Pergamon

Tetrahedron Letters, Vol. 35, No. 29, pp. 5153-5156, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01026-9

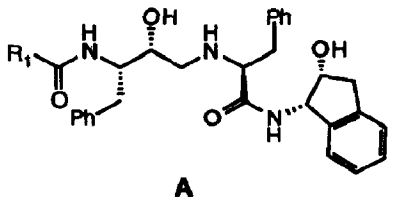
A CONVERGENT SYNTHESIS OF NOVEL CONFORMATIONALLY RESTRICTED HIV-1 PROTEASE INHIBITORS

B. Moon Kim*, James P. Guare, Colleen M. Hanifin, Deborah J. Arford-Bickerstaff, Joseph P. Vacca and Richard G. Ball†

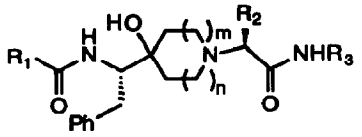
Merck Research Laboratories, Department of Medicinal Chemistry, West Point, Pennsylvania 19486 and †Department of Biophysical Chemistry, P.O. Box 2000, Rahway, New Jersey 07065

Abstract: Conformationally restricted HIV-1 protease inhibitors containing the transition state hydroxyl group in pyrrolidine or piperidine ring systems were synthesized stereoselectively utilizing the inherent stereochemistry of an amino acid derivative. A convergent double reductive amination strategy was used to construct the heterocyclic rings.

Human immunodeficiency virus type-1 (HIV-1) is the etiologic agent for the acquired immunodeficiency syndrome (AIDS).[1] The virus encodes a homodimeric aspartyl protease (HIV-1 protease) responsible for processing the *gag* and *gag-pol* gene products that allow for the organization of core structural proteins.[2] For this reason, HIV-1 protease has been recognized as one of the most attractive therapeutic targets for AIDS.[3] Much effort has been concentrated on the development of efficient protease inhibitors, and a number of these compounds have been reported in the literature.[4] Most inhibitors incorporate transition state isosteres to mimic the cleavage site of the natural substrate of the enzyme.



