel dysfunction (OBD) or opioid-induced constipation (OIC). Methylnaltrexone bromide is a quaternary ammonium salt derivative of naltrexone that does not cross the blood-brain barrier and thus acts as a selective antagonist at peripheral opioid receptors. As such, methylnaltrexone bromide is used to minimize GI side effects elicited by opioid analgesics [57]. Methylnaltrexone bromide was discovered at the University of Chicago which licensed it to UR labs which in turn licensed it to Progenics. In 2005, Progenics partnered with Wyeth for the joint development of methylnaltrexone bromide which was approved in many nations in 2008 for the treatment of OBD/OIC. Methylnaltrexone bromide is also in development for the treatment of post-operative ileus. The synthesis of methylnaltrexone bromide proceeds in a straightforward manner via the alkylation of naltrexone **90** (Scheme 12) [58]. Naltrexone **90** was reacted with methyl bromide in 1-methyl-2-pyrrolidinone at 60 °C. The resulting crude product was treated with sodium methoxide in methanol/water at 55 °C to remove any undesired phenolic (*O*-alkylated) side-products. The resulting crude sodium salt was treated with hydrobromic acid in methanol/water and upon crystallization gave methylnaltrexone bromide (**XII**) in 35% overall yield.

Pirfenidone (*Pirespa*®)

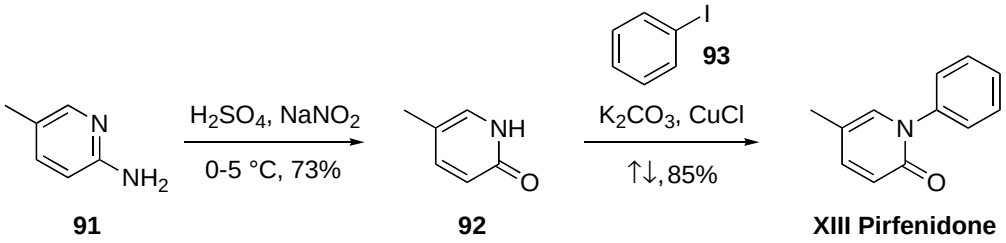
Pirfenidone is an orally active TNF-alpha production inhibitor discovered by Marnac. The drug is approved for the treatment of idiopathic pulmonary fibrosis (IPF). The National Cancer Institute (NCI) is evaluating the compound in phase III clinical trials for the treatment of neurofibromatosis type I and progressive plexiform neurofibromas. Pirfenidone may inhibit collagen synthesis, down-regulate production of multiple cytokines, and block fibroblast proliferation and



Scheme 11. Synthesis of Lacosamide (XI).



Scheme 12. Synthesis of Methylnaltrexone bromide (XII).



Scheme 13. Synthesis of Pirfenidone (XIII).

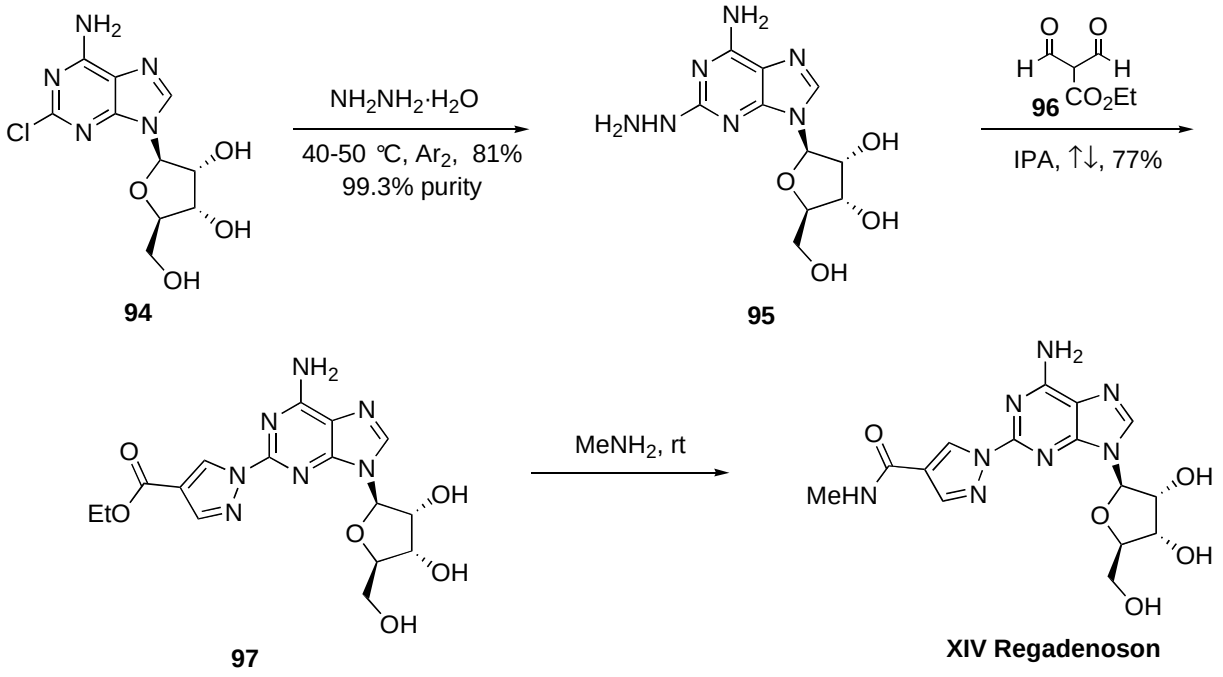
stimulation in response to cytokines [59]. Pirfenidone was prepared via a two step sequence as detailed in Scheme 13 [60]. 2-Amino-5-methylpyridine (**91**) was converted to pyridone **92** by reaction with sulfuric acid and sodium nitrate at low temperature in 73% yield. Condensation of 5-methyl-2-(1H)-pyridone (**92**) with iodobenzene (**93**) in the presence of K_2CO_3 and CuCl at reflux gave pirfenidone (**XIII**) in 85% yield.

