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SYNTHESIS OF A RADIOLABELED TYPE A CHOLECYSTOKININ RECEPTOR ANTAGONIST, (*R*)-N-PENTYL-N-(4,5-DI[^{3}H]PENTYL) N_α-(3-QUINOLINOYL)GLUTAMIC ACID AMIDE

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Summary

A method for the preparation of a radiolabeled CCK_A-specific antagonist, (*R*)-N-pentyl-N-(4,5-di[^{3}H]pentyl) N_α-(3-quinolinoyl)glutamic acid amide, [^{3}H]-A-65186, is described. (*R*)-γ-Benzyl-N-BOC-glutamic acid was coupled with N-(4-pentenyl)-N-pentylamine using BOPCl and TEA in dichloromethane to provide the corresponding amide. Deprotection of the α-amino moiety followed by coupling with 3-quinolinecarboxylic acid in the presence of EDCI, TEA, and HOBt in dichloromethane resulted in (*R*)-N-(4-pentenyl)-N-pentyl γ-benzyl-N_α-(3-quinolinoyl)glutamic acid amide. Tritiation with concomitant hydrogenolysis of the benzyl ester proceeds smoothly to provide [^{3}H]-A-65186.

Key words: *CCK_A antagonist, benzodiazepinone, cholecystokinin, ^{3}H, amide coupling*

Introduction

Cholecystokinin (CCK) is a peptide that is found throughout the central nervous system and in neurons and endocrine cells of the gastrointestinal tract.[1] Two CCK receptor subtypes have been identified. A CCK_A subtype is found in various peripheral

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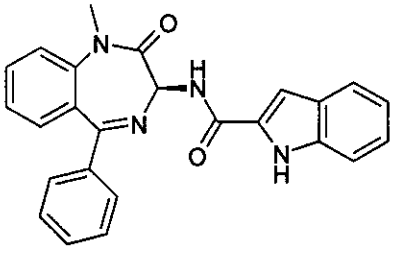
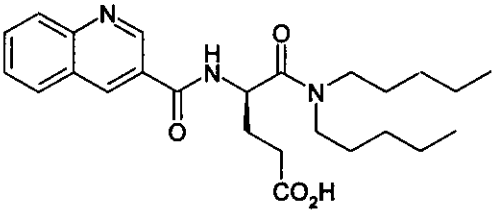
tissues and in discrete regions of the brain. A separate CCK_B subtype is found throughout the central nervous system and in the stomach. Highly selective antagonists have been developed for each subtype, including CCK_A-selective devazepide[2] (also called L364,718 and MK-329) and A-65186[3] (**1**) and CCK_B-selective L-365,260[4] and PD-134308.[5]



