Synthetic Approaches to the 2005 New Drugs

Subas M. Sakya[1,*], Jin Li[2,*] and Kevin K.-C. Liu[3,*]

[1]*Pfizer Global Research and Development, Pfizer Inc., Groton, CT 06340, USA;* [2]*BioDuro LLC, Beijing, China;* [3]*Pfizer Global Research and Development, Pfizer Inc., La Jolla, CA 92121, USA*

Abstract: New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biological target. In addition, these new chemical entities (NCEs) not only provide insights into molecular recognition, but also serve as drug-like leads for designing future new drugs. To these ends, this review covers the syntheses of 22 NCEs marketed in 2005.

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 1998 Nobel prize in physiology and medicine [1].

Inaugurated four 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 article [2]. Briefly, drugs that are approved worldwide tend to have structural similarity across similar biological targets. We strongly believe that knowledge of new chemical entities and their syntheses will greatly enhance our abilities to design new drug molecules in shorten period of time. With this hope, we continue to profile these NCEs that were approved for the year 2005.

In 2005, 41 NCEs including biological drugs [3], and two diagnostic agents reached the market. Among them, some products were approved for the first time in 2005 but were not launched before year end. Synthesis of those drugs will be covered in 2006's review. This review will focus on the syntheses of 22 new drugs marketed last year (Fig. **1**), but excludes new indications for known drugs, new combinations and new formulations. Natural products, diagnostic agents and drugs synthesized *via* bio-process and peptide synthesizers will also be excluded. The syntheses of these new drugs were published sporadically in different journals and patents. The synthetic routes cited here represent either the most scalable methods based on the author's judgment or currently available publications, and appear in alphabetical order by generic names.

CICLESONIDE (*ALVESCO*®)

Ciclesonide, a newer generation inhaled corticosteroid for the treatment of persistent asthma, was discovered and developed by Altana Pharma and launched in January 2005 in England [3]. Besides being approved in a number of other countries, Altana and Aventis has received an approvable letter in the US. It's novel release and distribution properties help target the lung specifically, resulting in an efficacious anti-inflammatory effects. Two separate approaches to the syntheses of the chiral ciclesonide have been described in the patent literature [4,5]. The first route involves a chiral resolution step [4] and the second approach highlights a stereoselective *trans* acetalization approach[5]. The first synthesis of ciclesonide (Scheme **1**) started by reacting (11β,16α)-11, 16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (**1**) with *iso*butyric anhydride to make the tri-*iso*butyl ester in 87% yield. Reaction of the tri-ester with cyclohexane carboxaldehyde in the presence of HCl and 70% perchloric acid gave the cyclohexane acetal **3**, which was then separated into the desired isomer ciclesonide (**I**) by HPLC or recrystallization.

In the second route (Scheme **2**), desonide (**4**) was reacted with cyclohexane carboxaldehyde in the presence of 70% perchloric acid in nitropropane, a key solvent required for selectivity, to give the isomers **5** (*R/S* in 88:2 ratio). The alcohol was subsequently capped with *iso*butyric anhydride to give the desired product ciclesonide (**I**) in good yields. Enrichment of the desired isomer, if required, was done by either recrystallization or HPLC purification.

CLOFARABINE (*CLOLAR*®)

Clofarabine, a purine nucleoside analogue, is an anticancer agent approved in December 2004 for the treatment of refractory or relapsed lymphoblastic leukemia with at least two years of prior treatment in pediatric patients. The drug was discovered by Ilex oncology (now Genzyme) and currently marketed by Genzyme [3,6]. Several routes to the synthesis of clofarabine have been published, including a process scale-up chemistry as shown in Scheme **3** [7,8,9]. Treatment of commercially available 2-deoxy-2-β-fluoro-1,3,5-tri-O-benzoyl-1-R-D-arabinofuranose (**6**) with 33%HBr in acetic acid provided the bromo sugar **7** in 88% yield. The bromide **7** was reacted with 2-chloroadenine (**8**) in optimized mixed solvent system in the presence of calcium hydride and potassium *t*-butoxide to give the desired β-anomeric product **9** in 50:1 ratio. Deprotection of the benzoyl groups with sodium methoxide then provided clofarabine (**II**).

CONIVAPTAN (*VAPRISOL*®)

Conivaptan, a vasopressin antagonist, was discovered and developed by Yamanouchi for the treatment of hyponatraeum associated with congestive heart failure [3,10]. After

*Address correspondence to these authors at the Pfizer Global Research and Development, Pfizer Inc., Groton, CT 06340, USA; Tel: 1-860-715-0425; E-mail: subas.m.sakya@pfizer.com; BioDuro LLC, Beijing, China; Tel: 86-1062948830; E-mail: jin.li@bioduro.com; Pfizer Global Research and Development, Pfizer Inc., La Jolla, CA 92121, USA; Tel: 1-858-622-7391; E-mail: kevin.k.liu@pfizer.com

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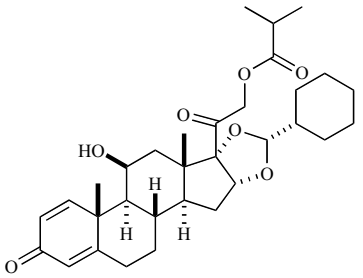
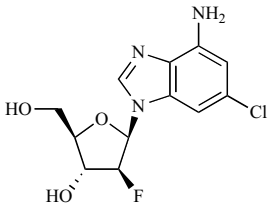
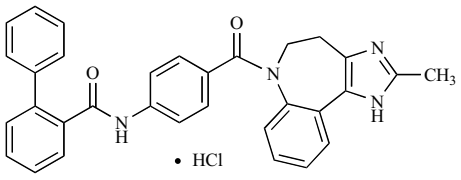


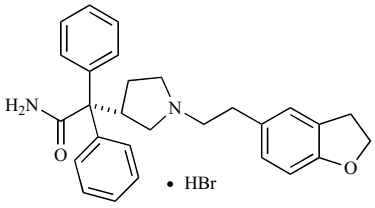
I. Ciclesonide (Alvesco)
(Scheme 1 & 2)



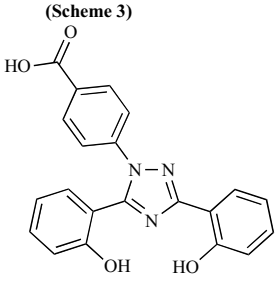
II. Clofarabine (Clolar)
(Scheme 3)



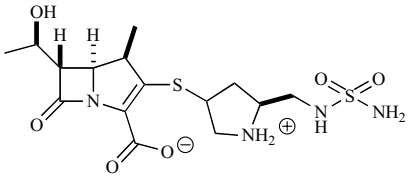
III. Conivaptan hydrochloride (Vaprisol)
(Scheme 4)



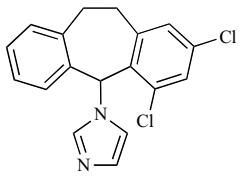
IV. Darfenacin hydrobromide (Emselex)
(Scheme 5)



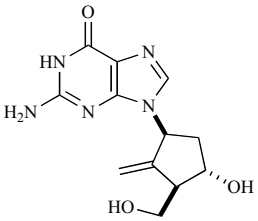
V. Deferasirox (Exjade)
(Scheme 6)



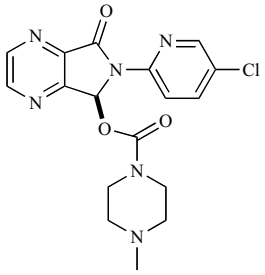
VI. Doripenem (Finibax)
(Scheme 7-9)



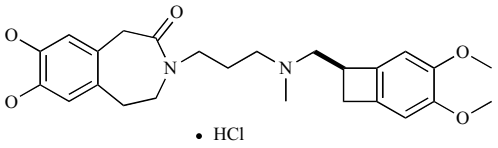
VII. Eberconazole (Ebernet)
(Scheme 10)



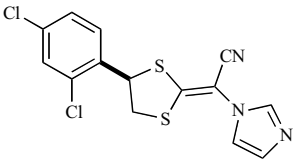
VIII. Entecavir (Baraclude)
(Scheme 11)



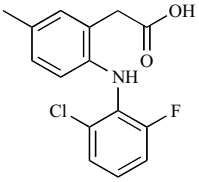
IX. Eszopiclone (Lunesta)
(Scheme 12)



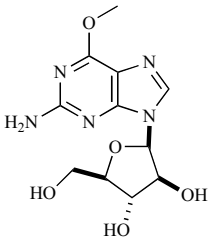
X. Ivabradine hydrochloride (Procorala)
(Scheme 13)



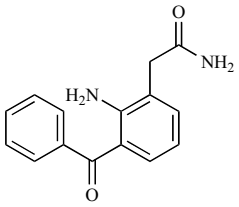
XI. Luliconazole (Lulicon)
(Scheme 14)



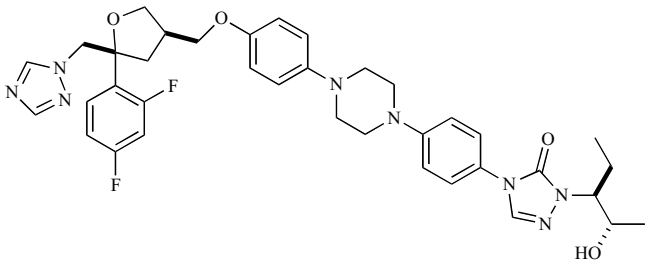
XII. Lumiracoxib (Prexige)
(Scheme 15)



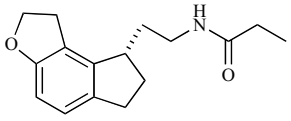
XIII. Nelarabine (Arranon)
(Scheme 16)



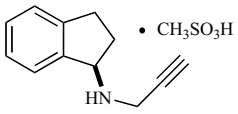
XIV Nepafenac (Nevanac)
(Scheme 17)



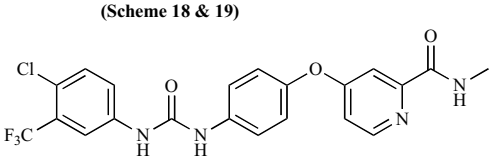
XV. Posaconazole (Noxafil)
(Scheme 18 & 19)



XVI. Ramelteon (Rozerem)
(Scheme 20)

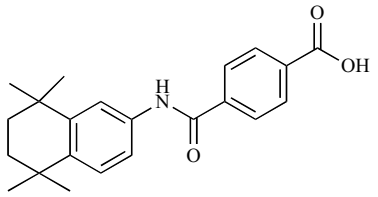


XVII. Resagiline mesilate (Azilect)
(Scheme 21)

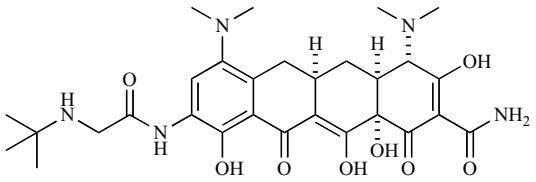


XVIII. Sorafenib (Nexavar)
(Scheme 22)

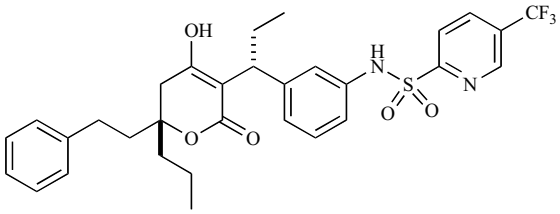
(Fig. 1. Contd….)



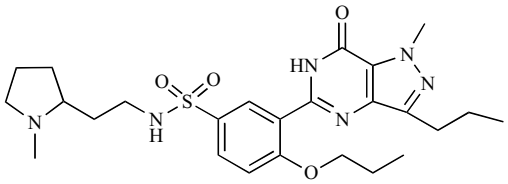
XIX. Tamibarotene (Amnolake)
(Scheme 23)



XX. Tigecyline (Tygacil)
(Scheme 24)

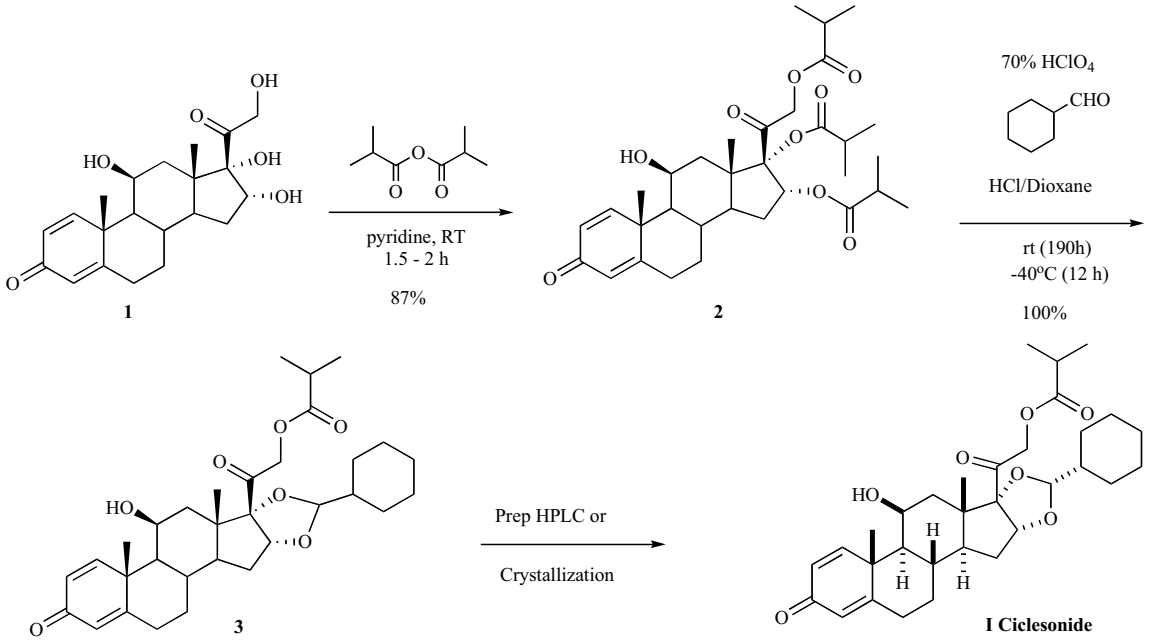


XXI. Tipranavir (Aptivus)
(Scheme 25)

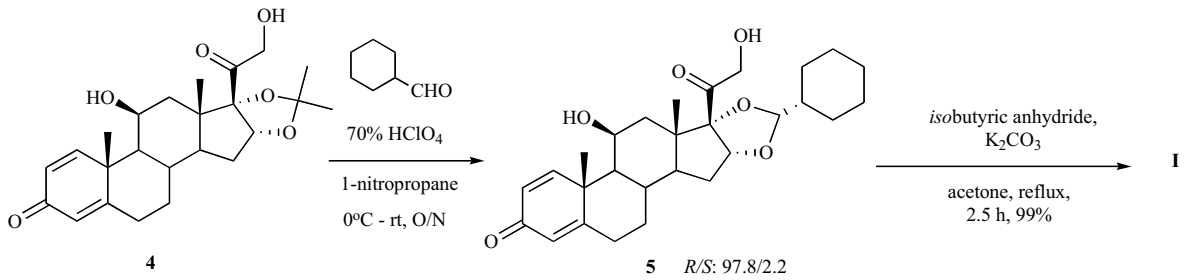


XXII Udenafil (Zydena)
(Scheme 26)

