Pergamon

Tetrahedron Letters, Vol. 36, No. 6, pp. 819-822, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02416-X

Synthesis and Activity of an HIV-1 Protease Inhibitor Containing a Contiguous (E)-Olefin-Hydroxyethylene Peptide Mimetic

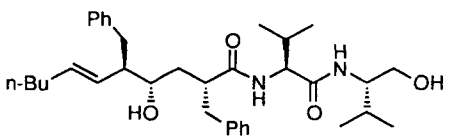
Richard M. Keenan*, Daniel F. Eppley, and Thaddeus A. Tomaszek, Jr.

Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, P.O. Box 1539, King of Prussia, Pennsylvania 19406 USA

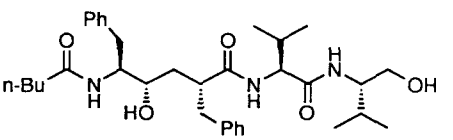
ABSTRACT: To investigate the contribution of a key amide bond to HIV Protease inhibition, we designed and synthesized a novel (E)-olefin hydroxyethylene analog. The stereoselective synthesis of this interesting homoallylic alcohol structural motif as well as its biological activity are discussed.

Inhibition of human immunodeficiency virus type 1 (HIV-1) protease, an aspartyl protease responsible for viral maturation and replication, has become an attractive strategy for the design of therapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS).[1] A well studied class of potent HIV-1 protease inhibitors contains a hydroxyethylene dipeptide isostere in place of the scissile amide bond.[2] Crystal structures of hydroxyethylene inhibitors complexed with HIV-1 protease have revealed that both the carbonyl oxygen and the amide N-H of the P_2-P_1 amide bond interact with portions of the enzyme active site.[3] The carbonyl oxygen is one of two oxygens involved in accepting hydrogen bonds from an embedded water molecule, which in turn accepts two hydrogen bonds from the flap regions of the enzyme enclosing the inhibitor in the active site. Likewise, the amide N-H has been shown in crystal structures of enzyme-inhibitor complexes to form a hydrogen bond to an amide carbonyl in the enzyme.

To evaluate the contribution of the P_2-P_1 amide bond to HIV-1 protease inhibition, we designed a novel hydroxyethylene analog containing an (E)-olefin replacement for the amide bond at this position. The replacement of an amide bond with the isosteric (E)-olefin is recognized as a useful method for investigating the importance of the amide bond to biological activity.[4] Herein, we describe the synthesis of the novel (E)-olefin hydroxyethylene peptide mimetic **1** and compare its biological activity to the corresponding amide **2**.



