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Diastereoselective synthesis of *syn*-aminoalcohols via contributing CH-π interaction: simple synthesis of (−)-bestatin

Byong Won Lee,[a] Jin Hwan Lee,[a] Ki Chang Jang,[a] Jae Eun Kang,[a] Jin Hyo Kim,[a] Ki-Min Park[b] and Ki Hun Park[a,*]

[a]*Division of Applied Life Science (BK21 program), Department of Agricultural Chemistry, Gyeongsang National University, Chinju 660-701, South Korea*

[b]*The Research Institute of Natural Science, Gyeongsang National University, Chinju 660-701, South Korea*

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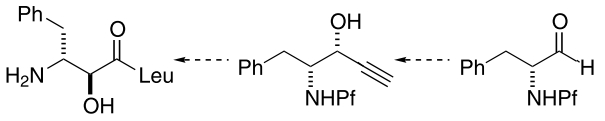
Abstract—^{1}H NMR and X-ray crystallography studies revealed that a CH-π and chelation control in aromatic aminoaldehydes (**1**–**6**) effects a highly diastereoselective addition to afford optically active *syn*-aminoalcohols (**1a**–**6a**). This methodology was applied to the synthesis of (−)-bestatin.

The stereoselective transformation of aromatic α-aminoaldehydes to *syn*-aminoalcohols is attractive synthetic strategy, since aromatic *syn*-α-hydroxy-β-amino acid is a key unit of small peptides (e.g. bestatin, phebestin and probestin) which function as aminopeptidase inhibitor.[1] In the stereoselective transformation of α-aminoaldehydes to aminoalcohols using organometallic reagent, the most frequently used protecting group is benzyl (Bn) group. The benzyl group allowed a high degree of diastereoselectivity in nucleophilic addition of α-aminoaldehydes, but produced an *anti*-aminoalcohols with non-chelating control.[2] Thus, aromatic α-amino acids have been modified by a number of methods[3] such as asymmetric dihydroxylation,[4] Ojimas' ring opening procedure,[5] etc. Our previous work has demonstrated that a diastereoselective addition utilizing the 9-phenylfluoren-9-yl (Pf) group affords *syn*-aminoalcohol.[6] The extension and application of this methodology for the asymmetric synthesis of a *syn*-α-hydroxy-β-amino acid is described herein. We also described the first evidence for a CH-π interaction to contribute a highly diastereoselective addition using NMR technique and X-ray study.



(-)-Bestatin

The requisite substrates (**1**–**10**) were prepared easily by the usual method from commercially available phenylalanine, *p*-nitrophenylalanine, tyrosine, valine, leucine, alanine, and serine. We chose the 9-phenylfluoren-9-yl (Pf) group for protection of amine since this protecting group has been shown to inhibit deprotonation at the α-position of α-aminoaldehyde.[7] α-Aminoaldehydes having the Pf group are stable to Grignard reaction condition.[8]

(*R*)-Phenylalaninal **1** was treated with ethynylmagnesium bromide at −40°C for 10 min to give *syn*-aminoalcohol **1a** as a 9.5:1 ratio in 96% yield via a diastereoselective addition (vida infra). As shown in Table 1, other aromatic α-aminoaldehydes (**2**–**6**) were also exposed to the same reaction conditions to give *syn* products (**2a**–**6a**) in high selectivity and quantitative yields. While, treatments of aliphatic α-aminoaldehydes (**7**–**10**) under same condition afforded a less than 3:1 ratio of the *syn* and *anti* isomers. The above results show that aromatic aminoaldehydes (**1**–**6**) provide much higher selectivity than aliphatic aminoaldehydes (**7**–**10**). Each diastereomeric aminoalcohol given by the Grignard reaction could easily be isolated in pure form by column chromatography. The structures of all aminoalcohols (**1a/b**–**10a/b**) were confirmed by their characteristic spectroscopic data. The relative stereochemistries of the products **1a** and **1b** were determined

Keywords: bestatin; AHPBA; *syn*-aminoalcohol; CH-π interaction; α-hydroxy-β-amino acid.

* Corresponding author. Tel: +82-55-7515472; fax: +82-55-7570178; e-mail: khpark@gshp.gsnu.ac.kr

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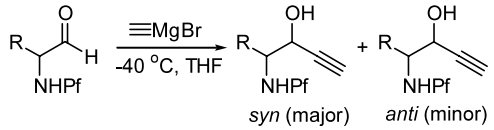
from their ^{1}H NMR spectra based on the coupling constant values and 2D NOE experiments.†

Table 1. Diastereoselective addition of ethynylmagnesium bromide to aminoaldehyde [a]

