Bis-Allylic Templates for Pd(0)-Catalyzed Solid Phase Synthesis of Tertiary Amines

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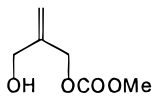
Introduction

Combinatorial solid phase synthesis of new lead compounds and drug candidates is a topic of much current interest.[1] There are two major challenges facing contemporary combinatorial chemistry: (1) structural design of potential ligands and (2) solid phase chemistry available to synthesize the desired structures. Creating libraries of structural analogs of known active compounds (β-turn mimetics, transition state analogs, benzodiazepines) is one efficient strategy to generate collections of new promising drug leads.[2] Alternatively, "generic" molecular constructs based on a variety of nonpeptide scaffolds have been used to explore the steric requirements for sets of pharmacophores interacting with target biological macromolecules.[3] Such scaffolds are usually designed to cover diverse conformational space allowing further "improvements" based on structural data obtained from NMR, X-ray, and computational studies. Structures of molecular probes thus range from fairly flexible to quite constrained assemblies of pharmacophores. Another fundamental requirement for the successful generation of molecular diversity on a solid support is the availability of a broad repertoire of well-documented organic reactions providing the desired molecules in high yield and with predictable stereochemistry.[4] In the last three years, a number of efficient C−C, C−N, and C−S bond-forming strategies on solid phase have been explored and validated in the synthesis of compound libraries.[5]

Tertiary amines are prominent structural components in a variety of synthetic and naturally occurring biologically active compounds.[6] For example, they are useful agents for potentiation of opiate analgesia, treatment of extrapyramidal movement disorders, besides, of course, their use as antifungal, general anesthetic, antipsychotic, antihistaminic, and calcium channel blocking agents.[7] Here we report a general method for the solid phase synthesis of tertiary amines based on the Pd(0)-catalyzed nucleophilic substitution employing bis-allylic templates **1** and **2**. The Pd(0)-catalyzed allylic substitution reactions of allyl halides, carbonates, or acetates have become a powerful tool for the C-heteroatom bond formation due to the functional group tolerance, high yield, and control of stereochemistry generally displayed by these transformations.[8] Furthermore, studies defining the scope, limitations, and mechanistic aspects of (η^3-allyl)palladium complexes have led to a very good understanding of the overall process.[9]



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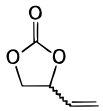

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Results and Discussion

Much of our model work has centered on developing routes to the simple substituted allylic amines **7**. We endeavored first to find a reliable solid phase procedure for N-allylation of *N*-benzylglycine **4** using template **1,** followed thereafter by O-acetylation of allyl alcohol **5**, as shown in Scheme 1. Thus, BocN(Bn)CH_2COOH was first activated with DIC/HOBt in DMF and then coupled to the TentaGel S-OH resin using DMAP as an acylation catalyst. Subsequent TFA-mediated removal of the *N*-

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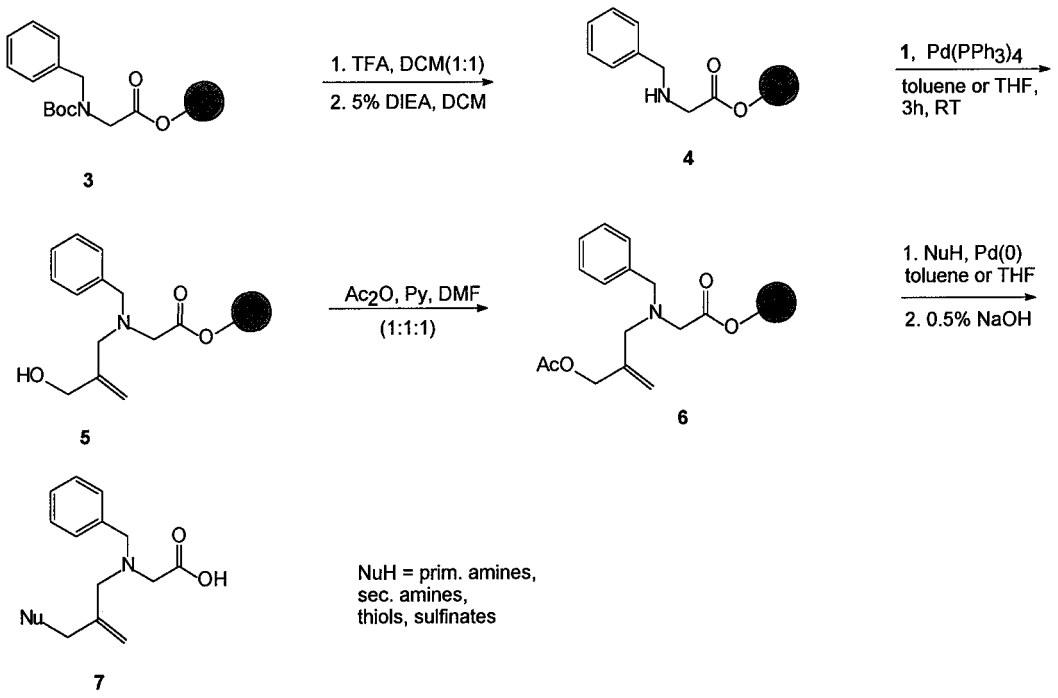
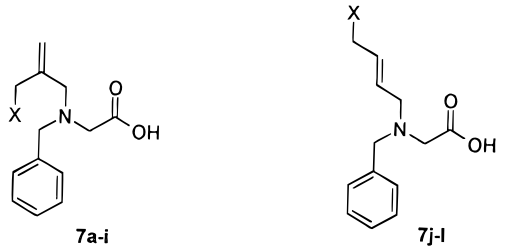
Scheme 1



Boc group from **3** and concomitant DIEA/DCM neutralization afforded solid phase bound *N*-benzylglycine **4**. Reactions with template **1** were performed with Pd(PPh$_3$)$_4$ (10−20% mol)[10] in 2% AcOH/THF or toluene as solvent[11] providing intermediate **5** in nearly quantitative yield (92−98%) within 3 h at room temperature. Acetylation of the resulting amino alcohol **5** with acetic anhydride/pyridine/DMF (1:1:1 v/v/v) afforded the polymer-supported "allyl-activated" intermediate **6**. Optimization of the second allylic acetate displacement was performed at room temperature using combinations of Pd(PPh$_3$)$_4$, Pd(acac)$_2$, Pd(OAc)$_2$, and Pd$_2$(dba)$_3$·CHCl$_3$ for the catalyst, with PPh$_3$, dppb, dppp, dppe, and P(O^{i}Pr)$_3$ for the phosphine (phosphite) ligands in both toluene and THF as solvents. The results of these experiments are summarized in Table 1. The optimal catalytic system and reaction solvent were Pd(PPh$_3$)$_4$ (10−20%)/THF[10] for secondary amines and Pd(acac)$_2$ (5−10%)/2dppb/THF for primary amines. Inspection of the data in Table 1 shows that the second allylic displacement proceeds readily with various structurally diverse primary and secondary amines and somewhat slowly with less nucleophilic substrates. In general, the reactivity can be rationalized by invoking both electronic and steric factors. Both reaction steps were monitored for complete conversion of the starting *N*-benzylglycine and the corresponding *O*-acetyl-*N*-monoallyl-*N*-benzylglycine by HPLC after cleavage of the material from a small sample of resin. Final cleavage of the material from the solid support with 0.1% NaOH in water/methanol (80:20) for 30 min provided derivatives **7a**−**l** in 36−88% overall yield. Due to the nature of cleaved compounds, RP-HPLC was used for the preparative workup.[12] Although the isolated yields are only modest to good, the purity (60−96%)[13] of crude products is in most cases quite high. The lower yields of relatively pure products can be attributed to the partial cleavage of ester bond during the treatment with amines and incomplete mass recovery after preparative HPLC. Difficulties were encountered in our initial attempts involving the second Pd(0)-catalyzed nucleophilic dis-

Table 1. *N*-Benzylglycine Derivatives 7 (Scheme 1)



7a-i **7j-l**

entry	X	reactn time[a] (h)	purity[b] (%)	yield[c] (%)
7a	*N*-morpholino	2	90	88
7b	HO(CH$_2$)$_2$MeN-	6	94	80
7c	*N*-tetrahydroisoquinolino	16	80	36
7d	C$_6$H$_5$CH$_2$MeN-	5	82	37
7e	C$_6$H$_5$CH$_2$NH-	2	70	43
7f	4-MeOC$_6$H$_4$NH-	40	96	46
7g	2-HO$_2$CC$_6$H$_4$S-	16[d]	90	51
7h	*t*-BuNH-	8	87	44
7i	4-MeC$_6$H$_4$SO$_2$-	6[d]	92	56
7j	Ac(Et)N-	2	60	40
7k	HO(CH$_2$)$_2$MeN-	2	96	48
7l	*i*-PrNH-	2	85	57

[a] Reaction time for second allylic acetate displacement. [b] Purity determined by C18 RP HPLC at 215 nm. [c] Overall isolated yields of purified materials are based on the initial loading of resin. [d] Pd(PPh$_3$)$_4$/THF.

(10) This amount is a crude estimate only necessitated by the handling difficulties with Pd(PPh$_3$)$_4$ caused by its air and moisture sensitivity.

(11) When the reaction was carried out in the absence of acetic acid, an appreciable amount of the (((3-hydroxy-2-methylenepropyl)oxy)-carbonyl)-*N*-benzylglycine was obtained.

(12) Analysis of ^{19}F NMR spectra of *N*-(4-fluorobenzyl)-*N*-(3-(tetrahydroisoquinolino)-2-methylenepropyl)glycine and *N*-(4-fluorobenzyl)-*N*-(3-(benzylamino)-2-methylenepropyl)glycine revealed the stoichiometry corresponding to bis-trifluoroacetates after the preparative HPLC. Isolated yields are therefore based on stoichiometric amounts of trifluoroacetic acid per amine functionality.

(13) The purities of compounds **5**, **7a**−**l** were calculated from integrated peak areas recorded by the HPLC analysis (215 nm) of the crude product which was cleaved from the solid support after complete conversion of the starting material.

placement of the acetate group with 2-mercaptopyridine and 2-mercaptobenzoic acid, as no detectable S-alkylation occurred when the standard protocol is followed. These difficulties can be overcome to some extent by adding acetic acid into the reaction mixture. Unfortunately, prolonged treatment of acetate **6** with 2-mercaptobenzoic acid under such "acidic" conditions yielded the starting material, *N*-benzylglycine, in amounts of 30−50% after alkaline hydrolysis. We suspect that effective N-deallylation of the protonated structure **7** takes place under these conditions.[14] On the other hand, the desired product from the reaction with 2-mercaptopyridine was detected in only minute amounts along with the unchanged template **5**, suggesting that the protonated 2-allylthiopyridine is a good leaving group in the S-deallylation. Reaction of substrate **6** with sodium *p*-toluenesulfinate and $Pd(PPh_3)_4$ at room temperature in toluene gave only sulfone **7i** without any indication (HPLC traces after alkaline hydrolysis, ^1H and ^{13}C NMR spectra) of sulfinic acid ester formation.[8g]

The reactivity and selectivity of template **2** toward Pd(0)-catalyzed nucleophilic displacement was also briefly studied. Under similar conditions, reaction of cyclic carbonate **2** with solid phase bound *N*-benzylglycine **4** followed by acetylation and second allylic acetoxy displacement with (hydroxyethyl)methylamine and isopropylamine afforded the corresponding derivatives **7k**,**l** as single isomeric products in acceptable yields.[15] To demonstrate the potential for enhanced diversity at the end of synthesis, the second allylic acetoxy displacement with ethylamine followed by N-acylation (acetic anhydride/pyridine/DMF, 16 h) of secondary allylic amine was performed on the solid phase, producing **7j** in 40% overall yield.

In conclusion, we have demonstrated that solid phase bis-allylation reactions provide the corresponding products in satisfactory yields and purity. The general availability of amines and *N*-alkylamino acids as well as other templates derived from vinyl epoxides, cycloalkene monoepoxides, and 5-acetoxy-3-(cyclo)alken-2-ols further enhances the utility of these reactions in the construction of combinatorial libraries containing tertiary amine functionalities. Studies are currently underway to improve the yields and to explore other templates and alternatives for remaining allylic double-bond transformations.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and are referenced to an internal standard of tetramethylsilane. Low-resolution mass spectra were obtained under electrospray (ES) ionization conditions, while high-resolution mass spectra were obtained using the MALDI technique. Unless otherwise noted, solvents were of reagent grade, available from commercial sources, and used without further purification. For anhydrous reactions, flasks were equipped with ruber septa and maintained under a positive argon presssure. (±)-4-Ethenyl-1,3-dioxolan-2-one was purchased from Eastman Chemical Co. TentaGel S OH (130 μm, 0.28 mmol/g; Rapp Polymere, Tübingen, Germany) resin was used in all experiments.