devazepide



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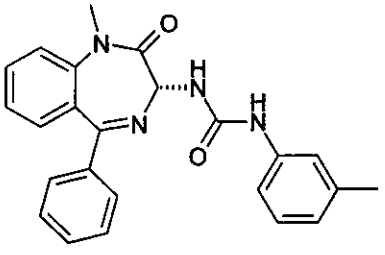
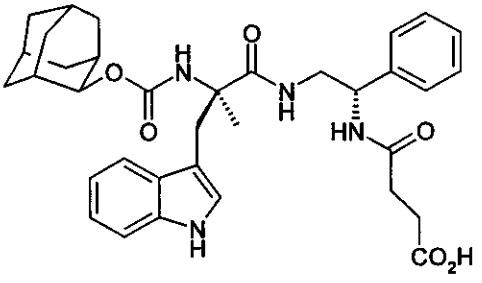
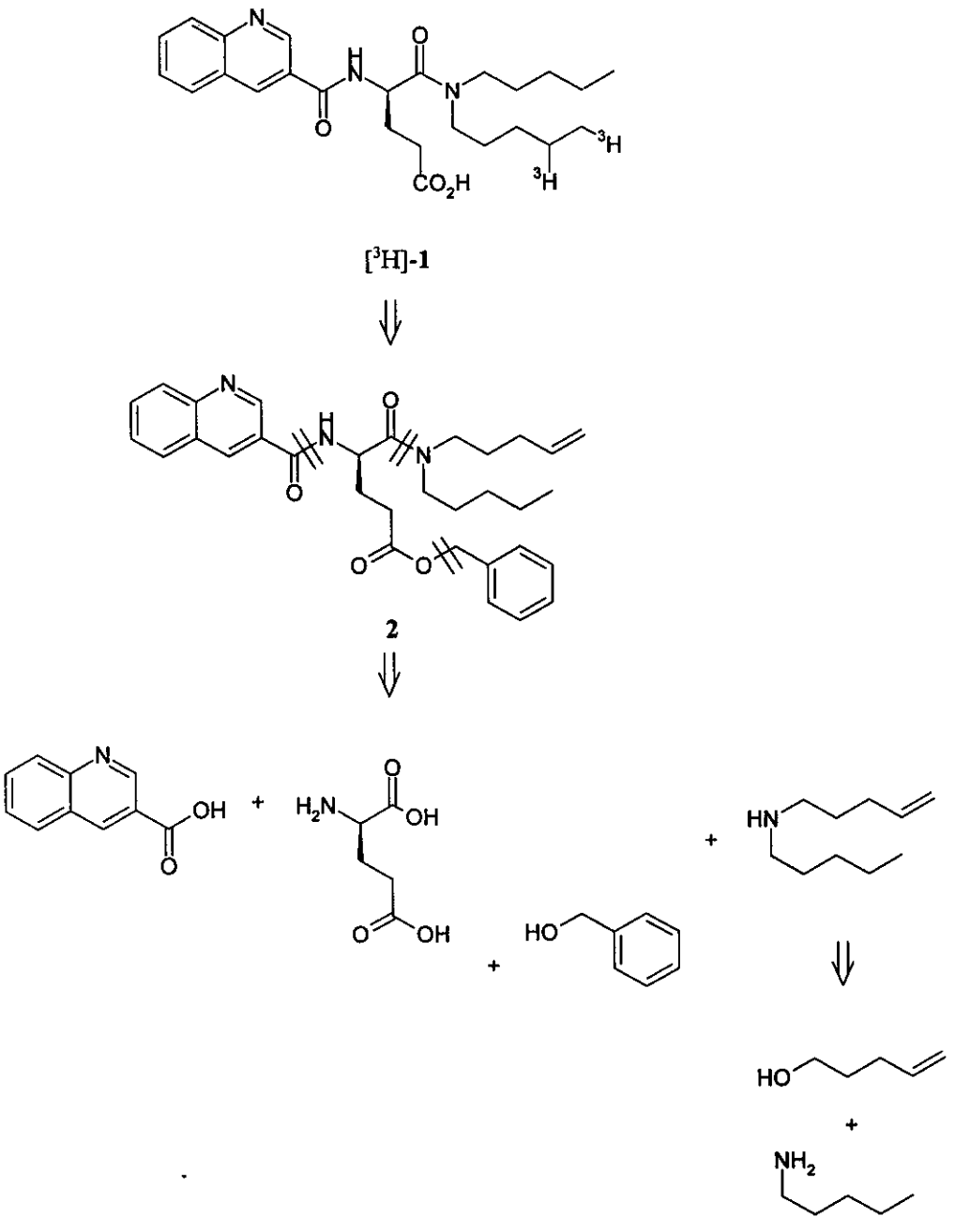


L-365,260



PD-134308

Peripheral administration of the CCK_A antagonist devazepide stimulates food intake in a variety of species,[6] suggesting that CCK plays an essential role in mediating satiety. Where or how CCK is acting is not clear, however. Devazepide penetrates the blood brain barrier,[7] suggesting that CCK may produce satiety by acting peripherally or in the brain. To clarify the relative importance of central versus peripheral CCK mechanisms in control of food intake, a study was designed to compare the feeding effects of systemic administration of CCK_A-specific antagonists that differ in their ability to penetrate the blood-brain barrier. Central to this study was quantitation of the blood-brain barrier permeabilities of devazepide and **1**.[8] To this end, a synthesis of (*R*)-N-pentyl-N-(4,5-di[^{3}H]pentyl)N_α-(3-quinolinoyl)glutamic acid amide, [^{3}H]-A-65186 ([^{3}H]-**1**) was designed and executed.

