3,5-$(NO_2)_2C_6H_3CO_2H$, 99-34-3; C_6H_5COOH, 65-85-0; $C_6H_5CO_2OH$, 93-59-4; 4-$FC_6H_4CO_2OH$, 1514-03-0; 3-$ClC_6H_4CO_2OH$, 937-14-4; 4-$CNC_6H_4CO_2OH$, 1711-43-9; 3-$NO_2C_6H_4CO_2OH$, 2453-41-0; 4-$NO_2C_6H_4CO_2OH$, 943-39-5; 3,5-$(NO_2)_2C_6H_3CO_2OH$, 66358-48-3; F_3CCO_2OH, 359-48-8; $ClCH_2COOMe$, 96-34-4; 3-$BrCH_2C_6H_4COOMe$, 1129-28-8; 1-hydroxyadamantane, 768-95-6; deuterium, 7782-39-0; 3-(bromomethyl)-4-nitrobenzoic acid methyl ester, 88071-90-3.

Supplementary Material Available: Experiments with macrocyclic hosts for hydrocarbon oxidation and tables of ^{13}C NMR shifts and kinetic parameters (12 pages). Ordering information is given on any current masthead page.

A Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosteres Using Novel, Chiral Aminoalkyl Epoxides and γ-(Aminoalkyl) γ-Lactones

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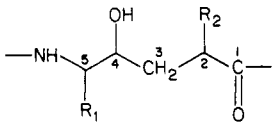
Received April 3, 1985

A stereocontrolled synthesis of the hydroxyethylene dipeptide isosteric unit 1 is described. This synthesis is capable of providing all eight stereoisomers of 1 and is amenable to variation of substituents R_1 and R_2. Also described are the novel chiral epoxides 2 and substituted γ-lactones 3, key intermediates in this synthesis having potentially broad application.

In the course of our work on peptidase inhibitors, we sought to prepare peptides containing suitable analogues in place of specific peptide bonds. Of particular interest were compounds incorporating the 2,5-disubstituted-5-amino-4-hydroxypentanoic acid unit, 1, the "hydroxyethylene dipeptide isostere", in this capacity. Only recently has interest in such subunits resulted in published syntheses,[1] and these have been of limited scope in terms of both variability of substituents and control of stereochemistry. The following method for synthesis of 1 allows wide and independent variation of the 2- and 5-substituents, as well as independent and controlled variation of stereochemistry at each of the stereocenters (2, 4, and 5) in 1.

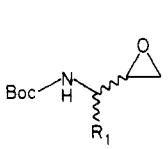


1

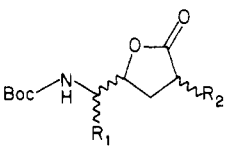
Results and Discussion

tert-Butylcarbonyl-(Boc) protected chiral α-amino aldehydes have served us well as useful intermediates in the preparation of statine ((3*S*,4*S*)-4-amino-3-hydroxy-5-methylhexanoic acid, Sta) and its analogues.[2] In extending our studies to include the statine homologues, 5-amino-4-hydroxy acids 1, we turned to these same aldehydes as potential intermediates. In preparing statine,[2] we had followed the example of Rich,[3] who had found that Boc-α-amino aldehydes could be synthesized and added to the enolate anion of ethyl acetate without significant loss of chirality, provided certain conditions of time (brief) and temperature (low) were observed.

Extending this observation, we surmised that the epoxides 2, synthetic intermediates of potentially broad utility, might also be prepared with retention of chirality by similarly careful addition of Boc-α-amino aldehydes to a suitably reactive ylide (Scheme I). To test this hypothesis most effectively, we chose as a pilot substrate the most chirally labile of the Boc-α-amino aldehydes we had so far encountered,[4] the compound **4a**, derived from Boc-L-Phe. It was with some surprise that we found dimethylsulfonium methylide[5] reacted with **4a** to give the desired epoxide **2**, not only in respectable yield but with virtually complete retention of chirality (see below).



2



3

Ylide attack on the diastereotopic faces of the aldehyde proved largely nonspecific, so that the product obtained was in fact a separable mixture of two diastereomers, easily distinguished by the NMR absorption of the C_2 proton (δ 3.7 and 4.1). To distinguish the "erythro" (2*S*,3*S* = **2a** and/or 2*R*,3*R* = **2d**) from the "threo" (2*R*,3*S* = **2b** and/or 2*S*,3*R* = **2c**) diastereomers, X-ray crystallographic analysis of one of these separated isomers (C_2H = δ 4.1) was carried out, showing the compound to have the "threo" configuration (Figure 1). Thus, the "erythro" and "threo" isomers could be separated and identified readily by the NMR absorption of their C_2 proton ("threo" = δ 4.1, "erythro" = δ 3.7).

† Rahway, NJ.

(1) (a) Szelke, M.; Jones, D. M.; Hallett, A. *European* Patent Application EP45 665, 1982; *Chem. Abstr.* **1982**, *97*, 39405. (b) Holladay, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401. (c) Szelke, M.; Jones, D. M.; Atrash, B.; Hallett, A.; Leckie, B. *Proc.* of the *Am. Pept. Symp.* (*8th*) **1983**, 579.

(2) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016.

(3) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624.

(4) See: ref 14 cited in ref 2.

(5) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

0022-3263/85/1950-4615$01.50/0

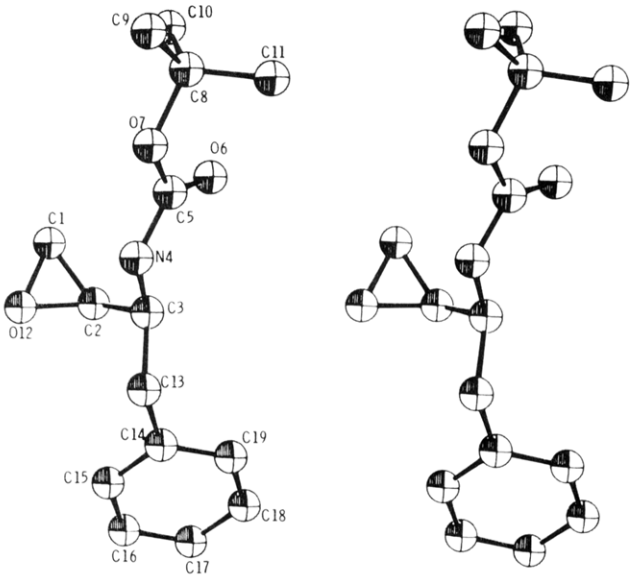
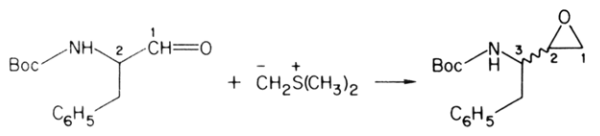


Figure 1. Computer-generated ORTEP drawing of the asymmetric unit of structure **2b** with crystallographic numbering scheme.

Scheme I



4a, 2*S*
4b, 2*R*

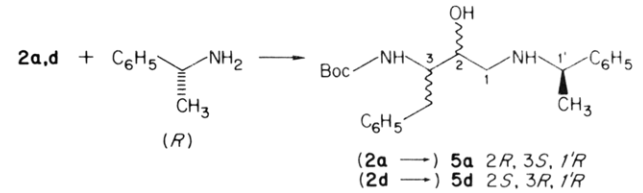
2a, 2*S*, 3*S*
2b, 2*R*, 3*S*
2c, 2*S*, 3*R*
2d, 2*R*, 3*R*

Neither chiral shift NMR or HPLC on a chiral support proved capable of distinguishing enantiomeric forms of **2** (**2a** from **2d** or **2b** from **2c**). To make this distinction, the epoxides **2** were first prepared from Boc-L-Phe and Boc-DL-Phe. The separated erythro diastereomers from each (**2a** and **2a**/**d**, respectively) were then added to *d*-(+)-α-methylbenzylamine to give the diastereomeric carbinolamines **5a** and **5a**/**d** (Scheme II). Conventional 360-MHz NMR spectroscopy resolved these two diastereomers without difficulty. This technique verified the chiral purity of the carbinolamine **5a** and hence of the starting epoxide **2a**, as >95% and demonstrated that the epoxidation of chirally labile aldehyde **4a** had taken place with high retention of stereochemical integrity at the α-carbon of the protected amino aldehyde. Since the stereochemistry at C_3 of the epoxides **2** could now be reliably equated to that of the starting Boc-amino acids, these results could be combined with the NMR studies above to assign absolute stereochemistry to each of the four diastereomers of **2**.

The epoxides **2** are previously unreported[6] and potentially useful synthetic intermediates. Aside from the uses to which they are put in this work, these compounds are potentially general sources of the pharmacologically important ethanolamine unit[8] with versatile substitution and controlled chirality (**5**, for example). Containing a moderately active electrophile in the epoxide group, the epoxides **2** are also of potential interest, both alone and incorporated into peptides, as suicide substrate[9] or simple active-site-directed[10] irreversible inhibitors of enzymes using amino acid or peptide substrates.

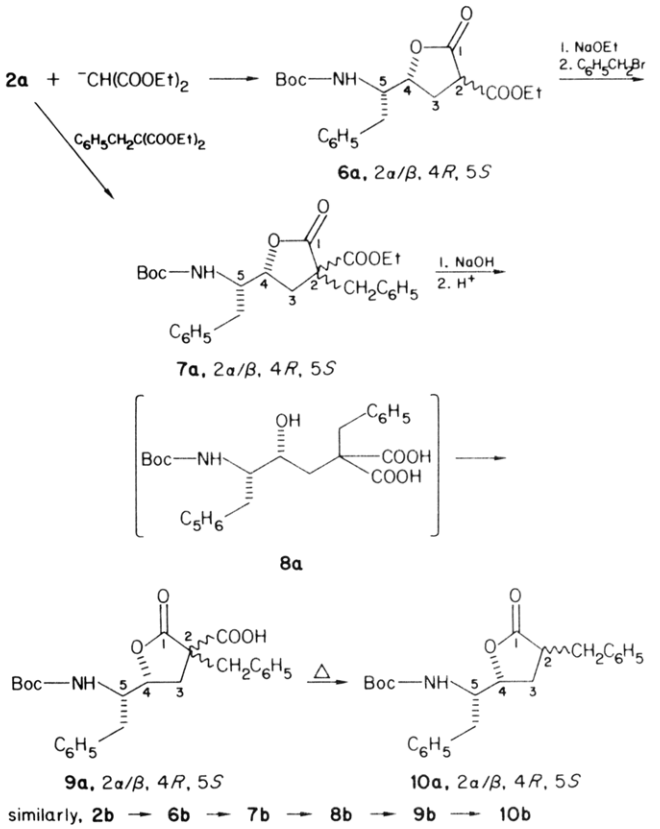
In the present application it was envisioned that these epoxides, like their precursor aldehydes **4**, might be used to alkylate directly the α-anion of an acetate derivative. However, with α-lithioethyl acetate,[11] dilithioacetate,[12] or α-lithiodimethylacetamide,[13] no alkylation by **2** was observed. With the sodium salt of diethyl malonate, efficient alkylation of **2a** and **2b** did take place to give, after spontaneous lactonization, the carbethoxy lactones **6a** and **6b** (Scheme III, illustrated for single isomer). It should be noted that this reaction introduced yet another chiral center (C_2) offering the potential for two diastereomeric

Scheme II



(**2a** →) **5a** 2*R*, 3*S*, 1′*R*
(**2d** →) **5d** 2*S*, 3*R*, 1′*R*

Scheme III



6a, 2*α*/*β*, 4*R*, 5*S*

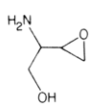
7a, 2*α*/*β*, 4*R*, 5*S*

8a

9a, 2*α*/*β*, 4*R*, 5*S* **10a**, 2*α*/*β*, 4*R*, 5*S*

similarly, **2b** → **6b** → **7b** → **8b** → **9b** → **10b**

(6) The only other example of this class of compounds of which we are aware is the hydroxymethyl analogue i described in a recent publication.[7] This compound was prepared by a route unrelated to the present work.



i

(7) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587.

(8) This is the core functional group in the much studied β-bocker drugs, for example. An important member of this class with reference to its congeners is described by Wasson, B. K.; Gibson, W. K.; Stuart, R. S.; Williams, H. W. R.; Yates, C. H. *J. Med. Chem.* **1972**, *15*, 651.

(9) Rando, R. R. *Science (Washington, D.C.)* **1974**, *185*, 320. Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313. Walsh, C. *Horiz. Biochem. Biophys.* **1977**, *3*, 36. Metcalf, B. *Annu. Rep. Med. Chem.* **1981**, *16*, 289.

