Synthetic Approaches to the 2002 New Drugs

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Abstract: New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biological target. 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. Therefore, it is important to be acquainted with these new structures as well as their syntheses. To these ends, this review covers the syntheses of 28 NCEs marketed in 2002.

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

INTRODUCTION

Dozens of new drugs are registered and launched every year around the world. Although thousands of drugs have been marketed historically, the structure similarity among some drugs is obvious and even more so for drugs targeting in the same gene family. Furthermore, it has been demonstrated that molecules which share the same or similar chemical template can be further modified for different therapeutic indications against the similar gene family. Therefore, medicinal chemists, being aware of these new drug structures, can strike and adopt ideas for their own innovations. In addition, preparation of these drug molecules has been studied extensively to make it concise due to the cost of goods consideration and to ensure environment-friendliness. Having such robust and reliable synthetic methods in hand to access these core structures will steer synthetic efforts more effectively toward the most promising compounds and help focus the optimization toward other challenging properties such as ADME.

In 2002 alone, 33 NCEs including biological drugs, and two diagnostic agents reached the market [1-5]. This review article will focus on the syntheses of the 28 new drugs marketed last year (Figure **1**), but excludes new indications for known drugs, new combinations and new formulations. The syntheses of these new drugs were published sporadically in different journals and patents. It is our intention to compile the syntheses of new drugs yearly into an annual review for the readers' advantage. The synthetic routes cited here represent the most scalable methods according to the best of the authors' knowledge and appear in alphabetical order by generic name.

Adefovir Dipivoxil (*Hepsera*™)

Adefovir dipivoxil (**1**), discovered by Gilead, became the first nucleoside analogue to gain FDA approval for the treatment of chronic hepatitis B infection [6]. Adefovir works by blocking viral replication [6]. The synthesis [7,8] of adefovir dipivoxil (**1**) involves a four-step process [9,10] as depicted in Scheme 1. Adenine (**29**) was condensed with ethylene carbonate (**30**) in hot DMF to afford intermediate 9-(2-hydroxyethyl)-adenine **31** in 83-95% yield. Alkylation of **31** was carried out using diethyl-*p*-toluenesulfonyloxy-methanephosphonate (**32**) and sodium *t*-butoxide in DMF. Phosphonate ester **33** was then cleaved with bromotrimethylsilane to furnish **34** and esterification of the phosphoric acid to append the pivaloyloxymethyl group provided adefovir dipivoxil (**1**).

Amrubicin Hydrochloride (*Calsed*)

This drug is the first anthracycline anticancer antibiotic produced by purely synthetic methods. It was discovered by Sumitomo Pharmaceuticals, and is for the treatment of non-small cell lung cancer and small cell lung cancer [11]. Tetralone **35** was treated with ammonium carbonate and potassium cyanide (Strecker reaction) to give the corresponding aminonitrile intermediate, which was hydrolyzed under basic conditions to afford amino acid **36** in excellent yield [12]. The carboxylic acid in **36** was esterified with HCl in methanol to the corresponding methyl ester, which was treated with *D*-(-)-mandelic acid in toluene to give optically pure levorotatory ester **37** in 33% yield. Sodium methylsulfinylmethide treatment of **37** followed by reduction with zinc yielded amino ketone **38**, which was acylated to give amido ketone **39** in 81 % yield from **37**. Compound **39** was converted to tetracyclic amido ketone **40** in one step (90% yield) by heating with phthalic anhydride in the presence of $AlCl_3$-NaCl at 170°C. Ketone **40** was protected as its ketal **41** in order to provide for subsequent regiospecific bromination. Treatment of **41** with 1,3-dibromo-5,5-dimethylhydantoin (DDH) under illumination in refluxing benzene formed oxazine **42** in 89% yield. Hydrolysis of the oxazine ring and deketalization were simultaneously affected by heating **42** with 3N sulfuric acid to give *cis*-amino alcohol **43** in 82% yield. Modified Arcamone conditions ($AgOSO_2CF_3$ in ether/tetramethylurea /DCM) were employed for the stereoselective glycosidation of **43** with 2-deoxy-3,4-di-O-acetyl-D-erythro-pentopyranosyl bromide (**44**) [13] to give the protected β-glycoside in 86% yield. Basic hydrolysis of the protected coupling product followed by HCl salt formation gave amrubicin hydrochloride (**2**) in 90% yield.

Aripiprazole (*Abilify*™)

This atypical antipsychotic agent was originally discovered by Otsuka and was co-developed and co-marketed

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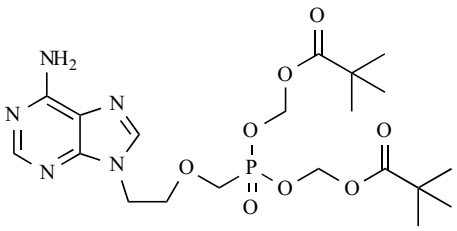
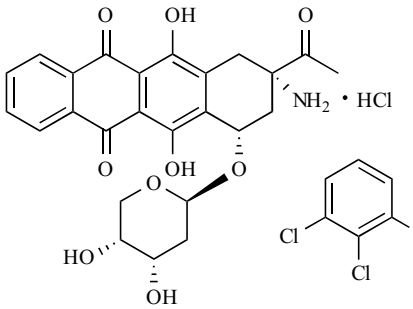
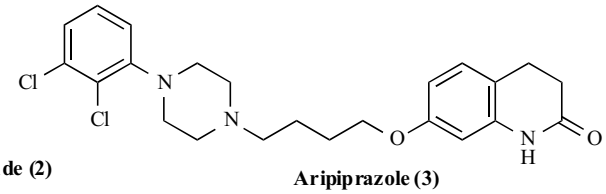


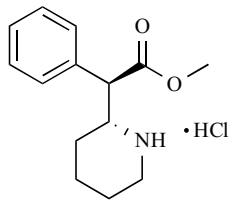
Adefovir dipivoxil (1)



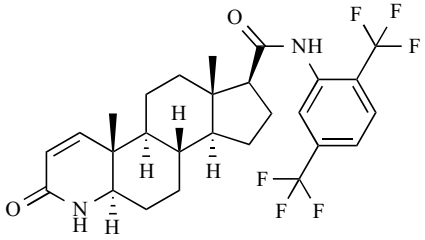
Amrubicin hydrochloride (2)



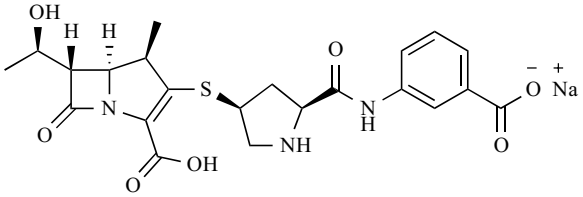
Aripiprazole (3)



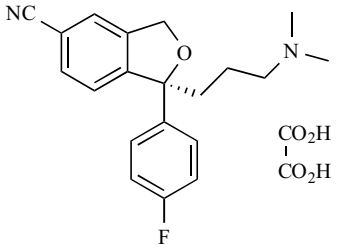
Dexmethylphenidate HCl (4)



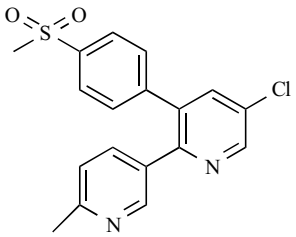
Dutasteride (5)



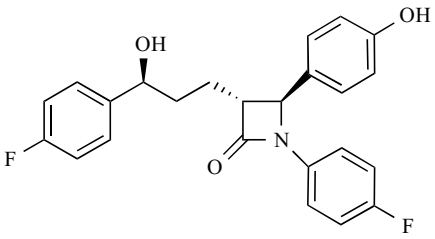
Ertapenem sodium (6)



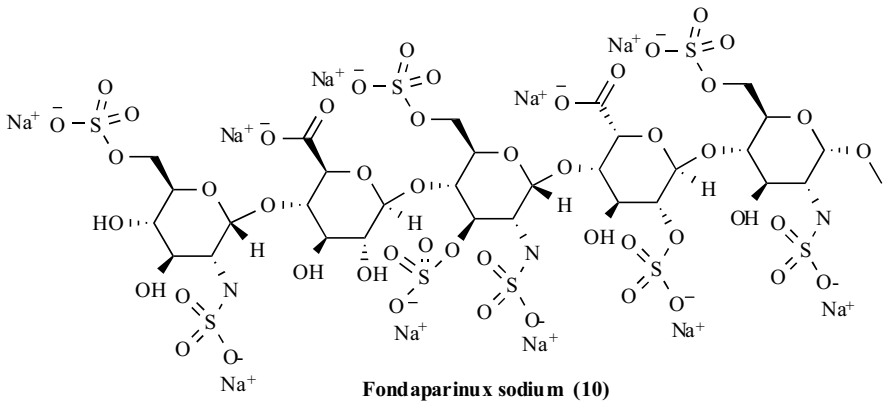
Escitalopram oxalate (7)



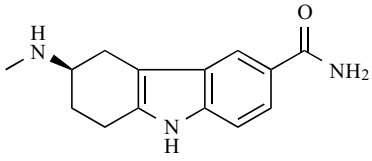
Etoricoxib (8)



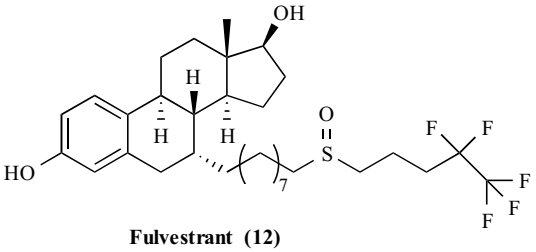
Ezetimibe (9)



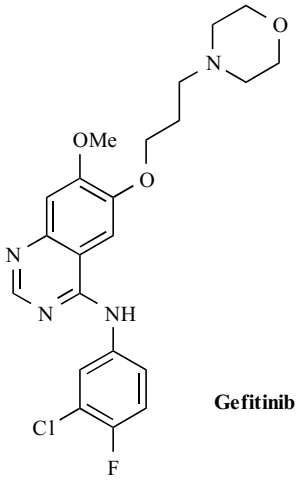
Fondaparinux sodium (10)



Frovatriptan (11)

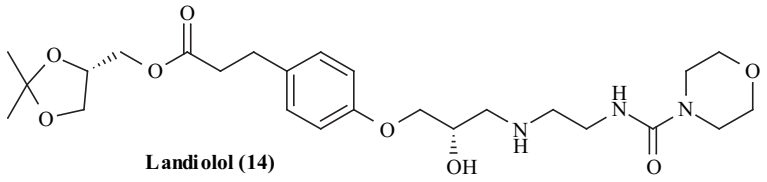


Fulvestrant (12)

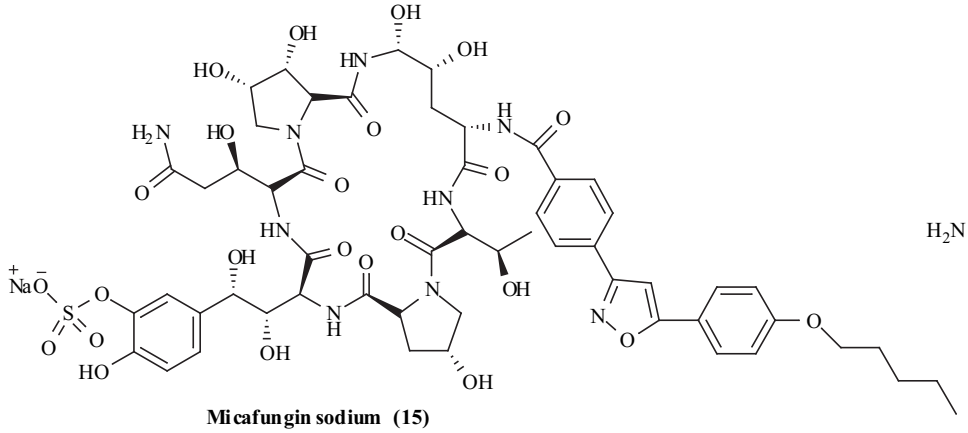


Gefitinib (13)

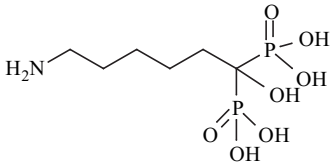
(Fig. 1). contd.....



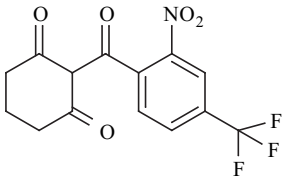
Landiolol (14)



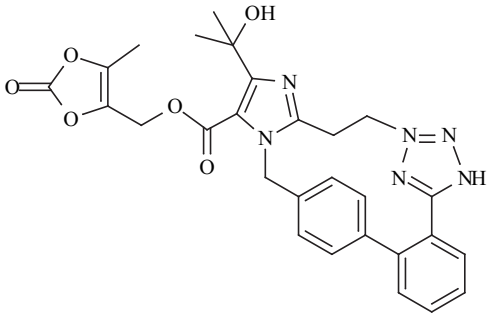
Micafungin sodium (15)



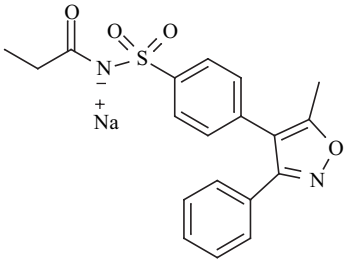
Neridronate (16)



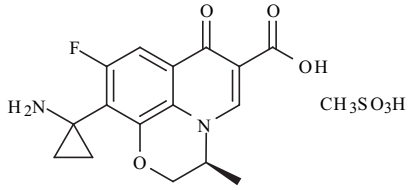
Nitisinone (17)



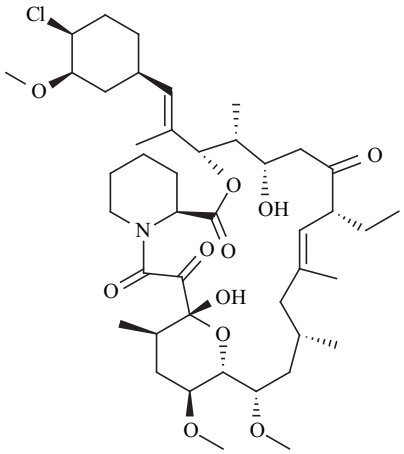
Olmesartan medoxomil (18)



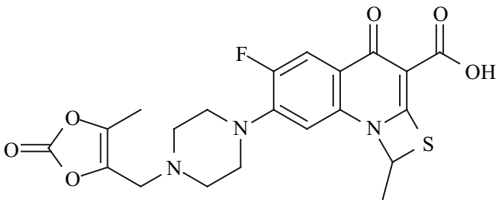
Parecoxib sodium (19)



Pazufloxacin mesilate (20)



Pimecrolimus (21)



Prulifloxacin (22)

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

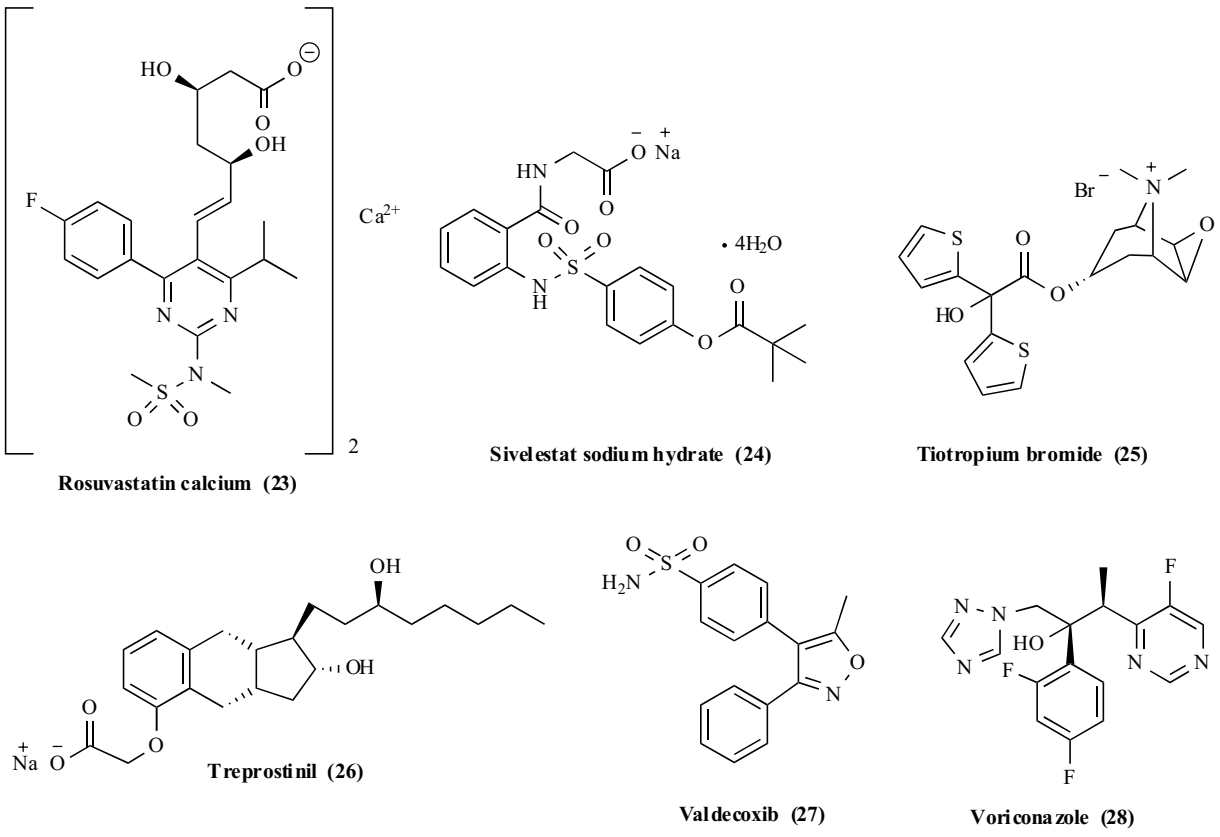
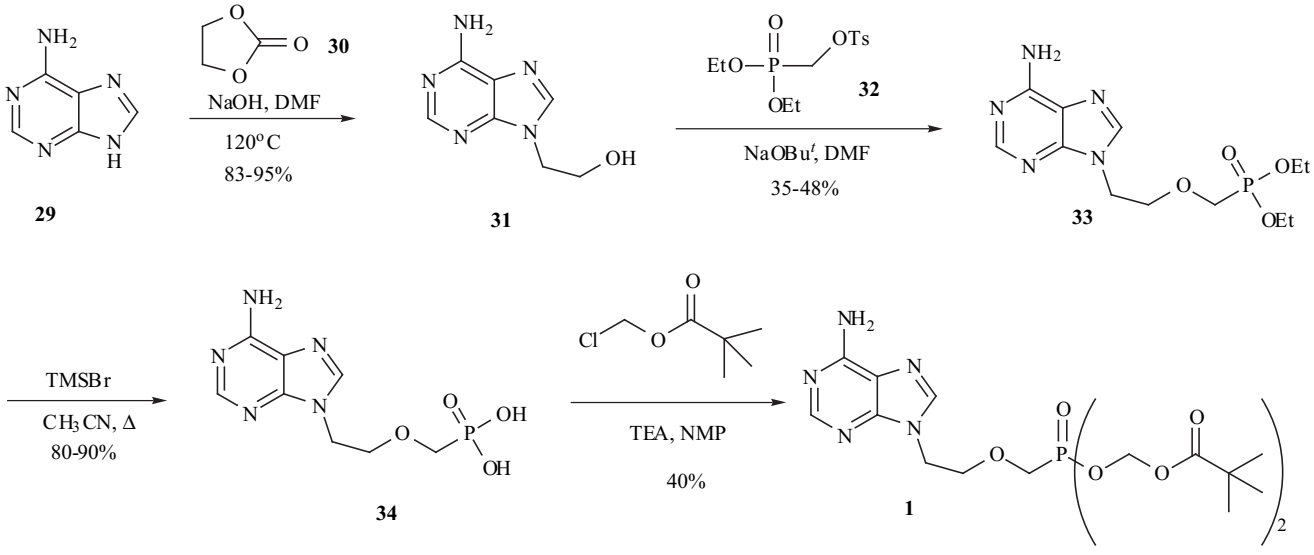


Fig. (1). Structures of 28 new drugs marketed in 2002.