3-Hydroxy-2-methylenepropyl Methyl Carbonate (1). To a stirred, cooled (−10 °C) solution of 2-methylene-1,3-propanediol (5.0 g, 57 mmol) in pyridine (20 mL) and CH_2Cl_2 (50 mL) was slowly added a solution of methyl chloroformate (4.6 mL, 59 mmol) in CH_2Cl_2 (50 mL). After being stirred for 2 h at 0 °C, the mixture was allowed to warm to 10 °C and diluted with dry diethyl ether (100 mL). Filtration and concentration gave a colorless residue which was purified by flash chromatography (hexane:ethyl acetate 60:40). After removal of the solvent in vacuo the residue was dissolved in methanol and passed through Amberlite IR-120(H^+) column (elution with methanol) to remove traces of pyridine. Final purification by Kugelrohr distillation (75 °C, 0.6 mm) afforded 3-hydroxy-2-methylenepropyl methyl carbonate (**1**) (4.84 g, 58%) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.18 (s, 2H), 4.71 (s, 2H), 5.23 (s, 1H), 5.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 54.9, 63.4, 68.1, 114.6, 142.8, 155.8; MS *m*/*e* 147 (M + H), 129, 101, 73, 59; IR (neat) 3435, 1751, 1445, 1272. Anal. Calcd for $C_6H_{10}O_4$: C, 49.30; H, 6.90. Found: C, 48.95; H, 7.10.

Resin Esterification (4). A mixture of Boc-protected *N*-benzylglycine (223 mg, 0.84 mmol), HOBt (114 mg, 0.84 mmol), DIC (132 μL, 0.84 mmol), and DMAP (10 mg, 0.08 mmol) in DMF (2 mL) was added to a suspension of TentaGel S OH resin (1.00 g, 0.28 mmol) in DMF (3 mL). After 16 h, the resin was washed with DMF (5 × 5 mL) and DCM (5 × 5 mL) and treated with TFA−water (95:5) for 1 h. The polymer was then washed with 5% DIEA in DCM (2 × 5 mL), DCM (5 × 5 mL), and toluene (5 × 5 mL).

Representative Procedure. Resin-Bound *N*-Benzyl-*N*-(3-hydroxy-2-methylenepropyl)glycine (5). 3-Hydroxy-2-methylenepropyl methyl carbonate (**1**) (123 mg, 0.84 mmol) was added to a suspension of resin-bound *N*-benzylglycine **4** (1.00 g, 0.28 mmol) in toluene (5 mL) containing acetic acid (0.1 mL). $Pd(PPh_3)_4$ (48 mg, 0.04 mmol) was then added in three equal portions in hour intervals while the suspension was shaken under an argon atmosphere at room temperature. Conversion of the starting *N*-benzylglycine to **5** (2−3 h) was monitored by HPLC after cleavage of the material from a small sample of resin with 0.1% NaOH in water/methanol (80:20): ^1H NMR ($CDCl_3$) δ 3.90 (s, 2H), 3.95 (s, 2H), 4.33 (s, 2H), 4.43 (s, 2H), 5.36 (s, 1H), 5.49 (s, 1H), 7.29−7.45 (m, 5H), 8.33 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 52.6, 57.8, 59.2, 65.8, 124.0, 128.5, 129.6, 130.5, 130.8, 136.5, 168.2; MS *m*/*e* 236 (M + H), 206, 190, 144, 91, 88; HRMS calcd for $C_{13}H_{18}NO_3$ *m*/*z* 236.1287, measured 236.1285.

Representative Procedure. Preparation of 6. The resin was washed with toluene (3 × 5 mL) and DMF (3 × 5 mL) and then treated with a mixture of acetic anhydride/pyridine/DMF (5 mL, 1:1:1) for 16 h.

