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Dipeptide Analogues: Versatile Synthesis of the Hydroxyethylene Isostere

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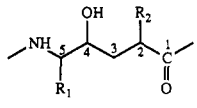
A general synthesis of the hydroxyethylene dipeptide isostere is described. Titanium-mediated condensation of *N*-alkylmethacrylamide dianions with protected α-amino aldehydes followed by pyrolytic cyclization affords key intermediate α-methylenebutyrolactones **7** and **8**. Conjugate addition leads to fully protected analogues **11–14**. Application of the methodology to a variety of dipeptides and the unambiguous determination of stereochemistry is discussed.

The replacement of peptide bonds by isosteres which impart greater activity, selectivity, and stability to peptides with interesting pharmacological properties has received considerable attention in recent years.[1] In the course of our work on inhibitors of aspartic proteinases, we required a general synthesis of dipeptide analogues **1** in which the



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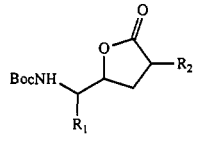

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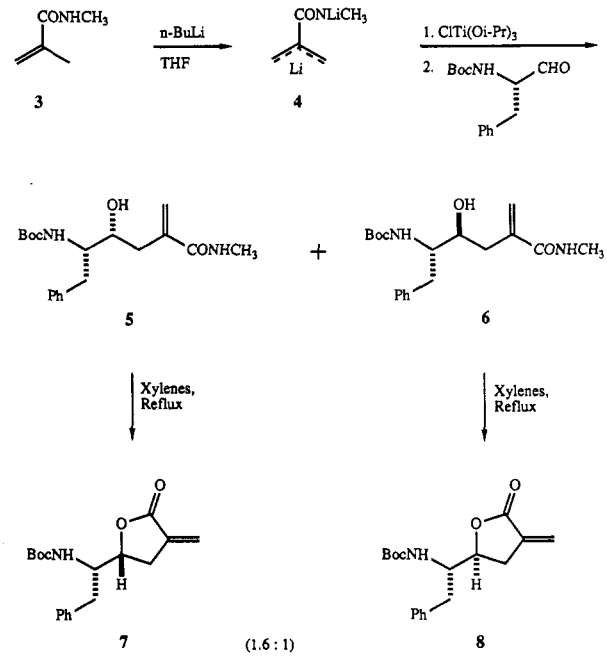
peptide bond has been replaced by the hydroxyethylene isostere. A recent report has described an example of **1** prepared through the intermediacy of lactone **2**.[2a] Our approach, which is complementary to existing methods,[2] involves a rapid, novel route to **2** and allows for wide variation of the two side chains R_1 and R_2 as well as the facile determination and independent control of stereochemistry at each of the three asymmetric centers.

Results and Discussion

In a fashion similar to previous methods,[2] our synthesis employs available amino acids as the source of both the identity and the chirality of the R_1 side chain in **1** as well as C_4 and C_5 of the carbon framework. The remainder of the backbone (C_1–C_3) is efficiently introduced through use of a novel metalation strategy. Finally, the side chain R_2 is appended via conjugate addition, in contrast to existing procedures which employ enolate alkylation to introduce R_2.

Scheme I



The synthesis of key intermediate α-methylene-γ-butyrolactones **7** and **8** is detailed in Scheme I. Dilithiation of *N*-methylmethacrylamide (**3**) with 2 equiv of *n*-butyllithium (THF, 0 °C) proceeds to give the β′-metalated[3] species **4**. Condensation of **4** with the aldehyde derived from Boc-phenylalanine[4] in the presence of chlo-

(1) Recent reviews: (a) Spatola, A. F. *Chem. Biochem. Amino Acids, Pept.; Proteins* **1983**, *7*, 267. (b) Tourwe, D. *Janssen Chim. Acta* **1985**, *3*, 3.

(2) (a) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (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. Am. Pept. Symp. (8th)* **1983**, 579.

(3) (a) Beak, P.; Kempf, D. J.; Wilson, K. D. *J. Am. Chem. Soc.* **1985**, *107*, 4745. (b) Beak, P.; Kempf, D. J. *Ibid.* **1980**, *102*, 4550. (c) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1980**, *45*, 4257.

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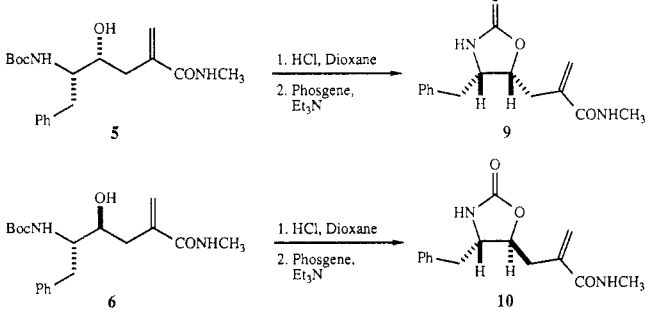
Table I. Preparation of Protected Hydroxyethylene Dipeptide Isosteres 11–17

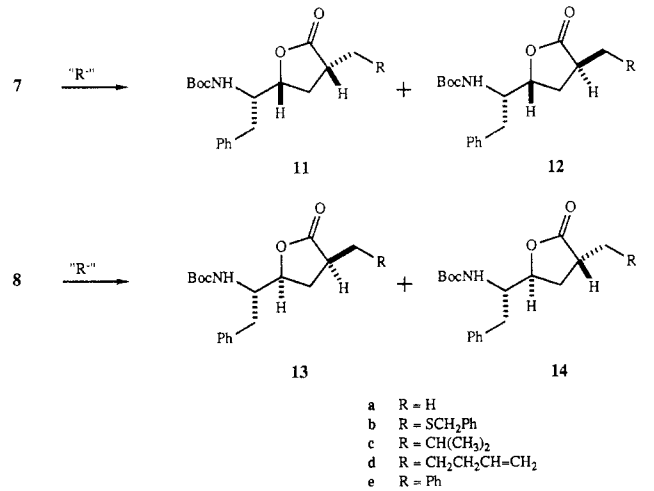
entry	starting material	nucleophile	products	R	ratio	yield,[a] %
1	7	H_2, Pd/C	**11a**	H	>20:1	100
2	8	H_2, Pd/C	**13a**	H	>20:1	100
3	5	H_2, Pd/C	**11a/12a**	H	1:1.2	74
4	6	H_2, Pd/C	**13a/14a**	H	1:1.4	63
5	7	$PhCH_2SH$	**11b/12b**	SCH_2Ph	1.9:1	90
6	8	$PhCH_2SH$	**13b/14b**	SCH_2Ph	3.9:1	93
7	7	$(CH_3)_2CHMgCl$, CuCN	**11c/12c**	$CH(CH_3)_2$	1.1:1	60
8	8	$(CH_3)_2CHMgCl$, CuCN	**13c/14c**	$CH(CH_3)_2$	1:1	84
9	7	$CH_2{=}CHCH_2CH_2MgBr$, CuCN	**11d/12d**	$CH_2CH_2CH{=}CH_2$	1.3:1	49
10	8	$CH_2{=}CHCH_2CH_2MgBr$, CuCN	**13d/14d**	$CH_2CH_2CH{=}CH_2$	1:1.5	54
11	7	$Ph_2Cu(CN)Li_2$	**11e/12e**	Ph	2.7:1	66
12	8	$Ph_2Cu(CN)Li_2$	**13e/14e**	Ph	2.3:1	50
13	13	OH^-	**16/17**		2:1	69[b]

[a] Yields represent isolated, spectrally homogeneous material. [b] Based on 28% yield of recovered intermediates.

