CHEMICAL REVIEWS

Review

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Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011)

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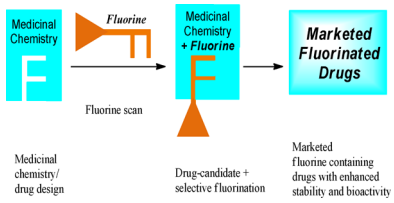

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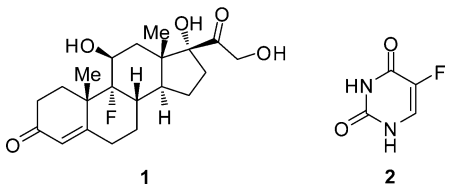
1. INTRODUCTION

1.1. Brief Historical Overview

As expected from the fluorine position on the periodic table of elements, it possesses some extreme properties, in particular, ultimate electronegativity and oxidation potential. Therefore, elemental fluorine cannot be prepared by chemical reaction,[1] and its isolation in 1886 by Henri Moissan required scientific ingenuity and great personal courage.[2] His historic effort earned him a Noble Prize (1906), and the developed electrolysis method is still in use for industrial production of fluorine gas. However, further development of fluorine chemistry was extremely sluggish, pursued by a handful of experts capable of handling the violent gas using specially designed laboratory equipment. Industrial-scale production of fluorochemicals dates back to late 1930s.[3] Truly larger scale production of elemental fluorine culminated with the necessity for production of fissile U-235. It was found that uranium hexafluoride (UF_6) possessed optimal physicochemical properties for separation of the fissile U-235 from heavier U-238 via centrifugation. Due to the very corrosive nature of UF_6 its production and use required development of inert fluorine-based special materials, in particular, polymers such as Teflon. During that time, many methodological discoveries have been made, including development of electrophilic fluorinating agents, electrochemical fluorination, and strategies to tame the violent reactivity of fluorine gas, which paved the way to fine synthetic fluoroorganic chemistry and availability of the fluorine-containing building blocks.[4]

However, in late 1940−1950s the idea of introducing fluorine into molecules of natural products was rather unconceivable. The prevailing wisdom of that time clearly suggested that fluorine is abiotic element, and its application is limited to military and special materials needs. Furthermore, quite poisonous properties of a few naturally occurring fluoroorganic compounds (vide infra) are very well known. It is interesting to note that discovery of fludrocortisone (**1**), the first fluorine-containing pharmaceutical product, was a result of a systematic study of series of 9α-halogenated cortisone derivatives, and the fluorinated compound was not included in the original study (Figure 1). In 1953 Fried



1 2

Figure 1. Structures of fludrocortisone (**1**) and 5-fluorouracil (**2**).

and Sabo noticed the relationship between the bioactivity of 9α-halo cortisones and the size of the halogen atom.[5] Thus, the anti-inflammatory activity of 9α-halo-17α-hydroxycorticosterone acetates was found to be in the following order: 1.0 (H, cortisone acetate), 0.1 (I), 0.28 (Br), 4.0 (Cl). This trend obviously prompted the authors to study the last remaining member of this group, the 9α-fluoro derivative, which was prepared by reaction of the corresponding alcohol with anhydrous hydrogen fluoride.[6] This compound, latter known as fludrocortisone, was found to possess a remarkable glucocorticoid activity, which exceeded by a factor of 10 that of the parent hormones. A few years later (1957), Heidelberger et al. demonstrated that 5-fluorouracil (5-FU) (**2**) can act as an antimetabolite of natural uracil.[7] Further studies have shown that 5-FU and many of its derivatives serve as potent mechanism-based inhibitors of thymidylate synthase (TS), the enzyme responsible for transformation of 20-deoxyuridine-5-monophosphate (dUMP) into 2-deoxythymidine-5-monophosphate.[8] Due to the remarkable antitumor-inhibiting activity of 5-FU, the search for its more potent and tumor-selective analogs is still a very active area of research, and one of the most recent examples will be discussed in this review. These two drugs, fludrocortisone and 5-FU, constituted the fundamental paradigm change in the view of fluorine's place in biology-related research, assuring that the role of fluorine in life sciences would ever increase. In fact, the research done in the 1950s demonstrated three general principles of fluorine application in the design and development of biologically active compounds: substitution of fluorine for hydrogen and hydroxy group, and use of fluorinated derivatives of natural compounds as antimetabolites. These breakthroughs in medicinal chemistry of fluorine represent the major strategies currently used in drug design to rationally impart some special properties, such as an enhancement of the therapeutic efficacy and improvement of pharmacological properties.[9]

1.2. Natural Organofluorine Compounds

As mentioned in the previous section, before 1954 it was inconceivable to expect that introduction of fluorine into natural products can result in beneficial biological properties. Some origins of this prevailing paradigm deserve a brief discussion. Thus, an overwhelming number of past and current pharmaceutical products are either directly derived from or inspired by natural products.[10] On the other hand, until 1943, fluorine-containing natural products have not been known to science. Furthermore, sodium monofluoroacetate, the first isolated fluorinated naturally occurring compound, was shown to be exceptionally toxic being the source of the poisonous properties of numerous Australian, Brazilian, and African shrubs.[11] As demonstrated by O'Hagan, a handful of other known fluorine-containing natural products are actually derived from a single precursor 5′-fluoro-5′-deoxyadenosine produced by just a single enzyme, named fluorinase.[12] These compounds share structural similarity being derivatives of carboxylic acids, including 4-fluoro-threonine, a unique amino acid isolated from bacterium *Streptomyces cattleya* in 1986.[13] By contrast, about 5000 other halogen-containing (Cl, Br, I) natural products have been identified and found in great structural diversity, containing one or multiple halogens, including the CCl_3 group.[14] Taking into account that fluorine is the 13th most common element on Earth's crust and significantly more abundant than other halogens, the extreme rarity of fluorine-containing natural products seems a bit puzzling. Actually, the answer can be easily found considering the chemical properties of fluorine. First, most of fluorine exists in the form of the insoluble salts fluorspar (CaF_2) and cryolite (Na_3AlF_6), rendering its delivery to aqueous biological systems quite limited. Biochemically, one common pathway for enzymatic halogenation includes formation of intermediate hypohalous species produced by vanadium-dependent halogenases and H_2O_2. As discussed above, fluorine has the highest possible oxidation potential [(−3.06 V vs −1.36 (Cl), −1.07 (Br), and −0.54 (I)] and therefore cannot enter this reaction. Another general enzymatic incorporation of halogens is a nucleophilic opening of epoxide intermediates with halide anion. In sharp contrast to other halogens, fluorine has an extraordinary high hydration energy [117 kcal/mol vs 84 (Cl), 78 (Br), and 68 (I)][15] and therefore behaves as a very poor nucleophile under aqueous biological conditions. One more and

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much less common pathway for biological halogenation involves a radical mechanism, like in the biosynthesis of trichloromethyl-containing barbamide.[16] While this mechanism is possible for fluorine, its radical is difficult to generate and its violent reactivity would prevent any regio/chemoselectivity. Finally, the C−F bond is one of the strongest chemical bonds, and its biological formation/cleavage would require extremely activated intermediates which are difficult to generate under biological conditions.[17] This quite rare feature can be of great value for rational design of molecules with a presupposed reactivity and biological activity.

1.3. Impact of Fluorine in Pharmaceuticals

There are many effects that fluorine and fluorine-containing substituents can impart on properties of organic compounds. It is well known that fluorine's electronegativity, size, omniphobicity/lipophilicity, and electrostatic interactions can dramatically influence chemical reactivity. Nowadays it is already not surprising that substitution of trifluoromethyl for a methyl group[18] or pentafluorophenyl for a phenyl group[19] can lead to a dramatically different chemical/stereochemical outcome. In a metabolic cascade of chemical reactions this effect can be significantly magnified, so even a single fluorine atom can completely change biological properties of a natural product. The classic example might be monofluoroacetic acid biological properties of which we now know well.[20] Generally, the effect of fluorine on the biological activity of organic compounds is rather subtle and difficult to predict. Accordingly, quite intense structure−activity relationship studies are usually necessary to pinpoint the correct position of fluorine in the target molecule. So-called fluorine scan is currently a routine approach in development of drug candidates. Nevertheless, the great wealth of research, biological, and medicinal data accumulated so far allows making some general predictions about an expected effect of fluorination on biological activity. This topic has been covered in an excellent review[21] and will be considered here only briefly. One of the major effects of fluorination is a modulation of acidity and basicity of a parent compound.[22] This can strongly influence binding affinity, pharmacokinetic properties, and bioavailability of a given drug candidate. Modulation of lipophilicity can also be effectively done with introduction of fluorine, in particular, CF_3, S−CF_3, and O−CF_3 groups. While substitution of fluorine for hydrogen results in minor steric alterations, electrostatic repulsive interaction or attraction of fluorine[23] or CF_3[24] with other functional groups in a molecule can lead to significant conformational changes. Another rather established effect of fluorination is a modulation of metabolic stability. In particular, replacing hydrogen with fluorine on aromatic rings is a very effective strategy to slow down significantly the oxidative metabolic step of a given drug by Cytochrome P450 monooxygenases. Hydrolytic metabolism can also be noticeably influenced by fluorination. In this case the electron-withdrawing property of fluorine plays a key role in effecting reaction rates and the stability of the intermediates. One may agree that these general areas of the fluorine effect provide quite attractive opportunities in drug design. Thus, in 1970 there were only about 2% of fluorine-containing drugs on the market, while the current number has grown to about 25%. It should be emphasized that fluorine is making an impact in pharmaceuticals not only in a fast-growing number of fluorinated drugs but also in development of best health care products. It is quite remarkable that three out of the five top-selling pharmaceuticals contain fluorine. In 2008 atorvastatin (Lipitor) (**3**) was registered as the best-selling drug globally with a revenue of $US 5.9 billion (Figure 2). Atorvastatin is used for treatment of high cholesterol

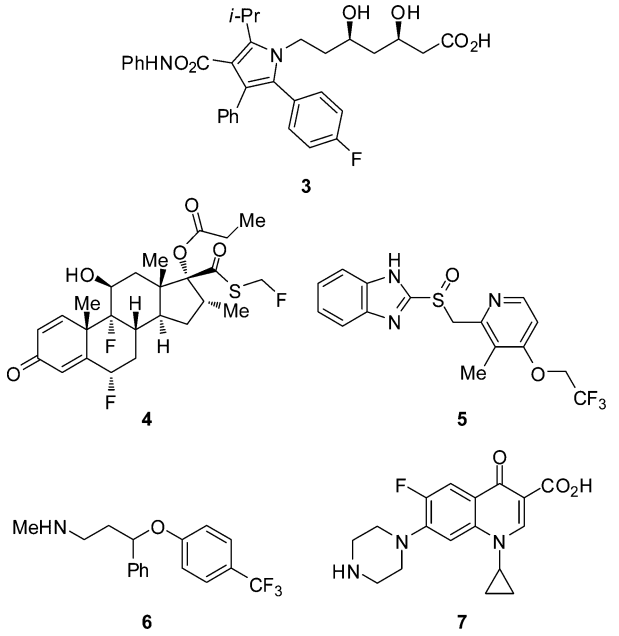

Figure 2. Structures of atorvastatin (**3**), fluticasone propionate (**4**), lansoprazole (**5**), fluoxetine (**6**), and ciprofloxacin (**7**).

and triglyceride levels and prevention of heart attacks and strokes. Steroidal anti-inflammatory drug fluticasone propionate (**4**) and lanzoprazole (Prevacid) (**5**) regulating gastric acid secretion make the list of top-selling fluorinated drugs. Furthermore, antidepressant fluoxetine (Prozac) (**6**) and the antibacterial ciprofloxacin (Ciprobay) (**7**) should also be mentioned among the most successful fluorine-containing drugs. In general, about one-third of the top-performing drugs, currently on the market, contain fluorine atoms in their structure. These statistic data clearly suggest that the paramount role of fluorine in medicinal chemistry and drug design has been firmly established, and we might see more and more fluorinated drugs in the near future.

Several excellent reviews covering various areas of fluorine in pharmaceuticals have been published in recent decades.[25] The major goal of this review is to profile 40 new fluorine-containing drugs introduced to the market from 2001 to 2011, according to information retrieved using the Thomson Pharma database. We provide detailed commentary on the mode of their biological activity and, where it is possible, by comparison with fluorine-free analogs, discuss the specific role of fluorine in development of a given drug. For each compound we illustrate synthetic routes and emphasize the source of organic fluorine. Considering that all these 40 compounds are structurally and synthetically very different we decided that the best order of their discussion would be based on their biological activity.

2. ANTICANCER DRUGS

2.1. Fulvestrant (Faslodex)

The most widely used therapy for treatment of breast cancer is administration of selective estrogen receptor modulators such as tamoxifen.[26] However, tamoxifen also acts as a partial estrogen receptor (ER) agonist in other tissues, increasing the risk of developing associated tumors, and at the same time patients may

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develop resistance to the drug effects. In the search for pure ER antagonists, devoid of any agonist activity, research work at ICI (currently Astra-Zeneca) showed that derivatives of estradiol containing an alkyl chain at the 7α position had a high affinity for the ER. This led to the discovery of ICI 164,384 (**8**) and eventually its fluorinated derivative fulvestrant (ICI 182,780) (**9**) as a more potent ER antagonist (Figure 3).[27] Their mechanism of

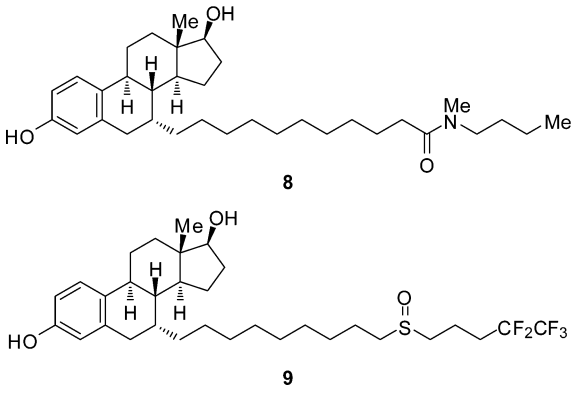


Figure 3. Structures of ICI 164,384 (**8**) and fulvestrant (**9**).

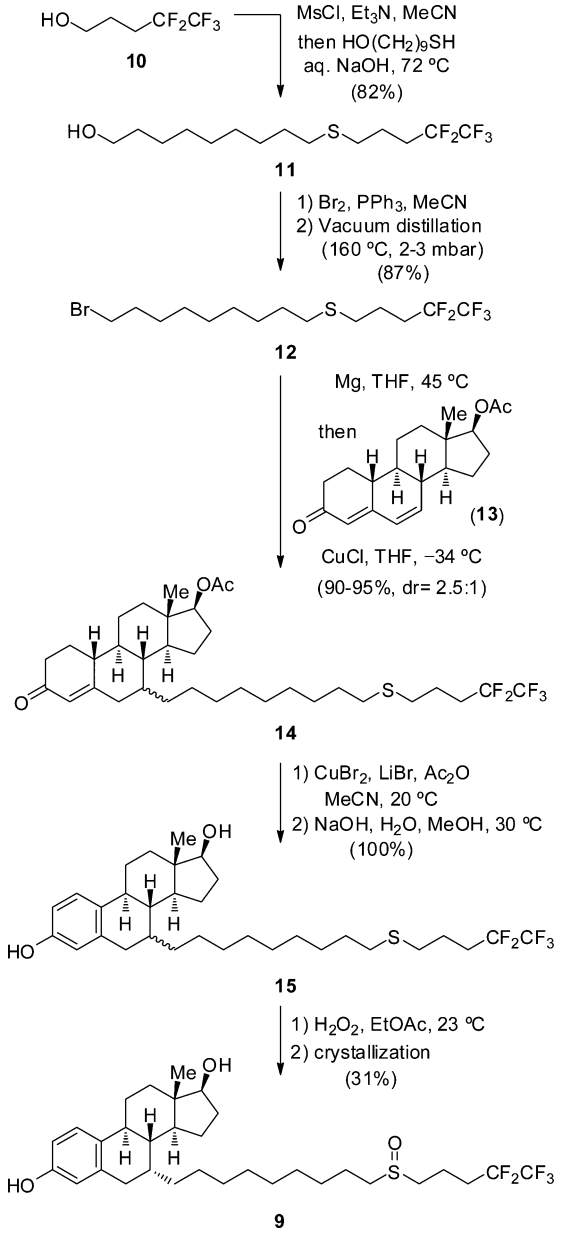
action is believed to proceed through degradation of ER after binding to the drug compound. Thus, introduction of fluorine atoms in fulvestrant at the end of the side chain may contribute to an increase in its metabolic stability during binding to ER. In fact, other fluorinated derivatives of estradiol have also been described recently as potential antiestrogen compounds.[28] Fulvestrant was approved by the FDA in 2002 as a second-line therapy for advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Sales for fulvestrant (Faslodex) reported by AstraZeneca for 2011 were $546.0 million, representing a year to year increase of 55% on 2010.

The synthetic route to fulvestrant developed by Astra-Zeneca for manufacturing use is outlined in Scheme 1.[29] The fluorinated precursor was commercially available 4,4,5,5,5-pentafluoropentan-1-ol (**10**), and its corresponding mesylate was reacted with 9-mercaptononan-1-ol to produce thioether **11**. After conversion into bromide **12**, the key step was the carbon−carbon bond formation at C-7 on the steroid nucleus by conjugate addition of the organocopper reagent derived from **12** to 17-acetoxyestra-4,6-dien-3-one (**13**), in turn derived from 19-nortestosterone. In this manner, compound **14** was obtained as a 2.5:1 diastereomeric mixture.[30] Fulvestrant (**9**) was finally accessed after subsequent and sequential aromatization of the steroid A ring and hydrolytic removal of the 17-acetate followed by oxidation of the side chain in sulfide **15** and recrystallization to remove the unwanted 7β-isomer.

2.2. Gefitinib (Iressa)

Gefitinib (ZD-1839) (**16**), developed and launched by Astra-Zeneca (formerly Zeneca), is an oral epidermal growth factor receptor (EGFR) inhibitor used for treatment of certain breast, lung, and other cancers (Figure 4). Gefitinib interrupts signaling through the EGFR in target cells,[31] and therefore, it is only effective in cancers with mutated and overactive EGFR.[32] It was first launched in Japan in July 2002 for treatment of inoperable or recurrent nonsmall cell lung cancer (NSCLC), and then, it was launched in the United States as a third-line monotherapy (after platinum-based and docetaxel therapies) for advanced NSCLC in May 2003. Current sales of the marketed drug (Iressa) reached $554.0 million in 2011.

Scheme 1. Synthetic Route to Fulvestrant (9)



Structurally, gefitinib contains a 3-chloro-4-fluoroaniline moiety linked to a quinazoline core.[33] X-ray studies showed that the 3-chloro-4-fluoroaniline substituent extends into the hydrophobic pocket in the back of the ATP binding cleft of EGFR, fitting better than less fluorinated aromatic rings. The fluorine substituent in the para position extends toward the side chains of Leu-788, Met-766, and Glu-762.[34] The potency and pharmacokinetics of fluorine regioisomers of gefitinib were also described.[35] Thus, introduction of a 2-fluoro substituent in **17** resulted in a potent inhibitor of EGFR at both enzyme and cellular levels, while 6-fluoro-substituted compound **18** resulted in a weaker inhibitor of EGFR. Compared to gefitinib (**16**), both the 2-fluoro- and the 6-fluoro-substituted compounds **17** and **18** show improved exposure, lower clearance, and improved bioavailability.

The early synthetic routes of gefitinib developed at Astra-Zeneca[36] have been recently adapted for preparation of a radiolabeled analogue.[37] Starting from 3-hydroxy-4-(methoxy)-

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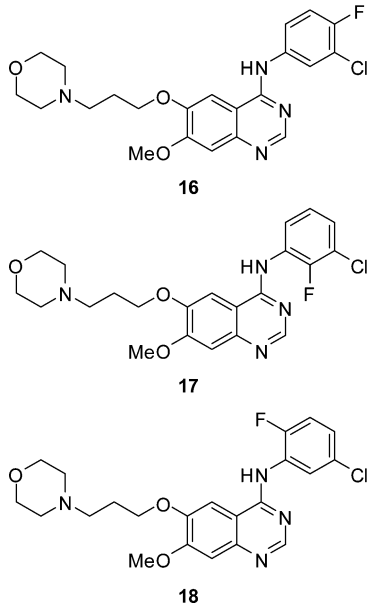
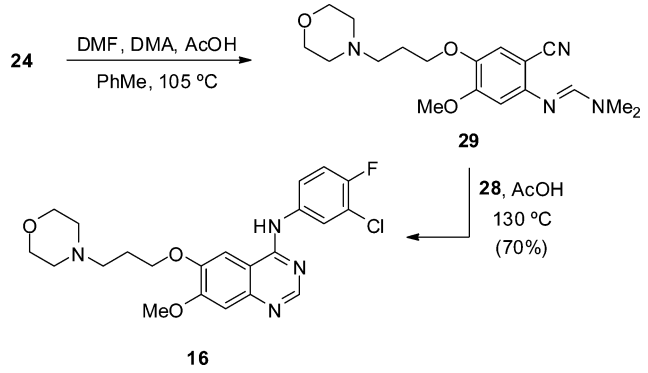


Figure 4. Structures of gefitinib (**16**) and its regioisomers **17** and **18**.

benzaldehyde (**19**), conversion into benzonitrile **20** was achieved by reaction with sodium formate/formic acid in the presence of hydroxylamine sulfate (Scheme 2). Next, chloride **21** was coupled to **20** to form morpholine **22**, which was further nitrated to afford **23**. Reduction of the nitro group with sodium dithionite produced aniline **24**, and its subsequent reaction with *tert*-amyl alcohol resulted in formation of amide **25**. Ring closure to quinazolinone **26** was carried out by treatment of **25** with formic acid and formamide. Final steps of synthesis included chlorination of **26** and coupling of the resulting chloride **27** with 3-chloro-4-fluoroaniline (**28**) to furnish gefitinib (**16**).

For large-scale purposes, synthesis of gefitinib has also been accomplished starting from intermediate **24** using a lower number of steps.[38] In this case, formamidine **29** was obtained by reaction of **24** with DMF and DMA and next coupled with aniline **28** to produce the target compound gefitinib in over 300 g scale (Scheme 3).

Scheme 3. Large-Scale Synthesis of Gefitinib (16)



2.3. Sorafenib (Nexavar)

Bayer and Onyx developed and launched sorafenib (BAY 43-9006) (**30**), the first oral multikinase inhibitor that targets Raf and affects tumor signaling and the tumor vasculature (Figure 5).[39] This drug is indicated for treatment of advanced renal cell

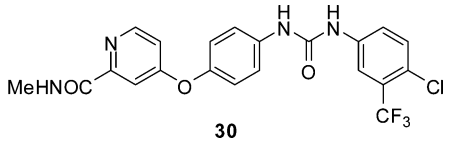
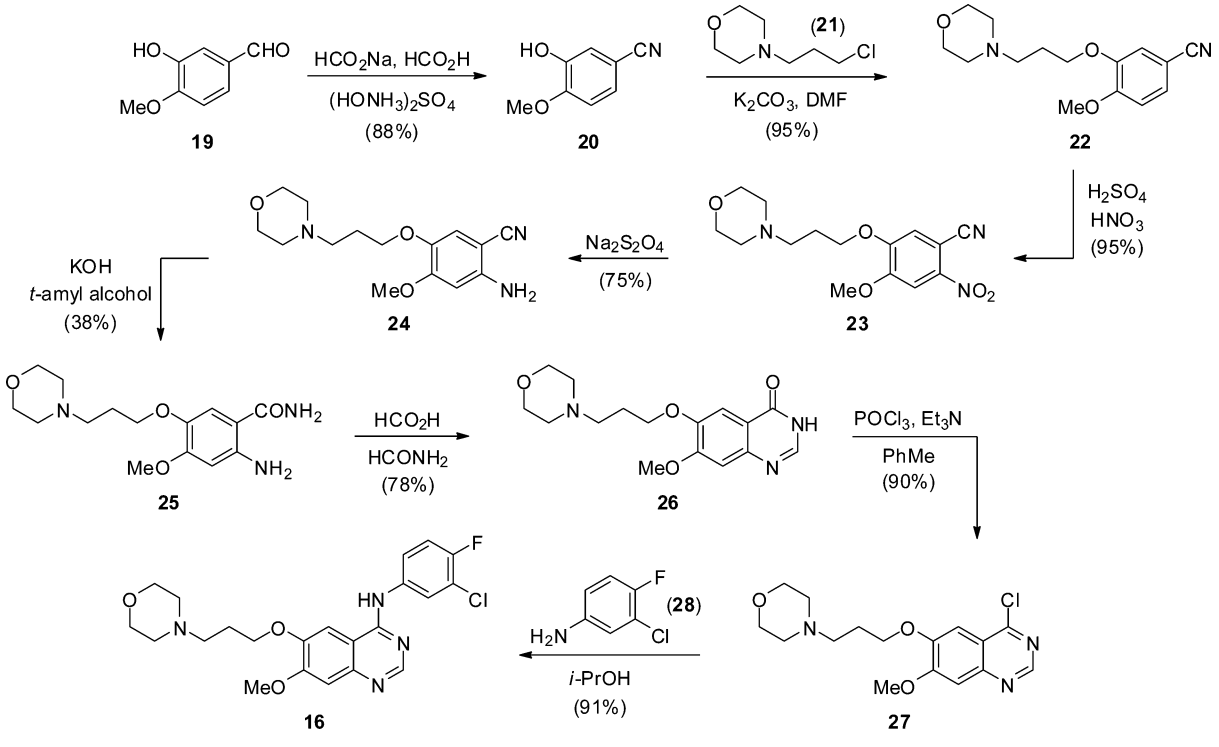


Figure 5. Structure of sorafenib (**30**).

Scheme 2. Early Synthetic Route to Gefitinib (16)



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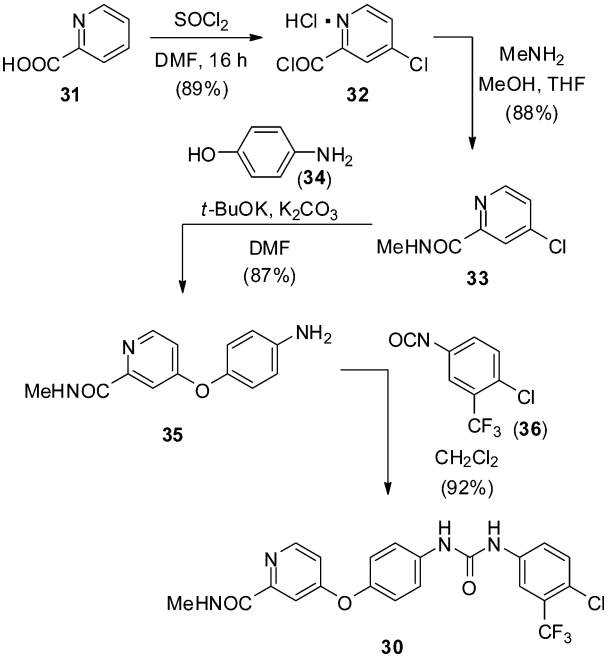
carcinoma (RCC) and unresectable hepatocellular carcinoma (HCC).[40] Bayer launched sorafenib for RCC in the United States in December 2005 and in the United Kingdom in October 2006. By May 2005, Bayer and Onyx were also developing sorafenib for breast, ovarian, peritoneal, prostate, skin, and pancreatic cancers. In June 2007, launches for NSCLC and breast cancer were planned for 2009 and 2013, respectively. Sales for sorafenib (Nexavar) reported by Bayer for 2011 were $1.009 billion, representing a year to year increase of 2.8% on 2010.

Sorafenib was prepared in four steps from picolinic acid (**31**) with an overall yield of 63% without any chromatographic purification (Scheme 4).[41] Acid chloride **32** was obtained by

Scheme 4. Synthesis of Sorafenib (30) from Picolinic Acid (31)

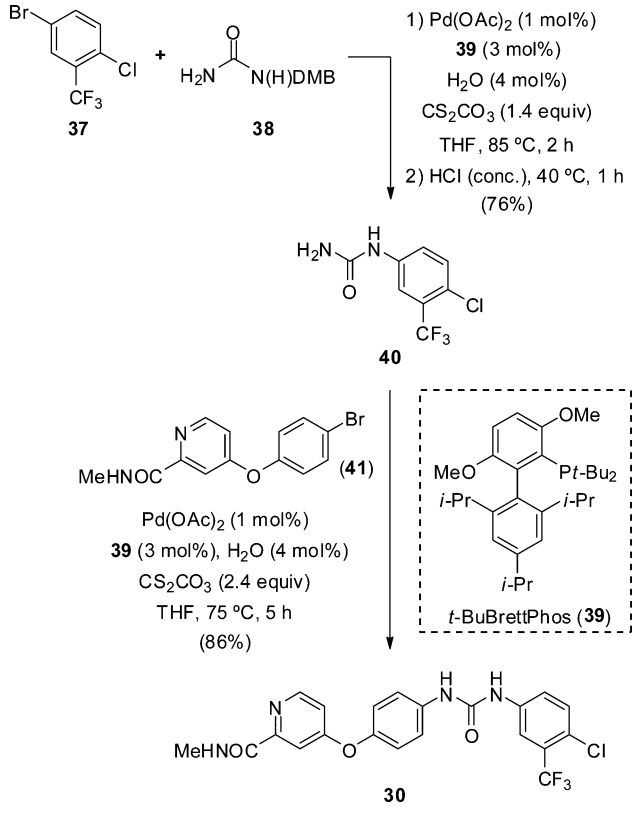


treatment of **31** with the Vilsmeier reagent, and then reacted with methylamine to produce amide **33**. Biaryl ether **35** was next formed by coupling of **33** with 4-aminophenol (**34**), and final urea formation by reaction with isocyanate **36** yielded sorafenib (**30**).

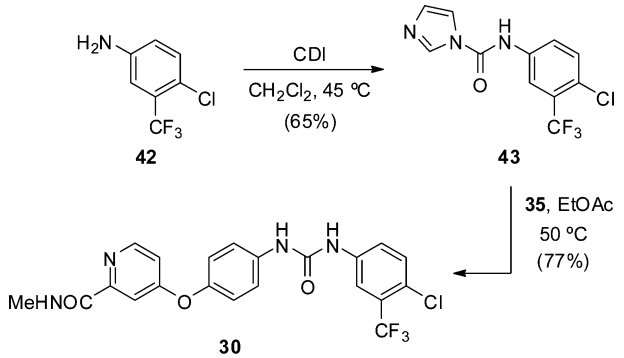
A facile route to unsymmetrical *N*,*N*′-diarylureas was recently developed, also serving for straightforward access to sorafenib in two steps from 4-bromo-2-(trifuoromethyl)chlorobenzene (**37**) in 65% overall yield (Scheme 5).[42] Pd-catalyzed C−N cross-coupling of **37** with 2,4-dimethoxybenzyl (DMB) urea (**38**) was carried out in the presence of *t*-BuBrettPhos ligand (**39**) to give urea **40** after HCl-mediated deprotection. Next, second arylation with bromide **41** under the same reaction conditions afforded sorafenib.

Final synthesis of sorafenib was easily achieved without the need of chromatographic purifications through an *N*-carbonyldiimidazole intermediate in order to build the unsymmetrical urea moiety.[43] Starting from 4-chloro-3-(trifluoromethyl)aniline (**42**), reaction with 1,1′-carbonyldiimidazole (CDI) afforded **43** and final coupling with biaryl aniline **35** furnished sorafenib (Scheme 6).

Scheme 5. Pd-Catalyzed Synthesis of Sorafenib (30)



Scheme 6. Final Synthesis of Sorafenib (30)



2.4. Capecitabine (Xeloda)

As mentioned in the Introduction, with the discovery of 5-fluorouracil (**2**) in 1957, fluorine substitution for hydrogen has become a common strategy in the drug discovery process. However, 5-fluorouracil has a strong toxicity and poor tumor affinity. Therefore, use of prodrug strategies to reduce such side effects has been highly pursued. In this context, capecitabine (RG-340) (**44**) is an *N*-4 carbamate pyrimidine prodrug created to improve the selectivity and bioavailability of the parent compound by a selective delivery of the cytotoxic agent (Figure 6).[44] This selectivity is due to its sequential metabolism by three enzymes, namely, carboxylesterase, cytidine deaminase, and thymidine phosphorylase, highly expressed in the liver and tumors.[45] Capecitabine was developed and launched by Roche, and it is an important drug used for treatment of breast and colorectal cancers. It is indicated in the United States as first-line treatment in metastatic colorectal cancer (mCRC) when treatment with fluoropyrimidine therapy alone is preferred and

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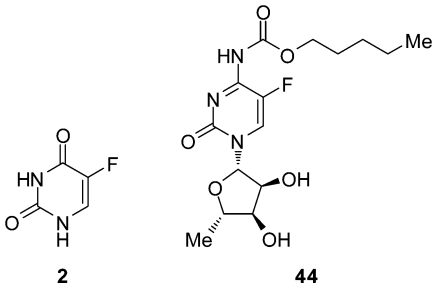
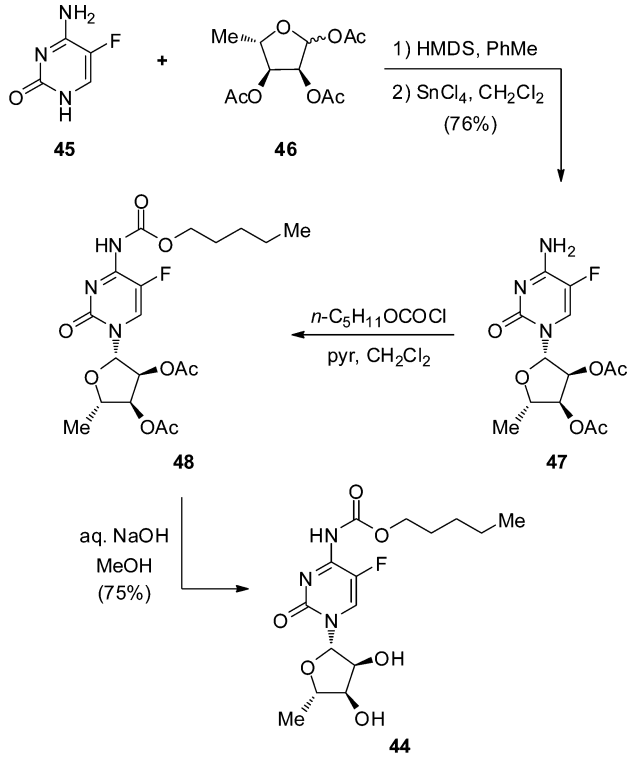


Figure 6. Structures of fluorouracil (**2**) and capecitabine (**44**).

as a single agent for adjuvant treatment in patients with Dukes C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. Sales of capecitabine (Xeloda) reported by Roche for 2011 were $1.532 billion, representing a year to year increase of 8% on 2010.

Synthesis of capecitabine is outlined in Scheme 7.[46] Coupling of 5-fluorocytosine (**45**) and 1,2,3-tri-*O*-acetyl-5-deoxyribose

Scheme 7. Synthetic Route to Capecitabine (44)



(**46**)[47] in the presence of $SnCl_4$[48] yielded nucleoside **47**. The carbamate functionality was installed by treatment with *n*-pentylchloroformate to afford **48** with the complete skeleton of the drug. Removal of the acetyl groups was performed with NaOH, and capecitabine (**44**) was obtained upon acidification workup.

A green and very efficient process for preparation of capecitabine has been very recently reported.[49] The process consists of an organocatalytic glycosylation in continuous flow by means of a Brønsted-acid-catalyzed procedure. On the basis of the finding that pyridinium triflates are superior catalysts for glycosylation of nucleobases, a one flow-three step synthesis of capecitabine was completed in 1 h in 72% overall yield, circumventing purification of the intermediate products. It comprised the use of sugar derivative **46**, silylated pirimidine **50**, *n*-pentylchloroformate, and piridinium triflate **49** as the catalyst (Scheme 8).

2.5. Sunitinib (Sutent)

Sunitinib (SU11248) (**51**) is a pyrrole-substituted 2-indolinone derivative developed and commercialized by Sugen and Pfizer (Figure 7).[50] Most notably, sunitinib was the first anticancer drug simultaneously approved by the FDA in 2006 for two different indications, namely, advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumor (GIST) after disease progression or imatinib resistance. Sunitinib targets both vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases, being highly successful in a number of preclinical tumor models. It has very good oral bioavailability and is well tolerated at efficacious doses.[51] Also, sunitinib is being studied for other indications, alone or in combination with other drugs, such as pulmonary hypertension and for Von Hippel–Lindau syndrome. Current sales of the marketed drug (Sutent) reported by Pfizer for 2011 were $1.187 billion, representing a year to year increase of 11% on 2010.

The biological activities of sunitinib analogues were first evaluated in biochemical assays measuring tyrosine phosphorylation of VEGF-R2, PDGF-Rβ, fibroblast growth factor receptor-1 (FGF-R1), and epidermal growth factor receptor (EGFR) and solubility at pH 2 and 6.[52] Different halogen substitutions had little effect on the biochemical activities against VEGF-R2 and PDGF-Rβ but affected the cytotoxicity profiles. The bulkier Cl and Br substitutions at the 5 position of the indole ring showed some extent of cytoxicity when compared to sunitinib.

The original medicinal chemistry route to sunitinib employed the classical Knorr method (Zn/AcOH) for construction of a fully substituted pyrrole ring and installment of the amine side chain afterward.[52] However, this was considered rather problematic for scale-up production, and therefore, a more efficient synthesis was pursued.[53] Reaction of diketene (**52**) with *N*,*N*-diethylethylenediamine afforded the highly unstable ketoamide **53**, which was reacted with oxime **55** [derived from *tert*-butyl acetoacetate (**54**)] under hydrogenation conditions to form pyrrole **56** in good yield (Scheme 9). It should be noted that the Zn/AcOH method was also tested but provided a lower chemical yield (53%) and also produced a big excess of zinc salts that were difficult to remove on a large scale. Pyrrole **56** was next decarboxylated under acidic conditions, and the resulting trisubstituted pyrrole **57** was subjected to a Vilsmeier–Haack reaction where the corresponding adduct **58** was reacted in situ with 5-fluorooxindole (**59**) (available by decarboxylation of 5-fluoroisatin) by means of an Eschenmoser-type condensation to finally produce sunitinib (**51**). Adaptation of this synthetic strategy has also allowed preparation of an ^{18}F-labeled analogue of sunitinib for positron emission tomography (PET) diagnosis techniques.[54]

2.6. Nilotinib (Tasigna)

Nilotinib (AMN107) (**60**) is a second-generation Bcr-Abl tyrosine kinase inhibitor (TKI) developed to overcome resistance or intolerance to imatinib (**61**) in patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in chronic phase (Figure 8).[55] Nilotinib was first approved in Switzerland for previously treated CML in July 2007. The drug was launched for second-line CML in the United States and European Union during fourth quarter 2007. Sales for

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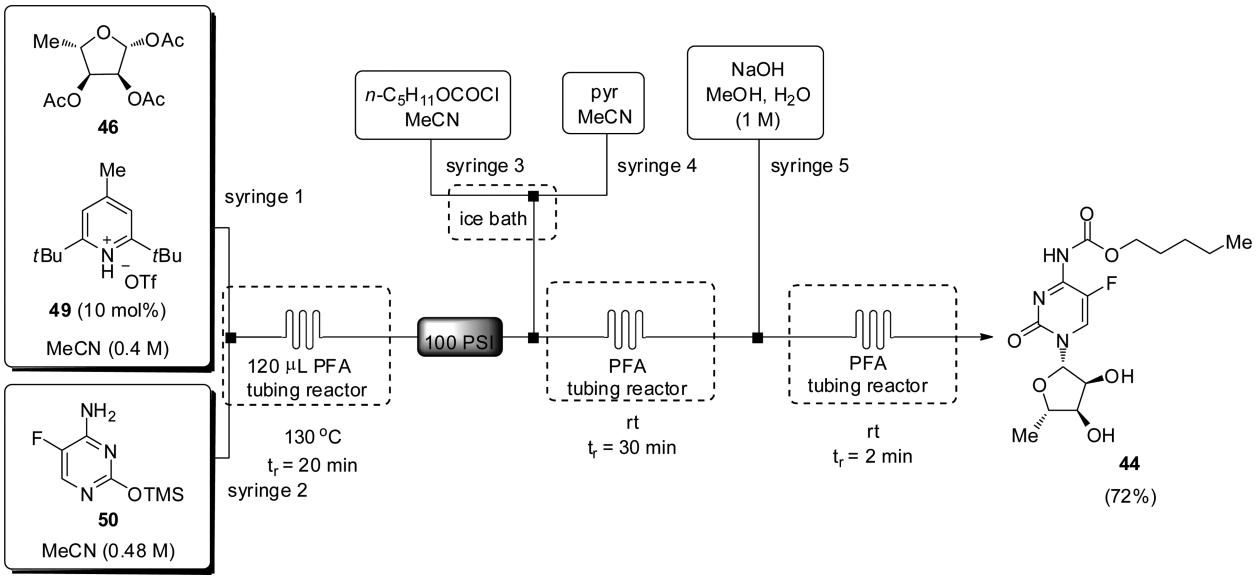
Scheme 8. Continuous Flow Synthesis of Capecitabine (44)



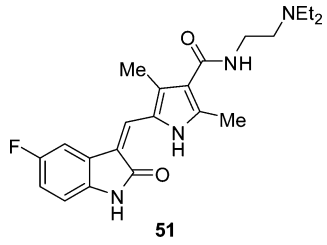


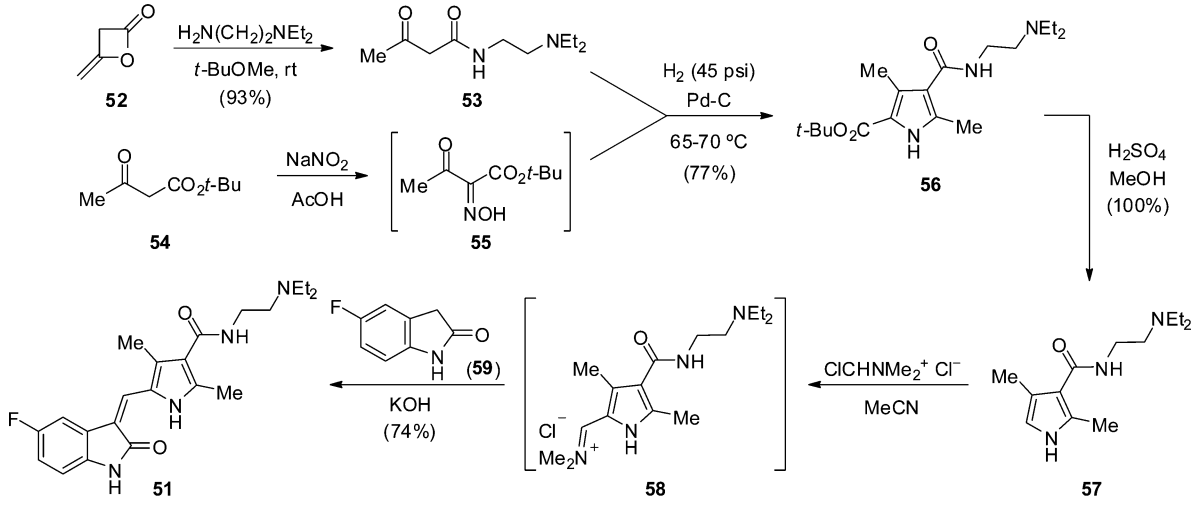
Figure 7. Structure of sunitinib (**51**).

nilotinib (Tasigna) reported by Novartis for 2011 were $716.0 million, representing a year to year increase of 79.0% on 2010.

Nilotinib was developed using a rational design strategy, which based on the premise that Bcr-Abl inhibitors more potent and selective than imatinib could be developed by making modest changes in this molecule.[56] Analysis of the structure of imatinib and that of the Abl kinase domain indicated that changes to the ATP-binding structure would be likely to decrease its efficacy, but some modification of the methylpiperazinyl group of imatinib might improve its binding characteristics. Replacement of the 4-methylpiperazine ring with 4-methylimidazolyl and adding a trifluoromethyl group on the phenyl ring resulted in the discovery of nilotinib, which is structurally similar to imatinib. Nilotinib, like imatinib, binds to a catalytically inactive conformation of Bcr-Abl kinase but is 30 times more potent at inhibiting Bcr-Abl activity. Nilotinib has more favorable binding energetics and higher selectivity than imatinib. In the active site pocket of the Abl kinase domain, one of the fluorine atoms of the CF_3 group of nilotinib interacts with the imidazole NH of a histidine as well as an isoleucine side chain. The CF_3 derivative is over 5-fold more active than the corresponding methyl derivative in an autophosphorylation assay.

Novartis' preparation of nilotinib has been disclosed only in a patent application, and thus, some synthetic details, such as chemical yields, were not given.[57] The eight-step synthesis comprised a convergent approach based on a late-stage coupling of fragments **66** and **72** (Scheme 10). Starting from benzoate **62**, formation of guanidine salt **63** was followed by condensation with enone **64** to create the pyrimidine ring in **65**. NaOH-mediated ester hydrolysis afforded key fragment **66**. The second

Scheme 9. Synthetic Route to Sunitinib (51)



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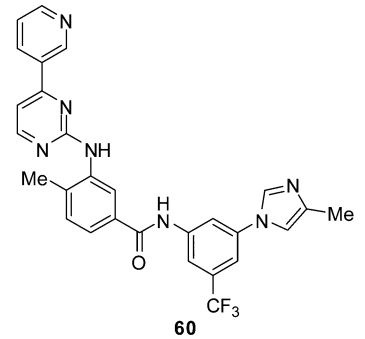
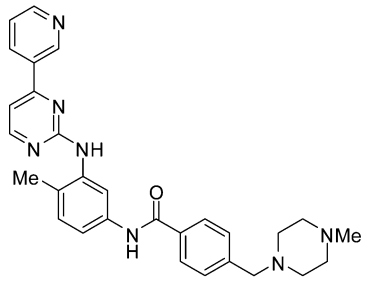
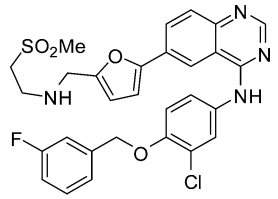


60



61

Figure 8. Structures of nilotinib (**60**) and imatinib (**61**).



83

Figure 9. Structure of lapatinib (**83**).

half of the molecule was obtained from an S_NAr reaction between 3-fluoro-5-(trifluoromethyl)benzonitrile (**67**) and 4-methylmidazole (**68**), leading to two regioisomeric imidazoles substituted at *N*-1 or *N*-3, and although separable their ratio was not reported. From imidazole **69**, hydrolysis of the nitrile function into carboxylic acid **70** was followed by a Curtius rearrangement to afford *N*-Boc-protected aniline **71**. After Boc removal, coupling of **66** and **72** in the presence of diethyl phosphorocyanidate furnished the target compound nilotinib (**60**).

An improved synthetic route was later described starting from the Cu-mediated coupling between bromoaniline **73** and 4-methylimidazole (**68**), proceeding with 85:15 selectivity at the *N*3−*N*1 atoms of the imidazole ring (Scheme 11).[58] Amide bond formation of the resulting major regioisomer **74** with acid chloride **75** afforded **76**, and its Pd-mediated Buchwald coupling with aminopyrimidine **77** using Xantphos (**78**) as ligand finally produced nilotinib.

More recently, a new synthesis of nilotinib was developed based on a fully regioselective Pd-catalyzed arylation of 4-methylimidazole (**68**) with aryl bromide **73** leading to *N*-1-substituted imidazole **74** as a single regioisomer in good yield (Scheme 12).[59] Because imidazoles can inhibit formation of Pd(0) catalytic species, the success of this method relied on preactivation of $Pd_2(dba)_3$ in the presence of ligand **79** prior to addition of reagents **68** and **73**. A second Pd-catalyzed reaction between aminopyrimidine **77** and aryl bromide **80** allowed access to ester **82**, this time using ligand **81** (BrettPhos). Final amide bond formation by reaction of **82** with **74** led to nilotinib.

2.7. Lapatinib (Tykerb)

Lapatinib (GW-572016) (**83**), developed and launched by GlaxoSmithKline (GSK), is an orally active epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER2) inhibitor and a dual tyrosine kinase inhibitor for breast cancer and other solid tumors (Figure 9).[60] Lapatinib ditosylate monohydrate was approved by the FDA for treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and have received prior therapy including an anthracycline, a taxane, and trastuzumab.[61] It was launched in the United States for use in second-line breast cancer in March 2007. Current sales of the marketed drug (Tykerb) reported by GSK reached $370.5 million in 2011.

Structurally, lapatinib contains a 4-(3-fluorobenzyloxy)aniline moiety on a quinazoline core. It was demonstrated that the 3-anilino and 3-benzyloxy positions were optimal for dual ErbB-1 and ErbB-2 inhibition.[62] A chlorine atom at the 3-anilino position afforded insignificant increases in enzyme potency but appeared to offer improvements in cellular efficacy. Larger groups in the 3-anilino position generally diminished activity. In combination with suitable substituents at the 3-anilino position, fluorine at the 3-benzyloxy position yielded compounds with greater potency in the cellular assay panel. Removal of the fluorine atom results in a 2-fold decrease in inhibition activity, whereas larger groups at the 3-benzyloxy position such as bromine also reduced the activity. X-ray crystal structure studies showed that the 3-F-Ar ring was accommodated well in a lipophilic pocket of ErbB-1, which is better than 3-H-Ar rings.[63] The importance of this single fluorine atom also relies on the better cellular activity and pharmacokinetics of lapatinib, compared to nonfluorinated derivatives.

Synthetic access to lapatinib has been disclosed by GSK, but again, the corresponding patent procedure does not provide chemical yield data.[62,64] Thus, starting from 2-chloro-5-nitrophenol (**84**) and 1-(bromomethyl)-3-fluorobenzene (**85**), the nitro group of the resulting coupled product **86** was hydrogenated to afford aniline **87** (Scheme 13). 4-Chloro-6-iodoquinazoline (**88**) was available by chlorination of the corresponding quinazolone precursor, and its reaction with **87** gave compound **89**. The Stille coupling described in the original patent was later replaced by a more environmentally friendly Suzuki reaction using boronic acid **90**. Final reductive amination reaction of aldehyde **91**[65] with sulfonylethylamine gave the target product lapatinib (**83**).

