Dipeptide Isosteres. 1. Synthesis of Dihydroxyethylene Dipeptide Isosteres via Diastereoselective Additions of Alkyllithium Reagents to *N,N*-Dimethylhydrazones. Preparation of Renin and HIV-1 Protease Inhibitor Transition-State Mimics

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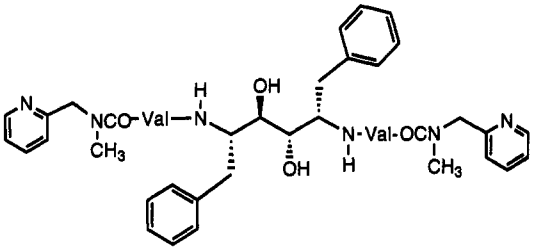
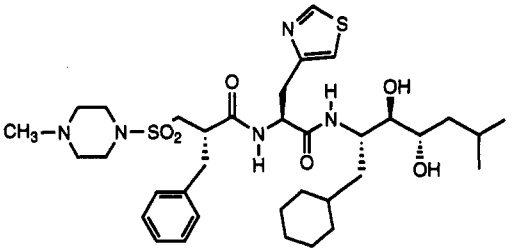
The amino and diamino dihydroxyethylene dipeptide isosteres **19a,b** and **23** are important intermediates for the preparation of inhibitors of human renin and HIV-1 protease, respectively. A general synthetic strategy was developed to access both dipeptide isosteres. The key step was a diastereoselective addition of an alkyllithium reagent to an aldehyde hydrazone. Thus, isosteres **19a** and **19b** were synthesized by addition of either benzyllithium or (cyclohexylmethyl)lithium to (4*S*,5*R*)-2,2-dimethyl-4-(2-methylpropan-1-yl)-5-formyl-1,3-dioxolane *N,N*-dimethylhydrazone (**4**) in diethyl ether at −10 °C. The hydrazine addition product was reduced to the amine, and the acetonide protecting group was removed. The resulting amino diol was derivatized as either a *N*-Boc analogue or coupled to *N*-(*tert*-butyloxycarbonyl)-3-(thiazol-4-yl)alanine. The addition reactions were completely diastereoselective, affording only the chelation-controlled products (*β* attack, *S* configuration at C(2)). Hydrazone **4** was prepared from either D-isoascorbic acid (**1**), divinyl carbinol (**5**), or chlorobenzene (**9**). Application of the hydrazone/alkyllithium reaction to the synthesis of the diamino dihydroxyethylene dipeptide isostere **23** was also achieved. Reaction of the bis-hydrazone **22** with benyllithium, followed by Raney nickel reduction of the hydrazine addition product, formation of the bis-benzyl carbamate, and deprotection of the acetonide with methanolic HCl gave the diamino dihydroxyethylene dipeptide isostere **23** in 36% overall yield (four steps). Isostere **23** is an intermediate useful for the preparation of C_2 symmetric HIV-1 protease inhibitors.

Introduction

A large number of inhibitors of the aspartic acid proteases, renin and HIV-1, have structures which incorporate a dihydroxyethylene dipeptide (DHED) isostere into the inhibitor molecule. The 1,2-diol moiety of the DHED isostere binds to the enzyme by forming tight hydrogen bonds to the aspartic acid residues which are present in the active site.[2] Thus, the DHED isostere functions as a stable transition-state mimic. Recent reports from our laboratories have disclosed two aspartic acid protease inhibitors, A-77003 and A-72517, which possess a DHED isostere as a transition-state mimic. A-77003 is an HIV-1 protease inhibitor which is currently under clinical development for potential use in the treatment of acquired immunodeficiency syndrome (AIDS).[3] A-72517, a potent inhibitor of human renin, is undergoing clinical evaluation as therapeutic agent for the treatment of hypertension and congestive heart failure (CHF).[4]



HIV-1 protease inhibitor A-77003



renin inhibitor A-72517

As part of a program aimed at identifying a practical and cost-effective synthesis of the dihydroxyethylene dipeptide isostere, we were interested in developing a general synthetic approach to both the amino and diamino DHED isosteres **A** and **D**. Previous synthetic approaches to isosteres **A** and **D** have utilized optically active *α*-amino aldehydes as starting materials and as a source of chirality *α* to nitrogen. The diol stereochemistry for isostere **A** was created by either a selective osmylation reaction of a cis olefin[5a] or a selective reduction of a *α*-hydroxy ketone.[5b] For the preparation of intermediate **D**, the 1,2-diol functionality and stereochemistry was obtained by a selective pinacol coupling.[6] Our strategy for the synthesis of isosteres **A** and **D** involved the creation of the chiral

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(2) (a) Blundell, T. L.; Cooper, J.; Foundling, S. I.; Jones, D. M.; Atrash, B.; Szelke, M. *Biochemistry* **1987**, *26*, 5585–5590. (b) Abad-Zapatero, C.; Rydel, T. J.; Neidart, D.; Luly, J.; Ericson, J. W. *Structure and Function of the Aspartic Proteinases*; Dunn, B. M., Ed.; Plenum Press, New York, 1991; pp 9–21. (c) Chen, L.; Erickson, J. W.; Rydel, T. J.; Park, C. H.; Neidhart, D.; Luly, J.; Abad-Zapatero, C. *Acta Crystallogr.* **1992**, B48, 476–488.

(3) Kempf, D. J.; Marsh, K. C.; Paul, D. A.; Knigge, M. F.; Norbeck, D. W.; Kohlbrenner, W. E.; Codacovi, L.; Vasavanonda, S.; Bryant, P.; Wang, X. C.; Wideburg, N. E.; Clement, J. J.; Plattner, J. J.; Erickson, J. *Antimicrob. Agents Chemother.* **1991**, *35*, 2209.

(4) Kleinert, H. D.; Rosenberg, S. H.; Baker, W. R.; Stein, H. H.; Klinghofer, V.; Barlow, J.; Spina, K.; Polakowski, J.; Kovar, P.; Cohen, J.; Denissen, J. *Science* **1992**, *257*, 1940–1944.

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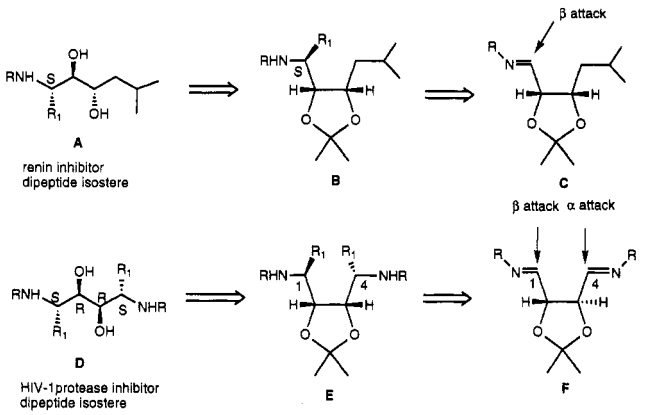
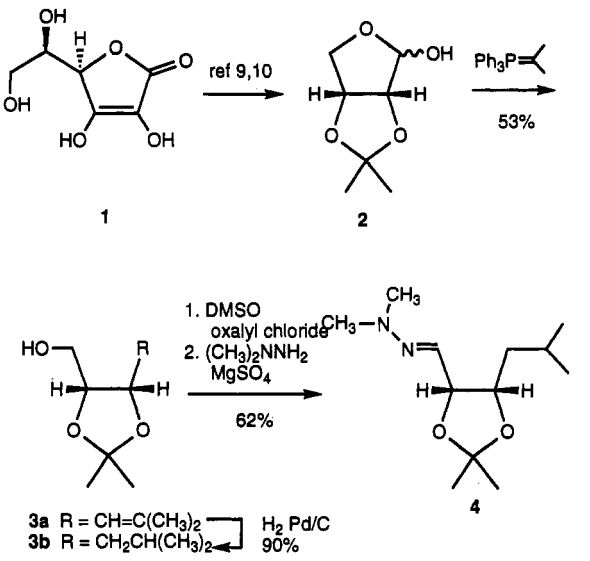


center α to the amino group by a diastereoselective organometallic addition to hydrazone **C**[7] and bis hydrazone **F**. Chelation-controlled addition to hydrazone **C** (β attack) and bis hydrazone **F** (β and α attack) would produce hydrazines **B** and **E**, respectively. The desired *S* configuration at the newly formed stereogenic center would be produced.[8] The 1,2-diol stereochemistry for intermediates **C** and **F** would be derived from either the chiral pool or stereoselective syntheses. We have previously reported the preparation of the dihydroxyethylene dipeptide isostere **19b** from D-isoascorbic acid.[7e] In this paper, we describe alternatative synthesis of intermediate **4** and the extension of the *N,N*-dimethylhydrazone/alkyllithium reaction methodology to the synthesis of the diamino diol DHED isostere **23**.