Scheme II



Scheme III



a R = H
b R = SCH_2Ph
c R = $CH(CH_3)_2$
d R = $CH_2CH_2CH{=}CH_2$
e R = Ph

rotitanium triisopropoxide affords a ca. 1.6:1 mixture of hydroxy amides **5** and **6** in 79% yield. The addition of the titanium reagent is necessary to ensure clean reaction with the aldehyde. Although the exact role of the titanium is unclear, it appears that mediation of the basicity of **4** is necessary since varying amounts of aldehyde are recovered if the lithium reagent is used directly. Other metal salts such as zinc chloride are equally effective but offer no apparent advantage. Products **5** and **6** can be separated by careful column chromatography and independently characterized. However, it is more expedient to convert the mixture of **5** and **6** in 74% yield to lactones **7** and **8** by heating at reflux in xylenes.[5] Separation of diastereomers by column chromatography is facile at this stage.

The relative stereochemistry of **5** and **6** (and therefore **7** and **8**) is established as shown in Scheme II. Removal of the Boc group in **5** and **6** followed by acylation of the intermediate amino alcohols with phosgene leads to the corresponding oxazolidinones **9** and **10**, respectively. The stereochemistry can be readily assigned by comparison of the ring-proton coupling constants (J_{H4-H5}). Thus, the cis isomer **9** has a coupling constant of 7.5 Hz while the corresponding value in the trans isomer **10** is 5.0 Hz, both in good agreement with literature values.[6] The integrity of the absolute stereochemistry in **7** and **8** is determined by conversion to the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) amides.[7] Removal of the Boc group in **7** followed by reaction with both (+)- and (−)-MTPA chlorides leads to diastereomeric amides. Examination of the crude proton and fluorine NMR spectra of each amide shows no evidence of the other diastereomer whereas the addition of 5% of the (−) isomer to a solution of the (+) isomer is readily apparent. The titanium-mediated condensation of **4** with the protected amino aldehyde is thus estimated to proceed with <1% racemization.

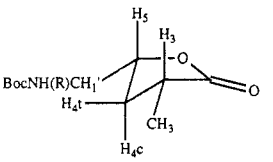


Figure 1. Predominant conformation of **11a**.

With α-methylene lactones **7** and **8** readily available, elaboration of the second side chain R_2 to give the fully protected dipeptide analogues **2** is easily accomplished as shown in Scheme III. The yields and ratios of diastereomers obtained in preparing analogues with a variety of different side chains are given in Table I. Hydrogenation of **7** and **8** leads to the Phe-Ala analogues **11a** and **13a**, respectively, in quantitative yield. As expected, in each case the addition of hydrogen occurs with high stereoselectivity from the less hindered face to give the cis isomer as the only product detected by TLC and ^1H NMR. The corresponding trans isomers **12a** and **14a** can be prepared by nonstereoselective hydrogenation of acyclic precursors **5** and **6**, respectively. Subsequent lactonization of the resulting saturated hydroxy amides leads to mixtures **11a/12a** and **13a/14a** (Table I, entries 3 and 4) which can be chromatographically separated and independently characterized.

The assignment of stereochemistry at C_3 in **11a–14a** is based on extensive decoupling and NOE experiments. A predominant feature of the ^1H NMR spectra of cis isomers **11a** and **13a** is the appearance of a broad quartet (J = 11–12 Hz) at 1.73 ppm, assigned to H_{4c} (Figure 1), which

(4) Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921.
(5) The mixture of **5** and **6** should be passed through a short column of silica gel to remove polar impurities which substantially lower the yield of the subsequent step.
(6) Rich, D. H.; Sun, E. T. O. *J. Med. Chem.* **1980**, *23*, 27.
(7) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

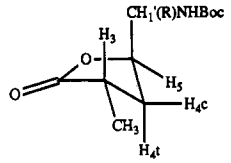


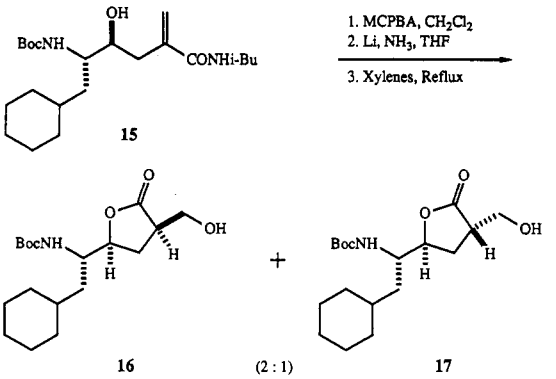
Figure 2. One contributing envelope conformation of **12a**.

results from splitting by one geminal and two vicinal coupling constants of nearly equal value. This general phenomenon (vide infra) is presumbly a consequence of the preponderance of the envelope conformer shown in Figure 1 wherein the two substituents adopt pseudoequatorial positions and thus produce large dihedral angles between H_{4c} and both H_3 and H_5. The vicinal couplings in the spectra of trans isomers **12a** and **14a** are significantly smaller (7–9 Hz) and are consistent with the population of a number of conformations. The stereochemical assignment is corroborated by NOE studies. In particular, irradiation of H_3 in **11a** and **13a** causes an enhancement of the signal corresponding to H_5, establishing a cis relationship between the two substituents. In the trans isomer **12a** (Figure 2), the H_3 resonance is enhanced upon irradiation of $H_{1'}$ while in the spectrum of **14a**, the NH signal is enhanced upon irradiation of H_3. Both of the above observations establish the proximity of the C_5 side chain and H_3 and are thus consistent with a trans relationship of substituents.

Other dipeptide analogues are available by varying the nucleophile. The results are given in Scheme III and Table I. Protected Phe-Cys analogues **11b–14b** are produced in high yield by addition of benzyl mercaptan to **7** and **8**. Copper-catalyzed addition of carbon nucleophiles is also feasible. Treatment of **7** and **8** with isopropylmagnesium chloride and cuprous cyanide affords the Phe-Leu isosteres **11c–14c**. In an analogous fashion, addition of 3-butenylmagnesium bromide[8] leads to **11d–14d**, which are masked forms of Phe-Lys dipeptide analogues, presumably unmasked by ozonolysis and reductive amination. The known[2a] Phe-Phe analogues **11e–14e** are readily prepared from **7** and **8** by reaction with the higher order mixed cuprate $Ph_2CuCNLi$.[9] In each of the above cases, the diastereomeric products can be conveniently separated chromatographically and assigned by analogy to **11a–14a**. For example, the ^1H NMR spectra of **11b** and **13b** contain a broad quartet ($J \approx 12$ Hz) at 1.81 and 1.93 ppm, respectively, identifying each as the cis isomer. Isomers **11c–e** and **13c–e** are assigned in the same fashion. With a few exceptions, there appears to be a small preference for formation of the cis products **11** and **13**. In the cuprate additions (Table I, entries 7–12), this preference probably represents a predisposition for kinetic protonation from the less hindered face of the lactone enolate. In contrast, the ratios in entries 5 and 6 presumably represent thermodynamic control and probably result from the stability of the envelope conformation in cis isomers **11b** and **13b** as indicated in Figure 1.

