Conversion of Serine β-Lactones to Chiral α-Amino Acids by Copper-Containing Organolithium and Organomagnesium Reagents†

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Abstract: A method for synthesis of optically pure α-amino acids has been developed. Mono- and di-N-protected α-amino-β-lactones **3a** (L, R_1 = H, R_2 = $COOCH_2Ph$ (Z)), **3b** (D, R_1 = H, R_2 = Z), **3c** (L, R_1 = CH_2Ph, R_2 = Z), and **3d** (D, R_1 = CH_2Ph, R_2 = Z) are readily produced by cyclization of the corresponding serine derivatives **2** under modified Mitsunobu conditions without loss of optical purity. Stereochemical integrity was demonstrated by conversion of **3** to 2-methoxy-2-(trifluoromethyl)phenylacetate esters **6** and analysis by HPLC, ^{19}F NMR, and ^1H NMR. Reaction of **3** with organolithium-derived cuprate reagents (R_2CuLi or $R_2Cu(CN)Li_2$) at low temperature produces N-protected α-amino acids by attack at the β-methylene group. Yields of di-N-protected amino acids are generally higher (ca. 50–75%), but some decrease in enantiomeric excess (ee) can occur (0–27%). In contrast, the mono-N-protected β-lactones **3a** and **3b** give slightly lower yields (ca. 44–62%) but negligible decrease in ee (0–1.7%) with the exception of $Ph_2Cu(CN)Li_2$ (67% loss of ee). However, the use of Cu(I)-catalyzed Grignard (RMgCl) additions gives better yields (44–83%), complete retention of optical purity (>99.4%), and fewer side products. Reductive removal of the protecting groups in a single step (H_2/Pd–C or Na/NH_3) affords the free α-amino acids in 91–99% yield. Their stereochemical purity was determined by conversion to the corresponding *N*-(−)-camphanoyl methyl esters and analysis by gas chromatography and ^1H NMR spectroscopy.

A staggering number of amino acids (>700) has been discovered in nature.[1] This represents an enormous pool of optically pure chiral units for organic chemists, who have begun to use them and their derivatives as chiral synthons, catalysts, and auxiliaries in asymmetric syntheses.[1a,2-4] Since relative few (2–3%) of the known amino acids occur abundantly in nature,[1] much recent work has focussed on both achiral[5] and enantioselective syntheses of them.[1,6,7] In many instances derivatives of readily available proteinogenic amino acids provide chiral synthons for other rare or unusual amino acids.[3,8]

Since both enantiomeric forms of the amino acid serine are available in high optical purity at relatively low expense, they are especially attractive chiral starting materials.[3] We recently demonstrated that readily accessible N-protected serine β-lactones (**3**, Scheme I) can act as chiral electrophilic alanine cation equivalents and eagerly accept heteroatom nucleophiles to produce a wide variety of optically pure β-substituted alanines.[3e,9]

An obvious extension of the serine β-lactone methodology is the formation of carbon–carbon bonds through reactions with C-nucleophiles to produce amino acids with homologated side chains. Early work on β-propiolactone[10] indicated that most Grignard and organolithium reagents attack the carbonyl of the lactone with acyl–oxygen cleavage to generate the corresponding ketone or tertiary alcohol products. While some organocadmium compounds reacted to produce β-substituted carboxylic acids, the method was not generally applicable.[10b] More recently Normant et al.[11] established that the desired regiospecific ring openings of β-propiolactone could be accomplished with either stoichiometric (i.e., R_2CuLi or R_2CuMgX) or catalytically generated (10 mol % Cu(I) salt/RMgX) organocuprate reagents in excellent yield (R = *n*-Bu, *i*-Pr, *t*-Am, Ph). Such approaches to three carbon homologation have proven successful in the synthesis of numerous natural products,[11-13] although they have not yet been applied to optically active 3-substituted 2-oxetanones.

Herein we examine the ring-opening reactions of optically pure N-protected serine β-lactones by organometallic reagents with respect to regiospecificity and stereochemical integrity. We report conditions under which these serine β-lactones react with aliphatic and aromatic carbanions, with essentially no loss in optical purity, to produce N-protected amino acids suitable for direct incorporation into peptides (Scheme II).

† Dedicated to Professor George Büchi, Massachusetts Institute of Technology, on the occasion of his birthday.

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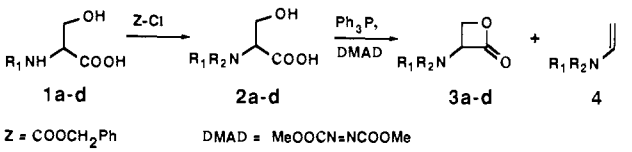
Scheme I



Results and Discussion

Synthesis of Serine β-Lactones. N-Protected serines **2** react quantitatively with the preformed *N*-phosphonium adduct of Ph_3P and dimethyl azodicarboxylate (DMAD) at low temperatures to produce either the corresponding β-lactone **3**[3e,9] or enamine **4** resulting from decarboxylative dehydration (Scheme I). At room temperature **4** is the major product. A study of temperature and solvent effects on product distribution indicates that decreasing the temperature (+20 °C → −78 °C) and/or increasing solvent polarity (Et_2O → MeCN) favors lactonization and minimizes elimination. The use of MeCN solvent at −55 °C rather than THF at −78 °C allows isolation of *N*-(phenylacetyl)-[14a] and *N*-(benzyloxycarbonyl (Z) serine β-lactones (**3a**) and (**3b**) in yields of 76–81%. This represents a 10–20% increase over our previously reported conditions[3e] and contrasts a 1.4% yield of *N*-(phenylacetyl)serine β-lactone obtained by using more typical Mitsunobu conditions.[14b]

With mono-N-protected serine β-lactones, an organometallic reagent may abstract the relatively acidic NH proton to form an amidate anion (see Scheme VII, X) which could open the lactone or repel attack by another equivalent of organometallic species. To assess the influence of the NH on the outcome of reactions of serine β-lactones with organometallics, the diprotected *N*-benzyl-*N*-(benzyloxycarbonyl)serine β-lactones (**3c**) and (**3d**) which lack an acidic NH proton were prepared (Scheme I). Reaction of *N*-benzylserines **1c** and **1d**[15] with benzyl chloroformate under Schotten–Baumann conditions provided **2c** and **2d**, respectively (40–47%). In the lactonization of di-N-protected serines **2c,2d** to **3c,3d**, temperature effects outweighed those of solvent, and the best yields (71%) were obtained by using THF at −78 °C according to our original general procedure.[3e] The choice of *N*-benzyl (Bn) and *N*-benzyloxycarbonyl (Z) as protecting groups allows deprotection of products in a single step under conditions identical with those employed for the monoprotected analogues (i.e., H_2/Pd–C or Na/NH_3). The *N*-Bn-*N*-Z-serine β-lactones (**3c**) and (**3d**) undergo all of the same reactions with heteroatom nucleophiles as their monoprotected Z-serine counterparts **3a** and **3b**[3e] with roughly equivalent yields but generally require longer reaction times under identical conditions.[16]

Stereochemical Purity Determinations. If the N-protected amino acids **8**, **10**, **12**, **13**, **15**, **17**, **18a–d** resulting from carbanion-mediated ring opening of serine β-lactones **3a–d** (Scheme II) are to be directly useful in peptide syntheses or as chiral synthons, their optical purity is of paramount importance.[1a,17] In order to quantitate any losses in stereochemical purity encountered in the addition of organometallics to the β-lactones a measure of the enantiomeric excess (ee) of both the starting lactones **3a–d** and the addition products is required. The assay of the optical purity of the serine β-lactones **3a–d** utilizes regiospecific ring opening by the potassium salt **5** of (*S*)-2-methoxy-2-(trifluoromethyl)-phenylacetate[18] (MTPA) in DMF to produce diastereomers from enantiomers (Scheme III).[19] Acidification, extraction, and esterification with diazomethane produces mixtures of **6a,b** or **6c,d**, along with **7**. Elimination of the ring-opened products to N-protected dehydroalanine is minimized (i.e., <0.6% of product) by performing the reaction with K^+MTPA^- **5** in DMF at 0–5 °C. Diastereomers **6a,b** or **6c,d** in the product mixture were directly separated and quantitated by using HPLC. Complementary ^{19}F and ^1H NMR results were obtained after separation of the MTPA derivatives **6** from methyl MTPA **7** by chromatography.

The accuracy and validity of the HPLC and ^{19}F NMR analyses on **6** was determined by subjecting known mixtures of the enantiomers of **3** to the analysis. In the case of the mono-N-protected β-lactones **3a,b**, derivatization and analyses of a standard mixture containing 65.22% **3a**[20] and 34.78% **3b**[21] provided ratios of 65/35 by ^1H NMR (δ 3.66 and 3.73 ppm, respectively, for $COOCH_3$'s) and ^{19}F NMR (δ −76.26 and −76.23 ppm, respectively, for CF_3's)[22] and 64.8/35.2 (±0.11) by HPLC. Reported values for the optical purity of **3a** and **3b** were obtained by HPLC and, when possible, confirmed by NMR.

For the di-N-protected β-lactones **3c** and **3d** a reference standard containing 67.12% **3c** (*S*)[23] and 32.88% **3d**[24] was derivatized and analyzed to yield ratios of 2/1 by ^1H NMR (δ 3.46 and 3.43 respectively for $COOCH_3$'s), 67/33 by ^{19}F NMR (δ −72.14, −71.96, and −72.04 respectively for CF_3's),[25] and 67.4/32.6 (±0.30) by HPLC. Although HPLC and ^{19}F NMR results complemented each other, the excellent resolution and accuracy of ^{19}F NMR[26] with the di-N-protected derivatives made it the method of choice. In all cases the measured optical purity of the serine β-lactones **3a–d** exactly matched that of the starting materials (**1** or **2a–d**), thereby indicating no detectable loss in optical purity in lactonization.[28]

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(14) (a) For *N*-(phenylacetyl)-L-serine β-lactone: mp 118–119 °C (lit.[14b] mp 122–123 °C; $[\alpha]^{25}_D$ −31.7° (*c* 2.0, CH_3CN); prepared by using DEAD as outlined for **3a** and **3b** in 77% yield. The balance of product was 2-(2-phenylacetamido)ethylene: mp 82–83 °C; IR ($CHCl_3$ cast) 3235 (m), 3145 (m), 3030 (m), 1662 (m), 1635 (vs), 1530 (m), 1263 (s), 1190 (m), 980 (m), 869 (m), 697 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1 H, 9.2 Hz, N*H*), 7.07 (m, 5 H, *Ph*), 6.76 (m, 1 H, CH_2CH), 4.47 (d, 1 H, 15.4 Hz, *Z*-CH*H*), 4.26 (d, 1 H, 8.4 Hz, *E*-C*H*H), 3.40 (s, 2 H, PhCH_2); EI-MS, 161.0832 (161.0841 calcd). Anal. ($C_{10}H_{11}NO$) C, H, N. (b) Parker, W. L.; Rathnum, M. L.; Liu, W. *J. Antibiot.* **1982**, *35*, 900–902.

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(19) The ring-opening by the MTPA salt is analogous to the previously reported reaction of Z-serine β-lactones with acetate.[3e,9]

(20) Compound **3a** determined to be 94.4(±0.4)% optically pure by HPLC analysis of **6a**.

(21) Compond **3b** determined to be 97.0(±.2)% optically pure by HPLC analysis of **6b**.

(22) ^{19}F NMR was only useful and accurate above 3% contamination due to partial overlap of the resonances of the (*S,S*)- and (*R,S*)-diastereomers.

(23) Compound **3c** determined to be 99% optically pure by ^{19}F NMR analyses on **6c**.

(24) Compound **3d** determined to be 97% optically pure by ^{19}F NMR analyses on **6d**.

(25) NMR spectra are complicated by broadening and/or multiple peaks due to conformational equilibria.

(26) Compound **6c** prepared from L-serine[27] contained <1% (*R,S*)-isomer according to ^{19}F NMR. HPLC also indicates <1.0%.

(27) Obtained from Sigma Chemical Co., St. Louis, MO, USA.