Results and Discussion

1. Synthesis of the Amino Dihydroxyethylene Dipeptide Isostere 19a and 19b from (4*S*,5*R*)-2,2-Dimethyl-4-(2-methylpropan-1-yl)-5-formyl-1,3-dioxolane *N,N*-Dimethylhydrazone (4). a. Preparation of Hydrazone 4 from D-Isoascorbic Acid (1). From the beginning, it was clear that a consise and inexpensive synthesis of the key hydrazone intermediate **4** was needed, one that could be readily scaled up to a manufacturing process and involve minimal to no purification of synthetic intermediates. D-Isoascorbic acid was selected as a starting material for the preparation of hydrazone **4**. D-Isoascorbic acid is an inexpensive compound, available in large quantities, and it is easily converted to D-erythronolactone, the precursor to 2,3-*O*-isopropylidene-D-erythrose (**2**), on large scale in excellent yield.[9] As outlined in Scheme I, D-isoascorbic acid (**1**) was transformed to the known acetonide lactol by published procedures.[10] The crude lactol **2** was reacted with (2-isopropylidene)triphenylphosphorane[11] using the procedure of Kang et al.[12] to give alcohol **3a** as a water-white liquid in 53% yield. Purification of **3a** was achieved by high vacuum distillation. Catalytic hydrogenation of the double bond produced the saturated alcohol **3b** in 90% yield. Swern oxidation of **3b** afforded the aldehyde, and addition of excess 1,1-dimethylhydrazine/$MgSO_4$[13] to the crude Swern reaction mixture produced hydrazone **4** which was purified by silica gel chromatography for characterization (64% yield for the two steps). For practical purposes, the crude hydrazone **4** was used in the organometallic addition reactions without further purification.

Scheme I



b. Preparation of Hydrazone 4 from Divinylcarbinol (5). The synthesis of hydrazone **4** from divinylcarbinol was investigated next. An asymmetric epoxidation reaction was employed to produce the 1,2-diol stereochemistry. Thus, Sharpless oxidation of divinylcarbinol (**5**) using D-(−)-diisopropyl tartrate as catalyst produced the (3*R*,4*S*)-epoxy alcohol **6** in 48% yield (Scheme II).[14] The epoxide ring was opened by the reaction of the alcohol **6** with isopropylmagnesium chloride in the presence of cuprous iodide. The resulting diol **7** was protected as the acetonide, affording dioxolane **8** (bp 54 °C (30 mmHg)) in 38% yield from epoxide **6**. Ozonolysis of **8**, followed by reductive workup with zinc metal, gave the crude aldehyde. Reaction of the aldehyde with 1,1-dimethylhydrazine as previously described furnished hydrazone **4** in 61% yield.

c. Preparation of Hydrazone 4 from Chlorobenzene (9). An intriguing approach to hydrazone **4** involved

(5) (a) Luly, J. R.; BaMaung, N.; Soderquist, J.; Fung, A. K. L.; Stein, H.; Kleinert, H. D.; Marcotte, P.; Egan, D. A.; Bopp, B.; Mertis, I.; Bolis, G.; Greer, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1988**, *31*, 2264–76. (b) Luly, J. R.; Hsiao, C.; BaMaung, N.; Plattner, J. J. *J. Org. Chem.* **1988**, *53*, 6109–6112.

(6) Kempf, D. J.; Norbeck, D. W.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook, W., Jr.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687–2689.

(7) For related syntheses of isostere **A** and other analogous dihdyroxyethylene dipeptide isosteres from starting materials other than α-amino acids, see the following. (a) From (*E*)-5-methyl-2-hexen-1-ol using Sharpless oxidation: Wood, J. L.; Jones, D. R.; Hirschmann, R.; Smith, A. B., III *Tetrahedron Lett.* **1990**, *31*, 6329–6330. (b) From divinyl carbinol: Atsuumi, S.; Masato, N.; Koike, Y.; Tanaka, S.; Funabashi, H.; Hashimoto, J.; Morishima, H. *Chem. Pharm. Bull.* **1990**, *38*, 3460–3462. (c) From (2*S*,3*S*)-tartaric acid: Kobayashi, Y.; Matsumoto, T.; Takemoto, Y.; Nakatani, K.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2550–2555 and references sited therein. (d) From D-ribose: Chan, M. F.; Hsiao, C. *Tetrahedron Lett.* **1992**, *33*, 3567–3570. (e) From D-isoascorbic acid: Baker, W. R.; Condon, S. L. *Tetrahedron Lett.* **1992**, *33*, 1581–1584.

(8) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.

(9) Dunigan, J.; Weigel, L. O. *J. Org. Chem.* **1991**, *56*, 6225–6227.

(10) (a) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* **1984**, *63*, 127. (b) Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberger, M.; Liu, Y. Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661–72.

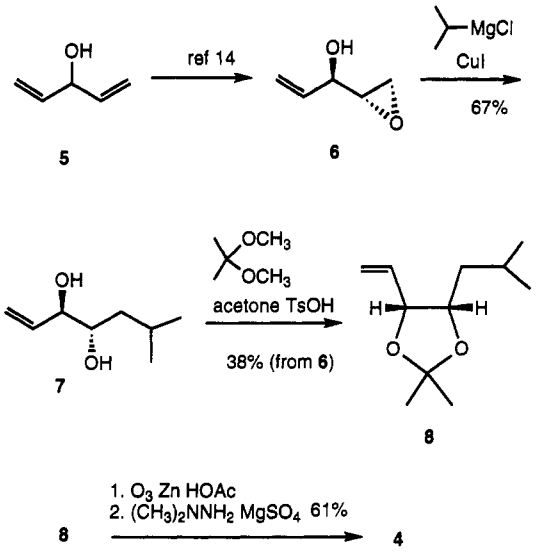
(11) Fagerlund, U. H. M.; Idler, D. R. *J. Am. Chem. Soc.* **1957**, *79*, 6473–6475.

(12) Kang, S.; Lee, D.; Kim, S. Org. Prep. Proced. Int. 1990, 22, 651–654.

(13) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677–681.

(14) (a) Babine, R. E. *Tetrahedron Lett.* **1986**, *27*, 5791–5794. (b) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793–4808. (c) Jager, V.; Hummer, W.; Stahl, U.; Gracza, T. *Synthesis* **1991**, 769–782.

