A Tandem Michael Addition Ring-Closure Route to the Metabotropic Receptor Ligand α-(Hydroxymethyl)glutamic Acid and Its γ-Alkylated Derivatives

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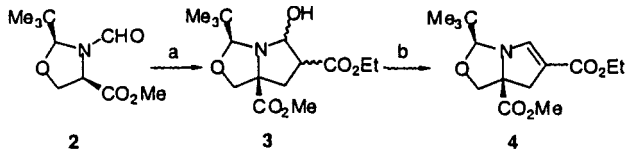
Introduction

L-Glutamate is one of the most abundant excitatory amino acid neurotransmitters found in the mammalian brain. This amino acid acts on diverse glutamate receptors, including members of both the ionotropic and the metabotropic glutamate receptor (mGluR) families.[1,2] Because of the possibility of identifying ligands that may prove useful in disease intervention, considerable attention has been given to the discovery of both selective agonists and antagonists of these glutamate receptors over the past decade.[3] As part of our ongoing efforts to discover subtype-selective mGluR agonists and antagonists, we have found that a 2-substituted L-glutamate analogue, namely, (2*S*)-α-(hydroxymethyl)glutamate (**1**, HMG), is able to act as a relatively potent agonist of the group 2 receptor mGluR3 while functioning as a weak antagonist of mGluR2. This compound has, in contrast, little or no effect on the Group 1 and Group 3 mGluRs.[4] Since our first synthetic approach to HMG required 10 synthetic steps, we sought a more practical route to this molecule, and in particular, a route that could produce not only the parent structure but its γ-substituted analogues as well. Herein, we describe a general approach to such molecules that starts from D-serine.

Results and Discussion

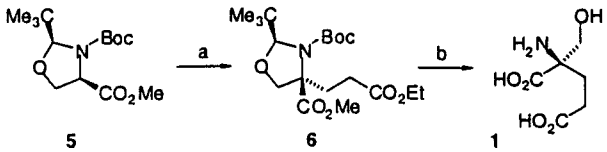
In our initial efforts to discover an expedient route to HMG, we first examined a simple Michael addition reaction of the serine-derived oxazolidine **2**[5] with ethyl acrylate (Scheme 1). The major product of the reaction was found to be the bicycle **3**, which was formed in 27% yield, together with the unsaturated ester **4** in 14% yield. We sought to oxidize intermediate **3** to the corresponding lactam in order to subsequently effect hydrolysis and decarboxylation to afford HMG. However, attempts to bring about this oxidation with either PDC or the Dess−Martin reagent resulted only in formation of the elimination product **4**.

Scheme 1[a]



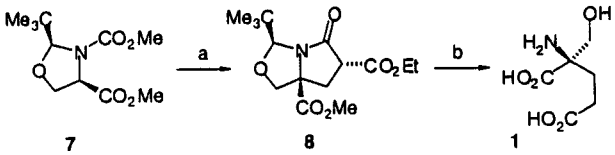
[a] Conditions: (a) (i) LDA, THF, −78 °C, 1 h, (ii) ethyl acrylate, −78 °C, 12 h, 41%; (b) Dess−Martin reagent, CH_2Cl_2, room temperature, or PDC, CH_2Cl_2, room temperature.

Scheme 2[a]



[a] Conditions: (a) (i) LDA, THF, −78 °C, 1 h, (ii) ethyl acrylate, −78 °C, 12 h, 10%; (b) 6 N HCl, reflux, overnight, 90%.

Scheme 3[a]



[a] Conditions: (a) (i) LDA, THF, −78 °C, 1 h, (ii) ethyl acrylate, −78 °C, 12 h, 62%; (b) 6 N HCl, reflux, overnight, 90%.

Upon replacement of the *N*-formyl group of **2** with the larger, less electrophilic Boc protecting group, the Michael addition reaction of carbamate **5**[6] with ethyl acrylate was found to take place, albeit in a very low yield (15% yield based on 67% conversion). The intermediate **6** was then hydrolyzed with 6 N HCl to afford the required HMG (Scheme 2).

Upon consideration of the somewhat disappointing results stemming from the use of the *N*-formyl and *N*-Boc derivatives, it appeared reasonable to attempt the same reaction using a methoxycarbonyl group for nitrogen protection. We believed that the smaller protecting group might allow the ring closure to the lactam to ensue, thus providing a means to drive the reaction to completion. The lactam intermediate might in turn allow for the stereocontrolled introduction of additional substituents through further carbanion-based alkylation chemistry.

In the event, the carbamate **7**[7] was converted to its enolate anion by the use of LDA and the anion reacted in turn with ethyl acrylate (Scheme 3). The desired Michael addition ring closure was indeed found to take place smoothly to provide the bicycle **8** as a single isomer in 62% yield after recrystallization. The configurations of the newly formed chiral centers were assigned as shown on the basis of an X-ray analysis. Adduct **8** was

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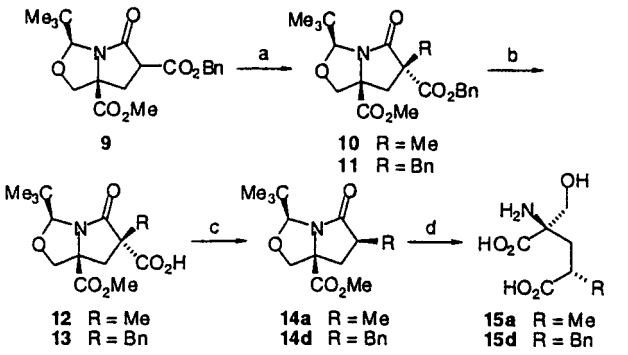
Scheme 4[a]



[a] Conditions: (a) NaH, DMF, MeI or BnBr, room temperature, overnight; (b) H_2, $Pd(OH)_2$/C, *t*-BuOH, room temperature, overnight; (c) 220 °C, 5 min; (d) 6 N HCl, reflux, 2 h.

