Synthesis of Optically Active 4-Substituted 2-Aminobutyrolactones and Homoserines by Combined Aldol/Photocyclization Reactions of Chromium Aminocarbene Complexes

Carsten Schmeck and Louis S. Hegedus*

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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Abstract: Aldol reactions of optically active chromium aminocarbene complexes proceeded with moderate to high diastereoselectivity. Photolysis of the aldol product gave optically active 4-substituted 2-aminobutyrolactones which could be hydrolyzed to γ-hydroxy-α-amino acids. Using this procedure, (+)-bulgecenine was synthesized.

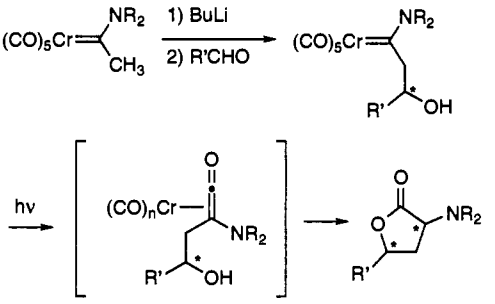
Introduction

The γ-hydroxy-α-amino acid fragment is found in a number of biologically active peptides including the antifungal agents theonellamide F[1] and neopolyoxins,[2] the antibiotic WS-43708A,[3] the bulgecin glycopeptide antibiotics,[4] and the calcium antagonist scytonemin A.[5] It occurs naturally in the mushroom *Boletus santanas*.[6] The related 4-substituted α-aminobutyrolactones have been used as intermediates in the synthesis of the β-lactam antibiotic clavalanine.[7] The widespread occurrence of this structural unit has led to the development of a number of stereoselective synthetic approaches.[8]

Research in these laboratories has centered on the development of photochemical reactions of optically active chromium aminocarbene complexes for the synthesis of α-amino acids[9] and peptides.[10] These reactions are thought to proceed through reactions of nucleophiles with a photogenerated ketene complex,[11] and both inter- and intramolecular trapping of these reactive intermediates has been developed. α-Carbanions of optically active (prolinol-derived) aminocarbene complexes undergo asymmetric Michael reactions with conjugated enones with fair to excellent enantioselectivity (~60–95% enantiomeric excess (ee)),[12] and those of achiral (dimethylamino)carbene complexes undergo aldol reaction with high diastereoselectivity using chiral aldehydes.[13] One of these aldol products was photolyzed to give a modest yield of the α-aminobutyrolactone. Below, we describe the asymmetric aldol condensation/photolysis of optically active chromium aminocarbene complexes to produce 4-substituted α-aminobutyrolactones with fair to excellent diastereoselectivity.

Results and Discussion

The general approach developed is shown in eq 1. For this approach to be of use, a high degree of stereoselectivity in both the aldol reaction step and the photocyclization step must be achieved. Control of *absolute* stereochemistry in aldol reactions



(1)

with chromium carbene complexes has not previously been reported, nor have the effects of chirality resident in the nucleophilic terminus in an intramolecular photocyclization been thoroughly examined. Previous experience[9,10] suggested that a chiral oxazolidine auxiliary on the carbene complex could control the absolute stereochemistry of the α-amino position in the resulting lactone, but its effect on the stereoselectivity of the aldol reaction was unknown.

The aldol reaction between oxazolidinyl carbene complex (*S*)-**1** and benzaldehyde produced two aldol products in a 92:8 ratio (Scheme 1, entry 1). Irradiation of this crude reaction mixture produced two lactones, (*S*,*R*,*R*)-**2a** and (*S*,*S*,*S*)-**2b**, which were

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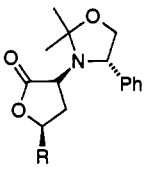
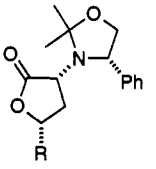
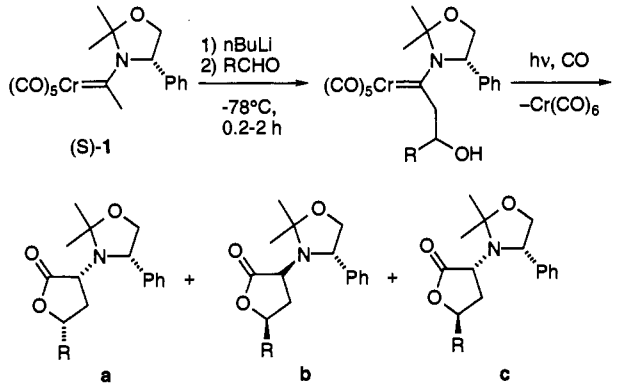
Table 1. Comparison of the ^1H NMR Spectra of Substituted Aminobutyrolactones





	R	H_A	H_B	Δδ	Me_A	Me_B	Δδ	H_A	H_B	Δδ	Me_A	Me_B	Δδ
2	Ph	1.66	2.36	0.70	1.48	1.48	0	2.32	2.54	0.22	1.38	1.54	0.16
3	*P*-(MeO)Ph							2.30	2.48	0.18	1.37	1.54	0.17
4	furyl							2.44	2.75	0.31	1.46	1.57	0.11
5	*t*-Bu							2.00	2.08	0.08	1.35	1.51	0.16
6	Me	1.16	2.11	0.95	1.44	1.45	0.01	1.96	2.26	0.28	1.36	1.50	0.14
7	*i*-Pr	1.98	1.30	0.68	1.44	1.46	0.02	2.02	2.13	0.11	1.36	1.51	0.15
8	vinyl	1.34	2.15	0.81	1.44	1.45	0.01	2.13	2.32	0.19	1.36	1.51	0.15
9	D-glyceryl	1.47	2.20	0.73	1.43	1.45	0.02	2.11	2.34	0.23	1.36	1.50	0.14

Scheme 1[a]



entry	R	yield (%)[a]		a	b	c
1	C_6H_5	78	2	92	8	---
2	$(p\text{-OMe})C_4H_6$	39[b]	3	100	---	---
3	2-furyl	44	4	100	---	---
4	$C(CH_3)_3$	32(50)[c]	5	100	---	---
5	Me	61	6	22	67	11
6	$CH(CH_3)_2$	59	7	22	68	10[d]
7	$CH{=}CH_2$	37[e]	8	41	41	18

[a] Combined yield of separated, isolated, pure diastereoisomers. [b] Aldol product was purified before photolysis; yield for the aldol reaction 53%, yield for the photolysis 74%. [c] The aldol reaction was stirred at 0 °C for 4 h under artificial light. After recooling to -78 °C and quenching, only the lactone and starting carbene were isolated. [d] Ratio determined by GC. [e] Aldol reaction was carried out at −100 °C.

separated and isolated in yields of 72% and 6%, respectively. From ^1H NMR spectroscopy each appeared to have the same relative *cis* disposition of the amino and phenyl groups,[14] but they were clearly isomers of each other. The major diastereoisomer was assigned as the (*S*,*R*,*R*)-**2a** from an X-ray crystal structure, and its ^1H NMR spectrum was consistent with this, compared with other members of the series (see below). Uniformly, the *cis*-lactones having 2*R* absolute configuration have the oxazolidine methyl group signals separated by ~0.15 ppm and the lactone CH_2 signals by ~0.2 ppm, while the *cis* 2*S* series have the oxazolidine methyl signals coincident and the lactone CH_2 signals separated by ~0.6–0.9 ppm (Table 1).

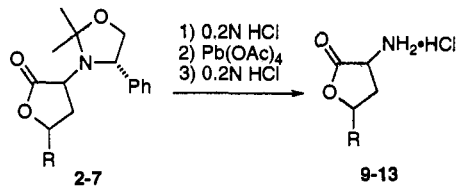
With benzaldehyde as substrate, the chiral auxiliary on nitrogen was relatively efficient at inducing stereochemistry in the aldol step, the reaction having a diastereomeric excess (de) of 84%, with the (*S*)-oxazolidine inducing the *R* absolute configuration at the aldol center (diastereoisomer **2a**). The same sense of asymmetric induction was observed with other aromatic aldehydes (entries 2 and 3) and with pivaldehyde (entry 4), for which single *cis* diastereoisomers **3a–5a** were obtained. In intermolecular photochemical reactions, it is the absolute configuration of the oxazolidine group on the carbene carbon which controls the absolute configuration of the newly formed stereogenic center, with the *S* complex inducing α*R* stereochemistry regardless of the absolute configuration of the attacking nucleophile.[9,10] For lactones **2–5** this was also the case, and the major (sole) diastereoisomer of the lactone had the expected α*R* absolute configuration.

