Synthetic Approaches to the 2003 New Drugs

Kevin K.-C. Liu*, Jin Li* and Subas Sakya*

Pfizer Global Research and Development, Pfizer Inc, Groton CT 06340, USA

Abstract: New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biological target. In addition, these new chemical entities (NCEs) not only provide insights into molecular recognition, but also serve as drug-like leads for designing new future drugs. To these ends, this review covers the syntheses of 23 NCEs marketed in 2003.

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 1998 Nobel prize in physiology and medicine [1].

Inaugurated last year, this annual review presents synthetic methods for molecular entities that were launched or approved in various countries for the first time during the past year. The motivation to write such a review is the same as stated in the previous article [2]. Briefly, drugs that are approved worldwide tend to have structural similarity across similar biological targets. We strongly believe that knowledge of new chemical entities and their syntheses will greatly enhance our abilities to design new drug molecules in short period of time. With this hope, we continue to profile these NCEs that were approved for the year 2003.

In 2003, 30 NCEs including biological drugs, and two diagnostic agents [3,4] reached the market. This review article will focus on the syntheses of 23 new drugs marketed last year (Figure 1), but excludes new indications for known drugs, new combinations and new formulations. Drugs synthesized *via* bio-processes (i.e., daptomycin and talaporfin sodium) and peptide synthesizers (i.e., abarelix and enfuvirtide) will be excluded as well. The syntheses of these new drugs were published sporadically in different journals and patents. The synthetic routes cited here represent the most scalable methods based on the author's judgment and appear in alphabetical order by generic names.

Alfuzosin Hydrochloride (*Uroxatral*™)

Alfuzosin (SL-77499) (**I**), a quinazoline derivative which is a uroselective alpha-1 adrenoreceptor antagonist, has been developed and launched worldwide by Sanofi-Synthelabo, for the treatment of benign prostate hyperplasia (BPH) [5]. In November 2003, alfuzosin (**I**) was launched as an extended release formulation in the US as Uroxatral utilizing Skyepharma's oral controlled release technology. Although syntheses of alfuzosin (**I**) have appeared in several reports [6-8], an optimized route used for the manufacture of the compound does not appear in the literature. The synthesis reported by the Sanofi group for alfuzosin will be described and is shown in Scheme 1. The commercially available 4-amino-2-chloro-6,7-dimethoxyquinazoline (**1**) was treated with 3-methylaminopropionitrile (**2**) in isoamyl alcohol and refluxed for 5 hrs. Filtration of the precipitated product and washing with ethanol gave nitrile **3** in 62% yield. Hydrogenation of the nitrile was done in 15% ammonia solution in ethanol with Raney nickel as catalyst at 70ºC and 1000 psi to obtain the corresponding amine free base. Conversion of the free base to the hydrochloride salt was done in ethanol to give the HCl salt **4** in 52% yield. The final acylation of amine **4** was done with the imidazolyl anhydride of furan **5**. Thus, 2-carboxyfuran was treated with carbonyldiimidazole in THF at 40°C for 1 hr and then cooled to 10°C. Addition of amine **4** in THF in the presence of triethylamine at 10°C, then refluxing the reaction for 1 hr, and aqueous workup gave the alfuzosin free base. After conversion to the hydrochloride salt and recrystallization from 2-propanol alfuzosin hydrochloride (**I**) was obtained in 44% yield.

Aprepitant (*Emend*™)

Aprepitant (MK-869, L-754030) (**II**), a functionalized morpholine acetal derivative with potent neurokinin receptor 1(NK-1) antagonist activity, has been developed and launched in April, 2003 in the US and February, 2004 in the UK for the treatment of chemotherapy-induced nausea and vomiting (CINV) [9] under the trade name Emend™. Several variations to the synthesis of aprepitant (**II**) have been published by the Merck group [10-16]. The latest optimized synthesis utilizing a novel crystallization-induced diastereoselective synthesis of aprepitant is highlighted in Scheme 2 [11]. The synthetic approach entailed (1) the synthesis and coupling of the key pieces, *N*-benzyl lactam lactol **13** and *sec*-phenethyl alcohol **7**, to provide lactam acetal **14**, (2) stereoselective elaboration to the key intermediate **14**, and (3) conversion to the final compound *via* either intramolecular cyclization or intermolecular coupling with triazolinone chloride **24**. The intermediate *sec*-phenethyl alcohol **7** was synthesized in 97% yield and 95% e.e. (improved to 99% e.e. after recrystallization) *via* the enantioselective borane reduction of ketone **6** in the presence of 2 mol % of (*S*)-oxazaborolidine catalyst **8**. The optimized conditions involved the slow addition of ketone **6** to a

*Address correspondence to these authors at the Pfizer, Groton, CT 06340, USA; KKL: Tel: 1-860-441-5498;
E-mail: kevin_k_liu@groton.pfizer.com; JL: Tel: 1-860-715-3552,
E-mail: jin_li@groton.pfizer.com; SMS: Tel: 1-860-715-0425,
E-mail: subas_m_sakya@groton.pfizer.com

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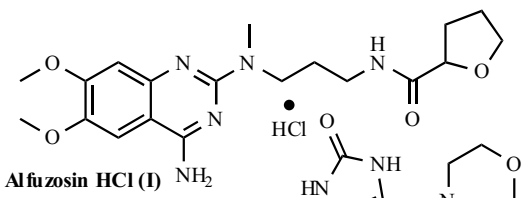
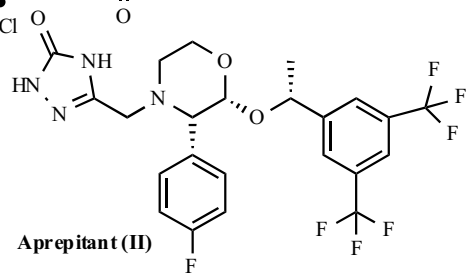
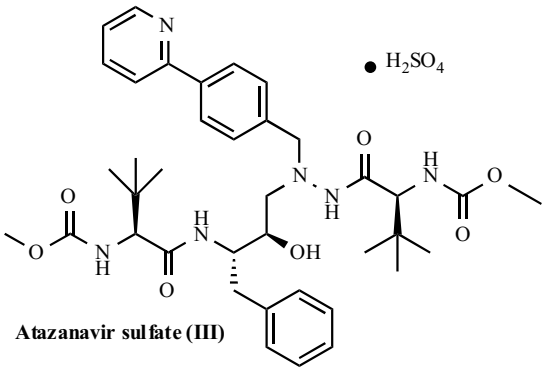


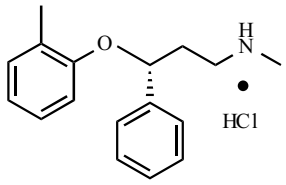
Alfuzosin HCl (I)



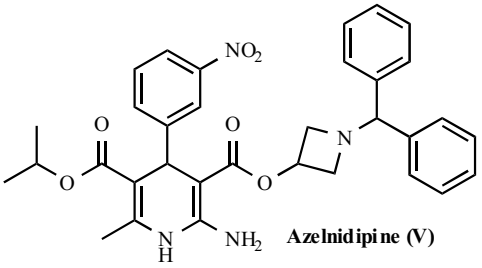
Aprepitant (II)



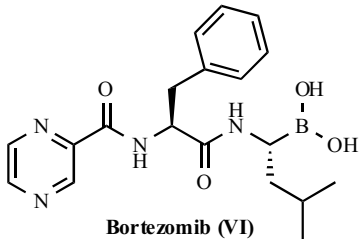
Atazanavir sulfate (III)



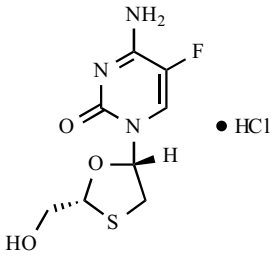
Atomoxetine hydrochloride (IV)



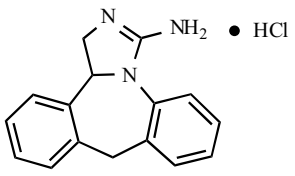
Azelnidipine (V)



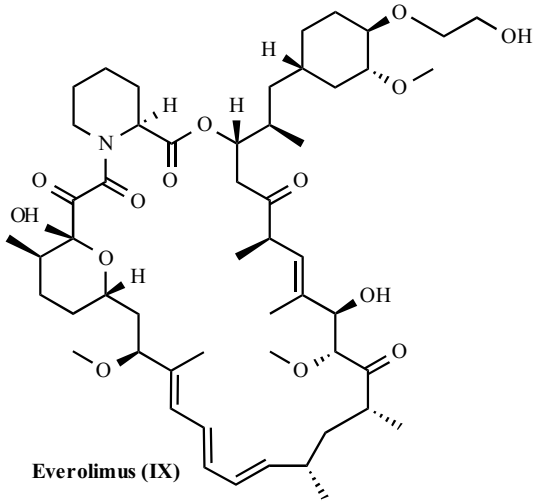
Bortezomib (VI)



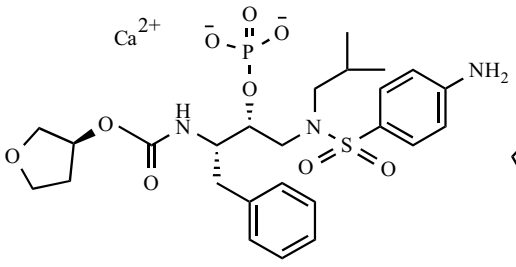
Emtricitabine HCl (VII)



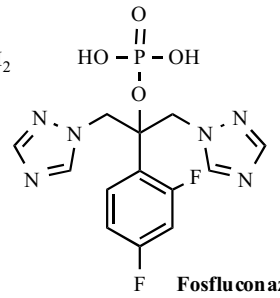
Epinastine HCl (VIII)



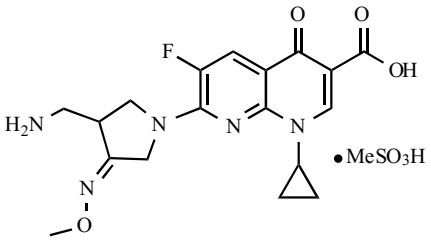
Everolimus (IX)



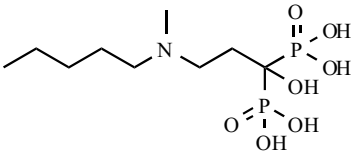
Fosamprenavir calcium (X)



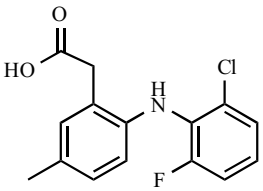
Fosfluconazole (XI)



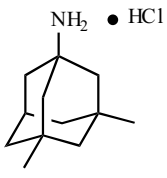
Gemifloxacin mesylate (XII)



Ibandronate Sodium (XIII)



Lumiracoxib (XIV)



Memantine HCl (XV)

Fig. (1). contd.....

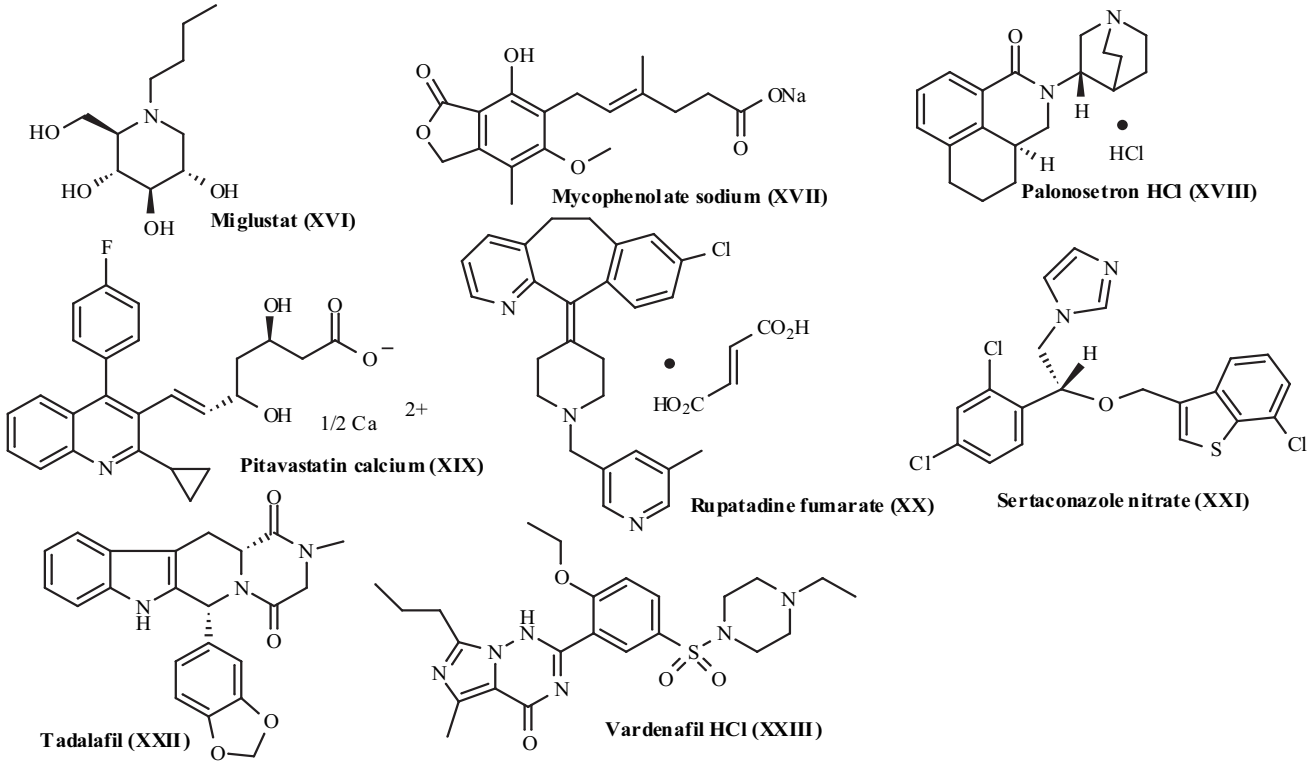
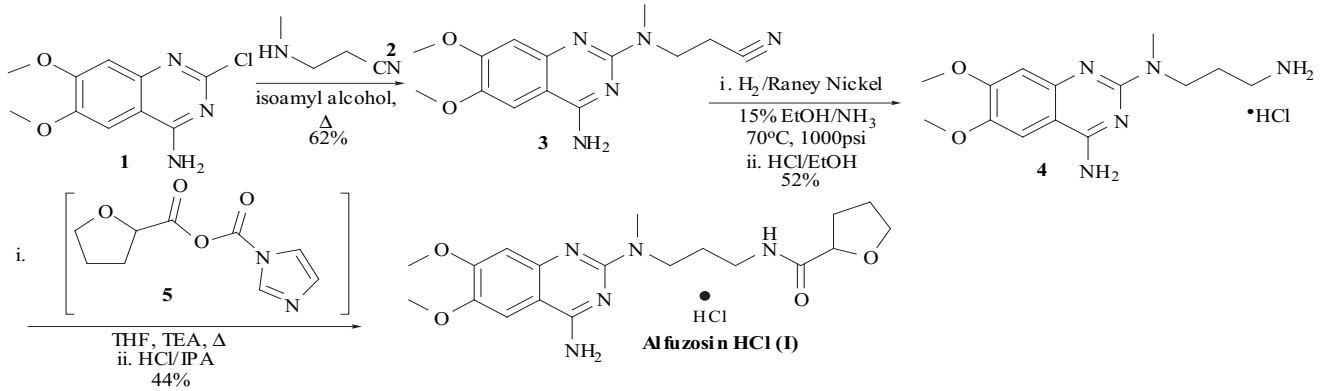
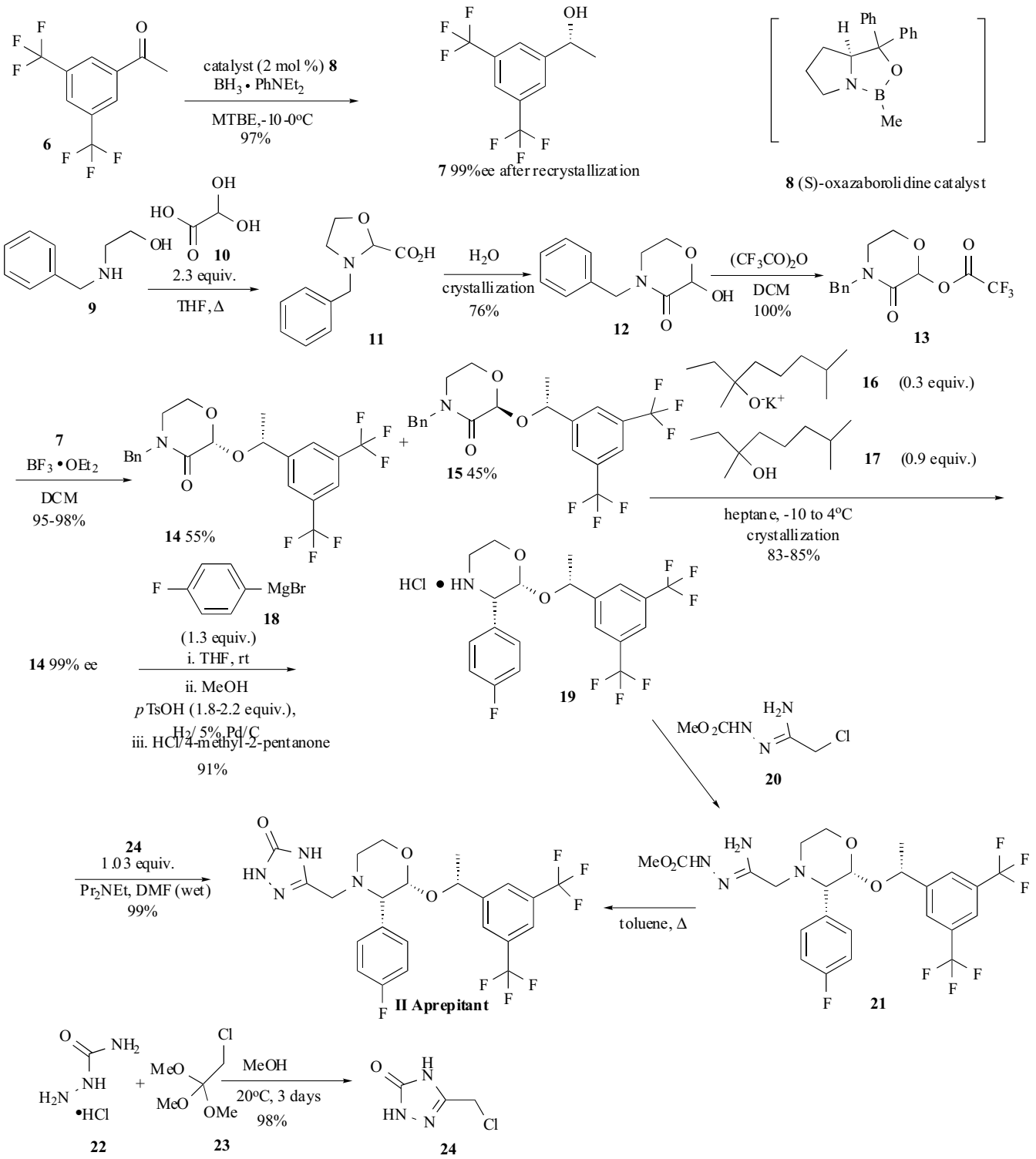