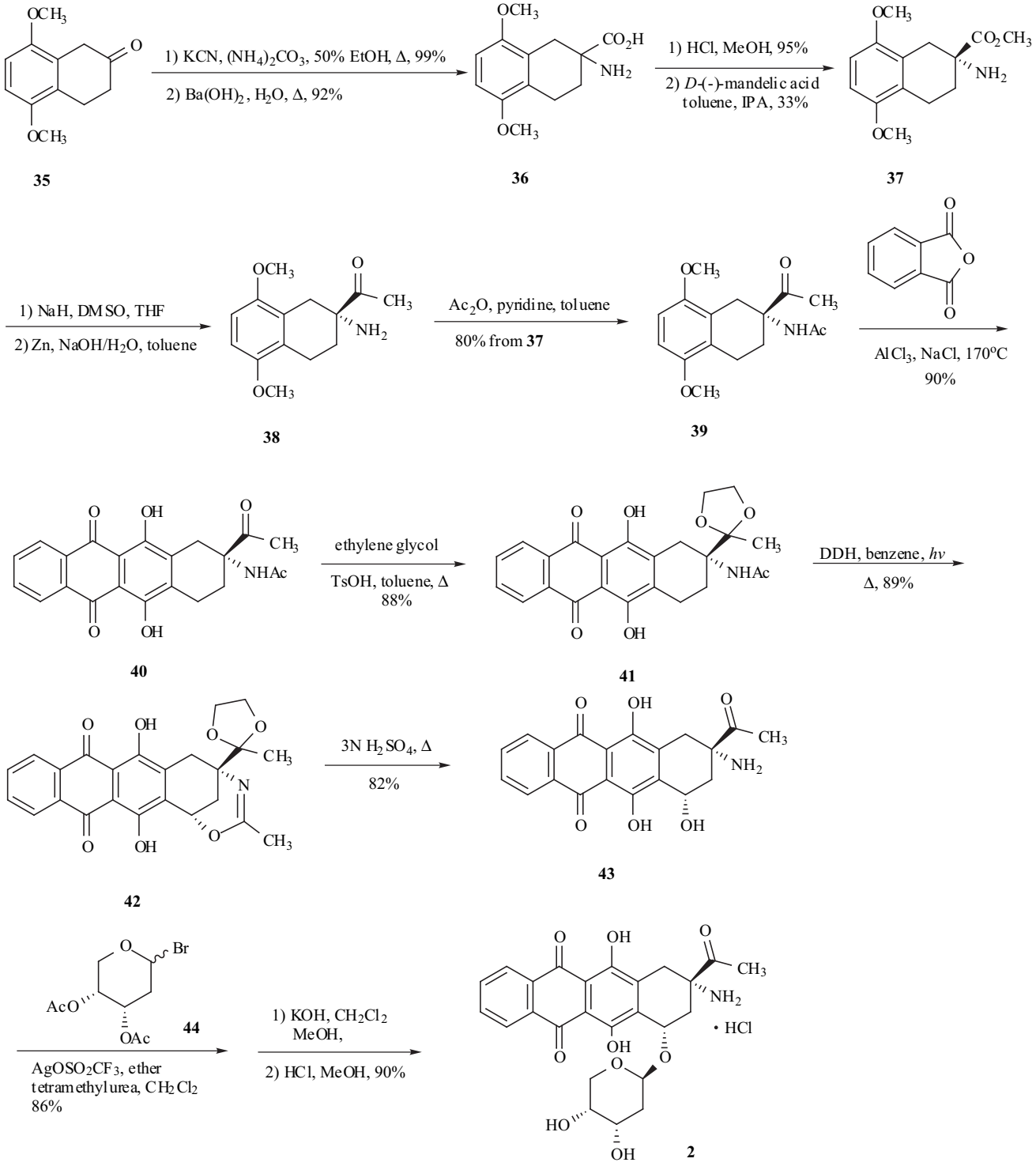
by Bristol-Myers Squibb. The compound is a partial agonist at dopamine D_2 and $5HT_{1a}$ and an antagonist at $5\text{-}HT_{2a}$ receptors [14]. It is indicated for the treatment of schizophrenia. Hydroxyl quinolinone **45** was alkylated with 1,4-dibromobutane in the presence of potassium carbonate in DMF to give **46** in 78% yield [15]. Bromide **46** was condensed with 1-(2,3-dichlorophenyl)piperazine [16] (**47**) in the presence of NaI and TEA to give aripiprazole (**3**) in 87% yield.

Dexmethylphenidate Hydrochloride (*Focalin*™)

Dexmethylphenidate (**4**) is the more pharmacologically active *d-threo*-enantiomer of methylphenidate which was marketed for the treatment of attention deficit/hyperactivity disorder (ADHD) in 1954 [17]. In addition, it has been shown that there are significant metabolic differences between the two enantiomers. This drug was discovered by Cangene and is marketed by Novartis. To date, several methods have been disclosed in the literature for preparing

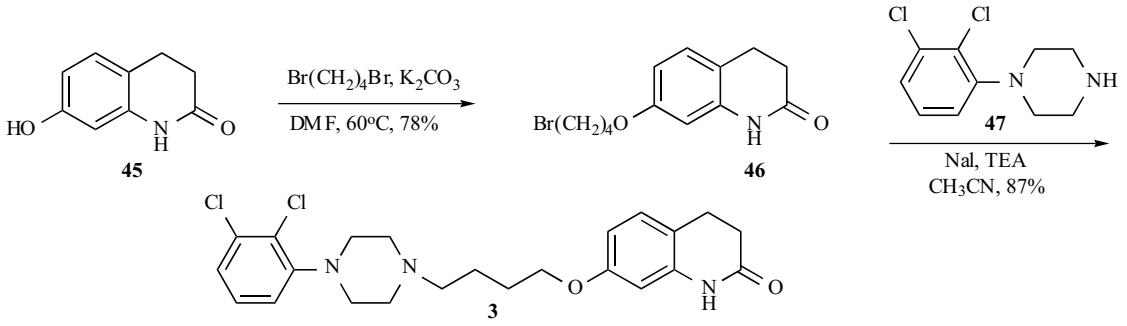


Scheme 1. Synthesis of adefovir dipivoxil.

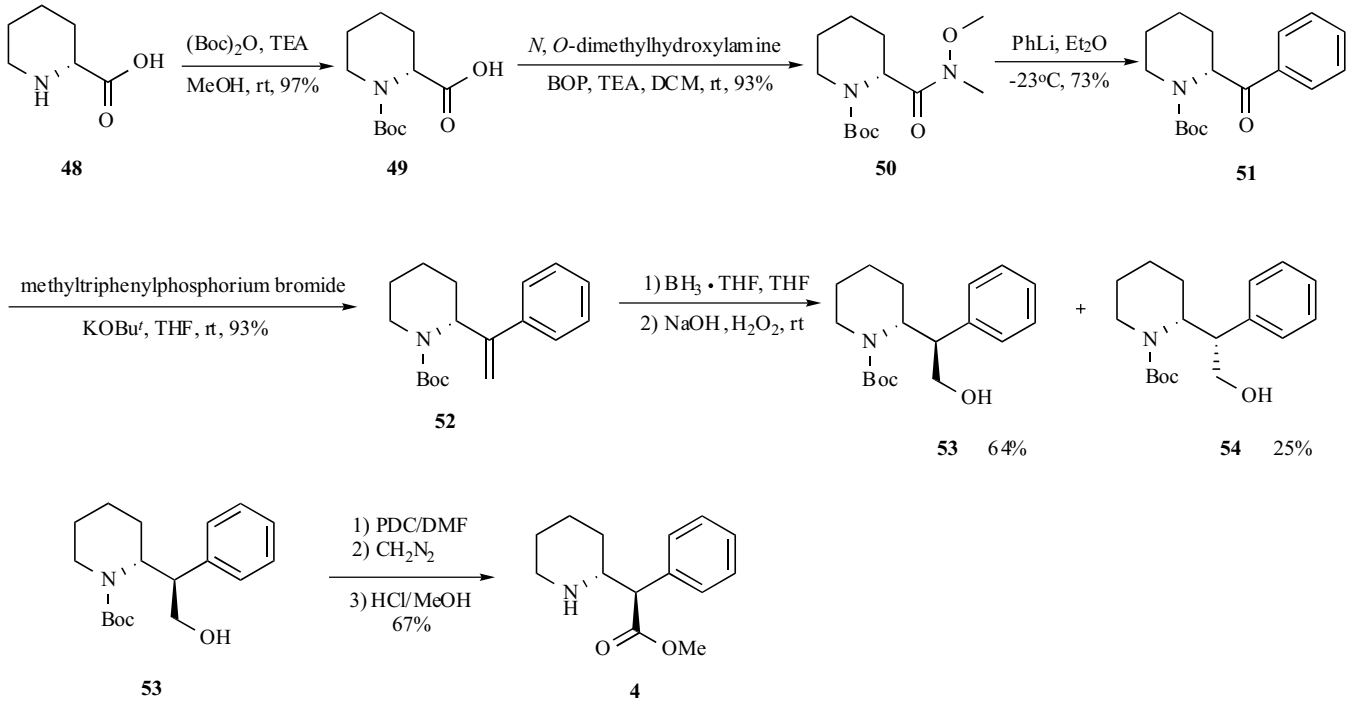


Scheme 2. Synthesis of amrubicin hydrochloride**.**

the *d-threo*-enantiomer of methylphenidate, most involving with enzymatic resolution [18], or crystallization/ recrystallization methods [19,20]. An asymmetric synthesis [21] route is depicted in Scheme 4. *R*-Pipecolic acid (**48**) was reacted with $(Boc)_2O$ to afford *N*-Boc pipecolic acid **49**. Treatment of **49** with *N,O*-dimethylhydroxylamine in DCM provided the Weinreb amide **50** in 93% yield. Reaction of amide **50** with phenyllithium at –23°C in Et_2O furnished enantiopure ketone **51** in 73% yield. Ketone **51** was converted to chiral aromatic alkene **52** using methylenetriphenylphosphorium ylide in THF at rt. The transformation of olefin **52** to diastereomeric alcohols **53** and **54** was achieved using BH_3-THF complex in 89% overall yield. Diastereomerically pure alcohol **53** was subjected to PDC-mediated oxidation in DMF followed by treatment with excess ethereal diazomethane. The resulting *N*-Boc-methylphenidate was deprotected with 3N methanolic HCl to give dexmethylphenidate (**4**) as a white solid in 67% yield.



Scheme 3. Synthesis of aripiprazole.



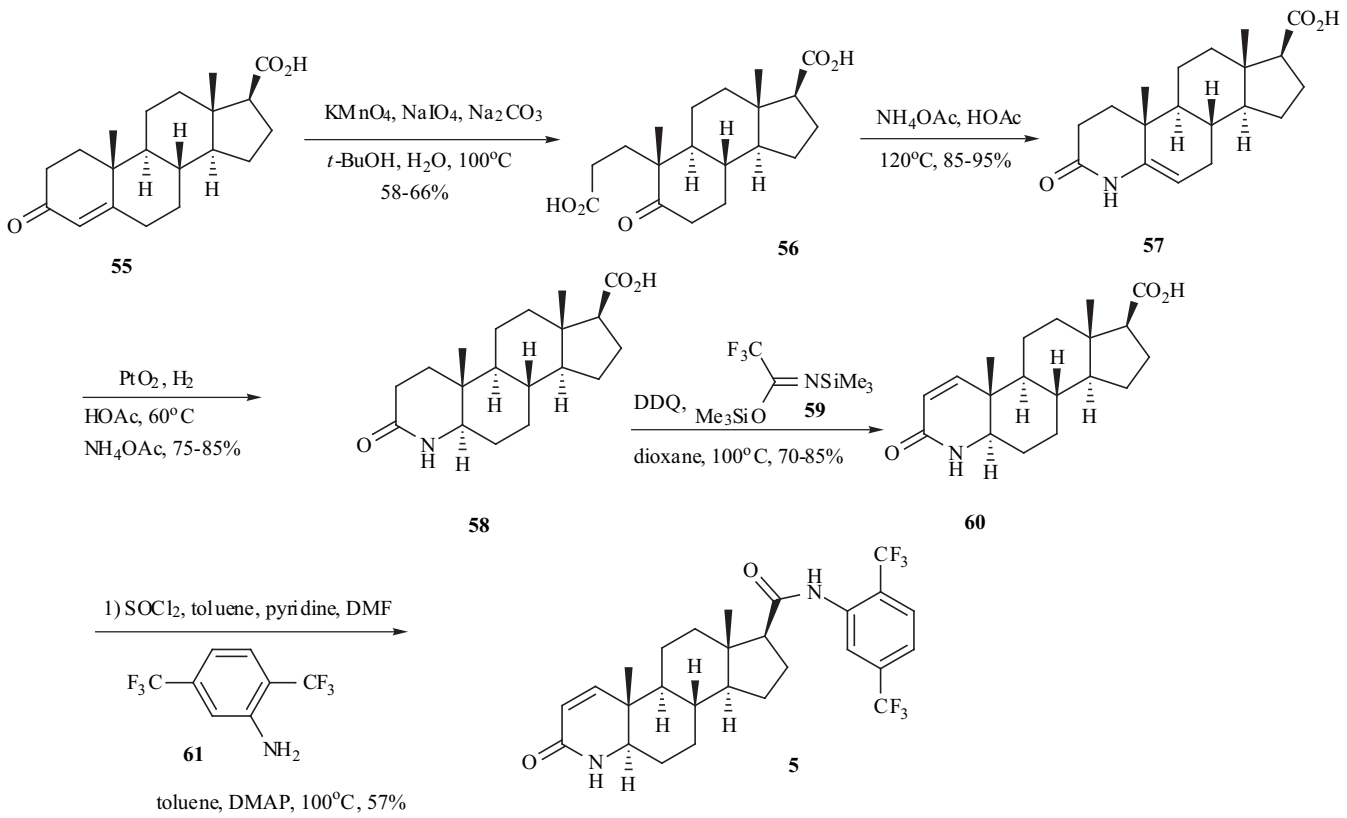
Scheme 4. Synthesis of dexmethylphenidate.

Dutasteride (*Avodart*^{TM})

This steroid 5α-reductase type 1 and 2 inhibitor was patented by GlaxoSmithKline. It is used for the treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate to improve urinary symptoms, reduce the risk of acute urinary retention and BPH-related surgery [22]. Steroidal dutasteride (**5**) was synthesized from 3-oxo-4-androstene-17β–carboxylic acid (**55**) [23]. Oxidation of **55** with potassium permanganate, sodium periodate and sodium carbonate in refluxing *t*-butyl alcohol and water gave seco-steroid **56** which was cyclized with ammonium acetate in acetic acid to give 4-aza-steroid **57** in good yield. Stereo-selective hydrogenation of **57** with H_2 over PtO_2 in hot acetic acid and in the presence of ammonium acetate yielded saturated azasteroid **58**, which was dehydrogenated with DDQ in the presence of bis(trimethylsilyl)trifluoroacetamide (BSTFA) **59** in refluxing dioxane to give **60**. Treatment of **60** with thionyl chloride gave the corresponding acyl chloride intermediate, which was then condensed with 2,5-bis(trifluoromethyl)aniline (**61**) by means of DMAP in heated toluene to give dutasteride (**5**) in 57% yield from intermediate **60**.

Ertapenem Sodium (*Invanz*^{TM})

Ertapenem sodium (**6**) was introduced in the U.S. and Europe by Merck & Co. as a once daily injectable carbapenum antibiotic drug. Ertapenem (**6**) is indicated for the treatment of moderate to severe infections in adults caused by susceptible strains of a range of Gram-positive and Gram-negative aerobic and anaerobic bacteria [24]. Following a conventional carbapenem synthetic strategy, ertapenem sodium (**6**) can be assembled from 4-nitrobenzyl-protected β-methyl carbapenemenolphosphate **71** and 2-aminocarbonylpyrrolidine-4-ylthio-containing side chain **70**. Many efficient approaches to **71** have been reported in the literature [25], and this compound is now commercially available on a large scale [26]. The synthesis of **70** is outlined in Scheme 6 [27,28]. Protection of the amino group in *trans*-4-hydroxy-*L*-proline (**62**) with diisopropyl phosphite followed by NaClO oxidation gave *N*-DIPP protected hydroxyl proline **63** in 80% yield. The carboxyl group in **63** was activated *via* reaction with diphenylphosphinic chloride (DPPC) in the presence of diisopropylethylamine (DIPEA). This intermediate **64** was directly reacted with methanesulfonyl chloride in the



Scheme 5. Synthesis of dutasteride.