2.8. Crizotinib (Xalkori)

Selective dual inhibitors of mesenchymal-epithelial transition factor (c-MET) kinase[66] and anaplastic lymphoma kinase (ALK)[67] are promising drug candidates for development of anticancer compounds. Several molecules belonging to this group of inhibitors have recently been introduced to clinical studies. Crizotinib (PF-02341066) (**92**) (Figure 10), developed and launched by Pfizer (trade name Xalkori),[68] was the first of this class approved by the FDA in 2011 for treatment of nonsmall cell lung cancer.[69] It is an oral ATP-competitive dual inhibitor of hepatocyte growth factor receptor tyrosine kinase (HGFR, c-Met) and ALK tyrosine kinase. Crizotinib is indicated in the United States for treatment of patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC), which is ALK positive. In preclinical tumor xenograft studies, crizotinib inhibited the growth and survival of cell lines dependent upon c-Met or ALK enzymatic activity. Crizotinib has been particularly effective against anaplastic large cell lymphoma and NSCLC cell

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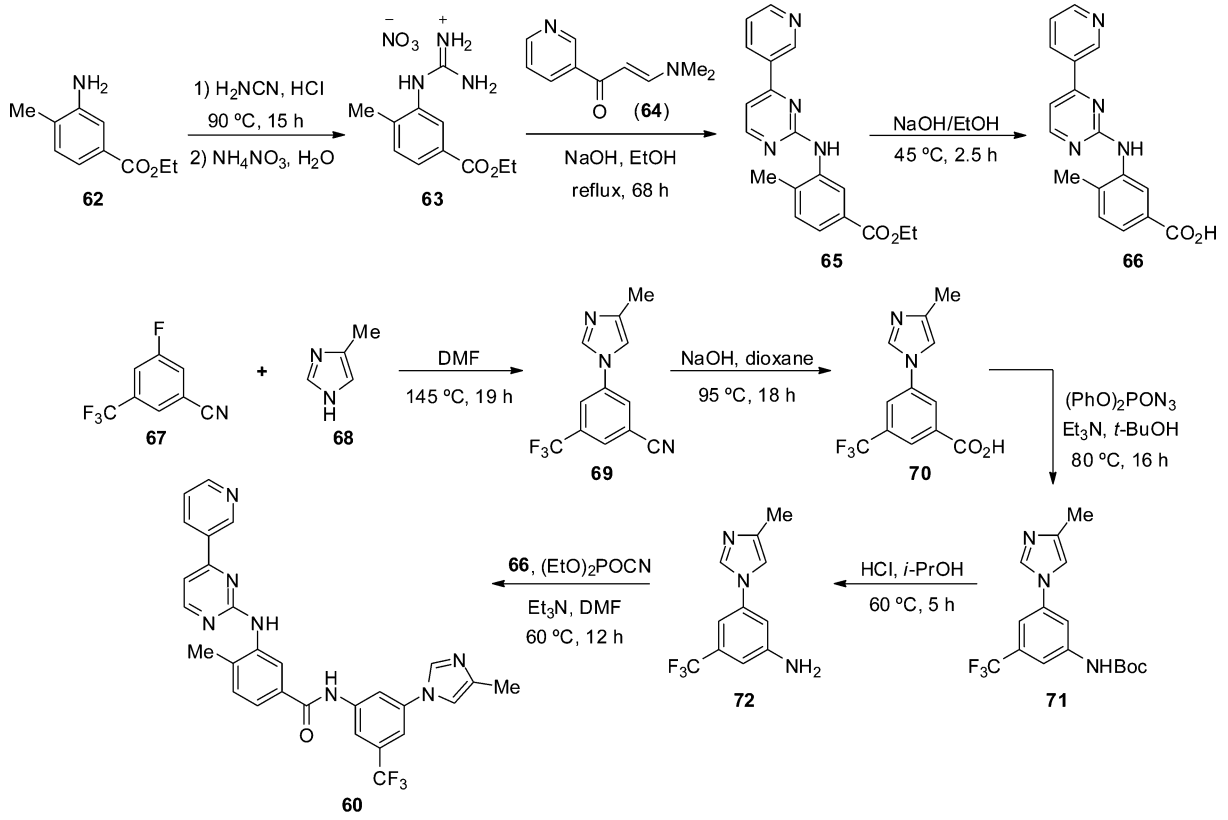
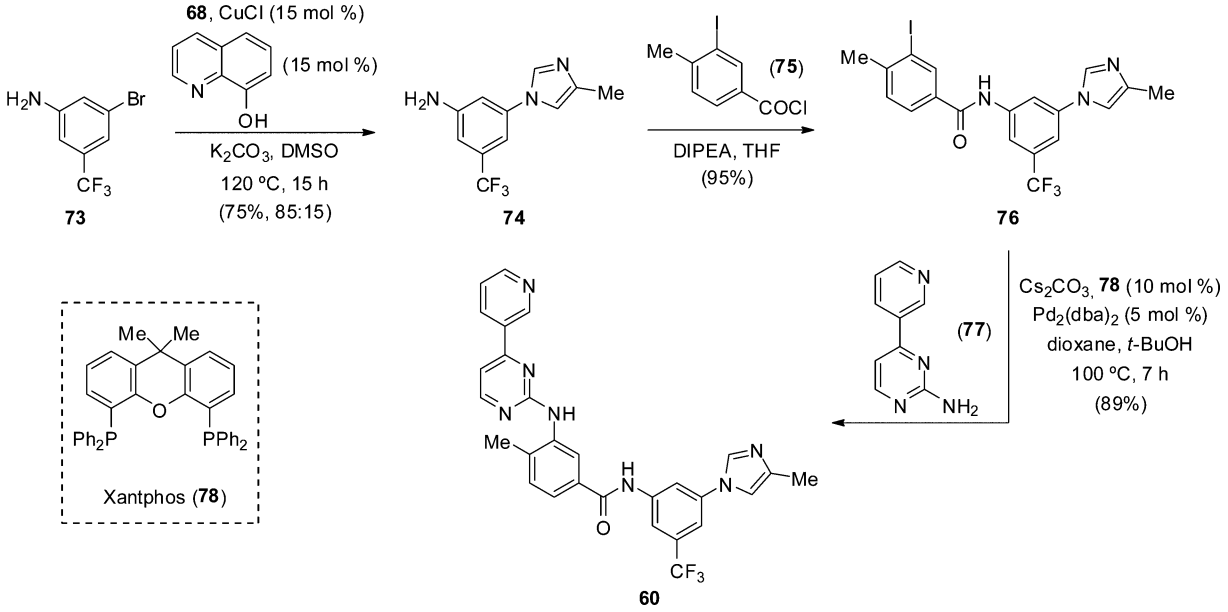
Scheme 10. Novartis Preparation of Nilotinib (60)



Scheme 11. Cu-Mediated Improved Route to Nilotinib (60)



lines that harbor ALK translocations resulting in expression of oncogenic ALK fusion proteins.

Crizotinib belongs to a second generation of selective c-Met inhibitors. Its structure was derived from that of the first selective and potent c-Met inhibitor to be identified, PHA-665752 (**93**).[70] A cocrystal structure of PHA-665752, bound to the c-Met kinase domain, revealed a novel ATP binding pocket, which enabled rational design of inhibitors that bind to this active pocket with improved drug-like properties. In the 2-amino-5-aryl-3-benzyloxypyridine series, the oxindole substituent of PHA-665752 was replaced by a 2-aminopyridine moiety as the hinge binder. In addition, the benzylsulfonyl group of PHA-665752 occupies the hydrophobic cavity of the kinase domain. This benzylsulfonyl group was substituted for a 3-benzyloxy group that occupied the cavity from a more direct angle, resulting in compounds with a lower molecular weight and reduced conformational constraint. The lead compound from the 2-amino-5-aryl-3-benzyloxypyridine series was designated PHA-806114. Further optimization

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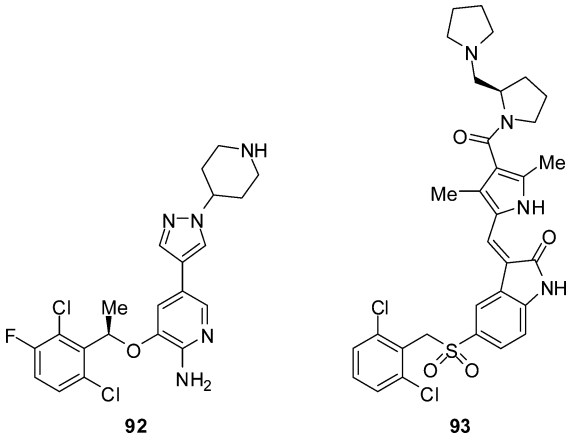
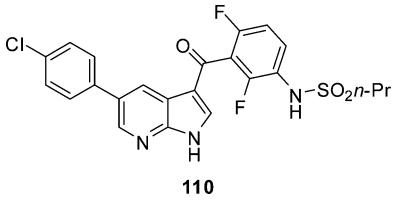


92 93

Figure 10. Structures of crizotinib (**92**) and PHA-665752 (**93**).



110

Figure 11. Structure of vemurafenib (**110**).

to improve the potency of c-Met inhibition as well as ADME properties led to discovery of the 2-amino-3-benzyloxy-5-(pyrazol-4-yl)pyridine series. SAR studies of various substitutions on the pyrazole ring led to identification of crizotinib.

The SAR of crizotinib has been investigated using an analysis of the kinase selectivity of derivatives of crizotinib.[71] This study demonstrated that the 2-aminopyridine moiety of crizotinib binds to the hinge region of c-Met in a bidentate manner; the primary amine forms hydrogen bonds with the carbonyl oxygen of Pro1158 and the pyridine nitrogen with the amide NH of Met1160. The (*R*)-methyl group occupied a hydrophobic pocket. In addition, the 2,6-dichloro-3-fluorophenyl ring is $\pi-\pi$ stacked against the Tyr1230 and forms a hydrogen-bond interaction with Met1211. The investigators suggested that these hydrophobic interactions may have a role in selective inhibition of c-Met because the Tyr1230 and Met1211 residues are conserved in only three (c-Met, Axl, and Mer) of the 491 kinases analyzed.

The initial medicinal chemistry route to crizotinib is shown in Scheme 14.[72] Mitsunobu reaction of **94** with chiral alcohol **95**[73] led to **96** in high yield, and the nitro group was subsequently reduced to afford aminopyridine **97**. Regioselective bromination of the pyridine ring then led to compound **98**. After protection of the amino group, reaction of bromide **99** with bis(pinacolato)-diboron (**100**) furnished boronate **101**. Removal of the di-*N*-Boc protecting group was followed by Suzuki coupling of **102** with bromopyrazole **103** to give compound **104**, which upon deprotection furnished crizotinib (**92**) in good yield.

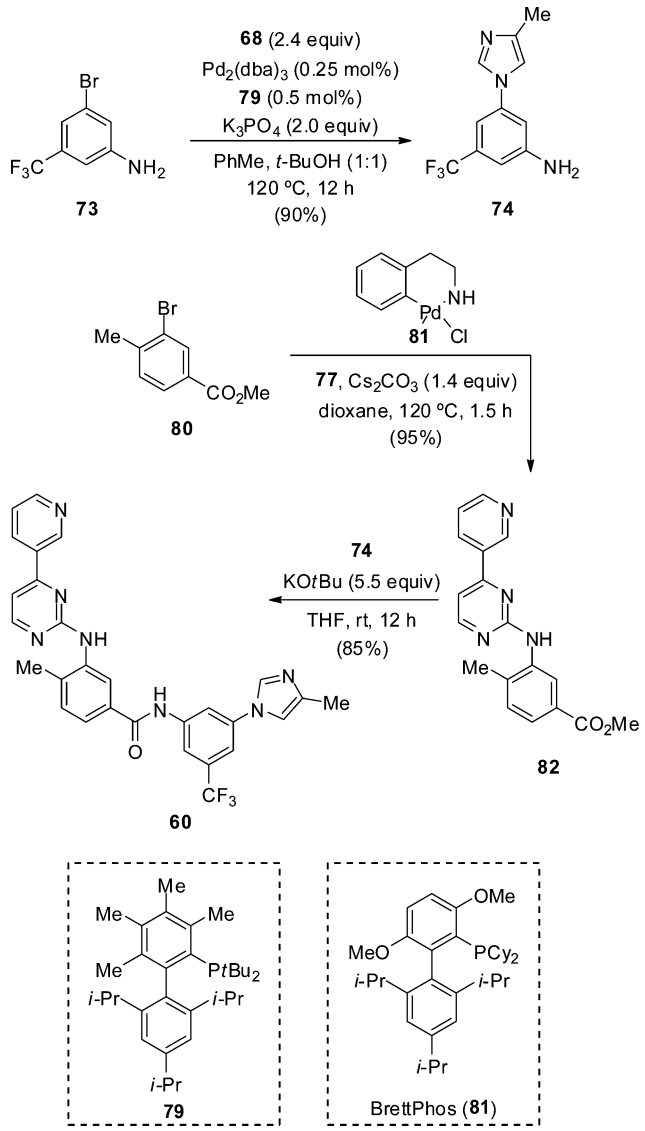
Pfizer researchers have also described a manufacturing route that enabled them to obtain crizotinib on multikilogram scale.[74] In this case, the key Suzuki coupling was carried out using bromide **98** and boronate **109**, the latter prepared in turn from hydroxypiperidine **105** and iodopirazole **107** (Scheme 15).

2.9. Vemurafenib (Zelboraf)

Roche and Plexxikon codeveloped and launched Vemurafenib (PLX-4032) (**110**), which is an orally available ^{V600E}BRAF-selective small-molecule inhibitor for treatment of late-stage melanoma, thyroid tumor, cancer, solid tumor, and colorectal tumor (Figure 11).[75] BRAF is a key protein kinase component of the RAS-RAF pathway. Around 8% of all solid human tumors are thought to harbor mutated BRAF, and over 30 mutations in the BRAF gene have been associated with human cancers, including 50% of melanomas, 30−70% of thyroid cancers, 30% of serous low-grade ovarian cancers, and 10% of colorectal cancers.[76] Vemurafenib received FDA approval for treatment of late-stage melanoma on August 17, 2011. In March 2012, vemurafenib was launched in the United Kingdom. The European Commission approved vemurafenib as a monotherapy for treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, the most aggressive form of skin cancer. In August 2011, Japanese licensee Chugai planned to conduct a phase I trial in Japan for BRAF V600E mutation-positive metastatic melanoma in 2012. Current sales of the marketed drug (Zelboraf) reached $ 35.1 million in 2011.

It was reported that the sulfonamide moiety of vemurafenib makes crucial hydrogen-bond interactions with the DFG loop of BRAF kinase.[77] The sulfonamide NH appeared to be a key pharmacophore for potent in vitro activity in this series. The

Scheme 12. Pd-Catalyzed Synthesis of Nilotinib (60)



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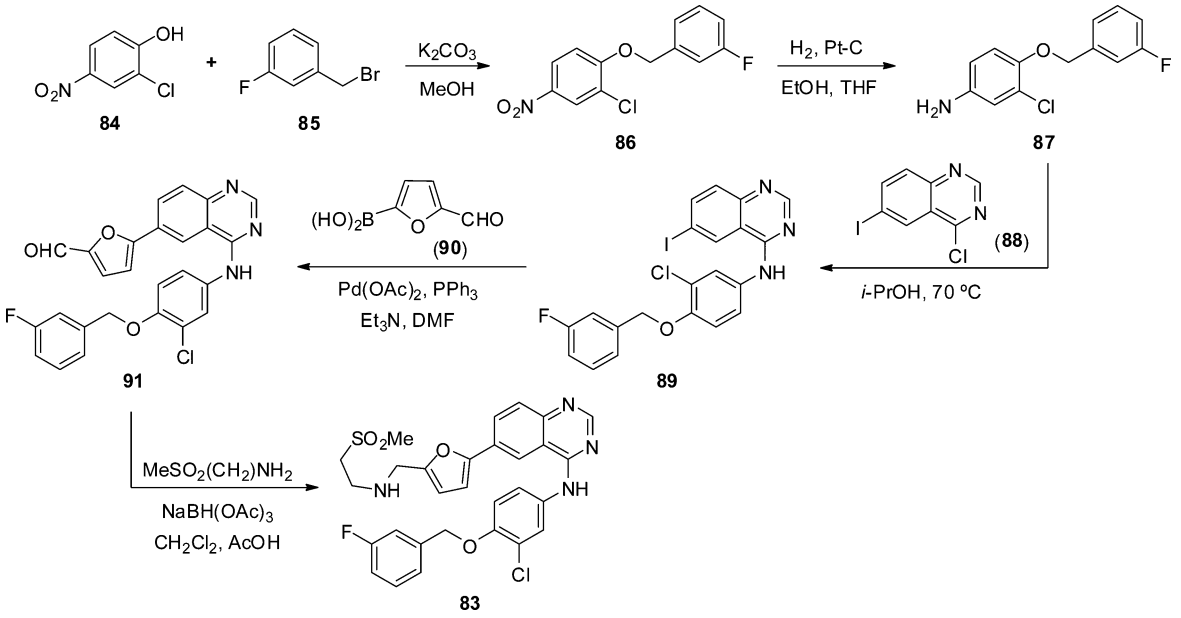
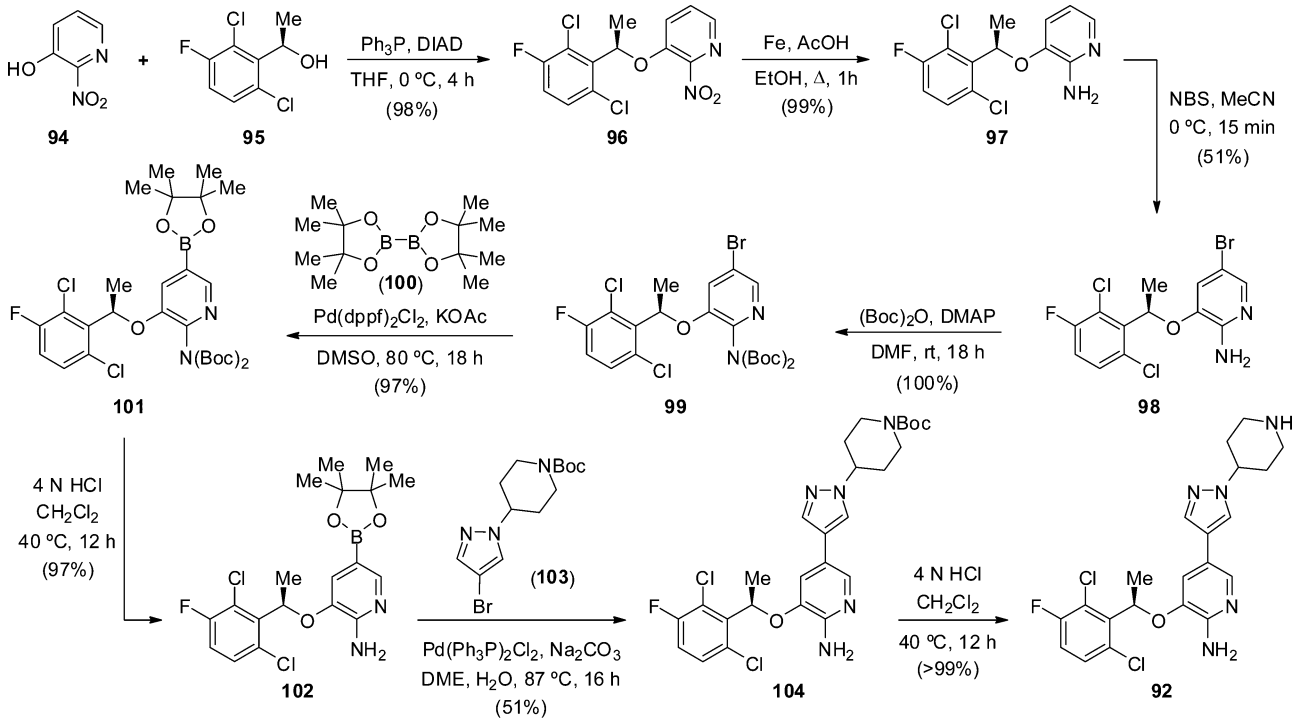
Scheme 13. GSK Synthetic Route to Lapatinib (83)



Scheme 14. Medicinal Chemistry Route to Crizotinib (92)



arylsulfonamide nitrogen exists as a deprotonated species, making hydrogen-bonding interactions with the backbone NH of Asp 594. The arylsulfonamide group forms two hydrogen-bonding interactions with Lys 483 and Phe 595.[78] Addition of a fluorine atom in either the 2 or the 3 position of the aryl ring was found to improve both the BRAF enzyme activity and the potency in the SKMEL proliferation assay. Fluorine substitution in the 4 position of the ring, or a larger substituent, such as a chlorine, led to a moderate reduction in potency in both enzyme and cellular assays. The difluorinated analogs mirrored the high potencies observed for the monofluorinated analogs.

Vemurafenib was synthesized from 5-bromo-7-azaindole (**111**) and 2,4-difluoroaniline (**114**) as described in Scheme 16.[75b] Suzuki coupling between azaindole **111** and 4-(chlorophenyl)boronic acid (**112**) gave compound **113**, whereas aniline **114** was transformed into **115** by reaction with propane-1-sulfonyl chloride and then formylated with *N*-formylmorpholine to produce aldehyde **116**. Aldol-like coupling of fragments **113** and **116** afforded alcohol **117**, which upon DDQ-mediated oxidation furnished the target molecule vemurafenib (**110**). Most notably, this method has been recently adapted using microwave irradiation on each synthetic step in order to reduce

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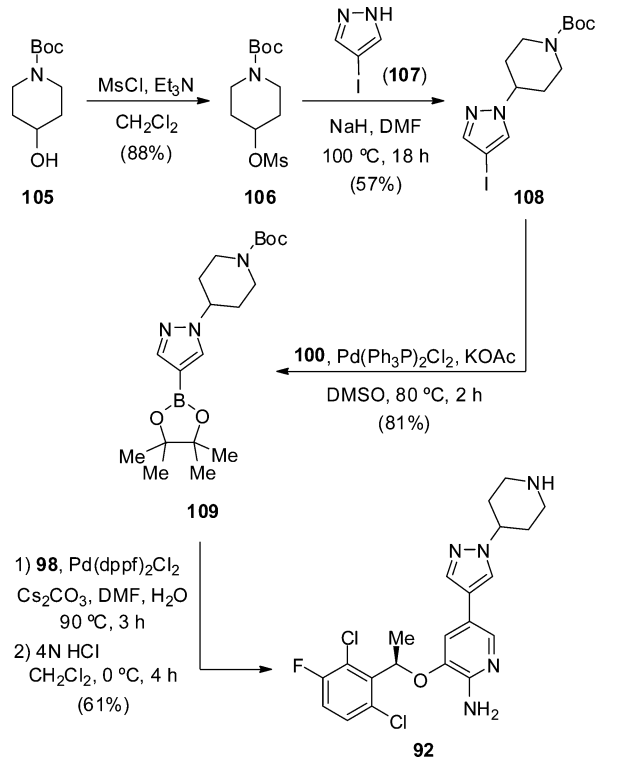
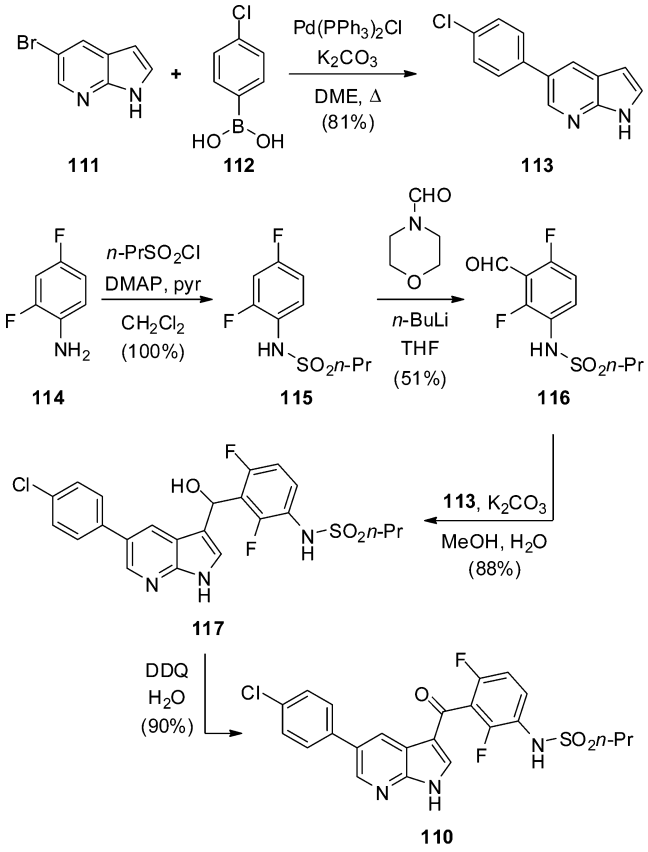
Scheme 15. Pfizer Manufacturing Route to Crizotinib (92)



Scheme 16. Synthetic Route to Vemurafenib (110)



considerably the reaction times while maintaining the chemical yields.[79]

2.10. Vandetanib (Caprelsa)

Vandetanib (**118**), also known as ZD6474, is an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR) (Figure 12).[80] It is an

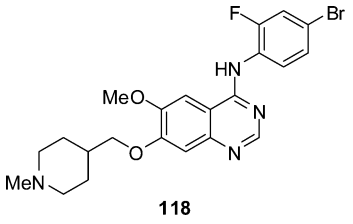


Figure 12. Structure of vandetanib (**118**).

oral tyrosine kinase inhibitor for thyroid tumor, nonsmall-cell lung cancer, and transitional cell carcinoma, being developed and launched by AstraZeneca.[81] Vandetanib is indicated for treatment of symptomatic or progressive medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.[82] In April 2011, vandetanib was launched in the United States for unresectable MTC, under the trade name Caprelsa. Sales for vandetanib reported by AstraZeneca for 2011 were $8.0 million.

Structurally, vandetanib contains a 4-bromo-2-fluoroaniline moiety linked to the quinazoline pharmacophore.[83] Substitution on the aniline moiety was investigated and clearly indicated that small lipophilic substituents such as halogens or methyl were preferred at the C-4′ position. On the other hand, small substituents such as hydrogen and fluorine were preferred at the C-2′ position. The 3-bromo-4-fluorophenylamino residue was shown to penetrate deeply in the back of the ATP-binding site, making predominantly hydrophobic interactions with the protein. It was shown also that increasing this type of hydrophobic interaction might increase the desired activity. In vitro studies revealed that vandetanib inhibits the activity of tyrosine kinases including members of the epidermal growth factor receptor (EGFR) family, vascular endothelial cell growth factor (VEGF) receptors, rearranged during transfection (RET) protein, protein tyrosine kinase 6 (BRK), TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases.

The synthetic route to vandetanib is illustrated in Scheme 17.[84] The *N*-Boc-protected 4-piperidine tosylate **119** was coupled with the *N*-3-pivaloyloxymethyl (POM)-protected quinazolone **120** at the C-7 position to give compound **121**. Subsequent selective deprotection of the Boc group led to free piperidine **122**, and *N*-methylation using formaldehyde under reductive conditions produced **123**. The quinazolone moiety of **123** was then unmasked using ammonia in methanol to afford **124**, and further chlorination using thionyl choride produced **125**. Finally, reaction of **125** with 4-bromo-2-fluoroaniline (**126**) under hydrochloric acid catalysis in isopropanol led to vandetanib (**118**).

3. DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

3.1. Escitalopram (Lexapro)

Escitalopram (**127**) is a highly selective serotonin reuptake inhibitor (SSRI) that is approved by the FDA for treatment of major depression and generalized anxiety disorder. Its therapeutic usefulness is expanding to other diseases such as

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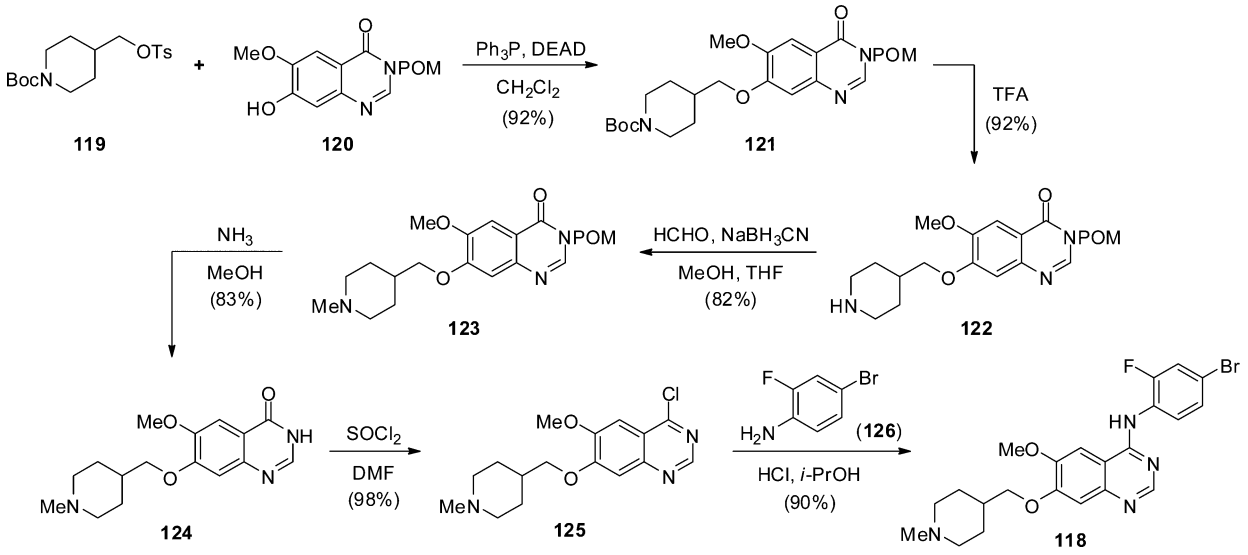
Scheme 17. Synthetic Route to Vandetanib (118)



social anxiety disorder, panic disorder, and obsessive-compulsive disorder. Escitalopram is the (*S*)-enantiomer of the earlier racemic drug citalopram which has similar pharmacology. The (*S*)-enantiomer (escitalopram) has an improved clinical effect as compared to the racemic mixture (citalopram).[85] The serotonin reuptake inhibitors exercise their effect by selectively inhibiting of serotonin transporter that facilitates reuptake of the neurotransmitter serotonin from the extracellular space into neurons. Therefore, serotonin transporter is an important drug target for treatment of psychiatric diseases such as depression and anxiety.

Escitalopram has an *N*,*N*-dimethyl propylamine group, a primary aromatic moiety with electronegative but not hydrogen-bond-donating cyano group, and a secondary aromatic ring with a fluorine substituent (Figure 13).[86] Systematic structure–activity relationship studies have shown that the aromatic CN substituent is important for high serotonin transporter inhibitory activity, while the aromatic fluorine atom and the amino substitution are less important factors for serotonin transporter inhibition. Further studies demonstrated that (*S*)-enantiomers of escitalopram analogues are also more selective and potent inhibitors of serotonin transporter as compared to (*R*)-enantiomers. Meanwhile, escitalopram remains the most potent and selective compound among phenyl-substituted phtalanes as an inhibitor of serotonin transporter.[87]

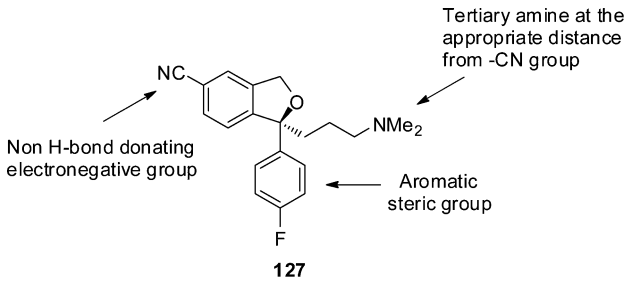


Figure 13. Structure of escitalopram (**127**).

Several syntheses of escitalopram (*S*)-**127** using either resolution of the diols (±)-**128** and diol monoesters (±)-**129** followed by ring-closure or resolution of cyclic ethers (±)-**127** have been published (Scheme 18). Resolution procedures included (a) fractional crystallization of diastereomeric esters of diols (±)-**128**,[88] (b) resolution of diols (±)-**128** by diastereomeric salt formation,[89] (c) resolution of cyclic ethers (±)-**127** by diastereomeric salt formation,[90] and (d) enzymatic resolution of diols (±)-**128** and diol monoesters (±)-**129**.[91]

Enantioselective synthesis of escitalopram was carried out using diaryl ketone **130** as starting material (Scheme 19).[92] This diaryl ketone was initially complexed with methyl boronic acid and *N*-methylpseudoephedrine (**131**). Subsequent Grignard addition of [(3-(dimethylamino)propyl]magnesium chloride to the complexed ketone **132** occurred with high selectivity leading to the tertiary alcohol (*S*)-**128** in 77% yield and 92% ee. The ee was further enhanced to 99.3% by resolution with (+)-di-*p*-toluoyl-D-tartaric acid [(+)-DPTTA]. Finally, the ring-closure reaction by treatment of (*S*)-**128** with *p*-toluenesulfonyl chloride and triethylamine gave target (*S*)-**127**.

Quite recently, a lithiation–borylation methodology for synthesis of enantioenriched tertiary alcohols has been used successfully in asymmetric synthesis of escitalopram.[93] Boc protection of the commercially available propargylamine **133** and zinc-mediated addition of the alkyne **134** to 4-fluorobenzaldehyde (**135**) using (+)-*N*-methylephedrine [(+)-NME)] as a chiral ligand gave the alcohol (*R*)-**136** with an enantiomeric ratio of 98:2 (Scheme 20). Hydrogenation using PtO_2 and carbamoylation of (*S*)-**137** led to the carbamate (*S*)-**138** in 74% yield over four steps with 98:2 enantiomeric ratio. Deprotonation of carbamate (*S*)-**138** with *s*-BuLi followed by addition of boronic ester **139** and further addition of $MgBr_2$/MeOH gave the tertiary alcohol (*S*)-**140** in 42% isolated yield and excellent 93:7 enantiomeric ratio after oxidation. The starting carbamate (*S*)-**138** was also isolated in 27% yield. The lithiation–borylation reaction was found to tolerate nitrile, benzylic alcohol, and *N*-Boc functionalities. Addition of $MgBr_2$/MeOH not only prevented racemization and recombination of the lithiated carbamate generated by the reverse process but also promoted the 1,2-metalate rearrangement. In the absence of $MgBr_2$ the tertiary alcohol was obtained in low yield (21%). The tertiary alcohol was converted to escitalopram (*S*)-**127** in three further steps. Intramolecular etherification of (*S*)-**140** mediated by $Pb(OAc)_4$ and I_2 gave cyclic ether (*S*)-**141** without racemization. Synthesis was completed by Boc deprotection and reductive *N*-methylation to give escitalopram.

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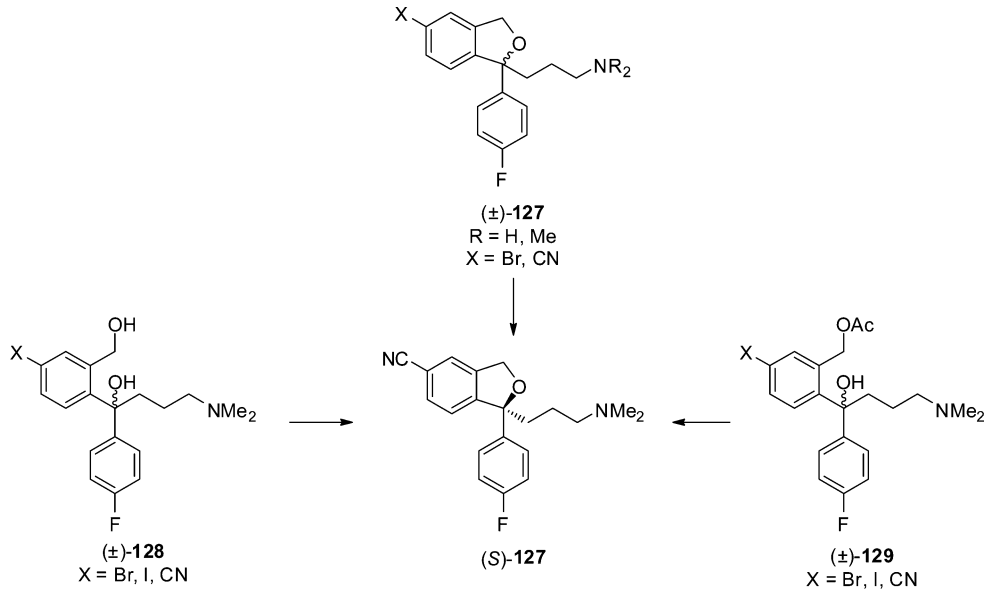
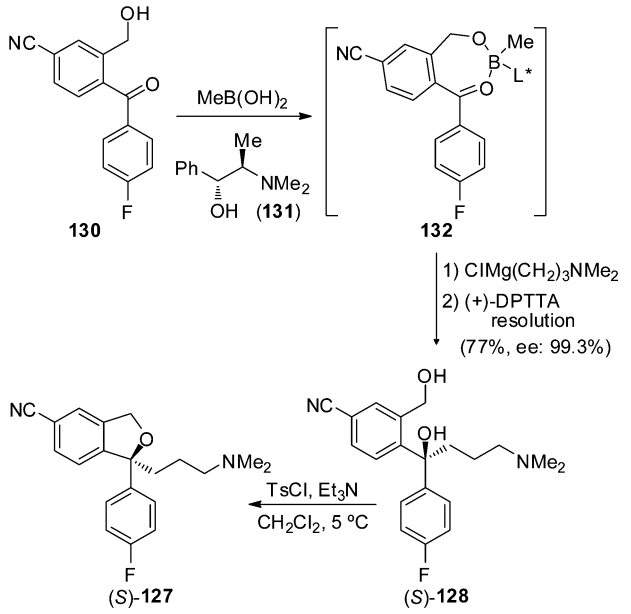
Scheme 18. Resolution Procedures To Access Escitalopram (127)



Scheme 19. *N*-Methylpseudoephedrine-Mediated Asymmetric Synthesis of Escitalopram (127)



3.2. Aprepitant (Emend)

Aprepitant (**142**) is a potent nonpeptide neurokinin-1 (NK_1) receptor antagonist approved by the FDA in 2003 for prevention of chemotherapy-induced nausea and vomiting under the trade name Emend. In 2008 the FDA approved a water-soluble phosphoryl prodrug for intravenous use called fosaprepitant, which is sold under the trade name Emend Injection in the United States and as Ivemend in some other countries.[94] Aprepitant is classified as an NK_1 antagonist because it blocks signals given off by NK_1 receptors. These receptors have a dominant ligand known as Substance P (SP). SP along with its cognate NK_1 receptor is located in the central nervous system and the peripheral nervous system acting as both neurotransmitter and neuromodulator. This neuropeptide is implicated in a variety of biological functions in the central nervous system such as regulation of affective behavior and mediation of stress responses including anxiety and depression. In addition, SP plays a critical role in pain transmission and emetic reflex.[95] It should be noted that aprepitant and some other potent and selective NK_1 receptor antagonists (**143**−**146**) contain a 3,5-bis-(trifluoromethyl)phenyl group improving central nervous system penetration (Figure 14). On the other hand, installation of fluorine atom at the para position of the phenyl ring serves to block the most likely point for oxidative metabolism as well as minimize oxidation at other positions of the phenyl ring.[96]

Several synthetic approaches to aprepitant containing the unusual cis-substituted 2-alkoxy-3-arylmorpholine acetal core linked to 3-oxo-1,2,4-triazole moiety have been described. Original preparation of aprepitant was accomplished using reduction/acylation of morpholinone **147** as a key step in the synthetic sequence (Scheme 21).[97] Morpholinone **147** was first treated with L-Selectride in THF at −78 °C, and the resulting intermediate was reacted at low temperature with 3,5-bis-(trifluoromethyl)benzoyl chloride to afford acyl acetal **148**. Compound **148** was reacted with dimethyl titanocene to provide the stable vinyl ether intermediate **149**.[98] Then concomitant reduction of the double bond and the *N*-benzyl substituent by hydrogenation of **149** in the presence of palladium on carbon catalyst resulted in formation of **150** which had the required *α*-(*R*)-methyl stereochemistry. Elaboration of **150** to aprepitant was carried out by initial alkylation of **150** in the presence of a base with hydrazone chloride **151** to give the intermediate **152**. Thermolysis of **152** provided aprepitant (**142**) in 71% yield from **150**.

The crucial steps of another synthesis of aprepitant involved a highly stereoselective Lewis-acid-catalyzed trans acetalization of trichloroacetimidate **155** with chiral alcohol **156** followed by inversion of the adjacent chiral center on the morpholine ring (Scheme 22).[99]Thus, morpholinone **153** was reduced with DIBAL in a mixture of toluene and THF at −20 °C to the lactol **154** which was directly activated by treatment with trichloroacetonitrile and K_2CO_3 affording the trichloroacetimidate **155**. Treatment of **155** and the chiral alcohol **156** with a catalytic amount of $BF_3{\cdot}Et_2O$ in toluene/THF at a temperature between −30 and −20 °C afforded the acetalization product **157**. In these reaction conditions a 96:4 mixture of the trans and cis

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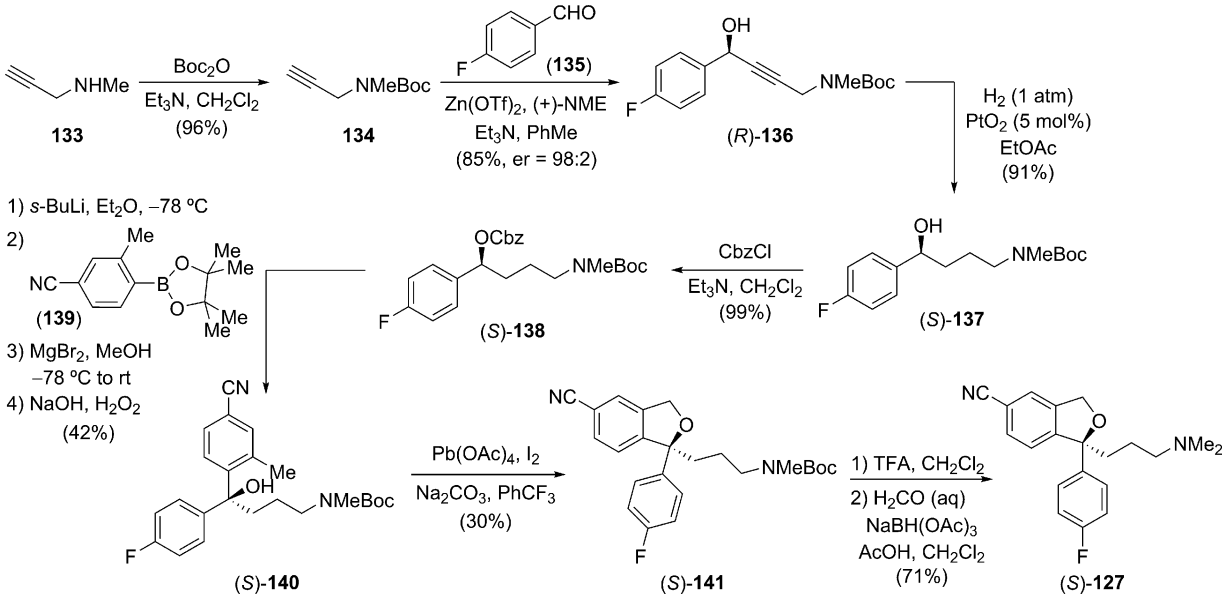
Scheme 20. Enantioselective Alkynilation Route To Access Escitalopram (127)



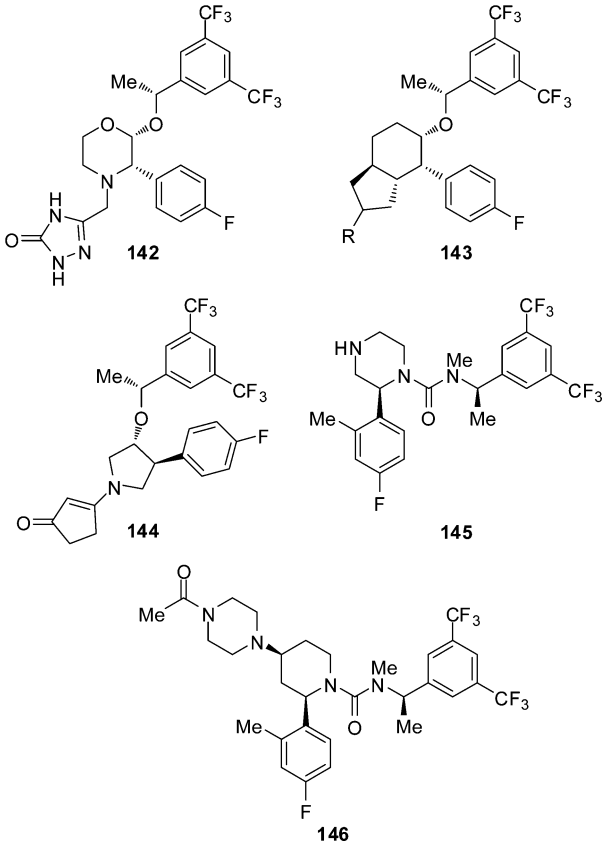
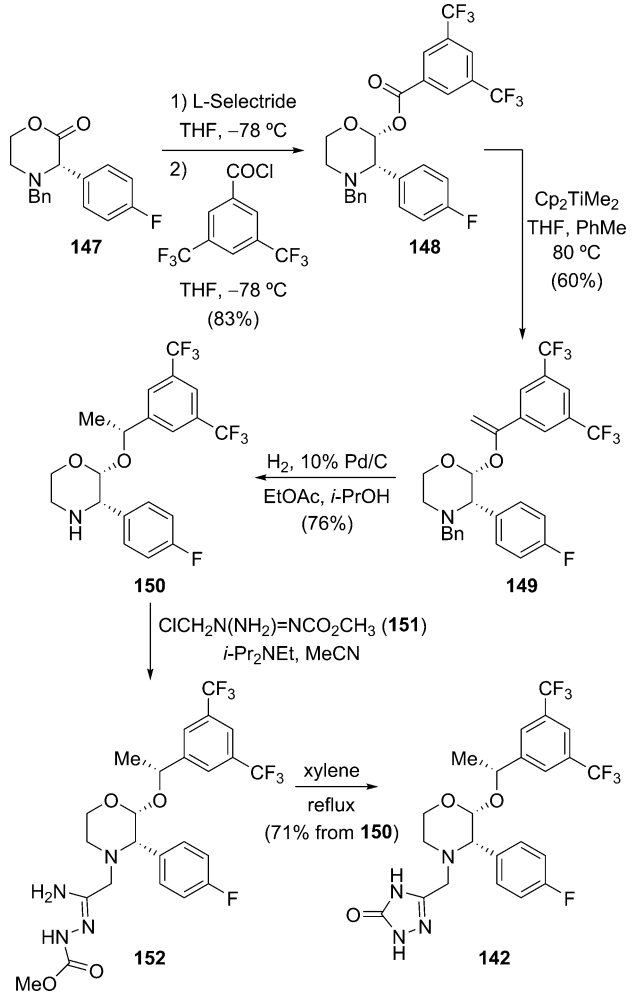


Figure 14. Chemical structures of aprepitant (**142**) and other selective NK_1 receptor antagonists **143**–**146**.

Scheme 21. Original Preparation of Aprepitant (142)



diastereomers was obtained. The desired diastereomer **157** was isolated with high purity in 85–87% yield from morpholinone **153** after crystallization from ethanol/water. The chiral auxiliary on **157** was easily cleaved by Pd/C-catalyzed hydrogenolysis in the presence of a strong acid such as *p*-TsOH yielding the *trans*-amine **158**.[100] Compound **158** was converted to the imine **159** by successive treatment with NCS and DBU in a mixture of toluene/DMF. The crude solution of **159** was used directly for hydrogenation to set the critical cis stereochemistry in amine **150**. Intermediate **150** was converted into aprepitant by a simple alkylation with triazolinonyl chloride **160** using K_2CO_3 or *i*-

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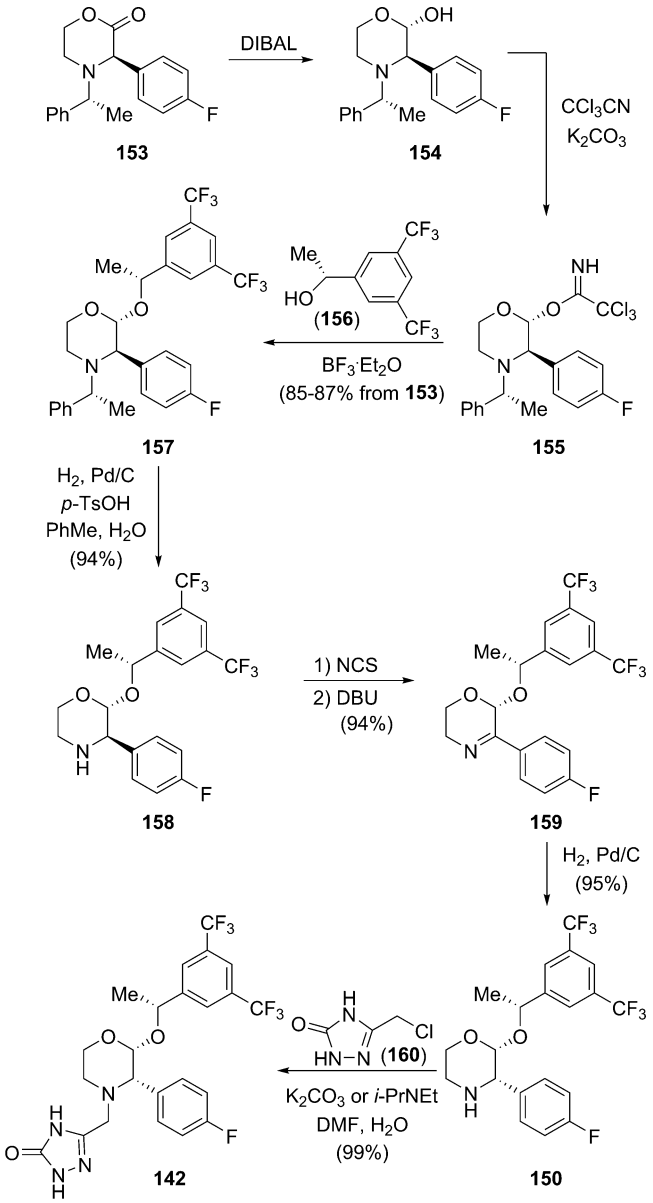
Scheme 22. Transacetylation Route to Aprepitant (142)



Pr_2NEt as a base, and the final product **142** was isolated in 99% yield.

The key step of an alternative practical approach to aprepitant was the stereoselective convertion of lactam acetal **163** to α-arylamine **150** via addition of a Grignard reagent followed by hydrogenation (Scheme 23).[101] The (*R*)-α-methyl bis-(trifluoromethyl)benzyl ether group was installed by nucleophilic displacement on trifluoroacetate **162** with the chiral alcohol **156**. Thus, treatment of lactam **161**[102] with trifluoroacetic anhydride gave trifluoroacetate **162**, which was reacted in situ with chiral alcohol **156** in the presence of $BF_3{\cdot}OEt_2$ to give, after workup, a 55:45 mixture of the acetals **163** and **164** in 95–98% overall yield. To obtain the desired diastereomer the crude mixture was dissolved in heptane and 3,7-dimethyl-3-octanol was added. After cooling to −10 and −5 °C and seeding with **163**, the potassium salt of 3,7-dimethyl-3-octanol was added to initiate the crystallization-induced epimerization of **164** to **163**. After 5 h **163** was isolated in 83–85% yield and >99% ee, thus overcoming the limitation of a nonselective reaction. Under an optimized condition, the lactam **163** was reacted with 4-fluorophenylmagnesium bromide in THF at ambient temperature followed by immediate hydrogenation of the reaction mixture in the presence of 5% Pd/C to give the addition product **150**, which was isolated as its hydrochloride salt in 91% yield, indicating that both Grignard addition and reduction occurred quantitatively. Conversion of morpholine **150** to aprepitant was carried out following the described above process.

3.3. Paliperidone (Invega) and Iloperidone (Fanapt, Fanapta, Zomaril)

Atypical antipsychotics are a class of drugs widely used in recent decades for treatment of schizophrenia and related CNS diseases by decreasing the dopamine levels in the brain.[103] Although they usually target numerous dopamine and serotonine receptors in order to bring about their therapeutical action, they proved to be superior to the so-called "typical" antipsychotics in reducing their associated side effects (extrapyramidal symptoms). Among these structurally diverse compounds, much attention has been addressed to the group that share a 3-(piperidin-4-yl)benzo[d]-isoxazole scaffold and more specifically to those compounds comprising a 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole moiety.[104] The first compound of this family eventually reaching the market in the 1990s was risperidone (trade name Risperdal, Janssen-Cilag) (**165**), becoming one of the most successful drugs for treating schizophrenia and bipolar disorder (Figure 15). Subsequent work at Janssen produced paliperidone or 9-hydroxyrisperidone (**166**), a major and active metabolite of risperidone and regarded as an improved drug not only because of its reduced side effects but also because of its better pharmacokinetic properties. The therapeutic efficacy of paliperidone in schizophrenia is mediated through a combination of serotonin Type 2 (5-HT_2) and dopamine Type 2 (D_2) receptor antagonism. In vitro receptor binding studies showed that paliperidone has high affinity for 5-HT_2, D_2, α_1, and α_2 adrenergic receptors.[105] However, the specific mechanism of action of paliperidone is unknown. Paliperidone is marketed in tablets for oral administration under the trade name Invega and was approved by the FDA for treatment of schizophrenia in 2006. Moreover, the longer acting injectable formulation of paliperidone palmitoyl ester was approved by the FDA in 2009 (marketed as Invega Sustenna) and in Europe in 2011 (marketed as Xeplion).

In addition, iloperidone (**167**) (trade names Fanapt, Fanapta, and Zomaril) is a close analogue of risperidone and paliperidone developed by Vanda Pharmaceuticals and approved by the FDA in 2009 for treatment of acute schizophrenia in adults. Like other atypical antipsychotics iloperidone shows significantly greater affinity for serotonin type 2A (5-HT_{2A}) than dopamine type 2 (D_2) receptors.[106] This ratio of affinities has been suggested to account for its enhanced efficiency with less extrapyramidal symptoms than D_2 receptor antagonist antipsychotics. In addition to its affinities for serotonin and dopamine receptors, iloperidone has moderate affinity for α_1- and α_{2C}-adrenoceptors. A blockade of α_{2C}-adrenoceptors might translate into antidepressant and anxiolytic activity.