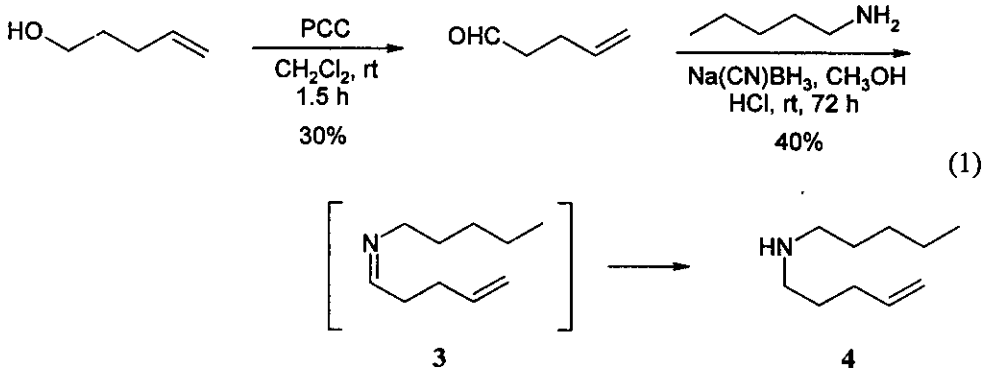


Scheme 1. Retrosynthesis of [^{3}H]-**1**.

Results and Discussion

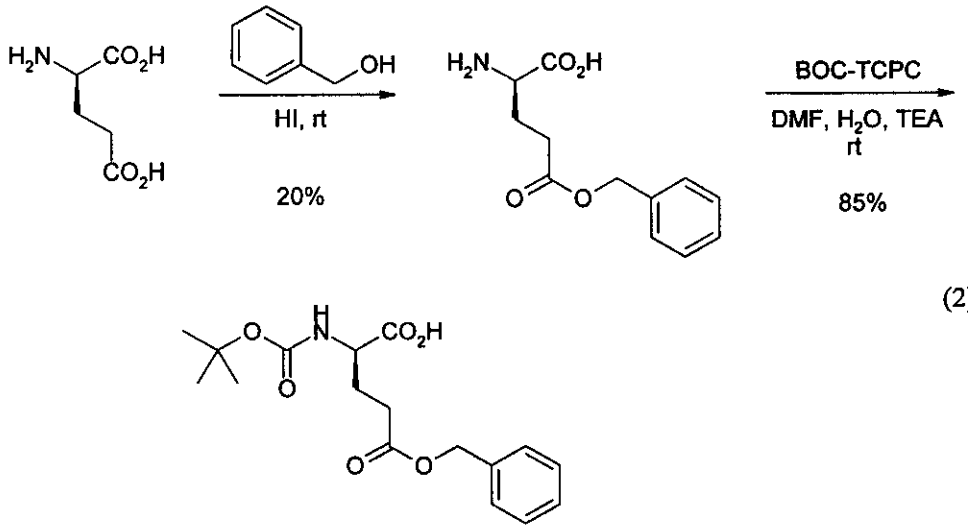
Retrosynthetic analysis. [^{3}H]-A-65186 ([^{3}H]-**1**) should be available in a manner analogous to the nontritiated compound.[3] Three straightforward disconnections (Scheme 1) indicate that [^{3}H]-**1**can be derived from γ-O-benzylated (*R*)-glutamic acid, coupling with an unsaturated amine to provide a glutamic acid 1-amide, and final couping with 3-quinolinecarboxylic acid. Tritium labeling of resultant **2** *via* tritiation, with concomitant debenzylation, would provide the target CCK_A ligand. The approach offers additional flexibility for increased specific activity of [^{3}H]-A-65186 if required: coupling with a polyunsaturated amine allows for incremental, two-fold increases in the initial desired specific activity of 50 Ci/mmol.

Synthesis of N-(4-pentenyl)-N-pentylamine (**4**). Essentially unknown,[9] two approaches to secondary amine **4** were investigated: direct displacement of a primary tosylate by pentylamine and reductive amination. Conversion of commercially available 4-penten-1-ol to the corresponding tosylate[10] proceeded in 88% yield, but S_N2 displacement of this tosylate by pentylamine[11] was largely unsuccessful, as expected.[12] Alternatively and more successfully, 4-penten-1-ol first was oxidized to the corresponding aldehyde using pyridinium chlorochromate (PCC)[13] in CH_2Cl_2 (eq 1). Reductive amination using pentylamine at pH 7 with sodium cyanoborohydride[14] provided **4** directly, *via* corresponding imine **3**.



(1)

Synthesis of (R)-γ-benzyl-N_α-t-butoxycarbonylglutamic acid (**5**). Coupling of **4** to (*R*)-glutamic acid required that the amino acid be appropriately protected. γ-Benzylation was performed using the method described for the (*S*)-enantiomer.[15] This method was determined to be effective in monoesterification, but otherwise relatively nonregioselective: although monoesters were found by titrimetry to have formed in 70% yield, only about 30% of this mixture was the desired γ-benzyl ester, the balance presumably being the unwanted regioisomer. The γ-benzyl ester was easily converted to its N_α-BOC derivative **5** using *t*-butyl 2,4,5-trichlorophenylcarbonate (BOC-TCPC, eq 2).[16] Compound **5** was obtained as a very thick oil even when determined to be solvent- and impurity-free by HPLC, TLC, and ^{1}H NMR. Crystalization ultimately occurs upon prolonged standing (≥ 5 months).

