# An Efficient Synthesis of *cis*- and *trans*-Methyl-3-hydroxy-2-pyrrolidone-5-carboxylates, Key Intermediates for the Synthesis of γ-Substituted Glutamic Acid Analogs

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Glutamic acid is the principle excitatory neurotransmitter in the mammalian central nervous system.[1] Receptors which modulate both the presynaptic release of glutamate and postsynaptic sensitivity to glutamate excitation are known as excitatory amino acid (EAA) receptors.[2] These can be subdivided into two classes, ionotropic glutamate receptors (iGluR) and metabotropic glutamate receptors (mGluR). Ionotropic glutamate receptors mediate fast synaptic transmission through ligand-gated ion channels while metabotropic glutamate receptors modulate intracellular second messengers through G protein-coupled processes. Excessive stimulation of these receptors by glutamic acid, a phenomenon known as excitotoxicity, can lead to neuronal cell damage or cell death.[3] Therefore, EAA receptor antagonists may be useful in the treatment of acute or chronic neurodegenerative disorders such as global or focal cerebral ischemia and Alzheimer's disease.[4]

Recently (2*S*,4*S*)-2-amino-4-(4,4-diphenylbut-1-yl)pentane-1,5-dioic acid (Figure 1), a glutamic acid analog, has been disclosed as a potent mGluR antagonist.[5] This observation prompted us to develop an efficient, multigram, stereochemically controlled synthesis of racemic methyl *trans*-3-hydroxy-2-pyrrolidone-5-carboxylate (**1**) (Scheme 1), thereby providing us with a key intermediate for preparing γ-substituted glutamic acid analogs. The preparation of the corresponding ethyl derivative of **1** has been described via a five step synthesis starting from ethyl 2,3-dibromopropionate and diethyl acetamido malonate.[6] This procedure suffers from divergent synthetic pathways and poor overall yield (3%). Recent papers[7] prompted us to explore the possibility of using acyl nitroso dienophiles in the synthesis of **1**. Following a

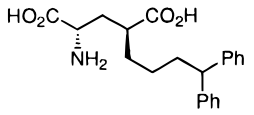
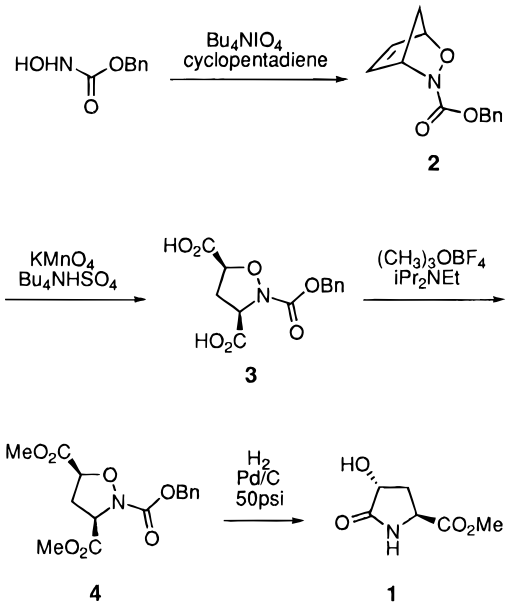


**Figure 1.**

**Scheme 1**



modified procedure,[8] commercially available benzyl *N*-hydroxycarbamate was oxidized *in situ* with tetrabutylammonium periodate forming the transient acyl nitroso dienophile. This intermediate readily underwent [4 + 2] cycloaddition to cyclopentadiene, affording the hetero Diels−Alder adduct **2** in 93% yield on a large (1 mol) scale. Our modification of this procedure led to a modest 22% increase in yield of **2** with respect to the published procedure.[8] Subjecting **2** to potassium permanganate[9] gave the diacid **3** which was readily converted to the diester **4** (65%) by treatment with trimethyloxonium tetrafluoroborate. Initial attempts to reductively cleave the N−O bond of **4** with aluminum amalgam[10] failed. Attempts to cleave the N−O bond, employing molybdenum hexacarbonyl[11] proved successful, albeit with major drawbacks, such as formation of multiple byproducts and low overall yields. Finally, we found that when the diester **4** was subjected to catalytic hydrogenation in the presence of palladium on carbon, both the N−O bond and the resulting benzyl carbamate were cleaved. This intermediate readily underwent intramolecular cyclization *in situ*, in a highly stereocontrolled fashion, affording methyl *trans*-3-hydroxy-2-pyrrolidone-5-carboxylate (**1**) (77%). The overall yield of **1** over four steps was 40%.

