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Review

Synthetic approaches to the 2010 new drugs

Kevin K.-C. Liu [a,†], Subas M. Sakya [b,‡], Christopher J. O'Donnell [b,*], Andrew C. Flick [b,§], Hong X. Ding [c,¶]

[a] Pfizer Inc., La Jolla, CA 92037, USA
[b] Pfizer Inc., Groton, CT 06340, USA
[c] Shenogen Pharma Group, Beijing, China

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ABSTRACT

New drugs are introduced to the market every year and each represents a privileged structure for its biological target. These new chemical entities (NCEs) provide insights into molecular recognition and also serve as leads for designing future new drugs. This review covers the synthesis of 15 NCEs that were launched anywhere in the world in 2010.

Contents

1. Introduction

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

This annual review was inaugurated nine years ago[2–9] and presents synthetic methods for molecular entities that were launched in various countries during 2010.[10] Given that drugs tend to have

* Corresponding author. Tel.: +1 860 715 4118.
E-mail addresses: Kevin.k.liu@pfizer.com (K.K.-C. Liu), subas.m.sakya@pfizer.com (S.M. Sakya), christopher.j.odonnell@pfizer.com (C.J. O'Donnell), andrew.flick@pfizer.com (A.C. Flick), Hongxia.ding@shenogen.com (H.X. Ding).
† Tel.: +1 858 622 7391.
‡ Tel.: +1 860 715 0425.
§ Tel.: +1 860 715 0228.
¶ Tel.: +86 10 8277 4069.

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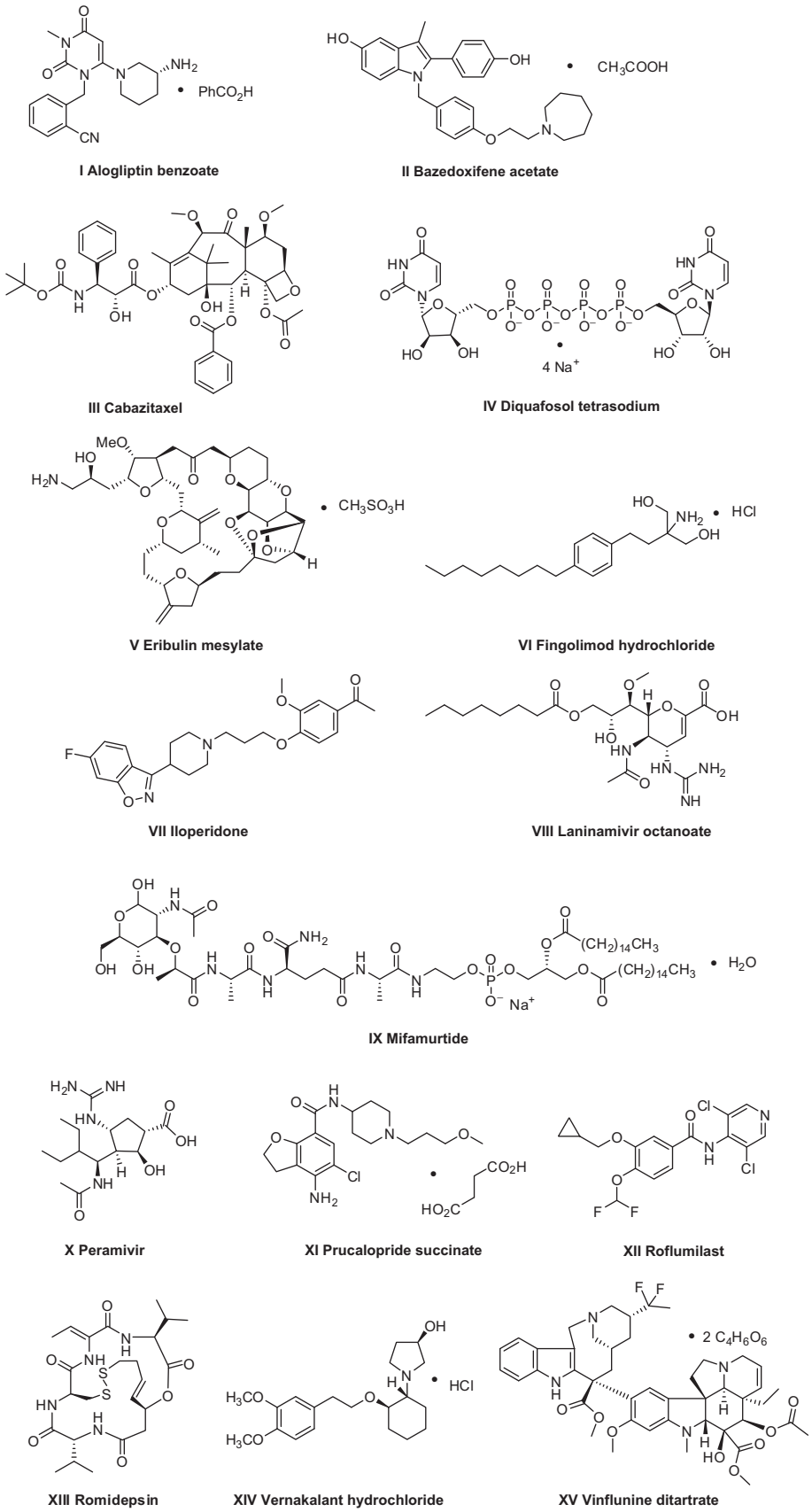


Figure 1. Structures of 15 new drugs marketed in 2010.

structural homology across similar biological targets, it is widely believed that the knowledge of new chemical entities and their syntheses will greatly accelerate drug design. In 2010, 29 new products, including new chemical entities, biological drugs, and diagnostic agents reached the market.[10] This review focuses on the syntheses of 15 new chemical entities that were launched anywhere in the world for the first time in 2010 (Fig. 1) and excludes new indications for previously launched medications, new combinations, new formulations and drugs synthesized via bio-processes or peptide synthesizers. Although the scale of the synthetic routes were not disclosed in all cases, this review attempts to highlight the most scalable routes based on the patent or primary literature and appear in alphabetical order by generic name. The syntheses of new products that were approved for the first time in 2010 but not launched before year's end, will be covered in the 2011 review.

2. Alogliptin benzoate (*Nesina*®)

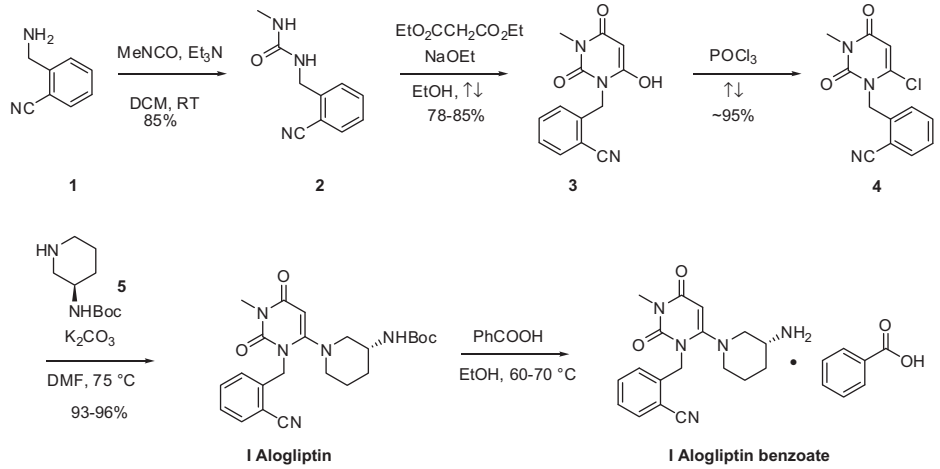
Alogliptin benzoate is a dipeptidyl peptidase IV (DPPIV) inhibitor discovered by Takeda Pharmaceuticals and approved in Japan in 2010 for the treatment of type II diabetes mellitus.[10] Alogliptin is an oral drug for once a day dosing to complement diet and exercise. Alogliptin is the most selective marketed DPPIV inhibition and has similar PK and PD properties compared to previous entries.[11,12] The discovery, structure–activity relationship of related analogs, and synthesis of this compound have been recently published.[13] The most convenient synthesis for scale-up will be highlighted from several published routes (Scheme 1).[13–16] Commercially available 2-cycanobenzyl amine **1** was reacted with methylisocyanate in DCM at ambient temperature to provide *N*-methyl urea **2** in 85% yield. Reaction of the urea **2** with dimethyl malonate in refluxing ethanol with sodium ethoxide as base gave the cyclized trione **3** in 78–85% yield. The trione **3** was then refluxed in neat $POCl_3$ to provide the penultimate chloride crude **4** in 95% yield which was reacted with Boc-protected diamine **5** in the presence of potassium carbonate in DMF to furnish alogliptin **I** in 93–96% yield. Treatment of alogliptin with benzoic acid in ethanol at 60–70 °C followed by crystallization delivered the desired alogliptin benzoate (**I**).

3. Bazedoxifene acetate (*Conbriza*®)

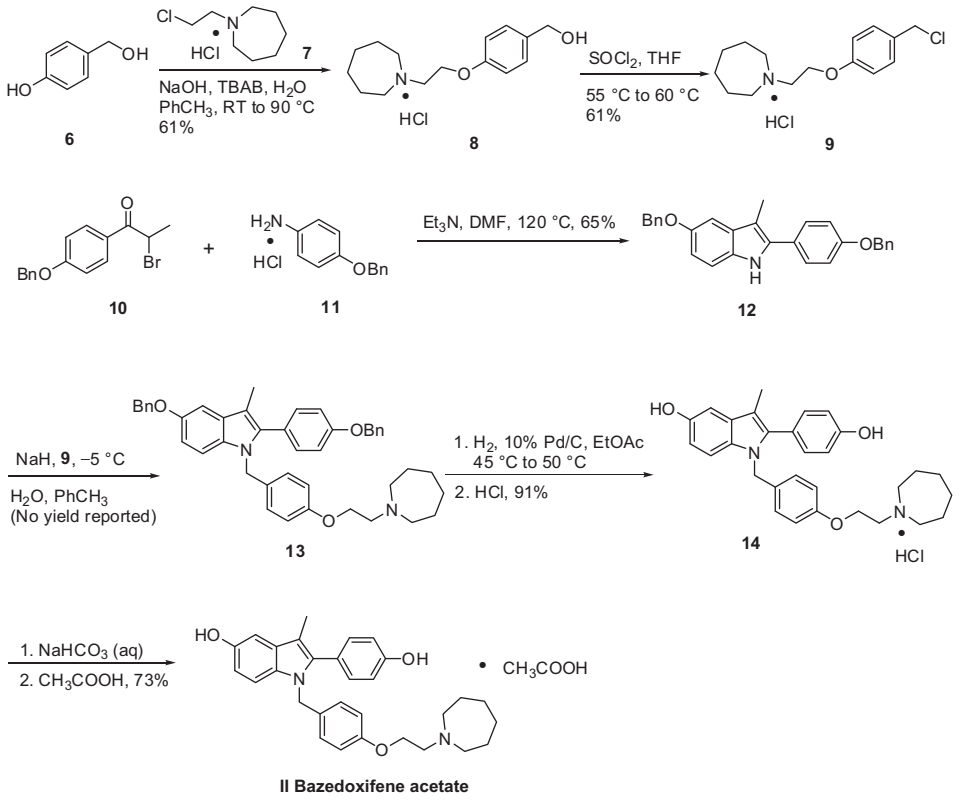
The selective estrogen receptor modulator bazedoxifene acetate was approved in Spain for the treatment of osteoporosis in postmenopausal women.[10] The drug was discovered by Wyeth (now Pfizer) and licensed to Almirall.[10] Clinical trials with bazedoxifene along with conjugated estrogens demonstrated significant improvement in bone mineral density and prevented bone loss in postmenopausal women without osteoporosis. It also reduces fracture risks among women with postmenopausal osteroporosis.[10] Among many syntheses reported for this drug,[17–22] the most recent process scale synthesis (multi-kg scale) is highlighted[22] and involves the union of azepane ether **9** and indole **12**. 4-Hydroxybenzyl alcohol (**6**) was converted in two steps to chloride **9** (Scheme 2). The reaction of **6** with 2-chloroethyl azepane hydrochloride (**7**) in a biphasic mixture of sodium hydroxide and toluene in the presence of tetrabutylammonium bromide (TBAB) gave the desired intermediate alcohol **8** in 61% yield. Treatment of **8** with thionyl chloride ($SOCl_2$) gave the requisite chloride **9** in 61% yield. The reaction of 2-bromopropiophenone (**10**) with an excess of 4-benzyloxy aniline hydrochloride (**11**) in the presence of triethylamine (TEA) in *N*,*N*-dimethylformamide (DMF) at elevated temperatures resulted in indole **12** in 65% yield. Alkylation of **12** with benzylchloride **9** in the presence of sodium hydride (NaH) afforded N-alkylated compound **13**. The benzyl ether functionalities from compound **13** were removed via hydrogenolysis and subsequently subjected to acidic conditions, providing diol **14** as the hydrochloride salt in 91% yield. The hydrochloride was then exchanged for the acetate via free base preparation with 5% sodium bicarbonate or triethylamine, followed by treatment with acetic acid giving bazedoxifene acetate (**II**) in 73–85% yield.

