Pergamon

Tetrahedron Letters 40 (1999) 6163–6166

TETRAHEDRON LETTERS

Synthesis of the peptidic α-hydroxy amides phebestin, probestin, and bestatin from α-keto amide precursors

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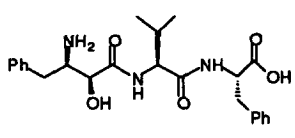
Received 10 May 1999; accepted 9 June 1999

Abstract

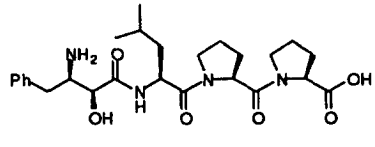
Aminopeptidase inhibitors, phebestin, probestin and bestatin have been prepared by stereospecific reduction of α-keto amide precursors using zinc borohydride.

In recent years a number of natural products have been isolated from bacterial cultures showing marked inhibition of aminopeptidases. These products such as phebestin,[1] probestin,[2] bestatin[3] and amastatin[4] contain β-amino α-hydroxy amide residues which are key units in their biological activity. Because of current interest in this class of bioactive systems, attention has been directed toward methods for synthesizing them efficiently and in enantiomerically pure form. Earlier synthetic work on the formation of β-amino α-hydroxy amides has included Sharpless asymmetric aminohydroxylation of α,β-unsaturated amides,[5] Ojima's β-lactam ring-opening procedure,[6] as well as microbial[7] or asymmetric catalytic[8] reduction of α-keto carboxylic acid derivatives. In addition, aldehydes or Weinreb amides have been homologated using 2-(trimethylsilyl)thiazole[9] or lithium tris(alkylthio)methanes.[10]

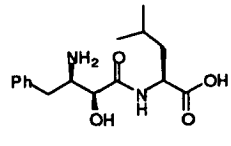
We have recently developed methods[11] for the synthesis of α-keto amides of interest as protease inhibitors using the coupling of carboxylic acids with ylides. The ready availability of these products by this facile procedure has prompted us to study the reduction of the α-keto amides to the corresponding enantiomerically pure α-hydroxy counterparts. We now report our synthesis of phebestin, probestin and bestatin, aminopeptidase inhibitors containing β-amino α-hydroxy amides.



Phebestin



Probestin



Bestatin

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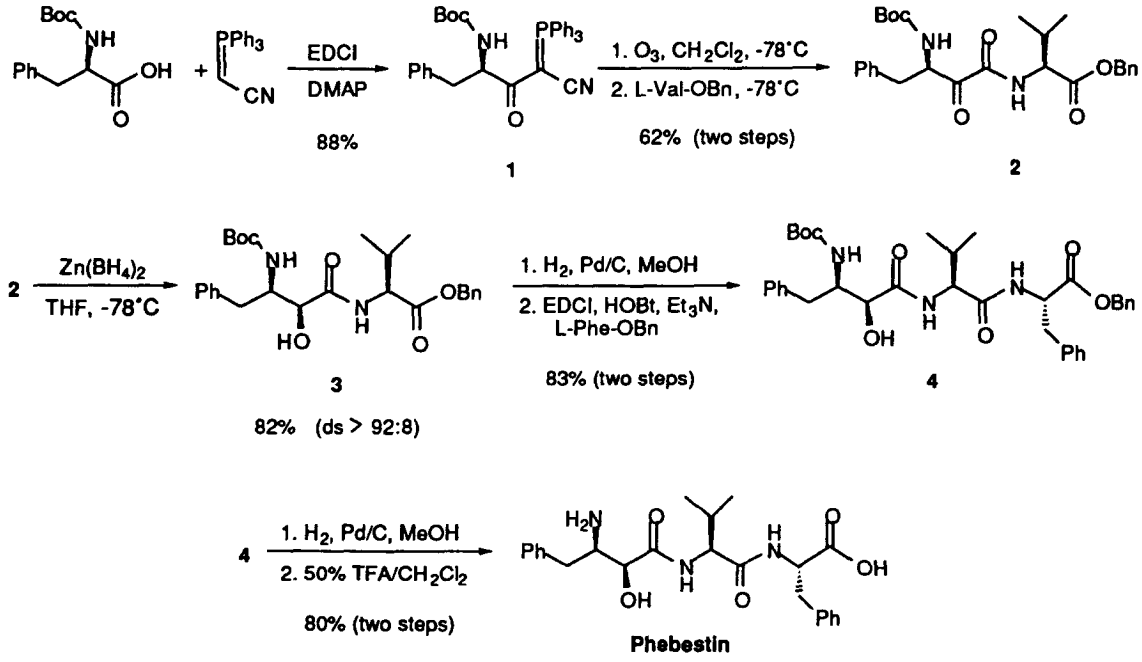
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01143-0