The common structural feature of both paliperidone and iloperidone, namely, the fluorinated benzoisoxazole fragment, was first prepared by formylation of isonipecotic acid (**168**) followed by conversion to the acyl chloride **169** in 76% yield for the two stages (Scheme 24).[104] Friedel–Crafts acylation of 1,3-difluorobenzene with **169** without solvent provided ketone **170** in 32% yield. Synthesis of the benzoisoxazole system was

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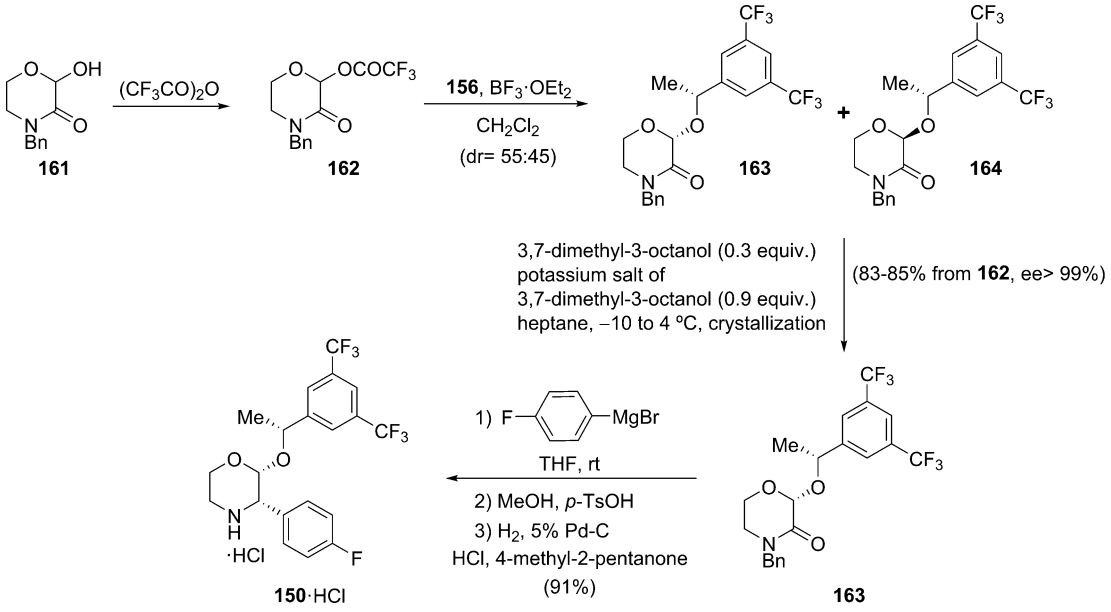
Scheme 23. Crystallyzation-Induced Epimerization Route to Aprepitant (142)



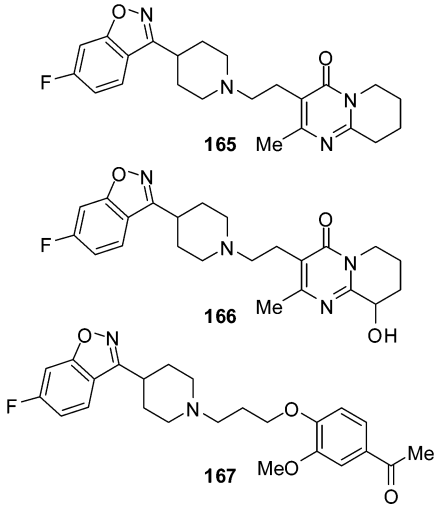
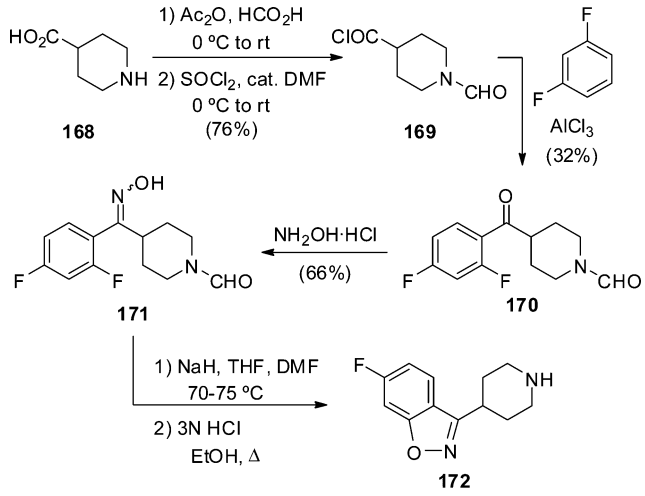


Figure 15. Structures of risperidone (**165**), paliperidone (**166**), and iloperidone (**167**).

Scheme 24. Synthesis of Common Structural Motif of Paliperidone (166) and Iloperidone (167)



accomplished by refluxing the ketone **170** with hydroxylamine under standard conditions to give the corresponding oxime **171**, which upon cyclization with sodium hydride and cleavage of the *N*-formyl group afforded benzoisoxazole **172**.

Despite the presence of a stereogenic center, paliperidone is marketed as a racemic mixture. It was first synthesized using 2-aminopyridine derivatives **173** and 2-acetylbutyrolactone (**174**) as starting compounds (Scheme 25).[107] Condensation of **173** with lactone **174** catalyzed by *p*-toluenesulfonic acid with azeotropic removal of water gave pyridopyrimidinones **175**. The hydroxy group was substituted with a good leaving group by treatment of **175** with chlorinating agents in organic solvents affording intermediates **176**. Compounds **176** so obtained were further transformed by hydrogenation of the pyridine ring (R = H) or simultaneous hydrogenation and hydrogenolysis (R = benzyl) over palladium on carbon catalyst to pyrimidinone derivative **177**, which was then coupled with benzoisoxazole **172** in the presence of organic or inorganic bases to provide paliperidone (**166**) as the final product. The reaction can be carried out in the presence of catalysts such as potassium iodide.

An alternative approach to paliperidone involved conversion of pyrimidinone derivative **178** with isoamyl nitrite (**179**) to produce oxime **180** as a mixture of syn and anti stereoisomers (Scheme 26).[108] The oximation reaction proceeded under heating to 85−90 °C, providing oxime **180** of high purity in high yield. The oxime **180** underwent alkylation reaction with benzoisoxazole **172** in the presence of base to provide **181**. In the next step, reductive deoximation of **181** using a stoichiometric amount of titanium trichloride led to the corresponding carbonyl compound which was converted in situ into the desired final product **166**. The deoximation/reduction process proceeded in water in the presence of $TiCl_3$.

A short and effective synthesis of paliperidone has been achieved by oxidation of risperidone with air under basic conditions.[109] Careful optimization of the hydroxylation of **165** in the presence of $P(OMe)_3$ as reducing agent led directly to paliperidone (**166**) in 70% yield after chromatographic

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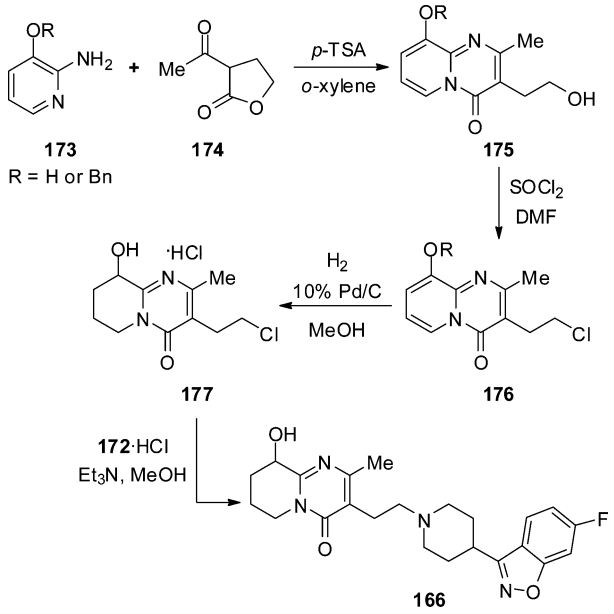
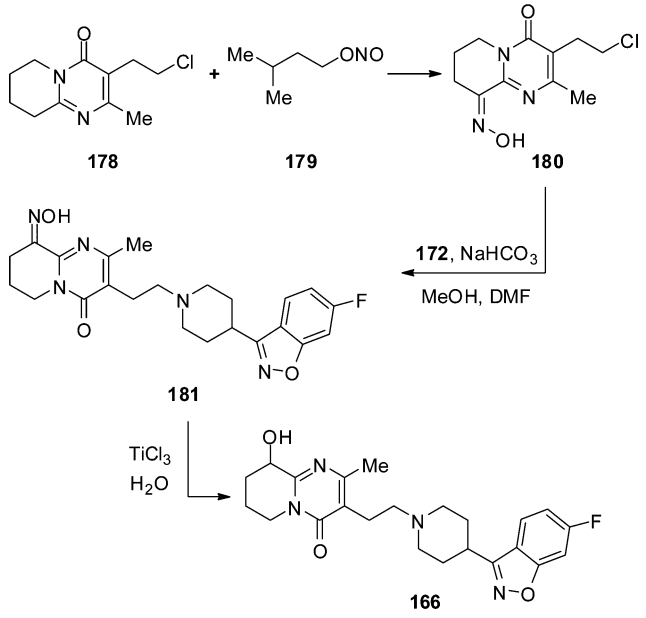
Scheme 25. Initial Synthesis of Paliperidone (166)



Scheme 26. Alternative Approach to Paliperidone (166)



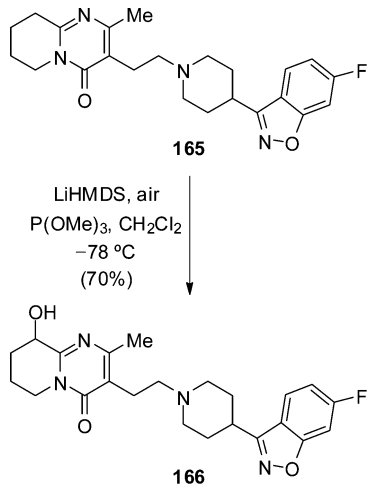
purification (Scheme 27). Chemically pure paliperidone can also be obtained with only a slight decrease in yield by crystallization of the crude product without the need for chromatography.

Preparation of iloperidone was carried out by alkylation of benzoisoxazole **172** with alkyl aryl ether **182** in the presence of K_2CO_3 in DMF at 70−90 °C to give iloperidone (**167**) in 58% yield (Scheme 28).[104,110] Alternatively, alkylation of **172** with 1-chloro-3-bromopropane in DMF in the presence of potassium carbonate provided the chloride **183**, and subsequent reaction with 4-hydroxy-3-methoxy acetophenone (**184**) under basic conditions gave iloperidone in slightly better overall yield.[111]

3.4. Rufinamide (Banzel, Inovelon)

Rufinamide (**185**) is an anticonvulsant medication approved by the FDA in 2008 as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, a severe form of epilepsy. Rufinamide was initially discovered by Novartis Pharmaceuticals

Scheme 27. Synthesis of Paliperidone (166) from Risperidone (165)



and is currently manufactured by Eisai Co., Japan, and marketed under the brand name Banzel (Figure 16). It is also marketed in the European Union under the brand name Inovelon.[112] The mechanism of action of rufinamide is considered to be modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Since it does not exhibit measurable binding to monoamine, acetylcholine, histamine, glycine, AMPA/kainate, NMDA, or GABA receptors, these receptor-mediated pathways are not anticipated to be involved in the exertion of rufinamide's effects.[113]

Rufinamide has an acetamide moiety along with a triazole pharmacophore and is structurally different from other antiepileptic drugs. In terms of interaction at the binding site, the title compound has structural features such as an aromatic hydrophobic domain, a nitrogen atom as an electron donor atom, a carbonyl group as hydrogen-bond acceptor, and a N−H moiety as hydrogen-bond donor. Anticonvulsant screening of substituted *N*-benzyl-1,2,3-triazole-4-formamide derivatives has shown that compounds containing chlorine atoms on the phenyl ring were less potent, while introducing one or two fluorine atoms on the benzyl system increased its activity. Furthermore, substituents on the nitrogen atom of the carboxamide decreased the anticonvulsant activity.[114]

All reported synthetic approaches to rufinamide began with 2,6-difluorobenzyl azide (**186**), which could be prepared by reacting the corresponding commercially available chloride with sodium azide (Scheme 29). The various syntheses of rufinamide differed by the dipolarophiles that underwent cycloaddition with 2,6-difluorobenzyl azide to form the triazole ring. The appropriate dipolarophiles were propiolic acid derivatives,[114,115] 2-chloroacrylonitrile,[116] methyl 3-methoxyacrylate,[117] methyl 2-(dimethylamino)acrylate,[118] alkyl 2-bromoacrylates,[119] and propargyl alcohol.[120] In the case of the carboxylic acid derivative, the corresponding intermediate was treated with thionyl chloride followed by concentrated aqueous ammonium hydroxide, providing rufinamide. Conversion of the nitrile intermediate to rufinamide has been accomplished by heating with sodium hydroxide in toluene/water. Ammonolysis of alkyl esters to the corresponding amide smoothly proceeded in methanolic ammonia. Methods based on cycloaddition of 2,6-difluorobenzyl azide **186** with 2-chloroacrylonitrile (**187**), methyl 3-methoxyacrylate (**189**), and methyl 2-(dimethylamino)acrylate (**190**)

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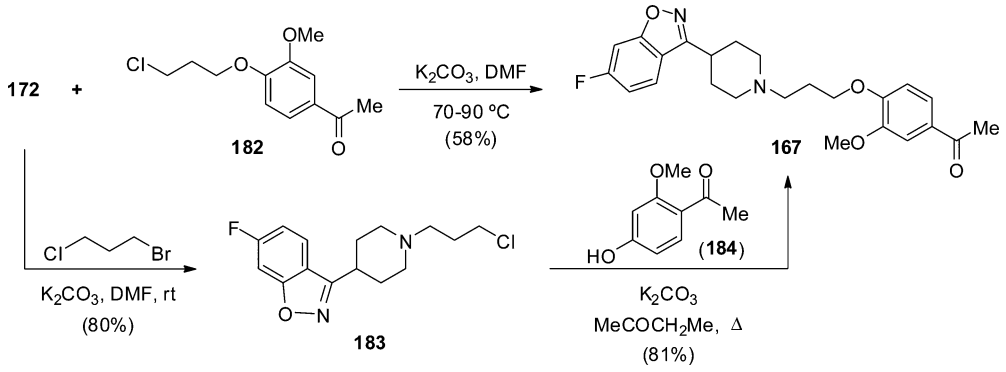
Scheme 28. Synthetic Routes to Iloperidone (167)



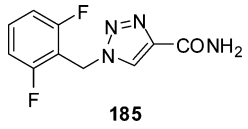


Figure 16. Structure of rufinamide (**185**).

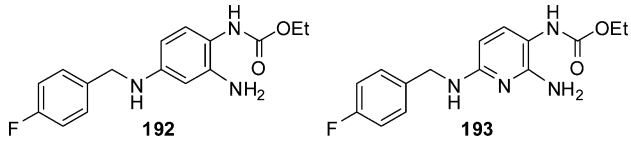


Figure 17. Chemical structures of ezogabine (**192**) and flupirtine (**193**).

have been developed as a two-step, one-pot process giving rise to rufinamide (**185**) of high purity and in high overall yield.

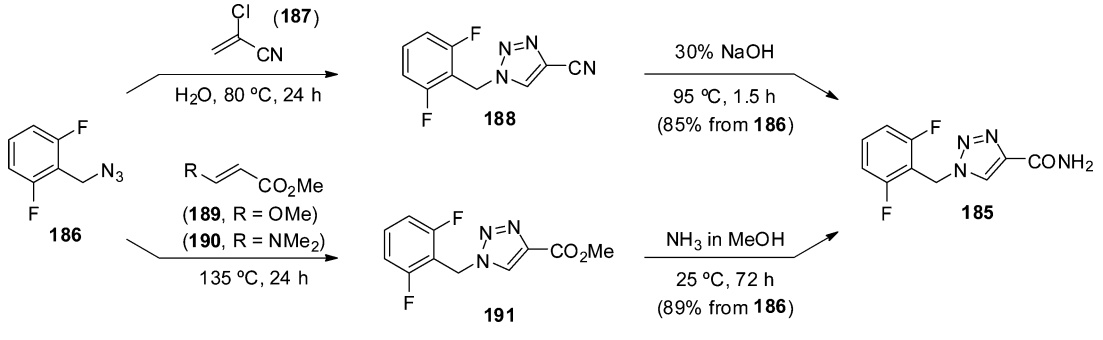
3.5. Ezogabine/Retigabine (Potiga, Trobalt)

Ezogabine (**192**), also known as retigabine, is an antoconvulsant approved by the FDA under the trade name Potiga in 2011 and the European Medicines Agency under the trade name Trobalt in 2011 for adjunctive treatment of partial-onset seizures (Figure 17). Ezogabine was developed as a close structural analog of the centrally acting analgesic flupirtine (**193**), which was also shown to have anticonvulsant effects in animal models of epilepsy and in patients with refractory seizures. Molecular modeling studies resulted in development of ezogabine with anticonvulsant activity substantially higher than that obtained with flupirtine.[121]

Ezogabine has shown a unique mechanism of action among other antiepileptic drugs by enhancing neuronal-specific M-type potassium currents mediated by Kv7.2−7.5 voltage-activated channels.[122] At the molecular level, ezogabine acts by binding into a hydrophobic pocket within the "gate" region of the K_V7.2 and 3 channels which is the site of a molecular "hinge". It should be noted that the most important effect of ezogabine is to keep the neuronal potassium channel in the open state, stabilizing the resting membrane potential, thereby reducing excitability of the brain cells. Ezogabine does not affect cardiac potassium channels K_V7.1, possibly because those channels are missing a glycine component which is essential for ezogabine binding. Ezogabine also possesses weak sodium and calcium channel blocking activity, albeit in 10−100-fold higher concentrations than required to activate Kv7 channels. Use of F and CF_3 substituents has proved to be fruitful for improving activity and selectivity of new Kv7 activators related to ezogabine (Figure 18).[123]

Ezogabine was easily prepared by a three-step procedure.[124] Condensation of 4-fluorobenzaldehyde (**135**) with 2-nitro-1,4-phenylenediamine (**200**) yielded imine **201**, which was reduced using sodium borohydride under standard conditions to give nitro compound **202** (Scheme 30). In turn, reduction of the nitro compound **202** to the aryldiamine using palladium on carbon followed by carbamoylation gave ezogabine. It was then precipitated by addition of hydrogen chloride in ethanol as its dihydrochloride in 73% yield. Alternatively, reaction of nitro compound **201** with diethylcarbonate in the presence of base resulted in selective carbamoylation of the amino group to give compound **203**.[125] Finally, ezogabine was prepared from compound **203** by standard reduction procedure using Pt/V on carbon in 70−90% yield. Ezogabine dihydrochloride appeared to be hygroscopic and unstable under long-term storage (several months at −18 °C), producing significant amounts of the ring-closed product 5-(4-fluorobenzylamino)-1,3-dihydro-benzimidazol-2-one (**204**). Therefore, it is preferably stored as the free base isolated from light. Crystallization of the free base from isopropanol at temperatures ranging from 20 to 100 °C afforded three different crystalline forms named A,

Scheme 29. Synthetic Approaches to Rufinamide (185)



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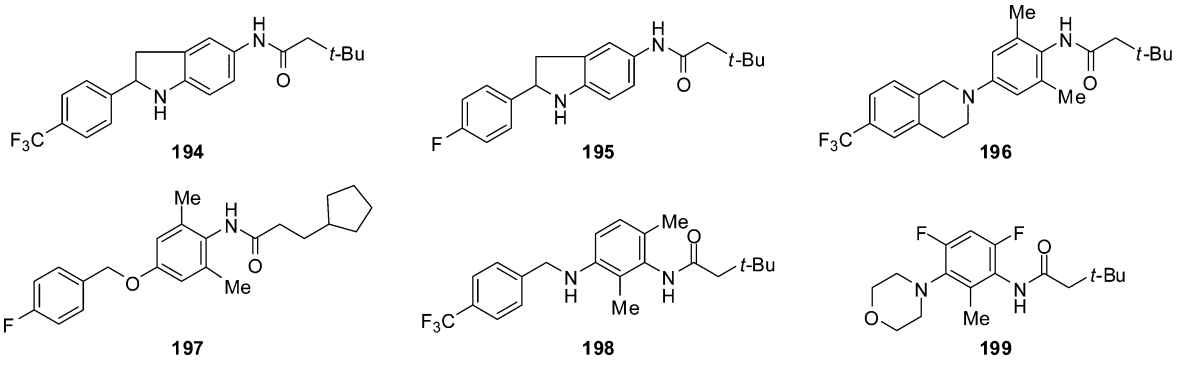
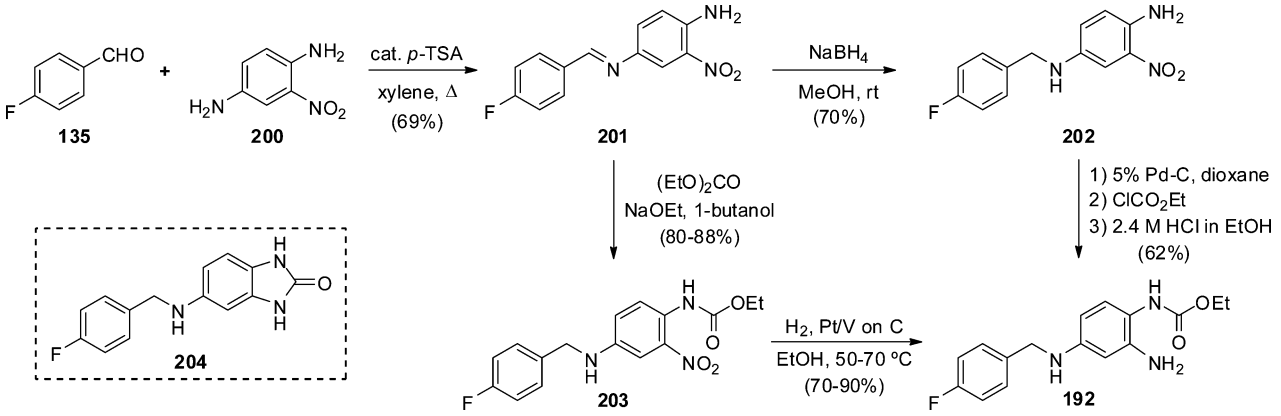


Figure 18. Structures of Kv7 activators **194**–**199**.

Scheme 30. Three-Step Procedure to Ezogabine (192)



B, and C.[126] Modification A has a crystal structure that is stable under long-term storage at temperatures up to 60 °C.

3.6. Ioflupane (DaTSCAN)

Radioligand ^{123}I-ioflupane (*β*-CIT-FP) (**208**) has been used successfully for single-photon emission computed tomography (SPECT) imaging of membrane dopamine transporters in human brain tissue.[127] Since its approval by the FDA in 2011, dopamine transporter imaging using the radioligand ^{123}I-ioflupane and SPECT is the most favored nuclear medicine method to support diagnosis of Parkinson's disease and differentiating Parkinson's disease from other clinically similar disorders.[128] ^{123}I-ioflupane is sold under the trade name DaTSCAN. Ioflupane belongs to ^{123}I-labeled *N*-substituted tropane (8-azabicyclo[3.2.1]octane) derivatives in which the benzoate ester linkage of cocaine (**205**) is replaced with a substituted aromatic ring at the 3 position of the tropane moiety (Figure 19). Among these compounds ioflupane has been selected for clinical application due to its fast and high-affinity binding to dopamine transporters as well as resistance to enzymatic hydrolysis. In addition, introduction of the *N*-fluoropropyl group results in increased selectivity for dopamine over both serotonin and norepinephrine transporters compared, for example, to the corresponding *N*-Me analogue (**206**) (*β*-CIT). The iodine atom in ioflupane is located in a metabolically resistant position, resulting in a slow in vivo rate of deiodination.

Natural cocaine (**205**) is an appropriate starting material for preparation of ioflupane (Scheme 31).[127,129−131] Hydrolysis of **205** by refluxing in HCl gave ecgonine (**210**), which was transformed into the corresponding ecgonidine methyl ester (**211**) with $POCl_3$ and MeOH. Conjugate addition of phenylmagnesium bromide to **211** in anhydrous ether at −40 °C led to

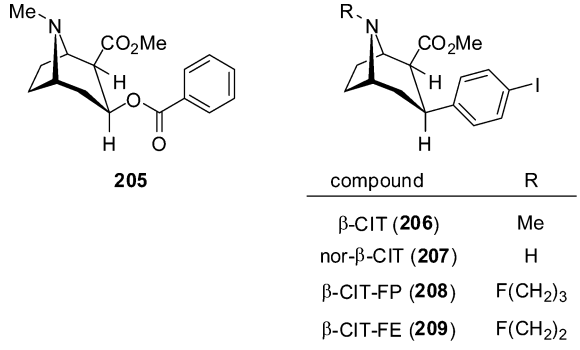


Figure 19. Structures of cocaine (**205**) and *N*-substituted-2*β*-carbomethoxy-3*β*-(4-iodopheny)tropanes **206**–**209**.

a 1.6:l mixture of the 3*β*-phenyltropane-2*β*-carboxylic acid methyl ester (**212**) and 3*β*-phenyltropane-2*α*-carboxylic acid methyl ester (**213**) in 79% yield, which were separated by flash chromatography on silica gel. *β*-CIT (**206**) was prepared by direct iodination of the solution of **212** in a mixture of acetic and perchloric acids containing mercuric oxide. *N*-Demethylation of **206** was selectively achieved by the action of 1-chloroethyl chloroformate (ACE-Cl) and methanol to generate intermediate carbamate, which was then hydrolyzed to nortropane derivative **207**. *N*-Alkylation of nor-*β*-CIT (**207**) with either 1-bromo-3-fluoropropane or 3-fluoro-1-iodopropane in the presence of triethylamine in toluene under reflux afforded *β*-CIT-FP (**208**). ^{123}I *β*-CIT-FP (^{123}I-**208**) was synthesized from nonradioactive *β*-CIT-FP after conversion to the corresponding trimethylstannyl *β*-CIT (**214**) by Pd(0)-catalyzed reaction with hexamethylditin. Reaction of **214** with ^{123}NaI in the presence of peracetic acid at

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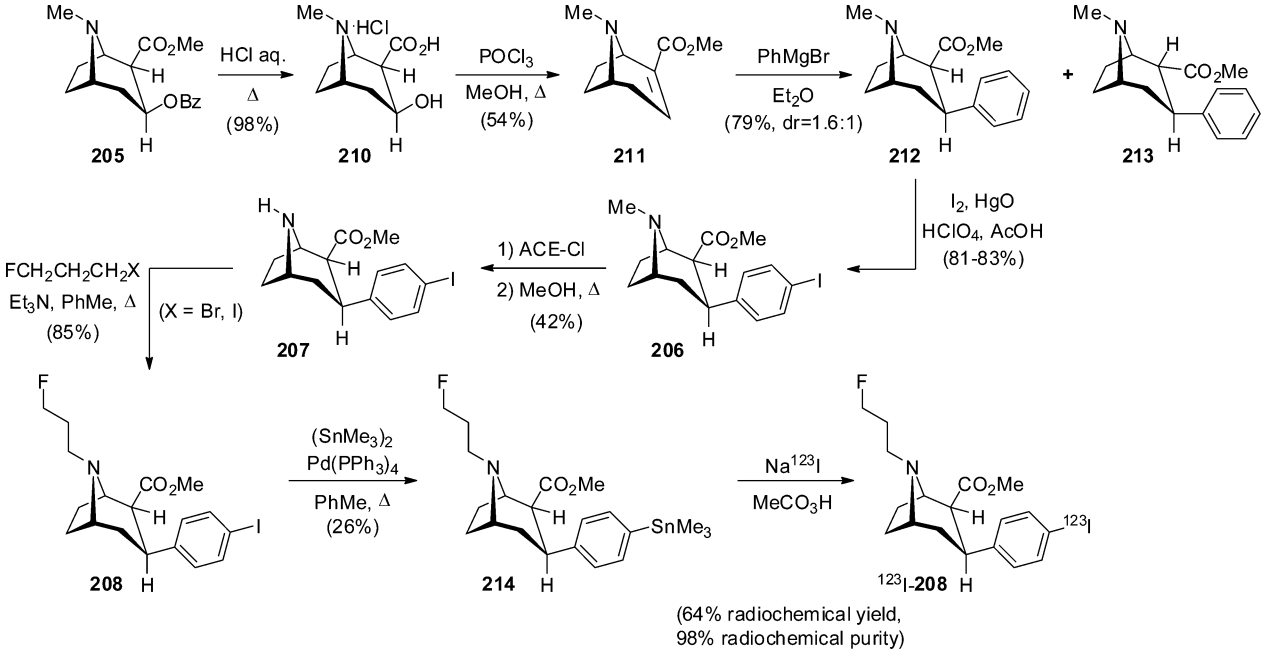
Scheme 31. Synthesis of Ioflupane (208) from Natural Cocaine (205)



pH 3−4 gave ^{123}I β-CIT-FP (^{123}I-**208**), which was purified by preparative HPLC and formulated in a 5% ethanol/isotonic saline solution containing 0.1 mM L-ascorbic acid. ^{123}I β-CIT-FP (^{123}I-**208**) was obtained in 64% radiochemical yield and with radiochemical purity of 98%.

4. DRUGS AFFECTING THE CARDIOVASCULAR SYSTEM

4.1. Ezetimibe (Zetia)

Ezetimibe (**216**) (Figure 20) is the first of a new class of compounds that inhibits biliary and dietary cholesterol absorption in the small intestine. It produces a significant reduction in total cholesterol, LDL cholesterol, and triglycerides as well as a small but significant increase in HDL cholesterol. Additionally, coadministration of **216** with statins (that inhibit cholesterol biosynthesis in the liver) has additive effects, showing a better profile for reducing cholesterol levels than statins alone.[132] Ezetimibe was approved by the FDA in October 2002 for reduction of cholesterol levels in patients with hypercholesterolaemia, thus reducing the risk of coronary heart disease.[133] Current sales of the marketed drug (Zetia, Schering-Plough) reached $2.428 billion in 2011.

Discovery of ezetimibe is the result of serendipity and design within a program aimed at identifying cholesterol acylCoA:acyltransferase (ACAT) inhibitors. These experiments demonstrated that β-lactam **215** inhibits cholesterol absorption by a unique mechanism that still remains not fully elucidated at the molecular level.[134] Intensive optimization of the structure promoted by SAR studies as well as by identification of its sites of metabolism led to the final derivative **216** which showed a 50-fold increase in activity when compared to the parent β-lactam **215**.[135] Use of halogen atoms to block sites of metabolism is a well-known strategy in drug design. In this case, fluorine was chosen due to its small steric demand and its deactivating toward oxidation effect to deter P450-mediated aromatic hydroxylation. Incorporation of two fluorine atoms in the parent compound **215** together with benzylic oxidation and demethylation of the remaining methoxy

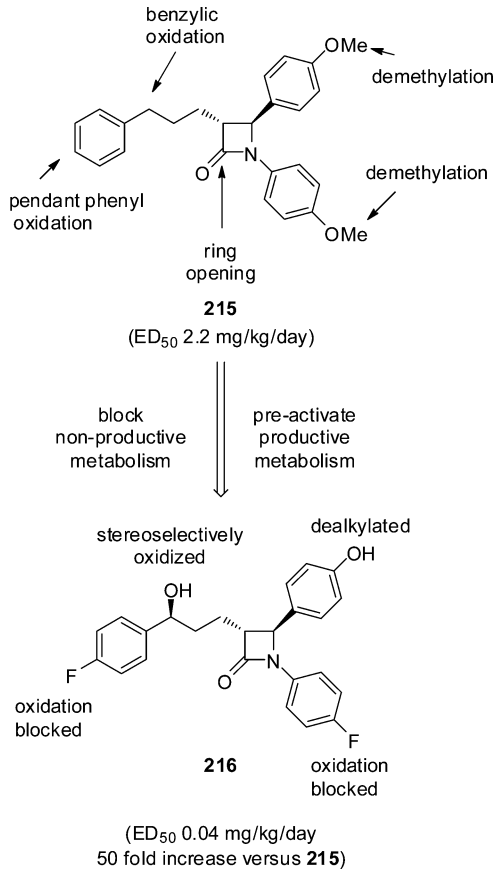


Figure 20. Structures of β-lactam **215** and ezetimibe (**216**).

group gave a derivative with improved pharmacokinetic and pharmacodynamic profiles and significant increased activity.

The novel structure and potent biological activity of ezetimibe prompted the chemical community to optimize synthesis of this molecule. First synthesis of ezetimibe was based on a Staudinger-type reaction.[136] Treatment of acyl chloride **217** with imine **218**

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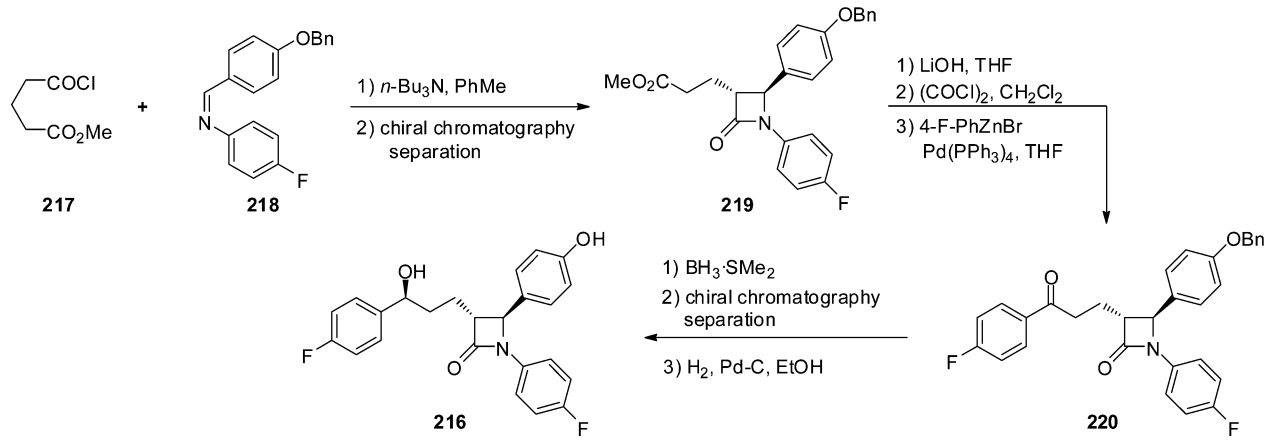
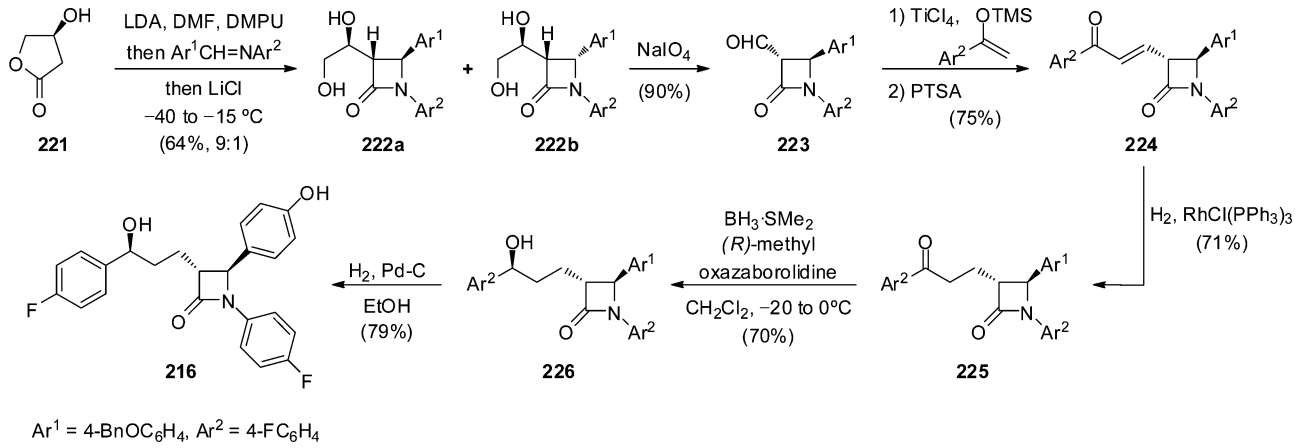
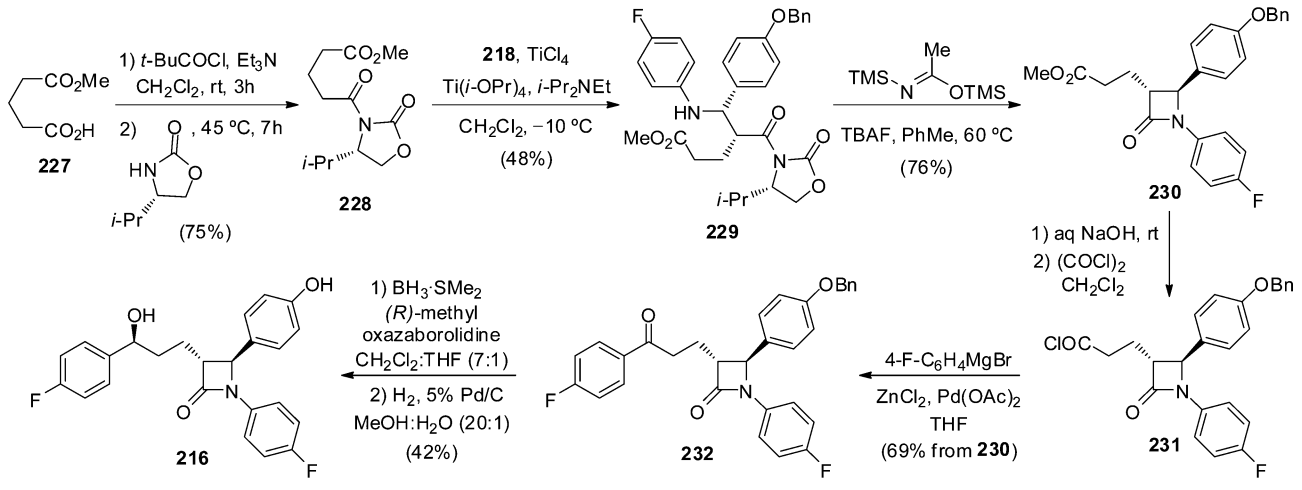
Scheme 32. Staudinger Reaction as Key Step in the First Synthesis of Ezetimibe (216)



Scheme 33. First Asymmetric Synthesis of Ezetimibe (216)



Scheme 34. Large-Scale Synthesis of Ezetimibe (216)



in the presence of a base afforded *trans*-β-lactam **219** containing adequate substitution at N and C4 (Scheme 32). Pure enantiomers were isolated by means of chiral chromatography. Ester hydrolysis, formation of the corresponding acyl chloride, and subsequent Negishi-type coupling gave ketone **220**, which was reduced with borane-methyl sulfide complex affording a mixture of diastereoisomers that were again separated by chiral chromatography. Final debenzylation led to the desired product **216**.

The first asymmetric synthesis of ezetimibe started from commercially available (*S*)-3-hydroxy-γ-lactone (**221**) by means of an enolate-imine condensation reaction for construction of the β-lactam core (Scheme 33).[137] The resulting diasteroisomeric mixture of β-lactams **222**—scaled up to 300 g—was oxidized with $NaIO_4$. The cis aldehyde was not stable and epimerized under the reaction conditions to the trans isomer **223**. A Mukaiyama aldol condensation was used to install the proper substituent at C3, which after dehydration and double-bond

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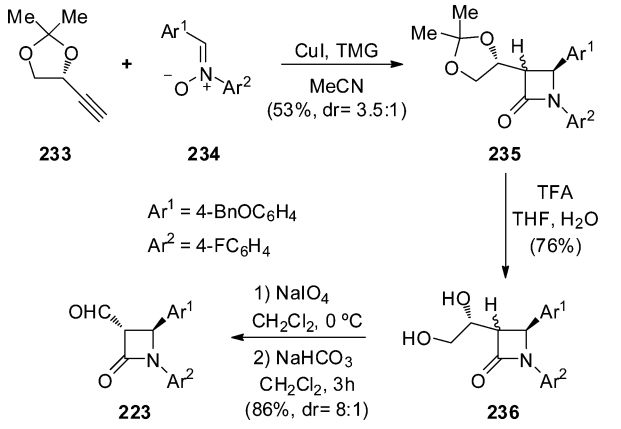
hydrogenation gave ketone **225**. Enantioselective reduction with the CBS reagent led to the benzylic alcohol **226** with the correct stereochemistry. Finally, ezetimibe was obtained by catalytic hydrogenolysis of the benzyl group on the aromatic ring at C4.

For large-scale purposes—69 g of **216**—chiral oxazolidinone chemistry was used to set the required stereochemistry of the β-lactam ring.[138] Monomethyl glutarate **227** was transformed into the corresponding acyl chloride that in turn was condensed to form oxazolidinone **228** (Scheme 34). Its titanium enolate was treated with imine **218** to afford the β-lactam precursor **229** as a single diastereoisomer. Cyclization of **229** with *N*,*O*-bis-(trimethylsilyl)acetamide and TBAF followed by ester hydrolysis and treatment with oxalyl chloride gave acyl chloride **231**. Negishi coupling with 4-fluorophenylmagnesium bromide in the presence of $ZnCl_2$ and $Pd(OAc)_2$ led to ketone **232**. Again, chiral oxazaborolidine chemistry was used to set the hydroxyl group stereochemistry,[139] and final benzyl deprotection gave ezetimibe.[140]

Two different strategies for synthesis of ezetimibe have been recently reported in the literature. The first one was based on a Kinugasa-type reaction as the key step.[141] It consists of a Cu(I)-mediated cycloaddition/rearrangement cascade process of nitrones and terminal alkynes in the presence of a base. Thus, chiral alkyne **233** and nitrone **234** were subjected to the copper-catalyzed Kinugasa reaction giving rise to β-lactam **235** as a 3.5:1 mixture of diastereomers (Scheme 35). Next, the acetonide was

Scheme 35. Kinugasa-Type Reaction as Key Step in Synthesis of Ezetimibe (216)



released with trifluoroacetic acid, and diol **236** was oxidized to the corresponding aldehyde. The resulting diastereomeric mixture of β-lactams was treated with $NaHCO_3$, leading to the more stable trans diastereoisomer **223** from which it is possible to access ezetimibe following the sequence depicted in Scheme 33.

The latest synthesis of ezetimibe, reported very recently, is the only enantioselective synthesis of this compound described to date.[142] The process relies on a palladium-catalyzed enantioselective allylic amination of Morita–Baylis–Hillman (MBH) adducts employing a new class of aromatic spiroketal-based bisphosphine chiral ligands. By means of this procedure, conjugated ester **237** was transformed into β-amino ester **239** in high yield and enantioselectivity (Scheme 36). Conjugated addition of dicarbonyl derivative **240** followed by palladium-catalyzed allyl group removal afforded amino ester **241**, which was converted in the β-lactam **220** by treatment with LiHMDS. From compound **220** and following the sequence illustrated in Scheme 32, ezetimibe was easily obtained.

4.2. Rosuvastatin (Crestor)

Rosuvastatin (**242**) (Figure 21) is the newest oral 3-hydroxy-3-methyl glutaryl coenzime A (HMG-CoA) reductase inhibitor. It is the seventh drug in the statin class, called a "super statin" because it appears to reduce low-density lipoprotein (LDL) cholesterol to a greater degree than rivals in its class without additional adverse effects.[143] It was approved by FDA in August 2003 for treatment of patients with primary hypercholesterolemia (type IIa, including heterozygous familiar hypercholesterolemia) or mixed dyslipidemia (type IIb) as an adjunct to diet when response to exercise and diet is inadequate.[144] It was originally discovered by Shionogi and subsequently codeveloped and comarketed by Astra-Zeneca with the name Crestor as its calcium salt. Current sales of the marketed drug reached $6622 billion in 2011.

Rosuvastatin is the result of an intensive effort on replacing the complex decalin portion of mevinic acids with structurally simpler and achiral aromatic and heteroaromatic surrogates. Structurally, rosuvastatin shares with the rest of synthetic statins the presence of the chiral 3,5-dihydroxyheptanoic acid substructure but in this case attached to a pyrimidine ring. Introduction of this heterocycle was translated into an improved activity for HMG-CoA reductase inhibition. Additionally, the sulfonyl moiety was introduced to lower lipophilicity, thereby improving the selectivity of statins for the liver.[145] Regarding the 4-fluorophenyl moiety, this is a strict structural requirement of all synthetic statins. Rosuvastatin calcium was found to be more potent than lovastatin, fluvastatin, and pravastatin in inhibiting HMG-CoA reductase in vitro and more potent than pravastatin in reducing plasma LDL levels in vivo. At the same time, recent studies demonstrated that rosuvastatin is cost effective compared with atorvastatin in reducing cholesterol levels.[146]

The side chain, 3,5-dihydroxyheptanoic acid moiety, was first assembled by means of a desymmetrization reaction of anhydride **244**, which in turn was prepared from diethyl-3-hydroxyglutarate (**243**) in three steps, including hydroxyl protection, saponification, and cyclization by treatment with acetic anhydride (Scheme 37).[147] Reaction of **244** with the lithium salt of benzyl-(*R*)-mandelate (**245**) afforded the desymmetrized product **246**, obtained as a single enantiomer after hydrogenation of the benzyl ester and recrystallization. Chiral diacid **247** was treated with NaOMe to release the chiral auxiliary, and compound **248** was transformed into the desired Wittig ylide **250** via the mixed anhydride **249**.

In the first enantioselective synthesis of rosuvastatin, preparation of the heterocyclic fragment started with the condensation between β-ketoester **251** and 4-fluorobenzaldehyde (**135**) to render keto ester **252** (Scheme 38).[148] Condensation of **252** with *S*-methyl thiourea hemisulfate in HMPA and subsequent oxidation with DDQ afforded compound **253**, bearing the pyrimidine core. Sulfide **253** was oxidized to sulfone **254** and then treated with methylamine to render the corresponding secondary amine that was sulfonylated with $MeSO_2Cl$ to yield pyrimidine **255**. Preparation of the aldehyde **256** for the key Wittig reaction was accomplished by DIBAL reduction followed by TPAP oxidation. Aldehyde **256** was treated with phosphorus ylide **250** to afford the conjugated ketone **257**. TBS deprotection, stereoselective reduction of the β-hydroxy ester with $NaBH_4$ in the presence of Et_2BOMe, and final ester hydrolysis afforded rosuvastatin calcium salt.

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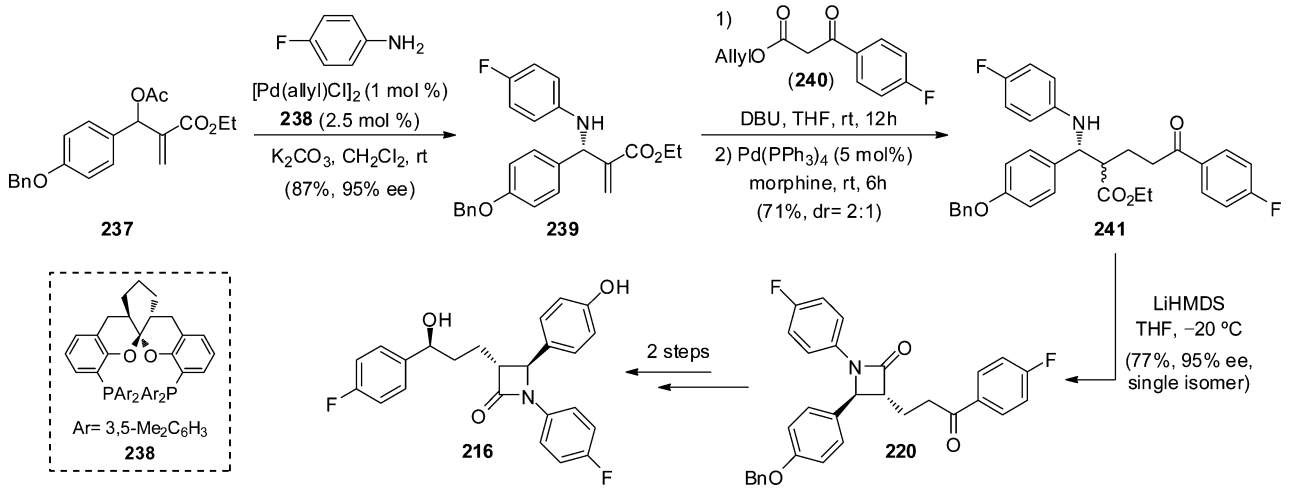
Scheme 36. Enantioselective Allylic Allylation as Key Step in Synthesis of Ezetimibe (216)



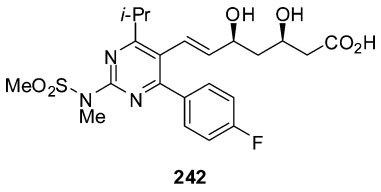


Figure 21. Structure of rosuvastatin (**242**).

More recently, two synthetic strategies have been devised for synthesis of rosuvastatin. The first one comprised two highly stereoselective hydrogenations as key steps.[149] Thus, 3,3-dimethoxypropanoate (**258**) was hydrolyzed and treated with carbonyl diimidazole (CDI) to afford amide **259**, which was converted into keto ester **260** by treatment with $(EtO_2CCH_2CO_2)_2Mg$ (Scheme 39). Asymmetric hydrogenation catalyzed by Ru(BINAP)Cl_2 afforded hydroxy ester **261** in excellent yield and enantiomeric excess. Then, the hydroxy group was protected as the silyl derivative **262** and treated with Jones reagent to afford acid **263**, which was transformed into the phosphorus ylide **264**, via conversion in its mixed anhydride, by reaction with $Ph_3P{=}CH_2$. Wittig reaction of **264** with aldehyde **256** gave rise to compound **265**, which after silyl group deprotection, stereoselective reduction of the β-hydroxy ketone, and saponification was converted into rosuvastatin as its calcium salt.

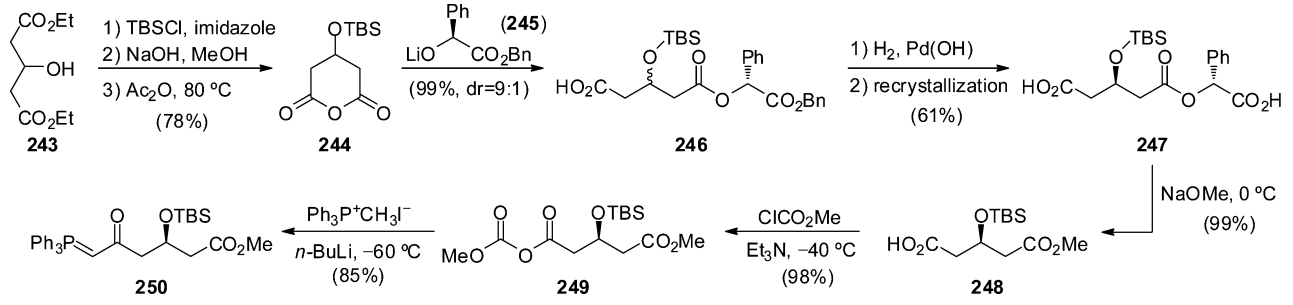
The last synthesis of rosuvastatin also employed a Wittig reaction to couple the side chain with the heterocyclic core, but in this case, the phosphorus ylide was generated on the heterocyclic terminus.[150] Starting from commercially available chlorohydrin ethyl ester **266**, the chlorine atom was substituted by iodine and the alcohol protected as its TBS group (Scheme 40). The resulting iodide **267** was transformed into allylic derivative **268** by treatment with vinyl magnesium chloride in the presence of CuI followed by ester hydrolysis. Iodolactonization of **268** afforded a mixture of diastereomeric lactones that was separated by either crystallization or chromatography. Enantiomerically pure lactone **269** was transformed into acetate **270** with silver acetate in refluxing acetic acid. At this point, acetate deprotection was troublesome in order to maintain the integrity of the chiral centers. Initially, this hydrolysis was performed with a tin derivative to afford alcohol **271** in 66% yield (Scheme 40, method A). Later, this procedure was improved employing a chemoenzymatic method using pancreatin powder to perform the hydrolysis process. In this case, the corresponding alcohol **271** was obtained in 96% yield (Scheme 40, method B).[151] Oxidation of **271** with Dess−Martin periodinane afforded *gem*-diol **272**, which was converted into aldehyde **273** simply by dissolving in dichloromethane and evaporating the solvents.

Pyrimidine ester **255** was converted into phosphonium salt **274**, and the key Wittig reaction with aldehyde **273** afforded compound **275**, which was readily transformed into rosuvastatin calcium salt in three steps (Scheme 41). The authors noted that this new convergent route was free of any steps requiring cryogenic conditions and therefore superior to other methods for preparation of rosuvastatin with industrial purposes.