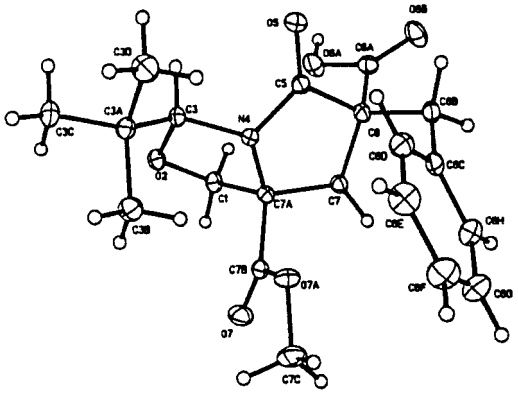


Figure 1. Crystal structure of **13**.

in turn directly hydrolyzed to the final product HMG in a high yield.

After successfully obtaining the desired parent molecule, HMG, we examined the possibility of using the bicycle **8** in the preparation of γ-substituted analogues of HMG. This was of interest to us as several γ-substituted glutamate analogues have been shown to exhibit selective mGluR2 antagonist activity.[8] After some experimentation, we found that the best way to carry out this chemistry was to use benzyl acrylate in the tandem reaction to generate the bicycle **9** in 63% yield (Scheme 4). Next, crude **9** was used directly without further purification in an alkylation reaction with either iodomethane or benzyl bromide. In both cases, single isomeric products, **10** and **11**, respectively, were generated. Hydrogenation of the benzyl esters **10** and **11** afforded the crystalline acids **12** and **13**, respectively, the structures of which were established by X-ray analysis. As is apparent from Figure 1, the crystal structure analysis of compound **13** shows that the alkyl substituent has been introduced cis to the methoxycarbonyl group. Next, decarboxylation was brought about by heating the intermediates **12** and **13** at 220 °C for several minutes[9] to afford **14a** and **14d**, respectively, as single isomers. Decarboxylation occurred with maintenance of the substituent on the convex face of the bicycle as revealed by X-ray analysis (Figure 2). Finally, hydrolysis with 6 N HCl under reflux conditions gave the desired 4-alkylated HMG analogues **15a** and **15d**. The purity of these compounds was confirmed by their ^{1}H NMR spectra.

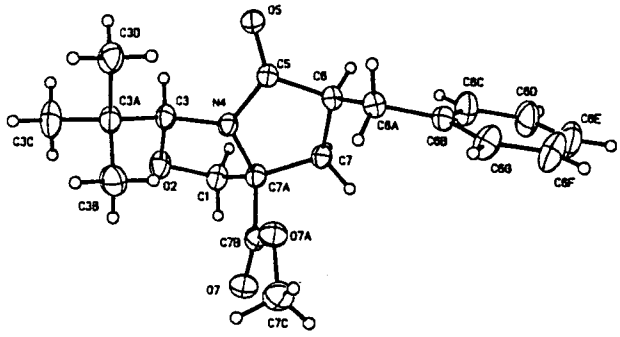
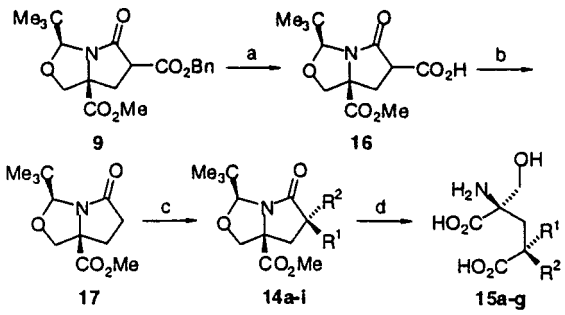


Figure 2. Crystal structure of **14d**.

Scheme 5[a]



[a] Conditions: (a) H_2, $Pd(OH)_2$/C, *t*-BuOH, room temperature, overnight; (b) 220 °C, 5 min; (c) (i) LDA, THF, −78 °C, 1 h, (ii) RX, −78 °C, 4 h; (d) 6 N HCl, reflux, 2 h.

For the pharmacological studies, we were also interested in obtaining the 4*R*-isomers of **15a** and **15d** in order to ascertain the contribution of this stereocenter to mGluR subtype selectivity and potency. To accomplish this, we chose to explore the alkylation chemistry of bicycle **17**, which was obtained from **9** by hydrogenation and decarboxylation (Scheme 5). Interestingly, when the methylation reaction of **17** was carried out using methyl trifluoromethanesulfonate as the electrophile, only a single product **14a** was obtained. On the other hand, when either methyl iodide or benzyl bromide was employed as the electrophile, mixtures of mono- and disubstituted products resulted. In the case of methyl iodide, the ratio of **14a**:**14b**:**14c** was 32:32:21, while **14d**, **14e**, and **14f** were formed in a ratio of 57:22:8 in the case of benzyl bromide. When the larger electrophilic reagent, 4,4-diphenyl-1-bromobutane,[10] was used (THF as the solvent and HMPA as the chelating agent),[11] **14g** was obtained in 32% yield, together with a small amount of **14h** and **14i** (both less than 1% yield). The structures of compounds **14g** and **14h** were assigned on the basis of their ^{1}H NMR spectra. As can be seen from Table 1, the proton in the α-position relative to the lactam carbonyl group (6-H) resonates at lower field when it is situated on the convex face of the bicycle. This is observed for **14b** and **14e** in comparison to **14a** and **14d**, respectively. As the stereochemistry of these compounds has been firmly established by X-ray analysis, we thus conclude that the

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Table 1. ^{1}H Chemical Shifts of 6-H of the 6-Monoalkylated Bicycles

compd	R^1	R^2	δ(6-H)
14a	Me	H	2.75
14b	H	Me	3.33
14c	Me	Me	
14d	Bn	H	3.00
14e	H	Bn	3.51
14f	Bn	Bn	
14g	$Ph_2CH(CH_2)_3$	H	2.58
14h	H	$Ph_2CH(CH_2)_3$	3.08
14i	$Ph_2CH(CH_2)_3$	$Ph_2CH(CH_2)_3$	

alkylation reaction using 4,4-diphenyl-1-bromobutane as the electrophile occurs predominantly on the convex face of the bicycle. The final HMG analogues were obtained from the bicyclic precursors by hydrolysis with 6 N HCl under reflux conditions followed by purification on a C_{18} column.