Scheme II

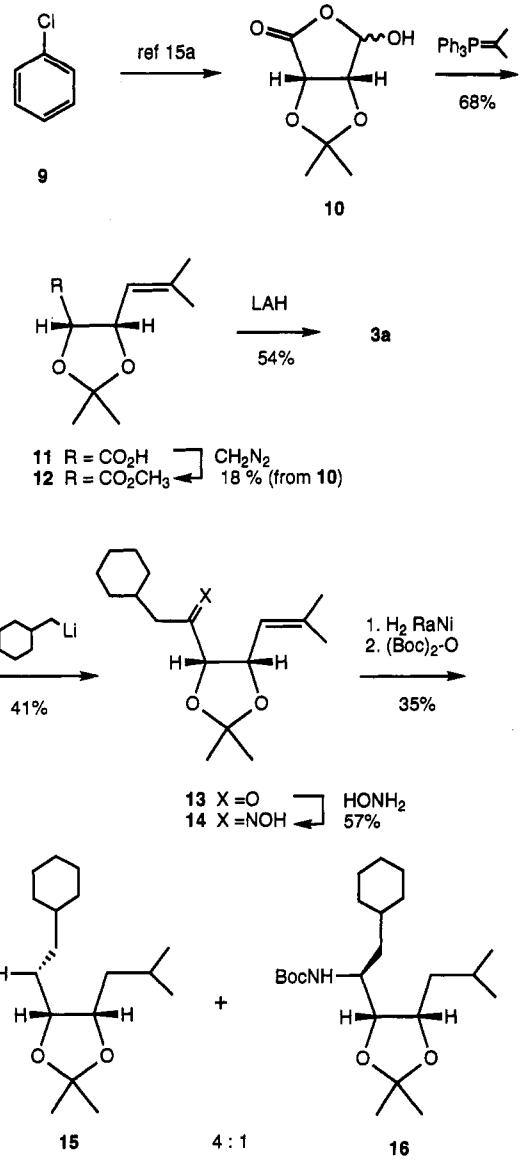


setting the desired stereochemistry of the vicinal 1,2-diol via a microbial oxidation. Hudlicky has described an efficient three-step synthesis of lactone **10** from chlorobenzene using *Pseudomonas putida* 39D as the microorganism for the oxidation reaction.[15a] Treatment of **10**[16] with (2-isopropylidene)triphenylphosphorane in THF at reflux temperature gave crude carboxylic acid **11**[15b] which was converted to the methyl ester **12**. Unfortunately, a rather low overall yield of ester **12** was realized (18% from lactone **10**). Lithium aluminum reduction of methyl ester **12** gave alcohol **3a** in 54%, thereby completing a formal synthesis of hydrazone **4**.

With carboxylic acid **11** in hand, we were interested in preparing oxime **14** from ketone **13** to determine if catalytic hydrogenation of the oxime would produce the desired amine diastereomer **16**. Reaction of crude acid **11** with cyclohexylmethyllithium, prepared from cyclohexylmethyl iodide and *tert*-butyllithium according to the procedure of Negishi,[17] gave ketone **13** in 41% yield.[18] Reaction of ketone **13** with $HCl{\cdot}NH_2OH$ in pyridine produced both oxime diastereomers. Reduction of the oxime diastereomers and olefin were accomplished simultaneously (H_2, RaNi, 4 atm) to yield the saturated amine. Protection of the amine as the Boc derivative give a 4:1 mixture of acetonides **15** and **16**, respectively. The lack of stereochemical control for the reduction of oxime **14** and the chemical instability of ketone **13** encouraged us to abandon this approach for the synthesis of isostere **19b**.

The synthesis of the amino DHED isosteres **19a** and **19b** from hydrazone **4** is outlined in Scheme IV. The key step required for the synthesis was a diastereoselective addition of an organometallic reagent to hydrazone **4**. Several experiments were attempted utilizing the reaction of a cerium-based organometallic reagent prepared from (cyclohexylmethyl)magnesium chloride and anhydrous $CeCl_3$ with hydrazone **4**. Although additions of organocerium reagents to imines[7c] and SAMP hydrazones[19] have been documented, we were unable to successfully obtain

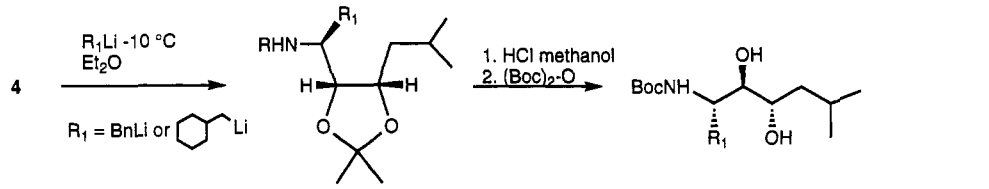
Scheme III



useful yields of hydrazine **17b** using the cerium-based organometallic reagent. We next investigated the reaction of organolithium reagents with hydrazone **4**. Claremon has reported high diastereoselectivities and excellent yields in the addition reactions of organolithium reagents to α-alkoxy aldehyde hydrazones.[20] He also evaluated 2,3-dihydroxy aldehyde acetonide hydrazones in the alkyllithium addition reactions. For example, reaction of methyllithium with the *N,N*-dimethylhydrazone of (*R*)-glyceraldehyde acetonide[21] in diethyl ether at −10 °C gave the hydrazine addition product in 95% yield. However, the diastereoselectivity was only a modest 3:1 (*S*/*R*). We were able to obtain an excellent yield for the reaction of (cyclohexylmethyl)lithium with the *N,N*-dimethylhydrazone of (*R*)-glyceraldehyde acetonide using identical reaction conditions. Unfortunately, the diastereoselectivity was the same (3:1). We were not discouraged by this result, and an addition reaction of cyclohexylmeth-

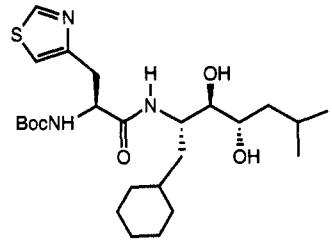
(15) (a) Hudlicky, T.; Price, J. D. *Synlett* **1990**, 159–160. (b) Hudlicky, T.; Luna, H.; Price, John D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683–4687.
(16) A 10-g sample of lactone **10** was kindly provided by Genencor International, Inc., 1100 Ridgeway Ave., Rochester, NY 14652-3615.
(17) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406–5409.
(18) Pure ketone **13** undergoes decomposition at rt over 18 h as judged by TLC.
(19) For addition reactions of organocerium reagents to hydrazones, see: (a) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219–6223. (b) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224–2225 and references cited therein.
(20) Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265–8266.
(21) Baer, E.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463–473.

Scheme IV



17a R = $(CH_3)_2N$, $R_1 = CH_2C_6H_5$
17b R = $(CH_3)_2N$, R_1 = CH_2cyclohexyl
18a R = H, $R_1 = CH_2C_6H_5$
18b R = H, R_1 = CH_2cyclohexyl
16 R =Boc, R_1 = CH_2cyclohexyl 36% from **3b**

19a $R_1 = CH_2C_6H_5$ 41% (from **4**)
19b R_1 = CH_2cyclohexyl 24% (from **3b**)



20 32% (from **3b**)

yllithium to hydrazone **4** was attempted. To our surprise, the reaction of (cyclohexylmethyl)lithium with hydrazone **4** in diethyl ether at −10 °C provided crude hydrazine **17b** as a single diastereomer. Reduction of **17b** to amine **18b** (H_2, RaNi) and formation of the *N*-Boc derivative with di-*tert*-butyl dicarbonate gave the Boc acetonide **16** (36% from **3b**) which was identical by TLC to the minor Boc acetonide formed from the reduction of oxime **14**. Apparently, the control of diastereoselectivity in the alkyllithium addition reaction was influenced by the isobutyl group on the dioxolane ring. The stereochemistry at the newly formed stereogenic centered was confirmed by conversion of **18b** to authentic *N*-Boc diol.[5a] Thus, hydrolysis of the crude amine **18b** and protection of the amino diol as the *N*-Boc derivative gave **19b** in 24% yield from hydrazone **4**. The TLC and ^1H and ^{13}C NMR of **19b** were identical to authentic *N*-Boc diol. Reaction of crude amino diol with *N*-Boc-3-(thiazo-4-yl)alanine afforded derivative **20** in 32% overall yield from **3b**.[7e]