4.3. Nebivolol (Bystolic)

Nebivolol (**276**) is a third-generation β-adrenergic receptor antagonist (β-blocker) that has been available in Europe for a decade, but it was only approved by FDA for hypertension

Scheme 37. Synthesis of the 3,5-Dihydroxyheptanoic Acid Side Chain of Rosuvastatin (232)



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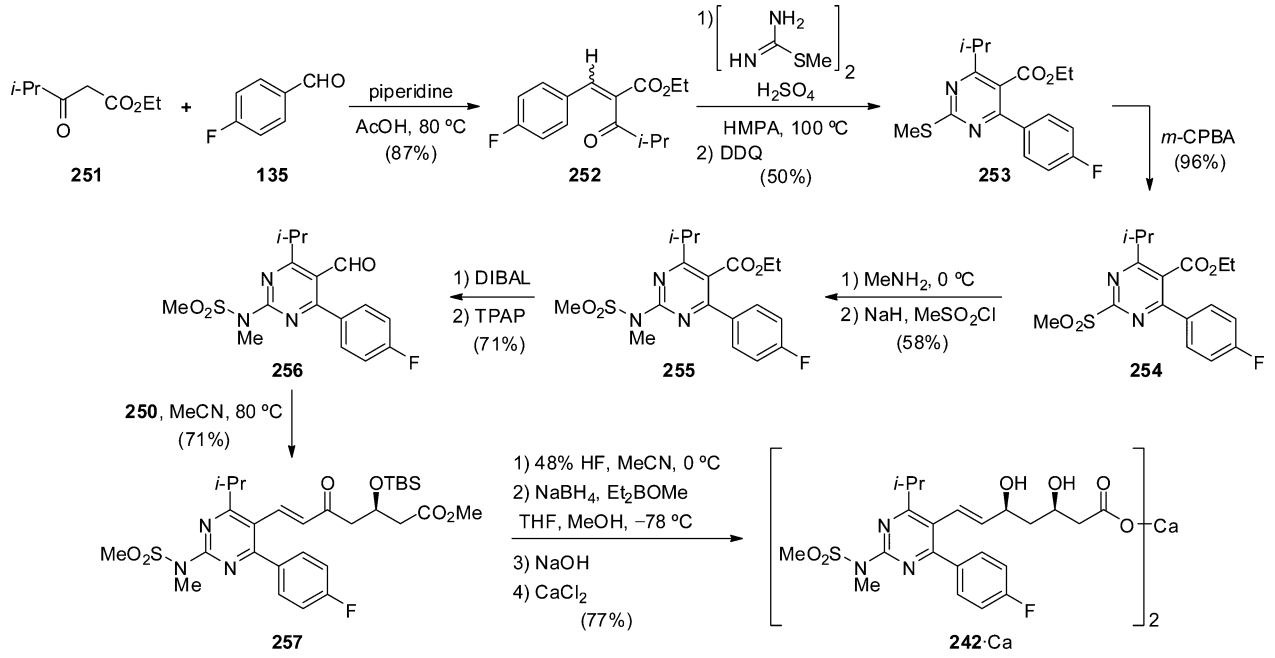
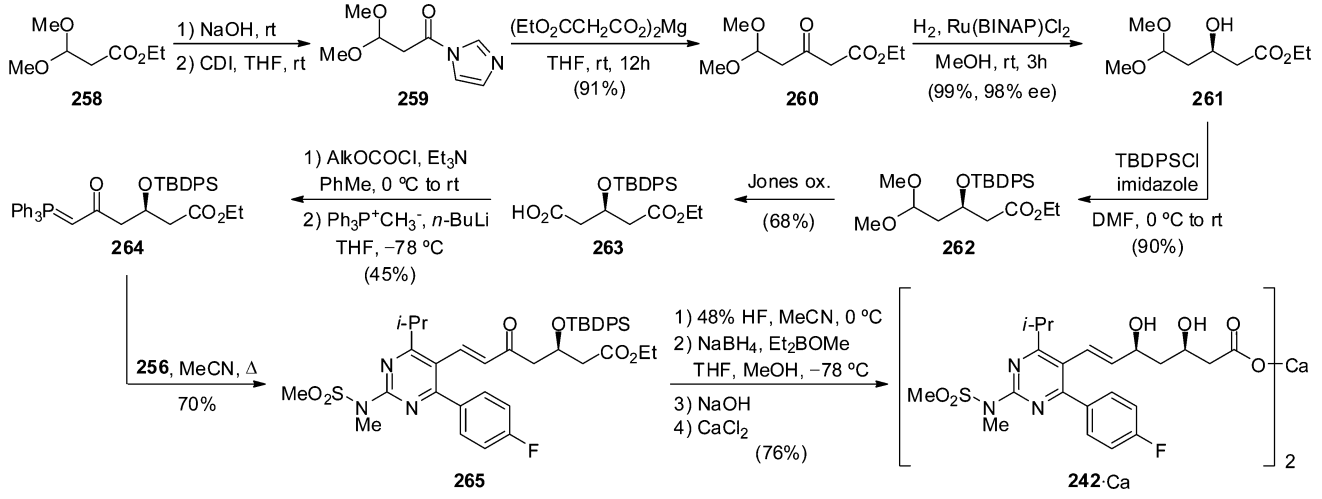
Scheme 38. First Enantioselective Synthesis of Rosuvastatin (232)



Scheme 39. Enantioselective Ru-Catalyzed Hydrogenation as Key Step in Synthesis of Rosuvastatin (232)



treatment in the United States in 2007. The drug, originally discovered at Janssen Pharmaceutica, is currently marketed in the United States under the brand name Bystolic from Mylan Laboratories and Forest Laboratories.[152]

Nebivolol has a unique hemodynamic profile, combining highly selective β_1-adrergenic receptor antagonism with nitric oxide-mediated vasodilatory activity. Therefore, it is an effective antihypertensive agent.[153] The nebivolol molecule contains four stereocenters and is marketed as a racemate of D-(+) and L-(−)-nebivolol **276** (Figure 22). Both isomers contribute to the antihypertensive action of the drug. However, the D-isomer is responsible for the β_1 adrenoreceptor blocking activity, while both isomers, but particularly L-nebivolol, contribute to the vasodilatory action.[154] Furthermore, recent clinical evaluation shows that the active (*S*,*R*,*R*,*R*) enantiomer[155] and racemic nebivolol produce equal reductions in blood pressure in hypertensive patients.

Nebivolol differs from all other β-blockers with a chiral hydroxypropanolamine substructure in that its antihypertensive activity resides in the (*R*)-enantiomer at the hydroxy group. This divergence may be due to the increased rigidity imposed by two of the four chiral centers that are part of the ring structures.[156]

There are several methods dealing with synthesis of nebivolol. An efficient, facile, and industrially feasible approach started from 6-fluoro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**277**), which was first hydrogenated to the chromane derivative **278** (Scheme 42).[157] Next, alcohol **279** was prepared by reduction of the mixed anhydride of **278** with $NaBH_4$, and subsequent oxidation afforded aldehyde **280**. The key epoxide derivative **281** was obtained using trimethylsulfonium iodide in quantitative yield. Finally, nebivolol was prepared in racemic form by the coupling reaction of two fragments, epoxide **281** and hydroxy amine **282**, obtained via the nucleophilic opening of epoxide **281** with benzylamine.

The first enantioselective total synthesis of (*S*,*R*,*R*,*R*)-nebivolol[158] involved a Zr-catalyzed kinetic resolution of cyclic allylic styrenyl ethers[159] and their Mo-catalyzed ring-opening and ring-closing metathesis as key steps of the synthesis.[160] In this

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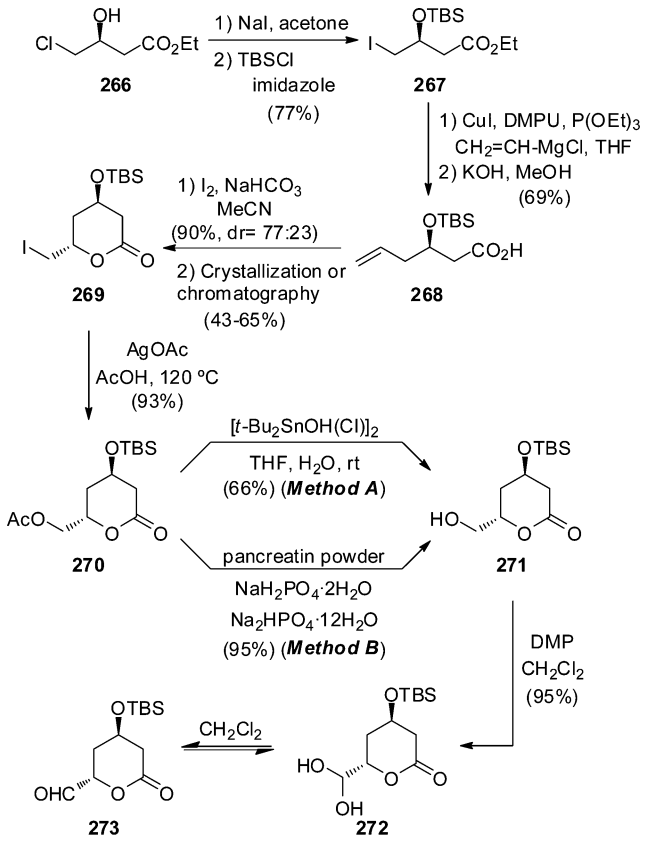
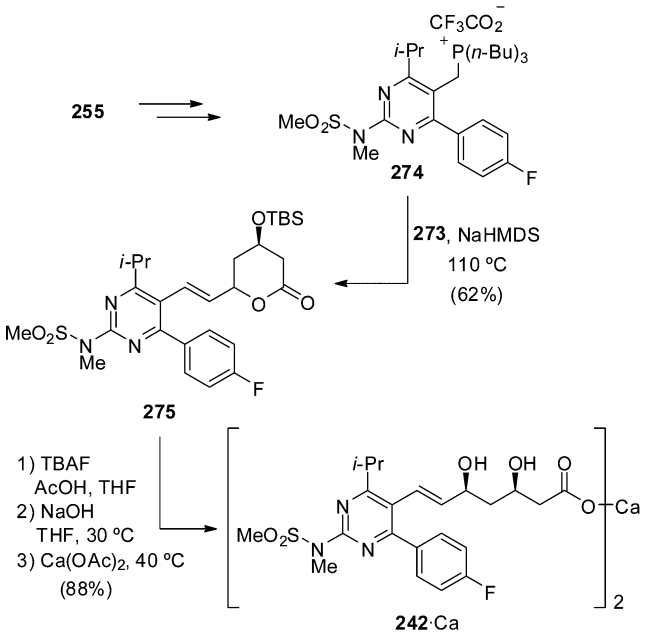
Scheme 40. Chlorohydrin Ethyl Ester 266 as Starting Material in Preparation of Rosuvastatin (232)

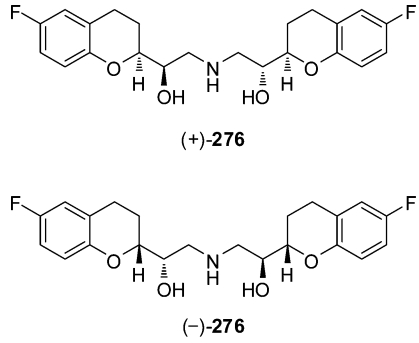


Scheme 41. Synthesis of Rosuvastatin (232) for Industrial Purposes



convergent approach, 2-substituted chiral chromanes **284** and **285** were coupled by means of a reductive amination reaction (Scheme 43).

Synthesis of chromane derivative (*R*,*R*)-**285** started with the regio- and stereoselective nucleophilic opening of allylic epoxide *rac*-**286** with styrenyl phenol **287** followed by protection of the



(+)-**276**

(−)-**276**

Figure 22. Structures of (+)-(*S*,*R*,*R*,*R*)-nebivolol ((+)-**276**) and (−)-(*R*,*R*,*R*,*S*)-nebivolol ((−)-**276**).

resulting secondary carbinol with TBS triflate (Scheme 44). Treatment of *rac*-**288** with EtMgCl and 10 mol % (*R*)-(EBTHI)Zr-binol (**289**) resulted in isolation of the recovered starting material (*R*,*R*)-**288** in >98% ee. This chiral compound was converted to the unsaturated chromene (*R*,*R*)-**291** in the presence of the Mo catalyst **290** under an atmosphere of ethylene. The two alkene sites in chromene (*R*,*R*)-**291** were differentiated through an efficient Pd-catalyzed Wacker oxidation of the terminal olefin to afford the corresponding methyl ketone and subsequent catalytic hydrogenation to give chromane derivative (*R*,*R*)-**292**. The necessary shortening of the chromane side chain was accomplished by means of a photochemical Norrish type II cleavage.[161] After optimization of the reaction conditions, when the photolysis was performed at −10 °C, the desired product was obtained in acceptable yield. Finally, synthesis of fragment (*R*,*R*)-**285** was completed in three steps comprising an ozonolytic cleavage−reduction sequence on olefin (*R*,*R*)-**293** followed by conversion of the resulting primary alcohol into a primary amine through a modified Mitsunobu procedure and a hydrazine-mediated deprotection.

Again, allylic epoxide *rac*-**286** was the starting material for synthesis of the (*S*,*S*)-chromane segment **284** (Scheme 45). However, in this case the opening of the oxirane ring should proceed with syn stereochemistry. To this aim, a directed Pd-catalyzed coupling of allylic epoxides with tin alkoxides was employed since it is known that the reaction occurs in a 1,2-syn fashion (vs the 1,4-allylic substitution).[162] In this manner, treatment of *rac*-**286** with n-$Bu_2Sn(OMe)_2$ in the presence of $Pd(PPh_3)_4$ and phenol **287** led to the desired compound *rac*-**294** in very good yield and excellent regio- and stereoselectivity. Then, conversion of *rac*-**294** to (*S*,*S*)-**284** was carried out efficiently in a similar fashion to that of the synthesis of (*R*,*R*)-**285**. It is worth noting that the Zr-catalyzed resolution was performed with the (*S*)-enantiomer of the Zr complex **289**.

Another approach to synthesis of (*S*,*R*,*R*,*R*)-nebivolol involved coupling of fragments **297** and **298** through the nucleophilic opening of an epoxide with an amine (Scheme 46).[163]

Synthesis began from commercially available *p*-fluorophenol (**299**), which was treated with allyl bromide in the presence of K_2CO_3 and furnished *O*-allyl ether **300** (Scheme 47). A Claisen rearrangement followed by protection of the hydroxy group generated compound **301**. Then, a hydroboration reaction gave primary alcohol **302**, which upon one-pot oxidation with Dess−Martin periodinane and Wittig olefination with ethyltriphenylphosphorane afforded α,β-unsaturated ester **303**. DIBAL reduction produced the corresponding alcohol, and desilylation yielded allyl alcohol **304**. Sharpless asymmetric epoxidation with (−)-DET followed by sodium hydroxide workup gave access to

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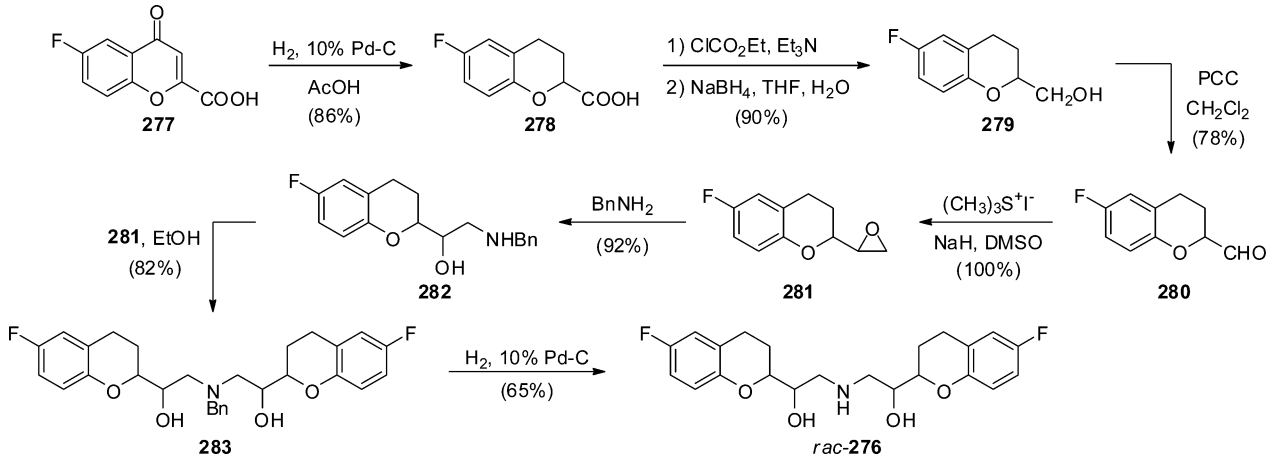
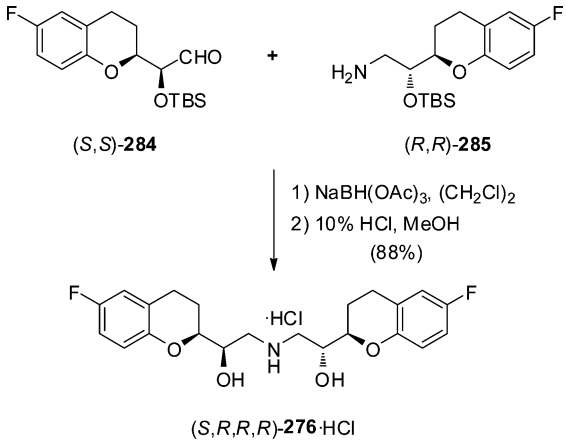
Scheme 42. Industrial Feasible Approach to Racemic Nebivolol (276)



Scheme 43. First Asymmetric Synthesis of (+)-Nebivolol (276)



the chromane skeleton (*S*,*R*)-**305**. Finally, the desired fragment (*S*,*R*)-**297** was obtained upon treatment with tosyl chloride followed by NaN_3 and reduction.

Similarly, chromane (*R*,*S*)-**305** was obtained from **304** employing (+)-DET in the Sharpless asymmetric epoxidation (Scheme 48). Under Mitsunobu conditions, (*R*,*S*)-**305** gave benzoate derivative (*R*,*R*)-**306** with inversion at C2, and finally, deprotection followed by tosylation and base treatment allowed formation of epoxide (*R*,*R*)-**298**.

A different approach started from the readily available compound **307** that was converted into (*R*)-2,3-isopropylideneglyceraldehyde (**309**) in two steps (Scheme 49).[164] The key cyclization reaction between (*R*)-**309** and 2-acetyl-4-fluorophenol (**310**) took place in the presence of pyrrolidine, yielding a 60:40 diastereomeric mixture of the key building blocks **311** and **312** that were easily separated by chromatography. On one hand, compound (*R*,*R*)-**312** was treated with zinc powder in HCl to form the corresponding diol that was tosylated to give (*R*,*R*)-**314**. On the other hand, (*S*,*R*)-**311** was subjected to the same sequence followed by nucleophilic substitution with ammonia to give (*S*,*R*)-**313**. Final substitution of amino alcohol (*S*,*R*)-**313** with tosylate (*R*,*R*)-**314** furnished the desired compound (*S*,*R*,*R*,*R*)-**276**.

Finally, a more recent strategy for asymmetric construction of the 2-substituted chromane ring from a phenol derivative employed chiral sulfoxides to control the stereochemical outcome.[165] This strategy relied on reaction of **6**-fluorochroman-2-one (**315**) with the lithium anion of (*R*)-methyl-*p*-tolyl sulfoxide (*R*)-**316** to obtain lactol (*R*)-**317** as a mixture of C-2 epimers (Scheme 50). When this mixture was treated with Et_3SiH and TMSOTf, a stereoselective reductive deoxygenation process took place, affording 2*H*-chroman (*S*,*R*)-**318**. This was then converted into aldehyde (*S*)-**319** through a Pummerer reaction. Following the same sequence but changing the absolute configuration at the sulfur atom, the enantiomer (*R*)-**319** was also synthesized in order to assemble the nebivolol molecule.

Further transformations on compound (*S*)-**319** included addition of the lithium anion derived from (*S*)-methyl-*p*-tolyl sulfoxide (*S*)-**316** (Scheme 51). Under these conditions, compound (*S*,*S*,*S*)-**320** could be isolated in 75% yield after chromatographic separation of the initially formed 85:15 mixture of epimeric β-hydroxy sulfoxides. Protection of carbinol (*S*,*S*,*S*)-**320** followed by Pummerer reaction gave aldehyde (*S*,*S*)-**321**. Subsequent reductive amination using benzylamine and $NaBH(OAc)_3$ afforded protected amino alcohol (*S*,*R*)-**322**, the left fragment of nebivolol.

For synthesis of the right fragment of nebivolol, that is, epoxy chromane (*R*,*R*)-**325**, Wittig reaction on aldehyde (*R*)-**319** yielded vinyl chromane (*R*)-**323** (Scheme 52). Then, Sharpless asymmetric dihydroxylation of the double bond with AD-mix-α gave rise to a 91:9 mixture of the corresponding diastereoisomeric diols, from which (*R*,*R*)-**324** was isolated in 88% yield. Selective tosylation of the primary hydroxy group followed by treatment with NaH led to epoxy chromane (*R*,*R*)-**325**.

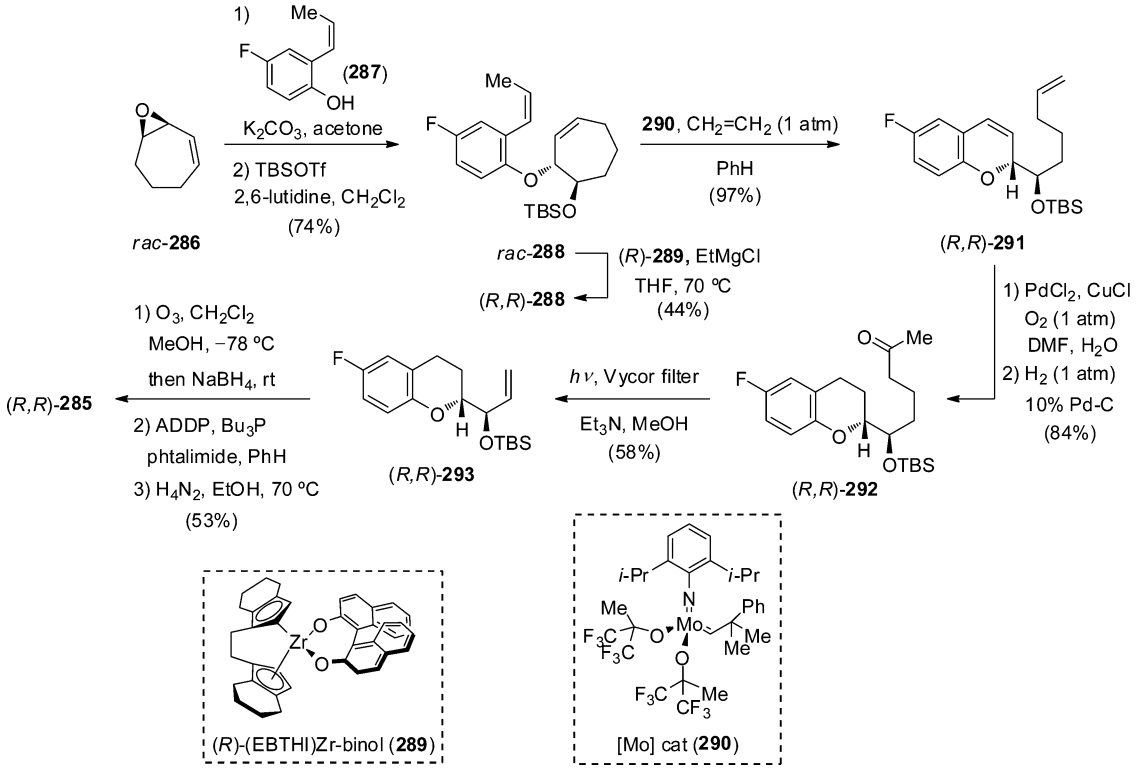
Assembly of benzylamine (*S*,*R*)-**322** with epoxide (*R*,*R*)-**325** was effected by heating a mixture of both compounds in refluxing ethanol (Scheme 53). Finally, removal of the benzyl protecting groups by hydrogenolysis followed by acidic treatment allowed obtention of (*S*,*R*,*R*,*R*)-nebivolol hydrochloride.

4.4. Pitavastatin (Livalo)

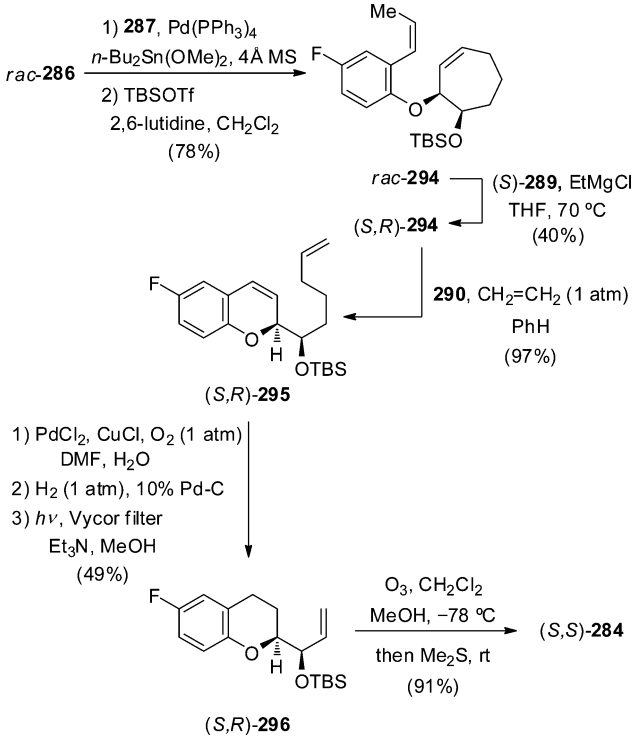
Pitavastatin (**327**) is an oral 3-hydroxy-3-methyl glutaryl coenzime A (HMG-CoA) reductase inhibitor (Figure 23). It belongs to the statin family, which includes drugs that inhibit conversion of HMG-CoA to mevalonate, an intermediate of the biosynthesis of cholesterol. It was launched in Japan in 2003 and approved by the FDA in 2009, entering the U.S. market in 2010 for treatment of primary hyperlipidemia and mixed dyslipidemia. It was marketed by Kowa and Sankio with the name Livalo as its calcium salt.[143a,166]

dx.doi.org/10.1021/cr4002879 | *Chem. Rev.* 2014, 114, 2432−2506

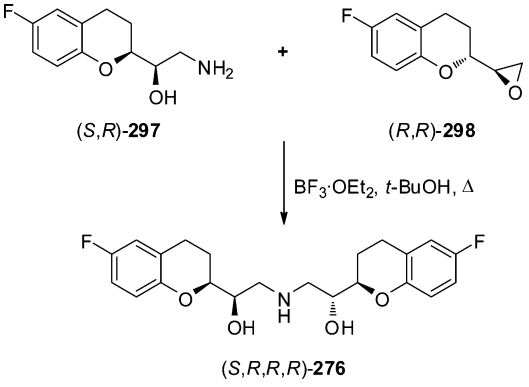
Scheme 44. Zr-Catalyzed Kinetic Resolution as Key Step in Synthesis of Chromane Intermediate (*R,R*)-285



Scheme 45. Asymmetric Synthesis of the (*S,S*)-Chromane Segment 284



Scheme 46. Synthesis of (+)-Nebivolol (276) from Fragments (*S,R*)-297 and (*R,R*)-298



Pitavastatin is the last member of the statin family that entered the U.S. market. It is a completely synthetic compound developed to increase the potency and efficiency of previous statins, such as pravastatin or symvastatin. In comparison with other synthetic statins, like atorvastatin or rosuvastatin, pitavastatin contains a cyclopropyl moiety attached to the heterocyclic core. This structural difference is translated into a high resistance to metabolization through the cytochrome P-450 pathway in the liver and better bioavailavility than their counterparts. Regarding the presence of the 4-fluorophenyl moiety, this is a strict structural requirement of all synthetic statins; SAR studies performed in this position of pitavastatin revealed that this substituent was the most active one in this system.[167]

Structurally, pitavastatin consists of a quinoline core attached to a chiral 3,5-dihydroxy-6-heptenoic acid residue. Since all second-generation synthetic statins share the same lateral chain, its preparation was the subject of intensive research. Several methodologies involving chemoenzymatic resolution,[168] chemical resolution,[169] asymmetric synthesis based on starting materials derived from the chiral pool,[170] or enantioselective synthesis[171] have been devised. However, discussion of all these

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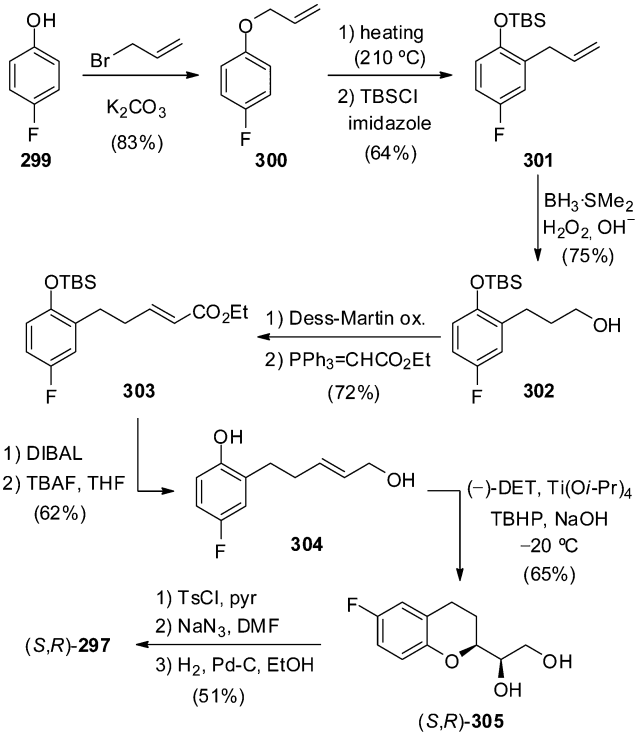
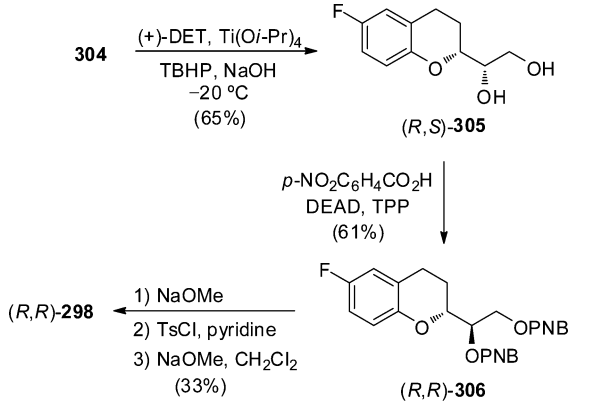
Scheme 47. Synthesis of Aminoalcohol (*S,R*)-297



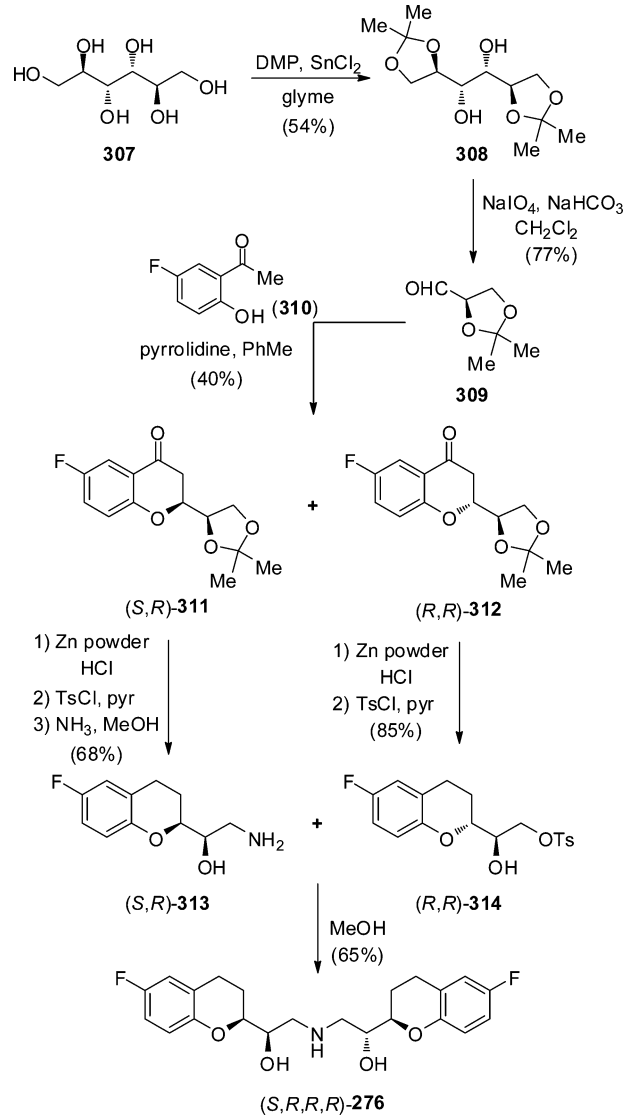
Scheme 48. Sharpless Asymmetric Epoxydation as Key Step in Synthesis of Epoxyde (*R,R*)-298



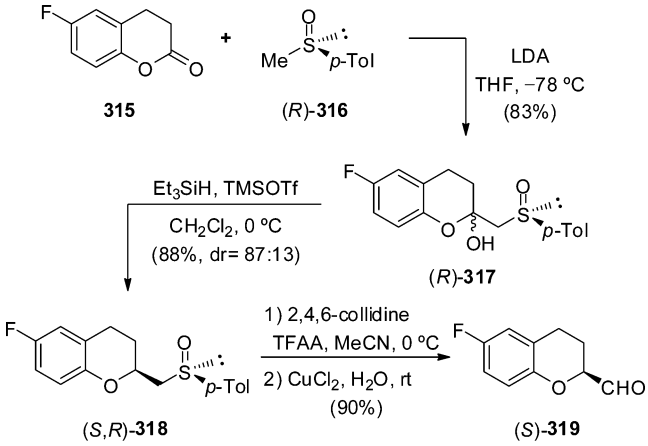
methods might be beyond the scope of this review, and only the approaches specifically related to synthesis of pitavastatin will be mentioned. Synthetic strategies employed to access **327** were summarized in Scheme 54. In all cases, a convergent approach involving preparation of two separated fragments, the heterocyclic core and the side chain, was used. Coupling of these two fragments was performed by means of a Wittig-type reaction by formation of the corresponding phosphorus ylide either at the heterocyclic terminus (Scheme 54, a) or at the side chain terminus (Scheme 54, e). Alternatively, palladium-catalyzed cross-coupling reactions of the corresponding aryl iodides (Scheme 54, c), an aldol-type reaction (Scheme 54, d), or nucleophilic addition to an epoxide (Scheme 54, b) were also employed.

Anthranilic acid (**328**) was used as starting material for preparation of the quinoline moiety of pitavastatin.[172] On one hand, **328** was transformed into its acyl chloride, and subsequent Friedel−Crafts acylation with fluorobenzene provided amino-

Scheme 49. Asymmetric Synthesis of (+)-Nebivolol (276) from (*R*)-2,3-Isopropylideneglyceraldehyde (309)



Scheme 50. Sulfoxide-Mediated Synthesis of Intermediate (*S*)-319



benzophenone **329** (Scheme 55). On the other hand, cyclopropyl methyl ketone (**330**) was transformed into keto ester **331**

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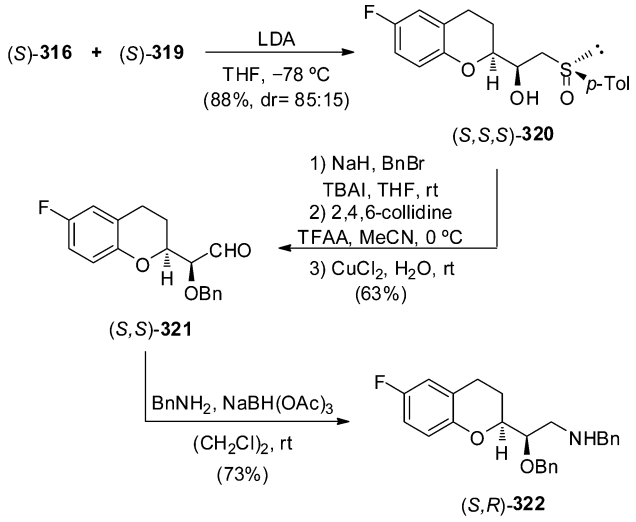
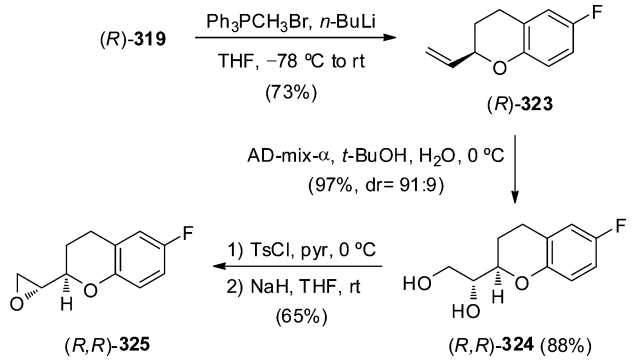
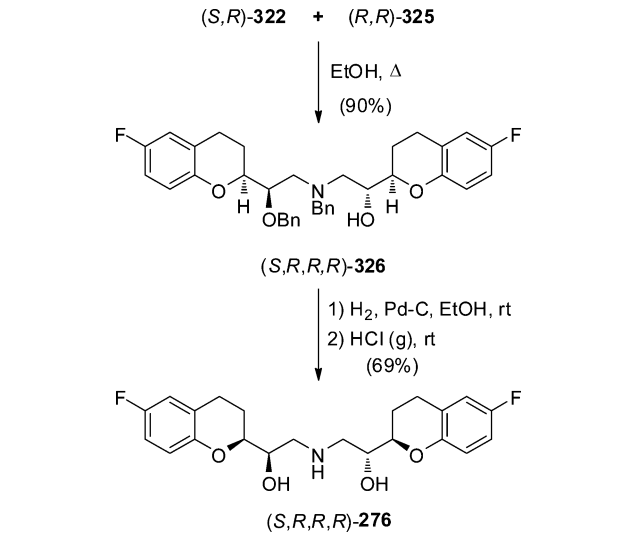
Scheme 51. Sulfoxide-Mediated Synthesis of Intermediate (*S,R*)-322



Scheme 52. Asymmetric Dihydroxylation Approach to Diol Intermediate (*R,R*)-325



Scheme 53. Synthesis of (+)-Nebivolol (276) from Fragments (*S,R*)-322 and (*R,R*)-325



by treatment with diethyl carbonate, and **331** was in turn condensed with **329** under acidic conditions to render quinoline carboxylate **332**. Next, ester **332** was reduced with $LiAlH_4$ to give alcohol **333**, which was in turn transformed into bromide **334** by

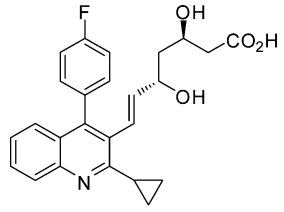


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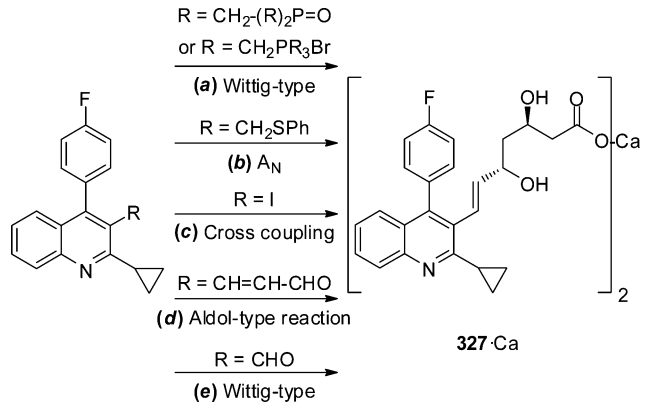
Figure 23. Structure of pitavastatin (**327**).

Scheme 54. Synthetic Strategies toward Pitavastatin (327)



treatment with PBr_3. Phosphonate **335** was prepared in quantitative yield by refluxing bromide **334** with Ph_2POEt in toluene. Alternatively, alcohol **333** was treated with *n*-Bu_3P and diphenyldisulfide to yield sulfide **336**. Furthermore, saponification of the ester **332** gave the corresponding acid that was converted into iodide **337** by treatment with acetoxyiodobenzene and iodine under UV irradiation.

The first synthesis of pitavastatin was performed employing a Wittig reaction as the key step (Scheme 54, strategy a).[173] The side chain was prepared starting from Taber's alcohol **338** as a chiral auxiliary (Scheme 56).[174] Transesterification with methyl acetoacetate in the presence of DMAP gave ester **339**. Its sodium lithium salt **340** was treated with Weinreb amide **341** to afford **342**, which was stereoselectively reduced to the *cis*-1,3-diol **343** by successive reduction with DIBAL and $NaBH_4/Et_2BOMe$. The chiral auxiliary was then removed, the resulting acid esterified with CH_2N_2, and the 1,3-diol moiety protected as the acetonide **344** that was converted into aldehyde **345** by ozonolysis. Next, phosphonate **335** was treated with lithium 2,2,6,6-tetramethylpiperidide (LTMP) to generate the corresponding phosphorus ylide, and then aldehyde **345** was added to the reaction mixture. This Wittig-type reaction rendered compound **346**, which was converted by acetonide deprotection and ester saponification into pitavastatin, which was isolated as its lactone **347** by heating in toluene.

Sulfide **336** was used for the second synthesis of pitavastatin.[175] It involved nucleophilic addition of its anion to a chiral epoxide that allowed asymmetric generation of one of the hydroxy groups present in the side chain (Scheme 54, strategy b). Thus, (*S*)-epichlorohydrin (**348**) was opened with the lithium anion of trimethylsilylacetylene in the presence of $BF_3{\cdot}OEt_2$ as a catalyst (Scheme 57). Alcohol **349** was transformed into epoxide **350** under basic conditions and subsequently opened by nucleophilic addition of the anion of sulfide **336** to render **351** as a mixture of diastereomers. Upon treatment with $PdCl_2$ and $CuCl_2$ in MeOH under CO atmosphere, the terminal alkyne was

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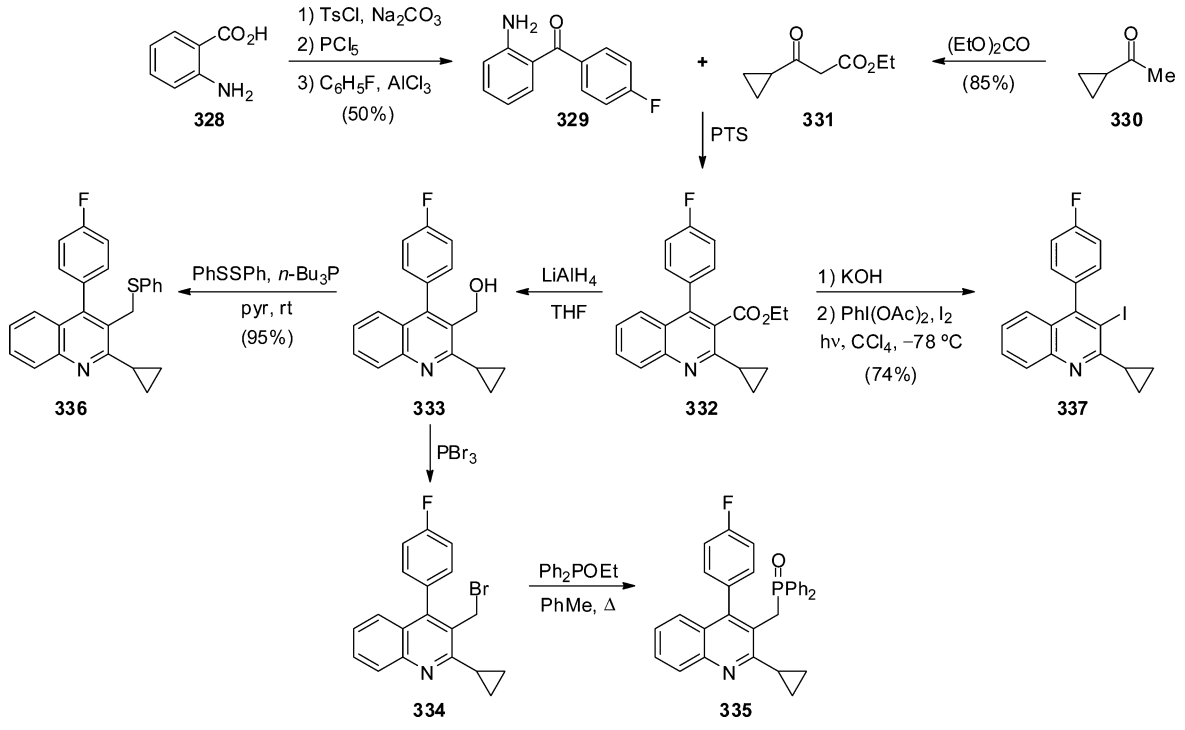
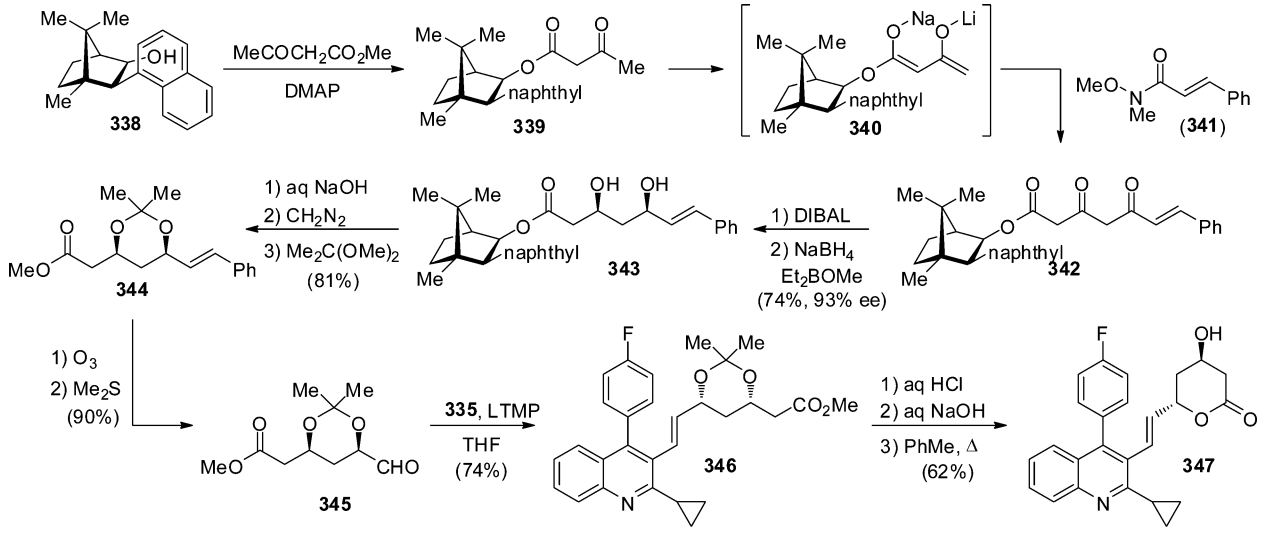
Scheme 55. Synthesis of Quinoline Moieties 225 and 337



Scheme 56. Wittig Reaction as Key Step in the First Synthesis of Pitavastatin (327)



methoxycarbonylated to give ester **352**. Then, the triple bond was reduced with Lindlar catalyst and lactonization by heating in the presence of PPTS afforded compound **353**. Oxidation of the sulfide followed by thermolysis in refluxing toluene furnished α,β-unsaturated lactone **354**. This conjugated lactone was epoxidized with H_2O_2 in basic media, affording **355** as a single diastereoisomer. The resulting epoxide was opened by treatment with diphenyl diselenide and $NaBH_4$ in the presence of a catalytic amount of acetic acid to render the desired lactone **347**.

The following two syntheses of pitavastatin were based on a quite innovative protocol, not used before in preparation of other synthetic statins, consisting of installation of the side chain by a palladium cross-coupling reaction of heteroaryl iodide **337** (Scheme 54, strategy c). Starting from (*R,R*)-diethyl tartrate (**356**),[176] acetonide formation and diester reduction afforded protected diol **357**, which was monobenzylated and chlorinated to compound **358** (Scheme 58). Reaction with lithium amide in liquid ammonia converted **358** into propargyl derivative **359** that was protected as its TBS derivative **360**. Next, treatment of **360** with BBr_3 afforded bromide **361** with inversion of the configuration, a reaction that also produced benzyl deprotection under the reaction conditions. Bromide **361** was then converted into nitrile **362** upon epoxide formation in the presence of a base followed by opening with potassium cyanide. The next step of the synthetic sequence was a Blaise reaction employing the organozinc derivative of *tert*-butyl bromoacetate to give, after acidic hydrolysis, keto ester **363**. Stereoselective syn reduction of the β-hydroxy ketone **363** was achieved by reaction with $NaBH_4$ and Et_2BOMe at low temperature, affording *syn*-diol **364**, the alkyne of which was deprotected and the diol protected as the

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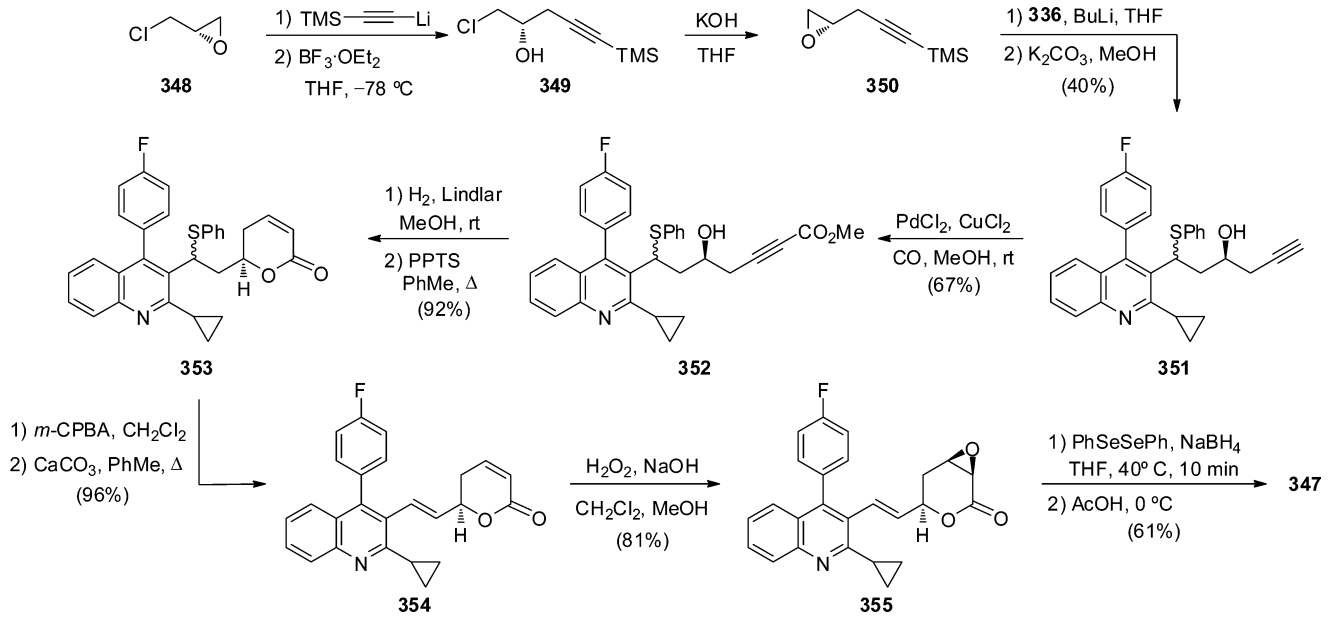
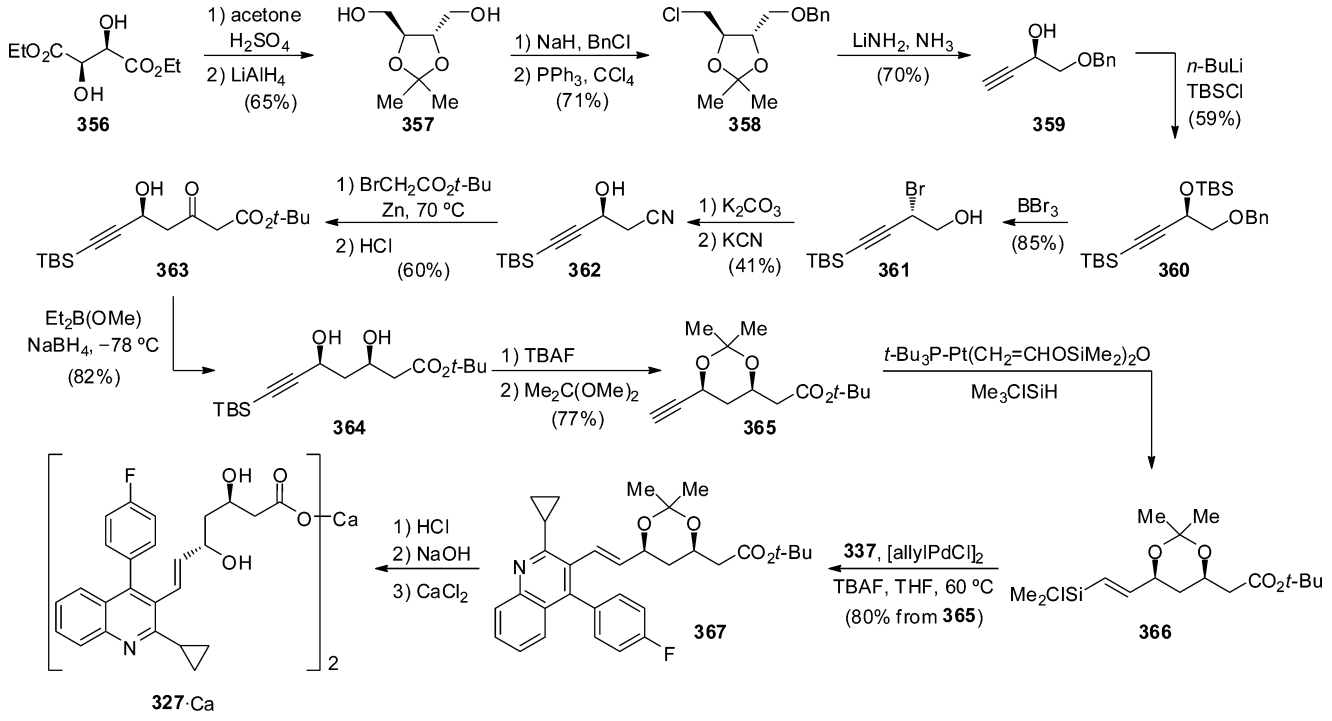
Scheme 57. (*S*)-Epichlorohydrin (348) as Starting Material in the Second Synthesis of Pitavastatin (327)



Scheme 58. Hiyama Coupling as Key Step in Synthesis of Pitavastatin (327)



acetonide **365**. The terminal triple bond was transformed into vinyl silane **366** by means of a hydrosilylation reaction catalyzed by a platinum complex. Palladium coupling of vinyl silane **366** with aryl iodide **337** afforded compound **367**, containing the complete skeleton of the final product, which was obtained as its calcium salt after protecting group removal.