4. Cabazitaxel (*Jevtana*®)

Cabazitaxel was developed by Sanofi-Aventis as an intravenous injectable drug for the treatment of hormone-refractory metastatic prostate cancer.[23] As a microtubule inhibitor, cabazitaxel differs from docetaxel because it exhibits a much weaker affinity for P-glycoprotein (P-gp), an adenosine triphosphate (ATP)-dependent drug efflux pump.[24] Cancer cells that express P-gp become resistant to taxanes, and the effectiveness of docetaxel can be limited by its high substrate affinity for P-gp.[24] Clinical studies confirmed that cabazitaxel retains activity in docetaxel-resistant tumors.[23] Common adverse events with cabazitaxel include diarrhea and neutropenia. Cabazitaxel in combination with prednisone is an important new treatment option for men with docetaxel-refractory metastatic CRPC (castration-resistant prostate cancer).[23] The semi-synthesis of cabazitaxel[25] started from 10-deacetylbaccatin III (**15**) which can be prepared from 7-xylosyl-10-deacetylbaccatin natural product mixture according to a literature process procedure (Scheme 3).[26] 10-Deacetylbaccatin III was protected with triethylsilyl chloride (TESCl) in pyridine to afford the corresponding 7,13-bis-silyl ether in 51% yield, which was methylated with MeI



Scheme 1. Synthesis of alogliptin benzoate (**I**).



Scheme 2. Synthesis of bazedoxifen acetate (**II**).

and NaH in DMF to give 10-methoxy-7,13-bis silyl ether **16** in 76% yield. After de-silylation of **16** with triethylamine trihydrofluoride complex at room temperature, triol **17** was obtained in 77% yield. Selective methylation of **17** with MeI and NaH in DMF at 0 °C provided 7,10-dimethyl ether **18** in 74% yield. Compound **18** was condensed with commercially available oxazolidinecarboxylic acid **19** in the presence of dicyclohexylcarbodiimide/dimethylaminopyridine (DCC/DMAP) in ethyl acetate at room temperature to generate ester **20** in 76% yield. The oxazolidine moiety of compound **20** was selectively hydrolyzed under mild acidic conditions to yield the hydroxy Boc-amino ester derivative cabazitaxel (**III**) in 32% yield.

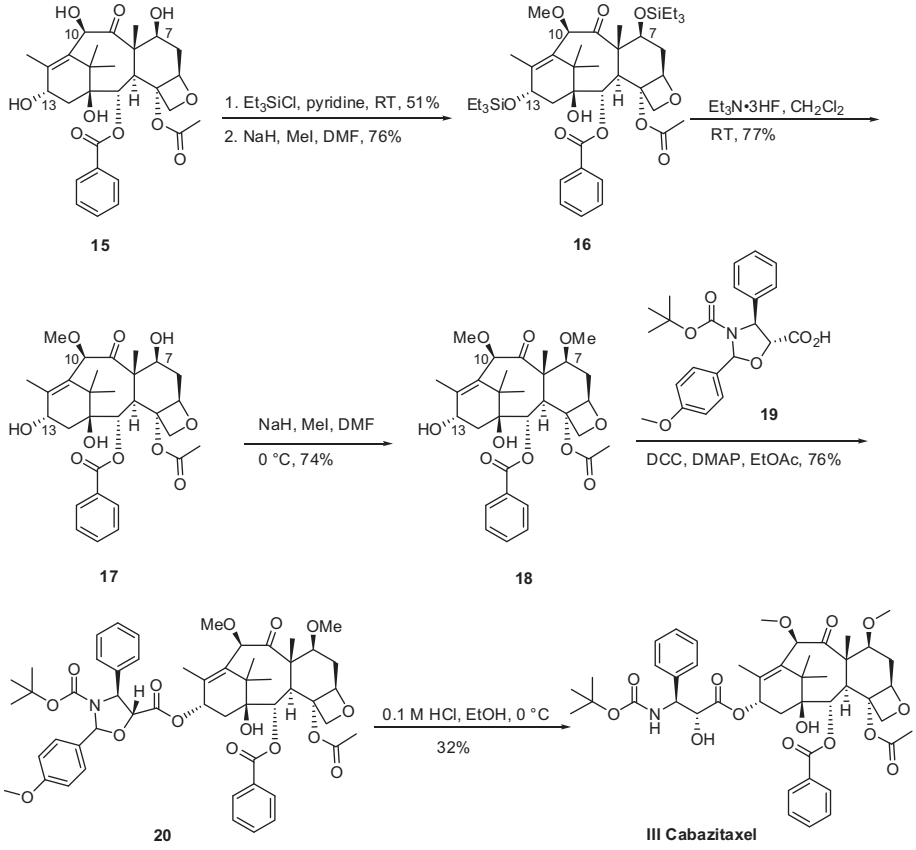
5. Diquafosol tetrasodium (*Diquas*®)

Diquafosol tetrasodium was approved in April 2010 as Diquas® ophthalmic solution 3% for the treatment of dry eye syndrome and launched in Japan by Santen Pharmaceuticals.[10] Diquafosol tetrasodium was originally discovered by Inspire Pharmaceuticals. In 2001, it was licensed to Santen for co-development and commercialization in Asian countries, and co-developed in collaboration with Allergan for the countries outside of Asia. In the US, diquafosol tetrasodium was submitted for a New Drug Application (NDA) as Prolacria® (2% ophthalmic formulation) in June 2003. However, it is still in Phase III clinical development for dry eye syndrome. Diquafosol tetrasodium, also known as INS-365, is a $P2Y_2$ receptor agonist, which activates $P2Y_2$ receptor on the ocular surface, leading to rehydration through activation of the fluid pump mechanism of the accessory lacrimal glands on the conjunctival surface.[27] The large-scale synthesis route of diquafosol tetrasodium is described in Scheme 4.[28,29] Commercially available uridine 5′-diphosphate disodium salt (**21**) was transformed into the corresponding tributylamine salt by ion exchange chromatography on Dowex 50 using Bu_3NH^+ phase, and then dimerized by means of CDI in DMF at 50 °C. The crude product was purified by Sephadex DEAE column followed by ion exchange using a Dowex 50W resin in Na^+ mode. The one-pot process provided diquafosol tetrasodium (**IV**) in 25% yield.[29]

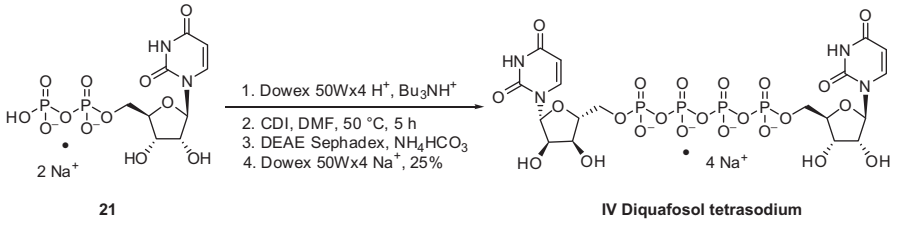
6. Eribulin mesylate (*Halaven*®)

Eribulin is a highly potent cytotoxic agent approved in the US for the treatment of metastatic breast cancer for patients who have received at least two previous chemotherapeutic regimens.[30] Eribulin was discovered and developed by Eisai and it is currently undergoing clinical evaluation for the treatment of sarcoma (PhIII) and non-small cell lung cancer which shows progression after platinum-based chemotherapy and for the treatment of prostate cancer (PhII). Early stage clinical trials are also underway to evaluate eribulin's efficacy against a number of additional cancers. Eribulin is a structural analog of the marine natural product halichondrin B. Its mechanism of action involves the disruption of mitotic spindle formation and inhibition of tubulin polymerization which results in the induction of cell cycle blockade in the G2/M phase and apoptosis.[31] Several synthetic routes for the preparation of eribulin have been disclosed,[32–35] each of which utilizes the same strategy described by Kishi and co-workers for the total synthesis of halichondrin B.[36] Although the scales of these routes were not disclosed in all cases, this review attempts to highlight what appears to be the production-scale route based on patent literature.[37,38] Nonetheless, the synthesis of eribulin represents a significant accomplishment in the field of total synthesis and brings a novel chemotherapeutic option to cancer patients.

The strategy to prepare eribulin mesylate (**V**) employs a convergent synthesis featuring the following: the late stage coupling of sulfone **22** and aldehyde **23** followed by macrocyclization under Nozaki–Hiyami–Kishi coupling conditions, formation of a challenging cyclic ketal, and installation of the primary amine (Scheme 5). Sulfone **22** was further simplified to aldehyde **24** and vinyl triflate



Scheme 3. Synthesis of cabazitaxel (**III**).

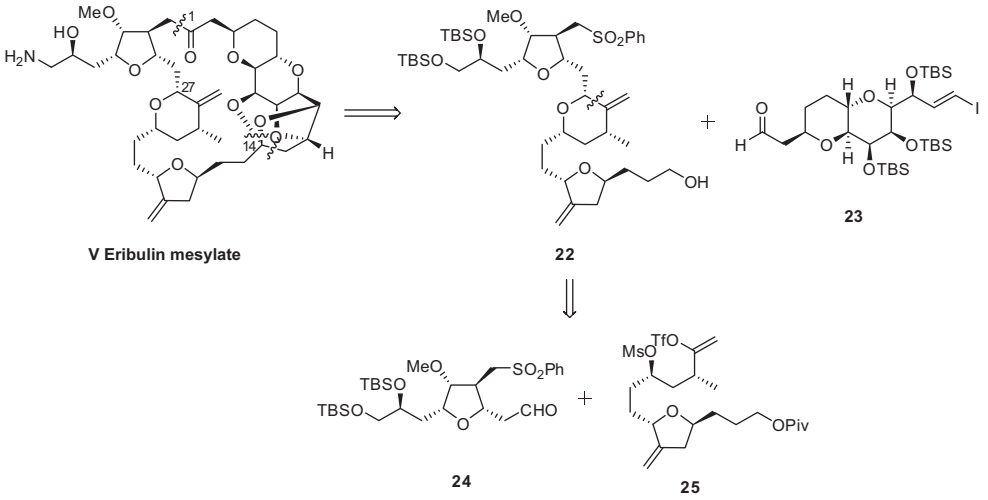


Scheme 4. Synthesis of diquafosol tetrasodium (**IV**).