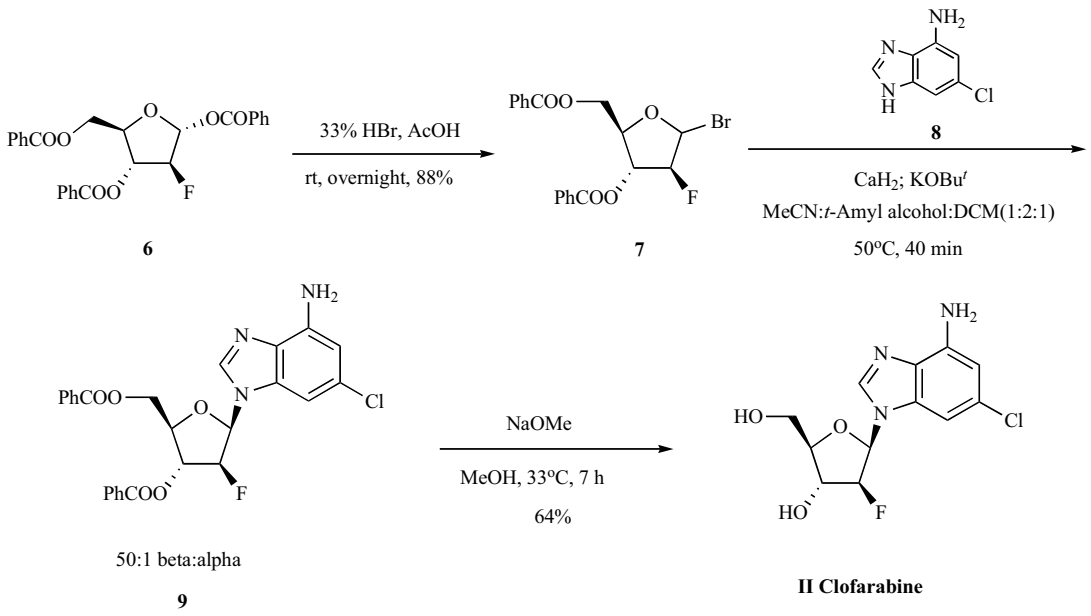
Fig. (1). Structures of 22 new drugs marketed in 2005.



Scheme 1. Racemic synthesis of Ciclesonide.

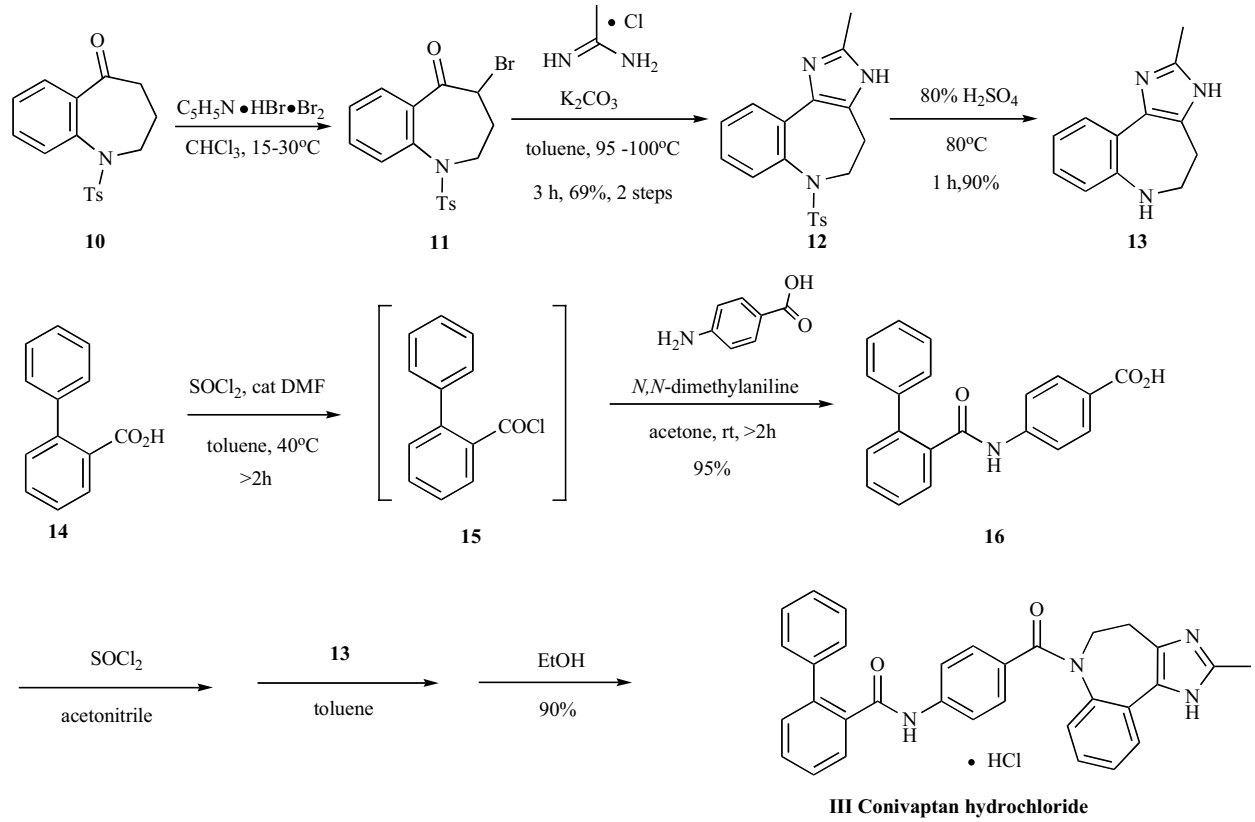


Scheme 2. Stereoselective synthesis of Ciclesonide.



Scheme 3. Synthesis of Clofarabine.

looking at several different approaches to the synthesis [11-13], a convergent approach, shown in Scheme **4**, was developed for large scale synthesis [15]. Bromination of benzazepinone **10** with pyridinium hydrobromide perbromide in chloroform followed by recrystallization gave bromide **11**. Reaction of bromide **11** with ethaneimidate hydrochloride in the presence of potassium carbonate in toluene or chloroform gave the desired imidazole **12** in 69% yield. Although chlo-



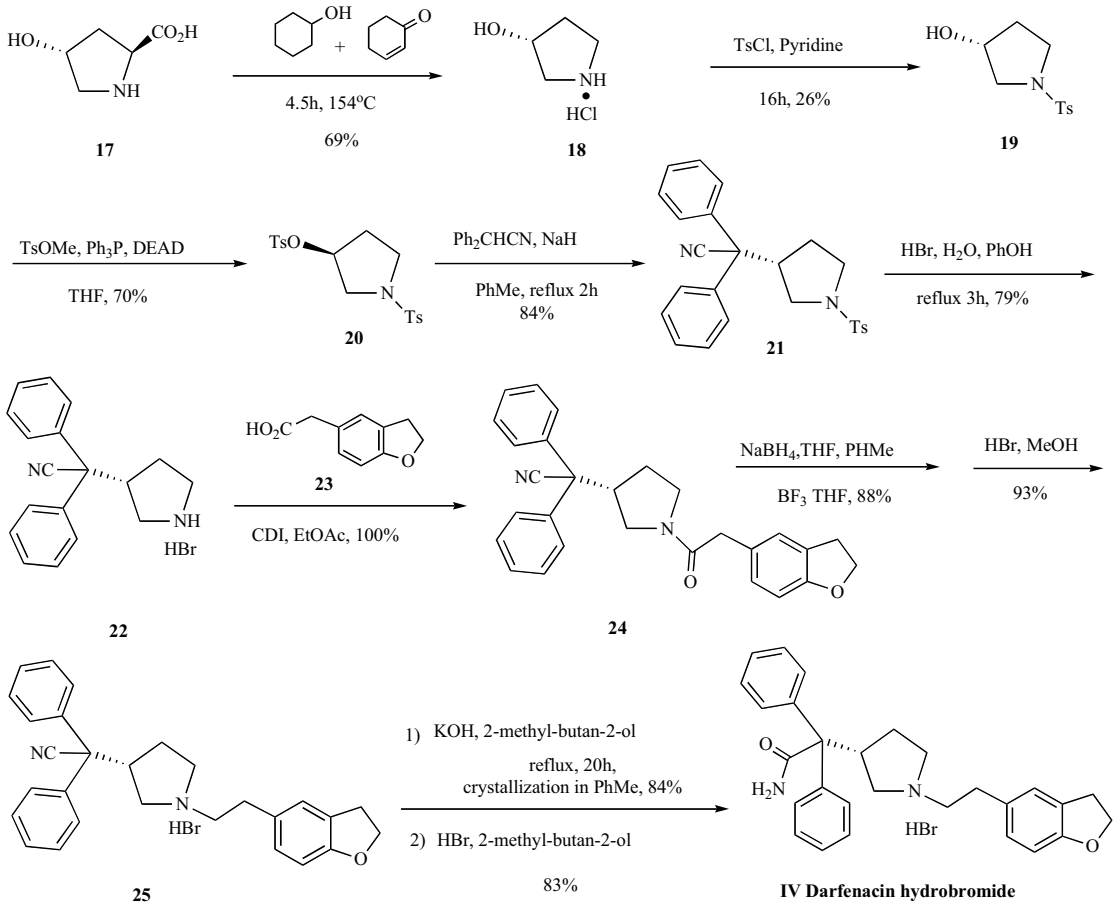
Scheme 4. Synthesis of Conivaptan.

roform provided a slightly better yield, for large scale preparation, toluene was used to minimize halogenated solvent waste and because the quality of product was similar or better than with use of chloroform. Deprotection of the tosylate was found to be effective with heating the sulfonamide **12** in 80% sulfuric acid at 80°C. The benzazepinone product **13** was obtained in 90% yield after crystallization from acetonitrile and water mixture.

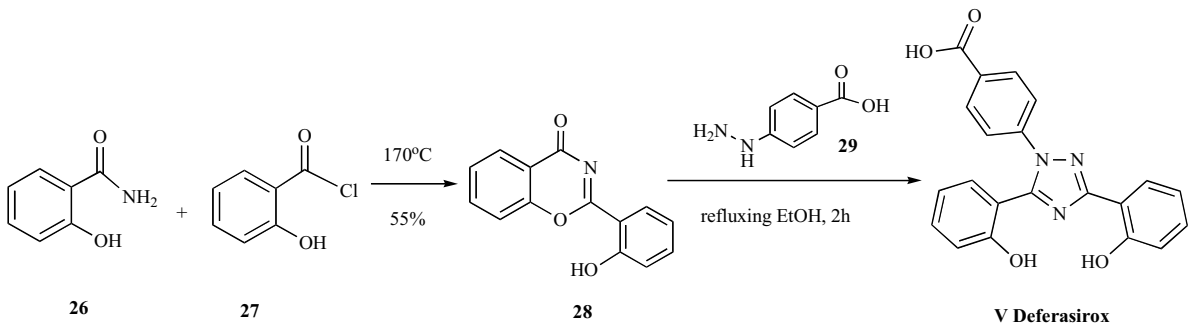
Synthesis of the coupling partner **16** required to provide conivaptan was synthesized in 95% yield from biphenyl 2-benzoic acid (Scheme **4**) *via* sequential reaction with thionyl chloride in toluene followed by coupling with aminobenzoic acid in acetone with *N,N*-dimethylaniline as a base. High quality acid **16** was obtained by crystallization from DMF and water. The acid **16** was activated by converting it into acid chloride with thionyl chloride in acenonitrile, to which was added imidazo benzazepine **13** in toluene and, after recrystallization in acidic ethanol, gave conivaptan hydrochloride (**III**) in 90% yield.

DARIFENACIN HYDROBROMIDE (*EMSELEX*®)

Darifenacin, an orally active, once a day selective M_3 receptor antagonist, was launched for the treatment of overactive bladder in patients with symptoms of urge urinary incontinence, urgency and frequency [16]. The drug selectively inhibits M_3 receptor in the detrusor muscle while sparing the M_1 and M_2 receptors that are believed to be involved in central nervous system and cardiovascular function respectively. The compound was originally developed by Pfizer and licensed to Novartis and Bayer. The synthesis of darifenacin [17] is depicted in Scheme **5**. Commercially available (2*S*,4*R*)-(-)-4-hydroxy-2-pyrrolidinecarboxylic acid (**17**), anhydrous cyclohexanol and 2-cyclohexen-1-one were heated at 154°C to give de-carboxylated compound **18** in 69 % yield. The 3-(*R*)-hydroxypyrrolidine (**18**) was *N*-tosylated with *p*-toluenesulfonyl chloride in pyridine yielding compound **19** in 26 % yield . The *N*-tosylated alcohol **19** was subjected to Mitsunobu reaction in the presence of methyl *p*-toluenesulfonate, triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF to afford *N*-tosyl-3(*S*)-(tosyloxy) pyrrolidine (**20**) in 70% yield, which was then condensed with 2,2-diphenylacetonitrile with NaH in refluxing toluene to give 2,2-diphenyl-2-[1-(*p*-toluenesulfonyloxy)pyrrolidin-2(S)-yl]acetonitrile (**21**). The tosyl group of **21** was removed with 48% HBr and phenol in refluxing water to yield 2,2-diphenyl-2-[2(S)-pyrrolidinyl] acetonitrile as its corresponding hydrogen bromide salt (**22**), which was coupled to 2-(2, 3-dihydrobenzofuran-5-yl) acetic acid (**23**) by treatment with carbonyldiimidazole (CDI) in ethyl acetate to the corresponding amide **24** in a quantitative yield. The amide (**24**) was dissolved in toluene and reduced with sodium borohydride in THF with slow addition of boron trifluoride THF



Scheme 5. Synthesis of Darifenacin.



Scheme 6. Synthesis of Deferasirox.