Assignment of **1** as the *trans* isomer was made through $^1$H NMR coupling constant measurements and NOE studies. The proton $H_5$ (4.29 δ) in Figure 2 displays coupling constants of 9.3 and 2.6 Hz to $H_{4b}$ (2.37 δ), and $H_{4a}$ (2.61 δ), respectively. The larger coupling is indicative of cis stereochemistry. The coupling constants of $H_3$

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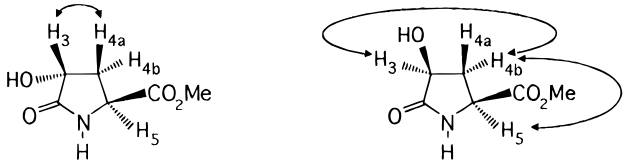
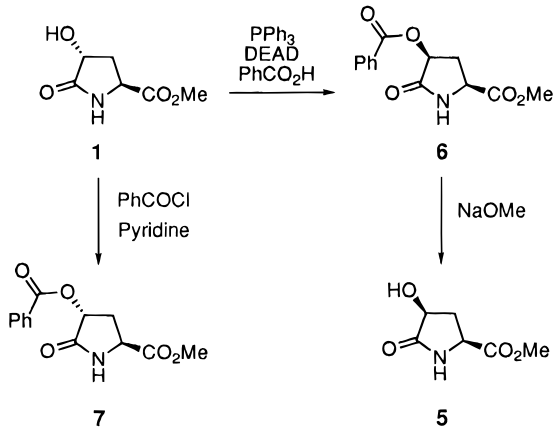


**Figure 2.** Observed NOEs for **1** and ROEs for **5**.

**Scheme 2**



(4.41 $\delta$) are 8.1 Hz to both $H_{4a}$ and $H_{4b}$, which cannot be used to determine stereochemistry at the C-3 position. However, results of the NOE experiments shown in Figure 2 were used to determine stereochemistry at the C-3 position. There are NOEs between $H_{4b}$ and $H_5$ and between $H_3$ and $H_{4a}$. The observed NOEs indicate that the C3 hydroxyl functionality and $H_{4a}$ are situated on opposite faces of the pyrrolidone ring system. Similarly, $H_{4a}$ and $H_5$ are also situated on opposite faces of the pyrrolidone ring system. Therefore, the C3-hydroxyl functionality is deduced to be trans to the C5-carbomethoxy group.

The corresponding *cis* isomer **5** was readily synthesized from **1** in two steps (Scheme 2). Employing standard Mitsunobu conditions,[12] treatment of **1** with benzoic acid afforded the *cis* benzoate **6** in 69% yield with inversion of configuration. The corresponding *trans* benzoate **7** (64%) was prepared from **1** with benzoyl chloride in pyridine. Examination of the cis and trans benzoates by $^1$H NMR revealed clear differences between the C4 methylene protons (see Experimental Section for peak positions and the supporting information for the NMR spectra). Next, the *cis* benzoate **6** was subjected to methanolysis to yield methyl *cis*-3-hydroxy-2-pyrrolidone-5-carboxylate (**5**). Examination of the crude *cis* isomer **5** by $^1$HNMR indicated no epimerization had resulted during methanolysis of the benzoate **6**. Pure **5** was isolated by crystallization followed by purification using Florisil column chromotography. The mother liquor was subjected to silica gel column chromotography. In the latter process, epimerization occurred affording a 87:13 mixture of *cis* and *trans* isomers. We were able to separate **5** from the mixture by exploiting the differences in solubility between the two diastereomers. The *cis* isomer **5** was water soluble and relatively insoluble in organic solvents, while the *trans* isomer **1** exhibited opposite solubilities to that of **5**. Trituration of the mixture in THF followed by filtration afforded pure **5** as a solid. Combining the isolated lots of **5** afforded a 53% yield of this product from **6**.