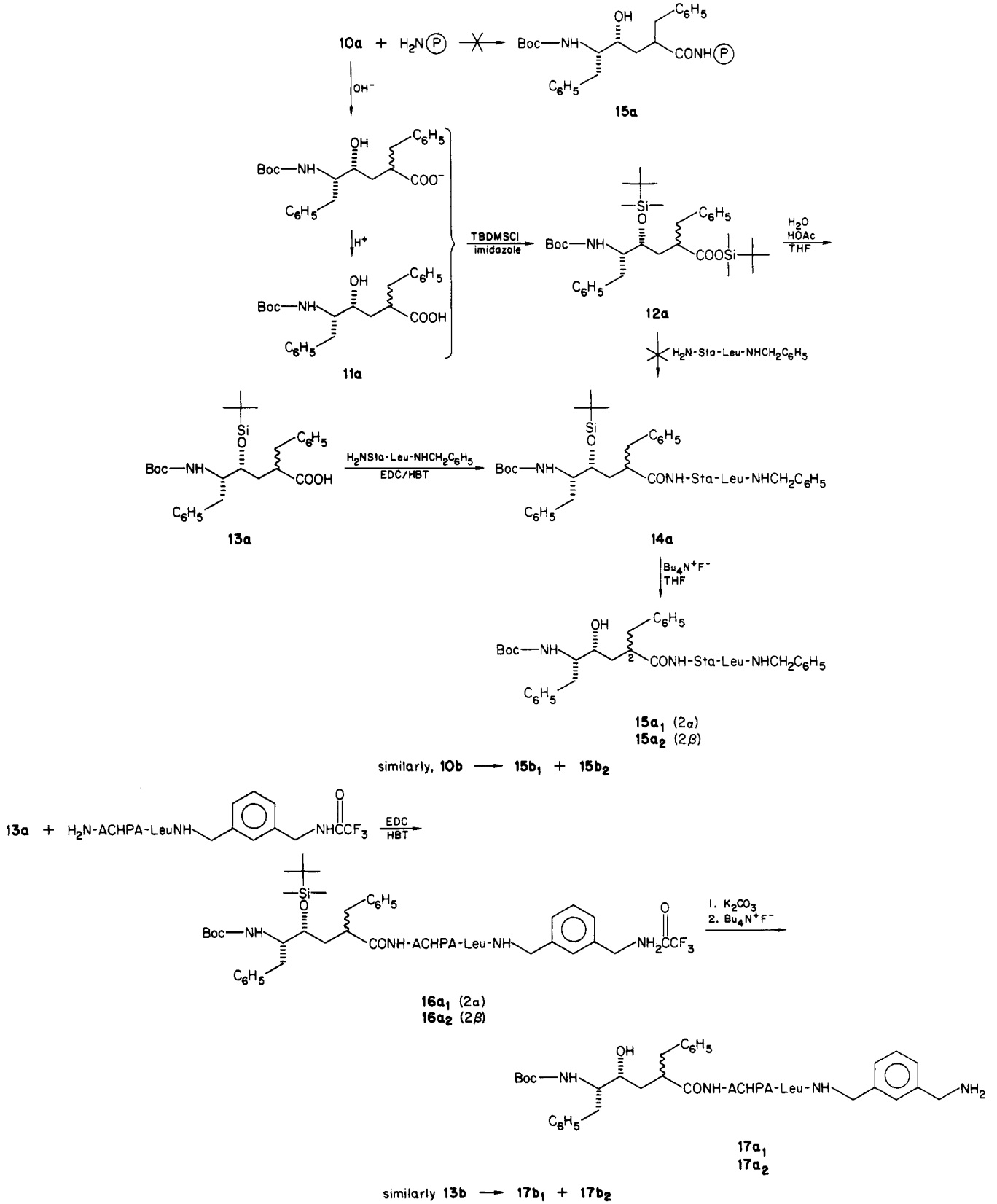
(10) Baker, B. R. "Design of Active-Site-Directed Irreversible Enzyme Inhibitors"; Wiley: New York, 1967.

(11) Montforts, F.-P.; Ofner, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 632.

(12) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M. *J. Org. Chem.* **1972**, *37*, 451.

(13) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688. Sauriol-Lord, F.; Grindley, T. B. *J. Org. Chem.* **1981**, *46*, 2831.

Scheme IV



products from each epoxide. No separation of such isomers could be observed by silica gel chromatography, but the NMR spectra did provide tenuous evidence for a pair of diastereomers (2α and 2β) in each lactone. In any event, since this third chiral center was destined to be the site of several subsequent reactions, its stereochemistry was ignored for the time being.

While the stereochemistry at C_2 appeared not to have a significant influence on the physical properties of **6**, that at C_4 did. Thus **6a** and **6b** were readily separated by silica gel chromatography, and in the overall sequence, separation of these isomers prepared from mixed **2a/b** proved operationally superior to separation of the precursor epoxides **2a** and **2b**.

The extra carbethoxy function in **6** also served a useful function; it permitted easy introduction of the second amino acid side-chain unit, in this case benzyl, by alkylation of the sodium salt of **6** with benzyl bromide to give **7** (the alternate direct synthesis of **7** from **2** using diethyl benzylmalonate, while successful, was operationally inferior to this two-step sequence). With this alkylation, all of the desired skeletal units and functional groups in **1** were now in place in **7**, and what remained was to remove the extra ester function and manipulate the protecting groups toward the desired end.

With aqueous base followed by aqueous acid, the lactones **7** provided the open-chain acids **8**, which cyclized spontaneously to give the carboxy lactones **9**. As anticipated, these were each obtained as a mixture of two diastereomers ($2\alpha + 2\beta$). The further utility of these acids was in some doubt since the next required transformation, decarboxylation, necessitated heating the acids in the presence of their own acid-labile Boc protecting groups. Thermogravimetric analysis indicated that at ~120 °C, the carboxy lactones **9** underwent a clean transformation corresponding to loss of CO_2. Duplication of this process on a preparative scale verified this finding and provided the free lactones **10** in good yield. These compounds again were each obtained as a mixture of two diastereomers (2α and 2β) and were used as such, separation being deferred until after final peptide coupling. Thus, in principle, all eight individual stereoisomers of **10** were accessible. These compounds are in fact the desired isostere units **1** in which the acid, carbinol, and amino groups are held in protected form.

The initial targets of this work were peptides of structures **15** and **17** (Scheme IV) which required no further elaboration of the N-terminus. For synthesis of such compounds, the two lactones **10a** and **10b** appeared to be potentially useful penultimate intermediates themselves. Repeated attempts to effect acylation of a free peptide N-terminal amine with these compounds proved unsuccessful, however. Therefore, a more conventional approach was adopted, one in which the lactone ring would be opened to provide the free acid (e.g., **11**) which would then be coupled by standard techniques. To forestall competing relactonization upon activation of the γ-hydroxy acid **11**, hydroxy protection was added as a refinement to this approach. In practice, then, lactone **10** was opened to acid **11** which, itself or as its sodium salt, was immediately silated to give the ether-ester **12**.[14] Again, attempts to effect reaction of these esters directly with peptide N-termini failed.

Selective hydrolysis of the ether-ester **12** to the corresponding ether acids **13** by the method of Corey and Venkateswarlu[15] took place in good yield, however, and coupling of the acids to previously synthesized peptide fragments proceeded smoothly with conventional peptide coupling techniques. Deprotection of the resulting silyl peptides **14** and **16** provided the completed peptides **15** and **17**, each as a mixture of two diastereomers (C_2); these were separated by silica gel chromatography or by HPLC.

This approach proved less well-suited to preparation of peptides in which the hydroxyethylene isosteric unit was wholly contained within the peptide chain. The reason is illustrated in Scheme V. In this sequence, the 5*S* Boc-protected isostere peptides **18** were prepared as starting intermediates by using the procedures described above for synthesis of **15** and **17**. One of these compounds (**18b**$_1$) was deprotected, and the resulting crude product coupled with Boc-Phe, according to standard procedures. What was obtained was not the expected peptide, but the lactone **21b** and the shorter peptide **22**. The source of these compounds was traced to a facile intramolecular cleavage of a peptide amide bond in **18** by the C_4-hydroxy group during the acid-catalyzed deprotection. This cleavage gave the amino lactones **19** and the peptide fragment **20**, both of which coupled with Boc-Phe in the coupling step to give the observed products.

That it was the amide-lactone **21** and not the lactam-ester **23** that was obtained from this reaction was suggested by a TLC experiment. Thus, exposure of this product to sodium hydroxide at pH 10 provided a single, new, very polar material, presumably the sodium salt of the ring-opened acid, **24**. Acidification gave a less polar compound (the free acid **24**), which upon standing, reverted virtually completely to the original material (lactone **21**). Had the product been in fact the lactam-ester, **23**, exposure to base should have effected irreversible conversion to free lactam **25** and Boc-Phe. The structure of lactone **21** was subsequently confirmed by its identity to a sample prepared in the synthesis of **28**.

This cleavage reaction is somewhat analogous to the cleavage of serine-containing peptides upon exposure to HF.[16,17] In that case, as in the present instance, an *N*-acyl function is transferred to a hydroxy group four atoms removed. The effect is to convert the *N*-acylserine residue to its *O*-acyl isomer.

While the cleavage reaction **18** → **19** does present a problem for synthesis of the desired peptides, it is a problem which contains the germ of its own solution. Specifically, identification of the coupled lactone **21** implied that the free amino-lactone **19** had been generated and coupled successfully. Thus, the approach to analogues containing peptide chains on both the C- and N-termini of the hydroxyethylene unit was built around this intermediate, as shown in Scheme VI.

Here, the two Boc-lactones **10a** and **10b** were first deprotected[18] to give **19** and then elaborated on the free nitrogen to give the peptidyl lactones **26**. Ring opening–silation–desilation of **26** provided the silyl free acids **27** which were coupled to the appropriate C-terminal segments by using conventional methods. Deprotection with fluoride as before gave the desired peptides **28**, in each case as a mixture of two diastereomers (at C_2). These were separated by silica gel chromatography, providing all four individual diastereomers of the desired 5*S* peptides with known stereochemistry at C_4 and C_5 of the hydroxyethylene unit. Assignment of absolute stereochemistry at C_2 has not yet been accomplished unambiguously. Efforts toward this end are in progress.

The effectiveness of the peptides prepared in this work as inhibitors of the key blood pressure controlling enzyme, renin, is the subject of a separate paper.

Conclusions. The methods presented in this paper provide access to the hydroxyethylene dipeptide isostere unit **1** in each of its stereochemical modifications. Chirality at C_5 and the substituent R_1 are set by the choice of starting amino acid. Chiralities at C_2 and C_4 are selected by separation of diastereomers, and the substituent(s) R_2 is subject only to the limitations of a malonate alkylation

(14) Reclosure of the hydroxy acid **11** to lactone **10** was sufficiently slow to permit virtually complete silation.

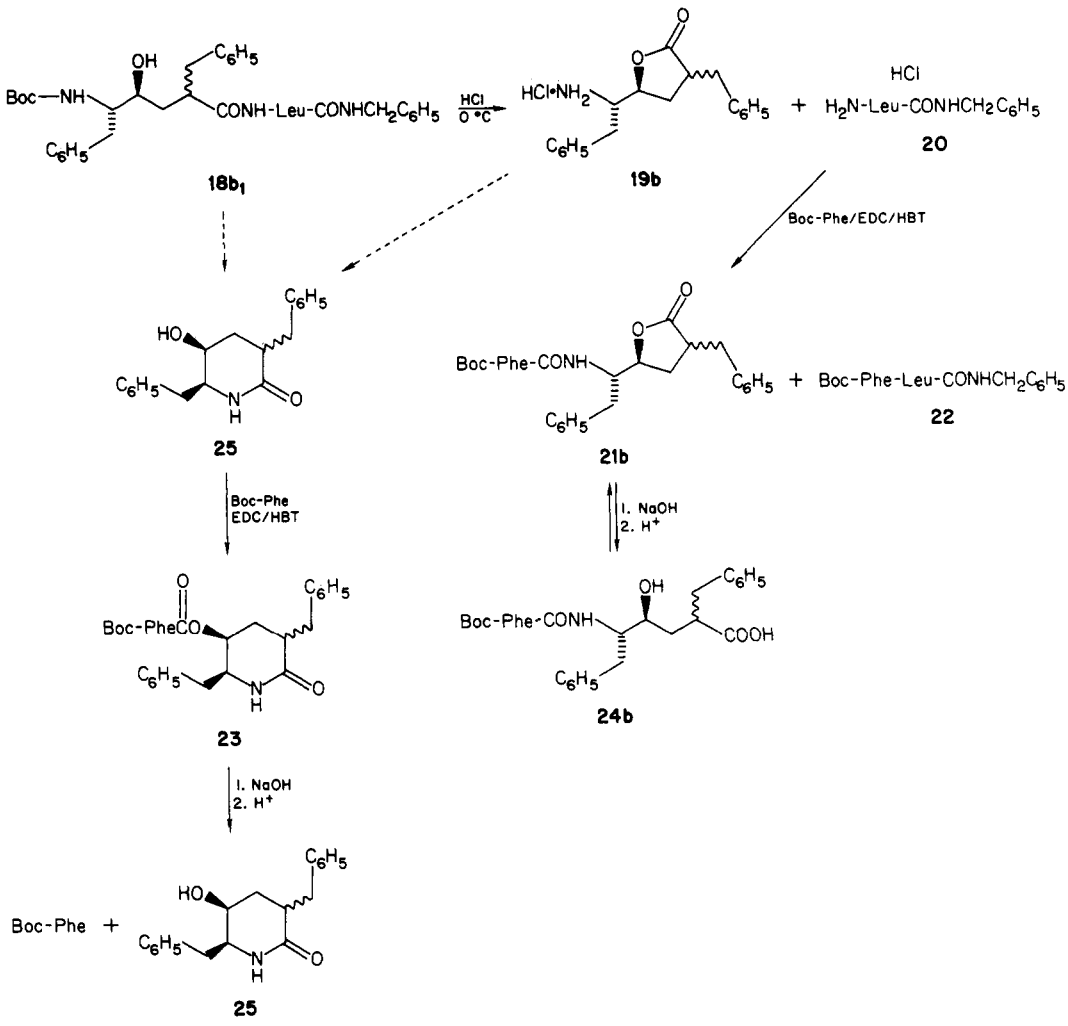
(15) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(16) Sakakibara, S.; Shin, K. H.; Hess, G. P. *J. Am. Chem. Soc.* **1962**, *84*, 4921.