A variation of the above methodology to produce a serine side chain is shown in Scheme IV. Hydroxy amide **15**, generated from *N*-isobutylmethacrylamide and Boc-cyclohexylalaninal in a manner analogous to the preparation of **5** and **6**, undergoes quantitative epoxidation upon reaction with *m*-chloroperoxybenzoic acid. Reductive opening of the resulting diastereomeric α,β-epoxy amides with lithium in ammonia affords an inseparable mixture of 1,4-diols. Cyclization in the previous fashion (xylenes, reflux) leads to the protected (cyclohexyl)Ala-Ser analogues **16** and **17** in 50% overall yield (69% based on recovered epoxy amide intermediates). As in previous cases, the stereochemistry is readily assigned by the appearance of a broad quartet ($J \approx 12$ Hz) at 2.00 ppm in the ^1H NMR spectrum of **16**.

Scheme IV



The examples above serve to illustrate a new, powerful method for stereocontrolled synthesis of protected dipeptide analogues of general structure **2**, which can be elaborated as previously described[2a] into hydroxyethylene isostere **1**. This methodology should allow access to analogues with a great deal of structural diversity in side chains R_1 and R_2. Although the exclusive production of a single desired diastereomer is not possible in every case, the facile separation and assignment of all possible stereoisomers of **1** will be highly valuable for studies of structure–activity relationships. Extensions of this methodology and its use for the modification of pharmacologically important peptides will be reported in due course.

Experimental Section

^1H NMR spectra were recorded at 300 MHz in $CDCl_3$ using tetramethylsilane as an internal standard. ^{19}F NMR were recorded at 340 MHz in $CDCl_3$ using C_6F_6 as an internal standard. All reactions involving organometallics were performed in flame-dried glassware under an N_2 atmosphere. Tetrahydrofuran and ether were freshly distilled from sodium benzophenone ketyl before use.

(4*R*,5*S*)- and (4*S*,5*S*)-*N*-Methyl-4-hydroxy-5-[[(*tert*-butyloxy)carbonyl]amino]-6-phenylhex-1-ene-2-carboxamide (5 and 6). Boc-phenylalaninal was prepared from Boc-phenylalaninol by a variation of the method of Hamada and Shioiri.[4] Sulfur trioxide–pyridine complex (9.5 g, 60 mmol) was added to 30 mL of Me_2SO and the solution was stirred for 10 min until completely dissolved. The solution was then added to a precooled (0 °C) solution of Boc-phenylalaninol (5.00 g, 19.9 mmol) and triethylamine (8.3 mL, 60 mmol) in 175 mL of dry dichloromethane. After being stirred at 0 °C for 1 h, the mixture was poured into 200 mL of ice water, extracted with one 400-mL and two 200-mL portions of ether, washed consecutively with two 50-mL portions of 10% citric acid, 100 mL of water, 100 mL of saturated $NaHCO_3$, and 100 mL of saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo at 25 °C to give 4.73 g (95%) of a nearly white solid which was used without further purification.

A solution of 3.76 g (38 mmol) of *N*-methylmethacrylamide (**3**) in 350 mL of dry tetrahydrofuran was cooled to −78 °C and treated in a rapid dropwise manner with 31.2 mL (78 mmol) of *n*-butyllithium in hexane. After addition of one-half of the *n*-butyllithium solution, a large amount of white precipitate appeared and it became necessary to manually swirl the mixture until part of the second equivalent was added whereupon the precipitate dissolved to give a yellow solution. After addition was complete, the solution was placed in an ice bath and stirred for 30 min. Subsequently, the red-orange solution was recooled to −78 °C, treated via cannula with 78 mL (78 mmol) of chlorotitanium triisopropoxide in hexane (whereupon the solution became black),

(8) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1978**, *43*, 4247.
(9) Lipshutz, B. H. *Tetrahedron Lett.* **1983**, *24*, 127.

stirred at −78 °C for 15 min, treated with a solution of Boc-phenylalaninal (4.43 g, 19 mmol) in 50 mL of tetrahydrofuran, stirred at −78 °C for 15 min at 0 °C for 30 min, and quenched by addition of 100 mL of 10% citric acid. After dilution with ether and water, the dark mixture was allowed to stir overnight at ambient temperature whereupon the salts became white. After separation, the aqueous layer was extracted with ether and the combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo to a nearly colorless oil. Purification by flash column chromatography using 4:1 ethyl acetate/chloroform gave 0.89 g (13%) of **5** (R_f 0.16, 3:1 ethyl acetate/hexane), 0.60 g (9%) of **6** (R_f 0.21), and 3.76 g (57%) of a 1.6:1 mixture of **5** and **6**, respectively, also containing a small amount of **3**. **5**: ^{1}H NMR δ 1.34 (s, 9 H), 2.41 (dd, J = 14, 9 Hz, 1 H), 2.54 (dd, J = 14, 2 Hz, 1 H), 2.84 (m, 1 H), 2.89 (d, J = 5 Hz, 3 H), 2.98 (dd, J = 14, 4 Hz, 1 H), 3.69 (m, 1 H), 3.82 (m, 1 H), 4.4 (br, 1 H), 4.66 (br d, J = 9 Hz, 1 H), 5.43 (s, 1 H), 5.64 (s, 1 H), 6.28 (br, 1 H), 7.15–7.35 (m, 5 H); IR ($CDCl_3$) 1701, 1500 cm^{-1}; MS, m/e 348 (M^+), 292, 275, 257, 248. Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.15; H, 8.16; N, 8.00.

6: ^{1}H NMR δ 1.38 (s, 9 H), 2.31 (dd, J = 14, 2 Hz, 1 H), 2.49 (dd, J = 14, 9 Hz, 1 H), 2.87 (d, J = 5 Hz, 3 H), 2.89 (br d, J = 8 Hz, 2 H), 3.62 (br d, J = 9 Hz, 1 H), 3.77 (br q, J = 9 Hz, 1 H), 4.8 (br, 1 H), 5.03 (d, J = 10 Hz, 1 H), 5.35 (s, 1 H), 5.52 (s, 1 H), 6.10 (br, 1 H), 7.15–7.3 (m, 5 H); IR ($CDCl_3$) 1701, 1650, 1612, 1496 cm^{-1}; MS, m/e 348 (M^+), 292, 275, 257, 248. Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 64.99; H, 8.10; N, 7.73.