The stereochemistry at the C3 position of **5** could not be determined using $^1$H NMR coupling constant measurements because of similarities in the couplings between $H_5$ to $H_4$ and $H_3$ to $H_4$. The proton $H_5$ (4.19 $\delta$) in Figure 2 displayed coupling constants of 7.5 Hz to $H_{4b}$ (2.85 $\delta$) and 8.5 Hz to $H_{4a}$ (2.08 $\delta$). The coupling constants of $H_3$ (4.38 $\delta$) were 7.8 Hz to $H_{4b}$ (2.85 $\delta$) and 8.5 Hz to $H_{4a}$ (2.08 $\delta$). With this, the stereochemistry at C-3 was assigned by a 2-D ROESY[13] experiment. ROEs between $H_5$ and $H_{4b}$ as well as $H_3$ and $H_{4b}$ were found. Protons $H_3$, $H_{4b}$, and $H_5$ are situated on the same face of the pyrrolidone ring system thus inferring cis stereochemistry between the C3-hydroxyl group and C5-ester functionality (Figure 2).

Additional supporting data for the stereochemical assignments of isomers **1**, **5**, **6**, and **7** can be drawn by comparison of their $^1$H NMR spectra. Close examination of protons $H_{4a}$ and $H_{4b}$ reveal clear differences in chemical shifts when these protons are influenced by highly shielded or deshielded electronic environments. The $H_{4a}$ proton in *trans* isomer **1** resonates at 2.61ppm. When $H_{4a}$ is situated on the same face of the pyrrolidone ring as the C3-hydroxy and C5-ester functionality, as in **5**, the resulting highly shielded electronic environment causes an upfield shift of 0.53 ppm for this proton compared to **1**. Analogously, when $H_{4b}$ is no longer situated on the same face of the ring system as the C3-hydroxy and C5-ester functionality, as in **5**, the resulting deshielded electronic environment causes a downfield shift of 0.48 ppm for this proton compared to $H_{4b}$ in **1**. The same phenomenon was observed for the benzoyl isomers **6** and **7** (see Experimental Section for peak positions and the Supporting information for the NMR spectra).

In conclusion, we have been able to selectively prepare methyl *trans*-3-hydroxy-2-pyrrolidone-5-carboxylate (**1**) in a concise, stereochemically controlled manner from cyclopentadiene. As demonstrated, our approach is amenable to large scale synthesis and is a 13 fold improvement in yield over a previously described procedure for the corresponding ethyl ester derivative.[6] The corresponding *cis* isomer **5** was also synthesized in a stereochemically controlled fashion from **1** in two steps, a 2 fold improvement in yield from a previously described procedure.[6] Both isomers serve as useful synthetic intermediates for synthesizing $\gamma$-substituted glutamic acid analogs. Subsequent application of these intermediates to our EAA antagonist structure activity studies are ongoing and will be reported elsewhere.

## Experimental Section

Melting points are uncorrected. THF was distilled from sodium benzophenone ketyl prior to use. All other reagents were purchased from commercial sources and used as obtained. $^1$H NMR spectra were obtained at 300 MHz. $^{13}$C NMR spectra were obtained at 75 MHz. The COESY and ROESY experiments were obtained at 500 MHz. Field desorption mass spectral data was recorded on a VG 70se instrument. Separations by flash chromatography were performed on silica gel (230−400 mesh). Flash silica gel filtration refers to Harwood's technique.[14]

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***N*-(Benzyloxycarbonyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (2).** To a suspension of benzyl *N*-hydroxycarbamate (166.5 g, 1.0 mol) in $CH_2Cl_2$ (1000 mL) cooled to −10 °C was added freshly distilled cyclopentadiene (59.6 g, 0.9 mol). The solution was then treated with a suspension of tetrabutylammonium periodate (429 g, 1.0 mol) in $CH_2Cl_2$ (900 mL) at a rate such that the temperature remained below 3 °C. After the addition of the periodate was complete (ca. 20 min), the resulting mixture was stirred at −5 °C for 2 h. A solution of $NaHSO_3$ (340.5 g, 3.3 mol) in water (1350 mL) was carefully added (caution—highly exothermic reaction!) at such a rate to maintain the reaction temperature between −2 °C and 6 °C. Once the addition of the $NaHSO_3$ was complete (ca. 50 min), the organic phase was removed. The aqueous phase was treated with water (1600 mL), causing further separation of the organic and aqeuous phases. The combined organic phases were washed with water (3 × 1600 mL), saturated $NaHCO_3$ solution (1050 mL), water (1600 mL), and 1 N HCl solution (1200 mL). The organic phase was dried over NaCl and then $MgSO_4$ and concentrated *in vacuo* to afford 547 g of a brown residue. This residue was treated with $Et_2O$ (1400 mL) and the resulting mixture filtered. The filtrate was evaporated to a solid (206.0 g). The solid was subjected to flash silica gel filtration, eluting with hexane:EtOAc (4:1, 4 × 3 L) and then hexane:EtOAc (2:1, 6 × 3 L). The fractions containing the title compound were combined and concentrated *in vacuo* to afford a yellow oil. The title compound crystallized from the oil yielding 194.9 g (93%) of a solid: mp 34−36 °C. $^1$H ($CDCl_3$) $\delta$ 7.31 (m, 5H), 6.38 (s, 2H), 5.24 (s, 1H), 5.19 (d, $J$ = 12.2 Hz, 1H), 5.12 (d, $J$ = 12.2 Hz, 1H), 5.05 (s, 1H), 2.01 (d, $J$ = 8.7 Hz, 1H), 1.75 (d, $J$ = 8.7 Hz, 1H); APT $^{13}$C (DMSO-$d_6$) $\delta$ up: 158.6, 136.0, 66.8, 47.9; down: 134.5, 133.2, 128.4,128.1, 127.8, 83.1, 64.8; FDMS $m/z$ (relative intensity) 231 (100, $M^+$). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.25; H, 5.69; N, 5.96.

***N*-(Benzyloxycarbonyl)-3,5-dicarboxy-1,2-oxazoline (3).** A biphasic solution of **2** (69.4 g, 0.30 mol) in toluene (694 mL) and water (150 mL) was treated with tetrabutylammonium hydrogen sulfate (10.2 g, 0.03 mol). The resulting mixture was cooled to approximately 2 °C, and a solution of $KMnO_4$ (123.2 g, 0.78 mol) in water (800 mL) was added at a rate such that the temperature was kept below 6 °C. After the addition of the permanganate was complete (ca. 50 min), the resulting mixture was mechanically stirred at 0 °C for 2.2 h. The reaction mixture was then treated with Celite 521 (348 g) and filtered through a dry Celite pad. The insolubles were washed with MeOH:$H_2O$ (3600 mL, 4:1). The filtrate was concentrated *in vacuo* to a volume of about 400 mL. This concentrate was treated with $H_2O$ (100 mL) and EtOAc (600 mL). The pH of this mixture was adjusted to 0.81 by the addition of 18 N $H_2SO_4$ (110 mL). The phases were separated and the aqueous phases extracted with EtOAc (2 × 500 mL). The combined organics were dried over NaCl and $MgSO_4$, filtered, and concentrated *in vacuo* to afford 81.3 g of the crude title compound. This material was used in the next reaction without further purification. $^1$H ($CDCl_3$) $\delta$ 7.32 (m, 5H), 5.19 (s, 2H), 4.83 (t, $J$ = 6.3 Hz, 1H), 4.68 (t, $J$ = 6.9 Hz, 1H), 2.85 (dd, $J$ = 6.9, 6.3 Hz, 2H); FDMS $m/z$ (relative intensity) 296 (100, $M^+$).

***N*-(Benzyloxycarbonyl)-3,5-bis(methoxycarbonyl)-1,2-oxazoline (4).** A solution of crude **3** (69.7 g, 0.27 mol) in $CH_2Cl_2$ (1000 mL) was cooled to −40 °C with an $CH_3CN$/dry ice bath. The solution was then treated with diisopropylethylamine (68.7 g, 0.53 mol) over a 5 min period. The solution was treated with trimethyloxonium tetrafluoroborate (78.5 g, 0.53 mol) while maintaining the reaction temperature below −37 °C. After 3 h, the reaction was allowed to warm to −25 °C for 1 h, and then the cooling bath was removed. The reaction was treated with $H_2O$ (500 mL) and the phases were separated. The organic phase was washed with $NaHSO_4$ solution (3 × 400 mL). The organic phase was dried over NaCl and concentrated *in vacuo* to give 81.2 g of crude product. The material was subjected to flash silica gel filtration, eluting with hexane:EtOAc (4:1, 8 L) and then hexane:EtOAc (2:1, 19 L). The fractions containing the desired product were combined and concentrated *in vacuo* to afford 49.4 g (65%) of a yellow oil. $^1$H ($CDCl_3$) $\delta$ 7.33 (m, 5H), 5.22 (s, 2H), 4.85 (t, $J$ = 6.3 Hz, 1H), 4.60 (t, $J$ = 6.3 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.82 (dd, $J$ = 6.3, 6.3 Hz, 2H); APT $^{13}$C (DMSO-$d_6$) $\delta$ up: 169.8, 168.3, 156.1, 135.6, 67.6, 35.2; down: 128.4, 128.2, 128.0, 77.0, 60.0, 52.5, 52.3; FDMS $m/z$ (relative intensity) 323 (100, $M^+$); Anal. Calcd for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33. Found: C,55.63; H, 5.34; N, 4.38.

**Methyl *trans*-3-Hydroxy-2-pyrrolidone-5-carboxylate (1).** A mixture of **4** (100.5 g, 0.31 mol) and 5% palladium on carbon (40.0 g) in THF (1.2 L) was hydrogenated at 50 psi and at rt. After 18 h the reaction mixture was filtered and the filtrate concentrated *in vacuo* to a solid. Recrystallization from EtOAc gave 38.3 g (77%) of the title compound: mp 86 °C. $^1$H ($CDCl_3$) $\delta$ 7.03 (s, $CD_3OD$ exchangeable), 4.41 (dd, $J$ = 8.3, 8.2 Hz, 1H), 4.29 (ddd, $J$ = 9.3, 2.5, 1.1 Hz, 1H), 3.77 (s,3H), 2.61 (ddd, $J$ = 13.5, 8.2, 2.5 Hz, 1H), 2.37 (ddd, $J$ = 13.5, 9.3, 8.3 Hz, 1H); APT $^{13}$C NMR (DMSO-$d_6$) $\delta$ up: 176.6, 173.1, 34.0; down: 67.0, 52.1, 51.5; FDMS $m/z$ (relative intensity) 160 (100, $M^+$). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.54; H, 5.70; N, 8.54.

**Methyl *cis*-3-Benzoyl-2-pyrrolidone-5-carboxylate (6).** A mixture consisting of **1** (1.56 g, 9.8 mmol), triphenylphosphine (3.08 g, 11.8 mmol), and benzoic acid (1.44 g, 11.8 mmol), in THF (36 mL) at −5 °C was treated with DEAD (2.05 g, 11.8 mmol), while maintaining the reaction temperature below 7 °C. After stirring 4 h at rt, the reaction was concentrated *in vacuo* to an oil. The oil was treated with $CHCl_3$ (5 mL), resulting in the precipitation of dicarbethoxyhydrazine. The crystalline dicarbethoxyhydrazine was collected by filtration and washed with 1:1 $CHCl_3$:hexane (5 mL). The filtrate was concentrated *in vacuo* and purified on a flash silica gel column (5.5 × 8.5 cm), eluting with acetone to afford the title compound. Recrystallization from acetone:diisopropyl ether afforded 1.78 g (69%): mp 108−109 °C. $^1$H ($CDCl_3$) $\delta$ 8.07 (d, $J$ = 8.3 Hz, 2H), 7.58 (m, 1H), 7.44 (m, 2H), 6.41 (bs, 1H), 5.54 (dd, $J$ = 8.3, 8.2 Hz, 1H), 4.30 (dd, $J$ = 7.8, 7.8 Hz, 1H), 3.80 (s,3H), 3.10 (ddd, $J$ = 13.6, 8.2, 8.2 Hz 1H), 2.29 (ddd, $J$ = 13.5, 7.8, 7.8 Hz, 1H); APT $^{13}$C NMR (DMSO-$d_6$) $\delta$ up: 172.9, 172.5, 165.8, 130.1, 32.0; down: 134.6, 130.2, 129.8, 71.1, 53.1, 52.5; FDMS $m/z$ (relative intensity) 263 (100, M), 204 (10). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C,59.45; H, 5.01; N, 5.49.

