Synthesis M. Barniol-Xicota et al. Review

Syntheses of Cinacalcet: An Enantiopure Active Pharmaceutical Ingredient (API)

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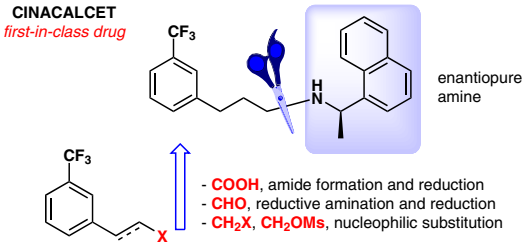

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Abstract Cinacalcet hydrochloride is the only approved drug acting as calcimimetic, a new class of compounds used in the therapy of secondary hyperparathyroidism and parathyroid carcinoma. Several generic drug manufacturers and research groups from academia have reported alternative approaches to this molecule, mainly from (*R*)-(+)-1-(1-naphthyl)ethylamine. There are mainly three strategies that have been used to couple this readily accessible enantiopure amine to the other part of the molecule: amide formation followed by reduction, reaction with an aldehyde and reduction of the resulting imine, and nucleophilic substitution with a suitable partner that carries a leaving group. More exotic approaches have also been disclosed. In the present review all of them are discussed.

Key words amides, amines, drugs, Mannich bases, reduction

1 Introduction

Cinacalcet (**1**), discovered by NPS Pharmaceuticals twenty years ago,[2] is the first drug in a new class of therapeutic agents (calcimimetics), which increase the sensitivity of calcium-sensing receptors (CaR) to the extracellular calcium ions, thus lowering the parathyroid hormone (PTH) production and release (Figure 1). This process results in a simultaneous decrease of serum calcium and phosphorus levels.[3] The drug was approved by the FDA and the EMA in 2004 for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on dialysis and hypercalcemia in patients with parathyroid carcinoma.[4] Currently it is marketed by Amgen as Sensipar® (USA, Australia) and Mimpara® (Europe), and by Kyowa Kirin as Regpara® (Asia). Tablets are formulated in strengths of 30, 60 and 90 mg of cinacalcet as the free base equivalent (33, 66 and 99 mg as the hydrochloride salt, respectively). Cinacalcet hydrochloride (**1**·HCl) is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and slightly soluble in water. It has one chiral center, having an *R*-absolute configuration. Its chemical name is *N*-[(*R*)-1-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine hydrochloride.

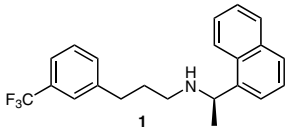

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Figure 1 Structure of cinacalcet (**1**)

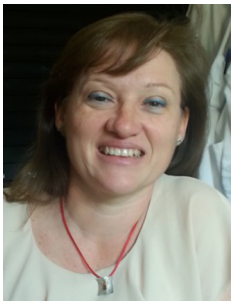
Given that cinacalcet a first-in-class drug, it is not a surprise that several academic groups and generic drug manufacturers have searched for alternative synthetic procedures. In fact, cinacalcet provides an excellent example of

how a blockbuster drug is severely scrutinized by generic manufacturers looking for the best synthetic route. So far, however, all but one synthesis of cinacalcet revolve around the use of (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**) as the source of chirality (see Scheme 24). This enantiopure amine is readily accessed through classical or enzymatic resolution of the racemic precursor,[5] and it is coupled to the other part of the molecule mainly by three strategies: formation of an amide followed by reduction, reaction with an aldehyde followed by reduction of the resulting imine, or, finally, nucleophilic substitution with a suitably substituted partner that carries a leaving group. More exotic approaches have also been disclosed. These synthetic strategies are discussed in detail below.

Biographical Sketches

Marta Barniol-Xicota studied pharmacy at Universitat de Barcelona (2006–2011), where she joined Dr. Vázquez's research group as an undergraduate student in 2009. In 2013 she obtained an MSc in 'industrial and experimental organic chemistry'. Currently she is in the last year of her PhD studies, under the supervision of Dr. Vázquez. She has also worked abroad at University College of London (UCL) in the group of Dr. Steve Hilton and at University of California San Francisco (UCSF) under the supervision of Prof. William F. DeGrado. Her scientific interests range from synthetic organic chemistry to chemical biology, specifically in the ion-channel field.

Rosana Leiva obtained a Degree in Pharmacy (Extraordinary Award) from the Universitat de Barcelona in 2013. She has always been interested in applied organic synthesis so she commenced doctoral studies in medicinal chemistry at the same university under the supervision of Dr S. Vázquez. She is currently placed in the University of Edinburgh doing a research stay in the laboratory of Prof. Scott P. Webster where she is learning pharmacological techniques to profile the compounds synthesized in Barcelona. After presenting her thesis, her plan is to carry out postdoctoral studies abroad.



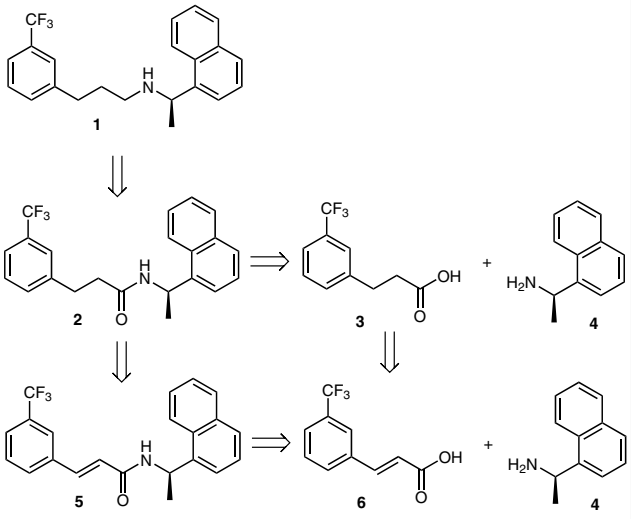
Carmen Escolano studied pharmacy at the Universitat de Barcelona, where she also obtained her PhD degree in 1998 under the guidance of Prof. J. Bonjoch and Dr. J. Quirante. After spending the summer of 1998 doing QSAR studies in the team of Prof. C. R. Ganellin (University College London), she joined the group of Prof. K. Jones at Kingston University (Surrey, United Kingdom) as Marie Curie Research Fellow (1999–2000) working on the synthesis of martinelline. In 2001 she returned to Universitat de Barcelona, joining the group of Prof. J. Bosch and Prof. M. Amat, as 'Investigador Ramón y Cajal'. In 2007 she took up her current permanent position as 'Professor Agregat'. Her present research interest is focused on the reactivity and therapeutic interest of aminophosphonates.

Santiago Vázquez studied Pharmacy (1986–1991) at the Universitat de Barcelona. He obtained his PhD in organic and medicinal chemistry at the same university in 1996 under the guidance of Professor P. Camps working on highly pyramidalized alkenes. After spending two years (1998–1999) in the Christopher Ingold Laboratories (University College London) with Professor William B. Motherwell as a Marie Curie Research Fellow working on novel radical reactions, he returned to Barcelona as 'Investigador Ramón y Cajal'. In 2005 he took up his current position as 'Professor Agregat' at Universitat de Barcelona. His scientific interests include polycyclic cage compounds of potential biological activity, drug synthesis and free-radical chemistry.

2 Synthetic Approaches Involving the Synthesis of an Amide Followed by Its Reduction

In addition to (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**), the key reagent for the synthesis of cinacalcet using an amide intermediate is the 3-(trifluoromethyl)cinnamic acid (**6**),[6] easily available from 3-trifluoromethylbenzaldehyde by Perkin condensation with acetic anhydride and sodium acetate,[7] or by Knoevenagel–Doebner condensation with malonate, acetic acid, and piperidine.[8] A Heck reaction of a 3-(trifluoromethyl)aryl halide with acrylic acid has also been used for the synthesis of **6**.[9]

From these two precursors, in order to accomplish cinacalcet synthesis, three transformations are required: catalytic hydrogenation of unsaturated acid **6** to acid **3**, amide formation, and, finally, amide reduction. Alternatively, acrylamide **5** can be synthesized from amine **4** and unsaturated acid **6**, followed by catalytic hydrogenation of the carbon–carbon double bond to amide **2** and amide reduction (Scheme 1). Amgen, Boehringer Ingelheim, Dr Reddy's, IndSwift, MacLeods, Sandoz and Evans and co-workers have all disclosed processes, which are assessed next, involving amides **2** or **5**. Alternative processes involving other amides, developed by Amgen, Optimus and Beller and co-workers, are considered separately.

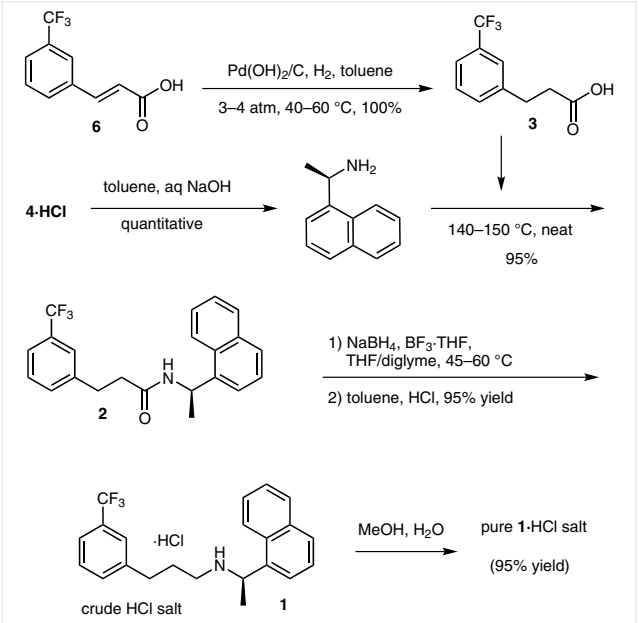


Scheme 1 Retrosynthetic analysis of cinacalcet from cinnamic acid derivative **6** and amine **4**

2.1 Approaches Involving Saturated Amide 2 from Acid 3

Process chemists from Amgen have reported a safe, practical, atom-economical and highly efficient approach to cinacalcet. The procedure involves only three synthetic steps with an overall yield of 85%.[10]

They first studied the catalytic hydrogenation of 3-(trifluoromethyl)cinnamic acid (**6**) in the presence of palladium hydroxide (20 wt% on carbon) under moderate hydrogen pressure (3–4 atm). A solvent survey concluded that rapid conversions (2 h at r.t.) were observed with primary alcohols (MeOH or EtOH), however alkyl ester by-products were formed. This side reaction was suppressed by using isopropanol as solvent, which decreased the reaction rate (>12 h for full conversion). Ultimately, toluene was chosen as an ideal solvent for this hydrogenation, as it allowed for an increase in the reaction temperature which compensated for the decrease in the reaction rate. The complete conversion was accomplished at 50 °C within 1–3 hours. After catalyst filtration the crude product was used directly in the next step (Scheme 2).



Scheme 2 Retrosynthetic analysis of cinacalcet from cinnamic acid derivative **6** and amine **4**

The coupling was successfully performed by heating an equimolar mixture of (*R*)-1-(1-naphthyl)ethylamine (**4**) and 3-[(3-trifluoromethyl)phenyl]propionic acid (**3**), in the absence of solvent, to 140–150 °C. The water formed was removed by continuous distillation. According to the authors, the key to this reaction is that the amide **2** remains liquid throughout the condensation. A clean reaction profile was observed despite the rather forcing conditions employed. After extractive removal of low residual starting materials by aqueous basic and acidic washes, the crude amide (95% solution yield, >99% HPLC purity) was used directly in the subsequent reaction. However, taking into account that the free amine is sensitive to oxidation, and that carbonate formation occurs when exposed to air,[10] amine **4** was used in its hydrochloride form. This alternative form of the starting material is a stable, crystalline, non-hygroscopic salt, and

can be conveniently converted, in quantitative yield, into the free base by treatment of a toluene solution with aqueous 20% sodium hydroxide. A solution of the amine is then mixed with a solution of the propionic acid. Removal of the toluene by distillation is followed by direct condensation to amide **2** (Scheme 2).

The reduction was investigated with lithium aluminum hydride or borane as reducing agents. Dr. Reddy's and academic researchers from the University College Dublin have independently reported yields of up to 80% using lithium aluminum hydride,[11,12] while Amgen's chemists found that cleaner reactions (<1% starting material, no impurity >0.5%) were usually observed with borane. Initially the borane was generated in situ from sodium borohydride in the presence of sulfuric acid, but this protocol led to the formation of impurities **7** and **8** in low quantities (Figure 2).

