Transition-State Mimetics for HIV Protease Inhibitors: Stereocontrolled Synthesis of Hydroxyethylene and Hydroxyethylamine Isosteres by Ester-Derived Titanium Enolate Syn and Anti-Aldol Reactions

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Stereocontrolled syntheses of hydroxyethylene dipeptide isostere and aminoalkyl epoxides for hydroxyethylamine isosteres are described. The stereochemistry of both stereogenic centers of the aminoalkyl epoxides **10** and **15** as well as the γ-lactone **17** was assembled by our recently developed highly selective ester-derived titanium enolate aldol reactions. The Ti-enolate of **6** reacted with (benzyloxy)acetaldehyde and cinnamaldehyde to provide the syn-aldol product **7** and anti-aldol product **12**, respectively. Removal of the chiral template followed by Curtius rearrangement of the resulting acid provided the desired amine functionality. The present syntheses represent practical and enantioselective entry to a range of other dipeptide isosteres, which are not limited to amino acid derived substituents.

Ever since the recognition that the virally encoded HIV protease is essential for the replication of infective virus, design and synthesis of protease inhibitors has become the subject of immense interest.[2] Consequently, numerous potent and selective HIV protease inhibitors have been designed based upon the transition-state mimetic concept which incorporates hydroxyethylene and hydroxyethylamine dipeptide isosteres at the scissile site.[3] Recently, three peptidomimetic protease inhibitors incorporating dipeptide isosteres have been approved by the U.S. Food and Drug Administration for the treatment of AIDS.[4] In general, the absolute configuration of the hydroxyl-bearing asymmetric center of these dipeptide isosteres has a pronounced effect on HIV protease inhibitory potencies. Protease inhibitors based upon the hydroxyethylene isostere have shown a distinct preference for the *S*-configuration at the hydroxyl-bearing center.[5] Protease inhibitors with a hydroxyethylamine isostere, however, have shown a marked preference for the *R*-configuration at the hydroxyl group.[6] In either event, stereoselective synthesis of hydroxyethylene or hydroxyethylamine isosteres with defined absolute configuration is very important for biological activity.

It is not surprising that since the first synthesis of these dipeptide mimics, a considerable effort has been devoted to synthesizing these dipeptide isosteres and their structural variants.[7] The majority of previous

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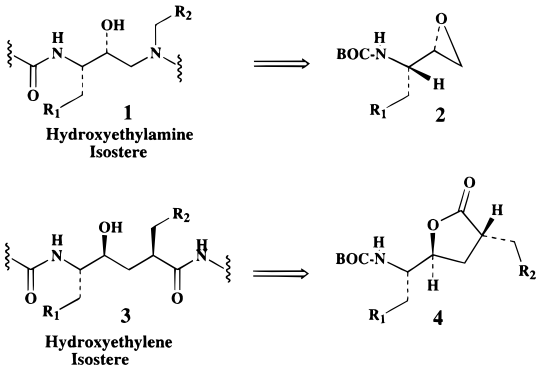
syntheses involved the N-protected L-amino acids as the starting materials.[8] Beside limitations with regard to stereochemical controls at the hydroxyl-bearing centers, these syntheses are confined to natural amino acid derived substitutents. Herein we report the stereocontrolled synthesis of hydroxyethylamine and hydroxyethylene isosteres in which all the stereogenic centers were constructed by asymmetric synthesis. The present synthesis is easily amenable to a range of dipeptide isosteres with a wide variety of substituents that are not limited to natural amino acid derived side chains.[9]

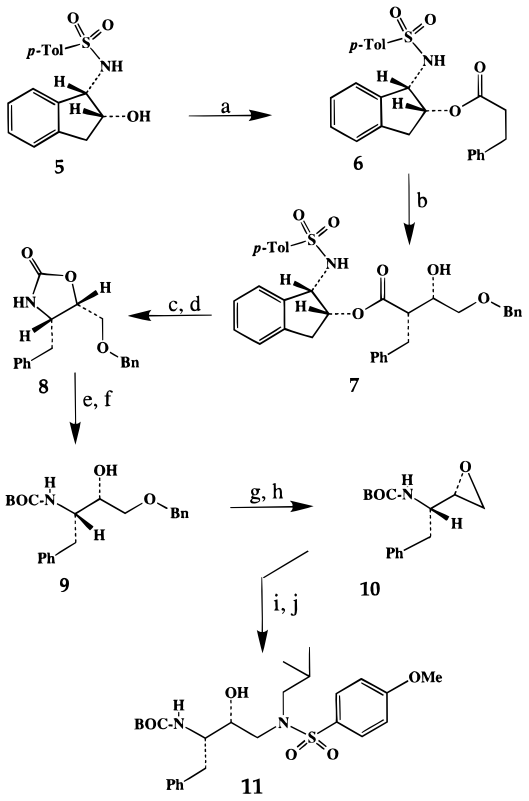
The key element of our synthesis involved the asymmetric aldol reaction to set the C-5 and C-2, C-3 stereogenic centers of the hydroxyethylene and hydroxyethylamine isosteres, respectively. The corresponding C-5 and C-3 amine functionalities were planned to be introduced by a Curtius rearrangement of the resulting β-hydroxy acids.[10] Therefore, stereocontrolled asymmetric syn-aldol and anti-aldol reactions will provide access to appropriate stereochemistry for the synthesis of hydroxyethylamine and hydroxyethylene isosteres, respectively. We recently demonstrated *cis*-1-arylsulfonamido-2-indanyl ester-derived titanium enolate reacts with monodentate and bidentate aldehydes to provide anti-aldol[11] and syn-aldol[12] products with high diastereofacial selectivity. Thus, the syn- or the anti-aldol product will be prepared from the same chiral template depending upon the choice of aldehyde. These aldol reactions have already been shown to be amenable to a variety of side chains.[11,12] The aminoalkyl epoxide **2** is the precursor for the synthesis



of hydroxyethylamine isostere **1**, and the γ-lactone **4** is intermediate for the synthesis of hydroxyethylene dipeptide isostere **3**.[5,6,13]

As shown in Scheme 1, acylation of enantiomerically pure (1*S*,2*R*)-sulfonamide **5**[12] with dihydrocinnamic acid

Scheme 1[a]



