Enantiomerically Pure Tetrahydropyrimidinones in Asymmetric Synthesis: Preparation of a Protected α-Methylasparagine Derivative and Corresponding Dipeptides

Stephanie A. Hopkins, Todd A. Ritsema, and Joseph P. Konopelski*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

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Methyl ester **5a**, available in enantiomerically pure form from the amino acid asparagine via a one-pot cyclization/protection sequence, followed by esterification, can be effectively deprotonated with LDA/DMPU/LiCl. Treatment with MeI affords the corresponding alkylated adduct in enantiomerically pure form, from which α-methylaspartic acid is obtained. Variation of the amine protection group allows for the isolation of a protected carboxylic acid/free amine derivative of α-methylasparagine. The utility of H-MeAsn-OMe is demonstrated in the formation of dipeptides.

One of the attractions of the chemical approach to biological molecules is the ability to prepare derivatives with novel designed properties. In recent years there has been considerable interest in the synthesis of unnatural amino acids, fueled by the desire for synthetic polypeptides with increased hydrolytic stability,[1] enzyme inhibition properties, and/or unique conformational restrictions.[2] One class of monomer that has been the focus of intense synthetic effort is the α-methyl amino acids. The restricted conformational space available to these relatively simple derivatives of the common building blocks of proteins and polypeptides, coupled with their resistance to hydrolytic attack, make them attractive components in tailored biologically active materials.[3]

The side chain amide of the amino acid asparagine is the attachment point for the polysaccharide antenna in *N*-linked glycopeptides,[4] ubiquitous cell surface macromolecules that mediate cell−cell interactions. It is believed that the mobility of the oligosaccharide chain is largely determined by the conformational flexibility of the asparagine side chain.[5] Specific conformations also play an important role in the stabilization of local structures in polypeptides when asparagine is present either as an N-[6] or a C-terminal[7] α-helix cap, and in the formation of *β*-hairpin loops by the Asn-Gly dipeptide.[8] Given the flexibility of the asparagine side chain, both glycopeptide and peptide secondary structure conformational studies would benefit from the availability of conformationally restricted asparagine derivatives.

Herein we disclose our work on the asymmetric synthesis of enantiomerically pure α-methylasparagine derivatives.[9] We note that this appears to be one of the last of the common amino acids to be made available in the α-methylated form. Undoubtedly this is due to the nature of asparagine as "an interesting, quirky, opinionated residue with many unique properties",[10] something we have experienced directly (vide supra). In addition, α-methylaspartic acid, an important compound in the synthesis of novel peptide-based therapeutics[11] and peptide structure,[12] is available from this protocol.[13] Finally, methods for the formation of α-Me-Asn-containing dipeptides are described.

Some years ago we began a study of enantiomerically pure dihydropyrimidinones and their chemistry that resulted in an efficient synthesis of both enantiomers of 2-*tert*-butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (**1**).[14] Since that time, synthetic pathways from reagent **1** to enantiomerically pure *β*-aryl[15] and *β*-alkyl-*β*-amino acids[16] have been defined in this laboratory as well as others.[17] In addition, **1** functions as an efficient chiral auxiliary for the synthesis of enantiomerically pure

* Corresponding author. Phone 831-459-4676; Fax 831-459-2935; e-mail joek@chemistry.ucsc.edu.

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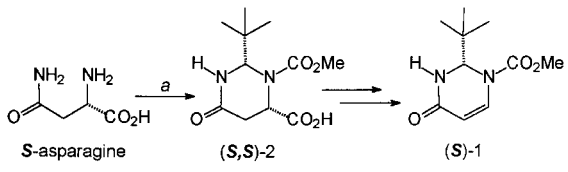
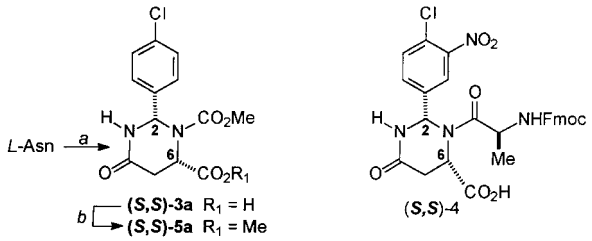
α-substituted carboxylic acids.[18] The synthesis of **1** begins with the one-pot formation of **2** from the amino acid asparagine, which is available at low cost in both enantiomeric forms. Such ready availability of a "protected" form of asparagine (i.e., **2**) opened the possibility for synthetic modifications to the amino acid itself.



a) 1) KOH, H_2O; 2) Me_3CCHO; 3) $ClCO_2Me$, $NaHCO_3$

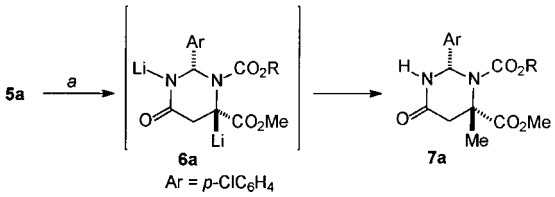
Initial Studies. Recrystallization brings **1** to enantiomeric purity without chromatography through the entire reaction sequence, as verified by analysis of the corresponding *O*-methyl mandelic acid derivative.[14b] Investigations of **2** indicate high enantiomeric purity as well.[14a] However, our more recent work has focused on the use of aromatic aldehydes in a two-step synthesis of the tetrahydropyrimidinone ring system.[19] We were intrigued with the prospect of extending our one-pot procedure to aromatic aldehydes. A number of aromatic aldehydes were investigated, as well as a wide variety of cyclization conditions. As opposed to the synthesis of **2**, water alone is no longer an acceptable solvent for this reaction. The best results involve the addition of *p*-chlorobenzadehyde (dissolved in DME) to a solution of the potassium salt of asparagine in water (3:5 ratio of DME to water). After 48 h, 1 equiv of $NaHCO_3$ is added, along with methyl chloroformate. Product **3a** is isolated in a modest 40% yield, but the ease of the reaction and the lack of expensive reagents allows for the production of large quantities of the desired material, which now possesses a UV-active chromophore. Proton and ^{13}C NMR analysis indicates the presence of a single diastereomer.[20] In addition, a single-crystal X-ray analysis of the related compound **4** verifies the expected cis relationship of the substituents at C2 and C6 of the newly formed heterocycle.[19] Methyl ester formation occurs in straightforward fashion with K_2CO_3/MeI in DMF to afford **5a** in good yield.



a) 1) KOH, H_2O/DME (5/3), *p*-ClC_6H_4CHO; 2) $ClCO_2Me$, $NaHCO_3$, *b*) K_2CO_3, MeI, DMF

Alkylation of **5a** follows the theme of "self-reproduction of chirality" pioneered by Seebach and co-workers[21] in that the C2 aromatic substituent directs the alkylation stereochemistry at C6. Based on the X-ray structure determinations of **1**,[14b] **4**, and related compounds,[22,23] as well as the stereochemistry of the product *β*-amino acids derived from **1**, the absolute stereochemistry of the product of the alkylation event is predicted to be that of the starting material. That is, the incoming alkyl electrophile is expected to approach the nucleophilic C6 position from the face of **5a** opposite to the aromatic group, regenerating the original absolute configuration at C6.

Deprotonation of **5a** results in the formation of dianion **6a**. While deprotonation of N3 ensures that there will be no reaction at C5 (α-position to a lactam anion), the formation of insoluble aggregates was expected to pose serious problems for reactivity. Indeed, deprotonation with 2.3 equiv of LDA at −75 °C afforded a solid mass from which no methylated product was isolated upon addition of MeI. Alkyllithium reagents were not effective, either giving low yield of methylated product (*t*-BuLi, lithium mesitylide) or reacting with the ester functionality (*n*-BuLi). Potassium hydride led to dimethylated product (N3 and C6) in 72% yield. With limited amounts of MeI (1.7 equiv vs 6 equiv), N3 methylation dominates the product mixture, with unreacted starting material making up the bulk of the remaining material. The use of LiHMDS as base was completely ineffective, presumably due to steric problems, and resulted in no methylated product. A mixture of LDA and LiCl[24] led to monoalkylation at long reaction times (18 h at −75 °C) with yields between 35 and 50%. Addition of DMPU afforded dialkylation product after 18 h, but a high yield of desired product **7a** was obtained after only 7 h reaction time. Analysis of the crude reaction material by GC and enantiomerically pure stationary phase HPLC[20] indicated small amounts of impurities that were removed by a single recrystallization from EtOAc/hexane to give analytically pure material. Enantiomeric product *ent*-**7a** was prepared from (*R*)-asparagine in similar fashion.



a) 1) 2.3 equiv LDA, excess LiCl, DMPU; 2) MeI

Acid hydrolysis of **7a** (6 N HCl, ion-exchange resin) led to the isolation of α-methylaspartic acid **8** in 77% yield, identical to the material described in the literature[13] by NMR and optical rotation.[25] Hydrogenolysis experiments on **7a**, designed to cleave the benzylic bonds of the *N*,*N*-

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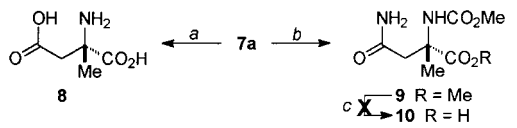
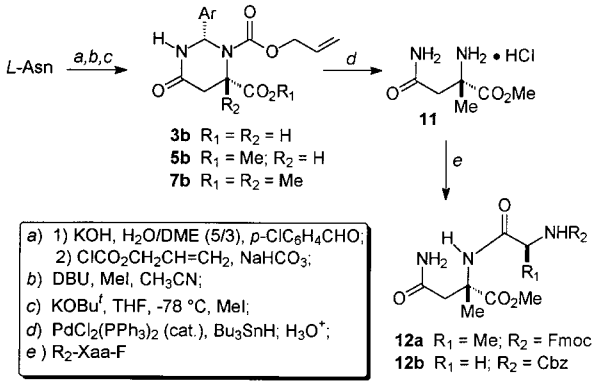
acetal, were not successful under a variety of conditions. However, treatment of **7a** with mild aqueous HCl (0.25 N) under reflux for only 1 h resulted in cleavage of the *N*,*N*-acetal while leaving both the carbamate and ester functionalities intact. Flash column chromatography afforded a 68% yield of MeO_2C-MeAsn-OMe **9**. Much to our dismay, however, none of the desired protected amine/free carboxylic acid derivative **10** was isolated upon treatment of **9** with a 0.025 N solution of KOH in MeOH/H_2O (3:1) at 0 °C. Rather, the corresponding succinimide was isolated in excellent yield, with no indication of free acid formation. To date, no conditions have been found to prepare **10** in acceptable yield. This cyclization proclivity of asparagine is well-known and thought to be involved in the accelerated racemization of this amino acid in biological systems.[26]



a) 6*N* HCl, 100 °C; *b*) 0.25*N* HCl, reflux, 1h;
c) 0.025 *N* KOH/MeOH, 0 °C

Preparation of α-Methylasparagine Derivative. Given the difficulty of working with α-methylasparagine derivatives once the pyrimidinone ring is opened, we opted for a different amine protection scheme that would allow for clean deprotection prior to ring opening via *N*,*N*-acetal cleavage. To this end, heterocycle **3b** was prepared according to the procedure defined for **3a**. The allyloxycarbonyl (Alloc) group was chosen for protection of the amine nitrogen because of its easy removal under standard palladium chemistry conditions.[27] Treatment of **3b** with DBU/MeI in CH_3CN afforded methyl ester **5b** without difficulty. For the preparation of **7b**, LDA proved inffective. Optimum alkylation conditions involved an in situ quench with MeI of the enolate formed from treatment of **5b** with KOBu^t/THF at −78 °C.[28] Again, the desired material was obtained in analytically pure form following a single recrystallization. Treament of **7b** with catalytic dichloro-bis-triphenylphosphine palladium (0.02 mol %) and Bu_3SnH, followed by acid hydrolysis of the intermediate tin carbamate, resulted in an 84% yield of **11** as the corresponding hydrochloride salt.

Free amine **11** was an ideal building block for further elaboration of α-methylasparagine peptides. Of the many methods available for peptide coupling, a subset of special conditions have been developed for use with hindered amino acids, including *N*- and α-alkylated amino acids.[29] Silylation of the free amine terminus, as an activation method to facilitate/accelerate the coupling process, has been reported many times for both solution[30] and solid phase[31] peptide synthesis. In the event, H-MeAsn-OMe·HCl **11** was subjected to silylation, followed by treatment with the desired amino acid fluoride.[32,33] Following standard workup, the coupled dipeptides **12a,b** were isolated in 40−50% yield. Even better results were obtained from the direct reaction of the amino acid fluoride with **11** without silylation. These conditions afforded the desired material in 66% yield.



In conclusion, the synthesis of a protected derivative of α-methylasparagine in enantiomerically pure form, and its use in the synthesis of model dipeptides, has been accomplished. The further use of **11** and related derivatives in the synthesis of polypeptides is underway in our laboratory and will be reported in due course.

