Tetrahedron Letters, Vol. 34, No. 9, pp. 1457-1460, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

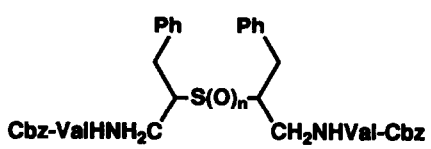
Synthesis Of C_2-Symmetric HIV-Protease Inhibitors With Sulfur-Containing Central Units.

Andrew Spaltenstein*[a], Johann J. Leban[a], and Eric S. Furfine[b]

Divisions of [a] *Organic Chemistry and* [b] *Experimental Therapy* Burroughs Wellcome Co, 3030 Cornwallis Rd., Research Triangle Park, NC 27709

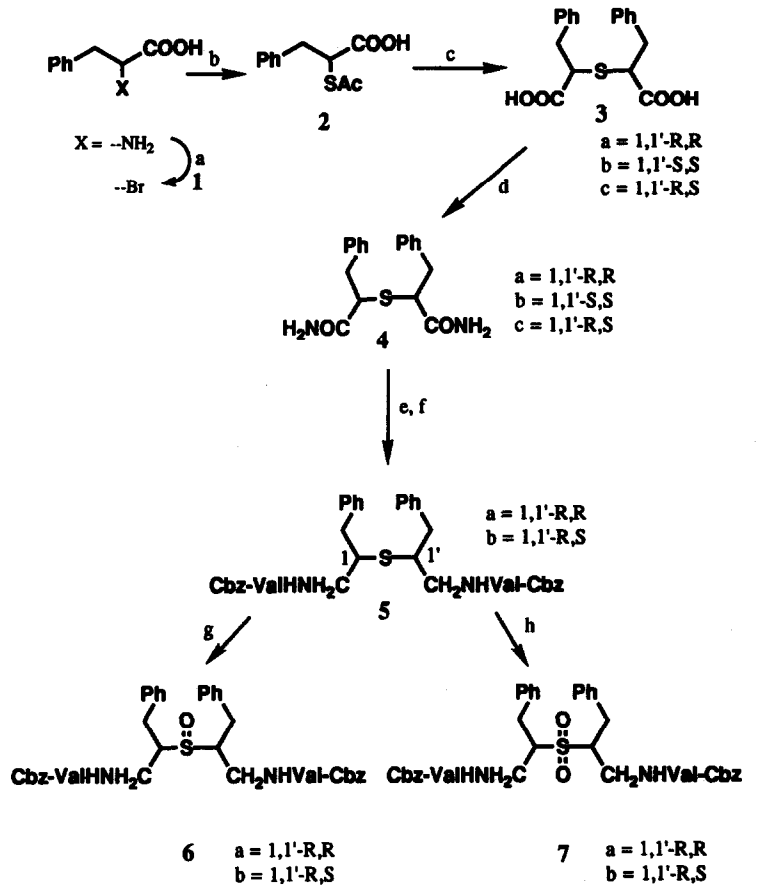
ABSTRACT: Sulfide-, sulfoxide-, and sulfone- containing C_2-symmetric peptide analogs were obtained stereospecifically starting from phenylalanine. The compounds were evaluated as potential HIV-protease inhibitors and found to be inactive within the limits of the assay.

HIV protease is a virus specific enzyme essential for the proliferation of the human immunodeficiency virus.[1] Inhibitors of HIV protease are attractive drug candidates because they provide a novel mechanism of action for blocking the viral reproduction.[2] A substantial number of selective protease inhibitors have been described in the literature and it was shown that many of them are able to supress the spread of HIV infection in vitro.[3] Recently, the concept of C_2-symmetric peptidic inhibitors of HIV protease was introduced by a group at Abbott.[4] Such compounds of the general formula R'HN-(CHR)-X-(CHR)-NHR', where the core unit X is either -CH(OH)-, or -CH(OH)CH(OH)- , were found to be highly potent inhibitors of HIV protease. Based on these results and on our own molecular modelling studies, we sought to synthesize pseudopeptide **5** to explore the effects of incorporating a sulfide functionality into the central unit of such inhibitors. Oxidation to the sulfoxide or the sulfone oxidation level would then provide the possibility of fine-tuning the electronic environment of the inhibitor core.[5]