[a] Key: (a) dihydrocinnamic acid, 4-DMAP, DCC, CH_2Cl_2, 0 to 23 °C, 85%; (b) $TiCl_4$, *i*Pr_2NEt, then $BnOCH_2CHO$, $TiCl_4$, CH_2Cl_2, −78 °C, 97%; (c) 30% H_2O_2, LiOH, THF:H_2O (3:1), 23 °C, 82%; (d) DPPA, Et_3N, CH_2Cl_2, 23 °C, 92%; (e) aq KOH, EtOH, 70 °C; (f) Boc_2O, CH_2Cl_2, 23 °C, 87%; (g) H_2, $Pd(OH)_2$, EtOAc:MeOH (4:1), 23 °C, quantitative; (h) PPh_3, DEAD, $CHCl_3$, reflux, 61%; (i) $Me_2CHCH_2NH_2$, 2-propanol, reflux, 3−5 h; (j) *p*-MeO-$PhSO_2Cl$, CH_2Cl_2, aq $NaHCO_3$, 23 °C, 83% (from **10**).

with DCC and DMAP afforded the 3-phenylpropionate ester **6** in 85% yield. Generation of titanium enolate of **6** and subsequent reaction with (benzyloxy)acetaldehyde afforded the aldol adduct **7** as a single diastereomer in 97% yield after silica gel chromatography.[12] The chiral auxiliary was removed by exposure to lithium hydroperoxide in aqueous THF at 23 °C for 3 h. The resulting acid was subjected to Curtius rearrangement with diphenylphosphoryl azide and triethylamine in methylene chloride to afford the oxazolidinone **8** in 75% yield (from **7**). The stereochemistry of the oxazolidinone was set by the precedence of the Curtius rearrangement proceeding with retention of configuration at the migrating carbon.[10] Also, the coupling constants of the vicinal protons at C-4 and C-5 of the oxazolidinone, which were established by homonuclear decoupling experiments, are consistent with syn stereochemistry (J_{AB} = 8 Hz).[14] The oxazolidinone **8** was converted to protected amino alcohol derivative **9** by hydrolysis of the oxazolidinone with aqueous KOH at 70 °C followed by reaction of the resulting amine with di-*tert*-butyl dicarbonate in a mixture of CH_2Cl_2 and water in a one-pot procedure (87% yield). Catalytic hydrogenation of benzyl ether **9** over $Pd(OH)_2$/C (Pearl-

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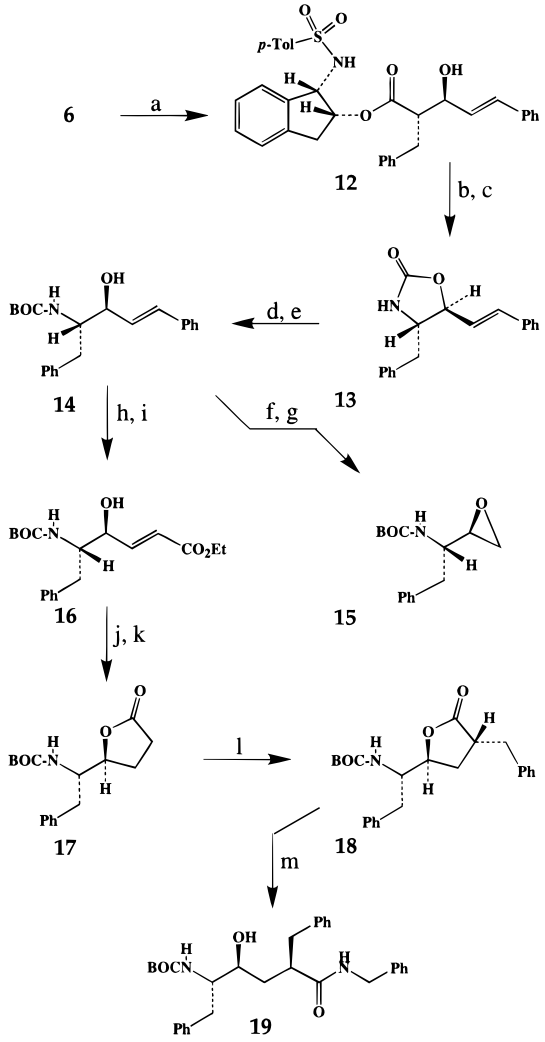
man's catalyst) in a mixture of ethyl acetate and MeOH (4:1) furnished the corresponding diol quantitatively. Exposure of the resulting diol to Mitsunobu reaction conditions with triphenylphosphine and diethyl azodicarboxylate in chloroform afforded the aminoalkyl epoxide **10** in 61% yield after chromatography.[15] Epoxide **10** is the versatile precursor for the synthesis of numerous hydroxyethylamine-derived potent HIV protease inhibitors including recently approved saquinavir.[4c,6,13] Reaction of the epoxide **10** with isobutylamine in 2-propanol at reflux provided the corresponding amino alcohol which, upon reaction with *p*-methoxybenzenesulfonyl chloride, furnished the protected hydroxyethylsulfonamide isostere **11**.[6e]

The synthesis of hydroxyethylene isostere is depicted in Scheme 2. Titanium enolate of **6** was prepared as described previously. Reaction of this enolate with cinnamaldehyde precomplexed with $TiCl_4$ afforded the anti-aldol product **12** exclusively in 48% yield. When the same titanium enolate was reacted with 2.5 equiv of cinnamaldehyde precomplexed with 2.5 equiv of di-*n*-butyl boron triflate, the anti-aldol product **12** was obtained as a major product (6.1:1 mixture ratio by ^{1}H NMR and HPLC) in 68% isolated yield after silica gel chromatography.[16] Removal of the chiral auxiliary, followed by Curtius rearrangement as described above, provided the oxazolidinone **13** in 78% yield from **12**. The vicinal coupling constant of oxazolidinone **13**, which was also established by homonuclear decoupling experiments, is consistent with an anti stereochemical relationship (J_{AB} = 6.3 Hz).[14] At this point, ^{1}H and ^{13}C NMR data showed only a single diastereomer. Basic hydrolysis of **13** and subsequent protection of amine furnished the protected amino alcohol **14**. BOC-protected amino alcohol **14** was converted to aminoalkyl epoxide **15** as well as the γ-lactone **18**, a precursor for the hydroxyethylene isostere. Thus, ozonolytic cleavage of the double bond followed by reductive workup with $NaBH_4$ afforded the corresponding diol.[17] The resulting diol was subjected to Mitsunobu conditions to afford the 2*R*,3*S*-epoxide **15** which has been previouly converted to both hydroxyethylene and hydroxyethylamine isosteres.[5,6,13]