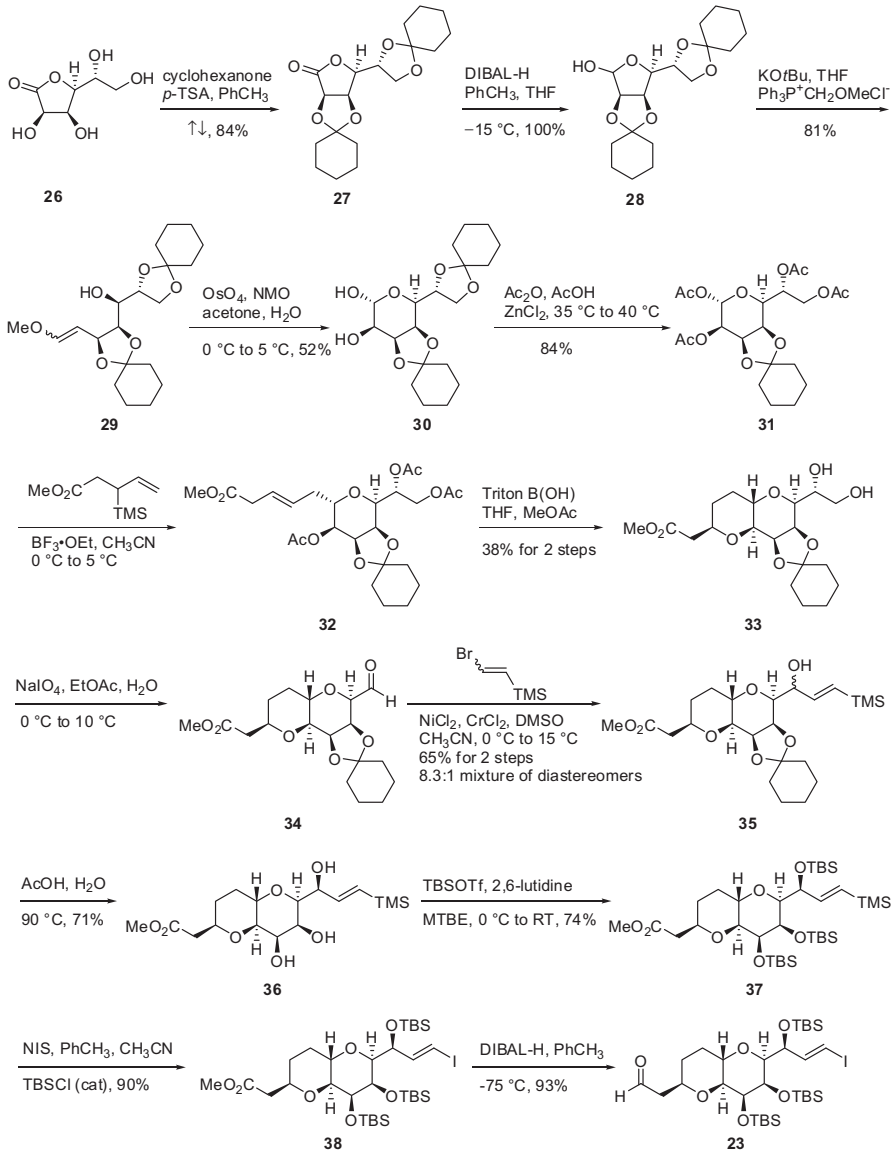
25 which were coupled through a Nozaki–Hiyami–Kishi reaction. The schemes that follow will describe the preparation of fragments **23**, **24** and **25** along with how the entire molecule was assembled.

The synthesis of the C1–C13 aldehyde fragment **23** is described in Scheme 6. L-Mannonic acid-lactone **26** was reacted with cyclohexanone in *p*-toluene sulfonic acid (*p*-TSA) to give the biscyclohexylidene ketal **27** in 84% yield. Lactone **27** was reduced with diisobutylaluminum hydride (DIBAL-H) to give lactol **28** followed by condensation with the ylide generated from the reaction of methoxymethylene triphenylphosphorane with potassium *tert*-butoxide to give a mixture of *E* and *Z* vinyl ethers **29** in 81% yield. Dihydroxylation of the vinyl ether of **29** using catalytic osmium teteroxide and *N*-methylmorpholine-*N*-oxide (NMO) with concomitant cyclization produced diol **30** in 52% yield. Bis-acetonide **30** was then reacted with acetic anhydride in acetic acid in the presence of $ZnCl_2$ which resulted in selective removal of the pendant ketal protecting group. These conditions also affected peracylation, giving rise to tetraacetate **31** in 84% yield. Condensation of **31** with methyl 3-(trimethylsilyl)pent-4-enoate in the presence of boron trifluoride etherate in acetonitrile provided alkene **32**. Saponification conditions using Triton B(OH) removed the acetate protecting groups within **32** and presumably induced isomerization of the alkene into conjugation with the terminal ester, triggering an intramolecular Michael attack of the 2-hydroxyl group, ultimately resulting in the bicylic-bispyranyl diol methyl ester **33** as a crystalline solid in 38% yield over two steps. Oxidative cleavage of the vicinal diol of **33** with sodium periodate gave aldehyde **34** which was coupled to (2-bromovinyl)trimethylsilane under Nozaki–Hiyami–Kishi conditions to give an 8.3:1 mixture of allyl alcohols **35** in 65% yield over two steps. Hydrolysis of the cyclohexylidine ketal **35** with aqueous acetic acid followed by recrystallization gave diastereomerically pure triol **36** which was reacted with *tert*-butyldimethylsilyl triflate (TBSOTf) to afford the *tris*-TBS ether **37** in good yield. Vinyl silane **37** was treated with NIS and catalytic *tert*-butyldimethylsilyl chloride (TBSCl) to give vinyl iodide **38** in 90% yield. Reduction of the ester with DIBAL-H produced the key C1–C14 fragment **23** in 93% yield.

The preparation of the tetra-substituted tetrahydrofuran intermediate **24** is described in Scheme 7. D-Glucurono-6,3-lactone **39** was reacted with acetone and sulfuric acid to give the



Scheme 5. Synthesis strategy of eribulin mesylate (**V**).

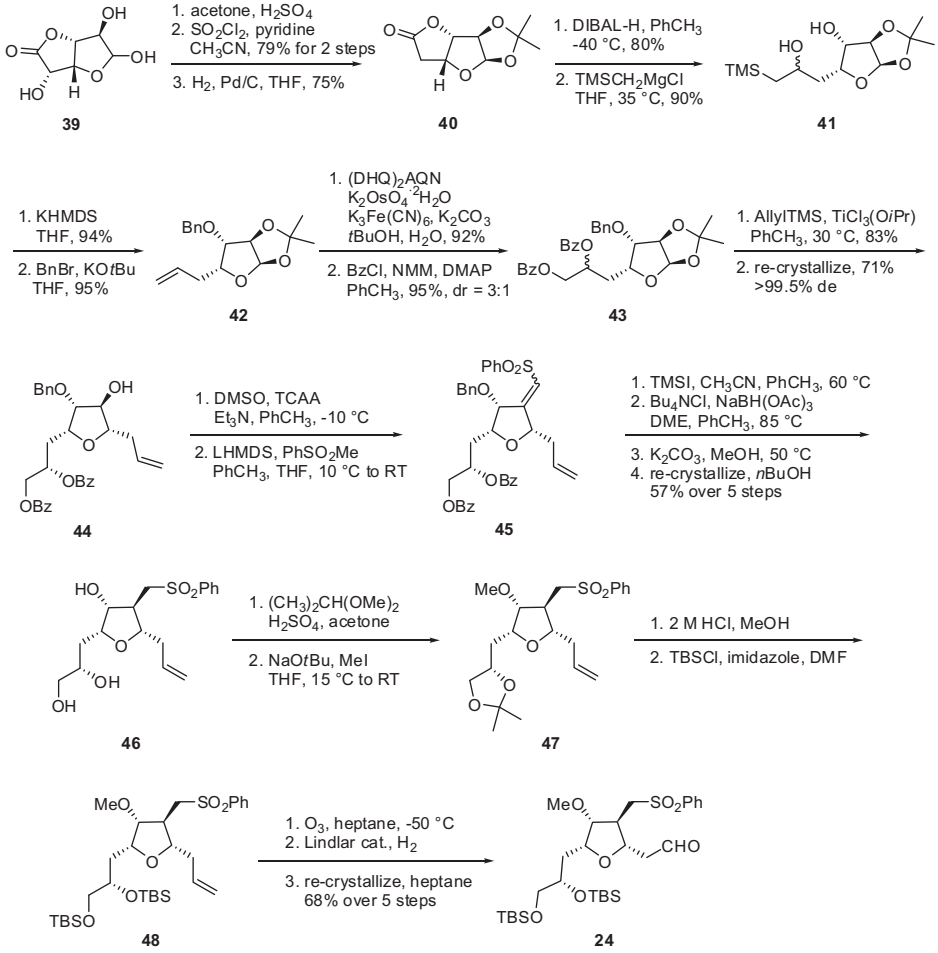


Scheme 6. Synthesis of fragment **23** of eribulin mesylate (**V**).

corresponding acetonide and the 5-hydroxyl group was then removed by converting it to its corresponding chloride through reaction with sulfuryl chloride (SO_2Cl_2) followed by hydrogenolysis to give lactone **40** in good overall yield. Reduction of the lactone **40** with DIBAL-H gave the corresponding lactol which was condensed with (trimethylsilyl)methylmagnesium chloride to afford silane **41**. Elimination of the silyl alcohol of **41** was accomplished under Peterson conditions with potassium hexamethyldisilazide (KHMDS) to afford the corresponding terminal alkene in 94% yield. The secondary alcohol of this intermediate was alkylated with benzyl bromide to afford ether **42** in 95% yield. Asymmetric dihydroxylation of the alkene of **42** under modified Sharpless conditions using potassium osmate (VI) dehydrate (K_2OsO_4), potassium ferricyanide ($K_3Fe(CN)_6$) and the $(DHQ)_2AQN$ ligand produced the vicinal diol which was then reacted with benzoyl chloride, *N*-methylmorpholine, and DMAP to give di-benzoate **43** in excellent yield as a 3:1 mixture of diastereomeric alcohols. Allyl trimethylsilane was added to the acetal of **43** using $TiCl_3(OiPr)$ as the Lewis acid to give **44** in 83% yield. Re-crystallization of **44** from isopropanol and *n*-heptane afforded **44** in >99.5% de in 71% yield. Oxidation of the secondary alcohol of **44** under the modified Swern conditions generated the corresponding ketone which was condensed with the lithium anion of methyl phenyl sulfone to give a mixture of *E* and *Z* vinyl sulfones **45**. Debenzylation of **45** using iodotrimethylsilane (TMSI) followed by chelation-controlled reduction of the vinyl sulfone through reaction with $NaBH(OAc)_3$, and then basic hydrolysis of the benzoate esters using K_2CO_3 in MeOH resulted in triol **46** as a white crystalline solid in 57% yield over the five steps after re-crystallization. The vicinal diol of **46** was protected as the corresponding acetonide through reaction with 2,2-dimethoxypropane and sulfuric acid and this was followed by methyl iodide-mediated methylation of the remaining hydroxyl group to give methyl ether **47**. The protecting groups within acetonide **47** were then converted to the corresponding bis-*tert*-butyldimethylsilyl ether by first acidic removal of the acetonide with aqueous HCl and reaction with TBSCl in the presence of imidazole to give bis-TBS ether **48**. Then, ozonolysis of the olefin of **48** followed by hydrogenolysis in the presence of Lindlar catalyst afforded the key aldehyde intermediate **24** in 68% yield over the previous five steps after re-crystallization from heptane.