Regadenoson (*Lexiscan*™)

Lexiscan™ (regadenoson) is an injectable adenosine A_{2A} receptor agonist for use as a pharmacologic stress agent in myocardial perfusion imaging (MPI) studies in patients unable to undergo adequate exercise induced stress. Regadenoson is the first adenosine A_{2A} receptor agonist shown to be safe and effective as a pharmacologic stress agent in MPI studies. It is delivered as a rapid bolus (approximately 10 seconds) with no dose adjustment required for body weight. The product was developed under a license and collaboration agreement between CV Therapeutics and Astellas, and was launched by Astellas in June of 2008. The synthesis of regadenoson has been reported in several papers and patents [61-65] and a scalable procedure is detailed in Scheme 14 [63]. The synthesis was initiated with the reaction of 2-chloroadenosine hemihydrate (**94**) and hydrazine monohydrate at 40-50 °C to provide **95** in 81% yield with 99.3% purity. Hydrazine **95** was condensed with ethyl-2-formyl-3-oxopropionate (**96**) under refluxing IPA to furnish the pyrazole **97** in 77% yield which was collected by filtration and used in next step without further purification. Pyrazole **97** was then reacted with methyl amine at room temperature to provide regadenoson (**XV**). Although the yield was not reported, the product was collected by simple filtration.

Rivaroxaban (*Xarelto*®)

Rivaroxaban is a coagulation factor Xa inhibitor for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Rivaroxaban has been shown to inhibit free factor Xa and prothrombinase activity to prevent thrombin generation in the coagulation pathway. Unlike most anticoagulants, which are available only in injectable form and are therefore not suitable for long-term treatment, rivaroxaban is an orally active drug. Warfarin, the only other commercialized oral



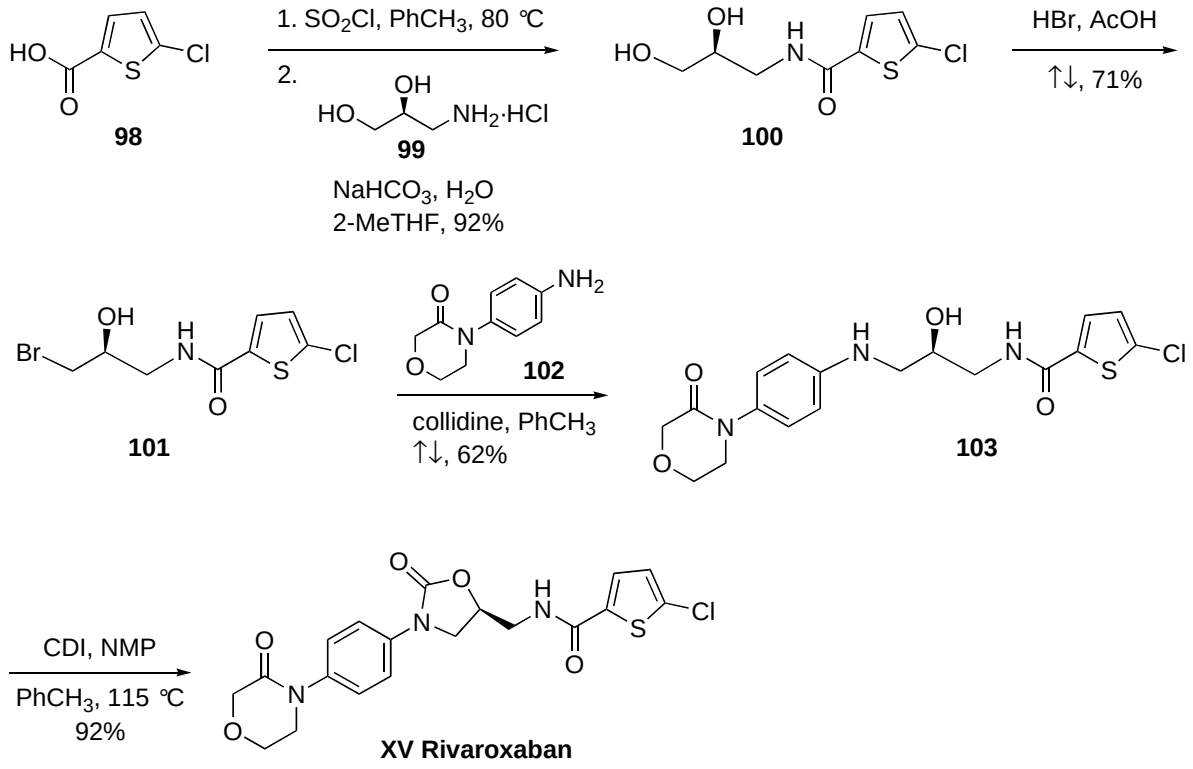
Scheme 14. Synthesis of Regadenoson (XIV).