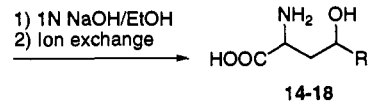
Remarkably, with acetaldehyde, 2-methylpropanal, and acrolein, the sense of asymmetric induction in the aldol reaction was *reversed, as was the sense of asymmetric induction in the photocyclization*! For these substrates the *other cis* diastereoisomeric lactone (**b** series) having 2*S* absolute configuration was the major product, along with smaller amounts of the (2*R*)-lactone (**a** series) and even a small amount of a *trans* isomer. The absolute configurations of lactones **6b–8b** were assigned as in Table 1. These results imply that it is the absolute configuration of the *aldol* center which controls the absolute configuration of the cyclization step, since for lactones **6–8** the absolute configuration at the 2-position is opposite that expected for the (*S*)-oxazolidinone. This places lactones **6–8** in the mismatched series, since the aldol center and the oxazolidine center have conflicting rather than reenforcing senses of asymmetric induction, accounting for the overall lower stereoselectivity, and the formation of some of the *trans* isomer. Lactones **2–5** thus represent matched cases, wherein both centers induce the same sense of chirality at the α-position.

Lactones **2a**, **3a**, **5a**, **6b**, and **7b** were converted to the free amino lactones **9–13** by hydrolysis of the oxazolidine followed by oxidative cleavage of the intermediate amino alcohol. Hydrolysis under basic conditions followed by purification by ion exchange gave the γ-hydroxy-α-amino acids **14–18** in excellent yield (eq 2). These transformations confirmed the assignments of the absolute configurations of lactones **6a** and **6b**. Amino acid **17** and lactone **12** had identical ^1H NMR spectra and similar specific rotations to those reported[6] for (2*S*,4*R*)-(−)-γ-hydroxynorvaline (reported $[\alpha]_D$ −35.5°, found −32.8°) isolated from the mushroom *B. santanas*, confirming the 2*S*,4*R* assignment for **6b** and for the corresponding (2*S*,4*R*)-(−)-lactone (reported $[\alpha]_D$ −3.0°, found −2.4°). The lactone and γ-hydroxyamino acid derived from **6a** had identical physical properties, but specific rotations were equal but opposite in sign to those derived from **6b**, confirming the enantiomeric 2*R*,4*S* assignment.

The effect of a chiral center resident on the aldehyde was next addressed. Wulff[13] has shown that the simple chromium (dimethylamino)methylcarbene complex underwent aldol reaction with racemic 2-phenylpropanal with high diastereoselectivity

(14) The use of ^1H NMR spectroscopy to assign relative (*cis–trans*) stereochemistry in 2,4-disubstituted γ-butyrolactones has been extensively studied. For example, see ref 6, and 8a and Tayyeb Hussain, S. A. M.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480.





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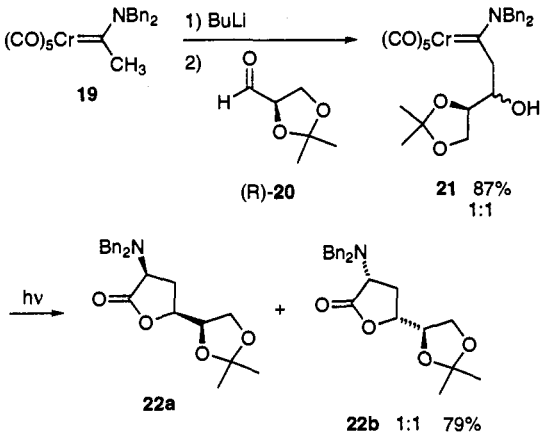
R		yield (%)		yield (%)	
2a - C_6H_5	(2R,4R)	**9**	80	**14**	93
3a - (p-OMe)C_4H_6	(2R,4R)	**10**	78	**15**	---
5a - $C(CH_3)_3$	(2R,4R)	**11**	89	**16**	86
6b - CH_3	(2S,4R)	**12**	67	**17**	92
7b - $CH(CH_3)_2$	(2S,4S)	**13**	79	**18**	91

(>40:1) and with racemic 2-methyl-3-phenylpropanal with considerably less (~4:1) diastereoselectivity. In marked contrast to these results chromium (dibenzylamino)methylcarbene complex **19** underwent aldol reaction with (*R*)-glyceraldehyde acetonide **20** with *no* diastereoselectivity, producing a 1:1 mixture of diastereoisomers of carbene complex **21** in excellent yield. Photolysis of this mixture gave an easily separated 1:1 mixture of *cis* α-amino lactones **22** (eq 3).

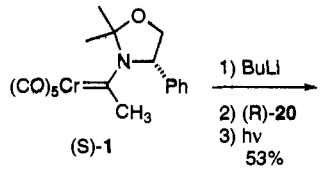


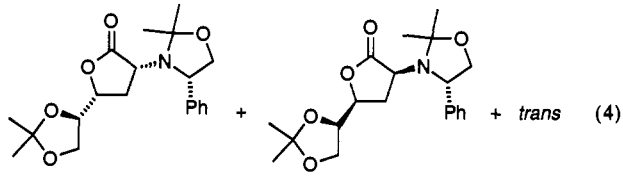
(3)

Aldol reactions of (*R*)-aldehyde **20** with optically active aminocarbene complexes (*S*)-**1** and (*R*)-**1** were somewhat more selective, giving a ~6:2:1 mixture of the expected *cis*- and *trans*-lactones (eqs 4 and 5). (The absolute configurations were again assigned on the basis of NMR spectroscopy; see Table 1.) Presumably, starting with (*S*)-glyceraldehyde acetonide, the complementary set of *cis*-aminolactones would be available, making all four *cis* diastereoisomers readily available in a few steps.

Provided the functional groups in **23** and **24** can be manipulated independently, these compounds should be useful intermediates for the synthesis of all epimers of bulgecinine[15,16] in a relatively direct manner. As shown in eq 6 such functional group manipulations are possible.

Although less elegant, the most direct access to the bugecinine family is via the chemistry in eq 3. Achiral carbene complex **19** is easily synthesized in high yield on a large scale. The aldol reaction and photocyclizations are efficient, and the diastereoisomers **22a** and **22b** are easily separated. Compound **22b** was converted to (+)-bulgecinine (**30**) in five steps (seven overall)





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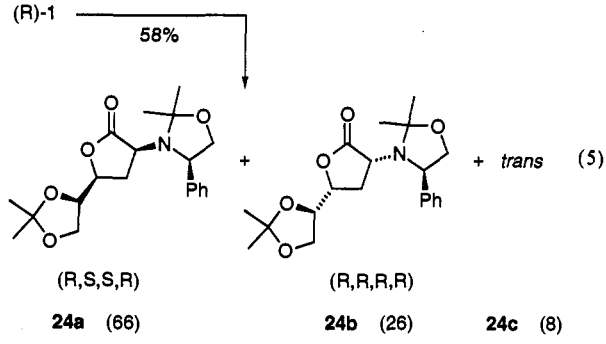

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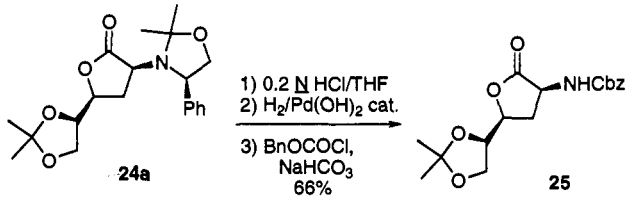

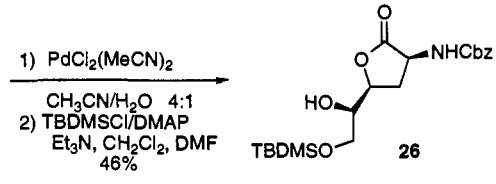

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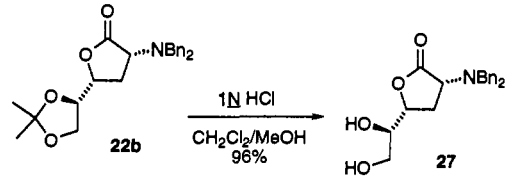

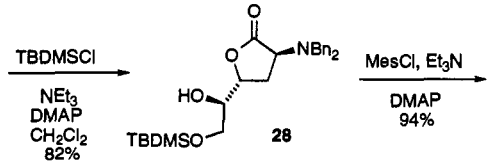

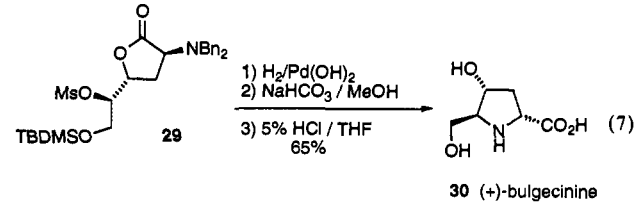

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and overall 17% yield from **19** (eq 7). Although this is not an asymmetric synthesis, the low number of steps and good overall yield make it attractive.

Experimental Section

General Procedure. Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker ACE-300 spectrometer. NMR spectra were recorded in $CDCl_3$, D_2O, DMSO-d_6, and CD_3OD, and chemical shifts are given in parts per million relative to $CHCl_3$ (7.24 ppm, ^{1}H), $CDCl_3$ (77.0 ppm, ^{13}C), HDO (4.65 ppm, ^{1}H), dioxane (67.6 ppm, ^{13}C), DMSO-d_6 (39.5 ppm, ^{13}C), or CD_3OD (49.0 ppm, ^{13}C). IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III. Specific rotations, $[\alpha]_D$ are reported in degrees per decimeter at 25 °C, and the concentration (c) is given in grams per 100 mL in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All the reactions involving chromium carbene complexes were performed under an atmosphere of argon. The crude reaction mixtures were purified by column chromatography with silica gel (ICN Biomedicals Silitech 32–63 μm). THF (Mallinckrodt) was distilled under an atmosphere of argon from sodium/benzophenone prior to use. CH_2Cl_2 (technical grade) was distilled from CaH_2. Carbene complexes (*S*)-**1**[9a] and **19**[9a] and (*R*)-2,3-*O*-isopropylideneglyceraldehyde [(*R*)-**20**][17] were prepared by literature procedures.

General Procedure for the Preparation of the 2-Aminobutyrolactones. The aminocarbene (*S*)-**1** (0.5 mmol) was dissolved in dry THF (10 mL). The solution was cooled to −78 °C, deoxygenated *in vacuo* (three cycles), and kept under argon. Butyllithium (1.25 equiv, 1.6 M in hexane) was added at −78 °C. After 30 min, the aldehyde (1.5–2.0 equiv) was added and stirring was continued at the temperature and for the time indicated below. A solution of a saturated NH_4Cl_{aq}/MeOH mixture (1:1, 0.5 mL) was added at −78 °C, and the reaction mixture was warmed to room temperature within 10 min. The solution was diluted with ether (10 mL), dried over magnesium sulfate, and filtered through a short bed of silica gel (elution with ether). The yellow to orange colored fitrate was concentrated *in vacuo* to give the crude aldol products which could be purified and characterized, if desired. More practically, the residue was taken up in dry, deoxygenated THF and was transferred under argon into an oven-dried pressure tube (Ace Glass) via a cannula. A pressure head was attached, and the system was pressurized with 60 psi of CO. Irradiation was performed with a 450 W Conrad Hanovia medium-pressure UV lamp at room temperature until the aldol product was consumed (TLC, hexane/ethyl acetate, 3:1). The solvent was removed under reduced pressure, and $Cr(CO)_6$ was removed by sublimation *in vacuo*. The residue was taken up in ether/hexane (100 mL, 1:1) and was air oxidized in a light box, equipped with six 20 W Vitalite fluorescent lamps for 20 h, followed by filtration through a bed of silica gel (elution with ether) and removal of the solvents *in vacuo*. Purification of the crude products by flash chromatography using a gradient of ethyl acetate in hexane afforded the pure 2-aminobutyrolactones.

2(*R*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*R*)-phenyl-1-oxotetrahydrofuran (2a). According to the general procedure, the aminobutyrolactone **2a** was prepared from 309 mg (0.78 mmol) of (*S*)-**1**, 613 μL (0.98 mmol) of butyllithium, and 159 μL (1.56 mmol) of benzaldehyde. The time for the aldol reaction at −78 °C was 10 min. Photolysis in THF for 48 h afforded after chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) the compound **2a** (190 mg, 72%) as a white solid. The crude reaction mixture consisted of a 92:8 ratio of two diastereomers (84% de), determined by integration of the singlets of the *gem*-dimethyl group. Data for **2a**: mp 149–150 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.32 (ddd, J = 12.6, 12.6, and 10.8 Hz, 1H, lactone CH_2), 2.54 (ddd, J = 12.6, 8.5 and 5.9 Hz, 1H, lactone CH_2), 3.73 (ap t, J = 8.3 Hz, 1H, OCH_2), 3.83 (dd, J = 12.7 and 8.6 Hz, 1H, NCH), 4.15 (dd, J = 7.8 and 6.6 Hz, 1H, OCH_2), 4.43 (dd, J = 8.6 and 6.5 Hz, 1H, NCHPh), 5.15 (dd, J = 10.7 and 5.9 Hz, 1H, OCH), 6.92 (m, 2H, Ar), 7.24–7.45 (m, 8H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8 (CH_3), 28.8 (CH_3), 34.3 (lactone CH_2), 55.5 (NCH), 62.5 (NCHPh), 72.3 (OCH_2), 77.6 (OCH), 95.5 (C_q), 125.4, 128.2, 128.5, 128.6, 138.0, 138.9 (Ar), 175.8 (C=O); IR (KBr) ν 1782 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75: H, 6.87; N, 4.15. Found: C, 74.81; H, 6.96; N, 4.04. Data for **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 6H, 2 CH_3), 1.66 (ddd, J = 13.0, 12.8, and 11.4 Hz, 1H, lactone CH_2), 2.36 (ddd, J = 13.0, 8.5 and 5.5 Hz, 1H, lactone CH_2), 3.80 (dd, J = 8.1 and 6.5 Hz, 1H, OCH_2), 4.01 (dd, J = 12.7 and 8.5 Hz, 1H, NCH), 4.31 (ap t, J = 7.7 Hz, 1H, OCH_2), 4.67 (ap t, J = 6.9 Hz, 1H, NCHPh), 5.07 (dd, J = 11.3 and 5.5 Hz, 1H, OCH), 6.81 (m, 2H, Ar), 7.20–7.42 (m, 8H, Ar).

2(*R*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*R*)-(*p*-methoxyphenyl)-1-oxotetrahydrofuran (3a). The aldol reaction of 165 mg of (*S*)-**1** (0.42 mmol), 325 μL of butyllithium (0.52 mmol), and 63 μL (0.52 mmol) of *p*-methoxybenzaldehyde was performed according to the general procedure for 2 h at −78 °C. The crude product was purified by flash chromatography under argon (SiO_2, 50 g, elution with 3:1 hexanes/EtOAc) to give the aldol product (118 mg, 53%) as an orange oil and recovered (*S*)-**1** (68 mg, 41%) as a yellow solid. The carbene was then photolyzed for 24 h following the general procedure. After chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) of the aminolactone, **3a** (60 mg, 74% for the photoreaction, 39% overall) was obtained as a white solid in diastereomerically pure form: mp 123 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.30 (ddd, J = 12.6, 12.6, and 10.8 Hz, 1H, lactone CH_2), 2.48 (ddd, J = 12.6, 8.5, and 5.8 Hz, 1H, lactone CH_2), 3.70–3.84 (m, 2H, NCH and OCH_2), 3.79 (s, 3H, OCH_3), 4.15 (dd, J = 7.8 and 6.5 Hz, 1H, OCH_2), 4.43 (dd, J = 8.6 and 6.5 Hz, 1H, NCHPh), 5.08 (dd, J = 10.6 and 5.8 Hz, 1H, OCH), 6.78 (d, J = 9.0 Hz, 2H, Ar), 6.82 (d, J = 9.0 Hz, 2H, Ar), 7.28–7.46 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (CH_3), 28.8 (CH_3), 34.3 (lactone CH_2), 55.3 (NCH), 55.5 (OCH_3), 62.5 (NCHPh), 72.3 (OCH_2), 77.5 (OCH), 95.5 (C_q), 114.0, 127.1, 128.2, 128.5, 128.6, 130.8, 138.1, 159.8 (Ar), 175.9 (C=O); IR (neat) ν 1782 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.95; H, 6.85; N, 3.80.