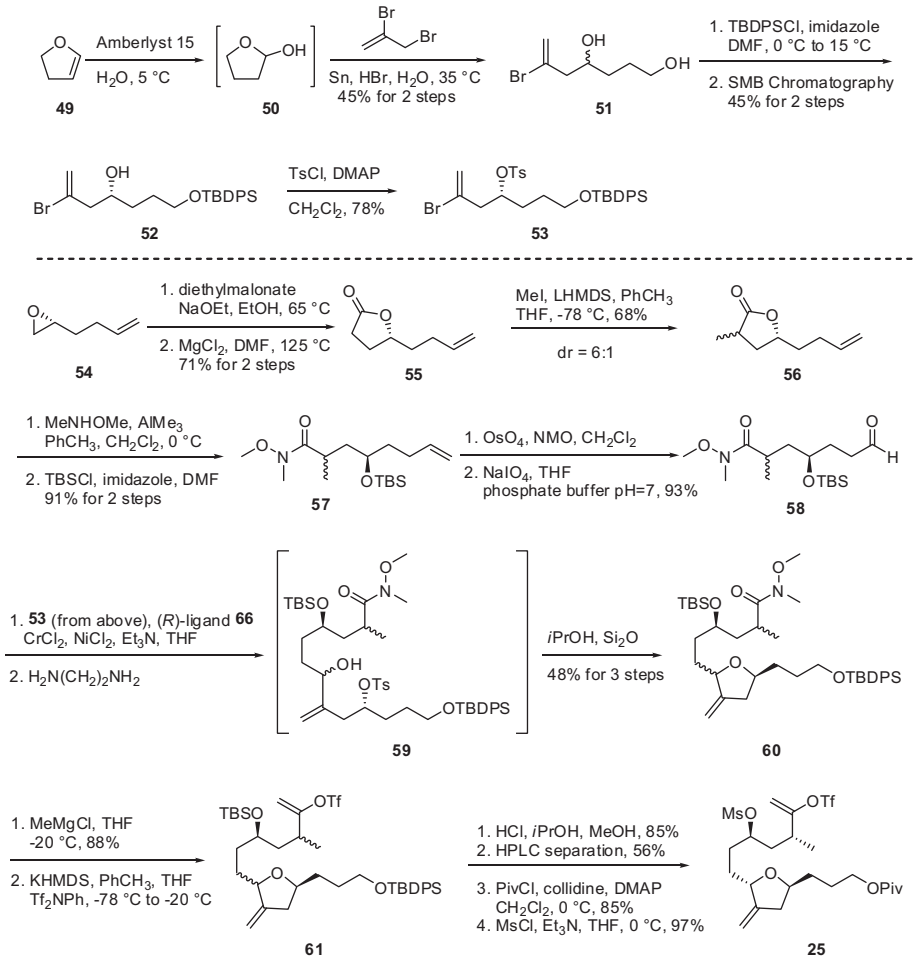
Two routes to the C14–C26 fragment **25** will be described as both are potentially used to prepare clinical supplies of eribulin. The first route features a convergent and relatively efficient synthesis of **25**, however it is limited by the need to separate enantiomers and mixture of diastereomers via chromatographic methods throughout the synthesis.[37] The second route to **25** is a much lengthier synthesis from a step-counting perspective; however it takes full advantage of the chiral pool of starting materials and requires no chromatographic separations and all of the products were carried on as crude oils until they could be isolated as crystalline solids.[38]

The first route to fragment **25** is described in Scheme 8 and was initiated by the hydration of 2,3-dihydrofuran (**49**) using an aqueous suspension of Amberlyst 15 to generate the intermediate tetrahydro-2-furanol (**50**) which was then immediately reacted with 2,3-dibromopropene in the presence of tin and catalytic HBr to

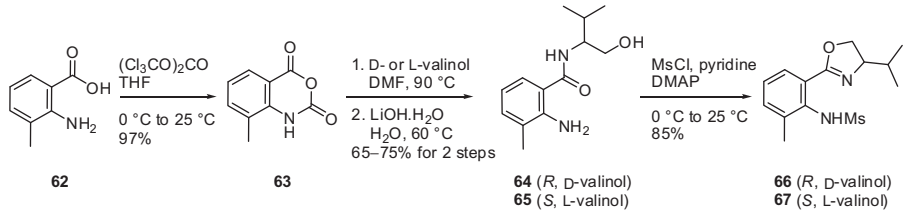


Scheme 7. Synthesis of fragment **24** of eribulin mesylate (**V**).

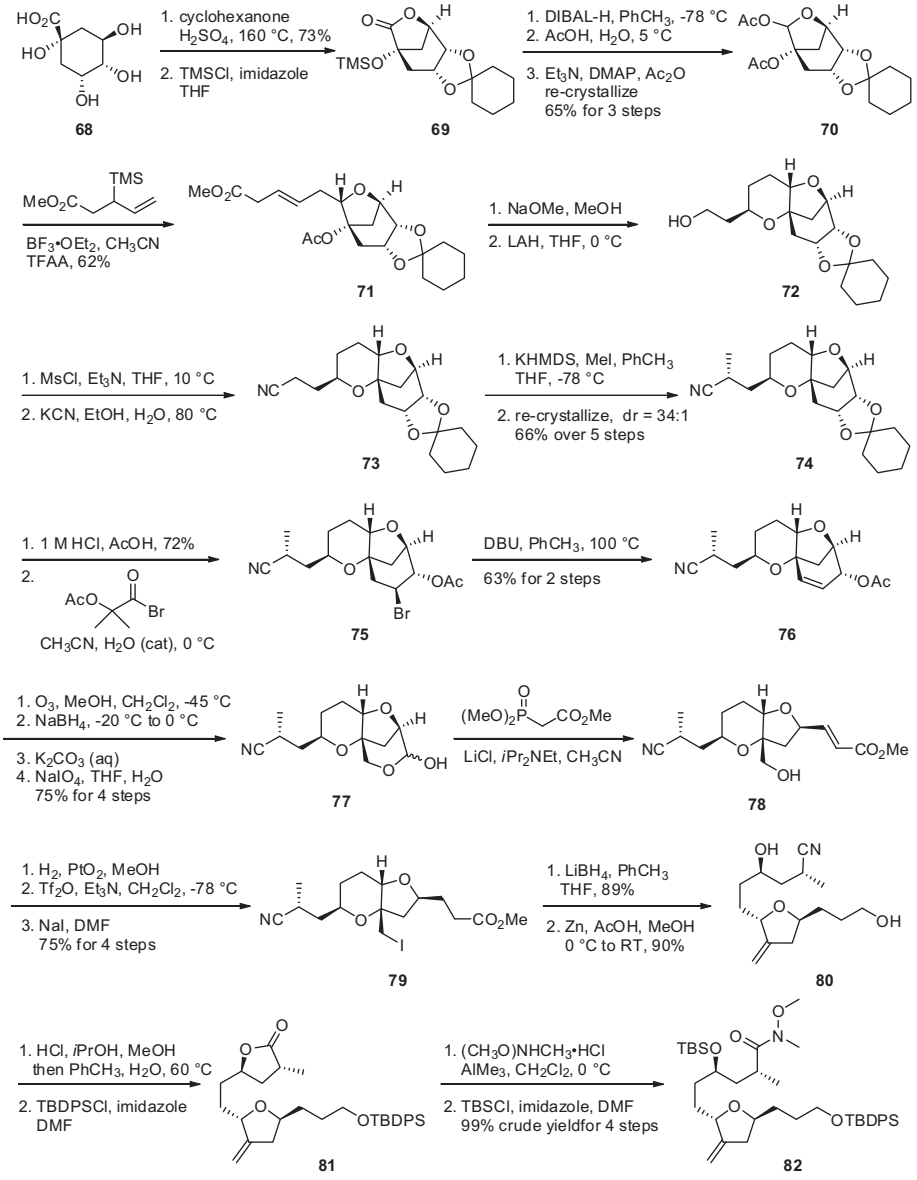
afford diol **51** in 45% for the two steps. The primary alcohol of **51** was selectively protected as its *tert*-butyldiphenylsilyl ether using TBDPSCl and imidazole and the racemate was then separated using simulated moving bed (SMB) chromatography to give enantiopure **52** in 45% yield over the two steps. The secondary alcohol of **52** was reacted with *p*-toluenesulfonyl chloride and DMAP to give tosylate **53** in 78% yield which was used as a coupling partner later in the synthesis of this fragment. The synthesis of the appropriate coupling partner was initiated by condensing diethylmalonate with (*R*)-2-(3-butenyl)oxirane (**54**), followed by decarboxylation to give lactone **55** in 71% yield for the two step process. Methylation of the lactone with LHMDS and MeI provided **56** in 68% yield as a 6:1 mixture of diastereomers. The lactone **56** was reacted with the aluminum amide generated by the reaction of $AlMe_3$ and *N*,*O*-dimethylhydroxylamine to give the corresponding Weinreb amide which was protected as its *tert*-butyldimethylsilyl ether upon reaction with TBSCl and imidazole to give **57** in 91% yield over the two steps. Dihydroxylation of the olefin of **57** by reaction with OsO_4 and NMO followed by oxidative cleavage with $NaIO_4$ gave the desired coupling partner aldehyde **58** in 93% yield. Aldehyde **58** was coupled with vinyl bromide **53** using an asymmetric Nozaki–Hiyami–Kishi reaction using $CrCl_2$, $NiCl_2$, Et_3N and chiral ligand **66** (described in Scheme 9 below). The reaction mixture was treated with ethylene diamine to remove the heavy metals and give the secondary alcohol **59**. This alcohol was stirred with silica gel in isopropanol to affect intramolecular cyclization to give the tetrahydrofuran **60** in 48% yield over the three step process. The Weinreb amide of **60** was reacted with methyl magnesium chloride to generate the corresponding methyl ketone which was converted to vinyl triflate **61** upon reaction with KHMDS and Tf_2NPh. De-silylation of the primary and secondary silyl ethers with methanolic HCl gave the corresponding diol in 85% yield over two steps and the resulting mixture of diastereomers was separated using preparative HPLC to provide the desired diastereomer in 56% yield. The primary



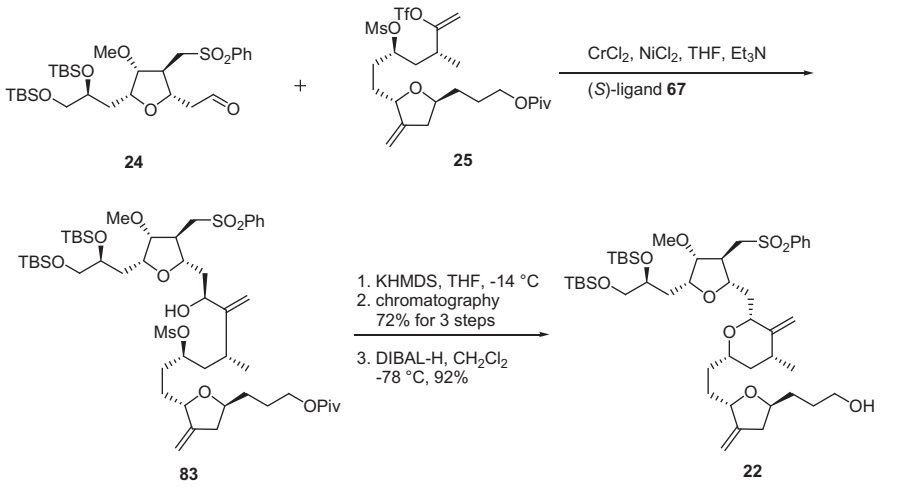
Scheme 8. First synthesis route of fragment **25** of eribulin mesylate (**V**).



Scheme 9. Synthesis of intermediates **66** and **67** of eribulin mesylate (**V**).



Scheme 10. Second synthesis route of fragment **25** of eribulin mesylate (**V**).

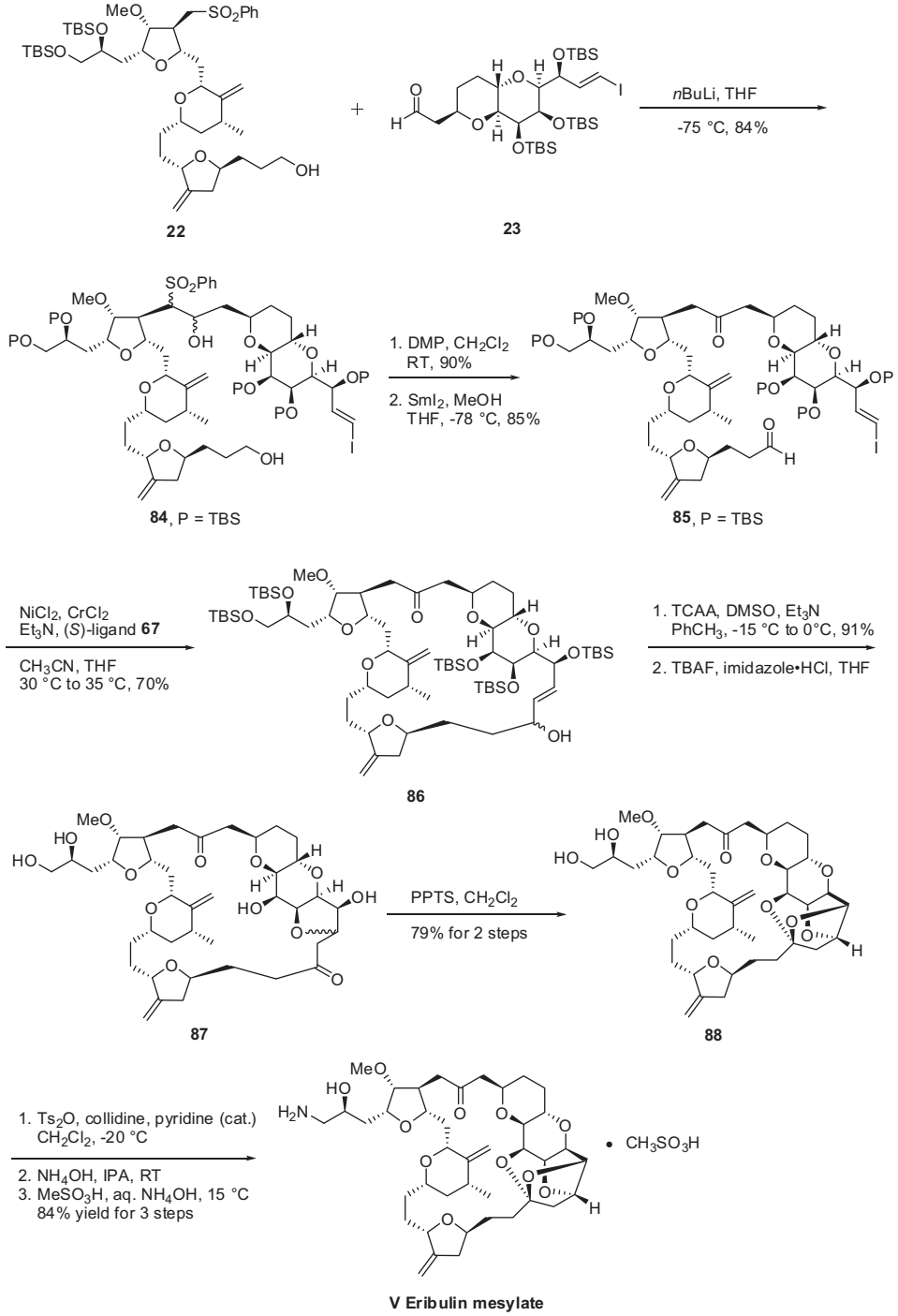


Scheme 11. Synthesis of fragment **22** of eribulin mesylate (**V**).