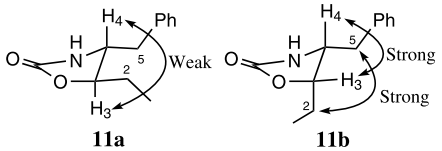


Compound	R	Ratio [b] a/b (*syn*/*anti*) [c]	Yield (%) [d]
1	Benzyl (*R*) [e]	**1a**/**1b** (9.5/1)	96
2	Benzyl (*S*) [f]	**2a**/**2b** (9.7/1)	97
3	4-Methoxybenzyl (*R*)	**3a**/**3b** (9.5/1)	94
4	4-Methoxybenzyl (*S*)	**4a**/**4b** (10/1)	96
5	4-Nitrobenzyl (*R*)	**5a**/**5b** (10/1)	97
6	4-Nitrobenzyl (*S*)	**6a**/**6b** (10/1)	97
7	2-Propyl (*S*)	**7a**/**7b** (1.8/1)	94
8	*iso*-Butyl (*S*)	**8a**/**8b** (2.5/1)	95
9	Methyl (*S*)	**9a**/**9b** (2.2/1)	93
10	Benzyloxymethyl (*S*)	**10a**/**10b** (1.5/1)	94

[a] All aminoaldehydes are enantiomeric pure.
[b] The ratio was defined by ^{1}H NMR spectrum of crude mixture.
[c] The stereochemistry was assigned by 2D-NOE experiment.
[d] Isolated yield.
[e] *R*-configuration.
[f] *S*-configuration.

Reetz reported that *anti*-aminoalcohols were obtained from nucleophilic addition of α-aminoaldehydes protected with Bn group through non-chelating control, due to the steric effect of Bn group.[9] Even though *anti*-aminoalcohols were expected from α-aminoaldehydes protected with Pf because of same reason, *syn*-aminoalcohols were obtained in this study. The *syn*-diastereoselectivity observed in conversion of aromatic aminoaldehydes (**1**–**6**) to aminoalcohols (**1a**–**6a**) may rationalize that the chelation controlled Cram cyclic model[10] is more favorable than the Felkin–Anh transition state model[11] as shown in Figure 1. Why could there not be observed a high selectivity in aliphatic α-aminoaldehydes?

† The compounds **1a** and **1b** were cyclized with carbonyldiimidazole after hydrogenation in Pd/H_2 condition to give **11a** and **11b**, respectively. Based on the coupling constant values in the ^{1}H NMR spectra of cyclized *syn* and *anti* isomers as like **1a**/**1b**, the stereochemistries of *syn* isomer ($J_{3,4}$ = 11–13 Hz) and *anti* isomers ($J_{3,4}$ = 6–8 Hz) could be determined from each coupling constant values.



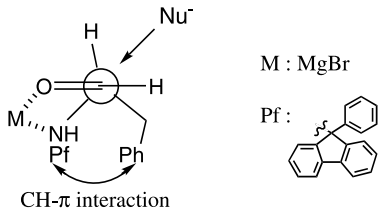


Figure 1. Transition state of diastereoselective addition.

Based on the chemical shifts in ^{1}H NMR spectra, upfield shifts of aromatic region were observed at aromatic α-aminoaldehydes (**1**–**6**) which showed a high selectivity, but were not observed at aliphatic aminoaldehydes (**7**–**10**). As shown in Figure 2, obvious upfield shift[12] appeared at only (d) and expected a CH-π interaction between Pf and nitrophenyl groups. This upfield shift should be caused by a CH-π interaction[13] between both aromatic groups. Furthermore, the structure of Pf-L-Phe-OCH_3 **12** was confirmed by X-ray crystallography‡ as shown in Figure 3. In the crystal structure, the distances which could be considered as typical intramolecular CH-π interactions (3.13–3.45 Å)[14] between benzyl (C20–C25) and Pf group (C2–C7) were observed: H3···centroid 3.00 Å, ∠C3–H3···centroid 117.0°, centroid···centroid 4.58 Å. This CH-π interaction may contribute to chelation control and a high selectivity.

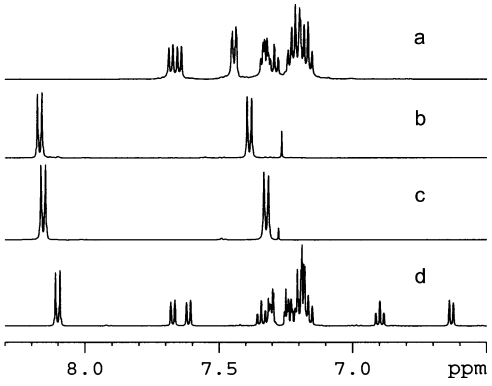


Figure 2. Aromatic region in ^{1}H NMR (500 MHz, $CDCl_3$). (a) N-Pf-Leu-OCH_3; (b) *p*-NO_2-Phe-OCH_3; (c) N-Boc-*p*-NO_2-Phe-OCH_3; (d) N-Pf-*p*-NO_2-Phe-OCH_3.

