Total Synthesis of *N*-Methyl LTC_4: A Novel Methodology for the Monomethylation of Amines

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Introduction

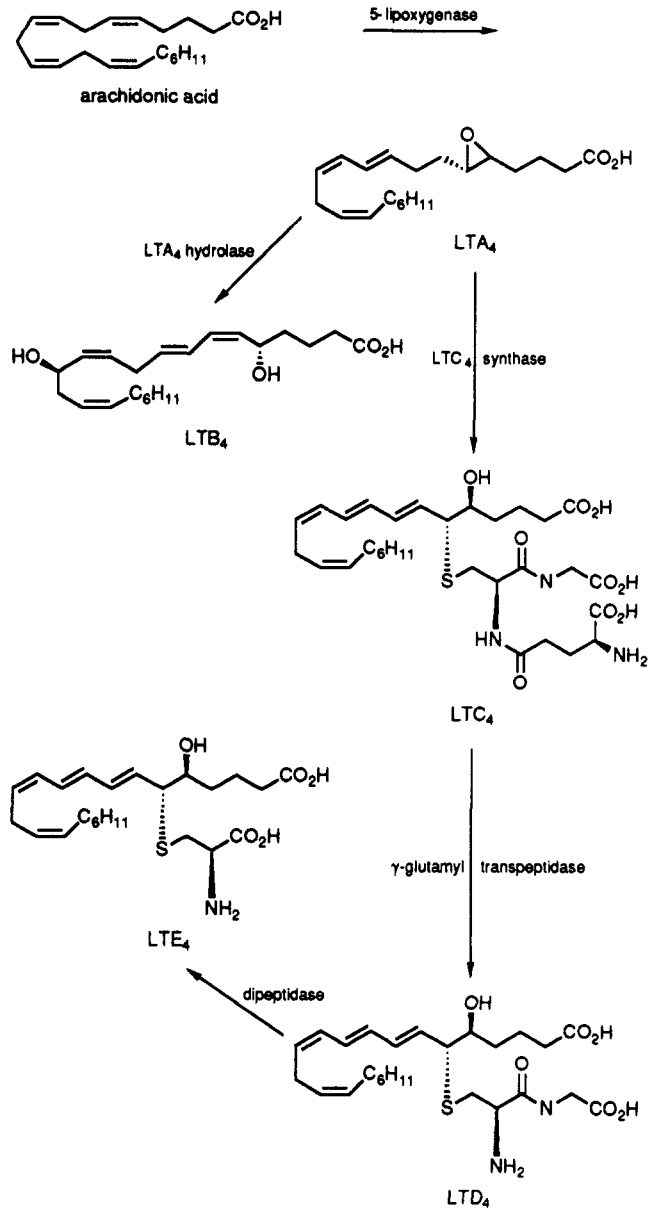
Since the history of leukotrienes began in 1938 with the discovery of a slow reacting substance released from lung by Feldberg and Kellaway,[1] the work done in this area has been enormous. First found in leukocytes, the term leukotriene would not be pronounced for the next 40 years until Samuelson noticed the indicative pattern of absorption of a triene unit by ultraviolet light and ascribed the term leukotriene.[2] Leukotrienes are believed to be involved in such diseases as bronchial asthma, psoriasis, and ulcerative colitis.[3] LTB_4 has been shown to be a potent chemotactic agent and a modulator of inflammatory responses. LTC_4, D_4, and E_4 are collectively known as slow reacting substances of anaphylaxis, SRS-A, or peptido-leukotrienes. They have potent acute pharmacological effects such as smooth muscle contraction and stimulation of bronchial constriction.

Arachidonic acid is transformed via the enzyme 5-lipoxygenase to LTA_4 which is transformed into two other leukotrienes (Scheme I). LTB_4 is formed by the action of LTA_4 hydrolase and LTC_4 synthase adds glutathione across the epoxide producing LTC_4. This in turn is cleaved at the glutamyl amide linkage by a second enzyme, glutamyl transpeptidase, to yield LTD_4. Finally, LTD_4 is cleaved at the amide level by a dipeptidase to give LTE_4.

