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DIASTEREOSPECIFIC SYNTHESIS OF (-)-STATINE

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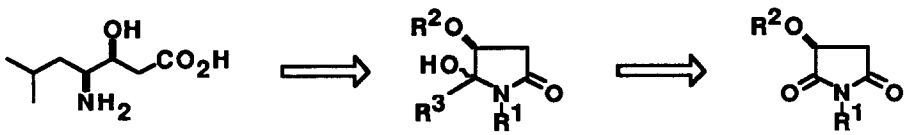
Summary: Reductive deoxygenation at quarternary α-carbon of α-hydroxy lactam was found to proceed under mild condition. Making an advantage of this procedure, (-)-statine was synthesized from *L*-malic acid in a diastereospecific manner.

(-)-Statine (**1**), an unusual amino acid component of pepstatine[1] is known as a key unit for the inhibitory activity of the aspartyl protease such as renin.[2] Because of the increasing interest in a renin inhibitor for an antihypertensive agent, statine and its analogues have been synthesized with excellent procedures.[3] Most of those methods deal with a construction of a β-amino alcohol structure whose stereochemistry is important for biological activity. We chose, as an appropriate starting chiron having a β-amino alcohol equivalent, the malimide (**2**) which was easily derivable from *L*-malic acid.[4] Although alkylation of an imide such as **2** has been known,[4,5] no reductive deoxygenation at the quarternary carbon center of the *N*-acylaminal represented as the α-hydroxy lactam (**3**) has been successful for a practical use. In this paper, we report a concise synthesis of (-)-statine (**1**) which relies on an efficient and chirospecific reduction of aminal carbon center in the lactam (**3a**) as illustrated in scheme 2.

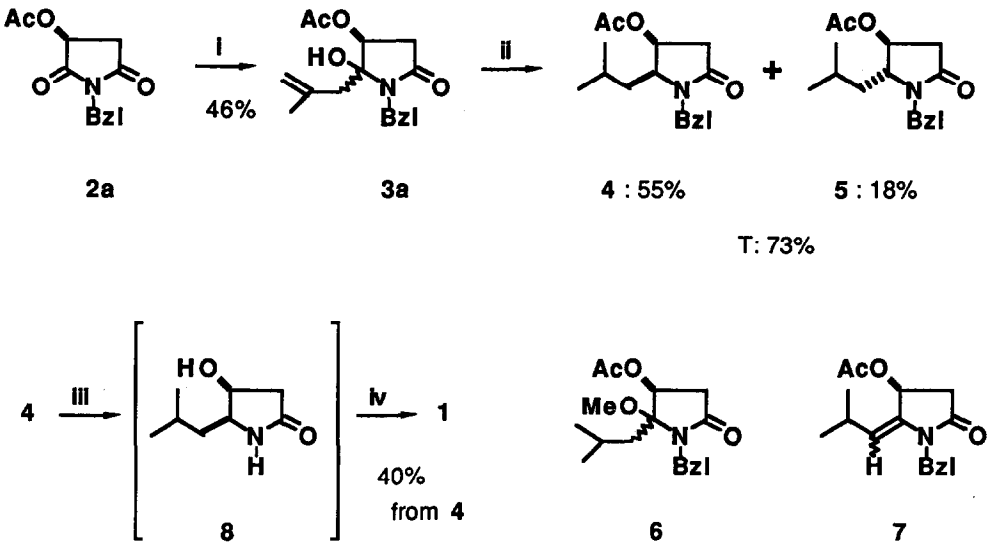
The malimide (**2a**) prepared in one pot from *L*-malic acid was alkylated with methallyl magnesium chloride at -50 °C to give the lactam (**3a**) in 46%. No regioisomer was detected. The fact that the lactam (**3a**) was recovered on $NaBH_4$ treatment in MeOH indicated that **3a**

Scheme 1



1 **3** **2**

Scheme 2 [a]



[a] (i) $CH_2C(CH_3)CH_2MgCl$/THF, -50 °C; (ii) H_2/Pd-C/CH_2Cl_2, 4.5 kg/cm^2; (iii) 1) HCl/MeOH, 60 °C, 3h; 2) Na/NH_3, -78 °C, 1h; iv) 6N HCl, 110 °C, 1h.

was not in the corresponding tautomeric keto amide form. After unsuccessful attempts to obtain the lactam (**4**) under several other conditions such as $NaBH_3CN$ or Et_3SiH treatment in acidic medium, or catalytic hydrogenation in acid,[6] we found that the aminal (**3a**) was reduced with hydrogen under medium pressure in CH_2Cl_2. In a typical reduction procedure, the mixture of the lactam (**3a**, 1.39 g, 4.58 mmol) and 10% Pd-C (139 mg) in CH_2Cl_2 (25 ml) was shaken under hydrogen atmosphere at 4.5 kg/cm^2 for 68 h. The mixture was filtered through a celite pad and evaporated. Chromatography of the residue on silica gel with *n*-hexane-EtOAc (7:3) was followed by reversed phase HPLC[7] to give lactams **4** (720 mg, 55%) and **5** (240 mg, 18%).[8]