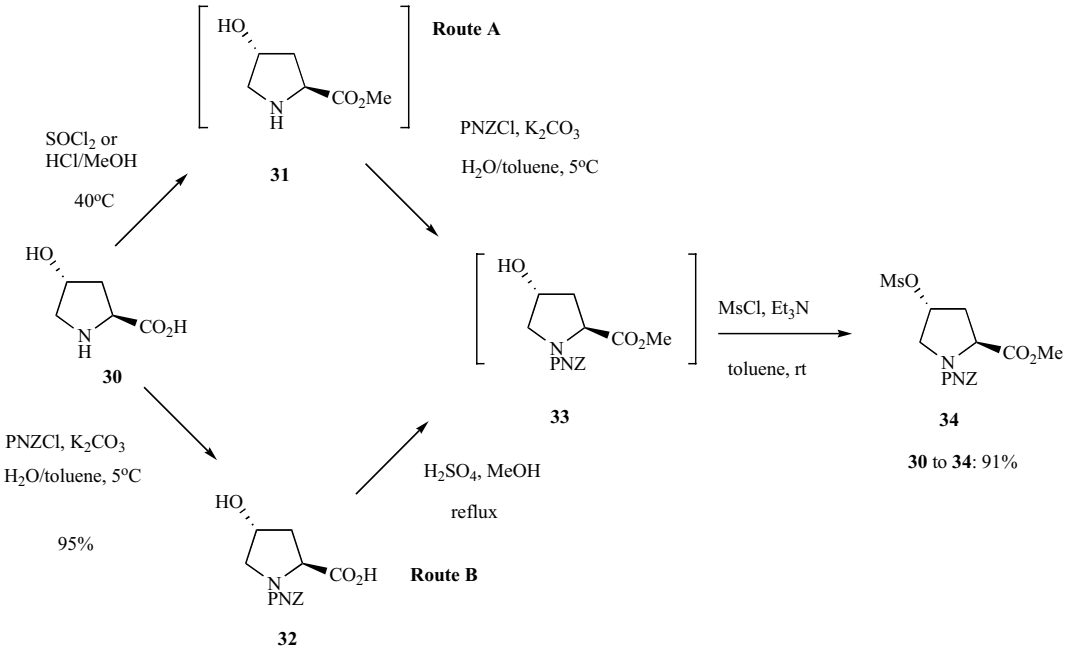
complex to keep the temperature below 10°C to give free amine in 88% yield. The free amine was converted to corresponding hydrogen bromide salt (**25**) with 48% HBr in methanol. Compound **25** was hydrolyzed with potassium hydroxide in refluxing 2-methyl-butan-2-ol for twenty hours to give acetamide which was crystallized from toluene as a toluene solvated form in 84% yield. Finally, the toluene solvated compound was converted to darfenacin hydrobromide (**IV**) with 48% HBr in 2-methyl-butan-2-ol.

DEFERASIROX (*EXJADE*®)

Deferasirox, an orally active iron chelator, was approved for the treatment of chronic iron overload because of blood transfusions in chronic anemia in adult and pediatric patients iron chelator two years of age and older [19]. Deferasirox, developed by Novartis, is the only drug administered as a drink, compared to the current standard treatment which often requires a subcutaneous infusion lasting 8 to 12 hours per night, for 5 to 7 nights a week for as long as the patient continues to receive blood transfusions or has excess iron within the patient body. Synthesis of deferasirox [20] (Scheme **6**) started with cyclization of salicylamide (**26**) with salicyloyl chloride (**27**) by heating at 170 C without any solvents to give 2-(2-hydroxyphenyl)-benz[*e*][1,3]oxazin-4-one (**28**) in 55% yield. Compound **28** was reacted with 4-hydrazinobenzoic acid (**29**) in refluxing ethanol for 2 hours to give deferasirox **V** as colorless crystals.

DORIPENEM (*FINIBAX*®)

Doripenem, a carbapenem antibiotic approved in Japan 2005, was developed and marketed by Shionogi Pharmaceuticals in Japan for the treatment of serious infections caused by both gram positive and negative bacteria including *pseudomonas aeruginosa*. It is currently being developed in the U.S. by Peninsula Pharmaceuticals [3]. Two process syntheses have been reported for the preparation of doripenem (Scheme **7**) [21]. Both methods utilize a common commercially available starting material, 3-hydroxy proline (**30**). In method A, compound **30** was initially reacted with thionyl chloride or HCl in methanol to provide methylester **31**, which was immediately protected with *p*-nitrobenzylchloroformate (PNZCl) to give PNZ *N*-protected 3-hydroxy proline ester **33**



Scheme 7. Synthesis of intermediate mesylate **34**.

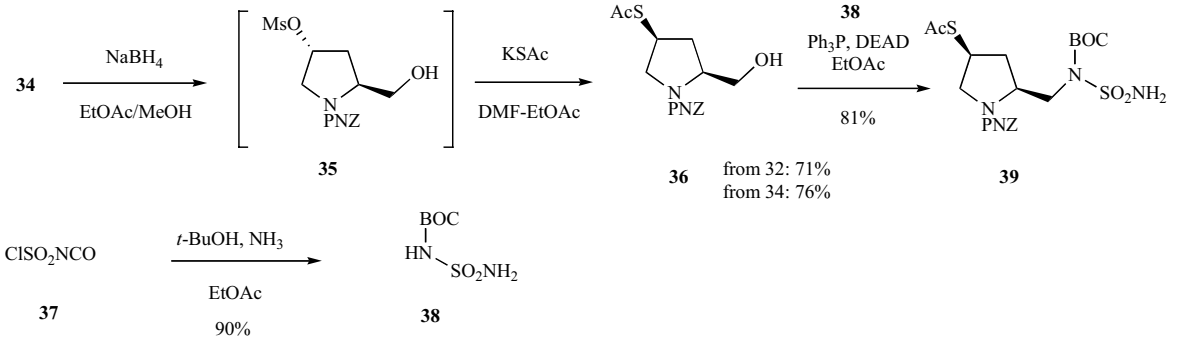
and finally the alcohol was converted to mesylate **34** before isolation in 91% overall yield. Alternatively, in method B, the hydroxyl proline is protected as the PNZ ester **32** first in 95% yield. The protected proline acid **32** was converted to the methyl ester with refluxing sulfuric acid in methanol followed by conversion of the alcohol to the mesylate **34** in 91% overall yield from **30**. The mesylate ester was reduced with sodium borohydride to provide alcohol **35**, which was converted without purification to thiol ester **36** by reacting with potassium thioacetate (Scheme **8**). Mitsunobu reaction of alcohol **36** with BOC-sulfonyl urea **38**, which was prepared from chlorosulfonyl *iso*cyanate with ammonia in t-butanol in 90% yield, provided the key thioacetate intermediate **39**. Finally, protected doripenem **42** was prepared by coupling thiol **40**, obtained by hyrolysis of thioacetate **39**, with enolphosphate **41** (Scheme **9**) in 88% yield [20]. Deprotection of intermediate ester and carbamate protecting groups *via* hydrogenation gave the desired carbapenem **VI**, which was isolated after crystallization. Final form of the drug doripenem was prepared by sterilization, crystallization and granulation.

EBERCONAZOLE (*EBERNET*®)

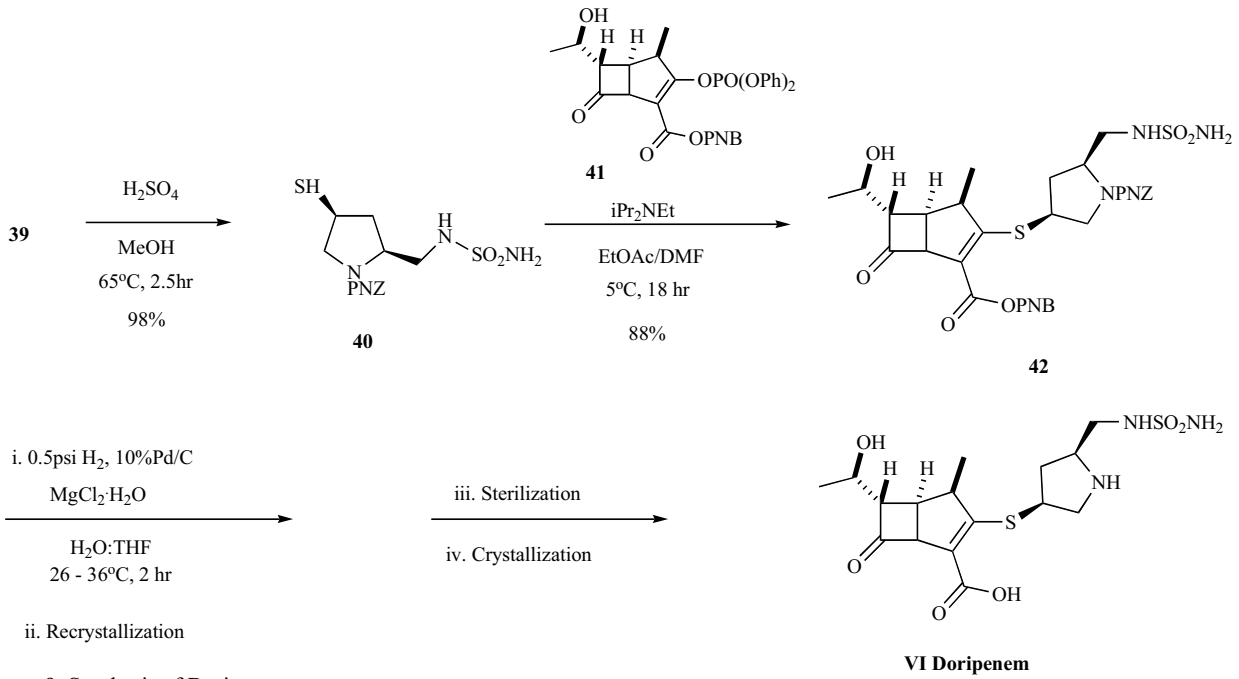
Eberconazole is an azole antifungal agent developed by Salvat and approved in Spain in 2005 for the topical treatment of cutaneous fungal infections, including *tinea corporis, tinea cruris* and *tinea pedis* [3]. The synthesis (Scheme **10**), started with the Wittig reaction of the phosphonium bromide **43** with the 3,5-dichlorobenzaldehyde to give the olefin mixture **44**. Hydrolysis of the ester followed by hydrogenation gives acid **46**, which was cyclized to tricyclized ketone **47**. Completion of the synthesis was accomplished in three steps *via* reduction of the ketone **47** with sodium borohydride, chlorination of resulting alcohol **48** with thionyl chloride and alkylation of the chloride **49** with imidazole to give eberconazole (**VII**) [23].

ENTECAVIR (BARACLUDE™)

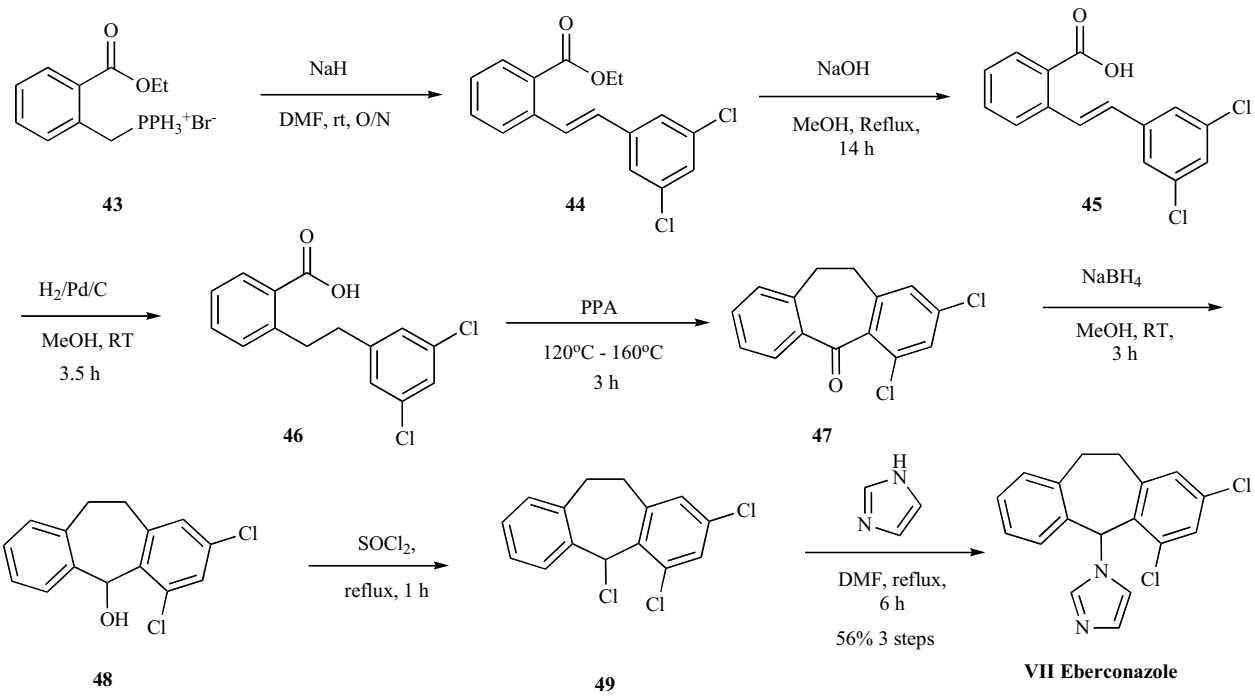
Entecavir, an orally activity nucleoside analogue launched in the U.S. by Bristol-Myers Squibb, is for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in



Scheme 8. Synthesis of key intermediate thioacetate **39**.



Scheme 9. Synthesis of Doripenem.