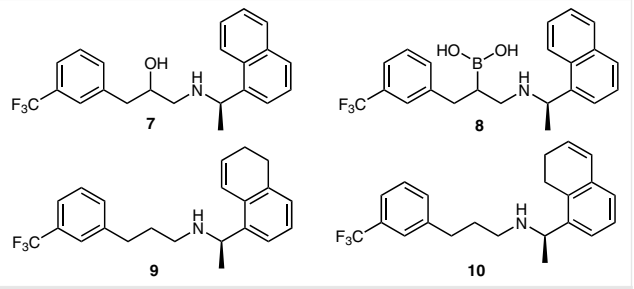
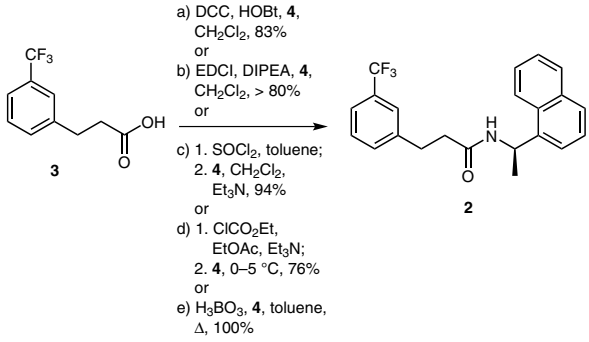


Figure 2 Impurities detected during Amgen's process

Fortuitously, these side products were not observed when boron trifluoride was used under anhydrous conditions. In the optimized process, the reaction was carried out by the addition of boron trifluoride–tetrahydrofuran to sodium borohydride in a mixture of diglyme and tetrahydrofuran at 45–60 °C. After hydrolysis of the amine–borane complex and subsequent treatment of the crude reaction mixture, the product was isolated as its hydrochloride salt. The latter was recrystallized from aqueous methanol to furnish material of a very high purity (>99.5%). Prior to the recrystallization, impurities **9** and **10** (Figure 2), arising from reduction of the naphthalene ring, were observed in low levels (<0.1%).[10] Both structures were established by independent synthesis.[13]

Alternative procedures seem to be less efficient. For example, Dr. Reddy's has reported the formation of amide **2** by condensation of acid **3** with amine **4** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) in 83% yield. Without HOBt the yield was slightly lower (73.5%).[11] Geoghegan et al. have used 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane for the coupling.[12] The amide has also been synthesized by previous activation of acid **3** with ethyl chloroformate, as reported by scientists at Sandoz.[14] Reaction of acid **3** with ethyl chloroformate in ethyl acetate at 0–5 °C in the presence of triethylamine, followed by addition of the enantiopure amine **4** at this temperature and subsequent work-up, led to the saturated amide **2** in 76% yield. Amide **2** has also been synthesized by conversion of acid **3** into its corresponding acyl chloride with thionyl chloride in toluene, followed by reaction with the enantiopure amine in dichloromethane in the presence of triethylamine. Both Ind-Swift and McLeods have reported very high yields for this transformation.[15,16] Finally, a direct conversion of acid **3** into amide **2** has been claimed by Ind-Swift by using a catalytic amount of boric acid in toluene at reflux and with azeotropic distillation of water. According to the work from this company, amide **2** is obtained in quantitative yield (Scheme 3).[15]



Scheme 3 Alternative syntheses of amide **2** from propionic acid **3**

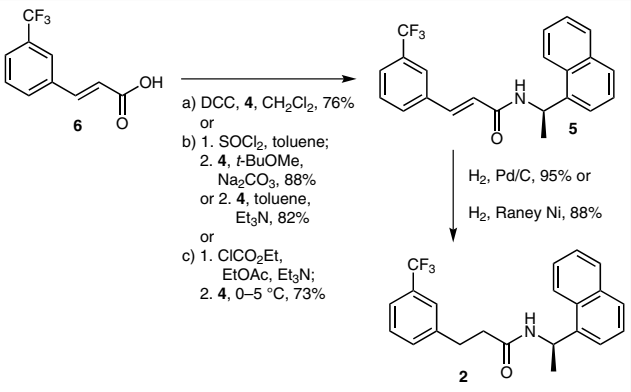
Regarding the reduction of the amide to cinacalcet, in addition to the aforementioned Amgen procedure, several conditions and reagents have been explored. For example, alternative sources for borane have been investigated by Ind-Swift, leading to the disclosure of a quantitative reduction using $BH_3{\cdot}Me_2S$ complex in refluxing tetrahydrofuran.[15] The Macleods procedure, using a mixture of sodium borohydride and molecular iodine in tetrahydrofuran at reflux, led to 90% yield and with a purity higher than 99.9%.[16]

Recently, Boehringer Ingelheim's process chemists have reported a new method for the reduction of primary, secondary and tertiary amides to amines using catalytic triruthenium dodecacarbonyl and 1,1,3,3-tetramethyldisiloxane (TMDS). In this context, reduction of the amide **2** using $Ru_3(CO)_{12}$ (1% mol) and TMDS in toluene at 50 °C for 18 hours, followed by the addition of hydrochloric acid, gave cinacalcet hydrochloride in 93% yield.[17]

2.2 Approaches Involving Acrylamide 5

As already discussed, it is possible to carry out first the coupling between unsaturated acid **6** and the amine **4**, followed by the stepwise reduction of the carbon–carbon double bond and the amide.

Dr. Reddy's has reported the condensation of 3-(trifluoromethyl)cinnamic acid (**6**), with (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**) in the presence of DCC in dichloromethane, obtaining 76% yield and an HPLC purity of 97%.[11] As already mentioned, it is possible to activate the propionic acid derivative **3** with ethyl chloroformate or through its conversion into the corresponding acyl chloride. Both possibilities have been also explored with unsaturated acid **6**. Reaction of **6** with ethyl chloroformate in ethyl acetate at 0–5 °C, followed by addition of the enantiopure amine **4** at this temperature, led to the acrylamide derivative **5** in 73% yield.[14] When the acid was activated as its acyl chloride and the coupling was carried out in toluene in the presence of triethylamine, the acrylamide derivative was obtained in 82% yield.[18] A similar yield (88%) were reported by IndSwifts who used *tert*-butyl methyl ether and sodium carbonate (Scheme 4).[15] Finally, the activation of **6** with 1,1′-carbonyldiimidazole in ethyl acetate at room temperature for three hours furnished **5** in only 14% yield.[18]



Scheme 4 Alternative syntheses of amide **5** from acid **6** and reduction to amide **2**

The acrylamide **5** was hydrogenated (5 atm H_2, MeOH) using either Pd/C or Raney nickel as catalyst, to furnish the saturated amide **2** in 95 or 88% yield, respectively (Scheme 4).[11,14] The reduction of amide **2** to cinacalcet has already been discussed in the previous section.

The earlier attempts to reduce **5** directly to cinacalcet using either lithium aluminum hydride in tetrahydrofuran, Vitride® in toluene or diisobutylaluminum hydride in toluene–dichloromethane, furnished 49, 39 and 60% yields, respectively.[11,18] More recently, Amgen achieved a 93% yield for this transformation using borane generated in situ from borane–dimethylsulfide complex (Scheme 5).[18]

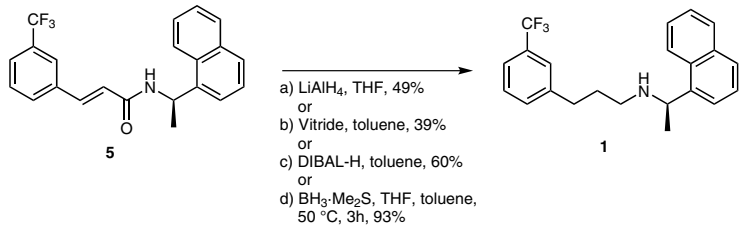
In summary, Amgen has developed both the shortest and the highest overall yielding sequences for the synthesis of **1**.

2.3 Alternative Approaches Involving Amides

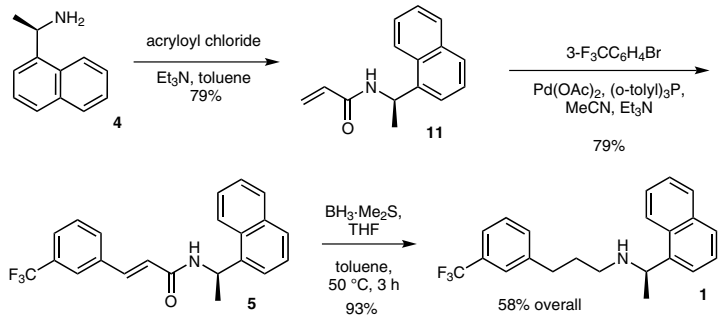
Amgen has claimed in a patent several alternative approaches to cinacalcet. Most of them have limited industrial interest as expensive reagents and/or low yields are involved.[18]

In their first approach, (*R*)-1-(1-naphthyl)ethylamine reacted with acryloyl chloride to give acrylamide **11** in 79% yield. The key step of the process is a metal-catalyzed cross-coupling reaction between acrylamide **11** and 1-bromo-3-(trifluoromethyl)benzene, using palladium(II) acetate (5% catalyst) and tri-*o*-tolylphosphine (10% catalyst) in acetonitrile; amide **5** was isolated in 79% yield. Of note, when 3-(trifluoromethyl)phenylboronic acid was used instead of the bromo derivative, the yield was much lower (only 9%). An alternative approach to acrylamide **5**, using a metathesis reaction of acrylamide **11** with 3-(trifluoromethyl)styrene in the presence of the Grubbs second-generation catalyst (15% mol), furnished amide **5** in a mere 7%. The last step is the reduction of amide **5** to cinacalcet in 93% yield using borane generated from borane–dimethylsulfide complex (Scheme 6).[18]

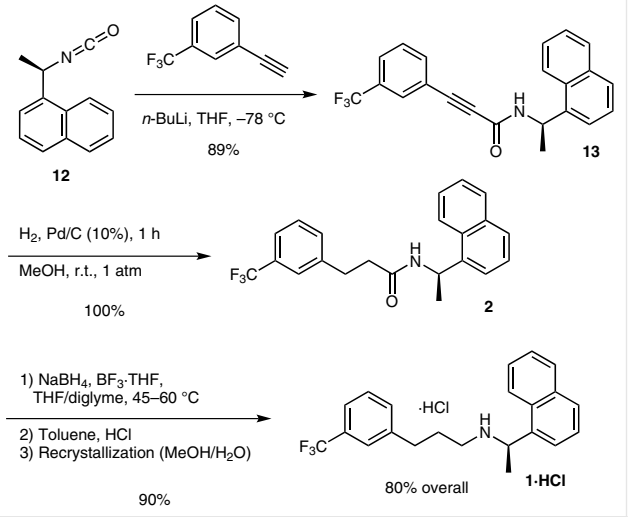
In the same patent, Amgen also disclosed the synthesis of cinacalcet from a propynamide.[18] First, 1-ethynyl-3-(trifluoromethyl)benzene is deprotonated with *n*-butyllithium, and added to a solution of (*R*)-1-(1-isocyanatoethyl)naphthalene (**12**; synthesis not described) to give propynamide **13** in 89% yield. In this case, the direct reduction of the propynamide with borane led to cinacalcet in only 22% yield. However, catalytic hydrogenation of the alkyne (Pd/C, MeOH) yielded the saturated amide in quantitative yield. The reduction of the amide is not described in this patent, but give the yield (90%) claimed by Amgen in reference 10 (see above), we can estimate a roughly 80% overall yield for this approach (Scheme 7).



Scheme 5 Direct reduction of amide **5** to cinacalcet

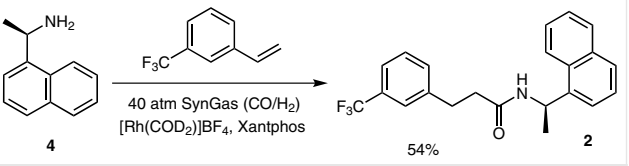


Scheme 6 Synthesis of cinacalcet through acrylamide **11**



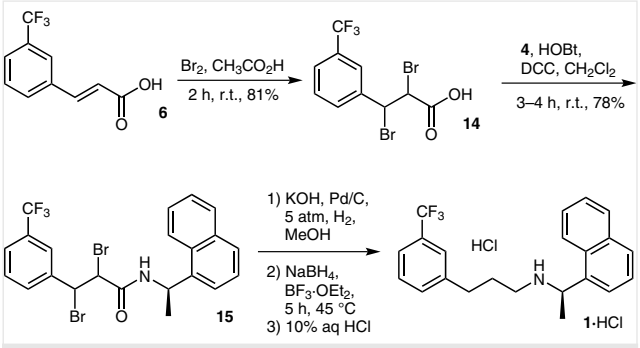
Scheme 7 Synthesis of cinacalcet through propynamide **13**

A third approach disclosed by Amgen revolves around a rhodium-catalyzed hydroformylation reaction between (*R*)-1-(1-naphthyl)ethylamine (**4**) and 3-(trifluoromethyl)styrene. The amide **2** is isolated in only 54% yield (Scheme 8).[18]



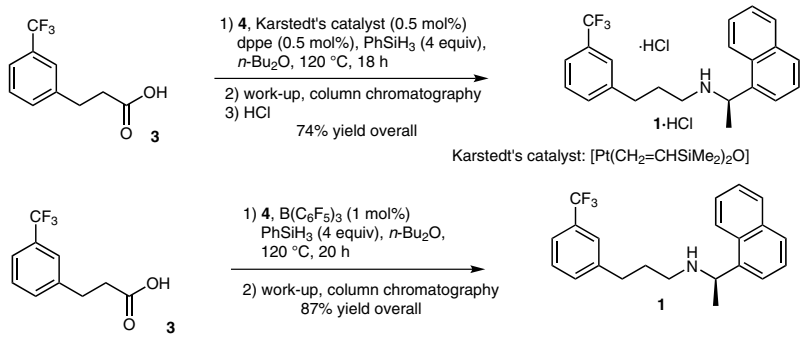
Scheme 8 Synthesis of **2** by a rhodium-catalyzed hydroformylation

Optimus has applied for an Indian patent with a four-step synthesis of cinacalcet from **6** (Scheme 9). Bromination of **6** in acetic acid led to its dibromo derivative **14** in 81% yield which, after coupling with enantiopure amine **4** in dichloromethane using HOBt and DCC, furnished amide **15** in 78% yield. Catalytic hydrogenation (5 atm, Pd/C, KOH) of a methanolic solution of amide **15** gave crude saturated amide **2** that, without further purification, was reduced to cinacalcet by borane generated from sodium borohydride and boron trifluoride–diethyl ether complex in anhydrous tetrahydrofuran. After the work-up, cinacalcet hydrochloride was isolated in 56% yield (from **15**) and 99.8% purity.[19]



Scheme 9 Synthesis of cinacalcet through dibromo derivatives **14** and **15**

Recently, Beller and co-workers developed a straightforward process for the *N*-alkylation of amines from readily available carboxylic acids and using silanes as the hydride source. The reaction proceeds through the direct condensation of the amine with the carboxylic acid to produce a carboxamide, followed by in situ reduction.[20] The reaction of the enantioenriched **4** (88% ee) and acid **3** with phenylsilane in the presence of an in situ formed platinum catalyst, generated from commercially available Karstedt's catalyst and 1,2-bis(diphenylphosphino)ethane (dppe), afforded **1**·HCl in 74% isolated yield without any observed racemization. This process is the first one-pot catalytic synthesis of cinacalcet (Scheme 10). Shortly thereafter, Fu and co-workers reported a metal-free alternative that involves a boron-based catalyst, tris(pentafluorophenyl)borane, that furnishes cinacalcet in 87% yield.[21]