In conclusion, we have developed a straightforward method to synthesize HMG and its γ-substituted analogues starting from D-serine. The method is based on a tandem Michael addition ring-closure protocol followed by a stereoselective alkylation reaction that takes place from the convex face of the bicycle. The biological evaluation of these novel amino acids as mGluR ligands will be reported separately.

Experimental Section

General Methods. THF was freshly distilled under N_2 from sodium benzophenone. ^{1}H and ^{13}C NMR spectra were acquired at a proton frequency of 300 MHz, using $CDCl_3$ as the solvent unless noted otherwise. ^{1}H chemical shifts (parts per million, ppm) were obtained using $CHCl_3$ (δ = 7.26, for $CDCl_3$ as the solvent) or HDO (δ = 4.80, for D_2O as the solvent) as the internal standard. ^{13}C chemical shifts (ppm) were determined with $CHCl_3$ (central peak δ = 77.00, for $CDCl_3$ as the solvent) or MeOH (δ = 49.15, for D_2O as the solvent) as the internal standard. Melting points were determined in Pyrex capillaries with a Thomas−Hoover Unimelt apparatus and are uncorrected. Mass spectra were measured in the EI mode at an ionization potential of 70 eV. X-ray data were collected on a computer-controlled Bruker P4 automatic four-circle diffractometer. The structures were solved by direct methods and refined, using all independent data, with full matrix least-squares on F2 values using the SHELXTL program package. TLC was performed on Merck silica gel 60F_{254} glass plates. Optical rotations were measured at room temperature.

(3*S*,7a*R*)-3-*tert*-Butyl-7,7a-dihydro-1*H*-pyrrolo[1,2-*c*]oxazole-6,7a-dicarboxylic Acid 6-Ethyl Ester 7a-Methyl Ester (4). To a solution of **2** (350 mg, 1.63 mmol) in THF (6.0 mL) stirred at −78 °C under nitrogen was added a solution of lithium diisopropylamide in THF (0.51 M, 3.4 mL, 1.7 mmol). After the reaction mixture had been stirred at −78 °C for 30 min, ethyl acrylate (188 mg, 1.88 mmol) in THF (2.6 mL) was added, and stirring was continued for 1 h at −78 °C. The reaction mixture was poured into NH_4Cl solution and extracted with EtOAc three times. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 1:15 EtOAc/hexane) afforded unreacted compound **2** (113 mg, 32% recovery) and products **3** (135 mg, 39% based on 68% conversion) and **4** (70 mg, 21% based on 68% conversion) as colorless oils. Compound **4**: ^{1}H NMR δ 6.82 (s, 1H), 4.70 (d, 1H, J = 8.7 Hz), 4.18−4.11 (m, 3H), 3.74 (s, 3H), 3.39 (d, 1H, J = 8.7 Hz), 2.84 (br, 2H), 1.25 (t, 3H, J = 6.9 Hz), 0.87 (s, 9H); ^{13}C NMR δ 172.74, 164.76, 149.77, 110.53, 101.88, 75.41, 71.33, 59.88, 52.59, 34.85, 24.19, 14.38.

(2*S*,4*R*)-2-*tert*-Butyl-4-[2-(ethoxycarbonyl)ethyl]oxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (6). To a solution of **5** (550 mg, 1.91 mmol) in THF (10 mL) stirred at −78 °C under nitrogen was added a solution of lithium diisopropylamide in THF (0.53 M, 4.0 mL, 2.1 mmol). After the reaction mixture had been stirred at −78 °C for 30 min, ethyl acrylate (280 mg, 2.80 mmol) in THF (2.5 mL) was added, and stirring was continued for 9 h at −78 °C. The reaction mixture was poured into NH_4Cl solution and extracted with EtOAc three times. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 1:15 EtOAc/hexane) afforded **5** (178 mg, 33% recovery) and product **6** (75 mg, 15% based on 67% conversion) as a colorless oil: $[\alpha]_D$ −50.0° (*c* 0.5, $CHCl_3$); IR (film) 2961, 1740, 1711 cm^{-1}; ^{1}H NMR δ 5.13 (s, 1H), 4.26 (d, 1H, J = 8.7 Hz), 4.13 (q, 2H, J = 6.9 Hz), 4.02 (d, 1H, J = 8.7 Hz), 3.76 (s, 3H), 2.73 (br, 1H), 2.49 (m, 1H), 2.31 (m, 1H), 2.16 (m, 1H), 1.45 (s, 9H), 1.25 (t, 3H, J = 6.9 Hz), 1.00 (s, 9H); ^{13}C NMR δ 172.76, 171.98, 153.15, 98.12, 81.08, 75.72, 68.10, 60.49, 52.45, 39.49, 30.06, 28.66, 28.01, 26.41, 14.13; MS *m*/*z* (%) 330 (6), 230 (100), 184 (46), 57 (95).