alcohol was protected as its pivalate ester with the use of pivaloyl chloride, DMAP and collidine; the secondary alcohol was converted to a mesylate upon treatment with methanesulfonyl chloride (MsCl) and Et_3N to give the C15–C27 fragment **25** in high yield.

The preparations of the chiral ligand **66** used in the coupling reaction in Scheme 8 along with the chiral ligand **67** utilized later in the synthesis are described in Scheme 9. 2-Amino-3-methylbenzoic acid (**62**) was reacted with triphosgene to give benzoxazine dione **63** in 97% yield, which then was reacted with either D- or L-valinol in DMF followed by aqueous LiOH to give alcohols **64** and **65**, respectively in 65–75% yield for the two steps. Reaction of alcohol **64** or **65** with MsCl in the presence of DMAP effected formation of the dihydrooxazole ring and mesylation of the aniline to give the corresponding (*R*)-ligand **66** derived from D-valinol or the (*S*)-ligand **67** derived from L-valinol, respectively in high yield.

An alternative route to intermediate **25** is described in Scheme 10 and although much lengthier than the route described in Scheme 8, it avoids chromatographic purifications as all of the products are carried on crude until a crystalline intermediate was isolated and purified by re-crystallization. Quinic acid (**68**) was reacted with cyclohexanone in sulfuric acid to generate a protected bicyclic lactone in 73% yield and the resulting tertiary alcohol was protected as its trimethylsilyl ether **69**. Reduction of the lactone **69** was accomplished with DIBAL-H and the resulting lactol



Scheme 12. Synthesis of eribulin mesylate (**V**).

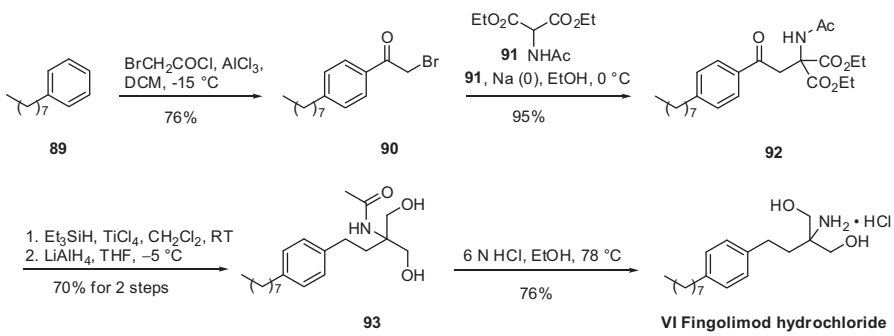
was treated with acetic acid to remove the TMS group and the resulting compound was reacted with acetic anhydride, DMAP and Et_3N to give bis-acetate **70** in 65% yield for the three steps after re-crystallization. Methyl 3-(trimethylsilyl)pent-4-enoate was coupled to the acetylated lactol **70** in the presence of boron trifluoride etherate and trifluoroacetic anhydride to give adduct **71** in 62% yield. The acetate of **71** was removed upon reaction with sodium methoxide in methanol and the resulting tertiary alcohol cyclized on to the isomerized enone alkene to give the fused pyran ring. Reduction of the methyl ester with lithium aluminum hydride provided pyranyl alcohol **72**. Mesylation of the primary alcohol was followed by displacement with cyanide anion to give nitrile **73**. The nitrile was methylated upon reaction with KHMDS and MeI and the resulting product was purified by re-crystallization to provide nitrile **74** in 66% over the previous five steps in a 34:1 diastereomeric ratio. Acid hydrolysis of the ketal of **74** liberated the corresponding diol in 72% yield and this was reacted with 2-acetoxy-2-methylpropionyl bromide to give bromo acetate **75**. Elimination of the bromide was accomplished upon treatment with 1,8-diazabicycloundec-7-ene (DBU) to give alkene **76** in 63% yield for two steps. Ozonolysis of the cyclohexene ring followed by reductive work-up with $NaBH_4$ and basic hydrolysis of the acetate produced a triol which upon reaction with $NaIO_4$ underwent oxidative cleavage to give cyclic hemiacetal **77** in 75% yield over the previous four steps. Wittig condensation with carbomethoxymethylene triphenylphosphorane gave the homologated unsaturated ester **78**. Catalytic hydrogenation of the alkene using PtO_2 as the catalyst was followed by converting the primary alcohol to the corresponding triflate prior to displacement with sodium iodide resulted in iodide **79** in 75% yield over four steps. The ester of **79** was reduced to the corresponding primary alcohol upon reaction with $LiBH_4$ in 89% yield and the resulting iodoalcohol was treated with Zn dust to affect reductive elimination of the iodide and decomposition of the pyran ring system to give the tetrahydrofuran diol **80** in 90% yield. This diol was treated with methanolic HCl to affect an intramolecular Pinner reaction and this was followed by protection of the primary alcohol as its *tert*-butyldiphenylsilyl ether to give lactone **81**. The lactone was reacted with the aluminum amide generated from $AlMe_3$ and *N,O*-dimethylhydroxylamine and the resulting secondary alcohol was protected as its *tert*-butyldimethylsilyl ether to give Weinreb amide **82** in 99% crude yield over four steps. Compound **82** is the diastereomerically pure version of compound **60** and can be converted to compound **25** by the methods described in Scheme 8 absent the required HPLC separation of diastereomers.

With the three key fragments completed, the next step was to assemble them and complete the synthesis of eribulin. Aldehyde **24** was coupled to vinyl triflate **25** using an asymmetric Nozaki–Hiyami–Kishi reaction using $CrCl_2$, $NiCl_2$, Et_3N and chiral ligand **67** (Scheme 9) to give alcohol **83** (Scheme 11). Formation of the THP ring was accomplished by reaction with KHMDS which allowed for displacement of the mesylate with the secondary alcohol and provided the THP containing product in 72% yield for the three steps. The pivalate ester group was removed with DIBAL-H to give the western fragment **22** in 92% yield.

The completion of the synthesis of eribulin is illustrated in Scheme 12. The lithium anion of sulfone **22** generated upon reaction with *n*BuLi was coupled to aldehyde **23** to give diol **84** in 84% yield. Both of the alcohol functional groups of **84** were oxidized using a Dess–Martin oxidation in 90% yield and the resulting sulfone was removed via a reductive cleavage upon reaction with SmI_2 to give keto-aldehyde **85** in 85% yield. Macrocyclization of **85** was accomplished via an asymmetric Nozaki–Hiyami–Kishi reaction using $CrCl_2$, $NiCl_2$, Et_3N and chiral ligand **67** to give alcohol **86** in 70% yield. Modified Swern oxidation of the alcohol provided the corresponding ketone in 91% yield and this was followed by removal of the five silyl ether protecting groups upon reaction with TBAF and subsequent cyclization to provide ketone **87**. Compound **87** was treated with PPTS to provide the 'caged' cyclic ketal **88** in 79% over two steps. The vicinal diol of **88** was reacted with Ts_2O in collidine to affect selective tosylation of the primary alcohol and this crude product was reacted with ammonium hydroxide to install the primary amine to give eribulin which was treated with methanesulfonic acid in aqueous ammonium hydroxide to give eribulin mesylate (**V**) in 84% yield over the final three steps.

7. Fingolimod hydrochloride (*Gilenya*®)

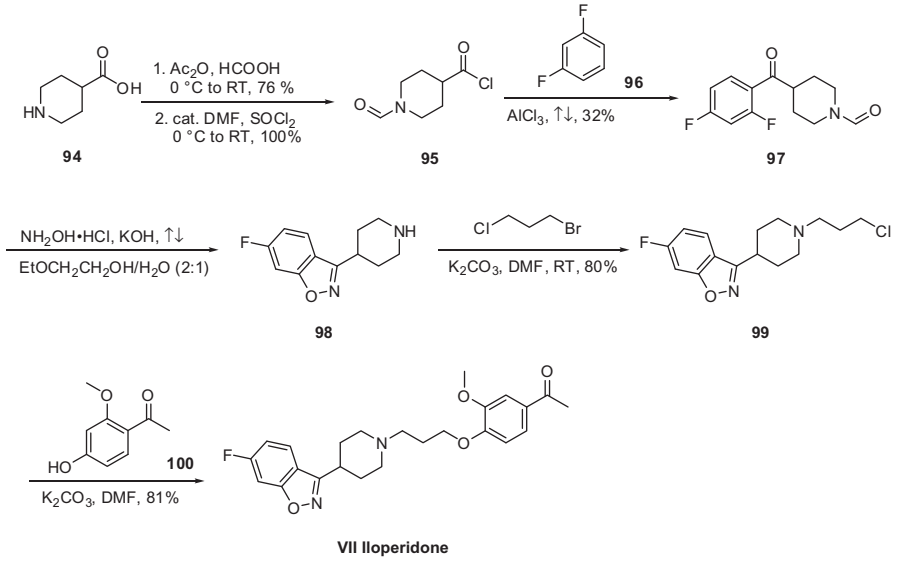
Fingolimod hydrochloride is an immunosuppressive drug developed by Novartis and approved in the US, Europe, and Australia in 2010 for the treatment of multiple sclerosis.[39] The structure of fingolimod derives from the naturally-occurring myriocin (ISP-1) metabolite of the fungus *I. sinclairii* and the aminoalcohol functionality within the drug possesses structural similarity to the sphingosine family of natural products.[40–42] Although several convenient preparations of fingolimod (FTY720) have been reported in the literature,[43–62] the route most closely resembling the process-scale approach[63] is described in Scheme 13. Friedel–Crafts acylation of commercial toluene derivative **89** with bromoacetyl chloride followed by ethoxide-mediated N-acylated aminomalonate (**91**) attack onto the resulting α-bromoketone **90** gave rise to ketoamide **92** in good overall yield. Next, separate hydride reduction protocols were employed to furnish diol **93**. Presumably, triethylsilyl hydride reduced the ketone and both ethyl esters within **92** to the corresponding diacid, which then underwent lithium aluminum hydride treatment to arrive at diol **93**. Careful attention to stoichiometry was required to avoid over reduction of amide **93**, which was critical to achieve high-yielding (76%) salt formation of fingolimod HCl (**VI**) through the use of 6 N ethanolic hydrochloric acid.



