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Dipeptide Isosteres. 2. Synthesis of Hydroxyethylene Dipeptide Isostere Diastereomers From a Common γ-Lactone Intermediate. Preparation of Renin and HIV-1 Protease Inhibitor Transition State Mimics.§

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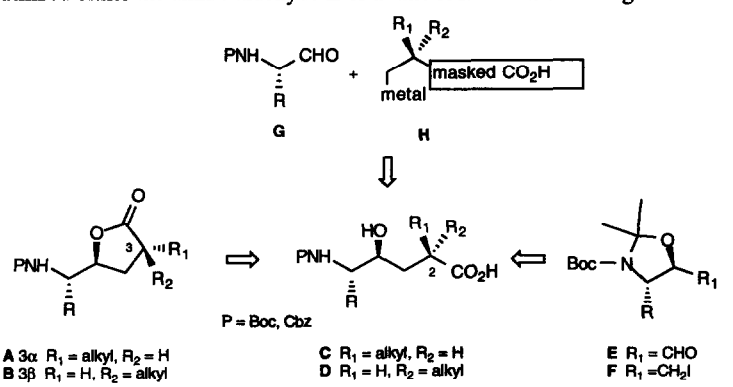
Abstract A general strategy for the synthesis of the hydroxyethylene dipeptide isostere diastereomers **C** or **D** has been developed. The syntheses proceeded through a common γ-lactone intermediate **A** or **B** The C(3α) γ-lactone diastereomer **A** was prepared from the N-Cbz protected α-amino aldehyde and 2-(2-isopropylpropen-2-yl)trimethylsilane in five steps The C(3β) γ-lactone diastereomer **B** was obtained by kinetic protonation of the lactone enolate using malonate derivatives

INTRODUCTION

Hydroxyethylene dipeptide (HED) isosteres function as transition state mimics for the hydrolysis of an amide bond and, when incorporated into peptides, render the peptides stable toward enzymatic cleavage. HED isosteres have been effectively utilized in the design of potent inhibitors of both the aspartic acid proteinases renin[2] and HIV-1[3]. Three general approaches for the synthesis of hydroxethylene dipeptide isosteres **C** and **D** have been developed. The first approach involved the reaction of a N-protected α-amino aldehyde **G** with a 2-substituted-3-(metal)propionate **H**. The carboxylate group of the propionate was masked as either an alcohol,[4] a phenyl ring,[5] or amide.[6] Reaction of the organometallic propionate reagent with the aldehyde **G** proceeded with chelation control, affording as the major diastereomer the secondary alcohol with the S configuration. A second approach utilized either the amino aldehyde **E** or amino iodide **F** as a starting materials. Thus, Evans



aldol[7] or thioester ketene acetal/BF_3•Et_2O[8] condensation using aldehyde **E** followed by deoxygenation of the

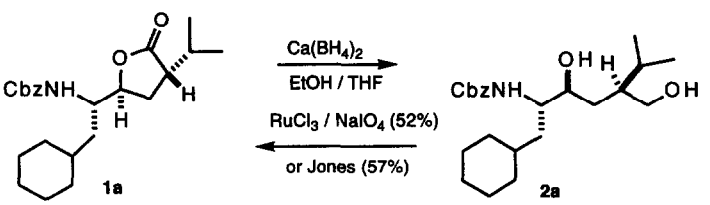
aldol product gave the diprotected hydroxyethylene dipeptide isostere. Alternatively, the HED isostere was assembled either via Wittig olefination of **E** with triethyl 2-alkyl-2-phosphonoacetate and hydrogenation of the resulting α,β-unsaturated ester[9] or alkylation of iodide **F** with an ester enolate.[10] However, no diastereoselectivity at C(2) was obtained in the alkylation reaction. The third approach, and the one most frequently exploited for the synthesis of HED isosteres, involved the synthesis and subsequent opening of the N-Boc γ-lactones **A** or **B** with hydroxide or amines. The preparation of the γ-lactone precursors **A** or **B** was achieved using a variety of approaches: 1) iodolactonization of an γ,δ-unsaturated amide[11] or acyloxazolidinones;[12] 2) Wittig olefination, cyclization, and hydrogenation of the unsaturated γ-lactone[13,14] or δ-lactam;[15] 3) epoxide opening and cyclization; [16] 4) homoenolate addition to an α-amino aldehyde using either ethyl propiolate,[17] dichloroisopropoxy-2-ethoxycarbonylethyl titanium,[18] or (Z)-3-dimethylphenylsilyl-1-lithio-2-propenyl N,N-diisopropylcarbamate;[19] and 5) reduction of γ-keto esters using homogeneous asymmetric hydrogenation, cyclization of the resulting γ-hydroxy ester and alkylation.[20] In addition, lactones **A** and **B** were also prepared from D-glucose,[21] D-ribose,[22] and D-mannose[23] and by addition of 2-(trimethylsilyloxy)furan to N-acyl-N, O-acetals.[24]

In this paper, we describe a concise and general strategy for the synthesis of hydroxyethylene dipeptide isosteres **C** and **D** from the γ-lactone precursors **A** and **B**, respectively. The key step of the synthesis of γ-lactone **A** (R_1 = isopropyl, R = H, and P = Cbz) was the hydroboration of a homoallylic alcohol protected as a TBDMS ether. Oxidation of the resulting alcohol gave a mixture of 3α and 3β substituted γ-lactones. The 3α diastereomer **A** (R_1 = isopropyl, R = H, P = Cbz) was obtained in a ratio of 9:1 by selective crystallization from methanol. The 3β substituted diastereomers **1b** and **17b** were obtained by kinetic protonation of the lithium enolates in a ratio of 13:1 and 9.5:1, respectively. Both diastereomeric γ-lactones **A** and **B** were available from a common intermediate and synthetic sequence. Application of this methodology for the synthesis of hydroxyethylene dipeptide isosteres as intermediates for both renin and HIV-1 protease inhibitors is now described.

RESULTS AND DISCUSSION

Synthesis of the Hydroxyethylene Dipeptide Isostere via the γ-Lactone Intermediate A

As shown in Scheme 1, preliminary results revealed that the 1,4-diol **2a** served as a relay intermediate

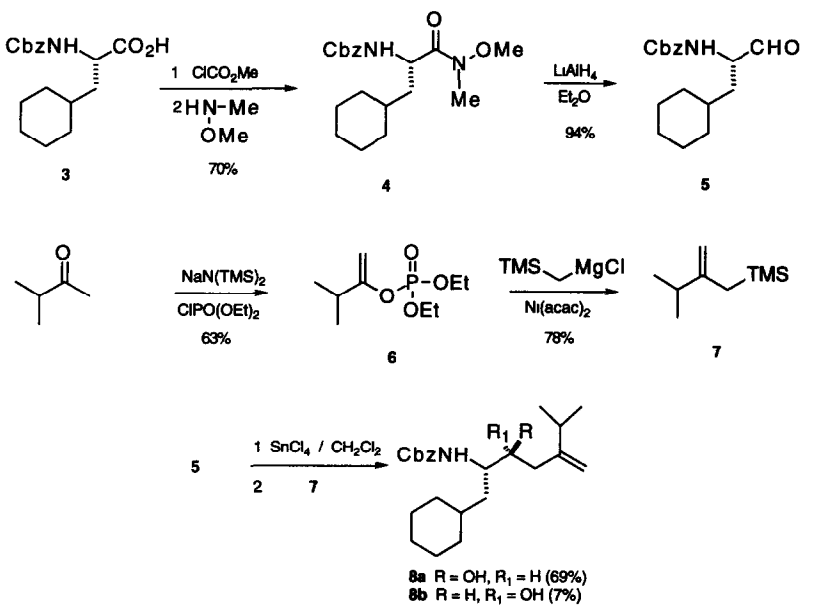


Scheme 1

for the synthesis of lactone **1a**. Thus, calcium borohydride reduction of the known N-Cbz γ-lactone **1a**[10] afforded the 1,4-diol **2a** which, when oxidized with either Jones reagent or ruthenium tetraoxide[25] gave the starting lactone **1a** in 57% and 52% yield, respectively. A two-step synthesis of the key intermediate **2a** was

envisioned. The first step was a Lewis acid promoted, chelation-controlled addition of a 2-substituted allylsilane to an α-amino aldehyde.[26] The second, and key step, was a diastereoselective intramolecular hydroboroation reaction of the homoallylic alcohol **8a**. Preparation of the homoallylic alcohol **8a** is shown in Scheme 2.