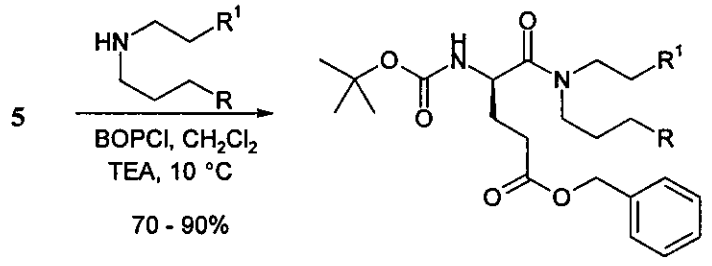


(2)

5

Synthesis of (R)-N-(4-pentenyl)-N-pentyl γ-benzyl-N_α-t-butoxycarbonylglutamic acid amide (**7**). Protected amino acid **5** was found to undergo efficient amide formation upon treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, eq 3).[17] Small-scale investigations using dipropylamine proceeded very cleanly to provide **6** (mp 58-59 °C); on gram scale, amide formation was incomplete but starting acid could

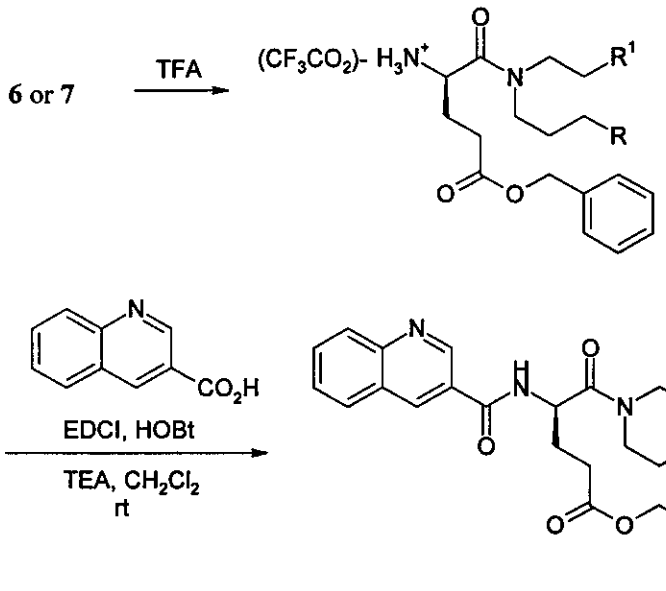
be removed by simple washing with aq Na_2CO_3. When 1.0 g of amine **4** was condensed with **5**, amide **7** was isolated in 70% yield.



(3)

6 (R = H, $R^1 = CH_3$)
7 (R = CH_2CH_3, $R^1 = CH_2CH{=}CH_2$)

Synthesis of (R)-N-(4-pentenyl)-N-pentyl γ-benzyl-$N_α$-(3-quinolinoyl)glutamic acid amide (**2**). Removal of the $N_α$-BOC protecting group prior to final coupling using 3-quinolinecarboxylic acid with 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) proved to be troublesome: typical conditions to prepare the hydrochloride[18] resulted in substantial recovery of starting material. A series of small-scale optimization studies was performed wherein a *ca.* 100 mg sample of **6** was deprotected using either 4 M HCl in 1,4-dioxane or trifluoroacetic acid (TFA).[19] After work-up, drying of the resultant salt overnight *in vacuo* was followed by amide coupling using EDCI and HOBt with triethylamine (TEA) as an acid scavenger (eq 4).[20] Couplings were monitored colorimetrically using ninhydrin.[21] The data (Table 1) clearly indicated optimal conditions for deprotection and coupling of **6** to be deprotection using TFA in CH_2Cl_2 at 0 °C for 30 min followed by removal of the solvent, excess TFA, and any isobutylene and CO_2 that had formed *in vacuo*. The resultant trifluoroacetic acid salt was coupled with a 10% excess of 3-quinolinecarboxylic acid using a 1.1/3.3/1.1 equiv ratio of HOBt/TEA/EDCI. Standard aqueous work-up, followed by preparative TLC, gave pure **8** (eq 4). Amide **7** was found to behave similarly (Table 2); application of these optimized conditions to a 2 g sample of amide **7** provided **2** in 65% isolated chemical yield (entry 3, Table 2).



(4)

8 (R = H, $R^1 = CH_3$)
2 (R = CH_2CH_3, $R^1 = CH_2CH{=}CH_2$)

Table 1. Synthesis of **8** from **6**.

equiv **6**	deprotection	work-up	R^2CO_2H[a]	equiv HOBt	equiv TEA	equiv EDCI	% yield
1.0	4 M HCl	aq	1.0	0.1	2.0	1.0	0
1.0	4 M HCl	aq	1.0	0.2	2.0	2.0	19
1.0	4 M HCl	aq	1.1	1.0	2.2	1.1	10
1.0[b]	4 M HCl	aq	1.1	1.1	3.3	1.1	6
1.0	4 M HCl	direct	1.1	1.1	2.2	1.1	17
1.0	TFA	aq	1.1	1.1	2.2	1.1	28
1.0	4 M HCl	aq	1.1	1.1	3.3	1.1	14
1.0	TFA	aq	1.1	1.1	3.3	1.1	58
1.0	TFA	direct	1.1	1.1	3.3	1.1	54

a. R^2 = 3-quinolinoyl.
b. R^2CO_2H was preactivated by mixing with HOBt/TEA/EDCI for 1 h before adding **6**.

Table 2. Synthesis of **2** from **7**.

equiv 7	deprotection	work-up	R^2CO_2H[a]	equiv HOBt	equiv TEA	equiv EDCI	% yield
1.0	4 M HCl	direct	1.1	1.1	2.2	1.1	33
1.0	TFA	direct	1.1	1.1	2.2	1.1	51
1.0[b]	TFA	direct	1.1	1.0	3.3	1.1	65

a. R^2 = 3-quinolinoyl.
b. 1.99 g **7** used.

Synthesis of (R)-N-pentyl-N-(4,5-di[^{3}H]pentyl) N_α-(3-quinolinoyl)glutamic acid amide, [^{3}H]-A-65186 ([^{3}H]-**1**). Hydrogenolysis of benzyl–oxygen bonds occurs readily using 10% Pd on C and low pressures of H_2, typical conditions for hydrogenation of isolated alkenes.[22] An analog of **2** with a N_α-(4,8-dihydroxy-2-quinolinoyl) substituent is known to undergo transfer hydrogenation: the glutamic acid side chain is debenzylated in 60% isolated chemical yield.[3b] It was expected, then, that radiolabeling with ^{3}H by $^3H_2$ over Pd on C in ethanol would proceed efficiently and with debenzylation (eq 5). Thus, a 130 mg sample of **2** was submitted to the Du Pont/Merck Pharmaceuti-

$$\mathbf{2} \xrightarrow[\substack{10\%\ Pd/C,\ rt \\ EtOH}]{^3H_2} [^3H]\text{-}\mathbf{1} \qquad (5)$$

cals Radiopharmaceutical Division for synthesis of [^{3}H]-**1**. In the event, tritium incorporation with concomitant hydrogenolysis of the benzyl ester proceeded smoothly to provide 2.1 mCi of a 1.9 mCi · mL^{-1} ethanol solution of [^{3}H]-**1** with specific activity of 92.0 Ci · mmol^{-1}. A radiochemical purity of 98.9 % was determined by thin layer chromatography/autoradiography versus authentic **1**[23] and was in agreement with the results of HPLC analyses using coinjections of [^{3}H]-**1** and **1** with dual detection by radioactivity and UV absorption, which provided a radiochemical purity of 99.6%.

Conclusion

A concise, convergent gram-scale synthesis of (*R*)-N-(4-pentenyl)-N-pentyl γ-benzyl-N_α-(3-quinolinoyl)glutamic acid amide (**2**) for preparation of the radiolabeled CCK_A ligand (*R*)-N-pentyl-N-(4,5-di[^{3}H]pentyl) N_α-(3-quinolinoyl)glutamic acid amide, [^{3}H]-A-65186 ([^{3}H]-**1**), has been developed. Tritiation with concomitant hydrogenolysis of the benzyl ester proceeds smoothly to provide the title compound.