1

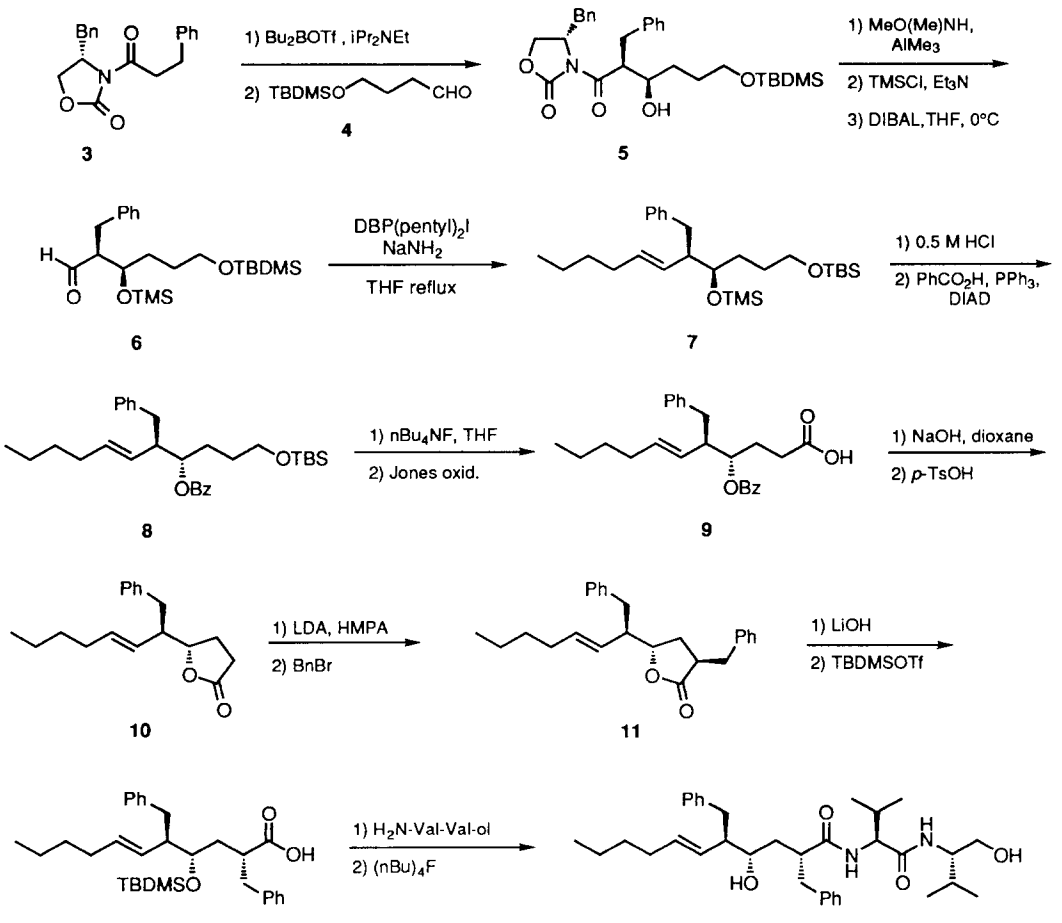


2

Although a number of routes have been developed for the synthesis of both (E)-olefin[5] and hydroxyethylene[6] dipeptide isosteres, the synthesis of an (E)-olefin in conjunction with a hydroxyethylene unit to mimic three contiguous amino acid residues has not been reported. The challenging feature in the target **1** is the stereospecific synthesis of the homoallylic alcohol portion of the molecule containing the threo related benzyl and hydroxyl groups adjacent to the (E)-olefin. Our strategy was to form the key bond

between the benzyl and hydroxyl centers in a stereocontrolled fashion using Evans aldol chemistry[7] and then invert the alcohol under Mitsunobu conditions[8] to arrive at the desired threo configuration. The required (E)-olefin would then be introduced via elaboration of the carbonyl functionality present as a result of the Evans chemistry.

Scheme 1



The synthesis of the desired target following our general strategy is outlined in Scheme 1. Condensation of oxazolidinone **3** with aldehyde **4**[9] following the Evans procedure using dibutylboron triflate and diisopropylethylamine[7] provided the erythro aldol product **5** in 75% yield[10] with >95:5 diastereoselectivity. Transamidation[11] afforded the N-methoxy-N-methyl amide in 97% yield which, after protection of the

secondary alcohol with trimethylsilyl chloride (90%), was reduced to the aldehyde **6** with DIBAL (73%). Incorporation of the (E)-hexenyl moiety was accomplished stereospecifically using dibenzophosphole ylide chemistry. Thus, treatment of aldehyde **6** with the phosphorous ylide of DBP(pentyl)$_2$I[12] ($NaNH_2$ in refluxing THF)[13] gave only a single product **7** in 50% yield, which, by analysis of the ^{1}H NMR spectrum of a subsequent intermediate (*vide infra*), possessed the requisite (E)-stereochemistry. Alternatively, the aldehyde could be reacted with 1,1-diiodopentane in the presence of $CrCl_2$[14] in DMF to afford **7** in slightly lower yield (35%).

Establishment of the desired threo stereochemistry required inversion of the secondary alcohol center. Mild acidic treatment (0.5 M aq. HCl in EtOAc) selectively deprotected the TMS group (86%). Subsequent reaction under Mitsunobu conditions[8] using DIAD and Ph_3P yielded the benzoate **8** (50%) containing the necessary threo substituted homoallylic alcohol system. Deprotection of the TBDMS group with fluoride (93%) and Jones oxidation (98%) provided the carboxylic acid **9**. Basic hydrolysis of the benzoate (NaOH,) and treatment with acid (*p*-TsOH) at room temperature gave the lactone **10** in 88% overall yield from **9**. In the lactone **10**, the ^{1}H NMR coupling constants of the two olefinic protons (J = 15.4 Hz) supported the *trans* geometry of the olefin.