Scheme 10 One-pot catalytic syntheses of cinacalcet from acid **3** and amine **4**

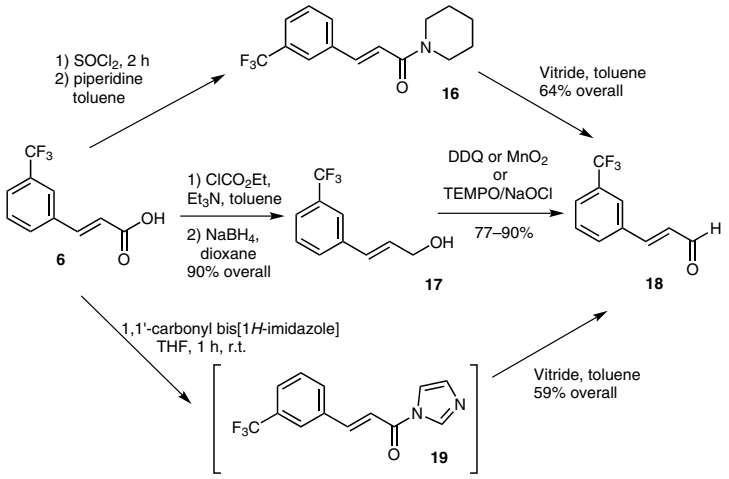
3 Synthetic Approaches Involving a Reductive Amination

In these approaches, (*R*)-(+)-1-(1-naphthyl)ethylamine reacts with either 3-(trifluoromethyl)cinnamaldehyde (**18**) or 3-[3-(trifluoromethyl)phenyl]propanal (**20**), both available in bulk quantities. Actavis, Aurobindo, Erregierre and Shasun have applied for patents involving aldehyde **18**, while Dipharma, DrReddy's, Heterodrugs, Jubilant, Medichem, MacLeods, NPS, Piramal, Teva, Torrent, Tyche and Wockhardt have all disclosed procedures involving aldehyde **20**. First, we will briefly discuss the reported procedures for the synthesis of aldehydes **18** and **20**. Next, we will focus on the synthesis of cinacalcet from them.

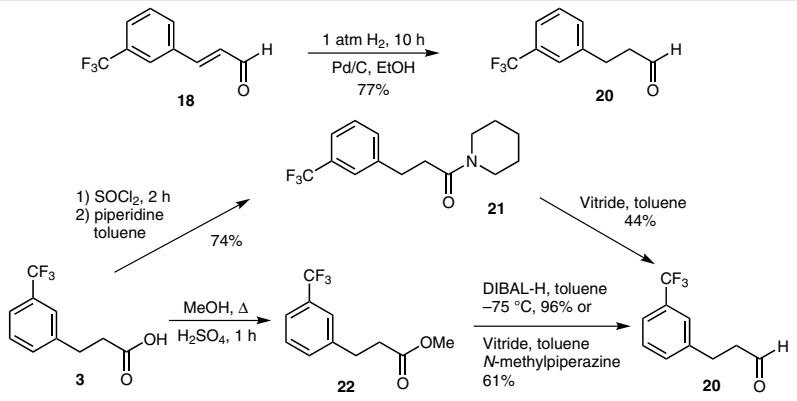
3.1 Processes for the Synthesis of 3-(Trifluoromethyl)cinnamaldehyde (18), and 3-[3-(Trifluoromethyl)phenyl]propanal (20)

3-(Trifluoromethyl)cinnamaldehyde (**18**) is easily available by reduction of a suitable derivative of 3-(trifluoromethyl)cinnamic acid (**6**). For example, Aurobindo has disclosed that activation of the acid with ethyl chloroformate followed by reduction with sodium borohydride led to the allylic alcohol **17** in 90% yield. Oxidation of the alcohol with sodium hypochlorite/TEMPO, DDQ or manganese(IV) oxide furnished the required aldehyde in 88, 90 and 77% yields, respectively.[22] Alternatively, treatment of the carboxylic acid with thionyl chloride followed by reaction of the acyl chloride with piperidine led to amide **16** that was reduced with Vitride® in toluene to the aldehyde **18** in 64% overall yield. Also, reaction of the carboxylic acid with carbonyldiimidazole followed by reduction with Vitride® in toluene led to aldehyde **18** in 59% yield (Scheme 11).[23]

There are several methods for the synthesis of 3-[3-(trifluoromethyl)phenyl]propanal (**20**). Most of these procedures involve the oxidation of 3-[3-(trifluoromethyl)phenyl]propanol (**25**). However, there is also one example reporting the catalytic hydrogenation of **18** to **20** in 77% yield,[23] and several low-yielding procedures dealing with the direct reduction of suitable derivatives (e.g., ester **22**,[24,25] amide **21**[23]) of acid **3** (Scheme 12).

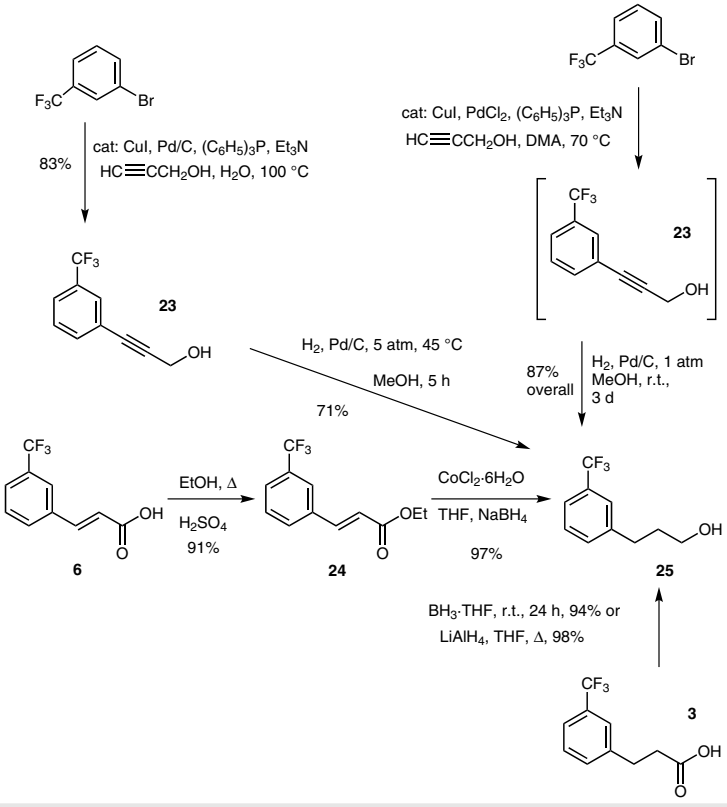


Scheme 11 Syntheses of aldehyde **18** from acid **6**



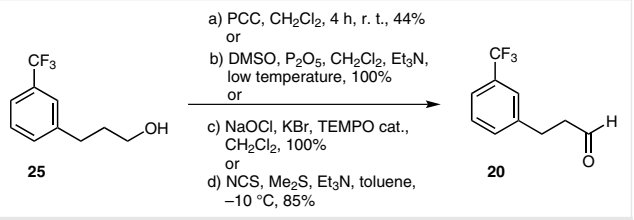
Scheme 12 Syntheses of aldehyde **20** from aldehyde **18** or derivatives of acid **3**

Scheme 13 collects several approaches to alcohol **25**. Actelion Pharmaceuticals has disclosed that reduction of the acid **3** with borane led to alcohol **25** in 94% yield.[26] The same transformation has also been described in higher yield (up to 98%) using lithium aluminum hydride in tetrahydrofuran.[11] In another process, Unichem has disclosed the direct reduction of ethyl 3-(trifluoromethyl)cinnamate (**24**) to the saturated alcohol in nearly quantitative yield using cobalt chloride hexahydrate and sodium borohydride in tetrahydrofuran, in the presence of a catalytic amount of diisopropylamine.[27] Alternatively, both Dipharma and Medichem have reported very similar procedures for the synthesis of alcohol **25**. First, 1-bromo-3-(trifluoromethyl)benzene reacts with propargyl alcohol in the presence of a base and a catalytic mixture of copper(I) iodide, triphenylphosphine and a source of palladium ($PdCl_2$ or Pd/C) to give alkyne **23**. Dipharma does not mention the yield of the coupling, as they reduced **23** directly to the saturated alcohol **25** in 87% overall yield.[28] Medichem reports an 83% yield for the coupling and a 71% yield for the hydrogenation.[29]



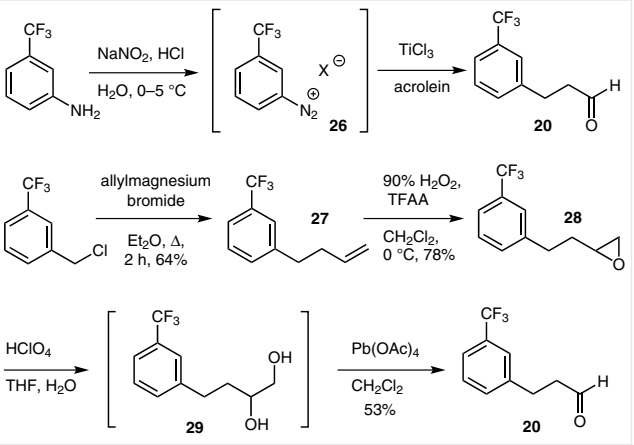
Scheme 13 Syntheses of saturated alcohol **25**

From alcohol **25**, several oxidation procedures have been reported (Scheme 14). While the oxidation of the alcohol to the aldehyde with PCC worked only in moderated yield,[26] both Dipharma and Medichem have reported quantitative yields using either dimethyl sulfoxide and phosphorus pentoxide at room temperature or a TEMPO-catalyzed process using bleach as stoichiometric oxidant.[28,29] Tyche has reported an 88% yield using the Corey–Kim oxidation (DMS, Et_3N, and NCS in toluene at –10 °C).[30]



Scheme 14 Oxidation of alcohol **25** to aldehyde **20**

Finally, Scheme 15 collects two alternative approaches to aldehyde **20**. Jubilant has synthesized aldehyde **20** from 3-trifluoromethylaniline and acrolein via a diazonium salt, although the yield was not disclosed.[31]



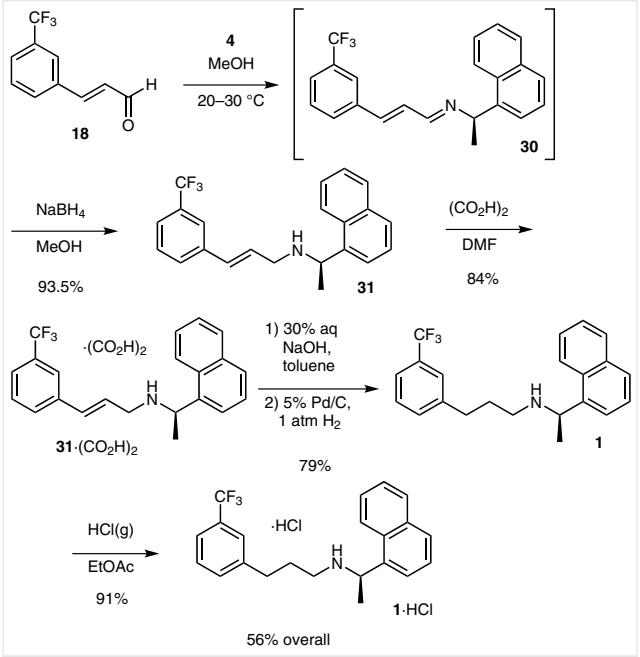
Scheme 15 Alternative syntheses of aldehyde **20**

The first reported synthesis of aldehyde **20** involved a four-step approach from allylmagnesium bromide and 3-(trifluoromethyl)benzyl chloride in 26% overall yield. Epoxidation with hydrogen peroxide and trifluoroacetic anhydride led to epoxide **28** which was converted into **20** by formation of glycol **29** and cleavage with lead(IV) acetate.[32]

3.2 Processes Involving 18

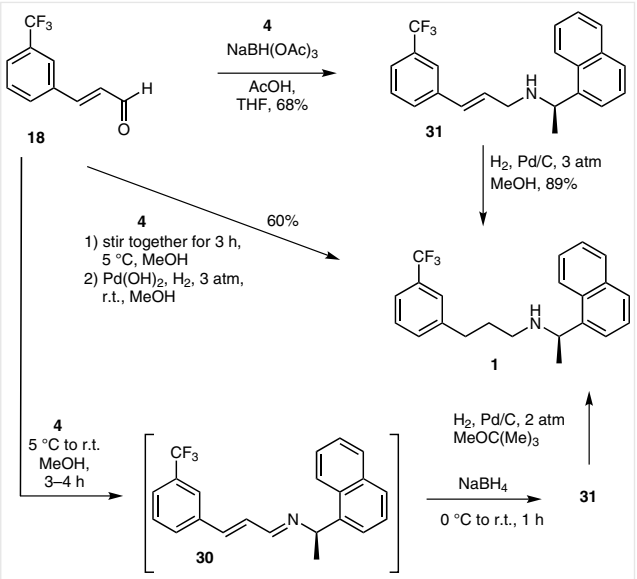
All these processes involve a reductive amination of 3-(trifluoromethyl)cinnamaldehyde (**18**) with (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**). Each process differs with respect to the reductive agent used, the purification conditions, and wether the imine is isolated before the reduction. After the reductive amination, a hydrogenation furnishes cinacalcet.