Fig. (1). Structures of 23 new drugs marketed in 2003.

solution containing catalyst **8** and BH_3•$PhNEt_2$ complex in MTBE at –10 to 0°C. The synthesis of lactam **12** was done by reacting *N*-benzylethanolamine (**9**) with slight excess of aqueous glyoxylic acid (**10**, 2.3 equivalent of 50% aqueous solution) in refluxing THF. Adjustment of the solvent composition from predominantly THF to predominantly water resulted in the crystallization of lactam **12** directly from **11** in the reaction mixture in 76% yield. Lactam **12** was treated with trifluoroacetic anhydride (1 equiv) to give trifluoroacetate **13**, which was reacted in *situ* with chiral alcohol **7** in the presence of BF_3•OEt_2 to give, after workup, a 55:45 mixture of the acetals **14** and **15** in 95-98% overall yield. To obtain the desired diastereomer from the 55:45 mixture of **14** and **15**, an optimized crystallization sequence was developed. To a solution of the crude mixture in heptane, 3,7-dimethyl-3-octanol (**17**) (0.9 equiv) was added, cooled to –10 to –5°C and, after seeding the mixture with pure **14**, potassium salt of 3,7-dimethyl-3-octanol (**16**) (0.3 equiv) was added to initiate the crystallization-induced epimerization of **15** to **14**. After 5 hr, the mixture was transformed into a 96:4 mixture from which **14** was isolated in 83-85% yield and >99% e.e. Under an optimized condition, the lactam **14** was reacted with 4-fluorophenylmagnesium bromide (**18**) (1.3 equiv) in THF at ambient temperature followed by methanol quench and addition of *p*-toluenesulfonic acid (1.8-2.2 equiv). Immediate hydrogenation of this mixture in the presence of 5% Pd/C gave the addition product **19**, which was isolated as hydrochloride salt in 91% yield. Under these conditions, no cleavage of the benzylic ether group was seen, even after extended hydrogenation periods. Elaboration to aprepitant (**II**) was done by the initial alkylation of **19** in the presence of a base with amidrazone chloride **20**, which was prepared from chloroacetonitrile, to give the intermediate **21**. Thermolysis of **21** in toluene provided aprepitant (**II**) in 85% overall yield. Alternatively, the hydrochloride salt **19** has also been alkylated directly with the triazolinone chloride **24** to give aprepitant (**II**) [17].



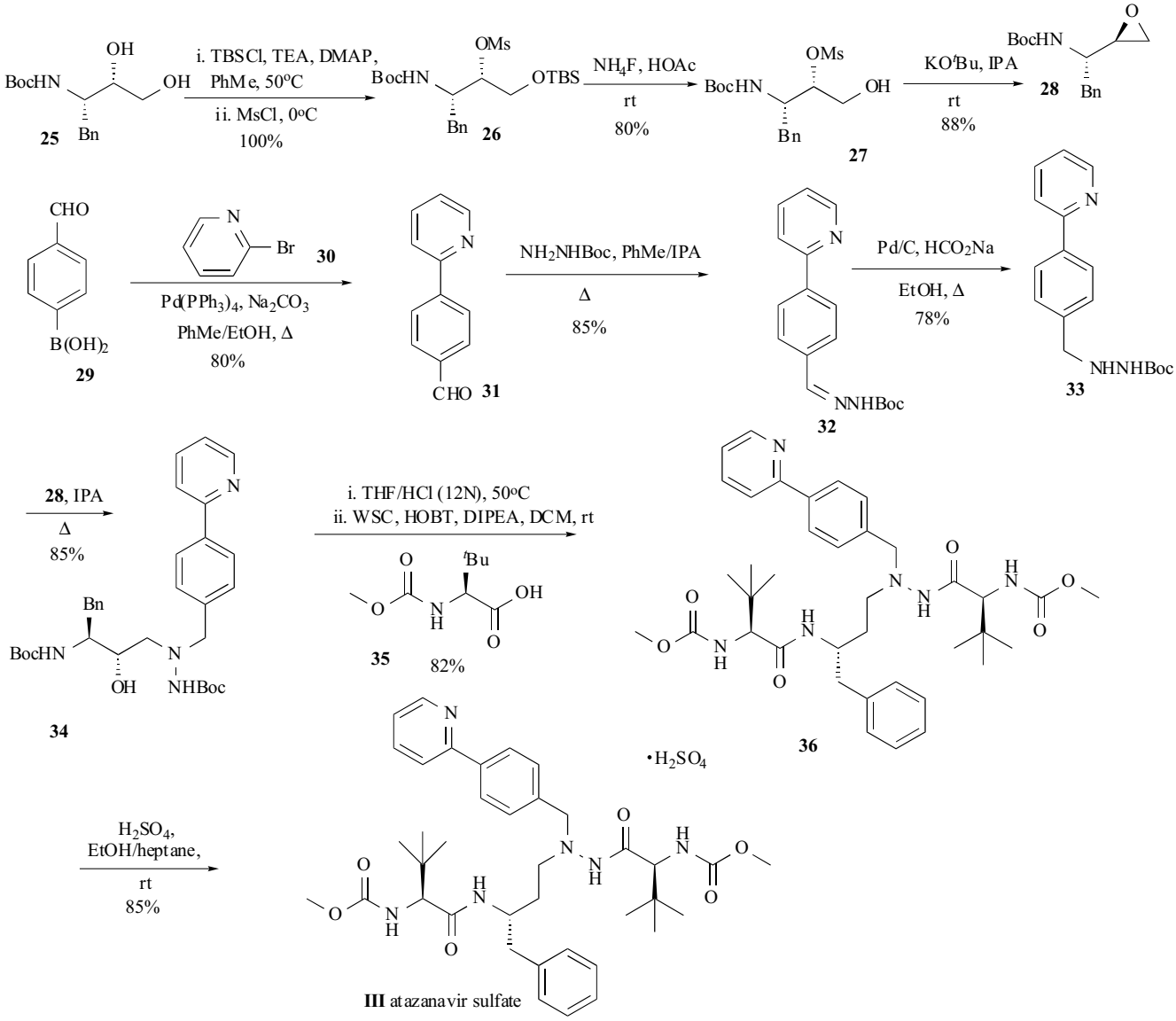
Scheme 1. Synthesis of alfuzosin hydrochloride (**I**).



Scheme 2. Synthesis of aprepitant (**II**).

Atazanavir Sulfate (*Reyataz*™)

Atazanavir (BMS-232632, **III**), an azapeptide HIV protease inhibitor, has been developed and launched by Bristol-Myers Squibb (BMS), under worldwide license from Novartis, for the treatment of HIV infection [18]. Atazanavir was launched in the US as Reyataz™ in July 2003. The synthesis of atazanavir (**III**) appeared in several reports [19-22]. The synthetic route depicted in Scheme 3 was one of the best routes which was suitable for large scale production [22]. The commercially available chiral diol **25** was converted to its silyl mesylate **26** in one pot *via* selective silylation and subsequent mesylation. This oily intermediate **26** was carried into the next step without further purification. The desilylation of **26** was achieved by using inexpensive ammonium fluoride. The resulting solid product **27** was readily isolated and further purified through recrystallization from IPA/H_2O in 80% yield. The epoxide formation from **27** was affected by KO^{t}Bu in THF/IPA to provide

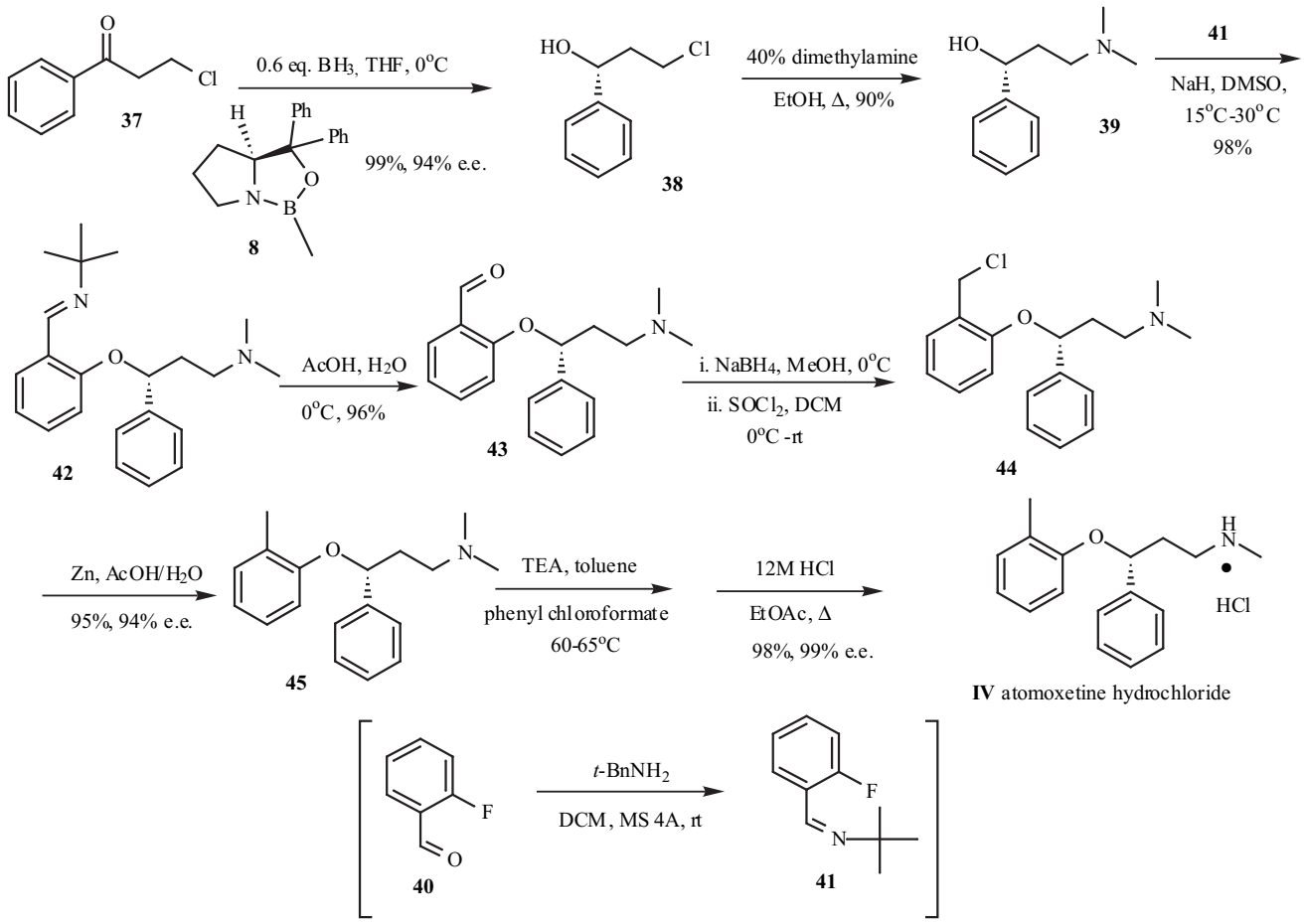


Scheme 3. Synthesis of atazanavir sulfate (**III**).

enantiomerically pure epoxide **28** in 88% yield. Suzuki coupling of boronic acid **29** with bromopyridine (**30**) provided pyridyl benzaldehyde **31** in 80% yield after crystallization. The subsequent condensation of aldehyde **31** with *t*-butylcarbamate was carried out by refluxing in toluene/IPA and Shiff base **32** was collected by filtration upon cooling. Reduction of hydrazone **32** to hydrazine **33** was accomplished by employing a catalytic phase-transfer hydrogenation protocol (Pd/C, HCOONa) to furnish hydrazine **33** in 78% yield after crystallization. Coupling of the hydrazinocarbamate **33** with epoxide **28** was performed in refluxing IPA, followed by the addition of water to precipitate the crude product. Subsequent recrystallization from MeCN/H_2O furnished **34** in 85% yield. Treatment of **34** with concentrated HCl in THF at 50ºC removed the two Boc groups in **34** to give the product as an oil, which was then dissolved in a mixture of DCM/DIPEA and slowly transferred into a premixed solution of *N*-methoxycarbonyl-L-*tert*-leucine (**35**), HOBT, and WSC in DCM. After removal of the solvent the crude product was crystallized from IPA/EtOH to furnish the freebase **36** in 82% yield. The sulfate **III** was obtained by stirring the free base **36** with concentrated H_2SO_4 in EtOH at ambient temperature. Direct crystallization by addition of *n*-heptane provided the sulfate salt **III** as an easily filterable solid in 85% yield.