(17) Lenard, J.; Hess, G. P. *J. Biol. Chem.* **1964**, *239*, 3275.

(18) In practice, this deprotection was demonstrated only on a probe scale; the major portion of each lactone **10** had been converted to the acid **13**, and **19** was in fact prepared from this acid by the same HCl/EtOAc procedure.

Scheme V



and the availability of a suitable alkylating agent. This work also introduces the chiral epoxides **2** which are easily prepared by addition of dimethylsulfonium methylide to protected α-amino aldehydes **4**. All four individual diastereomers of the epoxide are accessible, and the absolute stereochemistry at both chiral centers may be ascertained. The new γ-substituted-γ-lactones **10** (**19**, **21**, and **26**) are also prepared, again with control of stereochemistry and substituent pattern.

Experimental Section

Melting points (Thomas-Hoover melting point apparatus) are uncorrected. Spectra were obtained as follows: IR spectra on a Perkin-Elmer 237 spectrophotometer, EI mass spectra on a VG MM 7035 mass spectrometer, FAB mass spectra on a Varian MAT 731 spectrometer with xenon gas in the FAB gun, ^{1}H NMR spectra on a Varian EM-390 or Nicolet NT-360 spectrometer. HPLC was carried out on a Hewlett-Packard Model 1084B liquid chromatograph using a Waters C-18 column. Thermogravimetric analysis (TGA) was performed on a Perkin-Elmer TGS-1 analyzer. Analyses were conducted at a heating rate of 10°/min. The rate of change of weight and total weight loss vs. temperature were recorded.

Analytical TLC was carried out on 250 mm, 5 × 20 cm silica gel plates (E. Merck) using ultraviolet light and either phosphomolybdic acid or *tert*-butyl hypochlorite/potassium iodide/starch for visualization.

Sta-Leu-NHCH$_2$C$_6$H$_5$ was prepared by conventional EDC (1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide)/HBT (1-hydroxybenzotriazole) coupling of *t*-Boc-L-leucine to benzylamine, deprotection with HCl/EtOAc, recoupling to Boc-Sta,[2] and HCl deprotection. In similar fashion, (3*S*,4*S*)-4-(*t*-Boc-amino)-5-cyclohexyl-3-hydroxypentanoic acid (Boc-ACHPA)[19] was converted to ACHPA-Leu-2-[[(trifluoroacetyl)amino]methyl]-benzylamide by coupling to Leu-2-[(trifluoroacetyl)amino]-methylbenzylamide. The latter intermediate was synthesized by dicyclohexylcarbodiimide (DCC) coupling of *t*-Boc-L-Leu to a fourfold excess of 2-(aminomethyl)benzylamine followed by trifluoroacetylation (trifluoroacetic anhydride/triethylamine) and N-deprotection of the water washed product.

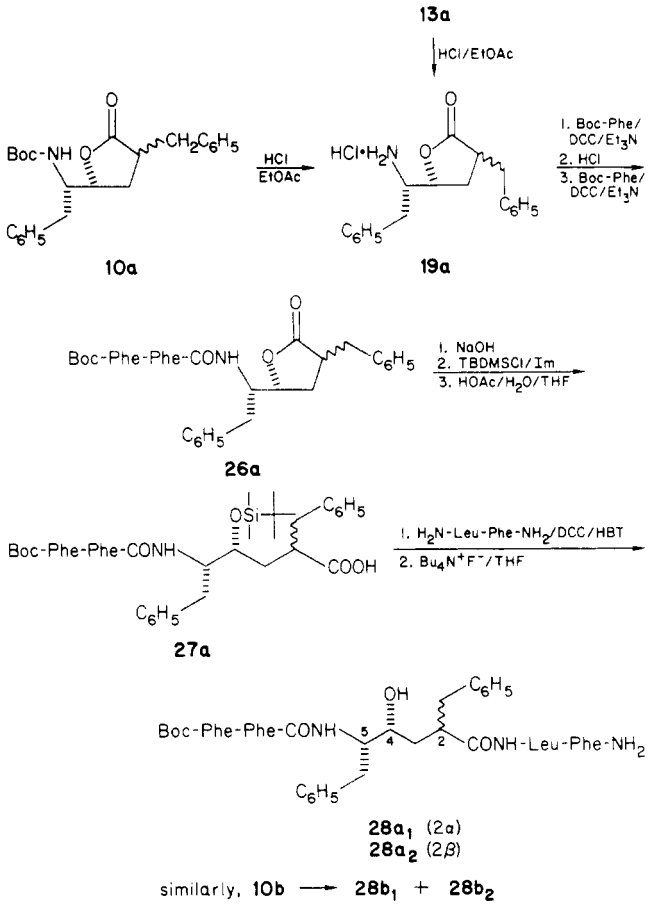
1-[1-(Boc-amino)-2-phenylethyl]oxirane (2). Boc-L-phenylalanine (25 g, 0.1 mol) was reduced to the carbinol and reoxidized to the aldehyde **4a** by using the procedures previously described.[2,3] The crude aldehyde was used immediately, without purification.

Dimethylsulfonium methylide (210 mmol) was prepared in Me$_2$SO/THF according to the procedure of Corey and Chaykovsky.[5] After being stirred for 1 min at −5 °C, the mixture was treated with the crude aldehyde dissolved in THF (135 mL), added fairly rapidly. The resulting mixture was stirred in the cold for 30 min and then quenched in cold H$_2$O (3 L). The suspension was extracted with ether (3 × 100 mL) and the combined organic layers were washed with H$_2$O (2 × 100 mL), dried over Na$_2$SO$_4$, filtered, and evaporated to dryness in vacuo. The product was chromatographed on silica gel eluted with 3:1 (v/v) hexane/ethyl acetate. Evaporation of the product fractions in vacuo gave the epoxide **2a/b** as a white solid (12 g, 46% from Boc-L-Phe). The ratio of **2a** to **2b** as determined by the relative intensities of the protons at δ 3.7 and 4.1 (see below) was ca. 1:1. This material was used in subsequent reactions without further refinement.

2a. A sample of this mixture was crystallized from ether by addition of petroleum ether (10×), and the resulting solid was

(19) Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; LaMont, B. I.; Lin, T.-Y.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.*, in press.

Scheme VI



recrystallized from hexane to give **2a**: mp 121.5–123.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.389 (s, 9 H, $(CH_3)_3$), 2.77 (br s), 2.80 (t), 2.82–2.95 (m), 2.98 (dd), (total 5 H, CH_2O, CH_2C, CHN), *3.7* (br s, 1 H, C_2H), 4.45 (br, 1 H, NH), 7.2–7.4 (m, 5 H, Ar); TLC (silica gel GF, 2:1 (v/v) hexane/ethyl acetate), single spot R_f 0.53; HPLC t_R 15.78 min = 97.5%, 15.98 min = 2.5%. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.25; H, 8.31; N, 5.37.

2b. The petroleum ether/ether recrystallization filtrate was evaporated to dryness in vacuo and the residue was recrystallized twice from ether to give a mixture of **2a** and **2b** in which **2b** was dominant (70%): mp 85–89 °C; ^{1}H NMR ($CDCl_3$) δ 1.390 (s) and 1.396 (s) (total 9 H $(CH_3)_3$), 2.59 (br s), 2.70 (t), 2.77 (br s), 2.80 (t), 2.82–3.05 (m) (total 5 H, CH_2O, CH_2C, CHN), *3.7* (br s, 0.3 H $(C_2H)_{2a}$), *4.13* (br s, 0.7 H $(C_2H)_{2b}$), 4.48 (br s, 1 H, NH), 7.2–7.4 (m, 5 H, Ar); TLC (silica gel GF, 2:1 (v/v) hexane/ethyl acetate), single spot identical with **2a**; HPLC t_R 15.77 min = 29.0%, 15.97 min = 71.0%. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.15; H, 8.16; N, 5.63.

The filtrate from these crystallizations was evaporated to provide **2b** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.396 (s), 2.59 (br s), 2.70 (t), 2.88 (dd, J_1 = 14 Hz, J_2 = 8 Hz), 2.93–2.99 (br m), 2.99–3.04 (m), *4.13* (br q), 4.48 (br d), 7.2–7.35 (m).

2b/c. Racemic aldehyde **4a/b** was prepared and converted to the epoxide mixture **2a–d** by using the procedures described above. The chromatographed product was evaporated to an oil which deposited a diastereomer mixture (1:1) from ether/hexane (1:10). The filtrate was evaporated, redissolved in ether/hexane and boiled gently to remove the bulk of the ether. After removal of a second mixed diastereomer crop (**2a/d:2b/c** = 5:1) by filtration, the filtrate deposited a final portion consisting of one (**2b/c**) racemate (mp 94–97.5 °C): ^{1}H NMR ($CDCl_3$) δ 1.396 (s, Boc), 2.59 (br s), 2.70 (t), 2.88 (dd, J_1 = 14 Hz, J_2 = 8 Hz), 2.93–2.99 (br m), 2.99–3.04 (m), *4.13* (br q), 4.48 (br d), 7.2–7.35 (m). Single-crystal X-ray analysis revealed a structure with *R* configuration at the substituted epoxide carbon and *S* configuration at carbon α to nitrogen.

The single-crystal solution of structure **2b/c** was carried out by an X-ray diffraction experiment at room temperature on a fully automated CAD-4 Enraf-Nonius diffractometer on a specimen grown in hexane/ethyl ether (approximately 6:1, v/v) and mounted in air. The unit cell parameters (with standard deviations in parentheses) are a = 6.205 (2) Å, b = 11.932 (7) Å, c = 20.039 (13) Å, β = 94.14 (5)°, and V = 1480 (2) Å^3 in the monoclinic, centrosymmetric space group $P2_1/n$ (Z = 4).

A correct trial structure was provided by MULTAN[20] and refined by full matrix least squares (minimizing the function $\sum w(|F_o| - |F_c|)^2$ where w = unit weight) to an unweighted residual index R ($=\sum||F_o| - |F_c||/\sum|F_o|$) of 0.046 using anisotropic temperature factors. A total of 1827 of 2016 symmetry independent reflections were considered observed at the level $I \geq 3\sigma(I)$. Hydrogen atoms were obtained by difference electron density syntheses, assigned equivalent isotropic temperature factors of the atoms to which they were bound (multiplied by a factor of 1.2), and refined for positional parameter variation only.

Data reduction, least squares, electron density syntheses, and other related software programs were provided by SDP[21] and were run on a PDP 11/60 computer. Three tables containing fractional crystallographic coordinates, bond lengths and bond angles have been included for structure **2b** in the supplementary material section. Figure 1 is a computer-generated ORTEP[22] drawing of the asymmetric unit of structure **2b** with the crystallographic numbering scheme.

2a/d. Recrystallization of the 5:1 mixed isomer from hexane provided the other racemate (**2a/d**): mp 101–102.5 °C, ^{1}H NMR ($CDCl_3$) δ 1.39 (s, Boc), 2.76 (br m), 2.81 (t), 2.82–2.94 (m), 2.98 (dd, J_1 = 14 Hz, J_2 = 5 Hz), *3.7* (br s), 7.2–7.36 (m).