Scheme II

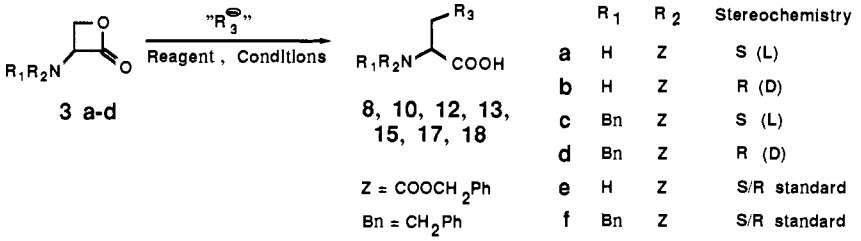


Table I

entry	starting β-lactone[a]	R_2	reagent[n]	conditions[b]	R_3	product (Yield)	% decrease in ee[c]
1	**3a**	H	5 eq CuCN, 8 eq MeLi	−23° (2 h), 0° (15 min)	Me	**8a** (47%)	1.7 (±0.4)%
2	**3c**	Bn	3.5 eq CuBr·SMe_2, 6.7 eq MeLi	−45° (2.5 h)	Me	**8c** (70%)	2.4 (±0.4)%[d]
3	**3c**	Bn	1.8 eq CuCN, 3.0 MeLi	−78° (40 min), −46 (3 h)	Me	**8c** (72%)[i]	17.5 (±0.6)%
4	**3d**	Bn	1.8 eq CuCN, 3.0 MeLi	−78° (1 h), −45 (0.5 h)	Me	**8d** (92%)[e]	1.0 (±0.7)%
5	**3b**	H	5.2 eq CuCN, 10 eq *n*-BuLi	−23° (2 h)	*n*-Bu	**10b** (62%)[i]	0[f,m]
6	**3c**	Bn	2.1 eq CuCN, 3.5 eq *n*-BuLi	−78° (40 min), −46° (1 h)	*n*-Bu	**10c** (76%)[i]	11.7 (±0.9)%
7	**3a**	H	0.19 eq CuBr·SMe_2, 6 eq *i*-PrMgCl	−23° (1.5 h)[h]	*i*-Pr	**12a** (44%)[i]	<0.5%
8	**3c**	Bn	0.21 eq CuBr·SMe_2, 5.2 eq *t*-PrMgCl	−23° (2 h)[h]	*t*-Pr	**12c** (83%)[i]	0[f]
9	**3c**	Bn	2.3 eq CuCN, 4.5 eq *sec*-BuLi	−78° (20 min), −45° (1.2 h), −18° (1 h)	*sec*-Bu	**13c** (76%)[j]	n.d.[g]
10	**3a**	H	3.3 eq CuCN, 3.1 eq MeLi, 3.1 eq *t*-BuLi	−23° (1 h)	*t*-Bu	**15a** (48%)	0[f]
11	**3c**	Bn	1.9 eq CuCN, 3.4 eq *t*-BuLi	−78° (1 h), −46° (1 h), −15 (0.5 h)	*t*-Bu	**15c** (38%)[j,k]	5.6 (±0.6)%[d]
12	**3c**	Bn	4.4 eq CuBr·SMe_2, 7.8 eq *t*-BuLi	−46° (7 h), −10° (1 h)	*t*-Bu	**15c** (51%)[j,k]	0[f]
13	**3a**	H	0.25 eq CuBr·SMe_2, 5 eq $CH_2CHMgCl$	−23° (2 h)[h]	CH_2CH–	**17a** (47%)	0[f]
14	**3c**	Bn	1.8 eq CuCN, 3.0 eq CH_2CHLi	−78° (1 h), −45° (3 h), 0° (0.5 h)	CH_2CH–	**17c** (56%)	27.2 (±0.8)%
15	**3a**	H	0.3 eq CuBr·SMe_2, 6.0 eq PhMgCl	−23° (2 h)[h]	Ph	**18a** (55%)[l]	0[f]
16	**3b**	H	5.13 eq CuCN, 10 eq PhLi	−15° (2 h)	Ph	**18b** (46%)	67.4 (±0.4)%
17	**3c**	Bn	2.5 eq CuBr·SMe_2, 4.9 eq PhMgBr	−12° (4 h)[h]	Ph	**18c** (60%)	3.3 (±0.8)%
18	**3c**	Bn	1.8 eq CuCN, 3.1 eq PhLi	−78° (1 h) → −15° (over 3 h)	Ph	**18c** (25%)	4.7 (±0.6)%
19	**3c**	Bn	3.0 eq CuBr·SMe_2, 6 eq PhLi	−35° (4 h)	Ph	**18c** (36%)	14.2 (±0.8)%[d]

[a] Unless noted optical purities of β-lactones **3a**, **3b**, **3c**, and **3d** were ≥99.5%, 97.0(±0.2)%, 98.7(±0.3)%, and 96.9(±0.3)%, respectively. [b] THF solvent unless indicated. [c] Determined by comparison with enantiomeric excess (ee) of starting β-lactone (see a). [d] By comparison of $[\alpha]^{25}_D$. [e] On the basis of 22% recovered β-lactone, 72% isolated yield of **8d**. [f] Within experimental error (±0.3%). [g] Mixture of at least two diasteromers. [h] THF/Me_2S (20:1) solvent. [i] Ketone product isolated: 5% (entry 3 (**9**), 6 (**11**)), 14% (entry 5), 8% ketone (entry 7), 16% (entry 8). [j] Z-NH-Bn (**14**) isolated: 4% (entry 9), 19% (entry 11), 18% (entry 12). [k] *N*-Z-*N*-Bn-Alanine **16** isolated: 14% (entry 11), 23% (entry 12). [l] Tertiary alcohol sideproduct **19** isolated in 43% yield. [m] The *S*-isomer produced under analogous conditions also exhibited no detectable decrease in optical purity. Identical yield using DME solvent at −23 °C. [n] eq is the abbreviated form for equivalent.

To assess the optical purity of the amino acid derivatives resulting from organometallic additions to the serine β-lactones (Scheme II), the corresponding free amino acids were liberated from mono- and di-N-protected products by hydrogenolysis (for **8**, **10**, **12**, **15**, **18 a–d**) or Na/NH_3 reduction (for **17a**, **17c**) and then analyzed as their *N*-(1*S*,4*R*)-camphanoyl methyl esters (Scheme IV).[30,6i] Derivatization of as little as 1 mg of amino acid is conveniently effected in 80–95% yield by using (−)-camphanoyl chloride (2 equiv) in 1 M sodium carbonate/bicarbonate buffer (pH 10, 20 mole equiv) and toluene (0.2 volumes). These mild conditions eliminate the need to monitor and adjust the pH during the reaction.[30a] Following esterification of the intermediate acids with diazomethane, a mixture of diastereomers **22**, **23**, **25-28 a,b** and methyl camphanoate (**21**) is produced. ^{1}H NMR and gas chromatographic (GC) analyses may be carried out directly on this mixture or after removal of **21** by sublimation or chromatography.

Although excellent resolution of 8′-CH_3 peaks of the (2*S*)- and (2*R*)-isomers of *N*-camphanoylamino acid methyl esters **22**, **23**, **25–28 a,b** in ^{1}H NMR[31,32] easily allows accurate estimation of the diastereomeric ratio down to approximately 2(±1)% cross-contamination, the results of GC analysis are reported because of their greater sensitivity and accuracy. In all cases standard mixtures of (2*R*)- and (2*S*)-isomers of *N*-camphanoylamino acid methyl esters **22**, **23**, **25–28 e** were used to develop GC conditions and estimate accuracy. Invariably the (2*R*)-isomer emerged ahead of the (2*S*)-isomer, and sufficient resolution to establish limits of detection at 0.2 → 0.5% of diastereomeric impurity was easily obtained. With the exception of the 2-aminoheptanoate reference standard **23e**, all GC standards (**22**, **25–28e**) were generated by derivatization of known mixtures of commercially available amino acids.[27] Since 2-aminoheptanoic acid was not commercially available, a standard mixture of (*S*)- and (*R*)-isomers **23e** was produced by diastereoselective alkylation of the corresponding glycine derivative according to Scheme V.[33] The ^{1}H NMR spectrum of **23e** suggested an *S*/*R* ratio of 70/30 in agreement with the result of 69.8/30.2 (±0.1) by GC analysis. When sufficient amino acid was deprotected to allow accurate measurement of optical rotation, the ratios agreed with those obtained by GC and ^{1}H NMR analyses within experimental error. Values for the percent decrease in enantiomeric excess (ee) reported in Table I are obtained by subtraction of the optical purity of the products (Scheme IV) from that of the serine β-lactone starting materials (Scheme III).

General Features of Reactions of Serine β-Lactones with Organometallic Reagents. Organometallic reagents may attack serine

(28) For example, 99.8% optically pure Z-L-serine obtained from Institut Armand Frappier[29] produced **3a** which contained <0.23% D-(*R*)-isomer (limit of detection) when analyzed as **6a** by HPLC. Compound **3a** prepared from Z-L-serine from Sigma[27] typically contained 0.75–2.80% D-isomer.

(29) Obtained from Institut Armand-Frappier, Laval, Quebec, Canada.

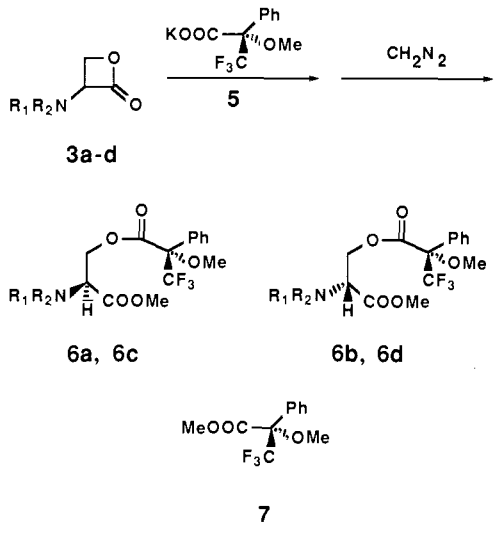
(30) (a) Armarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2229–2237. (b) In all cases both the protected derivations and the free amino acids obtained by deprotection were analyzed for optical purity after chromatographic purification but before crystallization to avoid possible enrichment of one enantiomer. In two cases both recrystallized and uncrystallized materials were subjected to analysis and gave identical results.

(31) ^{1}H NMR assignments of the camphanoyl moiety were made by analogy with confirmed assignments for **21** and **28a**.

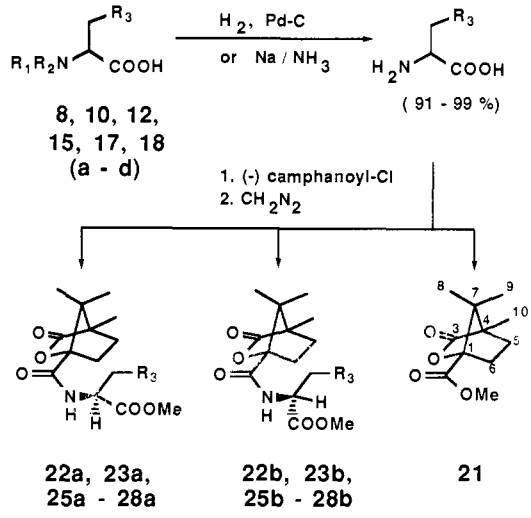
(32) The 8′-CH_3 of the (2*S*)-isomer appeared upfield of the (2*R*)-isomer by 0.05–0.27 ppm in all cases investigated. No other peak was as reliable.

(33) The method was adapted from Piotrowska and Abramski (Piotrowska, K.; Abramski, W. *Pol. J. Chem.* **1979**, *53*, 2397–2399).

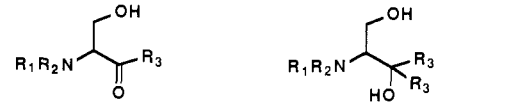
Scheme III



Scheme IV

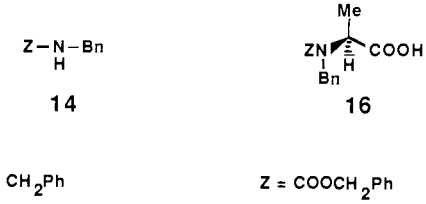


β-lactones at two sites (Scheme VI). Undesirable attack at the carbonyl carbon (path a) produces the corresponding ketone (A, e.g., **9**, **11**) which may add a second equivalent of organometallic



9 R_1 = Bn, R_2 = Z, R_3 = Me **19** R_1 = H, R_2 = Z, R_3 = Ph

11 R_1 = Bn, R_2 = Z, R_3 = n-Bu **20** R_1 = Bn, R_2 = Z, R_3 = Me



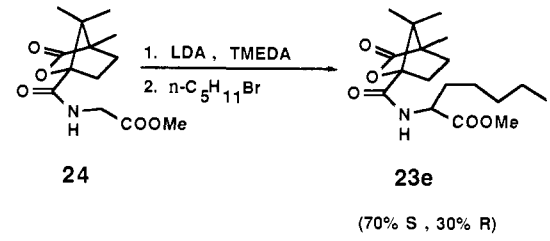
14 **16**

Bn = CH_2Ph Z = $COOCH_2Ph$

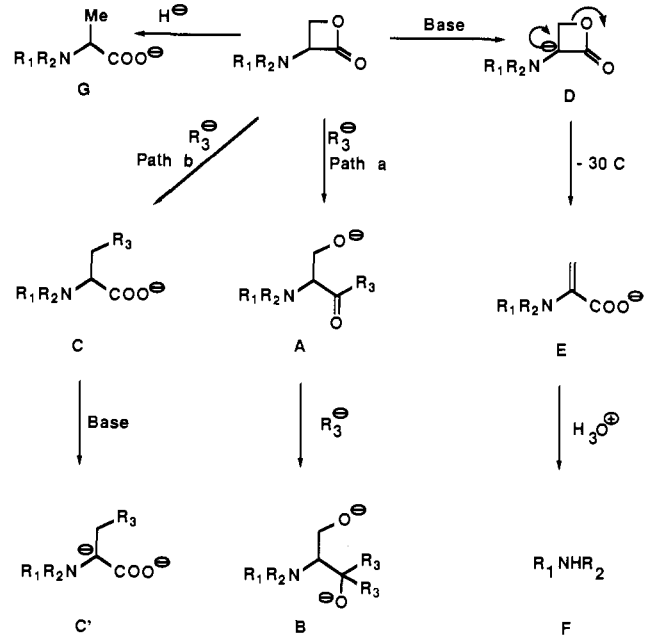
species to generate a tertiary alcohol (B, e.g., **19**, **20**). To produce the desired N-protected amino acids, the serine β-lactones must behave like "chiral enone equivalents" with "1,4-attack" of the carbanion at the β-methylene group (path b) and concomitant ring opening to liberate the carboxylate functionality (C).

Organometallic substitutions on N-protected *O*-tosyl or ω-halogen derivatives of serine or homoserine methyl esters give products which are susceptible to racemization under the reaction conditions or in the subsequent hydrolysis.[3c] In contrast, the N-protected 2-aminocarboxylates (C) derived from β-lactone cleavage should be rather resistant to racemization since it requires a proximal dianion (C', Scheme VI). Interestingly, previous work[10-13] with β-propiolactones indicated that organocuprate reagents which add in 1,4-fashion to α,β-unsaturated carbonyl systems also add to the methylene group of β-lactones. The same organometallic reagents are also useful in alkylations by primary alkyl halides and tosylates.[3c] To gain further insight into the behavior of β-lactones with organometallic reagents, the reactions of some of the more contemporary reagents with the serine β-lactones (**3a–d**) were examined. Recently, BF_3-etherate has been reported to promote addition of alkyllithiums to oxetanes and oxiranes.[34] Under similar conditions the attack of RLi/BF_3–OEt_2 on **3c** is *not* directed toward the β-methylene carbon, but instead the only products are ketones A and alcohols B resulting from reaction at the carbonyl (path a, Scheme VI). Organocerium reagents $RCeX_2$,[35] which display enhanced oxaphilicity and reduced basicity relative to their RLi and RMgX counterparts, similarly add in 1,2-fashion to the serine β-lactones (path a, Scheme VI), in direct analogy to their behavior with enones. For example, reaction of $MeCeCl_2$ (1 equiv) with **3c** yields only the ketoalcohol **9** (11%), diol **20** (19%), and unreacted β-lactone (57%). Lower order cyanocuprates RCu(CN)Li, in which CN^- economically functions as the residual ligand, have been reported to possess reactivity comparable to R_2CuLi, but with higher thermal stability.[36,37] Disappointingly, PhCu(CN)Li (7 equiv)

Scheme V



Scheme VI



(34) Eis, M. J.; Wrobel, J. E.; Ganem, B. J. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.