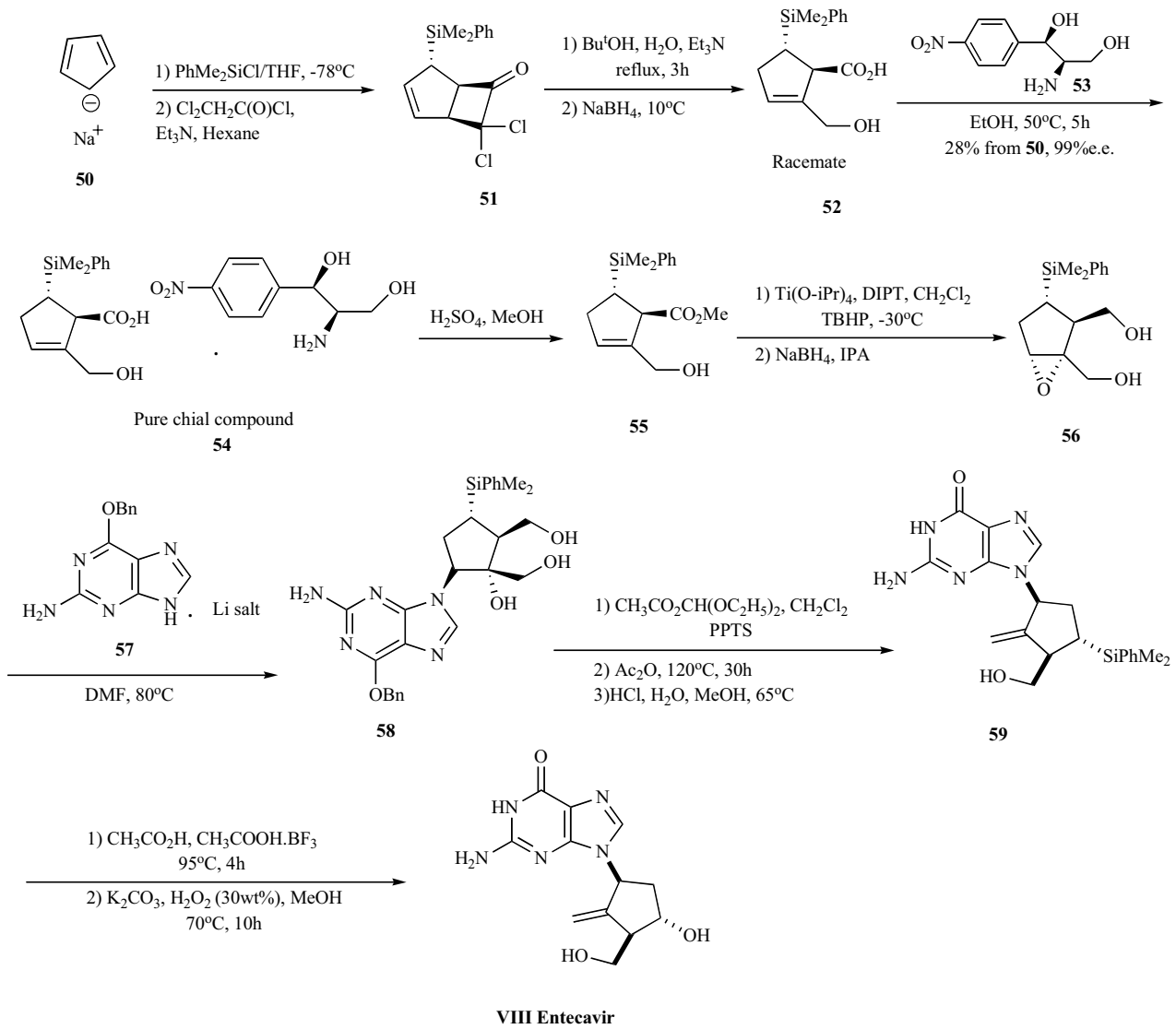


Scheme 10. Synthesis of Eberconazole.

serum aminotransferases (ALT or AST) or histologically active disease [26]. Entecavir is designed to selectively block the replication of hepatitis B virus (HBV) by inhibiting the virus' ability to infect cells. Several syntheses of entecavir have been reported and the synthesis described below is based on the most recent patents [25,26] (Scheme **11**). Commercial sodium cyclopentadienide (**50**) was treated with phenyldimethylchlorosilane in anhydrous THF at –78°C. The resulting silane moiety serves as a masked hydroxyl group that will be revealed later in the synthetic process. The silylated product was subsequently reactive with dichloroacetyl chloride to a 2+2 cycloaddition reaction to give cyclobutanone **51** as crude dark oil. The cyclobutanone **51** was then opened under a basic condition, and the resulting intermediate reduced with sodium borohydride at low temperature to yield racemic free carboxylic acid **52**. The racemic **52** was subjected to chiral resolution with a chiral amine, *R, R*-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**53**), to give chiral salt **54** in 99% e.e. and 28% overall yield from the starting material **50** as crystals. The chiral salt **54** was de-salted and converted to corresponding methyl ester **55** with sulfuric acid in methanol. The double bond in compound **55** was then expoxidized with titanium(IV) *iso*propoxide/TBHP at –30°C in dichloromethane to give an epoxyl ester which was selectively reduced with sodium borohydride in IPA to give epoxyl diol **56** as light yellow oil. Lithium salt of 2-amino-6-O-benzyl-oxypurine (**57**) was added to the epoxide **56** to give the ring-opening product **58**. The vicinal diol moiety of **58** was converted to an alkene by a two-step procedure. Compound **58** was reacted with diethoxymethyl acetate and PPTS in dichloromethane to give a mixture of dioxolanes as a viscous brown oil which was subsequently reacted with acetic anhydride at 120°C for 30 hours to an alkene. Concentrated HCl was added to the alkene mixture to hydrolyze the 6-benzyl-oxy group and an 2-N-acetyl group formed in the previous acetic anhydride reaction to give compound **59** as a light brown colored product. Finally, compound **59** was converted to entecavir by protodesilylation of the silane moiety followed by oxidation to convert the silane moiety to the hydroxyl group. Therefore, **59** was treated with boron trifluoride-acetic acid complex in acetic acid at high temperature and followed by basic hydrogen peroxide oxidation to give entecavir (**VIII**).

ESZOPICLONE (LUNESTA™)

Eszopiclone is a non-benzodiazepine hypnotic discovered by Aventis Pharma and licensed exclusively in the U.S. to Sepracor. Eszopicolone is the *S*-isomer of zopicolone. The parent compound, zopicolone, is a short acting hypnotic agent of cyclopyrrolone class which has been marketed in Europe for the treatment of insomnia under the brand name Imovane® or Amoban®. Therefore, Eszopicolone is for the treatment of transient and chronic insomnia. The hypnotic effect of eszopiclone is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors [27]. The synthesis of eszopicolone involves enzymatic resolution of a zopicolone [28] derivative to give the chiral compound as depicted in the Scheme **12** [27]. Pyrazine-2,3-dicarboxylic acid anhydride (**60**) was reacted with 2-amino-5-chloropyridine (**61**) in refluxing acetonitrile to generate 3-(5-chloro-2-pyridyl)carbamoyl pyrazine-2-carboxylic acid (**62**) in 95% yield. Compound **62** was cyclized by treating with refluxing $SOCl_2$ to give 6-(5-chloropyrid-2-yl)-5,7-dioxo-5,6-dihydropyrrolo[3,4-b]pyrazine (**63**) in 79% yield.

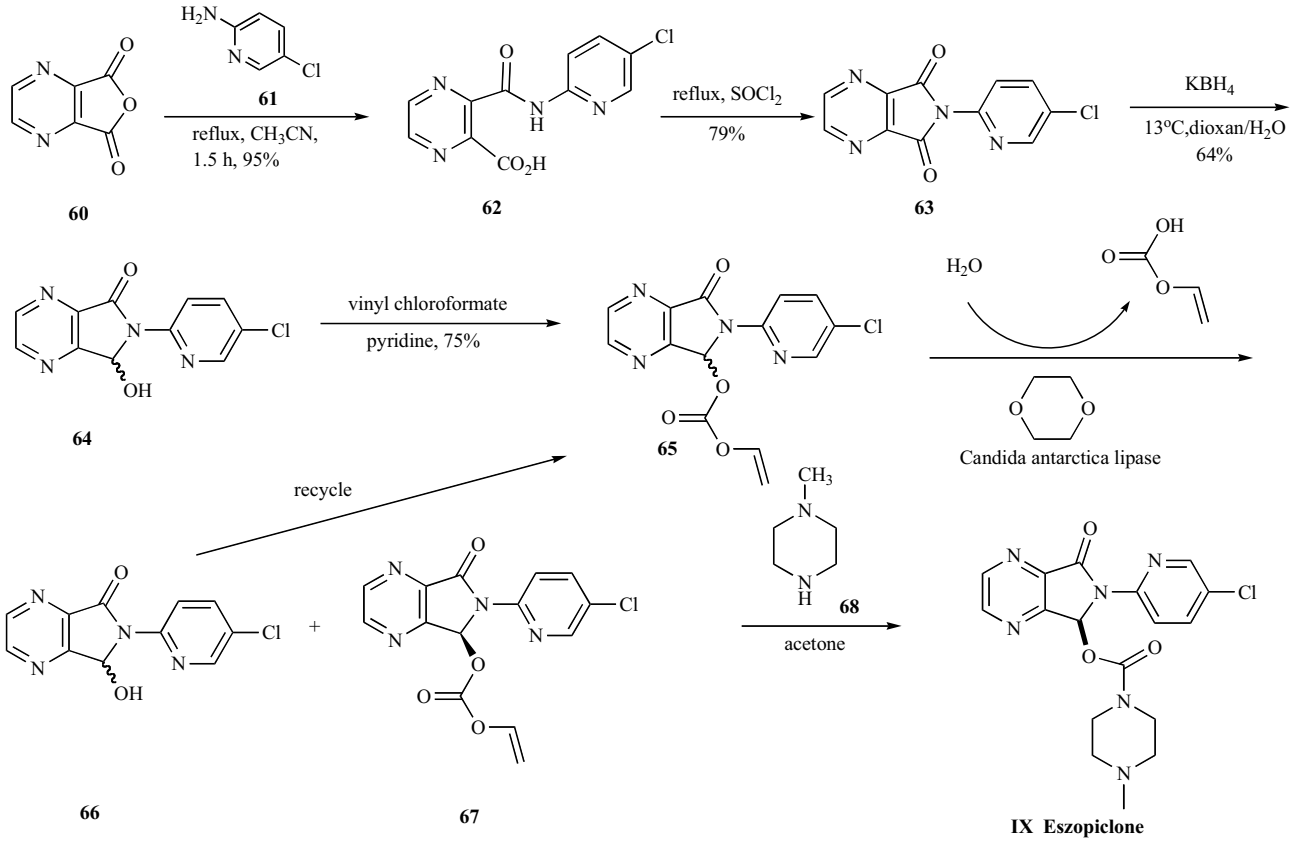


Scheme 11. Synthesis of Entecavir.

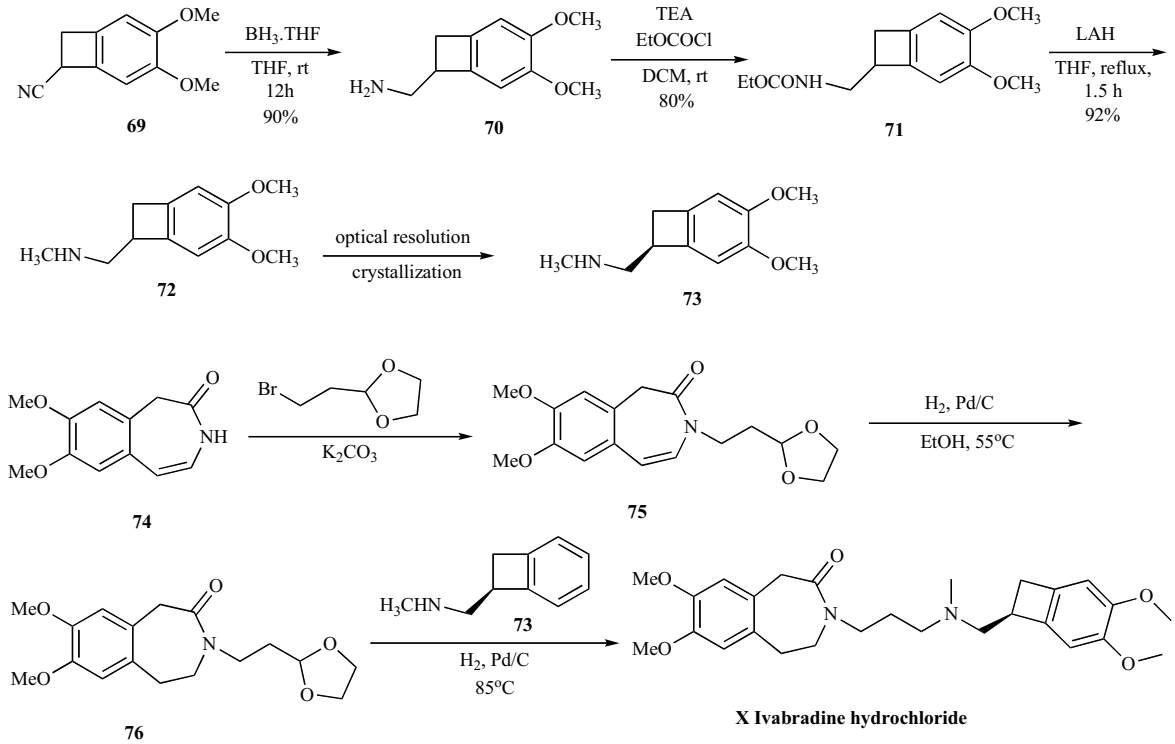
Compound **63** was subjected to partial reduction with KBH_4 in dioxane-water at low temperature to give 6-(5-chloro-2-pyridyl)-7-hydroxy-5,6-dihydropyrrolo[3,4-b]pyrazin-5-one (**64**) in 64% yield, which was esterified with vinyl chloroformate in pyridine to give corresponding vinyl acetate **65** in 75% yield. The racemic **65** was then subjected to kinetic resolution by a highly enantioselective enzymatic hydrolysis process. Chiral vinyl acetate **67** with desired stereochemistry was obtained when *candida antarctica* lipase was employed for hydrolysis of **65** in dioxane/water at 60°C for 2 days. Interestingly, the enzymatic hydrolysis stopped at 50% conversion and the hydrolyzed alcohol was recovered as the starting substrate **65** because of spontaneous racemization of the alcohol in the reaction medium. Therefore, although a maximum yield of kinetic resolution is 50%, the overall efficiency of this enzymatic process is 100% because of substrate recycling. Finally, the chiral vinyl acetate **67** was condensed with methyl piperazine in acetone to give eszopiclone (**IX**).

IVABRADINE (PROCORALAN®)

Ivabradine is a first selective and specific I_f inhibitor that was approved by EMEA in November for symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm. This is the first agent to lower heart rate by inhibiting the cardiac pacemaker I_f current. The compound was discovered and developed by Servier and is currently being marketed in Ireland [3,30]. The convergent synthesis of ivabradine was accomplished by coupling the key benzocylclobutanyl amine **73** with oxadioxalane **76** in an *in situ* deprotection and amination as shown in Scheme **13** [29]. For the synthesis of the key amine **73**, cyano group of compound **69** is reduced with borane-THF to give amine **70** in 90% yield, which was reacted with ethyl chloroformate to give carbamate **71** in 80% yield. Complete reduction of the carbamate was accomplished by refluxing with LAH in THF to give racemic methyl amine **72** in 92% yield, which was then resolved by crystallizing with N-acetyl –L-glutamic



Scheme 12. Synthesis of Eszopicolone.