In a first approach, Erregierre disclosed a synthesis of cinacalcet hydrochloride that involves the amination of aldehyde **18** with amine **4** in methanol to give a non-isolated imino intermediate, **30**, that is reduced in situ with sodium borohydride to the corresponding allylic amine, **31**, in 93.5% yield (Scheme 16). After purification of the amine throughout its oxalate salt, catalytic hydrogenation leads to cinacalcet free base in 79% yield; the latter is dissolved in ethyl acetate and treated with hydrogen chloride gas, leading to cinacalcet hydrochloride in 91% yield.[33]



Scheme 16 Erregierre's method for the synthesis of cinacalcet

Actavis has reported a one-pot three-step synthesis of cinacalcet base from **18** with **4**. The reaction is carried out in methanol, at 5–10 °C under hydrogen (3 atm) and in the presence of palladium hydroxide. After an extractive work-up, a 60% yield of cinacalcet base with a purity of 91% is obtained (Scheme 17).[34]



Scheme 17 Alternative methods for the synthesis of cinacalcet from aldehyde **18**

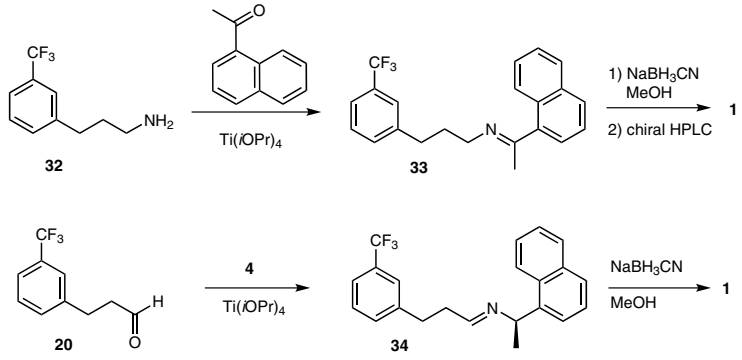
Alternatively, the two reductive steps can be carried out separately. In this vein, Aurobindo has disclosed a process that involves a reductive amination of aldehyde **18** with amine **4** using sodium triacetoxyborohydride in tetrahydrofuran. The allylic amine obtained was further reduced by catalytic hydrogenation to furnish cinacalcet hydrochloride. The overall yield from the aldehyde to cinacalcet hydrochloride is 60% and the product is isolated with a purity of 99.9% (Scheme 17).[22] The reductive amination can also be carried out in the presence of $Ti(iPrO)_4$ to give an intermediate that, without isolation, is hydrogenated to give cinacalcet in 44% overall yield. In a very similar fashion, Shasun Pharmaceuticals has disclosed the use of sodium borohydride for the reduction of the imine. In this process, the imine is formed first and directly reduced to the allyl amine that is isolated as its corresponding phosphate. Further reduction by catalytic hydrogenation led to cinacalcet. Unfortunately, as it is often encountered in the patent literature, the yields for this process have not been reported (Scheme 17).[35]

3.3 Processes Involving 20

The discovery synthesis route for cinacalcet and its congeners by NPS Pharmaceuticals relied on two reductive amination approaches (Scheme 18).[36] Without giving any specific example, the first patent described a general route for all the congeners that, for cinacalcet, would involve the condensation of methyl 1-(naphthyl) ketone with 3-[(3-trifluoromethyl)phenyl]propyl-1-amine (**32**) in the presence of titanium(IV) isopropoxide to give imine **33** that, by reduction with sodium cyanoborohydride would lead to racemic cinacalcet, that itself would be resolved by chiral HPLC. Alternatively, the same patent reports that condensation of aldehyde **20** with enantiopure amine **4** followed by reduction of the enantiopure imine **34** with sodium cyanoborohydride would afford enantiopure cinacalcet. This second approach was experimentally accomplished later on by researchers at Heterodrugs, who reported a 65% yield for the reductive amination of aldehyde **20** by amine **4** in the presence of titanium(IV) isopropoxide.[25] Unichem has reported that, after the titanium-induced coupling, the imine **34**, without isolation, can alternatively be reduced with sodium borohydride in tetrahydrofuran to give cinacalcet base in 91% yield.[27]

Alternatively, according to a procedure disclosed by Piramal, the imine **34** can be obtained using sulfuric acid as the catalyst in dichloromethane at 0–5 °C for one hour. Without isolation, imine **34** can be reduced to cinacalcet using sodium borohydride in methanol. After work-up, the hydrochloride salt of cinacalcet is obtained in 86% yield and 95% purity.[37]

In 2012, DrReddy's reported a direct reductive amination of aldehyde **20** with amine **4** in dichloromethane–methanol with sodium borohydride in the presence of a catalytic amount (1% mol) of iron(III) triflate. The reaction was very fast (about 5 minutes) and furnished cinacalcet base in 80% yield.[38]



Scheme 18 Firsts approaches to cinacalcet (**1**)

The same year, Wockhardt disclosed a reductive alkylation of amine **4** with aldehyde **20** in the presence of zinc chloride and formic acid in methanol, using sodium cyanoborohydride as the reducing agent. The process gave 95% yield of cinacalcet base.[39]

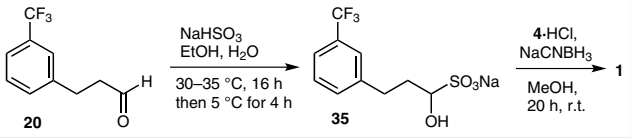
More recently, Zhong and co-workers reported that the reaction of aldehyde **20** with amine **4** in the presence of titanium(IV) chloride and 4 Å molecular sieves in toluene at room temperature gave the expected imine in 85% yield. Metal-free catalytic hydrogenation at 20 atmospheres using a [2.2]paracyclophane-derived frustrated Lewis pair catalyst afforded cinacalcet in 80% yield.[40]

Although the previous examples used a catalyst for the imine formation, according to several reports, there is no need for such a catalyst. Several generic manufacturers have reported procedures revolving around the direct condensation of amine **4** and aldehyde **20** without any catalyst. The imine, without isolation, has been reduced under several conditions (Table 1).[24,28,41–44]

Table 1 Reduction of Imine Generated in Situ from **4** and **20**

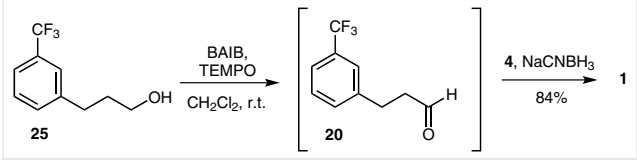
Reagent	Conditions	Yield	Manufacturer	Ref.
$NaBH(OAc)_3$	*i*-BuOAc	64%	Medichem	41,42
$NaBH(OAc)_3$	MeOH	72%	Dipharma	28
$NaBH_4$	toluene–MeOH, 2–3 °C	96%	Torrent Pharma	24
$NaBH_4$, H_3BO_3	no solvent	85%	Tyche	43
H_2 (2–4 atm), Raney Ni	MeOH	not reported	Cadila Healthcare	44

It should be noted that the oily nature of aldehyde **20** limits its purification. For this reason, very recently we have developed a process for the synthesis of cinacalcet from the sodium bisulfite adduct of aldehyde **20**. The aldehyde was first converted into its bisulfite adduct, **35**, by reaction with sodium bisulfite (1 equiv) in ethanol–water in 93% yield. Of note, the reductive alkylation was carried out directly from **35** with the hydrochloride of amine **4** (0.9 equiv) in methanol at room temperature, using sodium cyanoborohydride as the reducing agent. After work-up, the hydrochloride of cinacalcet was obtained in 90% yield (Scheme 19).[45]



Scheme 19 Synthesis of cinacalcet from **4**·HCl and the bisulfite adduct of aldehyde **20**

Another way to circumvent the purification and stability issues related to aldehyde **20** (e.g., oxidation) and imine **34** (e.g., hydrolysis) was recently reported by Cossy and co-workers. Their process involves a one-pot oxidation, imine–iminium formation, and reduction from alcohol **25**: the oxidation of alcohol **25** with [bis(acetoxy)iodo]benzene (BAIB), in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) in dichloromethane, is followed by the simultaneous addition of amine **4** and sodium triacetoxyborohydride. Although the reaction has unquestionable academic interest and the overall yield is 84%, some issues should be addressed before it can be applied in an industrial setting: cost of the stoichiometric oxidant, use of an excess of amine **4** (2 equiv) and use of column chromatography for final purification of cinacalcet (Scheme 20).[46]



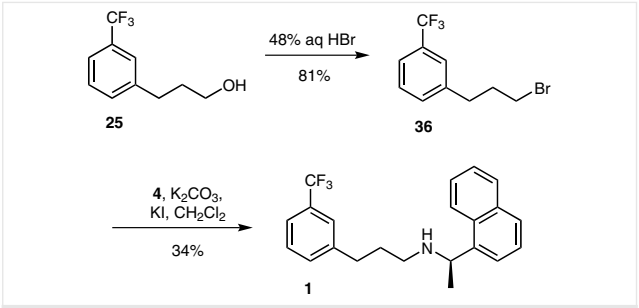
Scheme 20 Synthesis of cinacalcet from alcohol **25**

4 Synthetic Approaches Involving a Substitution Reaction

Cinacalcet has also been synthesized by nucleophilic substitution reactions. In these approaches, (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**) reacts with either an activated (mesylate, tosylate, etc.) derivative of 3-[3-(trifluoromethyl)phenyl]propan-1-ol, the mesylate derivative of 3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-ol, or an allyl halide or pseudohalide. Cipla, Dipharma, Dr. Reddy's, Ind-Swift, Ranbaxy and Teva have all applied for patents involving a substitution reaction.

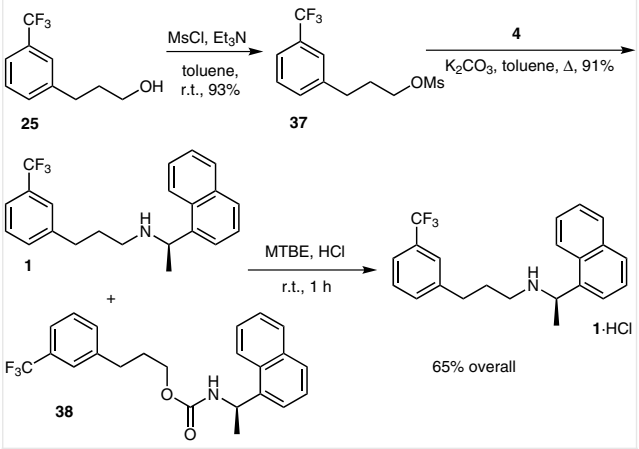
4.1 Substitutions Involving Alkyl Halides or Pseudohalides

In this area, several leaving groups have been explored. The reaction of the hydroxy group of alcohol **25** with 48% aqueous hydrobromic acid led to 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (**36**) in 81% yield. However, reaction of this bromo derivative with the enantiopure amine **4** led to cinacalcet hydrochloride in only 34% yield (Scheme 21).[11]



Scheme 21 Synthesis of cinacalcet from bromoalkyl derivative **36**

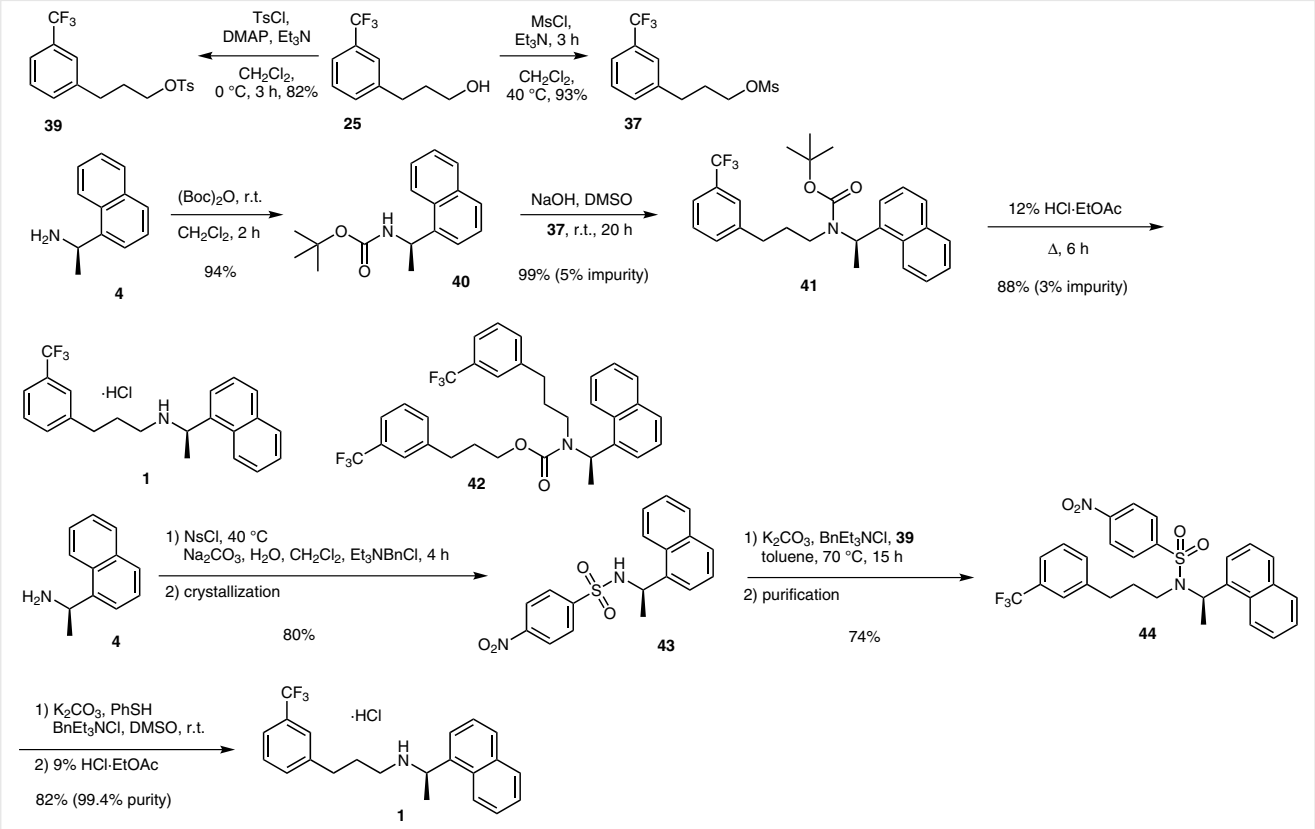
Teva and Cipla have obtained much better yields (>85%) in the substitution reaction, using the corresponding mesylate **37** as the leaving group.[46b,47–50] The reaction of alcohol **25** with mesyl chloride in toluene at 25 °C in the presence of triethylamine gave **37** as an oil in 93% yield. Several alternative conditions (solvents, bases, etc.) for this substitution reaction were studied. Toluene seemed to be the solvent of choice, while potassium carbonate gave higher yields than other bases. Of note, in several experimental protocols, the carbamate **38** appeared as an important impurity (typically around 3%, but up to 40% working under phase-transfer conditions).[46b] As usual, cinacalcet base was purified through crystallization of its hydrochloride salt. The overall yield from the mesylate to cinacalcet hydrochloride is about 62–70% (Scheme 22).



