Pergamon

Tetrahedron Letters, Vol. 38, No. 29, pp. 5223-5224, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01108-8

Stereoselective Synthesis of (-)-N-Boc-Statine and (-)-N-Boc-Norstatine

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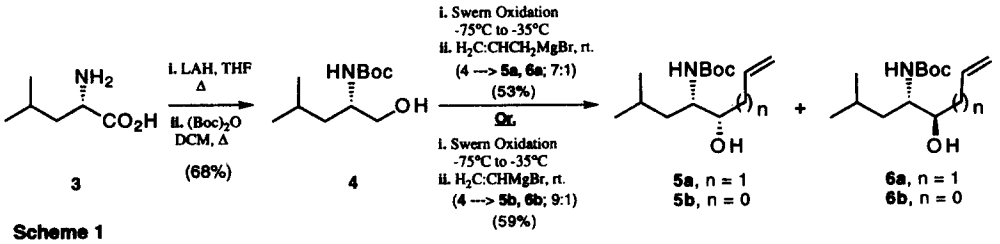
Abstract : An efficient synthesis of optically pure N-Boc-statine (**9**) and N-Boc-norstatine (**11**) has been developed *via* a *syn* selective Grignard reaction of N-Boc-leucinal with allyl- or vinylmagnesium bromide.

Statine, (3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (**1**), a naturally occuring amino acid of nonproteogenic origin, is a key component in the pepstatin family of aspartic protease inhibitors.[1] Statine and its structurally modified analogues have been widely used in the design of peptide mimics as potential inhibitors of renin and other aspartic proteases.[2] Similarly, norstatine, (2*R*, 3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (**2**), constituent amino acid of KRI-1230, a human renin inhibitor peptide[3], has also attracted a great deal of attention in efforts to prepare modified peptides with improved properties as drugs. Interestingly, the *syn* configuration in statine is essential for its bioactivity. Among the various methods for the preparation of statines[4], the most common one involves stereoselective aldol condensation of ester enolates with α-amino aldehydes[5], whereas, norstatines are generally synthesized *via* the cyanohydrin derivatives of the above aldehydes.[3]

Recently, in separate studies concerning the synthesis of paclitaxel side chain and its modified analogues, the research groups of Greene[6] and Georg[7] has shown that, *in-situ* generation of N-protected α-amino aldehydes *via* Swern oxidation of the corresponding amino alcohol, and subsequent addition to Grignard reagents afford the respective 1,2-amino alcohols with good *syn* diastereoselection and complete retention of enantiomeric purity. It was thus considered worthwhile to study and extend this protocol towards synthesizing statine and norstatine. We reasoned that, according to the above observations, stereoselective addition of allylmagnesium bromide (for statine) or vinylmagnesium bromide (for norstatine) to N-Boc-leucinal, should afford the *syn* amino alcohol functionality with the required stereochemistry, which can then be elaborated to the title compounds. The results of the studies thus undertaken are reported in this communication.

N-Boc-leucinol (**4**) was prepared in a one-pot reaction by lithium aluminium hydride reduction and *in-situ* derivatization of L-leucine (**3**). Tandem Swern oxidation - chelation controlled reaction of the resulting aldehyde with allyl- or vinylmagnesium bromide yielded the amino alcohols **5** and **6** (Scheme 1), with good *syn* selectivity[8], which is in accordance with the reported observations [6, 7]. Separation of the *syn* amino alcohol **5** by

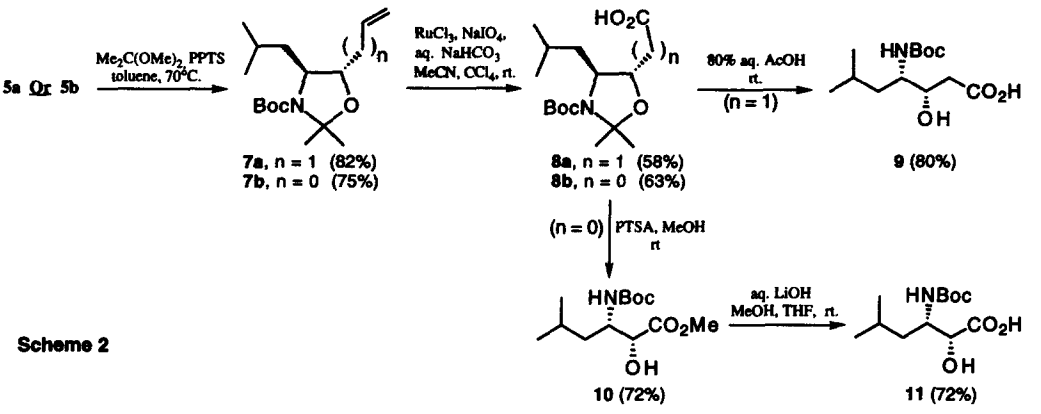


3 4 **5a**, n = 1 **5b**, n = 0 **6a**, n = 1 **6b**, n = 0

Scheme 1

column chromatrography followed by reaction with 2,2-dimethoxypropane provided the oxazolidine derivative **7** (Scheme 2). Degradative oxidation of the terminal olefin under standard reaction conditions formed the corres-

ponding carboxylic acid **8**. N,O- deprotection of the acetonide linkage of **8a** completed the proposed synthesis of N-Boc Statine (**9**) [mp. 119-120°C (lit. mp.[9] 117-119°C)]. Specific rotation of **9** {$[\alpha]_D$ = - 40.8 (0.3, MeOH)} was identical with the literature value {$[\alpha]_D$ = - 41 (1, MeOH)}[9], thereby confirming the optical purity of **9**. The



Scheme 2

norstatine precursor **8b** was next converted to the methyl ester derivative **10** (mp. 85-86°C) and was found to be of high optical purity by comparision of its specific rotation {$[\alpha]_D$ = - 72.3 (0.5, MeOH)} with that of *ent* - **10**{$[\alpha]_D$ = +74.7 (1, MeOH)}[10], furthermore, these results also confirmed the stereochemical assignments of **5a** and **5b**. Hydrolysis of ester **10** provided N-Boc norstatine (**11**)[11], {$[\alpha]_D$ = - 47.7 (0.75,$CHCl_3$)}, culminating in an efficient general approach for the syntheses of the title compounds.

Acknowledgments : We thank Dr. M. K. Gurjar for his support and encouragement. GV also thanks CSIR, New Delhi for a research fellowship.

References and Notes

IICT communication No. 3826.

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8. Assignment of *syn* stereochemistry to the major isomers **5a** and **5b**, initially based on analogy (Ref. 6 and 7), was proved conclusively by matching the specific rotations of the subsequent reaction products **9** and **10** with their literature reported values (*vide infra*).
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11. All the new compounds synthesized were fully characterized by their IR, ^1H NMR, ^{13}C NMR and mass spectral data.

(*Received in UK* 15 *May* 1997; *accepted* 6 *June* 1997)