eluent. 3α-O-Butanoyldeoxycholic acid, methyl ester was obtained in 85% yield. The product was crystallized from diethyl ether–hexane: mp 110–2 °C. ^{1}H NMR: δ 0.60 (3 H, s, C-18 Me), 0.86 (3 H, s, C-19 Me), 3.94 (1 H, t, J = 2.8 Hz, H-12β), 4.67 (1 H, sept, J_1 = 10.6 Hz, J_2 = 4.9 Hz, H-3β). Anal. Calcd for $C_{29}H_{48}O_5$: C, 73.47; H, 10.20. Found: C, 73.75; H, 10.03.

The acylations of **12**, **13**, and **14** were carried out similarly. The products were recovered (yields between 70 and 78%) and characterized.

3α-O-Butanoylchenodeoxycholic acid, methyl ester: oil. ^{1}H NMR; δ 0.62 (3 H, s, C-18 Me), 0.88 (3 H, s, C-19 Me), 3.83 (1 H, q, J = 2.5 Hz, H-7β), 4.56 (1 H, sept, J_1 = 10.6 Hz, J_2 = 5 Hz, H-3β). Anal. Calcd for $C_{29}H_{48}O_5$: C, 73.47; H, 10.20. Found: C, 72.71; H, 9.80.

3α-O-Butanoylursodeoxycholic acid, methyl ester: oil. ^{1}H NMR: δ 0.65 (3 H, s, C-18 Me), 0.90 (3 H, s, C-19 Me), 4.10 (1 H, t, J = 3.0 Hz, H-7α), 4.65 (1 H, sept, J_1 = 10.6 Hz, J_2 = 4.9 Hz, H-3β). Anal. Calcd for $C_{29}H_{48}O_5$: C, 73.47; H, 10.20. Found: C, 72.84; H, 9.82.

3α-O-Butanoylcholic acid, methyl ester: mp 116–118 °C (from diethyl ether–hexane). ^{1}H NMR: δ 0.62 (3 H, s, C-18 Me), 0.86 (3 H, s, C-19 Me), 3.84 (1 H, q, J = 2.5 Hz, H-7β), 3.97 (1 H, t, J = 2.8 Hz, H-12β), 4.57 (1 H, sept, J_1 = 10.6 Hz, J_2 = 4.9 Hz, H-3β). Anal. Calcd for $C_{29}H_{48}O_6$: C, 71.15; H, 9.88. Found: C, 70.98; H, 9.93.

Preparation of 3β-O-Butanoylrockogenin. Rockogenin (**20**, 400 mg) was dissolved in 20 mL of anhydrous benzene containing 3 molar equiv of TCEB. Cn.c lipase (1 g) was added and the suspension was shaken at 250 rpm and at 45 °C for 24 h. The enzyme was filtered out, the solvent evaporated, and the crude residue purified by flash chromatography ($CHCl_3$–AcOEt, 9:0.6), yielding 413 mg (89%) of 3β-O-butanoylrockogenin: mp 195 °C (from MeOH). ^{1}H NMR: δ 4.68 (1 H, sept, J_1 = 11 Hz, J_2 = 5.7 Hz, H-3α). Anal. Calcd for $C_{31}H_{50}O_5$·MeOH: C, 71.91; H, 10.11. Found: C, 71.06, H, 9.83.

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Conformationally Constrained Peptides. Chirospecific Synthesis of 4-Alkyl-Substituted γ-Lactam-Bridged Dipeptides from L-Aspartic Acid

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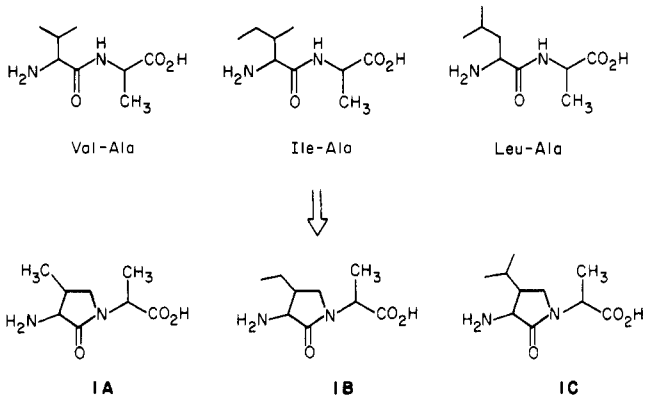
The synthesis of enantiomerically pure γ-lactam-bridged dipeptide analogues of Val-Ala, Ile-Ala, and β-MeLeu-Ala starting from L-aspartic acid is presented. *N*-(9-Phenylfluorenyl)-L-aspartic acid α-*tert*-butyl β-methyl diester and *N*-(9-Phenylfluorenyl)-L-aspartic acid dimethyl ester serve as the educts. They have been successfully alkylated at the β-carbon, C-3, with a variety of electrophiles and with total retention of asymmetric integrity at the α-carbon, followed by a regiospecific reduction of the β-methyl ester. Subsequent oxidation and reductive amination with alanine methyl ester affords the precursors of γ-lactam-bridged dipeptides which have been readily cyclized to the γ-lactams bearing the corresponding valine, isoleucine, and leucine side chains.

Introduction

Lactams as conformational constraints in peptide backbones are effective structural tools for probing the active conformations of bioactive peptides.[1-8] In a number of instances, locking bioactive peptides into active conformers by lactam backbone modification has led to increases in their potency.[1,9,10] Although several synthetic routes to lactam backbone modified peptides are known,[1,2,4,5-8,11-17] these methods commonly lack provision for retention of the amino acid side chain as a substituent on the lactam, place it at C-3 of the lactam, or do not permit continuing extension of the peptide chain. We now present a general synthetic methodology for preparation

Scheme I. Projections for γ-Lactam-Bridged Dipeptide Analogues



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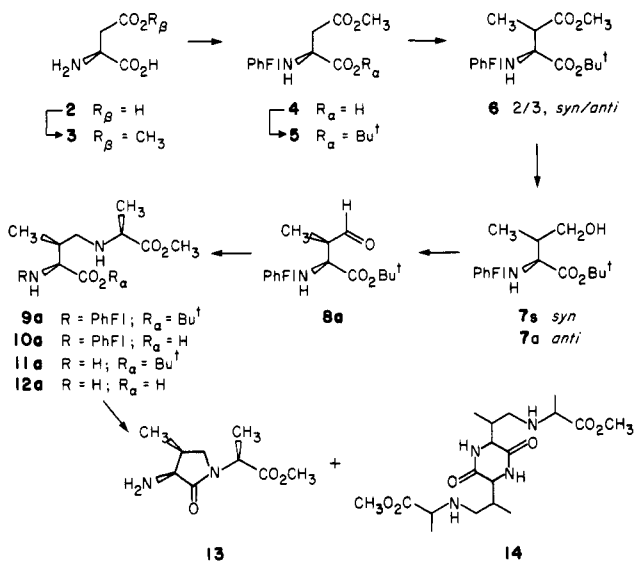
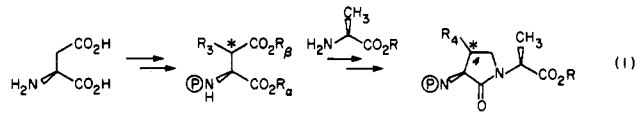
Scheme II. Synthesis via α-*tert*-Butyl β-Methyl Aspartate



of enantiomerically pure 4-alkyl-substituted γ-lactam-bridged dipeptides (1) where the alkyl group at C-4 of the γ-lactam represents the side chain of the former amino acid residue. To demonstrate the versatility of our method, we proposed to synthesize the γ-lactam-bridged analogues of the dipeptides Val-Ala (**1A**), Ile-Ala (**1B**), and Leu-Ala (**1C**) as reflected in Scheme I.

The γ-lactam-bridged dipeptides were to be obtained as projected in sequence 1 from amino acids in a protected form suitable for incorporation into standard peptide synthesis. L-Aspartic acid (**2**) was chosen as the chiral



(1)

educt for the γ-lactam unit because (a) its carbon chain already has all the necessary carbons of the future γ-lactam, (b) it has a β-carboxyl group which allows introduction of an alkyl group via the β-ester enolate, and (c) if differentially esterified, it permits chemical manipulation on each ester separately. The 9-(9-phenylfluorenyl) (PhFl) group[18] was chosen as the N-protecting group. This mode of N-protection insulates the α-center by obstructing removal of the α-proton, thus leading to exclusive formation of the β-ester enolate.[19,20]

Results and Dicussion

Preparation of γ-Lactam-Bridged Dipeptide Val-Ala (3*S*,4*S*,2′*S*)- and (3*S*,4*R*,2′*S*)-19. Via the sequence of Scheme II, *N*-(PhFl)-L-aspartic acid α-*tert*-butyl β-methyl diester (**5**) was readily prepared from L-aspartic acid (**2**).[21] Treating diester **5** with potassium hexamethyldisilazide (KHMDS) in THF at −78 °C followed by trapping the enolate with excess methyl iodide gave alkylated diester **6** in 95% yield as a 2/3, syn/anti[22] mixture of diastereoisomers, whose stereochemistry was established subsequently. Similar ratios but lower yields of **6** were obtained with lithium diisopropylamide (LDA) as a base in the presence of HMPT; no reaction was observed when HMPT was absent. Regioselective reduction of the β-methyl ester of **6** to alcohol **7** was achieved by treating **6** with DIBAL at −25 °C in THF. The diasteroisomeric alcohols **7a** (major isomer, anti) and **7s** (minor isomer, syn) were easily separable by chromatography. In contrast to other observations[23] of DIBAL reduction of N-protected aspartic acid diesters, **6** could be reduced in THF without concomitant formation of 4-methylhomoserine lactone. Repeated efforts to reduce diester **6** directly to aldehyde **8** failed; therefore, diastereomerically pure alcohol **7a** was oxidized to aldehyde **8a** by the dimethyl sulfide–*N*-chlorosuccinimide procedure.[24] Reductive amination[25] with L-alanine methyl ester in the presence of sodium cyanoborohydride than gave amination product **9a** in 85% yield as a single diastereoisomer.

At this point our synthetic plan was to cleave the *tert*-butyl ester of **9** to acid **10** and to form the γ-lactam-bridged dipeptide by heating.[11] Although many reaction conditions[26] were examined, we were unable to find any for hydrolysis of the *tert*-butyl ester without partial cleavage of the PhFl-protected amine. By heating a very dilute solution of free amino acid **12a** in DMF in the presence of pyridine, γ-lactam-bridged dipeptide **13** was obtained in very low yield. The major product isolated from this reaction was diketopiperazine **14**.

Due to the instability of the *N*-PhFl group to acidic reaction conditions needed to cleave the *tert*-butyl ester, the N-protecting group was changed at this stage of the synthesis, where the PhFl group is no longer needed. It had served its function of preventing enolization at the α-carbon of diester **5** and had protected the α-*tert*-butyl ester in **6** from reduction by DIBAL. Thus alcohol **7a** (Scheme III) was first deprotected by hydrogenolysis using Pd/C as catalyst in CH_3OH/HOAc. Reprotection of crude amino alcohol **15a** with benzoxycarbonyl chloride (CBZ-Cl) afforded *N*-CBZ protected amino alcohol **16a** in 92% yield. Oxidation[24] to aldehyde **17a**, followed by reductive amination[25] as previously with L-alanine methyl ester produced **18a** in yields comparable to those obtained with the *N*-PhFl-protected compounds. Exposure of aldehyde **17a** to silica gel led to slow epimerization at C-3. Therefore, the chromatographic purification of **17a** was done rapidly, and traces of the undesired C-3 epimer could be removed at the alkylated amine stage **18a**.

Formation of γ-lactam-bridged dipeptide **19a** was achieved by first hydrolyzing the *tert*-butyl ester of **18a** in warm formic acid and then neutralizing with pyridine in DMF. γ-Lactam-bridged dipeptide **19a** was isolated in 66% yield as a single diastereoisomer. Exactly the same sequence of reactions was used to transform the diastereomeric syn alcohol **7s** into the corresponding γ-lactam bridged dipeptide **19s**.