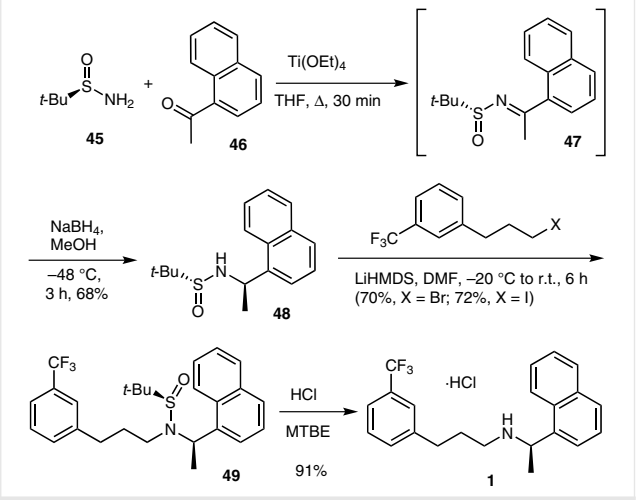
Scheme 22 Synthesis of cinacalcet from mesylate **37** and structure of carbamate **38**

Ind-Swift has disclosed a variation of the previous approaches using two protected derivatives of **4**, the *N*-Boc derivative **40** or the *p*-nitrobenzene sulfonamide derivative **43**.[51] The alcohol is activated either as the mesylate or as the tosylate. The protection of **4** works very well as the *N*-Boc carbamate, however the sulfonamide is obtained in only 80% yield. Both approaches presented some problems: the reaction of the *N*-Boc carbamate **40** with the mesylate gave *N*-Boc cinacalcet derivate **41** in a very high yield, but containing impurity **42** in about 5%, which remains in cinacalcet after the deprotection of the amine. The attack of some adventitious alcohol **25** either to the starting carbamate **40** followed by *N*-alkylation with **37**, or to the final carbamate **41**, may account for the formation of impurity **42**. Several crystallizations must be done in order to assure a good-quality product (Scheme 23). In the second approach, the reaction of the sulfonamide **43** with the tosylate **39** in toluene using triethylbenzylammonium chloride as a catalyst gave, after purification, the *p*-nitrobenzene sulfonamide of cinacalcet, **44**, in 74% yield. This product was transformed into cinacalcet hydrochloride in 82% yield by reaction with an excess of thiophenol in dimethyl sulfoxide, in the presence of potassium carbonate and a catalytic amount of triethylbenzylammonium chloride (Scheme 23).

Interestingly, in a very different approach, chemists at Suven Life Sciences reported a novel route for the asymmetric synthesis of cinacalcet hydrochloride. It consists in the application of (*R*)-*tert*-butanesulfinamide (**45**) and the regioselective *N*-alkylation of the naphthylethyl sulfinamide intermediate.[52] The uniqueness of this approach is that prochiral 1-acetylnaphthalene (**46**) is used as starting material, instead of (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**). First, the enantiopure 2-methylpropane-2-sulfinic acid 1-(1-naphthyl)ethylamide (**48**) is prepared with a diastereomeric ratio of 73:27, and by recrystallization of the crude, **48** is obtained in 99.94% ee in 68% yield. The reaction of this intermediate with 1-(3-bromopropyl)-3-(trifluoromethyl)benzene and lithium hexamethyldisilazide in *N*,*N*-dimethylformamide leads to the expected alkylated product, **49**, in 70% yield. A similar yield was obtained starting from intermediate **48** with 1-(3-iodopropyl)-3-(trifluoromethyl)benzene. As a last step, hydrolysis in *tert*-butyl methyl ether with concentrated hydrochloric acid at room temperature furnishes pure cinacalcet hydrochloride in 91% yield and 99.9% ee (Scheme 24).



Scheme 23 Synthesis of cinacalcet from mesylate **37** or tosylate **39** and structure of carbamate **42**

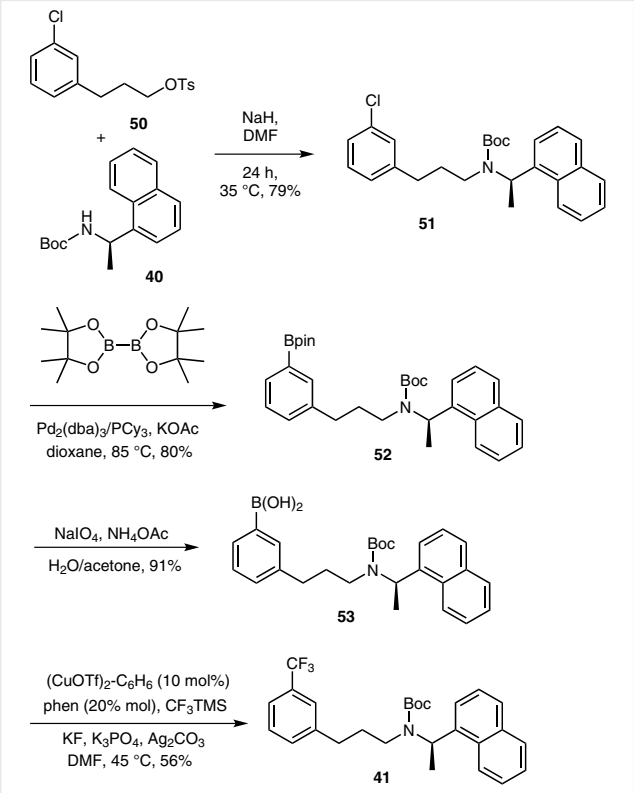


Scheme 24 Synthesis of cinacalcet from ketone **26** and (*R*)-*tert*-butanesulfinamide (**45**)

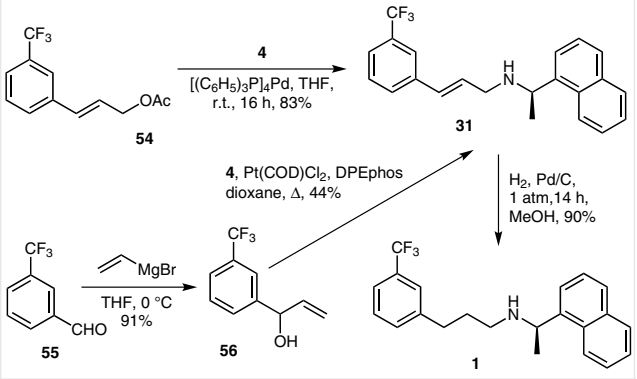
Finally, it should be mentioned that, as an example of a novel copper-catalyzed oxidative trifluoromethylation of aryl boronic acids, Qing and co-workers have reported a formal synthesis of cinacalcet which has academic interest (Scheme 25).[53] The synthesis parallels the previously discussed approaches but with a chlorine atom instead of the trifluoromethyl group. After incorporating the basic scaffold of cinacalcet in the *N*-Boc-protected analogue **51**, the trifluoromethyl group was introduced using the novel protocol developed by the authors, leading to *N*-Boc derivative **41**, the conversion of which to cinacalcet was already known (Scheme 23).

4.2 Substitutions Involving Allyl Halides or Pseudohalides

Amgen has disclosed two approaches to cinacalcet that involve substitution reactions (Scheme 26).[18] In a first approach, amine **4** reacts with allyl acetate **54** in the presence of palladium(0) to give **31** in 83% yield. Alternatively, amine **4** reacts with 1-[3-(trifluoromethyl)phenyl]prop-2-en-1-ol (**56**) in the presence of a platinum catalyst to give unsaturated amine **31** in 44% yield. We have already seen that **31** can be easily reduced to cinacalcet by catalytic hydrogenation (see Schemes 16 and 17).

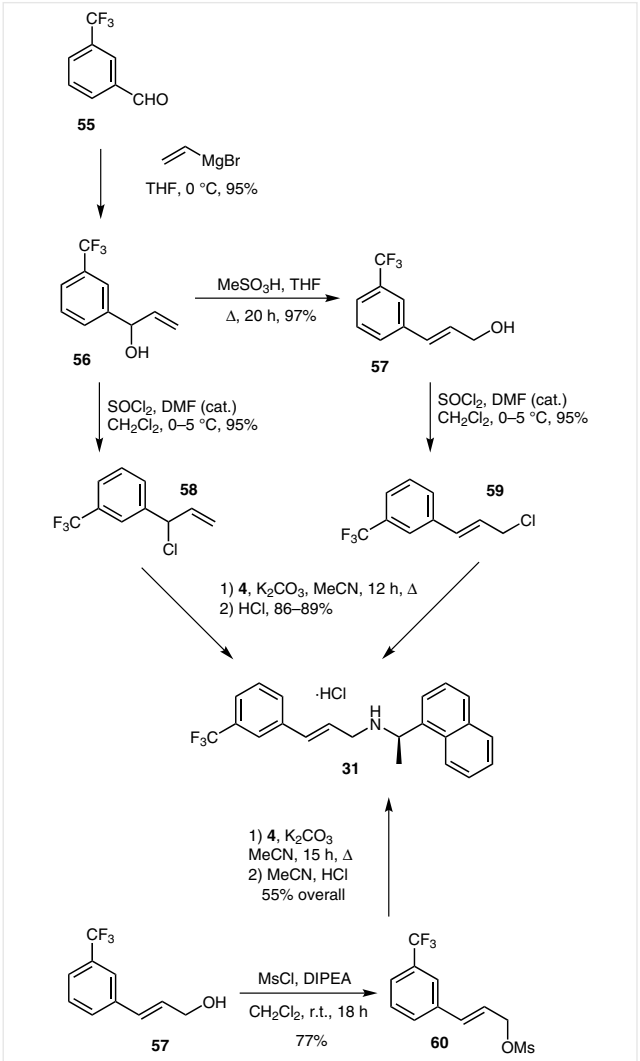


Scheme 25 Late introduction of the trifluoromethyl group in a synthesis of *N*-Boc-protected cinacalcet, **41**



Scheme 26 Synthesis of cinacalcet involving a substitution reaction in an allyl derivative

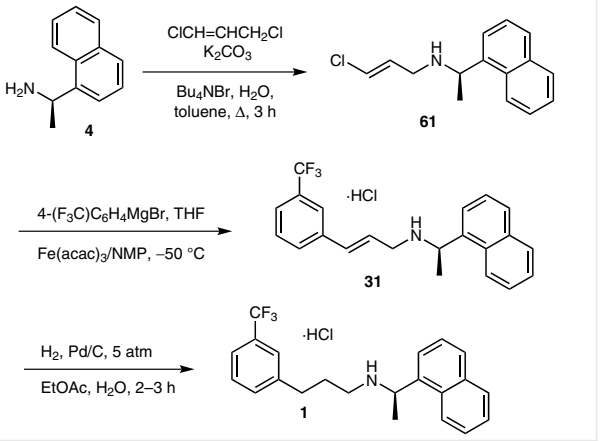
The use of an allyl chloride has also been reported. Ranbaxy has shown that unsaturated amine **31** can be synthesized in high yields by reaction of **4** with either 1-(1-chloroallyl)-3-(trifluoromethyl)benzene (**58**) or 1-(3-chloroprop-1-en-1-yl)-3-(trifluoromethyl)benzene (**59**). Both electrophilic partners can be synthesized, in very high yield, from 3-(trifluoromethyl)benzaldehyde (**55**), as shown in Scheme 27.[54] Also, **31** is easily synthesized from mesylate **60**, which in turn is easily prepared from alcohol **57**. The reported yield obtained for the substitution reaction using mesylate **60** is lower (55%) than that using **59** (86%).[22b,d]



Scheme 27 Syntheses of **31** involving a substitution reaction in allyl derivatives **58**–**60**

In a more original approach, Ranbaxy reported a synthesis of cinacalcet involving a carbon–carbon bond formation in a process catalyzed by an iron acetylacetonate–1-methyl-2-pyrrolidinone (NMP) complex. Reaction of 1,3-dichloropropene with amine **4** in toluene/water led to 3-chloro-*N*-[(1*R*)-1-(1-naphthyl)ethyl]prop-2-en-1-amine (**61**). Next, amine **61** was coupled with in situ prepared 3-(trifluoromethyl)phenylmagnesium bromide in tetrahydrofuran at –50 °C in the presence of a catalytic amount of iron acetylacetonate/NMP to give a mixture of *cis* and *trans* unsaturated cinacalcet in a 1:10 ratio. The *trans* isomer, **31**, was isolated as its hydrochloride in 99% purity with 1% of the *cis* isomer. Finally, catalytic hydrogenation with Pd/C in

ethyl acetate and water at moderate pressure furnished cinacalcet hydrochloride in 56% overall yield from **4** (Scheme 28).[55]



Scheme 28 Synthesis of cinacalcet from 1,3-dichloropropene and amine **4**

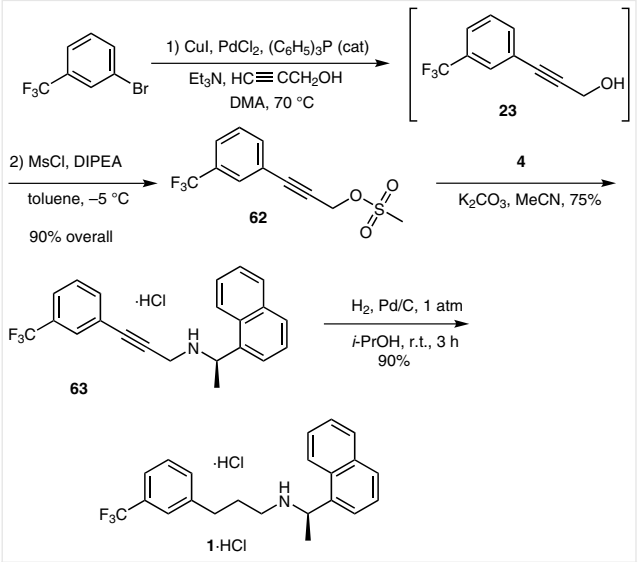
4.3 Substitution Involving a Propynyl Mesylate

We have already seen that Dipharma has disclosed a procedure for the synthesis of 3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-ol (**23**) from 1-bromo-3-(trifluoromethyl)benzene (Scheme 13).[28] The reaction of **23** with mesyl chloride in toluene in the presence of DIPEA furnished the corresponding mesylate, **62**, in 90% yield. Alternatively, the synthesis of **62** can be carried out without isolating **23** with the same overall yield.