A second alternative synthesis of pitavastatin, employing the same strategy, was simultaneously reported.[172a] In this case, a Suzuki-type coupling of the two fragments was the key step in the synthetic sequence. The side chain was constructed by reaction of the dianion of 3-oxobutyric acid ethyl ester (**369**) with protected propynal **368** (Scheme 59). In this manner, racemic keto ester **370** was obtained and stereoselectively reduced with $NaBH_4$ and Et_2BOMe to give diol **371**. The 1,3-diol moiety was protected as acetonide **372**, with concomitant loss of the TMS group, and the ester group was hydrolyzed yielding acid **373**. The next step was the resolution of **373**, which was accomplished by crystallization with (*R*)-(naphthyl)ethylamine. The corresponding acid moiety was esterified again as its ethyl ester **374**, and the precursor of the Suzuki reaction **375** was obtained by hydroboration of the triple bond with disiamyl borane. Palladium coupling with iodide **337** afforded derivative **376** that gave, after acetonide removal and ester deprotection, the target pitavastatin as its calcium salt.

A different strategy for preparation of pitavastatin and several derivatives in racemic form for SAR purposes was also

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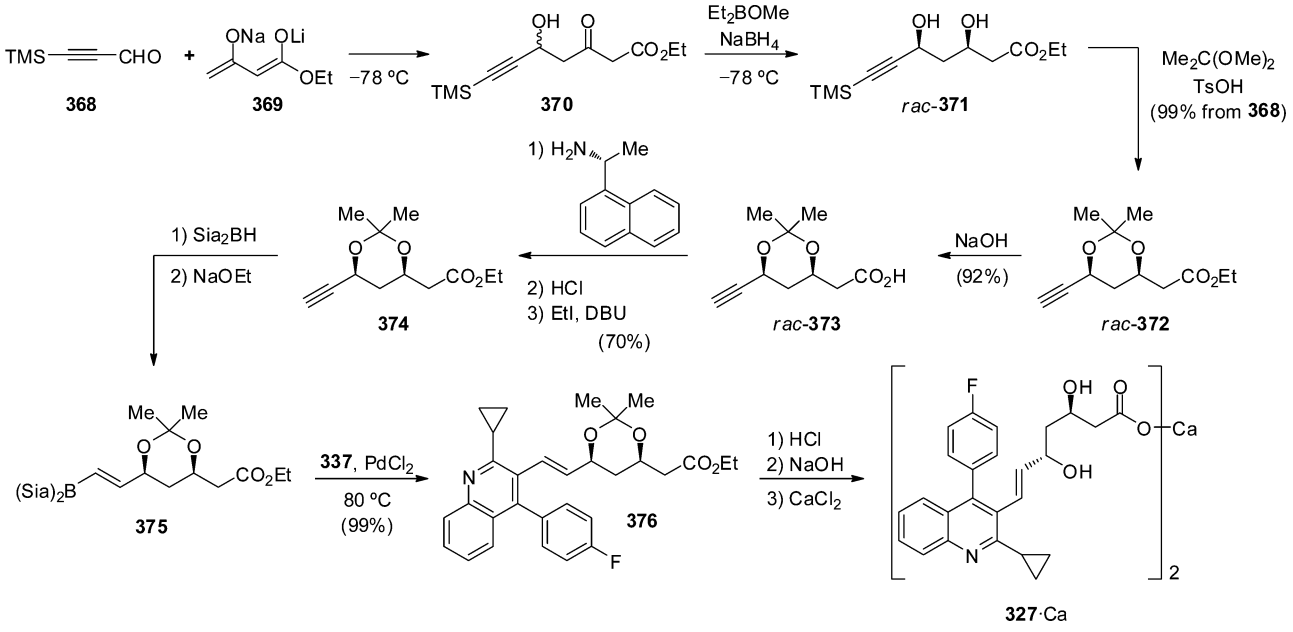
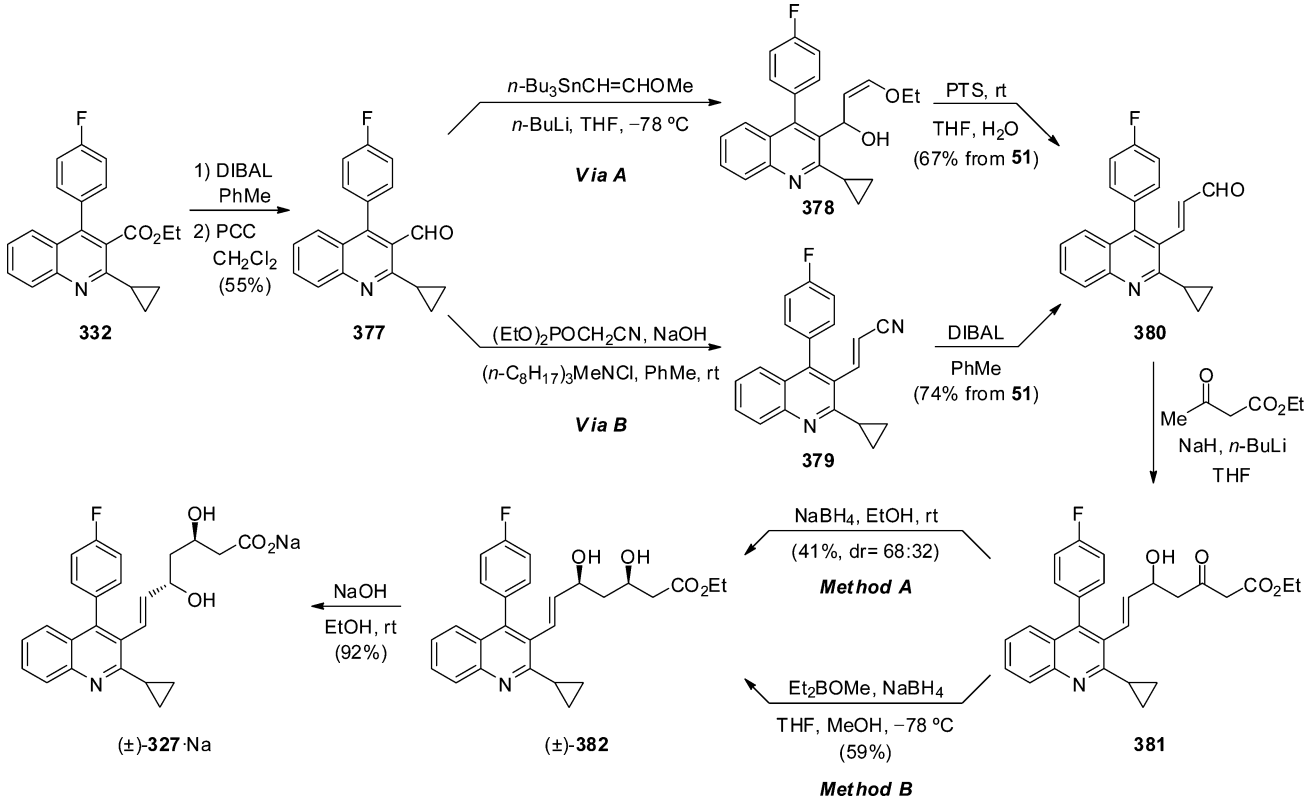
Scheme 59. Suzuki Coupling as Key Step in Synthesis of Pitavastatin (327)



Scheme 60. Synthesis of Pitavastatin (327) by Aldol Reaction with Aldehyde 380



reported.[177] In this case, an aldol-type reaction was used (Scheme 54, strategy d) as the key step in the synthetic sequence. The reduction−oxidation sequence of the ester group in **332** gave rise to quinoline aldehyde **377** (Scheme 60). Transformation of **377** into the precursor of the aldol-type reaction **380** can be accomplished by two different ways: by treatment with *cis*-ethoxyvinyl lithium obtained from trans-metalation of the corresponding stannane with BuLi followed by hydrolysis of enol ether **378** (Scheme 60, via A) or, alternatively, by Horner−Wadsworth−Emmons reaction with cyanomethyl phosphonate followed by DIBAL reduction of **379** (Scheme 60, via B). Aldol reaction between ethyl acetoacetate and aldehyde **380** yielded aldol **381**, which was reduced to generate the 1,3-diol derivative **382**. With $NaBH_4$ this reduction afforded a 68:32 mixture of diastereomers (Scheme 60, method A), while the same reaction in the presence of Et_2BOMe at −78 °C occurred with completed stereoselectivity (Scheme 60, method B).

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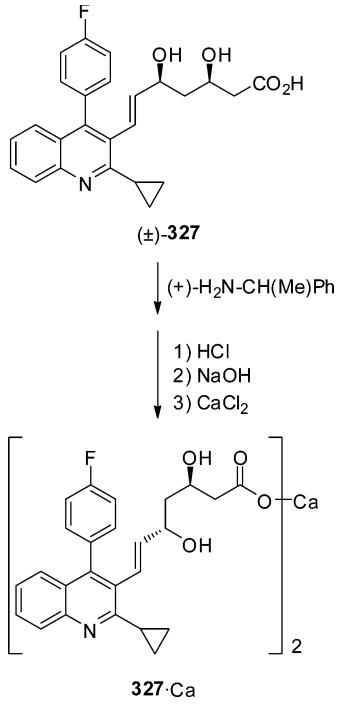
Finally, saponification of the ester group afforded racemic pitavastatin.

Synthesis of all stereoisomers of pitavastatin was also reported.[178] Synthesis of both racemic isomers (erythro and threo) was carried out followed by enantiomeric resolution using (+)-(phenyl)ethylamine. Acidification and formation of calcium salt afforded enantiomerically pure pitavastatin (Scheme 61).

Scheme 61. Synthesis of Pitavastatin (327) by Chemical Resolution



Two more synthetic strategies to access pitavastatin have been developed recently. The first one is based on a Wittig-type reaction (Scheme 54, strategy e) that involves preparation of phosphonate **385** bearing the side chain.[179] This chain was assembled by desymmetrization of prochiral anhydride **244** with (*S*)-(phenyl)ethylamine to obtain acid **383** in 93:7 enantiomeric ratio (Scheme 62). Using the mixed anhydride strategy, acid **383** was transformed into Weinreb amide **384** that was then treated with the lithium anion of methoxymethyl phosphonate to afford compound **385**. Horner–Wadsworth–Emmons reaction with aldehyde **377** yielded derivative **386** in good yield. Generation of the 1,3-diol moiety of **387** was again accomplished by reduction with $NaBH_4$ in the presence of Et_2BOMe at low temperature. Amide hydrolysis and addition of calcium chloride afforded pitavastatin as its calcium salt.

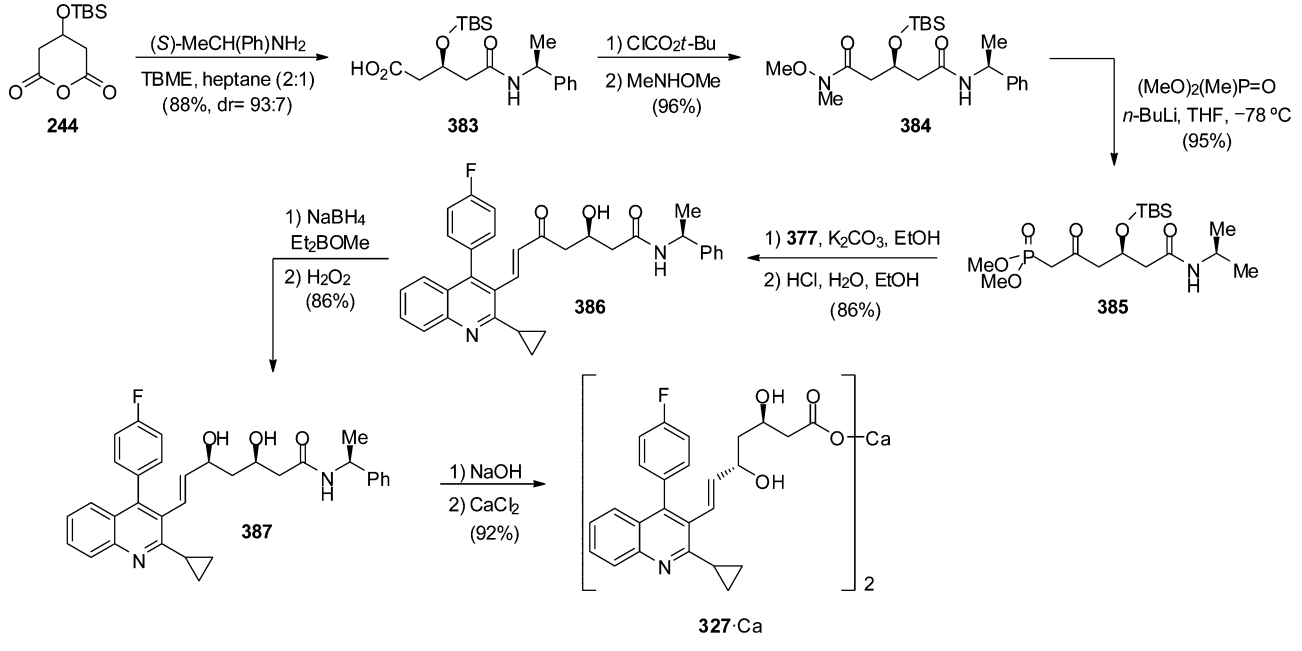
One more synthesis of **327** was reported very recently.[180] It involved a Wittig-type reaction with a phosphonium salt attached to the quinoline moiety as the key step (Scheme 54, strategy a). Bromide **334** was converted into its phosphonium salt **388**, and Wittig reaction with aldehyde **273** afforded intermediate **389** that was tranformed into pitavastatin calcium salt after silyl group removal and basic hydrolysis of the lactone nucleus followed by treatment with $CaCl_2$ (Scheme 63).

4.5. Prasugrel (Effient)

Prasugrel (**391**) is a new orally active thienopyridine class of adenosine diphosphate (ADP) receptor inhibitors (Figure 24).[181] Like clopidogrel (**392**), prasugrel inhibits platelet activation and aggregation through irreversible binding to $P2Y_{12}$ receptors. It was approved by the FDA in 2009 for reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention.[182] Current sales of the marketed drug (Effient, Eli-Lilly) reached $302.5 million in 2011.

Prasugrel belongs to the third generation of thienopyridines bearing a racemic stereogenic carbon center adjacent to the piperidine nitrogen. It is a prodrug, not therapeutically active itself, that is metabolized in the liver to give the pharmacologically active metabolite **395** (Scheme 64).[183] First, it is

Scheme 62. Synthesis of Pitavastatin (327) by Wittig Reaction with Phosphonate 385



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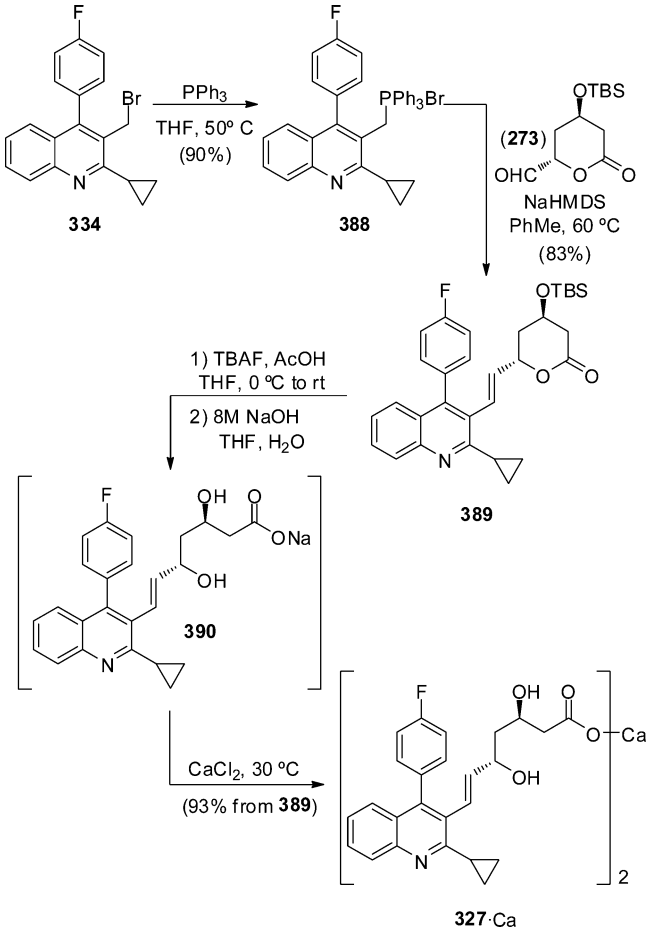
Scheme 63. Synthesis of Pitavastatin (327) by Wittig Reaction with Phosphonate 388



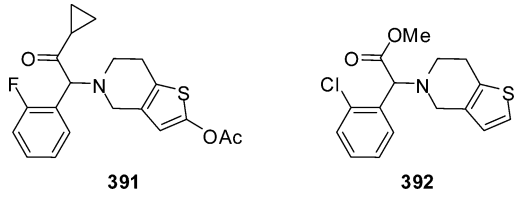


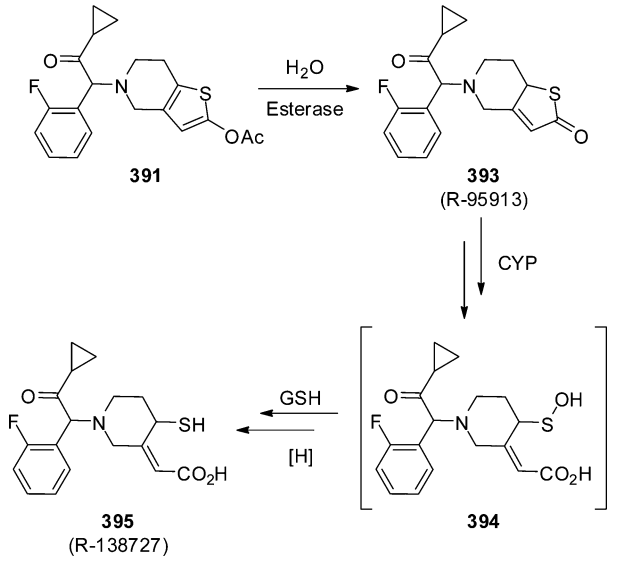
Figure 24. Structures of prasugrel (**391**) and clopidogrel (**392**).

transformed into the thiolactone **393** via an esterase-mediated hydrolysis. The active metabolite, that is, thiol **395**, is formed by several CYP-mediated oxidative events, and it is made up of four stereoisomers resulting from the presence of two chiral carbons in the structure. All four stereoisomers have antiplatelet activity, the (*R*,*S*)-isomer being the most potent one—at least 16 times more than the other three.

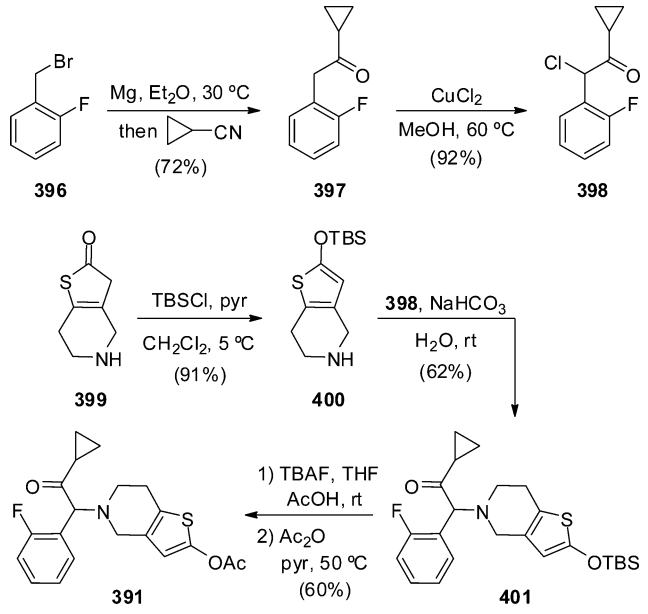
Both prasugrel and clopidogrel belong to the thienopyridine family, sharing a very similar chemical structure. However, prasugrel has a safer, higher, faster, and more consistent level of inhibition of platelet aggregation than clopidogrel. The small differences in structure between them, including replacement of the chlorine atom in **392** by a fluorine in **391**, are apparently translated into improved safety profile and pharmacokinetic properties, indicating that the limiting step for a maximal effect of the drug is not bioavailability but biotransformation.[184]

Synthesis of prasugrel involved coupling of fragments **398** and **400** (Scheme 65).[185] Fragment **398** was prepared by addition of the Grignard derivative of *o*-fluorobenzyl bromide (**396**) to

Scheme 64. Transformation of Prodrug Prasugrel (391) into Its Active Metabolite 395



Scheme 65. Synthesis of Prasugrel (391) by Coupling of Fragments 398 and 400



cyclopropylnitrile. Introduction of a chlorine atom into the α-position of the ketone was achieved in excellent yield using $CuCl_2$. On the other hand, fragment **400** was prepared from commercially available thiolactone **399** by treatment with TBSCl. Coupling of the two fragments was achieved in the presence of $NaHCO_3$. TBS deprotection and acetylation of derivative **401** rendered the final product **391**.

A large-scale procedure for preparation of prasugrel (5.8 kg) in 58% overall yield and 99.9% purity[186] has been recently reported using a similar protocol to that shown in Scheme 65. Commercially available thiolactone **399** and bromo derivative **402** were coupled in the presence of Na_2CO_3 (Scheme 66). Intermediate **403** was in situ acetylated to yield prasugrel in one step. Finally, it was converted into the hydrochloride salt by treatment with isopropanolic hydrochloride.

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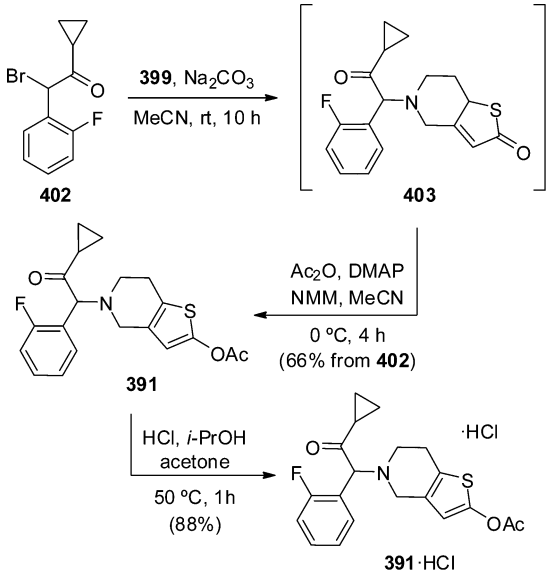
Scheme 66. Large-Scale Procedure for Preparation of Prasugrel (391)



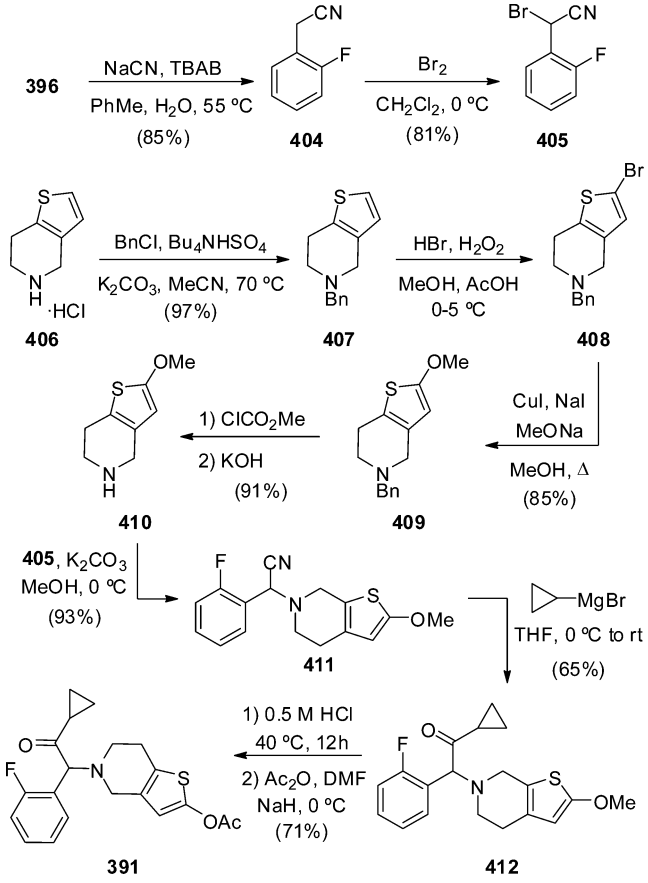
Finally, a new synthesis of prasugrel has been recently reported.[187] The major modification in this procedure was introduction of the cyclopropyl moiety at the end of synthesis. Again, two fragments were coupled to access the skeleton of prasugrel. Fragment **405** was prepared from *o*-fluorobenzyl bromide (**396**), which was transformed into nitrile **404**, and then, a bromine atom was introduced at the α-position (Scheme 67). Fragment **410** was synthesized from thienopyridine **406**. Nitrogen protection followed by electrophilic aromatic substitution gave the bromine-containing compound **408**. Then, the bromine atom was replaced by a methoxy group, and compound **409** was debenzylated to afford fragment **410**. Coupling of both fragments, **405** and **410**, was achieved in the presence of a base to yield nitrile **411**, which was then reacted with cyclopropyl magnesium bromide, affording ketone **412**. Synthesis was completed with hydrolysis of the methoxy group and subsequent acetylation.

4.6. Ticagrelor (Brilique, Brilinta)

Ticagrelor (**413**) belongs to the new chemical class of cyclopentyl-triazolo-pyrimidines that display effective inhibition of platelet aggregation (Figure 25).[188] It is the first reversible $P2Y_{12}$ receptor antagonist blocking adenine diphosphate (ADP)-induced platelet aggregation—in contrast with the currently available thienopyridines which display irreversible receptor binding—via a mechanism which is not competitive with ADP, thus suggesting the existence of an independent receptor binding site.[189] It was approved by the FDA in 2011 for prevention of thrombotic events such as stroke or heart attack in patients with acute coronary syndrome (ACS) or myocardial infarction with ST elevation.[190] Current sales of the marketed drug (Brilique and Brilinta, Astra-Zeneca) reached $21 million in 2011.

Discovery of ticagrelor was based on the fact that ATP is the natural antagonist of $P2Y_{12}$ receptor. Used as a chemical starting point, ATP modification led to identification of cangrelor (**414**) as a novel and promising candidate for antithrombotic therapy.[191] However, compound **414** was found to be a selective receptor antagonist suitable for intravenous use only. Extensive SAR studies of cangrelor, with modification of its physical and chemical properties, ended in development of the selective and

Scheme 67. Late Introduction of the Cyclopropyl Moiety in Synthesis of Prasugrel (391)



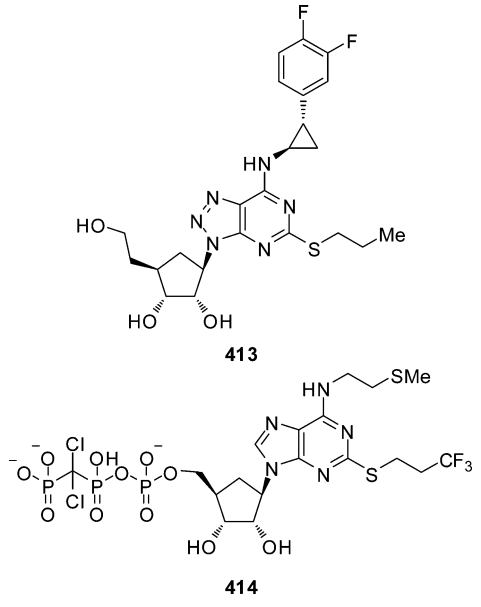


Figure 25. Structures of ticagrelor (**413**) and cangrelor (**414**).

orally active $P2Y_{12}$ antagonist ticagrelor. Thus, the triazolopyrimidine heterocycle was identified as an isostere of purine, the potential instability of the glycosidic bond to enzymatic cleavage induced replacement of the sugar by the cyclopentyl unit, propyl substitution at the S atom solved the problem of the oral absorption of cangrelor, and introduction of the lipophilic

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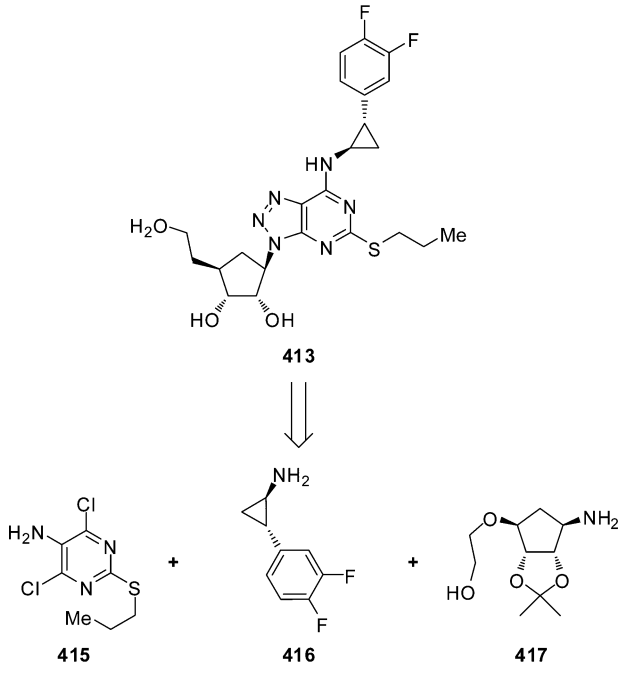
difluorophenyl cyclopropyl group was crucial for achieving good potency and good preclinical metabolic properties. As a result, ticagrelor shows excellent metabolic stability, and it does not require conversion to an active metabolite.

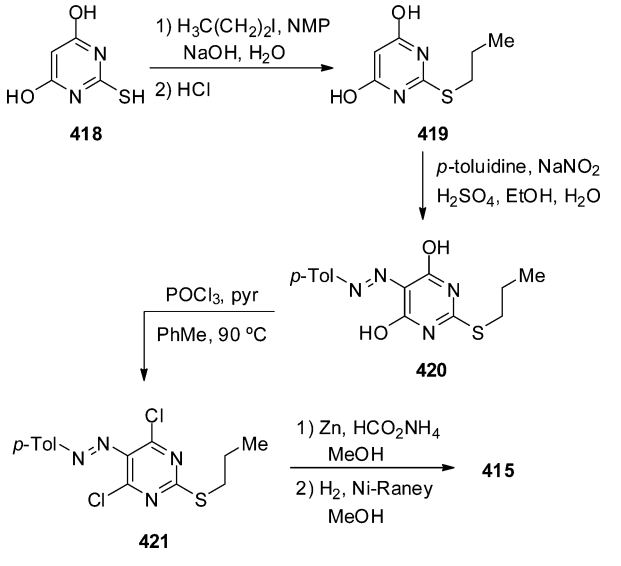
Retrosynthetic analysis of ticagrelor is shown in Scheme 68. It is a convergent protocol that involves reaction between pyrimidine **415**, fluorinated cyclopropylamine **416**, and sugar derivative **417**.[192]

Scheme 68. Retrosynthetic Analysis of Ticagrelor (413)



Pyrimidine **415** was prepared from 2-thiobarbituric acid (**418**) (Scheme 69). After alkylation of the thiol moiety, compound **419** was treated with the diazonium salt of *p*-toluidine, affording diazo-compound **420**. Introduction of chlorine was performed by treatment with $POCl_3$, and finally, reduction of the diazo

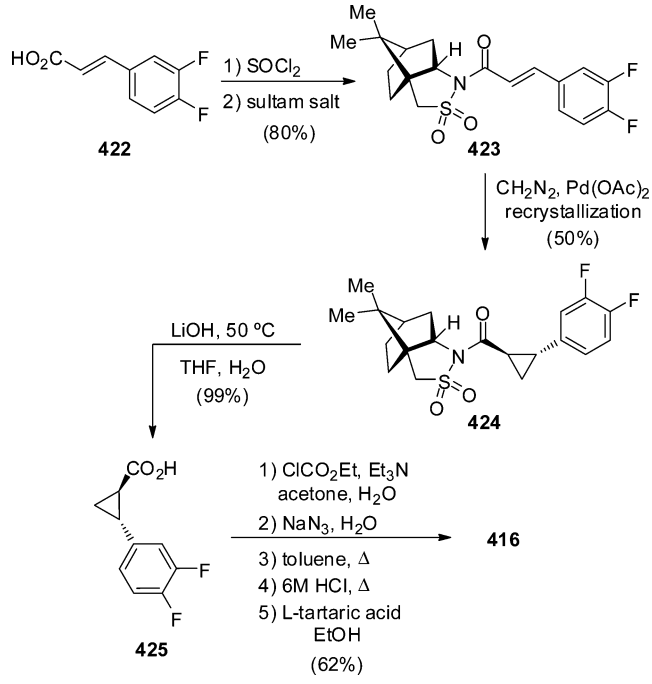
Scheme 69. Synthesis of the Pyrimidine Fragment 415



moiety in **421** with Zn followed by N−N cleavage with Ni-Raney gave the desired pyrimidine **415**.

3,4-Difluorocynnamic acid (**422**) was used as starting material to access cyclopropyl derivative **416** (Scheme 70). The

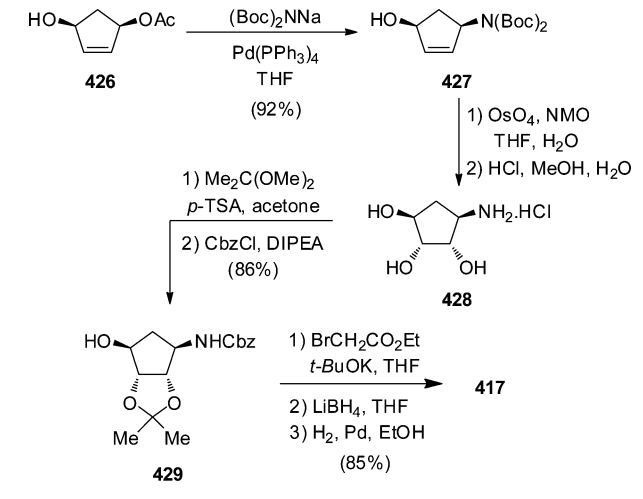
Scheme 70. Synthesis of the Cyclopropyl Amine Fragment 416



corresponding Oppolzer's sultam **423** was chosen as a chiral auxiliary to perform diastereoselective cyclopropanation to **424**. Chiral auxiliary removal afforded acid **425**, which was subjected to Curtius rearrangement, rendering the desired amine **416**, isolated as the tartrate salt.

Synthesis of fragment **417** started with commercially available monoprotected diol **426** (Scheme 71). First, the acetate group was substituted with Boc-protected sodium amide under palladium catalysis to afford derivative **427**. Diastereoselective dihydroxylation followed by carbamate cleavage yielded compound **428**. *cis*-1,2-Diol was protected as its acetonide and

Scheme 71. Synthesis of Amino Alcohol Fragment 417



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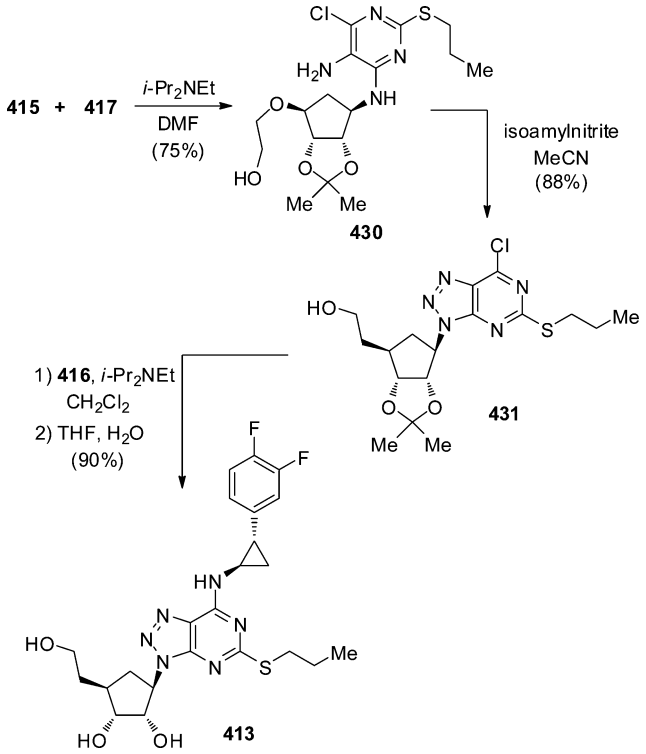
the nitrogen reprotected with the Cbz group to render compound **429**. Synthesis of **417** was completed by reaction with ethyl bromoacetate followed by ester reduction and nitrogen deprotection.

Coupling of the fragments started with reaction of amine **417** with pyrimidine **415** by chlorine displacement in the presence of diisopropylethylamine (Scheme 72). Compound **430** was converted, under diazotization conditions, into the triazolo pyrimidine heterocycle **431**. Another chlorine displacement on **431** with fragment **416** followed by acetonide deprotection yielded the desired compound ticagrelor.

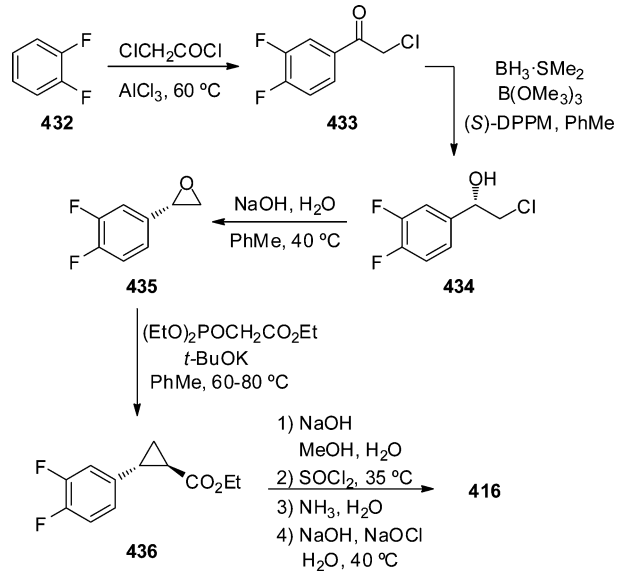
Scheme 72. Synthesis of Ticagrelor (413) by Coupling of Fragments 415, 416, and 417



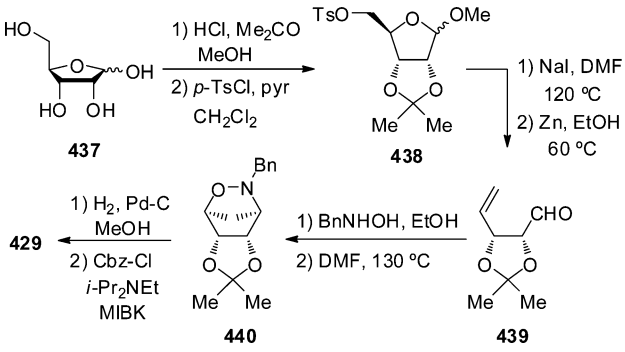
Subsequent process chemistry studies allowed for further improvement in the synthesis of the target drug in terms of more efficient preparation of the fragments **416** and **417** and final coupling.[193] Thus, 1,2-difluorobenzene (**432**) was transformed into the α-chloro ketone **433**, which was reduced with borane in the presence of (*S*)-diphenylprolinol to afford chiral chlorohydrin **434** possessing the correct configuration of the secondary alcohol's stereogenic center (Scheme 73). Further epoxidation under basic conditions was followed by triethyl phosphonoacetate-mediated Wadsworth–Emmons cyclopropanation to give ester **436** and, finally, compound **416** upon saponification and Hofmann degradation.

For preparation of fragment **417** D-ribose (**437**) was used as starting material. Initially, the anomeric carbon was transformed into the corresponding acetal, the *cis*-1,2 diol protected as its acetonide, and the primary alcohol tosylated to yield compound **438** (Scheme 74). Displacement of the tosylate by iodide followed by treatment with activated zinc in refluxing ethanol gave access to aldehyde **439**. Reaction with benzyl hydroxyl amine afforded the corresponding oxime which, upon heating, was converted into the nitrone that reacted intramolecularly with the olefin to render bicycle **440**. Reductive cleavage of the N–O bond afforded an amino alcohol, which was protected as its Cbz derivative **429**. Finally, introduction of the side chain to access fragment **417** was performed as depicted in Scheme 71. Final coupling of the fragments was carried out with little modifications in comparison with the conditions depicted in Scheme 72.

Scheme 73. Process Chemistry Improvement of Fragment 416



Scheme 74. Process Chemistry Improvement of Fragment 417



5. DRUGS FOR INFECTIOUS DISEASES

5.1. Voriconazole (Vfend)

During the last few decades, fungi have become a major threat to many hospitalized patients, particularly for those who are severely immunocompromised and therefore highly susceptible to systemic fungal infections, most often caused by *Candida* and *Aspergillus* species.[194] For this reason and also because of a rapid emergence of resistant and new opportunistic fungi, development of new antifungal agents targeting specific structures or functions has been actively pursued. Among the different chemical families used for treatment of invasive fungal infections, azoles and, specifically, triazoles are the largest class of antifungal agents in clinical use.[195] These compounds block synthesis of ergosterol, a major component of fungal cell membranes. Specifically, they act by inhibition of the fungal cytochrome P450-dependent conversion of lanosterol to ergosterol through 14-α-demethylation.[196] This inhibition leads to depletion of

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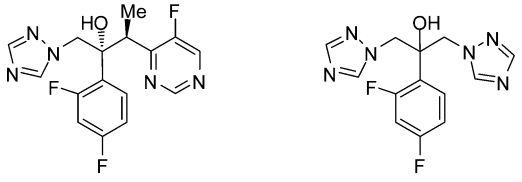
ergosterol in the cell membrane and accumulation of toxic intermediate sterols, causing increased membrane permeability and inhibition of fungal growth.[197]

Voriconazole (**441**) is a modern triazole related to fluconazole (**442**) that was first marketed by Pfizer (Vfend) in 2002 for treatment of fungal infections in patients intolerant or refractary to other therapies and for treatment of invasive aspergillosis (Figure 26). Although fluconazole is the antifungal of choice for



441 **442**

Figure 26. Structures of voriconazole (**441**) and fluconazole (**442**).

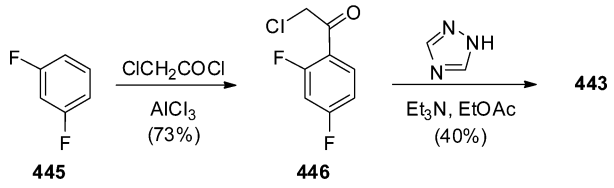
treatment of infections from two of the main human fungal pathogens (*Candida albicans* and *Cryptococcus neoformans*), it is poorly effective against infections caused by the third major pathogen, *Aspergillus fumigatus*. Pfizer scientists found that introduction of a methyl group adjacent to one of the triazole rings of fluconazole increased potency against *A. fumigatus* as it would function as an equivalent of the 13β-methyl group of lanosterol.[198] Replacement of the triazole ring adjacent to the branch point with six-membered heterocycles provided compounds with broad-spectrum in vitro activity and a fungicidal mechanism of action against *A. fumigatus*, with the 5-fluoro-4-pyrimidinyl substituent present in voriconazole being the best one.[199] Additionally, the 2,4-difluorophenyl moiety was maintained for retaining high activity against the other fungal pathogens.[200]

Synthesis of voriconazole also demonstrates its evolution from fluconazole as both make use of the same triazolyl difluoroacetophenone **443**. This is coupled with 4-chloro-5-fluoro-6-ethylpyrimidine (**444**) to access the desired compound (Scheme 75).

For preparation of compound **443**, aluminum chloride-catalyzed chloroacetylation of 1,3-difluorobenzene (**445**) afforded 1′-chloro-2,4-difluoroacetophenone (**446**) in good yield (Scheme 76). Displacement of the chloride with 1,2,4-triazole using triethylamine in refluxing ethyl acetate gave the desired triazolyl ketone **443**.

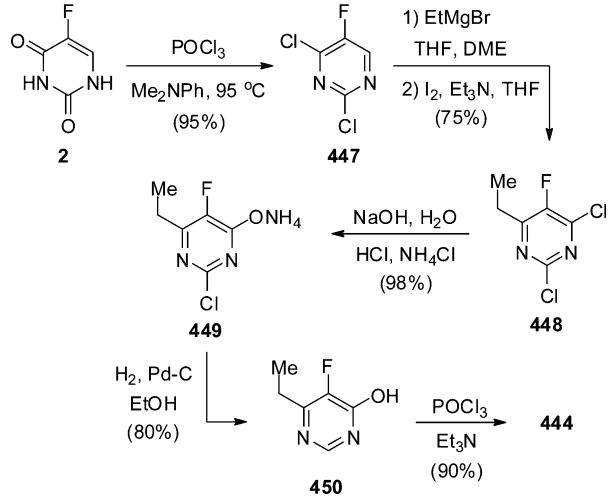
Regarding synthesis of the pyrimidine fragment, a variety of ethyl pyrimidine analogs were synthesized and investigated in their reaction with **443** under different metalation conditions.[201] These analogs were all prepared starting from 5-fluorouracil (**2**)

Scheme 76. Preparation of Intermediate 443



(Scheme 77). Key condensation of anions derived from the various ethyl pyrimidines was the subject of extensive

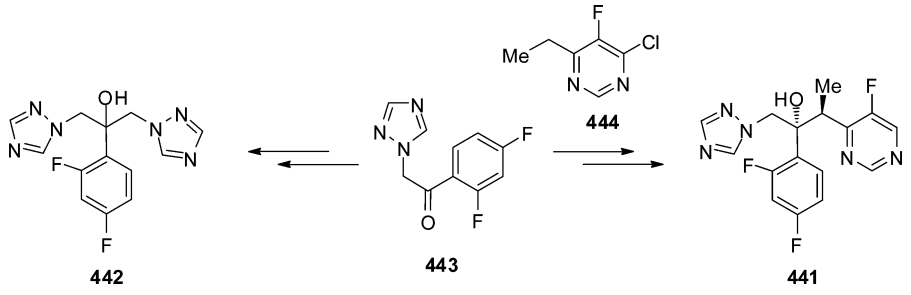
Scheme 77. Synthesis of the Pyrimidine Fragment 444



investigation in order to minimize different competing reactions. From these experiments, 4-chloro-5-fluoro-6-ethyl-pyrimidine (**444**) was found to be the best one. Accordingly, 5-fluorouracil was chlorinated in both the 2- and the 4- positions using a mixture of phosphorus oxychloride and *N*,*N*-dimethylaniline. Dichloro pyrimidine **447** was reacted with ethyl magnesium bromide, and the resulting adduct was oxidized using a mixture of iodine and triethylamine to give 2,4-dichloro-6-ethyl-5-fluoro pyrimidine (**448**) in good yield. Reaction of **448** with aqueous NaOH gave selective displacement of the chloro functionality at position 4. Next, dechlorination of the resulting pyrimidine **449** by catalytic hydrogenation followed by rechlorination with phosphorus oxychloride afforded compound **444**.

A more efficient route to pyrimidine **450** was also developed in which methyl 3-oxopentanoate (**451**) was fluorinated[202] with fluorine gas to give methyl 2-fluoro-3-oxopentanoate (**452**) (Scheme 78). This ester was then cyclized[203] with formamidine

Scheme 75. Synthetic Strategy To Access Voriconazole (441) and Fluconazole (442) from the Common Triazolyl Difluoroacetophenone Intermediate 443



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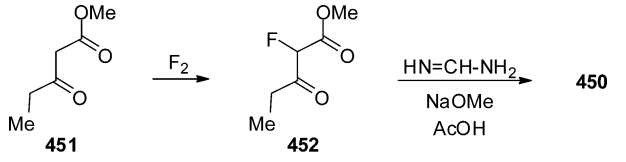
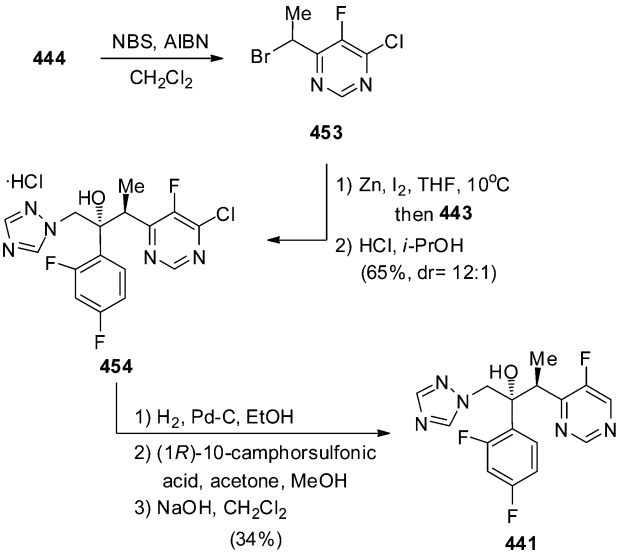
Scheme 78. Improved Route to Pyrimidine Fragment 444



acetate in the presence of NaOMe to give **450** directly. This chemistry was successfully scaled up to provide 100 kg quantities of pyrimidinone **450**.

Radical bromination of ethyl derivative **444** with NBS in the presence of AIBN provided compound **453** (Scheme 79). Then,

Scheme 79. Synthesis of Voriconazole (441) by Coupling of Fragments 443 and 444



a Reformatsky protocol was employed in the condensation of **453** with ketone **443** using zinc dust activated with iodine/THF. Conducting the reaction at 10 °C improved the diastereoselectivity of the process up to 12:1. Finally, compound **454** was dechlorinated using standard hydrogenation conditions to give the racemic voriconazole. This was resolved using (1*R*)-10-camphorsulfonic acid in an acetone/methanol solvent mixture, yielding an enantiopure salt after recrystallization, from which voriconazole free base could be regenerated.

5.2. Emtricitabine (Emtriva)

Emtricitabine (**455**) is an orally administered nucleoside reverse transcriptase inhibitor (NRTI) that selectively and potently inhibits human immunodeficiency virus type 1 (HIV-1) replication[204] and hepatitis B virus (HBV) (Figure 27).[205] It is an optically active drug approved by the FDA in July 2003 for

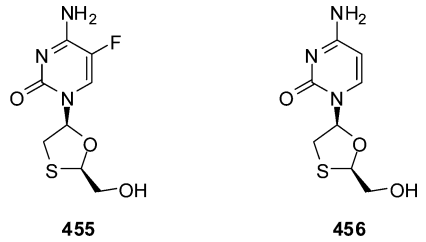


Figure 27. Structures of emtricitabine (**455**) and lamivudine (**456**).

treatment of HIV and hepatitis B infections. It is also used in combination with other drugs in highly active antiretroviral therapy (HAART). It was developed by Gilead Sciences Pharmaceuticals and marketed with the name of Emtriva.

Since the discovery of AZT (3′-azido-3′-deoxythimidine) as an effective agent against HIV-1, a number of nucleosides have been developed as potential anti-HIV agents. The toxicity associated with its use, together with the emergence of AZT-resistant strains, explains the critical need for development of new HIV agents with improved activity and selectivity. This is the case of the cytidine derivative lamivudine (**456**). Emtricitabine is the result of the search for more active HIV-1 agents derived from lamiduvine. In this context, introduction of a fluorine atom in the 5 position of the cytidine ring of **456** was translated into 4−10 times more potency and a higher therapeutic index than the parent compound against HIV-1.[206]

Synthesis of emtricitabine was performed employing L-gulose (**457**) as chiral starting material (Scheme 80).[207] After tosylation of the primary alcohol and peracetylation, treatment with HBr converted **457** into bromide **458**. Reaction with potassium *O*-ethyl xantate in refluxing acetone and deacetylation under basic conditions transformed **458** into bicyclic derivative **459**. Then, degradation with $NaIO_4$ followed by reduction with $NaBH_4$ and 1,2-diol protection as the corresponding acetonide rendered compound **460**, the primary alcohol which was protected with TBDPSCl along with removal of the acetonide group. Afterward, the 1,2-diol was degradated with $Pb(OAc)_4$ and the resulting aldehyde oxidized to acid **461**. Another degradation with $Pb(OAc)_4$ converted **461** into **462**, which was used to couple the heterocyclic fragment. Thus, treatment of **462** with cytosine derivative **463** gave compound **464** as a 1.3:1 mixture of diastereoisomers. The desired cis isomer was isolated via chromatography and, after silyl group removal and benzoyl amide hydrolysis, converted into the desired molecule, emtricitabine (**455**).

