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Synthesis of Cinacalcet congeners

Xin Wang,* Ying Chen, Richard Crockett, Jorge Briones, Tony Yan, Carlos Orihuela, Benxin Zhi and John Ng

Chemical Process Research & Development, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA

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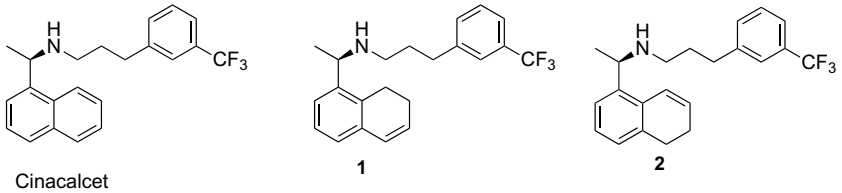
Abstract—Two racemic isomeric dihydronaphthalenes **1** and **2** were prepared from commercially available 5-hydroxytetralone in five linear steps. A key palladium-catalyzed double bond migration led to the synthesis of both isomers from the same starting material. Preparative chiral HPLC separation provided the enantiomerically pure materials. An asymmetric synthesis employing CBS reduction to furnish **1** was also developed.

During the late phase manufacturing studies of Cinacalcet,[1] low levels (<0.1%) of two new isomeric dihydronaphthalene related substances **1** and **2** were discovered (Scheme 1). Their structures have been assigned based on NMR spectroscopic studies of a small sample isolated by preparative HPLC from the original drug substance. To further establish the structural assignment, we prepared these two impurities via an unambiguous total synthesis approach.

Based on retro-synthetic analysis, we decided to take advantage of the commercially available 5-hydroxytetralone[2] (**3**). Our first approach relies on a key carbon–carbon bond formation as reported by Vogl and Buchwald,[3] in which monoarylation of nitroalkane was catalyzed by palladium (Scheme 2). Although this reference reported alkylation with aryl bromide substrates, our aryl triflate was unfortunately not a suitable partner for this type of coupling. We observed no desired product **5** under the reported Buchwald reaction conditions or slight variations. Through subsequent communication with Professor Buchwald, it was confirmed that similar observations were reported in their laboratories.

Our second approach also utilized 5-hydroxytetralone (**3**), which was first reduced with $NaBH_4$ to the alcohol **6** in 93% yield (Scheme 3). Formation of the bis-triflate and the elimination step were carried out in one pot using 2 equiv of triflic anhydride and Et_3N in CH_2Cl_2 to give the triflate **7** in overall 46% yield. The reaction conversions were nearly quantitative, but the low isolated yield is attributed to partial decomposition of the triflate **7**[4] during silica gel chromatography purification. The triflate **7** was converted to a mixture of two isomeric enol vinyl ethers **8a/b** via a Heck coupling protocol.[5] The partial double bond shift is not entirely surprising and similar examples have been precedented.[6] The Heck



Scheme 1.

Keywords: Dihydronaphthalene; Double bond migration; Cinacalcet.
* Corresponding author. Tel.: +1 805 447 6522; fax: +1 805 375 8753; e-mail: xinw@amgen.com

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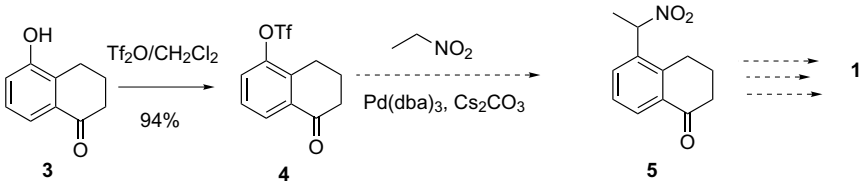
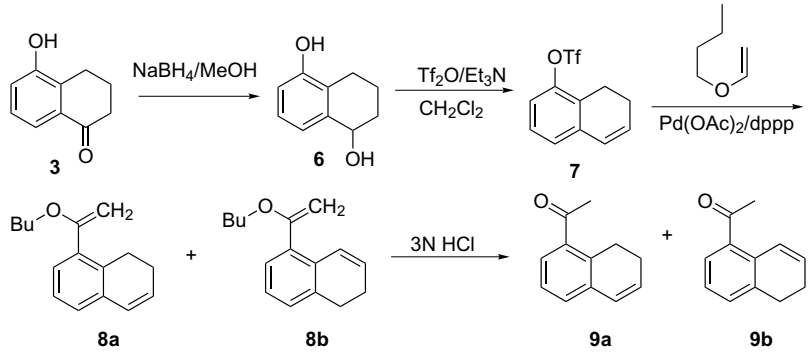


Scheme 2.