Absolute Stereochemistry of *N*-CBZ γ-Lactam-Bridged Dipeptides 19s and 19a. The initial assignment of absolute stereochemistry was accomplished by ^1H NMR study of the readily available cyclic carbamates **20s,a** of the diastereoisomeric alcohols **7** (Scheme III). Alcohol **7**, as a pure diastereomer, was hydrogenolyzed using Pd/C as catalyst, and the crude amino alcohol **15** was converted

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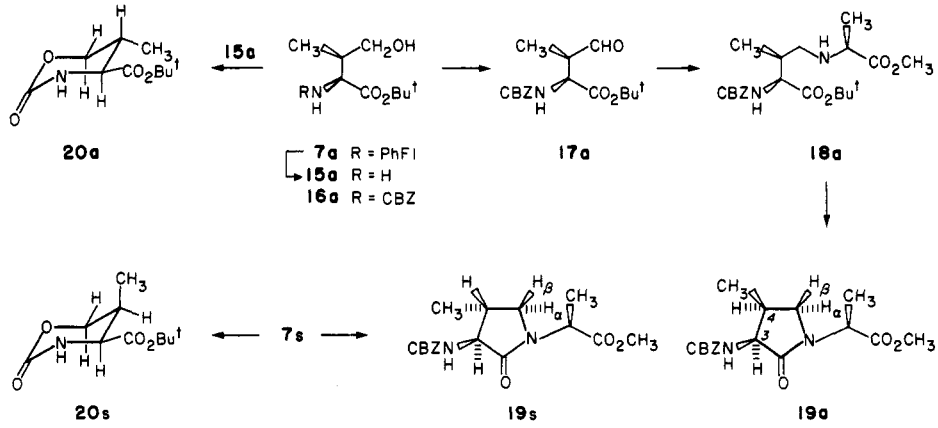
(26) (a) TFA/CH_2Cl_2, 1/1, at room temperature; (b) TFA at room temperature; (c) catalytic TsOH·H_2O in refluxing benzene; (d) formic acid (95–97%) at room temperature; (e) formic acid (95–97%) at 60 °C; (f) i-PrOH/H_2O/HOAc, 9/9/2, at 95 °C.

Scheme III. Synthesis and Stereochemistry of Val-Ala γ-Lactam-Bridged Analogues



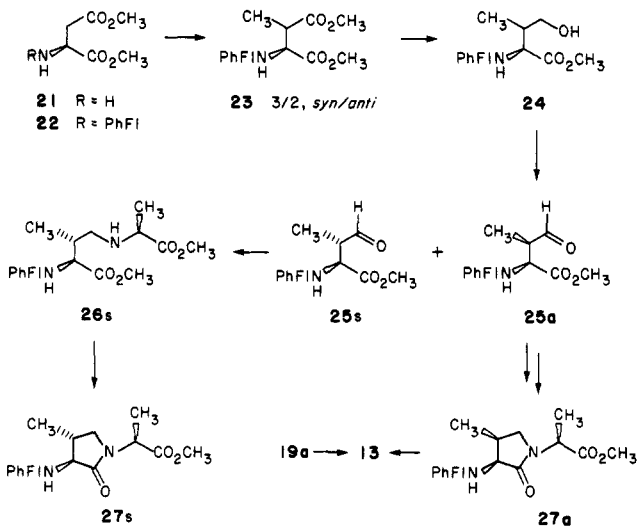
to its cyclic carbamate **20** by reaction with phosgene in toluene in the presence of triethylamine. We considered that **20** should have a chair conformation with the α-*tert*-butyl ester equatorial in both diastereomers and the vicinal methyl group axial in one and equatorial in the other. Analysis by ^1H NMR of cyclic carbamate **20a**, derived from the major alcohol **7a**, shows two large coupling constants of 7.14 and 8.02 Hz, corresponding to two vicinal axial-H, axial-H couplings, and a small coupling constant of 3.72 Hz corresponding to a vicinal axial-H, equatorial-H coupling. Carbamate **20s**, derived from the minor alcohol **7s**, shows three small coupling constants of 4.74, 3.52, and 2.8 Hz, corresponding to two vicinal equatorial-H, equatorial-H and one axial-H, equatorial-H coupling. Based on the previous conformational assignment for carbamate **20** and L-aspartic acid as the educt, the major diastereoisomer alcohol is anti, **7a**, and has the absolute configuration 2*S*,3*R*. The minor alcohol is syn, **7s**, and is assigned the configuration 2*S*,3*S*.

This assignment of the absolute stereochemistry was confirmed by 2D ^1H NMR NOESY experiments on the diastereoisomeric γ-lactam-bridged dipeptides **19**. Major γ-lactam **19a** (synthesized from **7a**) shows strong dipolar exchange of magnetization (NOE) between protons H_3–H_4, H_4–$H_{5\alpha}$, and $H_{5\beta}$–$H_{5\alpha}$ and a small NOE between H_3–$H_{5\alpha}$. For the minor γ-lactam **19s** (synthesized from **7s**) strong NOE's are observed between protons H_4–$H_{5\beta}$ and $H_{5\beta}$–$H_{5\alpha}$ and only very small NOE's between protons H_3–H_4 and H_3–$H_{5\alpha}$. These results confirm the assignment of the absolute configuration for alcohols **7s,a** based on cyclic carbamates **20**. Therefore, dipeptide **19a** has the absolute stereochemistry 3*S*,4*S*,2′*S* and **19s** is 3*S*,4*R*,2′*S*.

Preparation of *N*-PhFl γ-Lactam-Bridged Dipeptides Val-Ala (3*S*,4*S*,2′*S*)- and (3*S*,4*R*,2′*S*)-27. Our initial route to the γ-lactam-bridged dipeptide Val-Ala, using *N*-(PhFl)-L-aspartic acid α-*tert*-butyl β-methyl diester (**5**) as a key intermediate, required a detour to change the N-protecting group from PhFl to CBZ due to the instability of the *N*-PhFl group to acidic hydrolysis conditions needed to cleave the *tert*-butyl ester. Changing the *tert*-butyl ester in **9** to a methyl ester should make the γ-lactam available by thermolytic intramolecular condensation with loss of methanol.[11] Encouraged by our results in the selective alkylation of diester **5** at C-3 followed by almost total regioselective reduction of the β-methyl ester of **6**, we applied the same synthetic strategy to *N*-(PhFl)-L-aspartic acid dimethyl ester (**22**) as the new intermediate (Scheme IV).

L-Aspartic acid dimethyl ester hydrochloride (**21**) was obtained from L-aspartic acid in 98% yield by esterification with methanol/thionyl chloride. N-Alkylation with 9-

Scheme IV. Synthesis via Dimethyl Aspartate



bromo-9-phenylfluorene proceeded in 90% yield to *N*-(PhFl)-L-aspartic acid dimethyl ester (**22**).[21] Then C-alkylation of dimethyl ester **22** with CH_3I was carried out under identical conditions as in the previous alkylation of α-*tert*-butyl β-methyl diester **5**, producing **23** in 82% yield as a 3/2, syn/anti (see below) mixture of diastereoisomers together with 15% of the easily separated C-3 dialkylated product. Reduction of mixture **23** with DIBAL in THF at −35 °C occurred highly regiospecifically to give mixed alcohols **24** in 93% yield without any formation of 4-methylhomoserine lactone.[23] Oxidation of the 3/2 mixture of alcohols **24** as previously described gave 78% of diastereoisomeric aldehydes **25**, easily separable by MPLC. Reductive amination of major aldehyde **25s** (pure syn diastereoisomer) with L-alanine methyl ester using $NaCNBH_3$ as the reducing agent afforded a 95% yield of amination product **26s**. Conversion of **26s** to γ-lactam **27s** was best achieved by refluxing in toluene for 20 h. The absolute configuration of the diastereoisomeric γ-lactams **27a,s** could not be assigned unambiguously by ^1H NMR spectroscopy, due to overlapping chemical shifts of protons HC-3 and H_2C-5 and the small differences between the coupling constants of these protons in **27a** and **27s**.

The absolute configuration of the diastereoisomeric γ-lactams **27a,s** could be assigned, however (Scheme IV), by hydrogenolytic removal of the N-protecting group of *N*-PhFl γ-lactam **27a** and *N*-CBZ γ-lactam **19a**, the stereochemistry of the latter being known. Comparison of their ^1H NMR spectra showed them to be identical. Thus the absolute stereochemistry can be assigned at 3*S*,4*S*,2′*S*

Table I. ^{1}H NMR Data for γ-Lactam-Bridged Dipeptides

compound	δ, ppm (J, Hz)							
	CH_3C-4	CH_3C-2′	HC-4	HC-5		CO_2CH_3	HC-3	HC-2′
(3*S*,4*R*,2′*S*)-**19**	1.25 (d, 6.4)	1.41 (d, 7.5)	2.27 (m)	2.95 (t, 9.3)	3.50 (dd, 9.2, 8.1)	3.71	4.08 (t, 8.8)	4.85 (q, 7.5)
(3*S*,4*S*,2′*S*)-**19**	0.98 (d, 7.0)	1.42 (d, 7.5)	2.88 (m)	3.08 (d, 9.6)	3.54 (dd, 9.5, 5.9)	3.72	4.42 (t, 5.8)	4.84 (q, 7.5)
(3*S*,4*R*,2′*S*)-**27**	0.17 (d, 6.7)	1.27 (d, 7.3)	2.07 (m)	2.52 (dd, 9.3, 8.4)	3.32 (dd, 9.3, 8.3)	3.72	2.50 (d, 8.6)	4.75 (q, 7.4)
(3*S*,4*S*,2′*S*)-**27**	1.09 (d, 7.0)	1.23 (d, 7.4)	1.50 (m)	2.77 (d, 9.4)	3.00 (dd, 9.4, 5.4)	3.69	2.75 (d, 6.7)	4.73 (q, 7.4)
(3*S*,4*R*,2′*R*)-**27**	0.13 (d, 6.7)	1.37 (d, 7.4)	1.93 (m)	2.62 (dd, 8.4, 7.8)	3.29 (t, 8.8)	3.61	2.58 (d, 7.8)	4.83 (q, 7.4)
(3*S*,4*S*,2′*R*)-**27**	0.99 (d, 7.0)	1.30 (d, 7.4)	1.48 (m)	2.69 (d, 9.7)	3.11 (dd, 9.7, 5.2)	3.58	2.79 (d, 6.7)	4.80 (q, 7.4)
(3*S*,4*R*,2′*S*)-**32**		1.29 (d, 7.4)	1.93 (m)	2.61 (dd, 9.5, 7.6)	3.37 (t, 8.8)	3.73	2.59 (d, 8.5)	4.76 (q, 7.4)
(3*S*,4*R*,2′*S*)-**39**		1.42 (d, 7.5)	2.07–2.15 (m)	3.04 (t, 9.2)	3.44 (t, 9.0)	3.72	4.29 (dd, 9.9, 9.4)	4.87 (q, 7.5)

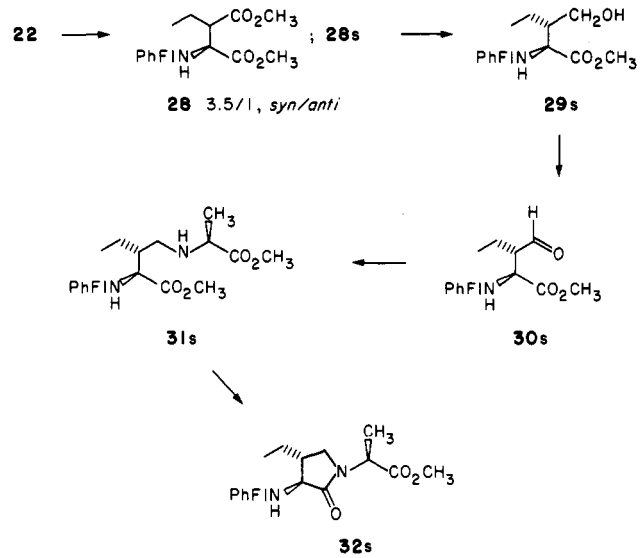
for **27a** and 3*S*,4*R*,2′*S* for **27s**.

Optical Purity of 27. To test if steric integrity had been lost at any of the chiral centers in **27** during its preparation or chromatographic purification, one enantiomer of each diastereomeric pair of **27** was synthesized. HPLC analysis of (3*S*,4*S*,2′*S*)-, (3*S*,4*R*,2′*S*)-**27** and (3*S*,4*S*,2′*R*)-, (3*S*,4*R*,2′*R*)-**27**, obtained from aldehydes **25s** and **25a**, respectively, by reductive amination with D-alanine methyl ester proved that the *N*-PhFl-protected γ-lactam-bridged dipeptides Val-Ala (**27**) are >99.5% enantiomerically pure. This establishes that the *N*-CBZ-protected γ-lactam-bridged dipeptides **19** also are >99.5% enantiomerically pure, since N-deprotection of **27** and **19** give identical products.

Preparation of *N*-PhFl-Protected γ-Lactam-Bridged Dipeptide Ile-Ala (3*S*,4*R*,2′*S*)-32. Extension of our synthetic methodology to the preparation of the *N*-PhFl-protected γ-lactam-bridged dipeptide Ile-Ala (3*S*,4*R*,2′*S*)-**32**, starting from *N*-(PhFl)-L-aspartic acid dimethyl ester (**22**), is shown in Scheme V. Alkylation of **22** as previously but using ethyl iodide led to dialkylation at C-3, and **28** was isolated as the minor reaction product in low yields. Changing the electrophile to ethyl triflate[27] resulted in a dramatic decrease in reaction time, and **28** was isolated in 80% yield as a 3.5/1 mixture of syn/anti diastereoisomers, separable by MPLC; dialkylation at C-3 of **22** was observed only to the extent of 5%. The regioselective reduction of **28s** (syn, major isomer) using DIBAL in THF failed. Instead of alcohol **29s**, 4-ethylhomoserine lactone was isolated as the major product.[23] No lactone formation had been observed in the DIBAL reduction of ester **23** to alcohol **24**; therefore, lactone formation is strongly dependent on the size of the alkyl group at C-3. Lactone formation could be minimized, however, by conducting the DIBAL reduction in toluene at −50 °C for 20 min and oxidizing crude alcohol **29s** directly to aldehyde **30s** in 59% yield from diester **28**. Reductive amination with L-alanine methyl ester and $NaCNBH_3$ afforded a 64% yield of amination product **31s**. Condensation to γ-lactam **32s** was then achieved in 86% yield by refluxing **31** for 3 h in *p*-xylene.

Assignment of the absolute configuration at C-4 of γ-lactam **32s** was made by correlation of its ^{1}H NMR spectrum with those for the C-4 epimeric γ-lactams **27s,a**. Pertinent chemical shifts and coupling constants are collected in Table I. The close coincidence of the coupling constants for HC-3 and H_2C-5 of **32s** with those of

Scheme V. Synthesis of Ile-Ala Analogue



(3*S*,4*R*,2′*S*)-**27**, and the fact that the protons of the C-4 alkyl group show the same upfield shift due to an anisotropic shielding effect of the *N*-PhFl group, allow assignment of 3*S*,4*R*,2′*S* as the configuration of **32s** (Table I).

Preparation of *N*-CBZ γ-Lactam-Bridged Dipeptide β-MeLeu-Ala (3*S*,4*R*,2′*S*)-39. As demonstrated in the previous syntheses, γ-lactam-bridged dipeptide Val-Ala can be prepared either from *N*-(PhFl)-L-aspartic acid α-*tert*-butyl β-methyl diester (**5**) to give the *N*-CBZ γ-lactams **19** (Scheme III) or, in fewer steps, from *N*-(PhFl)-L-aspartic acid dimethyl ester (**22**) to give *N*-PhFl γ-lactams **27** (Scheme IV). Although dimethyl ester **22** is a versatile educt for the synthesis of *N*-PhFl γ-lactam-bridged dipeptide Ile-Ala **32s** (Scheme V), its synthetic utility is somewhat diminished because of the instability of alcohol **29** toward lactone formation. Anticipating similar problems during the preparation of γ-lactam-bridged dipeptide β-MeLeu-Ala **39**, we chose *N*-(PhFl)-L-aspartic acid α-*tert*-butyl β-methyl diester (**5**) as the educt and, at the same time, demonstrated another synthetic application of **5** (Scheme VI).

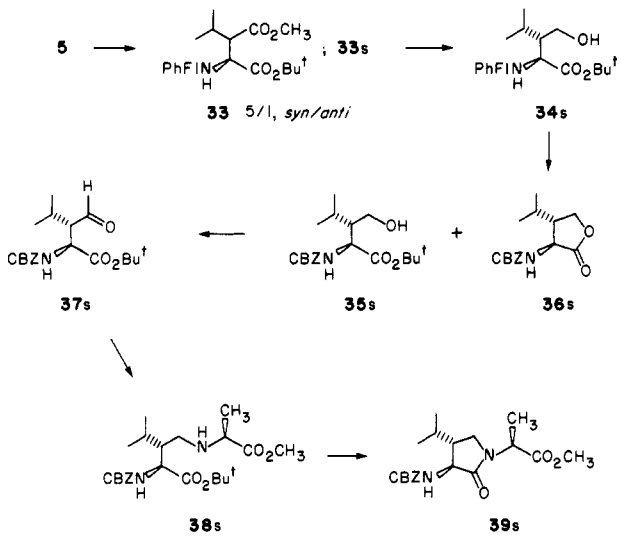
The alkylation of **5** was carried out using 200 mol % of KHMDS in THF at −78 °C and trapping the enolate with 200 mol % of isopropyl triflate, added as a freshly prepared 0.6 M solution in hexane.[27] The process of deprotonation with KHMDS and trapping the enolate with isopropyl triflate was repeated twice. After the reaction was quenched with 1 M H_3PO_4, **33** was isolated in 43% yield

(27) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 3673.

Table II. ^{1}H NMR Data for 2-Amino-4-hydroxy-3-methylbutanoates and β-Substituted Aspartates

	δ, ppm (J, Hz)							
compound	CH_3C-3	HC-1′	CH_3C-1′	HC-2	HC-3	HC-4	CO_2Bu^t	CO_2CH_3
(2S,3S)-7	0.86 (d, 7.2)			2.70 (s)	1.65 (m)	3.40 (dd, 11, 3.2) 3.51 (t, 11)	1.17	
(2S,3R)-7	0.65 (d, 7.0)			2.45 (d, 8.3)	1.85 (m)	3.40 (dd, 11, 8.5) 3.54 (dd, 11, 3.3)	1.16	
(2S,3S)-16	0.65 (d, 6.9)			4.59 (dd, 7.8, 2.7)	2.35 (m)	3.23 (m) 3.45 (m)	1.47	
(2S,3R)-16	1.01 (d, 7.0)			4.26 (dd, 8.4, 6.3)	2.06 (m)	3.52 (d, 10.5) 3.67 (dd, 11.5, 2.9)	1.47	
(2S,3S)-28		1.56–1.79 (m)	0.77 (t, 7.4)	2.79 (dd, 10.2, 6.6)	2.37 (m)			3.24 3.51
(2S,3R)-28		1.14 (m) 1.41 (m)	0.74 (t, 7.4)	2.85 (dd, 11.4, 8.8)	2.47 (m)			3.13 3.76
(2S,3S)-33		1.96 (m)	0.41 (d, 6.5) 0.67 (d, 6.5)	2.66 (d, 4.9)	2.14 (dd, 10, 4.9)		1.24	3.68
(2S,3R)-33		2.05 (m)	0.54 (d, 6.6) 0.83 (d, 6.6)	2.90 (d, 5.3)	2.24 (dd, 8.0, 6.0)		1.10	3.71

Scheme VI. Synthesis of Leu-Ala Analogue



as a 5/1, syn/anti, mixture of diastereoisomers, separable by MPLC, together with 45% of recovered diester **5**. Reduction of major isomer **33s** to alcohol **34s** was done as previously described in the reduction of **28**. Alcohol **34s** was isolated in 78% yield and showed no tendency to form lactone even under chromatographic purification. Hydrogenolytic (H_2, Pd/C) deprotection of alcohol **34s** in CH_3OH/HOAc followed by reprotection afforded *N*-CBZ alcohol **35s** in 66% yield together with 30% of 4-isopropylhomoserine lactone **36s**. Acid-catalyzed lactone formation occurred during the hydrogenolysis of **34s** and can be minimized by shortening the reaction time and omitting the acetic acid. Oxidation to aldehyde **37s** (80% yield) and reductive amination to **38s** (52% yield) with L-alanine methyl ester was carried out in the same way as described earlier for compounds **17** and **18**. Heating **38s** neat to 60 °C led to slow conversion to γ-lactam **39s**, which was prepared in 62% yield analogously to the previously described preparation of γ-lactam **19**. Assignment of the absolute configuration at C-4 of γ-lactam **39s** was made by a 2D ^{1}H NMR NOESY analysis. γ-Lactam **39s** shows a strong NOE only between protons H_4–$H_{5\beta}$ and $H_{5\beta}$–$H_{5\alpha}$ and a weak NOE between protons H_3–H_4 and H_3–$H_{5\alpha}$. Therefore the absolute configuration of γ-lactam **39s** is 3*S*,4*R*,2′*S* (Table I).

Synthesis of 3-alkylaspartic acids has been reported,[28,29] and recently 3-methylaspartic acid was found in the cyclic peptide toxin cyanogenosin RR, isolated from *Microcystis aeruginosa*.[30] The first synthesis[28] proceeded from di-*tert*-butyl *N*-formylaspartate and gave a mixture of α- and β-alkylated products. For the β-diastereomer, erythro configuration was assigned by analogy[31] and absolute stereochemistry derived by conversion to 3-methylaspartic acid and comparison of specific rotations.[32] The second synthesis[29] involves incubation of 3-alkylfumaric acid with the enzyme 3-methylaspartate ammonia-lyase (EC 4.3.1.2) for several days. The overall yield of purified 3-alkylaspartic acid varies from 20 to 40% depending on the alkyl group, and in the case of *n*-butyl, no amination occurred. The relative stereochemistry of 3-methyl- and 3-ethylaspartic acid has been assigned from the coupling constants of HC-2 and HC-3 of their *N*-(trifluoroacetyl)aspartic anhydrides. The absolute configuration at C-3 was assigned by degrading 3-ethylaspartic acid to 3-ethylsuccinic acid for which specific rotations have been reported.[33-35] The

(28) Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.
(29) Akhtar, M.; Botting, N. P.; Cohen, M. A.; Gani, D. *Tetrahedron* **1987**, *43*, 5899.
(30) Painuly, P.; Perez, R.; Fukai, T.; Shimizu, Y. *Tetrahedron Lett.* **1988**, *29*, 11.
(31) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197.
(32) Bodansky, M.; Marconi, G. G. *J. Antibiot.* **1970**, *23*, 238.
(33) Wren, H.; Crawford, J. *J. Chem. Soc.* **1937**, 230.
(34) Fredga, A. *Arkiv Kemi* **1947**, *24A*, 1.
(35) Berner, E.; Leonardsen, R. *Justus Liebigs Ann. Chem.* **1939**, *538*, 1.

correlation between the specific rotation and the absolute configuration was established by X-ray analysis of an ergoflavine derivative which gave (−)-methylsuccinic acid on oxidation.[36] The synthetic methodology described in the present work not only has the advantage of affording a variety of 3-alkylaspartic acids in high yields and in a fully protected form suitable for peptide synthesis, but also allows the unambiguous determination of their absolute stereochemistry by definitive NMR experiments. In Table II, the NMR data for the diastereoisomeric *N*-PhFl-protected 3-ethyl- and 3-isopropylaspartic acid diesters **28s,a** and **33s,a** are summarized together with the data for the diastereoisomeric *N*-PhFl- and *N*-CBZ-2-amino-4-hydroxy-3-methylbutanoic acid *tert*-butyl esters **7s** and **7a** and **16s** and **16a**.

Summary

The protected γ-lactam-bridged dipeptides Val-Ala, Ile-Ala, and β-MeLeu-Ala have been prepared in enantiomerically pure form starting from *N*-(PhFl)-L-aspartic acid α-*tert*-butyl β-methyl diester (**5**) or *N*-(PhFl)-L-aspartic acid dimethyl ester (**22**), both readily available from L-aspartic acid (**2**).[21] The *N*-PhFl protecting group directs regiospecific alkylation of **5** and **22** to C-3, without any loss of steric integrity at the α-chiral center. Furthermore, the bulk of the PhFl group contributed to the specific reduction of the β-methyl ester in **6**, **23**, **28**, and **33** without reducing the α-methyl or α-*tert*-butyl ester.

The synthetic routes described in this paper represent efficient and general methodology for the synthesis of enantiomerically pure 4-alkyl γ-lactam-bridged dipeptides. Such peptides then can be incorporated into polypeptides to induce a degree of conformational constraint.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately before use; chloroform was distilled from P_2O_5; methylene chloride, acetonitrile, isopropyl alcohol, triethylamine, pyridine, and trimethylsilyl chloride were distilled from CaH_2; toluene and hexane were distilled from NaH; methanol from magnesium; and dimethylsulfide (Me_2S) from sodium. *N*-Chlorosuccinimide (NCS) was crystallized from benzene. Column chromatography was performed with 230–400 (low-pressure chromatography) and 70–230 (gravity chromatography) mesh silica gel. Preparative medium-pressure liquid chromatography (MPLC) was performed with glass columns and 230–400 mesh silica gel. High-pressure liquid chromatography (HPLC) was done on a 4.6 × 250 mm, 5 μm LiChrosorb Si 60 normal-phase silica gel column at a flow rate of 1 mL/min. Thin-layer chromatography (TLC) was done on silica 60/F-254 aluminum-backed plates (E. Merck). ^{1}H NMR spectra were recorded at 250 MHz or 500 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in ppm (δ units) downfield from internal tetramethylsilane or internal sodium 3-(trimethylsilyl)propionate-d_4 (TSP) for spectra taken in D_2O. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley. Unless otherwise noted, reactions were conducted under a nitrogen atmosphere. Final product solutions were dried over $MgSO_4$ or Na_2SO_4, filtered, and evaporated under reduced pressure on a Berkeley rotary evaporator. In cases where identical reactions have been carried out with diastereomeric educts, only the experimental procedure for the major diastereomer is described.

***N*-(9-Phenylfluorenyl)-L-aspartic acid α-*tert*-butyl β-methyl diester (5)** was prepared from L-aspartic acid via the β-methyl ester **3** and its *N*-(9-phenylfluorenyl) derivative **4** as described.[21]

***N*-(9-Phenylfluorenyl)-3-methyl-L-aspartic Acid α-*tert*-Butyl β-Methyl Diester (6).** To a stirred solution of KHMDS (5.6 mL, 3.35 mmol, 0.6 M in toluene) in 50 mL of THF was added **5** (1.06 g, 2.4 mmol) dissolved in 10 mL THF at −78 °C dropwise. The pale yellow solution was stirred at −78 °C for 45 min, CH_3I (0.46 mL, 7.2 mmol) was added, and the resulting solution was stirred at −78 °C for 1 h. The reaction was quenched with 1 mL of MeOH at −78 °C, warmed up to room temperature, and partioned between 80 mL of 1 M H_3PO_4 and 80 mL of Et_2O. The organic layer was washed with 50 mL of H_2O and 50 mL of saturated $Na_2S_2O_3$, dried, and evaporated. The oily residue was chromatographed (low pressure, hexane/EtOAc, 12/1) to give **6** as a thick oil in 95% yield and a 2/3 ratio of syn/anti diastereoisomers according to ^{1}H NMR: ^{1}H NMR δ 0.96 (d, J = 7.0, CH_3C-3), 1.04 (d, J = 7.4, CH_3C-3), 1.08, 1.12 (2 s, CO_2Bu^t), 2.47 (m, HC-3), 2.86 (m, HC-2), 3.40, 3.53 (2 s, CO_2CH_3), 7.11–7.33 (m, 11 H, Ar), 7.58–7.66 (m, 2 H, Ar). Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8; N, 3.1. Found: C, 76.2; H, 6.9; N, 3.1.

***tert*-Butyl (2*S*,3*S*)-2-[(9-Phenylfluorenyl)amino]-3-methyl-4-hydroxybutanoate [(2*S*,3*S*)-7] and *tert*-Butyl (2*S*,3*R*)-2-[(9-Phenylfluorenyl)amino]-3-methyl-4-hydroxybutanoate [(2*S*,3*R*)-7].** Into a solution of **6** (1.02 g, 2.23 mmol, mixture of diastereomers) in 75 mL of THF was dropped DIBAL (6.9 mL, 6.9 mmol, 1 M in hexane) at −30 °C. The clear solution was stirred at −30 °C for 4 h, 0.33 mL of acetone and, after 10 min, 2 mL of MeOH were added, and the reaction mixture was partitioned between 75 mL of 1 M H_3PO_4 and 150 mL of Et_2O. Saturated $NaHCO_3$ (50 mL) was added, the mixture was filtered, and the organic phase was washed with brine, dried, and evaporated. The residue was chromatographed (low pressure, hexane/EtOAc, 5/1) to give 350 mg of (2*S*,3*S*)-**7** and 460 mg of (2*S*,3*R*)-**7** (85% yield).

(2*S*,3*R*)-7: ^{1}H NMR δ 0.65 (d, 3 H, J = 7.0, CH_3C-3), 1.16 (s, 9 H, CO_2Bu^t), 1.85 (m, 1 H, HC-3), 2.45 (d, 1 H, J = 8.3, HC-2), 3.40 (dd, 1 H, J = 11, 8.5, HC-4), 3.54 (dd, 1 H, J = 11, 3.3, HC-4), 7.15–7.47 (m, 11 H, Ar), 7.68–7.71 (m, 2 H, Ar). Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.3; H, 7.3; N, 3.3. Found: C, 78.4; H, 7.2; N, 3.3.

(2*S*,3*S*)-7: ^{1}H NMR δ 0.86 (d, 3 H, J = 7.2, CH_3C-3), 1.17 (s, 9 H, CO_2Bu^t), 1.65 (m, 1 H, HC-3), 2.70 (s, 1 H, HC-2), 3.0 and 3.3 (2 s, br, OH, NH), 3.40 (dd, 1 H, J = 11, 3.2, HC-4), 3.51 (t, 1 H, J = 11, HC-4), 7.19–7.53 (m, 11 H, Ar), 7.67–7.71 (m, 2 H, Ar).

***tert*-Butyl (2*S*,3*R*)-2-[(9-Phenylfluorenyl)amino]-3-methyl-4-oxobutanoate [(2*S*,3*R*)-8].** To a stirred suspension of *N*-chlorosuccinimide (560 mg, 4.2 mmol) in 10 mL of toluene was added $(CH_3)_2S$ (0.42 mL, 5.7 mmol) at 0 °C. The suspension was cooled to −25 °C, and a solution of (2*S*,3*R*)-**7** (450 mg, 1.05 mmol) in 4 mL of toluene was added dropwise. The reaction mixture was stirred for 4 h at −25 °C, and then Et_3N (0.56 mL, 4.2 mmol) in 1 mL of toluene was added. The cooling bath was removed and after 5 min 25 mL of Et_2O was added, and the mixture was washed with 0.5 M H_3PO_4 (25 mL) and H_2O (25 mL), dried, and evaporated. The oily residue was chromatographed (low pressure, hexane/EtOAc, 10/1) to leave (2*S*,3*R*)-**8** as a thick oil (360 mg, 80%): ^{1}H NMR δ 0.95 (d, 3 H, J = 6.9, CH_3C-3), 1.17 (s, 9 H, CO_2Bu^t), 2.33 (m, 1 H, HC-3), 2.94 (t, 1 H, J = 6.7, HC-2), 3.28 (s, 1 H, J = 7.5, NH), 7.17–7.42 (m, 11 H, Ar), 7.67–7.73 (m, 2 H, Ar), 9.37 (d, 1 H, J = 1.5, CHO).

(2*S*,3*S*)-8: ^{1}H NMR δ 1.01 (d, 3 H, J = 6.9, CH_3C-3), 1.19 (s, 9 H, CO_2Bu^t), 2.35 (m, 1 H, HC-3), 3.13 (m, 2 H, HC-2, NH), 7.17–7.40 (m, 11 H, Ar), 7.66–7.71 (m, 2 H, Ar), 9.14 (s, 1 H, CHO).

Reductive Amination Product. (2*S*,3*S*,2′*S*)-9. A solution of (2*S*,3*R*)-**8** (700 mg, 1.64 mmol), L-alanine methyl ester hydrochloride (1.12 g, 8.2 mmol), and $NaCNBH_3$ (82 mg, 1.3 mmol) in 50 mL of MeOH was stirred at room temperature for 45 min. The reaction mixture was evaporated, and the oily residue was partitioned between 50 mL of saturated $NaHCO_3$ and 100 mL of Et_2O. The H_2O layer was extracted with 40 mL of Et_2O, and the combined organic phase was washed with 30 mL of H_2O, dried, and evaporated. The residue was chromatographed (low pressure, hexane/EtOAc, 4/1) to leave 642 mg (76% yield) of (2*S*,3*S*,2′*S*)-**9** as a thick oil: ^{1}H NMR δ 0.80 (d, 3 H, J = 6.9, CH_3C-3), 1.16 (s, 9 H, CO_2Bu^t), 1.19 (d, 3 H, J = 6.9, CH_3C-2′), 1.71 (m, 1 H, HC-3), 2.36 (dd, 1 H, J = 11.7, 7.4, HC-4), 2.46 (dd, 1 H, J = 11.7, 6.3, HC-4), 2.48 (d, 1 H, J = 5.0, HC-2), 3.15 (q, 1 H, J = 6.9, HC-2′),

(36) McPhail, A. T.; Sim, G. A.; Asher, J. D. M.; Robertson, J. M.; Silverton, J. V. *J. Chem. Soc. B* **1966**, 18.

3.70 (s, 3 H, CO_2CH_3), 7.18–7.41 (m, 11 H, Ar), 7.64–7.67 (m, 2 H, Ar).

(2*S*,3*R*,2′*S*)-9: ^{1}H NMR δ 0.84 (d, 3 H, J = 6.9, CH_3C-3), 1.15 (d, 3 H, J = 7.0, CH_3C-2′), 1.17 (s, 9 H, CO_2Bu^t), 1.60 (m, 1 H, HC-3), 2.27 (dd, 1 H, J = 12, 7.2, HC-4), 2.42 (dd, 1 H, J = 12, 6.7, HC-4), 2.51 (s, br, 1 H, HC-2), 3.05 (s, br, 1 H, NH), 3.21 (q, 1 H, J = 7.0, HC-2′), 3.70 (s, 3 H, CO_2CH_3), 7.18–7.49 (m, 1 H, Ar), 7.64–7.73 (m, 2 H, Ar).

(2*S*,3*S*,2′*S*)-11. A solution of (2*S*,3*S*,2′*S*)-**9** (600 mg, 1.17 mmol) and Pd/C (10%, 300 mg) in 50 mL of MeOH/HOAc, 20/1, was shaken under 50 psi of H_2 for 16 h. The reaction mixture was filtered, the filtrate was evaporated, and the residue was partitioned between 30 mL of H_2O and 30 mL of Et_2O. The H_2O layer was basified with saturated $NaHCO_3$ and extracted with $CHCl_3$ (3 × 30 mL), and the organic layer was dried and evaporated to leave (2*S*,3*S*,2′*S*)-**11** as a colorless oil in 96% yield: ^{1}H NMR δ 0.96 (d, 3 H, J = 7.0, CH_3C-3), 1.27 (d, 3 H, J = 7.1, CH_3C-2′), 1.47 (s, 9 H, CO_2Bu^t), 2.02 (m, 1 H, HC-3), 2.53 (dd, 2 H, J = 7.0, 3.5, H_2C-4), 3.29 (m, 2 H, HC-2, HC-2′), 3.71 (s, 3 H, CO_2CH_3).

Deprotected γ-Lactam Dipeptide (3*S*,4*S*,2′*S*)-13. From (3*S*,4*S*,2′*S*)-27. A solution of 30 mg (0.07 mmol) of (3*S*,4*S*,2′*S*)-**27** and 20 mg of Pd/C (10%) in 8 mL of MeOH/HOAc (20:1) was mechanically shaken under 50 psi of H_2 for 16 h. The reaction mixture was filtered through Celite and evaporated, the residue was partitioned between 10 mL of H_2O and 10 mL of Et_2O, and the water layer was basified with saturated $NaHCO_3$ and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layer was dried and evaporated to leave 12 mg (88%) of (3*S*,4*S*,2′*S*)-**13** as a pale yellow oil. **From (3*S*,4*S*,2′*S*)-19.** A suspension of 15 mg of (3*S*,4*S*,2′*S*)-**19** and 4 mg of Pd/C (10%) in 2 mL of EtOAc was hydrogenolyzed with H_2 at 1 atm for 30 min. The reaction mixture was filtered through Celite and evaporated to give 5 mg of (3*S*,4*S*,2′*S*)-**13** as a pale yellow oil: ^{1}H NMR δ 1.08 (d, 3 H, J = 7.1, CH_3C-4), 1.41 (d, 3 H, J = 7.6, CH_3C-2′), 2.61 (m, 1 H, HC-4), 3.04 (dd, 1 H, J = 9.4, 1.8, HC-5), 3.47 (dd, 1 H, J = 9.4, 6.1, HC-5), 3.60 (d, 1 H, J = 7.4, HC-3), 3.73 (s, 3 H, CO_2CH_3), 4.85 (q, 1 H, J = 7.5, HC-2′).

