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The *N*-Hydroxymethyl Group for Stereoselective Conjugate Addition: Application to the Synthesis of (−)-Statine

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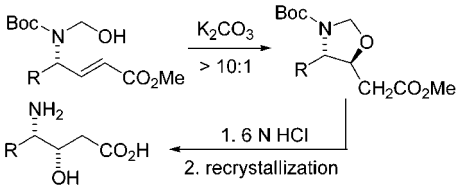
ABSTRACT



Efficient synthesis of enantiomerically pure (−)-statine was achieved with the stereoselective intramolecular conjugate addition of the hydroxyl group tethered to the amino group of a configurationally stable *N*-Boc-L-leucinal derivative.

The *N*-hydroxymethyl group of α-amino aldehydes has been shown to stabilize the labile stereogenic α-carbon by shifting the equilibrium from **1** to **2** (Figure 1).[1]

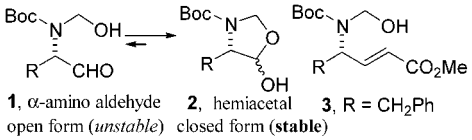


Figure 1. Stabilization of unstable α-amino aldehydes with the *N*-hydroxymethyl group.

The stability of **2** was supported by the successful Wittig reaction to give (*E*)-alkene **3** in refluxing benzene without racemization. We envisioned that the *N*-hydroxymethyl group of **3** could be useful for stereoselective introduction of the *β*-hydroxyl group in natural products such as statine with a *γ*-amino-*β*-hydroxycarboxylic acid moiety.[2,3] We wish to report herein an efficient synthesis of (−)-statine using a stereoselective intramolecular conjugate addition of the *N*-hydroxymethyl group to the α,*β*-unsaturated ester. Statine is a key component of pepstatin, a natural hexapeptide antibiotic isolated by Umezawa and co-workers from various species of actinomyces (Scheme 1).[4] Pepstatin was demonstrated to be a strong inhibitor of aspartic acid proteinases such as pepsin, renin, and cathepsin D.[5] (−)-Statine has

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(2) For a review, see: Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1992**, *33*, 1051.

(3) For recent synthetic studies for statine, see: (a) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292 and references therein. (b) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5593 (c) Veeresha, G.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 5223. (d) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 10419. (e) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 775. (f) Alemany, C.; Bach, J.; Farràs, J.; Garcia, J. *Org. Lett.* **1999**, *1*, 1831. (g) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450. (h) Sengupta, S.; Sarma, D. S. *Tetrahedron: Asymmetry* **1999**, *10*, 4633. (i) Pesenti, C.; Bravo, P.; Corradi, E.; Frigerio, M.; Meille, S. V.; Panzeri, W.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 5637 and references therein. (j) Kwon, S. J.; Ko, S. Y. *Tetrahedron Lett.* **2002**, *43*, 639.

(4) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259. For a review, see: Rich, D. H. In *Proteinase Inhibitors*; Barrett, A. J., Salvesen, G., Eds.; Elsevier: New York, 1986; p 179.

(5) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263.

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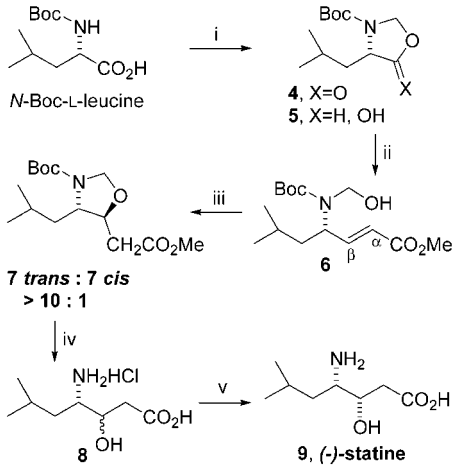
Scheme 1[a]



[a] Reagents and conditions: (i) cat. CSA, $(CH_2O)_n$, PhH, reflux (80%) and then $NaBH_4$, MeOH, 0 °C (85%); (ii) $Ph_3P{=}CHCO_2Me$, PhH, reflux (95%); (iii) K_2CO_3, MeOH, rt (85%); (iv) 6 N HCl, reflux; (v) ion-exchange resin column and then recrystallization (41%).