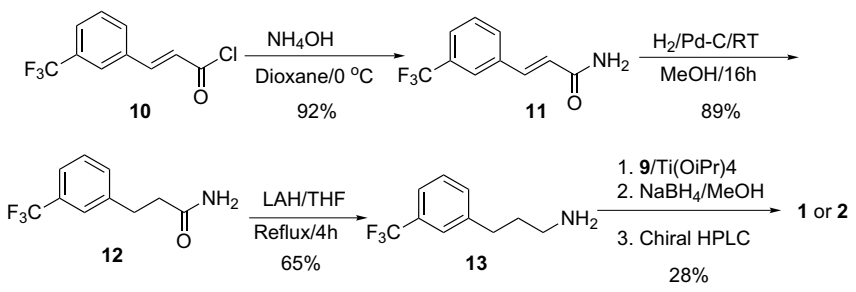


Scheme 3.

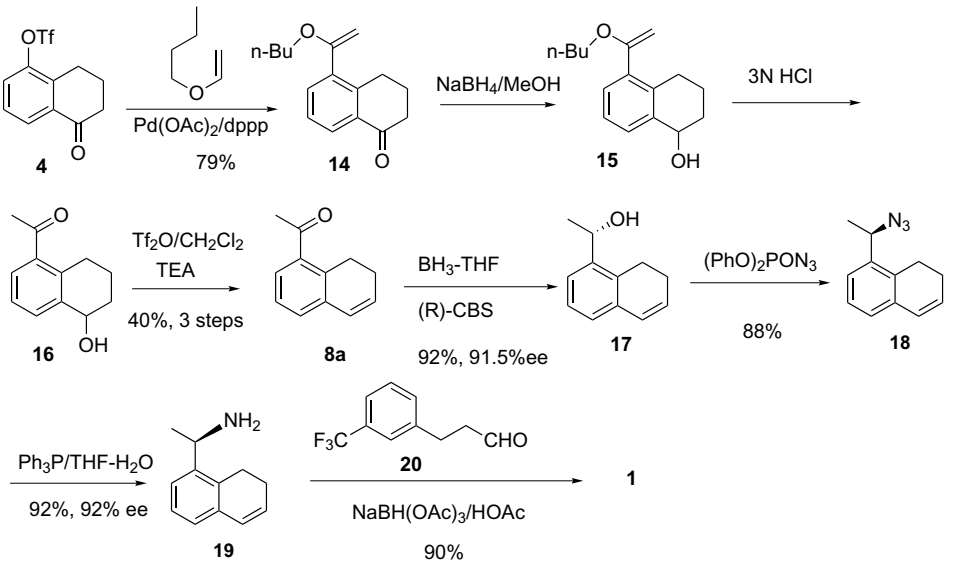
reaction required 16 h to complete, at which time the ratio of two isomers (**8a**:**8b**) was 6:1. This mixture was treated with HCl to afford the ketones **9a** and **9b**. The isolated yield for the ketone **9a** was 67% after preparative HPLC isolation. However, when the Heck reaction time was increased to 48 h, we believe the thermodynamic equilibrium ratio of two isomers (**8a**:**8b**) was terminal at 1.7:1. After the hydrolysis with HCl and the preparative HPLC separation, the ketone **9b** was obtained in 30% yield over two steps.[7]

The amino component was accessed via commercially available *trans*-3-(trifluoromethyl)-cinnamoyl chloride (**10**), which was treated with NH_4OH/dioxane to give the desired amide **11** in 92% yield (Scheme 4). The double bond was hydrogenated in 89% yield, and LAH reduced the amide **12** to afford the amine **13** in 65% yield. The direct reductive amination of **9** with **13** was sluggish due to the low reactivity of aryl methyl ketone **9**. Therefore, a stepwise reductive amination was employed. The amine **13** and the ketone **9** were mixed in neat $Ti(OiPr)_4$ overnight and the resulting imine was reduced by $NaBH_4$ in MeOH to give the desired products racemic **1** and racemic **2** from **9a** and **9b**, respectively, in 56% isolated yield. Finally, preparative chiral HPLC separation of **1** and **2** furnished the desired enantiomerically pure (*R*)-isomers, of the same configuration as Cinacalcet. Their spectroscopic data[8] was identical with the compounds isolated from drug substance in every aspect.

An alternative asymmetric synthesis of **1** was also developed to avoid the chiral HPLC purification (Scheme 5). The triflate **4** was subjected to the Heck conditions to afford **14**. HCl hydrolysis of the vinyl ether and ketone reduction followed by elimination produced the ketone **8a**. After much experimental effort with different chiral reducing agents, we found that methyl oxazaborolidine-catalyzed borane reduction[9] (Me-CBS/BH_3 or Me-CBS/catecholborane) was effective for the chiral reduction. Under optimal conditions [(*R*)-Me-CBS (1 equiv), BH_3/THF (1 equiv), toluene], the alcohol **17** was obtained in 92% yield and 91.5% ee.[11] The alcohol **17** was converted to the azide **18** using $(PhO)_2PON_3$[10] in 88% yield, which was then reduced to amine **19** using the conventional Ph_3P conditions in 92% yield and 92% ee. Reductive amination with the aldehyde **20**[12] afforded **1** in 90% yield and 92% ee.[11]



Scheme 4.



Scheme 5.