anticoagulant, needs close monitoring and interacts with food and numerous other drugs. On the other hand, rivaroxaban offers predictable anticoagulation across a wide range of parameters, suggesting that routine coagulation monitoring will not be required. Data also indicates that rivaroxaban does not interact with a wide variety of drugs that are commonly given concomitantly with anticoagulants [66]. The synthesis of rivaroxaban is described in Scheme **15**. 5-Chlorothiophene-2-carboxylic acid (**98**) was treated with $SOCl_2$ to generate the corresponding acid chloride, which was used directly to couple with (*S*)-3-amino-1,2-propanediol hydrochloride (**99**) in the presence of $NaHCO_3$ in 2-methyltetrahydrofuran to give dihydroxy amide **100** in 92% yield [67]. Compound **100** was then selectively brominated with a solution of HBr in refluxing AcOH to produce bromohydrin **101** in 71%, which was then condensed with morpholinoaniline **102** in the presence of collidine in refluxing toluene to yield the corresponding *N*-alkylated product **103** in 62% yield. Amino alcohol **103** was reacted with 1,1'-carbonyldiimidazole (CDI) in hot NMP/toluene to form the oxazolidinone and give rivaroxaban (**XV**) in 92% yield.

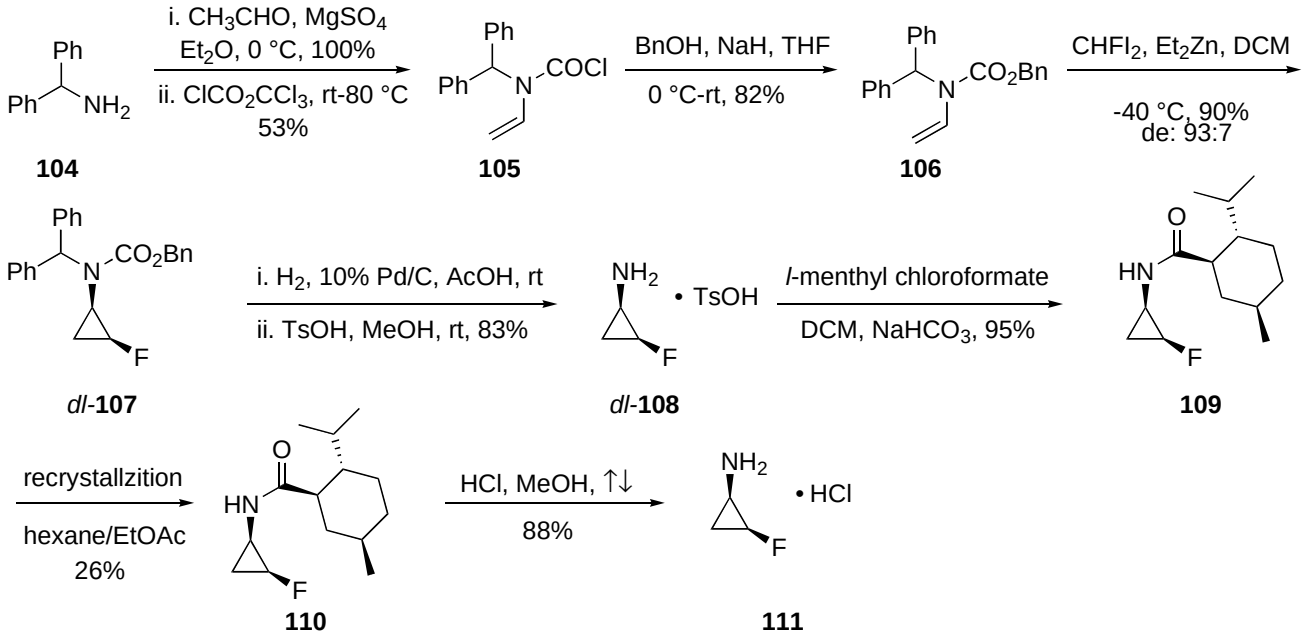
Sitafloxacin Hydrate (*Gracevit*®)