For scale-up purposes, two methodologies have been devised for preparation of the target drug in racemic form. The first one[208] started with allyl alcohol (**467**), which was protected and oxidized with ozone to render aldehyde **468** (Scheme 81). Reaction with mercaptoacetic acid gave rise to the heterocycle **469**, which was converted into **470** by reduction with DIBAL and acetylation. Treatment of **470** with protected fluorocytosine **466** (obtained from **465** by reaction with HMDS) in the presence of $SnCl_4$ and final silyl group removal rendered the desired compound **455**.

Alternatively, another route starting from 2-butene-1,4-diol (**471**) has been developed (Scheme 82).[209] Diol **471** was diacylated with butyryl chloride to give diester **472**. Treatment with ozone followed by addition of thiourea gave hemiacetal **473**, which was treated in situ with mercaptoacetic acid to furnish heterocycle **474**. Reduction and acetylation gave the key intermediate **475**, which was treated with protected cytosine **466** to afford an equimolecular mixture of anomers. Compound **476** was isolated after crystallization and converted into emtricitabine using resin DOWEX SBR.

Synthesis of emtricitabine in enantiomerically pure form was accomplished by means of an enzyme-mediated resolution. Thus, when butyl ester **476** was treated with pig liver esterase, clean hydrolysis of the undesired enantiomer (+)-**455** took place and compound (−)-**476** was isolated in excellent enantiomeric purity. After chromatographic separation, compound (−)-**476** was hydrolyzed to emtricitabine (−)-**455** (Scheme 83).[210] It is important to mention that compound (−)-**455** was about 20-

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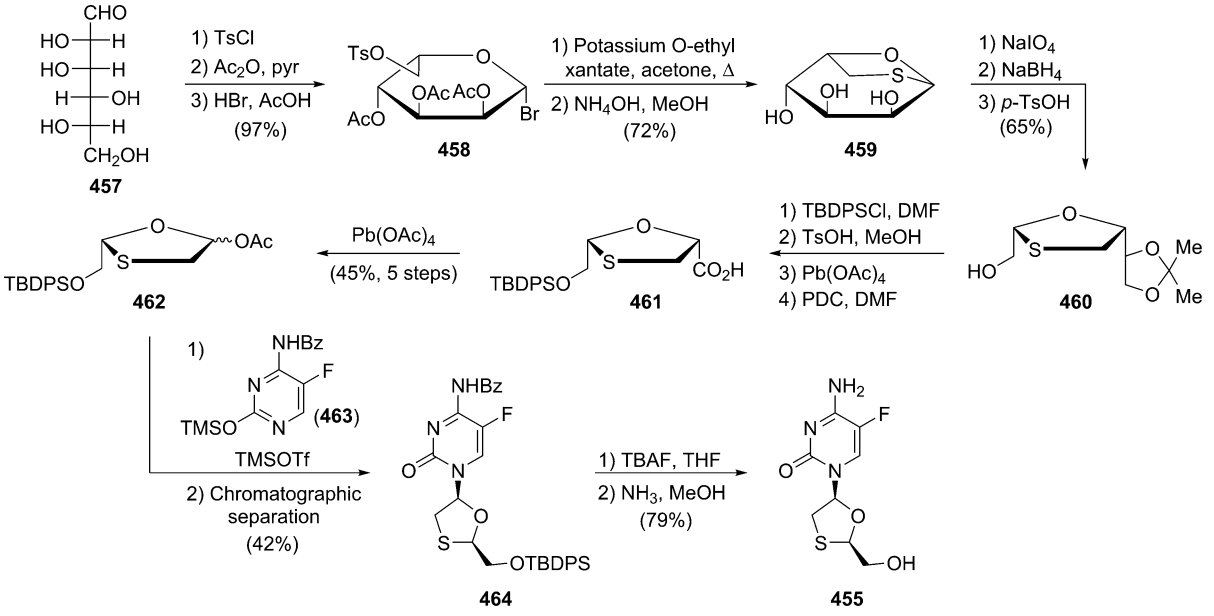
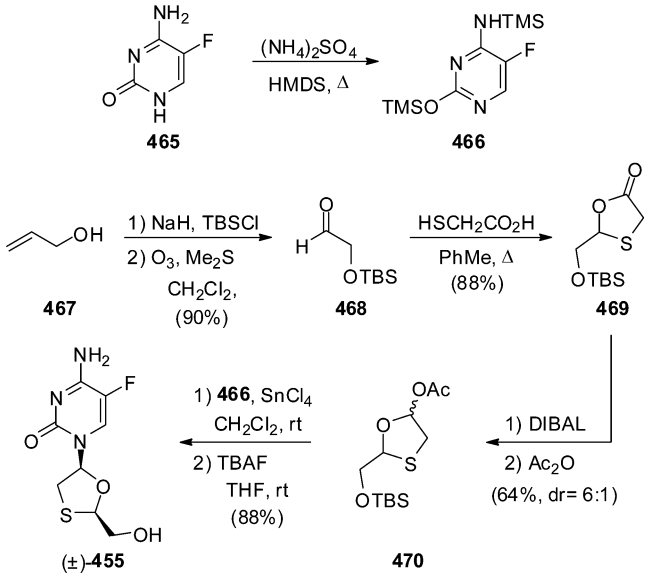
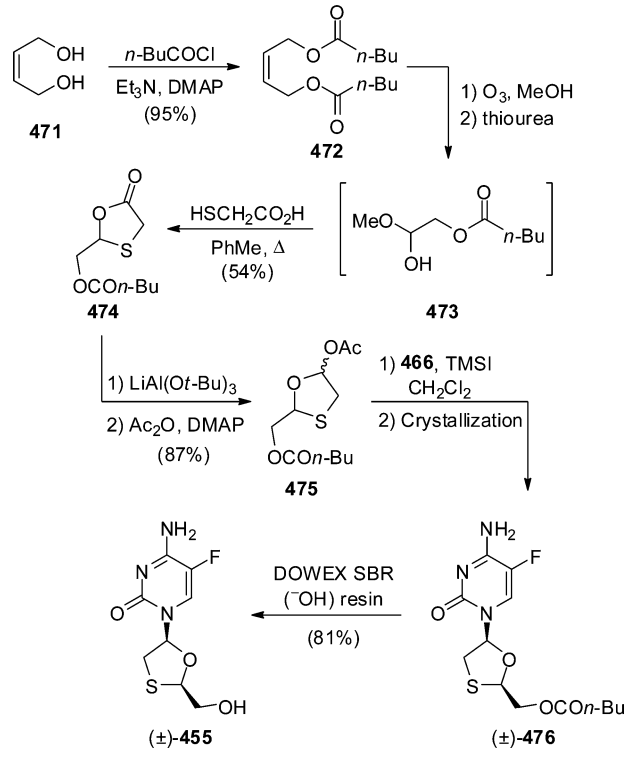
Scheme 80. Synthesis of Emtricitabine (455) from L-Gulose (457)



Scheme 81. Scale-Up Synthesis of Emtricitabine (455) from Allylic Alcohol (467)



Scheme 82. Scale-Up Synthesis of Emtricitabine (455) from 2-Butene-1,4-diol (471)



fold more potent that its enantiomer.[211] Use of an animal-derived enzyme in the generation of this pharmaceutical ingredient raises concern about the security, since final product could be contaminated with viruses. To avoid this problem, an immobilized enzyme obtained from microbial source was obtained, giving excellent results in the resolution protocol.[212]

Finally, emtricitabine was recently employed to generate dinucleoside−glutamate conjugates such as **477**, showing better antiviral profiles than the parent nucleosides (Figure 28).[213] Likewise, fatty acid conjugates of emtricitabine **478** with myristic acid, 12-azido dodecanoic acid, and 12-thioethyl dodecanoic acid were synthesized; the myristoylayed conjugate showed up to 6 times more activity than the parent compound.[214]

5.3. Tripanavir (Aptivus)

Tripanavir (**479**) is a selective nonpeptidic HIV-1 protease inhibitor (PI), indicated for use in highly treatment experienced patients with multiple PI resistance (Figure 29). In June 2005, the U.S. FDA granted accelerated approval to tipranavir based on data from the RESIST-1 and RESIST-2 studies (RESIST, Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients with tripanavir). The drug, originally discovered at Pfizer and then developed by Boehringer Ingelheim, was marketed with the name Aptivus.[215]

There are currently 10 FDA-approved protease inhibitors. Most of them are peptidomimetics, and therefore, their therapeutic utility is often compromised by low oral bioavailo-

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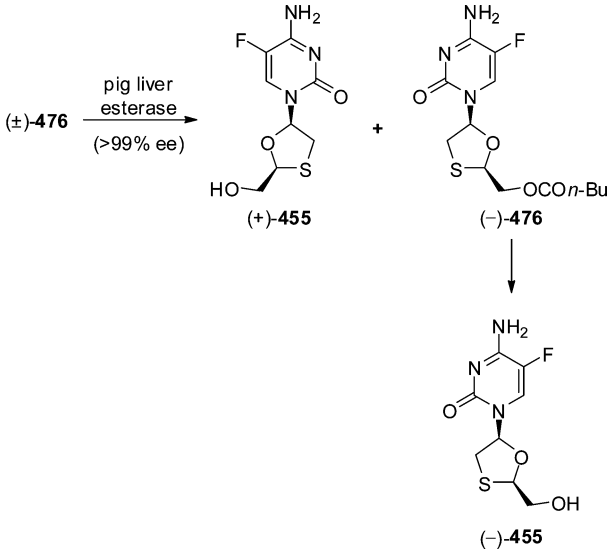
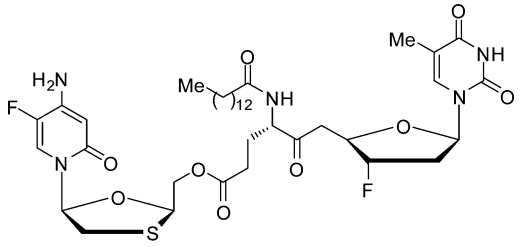
Scheme 83. Enzyme-Mediated Resolution Synthesis of Enantiomerically Pure Emtricitabine (455)





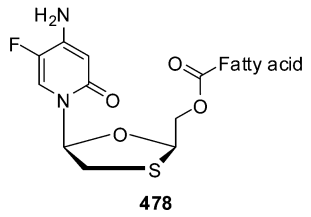
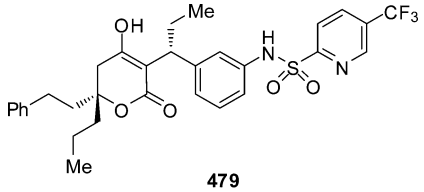


Figure 28. Structures of emtricitabine conjugates **477** and **478**.



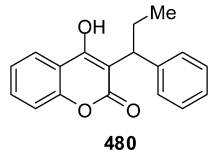


Figure 29. Structures of tripanavir (**479**) and lead compound **480**.

ability and rapid excretion. Tripanavir is the first antiretroviral agent with nonpeptidic nature that exhibits a good profile as protease inhibitor. After identification of compound **480** as an active HIV-protease inhibitory template, several iterative cycles of structure-based design led to the discovery of sulfonamide-containing 5,6-dihydro-4-hydroxy-2-pyrones as promising candidates. SAR studies over the sulfonamide moiety indicated that the 4-trifluoromethyl-2-pyridyl substituent gave nanomolar values of inhibition over the HIV-protease, with the *R* absolute configuration being preferred at the two stereocenters of **479**. Additionally, the crystal structure of the HIV-1 protease triple mutant (Q7K/L33I/L63I) complexed with tripanavir was determined, indicating an appropriate binding with the enzyme active site.[216]

Initially, tripanavir was synthesized in racemic form starting from 1-phenyl-3-hexanone (**481**), which was treated with the sodium anion of ethyl acetoacetate, followed by basic ester hydrolysis (Scheme 84). Upon acidification, pyrone **482** was obtained and condensation with the corresponding aromatic aldehyde gave unsaturated ketone **483**, which was treated with Et_3Al in the presence of $CuBr{\cdot}SMe_2$ to effect the conjugated addition affording compound **484**. Transformation of the nitro group to the amine functionality of tripanavir was achieved by catalytic hydrogenation and coupling with sulfonyl chloride **485**. This procedure, developed with SAR purposes, led to the discovery that the isomer with absolute configuration (3α*R*,6*R*) was the most active one.[217]

The first asymmetric synthesis of tripanavir was based on the use of Evans oxazolidinones as chiral auxiliaries.[218] Oxazolidinone **486** was acylated to give the Michael acceptor **487**,[219] which was treated with the aryl cuprate derived from {3-[bis(trimethylsilyl)amino]phenyl}magnesium bromide to set the first stereocenter (Scheme 85). Compound **488** was obtained as a single diastereomer after removal of the silyl groups and dibenzylation of the nitrogen. Formation of the titanium enolate followed by addition of 2-methyl-2-methoxy-1,3-dioxolane afforded, after acidic hydrolysis, acylated compound **489**. The quaternary stereocenter was generated by means of an aldol condensation of the titanium enolate of **489**, prepared by treatment with $Ti(O\textit{n}\text{-Bu})Cl_3$ and Hünig's base, with ketone **490**. In this manner, compound **491** was formed with excellent diastereoselectivity. Lactonization was effected by treatment with *t*-BuOK, and finally, lactone **492** was debenzylated and the triple bond hydrogenated to furnish, after reaction with sulfonyl chloride **485**, tripanavir (**479**).

Scalable synthesis of **479** was achieved by means of an aldol condensation as the key step between aldehyde **497** bearing the quaternary sterocenter and ester **502** containing the ethyl-substituted stereocenter.[220] In Scheme 86 synthesis of fragment **497** is depicted. The synthetic sequence started with reaction of 1-phenyl-3-hexanone (**481**) with the lithium enolate of ethyl acetate, followed by ester hydrolysis in basic media. Acid **493** was resolved by crystallization with (1*R*,2*S*)-norephedrine (**494**) to give hydroxyl acid **495** as the corresponding salt. After releasing the acid functionality, the secondary hydroxyl group was protected and the acid reduced to the primary alcohol **496**, which was in turn oxidized to aldehyde **497**.

For preparation of fragment **502** two different approaches have been devised. The first one involved Knoevenagel condensation of aldehyde **499** with methyl malonate **498** to render conjugated diester **500**. Then, conjugate addition of Et_2Zn in the presence of CuBr·DMS afforded diester **501**, which was decarboxylated and esterified to racemic ester **502**. Enantiomers of **502** were separated by means of chiral column chromatography (Scheme 87, Method A). Alternatively, an enzymatic approach was developed for preparation of **502**. Thus, alcohol **503** (arising from reduction of propiophenone) was resolved by reaction with isoprenyl acetate in the presence of Amano P30 lipase to furnish acetyl derivative **504** and alcohol

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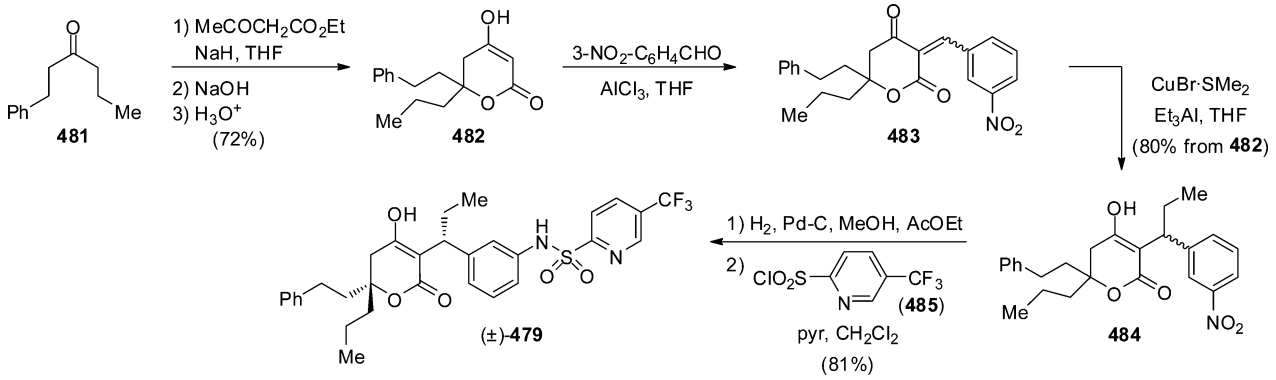
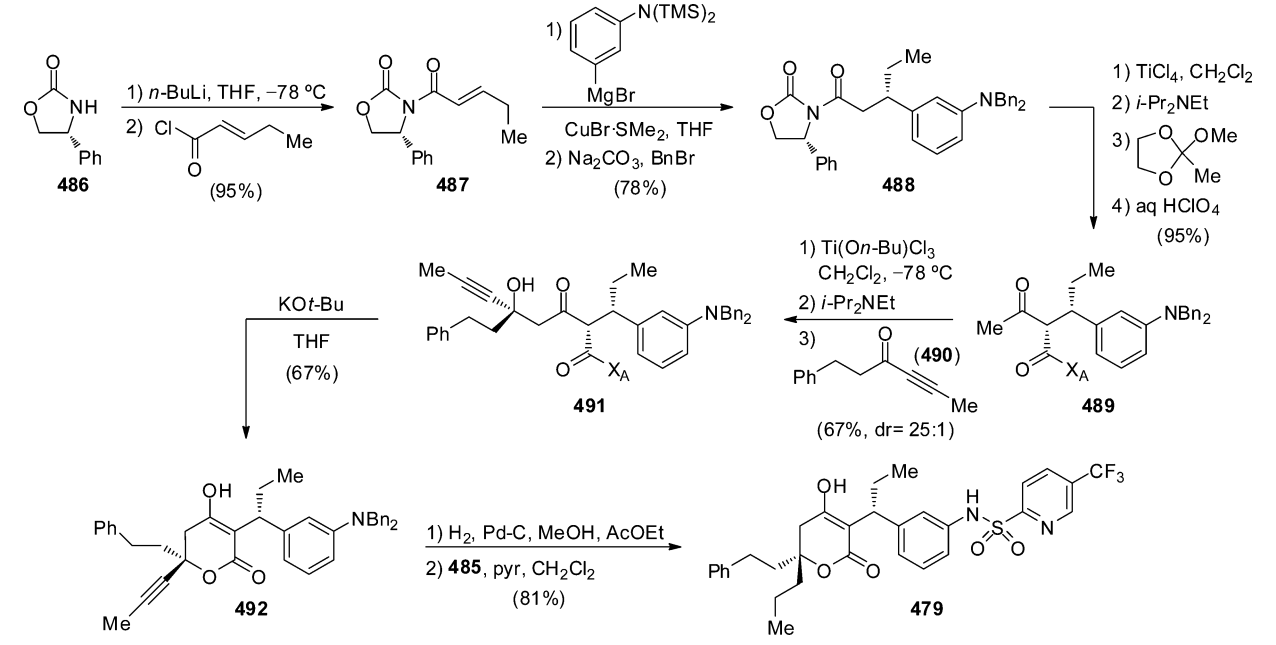
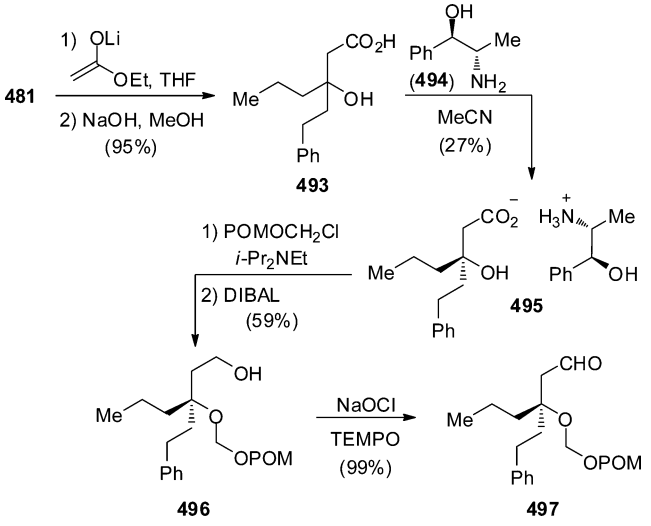
Scheme 84. Initial Racemic Synthesis of Tripanavir (479) Starting from 1-Phenyl-3-hexanone (481)



Scheme 85. First Asymmetric Synthesis of Tripanavir (479) Based on Evans Oxazolidinone 486



Scheme 86. Aldol Condensation as Key Step in the Scalable Synthesis of Tripanavir (479): Preparation of Intermediate 497



505. Mesylation of **505** and reaction with the sodium enolate of diethyl malonate afforded diester **506**, which was decarboxylated and esterified to the desired ester **502** (Scheme 87, Method B).

Coupling of both fragments was performed by reaction of the sodium enolate of **502** with aldehyde **497** to afford compound **507** as a mixture of diastereoisomers (Scheme 88). This mixture was oxidized and the POM protecting group released by treatment in acidic media to render compound **508**, which was lactonized under basic conditions to lactone **509**. Final hydrogenation of the nitro group and coupling with sulfonyl chloride **485** afforded the desired product **479**.

More recently, two new enantioselective syntheses of tripanavir have been devised. By means of the chiral molybdenum carbene **511**, an enantioselective tandem ring-opening−ring-closing metathesis was used as the key step to generate the quaternary stereocenter of tripanavir (Scheme 89).[221] Thus, when substrate **510** was heated in benzene with molybdenum catalyst **511**, unsaturated pyran **512** was obtained in excellent yield and enantiomeric excess. Oxidation with PCC afforded unsaturated lactone **513**, which was oxidized to the corresponding epoxide, which was opened regioselectively with diphenyldiselenide. Further reaction with $NaBH_4$ furnished

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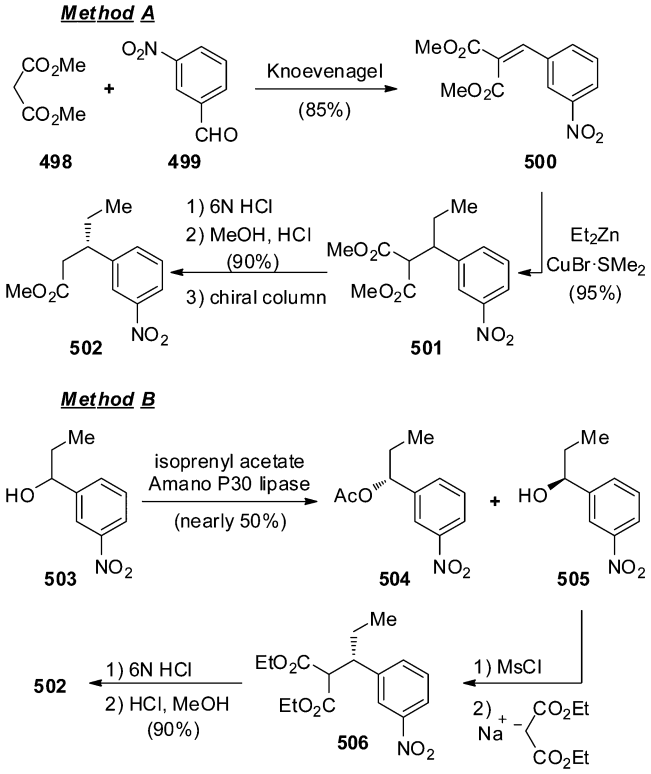
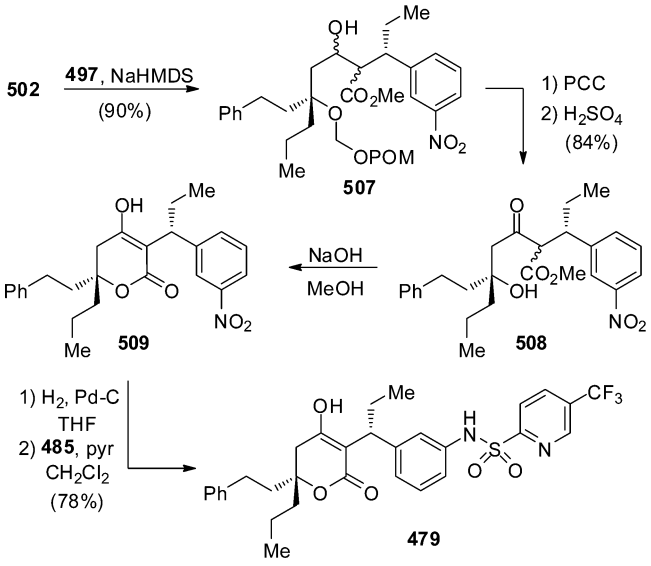
Scheme 87. Aldol Condensation as Key Step in the Scalable Synthesis of Tripanavir (479): Preparation of Intermediate 502



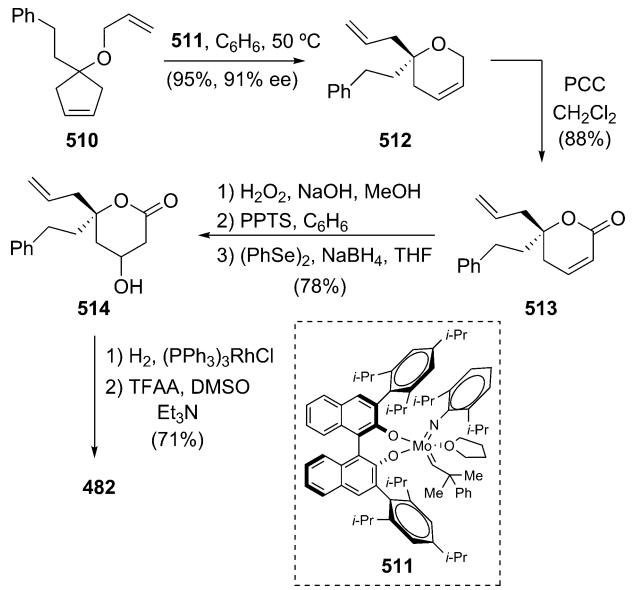
Scheme 88. Synthesis of Tripanavir (479) by Coupling of Fragments 497 and 502



alcohol **514**. Hydrogenation of the double bond and alcohol oxidation gave the advanced synthetic intermediate **482**.

Finally, the most recent synthesis of tripanavir was based on a highly convergent double dynamic kinetic asymmetric transformation (DYKAT) strategy by formation of the pyrone in a late stage of the synthetic sequence (Scheme 90).[222] Chloroketone **515** was treated with vinyl magnesium bromide, giving rise to the corresponding alcohol that cyclized upon basification to epoxide **516**. This epoxide was subjected to a palladium−boron

Scheme 89. Chiral Molybdenum Carbene 511-Mediated Enantioselective Synthesis of Tripanavir (479)



cocatalyzed DYKAT reaction in the presence of chiral phosphine **517** and *p*-methoxybenzyl alcohol to afford alcohol **518** in good yield and excellent enantiomeric excess. Heck reaction with phenyl iodide rendered compound **519**, which was hydrogenated and the alcohol oxidized to the corresponding aldehyde and treated with the Wittig reagent to give olefin **520**. Hydroboration and oxidation gave aldehyde **521**, which is the substrate for subsequent aldol condensation. The enolate partner for this reaction was prepared starting from alcohol **522**, initially converted to its carbonate **523**. Enantioselective allylic alkylation with the sodium salt of methyl malonate in the presence of the chiral ligand **524** and $Mo(CO)_3(C_7H_8)$ as catalyst afforded the corresponding chiral diester with excellent ee and compound **525** after decarboxylation. Formation of the sodium enolate of **525** and treatment with aldehyde **521** at −78 °C afforded the corresponding alcohol, which was oxidized to yield keto ester **526**. PMB deprotection and basification induced lactonization to form compound **527**. In order to finish the synthesis, it was necessary to perform hydrogenation of both the double bond and the nitro group and subsequent coupling with sulfonyl chloride **485**.

5.4. Posaconazole (Noxafil)

Azole antifungals, discovered around 30 years ago, are currently the largest class of antifungal agents in clinical use. Among this class of compounds, posaconazole (Sch 56592) (**528**) is a second-generation triazole antifungal drug that was approved by the FDA in 2006 (trade name Noxafil; Schering-Plough) for prophylaxis against invasive *Aspergillus* and *Candida* infections in highly immunocompromised adult patients (Figure 30).[223] It was discovered as a hydroxylated derivative of Sch 51048,[224] a structurally resembling compound to itraconazole (**529**) (first generation triazole) and developed to enhance the antifungal spectrum and bioavailability of the azole antifungal class. Posaconazole (**528**) shares the same mechanism of action as the rest of azoles (see section 5.1).[194,225]

Posaconazole has a broad spectrum of antifungal activity; in fact, it is the first azole agent to demonstrate activity against the zygomycetes, a family including species such as *Mucor* and *Rhizopus*, which have been very difficult to combat.

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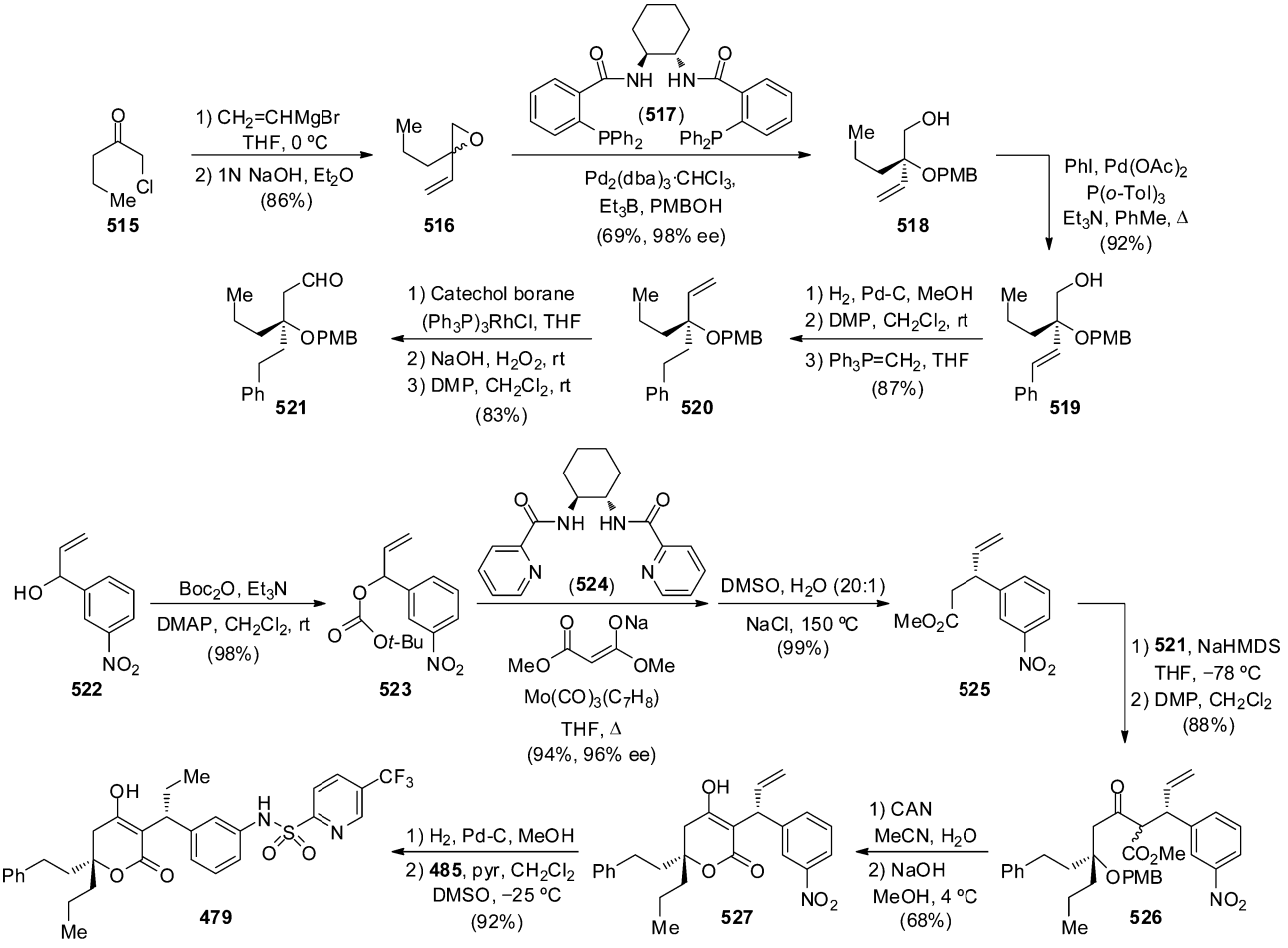
Scheme 90. Enantioselective Synthesis of Tripanavir (479) Based on the Double Dynamic Kinetic Asymmetric Transformation (DYKAT) Strategy



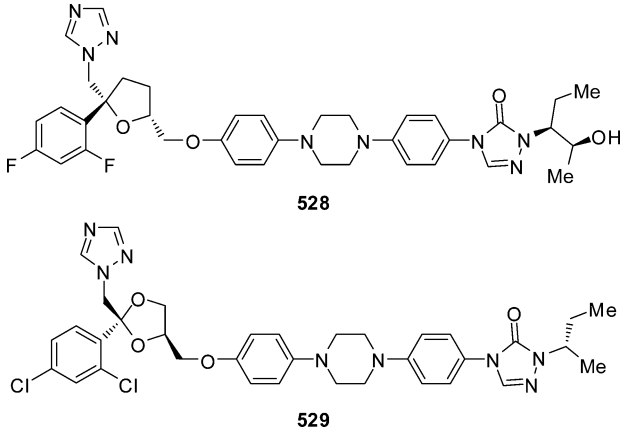
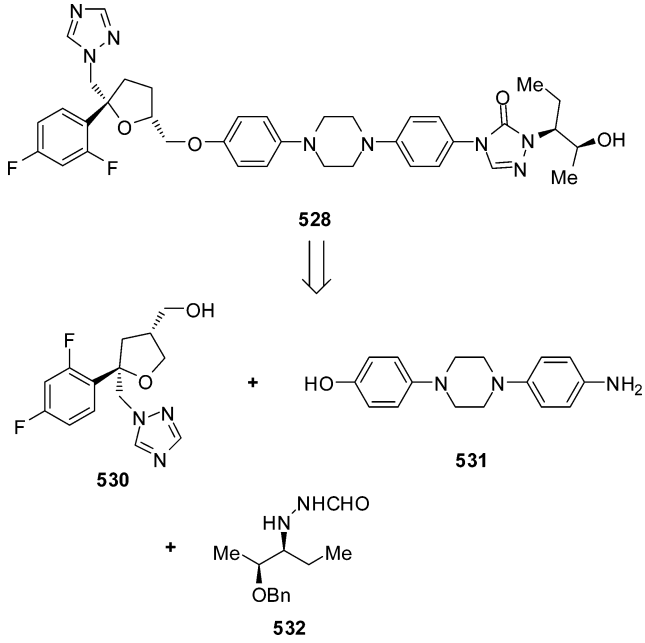


Figure 30. Structures of posaconazole (**528**) and itraconazole (**529**).

Scheme 91. Retrosynthetic Analysis for Synthesis of Posaconazole (528)



The most convenient synthetic route of **528** involves a convergent procedure comprising the key chiral THF subunit **530** and aryl piperazine amine **531**, followed by introduction of the triazolone subunit at the end of the synthesis by means of the chiral fragment **532** (Scheme 91).

For preparation of the 2,2,4-trisubstituted tetrahydrofuran derivative **530**, allyl alcohol **533**[226] was brominated to give compound **534**, which was then alkylated with sodium diethylmalonate (Scheme 92). The resulting diester **535** was reduced with $NaBH_4$/LiCl to afford diol **536**, which was efficiently desymmetrized to the chiral monoacetate **537** via selective acylation catalyzed by hydrolase Novo SP 435 in

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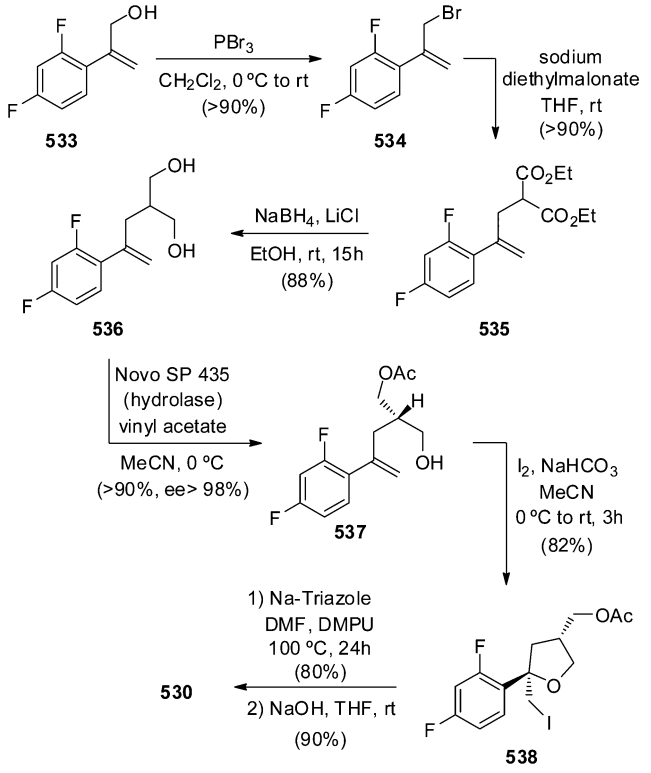
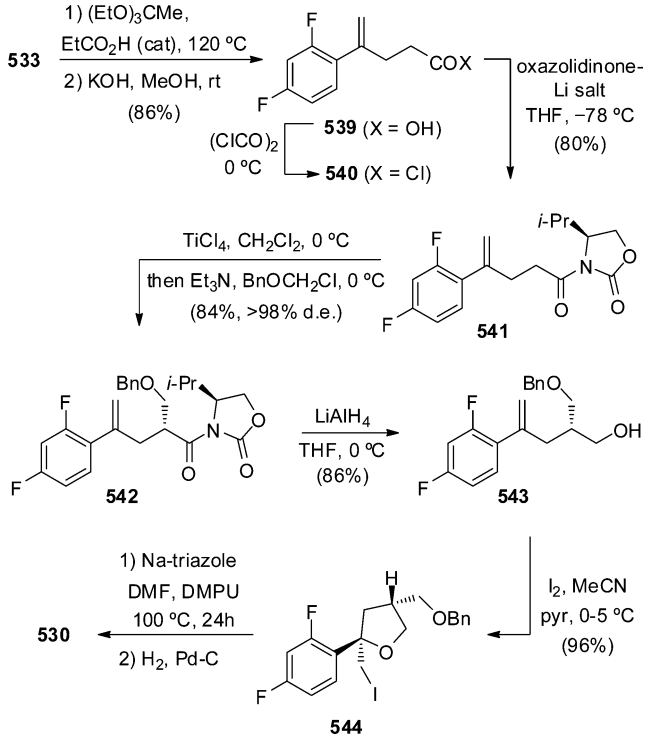
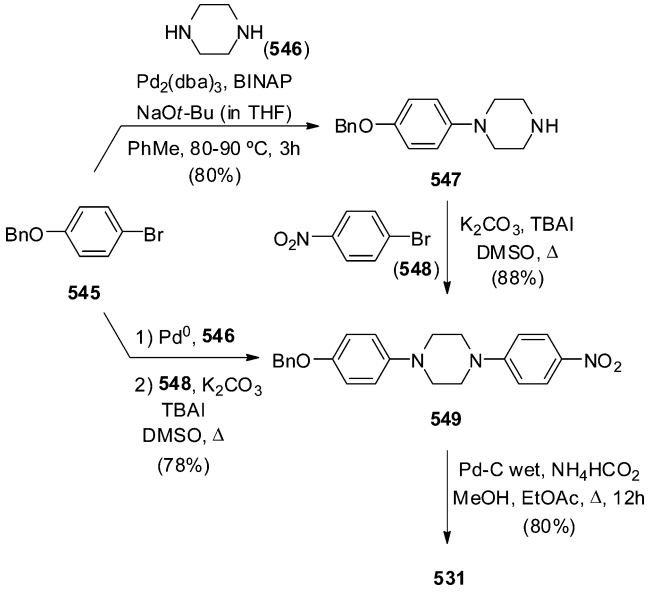
Scheme 92. Chemoenzymatic Synthesis of the Tetrahydrofurane Fragment 530



Scheme 93. Diastereoselective Chemical Routes to Tetrahydrofurane Fragment 530



Scheme 94. Pyperazine Palladium-Catalyzed Arylation for Synthesis of Fragment 531



acetonitrile.[227] Iodine-mediated cyclization of **537** gave the chiral iodo acetate **538** in good yield. This iodide was displaced with sodium−triazole in DMF/DMPU to afford the corresponding triazole, the acetate group of which was immediately hydrolyzed with sodium hydroxide to provide alcohol **530**.[228]

Besides the chemoenzymatic route depicted in Scheme 92, diastereoselective chemical routes to **530** were also investigated using the chiral imide enolate chemistry developed by Evans.[229] An example employing the chiral oxazolidinone derived from (*S*)-valinol is shown in Scheme 93. In a one-pot sequence, alcohol **533** was subjected to Claisen−Johnson orthoester rearrangement[230] with triethyl orthoacetate followed by basic hydrolysis of the resulting ethyl ester to provide acid **539** in good yield. Treatment of the acid chloride **540** with the lithium salt of (4*S*)-(−)-4-isopropyl-2-oxazolidinone under standard conditions[231] gave the chiral imide **541**. Alkylation with benzyloxymethyl chloride via Evans' titanium enolate protocol[232] gave benzyl ether **542** in good yield and diastereoselectivity. Next, **542** was reduced with $LiAlH_4$ in THF, affording the monoprotected diol **543**. Iodocyclization proceeded in excellent yield to give the tetrahydrofuran iodide **544**, which was converted into the corresponding triazole derivative and then debenzylated to compound **530**.

Although amino alcohol piperazine **531** is commercially available, scientists from Schering-Plough reported a short and convenient synthesis of that fragment by means of a Pd-catalyzed arylation of piperazines.[233] Thus, reaction of aryl bromide **545** with piperazine **546** in the presence of a Pd^0 catalyst resulted in the mono-*N*-arylated piperazine **547**, which readily reacted with aryl bromide **548** under conditions previously reported[234] to give compound **549** (Scheme 94). This was converted into **531** under hydrogenation conditions. Isolation of **547** was unnecessary as this, prepared in situ, reacted with **548** to form compound **549** in a one-pot procedure. This two-pot synthesis is the largest scale amenable preparation of **531** reported to date.

For synthesis of the chiral hydrazine **532**, needed to make the triazolone subunit of posaconazole, (*S*)-*N*,*N*-tetramethylenepropanamide **550**[235] was reduced with Red-Al to give (*S*)-benzyloxy propanal (**551**), which was then reacted with formyl hydrazine to afford hydrazone **552** (Scheme 95). Addition of ethylmagnesium bromide gave a mixture of the desired (*S*,*S*)-diastereomer **532** and its epimer **553** in 55% yield and good diastereoselectivity. However, protection of the formyl group as the *tert*-butyldimethylsilyl (TBS) ether **554** followed by treatment with

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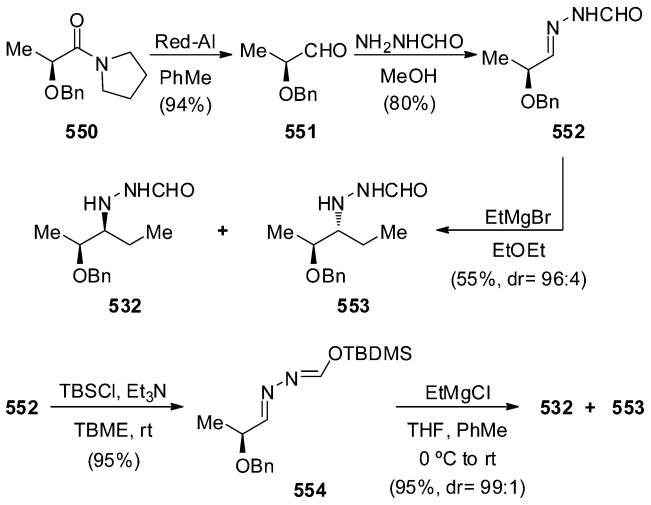
Scheme 95. Synthesis of Chiral Hydrazine Fragment 532



ethylmagnesium chloride gave both diastereomers in 95% yield and 99:1 ratio.

With fragments **530**, **531**, and **532** in hand, synthesis of posaconazole required several steps. First, activation of alcohol **530** as the *p*-chlorobenzene sulfonate (CBs) gave compound **555**, which was coupled with piperazine **531** employing aqueous sodium hydroxide in DMSO (Scheme 96). The resulting amine intermediate **556** was reacted with benzoyl chloride, thus yielding benzoate **557**. Finally, formyl hydrazine **532** was coupled with **557** to afford benzyloxy triazolone **558**, which was deprotected to access posaconazole in very good yield.

5.5. Raltegravir (Isentress)

Raltegravir (**559**) is the first member of a new class of integrase inhibitor drugs.[236] Human immunodeficiency virus type-1 (HIV-1) integrase is one of the three virally encoded enzymes required for virus replication and therefore a rational target for treatment of HIV-1 infection (Figure 31). This pyrimidone carboxamide exhibits a potent inhibition of the strand transfer process

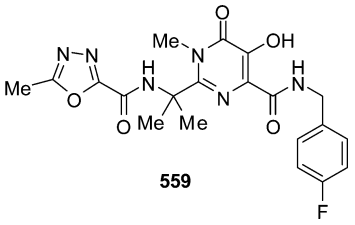


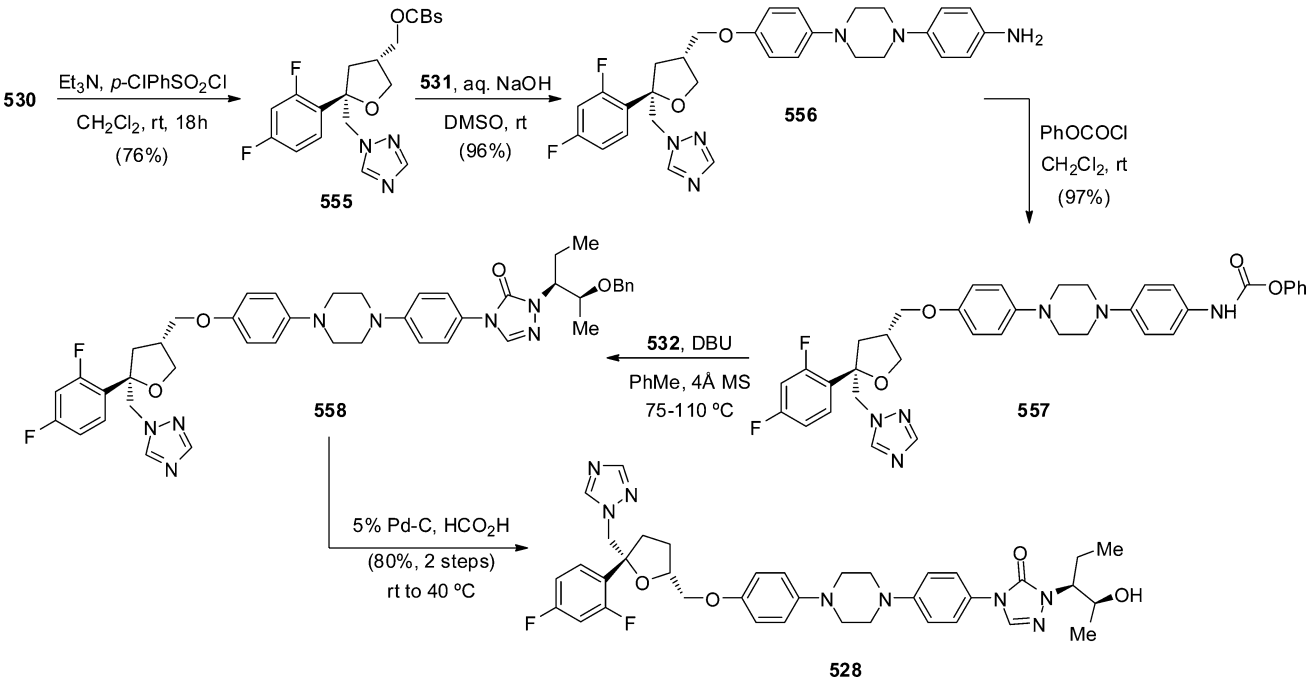
Figure 31. Structure of raltegravir (**559**).

catalyzed by the HIV-integrase. It was approved by the FDA in 2007 as a first-line anti-HIV therapy in patients who fail to benefit from the highly active antiretroviral therapy regimen.[237] Current sales of the marketed drug (Isentress, Merck) reached $1359 billion in 2011.

The HIV-integrase promotes insertion of proviral DNA into the host genome. Specifically, it catalyzes cleavage of a dinucleotide from each 3′ terminus of the viral DNA in the citosol and, subsequently, inserts the processed viral DNA into the host cell genome in a hydroxyl-mediated nucleophilic reaction termed "strand transfer". Raltegravir blocks the second step by means of an allosteric inhibition of the enzyme.[238]

HIV-integrase together with the related enzyme of the hepatitis C virus (HCV) NS5b polymerase share a common mechanism of action. Their catalytic activity is mediated by Mg^{2+} ions present in their active sites. Merck medicinal chemists found that while pyrimidine carboxylic acids are good inhibitors of HCV with no activity against HIV, the analogous pyrimidine carboxamides display promising activity against HIV being inactive toward HCV (Figure 32). With this starting point, careful optimization of these carboxamides in an extensive medicinal chemistry program led to the discovery of raltegravir.[239] In this context, more than 200 derivatives at the

Scheme 96. Synthesis of Posaconazole (528) by Coupling of Fragments 530, 531, and 532



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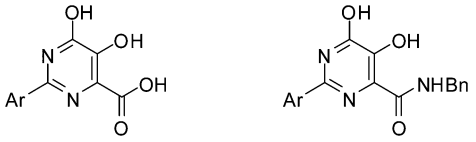


Figure 32. Structures of pyrimidine carboxylic acids and carboxamides as integrase inhibitors.

carboxamide moiety were prepared and screened. Their evaluation suggested that this part of the molecule binds in an apolar environment, with the *p*-fluorobenzyl being the optimal amide residue. This substituent displayed 8-fold improvement in potency (when compared with benzyl group) and acceptable pharmacokinetics.[240] SAR studies on the rest of the molecule were performed with this fluorinated amide.

The medicinal chemistry synthesis of raltegravir started from cyanohydrin **560**, arising from the Strecker reaction of acetone (Scheme 97).[241] Amination of **560** was followed by nitrogen protection to afford **562**. This nitrile was transformed into the corresponding amidoxime **563** by reaction with hydroxylamine. Compound **563** was condensed with dimethylacetylenedicarboxylate (DMAD) to render intermediate **564**, which was in turn cyclized by heating in xylene.[242] The hydroxyl group at C5 of pyrimidine **565** was selectively protected with benzoic anhydride and then methylated at N3 by treatment with dimethylsulfate, thus yielding pirimidone **567**. Next, removal of the Cbz protecting group and coupling with acid chloride **569** afforded amide **570**. Finally, introduction of the fluorobenzyl moiety by reaction with **571** and hydrolysis of the benzoate at C5 gave the desired product **559**.

A robust route for a large-scale manufacturing process—104 g—was necessary to avoid some environmental issues, and best performance was achieved by installation of the fluorinated benzyl amide at an earlier stage.[243] Thus, pirimidone **565** was coupled with 4-fluorobenzyl amine (**571**) in refluxing methanol to render amide **573** quantitatively (Scheme 98). N3 methylation required a big optimization effort in order to avoid the undesired *O*-methylation. Using MeI as an alkylating agent and $Mg(OMe)_2$ as a Lewis acid in DMSO, the side reaction was almost completely minimized and methyl derivative **574** was isolated in 90% yield. Regarding the phenolic oxygen at C5, it was protected with pivaloyl chloride[244] and the protected derivative **575** was hydrogenated to cleave the Cbz protecting group.

