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New stereoselective synthesis of the peptidic aminopeptidase inhibitors bestatin, phebestin and probestin

Giuliana Righi,[a,*] Claudia D'Achille,[a] Giovanna Pescatore[a] and Carlo Bonini[b]

[a]*CNR Istituto di Chimica Biomolecolare—Sezione di Roma, c/o Dip. di Chimica, Università 'La Sapienza', P. le A. Moro 5, Box 34, 00185 Roma 62, Italy*

[b]*Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy*

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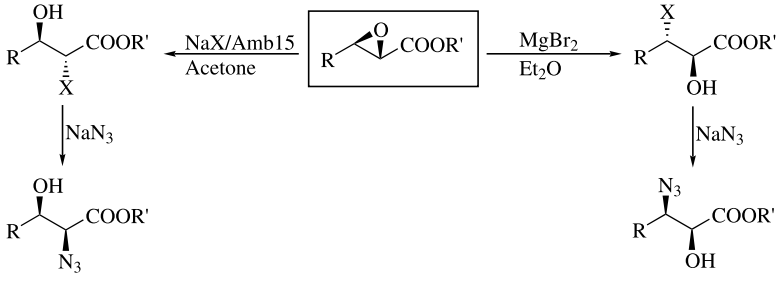
Abstract—Peptidic aminopeptidase inhibitors, bestatin, phebestin and probestin have been prepared by stereo- and regiocontrolled reactions from a common α,β-epoxy ester precursor.

A recent screening for new amino peptidase inhibitors has allowed the isolation of some β-amino α-hydroxy amides from *Streptomyces* cultures having this biological activity.[1] Structure-modification studies on these compounds indicated that the presence of *syn* amino alcohol fragments and the 2*S* configuration of the α-hydroxy group are the most important factors for a tight interaction with the enzyme.[2] The current interest in the synthesis of these bioactive compounds and the need of having stereocontrolled structures,[3] prompted us to employ our well-known methodologies to prepare these types of fragments.

Among the methods already reported for obtaining *syn* amino alcohols, the recently developed Sharpless asymmetric amino hydroxylation of olefins is the most straightforward route to build up the chiral β-amino alcohol moiety;[4] however, the use of this asymmetric procedure still suffers from some drawbacks, especially as to the regioselectivity of the reaction. Also, the Salen asymmetric epoxidation, followed by opening of the epoxide by nitrogen nucleophiles, appears suitable for this purpose.[5] However, in this methodology the limitations in the choice of the olefinic substrate (*cis* conjugated olefins) and the unpredictable regioselectivity in the opening of the epoxide with nitrogen nucleophiles still limit this approach to a small number of substrates.

By way of contrast, the older Sharpless asymmetric epoxydation[6] allows a more flexible access to a large variety of regio- and diastereoisomers than the direct AA and Salen-ae, despite the number of steps required for the transformation of the starting chiral epoxy alcohols into the final amino alcohols.



Scheme 1.

Keywords: asymmetric synthesis; α,β-epoxy esters; aminopeptidase inhibitors.
* Corresponding author.

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Following this last approach, our method, starting from a suitable chiral α,β-epoxy ester, affords *syn* 3-amino-2-hydroxy esters[7] or *syn* 2-amino-3-hydroxy esters[8] with virtually all kinds of R substituents.

Indeed, during our studies we succeeded in finding proper conditions for effecting the stereo- and regioselective ring opening of the α,β-epoxy esters by metal halides.

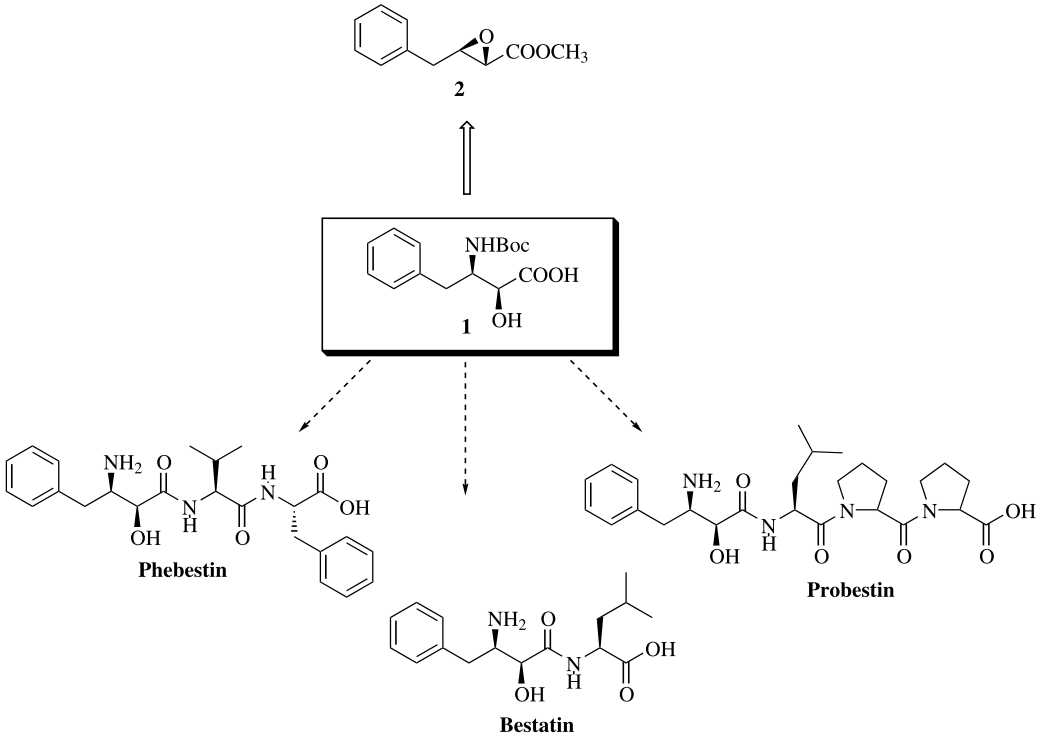
As shown in Scheme 1, the substitution of the halogen by azide (the most used precursor of an amino group) gives vicinal azido alcohols with a *syn* relationship between the stereocenters, which is not an easy goal to reach with other approaches.