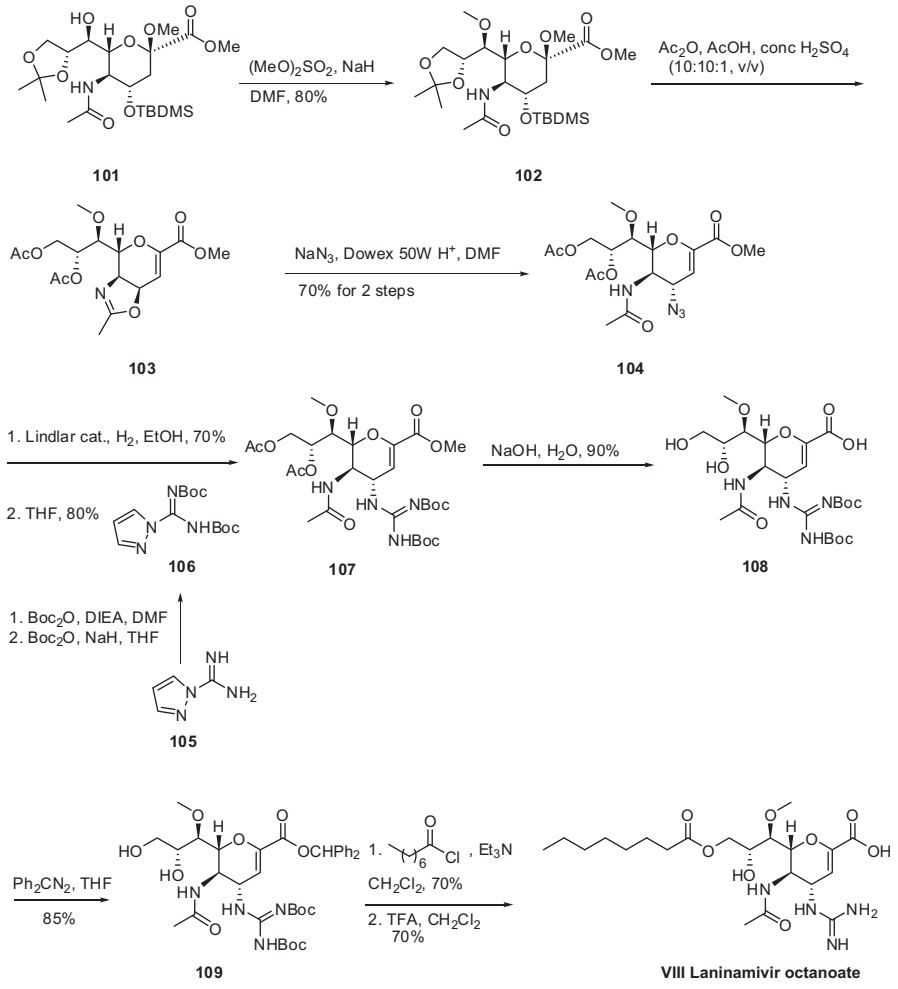
Scheme 13. Synthesis of fingolimod hydrochloride (**VI**).

8. Iloperidone (*Fanapt*®)

Acting as an antagonist on serotonin (5-HT_2) and dopamine receptor subtypes, iloperidone is an antipsychotic indicated for the treatment of acute schizophrenia in adults. Based on its in vitro and in vivo binding properties against both serotonin and dopamine receptors, it is expected that iloperidone will show fewer extrapyramidal symptoms than currently marketed



Scheme 14. Synthesis of iloperidone (**VII**).

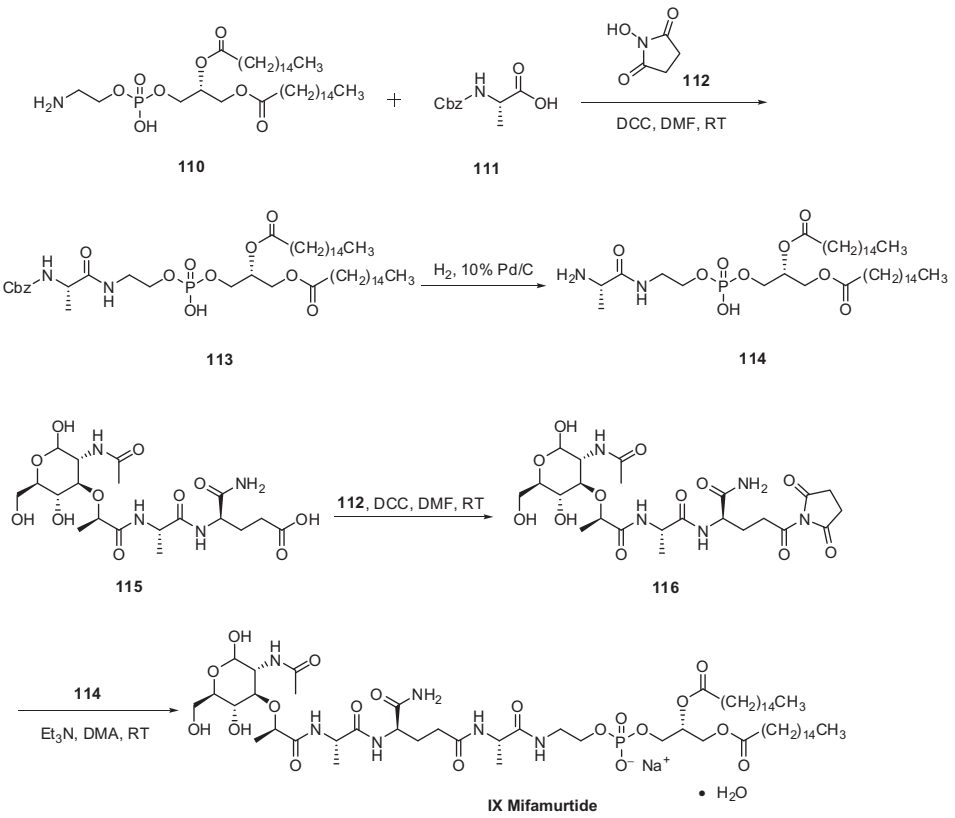


Scheme 15. Synthesis of laninamivir octanoate (**VIII**).

antipsychotics such as haloperidol and clozapine.[64] The original discovery was made by Hoechst-Roussel Pharmaceuticals who passed the developing rights to Vanda Pharmaceuticals and subsequently Novartis for marketing in the US and Canada.[10] While this drug was originally approved in the US in 2009, the marketing was only initiated in the US in 2010. Although a number of syntheses are reported in the literature, the process enabled route from a key intermediate **98** is described in Scheme 14.[65–72] The key intermediate **98** was synthesized from isonipecotic acid (**94**) in four steps.[65] Formylation of isonipecotic acid (76% yield) followed by conversion of the acid to the acyl chloride gave **95** in 100% yield. Friedel–Crafts acylation of 1,3-difluorobenzene (**96**) with the acid chloride **95** provided ketone **97** in 32% yield.[65,68] Treatment of ketone **97** with hydroxylamine hydrochloride in the presence of potassium hydroxide gave the corresponding oxime, which upon refluxing in 2-ethoxylethanol and water cyclized to piperidine benzisoxazole **98** with concomitant loss of the *N*-formyl group. Alkylation of piperidine **98** with 1-chloro-3-bromo propane in DMF in the presence of potassium carbonate provided the chloride intermediate **99** in 80% yield. Subsequent reaction with phenol **100** under basic conditions gave the desired product iloperidone (**VII**) in 81% yield.[71]

9. Laninamivir octanoate (*Inavir*®)

Laninamivir octanote, a prodrug of a potent neuraminidase inhibitor (LANI), was approved and launched in 2010 in Japan for the treatment of influenza A and influenza B. This ester prodrug of a potent neuraminidase inhibitor was designed to permeate from the lung tissue to the plasma and then hydrolyze at such a rate to reveal the active form (laninamivir) as a long-acting therapeutic agent. Neuraminidase cleaves the glycosidic linkages of neuraminic acids which are responsible for binding new viruses to infected cells, thereby allowing viruses to release and infect other cells. Neuraminidase is essential for the replication of all influenza viruses. Like other neuraminidase inhibitors, laninamivir octanoate is a sialic acid analogue which is structurally similar to zanamivir, differing only by changing one of the hydroxy groups with a methyl ether substitution on the triol side chain. Laninamivir is administered via an inhalable formulation (20 mg, dry powder inhaler) and results from clinical trials of the drug have demonstrated that a single inhaled dose is as effective as a 5-day course of oseltamivir for treatment of influenza.[73] The synthesis of laninamivir octanoate began with the well-documented sugar intermediate **101** (Scheme 15).[74,75] Alcohol **101** was alkylated with dimethyl sulfate in the presence of NaH in DMF to give methyl ether **102** in 80% yield.[76] Acetonide **102** was then de-protected and subsequently acylated with Ac_2O, AcOH, and H_2SO_4 (10:10:1, v/v) which resulted in oxazoline formation along with elimination of the methoxy functionality to furnish α,β-unsaturated ester **103**. Exposure of oxazoline **103** to NaN_3 in the presence of Dowex 50W/H^+ produced the *trans*-amidoazide **104** in 70% yield over two steps. Azide **104** was then subjected to guanidine formation conditions utilizing *N*,*N*-bis(tertbutoxycarbonyl)-1*H*-pyrazole-1-carboxyamidine (**106**), which was prepared from pyrazole-1-carboxamidine (**105**) by consecutive protection of the amidine nitrogens, first by treatment with Boc anhydride and diisopropylethyl amine (DIEA) in DMF, and then subsequent treatment to Boc anhydride in the presence of NaH in THF to give **107** in 80% yield. The protected guanidine **107** was hydrolyzed under basic conditions to give the corresponding acid **108** in good yield. Acid **108** was esterified with diphenyl diazomethane in THF to provide **109** in 85% yield.[77] Finally, the primary alcohol within diol **109** was selectively acylated with octanoyl chloride in the presence of TEA, followed by de-protection with TFA in CH_2Cl_2 to give laninamivir octanote (**VIII**) in 70% yield.



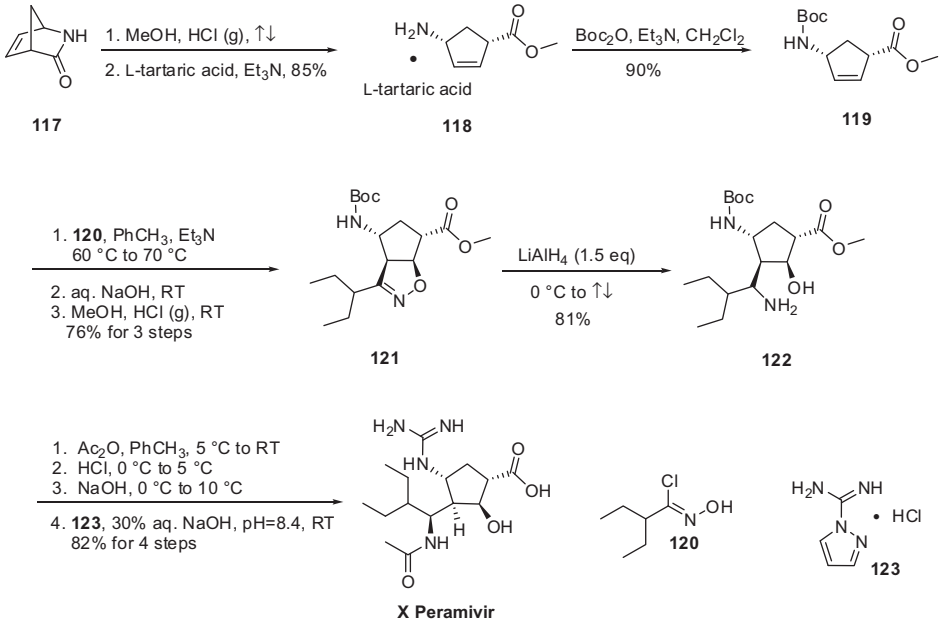
Scheme 16. Synthesis of mifamurtide (**IX**).