Atomoxetine (*Strattera*™)

This is a selective norepinephrine reuptake inhibitor for the treatment of attention deficit hyperactivity disorder (ADHD) and was discovered and launched by Lilly. Although it is a prescription drug, it is not classified as a controlled substance because the drug does not appear to have the potential for abuse [23]. The 3-aryloxy substituent was introduced utilizing a chiral alcohol by either the Mitsunobu reaction or by nucleophilic aromatic displacement. Because of the expense and difficulty of the Mitsunobu reaction on large scale, the commercial process adopts the nucleophilic aromatic substitution method. 3-Chloropropiophenone (**37**) was asymmetrically reduced with borane and catalytic amount of (*S*)-oxazaborolidine (**8**) in THF at 0°C to give chiral alcohol **38** in 99% yield and 94%



Scheme 4. Synthesis of atomoxetine hydrochloride (**IV**).

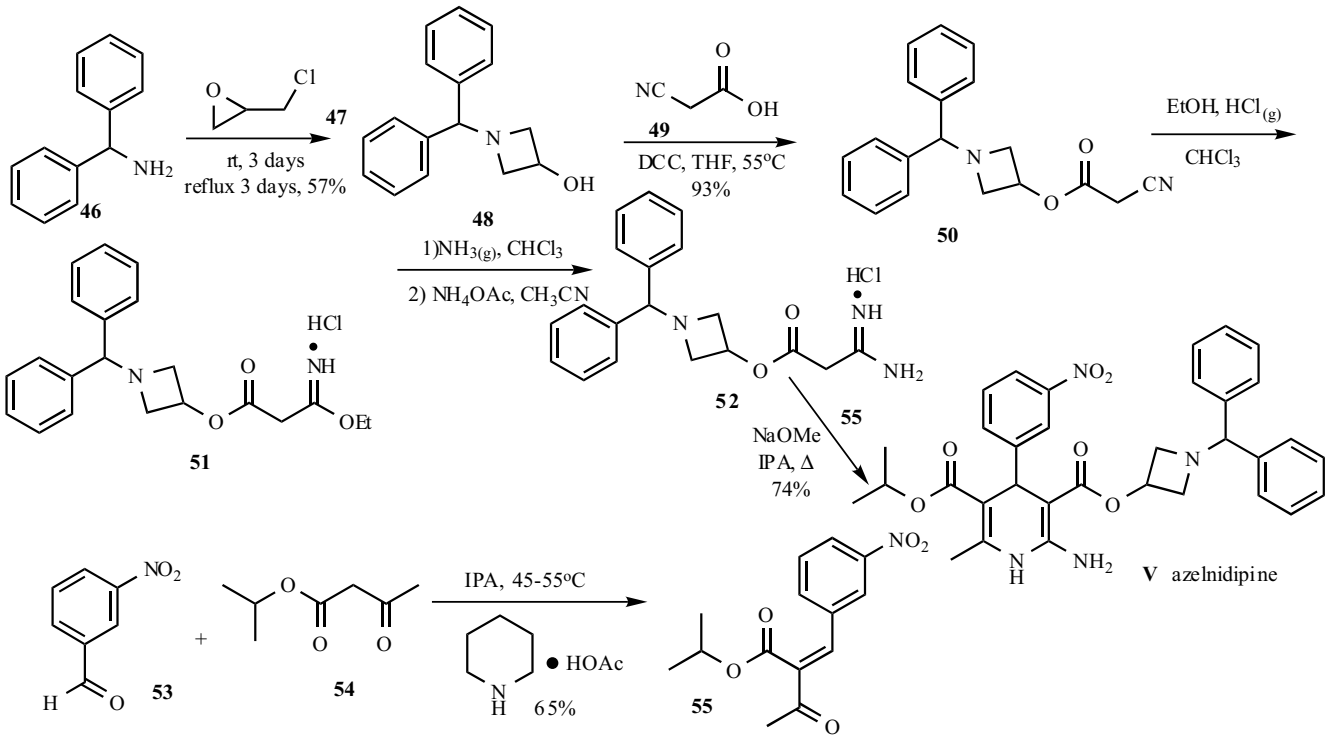
e.e. The chiral alcohol was further purified by recrystallization to greater than 99% e.e. [24]. Subsequent treatment of chloride **38** with excess dimethylamine (40% in water) in ethanol gave dimethylamine alcohol **39** in 90% yield. Alcohol **39** was then subjected to nucleophilic aromatic displacement [25] in the presence of NaH in DMSO with 1-fluoro-2-(*t*-butylimino)benzene (**41**), which was prepared in high yield from 2-fluorobenzaldehyde (**40**). The displacement product **42** was obtained in 98% yield, and the imine **42** was subsequently hydrolyzed with acetic acid in water at low temperature to give the corresponding aldehyde **43** in 96% yield. Sodium borohydride was employed to reduce aldehyde **43** to alcohol in cold methanol and the intermediate alcohol was converted to chloride **44** with thionyl chloride. Chloride **44** was then reduced with zinc metal under acidic conditions to give methyl adduct **45** in 95% yield and 94% e.e. Finally, phenyl chloroformate and triethylamine was used to transform dimethylamine **45** to monomethyl amine, which was subsequently treated with HCl in EtOAc under reflux to give atomoxetin hydrochloride (**IV**) in 98% yield and 99% e.e. from **45**.

Azelnidipine (*Calblock*^{TM})

It is a calcium channel antagonist, co-developed by Sankyo and Ube. It is a long-acting (slow onset), once-daily drug for the treatment of hypertension, and is only available in Japan now. Unlike other anti-hypertension drugs in its class, it does not produce an associated increase in heart rate when dosed chronically [26]. A solution of benzhydrylamine (**46**) and epichlorohydrin (**47**) was mixed without adding solvent to give azetidinol **48** in 57% yield [27]. DCC coupling between cyanoacetic acid (**49**) and azetidinol **48** in hot THF gave ester **50** in 93% yield. Cyanoester **50** was treated with ethanol and HCl gas in chloroform to give imidate HCl salt **51,** which was treated with ammonia gas in chloroform and ammonium acetate in acetonitrile to give the corresponding amidinoacetate **52**. A modified Hantzsch reaction was employed to construct the 2-amino-1,4-dihydropyridine core structure. Compound **52** was condensed with 2-(3-nitrobenzylidene)acetic acid isopropyl ester (**55**) in the presence of NaOMe in refluxing isopropanol to give the cyclized product, azelnidipine (**V**) in 74% yield. Benzylideneacetoacetate **55** was obtained through the Knoevenagel reaction employing 3-nitrobenzaldehyde (**53**) and isopropyl acetoacetate (**54**) in isopropanol containing a catalytic amount of piperidinium acetate at 45-55ºC in 65% yield.

Bortezomib (*Velcade*^{TM})

Millennium (formerly LeukoSite) has developed and launched bortezomib **VI** (Velcade; formerly known as MLN-341, LDP-341 and PS-341), a ubiquitin proteasome inhibitor, for the treatment of multiple myeloma (MM) in the US. Although the synthesis of dipeptidyl boronic acids have appeared on several reports [28-30], the synthetic details for bortezomib were not revealed. The synthetic route for the preparation of bortezomib is depicted in Scheme 6.

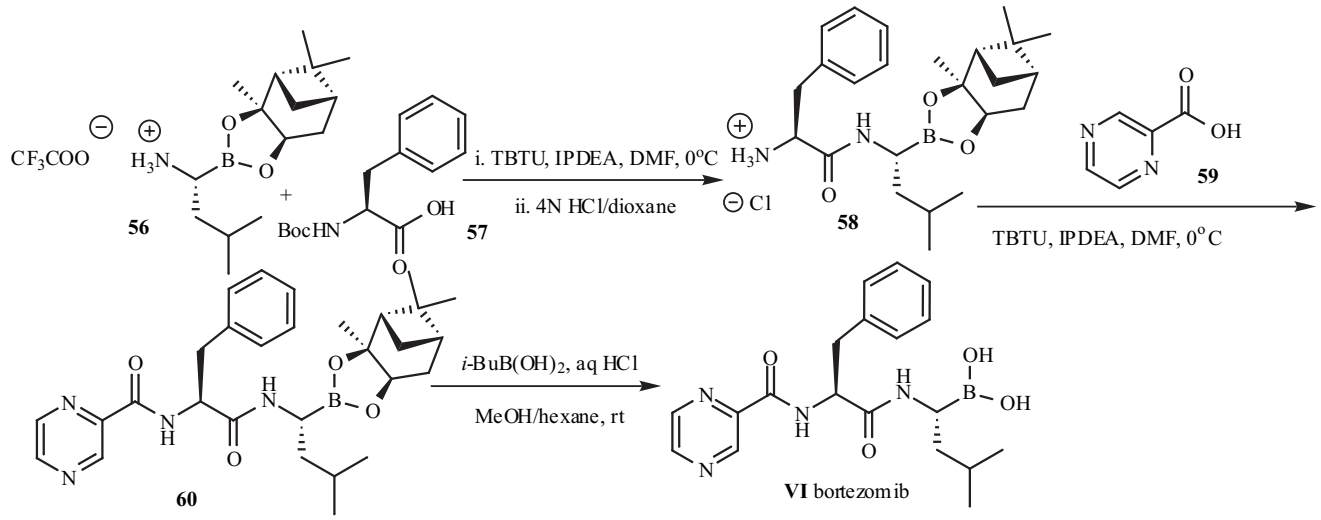


Scheme 5. Synthesis of azelnidipine (**V**).

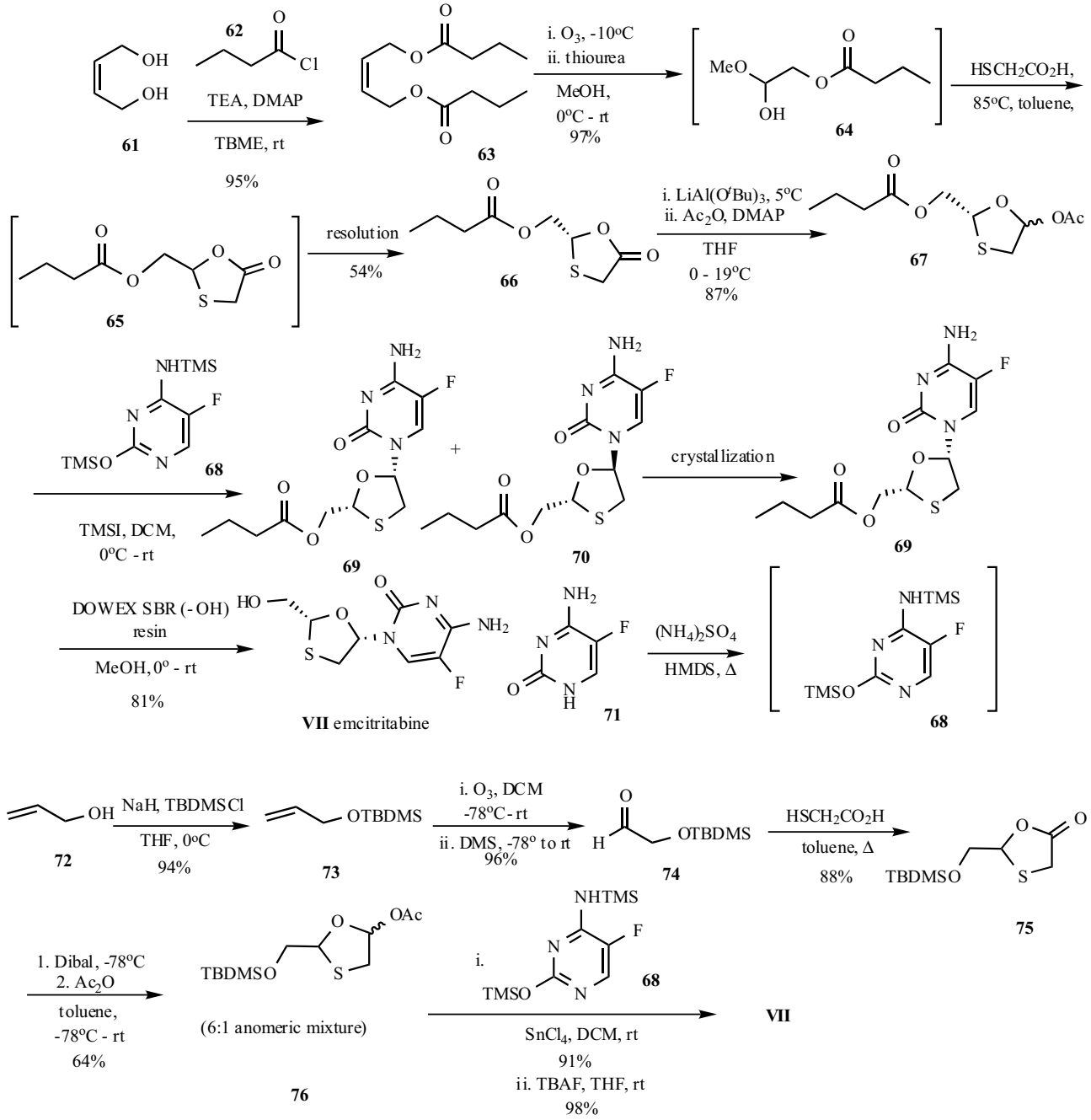
The pinanediol ester of leucine boronic acid (**56**) [31] was coupled with *N*-Boc phenylalanine (**57**) in the presence of TBTU followed by deprotection of the Boc group to provide **58**. *N*-Acylation of **58** then furnished the dipeptide boronate ester **60**. Deprotection of the boronic ester functionality was achieved by bi-phase transfer esterification with isobutyl boronic acid. Bortezomib (**VI**) was isolated by extractive workup.

