Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 9, pp. 949-952, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00150-6

SYNTHESIS OF α-HYDROXY STATINE THROUGH A FACIALLY SELECTIVE OSMYLATION OF A CHIRAL α-AMIDO CROTONATE

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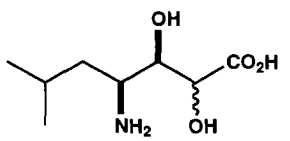
Abstract: α-hydroxy statine **5** was synthesized by osmylation of amido crotonate **6** and incorporated into peptide framework **9**, resulting in an active renin inhibitor; predicted stereochemical preferences for renin inhibition were confirmed by x-ray analysis and biochemical determinations. The facial selectivity of the osmylation is consistent with the Vedejs model.

In connection with our research in the renin inhibitor area,[1] we became interested in the synthesis of the transition state mimic α-hydroxy statine **1**, which is a hybrid of statine **2**[2] and norstatine **3**.[3] This α-hydroxy statine structural type has been generally disclosed[4], but not exemplified; the corresponding cyclohexyl segment **4** however was reported therein to be incorporated into a peptide and deblocked to afford a renin inhibitory agent of undefined stereochemistry within the statine segment at C-2 and C-3. In particular, we targeted the preparation of the 2-S, 3-R stereoisomer **5**, which computer modeling (employing Blundell's model[5] of human renin) had predicted to be compatible with the active site.



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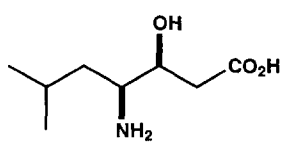

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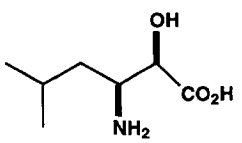

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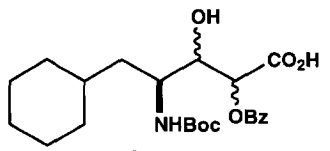

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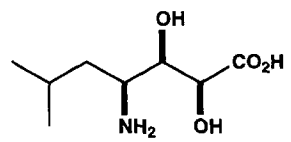

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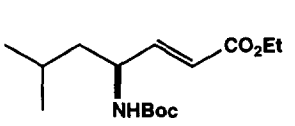
Our potentially stereoselective route to the α-hydroxy statine segment involved osmylation of known[6] E enone **6**, which we prepared in 96% yield by dehydration of Boc epi-statine ethyl ester[2] **7** with mesyl chloride/triethylamine (0°-25°C). When **6** was subjected to catalytic osmylation employing N-methylmorpholine oxide[7] in aqueous acetone, two diastereomeric diols were formed which were separated by column chromatography to afford a major and minor diol in a 71/29 ratio (66% yield together). The key question now is the identification of the isomer with the same relative configuration as statine at C-3; such a consideration is crucial since only the 3-S configuration of natural statine[8] can lead to an active renin inhibitor.



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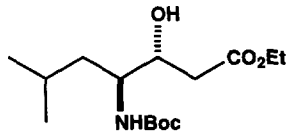

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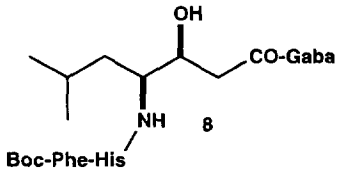
There is a chemical/spectral method[9] that was available for distinguishing the 3-S from the 3-R configuration, which involves conversion to oxazilidinones with phosgene followed by analysis of NMR coupling constants. Because of the possibility that the 2-OH of α-hydroxy statine might complicate the course of the phosgenation and cause ambiguity, we decided to use human renin to determine the absolute configuration at C-3 by constructing a peptide with each diol; after measurement of the renin inhibitory potency,[1] the more active member of the peptide pair should possess the same relative configuration as natural statine.[8] Accordingly, two peptides (using the major and minor α-hydroxy statine diastereomers) were constructed containing the same peptide framework as statine-containing reference **8** (IC_{50} = 3.2 μM) (Preparation-Scheme 1)[10]; the relative human renin potencies suggested that peptide **9** (IC_{50} = 3.0 μM) and therefore its precursor minor diol **11** possess the 3R configuration at C-3 (relative configuration identical to statine), while **10** (IC_{50} = 63 μM) and **12** possess the opposite relative configuration.