3-(*t*-Boc-amino)-2-hydroxy-4-phenyl-1-[(1-phenylethyl)-amino]butane (5). 5a. Epoxide **2a** (52 mg, 0.2 mmol) and *d*-(+)-(*R*)-α-methylbenzylamine (27 mg, 0.22 mmol) were combined in 2-propanol (1 mL) and heated for 5 h in an oil bath thermostatted at 70 °C. The mixture was cooled and evaporated in vacuo. The residue was chromatographed on silica gel (5% methanol in methylene chloride) and the combined product fractions were evaporated in vacuo to give **5a** (57 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 1.35 (s), 1.43 (d, J = 7 Hz), 2.0 (br s), 2.58 (d, J = 4 Hz), 2.78 (dd, J_1 = 14 Hz, J_2 = 8 Hz), 2.83–3.0 (m), 3.40–3.47 (m), 3.73–3.85 (m), *4.62* (d, $J \sim$ 10 Hz), 7.15–7.40 (m); TLC (4% $MeOH/CH_2Cl_2$) single component, R_f 0.27; MS, m/e 385 (M + H), 384 (M$^+$). Anal. Calcd for $C_{23}H_{32}N_2O_3 \cdot 0.3\ H_2O$: C, 70.84; H, 8.43; N, 7.18. Found: C, 70.54; H, 8.45; N, 7.14.

5a/d. Repetition of the same procedure using achiral epoxide **2a/d** (1:1) provided the corresponding carbinolamines **5a/d** (55 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 1.35 (s), 1.38 (d, J = 7 Hz), ~2.0 (br s), 2.55 (br d, $J \sim$ 5 Hz), 2.62 (dd), 2.72–2.89 (m), 2.94 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 3.36 (br s), 3.42 (br s), 3.53 (br s), 3.64 (br s), 3.72 (p, $J \sim$ 6 Hz), 3.79 (br s), *4.58* (d, $J \sim$ 10 Hz), *4.63* (d, $J \sim$ 10 Hz), 7.15–7.4 (m); TLC (4% $MeOH/CH_2Cl_2$) single component, R_f 0.27; MS, m/e 385 (M + H), 384 (M$^+$).

In general, the chemical shifts and some of the multiplet resolutions in the NMR spectra of these compounds were exquisitely sensitive to pH and difficult to reproduce. However, the NH doublets in the region δ 4.5–5, while somewhat variant in chemical shift, always provided a reliable indication of isomer composition. Thus, a sample containing all four isomers of epoxide **2** (**a:b:c:d** = 1:2:2:1) gave carbinolamine **5** (**a:b:c:d** = 1:2:2:1), showing four clearly distinct doublets in the NMR spectrum at δ *4.99*, *4.92*, *4.77*, and *4.70* (2:2:1:1, respectively, all J = ~10 Hz): TLC (4% $MeOH/CH_2Cl_2$) single component, R_f 0.27; MS, m/e 385 (M + H), 384 (M$^+$). Anal. Calcd for $C_{23}H_{32}N_2O_3 \cdot 0.3H_2O$: C, 70.84; H, 8.43; N, 7.18. Found: C, 70.67; H, 8.33; N, 7.51. Similarly, the chiral mixed isomers **2** (**a + b**) provided **5** (**a + b**) showing NH doublets at δ *4.83* ($J \sim$ 10 Hz) and *5.02* ($J \sim$ 10 Hz).

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5-[1-(*t*-Boc-amino)-2-phenylethyl]-3-carbethoxydihydrofuran-2(3*H*)-one (6). Epoxide **2** (mixed isomers **a** + **b**, 21.9 g, 83 mmol) and diethyl malonate (16 g, 100 mmol) were combined in 60 mL of dry ethanol. The solution was stirred in an ice bath under nitrogen and treated with a solution of sodium ethoxide (prepared from 1.84 g, 80 mmol of metallic sodium, and 31 mL of dry ethanol), added dropwise. The mixture was stirred overnight at room temperature. (In cases where TLC indicated the reaction was not complete, an extra 10% of diethyl malonate was added and the mixture heated in an oil bath thermostatted at 50 °C for 2 h.) The solution was quenched in 200 mL of cold H_2O containing 5 g of citric acid. The mixture was extracted with ether (4 × 70 mL) and the combined ether layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was separated and purified by chromatography on silica gel (750 g, 230–400 mesh, 55 mm i.d. column, medium pressure, 6:1 → 3:1 (v/v) hexane/ethyl acetate elution). The products fractions were evaporated in vacuo to give the 4*R*,5*S* lactone **6a** (10.0 g, 32%) and the 4*S*,5*S* isomer **6b** (12.4 g, 40%), each as a white solid homogeneous to TLC (silica gel GF, 3:1 (v/v) hexane/ethyl acetate). Samples of each were recrystallized from hexane/ethyl acetate (10:1).

6b: mp 104–106 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz, CH_3CH_2), 1.42 (s + s, 9 H, $(CH_3)_3C$), 2.3–2.42 (ddd, J_1 = 12 Hz, J_2 = 10 Hz, J_3 = 7 Hz, 1 H, C_3H_a), 2.49–2.62 (q, J = 11 Hz, 1 H, C_3H_b), 2.84–2.94 (dd, J_1 = 9 Hz, J_2 = 14 Hz, 1 H, $C_6H_5CH_a$), 2.96–3.06 (dd, J_1 = 7 Hz, J_2 = 14 Hz, 1 H, $C_6H_5CH_b$), 3.53–3.62 (dd, J_1 = 10 Hz, J_2 = 11 Hz, 1 H, C_2H), 3.98–4.1 (br q, J = 9 Hz, 1 H, C_5HN), 4.2–4.3 (q, J = 7 Hz, 2 H, CH_3CH_2O), 4.38–4.46 (ddd, J_1 = 9 Hz, J_2 = 7 Hz, J_3 = 2 Hz, 1 H, C_4HO), 4.66–4.73 (br d, J = 9 Hz, 1 H, NH), 7.2–7.35 (m, 6 H, ArO); MS, *m/e* 378 (M + H), 377 (M^+). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.57; H, 7.32; N, 3.40.

6a: mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.5 Hz), 1.33 (t, J = 7 Hz), 1.38 (s), 2.3–2.45 (br s), 2.55 (t + t, J = 9 Hz), 2.65 (q + q, J = 6 Hz), 2.8–2.95 (br s), 3.03 (dd, J_1 = 14 Hz, J_2 = 5 Hz), 3.60–3.68 (m), 3.92–4.07 (br s), 4.27 (sextet, J = 7 Hz), 4.35–4.45 (br s), 4.48 (q, J = 7.5 Hz), 4.53–4.63 (br s), 7.18–7.38 (m); MS, *m/e* 378 (M + H), 377 (M^+). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.65; H, 7.40; N, 3.77.

In Me_2SO-d_6 several of the NMR absorptions were separated into close pairs of approximately equal intensity. This separation was not compromised upon heating to 78 °C. The results suggest the presence of two diastereomers (2α and 2β) of **6a**.

The isomers **6a** and **6b** were each homogeneous by TLC (3:1 hexane/ethyl acetate, silica gel) and easily distinguished from each other (**6a**, R_f 0.23; **6b**, R_f 0.27). The absolute configurations were established by comparison with pure samples of **6a** and **6b** prepared from the separated epoxides **2a** and **2b**, respectively.

5-[1-(*t*-Boc-amino)-2-phenylethyl]-3-carbethoxy-3-(phenylmethyl)dihydrofuran-2(3*H*)-one (7). 7a. Lactone **6a** (0.1 g, 0.26 mmol) in dry ethanol (0.5 mL, distilled from sodium ethoxide) was treated with sodium ethoxide (0.1 mL of a 2.5 M solution in ethanol, 0.25 mmol) followed by benzyl bromide (0.044 g, 0.26 mmol), and the mixture was stirred under nitrogen in an oil bath thermostatted at 50 °C. Periodic TLC assay (3:1 hexane/ethyl acetate, silica gel) indicated that the reaction was complete after 1 h. At this time, the mixture was cooled, quenched in cold, dilute citric acid solution (10 mL), and extracted with ether (2 × 10 mL). The combined ether layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give the lactone **7a** as a white foam (0.13 g, 100%).

A sample of this material, chromatographed on silica gel (3:1 hexane/ethyl acetate) to remove a trace of a base-line contaminant was obtained as a sticky solid: ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7 Hz, EtOOC), 1.34 (m, 12 H, Boc), 2.15 (br t, J = 10 Hz), 2.33 (d, J = 7 Hz), 2.37 (d, J = 7 Hz), 2.5–2.8 (m), 2.85 (br d, J = 5 Hz), 2.89 (br d, J = 5 Hz), 3.17 (d, J = 14 Hz), 3.31 (s), 3.40 (d, J = 14 Hz), 3.72 (br s), 3.91 (br s), 4.24 (t, J = 7 Hz) and 4.30 (t, J = 7 Hz), 4.48 (br s), 7.06 (t, J = 8 Hz), 7.15–7.35 (m); IR (CH_2Cl_2, cm^{-1}) 3430, 2800–3100, 1775 (s), 1708 (br s), 1490, 1360, 1240, 1160; TLC (3:1 hexane/ethyl acetate), dumbbell, R_f 0.36 + 0.39; MS, *m/e* 468 (M + H), 467 (M^+). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.53; H, 7.43; N, 3.09.

7b. Lactone **6b** was alkylated with benzyl bromide as described in the preparation of **7a**. A chromatographed sample of **7b** was obtained as a sticky solid: ^{1}H NMR ($CDCl_3$) δ 1.23 (t J = 7 Hz) and 1.33 (t, J = 7 Hz) (EtOOC), 1.34 (s) and 1.38 (s) (Boc), 2.1–2.22 (m), 2.34 (d, J = 6 Hz) and 2.37 (d, J = 6 Hz), 2.55–2.70 (m), 2.75–2.91 (m), 3.12 (d, J = 14 Hz), 3.22–3.34 (m), 3.37 (d, J = 14 Hz), 3.74 (br q, J ~ 8 Hz) and 3.87 (br q, J ~ 8 Hz), 4.19 (q, J = 8 Hz), 4.22–4.32 (m), 4.47–4.55 (dd + dd, J_1 = 10 Hz, J_2 = 2 Hz), 4.62 (d, J = 10 Hz), 7.0 (d + d, J = 2 Hz, 7.12–7.32 (m); IR (CH_2Cl_2, cm^{-1}) 3430, 2880–3120, 1775 (s), 1730 (sh), 1708 (s), 1495, 1365, 1235 (br), 1162 (s); TLC (3:1 hexane/ethyl acetate) single component, R_f 0.46; MS, *m/e* 468 (M + H), 467 (M^+). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.32; H, 7.23; N, 3.03.

5-[1-(*t*-Boc-amino)-2-phenylethyl]-3-(phenylmethyl)dihydrofuran-2(3*H*)-one (10). 10b. Lactone **7b** (3.3 g, 7.1 mmol) in dioxane (60 mL) was diluted with H_2O (60 mL) and stirred in an open vessel. The pH of the mixture was monitored with a pH meter standardized with a 1:1 mixture of dioxane and pH 10 buffer. Sodium hydroxide (14 mL of 1 N solution, 14 mmol) was added dropwise, the pH rising to ca. 12.5. After 3 h the mixture was evaporated in vacuo to remove the bulk of the dioxane and then washed twice with ether. The aqueous phase was acidified to pH ~2 with 1 N HCl and extracted with ether (3 × 50 mL). The combined ether layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated in vacuo to give **9b** as a sticky solid (3.3 g): ^{1}H NMR (Me_2SO-d_6) δ 1.13 (s) and 1.16 (s) (Boc), 1.25 (s) and 1.27 (s) (Boc), 2.02 (d, J = 10 Hz), 2.06 (d, J = 10 Hz), 2.24 (d, J = 7 Hz), 2.28 (d, J = 7 Hz), 2.36 (d, J = 6 Hz), 2.39 (d, J = 6 Hz), 2.48–2.70 (m), 3.05 (d, J = 14 Hz), 3.12 (d, J = 14 Hz), 3.17 (d, J = 14 Hz), 3.27 (d, J = 14 Hz), 3.35 (br s), 3.55–3.76 (m), 4.45–4.55 (p, J = 5 Hz), 6.88 (d, J = 9 Hz), 6.93 (d, J = 9 Hz), 7.08–7.35 (m).