‡ Crystal data for **12**; $C_{29}H_{25}NO_2$ M = 419.50, orthorhombic, space group $P212121$, a = 7.9757(6), b = 15.4702(12), c = 18.4058(14) Å, U = 2271.0(3) Å^3, Z = 4, μ = 0.076 mm^{-1}, R_{int} = 0.0326. A total of 14347 reflections were measured for the angle range $3.44<2\theta<56.58$ and 5294 independent reflections were used in the refinement. The final parameters were wR_2 = 0.0871 and R_1 = 0.0398 [$I>2\sigma(I)$]. Data were collected on a Bruker SMART diffractometer equipped with a graphite monochromated Mo Kα (λ = 0.71073 Å) radiation source and a CCD detector using the SAINT-NT software.[15] The structures were solved by direct methods and refined by full matrix least-squares against F^2 for all data using the SHELXTL program package.[15] CCDC reference number 200283.

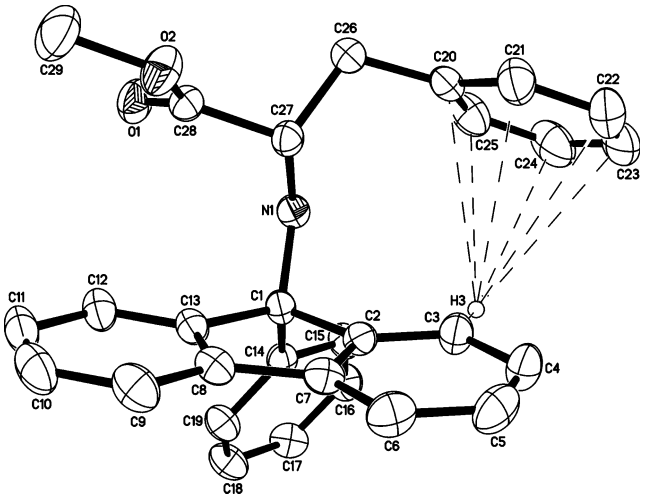
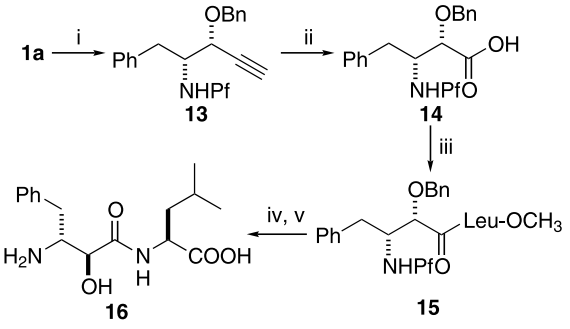


Figure 3. Molecular structure and atomic numbering scheme of **12**. Thermal ellipsoids are drawn at the 30% probability level and the H-atoms omitted for clarity. The dihedral angle between the aromatic planes of benzyl and Pf group (C(2)–C(7)) is 34.41(5)°. Selected H···C distances (Å): H(3)···C(20) 3.22, H(3)···C(21) 3.45, H(3)···C(22) 3.44, H(3)···C(23) 3.29, H(3)···C(24) 3.13, H(3)···C(25) 3.16.

This methodology has been applied to the synthesis of (−)-bestatin **16** which requires the coupling of two structural unit, N-terminal β-amino-α-hydroxy phenylbutanoic acid (AHPBA) and C-terminal amino acid leucine. After protection of hydroxy group in **1a** with BnBr, resulting benzylate was oxidized with $KMnO_4$ to give AHPBA derivative **14** as N-terminal part in 84% yield. The coupling reaction of **14** with (*S*)-leucine methyl ester was carried out in the presence of DCC to afford the dipeptide product **15** in 91% yield. Treatment of **15** with lithium hydroxide followed by exposure of resulting crude acid to H_2 over Pd/C gave (−)-bestatin in 93% yield, which was identical with a previous report (Scheme 1).[1]



Scheme 1. *Reagents and conditions*: (i) BnBr, NaH, Bu_4NI, THF, 0°C, 97%; (ii) $KMnO_4$, HOAc, H_2O, pentane, 87%; (iii) L-Leu-OCH_3, DCC, HOBT, TsOH, Et_3N, THF, 0°C, 91%; (iv) LiOH, THF/H_2O, 0°C, 95%; (v) H_2, Pd/C, MeOH, 50°C, 93%.

To summarize the above results, we developed an efficient method for the preparation of *syn*-aminoalcohol (**1a**–**6a**) from readily available aromatic α-amino acids through chelation control contributed by a CH-π interaction. These species can be easily converted to each corresponding *syn*-α-hydroxy-β-amino acids as key component of small peptide. We have also applied **1a** to enantiomerically pure (−)-bestatin.

Acknowledgements

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