Synthesis of Enantiomerically Pure β- and γ-Amino Acid Derivatives Using Functionalized Organozinc Reagents

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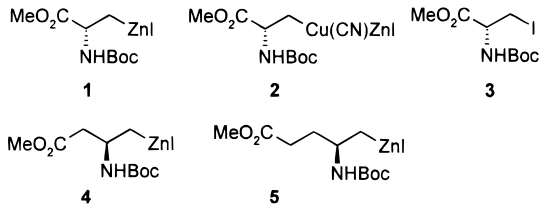
β-Amido zinc reagents **4** and **5** readily undergo β-elimination when prepared in THF, but when a polar aprotic solvent such as DMF is employed, β-elimination is suppressed. Using DMF, reaction of **4** with aryl iodides provides β-homophenylalanine derivatives (12 examples, 20−89% yield), and analogous reactions of **5** give γ-bishomophenylalanine derivatives (7 examples, 34−80% yield). The related zinc/copper reagents **17** and **18** are also useful intermediates that undergo subsequent cross-coupling reactions with a wide range of electrophiles (9 examples, 28−87% yield).

Introduction

The synthesis of nonproteinogenic amino acids continues to provide a challenge for organic chemists. Increasingly, β- and γ-amino acids have been attracting attention as a result of their presence in biologically active compounds[1] and their usefulness as components of modified peptides and natural products.[2] Recently, short-chain peptides comprising β-amino acids have been shown to form stable helical secondary structures in solution and the solid phase,[3−9] as well as showing resistance to the peptidase pepsin. γ-Amino acids have also been shown to form peptides with helical secondary structures.[10,11] γ-Aminobutyric acid, GABA, is present in the mammalian brain as an inhibitory neurotransmitter; low levels may lead to the convulsive behavior observed in Parkinson's disease and epilepsy.

There exist many approaches toward the synthesis of enantiomerically pure β-amino acids, and an excellent review describes the principal routes.[12]

The benefits of using organozinc intermediates in the synthesis of highly functional molecules are now well known and documented.[13,14] The outstanding functional group tolerance of such species has allowed us to develop the nucleophilic α-amino acid organozinc reagent **1**[15] and zinc/copper reagent **2**,[16] prepared in each case from protected iodoalanine **3** (which in turn is synthesized from serine). Similarly, side chain manipulation of aspartic acid and glutamic acid derivatives provides α-amino acid γ- and δ-anion equivalents, respectively.[17,18] This has led to routes for the synthesis of a variety of enantiomerically pure alkyl-, aryl-, heteroaryl-, and acyl-substituted α-amino acids by means of transition-metal-catalyzed cross-coupling reactions.[19] The success of these developments led us to investigate the synthesis of β- and γ-amino acids in an analogous fashion using the new organozinc reagents **4** and **5**.[20]



Results and Discussion

The iodide precursors **6** and **7** containing the necessary β- and γ-amino acid moieties, respectively, were synthesized from commercially available protected L-aspartic and L-glutamic acids. Reduction of the α-carboxylate was achieved by treating *N*-(*tert*-butoxycarbonyl)-L-glutamic

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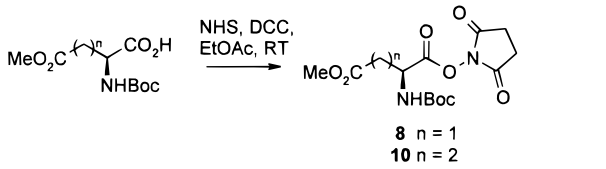
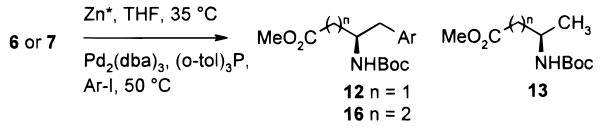
Scheme 1



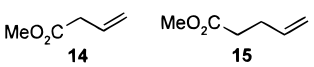
Scheme 2



acid β-methyl ester with *N*-hydroxysuccinimide/DCC to give succinimide ester **10**.[21] which was subsequently reduced with sodium borohydride by using a minor modification of the literature procedure.[21] Conversion of the alcohol **11** into iodide **7** was accomplished by using iodine, triphenylphosphine, and imidazole.[22] In an analogous manner, *N*-(*tert*-butoxycarbonyl)-L-aspartic acid γ-methyl ester was converted into alkyl iodide **6** via succinimide **8** and alcohol **9** (Scheme 1).

With the alkyl iodides in hand we attempted to prepare the zinc reagents **4** and **5**, using the protocol successfully developed for the serine-derived reagent **1**. Iodide **6** was added to zinc dust activated by the Knochel procedure using THF as solvent.[13] Subsequent palladium(0)-catalyzed cross coupling with iodobenzene gave the β-homophenylalanine derivative **12** (Ar = Ph) in poor yield (20%). The corresponding β-amino butanoate derivative **13** (5%), which is formed by protonation of the zinc reagent, was also isolated (Scheme 2). Similarly, the homologous zinc reagent **5** yielded disappointingly low yields of coupled product. The poor mass balance was of particular concern, and this prompted us to investigate the stability of the zinc reagents **4** and **5**.

NMR Studies of the Zinc Reagents in THF-d_8. The two new zinc reagents **4** and **5**, together with the existing serine-derived species **1**, all bear the same structural motif, i.e., they are all β-amido zinc reagents, although they appeared to exhibit markedly different stabilities. We decided that further studies of the structures of **4** and **5** were needed to understand the evident lack of stability. A survey of the ^{1}H and ^{13}C NMR spectra of these zinc reagents (**1**, **4**, and **5**) was conducted using THF-d_8 as the solvent. ^{1}H NMR spectra of **1** indicated the clean formation of the zinc reagent with no degradation products present. However, the ^{1}H NMR spectra of the homologous reagents **4** and **5** showed the occurrence of significant β-elimination of the carbamate group from each of the zinc reagents, yielding methyl but-3-enoate **14** and methyl pent-4-enoate **15**, respectively, and in both cases, Boc-NH_2.

