Bioorganic & Medicinal Chemistry Letters, Vol.2, No.4, pp. 353-356, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

SYNTHESIS OF C_2-SYMMETRIC HIV-1 PROTEASE INHIBITORS FROM D-MANNITOL

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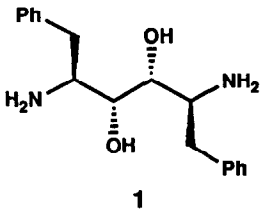
(*Received* 30 *December* 1991)

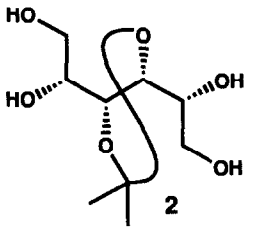
Abstract- Synthesis of C_2-symmetric HIV-1 protease inhibitors from D-mannitol is described.

Human Immunodeficiency Virus type-1 (HIV-1), the causative agent of acquired immunodeficiency syndrome (AIDS) encodes a proteinase (HIV-1 protease) which proteolytically processes the *gag* and *gag-pol* polyproteins.[1] The action of this enzyme is essential for the proper assembly and maturation of fully infectious virions.[2] HIV-1 protease is an aspartic protease dimer with C_2 axis of symmetry.[3,4] Several groups have designed inhibitors to take advantage of the C_2-symmetry of the enzyme.[5] These compounds have been shown to be very potent inhibitors of HIV-1 protease.[5] In view of the recent reports by Chenera et al[6a] and Ghosh et al[6b] we disclose synthesis of C_2-symmetric HIV-1 protease inhibitors from readily available D-mannitol.

The synthesis of **1** from commercially available D-mannitol derivative **2** appeared very attractive to us as it had the four chiral centers with desired absolute and relative configurations.



1

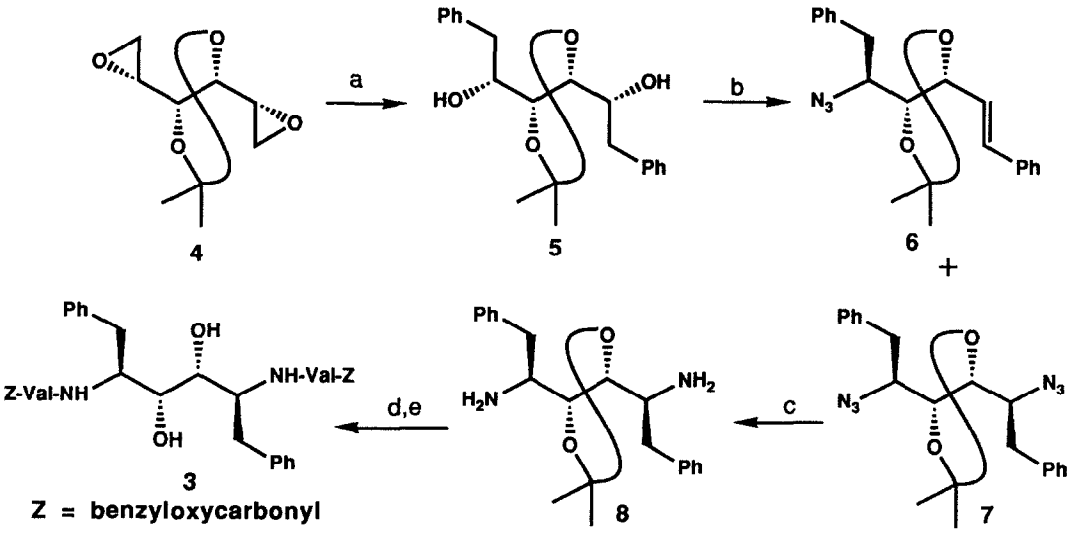


2

The amino acid residues[7] at P_1 or P_1' could be varied by appropriate selection of a nucleophile for opening of the diepoxide **4** (Scheme 1). Similarly the amino terminals of **1** at both ends could be derivatized with amino acids in order to probe the enzyme active site.

The HIV-1 protease inhibitor **3** was synthesized as shown in Scheme 1. The starting diepoxide **4** was prepared from D-mannitol following the literature procedure.[8] Addition of diphenyl cuprate (prepared by reaction of PhLi with either CuBr.S(CH3)2 or CuCN) to the epoxide **4** provided diol **5** in 90% yield. Conversion of diol **5** to diazido derivative **7** was found to be difficult. The diazido compound **7** was always accompanied by elimination product **6**.