N-Cbz-L-cyclohexylalanine (**3**) was reacted first with methyl chloroformate followed by N,O-dimethylhydroxylamine to give the L-cyclohexylalanine amide **4** in 70% yield. Reduction of amide **4** with LAH (-50 °C, diethyl ether) afforded the N-Cbz-L-cyclohexylalanal **5** as a white semisolid in 94% crude yield.[27] The crude aldehyde was used in the allylsilane addition reaction without further purification. Our first attempt to prepare (2-isopropylpropen-2-yl)trimethylsilane (**7**) using a cerium (III) chloride mediated addition of trimethylsilylmethylmagnesium chloride to ethyl 2-methylpropionate met with limited success.[28] Although we were able to obtain the allylsilane **7**, the yield was poor and the product was contaminated with unidentifiable impurities. We discovered that $Ni(acac)_2$ catalyzed coupling of the enol phosphonate **6** and trimethylsilylmethylmagnesium chloride gave the best yield of allylsilane **7** (49% from 3-methyl-2-butanone).[29] Lewis acid promoted condensation of allylsilanes with N-protected α-amino aldehydes has been reported.[26,30] Our results were consistent with the literature. A survey of Lewis acids and reaction conditions established that 1.2 to 1.8 molar equivalents of $SnCl_4$ gave the highest diastereomeric ratio of of alcohols

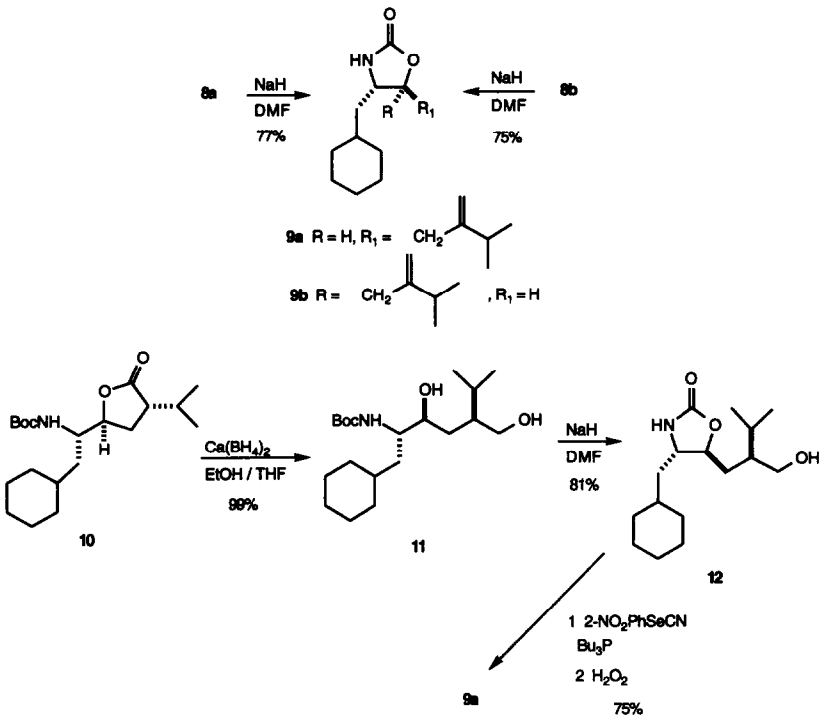


Scheme 2

8a:8b. One molar equivalent of $SnCl_4$ gave complete reaction with reduced stereoselectivity. The reaction yield of **8a:8b** was highest when $TiCl_4$ was employed as a Lewis acid catalyst, however, no stereoselectivity was observed. The Lewis acids $BF_3 \cdot Et_2O$ and $EtAlCl_2$ gave only a modest ratio of **8a:8b**. Again, the reaction yields were low. $ZnCl_2$ gave no observable reaction by TLC. The optimum conditions for the

reaction of aldehyde **5** with the allylsilane **7** were 1.5 molar equivalents of stannic chloride in CH_2Cl_2 at -78 °C for 1.5 hours. The diastereomeric ratio of alcohols **8a:8b** obtained was 9:1.

The stereochemistry of each alcohol diastereomer **8a** and **8b** was determined by synthesis of oxazolidinones **9a** and **9b** and comparison of the coupling constants between the C(4) and C(5) protons with known *cis* and *trans* 4,5-disubstituted oxazolidin-2-ones (Scheme 3).[30a] Oxazolidinones **9a** and **9b** had *J* values between the C(4) and C(5) protons of 5.7 and 7.5 Hz, respectively. This data suggested that the C(4) cyclohexylmethyl and the C(5) 2-isopropylpropen-2-yl groups was *trans* in **9a** and *cis* in **9b** . The absolute stereochemistry for alcohol **8a** was unambiguously assigned by correlation to the known lactone **10**.[12] Thus, calcium borohydride reduction of lactone **10** produced the Boc diol **11**, which was cyclized with NaH to give the oxazolidinone **12**. Elimination of the primary alcohol via the *o*-nitrophenylselenoxide produced an



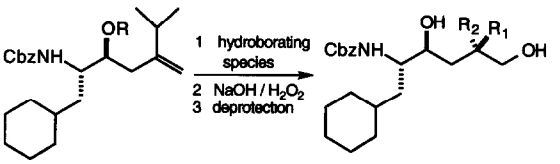
Scheme 3

oxazolidinone (mp 75 °C, $[\alpha]^{25}_D$ -69.4 (c = 0.93 $CHCl_3$) which was identical by ^1H NMR to oxazolidinone **9a** (mp 75 °C, $[\alpha]^{25}_D$ -64.3 (c = 0.795 $CHCl_3$) prepared from **8a**. Both oxazolidinones had specific rotations which were within experimental error, indicating that little to no racemization of the α-amino aldehyde occurred during the allylsilane addition reaction.

With the homoallylic alcohol **8a** in hand, a series of hydroboration experiments were conducted to determine the effect of the hydroxyl, hydroxyl protecting group, and hydroborating species on the diastereoselectivity of the hydroboration process (Table 1). The ratio of diastereomers **2a:2b** was based on

proton integration of the carbamate NH and/or methine proton alpha to the carbamate nitrogen in benzene-d_6. The absolute stereochemistries of the two hydroboration products were assigned by comparison of the ^1H NMR to a sample of authentic diol **2a**. For entries 7, 10, 11, 12, and 13 the protecting groups were removed prior to ^1H NMR evaluation. Entries 1 and 2 were an attempt to perform the hydroboration in an intramolecular fashion.[31, 32] For an intramolecular hydroboration reaction to take place, borane would react with the OH group at low temperature to give a -OBH_2 species which would then hydroborate the terminal olefin intramolecularly. The -OBH_2 species could also be formed by reaction of alcohol **8a** with BF_3 to give -OBF_2 and then addition of $NaBH_4$ to generate the OBH_2 species *in situ*. Reaction of alcohol **8a** with either one equivalent of BH_3•DMS (-30 °C, warming to 0 °C and oxidation of H_2O_2) or BF_3 (-78 °C to rt) then $NaBH_4$ (-78 °C to rt) gave an equal mixture of the two diastereomeric diols **2a:2b**. However, when the more sterically demanding hydroborating reagent 9-BBN was reacted with alcohol **8a**, diols **2a:2b** were obtained

Table 1. Synthesis of 1,4-Diols (2a/2b) by Hydroboration of Alcohol 8a and 8a Ethers.



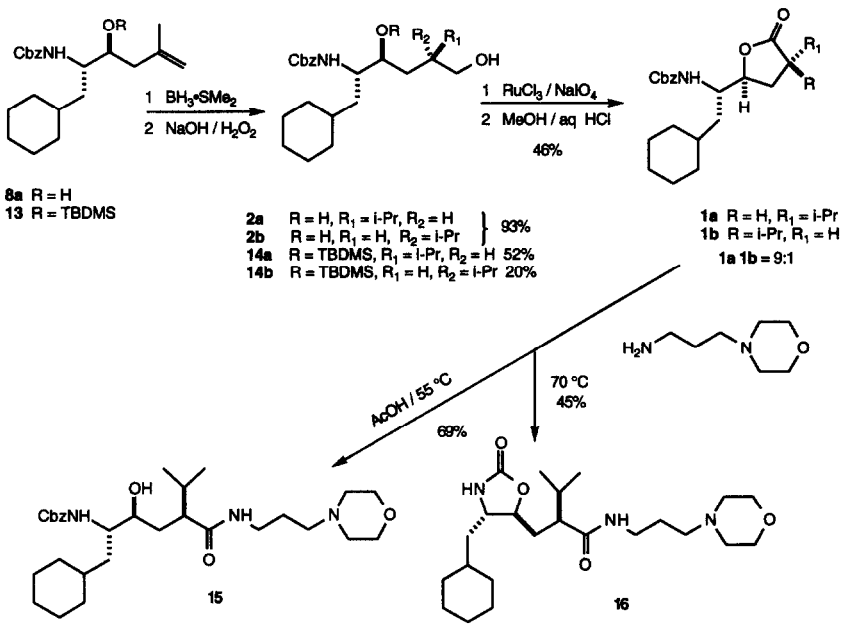
2a R_1 = i-Pr, R_2 = H
2b R_1 = H, R_2 = i-Pr

entry	R	hydroborating[a] species	product ratio[b] (2a:2b)
1	H	BH_3•SMe_2[c]	1:1
2	H	BF_3•Et_2O/$NaBH_4$	1:1
3	H	BH_3•SMe_2	1:1
4	H	9-BBN	2·1
5	H	thexylborane	1:1
6[d]	H	catecholborane	f
7[d]	TBDMS	catecholborane	1 5:1
8[d]	H	BH_3•SMe_2	1.1
9[d]	H	9-BBN	1:1
10	TBDMS	BH_3•SMe_2	2.6:1[f]
11	Si*t*-BuPh$_2$	BH_3•SMe_2	1:1
12	CPh_3	BH_3•SMe_2	1.4:1
13	TMS	BH_3•SMe_2	2:1