Experimental Section

MeO_2C-(cyclo-*p*-ClC_6H_4CH)-Asn-H (3a). In an Erlenmeyer flask equipped with a magnetic stir bar, KOH (3.30 g, 50 mmol, 1 equiv, 85% assay) was dissolved in water (75 mL). L-Asparagine monohydrate (7.51 g, 50 mmol, 1 equiv) was added with vigorous stirring, followed by a solution of 4-chlorobenzaldehyde (8.64 g, 60 mmol, 1.2 equiv) in DME (45 mL). At the end of 2 days, the solution was placed in an ice bath, and $NaHCO_3$ (4.2 g, 50 mmol, 1 equiv) was added, followed by methyl chloroformate (4.0 mL, 50 mmol, 1 equiv). After 1 h of vigorous stirring at ice temperature, additional sodium bicarbonate (2.1 g, 25 mmol, 0.5 equiv) and methyl chloroformate (2.0 mL, 25 mmol, 0.5 equiv) was added. The ice bath was removed, and the solution was allowed to warm to room temperature for 2 h. Sodium bicarbonate was added until the solution reached pH 8. Excess 4-chlorobenzaldehyde was extracted with 3 × 20 mL of CH_2Cl_2. The aqueous layer was cooled to 0 °C and acidified slowly with 10% HCl to pH 2. The resulting two-phase system was extracted with 80% $CHCl_3$/MeOH, and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated. The resulting solid (40% yield) could be used in the next step without further purification. An analytical sample was obtained by column chromatography with silica gel (100:1:1 $CHCl_3$, MeOH, AcOH): mp 183−84 °C (dec); $[\alpha]_D = -19.5$ (*c* 3.3, MeOH); ^{1}H NMR (D_2O, K_2CO_3) δ 2.59−2.75 (m, 2 H), 3.87 (s, 3 H), 4.54−4.57 (m, 1 H), 6.58 (s, 1 H), 7.47 (d, J = 8.5 Hz, 2 H), 7.65 (d, J = 9 Hz, 2 H); ^{13}C NMR (D_2O, K_2CO_3) δ 34.2, 54.7, 56.3, 57.0, 66.0, 129.1, 129.5, 134.6, 138.7, 158.4, 166.1, 174.7, 177.7; IR (thin film): 3398, 2916, 1868, 1690, 1449, 1091 cm^{-1}. Anal. Calcd for $C_{13}H_{13}ClN_2O_5$: C, 49.93; H, 4.19. Found: C, 49.76; H, 4.26.

Alloc-(cyclo-*p*-ClC_6H_4CH)-Asn-H (3b). Following the procedure given above, the title compound was obtained in 40% yield through the use of allyl chloroformate. The solid was employed in the next step without purification: ^{1}H NMR (CD_3-

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OD) δ 2.38 (br dd, 2H), 2.64 (dd, J = 5 Hz, J = 15 Hz, 2H), 4.58 (br m, 1H), 4.66 (d, J = 5 Hz), 5.18 (apparent dq, J = 1.4, J = 10.5), 5.36 (br m, 1H), 5.94 (m, 1H), 6.48 (s, 1H), 7.35 (d, J = 9.5 Hz, 2H), 7.62 (d, J = 9.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 33.9, 55.0, 66.5, 68.3, 118.5, 129.4, 129.6, 133.5, 135.4, 139.8, 156.8, 172.0, 173.2; IR (thin film) 3302, 2360, 1713 cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_{15}H_{15}ClN_2O_5$: 339.07480; found 339.07478.

MeO_2C-(cyclo-*p*-ClC_6H_4CH)-Asn-OMe (5a). To a suspension of **3a** (3.11 g, 10 mmol, 1 equiv) and oven-dried K_2CO_3 (1.66 g, 12 mmol, 1.2 equiv) in DMF (50 mL) was added CH_3I (3 mL, 50 mmol, 5 equiv) in DMF (50 mL) at room temperature. The mixture was allowed to react for 24 h, water was added, and **5a** was extracted with CH_2Cl_2. The organic phase was washed with water, dried with Na_2SO_4, evaporated to a small volume, and passed through a small amount of silica gel to remove residual DMF and provide the title compound in 60% yield: mp 131−33 °C; $[\alpha]_D$ = −17.9 (*c* 4, $CHCl_3$); ^{1}H NMR δ 2.35−2.67 (m, 2H), 3.57 (s, 3H), 3.82 (s, 3H), 4.48 (br s, 1H), 6.52−6.66 (br s, 1H), 7.33 (d, J = 10 Hz, 2H), 7.47 (d, J = 10 Hz, 2H), 8.15−8.46 (s, 1H); ^{13}C NMR δ 41.7, 52.9, 53.3, 61.4, 65.1, 76.5, 127.4, 128.5, 134.0, 138.4, 170.7, 172.3; IR (thin film) 3260, 2954, 2847, 1746−1693, 1746−1693, 770 cm^{-1}. Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63. Found: C, 51.62; H, 4.77.