(35) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763–4766, and references therein.

(36) (a) Gorlier, J. P.; Hamon, L.; Levisalles, J.; Wagnon, J. *J. Chem. Soc., Chem. Commun.* **1973**, 88–89. (b) Hamon, L.; Levisalles, J. *J. Organomet. Chem.* **1983**, *251*, 133–138.

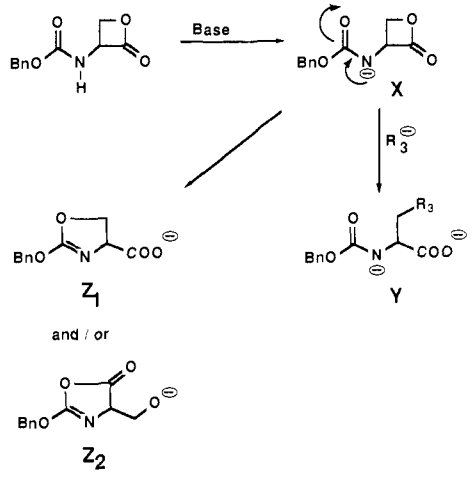
reacts with **3a** to provide only a 4% yield of Z-phenylalanine (**18a**). In contrast, higher order cyanocuprates $R_2Cu(CN)Li_2$[37,38] add to the mono- and di-N-protected β-lactones to give the desired amino acids (Table I) and are discussed below.

Organolithium-Derived Cuprate Reagents. Lipshutz and co-workers have illustrated the advantages and utility of higher order cyanocuprates $R_2Cu(CN)Li_2$ in reactions with primary and secondary alkyl halides and tosylates and in conjugate additions to α,β-unsaturated carbonyl systems.[37,38] Earlier work by Normant et al.[11] had also established that R_2CuLi reagents add to β-propiolactones in the desired manner. The results in Table I show that both types of reagents add to N-protected serine β-lactones in the required fashion. Similar yields were obtained with both reagents, but the cyanocuprates $R_2Cu(CN)Li_2$ may be preferred due to their higher thermal stability.

Yields of $R_2Cu(CN)Li_2$ additions are usually higher with di-protected β-lactones **3c,d** than with monoprotected β-lactones **3a,b** (e.g., compare Table I entries 1/4, 5/6, but 16/18). In the case of vinyllic transfer from $(CH_2{=}CH)_2Cu(CN)Li_2$ to **3a** none of the desired allylglycine derivative was detected, while a 56% yield was secured with **3c** (entry 14). In order to obtain comparable yields with mono-N-protected serine β-lactones, an excess of cuprate reagent was required (typically 5 equiv were employed). This is due in part to consumption of an equivalent of reagent in removing the "acidic" NH proton from **3a,b** to form X or from product to form Y (Scheme VII). In some cases a 20–25% excess of CuCN relative to RLi was also required to suppress attack at the carbonyl (path a, Scheme VI). For example, when exactly 2:1 MeLi/CuCN was employed with **3a**, 28% ketone A, 37% tertiary alcohol B, and 18% of the desired acid C were obtained (cf. entry 1). Lipshutz et al.[37,38] have observed the equilibrium between $R_2Cu(CN)Li_2$ and a mixture of $RCu(CN)Li$ and RLi. They found that the percentage of free RLi increases with temperature. Presumably, this equilibrium accounts for the increase in path a (Scheme VI) products encountered at the higher reaction temperature (−23 °C) used with the monoprotected lactones, and the corresponding reduction in these undesired products on addition of excess CuCN. A reduction in the equilibrium concentration of RLi on switching from THF to DME might also be expected;[37,38] however, such a solvent substitution for entry 5 had no effect on product yields. Even under optimal conditions with $R_2Cu(CN)Li_2$, between 5 and 15% of ketone products (e.g., **9**, **11**; A of Scheme VI) were usually observed.

With the mono-N-protected β-lactones **3a** and **3b** additional temperature-dependent side reactions require that the addition of β-lactone to $R_2Cu(CN)Li_2$ be done at −23 to −15 °C for optimum yield. At −78 °C no observable reaction occurs in 1.5 h. Upon warming to −46 °C the β-lactones are slowly consumed, but considerable amounts (18–35%) of optically pure Z-serine are generated on aqueous workup by using conditions which do *not* hydrolyze the β-lactones. At temperatures greater than −15 °C the yield of desired products is lowered by increasing production of Z-dehydroalanine[39] (Scheme VI, E). The formation of Z-serine at low temperatures suggests intramolecular rearrangement to an oxazoline (Z_1) or oxazolone (Z_2) (Scheme VII) which would readily hydrolyze to Z-serine in the acidic workup.[40] This reaction predominates only at low temperatures where intermolecular nucleophilic addition to the anion X is retarded by

Scheme VII



Coulombic repulsion.[41] As expected, no corresponding serine derivative **2c** or **2d** is produced in reactions of N-diprotected β-lactones **3c** or **3d**.

Although $R_2Cu(CN)Li_2$ and R_2CuLi additions to the di-N-protected β-lactones **3c** and **3d** appear superior with respect to yield and amount of organometallic reagent required, they often suffer from major losses in optical purity. In contrast, with the exception of entry 16, additions of $R_2Cu(CN)Li_2$ reagents to the monoprotected serine β-lactones **3a** and **3b** proceed with little or no decrease in enantiomeric excess (e.g., entries 1, 5, 10). Comparison of entries 3 and 4 which differ only in reaction times suggests that racemization of the di-N-protected products may occur on prolonged exposure to the organometallic reagent at −46 °C. Despite the fact that $R_2Cu(CN)Li_2$ additions to the mono-N-protected lactones were done at higher temperatures (e.g., −23 °C), little or no racemization is observed, presumably because deprotonation of species X or Y (Scheme VII) which already possess an anionic nitrogen is disfavored. Racemization could in principle also occur by formation of the α-carbanions D (Scheme VI), which are known to undergo rapid "forbidden" elimination to E at temperatures above −30 °C.[42] Although reaction of **3c** and **3d** with hindered *sec*- or *tert*-butyl reagents produced some benzyl *N*-benzylcarbamate (**14**) (F, Scheme VI) after hydrolytic workup due to this elimination (entries 9 (4%), 11 (19%), 12 (18%)), nucleophilic addition to the anion E seems unlikely and probably does not account for loss of stereochemical purity.

Lipshutz and co-workers have noted that relative to other $R_2Cu(CN)Li_2$, $Ph_2Cu(CN)Li_2$ exhibits low reactivity, poor yields, and lack of regiospecificity with enones.[38] Additions of $Ph_2Cu(CN)Li_2$ to the diprotected β-lactone produced only a low yield of the desired product (25%, entry 18) as did Ph_2CuLi reagent (36%, entry 19). A moderate yield of Z-phenylalanine **18b** was obtained with the monoprotected lactone **3b** (46%, entry 16); however, substantial losses (5–67%) in optical purity were apparent in all three cases.

In the reactions of $(t\text{-Bu})_2Cu(CN)Li_2$ (entry 11) and $(t\text{-Bu})_2CuLi$ (entry 12) with β-lactone **3c**, yields of the desired neopentylglycine derivative **15c** were reduced considerably (i.e., 14–23%) due to the formation of *N*-Z-*N*-Bn-alanine (**16**). Since **16** is optically active, the alanine derivative probably arises from hydride transfer to the β-lactone (G, Scheme VI) from the organometallic compound or from "CuH" type reagents which are generated in the thermal decomposition of labile cuprates such as $(t\text{-Bu})_2CuM$.[37,43,44] Sato et al. previously found pivalic acid was the major product of the Cu(I)-catalyzed ring opening of

(37) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038.

(38) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928–3938. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Ibid.* 3938–3942, and 3943–3949.

(39) Z-Dehydroalanine was determined by ^1H NMR spectra of the reaction mixtures.

(40) For various examples of oxazoline formation from serine derivatives, see: (a) Benoiton, L. N.; Hanson, R. W.; Rydon, H. N. *J. Chem. Soc.* **1964**, 824–836. (b) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026–7032. (c) Gordon, E. M.; Ondetti, M. A.; Pluscec, J.; Cimarusti, C. M.; Bonner, D. P.; Sykes, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 6053–6060. For examaples of 2-alkoxy-5(4*H*)-oxazolones: (d) Jones, J. H.; Witty, M. J. *J. Chem. Soc., Chem. Commun.* **1977**, 281–282. (e) Benoiton, L. N.; Chen, F. M. F. *Can. J. Chem.* **1981**, *59*, 384–389 and *J. Chem. Soc., Chem. Commun.* **1981**, 1225–1227.

(41) Reaction of di-N-protected β-lactones **3c** and **3d** with organometallic reagents is generally much more rapid than with corresponding mono-N-protected β-lactones.

(42) Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620–3622, and references therein.

(43) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J. *J. Am. Chem. Soc.* **1970**, *92*, 1426–1427.

(44) Normant, J. F. *Synthesis* **1972**, 63–80.

α,α-dimethyl-β-propiolactone by *t*-BuMgCl.[13c] The hydride-transfer reaction was abolished in *tert*-butyl addition to the mono-N-protected β-lactone **3a** through use of the mixed cuprate, *t*-Bu(Me)Cu(CN)Li_2, and provided Z-L-neopentylglycine in 48% yield. In accord with the findings of Lipshutz et al.[37,38] with enones, this reagent exclusively transfers its *tert*-butyl ligand, and no product of methyl transfer (i.e., **8a**) was detected.

Initially problems were encountered with Cu^{2+} contamination of the products since they chelate this cation. Removal of cupric ion from products with Chelex resin (BioRad) was successful but also resulted in significant product losses. To avoid this, reactions were quenched by addition to cold *degassed* 0.5 N HCl, which precipitates most of the copper as cuprous chloride. The use of ether rather than ethyl acetate in extractions and washing of the extracts with aqueous EDTA (pH 3.0) and saturated brine efficiently removes any residual copper. Purification by reverse phase chromatography (RP-8 MPLC) was generally most effective at resolving all of the products of the reactions.

Grignard-Derived Organocuprates. Many of the disadvantages associated with organolithium cuprate reagents can be avoided by the use of organomagnesium-derived reagents.[44] Utilization of the stoichiometric cuprate $Ph_2CuMgBr$ derived from PhMgBr and CuBr–SMe_2[45] (entry 17) with the di-N-protected β-lactone **3c** resulted in a considerable increase in both the yield (60%) and optical purity relative to the PhLi-derived cuprates (entries 18 (25%) and 19 (36%)).

Whereas organolithiums RLi are generally more reactive with enones than their respective cuprate adducts R_2CuLi, Grignard reagents RMgX are considerably less reactive than the corresponding cuprate R_2CuMgX.[44] This difference in reactivities has been exploited for Cu(I)-catalyzed 1,4-additions of Grignard reagents to enones[44] and to β-propiolactones.[11,12c]

Enlistment of only a catalytic amount of CuBr–SMe_2[45] in the reactions (entries 7, 8, 13, 15) simplifies workup and reduces the amount of organometallic reagent required by at least 50%. Furthermore, Grignard reagents RMgCl are less expensive than their organolithium counterparts, more stable, and easier to generate and handle. The use of Grignard reagents derived from alkyl chlorides rather than bromides is advantageous because $MgBr_2$-etherate reacts much more rapidly with β-lactones **3a** and **3b** than the corresponding dichloride.[3e,46] The unoptimized yields of desired products (44–83%) are superior in all instances to those obtained with $R_2Cu(CN)Li_2$ and R_2CuLi_2. For example, a 47% yield of Z-L-allylglycine **17a** was secured (entry 13) with catalytic $CuBr/CH_2CHMgCl$, whereas none of this desired material was detected with $(CH_2CH)_2Cu(CN)Li_2$. As before, yields obtained with mono-N-protected β-lactones **3a** and **3b** are somewhat lower than with **3c** and **3d** (e.g., 44% vs. 83% for *i*-PrMgCl, entries 7, 8). Further refinement of mole ratios should increase yields and reduce ketone (entries 7, 8) and tertiary alcohol (43% in entry 15) side products resulting from organometallic additions at the carbonyl (path a, Scheme VI). Unlike reactions involving organolithiums, the copper-catalyzed RMgCl additions were conveniently carried out at −23 °C with no observable formation of elimination products.

Most importantly, in all cases in which Cu(I)-catalytic RMgCl additions were employed (entries 7, 8, 13, 15), greater than 99.4% retention of optical purity was observed. The phenyl addition results (entry 15) dramatically contrast the large decrease in optical purity measured with $Ph_2Cu(CN)Li_2$ (entry 16). In virtually all respects, copper-catalyzed organomagnesium chloride additions to both mono- and di-N-protected serine β-lactones **3** are superior to alternative stoichiometric cuprate additions (R_2CuLi, $R_2Cu(CN)Li_2$, or R_2CuMgX) for production of N-protected amino acids.

(45) For a discussion of elimination and reduction side reactions in RLi/Cu(I) systems and their dependence on handling of CuBr·SMe_2, see: Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1986**, *27*, 4273–4276. See ref 54.

(46) Treatment of β-propiolactone with RMgBr gives up to 60% β-bromopropionic acid, see: ref 11.

Summary

These investigations have established conditions for the additions of organometallic reagents to both mono- and di-N-protected serine β-lactones **3** to afford N-protected amino acids in fair to excellent yields with 99–100% retention of optical purity. The use of Cu(I)-catalyzed Grignard (RMgCl) additions avoids low yields, loss of optical purity, and cupric ion contamination which are often encountered with stoichiometric cuprates (R_2CuLi, $R_2Cu(CN)Li_2$, R_2CuMgX). Our procedure conveniently produces derivatives which are suitable for direct incorporation into peptides (i.e., in terms of optical purity and protecting groups) or can be deprotected in a single step (91–99% yield) to the free amino acids. The general synthetic utility of this methodology in providing access to most major classes of amino acids bearing aliphatic or aromatic side chains[1b] has been demonstrated by the addition of methyl,[47] primary (*n*-Bu),[49] secondary (*i*-Pr,[50] *sec*-Bu[51]), tertiary (*t*-Bu[52]), vinyllic (CH_2CH),[53] and aromatic (Ph)[50] carbanion reagents to both the D- and L-isomers of the readily accessible N-protected serine β-lactones **3**.

