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Review

Synthetic approaches to the 2009 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 21 NCEs marketed in 2009.

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Abbreviations: AIBN, 2,2'-azobisisobutyronitrile; Boc, *t*-butoxycarbonyl; CBZ, benzyloxycarbonyl; CDI, *N,N'*-carbonyldiimidazole; CMHP, cumene hydroperoxide; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBTA, dibenzoyl tartaric acid; DCE, dichloroethane; DCM, dichloromethane; DET, diethyl tartrate; DIAD, diisopropyl azodicarboxylate; DIBAL-H, diisobutylaluminum hydride; DIC, *N,N'*-diisopropylcarbodiimide; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DMPU, *N,N'*-dimethylpropyleneurea; DMSO, methyl sulfoxide; DPPC, diphenylphosphinic chloride; EDCl, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide; HMTA, hexamethylenetetramine; HOBt, 1-hydroxybenzotriazole hydrate; IPA, isopropyl alcohol; IPAC, isopropyl acetate; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide; MCPBA, *meta*-chloroperoxybenzoic acid; MEK, methyl ethyl ketone; MS, molecular sieves; 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-methoxybenzyl; PPA, polyphosphoric acid; (*S,S*)-DET, (*S,S*)-(-)-diethyl tartrate; TBAF, *t*-butyl ammonium fluoride; TBDMSCl, *t*-butyldimethylsilyl chloride; TEA, triethylamine; TFA, trifluoroacetic acid; TFAA, trifluoroacetic acid anhydride; THF, tetrahydrofuran; THP, tetrahydropyran; TIPS, triisopropyl silyl; TPAP, tetrapropylammonium perruthenate; TMG, 1,1,3,3-tetramethylguanidine; TMSCl, trimethylsilyl chloride; *p*-TSA, *para*-toluene sulfonic acid; Ts-DAEN, *N*-[(1*S*,2*S*)-2-amino-1,2-bis(4-methoxyphenyl)ethyl]-4-methyl-benzenesulfonamide.

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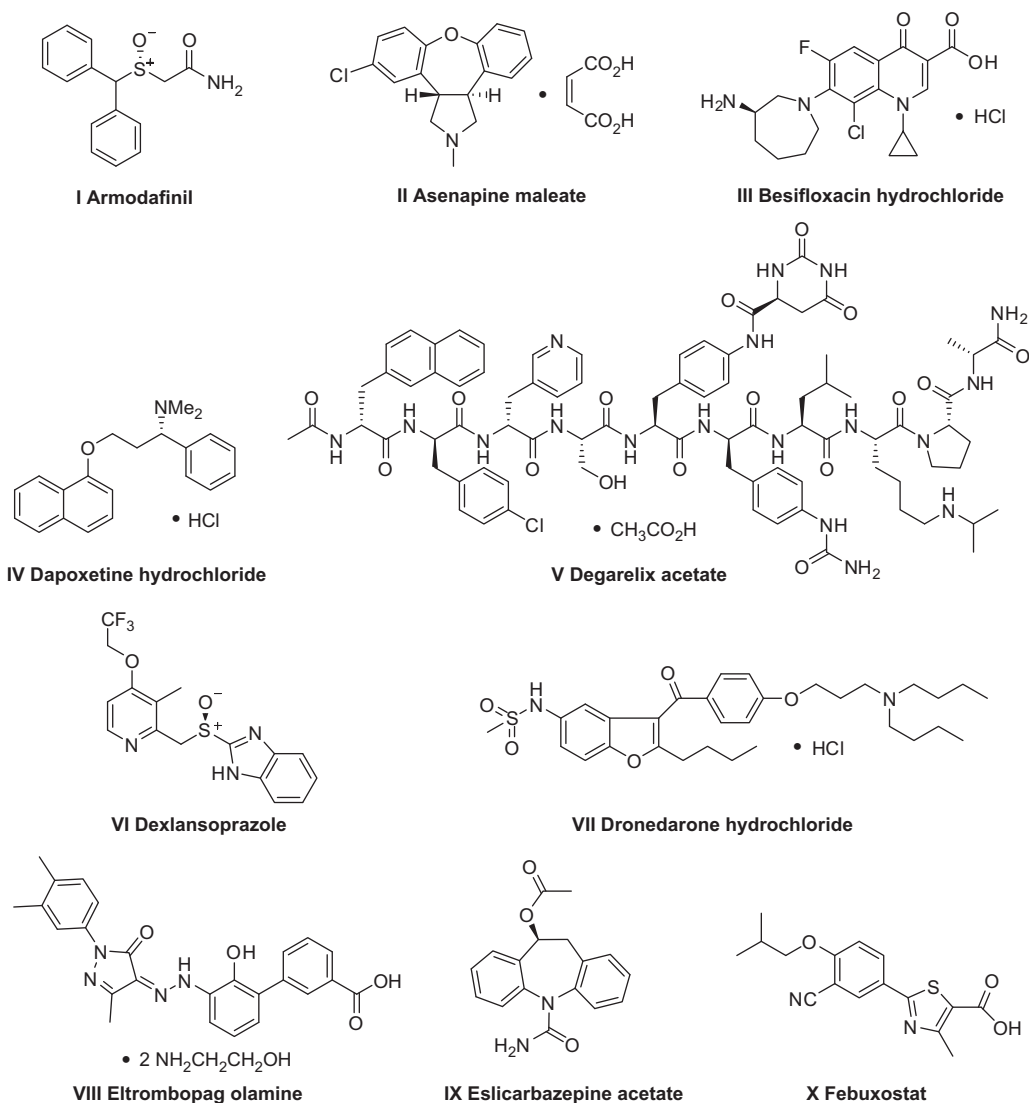
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1. Introduction

'The most fruitful basis for the discovery of a new drug is to start with an old drug.'—Sir James Whyte Black, winner of the 1988 Nobel Prize in physiology and medicine.¹

Inaugurated eight 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.^{2–8} 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 facilitate drug design. In 2009, 51 new products including new chemical entities, biological drugs, and diagnostic agents reached the market,⁹ the largest number in the last decade. Twelve additional products were approved for the first time in 2009; however, they were not launched before year's end and thus the syntheses of those drugs will be covered in 2010s review. This review focuses on the syntheses of



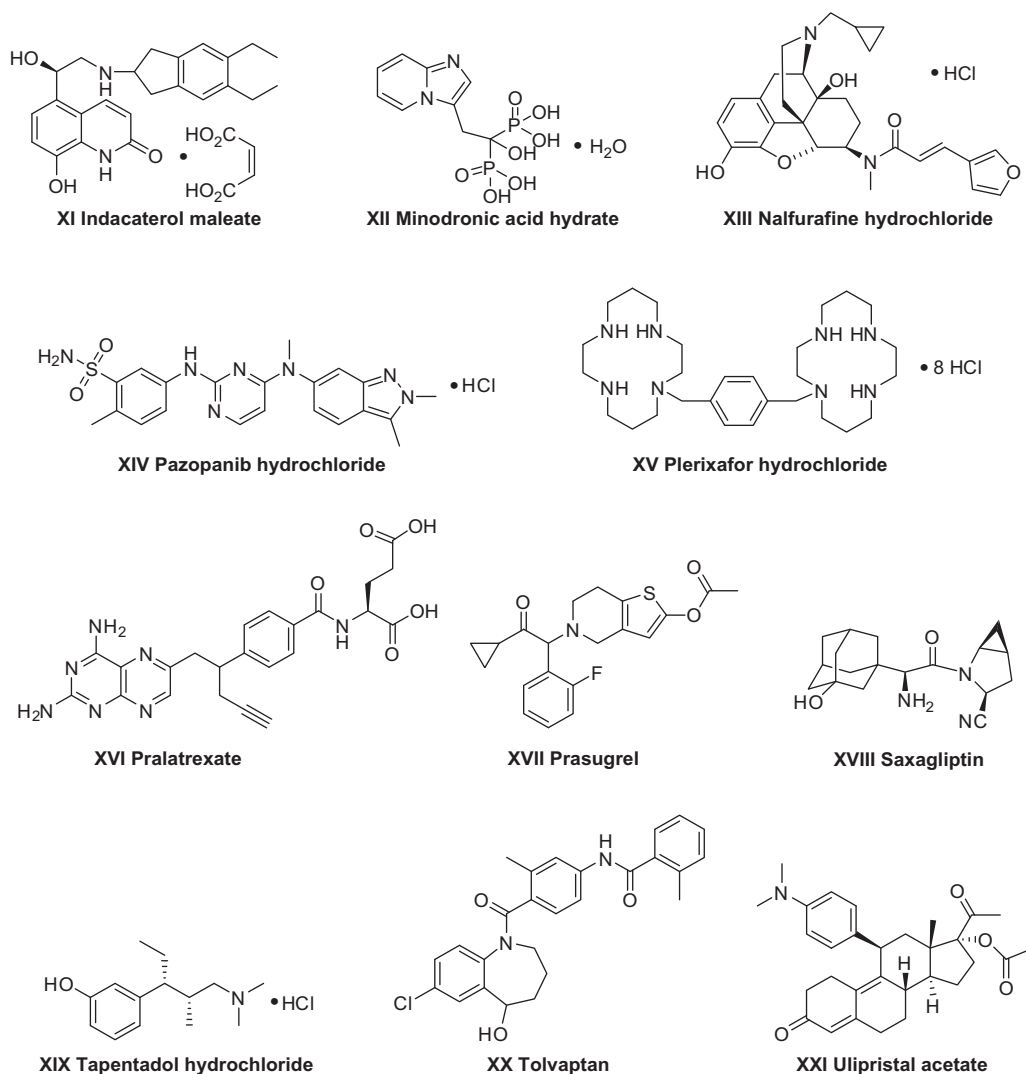
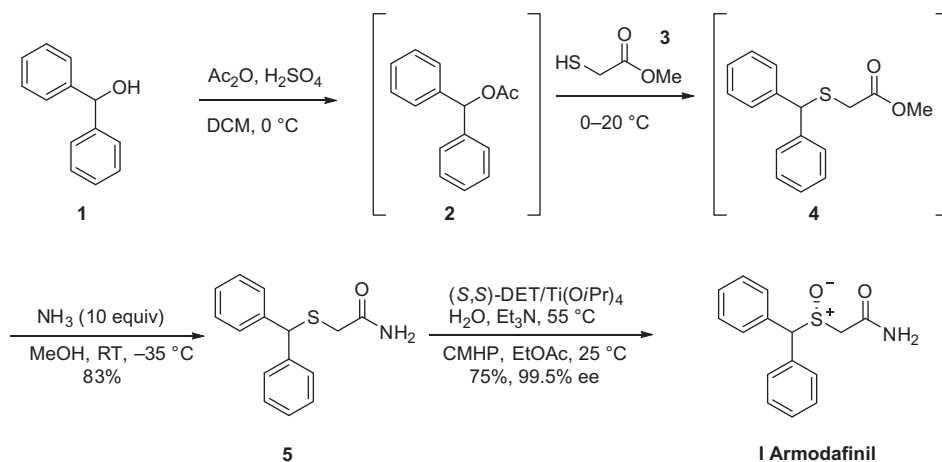


Fig. 1 (continued)

21 new drugs marketed in 2009 (Fig. 1) and excludes new indications for known drugs, new combinations, new formulations and drugs synthesized via bio-processes or peptide synthesizers. The synthetic routes cited herein represent the most scalable methods reported and appear in alphabetical order by generic name.