(3*S*,7a*R*)-3-*tert*-Butyl-1,6,7,7a-tetrahydro-5-oxopyrrolo-[1,2-*c*]oxazole-6,7a-dicarboxylic Acid 6-Ethyl Ester 7a-Methyl Ester (8). To a solution of compound **7** (3.90 g, 15.9 mmol) in 60 mL of THF stirred at −78 °C under nitrogen was added a 0.61 M solution of lithium diisopropylamide in THF (31.0 mL, 18.9 mmol, 1.2 equiv). After the reaction mixture had been stirred at −78 °C for 30 min, ethyl acrylate (2.0 g, 20.0 mmol) in THF (10 mL) was added, and stirring was continued for 12 h at −78 °C. The reaction mixture was poured into NH_4-Cl solution and extracted with EtOAc three times. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 1:10 EtOAc/hexane) afforded starting material **7** (1.10 g, 28% recovery) and product **8** (2.92 g, 86% based on 72% conversion). Compound **8**: mp 105−107 °C (from acetone/hexane); $[\alpha]_D$ −15.2° (*c* 1.2, MeOH); IR (KBr) 2977, 1732, 1720 cm^{-1}; ^{1}H NMR δ 4.86 (s, 1H), 4.82 (d, 1H, J = 8.7 Hz), 4.29−4.15 (m, 3H), 3.77 (s, 3H), 3.54 (d, 1H, J = 8.7 Hz), 2.64 (m, 1H), 2.44 (dd, 1H, J = 9.0, 13.2 Hz), 1.30 (t, 3H, J = 7.2 Hz), 0.85 (s, 9H); ^{13}C NMR δ 172.94, 172.17, 168.49, 96.59, 73.84, 70.04, 61.94, 52.88, 51.90, 35.78, 33.16, 24.71, 14.15; MS *m*/*z* (%) 298 (2), 256 (91), 210 (100). Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.37; H, 7.67; N, 4.41.

(3*S*,6*R*,7a*R*)-3-*tert*-Butyl-1,6,7,7a-tetrahydro-6-methyl-5-oxopyrrolo[1,2-*c*]oxazole-6,7a-dicarboxylic Acid 6-Benzyl Ester 7a-Methyl Ester (10). To a solution of compound **7** (3.60 g, 14.7 mmol) in THF (40 mL) stirred at −78 °C under nitrogen was added a solution of LDA in THF (1.5 M, 12.0 mL, 18.0 mmol). After the reaction mixture had been stirred at −78 °C for 30 min, benzyl acrylate (2.88 g, 17.8 mmol) in THF (10 mL) was added, and stirring was continued for 12 h at −78 °C. The reaction mixture was poured into NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford an inseparable mixture of **7** and **9** (4.80 g).

To a solution of this mixture (95 mg) in DMF (5 mL) was added NaH (60% in oil, 15 mg, 0.38 mmol) under nitrogen. Methyl iodide (40 μL, 0.64 mmol) was added 5 min later. The mixture was stirred overnight, poured into saturated NH_4Cl solution, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 1:20 EtOAc/hexane) to afford compound **10** as a colorless oil: $[\alpha]_D$ −6.0° (*c* 0.5, $CHCl_3$); IR (film) 2987, 1745, 1718 cm^{-1}; ^{1}H NMR δ 7.38−7.28 (m, 5H), 5.23 (d, 1H, J = 9.0 Hz), 5.13 (d, 1H, J = 9.0 Hz), 4.84 (s, 1H), 4.76 (d, 1H, J = 8.7 Hz), 3.78 (s, 3H), 3.47 (d, 1H, J = 8.7 Hz), 2.78 (d, 1H, J = 14.1 Hz), 2.12 (d, 1H, J = 14.1 Hz), 1.70 (s, 3H), 0.89 (s, 9H); ^{13}C NMR δ 178.97, 172.71, 171.36, 135.23, 128.64, 128.43, 128.42, 128.02, 98.21, 73.35, 69.79, 67.65, 56.22, 52.86, 38.73, 35.31, 24.82, 21.90; MS *m*/*z* (%) 332 (86), 91 (100), 43 (16).

(3*S*,6*R*,7a*R*)-6-Benzyl-3-*tert*-butyl-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-6,7a-dicarboxylic Acid 6-Benzyl Ester 7a-Methyl Ester (11). To a solution of crude compound **9** (480 mg) in DMF (10 mL) was added NaH (60% in oil, 60 mg, 1.5 mmol) under nitrogen. Benzyl bromide (0.20 mL, 1.7 mmol) was added 5 min later. The mixture was stirred overnight, poured into saturated NH_4Cl solution, and extracted with EtOAc. After evaporation, the crude oil was purified by column chromatography (SiO_2, 20:1 hexane/EtOAc) to afford compound **11** (300 mg) as a colorless oil: $[\alpha]_D$ −7.4° (*c* 2.0, $CHCl_3$); IR (film) 2956, 1742, 1724 cm^{-1}; ^{1}H NMR δ 7.40−7.10 (m, 10H), 5.23 (s,

2H), 4.81 (s, 1H), 4.68 (d, 1H, J = 8.4 Hz), 3.56 (s, 3H), 3.52−3.41 (m, 3H), 2.68 (d, 1H, J = 8.4 Hz), 2.27 (d, 1H, J = 8.4 Hz), 0.88 (s, 9H); ^{13}C NMR δ 177.91, 172.59, 170.39, 135.99, 134.96, 130.24, 128.67, 128.56, 128.40, 127.01, 98.63, 73.08, 69.64, 68.03, 61.19, 52.78, 39.53, 35.27, 33.18, 24.91; MS *m*/*z* (%) 450 (0.5), 408 (58), 91 (100).

