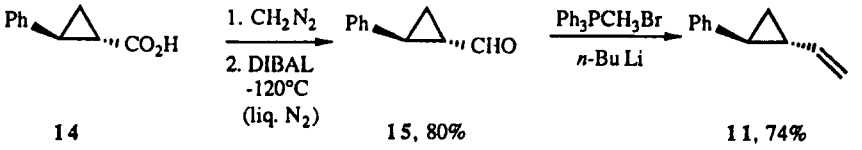
Scheme III



14 15, 80% 11, 74%

ticipation of using it for delineating the mechanism of enzymatic oxidations that require terminal olefin substrates.[21]

The vinylcyclopropane probe 11 was constructed, as outlined in Scheme III, in three steps and 59% yield from commercially available 14. The probe contained ~3% of the cis cyclopropyl isomer, reflecting the ratio of cis to trans isomers in the starting acid 14.

The epoxidation reactions were performed at 0.18 mmol scale[2] and were followed by GLC using response factors determined from authentic samples using decane as an internal standard.[22] Additionally, several control experiments were performed with and without catalyst, oxidant, and substrate. After 12 h, the reactions were quenched and the mixtures were analyzed by GLC and GC/MS. The chromatograms of the reaction mixtures were compared to those of authentic products. The identity of each component of the reaction mixtures was verified by GC/MS, co-injection, thin layer chromatography (TLC), and ^{1}H NMR comparison of the isolated products. The major product observed was the cyclopropane epoxide (72% yield by GLC, 83% conversion),[23] *and no products of cyclopropyl ring opening were observed by ^{1}H NMR analysis of the crude reaction mixture.* An unidentified peak on the GLC was determined as having arisen from the decomposition of the product epoxide as evidenced by the observation of this peak when an authentic sample of epoxide was subjected to the reaction conditions.

The formation of the epoxides in lieu of the cyclopropyl radical or cation rearrangement products strongly supports a concerted mechanism of epoxidation for 11 in which C–O bond formation occurs in a concerted manner at both ends of the olefin. This conclusion is consistent with observations we have made with aliphatically substituted internal *cis*-alkenes such as *cis*-2-octene and *cis*-2,2-dimethyl-3-hexene, which are epoxidized stereospecifically, with the corresponding cis epoxides as sole products. In contrast, aryl-substituted acyclic *cis*-alkenes always provide measurable (3–20%) amounts of the corresponding trans epoxides as byproducts.[1,6] Since neither the *cis*-alkenes nor the cis epoxides isomerize under the reaction conditions, the trans epoxides are primary products.[24] This strongly suggests that aryl-substituted alkenes may proceed by a different, nonconcerted mechanism (e.g. pathways A or D in Scheme I), with benzylic stabilization of the intermediate radical or with stepwise formation of the two C–O bonds in the product epoxide. This is supported by the fact that aryl-substituted olefins react much faster than aliphatically substituted olefins (k_{rel} = 30:1 in sterically similar cases). Enantioselectivities are also very different for these two substrate classes.[25]

In summary, with the use of a hypersensitive probe as a substrate, the Mn(III) salen mediated epoxidation of unfunctionalized alkyl-substituted olefins indicates a concerted process (pathway B or C), and a stepwise process is suggested for the epoxidation of aryl-substituted olefins. Given the ease with which 11 is prepared, this radical probe should prove to be invaluable in the mechanistic evaluation of other monooxygenases and their models.

Supplementary Material Available: Experimental procedures and characterization data for compounds 11, 12, and 15 and GLC data for catalyzed and control reactions (4 pages). Ordering information is given on any current masthead page.

(21) Bruice's (*Z*)-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radical probe[12a,b] would not be a substrate for monooxygenases such as that from *P. oleovorans* since these enzymes are specific for terminal olefins. 11 was not a substrate for *P. oleovorans* monooxygenase, chloroperoxidase, horseradish peroxidase, and cytochrome *c* oxidase. Reaction with other monooxygenases is under investigation.

(22) For these studies, racemic catalyst 1 was employed. Similar results were observed with 2.

(23) Only one epoxide is formed from the reaction as evidenced by GLC and ^{1}H NMR analyses. Efforts are currently underway to determine the stereochemistry of this compound. The reactions were stopped after 12 h and 83% conversion due to the gradual decomposition of epoxide 12 under the reaction conditions. Taking into account the epoxide decomposition product, total mass recovery is estimated to be ~96%.

(24) No isomerization of *cis*-β-methylstyrene oxide is observable when the epoxide is stirred with either 1 or 2 in the presence or in the absence of NaOCl, or if authentic pure cis epoxide is added to an ongoing catalytic epoxidation reaction. These control experiments rigorously rule out the possibility of epoxide cis–trans isomerization to account for the observed trans epoxide byproducts with aryl olefins.