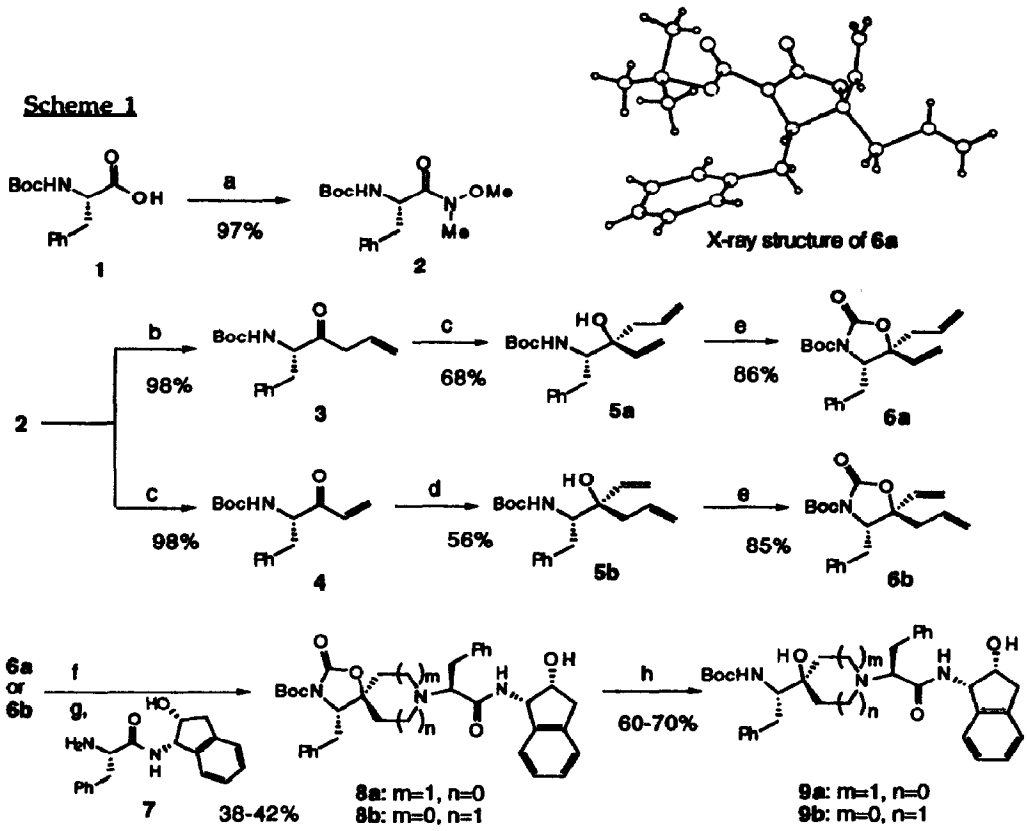
A



B, m=0,1; n=0,1

Recently, Tucker et al. have reported a new series of HIV-1 protease inhibitors (A)[5] which combine the hydroxyethylamine transition state mimic with the novel amino acid surrogate 1-amino-2-hydroxyindan.[6] Examination of a modeled structure of **A** in the enzyme active site[5] indicated that a pyrrolidine or piperidine ring could be formed between the hydroxyl carbon and the secondary amine to give compounds of general structure **B**. This ring might enforce a bioactive conformation and lead to an increase in inhibitory potency. In this communication, we wish to report a highly convergent synthesis of such conformationally restricted HIV protease inhibitors containing hydroxypyrrolidine or hydroxypiperidine heterocycles. The synthesis involves as a key step a double reductive amination[7] of a dialdehyde and an amine fragment, both of which are derived from L-amino acids.

Scheme 1 shows a general synthetic sequence leading to both of the two diastereomeric 3-hydroxypyrrolidines **9a** and **9b**.



a: N-methylpiperidine, methyl chloroformate, CH_2Cl_2-THF, -20°C; N-methylpiperidine, N-methoxy-N-methylamine, b: allyl magnesium bromide, THF, -40°C, c: vinyl magnesium bromide, -40°C, d: allyl magnesium bromide, anhyd $CeCl_3$, THF, e: NaH, THF; Boc_2O, Et_3N, CH_2Cl_2, f: O_3, MeOH, -78°C; Me_2S, g: $NaB(CN)H_3$, amine 7, AcOH, MeOH, pH 6, h: NaOH, MeOH

N-Methoxy-N-methyl amide **2** derived from N-*tert*-butoxycarbonylphenylalanine **1** served as a common starting material for the two isomeric 3-hydroxypyrrolidines **9a** and **9b**. Preparation of 2-propenyl ketone **3** and vinyl ketone **4** from the amide **2** was achieved in excellent yields (both ~98%) by the use of allyl- and vinyl Grignard reagents, respectively.

Addition of vinyl Grignard to ketone **3** afforded **5a** as a major product in a 4:1 ratio[8] in 68% combined yield, while formation of the isomeric tertiary alcohol **5b** was favored (3/1, 56% combined yield) in the addition reaction of allyl Grignard to ketone **4** in the presence of cerium chloride.[9] Control of the stereochemistry of **5a** and **5b** at the tertiary hydroxyl carbon was accomplished by utilizing the inherent stereogenic center of the starting amino acid. In the former case the product was accompanied by 1-propenyl ketone (16%) arising from base-induced double bond isomerization of the starting ketone. In the latter case, the product from 1,4-addition of vinyl Grignard was isolated in 20% yield. The hydroxyl groups in **5a** and **5b** were protected as