[a] Typical conditions were 3 molar equivalents of borane reagent in THF at -30 °C, warmed to 0 °C, and addition of basic H_2O_2 [b] Product ratios determined by ^1H NMR (C_6D_6) integration of the carbamate NH and/or methine alpha to carbamate nitrogen. For entries 7 and 10-13 the protecting group was removed prior to NMR evaluation. [c] Only 1 molar equivalent of BH_3•SMe_2. [d] Reactions performed with Wilkinson's catalyst. [e] No reaction observed. [f] Isolated ratio.

in a ratio of 2:1 (entry 4). In contrast, thexylborane gave no selectivity (entry 5). Catechol borane in conjunction with Wilkinson's catalyst ($ClRh(Ph_3)_3$) has been shown to impart high diastereoselectivity in the hydroboration of terminal olefins.[33] We found that catechol borane (entry 6), BH_3•DMS (entry 8), and 9-BBN (entry 9) with $ClRh(Ph_3)_3$ had no effect on the diol stereoselectivity using either alcohol **8a** or the TBDMS protected alcohol (entry 7) as substrates. We next considered increasing the steric bulk of the protecting group in order to effect diastereoselectivity in the hydroboration reaction. Acyclic stereocontrol on the hydroboration of terminal olefins with sterically dominant and subordinate groups at the homoallylic position has been documented.[34] A series of protected alcohols were prepared in order to examine the effect of steric bulk at the homoallylic position on the intermolecular hydroboration reaction (entries 10-13). The TBDMS protecting group and BH_3•DMS as the hydroborating reagent afforded the best ratio of diastereomers **2a:2b** (2.6:1). These conditions were employed for the completion of the synthesis of isostere **15**.

The synthesis of lactone **1a** and its conversion to the hydroxyethylene dipeptide isostere **15** was completed in four steps starting from the TBDMS ether **13** (Scheme 4). As previously described, hydroboration of ether **13** with borane/dimethylsulfide gave a 2.6:1 mixture of diastereomeric alcohols **14a:14b**. Oxidation of **14a:14b** mixture with catalytic RuO_4 gave the crude carboxylic acid which was



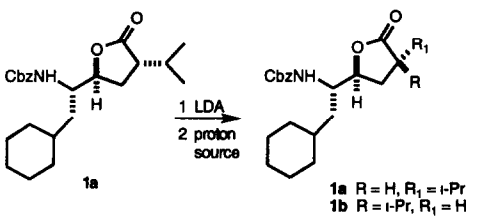
Scheme 4

cyclized with 3 M HCl in methanol, at reflux temperature. Upon cooling, lactone **1a** crystallized from the methanol solution as white needles (mp 167-8 °C). The ease of crystallization of the desired lactone **1a** from aqueous methanol, prompted us to perform the entire reaction sequence without purification of the diastereomeric alcohols **14a** and **14b**. Thus, hydroboration of a 4.6 g sample of ether **13** gave a 2.6:1

mixture (3.35 g) of alcohols **14a:14b**. The crude alcohol mixture was oxidized, cyclized, and crystallized as previously described to give 1.2 g (46%) of γ-lactones **1a** and **1b** in a ratio of 9:1. The synthesis of the renin inhibitor hydroxyethylene dipeptide isostere **15** and removal of the 10% unwanted diastereomer **1b** was accomplished by reaction of the (9:1) lactone mixture **1a:1b** with 3 equivalents of acetic acid and 3-(4-morpholin-4-yl)propylamine at 55 °C. The acetic acid was critical for the success of the lactone ring opening. In the absence of acetic acid, higher reaction temperatures were required which caused the formation of unwanted oxazolidinone **12**. Optically pure dipeptide isostere **15** (0.95 g) was obtained after recrystallization from ethyl acetate/hexane. The overall yield of amide **15** from ether **13** was 19%.

Since the selectivity of the hydroboration reaction (**13 -> 14a/14b**) was only modest, we speculated that the diastereomeric ratio might be further increased if the lactone enolate could be selectively protonated. Stereoselectivity in the protonation of achiral ketone enolates has been investigated using optically active α-hydroxy esters as chiral proton sources.[35] We hypothesized that similar selectivity might be achieved on kinetic protonation of the lactone enolate derived from **1a**.[36] The formation of the 3α **10a** or 3β **10b** diastereomer would then be controlled by the absolute stereochemistry of the α-hydroxy ester. As a control experiment, lactone **10a** was reacted with LDA at -78 °C and addition of acetic acid gave the C(3β:3α)

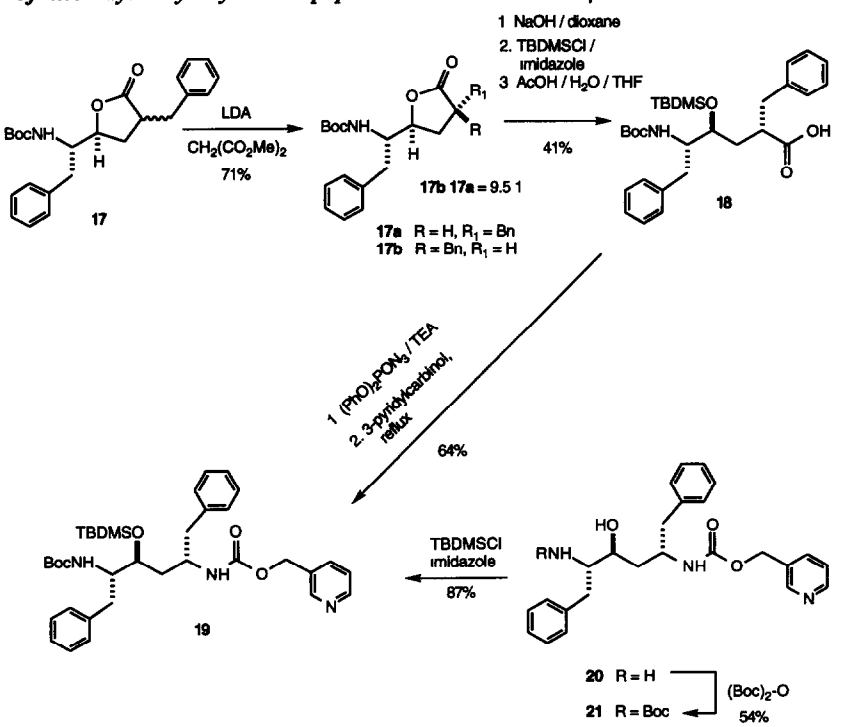
Table 2. Ratio of Diastereomers 1b:1a Obtained From the Protonation of Lactone 10a Enolate with Various Proton Sources.



entry	proton source	ratio (1b:1a)
1	$MeCO_2$	2:1
2	(S)-Methyl, 2-hydroxy-4-metylpentanoate	2:1
3	$CH_2(CO_2Me)_2$	10:1
4	$CH_2(CO_2Et)_2$	11:1
5	$CH_2(CO_2{}^tBu)_2$	11:1
6	$CH_2(CO_2Bn)_2$	13:1
7	$CHMe(CO_2Et)_2$	8:1
8	$CHPh(CO_2Et)_2$	8:1
9	i-$PrCH(CO_2Et)_2$	10:1
10	Meldrum's Acid	13.1
11	$CH_2(CN)_2$	9:1
12	$EtO_2CCH_2PO(OEt)_2$	9:1
13	$CNCH_2SO_2Ph$	5 1

diastereomers **1b:1a** in a ratio of 2:1 (Table 2). When (S) methyl 2-hydroxy-4-methylpentanoate (entry 2) was used as a chiral proton source the selectivity was the same. We concluded that the lack of stereoselectivity resulted from protonation on oxygen to form the enol which underwent a nonselective enol-keto tautomerism. Since oxygen-based acids gave no selectivity, we hypotesized that carbon-based acids would protonate the enolate on carbon and thus offer selectivity in the kinetic protonation reaction.[37] Malonates and malonate derivatives were selected as proton sources due to their high acidity and the possibility that the two carboxylate oxygens might complex with the lithium dianion and deliver the proton from the β face.[38] A series of malonate derivatives (entries 3-10) and three malonate-type carbon-based acids (entries 11-13) were evaluated. Except for phenylsulfonylacetonitrile (entry 13), all of the malonate esters (entries 3-6), 2-substituted malonate esters (entries 7-9), and malonate-type carbon acids (entries 10-12) gave excellent ratios of the C(3β) diastereomer (8-13:1). These results confirmed our hypothesis that protonation of the γ-lactone enolate with carbon-based acids occured directly on carbon and the facial selectivity was controlled by the C(5) substituent on the lactone ring. Unfortunately, the undesired diastereomeric lactone **1b** predominated from these experiments. The kinetic protonation approach could not be employed for the synthesis of lactone **1a** and hence, renin inhibitor hydroxyethylene dipeptide isostere **15**. However, these results encouraged us to apply the kinetic protonation methodology to the synthesis of the hydroxyethylene dipeptide isostere **19**, an intermediate found in HIV-1 protease inhibitors.[39]