The BOC-derivative **14** was then transformed into the hydroxyethylene isostere. As shown, ozonolytic cleavage of the olefin **14** followed by reductive workup with triphenylphosphine gave the corresponding aldehyde. The crude aldehyde was then subjected to a Horner−Emmons olefination with triethyl phosphonoacetate and sodium hydride to provide the unsaturated ester **16** in 44% yield in a two-step sequence. Catalytic hydrogenation of **16** over 10% Pd/C provided the saturated ester quantitatively. The resulting ester was then lactonized with acetic acid in refluxing toluene to afford the γ-lactone **17** in 68% yield. The lactone **17** is the versatile intermediate for the synthesis of numerous hydroxyethylene isostere-derived HIV protease inhibitors as well as renin inhibitors.[5,8g] For introduction of a suitable substituent at C-5, stereoselective alkylation of a similar lactone has been accomplished previously.[8b] For the preparation of hydroxyethylene Phe-Phe isostere, alkylation of **17** was carried out with lithium hexamethyldisilazide and benzyl iodide in THF at −78 °C to afford the alkylated lactone **18** as the major diastereomer (about 5% cis-alkylation product) which was separated by silica gel chromatography. The reaction of lactone **18** with benzylamine in the presence of trimethylaluminum in CH_2Cl_2 according to Weinreb procedure furnished the hydroxyamide **19** in 72% yield.[18] Compounds **11** and **19** have exhibited enzyme inhibitory potencies of (IC_{50} values) 34 and 75 nM, respectively, in the assay protocol developed by Toth and Marshall.[19] The lactone **18** has been previously

Scheme 2[a]



[a] Key: (a) $TiCl_4$, *i*Pr_2NEt, then (*E*)-PhCH=CHCHO, Bu_2BOTf, CH_2Cl_2, −78 °C, 68%; (b) 30% H_2O_2, LiOH, THF:H_2O (3:1), 23 °C, 85%; (c) DPPA, Et_3N, benzene, reflux, 92%; (d) aq KOH, EtOH, 70 °C; (e) BOC_2O, CH_2Cl_2, 23 °C, 85%; (f) O_3, EtOH, −78 °C, then $NaBH_4$, EtOH, 23 °C, 71%; (g) PPh_3, DEAD, $CHCl_3$, reflux, 88%; (h) O_3, CH_2Cl_2, PPh_3, −78 to 23 °C; (i) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 to 23 °C, 44% (from **14**); (j) H_2, 10% Pd/C, EtOAc:MeOH (1:1), 23 °C, 99%; (k) AcOH, toluene, 110 °C, 68%; (l) LiHMDS, BnI, THF, −78 °C, 77%; (m) Me_3Al, $PhCH_2NH_2$, CH_2Cl_2, 40 °C, 2 h, 72%.

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converted into potent and selective HIV protease inhibitors.[4]

In conclusion, we have achieved convenient and enantioselective syntheses for aminoalkyl epoxides **10** and **15** as well as the substituted γ-lactone **18**. The important utility of these intermediates in the synthesis of various potent HIV protease inhibitors has been previously documented.[2] The key steps of the current synthesis are the ester-derived Ti-enolate-based asymmetric syn- or anti-aldol reaction and Curtius rearrangement of the resulting β-hydroxy acid. The present syntheses should provide access to a structurally diverse class of inhibitors of HIV protease and other important aspartyl proteases. Application of these methods in the synthesis of novel HIV protease inhibitors is currently in progress.

Experimental Section

All melting points are uncorrected. Analytical HPLC analyses were performed on a μBondapak C-18 column, 4.6 mm × 25 cm, 40% CH_3CN/H_2O as solvent, flow rate 1.5 mL/min. Anhydrous solvents were obtained as follows: methylene chloride and chloroform, distillation from CaH_2; tetrahydrofuran, distillation from sodium/benzophenone. All other solvents were HPLC grade. All air-sensitive reactions were run under a N_2 atmosphere. Column chromatography was performed with Whatman 240−400 mesh silica gel under low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

(1*S*,2*R*)-*cis*-*N*-(2,3-Dihydro-2-hydroxy-1*H*-inden-1-yl)-4-methylbenzenesulfonamide (5). To a stirred mixture of optically active (1*S*,2*R*)-1-aminoindan-2-ol (5.00 g, 33.5 mmol), *p*-toluenesulfonyl chloride (6.50 g, 33.6 mmol), and DMAP (0.24 g, 2.4 mmol) in CH_2Cl_2 (200 mL) at 23 °C was added triethylamine (14.0 mL, 101 mmol). The resulting mixture was stirred for 2 h at 23 °C. After this period, the reaction mixture was washed with water, saturated aqueous sodium bicarbonate, and brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded a pale yellow residue, which was recrystallized from $CHCl_3$/hexane to provide the title sulfonamide (9.37 g, 92% yield) as a white solid (mp 135−136 °C). $[\alpha]^{23}_D$ +38.4 (c = 1.12, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ, 1.87 (br s, 1H), 2.46 (s, 3H), 2.88 (dd, 1H, J = 1.5, 16.6 Hz), 3.07 (dd, 1H, J = 4.9, 16.6 Hz), 4.34 (td, 1H, J = 1.6, 5.0 Hz), 4.70 (dd, 1H, J = 4.8, 9.2 Hz), 5.22 (d, 1H, J = 8.7 Hz), 7.08−7.26 (m, 4H), 7.35 (d, 2H, J = 8.2 Hz), 7.88 (d, 2H, J = 8.3 Hz); IR (neat): 3434, 1644, 1430, 1333, 1157 cm^{-1}; mass (EI) m/z 302 (M^+ − H), 148, 130, 103, 91. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.73; H, 6.02; N, 4.42.

(1*S*,2*R*)-*cis*-*N*-[2,3-Dihydro-2-(3-phenyl-1-oxopropoxy)-1*H*-inden-2-yl]-4-methylbenzenesulfonamide (6). To a stirred solution of *N*-tosyl-1-aminoindan-2-ol **5** (2.00 g, 6.57 mmol), DMAP (0.40 g, 3.29 mmol), and dihydrocinnamic acid (0.99 g, 6.57 mmol) in CH_2Cl_2 (30 mL) was added *N*,*N*′-dicyclohexylcarbodiimide (2.03 g, 9.86 mmol) in CH_2Cl_2 (5 mL). The resulting slurry was stirred at 23 °C for 18 h. The slurry was then filtered through a cotton plug and concentrated to afford a residue which was purified by silica gel chromatography to yield the title ester **6** (2.40 g, 85% yield) as a white solid (mp 152−153 °C). $[\alpha]^{23}_D$ −68.9 (c = 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ, 2.43 (s, 3H), 2.50 (t, 2H, J = 7.6 Hz), 2.80 (m, 3H), 3.04 (dd, 1H, J = 5.0, 17.2 Hz), 4.86 (d, 1H, J = 10.3 Hz), 4.95 (dd, 1H, J = 5.0, 10.3 Hz), 5.10 (t, 1H, J = 4.9 Hz), 7.07−7.28 (m, 11H), 7.74 (d, 2H, J = 8.2 Hz); IR (neat): 3503, 3275, 1713, 1643, 1338, 1162 cm^{-1}; mass (EI) m/z 435 (M^+), 355, 302, 130, 91. Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 68.73; H, 6.07; N, 3.51.