The fluoroquinolone antibacterial agent sitafloxacin hydrate was developed by Daiichi Sankyo and was approved and launched last year in Japan. Sitafloxacin's mode of action is through inhibition of DNA gyrase and topoisomerase IV. It is indicated for the treatment of inflammatory infections such as laryngopharyngitis, adenoiditis, acute bronchitis, pneumonia, secondary infections due to chronic respiratory lesions, cystitis, pyelonephritis, urethritis, cervicitis, otitismedia, sinusitis, periodontitis, and pericoronitis and jaw inflammation. Due to its broad spectrum of potent antibacterial activity, sitafloxacin is expected to be clinically effective in treating severe cases of bacterial infection, relapse/recrudescence of infection and infections in which resistant bacteria are suspected to be the cause. Several routes to the synthesis of sitafloxacin have been reported and the enantiopure route is described in Schemes **16.1-16.3** [68-71]. The optically pure fluorocyclopropylamine **111** intermediate was prepared as described in Scheme **16.1**. Condensation of diphenylmethyl amine **104** with acetaldehyde followed by treatment with trichloromethyl chloroformate in the presence of triethylamine gave *N*-vinyl carbamoyl chloride **105** in 53% yield. This intermediate was reacted with sodium benzyloxide (generated *in situ*) to afford *N*-vinylcarbamate **106** in 82% yield. Fluorocyclopropanation of **106** with zinc–monofluorocarbenoid generated from fluorodiiodomethane and diethylzinc provided *N*-(2-fluorocyclopropyl)carbamate **107** in 90% yield and with a diastereomeric ratio of 93:7 favoring the *cis*-isomer. Hydrogenolysis of the CBz and the diphenylmethyl groups was accomplished with catalytic 10% palladium on charcoal and was followed by treatment with TsOH to afford *dl*-**108** as its tosylate salt. Acylation of *dl*-**108** TsOH with *l*-menthyl chloroformate gave a 1:1 mixture of the diastereomeric carbamate **109** which upon four repeated recrystallizations from hexane/ethyl acetate afforded optically pure **110** in 26% yield. Acidic hydrolysis of **110** furnished **111** as its HCl salt in 88% yield.

The synthesis of enantiopure 7-[(*tert*-butoxycarbonyl)-amino]-5-azaspiro[2.4]heptanes **122** was achieved as described in Scheme **16.2**. 1-Acetyl-1-cyclopropanecarboxylic acid **112** was converted to (*R*)-(1-phenylethyl)amide **113** via the corresponding acid chloride. Protection of **113** as the ketal **114** proceeded in high yield and this was followed by reaction with bromine to give the stable bromide **115**. Cyclization of **115** was accomplished by reaction with sodium hydride to afford lactam **116**. Acidic hydrolysis of **116** gave 4,7-dioxo-5-azaspiro[2.4]heptane **117** in 45% yield. The keto group of **117** was converted to the corresponding hydroxyl



