Synthetic Approaches to the 2007 New Drugs

Kevin K.-C. Liu[1], Subas M. Sakya[2], Christopher J. O'Donnell[2] and Jin Li[3,*]

[1]*Pfizer Inc, La Jolla, CA 92037, USA;* [2]*Pfizer Inc, Groton, CT 06340, USA;* [3]*Shenogen Pharma Group, Beijing, China*

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 19 NCEs marketed in 2007.

Key Words: Synthesis, new drug, new chemical entities, medicine, therapeutic agents.

INTRODUCTION

"*The most fruitful basis for the discovery of a new drug is to start with an old drug*." ─ Sir James Whyte Black, winner of the 1988 Nobel prize in physiology and medicine [1].

Inaugurated six 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. The motivation to write such a review is the same as stated in the previous articles [2-5]. Generally, 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 drugs in shorter periods of time. With this hope, we continue to profile the NCEs that were approved in 2007.

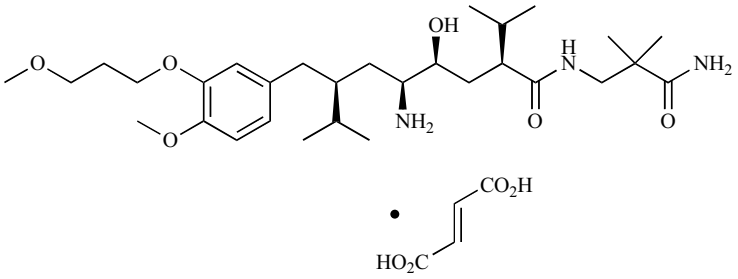
In 2007, 30 new products including new chemical entities, biological drugs, and diagnostic agents reached the market [6]. Six additional products were approved for the first time in 2007, however they were not launched before year's end and therefore, the syntheses of those drugs will be covered in 2008's review. This article will focus on the syntheses of 19 new drugs marketed in 2007 (Fig. **1**) and exclude new indications for known drugs, new combinations, and new formulations and drugs synthesized *via* bioprocesses, or peptide synthesizers. The synthetic routes cited herein represent the most scalable methods reported and appear in alphabetical order by generic names.

Aliskiren Fumarate (*Tekturna*®)

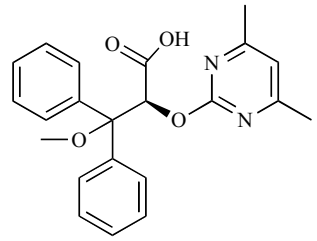
Last March, the U.S. became the first country to approve *Tekturna*® (aliskiren fumarate; Novartis/Speedel), a first-in-class antihypertensive agent. The once-daily, oral, direct renin inhibitor received FDA approval for treatment of high blood pressure as mono therapy or in combination with other antihypertensive medications. In an extensive clinical trial program involving more than 6,400 patients, aliskiren provided significant blood pressure reduction for a full 24 hour period. Furthermore, aliskiren demonstrated increased efficacy when used in combination with other commonly used blood pressure-lowering medications. Novartis is conducting a large outcome trial program to evaluate the long-term effects of aliskiren and of direct renin inhibition in general. The product, which is known as *Rasilez*® outside the U.S., was approved in the E.U. in August. Aliskiren has been synthesized by several different routes [7-11] and a convergent synthesis of aliskiren by Wuxi PharmaTech was performed on large scale; however, the yields were not reported [12]. The synthesis of aliskiren by Novartis is depicted in Scheme **1** [9]. Aliskiren (**I**) was synthesized through a convergent synthetic strategy by coupling key intermediate chloride **5** with aldehyde **10**. Hydrogenation of cinnamic acid **1**, followed by generation of the acid chloride of the corresponding acid and reaction with (+)-pseudoephedrine provided amide **2** in 91% yield. Deprotonation of amide **2** with LDA followed by alkylation with 2-iodopropane in refluxing THF gave **3** as a single diastereomer in 52% yield. Reduction of the amide functionality in **3** using *n*-butyl lithium boron trifluoride ammonium complex proceeded without epimerization of the chiral center to give alcohol **4** in 66% yield. Chlorination of **4** using phosphorus oxychloride gave chloride **5**, in 78% yield as the organometallic precursor for the eventual coupling to aldehyde **10**. Synthesis of fragment **10** commenced with (+)-pseudoephedrine isovaleramide **6**, which was efficiently deprotonated with LDA and alkylated using allyl bromide; diastereomerically pure **7** was obtained upon crystallization of the crude reaction mixture in 78% yield. Bromolactonization of **7**, using *n*-bromosuccinimide in the absence of acetic acid gave amide acetal **8** with a single configuration at the spirocenter and a 6:1 mixture of *trans:cis* ring substituents. Displacement of the bromide using tetrabutylammonium acetate followed by basic hydrolysis provided alcohol **9** in 85% yield. Oxidation of **9** using dimethyl sulfoxide-sulfur trioxide/pyridine proceeded without epimerization to furnish the masked lactone aldehyde **10** in 60% yield. Coupling of fragments **5** and **10** was achieved by treatment of **10** with the organocerium reagent of the corresponding Grignard reagent prepared from **5**. Hydrolysis of the crude spirocyclic addition product revealed that the hydroxylactone **11** was formed in 51% overall yield as an inseparable epimeric mixture with a Felkin-Anh selectivity of 85:15. The requisite nitrogen functionality was installed *via* the brosylate to give azido lactone **12** in 68% yield. Aminolysis with 3-amino-2,2-dimethylpropionamide led to formation of the open chain azido alcohol **13** in 76% yield. The

*Address correspondence to this author at the Shenogen Pharma Group, Beijing, China; tel: 8610-8277-4069; E-mail: jin.li@shenogen.com

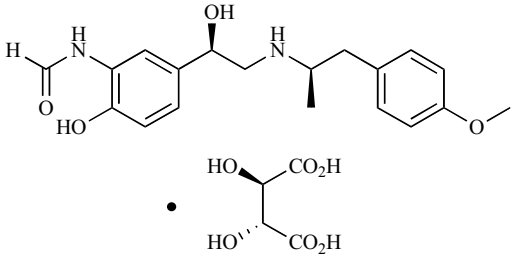
1389-5575/08 $55.00+.00



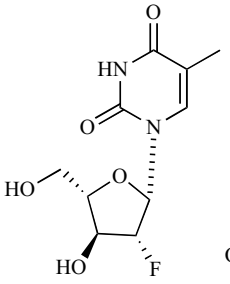
I Aliskiren Fumarate



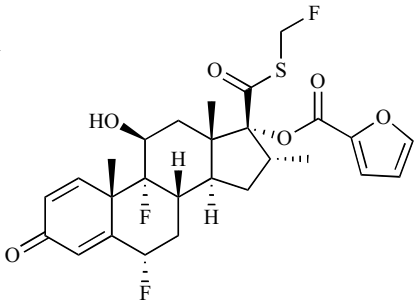
II Ambrisentan



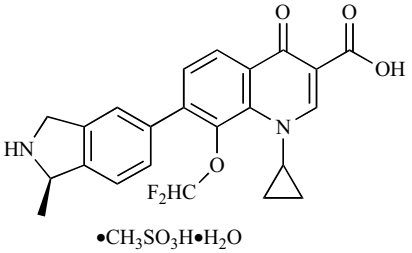
III Arformoterol tartrate



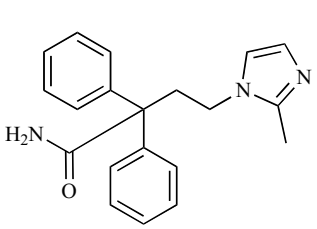
IV Clevudine



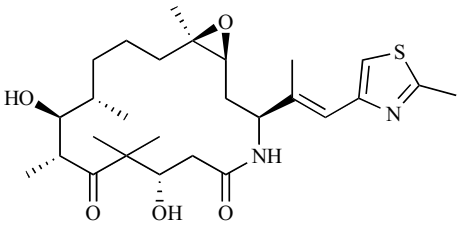
V Fluticasone furoate



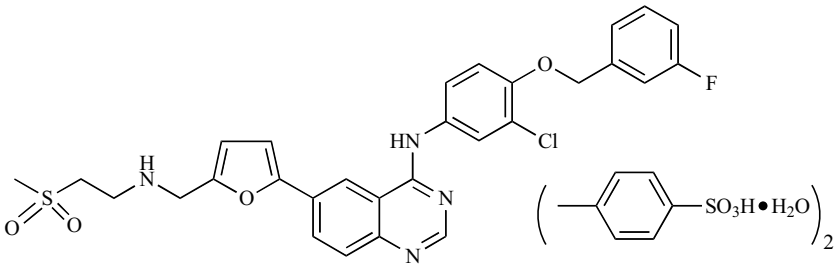
VI Garenoxacin mesilate hydrate



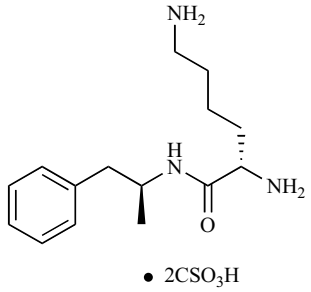
VII Imidafenacin



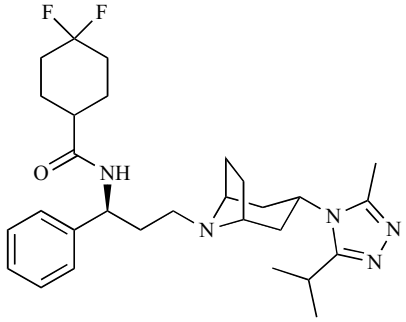
VIII Ixabepilone



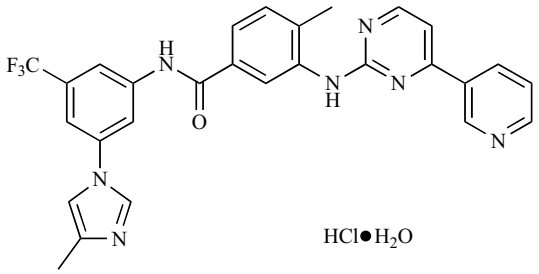
IX Lapatinib ditosylate hydrate



X Lisdexamfetamine dimesilate



XI Maraviroc



XII Nilotinib hydrochloride monohydrate

(Fig. (1). Contd….)

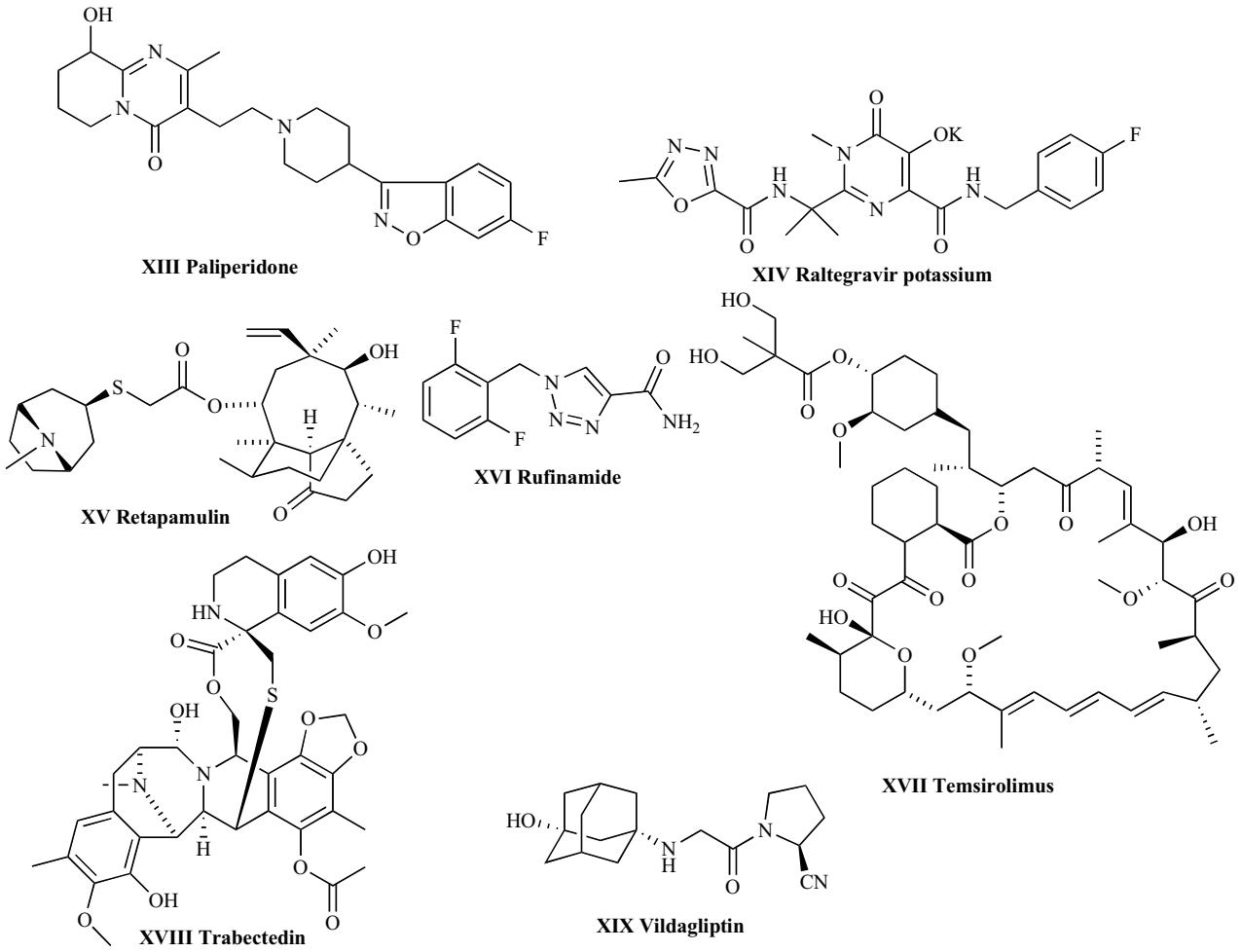


Fig. (1). Structures of 19 new drugs marketed in 2007.

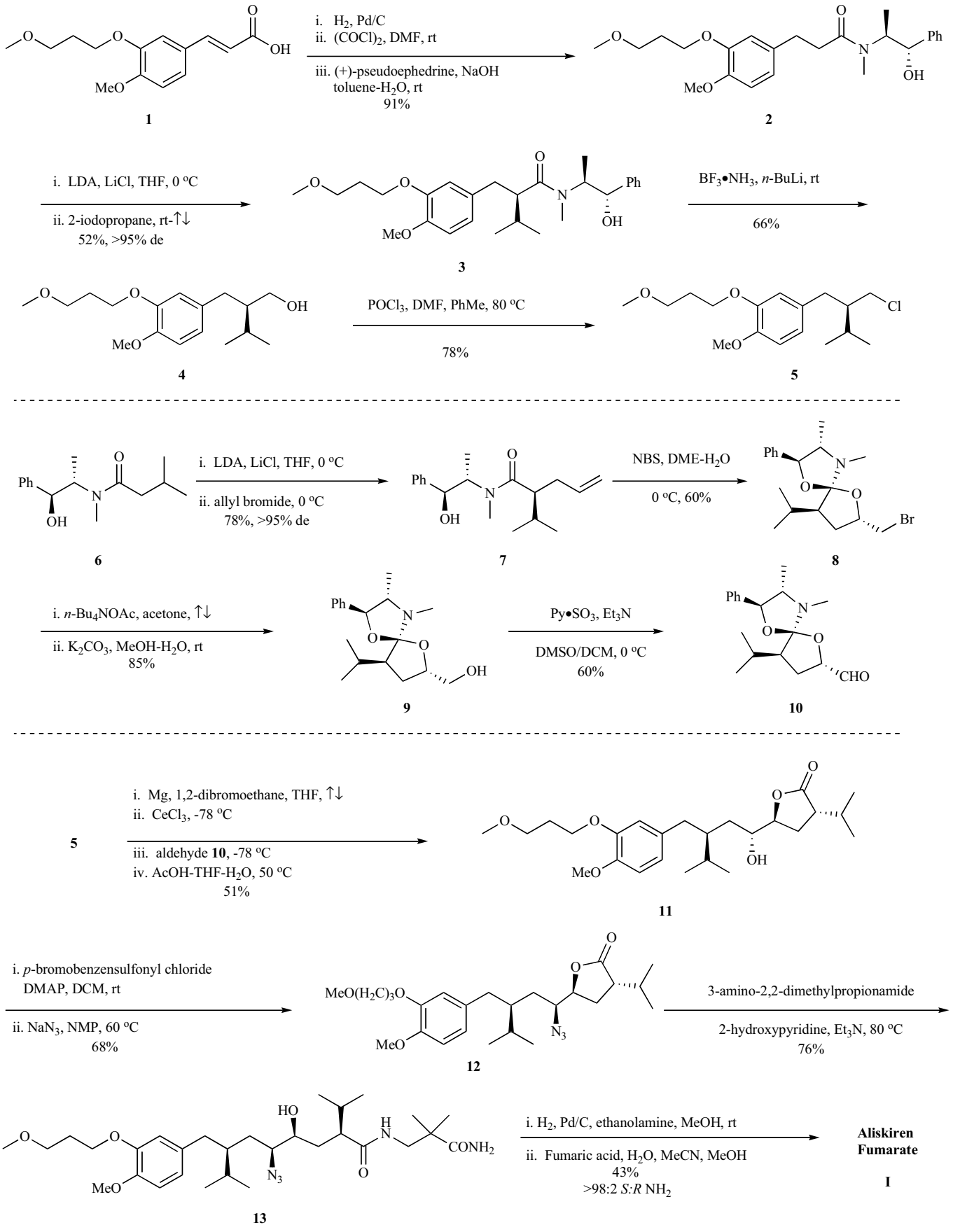
synthesis of aliskiren was completed by azide hydrogenolysis and formation of the hemifumarate salt. Generation of pure aliskiren was achieved *via* crystallization which removed the residual minor (*R*)-epimer carried through from the Grignard addition step to afford aliskiren (**I**) in 43% yield.