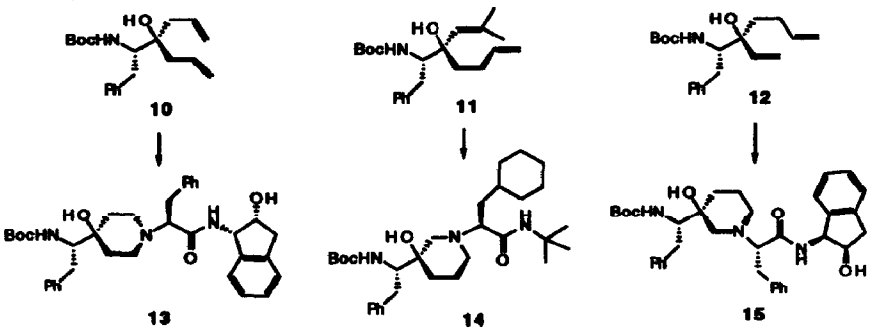
oxazolidinones **6a** and **6b**, respectively.[10] An X-ray crystallographic study performed on oxazolidinone **6a** (m.p. 104-105.5°C) confirmed the *S* configuration of the tertiary hydroxyl carbon of **5a**.[11]

Assembly of the two P_1P_2 and $P_1'P_2'$ fragments was accomplished in one step by the double reductive amination of the crude dialdehyde obtained from the ozonolysis of **6** and amine **7**.[12] Although the yields of this crucial step (38-42%) still need to be optimized, it is noteworthy that the convergent nature of the coupling step should allow one to incorporate various $P_1'P_2'$ groups into the inhibitor molecule in a later stage of the synthesis.

Final hydrolysis of the protecting oxazolidinone group provided the 3-hydroxypyrrolidine **9a** and **9b** in 60-70% yields along with minor products (15-20%) arising from the hydrolysis of the Boc group, which was easily separated by silica gel column chromatography.

Synthesis of hydroxypiperidine derivatives was more straightforward. As outlined in Scheme 2, hydroxydienes **10**, **11**, and **12** were directly utilized without protecting the hydroxyl groups in the ozonolysis step to furnish the crude dialdehydes. Reductive amination reaction of the dialdehydes with an amine such as **7** subsequently provided hydroxypiperidines **13**, **14**, and **15**, in 60, 55 and 54% yields, respectively.

Scheme 2



In summary, a series of conformationally restricted cyclic HIV-1 protease inhibitors were prepared through a convergent double reductive amination strategy. Some of these inhibitors exhibited submicromolar inhibitory activity (e.g. compound **9a**: IC_{50}=0.6 μM) towards the enzyme. Detailed structure-activty relationship of these types of inhibitors and crystallographic structure analysis of inhibitor-bound HIV-1 protease will be reported in due course.

Acknowledgment: We are grateful to Dr. H. Ramjit, Mr. A. Codington, and J. P. Moreau for analytical support and Ms. J. Kaysen for the preparation of this manuscript.

References and notes

1. (a) Gallo, R. C..; Montagnier, L. *Sci. Am.* **1988**, *259*, 40; (b) Coffin, J.; Hasse, A.; Levy, J. A..; Montagnier, L.; Oroszlan, S.; Teich, N.; Temin, H.; Toyashima, K.; Varmus, H.; Vogt, P.; Weiss, R. *Science* **1986**, *232*, 697.