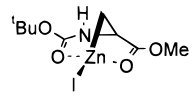


The ^{13}C NMR spectra also proved to be informative. Upon formation of the zinc reagent **1**, the ester and carbamate carbonyl group signals are observed to shift downfield relative to their parent iodide (Table 1). This probably indicates that coordination occurs between both the carbonyl groups and the zinc. The same is seen for the zinc species **4** and **5,** but the magnitude of $\Delta\delta$ decreases as the separation between the zinc and ester increases, suggesting that the coordination is intramolecular, i.e., as the ring size increases from 5 (zinc reagent **1**) to 7 (zinc reagent **5**) the coordination becomes less favorable. The magnitude of the carbamate−zinc coordination (as implied by $\Delta\delta$) increases through the series despite the fact that the size of the ring formed by coordination remains constant. The increase in magnitude of $\Delta\delta$ for the carbamate corresponds to a fall in $\Delta\delta$ for the ester, suggesting that the zinc is more Lewis acidic when the ester is further away and less able to donate electron density onto the metal. The consequence of the coordination of the carbamate to the zinc is an increased leaving group ability, which promotes β-elimination.

Table 1. Changes in ^{13}C Chemical Shift of Carbonyl Groups on Zinc Reagent Formation in THF-d_8

	$\Delta\delta$ ($\delta_{(R-ZnI)} - \delta_{(R-I)}$)		
	1	**4**	**5**
carbamate	+2.711	+3.747	+3.923
ester	+5.347	+1.464	+0.675

The remaining question is why the structurally related serine-derived zinc reagent **1** exhibits greater resistance to β-elimination. The $\Delta\delta$ for the carbamate, although less than for **4** and **5**, shows that there is significant coordination to the zinc. We believe that the strong ester coordination forces **1** to adopt a rigid bicyclic structure in which the C−NHBoc bond cannot be either syn or anti



to the C−Zn bond and thus cannot undergo elimination. Further evidence supporting this proposed structure is described in an earlier paper.[18]

NMR Studies of the Zinc Reagents in DMF-d_7. There is evidence that there are distinct advantages in the use of polar aprotic solvents in the formation of organozinc species. Aryl, heteroaryl, and benzylic zinc halides may be generated in the presence of DMF or DMA,[23,24] whereas they can otherwise only be formed in other solvents with highly reactive zinc. The use of dipolar aprotic solvents either as the solvent or as a cosolvent allows formation of β-amido zinc reagents at lower temperatures,[25] with reduced Wurtz coupling and with greater reliability. Nakamura and co-workers have carried out spectroscopic investigations on bis[2-(isopropoxycarbonyl)ethyl]zinc.[26] They demonstrated that in CCl_4 both carbonyl groups are bound to the zinc. In the presence of Et_2O, a solvent of moderate Lewis basicity,

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Table 2. Changes in ^{13}C Chemical Shift of Carbonyl Groups on Zinc Reagent formation in DMF-d_7

	$\Delta\delta$ ($\delta_{(R-ZnI)} - \delta_{(R-I)}$)		
	1	**4**	**5**
carbamate	−0.868	−0.535	−0.687
ester	+5.786	+0.872	+0.115

just one of the carbonyl groups was displaced to form the etherate. However, the use of pyridine disrupted all internal coordination between the carbonyl groups and the metal. Yoshida has also observed that β-zinc ketones do not show significant coordination between the carbonyl and metal when formed in benzene with a mandatory equivalent of HMPA as cosolvent.[27] Because the source of the instability of **4** and **5** is coordination of the carbamate to zinc, these results suggest that the use of dipolar aprotic solvents may improve stability by disrupting coordination.

In accordance with our previous experiment, we decided to generate the amino acid derived zinc reagents **4** and **5**, but using DMF-d_7 as the solvent. Once again, zinc dust was activated by treatment with 1,2-dibromoethane and chlorotrimethylsilane. Pleasingly, the zinc insertion proceeded under the same conditions as before (insertion occurring at ambient temperature), and so ^1H and ^{13}C NMR spectra were obtained for the series. ^1H NMR results indicate that in all cases insertion of zinc into the carbon−iodine bond occurred efficiently, with evidence for the presence of substantially less eliminated product than in THF-d_8. The ^{13}C NMR spectra show that the carbamate carbonyl groups experienced a very small upfield shift, which suggests that the coordination between the zinc and carbamate was suppressed (Table 2). Ester coordination was still observed and (as in THF-d_8) became weaker as the ester became more remote from zinc.

Synthesis of β- and γ-Amino Acid Homologues of Phenylalanine. Having established that our new β-amidozinc reagents can be generated conveniently with reduced tendency to eliminate by the use of dipolar aprotic solvents, we returned to the question of coupling the zinc species **4** and **5** with appropriate aromatic iodides. This class of coupled product represents a significant proportion of the β-amino acids found to be biologically important.[28,29] Our use of polar aprotic solvents also appeared to be beneficial given that palladium-catalyzed cross-coupling reactions often benefit from being carried out in DMF or DMA.[30] Organozinc reagent **4** was generated from alkyl iodide **6** by using zinc dust activated by the Knochel method, in DMF. Total conversion of the starting iodide was observed within 15 min at room temperature. Aromatic iodides were added using the active catalyst generated in situ from $Pd_2(dba)_3$ and tri-*o*-tolylphosphine. The coupling reaction was carried out at room temperature, which appears to be the best

Scheme 3

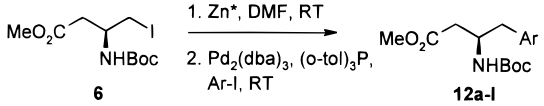
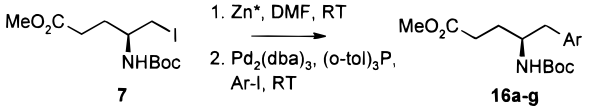


Table 3. Preparation of β-Homophenylalanine Derivatives

Ar	product	yield (%)
Ph	**12a**	73
1-naphthyl	**12b**	61
4-Me-C_6H_4	**12c**	73
2-MeO-C_6H_4	**12d**	56
4-MeO-C_6H_4	**12e**	68
2-NH_2-C_6H_4	**12f**	33
4-Br-C_6H_4	**12g**	58
2-F-C_6H_4	**12h**	46
4-F-C_6H_4	**12i**	65
2-NO_2-C_6H_4	**12j**	20
3-NO_2-C_6H_4	**12k**	47
4-NO_2-C_6H_4	**12l**	89

compromise for an efficient coupling reaction while minimizing β-elimination (Scheme 3). All other polar aprotic solvents that were screened (DMA, NMP, and DMSO) gave comparable results. 1,2-Dimethoxyethane behaved in the same manner as THF, with a substantial amount of β-elimination observed. Following standard workup and purification by flash chromatography, the cross-coupled products **12a**−**l** were isolated in good yield (Table 3). Not unexpectedly, the poorer yields occur when the electrophiles have bulky ortho substituents, with *o*-iodonitrobenzene being the worst example. Even so, the reasonable yield obtained with 2-fluoroiodobenzene is in stark contrast to the reaction in THF, which gave no isolated product using the previous protocol. The optical purity of **12a** was established by the close agreement of its specific rotation with that reported in the literature.[31] As an additional measure, the enantiomeric excess of **12a** was determined as being >98% (by comparison with a racemic sample) by capillary electrophoresis using α-cyclodextrin as a chiral selector.[32] We have therefore presumed that all of the other derivatives **12b**−**l** have also been formed without racemization, especially in view of all previous precedents for the lack of racemization in the use of amino acid derived zinc reagents.[15,18]