Diketopiperazine 14. A solution of (2*S*,3*S*,2′*S*)-**11** (154 mg, 0.56 mmol) in 4 mL of formic acid (95–97%) was heated to 75 °C for 3.5 h. After 3.5 h, no **11** could be detected by TLC (silica gel, $CHCl_3$/MeOH/pyridine, 10:1:0.5), and the reaction mixture was evaporated and dried (Kugelrohr, 55 °C, 0.1 mmHg, over night), to leave crude (2*S*,3*S*,2′*S*)-**12** as a thick syrup. A heterogeneous mixture of 125 mg (0.404 mmol) of crude (2*S*,3*S*,2′*S*)-**12** and 65 μL (0.808 mmol) of pyridine in 4 mL of cold DMF was added slowly (syringe pump, 1 h) to 150 mL of DMF at 75 °C. After complete addition, the homogeneous solution was stirred at 75 °C for 3 h, the reaction mixture was evaporated, and the residue was partitioned between 40 mL of $CHCl_3$ and 30 mL of saturated $NaHCO_3$. The organic layer was dried and evaporated to leave 60 mg (75%) of a mixture of **14** and (3*S*,4*S*,2′*S*)-**13** (95/5, according to ^{1}H NMR): ^{1}H NMR δ 0.98 (d, 3 H, J = 7.1, CH_3C-3), 1.44 (d, 3 H, J = 7.5, CH_3C-2′), 2.94 (m, 1 H, HC-3), 3.12 (d, 1 H, J = 9.7, HC-4), 3.58 (dd, 1 H, J = 9.7, 5.7, HC-4), 3.74 (s, 3 H, CO_2CH_3), 4.62 (t, 1 H, J = 6.1, HC-2), 4.84 (q, 1 H, J = 7.5, HC-2′), 6.58 (s, br, 1 H, CONH), 8.32 (d, 1 H, J = 1, NH···O).

***tert*-Butyl (2*S*,3*R*)-2-Amino-3-methyl-4-hydroxybutanoate [(2*S*,3*R*)-15].** A solution of (2*S*,3*R*)-**7** (180 mg, 0.42 mmol) and 90 mg of Pd/C (10%) in 12 mL of MeOH/HOAc (20/1) was mechanically shaken under 50 psi of H_2 for 16 h. The reaction mixture was filtered through Celite and evaporated, and the residue was partitioned between 20 mL of H_2O and 20 mL of Et_2O. The water layer was basified with saturated $NaHCO_3$ and extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried and evaporated to leave (2*S*,3*R*)-**15** as a colorless oil in quantitative yield: ^{1}H NMR δ 0.90 (d, 3 H, J = 7.0, CH_3C-3), 1.48 (s, 9 H, CO_2Bu^t), 1.98 (m, 1 H, HC-3), 2.83 (s, br, NH_2, OH), 3.27 (d, 1 H, J = 7.9, HC-2), 3.64 (m, 2 H, H_2C-4).

(2*S*,3*S*)-15: ^{1}H NMR δ 0.94 (d, 3 H, J = 7.2, CH_3C-3), 1.47 (s, 9 H, CO_2Bu^t), 2.14 (m, 1 H, HC-3), 2.48 (s, br, NH_2, OH), 3.62 (dd, 1 H, J = 10.9, 4.9, HC-4 and d, 1 H, J = 3.1, HC-2), 3.90 (dd, 1 H, J = 10.9, 3.0, HC-4).

***tert*-Butyl (2*S*,3*R*)-2-[(Benzoxycarbonyl)amino]-3-methyl-4-hydroxybutanoate [(2*S*,3*R*)-16].** To a stirred solution of (2*S*,3*R*)-**15** (132 mg, 0.7 mmol) and pyridine (85 μL, 1.05 mmol) in 5 mL of dry CH_3CN was added CBZ-Cl (120 μL, 0.84 mmol) dissolved in 0.5 mL of CH_3CN drop-by-drop at 0 °C under N_2. The mixture was stirred for 2 h at 0 °C, and then again pyridine (85 μL, 1.05 mmol) followed by CBZ-Cl (120 μL, 0.84 mmol) in 0.5 mL CH_3CN were added. Stirring was continued for 1 h, the reaction mixture was evaporated, and the residue was partitioned between 25 mL of 1 M H_3PO_4 and 25 mL of $CHCl_3$. The H_2O layer was extracted with $CHCl_3$ (2 × 20 mL), and the combined organic layer was dried and evaporated. The crude product was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 2/1) to leave (2*S*,3*R*)-**16** (230 mg, 92%) as a pale yellow oil: ^{1}H NMR δ 1.01 (d, 3 H, J = 7.0, CH_3C-3), 1.47 (s, 9 H, CO_2Bu^t), 2.06 (m, 1 H, CH-3), 2.45 (s, br, 1 H, OH), 3.52 (d, br, 1 H, J = 10.5, HC-4), 3.67 (dd, 1 H, J = 11.5, 2.9, HC-4), 4.26 (dd, 1 H, J = 8.4, 6.3, HC-2), 5.11 (s, 2 H, CH_2Ar), 5.76 (d, 1 H, J = 8.4, NH), 7.31–7.37 (s, 5 H, Ar). Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.1; H, 7.8; N, 4.3. Found: C, 63.1; H, 7.9; N, 4.3.

(2*S*,3*S*)-16: ^{1}H NMR δ 0.65 (d, 3 H, J = 6.9, CH_3C-3), 1.47 (s, 9 H, CO_2Bu^t), 2.35 (m, 1 H, HC-3), 3.23 (m, 1 H, HC-4), 3.45 (m, 1 H, HC-4), 4.0 (s, br, 1 H, OH), 4.59 (dd, 1 H, J = 7.8, 2.7, HC-2), 5.12 (s, 2 H, CH_2Ar), 5.58 (d, 1 H, J = 7.3, NH), 7.34–7.37 (s, 5 H, Ar).

***tert*-Butyl (2*S*,3*R*)-2-[(Benzoxycarbonyl)amino]-3-methyl-4-oxobutanoate [(2*S*,3*R*)-17].** To a stirred suspension of NCS (314 mg, 2.35 mmol) in 10 mL of dry toluene was added Me_2S (235 μL, 3.21 mmol) at 0 °C under N_2. The suspension was cooled to −25 °C, and (2*S*,3*R*)-**16** (190 mg, 0.59 mmol) in 2 mL of toluene was added drop-by-drop. Stirring was continued for 4 h at −25 °C, Et_3N (327 μL, 2.35 mmol) in 0.5 mL of toluene was added, the cold bath was removed, and after 10 min, the reaction mixture was partitioned between 25 mL of 1 M H_3PO_4 and 30 mL of Et_2O. The organic layer was washed with 20 mL of H_2O, dried, and evaporated. The oily residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 5/1) to leave (2*S*,3*R*)-**17** in 75% yield as a colorless oil: ^{1}H NMR δ 1.12 (d, 3 H, J = 7.2, CH_3C-3), 1.42 (s, 9 H, CO_2Bu^t), 3.09 (m, 1 H, HC-3), 4.69 (dd, 1 H, J = 7.9, 3.7, HC-2), 5.13 (s, 2 H, CH_2Ar), 5.57 (d, 1 H, J = 8.0, NH), 7.36 (s, 5 H, Ar), 9.69 (s, 1 H, CHO). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.5; H, 7.2; N, 4.4. Found: C, 63.5; H, 7.3; N, 4.3.

(2*S*,3*S*)-17: ^{1}H NMR δ 1.08 (d, 3 H, J = 7.1, CH_3C-3), 1.47 (s, 9 H, CO_2Bu^t), 2.90 (m, 1 H, HC-3), 4.79 (dd, 1 H, J = 7.9, 3.2, HC-2), 5.08 (s, 2 H, CH_2Ar), 5.46 (d, 1 H, J = 7.9, NH), 7.34 (s, 5 H, Ar), 9.76 (s, 1 H, CHO).

Reductive Amination Product (2*S*,3*S*,2′*S*)-18. To a stirred solution of (2*S*,3*R*)-**17** (140 mg, 0.436 mmol) in 10 mL of dry MeOH was added a mixture of L-alanine methyl ester hydrochloride (300 mg, 2.18 mmol) and $NaCNBH_3$ (22 mg, 0.35 mmol) at room temperature. The homogeneous reaction mixture was stirred for 45 min, the solvent was evaporated, and the residue was partitioned between 25 mL of saturated $NaHCO_3$ and 40 mL of Et_2O. The organic layer was dried and evaporated, and the residue was purified by filtration through a short column of silica gel (hexane/EtOAc, 2/1) to leave (2*S*,3*S*,2′*S*)-**18** as a colorless oil in 89% yield: ^{1}H NMR δ 0.97 (d, 3 H, J = 6.9, CH_3C-3), 1.26 (d, 3 H, J = 7.0, CH_3C-2′), 1.46 (s, 9 H, CO_2Bu^t), 2.20 (m, 1 H, HC-3), 2.39 (dd, 1 H, J = 11.8, 7.5, HC-4), 2.62 (dd, 1 H, J = 11.8, 5.4, HC-4), 3.28 (q, 1 H, J = 7.0, HC-2′), 3.70 (s, 3 H, CO_2CH_3), 4.24 (dd, 1 H, J = 8.3, 4.2, HC-2), 5.11 (s, 2 H, CH_2Ar), 6.05 (d, 1 H, J = 8.3, NH), 7.36 (s, 5 H, Ar). Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.8; H, 7.9; N, 6.9. Found: C, 62.0; H, 7.7; N, 6.6.

(2*S*,3*R*,2′*S*)-18: ^{1}H NMR δ 0.83 (d, 3 H, J = 6.8, CH_3C-3), 1.30 (d, 3 H, J = 7.0, CH_3C-2′), 1.46 (s, 9 H, CO_2Bu^t), 2.20 (m, 1 H, HC-3), 2.30 (dd, 1 H, J = 12.2, 5.6, HC-4), 2.64 (dd, 1 H, J = 12.2, 8.7, HC-4), 3.34 (q, 1 H, J = 7.0, HC-2′), 3.70 (s, 3 H, CO_2CH_3), 4.45 (dd, 1 H, J = 8.8, 3.0, HC-2), 5.11 (s, 2 H, CH_2Ar), 5.72 (d, 1 H, J = 8.8, NH), 7.35 (s, 5 H, Ar).

γ-Lactam Dipeptide (3*S*,4*S*,2′*S*)-19. A solution of (2*S*,3*S*,2′*S*)-**18** (45 mg, 0.11 mmol) in formic acid (2.5 mL, 95–97%) was heated to 65–70 °C for 90 min. Excess formic acid was evaporated, and the residue was dried for 0.5 h at 50 °C (0.5 mmHg) (Kugelrohr). The solid residue was dissolved in 2 mL of DMF, and pyridine (10 μL, 140 mol %) was added. The clear solution was stirred at 55–60 °C for 90 min, the DMF was evaporated, the oily residue was dissolved in 30 mL Et_2O, and the organic layer was washed with 15 mL of saturated $NaHCO_3$

and 15 mL of 1 M H_3PO_4, dried, and evaporated. The residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 2/3) to leave (3*S*,4*S*,2′*S*)-**19** as a oil in 66% yield: ^{1}H NMR δ 0.98 (d, 3 H, *J* = 7.0, CH_3C-4), 1.42 (d, 3 H, *J* = 7.5, CH_3C-2′), 2.88 (m, 1 H, HC-4), 3.08 (d, 1 H, *J* = 9.6, H_βC-5), 3.54 (dd, 1 H, *J* = 9.5, 5.9, H_αC-5), 3.72 (s, 3 H, CO_2CH_3), 4.42 (t, 1 H, *J* = 5.8, HC-3), 4.84 (q, 1 H, *J* = 7.5, HC-2′), 5.13 (s, 2 H, CH_2Ar), 5.31 (d, br, 1 H, NH), 7.36 (s, 5 H, Ar). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.1; H, 6.6; N, 8.4. Found: C, 61.2; H, 6.2; N, 8.4.

(3*S*,4*R*,2′*S*)-**19**: ^{1}H NMR δ 1.25 (d, 3 H, *J* = 6.4, CH_3C-4), 1.41 (d, 3 H, *J* = 7.5, CH_3C-2′), 2.27 (m, 1 H, HC-4), 2.95 (t, 1 H, *J* = 9.3, H_αC-5), 3.50 (dd, 1 H, *J* = 9.2, 8.1, H_βC-5), 3.71 (s, 3 H, CO_2CH_3), 4.08 (t, 1 H, *J* = 8.8, HC-3), 4.85 (q, 1 H, *J* = 7.5, HC-2′), 5.13 (s, 2 H, CH_2Ar), 5.19 (s, br, 1 H, NH), 7.35 (s, 5 H, Ar).

Cyclic Carbamate (4*S*,5*R*)-20. To a stirred solution of (2*S*,3*R*)-**15** (66 mg, 0.35 mmol) and Et_3N (0.41 mL, 3.15 mmol) in 5 mL of CH_2Cl_2 was added $COCl_2$ (1.27 mL, 10 wt% $COCl_2$ in toluene) at 0 °C under N_2. The ice bath was removed, stirring was continued for 30 min, 10 mL of saturated $NaHCO_3$ and 10 mL of CH_2Cl_2 were added, and the layers were separated. The organic layer was dried and evaporated, and the residue was chromatographed (silica gel, hexane/EtOAc, 1/2) to leave (4*S*,5*R*)-**20** as a white solid in 50% yield: mp 129–131 °C; ^{1}H NMR δ 1.20 (d, 3 H, *J* = 6.8, CH_3C-5), 1.50 (s, 9 H, CO_2Bu^t), 2.30 (m, 1 H, HC-5), 3.65 (dd, 1 H, *J* = 7.2, 1.3, HC-4), 3.94 (dd, 1 H, *J* = 11.1, 8.0, HC-6), 4.21 (dd, 1 H, *J* = 11.2, 3.7, HC-6), 5.7 (s, br, 1 H, NH). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.8; H, 8.0; N, 6.5. Found: C, 56.8; H, 8.0; N, 6.3.

(4*S*,5*S*)-**20**: mp 118–120 °C; ^{1}H NMR δ 1.06 (d, 3 H, *J* = 7.0, CH_3C-5), 1.51 (s, 9 H, CO_2Bu^t), 2.48 (m, 1 H, HC-5), 4.11 (d, 1 H, *J* = 4.7, HC-5), 4.16 (dd, 1 H, *J* = 11.1, 3.5, HC-6), 4.32 (dd, 1 H, *J* = 11.1, 2.8, HC-6), 5.59 (s, 1 H, NH).

Dimethyl *N*-(9-Phenylfluorenyl)-3-methyl-L-aspartate (23). To a stirred solution of KHMDS (5.5 mL, 3.24 mmol, 180 mol %, 0.6 M in toluene) in 40 mL of dry THF was added **22** (720 mg, 1.8 mmol, prepared via dimethyl aspartate (**21**) as described [21]) dissolved in 5 mL of THF drop-by-drop at under N_2 at −72 °C. The pale yellow solution was stirred at −75 °C for 1 h, and then CH_3I (0.57 mL, 9 mmol) in 1.3 mL of THF was added at −75 °C. The reaction mixture was stirred for 2 h at −75 °C, 2 mL of MeOH were added at −75 °C, the reaction mixture was partitioned between 40 mL of 1 M H_3PO_4 and 40 mL of Et_2O, and the water layer was extracted with Et_2O (2 × 40 mL). The combined organic layer was washed with 40 mL of saturated $Na_2S_2O_3$ and brine, dried, and evaporated, and the residue was purified by MPLC (silica gel, hexane/EtOAc, 8/1) to leave **23** (600 mg, 82%) as a mixture of diastereoisomers (3/2, according to ^{1}H NMR): ^{1}H NMR δ 0.92 (d, *J* = 7.0, CH_3C-3), 1.46 (d, *J* = 7.0, CH_3C-3), 2.5–2.7 (m, 2 HC-3), 2.85–3.12 (m, br, 2 HC-2 and 2 NH), 3.17, 3.26, 3.48, 3.72 (4 s, CO_2CH_3) 7.17–7.43 (m, 11 H, Ar), 7.64–7.71 (m, 2 H, Ar). Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.2; H, 6.1; N, 3.4. Found: C, 75.1; H, 6.1; N, 3.4. As a side product, 117 mg (15%) of dimethylated product was isolated.

Methyl (2*S*)-2-[(9-Phenylfluorenyl)amino]-3-methyl-4-hydroxybutanoate (24). To a stirred solution of **23** (580 mg, 1.4 mmol) in 50 mL of dry THF was added DIBAL (4.2 mL, 4.2 mmol, 1 M in hexane) dropwise at −35 °C under N_2. The reaction mixture was stirred at −30 °C for 1 h, it was poured into a stirred mixture of 50 mL of 1 M H_3PO_4 and 50 mL of Et_2O, and the phases were separated. The water layer was extracted with 30 mL of Et_2O, and the combined organic layer was dried and evaporated. The residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 2/1) to leave 508 mg (93%) of **24** as a mixture of diastereoisomers (3/2, according to ^{1}H NMR): ^{1}H NMR δ 0.53 (d, *J* = 7.0, CH_3C-3), 0.90 (d, *J* = 7.2, CH_3C-3), 1.65 (m, HC-3), 1.93 (m, HC-3), 2.48 (d, *J* = 9.9, HC-2), 2.76 (d, *J* = 3.8, HC-2), 3.19, 3.28 (2 s, CO_2CH_3), 3.29–3.63 (m, H_2C-4), 7.15–7.44 (m, 11 H, Ar), 7.67–7.71 (m, 2 H, Ar). Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.5; H, 6.5; N, 3.6. Found: C, 77.4; H, 6.6; N, 3.6.

Methyl (2*S*,3*S*)-2-[(9-Phenylfluorenyl)amino]-3-methyl-4-oxobutanoate [(2*S*,3*S*)-25] and Methyl (2*S*,3*R*)-2-[(9-Phenylfluorenyl)amino]-3-methyl-4-oxobutanoate [(2*S*,3*R*)-25]. To a stirred suspension of NCS (682 mg, 5.12 mmol) in 20 mL of toluene was added Me_2S (512 μL, 6.35 mmol) at 0 °C under N_2. The suspension was cooled to −25 °C, and **24** (495 mg, 1.28 mmol) in 4 mL of toluene was added dropwise. Stirring was continued for 4 h at −25 °C, and then Et_3N (717 μL, 5.12 mmol) in 2 mL of toluene was added. The cold bath was removed, and after 10 min, the reaction mixture was partitioned between 50 mL of 1 M H_3PO_4 and 50 mL of Et_2O. The organic layer was washed with 20 mL of H_2O, dried, and evaporated, and the diastereoisomeric aldehydes were purified by chromatography (low pressure, silica gel, hexane/EtOAc, 6/1) in 78% yield and separated by MPLC (silica gel, hexane/EtOAc, 16/1).

Major isomer (2*S*,3*S*)-**25**: ^{1}H NMR δ 1.06 (d, 3 H, *J* = 6.9, CH_3C-3), 2.35 (m, 1 H, HC-3), 3.0–3.2 (m, 2 H, HC-2, NH), 3.32 (s, 3 H, CO_2CH_3), 7.18–7.40 (m, 11 H, Ar), 7.66–7.73 (m, 2 H, Ar), 9.21 (s, 1 H, CHO). Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.8; H, 6.0; N, 3.6. Found: C, 77.8; H, 6.1; N, 3.6.

Minor isomer (2*S*,3*R*)-**25**: ^{1}H NMR δ 0.81 (d, 3 H, *J* = 6.9, CH_3C-3), 2.42 (m, 1 H, HC-3), 2.90 (t, br, 1 H, *J* = 9.0, HC-2), 3.10 (d, br, 1 H, NH), 3.24 (s, 3 H, CO_2CH_3), 7.18–7.39 (m, 11 H, Ar), 7.67–7.74 (m, 2 H, Ar), 9.47 (d, 1 H, *J* = 3.2, CHO).

Reductive Amination Product (2*S*,3*R*,2′*S*)-26. To a stirred solution of (2*S*,3*S*)-**25** (355 mg, 0.92 mmol) in 15 mL of dry MeOH was added a mixture of L-alanine methyl ester hydrochloride (640 mg, 4.6 mmol) and $NaCNBH_3$ (50 mg, 0.8 mmol) at room temperature. The pale yellow reaction mixture was stirred for 1 h, the solvent was evaporated, and the residue was partitioned between 40 mL of saturated $NaHCO_3$ and 50 mL of Et_2O. The water layer was extracted with 20 mL of Et_2O, and the combined organic layer was washed with H_2O, dried, and evaporated. The residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 3/1) to give 417 mg (95%) of (2*S*,3*R*,2′*S*)-**26** as a thick oil.

(2*S*,3*R*,2′*S*)-**26**: ^{1}H NMR δ 0.87 (d, 3 H, *J* = 6.8, CH_3C-3), 1.11 (d, 3 H, *J* = 7.0, CH_3C-2′), 1.58 (m, 1 H, HC-3), 2.19 (dd, 1 H, *J* = 12.2, 6.1, HC-4), 2.52 (dd, 1 H, *J* = 12.2, 7.3, HC-4), 2.60 (d, 1 H, *J* = 4.0, HC-2), 3.17 (q, 1 H, *J* = 7.0, HC-2′), 3.24 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 7.12–7.46 (m, 11 H, Ar), 7.64–7.70 (m, 2 H, Ar).

(2*S*,3*S*,2′*S*)-**26**: ^{1}H NMR δ 0.69 (d, 3 H, *J* = 6.9, CH_3C-3), 1.24 (d, 3 H, *J* = 6.9, CH_3C-2′), 1.72 (m, 1 H, HC-3), 1.99 (s, br, 1 H, NH), 2.41 (d, 1 H, *J* = 7.6, HC-2, and dd, 1 H, *J* = 11.3, 6.6, HC-4), 2.60 (dd, 1 H, *J* = 11.7, 5.6, HC-4), 3.19 (s, 3 H, CO_2CH_3), 3.28 (q, 1 H, *J* = 6.9, HC-2′), 3.74 (s, 3 H, CO_2CH_3), 7.14–7.43 (m, 11 H, Ar), 7.65–7.71 (m, 2 H, Ar).

γ-Lactam Dipeptide (3*S*,4*R*,2′*S*)-27. A solution of (2*S*,3*R*,2′*S*)-**26** (150 mg, 0.32 mmol) in 15 mL of toluene was refluxed at 120 °C bath temperature for 22 h. The solvent was evaporated, and the residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 3/1) to give 104 mg (75%; 95% based on recovered starting material) of (3*S*,4*R*,2′*S*)-**27** as a thick oil.

(3*S*,4*R*,2′*S*)-**27**: ^{1}H NMR δ 0.17 (d, 3 H, *J* = 6.7, CH_3C-4), 1.27 (d, 3 H, *J* = 7.3, CH_3C-2′), 2.07 (m, 1 H, HC-4), 2.50 (d, 1 H, *J* = 8.6, HC-3), 2.52 (dd, 1 H, *J* = 9.3, 8.4, HC-5), 3.24 (s, br, NH), 3.32 (dd, 1 H, *J* = 9.3, 8.3, HC-5), 3.72 (s, 3 H, CO_2CH_3), 4.75 (q, 1 H, *J* = 7.4, HC-2′), 7.17–7.5 (m, 11 H, Ar), 7.64–7.73 (m, 2 H, Ar). Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.3; H, 6.4; N, 6.4. Found: C, 76.4; H, 6.5; N, 6.3.

(3*S*,4*S*,2′*S*)-**27**: ^{1}H NMR δ 1.09 (d, 3 H, *J* = 7.0, CH_3C-4), 1.23 (d, 3 H, *J* = 7.4, CH_3C-2′), 1.50 (m, 1 H, HC-4), 2.75 (d, 1 H, *J* = 6.7, HC-3), 2.77 (d, 1 H, *J* = 9.4, HC-5), 3.0 (dd, 1 H, *J* = 9.4, 5.4, HC-5), 3.69 (s, 3 H, CO_2CH_3), 4.73 (q, 1 H, *J* = 7.4, HC-2′), 7.1–7.5 (m, 1 H, Ar), 7.64–7.75 (m, 2 H, Ar).

(3*S*,4*R*,2′*R*)-**27**: ^{1}H NMR δ 0.13 (d, 3 H, *J* = 6.7, CH_3C-4), 1.37 (d, 3 H, *J* = 7.4, CH_3C-2′), 1.93 (m, 1 H, HC-4), 2.58 (d, 1 H, *J* = 7.8, HC-3), 2.62 (dd, 1 H, *J* = 8.4, 7.8, HC-5), 3.29 (t, 1 H, *J* = 8.8, HC-5), 3.61 (s, 3 H, CO_2CH_3), 4.83 (q, 1 H, *J* = 7.4, HC-2′), 7.17–7.49 (m, 11 H, Ar), 7.64–7.73 (m, 2 H, Ar).

(3*S*,4*S*,2′*R*)-**27**: ^{1}H NMR δ 0.99 (d, 3 H, *J* = 7.0, CH_3C-4), 1.30 (d, 3 H, *J* = 7.4, CH_3C-2′), 1.48 (m, 1 H, HC-4), 2.69 (d, 1 H, *J* = 9.7, HC-5), 2.79 (d, 1 H, *J* = 6.7, HC-3), 3.01 (s, 1 H, NH), 3.11 (dd, 1 H, *J* = 9.7, 5.2, HC-5), 3.58 (s, 3 H, CO_2CH_3), 4.80 (q, 1 H, *J* = 7.4, HC-2′), 7.15–7.47 (m, 11 H, Ar), 7.64–7.72 (m, 2 H, Ar).