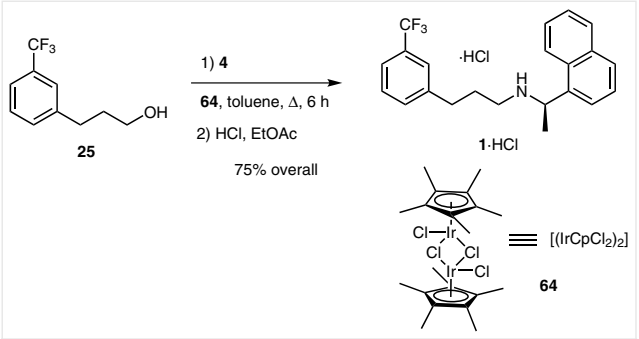
The reaction of **62** with **4** in acetonitrile in the presence of potassium carbonate led, after work-up and addition of hydrochloric acid, to the hydrochloride of the alkyne, **63**, which contains the cinacalcet skeleton, in 75% yield. Finally, catalytic hydrogenation of **63** furnished cinacalcet hydrochloride in 90% yield and in a purity higher than 99.5% (Scheme 29).[56]

4.4 Direct Substitution without Activating the Hydroxyl Group

Zentiva has disclosed a method that involves the direct coupling of (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**) with 3-[3-(trifluoromethyl)phenyl]propan-1-ol (**25**) in the presence of the iridium catalyst [dichloro(pentamethylcyclopentadienyl)iridium(III) dimer] (**64**) in refluxing toluene to give cinacalcet hydrochloride in 75% yield and 99.5% purity (Scheme 30). The product was recrystallized from ethyl acetate. This reaction can also be catalyzed by [Ru(*p*-cymene)Cl_2]$_2$, although this lowers the yield to 60%.[57]



Scheme 29 Synthesis of cinacalcet hydrochloride through propynyl mesylate **62**



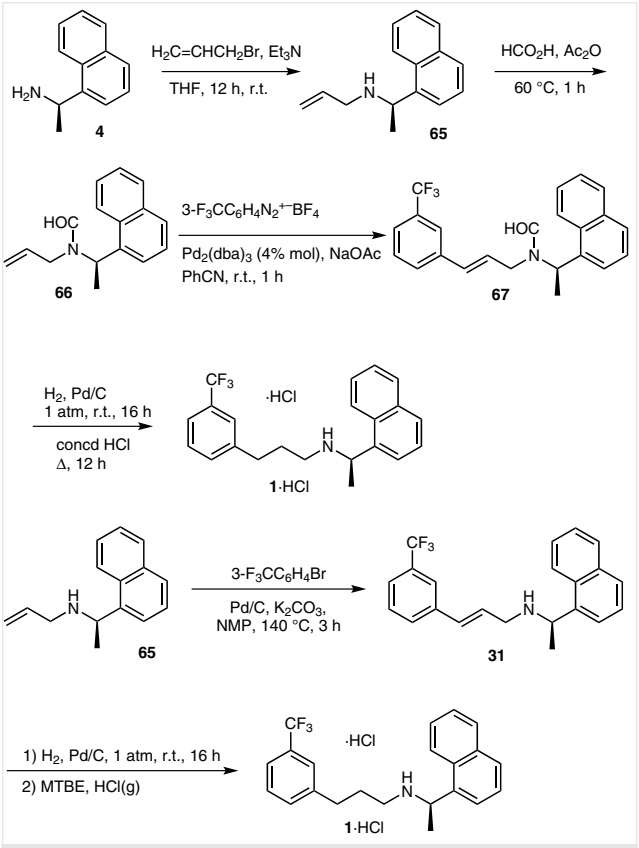
Scheme 30 Zentiva's approach to cinacalcet hydrochloride from alcohol **25**

5 Miscellaneous Synthetic Approaches

In this section we summarize some alternative approaches that do not fall into any of the previous synthetic approximations to cinacalcet. While most of them are of questionable industrial interest, there are some procedures worthy of being highlighted.

In 2014, a Brazilian group reported an approach to cinacalcet that revolved around a Heck reaction. They started with the allylation of **4** with allyl bromide, which led to (*R*)-*N*-[1-(1-naphthyl)ethyl]allylamine (**65**) in 85% yield. After protection of the amine as the corresponding formamide (in 90% yield), a Heck–Matsuda reaction with 3-(trifluoromethyl)benzene diazonium salt in the presence of a catalytic amount (4 mol%) of $Pd_2(dba)_3$ led to amide **67** that was converted into cinacalcet hydrochloride by catalytic hydro-

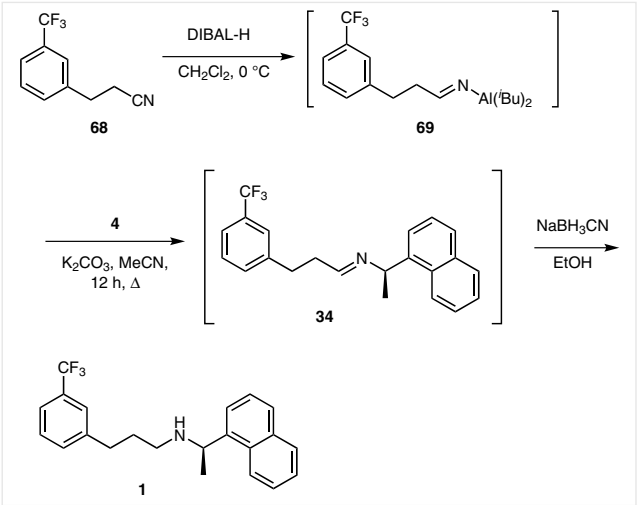
genation followed by deprotection and salt formation. Overall, the authors reported a 75% yield for the five steps from amine **4** (Scheme 31).[58]



Scheme 31 Syntheses of cinacalcet hydrochloride involving Heck reactions

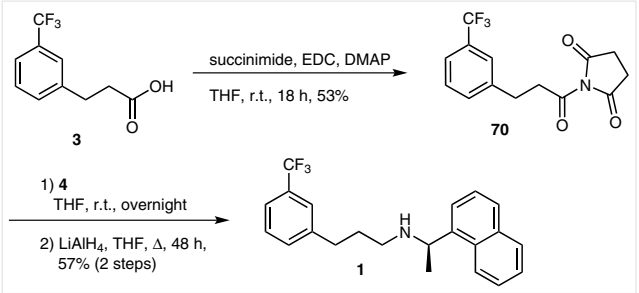
It should be mentioned that, previously, Teva disclosed a very similar procedure involving the Heck reaction of 1-bromo-3-(trifluoromethyl)benzene with amine **65** in the presence of a catalytic amount of Pd/C in NMP.[59] Unfortunately, no yields were reported for this procedure (Scheme 31).

NPS disclosed a very interesting synthesis involving a one-pot reduction–transimination–reduction protocol.[36] The reaction of nitrile **68** with diisobutylaluminum hydride, followed by treatment of the resultant aluminum–imine complex **69** with **4**, gave an imine that, on further reduction with ethanolic sodium cyanoborohydride, led to cinacalcet. Unfortunately, neither the yields nor experimental details were reported (Scheme 32).



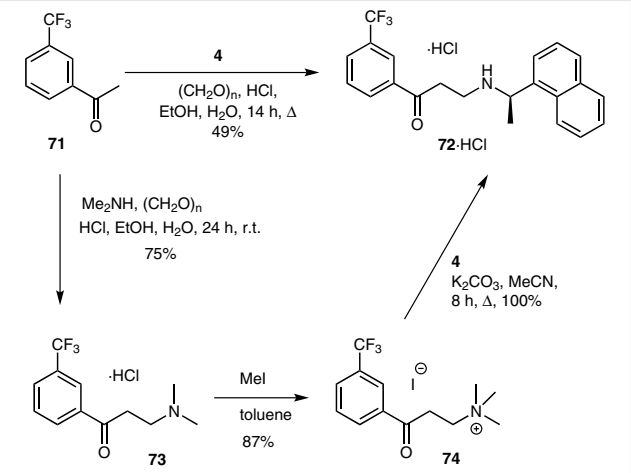
Scheme 32 Synthesis of cinacalcet from nitrile **68**

In another reductive approach, Hitchcock and co-workers reported a two-step, one-pot synthesis of cinacalcet by way of an acyl succinimide. The coupling of acid **3** with succinimide furnished acyl succinimide **70**, as a crystalline solid. The one-pot coupling of **70** with amine **4** followed by reduction with lithium aluminum hydride (2 M in THF) provided cinacalcet in 57% yield (Scheme 33).[60]



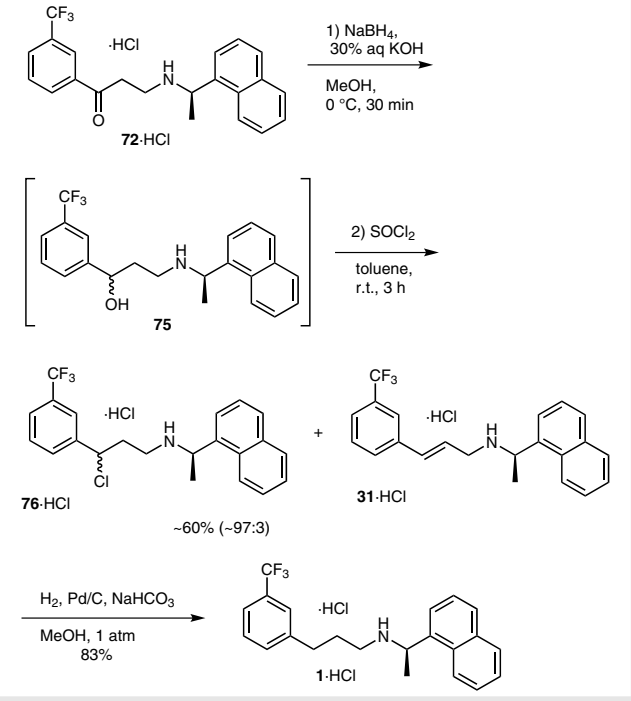
Scheme 33 Synthesis of cinacalcet through acyl succinimide **70**

Zach has filed several patents disclosing an original approach to cinacalcet that revolves around a Mannich reaction of 3-(trifluoromethyl)acetophenone (**71**), paraformaldehyde and amine **4**.[61] Alternatively, the β-amino ketone **72** can also be obtained by Mannich reaction of **71**, with paraformaldehyde and dimethylamine followed by methylation of **73** to give the ammonium salt **74**. The trimethylammonium group is finally substituted by **4**. According to the authors, the last reaction gave the β-amino ketone **72** in quantitative yield before purification (Scheme 34).



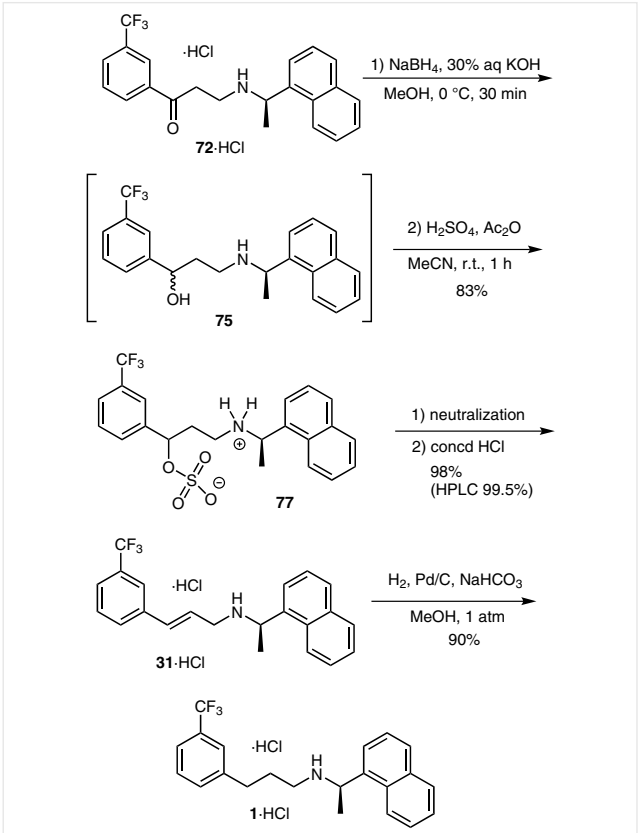
Scheme 34 Syntheses of β-amino ketone **72**

From the Mannich adduct, several possibilities have been explored. One of them is to reduce the carbonyl group of β-amino ketone **72** to a diastereomeric mixture of alcohols **75** that can be substituted by chlorine. In the reported procedures, mixtures of **75** and **76** are isolated. However, this is not a problem as catalytic hydrogenation of these mixtures followed by acidic work-up leads to cinacalcet hydrochloride. Interestingly, it is possible to carry out the reduction of the ketone and the introduction of the chlorine atom in a two-step one-pot procedure (Scheme 35).