When MeOH was used on hydrogenation, only *O*-methylated dihydro derivative (**6**) was obtained in 61% yield. In contrast with the above case, the aminal (**3a**) in CH_2Cl_2 was dehydrated completely within 12 h. The composition of reduction products was shown in Table 1. The *N*-acylenamide (**7**) was disappeared during the prolonged treatment with hydrogen. Hence hydrogenation of the *N*-acylenamide (**7**) was thought to be a rate-limiting step in this process. Since the *N*-benzyl lactam (**4**) was not hydrolyzable efficiently with hydrochloric acid, benzyl substituent was removed prior to the lactam ring opening. The lactam (**8**) was readily hydrolyzed in a sealed tube to give (2*S*,4*S*)-(−)-statine (**1**), $[\alpha]_D^{28}$

-17.3° (c 0.15, H_2O).[9] The yield from the lactam (**4**) was 40% in 3 steps. Application of the present procedure to a synthesis of other useful β-amino alcohol derivatives is currently under investigation.

Table 1. Reduction of The α-Hydroxy Lactam (**3a**)[a]

			Recovery	Products			
Entry	Solvent	Time (h)	**3a**	**4** (%)	**5** (%)	**6** (%)	**7** (%)
1	MeOH	17	-	-	-	61	-
2	CH_2Cl_2	12	-	50	16	-	16
3	CH_2Cl_2	68	-	55	18	-	-
4	CH_2Cl_2[b]	16	-	-	-	-	43

[a] 10% (wt/wt) of 10% Pd-C to **3a** was used. Reaction mixture was shaken at 4.5 kg/cm^2 of hydrogen pressure.

[b] Trifluoroacetic acid (10 equiv. to **3a**) was added.

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References and Notes

1) H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, H. Hamada, and T. Takeuchi, *J. Antibiot.*, **23**, 259 (1970).

2) J. Boger, N. S. Lohr, E. H. Ulm, M. Poe, E. H. Blaine, G. M. Fanelli, T. Y. Lin, L. S. Payne, T. W. Schorn, B. I. LaMont, T. C. Vassil, I. I. Stabilito, D. F. Veber, D. H. Rich, A. S. Boparai, *Nature*, **303**, 81 (1983).

3) Recent publications for syntheses of statine and its analogues: (a) H. Takahata, K. Yamazaki, T. Takamatsu, T. Yamazaki, and T. Momose, *J. Org. Chem.*, **55**, 3947 (1990). (b) S. Kano, T. Yokomatsu, and S. Shibuya, *J. Org. Chem.*, **54**, 515 (1989). (c) H. Yanagisawa, T. Kanazaki, and T. Nishi, *Chemistry Lett.*, 687 (1989). (d) Y. Yamamoto

and M. Schmid, *J. Chem. Soc., Chem. Commun.*, 1310 (1989). (e) M. T. Reetz, M. W. Drewes, B. R. Matthews, and K. Lennick, *J. Chem. Soc., Chem. Commun.*, 1474 (1989). (f) M. M. Midland and M. M. Afonso, *J. Am. Chem. Soc.*, **111**, 4368 (1989). (g) T. Kunieda, T. Ishizuka, T. Higuchi, and M. Hirobe, *J. Org. Chem.*, **53**, 3383 (1988). (h) S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibuya, *J. Org. Chem.*, **53**, 3865 (1988).

4) W. N. Speckamp and H. Hiemstra, *Tetrahedron*, **41**, 4367 (1985).

5) (a) D. A. Evans, E. W. Thomas, and R. E. Cherpeck, *J. Am. Chem. Soc.*, **104**, 3695 (1982). (b) J. Dijkink and W. N. Speckamp, *Heterocycles*, **12**, 1147 (1979).

6) J. Auerbach, M. Zamore, and S. M. Weinreb, *J. Org. Chem.*, **41**, 725 (1976).

7) HPLC conditions were as follows. Column: RP-18®, 8 X 250 mm. Eluent : MeOH-H_2O (7:3), 1 ml/min. Detection: UV at 254 nm.

8) ^1H NMR data ($CDCl_3$, 90 MHz) for **4**. **4a**: δ 0.72 (3H, d, *J*=8.0 Hz), 0.88 (3H, d, *J*=8.0 Hz), 1.32 (1H, m), 1.60 (2H, m), 2.10 (3H, s), 2.58 (1H, m), 2.70 (1H, m), 3.80 (1H, m), 3.98 (1H, d, *J*=15.7 Hz), 5.10 (1H, d, *J*=15.7 Hz), 5.39 (1H, m), 7.32 (5H, m). **4b**: δ 0.75 (3H, d, *J*=8.0 Hz), 0.90 (3H, d, *J*=8.0 Hz), 1.30 (1H, m), 1.60 (2H, m), 2.18 (3H, s), 2.60 (1H, m), 2.78 (1H, m), 3.40 (1H, m), 4.09 (1H, d, *J*=15.7 Hz), 5.02 (1H, d, *J*=15.7 Hz), 5.30 (1H, m), 7.25 (5H, m).

9) H. Morishima, T. Takita, T. Aoyagi, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, **23**, 263 (1970).

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