In summary, we discovered a novel palladium catalyzed double bond migration to afford a mixture of dihydronaphthalene isomers that was conducted in tandem with the key Heck coupling reaction in a single operation. Subsequent reductive amination was developed to afford the target isomers. In parallel, we established an asymmetric synthesis of the desired (*R*)-isomer, to unambiguously correlate the stereochemical assignment.

Acknowledgements

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References and notes

1. Cinacalcet HCl is an oral calcimimetic drug, first in class agent for the treatment of hyperparathyroidism and the preservation of bone density in patients with kidney failure or hypercalcemia due to cancer. Cinacalcet received the FDA approval on March 8, 2004. Franceschini, N.; Joy, M. S.; Kshirsagar, A. *Expert Opin. Invest. Drugs* **2003**, *12*, 1413.
2. 5-Hydroxy-1-tetralone was purchased from Aldrich at 5 g/$124.40.
3. Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106.
4. The crude triflate **7** is not suitable for the next step and needs purification before use.
5. Pendrak, I.; Chambers, P. A. *J. Org. Chem.* **1995**, *60*, 3249.
6. Cruikshank, B. I.; Davies, N. R. *Aust. J. Chem.* **1973**, *26*, 1935, Olefin isomerization can also be catalyzed by other transition metals.
7. The two isomers were separated by preparative HPLC. Column = X-terra C-18 RP, 10 μ; column size = 5 cm × 30 cm; particle size = 10 μ; wavelength = 220 nm; cycle time/per cycle = 20 min; total separation time for each injection = 80 min; sample loading/per injection: 0.55 g; mobile phase = 45/55/MeCN/H_2O; temperature = 25 °C; sample concentration = 22 mg/mL; injection volume = 25 mL; flow rate = 120 mL/min. Compound **9a**: ^{1}H NMR (300 MHz, $CDCl_3$): 2.25 (2H, dt), 2.57 (3H, s), 3.01 (2H, t), 6.05 (1H, dt), 6.45 (1H, d), 7.12 (1H, d), 7.19 (1H, dd), 7.45 (1H, d). ^{13}C NMR (75 MHz, $CDCl_3$): 23.2, 24.6, 30.4, 125.6, 127.1, 127.3, 127.9, 129.5, 135.3, 135.7, 138.2, 202.8. Compound **9b**: ^{1}H NMR (300 MHz, $CDCl_3$): 2.21 (2H, m), 2.59 (3H, s), 2.79 (1H, t), 6.15 (1H, dt), 7.02 (1H, d), 7.12 (1H, d), 7.19 (1H, dd), 7.45 (1H, d). ^{13}C NMR (75 MHz, $CDCl_3$): 22.3, 28.1, 29.9, 125.6, 127.1, 127.3, 127.9, 129.5, 135.3, 135.7, 138.2, 202.1.
8. Chiral HPLC separation was achieved: Chirobiotic V column 150 × 4.6 mm; wavelength = 260 nm; mobile phase = MeOH/HOAc/TEA 1000/0.2/0.2 (v:v:v); flow rate = 1 mL/min; column temperature = ambient. Compound **1**: ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (1H, s); 7.26 (3H, m); 7.21 (2H, m); 7.0 (1H, d); 6.45 (1H, d); 6.05 (1H, q); 4.59 (1H, m); 2.95 (1H, m); 2.68 (5H, m); 2.25 (2H, m); 1.91 (1H, m); 1.52 (3H, d); ^{13}C NMR (100 MHz, $CDCl_3$): 140.9, 134.8, 133.1, 132.9, 131.7, 130.7, 129.0, 128.8, 127.9, 127.0, 125.1, 125.0, 124.0, 123.2, 53.7, 45.2, 32.6, 27.2, 23.1, 22.9, 20.6. Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (1H, d); 7.43 (1H, s); 7.38 (1H, t); 7.34 (1H, d); 7.32 (1H, d); 7.15 (1H, t); 7.02 (1H, d); 6.84 (1, d); 6.14 (1H, m); 4.16 (1H, q); 2.81 (2H, t); 2.71 (2H, m); 2.55 (2H, m); 2.29 (2H, m); 1.83 (2H, m); 1.35 (3H, d); ^{13}C NMR (100 MHz, $CDCl_3$): 143.5, 140.9, 140.6, 136.5, 132.2, 131.7, 129.7, 129.0, 127.3, 126.5, 124.0, 125.5, 123.9, 123.0, 53.6, 47.5, 33.8, 32.2, 28.9, 23.8, 23.0.
9. For a recent example utilizing a CBS reduction of a ketone on a kilogram scale, see: Duquette, J.; Zhang, M.; Zhu, L.; Reeves, R. S. *Org. Process Res. Dev.* **2003**, *7*, 285.
10. Thompson, A. S.; Humphrey, G. R.; Demarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.

11. Enantiomeric excess of all the relevant compounds was determined by chiral HPLC. Two types of chiral columns were used: OD-H 250 × 4.6 mm or OJ-H 250 × 4.6 mm; mobile phase = hexane/IPA 90/10 or 95/5 (v:v); flow rate = 0.5 mL/min; wavelength = 260 nm; column temperature = ambient.

12. The aldehyde **20** is prepared by the following scheme in good yield: