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Practical synthesis of the calcimimetic agent, cinacalcet

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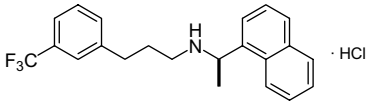
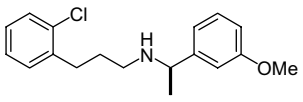
Abstract—A practical synthesis of cinacalcet (Sensipar®, Mimpara®) is described. The synthesis starts from readily available starting materials and relies on safe and practical reaction conditions. The sequence comprises three synthetic steps and only one isolation point. The overall yield for the sequence is 85%.

Cinacalcet HCl (AMG 073, Sensipar®, Mimpara®) **1**, a selective calcimimetic agent, acts on the calcium-sensing receptor of the parathyroid, the principal negative regulator of parathyroid hormone release, to increase its sensitivity to activation by extracellular calcium, thus decreasing parathyroid hormone.[1] Cinacalcet is effective in the clinical setting, and is approved for the treatment of secondary hyperthyroidism in patients with chronic kidney disease on dialysis, and for the treatment of elevated calcium levels in patients with parathyroid carcinoma.

Cinacalcet **1** and R-568 **2** (Fig. 1) are structurally related type II calcimimetics.[2] The original synthetic approaches for these types of compounds rely on various reductive amination approaches. Condensation of an aromatic ketone with the suitable 3-aryl propylamine followed by reduction with sodium cyanoborohydride requires resolution of the racemic product, generally achieved by chiral HPLC separation. Alternatively a chiral arylethylamine can be condensed with a 3-arylpropionaldehyde followed by reduction to afford the enantiomerically pure compounds (Scheme 1). Several alternative approaches to R-568 **2** have also been described over recent years. VanWagenen and co-workers used a one-pot reduction–transimination–reduction protocol to obtain **2** directly from 3-(2-chlorophenyl)propionitrile and (*R*)-1-(3-methoxyphenyl)ethylamine.[3] Buchwald and Hansen reported a titanium-catalyzed asymmetric hydrosilylation of an imine for the synthesis of **2**.[4] Kibayashi and co-workers used an auxiliary based approach for the synthesis of (*R*)-1-(3-methoxyphenyl)ethylamine, further functionalization by DCC-mediated peptide coupling with 3-(2-chlorophenyl)propionic acid, followed by reduction with DIBAL afforded **2** in acceptable yield (68%).[5] Herein, we disclose an alternative and practical, atom-economical synthesis of **1**, which relies exclusively on readily available starting materials.



Cinacalcet **1**



R-568 **2**

Figure 1. Type II calcimimetics.

Retrosynthetically, the target compound **1** is divided into the building blocks (*R*)-1-(1-naphthyl)ethylamine (**3**) and 3-(trifluoromethyl)cinnamic acid (**4**) (Scheme 2). The chiral amine **3** is readily accessed through classical or enzymatic resolution of the racemic precursor.[6]

3-(Trifluoromethyl)cinnamic acid (**4**) is also commercially available.[7] It is derived from 3-trifluoromethylbenzaldehyde by Perkin condensation with acetic anhydride/sodium acetate[8] or Knoevenagel–Doebner condensation with malonate/acetic acid/piperidine.[9]