Experimental Section

***N*-Benzyl-*N*-[(benzyloxy)carbonyl]serines (2c, 2d).** Benzyl chloroformate (3.4 mL, 4.06 g, 23.8 mmol) was added dropwise over 30 min to a chilled (5 °C) solution of *N*-benzyl-D-serine (**1d**) (3.0 g, 15.4 mmol) in 2 N NaOH (7.5 mL) and THF (2.5 mL) with vigorous stirring. Throughout the addition the apparent pH was maintained between 9.5–10.5 with 1 N NaOH. The mixture was stirred 20 min, acidified to pH 2.0 with 2 N HCl at 5 °C, and extracted with EtOAc (3 × 75 mL). The crude product obtained on evaporation of the organic phases was purified by reverse phase MPLC (65% MeCN/H_2O, 3.0 mL/min) to afford 2.0–2.38 g (40–47%) of **2d** as a colorless syrup: $[\alpha]^{25}_D$ +25.2° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$ cast) 3640–3100 (m, br), 1740 (m), 1702 (s), 1685 (s), 1454 (m), 1428 (m), 1247 (s), 699 (s) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$)[25] δ 7.27 (br s, 10 H, *Ph*), 6.72 (br s, 2 H, COO*H*, O*H*), 5.12 (s, 2 H, OCH_2Ph), 4.65 (s, 0.75 × 2 H) and 4.59 (s, 0.25 × 2 H) (NCH_2), 4.30–3.50 (m, 3 H, $CHCH_2OH$);EI-MS, M^+ 329.1265 (329.1263 calcd). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.64; H, 5.75; N, 4.06.

The L-isomer **2c** was prepared in an analogous manner from **1c** and possessed chromatographic and spectral properties identical with **2d**: $[\alpha]^{25}_D$ −24.4° (*c* 1.3, $CHCl_3$). Anal. Found: C, 65.42; H, 5.72; N, 4.25.

***N*-[(Benzyloxy)carbonyl]serine β-Lactones (3a, 3b) and Benzyl *N*-Vinylcarbamate (4).** The β-lactones were prepared from Z-serines **2a** and **2b** as previously described,[3e,9] except that MeCN/THF (9:1) was employed as the reaction solvent at −55 °C (rather than THF at −78 °C), to provide **3a** (L) and **3b** (D) in 76–81% yields.[28] Material (**3a**) produced from high optical purity Z-L-serine (≥99.8% L)[29] exhibited the following: mp 133–134 °C; $[\alpha]^{25}_D$ −26.8° (*c* 1.0, MeCN).[58] Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.60; H, 5.10; N, 6.21; other spectral properties identical with those previously reported.[3e]

(47) Optically pure 2-aminobutanoic acid occurs in Nature (e.g., the antibiotic virginiamycin S).[1a,48]

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(51) Homoisoleucine and related unsaturated derivatives are antimetabolites of leucine: Snider, B. B.; Duncia, J. V. *J. Org. Chem.* **1981**, *46*, 3223–3226.

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(58) Compound **3a** determined to be >99.5% optically pure by HPLC analysis of **6a**.

Early fractions from the column yielded moisture-sensitive benzyl vinylcarbamate (**4**) in 13–17% yield which was further purified by bulb-to-bulb distillation (0.1 mmHg/90 °C): mp 41–43 °C (lit. mp 43–44 °C[59]); IR ($CHCl_3$ cast) 3320 (s, br), 1706 (vs), 1649 (s), 1520 (s), 1499 (s), 1450 (m), 1402 (s), 1260 (vs), 1090 (s), 696 (s) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.34 (s, 5 H, *Ph*), 7.30 (br s, 1 H, N*H*), 6.90–6.48 (m, 1 H, N-C*H*), 5.15 (s, 2 H, CH_2Ph), 4.48 (~d, 1 H, ~16 Hz, *cis*-C*H*H), 4.27 (~d, 1 H, ~8 Hz, *trans*-CH*H*); EI-MS, M^+ 177.0792 (177.0790 calcd for $C_{10}H_{11}NO_2$).

***N*-Benzyl-*N*-[(benzyloxy)carbonyl]serine β-Lactones (3c, 3d).** These compounds were prepared in THF from **2c** and **2d**, respectively, according to the previously outlined procedure for Z-serine β-lactones.[3e] Isolation by flash chromatography on silica[60] (25% EtOAc/hexanes) afforded β-lactone (71%) which was recrystallized from Et_2O or CCl_4/hexane: mp 73–74 °C (L, **3c**), 75.5–76.0 °C (D, **3d**); $[\alpha]^{25}_D$ −9.3° (**3c**),[23] +9.5° (**3d**)[24] (*c* 1.1, THF); IR ($CHCl_3$ cast) 1833 (vs), 1702 (vs), 1454 (m), 1423 (m), 1246 (s), 1107 (m), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[25] δ 7.50–7.10 (m, 10 H, 2 *Ph*), 5.40–5.12 (m, 2 H, PhCH_2O), 5.00–4.82 (m, 1 H, C*H*), 4.58 (br s, 2 H, PhCH_2N), 4.42 (~br s, 0.63 H) and 4.27–4.08 (m, 1.37 H) (CHC*HH*O); ^{13}C NMR (75.5 MHz, $CDCl_3$)[25] 168.5 and 167.1, 155.4, 136.5, 129.1, 128.7, 128.5, 128.1, 127.5, 127.2, 69.0, 68.4, 65.8, 64.9, 51.9; EI-MS, 311.1157 (311.1157 calcd); CI-MS (NH_3) 329 ($M + NH_4^+$), 312 (MH^+). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.44; H, 5.49; N, 4.44 (**3c**) and C, 69.57; H, 5.43; N, 4.73 (**3d**).

General Procedure for Determination of Optical Purity of β-Lactones 3a, 3b, 3c, and 3d as (*S*)-MTPA Derivatives 6a, 6b, 6c, and 6d. A solution of the β-lactone **3** (0.271 mmol) and **5** (147.7 mg, 0.542 mmol) was stirred 18 h in dry DMF at 3 °C. The DMF was removed in vacuo, and the residue was treated with an excess of etheral diazomethane. The syrup obtained after evaporation of the solvent was redissolved in $CHCl_3$, and an aliquot was submitted to analysis by HPLC. For ^{19}F NMR analysis, the remainder of the sample was purified by MPLC (silica, EtOAc/hexanes (35:65) for **6a**, **6b**, and **6e**; (26:74) for **6c**, **6d**, and **6f**) to yield the appropriate N-protected *O*-[(*S*)-2-methoxy-2-(trifluoromethyl)phenylacetyl]serine methyl ester (**6a–f**) (typically 63–68% isolated) and methyl (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetate (**7**)[18,62] (typically 64.6 mg, 48%) as liquids. For **7**: $[\alpha]^{25}_D$ −72.2° (*c* 0.34, acetone); IR ($CHCl_3$ cast) 1752 (vs), 1450 (m), 1273 (s), 1170 (vs), 1030 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 2 H, *o-Ph*), 7.40 (m, 3 H, *m*, *p-Ph*), 3.90 (s, 3 H, COOCH_3), 3.55 (~q, 3 H, ~1.5 Hz, OCH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.31 (CF_3); EI-MS, M^+ 248.0661 (248.0661 calcd for $C_{11}H_{11}F_3O_3$).

Data for 6a (*S,S*-Isomer) from 3a:[28] IR ($CHCl_3$ cast) 3470–3200 (w, br), 1754 (vs), 1728 (s), 1510 (m), 1271 (s), 1220 (s), 1170 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 2 H, *o-Ph*), 7.37 (m, 3 H, *m*, *p-Ph*), 7.35 (s, 5 H, *Ph*CH$_2$O), 5.51 (d, 1 H, 7 Hz, N*H*), 5.12 (s, 2 H, CH_2Ph), 4.72 (dd, 1 H, 10.5, 3.5 Hz, CHC*H*HO), 4.68 (m, 1 H, C*H*), 4.60 (dd, 1 H, 2.5, 10.5 Hz, CHCH*H*O), 3.66 (s, 3 H, COOCH_3), 3.47 (~q, 3 H, ~1.5 Hz, OCH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −72.76 (CF_3);[22] EI-MS, M^+ 469.1345 (469.1349 calcd). Anal. Calcd for $C_{22}H_{22}NO_7F_3$: C, 56.29; H, 4.72; N, 2.98. Found: C, 56.11; H, 4.76; N, 2.91.

Data for 6b (*R,S*-Isomer) from 3b:[63] IR and EI-MS as described for **6a**. ^1H NMR (300 MHz, $CDCl_3$) was indistinguishable from **6a** except for δ 3.73 (s, 3 H, COOCH_3), 3.49 (~q, 3 H, ~1.5 Hz, OCH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −72.23 (CF_3).[22] Anal. Found: C, 56.20; H, 4.72; N, 2.94.

Data for 6e: This standard was prepared by subjecting a mixture of **3a**[20] (65.22%, 0.1768 mmol) and **3b**[21] (34.78%, 0.0942 mmol) to the above general procedure. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −76.26 (65% (*S,S*)-CF_3), −76.23 (35% (*R,S*)-CF_3).[22] HPLC analysis (9% EtOAc/91% hexane, 0.8 mL/min) provided a ratio of 64.80(±0.11)% *S,S*- (t_R = 78 min) and 35.20% *R,S*-isomer (t_R = 85 min).

Data for 6c (*S,S*-Isomer) from 3c:[26] IR ($CHCl_3$ cast) 1754 (vs), 1706 (s), 1273 (s), 1244 (s), 1183 (s), 1172 (s), 1028 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[25] δ 7.50–7.10 (m, 15 H, 3 *Ph*), 5.13 (m, 2 H, PhCH_2O), 4.82–4.00 (m, 5 H, C*H*-CH_2O, PhCH_2N), 3.60 (s, 0.59 × 3 H) and 3.33 (s, 0.41 × 3 H), (COOCH_3 conformers), 3.40 (br s, 3 H, OCH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −72.14 (CF_3); CI-MS, (NH_3) 577 ($M + NH_4^+$), 560 (MH^+). Anal. Calcd for $C_{29}H_{28}NO_7F_3$: C, 62.25; H, 5.04; N, 2.50. Found: C, 62.43; H, 4.98; N, 2.46.

Data for 6d (*R,S*-Isomer) from 3d:[64] IR ($CHCl_3$ cast) 1754 (vs), 1705 (s), 1270 (m), 1237 (s), 1182 (s), 1171 (s), 1026 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)[25] δ 7.53–7.05 (m, 15 H, 3 *Ph*), 5.16 (m, 2 H, PhCH_2O), 4.91–4.01 (m, 5 H, C*H*-CH_2O, PhCH_2N), 3.61 (s, 0.58 × 3 H) and 3.34 (s, 0.42 × 3 H) (COOCH_3 conformers), 3.40 (br s, 3 H, OCH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −72.04 (s, 0.58 × 3 F) and −71.96 (s, 0.42 × 3 F) (CF_3 conformers); CI-MS, (NH_3) 577 ($M + NH_4^+$), 560 (MH^+). Anal. Found: C, 61.90; H, 5.03; N, 2.37.

Data for 6f: This reference sample was prepared by submitting a mixture of **3c**[23] (67.12%, 0.1292 mmol) and **3d**[24] (32.88%, 0.0633 mmol) to the above general procedure. ^1H NMR (200 MHz, $CDCl_3$)[25] δ 3.46 (s, (*S,S*)-OCH_3), 3.43 (s, (*R,S*)-OCH_3) (total 3 H, ~2:1, incomplete resolution) with the remainder of spectrum as described for **6c** and **d** above; ^{19}F NMR (376.5 MHz, $CDCl_3$)[25] δ −72.14 (s, 67% (*S,S*)-CF_3), −71.96 (s), −72.04 (s) (58:42 ratio of conformers) 33% (*R,S*)-CF_3). HPLC analysis (6% EtOAc/94% hexane, 1.0 mL/min) provided a ratio of 67.4(±0.3)% *S,S*- (t_R = 79.5 min and 32.6% *R,S*-isomers (t_R = 73.8 min).

Reactions of Higher Order Organocyanocuprates $R_2Cu(CN)Li_2$ with β-Lactones. These reagents were prepared immediately before use as outlined by Lipshutz et al.[38a] Reactions were routinely followed by spotting onto TLC silica plates which had previously been wetted with HOAc. Following removal of HOAc in vacuo, the plate was developed (EtOAc/hexane), sprayed with alkaline bromocresol green spray,[65] and heated. The β-lactones appear as a yellow spot on a blue background. When β-lactone could no longer be detected, the reaction was terminated by addition to degassed 0.5 N HCl (~15 mol equiv relative to β-lactone) at 0–5 °C, 0.25 vol MeOH were added, and the mixture was stirred 20 min under Ar. The CuCl precipitate was removed by suction filtration and washed with Et_2O (1 vol). The filtrate was partitioned, and the aqueous layer was further extracted with Et_2O (3 × 1 vol). Ether phases were pooled, washed successively with saturated brine, pH 3.0 saturated EDTA solution, and again with brine (0.25 vol of each), dried over Na_2SO_4, and evaporated in vacuo. Chromatographic purification of the residue afforded the results indicated below.