Synthesis of the Hydroxyethylene Dipeptide Isostere via the γ-Lactone Intermediate B



Scheme 5

The γ-lactone precursor **B** (R = R_2 = benzyl, R_1 = H) was required for the synthesis of isostere **19** and was readily obtained by kinetic protonation of lactone **17**.[40] Reaction of **17** with LDA at -78 °C in THF followed by addition of dimethyl malonate at the same temperature gave in 71% yield lactones **17b:17a** (9.5:1). Lactone **17b** was hydrolyzed with aq. NaOH, the aqueous solution was carefully acidified with 10% citric acid to pH 2, and the secondary alcohol protected as the TBDMS ether (TBDMSCl, imidazole).[16,41] Carboxylic acid **18** was obtained in 41% yield after silica gel chromatography. Curtius rearrangement of acid **18** afforded the isocyanate intermediate which was trapped with 3-pyridinemethanol to produce the fully protected hydroxyethylene dipeptide isostere **19** (64%).[42] The relative stereochemistry of **19** was determined by correlation to the known amino alcohol **20**.[39] Reaction of the amino alcohol **20** with di-*t*-butyl dicarbonate (CH_2Cl_2, rt, 18 h) and protection of alcohol **21** as the TBDMS ether yielded isostere **19** which was identical by TLC, ^1H, and ^{13}C NMR to **19**.

CONCLUSION

The synthetic schemes described illustrate a versatile method for the synthesis of C(3) γ-lactone diastereomers from N-Cbz α-amino aldehydes and 2-substituted allylsilanes. In addition, the synthetic methodology should allow access to a wide variety of structurally diverse hydroxyethylene dipeptide isosteres having either R or S stereochemistry at the P_1' position.

EXPERIMENTAL

All reactions requiring anhydrous conditions were carried out in oven-dried (110 °C) glassware under dry N_2. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 F-254 glassbacked plates, 250 micron thickness (analytical). Flash chromatography was performed using E. Merck Kieselgel 60 (230-400 mesh) and eluent systems are reported as v/v %. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at 300 MHz in either $CDCl_3$ or C_6D_6, as noted in each experimental, using tetramethylsilane as an internal standard. Mass spectra were determined on a Kratos MS50 spectrometer. Combustion analyses were performed by the Analytical Research Department, Pharmaceutical Products Division, Abbott Laboratories. Optical rotations were performed on a Perkin-Elmer 241-polarimeter.

Diethyl 2-(3-Methylbuten-1-yl)phosphonate (6). 3-Methyl-2-butanone (32.4 mmol, 3.47 mL) was dissolved in 25 mL of dry THF and added via cannula to a cooled (-78 °C) solution of sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 36 mL, 35.6 mmol). The resulting solution was stirred at -78 °C for 50 min and added via cannula to a solution of diethyl chlorophosphonate (7.0 mL, 48.6 mmol) at -78 °C. The mixture was stirred at -78 °C for 10 min, warmed to ambient temperature over 50 min, and partitioned between saturated aqueous NH_4Cl and diethyl ether. The organic solution was washed with saturated NH_4Cl, saturated $NaHCO_3$, dried ($MgSO_4$), and filtered. The solvent volume was reduced from 250 to 100 mL by distillation at atmospheric pressure to remove the diethyl ether and THF. The product was distilled to give 4.5 g of a clear oil (63%): bp 94 °C (0.15mm); ^1H NMR ($CDCl_3$) δ 1.11 (d, J = 6.3 Hz, 6 H)

1.36 (t, J = 6.3 Hz, 3 H), 1.37 (t, J = 6.3 Hz, 3 H), 2.42 (7-line multiplet, J = 6.3 Hz, 1 H), 4.17 (q, J = 6.3 Hz, 2 H), 4.19 (q, J = 6.3 Hz, 2 H), 4.50 (m, 1 H), 4.81 (m, 1H); LRMS *m/e* 223 (M^+).

(2-Isopropylpropen-2-yl)trimethylsilane (7). Trimethylsilylmethylmagnesium chloride was generated by reacting chloromethyltrimethylsilane (63 ml, 451 mmol) in 150 mL of dry THF with magnesium turnings (11g, 453 mmol) and a catalytic amount of 1,2 dibromoethane (250 μL).[28] After most of the magnesium had reacted, the mixture was heated to reflux temperature for 30 min, cooled to 25 °C, and nickel acetylacetonate (0.05 eq, 1.93 g, 7.5 mmol) was added followed by dropwise addition of **6** (33.4 g, 150 mmol) in 150 mL of THF. The resulting black solution was stirred at room temperature for 1.5 h and then cannulated into a two-phase mixture of saturated NH_4Cl (200 mL) and diethyl ether (200 ml). The organic layer was separated and the green aqueous layer was extracted three times with ether. The combined organic layers were washed with saturated NH_4Cl, saturated NaCl, dried ($MgSO_4$) and filtered. The diethyl ether and THF were removed by distillation at atmospheric pressure (35-70 °C). Vacuum distillation of the residue gave 18.1 g (78%) of a clear liquid: bp 64-69 °C (40 mm); IR ($CDCl_3$) 2840-3000, 1623, 1240, 800-880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, J = 6.3 Hz), 1.53 (s, 2 H), 2.05 (7- line multiplet, J = 6.3 Hz, 1 H), 4.48 (m, 1 H), 4.60 (m, 1 H); LRMS *m/e* 156 (M^+).

N-Methyl, N-Methoxy Amide of N-Cbz-L-Cyclohexylalanine (4). To a suspension of N,O-dimethylhydroxylamine hydrochloride (19.5 g, 200 mmol) in 120 mL CH_2Cl_2 at 0 °C was added dropwise N-methylpiperidine (25.5 mL, 210 mmol) while the reaction temperature was maintained at 5 °C or below during the addition. The resulting clear solution was kept at 0 °C and used in the following procedure.

A solution of N-Cbz-L-cyclohexylalanine (**3**) (61.1 g, 200 mmol) in 900 mL of CH_2Cl_2 and 230 mL of THF was stirred at -20 °C. N-methypiperidine (25.5 mL, 210 mmol) was added followed by methyl chloroformate (15.4 mL, 200 mmol) maintaining the reaction temperature at -15 to -20 °C during the additions. After 2 min the amine solution prepared above was added and the reaction was warmed to ambient temperature over a period of 4 h. The reaction was then recooled to 0-5 °C and washed with 0.2 N HCl (2 X 250 mL), 0.5 N NaOH (2 X 250 mL), and with 200 mL of saturated NaCl. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* at 30-35 °C. HPLC chromatography on the Waters Prep 500A (7:3 hexane/ethyl acetate) gave 48.8 g (70% yield) of the desired amide as a viscous oil: $[\alpha]^{25}_D$ = +5.5°; ^1H NMR ($CDCl_3$) δ 0.80-1.74 (complex, 12 H), 1.84-1.95 (m, 1 H), 3.20 (s, 3 H), 3.80 (s, 3 H), 4.76-4.88 (m, 1 H), 5.10 (q, J= 11.4 Hz, 2 H), 5.28 (d, J= 8.7 Hz, 1 H), 7.28-7.44 (complex m, 5 H); LRMS *m/e* 349 (M^+), 366 ($M+NH_4^+$). Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.68; H, 8.09; N, 8.01.