2(*R*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*R*)-(2-furyl)-1-oxotetrahydrofuran (4a). According to the general procedure, the aminobutyrolactone **4a** was prepared from 205 mg (0.52 mmol) of (*S*)-**1**, 406 μL (0.65 mmol) of butyllithium, and 65 μL (0.78 mmol) of furfural. The time for the aldol reaction at −78 °C was 30 min. Photolysis in THF for 40 h afforded after chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) the compound **4a** (76 mg, 44%) as a white solid. The product was obtained in diastereomerically pure form: mp 110–112 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.44 (ddd, J = 12.7, 8.7, and 6.0 Hz, 1H, lactone CH_2), 2.75 (ddd, J = 12.7, 12.6, and 11.0 Hz, 1H, lactone CH_2), 3.75 (ap t, J = 8.2 Hz, 1H, OCH_2), 3.84 (dd, J = 12.7 and 8.7 Hz, 1H, NCH), 4.21 (ap t, J = 7.3 Hz, 1H, OCH_2), 4.64 (ap t, J = 7.5 Hz, 1H, NCHPh), 5.18 (dd, J = 10.9 and 6.0 Hz, 1H, OCH), 6.26 (d, J = 3.2 Hz, 1H, furyl 3-CH), 6.33 (dd, J = 3.2 and 1.8 Hz, 1H, furyl 4-CH), 7.25–7.48 (m, 6H, phenyl CH and furyl 5-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_3), 29.2 (CH_3), 29.7 (lactone CH_2), 55.0 (NCH), 62.8 (NCHPh), 70.5 (OCH), 72.0 (OCH_2), 95.4 (C_q), 109.8, 110.5, 128.0, 128.2, 128.5, 138.6, 143.5, 149.9 (Ar), 175.2 (C=O); IR

(17) LeCocq, J.; Bellou, C. E. *Biochemistry* **1968**, *33*, 728.

(neat) ν 1781 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.71; H, 6.33; N, 4.07.

2(*R*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*R*)-*tert*-butyl-1-oxotetrahydrofuran (5a). The aminobutyrolactone **5a** was prepared from 285 mg (0.72 mmol) of (*S*)-**1**, 563 μL (0.90 mmol) of butyllithium, and 119 μL (1.08 mmol) of trimethylacetaldehyde. The time for the aldol reaction at −78 °C was 1 h and an additional 15 min at −78 to 20 °C. Photolysis in THF for 24 h afforded after chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) the compound **5a** (74 mg, 32%) as a white solid. The product was obtained in diastereomerically pure form: **5a**: mp 163–165 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (s, 9H, $C(CH_3)_3$), 1.35 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.99 (m, 1H, lactone CH_2), 2.08 (m, 1H, lactone CH_2), 3.67 (dd, J = 12.5 and 8.8 Hz, 1H, NCH), 3.69 (dd, J = 8.5 and 8.0 Hz, 1H, OCH_2), 3.86 (dd, J = 10.7 and 5.7 Hz, 1H, OCH), 4.14 (dd, J = 7.9 and 6.6 Hz, 1H, OCH_2), 4.45 (dd, J = 8.6 and 6.6 Hz, 1H, NCHPh), 7.18–7.43 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6 (CH_3), 24.6 ($C(CH_3)_3$), 26.4 (CH_2), 28.8 (CH_3), 33.2 ($C(CH_3)_3$), 55.5 (NCH), 62.5 (NCHPh), 72.3 (OCH_2), 83.7 (OCH), 95.4 (C_q), 127.9, 128.2, 128.4, 138.2 (Ar), 176.3 (C=O); IR (KBr) ν 1764 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.67; H, 8.42; N, 4.29.

2(*S*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*R*)-methyl-1-oxotetrahydrofuran (6b). According to the general procedure, the amino butyrolactone **6b** was prepared from 395 mg (1.00 mmol) of (*S*)-**1**, 781 μL (1.25 mmol) of butyllithium, and 113 μL (2.00 mmol) of acetaldehyde. The time for the aldol reaction at −78 °C was 10 min. Photolysis in THF for 48 h afforded after chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) the compounds **6b** (112 mg, 41%), **6a** (37 mg, 13%), and **6c** (19 mg, 7%) as white solids. The crude reaction mixture consisted of a 58:26:16 ratio of three diastereomers, determined by integration of one of the lactone methylene protons. Data for **6b**: mp 104 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, J = 6.1 Hz, 3H, $CHCH_3$), 1.16 (ddd, J = 12.7, 11.9, and 10.8 Hz, 1H, lactone CH_2), 1.44 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.11 (ddd, J = 10.8, 8.7, and 5.3 Hz, 1H, lactone CH_2), 3.77 (dd, J = 8.2 and 5.8 Hz, 1H, OCH_2), 3.88 (dd, J = 12.6 and 8.7 Hz, 1H, NCH), 4.24 (m, 1H, $OCHCH_3$), 4.30 (dd, J = 8.1 and 7.4 Hz, 1H, OCH_2), 4.49 (dd, J = 7.3 and 5.8 Hz, 1H, NCHPh), 7.24–7.37 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 ($CHCH_3$), 23.7 (CH_3), 28.1 (CH_3), 37.7 (CH_2), 56.7 (NCH), 60.3 (NCHPh), 72.1 (OCH_2), 73.4 (OCH), 96.1 (C_q), 127.7, 127.9, 128.5, 139.7 (Ar), 174.8 (C=O); IR (KBr) ν 1779 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.79; H, 7.89; N, 4.97. Data for **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.1 Hz, 3H, $CHCH_3$), 1.36 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.96 (ddd, J = 12.5, 12.4, and 10.3 Hz, 1H, lactone CH_2), 2.26 (ddd, J = 12.4, 8.6, and 5.5 Hz, 1H, lactone CH_2), 3.64–3.77 (m, 2H, OCH_2 and NCH), 4.15 (dd, J = 7.9 and 6.6 Hz, 1H, OCH_2), 4.30 (m, 1H, $OCHCH_3$), 4.48 (dd, J = 8.4 and 6.6 Hz, 1H, NCHPh), 7.24–7.37 (m, 5H, Ar). Data for **6c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 6.4 Hz, 3H, $CHCH_3$), 1.36 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.80 (ddd, J = 13.4, 9.5, and 5.2 Hz, 1H, lactone CH_2), 2.50 (ddd, J = 13.4, 7.5, and 7.5 Hz, 1H, lactone CH_2), 3.68 (ap t, J = 7.9 Hz, 1H, OCH_2), 3.75 (dd, J = 9.5 and 7.3 Hz, 1H, NCH), 4.17 (dd, J = 8.0 and 6.8 Hz, 1H, OCH_2), 4.29 (m, 1H, $OCHCH_3$), 4.35 (ap t, J = 7.3 Hz, 1H, NCHPh), 7.25–7.41 (m, 5H, Ar).

2(*S*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*S*)-isopropyl-1-oxotetrahydrofuran (7b). According to the general procedure, the aminobutyrolactone **7b** was prepared from 300 mg (0.76 mmol) of (*S*)-**1**, 593 μL (0.95 mmol) of butyllithium, and 139 μL (1.52 mmol) of isobutyraldehyde. The time for the aldol reaction at −78 °C was 10 min. Photolysis in THF for 60 h afforded after chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) the compound **7b** (94 mg, 41%) as a white solid and a mixture of **7a** and **7c** (42 mg, 18%). The crude reaction mixture consisted of a 68:22:10 ratio of three diastereomers, determined by GC–MS. Data for **7b**: mp 144–145 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (d, J = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.73 (d, J = 6.9 Hz, 3H, $CH(CH_3)_2$), 1.44 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.23–1.46 (m, 2H, $CH(CH_3)_2$ and lactone CH_2), 1.98 (ddd, J = 12.7, 8.7, and 5.3 Hz, 1H, lactone CH_2), 3.77 (dd, J = 8.1 and 6.0 Hz, 1H, OCH_2), 3.81–3.89 (m, 2H, NCH and OCH), 4.29 (ap t, J = 7.7 Hz, 1H, OCH_2), 4.53 (ap t, J = 6.7 Hz, 1H, NCHPh), 7.22–7.34 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7 (CH_3), 17.7 (CH_3), 23.6 (CH_3), 28.1 (CH_3), 32.1 ($CH(CH_3)_2$), 32.2 (lactone CH_2), 56.5 (NCH), 60.2 (NCHPh), 72.2 (OCH_2), 81.8 (OCH), 96.1 (C_q), 127.7, 128.0, 128.5, 142.6 (Ar), 174.8 (C=O); IR (KBr) ν 1765 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{24}NO_3$: C, 71.49; H, 8.01; N, 4.63. Found: C, 71.28; H, 8.18; N, 4.55. Data for **7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, J = 6.7 Hz, 3H, $CH(CH_3)_2$), 0.83 (d, J = 6.7 Hz, 3H, $CH(CH_3)_2$), 1.36 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.02 (m, 1H, lactone CH_2), 2.08 (m, 1H, $CH(CH_3)_2$), 2.13 (m, 1H, lactone CH_2), 3.68 (dd, J = 12.6 and 8.6 Hz, 1H, NCH), 3.70 (dd, J = 8.2 and 8.2 Hz, 1H, OCH_2), 3.90 (m, 1H, OCH), 4.16 (dd, J = 7.9 and 6.6 Hz, 1H, OCH_2), 4.48 (dd, J = 8.5 and 6.7 Hz, 1H, NCHPh), 7.23–7.43 (m, 5H, Ar).