(*S*)-2-[(Benzyloxycarbonyl)amino]butanoic Acid[4(**(8a, Table I, Entry 1).** The cuprate $Me_2Cu(CN)Li_2$ was formed by addition of MeLi in Et_2O (7.23 mmol, 4.13 mL) to CuCN (417 mg, 4.65 mmol) in THF (8 mL) at −78 °C.[38a] The mixture was stirred at −23 °C for 20 min, and β-lactone **3a**[58] (200 mg, 0.904 mmol) was added dropwise in THF (2.5 mL) over 5 min. The mixture was stirred 2 h at −23 °C and 15 min at 0 °C. The reaction mixture was then quenched and extracted as outlined above. Reverse phase MPLC (45% MeCN/H_2O, 3.0 mL/min) yielded 100.8 mg (47%) of **8a** as a syrup which crystallized from Et_2O/hexane: mp 78.5–79.0 °C (lit.[56] mp 78–79 °C); $[\alpha]^{25}_D$ −31.3 (±0.2)° (*c* 2.0, EtOH) (lit.[56] $[\alpha]^{25}_D$ −32° (*c* 2, EtOH)); IR (CH_2Cl_2 cast) 3350–2200 (m, br), 1717 (vs), 1526 (s), 1456 (m), 1415 (m), 1345 (m), 1231 (m), 1216 (s), 1085 (m), 1054 (m), 697 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)[25] δ 7.70 (br s, 1 H, COO*H*), 7.33 (s, 5 H, *Ph*), 6.30 (br s, 0.2 H) and 5.35 (d, 0.8 H, 8 Hz) (rotomeric N*H*), 5.11 (s, 2 H, PhCH_2O), 4.46–4.15 (m, 1 H, C*H*), 2.07–1.62 (m, 2 H, C*HH*Me), 0.96 (t, 3 H, 7.5 Hz, CH_3); EI-MS, 237.1004 (237.1001 calcd for $C_{12}H_{15}NO_4$); CI-MS, (NH_3) 255 ($M + NH_4^+$). Deprotection to (*S*)-2-aminobutanoic acid and GC analysis as the camphanamide methyl ester derivative **22a** indicated 97.83(±0.14)% enantiomeric excess (i.e., 1.08% D-isomer present).

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]butanoic Acids (8c and 8d). 8c, Entry 2. MeLi in Et_2O (2.72 mmol, 1.90 mL) was added to a stirred slurry of CuBr·SMe_2 (295 mg, 1.43 mmol) at −78 °C in THF (3 mL). The mixture was stirred 20 min at 0 °C and cooled to −45 °C, and β-lactone (**3c**)[23] (126 mg, 0.406 mmol) in THF (4 mL) was added dropwise over 8 min. Stirring was continued for 2.5 h at −45 °C, and 1 N HCl (5 mL) was added to quench. The mixture was extracted with EtOAc (3 × 30 mL). The organic layers were pooled, washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography on silica[60] (95 $CHCl_3$/5 MeOH) yielded 93.5 mg (70%) of **8c** as an oil: $[\alpha]^{25}_D$ −36.5° (*c* 0.49, $CHCl_3$); IR ($CHCl_3$ cast) 3030 (m, br), 1741 (m), 1705 (vs), 1670 (m), 1454 (m), 1420 (m), 1250 (m), 698 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)[25] δ 9.12 (br s, 1 H, COO*H*), 7.27 (br s, 10 H, 2 *Ph*), 5.17 (s, 2 H, PhCH_2O), 4.80–4.00 (m, 3 H, C*H*, PhCH_2N), 2.14–1.60 (m, 2 H, CH_2CH$_3$), 0.81 (m, 3 H, CH_3); EI-MS, 327.1469 (327.1471 calcd for $C_{19}H_{21}NO_4$).

8c, Entry 3. The cuprate $Me_2Cu(CN)Li_2$ was prepared from CuCN (105 mg, 1.17 mmol) in THF (2 mL) and MeLi in Et_2O (2.0 mmol, 1.90 mL).[38a] The β-lactone **3c**[23] (204 mg, 0.656 mmol) was introduced in THF (5 mL) dropwise at −78 °C over 5 min, and the mixture was stirred at −78 °C (90 min) and −45 °C (40 min). Quenching and extraction in

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(60) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(61) Obtained from Aldrich Chemical Co., Milwaukee, WI, USA.
(62) Mioskowski, C.; Solladie, G. *Tetrahedron* **1973**, *29*, 3669–3674.
(63) Compound **6b** prepared from D-serine[27] contained 1.49(±0.09)% (*S,S*)-isomer by HPLC.
(64) Compound **6d** prepared from D-serine[27] contained 1.5% (*S,S*)-isomer by ^{19}F NMR. HPLC suggests 1–2%.
(65) Krebs, K. G.; Heusser, D.; Wimmer, H. In *Thin-Layer Chromatography*, 2nd ed.; Stahl, E., Ed.; Springer-Verlag: New York, 1969; pp 854–909.

the usual fashion, followed by reverse phase MPLC (56% MeCN/H_2O, 3.0 mL/min) afforded 155 mg of **8c** (72%) with spectral and chromatographic properties identical with entry 2 above: $[\alpha]^{25}_D$ −35.1° (*c* 0.52, $CHCl_3$). Deprotection to (*S*)-2-aminobutanoic acid and GC analysis as the camphanamide methyl ester (**22a**) indicated 9.4(±1)% D-isomer present (i.e., 81.2% ee).

In addition, chromatography also yielded 10.5 mg (5%) of the ketone **9**: IR ($CHCl_3$ cast) 3450 (m), 1697 (s), 1238 (s), 1127 (m), 700 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)[25] δ 7.30 (m, 10 H, 2 *Ph*), 5.20 (m, 2 H, $PhCH_2O$), 4.56 (m, 2 H, $PhCH_2N$), 4.12 (m, 1 H, C*H*), 3.8–3.4 (m, 2 H, $CHCH_2O$), 3.26 (br s, 0.6 H) and 2.36 (br s, 0.4 H, CH_2OH), 2.00 (s, 1.8 H) and 1.74 (s, 1.2 H, $C(O)CH_3$); CI-MS, (NH_3) 345 (M + NH_4^+), 328 (MH^+). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.78; H, 6.42; N, 4.08.

8d, Entry 4. The cuprate $Me_2Cu(CN)Li_2$ was prepared from CuCN (59.3 mg, 0.636 mmol) in THF (3 mL) and MeLi in Et_2O (1.06 mmol, 0.95 mL).[38a] The (*R*)-β-lactone **3d**[24] (110 mg, 0.353 mmol) was added in THF (2 mL) dropwise over 5 min at −78 °C, and the mixture was stirred at −78 °C (1 h) and −45 °C (30 min). Workup and chromatography as in entry 3 provided 24.0 mg of unreacted β-lactone **3d** (22%), 6.9 mg of ketone **9** (6%), and 75.7 mg (72%) of the (*R*)-acid **8d**: $[\alpha]^{25}_D$ +37.3 (±0.7)° (*c* 0.46, $CHCl_3$); ^1H NMR, IR, and EI-MS identical with **8c**: CI-MS, (NH_3) 345 (M + NH_4^+), 328 (MH^+). Optical purity analysis (GC) as derivative **22b** indicated 2.07(±0.21)% of the *S*-isomer or 95.9% ee.

(*R*)-2-[(Benzyloxycarbonyl)amino]heptanoic Acid (10b, Entry 5). The cuprate *n*-$Bu_2Cu(CN)Li_2$ was formed from CuCN (528 mg, 5.90 mmol) in THF (6.0 mL) and *n*-BuLi in hexanes (11.3 mmol, 4.30 mL).[38a] The β-lactone **3b**[21] (250 mg, 1.13 mmol) was introduced in THF (4 mL) dropwise over 7 min at −23 °C, and the mixture was stirred 2 h. Workup in the usual manner and reverse phase MPLC (40 MeOH/25 MeCN/35 H_2O, 3 mL/min) yielded 196 mg of **10b** (62%) which was recrystallized from CCl_4/hexane: mp 63–64 °C (lit.[49] mp 63–65 °C for *S*-isomer; $[\alpha]^{25}_D$ +3.4 (±0.1)° (*c* 1.43, 95% EtOH) (lit.[49] $[\alpha]^{22}_D$ −3.5° (*c* 2, 95% EtOH) for *S*-isomer); IR ($CHCl_3$ cast) 3320 (m, br), 1717 (vs, br), 1521 (m), 1453 (m), 1412 (m), 1340 (m), 1230 (m), 1212 (m), 1053 (m), 695 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[25] δ 10.20 (br s, 1 H, COO*H*), 7.36 (s, 5 H, *Ph*), 5.80 (br s, 0.3 H) and 5.22 (d, 0.7 H, 8.2 Hz) (N*H*), 5.18–5.07 (m, 2 H, $PhCH_2O$), 4.45–4.34 (m, 0.7 H) and 4.34–4.20 (m, 0.3 H), (C*H*), 1.95–1.79 (m, 1 H, CHC*H*H-Bu), 1.77–1.60 (m, 1 H, CHCH*H*-Bu), 1.45–1.20 (m, 6 H, $(CH_2)_3$), 0.88 (~t, 3 H, CH_3); EI-MS, 279.1468 (279.1470 calcd for $C_{15}H_{21}NO_4$). Optical purity analysis (GC) as **23b** indicated 1.24(±0.16)% *S*-isomer or 97.5% ee.

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]heptanoic Acid (10c, Entry 6). The cuprate was formed from CuCN (101 mg, 1.13 mmol) in THF (2.2 mL) and *n*-BuLi in hexanes (1.9 mmol, 1.6 mL).[38a] A solution of β-lactone **3c**[23] (171 mg, 0.548 mmol) in THF (3.3 mL) was added dropwise over 5 min at −78 °C, the mixture was stirred 40 min at −78 °C, warmed to −46 °C, and allowed to reach −36 °C over 1 h. Workup and reverse phase MPLC (65% MeCN/H_2O, 3 mL/min) gave 154 mg (76%) of acid **10c** and **11** mg (5%) of ketone **11**. **For 10c**: $[\alpha]^{25}_D$ −32.3° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$ cast) 3100 (m), 1706 (s), 1235 (m), 1100 (m), 698 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)[25] δ 9.84 (br s, 1 H, COO*H*), 7.26 (m, 10 H, 2 *Ph*), 5.18 (s, 2 H, $PhCH_2O$), 4.64 (m, 1 H, C*H*), 4.5–4.15 (m, 2 H, $PhCH_2N$), 1.91 (m, 1 H, CHC*H*H-Bu), 1.74 (m, 1 H, CHCH*H*-Bu), 1.11 (m, 6 H, $(CH_2)_3$), 0.78 (m, 3 H, CH_3); EI-MS, 369.1935 (369.1940 calcd). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.30; H, 7.43; N, 3.55. Optical purity analysis (GC) as derivative **23a** indicated 87.0(±0.6)% ee.

For ketone 11: IR ($CHCl_3$ cast) 3440 (m, br), 1700 (s), 1233 (m), 1125 (m), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[25] δ 7.34 (m, 10 H, 2 *Ph*), 5.20 (m, 2 H, $PhCH_2O$), 4.53 (m, 2 H, $PhCH_2N$), 4.11 (m, 1 H, C*H*), 3.8–3.5 (m, 2 H, $CHCH_2$), 3.24 (m, 0.6 H) and 1.85 (m, 0.4 H) (O*H*), 2.25 (m, 2 H, $C(O)CH_2$-Pr), 1.40 (m, 1 H, CH*H*), 1.17 (m, 2 H, CH_2), 1.00 (m, 1 H, C*H*H), 0.77 (m, 3 H, CH_3); EI-MS, 369.1943 (M^+, 369.1940 calcd), 284.1286 (M–C(O)Bu). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.52; H, 7.28; N, 3.67.

***N*-(Benzyloxycarbonyl)-L-leucine[50] (12a, Entry 7).** Isopropylmagnesium chloride in Et_2O (5.42 mmol, 1.80 mL) was added dropwise over 5 min to β-lactone **3a**[58] (200 mg, 0.904 mmol) and $CuBr{\cdot}SMe_2$ (35.0 mg, 0.17 mmol) in THF (8 mL)/Me_2S (0.4 mL) at −23 °C. The mixture was stirred 1.5 h at −23 °C and quenched by addition to cold degassed 0.5 N HCl (20 mL). Extraction and washing in the usual fashion followed by reverse phase MPLC (46% MeCN/H_2O, 3.5 mL/min) afforded 106 mg (44%) of **12a** as a syrup: $[\alpha]^{25}_D$ −16.8(±0.2)° (*c* 1.0, 95% EtOH) (lit.[66] $[\alpha]_D$ −16.5(±1)° (*c* 1.0, EtOH)). Spectral and chromatographic properties were identical with that of authentic Z-L-leucine. Optical purity analysis (GC) as the camphanamide methyl ester derivative **25a** indicated no detectable *R*-isomer (i.e., ≥99.4% ee).

***N*-Benzyl-*N*-(benzyloxycarbonyl)-L-leucine (12c, Entry 8).** Isopropylmagnesium chloride in Et_2O (3.0 mmol, 1.0 mL) was added dropwise over 5 min to β-lactone **3c**[23] (180 mg, 0.578 mmol) and $CuBr{\cdot}SMe_2$ (25 mg, 0.122 mmol) in THF (6 mL)/Me_2S(0.3 mL) at −23 °C. The mixture was stirred 2 h at −23 °C and quenched by addition to cold degassed 0.5 N HCl (20 mL). Extraction and washing of the etheral phases followed by reverse phase MPLC (55% MeCN/H_2O, 3.3 mL/min) yielded 170 mg (83%) of **12c** as an oil: $[\alpha]^{25}_D$ −44.7° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$ cast) 3160 (m br), 1740 (s), 1705 (vs), 1680 (s), 1498 (m), 1468 (s), 1454 (s), 1418 (s), 1315 (s), 1240 (vs), 1208 (s), 1179 (s), 699 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[25] δ 9.75 (br s, 1 H, COO*H*), 7.45–7.10 (m, 10 H, 2 *Ph*), 5.19 (s, 2 H, $PhCH_2O$), 4.87–4.62 (m, 1 H, C*H*), 4.60–4.30 (m, 2 H, $PhCH_2N$), 1.90–1.20 (m, 3 H, CH_2CHMe_2), 0.94–0.53 (m, 6 H, 2 CH_3); EI-MS, 355.1785 (355.1784 calcd); CI-MS (NH_3) 373 (M + NH_4), 356 (MH^+). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.97; H, 7.09; N, 3.94. Found: C, 70.68; H, 7.10; N, 3.87. Optical purity analysis (GC) as **25a** showed no detectable *R*-isomer (i.e, ≥99.4% ee).

