Published in final edited form as:

J Org Chem. 1991 November ; 56(23): 6500–6503. doi:10.1021/jo00023a009.

An Efficient Synthesis of Hydroxyethylene Dipeptide Isosteres: The Core Unit of Potent HIV-1 Protease Inhibitors

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Summary:

An efficient and stereocontrolled synthesis of hydroxyethylene dipeptide isosteres **1** from commercially available, optically pure D-mannose is described. This synthesis represents a practical and enantioselective entry to a range of other dipeptide isosteres, which are not limited to amino acid derived substituents.

Since the advent of acquired immunodeficiency syndrome (AIDS) and the discovery of its causative agent, human immunodeficiency virus (HIV-1),¹ the design and synthesis of mechanism-based HIV-1 protease inhibitors has intensified tremendously. The HIV-1 protease, an aspartic protease, is a proteolytic enzyme that cleaves the gag and gag-pol precursor polyproteins into the functional proteins of infectious virus particles.² In vitro disruption of this protease-dependent processing step results in the production of protease-defective virions which are immature and noninfectious.³ Therefore, therapeutic intervention of this enzyme represents a powerful strategy for the treatment of AIDS and related ailments.

Recently, we⁴ and others⁵ have reported a series of potent and selective HIV-1 protease inhibitors which are designed based on the transition-state mimetic concept.⁶ This approach incorporates the natural amino acid statine⁷ and hydroxyethylene dipeptide isostere^{8,9} at the scissile site, an approach that has been successfully utilized in the design and synthesis of potent inhibitors of renin¹⁰ and other aspartic proteases.¹¹ Since the first synthesis of hydroxyethylene dipeptide mimics, by Szelke⁸ and Rich⁹ in 1983, several other syntheses of dipeptide isosteres have appeared in the literature.¹² The majority of previous syntheses, however, have limitations with regard to stereochemical controls and variations of the substituents at C-2 and C-5 positions. In connection with the synthesis of potent and selective inhibitors of HIV-1 protease, we required an efficient, flexible and enantioselective synthesis of hydroxyethylene dipeptide mimics which were not limited to amino acid derived substituents. We describe here a new synthesis of Phe-Phe isostere **1** through the inter-mediacy of lactone **2**, with absolute stereocontrol at the C-4 and C-5 positions, utilizing commercially available and optically pure D-mannose as starting material. This synthesis is

Supplementary Material Available:

Experimental procedures and spectral data for compounds 5–14 (7 pages). Ordering information is given on any current masthead page.

potentially versatile and represents a practical and enantioselective entry to other dipeptide isosteres with a wide variety of substituents at C-2 and C-5 positions.

As shown in Scheme I, optically active D-mannose presents a unique opportunity for the synthesis of enantiomerically pure Phe-Phe dipeptide isostere **1** and related analogues. D-Mannose **3** already possesses the C-4 hydroxy group of hydroxyethylene isostere **1** with appropriate absolute configuration. Synthesis of isosteric lactone **2** requires deoxygenation of the C-2 and C-3 hydroxy groups, incorporation of phenyl and benzyl groups at C-6 and C-2, and introduction of nitrogen with inversion of configuration at C-5. Thus, D-mannOSe **3** was converted to 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranose **4** according to the reported procedure of Freudenberg.¹³ Required deoxygenation of **4** at the C-2 position was readily achieved utilizing Ireland's procedure.¹⁴ Accordingly, reaction of mannofuranose **4** with carbon tetrachloride (1.2 equiv) and tris(dimethylamino)phosphine (1.2 equiv) in tetrahydrofuran (-78°C for 30 min and then 23°C for 30 min) and subsequent reduction of the resulting furanosyl chloride with lithium in liquid ammonia at -78 to 0°C for 5 h afforded the glycol **5** (72% yield) along with a small amount of dehalogenation byproduct **6** (3% yield) after flash chromatography over silica gel. Although the reduction of furanosyl chloride with di-*tert*-butylbiphenyl radical anion resulted in **5** in excellent yield (85%), use of lithium in liquid ammonia was found to be operationally more convenient for large-scale preparation.