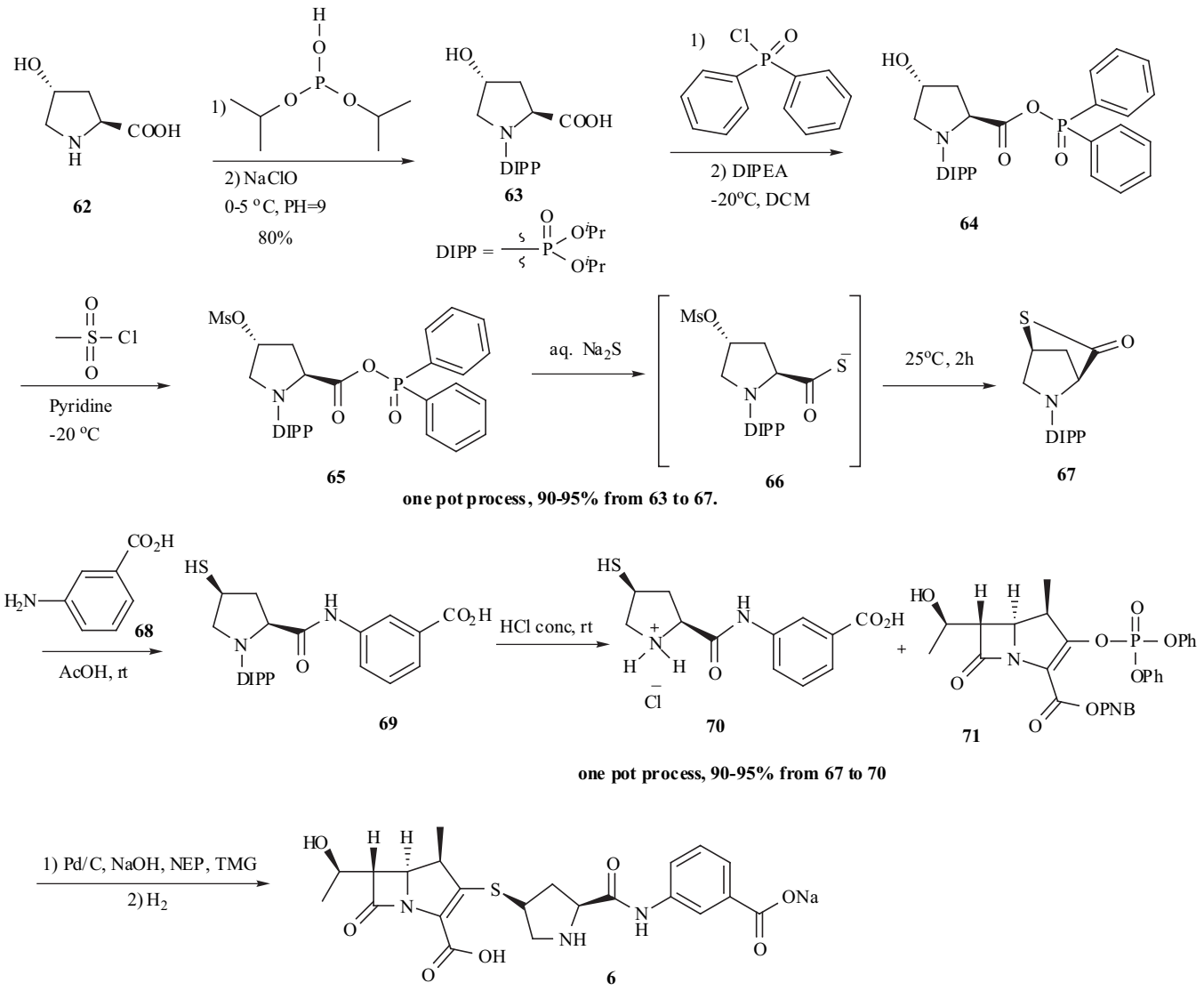
presence of pyridine to furnish mesylate **65.** Mesylate **65** was then quenched with aqueous sodium sulfide yielding **66** instantaneously, which then slowly cyclized to **67.** Aminolysis of **67** with *m*-aminobenzoic acid (**68**) and subsequent deprotection of the DIPP group with concentrated HCl provided **70** in 90-95% yield in a one-pot process. The coupling reaction between **70** and **71** followed by deprotection of PNB group was completed in one reaction vessel to furnish ertapenem sodium (**6**) (yield was not disclosed) [28].

Escitalopram Oxalate (*Cipralex*®)

Escitalopram (**7**) is a selective serotonin reuptake inhibitor (SSRI) and was launched first in Switzerland. It is the more active *S*-enantiomer of citalopram which is a well-known antidepressant drug that has been on the market for some years [29]. It is for the treatment of major depressive episodes and panic disorder with or without agoraphobia. The synthesis of escitalopram was carried out in several different routes [30-33]. 5-Cyanophthalide (**72**) was treated with Grignard reagent **73** at 0°C to provide intermediate **75** which was reacted *in situ* with another Grignard reagent **76** to afford the diol in a one-pot process. Racemic diol **77** was resolved using (+)-*p*-toluoyltartaric acid to afford desired S isomer **78** in 55% yield. The ring closure reaction was carried out at 0°C using methanesulfonyl chloride in toluene to furnish escitalopram (**7**) in 60% yield.

Etoricoxib (*Arcoxia*™)

Merck & Co.'s etoricoxib (**8**) was launched for the first time in the U.K. last May as a new COX-2 inhibitor. Etoricoxib (**8**) is indicated for the symptomatic relief of osteoarthritis and rheumatoid arthritis, treatment of acute gouty arthritis, relief of chronic musculoskeletal pain including low back pain, relief of acute pain associated with dental surgery and treatment of primary dysmenorrhea [34]. The synthesis of etoricoxib (**8**) was explored extensively by the Merck process research group [35]. Key intermediate **85** was synthesized through at least three different routes. In the Horner-Wittig approach, 6-methyl methylnicotinate (**79**) was converted into Weinreb amide **80** in 95% yield. Amide **80** was then converted to aldehyde **81** *via* a DIBAL-H mediated reduction. Subsequent treatment of a solution of aldehyde **81** in isopropyl acetate with aniline and diphenyl phosphite provided *N,P*-acetal **82** in 87% yield. The Horner-Wittig reaction of *N,P*-acetal **82** with 4-methanesulfonyl-benzaldehyde (**83**) furnished enamine **84**, which was hydrolyzed to ketosulfone **85**. A Grignard approach was also developed in the preparation of ketosulfone **85**. Addition of Grignard reagent **86** to Weinreb amide **80** in toluene/THF provided ketosulfide **85** in 80% yield. Tungstate-catalyzed oxidation of ketosulfide **87** using hydrogen peroxide provided ketosulfone **85** in 89% yield by simple filtration. Ketosulfone **85** was prepared through Claisen condensation protocol as well. Thus, reaction of 4-methanesulfonyl phenyl acetic acid (**88**) with methyl nicotinate **79** under Ivanoff condition, *i.e.,* the magnesium dianion in THF, resulted 58% yield of ketosulfone **85**. Treatment of ketosulfone **85** with a three-carbon electrophile, 2-chloro-*N,N*-dimethylaminotrimethinium hexafluorophos-phate (**89**) in the presence of potassium *t*-butoxide at ambient temperature resulted adduct **90**. Inverse quench of adduct **90** into a mixture of HOAc /TFA led to the putative intermediate **91**. Ring closure of the pyridine ring occurred upon heating at

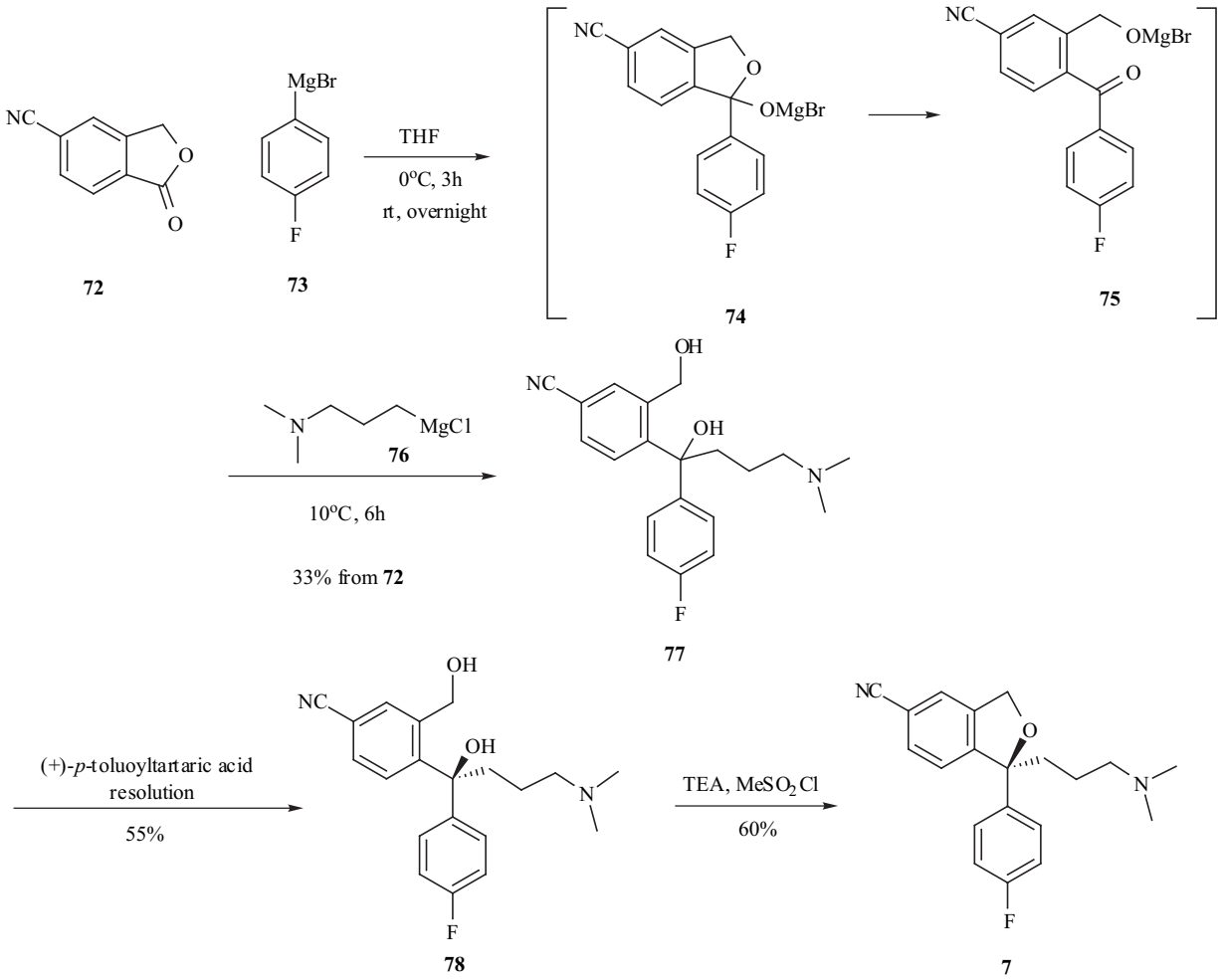


Scheme 6. Synthesis of ertapenem sodium.

reflux in the presence of an excess of aqueous ammonium hydroxide to give desired etoricoxib (**8**) in 97% yield in a one-pot process from **85**.

Ezetimibe (*Zetia*)

Ezetimibe (**9**) was approved as the first hypolipidemic drug to act by blocking the absorption of dietary cholesterol. This drug was discovered by Schering-Plough and is co-developed and co-marketed by Merck and Schering-Plough for the treatment of hypercholesterolemia and also two less common forms of hyperlipidemia: homozygous familial hypercholesterolemia and homozygous sitosterolemia [36]. The synthesis of ezetimibe (**9**) begins with the one-step diastereoselective and practical synthesis [37] of the *trans* β-lactam from commercially available (*S*)-3-hydroxy-γ-lactone (**92**). Lactam **95** was obtained by generation of a dianion of lactone **92** with LDA in THF followed by addition of the imine and *N,N'*-dimethylpropyleneurea (DMPU) to give predominately adduct **93** (**93**:**94** = 79:21). However, intermediate **93** and **94** did not cyclize to their respective lactams due to formation of stable lithium aggregates. Addition of lithium chloride/DMF was employed to cyclize the intermediates into *trans*-lactam **95** as the major product (*trans:cis* = 95:5) in a one-pot process from **92** in 64% yield. The 95:5 ratio of compound **95** was oxidatively cleaved with $NaIO_4$ to give aldehyde **96**. Mukaiyama aldol condensation was adopted to elaborate the 4-fluoro-phenylpropyl side chain to give alcohol **98**. Without isolation, the reaction mixture was subjected to dehydration using *p*-TSA to give enone **99** in 75% yield from compound **96**. Reduction of the double bond in **99** with Wilkinson's catalyst yielded ketone **100**, which was subjected to the highly enantioselective CBS reduction to give alcohol **101** with a 98:2 selectivity of *S:R* at the benzylic position. Catalytic hydrogenation of compound **101** gave ezetimibe (**9**) in 79% yield. Alternatively, a palladium-catalyzed double reduction in EtOAc/MeOH of both the double bond and the benzyl protecting group in enone **99** produced free phenol **107** in 90% yield. A three-step one-pot procedure was subsequently developed to transform **107** into ezetimibe (**9**) in 79% yield. That is, free phenol **107** was protected *in situ* as its TMS ether using BSU followed by a highly selective CBS reduction of the ketone group to give the

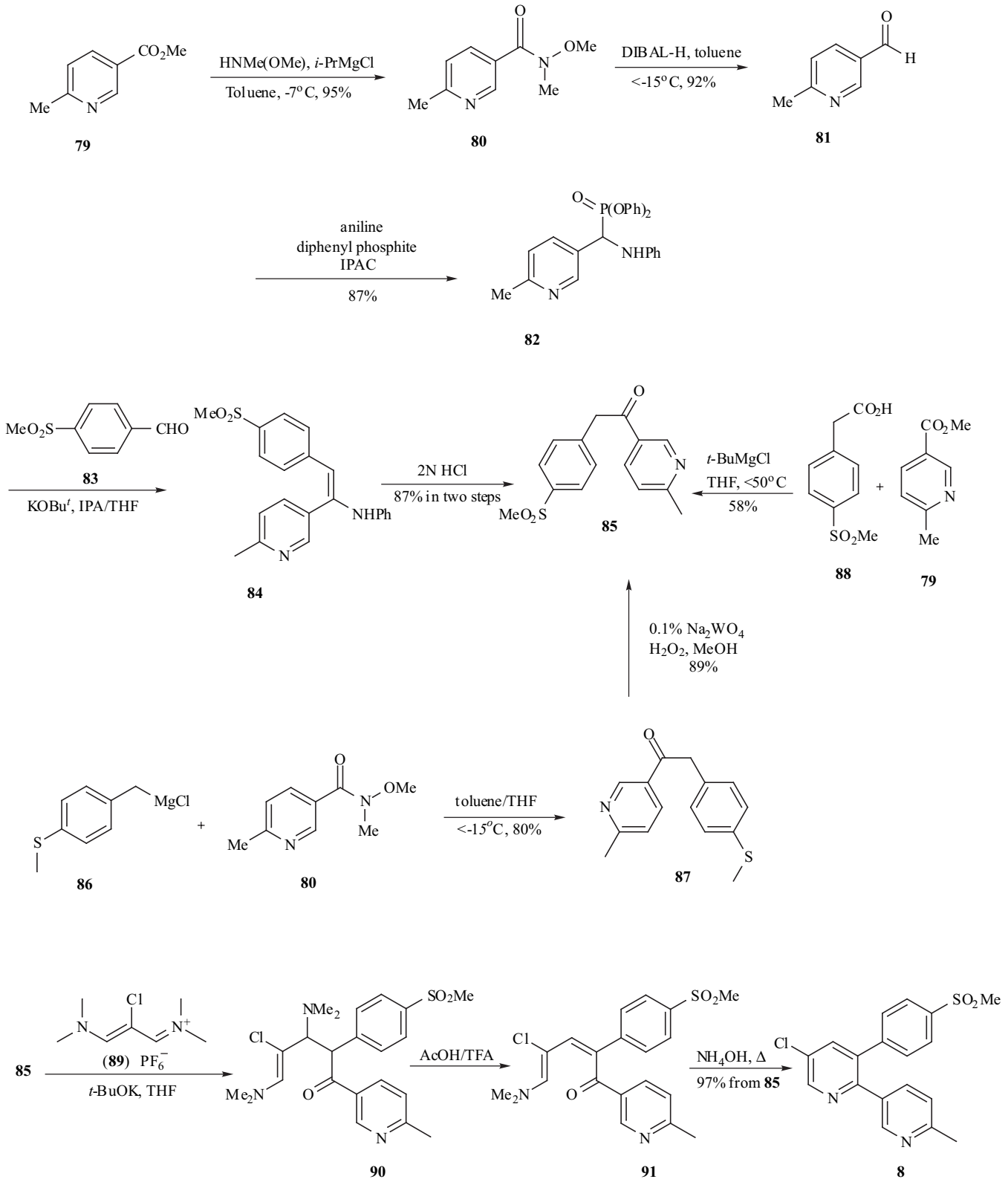


Scheme 7. Synthesis of escitalopram.

desired alcohol in 97% ee. The TMS group was removed during acidic workup to give ezetimibe (**9**). A more convergent approach to this drug was also developed by preparing the (*S*)-hydroxy side chain before the ring construction [38]. Therefore, *p*-fluorobenzoylbutyric acid (**102**) was reacted with pivaloyl chloride and the acid chloride thus obtained was acylated with chiral auxiliary **103** to give the corresponding amide. The ketone group in the amide was reduced with (*R*)-MeCBS/BH_3-THF (**104**) in the presence of *p*-TSA to give desired alcohol **105** in high yield (99%) and stereoselectivity (96 % d.e.) [39]. Chiral alcohol **105** was then mixed with the imine in the presence of TMSCl and DIPEA to protect the alcohols as TMS ethers. In the same pot, $TiCl_4$ was added to catalyze the condensation reaction and gave compound **106** in 65% yield. Compound **106** was reacted with TBAF and a fluoride-catalyzed cyclization took place to give the corresponding lactam. Finally, the TMS protecting group was removed under acidic conditions to give ezetimibe (**9**) in 91% yield over two steps.