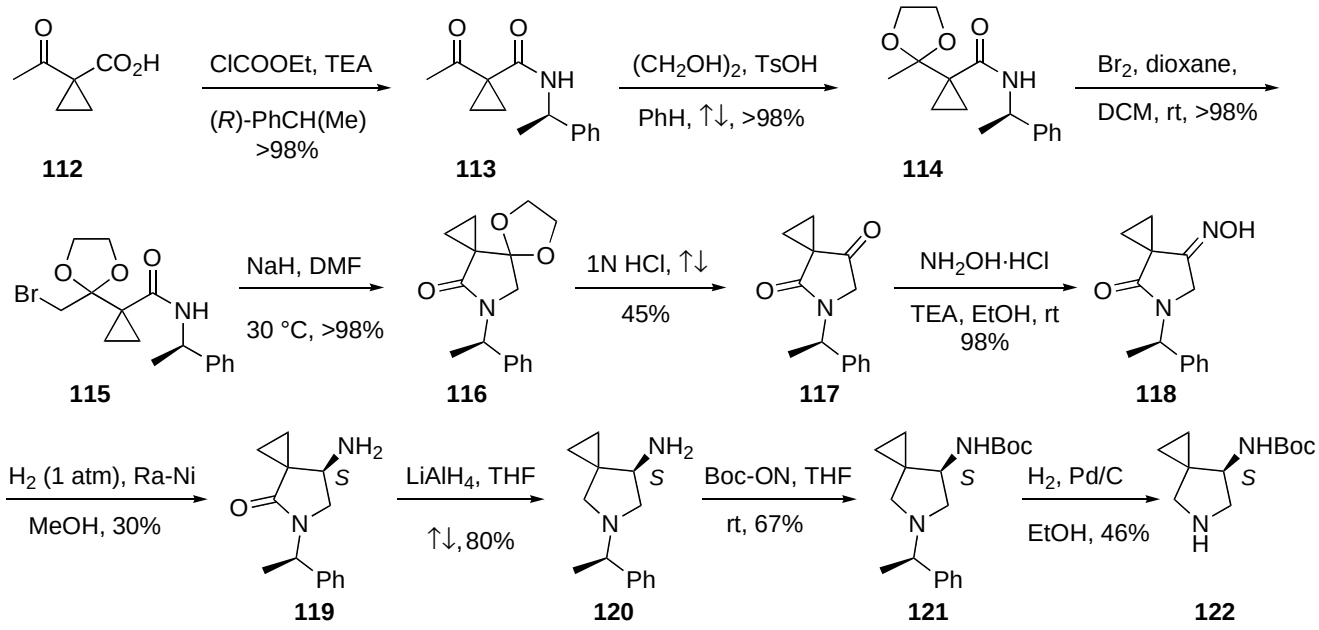
Scheme 15. Synthesis of Rivaroxaban (XV).



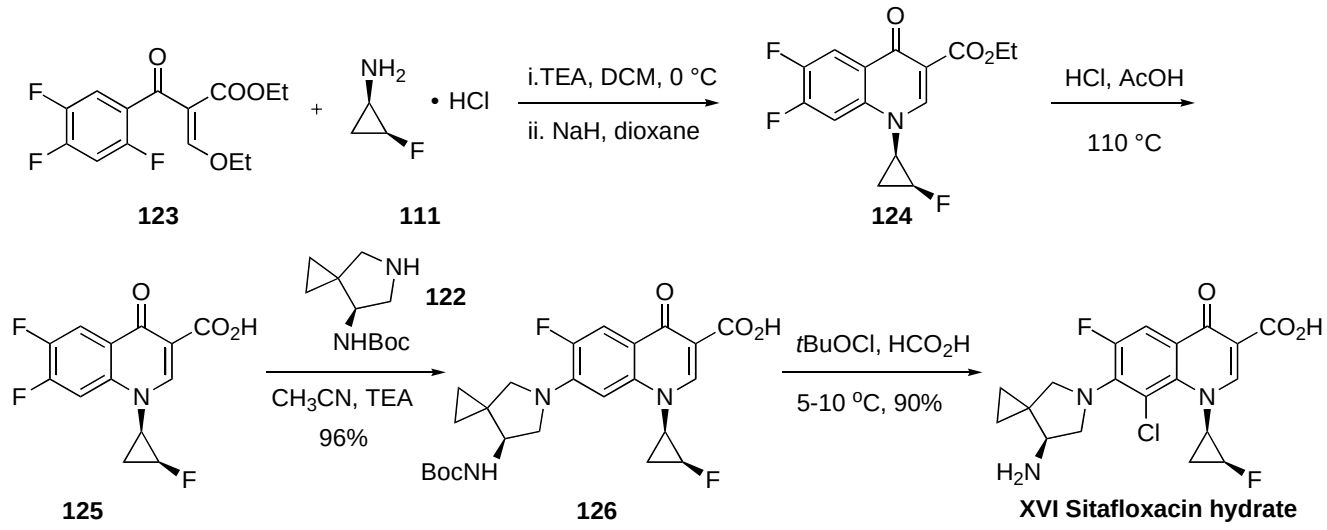
Scheme 16.1. Synthesis of Sitafloxacin hydrate intermediate 111.

amine **118**, followed by reduction to the primary amine via hydrogenolysis using catalytic Ra-Ni. The resulting diastereomeric mixture of amines was separated by chromatography to provide **119** in 30% isolated yield. Reduction of lactam **119** with lithium aluminum hydride produced aminopyrollidine **120** in 80% yield. Reaction of amine **120** with Boc-ON provided protected amine **121** in 67% yield. Hydrogenolysis with catalytic Pd/C affected debenzylation to give chiral amine **122** in 46% yield.

The synthesis of sitafloxacin hydrate was completed as described in Scheme 16.3. Condensation of intermediate **123** with cyclopropyl amine **111** provided quinolone **124**. Acidic hydrolysis of the ester of quinolone **124** provided quinolone



Scheme 16.2. Synthesis of Sitafloxacin hydrate intermediate 122.