Scheme 13. Synthesis of Ivabradine.

acid to give chiral salt **73**. Prior to the next step, the amine is converted to the hydrochloride salt.

The coupling partner **76** to make ivabradine was prepared from the azepinone **74** by first reacting with bromoethyldioxalane to give **75**. The olefin in **75** was reduced by hydrogenating with palladium/carbon catalyst at 55°C to give **76**. To the same pot, the amine **73** was added and hydrogenated to give reductive amination product ivabradine hydrochloride (**X**) in very good yields.

LULICONAZOLE (LULICON®)

Luliconazole is a topical imidazole related antifungal agent which was approved for use to treat tinea pedis, candidiasis and pityriasis in Japan [3]. Synthesis of luliconazole (Scheme **14**) started with diol **77**, prepared according to literature procedure in 98%ee [32] which was activated by converting to dimesylate **78** in 99% yield and coupled to dipotassium enolate **80**, prepared *in situ* by reacting cyano methylimidazole **79** with carbon disulfide, to give luliconazole (**XI**), 99% ee in 48% yield [33].

LUMIRACOXIB (PREXIGE)

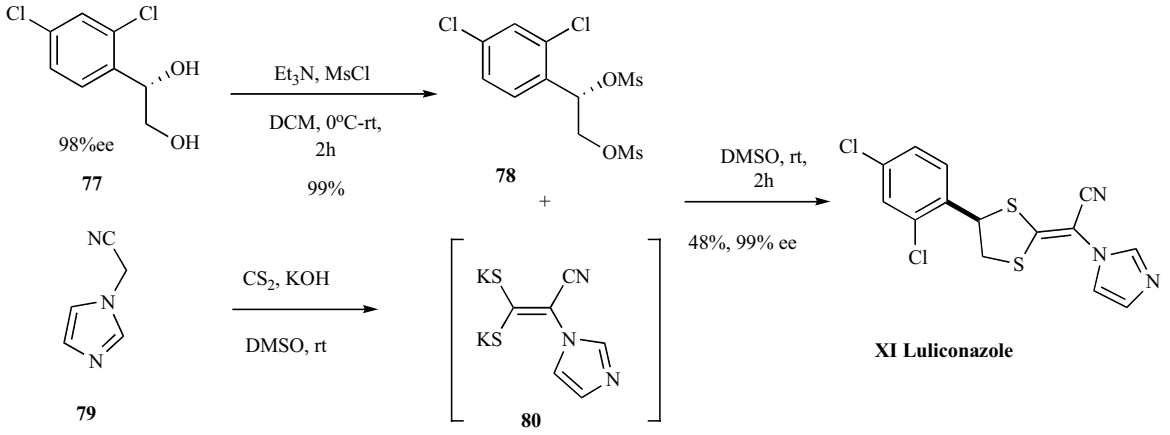
Lumiracoxib, a orally active cyclooxygenase-2 (COX-2) inhibitor launched by Novartis in Brazil in 2005, is for the treatment of osteoarthritis and acute pain. In 2004, Novartis withdrew its application for the European mutual recognition procedure for the compound to await the outcome of a review from the EMEA of all selective COX-2 inhibitors. Novartis expects to resubmit in 2006 the application with added safety and efficacy data according to the EMEA's recommendations. In addition, phase III clinical trials of lumiracoxib are still under way in the U.S., Japan and Europe for the treatment of dysmenorrhea, rheumatoid arthritis (RA) and gout [34]. Synthesis of lumiracoxib is rather straightforward (Scheme **15**) [35]. 2-Iodo-5-methylbenzoic acid (**81**) was reduced with BH_3/THF in THF to give 2-iodo-5-methylbenzyl alcohol as a white solid, which was treated with 48% HBr under refluxing to yield benzyl bromide **82** as a yellow solid. The benzyl bromide **82** was reacted with NaCN in ethanol/water to afford corresponding phenylacetonitrile as a white solid, which was hydrolyzed with NaOH in refluxing EtOH/water to provide phenylacetic acid **83**. The solid phenylacetic acid **83** was reacted with $SOCl_2$ in refluxing dichloromethane with a few drop of DMF to give corresponding acyl chloride as a yellowish oil, which is treated with dimethylamine in diethyl ether/THF to yield 2-(2-iodo-5-methylphenyl)-N,N-dimethylacetamide (**84**). Condensation of compound **84** with 2-chloro-6-fluoroaniline (**85**) in the presence of Cu powder, Cu_2I_2 and K_2CO_3 in refluxing xylene afforded 2-[2-(2-chloro-6-fluorophenylamino)-5-methylphenyl]-*N,N*-dimethyl-acetamide (**86**) as an off white crystalline solid that was finally hydrolyzed with NaOH in refluxing butanol/water to yield lumiracoxib (**XII**).

NELARABINE (ARRANON®)

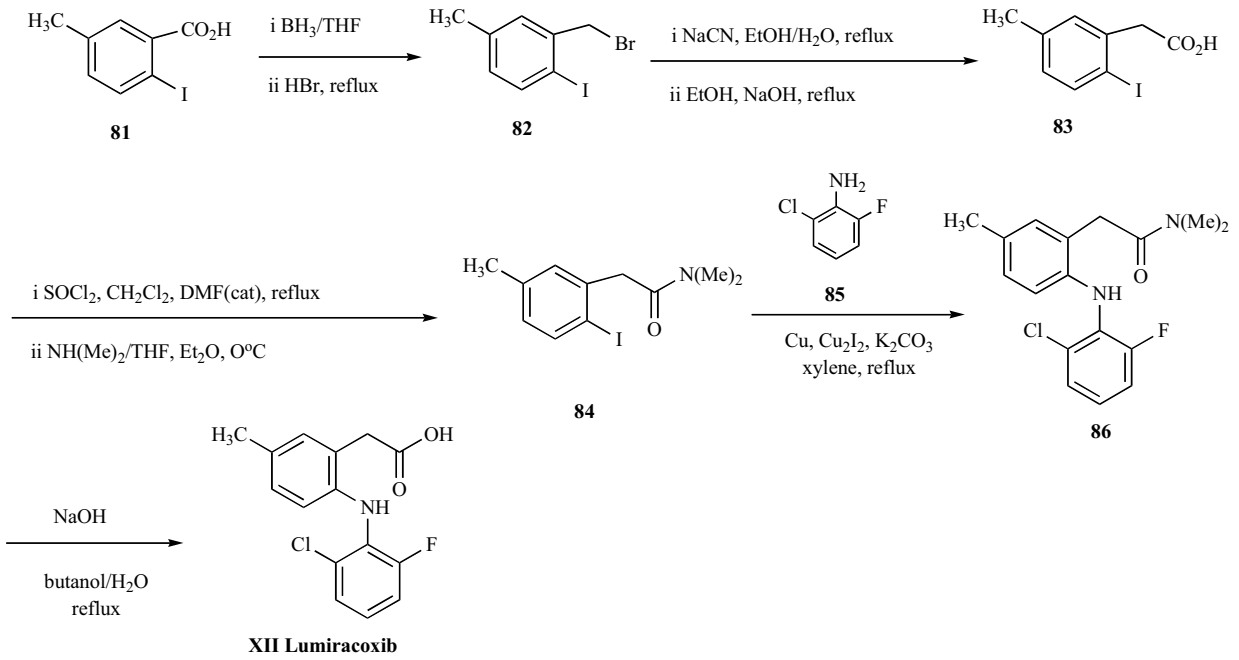
Nelarabine, a novel water soluble nucleoside analog prodrug of ara-G with T- cell selectivity, was approved by the FDA in October, 2005 for treatment of T-cell acute lymphobalstic leukemia (T-ALL). After accumulation in cancer cells, it is converted to its corresponding arabinosylguanine nucleoide triphosphate (araGTP) which results in inhibition of DNA synthesis and cytotoxicity [3,36]. The drug was synthesized (Scheme **16**) by enzymatic coupling of arabinosyluracil **87**, prepared according to literature [37] and 2-amino-6-methoxy purine **88** using purine nucleoside phosphorylase (PNP) and uridine phosphorylase (UP) in phosphate buffer for 30 days to give the nelarabine (**XIII**) in 48% yield [38].

NEPAFENAC (NEVANAC™)

Nepafenac originated from Wyeth is a non-steroidal anti-inflammatory drug (NSAID) that was launched by Alcon in 2005 for the treatment of pain and inflammation associated with cataract surgery [39]. The drug, which rapidly penetrates ocular tissues, is the first ophthalmic NSAI prodrug to receive FDA approval. Nepafenac is metabolically converted to 2-amino-3-benzoylbenzeneacetic acid, amfenac, a potent cyclooxygenase inhibitor and clinically approved anti-inflammatory drug. The synthesis of nepafenac (Scheme **17**) [40] started with commercially available 2-amino-benzophenone (**89**). Compound **89** was reacted with *t*-butyl hypochrite at –65°C in DCM to give a mono-*N*-chloroaniline (**90**) which was subsequently treated with methylthioacetamide in THF at –65°C in the same pot to give an aza-sulfonium salt **91** as a solid. Compound **91** was slurred in DCM and triethylamine was added to give sulfer ylide **92** intermediate which under-



Scheme 14. Synthesis of Luliconazole.

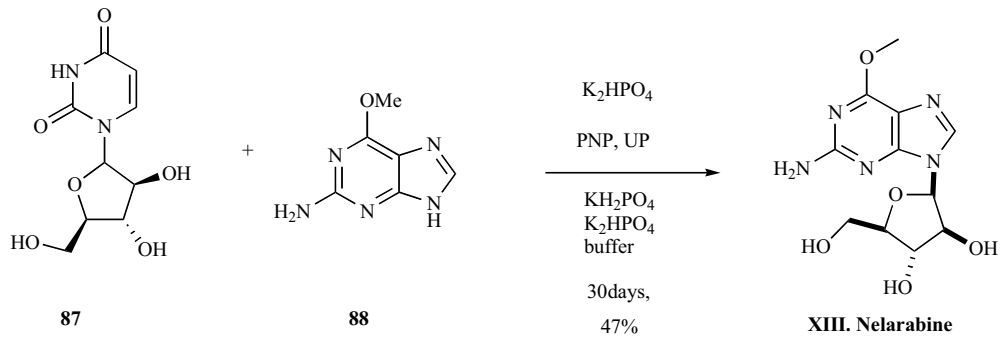


Scheme 15. Synthesis of Lumiracoxib.

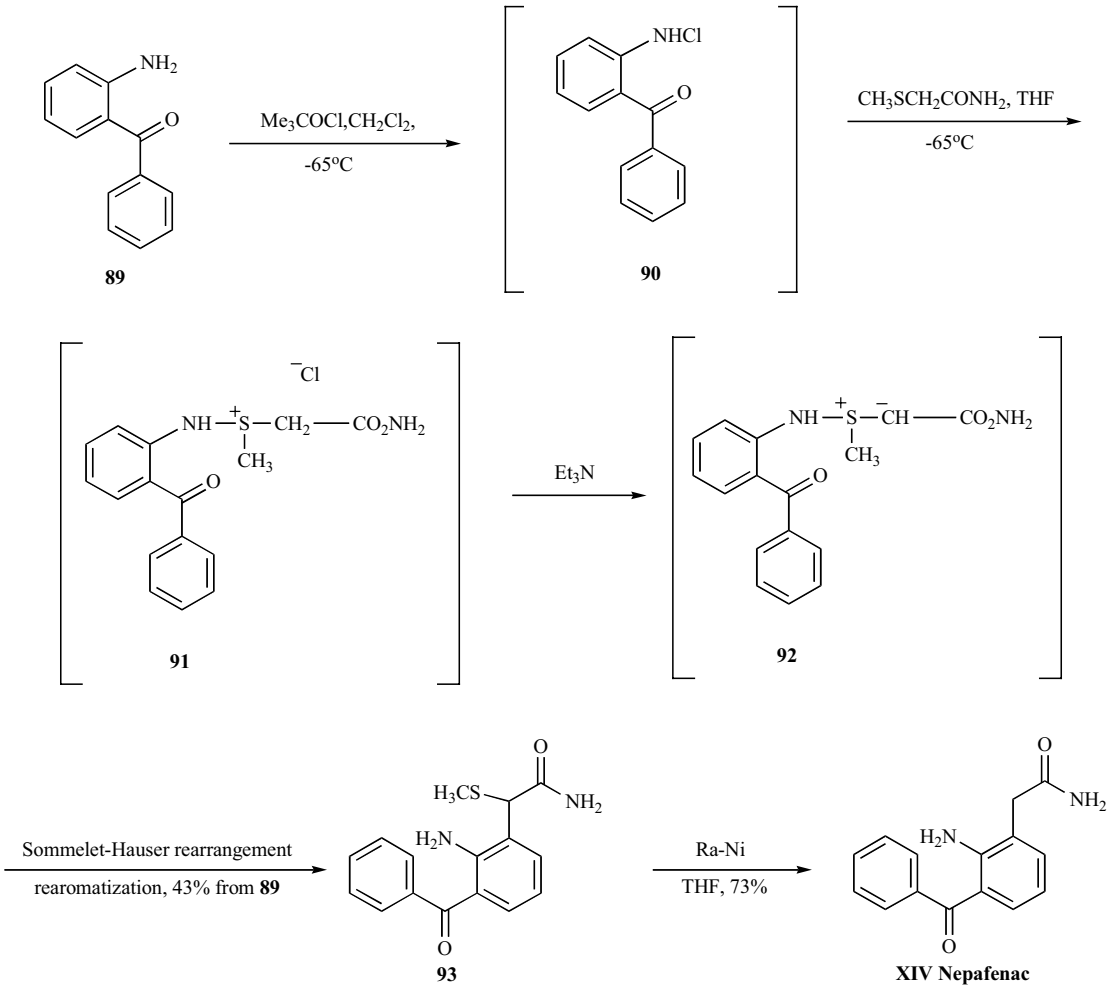
went a Sommelet-Hauser type rearrangement to give compound **93** after re-aromatization of the intermediate cyclohexadienone imine. Compound **93** was finally reduced with Raney nickel to give nepafenac (**XIV**) in 73% yield as yellow needles.