(3*S*,6*R*,7a*R*)-3-*tert*-Butyl-1,6,7,7a-tetrahydro-6-methyl-5-oxopyrrolo[1,2-*c*]oxazole-6,7a-dicarboxylic Acid 7a-Methyl Ester (12). To a solution of compound **10** (110 mg, 0.33 mmol) in *tert*-butyl alcohol (10 mL) was added 20% $Pd(OH)_2/C$ (50 mg), and the mixture was hydrogenated at 1 bar and room temperature overnight. Filtration from the catalyst and concentration afforded the product **12**: mp >132 °C dec (from EtOAc/hexane); $[\alpha]_D$ −47.4° (*c* 0.14, $CHCl_3$); IR (KBr) 3118, 2938, 1748, 1716 cm^{-1}; ^{1}H NMR δ 10.0 (br, 1H), 4.85 (s, 1H), 4.82 (d, 1H, J = 8.7 Hz), 3.82 (s, 3H), 3.49 (d, 1H, J = 8.7 Hz), 2.81 (d, 1H, J = 14.4 Hz), 2.25 (d, 1H, J = 14.4 Hz), 1.76 (s, 3H), 0.90 (s, 9H); ^{13}C NMR δ 180.10, 174.45, 172.17, 97.88, 73.90, 69.42, 55.33, 53.03, 38.30, 35.33, 24.81, 23.69; MS *m*/*z* (%) 255 (0.1), 198 (4), 83 (100).

(3*S*,6*R*,7a*R*)-6-Benzyl-3-*tert*-butyl-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-6,7a-dicarboxylic Acid 7a-Methyl Ester (13). Compound **11** (250 mg, 0.54 mmol) was dissolved in *tert*-butyl alcohol (10 mL); then, 20% $Pd(OH)_2/C$ (90 mg) was added, and the mixture was hydrogenated at 1 bar and room temperature overnight. The catalyst was filtered off, and the solvent was removed under vacuum to give product **13** (200 mg, 100%): mp >133 °C dec (from hexane/EtOAc); $[\alpha]_D$ +9.1° (*c* 0.4, $CHCl_3$); IR (KBr) 3141, 2973, 1736, 1718 cm^{-1}; ^{1}H NMR δ 7.33−7.14 (m, 5H), 6.5 (br, 1H), 4.84 (s, 1H), 4.80 (d, 1H, J = 8.7 Hz), 3.77 (s, 3H), 3.54−3.38 (m, 3H), 2.67 (d, 1H, J = 14.7 Hz), 2.43 (d, 1H, J = 14.7 Hz), 0.93 (s, 9H); ^{13}C NMR δ 179.77, 172.03, 171.80, 134.52, 130.02, 128.50, 127.70, 97.94, 74.25, 69.22, 60.24, 53.09, 42.94, 35.34, 35.15, 24.93; MS *m*/*z* (%) 331 (0.3), 274 (36), 58 (72), 43 (100). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.33; H, 6.47; N, 3.57.

(3*S*,7a*R*)-3-*tert*-Butyl-1,6,7,7a-tetrahydro-5-oxopyrrolo-[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (17). To a solution of crude compound **9** (1.35 g) in *tert*-butyl alcohol (15 mL) was added 20% $Pd(OH)_2/C$ (0.45 g), and the mixture was hydrogenated at 1 bar and room temperature for 1 h. Filtration from the catalyst and concentration afforded the crude acid **16**, which was heated to 220 °C for 5 min. The crude product was purified by column chromatography (SiO_2, 10:1 hexane/EtOAc) to afford the bicycle **17** (650 mg, 75% over two steps): mp 82−83 °C (from EtOAc/hexane); $[\alpha]_D$ −50.2° (*c* 2.0, $CHCl_3$); IR (KBr) 2965, 1741, 1708 cm^{-1}; ^{1}H NMR δ 4.87 (s, 1H), 4.81 (d, 1H, J = 8.4 Hz), 3.79 (s, 3H), 3.44 (d, 1H, J = 8.4 Hz), 3.10 (m, 1H), 2.52 (m, 1H), 2.32 (m, 1H), 2.16 (m, 1H), 0.88 (s, 9H); ^{13}C NMR δ 178.42, 172.77, 96.43, 73.97, 72.01, 52.65, 35.72, 34.40, 29.68, 24.74; MS *m*/*z* (%) 226 (0.3), 184 (22), 58 (30), 43 (100). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.62; H, 7.84; N, 5.61.

Representative Procedure for the Alkylation of Bicycle 17. To a solution of compound **17** (146 mg, 0.61 mmol) in THF (7 mL), which was stirred at −78 °C, was added a solution of LDA in THF (1.0 M, 0.8 mL, 0.8 mmol). After the reaction mixture had been stirred at −78 °C for 1 h, iodomethane (45 μL, 0.73 mmol) was added, and stirring was continued for 3 h. The reaction was quenched with saturated NH_4Cl solution (20 mL) at −78 °C, and the mixture was extracted with 3 × 20 mL of diethyl ether. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Column chromatogaphy (SiO_2, 10:1 hexane/EtOAc) afforded the products **14a** (50 mg, 32%), **14b** (50 mg, 32%), and **14c** (35 mg, 22%).

(3*S*,6*S*,7a*R*)-3-*tert*-Butyl-1,6,7,7a-tetrahydro-6-methyl-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14a): mp 107−108 °C (from EtOAc/hexane); $[\alpha]_D$ −58.3° (*c* 0.42, $CHCl_3$); IR (KBr) 2956, 1738, 1707 cm^{-1}; ^{1}H NMR δ 4.81 (s, 1H), 4.79 (d, 1H, J = 9.0 Hz), 3.78 (s, 3H), 3.31 (d, 1H, J = 9.0 Hz), 2.75 (m, 1H), 2.39 (dd, 1H, J = 10.8, 13.8 Hz), 1.95 (dd, 1H, J = 10.8, 13.8 Hz), 1.43 (d, 3H, J = 7.8 Hz), 0.89 (s, 9H); ^{13}C NMR δ 183.32, 173.20, 97.70, 73.52, 70.85, 52.62, 40.19, 35.27, 34.61, 24.82, 18.41; MS *m*/*z* (%) 240 (0.6), 198 (40), 58 (72), 43 (100). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.11; H, 8.31; N, 5.31.