Emtricitabine (*Emtriva*™)

Emtricitabine (BW-524W91, (-)-FTC) (**VII**), *cis*-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine, a novel enantiomerically pure oxathiolanyl nucleoside analog was recently approved in the US in July, 2003, for the treatment of HIV infection [32]. This novel HIV nucleoside reverse transcriptase inhibitor (NRTI) was developed and marketed under the trade name *Emtriva*^{TM} by Gilead Pharmaceuticals. Emcitritabine (**VII**) was discovered by researchers at Emory University and licensed to Triangle Pharmaceuticals, which started the development work before being acquired by Gilead. Because emcitritabine (**VII**) belongs to an important structural class of nucleosides with marketed drugs, such as 3TC, several processes for the manufacture of this class of oxathiolane nucleosides have appeared in patents and scientific literature [33-41]. However, only the synthesis described in the latest patent filed for the manufacture of emcitritabine (**VII**) and one other efficient synthesis from the Liotta group will be described (Scheme 7) [38,39]. The synthesis started with diacylation with butyryl chloride (**62**) of the 2-butene-1,4-diol (**61**) in methyl *t*-butylether at 0°C to room temperature in the

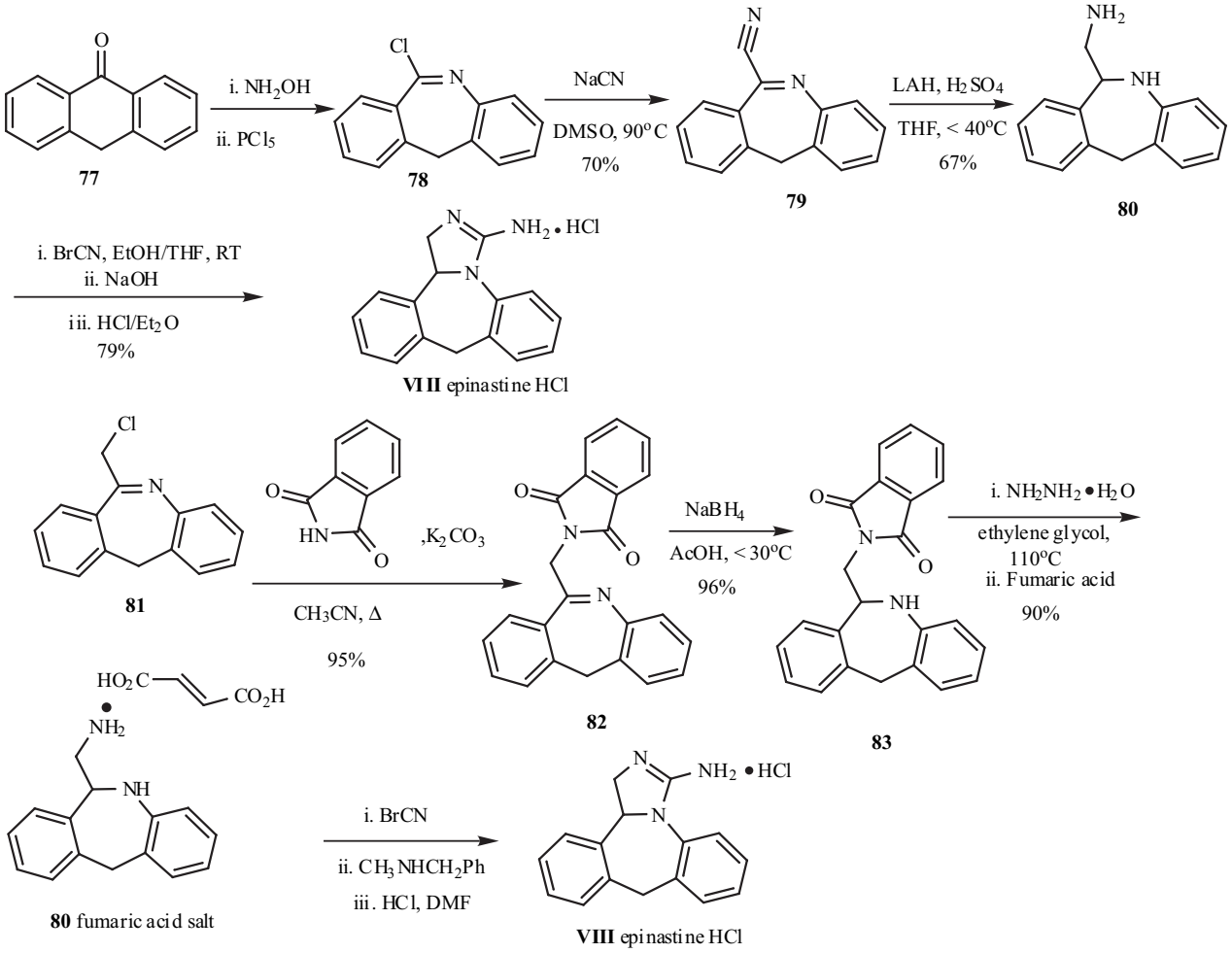


Scheme 6. Synthesis of bortezomib (**VI**).



Scheme 7. Synthesis of emcitritabine (**VII**).

presence of triethylamine to give diacylated product **63** in 95% yield. Ozonolysis followed by reduction with thiourea provided a mixture of hemiacetal **64** mixed with acetals, dimers and trimers in 97% yield, which was used in the next step directly. The hemiacetal mixture was reacted with thioacetic acid in toluene at 85°C for 3 hr to give the crude keto oxathiolane mixture, which was purified by vacuum distillation in a 2-in Pope Scientific wiped film still to remove impurities and collect about 92% pure **66** in 54% yield. Also mentioned in the patent is the potential use of enzymatic resolution of the isomers as reported previously [37]. This keto oxathiolane **66** was reduced at 5°C with lithium aluminum *t*-butoxide, which was prepared in *situ via* reaction of LAH and *t*-butanol, and the resulting lactol was trapped with acetic anhydride in the presence of DMAP in the same reaction vessel to give, after workup, 87% yield of the key intermediate acetate **67**. The bis-silyl protected 5-fluorocytosine **68**, prepared *in situ* by reacting 5-fluorocytosine (**71**) with HMDS, was reacted with acetate **67** in the presence of trimethylsilyliodide at 0°C to room temperature to give a 1:1 mixture of *alpha* and *beta*-anomers **69** and **70**. Pure **69** could be isolated by recrystallization from toluene. Cleavage of the butyryl group with a strongly basic DOWEX SBR resin in methanol at room temperature gave emcitritabine (**VII**) in 81% yield. An alternate concise synthesis reported by Liotta *et al* is worth mentioning [39]. This synthetic route accessed the key thioxalane acetate **76** as the TBDMS ether in four steps from allyl alcohol **72**. The



Scheme 8. Synthesis of epinastine (**VIII**).

key step to the preparation of the final compound was the coupling of the bis-silyl 5-fluorocytosine (**68**) with acetate **76** with tin tetrachloride in a stereoselective manner, after cleavage of the silyl groups and recrystallization, to give pure *cis* isomer emcitritabine (**VII**) in excellent yield.

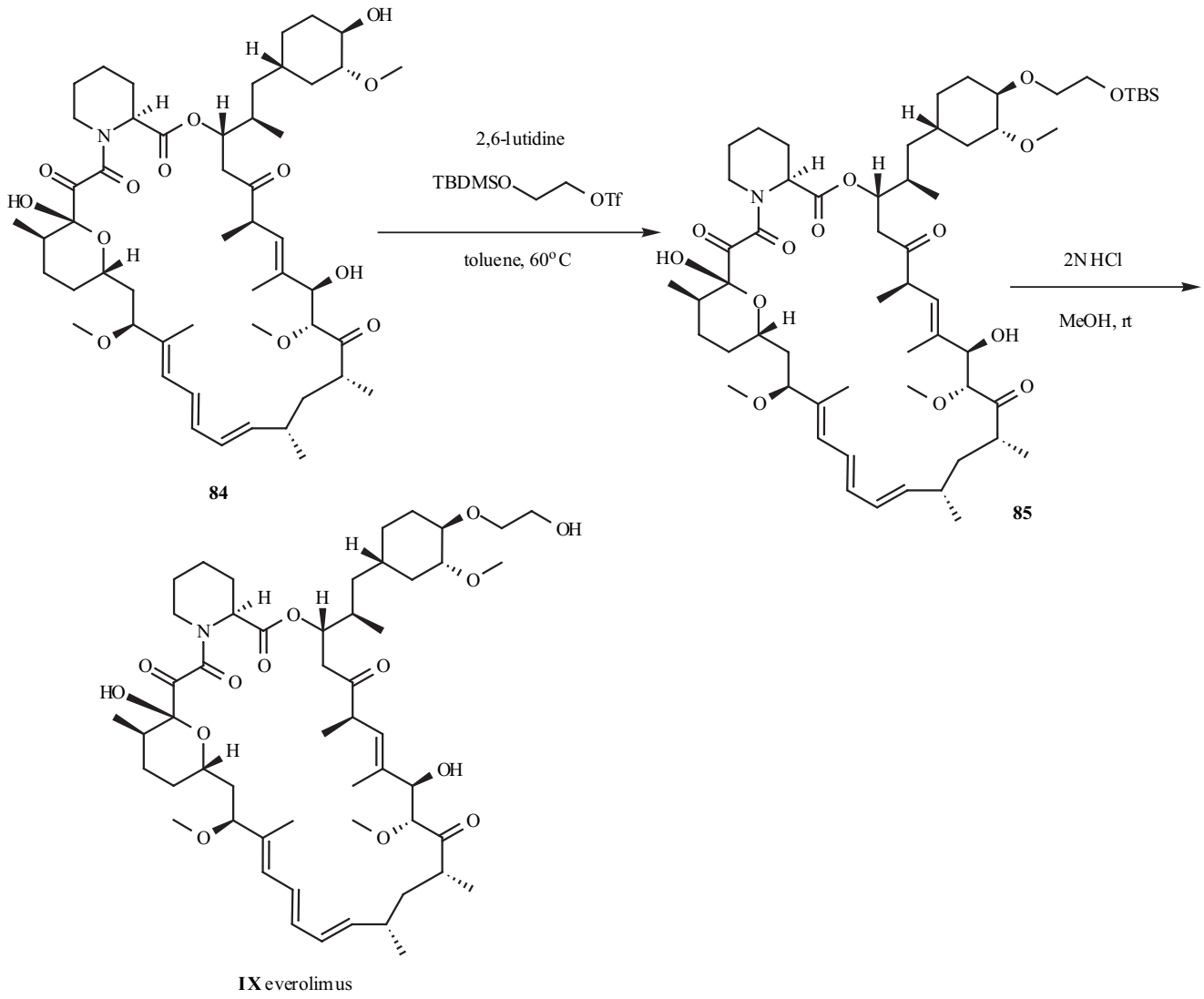
Epinastine (*Alesion*™)

Epinastine (WAL-801), a non-sedating, histamine H_1 antagonist, was developed by Allergan, after licensing from Boeringer Ingelheim, and approved in the US in October, 2003 as an ophthalmic formulation for the prevention of itching associated with allergic conjunctivitis [42]. This drug was first introduced in Japan in 1993 and followed shortly by an introduction in several Asian and South American markets. Several patents on the synthesis of epinastin (**VIII**) have appeared in Europe and Japan [43-48]. The synthesis described below is taken partly from the US patent [43] and a Japanese patent [44]. All the syntheses utilized 6-aminomethyl-6,11-dihydro-5H-dibenzo[*b.e*]azepine (**80**) as the key intermediate which was converted to the final guanidine epinastine by reacting with cyanogen bromide. The solution of **80** in ethanol was treated with a solution of cyanogen bromide in THF at room temperature and stirred overnight. The hydrobromide salt was collected in 79% yield after adding ether to the reaction mixture. The salt was free based with a solution of sodium hydroxide and then treated with an ethereal solution of HCl to obtain the epinastine hydrochloride salt **VIII**. For the preparation of the key intermediate, chloroimine **78**, presumably obtained from ketone **77** *via* Beckmann rearrangement [49,50], was reacted with sodium cyanide in DMSO to give the nitrile **79** in 70% yield. Reduction of the imino nitrile was carried out in THF in the presence of an acid with LAH to give the key intermediate **80** in 67% yield.

An alternate approach to preparation of **80** is shown in Scheme **8** as well. Reaction of the commercially available chloride **81** with phthalimide [46,48] in the presence of a base gave the phthalimide **82**. Reduction of the imine with sodium borohydride gave **83,** which was then reacted with hydrazine hydrate to free up the amine in 90% yield. The amine intermediate was isolated as the fumarate salt.

Everolimus (*Certican*™)

Everolimus (**IX**) (SDZ-RAD), was developed by Novartis as an immunosuppressant [51] to be used in conjunction with cyclosporin in transplantation allograft rejection and was recently approved in the US in 2003. Another natural product that had been approved for use in transplantation is rapamycin (sirolimus) as an inejectable agent. In an attempt to develop an orally bioavailable

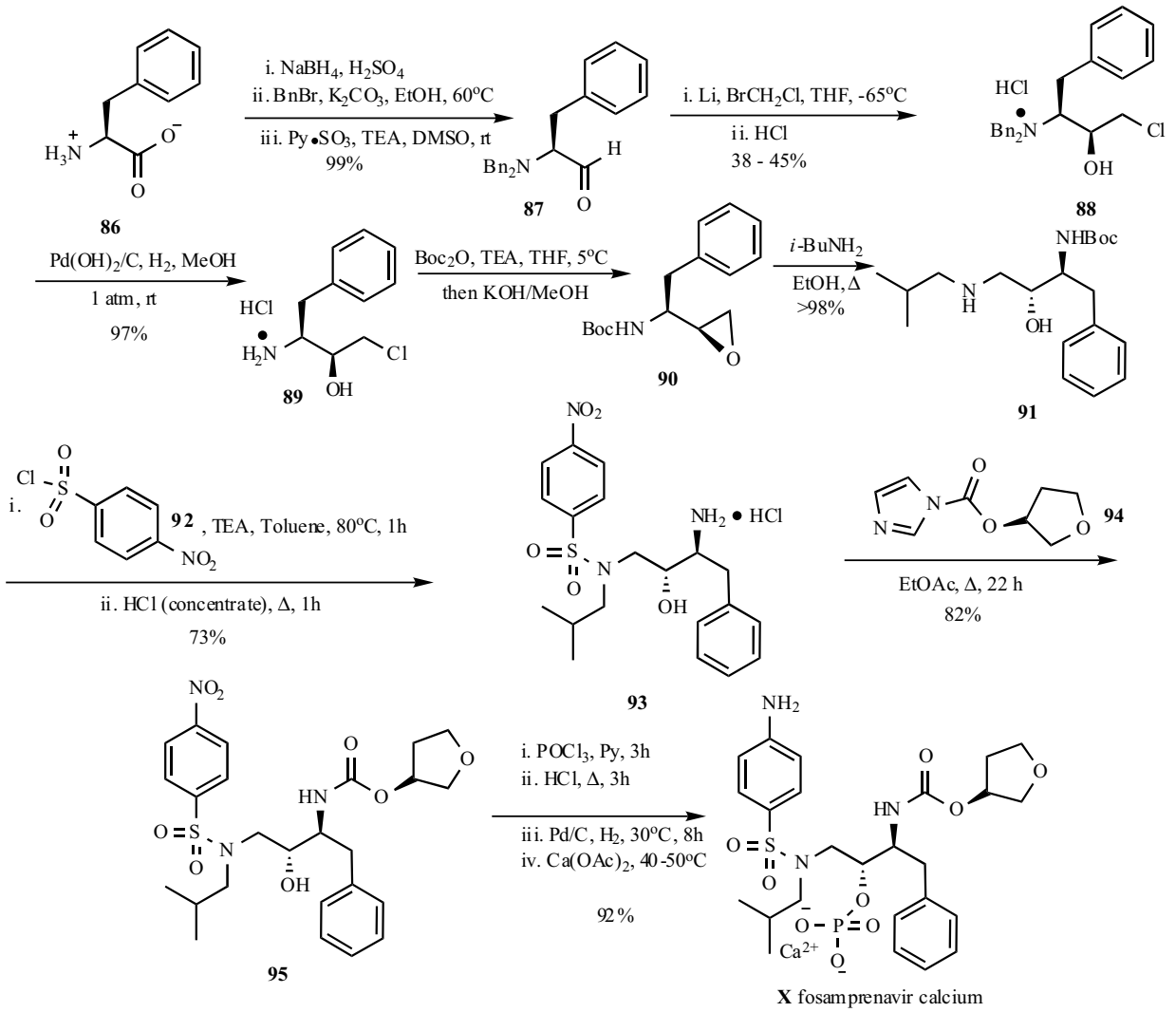


Scheme 9. Synthesis of everolimus (**IX**).

immunosuppressant agent, many companies attempted modification of rapamycin itself [52]. Everolimus (**IX**) was discovered by Sandoz (Novartis) scientists by modifying rapamycin drug in the 40-hydroxyl position [53]. Thus, treatment of rapamycin (**84**) with *t*-butyldimethylsilyloxy ethyl triflate in the presence of 2,6-lutidine at 60°C for 3.5 hrs gave ether **85**. Deprotection of the silyl group was done by treating silyloxy ether **85** in methanol with 2N HCl to give the product **IX** (everolimus), which was purified by chromatography. No yields were given for the reactions.