Fondaparinux Sodium (*Arixtra*^{TM})

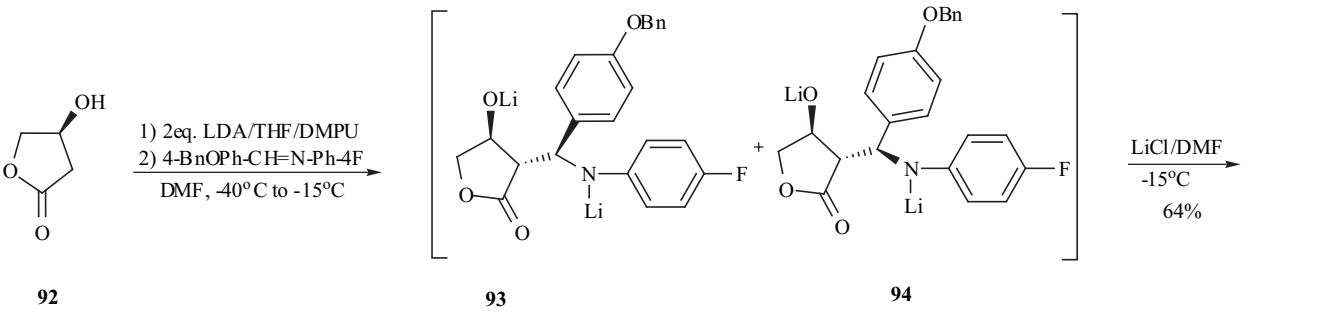
Fondaparinux sodium (Arixtra; formerly fondaparin sodium, **10**) is a synthetic pentasaccharide heparinoid Factor Xa antagonist and thrombokinase inhibitor launched extensively by Sanofi-Synthélabo (formerly Sanofi) and Organon as a treatment and prophylaxis for deep vein thrombosis (DVT) and symptomatic pulmonary embolism following hip or knee surgery. It is also being developed as a potential treatment for coronary artery diseases [40]. Fondaparinux has a complex structure. Starting from *D*-glucose, *D*-cellobiose, and *D*-glucosamine, the production process for the synthesis of the pentasaccharide involves about 55 steps. The synthesis was accomplished by preparing a fully-protected pentasaccharide, and then converting it into the final product. The choice of protecting groups was dictated by two factors: the need to introduce sulfate substituents (*O*- as well as *N*-linked), carboxylate groups and hydroxyl groups, in the proper positions on the target molecule, and the constraints of current methods for oligosaccharide synthesis, particularly the use of 2-azido glucose derivatives to achieve stereoselective introduction of α-*D*-linked glucosamine units. All the monosaccharide synthons were obtained from glucose or from glucosamine [41,42], and the synthesis [42-44] is outlined in Scheme 10. Trisaccharide **108** and disaccharide **109** are the two key building blocks in the synthesis. Coupling **108** and **109** was carried out at -20°C in DCE. Fully protected pentasaccharide **110** was then converted into the target compound **10** using traditional methods: saponification, *O*-sulfation, cleavage of benzyl ethers with simultaneous reduction of azido into



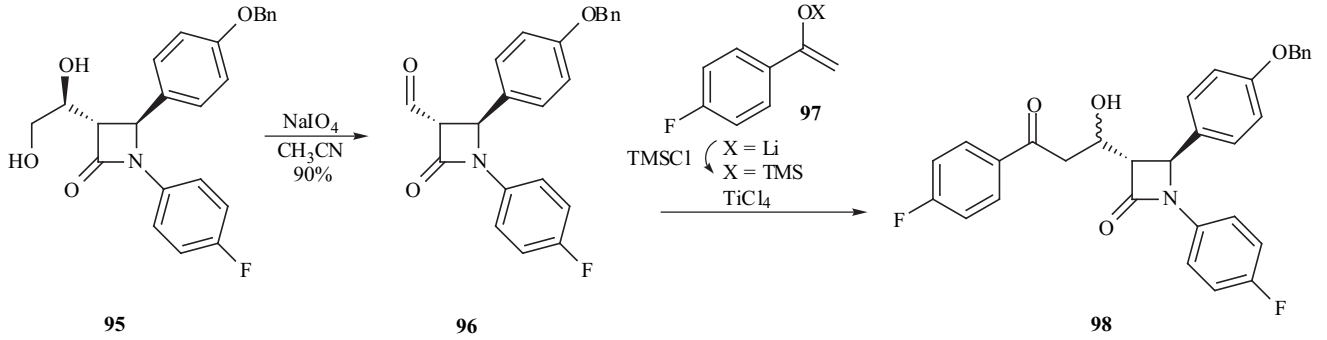
Scheme 8. Synthesis of etoricoxib.

amino functions and finally *N*-sulfation. Preparation of trisaccharide building block **108** started from 1,6-anhydro-cellobiose (**111**). Selective protection at 4',6' position was achieved through benzylidenation to provide crude **112** which was converted into epoxide **113** by treatment with sodium methoxide and benzylation. Compound **113** was isolated after filtration on silica gel and crystallization (m.p. 184-5°C). *Trans*-diaxial opening of the epoxide yielded the 2-azido derivative (66%) which was acetylated to give **114** (99%). The benzylidene was cleaved (92%) and the diol was then converted into **115** by successive tritylation, levulinoylation, detritylation, oxidation, methylation and

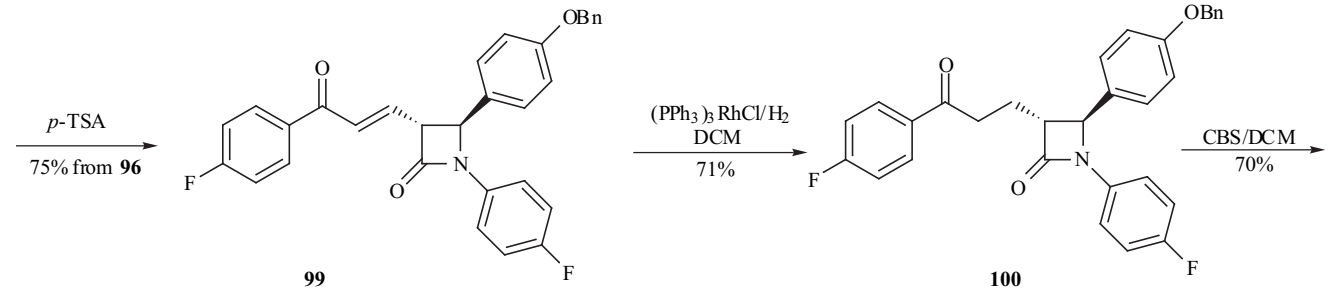
hydrazinolysis (60% over the 6 steps). Imidate **116** was prepared in the usual way from its hydroxyl precursor and coupled with **115** to give *O*-linked trisaccharide **117** in 78% yield. Compound **117** was acetolysed (91%), the anomeric acetate was cleaved by benzylamine in ether (100%) and imidate **108** was obtained by reaction with potassium carbonate and trichloroacetonitrile at room temperature (α, β– mixture with α as the predominant isomer, 76%). The preparation of the other building block **109** is described as following. Selective 6-acetylation of **118** by *N*-acetylimidazole in DCE gave **119** in 60% yield. Treatment of **119** with **120** using DCE/pyridinium perchlorate and followed dechloroacetylation using hydrazinedithiocarbonate afforded the crystalline disaccharide **109** [43].



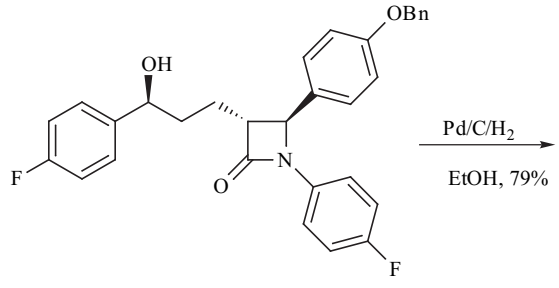
92 **93** **94**



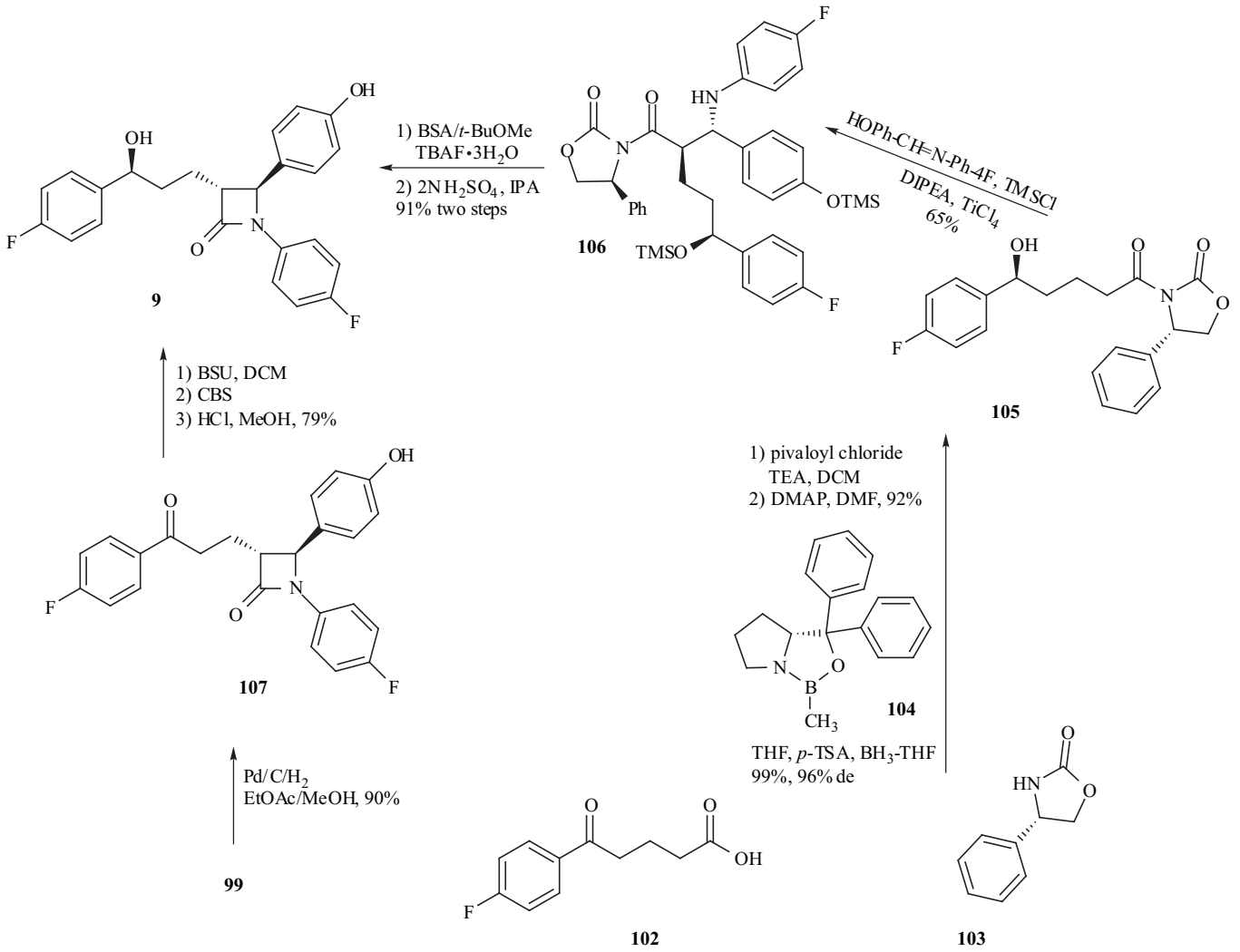
95 **96** **98**



99 **100**



101



Scheme 9. Synthesis of ezetimibe.

Frovatriptan Succinate (*Frova*™)

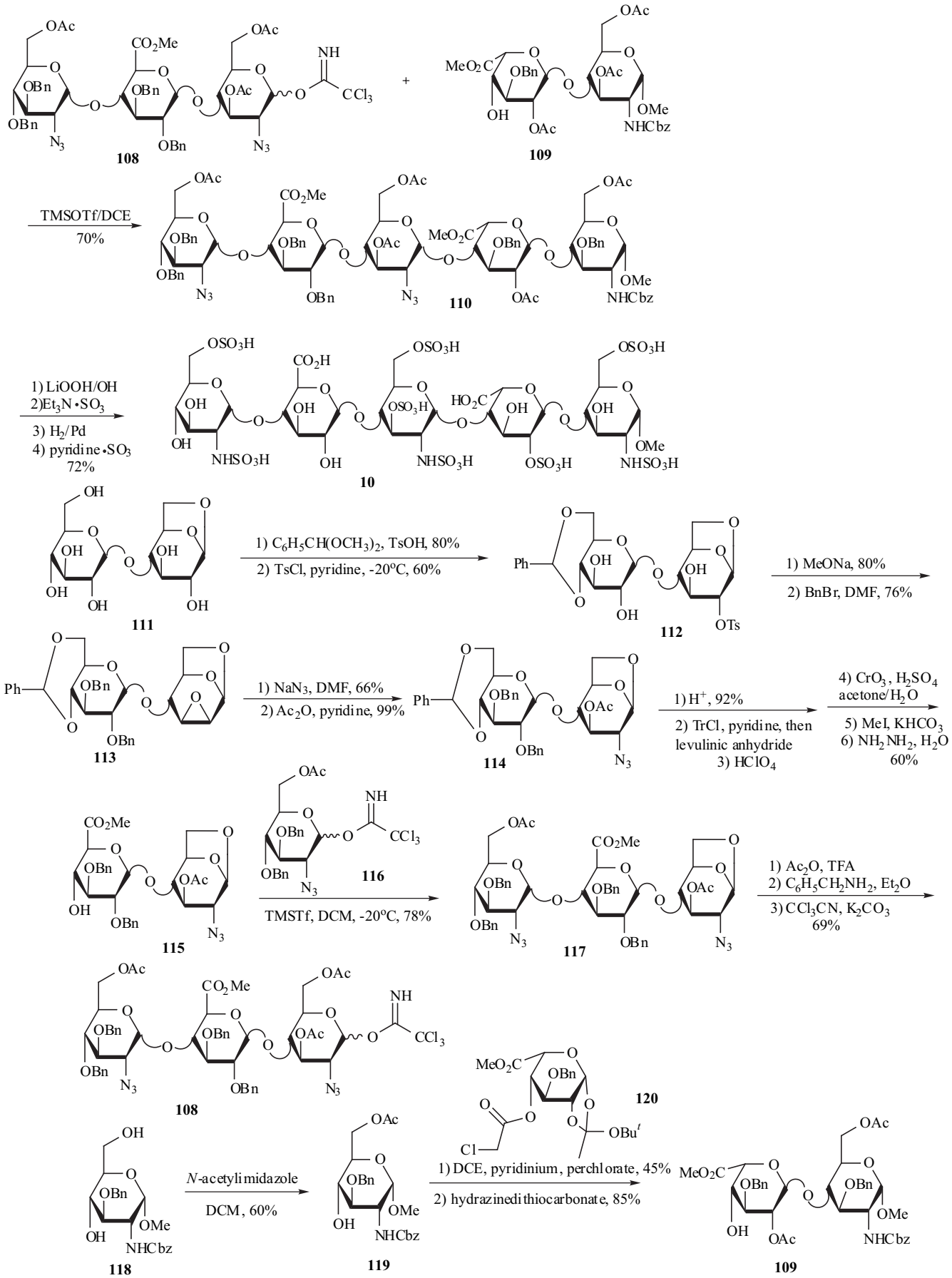
The serotonin 5-HT_{1D} receptor agonist frovatriptan succinate (**11**) was launched last year in the U.S. for the acute treatment of migraine attacks. This drug was discovered at Vernalis and is marketed by UCB Pharm and Elan. Frovatriptan treats migraine by constricting blood vessels in the brain [45]. The synthesis of frovatriptan (**11**) appeared in a patent in multi-kilo scale [46]. Cyclohexanedione monoketal (**121**) was converted to amine **122** by reductive amination. The Fischer indolization of amine **122** with hydrazine **123** furnished indole nitrile **124** in 72% yield. The desired *R* isomer of the indole nitrile was obtained *via* a chiral salt formation/recrystallization process using chiral lactam **125** and isolated as a *L*-pyroglutamic acid salt **126**. Hydrolysis of the nitrile functional group in **126** provided carboxamido indole **127**, which was converted to succinate **11** *in situ*.