Ambrisentan (*Letairis*™)

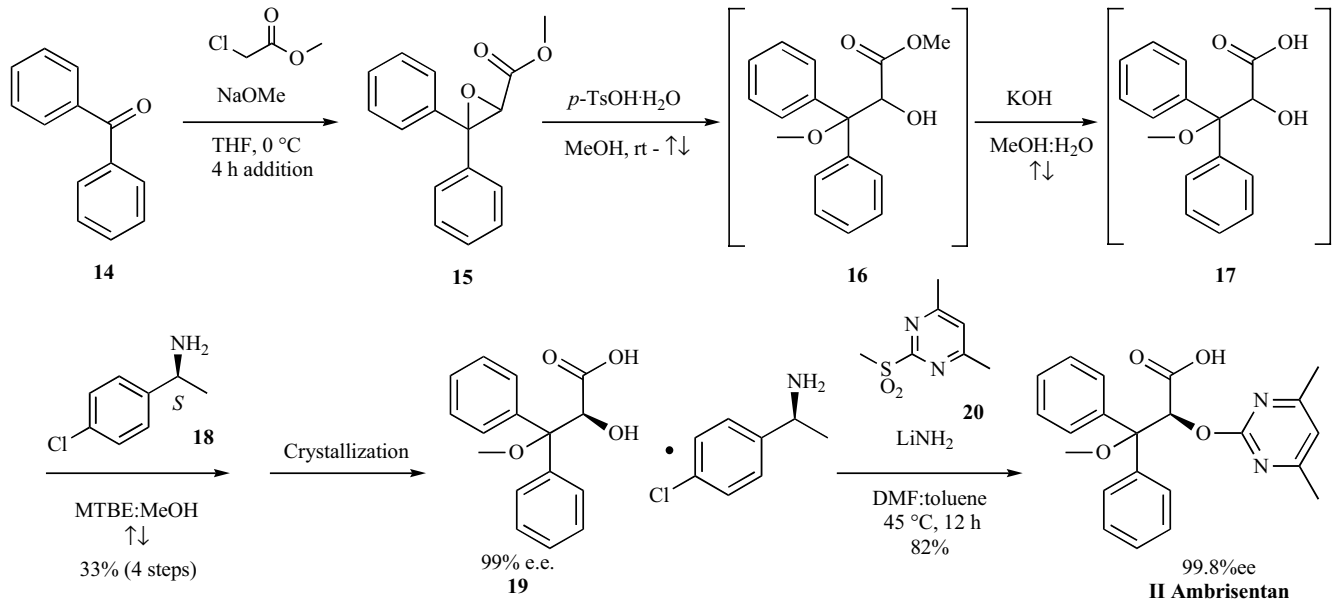
Ambrisentan (BSF-208075) is an endothelin-1a antagonist developed by Gilead (formerly Myogen) under license from Abbott Laboratories and received FDA approval for the treatment of pulmonary arterial hypertension in June 2007 [6,13]. Both the discovery [14] and process routes to the synthesis of ambrisentan have been published and the process route is described as shown in Scheme **2** [15]. Reacting a mixture of benzophenone (**14**) and sodium methoxide in THF at 0 °C with methylchloroacetate over a four hour period provided glycidate **15** which was taken forward without purification to the subsequent step. Addition of *p*-toluenesulfonic acid monohydrate to a solution of glycidate **15** in methanol was followed by heating at reflux and distilling out the solvent until the temperature reached 66°C. While the solution was still refluxing, 10% potassium hydroxide was added and the remaining organic solvent was distilled out until the temperature reached 94°C, providing complete hydrolysis to acid **16**. The reaction was cooled to room temperature and diluted with water and methyl *tert*-butylether (MTBE) then acidified with 10% sulfuric acid. The MTBE layer was separated and taken to the next step. Additional MTBE and methanol were added to the crude acid **17** and the resulting mixture was heated at reflux. (*S*)-1-(4-chlorophenyl)ethylamine was added to the refluxing solution and the resulting mixture was allowed to cool to 0-5°C slowly at a rate of 10°C/h which resulted in crystallization of the salt **19** in 33% overall yield from benzophenone and 99% e.e. The chiral hydroxyl acid salt **19** was mixed with sulfone **20** and lithium amide in a toluene/DMF mixture and heated at 45 °C for 12 hours to give, after acidic workup and crystallization, ambrisentan (**II**) in 84% yield as a colorless powder with 99.8% e.e.

Arformoterol Tartrate (*Brovana*™)

Sepracor's *Brovana*™, a nebulized long acting bronchodilator, was launched in the U.S. in April 2007. The β2-adrenoceptor agonist is indicated for the twice-daily, long-term maintenance treatment of bronchoconstriction in patients

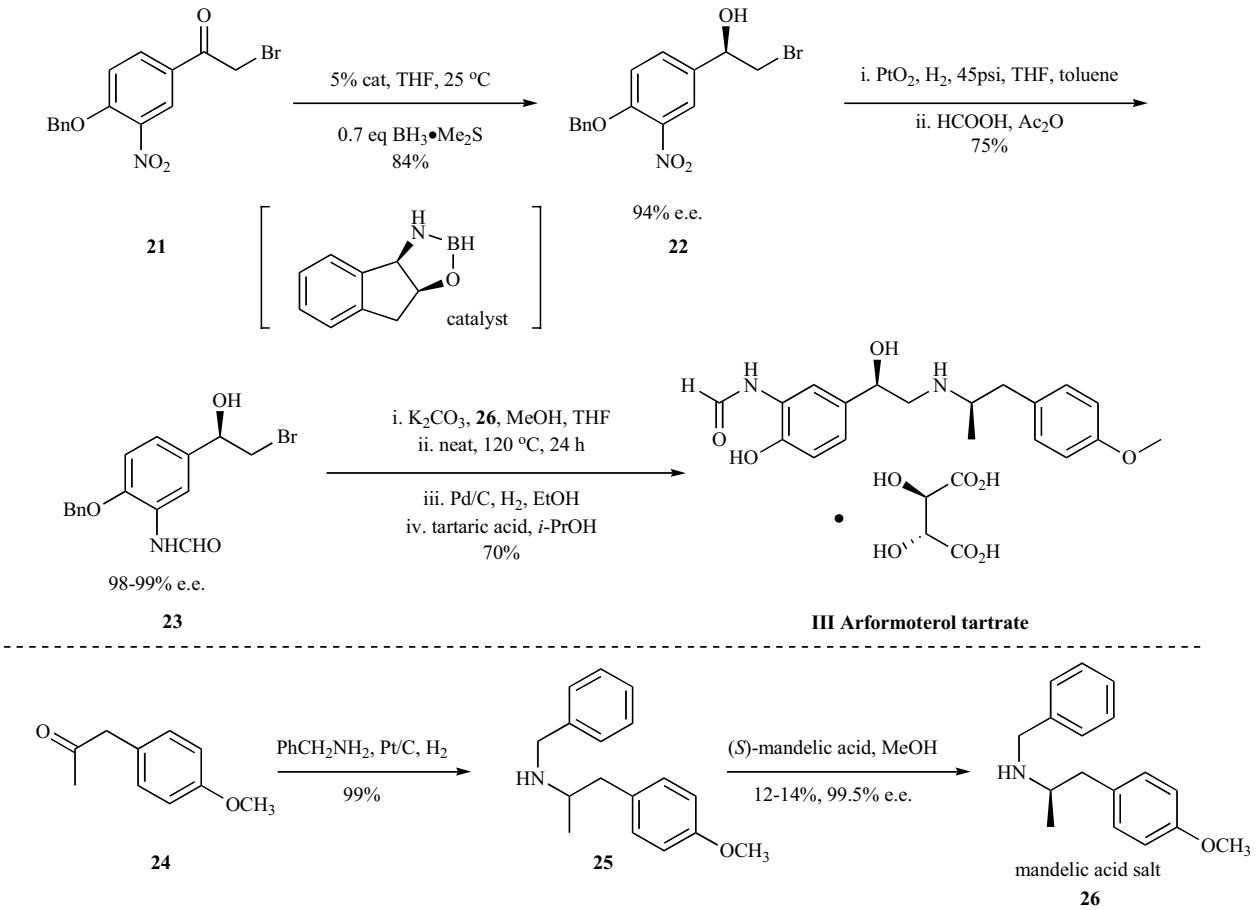


Scheme 1. Synthesis of Aliskiren Fumarate.



Scheme 2. Synthesis of Ambrisentan.

with chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema. It is the first long-acting nebulized bronchodilator approved by the FDA for this indication [16]. There are several reports on the synthesis of arformoterol [16-24]. A large-scale synthesis of enantio/diastereomerically pure (*R*,*R*)-formoterol is cited here (Scheme **3**) [21a]. Bromoalcohol **22** was synthesized in 84% yield with 94% e.e. through the catalytic enantioselective reduction of bromo ketone **21**[21b]. The nitro functional group in **22** was reduced in quantitative yield by hydrogena-



Scheme 3. Synthesis of Arformoterol Tartrate.

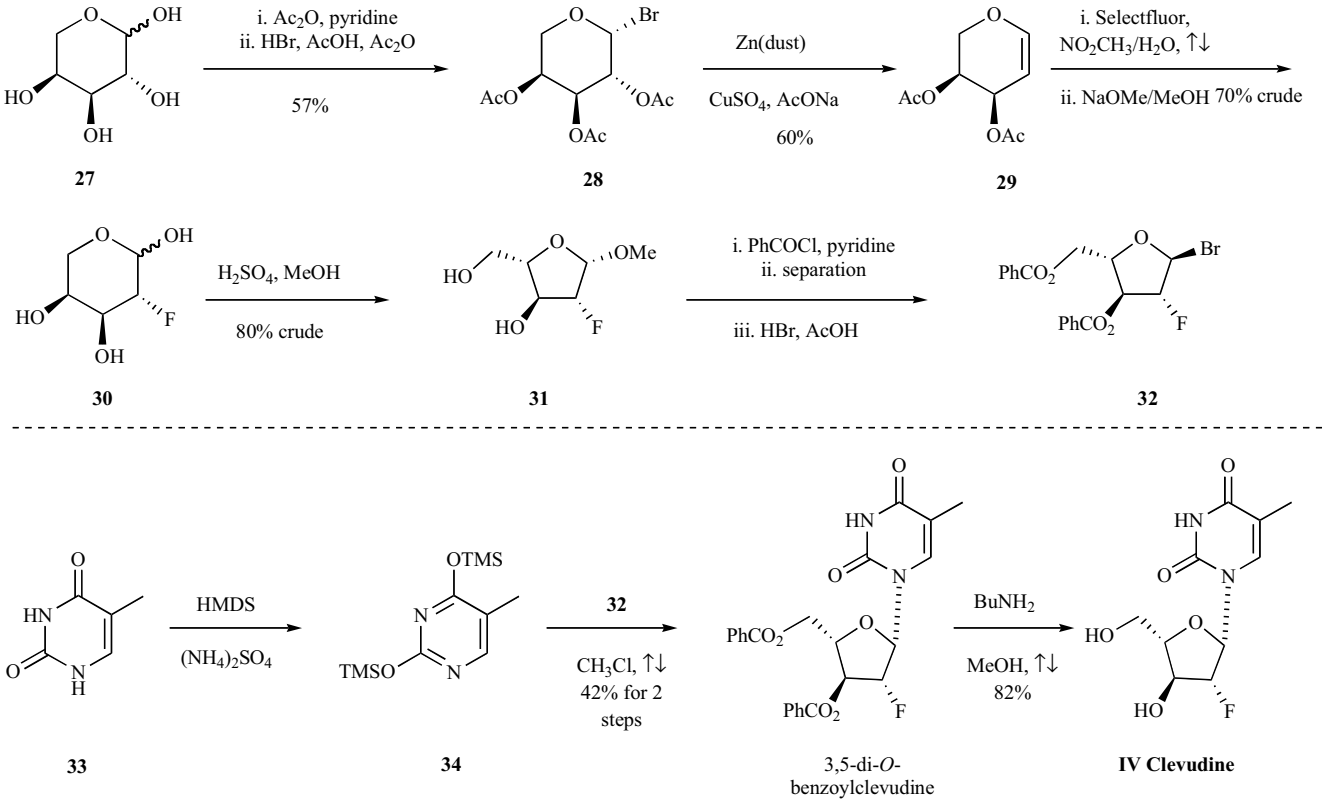
tion in the presence of Adams catalyst and the resulting aniline was isolated by filtration of the catalyst and removal of the solvent. In order to avoid auto-oxidation, the aniline was treated with a mixture of formic acid and acetic anhydride immediately after the removal of the platinum catalyst. Upon concentrating the reaction mixture, bromohydrin **23** crystallized and could be isolated in 75% yield with 98.6% e.e. It was further enriched to >99.5% e.e. by a single re-crystallization from ethylacetate. Next, a mixture of bromohydrin **23** and amine salt (*R*)-**26**-(*S*)-mandelic acid was treated with K_2CO_3 resulting in generation of the corresponding epoxide of **23** and liberation of the free base of (*R*)-**26**. After an aqueous work up to remove salts and mandelic acid, the reaction mixture was heated to 120 °C to affect epoxide opening with the amine of **26**. Removal of the benzyl protecting groups of the resulting crude product *via* catalytic hydrogenation followed by salt formation with tartaric acid afforded arformoterol tartrate (**III**) in 70% yield upon crystallization.

Clevudine (*Levovir*®)

Clevudine, a DNA polymerase inhibitor, was launched in South Korea for the treatment hepatitis B [25]. The hepatitis B virus (HBV) belongs to the family of hepadnaviruses. The HBV genome is a relaxed circular, partially double-stranded DNA of approximately 3,200 base pairs. The drug was originally discovered at the University of Georgia and Yale University. Bukwang acquired the rights and Eisai in-licensed clevudine from Bukwang. The synthesis is depicted in Scheme **4** [26]. L-Arabinose (**27**) was treated with acetic anhydride and pyridine at room temperature for four hours to give acetylated arabinose, which was then brominated using 30% HBr in AcOH/Ac_2O at room temperature for 36 hours to afford bromo-sugar **28** as a white solid in 57% yield after crystallization in ethyl ether. Bromo-sugar **28** was then treated with Zn dust, $CuSO_4$ and NaOAc in AcOH/H_2O, followed by chromatographic separation to give L-arabinal **29** in 60% yield. L-arabinal **29** was converted to the fluoro derivative in 70% crude yield by reaction with Selectfluor® (F-TEDA-BF_4) in refluxing nitromethane/H_2O, and the resulting fluoroalcohol was deacetylated with NaOMe in MeOH to give compound **30** in 100% crude yield. Compound **30** was then treated with H_2SO_4 in refluxing MeOH to afford methyl furanoside **31** in 80% crude yield. Furanoside **31** was benzoylated with benzoyl chloride in pyridine to give a mixture of isomers, from which the α-anomer was isolated by chromatography and then brominated with 30% HBr/AcOH in CH_2Cl_2 to provide the crude bromo-sugar **32** which was dissolved in chloroform and used without further purification in the next step. Compound **34** was obtained by treatment of thymine (**33**) with HMDS and ammonium sulfate in refluxing chloroform for 16 hours. The sugar **32** was condensed with silylated pyrimidine derivative **34** in refluxing chloroform to afford 3,5-di-*O*-benzoylclevudine in 42% yield after recrystallization from ethanol. The benzoyl groups were removed upon treatment with *n*-butylamine in refluxing methanol to give clevudine (**IV**) in 82% yield.