2(*R*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*R*)-vinyl-1-oxotetrahydrofuran (8a). According to the general procedure, the amino butyrolactone **8a** was prepared from 250 mg (0.63 mmol) of (*S*)-**1**, 492 μL (0.79 mmol) of butyllithium, and 84 μL (1.26 mmol) of acrolein. The time for the aldol reaction at −100 °C was 10 min. Photolysis in THF for 36 h afforded after chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) the compounds **8a** (27 mg, 15%), **8b** (27 mg, 15%), and **8c** (12 mg, 7%) as white solids. Data for **8b**: mp 92–94 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (ddd, J = 12.7, 12.7, and 11.0 Hz, 1H, lactone CH_2), 1.44 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.15 (ddd, J = 12.9, 8.5, and 5.5 Hz, 1H, lactone CH_2), 3.78 (dd, J = 8.1 and 5.8 Hz, 1H, OCH_2), 3.90 (dd, J = 12.6 and 8.6 Hz, 1H, NCH), 4.29 (dd, J = 8.1 and 7.4 Hz, 1H, OCH_2), 4.50 (dd, J = 7.2 and 5.8 Hz, 1H, NCHPh), 4.53 (m, 1H, OCH), 5.05 (dt, J = 10.2 and 1.0 Hz, 1H, $CH=CH_2$), 5.11 (dt, J = 17.1 and 1.0 Hz, 1H, $CH=CH_2$), 5.34 (ddd, J = 17.1, 10.2 and 6.8 Hz, 1H, $CH=CH_2$), 7.23–7.36 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (CH_3), 28.1 (CH_3), 36.1 (CH_2), 56.2 (NCH), 60.2 (NCHPh), 72.1 (OCH_2), 77.3 (OCH), 96.1 (C_q), 118.3 ($CH=CH_2$), 127.7, 127.8, 128.5, 142.4 (Ar), 135.0 ($CH=CH_2$), 174.3 (C=O); IR (film) ν 1766-(C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.23; H, 7.21; N, 4.68. Data for **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.13 (ddd, J = 12.5, 12.5, and 10.5 Hz, 1H, lactone CH_2), 2.32 (ddd, J = 12.5, 8.6, and 5.9 Hz, 1H, lactone CH_2), 3.72 (m, 2H, OCH_2 and NCH), 4.16 (dd, J = 7.9 and 6.7 Hz, 1H, OCH_2), 4.48 (dd, J = 8.4 and 6.7 Hz, 1H, NCHPh), 4.59 (m, 1H, OCH), 5.16 (ap d, J = 10.5 Hz, 1H, $CH=CH_2$), 5.21 (ap d, J = 17.0 Hz, 1H, $CH=CH_2$), 5.61 (ddd, J = 17.0, 10.5, and 6.4 Hz, 1H, $CH=CH_2$), 7.22–7.42 (m, 5H, Ar).

2(*R*)-(1-Aza-2,2-dimethyl-3-oxa-5(*S*)-phenylcyclopent-1-yl)-4(*R*)-(1,3-dioxa-2,2-dimethylcyclopent-5(*R*)-yl)-1-oxotetrahydrofuran (23a). The aldol reaction of 200 mg of (*S*)-**1** (0.51 mmol), 400 μL of butyllithium (0.64 mmol), and 133 mg (1.02 mmol) of (*R*)-**20** was performed according to the general procedure for 1.5 h at −78 °C. Photolysis in THF for 16 h afforded after chromatography (SiO_2, 30 g, elution with 3:1 hexane/EtOAc) the compounds **23a** (63 mg, 34%), **23b** (22 mg, 12%), and **23c** (11 mg, 6%) as white solids. Data for **23a**: mp 178–181 °C (recrystallized from hexane/ether); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.11 (ddd, J = 12.4, 8.9, and 5.9 Hz, 1H, lactone CH_2), 2.34 (ddd, J = 12.5, 12.5, and 10.5 Hz, 1H, lactone CH_2), 3.55 (dd, J = 8.7 and 6.0 Hz, 1H, OCH_2), 3.67 (m, 2H, dioxolane CH_2 and NCH), 3.87 (dd, J = 8.7 and 6.9 Hz, 1H, OCH_2), 4.04 (ddd, J = 6.4, 6.4, and 3.8 Hz, 1H, dioxolane CH), 4.15 (dd, J = 7.9 and 6.6, 1H, dioxolane CH_2), 4.22 (ddd, J = 10.1, 6.1, and 3.8 Hz, 1H, OCH), 4.50 (dd, J = 8.3 and 6.7 Hz, 1H, NCHPh), 7.22–7.43 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (CH_3), 25.2 (CH_3), 25.9 (CH_3), 26.4 (CH_2), 29.0 (CH_3), 54.7 (NCH), 62.5 (NCHPh), 64.5 (OCH_2), 72.2 (OCH_2), 74.8 (OCH), 75.3 (OCH), 95.4 (C_q), 110.0 (C_q), 128.0, 128.2, 128.4, 138.4 (Ar), 175.4 (C=O); IR (film) ν 1778 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.24; H, 7.43; N, 3.61. Data for **23b**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.47 (m, 1H, lactone CH_2), 2.20 (ddd, J = 13.0, 8.9, and 5.6 Hz, 1H, lactone CH_2), 3.51 (m, 1H, dioxolane CH_2), 3.61 (m, 1H, OCH_2), 3.77 (m, 2H, dioxolane CH and OCH_2), 3.90 (dd, J = 12.5 and 8.9 Hz, 1H, NCH), 4.08 (m, 1H, OCH), 4.28 (dd, J = 7.9 and 7.5 Hz, 1H, dioxolane CH_2), 4.50 (dd, J = 7.1 and 6.1 Hz, 1H, NCHPh), 7.20–7.37 (m, 5H, Ar).

2(*S*)-(1-Aza-2,2-dimethyl-3-oxa-5(*R*)-phenylcyclopent-1-yl)-4(*S*)-(1,3-dioxa-2,2-dimethylcyclopent-5(*R*)-yl)-1-oxotetrahydrofuran (24a). The aldol reaction of 260 mg of (*R*)-**1** (0.66 mmol), 514 μL of butyllithium (0.82 mmol), and 172 mg (1.32 mmol) of (*R*)-**20** was performed according to the general procedure for 1.5 h at −78 °C. Photolysis in THF for 20 h afforded after chromatography (SiO_2, 30 g, elution 3:1 hexane/EtOAc) the compounds **24a** (91 mg, 38%), **24b** (36 mg, 15%), and **24c** (11 mg, 5%) as white solids. Data for **24a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.24 (ddd, J = 12.6, 12.5, and 9.9 Hz, 1H, lactone CH_2), 2.32 (ddd, J = 12.6, 9.1, and 6.2 Hz, 1H, lactone CH_2), 3.70 (m, 4H, OCH_2, dioxolane CH_2 and NCH), 3.91 (m, 1H, dioxolane CH), 4.09 (m, 1H, OCH), 4.15 (dd, J = 7.9 and 6.6 Hz, 1H, OCH_2), 4.46 (dd, J = 8.5 and 6.6 Hz, 1H, NCHPh), 7.22–7.43 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (CH_3), 24.8 (CH_3), 26.5 (CH_3), 27.7 (CH_2), 28.8 (CH_3), 54.4 (NCH), 62.3 (NCHPh), 66.4 (OCH_2), 72.1 (OCH_2), 75.8 (OCH), 77.0 (OCH), 95.3 (C_q), 109.8 (C_q), 128.1, 128.3, 128.4, 138.0 (Ar), 175.5 (C=O); IR (film) ν 1772(C=O) cm^{-1}. Data for **24b**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.41 (m, 1H, lactone CH_2), 1.44 (s, 3H, CH_3), 1.99 (ddd, J = 12.8, 9.1, and 5.1 Hz, 1H, lactone CH_2), 3.32 (m, 1H, dioxolane CH), 3.67 (m, 2H, dioxolane CH_2), 3.77 (dd, J = 8.1 and 6.2 Hz, 1H, OCH_2), 3.88 (dd, J = 12.4 and 9.1 Hz, 1H, NCH), 4.16 (ddd, J = 10.9, 5.7, and 5.5 Hz, 1H, OCH), 4.27 (dd, J = 8.0 and 7.4 Hz, 1H, OCH_2), 4.50 (dd, J = 7.1 and 6.4 Hz, 1H, NCHPh), 7.25–7.38 (m, 5H, Ar).