We explored two methods for forming the peptidic β-amino α-hydroxy products. In one procedure, we synthesized the α-keto tripeptidic analog of phebestin and then studied methods for reducing this keto precursor into the natural product using reducing agents such as complexes of rhodium with chiral ligands, Dip-Cl, DIBAL-H, zinc borohydride, L-Selectride®, K-Selectride® and $(Bu^tO)_3BH$-Li. This approach appeared to be less satisfactory than an alternative method which accomplished the stereospecific reduction at an early stage using a dipeptidic intermediate. In the following, we describe the synthesis of our target molecules by the second route involving reduction of the dipeptides **2** and **5**, both containing the 3-amino-2-oxo-4-phenylbutanoic acid amide residue.

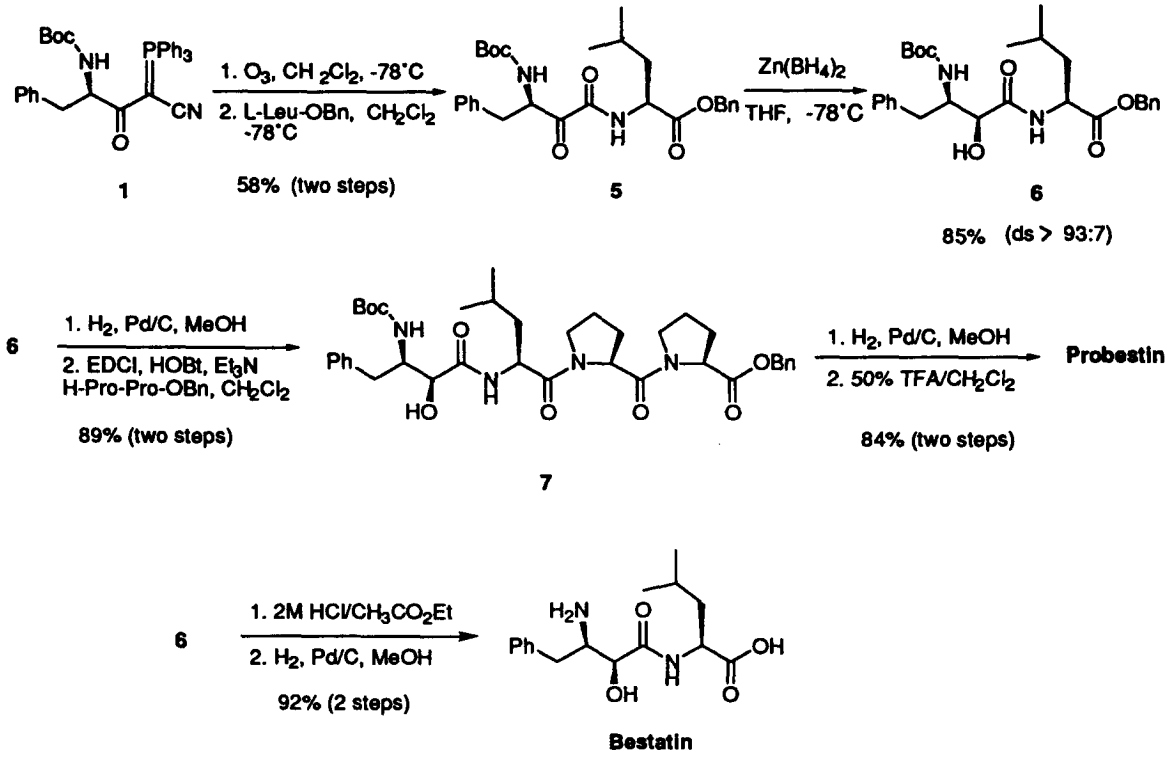
Phebestin. Our synthesis, outlined in Scheme 1, began with *N*-Boc-D-phenylalanine, which was coupled with triphenylphosphoranylideneacetonitrile to form the acyl cyano ylide **1** (88%). Ozonolysis of **1** at −78°C was followed by coupling with the benzyl ester of L-valine at low temperature to yield the dipeptidic α-keto amide **2**. At this early point in the synthesis, we explored the use of reducing agents for stereospecific conversion of the α-keto group to the α-hydroxy counterpart.



Scheme 1.