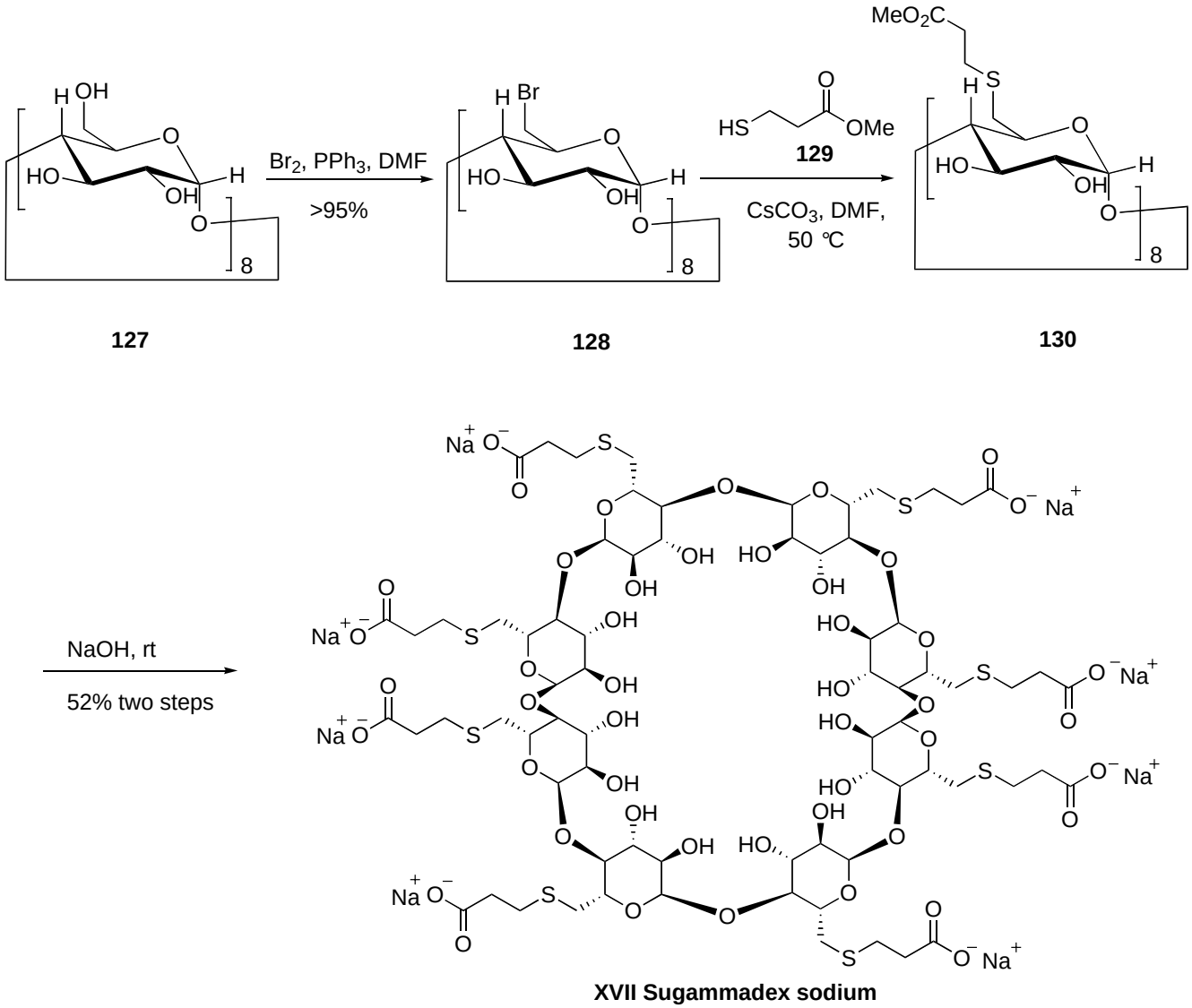


Scheme 16.3. Synthesis of Sitafloxacin hydrate (XVI).

125 which was reacted with amine **122** to give **126** in 96% yield. The C-8 chlorine was introduced onto **126** by using *tert*-butyl hypochlorite in formic acid, conditions which also affected removal of the amine protecting group, to afford sitafloxacin (**XVI**) in 90% yield.