Fluticasone Furoate (*Veramyst*™)

In April 2007, the FDA approved GlaxoSmithKline's once-daily *Veramyst*™ (fluticasone furoate) nasal spray to treat seasonal and year-round allergy symptoms in adults and

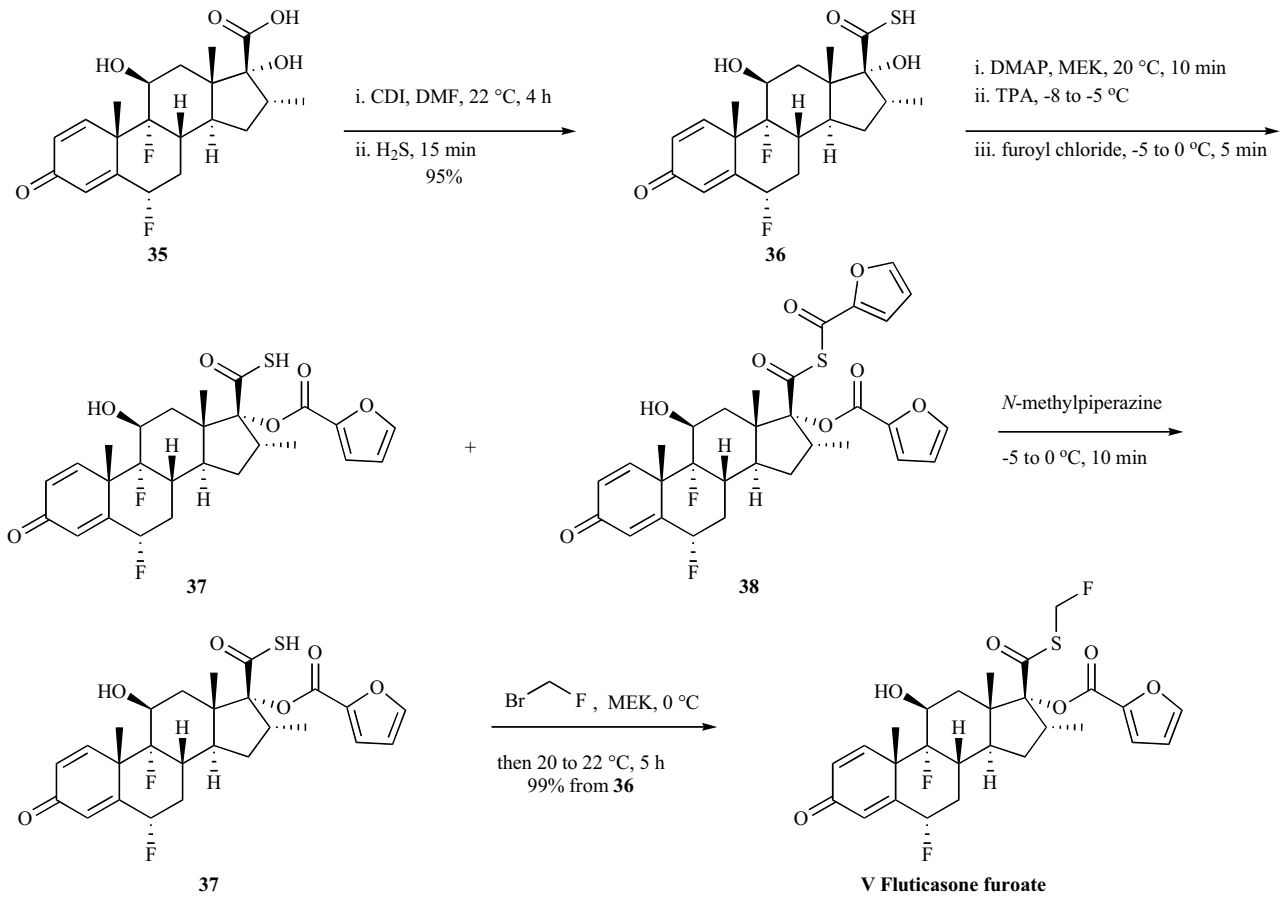


Scheme 4. Synthesis of Clevudine.

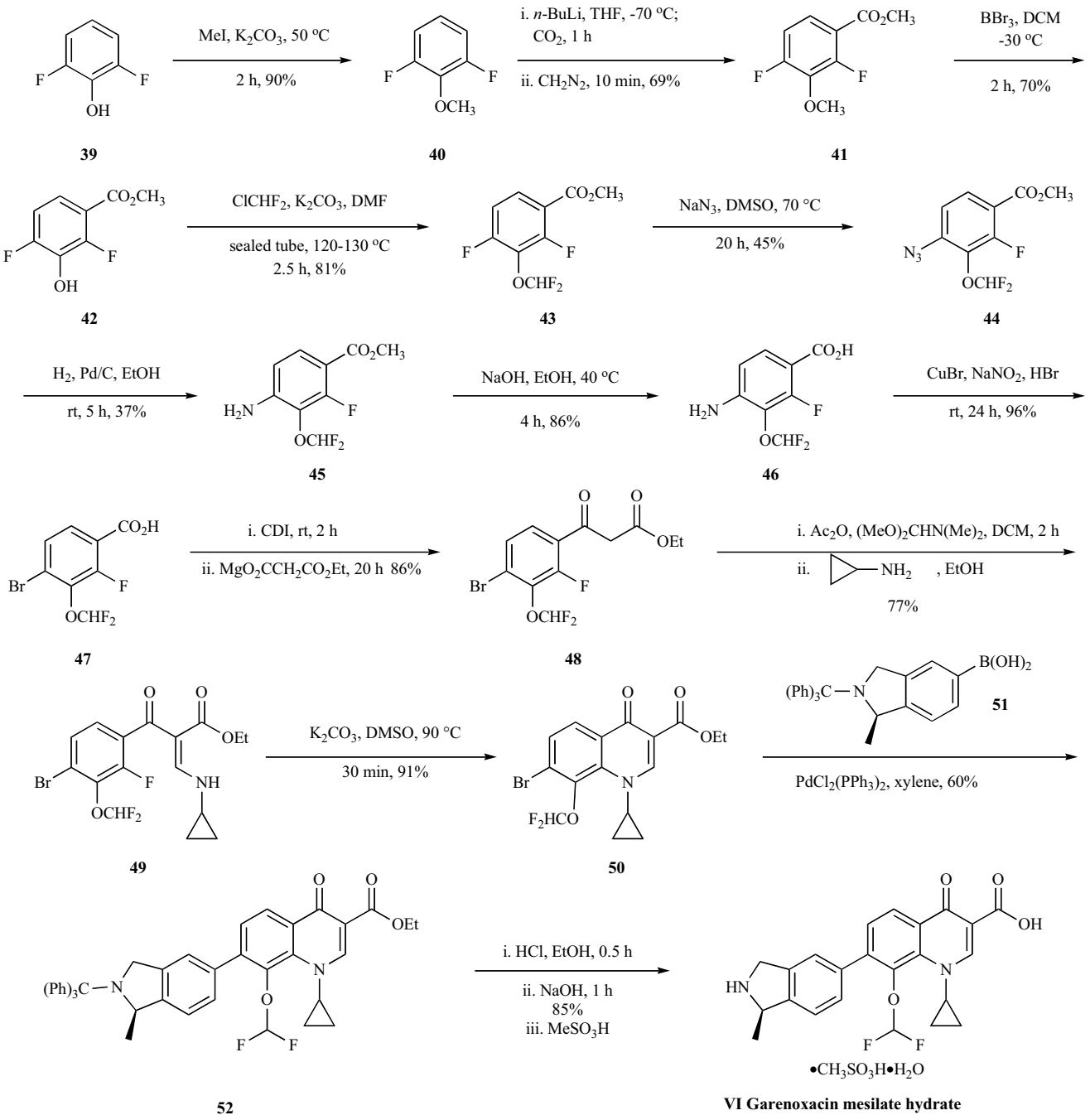
children 2 years of age and older. Fluticasone furoate is an intranasal corticosteroid that works throughout the allergy process to block an entire range of inflammatory mediators that may lead to nasal allergy symptoms, although the precise mechanism through which the drug affects allergy symptoms is not known. The approval of fluticasone furoate was based on clinical trials in more than 2,900 adults and children suffering from seasonal or year-round allergies. The product was launched in May. In October the European Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion for fluticasone furoate, which will be marketed upon approval in Europe under the trade name *Avamys*™. The synthesis of fluticasone on large scale was disclosed in the patent literature [27-29]. The starting 6α,9α-difluoro-11β-17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid **35** [27a] was converted to the analogous carbothioic acid **36** in 95% yield *via* activation with carbonyl diimidazole, followed by reaction with hydrogen sulfide gas (Scheme **5**). Conversion of the carbothioic acid to fluticasone was completed through a three-step sequence in a one pot process in 99% overall yield. Carbothioic acid **36** and DMAP were dissolved in MEK. Tripropylamine (TPA) was then added to the mixture at -8 to -5 °C. Neat furoyl chloride was then added dropwise over 2-3 minutes and the resulting mixture was then stirred at -5 to 0 °C for 15 minutes generating a mixture of desired ester **37** and thioanhydride **38**. A solution of *N*-methylpiperazine in water was then added dropwise over 2-3 minutes at -5 to 0 °C to the crude reaction mixture and stirred for 10 minutes, which enabled the conversion of thioanhydride **38** to the ester **37**. A solution of bromofluoromethane in MEK was then added rapidly at 0 °C and the resulting solution was stirred at 20 °C for 5 hours. After a simple work-up, fluticasone furoate (**V**) was obtained in 99% overall yield from **36** with 97% purity.

Garenoxacin Mesilate Hydrate (*Geninax*®)

Toyama, Astellas Pharma and Taisho Toyama launched *Geninax*® (garenoxacin mesilate hydrate), an orally formulated quinolone, last year in Japan. The product is indicated for pharyngitis, laryngitis, tonsillitis, acute bronchitis, pneumonia, secondary infection in chronic respiratory lesion, otitis media and sinusitis. Garenoxacin is the first synthetic antibacterial agent indicated for treatment of penicillin-resistant *S. pneumoniae*. Garenoxacin, discovered by Toyama, displays good oral absorption and tissue distribution, providing for once-daily administration. Several syntheses of garenoxacin have been reported and the largest scale synthesis is reported herein [30-32]. The synthesis was initiated by methylation of 2,6-difluorophenol (**39**) with methyl iodide and K_2CO_3 in DMF giving 2,6-difluoroanisole (**40**) in 90% yield (Scheme **6**). Deprotonation of **40** with *n*-butyl lithium and reaction with CO_2 yielded 2,4-difluoro-3-methoxybenzoic acid which was methylated with diazomethane in ether to afford methyl ester **41** in 69% yield. Liberation of the phenol was accomplished by reaction with BBr_3 in dichloromethane resulting in 2,4-difluoro-3-hydroxybenzoic acid methyl ester

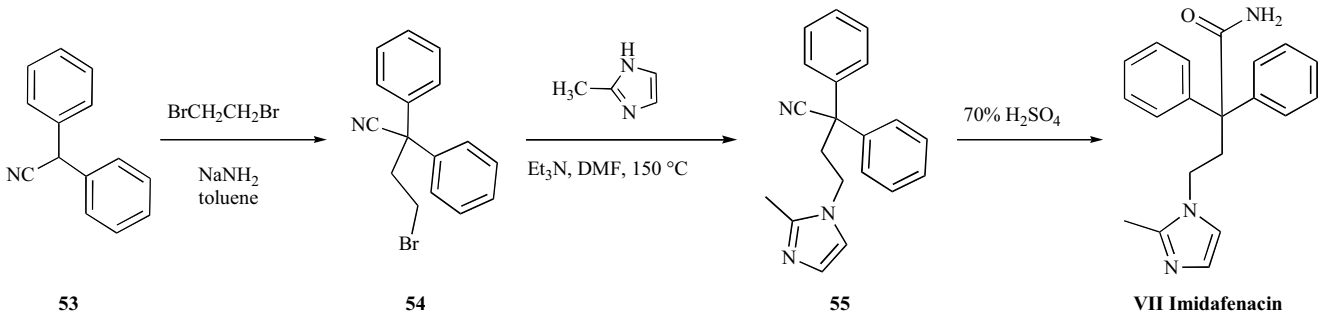


Scheme 5. Synthesis of Fluticasone Furoate.



Scheme 6. Synthesis of Garenoxacin.

42 in 70% yield. Alkylation of **42** with chlorodifluoromethane and K_2CO_3 in DMF gave 3-(difluoromethoxy)-2,4-difluorobenzoic acid methyl ester **43** in 81% yield, which was then treated with sodium azide in DMSO, yielding the azido derivative **44** in 45% yield. Reduction of **44** with H_2 over Pd/C in ethanol afforded 3-amino-2,4-difluorobenzoic acid methyl ester **45** in 37% yield and **45** was hydrolyzed with NaOH in ethanol, giving the free acid **46** in 86% yield. Diazotization of **46** with $NaNO_2$ followed by reaction with HBr yielded 4-bromo-3-(difluoromethoxy)-2-fluorobenzoic acid **47** in 96% yield. Acid **47** was then condensed with the magnesium salt of malonic acid monoethyl ester by means of CDI in THF affording 3-oxopropionate **48** in 86% yield. The reaction of **48** with dimethylformamide dimethylacetal and cyclopropylamine by means of acetic anhydride in dichloromethane gave the 3-(cyclopropylamino) acrylate **49** in 77% yield, and this was followed by cyclization using K_2CO_3 in hot DMSO, yielding quinolone **50** in 91% yield. Coupling of **50** with the isoindolylboronic acid derivative **51**, which was obtained by reaction of 5-bromo-1-(*R*)-methyl-2-tritylisoindoline with triisopropyl borate and *n*-butyl lithium, in THF using bis(triphenylphosphine)palladium(II) chloride as catalyst in refluxing toluene afforded the protected compound **52** in 60% yield. Removal of the trityl group with HCl in etha-



Scheme 7. Synthesis of Imidafenacin.

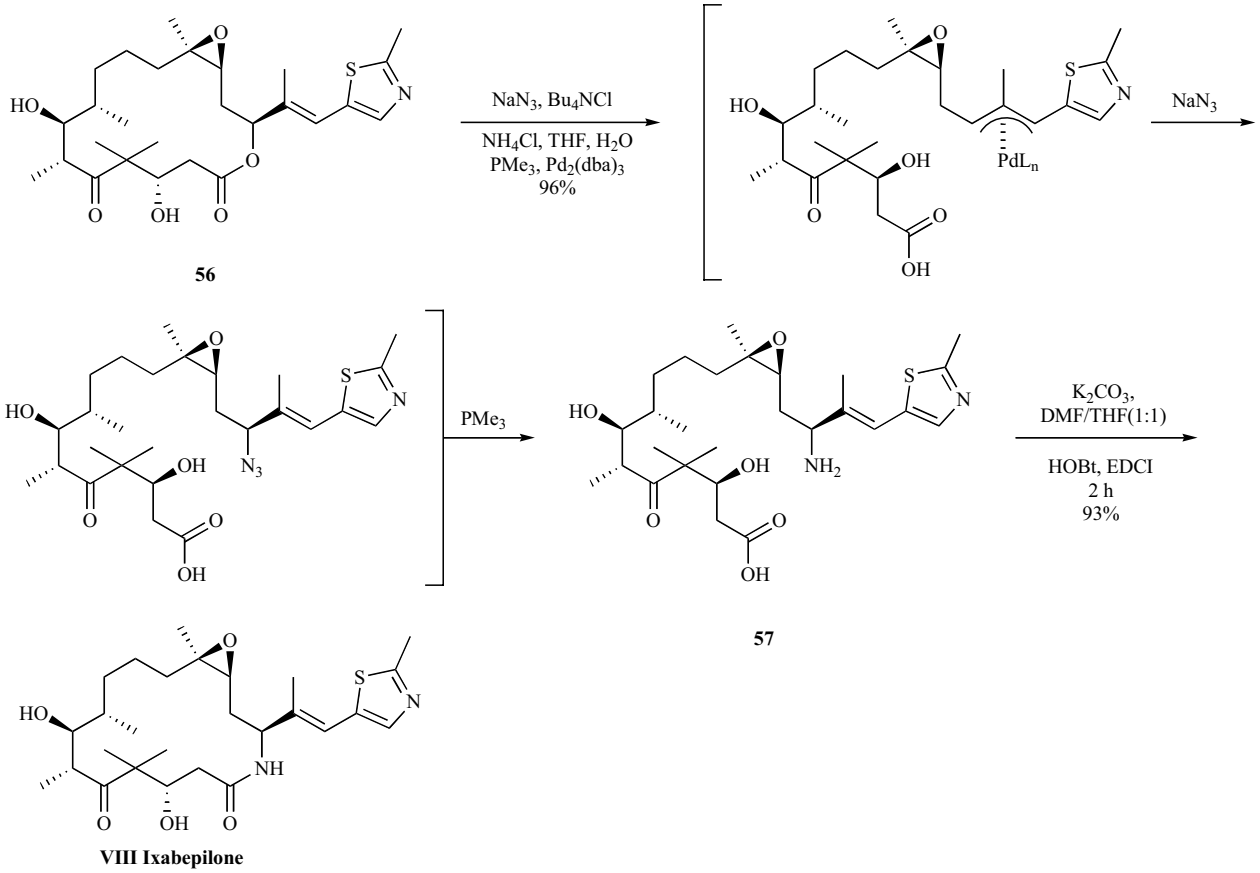
nol, followed by saponification of the ethyl ester and formation of the mesylate salt provided garenoxacin mesilate hydrate (**VI**).

Imidafenacin (Staybla, Uritos®)

Imidafenacin, an orally active muscarinic M1/M3 antagonist, was launched in Japan for the treatment of overactive bladder (OAB) [33]. Overactive bladder alone incurs annual costs of $12.6 billion [USD]. The drug was originally developed by Kyorin and it has selective action on bladder smooth muscle. Subsequently, Kyorin signed an agreement with Ono Pharmaceutical for co-development and co-marketing of imidafenacin. To date, the synthesis reported [34], gives no information on chemical yields. Diphenylacetonitrile (**53**) was alkylated with dibromoethane in the presence of $NaNH_2$ in toluene to give bromide compound **54** (Scheme **7**). The bromide **54** was condensed with 2-methylimidazole in the presence of Et_3N in hot DMF to afford 2-methylimidazole derivative **55**. Hydrolysis of the cyano group of **55** with 70% sulfuric acid provided imidafenacin (**VII**).

