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# A STEREOSELECTIVE SYNTHESIS OF CYCLOHEXYLNORSTATINE, THE KEY COMPONENT OF A RENIN INHIBITOR

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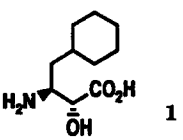
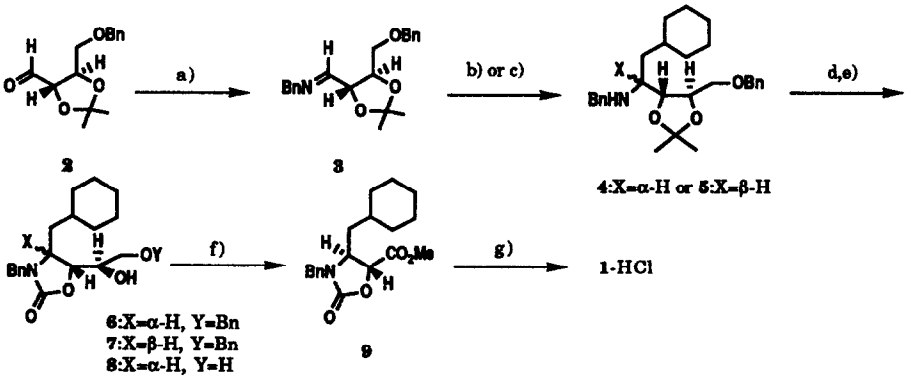
**Abstract**: The title synthesis could be accomplished by employing the novel addition reaction of a Grignard reagent with an imine in the presence of cerium(III) chloride.

Cyclohexylnorstatine [(2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid] (**1**) constitutes the C-terminal moiety of the renin inhibitor currently being developed as a promising antihypertensive agent.[2] We wish to report here a stereoselective synthesis of **1** employing the novel addition reaction of a Grignard reagent with an imine in the presence of cerium(III) chloride as a key step.[3]



**1**

The explored synthetic scheme starts from 4-*O*-benzyl-2,3-isopropylidene-*D*-threose (**2**) readily obtainable from unnatural (2*S*,3*S*)-tartaric acid in 5 steps according to the reported procedure.[4] Condensation of **2** with benzylamine afforded the imine (**3**). Contrary to our expectation, cyclohexylmethylmagnesium bromide was found to undergo no addition reaction with **3**. However, when cyclohexylmethylmagnesium bromide (5.0 equiv.) was first treated with cerium(III) chloride (5.0 equiv.) ($Et_2O$-THF, -30°C, 0.5 h) and the resulting cerium(III) complex was allowed to react with **3** ($Et_2O$-THF, -30°C, 2 h, then, rt, 12 h), the addition reaction proceeded smoothly in a highly stereoselective manner, giving rise to the amine (**4**), $[\alpha]_D^{20}$ +12.3° (c=1.22, $CHCl_3$), as a sole product in 75% yield.[5,6] The $^1$H-NMR spectrum of the crude addition product definitely disclosed the complete absence of the undesired diastereomer (**5**). Being different from the above case, treatment of **3** with cyclohexylmethylcopper(I) in the presence of $BF_3 \cdot Et_2O$ (2.7 equiv.) ($Et_2O$-THF, -78°C, 1 h, then, rt, 15 h),




a) $BnNH_2$ (1.0 equiv.)-anhyd. $MgSO_4$ in PhMe, 0°C, 1.5h, 100% b,c) see text d) i) $ClCO_2Me$-anhyd. $K_2CO_3$ in THF, 0°C, 7h ii) 80% aq AcOH, 80°C, 5h iii) 10% KOH in MeOH, rt, 3.5h, 90% (6) from 4 or 94% (7) from 5 e) $H_2$(1atm)-20% $Pd(OH)_2$/C in MeOH, rt, overnight, 100% f) i) $RuCl_3 \cdot 3H_2O$-$NaIO_4$ in $CCl_4$-MeCN-$H_2O$, rt, 2h ii) $TMSCHN_2$ in PhH-MeOH, rt, 1h, 73% from 8 g) i) NaOH in MeOH-$H_2O$, 90°C, overnight ii) aq HCl iii) $H_2$(1atm)-20% $Pd(OH)_2$/C in MeOH, rt, overnight iv) Dowex AG 50WX2, $H^+$-form v) aq HCl, 76% from 9