**Methyl *cis*-3-Hydroxy-2-pyrrolidone-5-carboxylate (5).** A solution of sodium methoxide (0.08 g, 1.5 mmol) in MeOH (11 mL) was treated with **6** (1.34 g, 5.1 mmol). The reaction was stirred at 22 °C for 3.2 h, treated with 1 N HCl (1.5 mL, 1.5 mmol), and then concentrated *in vacuo* to afford an oil. $^1$H NMR of this material indicates no epimerization has occurred. The oil was cooled to −20 °C, resulting in crystal formation. The crystals were collected by filtration, washed with $CHCl_3$, taken up into methanol, purified on a Florisil column (3 × 7 cm), eluting with $CHCl_3$:MeOH (9:1), to afford 354 mg of the title compound. The filtrate was concentrated *in vacuo*, taken up into MeOH, and subjected to silica gel chromtography (3 × 7 cm, 90:10:1 $CHCl_3$:MeOH:$NH_4OH$). The product eluted as a mixture of 6.7:1 cis:trans methyl 3-hydroxy-2-pyrrolidone-5-carboxylate. This mixture was triturated in THF (4 mL), filtered and washed with THF (1 mL) to afford 75 mg of the title compound. Combining both lots of **6** afforded 429 mg (53%) of pure methyl *cis*-3-hydroxy-2-pyrrolidone-5-carboxylate: mp 71−72 °C. $^1$H ($CDCl_3$) $\delta$ 6.62 (bs, 1H), 4.38 (dd, $J$ = 8.5, 7.8 Hz, 1H), 4.19 (ddd, $J$ = 8.5, 7.8, 7.6 Hz, 1H), 3.80 (s, 3H), 2.85 (ddd, $J$ = 13.0, 7.8, 7.6 Hz, 1H), 2.08 (ddd, $J$ = 12.9, 8.9, 8.9 Hz, 1H); APT $^{13}$C (DMSO-$d_6$) $\delta$ up: 175.8, 172.2, 34.0; down: 67.7, 51.8, 50.9; FDMS $m/z$ (relative intensity) 159 (100, M). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C,45.52; H, 5.70; N, 8.57.

**Methyl *trans*-3-Benzoyl-2-pyrrolidone-5-carboxylate (7).** To a solution of **1** (0.56 g, 3.5 mmol) in pyridine (7 mL) at 22 °C was added benzoyl chloride (0.49 g, 3.5 mmol). The reaction was stirred at 22 °C for 6 h and then concentrated *in vacuo* to afford a solid. The solid was treated with $CH_2Cl_2$ (30 mL) and $H_2O$ (30 mL), phases were separated, and the aqueous phases were extracted with additional $CH_2Cl_2$ (2 × 10 mL). The combined organic phases were dried over $Na_2SO_4$ and then filtered. The filtrate was boiled down to approximately 10 mL and cooled to 22 °C, and the resulting crystals were collected by filtration to afford 450 mg (64%) of the title compound: mp 187−189 °C. $^1$H ($CDCl_3$) $\delta$ 8.08 (d, $J$ = 7.4 Hz, 2H), 7.59 (m, 1H), 7.45 (m, 2H), 6.89 (bs, 1H), 5.58 (dd, $J$ = 8.2, 8.2 Hz, 1H), 4.39 (dd, $J$ = 9.1, 2.8, Hz, 1H), 3.82 (s, 3H), 2.88 (ddd, $J$ = 13.8, 8.2, 2.8 Hz, 1H), 2.53 (ddd, $J$ = 13.9, 9.1, 7.8 Hz, 1H); APT $^{13}$C NMR (DMSO-$d_6$) $\delta$ up: 172.6, 172.0, 164.9, 128.9, 30.9; down: 133.7, 129.3, 128.8, 69.6, 52.4, 51.8; FDMS $m/z$ (relative intensity) 264 (100, $M^+$),

204 (24). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C,59.36; H, 5.03; N, 5.51.

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**Supporting Information Available:** $^1$H NMR spectra for **1**, **5**, **6**, and **7** (4 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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