All leukotrienes are contractile on the guinea pig ileum assay. Their potency is as follows $D_4 > C_4 \gg E_4$. LTC_4 is metabolized to LTD_4 and LTE_4 and makes their specific pharmacology study more difficult. Although there is no doubt as to the presence of a LTD_4 receptor, controversy still remains over the existence of one for LTC_4. It was clear that a synthetic analogue of C_4 that would not be metabolized to D_4 and E_4 would be a powerful tool in the characterization of the LTC_4 receptor.

It has been reported recently that the metabolism of LTC_4 can be blocked by adding a methyl group on the nitrogen of the glutamyl moiety.[4] However this analogue still retained the effects of the natural molecule, albeit at a lower level. This makes *N*-methyl LTC_4 a good mimetic for use in the research of the pharmacology of LTC_4. Herein we wish to report an efficient and practical synthesis of *N*-methyl LTC_4 and the application of this methodology to glutamic acid.

Scheme I



Results and Discussion

Methylation of primary amines is well documented in the literature.[5] The most used method is by treatment of an amine with formaldehyde and sodium cyanoborohydride.[5b,c] Unfortunately, this does not stop at the first alkylation but goes on to a dimethylated adduct. However, *N*-methyl amino acids can be prepared by the method of Quitt et al.[6] in which a temporary benzylation and a reductive methylation are involved. The yields reported on various amino acids vary from 3% to 42%.[5d] The lowest yield was obtained for *N*-methylglutamic acid. In our hands this approach was unsuccessful. A recent paper described the selective monoalkylation of amines using the Nakayama reagent, 1,3-benzodithiothiolylium tet-

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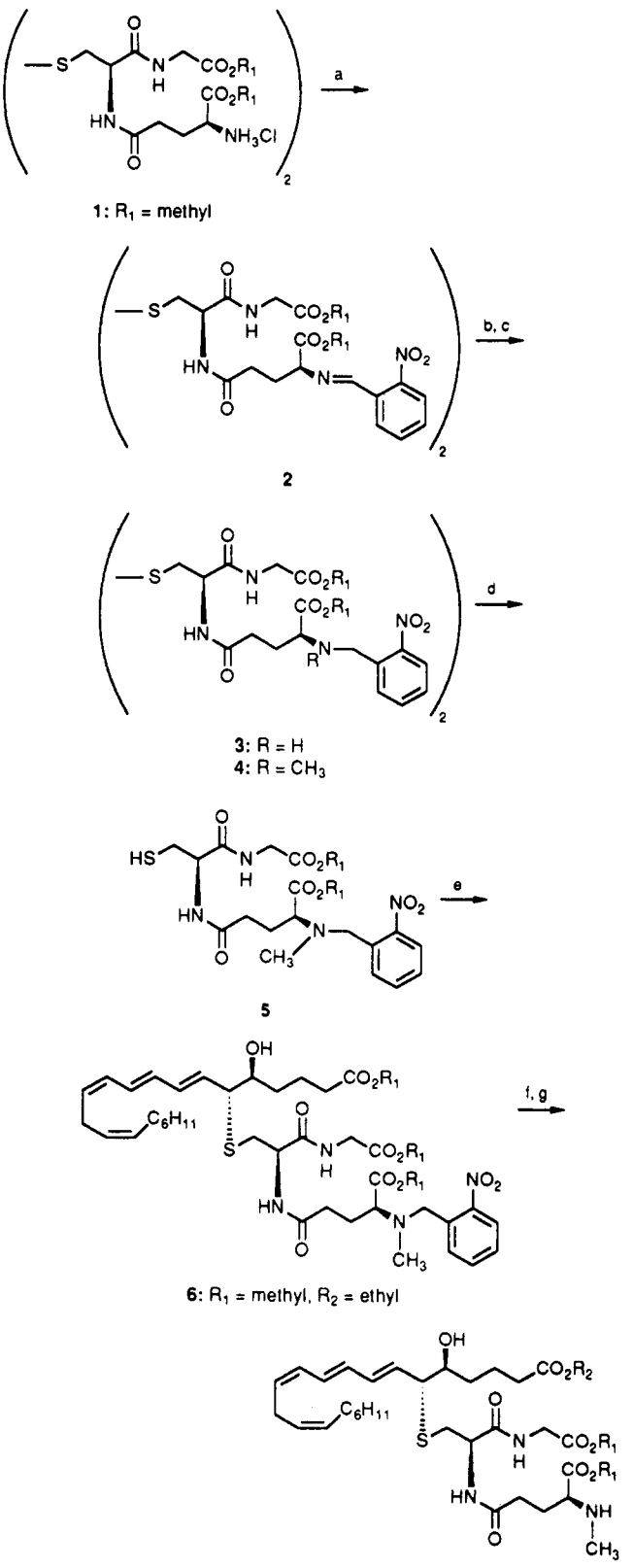
0022-3263/93/1958-1582$04.00/0