Representative Procedure. Preparation of *N*-Benzyl-*N*-(3-(benzylamino)-2-methylenepropyl)glycine (7e). Resin-bound allylic template **6** (0.1mmol) was washed with dry THF (5 × 3 mL). Benzylamine (55 μL, 0.5 mmol), $Pd(acac)_2$ in THF (400 μL, 0.025 M, 0.01 mmol), and dppb in THF (200 μL, 0.1 M, 0.02 mmol) were added to a slurry of the resin in dry THF (3 mL) agitated with argon. Upon completion of the reaction as monitored by HPLC (2−4 h), final cleavage of the product from the resin was accomplished by hydrolysis with 0.1% NaOH in water/methanol (80:20, 2.5 mL, 30 min) to give, after preparative HPLC, 24 mg (43%) of **7e** as a colorless oil.

***N*-Benzyl-*N*-(3-morpholino-2-methylenepropyl)glycine (7a)** was isolated in 88% yield as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.1−2.3 (bs, 4H), 3.59 (s, 2H), 3.70 (s, 2H), 3.88 (s, 2H), 3.96 (bs, 4H), 4.06 (s, 2H), 5.66 (s, 1H), 5.70 (s, 1H), 7.3−7.8 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 51.8, 53.4, 57.7, 58.0, 59.6, 63.5, 117.7, 126.2, 128.3, 128.7, 133.1, 134.7, 172.0; MS *m*/*e* 305 $(M + H)^+$, 218, 140, 128, 100, 91; HRMS calcd for $C_{17}H_{25}N_2O_3$ *m*/*z* 305.1865, measured 305.1867.

***N*-Benzyl-*N*-[3-(*N*′-methyl-*N*′-(hydroxyethyl)amino)-2-methylenepropyl]glycine (7b)** was isolated in 80% yield as a colorless oil: ^1H NMR (DMSO) δ 2.80 (s, 3H), 3.20 (bs, 2H), 3.24 (s, 2H), 3.35 (s, 2H), 3.76 (s, 2H), 3.78 (bs, 2H), 5.47 (s, 1H), 5.53 (s, 1H), 7.3−7.4 (m, 5H); ^{13}C NMR (DMSO) δ 40.1, 53.7, 55.5, 57.5, 57.7, 57.9, 59.6, 124.2, 127.5, 129.1, 129.8, 136.3, 137.2, 173.3; MS *m*/*e* 293 $(M + H)^+$, 218, 164, 128, 91, 74; HRMS calcd for $C_{16}H_{25}N_2O_3$ *m*/*z* 293.1865, measured 293.1868.

***N*-Benzyl-*N*-(3-tetrahydroisoquinolino-2-methylenepropyl)glycine (7c)** was isolated in 36% yield as a colorless oil: ^1H NMR (DMSO) δ 3.13 (bs, 2H), 3.23 (s, 2H), 3.35 (s, 2H), 3.55

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(15) Based on ^1H NMR spectra and HPLC profiles of **7j** and analogous ethylamine derivative of **7**; no detectable amounts (>5%) of other geometric isomer were observed in ^1H and ^{13}C NMR spectra of compounds **7j**−**l**. Assignment of *E*-stereochemistry is supported by the magnitude of J^3 coupling constant (J^3 = 15.4 Hz) for vinylic protons after selective irradiation of CH_2-allylic protons.

(bs, 2H), 3.74 (s, 2H), 4.00 (s, 2H), 4.43 (s, 2H), 5.23 (s, 1H), 5.57 (s, 1H), 7.2−7.4 (m, 9H); ^{13}C NMR (DMSO) δ 25.4, 49.7, 53.0, 54.0, 56.7, 58.1, 59.3, 124.9, 127.2, 127.4, 128.2, 128.4, 128.6, 129.1, 131.7, 136.1, 137.6, 174.3; MS *m/e* 351 $(M + H)^+$, 218, 186, 146, 132, 91; HRMS calcd for $C_{22}H_{27}N_2O_2$ *m/z* 351.2073, measured 351.2079.