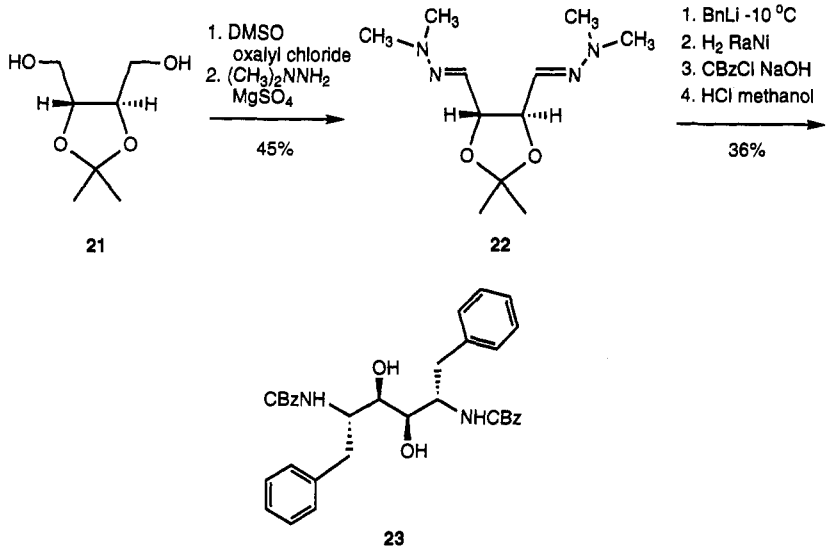
The generality of the hydrazone/alkyllithium reaction for the preparation of DHED isosteres was demonstrated by the synthesis of analogue **19a**. Benzyllithium was prepared via a tin/lithium exchange reaction of triphenylbenzyltin and phenyllithium in diethyl ether.[22] Addition of hydrazone **4** to the benzyllithium solution produced the crude hydrazine **18a**. Again, the proton NMR (300 MHz) of crude **18a** indicated the existence of only one diastereomer, and by analogy to **18b**, the new stereogenic center was assigned the *S* configuration. Hydrazine **18a** was then converted to isostere **19a** using the previously described procedures in 41% overall yield from hydrazone **4**.

2. Synthesis of the Diamino Dihydroxyethylene Dipeptide Isostere 23 from (−)-2,3-*O*-Isopropylidene-D-threitol (21). An expeditious synthesis of isostere **23** has been described by Kempf and Sowin et al.[23] Their approach utilized an intermolecular Pedersen pinacol coupling of Cbz-phenylalanal to give a mixture of all three possible 1,2-diol diastereomers in a ratio of 8:1:1. The syn diol **23** was obtained as the major product. We were interested in applying the hydrazone/alkyllithium reaction methodology to the synthesis of isostere **23** (Scheme V). In order to achieve a synthesis of isostere **23**, a bis diastereoselective addition reaction of benzyllithium to hydrazone **22** would be required. As in the pinacol coupling reaction of *N*-Cbz phenylalinal, three diastereomers are possible from the reaction of benzyllithium with hydrazone **22**: (1) the desired 1*S*,4*S* diastereomer **23** (chelation-controlled addition product, β and α attack); (2) the 1*R*,4*R* diastereomer (non-chelation-controlled addition product, α and β attack); and (3) the 1*R*,4*S* or 1*S*,4*R* diasteromers which are the same compound by C_2 symmetry ($\alpha\alpha$ or $\beta\beta$ attack). Treatment of hydrazone **22** with benzyllithium using the standard procedure gave the crude bis-hydrazine addition product. Reduction of the hydrazine moiety (H_2/RaNi, 4 atm) and protection of the diamine (CbzCl, NaOH) afforded the crude bis *N*-Cbz acetonide. Deprotection of the acetonide with methanolic HCl gave crystalline diol **23** (mp 214–215 °C) which was identical by TLC and ^1H and ^{13}C NMR to authentic diol diastereomer.[23] HPLC examination of the crude bis-*N*-Cbz diol reaction mixture showed only one peak in the chromatogram which corresponded to authentic bis-Cbz-diol prepared by the Pedersen pinacol coupling procedure.[6] The other two 1,2-diol diastereomers were not detected by HPLC.

Conclusion. We have developed a general synthetic approach to amino and diamino dihydroxyethylene dipeptide (DHED) isosteres. The syntheses featured a diastereoselective addition of an alkyllithium reagent to N,N-dimethylhydrazone **4** and bis hydrazone **22**. For the preparation of isosteres **19a** and **19b**, the key hydrazone intermediate **4** was synthesized by three independent routes, starting from either D-isoascorbic acid, divinyl carbinol, or chlorobenzene. All three syntheses of **4** allowed for the ready substitution at the C(4) position of the dioxolane ring. For the preparation of the C_2 symmetric diamino dihydroxyethylene dipeptide isostere **23**, the starting material, bis-hydrazone **22**, was prepared from

(22) Gilman, H.; Rosenberg, S. D. *J. Org. Chem.* **1959**, *24*, 2063–2064.
(23) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692–5700.

Scheme V



(−)-2,3-*O*-isopropylidene-D-threitol (**21**) and converted into isostere **23** in four steps with an excellent overall yield.

Experimental Section

Solvents were reagent grade and used without purification unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Methylene chloride was purified by distillation from calcium hydride. All ^1H and ^{13}C NMR were obtained on a GE QE-300 (300-MHz) spectrometer, unless otherwise stated. Chemical shifts are reported as δ values (parts per million) relative to Me_4Si as an internal standard. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter. Column chromatographies were performed on silica gel 60, 0.04–0.063 mm (E. Merck), using 10–12 psi of air pressure. Thin-layer chromatograms were visualized using 20% ethanolic phosphomolybdic acid. HPLC was carried out on a Spectra Physics Model SP8800 HPLC system using a 25-cm Jones C-18 column. HPLC solvent used was 70:30 methanol/0.025 M KH_2PO_4 buffer pH 3.5. Eluent flow was 1.0 mL/min and monitored by a Spectra Physics Spectra 100 variable-wavelength UV spectrophotometer at 254 nM. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions were performed under an atmosphere of dry nitrogen. Elemental analyses were performed by the Analytical Research Department, Abbott Laboratories.

2,3-*O*-Isopropylidene-D-erythrose (2). Lactol **2** was prepared in 60% overall yield from D-isoascorbic acid according to literature procedures:[9,10] ^1H NMR ($CDCl_3$) δ 1.33 (s, 1H), 1.48 (s, 3H), 4.16 (m, 2H), 4.59 (d, 1H, J = 6 Hz), 4.85 (dd, 1H, J = 3, 6 Hz), 5.43 (d, 1H, J = 1.5 Hz); TLC analysis (1:1 diethyl ether–hexanes) gave a single spot, R_f = 0.33.

(4*S*,5*R*)-2,2-Dimethyl-4-(2-methylpropen-1-yl)-5-(hydroxymethyl)-1,3-dioxolane (3a). To a suspension of (2-isopropyl)triphenylphosphonium bromide[11] (121 g, 0.31 mol) in 1.5 L of THF which was cooled to −40 °C was added a hexane solution of *n*-butyllithium (1.6 M, 197 mL, 0.31 mol). The resulting red suspension was stirred for 1.5 h, and lactol **2** (21 g, 0.131 mol) in 231 mL of THF was added dropwise while the reaction temperature was maintained at −40 °C. The suspension was allowed to warm to rt and stirred for 20 h, and solid NH_4Cl (77 g) was added. Insoluble material was removed by filtration through Celite and the filtrate concentrated under reduced pressure. The crude residue was extracted (4×) with diethyl ether, and the combined organic extracts were washed with water and saturated NaCl, dried ($MgSO_4$), and concentrated to give a yellow oil. Chromatography of the oil using 1:4 ethyl acetate–hexanes as eluent afforded 13.0 g (53%) of alcohol **3a** as a water white liquid: bp 81 °C (0.6 mm); $[\alpha]^{25}_D$ = +43.1° (*c* 1.65 $CHCl_3$); IR ($CDCl_3$) 3680–3320 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.51 (s, 3H), 1.72 (s, 3H), 1.78 (s, 3H), 3.57 (m, 2H), 4.21 (dd, 1H, J = 6, 12 Hz), 4.94 (dd, 1H, J = 6, 9 Hz), 5.26 (dt, 1H, J = 1, 9 Hz); LRMS *m/e* 204 (M + NH_4). Anal. Calcd for $C_{10}H_{22}O_3$: C, 64.49; H, 9.74. Found: C, 64.29; H, 9.92.