Ixabepilone (*Ixempra*™)

Ixabepilone is a semi-synthetic analog of epothilone developed by Bristol-Myers Squibb for the treatment of metastatic breast cancer and has a mode of action similar to paclitaxel which involves stabilizing microtubules by promoting tubulin polymerization [35]. Ixabepilone is indicated for use as monotherapy in metastatic or locally advanced breast cancer after failure of an anthracycline, a taxane, or capecitabine treatment. Additionally, ixabepilone is currently undergoing clinical trials targeting a variety of additonal cancer indications. The synthesis [36] is described in Scheme **8**, and was

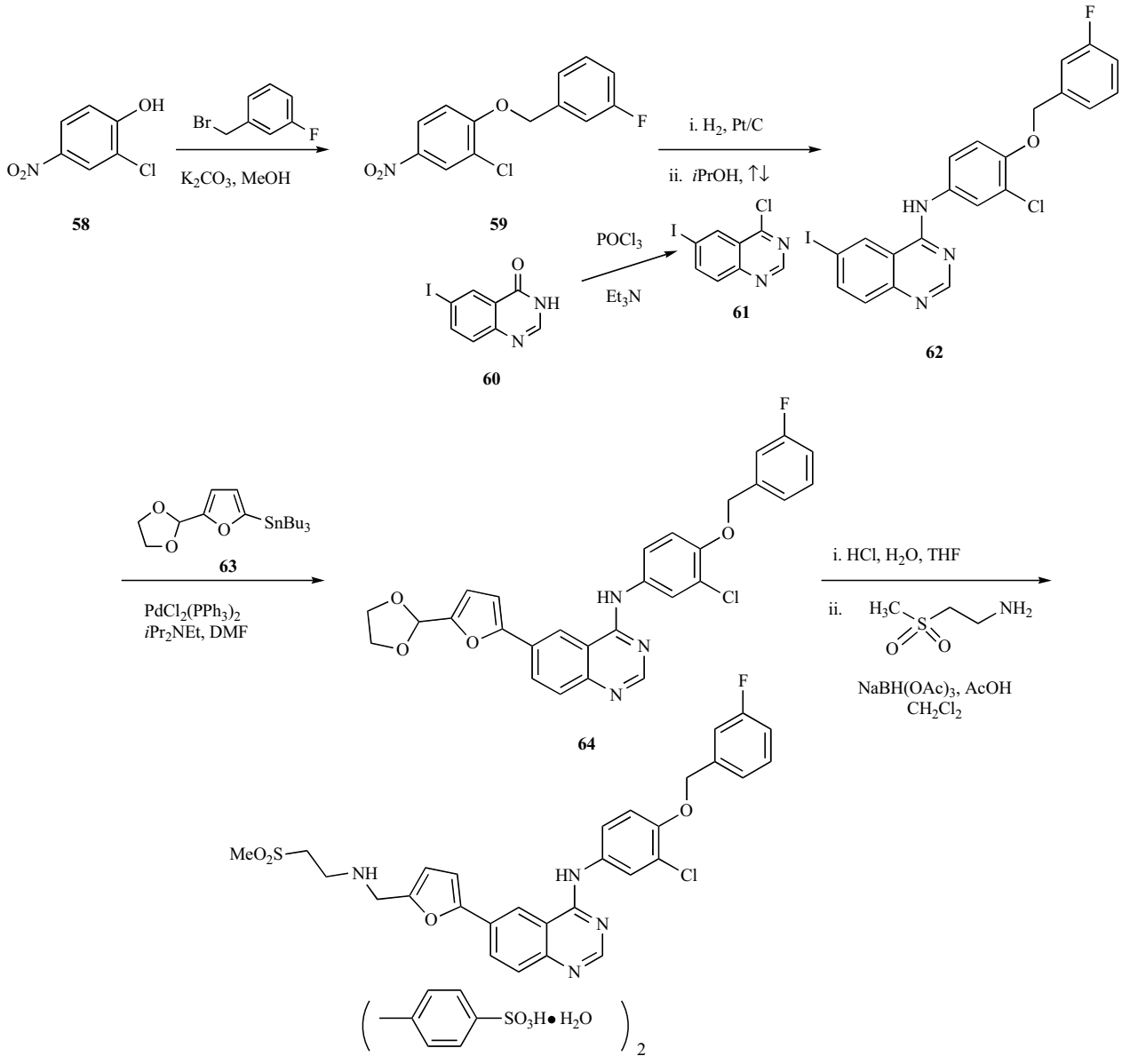


Scheme 8. Synthesis of Ixabepilone.

initiated by treating epothilone B (**56**) with sodium azide, tetrabutylammonium chloride, ammonium chloride, trimethylphosphine and tris-(dibenzylideneacetone)-dipalladium(0) chloroform which gave the ring-opened amino acid **57** in 96% yield. It has been proposed that this reaction proceeds *via* initial ring-opening π-allyl palladium complex formation followed by trapping with azide and subsequent reduction to the desired amine [36b]. Lactamization of the acyclic amino carboxylic acid **57** by reaction with K_2CO_3, HOBt and EDCI provided ixabepilone (**VIII**) in 93% yield. Re-crystallization from cyclohexane/ethyl acetate afforded ixabepilone in 56% overall yield from epothilone B.

Lapatinib Ditosylate (*Tykerb*®)

Lapatinib, an ErB-1 and ErB-2 dual kinase inhibitor, was launched for the treatment of advanced or metastatic HER2 (ErbB2) positive breast cancer in women who have received prior therapy [37]. The drug was discovered and developed by GlaxoSmithKline and is also currently being evaluated for several additional cancer indications. The synthesis started with Williamson ether synthesis between 2-chloro-4-nitrophenol (**58**) and 3-fluorobenzyl bromide to give ether **59** (Scheme **9**); however, no specific yields were provided [38]. Reduction of the nitro group of compound **59** by catalytic hydrogenation over Pt/C and subsequent condensation of the resulting aniline with 4-chloro-6-iodoquinazoline (**61**) in refluxing *i*-PrOH afforded compound **62**. 4-Chloro-6-iodoquinazoline (**61**) was prepared by reacting 6-iodoquinazolin-4(3H)-one (**60**) with $POCl_3$ in the presence of triethylamine. Compound **62** was subjected to Stille coupling with 5-dioxolanyl-2-(tributylstannyl)furan (**63**) in the presence of $PdCl_2(PPh_3)_2$ to give **64**. Acidic hydrolysis of acetal **64** using HCl in THF/H_2O provided the corresponding aldehyde which was further subjected to reductive amination with 2-(methan-



Scheme 9. Synthesis of Lapatinib ditosylate.

esulfonyl)ethylamine in the presence of sodium triacetoxyborohydride to yield lapatinib. Lapatinib was treated with *p*-toluenesulfonic acid solution to give lapatinib ditosylate (**IX**).

Lisdexamfetamine Mesilate (*Vyvanase*®)

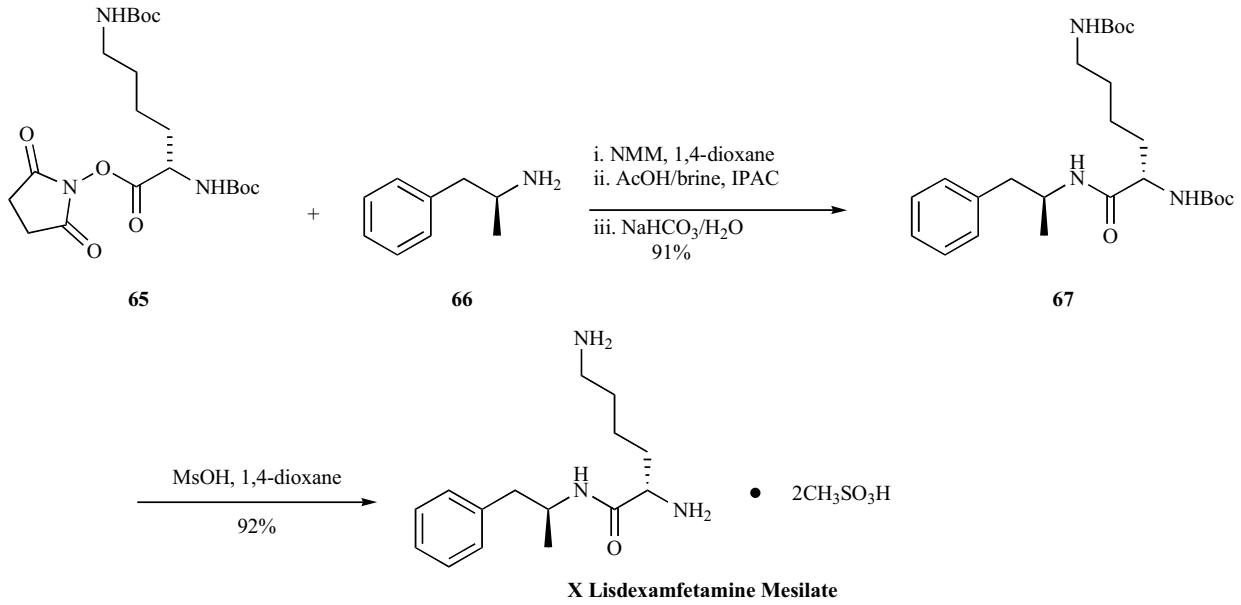
Lisdexamfetamine, a prodrug consisting of *d*-amphetamine conjugated to L-lysine, is a stimulant for the treatment of ADHD in children. Lisdexamfetamine was discovered, developed, and launched in the US in 2007 by New River Pharmaceuticals and marketed by Shire after their merger. Lisdexamfetamine offers the advantage of prolonged duration of action and reduced abuse potential liability versus traditional stimulant agents for the treatment of ADHD [39]. The straightforward synthesis of lisdexamfetamine mesilate was initiated by adding a solution of D-amphetamine (**66**) to a solution of Boc-L-Lys(Boc)-OSu (**65**), *N*-methylmorpholine and 1,4-dioxane (Scheme **10**) [40]. The resulting mixture was partitioned between isopropyl acetate and an acetic acid/brine solution, and the organic layer was washed with aqueous sodium bicarbonate to give Boc-L-Lys(Boc)-D-amphetamine (**67**) in 91% yield. The two primary amine groups were liberated by reacting a solution of **67** in 1,4-dioxane with methanesulfonic acid providing lisdexamfetamine mesilate (**X**) in 92% yield.

Maraviroc (*Selzentry*®)

Maraviroc, a chemokine CCR5 antagonist, was discovered and developed by Pfizer for the treatment of HIV-infected adults who are infected with only CCR5-tropic HIV-1 virus and who have HIV-1 strains resistant to multiple antiretroviral agents [41]. Maraviroc was launched in the U.S. and the E.U. in 2007. In addition to treating HIV-1, Pfizer is currently developing maraviroc for the potential oral treatment of rheumatoid arthritis. Two separate but similar approaches to the synthesis of enantiomerically pure maraviroc have been described, differing only in the end game strategy, the largest scale synthesis is reported herein [42,43]. The preparation of the azabicyclic triazole core of maraviroc (**75**) is described in Scheme **11**. Cyclization of 2,5-dimethoxytetrahydrofuran **68** with benzylamine **69** and 1,3-acetonedicarboxylic acid **70** under aqueous HCl and NaOAc produced benzyl protected tropanone **71** in 47% yield. Reaction of **71** with ammonium hydroxide in pyridine generated the corresponding oxime in 96% yield which was reduced using sodium in refluxing pentanol to give *exo*-amine **72** in 92% yield. Acetylation of **72** with isobutyric acid using EDC gave amide **73** in 53% yield. Triazole **74** was then prepared in a one-pot, two step procedure by first reacting amide **73** with phosphorus oxychloride followed by acetohydrazide to affect the desired cyclization in 30% yield. Removal of the benzyl protecting group of the amine under standard transfer hydrogenolysis conditions using ammonium formate as the hydrogen source gave azabicyclic triazole intermediate **75**.

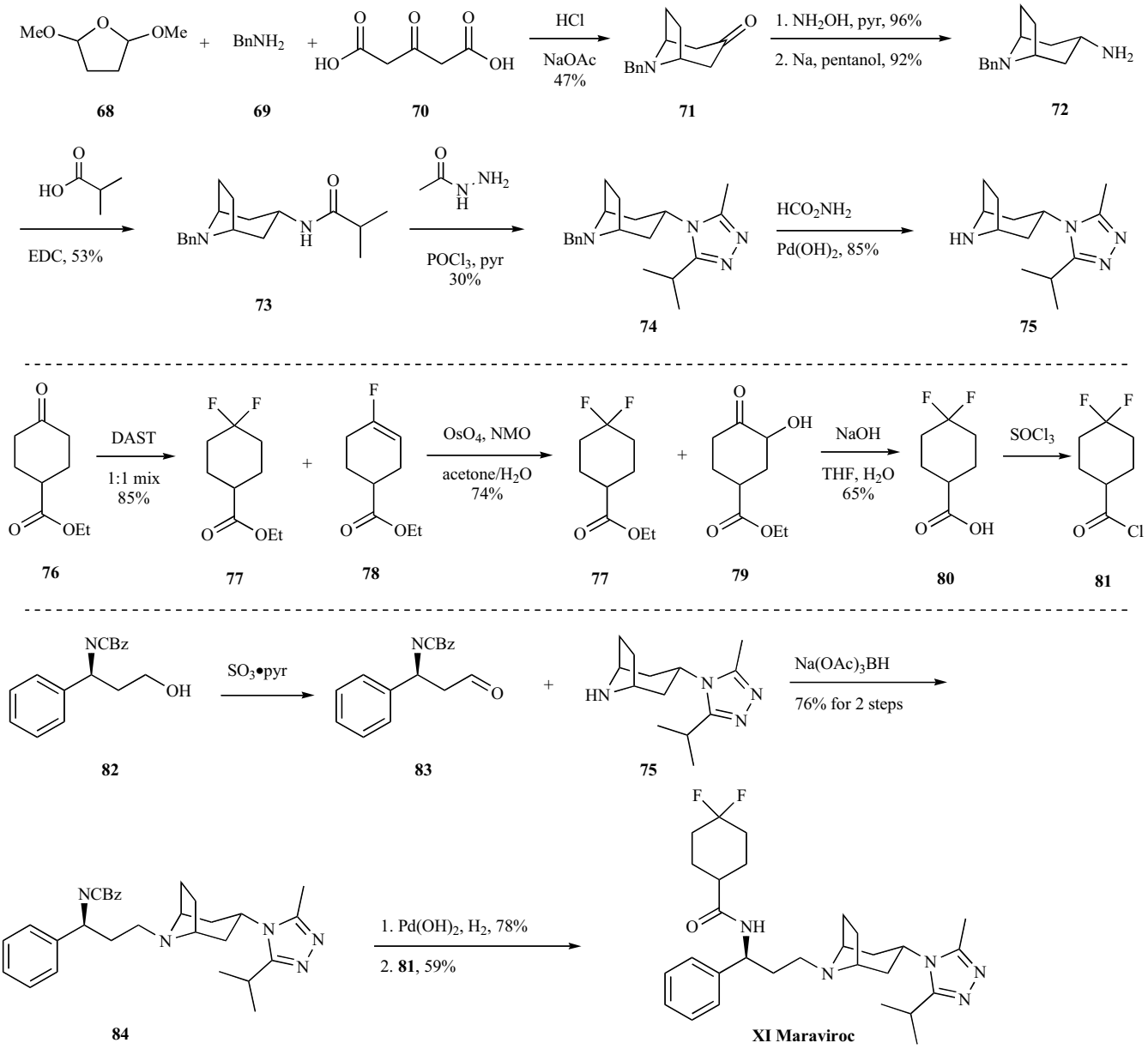
The preparation of the 4,4-difluorocyclohexane carboxylic acid chloride coupling partner **81** is described as follows (Scheme **11**). Difluorination of cyclohexanone-4-carboxylic acid ethyl ester **76** was accomplished through the reaction with diethylaminosulfur trifluoride (DAST) to give a inseparable 1:1 mixture of the desired difluorinated product **77** and undesired fluoroalkene **78** in 85% yield. This mixture was reacted with osmium tetroxide and NMO to affect complete dihydroxylation of the alkene functional group of **78** to keto alcohol **79** with concomitant no reaction of the difluorinated ester **77**. Purification of **77** from the reaction mixture followed by saponification under basic conditions gave acid **80** in 65% yield. Reaction of **80** with thionyl chloride produced the 4,4-difluorocyclohexane carboxylic acid chloride coupling partner **81** which was carried on without further purification.

The endgame strategy to maraviroc is described as follows (Scheme **11**). Readily available alcohol **82** was oxidized to aldehyde **83** using sulfur trioxide pyridine complex [44]. Aldehyde **83** was reacted with azabicylic triazole **75** and sodium triacetoxyborohydride to give the protected



X Lisdexamfetamine Mesilate

Scheme 10. Synthesis of Lisdexamfetamine Mesilate.