(3*S*,6*R*,7a*R*)-3-*tert*-Butyl-1,6,7,7a-tetrahydro-6-methyl-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14b): $[\alpha]_D$ −27.1° (*c* 0.76, $CHCl_3$); IR (film) 2961, 1743, 1718 cm^{-1}; ^{1}H NMR δ 4.87 (s, 1H), 4.82 (d, 1H, J = 8.7 Hz), 3.78 (s, 3H), 3.40 (d, 1H, J = 8.7 Hz), 3.33 (m, 1H), 2.54 (dd, 1H, J = 8.7, 13.2 Hz), 1.78 (dd, 1H, J = 8.7, 13.2 Hz), 1.18 (d, 3H, J = 6.9 Hz), 0.88 (s, 9H); ^{13}C NMR δ 180.01, 172.78, 96.19, 74.71, 69.61, 52.64, 39.85, 39.46, 35.81, 24.75, 14.92; MS *m*/*z* (%) 256 (0.3), 198 (100), 138 (40). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.96; H, 8.45; N, 5.27.

(3*S*,7a*R*)-3-*tert*-Butyl-1,6,7,7a-tetrahydro-6,6-dimethyl-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14c): $[\alpha]_D$ −28.5° (*c* 0.80, $CHCl_3$); IR (film) 2965, 1744, 1718 cm^{-1}; ^{1}H NMR δ 4.84 (s, 1H), 4.81 (d, 1H, J = 8.7 Hz), 3.78 (s, 3H), 3.28 (d, 1H, J = 8.7 Hz), 2.20 (d, 1H, J = 14.1 Hz), 2.05 (d, 1H, J = 14.1 Hz), 1.42 (s, 3H), 1.20 (s, 3H), 0.90 (s, 9H); ^{13}C NMR δ 184.62, 173.23, 97.52, 75.20, 68.67, 52.60, 44.98, 43.08, 35.34, 27.09, 26.59, 24.90; MS *m*/*z* (%) 270 (0.1), 212 (34), 58 (79), 43 (100).

Compounds 14d−f. Compounds **14d−f** were obtained analogously in yields of 57%, 22%, and 8%, respectively. Compound **14d** can also be prepared in 91% yield by heating acid **13** to 220 °C under nitrogen for 5 min.

(3*S*,6*S*,7a*R*)-6-Benzyl-3-*tert*-butyl-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14d): mp 130−131 °C (from EtOAc/hexane); $[\alpha]_D$ +32.9° (*c* 0.90, $CHCl_3$); IR (KBr) 2977, 1736, 1706 cm^{-1}; ^{1}H NMR δ 7.39−7.18 (m, 5H), 4.88 (s, 1H), 4.78 (d, 1H, J = 8.7 Hz), 3.80 (s, 3H), 3.32 (d, 1H, J = 8.7 Hz), 3.30 (br, 1H), 3.11−2.97 (m, 2H), 2.20−2.02 (m, 2H), 0.94 (s, 9H); ^{13}C NMR δ 181.68, 172.97, 138.69, 128.79, 128.53, 128.36, 126.49, 97.61, 73.53, 70.73, 52.59, 47.13, 37.97, 35.25, 31.31, 24.81; MS *m*/*z* (%) 331 (0.1), 316 (1), 274 (48), 43 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.55; H, 7.23; N, 4.00.

(3*S*,6*R*,7a*R*)-6-Benzyl-3-*tert*-butyl-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14e): $[\alpha]_D$ −28.8° (*c* 0.16, $CHCl_3$); IR (film) 2957, 1740, 1705 cm^{-1}; ^{1}H NMR δ 7.32−7.15 (m, 5H), 4.88 (s, 1H), 4.76 (d, 1H, J = 8.7 Hz), 3.73 (s, 3H), 3.51 (m, 1H), 3.29−3.23 (m, 2H), 2.63 (m, 1H), 2.32 (m, 1H), 1.85 (t, 1H, J = 12.6 Hz), 0.89 (s, 9H); ^{13}C NMR δ 178.67, 172.55, 138.78, 128.87, 128.57, 126.47, 96.29, 74.53, 69.64, 52.65, 46.70, 36.76, 36.25, 35.79, 24.76; MS *m*/*z* (%) 331 (0.4), 274 (100), 91 (29), 43 (32). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.51; H, 7.21; N, 3.90.

(3*S*,7a*R*)-6,6-Dibenzyl-3-*tert*-butyl-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14f): $[\alpha]_D$ −5.4° (*c* 0.28, $CHCl_3$); IR (film) 3028, 2957, 1742, 1712, 1732, 1720 cm^{-1}; ^{1}H NMR δ 7.36−7.09 (m, 10H), 4.60 (s, 1H), 4.24 (d, 1H, J = 8.4 Hz), 3.59 (s, 3H), 3.35 (d, 1H, J = 13.5 Hz), 3.30 (d, 1H, J = 13.2 Hz), 3.01 (d, 1H, J = 13.2 Hz), 2.48 (d, 1H, J = 13.5 Hz), 2.18 (d, 1H, J = 14.1 Hz), 2.05 (d, 1H, J = 14.1 Hz), 1.68 (d, 1H, J = 8.4 Hz), 0.85 (s, 9H); ^{13}C NMR δ 183.04, 173.34, 137.30, 136.74, 130.86, 130.81, 128.52, 128.25, 127.17, 126.89, 97.31, 72.27, 68.60, 55.43, 52.63, 45.05, 42.13, 35.22, 32.02, 24.93; MS *m*/*z* (%) 406 (1), 364 (100), 91 (54), 43 (49).