gave **5**, $[\alpha]_D^{20}$ +26.7° (c=1.05, $CHCl_3$), as a sole product in 52% yield.[7] The Organocopper(I) reagent could be *in situ* produced from cyclohexylmethylmagnesium bromide (2.7 equive.) and copper(I) iodide (2.7 equiv.) ($Et_2O$-THF, -78°C, 10 min) prior to the addition reaction. The $^1$H-NMR spectrum obviously showed that **5** was not contaminated with **4**. Similar diastereoselective addition reaction of an organocopper(I) reagent with an imine has been reported.[8] The stereochemistries of diastereomeric **4** and **5** could be firmly established at the stages of the oxazolidin-2-one derivatives (**6** and **7**) (*vide infra*).

With **4** in hand, the elaboration of **4** to **1** was next attempted. Thus, methoxycarbonylation of **4** followed by deacetalization and oxazolidin-2-one formation produced **6**, $[\alpha]_D^{20}$ −29.7° (c=1.25, $CHCl_3$). The same sequential treatments of **5** gave **7**, $[\alpha]_D^{20}$ −31.6° (c=0.823, $CHCl_3$). Since the coupling constants of $C_4$- and $C_5$-protons in **6** and **7** were found to be 5.1 and 8.5 Hz (in $C_6D_6$), respectively, (4*S*)- and (4*R*)-configurations could be assigned for **6** and **7**. Based on these spectral features as well as successful synthesis of **1** from **6**, the stereochemistries of **4** and **5** could be rigorously determined as depicted. Hydrogenolysis of **6** gave the well-crystalline diol (**8**), mp 101-102°C and $[\alpha]_D^{20}$ −43.1° (c=0.594, $CHCl_3$). Sequential oxidation of **8** and esterification of the formed acid gave the methyl ester (**9**). This was readily derived to the hydrochloride of **1** (**1**-HCl) by the following five sequential operations; 1) alkaline hydrolysis of **9**, 2) salt formation, 3) hydrogenolysis, 4) removal of inorganic salts with an ion exchange resin, and 5) salt formation. The hydrochloride of **1** (**1**-HCl) obtained as colorless crystals,[9] showed mp 191-192°C (decomp.) and $[\alpha]_D^{20}$ −13.6° (c=0.633, 1M HCl) (lit.[3d], mp 190°C (decomp.) and $[\alpha]_D^{20}$ −12.4° (c=0.482, 1M HCl)).

As mentioned above, we have succeeded in developing a stereoselective synthetic route to **1**. The explored addition reaction of a Grignard reagent with an imine in the presence of cerium(III) chloride may find a wide application in the syntheses of various optically active amines.

**References and Notes**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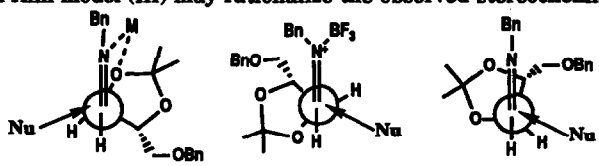
6) Highly stereoselective formation of **4** may be explained by the chelation-controlled mechanism (**i**).
7) The dipolar model (**ii**) or the Felkin-Anh model (**iii**) may rationalize the observed stereochemical feature.
8) M.Wada, The 55th Symposium on Organic Synthesis, Japan, Tokyo, **1989**, June, Abstract p 71.
9) The $^1$H-NMR spectrum (in $D_2O$) cleary disclosed that this sample ($C_2$-H: δ 4.26ppm) was not contaminated with its $C_2$-epimer ($C_2$-H: δ 4.38ppm).[3d]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