2. Armodafinil (Nuvigil®)

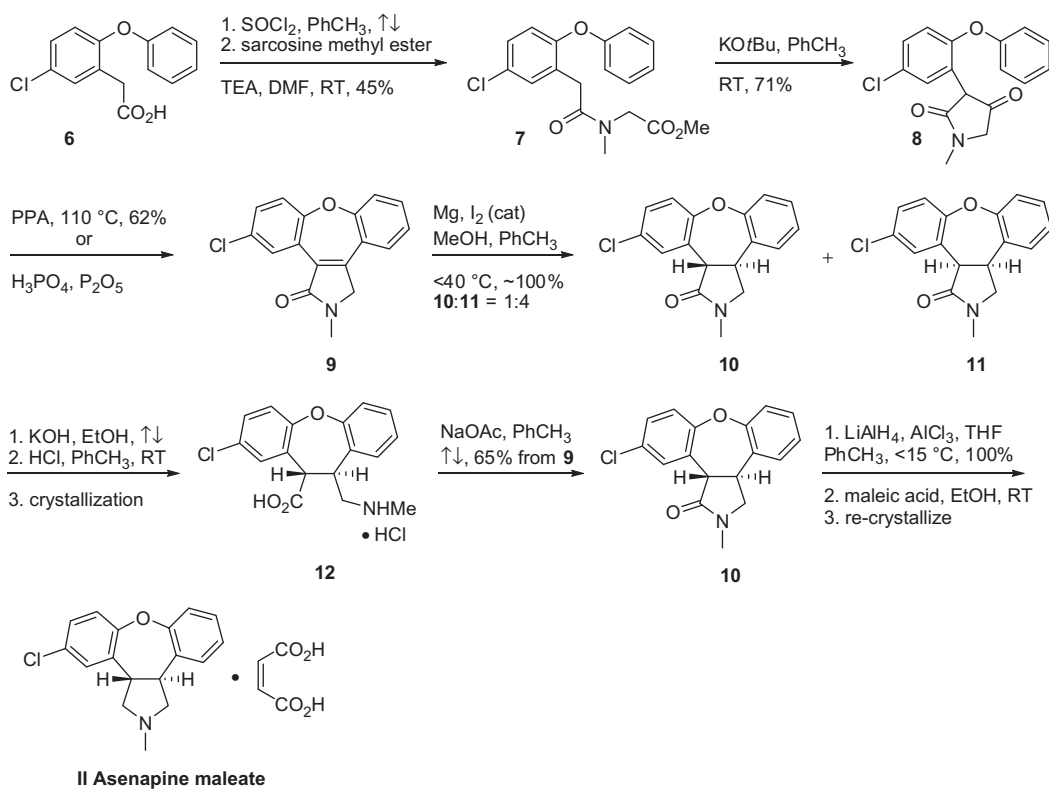
Armodafinil, the *R*-enantiomer of the racemic marketed drug modafinil, was approved in June 2007 for treatment of excessive sleepiness associated with shift work sleep disorder, narcolepsy



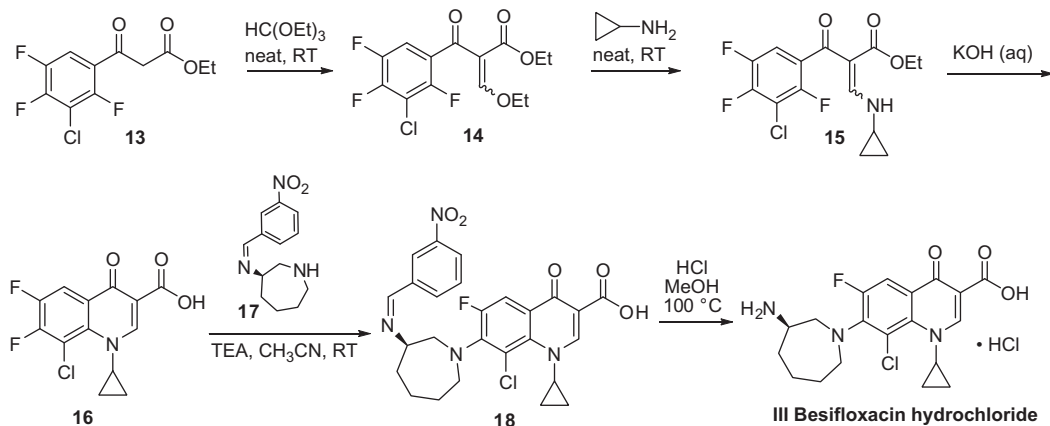
Scheme 1. Synthesis of armodafinil (I).

and obstructive sleep apnea/hypoapnea syndrome (OSAHS).⁹ The marketing of this drug was started in June 2009 by Cephalon, who discovered and developed the drug. In comparison to modafinil, armodafinil has a long half-life due to its slower metabolism and excretion, resulting in greater exposure of the drug and consequently a longer duration of action.¹⁰ Since the drug is the enantiomerically pure form of an existing racemic drug, multiple synthetic approaches to the enantiopure drug were utilized to progress the compound.¹¹ To facilitate preparation of the enantiopure drug for Phase 1 studies, a continuous chiral separation method was developed on large scale.¹² However, due to the cost of this process, this route was abandoned in favor of a crystallization method.¹³ While exploring crystallization of various intermediates of the racemic sulfoxide, it was discovered that the acid intermediate formed a eutectic mixture. Seeding of this mixture with the desired *R*-enantiomer provided the pure, desired enantiomer via an auto-seeded programmed polythermal preferential crystallization (AS3PC) method.¹⁴ Again, however, this route was deemed unsuitable for industrial scale because the *S*-enantiomer was still discarded in the process. Thus, an alternate catalytic oxidation method, based on initial work from Kagan and co-workers¹⁵ was developed and utilized in the industrial process.¹⁶ The resulting synthesis is a four-step sequence that requires only two isolations and delivers the final target in high chemical and chiral purity (Scheme 1). Benzhydrol (**1**) was added to a mixture of acetic anhydride and catalytic sulfuric acid in DCM at 0 °C to give acetate **2**. Crude **2** was reacted with methyl thioglycolate (**3**) and the reaction mixture was warmed to 20 °C to provide ester **4**, carried on to the next step without isolation. Ester **4** was then subjected to three volumes of ammonia in methanol at room temperature (rt) and warmed to 35 °C. Upon completion

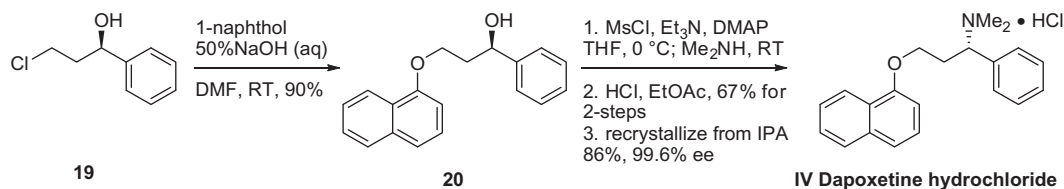
mer provided the pure, desired enantiomer via an auto-seeded programmed polythermal preferential crystallization (AS3PC) method.¹⁴ Again, however, this route was deemed unsuitable for industrial scale because the *S*-enantiomer was still discarded in the process. Thus, an alternate catalytic oxidation method, based on initial work from Kagan and co-workers¹⁵ was developed and utilized in the industrial process.¹⁶ The resulting synthesis is a four-step sequence that requires only two isolations and delivers the final target in high chemical and chiral purity (Scheme 1). Benzhydrol (**1**) was added to a mixture of acetic anhydride and catalytic sulfuric acid in DCM at 0 °C to give acetate **2**. Crude **2** was reacted with methyl thioglycolate (**3**) and the reaction mixture was warmed to 20 °C to provide ester **4**, carried on to the next step without isolation. Ester **4** was then subjected to three volumes of ammonia in methanol at room temperature (rt) and warmed to 35 °C. Upon completion



Scheme 2. Synthesis of asenapine maleate (II).



Scheme 3. Synthesis of besifloxacin hydrochloride (III).



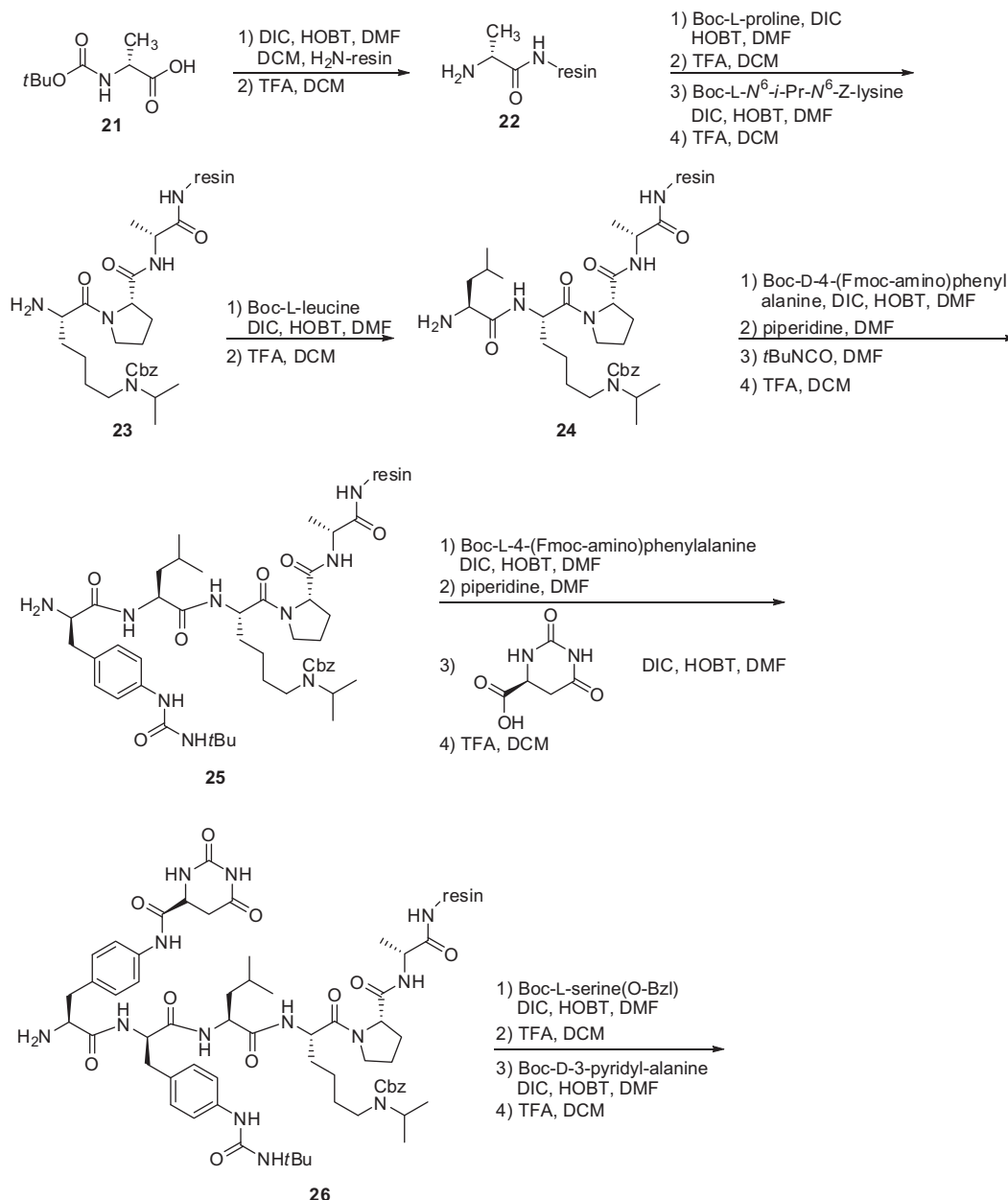
Scheme 4. Synthesis of dapoxetine hydrochloride (IV).

of the reaction, the mixture was cooled to 25 °C and water was added to precipitate the desired amide **5**, obtained by filtration in 83% yield. Amide **5** was then poised for the aforementioned asymmetric oxidation step, and thus dissolved in ethyl acetate and treated with (*S,S*)-(–)-diethyl tartrate, titanium(IV) isopropoxide, and water and stirred at 55 °C for 50 min. The mixture was then cooled to room temperature (25 °C) and triethylamine and cumene hydroperoxide (CMHP) were added. The reaction mixture was stirred for 1 h and

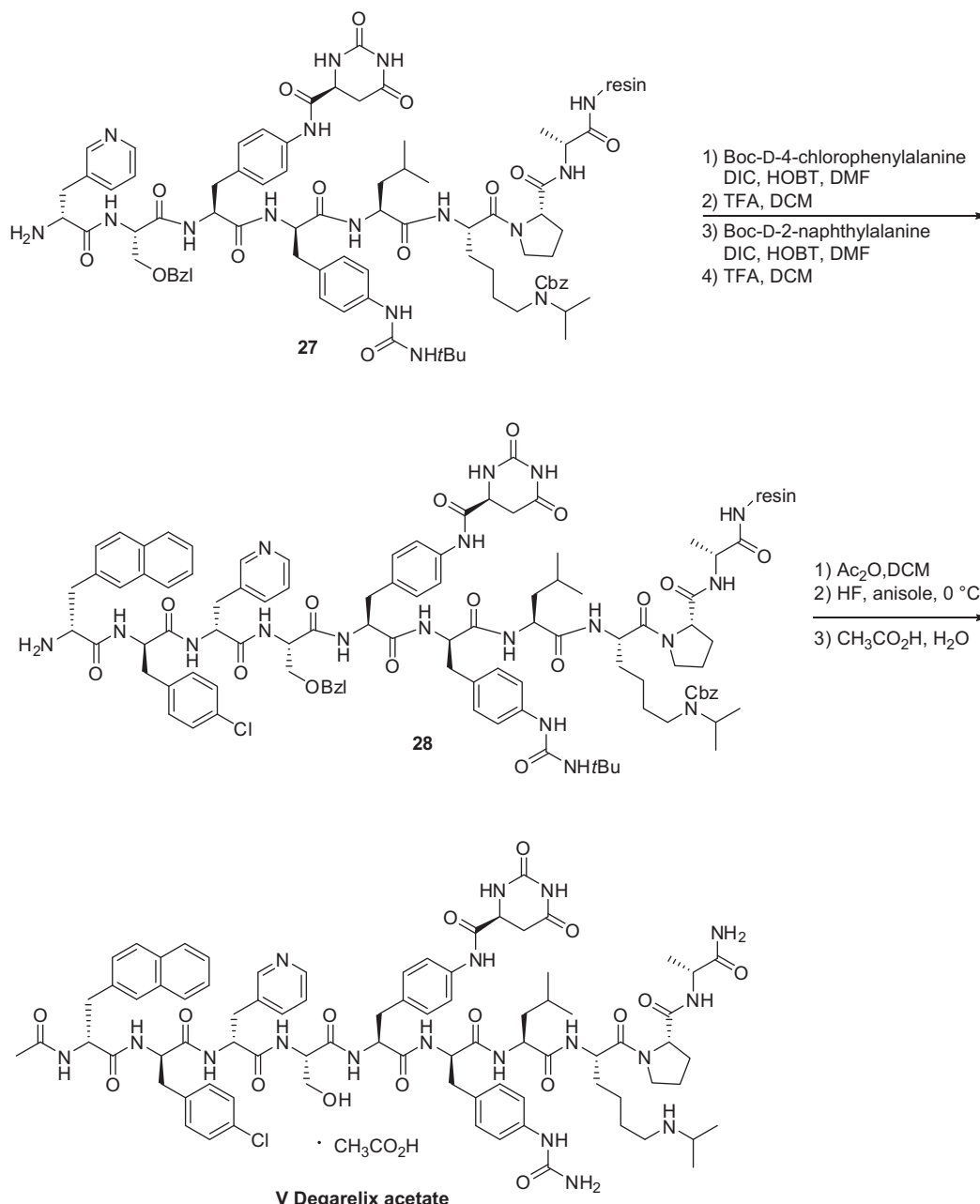
the resulting product precipitated and collected by filtration to provide the armodafinil (**I**) in 75% yield with 99.5% ee.

3. Asenapine maleate (Saphris®)

Asenapine is an atypical antipsychotic approved in the U.S. for acute treatment of schizophrenia in adults and the acute treatment of mania or mixed episodes associated with bipolar I disorder in



Scheme 5. Synthesis of degarelix acetate (V).



Scheme 5 (continued)

adults. Although asenapine potently antagonizes a wide variety of serotonin and dopamine receptors, its pharmacological activity is attributed to its antagonism of the 5-HT_{2A} and D1/D2 receptors.¹⁷ Asenapine was discovered and developed by Organon and later co-developed in collaboration with Pfizer. In 2006, however, Pfizer discontinued co-development of asenapine and in 2007 Organon was acquired by Schering-Plough who completed the development. The drug is now marketed by Merck & Co. after their acquisition of Schering-Plough in 2009. Several synthetic routes for the preparation of asenapine have been disclosed,^{18,19} and the largest reported process scale route is described in Scheme 2.^{20–23} 5-Chloro-2-phenoxyphenylacetic acid (**6**) was treated with thionyl chloride to generate the corresponding acid chloride that was subsequently treated with sarcosine methyl ester to give amide **7** in 45% overall yield. Treatment of compound **7** with potassium *tert*-butoxide in toluene effected a Dieckmann-like

condensation to provide oxo-lactam **8** in 71% yield. An intramolecular Friedel–Crafts alkylation-dehydration sequence was then performed by subjecting **8** to polyphosphoric acid, affording unsaturated lactam **9** in 62% yield. Alternatively, reacting **8** with phosphoric acid and phosphorous pentoxide would also deliver **9**. Reduction of **9** with magnesium in methanol and catalytic iodine gave a 1:4 mixture of the desired *trans*-lactam **10** to the undesired *cis*-lactam isomer **11** in quantitative conversion. In the initial route, **10** was separated from **11** via column chromatography and **11** could be epimerized to **10** upon treatment with DBU. After two recycling steps, compound **10** was prepared in 32% yield. However, a higher-yielding route that avoided the epimerization of **11** and column chromatography was later developed. The mixture of lactams (**10** and **11**) were treated with KOH in refluxing ethanol to affect lactam ring-opening. These basic conditions facilitated concomitant epimerization of the corresponding *cis*-amino acid

product to the *trans*-amino acid **12**, which upon treatment with sodium acetate in refluxing toluene regenerated *trans*-lactam **10** as a single isomer in 65% yield from **9**. Reduction of **10** with lithium aluminum hydride followed by maleic acid co-crystallization provided asenapine maleate (**II**) in 70% yield.

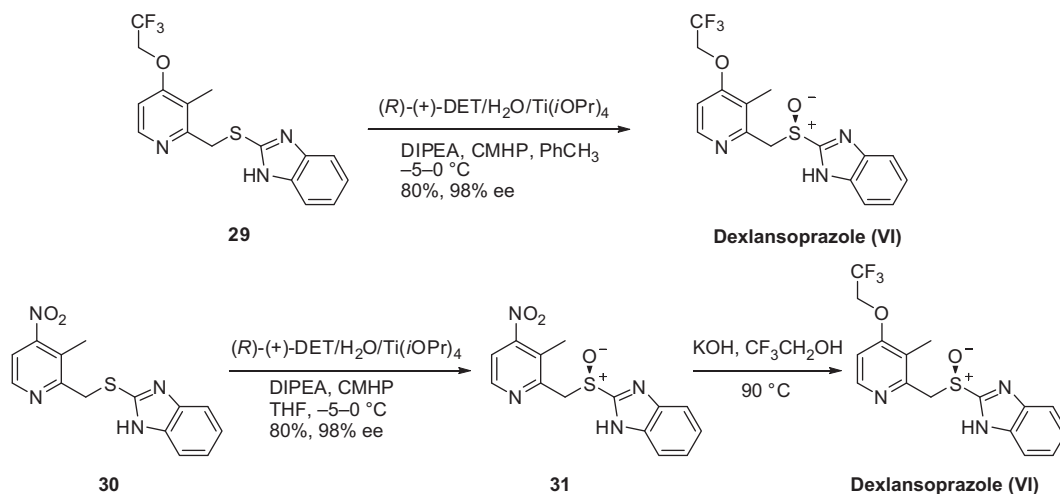
4. Besifloxacin hydrochloride (Besivance®)

Besifloxacin is a fourth-generation fluoroquinolone antibiotic which is marketed as besifloxacin hydrochloride. It was originally developed by the Japanese firm SSP Co. Ltd and designated SS734. SSP then licensed U.S. and European rights of SS734 for ophthalmic use to InSite Vision, Inc., in 2000, who then developed an eye drop formulation (ISV-403) and conducted preliminary clinical trials before selling the product and all rights to Bausch & Lomb in 2003. The eye drop was approved by the United States Food and Drug Administration (FDA) on May 29, 2009 and marketed under the trade name Besivance.^{24a} Besifloxacin has been found to inhibit production of pro-inflammatory cytokines in vitro. The synthesis of besifloxacin commences with commercially available ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoate (**13**, Scheme

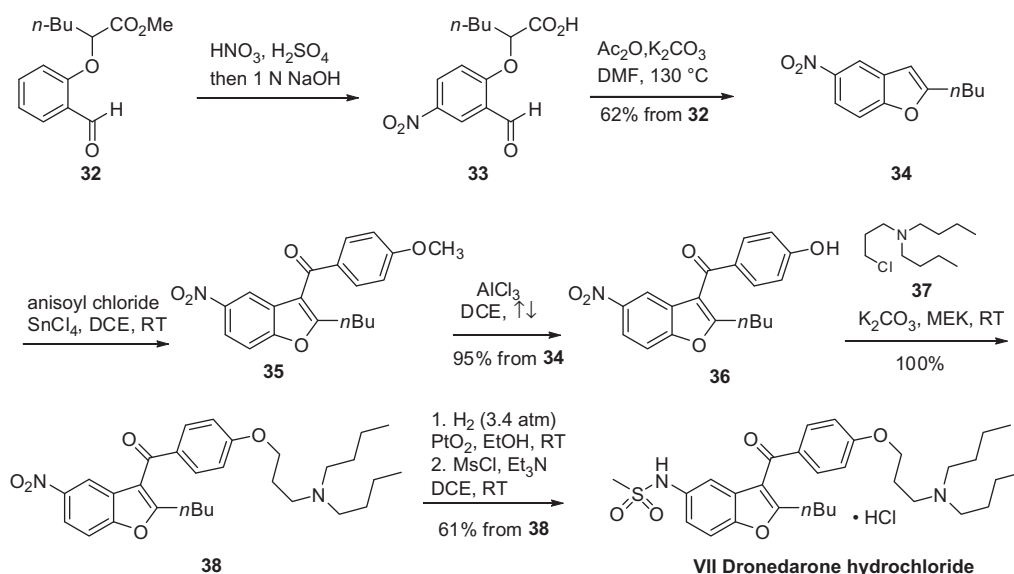
3).^{24b} Condensation of this ketoester with triethyl orthoformate resulted in a mixture of vinylogous esters **14**. Substitution with cyclopropanamine converts **14** to the vinylogous amide **15** as an unreported distribution of *cis*- and *trans*-isomers. This mixture was treated with base at elevated temperature to give **16**. Presumably, the *trans*-isomer isomerizes to the *cis*-isomer, which subsequently undergoes an intramolecular nucleophilic aromatic substitution with concomitant saponification to construct quinolone acid **16**. Quinolone **16** is then subjected to another nucleophilic substitution involving readily available iminoazepine **17** and the displacement reaction proceeds regioselectively to furnish the atomic framework of besifloxacin (**18**). Acidic methanolysis of **18** at elevated temperature gave besifloxacin (**III**).

5. Dapoxetine hydrochloride (Priligy®)

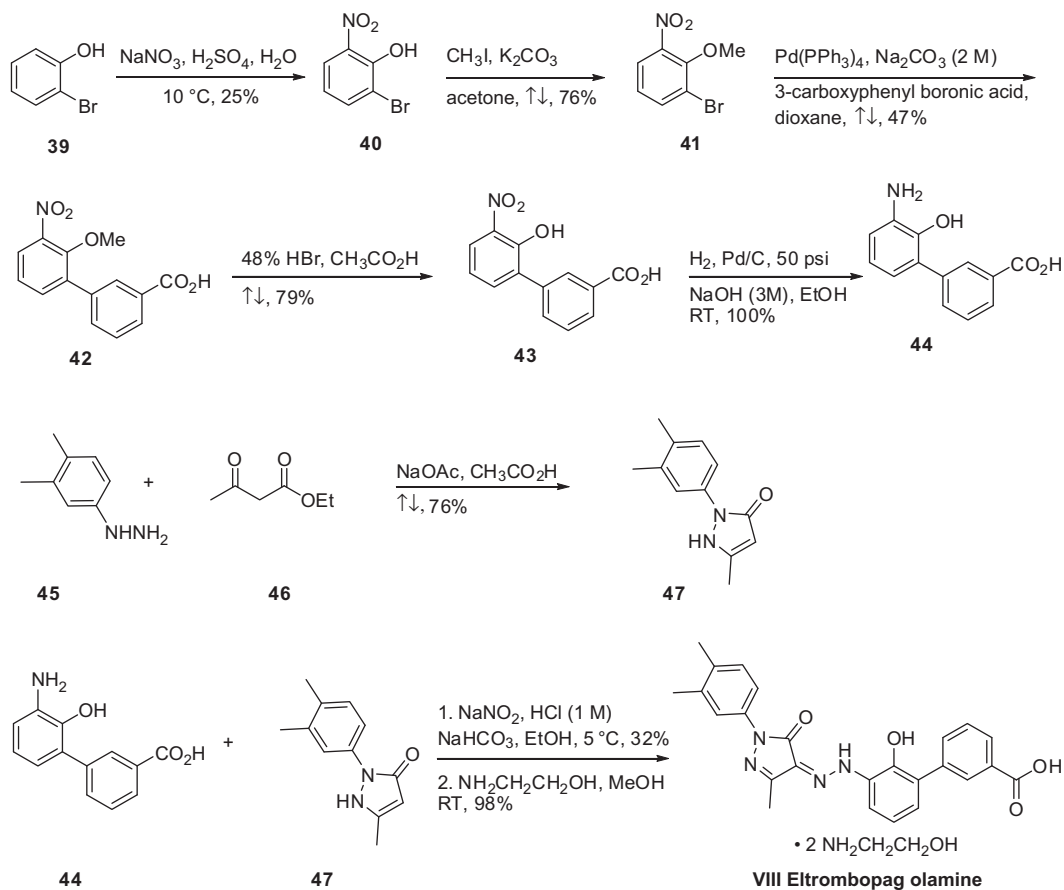
Dapoxetine is a selective serotonin re-uptake inhibitor (SSRI) which has been approved in Finland and Sweden for the treatment of premature ejaculation.²⁵ Dapoxetine was discovered and developed by Lilly and was licensed to Alza, a wholly-owned subsidiary of Johnson & Johnson. Several synthetic routes for the preparation



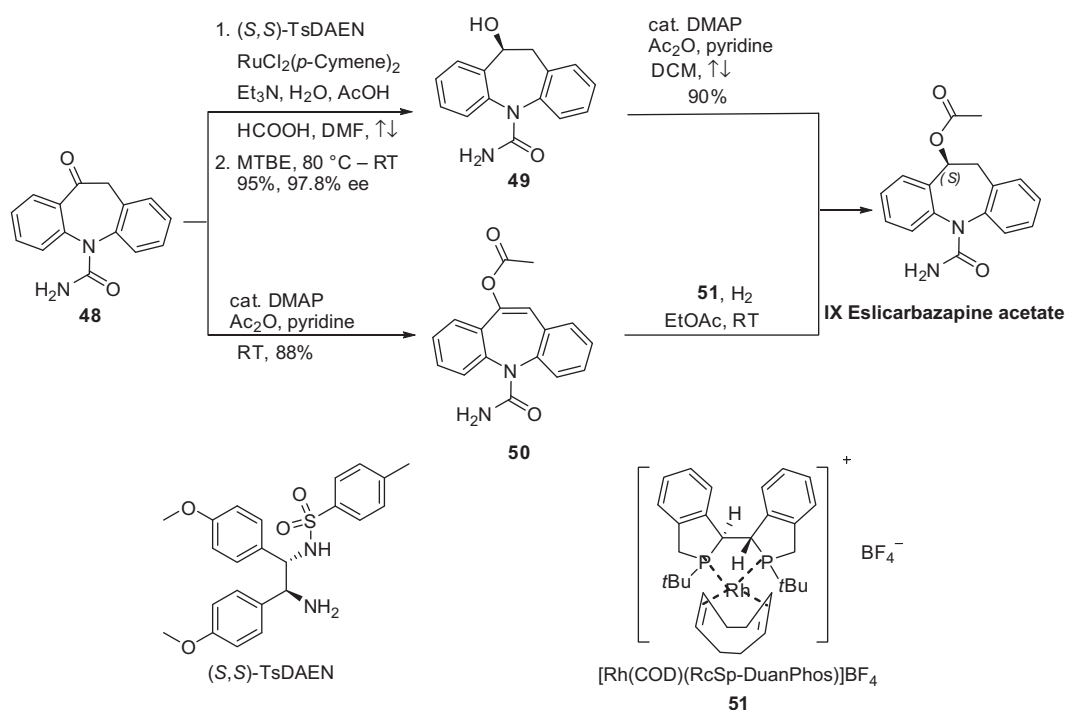
Scheme 6. Synthesis of dextansoprazole (VI).



Scheme 7. Synthesis of dronedarone hydrochloride (VII).



Scheme 8. Synthesis of eltrombopag olamine (VIII).



Scheme 9. Synthesis of eslicarbazepine acetate (IX).

of dapoxetine have been disclosed, all on gram scale.²⁶ Based on the routes and yields, the most likely process route is described in Scheme 4.²⁷ Commercially available (*R*)-(+)-3-chloro-1-phenyl-1-propanol (**19**) was reacted with 1-naphthol in the presence of 50% aqueous sodium hydroxide in DMF to give ether **20** in 90% yield. Activation of the secondary alcohol was accomplished through treatment of **20** with methane sulfonyl chloride and triethylamine with catalytic DMAP. Upon complete conversion to the corresponding mesylate, dimethylamine was added to the reaction mixture. The addition of hydrochloric acid in ethyl acetate to the resultant crude product gave dapoxetine hydrochloride (**IV**) in 67% yield. Purification of this material by re-crystallization from isopropanol provided **IV** in 86% yield and in 99.6% ee.

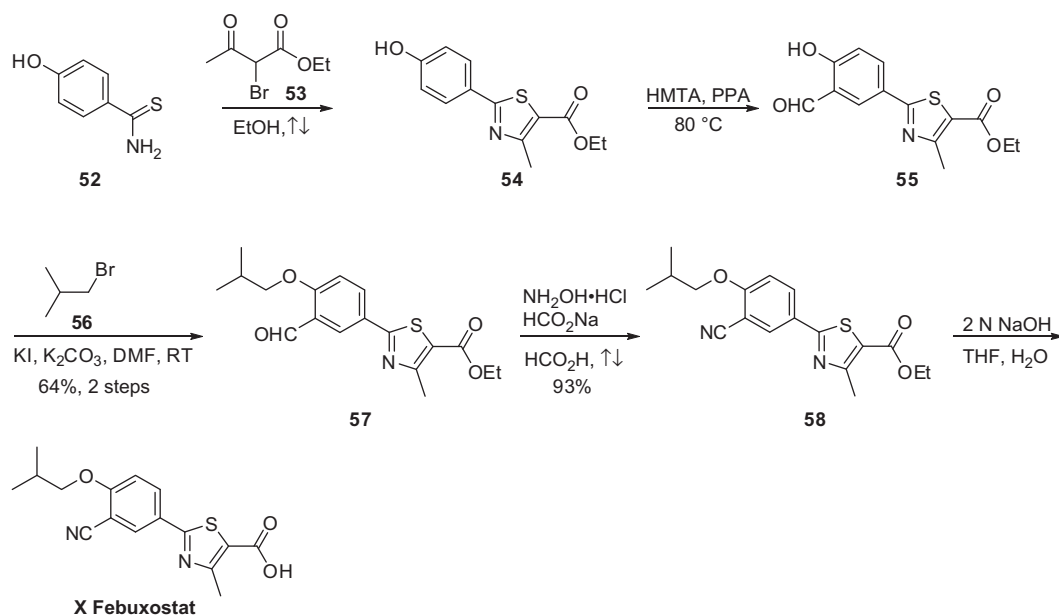
6. Degarelix acetate (Firmagon®)

Ferring launched degarelix acetate, a gonadotrophin-releasing hormone (GnRH) antagonist, in 2009 in the U.S. for the treatment of prostate cancer.²⁸ The compound has been approved by the E.U. for the same indication, and in the same year it was launched in the UK and Germany. Degarelix has been developed as a one-month or three-month sustained-release injectable formulation. Compared to other GnRH antagonists, degarelix displays improved aqueous solubility, longer acting effects and weaker histamine-releasing properties. The synthesis of degarelix acetate employed iterative peptide coupling and protection/de-protection sequences in high yields (85–99%), and this sequence is described in Scheme 5.^{29,30} Boc-D-alanine (**21**) was immobilized via MBHA resin (Bachem) by reaction with diisopropyl carbodiimide (DIC) and 1-hydroxybenzotriazole (HOBT). The resulting product was treated with trifluoroacetic acid (TFA) to remove the *N*-Boc protecting group to reveal amine **22**. The N-terminus of **22** was then subjected to sequential coupling and de-protection cycles with the following protected amino acids: *N*-Boc-L-proline, *N*- α -Boc-*N*⁶-isopropyl-*N*⁶-carbobenzoxy-L-lysine and *N*-Boc-L-leucine to give **23** and **24**, respectively. The N-terminus of **24** was coupled with *N*- α -Boc-D-4-(Fmoc-amino)phenylalanine, followed by removal of the Fmoc group with piperidine in DMF to give the corresponding free aniline. The free aniline resin was then reacted with *t*-butyl isocyanate to generate the corresponding *t*-butyl urea

followed by reaction with TFA to remove the Boc group to give the *t*-butyl urea amine **25**. The N-terminus of **25** was coupled with *N*- α -Boc-L-4-(Fmoc-amino)phenylalanine, followed by removal of the Fmoc group with piperidine in DMF to generate the corresponding free aniline. The free aniline was reacted with L-hydroxyrotic acid, followed by reaction with TFA to liberate amine **26**. Amine **26** was then coupled with *O*-benzylated-*N*-Boc-serine, followed by removal of the Boc group with TFA and reacting the resulting amine with *N*- α -Boc-D-(3-pyridyl)alanine and subsequent removal of the Boc group with TFA gave amine **27**. Amine **27** was coupled with *N*-Boc-D-(4-chlorophenyl)alanine, followed by removal of the Boc group with TFA, and the resulting amine was then coupled with *N*-Boc-D-(2-naphthyl)alanine, followed by removal of its Boc group with TFA to give **28**. Acylation of **28** with acetic anhydride followed by sequential treatment with HF and TFA resulted in cleavage from the resin, removal of the *O*-benzyl group, and conversion of the *t*-butyl urea to the corresponding NH₂-urea, resulting in free degarelix. Finally, treatment with acetic acid provided degarelix acetate (**V**).

7. Dexlansoprazole (Dexilant®)

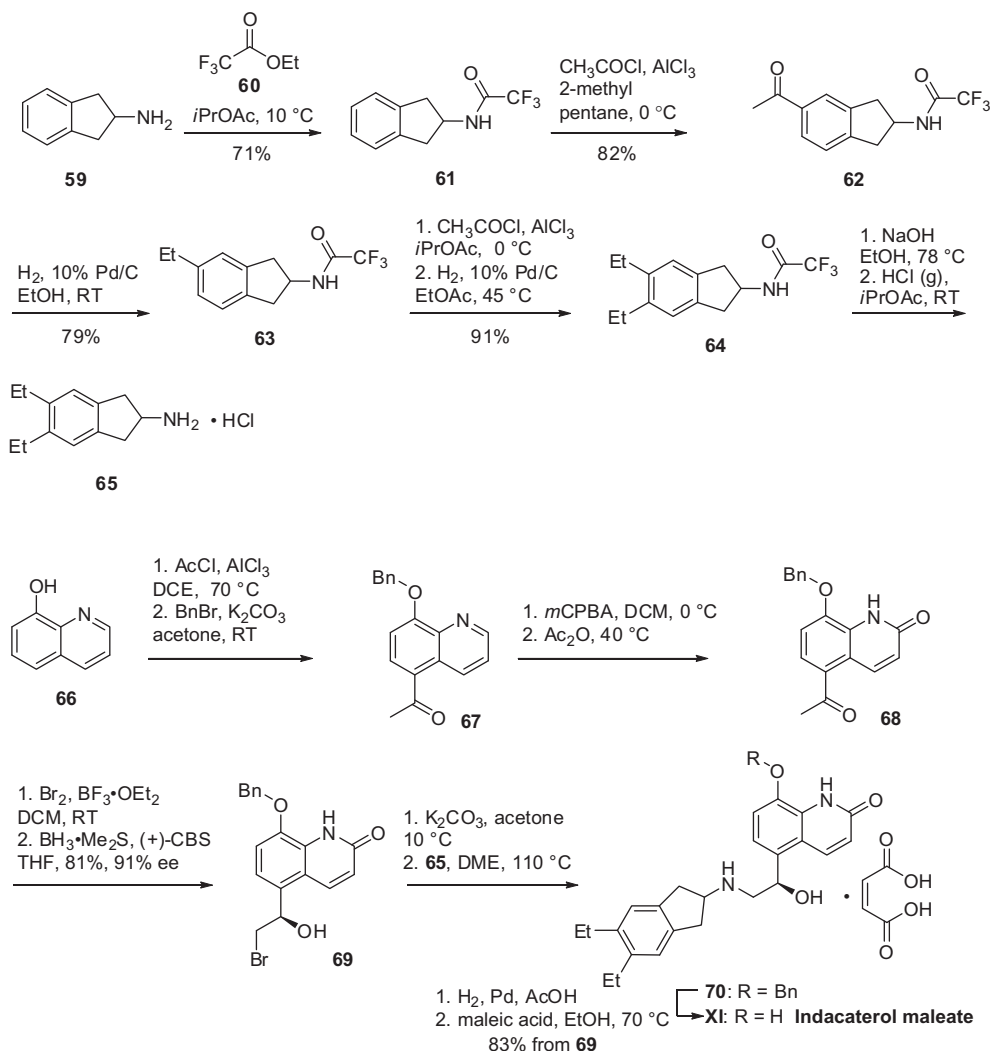
Takeda Pharmaceuticals received approval of dexlansoprazole, a dual release formulation of the (*R*)-isomer of lansoprazol proton pump inhibitor (PPI) already in the market, from the FDA in January 2009.⁹ Dexlansoprazole is a delayed release capsule for the once-daily, oral treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD), the healing of erosive esophagitis (EE) and the maintenance of healed EE.^{31,32} The dual release formulation is designed to provide two separate releases of medication, one at 1–2 h and then another at 4–5 h after treatment, for extended efficacy in the treatment of GERD.³³ Similar to the synthesis of the chiral sulfoxide of armodafinil vide supra, the preparation of the chiral sulfoxide of lansoprazole utilized the catalytic oxidation method developed by Kagan and co-workers (Scheme 6).¹⁵ Two routes have been reported that describe the preparation of dexlansoprazole on large scale. The first route developed by Takeda reacts commercially available thioether **29**, also used to make lansoprazole, under the Kagan asymmetric oxidation conditions³⁴ and the alternative route utilizes the cheaper