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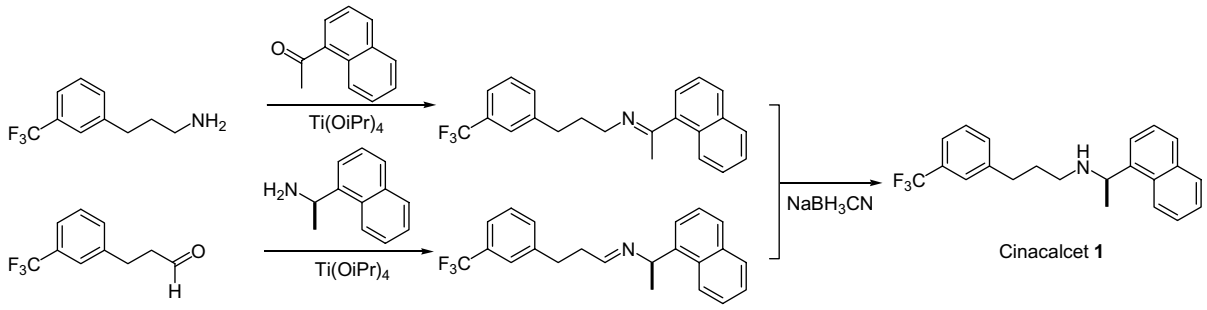
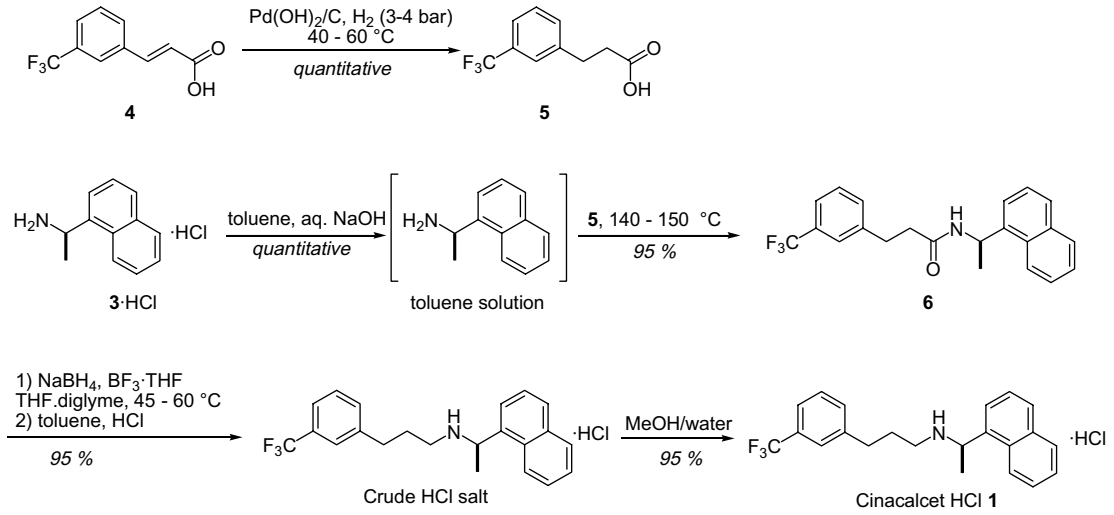


Scheme 1. Discovery route to cinacalcet **1**.



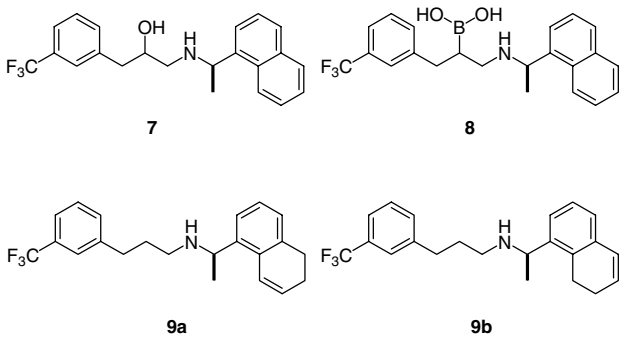
Scheme 2. Practical synthesis of cinacalcet **1**.