(1*S*,2*R*)-*cis*-*N*-(2,3-dihydro-2-((2S,3S)-3-hydroxy-2-(phenylmethyl)-4-(phenylmethoxy)-1-oxobutoxy)-1*H*-inden-1-yl)-4-methylbenzenesulfonamide (7). To a stirred solution of phenylpropionate ester **6** (1.18 g, 2.71 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added a 1 M solution of $TiCl_4$ (3.28 mL, 3.28 mmol, Aldrich) in CH_2Cl_2. The resulting solution was allowed to warm to 23 °C and stirred an additional 15 min. To this solution was added *N*,*N*-diisopropylethylamine (1.79 mL, 10.3 mmol) in a dropwise manner. The mixture was stirred for 2.0 h at 23 °C. In a separate flask, to a stirred solution of (benzyloxy)acetaldehyde (880 mg, 5.85 mmol) in CH_2Cl_2 (30 mL) at −78 °C, was added a 1 M solution of $TiCl_4$ (5.91 mL, 5.91 mmol) in CH_2Cl_2. The resulting mixture was stirred for 30 min at −78 °C, and the above enolate solution was added to the aldehyde solution dropwise via syringe over a period of 5 min. The mixture was stirred at −78 °C for 2 h and then quenched by addition of aqueous ammonium chloride. The resulting mixture was warmed to 23 °C. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude aldol products. Silica gel chromatography of the crude product yielded the title aldol product **7** (1.54 g, 97% yield) as a white solid (mp 97−99 °C). $[\alpha]^{23}_D$ −25.5 (c = 2.51, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ, 2.42 (s, 3H), 2.55 (d, 1H, J = 17.1 Hz), 2.82 (m, 2H), 2.96 (m, 1H), 3.31 (d, 1H, J = 3.7 Hz), 3.43−3.55 (m, 2H), 4.13 (m, 1H), 4.48 (dd, 2H, J = 4.5, 17.2 Hz), 4.84 (dd, 1H, J = 4.8, 9.7 Hz), 5.18 (t, 1H, J = 4.5 Hz), 6.17 (d, 1H, J = 9.8 Hz), 6.92 (m, 2H), 7.18−7.42 (m, 14H), 7.77 (d, 2H, J = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ, 21.5, 31.5, 36.9, 50.1, 59.6, 70.6, 71.5, 73.3, 75.8, 124.3, 124.8, 126.3, 127.0, 127.3, 127.8, 128.3, 128.4, 128.7, 129.7, 137.6, 137.8, 138.5, 138.8, 140.0, 143.4, 171.9; IR: 3420, 3284, 1732, 1337, 1160 cm^{-1}; mass (CI) m/z 584 (M^+ − H), 302, 155. Anal. Calcd for $C_{34}H_{35}NO_6S$: C, 69.72; H, 6.02; N, 2.39. Found: C, 69.38; H, 6.23; N, 2.12.

(4*S*,5*S*)-4-(Phenylmethyl)-5-[(phenylmethoxy)methyl]-2-oxazolidinone (8). To a stirred solution of aldol adduct **7** (1.50 g, 2.56 mmol) in a mixture (3:1) of THF and H_2O (25 mL) were added 30% H_2O_2 (1.74 mL, 15.4 mmol) and LiOH·H_2O (322 mg, 7.68 mmol). The resulting mixture was stirred at 23 °C for 3 h. After this period, 1.5 M aqueous Na_2SO_3 and saturated aqueous sodium bicarbonate were added. The resulting mixture was concentrated under reduced pressure, and the residue was extracted with $CHCl_3$. The aqueous layer was then acidified with 1 N HCl to pH 3 and then extracted thoroughly with $CHCl_3$. This organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield the (2*S*,3*S*)-2-Benzyl-4-(benzyloxy)-3-hydroxybutanoic acid (633 mg, 82.3% yield) as a white solid (mp 96−97 °C). $[\alpha]^{23}_D$ −9.09 (c = 10.1, $CHCl_3$); ^{1}H NMR (200 MHz, CD_3COCD_3): δ, 3.00 (m, 3H), 3.60 (m, 2H), 4.11 (m, 1H), 4.54 (s, 2H), 7.22−7.42 (m, 10 H); ^{13}C NMR (50 MHz, CD_3COCD_3): δ, 33.7, 50.2, 70.4, 71.7, 73.4, 126.4, 127.8, 128.4, 128.9, 137.5, 138.8, 178.3. IR: 3420, 1645, 1239, 1186; mass (EI) m/z 300 (M^+), 149, 91.

To a stirred solution of the above acid (550 mg, 1.83 mmol) in CH_2Cl_2 (25 mL) were added diphenylphosphoryl azide (0.59 mL, 2.75 mmol) and triethylamine (0.38 mL, 2.75 mmol). The mixture was stirred at 23 °C for 48 h, and then the solvent was removed under reduced pressure. The residue was chromatographed over silica gel to afford the title oxazolidinone **8** as an oil (499 mg, 92% yield). $[\alpha]^{23}_D$ −65.4 (c = 0.52, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ, 2.7 (dd, 1H, J = 13.3, 11.1 Hz), 2.95 (dd, 1H, J = 3.5, 13.5 Hz), 3.74 (d, 2H, J = 5.6 Hz), 4.05 (m, 1H), 4.58 (s, 2H), 4.84 (q, 1H, J = 5.6 Hz), 5.83 (br s, 1H), 7.02−7.38 (m, 10H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 36.0, 55.8, 67.5, 73.6, 77.4, 126.9, 127.8, 128.5, 128.9, 137.0, 137.5, 158.5; IR (neat): 3446, 1643, 1071 cm^{-1}; mass (CI) m/z 298 (M^+ + H), 220, 155, 121.