10. Mifamurtide (*Mepact*®)

Mifamurtide is an anticancer agent for the treatment of osteosarcoma, the most common primary malignancy of bone tissue mainly affecting children and adolescents.[10] The drug was invented by Ciba-Geigy (now Novartis) in the early 1980s and the agent was subsequently licensed to Jenner Biotherapies in the 1990s. IDM Pharma bought the rights to the drug from Jenner in April 2003.[78] In March 2009, mifamurtide was approved in the 27 European Union member states plus Iceland, Liechtenstein and Norway via a centralized marketing authorization. After the approval, IDM Pharma was acquired by Takeda, which began launching mifamurtide, as Mepact®, in February 2010. Mifamurtide, a fully synthetic lipophilic derivative of muramyl dipeptide (MDP), is muramyl tripeptide phosphatidylethanolamine (MTP-PE), which is formulated as a liposomal infusion.[79] Being a phospholipid, mifamurtide accumulates in the lipid bilayer of the liposomes upon infusion. After application of the liposomal infusion, the drug is cleared from the plasma within minutes. However, it is concentrated in lung, liver, spleen, nasopharynx and thyroid, and the terminal half-life is 18 h, which is longer than the natural substance. Two synthetic routes have been reported,[80,81] and Scheme 16 describes the more process-amenable route. Commercially available 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (**110**) was coupled with *N*-Boc-L-alanine (**111**) by means of *N*-hydroxysuccinimide (**112**), DCC in DMF to give amide **113**, which was followed by hydrogenolysis of the CBZ group to give the corresponding L-alanyl-phosphoric acid **114**. Next, commercially available *N*-acetylmuramoyl-L-alanyl-D-isoglutamine (**115**) was subjected to hydroxybenzotriazole (HOBT) and DIC in DMF to provide the corresponding succinimide ester **116** which was condensed with compound **114** to provide mifamurtide (**IX**). No yields were provided for these transformations.

11. Peramivir (*Rapiacta*®)

The second drug added to the influenza treatment armamentarium last year was peramivir, a novel neuraminidase inhibitor acting as a transition-state analogue inhibitor of influenza neuraminidase and thereby preventing new viruses from emerging from infected cells. It was first discovered and developed by BioCryst Pharmaceuticals, and Johnson and Johnson licensed the global marketing and development rights in 1998. However, in early 2001, its development was discontinued due to low bioavailability of the oral formulation and failure in clinical trials, and all the rights were returned to BioCryst. The low bioavailability of oral formulation resulted in BioCryst developing an intramuscular and intravenous formulation of peramivir. Fortunately, as part of the US government's effort to prepare against the threat of the influenza pandemic, peramivir received strong support, including "Fast Track" designation from the FDA and a grant of $180 million from NIH, which accelerated the development of peramivir. Moreover, BioCryst entered into two agreements with Green Cross Pharmaceuticals and with Shionogi Pharmaceuticals in 2006–2007, for the development and marketing peramivir in South Korea and Japan, respectively. In October 2009, the FDA approved the use of intravenous peramivir for the treatment of 2009 H1N1 hospitalized patients under the Emergency Use Act (EUA) which expired on June 23th, 2010. Finally, the intravenous form of peramivir received approval in Japan in early of 2010 and launched for the first time with the commercial name Rapiacta®. Several syntheses of this drug have been reported[82–84] and the improved route disclosed in a recent patent is described (Scheme 17).[85] Ring opening of commercially available (±)-2-azabicyclo[2.2.1]hept-5-en-3-one (**117**) with methanolic HCl followed by classical resolution with L-tartaric acid gave the (1*S*,4*R*)-methyl ester **118** in 85% yield. Protection of **118** with Boc anhydride and TEA in CH_2Cl_2 afforded carbamate **119** in 90% yield. Alkene **119** was then subject to nitrone dipolar cycloaddition conditions involving 2-ethyl-*N*-hydroxybutanimidoyl chloride **120** and triethylamine, followed by the basic workup and then treatment with methanolic HCl, ultimately resulting in dihydroisoxazole **121**. Interestingly, the nitrone generated from **120** approached alkene **119** from the less hindered face and proceeded with remarkable regioselectivity to provide azacycle **121** in 76% yield for the three step sequence. Treatment of **121** with 1.5 equiv lithium aluminum hydride resulted in rupture of the *N–O* bond within this system, which afforded the amino alcohol **122** in 81% yield. It should be noted that neither the Boc group or the methyl ester were reduced under these reaction



Scheme 17. Synthesis of peramivir (**X**).

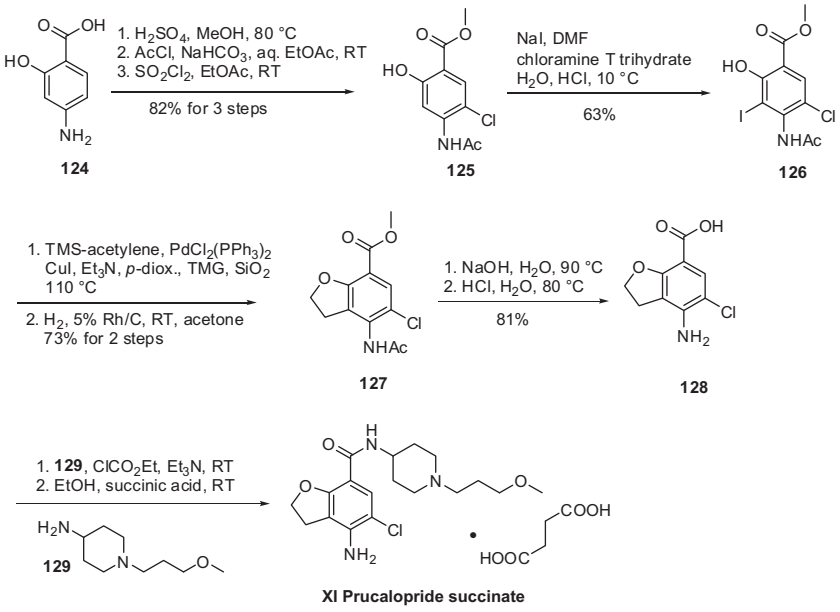
conditions. Then, a one-pot three step sequence involving acetylation of the amino group, removal of the Boc group, and hydrolysis of the carboxylic ester followed by guanylation with pyrazolecarboxamidine hydrochloride (**123**) provided peramivir (**X**) in 82% yield over the final four steps.

12. Prucalopride succinate (*Resolor*®)

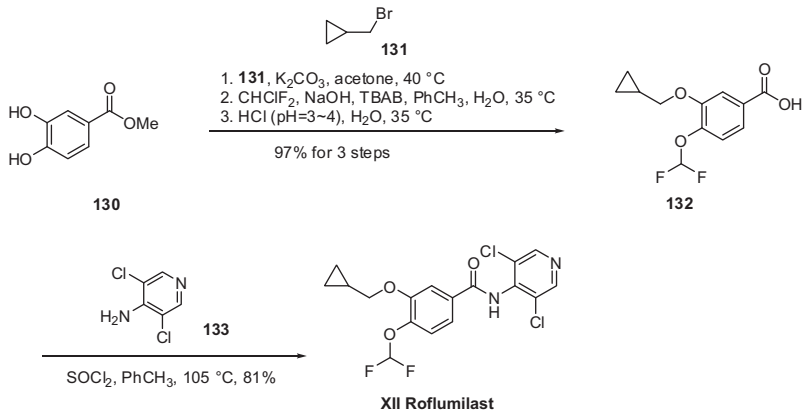
Prucalopride succinate, a first-in-class dihydrobenzofurancarboxamide, is a selective serotonin (5-HT_4) receptor agonist.[86–94] The drug, marketed under the brand name Resolor®, possesses enterokinetic activity and was developed by the Belgian-based pharmaceutical firm Movetis. Prucalopride alters colonic motility patterns via serotonin 5-HT_4 receptor stimulation, triggering the central propulsive force for defecation.[95–97] The preparation of prucalopride succinate begins with the commercially available salicylic aniline **124** (Scheme 18). Acidic esterification, acetylation of the aniline nitrogen atom, and ambient-temperature chlorination via sulfuryl chloride (SO_2Cl_2) converted aminophenol **124** to acetamidoester **125** in 83% yield over the course of three steps.[98–102] An unique set of conditions involving sodium tosylchloramide (chloramine T) trihydrate and sodium iodide were then employed to convert **125** to *o*-phenolic iodide **126**, which then underwent sequential Sonogashira/cyclization reaction utilizing TMS-acetylene with tetramethylguanidine (TMG) in the presence of silica gel to furnish the benzofuran progenitor of **127**.[103] Hydrogenation of this intermediate benzofuranyl Sonagashira product saturated the 2,3-benzofuranyl bond while leaving the chlorine atom intact, ultimately delivering dihydrobenzofuran **127** in excellent yield for the two step sequence. Base-induced saponification and acetamide removal gave rise to acid **128**. This acid was activated as the corresponding mixed anhydride and treated with commercial piperidine **129** to construct prucalopride which was stirred at room temperature for 24 h in ethanolic succinic acid to provide prucalopride succinate (**XI**). The yield for the formation of the salt was not provided.

13. Roflumilast (*Daxas*®)

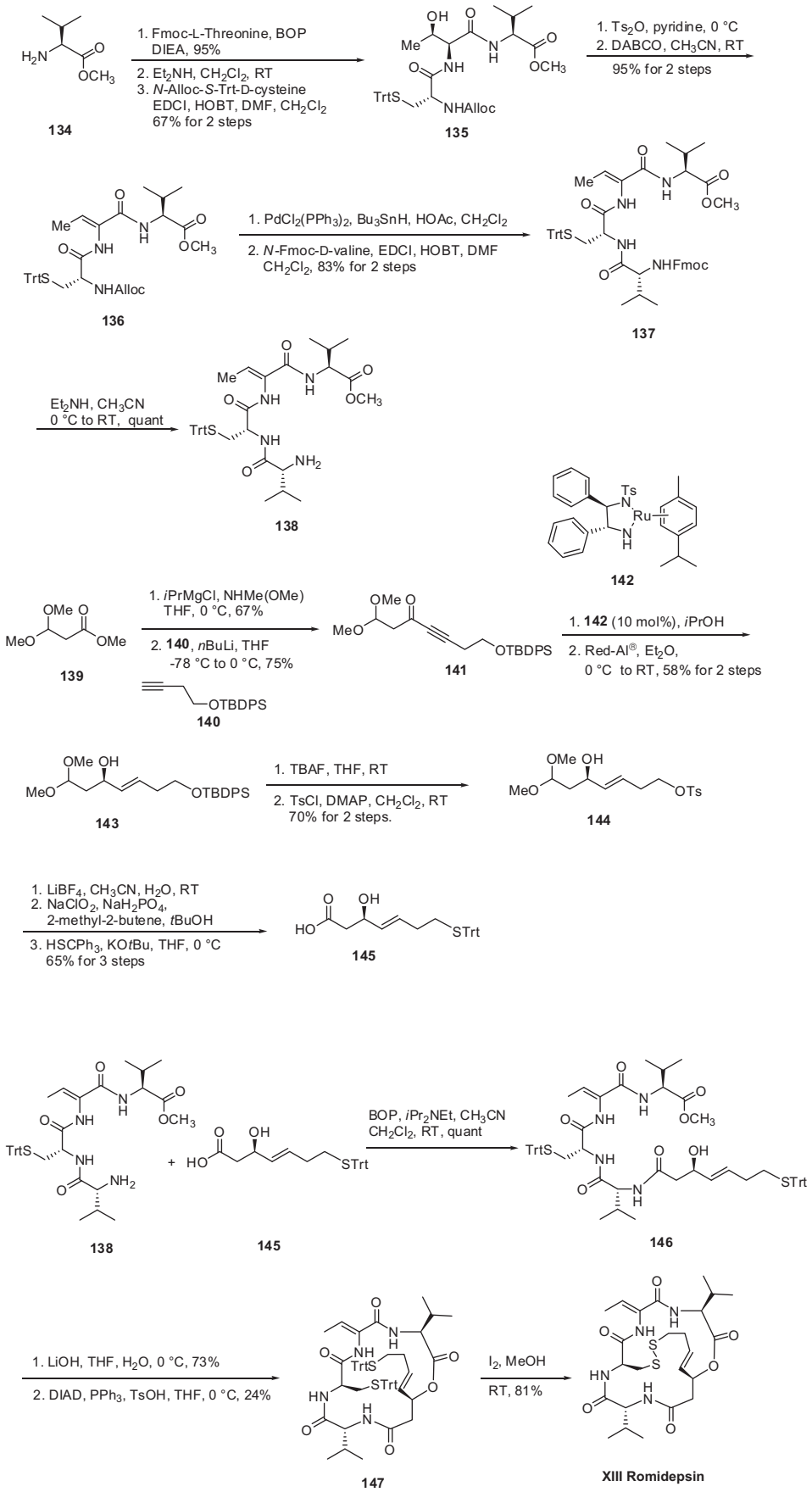
Roflumilast is a selective, long-acting PDE-4 inhibitor approved in 2010 for the treatment of inflammatory conditions of the lungs such as asthma and chronic obstructive pulmonary disorder.[104–108] Marketed under the trade name Daxas®, roflumilast was developed by researchers at the University of Liverpool in partnership with



Scheme 18. Synthesis of prucalopride succinate (**XI**).