(4*S*,5*R*)-2,2-Dimethyl-4-(2-methylpropan-1-yl)-5-(hydroxymethyl)-1,3-dioxolane (3b). A solution of the alcohol **3a** (13.5 g, 73 mmol) in 250 mL of methanol and 950 mg of 10% Pd on carbon (dry) was shaken under 1 atm of H_2 at the rt for 24 h. The catalyst was filtered and washed with methanol. The combined methanol solutions were filtered through a 0.45-mm millipore filter and evaporated to a purple oil. Distillation of the residue gave 12.3 g (90%) of alcohol **3b** as a clear oil: bp 63–65 °C (0.6 mm); $[\alpha]^{25}_D$ +26.3° (*c* 1.2, $CHCl_3$); IR ($CDCl_3$) 3680–3320 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 3H, J = 9 Hz, CH_3), 0.96 (d, 3H, J = 9 Hz, CH_3), 1.28–1.18 (eight-line m, 1H, CH_2), 1.37 (s, 3H, dioxolane CH_3), 1.47 (s, 3H, dioxolane CH_3), 1.59–1.48 (eight-line m, 1H, CH), 1.82–1.69 (14-line m, 1H, CH), 1.85 (dd, 1H, J = 4, 6 Hz, OH), 3.60 (m, 2H, OCH_2), 4.12 (dd, 1H, J = 6 Hz, OCH), 4.26 (seven-line m, 1H, OCH); LRMS *m/e* 189 (M + H), 206 (M + NH_4). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C. 64.10; H, 10.47.

(4*S*,5*R*)-2,2-Dimethyl-4-(2-methylpropan-1-yl)-5-formyl-1,3-dioxolane *N,N*-Dimethylhydrazone (4). Method A. To a solution of oxalyl chloride (0.51 mL, 5.84 mmol) in 14 mL of CH_2Cl_2 at −60 °C was added 0.904 mL (11.7 mmol) of DMSO in 1 mL of CH_2Cl_2. After 3 min, alcohol **3b** (1.0 g, 5.31 mmol) in 2.0 mL of CH_2Cl_2 was added in one portion to the reaction mixture. After the mixture was stirred, for 15 min, triethylamine (3.7 mL, 27 mmol) was added, the reaction mixture was stirred an additional 15 min and warmed to rt, and 1,1-dimethylhydrazine (1.61 mL, 21.2 mmol) and $MgSO_4$ (1.3 g, 10.6 mmol) were added. The reaction was stirred for 1 h at rt, and water (75 mL) was added. The organic layer was separated, washed with saturated NaCl, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave a yellow oil which was purified by chromatography using 7:93 ethyl acetate–hexane as eluent. The product hydrazone **4** was obtained in 62% yield (808 mg) as a clear oil: $[\alpha]^{25}_D$ = +99.2° (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) 2800–3000, 900–920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, 3H, J = 6 Hz, CH_3), 0.95 (d, 3H, J = 6 Hz, CH_3), 1.29–1.19 (eight-line m, 1H, CH_2), 1.38 (s, 3H, dioxolane CH_3), 1.53–1.42 (eight-line m and s, 4H, dioxolane CH_3 and CH_2), 1.85–1.67 (br m, 1H, CH), 2.82 (s, 6H, $N(CH_3)_2$), 4.33–4.25 (eight-line m, 1H, OCH), 4.6 (dd, 1H, J = 7, 8 Hz, OCHC=N); LRMS *m/e* 229 (M + H). Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 63.04; H, 10.62; N, 12.23.

Method B. A solution of olefin **8** (5 g, 27.1 mmol) was cooled to −70 °C, and stream of ozone was bubbled through the solution until a blue color persisted (10–15 min). Excess ozone was removed by ebullition with nitrogen gas, and the reaction mixture was cannulated into a solution of 200 mL of 1:1 methanol–water containing 6.7 mL of glacial acetic acid and 7.1 g (108 mmol) of zinc dust at −40 °C. Stirring was continued for 5 min, and the reaction mixture was allowed to warm to rt over 18 h. Saturated NaCl (50 mL) was added, and the layers were separated. The

aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried ($MgSO_4$) and filtered. 1,1-Dimethylhydrazine (8.2 mL, 108 mmol) and 6.5 g of $MgSO_4$ were added to the filtrate, and the mixture was stirred for 2.5 h. The CH_2Cl_2 was filtered and evaporated to yield an oil which was purified by chromatography using 7:93 ethyl acetate–hexanes as eluent. Hydrazone **4** was obtained in 61% yield (3.75 g). ^1H NMR and TLC were identical to the hydrazone prepared in method A: $[\alpha]^{25}_D = +93.2°$ (*c* 1.1, $CHCl_3$).

(3*R*,4*S*)-3,4-Dihydroxy-6-methylhept-1-ene (7). To a suspension of cuprous iodide (4.4 g, 23 mmol) in 1.0 L of THF and isopropylmagnesium chloride (2.0 M solution in diethyl ether, 436 mL, 875 mmol) cooled to −40 °C was added 29.2 (292 mmol) of epoxy alcohol **6**[14] in 500 mL of THF. The resulting mixture was stirred for 1.5 h, solid NH_4Cl was added, and the reaction was filtered through Celite. Solvent was evaporated under reduced pressure and the residue partitioned between EtOAc and saturated NH_4Cl. The aqueous layer was separated and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give 30 g (67% crude recovery) of diol **7** as a tan solid which was one spot by TLC (R_f = 0.2, 1:4 ethyl acetate–hexane). An analytical sample was prepared by chromatography purification using 3:7 EtOAc–hexanes as eluent: mp 42–46 °C; $[\alpha]^{25}_D = -9.8°$ (*c* 1.0 $CHCl_3$); IR ($CDCl_3$) 3600–3200, 3000–2800, 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = 6 Hz), 0.96 (d, 3H, *J* = 6 H), 1.20 (three d, 1H, *J* = 3, 9, 15 Hz), 1.38 (three d, 1H, *J* = 4.5, 9, 15 Hz), 1.81 (m, 1H), 3.80 (dt, 1H, *J* = 6, 9 Hz), 4.09 (m, 1H), 4.25 (brt, 1H, *J* = 4.5 Hz), 5.31 (m, 2H); ^{13}C NMR (75 MHz $CDCl_3$) δ 21.82, 23.56, 24.52, 41.06, 72.15, 76.27, 117.65, 136.05; LRMS *m/e* 162 (M + NH_4).

(4*S*,5*R*)-2,2-Dimethyl-4-(2-methylpropan-1-yl)-5-vinyl-1,3-dioloxane (8). Diol **7** (32 g, 222 mmol) in 435 mL of acetone, $MgSO_4$ (56 g, 0.466 mmol), *p*-TSOH·H_2O (464 mg, 2.4 mmol), and 2,3 dimethoxypropane (382 mL, 3.11 mmol) were stirred at rt for 18 h. Anhydrous Na_2CO_3 (254 mg, 2.4 mmol) was added to the reaction mixture, and the mixture was filtered. The solvent (1 L) was removed by distillation at ambient pressure to give 100 mL of a brown oil. Short-path distillation of the residue gave 24.4 g (60%) of a clear liquid: bp 54 °C (30 mm); $[\alpha]^{25}_D = -4.7°$ (*c* 1.0 $CHCl_3$); IR ($CDCl_3$) 3040–2840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, 3H, *J* = 6 Hz), 0.94 (d, 3H, *J* = 6 Hz), 1.16 (three d, 1H, *J* = 4.5, 9, 15 Hz), 1.48 (s, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.73 (m, 1H), 4.24 (three d, 1H, *J* = 4.5, 6, 10.5 Hz), 4.47 (dd, 1H, *J* = 6 Hz), 5.24 (m, 2H), 5.81 (three d, 1H, *J* = 7.5, 10.5, 18 Hz); LRMS *m/e* 204 (M + NH_4). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94; N, 12.27. Found: C, 71.67; H, 10.73.

