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Synthesis of NPS R-568 Utilizing Titanium-Catalyzed Asymmetric Hydrosilylation

Marcus C. Hansen and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts, USA 02139

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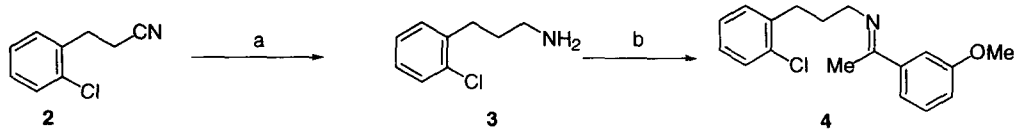
Abstract The enantioselective hydrosilylation of imines catalyzed by an (EBTHI) Ti (EBTHI= ethylene-bis(η^5-tetrahydroindenyl)) species was applied to the synthesis of NPS R-568, an active compound for the treatment of hyperparathyroidism.

Hyperparathyroidism occurs when the parathyroid glands fail to regulate the amount of calcium in the blood stream resulting in elevated calcium levels. Current treatment for this disease involves the surgical removal of one, or more, of the parathyroid glands that are abnormal. Unfortunately, there is currently no method for noninvasive treatment.

Chemotherapy may soon be possible with the discovery of a new class of compounds called calcimimetics. These compounds activate the calcium receptor in the parathyroid gland.[1] A representative of this class of compounds with potent activity is the hydrochloride salt of NPS R-568 (**5**). This compound has been shown to be effective against both primary and secondary hyperparathyroidism and is currently in Phase II clinical trials. The (*R*) isomer is 10 to 100 fold more potent than the corresponding (*S*) isomer.[2] The synthesis of this compound by addition of optically pure 3'-methoxyphenethyl amine to a diisobutylaluminum-imine complex formed from nitrile **2** and DIBAL-H was recently described.[3]

As part of our continued interest in the group 4-catalyzed hydrogenations and hydrosilylations, we recently described an improved asymmetric imine hydrosilylation procedure using air-stable ethylene-bis(tetrahydroindenyl)titanium difluoride ((EBTHI)TiF_2), **1**) as a catalyst precursor.[4] This procedure allows the reduction of imines containing a variety of nitrogen substituents with high enantioselectivity and in high yield. Herein, we report the application of our asymmetric reduction methodology to the synthesis of NPS R-568.

The imine substrate for the asymmetric reduction was synthesized in the two-step sequence shown below. The 2-chlorodehydrocinnamonitrile, **2**, was first reduced with lithium aluminum hydride to yield known amine **3**.[5,6] Condensation of **3** with 3'-methoxy acetophenone gave the desired imine, **4**, as a yellow liquid. Based on our stereochemical model,[7] (*R,R*)-**1** was selected as the precatalyst for the hydrosilylation. Subjecting **4** to our hydrosilylation protocol,[8] using PMHS (polymethylhydrosiloxane) as the stoichiometric reductant, for 17 h and normal workup provided NPS R-568 as a yellow oil in 83% yield. The ee was determined to be 97% by chiral HPLC analysis (Chiracel OD column). That the (*R*) isomer was produced was confirmed by polarimetry.[9]



2 **3** **4**

a: LAH, Et_2O, 30 min, 73% b: 3'-methoxyacetophenone, 5 Å molecular sieves, toluene, reflux 36 h, 51%.

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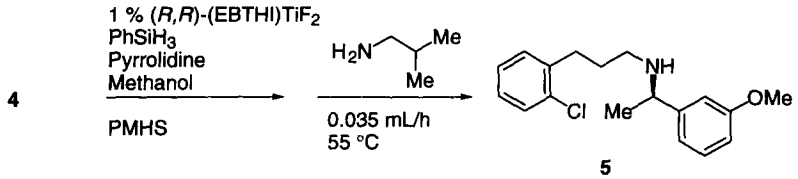

In conclusion, we have applied the (EBTHI) titanium-catalyzed hydrosilylation procedure to the synthesis of the calcimimetic compound NPS R-568 in good yield and with a high enantiomeric excess. Our model for the stereochemical outcome of the reduction correctly predicted that the use of (*R,R*)-**1** would yield (*R*)-**4**. Further applications of this reduction system are currently in progress.

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8. **Experimental Procedure**: Into an oven-dried resealable Schlenk flask was placed (*R,R*)-**1** (8.8 mg, 0.025 mmol). The Schlenk flask was cooled to RT under Ar, then evacuated and backfilled with argon. This cycle was repeated two additional times. THF (1 mL), $PhSiH_3$ (12 μL, 0.1 mmol), pyrrolidine (8 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol) were added sequentially. The Schlenk flask was placed in a 60 °C oil bath until activation of the catalyst occurred as signified by a color change from yellow to green. The Schlenk flask was cooled to RT and additional THF (1 mL) was added along with PMHS (1.8 mL, 30 mmol). The Schlenk flask was sealed and brought into a nitrogen-filled glovebox. The imine **3** (721 mg, 2.4 mmol) was added and the Schlenk flask was placed in a 55 °C oil bath. Isobutylamine (0.6 mL, 6 mmol) was added via syringe pump at a rate of 0.035 mL/h. After 17 h, GC analysis showed that no starting material remained. After cooling, the Schlenk flask was removed from the glovebox and the contents transferred to a 100 mL round bottom flask. Ether (25 mL) and 1 M NaOH (25 mL) were added and the resulting biphasic solution was stirred for 1 h. The layers were separated and the aqueous phase was extracted twice with ether (20 mL). The combined ether layers were dried over $MgSO_4$ and concentrated. Flash chromatography ($CHCl_3$/MeOH) yielded 602 mg (1.99 mmol, 83% yield) of the desired amine with 97% ee. The product was characterized by ^1H and ^{13}C NMR, IR, GC/MS, and EA.

9. Found: $[\alpha]_D$ +38.6 (*c* 1.1, $CHCl_3$) Reported: $[\alpha]_D$ +37.8 (*c* 6.80, $CHCl_3$) Van Wagenen, B. C. Personal Communication.