POSACONAOLE (NOXAFIL®)

Posaconazole, a tetrahydrofuran antifungal agent discovered and developed by Schering Plough, was approved in the European Union in October, 2005 for the treatment of invasive fungal infections in adult patients, especially those who have been refractory or are intolerant of other commonly used antifungal agents [3,41,42]. Several routes to the synthesis of posaconazole have been published in the literature [43-46]. The most likely route to large scale synthesis uses convergent synthesis of a key chiral THF subunit **101** and aryl piperazine amine **102** followed by introduction of the triazole subunit at the end (Scheme **19**) [44,46]. The readily accessible allyl alcohol **94** (Scheme **18**) was brominated (PBr_3) to give bromide **95** which was alkylated with sodium diethylmalonate and the resulting diester was reduced with $NaBH_4$/LiCl, to give the key diol **97** in very good yields. After scanning many hydrolases to desymmetrize the diol *via* selective acylation, hydrolase SP 435 was found to be suitable [47]. Thus reaction of the diol **97** in the presence of SP 435 with vinyl acetate in acetonitrile gave monoacetate **98** in greater than 90% yield. Iodine mediated cyclization of the monoacetate **98** with iodine in dichloromethane gave chiral iodide **99** in 86% yield. The iodide was converted to triazole (sodiumtriazole, DMF: DMPU) and immediately followed by hydrolysis of the acetate with sodium hydroxide to provide alcohol **100**. Activation of the alcohol to the *p*-chlorobenzene sulfonate **101** proceeded in 76% yield which was then coupled with commercially available amino alcohol piperazine **102** with aqueous sodium hydroxide in DMSO to give amine intermediate **103** in 96% yield. The amine was



Scheme 16. Synthesis of Nelarabine.



Scheme 17. Synthesis of Nepafenac.

reacted with benzoyl chloride to give benzoate **104** (97%), which was subsequently converted to triazine of posaconazole.

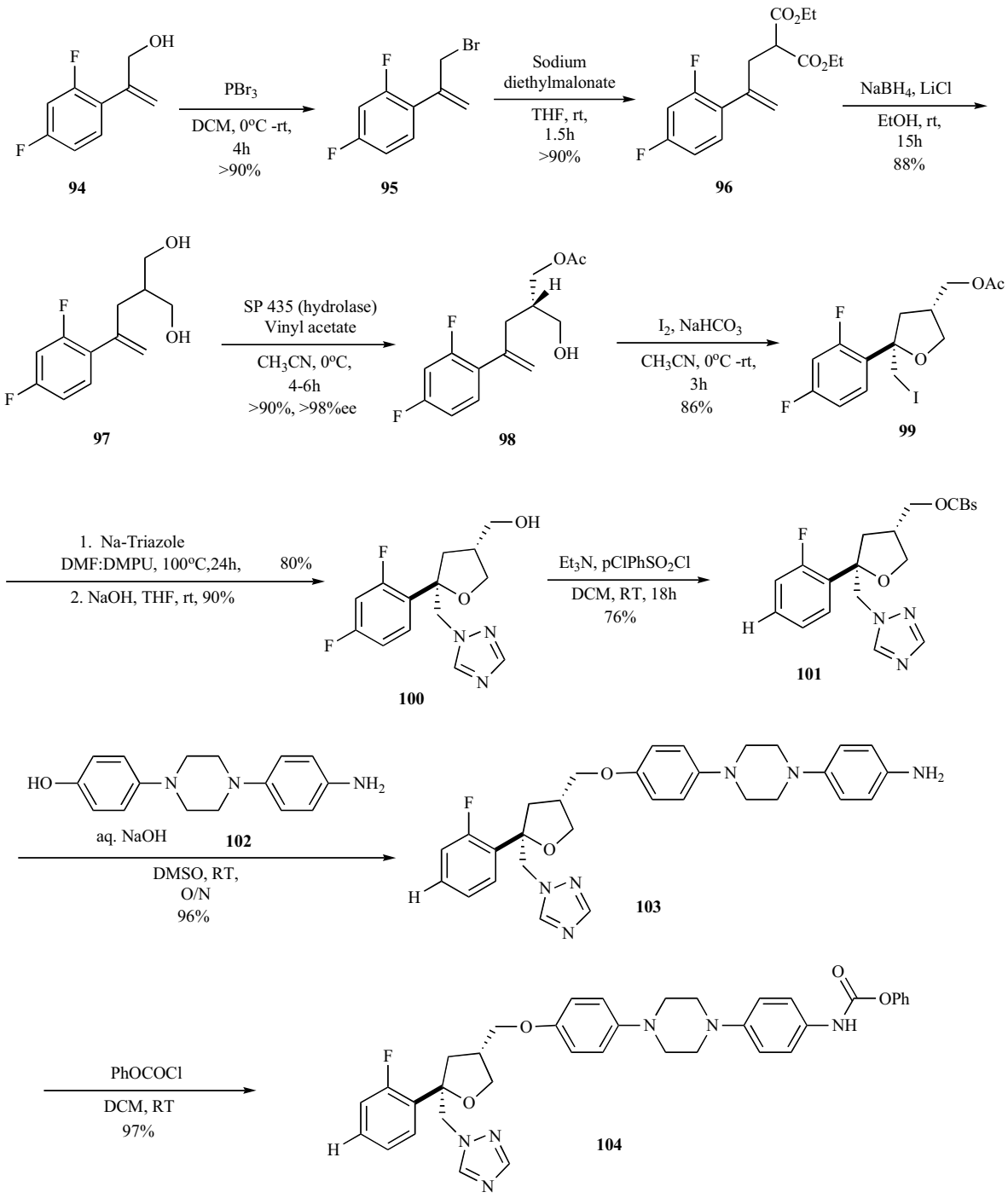
For the preparation of chiral hydrazine **107,** intermediate needed to make the triazolone, lactam **105** was reduced with Red-Al to give (*S*)-2-benzyloxy propanal **106** (94%) which was then reacted with formyl hydrazine to give hydrazone **107** in 81% yield. Addition of EtMgBr directly to formyl hydrozones **107** gave mixture of (*S,S*)stereoisomer **109** and (*S,R*)-diastereomer **110** in relative good diastereoselectivity (94:6) in 55% yield. However, protection of the formyl group as TBDMS ether **108** followed by treatment of the EtMgCl gave 95% yield of the (*S,S*)-diastereomer **109** and (*S,R*)-diastereomer **110** in 99:1 ratio.

For finishing off the synthesis, the formyl hydrazine **109** was coupled with the phenyl carbamate **104** in toluene at 75 - 85°C for 12 – 24 hrs. After the completion of coupling, the intermediate was heated at 100 – 110°C for 24 – 48 hrs to completely cyclize to the benzyloxy triazolone **108**, which was deprotected with 5% Pd/C and formic acid at room temperature overnight and 40°C for 24 h to give posaconazole (**XV**) in 80% overall yield.

RAMELTEON (ROZEREM™)

Ramelteon, a melatonin receptor (MT1/MT2) agonist, was approved in 2005 for the treatment of primary insomnia characterized by difficulty with sleep onset. Discovered and developed by Takeda, this drug is one of the first prescription medication in 35 years to reach US market with a novel mechanism targeting the melatonin receptors in the suprachiasmatic nucleus to modulate the sleep/wake cycle. This drug has shown no dependence liability and is not designated as a controlled substance [3,48]. Several routes to the synthesis of this drug have been published [49,50] including the process route as shown in Scheme **20** [51].

Vilsmeier-Haack reaction on benzofuran **112** provided aldehyde **113** (100%), which was converted to olefin **114** (88%) by Horner-Emmons reaction with triethylphosphonoacetate, and was followed by hydrogenation of the olefin to give ester **115** (100%). In order to avoid the cyclization of the acid chloride intermediate into the wrong position, the benzene ring was protected by bromination. Both bromination and hydrolysis of the ester is accomplished in a single pot to give acid **116**. Thus the ester is brominated with bromine in sodium acetate and acetic acid at 0°C and RT for



Scheme 18. Synthesis of key Intermediate **104**.

several hours followed by quenching of remaining bromide by sodium thiosulfate. The resulting acidic solution was taken up in acetonitrile and refluxed for 2hr to provide the acid **116** in 73% yield. The conversion of the acid to acid chloride was done by reacting with thionyl chloride in o-dichlorobenzene at 40°C for 30 to 40 min after which the reaction was cooled to 0°C . Aluminum trichloride was added and the reaction mixture was stirred at 0°C for 30 min to deliver cyclized ketone **117** in 92% yield. After completion of the cyclization, the bromines are removed by hydrogenation (86%) and resulting ketone **118** was then reacted under Horner-Emmons condition with diethyl cyano phosphonate to give vinyl nitrile **119** in 84% yield. Selective reduction of the nitrile was accomplished by hydrogenation under basic condition (sodium hydroxide in toluene) in the

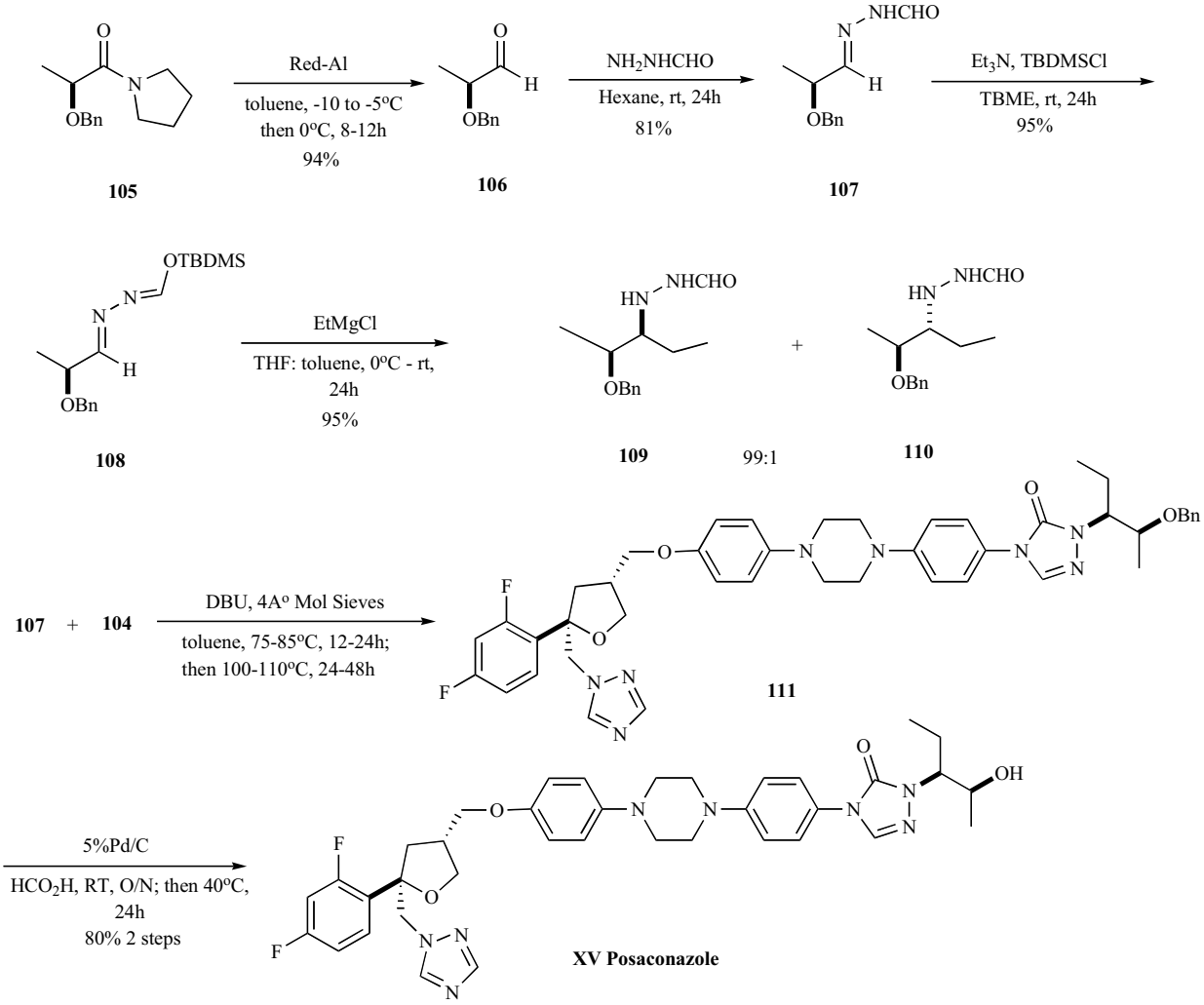
presence of the activated cobalt at 25-50°C for 6.5 hr. The amine was recovered as hydrochloride salt **120** (99% yield) by treating the amine with HCl in methanol. In the next step, the amine salt **120** was taken up in toluene and treated with sodium hydroxide followed by hydrogenation of the mixture with [RuCl(benzene)(*R*)-BINAP]Cl as catalyst to provide chiral amine **121**, after several work up and palladium catalyzed hydrogenations, in 73% overall yield. Final acylation of the amine with propionyl chloride in the presence of aqueous sodium hydroxide in THF at room temperature gave the desired product ramelteon (**XVI**), after crystallization, in 97% yield.

RESAGILINE MESILATE (AZILECT®)

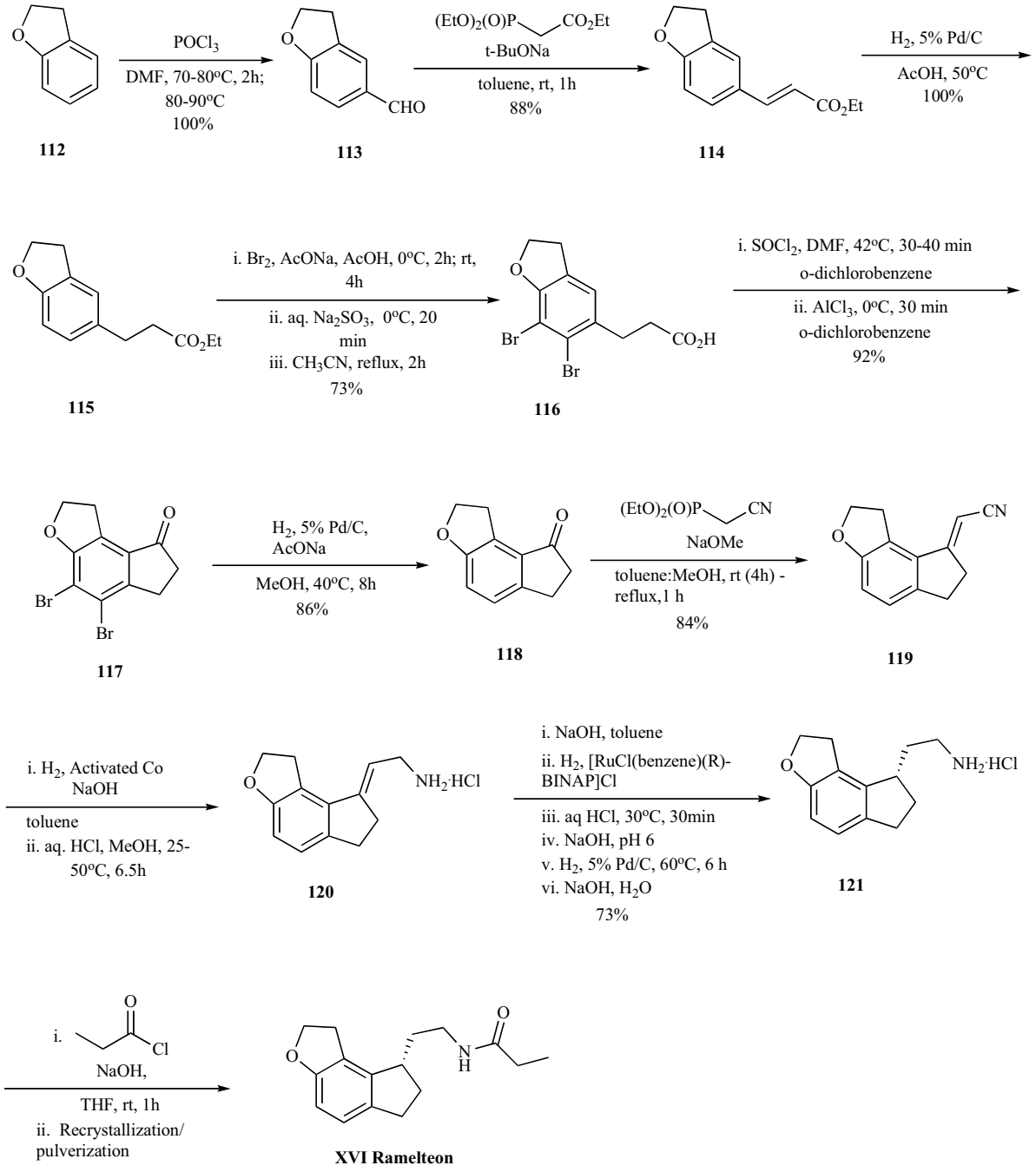
Rasagiline mesylate is a potent and selective irreversible monoamine oxidase B (MAO-B) inhibitor launched in 2005 in Israel by Teva as monotherapy in patients with early Parkinson's disease and as adjuvant treatment in moderate-to-advanced disease [52]. Lundbeck will market the drug throughout Europe. Rasagiline is in phase II clinical trials at Teva and Eisai for the treatment of Alzheimer's type dementia. 1-Indanone (**122**) was condensed with benzyl amine to give corresponding enamine (Scheme **21**) which was reduced with sodium borohydride in ethanol to give racemic *N*-benzyl-1-inda-namine (**123**) in 82% yield [51]. The racemic benzylamine **123** was resolved with *L*-tartaric acid and recrystallized from boiling water to give optical pure *R*-benzylamine **124** as a tartarate salt. The recovered *S*-isomer **125** can be racemized under basic condition to give back as the starting racemic **123**. Compound **124** was hydrogenated and basified to give free amine **126** in 72 % yield which was alkylated with propargyl chloride and K_2CO_3 in hot acetonitrile to yield free resagiline. Finally resagiline mesilate (**XVII**) was obtained by treating resagiline with methanesulfonic acid in refluxing IPA.

SORAFENIB (NEXAVAR®)

Sorafenib, an orally active potent multi-kinases inhibitor, was approved in the U.S. for the treatment of advanced renal cell carcinoma [54]. The drug targets both tumor cell proliferation and tumor angiogenesis kinases that include RAF, VEGFR-2, VEGFR-3, PDGFR-β, KIT and FLT-3. Sorafenib is being jointly developed by Bayer and Onyx in phase III trials as a single agent for the treatment of advanced hepato-

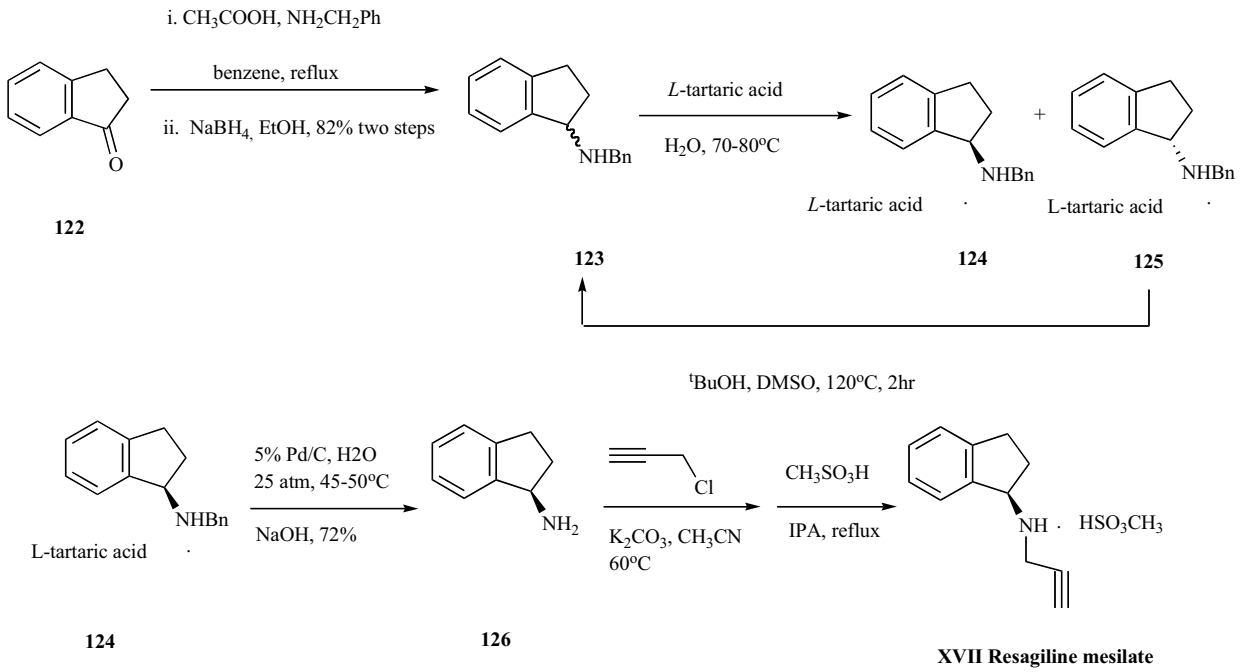


Scheme 19. Synthesis of Posaconazole.



Scheme 20. Synthesis of Ramelteon.

cellular carcinoma and in combination with carboplatin and paclitaxel in patients with advanced metastatic melanoma. Phase II trials in combination with doxorubicin for the treatment of advanced hepatocellular carcinoma are also under investigation. Additional phase II trials are ongoing for non-small cell lung cancer (NSCLC) and in postmenopausal women with estrogen receptor and/or progesterone receptor-positive metastatic breast cancer. In addition, the National Cancer Institute (NCI) is evaluating the compound both as a single therapy agent and in combination with other oncology agents in phase II trials for several cancer indications. An improved, four-step synthesis in 63% overall yield was published recently [55] and is illustrated in Scheme **22**. Picolinic acid (**127**) was heated with Vilsmeier reagent for 16 hr to give **128** in 89% yield as an off-white solid. The acid chloride **128** was treated with methylamine in methanol at low temperature to give amide **129** in 88% yield as pale-yellow crystals after its crystallization from ethyl acetate.

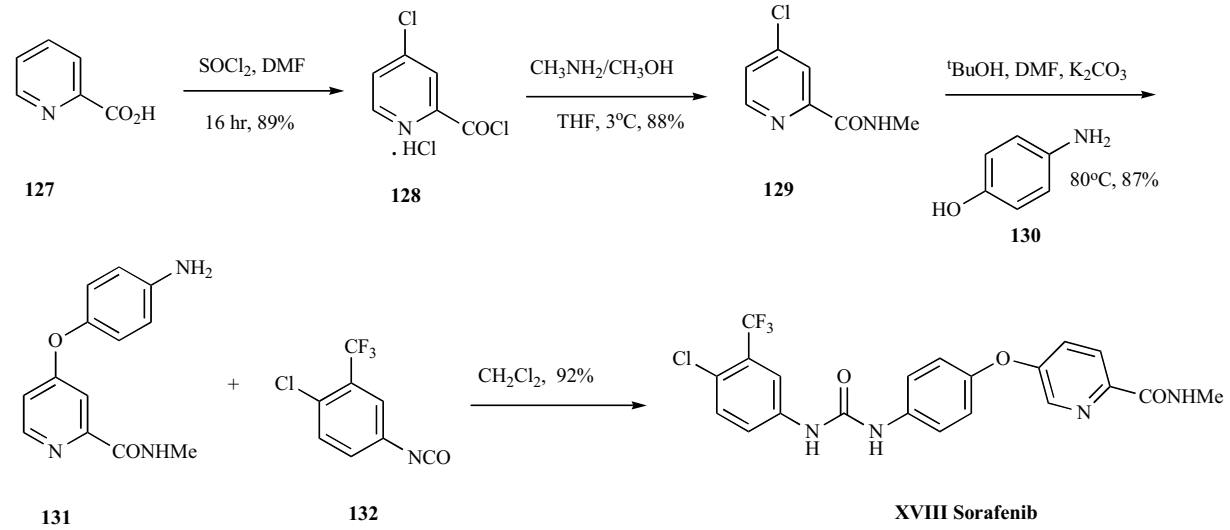


Scheme 21. Synthesis of Resagiline Mesilate.

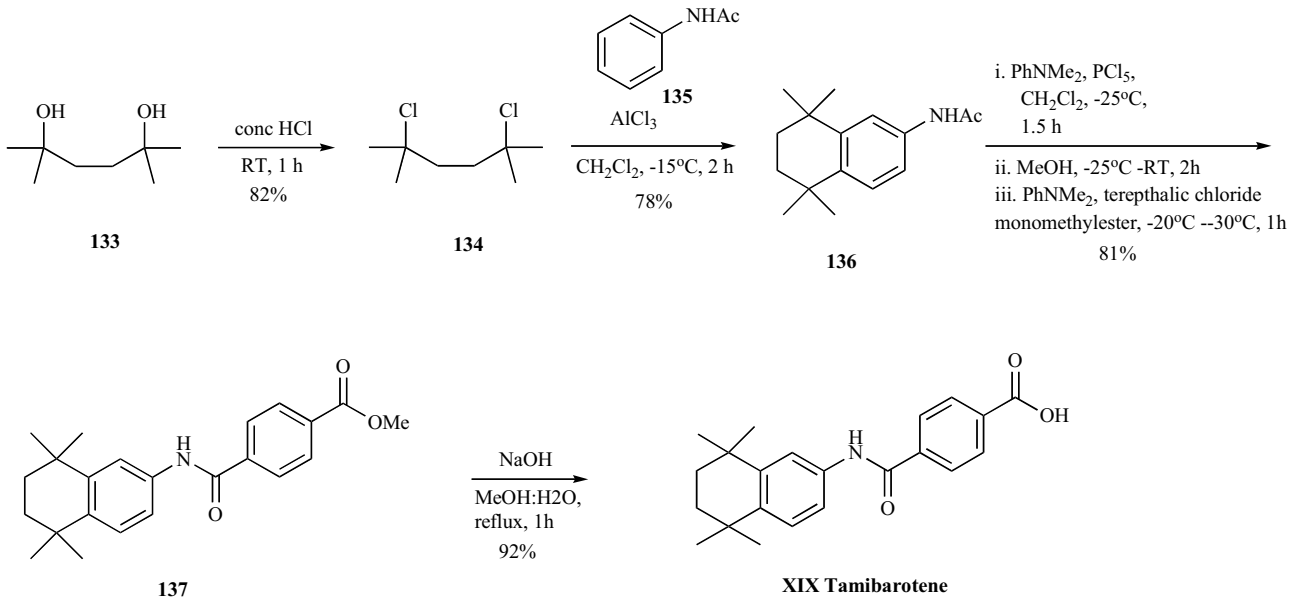
4-Aminophenol anion was generated under a basic condition and compound **129** was added to the anion solution to give corresponding addition compound **131** in 87% yield. For an unknown reason, potassium carbonate used in the reaction increased the reaction rate significantly. Finally, compound **131** was condensed with *iso*cyanate **132** in methylene chloride to give sorafenib (**XVIII**) in 92% yield as a white solid.

TAMIBAROTENE (*AMNOLAKE*®)

Tamibarotene, a retinoic acid receptor-α (RARα) agonist, was approved for the treatment of relapsed or refractory acute promyelocytic leukemia (APL) in Japan on June, 2005 and is currently marketed by Nippon Shinyaku Co. This novel drug has shown high remission rate among patients who have recurrent disease after all trans retinoic acid therapy [3,56]. Several synthesis of tamibarotene have been disclosed in the literature [57] including the process scale synthesis as shown in Scheme **23** [57]. The synthesis started with preparation of dichloride **134** in 82% yield from diol **133** by treating with concentrated HCL in DCM. Friedal Crafts reaction of dichloride **134** with acetanilide in the presence of aluminum chloride at -15°C for 2h provided acetanilide derivative **136** in 78% yield. In a single pot, the acetanilide was reacted with PCl_5 and dimethylaniline at -



Scheme 22. Synthesis of Sorafenib.

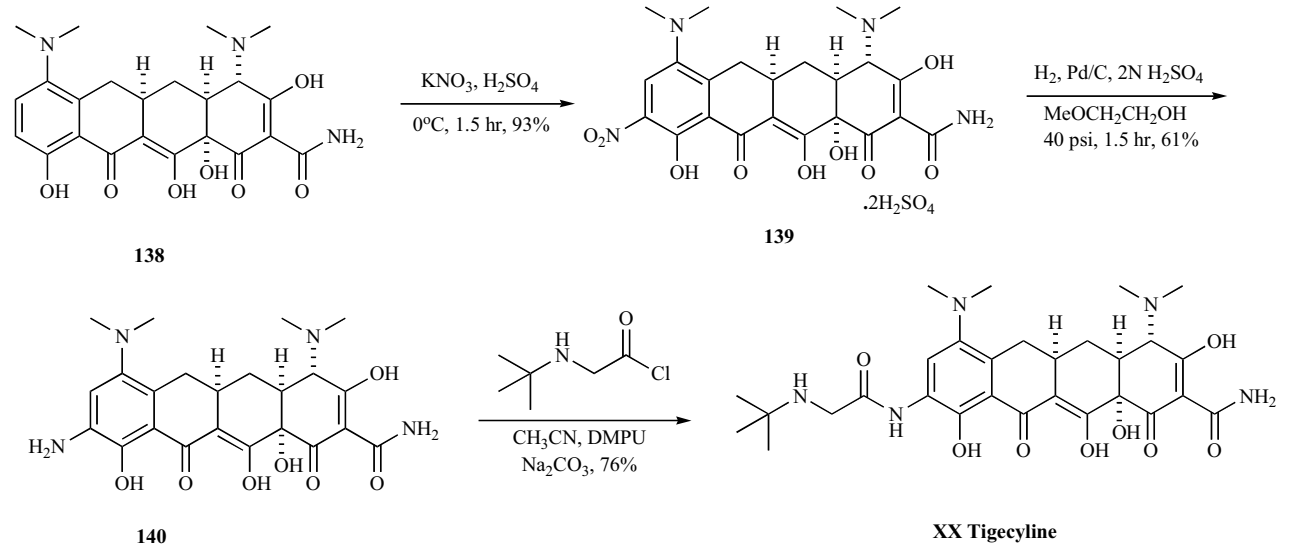


Scheme 23. Synthesis of Tamibarotene.