rafluoroborate (BDTF).[5a] This group attached to an amine can be converted to a methyl group by tributyltin hydride treatment in refluxing benzene.[5a] The major drawback is clear in the case of sulfur-containing peptides or with heat-sensitive molecules like leukotrienes. On the other hand, *o*-nitrobenzaldehyde derivatives have been used to protect nitrogen and carbonyl functions in peptides.[7] By irradiation at 350 nm the blocking group is readily removed. This deprotection is compatible with LTC_4 since the conjugated system of leukotrienes absorbs at wavelengths lower than 300 nm and therefore should not be affected. Our approach was to prepare the protected *N*-methyl peptide **5**. From there, standard addition to the epoxide of LTA_4 and removal of the photolabile group would give **8** (*N*-methyl LTC_4) after hydrolysis (Scheme II). Condensation of *o*-nitrobenzaldehyde with the esterified glutathione in water–MeOH gave, after vigourous stirring overnight, a white precipitate of the stable imine **2** (85%). Reduction of the imine using sodium cyanoborohydride while keeping the solution slightly acidic afforded the *o*-nitrobenzylamine **3** (75%). The reductive methylation used the same methodology of condensation–reduction with formaldehyde–$NaBH_3CN$. This one-pot reaction gave the protected *N*-methylglutathione **4** (85%). Reduction of the disulfide to the thiol **5** was accomplished using the Overman procedure.[8] Treatment of disulfide **4** with a mixture of triphenylphosphine, water, and HCl produced the thiol in 53% yield. Treatment of the thiol **5** with LTA_4 ethyl ester in methanol–triethylamine in the presence of a radical scavenger afforded 70% of protected *N*-methyl LTC_4 ester **6**.[9] The N-protecting group was cleanly removed by irradiation at 350 nm in a dioxane solution for 30 min. Chromatography on SiO_2 afforded the secondary amine **7** in 74% yield. The free acid was obtained after K_2CO_3 hydrolysis and purification by HPLC (33%). The UV spectra showed the characteristic pattern of LTC_4 with a λ_{max} = 281.4 nm.

In order to confirm that racemization does not occur using our monomethylation conditions,[7c] the sequence was repeated with glutamic acid (Scheme III). Condensation of glutamic acid dibenzyl ester hydrochloride (**9**)[10] with *o*-nitrobenzaldehyde followed by $NaBH_3CN$ reduction afforded the secondary amine **10** (64%). A second condensation/reduction with formaldehyde/$NaBH_3CN$ produced the *N*-methyl-protected glutamic acid **11** (80%). Removal of the photolabile group at 350 nm for 1 h gave the *N*-methylamine **12** (51%) which over a short period of time cleanly cyclized to the lactam **13**. Hydrogenolysis of γ-lactam **13** over palladium gave an almost quantitative yield of **14** (96%). The rotation of **14** $[\alpha]_D$ = −6.9°, compared very well with the published value of −7.6°.[11] This confirmed that the sequence occurs with little or no racemization. In summary, we developed a novel methodology for the selective monomethylation of amines which could be applied to a variety of amino acids and peptides. This methodology did not produce any racemization either

Scheme II[a]



[a] (a) *o*-Nitrobenzaldehyde, NaOH; 88%; (b) $NaBH_3CN$, 87%; (c) HCHO, $NaBH_3CN$; 85%; (d) Ph_3P, HCl; 53%; (e) LTA_4 ethyl ester, Et_3N; 70%; (f) *hν*; 74% (g) K_2CO_3; 33%.