Alloc-(cyclo-*p*-ClC_6H_4CH)-Asn-OMe (5b). To a solution of **3b** (5 g, 14.7 mmol) in CH_3CN (50 mL) were added DBU (2.23 g, 14.7 mmol) and MeI (10.4 g, 73.5 mmol). The resulting mixture was allowed to stir for 1−2 days. The solution was diluted with ethyl acetate, washed with 0.1 M $KHSO_4$ and water, dried, and evaporated under reduced pressure. The crude material was purified on silica gel (2:1 EtOAc/hexanes) to yield a clear oil. Yield 69% (3.56 g); $[\alpha]_D$ = −20.4 (*c* 2.91, $CHCl_3$); ^{1}H NMR δ 2.55 (m, 1H) 2.67 (dd, J = 5.5, 16 Hz, 1H), 3.57 (s, 3H), 4.68 (m, 3H), 5.27 (d, J = 10 Hz, 1H), 5.33 (d, J = 17.5 Hz, 1H), 5.91 (m, 1H), 6.66 (br d, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 32.6, 52.1, 53.3, 65.1, 67.2, 118.2, 127.8, 128.6, 131.8, 134.4, 137.7, 154.7, 169.4, 170.2; IR (film) 3281, 2953, 2360, 1752, 1692 cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_{16}H_{17}ClN_2O_5$: 353.09040; found 353.09043.

MeO_2C-(cyclo-*p*-ClC_6H_4CH)-MeAsn-OMe (7a). A dry, 50 mL, two-necked, round-bottom flask equipped with a magnetic stir bar was charged with LiCl (0.400 g, 9.4 mmol, 3 equiv), diisopropylamine (0.93 mL, 7 mmol, 2.3 equiv), DMPU (2 mL, 16 mmol, 5 equiv), and anhydrous THF (15 mL). The resulting suspension was cooled to −72 °C, and *n*-butyllithium (1.96 *M*, 3.60 mL, 7 mmol, 2.3 equiv) was added slowly via syringe. After stirring at −72 °C for 30 min, a solution of compound **5a** (1.0 g, 3 mmol, 1 equiv) was added dropwise via syringe. The resulting green solution was stirred at −72 °C for 2 h before the addition of CH_3I (2.0 mL, 30 mmol, 10 equiv). Following stirring at −72 °C for 3 h, the cold bath was removed, and the reaction mixture was stirred for 5 min at room temperature. The mixture was quenched with 10 mL of an aqueous solution of saturated NH_4Cl, followed by 30 mL of water. The solution was extracted with EtOAc, and the combined organic layers were washed with water, dried, and concentrated. Purification through a silica gel plug with ethyl acetate followed by recrystallization from 7:3 ethyl acetate/hexanes afforded the desired compound in analytically pure form. Additional material was obtained by chromatography (3:2 EtOAc/hexanes) of the mother liquors to give a total yield of desired product of 54%: mp 193−94 °C; $[\alpha]_D$ = −47 (*c* 1.2, EtOAc); ^{1}H NMR δ 1.70 (s, 3H), 2.72 (d, J = 16 Hz, 1H), 2.55 (d, J = 16 Hz, 1H), 3.74 (s, 3H), 6.40−6.50 (br s, 1H), 7.30 (d, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 2H), 8.75−8.79 (br s, 1H); ^{13}C NMR δ 42.0, 48.0, 53.1, 53.5, 61.8, 65.4, 77.0, 127.6, 128.0, 134.3, 138.7, 170.8, 172.6; IR (thin film) 3283, 2953, 1744, 1695, 1443, 600 cm^{-1}. Anal. Calcd for $C_{15}H_{17}ClN_2O_5$: C, 52.87; H, 5.03. Found: C, 53.02; H, 4.98.

