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Practical and Enantiospecific Synthesis of LY303870, a Novel NK-1 Antagonist

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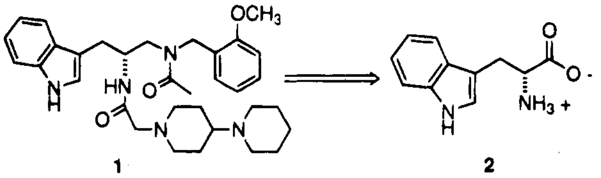
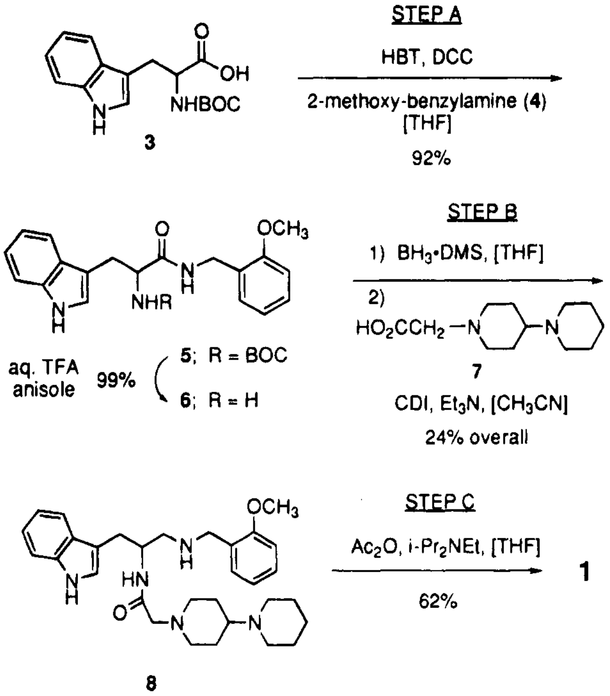
NK-1 antagonists have been postulated to be useful in a variety of human pathologies where NK-1 receptor overactivation has been implicated (i.e. persistent pain,[1] migraine,[2] and asthma[3]). In order to further develop and test this concept in humans, practical and highly enantiospecific syntheses of these agents are required. We recently discovered a series of 3-aryl-1,2-diacetamidopropane NK-1 antagonists.[4] This note describes an enantiospecific synthesis of one of the more interesting congeners of the series, LY303870 (**1**),[5] from (*R*)- tryptophan (**2**).



1 **2**

Frequently N_α-carbamate (*tert*-butyl (BOC) and benzyl (CBZ)) protective groups are called upon for the manipulation of α-amino acid starting materials with less than optimal results. Our own original racemic synthesis of (±)-**1** starting from N_α-BOC-tryptophan, outlined in Scheme 1 (five steps, 14% overall yield), stands as an example of the pitfall of such an approach. After smoothly coupling **3** with **4**, attempts to selectively reduce the resulting amide **5** were met with considerable difficulties. Typical outcomes were low yields of *deprotected* (both diamino- and methylamino-amino) reduction products. Under no circumstance was the BOC group found to be stable; therefore it was necessarily removed just after coupling (step A). Unfortunately this resulted in the need to rely on a low yielding and poorly selective reduction/acylation sequence (step B) as well as the requirement to confront highly polar, unprotected compounds later in the sequence. In essence, the BOC group was useful for only one of the five steps.

Scheme 1



To improve the situation, derivatization of the α-amine functionality of (*R*)-tryptophan with a protecting group stable to reductive conditions was indicated. The often overlooked triphenylmethyl (trityl)[6] and 9-phenylfluorenyl (9-PhFl)[7] amino protective groups were considered to allow for (1) the selective functional group reductive manipulation of the carboxylate carbon in the presence of the α-nitrogen, (2) faithful retention of the stereochemistry at the α-carbon of **2**, and (3) additional lipophilic character in otherwise polar materials. This conceptually different approach should allow us to operate at the level of a differentially functionalized diamine as well as proceed with the synthesis in an enantiospecific manner.