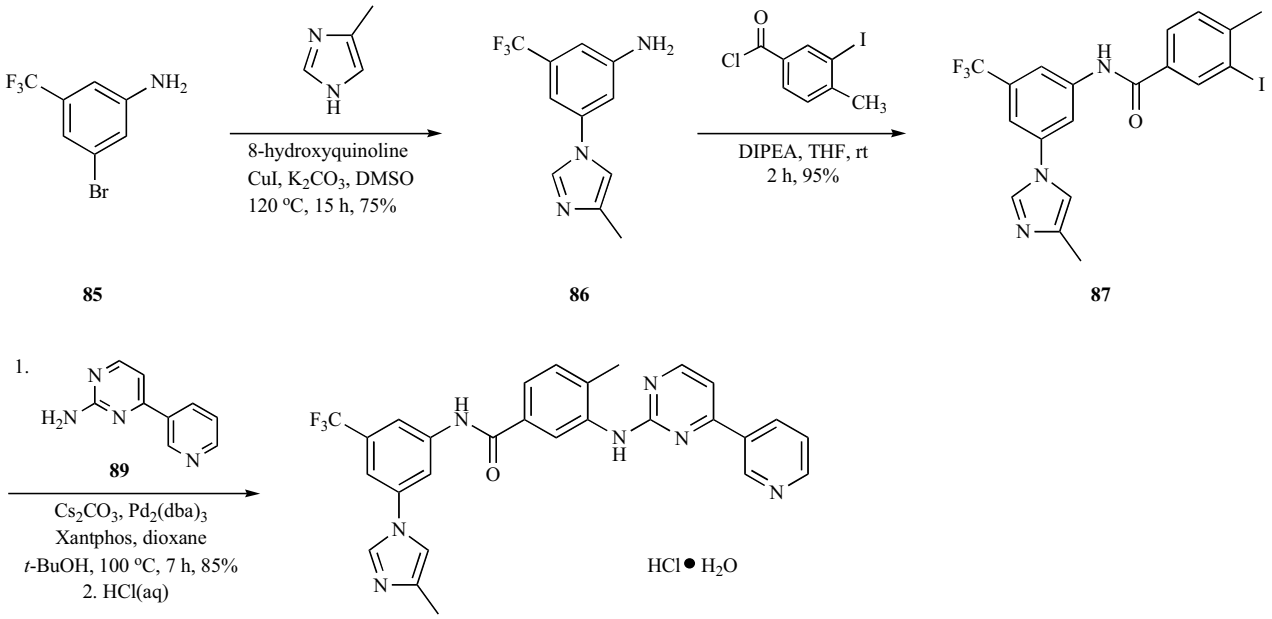


Scheme 11. Synthesis of Maraviroc.

amine **84** in 76% yield for the two step sequence. Removal of the CBz protecting group under standard catalytic hydrogenolysis conditions using Pearlman's catalyst gave the corresponding primary amine in 78% yield which was reacted with acid chloride **81** to give maraviroc (**XI**) in 59% yield.

Nilotinib (*Tasigna*®)

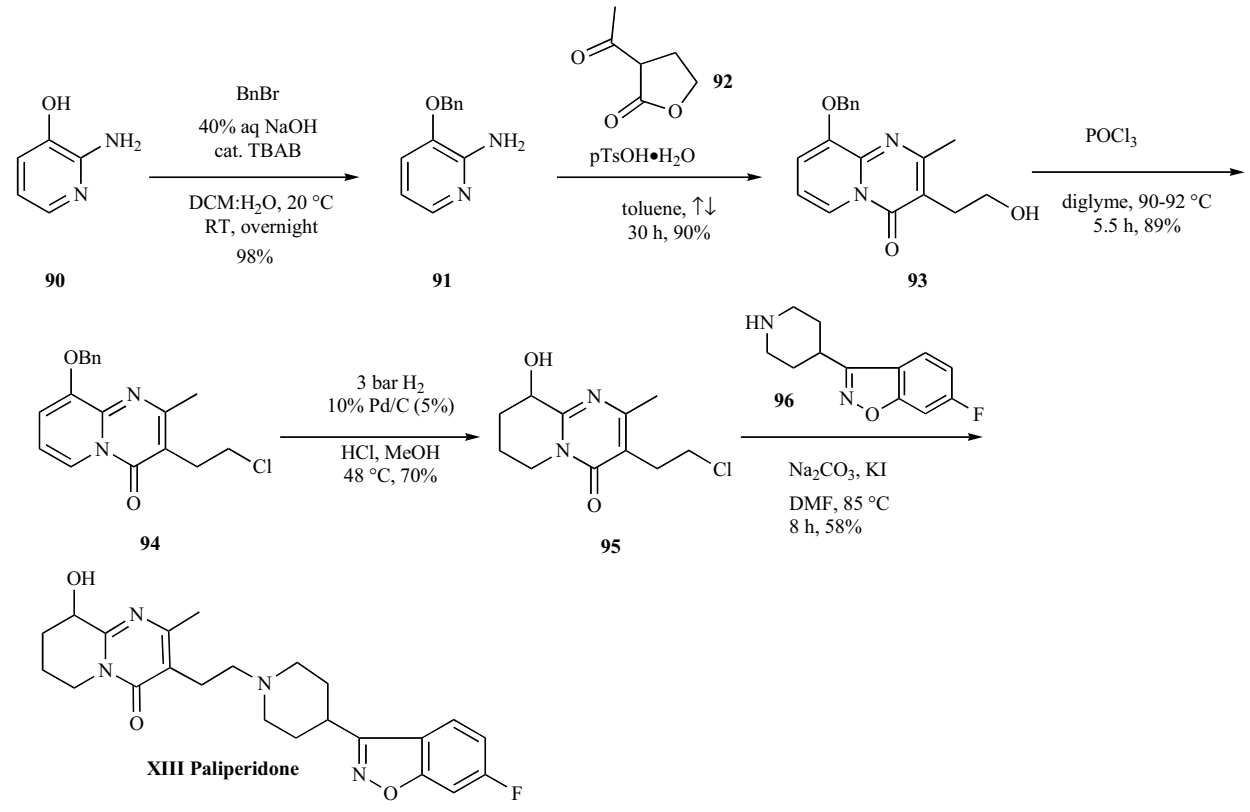
Nilotinib, an orally active signal transduction inhibitor that selectively inhibits the tyrosine kinase Bcr-Abl, was discovered and developed by Norvartis and was launched for the treatment of chronic myeloid leukemia (CML) in patients with Philadelphia chromosome-positive (Ph+) disease who are resistant or intolerant to imatinib mesilate [45]. Additional clinical trials are currently underway for the treatment of acute lymphoblastic leukemia (ALL) and gastrointestinal stromal tumors (GISTs). A concise synthesis of nilotinib was recently described (Scheme **12**) [46]. 3-Bromo-5-trifluoromethylaniline (**85**) was condensed with 4-methylimidazole in the presence of CuI, 8-hydroxyquinoline and potassium carbonate in hot DMSO to give compound **86** in 75% isolated yield. Aniline **86** was reacted with 3-iodo-4-methylbenzoic chloride and diisopropylethyl amine (DIPEA) in THF at room temperature to give amide **87** in 95% yield. Palladium catalyzed aryl amine coupling between **87** and commercially available 4-(pyridin-3-yl)pyrmidin-2-amine (**89**) was effectively carried out by using $Pd_2(dba)_3$/Xantphos as the catalyst system in the presence of cesium carbonate in dioxane/*t*-BuOH to give nilotinib in 89% yield as a while solid which was treated with aqueous HCl solution to give nilotinib hydrochloride monohydrate (**XII**).



Scheme 12. Synthesis of Nilotinib.

Paliperidone (*Invega*™)

Paliperidone, a metabolite of the marketed antipsychotic drug risperidone, is a dual inhibitor of $5HT_2$ and dopamine D_2 receptors developed by Johnson and Johnson for the treatment of schizophrenia [6,47]. It is formulated for once a day dosing with a proprietary OROS extended release formulation [6]. Among a number of publications on the preparation of paliperidone [48], the most recently described improved synthesis of the drug is shown in Scheme **13** [49,50]. 2-Amino-3-hydroxypiperidine (**90**) was treated with benzyl

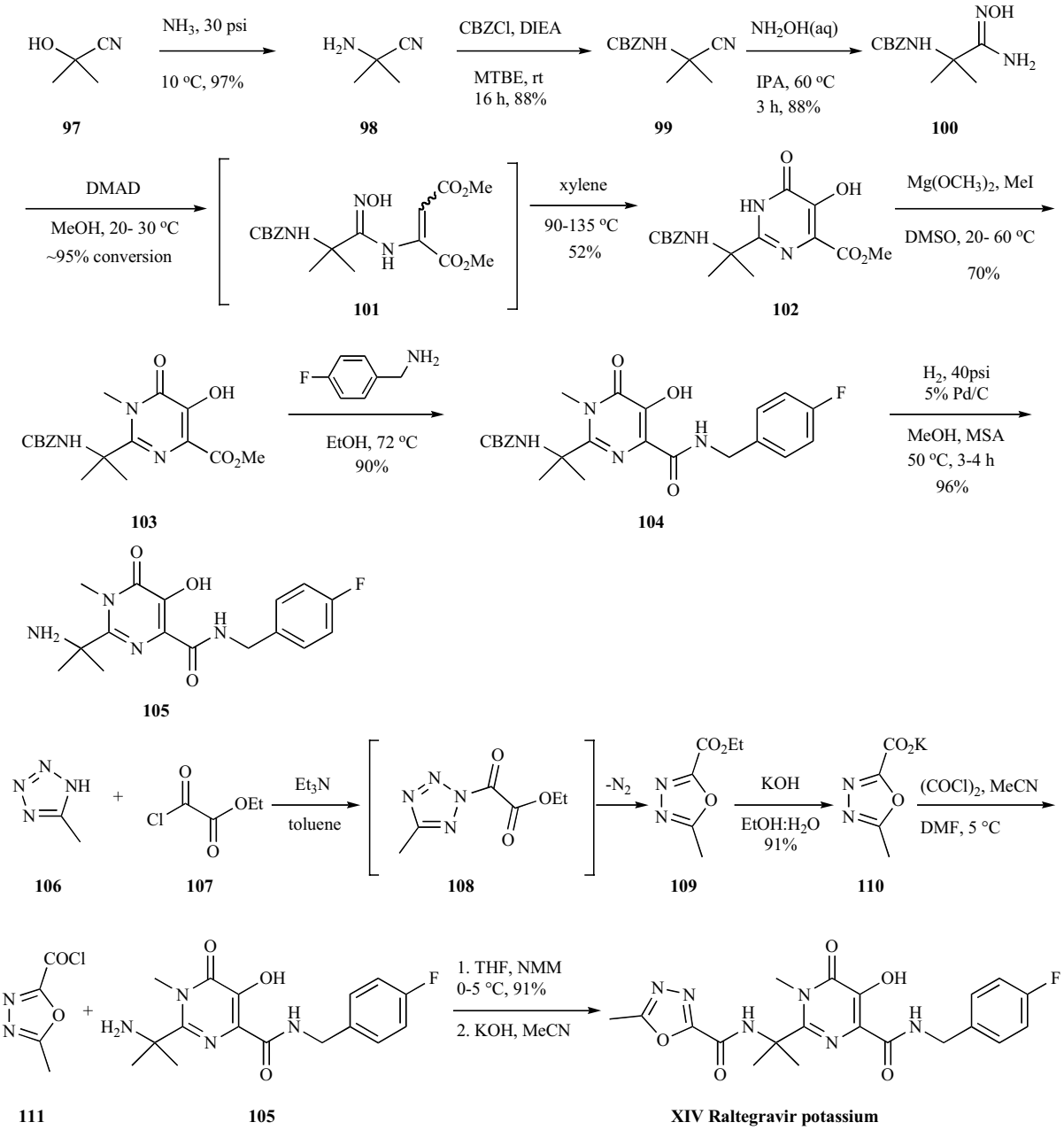


Scheme 13. Synthesis of Paliperidone XIII.

bromide, sodium hydroxide and a catalytic amount of *t*-butyl ammonium bromide (TBAB) in a biphasic mixture of water and DCM to afford benzyl ether **91** in 98% yield. Amino pyridine **91** was reacted with ketolactone **92** in refluxing toluene and catalytic *p*-TsOH·H_2O with azeotropic removal of water providing bicyclic pyrimidone **93** in 90% yield. Subsequent treatment of **93** with phosphorous oxychloride in diglyme gave the chloride **94** in 89% yield. The pyridine ring of chloride **94** was reduced by hydrogenation at 3 bar H_2 and 48 °C for 7.5 hours in the presence of 10%Pd/C and concentrated HCl giving **95** in 70% yield. Chloride **95** was coupled with benzisoxazole piperidine **96** in the presence of sodium carbonate and potassium iodide in DMF to give racemic paliperidone (**XIII**) in 58% yield.

Reltagravir (*Isentress*™)

Reltagravir is an HIV integrase inhibitor developed by Merck and approved in 2007 in the US for treatment of HIV-1 disease. Reltagravir is approved for the combination therapy with other antiretroviral agents for patients who have been exposed to other drugs and experienced resistance or patients that have growing viral loads [6,51,52]. Reltagravir was shown to be active in patients who had been unresponsive to other anti retroviral drugs and developed resistance [52]. Both the discovery [53] and process scale synthesis [54], have been published and the process synthesis is described in Scheme **14**. The synthesis follows a convergent approach with the preparation of two key intermediates, pyrimidone **105** and the oxadiazole acid chloride **111**, fol-



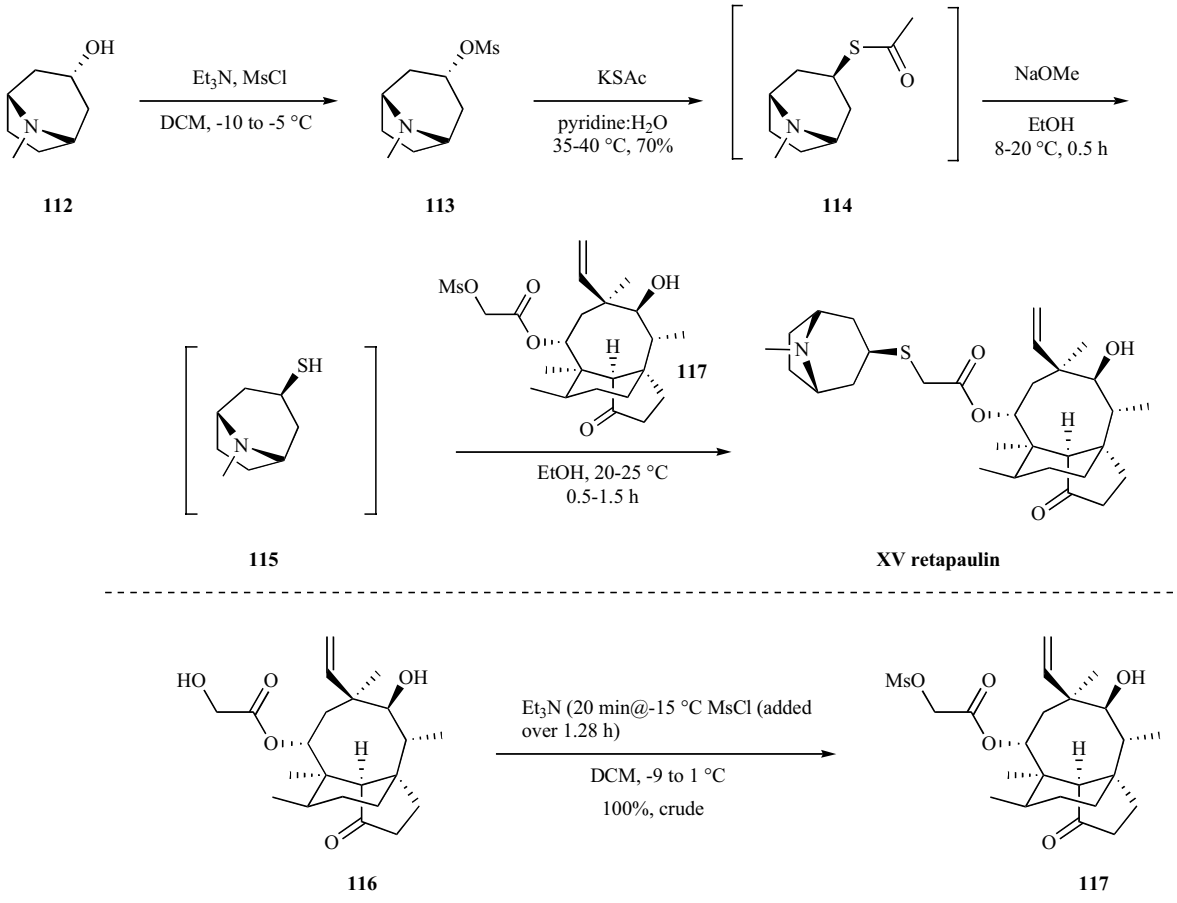
Scheme 14. Synthesis of Reltagravir.

lowed by amide coupling to make reltagravir. The synthesis of pyrimidone **105** began with amination of cyanohydrin **97** with ammonia at 10 °C using pressurized ammonia gas feed to give amino cyanohydrin **98** in 97% yield. Aminonitrile **98** was protected with benzylchloroformate in methyl tert-butyl ether (MTBE) at room temperature in the presence of DIPEA to provide protected aminonitrile **99** in 88% yield. Aminonitrile **99** was then reacted with aqueous hydroxyl amine in IPA at 60 °C to furnish amidoxime **100** in 88% yield. Initial reaction of amidoxime **100** with dimethylacetylene dicarboxylate (DMAD) in methanol at 20-30 °C provided clean conversion to intermediate **101**, which upon gradual warming to 90-135 °C in xylene gave pyrimidone **102** in 52% yield. Deprotonation of pyrimidone **102** in DMSO with magnesium methoxide, followed by removal of the residual methanol and treatment with methyliodide provided *N*-methyl pyrimidone **103** in 70% yield. Remarkably, there was less that 0.5% *O*-methylated side products after workup and methanol:MTBE (9:1) wash of the crude product. Heating pyrimidone ester **103** with *p*-fluorobenzylamine in ethanol at 72 °C followed by crystallization gave amide **104** in 90% yield. Hydrogenolysis of the CBZ protecting group of amide **104** at 40 psi H_2 using 5% Pd/C catalyst in the presence of methanesulfonic acid at 50 °C gave pyrimidone amine **105**, obtained as a hydrate, in 96% yield.