(2*S*,3*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-phenyl-1-(phenylmethoxy)butan-3-ol (9). To a stirred solution of oxazolidinone **8** (470 mg, 1.58 mmol) in 30 mL of EtOH:H_2O (1:1) was added powdered KOH (355 mg, 6.32 mmol). The resulting mixture was heated at reflux for 17 h. The solution was then neutralized to pH = 7 with 1 N HCl, and the

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resulting mixture was concentrated under reduced pressure to a small volume. To the resulting residue was added CH_2Cl_2 (15 mL) followed by di-*tert*-butyl dicarbonate (0.73 mL, 3.16 mmol). The resulting mixture was then stirred at 23 °C for 3 h. After this period, the layers were then separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed over silica gel to yield the title alcohol **9** (493 mg, 87% yield) as a white solid (mp 111−112 °C). $[\alpha]^{23}_D$ −21.7 (c = 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ, 1.40 (s, 9H), 2.90 (d, 2H, J = 4.4 Hz), 3.57 (m, 3H), 3.81 (m, 1H), 4.01 (m, 1H), 4.55 (s, 2H), 5.01 (d, 1H, J = 8.9 Hz), 7.22−7.42 (m, 10H). ^{13}C NMR (100 MHz, $CHCl_3$): δ, 28.3, 36.2, 53.9, 71.6, 71.8, 73.4, 79.2, 126.2, 127.8, 128.3, 128.4, 129.5, 137.8, 138.0, 155.8; IR (neat): 3426, 1689, 1527, 1172 cm^{-1}; mass (EI) m/z 372 (M^+ + H), 280, 180, 120.

2(*S*)-[1′-(*S*)-*N*-((*tert*-Butyloxycarbonyl)amino)-2-phenylethyl]oxirane (10). To a stirred solution of **9** (470 mg, 1.27 mmol) in 15 mL of EtOAc:MeOH (4:1) was suspended 20% $Pd(OH)_2$ (135 mg, 0.25 mmol), and the resulting mixture was hydrogenated under a balloon filled with hydrogen for 12 h. After this period, the reaction mixture was filtered through a Celite pad, and the pad was washed with EtOAc. The filtrate was concentrated under reduced pressure to provide the (2*S*,3*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-benzyl-2-hydroxypropan-1-ol (356 mg, quantitative) as a white solid (mp 118−119 °C). $[\alpha]^{23}_D$ +8.06 (c = 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ, 1.36 (s, 9H), 2.88 (dd, 1H, J = 7.9, 14.1 Hz), 3.06 (dd, 1H, J = 3.8, 14.1 Hz), 3.41 (d, 1H, J = 7.9 Hz), 3.53 (br, 2H), 3.66 (s, 2H), 3.86 (m, 1H), 4.70 (d, 1H, J = 8.7 Hz), 7.22−7.32 (m, 5H); ^{13}C NMR (100 MHz, $CHCl_3$): δ, 28.2, 36.4, 52.4, 63.0, 73.1, 80.2, 126.5, 128.5, 129.4, 137.4, 156.9; IR: 1658, 1536, 1169; mass (EI) m/z 282 (M^+ + H), 120, 57.

To a stirred solution of the above diol (350 mg, 1.24 mmol) and Ph_3P (326 mg, 1.24 mmol) in $CHCl_3$ (25 mL) at 23 °C was added diethyl azodicarboxylate (0.20 mL, 1.24 mmol). The resulting mixture was heated at reflux for 72 h. After this period, the reaction mixture was cooled to 23 °C and then quenched with water. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was purified by silica gel chromatography to furnish the title oxirane **10** (201 mg, 61% yield) as a white solid (mp 121−122 °C). $[\alpha]^{23}_D$ +6.45 (c =1.86, $CHCl_3$); ^{1}H NMR (200 MHz, $CHCl_3$): δ, 1.36 (s, 9H), 2.70−3.00 (m, 5H), 3.68 (m, 1H), 4.67 (d, 1H, J = 7.5 Hz), 7.16−7.33 (m, 5H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 28.2, 37.6, 46.6, 52.6, 53.2, 79.4, 126.5, 128.4, 129.3, 136.8, 155.2; IR (neat): 3387, 2981, 1680, 1546 cm^{-1}; mass (EI) m/z 264 (M^+ − H), 219, 131. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.21; H, 8.07; N, 5.12.

(2*S*,3*S*)-*N*-(2-Methylpropyl)-*N*-[2-hydroxy-4-phenyl-3-(*N*′-*tert*-butyloxycarbonyl)amino]-4-methoxybenzenesulfonamide (11). To a stirred solution of epoxide **10** (110 mg, 0.42 mmol) in 2-propanol (5 mL) was added isobutylamine (0.21 mL, 2.1 mmol), and the resulting solution was heated to 68 °C for 3.5 h. After this period, the reaction mixture was cooled to 23 °C and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL), and 4-methoxybenzenesulfonyl chloride (86.0 mg, 0.42 mmol) followed by concentrated aqueous sodium bicarbonate (1.0 mL) was added. The resulting mixture was stirred at 23 °C for 16 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel to afford the title sulfonamide **11** (177 mg, 83% yield) as a white solid (mp 112−114 °C). $[\alpha]^{23}_D$ +15.6 (c = 2.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ, 0.85 (dd, 6H, J = 6.6, 11.8 Hz), 1.31 (s, 9H), 1.84 (m, 1H), 2.77−2.93 (m, 3H), 2.99 (dd, 1H, J = 4.0, 14.2 Hz), 3.07 (d, 2H, J = 5.6 Hz), 3.75 (m, 2H), 3.82 (s, 3H), 4.74 (d, 1H, J = 8.3 Hz), 6.94 (d, 2H, J = 8.8 Hz), 7.15−7.27 (m, 5H), 7.68 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CHCl_3$): δ, 19.9, 20.0, 27.0, 28.2, 35.4, 53.5, 54.6, 55.5, 58.4, 72.7, 79.5, 114.2, 126.2, 128.3, 129.4, 129.5, 129.9, 137.9, 155.9, 162.9; IR (neat): 1695, 1597, 1496, 1259, 1155 cm^{-1}; mass (EI) m/z, 506 (M^+); HRMS: m/z (M^+) calcd for $C_{26}H_{38}N_2O_6S$, 506.2451, found 506.2466. Anal. Calcd for $C_{26}H_{38}N_2O_6S$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.79; H, 7.75; N, 5.61.