attracted a lot of interest because of its potential use in the treatment of hypertension and congestive heart failure. Considerable efforts have been devoted to the asymmetric synthesis of statine and its analogues.[3,6−8] However, there has been no successful synthetic study for (−)-statine with conjugate addition of the hydroxyl group, although this method looks conceptually simple and has been utilized with carbohydrates.[9]

A diastereomeric mixture of the L-leucinal derivative **5** was prepared from commercially available *N*-Boc-L-leucine in 68% overall yield in two steps (Scheme 1).[1] However, the $NaBH_4$ reduction[10] of **4** was employed in the present study to give higher yield (85%) of **5** because the reduction with DIBALH resulted in lower yield (75%). The Wittig olefination of **5** with the stabilized ylide afforded the desired (*E*)-γ-amino-α,β-conjugated ester **6** with the *N*-hydroxymethyl group in excellent yield and selectivity. No (*Z*)-alkene was detectable, and the *N*-hydroxymethyl group was stable under the reaction conditions. We were gratified that an intramolecular conjugate addition of the hydroxyl group of **6** was successful to give the expected cyclized product, oxazolidine **7**. The *N*-hydroxymethyl group was removed under similar conditions in the previous report.[1] It seems that the intramolecular addition is much faster here than the dehydroxymethylation. The initial reaction with KOH (1.0 equiv) as base showed moderate selectivity (about 5:1) for the desired *trans* diastereomer of **7**.

The optimal conditions for **7** ***trans*** in the cyclization step were then explored. The effects of the amount of base, the concentration of **6**, and the type of base on the diastereoselectivity of the conjugate addition were examined, and the results are shown in Tables 1 and 2. First, the effect of the amount of KOH was examined under constant concentration of **6** (0.33 M in MeOH). The results in Table 1 (entries 1, 2, and 4) indicate that increase of the amount of KOH gives better selectivity. The conjugate addition with KOH was usually complete within 30 min at room temperature. Next, the effect of concentration of **6** was investigated (entries 3−6). In all cases, 1 equiv of KOH was used. Increase of the reaction concentration produces better selectivities. However, the yield of the ester product is low at higher concentration (entry 6) because the ester is partially hydrolyzed to give the corresponding carboxylic acid as a byproduct.

Table 1. Effect of Amount of KOH and Concentration of Substrate **6** on Diastereoselectivity

entry	KOH (equiv)	concn of **6** (M)	ratio (**7** ***trans***:**7** ***cis***)[a]	yield (%)
1	0.1	0.33	2.5:1	82
2	0.5	0.33	5.6:1	95
3	1.0	0.10	3.8:1	88
4	1.0	0.33	8.0:1	85
5	1.0	0.44	9.6:1	86
6	1.0	1.00	10.4:1	57

[a] The ratio was determined by GC.

Table 2. Effect of Type of Base on Diastereoselectivity

entry	base[a]	reaction time (h)	ratio (**7** ***trans***:**7** ***cis***)[b]	yield (%)
1	Et_3N	20	1.7:1	88
2	DBU	1	4.3:1	87
3	$NaHCO_3$	60	2.1:1	83
4	K_2CO_3	1	10.7:1	85
5	NaOH	0.5	10.5:1	54
6	KOH	0.5	10.4:1	57

[a] One equivalent of base was used with 1.0 M of **6**. [b] The ratio was determined by GC.

To alleviate the problem of partial hydrolysis at higher concentration, we have conducted the conjugate addition with several weaker bases at 1.0 M concentration of **6** in MeOH (Table 2). The best diastereoselectivity was attained with K_2CO_3, and the yield was satisfactory, too (entry 4). Although NaOH gave selectivity comparable to that of KOH, the same

(6) (a) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248. (b) D'Aniello, F.; Mann, A.; Matii, D.; Taddei, M. *J. Org. Chem.* **1994**, *59*, 3762 and references therein.

(7) (a) Kessler, H.; Schudok, M. *Synthesis* **1990**, 457. (b) Kazmaier, U.; Krebs, A. *Tetrahedron Lett.* **1999**, *40*, 479.