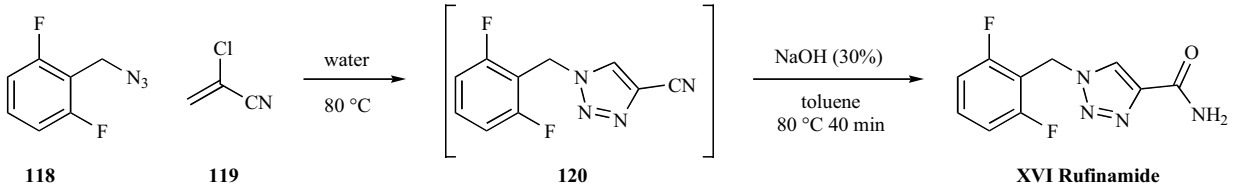
The synthesis of oxadiazole acid chloride **111** was initiated by reaction of ethyl oxalylchloride (**107**) with methyltetrazole (**106**) in the presence of triethylamine in toluene at 0 °C to give intermediate **108**. Slow addition of this intermediate to warm toluene at 50 °C followed by heating the reaction mixture at 65 °C for 1 hour resulted in loss of nitrogen and provided the oxadiazole ester **109**. Crude ester **109** was treated with KOH which resulted in saponification of the ester to give oxadiazole carboxylic acid potassium salt **110** in 91% yield from **106**. The synthesis was completed by first converting **110** to the corresponding acid chloride **111** using oxalyl chloride followed by reaction with pyrimidone **105** in the presence of *N*-methyl morpholine giving reltagravir in 91% yield after recrystallization from isopropanol/water. The reltagravir potassium salt **XIV** was then obtained by mixing KOH with reltagravir in acetonitrile and precipitating out the product *via* slow concentration and filtration of the potassium salt.

Retapamulin (*Altabax*™)

Antibacterial retapamulin is a derivative of the natural product pleuromutilin and was developed by Glaxo and approved in the US in 2007 for the treatment of skin infections [6]. It has a unique mechanism of action, inhibiting bacterial protein synthesis by inhibiting the larger subunit of the ribosome, and thus has no cross resistance to other antibacterial agents [55, 56]. A number of routes have been disclosed in the patent literature and all of them start with the natural product pleuromutilin [57, 58] and the process route is shown in Scheme **15** [58]. Commercially available tropinol



Scheme 15. Synthesis of Retapamulin XV.



118 **119** **120** **XVI Rufinamide**

Scheme 16. Synthesis of Rufinamide.

112 was mesylated under standard conditions (MsCl, Et_3N) to give mesylate **113**. Tropinol mesylate **113** was reacted with potassium thioacetate in pyridine and water giving intermediate **114** which was treated with sodium methoxide in ethanol to give intermediate **115**. Thiol **115** was reacted with pleuromutilin mesylate **117**, prepared by reacting pleuromutilin with methanesulfonyl chloride and triethylamine in DCM in 95% yield, giving crude retapamulin in 75% purity. Purification by crystallization in ethanol afforded retapamulin (**XV**) in >96-100% purity and 10.6% overall yield from tropinol mesylate **113**.

Rufinamide (*Inovelon*®)

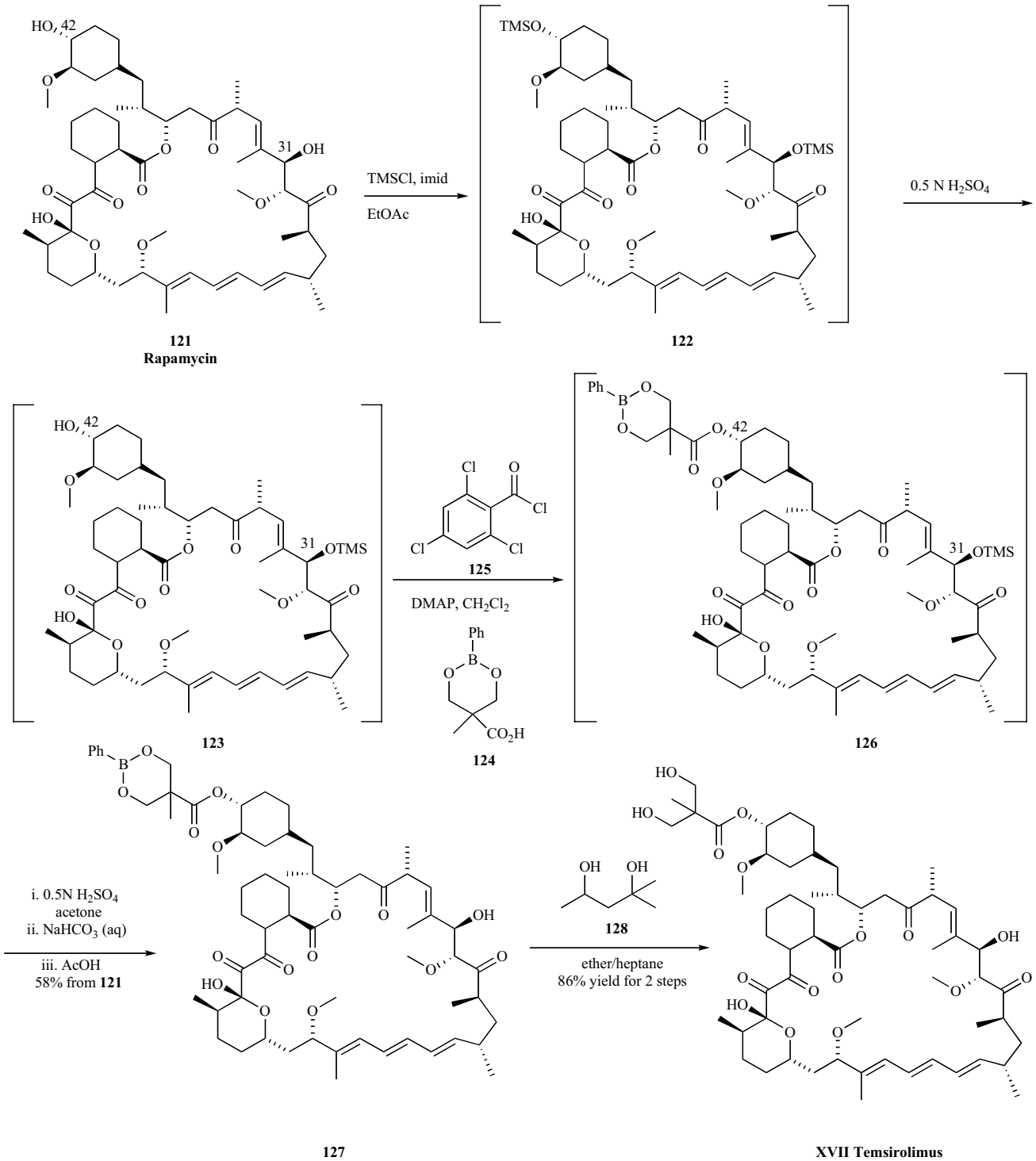
Rufinamide was developed by Novartis, and licensed by Eisai, for the treatment of epileptic seizures associated with Lennox-Gastaut Syndrome (LGS) [6]. Rufinamide is a sodium channel blocker and works by reducing the recovery of neuronal sodium-dependent action potential [59-62]. Although several different approaches have been reported in the literature [60, 63], a simple one pot synthesis of rufinamide is shown in Scheme **16** [64]. 2,6-Difluorobenzyl azide **118** was reacted with 2-chloroacrylonitrile **119** in water at 80 °C for 24 hours. The excess acrylonitrile was removed by heating and upon cooling, toluene was added. The resulting mixture was heated to 80 °C and sodium hydroxide was added to affect hydrolysis of the nitrile. After removal of toluene by distillation, the reaction mixture was cooled and the resulting product, rufinamide (**XVI**) was collected by filtration.

Temsirolimus *(Torisel®)*

Temsirolimus, a cell cycle inhibitor developed by Wyeth for the treatment of renal cell carcinoma, was launched in the US in 2007. Temsirolimus works by inhibiting mTOR (mammalian target of rapamycin)-driven cell proliferation [65]. Temsirolimus is also being developed for the treatment of mantle cell lymphoma (PhIII) and also as mono- or combination therapy for the treatment of ovarian and endometrium cancer (PhII). Additionally, temsirolimus is being evaluated for the treatment of several other types of cancer as well as multiple sclerosis and rheumatoid arthritis. The synthesis of temsirolimus was initiated by bis-silylation at positions 31 and 42 of rapamycin (**121**) using trimethylsilyl chloride and imidazole to give **122** (Scheme **17**) [66]. The silyl ether at positon 42 was regioselectively desilylated using dilute sulfuric acid producing intermediate **123**. The C42 position was acylated with the mixed anhydride derived from the 2-phenyl boronate acid **124** and 2,4,6-trichlorophenyl carboxylic acid chloride **125** using catalytic DMAP to give **126** [67]. Next, the silyl ether group at position 31 was removed using dilute sulfuric acid in acetone and after work up with aqueous sodium bicarbonate solution and acetic acid provided the deprotected intermediate **127**. The boronate ester was removed by reaction with excess 2-methyl-2,4-pentanediol **128** and the crude product was precipitated using ether/heptanes to afford pure temsirolimus (**XVII**) in 86% yield.

Trabectedin (*Yondelis*®)

Trabectedin is a novel marine-derived tetrahydroisoquinoline, an antitumor agent isolated from the colonial tunicate *Ecteinascidia turbinate*. Trabectedin binds to the minor groove of DNA and bends the DNA toward the major groove, blocking the activation of genes *via* several pathways. These pathways include selective inhibition of the expression of key genes (including oncogenes) involved in cell growth and drug resistance, inhibition of genetic repair pathways and inhibition of cell cycle progression leading to p53-independent programmed cell death [68]. Trabectedin was originally developed by PharmaMar, a subsidiary of Zeltia. Subsequently, the drug was co-developed and co-marketed with Ortho Biotech, a subsidiary of Johnson & Johnson. Trabectedin was approved as an orphan drug designation for the treatment of advanced soft tissue sarcoma and ovarian cancer. PharmaMar and Johnson & Johnson are exploring trabectedin for numerous additional cancer indications. Cyanosafracin B (**129**), available from the optimization of the fermentation of bacteria *Pseudomonas fluorescens* on kilogram scale, was used as the starting material for the synthesis (Scheme **18**) [69]. The amino and phenol groups of compound **129** were protected as their corresponding Boc and MOM derivatives, respectively giving compound **130** in 67% yield for the 2 steps. Compound **130** was subjected to NaOH in H_2O/MeOH, hydrolyzing the methoxy-*p*-quinone to give free hydroxyl compound **131** in 68% yield. Compound **131** was reduced with H_2 over Pd/C to give an unstable hydroquinone which was selectively alkylated with bromochloromethane in hot DMF in a sealed tube to give benzodioxolane **132**, which was used in the next step without purification. Compound **132** was subjected to a second alkylation with allylbromide to give allylic adduct **133** as a white solid in 56% yield from compound **131**. Removal of both the MOM and Boc protecting groups of **133** with TFA gave compound **134** in 95% yield. Compound **135**, the free amine product, was obtained by Edman degradation of the amide side chain of compound **134** by treating **134** with excess phenyl isothiocyanate to form the corresponding thiourea in 87% yield which was subsequently hydrolyzed with HCl in dioxane to give **135** in 82% yield. To set up the critical conversion of primary amine of compound **135** to its corresponding alcohol, the phenol of the E-ring needed to be protected as its MOM derivative. Therefore, the primary amine



121
Rapamycin

122

123

124

125

126

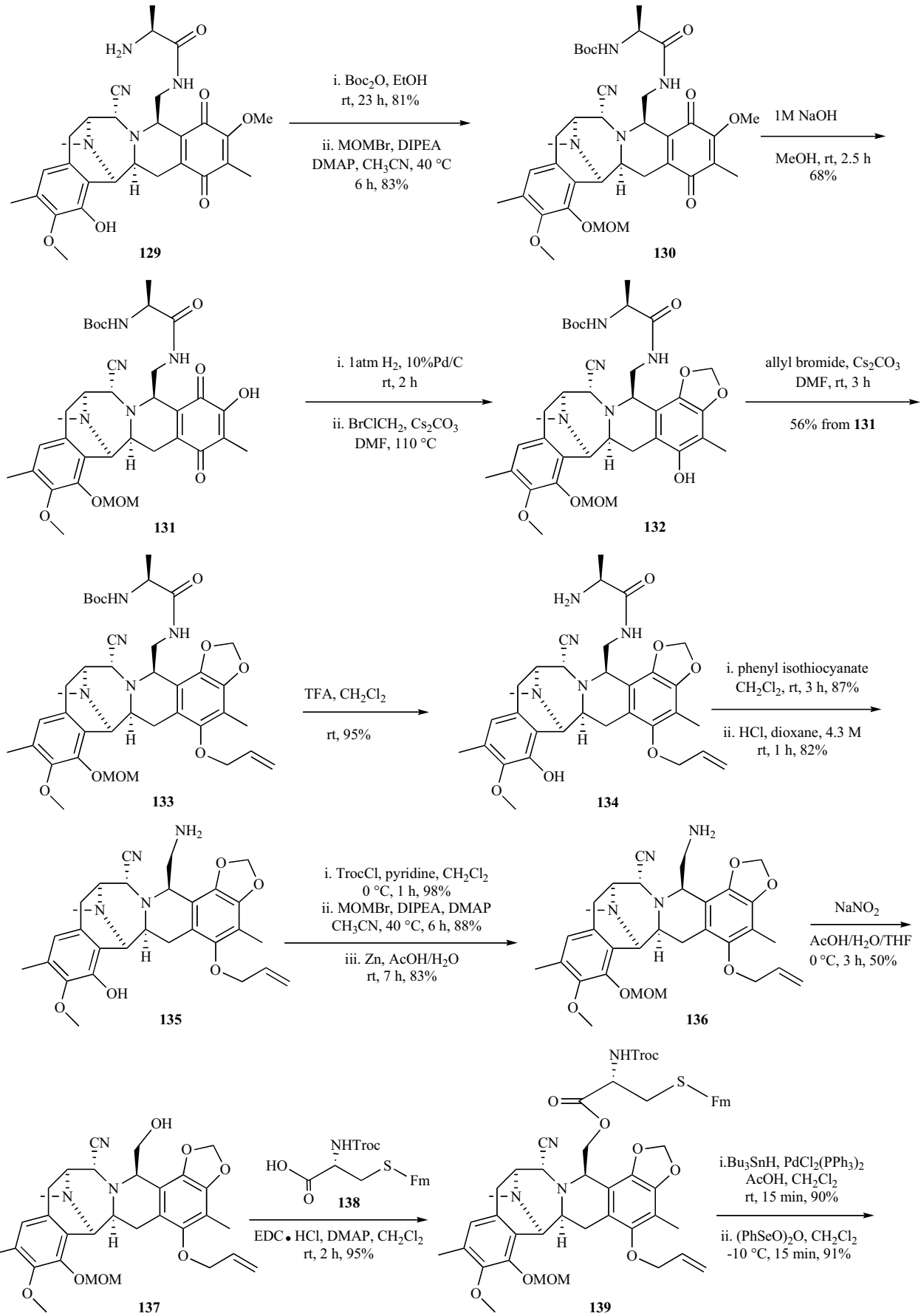
127

128

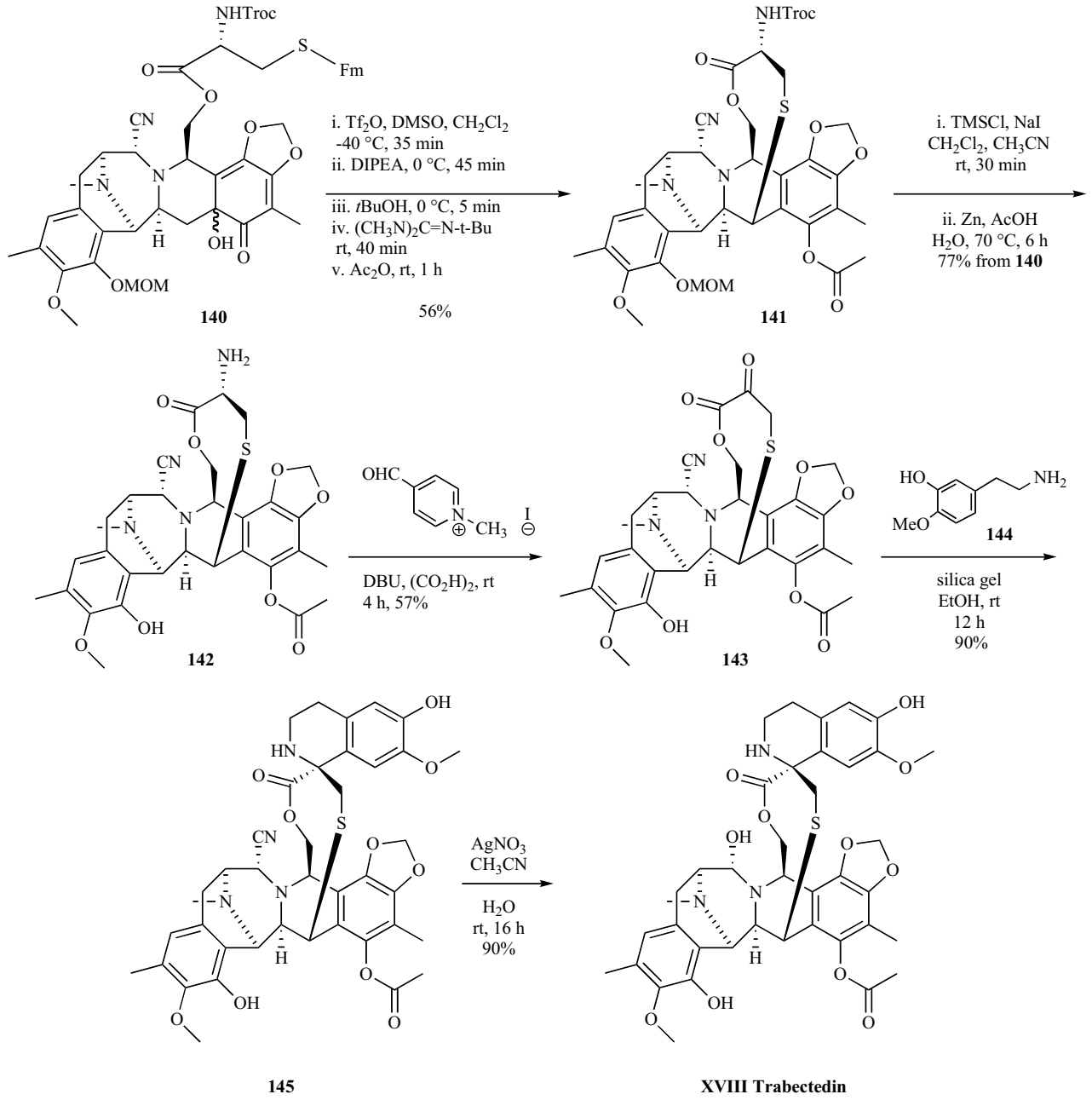
XVII Temsirolimus

Scheme 17. Synthesis of Temsirolimus.