For our synthesis, the trityl group was chosen; but to our surprise, an efficient and enantiospecific preparation of (*R*)-trityltryptophan directly from (*R*)-tryptophan had not been described in the literature.[8] Theodoropoulos *et al.* described a procedure wherein simple amino acids could be α-aminotritylated after *in situ* silylation of the carboxylate; however, trityltryptophan was notably missing as an example.[9] We were able to modify their procedures and apply it to (*R*)-tryptophan (Scheme 2). Careful and complete *in situ* protection of the carboxylate as the silyl ester in ethyl acetate was accomplished by

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(1) (a) Levine, J. D.; Fields, H. L.; Basbaum A. I. *J. Neurosci.* **1993**, *13*, 2273–2286. (b) Otsuka, M.; Yanagisawa, M. *Cell Molec. Neurobiol.* **1990**, *10*, 293–302. (c) Lotz, M.; Carson, D. A.; Vaughan, J. H. *Science* **1987**, *235*, 893–895. (d) Marabini, S.; Matucci-Cerinic, M.; Geppetti, P.; Del Bianco, E.; Marchesoni, A.; Tosi, S.; Cagnoni, M.; Partsch, G. *Ann New York Acad. Sci.* **1991**, *632*, 435–436.

(2) Moskowitz, M. A. *Trends Pharmacol. Sci.* **1992**, *13*, 307–311.

(3) (a) Bertrand, C.; Geppetti, P.; Baker, J.; Yamawaki, I.; Nadel, J. A. *J. Immunology* **1993**, *150*, 1479–1485. (b) Frossard, N.; Advenier, C. *Life. Sci.* **1991**, 19541–19543.

(4) Hipskind, P. A.; Howbert, J. J.; Nixon, J. A.; Lobb, K. L.; Waters, D. C.; Threlkeld, P. G.; Gitter, B. D. Unpublished results.

(5) Gitter, B. D.; Bruns, R. F.; Howbert, J. J.; Waters, D. C.; Threlkeld, P. G.; Cox, L. M.; Nixon, J. A.; Lobb, K. K.; Mason, N. R.; Stengel, P. W.; Cockerham, S. L.; Silbaugh, S. A.; Gehlert, D. R.; Schober, D. A.; Iyengar, S.; Calligaro, D. O.; Regoli, D.; Hipskind, P. A. *J. Pharmacol. Exp. Ther.* **1995**, in press.

(6) Allen, M. C.; Brundish, D. E.; Fullerton, J. D.; Wade, R. *J. Chem. Soc. Perkin Trans. 1* **1986**, 989. Matsoukas, J.; Tsefenidis, T.; Cordopatis, P.; Theodoropoulos, D. M. *Tetrahedron* **1984**, *40*, 1869. Halstrom, J.; Kovacs, K.; Brunfeldt, K. *Acta. Chem. Scand.* **1973**, *27*, 3085.

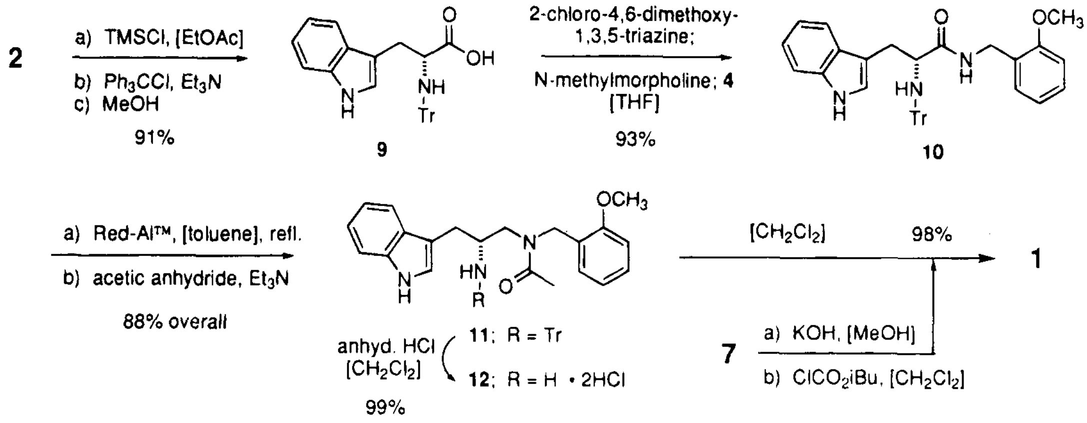
(7) Recent uses of the phenylfluorenyl amino protective group have been reported. See: Park, K. H. Rapoport, H. *J. Org. Chem.* **1994**, *59*, 394. Jamison, T. F. Rapoport, H. *Org. Synth.* **1993**, *71*, 226.

(8) The reviewers pointed out a low yielding procedure of unknown enantiospecificity. Stelakaos, G. C.; Theodoropoulos, D. M.; Zervas, L. *J. Am. Chem. Soc.* **1959**, *81*, 2884.

(9) Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324.

0022-3263/95/1960-7033$09.00/0

Scheme 2



heating the reaction mixture at reflux for 4 h with chlorotrimethylsilane.[10] This was followed by tritylation and desilylation to give (*R*)-trityltryptophan (**9**) in 91% yield. Assessment of the enantiomeric purity of this material was attempted by chiral HPLC, but proved to be inconclusive; therefore further derivatization was necessary. Coupling of **9** with **4** using 2-chloro-4,6-dimethoxy-1,3,5-triazine[11] (CDMT) produced the benzylamide **10** in 93% yield. This method was chosen only on the basis of cost over carbodiimide (DCC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI)) methods, which worked equally well. A high degree of overall enantiospecificity was indicated for the two first steps; compound **10** was obtained in greater than 99% enantiomeric excess as analyzed by chiral stationary phase HPLC.[12]

Attempted reductions of **10** with LAH or borane–dimethyl sulfide led to the observations of incomplete and no observed reaction, respectively. In both cases reaction mixtures were observed to be thick slurries upon addition of the reducing agent as well as after periods of elevated temperature. Subsequently, amide **10** was found to be smoothly reduced upon treatment with Red-Al in toluene at reflux.[13] In this case the reaction mixture was found to form and persist as a solution upon addition of Red-Al. The product amine was isolable in high yield; however, we found it more expedient to directly acylate the crude material. This provided tritylacetamide **11** in an 88% overall yield. Treatment of a solution of tritylacetamide **11** in methylene chloride with anhydrous hydrogen chloride removed the trityl group and generated the crystalline dihydrochloride salt of the product amine **12** in high yield.[14] This particular protocol eliminated a troublesome acetyl migration (secondary to primary amine) which was observed with formic acid deprotection conditions.[15]

Finally the 2-(4-(piperidin-1-yl)piperidin-1yl)acetate side chain (**7**) was installed. While stepwise strategies were initially investigated, a convergent approach was found to be much more acceptable. Mixed anhydride acylation procedures (potassium salt of **7**, isobutyl chloroformate) were used to directly couple **7** and **12** to give **1** in 98% yield.[16] Compound **7** was prepared by reacting methyl α-bromoacetate and 4-(piperidin-1-yl)piperidine under phase transfer conditions followed by saponification with KOH in methanol.

The enantiospecificity of the above process was further inspected at two additional stages. Both aminoacetamide **12** and the target compound **1** were found to be >98% and >99.5% enantiomeric excess, respectively, using chiral stationary phase HPLC analysis and asymmetric mobile phase capillary electrophoresis, respectively.[17]

While intermediates **9**, **10**, and **12** were crystalline materials and therefore may have undergone enantiomeric enrichment during the crystallization processes, the high overall chemical (73%) and final optical yield of this convenient, five-step process, is quite noteworthy. Further, the utility of the trityl amino protective group (verses carbamate groups) in the enantio- and regiospecific functional group transformation of amino acid building blocks as well as a direct preparation of (*R*)-N$_\alpha$-trityltryptophan (**5**) from (*R*)-tryptophan are exemplified. Anecdotally the trityl group also imparted additional beneficial physical properties (crystallinity) to many of the intermediates encountered in this synthesis (vs the original BOC based approach). This synthesis has been executed at a scale of 22 L (4 mol).