N-Cbz-L-Cyclohexylalanal (5). A suspension of LAH powder 95% (1.32 g, 33 mmol) in 150 mL of anhydrous Et_2O was stirred for 1 h at ambient temperature and then cooled to -50 °C. To the suspension was added a solution of **4** (10.5 g, 30 mmol) dissolved in 20 mL of Et_2O. The mixture was warmed to 5 °C, stirred for 30 min and then recooled to -50 °C. A solution of potassium bisulfate (7.2 g, 53 mmol) in 20 mL of water was added very slowly to the reaction mixture. Gas evolution and an exotherm to -10 °C was noted. The solution was stirred at ambient temperature for 1.5 h, filtered through a plug of Celite and the Celite plug was washed thoroughly with Et_2O. The combined organic extracts were washed with cold 1 N HCl (3 x 30 mL), saturated $NaHCO_3$, (2 x 30 mL), and with 30 mL of saturated NaCl. The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo* at 30 °C to give 8.2 g (94%) of a white semisolid. The

crude aldehyde **5** was stored under N_2 at -20 °C: ^{1}H NMR ($CDCl_3$) δ 0.83-1.86 (complex 13 H), 4.30-4.42 (m, 1 H), 5.12 (s, 3 H), 7.26-7.40 (m, 5 H), 9.59 (s, 1 H); MS, *m/e* 290 (M^+), 307 ($M+NH_4^+$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 69.44; H, 8.01; N, 4.84. Found: C, 69.44; H, 8.21; N, 4.83.

(2S,3S) and (2S,3R) 2-Benzyloxycarbonylamino-1-cyclohexyl-5-isopropyl-5-hexen-3-ol (8a and 8b). To a solution of $SnCl_4$ (1.0 M in CH_2Cl_2, 85.0 mL, 85.0 mmol) at -78 °C was added dropwise over 30 min a solution of aldehyde **5** (16.5 g, 57.0 mmol) in 100 mL of CH_2Cl_2. The resulting solution was stirred at -78 °C for 2 h and silane **7** (10.9 g, 70.0 mmol) in 50 mL of CH_2Cl_2 was added dropwise over 30 min. The reaction mixture was stirred at -78 °C for 1 h and quenched with 100 mL of distilled water. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The extracts were combined, washed with 50 mL of saturated NaCl, dried ($MgSO_4$), filtered and concentrated to give 19.7 g (92% recovery) of two diastereomeric alcohols. The crude alcohols were purified by flash chromatography (4:1 hexane/ethyl acetate) to give 14.7 g (69% yield) of **8a**: R_f = 0.34, 4:1 hexane/ethyl acetate; mp 63-65 °C; $[\alpha]^{25}_D$ = -35.0 ° (c 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75-1.00 (m, 1 H), 1.01 (d, J= 7.5 Hz, 3 H), 1.05 (d, J = 7.5 Hz, 3 H), 1.07-1.91 (complex m, 13 H), 2.06-2.34 (m, 3 H), 3.60-3.80 (m, 2 H), 4.79 (s, 1 H), 4.89-4.94 (m, 2 H), 5.12 (s, 2 H), 7.25-7.40 (m, 5 H); LRMS, *m/e* 374 (M^+), 391 ($M+NH_4^+$); HRMS *m/e* Calcd for $C_{23}H_{35}NO_3$ 374.2695. Found: 374.2682; Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.62; H, 9.14; N, 3.64. **8b** 1.4 g (7% yield): R_f = 0.26 (4:1 hexane/ethyl acetate); mp 74-76 °C; $[\alpha]^{25}_D$ = -43.8 ° (c 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.72-0.90 (m, 1 H), 1.00 (d, *J* = 7.5 Hz, 3 H), 1.04 (d, *J* = 7.5 Hz, 3 H), 0.92-1.92 (complex m, 12 H), 2.04-2.16 (m, 2 H), 2.18-2.30 (m, 2 H), 3.68-3.83 (m, 2 H), 4.82 (s, 1 H), 4.84 (d, *J* = 9.3 Hz, 1 H), 4.92 (s, 1 H), 5.09 (d, *J* = 10.5 Hz, 1 H), 5.13 (d *J* = 10.5 Hz, 1 H), 7.25-7.40 (m, 5 H); LRMS, *m/e* 374 (M^+), 391 $M+NH_4^+$), HRMS *m/e* Calcd for $C_{23}H_{35}NO_3$ 374.2695. Found 374.2689; Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 74.25; H, 9.53; N, 3.82.

(2S,3S) 3-Cyclohexylmethyl-2-(2-isopropylpropen-2-yl)-2,3,5-tetrahydro-4H- oxazole 5-one (9a). To a suspension of NaH (60% dispersion in oil, 90 mg, 2.2 mmol) in 3 mL of anhydrous DMF was added a solution of **8a** (374 mg, 1.0 mmol) in 2 mL of DMF at 0 °C. The mixture was stirred overnight at ambient temperature and partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. Chromatography (3:1 hexane/ethyl acetate) gave 205 mg (77%) of **9a** as a white solid. mp 75 °C; $[\alpha]^{25}_D$ = -64.3 ° (c 0.795, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80-1.02 (m, 2 H), 1.05 (d, J=7.5 Hz, 6 H), 1.10-1.76 (complex m, 11 H), 2.20-2.37 (m, 2 H), 2.50-2.59 (m, 1 H), 3.54-3.62 (m, 1 H), 4.25-4 33 (dt, J = 6.6, 5.7 Hz, 1H), 4.82 (s, 1 H), 4.93 (s, 1 H), 5.14 (bs, 1 H); LRMS *m/e* 266 (M^+), 283 ($M+NH_4^+$). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.54; H, 10.07 N, 5.36.

(2S,3R) 3-Cyclohexylmethyl-2-(2-isopropylpropen-2-yl)-2,3,5-tetrahydro-4H-oxazole 5-one (9b). In a manner analogous to the preparation of **9a**, NaH (60% dispersion in oil, 90 mg, 2.2 mmol) was reacted with **8b** (374 mg, 1.0 mmol) in 5 mL of anhydrous DMF. The crude product was chromatographed using 3:1 hexane/ethyl acetate and then recrystallized from cold hexanes to give **9b** as a white solid in 75% yield (200 mg). mp 89-90 °C; $[\alpha]^{25}_D$ = -34.6 ° (c 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75-1.03 (m, 2H), 1.05 (dd, J = 6.6, 2.4 Hz, 6H), 1.10-1.80 (complex m, 11 H), 2.20-2.34 (m, 2 H), 2.43-

2.54 (m, 1 H), 3.86-3.95 (m, 1 H), 4.75 (s, 1 H), 4.77-4.87 (dt, J = 7.5, 5.7 Hz, 1H), 4.91 (s, 1 H), 5.59 (bs, 1 H); LRMS, *m/e* 266 (M^+), 283 ($M+NH_4^+$); Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.10; H, 10.13; N, 5.23.

(2S,3S,5S)-2-tert-Butyloxycarbonylamino-1-cyclohexyl-5-isopropylhexan-3,6-diol (11). To a solution of **10** (35.3 g, 100 mmol) in a mixture of 140 mL of EtOH and 140 mL of THF at 0 °C was added $CaCl_2$ (22.2 g, 200 mmol). After 15 min, $NaBH_4$ (15.1 g, 400 mmol) was added portionwise. The milky solution was stirred for 4 h at 0 °C and warmed to ambient temperature over 18 h. The solution was recooled to 0 °C and 1M aqueous $KHSO_4$ was added until bubbling subsided. The solution was filtered and the filtrate partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), and concentrated to a clear oil (35.7 g, 99 % yield). The crude product was used without purification. R_f = 0.27, 7:3 hexane/ EtOAc; ^1H NMR ($CDCl_3$) δ 0.75-1.90 (complex m 17 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.91 (d *J* = 6.6 Hz, 3 H), 1.44 (s, 9 H), 3.54- 3.73 (m, 4 H), 4.68 (bd, *J* = 9.9 Hz, 1 H).

(2S,3S) 3-Cyclohexylmethyl-2-(2-isopropylpropen-2-yl)-2,3,5-tetrahydro-4H-oxazole 5-one (12). NaH (60%, 16.0 g, 400 mmol) was washed with hexanes to remove mineral oil and 200 mL of DMF was added. To this suspension was added dropwise alcohol **11** (35.7 g, 100 mmol) dissolved in 100 mL of DMF. The mixture was stirred at 0-10 °C for 4 h and then overnight at ambient temperature. The solution was slowly poured into 800 mL of cold saturated NH_4Cl and the aqueous phase was extracted with Et_2O (4 x 200 mL). The organic extracts were combined, washed with saturated NaCl, dried ($MgSO_4$), filtered and concentrated. The crude oxazolidinone was purified by HPLC chromatography on the Waters Prep 500 (3:2 hexane/ethyl acetate) to give **12** (23.0 g, 81% yield) as a white solid. mp 88-89 °C; $[\alpha]^{25}_D$ = -79.5 ° (c 1.075, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.91 (d, J = 7.5 Hz, 3 H), 0.92 (d, J = 7.5 Hz, 3 H), 0.95-1.85 (complex m, 18 H), 3.47-3.55 (m, 1 H), 3.61-3.76 (m, 2 H), 4.30-4.39 (m, 1 H), 5.19 (bs, 1 H). MS, *m/e* 284 (M^+), 301 ($M+NH_4^+$). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.97; H, 10.13; N, 4.93.