Thermogravimetric analysis (TGA) indicated that **9b** underwent a single thermal process corresponding to loss of CO_2 in the region 100–130 °C. Acid **9b** (1.0 g, 2.3 mmol) was heated under a nitrogen stream in a flask immersed in an oil bath thermostatted at 120 °C. After 30 min, TLC (80:10:1 CH_2Cl_2/MeOH/HOAc, silica gel plate) indicated complete conversion of the acid to a higher R_f material. Following chromatography on silica gel (CH_2Cl_2 and 1% MeOH in CH_2Cl_2) to remove a trace of a base-line component, the product fractions were evaporated in vacuo to give **10b** as a colorless oil (0.7 g, 78%): ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.40 (s + s, Boc), 1.80 (q, J = 12 Hz), 1.96 (m), 2.01–2.12 (m), 2.16–2.26 (m), 2.65–3.03 (m), 3.12 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 3.26 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 3.94 (br q, J = 7 Hz), 4.21 (q), 4.31 (ddd), 4.52 (br d, J = 10 Hz), 4.60 (br d, J = 10 Hz), 5.25 (s, ~0.1 H, CH_2Cl_2), 7.10–7.40 (m); IR ($CHCl_3$, cm^{-1}) 3440, 2850–3100, 1770 (s), 1710 (s), 1495 (s), 1455, 1365 (s), 1210 (br), 1160 (s); TLC (1% (v/v) MeOH/CH_2Cl_2) single component, R_f 0.51; MS, *m/e* 396 (M + H), 395 (M^+). Anal. Calcd for $C_{24}H_{29}NO_4$·0.05 CH_2Cl_2: C, 72.25; H, 7.33; N, 3.50. Found: C, 72.29; H, 7.52; N, 3.62.

10a. Lactone ester **7a** (3.3 g, 7.1 mol) was converted to the lactone acid **9a** as described for the isomer **9b**. The product was obtained as a colorless oil (3.4 g): ^{1}H NMR (Me_2SO-d_6) δ 1.11 (s) and 1.15 (s) (Boc), 1.24 (s) and 1.27 (s) (Boc), 2.04 (br), 2.16 (d, J = 10 Hz), 2.19 (d, J = 10 Hz), 2.31–2.66 (m), 2.74 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 3.07 (d, J = 14 Hz), 3.14 (d, J = 14 Hz), 3.19 (d, J = 14 Hz), 3.27 (d, J = 14 Hz), 3.36 (br), 3.6–3.75 (br m), 4.43 (t + t), 6.88 (d, J = 9 Hz), 6.96 (d, J = 9 Hz), 7.1–7.4 (m).

Decarboxylation of **9a** (1.0 g, 2.3 mmol) as described for **9b** and crystallization of the chromatographed product from ether gave **10a** as a white solid (0.66 g, 73%): ^{1}H NMR ($CDCl_3$) δ 1.32 and 1.34 (s + s, Boc), 1.69 (m), 1.80 (br q, J = 11 Hz), 1.95–2.05 (m), 2.12–2.27 (m), 2.65–3.0 (m), 3.06 (br s), 3.18 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 3.28 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 3.90 (br s), 4.13 (br s), 4.2–4.45 (br), 7.15–7.35 (m); IR ($CHCl_3$, cm^{-1}) 3440, 2840–3130, 1770 (s), 1710 (s), 1495 (s), 1450, 1365, 1200 (br), 1160 (s); TLC (1% (v/v) MeOH/CH_2Cl_2) single component, R_f 0.45; MS, *m/e* 396 (M + H). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.88; H, 7.39; N, 3.54. Found: C, 73.11; H, 7.62; N, 3.72.

5-(*t*-Boc-amino)-4-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-2-(phenylmethyl)hexanoic Acid (13). 13a. Lactone **10a** (6.95 g, 17.6 mmol), stirred in a mixture of dioxane (100 mL) and H_2O (50 mL), was treated with sodium hydroxide (19.3 mL, 1 M, 19.3 mmol) added dropwise over 5 min. The mixture was

stirred briskly for 30 min and the bulk of the dioxane removed in vacuo. The remaining mixture was acidified to pH ~2 with 10% citric acid and extracted with ether (3 × 30 mL). The combined ether layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was triturated with petroleum ether to yield **11a** as a white solid (7.3 g, 100%). This material was found to revert to the lactone **10a** at a detectable rate (10–20% by TLC after 41 days at 0 °C, solid phase; considerably faster in solution at ambient temperature) and was therefore immediately silated upon isolation.

11a (7.3 g, 17.7 mmol), *tert*-butyldimethylsilyl chloride (13.3 g, 87.9 mmol), and imidazole (11.4 g, 168 mmol) were combined in dry DMF (34 mL) and stirred at room temperature under nitrogen for 18 h. The mixture was evaporated in vacuo and the residue treated with ice H_2O. The resulting mixture was acidified to pH 4 with 10% citric acid and extracted with ether (3 × 60 mL). The combined ether layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated in vacuo to give the silyl ether–silyl ester **12a** as a colorless syrup. This material was dissolved in a mixture of THF (76 mL), glacial acetic acid (76 mL), and H_2O (25 mL) according to the procedure of Corey and Venkateswarlu,[15] stirred 1.5 h at ambient temperature, and refrigerated overnight. After an additional 1 h at ambient temperature, TLC (2% MeOH/CH_2Cl_2, silica gel) indicated the reaction was complete. The mixture was evaporated in vacuo and the residue was diluted with H_2O (60 mL) and extracted with ether (3 × 50 mL). The combined ether layers were dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (500 g) eluted with a gradient of 0–3% MeOH in CH_2Cl_2 to give the product, silyl acid **13a**, as a white solid (7.6 g, 14.4 mmol, 82% from **10a**), along with 1.3 g of recovered lactone **10a**. **13a**: ^{1}H NMR ($CDCl_3$) δ −0.01 (s) + 0.0 (s) + 0.03 (s) + 0.05 (1:1:3:3, 6 H, total, $SiCH_3$), 0.86 (s) + 0.90 (s) (1:3, 9 H total, $(CH_3)_3CSi$), 1.15–1.4 (br s + m) + 1.4–2.1 (m) (11 H, Boc + $-CH_2-$), 2.45–3.10 (m, 5 H, $C_6H_5CH_2$ + $CHCOOH$), 3.75–3.90 (br s, CHO), 4.45 (br) + 4.60 (br) (1 H, NH), 7.0–7.35 (m, 10 H, Ar); TLC (4% (v/v) MeOH/CH_2Cl_2) single component, R_f 0.56; MS, *m/e* 528 (M + H), 527 (M^+). Anal. Calcd for $C_{30}H_{45}NO_5Si$: C, 68.27; H, 8.59; N, 2.65. Found: C, 68.33; H, 8.68; N, 3.04.

13b. The same procedure was used to convert lactone **10b** (5.5 g, 13.9 mmol) to acid **11b** (white solid, 5.9 g). This compound appeared slightly more prone to relactonization than **11a**, reverting ~30–40% to lactone upon standing at 0 °C for 45 days (solid phase).

The entire lot of **11b** was converted to **12b** as described for **11a** → **12a**, and the product was deprotected to provide **13b** without the additional 1 h in the acidic solvent mixture. Chromatography as described gave **13b** as a white foam (5.1 g, 9.7 mmol, 70% from **10b**): ^{1}H NMR (CCl_4) δ 0.1 (s, 6 H, $SiCH_3$), 0.95 (s, 9 H, $(CH_3)_3CSi$), 1.1–2.0 (br s + br s + m, 11 H, Boc + $-CH_2-$), 2.4–3.1 (m, 5 H, $C_6H_5CH_2$ + $CHCOOH$), 3.6–4.5 (m, 2 H, NH + CH–O), 6.9–7.5 (m, 10 H, Ar); TLC (4% (v/v) MeOH/CH_2Cl_2), dumbbell, R_f 0.49 + 0.56; MS, *m/e* 528 (M + H), 527 (M^+). Anal. Calcd for $C_{30}H_{45}NO_5S$: C, 68.27; H, 8,59; N, 2.65. Found: C, 68.53; H, 8.75; N, 2.87.

N^{α}-[4-[[5-(*t*-Boc-amino)-4-hydroxy-6-phenyl-2-(phenylmethyl)hexanoyl]amino]-3-hydroxy-6-methylheptanoyl]-L-leucine Benzylamide (15). 15a. Acid **13a** (0.1 g, 0.19 mmol), Sta-Leu benzylamide hydrochloride (90 mg, 0.23 mmol), EDC (44 mg, 0.23 mmol), and HBT (31 mg, 0.23 mmol) were combined in dry, degassed DMF (0.5 mL) and stirred at room temperature. The pH of the mixture, measured by application of an aliquot to moistened colorpHast sticks (E. Merck), was adjusted to 9–9.5 with triethylamine, and the mixture was stirred 3 h. The solvent was removed in vacuo and the residue was treated with 10% citric acid solution (10 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with citric acid (2 × 5 mL), saturated sodium bicarbonate (2 × 5 mL), and brine (1 × 5 mL), dried over sodium sulfate, filtered, and evaporated in vacuo to give **14a** as a mixture of two diastereomers, ca. 3:1: ^{1}H NMR ($CDCl_3$) δ 0.05 (s) + 0.06 (s) + 0.08 (s) CH_3Si, 0.65–1.0 (m), 1.2–1.4 (m) (1.32 (s) + 1.33 (s)), 1.4–1.8 (m + m), 1.8–1.95 (m), 2.01 (d, *J* = 2 Hz), 2.12–2.23 (m), 2.3–2.4 (m), 2.42–2.68 (m), 2.75–2.9 (m), 3.26 (br s), 3.58 (br s), 3.69 (br q, *J* ~ 7 Hz), 3.78 (br d, *J* ~ 7 Hz), 3.85 (m + m, *J* ~ 10 Hz), 3.93 (br s), 4.11 (br s), 4.16–4.57 (m, including 4.48 (d, *J* = 6 Hz) and 4.52 (d, *J* = 6 Hz), ratio 3:1), 4.59 (br d, *J* = 6 Hz) and 4.65 (d, *J* = 9 Hz), ratio 1:3, 5.3 (br d, *J* = 9 Hz), 6.06 (br d, *J* = 7 Hz), 6.74 (br d, *J* = 9 Hz), 6.95–7.05 (br m), 7.10–7.40 (m), 8.2–8.27 (br s).

Silylpeptide **14a** (72 mg, 79 μmol) in THF (1 mL) was treated with tetrabutylammonium fluoride (1 M, 0.24 mL, 240 μmol) and stirred at room temperature for 3 days after which time TLC (2% MeOH in CH_2Cl_2) showed the starting **14a** to have been consumed. The mixture was evaporated in vacuo and chromatographed on silica gel (3% MeOH/CH_2Cl_2 elution) to give the isomer mixture **15a$_1$** + **15a$_2$** (43 mg): ^{1}H NMR (CD_3OD) δ 0.64 (d, *J* = 6 Hz) + 0.70 (d, *J* = 6 Hz) + 0.80 (d, *J* = 6 Hz) + 0.85 (d, *J* = 6 Hz), ratio 1:1:3:3, 0.89 (d, *J* = 6 Hz), 0.91 (d, *J* = 6 Hz), 0.92 (d, *J* = 6 Hz), 0.97 (d, *J* = 6 Hz), 1.13–1.23 (m), 1.29 (s) and 1.32 (s), ratio 3:1, 1.45–1.90 (m), 2.34 (d, *J* = 7 Hz), 2.43–2.96 (m), 3.11 (m), 3.17 (m), 3.50 (m), 3.55–3.72 (m), 3.75–3.90 (m), 3.97 (br t, *J* = 7 Hz), 4.34 (d, *J* = 15 Hz), 4.43 (d, *J* = 15 Hz), 4.42–4.47 (m), 4.52 (d, *J* = 15 Hz), 4.72 (s), 7.08–7.37 (m); FABMS, *m/e* 795 (M + Na), 774 (M + 2), 773 (M + 1), 675, 674, 673; HPLC two diastereomers, 65% and 26%. Calcd for amino acid analysis (μmol/mg): Leu, 1.29. Found: Leu, 1.31.

The mixture (~40 mg) was separated by preparative HPLC and the recovered fractions were evaporated and rechromatographed on silica gel. Only the major component was obtained in sufficient quantity for characterization: ^{1}H NMR (CD_3OD) δ 0.80 (d, *J* = 6 Hz), 0.85 (d, *J* = 6 Hz), 0.92 (d, *J* = 6 Hz), 0.97 (d, *J* = 6 Hz), 1.17–1.25 (m), 1.29 (s), 1.45–1.72 (m), 1.79 (br t, *J* = 6 Hz), 1.85–1.90 (m), 2.51 (dd, J_1 = 14 Hz, J_2 = 10 Hz), 2.73–2.92 (m), 3.55–3.72 (m), 3.81–3.89 (m), 4.34 (d, *J* = 15 Hz), 4.43 (d, *J* = 15 Hz), 4.74 (br m), 7.12–7.33 (m); FABMS, *m/e* 774 (M + 2), 773 (M + 1), 772 (M), 675, 674, 673; HPLC 99%. Calcd for amino acid analysis (μmol/mg): Leu, 1.29. Found: Leu, 1.12.