Scheme 4



In an analogous manner, γ-amino acids **16a**−**g** were synthesized from zinc reagent **5** (Scheme 4). Again, the zinc insertion into iodide **7** occurred smoothly at room temperature in DMF, and the subsequent palladium-catalyzed cross-coupling reactions, also at room temperature, afforded the desired products in good yield (Table 4). The previous trends were again observed, with ortho substituents giving rise to the lowest yields.

Reactivity of the Zinc/Copper Reagents 17 and 18. We wished to further explore the potential of the new zinc reagents. The extensive work of Knochel in the area

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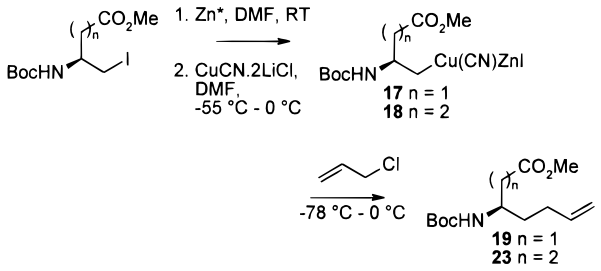
Table 4. Preparation of γ-Bishomophenylalanine Derivatives

Ar	product	yield (%)
Ph	**16a**	68
4-Me-C_6H_4	**16b**	68
2-MeO-C_6H_4	**16c**	69
4-MeO-C_6H_4	**16d**	68
2-NH_2-C_6H_4	**16e**	56
2-F-C_6H_4	**16f**	34
4-NO_2-C_6H_4	**16g**	80

Scheme 5



of zinc/copper reagents had led us in the past to prepare the serine-derived zinc/copper reagent **2**[16] which, like other such reagents, has enhanced reactivity over the corresponding zinc reagent. We wanted to investigate whether we could apply the existing methodologies to β- and γ-amino acid derivatives. Given the propensity for **4** and **5** to β-eliminate, the reactions were carried out wholly in DMF, whereas previously **2** had been generated and used in THF. An equimolar amount of a DMF solution of CuCN.2LiCl was added to a solution of **4** in DMF at −55 °C. The reaction was allowed to briefly warm to 0 °C to ensure formation of the cuprate, then it was recooled to −55 °C and allyl chloride was added (Scheme 5). Usual workup gave the allylated compound **19** in good yield (73%). The mass balance was accounted for by β-elimination and trace amounts of protonated zinc reagent (ca. 3−4%). Preparation and reaction of the reagent on a larger scale (3.0 mmol rather than 0.75 mmol) brought about an increase in yield to 82%. A representative selection of unsaturated alkyl halide electrophiles was further tested, all of which gave excellent yields of coupled product (Table 5).

Michael Reactions. Functionalized zinc/copper reagents generally undergo successful conjugate addition reactions.[33] More recent advances have seen copper being used catalytically[34−36] and enantioselectively.[37] We have shown previously that the serine-derived zinc/copper reagent **2** (generated and reacted in THF), added to methyl vinyl ketone in the presence of chlorotrimethylsilane, gave the Michael product in low yield (20%).[16] Recently, this same reagent has been reacted with a propyne iminium triflate, using DMF as solvent, to give α,β-unsaturated ketones upon aqueous workup.[38] It has also been reported that zinc/copper reagents derived from simple N-protected iodoethylamine derivatives (generated in THF) lack sufficient reactivity to perform Michael additions.[25] Both Knochel and Yoshida have previously commented on low observed reactivities of zinc/copper reagents containing either electron-withdrawing or coordinating groups. However, zinc/copper reagent **17** (generated in DMF) was reacted with a premixed THF solution of methyl vinyl ketone and chlorotrimethylsilane at −55 °C (Scheme 6), yielding the Michael adduct **25** (56%). The superior yield for this reaction over that attempted previously with the serine-derived zinc/copper reagent **2** may be a further reflection on the fact that a polar aprotic solvent was used in the coupling process. The use of a polar solvent such as NMP and HMPA has been shown to allow conjugate addition to β,β-disubstituted Michael acceptors.[39] These are much less reactive electrophiles and otherwise require more powerful activation such as BF_3-etherate for the addition to successfully occur.[40] Additions of zinc/copper reagent **17** to substituted enones, e.g., cyclohexenone and 4-hexen-3-one, were also successful but furnished **26** and **27**, respectively, in somewhat lower yield (33% and 28%, respectively) and with only a marginal diastereomeric excess as detected by ^1H NMR.

Given the use of a polar aprotic solvent, we questioned the necessity to include chlorotrimethylsilane. Zinc/copper species **17** was formed in DMF, and to this was added methyl vinyl ketone with no TMSCl. The reaction was otherwise treated as before. Following workup and chromatography it was discovered that two products were present, the anticipated Michael adduct **25** (30%) and a cyclized derivative **28** (21%). This presumably arises from the intramolecular reaction of the enolate that is formed on initial Michael addition (and is usually trapped as a silyl enol ether) with the methyl ester. Similar tandem conjugate addition−cyclization reactions have been observed by Crimmins upon addition of functionalized zinc/copper reagents to acetylenic esters, to yield ultimately 2-carboalkoxy cyclopentenones[41] and cyclohexenones.[42]

Conclusions

We have demonstrated that β- and γ-amino acids can be efficiently synthesized from the new functionalized organozinc reagents **4** and **5** in good yield. The use of a polar aprotic solvent is essential to minimize β-elimination of the carbamate group. Furthermore, the use of such solvents allows the convenient and reliable formation of these zinc reagents under mild conditions and successful cross-coupling reactions.