Some of the recently isolated β-amino α-hydroxy amide aminopeptidase inhibitors, viz. bestatin,[9] phebestin[10] and probestin,[11] contain a (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid fragment in their structure (Scheme 2). Thus, we deemed very convenient to employ our method for the synthesis of these compounds starting from a common optically active precursor, i.e. the (2*S*,3*R*)-3-[(*N*-*t*-butoxycarbonyl)amino]-2-hydroxy-4-phenylbutanoic acid, **1**, easily obtained from (2*S*,3*R*)-methyl-2,3-epoxy-4-phenylbutanoic acid, **2**.[12]

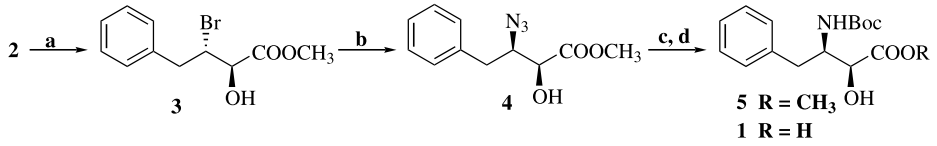
While the $MgBr_2$-mediated opening of **2** (Scheme 3) afforded, as expected, the bromohydrin **3** in nearly quantitative yield, several attempts were necessary until conditions were eventually found for the displacement of bromine by azide.[13] Finally, by employing NaN_3 in DMSO at 40°C,[14] **4** was readily obtained with complete inversion of configuration; its catalytic hydrogenation in the presence of di-*tert*-butyl carbonate[15] followed by hydrolysis afforded **1** (Scheme 3).[16]

As shown in Scheme 4, from **1** it is possible to synthesize the three peptidic aminopeptidase inhibitors using simple and well-known procedures. The coupling of the benzyl ester of L-valine with acid **1** and the subsequent deprotection by hydrogenation afforded the dipeptide **9**. Finally, its coupling with the benzyl ester of L-phenylalanine and the sequential removal of the protecting groups by hydrogenation and TFA treatment afforded the tripeptide phebestine.

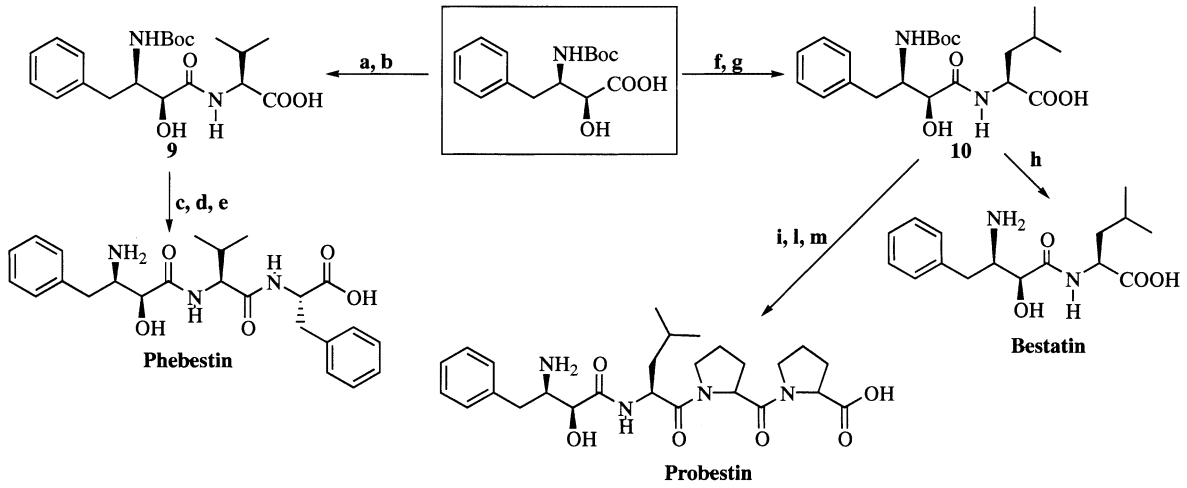
In order to prepare bestatin, **1** was coupled with the benzyl ester of L-leucine, hydrogenated to the dipeptide **10** and then deprotected with TFA. On the other hand, the coupling of **10** with the benzyl ester of prolylproline, followed by the removal of the protecting groups as usual, furnished the tetrapeptide probestin.