Preparation of Compounds 14g−i. To a solution of bicycle **17** (260 mg, 1.08 mmol) in THF (7.0 mL) under nitrogen were successively added solutions of LDA (1.5 M, 1.0 mL) and HMPA (1.0 mL) at −78 °C. After 1 h, 4-bromo-1,1-diphenylbutane (360 mg, 1.25 mmol) in THF (3.0 mL) was added. After 6 h at −78 °C, the reaction was quenched with saturated NH_4Cl solution. The product was extracted into EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Separation by column chromatography (SiO_2, 30:1 hexane/EtOAc) afforded starting material **17** (140 mg, 54% recovery) and compound **14g** (70 mg, 31%) besides traces of **14h** (2 mg) and **14i** (2 mg).

(3*S*,6*S*,7a*R*)-3-*tert*-Butyl-6-(4,4-diphenylbutyl)-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14g): colorless oil; $[\alpha]_D$ −19.0° (*c* 0.28, $CHCl_3$); IR (film) 2954, 1742, 1713 cm^{-1}; ^{1}H NMR δ 7.30−7.15 (m, 10H), 4.80 (s, 1H), 4.76 (d, 1H, J = 8.4 Hz), 3.92 (t, 1H, J = 4.8 Hz), 3.73 (s, 3H), 3.26 (d, 1H, J = 8.4 Hz), 2.58 (m, 1H), 2.28−1.69 (m, 6H), 1.42−1.32 (m, 2H), 0.88 (s, 9H); ^{13}C NMR δ 182.81, 173.18, 144.90, 144.76, 128.41, 127.78, 127.74, 126.13, 126.10, 97.90, 73.39, 70.83, 52.60, 50.93, 45.13, 35.21, 32.70, 32.40, 25.76, 24.86; MS *m*/*z* (%) 449 (6), 392 (100), 91 (16), 43 (18).

(3*S*,6*R*,7a*R*)-3-*tert*-Butyl-6-(4,4-diphenylbutyl)-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14h): colorless oil; $[\alpha]_D$ −29.6° (*c* 0.5, $CHCl_3$); ^{1}H NMR *δ* 7.30−7.14 (m, 10H), 4.84 (s, 1H), 4.78 (d, 1H, *J* = 8.7 Hz), 3.89 (t, 1H, *J* = 7.8 Hz), 3.75 (s, 3H), 3.33 (d, 1H, *J* = 8.7 Hz), 3.08 (m, 1H), 2.38 (m 1H), 2.11−1.24 (m, 7H), 0.86 (s, 9H); ^{13}C NMR *δ* 179.48, 172.76, 144.91, 128.44, 127.79, 127.74, 126.16, 126.13, 96.23, 74.67, 69.76, 52.68, 51.07, 44.93, 37.54, 35.83, 35.47, 30.36, 25.66, 24.78; MS *m*/*z* (%) 449 (6), 392 (94), 43 (18).

(3*S*,7a*R*)-3-*tert*-Butyl-6,6-bis(4,4-diphenylbutyl)-1,6,7,7a-tetrahydro-5-oxopyrrolo[1,2-*c*]oxazole-7a-carboxylic Acid Methyl Ester (14i): colorless oil; $[\alpha]_D$ −15.5° (*c* 1.2, $CHCl_3$); IR (film) 2953, 1742, 1714 cm^{-1}; ^{1}H NMR *δ* 7.29−7.12 (m, 20H), 4.67 (s, 1H), 4.63 (d, 1H, *J* = 8.4 Hz), 3.89 (t, 1H, *J* = 8.1 Hz), 3.83 (t, 1H, *J* = 8.1 Hz), 3.63 (s, 3H), 3.01 (d, 1H, *J* = 8.4 Hz), 2.03−0.96 (m, 14H), 0.84 (s, 9H); ^{13}C NMR *δ* 183.82, 173.26, 144.94, 144.92, 144.74, 144.72, 128.41, 128.40, 127.80, 127.77, 127.75, 126.15, 126.14, 126.07, 97.50, 74.11, 68.67, 52.42, 52.00, 50.85, 50.77, 37.79, 37.30, 35.86, 35.78, 35.74, 35.19, 24.93, 23.03, 22.39; MS *m*/*z* (%) 657 (5), 600 (45), 572 (12), 44 (100).

Representative Procedure for Hydrolysis: (*R*)-2-(Hydroxymethyl)glutamic Acid (1). A solution of compound **8** (930 mg, 2.97 mmol) in 6 N HCl (20 mL) was stirred under reflux overnight and then concentrated. Purification by reverse-phase column chromatography (C_{18}, 125 Å, Waters; H_2O as the eluent) and lyophilization afforded HMG (**1**; 580 mg, 91%): $[\alpha]_D$ −1.6° (*c* 1.0, H_2O); ^{1}H NMR (D_2O) *δ* 4.02 (d, 1H, *J* = 12.3 Hz), 3.75 (d, 1H, *J* = 12.3 Hz), 2.61−2.43 (m, 2H), 2.23−2.06 (m, 2H); ^{13}C NMR (D_2O) *δ* 176.13, 171.58, 64.35, 63.45, 28.15, 26.86. Anal. Calcd for $C_6H_{11}NO_5$·HCl·0.5H_2O: C, 32.37; H, 5.89; N, 6.29. Found: C, 32.22; H, 5.74; N, 6.16.

The following compounds were obtained analogously.

(2*R*,4*S*)-2-(Hydroxymethyl)-4-methylglutamic Acid (15a): $[\alpha]_D$ −18.2° (*c* 0.34, CH_3OH); IR (KBr) 3407, 1683 cm^{-1}; ^{1}H NMR (D_2O) *δ* 3.90 (d, 1H, *J* = 11.7 Hz), 3.70 (d, 1H, *J* = 11.7 Hz), 2.69 (m, 1H), 2.44 (dd, 1H, *J* = 9.3, 13.8 Hz), 1.96 (dd, 1H, *J* = 9.3, 13.8 Hz), 1.14 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD) *δ* 182.62, 176.34, 67.93, 67.05, 37.47, 37.08, 17.16. Anal. Calcd for $C_7H_{13}NO_5$·1.4HCl: C, 34.71; H, 5.99; N, 5.78. Found: C, 34.70; H, 5.59; N, 5.57.