Experimental Section

General. General experimental procedures have already been described.[18]

Methyl 3(*S*)-[(*tert*-Butoxycarbonyl)amino]-4-hydroxybutanoate (9). To a stirred solution of *N*-Boc aspartic acid β-methyl ester (12.66 g, 51.2 mmol) in ethyl acetate (100 mL) was added solid *N*-hydroxysuccinimide (6.29 g, 54.6 mmol) at 0 °C. A solution of dicyclohexylcarbodiimide (10.74 g, 52.0 mmol) in ethyl acetate (50 mL) was added slowly. The reaction

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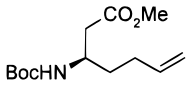
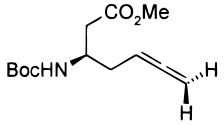
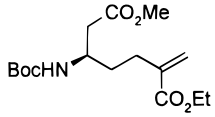
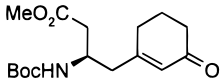
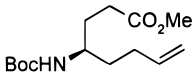
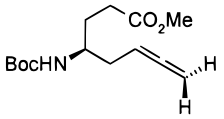
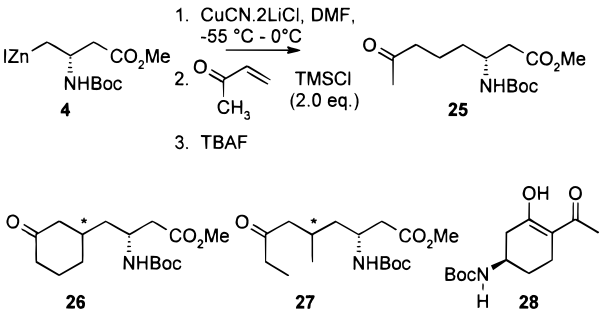
Table 5. Preparation of Unsaturated β- and γ-Amino Acid Derivatives

zinc/copper reagent	electrophile	product		yield (%)
17	allyl chloride	**19**		82
17	propargyl chloride	**20**		71
17	ethyl 2-bromomethylacrylate	**21**		71
17	3-iodocyclohex-2-enone	**22**		46
18	allyl chloride	**23**		87
18	propargyl chloride	**24**		82

Scheme 6



was allowed to attain room temperature and stirred overnight (convenience). The precipitate of dicyclohexylurea was filtered off, and the filtrate was washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried, and evaporated under reduced pressure to give crude succinimide ester **8** (17.9 g, 51.2 mmol, 100%). Sodium borohydride (0.63 g, 16.3 mmol) was dissolved in water (4 mL) and THF (30 mL) at 0 °C. A solution of **8** (3.44 g, 10.0 mmol) in THF (5 mL) was added dropwise over 30 s. The reaction was monitored by TLC (petroleum ether−ethyl acetate, 1:1), and after approximately 2 min, the reaction was observed to have gone to completion. Saturated aqueous ammonium chloride was added to quench the reaction. Extraction with ethyl acetate followed by washing of the combined organic extracts with brine, drying, and evaporation to dryness, afforded the crude product, which was purified by column chromatography on silica with petroleum ether−ethyl acetate (2:1) to give alcohol **9** as a colorless oil (1.94 g, 83%). Found C, 51.27; H, 8.52; N, 6.01. $C_{16}H_{19}NO_4$ requires C, 51.49; H, 8.21; N, 6.00. ν_{max} 3373 (s, br), 1717, 1692, 1523, and 1062; δ_H 1.38 (9 H, s) 2.57 (2 H, d, J = 6.1), 3.00 (1 H, br s), 3.61 (2 H, d, J = 5.1), 3.64 (3 H, s), 3.92−3.96 (1 H, m), and 5.30 (1 H, br d, J = 7.1); m/z (EI) 202.1080 (26, $M^+ - CH_3O$; $C_9H_{16}NO_4$ requires 202.1079), 146 (62), 102 (71), and 57 (100). $[\alpha]^{26}_D$ +1.8 (c 3.05 in CH_2Cl_2).

Methyl 4(*R*)-[(*tert*-Butoxycarbonyl)amino]-5-hydroxypentanoate (11). Prepared by the same method as described above for compound **9**. Alcohol **11** (66%) was isolated as a colorless oil. Found C, 53.41; H, 8.58; N, 5.84. $C_{11}H_{21}N_2O_5$ requires C, 53.43; H, 8.56; N, 5.66. ν_{max} 3358, 2977, 1737, 1714, 1691, and 1170; δ_H 1.40 (9H, s), 1.78−1.88 (2H, m), 2.35 (2H, t, J = 7.3), 2.67 (1H, br s), 3.50−3.62 (3H, m), 3.65 (3H, s), and 4.85 (1H, br d, J = 5.9); m/z (EI) 216.1229 (17, $M^+ - CH_3O$; $C_{10}H_{18}NO_4$ requires 216.1222), 160 (42), and 116 (65). $[\alpha]^{26}_D$ −7.0 (c 0.35 in $CHCl_3$) (lit.[21] $[\alpha]_D$ −10.48 (c 2.88 in $CHCl_3$)).

Methyl 3(*R*)-[(*tert*-Butoxycarbonyl)amino]-4-iodobutanoate (6). Triphenylphosphine (10.69 g, 40.3 mmol), imidazole (2.77 g, 40.3 mmol), and iodine (10.23 g, 40.3 mmol) were added to dry dichloromethane (120 mL) with stirring. Alcohol **9** was dissolved in dry dichloromethane (40 mL) under nitrogen and transferred to the reaction mixture via syringe. The reaction was monitored by TLC (petroleum ether−ethyl acetate, 2:1) and observed to have gone to completion after 1 h. The mixture was filtered before washing with aqueous sodium thiosulfate solution (1 M, 50 mL) and brine (50 mL) and drying ($MgSO_4$). The dichloromethane was evaporated under reduced pressure, and then the residue was slurried in diethyl ether and filtered through a bed of silica, with washing with additional ether. The filtrate was concentrated under vacuum, yielding the product as white needles in 73% yield, mp 58−59 °C. Found C, 35.55; H, 5.31; N, 4.15. $C_{10}H_{18}HNO_4I$ requires C, 35.00; H, 5.29; N, 4.08. ν_{max} 3342, 1731, 1682, and 1528; δ_H 1.45 (9 H, s), 2.64 (1 H, d, J = 6.4 and 16.5), 2.76 (1 H, dd, J = 5.5 and 16.5), 3.44 (2 H, m), 3.71 (3 H, s), 3.92 (1 H, m), and 5.10 (1 H, br d, J = 7.3); δ_C 11.16, 28.41, 38.59, 47.71, 52.02, 80.11, 154.79, and 117.24; m/z (EI) 286.9659 (37, $M^+ - C_4H_8$; $C_6H_{10}NO_4I$ requires 286.9654), 202 (51), 160 (78), and 146 (62). $[\alpha]_D$ +8.65 (c 2.105 in CH_2Cl_2).