was temporary protected as TROC carbamate in 98% yield. This was followed by reaction with MOMBr in the presence of DIPEA in 88% yield, and removal of the TROC protecting group with Zn in HOAc to give compound **136** in 83% yield. Compound **136** was treated with $NaNO_2$ in HOAc to give key primary hydroxy intermediate **137** in 50% yield which was coupled with **138** in the presence of EDC and DMAP to give ester **139** in 95% yield. Compound **139** was treated with *n*-tributyl tin hydride and a palladium catalyst removing the allylic protecting group to give the corresponding phenol in 90% yield which was subsequently oxidized with benzeneselenic anhydride in methylene chloride at low temperature to give **140** in 91% yield as a mixture of alcohol isomers. Compound **140** was converted to lactone **141** in 58% yield by the following transformations as developed by Corey [70]: a) reaction of compound **140** with *in situ* Swern


i. Boc2O, EtOH
rt, 23 h, 81%
ii. MOMBr, DIPEA
DMAP, CH3CN, 40 °C
6 h, 83%
1M NaOH
MeOH, rt, 2.5 h
68%
i. 1atm H2, 10%Pd/C
rt, 2 h
ii. BrClCH2, Cs2CO3
DMF, 110 °C
allyl bromide, Cs2CO3
DMF, rt, 3 h
56% from 131
TFA, CH2Cl2
rt, 95%
i. phenyl isothiocyanate
CH2Cl2, rt, 3 h, 87%
ii. HCl, dioxane, 4.3 M
rt, 1 h, 82%
i. TrocCl, pyridine, CH2Cl2
0 °C, 1 h, 98%
ii. MOMBr, DIPEA, DMAP
CH3CN, 40 °C, 6 h, 88%
iii. Zn, AcOH/H2O
rt, 7 h, 83%
NaNO2
AcOH/H2O/THF
0 °C, 3 h, 50%
EDC • HCl, DMAP, CH2Cl2
rt, 2 h, 95%
i.Bu3SnH, PdCl2(PPh3)2
AcOH, CH2Cl2
rt, 15 min, 90%
ii. (PhSeO)2O, CH2Cl2
-10 °C, 15 min, 91%
129
130
131
132
133
134
135
136
137
138
139

(Scheme 18. Contd….)

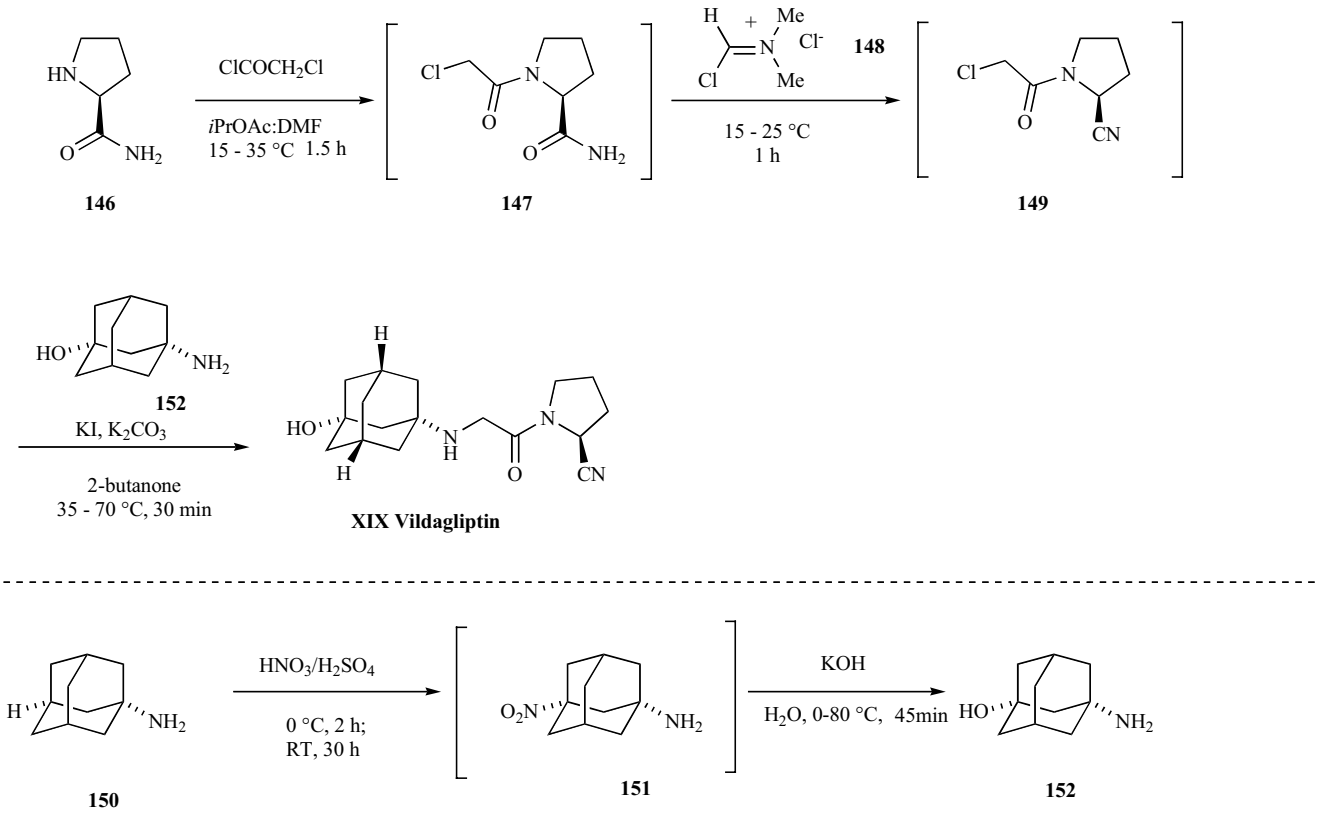


Scheme 18. Synthesis of Trabectedin.

reagent in DMSO at low temperature, b) addition of DIPEA to form the exendo quinine methide, c) quenching with *t*-BuOH to remove excess Swern reagent, d) addition of excess *N-t*-butyl-*N', N', N', N'*-tetramethylguanidine to convert the 9-fluorenylmethyl thioether to the thiolate ion and to initiate nucleophilic addition of sulfur to the quinine methide to generate the lactone ring, and e) addition of excess acetic anhydride to acetylate the resulting phenoxide group. The MOM and TROC protecting groups were removed with TMSCl/NaI and Zn in AcOH/H_2O, respectively to give compound **142** in 77% yield for these two steps. The α-amino lactone of compound **142** was oxidized to the corresponding α-keto lactone with the methiodide of pyridine-4-carboxaldehyde in the presence of DBU to give compound **143** in 57% yield. Compound **143** was reacted with **144** in the presence of silica gel in ethanol at room temperature to give stereospecifically the spiro-tetrahydroisoquinoline **145** in 90% yield which was finally reacted with $AgNO_3$ to replace the nitrile with a hydroxyl group to yield trabectedin (XVIII) in 90% yield.

Vildagliptan (*Galvus*®)

Vildagliptin, a dipeptidyl-peptidase IV (DPPIV) inhibitor discovered and developed by Novartis Pharmaceuticals, was approved for the treatment of type II diabetes in Mexico, Brazil and the E.U. Vildagliptin is the second DPPIV inhibi-



Scheme 19. Synthesis of Vildagliptin.

tor approved after last year's approval of sitagliptin developed by Merck [6,71,72]. Both the discovery [73] and process routes [74] toward the synthesis of this drug have been published, and the process route is shown in Scheme **19**. A solution of L-prolinamide **146** in DMF was added to a premixed solution of chloroacetyl chloride in isopropylacetate/DMF at 15 °C. Upon complete addition of **146** the reaction mixture was warmed to 35 °C, which generated intermediate **147**. After 1.5 hours, the reaction mixture was cooled to 15 °C and Vilsmeier reagent **148** was added portionwise to generate nitrile **149**. 3-Hydroxyaminoadamantane **152**, required for coupling with **149**, was prepared in two steps [74]. Aminoadamantane **150** was added in small portions to an ice cold solution of sulfuric acid and nitric acid. Upon complete addition, the reaction was stirred for 2 hours at 0 °C and for 30 hours at room temperature generating intermediate **151**. Next, the reaction mixture containing **151** was cooled in an ice-water bath and solid KOH was added portionwise over 45 minutes. After addition was complete, the reaction had reached 80 °C which resulted in the evolution of NO_2 gas and the reaction turned into a white slurry. After filtration of the slurry, the solid was washed with DCM, dried, and concentrated to give the desired 3-hydroxyaminoadamantane **152**. The synthesis was completed by adding a solution of **149**, prepared as described above, to a solution of 3-hydroxyaminoadamantane **152**, potassium carbonate, and potassium iodide in 2-butanone generating vildagliptin (**XIX**) in 31% crude yield. Pure vildagliptin was obtained upon re-crystallization from 2-butanone; however the yield was not reported.

ABBREVIATIONS

AIBN	=	2,2'-Azobisisobutyronitrile
BOC	=	*t*-Butyloxycarbonyl
CBZ	=	Benzyloxycarbonyl
CDI	=	*N,N'*-Carbonyldiimidazole
DBU	=	1,8-Diazabicyclo[5.4.0] undec-7-ene
DCE	=	Dichloroethane
DCM	=	Dichloromethane
DIAD	=	Diisopropyl azodicarboxylate
DIBAL-H	=	Diisobutylaluminum hydride
DIPEA	=	Diisopropylethylamine
DMAP	=	4-Dimethylaminopyridine
DMF	=	*N,N*-Dimethylformamide
DMPU	=	*N,N'*-Dimethylpropyleneurea
DMSO	=	Methyl sulfoxide
DPPC	=	Diphenylphosphinic chloride
EDC	=	*N*-(3-Dimethylaminopropal)-*N'*-ethylcarbodiimide
HOBT	=	1-Hydroxybenzotriazole hydrate
IPA	=	Isopropyl alcohol

IPAC = Isopropyl acetate

LDA = Lithium diisopropylamide

LIHMDS = Lithium bis(trimethylsilyl)amide

MEK = Methylethyl 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-Methoxylbenzyl

PPA = Polyphosphoric acid

TBAF = *t*-Butyl ammonium fluoride

TBAB = *t*-Butyl ammonium bromide

TBDMS = *t*-Butyldimethylsilyl

TEA = Triethyl amine

TFA = Trifluoroacetic acid

TFAA = Trifluoroacetic acid anhydride

THF = Tetrahydrofuran

THP = Tetrahydropyran

TIPS = Triisopropylsilyl

TPA = Triisopropylamine

TPAP = Tetrapropylammonium perruthenate

TROC = 2,2,2-Trichlorethoxycarbonyl

TMG = 1,1,3,3-Tetramethylguanidine

p-TSA = *para*-Toluene sulfonic acid

REFERENCES

[1] Raju, T. N. K. The Nobel chronicles. 1988: James Whyte Black, (b 1924), Gertrude Elion (1918-99), and George H Hitchings (1905-98). *Lancet,* **2000***, 355*, 1022.

[2] Li, J.; Liu, K.-C. Synthetic approaches to the 2002 new drugs. *Mini Rev. Med. Chem.,* **2004***, 4*, 207-33.

[3] Liu, K.-C.; Li, J.; Sakya, S. M. Synthetic approaches to the 2003 new drugs. *Mini Rev. Med. Chem.,* **2004***, 4*, 1105-25.

[4] Li, J.; Liu, K.-C.; Sakya, S. M. Synthetic approaches to the 2004 new drugs. *Mini Rev. Med. Chem.,* **2005***, 5*, 1133-44.

[5] a) Sakya, S. M.; Liu, K.-C.; Li, J. Synthetic approaches to the 2005 new drugs. *Mini Rev. Med. Chem.,* **2007***, 7*, 429-50. b) Liu, K.-C.; Sakya, S. M.; Li, J. Synthetic approaches to the 2006 new drugs. *Mini Rev. Med. Chem.,* **2007***, 7*, 1255-69.

[6] Graul, A. I.; Prous, J. R.; Barrionuevo, M.; Bozzo, J.; Castañer, R.; Cruces, E.; Revel, L.; Rosa, E.; Serradell, N.; Sorbera, L. A. The Year's New Drugs and Biologics-2007. *Drug News Perspect,* **2008***, 21*, 7-35.

[7] Mealy, N. E.; Castaner, J.; Castaner, R. M.; Silvestre, J. Aliskiren Fumarate. *Drugs Future,* **2001**, *26*, 1139-48.

[8] Rueger, H.; Stutz, S.; Goschke, R.; Spindler, F.; Maibaum, J. A convergent synthesis approach towards CGP60536B, a non-peptide orally potent renin inhibitor, *via* an enantiomerically pure ketolactone intermediate. *Tetrahedron Lett*., **2000**, *41*, 10085-9.

[9] Sandham, D. A.; Taylor, R. J.; Carey, J. S.; Fassler, A. A convergent synthesis of the renin inhibitor CGP60536B. *Tetrahedron Lett*., **2000**, *41*, 10091-4.

[10] Dondoni, A.; De Lathauwer, G.; Perrone, D. A convergent synthesis of the renin inhibitor SPP-100 using a nitrone intermediate. *Tetrahedron Lett*., **2001**, *42*, 4819-23.

[11] Goschke, R.; Stutz, S.; Heinzelmann, W.; Maibaum, J. The non-chiral bislactim diethoxy ether as a highly stereo-inducing synthon for sterically hindered, γ-branched α-amino acids: a practical, large-scale route to an intermediate of the novel renin inhibitor aliskiren**.** *Helv. Chim. Acta,* **2003**, *86*, 2848-70.

[12] Dong, H.; Zhang, Z.-L.; Huang, J.-H.; Ma, R.; Chen, S.-H.; Li, G. Practical synthesis of an orally active renin inhibitor aliskiren. *Tetrahedron Lett*., **2005**, *46*, 6337-40.

[13] Sorbera, L. A.; Castañer, J. Ambrisentan. Ambrisentan: treatment of pulmonary arterial hypertension endothelial ETA receptor antagonist. *Drugs Future,* **2005**, *30*, 765-70.

[14] Riechers, H.; Albrecht, H.-P.; Amberg, W.; Baumann, E.; Bernard, H.; Bohm, H.-J.; Klinge, D.; Kling, A.; Muller, S. ; Raschack, M.; Unger, L.; Walker, N.; Wernet, W. Discovery and optimization of a novel class of orally active nonpeptidic endothelin-A receptor antagonists. *J. Med. Chem.,* **1996**, *39,* 2123-8.

[15] Jansen, R.; Knopp, M.; Amberg, W.; Bernard, H.; Koser, S.; Muller, S.; Munster, I.; Pfeiffer, T.; Riechers, H. Structural similarity and its surprises: endothelin receptor antagonists – process research and development report. *Org. Proc. Res. Dev*., **2001**, *5,* 16-22.