Experimental Section

Preparation of (*R*)-N_α-Trityltryptophan (9). A stirred slurry of (*R*)-tryptophan (**2**) (801.7 g, 3.925 mol) in 10 L of ethyl acetate was warmed to 40 °C. Chlorotrimethylsilane (447.8 g, 1.05 equiv) was added over a 30 min period while maintaining good agitation. The reaction mixture was then heated to reflux temperature. After stirring for 2–4 h, the mixture was cooled to 40 °C, and triethylamine (834 g, 2.10 equiv) and trityl chloride

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[10] Incomplete initial carboxylate silylation clearly led to lower enantiospecificity as measured at the stage of compound **10**.

[11] Kaminski, Z. J. *Tetrahedron Lett.* **1985**, *26*, 2901–2904.

[12] Analysis of the enantiomeric purity of **10**: HPLC column, 25 cm × 4.6 mm Whelk 01 (Regis Chemical Co.); eluent 50% 2-propanol in hexane; flow 1.0 mL/min; temperature 45 °C; detection 230 nm. Retention times were as follows: (*R*) isomer, 5.5 min; (*S*) isomer, 6.5 min.

[13] For a review of alkoxyaluminohydride reductions see: Malek, J.; Cerny, M. *Synthesis* **1972**, 217–234.

[14] Applegate, H. E.; Cimarusti, C. M.; Dolfini, J. E.; Funke, P. T.; Koster, W. H.; Puar, M. S.; Slusarchyk, W. A.; Young, M. G. *J. Org. Chem.* **1979**, *44*, 811–818.

[15] Acetyl migration can be a problem during deprotections of amines. See: Fuentes, J. Cuevas, T. Pradera, M. A. *Synth. Commun.* **1994**, *24*, 2237–2245.

[16] Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1967**, *89*, 5012–5017.

[17] Conditions for analysis of enantiomeric purity of **12**: HPLC column, 15 cm Chiracel OD-H 316-11-21217; eluent 20% *n*-propyl alcohol in hexane; flow 1.0 min; temp 40 °C detection 278 nm. Retention times were as follows: (*R*) isomer, 9.8 min; (*S*) isomer, 12.6 min. Conditions for analysis of enantiomeric purity of **1**: capillary zone electrophoresis; column, open tube silica; eluant 1.2% methyl-β-cyclodextrin in a 100 mM phosphate buffer, pH adjusted to 2.5; running voltage 20 kV; detection 200 nm; temp 30 °C. Approximate retention times were as follows: (*R*) isomer, 18.2 min; (*S*) isomer, 17.7 min.

(1.3 kg, 1.03 equiv) were added. The reaction mixture was stirred overnight at 40 °C. Methanol (139.6 g, 1.11 equiv) was added while maintaining good agitation. After stirring for 30 min at 40 °C, the reaction mixture was cooled to room temperature and washed twice with an aqueous solution of 5% citric acid. Ethyl acetate was removed *in vacuo*, and heptane was added to crystallize the product. The crystalline product was isolated by filtration and the filter cake was washed with heptane and dried under vacuum at 40 °C to give 1.60 kg, a 91% yield of **9**: mp 210 °C dec; ^{1}H (300 MHz, CDCl$_3$) δ 2.9 (dd, 1H, J = 5.8, 14.5 Hz), 3.15 (dd, 1H, J = 5.9, 14.5 Hz), 3.77 (dd, 1H, J = 5.8, 5.9 Hz), 6.9−7.6 (m, 22H), 8.06 (s, 1H); IR (KBr) 3316, 1747 cm^{-1}; ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.4, 146.0, 135.9, 128.4, 127.6, 127.5, 127.4, 126.1, 123.9, 120.6, 118.5, 118.0, 111.1, 109.2, 70.6, 56.7, 30.6; mass spec 446 au; [α]$_D$ −23.9° (c = 1, MeOH). Anal. Calcd for C$_{30}$H$_{26}$N$_2$O$_2$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.94; H, 5.92; N, 6.02.