Scheme 35 Synthesis of cinacalcet from β-amino ketone **72**

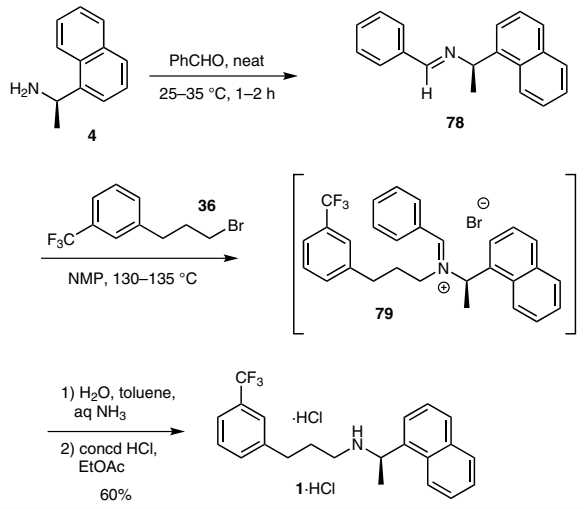
Alternatively, the alcohol **75** can be dehydrated via sulfate **77** which, after elimination, gives **31**. Hydrogenation of the latter furnishes cinacalcet (Scheme 36).



Scheme 36 Alternative synthesis of cinacalcet from β-amino ketone **72**

Megafine has reported an impressive one-pot synthesis of cinacalcet hydrochloride from **4**, benzaldehyde and substituted benzene **36** (Scheme 37),[62] which itself is prepared in high yield from 3-[3-(trifluoromethyl)phenyl]propan-1-ol (**25**) and aqueous hydrobromic acid as described in Scheme 21.

In this procedure the synthesis of cinacalcet hydrochloride was first carried out step by step, in order to identify and characterize impurities and to establish the reaction parameters at each step. The reaction of **4** with benzaldehyde was initially conducted in ethanol at reflux for five to six hours. The Schiff base **78** precipitated out and was isolated as a white crystalline solid by filtration of the reaction mass. The solid obtained was used directly in the next step without further purification. Although **78** was found to be unstable upon storage for a longer period in the presence of moisture, dried samples, stored under inert atmosphere, remained stable for longer periods. The reaction of the Schiff base **78** with bromoalkyl derivative **36** in NMP at 130–135 °C provided the iminium salt **79**, which upon treatment with water or an aqueous acid at room temperature, fol-



Scheme 37 Synthesis of cinacalcet from benzaldehyde, **4** and **36** using a Forster reaction

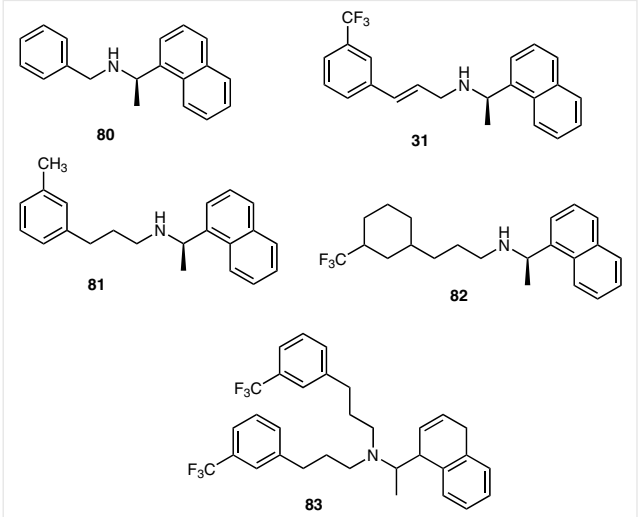
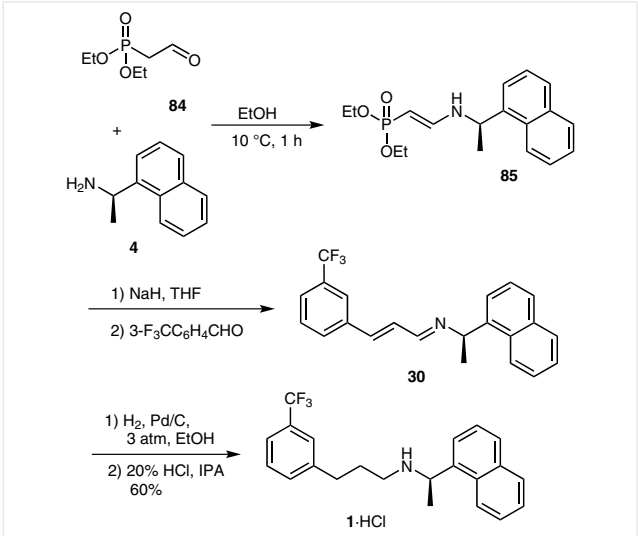


Figure 3 Impurities detected during Megafine's process



Scheme 38 Synthesis of cinacalcet from phosphonate **85**

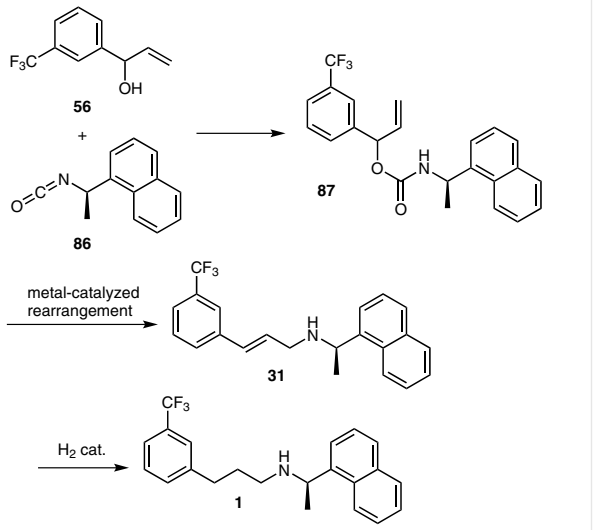
lowed by usual workup procedure, furnished cinacalcet hydrochloride. After additional purification and recrystallization, cinacalcet hydrochloride was obtained as a white crystalline solid with 99.9% purity by HPLC and with an overall yield of 60%. The use of a catalyst or a phase-transfer catalyst provided no enhancements to the established process. The original Forster reaction does not use any solvent for the formation of the iminium salt, but in this case, many impurities were formed when the reaction was performed without solvent.

After optimizing both reactions independently, a one-pot process was established by telescoping both reactions. While telescoping and setting up the one-pot process, the formation of the Schiff base was achieved at 25 °C within one to two hours without using any solvent. NMP was added to the reaction mass containing the Schiff base, followed by **36**, and the rest of the operations were performed in the same manner as described above to obtain the cinacalcet hydrochloride in one pot. Moreover, five potential impurities (Figure 3) were identified, synthesized, and characterized by LC-MS.

In a different approach to cinacalcet, French researchers disclosed a new synthesis that relies on the Horner–Wadsworth–Emmons olefination of vinyl phosphonate **85**, which is readily available from diethyl (2-oxoethyl)phosphonate (**84**) and amine **4**, with 3-(trifluoromethyl)benzaldehyde. It gives **30** in quantitative yield (Scheme 38). As previously mentioned, catalytic hydrogenation of imino intermediate **30** gives cinacalcet that is further processed to its hydrochloride.[63]

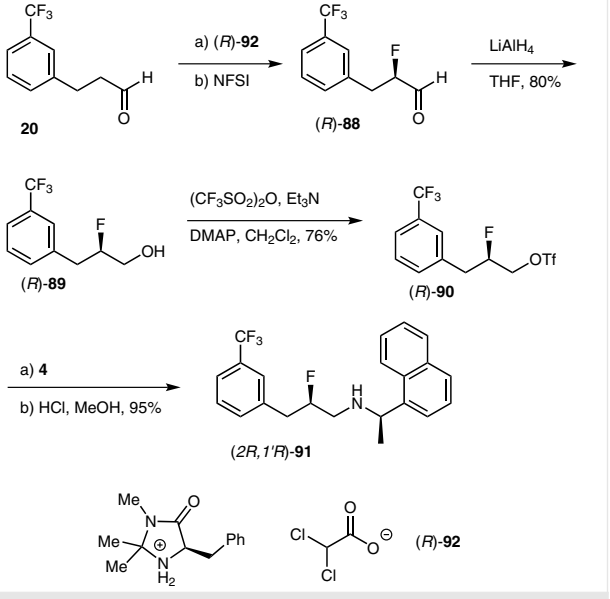
It should be noted that Angem has mentioned the possibility of preparing cinacalcet using a C–O to C–N rearrangement,[18] starting from the allyl alcohol **56** and (*R*)-1-(1-isocyanatoethyl)naphthalene (**86**). The carbamate **87** can be admixed with a metal catalyst to allow the C–O to C–N rearrangement to an unsaturated cinacalcet precursor, allylic amine **31**, the hydrogenation of which is known to give cinacalcet (Scheme 39). However, this patent application did not give experimental details for this approximation.

Finally, it is worth mentioning that O'Hagan and coworkers synthesized three novel analogues of cinacalcet.[50] Two of them, (2*R*,1′*R*)-**91** and its (2*S*,1′*R*) diastereoisomer (not shown) were synthesized from aldehyde **20** following the synthetic sequence shown in Scheme 40. A MacMillan asymmetric fluorination reaction of aldehyde **20** with *N*-



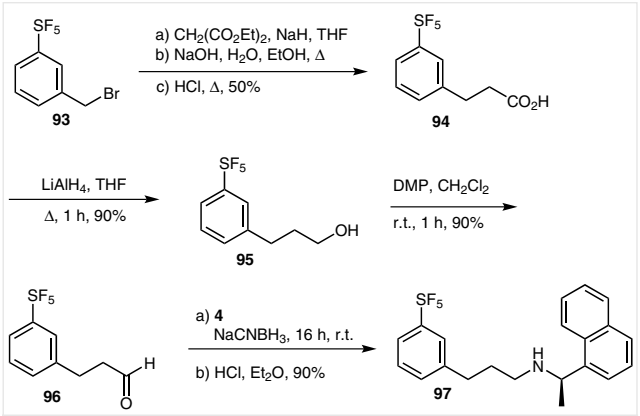
Scheme 39 Synthesis of cinacalcet using a C–O to C–N rearrangement

fluorobenzenesulfonimide (NFSI) and (*R*)-**92** as organocatalyst led to the monofluorinated aldehyde (*R*)-**88**, reduction of which with lithium aluminum hydride furnished alcohol (*R*)-**89** in 80% yield. Reaction of this alcohol with trifluoromethanesulfonic anhydride yielded triflate (*R*)-**90**. Finally, its reaction with enantiopure amine **4** furnished (2*R*,1′*R*)-**91** in high yield. In the same way, starting from aldehyde **20** and using organocatalyst (*S*)-**92** the corresponding (2*S*,1′*R*)-**91** diastereoisomer was obtained.



Scheme 40 Synthesis of fluorinated cinacalcet analogue (2*R*,1′*R*)-**91**

The synthesis of the pentafluorosulfanyl analogue **97** was started from known benzyl bromide **93**.[64] Nucleophilic substitution with diethyl malonate followed by hydrolysis and decarboxylation furnished acid **94** in moderate yield. Reduction of acid **94** with lithium aluminum hydride followed by Dess–Martin oxidation of alcohol **95** gave aldehyde **96** in 91% yield. Finally, reductive amination of aldehyde **96** with enantiopure **4** gave **97** in 90% yield (Scheme 41).[50]



Scheme 41 Synthesis of pentafluorosulfanyl cinacalcet analogue **97**

6 Conclusions

In this review, we have compiled an overview of the different procedures that have been reported for the synthesis of cinacalcet. Although there is significant diversity among the methods used to synthesize this drug, most the approaches that have industrial applicability can be placed into one or another of these three categories: processes involving the reduction of an amide, those featuring a reductive amination, and those involving a substitution reaction. As one might expect, the majority of the alternatives are found in the first two groups.

Although most of the relevant information arises from the patent literature, which makes yield comparison more difficult, and setting aside the purity of the final product between different approaches, it is probable that the two reductive approaches developed by Amgen (Schemes 2, 4 and 5) and the one-pot procedure disclosed by Megafine (Scheme 37) are the best alternatives. Also, several of the academic routes, albeit elegant, have not been fully optimized, so they cannot be compared with those developed in industry. Notwithstanding these caveats, the present review constitutes an instructive example of how generic manufacturers search for novel, non-infringing approaches to an API of interest. Hopefully, new reactions and novel imaginative ideas will provide further approaches to this drug in the coming years.