(1*S*,2*R*)-*N*-[2,3-Dihydro-2-((2*S*,2*S*)-(*E*)-3-hydroxy-5-phenyl-2-(phenylmethyl)-1-oxopent-4-enoxy)-1*H*-inden-1-yl]-4-methylbenzenesulfonamide (12). To a stirred solution of ester **6** (2.00 g, 4.59 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a 1 M solution of $TiCl_4$ (5.05 mL, 5.05 mmol) in CH_2Cl_2. The resulting solution was allowed to warm to 23 °C and stirred an additional 15 min. To this solution was then added *N*,*N*-diisopropylethylamine (3.04 mL, 17.4 mmol) dropwise over a period of 5 min, and the mixture was stirred for 2 h at 23 °C and then cooled to −78 °C. In a separate flask, to a stirred solution of cinnamaldehyde (1.45 mL, 11.5 mmol) in dry CH_2Cl_2 (120 mL) at −78 °C was added a 1 M solution of di-*n*-butyl boron triflate (11.5 mL, 11.5 mmol) in CH_2Cl_2. The resulting solution was stirred for 30 min at −78 °C and then added to the above enolate at −78 °C via cannula. The resulting mixture was continued to stir at −78 °C for an additional 1.5 h, MeOH (40 mL), pH 7 buffer (20 mL), and 30% H_2O_2 (10 mL) were added successively, and the mixture was allowed to warm to 23 °C. The resulting mixture was concentrated under reduced pressure to a small volume, and the residue was thoroughly extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a residue which was chromatographed over silica gel to yield the title aldol product **12** (1.80 g, 68% yield) as an inseparable mixture (anti:syn ratio, 6.1:1 by HPLC) of diastereomers, mp = 78−80 °C. ^{1}H NMR (major isomer, 400 MHz, $CHCl_3$): δ, 2.37 (s, 3H), 2.74 (d, 1H, J = 17.1 Hz), 2.81−2.97 (m, 4H), 3.71 (d, 1H, J = 4.4 Hz), 4.37 (m, 1H), 4.81 (dd, 1H, J = 4.8, 9.4 Hz), 5.24 (t, 1H, J = 4.7 Hz), 6.12 (dd, 1H, J = 7.1, 15.9 Hz), 6.55 (d, 1H, J = 15.8 Hz), 6.62 (d, 1H, J = 9.4 Hz), 7.02−7.45 (m, 16H), 7.77 (d, 2H, J = 12.2 Hz); ^{13}C NMR (100 MHz, $CHCl_3$): δ, 21.5, 34.9, 37.1, 53.8, 59.6, 73.4, 75.3, 124.5, 124.8, 126.6, 126.7, 127.2, 127.3, 127.9, 128.3, 128.4, 128.5, 128.7, 128.8, 129.0, 129.7, 132.7, 136.2, 137.5, 138.2, 138.4, 140.2, 143.4, 171.4. IR (neat): 3416, 3028, 2930, 1731, 1633, 1158 cm^{-1}; mass (EI) m/z 549 (M^+ − H_2O), 435, 378, 116, 91. Anal. Calcd for $C_{34}H_{33}NO_5S$: C, 71.93; H, 5.86; N, 2.47. Found: C, 72.23; H, 6.14; N, 2.22.

(4*S*,5*S*)-4-(Phenylmethyl)-5-[(*E*)-phenylvinyl]-2-oxazolidinone (13). To a stirred solution of aldol adduct **12** (1.80 g, 3.14 mmol) at 23 °C in a mixture (3:1) of THF:H_2O (28 mL) were added 30% H_2O_2 (2.14 mL, 18.9 mmol), and $LiOH\cdot H_2O$ (396 mg, 9.43 mmol). The resulting mixture was stirred at 23 °C for 48 h, and the reaction was quenched with 1.5 M aqueous Na_2SO_3 (25 mL). The mixture was concentrated under reduced pressure to a small volume, and the residue was extracted with $CHCl_3$. The aqueous layer was then acidified to pH 3 with 1 N HCl, and the resulting mixture was thoroughly extracted with $CHCl_3$. This organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the (2*S*,3*S*)-(*E*)-2-Benzyl-3-hydroxy-5-phenylpent-4-enoic acid (750 mg, 85% yield) as a white solid (mp 149−151 °C). ^{1}H NMR (200 MHz, CD_3COCD_3): δ, 2.93 (m, 3H), 4.46 (m, 1H), 6.39 (dd, 1H, J = 6.6, 15.9 Hz), 6.66 (d, 1H, J = 15.9 Hz), 7.11−7.44 (m, 10H); ^{13}C NMR (50 MHz, CD_3COCD_3): δ, 35.4, 55.0, 73.8, 126.8, 127.3, 128.2, 129.0, 129.3, 129.7, 130.0, 131.8, 137.8, 140.7, 174.8. IR (neat): 3420, 1704, 1622, 1210 cm^{-1}; mass (EI) m/z 282 (M^+), 133, 91, 55.

To a stirred suspension of the above acid (800 mg, 2.83 mmol) in benzene (30 mL) were added diphenylphosphoryl azide (0.92 mL, 4.25 mmol) and triethylamine (0.59 mL, 4.25 mmol). The resulting solution was heated at reflux for 16 h. The reaction mixture was cooled to 23 °C, washed with saturated aqueous sodium bicarbonate and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and silica gel chromatography of the residue yielded the title oxazolidi-

none **13** (728 mg, 92% yield) as an oil. ^{1}H NMR (200 MHz, $CHCl_3$): δ, 2.93 (m, 2H), 3.87 (m, 1H), 4.84 (m, 1H), 6.07 (ddd, 1H, J = 2.2, 7.0, 15.8 Hz), 6.52 (d, 1H, J = 15.8 Hz), 6.73 (s, 1H), 7.14−7.39 (m, 10H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 40.5, 59.7, 82.0, 124.9, 126.8, 127.1, 128.4, 128.6, 128.8, 129.0, 129.3, 133.8, 135.5, 135.8, 159.1; IR (neat): 1752, 1652, 1383, 981 cm^{-1}; mass (EI) m/z 279 (M^+), 188, 144, 91, 77.

(1*S*,2*S*)-(*E*)-4-[*N*-(*tert*-Butyloxycarbonyl)amino]-1,5-diphenylpent-1-en-3-ol (14). To a stirred solution of oxazolidinone **13** (760 mg, 2.72 mmol) in a mixture (1:1) of EtOH and H_2O (20 mL) at 23 °C was added powdered KOH (610 mg, 10.9 mmol). The resulting mixture was heated at reflux for 19 h. The reaction mixture was cooled to 23 °C and neutralized to pH 7 with 1 N HCl solution. The resulting mixture was concentrated under reduced pressure to a small volume. To the resulting residue was added CH_2Cl_2 (10 mL) followed by di-*tert*-butyl dicarbonate (1.25 mL, 5.44 mmol). The reaction mixture was stirred at 23 °C for 3.5 h. After this period, the layers were then separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed over silica gel to yield the title alcohol **14** (818 mg, 85% yield) as a white solid (mp 114−117 °C). ^{1}H NMR (200 MHz, $CHCl_3$): δ, 1.39 (s, 9H), 2.95 (m, 2H), 3.95 (m, 1H), 4.31 (m, 1H), 5.18 (d, 1H, J = 8.9 Hz), 6.24 (dd, 1H, J = 5.8, 15.8 Hz), 6.60 (d, 1H, J = 16.2 Hz), 7.23−7.36 (m, 10H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 28.2, 37.9, 56.4, 72.2, 79.5, 126.3, 126.5, 127.5, 128.4, 129.4, 129.7, 131.1, 136.7, 138.4, 156.2; IR (neat): 3409, 1683, 1495, 1166 cm^{-1}; mass (EI) m/z 354 (M^+ + H), 220, 164, 120, 57. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.67; N, 3.96. Found: C, 74.53; H, 7.42; N, 3.62.