Preparation of 3-(1*H*-Indol-3-yl)-*N*-(2-methoxybenzyl)-2-[*N*-(triphenylmethyl)amino]propanamide (10). A mixture of **9** (1.3 kg, 2.91 mol), *N*-methylmorpholine (309.3 g, 3.05 mol), and 2-chloro-4,6-dimethoxy-1,3,5-triazine (531.6 g, 3.03 mol) in 6.5 L of tetrahydrofuran was stirred at 25 °C for 1 h. Neat 2-methoxybenzylamine (431.3 g, 1.03 equiv) was added, and the reaction mixture was stirred until the reaction was complete as indicated by HPLC analysis.[18] On completion of the reaction, 6.5 L of methylene chloride was added to the reaction mixture, and the resulting solution was washed with 9.75 L of 5% citric acid solution. The reaction mixture was then washed sequentially with 4.5 L of 10% sodium bicarbonate solution and 4.5 L of deionized water. After separating the layers, the organic layer was concentrated *in vacuo* to a viscous oil. Heptane was added, and the resulting slurry was stirred overnight at 0−5 °C. It was then filtered and the filter cake washed with cold heptane. The wet cake was then dried under vacuum at 40 °C to give 1.53 kg, a 93% yield of **10**: mp 213−215 °C; ^{1}H (300 MHz, CDCl$_3$) δ 2.23 (dd, 1H, J = 6.5, 14.4 Hz), 2.65 (brs, 1H), 3.20 (dd, 1H, J = 5, 15.4 Hz), 3.47 (overlapping dd, 1H, J = 5.8 Hz, 6.5 Hz), 3.62, (s,3H), 4.00 (dd, 2H, J = 5.8, 14.2 Hz), 4.20 (dd, 1H, J = 7, 14.3 Hz), 6.6−7.5 (m, 24H), 7.85 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.7, 156.4, 146.1, 136.1, 128.4, 127.7, 127.6, 127.5, 126.6, 126.1, 124.3, 124.2, 119.9, 118.9, 118.0, 111.1, 110.1, 70.8, 57.2, 55.1, 37.3, 30.4; IR 3479, 1655 cm^{-1}; mass spec 566 (M + 1) au [α]$_D$ +1.18°, [α]$_{365}$ +15.5° (c = 1, CH$_2$Cl$_2$). Anal. Calcd for C$_{38}$H$_{35}$N$_3$O$_2$: C, 80.68; H, 6.24; N, 7.43. Found: C, 80.65; H, 6.46; N, 7.50.