(5*R*,1′*S*)- and (5*S*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]-amino]-2-phenylethyl]-3-methylenedihydrofuran-2(4*H*)-one (7 and 8). A solution of 3.69 g (10.6 mmol) of a 1.6:1 mixture of **5** and **6** in 125 mL of xylenes was heated at reflux under an N_2 atmosphere for 12 h. After cooling, the solvent was removed in vacuo and the crude mixture was separated by flash column chromatography using 3:1 hexane/ethyl acetate to give 1.57 g (47%) of **7** (R_f 0.13, 3:1 hexane/ethyl acetate) and 0.9 g (27%) of **8** (R_f 0.20). **7**: ^{1}H NMR δ 1.37 (s, 9 H), 2.8–2.9 (m, 2 H), 2.95–3.05 (m, 2 H), 3.97 (m, 1 H), 4.47 (m, 2 H), 5.68 (br t, J = 3 Hz, 1 H), 6.29 (br t, J = 3 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1764, 1710, 1501 cm^{-1}; CIMS (NH_3), m/e 335 (M + NH_4), 318 (M + H), 279, 262, 218. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.24; H, 7.33; N, 4.39.

8: ^{1}H NMR δ 1.42 (s, 9 H), 2.85–2.95 (m, 4 H), 4.04 (br q, J = 9 Hz, 1 H), 4.51 (td, J = 7, 1.5 Hz, 1 H), 4.55 (br d, J = 8 Hz, 1 H), 5.61 (br t, J = 3 Hz, 1 H), 6.21 (br t, J = 3 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1764, 1708, 1501 cm^{-1}; MS, m/e 317 (M^+), 261, 244, 226. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.23; H, 7.34; N, 4.37.

(4*S*,5*R*)-4-Benzyl-5-[2-(methylcarbamyl)-2-propenyl]oxazolidin-2-one (9). Hydroxy amide **5** (33 mg, 0.095 mmol) was treated with 0.8 mL of 4 M HCl in dioxane and 0.2 mL of absolute ethanol and allowed to stand at ambient temperature for 30 min. After removal of the solvent in vacuo, the residue was treated with 1 mL of chloroform and concentrated in vacuo to give the hydrochloride salt as a gum. The crude salt was treated with 0.5 mL of chloroform and 70 μL (0.5 mmol) of triethylamine, cooled to 0 °C, treated with 0.7 mL (0.8 mmol) of a solution of phosgene in toluene, and allowed to stir at ambient temperature. After 1.5 h, the mixture was treated with aqueous $NaHCO_3$, stirred for 0.5 h, extracted with ethyl acetate, washed consecutively with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated to a crude oil. Separation by MPLC using ethyl acetate afforded 21 mg (81%) of **9** (R_f 0.12, ethyl acetate): ^{1}H NMR δ 2.55–2.75 (m, 2 H), 2.90 (d, J = 5 Hz, 3 H), 2.85–3.05 (m, 2 H), 4.04 (ddd, J = 11.4, 7.5, 3.3 Hz, 1 H), 4.78 (br, 1 H), 4.89 (ddd, J = 10.7, 7.5, 2.8 Hz, 1 H), 5.55 (s, 1 H), 5.64 (s, 1 H), 6.03 (br, 1 H), 7.15–7.4 (m, 5 H) [Irradiation at 4.04 ppm decoupled the signal at 4.89 ppm to give a doublet of doublets, J = 11, 3 Hz. Irradiation at 4.8. ppm decoupled the signal at 4.04 ppm to give a doublet of doublets, J = 11, 3 Hz]; IR ($CDCl_3$) 1758, 1662, 1622 cm^{-1}; MS, m/e 274 (M^+), 183, 152, 91; exact mass calcd 274.1317, obsd 274.1320.

(4*S*,5*S*)-4-Benzyl-5-[2-(methylcarbamyl)-2-propenyl]oxazolidin-2-one (10). In a manner analogous to the preparation of **9**, 31 mg (0.089 mmol) of **6** was converted to 14.8 mg (61%) of **10** (R_f 0.12, ethyl acetate): ^{1}H NMR δ 2.63 (dd, J = 14, 8 Hz, 1 H), 2.7–2.8 (m, 2 H), 2.86 (d, J = 5 Hz, 3 H), 2.94 (dd, J = 14, 5 Hz, 1 H), 3.76 (dtd, J = 9, 5, 0.5 Hz, 1 H), 4.52 (dt, J = 7.8, 5.0 Hz, 1 H), 5.05 (br, 1 H), 5.45 (s, 1 H), 5.62 (s, 1 H), 5.91 (br, 1 H), 7.15–7.4 (m, 5 H) [Irradiation at 3.76 ppm decoupled the peak at 4.52 ppm to give a doublet of doublets, J = 8, 5 Hz. Irradiation of 4.52 ppm decoupled the peak at 3.76 ppm to give a broad doublet of doublets, J = 9, 5 Hz]; IR ($CDCl_3$) 1756, 1661, 1620 cm^{-1}; MS, m/e 274 (M^+), 183, 152, 91; exact mass calcd 274.1317, obsd 274.1320.

MTPA Amides Derived from 7. Lactone **7** (15 mg, 0.047 mmol) was treated with 0.3 mL of 4 M HCl in dioxane. After 30 min, the solvent was removed in vacuo, and the residue was treated with 0.5 mL of chloroform and concentrated. The resulting crude hydrochloride salt was dissolved in 0.5 mL of dichloromethane, treated sequentially with 21 μL (0.15 mmol) of triethylamine and 9 mL (0.05 mmol) of (+)-MTPA chloride, and stirred for 1 h at ambient temperature. The resulting mixture was partitioned between chloroform and 1 M HCl, washed sequentially with water and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give the crude product. In the same fashion, the amide from **7** and (−)-MTPA chloride was prepared. Examination of both ^{1}H and ^{19}F NMR spectra of each crude amide showed no evidence for the presence of the other diastereomer.

(+)-MTPA amide: ^{1}H NMR δ 2.80 (ddt, J = 18, 6, 3 Hz, 1 H), 2.89 (dd, J = 14, 9 Hz, 1 H), 2.97 (ddt, J = 18, 8, 3 Hz, 1 H), 3.04 (dd, J = 14, 4 Hz, 1 H), 3.15 (q, J_{H-F} = 1.5 Hz, 3 H), 4.42 (m, 1 H), 4.55 (dt, J = 8, 6 Hz, 1 H), 5.67 (t, J = 3 Hz, 1 H), 6.28 (t, J = 3 Hz, 1 H), 6.84 (br d, J = 9 Hz, 1 H), 7.2–7.45 (m, 10 H); ^{19}F NMR δ 93.0.

(−)-MTPA amide: ^{1}H NMR δ 2.80 (dd, J = 14, 10 Hz, 1 H), 2.90 (ddt, J = 18, 6, 3 Hz, 1 H), 3.05 (ddt, J = 18, 8, 3 Hz, 1 H), 3.15 (dd, J = 14, 4 Hz, 1 H), 3.20 (q, J_{H-F} = 1.5 Hz, 3 H), 4.45 (m, 1 H), 4.54 (m, 1 H), 5.72 (t, J = 3 Hz, 1 H), 6.32 (t, J = 3 Hz, 1 H), 6.97 (br d, J = 8 Hz, 2 H), 7.04 (br d, J = 9 Hz, 1 H), 7.0–7.4 (m, 8 H); ^{19}F NMR δ 92.7.