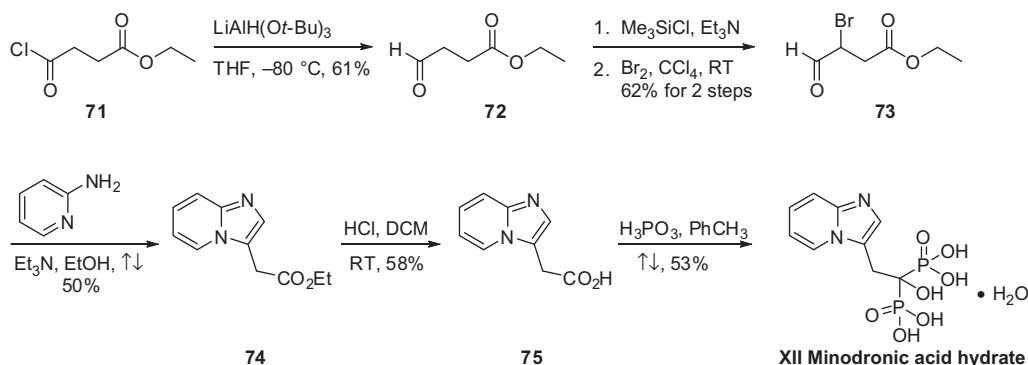
Scheme 10. Synthesis of febuxostat (X).

commercial intermediate nitrosulfide **30** in the analogous asymmetric oxidation by Kagan (Scheme 6).³⁵ Thus, the catalyst complex consisting of (+)-DET, Ti(OiPr)₄ and water was formed in the presence of thioether **29** in toluene at 30–40 °C. The reaction mixture was then cooled to –5 °C and DIPEA and cumene hydroperoxide (CMHP) were added to give, after aqueous work-up and in situ crys-

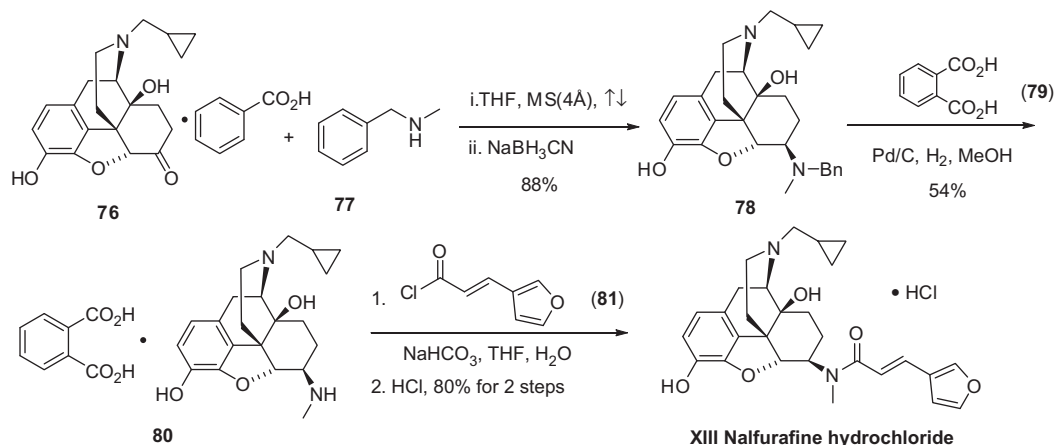
tallization from the organic layer, dexlansoprazole (**VI**) in 98% ee. No yield was given in the patent. An alternate, but similar, sequence was also described wherein the nitrosulfide intermediate **30** was subjected to similar oxidative conditions that gave intermediate nitro compound **31** in 80% yield and 98% ee. Compound **31** was treated with KOH and trifluoroethanol to provide dexlansoprazole (**VI**).



Scheme 11. Synthesis of indacaterol maleate (**XI**).



Scheme 12. Synthesis of minodronic acid hydrate (**XII**).



Scheme 13. Synthesis of nalfurafine hydrochloride (XIII).

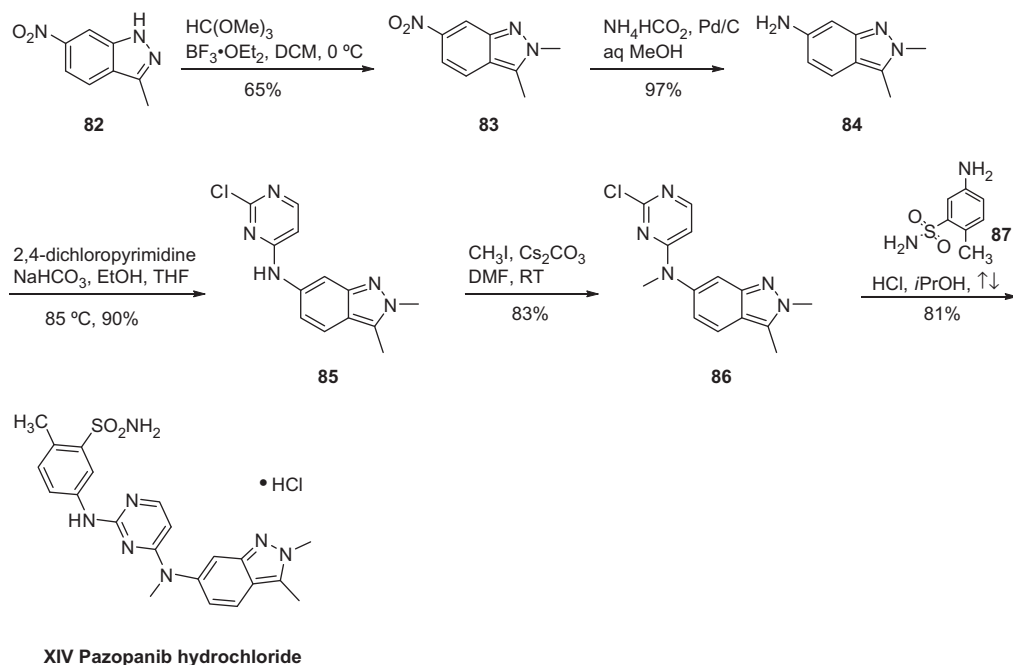
8. Dronedarone hydrochloride (Multaq®)

Dronedarone hydrochloride (also known as SR33589 and marketed as Multaq) is a drug developed by Sanofi-Aventis for cardiac arrhythmias (irregular heartbeat) that was approved by the FDA in July 2009. Dronedarone is used for the treatment of atrial fibrillation and atrial flutter in patients whose hearts have either returned to normal rhythm or who undergo drug therapy or electroshock treatment to maintain normal cardio rhythm. Dronedarone is less lipophilic than amiodarone, exhibits a much smaller volume of distribution and a half-life of 24 h, this stands in contrast to competitor amiodarone's half-life of several weeks.³⁶ As a result of these pharmacokinetic characteristics, dronedarone dosing may be less complicated than amiodarone. The synthesis of dronedarone relies on the preparation of the benzofuran core 34, of which three main routes have been reported, but two possess obvious overlap and are considered more process-amenable.³⁷ Starting from methyl 2-(2-formylphenoxy)hexanoate (32), this

aldehyde can either be nitrated, then saponified or saponified and then nitrated to procure nitroacid 33 (Scheme 7). The benzofuran ring is then secured through the use of acetic anhydride and base in the presence of DMF at elevated temperature. The key benzofuran 34 can be produced by either route in 62% yield on gram-scale by this method. Friedel–Crafts acylation involving anisoyl chloride and tin tetrachloride constructed the diaryl ketone 35. Cleavage of the methyl ether through the use of aluminum trichloride in refluxing DCE provided phenol 36. Alkylation of phenol 36 with aminoalkyl chloride 37 gave ether 38. Subsequent reduction of the nitro group via catalytic hydrogenation and sulfonylation of the resulting amine provided dronedarone (VII) which was isolated as its HCl salt.³⁸

9. Eltrombopag olamine (Promacta®)

Eltrombopag olamine, a thrombopoietin receptor (TpoR) agonist, was approved in late 2008 for the once-daily, oral short-term



Scheme 14. Synthesis of pazopanib hydrochloride (XIV).

and long-term treatment of adult patients with previously treated chronic idiopathic thrombocytopenic purpura (ITP). It is the first small-molecule TpoR agonist and was launched in the U.S. for this indication in 2009 by GlaxoSmithKline (GSK). Because eltrombopag is a small molecule, the drug is administered orally and has a reduced potential for causing an immune system reaction versus alternative protein-based therapies.³⁹ In 2010, eltrombopag was approved in Europe for the long-term treatment of adult patients with previously treated chronic ITP. The synthesis began with the nitration of 2-bromophenol (**39**) with sodium nitrate and sulfuric acid in water at 10 °C to give 2-bromo-6-nitrophenol (**40**) in 25% yield, which was methylated using methyl iodide and potassium carbonate in refluxing acetone providing 2-bromo-6-nitroanisole (**41**) in 76% yield (Scheme 8).⁴⁰ Suzuki coupling of compound **41** with 3-carboxyphenyl boronic acid with Pd(PPh₃)₄ and 2 M sodium carbonate in refluxing dioxane gave 2'-methoxy-3'-nitrobiphenyl-3-carboxylic acid (**42**) in 47% yield as a tan powder. Demethylation using 48% HBr (aq) in refluxing acetic acid resulted in a 79% yield of 2'-hydroxy-3'-nitrobiphenyl-3-carboxylic acid (**43**). The nitro group of compound **43** was reduced via catalytic hydrogenation at 50 psi at room temperature over Pd/C in mixed ethanol/3 M aq NaOH solution to give 3'-amino-2'-hydroxybiphenyl-3-carboxylic acid (**44**) in quantitative yield. The intermediate 1-(3,4-dimethylphenyl)-3-methyl-2,5-dihydro-1H-pyrazol-5-one (**47**) was prepared by condensing of 3,4-dimethylphenyl-hydrazine **45** with ethyl acetoacetate **46** with sodium acetate in refluxing acetic acid in 76% yield. Treatment of (**44**) with sodium nitrite in 1 M HCl at 5 °C, followed by condensation with 1-(3,4-dimethylphenyl)-3-methyl-2,5-dihydro-1H-pyrazol-5-one (**47**) at a constant pH of 7–8 via the addition of sodium bicarbonate and ethanol afforded eltrombopag in 32% yield. Finally, eltrombopag was treated with hydroxyl ethylamine to give eltrombopag olamine (**VIII**).

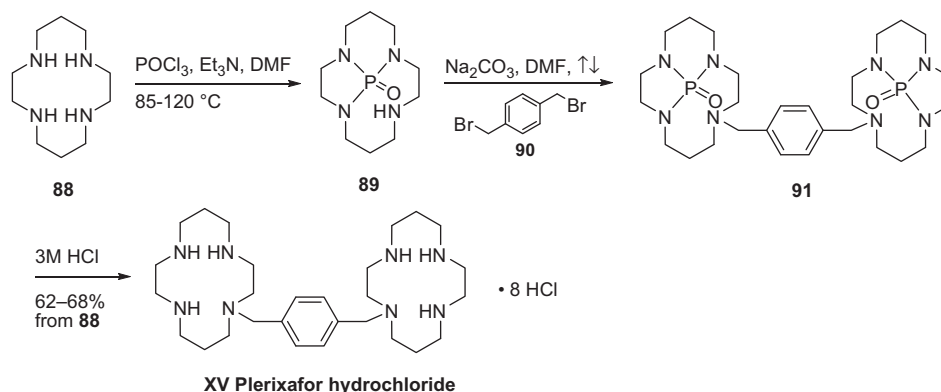
10. Eslicarbazepine acetate (Exelief®)

Eslicarbazepine acetate is a prodrug of eslicarbazepine (licarbazepine) which is a metabolite of oxcarbazepine. Eslicarbazepine acetate was recently approved in Europe for the treatment of adjunctive therapy for partial-onset of seizures, with or without secondary generalizations, in adults with epilepsy.⁹ The mechanism of its action is the inhibition of voltage gated sodium channels in the brain, making brain cells less prone to excitability.^{41,42} The drug was discovered and developed by Bial, a small privately held Portuguese pharmaceutical company, and is marketed in Europe by Eisai Pharmaceutical Co. A number of racemic syntheses have been reported that require separation using chiral auxiliaries along with several asymmetric

reduction methods starting with the commercially available (Bosche Scientific, LLC) oxcarbazepine **48**.^{43–45} Scheme 9 highlights two asymmetric approaches, asymmetric reduction of ketone **48** followed by esterification^{46,47} or asymmetric hydrogenation of vinyl acetate **50** to give the acetate directly.⁴⁸ Thus asymmetric reduction of oxcarbazepine **48** was accomplished using Ru(Cl₂)(*p*-cymene)₂ as the catalyst, (S,S)-TsDAEN with formic acid as the stoichiometric reductant in a mixed solvent system at reflux followed by cooling to 80 °C. Addition of MTBE, followed by a slow cooling to room temperature afforded the crystals of alcohol **49**, which were collected by filtration and dried to obtain a 95% isolated yield in 97.8% ee. Several experiments were described in the patent varying (1) catalyst loading, (2) equivalents of formic acid, (3) pH of the reaction, (4) reaction time and (5) the use of a phase transfer catalyst. Employment of the phase transfer catalyst gave 90% yield and >99.9% ee of the product with less than 2 ppm residual ruthenium content. Alcohol **49** was then converted to eslicarbazepine acetate **IX** by reacting with acetic anhydride in the presence of DMAP and pyridine in refluxing dichloromethane. After aqueous work-up, the crude product was crystallized from isopropanol to give the desired product eslicarbazepine acetate (**IX**) in 90% yield with 99.96% purity with undetectable amount of *R* isomer. In the second approach,⁴⁸ the acetate intermediate **50** was formed first in 88% yield which was then reduced via catalytic hydrogenation in the presence of the preformed catalyst **51** to give eslicarbazepine acetate (**IX**) in ~94% ee. No yield was given for the formation of the product using this route.