Preparation of 3-(1*H*-Indol-3-yl)-1-[*N*-(2-methoxybenzyl)acetylamino]-2-[*N*-(triphenylmethyl)amino]propane (11). Red-Al (1.36 kg, 4.5 equiv) was added to a stirred mixture of **10** (551.9 g, 0.97 mol) in 3.86 L of toluene, and the resulting mixture was warmed to reflux. The mixture was held at 110 °C for 2−4 h until the reaction was complete as demonstrated by HPLC analysis.[19] The reaction mixture was cooled to 0−10 °C and quenched with 2.75 L of chilled 7 M NaOH. The resulting mixture was stirred for 15−30 min, and the layers were separated. The toluene layer was dried over MgSO$_4$ and filtered to remove the drying agent. The filtrate was cooled to 5 °C, and triethylamine (98.7 g, 1.0 equiv) was added at a rate such that the temperature did not exceed 25 °C. Acetic anhydride (107.5 g, 1.08 equiv) was added at a rate such that the temperature did not exceed 25 °C. The resulting mixture was stirred for 1 h. The reaction was quenched by the addition of 1.87 L of deionized water, and the layers were separated. The organic layer was extracted with 1.65 L of 10% sodium bicarbonate solution. The reaction mixture was concentrated *in vacuo* to a thick oil. Ethyl acetate was added, and the reaction mixture was again concentrated, forming a thick slurry. Heptane was added to the slurry, and the resulting mixture was cooled to 0−5 °C. The product was isolated by filtration. The filter cake was washed with chilled heptane and dried under vacuum at 40 °C to give 507 g, an 88% yield of **11**: mp 174−175 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.95, 1.98 (singlets, 3H [rotamers]), 2.38−2.55 (doublet of quartets, 1H [rotamers]), 2.63−2.79 (multiplet, 2H), 3.16−3.33, (multiplet, 3H), 3.59, 3.71 (two s, 3H [rotamers], 3.72, 4.45 (doublets, 1H [rotamers]), 4.07, 4.68, (doublets, 1H [rotamers]), 6.42−7.56 (multiplet, 24H), 8.11, 8.20, (singlets, 1H-[rotamers]); ^{13}C NMR (75 MHz, DMSO) δ 171.1, 170.3, 156.7, 156.6, 147.1, 146.9, 136.0, 135.9, 128.5, 128.3, 127.6, 127.5, 127.3, 127.2, 126.7, 126.0, 125.9, 125.1, 124.0, 123, 122.7, 120.7, 120.6, 120.0, 119.9, 118.2, 118.1, 118.0, 117.9, 111.5, 111.4, 111.2, 111.1, 110.4, 110.2, 70.4, 70.3, 54.9, 53.4, 52.6, 48.5, 46.9, 40.3, 40.0, 29.6, 21.2; IR 1666.7 cm^{-1}; [α]$_D$ +3.57° (c = 1, MeOH). Anal. Calcd for C$_{40}$H$_{39}$N$_3$O$_2$: C, 80.91; H, 6.62; N, 7.08. Found: C, 81.20; H, 6.65; N, 7.31.

Preparation of 2-Amino-3-(1*H*-indol-3-yl)-1-[*N*-(2-methoxybenzyl)acetylamino]propane Dihydrochloride (12). A mixture of **11** (199.4 g, 0.33 mol) in 500 mL of methylene chloride was cooled to −8 °C, and anhydrous HCl (40 g, 1.10 mol) was added at a rate such that the temperature was controlled to less than 0 °C. The resulting mixture was stirred at −10 °C for 90 min, and 500 mL of methyl *tert*-butyl ether was added over a period of 1 h. The resulting slurry was stirred at 0−5 °C for 3 h. The product was isolated by filtration and washed with 800 mL of methyl *tert*-butyl ether. A total of 139 g (99%) of **12** as light pink crystals were obtained upon drying the wet cake under vacuum at 40 °C: mp 179 °C dec; ^{1}H (300 MHz, DMSO-d_6) δ 1.94, 2.08 (two singlets, 3H [rotamers]); 2.88 (dd, 1H, J =14 Hz, 9 Hz); 2.96 (dd, 1H, J = 14 Hz, 4 Hz), 3.42−3.49 (m, 3H); 3.49 (s, 3H); 3.69 (broad doublet, 1H, J = 5 Hz); 4.38 (d, 1H, J = 17 Hz); 4.48, (d, 1H, J = 17 Hz); 6.76−6.80 (m, 2H); 6.94 (m, 2H); 7.05 (t, 1H, J = 7 Hz); 7.18 (m, 2H), 7.36 (d, 1H, J = 8 Hz); 7.56 (d, 1H, J = 8 Hz); 8.45, 8.60 (two broad singlets [rotamers] 2H); 11.1 (broad singlet, 2H); ^{13}C NMR (75 MHz, DMSO) δ 171.9, 156.7, 136.2, 128.6, 127.9, 127.7, 127.6, 127.4, 127.1, 127.0, 126.98, 124.7, 124.5, 124.2, 124.1, 121.0, 120.2, 120.0, 118.4, 118.3, 118.2, 111.5, 110.7, 110.4, 108.2, 107.9, 55.1, 54.9, 49.8, 49.6, 49.4, 48.4, 47.6, 26.6, 21.5; IR 1643, 1604 (shoulder) cm^{-1}; [α]$_D$ +6.55° (c = 1, MeOH). Anal. Calcd for C$_{21}$H$_{27}$Cl$_2$N$_3$O$_2$: C, 59.44, H, 6.41; N, 9.90. Found: C, 59.86; H, 6.50; N, 9.80.