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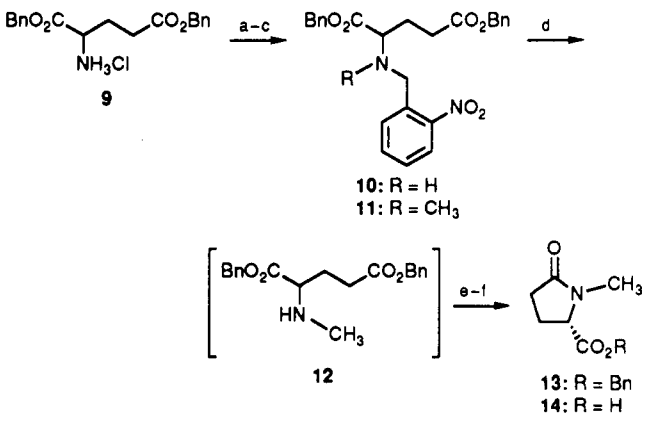
Scheme III[a]



[a] (a) *o*-Nitrobenzaldehyde, Et_3N; (b) $NaBH_3CN$; 64% (2 steps); (c) HCHO, $NaBH_3CN$; 80% (d) $h\nu$, 350 nm; 51%; (e) cyclization; (f) H_2/Pd–C; 96%.

during photoremoval of the *o*-nitrobenzyl group or two cyanoborohydride reductions.

Experimental Section

Preparation of Imine 2. A 1 M solution of NaOH (36 mL, 36 mmol) was added dropwise to a solution of oxidized glutathione dimethyl ester dihydrochloride (13.34 g, 18.0 mmol) in 100 mL of water and 20 mL of methanol, followed by solid *o*-nitrobenzaldehyde (5.44 g, 36 mmol) at 5 °C. The temperature was brought to 25 °C and the suspension was stirred vigorously for 6 h. The solid was filtered, washed with water, and dried overnight under high vacuum to give 14.40 g (88%) of the imine **2** as a white solid: ^{1}H NMR (DMSO-d_6, 250 MHz) δ 1.99 (m, 1 H), 2.17 (br s, 3 H), 2.78 (m, 1 H), 3.07 (m, 1 H), 3.59 (s, 3 H), 3.65 (s, 3 H), 3.81 (AB, 2 H, J = 14.4 Hz), 4.16 (m, 1 H), 4.59 (m, 1 H), 7.75 (m, 2 H), 7.97 (d, 1 H, J = 7.1 Hz), 8.06 (d, 1 H, J = 7.5 Hz), 8.30 (d, 1 H, J = 8.1 Hz), 8.45 (t, 1 H, J = 6.9 Hz) and 8.63 (s, 1 H).

Preparation of Amine 3. To a solution of imine **2** (14.04 g, 15.4 mmol) in 120 mL of CH_3CN and 60 mL of DMSO was added portionwise $NaBH_3CN$ (1.94 g, 30.8 mmol). The mixture was allowed to stir 3 h and was kept slightly acidic by the addition of acetic acid. The reaction mixture was then neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 200 mL). The organic phases were combined and dried ($MgSO_4$) and the solvent was removed leaving an oil which was purified by flash chromatography using a 95:5 dichloromethane–methanol mixture as the eluent. This afforded 12.25 g (87%) of amine **3**: ^{1}H NMR (CD_3OD, 250 MHz) δ 1.94 (m, 2 H), 2.39 (t, 2 H, J = 7.7 Hz), 2.89 (m, 1 H), 3.18 (m, 2 H), 3.63 (s, 3 H), 3.69 (s, 3 H), 3.94 (s, 2 H), 3.98 (AB, 2 H, J = 14.4 Hz), 4.85 (m, 1 H), 7.46 (m, 1 H), 7.64 (d, 2 H, J = 4.0 Hz) and 7.91 (d, 1 H, J = 7.8 Hz); MS, m/z 967 (M^+ + 1).