11. Febuxostat (Uloric®)

Febuxostat was discovered by Teijin Pharmaceuticals and licensed to TAP Pharmaceuticals (which is currently part of Takeda Pharmaceuticals) and was approved in the U.S. for the treatment of hyperuricemia in patients with gout.⁹ It is a once-daily non-purine based agent with potent inhibitory activity against xanthine oxidase. The safety profile of the drug also does not require dose adjustment for patients with mild to moderate renal or hepatic impairment. Febuxostat is the first new agent cleared for this indication in 40 years.^{49,50} There are a number of routes available to prepare this agent as discussed in recent publications.^{51,52} The synthesis shown in Scheme 10 is a short and concise route and does not require the use of toxic reagents.⁵³ Thus the commercially available and easily prepared 4-hydroxythiobenzamide (**52**) was reacted with ethyl bromoacetoacetate (**53**) in refluxing ethanol to provide the thiazole ester **54** in ~60% yield after crystallization. The phenolic ester **54** was then treated with hexamethylenetetramine (HMTA) in polyphosphoric acid at 80 °C to provide the crude



Scheme 15. Synthesis of plerixafor hydrochloride (XV).

aldehyde **55** (74% conversion by HPLC). Reaction of phenol **55** and isobutyl bromide (**56**) in the presence of potassium carbonate with catalytic potassium iodide in DMF gave isobutyl ether **57** (64%, two steps). This ether was then converted in one pot to nitrile **58** in 93% by reacting the aldehyde with hydroxylamine hydrochloride and sodium formate in refluxing formic acid. Saponification of the ester **58** with aqueous sodium hydroxide provided fabuxostat (**X**).

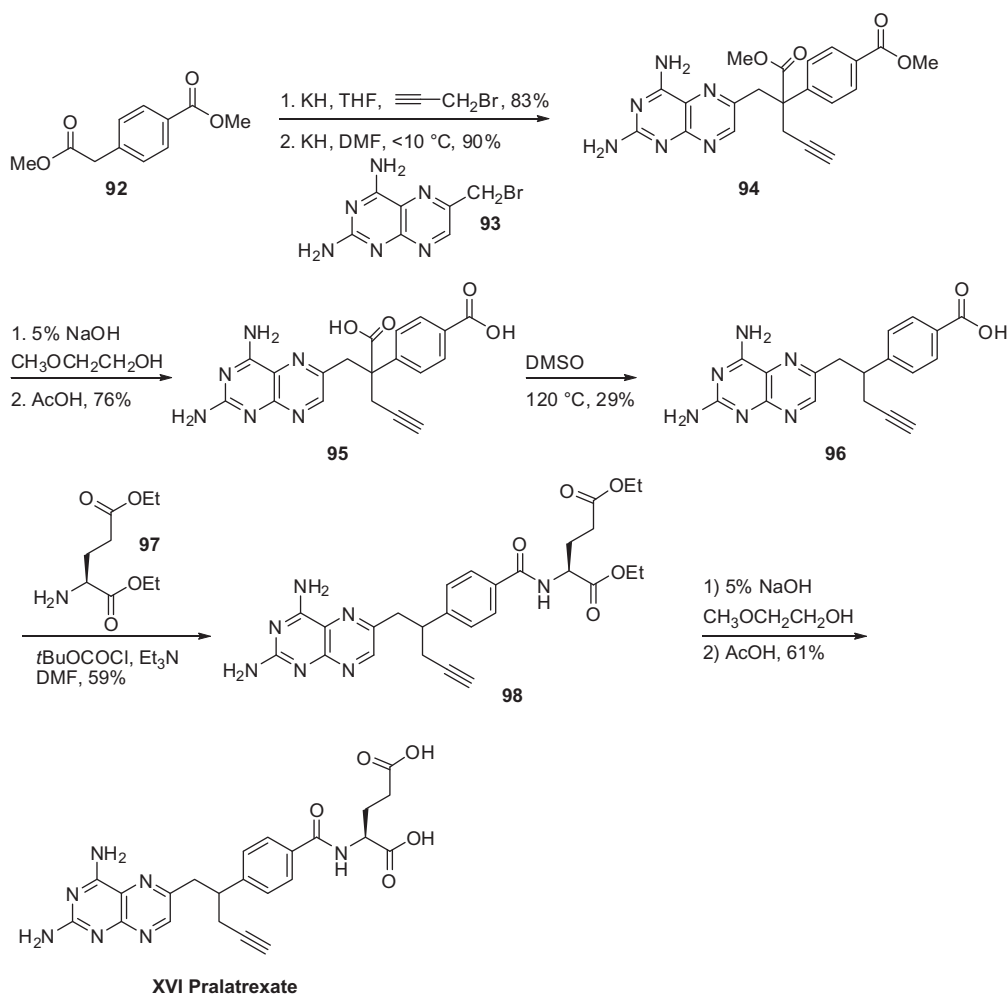
12. Indacaterol maleate (Onbrez®)

Indacaterol is a β -adrenoceptor agonist currently approved in Europe as Onbrez®, and is marketed by Novartis. It needs to be taken only once a day, unlike competitors formoterol and salmeterol. These drugs are used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma. Onbrez is administered via an aerosol formulation through a dry powder inhaler. A Phase III trial published in July 2010 suggested that indacaterol is significantly more effective than twice-daily formoterol in improving FEV₁ and reduces the need for rescue medication.⁵⁴ The synthesis of indacaterol relies on the union of the dihydroindeneamine region and the quinolinol region of the molecule. Preparation of the dihydroindene unit of indacaterol was reported by researchers at Novartis in 2006 and is summarized in Scheme 11.⁵⁵ 2,3-Dihydro-1*H*-inden-2-amine (**59**) was protected as its trifluoroacetamide **61** and was followed by Friedel–Crafts alkylation with acetylchloride to give **62**. Hydrogenative carbonyl reduction of this unsymmetrical dihydroindene provided amide **63**. An iterative

Friedel–Crafts acylation/hydrogenation sequence was used to install the second ethyl group, giving rise to trifluoroacetamide **64**. Basic hydrolysis to remove the trifluoroacetamide functionality, followed by salt formation by means of gaseous HCl furnished the dihydroindene amine **65**. The synthesis of the remaining portion of the molecule starts from 8-hydroxyquinoline (**66**). Friedel–Crafts alkylation with acetylchloride and trichloroaluminum installed the acetophenone functionality at the 5-position of the quinoline frame followed by benzyl protection of the hydroxyl group to give ether **67**. Oxidation of quinoline **67** with mCPBA and acylation of the resulting *N*-oxide with acetic anhydride and thermal rearrangement produced quinolone **68**. Bromination of the methyl ketone and subsequent asymmetric reduction provided (*R*)-alcohol **69**. Bromohydrin **69** was then converted to the epoxide using potassium carbonate prior to amination of the epoxide with dihydroindene intermediate **65** to furnish the indacaterol skeleton **70**. Hydrogenolytic debenzylation and maleate salt formation provided indacaterol maleate (**XI**).

13. Minodronic acid hydrate (Bonoteo® and Recalbon®)

The bone resorption inhibitor minodronic acid hydrate was approved and introduced last year in Japan, bringing the total number of bis-phosphonates marketed for this indication to seven. There are an estimated 10 million current and potential osteoporosis sufferers in Japan, a number that is expected to continue growing due to the country's aging population. Minodronic acid



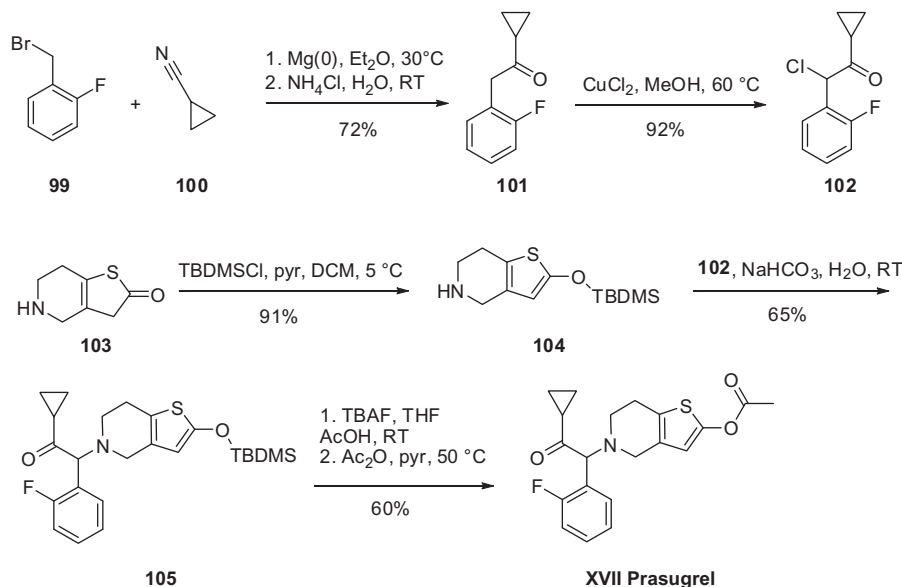
Scheme 16. Synthesis of pralatrexate (XVI).

is the first drug to show a significant effect in preventing bone fractures as compared to placebo in a Japanese patient population. Minodronic acid was co-developed by Astellas and Ono, who are marketing the drug as Bonoteo® and Recalbon®, respectively.⁹ Several syntheses of minodronic acid have been reported,^{56–61} a scalable preparation is described in Scheme 12.⁶¹ Commercially available acid chloride **71** was first reduced with lithium tritertbutoxy aluminum hydride to the aldehyde **72** at -80°C in 61% yield. Next, reaction of aldehyde **72** with TMSCl and triethylamine generated the corresponding silyl enol ether, which was then treated with bromine to give α -bromoaldehyde **73** in 62%

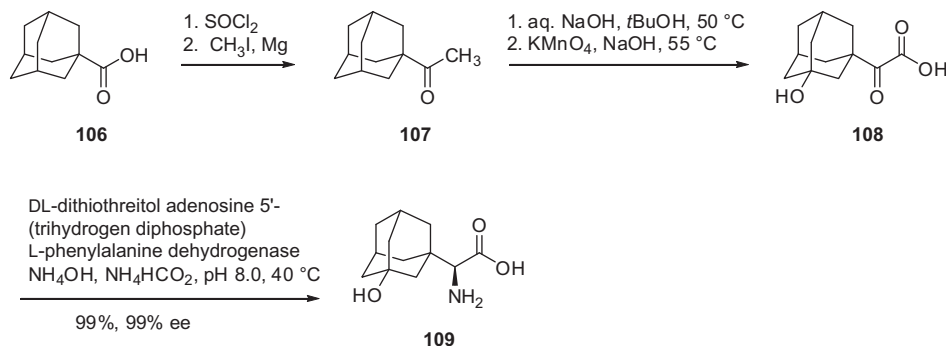
yield. Condensation with 2-amino pyridine furnished imidazopyridine **74**, which was hydrolyzed with HCl to acid **75** in 58% yield. Reaction with H_3PO_3 at 120°C to provide minodronic acid hydrate (**XII**) in 53% yield.