General Procedure for the Addition of Alkyllithium to 1,3-Dioxolane Hydrazones and Reductive Cleavage. (4*S*,5*R*)-2,2-Dimethyl-4-(2-methylpropan-1-yl)-5-[(1*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-cyclohexylethyl]-1,3-dioxolane (16). Oxalyl chloride (1.53 ml, 17.5 mmol) in 42 mL of CH_2Cl_2 was cooled to −60 °C, DMSO (2.71 ml, 35 mmol) in 3.0 mL of CH_2Cl_2 was added, and the reaction mixture was stirred for 3 min. Alcohol **3b** (3.0 g, 15.9 mmol) in 6.0 mL of CH_2Cl_2 was added in one portion while the reaction temperature was maintained at −40 °C. After 15 min, triethylamine (11 mL, 80 mmol) was added dropwise, the mixture was stirred for 5 min and warmed to rt, and 1,1-dimethylhydrazine (4.83 mL, 64 mmol) and magnesium sulfate (3.82 g, 32 mmol) were added. The mixture was stirred for 2 h at rt. Water (150 mL) was added, and the organic layer was separated, washed with saturated NaCl, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave the crude hydrazone **4** as a yellow oil which was used without further purification.

To a solution of *t*-BuLi (1.7 M in pentane, 27 mL) cooled to −80 to −90 °C (diethyl ether/liquid N_2) was added cyclohexylmethyl iodide[7e] (5.34 g, 24 mmol). After 5 min the temperature of the reaction mixture was allowed to rise to −10 °C and a solution of the crude hydrazone **4** in 17 mL of ether was added. After addition, the mixture was allowed to warm to rt over 1 h, recooled in an ice–water bath, and water was added. The aqueous layer was separated and the ether layer washed with aqueous saturated NaCl, dried ($MgSO_4$), filtered, and evaporated to give the hydrazine as a yellow oil (5.2 g) which was used without further purification: ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = 6 Hz), 0.97 (d, 3H, *J* = 6 Hz), 1.32 (s, 3H), 1.44 (s, 3H), 1.86 (m, 2H), 2.44 (s, 6H), 2.85 (td, 1H, *J* = 3, 9 Hz), 4.07 (m, 2H); LRMS *m/e* 327 (M + H).

The crude hydrazine was dissolved in 250 mL of methanol and 26 g of 2800 Raney nickel and submitted to 4 atm of hydrogen at rt for 24 h. After filtration, the catalyst was washed with water (3×) and methanol (3×) and filtered through a 0.45-μm filter, and the combined aqueous methanol was evaporated to give 2.92 g of the amine as a green oil (64% recovery): ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = 6 Hz), 0.98 (d, 3H, *J* = 6 Hz), 1.85 (m, 2H), 2.93 (m, 1H), 3.76 (t, 1H, *J* = 6 Hz), 4.15 (three d, 1H, *J* = 3, 6, 12 Hz); LRMS *m/e* 284 (M + H).

The crude amine was stirred in 23 mL of CH_2Cl_2, and di-*tert*-butyl dicarbonate (3.4 g, 15.5 mmol) in 23 mL of CH_2Cl_2 was added. The mixture was stirred at rt for 18 h. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated. The resulting oil was purified by chromatography using 4:96 ethyl acetate–hexanes as eluent. The Boc amino acetonide **16** was obtained in 36% yield from alcohol **3b** (2.2 g) as a clear oil: $[\alpha]^{25}_D = -18.5°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3440, 3000–2840, 2240, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 6H, *J* = 4.5 Hz), 1.44 (s, 9H), 1.95 (d, 1H, *J* = 12 Hz), 3.77 (m, 1H), 3.99 (d, 1H, *J* = 6 Hz), 4.24 (three d, 1H, *J* = 3, 6, 9 Hz), 4.68 (d, 1H, *J* = 9 Hz); LRMS *m/e* 384 (M + H). Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.06; H, 10.15; N, 3.58.

(2*S*,4*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (19b). (Cyclohexylmethyl)-lithium was prepared from *t*-BuLi (1.7 M in pentane, 91 mL, 154 mmol) and 17.9 g (80 mmol) of cyclohexylmethyl iodide as described previously. After 5 min, the temperature of the reaction mixture was warmed to −10 °C, and the crude hydrazone **4** (prepared from 10 g of **3b**) in 60 mL of ether was added. Workup as usual gave the crude hydrazine **17b** as a yellow oil (11.55 g, 66% crude recovery) which was used in the next step without further purification.

The crude hydrazine **17b** was reduced using 27 g of 2800 Raney nickel and 250 mL of methanol at 4 atm of H_2 at rt for 48 h to give 9.37 g of the crude amine as a green oil (80% recovery from starting alcohol **3b**): ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = 6 Hz), 0.98 (d, 3H, *J* = 6 Hz), 1.85 (m, 2H), 2.93 (m, 1H), 3.76 (t, 1H, *J* = 6 Hz), 4.15 (three d, 1H, *J* = 3, 6, 12 Hz).

The crude amine **18b** was dissolved in 220 mL of methanol and 27.5 mL of 6 N HCl and stirred at rt for 4 h. Evaporation of the methanol (0.25 mm) gave a brown foamy solid. A solution of amine hydrochloride in 100 mL of THF, *N*-methylmorpholine (7.21 mL, 65.6 mmol), and di-*tert*-butyl dicarbonate (10.7 g, 49.2 mmol) was stirred for 2 h at rt. The THF solution was evaporated, and the residue was redissolved in ethyl acetate. The ethyl acetate was washed with saturated $NaHCO_3$, filtered, and evaporated and the residue dissolved in hexane. The Boc amine diol **19b** crystallized on standing at rt (3.9 g, 24% from **3b**). TLC analysis using 2:98 methanol–methylene chloride showed one compound, R_f = 0.32. An analytical sample was obtained by recrystallization from 2:7 ethyl acetate–hexane to give a white solid: mp 124–127 °C (lit. 124–126 °C); $[\alpha]^{25}_D = -63.6°$ (*c* 2.20 $CHCl_3$) [lit.[5b] $[\alpha]^{25}_D = -64.91°$ (*c* 2.20 $CHCl_3$)]; IR ($CDCl_3$) 3640, 3620–3240, 3000–2840, 2240, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3H, *J* = 6 Hz), 0.94 (d, 3H, *J* = 6 Hz), 1.47 (s, 9H), 1.93 (m, 1 H), 3.2 (t, 1H, *J* = 6 Hz), 3.33 (m, 1H), 4.05 (m, 1H), 4.56 (d, 1H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 21.25, 23.98, 24.34, 26.10, 26.25, 26.46, 28.25, 32.76, 33.70, 34.22, 39.70, 42.03, 47.90, 69.11, 80.09, 157.61; LRMS *m/e* 344 (M + H). Anal. Calcd for $C_{19}H_{37}NO_3$: C, 66.43; H, 10.86; N, 4.08. Found: C, 66.42; H, 10.82; N, 4.07.

(2*S*,3*R*,4*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-phenyl-3,4-dihydroxy-6-methylheptane (19a). Benzyllithium was prepared using the procedure of Gilman et al.[22] Benzyltriphenyltin (5.8 g, 13.1 mmol) in 58 mL of diethyl ether was cooled to −40 °C while phenyllithium (7.2 mL, 12.9 mmol, 1.8 M in a 70:30 cyclohexane/diethyl ether solution) was slowly added. After 1 h, the solution was allowed to warm to −10 °C and hydrazone **4** (1 g, 4.38 mmol) in 5 mL of diethyl ether was added. The reaction mixture was allowed to warm to rt over 2 h, water was added, and the reaction mixture was filtered. The filtrate was dried ($MgSO_4$), filtered, and evaporated to give 1.94 g of the crude hydrazine **17a**: ^1H NMR ($CDCl_3$) δ 0.74 (d, 3H, *J* = 6 Hz), 0.84 (d, 3H, *J*

= 6 Hz), 1.28 (s, 3H), 1.41 (s, 3H), 1.73 (m, 1H), 2.46 (s, 6H), 2.75 (dd, 1H, J = 6, 15 Hz), 2.9 (dd, 1H, J = 6, 15 Hz), 3.1 (m, 1H), 3.9 (dd, 1H, J = 6, 12 Hz), 4.02 (three d, 1H, J = 6, 9, 12 Hz), 7.1–7.4 (sev. m, (5H); LRMS m/e 321 (M + H).