Experimental

NMR spectra were obtained on a Varian Inova 300 spectrometer. IR spectra were obtained as thin films, KBr pellets, or as solutions in $CHCl_3$ on Perkin-Elmer 1420 or Nicolet Impact 410 spectrometers. UV/Vis spectra were obtained using a Varian Carey Bio 3 spectrometer. High performance liquid chromatography (HPLC) was performed on a LDC Milton Roy chromatograph using an Alltech Econosphere™ 5 μ, 250 x 4.6 mm C_{18} column with detection at 254 nm. Medium pressure liquid chromatography (MPLC)[24] was performed using EM Separations Lobar® silica columns and TLC employed Analtech standard silica gel 60 plates. High resolution mass spectrometric analyses were performed by the Nebraska Center for Mass Spectrometry, Lincoln, NE. Diethyl ether was distilled from sodium-benzophenone; DMF and CH_2Cl_2 were distilled from CaH_2. All other reagents were used as received. (*R*)-γ-Benzylglutamic acid[15] and (*R*)-γ-benzyl-N_α-BOC-glutamic acid[16] (**5**) were prepared as described.

4-Penten-1-al. A 250 mL round bottom flask equipped with a magnetic stirring bar was charged with 18.77 g (87.08 mmol) of PCC and 116 mL of CH_2Cl_2. Stirring was begun as 5.01 g (58.16 mmol) of 4-penten-1-ol in 11.6 mL of CH_2Cl_2 was added in one portion. After stirring for 1.5 h, 116 mL of ether was added and the supernatant solution decanted off from the black oily residue which had formed. The oily residue was washed well three times with 30 mL portions of ether, and the combined ether supernatants filtered through Florisil.® Rotary evaporation at 40 °C afforded the crude aldehyde, which was fractionally distilled to yield 1.44 g (30%) of 4-pentenal: bp 65-70 °C (151 mm). ^{1}H NMR($CDCl_3$): δ 9.81 (s, 1H), 5.85 (m, 1H), 5.08 (m, 2H), 2.60 (t, *J*=5.5 Hz, 2H), 2.42 (apparent q, *J*=8.5 Hz, 2 H) ppm. ^{13}C NMR($CDCl_3$): δ 175.74, 136.40,

115.65, 42.72, 26.08 ppm. IR(thin film): 3080 (w), 2980 (w), 2910 (w), 2820 (w), 2730 (w), 1725 (s), 1645 (m), 995 (m), 920 (s) cm^{-1}.

N-(4-Pentenyl)-N-pentylamine (**4**). A 100 mL round bottom flask equipped with magnetic stirring bar, condenser, and N_2 inlet was charged with a solution of 11.9 mL (102.5 mmol) of pentylamine in 43 mL of anhydrous methanol. 6.9 mL of a 5 M solution of HCl in methanol was added carefully, followed by 1.44 g (17.1 mmol) of 4-pentenal, 512.7 mg (10.2 mmol) of $Na(CN)BH_3$, and *ca.* 1 mL of 3 Å molecular sieves. The mixture that resulted was left to stir at room temperature under N_2 for 72 h. After that time, the reaction was cooled in an ice-water bath, and conc. HCl was added to adjust the pH of the reaction mixture to 2. Rotary evaporation of the methanol was followed by the addition of 17 mL of water. Washing with three 35 mL portions of ether was followed by adjusting the pH of the aqueous layer to 10 using solid KOH. NaCl was added to near saturation, and the resultant mixture extracted five times with 25 mL portions of ether. The combined ether extracts were dried through $MgSO_4$; rotary evaporation afforded the crude product, which was purified by Kugelrohr distillation to provide 1.00 g (40%) of N-(4-pentenyl)-N-pentylamine: bp 85-85 °C (17 mm). ^1H NMR($CDCl_3$): δ 5.83 (m, 1H), 5.05 (m, 2H), 2.65 (q, *J*=7.2 Hz, 4H), 2.35 (br s, 1H, exchanges with D_2O), 2.13 (q, *J*=9.6 Hz, 2H), 2.65 (pentet, *J*=8.2 Hz, 2H), 1.58 (pentet, *J*=7.7 Hz, 2H), 1.37 (br s, 4H), 0.93 (t, *J*=7.0 Hz, 3H) ppm. ^{13}C NMR($CDCl_3$): δ138.31, 114.72, 49.82, 49.28, 31.52, 29.54, 29.42, 28.89, 22.56, 13.99 ppm. IR(thin film): 3300 (w), 3080 (w), 2920 (s), 1640 (m), 1460 (m), 1130 (m), 990 (w), 910 (s) cm^{-1}.