Fulvestrant (*Faslodex*®)

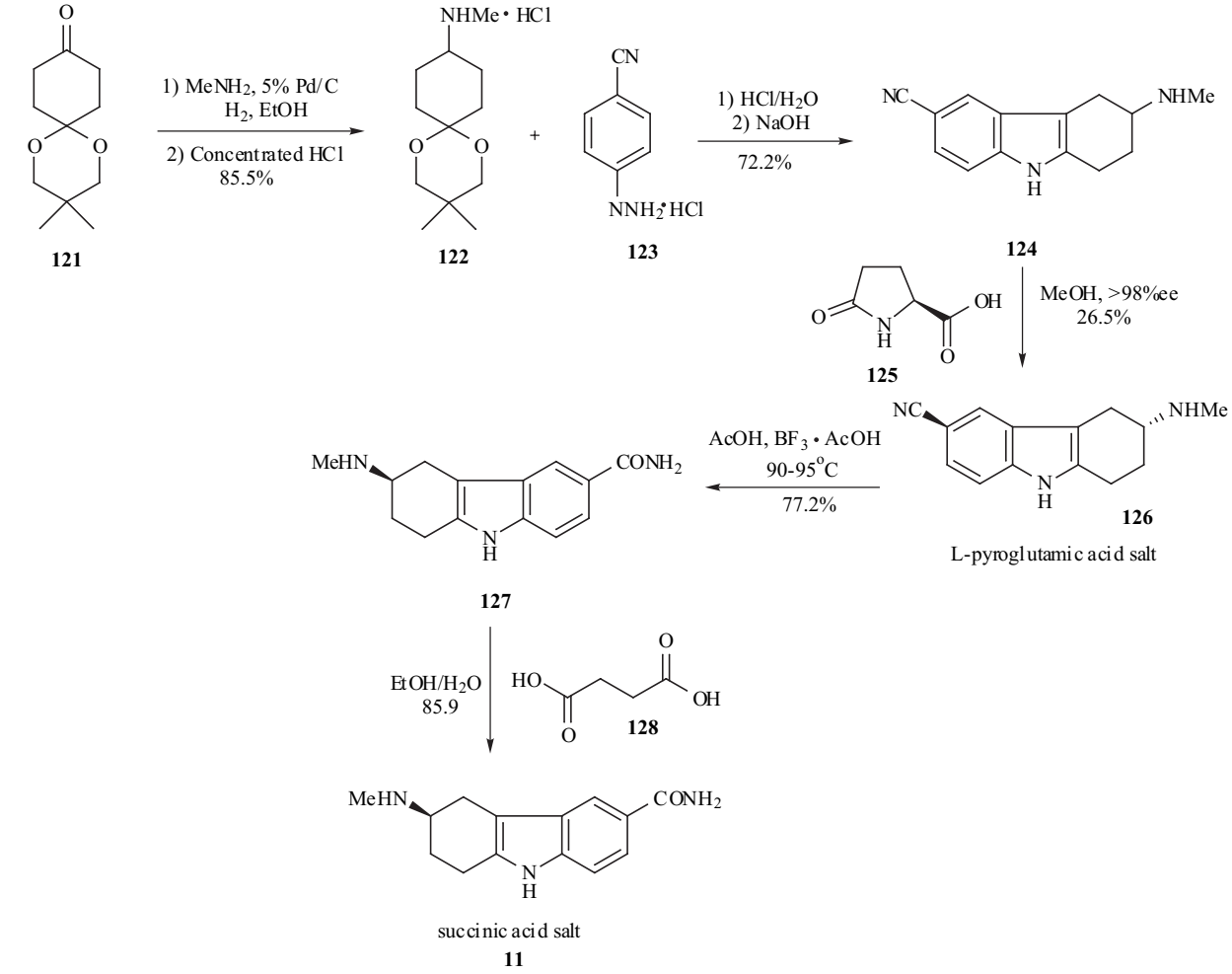
Fulvestrant (**12**) was launched for the first time in the U.S. for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. As an estrogen antagonist with no known agonist effects, it is the only compound in its class to be proven effective after tamoxifen failure [47]. It is administered as a once a month i. m. injection. Several routes for the synthesis of fulvestrant (**12**) were published [48,49]. One of the best routes [50] is depicted in Scheme 12. The conjugate addition of Grignard reagent derived from bromide **130** with dienone **129** gave adduct **131** as a mixture of 7α- and 7β-isomers in a ratio of 2.5:1 in 90-95% yield. Aromatization of the A-ring with copper bromide/lithium bromide in acetic acid followed by hydrolysis of the ester group provided diol **132** in 80-85% yield. Oxidation of the side chain from sulfite to sulfone followed by crystallization provided fulvestrant (**12**) in 30% overall yield from dienone **129**.

Gefitinib (*Iressa*)

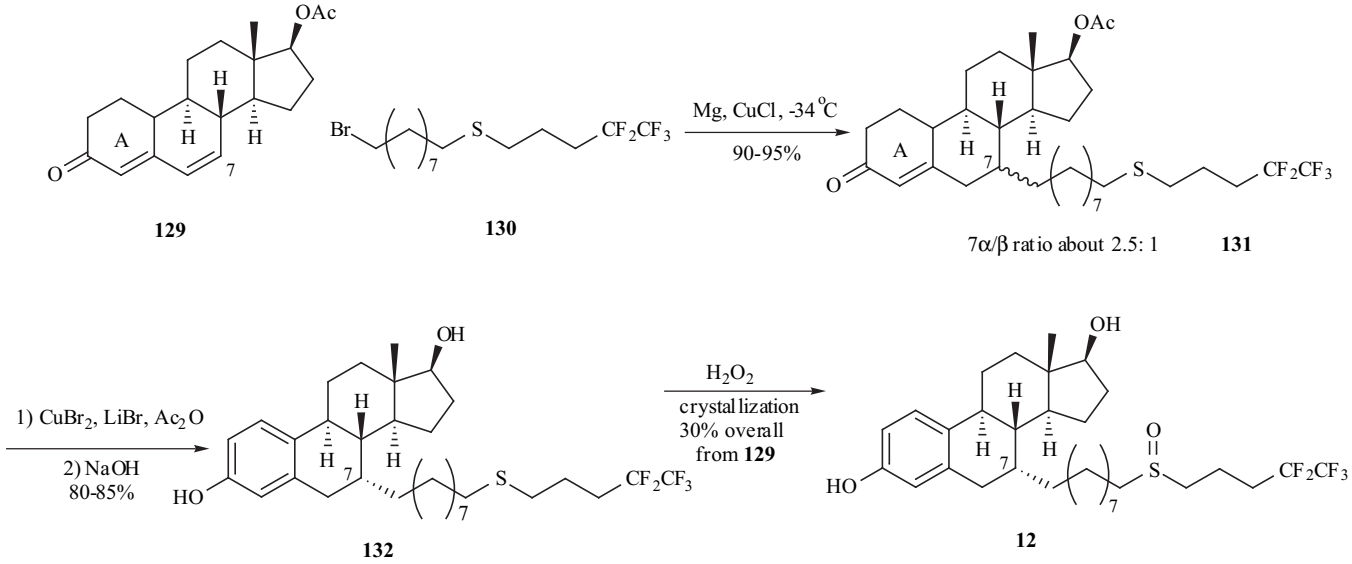
Gefitinib (**13**) is the first drug in a new class of anticancer agents known as epidermal growth factor receptor (EGFR) inhibitors. It was discovered by AstraZeneca and is for the treatment of inoperable or recurrent non-small cell lung cancer [51]. A mixture of 4,5-dimethoxyanthranilic acid (**133**) and formamide was heated to generate the cyclized quinazoline **134** [52]. The quinazoline was selectively mono-



Scheme 10. Synthesis of fondaparinux sodium.

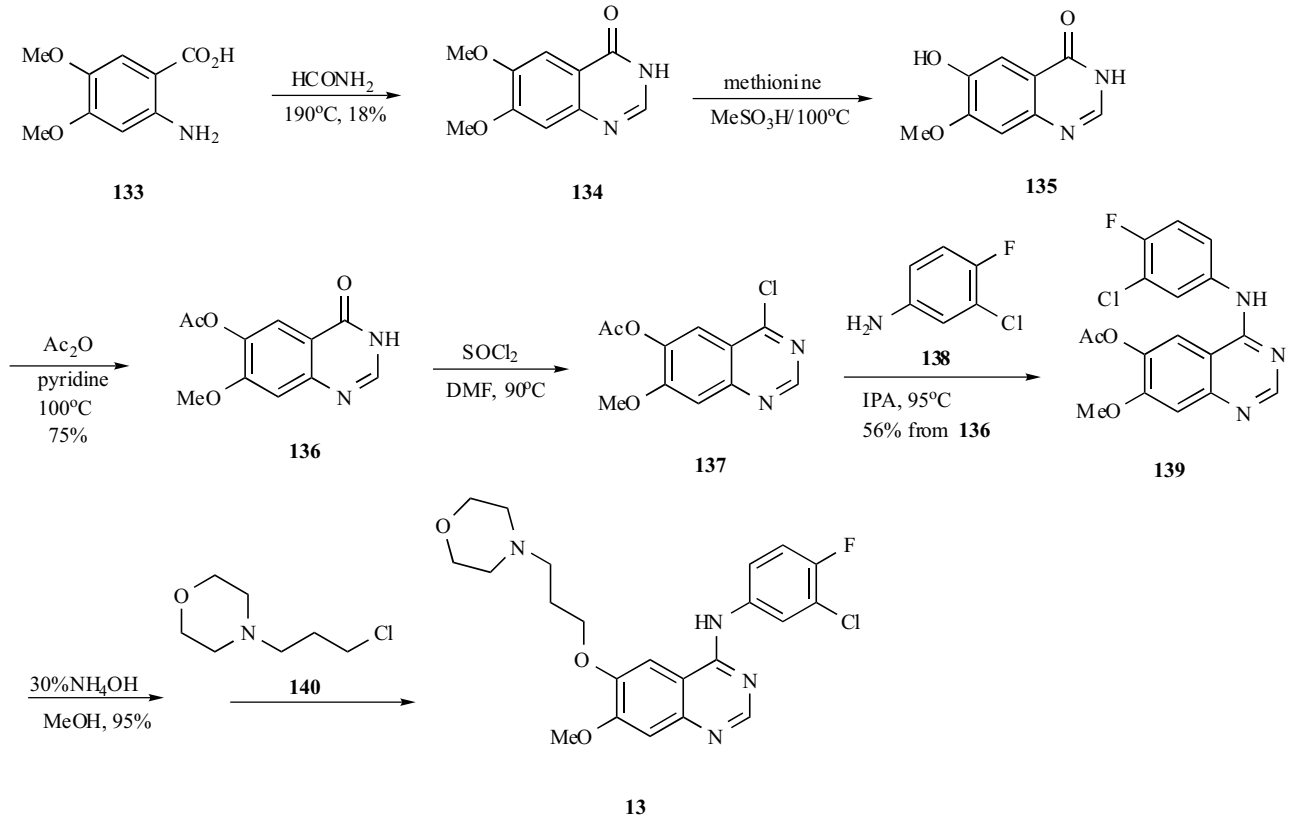


Scheme 11. Synthesis of frovatriptan.



Scheme 12. Synthesis of fulvestrant.

demethylated with methionine in refluxing methanesulfonic acid to afford **135** in 47% yield [53]. Compound **135** was acylated to give acetate **136**, which was treated with refluxing thionyl chloride to yield chloropyrimidine **137**. Chloride **137** was condensed with 3-chloro-4-fluoroaniline (**138**) in refluxing IPA to yield anilinoquinazoline **139** in 56% yield from **136**. The acetate protecting group in compound **139** was hydrolyzed with ammonium hydroxide in methanol, and the free phenol was alkylated with 3-(4-morpholinyl)propyl chloride (**140**) to give gefitinib (**13**) in 55% yield.

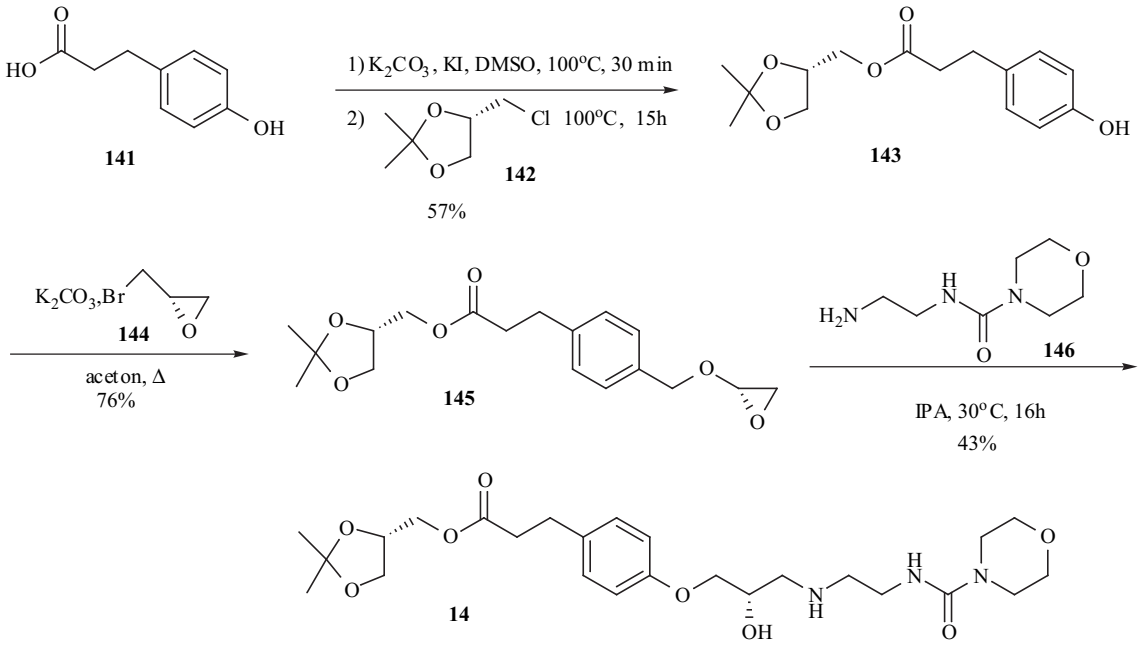


Scheme 13. Synthesis of gefitinib.

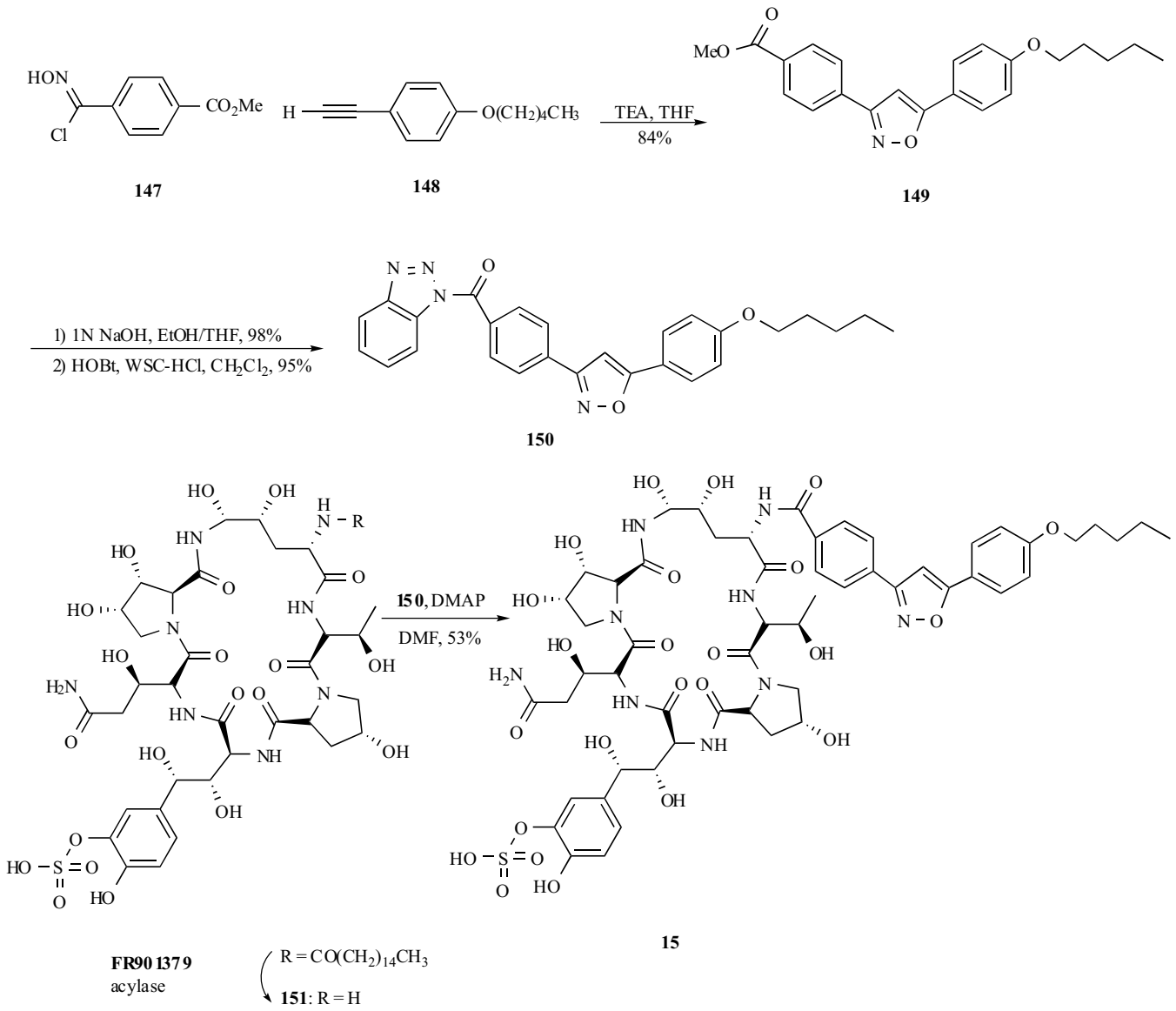
Landiolol Hydrochloride (*Onoact*®)

Landiolol hydrochloride (**14**) was launched in Japan by Ono for the treatment of intraoperative tachyarrhythmia. It improves tachyarrhythmia by selectively blocking β_1 receptors located mainly in the heart and by inhibiting the action of catecholamine [54]. The synthesis of landiolol appeared in an earlier patent in 1990 [55]. Esterification of 3-(4-hydroxyphenyl)propionic acid (**141**) with 2,2-dimethyl-1,3-dioxolan-4-ylmethyl chloride (**142**) in DMSO gave desired ester **143** in 57% yield. Treatment of phenol **143** with bromo epoxide **144** in the present of K_2CO_3 afforded ether **145** in 76% yield. Epoxide **145** was then reacted with free amine **146** *via* a neucleophilic ring opening process to provide landiolol (**14**).

Micafungin Sodium (*Funguarg*®)



Scheme 14. Synthesis of landiolol.

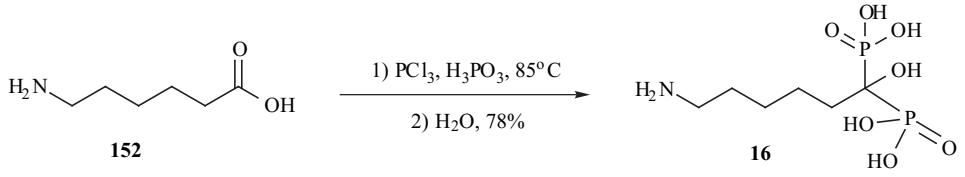


Scheme 15. Synthesis of micafungin sodium.