The crude hydrazine **17a** (1.94 g) was reduced in 150 mL of methanol using 3.9 g of 2800 Raney nickel, 4 atm of H_2, at rt for 48 h to give 1.20 g of the amine **18a** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, J = 6 Hz), 0.96 (d, 3H, J = 6 Hz), 1.16 (three d, 1H, J = 3, 6, 9 Hz), 1.37 (s, 3H), 1.48 (s, 3H), 1.68 (three d, 1H, J = 3, 6, 9 Hz), 1.85 (m, 1H), 2.59 (dd, 1H, J = 9, 9 Hz), 2.79 (dd, 1H, J = 4.5, 13.5 Hz), 3.15 (m, 1H), 3.93 (t, 1H), J = 6 Hz), 4.22 (three d, 1H, J = 3, 6, 6 Hz), 6.74 (d, 1H, J = 6 Hz), 7.2–7.47 (m, 5H); LRMS m/e 278 (M + H).

Amine **18a** (1.16 g) was dissolved in a mixture of 28 mL of methanol and 3.5 mL of 6 M HCl and stirred for 2.5 h, another 3.5 mL of 6 M HCl was added and stirring continued for 1 h, the solvent was evaporated to give 1.1 g of amine diol hydrochloride.

To a solution of the crude amine HCl salt in dry THF was added di-*tert*-butyl dicarbonate (6.3 mmol, 1.37 g) and *N*-methylmorpholine (8.4 mmol, 0.923 mL). After 18 h, the THF was evaporated, and the residue was partitioned between ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$), and evaporated. The resulting Boc amino diol was crystallized from 150 mL of ethyl acetate–hexanes to give 600 mg (41% from **4**) of white crystals: mp 136–137 °C; $[\alpha]^{25}_D$ = −57.4° (c 1.0 $CHCl_3$); IR (KBr) 3400, 3100–2800, 1720, 1660, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 6 Hz), 0.93 (d, 3H, J = 6 Hz), 1.42 (s, 9H), 1.88 (m, 1H), 2.9 (dd, 1H, J = 4.5, 7.5 Hz), 3.22 (t, 1H, J = 6 Hz), 3.39 (m, 1H), 3.85 (d, 1H, J = 3 Hz), 4.2 (m, 1H), 4.7 (d, 1H, J = 9 Hz), 7.18–7.33 (sev m 5H); LRMS m/e 338 (M + H). Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.67; H, 9.31; N, 3.92.

***N*-(*tert*-Butoxycarbonyl)-4-thiazoylalaninyl Amide of (2*S*,3*R*,4*S*)-2-Amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (20).** The crude amine diol hydrochloride salt was prepared from alcohol **3b** (12.3 g, 65.3 mmol) using the procedure described for the preparation of Boc amino diol **19b**: oxalyl chloride (6.3 mL, 72 mmol), DMSO (11.1 mL, 144 mmol), triethylamine (45 mL, 327 mmol), $MgSO_4$ (15.7 g), *N*,*N*-dimethylhydrazine (20 mL, 261 mmol), *t*-BuLi (1.7 M, 111 mL, 189 mmol), cyclohexylmethyl iodide (22 g, 98 mmol), 2800 Raney nickel (30 g), and 33 mL of 6 N HCl. The crude amine hydrochloride was dissolved in 113 mL DMF, and *N*-methylmorpholine (10 mL, 91 mmol), *N*-(*tert*-butoxycarbonyl)-3-(thiazo-4-yl)alanine (11.9 mg, 39.7 mmol), and 1-hydroxybenzotriazole hydrate (16.1 g, 119 mmol) were added. The reaction mixture was cooled to −23 °C, and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDC, 8.4 g, 43.6 mmol) was added in one portion. The mixture was stirred while warming to rt over 24 h. The reaction mixture was partitioned between ethyl acetate and saturated $NaHCO_3$, and the aqueous layer was separated and extracted with ethyl acetate. The combined organic extracts were dried ($NaSO_4$), filtered, and evaporated. The residue was crystallized from ethyl acetate–hexanes to give 10.25 g of the amino acid derivative **20** (32% yield from **3b**): mp 154–157 °C; $[\alpha]^{25}_D$ = −35.7° (c 1, $CHCl_3$); IR ($CDCl_3$) 3600–3200, 3000–2800, 2240, 1700, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 6 Hz), 0.95 (d, 3H, J = 6 Hz), 1.47 (s, 9H), 1.89 (m, 1H), 2.16 (m, 1H), 3.13–3.4 (sev m, 4H), 4.1 (m, 1H), 4.28 (m, 1H), 4.45 (m, 1H), 6.17 (d, 1H, J = 4.5 Hz), 6.22 (d, 1H, J = 9 Hz), 7.15 (d, 1H, J = 1 Hz), 8.78 (d, 1H, J = 1 Hz). Anal. Calcd for $C_{25}H_{43}N_3SO_5$: C, 60.33; H, 8.64; N, 10.29. Found: C, 60.34; H, 8.66; N, 8.40.

(2*S*,3*R*)-2,2-Dihydroxy-5-methyl-4-hexenoic Acid Acetonide (11). Following the procedure of Hudlicky et al.,[15b] lactol **10** (4.1 g, 23 mmol) in 100 mL of THF was added to a solution of isopropyltriphenylphosphorane [prepared from 27 g (70 mmol) of isopropyltriphenylphosphonium bromide and *n*-butyllithium (1.6 M in hexanes, 9.9 mmol, 44 mL) as previously described] in 200 mL of THF at rt. The mixture was heated to reflux for 1 h and cooled to rt. Water (600 mL) was added, and the resulting mixture was extracted 3× with diethyl ether. The aqueous layer was acidified with Amberlite IR-120 (plus) resin to pH 3 and filtered and the aqueous solution extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated to give a foam. Reextraction of the foam with diethyl ether afforded a yellow oil (3.2 g, 68% crude recovery): ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.63 (s, 3H), 1.77 (d, 6H, J = 4.5 Hz), 4.62 (m, 1H), 5.15 (m, 2H); LRMS (EI) m/e 201 (M + H).

Methyl (2*S*,3*R*)-Dihydroxy-5-methyl-4-hexenoate Acetonide (12). Diazomethane was generated by the addition of 1-methyl-3-nitro-1-nitrosoguanidine to a bilayer of 40% aqueous KOH and diethyl ether at 0–5 °C and added to an ether solution of crude carboxylic acid **11** (1.65 g, 8.24 mmol) at 0–5 °C. Excess diazomethane was removed by nitrogen ebullition, and the solvent was evaporated. The residue was purified by chromatography using 1:9 ethyl acetate–hexanes as eluent to give 452 mg of ester **12** (18% from **10**): $[\alpha]^{25}_D$ = +97.7° (c 1.2, $CHCl_3$); IR ($CDCl_3$) 3040–2840, 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.63 (s, 3H), 1.74 (d, 6H, J = 4.5 Hz), 3.71 (s, 3H), 4.63 (d, 1H, J = 6 Hz), 5.08 (m, 2H); LRMS m/e 232 (M + NH_4). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.36; H, 8.34.

Synthesis of Alcohol 3a from Methyl Ester 12. A solution of ester **12** (327 mg, 1.52 mmol) in 30 mL of dry THF was added to a suspension of LAH (1.0 M in THF, 1.52 mL, 1.52 mmol) at 0–5 °C. The reaction was quenched with 0.6 mL of H_2O, 0.6 mL of 15% aqueous NaOH, and 0.18 mL of water after 2.5 h. The reaction was filtered and the solvent evaporated to give 152 mg (54%) of the alcohol **3a** which was identical by ^{1}H NMR and TLC to alcohol **3a** previously prepared.