15b. Acid **13b** (0.1 g, 0.19 mmol) was coupled to Sta-Leu benzylamide by the same procedure described for **13a**, giving **14b** as a mixture of two diastereomers, ca. 1.5:1: ^{1}H NMR ($CDCl_3$) δ 0.11 (s) + 0.13 (s) + 0.15 (s) CH_3Si, 0.64 (d, *J* = 6 Hz) + 0.69 (d, *J* = 6 Hz) + 0.78 (d, *J* = 6 Hz), + 0.80 (d, *J* = 6 Hz), ratio 1.5:1.5:1:1, 0.88 (d, *J* = 6 Hz), 0.90–1.10 (m, including 0.96 (s) + 0.97 (s)), 1.15–1.45 (m, including 1.33 (s) + 1.36 (s)), 1.48–2.10 (m), 2.17 (d, *J* = 7 Hz) + 2.21 (d, *J* = 7 Hz), ratio 1.5:1, 2.48–3.0 (m), 3.24 (br s) + 3.29 (br s), 3.51 (br m), 3.60 (br q), 3.72–3.90 (m), 4.00–4.10 (br m), 4.35–4.50 (m), 4.66 (d, *J* = 10 Hz) and 4.78 (d, *J* = 10 Hz), ratio 1.5:1, 5.93 (br d), 6.00 (d, *J* = 9 Hz), 6.13 (d, *J* = 9 Hz), 6.52 (d, *J* = 7 Hz), 6.93–7.37 (m).

Silylpeptide **14b** (137 mg, 150 μmol) in THF (1 mL) was treated with tetrabutylammonium fluoride (1 M, 0.47 mL, 470 μmol) and stirred at room temperature for 3 days after which time TLC (2%, MeOH in CH_2Cl_2) showed the starting **14b** to have been consumed. The mixture was evaporated in vacuo and chromatographed on silica gel (2% MeOH/CH_2Cl_2 elution) to give the separated diastereomers (C_2) **15b$_1$** (25 mg) and **15b$_2$** (56 mg).

15b$_1$: ^{1}H NMR (CD_3OD) δ 0.80 (d, *J* = 6 Hz), 0.86 (d, *J* = 6 Hz), 0.93 (d, *J* = 6 Hz), 0.98 (d, *J* = 6 Hz) (0.9–0.95 m), 1.2–1.8 (m), 1.33 (s), 1.83 (d, *J* = 7 Hz), 2.6–2.85 (m), 3.10–3.15 (m), 3.50 (m), 3.56 (m), 3.58 (m), 3.66–3.73 (m), 3.77–3.83 (m), 3.86 (dt, J_1 = 7 Hz, J_2 = 2 Hz), 4.33 (d, *J* = 15 Hz), 4.36–4.39 (m), 4.42 (d, *J* = 15 Hz), 7.10–7.35 (m); HPLC 91% (contains 1.5% of isomer **15b$_2$**); FABMS, *m/e* 795 (M + Na), 774 (M + 2), 773 (M + 1), 675, 674, 673. Calcd for amino acid analysis (μmol/mg): Leu, 1.29. Found: 1.22.

15b$_2$: ^{1}H NMR (CD_3OD) δ 0.60 (d, *J* = 6 Hz), 0.68 (d, *J* = 6 Hz), 0.75–0.87 (m), 0.89 (d, *J* = 6 Hz), 0.93 (d, *J* = 6 Hz), 1.01–1.20 (m), 1.23 (br s), 1.33 (s), 1.55–1.77 (m), 1.8–2.0 (m), 2.32 (dd, J_1 = 14 Hz, J_2 = 7 Hz), 2.43 (dd, J_1 = 14 Hz, J_2 = 7 Hz), 2.61–2.77 (m), 2.86 (dd, J_1 = 13 Hz, J_2 = 5 Hz), 3.21 (br s), 3.69–3.80 (br m), 3.96 (dt, J_1 = 7 Hz, J_2 = 2 Hz), 4.36–4.45 (m), (4.35 d, *J* = 15 Hz + 4.42 d, *J* = 15 Hz), 7.07–7.13 (m); HPLC 89% (contains 3% of isomer **15b$_1$**); FABMS, *m/e* 795 (M + Na), 774 (M + 2), 773 (M + 1), 675, 674, 673. Calcd for amino acid analysis (μmol/mg): Leu, 1.29. Found: Leu, 1.31.

N^{α}-[4-[[5-(*t*-Boc-amino)-4-hydroxy-6-phenyl-2-(phenylmethyl)hexanoyl]amino]-5-cyclohexyl-3-hydroxypentanoyl]-L-leucine *m*-(Aminomethyl)benzylamide (17). Acid **13a** (0.56 g, 1.06 mmol), ACHPA-L-Leu-3-[[(trifluoroacetyl)amino]methyl]benzylamide hydrochloride (0.5 g, 0.86 mmol), EDC (0.166 g, 0.86 mmol), and HBT (0.116 g, 0.86 mmol) were combined in dry, degassed DMF (2 mL), the pH was adjusted to 9–9.5 with triethylamine, and the mixture was stirred 6 h at

room temperature. The reaction was quenched in a cold pH 4 buffer (50 mL) prepared by addition of sodium bicarbonate to a 10% citric acid solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, washed with the buffer (1 × 20 mL), with saturated sodium bicarbonate (1 × 20 mL), and with brine (1 × 20 mL), dried over sodium sulfate, filtered, and evaporated in vacuo to give a white foam (0.95 g). Chromatography on silica gel (2% MeOH/CH_2Cl_2 elution) gave the two separated diastereomers **16a**$_1$ (0.13 g) and **16a**$_2$ (0.24 g) as white amorphous solids. Flushing with 10% MeOH/CH_2Cl_2 provided an additional 0.22 g of material consisting mainly of **16a**$_1$, which was not processed further.

16a$_1$: ^{1}H NMR (CD_3OD) δ 0.14 (s) + 0.18 (s), 0.65–0.80 (m), 0.87 (d, J = 6 Hz), 0.92 (d, J = 6 Hz), 0.97 (s), 1.08–1.38 (m), 1.30 (s), 1.45–1.55 (m), 1.56–1.70 (m), 1.85–1.95 (m), 2.29 (dd, J_1 = 14 Hz, J_2 = 9 Hz), 2.38 (dd, J_1 = 14 Hz, J_2 = 5 Hz), 2.60–2.84 (m), 2.86 (s), 2.99 (s), 3.82–3.98 (m), 4.29 (s), 4.39 (d, J = 6 Hz), 4.42 (d, J = 6 Hz), 5.83 (d, J = 10 Hz), 7.10–7.30 (m); FDMS, m/e 1052 (M + 1), 1053 (M + 2), 994, 960, 832.

16a$_2$: ^{1}H NMR (CD_3OD) δ 0.05 (s) + 0.07 (s), 0.70–0.99 (m), 0.91 (s), 0.98 (d, J = 6 Hz), 1.06–1.37 (m), 1.29 (s), 1.36–1.50 (m), 1.56–1.78 (m), 1.82–2.03 (m), 1.98 (d, J = 7 Hz), 2.38 (dd, J_1 = 14 Hz, J_2 = 10 Hz), 2.52 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 2.60 (dd, J_1 = 14 Hz, J_2 = 7 Hz), 2.67–2.78 (m), 2.90 (t, J = 14 Hz), 2.95 (t, J = 14 Hz), 3.75 (dt, J_t = 9 Hz, J_d = 3 Hz), 3.93 (d, J = 14 Hz), 3.95 (d, J = 14 Hz), 4.34–4.50 (m), 4.70 (s), 7.03 (d, J = 7 Hz), 7.11–7.34 (m); FDMS, m/e 1052 (M + 1), 1053 (M + 2), 994, 960, 832.

Acid **13b** was coupled to ACHPA-L-Leu-3-[[(trifluoroacetyl)-amino]methyl]benzylamide by the same procedure. Chromatography provided **16b**$_1$ (0.46 g) and **16b**$_2$ (0.21 g) as amorphous white solids.

16b$_1$: ^{1}H NMR (CD_3OD) δ 0.04 (s) + 0.10 (s), 0.78 (d, J = 6 Hz), 0.83 (d, J = 6 Hz), 0.88 (s), 0.65–0.95 (m), 1.04–1.42 (m), 1.34 (s), 1.52–1.72 (m), 2.00–2.12 (m), 2.33 (dd, J_1 = 15 Hz, J_2 = 5 Hz), 2.42 (d, J = 9 Hz), 2.48 (t, J = 15 Hz), 2.51 (t, J = 15 Hz), 2.65 (dd, J_1 = 12 Hz, J_2 = 6 Hz), 2.75–2.93 (m), 2.87 (s), 3.00 (s), 3.45–3.52 (m), 3.64–3.74 (br m), 3.80 (br s), 3.90–3.97 (m), 4.02–4.07 (br t), 4.30–4.48 (m), 4.71 (s), 7.12–7.33 (m); FDMS, m/e 1052 (M + 1), 1053 (M + 2), 953, 952.

16b$_2$: ^{1}H NMR (CD_3OD) δ 0.15 (s) + 0.17 (s), 0.93 (d, J = 6 Hz), 0.98 (d, J = 6 Hz), 0.96 (s), 1.10–1.30 (m), 1.34 (s), 1.40–1.50 (m), 1.50–2.00 (m), 2.55–2.85 (m, including several d), 2.86 (s), 3.00 (s), 3.75–4.00 (m), 4.36 (d, J = 6 Hz), 4.37–4.47 (m), 4.75 (s), 5.96 (d, J = 9 Hz), 7.12–7.37 (m); FDMS, m/e 1052 (M + 1), 1053 (M + 2), 994, 960, 935.

Each of the four individual diastereomers of **16** was detrifluoroacetylated by stirring 6 days at room temperature in 5 mL of MeOH containing 5 mL of a 7% solution of potassium carbonate in 40% aqueous methanol. The reactions each showed a single product on TLC (90:10:1:1 CH_2Cl_2/MeOH/HOAc/H_2O, silica gel, PMA stain). Each reaction was evaporated in vacuo, and the residue was treated with H_2O (3 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over potassium carbonate, filtered, and evaporated to give the deprotected amines.

These amines were each desilated by stirring for 24 h at room temperature with a three-fold molar excess of tetrabutylammonium fluoride (1 M in THF). Each reaction mixture was evaporated in vacuo and the residue chromatographed on silica gel (170:10:1 CH_2Cl_2/MeOH/concentrated NH_3 elution) to give the final products **17a**$_1$,**a**$_2$,**b**$_1$,**b**$_2$ (63, 56%, 64%, and 67% from the respective **16**).

17a$_1$: ^{1}H NMR (CD_3OD) δ 0.65–1.05 (m), 0.90 (d, J = 6 Hz), 1.06–1.30 (m), 1.32 (s), 1.48–1.80 (m), 1.90 (t, J = 8 Hz), 2.35 (dd, J_1 = 7 Hz, J_2 = 5 Hz), 2.55 (dd, J_1 = 14 Hz, J_2 = 11 Hz), 2.65 (dd, J_1 = 13 Hz, J_2 = 5 Hz), 2.78 (d, J = 9 Hz), 2.81 (d, J = 9 Hz), 3.15 (s), 3.37–3.42 (br m), 3.45–3.52 (br), 3.56–3.67 (br m), 3.89 (s), 3.87–3.95 (br m), 4.01 (dt, J_t = 7 Hz, J_d = 1.5 Hz), 4.39 (d, J = 15 Hz), 4.47 (d, J = 15 Hz), 4.37–4.45 (m), 4.72 (s), 7.10–7.35 (m); HPLC 92.5% (contains 1.6% of **17a**$_2$); FABMS, m/e 844 (M + 3), 843 (M + 2), 842 (M + 1), 742. Calcd for amino acid analysis (μmol/mg): Leu, 1.19. Found: Leu, 1.07.

17a$_2$: ^{1}H NMR (CD_3OD) δ 0.65–1.05 (m), 0.93 (d, J = 6 Hz), 0.99 (d, J = 6 Hz), 1.05–1.36 (m), 1.28 (s), 1.49 (t, J = 9 Hz), 1.55–1.95 (m), 1.80 (br t, J = 5 Hz), 1.90 (t, J = 6 Hz), 2.52 (dd, J_1 = 14 Hz, J_2 = 10 Hz), 2.77 (d, J = 5 Hz), 2.80–2.92 (m), 3.15 (s), 3.55–3.72 (m), 3.80–3.88 (m), 3.90 (s), 4.36 (dd, J_1 = 9 Hz, J_2 = 6 Hz), 4.37 (d, J = 15 Hz), 4.46 (d, J = 16 Hz), 4.72 (s), 7.10–7.37 (m); HPLC 97.3% (contains 0.75% of **17a**$_1$); FABMS, m/e 844 (M + 3), 843 (M + 2), 842 (M + 1), 742. Calcd for amino acid analysis (μmol/mg): Leu, 1.19. Found: Leu, 1.07.