***N*-Benzyl-*N*-[3-(*N*′-methyl-*N*′-benzylamino)-2-methyleneprop yl]glycine (7d)** was isolated in 37% yield as a colorless oil: ^{1}H NMR (DMSO) δ 2.68 (s, 3H), 3.16 (s, 2H), 3.31 (s, 2H), 3.61 (s, 2H), 3.82 (s, 2H), 5.45 (s, 1H), 5.50 (s, 1H), 7.1−7.6 (m, 10H); ^{13}C NMR (DMSO) δ 39.8, 53.7, 56.9, 57.9, 58.1, 59.8, 123.6, 127.1, 127.4, 128.9, 130.3, 132.1, 136.9, 139.2, 174.1; MS *m/e* 339 $(M + H)^+$, 218, 174, 164, 131, 120, 91; HRMS calcd for $C_{21}H_{27}N_2O_2$ *m/z* 339.2073, measured 339.2080.

***N*-Benzyl-*N*-(3-(benzylamino)-2-methylenepropyl)glycine (7e)** was isolated in 43% yield as a colorless oil: ^{1}H NMR (DMSO) δ 3.16 (s, 2H), 3.28 (s, 2H), 3.65 (s, 2H), 3.71 (s, 2H), 4.22 (s, 2H), 5.35 (s, 1H), 5.38 (s, 1H), 7.2−7.5 (m, 10H); ^{13}C NMR (DMSO) δ 49.6, 50.3, 53.0, 56.5, 58.0, 69.7, 120.1, 127.3, 127.7, 128.3, 128.7, 129.0, 129.9, 131.6, 137.1, 173.1; MS *m/e* 325 $(M + H)^+$, 279, 218, 174, 160, 128, 120, 91; HRMS calcd for $C_{20}H_{25}N_2O_2$ *m/z* 325.1916, measured 325.1924.

***N*-Benzyl-*N*-[3-(4-methoxyanilino)-2-methylenepropyl]-glycine (7f)** was isolated in 46% yield as a colorless oil: ^{1}H NMR (DMSO) δ 3.50 (bs, 4H), 3.70 (s, 3H), 3.85 (s, 2H), 3.96 (s, 2H), 5.36 (bs, 2H), 6.8−7.4 (m, 9H); ^{13}C NMR (DMSO) δ 50.8, 53.2, 55.8, 57.7, 70.2, 115.3, 119.3, 120.0, 128.8, 130.2, 135.5, 136.1, 139.1, 155.5, 171.5; MS *m/e* 341 $(M + H)^+$, 295, 266, 250, 176, 123, 91; HRMS calcd for $C_{20}H_{25}N_2O_3$ *m/z* 341.1865, measured 341.1869.

***N*-Benzyl-*N*-[3-((2-carboxyphenyl)thio)-2-methylenepropyl]glycine (7g)** was isolated in 43% yield as a colorless oil: ^{1}H NMR (DMSO) δ 3.44 (s, 2H), 3.51 (s, 2H), 3.71 (s, 2H), 3.98 (s, 2H), 5.29 (s, 1H), 5.33 (1H, s), 7.2−7.5 (m, 8H), 7.85 (d, J = 7.4 Hz, 1H); ^{13}C NMR (DMSO) δ 52.4, 57.3, 66.9, 69.7, 118.6, 124.0, 126.2, 127.8, 128.3, 128.7, 129.5, 130.6, 131.9, 140.1, 167.4, 170.6; MS *m/e* 372 $(M + H)^+$, 326, 218, 207, 128, 100, 91; HRMS calcd for $C_{20}H_{21}NO_4SNa$ *m/z* 394.1089 $(M + Na)^+$, measured 394.1090.

***N*-Benzyl-*N*-(3-(*tert*-butylamino)-2-methylenepropyl)-glycine (7h)** was isolated in 44% yield as a colorless oil: ^{1}H NMR (DMSO) δ 1.58 (s, 9H), 3.23 (s, 2H), 3.32 (s, 2H), 3.64 (t, J = 6.5 Hz, 2H), 3.72 (s, 2H), 5.40 (s, 1H), 5.42 (s, 1H), 7.3−7.4 (m, 5H), 8.62 (bs, 2H); ^{13}C NMR (DMSO) δ 25.6, 44.6, 53.6, 57.4, 58.4, 63.2, 121.0, 127.9, 128.9, 129.5, 137.4, 137.9, 173.7; MS *m/e* 291 $(M + H)^+$, 235, 218, 189, 178, 160, 143, 91, 57; HRMS calcd for $C_{17}H_{27}N_2O_2$ *m/z* 291.2073, measured 291.2075.