5: n=0
6: n=1
7: n=2

The synthesis of target compounds **5-7** proceeded as outlined in Scheme 1[6]: [R]-and [S]-2-bromo-3-phenylacetic acid **1**, obtained in 80% yield from [R]-and [S]-phenylalanine ($NaNO_2$, NaBr, HBr) was converted to the S-acetyl intermediate **2** with inversion of stereochemistry (CH_3COSK, MeOH,).[7] Reaction of [R]-**2** with bromide [S]-**1**, [S]-**2** with bromide [R]-**1** , and of [S]-**2** with bromide [S]-**1**, in methanol, in the



Scheme 1 Reagents and conditions: a. $NaNO_2$, 2M NaBr, aq HBr, rt, 3h, 80% b. KSAc, MeOH, rt, 12h, 90% c. **1**, Na_2CO_3, MeOH, rt, 60h, 72% d. NH_4Cl, BOP, DMF, rt, 3h, 65% e. LAH, THF, rt, 24h f. Cbz-(L)-Val, BOP, DMF, rt, 3h, 45% over 2 steps g. $NaIO_4$, MeOH, H_2O, rt, 12h, 65% h. mCPBA, $CHCl_3$, rt, 36h, 80%

presence of sodium carbonate, afforded optically active diacids [R,R]-**3**, [S,S]-**3**, and the meso-diacid [R,S]-**3**, respectively.[8] The diacids **3** were converted to the diamides **4** with ammonium chloride in DMF / benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP), without loss of stereochemical integrity.[9,10] Reduction of the diamides **4** with lithium aluminum hydride in THF (25°, 24h), afforded the diamines, which were not normally purified, but instead treated directly with Cbz-Valine / BOP, to afford the corresponding sulfur bridged peptides **5**. Oxidation to the sulfoxides **6** and sulfones **7** was accomplished with sodium periodate in MeOH / water, and mCPBA in chloroform, respectively.

Compounds **5-7** were tested in an in vitro radiometric assay using a tritiated nonapeptide and purified HIV protease expressed from E. Coli. All compounds were found to be inactive at < 70 μM. Studies with higher inhibitor concentrations were precluded due to the low solubility of these compounds.

In conclusion, we have developed a stereocontrolled synthesis of a series of potential inhibitors of HIV protease with sulfide, sulfoxide and sulfone bearing central units. This class of compounds was found to be inactive to the extent that solubility permitted meaningful analysis.

ACKNOWLEDGEMENT: We thank Dr Kent Stewart for his assistance with molecular modelling and Drs K. Ingold and N. van Draanen for helpful discussions.

REFERENCES AND NOTES

1. Kohl, N.E.; Emini, E.A.; Schleif,W.A.; Davis,L.J.; Heimbach,J.C.; Dixon,R.A.F.; Scolnick,E.M.; Sigal,I.S. *Proc. Acad. Sci. USA* **1988**, *85*, 4686.
2. Kramer, R. A. *Science*, **1986**, *231*, 1580.
3. a. Moore,M.L.; Btyan,W.M.; Fakhoury,S.A.; Magaard,V.W.; Huffman,W.F.; Dayton,B.D.; Meek,T.D.; Hyland,L.; Dreyer,G.B.; Metcalf,B.W.; Strickler,J.E.; Gorniak,J.G.; Debouk,C. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 420. b. McQuade,T.J.; Tomasselli,A.G.; Lui,L.; Karacostas,V.; Moss,B.; Sawyer,T.K.; Heinrickson,R.L.; Tarpley,W.G. *Science*, **1990**, *247*, 454. c. Roberts,N.A.; Martin,J.A.; Kinchinton,D.; Broadhurst,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.; Thopmas,G.J Machin,P.J. *Science* **1990**, *248*, 358. d. Rich,D.H.; Green,J.; Toth,M.V.; Marshall,G.R.; Kent,S.B.H. *J. Med. Chem.* **1990**,*33*, 1285.
4. Kempf,D.J.; Norbeck,D.W.; Codacovi,L.M.; Wang,X.C.; Kohlbrenner,W.E.; Wideburg,N.E.; Paul,D.A.; Knigge,M.F.; Vasavanoda,S.; Craig-Kennard,A.; Saldivar,A.; Rosenbrook,Jr.,W.; Clement,J.J.;

Plattner,J.J.; Erickson,J. *J. Med. Chem.* **1990**, *33*, 2687.