Further dehydroxylation of glycol **5** at the C-3 position was efficiently carried out employing Ferrier-type rear-rangement¹⁵ with methanol in the presence of pyridinium *p*-toluenesulfonate in methylene chloride (0 – 23°C for 12 h) to provide a mixture (52:48 by ^1H NMR) of methyl glycoside **7** in 97% isolated yield. Reaction of **5** with 2-propanol in methylene chloride in the presence of *p*-toluenesulfonic acid at 0°C or stannic chloride promoted reaction at -78°C offered no enhancement of the anomeric effect;¹⁶ the ratio of anomers remained the same (1:1) after workup. Since the methyl glycoside **7** would eventually be converted to the corresponding γ -lactone, all subsequent reactions were carried out with the mixture of anomers. Catalytic hydrogenation of **7** with 10% palladium on charcoal under atmospheric pressure in 4:1 ethyl acetate-methanol afforded the corresponding saturated glycoside in quantitative yield. Removal of the isopropylidene group was then effected by heating the resulting glycoside with 40% aqueous acetic acid at 90°C for 3 h, followed by evaporation of solvents under reduced pressure and silica gel chromatography provided diol **8** (84% yield). Glycosidic diol **8** was then converted to the desired epoxide **9** in the following two-step sequence: (1) selective *O*-tosylation of the primary alcohol with *p*-toluenesulfonyl chloride (1.1 equiv) in pyridine at 0°C for 12 h and (2) treatment of the resulting crude tosylate with sodium methoxide (5 equiv) in chloroform at 23°C for 4 h to provide the epoxide **9** in 72% yield after silica gel chromatography.

Regiospecific epoxide ring opening of **9** with phenylmagnesium bromide (2.2 equiv) in the presence of cuprous iodide (1.1 equiv) at -40 to 0 °C for 3 h afforded glycosidic alcohol **10** in 91 % yield after flash chromatography over silica gel. Thus, nucleophilic opening of epoxide **9** allows the incorporation of a variety of substituents at the C-5 position, an option not afforded by previous syntheses of hydroxyethylene isosteres.

Conversion of glycosidic alcohol **10** to the corresponding azide **11** was readily accomplished by a Mitsunobu reaction.¹⁷ Thus, reaction of **10** with triphenylphosphine (1.2 equiv), diethyl azodicarboxylate (1.2 equiv), and diphenylphosphoryl azide (1.2 equiv) in toluene at -10 to 23 °C for 12 h furnished the azide **11** (92% yield) along with a small amount (<3%) of elimination product. Interestingly, formation of the mesylate of **10** with mesyl chloride in pyridine and subsequent displacement of the mesylate with sodium azide in DMF at 90 °C or tetramethylguanidinium azide in DMF at 80 °C resulted in **11** (65–70% yield) and 15–20% elimination product resulting from E₂ reaction. Grieco oxidation¹⁸ of methyl furanoside **11** with *m*-chloroperbenzoic acid (1.2 equiv) in dry methylene chloride at 0 °C for 3 h in the presence of boron trifluoride etherate (0.25 equiv) afforded the corresponding azido γ -lactone in 72% yield after silica gel chromatography. Catalytic hydrogenation¹⁹ of the resulting azido lactone with 10% palladium on charcoal in the presence of di-*tert*-butyl dicarbonate for 6 h furnished the *tert*-butyloxycarbonyl-protected amino lactone **12** (white solid, mp 95 °C) exclusively in 91 % yield. The γ -lactone **12** is a versatile intermediate for the synthesis of suitably substituted hydroxyethylene dipeptide isosteres.

Introduction of a benzyl group at C-2 was accomplished by stereoselective alkylation^{12b} of **12** with benzyl halide. Thus, generation of the dianion of lactone **12** with lithium hexamethyldisilazide (2.2 equiv) in tetrahydrofuran at -78 °C (30 min) and alkylation with benzyl iodide (1.1 equiv) for 30 min at -78 °C, followed by quenching with propionic acid (5 equiv), provided the desired alkylated lactone **2** (84% yield, mp 76 – 78 °C) along with a small amount (<4% by HPLC) of undesired *cis* isomer **13** (mp 112 – 115 °C). The minor *cis* lactone was conveniently removed by column chromatography over silica gel using a mixture (1:1) of ethyl acetate-hexanes as the solvent system. The stereochemical assignment of alkylated lactones **2** and **13** were made based on extensive ¹H NMR NOE experiments as well as by comparison of ¹H NMR spectra with that reported previously.¹² Weinreb amidation²⁰ of lactone **2** with benzylamine (2 equiv) and trimethylaluminum (2 equiv) in methylene chloride (23 °C for 10 min, then 40 °C for 3 h) afforded hydroxyamide **14** (74% yield, mp 179 – 182 °C) after silica gel chromatography.²¹ Lactone **2** was converted to potent and selective inhibitors of HIV-1 protease according to the previous literature procedure.⁴

In conclusion, an efficient, stereocontrolled, and economical synthetic route to dipeptide isostere **1** has been developed. Since the starting material of this synthesis is D-mannose rather than an amino acid, the present methodology should provide convenient access to other dipeptide isosteres with a great deal of structural diversity at C-2 and C-5 positions. Synthesis of a number of HIV-1 protease inhibitors containing hydroxyethylene isosteres and their biological evaluation is currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment.