Methyl 3(*R*)-[(*tert*-Butyloxycarbonyl)amino]-5-iodopentanoate (7). Compound **7** was prepared by the method described above for compound **6**. Iodide **7** (65%) was isolated as fine needles, mp 92−93 °C. Found C, 37.26; H, 5.76; N, 3.88. $C_{11}H_{20}NO_4I$ requires C, 36.99; H, 5.64; N, 3.92. ν_{max} 3351, 1730, 1682, and 1626; δ_H 1.45 (9 H, s), 1.81−1.91 (2 H, m), 2.37 (1 H, dd, J = 7.6 and 16.6), 2.43 (1 H, dd, J = 7.7 and 16.6), 3.30−3.32 (1 H, m), 3.39−3.45 (1 H, m), 3.69 (3 H, s), and 4.64 (1 H, br d, J = 8.5); δ_C 14.03, 28.34, 30.34, 30.48, 49.58, 51.82, 79.88, 155.09, and 173.44. m/z (EI) 283.9779 (3, $M^+ - C_4H_9O$; $C_7H_9NO_3I$ requires 283.9784), 301 (2.5), 170 (12), 130 (30), 116 (25), and 57 (100). $[\alpha]_D$ −15.6 (c 1.38 in CH_2Cl_2) and $[\alpha]_D$ −3.04 (c 2.53 in acetone) (lit.[43] $[\alpha]_D$ −5.2 (c 2.48 in acetone)).

Generation of Zinc Reagents (1, 4, and 5). General Procedure. Zinc dust (0.294 g, 4.5 mmol, 6.0 equiv) was weighed into a 50 mL round-bottom flask with sidearm which

(43) El Marini, A.; Roumestant, M. L.; Viallefont, P.; Razafindramboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, *11*, 1104−1108.

was flushed with nitrogen. Dry DMF (0.5 mL) and 1,2-dibromoethane (19 μL, 0.225 mmol) were added, and the mixture was stirred vigorously. The mixture was heated on a hot water bath for 20 min before being allowed to attain ambient temperature. Trimethylsilyl chloride (6 μL, 0.046 mmol) was added to the mixture, which was stirred for a further 30 min. Iodide **3**, **6**, or **7** (0.75 mmol) was dissolved in dry DMF (0.5 mL) under nitrogen. The iodide solution was transferred by syringe to the zinc mixture and stirred at room temperature. TLC (petroleum ether−ethyl acetate, 2:1) showed complete consumption of starting material within 15 min.

Preparation of Protected 4-Aryl β-Amino Acids (12a−l). General Procedure. The electrophile (1.0 mmol), tris-(dibenzylideneacetone)dipalladium (0.0228 g, 0.025 mmol, 0.025 equiv) and tri-*o*-tolylphosphine (0.0304 g, 0.10 mmol, 0.10 equiv) were added successively to the reaction mixture as solids. The reaction mixture was stirred at room temperature for 3 h and was subsequently diluted with ethyl acetate (50 mL), washed with brine, dried, and evaporated to dryness. Flash column chromatography over silica with an appropriate petroleum ether−ethyl acetate gradient furnished the protected 4-aryl-β-amino acid **12**.

Methyl 3(*R*)-[(*tert*-Butoxycarbonyl)amino]-4-phenylbutanoate (12a). Treatment with iodobenzene yielded **12a** (0.161 g, 73%), isolated as a white solid, mp 48−50 °C (lit. 51−52 °C).[31] Found C, 65.28; H, 8.05; N, 4.77. $C_{16}H_{23}NO_4$ requires C, 65.51; H, 7.90; N, 4.77. ν_{max} 3378, 1738, 1714, 1513, and 1168; δ_H 1.46 (9 H, s), 2.49 (1 H, dd, J = 5.8 and 15.9), 2.56 (1 H, dd, J = 5.5 and 15.9), 2.86 (1 H, J = 8.0, 13.5), 2.96−2.98 (1 H, m), 3.73 (3 H, s), 5.12 (1 H, br d, J = 6.7), and 7.23−7.38 (5 H, m); δ_C 28.17, 37.46, 40.30, 48.72, 51.53, 79.26, 126.51, 128.44, 129.30, 137.65, 155.05, and 172.06; *m*/*z* (EI) 220.0976 (36, $M^+ - C_4H_9O$; $C_{12}H_{14}NO_3$ requires 220.0974) 202 (62), 176 (46), and 146 (77). $[\alpha]_D$ +11.4 (*c* 1.34 in CH_2Cl_2). $[\alpha]_D$ +20.8 (*c* 1.28 in MeOH) (lit.[31] +19.9 (*c* 1.29 in MeOH)).

Preparation of Protected 5-Aryl γ-Amino Acids (16a−g). General Procedure. The same procedure as described above for the preparation of the protected 4-aryl-β-amino acids **12** was used in the preparation of 5-aryl γ-amino acid derivatives **16**, starting from iodide **7** (0.268 g, 0.75 mmol).

Aspartic Acid and Glutamic Acid Derived Zinc/Copper Reagents (17 and 18). Zinc dust (1.136 g, 18.0 mmol) was activated in dried DMF using the procedure described above but scaled up by a factor of 4. A solution of iodide **4** or **5** (3.0 mmol) in DMF was transferred under nitrogen via syringe to the reaction mixture at room temperature. The reaction was judged to be complete by TLC analysis (petroleum ether−ethyl acetate, 2:1) after approximately 20 min and was cooled to −55 °C (cryostat temperature). A solution of CuCN·2LiCl, prepared by dissolving copper(I) cyanide (0.2687 g, 3.0 mmol) and rigorously dried lithium chloride (0.2543 g, 6.0 mmol) in dry DMF (4.0 mL), was transferred via syringe to the reaction mixture, which was then allowed to warm to 0 °C for 10 min. After cooling to −55 °C again, the electrophile was introduced, and then the mixture was allowed to warm to −10 °C and stirred at this temperature for 3 h. The reaction mixture was partitioned between ethyl acetate (100 mL) and saturated aqueous ammonium chloride (40 mL) and then filtered. The organic layer was washed with water (40 mL) and brine (40 mL) and then dried, and the solvent was removed under reduced pressure. Flash column chromatography on silica gel, eluting with an appropriate petroleum ether−ethyl acetate gradient yielded the unsaturated protected amino acids.