2. (a) Ratner, L.; Haseltine, W.; Patarca, R.; Livak, K. J.; Starcich, B.; Josephs, S. F.; Doran, E. R.; Rafalsi, J. A.; Whitehorn, E. A.; Baumeister, K.; Ivanoff, L.; Petteway, Jr., S. R.; Pearson, M. L.; Lautenberger, J. A.; Papas, T. S.; Ghrayeb, J.; Chang, N. T.; Gallo, R. C.; Wong-Staal, F. *Nature*, **1985**, *313*, 277-284; (b) Kaplan, A. H.; Zack, J. A.; Knigge, M.; Paul, D. A.; Kempf, D. J.; Norbeck, D. W.; Swantrom, R. *J. Virol.* **1993**, 4050.
3. Kramer, R. A.; Schaber, M. D.; Skalka, A. M.; Ganguly, K.; Wong-Staal, F.; Reddy, E. P. *Science* **1986**, *231*, 1580-1584.
4. For reviews on protease inhibitors, see: (a) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305-2314; (b) Meek, T. D. *J. Enz. Inhib.* **1992**, *6*, 65-98; (c) Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543-85; (d) Martin, J. A. *Antiviral Research* **1992**, *17*, 265-78.
5. Tucker, T. J.; Lumma, Jr., W. C.; Payne, L. S.; Wai, J. M.; de Solms, J.; Giuliani, E. A.; Darke, P. L.; Heimbach, J. C.; Zugay, J. A.; Schleif, W.A.; Quintero, J. C.; Emini, E. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1992**, *35*, 2525-2533.
6. For the synthesis of 1(S)-amino-2(R)-hydroxyindane, see Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1685-1701.
7. For a convergent double reductive amination to form small size amine rings, see (a) Verardo, G.; Giumanini, A. G.; Favret, G.; Strazzolini, P. *Synthesis*, **1991**, 447; (b) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777-80; (c) Shim, S. C.; Huh, K. T.; Park, W. H. *Tetrahedron*, **1986**, *42*, 259.
8. Few examples exist in the literature for stereoselective, chelation-controlled nucleophilic addition to N-protected α-aminoketones: (a) Rich, D. H.; Sun, C.-Q.; Vara Prasad, J. V. N.; Pathiasseril, A.; Toth, M.V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Houseman, K. *J. Med. Chem.* **1991**, *34*, 1225; (b) Maugras, I.; Poncet, J.; Jouin, P. *Tetrahedron*, **1990**, *46*, 2807; (c) Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 4143. Excellent stereoselectivities were observed for the opposite stereochemistry in the case of nonchelation-controlled addition. See for example, Diedrich, A. M.; Ryckman, D. M. *Tetrahedron Lett.* **1993**, *34*, 6169.
9. Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.
10. Subsequent reductive amination reactions in the presence of this free hydroxyl group were sluggish and yields of the desired product were very low.
11. Crystal structure details: $C_{20}H_{25}NO_4$, $M_r = 343.43$, monoclinic space group $P2_1$, $a = 12.930$ (3), $b = 6.560$ (2), $c = 13.013$ (2) Å, $\beta = 113.21$ (1)°, $V = 1014.4$ Å^3, $Z = 2$, $D_{calc} = 1.124$ g cm^{-3}, monochromatized radiation λ(Cu K_α) = 1.54184 Å, $\mu = 0.60$ mm^{-1}, $F(000) = 368$, $T = 296$ K. Data collected on a Rigaku AFC5R diffractometer to a 2θ limit of 140° with 506 observed data, at the $I \geq 3\sigma(I)$ level, out of 2135 measured. Structure solved using direct methods and refined using full-matrix least-squares on F using 100 parameters. All non-hydrogen atoms refined with isotropic thermal displacements. Hydrogen atom contributions included in calculations. Final agreement statistics are: $R = 0.083$, $wR = 0.064$, $S = 2.76$, $(\Delta/\sigma)_{max} = 0.02$. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in a final difference Fourier map is (0.34(6) eÅ^{-3}) with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
12. Compound 7 was prepared from BocPhe and 1(S)-amino-2(R)-hydroxyindane under a standard peptide coupling condition (HOBT, EDC in DMF at pH=8.5 adjusted by adding Et_3N, 18 h, r.t.) follwed by deprotection of Boc group (HCl(g) in EtOAc, 0°C, 92% yield for two steps after recrystalization from 75% EtOAc/Hexane, mp 181.5-182.0°C).

(*Received in USA* 19 *April* 1994; *revised* 18 *May* 1994; *accepted* 25 *May* 1994)