Dimethyl 2-*N*-(9-Phenylfluorenyl)-3-ethyl-L-aspartate (28). To a stirred solution of KHMDS (8.65 mL, 5.2 mmol, 0.6

M in toluene) in 60 mL of dry THF was added **22** (1.6 g, 4.0 mmol) dissolved in 8 mL of THF dropwise at −75 °C under N_2. The pale yellow solution was stirred at −75 °C for 45 min, and then EtOTf (568 μL, 4.4 mmol) was added neat at once at −75 °C. After 10 min the reaction was quenched with 3 mL of MeOH and partitioned between 40 mL of 1 M H_3PO_4 and 50 mL of Et_2O. The water layer was extracted with 40 mL of Et_2O, the combined organic layers were dried and evaporated, and the residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 8/1) to leave 6% of **22** and 82% of a mixture of **28** (78%; 3.5/1 mixture of diastereoisomers) and dialkylation product (4%). The diastereoisomers of **28** and the dialkylation product were separated by MPLC (silica gel, hexane/EtOAc, 15/1) to yield 84% of **28** based on recovered **22** (6%).

(2*S*,3*S*)-**28**: ^{1}H NMR δ 0.77 (t, 3 H, *J* = 7.4, H_3C-2′), 1.56–1.79 (m, 2 H, H_2C-1′), 2.37 (m, 1 H, HC-3), 2.79 (dd, 1 H, *J* = 10.2, 6.6, HC-2), 3.04 (d, 1 H, *J* = 10.2, NH), 3.24 (s, 3 H, CO_2CH_3), 3.51 (s, 3 H, CO_2CH_3), 7.15–7.43 (m, 11 H, Ar), 7.63–7.70 (m, 2 H, Ar). Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.5; H, 6.3; N, 3.3. Found: C, 75.5; H, 6.2; N, 3.1.

(2*S*,3*R*)-**28**: ^{1}H NMR δ 0.74 (t, 3 H, *J* = 7.4, H_3C-2′), 1.14 (m, 1 H, HC-1′), 1.41 (m, 1 H, HC-1′), 2.47 (m, 1 H, HC-3), 2.85 (dd, 1 H, *J* = 11.4, 8.8, HC-2), 3.00 (d, 1 H, *J* = 11.5, NH), 3.13 (s, 3 H, CO_2CH_3), 3.76 (s, 3 H, CO_2CH_3e, 7.12–7.38 (m, 11 H, Ar), 7.65–7.71 (m, 2 H, Ar).

Methyl (2*S*,3*S*)-2-[(9-Phenylfluorenyl)amino]-3-ethyl-4-hydroxybutanoate [(2*S*,3*S*)-29]. To a solution of (2*S*,3*S*)-**28** (200 mg, 0.47 mmol) in 25 mL of toluene was added DIBAL (1.4 mL, 1.4 mmol, 1 M solution in hexane) at −49 °C drop-by-drop. The reaction mixture was stirred at −47 °C for 20 min, and then quenched by adding a mixture of 25 mL of 1 M H_3PO_4 and 30 mL of Et_2O at −47 °C. The phases were separated, and the organic layer was dried and evaporated to a residue of ca. 5 mL. This residue was filtered through a short column of silica gel (EtOAc), and the solvent was evaporated. Crude (2*S*,3*S*)-**29** was dried for 45 min at 40 °C (0.5 mmHg) (Kugelrohr) and used immediately for the next oxidation step: mass recovery 84%; ^{1}H NMR δ 0.80 (t, 3 H, *J* = 7.0, H_3C-2′), 1.22–1.52 (m, 2 H, H_2C-1′), 2.81 (d, 1 H, *J* = 3.4, HC-2), 3.28 (s, 3 H, CO_2CH_3), 3.42 (dd, 1 H, *J* = 11.3, 2.0, HC-4), 3.60 (dd, 1 H, *J* = 11.3, 5.5, HC-4), 7.14–7.46 (m, 11 H, Ar), 7.67–7.70 (m, 2 H, Ar).

Methyl (2*S*,3*S*)-2-[(9-Phenylfluorenyl)amino]-3-ethyl-4-oxobutanoate [(2*S*,3*S*)-30]. To a stirred suspension of NCS (200 mg, 1.5 mmol) in 10 mL of dry toluene was added Me_2S (150 μL, 2.04 mmol) at 0 °C under N_2. The suspension was cooled to −25 °C, and crude (2*S*,3*S*)-**29** (157 mg, 0.39 mmol) in 2 mL of toluene was added drop-by-drop. Stirring was continued for 4 h at −25 °C, and then Et_3N (208 μL, 1.5 mmol) in 0.5 mL of toluene was added. The cold bath was removed, and after 10 min the reaction mixture was partitioned between 25 mL of 1 M H_3PO_4 and 30 mL of Et_2O. The organic layer was dried and evaporated. Purification of the residue by chromatography (low pressure, silica gel, hexane/EtOAc, 6/1) afforded (2*S*,3*S*)-**30** in 59% yield based on (2*S*,3*S*)-**28**: ^{1}H NMR δ 0.78 (t, 3 H, *J* = 7.5, H_3C-2′), 1.50–1.60 (m, 1 H, HC-1′), 1.70–1.81 (m, 1 H, HC-1′), 2.20 (m, 1 H, HC-3), 2.98 (dd, 1 H, *J* = 9.0, 4.7, HC-2), 3.07 (d, 1 H, *J* = 10, NH), 3.29 (s, 3 H, CO_2CH_3), 7.17–7.41 (m, 11 H, Ar), 7.66–7.72 (m, 2 H, Ar), 9.35 (d, 1 H, *J* = 2.0, CHO).

Reductive Amination Product (2*S*,3*R*,2′*S*)-31. To a stirred solution of (2*S*,3*S*)-**30** (100 mg, 0.25 mmol) in 7 mL of dry MeOH was added a mixture of L-alanine methylester hydrochloride (175 mg, 1.25 mmol) and $NaCNBH_3$ (14 mg, 0.22 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h, the solvent was evaporated, and the residue was partitioned between 30 mL of saturated $NaHCO_3$ and 40 mL of Et_2O. The H_2O layer was extracted with 30 mL of Et_2O, and the combined organic layer was dried and evaporated. Purification of the residue by chromatography (low pressure, silica gel, hexane/EtOAc, 4/1) left (2*S*,3*R*,2′*S*)-**31** in 64% yield as a thick oil: ^{1}H NMR δ 0.67 (t, 3 H, *J* = 7.2, H_3C-2″), 1.13 (d, 3 H, *J* = 7.0, CH_3C-2′), 1.20–1.50 (m, 3 H, HC-3, H_2C-1″), 2.26 (dd, 1 H, *J* = 12.3, 4.3, HC-4), 2.58 (dd, 1 H, *J* = 12.3, 7.0, HC-4), 2.66 (d, 1 H, *J* = 3.6, HC-2), 3.18 (q, 1 H, *J* = 7.0, HC-2′), 3.24 (s, 3 H, CO_2CH_3), 3.69 (s, 3 H, CO_2CH_3), 7.15–7.45 (m, 11 H, Ar), 7.64–7.70 (m, 2 H, Ar).

γ-Lactam Dipeptide (3*S*,4*R*,2′*S*)-32. A solution of 70 mg of (2*S*,3*R*,2′*S*)-**31** in 10 mL of *p*-xylene was refluxed at 140–150 °C for 3 h. After evaporation of the solvent, (3*S*,4*R*,2′*S*)-**32** was isolated in 86% yield by MPLC (silica gel, hexane/EtOAc, 5/1) as a white foam: ^{1}H NMR δ 0.38 (m, 4 H, H_3C-2″), 0.59 (m, 1 H, HC-1″), 1.29 (d, 3 H, *J* = 7.4, CH_3C-2′), 1.93 (m, 1 H, HC-4), 2.59 (d, 1 H, *J* = 8.5, HC-3), 2.61 (dd, 1 H, *J* = 9.5, 7.6, HC-5), 3.16 (s, 1 H, NH), 3.37 (t, 1 H, *J* = 8.8, HC-5), 3.73 (s, 3 H, CO_2CH_3), 4.76 (q, 1 H, *J* = 7.5, HC-2′), 7.16–7.54 (m, 11 H, Ar), 7.63–7.71 (m, 2 H, Ar). Anal. Calcd for $C_{29}H_{30}N_2O_3$: C, 76.6; H, 6.7; N, 6.2. Found: C, 76.6; H, 6.7; N, 6.1.

2-*N*-(9-Phenylfluorenyl)-3-isopropyl-L-aspartic Acid α-*tert*-Butyl β-Methyl Diester [(2*S*,3*R*)- and (2*S*,3*S*)-33]. To a stirred solution of KHMDS (0.43 mL, 0.26 mmol, 0.6 M in toluene) in 5 mL of dry THF was added **5** (50 mg, 0.13 mmol) in 1 mL of THF drop-by-drop at −78 °C. After 45 min, i-PrOTf (0.4 mL, 0.26 mmol, 0.67 M in hexane) was added at −78 °C, and after 45 min another 0.43-mL portion of KHDMS was added, followed by 0.4 mL of i-PrOTf in hexane after 15 min. The reaction was stirred at −78 °C for 60 min and then quenched with 15 mL of 1 M H_3PO_4 and 20 mL of Et_2O. The phases were separated, the water layer was extracted with 20 mL of Et_2O, the combined organic layer was dried and evaporated, and the residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 12/1), affording 27.2 mg (43%) of **33** as a thick oil (ratio of diastereoisomers 5/1 by ^{1}H NMR) and 25.1 mg (45%) of recovered **5**. The diastereoisomers of **33** are separable by MPLC (silica gel, hexane/$CHCl_3$/EtOAc, 10/20/0.6).

Major isomer (2*S*,3*S*)-**33**: ^{1}H NMR δ 0.41 (d, 3 H, *J* = 6.5, CH_3C-1′), 0.67 (d, 3 H, *J* = 6.5, CH_3C-1′), 1.24 (s, 9 H, CO_2Bu^t), 1.96 (m, 1 H, HC-1′), 2.14 (dd, 1 H, *J* = 10, 4.9, HC-3), 2.66 (d, 1 H, *J* = 4.9, HC-2), 3.35 (br, 1 H, NH), 3.68 (s, 3 H, CO_2CH_3), 7.17–7.42 (m, 11 H, Ar), 7.65–7.70 (m, 2 H, Ar). Anal. Calcd for $C_{31}H_{35}NO_4$: C, 76.7; H, 7.3; N, 2.9. Found: C, 76.6; H, 7.3; N, 2.8.

Minor isomer (2*S*,3*R*)-**33**: ^{1}H NMR δ 0.54 (d, 3 H, *J* = 6.6, CH_3C-1′), 0.83 (d, 3 H, *J* = 6.6, CH_3C-1′), 1.10 (s, 9 H, CO_2Bu^t), 2.05 (m, 1 H, HC-1′), 2.24 (dd, 1 H, *J* = 8.0, 6.0, HC-3), 2.9 (d, 1 H, *J* = 5.3, HC-2), 3.10 (br, 1 H, NH), 3.71 (s, 3 H, CO_2CH_3), 7.13–7.41 (m, 11 H, Ar), 7.63–7.68 (m, 2 H, Ar).

***tert*-Butyl (2*S*,3*S*)-2-[(9-Phenylfluorenyl)amino]-3-isopropyl-4-hydroxybutanoate [(2*S*,3*S*)-34].** To a stirred solution of (2*S*,3*S*)-**33** (220 mg, 0.45 mmol) in 15 mL of toluene was added DIBAL (1.4 mL, 1.4 mmol, 1 M in hexane) at −30 °C. The reaction mixture was stirred at −30 °C for 20 min and then quenched by adding a mixture of 20 mL of 1 M H_3PO_4 and 30 mL of EtO_2 at −30 °C. The phases were separated, the water layer was extracted with 25 mL of Et_2O, and the combined organic layer was dried and evaporated to a residue of ca. 3 mL, which was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 7/1) to give 161 mg (78%) of (2*S*,3*S*)-**34** as a colorless oil: ^{1}H NMR δ 0.52 (d, 3 H, *J* = 6.7, CH_3C-1′), 0.82 (d, 3 H, *J* = 6.7, CH_3C-1′), 1.21 (s, 9 H, CO_2Bu^t), 1.2–1.35 (m, 1 H, HC-1′), 1.5–1.62 (m, 1 H, HC-3), 2.77 (d, 1 H, *J* = 3.8, HC-2), 3.61 (dd, 1 H, *J* = 11.4, 8.0, HC-4), 3.77 (dd, 1 H, *J* = 11.4, 3.1, HC-4), 7.18–7.42 (m, 11 H, Ar), 7.67–7.71 (m, 2 H, Ar). Anal. Calcd for $C_{30}H_{35}NO_3$: C, 78.7; H, 7.7; N, 3.1. Found: C, 78.7; H, 7.8; N, 3.0.