(R)-N-(4-Pentenyl)-N-pentyl γ-benzyl-N_α-t-butoxycarbonylglutamic acid amide (**7**). A 25 mL round bottom flask equipped with magnetic stirring bar and N_2 inlet was charged with 1.00 g (6.44 mmol) of N-(4-pentenyl)-N-pentylamine and a solution of 2.1780g (6.44 mmol) of (*R*)-γ-benzyl-N_α-BOC-glutamic acid in 13 mL of CH_2Cl_2. Stirring was begun as the flask was cooled to 10 °C. 1.6537 g (6.44 mmol) of BOPCl was added in one portion; the cooling bath then was removed and the reaction left to warm to room temperature over 3.5 h. After this time, 13 mL of water was added and the flask contents were transferred to a separatory funnel. The pH of the funnel contents was adjusted to 1-2 using 4 M HCl, 50 mL of CH_2Cl_2 was added, and the funnel contents shaken well. The organic layer was washed three times with 10 mL of 0.1 M Na_2CO_3,

until the pH of the aqueous layer was 10-11. Each time, before drawing off the organic layer 100 mL of water was added to facilitate separation. The organic layer then was dried through $MgSO_4$, and concentrated by rotary evaporation. 2.2106 g (72%) of (*R*)-N-(4-pentenyl)-N-pentyl γ-benzyl-N_α-t-butoxycarbonylglutamic acid amide was isolated as a semisolid having R_f = 0.35 (2:1 hexanes:ether): ^{1}H NMR($CDCl_3$): δ 7.39 (br s, 5H), 5.84 (m, 2H), 5.42 (two s, 1H), 5.23 (m, 2H), 5.17 (s, 2H), 4.67 (m, 1H), 3.52 (m, 2H), 3.32-3.04 (br m, 2H), 2.50 (m, 2H), 2.08 (m, 2H), 1.90-1.50 (br m, 5H), 1.44(s, 9H), 1.34 (m, 3H), 0.94 (two t, *J*=7.0 Hz, 3H) ppm. The latter two triplets presumably are due to rotational isomerism. Rotameric populations are also plainly apparent in the ^{13}C NMR spectrum: ^{13}C NMR($CDCl_3$): δ 172.76, 171.50, 155.46, 137.70, 137.22, 135.93, 128.49, 128.15, 115.58 and 115.06, 79.51, 66.32, 49.39, 47.72 and 46.98, 45.96 and 45.58, 31.03 and 30.76, 29.67, 29.04 and 28.85, 28.92, 28.29, 28.19, 27.20 and 26.68, 22.38, 13.94 ppm. IR($CHCl_3$): 3420 (w), 3020 (m), 2960 (m), 1725 (s), 1705 (s), 1635 (s), 1500 (s), 1450 (m), 1430 (m), 1170 (s) cm^{-1}.

(R)-N-(4-Pentenyl)-N-pentyl γ-benzyl-N_α-(3-quinolinoyl)glutamic acid amide (2). A 50 mL round bottom flask equipped with a magnetic stirring bar and N_2 inlet was charged with a solution of 1.9857 g (4.18 mmol) of (*R*)-N-(4-pentenyl)-N-pentyl γ-benzyl-N_α-t-butoxycarbonylglutamic acid amide in 17.6 mL of CH_2Cl_2. Stirring was begun as the flask was cooled to 0 °C using an ice-water bath. 17.6 mL of 0 °C TFA was added to the flask and the reaction stirred at 0 °C for 30 min. The stirring bar then was removed and the TFA and CH_2Cl_2 removed by rotary evaporation. The flask then was held at room temperature and evacuated overnight (16 h) at 0.1 mm. Venting to N_2 was immediately followed by addition of a solution of 0.7978 g (4.60 mmol) of 3-quinolinecarboxylic acid, 0.6247 g (4.60 mmol) HOBt, and 2.0 mL (13.8 mmol) of TEA in 51 mL of CH_2Cl_2. A stirring bar was added and stirring under N_2 begun. 0.8918 g (4.60 mmol) of EDCI was added in one portion and the reaction left to stir at room temperature overnight (16 h). After this time, a small aliquot of the reaction was assayed for remaining aminoamide using ninhydrin according to a modified version of Kaiser's method.[21] Essentially no aminoamide was found to remain. The solvents were removed by rotary evaporation and the crude product dissolved in 100 mL of ethyl acetate. The ethyl acetate solution was washed three times with 30 mL aliquots of 0.1 M citric acid,