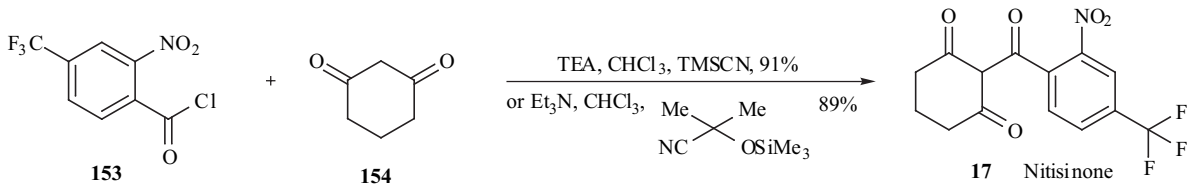
The semi-synthetic echinocandin antifungal agent, micafungin sodium (**15**), is a 1,3-β-glucan synthase inhibitor discovered by Fujisawa. It is for the treatment and prevention of infections caused by *Aspergillus* and *Candida* such as *fungemia*, respiratory mycosis and gastrointestinal mycosis [56]. The key intermediate for the side chain of micafungin (**15**) was prepared by regioselective 1,3-dipolar cycloaddition reaction of 4-methoxycarbonylbenzhydroxamic acid chloride (**147**) and 4-pentyloxyphenylacetylene (**148**) with TEA in THF [57]. Basic hydrolysis of thus obtained ester **149**, followed by condensation with 1-hydroxybenzotriazole (HOBT) gave the corresponding activated ester **150** in 95% yield. The cyclic peptide core **151**, obtained by acylase-catalyzed hydrolysis of the natural product **FR901379**, was acylated with **150** to give micafungin (**15**) in 53% yield.

Neridronate (*Nerixia*®)

This bisphosphonate compound was developed, and is marketed, by Abiogen Pharma. This drug is the first treatment ever for osteogenesis imperfecta [58]. 6-Aminohexanoic acid (**152**) was reacted with phosphorus trichloride and phosphorous acid at 85°C, and then water



Scheme 16. Synthesis of neridronate.



Scheme 17. Synthesis of nitisinone.

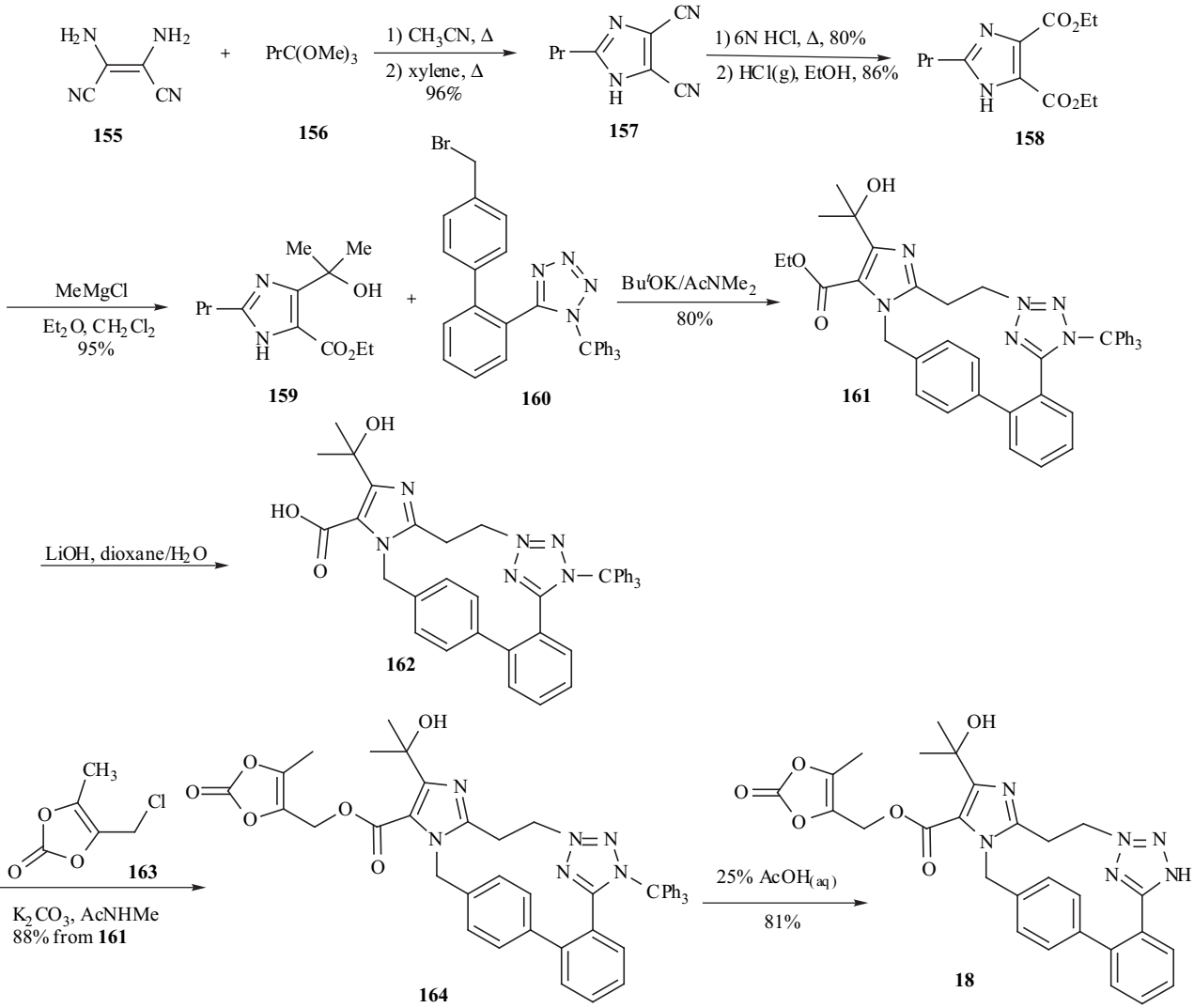
was added to generate free diphosphonic acid **16** in 78% overall yield [59].

Nitisinone (*Orfadin*®)

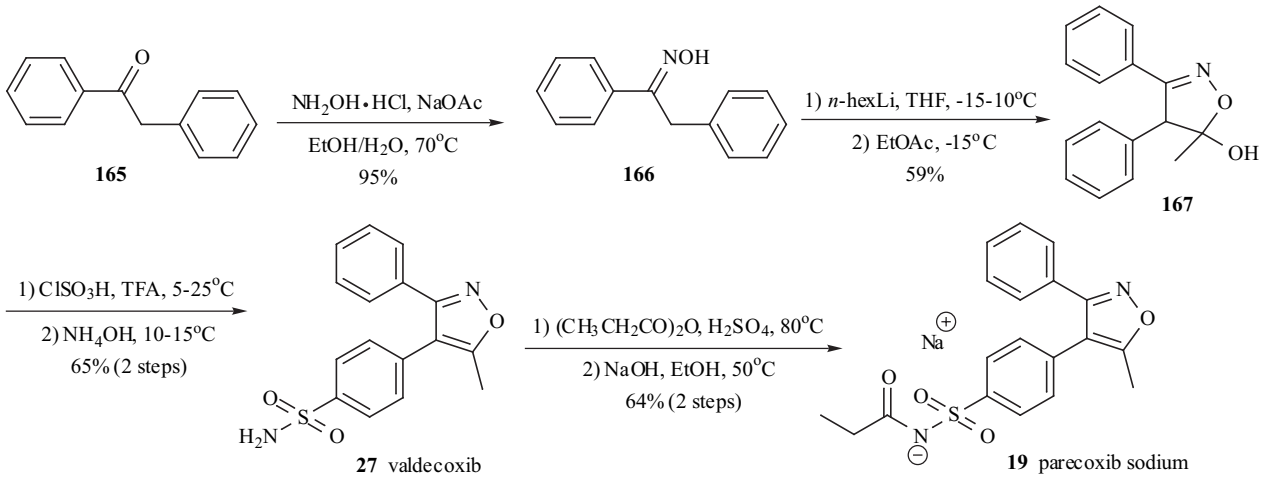
This reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase was discovered by Swedish Orphan and is co-marketed by Apoteket AB and Rare Disease Therapeutics. It is used as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1) disease [60]. Nitisinone (**17**) was synthesized in one step by reacting 2-nitro-4-trifluoromethylbenzoyl chloride (**153**) with cyclohexane-1, 3-dione (**154**) in the presence of TEA and trimethylsilylcyanide or 2-cyano-2-(trimethylsilyloxy)propane [61].

Olmesartan Medoxomil (*Benicar* TM)

This Angiotensin II antagonist was discovered by Sankyo and licensed to Forest for the treatment, alone or in combination with other antihypertensive agents, of high blood pressure [62]. The imidazole ring of olmesartan (**18**) was constructed with diaminomaleonitrile **155** and trimethylorthobutyrate (**156**) in CH_3CN then xylene to give **157** in 96% yield [63]. Acid hydrolysis of **157** in 6N HCl gave the dicarboxylic acid intermediate. After esterification of the diacid in ethanol in the presence of HCl, diester **158** was treated with MeMgCl to give 4-(1-hydroxyalkyl) imidazole **159** in 95% yield. Alkylation of **159** with biphenyl bromide **160** in the presence of potassium *t*-butoxide afforded **161** in 80% yield. Ester **161** was then hydrolyzed to free carboxylic acid **162** under basic

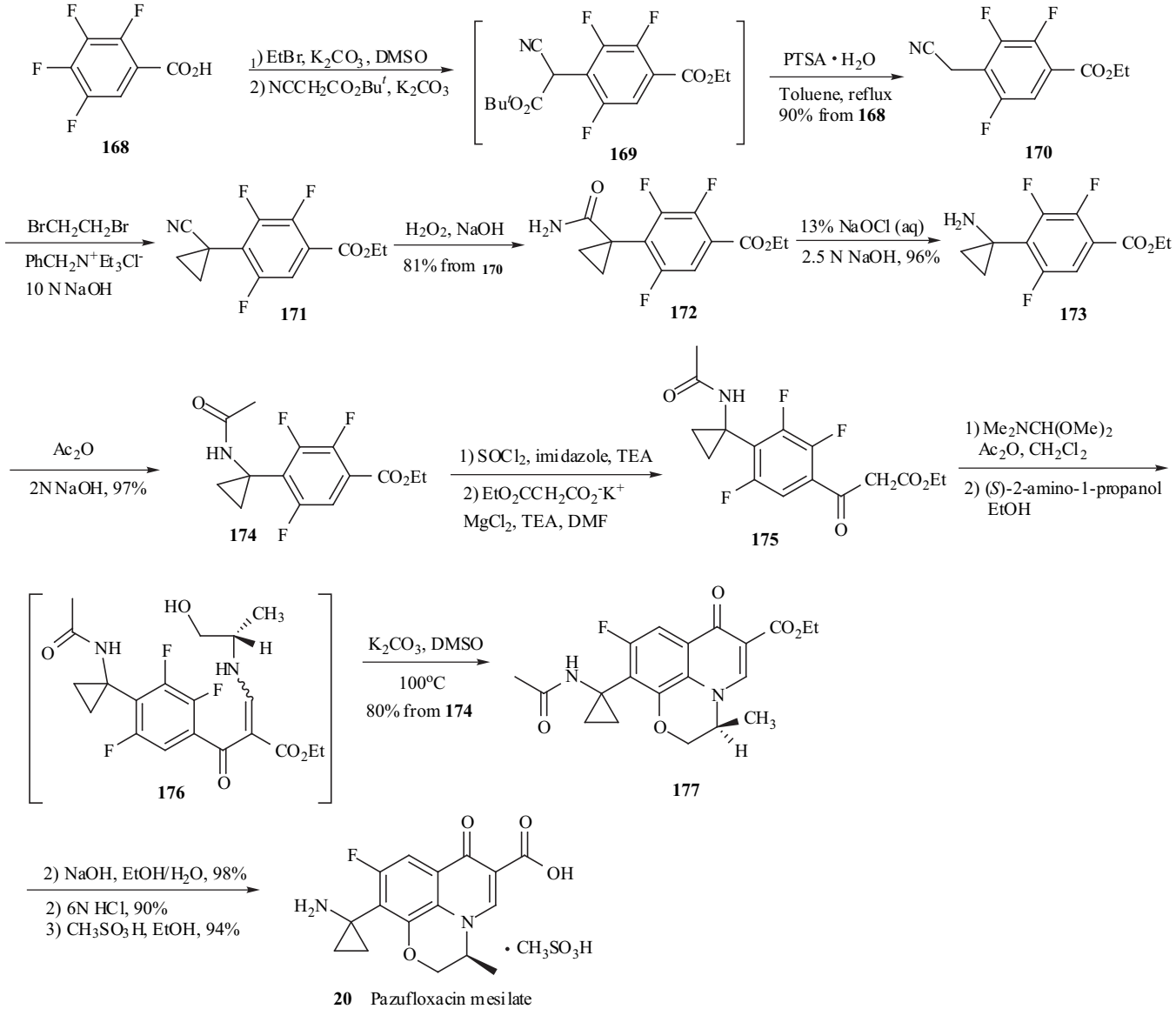


Scheme 18. Synthesis of olmesartan medoxomil.



Scheme 19. Synthesis of paracoxib sodium.

conditions, and **162** was treated with chloride **163** in the presence of K_2CO_3 to give ester **164** in 88% yield from **161**. Lastly, the trityl group was removed with 25% aqueous acetic acid to give olmesartan (**18**) in 81% yield.



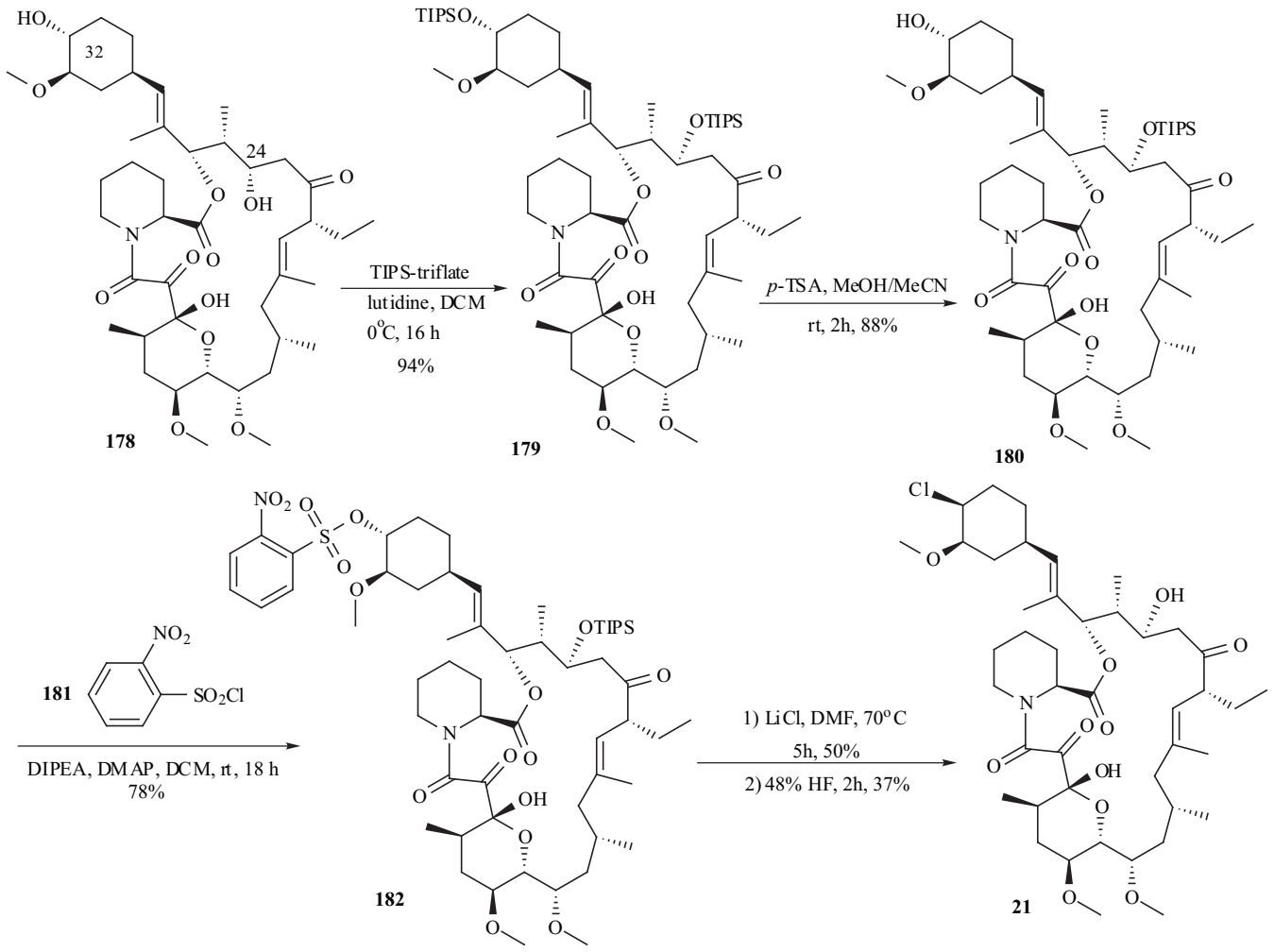
Scheme 20. Synthesis of pazufloxacin mesilate.

Parecoxib Sodium (*Dynastat*®)

Parecoxib sodium (**19**) is a cyclooxygenase 2 (COX-2) inhibitor and was introduced by Pharmacia (now Pfizer) as an injectable formulation for short-term treatment of postoperative pain [64]. Parecoxib is a water-soluble prodrug of valdecoxib (**27**) that undergoes biotransformation *in vivo* to release valdecoxib (**27**). The synthesis (Scheme 19) of parecoxib sodium (**19**) started from commercially available deoxybenzoin (**165**). Deoxybenzoin (**165**) was treated with hydroxylamine in EtOH/H_2O (3:1) to give deoxybenzoin oxime **166** in 95% yield. Deprotonation of oxime **166** with two equivalents of *n*-hexyllithium followed by condensation with ethyl acetate afforded isoxazoline **167** in 59% yield. Treatment of isoxazoline **167** with chlorosulfonic acid followed by reaction of the incipient sulfonyl chloride with aqueous ammonia furnished valdecoxib (**27**). Acylation of isoxazole sulfonamide **27** with propionic anhydride afforded parecoxib, which was converted to its sodium salt by titration with aqueous sodium hydroxide (64%) [65,66].