14. Nalfurafine hydrochloride (Remitch®)

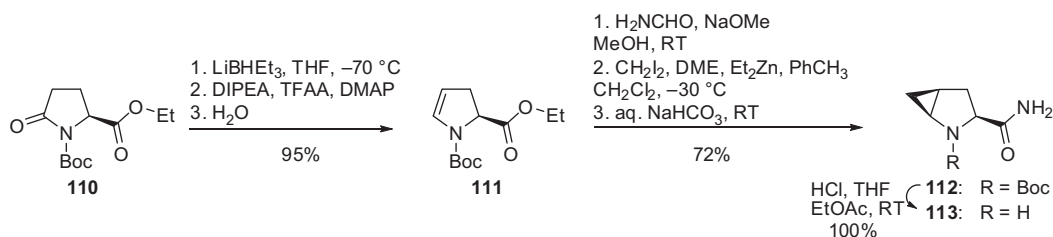
The κ opioid receptor agonist nalfurafine hydrochloride was approved and launched in 2009 for the first time in Japan. Nalfurafine is indicated for the treatment of pruritus in hemodialysis patients who have not responded to conventional therapies. Hemodialysis-



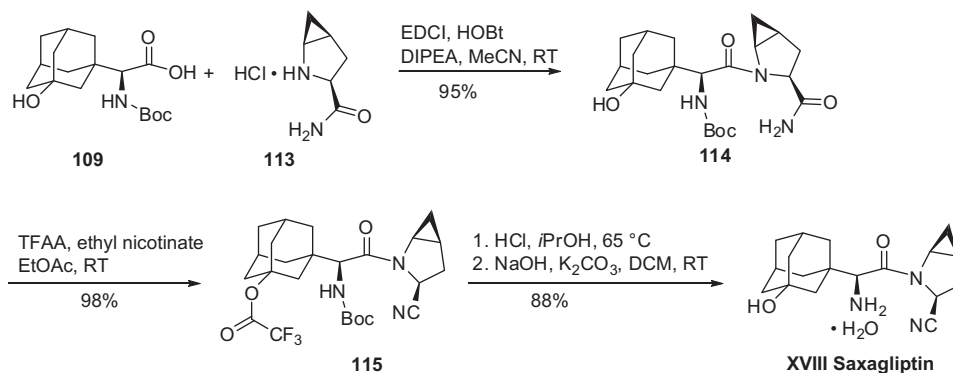
Scheme 17. Synthesis of prasugrel (XVII).



Scheme 18a. Synthesis of saxiglipitin precursor **109**.



Scheme 18b. Synthesis of saxiglipitin precursor **113**.



Scheme 18c. Synthesis of saxagliptin (XVIII).

related uremic pruritus is characterized by severe systemic itching without inflammation of the skin. Its cause has not been fully elucidated, and it often does not respond to treatment by conventional antipruritic drugs, such as antihistamines. Nalfurafine was co-developed by Toray, Japan Tobacco and Torii Pharmaceuticals and manufactured and marketed by Toray. It has orphan drug status in Japan for the approved indication. The preparation of nalfurafine hydrochloride started with naltrexone benzoate (**76**) which is available commercially from Aldrich.^{62–64} **76** was treated with benzylmethylamine (**77**) in refluxing THF in the presence of molecular sieves (4 Å) to form the intermediate imine which was subsequently reduced in situ using sodium cyanoborohydride to provide benzylmethyl amine **78** in 88% yield (Scheme 13). Removal of the benzyl group in **78** via catalytic hydrogenation and salting the resulting amine with phthalic acid (**79**) gave secondary amine **80** in 54% yield. Phthalate **80** was then combined with *trans*-3-(furyl)acryloyl chloride (**81**) and sodium bicarbonate in THF/water to provide nalfurafine which was then treated with HCl to provide nalfurafine hydrochloride (**XIII**) in 80% yield.

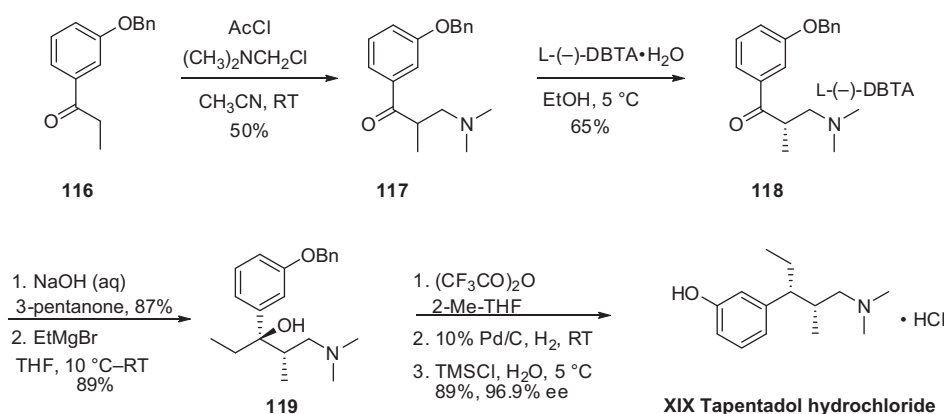
15. Pazopanib hydrochloride (Votrient®)

Pazopanib is a potent and selective multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α/β , and c-kit that blocks tumor growth and inhibits angiogenesis. It was approved for renal cell carcinoma by the U.S. Food and Drug Administration in 2009 and is marketed under the trade name Votrient® by the drug's manufacturer, GlaxoSmithKline. The synthesis of pazopanib begins with methylation of 3-methyl-6-nitroindazole (**82**) with trimethyl orthoformate in the presence of

BF₃·OEt to give indazole **83** in 65% yield (Scheme 14).⁶⁵ Reduction of the nitro group was achieved via transfer hydrogenation to give **84** in 97% yield, and this was followed by coupling the aniline with 2,4-dichloropyrimidine in a THF-ethanol mixture at elevated temperature to provide diarylamine **85** in 90% yield. The aniline nitrogen was then methylated using methyl iodide to give **86** in 83% yield prior to coupling with 5-amino-2-methylbenzenesulfonamide (**87**) and salt formation using an alcoholic solution of HCl to furnish pazopanib hydrochloride (**XIV**) in 81% yield.

16. Plerixafor hydrochloride (Mozobil®)

Plerixafor hydrochloride, a chemokine CXCR4 (SDF-1) antagonist, was launched by Genzyme for the treatment of enhancing mobilization of hematopoietic stem cells for autologous transplantation in patients with lymphoma and enhancing mobilization of hematopoietic stem cells for transplantation in patients with multiple myeloma.⁶⁶ Being a CXCR4 antagonist, a specific cellular chemokine receptor, plerixafor triggers the rapid movement of stem cells out of the bone marrow and into circulating blood where the stem cells can be collected for use in stem cell transplants. Regarding its use for cardiac applications, some clinical data suggests that the presence of stem cells circulating in the bloodstream or directly injected into the hearts of patients who have suffered a heart attack may result in improved cardiac function.⁶⁷ A concise one-pot synthesis was achieved by a rather novel nitrogen protecting strategy.^{68,69} Tetraazacyclotetradecane **88** was protected as its phosphorotriamide **89** by reaction with POCl₃ and Et₃N in hot DMF (Scheme 15). Without isolation, compound **89** was *bis*-alkylated with dibromide **90** in the presence of sodium carbonate in reflux-



Scheme 19. Synthesis of tapentadol hydrochloride (XIX).

ing DMF overnight to give bis-phosphoramidate **91**. The crude dimeric bis-phosphoramidate was hydrolyzed with 3 M HCl to afford plerixafor hydrochloride (**XV**) in 62–68% yield.

17. Pralatrexate (Foloty[®])

Pralatrexate, an injectable dihydrofolate reductase (DHFR) inhibitor, has a superior potency and toxicity profile compared to other DHFR inhibitors. In 2009, the compound was launched by Allos and approved in the U.S. for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) as a single agent. It is the first drug approved for this indication.⁷⁰ In 2010, orphan drug designation was received in the E.U. for the treatment of cutaneous T-cell lymphoma (CTCL). Preparation of pralatrexate is described in Scheme 16.⁷¹ Dimethyl homoterephthalate (**92**) was alkylated with propargyl bromide in the presence of KH in THF in 83% yield and then with 2,4-diamino-6-(bromomethyl)pteridine hydrobromide (**93**) in the presence of KH in DMF to afford 90% of crude product **94**. Hydrolysis of diester **94** with aqueous NaOH in 2-methoxyethanol, followed by acidification with AcOH gave 76% of crude dicarboxylic acid **95**, which upon thermally-induced decarboxylation in DMSO at 120 °C gave 10-deazapteroic acid derivative **96** in 29% yield as a tan solid. Activation of carboxylic acid **96** as a mixed anhydride using *t*-butyl chloroformate prior to coupling with diethyl L-glutamate hydrochloride (**97**) in the presence of Et₃N in DMF gave 10-propargyl-10-deaza-aminopterin diethyl ester **98** in 59% yield. Finally, saponification of diethyl ester **98** with aqueous NaOH in 2-methoxyethanol, followed by acidification with AcOH gave pralatrexate (**XVI**) in 61% yield.

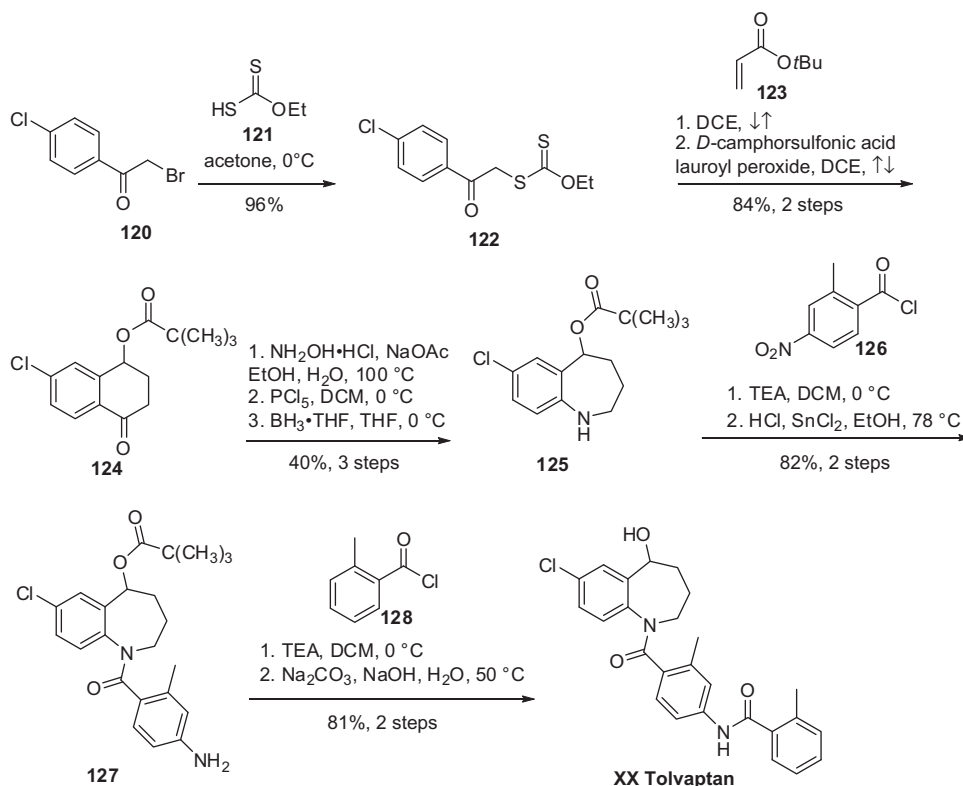
18. Prasugrel (Effient[®])

Prasugrel is a platelet inhibitor developed by Daiichi Sankyo Co. and is marketed in the United States in cooperation with Eli Lilly

and Company for acute coronary syndromes planned for percutaneous coronary intervention (PCI).⁷² Prasugrel was approved for use in Europe in February 2009, and is currently available in the UK. In the U.S. prasugrel is also approved for the reduction of thrombotic cardiovascular events, including stent thrombosis, in patients with acute coronary syndrome who are to be managed with PCI. Prasugrel is a member of the thienopyridine class of ADP receptor inhibitors, and irreversibly binds to P2Y₁₂ receptors. The synthesis of prasugrel begins with the preparation of the α -ketocyclopropane **102** which is prepared as summarized in Scheme 17.⁷³ Conversion of 1-(bromomethyl)-2-fluorobenzene (**99**) to the corresponding Grignard reagent through reaction with magnesium followed by condensation with nitrile **100** resulted in ketone **101** in 72% yield. Chlorination of ketone **101** with CuCl₂ resulted in the key prasugrel coupling component **102** in 92% yield. The piperidine coupling partner was prepared by treating thiolactone **103** with TBDMSCl and triethylamine to give thiophene **104** in 91% yield. Treatment of piperidine **104** with α -chloroketone **102** resulted in enol silane **105** in 65% yield. Reaction of silylenol ether **105** with acetic anhydride in the presence of triethylamine and catalytic DMAP resulted in the preparation of prasugrel (**XVII**) in 60% yield.