Fosamprenavir Calcium (*Lexiva*™)

Fosamprenavir is an amprenavir (APV, Agenerase; Vertex Pharmaceuticals Inc/GlaxoSmithKline plc) prodrug for the treatment of HIV infection. Fosamprenavir (**X**) was developed to overcome adherence barriers, such as pill size and burden, and food and water restrictions, which are common amongst all current FDA-approved protease inhibitors (PI). Fosamprenavir (**X**) can be administered without any food or water restrictions as two 700 mg tablets twice-daily; one 700 mg tablet plus one 100 mg capsule of ritonavir twice-daily; or two 700 mg tablets plus two 100 mg capsules of ritonavir once-daily. Ultimately, fosamprenavir (**X**) will offer patients and physicians a flexible and convenient PI backbone [54]. The synthesis of fosamprenavir (**X**) started with a known amino alcohol **91** [55,56]. *N,N*-Dibenzyl-*L*-phenylalaninal (**87**) was prepared by reduction of *L*-phenylalanine (**86**) to *L*-phenylalaninol followed by *N,N*-dibenzylation and oxidation to the aldehyde **87** using pyridine-sulfur trioxide complex at room temperature. A large excess of lithium shot was stirred in a solution of aldehyde **87** and bromochloromethane in THF at -65°C. The reaction mixture was subsequently allowed to warm up to room temperature to provide the diastereomeric epoxide mixture (6:1) which was quenched with 6N aqueous HCl and set standing overnight to provide the salt precipitate. Recrystallization from methanol gave optically pure dibenzylaminochlorohydrin hydrochloride (**88**) in 38-45% yield. Hydrogenolysis under standard conditions gave deprotected aminochlorohydrin hydrochloride **89** as a crystalline white solid. Conversion to desired *N*-Boc-epoxide **90** was accomplished by the introduction of the Boc group followed by cyclization [55]. *N*-Boc-epoxide **90** was then converted to amino alcohol **91** by refluxing with isobutylamine in EtOH [57]. Treatment of the amino alcohol

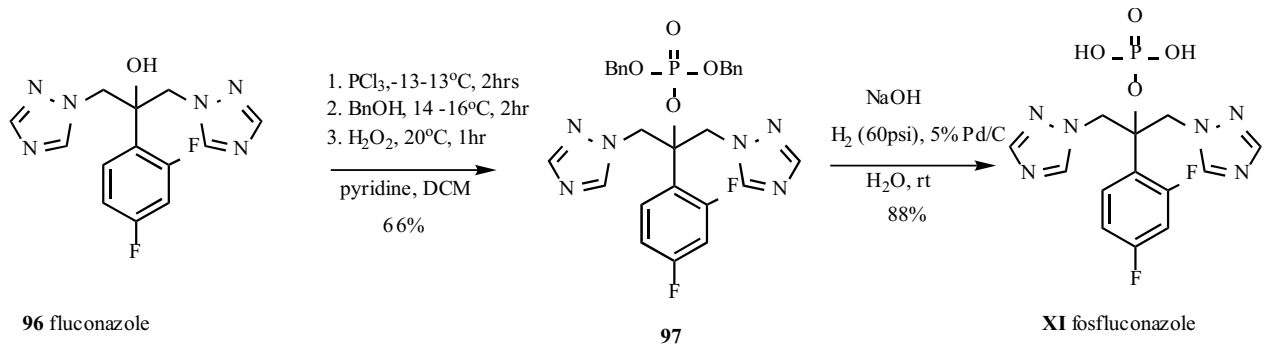


Scheme 10. Synthesis of fosamprenavir calcium (**X**).

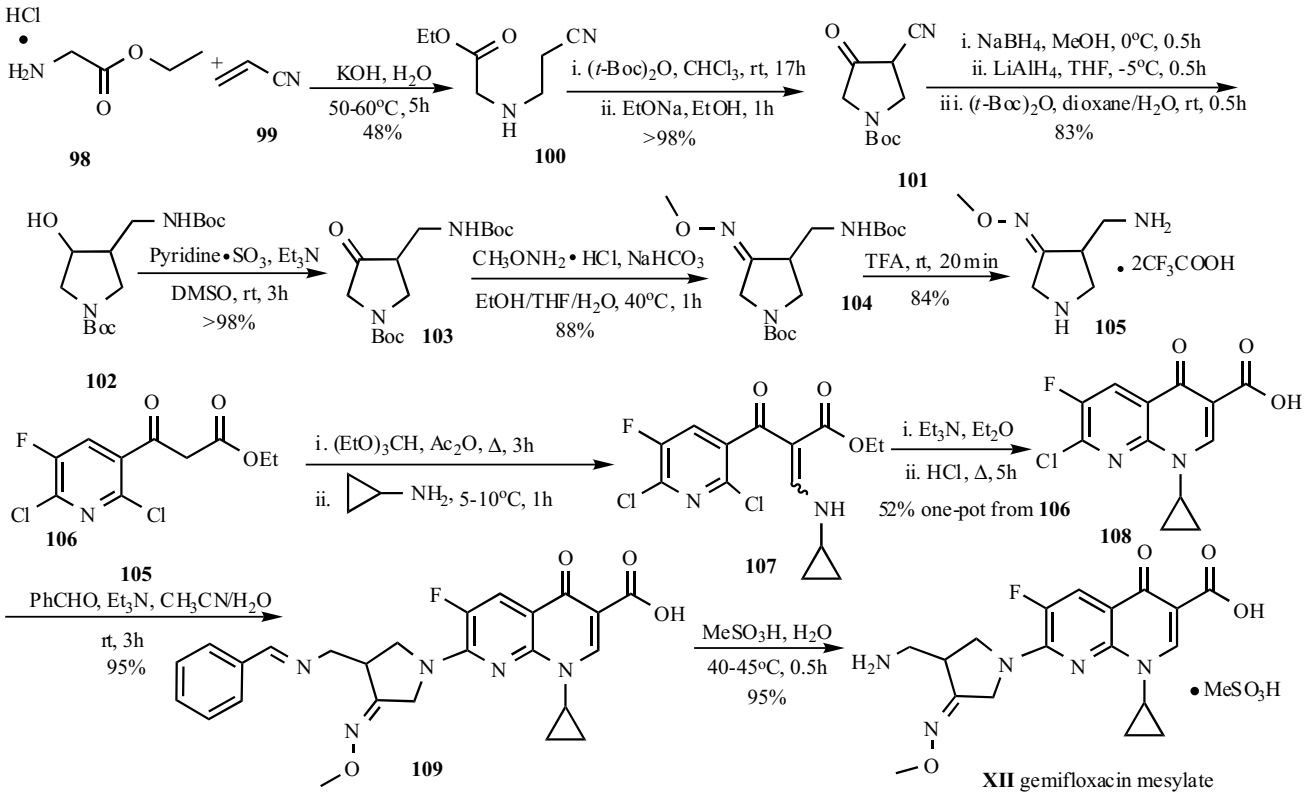
91 with *p*-nitrobenzene sulphonyl chloride in toluene at 80°C followed by acid hydrolysis of the Boc group furnished sulphonamide **93** in 73% yield. The carbamate **95** was prepared by refluxing **93** with (*S*)-tetrahydrofuryl imidazole carboxylate (**94**) in EtOAc. Treatment of the sulphonamide **95** with $POCl_3$ followed by aqueous HCl hydrolysis provided the phosphate intermediate, which was then reduced by hydrogenation and converted to fosamprenavir calcium salt **X** in a one-pot process in 92% yield.

Fosfluconazole (*Profif*™)

Fosfluconazole, a phosphate prodrug of fluconazole (**96**), was recently approved for intravenous use in Japan in October 2003. The drug was developed as a water-soluble prodrug by Pfizer as an enhancement to the injectable infusion formulation of fluconazole (**96**), a very potent antifungal agent, that could be used intravenously in bolus doses requiring smaller volumes of fluid and sodium. The disclosed manufacturing route of synthesis utilized



Scheme 11. Synthesis of fosfluconazole (**XI**).

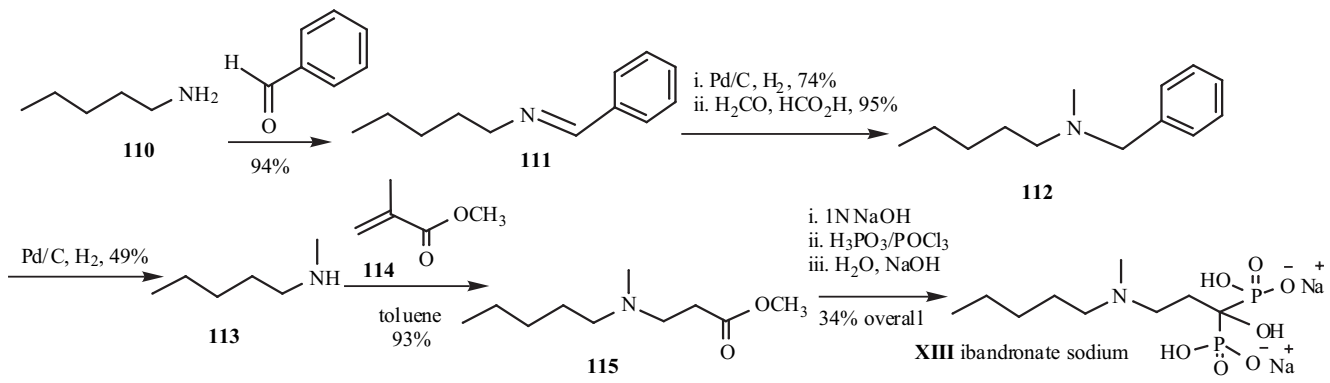


Scheme 12. Synthesis of gemifloxacin mesylate (**XII**).

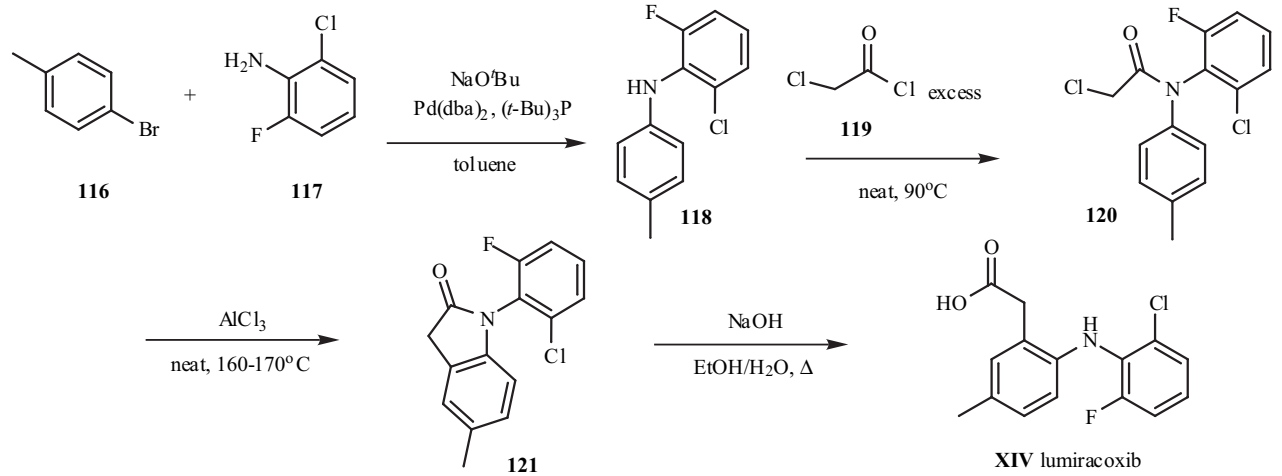
fluconazole (**96**) as a precursor and was prepared in two steps using inexpensive starting materials [58]. Fluconazole [59] was dissolved in dichloromethane with pyridine and was treated sequentially with phosphorus trichloride at –13°C and reacted at 13°C for 2 hr followed by an addition of benzyl alcohol at 14-16°C and reacted for 2 hrs at 10-15°C. The mixture was then cooled to 0°C and 30% hydrogen peroxide was added over three hours, maintaining the temperature below 20°C. After stirring the reaction at 20°C for 1hr, the intermediate **97** was isolated in 66% yield. Hydrogenation of the benzyl phosphate at 60 psi in water with 5% palladium on carbon gave the desired phosphate prodrug, fosfluconazole (**XI**) in 88% yield.

Gemifloxacin (*Zymar*™)

LG Life Sciences (formerly LG Chemical) has developed gemifloxacin (SB-265805, LB-20304a), a fluoronaphthyridone active against both Gram-positive and Gram-negative bacteria, including methicillin-resistant *staphylococci*, as a treatment for bacterial infection [60]. By December 2002, the drug had been approved in Korea. Oral gemifloxacin was approved by the FDA in April 2003. Two key intermediates, 3-aminomethyl-4-methoxyiminopyrrolidine (**105**) and 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**108**) were involved in the synthesis of gemifloxacin (**XII**). Michael addition of glycine ethyl ester hydrochloride (**98**) to acrylonitrile (**99**) in the presence of KOH furnished cyanoester **100** in 48% yield. Protection of the amino group and Dieckmann cyclization were accomplished in a one-pot process to furnish 4-cyano-1-(*N*-*t*-butoxycarbonyl)-pyrrolidine-3-one (**101**) in almost quantitative yield. The conversion of ketone **101** to alcohol **102** was achieved *via* three reaction sequences in a one-pot process in 83% yield. The hydroxy group was oxidized to ketone **103** with pyridine-sulfur trioxide complex in DMSO. Treatment of ketone **103** with methoxyamine in the presence of $NaHCO_3$ provided methyloxime **104** in 88% yield.