2(*SR*)-(*N,N*-Dibenzylamino)-4(*SR*)-(1,3-dioxa-2,2-dimethylcyclopent-5(*R*)-yl)-1-oxotetrahydrofuran (22). According to the general procedure, the amino butyrolactone **22** was prepared from 485 mg (1.17 mmol) of **19**, 914 μL (1.46 mmol) of butyllithium, and 190 mg (1.46 mmol) of (*R*)-**20**. The time for the aldol reaction at −78 °C was 2.5 h. The crude was purified by flash chromatography under argon (SiO_2, 100 g, elution with 4:1 hexanes/Et_2O) to give the aldol product (558 mg, 87%) as a 1:1 mixture of diastereomers. This carbene mixture was then photolyzed for 36 h following the general procedure. Chromatography (SiO_2, 50 g, elution with 3:1 hexane/EtOAc) afforded a 1:1 mixture of the compounds **22b** and **22a** (308 mg, 79% for the photoreaction, 69% overall) as a slightly yellow oil. Data for (2*R*,4*R*)-**22b**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.25 (m, 2H, lactone CH_2), 3.69 (d, J = 13.7 Hz, 2H, NCH_2Ph), 3.79–3.94 (m, 4H, NCH_2Ph and dioxolane CH_2), 4.05 (dd, J = 8.4 and 6.8 Hz, 1H, NCH), 4.17 (m, 1H, dioxolane CH), 4.24 (ap dt, J = 8.6 and 3.8 Hz, 1H, OCH), 7.18–7.44 (m, 10H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3 (CH_3), 26.1 (CH_3), 26.3 (CH_2), 54.6 ($N(CH_2Ph)_2$), 58.6 (NCH), 65.0 (OCH_2), 75.5 (OCH), 76.2 (OCH), 110.1 (C_q), 127.2, 128.4, 128.6, 138.9 (Ar), 174.9 (C=O); IR (film) ν 1777 (C=O) cm^{-1}. This material was carried on without further characterization. Data for (2*S*,4*S*)-**22a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.14 (ddd, J = 12.6, 12.2, and 9.4 Hz, 1H, lactone CH_2), 2.41 (ddd, J = 12.7, 9.0, and 5.7 Hz 1H, lactone CH_2), 3.65 (d, J = 13.7 Hz, 2H, NCH_2Ph), 3.83 (m, 2H, dioxolane CH_2), 3.90 (d, J = 13.7 Hz, 2H, NCH_2Ph), 4.11 (m, 3H, NCH, dioxolane CH and OCH), 7.18–7.44 (m, 10H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9 (CH_3), 26.5 (CH_3), 27.6 (CH_2), 54.7 ($N(CH_2Ph)_2$), 58.6 (NCH), 66.7 (OCH_2), 76.4 (OCH), 77.0 (OCH), 110.0 (C_q), 127.3, 128.4, 128.7, 138.8 (Ar), 175.1 (C=O); IR (film) ν 1777 (C=O) cm^{-1}.

General Procedure for the Removal of the Oxazolidine Chiral Auxiliary. The oxazolidine-protected aminobutyrolactones were dissolved in 10 mL of a 1:1 mixture of CH_2Cl_2/MeOH and were hydrolyzed at room temperature with 2 mL of 0.2 N HCl for 1 h. The solvents were removed under reduced pressure, and 5 mL of 5% aqueous $NaHCO_3$ solution was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$. After filtration through a plug of Celite the solvent was evaporated *in vacuo* to leave the crude amino alcohols. The product was dissolved in 20 mL of a 1:1 mixture of CH_2Cl_2/MeOH, and 1 equiv of $Pb(OAc)_4$ was added in one portion at 0 °C. After stirring at this temperature for 15 min, 10 mL of 5% aqueous $NaHCO_3$ was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried with $MgSO_4$. After filtration through a plug of silica gel the solvent was removed *in vacuo* to give the crude imines. The imines were hydrolyzed in 10 mL of a 1:1 mixture of CH_2Cl_2/MeOH with 1.5 mL of 0.2 N HCl at room temperature for 4 h (monitored by TLC). The solvent was removed under reduced pressure, and after drying under high vacuum, the crude hydrochlorides were obtained. These were dissolved in a minimal amount of MeOH and triturated with ether. The aminolactone hydrochlorides were removed by filtration from the solution and recrystallized from MeOH/ether, if needed.

Deprotection of 2a. The above general procedure was applied to aminobutyrolactone **2a** (85 mg, 0.25 mmol). Oxidative cleavage of the amino alcohol with $Pb(OAc)_4$ (76 mg, 0.25 mmol) and subsequent hydrolysis gave the aminolactone hydrochloride **9** as a white solid (43 mg, 80%): $[\alpha]_D$ = +7.1° (c = 1.3, H_2O); mp = 190–195 °C dec; ^1H NMR (300 MHz, D_2O) δ 2.33 (ddd, J = 12.4, 11.7, and 11.7 Hz, 1H, lactone CH_2), 3.06 (ddd, J = 12.7, 8.5, and 5.4 Hz, 1H, lactone CH_2), 4.57 (m, 1H, NCH), 5.60 (dd, 10.9 and 5.4 Hz, 1H, OCH), 7.38 (m, 5H, Ar); ^{13}C NMR (75 MHz, D_2O) δ 36.1 (CH_2), 51.1 (NCH), 81.4 (OCH), 127.5, 130.1, 130.7, 137.6 (Ar), 174.4 (C=O); IR (KBr) ν 1790 (C=O) cm^{-1}.

Deprotection of 3a. The above general procedure was applied to aminobutyrolactone **3a** (100 mg, 0.27 mmol). Oxidative cleavage of the amino alcohol with $Pb(OAc)_4$ (120 mg, 0.27 mmol) and subsequent hydrolysis gave the aminolactone hydrochloride **10** as a white solid (52 mg, 78%): $[\alpha]_D$ = −3.1° (c = 1.0, H_2O); mp 200–203 °C dec; ^1H NMR (300 MHz, D_2O) δ 2.34 (ddd, J = 12.3, 11.7, and 11.0 Hz, 1H, lactone CH_2), 2.98 (ddd, J = 12.7, 7.0, and 5.5 Hz, 1H, lactone CH_2), 3.70 (s, 3H, OCH_3), 4.53 (dd, J = 12.0 and 7.1 Hz, 1H, NCH), 5.52 (dd, J = 11.0 and 5.3 Hz, 1H, OCH), 6.92 and 7.31 (2d, J = 7.2 Hz, 4H, Ar); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.5 (CH_2), 49.7 (NCH), 55.2 (OCH_3), 78.7 (OCH), 114.0, 128.5, 129.7, 159.8 (Ar), 173.2 (C=O); IR (KBr) ν 1780 (C=O) cm^{-1}. Anal. Calcd (as the N-tBOC derivative) for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.45; H, 6.66; N, 4.53.

Deprotection of 5a. The above general procedure was applied to aminobutyrolactone **5a** (60 mg, 0.19 mmol). Oxidative cleavage of the amino alcohol with $Pb(OAc)_4$ (84 mg, 0.19 mmol) and subsequent hydrolysis gave the aminolactone hydrochloride **11** as a white solid (32 mg, 89%): $[\alpha]_D = +8.8°$ (c = 1.0, H_2O); mp 168–169 °C dec; ^1H NMR (300 MHz, D_2O) δ 0.82 (s, 9H, $C(CH_3)_3$), 2.02 (ddd, J = 12.2, 11.8, and 11.3 Hz, 1H, lactone CH_2), 2.58 (ddd, J = 12.6, 8.7, and 5.1 Hz, 1H, lactone CH_2), 4.33 (dd, J = 11.2 and 5.3 Hz, 1H, OCH), 4.35 (dd, J = 11.7 and 9.2 Hz, 1H, NCH); ^{13}C NMR (75 MHz, D_2O) δ 25.1 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 33.8 (CH_2), 49.9 (NCH), 87.9 (OCH), 175.2 (C=O); IR (KBr) ν 1781 (C=O) cm^{-1}.

Deprotection of 6b. The above general procedure was applied to aminobutyrolactone **6b** (100 mg, 0.36 mmol). Oxidative cleavage of the amino alcohol with $Pb(OAc)_4$ (160 mg, 0.36 mmol) and subsequent hydrolysis gave the aminolactone hydrochloride **12** as a white solid (37 mg, 67%): $[\alpha]_D = -2.4°$ (c = 1.0, H_2O); mp 190–194 °C dec (lit.[6] $[\alpha]_D = -3.0°$ (c = 1.5–2.0, H_2O); mp 194–195 °C dec); ^1H NMR (300 MHz, D_2O) δ 1.35 (d, J = 6.2 Hz, 3H, CH_3), 1.89 (ddd, J = 12.2, 12.2, and 10.7 Hz, 1H, lactone CH_2), 2.77 (ddd, J = 12.5, 8.3, 5.1 Hz, 1H, lactone CH_2), 4.37 (dd, J = 12.0 and 8.9 Hz, 1H, NCH), 4.68 (m, 1H, OCH); ^{13}C NMR (75 MHz, MeOH-d_4) δ 20.6 (CH_3), 36.2 (CH_2), 51.1 (NCH), 76.7 (OCH), 173.6 (C=O); IR (KBr) ν 1777 (C=O) cm^{-1}.