17b$_1$: ^{1}H NMR (CD_3OD) δ 0.55–1.05 (m), 0.89 (d, J = 6 Hz), 0.94 (d, J = 6 Hz), 1.05–1.25 (m), 1.21 (s), 1.32 (s), 1.45–1.80 (m), 1.85–1.97 (m), 2.33 (dd, J_1 = 14 Hz, J_2 = 7 Hz), 2.45 (dd, J_1 = 14 Hz, J_2 = 6 Hz), 2.62–2.90 (m), 2.73 (dd, J_1 = J_2 = 11 Hz), 2.86 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 3.17 (s), 3.67–3.77 (m), 3.80–3.92 (m), 3.88 (s), 3.99 (dt, J_t = 7 Hz, J_d = 2 Hz), 4.38 (d, J = 6 Hz), 4.37 (d, J = 15 Hz), 4.43 (d, J = 15 Hz), 4.74 (s), 7.10–7.35 (m); HPLC, 94.2% (contains 3.1% of **17b**$_2$); FABMS, m/e 844 (M + 3), 843 (M + 2), 842 (M + 1), 742. Calcd for amino acid analysis (μmol/mg): Leu, 1.19. Found: Leu, 1.04.

17b$_2$: ^{1}H NMR (CD_3OD) δ 0.70–1.08 (m), 0.93 (d, J = 6 Hz), 0.99 (d, J = 6 Hz), 1.10–1.55 (m), 1.32 (s), 1.55–1.95 (m), 1.85 (dd, J_1 = 6 Hz, J_2 ~ 2 Hz), 2.60–2.97 (m), 3.16 (br s), 3.58–3.73 (m), 3.82–3.90 (m), 3.86 (s), 4.33 (dd, J_1 = 15 Hz, J_2 = 6 Hz), 4.36 (d, J = 15 Hz), 4.45 (d, J = 15 Hz), 4.73 (s), 7.10–7.36 (m); HPLC, 85.7% (contains 5.5% of **17b**$_1$); FABMS, m/e 844 (M + 3), 843 (M + 2), 842 (M + 1), 742. Calcd for amino acid analysis (μmol/mg): Leu, 1.19. Found: Leu, 0.99.

Cleavage of N^{α}-[5-(*t*-Boc-amino)-4-hydroxy-6-phenyl-2-(phenylmethyl)hexanoyl]-L-leucine Benzylamide (18b). Acid **13b** (0.3 g, 0.57 mmol) and Leu benzylamide hydrochloride (0.18 g, 0.69 mmol) were coupled by using EDC (0.13 g, 0.69 mmol) and HBT (0.093 g, 0.69 mmol) in dry, degassed DMF (5 mL) according to the procedure described for **15**. Workup as described and chromatography on silica gel (20% EtOAc/hexane elution) provided the individual diastereomers A (0.18 g) and B (0.11 g) of the acylpeptide.

A: ^{1}H NMR ($CDCl_3$) δ 0.06 (s) + 0.12 (s) CH_3Si, 0.68 (d, J = 6 Hz) + 0.73 (d, J = 6 Hz), 0.94 (s), 1.13–1.42 (m, including 1.32 (s)), 1.60–2.05 (m), 2.55–2.85 (m), 3.68 (dd, J_1 = 10 Hz, J_2 = 5 Hz), 3.94 (dt, J_t = 10 Hz, J_d = 5 Hz), 4.13–4.22 (m), 4.29 (dd, J_1 = 15 Hz, J_2 = 6 Hz), 4.47 (dd, J_1 = 15 Hz, J 2 = 6 Hz), 4.61 (d, J = 10 Hz), 5.71 (d, J = 8 Hz), 6.4 (br t), 7.08–7.40 (m).

B: ^{1}H NMR ($CDCl_3$) δ 0.105 (s) + 0.11 (s) CH_3Si, 0.82–1.05 (m, including 0.95 (s)), 1.28 (d, J = 11 Hz), 1.35 (s), 1.50–1.95 (m), 2.46 (dd, J_1 = 13 Hz, J_2 = 5 Hz), 2.51–2.63 (m), 2.66 (d, J = 7 Hz) + 2.69 (d, J = 7 Hz) + 2.74 (d, J = 7 Hz) + 2.78 (d, J = 9 Hz) + 2.82 (d, J = 9 Hz), 3.72 (dd, J_1 = 10 Hz, J_2 = 4 Hz), 3.97 (dd, J_1 = 17 Hz, J_2 = 8 Hz), 4.17 (dd, J_1 = 15 Hz, J_2 = 6 Hz), 4.23–4.37 (m), 4.77 (d, J = 10 Hz), 6.18 (br t), 6.34 (d, J = 8 Hz), 6.95–7.37 (m).

Silyl ether A (0.18 g, 0.25 mmol) and tetrabutylammonium fluoride/THF (0.77 mL, 1 M, 0.77 mmol) were combined and stirred at room temperature under nitrogen for 40 h. The mixture was evaporated in vacuo and the residue was chromatographed on silica gel (180:10:1 CH_2Cl_2/MeOH/concentrated NH_3 elution) to give the deprotected acylpeptide **18b**$_1$ (0.15 g, 66%). Silyl ether B was similarly converted to **18b**$_2$ (64%).

18b$_1$ (0.1 g, 0.16 mmol) was stirred in EtOAc (1.5 mL) immersed in an ice bath. HCl (g) was passed through the solution for 10 min and the mixture was stirred an additional 15 min in the cold. The solvent was removed in vacuo and the residue was treated with EtOAc and evaporated (3×). Addition and evaporation of hexane provided a white foam. This material was combined with Boc-L-Phe (0.048 g, 0.18 mmol), EDC (0.034 g, 0.18 mmol), and HBT (0.024 g, 0.18 mmol) in dry, degassed DMF (1 mL) and stirred at room temperature. The pH was adjusted to 9–9.5 as described in the synthesis of **15**, and the mixture was stirred at room temperature for 40 h.

The mixture was evaporated in vacuo, stirred with 10% citric acid solution, then treated with concentrated Na_2CO_3, and extracted with EtOAc (3 × 5 mL). The EtOAc layer was washed with H_2O, dried over K_2CO_3, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (80:10:1 CH_2Cl_2/MeOH/concentrated NH_3 elution) to give Boc-Phe lactone **21b** (18 mg, 0.03 mmol), peptide **22** (44 mg, 0.09 mmol), and a third fraction (60 mg) containing a number of components including an estimated (NMR, TLC) 30% of **22**.

21b: ^{1}H NMR (CD_3OD) δ 0.85–0.95 (br), 1.2–1.45 (m, including 1.36 (s)), 1.52 (br d, J = 12 Hz), 1.59 (br d, J = 12 Hz), 1.89–2.0 (m), 2.55–2.68 (m), 2.73–3.08 (m), 3.14 (dd, J_1 = 14 Hz, J_2 = 4 Hz), 4.2–4.32 (m), 4.37–4.48 (m), 7.10–7.38 (m); MS, m/e 542 (M^+),

486, 451, 442. TLC (180:10:1:1 CH_2Cl_2/MeOH/HOAc/H_2O) single component, R_f 0.68, coelutes with a sample of this intermediate prepared in synthesis of **28**.

22: ^1H NMR (CD_3OD) δ 0.89 (d, J = 6 Hz), 0.93 (d, J = 6 Hz), 1.2–1.4 (m, including 1.35 (s)), 1.52–1.70 (m), 2.75–2.88 (m), 3.06 (d, J = 6 Hz), 3.09 (d, J = 6 Hz), 4.21–4.37 (m), 4.39–4.47 (m), 7.1–7.35 (m); FABMS, m/e 469 (M + 2), 468 (M + 1), 467 (M^+), 412, 369, 368. The compound coeluted (TLC, 80:10:1 CH_2Cl_2/MeOH/NH_3 and 90:10:1:1 CH_2Cl_2/MeOH/HOAc/H_2O, silica gel) with an authentic sample prepared by EDC coupling of Boc-Phe to Leu-$NHCH_2C_6H_5$.

5-(1-Amino-2-phenylethyl)-3-(phenylmethyl)dihydrofuran-2(3*H*)-one Hydrochloride (19). 19a. Acid **13a** (3.74 g, 7.1 mmol) was stirred in EtOAc (48 mL) immersed in an ice bath. HCl (g) was passed through the solution for 10 min and the mixture was stirred an additional 15 min in the cold. The solvent was removed under vacuum and the residue treated with EtOAc and evaporated (3×). After standing under hexane (90 mL), the mixture was filtered to give the amino lactone hydrochloride **19a** as a white solid (2 g, 61%): ^1H NMR (CD_3OD) δ 0.7–1.5 (br, hexane), 1.7–2.4 (br, 2 H), 2.6–3.3 (br, 4 H), 3.4–4.8 (br, 3 H), 6.7–7.0 (m, 10 H, Ar); IR (KBr, cm^{-1}) 3200–3600 (br), 2450–3150 (br), 1775 (br s), 1495, 1165. TLC (90:10:1:1, CH_2Cl_2/MeOH/HOAc/H_2O) single component, R_f 0.45; MS, m/e 295 (M^+, free base). Anal. Calcd for $C_{19}H_{21}NO_2$·HCl·0.1C_6H_{14}: C, 69.14; H, 6.93; N, 4.11. Found: C, 69.05; H, 7.19; N, 4.01.

19b. Applied to acid **13b**, this same procedure provided **19b** (62%): ^1H NMR (CD_3OD) δ 1.5–2.2 (br, 2 H), 2.2–3.5 (m, 5 H), 3.5–4.3 (br, 2 H), 6.8–7.2 (m, 10 H, Ar); IR (KBr, cm^{-1}) 3300–3650 (br), 2500–3250 (br), 1780 (s), 1495, 1175; TLC (90:10:1:1 CH_2Cl_2/MeOH/HOAc/H_2O) single component, R_f 0.40; MS, m/e 295 (M^+, free base). Anal. Calcd for $C_{19}H_{21}NO_2$·HCl: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.81; H, 6.86; N, 4.30.

***N*$^\alpha$-[5-[[*N*$^\alpha$-(*t*-Boc-amino)-L-phenylalanyl-L-phenylalanyl]amino]-4-hydroxy-6-phenyl-2-(phenylmethyl)hexanoyl]-L-leucyl-L-phenylalanine Amide (28).** Amino lactone hydrochloride **19b** (1.5 g, 4.5 mmol), Boc-L-phenylalanine (1.32 g, 5.0 mmol), EDC (0.96 g, 5.0 mmol), and HBT (0.68 g, 5.0 mmol) were combined in dry, degassed DMF (26 mL) and stirred at room temperature. The pH of the mixture, measured by spotting an aliquot on moistened colorpHast sticks (E. Merck), was raised to 9–9.5 by addition of triethylamine, and the mixture was stirred 2 h and then refrigerated overnight.

The mixture was evaporated in vacuo and the residue treated with cold 10% citric acid (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The resulting intermediate **21b** (see Scheme V) was used without further purification. The residue was stirred in ethyl acetate (30 mL), immersed in an ice bath, and saturated with HCl (g) for 10 min. The mixture was evaporated several times from ethyl acetate and then from ether. The residue was coupled with Boc-L-phenylalanine using the procedure described above for **19b**. Chromatography on silica gel (180:10:1 CH_2Cl_2/MeOH/HOAc elution) gave **26b** as a white foam (2.5 g).

This material was dissolved in dioxane (40 mL), treated with H_2O (20 mL) and aqueous sodium hydroxide (3.55 mL of 1 M), and stirred at room temperature for 18 h. The solvent was removed in vacuo and the residue dried under high vacuum for 18 h. The resulting salt (2.3 g, 3.2 mmol) was treated with *tert*-butyldimethylsilyl chloride (3.4 g, 22.5 mmol) and imidazole (3.6 g, 53 mmol) in dry DMF (40 mL) and stirred at room temperature. After 6 h, additional portions of the silyl chloride (1.5 g) and imidazole (1.5 g) were added and the mixture was stirred for 3 days. The mixture was evaporated in vacuo, treated with ice H_2O (100 mL), acidified to pH ~4 with citric acid solution, and extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (1% MeOH/CH_2Cl_2) to give the silyl ester as a white foam.

This solid was dissolved in THF (12 mL), treated with H_2O (4 mL) and glacial acetic acid (12 mL), and stirred 3 h at room temperature. The mixture was evaporated in vacuo, and the residue was diluted with H_2O, adjusted to pH ~3 (sodium bicarbonate + citric acid), and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with H_2O, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (1% → 5% MeOH in CH_2Cl_2) to give **27b** as a white foam (2.0 g); ^1H NMR (CD_3OD) δ 0.00 (s) + 0.09 (s) + 0.12 (s) + 0.16 (s) + 0.10–0.17 (m), 0.96 (s), 0.93–1.0 (m), 1.2 (br s), 1.33 (s), 1.3–1.4 (m), 1.99 (s), 2.52–3.0 (m), 3.69 (br t), 3.78 (br s), 4.24 (br s), 4.34 (br s), 4.60 (br t), 6.61 (br d), 7.05–7.35 (m), 7.40 (br d); FABMS, m/e 822 (M + 1); IR (CH_2Cl_2, cm^{-1}) 3420, 3300, 3070 (sh), 3030 (sh), 2930, 1750 (sh), 1715, 1675 (sh), 1495, 1370, 1160, 840.