(25) Groves has reported that styrene derivatives and *tert*-butylethylene display opposite facial selectivity in asymmetric epoxidation.[5]

(26) This research was supported by the NSF (CHE-8996249) to C. H.W. and an American Cancer Society Postdoctoral Fellowship (PF-3525, to G.C.L.). E.N.J. acknowledges a NSF Presidential Young Investigator Award (CHE-9057740) and support from the NIH (GM-4314-01A1).

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

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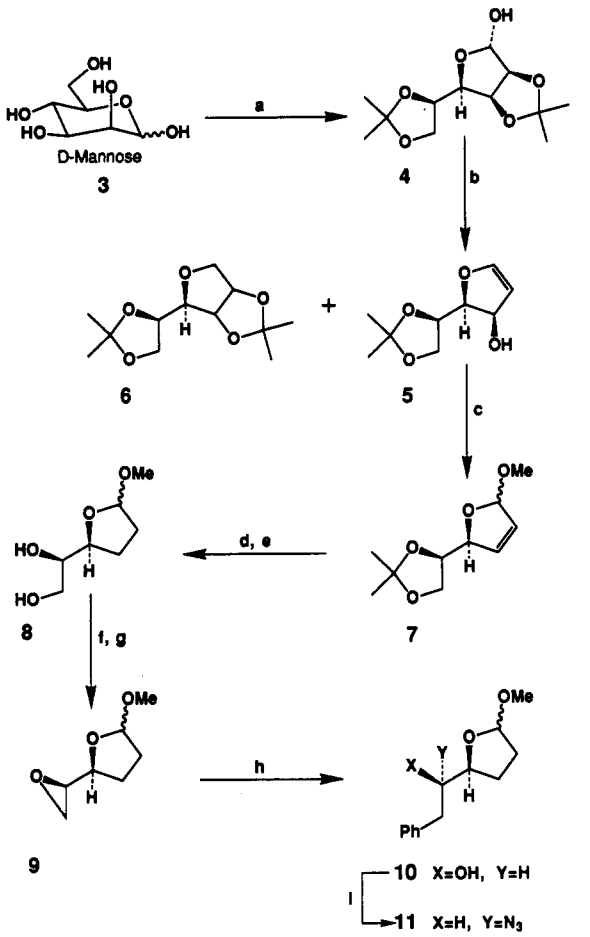
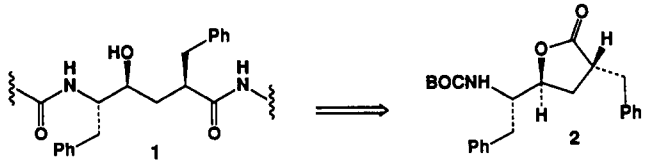
synthesis of mechanism-based HIV-1 protease inhibitors has intensified tremendously. The HIV-1 protease, an aspartic protease, is a proteolytic enzyme that cleaves the gag and gag-pol precursor polyproteins into the functional proteins of infectious virus particles.[2] In vitro disruption of this protease-dependent 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, we[4] and others[5] 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 statine[7] and hydroxyethylene dipeptide isosteres[8,9] at the scissile site, an approach that has been successfully utilized in the design and synthesis of potent inhibitors of renin[10] and other aspartic proteases.[11] Since the first synthesis of hydroxyethylene dipeptide mimics, by Szelke[8] and Rich[9] 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 intermediacy 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 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.

Scheme I[a]



[a] Reagents: (a) Me_2CO, 3% H_2SO_4, 23 °C, 12 h; (b) CCl_4, $(Me_2N)_3P$, THF, −78 to 23 °C, 1 h; then Li, NH_3, −78 to 0 °C, 5 h; (c) MeOH, PPTS, CH_2Cl_2, 0–23 °C, 12 h; (d) 10% Pd–C, H_2, EtOAC–MeOH (4:1), 5 h; (e) 40% aqueous AcOH, 90 °C, 3 h; (f) *p*-TsCl, pyridine, 0–23 °C, 12 h; (g) NaOMe, $CHCl_3$, 0 °C for 10 min; then 23 °C, 4 h; (h) PhMgBr, CuI, THF, −40 to 0 °C, 3 h; (i) Ph_3P, $EtO_2CN{=}NCO_2Et$, $Ph_2P(O)N_3$, PhMe, −10 to 23 °C, 12 h.