5. Rivero,R.A.; Greenlee,W.J.; Patchett,A.A. *Tetrahedron Lett.* **1991**, *32*, 5263.

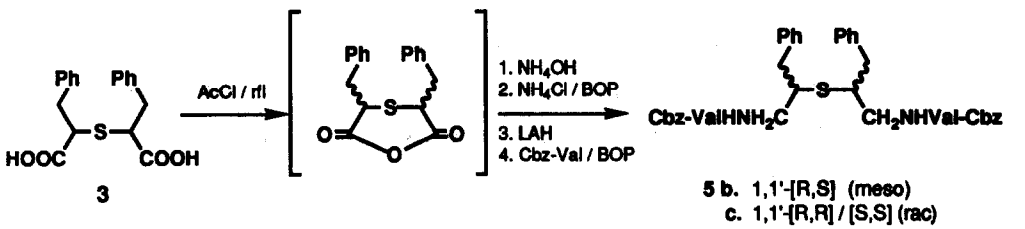
6. All compounds gave ^{1}H NMR, IR and low or high resolution FAB-MS spectra consistent with the proposed structures. Selected examples gave satisfactory elemental analyses.

7. Ondetti,M.A. German Patent **1980**, DE 3012140 A1

8. A general procedure for the coupling of **1** and **2** is given below: A solution of 2.0g (11 mMol) of S-**2** and 2.2g (12 mMol) of S-**1** in 20 mL of methanol was purged with nitrogen and treated with 2.7g (20 mMol) of sodium carbonate. After stirring for 60 h at 25°, the mixture was diluted with ether and extracted with 1N hydrochloric acid. The ether layer was dried (magnesium sulfate) and treated briefly with gaseous ammonia. The bis- ammonium salt of meso **3** was collected by filtration (2.2g; 60%)[9].

9. Analytical data for selected compounds: ^{1}H NMR: **3c** (D_2O) δ 2.97(2H,ddddJ=6,6,7,7Hz), 3.53(1H,dd,J=6,7Hz), 7.21(5H,m), **3a,b** (D_2O) 2.97(2H,d,J=7Hz), 3.56(1H,t,J=7Hz), 7.21(5H,m), **4c** (DMSO-d_6) 2.85(1H,dd,5,14Hz), 3.10(1H,dd,10,14Hz), 3.63(1H,dd,5,10Hz), 6.95(1H,bs,NH), 7.21(5H,m), 7.41(1H,bs,NH), **4a,b** 2.81(1H,dd,J=5,14Hz), 3.05(1H,dd,10,14Hz), 3.63(1H,dd,5,10Hz), 7.00(1H,bs,NH), 7.22(5H,m), 7.41(1H,bs,NH), **5b** (DMSO-d_6) 0.87(6H,dd), 1.98(1H,m), 2.54(1H,m), 2.85(2H,m), 3.00 and 3.15(1H,m), 3.82(1H,m), 5.00(2H,m), 7.16-7.36(10H,m),7.99(1H,bt,NH), **6b** ($CDCl_3$) 1:1 mixture of sulfur diastereomers:0.93(6H,m), 2.00 and 2.18(0.5H,m), 2.75(0.5H,m), 2.95(1H,m),3.06-3.18(2.5H,m), 3.5-3.7(1H,m),3.95(1H,m), 5.01(2H,dd), 5.4(0.5H,bd), 5.80(0.5Hbd), 7.0-7.4(11H,m), **7b** ($CDCl_3$) 0.85(6H,dd), 2.10(1H,m), 2.82(1H,m), 3.42(2H,m), 3.50(1H,m), 3.79(1H,m),4.99(2H,dd), 5.38(1H,bd,NH), 6.78(1H,bd,NH), 7.10(1H,d), 7.30(9H,m), $[\alpha]^{20}$ (as bis-ammonium salts,10mg/mL H_2O): **3a** +30.4°, **3b** -31.3°

10. Alternatively, if stereochemical control is not essential, the meso and racemic sulfides may be obtained by treating diacid **3** with refluxing acetyl chloride[11] which results in complete loss of optical activity and in the formation of the meso and racemic cyclic anhydrides in roughly equal amounts, as inferred from the mixture of diastereomers obtained after conversion to the corresponding peptides **5.**



11. Ksander,G.M.; Diefenbacher,C.G.; Yuan,A.M.; Clark,F.; Sakane,Y.; Ghai,R.D. *J. Med. Chem.* **1989**, *32*, 2519.

(Received in USA 16 November 1992; accepted 16 December 1992)