Preparation of Tertiary Amine 4. To a solution of the previous amine (8.89 g, 9.7 mmol) in 400 mL of CH_3CN and 100 mL of DMSO was added 4 mL of formaldehyde (37%), followed 5 min later by $NaBH_3CN$ (1.19 g, 18.9 mmol) portionwise as in the preparation of **3**. This afforded 7.77 g (85%) of the tertiary amine **4**: ^{1}H NMR (CD_3OD, 250 MHz) δ 1.98 (m, 2 H), 2.16 (s, 3 H), 2.32 (m, 2 H), 2.95 (m, 1 H), 3.18 (m, 1 H), 3.35 (m, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 3.96 (m, 4 H), 4.84 (m, 1 H), 7.48 (m, 1 H), 7.62 (d, 2 H, J = 4.0 Hz) and 7.80 (d, 1 H, J = 7.9 Hz). Anal. Calcd for $C_{40}H_{54}N_8O_{16}S_2$: C, 49.68; H, 5.63; N, 11.59. Found: C, 49.69; H, 5.69; N, 11.94.

Preparation of Thiol 5. To a solution of disulfide **4** (1.01 g, 1.1 mmol) and triphenylphosphine (0.50 g, 1.9 mmol) in 12 mL of peroxide-free DME and 5 mL of water was added 0.4 mL of concentrated HCl. The reaction mixture was stirred overnight and the DME was evaporated. The aqueous phase was washed with CH_2Cl_2 and was then neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were combined, dried ($MgSO_4$), and evaporated. The crude oil obtained was purified by flash chromatography using a 95:5 dichloromethane–methanol mixture as the eluent to afford 0.54 g (53%) of the thiol: ^{1}H NMR (CD_3OD, 250 MHz) δ 2.01 (m, 2 H), 2.17 (s, 3 H), 2.31 (m, 2 H), 2.86 (m, 2 H), 3.37 (m, 1 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 3.96 (m, 4 H), 4.53 (t, 1 H, J = 6.4 Hz), 7.55 (m, 1 H), 7.60 (m, 2 H) and 7.81 (d, 1 H, J = 7.8 Hz); MS, m/z 485 (M^+ + 1).

Preparation of *N*-Methyl-*N*-(*o*-nitrobenzyl) LTC$_4$ Dimethyl Ethyl Ester (6). To a solution of LTA_4 ethyl ester (0.300 g, 0.86 mmol) and 1 crystal of 4-hydroxytempo in 6 mL of methanol–triethylamine (3:1) was added thiol **5** (0.518 g, 1.20 mmol), and the mixture was allowed to stir overnight. The solvent was removed and the crude oil was purified by flash chromatography using a 50:50–2.5:2.5 hexane–ethyl acetate–methanol–triethylamine mixture as the eluent to afford 0.471 g (70%) of the eicosatetraene **6**: ^{1}H NMR (CD_3OD, 250 MHz) δ 0.91 (t, 3 H, J = 6.8 Hz), 1.14 (t, 3 H, J = 7.1 Hz), 1.28–2.10 (m, 13 H), 2.18 (s, 3 H), 2.32 (m, 4 H), 2.70 (m, 1 H), 2.95 (m, 3 H), 3.40 (m, 2 H), 3.66 (m, 1 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 3.97 (m, 2 H), 4.12 (m, 4 H), 4.58 (m, 1 H), 5.38 (m, 3 H), 5.66 (m, 2 H), 6.02 (t, 1 H, J = 10.9 Hz), 6.27 (m, 2 H), 6.60 (m, 1 H), 7.50 (m, 1 H), 7.62 (m, 2 H) and 7.83 (d, 1 H, J = 7.9 Hz); MS, m/z 831 (M^+).