2(*R*)-[1′-(*S*)-*N*((*tert*-Butyloxycarbonyl)amino)-2-phenylethyl]oxirane (15). To a stirred solution of allyl alcohol **14** (411 mg, 1.16 mmol) in EtOH (100 mL) at −78 °C was bubbled a stream of ozonized oxygen until the blue color persisted (45 min). After the solution was flushed with nitrogen for 5 min, $NaBH_4$ (3.05 g, 11.6 mmol) in EtOH (20 mL) was then added slowly, and the reaction mixture was allowed to warm to 23 °C. The mixture was continued to stir for 1 h, and acetone was added. The reaction mixture was concentrated under reduced pressure to a small volume. The residue was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous sodium bicarbonate and dried over anhydrous Na_2SO_4. Evaporation of the solvents afforded a residue which was chromatographed over silica gel to provide the (2*R*,3*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)-amino]-3-benzyl-2-hydroxypropan-1-ol (232 mg, 71% yield) as a white solid (mp 70−72 °C). $[\alpha]^{23}_D$ −32.5 (c = 1.17, $CHCl_3$); ^{1}H NMR (200 MHz, $CHCl_3$): δ, 1.36 (s, 9H), 2.87 (d, 2H, J = 7.5 Hz), 3.50 (m, 2H), 3.61 (m, 1H), 3.88 (m, 1H), 4.00 (br s, 2H), 5.25 (d, 1H, J = 9.3 Hz), 7.16−7.29 (m, 5H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 28.2, 38.1, 52.6, 63.9, 71.6, 79.7, 126.3, 128.4, 129.2, 138.1, 156.7; IR (neat): 3352, 1695, 1523, 1172 cm^{-1}; mass, (EI) m/z 282 (M^+ + H), 190, 90, 57.

To a stirred solution of the above diol (277 mg, 0.99 mmol) and Ph_3P (260 mg, 0.99 mmol) in $CHCl_3$ at 23 °C was added diethyl azodicarboxylate (0.16 mL, 0.99 mmol). The resulting solution was heated at reflux for 50 h. After this period, the reaction was cooled to 23 °C and quenched with water. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed successively with saturated aqueous sodium bicarbonate and brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvents under reduced pressure gave a residue which was chromatographed over silica gel to furnish the title epoxide **15** (205 mg, 88% yield) as an oil. $[\alpha]^{23}_D$ +2.53 (c = 1.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ, 1.37 (s, 9H), 2.54 (s, 1H), 2.66 (m, 1H), 2.82−3.00 (m, 3H), 4.12 (m, 1H), 4.62 (d, 1H, J = 8.1 Hz), 7.18−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CHCl_3$): δ, 28.2, 39.6, 44.4, 50.4, 52.5, 79.4, 126.5, 128.4, 129.3, 137.3, 155.4; IR (neat): 3338, 1682, 1648, 1247, 1168 cm^{-1}; mass (EI) m/z 264 (M^+ + H), 172, 91, 72, 57. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.10; H, 7.99; N, 5.27.

(4*S*,5*S*)-(*E*)-Ethyl-5-(*N*-(*tert*-butyloxycarbonyl)amino)-4-hydroxy-6-phenylhex-2-enoate (16). To a stirred solution of allyl alcohol **14** (1.20 g, 3.4 mmol) in CH_2Cl_2 (200 mL) at −78 °C was bubbled a stream of ozonized oxygen until the blue color persisted (15 min). After the solution was flushed with nitrogen for 5 min, a solution of Ph_3P (908 mg, 3.46 mmol) in CH_2Cl_2 (5 mL) was then slowly added, and the resulting mixture was allowed to warm to 23 °C. After stirring for 1.5 h, the reaction mixture was concentrated under reduced pressure, and the crude aldehyde was used for next reaction without further purification.

NaH (60% dispersion in mineral oil, 543 mg, 13.6 mmol) was washed with hexanes, then THF (30 mL) was added, and the resulting slurry was cooled to 0 °C. Triethyl phosphonoacetate (2.69 mL, 13.6 mmol) was added at 0 °C, and after stirring for 5 min, the resulting reaction mixture was allowed to warm to 23 °C. The mixture was stirred an additional 40 min at 23 °C and then cooled to 0 °C. The above crude aldehyde in THF (15 mL) was added dropwise in 2 min. The resulting reaction mixture was allowed to warm to 23 °C and stirred for 3 h. After this period, the reaction was quenched with aqueous NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvents under reduced pressure gave a residue which was chromatographed over silica gel to afford the title ester **16** (519 mg, 44% yield for two steps) as a viscous oil. $[\alpha]^{23}_D$ −62.2 (c = 0.45, $CHCl_3$); ^{1}H NMR (200 MHz, $CHCl_3$): δ, 1.23 (t, 3H, J = 7.2 Hz), 1.35 (s, 9H), 2.91 (m, 2H), 3.86 (m, 1H), 4.13 (q, 2H, J = 7.1 Hz), 4.28 (m, 1H), 5.07 (d, 1H, J = 9.0 Hz), 6.07 (dd, 1H, J = 1.4, 15.6 Hz), 6.91 (dd, 1H, J = 4.0, 15.6 Hz), 7.14−7.29 (m, 5H). ^{13}C NMR (50 MHz, $CHCl_3$): δ, 14.1, 28.1, 37.4, 55.8, 60.3, 70.7, 79.6, 121.4, 126.4, 128.4, 129.2, 138.0, 148.2, 156.0, 166.4; IR (neat): 2981, 1749, 1672, 1367, 1165 cm^{-1}; mass (EI) m/z 350 (M^+ + H), 164, 120, 91, 57.