(2S,3S) 3-Cyclohexylmethyl-2-(2-isopropylpropen-2-yl)-2,3,5-tetrahydro-4H-oxazole 5-one (9a). A solution of *o*-nitrophenylselenocyanate (409 mg, 1.8 mmol) and **11** (425 mg, 1.5 mmol) in 6 mL of THF was stirred at ambient temperature. To the solution was added dropwise tributylphosphine (450 μL, 1.8 mmol). After 1 h the reaction was cooled to 0 °C and cold 30% hydrogen peroxide (2.0 mL, 15 mmol) was added dropwise. After stirring overnight the reaction mixture was concentrated and the residue partitioned between water and diethyl ether. The ethereal layer was washed with aqueous Na_2CO_3, washed with saturated NaCl, dried ($MgSO_4$), and concentrated. The crude olefin was purified by chromatography using 7:3 hexane/ethyl acetate as eluent. An orange solid was obtained which was recrystallized from cold hexanes to give 200 mg (75%) of **9a** as a white solid: mp 75 °C. The ^1H NMR, melting point and TLC were identical to the oxazolidone prepared from **8a**: $[\alpha]^{25}_D$ = -69.4 ° (c 0.930, $CHCl_3$); LRMS, *m/e* 266 (M^+), 283 ($M+NH_4^+$); Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.62; H, 10.04; N, 5.36.

***tert*-Butyldimethylsilyl Ether of (2S,3S) 2-Benzyloxycarbonylamino-1-cyclohexyl-5-isopropyl-5-hexen-3-ol (13).** A solution of **8a** (374 mg, 1.0 mmol), *tert*-butyldimethylsilyl chloride (226 mg, 1.5 mmol) and imidazole (170 mg, 2.5 mmol) in 1 mL of DMF was heated at 35 °C for 8 h. The

solution was cooled, partitioned between Et_2O and water, and the aqueous phase was extracted with Et_2O (3 X 15 mL). The extracts were combined, washed with saturated NaCl, dried ($MgSO_4$) and concentrated to a viscous oil. The crude silyl ether was purified by chromatography (9:1 hexane/ethyl acetate) to give 460 mg (94%) of a colorless oil: $[\alpha]^{25}_D$ = -16.2 ° (c 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.89 (s, 9 H), 0.82-1.84 (complex, 19 H), 2.04-2.29 (m, 3 H), 3.67-3.90 (m, 2 H), 4.72 (s, 1H), 4.85 (s, 1 H), 4.89 (bd, *J* = 9.3 Hz, 1 H), 5.10 (s, 2 H), 7.27-7.39 (m, 5 H); LRMS, *m/e* 488 (M^+); Anal. Calcd for $C_{29}H_{49}NO_3Si$: C, 71.41; H, 10.13; N, 2.87. Found: C, 71.72; H, 10.19; N, 2.82.

(2S,3S,5S)-2-Benzyloxycarbonylamino-1-cyclohexyl-5-isopropylhexane-3,6-diol (2a). A solution of $CaCl_2$ (2.22g, 20.0 mmol) and lactone **1a** (3.88 g, 10.0 mmol) in 60 mL of ethanol and 60 mL of THF was cooled to 0 °C and $NaBH_4$ (1.5 g, 40.0 mmol) was added portionwise. Vigorous gas evolution and an exotherm was observed. The resulting solution was stirred at 0 °C for 1 h, ambient temperature for 1 h, diluted with 100 mL of diethyl ether and filtered through a plug of Celite. The filtrate was cooled to 0 °C and quenched by addition of 1M $KHSO_4$ until bubbling ceased. The organic phase was washed with saturated $NaHCO_3$ (2 x 20 mL), NaCl (2 x 20 mL), dried ($MgSO_4$), and concentrated to a give a white solid. Recrystallization from EtOAc/hexanes gave 3.67 g (94 %) of **2a**. mp 112-113 °C; $[\alpha]^{25}_D$ = -32.0 ° (c 1.025, $CHCl_3$); ^1H NMR (C_6D_6) δ 0.76 (d, *J* = 7.5 Hz, 3 H), 0.79 (d, *J* = 7.5 Hz, 3 H), 0.75-1.74 (complex m, 18 H), 1.98-2.09 (bd, *J* = 11.1 Hz, 1 H), 3.28-3.41 (m, 2 H), 3.62-3.70 (m, 1 H), 3.90-4.00 (m, 1 H), 4.88 (d, *J* = 9.6 Hz, 1 H), 5.12 (s, 2 H), 7.00-7.30 (m, 5 H); LRMS, *m/e* 392 (M^+), 409 ($M+NH_4^+$); Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.52; N, 3.58. Found: C, 70.78; H, 9.54; N, 3.56.

***tert*-Butyldimethylsilyl Ethers of (2S,3S,5S) and (2S,3S,5R)-2-Benzyloxycarbonylamino-1-cyclohexyl-5-(2-methylpropyl)hexan-3,6-diol (14a and 14b).** To a solution of borane/dimethylsulfide (583 μL, 6.2 mmol) in 5 mL of THF at -78 °C was added 1.0 g (2.1 mmol) of olefin **13**. The resulting solution was stirred at ambient temperature for 16 h, recooled to 0 °C, and aqueous 1M $NaHCO_3$ (24 mL, 24 mmol) was added followed immediately by careful addition of 30 % H_2O_2 (3.4 mL). The mixture was stirred vigorously for 3 h at ambient temperature and partitioned with Et_2O. The aqueous phase was extracted with Et_2O (3 X 20 mL), the organic extracts were combined, washed with saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by chromatography (4:1 hexane/ethyl acetate) to give 552 mg (52%) of **14a** and 216 mg (20%) of **14b.** Deprotection of **14a** with tetrabutylammonium fluoride (TBAF) gave a diol which was was identical by TLC to **2a**. Data for **14a:** R_f = 0.22, 4:1 hexane/ethyl acetate; $[\alpha]^{25}_D$ = -21.4 ° (c 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.85 (d, *J* = 7.5 Hz, 3 H), 0.88 (s, 9 H), 0.92 (d, *J* = 7.5 Hz, 3 H), 0.80-1.85 (complex m, 18 H), 3.30-3.92 (m, 4 H), 4.84 (d, *J* = 9.9 Hz, 1 H), 5.04 (d, *J* = 12.0 Hz, 1 H), 5.15 (d, *J* = 12.0 Hz, 1 H), 7.26-7.38 (m, 5 H); LRMS, *m/e* 506 (M^+), 523 ($M+NH_4^+$); HRMS Calcd for $C_{29}H_{51}NO_4Si$ 506.3666. Found 506.3677; Anal. Calcd for $C_{29}H_{51}NO_4Si$: C, 68.86; H, 10.16; N, 2.77. Found: C, 68.13; H, 9.89; N, 2.98. Data for **14b:** R_f = 0.33, 4:1 hexane/ethyl acetate; $[\alpha]^{25}_D$ = -10.2 ° (c 1.56, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.78-1.90 (complex, 18 H), 0.82 (d, *J* = 7.5 Hz, 3 H), 0.95 (d, *J* = 7.5 Hz, 3 H), 0.88 (s, 9 H), 3.52-3.63 (m, 2 H), 3.78-3.88 (m, 2 H), 3.81 (d, *J* = 12.0 Hz, 1 H), 5.10 (s, 2 H), 7.30-7.38 (m, 5 H); MS, *m/e* 506 (M^+). Anal. Calcd for $C_{29}H_{51}NO_4Si$: C, 68.86; H, 10.16; N, 2.77. Found: C, 68.34; H, 9.87; N, 2.72.

(2S,3S,5S) and (2S,3S,5R) 2-Benzyloxycarbonylamino-1-cyclohexyl-5-isopropyl-

hexane-3,6-diol (2a and 2b). A solution of borane/dimethylsulfide (380 μL, 4.0 mmol) in 2 mL of THF was cooled to -30 °C and a solution of **8a** (520 mg, 1.4 mmol) in 10 mL of THF was added. The reaction was stirred at room temperature for 4 h and recooled to 0 °C. To the reaction was added carefully 3N NaOH (700 μL) followed immediately by addition of 30 % H_2O_2 (700 μL). The mixture was stirred vigorously for 3 h at room temperature and partitioned with ether. The aqueous phase was extracted with Et_2O (3 X 20 mL). The extracts were combined, washed with saturated NaCl, dried ($MgSO_4$) and concentrated to give 511 mg (93 % yield) of a white solid. TLC analysis gave one spot. However, ^1H NMR (500 MHz) analysis in benzene-d_6 showed the diol to be a 1:1 mixture of diastereomers. Chromatography of the mixture (7:3 hexane/ethyl acetate) gave only partial separation of the diastereomers. ^1H NMR of the more polar diol diastereomer was identical to diol **2a** which was previously prepared by reduction of lactone **1a**. Data for **2a** (more polar diastereomer): mp 112-113 °C; $[\alpha]^{25}_D$ = -32.4 ° (c 1.0, $CHCl_3$); Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.52; N, 3.58. Found: C, 70.87; H, 9.16; N, 3.57. Data for **2b:** $[\alpha]^{25}_D$ = -8.1° (c 1.70, $CHCl_3$); ^1H NMR (C_6D_6) δ 0.70 (d, *J* = 7.5 Hz, 6 H), 0.62-1.74 (complex, 18 H), 2.02-2.09 (bd, *J* = 11.1 Hz, 1 H), 3.23 (dd, *J* = 9.6 Hz, *J* = 9.6 Hz, 1 H), 3.45 (dd, *J* = 9.6 Hz, *J* = 3.6 Hz, 1 H), 3.55-3.64 (m, 1 H), 3.94-4.06 (m, 1 H), 5.08 (s, 2 H), 5.18 (d, *J* = 9.6 Hz, 1 H), 6.95-7.26 (m, 5 H); LRMS, *m/e* 392 (M^+), 409 ($M+NH_4^+$); HRMS Calcd for $C_{23}H_{37}NO_4$: 392.2801. Found 392.2813.