three times with 30 mL aliquots of saturated Na_2CO_3, three times with 30 mL aliquots of water, and once with 30 mL of brine. Drying through $MgSO_4$ and removal of the ethyl acetate by rotary evaporation gave a thick oil, which was purified by MPLC (Lobar® size C column, 1% CH_3OH in $CHCl_3$) to give 1.45 g (65%) of pure (*R*)-N-(4-pentenyl)-N-pentyl γ-benzyl-N_α-(3-quinolinoyl)glutamic acid amide: R_f = 0.27 (1% CH_3OH in $CHCl_3$). HPLC retention time 3.5 min (1.5 mL/min 70/30 CH_3CN/H_2O). ^1H NMR($CDCl_3$): δ 9.22 (s, 1H), 8.49 (s, 1H), 8.36 (t, *J*=7.0 Hz, 1H), 8.06 (d, *J*=8.1 Hz, 1H), 7.73 (t, *J*=6.8 Hz, 1H), 7.70 (d, *J*=8.1 Hz, 1H), 7.52 (d, *J*=6.8 Hz, 1H), 7.30 (m, 5 H), 5.82 (m, 1H), 5.24 (br m, 1H), 5.12 (s, 2H), 5.00 (m, 2H), 3.60 (m, 2 H), 3.33 (m, 1H), 3.11 (sextet, *J*=7.3 Hz, 1H), 2.61 (m, 2H), 2.40-1.15 (br m, 14 H), 0.94 and 0.86 (two t, *J*=7.1 Hz, 3H) ppm. The latter two triplets coalesce when heated to 80 °C in DMSO-d_6. Rotameric populations are also plainly apparent in the ^{13}C NMR spectrum: ^{13}C NMR($CDCl_3$): δ 172.47 and 172.46, 171.40 and 171.34, 165.18 and 165.17, 148.88, 148.52, 137.34, 137.01, 135.21, 130.87, 129.01, 128.52, 128.28, 127.97, 127.95, 127.02, 126.41 and 125.83, 115.55 and 114.97, 66.25, 48.96 and 48.91, 47.78 and 47.00, 46.11 and 45.72, 30.81 and 30.60, 29.78, 28.83 and 28.71, 28.67, 27.93 and 27.81, 27.04 and 26.52, 22.14 and 22.12, 13.80 and 13.73 ppm. IR(thin film): 3280 (m), 3060 (w), 2920 (s), 1730 (s), 1630 (s), 1530 (m), 1300 (m), 1170 (m), 915 (m), 790 (m), 730 (s), 695 (m) cm^{-1}. λ_{max}(CH_3CN) 208 (ε=8300), 234 (ε=10,500), 276 (ε=1800), 318 (ε=900). HRMS (EI) calcd for $C_{32}H_{39}N_3O_4$: 529.2940; found 529.2923.

(R)-N-Pentyl-N-(4,5-di[^{3}H]pentyl) N_α-(3-quinolinoyl)glutamic acid amide, [^{3}H]-A-65186 ([^{3}H]-**1**). 130 mg (246 μmol) of (*R*)-N-(4-pentenyl)-N-pentyl γ-benzyl-N_α-(3-quinolinoyl)glutamic acid amide was submitted to the Du Pont/Merck Pharmaceuticals Radiopharmaceutical Division, Boston MA for radiolabeling with concomitant hydrogenolysis of the benzyl ester. An approximately 22.8 nmol sample was radiolabelled by hydrogenation in ethanol to provide 2.1 mCi of [^{3}H]-**1** at a concentration of 1.9 mCi · mL^{-1} and specific activity of 92.0 Ci · $mmol^{-1}$. Chemical and radiochemical purities were determined chromatographically versus authentic **1**.[23] TLC ($CHCl_3$:CH_3OH, 4:1): R_f 0.37. Autoradiography provided a radiochemical purity of 98.9%. HPLC (Zorbax SB-C18 #CL3804, pH 4.0 1% triethylammonium acetate solution:CH_3CN, 2:3 at 1 mL·min^{-1}) of a sample of [^{3}H]-**1** and authentic **1** with dual

channel detection using Pico-fluor 40 (channel 1) and UV (channel 2) serial detectors gave a single peak with channel 1, R_t 7.28 min, radiochemical purity 99.6 %, and channel 2, R_t 7.10 min. Instrument offset was determined to be 0.09 ± 0.2 min.

Acknowledgments

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