Alloc-(cyclo-*p*-ClC_6H_4CH)-MeAsn-OMe (7b). To a solution of **5b** (4 g, 11 mmol) in dry THF (110 mL) was added MeI (6.8 mL, 110 mmol). The solution was cooled to −78 °C. A 1 M solution of $KOBu^t$ (110 mmol) in THF was added via addition funnel over 2 h. The reaction mixture was diluted with EtOAc and quenched by addition of saturated NH_4Cl. The organic layer was washed with brine, dried, and evaporated. The resulting oil was passed through a plug of silica gel with EtOAc/hexanes (1:1) and the product evaporated to a light yellow foam, affording 3.33 g (80.4%, 9.0 mmol). This material is pure enough to be used in the next step or may be recrystallized in good yield from EtOAc/hexanes (1:2): mp 151−152 °C; $[\alpha]_D$ = −39.1 (*c* 2.03, $CHCl_3$); ^{1}H NMR δ 1.72 (s, 3H), 2.29 (d, J = 15 Hz, 1H), 2.58 (d, J = 15 Hz, 1H), 3.72 (s, 3H) 4.64 (m, 3H), 5.25 (m, 2H), 5.85 (m, 1H), 6.48 (br s, 1H), 7.31 (d, J = 8.5, 2H), 7.47 (d, J = 7 Hz, 2H); ^{13}C NMR δ 42.0, 53.1, 65.4, 67.2, 118.8, 127.6, 128.8, 131.7, 134.4, 138.6, 160.6, 170.7, 172.5; IR (film) 3284, 2951, 2361, 1745, 1697, 1491, 1092 cm^{-1}. Anal. Calcd for $C_{17}H_{19}ClN_2O_5$: C, 55.67; H, 5.22. Found: C, 55.80; H, 5.24.

MeO_2C-MeAsn-OMe (9). To a sample of **7a** (777 mg, 2.28 mmol) was added 0.25 M HCl (52 mL) in which the substrate was insoluble. The suspension was refluxed for 1 h (110 °C sand bath), during which time the solution became homogeneous and a white solid deposited on the glassware above the liquid. The solution was cooled to room temperature and concentrated under reduced pressure. Acetonitrile was added to the product and removed under reduced pressure to aid in water removal. The resulting crude material was purified on silica gel with 5% MeOH/$CHCl_3$ to afford the desired product (304 mg, 68%) as an oil: $[\alpha]_D$ = 14.5 (*c* 2.80, $CHCl_3$); ^{1}H NMR δ 1.61 (s, 3H), 2.88 (d, J = 15 Hz, 1H), 3.15 (d, J = 15 Hz, 1H), 3.64 (s, 3H), 3.80 (s, 3H), 5.91 (br s, 1H), 5.99 (br s, 1H), 6.12 (s, 1H); ^{13}C NMR δ 23.6, 42.0, 51.5, 52.6, 57.8, 155.5, 171.5, 173.7; IR (thin film) 3350, 2955, 2361, 1713, 1672, 1618, cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_8H_{15}N_2O_5$: 219.09810; found 219.09810.

H-MeAsn-OMe·HCl (11). To a solution of **7b** (580 mg, 1.58 mmol) in dry CH_2Cl_2 (5 mL) was added $PdCl_2(PPh_3)_2$ (22.4 mg, 0.032 mmol) and Bu_3SnH (638 uL, 2.37 mmol). The reaction was allowed to stir overnight. The resulting solution was passed through Celite and concentrated in vacuo to afford an oil. The oil was dissolved in THF (3 mL) and treated with 0.5 M aqueous HCl (3.7 mL) for 1 h with vigorous stirring. The aqueous layer was extracted with hexanes and evaporated under reduced pressure to yield a white foam (213 mg, 84%). This material was sufficiently pure to use directly in peptide coupling procedures. Analytically pure material was obtained from recrystallization from 2-propanol/CH_3CN: mp 84−87 °C; $[\alpha]_D$ = 44.6 (*c* 2.03, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.78 (s, 3H), 3.057 (d, J = 18 Hz, 1H), 3.35 (d, J = 18 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (CD_3OD) δ 23.1, 41.3, 55.3, 58.9, 174.5, 175.6; IR (film) 3176, 2359, 1748, 1670, 1230 cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_6H_{12}N_2O_3$: 161.09234; found 161.09262.