Pazufloxacin Mesilate (*Pazucross, Pasil*)

This fluoroquinolone was co-developed by Toyama and Mitsubishi Pharm and was launched for the intravenous therapy of respiratory, urinary, surgical, gynecological and systemic infections [67]. The drug is elegantly synthesized from commercially available 2,3,4,5-tetrafluorobenzoic acid (**168**) by an 11-step process with an overall yield 48% [68]. Starting material **168** was first treated with ethyl bromide and then with *t*-butyl cyanoacetate in the presence of potassium carbonate in DMSO in one flask to give acylated cyanoacetate **169**. Intermediate **169** thus obtained without purification was refluxed in toluene with *p*-TSA to yield 4-cyanomethylbenzoate **170** in 90% yield from **168**. Cyclopropanation at the benzylic position of **170** was performed by α,α-dialkylation with two equiv. of 1,2-dibromoethane under phase-transfer conditions to give cyanocyclopropyl compound **171**. Cyano compound **171** was subjected to hydration with alkaline H_2O_2 to afford carboxamide **172** in 81% yield from **170**. Subsequently, carboxamide **172** was treated with NaOCl for Hofmann rearrangement to give primary amine **173**, which was protected as its *N*-acetyl derivative **174** for the next reaction. Treatment of **174** with imidazole in the presence of thionyl chloride and TEA generated an imidazolide intermediate, which was converted to β-keto ester **175** by reacting with potassium ethyl malonate and $MgCl_2$. Enamine **176** was obtained without purification by successive treatment of **175** with DMF-dimethylacetal and (*S*)-(+)-2-aminopropanol. Crude **176** was heated in DMSO in the presence of potassium carbonate to efficiently give tricycle product **177** in 80% yield from **174**. Finally, the ethyl ester and



Scheme 21. Synthesis of pimecrolimus.

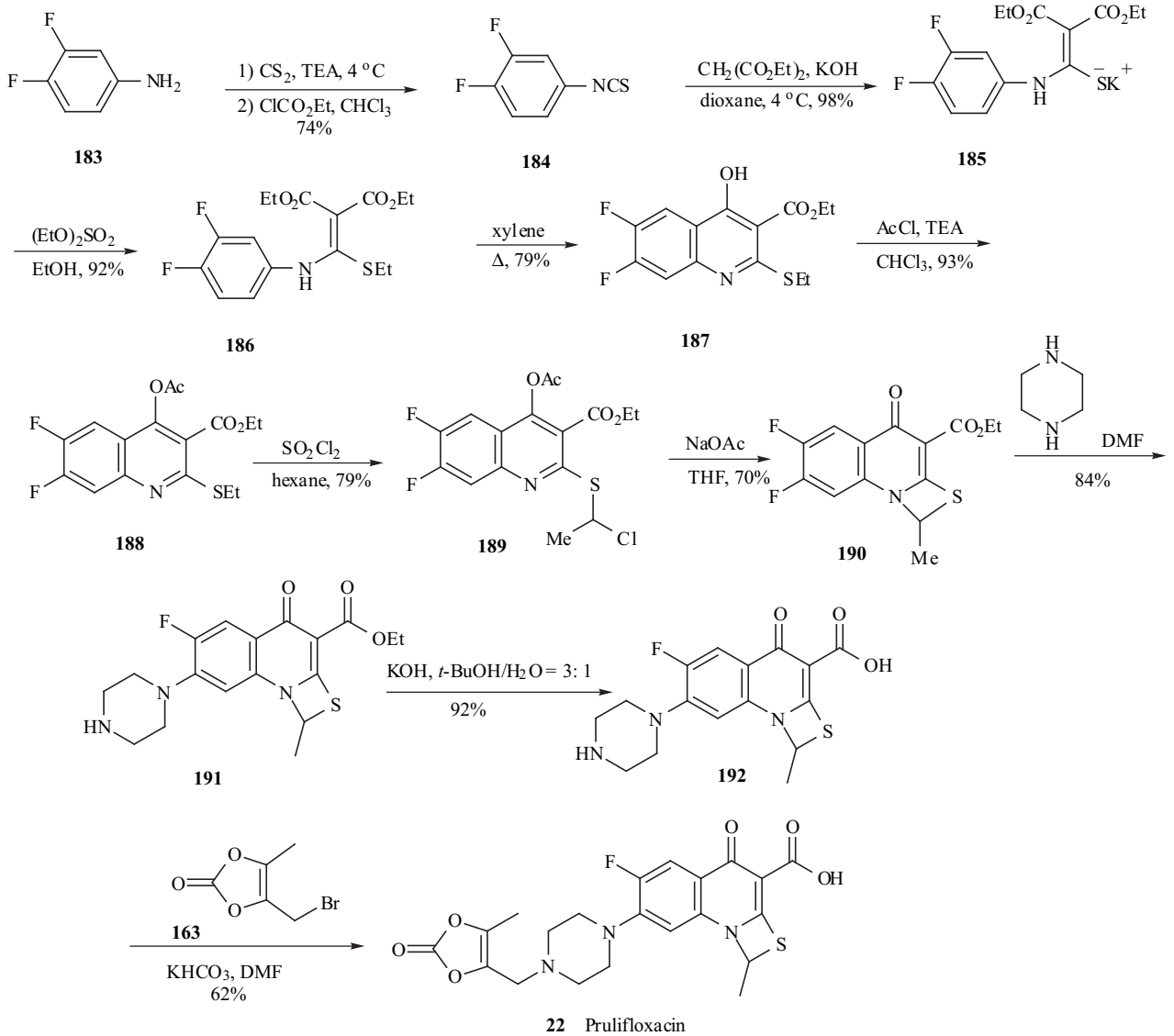
acetamide in **177** were hydrolyzed under basic and acidic conditions, respectively, to give the free amine. Pazufloxacin mesilate (**20**) was obtained in 94% yield by treatment of its corresponding free amine with methanesulfonic acid in ethanol.

Pimecrolimus (*Elidel*®)

Pimercrolimus (**21**) is the first non-steroid agent for the treatment of mild to moderate atopic dermatitis lunched by Novartis. It selectively blocks the production and release of cytokines from T-cells. These cytokines cause inflammation, redness and itching associated with eczema. Long-term therapy with pimecrolimus (**21**) was more effective than conventional treatment in reducing the incidence of disease flares and the use of corticosteroids. This drug is also safe and effective in pediatric patients and is approved for use in children as young as two years [69]. The syntheses of pimecrolimus (**21**) appeared in several patent applications [70-73]. Starting material **178** was prepared by either fermentation [74] or modification of a previously described synthetic method in the literature [75]. Treatment of macrolide **178** with triisopropylsilyl trifluoromethanesulfonate (TIPS-triflate) in the presence of lutidine in DCM at 0°C afforded di-protected compound **179** in 94% yield. Selective deprotection of the TIPS group at position 32 using *p*-TSA in MeOH at rt gave mono-protected macrolide **180** in 88% yield. Reaction of the hydroxyl group at position 32 with *o*-nitrobenzenesulfonyl chloride (**181**) in the presence of DMAP and DIPEA in DCM provided **182** in 78% yield with 20% recovered starting material **180**. Displacement of the sulfate with chloride using LiCl in DMF furnished the chlorinated compound, which was treated with aqueous HF to remove the TIPS group to provide pimecrolimus (**21**).

Prulifloxacin (*Sword*)

This fluoroquinolone antibacterial prodrug was originally discovered by Nippon Shinyaku and subsequently co-developed and co-marketed by Meiji Seika. The drug is used in the treatment of systemic bacterial infections including acute upper respiratory tract infection, bacterial pneumonia, cholecystitis, prostatitis, internal genital infections, bacterial

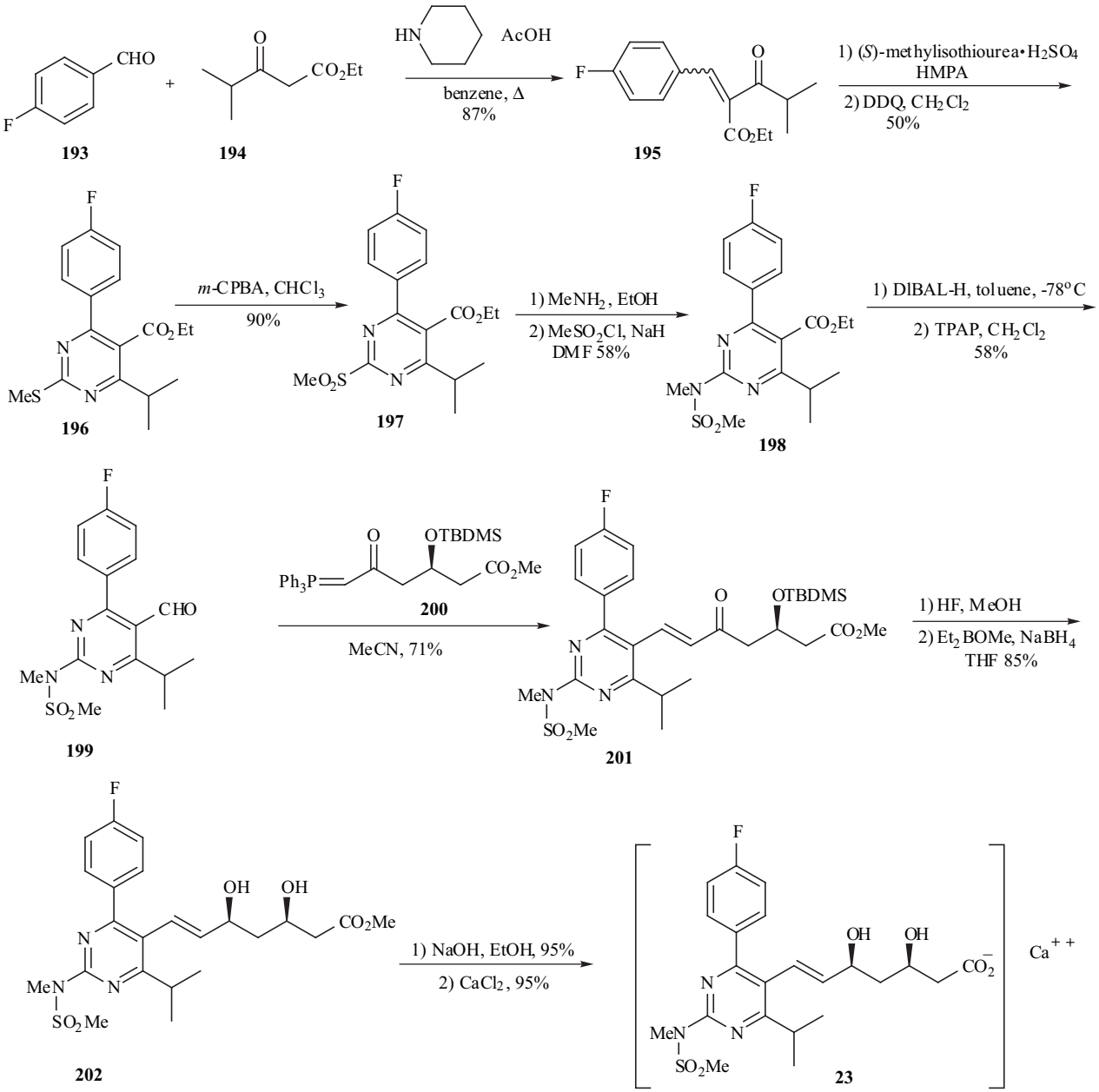


Scheme 22. Synthesis of prulifloxacin.

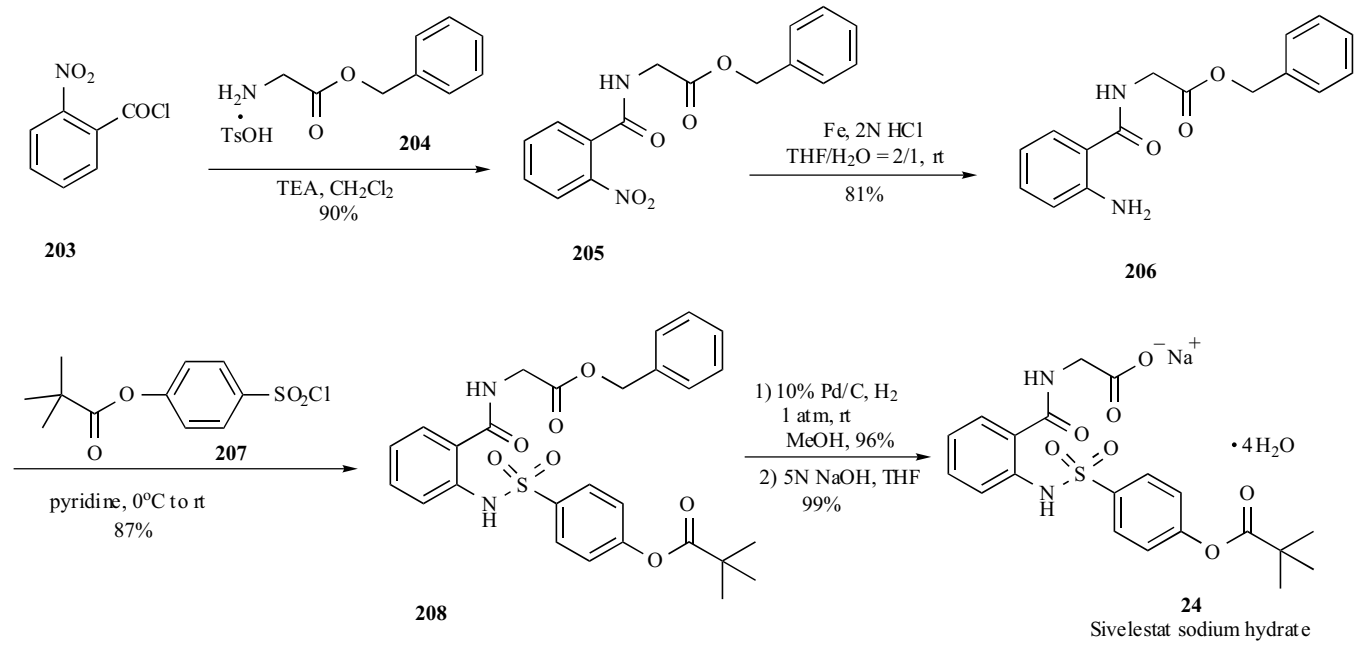
enteritis, otitis media and sinusitis [76]. The synthesis of prulifloxacin (**22**) [77] started with the treatment of 3,4-difluoroaniline (**183**) with carbon disulfide in the presence of TEA to give the triethylammonium dithiocarbamate, which by reaction with ethyl chloroformate and TEA in chloroform, was converted into isothiocyanate **184** in 74% yield. Reaction of **184** with diethyl malonate in the presence of KOH in dioxane yielded methylenemalonate **185** potassium salt, which was ethylated with ethyl sulfate in ethanol to give compound **186** in excellent yield. 6,7-Difluoroquinoline **187** was obtained with the highest yield and regioselectivity when precursor **186** was heated in refluxing xylene [78]. To suppress the side reaction in the subsequent chlorination, quinoline **187** was acylated to give **188** with acetyl chloride in chloroform. Chlorination of **188** with sulfuryl chloride gave compound **189** in 79% yield. Compound **189** was treated with sodium acetate in THF to afford cyclized compound **190,** which was condensed with piperazine in DMF to give compound **191**. The hydrolysis of ester **191** with KOH in hot *t*-butanol gave free acid **192**, which was finally condensed with 4-(bromomethyl)-5-methyl-1, 3-dioxol-2-one (**163**) by treatment of potassium bicarbonate in DMF to give prulifloxacin (**22**).

Rosuvastatin Calcium (*Crestor*®)

The HMG-CoA reductase inhibitor, known as Crestor® (**23**), was originally discovered by Shionogi and subsequently co-developed and co-marketed by AstraZeneca. The drug is for the treatment of patients with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidemia (type IIb) as an adjunct to diet when response to exercise and diet is inadequate. Crestor (**23**) is also used in patients with homozygous familial hypercholesterolemia either alone or as an adjunct to diet and other lipid-lowering treatments [79].



Scheme 23. Synthesis of rosuvastatin calcium sodium.

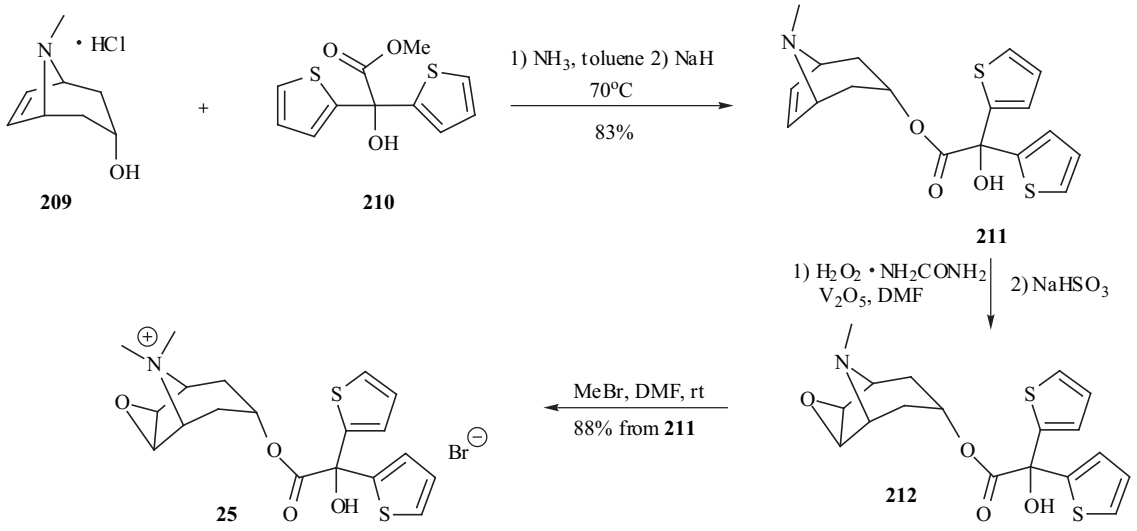


Scheme 24. Synthesis of sivelestat sodium hydrate.