Deprotection of 7b. The above general procedure was applied to aminobutyrolactone **7b** (100 mg, 0.33 mmol). Oxidative cleavage of the amino alcohol with $Pb(OAc)_4$ (146 mg, 0.33 mmol) and subsequent hydrolysis gave the aminolactone hydrochloride **13** as a white solid (46 mg, 79%): $[\alpha]_D = +2.0°$ (c = 3.0, H_2O); mp 130–133 °C dec; ^1H NMR (300 MHz, D_2O) δ 0.81 (d, J = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.89 (d, J = 6.8 Hz, 3H, $CH(CH_3)_2$), 1.82 (sept, J = 6.8 Hz, 1H, $CH(CH_3)_2$), 1.98 (ddd, J = 12.2, 12.2, and 11.0 Hz, 1H, lactone CH_2), 2.70 (ddd, J = 12.5, 8.7, and 5.2 Hz, 1H, lactone CH_2), 4.33 (ddd, J = 10.9, 7.3, and 5.2 Hz, 1H, OCH), 4.38 (dd, J = 12.2 and 8.8 Hz, 1H, NCH); ^{13}C NMR (75 MHz, D_2O) δ 17.2 ($CH(CH_3)_2$), 18.5 ($CH(CH_3)_2$), 31.9 (CH_2), 32.9 ($CH(CH_3)_2$), 51.0 (NCH), 85.5 (OCH), 175.6 (C=O); IR (KBr) ν 1781 (C=O) cm^{-1}.

Preparation of the Free γ-Hydroxyamino Acids. The aminolactone hydrochlorides were stirred at 25 °C in 5 mL of MeOH and 1 mL of 1 N NaOH. The MeOH was removed under reduced pressure, and the pH of the remaining solution was adjusted to 7 with 1 N HCl. The amino acids were purified by ion exchange chromatography (Dowex 50W-8X ion exchange resin, elution with 1 N NH_4OH, monitored by TLC; 20% aqueous MeOH, ninhydrin) to give the pure amino acids after lyophilization as a white fluffy powder.

Preparation of (+)-(2*R*,4*R*)-2-Amino-4-hydroxy-4-phenylbutanoic Acid (14). Following the general procedure, the aminolactone hydrochloride **9** (31 mg, 0.15 mmol) was hydrolyzed for 30 min. Ion exchange chromatography gave the pure amino acid **14** (27 mg, 93%): $[\alpha]_D = +19.0°$ (c = 0.45, H_2O); mp 150–155 °C dec; ^1H NMR (300 MHz, D_2O) δ 2.09 (ddd, J = 15.2, 6.9, and 3.9 Hz, 1H, CH_2), 2.19 (ddd, J = 15.2, 9.3, and 4.3 Hz, 1H, CH_2), 3.75 (dd, J = 6.9 and 4.3 Hz, 1H, NCH), 4.78 (dd, J = 9.3 and 3.9 Hz, 1H, OCH), 7.22–7.34 (m, 5H, Ar); ^{13}C NMR (75 MHz, D_2O) δ 38.9 (CH_2), 54.0 (NCH), 72.0 (OCH), 126.7, 129.1, 129.9, 144.1 (Ar), 175.0 (C=O); IR (KBr) ν 1592 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 57.36; H, 7.06; N, 6.83.

Preparation of (+)-(2*R*,4*R*)-2-Amino-4-hydroxy-5,5-dimethylhexanoic Acid (16). Following the general procedure, the aminolactone hydrochloride **11** (40 mg, 0.21 mmol) was hydrolyzed for 1 h. Ion exchange chromatography gave the pure amino acid **16** (32 mg, 86%): $[\alpha]_D = +39.3°$ (c = 1.4, H_2O); mp 193–195 °C dec; ^1H NMR (300 MHz, D_2O) δ 0.73 (s, 9H, $C(CH_3)_3$), 1.76 (ddd, J = 15.0, 6.9, and 3.9 Hz, 1H, CH_2), 1.97 (ddd, J = 15.3, 6.9, and 1.9 Hz, 1H, CH_2), 3.26 (dd, J = 11.2 and 1.9 Hz, 1H, OCH), 3.80 (dd, J = 6.8 and 3.5 Hz, 1H, NCH); ^{13}C NMR (75 MHz, D_2O) δ 25.8 ($C(CH_3)_3$), 31.8 ($C(CH_3)_3$), 35.3 (CH_2), 54.5 (NCH), 77.8 (OCH), 175.5 (C=O); IR (KBr) ν 1616 (C=O) cm^{-1}. Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 52.63; H, 9.89; N, 7.66.

Preparation of (–)-(2*S*,4*R*)-γ-hydroxynorvaline (17). Following the general procedure, the aminolactone hydrochloride **12** (20 mg, 0.13 mmol) was hydrolyzed for 1 h. Ion exchange chromatography gave the pure amino acid **17** (16 mg, 92%): $[\alpha]_D = -32.8°$ (c = 1.6, H_2O); mp 188–189 °C dec (lit.[6] $[\alpha]_D = -35.5°$ (c = 1.5–2.0, H_2O); mp 194–195 °C dec); ^1H NMR (300 MHz, D_2O) δ 1.08 (d, J = 6.2 Hz, CH_3), 1.84 (m, 2H, CH_2), 3.75 (m, 1H, NCH), 3.84 (ap dt, J = 12.4 and 5.2 Hz, 1H, OCH) (^1H NMR data are in good agreement with the literature);[6] ^{13}C NMR (75 MHz, D_2O) δ 23.6 (CH_3), 38.7 (CH_2), 54.1 (NCH), 66.1 (OCH), 175.6 (C=O); IR (KBr) ν 1617 (C=O) cm^{-1}.

Preparation of (–)-(2*S*,4*S*)-2-Amino-4-hydroxy-5,5-dimethylhexanoic Acid (16). Following the general procedure, the aminolactone hydrochloride **11** (40 mg, 0.22 mmol) was hydrolyzed for 1 h. Ion exchange chromatography gave the pure amino acid **16** (32 mg, 91%): $[\alpha]_D = -30.7°$ (c = 0.7, H_2O); mp 166–169 °C dec; ^1H NMR (300 MHz, D_2O) δ 0.73 (d, J = 6.7 Hz, 3H, $CH(CH_3)_2$), 0.74 (d, J = 6.7 Hz, 3H, $CH(CH_3)_2$), 1.53 (ap sept, J = 6.7 Hz, 1H, $CH(CH_3)_2$), 1.77 (ddd, J = 15.2, 10.7, and 3.8 Hz, 1H, CH_2), 1.93 (ddd, J = 15.3, 6.9, and 2.5 Hz, 1H, CH_2), 3.35 (ddd, J = 10.5, 6.0, and 2.5 Hz, 1H, OCH), 3.78 (dd, J = 6.9 and 3.7 Hz, 1H, NCH); ^{13}C NMR (75 MHz, D_2O) δ 18.0 ($CH(CH_3)_2$), 18.7 ($CH(CH_3)_2$), 34.1 (CH_2), 34.6 ($CH(CH_3)_2$), 54.3 (NCH), 74.9 (OCH), 175.5 (C=O); IR (KBr) ν 1606 (C=O) cm^{-1}. Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 51.94; H, 9.43; N, 8.52.

Removal of the Oxazolidine Chiral Auxiliary of 24a To Give 25. The aminolactone **24a** (90 mg, 0.25 mmol) was hydrolyzed in 10 mL of THF with 2 mL of 0.2 N HCl at room temperature for 1 h. The solvent was removed *in vacuo*, and 10 mL of 5% aqueous $NaHCO_3$ solution was added. The aqueous solution was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$. After filtration through a plug of Celite the solvent was evaporated *in vacuo* to leave the crude amino alcohol. This was dissolved in 10 mL of MeOH and was hydrogenated under 50 psi of H_2 in the presence of 40 mg of $Pd(OH)_2$ at room temperature for 24 h. This solution was filtered through a plug of Celite, and the filter cake was washed with 50 mL of MeOH. The solvent was removed *in vacuo* to give the crude amine, which was dissolved in 20 mL of EtOAc and cooled to 0 °C. Benzyl chloroformate (39 μL, 0.28 mmol) and 5 mL of saturated $NaHCO_3$ were added, and this mixture was stirred for 0.5 h at this temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and filtered through a plug of Celite. After removal of the solvent *in vacuo*, the crude product was purified by flash chromatography (SiO_2, 10 g, elution with 1:1 hexane/EtOAc) to give the Cbz-protected aminolactone **25** (55 mg, 66%) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.03 (m, 1H, lactone CH_2), 2.83 (m, 1H, lactone CH_2), 3.85–4.51 (m, 5H, dioxolane CH_2, dioxolane CH, OCH, and NCH), 5.10 (s, 2H, OCH_2Ph), 5.42 (br, m 1H, NH), 7.26–7.38 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9 (CH_3), 26.5 (CH_3), 32.5 (CH_2), 51.0 (NCH), 66.4 (OCH_2Ph), 67.3 (OCH_2), 70.0 (OCH), 71.4 (OCH), 110.2 (C_q), 128.1, 128.3, 128.5, 135.8 (Ar), 155.9 (carbamate C=O), 173.8 (C=O).