Methyl 3(*R*)-[(*tert*-butoxycarbonyl)amino]-hept-6-enoate (19). Treatment with allyl chloride yielded **19** (0.1375 g, 69%), isolated as a colorless oil. Found C, 59.99; H, 9.03; N, 5.29. $C_{13}H_{23}NO_4$ requires C, 60.06; H, 9.01; N, 5.44. ν_{max} 3360, 2978, 1739, 1715, 1521, 1366, 1247, 1171, and 1055; δ_H 1.44 (9 H, s), 1.57−1.63 (2 H, m), 2.06−2.16 (2 H, m), 2.51 (1 H, dd, J = 5.5 and 15.5), 3.68 (3 H, s), 3.92−3.93 (1 H, m), 4.98 (1 H and 1 H, dd and m, J = 1.5 and 10.0), 5.03 (1 H, ddd, J = 1.5, 3.5, and 17.0), and 5.75−5.84 (1 H, m); δ_C 28.34, 30.34, 33.71, 39.03, 47.10, 51.60, 79.20, 115.15, 137.55, 155.27, and 172.06; *m*/*z* 201.1002 (2.5, $M^+ - C_4H_8$; $C_9H_{15}NO_4$ requires 201.1001). $[\alpha]_D$ +20.8 (*c* 1.06 in CH_2Cl_2).

Methyl 3(*R*)-[(*tert*-Butoxycarbonyl)amino]-hept-5,6-dienoate (20). Treatment with propargyl chloride yielded **20** (0.1375 g, 69%), isolated as a colorless oil. ν_{max} 3363, 2978, 1956, 1738, 1715, 1520, 1366, 1249, and 1168; δ_H 1.44 (9 H, s), 2.23−2.30 (2 H, m), 2.58 (2 H, br d, J = 5), 3.67 (3 H, s), 3.97−4.04 (2 H, dt, J = 2.8 and 6.4), and 5.02−5.08 (2 H, m); δ_C 28.58, 33.74, 38.33, 47.68, 51.90, 75.20, 79.59, 85.99, 155.41, 172.20, and 209.79; *m*/*z* 199.0845 (7, $M^+ - C_4H_8$; $C_9H_{17}NO_4$ requires 199.0845), 146 (31), 108 (13), 102 (72), 82 (17), and 57 (100). $[\alpha]_D$ −7.9 (*c* 1.24 in CH_2Cl_2).

5(*R*)-[(*tert*-Butoxycarbonyl)amino]-2-methylene-heptanedioic Acid 1-Ethyl-7-methyl Diester (21). Treatment with ethyl bromomethylacrylate[44] yielded **21** (0.686 g, 72%), isolated as a colorless oil. ν_{max} 3371, 2979, 1739, 1716, 1631, 1519, 1366, 1246, and 1172; δ_H 1.30 (3 H, t, J = 7.1), 1.44 (9 H, s), 1.69 (2 H, m), 2.27−2.35 (1 H, m), 2.38−2.45 (1 H, m), 2.54 (2 H, d, J = 5.2), 3.68 (3 H, s), 3.92 (1 H, m), 4.20 (2 H, q, J = 7.1), 4.98 (1 H, br s), 5.57 (1 H, br s), and 6.16 (1 H, br s); δ_C 14.21, 28.38, 28.72, 33.39, 39.25, 47.32, 51.66, 60.68, 79.29, 125.28, 139.83, 155.35, 166.98, and 171.99; *m*/*z* (EI) 273.1219 (1.2, $M^+ - C_4H_8$; $C_{12}H_{19}NO_6$ requires 273.1212), 229 (24), 184 (22), 156 (47), 102 (100), and 57 (98). $[\alpha]_D$ +8.5 (*c* 0.80 in CH_2Cl_2).

Methyl 3(*R*)-[(*tert*-Butoxycarbonyl)amino]-4-(cyclohex-1′-en-3′-one) Butanoate (22). Treatment with 3-iodocyclohex-2-enone yielded **22** (0.423 g, 56%), isolated as fine white needles, mp 94−97 °C. Found C, 61.39; H, 8.09; N, 4.41. $C_{16}H_{25}NO_5$ requires C, 61.72; H, 8.09; N, 4.50. ν_{max} 3350, 2986, 1745, 1683, 1688, 1531, 1366, 1258 and 1162; δ_H 1.39 (9 H, s), 1.95−2.05 (2 H, m), 2.28 (1 H, dt, J = 5.5 and 1.8), 2.35 (2 H, t, J = 6.7), 2.38−2.50 (3 H, m), 2.55 (1 H, dd, J = 5.5 and 16.2), 2.60 (1 H, dd, J = 5.5 and 16.2), 3.70 (3 H, s), 4.17−4.24 (1 H, m), 5.08 (1 H, br d, J = 9.2), and 5.86 (1 H, br s); δ_C 22.71, 28.29, 29.15, 37.29, 38.74, 43.71, 45.37, 51.85, 79.67, 128.34, 155.20, 161.97 (C(1′)), 171.69, and 199.59; *m*/*z* 311.1747 (M^+; $C_{16}H_{25}NO_5$ requires 311.1733), 255 (2, $M^+ - C_4H_8$), 238 (5, $M^+ - C_4H_9O$), 224 (6), 195 (12), 146 (27), 110 (75), 102 (100), and 57 (65). $[\alpha]_D$ −13.8 (*c* 0.995 in CH_2Cl_2).

Methyl 4(*R*)-[(*tert*-Butoxycarbonyl)amino]-oct-7-enoate (23). Treatment with allyl chloride yielded **23** (0.722 g, 87%), isolated as a colorless oil. Found C, 62.47; H, 9.25; N, 5.18. $C_{14}H_{25}NO_4$ requires C, 61.97; H, 9.29; N, 5.16. ν_{max} 3356, 2977, 1740, 1713, 1690, 1522, 1366, and 1173; δ_H 1.43 (9 H, s), 1.45−1.50 (1 H, m), 1.52−1.57 (1 H, m), 1.59−1.67 (1 H, m), 1.82−1.89 (1 H, m), 2.04−2.15 (2 H, m), 2.37 (2 H, t, J = 7.5), 3.64−3.65 (1 H, m), 3.67 (3 H, s), and 4.29 (1 H, br s); δ_C 28.53, 30.30, 30.71, 30.95, 35.18, 50.14, 51.79, 79.25, 115.14, 138.03, 155.78, and 174.23; *m*/*z* (EI) 271.1790 (0.07; M^+ $C_{14}H_{25}NO_4$ requires 271.1784), 215 (4, $M^+ - C_4H_8$), 198 (9, $M^+ - C_4H_9O$), 170 (14), 160 (13), 116 (95), 84 (63), and 57 (100). $[\alpha]_D$ +2.3 (*c* 1.35 in CH_2Cl_2).