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-4-methylhexanoic Acid[51] (13c, Entry 9). The cuprate *sec*-$Bu_2Cu(CN)Li_2$ was prepared from CuCN (83.1 mg, 0.928 mmol) in THF (2.3 mL) and *sec*-butyllithium (1.7 mmol, 1.25 mL).[38a] The β-lactone **3c**[23] (123 mg, 0.396 mmol) in THF (7 mL) was added dropwise over 4 min at −78 °C, and the mixture was stirred 20 min at −78 °C, 70 min at −46 °C, and 1 h at −18 °C. Workup in the usual fashion followed by reverse phase MPLC (70% MeCN/H_2O, 3 mL/min) afforded 110 mg (76%) of **13c** as an oil and 4 mg (4%) of benzyl *N*-benzylcarbamate **14**.

For 13c: $[\alpha]^{25}_D$ −37.6° (*c* 0.47, $CHCl_3$); IR ($CHCl_3$ cast) 3100 (m br), 1705 (s), 1238 (s), 1102 (m), 975 (m), 698 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)[25] δ 9.60 (br s, 1 H, COO*H*), 7.26 (m, 10 H, 2 *Ph*), 5.18 (s, 2 H, $PhCH_2O$), 4.7–4.4 (m, 3 H, C*H*, $PhCH_2N$), 2.0–1.4 (m, 2 H, N-CH-CH_2), 1.4–0.84 (m, 3 H, $CHCH_3$, CH_2CH_3), 0.84–0.59 (m, 6 H, 2 CH_3); EI-MS, 369.1938 (369.1940 calcd). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.32; H, 7.42; N, 3.70.

For 14: mp 59–61 °C (lit.[67] mp 60 °C); IR ($CHCl_3$ cast) 3325 (m), 1690 (s), 1532 (m), 1454 (m), 1268 (s), 1140 (m), 748 (m), 697 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34 (m, 10 H, 2 *Ph*), 5.15 (s, 2 H, $PhCH_2O$), 5.10 (br s, 1 H, N*H*), 4.38 (d, 2 H, 6 Hz, CH_2N); EI-MS, 241.1103 (241.1102 calcd for $C_{15}H_{15}NO_2$).

(*S*)-[*N*-(Benzyloxycarbonyl)amino]-4,4-dimethylpentanoic Acid (15a, Entry 10). The higher order mixed organocuprate *t*-Bu(Me)$Cu(CN)Li_2$ was formed from CuCN (267 mg, 2.98 mmol) in THF (7.5 mL), MeLi in Et_2O (2.80 mmol, 1.65 mL), and *t*-BuLi in pentane (2.80 mmol, 1.55 mL).[38b] The β-lactone **3a**[58] (200 mg, 0.904 mmol) in THF (3.5 mL) was added dropwise over 5 min at −23 °C, and the mixture was stirred 1 h. Workup in the usual fashion and reverse phase MPLC (57% MeCN/H_2O, 3 mL/min) provided 121 mg (48%) of **15a** which crystallized from Et_2O/hexane: mp 95–97 °C; $[\alpha]^{25}_D$ −16.7(±0.2)° (*c* 1.17, MeOH);[52b] IR ($CHCl_3$ cast) 3320 (m br), 2957 (s), 1719 (vs), 1531 (s), 1245 (s), 1050 (m), 694 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[25] δ 7.90 (br s, 1 H, COO*H*), 7.30 (s, 5 H, *Ph*), 6.10 (br d, 0.20 H, 8 Hz) and 5.33 (d, 0.80 H, 8.5 Hz) (N*H*), 5.20–5.00 (m, 2 H, $PhCH_2O$), 4.45–4.20 (m, 1 H, C*H*), 1.85–1.70 (m, 1 H, C*H*H-*t*-Bu), 1.53–1.40 (dd, 1 H, 9, 14 Hz, CH*H*-*t*-Bu), 0.92 (br s, 9 H, *t-Bu*); EI-MS, 279.1470 (M^+, 279.1470 calcd), 234.1494 (M–CO_2H); CI-MS, (NH_3) 297 (M + NH_4^+), 280 (MH^+). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.54; H, 7.33; N, 5.21.

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-4,4-dimethylpentanoic Acid (15c, Entry 11). The cuprate *t*-$Bu_2Cu(CN)Li_2$ was prepared from CuCN (68.7 mg, 0.767 mmol) in THF (2 mL) and *t*-BuLi in pentane (1.38 mmol, 1.0 mL).[38a] The β-lactone **3c**[23] in THF (2 mL) was introduced dropwise at −78 °C over 5 min, and the mixture was stirred for 1 h at −78 °C, 1 h at −45 °C, and 30 min at −15 °C. Workup in the usual manner, followed by reverse phase MPLC (60% MeCN/H_2O, 3 mL/min) afforded 56.3 mg (38%) of **15c**, 18.4 mg (19%) of **14**, and 18 mg of *N*-benzyl-*N*-(benzyloxycarbonyl)-L-alanine (**16**).

For 15c: mp 109–112.5 °C; $[\alpha]^{25}_D$ −28.6(±0.2)° (*c* 1.0, $CHCl_3$) (cf. mp and $[\alpha]_D$ for entry 12 below); IR ($CHCl_3$ cast) 3100 (m, br), 2957 (s), 1742 (m), 1706 (vs), 1453 (m), 1367 (m), 1244 (m), 698 (s) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 10.20 (br s, 1 H, COO*H*), 7.30 (s, 10 H, 2 *Ph*), 5.22 (s, 2 H, $PhCH_2O$), 4.74–4.27 (m, 3 H, C*H*, $PhCH_2N$), 2.08 (dd, 1 H, 5, 14 Hz, C*H*H-*t*-Bu), 1.60 (dd, 1 H, 5, 14 Hz, CH*H*-*t*-Bu), 0.82 (s, 9 H, *t-Bu*); EI-MS, 369.1938 (369.1940 calcd for $C_{22}H_{27}NO_4$).

(66) *The 1986–87 Chemalog Catalog/Handbook of Chemicals*; Chemical Dynamics Corporation: South Plainfield, NJ, USA.

(67) Kunieda, T.; Higuchi, T.; Abe, Y.; Hirobe, M. *Chem. Pharm. Bull.* **1984**, *23*, 2174–2181.

For 16: IR ($CHCl_3$ cast) 3100 (m), 1704 (s), 1260 (m), 1213 (m), 1070 (m), 1015 (m), 698 (s) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.75 (br s, 1 H, COO*H*), 7.27 (s, 10 H, 2 *Ph*), 5.22 (s, 2 H, PhCH_2O), 4.9–4.2 (m, 3 H, PhCH_2N, C*H*), 1.37 (d, 3 H, 7 Hz, CH_3); EI-MS, 313.1311 (313.1314 calcd for $C_{18}H_{19}NO_4$).

15c, entry 12: *tert*-Butyllithium (3.0 mmol, 2.0 mL) was added dropwise to a suspension of CuBr·SMe_2 (0.340 g, 1.66 mmol) in THF (3 mL) at −78 °C, and the mixture was stirred for 40 min at −78 °C and 20 min at −45 °C. A solution of β-lactone **3c**[23] (199 mg, 0.382 mmol) in THF (3 mL) was added dropwise over 15 min, and stirring was continued 7 h at −46 °C and 1 h at −10 °C. Workup and chromatography as outlined for entry 11 afforded 71.9 mg (51%) of **15c**, 16.9 mg (18%) of urethane **14**, and 27.0 mg (23%) of alanine derivative **16**.

For 15c, entry 12: mp 114–116 °C; $[\alpha]^{25}_D$ −32.4° (*c* 1.0, $CHCl_3$) (cf. entry 11 above); IR, ^1H NMR, EI-MS identical with entry 11. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.25; H, 7.31; N, 3.74. Deprotection to (*S*)-2-amino-4,4-dimethylpentanoic acid and GC analysis as **26a** indicated 99.2(±0.1)% enantiomeric excess.

For 16: $[\alpha]^{25}_D$ −28.8° (*c* 0.88, $CHCl_3$); IR, ^1H NMR, EI-MS identical with those reported under entry 11 results.

(*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-4-pentenoic Acid[53] **(17a, Entry 13).** To β-lactone **3a**[68] (74.0 mg, 0.334 mmol) and CuBr·SMe_2 (17.2 mg, 0.084 mmol) in THF (3.0 mL) and Me_2S (0.15 mL) was added vinylmagnesium chloride in THF (1.67 mmol, 1.10 mL) dropwise over 5 min at −23 °C. The mixture was stirred 2 h at −23 °C and worked up in the usual manner. Reverse phase MPLC (43% MeCN/H_2O, 3.0 mL/min) yielded 39.1 mg (47%) of **17a** as a white solid which was recrystallized from Et_2O/hexane: mp 63.5–64.5 °C (lit.[69a] mp 65 °C); $[\alpha]^{25}_D$ +17.5(±0.2)° (*c* 2.0, $CHCl_3$) (lit.[69a] $[\alpha]^{25}_D$ +17.6(±0.6)° (*c* 5.0, $CHCl_3$)); IR, ^1H NMR, and EI-MS characteristics were identical with those in literature.[69b] Optical purity analysis (GC) of the derivative **27a** indicated 98.40(±0.20)% ee.

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-4-pentenoic Acid (17c, Entry 14). The cuprate $(CH_2CH)_2Cu(CN)Li_2$ was prepared from CuCN (103.6 mg, 1.16 mmol) in THF (5.0 mL) and vinyllithium in THF (1.93 mmol, 1.04 mL).[38a] The β-lactone **3c**[23] (200 mg, 0.642 mmol) in THF 2.5 mL) was added dropwise over 5 min at −78 °C, and the mixture stirred 1 h at −78 °C, 3 h at −46 °C, and 30 min at 0 °C. Workup in the usual manner and reverse phase MPLC (55% MeCN/H_2O, 3 mL/min) afforded 122 mg (56%) of **17c** as an oil: $[\alpha]^{25}_D$ −33.3° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$ cast) 3100 (m, br), 1742 (m), 1706 (vs), 1678 (m), 1498 (m), 1455 (m), 1421 (m), 1240 (s), 698 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (br s, 1 H, COO*H*), 7.27 (m, 10 H, 2 *Ph*), 5.71–5.44 (m, 1 H, vinylic-C*H*), 5.18 (s, 2 H, PhCH_2O), 5.07–4.81 (m, 2 H, vinylic-CH_2), 4.69 (m, 1 H, C*H*), 4.49–4.02 (m, 2 H, PhCH_2N), 2.80–2.40 (m, 2 H, CHCH_2); EI-MS, 298.1083 (M − C_3H_5, 298.1080 calcd for $C_{17}H_{16}NO_4$), 294.1491 (M − CO_2H, 294.1494 calcd), 254.1180 (M − (C_3H_5 + CO_2)), 204.1027 (M − CO_2Bn); CI-MS, (NH_3) 357 (M + NH_4^+), 340 (MH^+). Optical purity analysis (GC) as **27a** indicated 71.5(±0.5)% ee.

***N*-(Benzyloxycarbonyl)-L-phenylalanine (18a, Entry 15).** Phenylmagnesium chloride in THF (5.42 mmol, 2.71 mL) was added dropwise to β-lactone **3a**[58] (200 mg, 0.904 mmol) and CuBr·SMe_2 (55.8 mg, 0.271 mmol) in THF (8 mL) and Me_2S (0.4 mL) at −23 °C over 5 min, and the mixture was stirred 2 h at −23 °C. Workup and reverse phase MPLC (46% MeCN/H_2O, 3.5 mL/min) provided 149 mg (55%) of Z-L-phenylalanine (**18a**) and 147 mg (43%) of the tertiary alcohol **19**, which was recrystallized from $CHCl_3$/hexane.

For 18a, Entry 15: mp 86–87 °C (lit.[56] mp 88–89 °C); $[\alpha]^{25}_D$ +5.11° (*c*, 2.0, 98% EtOH) (lit.[56] $[\alpha]^{25}_D$ +5.1° (*c* 2.0, EtOH)); IR, ^1H NMR, EI-MS, and CI-MS were identical with authentic material. Optical purity determination (GC) as the derivative **28a** indicated no detectable *R*-isomer (i.e., ≥99.4% ee).

For (*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-1,1-diphenylpropane-1,3-diol (19): mp 134.0–134.5 °C; $[\alpha]^{25}_D$ −68.4 (±0.2)° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$ cast) 3360 (m, br), 1692 (s), 1538 (m), 1492 (m), 1448 (m), 1258 (m), 1062 (s), 747 (s), 695 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[25] δ 7.55–7.00 (m, 15 H, 3 *Ph*), 5.90 (d, 1 H, 9 Hz, N*H*), 4.98 (d, 1 H, 12.5 Hz, PhC*H*HO), 4.91 (d, 1 H, 12.5 Hz, PhCH*H*O), 4.88 (m, 1 H, C*H*Ph_2), 4.70 (m, 0.9 H) and 4.56 (m, 0.1 H) (N-C*H*), 3.74 (m, 1 H, C*H*HOH), 3.65 (m, 1 H, CH*H*OH), 3.04 (br s, 2 H, 2 O*H*); EI-MS, 183.0809 (Ph_2COH^+, base peak); CI-MS, (NH_3) 395 (M + NH_4^+), 378 (MH^+), 360 (MH^+ − H_2O, base peak). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.14; H, 6.31; N, 3.70.

***N*-(Benzyloxycarbonyl)-D-phenylalanine (18b, Entry 16).** The cuprate $Ph_2Cu(CN)Li_2$ was prepared from CuCN (311.5 mg, 3.48 mmol) in THF (7.0 mL) and PhLi in cyclohexane/Et_2O (7:3) (6.75 mmol, 3.55 mL).[38a] The β-lactone **3b**[21] (150 mg, 0.678 mmol) in THF (2.5 mL) was added dropwise over 5 min at −15 °C, and the mixture was stirred 2 h. Workup in the usual fashion followed by reverse phase MPLC (62% MeOH/H_2O, 3 mL/min) afforded 93.5 mg (46%) of Z-D-phenylalanine (**18b**): mp 100–101 °C (lit.[56] mp 88–89 °C; mp 103 °C for DL); $[\alpha]^{25}_D$ −1.6(±0.1)° (*c* 2.0, 95% EtOH) (lit.[56] $[\alpha]^{25}_D$ +5.1 (*c* 2, EtOH) for L-isomer); IR, ^1H NMR, and MS identical with authentic material. Optical purity determination (GC) as the derivative **28b** indicated 29.6(±0.1)% ee.