(3*R*,5*R*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-methyldihydrofuran-2(3*H*)-one (11a). A solution of 101 mg (0.32 mmol) of **7** and 15 mg of 10% palladium on carbon in 3 mL of ethyl acetate was stirred vigorously under a H_2 atmosphere for 24 h. The resulting mixture was filtered through Celite and concentrated to give 101 mg (100%) of pure **11a** (R_f 0.11, 3:1 hexane/ethyl acetate) as a single diastereomer: ^{1}H NMR δ 1.28 (d, J = 7.0 Hz, 3 H), 1.38 (s, 9 H), 1.73 (br q, J = 12 Hz, 1 H), 2.45 (ddd, J = 12.7, 8.7, 5.7 Hz, 1 H), 2.66 (ddq, J = 12.0, 8.7, 7.0 Hz, 1 H), 2.9 (m, 1 H), 3.29 (dd, J = 14.0, 4.5 Hz, 1 H), 3.95 (m, 1 H), 4.27 (m, 1 H), 4.45 (br, 1 H), 7.2–7.35 (m, 5 H); IR (KBr) 1775, 1675, 1525 cm^{-1}; MS, m/e 320 (M + 1), 228. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.96; H, 8.23; N, 4.23.

(3*S*,5*R*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-methyldihydrofuran-2(3*H*)-one (12a). In a manner analogous to the preparation of **11a**, 128 mg (0.37 mmol) of **5** was converted to 123 mg (96%) of a mixture of saturated hydroxy amides, a portion (117 mg, 0.33 mmol) of which was heated at reflux in 10 mL of xylenes for 9 h. After removal of the solvent in vacuo, separation by MPLC using 3:1 hexane/ethyl acetate afforded 42 mg (39%) of **12a** (R_f 0.14, 3:1 hexane/ethyl acetate), 34 mg (32%) of **11a**, and 4 mg (3%) of a mixture of **11a** and **12a**. **12a**: ^{1}H NMR δ 1.28 (d, J = 7.0 Hz, 3 H), 1.37 (s, 9 H), 1.92 (dt, J = 13.2, 8.2 Hz, 1 H), 2.37 (ddd, J = 13.2, 9.2, 4.1 Hz, 1 H), 2.75–2.9 (m, 2 H), 3.01 (dd, J = 14.1, 4.3 Hz, 1 H), 3.9 (m, 1 H), 4.31 (td, J = 8.2, 4.1 Hz, 1 H), 4.4 (br, 1 H), 7.2–7.35 (m, 5 H); IR (KBr) 1767, 1753, 1691, 1520 cm^{-1}; MS, m/e 319 (M^+), 263, 246, 228, 220. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.51; H, 8.11; N, 4.30.

(3*S*,5*S*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-methyldihydrofuran-2(3*H*)-one (13a). In a manner analogous to the preparation of **11a**, 101 mg of **8** was converted to 101 mg (100%) of **13a** (R_f 0.17, 3:1 hexane/ethyl acetate) as a single diastereomer: ^{1}H NMR δ 1.26 (d, J = 7.0 Hz, 3 H), 1.39 (s, 9 H), 1.73 (br q, J = 12 Hz, 1 H), 2.28 (ddd, J = 12.8, 9.0, 6.0 Hz, 1 H), 2.64 (m, 1 H), 2.88 (dd, J = 13.6, 8.9 Hz, 1 H), 2.98 (dd, J = 13.6, 7.0 Hz, 1 H), 3.98 (br q, J = 8 Hz, 1 H), 4.34 (ddd, J = 10.2, 6.0, 1.5 Hz, 1 H), 4.65 (br d, J = 10 Hz, 1 H), 7.2–7.35 (m, 5 H); IR (KBr) 1763, 1750, 1688, 1530 cm^{-1}; MS, m/e

320 (M + 1), 228. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.86; H, 8.22; N, 4.23.

(3*R*,5*S*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-methyldihydrofuran-2(3*H*)-one (14a). In a manner analogous to the preparation of **11a**, 125 mg of crude **6** was converted to 100 mg of a mixture of the corresponding saturated hydroxy amides. A solution of the latter in 10 mL of xylenes was heated at reflux for 14 h. After removal of the sovlent in vacuo, separation by MPLC using 9:1 hexane/ethyl acetate gave 34 mg (37%) of **14a** (R_f 0.21, 3:1 hexane/ethyl acetate), and 24 mg (26%) of **13a**. **14a**: ^{1}H NMR δ 1.25 (d, J = 7.0 Hz, 3 H), 1.37 (s, 9 H), 1.86 (ddd, J = 13.2, 8.2, 6.7 Hz, 1 H), 2.38 (ddd, J = 13.2, 9.8, 5.5 Hz, 1 H), 2.71 (m, 1 H), 2.9 (m, 2 H), 4.01 (br q, J = 8 Hz, 1 H), 4.48 (ddd, J = 8.2, 5.5, 1.7 Hz, 1 H), 4.53 (br d, J = 10 Hz, 1 H), 7.2–7.35 (m, 5 H); IR (KBr) 1772, 1685, 1528 cm^{-1}; MS, m/e 319 (M$^+$), 263, 246, 228, 220. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.40; H, 7.80; N, 4.32.

(3*R*,5*R*,1′*S*)- and (3*S*,5*R*,1′*S*)-3-[(Benzylthio)methyl]-5-[1-[[(*tert*-butyloxy)carbonyl]amino]-2-phenylethyl]dihydrofuran-2(3*H*)-one (11b and 12b). A solution of 187 mg (0.59 mmol) of **7**, 90 μL (0.77 mmol) of benzyl mercaptan, and 110 mL (0.77 mmol) of triethylamine in 3 mL of methanol was heated for 3 h at 60 °C. After removal of the solvent in vacuo, the mixture was separated by flash chromatography using 3:1 hexane/ethyl acetate to give 155 mg (59%) of **11b** (R_f 0.42, 2:1 hexane/ethyl acetate) and 81 mg (31%) of **12b** (R_f 0.52), both of which were recrystallized from dichloromethane/hexane. **11b**: ^{1}H NMR δ 1.32 (s, 9 H), 1.81 (br q, J = 12 Hz, 1 H), 2.36 (ddd, J = 13, 9, 6 Hz, 1 H), 2.55 (dd, J = 13, 8 Hz, 1 H), 2.7–2.85 (m, 2 H), 2.9 (m, 2 H), 3.70 (s, 2 H), 3.9 (m, 1 H), 4.26 (m, 1 H), 4.42 (br, 1 H), 7.1–7.3 (m, 10 H); IR (KBr) 1755, 1685, 1522 cm^{-1}; MS, m/e 385 (M − C_4H_8), 368, 341, 324. Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 68.00; H, 7.08; N, 3.17. Found: C, 67.79; H, 7.02; N, 3.01.