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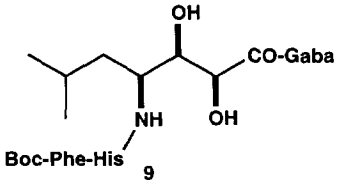

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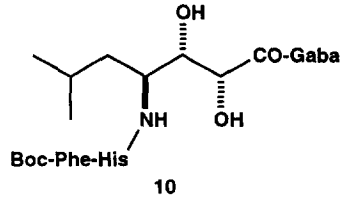

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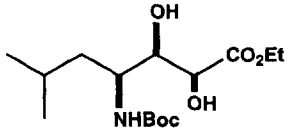

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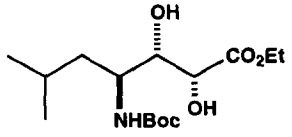

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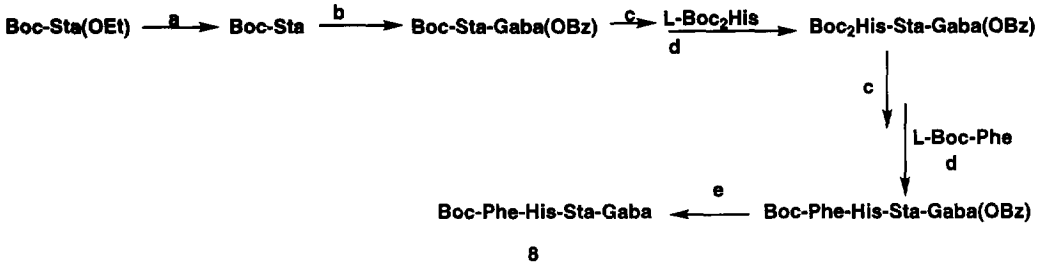
At the time that this information became available, we were able to unequivocally determine the relative configuration for the two contiguous asymmetric centers at C-2 and C-3 of **12** with respect to the known absolute configuration at C-4 through x-ray analysis;[11] major diol **12** is correct as drawn.

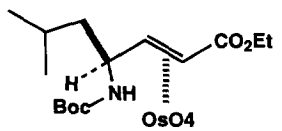
SCHEME 1



Reagents: (a) NaOH, aq.THF (b) DCC, Gaba(OBz) (c) HCl, dioxane (d) DCC, HOBt, N- methylmorpholine (e) H_2, $Pd(OH)_2/C$

Having identified a new transition state segment equipotent to statine and in so doing having confirmed the validity of deriving stereochemical preferences from the renin model, we now turned our attention to a chemical issue, namely the facial selectivity of the enone osmylation. Facial selectivity of electrophilic reactions in asymmetric allylic systems is an area of active research.[12] As a subset of this class of reactions, osmylation has been extensively studied with most effort directed to allylic alcohol and ether substrates, resulting in at least 5 different models for predicting stereochemical outcomes.[13] Apparently there are only a few examples in the literature of the osmylation of asymmetric allylic amides[12] and none for γ-amido crotonates like **6**.[14]

As previously mentioned, our osmylation affords two diastereomers, minor 2S, 3R **11** and major 2R, 3S **12**, formed in the ratio of 29:71, respectively. For the diastereofacial analysis of our result, we chose the Vedejs model because of better compatibility with the functionality of enone **6**. Formulation **13** was employed, which places the hydrogen at the chiral center in the sterically most demanding environment, and the amide N in the enone plane on the inside (for steric reasons) of the allylic system; we are then led to the prediction that the major diastereomer should be 2R, 3S **12** which in fact corresponds to the unnatural statine configuration at C-3. The



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observed ratio of diols **11/12** is similar to that seen in Hauser's allylic amide studies.[15]

In conclusion, a new statine replacement was synthesized which expands the scope of segments useful for the inhibition of aspartyl proteases. Our osmylation results further confirm the validity of the Vedejs model, and, in addition, extend its predictive usefulness to γ-amido crotonates which are potentially valuable intermediates of

the synthesis of medicinally interesting substances.

Acknowledgement: We are grateful to W. R. Murphy and I. M. Purcell for the measurement of renin inhibitory potencies.

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(*Received in USA* 1 *February* 1995; *accepted* 20 *March* 1995)