***N*-Benzyl-*N*-(benzyloxycarbonyl)-L-phenylalanine (18c, Entry 17).** Phenylmagnesium bromide in THF (1.87 mmol, 3.55 mL) was added dropwise over 10 min to a stirred suspension of CuBr·SMe_2 (197 mg, 0.957 mmol) in THF (5 mL) and Me_2S (0.2 mL) at −12 °C. The mixture was stirred 2 h at −12 °C, and β-lactone **3c**[70] (120 mg, 0.384 mmol) in THF (3 mL) was introduced dropwise over 5 min. The mixture was stirred 4 h at −12 °C and worked up in the usual fashion. Purification by reverse phase MPLC (60% MeCN/H_2O, 3 mL/min) afforded 24.6 mg (17%) of biphenyl (mp 68–70 °C; lit.[48] mp 69–71 °C), and 89.5 mg (60%) of **18c**: $[\alpha]^{25}_D$ −107° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$ cast) 3100 (m), 3025 (m), 1706 (s), 1238 (s), 1123 (m), 986 (m), 750 (m), 698 (s) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 9.95 (br s, 1 H, COO*H*), 7.25 (m, 15 H, 3 *Ph*), 5.26 (s, 2 H, PhCH_2O), 4.7–3.72 (m, 3 H, PhCH_2N, C*H*), 3.32 (m, 2 H, CH_2Ph); EI-MS, 389.1631 (389.1627 calcd). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.11; H, 6.03; N, 3.36. Optical purity determination (GC) as derivative **28a** indicated 88.5(±0.2)% ee.

18c, entry 18: The cuprate $Ph_2Cu(CN)Li_2$ was generated from CuCN (77.9 mg, 0.870 mmol) in THF (3 mL) and PhLi in cyclohexane/Et_2O (7:3) (1.5 mmol, 0.70 mL).[38a] The β-lactone **3c**[23] (151 mg, 0.485 mmol) in THF (6 mL) was added dropwise over 10 min at −78 °C, and the mixture was stirred 1 h at −78 °C and allowed to warm to −15 °C over 3 h. Workup and chromatography as outlined for entry 17 afforded 47.9 mg (25%) of **18c** as an oil. IR, ^1H NMR, and MS properties were identical with those described for entry 17. Optical purity determination (GC) as the derivative **28a** indicated 94.0(±0.6)% ee.

18c, entry 19: Phenyllithium in cyclohexane/Et_2O (7:3) (2.95 mmol, 1.40 mL) was added to CuBr·SMe_2 (308 mg, 1.50 mmol) in THF (3 mL) at −42 °C over 3 min. The mixture was stirred 15 min at −42 °C, β-lactone **3c**[71] (154 mg, 0.494 mmol) in THF (3.5 mL) was introduced dropwise over 3 min, and the resulting mixture was stirred 4 h at −35 °C. Quenching, extractive workup, and chromatography (see entry 17) yielded 69.4 mg (36%) of **18c**: $[\alpha]^{25}_D$ −101° (*c* 0.59, $CHCl_3$) (cf. entry 17). IR, ^1H NMR, and MS properties were identical with those for entry 17 above.

Reaction of β-Lactone 3c with Methylcerium(III) Dichloride To Form Ketone 9 and Alcohol 20. The organocerium reagent $MeCeCl_2$ was prepared according to Imamoto et al.[35] by dropwise addition of MeLi in Et_2O (0.42 mmol, 0.35 mL) to anhydrous $CeCl_3$ (155 mg, 0.416 mmol $CeCl_3$·$7H_2O$, dried 2 h at 140 °C, 0.05 mmHg) in THF (5 mL) at −78 °C. The mixture was stirred 35 min, β-lactone **3c**[71] (98.5 mg, 0.316 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred 2 h at −78 °C. Quenching, extraction, and flash chromatography on silica[60] (35 EtOAc/65 hexanes; EtOAc) afforded 55.9 mg (57%) of unreacted β-lactone **3c**, 11.3 mg (11%) of ketone **9**, and 20.4 mg (19%) of (*S*)-2-[*N*-(benzyloxycarbonyl)amino]-3-methylbutan-1,3-diol (**20**): $[\alpha]^{25}_D$ −29° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3410 (m, br), 1675 (s), 1499 (m), 1477 (m), 1347 (m), 1236 (m), 1144 (m), 1116 (m), 1050 (m), 698 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (m, 10 H, 2 *Ph*), 5.29 (d, 1 H, 12 Hz, PhC*H*HO), 5.21 (d, 1 H, 12 Hz, PhCH*H*O), 4.66 (d, 1 H, 14 Hz, PhC*H*HN), 4.58 (d, 1 H, 14 Hz, PhCH*H*N), 4.05 (m, 2 H, CHCH_2), 3.32 (br s, 0.83 H, O*H*), 2.05 (br s, 0.83 H, O*H*), 1.79 (s, 0.34 H, O*H*), 1.24 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3); CI-MS, (NH_3) 361 (M + NH_4^+), 344 (MH^+). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; H, 4.08. Found: C, 69.95; H, 7.39; N, 3.75.

General Procedures for Deprotection of Amino Acid Derivatives and Determination of Stereochemical Purity: Deprotection of 8, 10, 12, 15, and 18a–d to Free Amino Acids. Typically a solution of the N-protected amino acid (approximately 50 mg) in HOAc/H_2O (2:1, ~7 mL) was stirred with 5% Pd on carbon under an atmosphere of H_2 for 12–16 h. The catalyst was removed by filtration and washed with HOAc/H_2O (2:1, 3 × 1 mL). The filtrate was evaporated to dryness in vacuo (35–40 °C), and the residue was redissolved in H_2O and lyophilized. Further

(68) Compound **3a** determined to be 98.50(±0.30)% optically pure by HPLC analysis as **6a**.

(69) (a) Neuberger, A.; Tait, G. H. *J. Chem. Soc.* **1962**, 3963–3968. (b) Kamber, M.; Just, G. *Can. J. Chem.* **1985**, *63*, 823–827.

(70) Compound **3c** determined to be 93(±0.8)% optically pure based on $[\alpha]^{25}_D$ −8.7° (*c* 1.1, THF).

(71) Compound **3c** estimated to be 97.3(±0.5)% optically pure based on $[\alpha]^{25}_D$ −9.1° (c 1.1, THF).

drying to constant weight in vacuo over P_2O_5 and KOH pellets afforded the free amino acids in 91–99% yield. Where R_3 = Me, *i*-Pr, *t*-Bu, vinyl, or phenyl (see Scheme IV), the products possessed IR, ^1H NMR, POSFAB-MS (glycerol/HCl matrix), and chromatographic properties identical with the authentic amino acids.[27]

For (*R*)- and (*S*)-2-aminoheptanoic acids obtained by deprotection of **10b** and **10c**: $[\alpha]^{25}_D$ −32.3(±0.2)° (*c* 1.02, HOAc) (for *R*-isomer from **10b**), +28.5(±0.2)° (*c* 0.97, HOAc) (for *S*-isomer from **10c**) (lit.[72] $[\alpha]^{25}_D$ +33.0 (*c* 1.2, HOAc) for *S*-isomer); IR (KBr disc) 3425 (vs, br), 1620 (m), 1587 (s), 1409 (m), 1050 (m, br) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.74 (t, 1 H, 6.3 Hz, C*H*), 1.86 (br m, 2 H, CHCH_2), 1.35 (br m, 6 H, (CH_2)$_3$), 0.87 (t, 3 H, 7 Hz, CH_3); POSFAB-MS (glycerol/HCl) 146 (MH^+), 291 (M_2H^+).

Deprotection of 17a,c to (*S*)-2-Amino-4-pentenoic Acid. Compound **17a** (16.9 mg) or **17c** (23.0 mg) (0.068 mmol) in THF (1.5 mL) was added to a blue solution of $Na_{(s)}$ (~1 mg) in $NH_{3(l)}$ (6 mL). Tiny shavings of sodium (~0.3 mg each) were added to the mixture until the blue color obtained on dissolution of the metal persisted for about 1 min. A crystal of NH_4OAc was added to decolorize the solution, and the solvents were evaporated in a stream of dry argon. The residue was dried briefly in vacuo and dissolved in 1.5 mL of H_2O, and the pH was adjusted to 6.0 with acetic acid. The aqueous solution was extracted with CH_2Cl_2 (3 mL) to remove residual organic impurities and applied to a column of BioRad Ion Retardation Resin Ag 11 A8 (30 g, 1 × 40 cm)[73] packed in H_2O. Elution with H_2O (0.4 mL/min) provided the amino acid free of salts. Lyophilization of these fractions afforded 7.4–7.25 mg (93–95%) of (*S*)-2-amino-4-pentenoic acid which possessed IR, ^1H NMR, POSFAB-MS, and chromatographic properties identical with authentic material.[27]

Preparation of *N*-(1*S*,4*R*)-ω-Camphanoylamino Acid Methyl Esters for Determination of Stereochemical Purity. A modification of the procedure of Armarego et al.[30] was employed. Typically, (−)-(1*S*,4*R*)-camphanoyl chloride (46.9 mg, 0.216 mmol) was added to a mixture of the amino acid (0.108 mmol) in 1 M $NaHCO_3/Na_2CO_3$ buffer (pH 10, 2 mL) with toluene (0.4 mL). The mixture was stoppered and stirred vigorously for 2 h. Following acidification to pH 1 with 5.7 N HCl and extraction with CH_2Cl_2 (4 × 5 mL), the organic phases were dried over Na_2SO_4 and evaporated in vacuo. The residue was treated with an excess of CH_2N_2 in Et_2O, and the solvent and excess reagent were removed in vacuo to provide a crude sample for analytical GC separation of diastereomers. Analytical samples were secured by removal of the side product, methyl (−)-(1*S*,4*R*)-camphanoate (**21**), by sublimation (65 °C, 0.01 mmHg, ~6 h). *N*-camphanoyl amino acid methyl esters were obtained in yields of 78–95% in this manner, along with a sublimate of 22.0–33.4 mg (48–51%) of methyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate (**21**): mp 108.0–108.5 °C $[\alpha]^{25}_D$ −12.1° (*c* 2.0, 95% EtOH) (lit.[74] mp 108.4–108.5 °C; $[\alpha]^{25}_D$ −12.4° (*c* 2.2, EtOH)); IR ($CHCl_3$ cast) 1782 (vs), 1727 (s), 1277 (m), 1100 (m), 924 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3 H, COOCH_3), 2.47–2.36 (m, 1 H, 6-H_{exo}), 2.10–1.99 (m, 1 H, 6-H_{endo}), 1.98–1.88 (m, 1 H, 5-H_{exo}), 1.73–1.62 (m, 1 H, 5-H_{endo}), 1.13 (s, 3 H, 10-CH_3), 1.07 (s, 3 H, 9-CH_3), 0.97 (s, 3 H, 8-CH_3) (Absolute ^1H NMR assignments made on the basis of NOE enhancements and confirmed by ^1H decoupling experiments. See structure **21** (Scheme IV) for numbering system.); EI-MS, 212.1049 (212.1049 calcd). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.14; H, 7.55.

Methyl 2-([[(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]-heptyl]-1-carbonyl]amino)butanoates (22a, 22b, and 22e). These compounds were prepared from (*S*)- and (*R*)-2-aminobutanoic acids, respectively (using products from deprotection of **8a,c**, and **d** as well as authentic material[27]), as outlined above.

For the (2*S*)-isomer 22a: mp 74–76 °C; $[\alpha]^{25}_D$ −16.5° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$ cast) 3365 (m, br), 2960 (s), 1790 (vs), 1749 (s), 1672 (s), 1528 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[31] δ 6.92 (br d, 1 H, 8 Hz, N*H*), 4.59 (m, 1 H, C*H*), 3.76 (s, 3 H, COOCH_3), 2.56–2.43 (m, 1 H, 6′-H_{exo}), 2.03–1.86 (m, 3 H, 6′-H_{endo}, 5′-H_{exo}, C*H*HCH$_3$), 1.81–1.68 (m, 2 H, 5′-H_{endo}, CH*H*CH$_3$), 1.13 (s, 3 H, 10′-CH_3), 1.12 (s, 3 H, 9′-CH_3), 0.93 (s, 3 H, 8′-CH_3), 0.92 (m, 3 H, CH_2CH_3); EI-MS, 297.1576 (297.1577 calcd for $C_{15}H_{23}NO_5$).

For the (2*R*)-isomer 22b: oil; $[\alpha]^{25}_D$ −13.8° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$ cast) 3370 (m, br), 2968 (s), 1792 (vs), 1742 (s), 1675 (s), 1526 (s), 1265 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[31] δ 6.79 (d, 1 H, 8 Hz, N*H*), 4.61–4.52 (m, 1 H, C*H*), 3.74 (s, 3 H, OCH_3), 2.60–2.46 (m, 1 H, 6′-H_{exo}), 2.02–1.86 (m, 3 H, 6′-H_{endo}, 5′-H_{exo}, C*H*HCH$_3$), 1.78 (dd, 1 H, 7, 14.5 Hz, CH*H*CH$_3$), 1.75–1.68 (m, 1 H, 5′-H_{endo}), 1.13 (s, 3 H, 10′-CH_3), 1.09 (s, 3 H, 9′-CH_3), 0.98 (s, 3 H, 8′-CH_3), 0.95 (t, 3 H, 7 Hz, CH_2CH_3); EI-MS, 297.1576 (297.1577 calcd for $C_{15}H_{23}NO_5$).

Reference Standard 22e: This material was prepared from commercial racemic 2-aminobutanoic acid[27] as an oil which possessed spectral properties consistent with an equimolar mixture of **22a** and **22b**. GC analysis (RSL-300, 160 °C, 1.0 min, 1.5 °C/min to 200 °C, 50 °C/min to 250 °C, 6.6 psi) afforded a ratio of 48.25%:51.75 (±0.08)% for the 2*R*- (t_R = 17.54 min) and 2*S*-isomers (t_R = 18.57 min), respectively, in **22e**. Samples and standards established limits of detection at approximately 0.3%.