Scheme 19. Synthesis of roflumilast (**XII**).

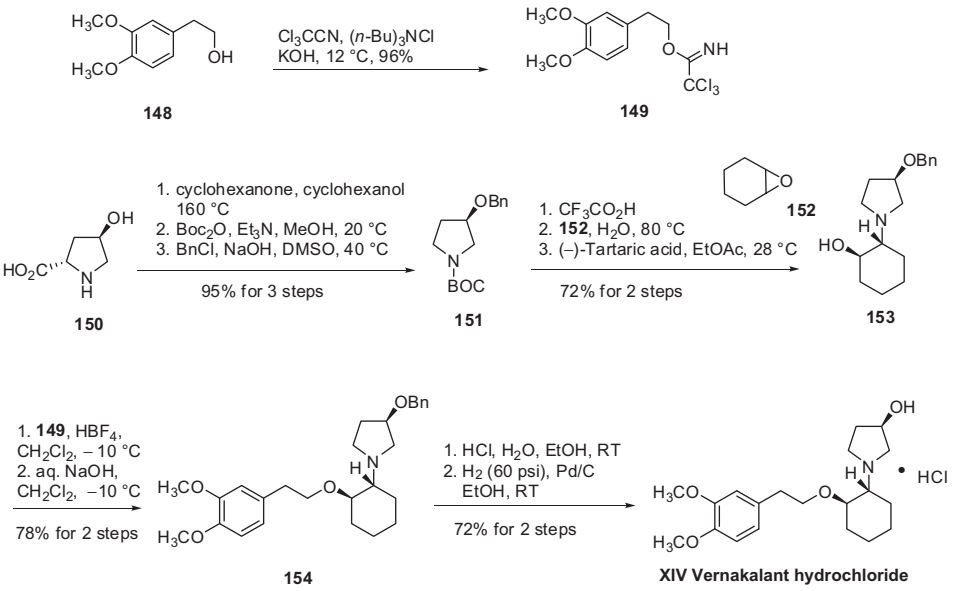


Scheme 20. Synthesis of romidepsin (**XIII**).

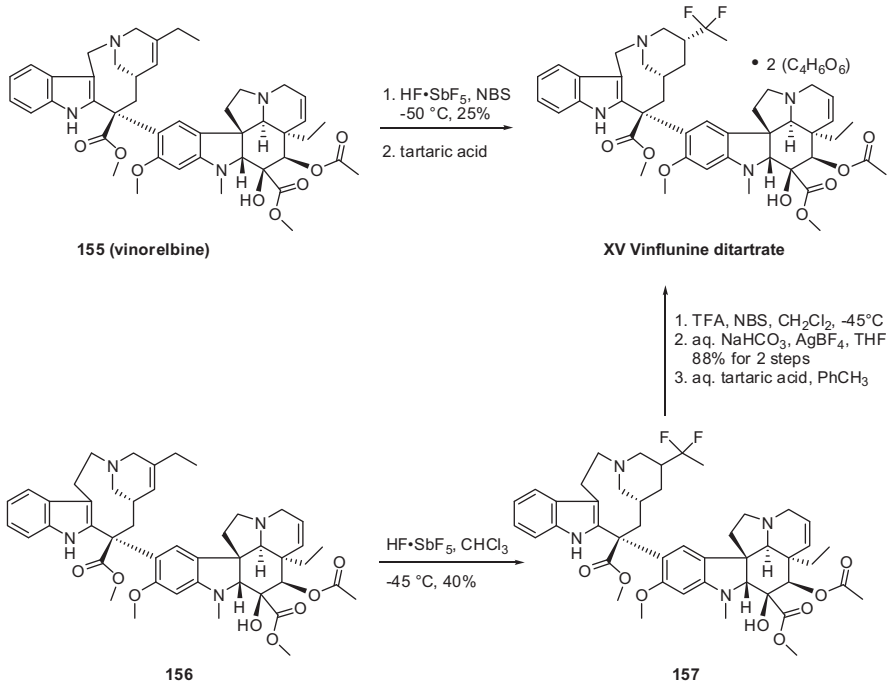
Nycomed. Although the dose-limiting side effects of the drug are mild nausea, diarrhea, and weight loss, these symptoms subsided after a few weeks of treatment.[106] The straightforward preparation of roflumilast begins with commercially available methyl 3,4-dihydroxybenzoate (**130**) (Scheme 19).[109,110] Alkylation of the more reactive 3-hydroxyl group with (bromomethyl)cyclopropane (**131**) preceded a second alkylation of the remaining *p*-phenol with chlorodifluoromethane in aqueous sodium hydroxide. These phase-transfer conditions saponified the ester within **130** and after acidic quench, carboxylic acid **132** was ultimately furnished in excellent yield (97%) over the three step protocol. Activation of **132** as the corresponding acyl halide through use of thionyl chloride ($SOCl_2$) and subsequent exposure to commercial aminopyridine **133** provided roflumilast (**XII**) in 81% yield.

14. Romidepsin (*Istodax*®)

Romidepsin, a histone deacetylase inhibitor, originally developed by Fujisawa (now Astellas Pharma), causes cell cycle arrest, differentiation, and apoptosis in various cancer cells.[111] In 2004, the FDA granted fast-track designation for romidepsin as monotherapy for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have relapsed following, or become refractory to, other systemic therapies. The FDA designated romidepsin as an orphan drug and it was approved in 2009 for this indication and it was commercialized in 2010. In 2007, another fast-track designation was granted for the product as monotherapy of previously treated peripheral T-cell lymphoma. Romidepsin (FR901228) was originally discovered and isolated from the fermentation broth of Chromobacterium violaceum No. 968. It was identified through efforts in the search for novel agents which selectively reverse the morphological phenotype of Ras oncogene-transformed cells since the Ras signaling pathway plays a critical role in cancer development. Therefore, the drug could also have multiple molecular targets for its anticancer activity besides HDAC.[112] FR901228 is a bicyclic depsipeptide which is structurally unrelated to any known class of cyclic peptides with an unusual disulfide bond connecting a thiol and D-cysteine. This drug is commercially produced by fermentation; however its interesting and novel structure warrants examination of its synthesis within the context of this review.[113,114] The synthesis of romidepsin described is based on the total synthesis reported by the Williams[115] and Simon groups (Scheme 20).[116] L-Valine methyl ester (**134**) was coupled to *N*-Fmoc-L-threonine in the presence of the BOP reagent in 95% yield. The *N*-Fmoc protecting group was removed with Et_2NH and the corresponding free amine was coupled to *N*-alloc-(*S*-triphenylmethyl)-D-cysteine with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and HOBT in DMF and CH_2Cl_2 to yield the tripeptide **135** in good yield. The threonine residue of tripeptide **135** was then subjected to dehydrating conditions to give alkene **136** in 95% yield. The *N*-alloc protecting group of the dehydrated tripeptide **136** was removed with palladium and tin reagents and the corresponding free amine was subsequently coupled with *N*-Fmoc-D-valine to give tetrapeptide **137** in 83% yield. After removal of the *N*-Fmoc protecting group of compound **137** with Et_2NH amine **138** was obtained in quantitative yield. The acid coupling partner **145** for amine **138** was prepared as follows: methyl 3,3-dimethoxypropionate (**139**) was converted to its corresponding Weinreb amide by standard conditions and reacted with lithium acetylide **140** to give propargylic ketone **141** in 75% yield. Noyori's asymmetric reduction of ketone **141** using ruthenium catalyst **142** gave the (*R*)-propargylic alcohol in 98% ee. This was followed by Red-Al reduction of the alkyne to selectively yield (*E*)-alkene **143** in 58% yield for the two steps. Liberation of the primary alcohol with tetrabutylammonium fluoride (TBAF) followed by selective tosylation gave **144** in 70% yield in two steps. Hydrolysis of the dimethyl acetal of **144** with $LiBF_4$ was followed by a Pinnick oxidation to give the corresponding carboxylic acid. The tosylate was displaced with trityl mercaptan in the presence of *tert*-butyl alcohol to give allylic alcohol **145** in 65% yield for the three steps. Aminoamide **138** was then coupled to acid **145** using BOP to give peptide **146** in quantitative yield. The methyl ester of compound **146** was hydrolyzed with lithium hydroxide to provide the free carboxylic acid which underwent macrolactonization under Mitsunobu conditions in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosine to give macrocycle **147** in 24% yield. Finally, the disulfide linkage was formed by treating *bis*-tritylsulfane **147** with iodine in methanol at room temperature to give romidepsin (**XIII**) in 81% yield.



Scheme 21. Synthesis of vernakalant hydrochloride (**XIV**).



Scheme 22. Synthesis of vinflunine ditartrate (**XV**).

15. Vernakalant hydrochloride (*Brinavess*® or *Kynapid*®)

Vernakalant is an investigational drug under regulatory review for the acute conversion of atrial fibrillation. The drug was initially developed by Cardiome Pharma under the trade names Kynapid® and Brinavess® and its intravenous formulation was further developed by Merck in April 2009.[117,118] Like other class III antiarrhythmics, vernakalant blocks atrial potassium channels, thereby prolonging repolarization.[119–121] It differs from typical class III agents by blocking the cardiac transient outward potassium current, with increased potency as the heart rate increases. It also slightly blocks the hERG potassium channel, leading to a prolonged QT interval, which may theoretically increase the risk of ventricular tachycardia.[122] The preparation of vernakalant entails the union of a prolinol derivative **150** with a 3,4-dimethoxyphenethyl alcohol (**148**) across a cyclohexanyl lynchpin **152** and is described in Scheme 21.[123–125] Decarboxylation of commercially available (*2S,4R*)-4-hydroxyprolinol (**150**) was effected using cyclohexanol and cyclohexanone at elevated temperatures. Subsequent protection of the nitrogen atom and the oxygen atom within this system resulted in carbamate **151**. Acid-mediated removal of the N-protective functionality preceded nucleophilic attack on epoxide **152** in hot water, and the ensuing mixture of diastereomers was separated by classical resolution via the tartrate salt. O-Benzylated vernakalant **154** was obtained when enantiomerically pure alcohol **153** was subjected to trichloroacetimidate **149** (which arose from the corresponding alcohol **148** under modified Williamson conditions[126]). Acidic hydrogenolysis, which the authors report as separate steps, furnished vernakalant hydrochloride (**XIV**) in excellent overall yield.

16. Vinflunine ditartrate (*Javlor*®)

Vinflunine ditartrate is a second generation difluorinated analog of the naturally-occurring substance vinorelbine and it is approved for the treatment of non-small cell lung cancer, metastatic breast cancer and ovarian cancer. Vinflunine, a tubulin polymerization inhibitor, belongs to the vinca alkaloid class of anti-cancer agents. Introduction of the difluoro group of vinflunine dramatically improved antitumor activity of the parent vinorelbine structure.[127] Vinflunine was discovered by Pierre Fabre Laboratories and in 2004 was licensed to Bristol-Myers Squibb for development and commercialization. In 2007, the rights to venflunine were returned to Pierre Fabre which completed its development. Vinflunine can be prepared directly from vinorelbine (**155**) through the use of superacid chemistry (Scheme 22). Reaction of **155** with antimony pentaflouride in hydrofluoric acid and *N*-bromosuccinimide followed by treatment with two equivalents of tartaric acid produced vinflunine ditartrate (**XV**) in 25% yield.[128] An alternative synthesis of vinflunine was realized through reaction of vinblastine or 3′,4′-dihydrovinblastine (**156**) with antimony pentaflouride and hydrofluoric acid in chloroform to give the difluoro alkaloid **157** in 40% yield.[128,129] Ring contraction was effected by reaction with trifluoroacetic acid and *N*-bromosuccinimide followed by aqueous sodium bicarbonate and silver tetrafluoroborate to give vinflunine in 88% yield. Vinflunine ditartrate (**XV**) was prepared by treating a solution of vinflunine in toluene with 2 equiv of tartaric acid.

Acknowledgment

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