Preparation of *N*-Methyl LTC$_4$ Dimethyl Ethyl Ester (7). A solution of **6** (0.130 g, 0.14 mmol) in 50 mL of dioxane was poured equally in three pyrex tubes under nitrogen. The tubes are disposed as to touch the UV lamp and irradiated at 350 nm for 40 min with no stirring. No cooling system was necessary during the course of the reaction. The solvent was removed and the crude oil purified by flash chromatography using a 2:3 hexane–ethyl acetate mixture as the eluent containing 5% of triethylamine and 5% of methanol to afford 0.083 g (76%) of the deprotected amine **7**: ^{1}H NMR (CD_3OD, 250 MHz) δ 0.92 (t, 3 H, J = 6.9 Hz), 1.20–1.85 (m, 13 H), 2.02 (m, 4 H), 2.13 (m, 7 H), 2.68 (m, 1 H), 2.96 (m, 3 H), 3.33 (m, 2 H), 4.65 (m, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.97 (AB, 2 H, J = 7.1 Hz), 4.11 (q, 2 H, J = 7.2 Hz), 4.55 (m, 1 H), 5.40 (m, 3 H), 5.66 (m, 1 H), 6.04 (t, 1 H, J = 10.9 Hz), 6.15 (m, 2 H) and 6.60 (m, 1 H); HRMS calcd for $C_{35}H_{58}O_9N_3S$ (M^+ + 1) 696.3893, found 696.3879.

Preparation of *N*-Methyl LTC$_4$ (8). To a solution of *N*-methyl LTC_4 triester **7** (0.190 g, 0.27 mmol) and 1 crystal of 4-hydroxytempo in 1 mL of methanol was added 2 mL of K_2CO_3 (2 M). The reaction mixture was stirred 2 days protected from light. It was then diluted with 8 mL of methanol–water (1:1) and the pH adjusted to 6 with acetic acid. The product was purified by HPLC on a Bondapak-C_{18} column (50 × 300 mm) with CH_3CN–NaH_2PO_4 buffer (2 g/L) at pH = 6.5 with a flow of 100 mL/min (t_R = 14.8 min). The solvents were removed until ca. 15 mL of water was left. The amount of product was determined to be 0.057 g (33%) by UV. An aliquot was taken and lyophilized to give a white solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (t, 3 H, J = 6.9 Hz), 1.28–1.41 (m, 7 H), 1.46 (m, 1 H), 1.59 (m, 2 H), 1.77 (m, 1 H), 2.06 (m, 3 H), 2.17 (t, 1 H, J = 6.9 Hz), 2.28 (t, 1 H, J = 6.6 Hz), 2.54 (m, 2 H), 2.68 (m, 7 H), 2.95 (m, 3 H), 3.37 (m, 1 H), 3.53 (m, 1 H), 3.66 (m, 1 H), 3.78 (m, 2 H), 4.53 (m, 1 H), 5.36 (m, 3 H), 5.64 (m, 1 H), 6.01 (t, 1 H, J = 11.0 Hz), 6.24 (m, 2 H) and 6.57 (m, 1 H); HRMS calcd for $C_{31}H_{50}O_9N_3S$ (M^+ + 1) 640.3262, found 640.3265.

Preparation of *N*-(*o*-Nitrobenzyl)-L-glutamic Acid Dibenzyl Ester (10). To a mixture of glutamic acid dibenzyl ester hydrochloride (4.60 g, 12.4 mmol) in 50 mL of THF was added 1.7 mL of triethylamine, followed by solid *o*-nitrobenzaldehyde (1.88 g, 12.4 mmol). After 2 h of stirring, the solvent was removed to give the crude imine. Some characteristic peaks by proton NMR are (250 MHz, CD_3OD) δ 4.1 (m, 1 H), 4.9 (s, 2 H), 5.0 (s, 2 H), 7.1 (m, 10 H), 7.7 (d, 1 H, J = 7.5 Hz), 7.9 (d, 1 H, J = 7.5 Hz) and 8.45 (s, 1 H). The crude imine was dissolved in 50 mL of DMSO and $NaBH_3CN$ (0.31 g, 49.6 mmol) was added. The reaction mixture was treated as in the preparation of **3**. The crude solid obtained was purified by flash chromatography using a 7:3 hexane–ethyl acetate mixture as the eluent to afford 3.66 g (64%) of the protected amine **10**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.03 (m, 1 H), 2.15 (m, 2 H), 2.60 (t, 2 H, J = 7.4 Hz), 3.42 (m, 1 H), 4.10 (AB, 2 H, J = 14.6 Hz), 5.19 (s, 2 H), 5.23 (s, 2 H), 7.44 (m, 11 H), 7.62 (m, 2 H) and 7.98 (d, 1 H, J = 7.9 Hz); MS, m/z 463 (M^+ + 1).