We found that among the above reducing agents, zinc borohydride[12] was particularly effective in the reduction of the keto substrate to the alcohol with high diastereomeric selectivity (92:8).[13] The zinc borohydride (0.15 M) in ether (2 equiv.) was added to the solution of the α-keto amide **2** in THF at −78°C under N_2, and the mixture was stirred for 30 min. After separation of the desired diastereomer by preparative TLC (ethyl acetate:hexane, 1:1), the product **3** was deprotected by hydrogenation and then coupled with the benzyl ester of L-phenylalanine to yield the tripeptide **4**. Removal of protecting groups from **4** sequentially using hydrogenation and TFA yielded a product (80%) identical in every respect with natural phebestin. The selectivity in the reduction of **2** to **3** may be explained on the basis of chelation control in which the two carbonyl groups coordinate with the zinc ion permitting hydride attack at the less hindered side of the α-carbonyl group.

Probestin and bestatin. In the synthesis of the tetrapeptide probestin we also prepared the unnatural β-amino α-hydroxy residue at the dipeptide stage for further coupling with a second dipeptidic unit. As shown in Scheme 2, the doubly protected dipeptide **5** containing the α-keto amide residue was subjected to reduction by zinc borohydride to give the α-hydroxy product **6** with diastereomeric selectivity 93:7 (85%) (preparative TLC, eluting with ethyl acetate:hexane, 1:1). Further transformation of **6** to probestin was accomplished by coupling with the benzyl ester of prolylproline followed by deprotection as indicated.



Scheme 2.

During the course of our probestin synthesis, we carried out the deprotection of the β-amino α-hydroxy intermediate **6**. The product was shown to be identical in every respect with an authentic sample (Sigma) of bestatin by comparison of spectroscopic properties.

Acknowledgements

This work was supported by grants from the National Institutes of Health and the National Science Foundation. We express our appreciation to Dr. Takaaki Aoyagi, Institute of Microbial Chemistry, Tokyo, Japan, for generous help in providing authentic samples of phebestin and probestin.

References

1. Nagai, M.; Kojima, F.; Naganawa, H.; Hamada, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 82.
2. (a) Aoyagi, T.; Yoshida, S.; Nakamura, Y.; Shigihara, Y.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 143; (b) Yoshida, S.; Nakamura, Y.; Naganawa, H.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 149.
3. (a) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97; (b) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 100.
4. Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 636.
5. (a) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637 and references cited therein; (b) Keding, S. J.; Dales, N. A.; Lim, S.; Beaulieu, D.; Rich, D. H. *Synth. Commun.* **1998**, *28*, 4463.
6. Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377.
7. (a) Patel, R. N.; Banerjee, A.; Howell, J. M.; McNamee, C. G.; Brozozowski, D.; Mirfakhrae, D.; Nanduri, V.; Thottathil, J. K.; Szarka, L. J. *Tetrahedron: Asymmetry* **1993**, *4*, 2069; (b) Kearns, J.; Kayser, M. M. *Tetrahedron Lett.* **1994**, *35*, 2845.
8. (a) Nozaki, K.; Sato, N.; Takaya, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2179; (b) For a review of reduction of carbonyl compounds with chiral oxazaborolidine catalysts, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.
9. Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181.
10. (a) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570 and references cited therein; (b) Iwanowicz, E. J.; Lin, J.; Roberts, D. G. M.; Michael, I. M.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607.
11. (a) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364; (b) Wasserman, H. H.; Petersen, A. K. *Tetrahedron Lett.* **1997**, *38*, 953; (c) Wasserman, H. H.; Petersen, A. K. *J. Org. Chem.* **1997**, *62*, 8972; (d) Wasserman, H. H.; Chen, J.-H.; Xia, M. *J. Am. Chem. Soc.* **1999**, *121*, 1401.
12. (a) For preparation of zinc borohydride, see: Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074; (b) for a review of synthetic application of zinc borohydride, see: Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19.
13. (a) We confirmed the assignment of the relative configuration of the two diastereomers derived from **2** by formation of the *threo-* and *erythro-* oxazolidone derivatives using phosgene in toluene. The larger $J_{4,5}$ coupling constant (9.0 Hz) was assigned to the *erythro* isomer, and the smaller (5.0 Hz) to the *threo* isomer. It is well known that oxazolidones derived from β-amino α-hydroxy esters (Ref. 3b) or α-amino β-hydroxy esters (Ref. 13b) exhibit larger $J_{4,5}$ coupling constants for the *erythro* isomers (8.0–10.0 Hz) than for the *threo* isomers (4.0–6.0 Hz); (b) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn* **1973**, *46*, 3308.