[16] Revill, P.; Serradell, N.; Bolos, J.; Bayes, M. Arformoterol tartrate: β2-Adrenoceptor agonist, bronchodilator, treatment of chronic obstructive pulmonary disease. *Drugs Future,* **2006**, *31*, 944-52.

[17] Tanoury, G. J.; Senanayake, C. H.; Kessler, D. W. Formoterol tartrate process and polymorph. US20006472563B1, 2002, p. 19.

[18] Tanoury, G, J.; Hett, R; Kessler, D. W.; Wald, S. A.; Senanayake, C. H. Taking advantage of polymorphism to effect an impurity removal: development of a thermodynamic crystal form of (*R,R*)-formoterol tartrate*. Org. Proc. Res. Dev*., **2002**, *6*, 855-62.

[19] Gao, Y.; Hett, R.; Fang, K. Q.; Wald, S. A.; Redmon, M. P.; Senanayake, C. H. Formoterol process. US20006040344A, 2000, p. 11.

[20] Gao, Y.; Hett, R.; Fang, K. Q.; Wald, S. A.; Senanayake, C. H. Process for the preparation of optically pure isomers of formoterol. WO21175A1, 1998, p. 30.

[21] a) Hett, R.; Fang, K. Q.; Gao, Y.; Wald, S. A.; Senanayake, C. H. Large-scale synthesis of enantio- and diastereomerically pure (*R*,*R*)-formoterol. *Org. Proc. Res. Dev*., **1998**, *2*, 96-9. b) Kaiser, C.; Colella, D. F.; Schwartz, M. S.; Garvey, E.; Wardell, J. R. Adrenergic agents. 1. Synthesis and potential beta.-adrenergic agonist activity of some catechol amine analogs bearing a substituted amino functionality in the meta position. *J. Med. Chem.,* **1974**, *17*, 49-57.

[22] Hett, R.; Senanayake, C. H.; Wald, S. A. Conformational toolbox of oxazaborolidine catalysts in the enantioselective reduction of α-bromo-ketone for the synthesis of (*R*,*R*,)-formoterol*. Tetrahedron Lett*., **1998**, *39*, 1705-8.

[23] Wilkinson, H. S.; Hett, R.; Tanoury, G. J.; Senanayake, C. H.; Wald, S. A. Modulation of catalyst reactivity for the chemoselective hydrogenation of a functionalized nitroarene: preparation of a key intermediate in the synthesis of (*R*,*R*)-formoterol tartrate. *Org. Proc. Res. Dev*., **2000**, *4*, 567-70.

[24] Wilkinson, H. S.; Tanoury, G. J.; Wald, S. A.; Senanayake, C. H. Diethylanilineborane: a practical, safe, and consistent-quality borane source for the large-scale enantioselective reduction of a ketone intermediate in the synthesis of (*R*,*R*)-formoterol. *Org. Proc. Res. Dev*., **2002**, *6*, 146-8.

[25] Chu, C. K.; Ma, T.; Shanmuganathan, K.; Wang, C.; Xiang, Y.; Pai, S. B.; Yao, G. Q.; Sommadossi, J. P.; Cheng, Y. C. Use of 2'-fluoro-5-methyl-beta-L-arabinofuranosyluracil as a novel antiviral agent for hepatitis B virus and Epstein-Barr virus. *Antimicrob. Agents Chemother*., **1995**, *39*(4), 979-81.

[26] Sznaidman, M. L.; Almond, M. R.; Pesyan, A. New synthesis of L-FMAU from L-arabinose. *Nucleosides Nucleotides Nucleic Acids,* **2002**, *21*, 155-63.

[27] a) Kertesz, D.; Marx, M. Thiol esters from steroid 17.beta.-carboxylic acids: carboxylate activation and internal participation by 17.alpha.-acylates. *J. Org. Chem*., **1986**, *51*, 2315-28. b) Phillipps, G. H.; Bain, B. M.; Williamson, C.; Steeples, I. P.; Laing, S. B. Androstane 17β-carbothioates. GB2088877, 1982, p. 30.

[28] Cross, W. I.; Hannan, M. L.; Johns, D. M.; Lee, M.-Y.; Price, C. J. Novel crystalline pharmaceutical product. WO108572, 2006, p. 38.

[29] Berry, M. B.; Hughes, M. J.; Parry-Jones, D.; Skittrall, S. J. Novel process. WO144363A2, 2007, p. 15.

[30] Graul, A.; Rabasseda, X.; Castañer, J. T-3811ME: quinolone antibacterial. *Drugs Future,* **1999**, *24*, 1324-31.

[31] Todo, Y.; Hayashi, K.; Takahata, M.; Watanabe, Y.; Narita, H. Quinolonecarboxylic acid derivatives or salts thereof. WO29102, 1997, p. 66.

[32] Yamada, M.; Hamamoto, S.; Hayashi, K.; Takaoka, K.; Matsukura, H.; Yotsuji, M.; Yonezawa, K.; Ojima, K.; Takamatsu, T.; Yamamoto, H.; Kiyoto, T.; Kotsubo, H. Processes for producing 7-isoindolinequinolonecarboxylic derivatives and intermediates therefor, salts of 7-isoindolinequinolonecarboxylic acids, hydrates thereof, and composition containing the same as active ingredient. WO21849, 1999, p. 388.

[33] Kobayashi, F.; Yageta, Y.; Yamazaki, T.; Wakabayashi, E.; Inoue, M.; Segawa, M.; Matsuzawa, S. Effects of imidafenacin (KRP-197/ONO-8025), a new anti-cholinergic agent, on muscarinic acetylcholine receptors. High affinities for M3 and M1 receptor subtypes and selectivity for urinary bladder over salivary gland. *Arzneim-Forsch Drug Res.,* **2007**, *57*, 147-54.

[34] Miyachi, H.; Kiyota, H.; Uchiki, H.; Segawa, M. Synthesis and antimuscarinic activity of a series of 4-(1-imidazolyl)-2,2-diphenylbutyramides: discovery of potent and subtype-selective antimuscarinic agents. *Bioorg. Med. Chem.,* **1999**, *7*, 1151-61.

[35] Lee, F. Y. F.; Borzilleri, R.; Fairchild, C. R.; Kim, S.-H.; Long, B. H.; Reventos-Suarez, C.; Vite, G. D.; Rose, W. C.; Kramer, R. A. BMS-247550: A novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. *Clin. Cancer Res.,* **2001**, *7*, 1429-37.

[36] a) Li, W. S.; Thornton, J. E.; Guo, Z.; Swaminathan, S. Process for the preparation of epothilone analogs US20030004338, 2003, p. 17. b) Borzilleri, R.M.; Zheng, X.; Schmidt, R.J.; Johnson, J.A.; Kim, S.-H.; DiMarco, J.D.; Fairchild, C.R.; Gougoutas, J.Z.; Lee, F.Y.F.; Long, B.H.; Vite, G.D. A novel application of a Pd(0)-catalyzed nucleophilic substitution reaction to the regio- and stereoselective synthesis of lactam analogues of the epothilone natural products. *J. Am. Chem. Soc.,* **2000**, *122*, 8890-7.

[37] Langdon, S. P.; Mullen, P.; Faratian, D.; Harrison, D. J.; Cameron D. A.; Hasmann, M. Pertuzumab: humanized anti-HER2 monoclonal antibody, HER dimerization inhibitor, oncolytic. *Drugs Future,* **2008**, *33*, 123-30.

[38] Whitehead, B. F.; Ho, P. T. C.; Suttle, A. B.; Pandite, A. Cancer treatment method WO143483, 2007, p. 49.

[39] a) Sorbera, L. A.; Serradell, N.; Rosa, E.; Bolos, J. Lisdexamfetamine Mesilate. Treatment of attention deficit hyperactivity disorder. *Drugs Future,* **2007**, *32*, 223-7. b) Elia, J.; Easley, C.; Kirkpatrick, P. Lisdexamfetamine dimesylate. *Nat. Rev. Drug Disc*., **2007**, *6*, 343-4.

[40] a) Mickle, T.; Krishnan, S.; Moncrief, J. S.; Lauderback, C. Pharmaceutical compositions for prevention of overdose or abuse. WO032474 (A2) 2005, p. 336. b) Mickle, T.; Krishnan, S.; Bishop, B.; Lauderback, C.; Moncrief, J. S.; Oberlender, R.; Piccariello, T. Abuse-resistant amphetamine prodrugs. US20070042955 (A1) 2007, p. 111.

[41] a) Fadel, H.; Temesgen, Z. Maraviroc. Maraviroc. *Drugs Today,* **2007**, *43,* 749-58. b) Kuritzkes, D.; Kar, S.; Kirkpatrick, P. Maraviroc. *Nat. Rev:Drug Disc.,* **2008**, *7*, 15-6.

[42] Perros, M.; Price, D. A., Stammen, B. L. C.; Wood, A. Tropane derivatives useful in therapy. WO90106 (A2), 2001, p. 79.

[43] Price, D. A.; Gayton, S.; Selby, M. D.; Ahman, J.; Haycock-Lewandowski, S.; Stammen, B. L.; Warren, A. Initial synthesis of UK-427,857 (Maraviroc). *Tetrahedron Lett.,* **2005**, *46*, 5005-7.

[44] For a synthesis of alcohol **82** see: Torre, O.; Gotor-Fernandez, V.; Gotor, V. Lipase-catalyzed resolution of chiral 1,3-amino alcohols: application in the asymmetric synthesis of (*S*)-dapoxetine. *Tetrahedron: Asymm.,* **2006**, *17*, 860-6.

[45] Davies, S.L.; Bolós, J.; Serradell, N.; Bayés, M. Nilotinib. *Drugs Future,* **2007**, *32*, 17-25.

[46] Huang, W. S.; Shakespeare, W. C. An Efficient synthesis of nilotinib (AMN107). *Synthesis,* **2007**, *14*, 2121-4.

[47] Owen, R. T. Extended-release paliperidone efficacy, safety and tolerability profile of a new atypical antipsychotic. *Drugs Today,* **2007**, *43*, 249-58.

[48] Spittaels, T. F. E.; Van Dun, J. P.; Verbraeken, J. A.; Wouters, B. Preparation of aseptic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyridio[1,2-a]pyrimidin-4-one palmitate ester. WO114384 A1, **2006**, p. 25.

[49] Dolitzky, B.-Z. Process for preparation of paliperidone by reaction of 3-(2-chloroethyl)-6,7,8,9 tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one with 6-fluoro-3piperidino-1,2-benzisoxazole. WO021345 A2, 2008, p. 14.

[50] Dolitzky, B-Z. Process for the synthesis of CMHTP, paliperidone, and intermediates thereof. WO024415 A2, 2008, p. 42.

[51] Anker, M.; Corales, R. B. Raltegravir (MK-0518): a novel integrase inhibitor for the treatment of HIV infection. *Expert Opin. Investig. Drugs,* **2008**, *17*, 97-103.

[52] Evering, T. H.; Markowitz, M. Raltegravir (MK-0518): an integrase inhibitor for the treatment of HIV-1. *Drugs Today,* **2007**, *43*, 865-77.

[53] a) Crescenzi, B.; Gardelli, C.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Petrocchi, A.; Poma, M.; Rowley, M.; Scarpelli, R. Summa, V. Preparation of *N*-substituted hydroxypyrimidinone carboxamide inhibitors of HIV integrase. WO035077A1, 2003, p. 217. b) Summa, V.; Petrocchi, A.; Bonelli, F.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Fiore, F.; Cardelli, C.; Paz, O. G.; Hazuda, D. J.; Jones, P.; Kinzel, O.; Laufer, R.; Monteagudo, E.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Scarpelli, R.; Stillmock, K.; Witmer, M. V.; Rowley, M. Discovery of raltegravir, a potent, selective orally bioavailable HIV-integrase inhibitor for the treatment of HIV-AIDS infection. *J. Med. Chem.,* **2008**, *51*, 5843-55.

[54] Belyk, K. M.; Morrison, H. G.; Jones, P.; Summa, V. Preparation of N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-1,6-dihydropyrimidine-4-carboxamide potassium salts as HIV integrase inhibitors. WO060712A2, 2006, p. 52.

[55] Boyd, B.; Castañer. J. Retapamulin. *Drugs Future,* **2006**, *31*, 107-13.

[56] Davidovich, C.; Bashan, A.; Auerbach-Nevo, T.; Yaggie, R. D.; Gontarek, R. R.; Yonath, A. Induced-fit tightens pleuromutilins binding to ribosomes and remote interactions enable their selectivity. *Proc. Nat. Acad. Sci. USA,* **2007**, *104*, 4291-6.

[57] Berry, V.; Dabbs, S.; Frydrych, C. H.; Hunt, E.; Woodnut, G.; Sanderson, F. D. Preparation of pleuromutilin derivatives as antimicrobials. WO21855*,* 1999, p. 70.

[58] Breen, G. F.; Forth, M. A.; Kopelman, S. S. H.; Muller, F. X.; Sanderson, F. D. Process for preparation of mutilin derivatives and their salts as antibacterial agents. WO023257*,* 2005, p. 66.

[59] Deeks, E. D.; Scott, L. J. Rufinamide. *CNS Drugs,* **2006**, *20*, 751-60.

[60] Sorbera, L. A.; Leeson, P. A.; Rabasseda, X.; Castañer, J. Rufinamide. *Drugs Future,* **2000**, *25*, 1145-9.

[61] Heaney, D.; Walker, M. C. Rufinamide. *Drugs Today,* **2007**, *43*, 455-60.

[62] Hakimian, S.; Cheng-Hakimian, A.; Anderson, G. D.; Miller, J. W. Rufinamide: a new anti-epilectic medication. *Expert Opin. Pharmacother*., **2007**, *8*, 1931-40.

[63] Portmann, R.; Hofmeier, U. C.; Burkhard, A.; Scherrer, W.; Szelagiewicz, M. Crystal modification of 1-(2,6-difluorobenzyl)-1H-1,2,3--triazole-4-carboxamide and its use as antiepileptic. WO56772*,* 1998, p. 26. and WO9856773, 1998, p. 25.

[64] Portmann, R. Process for preparing 1-substituted 4-cyano-1,2,3-triazoles. WO02423, 1998, p. 22.

[65] a) Rini, B.; Kar, S.; Kirkpatrick, P. Temsirolimus. *Nat. Rev.: Drug Disc.* **2007**, *6*, 599-600. b) Sorbera, L. A.; Castaner, J.; del Fresno, M. CCI-779. Oncolytic mTOR Inhibitor. *Drugs Future,* **2002**, *27*, 7-13.

[66] a) Chew, W.; Shaw, C.-C. Regioselctive synthesis of CCI-779. US0033046 (A1), 2005, p. 12; b) Zhang, C.; Coughlin, C. W.; Pilcher, A.; Michaud, A. P.; Farina, J. S.; Sahli, A. Scalable process for the preparation of a rapamycin 42-ester from a rapamycin 42-ester boronate. US29541(A1), 2007, p. 16. For an alternative syn-

thesis proceeding through a 1,3-dioxane protecting group of the diol off of positon 42 see: Shaw, C.-C.; Sellstedt, J. H.; Noureldin, R.; Cheal, G. K.; Fortier, G. Regioselective synthesis of rapamycin derivatives. WO23395(A2), 2001, p. 29.

[67] 2-phenyl boronate acid **124** was prepared by combining 2,2-bis(hydroxymethyl)propinoic acid with phenylboronic acid. See ref. 66a for a detailed description of the preparation.

[68] Jimeno, J. M.; Faircloth, G.; Cameron, L.; Meely, K.; Vega, E.; Gómez, A.; Fernández Sousa-Faro, J. M.; Rinehart, K. Progress in the acquisition of new marine-derived anticancer compounds: development of ecteinascidin-743 (ET-743). *Drugs Future,* **1996**, *21*, 1155-65.

[69] Cuevas, C.; Perez, M.; Martin, M. J.; Chicharro, J. L.; Fernandez-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; Garcia, J.; Polanco, C.; Rodriguez, I.; Manzanares, I. Synthesis of ecteinascidin ET-743 and phthalascidin Pt-650 from cyanosafracin B. *Org. Lett*., **2000**, *2*, 2545-8.

Received: 11 October, 2008 Revised: 11 November, 2008 Accepted: 12 November, 2008

[70] Corey, E. J.; Gin, D. Y.; Kania, R. S. Enantioselective total synthesis of ecteinascidin 743. *J. Am. Chem. Soc*., **1996**, *118*, 9202-3.

[71] McIntyre, J. A.; Castañer, J. Vildagliptin. *Drugs Future,* **2004**, *29*, 887-91.

[72] Garber, A. J.; Sharma, M. D. Update: vildagliptin for the treatment of Type 2 diabetes. *Expert Opin. Investig. Drugs,* **2008**, *17*, 105-13.

[73] Villhauer, E. B.; Brinkman, J. A.; Naderi, G. B.; Burkey, B. F.; Dunning, B. E.; Prasad, K.; Mangold, B. L.; Russell, M. E.; Hughes, T. E. 1-[[(3-Hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(*S*)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. *J. Med. Chem.,* **2003**, *46*, 2774-89.

[74] a) Villhauer, E. B. *N*-Substituted 2-cyanopyrrolidines. *WO* 34241 A1*,* 2000, p. 26.; b) Schaefer, F.; Sedelmeier, G. Process for the preparation of *N*-substituted 2-cyanopyrrolidines. WO092127, 2004, p. 20.