(3*R*,4*S*)-1-Cyclohexyl-3,4-dihydroxy-6-methyl-5-hepten-2-one Acetonide (13). Cyclohexylmethyl iodide[6] (2.8 g, 31 mmol) was dissolved in 50 mL of 3:2 pentane–diethyl ether and cooled to −70 °C, and *tert*-butyllithium (1.7 M in pentane 16.1 mL, 27.4 mmol) was added. After 5 min, the mixture was allowed to warm to 18 °C and stirred for 1 h. The reaction mixture was recooled to −70 °C, the crude carboxylic acid **11** (1.0 g, 4.99 mmol) in 25 mL of 3:2 pentane–diethyl ether was added, and the reaction mixture was warmed to rt and stirred for 3 h. The mixture was recorded to 0–5 °C, and 3 mL of water was added. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to give a yellow oil which was purified by chromatography using a gradient of 2:98 to 1:9 ethyl acetate–hexanes to give 576 mg (41%) of a light yellow oil: R_f = 0.57 1:9 ethyl acetate/hexanes; $[\alpha]^{25}_D$ = +8.64° (c 1.1, $CHCl_3$) 3000–2840, 1710 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3H), 1.63 (s, 3H), 1.72 (s, 6H), 1.83 (m, 1H), 2.24 (dd, 1H, J = 6, 18 Hz), 2.41 (dd, 1H, J = 6, 18 Hz), 5.01 (m, 1H), 5.12 (dd, 1H, J = 6, 7 Hz); LRMS m/e 298 (M + NH_4).

(3*R*,4*S*)-1-Cyclohexyl-3,4-dihydroxy-6-methyl-5-hepten-2-one Oximes (14). A solution of 200 mg (0.71 mmol) of ketone **13** and 55 mg (14.4 mmol) of hydroxylamine hydrochloride in 2 mL of pyridine was stirred at rt for 20 h. Saturated NH_4Cl was added, and the aqueous layer was extracted with diethyl ether. The ether extracts were dried ($MgSO_4$), filtered, and evaporated to give a light brown oil. Chromatography using 1:9 ethyl acetate–hexanes gave 120 mg (57%) of a mixture of two oxime isomers. TLC (1:9 ethyl acetate–hexanes) gave two spots, R_f = 0.26 and R_f = 0.34, respectively. Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.44 (s, 3H), 1.68 (d, 6H, J = 1 Hz), 2.13 (m, 2H), 4.68 (d, 1H), 5.32 (m, 1H). Minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.46 (s, 3H), 1.75 (d, 6H, J = Hz), 2.13 (m, 2H), 5.06 (d, 1H), 5.08 (1H), 5.22 (dd, 1H, J = 6, 9 Hz); LRMS m/e 296 (M + 1).

(2*S*- and 2*R*,3*R*,4*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-3,4-dihydroxy-6-methylheptane Acetonide (16) and (15). The mixture of oxime isomers **14** (107 mg, 0.362 mmol) and 320 mg of 2800 Raney nickel in 10 mL of methanol were hydrogenated at rt and 4 atm for 24 h. The methanol solution was filtered through a 0.45-mm millipore filter and evaporated to give the crude amine.

The crude amine was dissolved in 1 mL of CH_2Cl_2, and a solution of di-*tert*-butyl dicarbonate (103 mg, 0.473 mmol) in 1 mL of CH_2Cl_2 was added. The resulting mixture was stirred at rt for 18 h and evaporated, and the residue was purified by chromatography (5:95 ethyl acetate–hexanes). The less polar isomer **16** (11.6 mg, 4.2% from **13**, R_f = 0.53 1:9 ethyl acetate–hexanes) was identical by ^{1}H NMR and TLC to a sample of **16** previously prepared from the hydrazone **4**. More polar isomer **15**: 42 mg (15%); R_f = 0.36; $[\alpha]^{25}_D$ = +37.2° (c 0.68, $CHCl_3$); IR ($CDCl_3$) 3340, 3000–2840, 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, J = 6 Hz), 0.94 (d, 3H, J = 6 Hz), 1.44 (s, 6H), 1.97 (br d, 1H, J = 8 Hz), 3.77 (m, 1H), 3.97 (t, 1H, J = 4.5 Hz), 4.22 (three

d, 1H, J = 3, 6, 9 Hz), 4.34 (d, 1H, J = 9 Hz); LRMS m/e 384 (M + H): HRMS calcd for $C_{22}H_{42}NO_4$ 384.3114, found 384.3106.

(4*R*,5*R*)-2,2-Dimethyl-4,5-bisformyl-1,3-dioxolane *N*,*N*-Dimethylhydrazone (22). The bishydrazone **22** was prepared using the procedures previously described: oxalyl chloride (8.2 mL, 95.0 mmol), 210 mL CH_2Cl_2, DMSO (14.7 mL, 190 mmol), (−)-2,3-isopropylidene-D-threitol (**21**) in 36 mL of CH_2Cl_2, triethylamine (24.7 mL, 177 mmol), *N*,*N*-dimethylhydrazine (26 mL, 346 mmol), and $MgSO_4$ (21 g), rt for 2 h. Water was added, and the organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to give 7 g of a yellow oil. Chromatography of the oil using 1:99 methanol–CH_2Cl_2 afforded 4.85 g (45%) of the bishydrazone **22** as a yellow solid: mp 77–78 °C; $[\alpha]^{25}_D$ = +167.2° (c 1.1, $CHCl_3$); IR ($CDCl_3$) 3000–2800, 2240, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.85 (s, 12H), 4.46 (2H), 6.37 (2H); LRMS m/e 243 (M + H). Anal. Calcd for $C_{11}H_{23}N_4$: C, 54.52; H, 9.15; N, 23.12. Found: C, 54.61; H, 9.23; N, 22.89.

(2*S*,3*R*,4*R*,5*S*)-2,5-Bis[(benzyloxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane (23). Benzyltriphenyltin (26 g, 59 mmol) and phenyllithium (32.1 mL, 58 mmol, 1.8 M in a 70:30 cyclohexane/diethyl ether solution) in 792 mL of diethyl ether were stirred at −40 °C for 2 h. The reaction mixture was allowed to warm to −10 °C, and a solution of the bishydrazone **22** (4.75 g, 19.6 mmol) in 100 mL of ether was added in the reaction. Stirring was continued for 1 h at −10 °C, the reaction warmed to rt, water was added, and the reaction mixture was filtered. The organic layer was separated, dried ($MgSO_4$), and filtered. Evaporation of the solvent gave 12.3 g of the crude hydrazine: ^1H NMR ($CDCl_3$) δ 1.47 (s, 6H), 2.16 (s, 12H); LRMS m/e 427 (M + H).

The crude hydrazine was reduced with 98.4 g of 2800 Raney nickel and 4 atm of H_2 in 1 L of methanol for 48 h at rt. The solution was filtered, the catalyst was washed with aqueous methanol (3×), and the solution was evaporated to give 4.82 g of crude diamine.

The crude diamine was dissolved in 77 mL of dioxane, 38 mL of water, and 11 mL of 3 M NaOH and cooled to 0–5 °C. Benzyl chloroformate (8.6 mL, 60.2 mmol) in 2.75 mL of dioxane and 11 mL of 3 M NaOH were added to the reaction mixture in alternating portions. The mixture was stirred at 0–5 °C for 25 min and then allowed to warm to rt. The mixture was evaporated, and the resulting residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), and filtered. The filterate was evaporated to give 10.1 g of a crude oil.

The crude oil was dissolved in 100 mL of 1 M HCl/methanol (generated by adding 7.1 mL of acetyl chloride to methanol at 5 °C). The reaction mixture was stirred at rt overnight, during which time a precipitate formed. The mixture was filtered, and the precipitate was washed with methanol and dried under vacuum to give 4.01 g of diol **23** as a granular white solid (36% from **22**): mp 214–215 °C; $[\alpha]^{25}_D$ = −17.0° (c 0.62, DMSO); IR (KBr) 3600–3080, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.60 (dd, 2H, J = 6, 7.5 Hz), 2.73 (dd, 2H, J = 6, 9 Hz), 3.26 (d, 2H, J = 1 Hz), 4.18 (m, 2H), 4.49 (d, 2H, J = 1 Hz), 4.92 (dd, 4H, J = 6, 12 Hz), 6.78 (d, 2H, J = 4.5 Hz), 7.13–7.32 (sev m, 20 H); ^{13}C NMR (75 MHz DMSO-d_6) δ 38.24, 52.90, 64.79, 72.56, 125.63, 127.15, 127.42, 127.76, 128.13, 129.12, 137.43, 139.18, 155.75; LRMS m/e 569 (M + H). Anal. Calcd for $C_{34}H_{36}N_2O_6$: C, 78.81; H, 6.38; N, 4.93. Found: C, 71.69; H, 6.41; N, 4.88.

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