Methyl 4(*R*)-[(*tert*-Butoxycarbonyl)amino]-oct-6,7-dienoate (24). Treatment with propargyl chloride yielded **24** (0.664 g, 82%), isolated as a colorless oil. ν_{max} 3358, 2977, 1956, 1739, 1213, 1694, 1521, and 1172; δ_H 1.42 (9 H, s), 1.65−1.71 (1 H, m), 1.85−1.92 (1 H, m), 2.13−2.19 (2 H, m), 2.38 (2 H, t, J = 7.5), 3.66 (3 H, s), 4.10−4.12 (1 H, m), 4.68 (2 H, dt, J = 1.84 and 6.71), and 5.01−5.07 (2 H, m); δ_C 28.58, 31.06, 32.42, 34.81, 50.42, 51.87, 74.98, 79.42, 85.86, 155.77, 174.17, and 209.80; *m*/*z* (EI) 213.0991 (2, $M^+ - C_4H_8$; $C_{10}H_{19}NO_4$ requires 231.1001), 216 (7, $M^+ - C_4H_5$), 160 (21), 116 (71), and 57 (100). $[\alpha]_D$ −29.2 (*c* 1.05 in CH_2Cl_2).

Michael Additions. The zinc/copper reagent **17** was generated from iodide **6** using the procedure described above. A solution of the α,β-unsaturated ketone (4.0 mmol) and chlorotrimethylsilane (504 μL, 4.0 mmol) in freshly distilled THF (2.0 mL) was added at −55 °C to the reaction mixture, which was then allowed to warm to −10 °C and stir overnight. The reaction mixture was partitioned between ethyl acetate (100 mL) and saturated aqueous ammonium chloride (40 mL) and

(44) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924−925.

then filtered. The organic layer was washed with water (40 mL) and brine (40 mL) and then dried, and the solvent was removed under reduced pressure. Flash column chromatography on silica gel using an appropriate petroleum ether−ethyl acetate gradient furnished the desired protected Michael adducts.

Methyl 3(*R*)-[(*tert*-Butoxycarbonyl)amino]-7-oxo-octanoate (25). Treatment with methyl vinyl ketone yielded **25** (0.2452 g, 56%), isolated as a colorless oil. Found C, 57.62; H, 8.72; N, 4.99. $C_{14}H_{25}NO_5$ requires C, 57.52; H, 8.72; N, 4.87. ν_{max} 3360, 1712, 1520, 1452, 1366, and 1170; δ_H 1.43 (9 H, s), 1.48−1.69 (4 H, m), 2.11 (3 H, s), 2.42−2.48 (2 H, m), 2.51 (2 H, d, J = 5), 3.37 (3 H, s), 3.81−3.89 (1 H, m), and 4.89 (br s, NH); δ_C 20.29, 28.37, 29.83, 31.41, 34.04, 39.31, 43.02, 51.58, 79.41, 155.46, 171.94, and 208.19; *m/z* (EI) 231.1108 (3, $M^+ - C_4H_8$; $C_{10}H_{17}NO_5$ requires 231.1106), 186 (13), 146 (13), 102 (62), and 57 (100). $[\alpha]_D$ +17.2 (*c* 3.54 in CH_2Cl_2).

Methyl 3(*R*)-[(*tert*-Butoxycarbonyl)amino]-(3′-oxocyclohexyl)butanoate (26). Treatment with cyclohexenone yielded **26** as a mixture of diastereomers (0.254 g, 33%), isolated as a colorless oil. ν_{max} (cap. film) cm^{-1} 3356, 2976, 1737, 1711, 1521, 1366, and 1169; δ_H 1.36 (9 H, s), 1.55−1.75 (m), 1.82−1.95 (m), 1.98−2.14 (m), 2.20−2.30 (m), 2.35−2.40 (m), 2.50−2.65 (m), 3.68 and 3.69 (3 H *both diastereomers*, s), 3.95−4.05 and 4.05−4.15 (1 H *both diastereomers*, m), and 4.95−5.05 (1 H, m); δ_C 24.95, 25.06, 28.25, 30.30, 31.18, 35.75, 38.92, 39.52, 40.99, 41.29, 44.71, 44.91, 47.42 48.38 51.62, 79.36, 155.42, 171.84, 210.97, and 211.29; *m/z* (EI) 257.1263 (3.5, $M^+ - C_4H_8$; $C_{14}H_{19}NO_5$ requires 257.1257), 240 (10), 196 (20), 146 (14), 123 (15), 102 (47), and 57 (100).

Methyl 3(*R*)-[(*tert*-Butoxycarbonyl)amino]-5-methyl-7-oxononoate (27). Treatment with 4-hexen-3-one yielded **27** as a mixture of diastereomers (0.218 g, 28%), isolated as a colorless oil. ν_{max} (cap. film) cm^{-1} 3368, 1739, 1711, 1521, and 1170; δ_H 0.86 (3 H, t, J = 7), 0.97 (3 H, q, J = 7), 1.36 and 1.37 (9 H *both diastereomers*, s), 1.95−2.52 (9 H, m), 3.60 and 3.63 (3 H *both diastereomers*, s), 3.96 (1 H, br s), and 4.86−4.95 (1 H, m); δ_C 7.81, 19.70, 20.25, 25.86, 26.29, 28.42, 28.44, 36.3, 36.56, 39.13, 40.08, 41.43, 41.60, 45.28, 45.66, 48.72, 49.72, 51.67, 51.74, 79.42, 155.34, 155.50, 172.06, 172.18, and 211.21; *m/z* 315.2048 (M^+; $C16H_{29}NO_5$ requires 315.2046), 259 (0.45, $M^+ - C_4H_8$), 215 (2), 186 (3), 146 (5.5), 102 (35), and 57 (100).