Hydroxyethylene Phe-Phe isostere

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 re-

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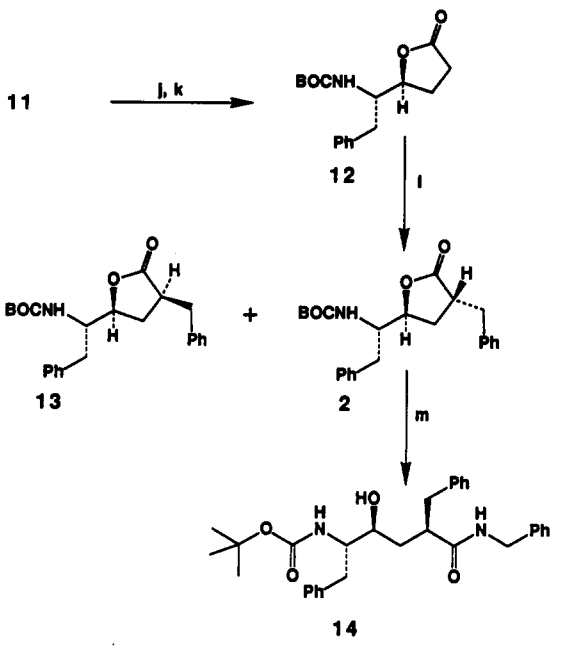
quires deoxygenation of the C-2 and C-3 hydroxy groups, incorporation of phenyl and benzyl groups at C-6 and C-2, and introduction of nitrogen with inversion of configuration at C-5. Thus, D-mannose **3** was converted to 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **4** according to the reported 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 glycal **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 glycal **5** at the C-3 position was efficiently carried out employing Ferrier-type rearrangement[15] 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 ^{1}H 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 E_2 reaction. Grieco oxidation[18] 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 hydrogenation[19] 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**

Scheme II[a]



[a] Reagents: (j) MCPBA, BF_3·OEt_2, CH_2Cl_2, 0 °C, 3 h; (k) 10% Pd–C, H_2, EtOAc, BOC_2O, 6 h; (l) $(TMS)_2NLi$, THF, −78 °C, 30 min; $PhCH_2I$, −78 °C, 30 min; then $MeCH_2CO_2H$, −78 to 23 °C, 15 min; (m) Me_3Al, $PhCH_2NH_2$, CH_2Cl_2, 40 °C, 3 h.

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were made based on extensive ^1H NMR NOE experiments as well as by comparison of ^1H NMR spectra with that reported previously.[12] Weinreb amidation[20] 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.

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.

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

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Enantiomeric Synthesis of (+)-BCH-189 [(+)-(2*S*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine] from D-Mannose and Its Anti-HIV Activity

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Summary: Enantiomerically pure (+)-BCH-189 has been synthesized from D-mannose via 1,6-thioanhydro-D-mannose and its anti-HIV activity has been determined in peripheral blood mononuclear cells.

Since the discovery of AZT[1] as a potent anti-HIV agent, a number of nucleosides have been identified as potentially useful antiviral agents for AIDS and AIDS-related complex.[2-4] More recently several unusual types of nucleosides have been shown to be potent anti-HIV agents, including (±)-BCH-189,[5] dioxolane-T,[5,6] 6-(phenylthio)acyclonucleosides (HEPT),[7,8] and 4′-azidothymidine.[9]

Dioxolane-T and BCH-189 are particularly interesting in that the 3′-CH_2 groups of the 2′,3′-dideoxyribose moieties are replaced by oxygen and sulfur atoms, respectively (Figure 1). (±)-Dioxolane-T[5,6] has been reported to exhibit a moderate anti-HIV activity (EC_{50} = 20 μM) in ATH8 cells as a racemic mixture. Recently, we have synthesized the enantiomerically pure (−)-β-dioxolane-T and evaluated the anti-HIV activity in human peripheral blood mononuclear cells (PBM).[10] In contrast to the previous report of (±)-dioxolane-T in the ATH8 cells,[6] the enantiomerically pure (−)-β-D-dioxolane-T exhibited a potent anti-HIV activity (EC_{50} = 0.3 μM) in human PBM cells.[10] (±)-BCH-189 is a promising nucleoside with potent anti-HIV activity and low toxicity in vitro. (±)-BCH-189 is currently undergoing preclinical toxicology and is expected to undergo clinical trials in the near future. Thus, it was of interest to synthesize the enantiomerically pure form of BCH-189 and determine its anti-HIV activity. We report here the first asymmetric synthesis of enantiomerically pure (+)-BCH-189 and its anti-HIV activity in human PBM cells.

Retrosynthetic analysis of BCH-189 suggests that 1,6-thioanhydro-D-mannose (5) can serve as a chiral intermediate for the synthesis of enantiomerically pure BCH-189. The 1,6-thioanhydro-D-mannose (5) was prepared in five steps from D-mannose (1) (Scheme I). Selective tosylation of the primary hydroxyl group of D-mannose followed by acetylation gave 1,2,3,4-tetra-*O*-acetyl-6-*O*-tosyl-D-mannose (2) in 96.7% yield as a foam, which, without further purification, was converted to the bromo sugar 3 (97.6%) by treatment with 2 molar equiv of HBr/HOAc (45% w/v) using acetic acid as solvent. The bromo sugar 3 was treated with 3 molar equiv of potassium *O*-ethylxanthate in DMF using a similar methodology as used previously by Akagi et. al.[11] and Whistler and Seib[12]

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