12b: ^{1}H NMR δ 1.37 (s, 9 H), 2.1 (m, 1 H), 2.28 (ddd, J = 13, 9, 5 Hz, 1 H), 2.60 (dd, J = 14, 9 Hz, 1 H), 2.8 (m, 1 H), 2.85–3.0 (m, 3 H), 3.75 (s, 2 H), 3.9 (m, 1 H), 4.3–4.4 (m, 2 H), 7.15–7.35 (m, 10 H); IR (KBr) 1790, 1684, 1526 cm^{-1}; MS, m/e 441 (M$^+$), 385, 368, 341, 324. Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 68.00; H, 7.08; N, 3.17. Found: C, 67.62; H, 7.03; N, 3.13.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-3-[(Benzylthio)methyl]-5-[1-[[(*tert*-butyloxy)carbonyl]amino]-2-phenylethyl]dihydrofuran-2(3*H*)-one (13b and 14b). In a manner analogous to the preparation of **11b** and **12b**, 186 mg (0.59 mmol) of **8** was converted to a crude mixture which was separated by flash chromatography using 3:1 hexane/ethyl acetate to give 191 mg (74%) of **13b** (R_f 0.23, 4:1 hexane/ethyl acetate) and 49 mg (19%) of **14b** (R_f 0.32), both of which were recrystallized from dichloromethane/hexane. **13b**: ^{1}H NMR δ 1.39 (s, 9 H), 1.93 (br q, J = 12 Hz, 1 H), 2.24 (ddd, J = 13, 9, 6 Hz, 1 H), 2.57 (dd, J = 13, 8 Hz, 1 H), 2.76 (m, 1 H), 2.8–3.0 (m, 3 H), 3.73 (s, 2 H), 3.98 (br q, J = 9 Hz, 1 H), 4.43 (ddd, J = 10, 6, 1.5 Hz, 1 H), 4.64 (br d, J = 10 Hz, 1 H), 7.2–7.35 (m, 10 Hz); IR (KBr) 1768, 1682 cm^{-1}; MS, m/e 441 (M$^+$), 385, 368, 341. Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 68.00; H, 7.08; N, 3.17. Found: C, 68.05; H, 7.03; N, 3.07.

14b: ^{1}H NMR δ 1.37 (s, 9 H), 2.08 (m, 1 H), 2.32 (m, 1 H), 2.57 (dd, J = 13, 8 Hz, 1 H), 2.8–2.95 (m, 4 H), 3.71 (AA′, 2 H), 4.00 (br q, J = 9 Hz, 1 H), 4.48 (m, 2 H), 7.2–7.35 (m, 10 H); IR ($CDCl_3$) 1765, 1710, 1494 cm^{-1}; MS, m/e 441 (M$^+$), 385, 368, 341. Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 68.00; H, 7.08; N, 3.17. Found: C, 67.81; H, 7.07; N, 3.03.

(3*R*,5*R*,1′*S*)- and (3*S*,5*R*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-isobutyldihydrofuran-2-(3*H*)-one (11c and 12c). A suspension of 5 mg (0.05 mmol) of CuCN in 2.5 mL of ether was cooled to −78 °C, treated with 235 μL (0.47 mmol) of isopropylmagnesium chloride, and allowed to warm to ca. 0 °C whereupon the mixture became homogeneous. After being recooled to −78 °C, the solution was treated dropwise with 49 mg (0.15 mmol) of **7** in 0.3 mL of tetrahydrofuran, stirred for 15 min, and quenched by addition of saturated NH_4Cl. The resulting mixture was partitioned between ether and 1 N NH_4OH, dried over $MgSO_4$, and concentrated in vacuo. Separation by MPLC using 13% ethyl acetate in hexane gave 19 mg (32%) of **11c** (R_f 0.46, 2:1 hexane/ethyl acetate) and 16 mg (28%) of **12c** (R_f 0.50), both of which were recrystallized from dichloromethane/hexane. **11c**: NMR δ 0.90 (d, J = 6 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 1.37 (s, 9 H), 1.6–1.85 (m, 4 H), 2.42 (m, 1 H), 2.62 (m, 1 H), 2.90 (m, 1 H), 3.03 (dd, J = 14, 5 Hz, 1 H), 3.95 (m, 1 H), 4.27 (m, 1 H), 4.43 (br, 1 H), 7.2–7.35 (m, 5 H); IR (KBr) 1775, 1693, 1520 cm^{-1}; MS, m/e 361 (M$^+$), 346, 305, 288, 270. Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 69.74; H, 8.59; N, 3.65.

12c: ^{1}H NMR δ 0.92 (d, J = 6 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 1.37 (s, 9 H), 1.6–1.8 (m, 3 H), 1.93 (m, 1 H), 2.31 (ddd, J = 13, 9, 4 Hz, 1 H), 2.74 (m, 1 H), 2.85 (m, 1 H), 3.02 (dd, J = 14, 4 Hz, 1 H), 3.94 (m, 1 H), 4.33 (m, 1 H), 4.41 (br, 1 H), 7.2–7.35 (m, 5 H); IR (KBr) 1782, 1690, 1525 cm^{-1}; MS, m/e 361 (M$^+$), 305, 288, 270. Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 69.75; H, 8.55, N, 3.63.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-isobutyldihydrofuran-2-(3*H*)-one (13c and 14c). In a manner analogous to the preparation of **11c** and **12c**, 51 mg (0.16 mmol) of **8** was allowed to react with isopropylmagnesium chloride in the presence of CuCN to give, after separation by MPLC using 9:1 hexane/ethyl acetate, 25 mg (42%) of **13c** (R_f = 0.50, 2:1 hexane/ethyl acetate) and 25 mg (42%) of **14c** (R_f 0.55) as colorless oils. **13c**: ^{1}H NMR δ 0.87 (d, J = 6 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 1.40 (s, 9 H), 1.65 (m, 2 H), 1.77 (m, 2 H), 2.25 (ddd, J = 12, 9, 6 Hz, 1 H), 2.60 (m, 1 H), 2.88 (dd, J = 14, 9 Hz, 1 H), 2.99 (dd, J = 14, 7 Hz, 1 H), 3.98 (br q, J = 9 Hz, 1 H), 4.35 (ddd, J = 10, 6, 1.5 Hz, 1 H), 4.65 (br d, J = 10 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1765, 1707, 1500 cm^{-1}; MS, m/e 361 (M$^+$), 346, 305, 288, 270; exact mass calcd 361.2253, obsd 361.2252.

14c: ^{1}H NMR δ 0.88 (d, J = 6 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 1.38 (s, 9 H), 1.66 (m, 3 H), 1.88 (m, 1 H), 2.35 (ddd, J = 13, 10, 5 Hz, 1 H), 2.67 (m, 1 H), 2.90 (br d, J = 8 Hz, 2 H), 4.02 (br q, J = 9 Hz, 1 H), 4.47 (ddd, J = 7, 5, 1.5 Hz, 1 H), 4.55 (br d, J = 9 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1765, 1708, 1596 cm^{-1}; MS, m/e 361 (M$^+$), 346, 305, 288, 270; exact mass calcd 361.2253, obsd 361.2255.