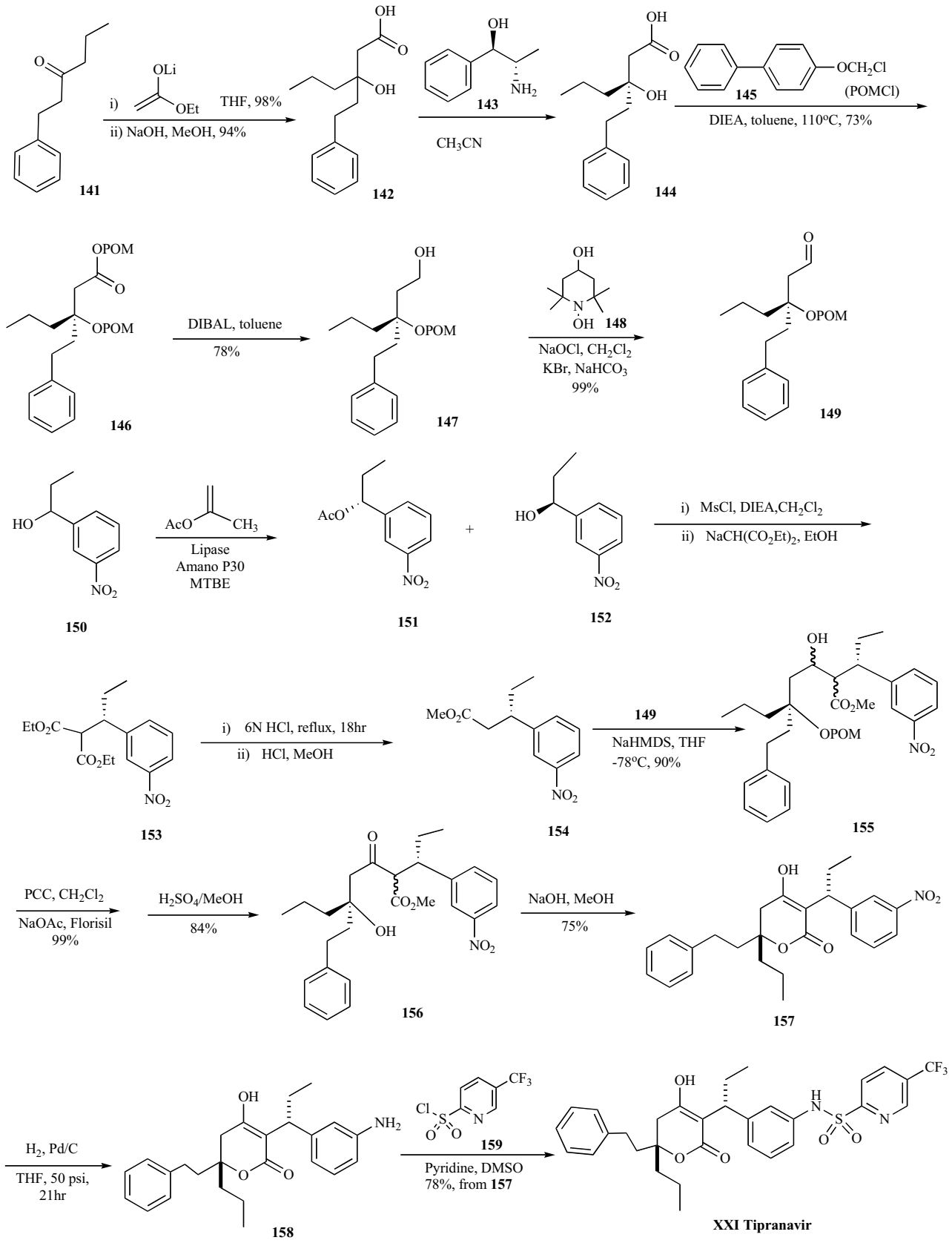
25°C for 1.5h followed by quenching the reaction with methanol for 2h after addition at -25°C. Addition of dimethylaniline and terepthalic chloride mono-methylester at -30 - -20°C for 1 hr provided the tamibarotene methyl easter **137** in 81% yield. Hydrolysis of the ester by heating with sodium hydroxide in MeOH:water mixture for 1h followed isolation and crystallization gave tamibarotene (**XIX**) in 92% yield.

TIGECYLINE (TYGACIL™)

Tigecycline, a new glycylcycline class of antibiotics, was initially launched in 2005 for the treatment of complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI). Originally discovered and developed by Wyeth, the intravenous antibiotic has an expanded broad spectrum of *in vitro* activity against many Gram-positive bacteria, Gram-negative bacteria, anaerobes and methicillin-resistant Staphylococcus aureus (MRSA). It does not require dosage adjustment in patients with impaired renal function and is conveniently dosed every 12 hours [59]. Synthesis of tigecycline (Scheme **24**) [60] started with nitration of **138** with potassium nitrate and concentrated sulfuric acid to give 9-nitro derivative **139** in 93 % yield as disulfate salt, which was hydrogenated over Pd/C in 2-methoxyethanol/2N sulfuric acid at 40 psi to provide 9-aminominocycline (**140**). Finally, 9-aminominocycline (**140**) is acylated directly with *N-tert*-butylglycyl chloride in a 1:5 mixture of acetonitrile and N, N-dimethylpropyleneurea (DMPU) with anhydrous sodium carbonate to give tigecycline (**XX**).



Scheme 24. Synthesis of Tigecycline.



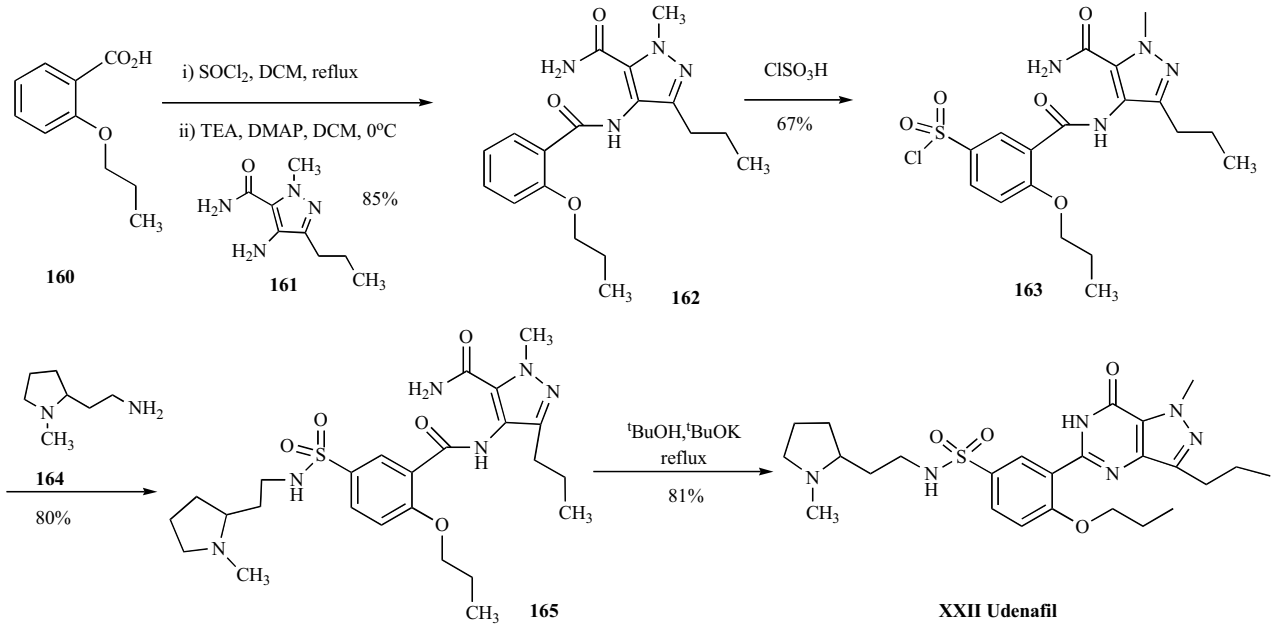
Scheme 25. Synthesis of Tipranavir.

TIPRANAVIR (APTIVUS®)

Tipranavir, an HIV protease inhibitor, is for the treatment of HIV-1-infected patient with evidence of viral replication who have HIV-1 strains resistant to multiple protease inhibitors or have extensive treatment already. The drug originally discovered at Pfizer and then developed by Boehringer Ingelheim gained accelerated approval from FDA based on analyses of plasma HIV-1 RNA levels in two controlled studies of tipranavir of six months duration [61]. Synthesis of tipranavir (Scheme **25**) was assembled by an aldol condensation between two chiral key intermediates, **149** and **154** [62]. Condensation of 1-phenylhexan-3-one (**141**) with ethyl acetate in the presence of butyllithium and di*iso*propylamine in THF gave racemic 3-hydroxy-3-(2-phenylethyl)hexanoic acid ethyl ester, which was directly hydrolyzed with NaOH in methanol to corresponding free acid **142** in 94% yield. The racemic **142** was subjected to optical resolution with (1*R*, 2*S*)-(-)-norephedrine to yield chiral compound **144** which was alkylated with 4-biphenylyloxymethyl chloride (POMCl) and di*iso*propylethylamine in toluene to give POM protected ester **146** in 73% yield . The choice of POM protection group is for the purification since the POM protected intermediates were highly crystalline compounds. The ester group of **146** was reduced with di*iso*butylaluminum hydride in toluene to give corresponding alcohol **147** in 78% yield, which was oxidized with 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy radical (TEMPO)/bleach (NaOCl) to yield corresponding aldehyde **149** in 99% yield. The other chiral intermediate **154** was synthesized as described below. Racemic compound **150** was subjected to kinetic enzymatic resolution with a lipase and *iso*propenyl acetate in dichloromethane to give chiral alcohol **152** which was converted to its mesylate and reacted with sodium diethyl malonate to give diester **153**. The diester **153** was decarboxylated under an acid condition and re-esterified to give optical pure intermediate **154**. Aldol condensation of **149** and **154** with sodium hexamethyldisilazide in THF at low temperature gave hydroxyester **155** in 90% yield as a mixture of four diastereomers. This mixture was oxidized with pyridinium chlorochromate (PCC) in dichloromethane to afford corresponding ketoester which was subsequently treated with sulfuric acid in methanol to remove the POM protecting group to yield hydroxy ketoester **156** in 84% yield. Compound **156** was cyclized with NaOH in methanol/water to afford dihydropyranone **157** in 75% yield. The nitro group of **157** was reduced with hydrogen over Pd/C in THF to give corresponding aniline **158**, which was finally amidated with 5-(trifluoromethyl)pyridine-2-sulfonyl chloride **159** and pyridine in DMSO to give tipranavir (**XXI**) in 78% yield from compound **149**.

UDENAFIL (ZYDENA®)

Udenafil, an orally active phosphodiesterase 5 (PDE5) inhibitor with pyrazolopyramidinone core structure, was launched by Dong-A in Korea for the treatment of erectile dysfunction (ED). Phase III trials are expected to begin in the U.S. in 2006. Udenafil has a unique pharmacokinetic profile with a relatively rapid onset and sufficiently long duration (Tmax 1-1.5 hr, $t_{1/2}$ 11-13 hr) to make it effective for up to 24 hours [63]. Synthesis of this racemic compound (Scheme **26**) started with commercially available 2-propoxybenzoic acid (**160**) [64]. The free acid **160** was converted to it acyl chloride with thinoy chloride in refluxing dichloromethane, which was condensed with 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (**161**) with TEA and DMAP in dichloromethane to yield carboxamide **162** in 85% yield from **160**. Compound **162** was sulfonated with chlorosulfonic acid to yield benzenesulfonyl chloride **163** in 67% yield, which was treated with racemic 2-(1-methylpyrrolidin-2-yl)ethylamine (**164**) in dichloromethane to afford sulfonamide **165** in 80% yield. Finally, compound **165** was cyclized with ^{t}BuOK in refluxing ^{t}BuOH to give udenafil (**XXII**) in 81% yield.



Scheme 26. Synthesis of Udenafil.

ABBREVIATIONS

ADME	=	Absorption, distribution, metabolism, excretion
CDI	=	Carbonyl diimidazole
DBU	=	1,8-Diazabicyclo[5, 5,0]undec-7-ene
DCE	=	Dichloroethane
DCM	=	Dichloromethane
DEAD	=	Diethylazodicarboxylate
DIBAL	=	Di*iso*butylaluminum hydride
DIEA	=	Di*iso*propylethylamine
DIPP	=	Di*iso*propylphosphoryl
DIPT	=	Di*iso*propyl tartrate
DMAP	=	4-Dimethylaminopyridine
DMF	=	*N,N*-Dimethylformamide
DMPU	=	N, N-dimethylpropyleneurea
DMSO	=	Methyl sulfoxide
IPA	=	*Iso*propyl alcohol
MsCl	=	Methansulfonyl chloride
MTBE	=	*tert*-Butyl methyl ether
NaHMDS	=	Sodium bis(trimethylsilyl)amide
NCE	=	New chemical entities
O/N	=	overnight
PCC	=	Pyridinium chlorochromate
PNP	=	Purine nucleoside phosphorylase
PNZCl	=	p-Nitrobenzylchloroformate
PPA	=	Polyphosphoric acid
Red-Al	=	Sodium bis(2-methoxyethoxy)aluminum hydride
TBHP	=	*tert*-Butyl hydrogen peroxide
TEA	=	Triethyl amine
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
TsCl	=	Toluenesulfonyl chlodire
p-TSA	=	*para*-Toluene sulfonic acid
UP	=	Uridine phosphorylase

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