The completion of the synthesis was accomplished using a protocol worked out for the synthesis of previous hydroxyethylene HIV protease inhibitors.[3a] Deprotonation of lactone **10** with LDA and alkylation with benzyl bromide afforded the desired dibenzyl lactone **11** in 75% yield along with a trace (4%) of its diastereomer. The major product was assigned as resulting from alkylation from the sterically less encumbered face, by analogy to the synthesis of related hydroxyethylene isosteres.[3a,6e] Lactone opening with LiOH and treatment with *tert*-butyldimethylsilyl triflate provided the free acid **12** (30%) along with recovered lactone **10** (65%). Coupling under standard conditions (HOBT, BOP reagent, 75%), then deprotection of the silyl group with fluoride (58% plus 33% recovered SM) afforded the final product **1**.

When assayed for inhibition of HIV-1 protease,[15] compound **1** displayed a K_i = 3.6 μM. For comparison, the n-butyl amide analog **2**[16] had a K_i = 37 nM. Thus, the amide bond appears to contribute approximately two orders of magnitude worth of binding to this class of HIV protease inhibitors. This result is consistent with the amide carbonyl playing a key role in engaging the flap regions of the enzyme and holding the inhibitor in the active site.

In summary, a novel (E)-olefin hydroxyethylene peptide mimetic has been synthesized. The synthesis of this compound, which contains four contiguous stereocenters as part of a homoallylic alcohol system, employed an Evans aldol reaction followed by a Mitsunobu inversion to set the desired threo stereochemistry, and a phosphorous ylide reaction to stereoselectively construct the (E)-olefin. Biological assay of this novel HIV-1 protease inhibitor revealed a loss of activity compared to its amide counterpart, supporting the notion that this amide carbonyl plays a key role in the binding of a hydroxyethylene inhibitor in the active site.

Acknowledgments

We acknowledge E. Reich for elemental analyses and the Department of Physical and Structural Chemistry for mass spectral data. The Boc-protected amine for the synthesis of **2** was kindly provided by D. Takata.

References and Notes

1. Debouck, C. *AIDS Research and Human Retroviruses* **1992**, *8*, 153-164.

2. Moore, M. L.; Dreyer, G. B. *Perspectives in Drug Discovery* **1993**, *1*, 85-108.

3. (a) Dreyer, G. B.; Lambert, D. M.; Meek, T. D.; Carr, T. J.; Tomaszek Jr., T. A.; Fernandez, A. V.; Bartus, H.; Cacciavillani, E.; Hassell, A. M.; Minnich, M.; Petteway, S. R.; Metcalf, B. W. Biochemistry **1992**, *31*, 6646-6659. (b) Jaskolski, M.; Tomasselli, A. G.; Sawyer, T. K.; Staples, D. G.; Heinrikson, R. L.; Schneider, J.; Kent, S. B.; Wlodawer, A. *Biochemistry* **1991**, *30*, 1600-1609.

4. Hann, M. H.; Sammes, P. J.; Kennewell, P. D.; Taylor, J. B. *J. C. S. Chem. Comm.* **1980**, 234-235; *J. C. S. Perkin Trans I* **1982**, 307-314.

5. See McKinney, J. A., Eppley, D. F., Keenan, R. M. *Tetrahedron Lett.*, in press, and references therein.

6. (a) Ciapetti, P.; Taddei, M.; Olivi, P. *Tetrahedron Lett.* **1994**, *35*, 3183-3186. (b) Armstrong III, J. D.; Hartner Jr., F. W.; DeCamp, A. E.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1992**, *33*, 6599-6602. (c) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirsfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615-4625. (d) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803-1806. (e) Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4823-4833.

7. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

8. Mitsunobu, O. *Synthesis* **1981**, 1-28.

9. Synthesized in two steps in 66% overall yield from 4-penten-1-ol: (i) TBDMSOTf, 2,6-lutidine (ii) O_3; dimethyl sulfide.

10. The structural assignments for all new products were consistent with 400 MHz ^{1}H NMR and MS data. In addition, CHN elemental analysis data were obtained for compounds **1** and **2**.

11. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3816.

12. Synthesized in two steps from tetraphenylphosphonium bromide: (i) LDA, THF; 4M HCl (ii) Li metal, THF; 1-iodopentane (6 equiv.)[13].

13. Vedejs, E.; Marsh, C. *Tetrahedron Lett.* **1987**, *28*, 3445-3448.

14. Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.

15. See reference 3a for a description of the assay conditions.

16. The amide **2** was prepared from the corresponding t-Boc-amine t-butyldimethylsilyl ether: (i) selective amine deprotection with TFA (ii) valeric anhydride, Et_3N (iii) n-Bu_4NF.

(*Received in USA* 29 *August* 1994; *revised* 28 *October* 1994; *accepted* 5 *December* 1994)