(5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butyloxycarbonyl)amino]-2′-phenylethyl]dihydrofuran-2(3*H*)-one (17). To a stirred solution of ester **16** (518 mg, 1.48 mmol) in a mixture (1:1) of EtOAc and MeOH (60 mL) was suspended 10% Pd/C (150 mg), and the resulting mixture was stirred under a balloon filled with hydrogen for 18 h. After this period, the catalyst was filtered off through a Celite pad, and the pad was washed with EtOAc. The filtrate was concentrated to yield the corresponding saturated ester (513 mg, 99% yield) as a white solid (mp 100−104 °C). $[\alpha]^{23}_D$ −17.2 (c = 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ, 1.19 (t, 3H, J = 7.1 Hz), 1.38 (s, 9H), 1.71 (m, 1H), 1.82 (m, 1H), 2.40 (m, 2H), 2.87 (m, 2H), 3.56 (m, 1H), 3.70 (m, 1H), 4.06 (q, 2H, J = 7.1 Hz), 5.01 (d, 1H, J = 9.1 Hz), 7.16−7.28 (m, 5H); ^{13}C NMR (100 MHz, $CHCl_3$): δ, 14.0, 28.2, 29.5, 31.0, 38.4, 56.0, 60.5, 70.9, 79.2, 126.2, 128.3, 129.2, 138.4, 156.1, 174.4; IR (neat): 2982, 1771, 1691, 1367, 1046; mass (EI) m/z 352 (M^+ + H), 260, 160, 114, 91.

To a stirred suspension of the above saturated ester (513 mg, 1.46 mmol) in toluene (15 mL) was added glacial acetic acid (0.44 mL, 7.74 mmol), and the mixture was heated at reflux for 5.5 h. The reaction mixture was cooled to 23 °C, and the solvents were removed under reduced pressure to provide a residue which was chromatographed over silica gel to yield the title lactone **17** (306 mg, 68% yield) as a white solid (mp 88−89 °C). $[\alpha]^{23}_D$ −4.1 (c = 0.73, $CHCl_3$); ^{1}H NMR (200 MHz, $CHCl_3$): δ, 1.36 (s, 9H), 2.09 (m, 2H), 2.48 (m, 2H), 2.89 (m, 2H), 3.98 (m, 1H), 4.45 (td, 1H, J = 1.3, 7.5 Hz), 4.78 (m, 1H), 7.15−7.31 (m, 5H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 24.0, 28.1, 28.6, 39.2, 54.0, 79.7, 79.9, 126.6, 128.5, 129.2, 137.2, 155.8, 177.1; IR (neat): 2979, 1759, 1682, 1647, 1169 cm^{-1}; mass (EI) m/z 305 (M^+), 214, 114, 91, 57. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.93; H, 7.82; N, 4.28.

(3*R*,5*S*,1′*S*)-5-[1′-[*N*-(*tert*-Butyloxycarbonyl)amino]-2′-phenylethyl]-3-(phenylmethyl)dihydrofuran-2(3*H*)-one (18). To a stirred solution of lactone **17** (115 mg, 0.38 mmol) in THF (2 mL) at −78 °C was added a 1 M solution of lithium bis(trimethylsilyl)amide (Aldrich, 0.75 mL, 0.75 mmol) in THF. After stirring for 0.5 h, benzyl iodide (82 mg, 0.38 mmol) in

THF (2 mL) was added. The resulting solution was stirred for 30 min, propionic acid (0.2 mL) was added, and the reaction mixture was stirred at −78 °C for 5 min. The mixture was then allowed to warm to 23 °C, and 10% citric acid and EtOAc were added. After separating the layers, the aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous Na_2SO_4, and concentrated. Silica gel chromatography of the residue yielded the title alkylated lactone **18** (115 mg, 77% yield) as a white solid (mp 75−77 °C). $[\alpha]^{23}_D$ −40 (c = 0.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CHCl_3$): δ, 1.36 (s, 9H), 1.97 (m, 1H), 2.23 (m, 1H), 2.81 (m, 3H), 2.97 (m, 1H), 3.12 (dd, 1H, J = 4.2, 13.2 Hz), 3.95 (q, 1H, J = 8.4 Hz), 4.22 (td, 1H, J = 0.8, 6.6 Hz), 4.84 (d, 1H, J = 9.7 Hz), 7.12−7.30 (m, 10 H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 28.1, 29.2, 36.8, 38.8, 41.2, 54.5, 78.4, 79.7, 126.6, 126.8, 128.5, 128.6, 128.8, 129.2, 137.2, 137.8, 155.8, 179.0; IR (neat): 1767, 1710, 1151; mass (EI) m/z 395 (M^+), 204, 120, 91, 57.

(2*R*,5*S*,6*S*)-2,*N*-Bis(phenylmethyl)-4-hydroxy-[5-*N*′-(*tert*-butyloxycarbonyl)amino]-6-phenylhexanamide (19). To a stirred solution of benzylamine (0.10 mL, 0.96 mmol) in CH_2Cl_2 (6 mL) at 23 °C was added a 2 M solution of trimethylaluminum (Aldrich, 0.48 mL, 0.96 mmol) in heptane. After stirring 10 min, a solution of lactone **18** (190 mg, 0.48 mmol) in CH_2Cl_2 was added, and the resulting solution was heated to 40 °C for 2.5 h. After this period, the reaction mixture was cooled to 23 °C and quenched with 1 N HCl (8 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with concentrated aqueous sodium bicarbonate and brine, dried over Na_2SO_4, and concentrated. Silica gel chromatography of the residue yielded the title amide **19** (173 mg, 72% yield) as a white solid (mp 179−180 °C). $[\alpha]^{23}_D$ −17.6 (c = 1.08, $CHCl_3$); ^{1}H NMR (200 MHz, $CHCl_3$): δ, 1.24 (s, 9H), 1.68 (m, 2H), 2.50−2.90 (m, 6H), 3.62 (m, 2H), 3.99 (dd, 1H, J = 4.7, 14.9 Hz), 4.30 (dd, 1H, J = 6.5, 14.9 Hz), 5.01 (d, 1H, J = 9.2 Hz), 6.54 (t, 1H, J = 5.4 Hz), 6.81−7.26 (m, 15H); ^{13}C NMR (50 MHz, $CHCl_3$): δ, 28.1, 37.0, 38.0, 38.4, 43.0, 45.9, 55.9, 68.4, 79.0, 126.0, 126.9, 127.3, 128.2, 128.7, 129.0, 129.2, 129.5, 137.9, 138.5, 139.4, 156.2, 175.2; IR (neat): 1670, 1626, 1524, 1248 cm^{-1}; mass (EI) m/z, 502 (M^+), 411, 355, 282; HRMS: m/z (M^+) calcd for $C_{31}H_{38}N_2O_4$, 502.2832, found 502.2839. Anal. Calcd for $C_{31}H_{38}N_2O_4$: C, 74.08; H, 7.62; N, 5.57. Found: C, 73.71; H, 7.55; N, 5.66.

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Supporting Information Available: ^{13}C NMR spectra for compounds **8**, **9**, **13**, **18** and ^{1}H NMR spectrum for compound **16** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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