Scheme 13. Synthesis of ibandronate sodium (**XIII**).



Scheme 14. Synthesis of lumiracoxib (**XIV**).

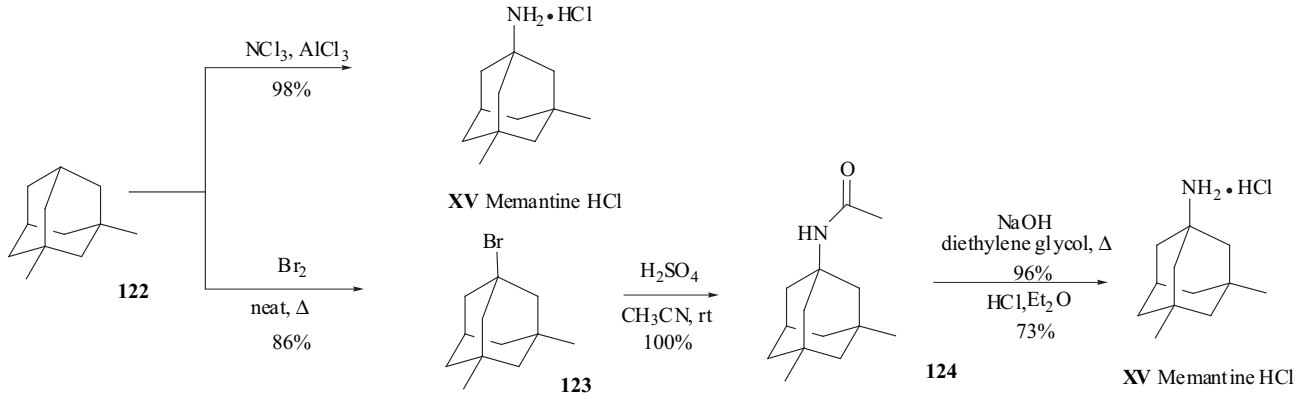
Deprotection of the Boc groups in **104** by TFA afforded pyrrolidine **105** in 84% yield [61]. Quinolone acid **108** was employed in the synthesis of ciprofloxacin and can be readily prepared according to literature methods [62,63]. A four step sequence/one-pot process [63,64] is depicted in Scheme 12. Nicotinoyl acetate **106** was converted to enaminoester **107** by reaction with ethyl orthoformate and acetic anhydride, followed by reaction with the cyclopropyl amine. 1,8-Naphthyridine **108** was obtained through base-assisted cyclization, followed by acid hydrolysis of the ester function *via* a one-pot process in 52% overall yield. The coupling reaction of quinolone **108** with pyrrolidine **105** was carried out in CH_3CN-H_2O in the presence of benzaldehyde and triethylamine. The benzaldehyde served as an important reagent to protect the primary amine selectively and therefore the desired gemifloxacin derivative **109** was obtained in high yield and purity, otherwise a 10% by-product was observed [65]. The deprotection and salt formation reactions were carried out in one step by treatment of **109** with methanesulfonic acid at 40-45ºC in water. The gemifloxacin mesylate (**XII**) was collected by filtration upon cooling in 95% yield [65].

Ibandronate (*Boniva*™)

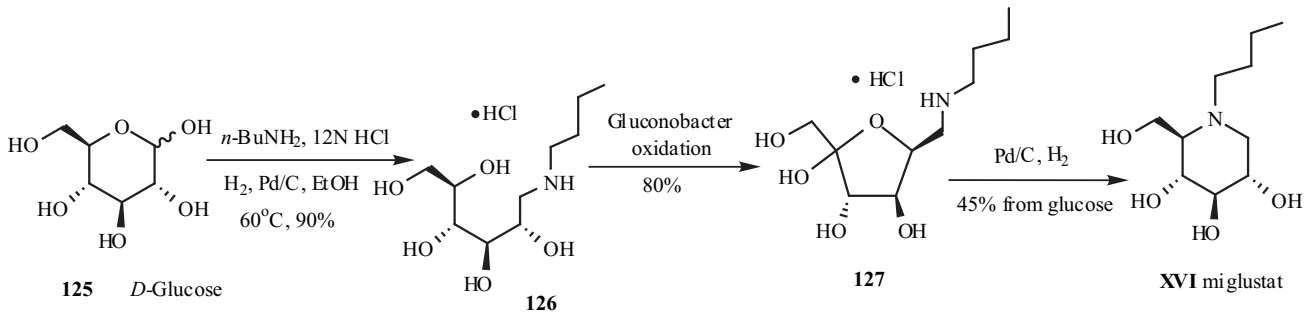
This bisphosphonate, a calcium metabolic inhibitor and osteogenesis inhibitor, was developed and launched by Boehringer Mannheim (now Roches) for the treatment of tumor-induced hypercalcemia (TIH) and is available in both injectable and oral formulations [66]. In collaboration with GlaxoSmithKline, the ibandronic acid was also developed in both *iv* and oral formulations for the treatment and prevention of postmenopausal osteoporosis. The synthesis of ibandronate sodium (**XIII**) is shown in Scheme 13 [67]. However some reaction details are not available in the literature. *N*-pentylamine (**110**) was reacted with benzaldehyde to give oily Schiff base **111** in 94% yield. Hydrogenation with palladium/charcoal gave *N*-benzyl-*N*-pentylamine as oil in 74% yield. The secondary amine was reductively alkylated with formaldehyde and formic acid to give the tertiary amine **112** in 95% yield. Hydrogenolytic cleavage of the benzyl group of **112** with palladium/charcoal gave secondary amine **113,** which was reacted with methyl acrylate (**114**) in toluene to give compound **115** in 93% yield. Methyl ester **115** was then saponified with 1N NaOH to give carboxylic acid. The acid was then heated to 80ºC with phosphorous acid. The melt was mixed with phosphorus oxychloride at the same temperature for 16 hours. Water was then added and the reaction mixture was stirred at 100°C for 24 hours to give free diphosphonic acid. The free diphosphonic acid was finally treated with sodium hydroxide to give ibandronate sodium (**XIII**).

Lumiracoxib (*Prexige*™)

Lumiracoxib, a selective COX-2 inhibitor discovered and developed by Novartis, was approved in September, 2003 in the UK for the symptomatic relief of osteoarthritis and short



Scheme 15. Synthesis of memantine (**XV**).

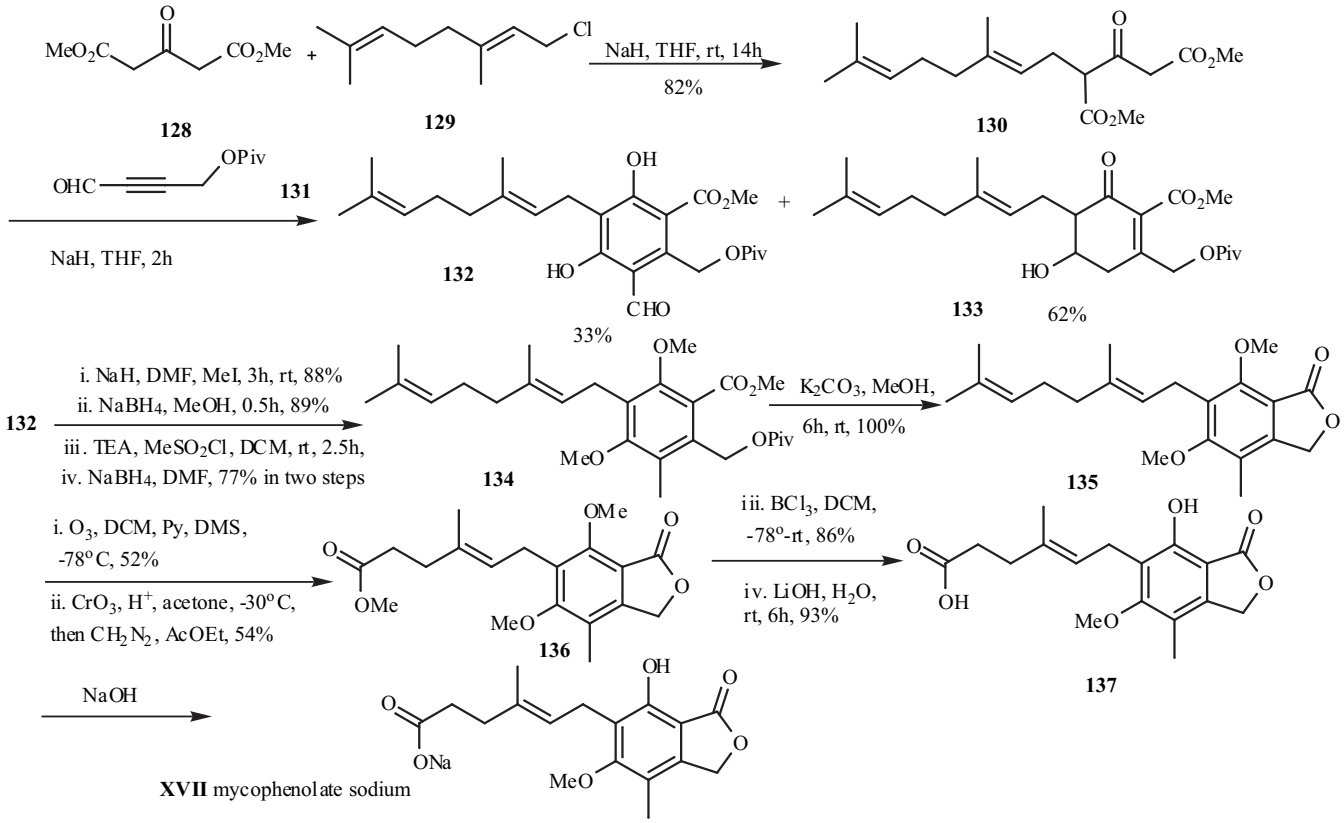


Scheme 16. Synthesis of miglustat (**XVI**).

term relief of moderate to severe acute pain associated with primary dysmenorrhea, dental surgery and orthopedic surgery [68]. After an initial not approvable letter issued by FDA in September 2003, Novartis expects to re-submit a NDA by early 2006 following the completion of several studies requested by FDA. Since the original patent on the discovery of lumiracoxib (**XIV**) disclosed the first synthesis of this compound [69], several approaches to the synthesis of lumiracoxib (**XIV**) have been detailed in the subsequent process patent [70]. In all the routes, the key to the synthesis was the ring opening of lactam **121**. Coupling of *p*-bromotoluene (**116**) with 2-chloro-6-fluoroaniline (**117**) in the presence of palladium catalyst $Pd(dba)_3$, tributyl phosphine and sodium *t*-butoxide in toluene provided aniline intermediate **118**. Acylation with chloroacetylchloride (**119**) at 90°C neat gave chloride intermediate **120**. Cyclization in the presence of aluminum chloride at 160 to 170°C gave the key lactam **121**, which was subsequently opened with sodium hydroxide in boiling ethanol water mixture to provide lumiracoxib (**XIV**).

Memantine HCl (*Namenda*^{TM})

Memantine, a NMDA receptor antagonist [71,72], was co-developed by Forest Laboratories with Merz Pharmaceuticals and marketed under the trade name Namenda for the treatment of Alzheimer's disease in the US after its approval in October, 2003. This drug has been available in many European and Asian markets before getting approval in the US. Memantine (**XV**) or 1-amino-3,5-dimethyladamantane hydrochloride was first synthesized by Lilly as an anti-diabetic agent but was ineffective in lowering blood sugar [73]. Several syntheses have been detailed in the literature [73-76]. However the simplest synthesis of the drug was done in one step from the commercially available 3,5-dimethyl adamantine (**122**). Treatment of **122** with nitrogen trichloride (CAUTION: very explosive gas!) in the presence of aluminum trichloride (ratio of 1.5:1.2) gave the desired amino adamantine in 86% yield. However, a much safer alternative has been reported by Lilly scientists. Heating the commercially available 3,5-



Scheme 17. Synthesis of mycophenolate sodium (**XVII**).

dimethyladamantane **122** in bromine gave the bromo derivative **123** (86%) which was then reacted with sulfuric acid in acetonitrile to provide quantitatively acetyl amino derivative **124** after aqueous workup. Hydrolysis of the acetyl group was done by heating **124** with sodium hydroxide in diethylene glycol to give 1-amino -3,5-adamantane (96%), which was then made into the hydrochloride salt in ether and recrystallized from ether and alcohol mixture to provide the final product memantine hydrochoride **XV**.

Miglustat (*Zavesca*™)

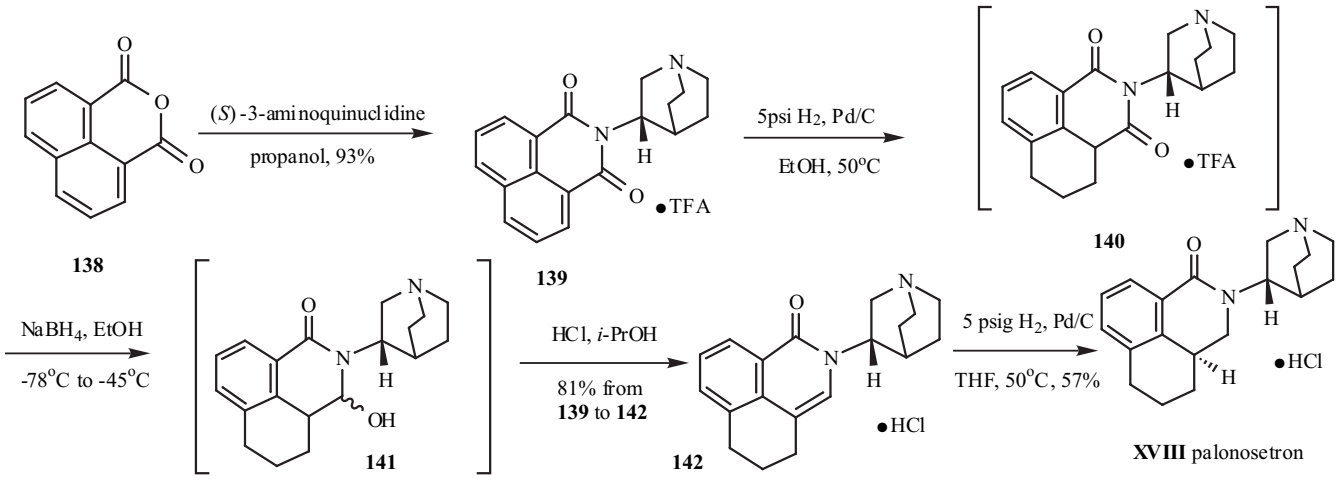
This orally active glucosylceramide glucosyltransferase inhibitor, was launched for the treatment of type I Gaucher's disease [77]. Miglustat (**XVI**) has been developed and launched by Oxford GlycoSciences (OGS; now Celltech) and Actelion. The drug was originally discovered at Searle (now Pfizer) and an enzymatic oxidation was employed in the synthesis [78]. *D*-Glucose (**125**) was subjected to reductive amination with *n*-butylamine in ethanol under 4 atm of hydrogen in the presence of Pd/C catalyst at 60 ºC to give *N*-butylglucamine HCl salt (**126**) in 90% yield. *N*-butylglucamine (**126**) then was submitted to a selective microorganism oxidation by *Gluconobacter Oxidans* (DSM 2003) cell paste in water to give 6-(butylamino)-6-deoxy-a-L-sorbofuranose HCl salt (**127**) in 80 % yield. Finally, compound **127** was cyclized and reduced *in situ* with hydrogen over Pd/C at 4000 atm in ethanol/water to give miglustat (**XVI**) in 45% overall yield from *D*-glucose (**125**).