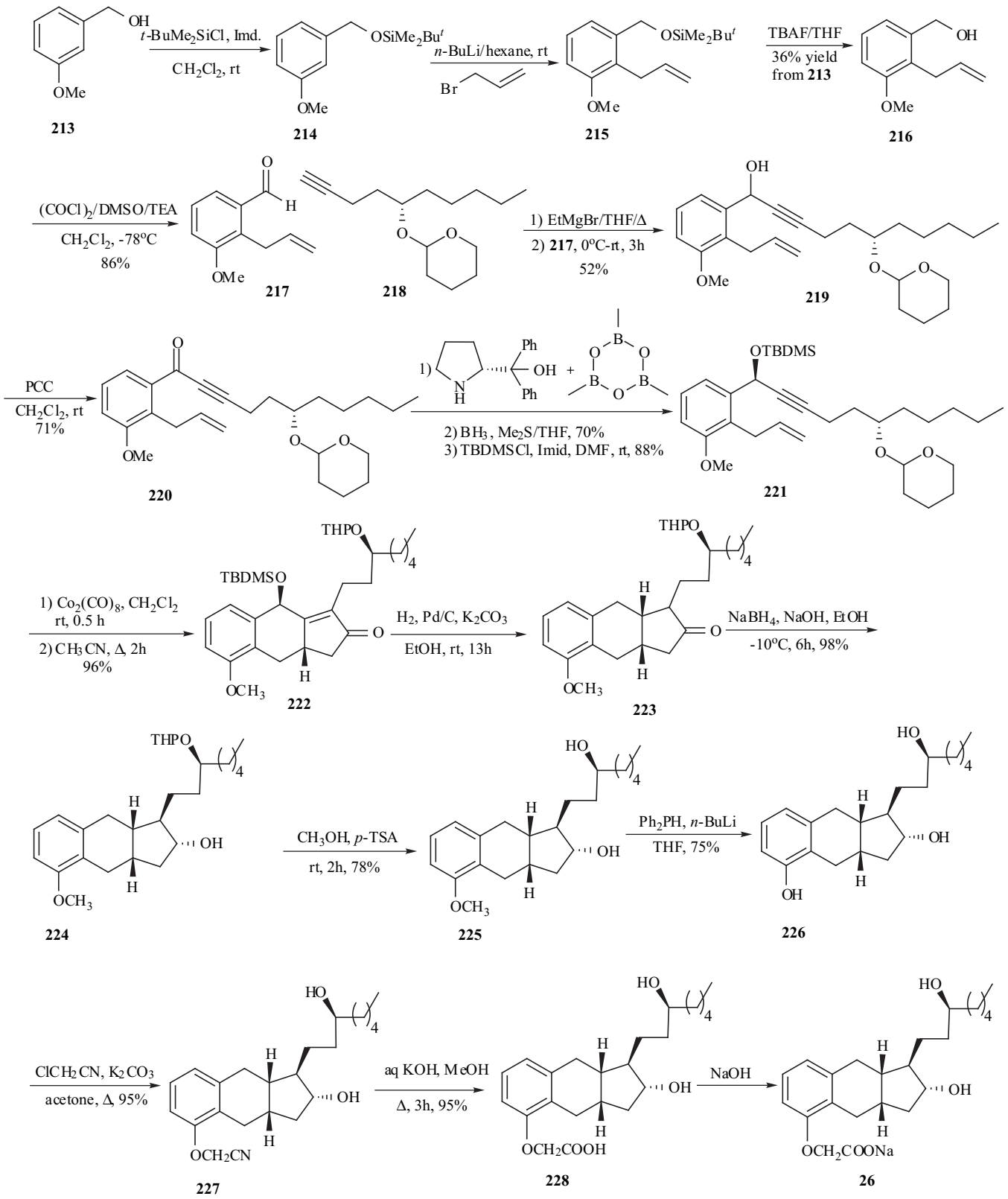
The synthesis of optically pure rosuvastatin (**23**) begins from the Knoevenagel reaction of *p*-fluorobenzaldehyde (**193**) with ethyl isobutylacetate (**194**) to give unsaturated ketoester **195** [80]. Compound **195** was condensed with (*S*)-methylisothiourea and then aromatized *in situ* using DDQ in methylene chloride to give pyrimidine **196** in 50% yield. Pyrimidine sulfide **196** was then oxided by *m*-CPBA to give sulfone **197** in 96% yield. Sulfone **197** was reacted with methylamine in methanol followed by treatment with methanesulfonyl chloride to give the *N*-methanesulfonylamino pyrimidine **198** in 58% yield. Reduction of ester **198** with DIBAL-H followed by TPAP oxidation afforded aldehyde **199** in 58% yield. Aldehyde **199** was subjected to Wittig reaction with optically pure ylide, (3*R*)-3-(*t*-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidenehexanoate (**200**) [81], to give heptenoate compound **201** in 71% yield. Compound **201** was deprotected with HF in acetonitrile, and stereoselective chelation-controlled reduction with Et_2BOMe and $NaBH_4$ in THF-MeOH mixed solvent gave methyl (3*R*, 5*S*, 6*E*)-dihydroxyheptenoate **202** in 85% yield. Diol **202** was hydrolyzed with aqueous NaOH to afford the corresponding sodium salt. Rosuvastatin calcium salt (**23**) was obtained as white powder from the sodium salt on treatment with aqueous $CaCl_2$.

Sivelestat Sodium Hydrate (*Elaspol*®)

A neutrophil elastase inhibitor, introduced by Ono Pharmaceutics as an injectable formulation, is for the treatment of acute lung injury accompanying systemic inflammatory response syndrome [82]. The synthesis [83] of sivelestat (**24**) started with the amide formation between 2-nitrobenzoyl chloride (**203**) and glycine benzyl ester *p*-tolene sulfonic acid salt (**204**) in the presence of TEA to give amide **205** in 90% yield. Amide **205** was then reduced with iron



Scheme 25. Synthesis of tiotropium sodium.



Scheme 26. Synthesis of treprostinil sodium.

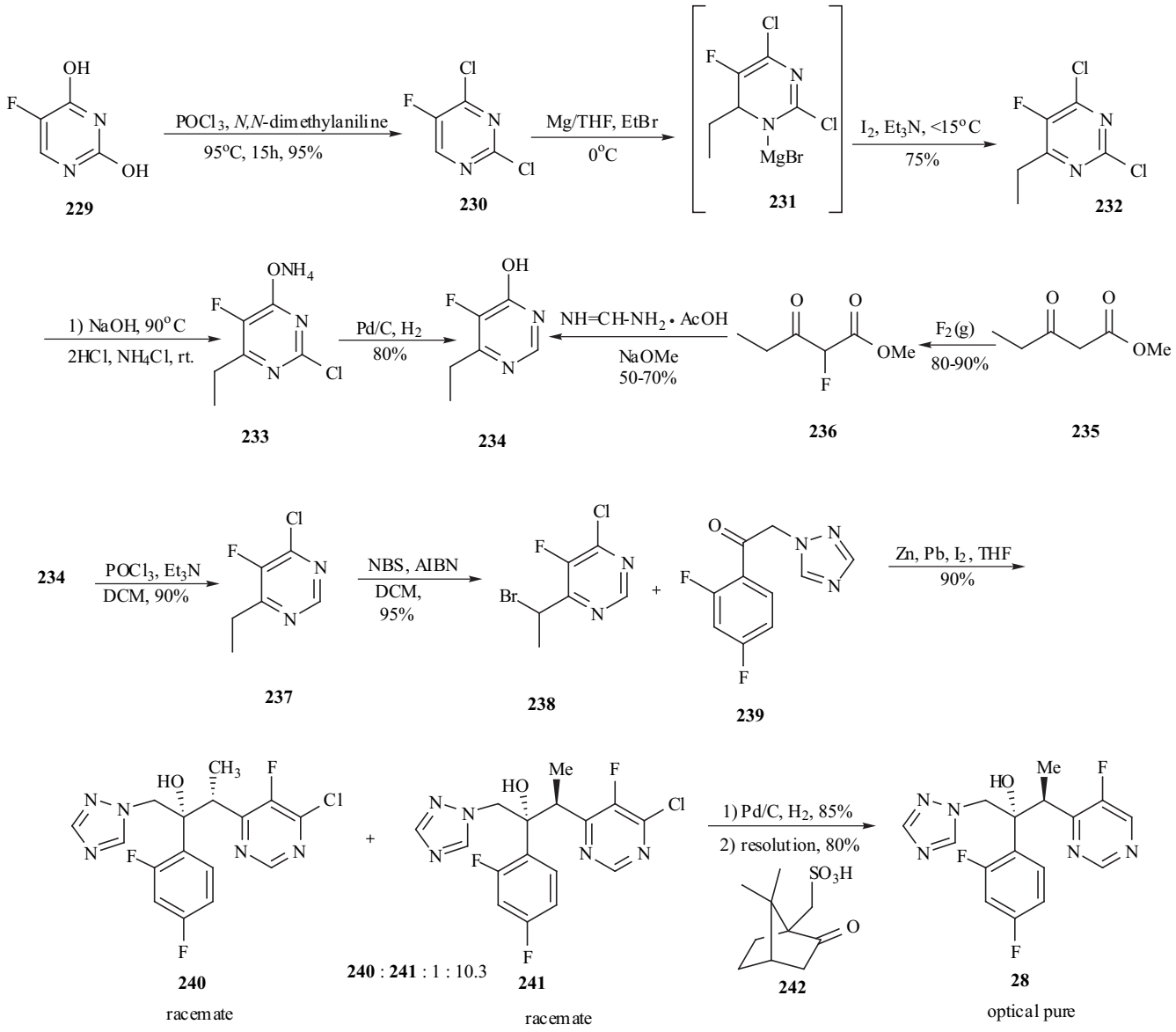
power under acidic conditions to give corresponding amine **206** in 81% yield. Alternatively, the mixture of activated Raney nickel, nitro compound **205**, acetic acid and 1,3-dimethyl-2-imidazolinone (DMI) under 25 atmospheric pressure of hydrogen at 40°C in an autoclave can give the same free amine **206** in 88% yield. Free amine **206** was treated with *p*-pivaloyloxybenzenesulfonyl chloride [84] (**207**) in pyridine to yield sulfonamide **208** in 87% yield. Benzyl ester **208** was converted to its free carboxylic acid under hydrogenation, and the carboxylic acid was subsequently basified to give sivelestat sodium (**24**).

Tiotropium Bromide (*Spiriva*®)

Boehringer Ingelheim's once-daily inhaled chronic obstructive pulmonary disease (COPD) therapy tiotropium bromide (**25**) was launched for the first time in the Netherlands and Philippines in 2002. Tiotropium (**25**), which acts through prolonged M_3 receptor blockade, is approved as a bronchodilator for the maintenance treatment of COPD [85]. At least two synthetic paths have been disclosed in the patent and literature [86-88]. The synthesis of tiotropium is depicted in Scheme 25. Tropenol hydrochloride **209** was first neutralized with ammonia in toluene and then the free base was reacted with methyl di-(2-thienyl)glycolate (**210**) in the presence of sodium hydride to furnish desired tropenol ester **211** in 83% yield. The vanadium-catalyzed oxidation of tropenol ester **211** using hydrogen peroxide-urea complex gave epoxide **212**, which was converted into its quaternary salt **25** with methyl bromide. The last two steps were carried out in a one-pot process in 88%yield.

Treprostinil Sodium (*Remodulin*™)

The prostacyclin analog, treprostinil sodium (**26**), was launched in the U.S. in June 2002 for the treatment of pulmonary hypertension. Developed and marketed by United Therapeutics, treprostinil is specifically approved for the treatment of pulmonary arterial hypertension in patients with NYHA class II-IV symptoms, to reduce symptoms associated with exercise [89]. The synthesis of treprostinil [90,91] starts from commercially available 3-methoxybenzyl alcohol (**213**). The hydroxyl group in **213** was protected as a *t*-butyldimethylsilyl ether *via* reaction with TBDMS chloride in DCM at rt. A regiospecific introduction of the allylic chain and deprotection of the silyl group *in situ* provided alcohol **216** in 36% yield in a three-step sequence. Swern oxidation of alcohol **216** using oxalyl chloride/DMSO furnished aldehyde **217** in 86% yield. Acetylene **218** was first treated with magnesium ethyl bromide and then reacted with aldehyde **217** to provide adduct **219** in 52% yield. The alcohol functional group in



Scheme 27. Synthesis of voriconazole.

219 was then transformed into a carbonyl group in **220** *via* a PCC-mediated oxidation. Ketone **220** was then reduced again using chiral boron reagent to give the chiral alcohol which was protected with TBDMS chloride *in situ* (**221**). Optically pure intermediate **221** underwent cobalt-mediated Pauson-Khand reaction to furnish tricyclic compound **222** in excellent yield. Catalytic hydrogenation was employed to reduce the double bond and the hydroxyl moiety to give ketone **223**. Sodium borohydride mediated reduction of the carbonyl group in **223** gave single diastereomer **224**. The THP and methyl ether protecting groups were then removed in a two-step process to give triol **226**. The more reactive hydroxyl group on the phenyl ring was then reacted with chloroacetonitrile to furnish nitrile **227.** A base mediated hydrolysis of the nitrile provided free acid, treprostinil (**228**), which was converted to its sodium salt **26** by titration with sodium hydroxide (no yield reported).

Voriconazole (*Vfend*®)

Voriconazole was launched by Pfizer in both oral and injectable formulations for the treatment of fungal infections in patients intolerant of, or refractory to, other therapy and for the treatment of invasive aspergillosis [92]. It is a triazole antifungal agent whose major mechanism of action is the inhibition of fungal cytochrome P450-mediated 14α-lanosterol demethylation [93]. The synthesis [94-96] of voriconazole is an excellent example of process research. As depicted in Scheme 27, 5-fluorouracil (**229**) was chlorinated in both the 2- and 4- positions using a mixture of phosphorus oxychloride and *N,N*-dimethylaniline at 95° C to afford **230** in 95% yield. Dichloro pyrimidine **230** was reacted with ethyl magnesium bromide to give dihydropyrimidine adduct **231**. Adduct **231** was oxidized prior to quenching using a mixture of iodine and TEA in THF to give 2,4-dichloro-6-ethyl-5-fluoro pyrimidine (**232)** in 75% yield. Reaction of **232** with two equiv of aqueous NaOH at reflux gave selective displacement of the chloro functionality at 4-position. Acidification of the reaction and extraction with DCM gave 2-chloro-6-ethyl-5-fluoro-4(*3H*)-pyrimidine which was conveniently isolated as its ammonia salt **233**. Dechlorination of **233** was achieved using catalytic hydrogenation at 50° C to provide **234** in 80% yield. Alternatively, 4-fluoro-6-ethyl-5-fluoropyrimidine (**234**) was prepared in a two-pot process in which methyl 3-oxopentanoate (**235**) was fluorinated with fluorine gas to give methyl 2-fluoro-3-oxopentanoate (**236**) in 80-90% yield [97]. This ester was then cyclized [98] with formamidine acetate in the presence of NaOMe to give **234** in a moderate yield (50-70%). Reaction of **234** with phosphorus oxychloride and TEA afforded 4-chloro-6-methyl-5-fluoropyrimidine (**237**) in 90% yield. Reaction of **237** with NBS in the presence of AIBN initiator provided bromide **238** in 95% yield. A Reformatsky protocol was employed in the condensation of **238** with ketone **239** which was an intermediate in the commercial synthesis of Diflucan [99]. A solution of iodine in THF was added to a slurry of zinc and lead at rt and then a mixture of bromide **238** and ketone **239** were added to the above mixture at 5°C for 30 min. This provided the best diastereomeric selectivity and the ratio of **241** and **240** enantiomeric pair reached approximately 10 to 1. Adduct **241** was de-chlorinated using standard hydrogenation condition (5% w/w Pd on carbon /15 psi hydrogen) to give the racemate of voriconazole. The racemic voriconazole was resolved using (*1R*)-10-camphorsulfonic acid (**242**) and crystallization of the required diastereomeric salt provided optically pure voriconazole (**28**) in 80% yield.

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ABBREVIATIONS

ADME	=	Absorption, distribution, metabolism, excretion
AIBN	=	2,2'-Azobisisobutyronitrile
BOP	=	Benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
BSA	=	Bistrimethyl acetamide
BSTFA	=	Bis(trimethylsilyl)trifluoroacetamide
BSU	=	Bistrimethylsilyl urea
CBS	=	Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-Pyrrolo[1,2-c][1,3,2]oxazaborole
DCE	=	Dichloroethane
DCM	=	Dichloromethane
DDH	=	1,3-Dibromo-5,5-dimethylhydantoin
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	=	Diisobutylaluminum hydride
DIPEA	=	Diisopropylethylamine
DIPP	=	Diisopropylphosphoryl
DMAP	=	4-Dimethylaminopyridine
DMF	=	*N,N*-Dimethylformamide
DMPU	=	*N,N'*-dimethylpropyleneurea
DMSO	=	Methyl sulfoxide
DPPC	=	Diphenylphosphinic chloride
HOBT	=	1-Hydroxybenzotriazole hydrate
I.M.	=	Intramuscularly
IPA	=	Isopropyl alcohol
IPAC	=	Isopropyl acetate
LDA	=	Lithium diisopropylamide
NBS	=	*N*-Bromosuccinimide
NCE	=	New chemical entities
NEP	=	*N*-Ethylpyrrolidinone
NMP	=	1-Methyl-2-pyrrolidinone
NYHA	=	New York Heart Association
PCC	=	Pyridinium chlorochromate
PDC	=	Pyridinium dichromate

TBAF = *t*-Butyl ammonium fluoride

TBDMS = *t*-Butyldimethylsilyl

TEA = Triethyl amine

TFA = Trifluoroacetic acid

THF = Tetrahydrofuran

THP = Tetrahydropyran

TIPS = Triisopropyl silyl

TPAP = Tetrapropylammonium perruthenate

TMG = 1,1,3,3-Tetramethylguanidine

p-TSA = *para*-Toluene sulfonic acid

WSC-HCl = 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride

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