Deprotection of the 1,2-Diol and Reprotection of the Primary Alcohol to Give 26. The Cbz-protected aminolactone **25** (55 mg, 0.19 mmol) was heated at 65 °C in 10 mL of a 1:1 mixture of acetonitrile/water in the presence of 10 mg of $PdCl_2(CH_3CN)_2$ for 24 h.[18] The solvents were removed *in vacuo* to leave the crude

product, which was purified by flash chromatography (SiO_2, 10 g, elution with EtOAc). The 1,2-diol was then stirred in 10 mL of CH_2Cl_2 with (TBDMS)Cl (31 mg, 0.21 mmol) and triethylamine (31 μL, 0.22 mmol) in the presence of catalytic amounts of DMAP at room temperature for 16 h. This mixture was directly applied to flash chromatography (SiO_2, 10 g, elution with hexanes/EtOAc, 1:1) to give **26** (35 mg, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 and 0.06 (2s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $C(CH_3)_3$), 2.16 (m, 1H, lactone CH_2), 2.74 (m, 1H, lactone CH_2), 2.76 (br, s 1H, OH), 3.66 (m, 2H, OCH_2), 3.86 (m, 1H, OCH), 4.48 (m, 2H, OCH and NCH), 5.10 (s, 2H, OCH_2Ph), 5.50 (br, *d* J = 6.8 Hz, 1H, NH), 7.29–7.35 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5 ($Si(CH_3)_2$), 18.2 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 31.0 (CH_2), 51.1 (NCH), 62.9 (OCH_2Ph), 67.3 (OCH_2), 71.8 (OCH), 77.2 (OCH), 128.1, 128.3, 128.5, 135.9 (Ar), 156.0 (carbamate C=O), 174.4 (C=O); IR (film) ν = 1789 (C=O), 1713 (carbamate C=O) cm^{-1}.

Deprotection of 22b To Give 27. The aminolactone **22b** (88 mg, 0.23 mmol) was hydrolyzed in 10 mL of a 1:1 mixture of CH_2Cl_2/MeOH with 2 mL of 1 N HCl at room temperature for 24 h. The solvents were removed *in vacuo*, and 10 mL of a 5% aqueous $NaHCO_3$ solution was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$. After filtration through a plug of Celite the solvent was evaporated *in vacuo* to leave the 1,2-diol **27** (70 mg, 96%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21–2.31 (m, 3H, lactone CH_2 and OH), 2.5–3.5 (br, s 1H, OH), 3.64–3.91 (m, 8H, $N(CH_2Ph)_2$, HOC*H*, OCH_2, and NCH), 4.27 (m, 1H, OCH), 7.18–7.43 (m, 10H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2 (CH_2), 54.7 ($N(CH_2Ph)_2$), 58.9 (NCH), 63.1 (OCH_2), 72.8 (OCH), 77.4 (OCH), 127.3, 128.4, 128.6, 138.7 (Ar), 175.5 (C=O).

Silylation of 27 To Give 28. The 1,2-diol **27** (70 mg, 0.22 mmol) was stirred in 10 mL of CH_2Cl_2 with (TBDMS)Cl (42 mg, 0.28 mmol) and triethylamine (39 μL, 0.28 mmol) in the presence of a catalytic amount of DMAP at room temperature for 16 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (SiO_2, 30 mg, elution with 4:1 hexane/EtOAc) to give **28** (79 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $C(CH_3)_3$), 2.17–2.44 (m, 3H, lactone CH_2 and OH), 3.58–3.71 (m, 5H, NCH_2Ph, OCH_2, and HOC*H*), 3.83 (dd, J = 11.7 and 9.2 Hz, 1H, NCH), 3.87 (d, J = 13.8 Hz, 2H, NCH_2Ph), 4.33 (ddd, J = 10.3, 6.4, and 3.1 Hz, 1H, OCH), 7.23–7.42 (m, 10 H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5 ($Si(CH_3)_2$), 18.2 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 26.3 (CH_2), 54.7 ($N(CH_2Ph)_2$), 58.8 (NCH), 63.5 (OCH_2), 72.4 (OCH), 77.2 (OCH), 127.2, 128.4, 128.7, 138.9 (Ar), 175.3 (C=O). IR (film) ν = 1770 (C=O) cm^{-1}.

Mesylation of 28 To Give 29. The aminolactone **28** (79 mg, 0.18 mmol) was dissolved together with methanesulfonyl chloride (18 μL, 0.23 mmol) and a catalytic amount of DMAP in 10 mL of CH_2Cl_2. Triethylamine (38 μL, 0.27 mmol) was added, and the mixture was allowed to stir at room temperature for 16 h. After adding 20 mL of 1N HCl, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were dried with $MgSO_4$ and filtered through a plug of SiO_2. The solvent was removed under reduced pressure to leave the amino mesylate **29** (93 mg, 94%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 and 0.07 (2s, 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 2.28 (m, 2H, lactone CH_2), 3.07 (s, 3H, CH_3SO_2), 3.64 (d, J = 13.6 Hz, 2H, NCH_2Ph), 3.78–3.94 (m, 3H, OCH_2 and NCH), 3.88 (d, J = 13.6 Hz, 2H, NCH_2Ph), 4.50 (ddd, J = 10.1, 6.5, and 4.4 Hz, 1H, OCH), 4.61 (ap q, J = 5.0 Hz, 1H, OCH), 7.21–7.47 (m, 10 H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6 ($Si(CH_3)_2$), 18.2 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 26.1 (CH_2), 38.7 (CH_3SO_2), 54.7 ($N(CH_2Ph)_2$), 58.7 (NCH), 62.2 (OCH_2), 74.3 (OCH), 81.8 (OCH), 127.3, 128.4, 128.7, 138.6 (Ar), 174.4 (C=O). IR (film) ν = 1779 (C=O) cm^{-1}.

Preparation of (2*R*,4*R*,5*S*)-4-Hydroxy-5-(hydroxymethyl)-proline (30). The amino mesylate **29** (93 mg, 0.17 mmol) was hydrogenated with 60 psi of H_2 in 10 mL of a 9:1 mixture of EtOAc/MeOH in the presence of 19 mg of $Pd(OH)_2$ at room temperature for 20 h. Filtration through a plug of Celite and removal of the solvents *in vacuo* gave the free amino lactone that was dissolved in 10 mL of MeOH. Saturated $NaHCO_3$ (2 mL) was added, and the mixture was allowed to stir at room temperature for 24 h. After neutralizing this solution (pH 7), the solvents were removed *in vacuo*. In order to remove the TBDMS group, the residue was treated with 2 mL of 5% HCl in 20 mL of THF at room temperature for 24 h. The pH was adjusted to 7, and the crude product was purified by ion exchange chromatography (Dowex 50W-8X ion exchange resin, elution with 1 N NH_4OH, monitored by TLC; 20% aqueous MeOH, ninhydrin). After lyophilization, (2*R*,4*R*,5*S*)-4-hydroxy-5-(hydroxymethyl)proline (**30**) (17 mg, 65%) was obtained as a clear oil: $[\alpha]_D$ = +13.9° (c = 0.9, H_2O) (lit.[16b] for (−)-bulgecine $[\alpha]_D$ = −13.1° (c = 0.95, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 2.02 (ddd, J = 13.8, 5.9, and 5.3 Hz, 1H, CH_2), 2.52 (ddd, J = 13.8, 9.0, and 5.9 Hz, 1H, CH_2), 3.58–3.79 (m, 3H, OCH_2 and NCH), 4.07 (dd, J = 6.6 and 9.1 Hz, 1H, C*H*CO_2H), 4.25 (m, 1H, HOC*H*); ^{13}C NMR (75 MHz, D_2O) δ 37.1 (CH_2), 58.7 (OCH_2), 59.9 ($CH(CH_2)$OH), 67.4 ($CHCO_2$H), 71.1 (HOCH), 174.7 (C=O) (^{1}H NMR and ^{13}C NMR data are in good agreement with the literature).[16b]

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