Alternatively, this cinnamic acid may be accessed by Heck reaction of a 3-trifluoromethylarylhalide with acrylic acid.[10]

The synthetic sequence to cinacalcet **1** starts with hydrogenation of 3-(trifluoromethyl)cinnamic acid (**4**) in the presence of palladium hydroxide (20 wt% on carbon) under moderate hydrogen pressure (40–60 psi). A solvent survey concludes that rapid conversions (2 h at ambient temperature) are observed with primary alcohols (methanol or ethanol) as solvent, but the formation of alkyl ester byproducts is problematic. This side reaction can be suppressed using isopropanol as solvent, but slower reaction rates are observed (>12 h for full conversion). Diglyme or xylenes are suitable alternatives for this hydrogenation, but these solvents lead to lower reaction rates in the second synthetic step. Ultimately toluene was chosen as an ideal solvent for this hydrogenation, where a declination in the reaction rate was compensated for by an increase in the reaction temperature. Complete conversion is accomplished at 50 °C within 1–3 h. After catalyst filtration the crude product can be used directly in the next reaction.

A variety of conditions could be suitable for the coupling of 3-(3-trifluoromethylphenyl)-propionic acid (**5**) with (*R*)-1-(1-naphthyl)ethylamine (**3**) to the amide. Although activation of the acid via an acid chloride or with peptide coupling reagents are typical methods, the most atom-economical process for the preparation of an amide is the direct condensation of a carboxylic acid with an amine.[11] The coupling was successfully performed by heating an equimolar mixture of (*R*)-1-(1-naphthyl)ethylamine (**3**) and 3-(3-trifluoromethylphenyl)-propionic acid (**5**) in the absence of solvent to 140–150 °C. The water formed is removed by continuous distillation. The key to this reaction is the amide remains liquid throughout the condensation. A clean reaction profile is observed despite the rather forcing conditions employed. The addition of a solvent (DMF, diglyme, xylenes) and the use of acidic (Amberlite IR-120, methane sulfonic acid) or basic promoters (sodium methoxide) offered no significant improvement. After extractive removal of low residual staring materials by aqueous basic and acidic washes, the crude amide (95% solution yield, >99% HPLC purity) was used directly in the subsequent reaction.

During the scale-up of the amide coupling reaction it was noted that the free amine (*R*)-1-(1-naphthyl)ethylamine (**3**) is sensitive to oxidation and carbonate formation when exposed to air. To address this potential stability issue, (*R*)-1-(1-naphthyl)ethylamine hydrochloride can be used as alternative form of the starting material. It is a stable, crystalline non-hygroscopic salt, and can be conveniently converted in quantitative yield to



Scheme 3. Impurities in the amide reduction.

the free base by treatment of a toluene solution with aq sodium hydroxide (20%). A solution of the amine is then mixed with a solution of the dihydrocinnamate. Distillative removal of the toluene is followed by direct condensation to the amide.

The key step of this synthetic sequence to **1** is the reduction of amide **6** to the corresponding amine. This reaction was investigated with lithium aluminum hydride or borane as reducing agents. The former led to the formation of significant amounts (up to 30%) of unidentified impurities. 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 the two impurities **7** and **8** in low quantities (Scheme 3).[12] Fortuitously, these side products were not observed when boron trifluoride was used as the acid source under anhydrous conditions. In the optimized process the reaction is carried out by the addition of boron trifluoride–THF to sodium borohydride in a mixture of diglyme/THF at 45–60 °C. After complete conversion the resulting amine–borane complex is hydrolyzed by the addition of water. The organic solvents are removed by vacuum distillation. The crude product is extracted into toluene, followed by washes of the organic phase with aq sodium hydroxide and water. The product is isolated by the formation of the HCl salt from a mixture of toluene and heptane. Two impurities **9a** and **9b** arising from reduction of the naphthalene substituent were observed in low levels (<0.1%). The structures of these impurities were established by independent synthesis.[13] The crude HCl salt of cinacalcet can be recrystallized from aqueous methanol to obtain material of very high purity (>99.5%).

In summary a short, atom-economical and highly efficient approach to cinacalcet was developed. The starting materials are readily available and the sequence involves only three synthetic steps with an overall yield of 85%. Only a single isolation and one recrystallization are necessary to obtain the material in high purity. This synthesis allows convenient access to kilogram quantities of cinacalcet.

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