Scheme 1



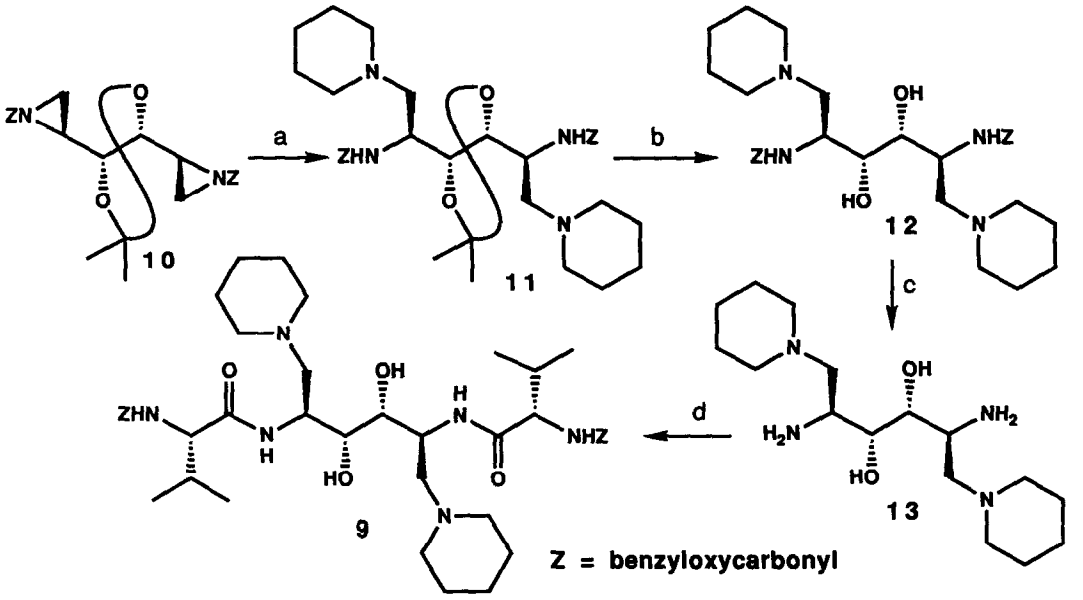
(a) PhLi/CuBr.S(CH_3)$_2$, 90% yield; (b) Ph_3P/ EtOOCN=NCOOEt/ $(PhO)_2P(O)N_3$; (c) H_2/ 10% Pd on C, 38% yield from **5**; (d) Z-L-Val, iBuOCOCl, N-methyl morpholine; (e) 4% HCl in anhydrous methanol, 60% yield from **8**.

Use of triphenylphosphine/ diethylazodicarboxylate/ diphenylphosphorylazide combination gave the best results.[9] The inseparable mixture of **6** and **7** was reduced to diaminoacetonide by catalytic hydrogenation and purified on silica gel (2% followed by 4% methanol in chloroform was used as eluent) to provide **8** in 38% overall yield from **5**. The diaminoacetonide **8** was readily coupled with Z-L-valine by using the mixed anhydride procedure[10] followed by removal of the acetonide with 4% wt./ wt. hydrogen chloride in anhydrous methanol to provide **3** [m. p. 216-218° C, $[\alpha]_D$ -29.4 (c, 0.74, DMSO)].

We also utilized the known D-mannitol derivative[11] **10** for the synthesis of compounds containing heterocyclic moieties at P_1 and P_1' as shown in Scheme 2. Diaziridine **10** on treatment with piperidine in DMF at room temperature furnished **11** which on exposure to acid in methanol provided **12**. Hydrogenolysis of **12** followed by coupling of the resulting diaminodiol to valine derivative furnished piperidine containing analog **9** [m. p. 160-162° C,

$[\alpha]_D$ -17.1 (c, 0.53, DMSO)]. It should be noted that unlike the literature report[6] we have established that D-mannitol can also be used for the synthesis of HIV-1 protease inhibitors with heterocycles at P1 and P1'.

Scheme 2



(a) piperidine in DMF, 54% yield; (b) 5% con H_2SO_4 in methanol, 50% yield; (c) H_2/ 10% Pd on C, 74% yield; (d) Z-L-Val-OSu/ DMF; 51% yield.

In conclusion highy efficient, versatile and stereocontrolled synthetic routes to C_2-symmetric HIV-1 protease inhibitors have been developed from inexpensive D-mannitol.

ACKNOWLEDGEMENTS

The authors thank Drs. Thomas R. Sharpe and David A. Jackson for encouragement and support during the course of this work.

REFERENCES AND NOTES

1. (a) Barre-Sinoussi, F.; Chermann, J. C.; Rey, R.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, 220, 868. (b) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. *Science* **1984**, 224, 500.
2. Kramer, R. A.; Schaber, M. D.; Skalka, A. M.; Ganguly, K.; Wong-Staal, F.; Reedy, E. P. *Science* **1986**, 231, 1580.