Preparation of *N*-Methyl-*N*-(*o*-nitrobenzyl)-L-glutamic Acid Dibenzyl Ester (11). To a solution of amine **10** (3.56 g,

7.7 mmol) in 100 mL of CH_3CN was added an aqueous solution of formaldehyde (3.1 mL, 37%). After 10 min $NaBH_3CN$ (0.48 g, 7.7 mmol) was added and the reaction mixture was treated as in the preparation of **3**. The crude oil was purified by flash chromatography using a 4:1 hexane–ethyl acetate mixture as the eluent to afford 2.92 g (80%) of the tertiary amine **11**: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.06 (m, 2 H), 2.17 (s, 3 H), 2.40 (dt, 2 H, J = 1.8 Hz and J = 7.9 Hz), 3.41 (m, 1 H), 4.03 (AB, 2 H, J = 14.7 Hz), 5.17 (AB, 4 H, J = 12.3 Hz), 7.33–7.49 (m, 13 H) and 7.79 (d, 1 H, J = 7.7 Hz); IR (neat) 3030, 2960, 1735, 1525, 1355, 1155, 725 and 695 cm^{-1}.

Preparation of *N*-Methyl-L-glutamic Acid Dibenzyl Ester (12). A solution of the previous *o*-nitrobenzyl **11** (0.171 g, 0.35 mmol) in 116 mL of dioxane was irradiated 1 h at 350 nm as described for compound **7**. The solvent was removed and the crude oil was purified by flash chromatography using a 7:3 hexane–ethyl acetate mixture as the eluent to afford 62 mg (51%) of the unprotected amine **12**: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.69 (br s, 1 H), 1.95 (m, 2 H), 2.32 (s, 3 H), 2.46 (t, 2 H, J = 7.4 Hz), 3.21 (m, 1 H), 5.10 (s, 2 H), 5.15 (s, 2 H), and 7.33 (m, 10 H). In most runs cyclization occurred to give *N*-methyl-L-2-oxopyrrolidine-5-carboxylic acid benzyl ester (**13**): ^1H NMR ($CDCl_3$, 250 MHz) δ 2.00–2.15 (m, 1 H), 2.30–2.50 (m, 3 H), 2.84 (s, 3 H), 4.15 (m, 1 H), 5.20 (s, 2 H) and 7.37 (m, 5 H); IR (neat) 2950, 1740, 1700, 1395, 1185, 750, and 695 cm^{-1}; MS, m/z 234 (M^+ + 1).

Preparation of *N*-Methyl-L-2-oxopyrrolidine-5-carboxylic Acid (14). A solution of benzyl ester **13** (0.423 g, 1.81 mmol) in 10 mL of methanol was hydrogenated over palladium (40 mg) overnight. The suspension was filtered and the solvent removed to give 0.250 g (96%) of lactam **14** as a white solid: ^1H NMR (CD_3OD, 250 MHz) δ 2.06–2.11 (m, 1 H), 2.30–2.45 (m, 3 H), 2.83 (s, 3 H), and 4.20 (m, 1 H); mp 157–158 °C (lit.[4] mp 158 °C), $[\alpha]^{23}_D$ = –6.9° (c 1.05, H_2O), (lit.[4] $[\alpha]_D$ = –7.6°); HRMS calcd for $C_6H_{10}O_3N$ (M^+ + 1) 144.0661, found 144.0677.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds described in the Experimental Section (24 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.