(2S,4S,5S)-5-Benzyloxycarbonylamino-6-cyclohexyl-4-hydroxy-2-isopropyl hexanolide (1a) from diol 2a. Catalytic RuO_4 Oxidation. Using the procedure of Sharpless et al. a mixture of diol **2a** (1.0g, 2.56 mmol) and $NaIO_4$ (2.24 g, 10.5 mmol) was dissolved in 8 mL of CCl_4, 8 mL of CH_3CN and 12 mL of water. To the resulting solution was added a catalytic amount of $RuCl_3 \cdot H_2O$ (11.6 mg, 0.056 mmol). The mixture was stirred for 6 h at ambient temperature and diluted with 40 mL of CH_2Cl_2. The organic solution was filtered through a pad of Celite, washed with saturated NaCl (2 x 20 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (1:4 ethyl acetate:hexane) gave 520 mg (52%) of **1a** as a white solid which was identical to an authentic sample of lactone **1a**:[10] mp 167-168 °C; $[\alpha]^{25}_D$ = -33.0° (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.75-0.85 (m, 1 H), 0.90 (d, *J* = 7.5 Hz, 3 H), 0.96 (d, *J* = 7.5 Hz, 3 H), 1.20-1.85 (complex, 12 H), 2.00-2.21 (m, 3 H), 2.47 (8 line m, 1 H), 3.88-3.96 (m, 1 H), 4.40-4.46 (m, 1 H), 4.58 (d, *J* = 9.6 Hz, 1 H), 5.12 (s, 2 H), 7.24-7.40 (m, 5 H); LRMS, *m/e* 405 ($M+NH_4^+$); Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.67; H, 8.52; N, 3.68.

Jones Oxidation. A solution of **2a** (500 mg, 1.3 mmol) and Jones Reagent (2.7 M, 1.9 mL, 5.2 mmol) in 10 mL of acetone was stirred vigorously at 10 °C for 3 h. The reaction mixture was filtered through a plug of Celite and the plug was washed repeatedly with diethyl ether. The ether layer was washed with saturated NaCl (2 x 5 mL), dried ($MgSO_4$) and concentrated to give a white solid. The solid was purified by chromatography (4:1 hexane/ethyl acetate) to give 286 mg (57% yield) of **1a** which was identical to lactone **1a** prepared by the RuO_4 oxidation procedure.

(2S,4S,5S)-5-Benzyloxycarbonylamino-6-cyclohexyl-2-isopropyl-4-hydroxy hexanolide (1a) from the TBDMS Ethers 14a and 14b. A mixture of alcohols **14a** and **14b** (2.6:1, 3.35 g, 6.6 mmol) and $NaIO_4$ (5 4 g, 25 mmol) in 30 mL of CCl_4, 30 mL of CH_3CN and 45 mL of water was stirred vigorously until all solids had dissolved. To the resulting solution was added a catalytic amount of $RuCl_3 \cdot H_2O$ (42 mg, 0.2 mmol). The mixture was stirred for 3 h at ambient temperature and diluted with 50 mL of CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 X 40 mL). The combined organic extracts

were filtered through a plug of Celite and the plug was washed repeatedly with CH_2Cl_2. The organic solution was washed with saturated NaCl (2 X 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 3.1 g (90 %) of a purple oil.

The crude oxidation product was dissolved in 150 mL of MeOH and 3M HCl (13.3 mL, 40 mmol) was added. This solution was heated at reflux temperature for 1.5 h and allowed to cool to room temperature. White needles crystallized from the methanol solution and were collected by filtration to give 1.20 g (46%) of lactones **1a/1b**. The ratio of **1a/1b** was 9:1 as determined by integration of the C-3 methine proton at δ 2.57. The lactone diastereomers were separated by chromatography: Data for **1a:** R_f = 0.22, 4:1 hexane/ethyl acetate; ^{1}H NMR spectrum was identical to lactone **1a** previously prepared. Data for **1b:** R_f = 0.18, 4:1 hexane/ethyl acetate; mp 117-118 °C; $[\alpha]^{25}_D$ = -20.7 ° (c 1.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (d, *J* = 7.5 Hz, 3 H), 0.82-1.0 (m, 1 H), 0.97 (d, *J* = 7.5 Hz, 3 H), 1.0-1.89 (complex, 13 H), 2.05-2.20 (m, 2 H), 2.57 (ddd, *J* = 12.5 Hz, *J* = 9 Hz, *J* = 5 Hz, 1 H), 3.89-3.99 (m, 1 H), 4.32-4.39 (m, 1 H), 4.67 (d, *J* = 9.6 Hz, 1 H), 5.07 (d, *J* = 12.6 Hz, 1 H), 5.13 (d, *J* = 12.6 Hz, 1 H), 7.29-7.38 (m, 5 H). LRMS, *m/e* 405 ($M+NH_4^+$); Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.61; H, 8.47; N, 3.92.

***N*-3-(4-Morpholinyl)propyl-(2S,4S,5S)-5-(benzyloxycarbonylamino)-6-cyclohexyl-4-hydroxy-2-isopropylhexanamide (15).** A 9:1 mixture of lactones **1a:1b** (1.0 g, 2.58 mmol), 3-(4-morpholinyl)propyl amine (3.3 g, 23.2 mmol) and glacial acetic acid (150 μL, 2.58 mmol) was heated at 55 °C for 8 h. The solution was partitioned between EtOAc and water. The organic layer was washed with saturated NaCl (2 X 20 mL), dried ($MgSO_4$), and concentrated. The crude product was recrystallized from hot ethyl acetate/hexane to give 940 mg (69%) of amide **15**: mp 145-146 °C; $[\alpha]^{25}_D$ = -26.9 ° (c 0.87 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75-1.03 (m, 2 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 1.07- 2.00 (complex m, 17 H), 2.40- 2.55 (m, 6 H), 3.23-3.44 (m, 2 H), 3.53-3.65 (m, 2 H), 3.71 (t, *J* = 4.8 Hz, 4 H), 4.94 (bd, *J* = 9.3 Hz, 1 H), 5.07 (d, *J* = 9.3 Hz, 2 H), 5.14 (d, *J* = 9.3 Hz, 2 H), 7.11 (m, 1 H), 7.27-7.38 (arom, 5 H); LRMS, *m/e* 532 (M^+); HRMS Calcd for $C_{30}H_{49}N_3O_5$: 532.3750. Found 532.3737. Anal. Calcd for $C_{30}H_{49}N_3O_5 \cdot$ C, 67.76; H, 9.29; N, 7.80. Found: C, 68.14; H, 9.13; N, 8.01.

Oxazolidone 16 A 9:1 mixture of lactones **1a:1b** (810 mg, 2.1 mmol) and 3-(4-morpholinyl)propyl amine (4.0 g, 28 mmol) was heated at 70 °C for 4 days. The solution was partitioned between EtOAc and water. The organic layer was washed with saturated NaCl (2 X 20 mL), dried ($MgSO_4$), and concentrated. The crude product was recrystallized from ethyl acetate/hexane to give 400 mg (45%) of the oxazolidinone **16**: mp 153 °C; $[\alpha]^{25}_D$ = -64.5 ° (c 0.35 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80-1.05 (m, 2 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.10-1.37 (m, 4 H), 1.43 (t, *J* = 6.6 Hz, 2 H), 1.58-2.14 (complex m, 11 H), 2.47 (m, 6 H), 3.36 (7 line m, 2 H), 3.49 (m, 1 H), 3.73 (m, 4 H), 3.99 (ddd, J = 8.4, 6.6, 2.4 Hz, 1 H), 5.13 (bs, 1 H), 7.02 (bs, 1 H); LRMS, *m/e* 424 (M^+); HRMS Calcd for $C_{23}H_{41}N_3O_4$: 424.3175. Found 424.3176. Anal. Calcd for $C_{23}H_{41}N_3O_4$: C, 65.22; H, 9.76; N, 9.92. Found: C, 65.28; H, 9.84; N, 9.82.