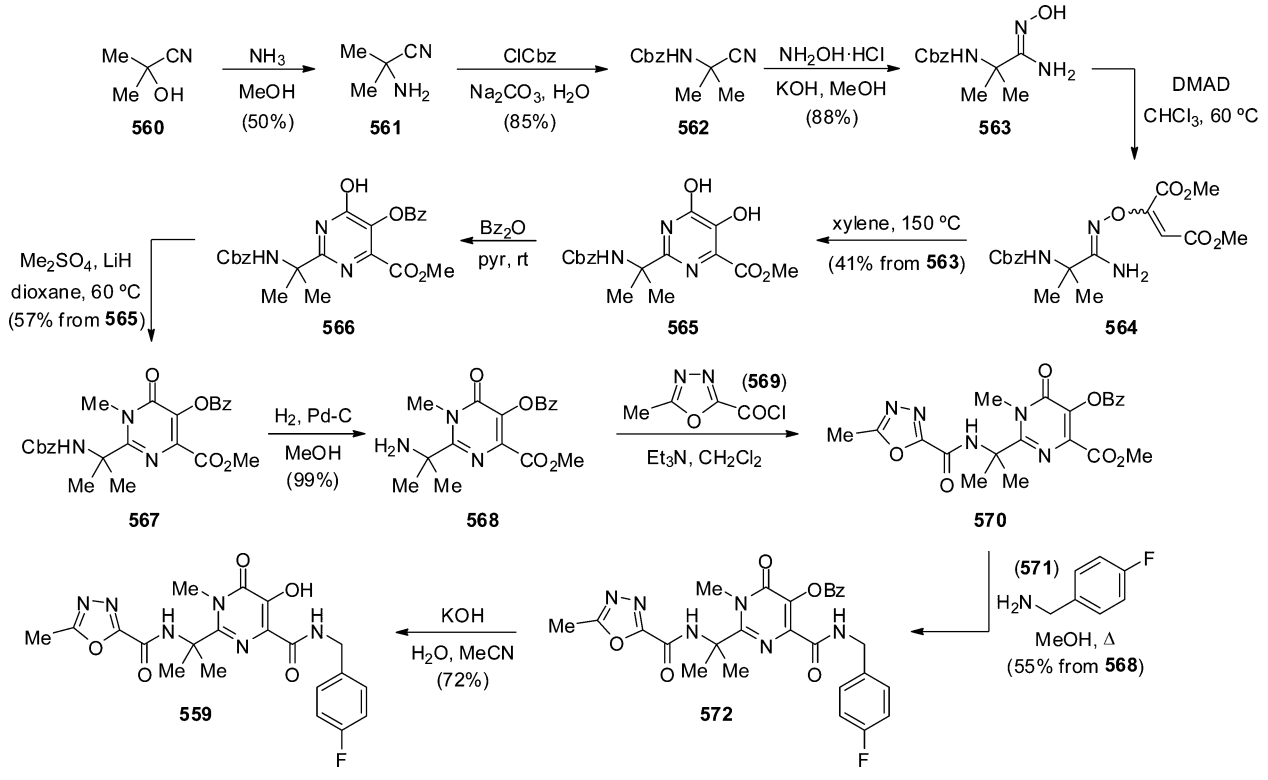
Oxadiazole intermediate **569** was prepared from tetrazole **577** (Scheme 99). Reaction with ethyl oxalyl chloride gave intermediate **578**, which, upon heating, was converted into the desired heterocycle **579**, which was isolated as its potassium salt. Treatment with oxalyl chloride and DMF afforded the desired acid chloride **569**.

Finally, reaction of amine **576** with the oxadiazole-containing acid chloride **569** gave intermediate **580** on which the pivaloyl functionality was in situ deprotected providing, after acidification, raltegravir in 35% overall yield (Scheme 100).

5.6. Maraviroc (Selzentry)

Maraviroc (**581**) is a specific, slowly reversible, and noncompetitive antagonist of the CCR5 chemokine receptor (Figure 33). It has been developed as a new HIV-1 therapeutic agent, targeting one of the early steps of the viral cycle infection since that chemokine receptor is essential for the HIV-1 entry to the host cell.[245] This is the first of a number of CCR5 antagonists approved by the FDA for treatment of HIV in 2007.[246] Current sales of the marketed drug (Selzentry, Pfizer) reached $176.4 million in 2011.

Scheme 97. Medicinal Chemistry Synthesis of Raltegravir (559) from Cyanohydrin 560



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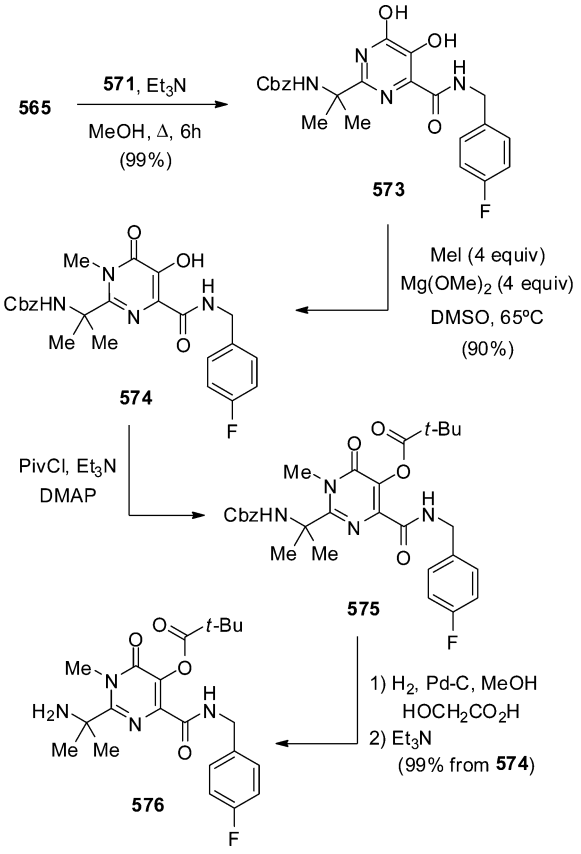
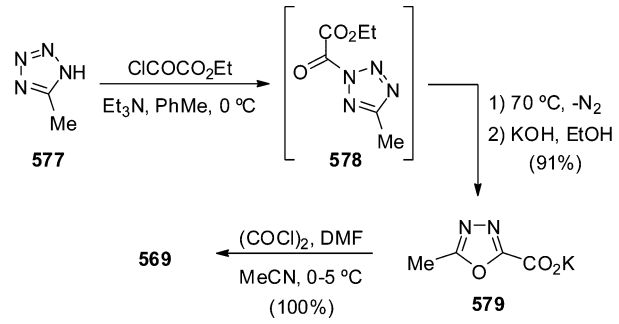
Scheme 98. Large-Scale Manufacturing Process for Raltegravir (559): Synthesis of Fragment 576



Scheme 99. Large-Scale Manufacturing Process for Raltegravir (559): Synthesis of Fragment 569



Traditionally the antiretroviral therapy was based on two key enzymes in the virus life cycle, namely, HIV-1 reverse transcriptase and HIV-1 protease. Despite impressive discoveries regarding development of effective inhibitors of both enzymes, an unmet medical need for new antiviral agents to combat the disease still remains owing to the emergence of drug-resistant viruses in many patients. Maraviroc has emerged as a new and promising drug that can be used in combined therapy with other antiretroviral agents. It is the result of an intensive medicinal chemistry program initiated after identification of an imidazopyridine CCR5 ligand from a high-throughput screening of the Pfizer compound file.[247]

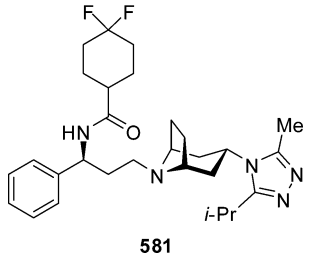


Figure 33. Structure of maraviroc (**1**).

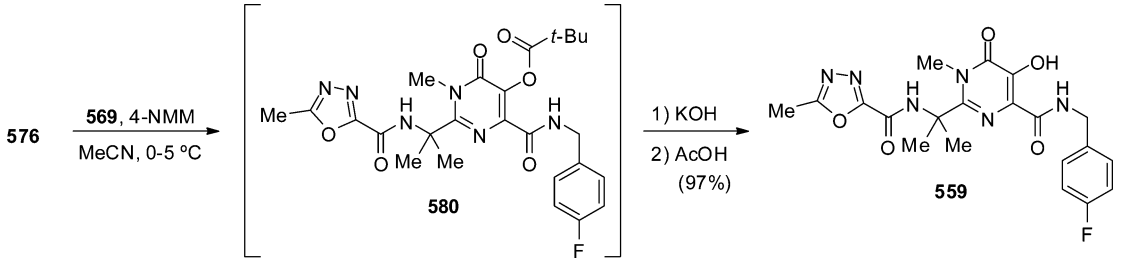
Discovery of CCR5 antagonists has to face a major challenge, that is, the affinity for the HERG potassium channel, which plays a key role in controlling the cardiac rhythm. Therefore, the ability of molecules to bind HERG channel is closely related to eventual cardiotoxicity. Among the substituents evaluated in the amide functionality, the 4,4-difluorocyclohexyl moiety was found to be outstanding, displaying a nanomolar antiviral activity in combination with nonbinding to the HERG channel. This lack of affinity is presumably due to the steric demand of the cyclohexyl group and also the dipole generated by the difluoro moiety along the ion channel.[248]

First synthesis of maraviroc was published in 2005,[249] and scale up of the process for commercial purposes—88.5 kg of the **581**-tosylate—was performed following the initial synthetic strategy, with improvements introduced by process chemists.[250] Retrosynthetic analysis is depicted in Scheme 101 and based on a convergent protocol that involves preparation of three fragments: tropane derivative **584**, chiral *β*-amino ester **583**, and difluorocyclohexyl carboxylic acid derivative **582**.

Preparation of fragment **584** started with commercially available tropane derivative **585** (Scheme 102). First, its oxime **586** was reduced with Na in refluxing toluene to afford a 10:1 mixture of exo/endo tropanes **587**. Compound **587**-*exo* was coupled with *i*-PrCOCl, and the resulting amide **588** was transformed into triazole **589** via imidoyl chloride formation by reaction with PCl_5.[251] Further reaction with acylhydrazine and acidification afforded the desired heterocyclic derivative **589** in 72% yield. Removal of the benzyl group by catalytic hydrogenation yielded fragment **584**.

β-Amino ester **583** was synthesized by a Rodionov reaction[252] starting from condensation of benzaldehyde (**590**) with malonic

Scheme 100. Synthesis of Raltegravir (559) by Coupling of Fragments 569 and 576



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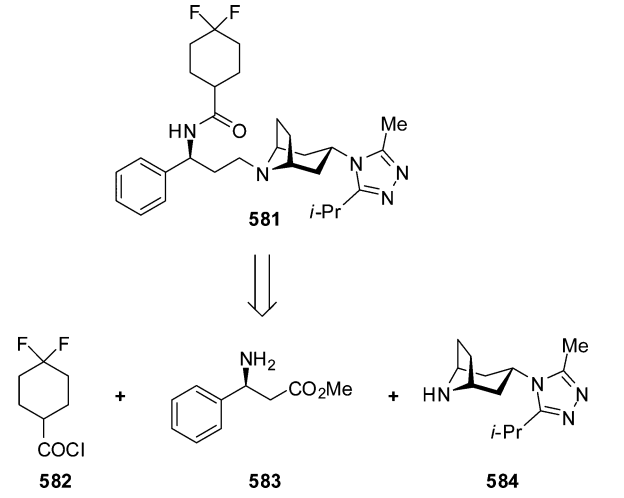
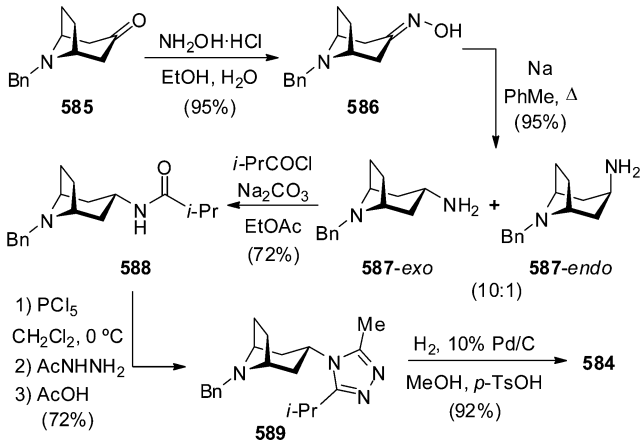
Scheme 101. Synthetic Strategy for Preparation of Maraviroc (581)

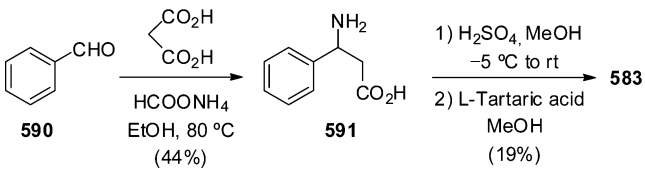


Scheme 102. Preparation of Triazole Fragment 584



acid and ammonium formate to render, after decarboxylation, β-amino acid **591** (Scheme 103). Racemic β-amino acids can be

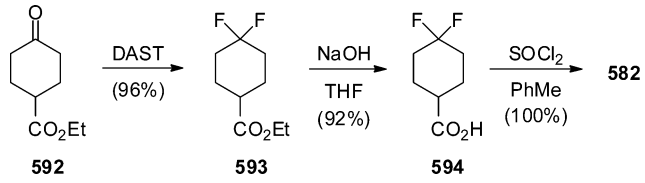
Scheme 103. Preparation of β-Amino Ester Fragment 583



easily resolved using penicillin acylase providing for quite inexpensive acess to enatiomerically pure derivatives.[253] However, in this particular procedure, resolution of racemic ester **583** was conducted via recrystallization with tartaric acid to afford the enantiomerically pure fragment **583** as the corresponding tartrate.

Finally, fragment **582** was synthesized from ethyl 4-oxocyclohexane carboxylate (**592**) by difluorination with diethylamino sulfur trifluoride (DAST) and subsequent ester saponification to acid **594** (Scheme 104). Acid **594** was transformed to the chloride **582** for the final coupling. In the fluorination step, appreciable amounts of the fluorinated alkene arising from HF elimination were also formed and could be separated after ester hydrolysis. Additionally, the fluorinating

Scheme 104. Preparation of Difluorocyclohexyl Carboxylic Acid Chloride Fragment 582



reagent was changed to HF in the scale-up process due to safety issues.

Prior to coupling of the fragments, amino ester **583** was protected as the Cbz derivative **595**, reduced to the alcohol **596**, and oxidized to aldehyde **597** using Parikh−Doering conditions (Scheme 105). Reductive amination of aldehyde **597** with amine **584** rendered compound **598**. Finally, *N*-deprotection and reaction of the free amine **599** with acid chloride **582** under basic conditions yielded maraviroc.

The first enantioselective synthesis of maraviroc was reported in 2007 by means of an enantioselective allylboration of acylimines as the key step.[254] In this case, the starting material was difluorinated acid **594**, which was converted into the difluorocyclohexane carboximide imine **600** (Scheme 106). Enantioselective allylboration of the imine functionality was successfully achieved by reaction with diisopropylallylborane in the presence of BINOL derivative **601**. In this manner, homoallylic amide **602** was obtained with 91% ee. Ruthenium-mediated oxidation of the double bond and reductive amination in the presence of fragment **584** afforded the final product **581** in good yield.

Finally, a novel organocatalytic enantioselective synthesis of maraviroc has been recently reported.[255] The key step was the organocatalytic aza-Michael reaction of fluorinated *N*-hydroxyl amine **604** with cinnamic aldehyde catalyzed by diaryl prolinol **605** to give 5-hydroxyisoxazolidine **606** in 91% yield and 80% ee (Scheme 107). N−O cleavage was performed with $Mo(CO)_6$ as reducing agent to render amino aldehyde **607**, which was coupled in a reductive amination sequence with tropane derivative **584** to give maraviroc.

6. EYE CARE DRUGS

6.1. Travoprost (Travatan) and Tafluprost (Zioptan)

The therapeutic utility of prostanoids (prostaglandins, prostacyclins, and thromboxanes) is sometimes compromised because of their low chemical stability.[256] As a result, the large number of fluorinated analogues of prostanoids that have been described in recent years with the aim to prepare molecules having a better stability profile than their naturally occurring counterparts is not surprising.[257] For instance, fluprostenol (**608**) (Figure 34) is a prostaglandin $F_{2\alpha}$ derivative developed in the 1970s as a luteolytic agent for veterinary uses.[258] More recently, it was shown that some aryl-substituted $PGF_{2\alpha}$ analogues also reduced the intraocular pressure, with latanoprost (**609**) being an illustrative example for successful treatment of glaucoma.[259] New derivatives of $PGF_{2\alpha}$ have since been investigated in order to increase the efficacy while reducing the side effects observed with latanoprost. For instance, travoprost (**610**) (the isopropyl ester of fluprostenol) was developed by Alcon Laboratories and marketed in 2001 with the trade name Travatan, showing the same or better results in lowering the intraocular pressure than latanoprost.[260] Another member of this family of compounds is tafluprost (**611**), which results from replacing the 15-OH group

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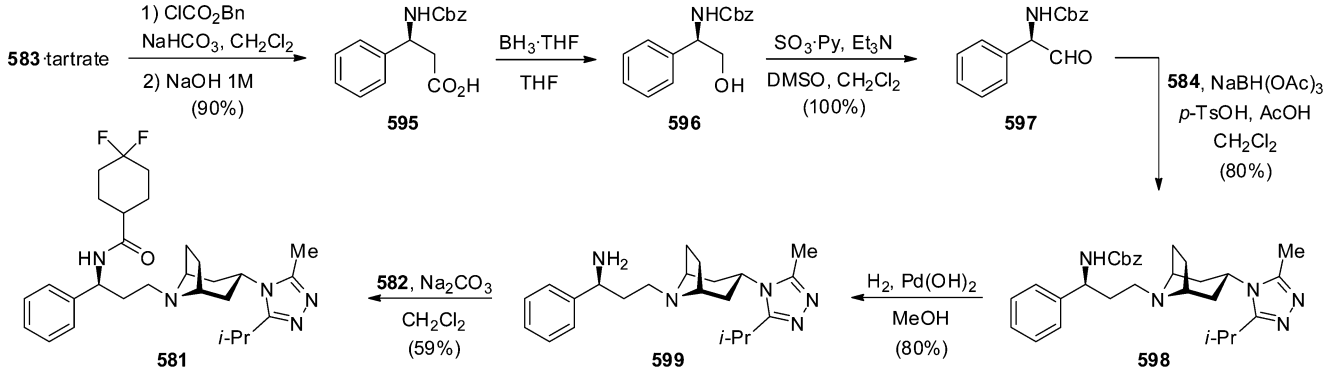
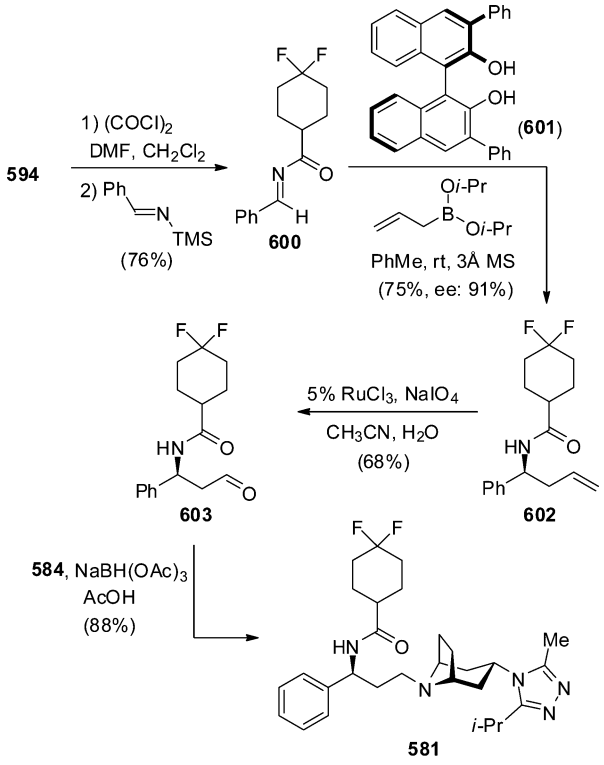
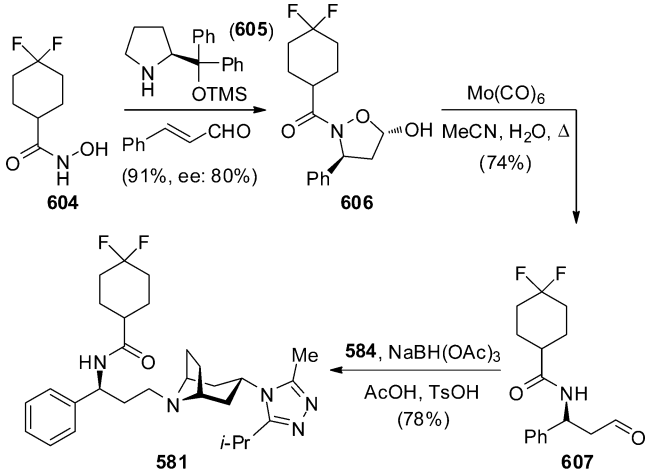
Scheme 105. Synthesis of Mavarivoc (581) by Coupling of Fragments 582, 583, and 584



Scheme 106. Enantioselective Acylimine–Allyl Boration as Key Step in the First Enantioselective Synthesis of Maraviroc (581)



Scheme 107. Organocatalytic Enantioselective Synthesis of Maraviroc (581)



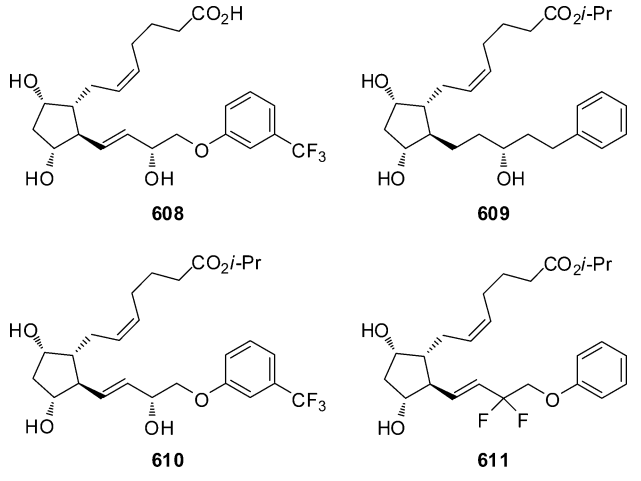


Figure 34. Structures of fluprostenol (**608**), latanoprost (**609**), travoprost (**610**), and tafluprost (**611**).

of $PGF_{2\alpha}$ by a difluoro moiety, reducing the risk of melanogenesis inherent to the use of latanoprost.[261] Tafluprost was developed by Santen and Asahi Glass, licensed to Merck in the United States (Zioptan) and approved by the FDA in early 2012.

As in many other syntheses of prostaglandin derivatives, most of the routes developed for preparation of travoprost and related molecules made use of the Corey methodology.[262] One of the key steps involved diastereoselective reduction of the 15-keto group (prostaglandin numbering) in compound **612** but always afforded mixtures of the desired alcohol **613** and its epimer (Scheme 108). An improved procedure for this process has been described using borane-*N*,*N*-diethylaniline complex and catalytic (*R*)-2-methyl-CBS-oxazaborolidine, thus yielding alcohol **613** with 95:5 diastereoselectivity.[263]

The only synthesis of tafluprost reported thus far also started from the Corey lactone.[264] Horner–Wadsworth–Emmons olefination of aldehyde **614** with phosphonate **615** produced enone **616** with the required *E* geometry, and its further reaction with morpholino-sulfur trifluoride allowed difluorination of the carbonyl group under mild reaction conditions (Scheme 109). After removal of the benzoyl protecting group, lactone **617** was reduced with DIBAL and the resulting lactol was subjected to a Wittig reaction to install the *Z*-unsaturated chain. Final esterification of the carboxylic acid moiety led to tafluprost (**611**) in good overall yield.

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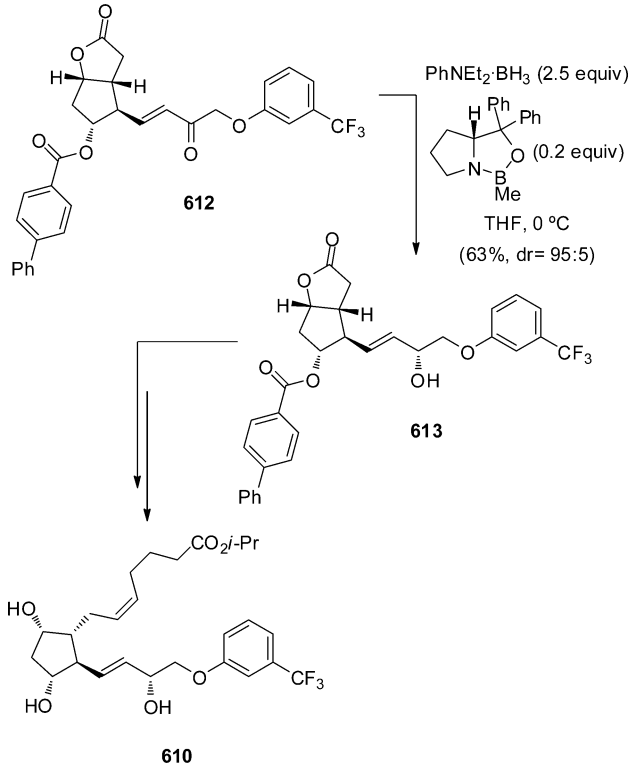
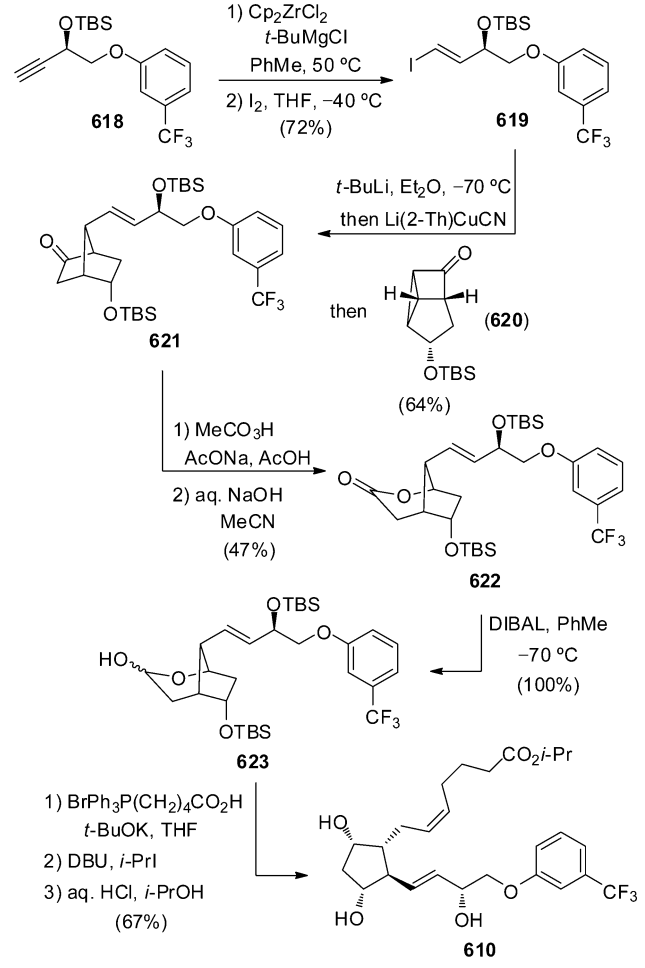
Scheme 108. Corey Prostanglandin Synthetic Methodology for Preparation of Travoprost (610)



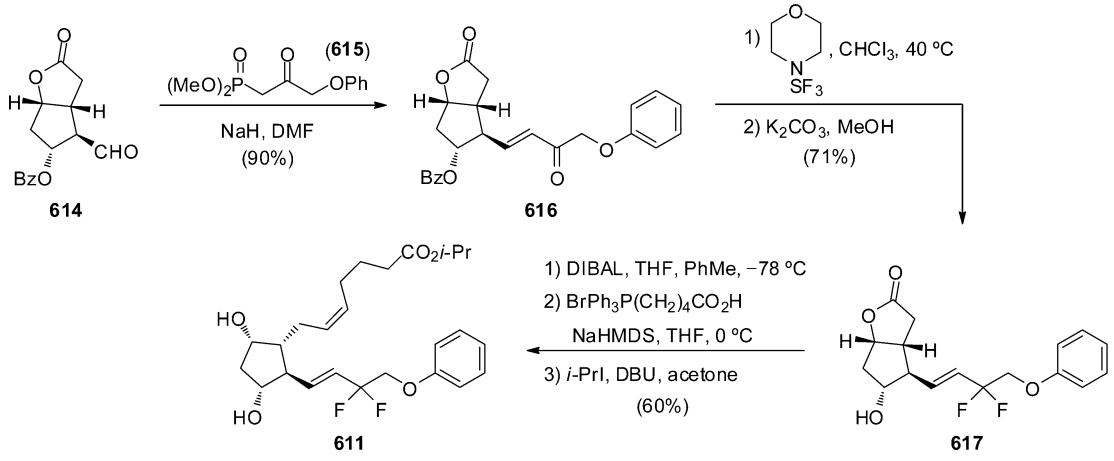
Because of the long route required for preparation of Corey lactone, other alternatives have been pursued. A multigram-scale synthesis of travoprost was described from enantioenriched (99.5% ee) alkyne **618**, available in turn by optical resolution of the alcohol precursor (Scheme 110).[265] Hydrozirconation/iodination of **618** afforded vinylic iodide **619**, which was transformed into its derived lithium 2-thienylcyanocuprate and reacted with tricyclic ketone **620**[266] to produce compound **621** via a homoconjugate addition reaction. Baeyer−Villiger oxidation of **621** yielded lactone **622**, which upon reduction gave lactol **623**. Synthesis of travoprost (**610**) was completed using a Wittig reaction followed by esterification and removal of the silicon protecting groups.

Scheme 110. Optical Resolution-Mediated Large-Scale Synthesis of Travoprost (610)



Finally, a synthetic approach to a late-stage intermediate for both travoprost and tafluprost has recently been described using furfural as starting material.[267] Thus, Wittig reaction on furfural-derived aldehyde **624** proceeded in good yield, followed by ester formation and TBS group deprotection to give alcohol **625** (Scheme 111). This compound served as substrate for a Piancatelli rearrangement to afford a mixture of isomeric enones, which on equilibration with chloral produced exclusively the

Scheme 109. Synthesis of Tafluprost (611) from Corey Lactone 614



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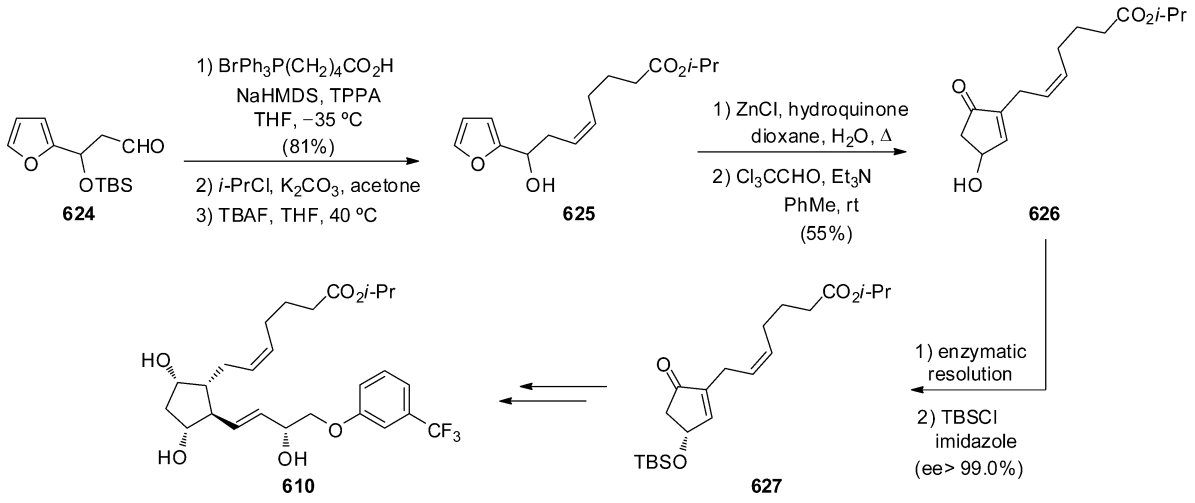
Scheme 111. Furfural as Starting Material for Synthesis of Travoprost (610) and Tafluprost (611)



most stable isomer **626**. Afterward, enzymatic resolution of this racemic compound produced optically enriched **627** (ee > 99.0%) after TBS protection. Introduction of a suitably substituted side chain via addition of the corresponding higher order cyanocuprate has produced travoprost[267b] and potentially would also serve for synthesis of tafluprost.

6.2. Difluprednate (Durezol)

Difluprednate (**628**) is a potent topical corticosteroid that displays relevant clinical efficacy in controlling postoperative inflammation (Figure 35). It is a difluorinated derivative of

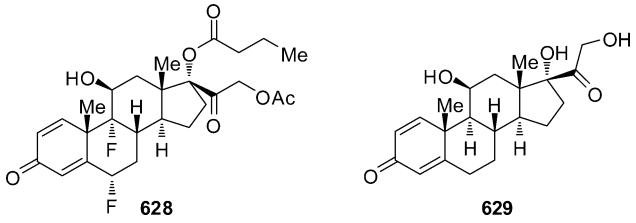


Figure 35. Structures of difluprednate (**628**) and prednisolone (**629**).

prednisolone (**629**), also designated as difluoroprednisolone butyrate acetate. It was approved by the FDA in June 2008 as the first topical steroid indicated for both inflammation and pain associated with ocular surgery, and it is also being studied for treatment of uveitis.[268] Difluprednate was introduced by Sirion and then acquired by Alcon, marketing the drug with the trade name Durezol.

Difluprednate is the ninth corticosteroid to be marketed in ophthalmic formulations for treating ocular inflammatory conditions. It exhibits enhanced penetration, better bioavailability, rapid local metabolism, and strong efficacy, with a lower incidence of adverse effects than the parent steroids. It is more potent than prednisolone acetate, which has been considered the "gold standard" for treatment of inflammation.[269] Difluprednate is a prodrug; it rapidly penetrates the corneal epithelium, where it quickly deacetylates to difluoroprednisolone butyrate (DFPB), the active metabolite. Fluorination at the C6 and C9 positions contributes to the potency of the drug,[270] and substituting the 21-hydroxyl group with acetic acid increases both the drug's lipophilicity and corneal penetration, while replacing the 17-hydroxyl group with butyric acid enhances the steroid's anti-inflammatory activity.[271]

Synthesis of difluprednate started from $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione (**630**) (Scheme 112).[272] Heating with methyl orthobutyrate in the presence of *p*-toluene sulfonic acid furnished orthoester **631**, which was hydrolyzed with 2*N* oxalic acid to hydroxy ketone **632**, which was in turn acetylated to give compound **633**. Introduction of the first fluorine atom in position 6 was accomplished with perchloryl fluoride to render, after acidic hydrolysis, compound **634**. Subsequent formation of bromohydrin **635** was performed with bromo acetamide in perchloric acid, and then **635** was converted into epoxide **636** under basic conditions. Epoxide ring opening with hydrogen fluoride followed by 1,2-dehydrogenation of **637** with DDQ gave rise to difluprednate (**628**). This sequence could also be performed in the reverse way, that is, 1,2-dehydrogenation of **636** with DDQ followed by epoxide ring opening of **638** with hydrogen fluoride also rendered the desired product **628**.

Difluprednate can also be synthesized from 6α,9α-difluoroprednisolone (**639**) following the aforementioned sequence, orthoester formation, hydrolysis, and acetylation of hydroxy ketone **641** (Scheme 113).

6.3. Besifloxacin (Besivance)

Besifloxacin (**642**), marketed as its hydrochloride salt (Besivance, Bausch & Lomb), is a broad-spectrum fluoroquinolone recently introduced for treatment of bacterial conjunctivitis (Figure 36).[273] The eye drop formulation of **642** was approved by the FDA on May 2009. Considered as the fourth generation of fluoroquinolones, besifloxacin has a uniquely dual-targeting activity as it inhibits both DNA gyrase and topoisomerase IV simultaneously.[274] Additionally, it was developed exclusively for topical ocular use, which reduces resistance development.

Since the discovery of nalidixic acid (**643**) in 1962,[275] quinolone antibacterials have emerged as a relevant class of chemotherapeutic agents. On account of SAR studies, a series of structural modifications of the quinolone scaffold allowed for identification of novel quinolones with improved activity, with more than 20 of them being marketed to date.[276] The most significant structural changes were introduction of a fluorine atom at C6 and a cyclopropyl group at the N (position 1).[277] It is known that quinolones not possessing the fluorine substituent at C6 undergo decarboxylation, oxidation, and dimerization under photolysis conditions in water, giving rise to antimicrobially inactive products. Additionally, it is generally believed that fluorine substitution conveys enhanced DNA gyrase potency and

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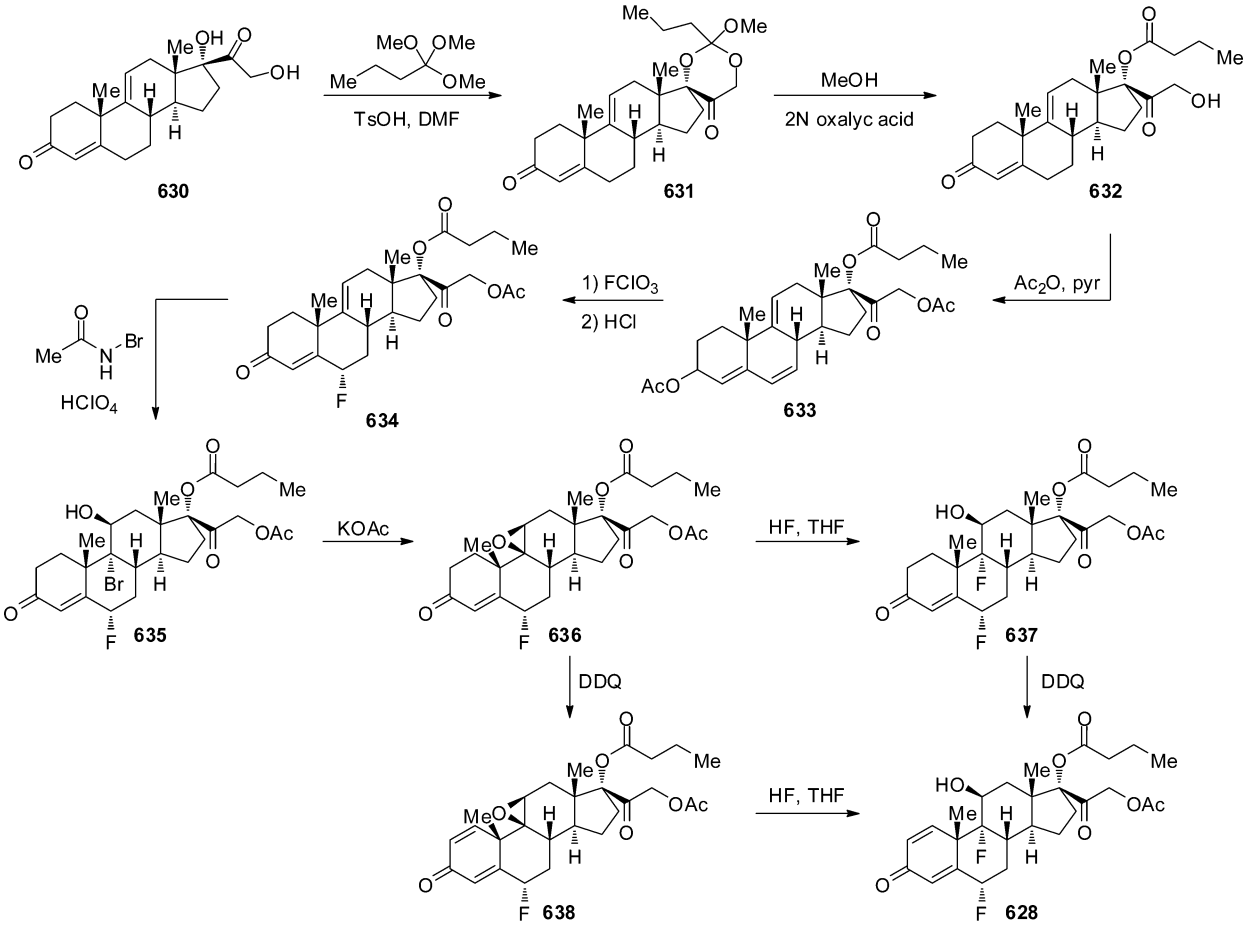
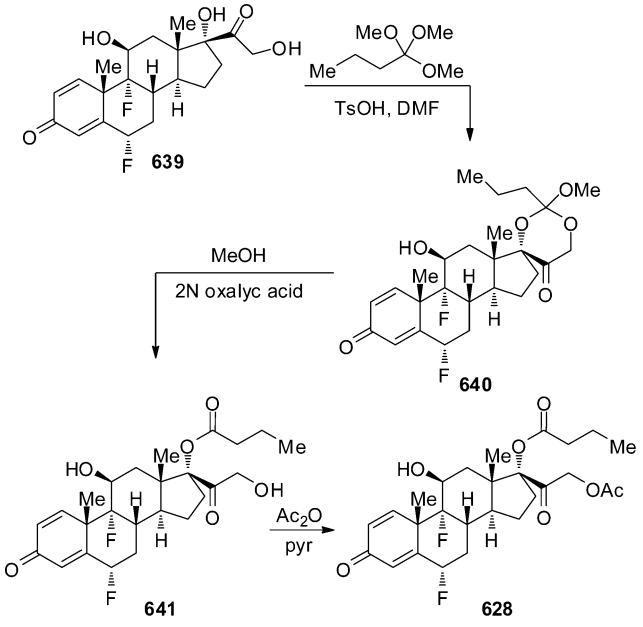
Scheme 112. Synthesis of Difluprednate (628) from Steroid Derivative 630



Scheme 113. Synthesis of Difluprednate (628) from Difluoroprednisolone 630



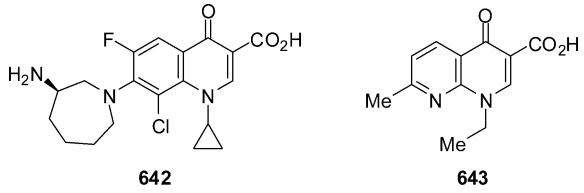


Figure 36. Structures of besifloxacin (**642**) and nalidixic acid (**643**).

enhances cell penetration.[278] On the other hand, the *N*-cyclopropyl moiety increases antigram negative potency. These structural modifications are present in besifloxacin. Moreover, the presence of a chlorine atom in C8 and an azepinyl substituent in C7 apparently further enhance potency against both type II topoisomerases found in bacteria.

Synthesis of besifloxacin[279] starts with commercially available ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoate **644** (Scheme 114). Condensation with orthoester afforded conjugated α-keto ester **645** as a mixture of diastereoisomers. This mixture was subjected to an addition−elimination sequence with cyclopropyl amine to render enamine **646**. Cyclization at the ortho position upon treatment with KOH afforded **647** with the complete fluoroquinolone heterocyclic core. Finally, introduction of the azepinyl fragment was performed by nucleophilic displacement of the fluorine at C7 by reaction with the chiral amine **648**. Hydrolysis of the imine protecting group afforded the final product **642** as its hydrochloride salt.

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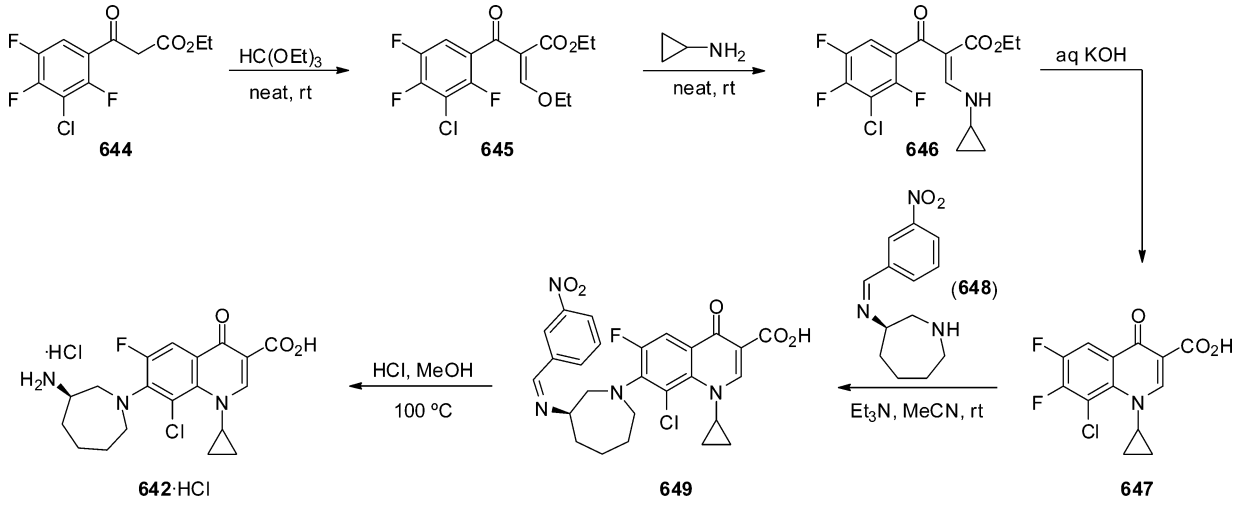
Scheme 114. Synthesis of Fluoroquinolone Besifloxacin (642)



7. DRUGS ACTING ON THE GENITO–URINARY SYSTEM

7.1. Dutasteride (Avodart)

Benign-prostatic hyperplasia (BPH) is a common dysfunction of the urinary system in male adults over 50 years old. BPH consists in an enlargement of the prostate, causing obstruction of the urethra and, as a result, difficulty urinating. Production of dihydrotestosterone (DHT) from testosterone by the enzyme 5α-reductase has long been linked to development of BPH, and therefore, discovery of new 5α-reductase inhibitors has been largely pursued as a clinically useful therapy for treatment of BPH.[280]

Many 5α-reductase inhibitors are designed to mimic the structure of natural steroid hormones. Particularly, the group of 4-azasteroids has provided the only examples of marketed drugs with this mechanism of action. The first example of this type was finasteride (**650**), released by Merck in the 1990s for treatment of BPH and later on for other DHT-dependent disorders such as male pattern baldness (Figure 37).[281] Later work showed that

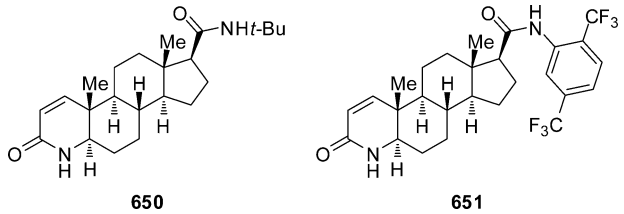


Figure 37. Structures of finasteride (**650**) and dutasteride (**651**).

modification of the carboxylic substituent increased the inhibition activity by fitting better to a lipophilic pocket of the enzyme.[282] Independently, workers at Glaxo developed dutasteride (**651**), having a 2,5-bis(trifluoromethyl)aniline moiety instead of a *tert*-butyl group and with a 72-fold more potent in vivo activity than finasteride, as well as improved metabolic stability.[283] Dutasteride (Avodart) was approved by the FDA in 2002 for treating BPH, and its yearly sales are $1.119 billion.

The synthetic route to dutasteride[284] started from 3-oxo-4-androstene-17β-carboxylic acid (**652**), which was activated as its corresponding acid chloride and then reacted with 2,5-bis(trifluoromethyl)aniline (**653**) to give amide **654** (Scheme 115). The enone functionality was next oxidized to ketoacid **655**, and this compound was then cyclized to lactam **656** by reaction with ammonia. Hydrogenation of the double bond was followed by dehydrogenation of **657** with DDQ and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) to afford dutasteride (**651**).

More recently, a chromatography-free modification of the synthetic process was established in order to improve the overall chemical yield as well as diminishing the number of byproducts associated to the original route.[285] First, dehydrogenation of commercially available 4-azasteroid **658** afforded unsaturated lactam **659** (Scheme 116). Conversion of **659** into the corresponding amide **660** was followed by Cu-mediated coupling with iodobenzene **661**, thus leading to dutasteride in multigram scale.

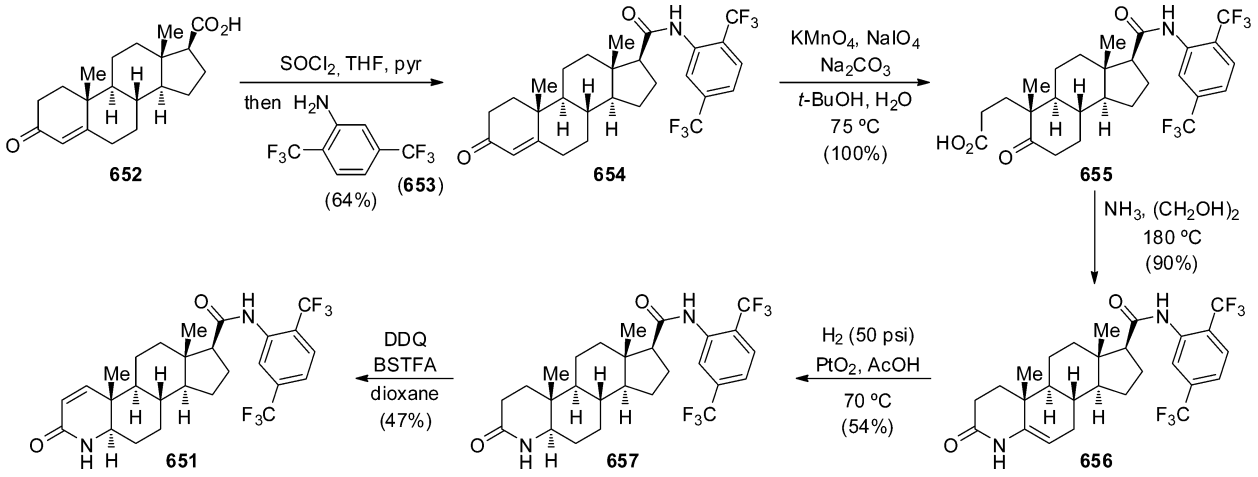
7.2. Silodosin (Rapaflo, Urief)

The α_1 adrenoreceptor antagonists, commonly referred as alpha blockers, constitute a second class of drugs widely employed for the pharmacological treatment of BHP.[280a,286] These compounds act relaxing the smooth muscle in the prostate and the bladder neck and hence favoring urinary flow. However, a subtype of α_1 adrenergic receptors is found in vascular smooth muscle, and therefore, their antagonists may also contribute to decrease the blood pressure.[287] Most of the structurally different alpha blockers developed thus far are nonselective over these receptor subtypes, and consequently, they also produce hypotension as a side effect. In contrast, tamsulosin (**662**) has been the most representative example of selective α_1-adrenergic blockers currently in use for treating BHP[288] until the more recent discovery of silodosin (KMD-3213) (**663**), a closely related molecule with a 38-fold increase in selectivity which may result from introduction of a trifluoroethoxy group (Figure 38).[289] Silodosin shows weaker cardiovascular effects than tamsulosin, although both compounds have been reported to produce ejaculatory disorders. Silodosin was developed by Kissei, first marketed in Japan (trade name Urief) in 2006 and licensed to Watson Pharmaceuticals for the United States market (trade name Rapaflo), reaching $27.6 million sales in 2011.

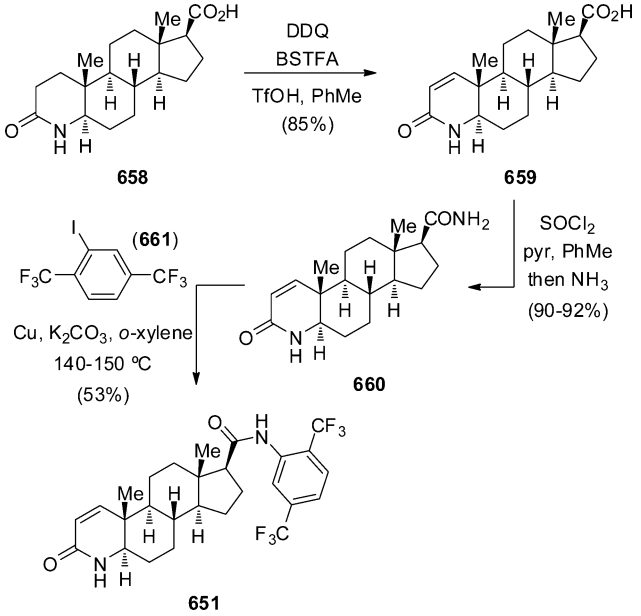
Kissei has disclosed the synthesis of silodosin only in a patent.[290] The most efficient procedure employs addition of Grignard reagent **664** to chiral oxazolidinone **665** to create the stereocenter found in the target compound (Scheme 117). Next, reduction of the carbonyl group in **666** to a methylene moiety

dx.doi.org/10.1021/cr4002879 | *Chem. Rev.* 2014, 114, 2432–2506

Scheme 115. Synthetic Route to Dutasteride (651) from Steroid Derivative 652



Scheme 116. Multigram-Scale Synthesis of Dutasteride (651)



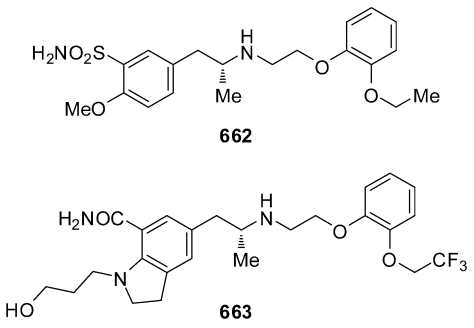


Figure 38. Structures of tamsulosin (**662**) and silodosin (**663**).

afforded compound **667**, which was brominated to produce **668**. Aromatic substitution with CuCN was followed by selective hydrogenation of the Cbz group to furnish free amine **669**, which was subsequently coupled with fluorinated mesylate **670** to give **671**. Finally, removal of the benzyl group and hydrolysis of the nitrile function yielded silodosin (**663**).