3. (a) Darke, P. L.; Leu, C. T.; Davis, L. J.; Heimbach, J. C.; Diehl, R. E.; Hill, W. S.; Dixon, R. A. F.; Sigal, I. S. *J. Biol. Chem.* **1989**, 264, 2307. (b) Meek, T. D.; Dayton, B. D.; Metcalf, B. W.; Dryer, G. B.; Strickler, J. E.; Gorniak, J. G.; Rosenberg, M.; Moore, M. L.; Maagard, V. W.; Debouck, C. *Proc. Natl. Acad. Sci. USA* **1989**, 86, 1841. (c) Navia, M. A.; Fitzgerald, P. M. D.; McKeever, B. M.; Leu, C.; Heimbach, J. C.; Gerver, W. K.; Sigal, I. S.; Darke, P. L.; Springer, J. P. *Nature.* **1989**, 337, 615. (d) Wlodawer, A.; Miller, M.; Jaskolski, M.; Satyanarayan, B. K.; Baldwin, E.; Weber, I. T.; Selk, L. M.; Clawson, L.; Schneider. J.; Kent, S. B. H. *Science* **1989**, 245, 616.
4. (a) Dryer, G. B.; Metcalf, B. W.; Tomaszek, T. A.; Carr, T. J.; Chandler, A. C.; Hyland, L.; Fakoury, S. Z.; Magaard, V. W.; Moore, M. L.; Strickler, J. E.; Debouk, C.; Meek, T. D. *Proc. Natl. Acad. Sci. USA* **1989**, 86, 9752. (b) Tomaselli, A. G.; Olsen, M. K.; Hue, J.; Staples, D. J.; Sawyer, T. K.; Heinrikson, R. L.; Tomich, C. -S. C. *Biochemistry* **1990**, 29, 264. (c) Rich, D. H.; Green, J.; Toth, M. V.; Marshal, G. R.; Kent, S. B. H. *J. Med. Chem.* **1990**, 33, 1285. (d) Meek, T. D.; Lambert, D. M.; Dryer, G. B.; Carr, T. J.; Tomaszek, T. A.; Moore, M. L.; Strickler, J. E.; Debouk, C.; Hyland, L. J.; Mathews, T. J.; Metcalf, B. W.; Pettway, S. R. *Nature* **1990**, 343, 90. (e) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Brodhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L; Thomas, G. J.; Machin, P. J. *Science* **1990**, 248, 358. (f) Ashorn, P.; McQuade, T. J.; Thaisrivongs, S.; Tomasselli, A. G.; Tarpley, W. G.; Moss, B. *Proc. Natl. Acad. Sci. USA* **1990**, 87, 7472. (g) Vacca, J. P.; Guare, J. P.; deSolms, S. J.; Sanders, W. M.; Guiliani, E. A.; Young, S. D.; Darke, P. L.; Zugay, J.; Sigal, I. S.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1991**, 34, 1225.
5. (a) Erickson, J.; Neidhart, D. J.; VanDrie, J.; Kempf, D. J.; Wang, X. C.; Norbeck, D.; Plattner, J. J.; Riittonhouse, J.; Turon, M.; Wideburg, N.; Kohlbrenner, W. E.; Simmer, R.; Helfrich, R.; Paul, D.; Knigge, M. *Science* **1990**, 249, 527. (b) Kemf, D. J.; Norbeck, D. W.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Paul, D.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook, W.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, 33, 2687. (c) Budt, K-H.; Stowasser, B.; Knolle, J.; Ruppert, D.; Meichsner, C.; Paessens, A.; Hansen, J. German Patent Application # 4030350, 1991. (d) Bone, R.; Vacca, J. P.; Anderson, P. S.; Holloway, M. K. *J. Amer. Chem. Soc.* **1991**, 113, 9382.
6. While our work was being cleared for publication within the company two publications involving synthesis of C_2-symmetric HIV-1 protease inhibitors from D-mannitol appeared in the literature. (a) Chenara, B.; Boehm, J. C.; Dreyer, G. B. *Biomed. Chem. Lett.* **1991**, 1, 333. (b) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *Tetrahedron Lett.* **1991**, 32, 5729.
7. The nomenclature of amino acid residues at the cleavage sites is according to: Berger, A.; Schechter, I. *Philos. Trans. R. Soc. London Ser. B* **1970**, 257, 249.
8. (a) Wiggins, L.F. *J. Chem. Soc.* **1946**, 384. (b) Merrer, Y. L.; Dureault, A.; Gravier, C.; Languin, D.; Depezay, J. C. *Tetrahedron Lett.* **1985**, 26, 319.
9. Mitsunobu, O. *Synthesis* **1981**, 1.
10. Meienhofer, J. in *The Peptides;* Gross, E.; Meienhofer, J. Eds; Academic Press: New York, 1979; Vol. 1, pp. 263-314.
11. Dureault, A.; Tranchepain, I.; Depezay, J. C. *J. Org. Chem.* **1989**, 54, 5324.