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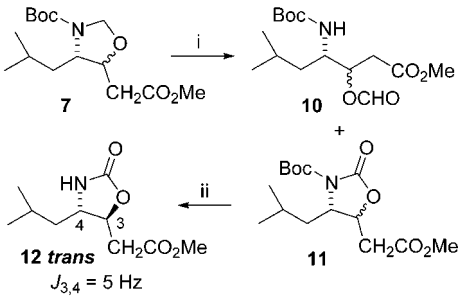
partial hydrolysis problem occurred (entry 5). Other weaker bases showed poor to low diastereoselectivity (entries 1−3), although the yields were very good. The efforts to improve the *trans* selectivity by equilibration of the diastereomeric mixture were fruitless under either acidic or basic conditions.

The configuration at the newly generated stereogenic center was determined with measurement of the vicinal coupling constant between the protons at C-3 and C-4 (Scheme 2). A diastereomeric mixture of the conjugate

Scheme 2[a]



[a] Reagents and conditions: (i) cat. $RuCl_3$, $NaIO_4$ (86%); (ii) TFA, CH_2Cl_2 (90%).

addition product **7** was converted to the known oxazolidinone **12** as follows. First, the ruthenium-catalyzed oxidation reaction of the *N*,*O*-methylene group gave a mixture of the desired oxazolidinone **11** and the *O*-formyl statine derivative **10** in about 1:1.7 ratio.[11] Then, the Boc protecting group of **11** was removed with trifluoroacetic acid (TFA) to afford **12**. The ^{1}H NMR analysis of the major diastereomer of **12** showed a $J_{3,4}$ of 5.0 Hz, which is the same as the reported value for the *trans* oxazolidinone. That of the minor isomer was 7.7 Hz, which is comparable with the literature value for the *cis* isomer of **12** (8 Hz).[12]

The diastereoselection observed here can be explained with the more favorable H-eclipsed allylic conformation (Figure 2).[13] The attack by the hydroxyl group on the same side of

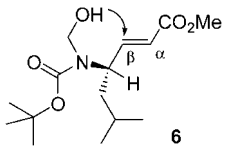


Figure 2. Favored conformation for the major product.

the amino group to the double bond would result in the *trans* product. The higher selectivity (13.7:1) for **7** ***trans*** was in fact observed with the (*Z*)-isomer of **6**.[14]

The synthesis of (−)-statine (**9**) was completed with hydrolysis of the diastereomeric mixture **7** followed by ion-exchange resin chromatography according to the literature procedure.[15] Only the desired isomer was isolated from the mixture of the two diastereomers after recrystallization in 41% yield. Overall, enantiomerically pure (−)-statine was prepared from *N*-Boc-L-leucine in five steps in more than 20% yield.[16]

In summary, we have shown the efficient synthesis of enantiomerically pure (−)-statine **9** via the stereoselective intramolecular conjugate addition of the *N*-hydroxymethyl group. The *N*-hydroxymethyl group has also been used for stabilization of the labile α-amino aldehyde. The method reported in the present study should be valuable for efficient synthesis of other pharmaceutically important γ-amino-β-hydroxycarboxylic acids with different side chains such as cyclohexylstatine, 4-amino-3-hydroxy-4-phenylbutanoic acid (AHPBA), and 4-amino-3-hydroxy-4-phenylpentanoic acid (AHPPA).[3d,g]

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Supporting Information Available: Experimental procedures and characterization data for compounds **4**−**7** and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Misiti, D.; Zappia, G. *Tetrahedron Lett.* **1990**, *31*, 7359. The same coupling constant of 5.0 Hz for the *trans* isomer was observed between the protons at C-3 and C-4 of the *trans* isomer of **12** prepared independently from (−)-statine in the present study (see below) by esterification and the following carbonylation.

(13) (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(14) The (*Z*)-isomer of **6** was selectively prepared with the Wittig olefination of **5** using $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ and 18-crown-6 with KHMDS according to: Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(15) Takemoto, Y.; Matsumoto, T.; Ito, Y.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2425.

(16) Characterization data for (−)-statine: the NMR (^{1}H and ^{13}C), $[\alpha]_D$, and mass data were identical with those in the literature.[15] HRMS (CI) calcd for $C_8H_{18}O_3N$ 176.1286 ($[M + 1]^+$), found 176.1280.