General Procedure for the Protonation of the Enolate Derived from Lactone 1a. LDA was prepared by dropwise addition of 2.5 M *n*-BuLi (880 μL, 2.2 mmol) to a solution of diisopropyl amine (310 μL, 2.2 mmol) in 3 mL of THF at - 60 °C. The LDA solution was stirred for 10 min at -78 °C and lactone **1a** (387 mg, 1.0 mmol) in 3 mL of THF was added dropwise. The reaction mixture was stirred for 20 min and the proton source (3 to 5 mmol) was added. The reaction was stirred for 20 min at -78 °C, warmed to ambient temperature and quenched with saturated NH_4Cl. The aqueous phase was extracted with diethyl ether

(3 x 30 mL). The extracts were combined, washed with saturated NaCl, dried ($MgSO_4$), and concentrated. The ratio of lactone **1a/1b** were determined by integration of the C-3 methine proton at δ 2.57.

(2R,4S,5S) and (2S,4S,5S)-2-Benzyl-5-Benzyloxycarbonylamino-6-cyclohexyl-4-hydroxyhexanolide (17a and 17b). A diastereomeric and racemic mixture of lactones **17a:17b** (1.0 g, 2.5 mmol) was reacted with LDA (5.5 mmol) according to the general procedure and the enolate was quenched with diethyl malonate (1.4 mL, 12.5 mmol). Workup afforded an oil which was purified by chromatography (3:1 hexane/EtOAc). Lactones **17b** C(3S) and **17a** C(3R) were isolated in a ratio of 9.5:1 and were identical by TLC and ^1H NMR to authentic lactones previously prepared.[40] **17a:** 67 mg (7%); R_f = 0.32 4:1 hexanes/EtOAc. **17b:** 634 mg (64 %); R_f = 0.23 4:1, hexane/EtOAc.

(2S,4S,5S) 2-Benzyl-5-Benzyloxycarbonylamino-6-cyclohexyl-4-hydroxy-hexanoic Acid *tert*-Butyldimethylsilyl Ether (18). A solution of **17b** (630 mg, 1.59 mmol) and NaOH 1.0 M (1.75 mL, 1.75 mmol) in 8 mL of dioxane and 4 mL of water was stirred vigorously for 30 min. The solution was concentrated and the residue was treated with 10% aqueous citric acid until the pH was 2. The aqueous phase was extracted with diethyl ether (3 X 20 mL). The extracts were combined, washed with saturated NaCl, dried (Na_2SO_4), and concentrated to give the crude carboxylic acid.

The crude acid was immediately combined with TBDMSCl (1.2 g, 8 mmol) and imidazole (950 mg, 14 mmol) in 5 mL of DMF and stirred overnight at ambient temperature. The solution was concentrated and the residue partitioned between water and diethyl ether. The pH of the solution was adjusted to 4 with 10% aqueous citric acid and the aqueous phase was extracted with diethyl ether (3X 20 mL). The organic extracts were combined, washed with saturated NaCl, dried (Na_2SO_4), and concentrated to give 710 mg (70%) of the crude diTBDMS ether/ester.

The crude diTBDMS ether/ester (710 mg, 1.1 mmol) was stirred in a mixture of 9 mL of glacial acetic acid, 3 ml of THF and 3 mL of water for 2 h at ambient temperature and concentrated. The residue was treated with ice water and extracted with diethyl ether (3 X 20 mL). The extracts were combined, washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (6:94 MeOH/CH_2CH_2) to give 240 mg (41 %) of acid **18**. mp 118-119 °C; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.93 (s, 9 H), 1.35 (s, 9 H), 1.65-1.92 (m, 3 H), 2.64- 2.98 (m, 5 H), 3.71 (m, 1 H), 4.04 (m, 1 H), 4.63 (m, 1 H), 7.08-7.28 (arom, 10 H); LRMS, *m/e* 528 (M^+), 545 ($M+NH_4^+$). Anal. Calcd for $C_{30}H_{45}NO_5Si$: C, 68.27; H, 8.59; N, 2.65. Found: C, 68.56; H, 8.73; N, 2.63.

(2S,3S,5S) 2-[(*tert*-Butyloxycarbonyl)amino]-1,6-diphenyl-3-hydroxy-5-[(3-pyridinylmethoxycarbonyl)amino]hexane *tert*-Butyldimethylsilyl Ether (19). A solution of acid **18** (105 mg, 0.20 mmol), triethylamine (22 mg, 31μL, 0.22 mmol) and diphenylphosphoryl azide (147 μL, 0.22 mmol) in 2 mL of dry toluene was heated at 70 °C for 1.5 h. To the solution was added 3-pyridylcarbinol (440 μL, 4.52 mmol) and the solution was heated at reflux temperature for 36 h, cooled and concentrated. The residue was partitioned between EtOAc and water. The organic layer was washed with 10 mL of 1 M HCl, 10 mL water, 10 mL of $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), and concentrated. The crude product was purified by chromatography (1.5:1, hexanes/EtOAc) to give 81 mg (64%) of carbamate **19**. R_f = 0.31, 3:2 hexane/ethyl acetate; ^1H NMR (d_6 DMSO) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.30 (s, 9 H), 1.49-1.75 (m, 3 H), 2.58-2.73 (bm, 4 H), 3.68-4.00 (bm, 3 H), 4.80-5.08 (m, 2 H), 6.44 (bd, J = 9 Hz, 1 H), 7.10-7.38 (m, 11 H), 7.62 (bm, 1 H), 8.50 (m, 2 H); ^{13}C NMR (75 MHz d_6 DMSO) δ 17.7, 25.82, 27.7, 28.2, 35.6, 49.3,

54.3, 62.5, 71.5, 77.5, 123.3, 125.6, 125.8, 127.8, 127.9, 128.8, 128.9, 132.9, 135.3, 138.9, 139.6, 148.8, 148.9, 155.3, 155.4; LRMS *m/e* 634 ($M+H^+$); HRMS Calcd for $C_{36}H_{52}N_3O_5Si$: 634.3676. Found 634.3687. Anal. Calcd for $C_{36}H_{51}N_3O_5Si \cdot 0.25\ H_2O$: C, 67.73; H, 8.13; N, 6.58. Found: C, 67.58; H, 7.98; N, 6.46.

(2S,3S,5S) 2-[(*tert*-Butyloxycarbonyl)amino]-1,6-diphenyl-3-hydroxy-5-[(3-pyridinylmethoxycarbonyl)amino]hexane (21). A solution of amino alcohol **20** (120 mg, 0.3 mmol) and di-*tert*-butyl dicarbonate (125 mg, 0.6 mmol) in 2 mL of CH_2Cl_2 were stirred at rt for 18 h, solvents were evaporated and the residue purified by flash silica gel chromatography (2-5:98-95 methanol-CH_2Cl_2) to give 80 mg (54 %) of Boc amino alchol **21**: mp 156-158 °C; $[\alpha]^{25}_D$ = -15.2 ° (c 0.88 $CHCl_3$); ^1H NMR (d_6 DMSO) δ 1.13-1.20 (bs, 2 H), 1.31 (s, 9 H), 1.46-1.58 (br t, 3 H), 2.54-2.75 (bm, 7 H), 3.48-3.59 (bm, 2 H), 3.70-97 (bm, 3 H), 4.55 (br d, 1 H), 4.92-5.02 (bm and s, 3 H), 6.25 (br d, 1 H), 7.07-7.27 (bm, 6 H), 7.34 (br dd, 1 H), 7.58 (br d, 1 H), 8.49 (br d, 1 H); LRMS *m/e* 520 ($M+H^+$). Anal. Calcd for $C_{30}H_{37}N_3O_5$: C, 69.36; H, 7.13; N, 8.09. Found: C, 69.17; H, 7.13; N, 8.04.

(2S,3S,5S) 2-[(*tert*-Butyloxycarbonyl)amino]-1,6-diphenyl-3-hydroxy-5-[(3-pyridinylmethoxycarbonyl)amino]hexane *tert*-Butyldimethylsilyl Ether (19). A solution of alcohol **21** (60 mg, 0.1 mmol), imidazole (9.4 mg, 0.12 mmol) and *tert*-butyldimethylsilyl chloride (21 mg, 0.12 mmol) in 0.5 mL of DMF were stirred at rt for 18 h. The DMF was evaporated and the residue purified by flash silica gel chromatography (1:2 ethyl acetate-hexane) to give 64 mg (87%) of the silyl ether **19**: $[\alpha]^{25}_D$ = +4.8 ° (c 0.82 $CHCl_3$); ^1H and ^{13}C NMR (d_6 DMSO) were identical to carbamate **19** that was prepared above. Anal. Calcd for $C_{36}H_{51}N_3O_5Si$: C, 68.25; H, 8.06; N, 6.64. Found: C, 67.73; H, 7.98; N, 6.51.

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