Sugammadex (*Bridion*®)

Schering-Plough's sugammadex sodium, the first selective relaxant binding agent (SRBA), was approved last year in the European Union. Sugammadex is a drug-specific cyclodextrin designed specifically to reverse the effects of the muscle relaxant rocuronium bromide (*Esmeron*®/*Zemuron*®) when used as a component of general anesthesia during surgical procedures. Unlike other reversal agents, sugammadex can achieve reversal following rocuronium bromide administration within three minutes, regardless of the depth of block. Schering-Plough, which acquired the product via its acquisition of Organon BioSciences in late 2007, began marketing sugammadex in Sweden in September, 2008. There are several reports on the syntheses of sugammadex, all following a similar three-step procedure [72-74]. Bromination of γ-cyclodexdrin **127** with the Vilsmeier-Haack reagent prepared by reaction of bromine with triphenylphospine in DMF gave the per-6-bromo-γ-cyclodextrin **128** in 95-98% yield [73]. Nucleophilic displacement of the bromines of **128** with methyl 3-mercaptopropionate (**129**) and cesium carbon-



127 **128** **130**

Scheme 17. Synthesis of Sugammadex (XVII).

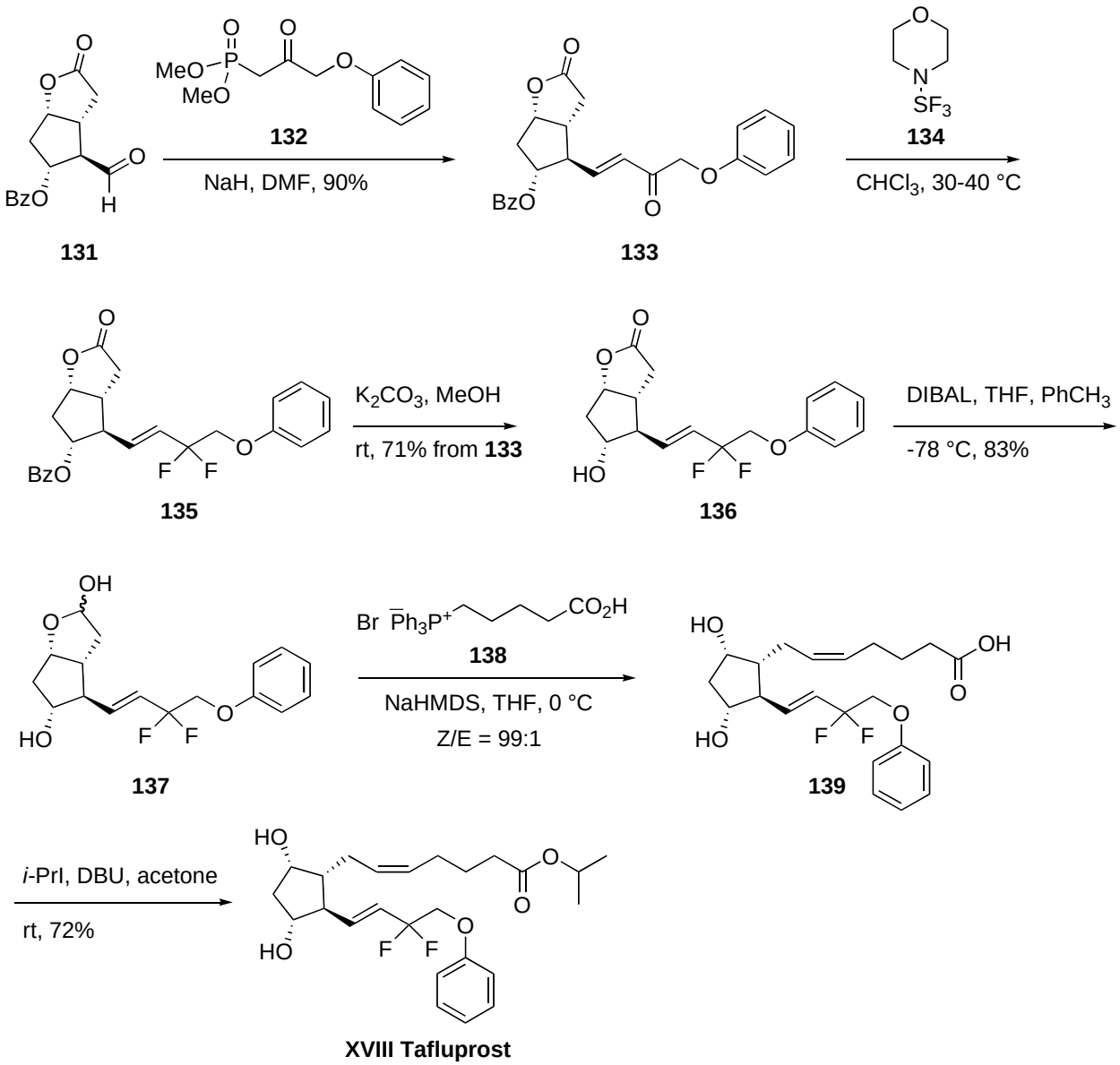
ate at 50 °C in DMF gave 6-perdeoxy-6-per(2-methoxycarbonylethyl) thio-γ-cyclodextrin **130** as a white powder. Saponification of the esters of **130** was accomplished by reaction with aqueous sodium hydroxide solution to provide sugammadex (**XVII**) as a glassy solid in 52% yield for the 2 steps [72,74].