NMR Experiments. Structural Studies of the Serine (1), Aspartic Acid (4), and Glutamic Acid (5) Derived Organozinc Reagents in THF-d_8 and DMF-d_7. The organozinc reagents were generated by means of the general procedure described above, but using DMF-d_7 and THF-d_8 in place of the nondeuterated solvents. When no starting material remained (as judged by TLC) the excess zinc dust was allowed to settle. The supernatant was transferred via syringe into a nitrogen-filled NMR tube fitted with a Young's tap. Generally, a small amount of excess zinc was unavoidably transferred into the NMR tube, although this did not appear to affect the quality of the spectra. References used for the deuterated solvents: DMF-d_7 (δ_H 2.90, δ_C 161.70) and THF-d_8 (δ_H 1.80, δ_C 26.70)

Serine Derived Iodide (3). δ_H (DMF-d_7) 1.42 (9 H, s), 3.49 (1 H, dd, J = 8.2 and 10.0), 3.62 (1 H, dd, J = 4.5 and 10.0), 3.71 (3 H, s), 4.40 (1 H, m), and 7.21 (1H, br d, J = 8.2); δ_C (DMF-d_7) 4.14, 27.39, 51.74, 55.32, 78.51, 155.11, and 169.57; δ_H (THF-d_8) 1.49 (9 H, s, $C(CH_3)_3$), 3.53 (1 H, dd, J = 6.1 and 10.0), 3.61 (1 H, dd, J = 4.5 and 10.0), 3.78 (3 H, s), 4.50 (1 H, m), and 6.59 (1 H, br d, J = 7.0); δ_C (THF-d_8) 8.11, 29.99, 57.02, 58.59, 81.05, 157.20, and 171.93.

Serine-Derived Zinc Reagent (1). δ_H (DMF-d_7) 0.38 (1 H, dd, J = 8.5 and 12.8), 0.42 (1 H, dd, J = 7.6 and 12.8), 1.31 (9 H, s), 3.53 (3 H, s), 4.09 (1 H, m), and 6.99 (1 H, br d, J = 6.7); δ_C (DMF-d_7) 11.95, 28.59, 50.00, 53.33, 76.80, 154.24, and 175.35; δ_H (THF-d_8) 0.44 (1 H, m, C(3)H), 0.58 (1 H, m), 1.47 (9 H, s), 3.70 (3 H, s), 4.16 (1 H, m), and 6.38 (1 H, br); δ_C (THF-d_8) 14.86, 30.34, 53.61, 57.19, 82.48, 159.91, and 177.28.

Aspartic Acid Derived Iodide (6). δ_H (DMF-d_7) 1.38 (9 H, s), 2.65 (1 H, dd, J = 7.9 and 15.9), 2.73 (1 H, dd, J = 5.8 and 15.9), 3.41 (1 H, dd, J = 6.7 and 10.0), 3.47 (1 H, dd, J = 5.5 and 10.0), 3.63 (3 H, s), 3.94 (1 H, m), and 6.97 (1 H, br d, J = 7.95); δ_C (DMF-d_7) 10.49, 27.48, 38.22, 48.96, 50.92, 77.86, 154.88, and 170.51; δ_H (THF-d_8) 1.47 (9 H, s), 2.63 (1 H, dd, J = 7.0 and 16.5), 2.71 (1 H, dd, J = 10.7 and 16.5), 3.47 (1 H, dd, J = 5.5 and 10.0), 3.53 (1 H, dd, J = 5.5 and 10.0), 3.71 (3 H, s), 3.89 (1 H, m), and 6.39 (1 H, br d, J = 6.7); δ_C (THF-d_8) 13.33, 28.00, 40.51, 50.78, 53.10, 80.39, 157.04, and 172.68.

Aspartic Acid Derived Zinc Reagent (4). δ_H (DMF-d_7) 0.31 (1 H, dd J 5.5 and 12.9), 0.37 (1 H, dd, J = 7.6 and 12.9), 1.32 (9 H, s), 2.40 (1 H, dd, J 6.4 and 14.0), 2.48 (1 H, dd, J = 7.0 and 14.0), 3.53 (3 H, s), 4.14 (1 H, m), and 6.48 (1 H, br d, J = 8.85); δ_C (DMF-d_7) 15.72, 27.07, 43.22, 48.59, 50.23, 76.65, 154.34, and 171.38; δ_H (THF-d_8) 0.20 (1 H, dd, J = 8.2 and 12.8), 0.40 (1 H, dd, J = 5.2 and 12.8), 1.46 (9 H, s), 2.42 (1 H, dd, J = 6.0 and 15.0), 2.59 (1 H, dd, J = 7.0 and 15.0), 3.63 (3 H, s), 3.96 (1 H, m), and 6.67 (1 H, br d); δ_C (THF-d_8) 16.62, 30.42, 40.96, 45.77, 53.26, 82.59, 160.79, and 174.14.

Glutamic Acid Derived Iodide (7). δ_H (DMF-d_7) 1.39 (9 H, s), 1.69−1.76 (1 H, m), 1.94−1.99 (1 H, m), 2.36−2.45 (2 H, m), 3.36 (1 H, dd, J = 6.4 and 9.8), 3.42 (1 H, dd, J = 5.5 and 9.8), 3.62 (3H, s), and 6.82 (1 H, d, J = 8). δ_C (DMF-d_7) 11.66, 27.51, 28.97, 29.89, 50.70, 50.97, 77.68, 155.24, and 172.71; δ_H (THF-d_8) 1.48 (9 H, s), 1.72−1.78 (1 H, m), 1.95−2.01 (1 H, m), 2.41 (2 H, t, J = 7.9), 3.37 (1 H, dd, J = 9.75 and 4.9), 3.44 (1 H, dd J 9.75 and 5.2), 3.47−3.53 (1 H, m), 3.67 (3 H, s), and 6.23 (1 H, d, J = 7); δ_C (THF-d_8) 14.65, 30.03, 31.93, 32.43, 52.81, 53.00, 80.22, 157.40, and 174.80.

Glutamic Acid Derived Zinc Reagent (5). δ_H (DMF-d_7) 0.24−0.33 (2 H, m), 1.31 (9 H, s), 1.61−1.76 (2 H, m), 2.25 (2 H, t, J = 7.6), 3.53 (3 H, s), 3.71−3.78 (1 H, m) and 5.78 (1 H, m); δ_C (DMF-d_7) 15.20 (CH_2ZnI), 76.31, 154.56 (carbamate) and 172.82 (CO_2CH_3), *assignment of remaining peaks difficult as a result of overlap with solvent signals;* δ_H (THF-d_8) 0.14−0.16 (1 H, m), 0.41 (1 H, dd, J = 4.3 and 12.8), 1.47 (9 H, s), 1.65−1.73 (1 H, m), 1.78−1.87 (1 H, m), 2.32−2.40 (2 H, m), 3.50−3.58 (1 H, m), 3.62 (3 H, m), 7.03 (1 H, br s); δ_C (THF-d_8) 15.91, 31.17, 36.77, 53.13, 55.86, 161.32, and 175.48.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all coupled products (**12a**−**l**, **16a**−**g**, and **19**−**27**), characterization data for coupled products **12b**−**l** and **16a**−**g**, and the NMR studies of **1**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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