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References

(1) These authors contributed equally to this work.
(2) Nemeth, E. F.; Van Wagenen, B. C.; Balandrin, M. F. PCT Int. Appl. WO9304373, **1993**; *Chem. Abstr.* **1993**, *119*, 63054.
(3) Locatelli, F.; Pontoriero, G.; Limardo, M.; Tentori, F. *Expert Rev. Endocrinol. Metab.* **2006**, *1*, 167.
(4) (a) Palmer, S. C.; Nistor, I.; Craig, J. C.; Pellegrini, F.; Messa, P.; Tonelli, M.; Covic, A.; Strippoli, G. F. *PLoS Med.* **2013**, *10*, e1001436. (b) Verheyen, N.; Pilz, S.; Eller, K.; Kienreich, K.; Fahrleitner-Pammer, A.; Pieske, B.; Ritz, E.; Tomaschitz, A. *Expert Opin. Pharmacother.* **2013**, *14*, 793.
(5) Catalog suppliers like Aldrich and Acros sell small-scale quantities. Larger quantities are available from BASF, Chiron and Finorga.
(6) Catalog suppliers like Aldrich and Acros sell small-scale quantities. Larger quantities are available, from Central Glass, Indofine and TCI.
(7) Brown, T. H.; Blakemore, R. C.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E.; Rawlings, D. A.; Walker, T. F. *Eur. J. Med. Chem.* **1988**, *23*, 53.
(8) (a) Knoevenagel, E. *Chem. Ber.* **1898**, *31*, 2585. (b) Doebner, O. *Chem. Ber.* **1900**, *33*, 2140. (c) See also references 16a and 24.
(9) (a) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *371*, 397. (b) Beller, M.; Kuehlein, K. *Synlett* **1995**, 441.
(10) Thiel, O. R.; Bernard, C.; Tormos, W.; Brewin, A.; Hirotani, S.; Murakami, K.; Saito, K.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Tetrahedron Lett.* **2008**, *49*, 13.
(11) (a) Padi, P. R.; Akundi, S. P.; Suthrapu, S. K.; Kolla, N. K.; Kotagiri, V. K.; Neelam, U. K.; Baddam, S. R.; Manne, N. PCT Int. Appl. WO2008058235, **2008**; *Chem. Abstr.* **2008**, *148*, 561587. (b) Padi, P. R.; Akundi, S. P.; Suthrapu, S. K.; Kolla, N. K.; Kotagiri, V. K.; Neelam, U. K.; Baddam, S. R.; Manne, N.; Devarakonda, S. N.; Thaimattam, R.; Raghupati, B.; Vasamsetti, S. K. PCT Int. Appl. WO2008058236, **2008**; *Chem. Abstr.* **2008**, *148*, 537933.
(12) Geoghegan, K.; Kelleher, S.; Evans, P. *J. Org. Chem.* **2011**, *76*, 2187.
(13) (a) Wang, X.; Chen, Y.; Crockett, R.; Briones, J.; Yan, T.; Orihuela, C.; Zhi, B.; Ng, J. *Tetrahedron Lett.* **2004**, *45*, 8355. (b) For the synthesis of related impurities, see: Lei, F.; Qu, B.; Li, X.; Guo, L.; Guan, M.; Hai, L.; Jin, H.; Wu, Y. *Synth. Commun.* **2014**, *44*, 2879.
(14) (Sandoz AG), EP 1990333, **2008**; *Chem. Abstr.* **2008**, *149*, 533935.
(15) Srinivasan, C. V.; Johar, P. S.; Wadhwa, L. PCT Int. Appl. WO2008035381, **2008**; *Chem. Abstr.* **2008**, *148*, 379220.
(16) (a) Agarwal, R. M.; Bhirud, S.; Pillai, C. B.; Maloyesh, B. PCT Int. Appl. WO2008117299, **2008**; *Chem. Abstr.* **2007**, *148*, 426540. (b) Bijukumar, G.; Maloyesh, B.; Bhaskar, B. S.; Rajendra, A. *Synth. Commun.* **2008**, *38*, 1512.
(17) Reeves, J. T.; Tan, Z.; Marsini, M. A.; Han, Z. S.; Xu, Y.; Reeves, D. C.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *Adv. Synth. Catal.* **2013**, *355*, 47.
(18) Thiel, O.; Bernard, C.; Larsen, R.; Martinelli, M. J.; Raza, M. T. PCT Int. Appl. WO2009002427, **2009**; *Chem. Abstr.* **2008**, *150*, 98009.
(19) Reddy, S. R. D.; Velivela, S. R.; Rane, D. R.; Punna, S.; Naini, V. Indian Pat. Appl. IN 2013CH02896, **2013**; *Chem. Abstr.* **2015**, *163*, 412018.
(20) Sorribes, I.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2014**, *136*, 14314.
(21) Fu, M.-C.; Cheng, W.-M.; Fu, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 9042.
(22) (a) Divvela, V. N. S. R.; Guntupally, S.; Deekonda, S.; Racha, L.; Ray, U. K.; Islam, A.; Meenakshisunderam, S. PCT Int. Appl. WO2010128388, **2010**; *Chem. Abstr.* **2013**, *159*, 608398. (b) Rao, D. V. N. S.; Lenin, R.; Satheesh, D.; Ray, U. K.; Sivakumaran, M. Indian Pat. Appl. IN 2009CH01069, **2009**; *Chem. Abstr.* **2013**, *161*, 389729. (c) Rao, D. V. N. S.; Lenin, R.; Satheesh, D.; Ray, U. K.; Sivakumaran, M. Indian Pat. Appl. IN 2009CH01070, **2009**; *Chem. Abstr.* **2013**, *161*, 404480. (d) Rao, D. V. N. S.; Lenin, R.; Satheesh, D.; Ray, U. K.; Sivakumaran, M. Indian Pat. Appl. IN 2009CH01071, **2009**; *Chem. Abstr.* **2013**, *161*, 375752.
(23) Shimpi, N.; Bijukumar, G. P.; Nadkami, S. S. Indian Pat. Appl. IN 2009MU00189, **2009**; *Chem. Abstr.* **2010**, *154*, 87954.
(24) Shimpi, N.; Bijukumar, G. P.; Prabhavat, M. D.; Nadkami, S. S. Indian Pat. Appl. IN 2009MU01367, **2009**; *Chem. Abstr.* **2010**, *154*, 409666.
(25) Parthasaradhi Reddy, B.; Rathnakar Reddy, K.; Muralidhara Reddy, D.; Raji Reddy, R.; Mukunda Reddy, J.; Vamsi Krishna, B. PCT Int. Appl. WO2012007954, **2012**; *Chem. Abstr.* **2012**, *156*, 175011.
(26) Aissaoui, H.; Boss, C.; Gude, M.; Koberstein, R.; Sifferlen, T. PCT Int. Appl. WO2007122591, **2007**; *Chem. Abstr.* **2007**, *147*, 502350.
(27) Bhobe, A. M.; Lamture, J. B.; Nair, D. S.; Kulkarni, S. R.. Indian Pat. Appl. IN 2011MU00087, **2011**; *Chem. Abstr.* **2012**, *158*, 11310.
(28) Allegrini, P.; Attolino, E.; Rossi, D. EP2327684, **2011**; *Chem. Abstr.* **2011**, *154*, 614838.
(29) Szekeres, T.; Répási, J.; Szabó, A.; Mangion, B. PCT Int. Appl. WO2008035212, **2008**; *Chem. Abstr.* **2008**, *148*, 402864.
(30) (a) Chavakula, R.; Mutyala, N. R.; Chennupati, S. R. *J. Indian Chem. Soc.* **2013**, *90*, 1259. (b) Narayana, R. M.; Ramadas, C.; Srinivasa, R. C.; Sandeep, G. PCT Int. Appl. WO2014016847, **2014**; *Chem. Abstr.* **2014**, *160*, 264927.
(31) Gupta, N.; Khairnar, P. K. K.; Lunagariya, J.; Kumar, P.; Dubey, S. K. Indian Pat. Appl. IN 2008DE02268, **2008**; *Chem. Abstr.* **2010**, *153*, 286719.
(32) Lednicer, D.; Emmery, D. E. *J. Med. Chem.* **1968**, *11*, 1258.
(33) Ferrari, M.; Ghezzi, M.; Bonaldi, M. PCT Int. Appl. WO2009153814, **2009**; *Chem. Abstr.* **2009**, *152*, 74740.
(34) Sebastian, S.; Peri, S. R. S.; Ramamurthy, K.; Pradhan, N. S. PCT Int. Appl. WO2010067204, **2010**; *Chem. Abstr.* **2010**, *153*, 97594.
(35) Veerappan, V.; Sankareswaran, S.; Viswanathan, S. K. R.; Sakthivelmurugan, S. PCT Int. Appl. WO2014020574, **2014**; *Chem. Abstr.* **2014**, *160*, 278695.
(36) (a) Nemeth, E. F.; Van Wagenen, B. C.; Balandrin, M. F.; Delmar, E. G.; Moe, S. T. PCT Int. Appl. WO9511221, **1995**; *Chem. Abstr.* **1996**, *125*, 142305. (b) Van Wagenen, B. C.; Moe, S. T.; Balandrin, M. F.; Delmar, E. G.; Nemeth, E. F. PCT Int. Appl. WO9612697, **1996**; *Chem. Abstr.* **1996**, *125*, 142305.
(37) Sinore, S.; Shah, C.; Jagtap, A.; Roy, M.; Hariharan, S. Indian Pat. Appl. IN 2012MU03068, **2012**; *Chem. Abstr.* **2014**, *162*, 287140.
(38) Kumar, N. U.; Reddy, B. S.; Reddy, V. P.; Bandichhor, R. *Tetrahedron Lett.* **2012**, *52*, 4354.

(39) Rai, V. C.; Naithani, P. K.; Merwade, A. Y.; Deo, K. Indian Pat. Appl. IN 2012MU03420, **2012**; *Chem. Abstr.* **2014**, *162*, 326943.
(40) Wang, G.; Chen, C.; Du, T.; Zhong, W. *Adv. Synth. Catal.* **2014**, *356*, 1747.
(41) Szekeres, T.; Répási, J.; Szabó, A.; Benito, M.; Mangion, B. PCT Int. Appl. WO2008068625, **2008**; *Chem. Abstr.* **2008**, *149*, 38959.
(42) Mangion, B. PCT Int. Appl. WO2009039241, **2009**; *Chem. Abstr.* **2009**, *150*, 359931.
(43) Chavakula, R.; Mutyala, N. R.; Chennupati, S. R. *J. Indian Chem. Soc.* **2013**, *90*, 2291.
(44) Dwivedi, S. P. D.; Prasad, A.; Desai, J. A.; Naik, A. V. PCT Int. Appl. WO2014178068, **2014**; *Chem. Abstr.* **2014**, *161*, 698287.
(45) Barniol-Xicota, M.; Turcu, A. L.; Codony, S.; Escolano, C.; Vázquez, S. *Tetrahedron Lett.* **2014**, *55*, 2548.
(46) (a) Guérin, C.; Bellosta, V.; Guillamot, G.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 2990. (b) Lifshitz-Liron, R.; Raizi, Y.; Ramaty, R. PCT Int. Appl. WO2006127932, **2006**; *Chem. Abstr.* **2006**, *146*, 27637.
(47) Gome, B.; Levenfeld, L. PCT Int. Appl. WO2008063645, **2008**; *Chem. Abstr.* **2008**, *148*, 568869.
(48) (a) Kankan, R. N.; Rao, D. R.; Birari, D. R. PCT Int. Appl. WO2010100429, **2010**; *Chem. Abstr.* **2010**, *153*, 382679. (b) Another of Cipla's patents discloses similar procedures but using racemic intermediates: Rao, D. R.; Kankan, R. N.; Birari, D. R. PCT Int. Appl. WO2010010359, **2010**; *Chem. Abstr.* **2010**, *152*, 191790.
(49) Xu, M.; Yue, H.; Min, Z. US Pat. Appl. Publ. US20150080608, **2015**; *Chem. Abstr.* **2015**, *162*, 437916.
(50) O'Hagan and co-workers have used this approach for the synthesis of two fluorinated analogues of cinacalcet, see: Chia, P. W.; Brennan, S. C.; Slawin, A. M. Z.; Riccardi, D.; O'Hagan, D. *Org. Biomol. Chem.* **2012**, *10*, 7922; see section 5 for details.
(51) Chidambaram, V. S.; Johar, P. S.; Prajapaty, R.; Sharma, E.; Wadhwa, L. PCT Int. Appl. WO2010004588, **2010**; *Chem. Abstr.* **2010**, *152*, 144330.
(52) Arava, V. R.; Gorentla, L.; Dubey, P. K. *Beilstein J. Org. Chem.* **2012**, *8*, 1366.
(53) Jiang, X.; Chu, L.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 1251.
(54) Mukhtar, S.; Nair, D. S.; Medhane, R. R.; Maheshwari, N.; Tewari, N.; Prasad, M. PCT Int. Appl. WO2011033473, **2011**; *Chem. Abstr.* **2011**, *154*, 360701.
(55) Tewari, N.; Maheshwari, N.; Medhane, R.; Nizar, H.; Prasad, M. *Org. Process Res. Dev.* **2012**, *16*, 1566.
(56) Allegrini, P.; Attolino, E.; Rossi, D. EP2022777, **2009**; *Chem. Abstr.* **2008**, *150*, 77352.
(57) (a) Vlasakova, R.; Hajicek, J. PCT Int. Appl. WO2013075679, **2013**; *Chem. Abstr.* **2013**, *159*, 42445. (b) For a possible mechanism for this reaction, see: Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943.
(58) Prediger, P.; da Silva, A. R.; Correia, C. R. D. *Tetrahedron* **2014**, *70*, 3333.
(59) Lifshitz-Liron, R. PCT Int. Appl. WO2007127449, **2007**; *Chem. Abstr.* **2007**, *147*, 502111.
(60) Goodman, C. A.; Janci, E. M.; Onwodi, O.; Simpson, C. C.; Hamaker, C. G.; Hitchcock, S. R. *Tetrahedron Lett.* **2015**, *56*, 4468.
(61) (a) Catozzi, N.; Foletto, J.; Forcato, M.; Giovanetti, R.; Soriato, G.; Verzini, M. PCT Int. Appl. WO2010049293, **2010**; *Chem. Abstr.* **2010**, *152*, 525525. (b) Catozzi, N.; Cotarca, L.; Foletto, J.; Forcato, M.; Giovanetti, R.; Soriato, G. PCT Int. Appl. WO2010094674, **2010**; *Chem. Abstr.* **2010**, *153*, 358731. (c) Catozzi, N.; Cotarca, L.; Foletto, J.; Forcato, M.; Giovanetti, R.; Soriato, G.; Verzini, M. PCT Int. Appl. WO2011029833, **2011**; *Chem. Abstr.* **2011**, *154*, 360700.
(62) (a) Mathad, V. T.; Niphade, N. C.; Shinde, G. B.; Ippar, S. S.; Deshmukh, S. P.; Panchangam, R. K. PCT Int. Appl. WO2010103531, **2010**; *Chem. Abstr.* **2010**, *153*, 431072. (b) Shinde, G. B.; Niphade, N. C.; Deshmukh, S. P.; Toche, R. B.; Mathad, V. T. *Org. Process Res. Dev.* **2011**, *15*, 455.
(63) Schneider, J.-M.; Madec, J.; Kreimerman, S.; Guillamot, G. PCT Int. Appl. WO2014037563, **2014**; *Chem. Abstr.* **2014**, *160*, 427611.
(64) For a very recent review on the preparation and utility of the pentafluorosylfanyl group in organic compounds, see: Savoie, P. R.; Welch, J. T. *Chem. Rev.* **2015**, *115*, 1130.