Fmoc-Ala-MeAsn-OMe (12a). Method 1. Compound **11** (86.4 mg, 0.441 mmol) was suspended in CH_2Cl_2 (2 mL). The suspended solid dissolved shortly after the addition of $(C_3H_7)_2$-NEt (77 μL, 0.441 mmol) and BSA (215 uL, 0.882 mmol). The solution was stirred for 2 h, followed by addition of Fmoc-Ala-F (124 mg, 0.397 mmol) dissolved in CH_2Cl_2 (1 mL). The mixture was stirred for 2 h. TLC (3:1 CH_2Cl_2/EtOAc) indicated disappearance of the acyl fluoride. Additional CH_2Cl_2 was added, and the organic phase was washed sequentially with 10% HCl, saturated $NaHCO_3$, and brine and dried ($MgSO_4$). The resulting residue was purified by column chromatography on silica gel with EtOAc/hexanes to afford 86.8 mg (43%) of dipeptide as an oil.

Method 2. To a solution of Fmoc-Ala-OH (508 mg, 1.63 mmol) and $(C_3H_7)_2NEt$ (852 μL, 4.89 mmol) in CH_2Cl_2 (8 mL) was added TFFH[33] (0.645 mg, 2.44 mmol). The resulting mixture was stirred for 2 h and used directly. In a separate flask, compound **11** (267 mg, 1.36 mmol) was dissolved in CH_2-Cl_2 (2 mL) and $(C_3H_7)_2NEt$ (237 μL, 1.36 mmol). Molecular sieves (3 Å) were added, and the mixture was stirred for 15 min. The solution of **11** was added to the solution of Fmoc-

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Ala-F, and the coupling was monitored by TLC (3:1 EtOAc/CH_2Cl_2; product $R_f \sim 0.2$) and judged to be complete after 2.5 h. The reaction mixture was washed with 10% HCl, $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated to an oil. The crude material was purified on silica gel with EtOAc/CH_2Cl_2 to yield 405 mg (0.89 mmol) of a white foam, 65.7%: $[\alpha]_D = 4.60$ (*c* 1.65, $CHCl_3$); ^{1}H NMR δ 1.37 (d, $J = 7$ Hz, 3H), 1.63 (s, 3H), 2.92 (d, $J = 15$ Hz, 1H), 3.20 (d, $J = 15$ Hz, 1H), 3.76 (s, 3H), 4.19 (t, $J = 10$ Hz, 1H), 4.32 (m, 1H), 4.36 (d, $J = 7.5$ Hz, 2H), 5.9 (br d, $J = 7.5$ Hz, 1H), 6.07 (br s, 1H), 6.22 (s, 1H), 7.28 (dt, $J = 7$, 1.5 Hz, 2H), 7.37 (t, $J = 10$ Hz, 2H), 7.58 (br m, 2H), 7.74, (d, $J = 8$ Hz, 2H), 7.78 (s, 1H); ^{13}C NMR δ 18.6, 23.1, 41.6, 47.3, 51.1, 52.7, 58.1, 67.1, 119.8, 125.0, 127.0, 127.6, 141.3, 143.9, 155.8, 172.0, 172.3, 173.7; IR (thin film) 3313, 1670 cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_{24}H_{28}N_3O_6$: 454.1978; found 454.1976.

Cbz-Gly-MeAsn-OMe (12b). Following the procedure for method 1 given above, the title compound was obtained in 40% yield: $[\alpha]_D = 9.70$ (*c* 1.73, $CHCl_3$); ^{1}H NMR δ 1.60 (s, 3H), 2.92 (d, $J = 10$ Hz, 1H), 3.18 (d, $J = 10$ Hz, 1H) 3.74 (s, 3H), 3.81 (m, 1H), 5.09 (s, 2H), 5.92 (br s, 1H), 6.05 (br s, 1H), 6.17 (br s, 1H), 7.30 (m, 5H), 7.64 (br s, 1H); ^{13}C NMR δ 23.3, 41.6, 44.9, 52.7, 58.3, 67.0, 127.9, 128.0, 128.4, 136.5, 156.5, 168.9, 171.9, 173.7; IR (thin film) 3326, 1735, 1664 cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_{16}H_{21}N_3O_6$: 352.1509; found 352.1510.

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Supporting Information Available: General experimental and synthetic procedures for α-methylaspartic acid and compounds not specifically numbered in the text, as well as ^{1}H and ^{13}C NMR spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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