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) $MgBr_2$, Et_2O, rt, 2 h, 92%; (b) NaN_3, DMSO, 40°C, 6 h, 73%; (c) H_2, Pd/C, EtOAc, $(BocO)_2O$, rt, 5 h, 95%; (d) Na_2CO_3, H_2O/MeOH, rt, 12 h, 79%.



Scheme 4. *Reagents and conditions*: (a) EDAC, HOBt, DIPEA, L-Val-OBn-TsOH, DMF, CH_2Cl_2, rt, 12 h, 87%; (b) H_2, Pd/C, MeOH, rt, 3h, 96%; (c) EDAC, HOBt, DIPEA, L-Phe-OBn-TsOH, DMF, CH_2Cl_2, rt, 12 h, 85%; (d) H_2, Pd/C, MeOH, rt, 3 h, 95%; (e) TFA, CH_2Cl_2, rt, 12 h, 85%; (f) EDAC, HOBt, DIPEA, L-Leu-OBn-TsOH, DMF, CH_2Cl_2, rt, 12 h, 87%; (g) H_2, Pd/C, MeOH, rt, 3 h, 95%; (h) TFA, CH_2Cl_2, rt, 12 h, 85%; (i) EDAC, HOBt, DIPEA, L-Pro-Pro-OBn-HCl, DMF, CH_2Cl_2, rt, 12 h, 86%; (l) H_2, Pd/C, MeOH, rt, 3 h, 94%; (m) TFA, CH_2Cl_2, rt, 12 h, 85%.

The physico-chemical properties of the three peptidic inhibitors were consistent with those reported in the literature for the same compounds.

In conclusion, the already successfully used highly regio- and stereoselective sequence from *trans* α,β-epoxy esters to *syn* β-amino-α-hydroxy esters proved to be also a straightforward approach for the synthesis of this type of molecules. Moreover, the generality of the method allows the preparation of a large number of variously substituted analogues.

Acknowledgements

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12. Compound **5** was easily prepared by standard procedure (Ref. 7a) in four high yielding steps starting from the commercially available phenylacetaldehyde.
13. Several reaction conditions failed: (a) NaN_3 in DMF; (b) NaN_3/R_4PBr in H_2O; (c) $TMSN_3/Bu_4NF$ in DMF. In the case (a) the reaction was not stereoselective and in the cases (b) and (c) the starting material **3** remained unchanged when the reaction temperature was ≈60°C and decomposed when it was heated to 80–90°C.
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16. NMR data for most significant new compounds. Compound **3**: ^{1}H NMR: δ 7.40–7.22 (m, 5H), 4.54–4.43 (m, 2H), 3.78 (s, 3H), 3.56 (d, J=6.7 Hz, 1H), 3.38 (dd, J=6.7, 13.9 Hz, 1H), 3.27 (dd, J=8, 13.9 Hz, 1H). ^{13}C NMR: δ 171.4, 137.3, 129.1, 128.5, 126.9, 73.3, 56.0, 52.7, 40.3. Compound **4**: ^{1}H NMR: δ 7.41–7.24 (m, 5H), 4.15 (dd, J=2.2, 5.8 Hz, 1H), 3.80 (s, 3H), 3.72 (dt, J=2.2, 8 Hz, 1H), 3.14 (d, J=7.3 Hz, 2H), 3.04 (d, J=5.8 Hz, 1H). ^{13}C NMR: δ 173.1, 136.5, 129.3, 128.8, 127.1, 71.3,

64.1, 53.0, 36.1. Compound **5**: ^{1}H NMR: δ 7.36 (m, 5H), 4.81 (bd, $J=9.5$ Hz, 1H), 4.32–4.18 (m, 1H), 4.05 (d, $J=4.4$ Hz, 1H), 3.75 (s, 3H), 3.15 (d, $J=4.4$ Hz, 1H), 2.95–2.78 (m, 2H), 1.35 (s, 9H). ^{13}C NMR: δ 172.4, 155.1, 143.8, 129.5, 128.5, 126.5, 79.6, 70.2, 54.2, 52.7, 38.1, 28.1. Compound **1**: ^{1}H NMR: δ 7.32 (m, 5H), 6.5 (bs, 1H), 5.05 (bd, $J=8.8$ Hz, 1H), 4.35–4.05 (m, 2H), 4.15 (d, $J=6.6$ Hz, 1H), 2.95 (d, $J=7.3$ Hz, 2H), 1.37 (s, 9H). ^{13}C NMR: δ 157.1, 156.1, 137.8, 129.4, 128.5, 126.5, 81.5, 70.4, 56.1, 54.4, 38.2, 28.1.