***tert*-Butyl (2*S*,3*S*)-2-[(Benzoxycarbonyl)amino]-3-isopropyl-4-hydroxybutanoate [(2*S*,3*S*)-35].** A solution of (2*S*,3*S*)-**34** (175 mg, 0.38 mmol) in 12 mL of MeOH/HOAc (15/1) was hydrogenolyzed overnight under 1 atm of H_2 using 80 mg Pd/C (10%) as the catalyst. The reaction mixture was filtered through Celite, the catalyst was washed with MeOH, the filtrate and washings were evaporated, and the residue was partitioned between 15 mL of H_2O and 20 mL of Et_2O. The organic layer was extracted with 10 mL of 0.5 M H_3PO_4, and the combined water layer was adjusted to pH 9 with saturated Na_2CO_3 and extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried and evaporated to give crude amine in ca. 85% yield.

To a stirred solution of 57 mg (0.26 mmol) of crude amine and 140 mg (1.3 mmol) of $NaHCO_3$ in 8 mL of H_2O/EtOAc, 1/1, was added CBZ-Cl (60 μL, 0.39 mmol) in 1 mL of EtOAc dropwise at 0 °C. The mixture was stirred at 0 °C for 90 min, the phases were separated, and the water layer was extracted with 20 mL of EtOAc. The combined organic layer was dried and evaporated, and the residue was purified by chromatography (low pressure,

silica gel, hexane/EtOAc, 9/2) to give 60 mg (66%) of (2*S*,3*S*)-**35** as a colorless oil and 22 mg (30%) of lactone (3*S*,4*S*)-**36**.

(2*S*,3*S*)-**35**: ^{1}H NMR δ 0.88 (d, 3 H, J = 6.8, CH_3C-1′), 0.97 (d, 3 H, J = 6.8, CH_3C-1′), 1.47 (s, 9 H, CO_2Bu^t), 1.68 (m, 1 H, HC-1′), 2.0 (m, 1 H, HC-3), 3.47 (dd, br, 2 H, J = 11.0, H_2C-4), 3.73 (s, br, 1 H, OH), 4.62 (dd, 1 H, J = 8.0, 3.1, HC-2), 5.12 (s, 2 H, CH_2Ar), 5.68 (d, 1 H, J = 7.7, NH), 7.31–7.37 (s, 5 H, Ar). Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.9; H, 8.3; N, 4.0. Found: 64.9; H, 8.1; N, 4.0.

(3*S*,4*S*)-**36**: mp 81–83 °C; ^{1}H NMR δ 0.94 (d, 3 H, J = 6.5, CH_3C-1′), 1.00 (d, 3 H, J = 6.6, CH_3C-1′), 1.85 (m, 1 H, HC-1′), 2.33 (m, 1 H, HC-4), 3.93 (t, 1 H, J = 10, HC-5), 4.26 (t, 1 H, J = 10, HC-5), 4.40 (t, 1 H, J = 8.5, HC-3), 5.14 (m, 2 H, CH_2Ar), 5.26 (d, 1 H, J = 8.5, NH), 7.31–7.36 (s, 5 H, Ar). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.0. Found: C, 64.9; H, 7.0; N, 4.9.

***tert*-Butyl (2*S*,3*S*)-2-[(Benzoxycarbonyl)amino]-3-isopropyl-4-oxobutanoate [(2*S*,3*S*)-37].** To a stirred suspension of NCS (77 mg, 0.57 mmol) in 4.5 mL of dry toluene was added Me_2S (58 μL, 0.72 mmol) at 0 °C under N_2. The suspension was cooled to −25 °C and (2*S*,3*S*)-**35** (45 mg, 0.128 mmol) in 0.5 mL of toluene was added dropwise. Stirring was continued for 4 h at −25 °C, and then Et_3N (80 μL, 0.57 mmol) in 0.5 mL of toluene was added. The cold bath was removed, and after 10 min, the reaction was partitioned between 20 mL of 1 M H_3PO_4 and 25 mL of Et_2O. The organic layer was washed three times with 20 mL of H_2O, dried, and evaporated. The residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 5/1) to give (2*S*,3*S*)-**37** in 80% yield, based on 14% recovered (2*S*,3*S*)-**35**: ^{1}H NMR δ 1.05 (d, 3 H, J = 6.9, CH_3C-1′), 1.09 (d, 3 H, J = 6.9, CH_3C-1′), 1.45 (s, 9 H, CO_2Bu^t), 2.16 (m, 1 H, HC-1′), 2.45 (m, 1 H, HC-3), 4.62 (dd, 1 H, J = 8.3, 6.0, HC-2), 5.11 (s, 2 H, CH_2Ar), 5.45 (d, 1 H, J = 8.3, NH), 7.31–7.36 (s, 5 H, Ar), 9.72 (d, 1 H, J = 2.9, CHO). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.3; H, 7.8; N, 4.0. Found: C, 64.8; H, 7.7; N, 4.0.

Reductive Amination Product (2*S*,3*R*,2′*S*)-38. To a stirred solution of (2*S*,3*S*)-**37** (20 mg, 0.057 mmol) in 2 mL of dry MeOH was added a mixture of L-alanine methyl ester hydrochloride (50 mg, 0.36 mmol) and $NaCNBH_3$ (6 mg, 0.1 mmol) at room temperature. After 2 h, the solvent was evaporated, and the residue was partitioned between 10 mL of saturated $NaHCO_3$ and 20 mL of Et_2O. The water layer was extracted with 10 mL of Et_2O, the combined organic layer was dried and evaporated, and the residue was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 4/1) to give 13 mg (52%) of (2*S*,3*R*,2′*S*)-**38** as a thick oil: ^{1}H NMR δ 0.91 (d, 3 H, J = 6.3, CH_3C-1″), 1.03 (d, 3 H, J = 6.1, CH_3C-1″), 1.27 (d, 3 H, J = 7.0, CH_3C-2′), 1.46 (s, 9 H, CO_2Bu^t), 1.62–1.79 (m, 2 H, HC-1″, HC-3), 2.54–2.70 (m, 2 H, H_2C-4), 3.34 (q, 1 H, J = 7.0, HC-2′), 3.70 (s, 3 H, CO_2CH_3), 4.56 (dd, 1 H, J = 8.7, 2.5, HC-2), 5.11 (s, 2 H, CH_2Ar), 6.48 (d, 1 H, J = 8.6, NH), 7.27–7.37 (s, 5 H, Ar).

γ-Lactam Dipeptide (3*S*,4*R*,2′*S*)-39. A solution of (2*S*,3*R*,2′*S*)-**38** (12 mg, 0.027 mmol) in formic acid (1.5 mL, 95–97%) was heated to 70 °C for 90 min. Excess formic acid was evaporated, and the residue was dried for 15 min at 40 °C (0.5 mmHg) (Kugelrohr). The oily residue was dissolved in 1.5 mL of DMF and two drops of pyridine, the clear solution was stirred at 65 °C for 2.5 h, and the solvent was evaporated. The residue was dissolved in 15 mL of Et_2O, washed with 10 mL of saturated $NaHCO_3$ and 10 mL of 1 M H_3PO_4, dried, and evaporated, leaving a residue that was purified by chromatography (low pressure, silica gel, hexane/EtOAc, 3/2) to give (3*S*,4*R*,2′*S*)-**39** as an oil in 62% yield: ^{1}H NMR δ 0.97 (d, 3 H, J = 7.0, CH_3C-1″), 0.99 (d, 3 H, J = 7.0, CH_3C-1″), 1.42 (d, 3 H, J = 7.5, CH_3C-2′), 1.86–1.94 (m, 1 H, HC-1″), 2.07–2.15 (m, 1 H, HC-4), 3.04 (t, 1 H, J = 9.2, $H_\alpha C$-5), 3.44 (t, 1 H, J = 9.0, $H_\beta C$-5), 3.72 (s, 3 H, CO_2CH_3), 4.29 (dd, 1 H, J = 9.9, 9.4, HC-3), 4.87 (q, 1 H, J = 7.5, HC-2′), 5.06 (d, 1 H, J = 9.4, NH), 5.14 (s, 2 H, CH_2Ar), 7.29–7.36 (s, 5 H, Ar). Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 63.0; H, 7.2; N, 7.7. Found: C, 62.7; H, 7.3; N, 7.5.

Preparation of Isopropyl Triflate in Hexane. A solution of 0.69 mL of i-PrOH (distilled from CaH_2) and 0.74 mL of pyridine (distilled from CaH_2) in 4.5 mL of hexane (distilled from NaH) was added over a period of 20 min to a stirred solution of 1.51 mL of $(Tf)_2O$ in 7.5 mL of hexane at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then filtered through a short pad of Na_2SO_4 to give a colorless, clear solution, 0.67 M in hexane, which was used immediately.

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Registry No. **5**, 120230-41-3; (2*S*,3*S*)-**6**, 120230-42-4; (2*S*,3*R*)-**6**, 120230-43-5; (2*S*,3*S*)-**7**, 120230-46-8; (2*S*,3*R*)-**7**, 120230-47-9; (2*S*,3*R*)-**8**, 120230-48-0; (2*S*,3*S*,2′*S*)-**9**, 120230-49-1; (2*S*,3*S*,2′*S*)-**11**, 120230-50-4; (2*S*,3*S*,2′*S*)-**12**, 120230-51-5; (3*S*,4*S*,2′*S*)-**13**, 120230-52-6; **14**, 120230-53-7; (2*S*,3*R*)-**15**, 120230-54-8; (2*S*,3*S*)-**15**, 120230-55-9; (2*S*,3*R*)-**16**, 120262-55-7; (2*S*,3*S*)-**16**, 120230-56-0; (2*S*,3*R*)-**17**, 120230-57-1; (2*S*,3*S*)-**17**, 120230-58-2; (2*S*,3*S*,2′*S*)-**18**, 120230-59-3; (2*S*,3*R*,2′*S*)-**18**, 120329-59-1; (3*S*,4*S*,2′*S*)-**19**, 120230-60-6; (3*S*,4*R*,2′*S*)-**19**, 120328-49-6; (4*S*,5*R*)-**20**, 120230-61-7; (4*S*,5*S*)-**20**, 120262-56-8; **22**, 120230-62-8; (*S*,3*S*)-**23**, 120230-63-9; (2*S*,3*R*)-**23**, 120230-64-0; (2*S*,3*S*)-**24**, 120230-68-4; (2*S*,3*R*)-**24**, 120230-69-5; (2*S*,3*S*)-**25**, 120230-71-9; (2*S*,3*R*)-**25**, 120230-72-0; (2*S*,3*R*,2′*S*)-**26**, 120230-74-2; (2*S*,3*S*,2′*S*)-**26**, 120328-50-9; (2*S*,3*R*,2′*R*)-**26**, 120328-51-0; (2*S*,3*S*,2′*R*)-**26**, 120328-52-1; (3*S*,4*R*,2′*S*)-**27**, 120230-76-4; (3*S*,4*S*,2′*S*)-**27**, 120328-53-2; (3*S*,4*R*,2′*R*)-**27**, 120328-54-3; (3*S*,4*S*,2′*R*)-**27**, 120328-55-4; (2*S*,3*S*)-**28**, 120230-65-1; (2*S*,3*R*)-**28**, 120230-66-2; (2*S*,3*S*)-**29**, 120230-70-8; (2*S*,3*S*)-**30**, 120230-73-1; (2*S*,3*R*,2′*S*)-**31**, 120230-75-3; (3*S*,4*R*,2′*S*)-**32**, 120230-77-5; (2*S*,3*S*)-**33**, 120230-44-6; (2*S*,3*R*)-**33**, 120230-45-7; (2*S*,3*S*)-**34**, 120230-78-6; (2*S*,3*S*)-**35**, 120230-79-7; (3*S*,4*S*)-**36**, 120230-80-0; (2*S*,3*S*)-**37**, 120230-81-1; (2*S*,3*R*,2′*S*)-**38**, 120230-82-2; (3*S*,4*R*,2′*S*)-**39**, 120230-83-3; H-Ala-OMe·HCl, 2491-20-5; L-(PhFl)NHCH(CO_2Me)CMe_2CO_2Me, 120230-67-3; H-D-Ala-OMe·HCl, 14316-06-4.