19. Saxagliptin (Onglyza[®])

Saxagliptin, previously identified as BMS-477118, is an oral hypoglycemic of the dipeptidyl peptidase-4 (DPP-4) inhibitor class developed by Bristol-Myers Squibb for the treatment of type 2 diabetes.⁷⁴ DPP-IV is the primary enzyme responsible for degradation of incretins, such as glucagon-like peptide-1 (GLP-1), which is a hormone responsible for the glucose-dependent stimulation of insulin in humans.⁷⁵ Inhibitors of DPP-IV serve as effective glucose regulators by increasing the endogenous concentration of GLP-1. The initial discovery route to saxagliptin was a 15-step, convergent



Scheme 20. Synthesis of tolvaptan (XX).

synthesis focused on the production and use of compounds **109** and **113** (Schemes 18a and 18b),^{74a,76,77} While the strategy of early drug delivery involved rapid synthesis to support preclinical activities and Phase I clinical trials, as saxagliptin entered Phase II, a greater emphasis was placed on defining and demonstrating a commercially viable synthetic process. Scheme 18a describes a more expedient route to the preparation of adamantylamino acid **109**.⁷⁸ Commercially available 1-adamantoic acid (**106**) was first converted to the corresponding acid halide through the use of thionyl chloride prior to a Grignard addition reaction utilizing iodomethane and magnesium metal to furnish ketone **107**. This ketone was then subjected to oxidizing conditions involving potassium permanganate to provide the hydroxylated ketoacid **108**. The amino acid **109** was furnished through the use of phenylalanine dehydrogenase in near-quantitative yield in 99% enantioselectivity.

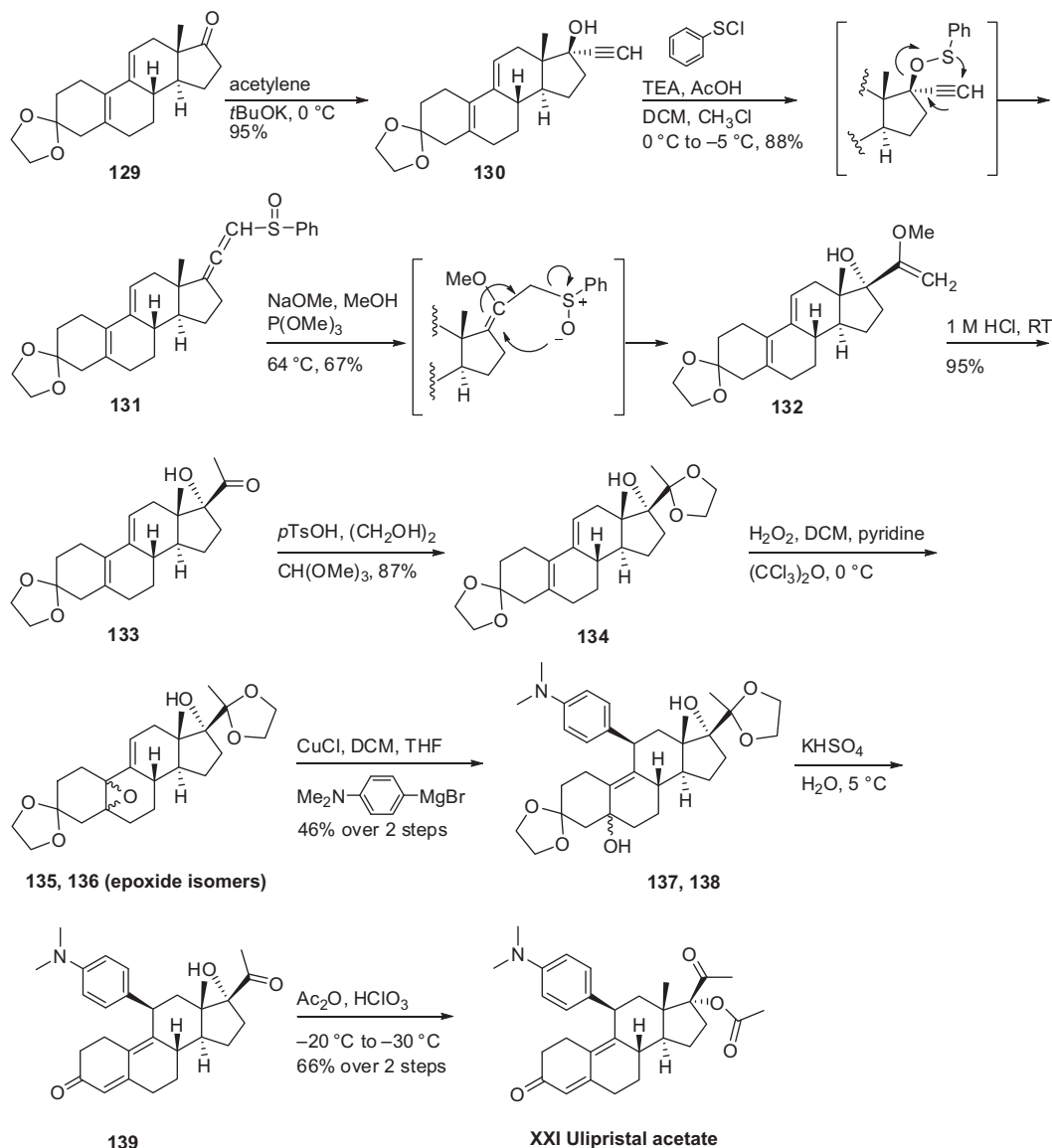
The synthesis of **113** began with commercially available ethyl *N*-*tert*-butoxycarbonylpyroglutamate (**110**) (Scheme 18b). Selective reduction of the amide carbonyl within **110** through the use of lithium triethylborohydride followed by acylation and base-induced elimination of the resulting amination and careful hydrolysis

gave rise to dihydropyrrole **111** with full retention of stereochemical configuration in 95% yield. Amidation followed by Simmons–Smith cyclopropanation employing methylene iodide converted **111** to the cyclopropanated product **112**, which was then converted to the key coupling partner **113**.⁷⁹

The core of saxagliptin was formed by the amide coupling of amino acid **109** and methanoprolineamide **113** to give amide **114** in 95% yield (Scheme 18c). Subsequent dehydration of the primary amide **114** using trifluoroacetic acid anhydride and ethyl nicotinate gave nitrile **115** in 98% yield. Removal of both the alcohol and amine protecting groups with HCl afforded saxagliptin (**XVIII**) in 88% yield.

20. Tapentadol hydrochloride (Nucynta®)

Tapentadol was approved by the FDA in November 2008 for the treatment of moderate to severe acute pain.⁹ It is a centrally acting analgesic that acts as both an agonist at the μ -opioid receptor and as a norepinephrine re-uptake inhibitor, allowing it to have efficacy similar to potent narcotic analgesics but without their side effects.⁸⁰ The drug was developed by Grunenthal and Johnson &



Scheme 21. Synthesis of ulipristal acetate (XXI).

Johnson and was marketed starting in 2009. Several syntheses of this drug have been reported^{81,82} and the improved route disclosed in a recent patent is described (Scheme 19).^{83,84} Ketone **116** was treated with Eschenmoser's salt in acetonitrile and acetyl chloride at room temperature and the resulting amine **117** was collected in 50% yield by adding ether and crystallizing the product. Amine **117** was crystallized with L-(–)-dibenzoyl tartaric acid monohydrate in ethanol at 6–8 °C to give the desired enantiomer as salt **118** in 65% yield. The free base of **118** was generated by reaction with aqueous sodium hydroxide in 87% yield and then treated with ethylmagnesium bromide in THF at 10 °C followed by stirring at room temperature overnight to give tertiary alcohol **119** in 89% yield. Alcohol **119** was treated with trifluoroacetic anhydride in 2-methyl THF at 40–45 °C to give the corresponding trifluoromethyl ester which was then treated with 10% Pd/C and hydrogenated at 3 bar at ambient temperature. These hydrogenolytic conditions effected reductive cleavage of the trifluoromethyl ester and removal of the benzyl protecting group with retention of stereochemistry. Filtration of the catalyst followed by the addition of water and trimethylchlorosilane to generate HCl in situ and allowing the product to crystallize out at 5–8 °C gave the desired terpendadol hydrochloride (**XIX**) in 89% yield with 99% purity and 96.9% ee.

21. Tolvaptan (Samsca®)

Tolvaptan, also known as OPC-41061, is a selective, competitive arginine vasopressin receptor 2 antagonist used to treat hyponatremia (low blood sodium levels) associated with congestive heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH).⁸⁵ Otsuka Pharmaceutical licensed tolvaptan under the trade name Samsca after the FDA approved the drug in May 2009. Tolvaptan has also shown efficacy against polycystic kidney disease. In a 2004 trial, tolvaptan administered with traditional diuretics was noted to increase excretion of excess fluids and improve blood sodium levels in patients with heart failure without producing side effects such as hypotension (low blood pressure) or hypokalemia (decreased blood levels of potassium). The drug also exhibited no adverse effect on kidney function.⁸⁶ Starting from commercially available 2-bromo-1-(4-chlorophenyl)ethanone (**120**), nucleophilic displacement of the bromide in the α -position with O-ethyl-S-hydrogen carbonodithioate (**121**) in acetone to give xanthate **122** in 96% yield (Scheme 20).⁸⁷ Next, the resulting α -keto xanthate **122** was treated with acrylate **123** to furnish an intermediate ester which upon treatment with acidic lauroyl peroxide affected a tandem Friedel–Crafts/mercaptyl reduction event to furnish tetralone **124** in 84% yield for the two-step sequence. Next, benzazepine **125** was obtained via a Beckmann rearrangement involving hydroxylamine-HCl mediated oxime formation followed by a phosphorous pentachloride-induced ring expansion. Removal of the carbonyl group within the resulting lactam using borane-THF as the reducing agent ultimately delivered benzazepine **125** in 40% over the three-step protocol. Next, acylation of aniline **125** with **126** followed by selective, tin-mediated nitro reduction constructed aniline **127** which was subsequently acylated with 2-methylbenzoyl chloride (**128**). Base hydrolysis removed the Boc protecting group which gave rise to tolvaptan (**XX**) in 81% yield over the two-step sequence.

22. Ulipristal acetate (ellaOne®)

Ulipristal acetate, a selective progesterone receptor modulator (SPRM), was developed at the Research Triangle Institute. In 2009, HRA Pharma received FDA approval for emergency contraception within 120 h (5 days) of unprotected sexual intercourse

or contraceptive failure. Ulipristal acetate is a well-known steroid that possesses antiprogesterational and antiglucocorticoid activity. It is the first SPRM that was specifically designed as an oral emergency contraceptive. Unlike earlier levonorgestrel-based emergency contraceptives, this SPRM drug maintains efficacy for 5 days after unprotected intercourse while having safety profile comparable to levonorgestrel.⁸⁸ Recently, an industrial scale route was published and is described in Scheme 21.⁸⁹ Alkylation of commercially available 3-(ethylenedioxy)-19-estra-5(10),9(11)-diene-17-one (**129**, multiple vendors) with *t*BuOK and acetylene in THF at 0 °C gave alcohol **130** in 95% yield, which was subsequently treated with phenylsulfonyl chloride in the presence of TEA and AcOH in DCM/CHCl₃ at –5 °C to 0 °C to effect thiolester formation followed by sulphinyl-sulphoxide rearrangement to give allene sulphoxide **131** in 88% yield. Compound **131** was treated with NaOMe/MeOH at 64 °C to give the corresponding enol ether and then the enol ether was treated with trimethyl phosphite at the same temperature for sulphoxide-sulphinyl rearrangement to furnish hydroxyl enol ether **132** in 67% yield. Compound **132** was demethylated with 1 M HCl in methanol to give the corresponding ketone **133** in 95% yield which was protected using ethylene glycol, *p*TsOH and trimethyl orthophosphate in DCM to afford cyclopentyl ketal **134** in 87% yield. Epoxidation of **134** in the presence of hexachloroacetone and H₂O₂ in pyridine and DCM at 0 °C provided a 55:45 mixture of the 5- α ,10- α epoxides (**135**, **136**). The crude epoxides **135** and **136** were reacted with 4-(*N,N*-dimethylamino)-phenyl magnesium bromide in THF in the presence of CuCl in DCM to furnish the mixture of diastereomers **137** and **138** in 46% yield over two steps. The mixture (**137** and **138**) was then treated with KHSO₄ in water at 5 °C to affect dehydration and liberation of the keto functional group to give **139** which was used in the next step without isolation. Compound **139** was acetylated with acetic anhydride and perchloric acid in DCM at –30 °C to afford the ulipristal acetate (**XXI**) in 66% yield over the final two steps.

Acknowledgments

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