***N*-Benzyl-*N*-[3-(4-toluenesulfonyl)-2-methylenepropyl]glycine (7i)** was isolated in 56% yield as a colorless oil: ^{1}H NMR (DMSO) δ 2.39 (s, 3H), 3.29 (s, 2H), 3.33 (s, 2H), 3.83 (s, 2H), 4.10 (s, 2H), 5.05 (s, 1H), 5.39 (s, 1H), 7.3−7.7 (m, 9H); ^{13}C NMR (DMSO) δ 21.5, 53.2, 57.7, 58.4, 59.1, 123.9, 128.1, 128.4, 128.8, 129.7, 130.1, 134.0, 136.0, 136.8, 144.8, 171.4; MS *m/e* 374 $(M + H)^+$, 328, 282, 238, 218, 172, 164, 139, 91; HRMS calcd for $C_{20}H_{23}NO_4SNa$ *m/z* 396.1245 $(M + Na)^+$, measured 396.1238.

***N*-Benzyl-*N*-[4-(*N*′-acetyl-*N*′-ethylamino)-2-butenyl]glycine (7j)** was isolated in 40% yield as a colorless oil: ^{1}H NMR (DMSO) δ 1.06 (t, 3H, J = 7 Hz), 1.99 (s, 3H), 3.21−3.32 (m, 2H), 3.77−3.83 (m, 2H), 3.91−3.97 (m, 4H), 4.35 (s, 2H), 5.61−5.66 (m, 1H), 5.94 (dt, 1H, J = 15 Hz, J = 5 Hz), 7.37−7.52 (m, 5H); ^{13}C NMR (DMSO) δ 13.3, 21.0, 45.6, 48.7, 51.5, 55.1, 57.2, 119.5, 128.9, 129.4, 129.8, 131.4, 137.8, 167.4, 169.2; MS *m/e* 305 $(M + H)^+$, 140, 98; HRMS calcd for $C_{17}H_{24}N_2O_3Na$ *m/z* 327.1685 $(M + Na)^+$, measured 327.1682.

***N*-Benzyl-*N*-[4-(*N*′-methyl-*N*′-(2-hydroxyethyl)amino)-2-butenyl]glycine (7k)** was isolated in 48% yield as a colorless oil: ^{1}H NMR (DMSO) δ 2.76 (s, 3H), 3.11−3.19 (m, 2H), 3.70−3.78 (m, 6H), 3.87 (s, 2H), 4.30 (s, 2H), 5.96−6.11 (m, 2H), 7.42−7.51 (m, 5H); ^{13}C NMR (DMSO) δ 49.8, 52.0, 54.3, 55.0, 56.2, 57.1, 128.0, 128.7, 129.3, 130.0, 130.4, 130.8, 168.0; MS *m/e* 293 $(M + H)^+$, 218, 164, 128, 101, 91, 74; HRMS calcd for $C_{16}H_{25}N_2O_3$ *m/z* 293.1865, measured 293.1869.

***N*-Benzyl-*N*-[4-(*N*′-isopropylamino)-2-butenyl]glycine (7l)** was isolated in 57% yield as a colorless oil: ^{1}H NMR (DMSO) δ 1.21 (d, J = 7.0 Hz, 6H), 3.24−3.30 (m, 1H), 3.58−3.70 (m, 4H), 3.74 (s, 2H), 4.19 (s, 2H), 5.85−6.09 (m, 2H), 7.4−7.5 (m, 5H), 8.83 (bs, 2H); ^{13}C NMR (DMSO) δ 19.0, 45.3, 49.3, 52.5, 54.7, 57.3, 129.1, 129.4, 129.7, 131.0, 132.5, 169.2; MS *m/e* 277 $(M + H)^+$, 218, 164, 131, 112, 91; HRMS calcd for $C_{16}H_{25}N_2O_2$ *m/z* 277.1916, measured 277.1923.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **7a**−**l** and the corresponding HPLC profiles (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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