Acid **27b** (0.8 g, 0.97 mmol), L-leucine benzylamide hydrochloride (0.33 g, 1.07 mmol), DCC (1 M in CH_2Cl_2, 1.02 mL, 1.02 mmol), and HBT hydrate (0.150 g, 1.02 mmol) were combined in dry DMF (12 mL), and the pH was adjusted to 8.5 with triethylamine. The mixture was stirred for 5 days at room temperature and then evaporated in vacuo. The residue was treated with dilute citric acid (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with citric acid (2 × 20 mL), sodium bicarbonate (2 × 20 mL), and brine, dried over potassium carbonate, filtered, and evaporated to dryness in vacuo (1.2 g).

The residue (0.95 g) was combined with 1 M tetrabutylammonium fluoride/THF (2.64 mL, 2.64 mmol) in 3 mL of THF and stirred at room temperature under nitrogen for 40 h. The mixture was evaporated in vacuo and the residue chromatographed on silica gel (390:10:1 CH_2Cl_2/MeOH/concentrated NH_3 elution) to give the two diastereomers **28b$_1$** and **28b$_2$** in a series of mixed fractions ranging from 1:500 to 3:1 (total ~0.43 g). A portion of this material (0.3 g) was separated by preparative HPLC to give the two diastereomers **28b$_1$** (210 mg) and **28b$_2$** (31 mg), each as an amorphous white solid.

28b$_1$: ^1H NMR (Me_2SO-d_6) δ 0.50 (d, J = 7 Hz), 0.65 (d, J = 7 Hz), 0.85–0.97 (m), 1.05–1.18 (m), 1.26 (s), 1.63–1.74 (m), 2.50–2.65 (m), 2.65–2.85 (m), 2.85–2.97 (m), 3.08 (dd, J_1 = 14 Hz, J_2 = 5 Hz), 3.2 (s), 3.6 (br m), 3.85 (q, J = 7 Hz), 4.0–4.15 (br m), 4.39 (dt, J_t = 9 Hz, J_d = 6 Hz), 4.56 (br q, J = 7 Hz), 5.13 (br d, J = 5 Hz), 6.90 (d, J = 9 Hz), 7.08–7.35 (m), 7.72 (d, J = 8 Hz), 7.90 (d, J = 7 Hz), 7.92 (s), 7.97 (d, J = 8 Hz); HPLC, 96.5%; FABMS, m/e 967 (M + 1), 968 (M + 2), 867, 803, 703/4/5, 590. Calcd for amino acid analysis (μmol/mg): Leu, 1.03; Phe, 3.09. Found: Leu, 1.02; Phe, 3.04.

28b$_2$: ^1H NMR (Me_2SO-d_6) δ 0.76 (d, J = 6 Hz), 0.83 (d, J = 6 Hz), 1.08 (s), 1.15 (s), 1.22–1.38 (m), 1.26 (s), 1.4–1.52 (br m), 2.39 (dd, J_1 = 13 Hz, J_2 = 7 Hz), 2.52–2.90 (m), 2.98 (dd, J_1 = 13 Hz, J_2 = 5 Hz), 3.18 (s), 3.82 (br m), 4.10 (dt, J_t = 10 Hz, J_d = 4 Hz), 4.20 (q, J = 7 Hz), 4.35–4.45 (m), 4.50–4.62 (br), 4.78 (d, J = 6 Hz), 6.86 (d, J = 9 Hz), 7.00–7.40 (m), 7.78 (d, J = 8 Hz), 7.85 (d, J = 9 Hz), 7.87–7.93 (m); HPLC, 89.3%; contains 3% **28b$_1$** and 4% de-Boc; FABMS, m/e 967 (M + 1), 968 (M + 2), 867 (M + 2 – Boc), 804, 704, 590. Calcd for amino acid analysis (μmol/mg): Leu, 1.03; Phe, 3.09. Found: Leu, 0.949; Phe, 2.89.

28b$_1$ and **28b$_2$** are separated by TLC on silica gel, 80:10:1 CH_2Cl_2/MeOH/concentrated NH_3 elution: **28b$_1$**, R_f, 0.48; **28b$_2$**, 0.45.

Amino lactone hydrochloride **19a** was coupled, deprotected, and coupled again with Boc-phenylalanine to give **26a** as described for **26b**. The resulting lactone was opened to the free acid, disilated, and monodesilated to give **27a**, again as described for **27b**. Chromatography provided 2.4 g of white solid: ^1H NMR (CD_3OD) δ 0.0–0.1 (s + s + s), 0.93 (s) + 0.97 (s), 0.93–1.03 (m), 1.29 (br s), 1.40 (s), 1.5–1.62 (m), 1.70–1.82 (m), 2.06 (s), 2.65–3.20 (m), 3.75 (br m), 4.2 (br), 4.30 (br m), 4.58–4.68 (br m), 7.13 (d), 7.15–7.40 (m); FABMS, m/e 822 (M + 1).

Acid **27a** was coupled to L-leucine benzylamide and the product desilated to give **28a$_1$** and **28a$_2$** using the procedure described for conversion of **27b** to **28b$_1$** + **28b$_2$**, except that the tetrabutylammonium fluoride desilation required 3 days to proceed to completion. A portion (0.26 g) of the chromatographed mixture of diastereomers was separated by preparative HPLC to give **28a$_1$** and **28a$_2$** as amorphous white solids (37 mg and 34 mg, respectively) along with considerable mixed material.

28a$_1$: ^1H NMR (Me_2SO-d_6) δ 0.57 (d, J = 6 Hz), 0.66 (d, J = 6 Hz), 0.8–0.95 (heptet, J = 6 Hz), 1.05–1.19 (m), 1.20–1.45 (m), 1.27 (s), 1.78 (br t, J = 7.5 Hz), 2.47–3.07 (m), 3.93 (br d), 4.02 (q, J = 8 Hz), 4.10 (dt, J_t = 10 Hz, J_d = 4 Hz), 4.44 (br q), 4.48–4.60 (m), 4.97 (br s), 6.86 (d, J = 9 Hz), 6.95–7.50 (m), 7.53 (s), 7.64 (d, J = 8 Hz), 7.88 (d, J = 9 Hz), 7.93 (d, J = 6 Hz); HPLC 96.6% (contains 1.1% of **28a$_2$**); FABMS, m/e 967 (M + 1), 968 (M + 2), 867, 803, 703/4/5, 590. Calcd for amino acid analysis

(μmol/mg): Leu, 1.03; Phe, 3.09. Found: Leu, 1.06; Phe, 3.23.

28a$_2$: ^{1}H NMR (Me_2SO-d_6) δ 0.75 (d, J = 6 Hz), 0.82 (d, J = 6 Hz), 1.08 (s), 1.15 (s), 1.25–1.45 (m), 1.27 (s), 1.45–1.58 (m), 1.58–1.70 (m), 2.48–2.90 (m), 2.99 (dd, J_1 = 14 Hz, J_2 = 5 Hz), 3.81 (br), 4.04–4.22 (m), 4.41 (q), 4.45–4.55 (br m), 4.78 (br s), 6.88 (d, J = 9 Hz), 7.05–7.33 (m), 7.35 (s), 7.69 (d, J = 8 Hz), 7.85–8.00 (m); HPLC 85% (contains 11% *N*-de-Boc'd compound); FABMS, m/e 967 (M + 1), 968 (M + 2), 867, 803, 703/4/5, 590. Amino acid analysis: Calcd (μmol/mg): Leu, 1.03; Phe, 3.09. Found: Leu, 1.03; Phe, 2.96.

Acknowledgment. We gratefully acknowledge the efforts of those who have assisted in this work including Dr. David Cochran and Mrs. Joan Murphy (NMR spectra), Dr. Harri Ramjit and Mr. Brian Haggert (EI mass spectra), Mr. Jack Smith (FAB mass spectra), Mr. John Moreau (CHN determinations), Mrs. Susan Fitzpatrick (amino acid analyses), Dr. Dominic Ip (TGA), and Mrs. Mary Banker (manuscript preparation). We are also indebted to Drs. Mark Bock and Roger Freidinger for valuable comments and suggestions and to Dr. Joshua Boger for a gift of BocACHPA.

Supplementary Material Available: Crystallographic data including tables of the atomic positional and thermal parameters, bond distances, and bond angles for **2b** (3 pages). Ordering information is given on any current masthead page.

Notes

Chiral Synthetic Intermediates via Asymmetric Hydrogenation of α-Methyl-α,β-unsaturated Aldehydes by Bakers' Yeast†

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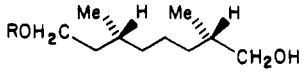
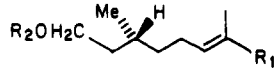
Received December 20, 1984

Microbial-mediated reactions are a useful means of preparing chiral intermediates for synthetic studies.[1] The enantioselective microbial hydrogenation of the double bond in α-[2] or β-methyl-α,β-unsaturated aldehydes[3] (or alcohols or acetals) is well documented: Common baker's yeast appears to be particularly versatile and is easy to use for this purpose.

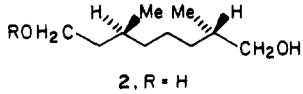
Herein we describe the preparation of (2*S*,6*R*)-2,6-dimethyl-1,8-octanediol (**1**) and of its 6-epimer (**2**) in an enantiomerically pure form by the yeast reduction (*Saccharomyces cerevisiae*) of **3** and **4**, which were prepared in their turn from (*R*)-citronellol (**5**)[4] and from its enantiomer (**6**),[5] respectively. By the same procedure **7** and **8** were obtained starting from the corresponding 8-acetoxy aldehydes **9** and **10** related to citronellyl acetates **11** and **12**.



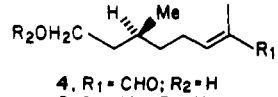
1, R = H
7, R = Ac



3, R_1 = CHO; R_2 = H
5, R_1 = Me; R_2 = H
9, R_1 = CHO; R_2 = Ac
11, R_1 = Me; R_2 = Ac

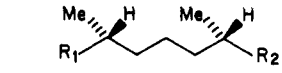


2, R = H
8, R = Ac

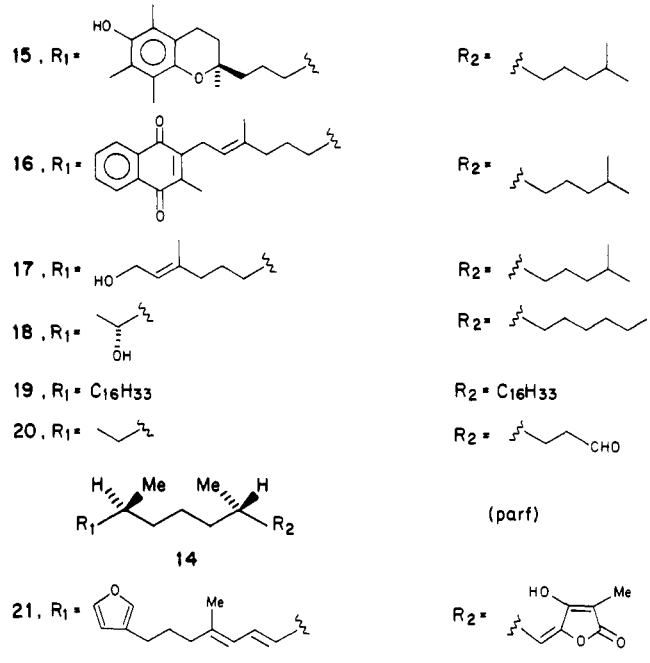


4, R_1 = CHO; R_2 = H
6, R_1 = Me; R_2 = H
10, R_1 = CHO; R_2 = Ac
12, R_1 = Me; R_2 = Ac

A 1,5-dimethylated acyclic unit (**13**, **14**) is present in a number of biologically important natural products: e.g., tocopherols (vitamin E, **15**); phylloquinones (vitamin K_1, **16**); phytol (**17**); insect pheromones of pine sawflies (**18**),[6] of tsetse flies (**19**),[7] and of red flour beetles (**20**);[8] fascicu-



13 (pref)



15, R_1 = ; R_2 =
16, R_1 = ; R_2 =
17, R_1 = ; R_2 =
18, R_1 = ; R_2 =
19, R_1 = $C_{16}H_{33}$; R_2 = $C_{16}H_{33}$
20, R_1 = ; R_2 =

14 (parf)

21, R_1 = ; R_2 =

† This work is dedicated to the memory of Professor Luigi Canonica, deceased unexpectedly (Aug 17 1984).

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(4) (*R*)-(+)-Citronellol was prepared by *S. cerevisiae* reduction of a readily available achiral compound, geraniol (**28**).[3] "Natural citronellal" from Java citronella oil is only 75–80% optically pure (Morrison, J. D. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, pp 2–3).

0022-3263/85/1950-4625$01.50/0