Mycophenolate Sodium (*Myfortic*™)

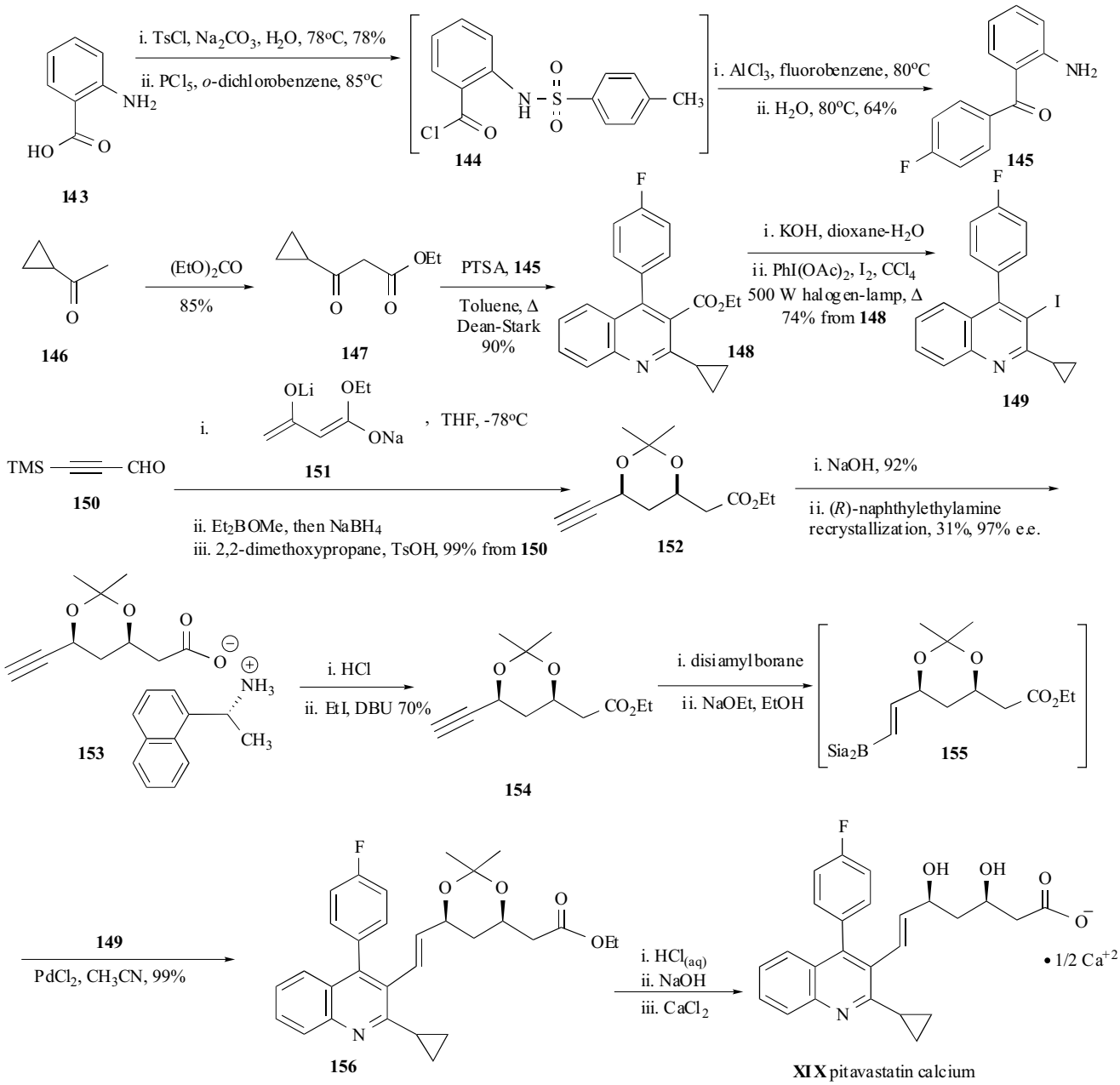
Novartis has developed and launched an enteric-coated formulation of mycophenolate sodium (Myfortic; ERL-080), an IMP dehydrogenase inhibitor, as an oral immunosuppressive agent for the prevention of kidney rejection during transplantation [79]. In November 2002, its first approval was gained in Switzerland; additional approvals were subsequently received in Brazil, India, Australia. By January 2004, approval had been received in 36 countries, and by March 2004, approval had been granted in the EU and US. Mycophenolic acid (**137**), a natural product, was discovered 107 years ago [80]. Mycophenolic acid (**137**) was originally synthesized by Birch and Wright [81] and has been the subject of several total [82-88] and formal syntheses [89-95]. The large production in industry is done *via* fermentation [96]. A concise synthesis of mycophenolic acid published recently is depicted in Scheme 17 [88]. Reaction of dimethyl 1,3-acetonedicarboxylate (**128**) with commercially available geranyl chloride (**129**) in the presence of NaH gave ketoester **130** in 82% yield. Treatment of ketoester **130** with 4-(pivolyloxy)-2-butynal (**131**) in the presence of NaH provided resorcinol **132** in a single step with all substituents in place in 33% yield along with two more compounds represented by **133** (62%). Resorcinol **132** was transformed into **134** *via* a four step sequences: methylation with NaH and MeI in dry DMF, reduction of the formyl group with $NaBH_4$, mesylation of the resulting alcohol and subsequent reduction of the mesylate. The preparation of phthalide **135** was affected in quantitative yield on treatment of **134** with K_2CO_3 in dry MeOH. Selective ozonolysis of compound **135,** followed by Jones oxidation and esterification afforded ester **136**. Demethylation with BCl_3 in DCM followed by hydrolysis of the ester function gave the mycophenolic acid (**137**). The mycophenolic acid was then converted to its sodium salt **XVII** (no conditions and yield available).

Palonosetron (*Aloxi*™)

This selective and conformationally restricted 5-HT_3 receptor antagonist was approved for the treatment of chemotherapy-induced nausea and vomiting [97]. The drug was originally developed by Syntex Corp (now Roche Bioscience) and is currently being developed by Helsinn and MGI Pharm. (*S*)-3-Aminoquinuclidine was condensed with inexpensive 1,8-naphthalic anhydride (**138**) to furnish imide **139** in 93% yield and isolated as its TFA salt [98]. Imide **139** was hydrogenated at 5 psi to give intermediate **140** with one of the reduced aromatic ring. The less hindered C-3 carbonyl group in **140** was selectively reduced to a hydroxy group by using sodium borohydride in ethanol under nitrogen at low temperature to give intermediate **141**. Intermediate **141** was not isolated because of the formation of a tight boron complex. Subsequently, acid was added to **141** in *i*-PrOH to decompose the boron complex and dehydrate intermediate **141** to **142,** which was conveniently



Scheme 18. Synthesis of palonosetron (**XVIII**).

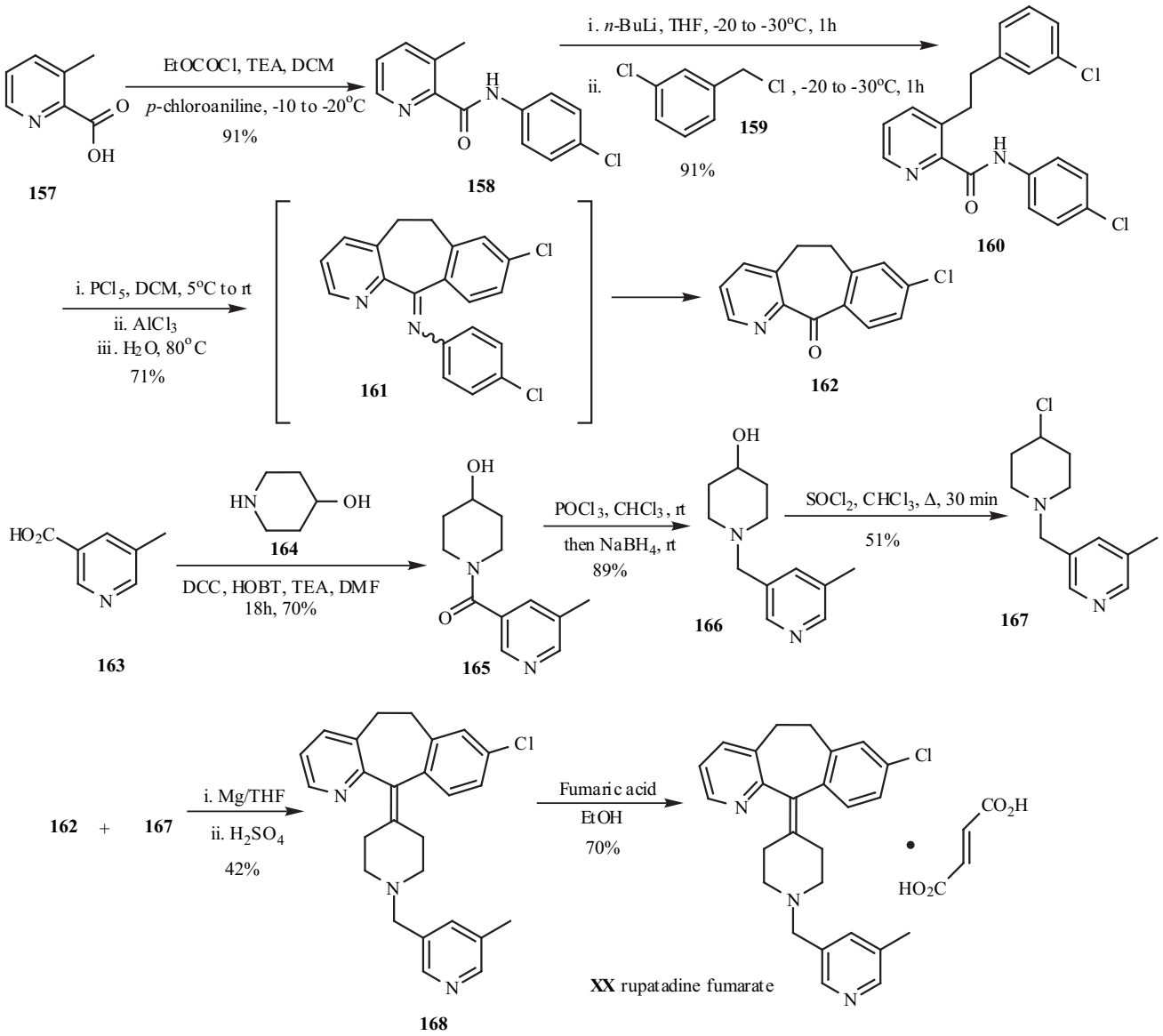


Scheme 19. Synthesis of pitavastatin calcium (**XIX**).

isolated as its HCl salt in 75% yield from **139**. Palonosetron (**XVIII**) was obtained in 57% yield by palladium-catalyzed hydrogenation of **142**.

Pitavastatin Calcium (*Livalo*™)

Pitavastatin calcium, another HMG-CoA reductase inhibitor in the statin family, is marketed by Kowa and Sankyo for the treatment of hyperlipidemia. Pitavastatin (**XIX**) is a liver-selective drug with higher cholesterol-lowering potency and longer action than pravastatin or simvastatin [99]. The convergent synthesis [100-102] was achieved by cross-coupling of aryl halide **149** with (*E*)-alkenyl borane **155** which was derived from terminal acetylene **154** by via hydroboration [102]. Anthranilic acid (**143**) was treated with TsCl and sodium carbonate in hot water to give *N*-tosylated intermediate in 78% yield, which was converted to the corresponding acid chloride **144** with PCl_5 in *o*-dichlorobenzene at 85°C. Intermediate **144,** without isolation, was reacted with fluorobenzene in the presence of $AlCl_3$ at 80°C to give the Friedel-Crafts product which was then hydrolyzed in hot water to give fluorobenzophenone free aniline **145** in 64% yield from the *N*-tosyl anthranilic acid. Acetyl cyclopropane (**146**) was reacted with diethyl carbonate to give the corresponding ethyl ester **147**. The quinoline core structure was obtained by condensing fluorobenzophenone **145** with **147** under acidic conditions with a Dean-Stark trap to give quinoline-3-carboxylic ethyl ester **148** in 90% yield. Ester **148** was hydrolyzed with potassium hydroxide, and the free carboxylic acid thus obtained was subsequently photo-iododecarboxylated with iodine and $PhI(OAc)_2$ to give aryl

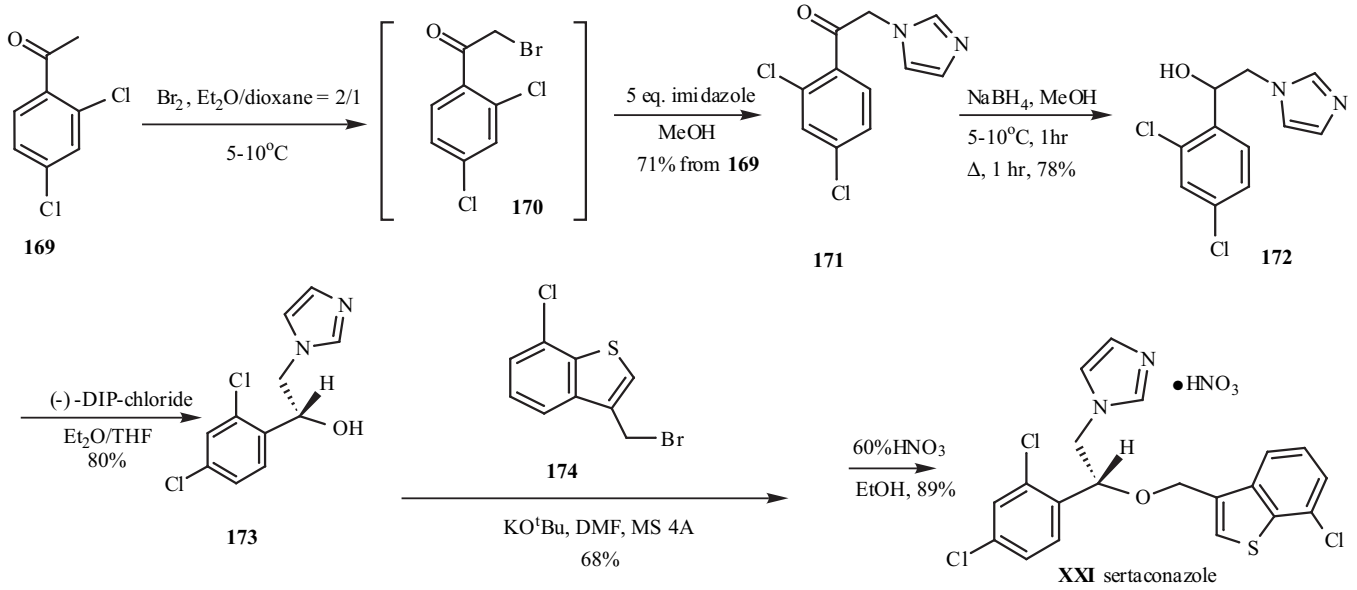


Scheme 20. Synthesis of rupatadine fumarate (**XX**).

iodide **149** in 74% yield. 3-Trimethylsilylpropynal (**150**) was used as the starting material to prepare the chiral side chain. Compound **150** was reacted with di-anion **151** in THF at low temperature to give the corresponding diol ester which was first reacted with Et_2BOMe and then reduced to acetylene with sodium borohydride. The free diol was protected as ketal with 2,2-dimethoxypropane in the presence of TsOH to give dimethylketal acetylene **152** in 99% yield. The ester functionality was hydrolyzed with sodium hydroxide to give the acid in 92% yield. The racemic free acid was resolved with (*R*)-(1-naphthyl)ethylamine to give the pure diastereomeric salt **153** which crystallized out in 31% yield and 97% e.e. Esterification of the free carboxylic acid liberated from the crystalline salt with ethyl iodide gave optically pure acetylene **154** in 70% yield. Hydroboration of acetylene **154** with disiamylborane gave (*E*)-alkenyl-disiamylborane **155** and the excess borane reagent was quenched with sodium ethoxide in ethanol. After evaporation of all volatile material, the residue was directly subjected to the cross-coupling reaction. Palladium (II) chloride and aryl iodide **149** were mixed in acetonitrile to give coupling product **156** in 99% yield. After the ketal in **156** was hydrolyzed under acid conditions and the ester was hydrolyzed with sodium hydroxide, the resulting carboxylic sodium salt was reacted with calcium chloride to yield pitavastatin calcium (**XIX**) with 99% e.e.