(3*R*,5*R*,1′*S*)- and (3*S*,5*R*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-(4-pentenyl)dihydrofuran-2(3*H*)-one (11d and 12d). A 1 M solution of 3-butenylmagnesium bromide in tetrahydrofuran was prepared according to the procedure of Salomon and Reuter.[8] A suspension of 18 mg (0.2 mmol) of CuCN in 8 mL of tetrahydrofuran was cooled to −78 °C, treated with 1.8 mL (1.8 mmol) of 3-butenylmagnesium bromide, and allowed to warm to ca. 0 °C, whereupon the mixture became homogeneous. After being recooled to −78 °C, the solution was treated dropwise with a solution of 100 mg (0.32 mmol) of **7** in 2 mL of tetrahydrofuran. The resulting solution was stirred at −78 °C for 5 min, warmed to −23 °C for 15 min, and quenched with saturated NH_4Cl. The mixture was partitioned between ether and 1 N NH_4OH, dried over $MgSO_4$, concentrated in vacuo, and separated by MPLC using 3:1 hexane/ethyl acetate to give 33 mg (28%) of **11d** (R_f 0.36, 2:1 hexane/ethyl acetate) and 25 mg (21%) of **12d** (R_f 0.43). **11d**: ^{1}H NMR δ 1.37 (s, 9 H), 1.47 (m, 3 H), 1.74 (br q, J = 12 Hz, 1 H), 1.43 (m, 1 H), 2.09 (br q, J = 7 Hz, 2 H), 2.41 (ddd, J = 13, 9, 6 Hz, 1 H), 2.60 (m, 1 H), 2.88 (m, 1 H), 3.03 (dd, J = 14, 4 Hz, 1 H), 3.94 (m, 1 H), 4.28 (m, 1 H), 4.44 (br d, J = 8 Hz, 1 H), 4.95–5.05 (AA′X, 2H), 5.79 (ddt, J = 17, 10, 7 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1768, 1708, 1498 cm^{-1}; MS, m/e 373 (M$^+$), 317, 300, 272; exact mass calcd 373.2253, obsd 373.2256. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; H, 3.75. Found: C, 70.57; H, 8.60; N, 3.89.

12d: 1.37 (s, 9 H), 1.50 (m, 3 H), 1.85 (m, 1 H), 1.97 (dt, J = 13, 8 Hz, 1 H), 2.09 (br q, J = 7 Hz, 2 H), 2.31 (ddd, J = 13, 9, 4 Hz, 1 H), 2.70 (m, 1 H), 2.83 (m, 1 H), 3.01 (dd, J = 14, 4 Hz, 1 H), 3.93 (m, 1 H), 4.32 (m, 1 H), 4.41 (br d, J = 9 Hz, 1 H), 4.95–5.05 (AA′X, 2 H), 5.78 (ddt, J = 17, 10, 7 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1793, 1687, 1525 cm^{-1}; MS, m/e 373 (M$^+$), 317, 300, 272; exact mass calcd 373.2253, obsd 373.2252.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-(4-pentenyl)dihydrofuran-2-(3*H*)-one (13d and 14d). In a manner analogous to the preparation of **11d** and **12d**, 101 mg (0.32 mmol) of **8** was allowed to react with 3-butenylmagnesium bromide in the presence of CuCN to give, after separation by MPLC using 4:1 hexane/ethyl acetate, 26 mg (22%) of **13d** (R_f 0.15, 4:1 hexane/ethyl acetate) and 39 mg (32%) of **14d** (R_f 0.21) as colorless oils. **13d**: ^{1}H NMR

δ 1.40 (s, 9 H), 1.4–1.5 (m, 3 H), 1.75 (br q, J = 12 Hz, 1 H), 1.89 (m, 1 H), 2.06 (br q, J = 7 Hz, 2 H), 2.23 (ddd, J = 13, 9, 6 Hz, 1 H), 2.57 (m, 1 H), 2.87 (dd, J = 14, 9 Hz, 1 H), 2.99 (dd, J = 14, 7 Hz, 1 H), 3.98 (br q, J = 8 Hz, 1 H), 4.35 (ddd, J = 10, 6, 1.5 Hz, 1 H), 4.65 (br d, J = 9 Hz, 1 H), 4.95–5.05 ($AA'X$, 2 H), 5.77 (ddt, J = 17, 10, 7 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1765, 1709, 1598 cm^{-1}; MS, m/e 317 ($M - C_4H_8$), 300, 282; exact mass calcd (M^+) 373.2253, obsd 373.2252.

14d: ^1H NMR δ 1.39 (s, 9 H), 1.4–1.5 (m, 3 H), 1.80 (m, 1 H), 1.90 (ddd, J = 13, 8, 7 Hz, 1 H), 2.06 (br d, J = 7 Hz, 2 H), 2.34 (ddd, J = 13, 10, 6 Hz, 1 H), 2.62 (m, 1 H), 2.90 (m, 2 H), 4.01 (br q, J = 9 Hz, 1 H), 4.47 (ddd, J = 8, 6, 1.5 Hz, 1 H), 4.54 (br d, J = 9 Hz, 1 H), 4.95–5.05 ($AA'X$, 2 H), 5.76 (ddt, J = 17, 10, 7 Hz, 1 H), 7.2–7.35 (m, 5 H); IR ($CDCl_3$) 1763, 1709, 1598 cm^{-1}; MS, m/e 373 (M^+) 317, 300, 282; exact mass calcd 373.2253, obsd 373.2252. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.66; H, 7.98; N, 3.51.

(3*R*,5*R*,1′*S*)- and (3*S*,5*R*,1′*S*)-3-Benzyl-5-[1-[[(*tert*-butyloxy)carbonyl]amino]-2-phenylethyl]dihydrofuran-2-(3*H*)-one (11e and 12e). A suspension of dry[9] CuCN (64 mg, 0.71 mmol) in 6 mL of ether was cooled to −78 °C, treated with 800 μL (1.42 mmol) of phenyllithium, and allowed to warm to ca. 0 °C, whereupon the mixture became homogeneous. The recooled (−78 °C) solution was treated dropwise with 66 mg (0.21 mmol) of **7** in 0.6 mL of tetrahydrofuran, warmed to −23 °C (CO_2/CCl_4), and stirred for 10 min prior to quenching with saturated NH_4Cl. The mixture was partitioned between ether and 1 N NH_4OH, dried over $MgSO_4$, and concentrated in vacuo. Separation by MPLC using 4:1 hexane/ethyl acetate gave 39 mg (48%) of **11e** (R_f 0.33, 2:1 hexane/ethyl acetate) and 15 mg (18%) of **12e** (R_f 0.38), both of which were recrystallized from dichloromethane/hexane. **11e:** ^1H NMR δ 1.34 (s, 9 H), 1.79 (br q, J = 12 Hz, 1 H), 2.23 (ddd, J = 13, 9, 6 Hz, 1 H), 2.7–2.95 (m, 4 H), 3.28 (dd, J = 14, 4 Hz, 1 H), 3.89 (m, 1 H), 4.28 (m, 1 H), 4.38 (m, 1 H), 7.15–7.35 (m, 10 H); IR (KBr) 1782, 1696, 1513 cm^{-1}; MS, m/e 395 (M^+), 339, 322, 304. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.88; H, 7.40; N, 3.23.

12e: ^1H NMR δ 1.56 (s, 9 H), 2.00 (m, 1 H), 2.17 (ddd, J = 14, 9, 5 Hz, 1 H), 2.81 (m, 2 H), 2.97 (dd, J = 14, 4 Hz, 1 H), 3.06 (m, 1 H), 3.18 (dd, J = 14, 5 Hz, 1 H), 3.90 (m, 1 H), 4.12 (m, 1 H), 4.33 (br, 1 H), 7.15–7.35 (m, 10 H); IR (KBr) 1775, 1685 cm^{-1}; MS, m/e 395 (M^+), 339, 322, 304. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 73.04; H, 7.44; N, 3.40.