The authors thank professor Samuel Danishefsky for helpful discussions and acknowledge the encouragement and support of Dr. Joel R. Huff and Dr. Paul S. Anderson.

References

- (1). (a)BarreSinouesi F; Chermann JC; Rey F; Nugeyre MT; Chamaret S; Gruest J; Dauguet C; Axler-Blin C; Vezinet-Brun F; Rouzioux C; Rozenbaum W; Montagnier L Science 1983,220,868. [PubMed: 6189183] (b)Gallo RC; Salahuddin SZ Popovic M; Shearer GM; Kaplan M; Haynes BF; Palker TJ; Redfield R; Oleske J; Safai B; White G; Foster P; Markham PD Science 1984,224,500. [PubMed: 6200936]
- (2). (a)Kramer RA; Schaber MD; Skalka AM; Ganguly K; Wong-Staal F; Reddy EP Science 1986,231,1580. [PubMed: 2420008] (b)Dunn BM; Kay JJ Anti. Chem 1990, 1, 3.
- (3). Kohl NE; Emini EA.; Schleif WA.; Davis LJ; Heimbach JC; Dixon RAF; Scolnick EM; Sigal IS Proc. Natl. Acad. Sci. U.S.A. 1988,85,4686. [PubMed: 3290901]
- (4). (a)Sigal IS; Huff JR; Darke PL; Vacca JP; Young SD; desolms JS; Thompson WJ; Lyle TA; Graham SL; Ghosh A K. Eur. Pat. Appl 0337714, 1988.(b)Lyle TA.; Wiscourt CM; Guare JP; Thompson WJ; Anderson PS; Darke PL; Zugay JA; Emini EA; Schleif WA; Quintero JC; Dixon RAF; Sigal IS; Huff JR J. Med. Chem 1991, 34, 1228 and references cited therein. [PubMed: 2002466]
- (5). (a)Dreyer GB; Metcalf BW; Tomaszek TA; Carr TJ; Chandler AC; Hyland L; Fakhoury SA; Magaard VW; Moore ML; Strickler JE; Debouck C; Meek TD proc. Natl. Acad. Sci. U.S.A. 1989, 88, 9752.(b)McQuade TJ; Tomasselli AG; Liu L; Karacostas V; Moss B; Sawyer TK; Heinrickson RL; Tarpley WG Science 1990, 247, 454. [PubMed: 2405486] (c)Roberts NA; Martin JA; Kinchington D; Broadhunt AV; Craig JC; Duncan IB; Galpin SA; Handa BK; Kay J; Krohn A; Lambert RW; Merrett JH; Mills JS; Parkes KEB; Redshaw S; Ritchie AJ; Taylor DL; Thomas GJ; Machin PJ Science 1990, 248, 358. [PubMed: 2183354] (d)Ashorn P; McQuade TJ; Thaisrivongse S; Tomasselli AG; Tarpley WG; Moss B Proc. Natl. Acad. Sci. U.S.A. 1990,87, 7472 and references cited therein. [PubMed: 2217178]
- (6). (a)Pauling L Chem. Eng. News 1946, 24, 1375.(b)Wolfenden R Nature 1969, 223, 704. [PubMed: 4979456] (c)Marciniszyn J; Hartsuck J; Tang JJBiol. Chem 1976, 251, 7088.
- (7). (a)Niahi T; Kitamura M; Ohkuma T; Noyori R Tetrahedron Lett. 1988, 29, 6327.(b)Bemardi A; Micheli F; Potenza D; Scolastico C; Villa R Tetrahedron Lett. 1990, 31, 4949 and references cited therein.
- (8). (a)Szelke M; Jones DM; Atrash B; Hallett A; Leckie B J. Proc. Am. Pept. Symp. 8th 1983,579. (b)Leckie BJ; Grant J; Hallett A; Hughes M; Jones DM; Szelke M; Tree M Scott. Med. J. 1984, 29, 125. [PubMed: 6397858]
- (9). (a)Rich DH; Salituro FG; Holliday MW hoc. Am. Pept. Symp. 8th 1983,511.(b)Holliday MW; Rich RH Tetrahedron Lett. 1983, 24, 4401.
- (10). Greenlee WJ J. Med. Res. Rev 1990, 10, 173 and references cited therein.
- (11). (a)Acid proteases: Structure, Function, and Biology; Tang J, Ed.; Plenum: New York, 1977. (b)Peach, M. J. Physiol. Rev. 1977, 57, 313.
- (12). (a)Evans BE; Rittle KE; Homnick CF; Sarin d. P.; Hirshfeld J; Veber DF J. Org. Chem 1985, 50, 4615.(b)Fray AH; Kaye RL; Kleinman EF J. Org. Chem 1986, 51, 4828.(c)Kempf DJ J. Org. Chem 1986, 51 3921.(d)Bradbury RH; Revill JM; Rivett JE; Waterson D Tetrahedron Lett. 1989, 30, 3845.(e)Herold P; Duthaler R; Rihs G; Angst CJ Org. Chem 1989,54, 1178(f)Chakravarty PK; de Laszlo SE; Sarnella CS; Springer JP; Schude PF Tetrahedron Lett. 1989, 30, 415.
- (13). Freudenberg K; Wolf A Ber. 1927,60, 232.