Rupatadine Fumarate (*Rupafin*™)

Uriach's rupatadine fumarate, a novel antiallergic drug with a dual mechanism of action, was launched for the first time in Spain in 2003. Rupatadine, which acts as a non-sedating histamine H_1 antagonist and platelet-activating factor antagonist, represents a novel approach to the treatment of allergic rhinitis [103]. One of the convergent syntheses [104-109] for rupatadine (**XX**) involved two key intermediates, tricyclic ketone **162** and chloropiperidine derivative **167**. 3-Methylpicoline acid (**157**) was reacted with *p*-chloroaniline in the presence of acid chloride and TEA to provide amide **158** in 91% yield. Amide **158** was then

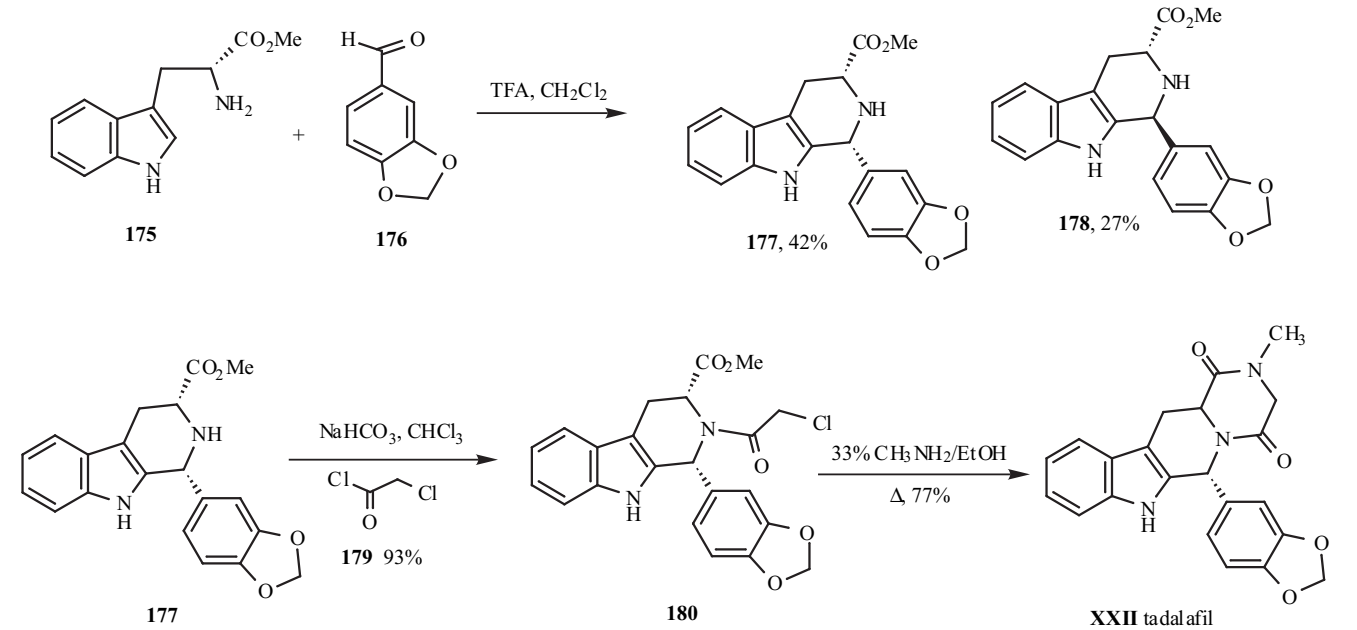


Scheme 21. Synthesis of sertaconazole (**XXI**).

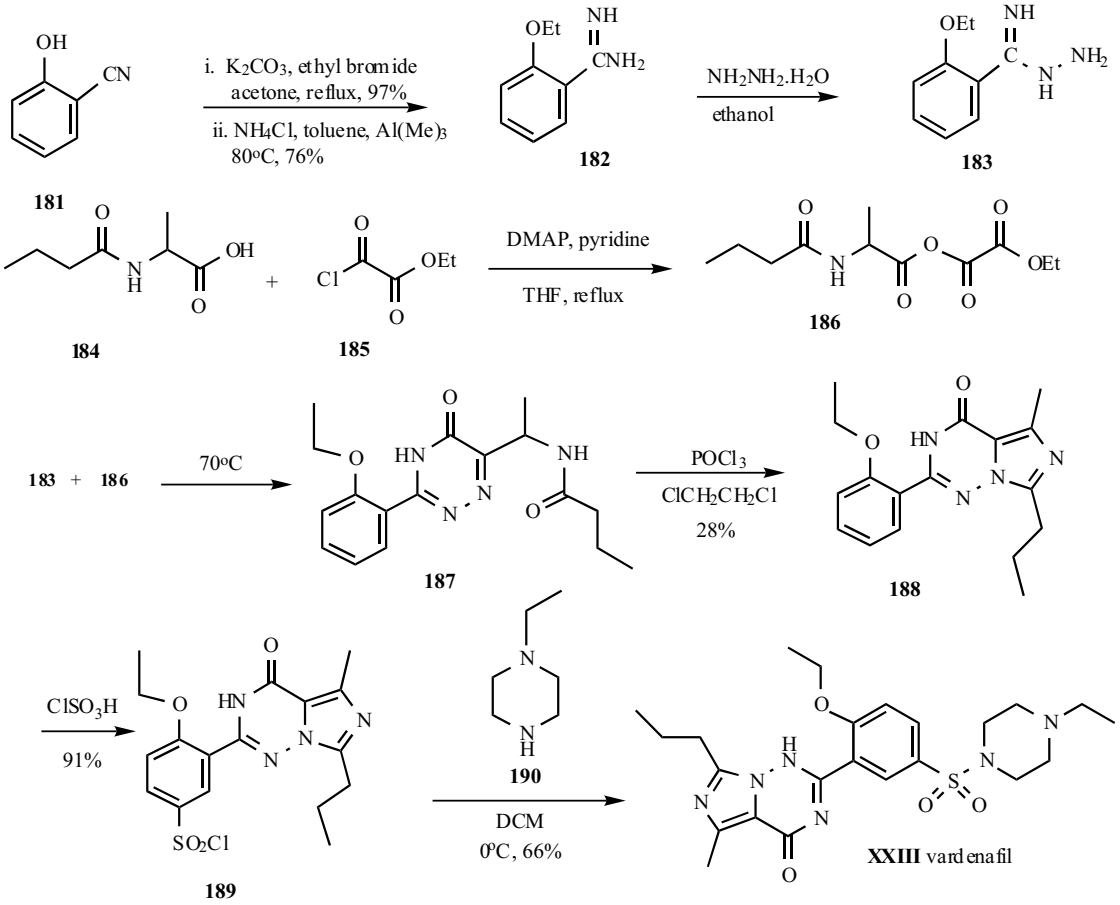
treated with *n*-BuLi at -20°C for 1h, followed by addition of 3-chlorobenzyl chloride (**159**) to furnish amide **160** in 91% yield after an aqueous workup. The cyclization of amide **160** was accomplished by treatment with **160** PCl_5 first followed by $AlCl_3$ mediated Friedel-Crafts cyclization. The cyclic intermediate **161** was directly subjected to hydrolysis without isolation and tricyclic ketone **162** was obtained in 71% yield *via* a one-pot process [107]. *N*-acylation of 5-hydroxypiperidine (**164**) with 5-methylnictonic acid (**163**) was accomplished by using HOBT, DCC to furnish amide **165**. The carbonyl group in **165** was reduced by chlorination/reduction sequence using $POCl_3$ and $NaBH_4$. Alcohol **166** was then converted to the chloride **167** by refluxing with $SOCl_2$ in $CHCl_3$. Coupling tricyclic ketone **162** and chloride **167** *via* a Grinard protocal followed by dehydration furnished the rupatadine **168**. Treatment of rupatadine with fumaric acid in EtOH gave rupatadine fumarate (**XX**) in 70% yield [109].

Sertaconazole (*Dermofix*™, *Ertaczo*™)

This drug has been developed and launched for the treatment of dermatological fungal infections by Ferrer Internacional S. A.[110]. Mylan received FDA approval for sertaconazole nitrate cream for the treatment of athlete's foot (*tinea pedis*) at the end of 2003. 2,4-Dichloro acetophenone **169** was brominated at low temperature to give bromide intermediate **170**, which was used without isolation. To the same pot, five-fold excess of imidazole was added to give imidazolylacetophenone **171** in 71% yield from **169**. Sodium borohydride was employed to reduce ketone **171** to alcohol **172** in 78% yield. Racemic alcohol **172** was



Scheme 22. Synthesis of tadalafil (**XXII**).



Scheme 23. Synthesis of vardenafil (**XXIII**).

resolved with (-)-DIP-chloride to give its corresponding chiral *R*-alcohol **173** in 80% yield. Compound **173** was then alkylated with 3-bromomethyl-7-chlorobenzo[*b*]thiophene (**174**) in dry DMF in the presence of potassium *t*-butoxide to give the alkylation product in 68% yield. Finally, 60% nitric acid was used to make sertaconazole mononitrate (**XXI**) in 89% yield [111].

Tadalafil (*Cialis*™)

Tadalafil is an orally active and structurally distinct phosphodiesterase (PDE) type 5 inhibitor. This drug has been developed and launched widely in several markets by Lilly ICOS LLC (a joint venture established in 1998) for the treatment of erectile dysfunction. Compared to Viagra, tadalafil (**XXII**) is more selective against PDE_6, has a significantly longer duration of action (24 hr vs. 2-4 hr) and has no food effect on its absorption [112]. Pictet-Spengler reaction was applied in the synthesis of tadalafil (**XXII**) [113]. *D*-(-)-Tryptophan methyl ester (**175**) and 1,3-benzodioxole-5-carboxaldehyde (**176**) were subjected to a modified Pictet-Spengler reaction to form *cis*- and *trans*-tetrahydro-β-carboline tricyclic compounds. The *cis*-compound **177** was isolated as a white solid in 42% yield. The basic nitrogen in the piperidine ring of **177** was acylated with chloroacetyl chloride (**179**) to give compound **180** in 93% yield. Finally, the diketonepiperazine ring was formed by adding **180** to 33% methylamine in ethanol under refluxing conditions and yielded tadalafil (**XXII**) in 77% as a white solid.

Vardenafil (*Levitra*™)

This is another orally active phosphodiesterase (PDE) type 5 inhibitor with better potency and selectivity for the PDE_5 isoform than Viagra. Vardenafil (**XXIII**) was originally discovered by Bayer and co-developed by Bayer and GlaxoSmithKline for the treatment of erectile dysfunction [114]. The synthesis [115] started with 2-hydroxybenzonitrile. 2-Hydroxybenzonitrile (**181**) was alkylated with ethyl bromide to give 2-ethoxybenzonitrile in 97% yield as a liquid which was subsequently treated with $AlMeClNH_2$, prepared from $AlMe_3$ and NH_4Cl, to give corresponding 2-ethoxybenzamidine (**182**) in 76% yield as a solid. Compound **182** was treated with hydrazine hydrate in ethanol to give hydrazide **183,** which was used in the next step without isolation. Dakin-West reaction of 2-butyrylaminopropionic acid (**184**) with ethyl oxalyl chloride (**185**) in the presence of DMAP in refluxing pyridine/THF to give corresponding α-oxoamino-acid ester **186** which was also used for next step without isolation. Hydrazide **183** was condensed with ester **186** in refluxing ethanol to give triazinone **187** intermediate which was then cyclized to the final core structure, imidazo[5,1-*f*][1,2,4]triazin-4-one, using $POCl_3$ to give **188** in 28% yield from **183**. Compound **188** was sulfonylated with chlorosulfonic acid to give sulfonyl chloride **189** in 91% yield. Finally, **189** was condensed with

N-ethylpiperazine (**190**) in dichloromethane to give vardenafil (**XXIII**) in 66% yield.

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ABBREVIATIONS

ADME	=	absorption, distribution, metabolism, excretion
Boc	=	*t*-butyloxycarbonyl
Dba	=	dibenzylideneacetone
DBU	=	1,8-diaza-7-bicyclo[5.4.0]undecene
DCC	=	*N,N'*-dicyclohexylcarbodiimide
DCM	=	dichloromethane
DIBAL-H	=	diisobutylaluminum hydride
DIP-chloride	=	B-chlorodiisopinocampheylborane
DIPEA	=	diisopropylethylamine
DMAP	=	4-dimethylaminopyridine
DMF	=	*N,N*-dimethylformamide
DMSO	=	methyl sulfoxide
HOBT	=	1-hydroxybenzotriazole hydrate
HMDS	=	hexamethyldisilazane
IPA	=	isopropyl alcohol
LDA	=	lithium diisopropylamide
LAH	=	lithium aluminum hydride
MTBE	=	*t*-butylmethyl ether
NCE	=	new chemical entities
TBAF	=	*t*-butyl ammonium fluoride
TBDMS	=	*t*-butyldimethylsilyl
TBTU	=	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEA	=	triethyl amine
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TMS	=	tetramethylsilyl
Ts	=	tosyl
p-TSA	=	*para*-Toluene sulfonic acid
WSC-HCl	=	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride

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