Tafluprost (*Santen, Taflotan*™)

Tafluprost is a prostaglandin analog first approved and commercialized in Germany in 2008 for the treatment of glaucoma and ocular hypertension [75]. Tafluprost was jointly discovered by Santen and Asahi. Tafluprost is a preservative-free drug, therefore, it is expected to benefit preservative intolerant patients with dry or sensitive eyes. The synthesis was initiated from the Corey aldehyde **131** [76]. Horner-Emmons condensation of the bicyclic carbaldehyde **131** with the dimethyl phosphonate **132** using NaH in DMF gave enone **133** in 90% yield. Fluorination of the enone **133** was accomplished upon reaction with morpholino-sulfur trifluoride (**134**) in chloroform to yield the corresponding difluorinated compound **135**. Hydrolysis of the benzoate ester group of **135** with K_2CO_3 in methanol at room temperature afforded alcohol **136** in 71% yield from **133**. Reduction of the lactone group of **136** with diisobutyl aluminum hydride (DIBAL) in THF/toluene gave lactol **137** in 83% yield. Lactol **137** was condensed with the phosphonium ylide prepared by deprotonation of phosphonium salt **138** with sodium bis(trimethylsilyl)amide (NaHMDS) in THF/toluene to give the prostaglandin F2-alpha derivative **139** in excellent *Z/E* selectivity (99:1). The synthesis was completed by esterification of compound **139** with isopropyl iodide and DBU in acetone to provide tafluprost (**XVIII**) in 72% yield.

ACKNOWLEDGEMENT

The authors thank Dr. Christopher Butler, Dr. Andrew Flick and Dr. Martin Pettersson for their helpful suggestions in preparing this review.



Scheme 18. Synthesis of Tafluprost (XVIII).

ABBREVIATIONS

AIBN	=	2,2'-Azobisisobutyronitrile
CBZ	=	Benzyloxycarbonyl
CDI	=	*N,N'*-Carbonyldiimidazole
DBU	=	1,8-Diazabicycloundec-7-ene
DCE	=	Dichloroethane
DCC	=	*N, N'*-Dicyclohexylcarbodiimide
DCM	=	Dichloromethane
DIAD	=	Diisopropyl azodicarboxylate
DIBAL	=	Diisobutylaluminum hydride
DIPEA	=	Diisopropylethylamine
DMAP	=	4-Dimethylaminopyridine
DMF	=	*N,N*-Dimethylformamide
DMPU	=	*N,N'*-Dimethylpropyleneurea
DMSO	=	Methyl sulfoxide
DTTS	=	Di-*p*-toluoyl-D-tartaric acid
DPPC	=	Diphenylphosphinic chloride
EDC	=	*N*-(3-Dimethylaminopropal)-*N'*-ethylcarbodiimide
HOBT	=	1-Hydroxybenzotriazole hydrate
IPA	=	Isopropyl alcohol
IPAC	=	Isopropyl acetate
LDA	=	Lithium diisopropylamide

LHMDS	=	Lithium bis(trimethylsilyl)amide
MS	=	Molecular sieves
2-Methyl-THF	=	2-Methyl tetrahydrofuran
NaHMDS	=	Sodium bis(trimethylsilyl)amide
NBS	=	*N*-Bromosuccinimide
NCS	=	*N*-Chlorosuccinimide
NEP	=	*N*-Ethylpyrrolidinone
NMM	=	*N*-methylmorpholine
NMP	=	1-Methyl-2-pyrrolidinone
PCC	=	Pyridinium chlorochromate
PDC	=	Pyridinium dichromate
PMB	=	4-Methoxylbenzyl
PPA	=	Polyphosphoric acid
pTSA	=	*para*-Toluene sulfonic acid
TBAF	=	*t*-Butylammonium fluoride
TBAB	=	*t*-Butylammonium bromide
TBDMS	=	*t*-Butyldimethylsilyl
TEA	=	Triethylamine
TEMPO	=	2,2,6,6-Tetramethylpiperidine-*N*-oxide
TFA	=	Trifluoroacetic acid
TFAA	=	Trifluoroacetic acid anhydride
THF	=	Tetrahydrofuran
THP	=	Tetrahydropyran
TIPS	=	Triisopropyl silyl
TPAP	=	Tetrapropylammonium perruthenate
TMG	=	1,1,3,3-Tetramethylguanidine
p-TSA	=	*para*-Toluene sulfonic acid

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