- (14). (a)Ireland RE; Thaisrivongs S; Vanier N; Wilcox CS J. Org. Chem 1980,45,48.(b)Ireland RE; Norbeck DW; Mandel GS; Mandel NS J. Am. Chem. SOC 1985, 107, 3285.
- (15). (a)Ferrier RJ; J. Chem. SOC 1964, 5443.(b)Ferrier RJ; Prasad NJ Chem. SOC. C 1969, 570.
- (16). (a)Lemieux RU Pure Appl. Chem 1971,27,527.(b)Zefirov NS; Shekhtman NM Russ. Chem. Rev 1971, 40, 315.
- (17). (a)Lal B; Pramanik BN; Manhas MS; Bose AK; Tetrahedron Lett. 1977, 23, 1977.(b)Shioiri T; Ninomiya K; Yamada s.; J. Am. Chem. SOC. 1972,94,6203. [PubMed: 5054412] (c)Mitsunobu O; Synthesis 1981, 1.
- (18). Grieco PA; Oguri T; Yokoyama Y Tetrahedron Lett. 1978, 419.
- (19). (a)Maaahiro S; Hori K; Ohfuné Y Tetrahedron Lett. 1988,29, 2983.(b)Saito S; Nakajima H; Inaba M; Moriwake T Tetrahedron Lett. 1989, 30, 837.
- (20). Basha A; Lipton M; Weinreb SM Tetrahedron Lett. 1977, 4171.
- (21). All new compounds gave satisfactory spectroscopic and analytical results.

Scheme Ia.

^a**Reagents:** (a) Me₂C=O, 3% H₂SO₄, 23 °C, 12 h; (b) CCl₄, (Me₂N)₃P, THF, -78 to 23 °C, 1 h; then Li, NH₃, -78 to 0 °C, 5 h; (c) MeOH, PPTS, CH₂Cl₂, 0–23 °C, 12 h; (d) 10% Pd-C, H₂, Et-OAc-MeOH (4:1), 5 h; (e) 40% aqueous AcOH, 90 °C, 3 h; (f) *p*-TsCl, pyridine, 0–23 °C, 12 h; (g) NaOMe, CHCl₃, 0 °C for 10 min; then 23 °C, 4 h; (h) PhMgBr, CUI, THF, -40 to 0 °C, 3 h; (i) Ph₃P, EtO₂CN=NCO₂Et, Ph₂P(O)N₃, PhMe, -10 to 23 °C, 12 h.

Scheme IIa.

^a**Reagents:** (j) MCPBA, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 0 °C, 3 h; (k) 10% Pd-C, H_2 , EtOAc, BOC_2O , 6 h; (l) $(\text{TMS})_2\text{NLi}$, THF, -78 °C, 30 min; PhCH_2I , -78 °C, 30 min; then $\text{MeCH}_2\text{CO}_2\text{H}$, -78 to 23 °C, 15 min; (m) Me_3Al , PhCH_2NH_2 , CH_2Cl_2 , 40 °C, 3 h.