(*S*)- and (*R*)-Methyl 2-([[(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptyl]-1-carbonyl]amino)heptanoates (23a and 23b). These compounds were produced by deprotection of **10b** and **10c** to (*R*)- and (*S*)-2-aminoheptanoic acids, respectively, followed by derivatization as outlined above.

For the (2*S*)-isomer 23a: IR ($CHCl_3$ cast) 3360 (w, br), 2959 (s), 2926 (s), 2850 (m), 1796 (vs), 1746 (s), 1678 (s), 1527 (m), 1260 (m), 1060 (m), 1015 (m), 921 (m), 795 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[31] δ 6.87 (d, 1 H, 8 Hz, N*H*), 4.62 (m, 1 H, C*H*), 3.75 (s, 3 H, COOCH_3), 2.60–2.42 (m, 1 H, 6′-H_{exo}), 2.04–1.79 (m, 3 H, 6′-H_{endo}, 5′-H_{exo}, CHC*H*H-Bu), 1.78–1.60 (m, 2 H, 5′-H_{endo}, CHCH*H*-Bu), 1.40–1.21 (m, 6 H, (CH_2)$_3$), 1.12 (s, 3 H, 10′-CH_3), 1.11 (s, 3 H, 9′-CH_3), 0.92 (s, 3 H, 8′-CH_3), 0.90–0.82 (m, 3 H, CH_2CH_3); EI-MS, 339.2042 (339.2046 calcd for $C_{18}H_{29}NO_5$); CI-MS, (NH_3) 357 (M + NH_4^+), 340 (MH^+).

For the (2*R*)-isomer 23b: IR and MS behavior were identical with **23a**. ^1H NMR (300 MHz, $CDCl_3$)[31] was virtually identical with **23a** except for the following: δ 6.75 (d, 1 H, 8 Hz, N*H*), 3.73 (s, 3 H, COOCH_3), 1.09 (s, 3 H, 9′-CH_3), 0.98 (s, 3 H, 8′-CH_3).

Reference Standard 23e: Since 2-aminoheptanoic acid was not commercially available, this compound was prepared by a diastereoselective alkylation of the corresponding glycine derivative. Methyl (1*S*,4*R*)-camphanoylglycinate (**24**) (mp 85.5–86.0 °C; lit.[30] mp 84 °C) was obtained in 95% yield from glycine by using the above general procedure, followed by MPLC purification (silica, 50% EtOAc in hexanes, 3 mL/min). The method of Piotrowska and Abramski[33] employing LDA (2 equiv) and TMEDA (2 equiv) was adapted to alkylate **24** (269 mg, 1 mmol) with 1-bromopentane (0.124 mL, 1 mmol). MPLC (silica, 25% EtOAc in hexanes, 3.0 mL/min) was used to isolate **23e** as a mixture of diastereomers in 11% yield (37.3 mg): IR and MS properties were identical with **23a** and **23b**. ^1H NMR (300 MHz, $CDCl_3$)[31] indicated 70% of (2*S*)- and 30% (2*R*)-isomers from the ratio of 8′-CH_3 (0.92 and 0.98 ppm) and COOCH_3 (3.75 and 3.73 ppm) integrals, respectively. GC analysis (DB 17$^+$, 170 °C, 2.0 min, 2 °C/min to 230 °C, 7.12 psi) afforded a ratio of 69.79(±0.10)% to 30.21% for the (2*S*)- (t_R = 24.65 min) and (2*R*)-isomers (t_R = 24.07 min), respectively. The estimated limit of detection is ≤0.5%.

Methyl 2-([[(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]-heptyl]-1-carbonyl]amino)-4-methylpentanoates (25a and 25e). (2*S*)-Isomer 25a. This compound was prepared by using the product of deprotection of **12a** or **12c** as outlined above: mp 51–52 °C; IR ($CHCl_3$ cast) 3438 (m, br), 3355 (m, br), 2955 (m), 1793 (vs), 1745 (m), 1675 (s), 1525 (m), 1167 (m), 1011 (m), 921 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[31] δ 6.76 (br d, 1 H, 8.4 Hz, N*H*), 4.70–4.60 (m, 1 H, C*H*), 3.75 (s, 3 H, COOCH_3), 2.56–2.43 (m, 1 H, 6′-H_{exo}), 2.02–1.89 (m, 2 H, 6′-H_{endo}, 5′-H_{exo}), 1.76–1.55 (m, 4 H, -CH_2C*H*Me$_2$, 5′-H_{endo}), 1.12 (s, 3 H, 10′-CH_3), 1.11 (s, 3 H, 9′-CH_3), 0.96 (d, 3 H, 2.8 Hz, CH(CH_3)-CH$_3$), 0.93 (d, 3 H, 3 Hz, CH(CH$_3$)CH_3), 0.91 (s, 3 H, 8′-CH_3); EI-MS, 325.1889 (325.1889 calcd). Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.80; H, 8.23; N, 4.19.

Reference Standard 25e: This material was prepared as an oil from authentic L-leucine (8.42 mg) and D-leucine (10.67 mg)[27] (0.146 mmol total) according to the general procedure: IR and MS behavior was essentially identical with **25a**. ^1H NMR (300 MHz, $CDCl_3$)[31] indicated 44% (2*S*)- and 56% (2*R*)-isomers, with resolved peaks due to the (2*R*)-isomer at δ 6.70 (br d, 1 H, 8.4 Hz, N*H*), 3.73 (s, 3 H, COOCH_3), 1.08 (s, 3 H, 9′-CH_3), 0.99 (s, 3 H, 8′-CH_3), and all other peaks as described for **25a** above. Anal. Found: C, 62.38; H, 8.07; N, 4.29. GC analysis (RSL-300, 110 °C, 1.0 min, 1.5 °C/min to 210 °C, 50 °C/min to 250 °C, 2.0 min, 6.7 psi) indicated 44.1(±0.30)% and 55.9% of the (2*S*)- (t_R = 53.80 min) and (2*R*)-isomers (t_R = 52.95 min), respectively. Limits of detection were established with additional standards as ≤0.5% of the (2*R*)-isomer.

Methyl 2-([[(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]-heptyl]-1-carbonyl]amino)-4,4-dimethylpentanoates (26a and 26e). (2*S*)-Isomer 26a. This compound was prepared by using the product of deprotection of **15a** and **15c** in the usual manner: IR ($CHCl_3$ cast) 3365 (m, br), 2957 (s), 1792 (vs), 1748 (s), 1675 (s), 1527 (s), 1274 (m), 1169 (m), 1060 (m), 923 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[31] δ 6.68 (d, 1 H, 8 Hz, N*H*), 4.59 (~d of t, 1 H, 8.4, 3.7 Hz, C*H*), 3.74 (s, 3 H,

(72) See: ref 56, p 2401.
(73) See: BioRad Bulletin no. 1005.
(74) Kuritani, H.; Takaoka, Y.; Shingu, K. *J. Org. Chem.* **1979**, *44*, 452–454.

$COOCH_3$), 2.54–2.38 (m, 1 H, 6′-H_{exo}), 2.03–1.87 (m, 2 H, 6′-$_{endo}$, 5′-H_{exo}), 1.81 (dd, 1 H, 14.6, 3.7 Hz, CHH-*t*-Bu), 1.76–1.66 (m, 1 H, 5′-H_{endo}), 1.52 (dd, 1 H, 14.5, 8.4 Hz, CH*H*-*t*-Bu), 1.13 (s, 3 H, 10′-CH_3), 1.12 (s, 3 H, 9′-CH_3), 0.97 (s, 9 H, *t-Bu*), 0.92 (s, 3 H, 8′-CH_3); EI-MS, 339.2045 (339.2046 calcd for $C_{18}H_{29}NO_5$).

Reference Standard 26e: This material was prepared from a mixture of authentic D- and L-γ-methylleucine (58.90 mg and 33.70 mg, respectively)[27] as outlined in the general procedure: IR and MS behavior were as described for **26a**. ^{1}H NMR (300 MHz, $CDCl_3$)[31] indicated 64% (2*R*)- and 36% (2*S*)-isomers, with resolved peaks due to the (2*R*)-isomer at δ 4.67 (d of t, 1 H, 3.0, 9.0 Hz, C*H*), 3.73 (s, 3 H, $COOCH_3$), 1.10 (s, 3 H, 9′-CH_3), 0.99 (s, 3 H, 8′-CH_3), and all other peaks as described for **26a** above. GC analysis (RSL-300, 160 °C, 1.0 min, 1.5 °C/min to 210 °C, 50 °C/min to 250 °C, 1.0 min, 6.6 psi) afforded a ratio of 64.43(±0.04)% and 35.57% of the (2*R*)- (t_R = 24.0 min) and (2*S*)-isomers (t_R = 25.2 min), respectively. Limits of detection were established as ≤0.25% of the (2*R*)-isomer.

Methyl 2-([[(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]-heptyl]-1-carbonyl]amino)-4-pentenoates (27a and 27e). (2*S*)-Isomer 27a. This compound was prepared from the product of deprotection of **17a** or **17c** by using the general procedure outlined above. Due to the volatility of **27a** under the usual sublimation conditions, purification by MPLC (35% EtOAc in hexane, 3 mL/min) was used to provide **27a** as an oil (91% yield): IR ($CHCl_3$ cast) 1793 (vs), 1746 (m), 1677 (s), 1524 (m), 920 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)[31] δ 6.94 (br d, 1 H, 8 Hz, N*H*), 5.77–5.59 (m, 1 H, vinylic-C*H*), 5.51–5.18 (m, 2 H, vinylic-CH_2), 4.78–4.64 (m, 1 H, C*H*), 3.77 (s, 3 H, $COOCH_3$), 2.68–2.43 (m, 3 H, 6′-H_{exo}, $CHCH_2$), 2.01–1.84 (m, 2 H, 6′-H_{endo}, 5′-H_{exo}), 1.76–1.63 (m, 1 H, 5′-H_{endo}), 1.11 (s, 3 H, 10′-CH_3), 1.10 (s, 3 H, 9′-CH_3), 0.91 (s, 3 H, 8′-CH_3); EI-MS, 309.1573 (309.1576 calcd). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.14; H, 7.30; N, 4.43.

Reference Standard 27e: This material was prepared from authentic D- (7.06 mg) and L-allylglycine (12.00 mg)[27] as described for **27a**: IR and MS behavior was identical with **27a**. ^{1}H NMR (300 MHz, $CDCl_3$)[31] provided a ratio of 37% (2*R*)- and 63% (2*S*)-isomers, with resolved peaks due to the (2*R*)-isomer at δ 6.83 (br d, 1 H, 8 Hz, N*H*), 3.75 (s, 3 H, $COOCH_3$), 1.12 (s, 3 H, 10′-CH_3), 1.09 (s, 3 H, 9′-CH_3), 0.98 (s, 3 H, 8′-CH_3), with all other peaks as described for **27a** above. GC analysis (RSL-300, 120 °C, 2.0 min, 2.0 °C/min to 220 °C, 50 °C/min to 250 °C, 7.10 psi) afforded a ratio of 37.47(±0.32)% and 62.53° of the (2*R*)- (t_R = 36.50 min) and (2*S*)-isomers (t_R = 37.26 min), respectively. Limits of detection were determined to be ≤0.6% of (2*R*)-isomer.

Methyl 2-([[(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]-heptyl]-1-carbonyl]amino)-3-phenylpropionates (28a, 28b, and 28e). (2*S*)-Isomer 28a. This compound was prepared from the deprotection product of **18a** or **18c** according to the general procedure, with purification by flash chromatography[60] (40% EtOAc in hexane) or sublimative removal of **21**: IR ($CHCl_3$ cast) 3360 (m, br), 2960 (m), 1789 (vs), 1752 (m), 1671 (s), 1523 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.18 (m, 3 H, *m*, *p-Ph*), 7.18–7.10 (m, 2 H, *o-Ph*), 6.81 (br d, 1 H, 8.5 Hz, N*H*), 4.94 (m, 1 H, C*H*), 3.73 (s, 3 H, $COOCH_3$), 3.22 (dd, 1 H, 5.5, 14 Hz, C*H*HPh), 3.02 (dd, 1 H, 8.5, 14 Hz, CH*H*Ph), 2.52–2.39 (m, 1 H, 6′-H_{exo}), 1.97–1.84 (m, 2 H, 5′-H_{exo}, 6′-H_{endo}), 1.72–1.57 (m, 1 H, 5′-H_{endo}), 1.07 (s, 3 H, 10′-CH_3), 1.01 (s, 3 H, 9′-CH_3), 0.61 (s, 3 H, 8′-CH_3) (Absolute assignments are based on NOE and ^{1}H-decoupling results.); EI-MS, 359.1735 (359.1733 calcd). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.63; H, 6.99; N, 3.87.

(**2*R*)-Isomer 28b**: This compound was prepared from the deprotection product of **18b** (entry 16) exactly as described for **28a** above. Spectral characteristics of the resulting stereochemically impure material (64.8% (2*R*)) were essentially as described for **28e** below.

Reference Standard 28e: The procedure outlined for **28a** was employed to derivatize a mixture of D- (0.209 g) and L-phenylalanine[27] (0.100 g): IR and MS behavior was identical with **28a**. ^{1}H NMR (300 MHz, $CDCl_3$) provided a ratio of 66% (2*R*)- and 34% (2*S*)-isomers, with resolved peaks due to the (2*R*)-isomer[32] at δ 3.72 (s, 3 H, $COOCH_3$), 1.09 (s, 3 H, 10′-CH_3), 1.06 (s, 3 H, 9′-CH_3), 0.88 (s, 3 H, 8′-CH_3) with all other peaks as described for **28a** above. Anal. Found: C, 66.47; H, 7.11; N, 3.89. GC analysis (RSL-300, 170 °C, 2.0 min, 2.0 °C/min to 250 °C, 3.0 min, 6.8 psi) indicated 66.07 (±0.36)% and 33.93% of the (2*R*)- (t_R = 32.3 min) and (2*S*)-isomers (t_R = 33.1 min), respectively. Limits of detection were established as ≤0.4% under these conditions.

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Supplementary Material Available: General experimental procedures and instrumentation and preparation of **1c, 1d, 2b,** and **5** (3 pages). Ordering information is given on any current masthead page.