8. RESPIRATORY SYSTEM DRUGS

8.1. Roflumilast (Daxas, Dalisrep)

Selective inhibitors of phosphodiesterase type 4 (PDE4) have been studied for many years as anti-inflammatory agents, especially in the area of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD).[291] While a first generation of such inhibitors is represented by rolipram (**672**) and piclamilast (**673**),[292] the first compound eventually reaching the market was roflumilast (**674**) (Figure 39), an orally available drug developed by Altana Pharma (currently Nycomed).[293] Roflumilast received approval in 2010 in the European Union (trade name Daxas) and in 2011 in the United States (licensed to Forest Laboratories, trade name Dalisrep) for treatment of COPD exacerbations. Although the structure of roflumilast closely resembled that of piclamilast, the benefits of introducing fluorine atoms on the biological or pharmacological effects of roflumilast have not been disclosed.

Most of the reported methods for preparation of roflumilast dealt with alkylation of catechol derivatives, leading to mixtures of compounds which required complex purification procedures.[292,294] For instance, reaction of catechol (**675**) with (bromomethyl)cyclopropane (**676**) afforded a mixture of mono- and bis-functionalized compounds from which the desired product **677** was separated by fractional distillation (Scheme 118).[294a] Next, bromination of **677** at low temperature produced bromophenol **678**, converted into difluoro derivative **679** by reaction with CHF_2Cl. A Pd-catalyzed carbonylation followed by hydrolysis of the resuling methyl ester led to acid **680**, and final coupling with 4-amino-3,5-dichloropyridine (**681**) furnished roflumilast (**674**).

Recently, an alternative synthetic approach was reported starting from 3-hydroxy-4-iodobenzoic acid (**682**).[295] Thus, the corresponding methyl ester reacted with (bromomethyl)-cyclopropane in excellent yield, and next, the iodine atom in compound **683** was replaced by a phenol functionality using a Cu-catalyzed hydroxylation (Scheme 119). In this reaction the ester was also hydrolyzed and carboxylic acid **684** had to be converted again into ester **685**. Introduction of the difluoromethyl ether function was accomplished by reaction of **685** with NaO_2CCF_2Cl, and subsequent ester hydrolysis led to acid **680**, immediate precursor of roflumilast.

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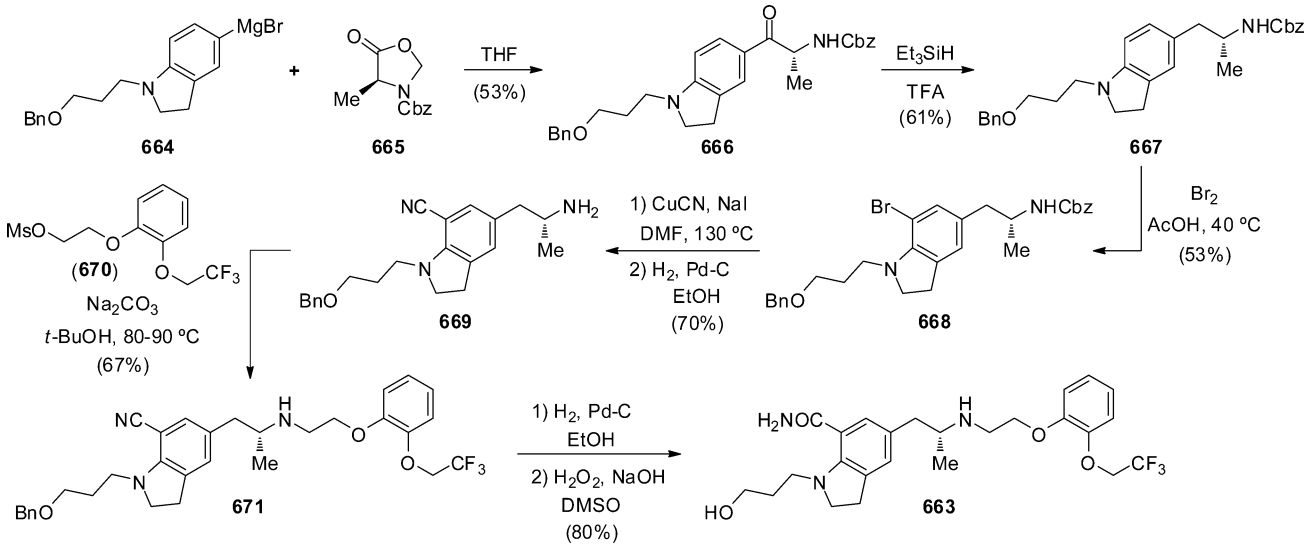
Scheme 117. Asymmetric Synthesis of Silodosin (653) from Chiral Oxazolidinone 665



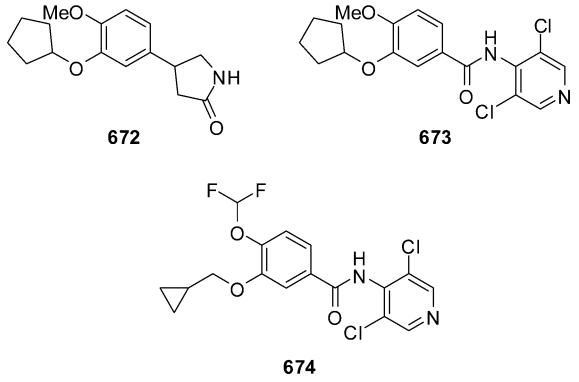
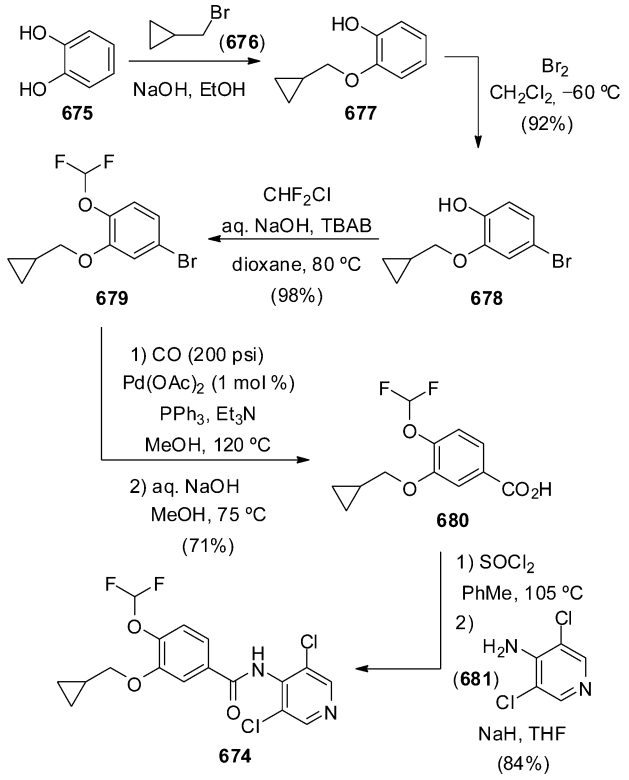


Figure 39. Structures of rolipram (**672**), piclamilast (**673**), and roflumilast (**674**).

Scheme 118. Synthesis of Roflumilast (674) from Catechol Derivative 675



9. ANTI-DIABETES DRUGS

9.1. Sitagliptin (Januvia, Janumet)

Inhibitors of dipeptidyl peptidase 4 (DPP-4) are promising drug candidates for development of antidiabetic compounds. Several molecules belonging to this group of inhibitors have recently been introduced on clinical studies, and sitagliptin (**686**), developed by Merck,[296] was the first of them approved by the FDA in 2006 for treatment of type 2 diabetes mellitus (Figure 40). Current sales of the marketed drugs (Januvia, sitagliptin phosphate; and Janumet, sitagliptin in combination with metformin) reached $3.324 billion in 2011.

Structurally, sitagliptin contains a trifluorinated β-amino acid moiety linked to a trifluoromethyl-containing triazolopyrazine. X-ray studies showed that the 2,4,5-trifluorophenyl ring accommodates into a hydrophobic pocket of DPP-4, fitting better than less fluorinated aromatic rings. Conversely, the presence of the CF_3 group in the triazole ring is fundamental for having good activity, as it interacts electrostatically[24a,297] with the side chains of arginine and serine residues of DPP-4. In fact, removal of the CF_3 group results in a 4-fold decrease in inhibition activity, whereas larger groups such as CF_3CF_2 were less effective. The importance of this CF_3 group also relies on the better pharmacokinetics of sitagliptin, compared to nonfluorinated derivatives.[296]

First syntheses of sitagliptin and analogues consisted of coupling of both β-amino acid and triazolopyrazine fragments, with the chirality of the β-amino acids already installed through an Arndt−Eistert homologation from the parent α-amino acids.[296] Correspondingly, preparation of the heterocyclic unit present in sitagliptin was initially achieved by hydrogenation of a pyrazine precursor, although a better procedure for large-scale production was subsequently developed starting from ethyl trifluoroacetate (**687**) (Scheme 120).[298] Reaction of **687** with hydrazine and 2-chloroacetyl chloride led to hydrazide **688**, which underwent dehydration to afford oxadiazole **689**. Amidine **690** was then formed from **689** and ethylenediamine, and final

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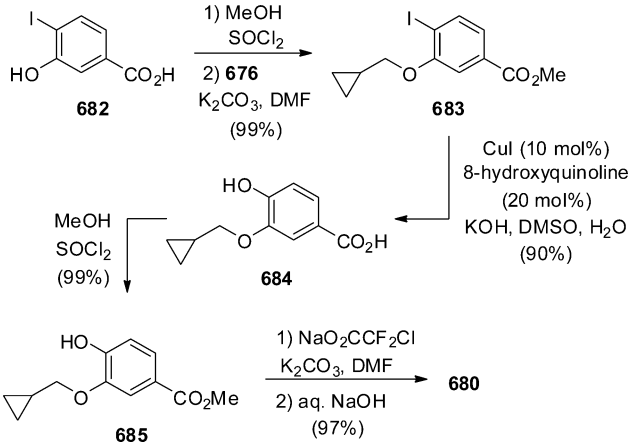
Scheme 119. Synthesis of Roflumilast (674) from Benzoic Acid Derivative 682



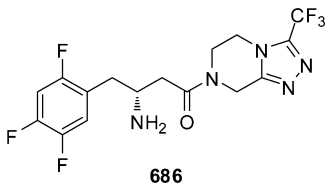
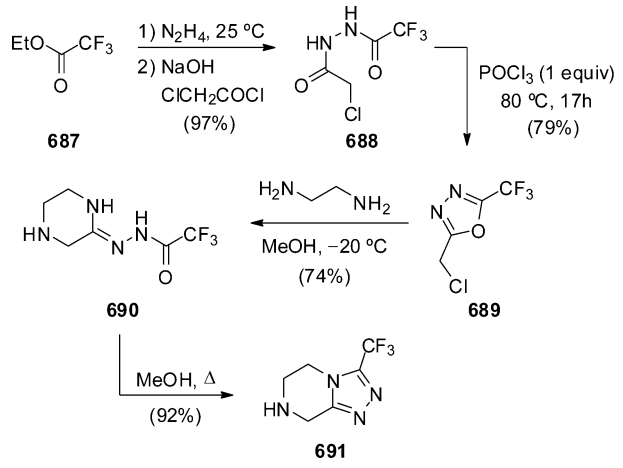


Figure 40. Structure of sitagliptin (**686**).

Scheme 120. Large-Scale Procedure for Heterocyclic Intermediate 691



cyclization to triazolopyrazine **691** was accomplished by heating in MeOH.

For large-scale purposes,[299] first-generation synthesis of sitagliptin employed an enantioselective Ru-catalyzed hydrogenation of β-ketoester **692** which proceeded with 94% ee (Scheme 121).[300] After ester hydrolysis, reaction of carboxylic acid **693** with *O*-benzylhydroxylamine gave compound **694**, which served for an intramolecular Mitsunobu reaction to yield β-lactam **695**. At this point, optical purity was enhanced to ee > 99% by recrystallization of **695** in MeOH/H_2O. Ring opening of this β-lactam produced β-amino acid **696**, and further coupling with triazolopyrazine **691** followed by removal of the benzyloxy group led to sitagliptin (**686**), isolated as its phosphoric acid salt.

Although this synthesis was scalable up to 100 kg of final product, a more efficient route was needed for manufacturing scale, based on the enantioselective reduction of an unprotected enamino amide precursor (Scheme 122).[301] Thus, a three-step, one-pot protocol from (2,3,5-trifluorophenyl)acetic acid (**698**) and Meldrum's acid (**699**) led to enamino amide **703** in 82% yield and >99.6% purity after crystallization from the reaction mixture. This process occurred through intermediate **700**, which in the presence of TFA afforded ketene **701**. In situ addition of the hydrochloride salt of **691** to this ketene gave ketoamide **702**, and by further reaction with NH_4OAc enamino amide **703** was finally formed. High-pressure hydrogenation of **703** in the presence of [(COD)$RhCl_2$] and a chiral diphosphine ligand (*t*-Bu-Josiphos) produced sitagliptin with 95% ee, subsequently increased to >99.9% after recrystallization.

In addition, a metal-free direct transformation of keto amide **702** into **686** was also recently reported (Scheme 123).[302] This third-generation synthesis employed a biocatalytic process using a modified transaminase (27 mutations from a previously known enzyme), which proved to be highly efficient in preparation of sitagliptin in terms of yield and enantioselectivity (99.95% ee), with this protocol also being amenable for industrial production. It is worth mentioning that this procedure can be also applied for synthesis of other chiral amines not accessible by direct amination of the parent carbonyl substrates.

A different synthetic approach was recently described by two independent groups using a highly diastereoselective Michael addition of (*R*)-*N*-benzyl-α-phenylethylamine to a conjugated α,β-unsaturated ester (Davies reaction).[303] In the second case, the Michael acceptor **706** was prepared from 2,4,5-trifluorobenzaldehyde (**704**) using two consecutive Wittig reactions (Scheme 124). Then reaction of **706** with the lithium amide derived from the aforementioned chiral amine proceeded in good yield and excellent stereocontrol. The resulting amino ester **707** was hydrolyzed and coupled with CF_3-triazole **691**, and final deprotection by hydrogenation afforded sitagliptin (**686**) in 43% overall yield. A related PMP-protected chiral amine was also equally efficient in this synthesis, allowing for an alternative deprotection strategy.[303b]

10. GASTROINTESTINAL TRACT DRUGS

10.1. Lubiprostone (Amitiza)

Prostones are a family of bicyclic prostaglandin derivatives developed for the search of new therapeutically useful selective activators of ion channels. In fact, it has been shown that activation of type-2 chloride channels may provide potentially effective agents against chronic constipation and irritable bowel syndrome (IBS).[304] Lubiprostone (**709**) is a difluorinated analogue of prostaglandin E1, FDA approved (2006) for treatment of chronic idiopathic constipation in adults and IBS with constipation in adult women (Figure 41).[305] Lubiprostone was developed by Sucampo Pharmaceuticals and marketed in collaboration with Takeda with the trade name Amitiza.

The original route for preparation of lubiprostone started from the Horner–Wadsworth–Emmons olefination between THP-protected Corey lactone aldehyde **710** and phosphonate **711** (in turn available by difluorination of a suitable α-keto ester precursor) in the presence of TlOEt to afford enone **712** in moderate yield (Scheme 125).[306] Next, double-bond hydrogenation and carbonyl reduction produced alcohol **713**, transformed into lactol **714** by DIBAL reduction. A Wittig reaction led to carboxylic acid **715**, which was conveniently protected and oxidized to furnish compound **716**. Final double-bond hydrogenation yielded lubiprostone (**709**) in equilibrium with its open-chain form **717**.

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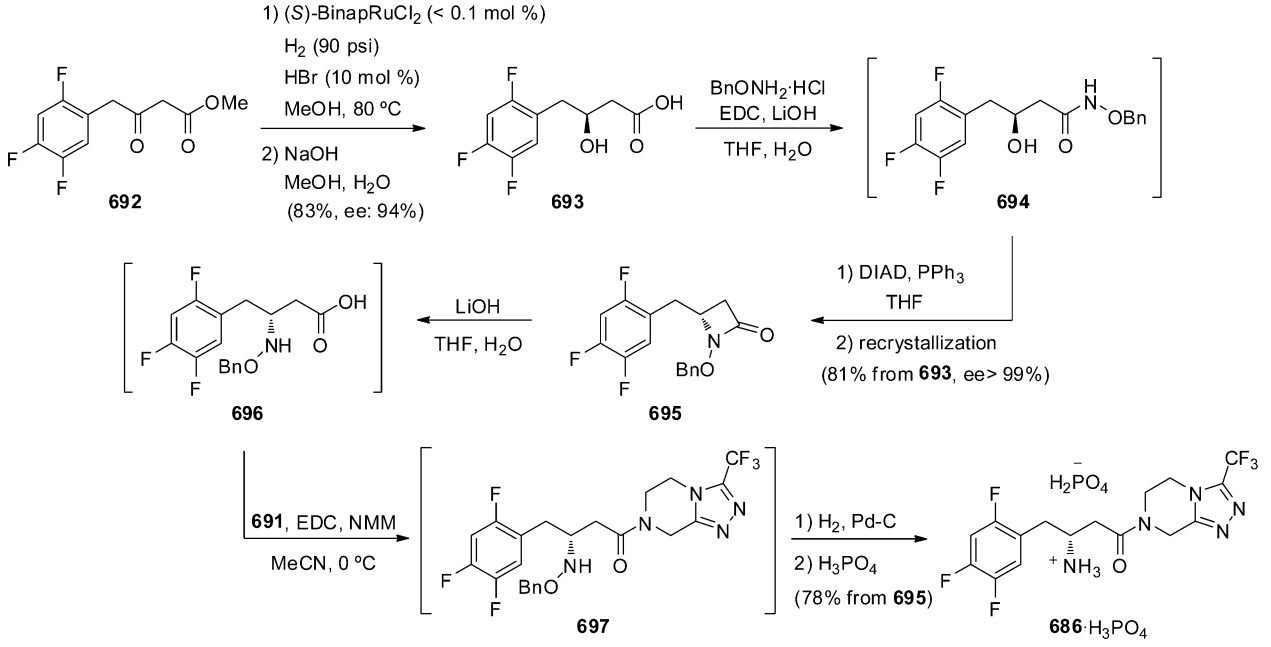
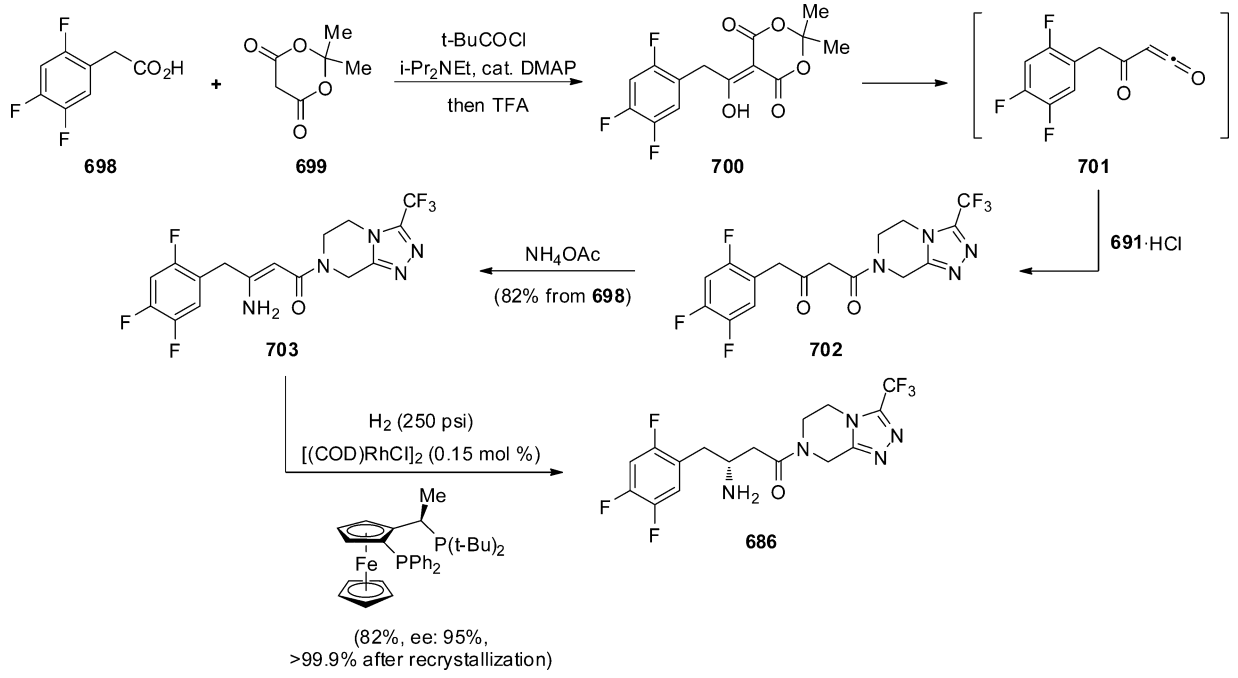
Scheme 121. Enantioselective Ru-Catalyzed Hydrogenation as Key Step in Synthesis of Sitagliptin (686)



Scheme 122. Manufacturing Enantioselective Synthesis of β-Amino Acid Derivative 686



The previously shown enone **627** (Scheme 111), advanced intermediate for synthesis of travoprost and tafluprost, has also been employed for preparation of lubiprostone (Scheme 126).[267a,307] The fluorinated chain of the target product was accessed from ethyl bromodifluoroacetate (**718**), through addition of its derived organozinc reagent to butanal (**719**) to afford alcohol **720**. Elimination of the hydroxyl group produced alkene **721**, and then addition of lithium trimethylsilylacetylide followed by carbonyl reduction and desilylation furnished propargyl alcohol **722**. Benzylation of the hydroxyl group and stannylation of the triple bond led to vinyl stannane **723**, which upon transformation into its derived higher order cyanocuprate, stereoselective conjugate addition to enone **627** proceeded in good yield, and the obtained compound **724** was later converted into lubiprostone by hydrogenation of the double bonds and functional group manipulations.

11. ENDOCRINE SYSTEM DRUGS

11.1. Cinacalcet (Sensipar, Minpara)

Secondary hyperparathyroidism is a disorder caused by high levels of parathyroid hormone (PTH) as a response to low blood calcium levels, mostly occurring as a result of kidney malfunctioning. The main consequence of secondary hyperparathyroidism is bone disease, either by the disorder itself or by therapeutic treatments based on calcium administration.

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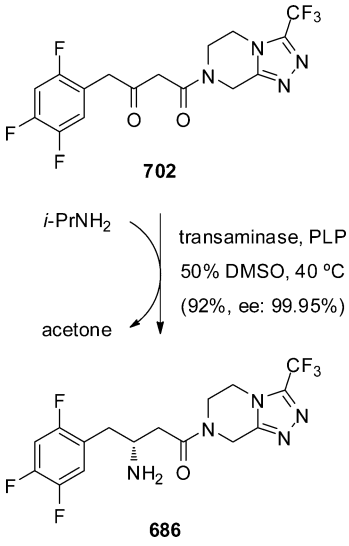
Scheme 123. Biocatalytic Process for Preparation of β-Amino Acid Derivative 686



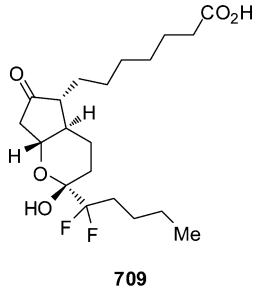


Figure 41. Structure of lubiprostone (**709**).

Calcimimetics are a group of compounds with a mechanism of action involving allosteric activation of calcium-sensing receptor (responsible for release of PTH) present on several tissues by mimicry of extracellular calcium.[308] Different calcimimetic agents have been investigated in recent years, with cinacalcet (**726**) being developed by NPS Pharmaceuticals and licensed to Amgen (Sensipar, Minpara), the first and only of its class approved thus far by the FDA in 2004 for treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis as well as treatment of hypercalcemia in patients with parathyroid carcinoma (Figure 42).[309] Sales of cinacalcet reached $808 million in 2011.

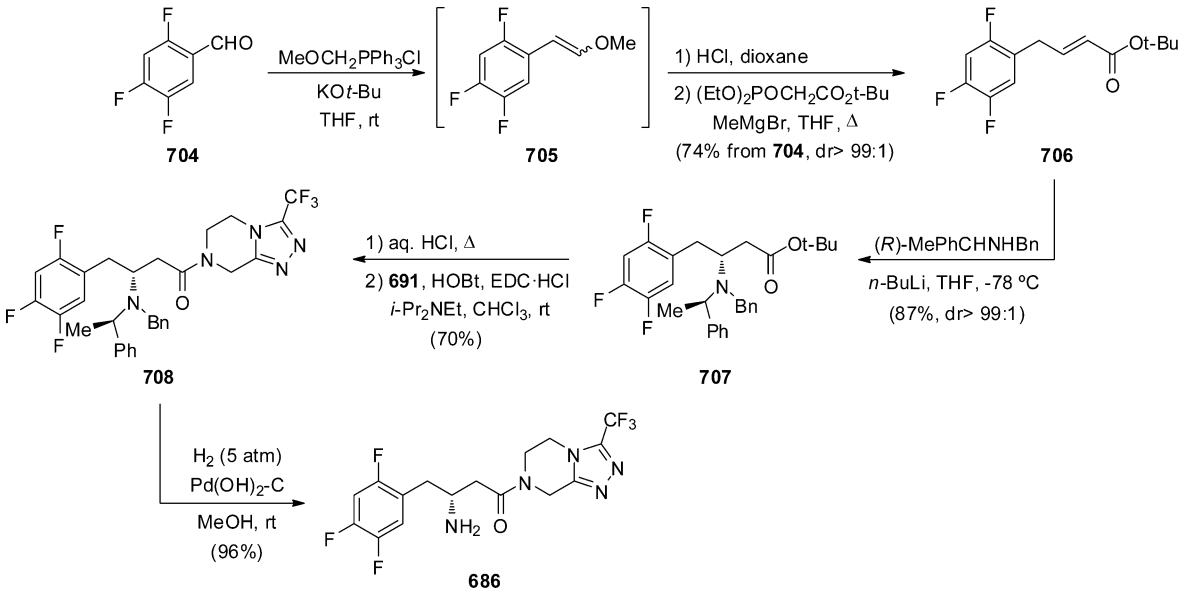
Early synthetic approaches to cinacalcet and related molecules involved reductive amination protocols.[310] For instance, reaction between a suitably substituted 3-arylpropanamine **727** and aromatic ketone **728** led to imine **729**, which was reduced with $NaBH_3CN$ followed by chiral HPLC separation of the resulting enantiomers (Scheme 127). Alternatively, use of (*R*)-methyl naphtylamine (**731**) on the reaction with arylpropanal **730** afforded chiral imine **732** leading on reduction to cinacalcet (**726**).

A related process was recently described from commercially available 3-(trifluoromethyl)cinnamic acid (**733**), also accessible using a Knoevenagel condensation of 3-(trifluoromethyl)-benzaldehyde with malonic acid.[311] Hydrogenation of compound **733** was followed by reduction of the carboxylic acid function (Scheme 128). Then a one-pot protocol consisting of oxidation of alcohol **735** and further reductive amination with amine **731** in the presence of $NaBH(OAc)_3$ led to cinacalcet in 60% overall yield.

A different strategy consisted of reduction of the parent amide **736** (Scheme 129).[312] For instance, a chromatography-free, scalable process was developed using condensation of acid **734** and neat amine **731** followed by reduction of amide **736** with in-situ-formed borane, allowing synthesis of cinacalcet hydrochloride salt in kilogram scale and high purity after recrystallization.[312a]

More recently, access to a CF_3-substituted 3-arylpropionate through a one-pot Heck reaction−hydrogenation was also described.[313] Starting from 1-bromo-3-(trifluoromethyl)-benzene (**737**), Pd-mediated coupling with methyl acrylate was followed by in situ hydrogenation to furnish ester **738** (Scheme 130). This compound was next transformed into amide **736**, a direct precursor of cinacalcet.

Scheme 124. Highly Diastereoselective Michael Addition as Key Step in Synthesis of Sitagliptin (686)



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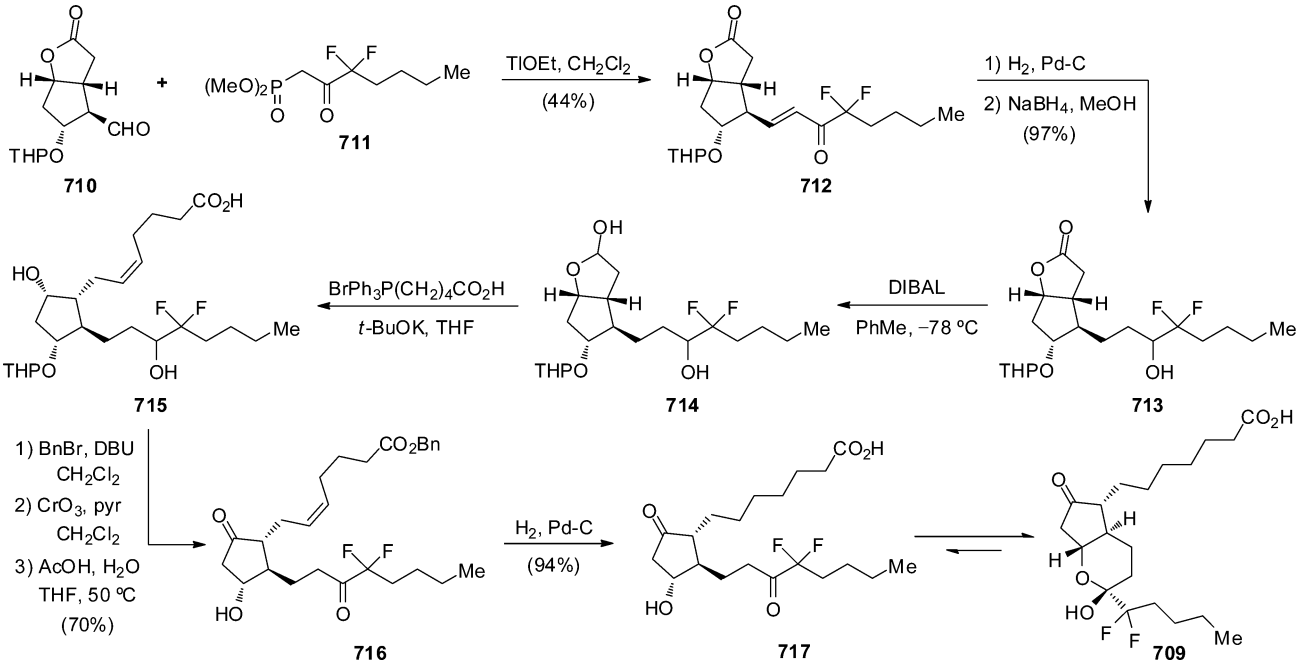
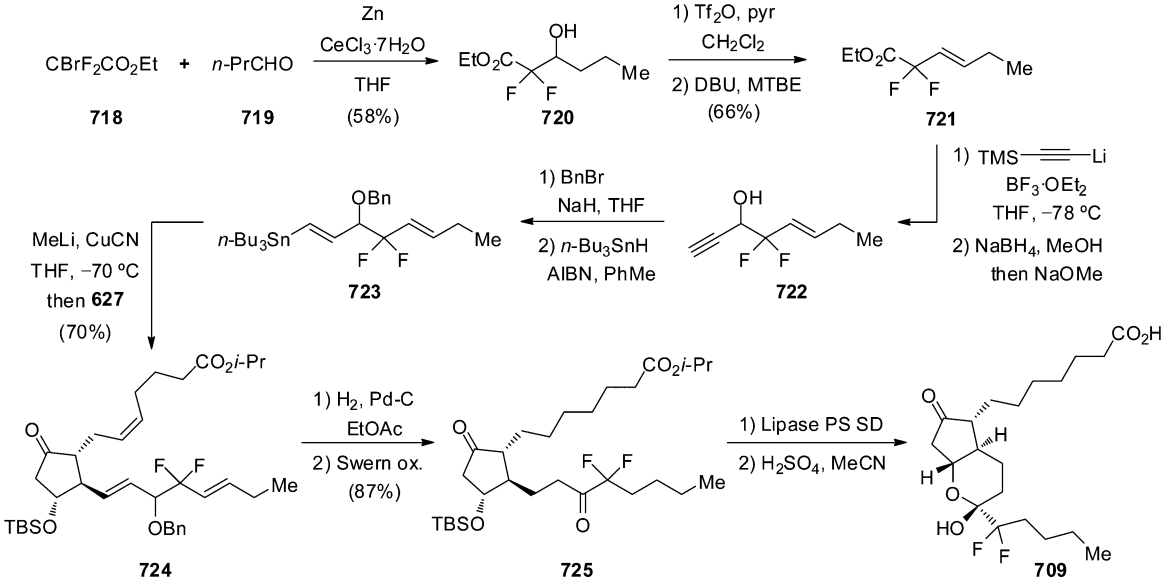
Scheme 125. Synthesis of Lubiprostone (709) from Corey Lactone Aldehyde 710



Scheme 126. Synthesis of Lubiprostone (709) from Enone 627



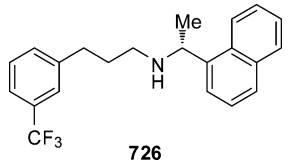


Figure 42. Structure of cinacalcet (**726**).

Another kilogram-scale, one-pot synthesis of cinacalcet was reported using a Forster reaction on imine **739** derived from benzaldehyde and the chiral amine **731** (Scheme 131).[314] Imine **739** reacted with bromide **740** to afford the highly unstable iminium salt **741**. Hydrolysis of **741** finally produced cinacalcet hydrochloride in 58% overall yield without purification of any synthetic intermediate.

Ellman's reagent **742** was employed recently as starting chiral substrate in the synthesis of cinacalcet (Scheme 132).[315] Its reaction with ketone **728** produced the corresponding sulfinimine **743**, leading to a mixture of diastereomeric amines (73:27 ratio) by its further reduction with $NaBH_4$. After separation by recrystallyzation, regioselective *N*-alkylation of the major isomer **744** with iodide **745** afforded compound **746**, and final removal of the sulfoxide moiety by acid treatment yielded cinacalcet hydrochloride.

Finally, cinacalcet was also accessible using an iron-promoted C−C bond-forming reaction between Grignard reagent **749** and vinyl chloride **748**, the latter available in turn from dichloride **747** and chiral amine **731** (Scheme 133).[316] The resulting compound **750** was hydrogenated to furnish cinacalcet hydrochloride in kilogram scale.

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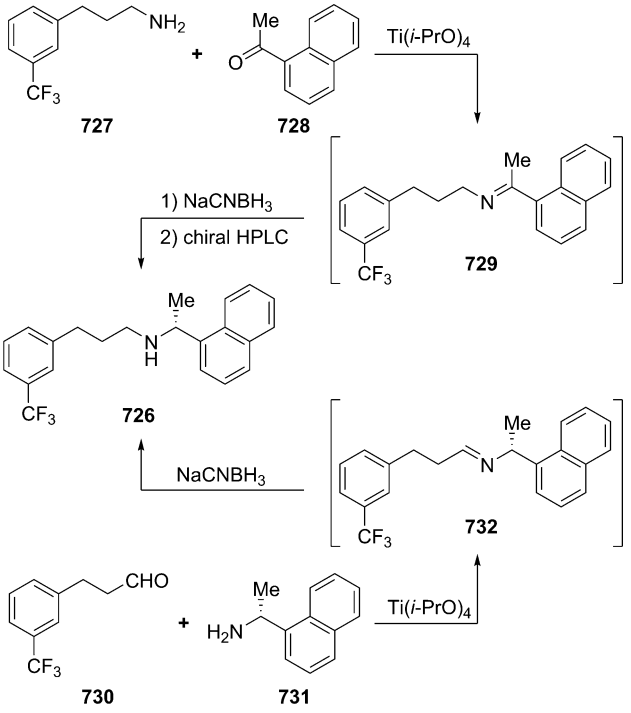
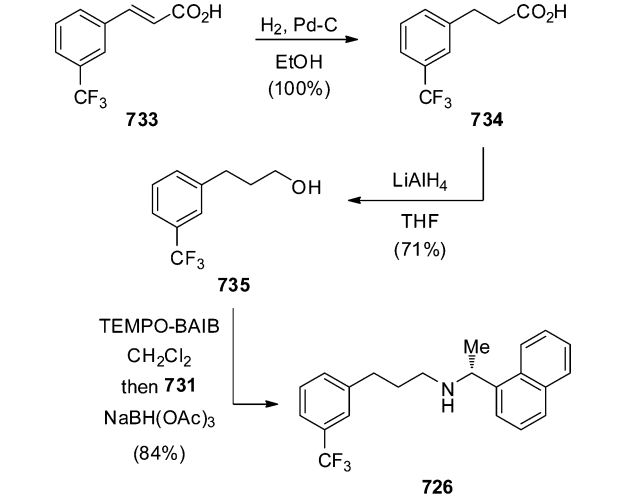
Scheme 127. Early Synthetic Approaches to Cinacalcet (726) by Means of Reductive Amination Protocols



Scheme 128. Synthesis of Cinacalcet (726) from 3-Trifluoromethylcinnamic Acid (733)

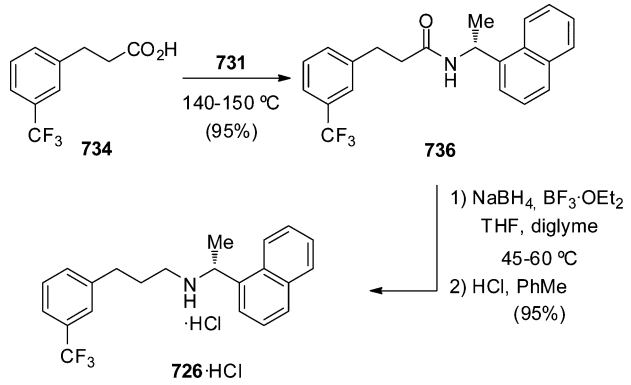


12. NUTRITION AFFECTING DRUGS

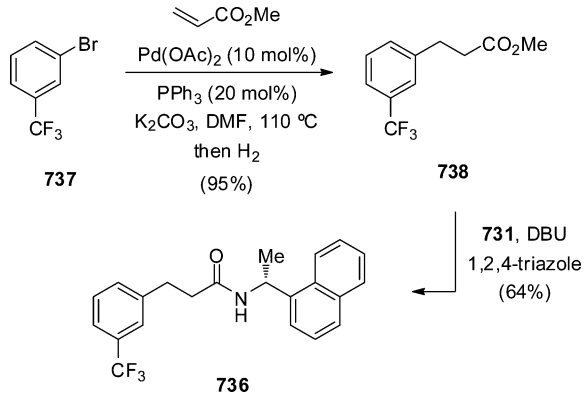
12.1. Nitisinone (Orfadin)

Hereditary tyrosinaemia type 1 (HT-1) is a genetic disorder originated by the lack of fumarylacetoacetate hydrolase, which is the ultimate enzyme in the catabolic pathway of the amino acid tyrosine. Although HT-1 is a very rare disease, affecting only 1 out of 100 000 people worldwide, it has severe clinical consequences mostly associated with liver malfunctioning. In fact, the only effective treatment for HT-1 before 2002 was liver transplantation. However, the FDA approved in that year the use of nitisinone (**751**) for HT-1 treatment, considerably increasing the life expectancy of patients (Figure 43).[317] Nitisinone (Orfadin) was originally licensed by Zeneca and is currently marketed by Swedish Orphan Viobitrum.

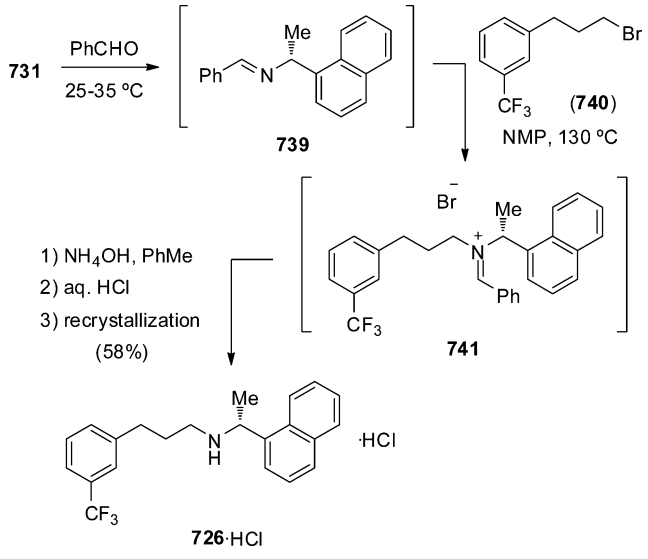
Scheme 129. Scalable Synthesis of Cinacalcet (726) from Amide 736



Scheme 130. Synthesis of Cinacalcet (726) by Means of a Tandem Heck-Hydrogenation Sequence



Scheme 131. Forster Kilogram-Scale Synthesis of Cinacalcet (726)



1,3,3′-Triketones such as nitisinone have been investigated for decades as herbicide agents.[318] Interestingly, when toxicity studies of nitisinone and related compounds were conducted in rats, they developed corneal lesions which eventually were linked to inhibition of 4-(hydroxyphenyl)pyruvate dioxygenase (HPPD). This enzyme acts in the tyrosine degradation route much earlier than fumarylacetoacetate hydrolase, and therefore,

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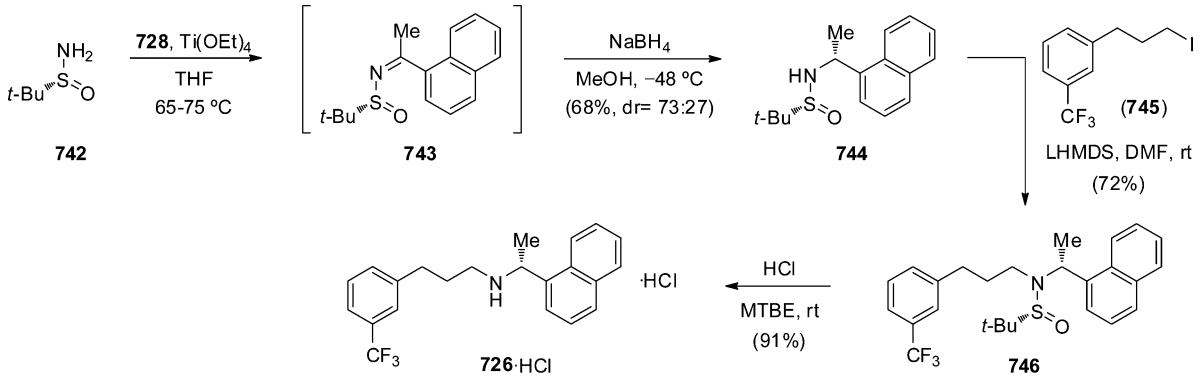
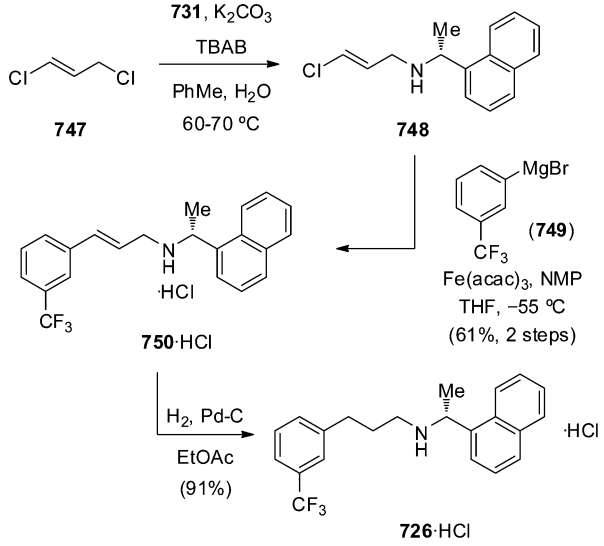
Scheme 132. Ellman's Sulfinamide 742-Mediated Asymmetric Synthesis of Cinacalcet (726)



Scheme 133. Iron-Catalyzed Synthesis of Cinacalcet (726)



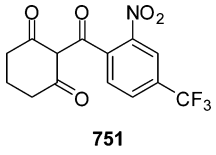


Figure 43. Structure of nitisinone (**751**).

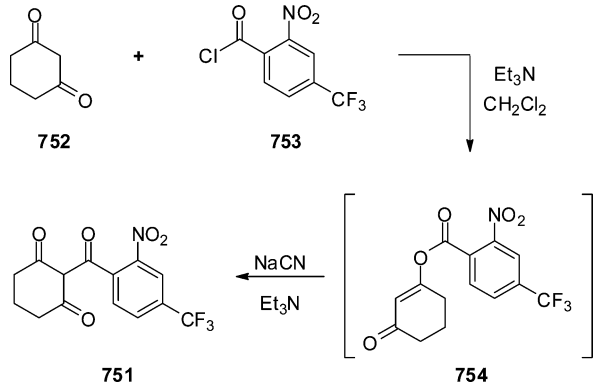
its inhibition prevents accumulation of toxic products in the liver of HT-1 patients.[319] Nitisinone interacts with Fe(II)-HPPD through its keto−enol form, which is the dominant tautomer in different solvents.[320] The relevance of the CF_3 group has been studied only in the context of herbicide activities, establishing that an electron-withdrawing group is preferred at the para position.

Synthesis of nitisinone is very straightforward from 1,3-cyclohexanedione (**752**) and 2-nitro-4-(trifluoromethyl)benzoyl chloride (**753**) through rearrangement of the resulting ester **754** by reaction with NaCN and Et_3N (Scheme 134).[321]

13. CONCLUSIONS

Currently, there are about 200 pharmaceuticals containing fluorine, including the 40 new compounds discussed in this review. One may agree that the contribution of the past decade indicates a significant 20% increase in the number of fluorinated drugs on the market. Accordingly, it is quite obvious to expect that the next decade will see an even greater number of new

Scheme 134. Synthesis of Nitisinone from 1,3-Cyclohexanedione (752)



fluorine-containing pharmaceuticals. Great resources are being invested in academia and industry for systematic studies of all biological aspects of fluorine substitution, metabolism, excretion properties, and protein−fluorine-containing ligand binding interactions. Fluorine scans of ligands will become a routine strategy in lead optimization of pharmaceutical and agrochemical products. This extraordinary potential puts pressure on synthetic fluorine chemistry to deliver new methodologies for selective introduction of fluorine in desirable structural positions.[322] One may observe an interesting tendency that a noticeable increase in the number of newly launched fluorine-containing pharmaceuticals usually follows some major advances in development of fluorine chemistry in a time frame that it is usually necessary to develop a drug.[25f] Recently, there has been explosive research activity in the area of trifluoromethylation,[323] including asymmetric versions.[324] As a result, many truly practical, scalable methods for selective introduction of CF_3 groups have been developed. Accordingly, in the next 5−10 years one may expect that many trifluoromethyl-containing drugs will appear on the pharmaceutical market. In general, however, synthetic methodology holds back a methodical, full exploration of this field, as selective fluorination is still rarely straightforward, using dangerous or expensive reagents. One may agree that the performance of any given drug can be meaningfully improved by selective fluorination, at least to increase a drug's biological half-life by impeding oxidative metabolism and increase bioabsorption by lipophilic effects, which are well understood and quite general strategies. This will, most definitely, improve the quality of healthcare and have tremendous positive economical and social effects. However, this potential is beyond the reach at present as needed fluorination methods are not yet developed or

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the target drug would be prohibitedly expensive. Therefore, it is rather clear that there is a gap between needs of the pharmaceutical industry and current methodological efficiency of fluorine chemistry. Substantial resources should be invested in synthetic fluoroorganic chemistry and developing a new brand of expertise overlapping synthetic fluorine methodology, drug design, and biochemistry.

Besides the dazzling potential of fluorinated pharmaceuticals there are two potential warning issues we believe should be addressed in this section. It is quite reasonable to assume that the increase in consumption of fluorine-containing drugs will eminently lead, due to their metabolic degradation, to higher than normal concentrations of fluoride in body fluids and tissues. The toxicological profile of fluoride is virtually unstudied; therefore, evaluation of the safety and benefits vs risks of the long-term effect of fluorine-containing pharmaceutical products on human health presents an important concern.[325] One of the known potential risks is a synergistic action between fluoride and aluminum ions forming aluminofluoride complexes.[326] The problem is that these complexes can act as analogs of phosphate groups, in the regulation of the activity of enzymes, energy metabolism, cell (G proteins) signaling cascades.[327] Aluminofluoride complexes are efficient in extremely low (nanomolar) concentrations and therefore may present some potential danger for living organisms, including humans, calling for this human fluoride overload concern to be studied in detail.[328]

Another issue is the phenomenon of self-disproportionation of enantiomers (SDE).[329] SDE is observed for nonracemic compounds and consists of a spontaneous or designed process of separation of racemate from the excess enantiomer under totally achiral conditions. For example, if an enantiomerically enriched sample is subjected to purification by achiral chromatography, it may be eluted as racemic and enantiomerically pure fractions.[330] Another common example of SDE is phase transitions, in particular, sublimation. It was shown that sublimation rates of racemic and enantiomerically pure crystals are different, similar to the differences in melting points and solubility, and lead to separation of racemic and enantiomerically pure forms in sublimate and the remainder.[331] Literature data on SDE clearly suggest that fluorine-containing compounds are particularly prone to SDE.[332] Thus, in the case of achiral chromatography,[333] the strongly polarizing effect of fluorine on chemical bonds leads to enhanced intermolecular homo/heterochiral interactions (dipole−dipole or H bonding) and therefore a high magnitude of SDE. In the case of sublimation,[334] the presence of fluorine renders compounds more volatile and consequently more susceptible to sublimation, even at normal pressure and ambient temperature.[335] Thus, if a practitioner is unaware of SDE, this effect can lead to problems with correct determination of the enantiomeric purity of a drug sample and cause marketing a compound of less than the specified enantiomeric purity. Of course, these problems can be avoided if appropriate precautions are made including the SDE test. Furthermore, if the SDE is properly investigated, it can be used as an unconventional enantiomeric purification method;[336] in this case, fluorinated compounds will advantage over fluorine-free analogs.

In general, fluorine-containing health care products are already making a notable impact on organic/medicinal chemistry, pharmaceutical, and chemical industries. Their economical and social effect will continue to increase, making it a very exciting time to work in this area.

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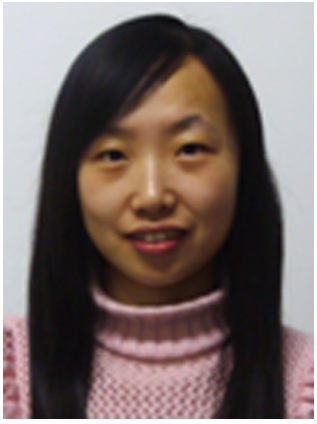
Notes

The authors declare no competing financial interest.

Biographies



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María Sánchez-Roselló was born in Valencia, Spain, in 1977. She studied Pharmacy and received her Ph.D. degree in 2005 from the University of Valencia under the supervision of Professor Santos Fustero, working in the field of organofluorine chemistry and focusing on synthesis of α- and β-amino acids through the olefin metathesis reaction. She spent 2 years as a postdoctoral researcher in the laboratories of Professor Scott J. Miller at Boston College and Yale University, working on peptide-based asymmetric catalysis. She then joined Professor Fustero's group with a *Juan de la Cierva* research contract, and currently she is an assistant professor in Organic Chemistry at the University of Valencia. Her scientific interests include asymmetric organocatalysis and organofluorine chemistry.

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Hong Liu received her M.S. and Ph.D. degrees in Medicinal Chemistry from the China Pharmaceutical University under the supervision of Professor Weiyi Hua. After a postdoctoral stay with Professor Ruyun Ji and Professor Kaixian Chen at Shanghai Institute of Materia Medica, she joined the Shanghai Institute of Materia Medica and is Group Leader now. As a visiting scientist, she stayed with Professor James Halpert at the University of Texas Medical Branch at Galveston. Her research interests include medicinal chemistry, organic chemistry, computer modeling, and pharmacologically active molecules, especially those targeting antitumor and antidiabetes. Her scientific efforts have found recognition by a variety of scientific prizes and research awards, international lectureships, and an invitation to join the advisory boards of scientific journals.

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