(2*R*,4*R*)-2-(Hydroxymethyl)-4-methylglutamic Acid (15b): $[\alpha]_D$ +8.9° (*c* 0.18, CH_3OH); ^{1}H NMR (D_2O) *δ* 3.94 (d, 1H, *J* = 11.7 Hz), 3.64 (d, 1H, *J* = 11.7 Hz), 2.67 (m, 1H), 2.55 (dd, 1H, *J* = 9.0, 12.6 Hz), 1.78 (dd, 1H, *J* = 9.0, 12.6 Hz), 1.14 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (D_2O) *δ* 183.82, 177.99, 67.03, 66.20, 35.89, 35.51, 15.55.

(*R*)-2-(Hydroxymethyl)-4,4-dimethylglutamic Acid (15c): $[\alpha]_D$ −18.5° (*c* 0.13, MeOH); ^{1}H NMR (D_2O) *δ* 3.93 (d, 1H, *J* = 11.4 Hz), 3.64 (d, 1H, *J* = 11.4 Hz), 2.28 (d, 1H, *J* = 13.8 Hz), 2.05 (d, 1H, *J* = 13.8 Hz), 1.16 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (D_2O) *δ* 188.10, 179.55, 68.88, 67.42, 43.73, 43.06, 27.66, 27.19. Anal. Calcd for $C_8H_{15}NO_5$·0.5HCl: C, 43.00; H, 6.99; N, 6.27. Found: C, 42.72; H, 6.34; N, 6.06.

(2*R*,4*S*)-4-Benzyl-2-(hydroxymethyl)glutamic Acid (15d): $[\alpha]_D$ +70.4° (*c* 0.16, CH_3OH); IR (KBr) 3363, 1683 cm^{-1}; ^{1}H NMR (D_2O) *δ* 7.36−7.24 (m, 5H), 3.81 (d, 1H, *J* = 11.7 Hz), 3.62 (d, 1H, *J* = 11.7 Hz), 3.12−2.92 (m, 2H), 2.77 (m, 1H), 2.23−2.05 (m, 2H). Anal. Calcd for $C_{13}H_{17}NO_5$·0.7H_2O·0.1HCl: C, 55.07; H, 6.58; N, 4.94. Found: C, 54.96; H, 6.68; N, 4.49.

(2*R*,4*R*)-4-Benzyl-2-(hydroxymethyl)glutamic Acid (15e): $[\alpha]_D$ −33.9° (*c* 0.13, MeOH); IR (KBr) 3386, 1701, 1664 cm^{-1}; ^{1}H NMR (D_2O) *δ* 7.40−7.27 (m, 5H), 3.77 (d, 1H, *J* = 11.7 Hz), 3.24 (d, 1H, *J* = 11.7 Hz), 3.09−2.96 (m, 2H), 2.80 (m, 1H), 2.33 (m, 1H), 1.85 (m, 1H); ^{13}C NMR (D_2O) *δ* 184.14, 178.85, 140.94, 131.74, 131.16, 129.20, 69.49, 68.17, 44.39, 37.91, 33.99.

(*R*)-4,4-Dibenzyl-2-(hydroxymethyl)glutamic Acid (15f): $[\alpha]_D$ −8.2° (*c* 0.12, MeOH); IR (film) 3415, 1682 cm^{-1}; ^{1}H NMR (CD_3OD) *δ* 7.25−7.13 (m, 10H), 3.16 (d, 1H, *J* = 10.5 Hz), 3.15 (d, 1H, *J* = 13.5 Hz), 3.01 (d, 1H, *J* = 13.2 Hz), 2.65 (d, 1H, *J* = 13.2 Hz), 2.53 (d, 1H, *J* = 13.5 Hz), 2.32 (d, 1H, *J* = 14.7 Hz), 2.19 (d, 1H, *J* = 10.5 Hz), 1.80 (d, 1H, *J* = 14.7 Hz); ^{13}C NMR (CD_3OD) *δ* 181.92, 175.97, 138.85, 138.02, 131.90, 131.80, 129.56, 129.53, 128.13, 128.11, 69.44, 65.46, 52.65, 45.31, 44.03, 33.25. Anal. Calcd for $C_{20}H_{23}NO_5$·1.7HCl: C, 57.28; H, 5.70; N, 3.34. Found: C, 57.31; H, 5.62; N, 3.03.

(2*R*,4*S*)-4-(4,4-Diphenylbutyl)-2-(hydroxymethyl)glutamic Acid (15g): $[\alpha]_D$ −9.5° (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD) *δ* 7.25−7.09 (m, 10H), 3.91 (t, 1H, *J* = 7.8 Hz), 3.68 (d, 1H, *J* = 11.1 Hz), 3.61 (d, 1H, *J* = 11.1 Hz), 2.45 (m, 1H), 2.28 (m, 1H), 2.11−2.01 (m, 2H), 1.89−1.78 (m, 2H), 1.42−1.27 (m, 3H); ^{13}C NMR (CD_3OD) *δ* 181.80, 180.02, 146.82, 146.78, 129.54, 129.52, 129.05, 129.02, 127.18, 127.16, 68.84, 68.52, 52.63, 43.16, 36.77, 35.95, 32.71, 27.01.

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Supporting Information Available: ^{1}H NMR spectra of compounds **15a**−**g** together with tables of experimental X-ray data and ORTEP plots for compounds **8**, **12**, **13**, **14a**, **14d**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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