(3*S*,5*S*,1′*S*)- and (3*R*,5*S*,1′*S*)-3-Benzyl-5-[1-[[(*tert*-butyloxy)carbonyl]amino]-2-phenylethyl]dihydrofuran-2-(3*H*)-one (13e and 14e). In a manner analogous to the preparation of **11e** and **12e**, 95 mg (0.30 mmol) of **8** was allowed to react with the cuprate derived from phenyllithium and CuCN to give, after separation by MPLC using 12% ethyl acetate in hexane, 42 mg (35%) of **13e** (R_f 0.43, 2:1 hexane/ethyl acetate) and 18 mg (15%) of **14e** (R_f 0.49) as colorless oils. **13e:** ^1H NMR δ 1.40 (s, 9 H), 1.80 (br q, J = 12 Hz, 1 H), 2.07 (ddd, J = 13, 9, 6 Hz, 1 H), 2.69 (dd, J = 13, 9 Hz, 1 H), 2.8–3.0 (m, 3 H), 3.26 (dd, J = 14, 3 Hz, 1 H), 3.94 (br q, J = 9 Hz, 1 H), 4.31 (ddd, J = 10, 6, 1.5 Hz, 1 H), 4.60 (br d, J = 10 Hz, 1 H), 7.1–7.3 (m, 10 H); IR ($CDCl_3$) 1765, 1705, 1492 cm^{-1}; MS, m/e 395 (M^+) 339, 322, 304; exact mass calcd 395.2096, obsd 395.2094.

14e: ^1H NMR δ 1.35 (s, 9 H), 1.96 (m, 1 H), 2.22 (ddd, J = 13, 10, 6 Hz, 1 H), 2.77 (dd, J = 13, 8 Hz, 1 H), 2.85 (m, 2 H), 2.97 (m, 1 H), 3.12 (dd, J = 14, 5 Hz, 1 H), 3.93 (br q, J = 9 Hz, 1 H), 4.20 (m, 1 H), 4.51 (br d, J = 10 Hz, 1 H), 7.1–7.3 (m, 10 H); IR ($CDCl_3$) 1765, 1707, 1492 cm^{-1}; MS, m/e 395 (M^+), 339, 322, 304; exact mass calcd 395.2096, obsd 395.2098.

(4*S*,5*S*)-*N*-Isobutyl-4-hydroxy-5-[[(*tert*-butyloxy)carbonyl]amino]-6-cyclohexylhex-1-ene-2-carboxamide (15). In a manner analogous to the preparation of **5** and **6**, *N*-isobutylmethacrylamide and [[(*tert*-butoxy)carbonyl]cyclohexyl]-alaninal were converted to a mixture of crude hydroxy amides. Partial separation of diastereomers by flash column chromatography using 20% ethyl acetate in chloroform gave a 24% yield of **15** (R_f 0.32, 40% ethyl acetate in chloroform) which was crystallized by trituration with hexane: ^1H NMR δ 0.94 (d, J = 7 Hz, 6 H), 1.1–1.55 (br m, 8 H), 1.44 (s, 9 H), 1.6–1.7 (m, 4 H), 1.8–1.9 (m, 2 H), 2.45 (m, 2 H), 3.11 (dt, J = 13, 7 Hz, 1 H), 3.18 (dt, J = 13, 7 Hz, 1 H), 3.62 (m, 1 H), 3.70 (m, 1 H), 4.55 (br, 1 H), 4.79 (br d, J = 10 Hz, 1 H), 5.44 (s, 1 H), 5.59 (s, 1 H), 6.17 (br t, J = 7 Hz, 1 H); IR (KBr) 1682, 1645, 1601, 1537 cm^{-1}; MS, m/e 396 (M^+), 339, 322, 296. Anal. Calcd for $C_{22}H_{40}N_2O_4$: C, 66.63; H, 10.17; N, 7.06. Found: C, 66.72; H, 10.32; N, 7.02.

(3*R*,5*S*,1′*S*)- and (3*S*,5*S*,1′*S*)-5-[1-[[(*tert*-Butyloxy)carbonyl]amino]-2-phenylethyl]-3-(hydroxymethyl)dihydrofuran-2(3*H*)-one (16 and 17). A solution of 267 mg (0.67 mmol) of **15** and 292 mg (1.4 mmol) of 3-chloroperoxybenzoic acid in 10 mL of dichloromethane was allowed to stand in the dark at ambient temperature for 24 h. After dilution with a few milliliters of ether, the solution was stirred vigorously with 10% aqueous $Na_2S_2O_3$ for 1.5 h, extracted with ether, washed sequentially with 3 N NaOH and saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo to a mixture of epoxy amides (R_f 0.54, 0.48, 3:1 ethyl acetate/chloroform). Lithium wire (ca. 30–40 mg) was added to a precooled (−78 °C) mixture of 10 mL of tetrahydrofuran and ca. 20 mL of ammonia. After being stirred for a few minutes, a solution of the crude epoxy amides in 5 mL of tetrahydrofuran was added dropwise, and the resulting solution was stirred for 6 min at −78 °C before being quenched by cautious addition to a rapidly stirred mixture of ether and saturated NH_4Cl. The product was extracted with 150 mL of ether, dried over $MgSO_4$, and concentrated in vacuo. Separation by flash chromatography using ethyl acetate gave 139 mg (50%, 69% based on recovered starting material) of a mixture of diastereomeric diols (R_f 0.29, 3:1 ethyl acetate/chloroform) as well as 78 mg (28%) of recovered epoxy amides. A solution of 62 mg (0.15 mmol) of the mixture of diols in 5 mL of xylenes was heated at reflux for 2.5 days. After removal of the solvent in vacuo, separation by flash chromatography using 40% ethyl acetate in chloroform afforded 29 mg (57%) of **16** (R_f 0.19, 40% ethyl acetate/chloroform), 13 mg (25%) of **17** (R_f 0.22), and 9 mg (18%) of a ca. 1.3:1 mixture of **16** and **17**. **16:** ^1H NMR δ 0.8–1.0 (m, 2 H), 1.1–1.7 (m, 10 H), 1.44 (s, 9 H), 1.82 (br d, J = 12 Hz, 1 H), 2.00 (br q, J = 12 Hz, 1 H), 2.29 (ddd, J = 13, 9, 6 Hz, 1 H), 2.48 (m, 1 H), 2.87 (m, 1 H), 3.77 (m, 1 H), 3.90 (m, 2 H), 4.46 (m, 2 H); IR (KBr) 2860, 1749, 1708, 1683 cm^{-1}; MS, m/e 341 (M^+), 268, 226, 170; exact mass calcd 341.2202, obsd 341.2203.

17: ^1H NMR δ 0.8–1.0 (m, 2 H), 1.1–1.75 (m, 10 H), 1.45 (s, 9 H), 1.82 (br d, J = 12 Hz, 1 H), 2.2–2.4 (m, 3 H), 2.84 (m, 1 H), 3.76 (m, 1 H), 3.93 (m, 2 H), 4.35 (br d, J = 10 Hz, 1 H), 4.56 (m, 1 H); IR (KBr) 2860, 1765, 1684 cm^{-1}; MS, m/e 341 (M^+), 268, 226, 170; exact mass calcd 341.2202, obsd 341.2206.

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