Preparation of 1-[*N*-(2-Methoxybenzyl)acetylamino]-3-(1*H*-indol-3-yl)-2-[*N*-[2-[4-(piperidin-1-yl)piperidin-1-yl]-acetyl]amino]propane. (1) Dihydrochloride, Trihydrate. A slurry of the potassium salt of 2-[4-(piperidin-1-yl)piperidin-1-yl)acetic acid (**7**) (97 g, 1.55 equiv) in 1.75 L of anhydrous methylene chloride was cooled to −10 °C, and isobutyl chloroformate (57.5 mL, 1.67 equiv) was added at a rate such that the temperature of the reaction mixture did not exceed −8 °C. The reaction mixture was stirred at a temperature of −10 °C for about 1.5 h. A mixture of **12** (100.8 g, 235 mmol) in 1 L of anhydrous methylene chloride was then added slowly to the reaction mixture. The resulting mixture was warmed to 15−20 °C over a period of 23 h, and the reaction was quenched by the addition of 1 L of deionized water. The pH of the mixture was adjusted to 1 by the addition of 1 N HCl. After separating the layers, the aqueous layer was washed with 1 L of methylene chloride. Additional methylene chloride (2 L) was added to the aqueous layer, and the resulting mixture was basified with 2 N sodium hydroxide to a pH of 13. The resulting mixture was stirred at 25 °C for 15 min. The layers were separated, and the aqueous layer was further extracted with additional methylene chloride. The combined methylene chloride washes were then concentrated *in vacuo*. Acetone was added to the resulting oil, and then a solution of 1.5 L of acetone, 47.5 mL of 10 N HCl, and 40 mL of deionized water was added dropwise to crystallize the product. The crystals were isolated by filtration and washed with dry acetone. A total of 159.8 g (98%) of **1** was obtained as the dihydrochloride salt trihydrate after drying this material under vacuum at 50 °C: mp 192−196 °C (loss of H$_2$O), 240 °C dec; ^{1}H (300 MHz, CDCl$_3$) δ 1.25−1.70 (m, 10H); 1.77−2.00 (m, 3H); 1.95, (s, 1.8 H [rotamer]), 2.04, (s, 1.2 H [rotamer]); 2.10−2.97, (m, 9H); 3.10−3.65, (m, 3H), 3.72, (s, 1.2H[rotamer]); 3.74, (s, 1.8 H[rotamer]); 4.26−4.58, (m, 3H); 6.76−7.12, (m, 6H); 7.13−7.35 (m, 2H), 7.42−7.66 (m, 2H); 10.80 (broad s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 169.9, 169.4, 169.3, 156.8, 156.7, 136.1,

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(18) HPLC analysis of the reaction mixture was accomplished using an isocratic mobile phase of 60% acetonitrile/40% 12 mM phosphate (pH 7) buffer with a LC-ABZ reverse phase column. At a flow rate of 2.0 mL/min and detection wavelength of 220 nm the retention times are as follows: compound **9**: 2.85 min, compound **10**: 9.8 min.

(19) HPLC analysis of the reaction mixture was accomplished using an isocratic mobile phase of 60% acetonitrile/40% 12 mM phosphate (pH 7) buffer with a Supelcosil LC-ABZ reverse phase column. At a flow rate of 2.0 mL/min and detection wavelength of 230 nm the retention times are as follows: Compound **10**: 15.7 min; product amine: 28.1 min.

128.5, 127.7, 127.5, 127.3, 127.2, 126.9, 125.4, 124.6, 123.2, 123.1, 120.08, 120.7, 120.2, 120.0, 118.4, 118.2, 118.1, 111.2, 110.6, 110.5, 110.4, 110.3, 79.1, 61.7, 61.4, 61.3, 55.1, 53.4, 53.3, 53.2, 51.2, 49.7, 47.9, 47.7, 47.6, 47.5, 47.2, 43.1, 27.8, 27.6, 27.5, 27.4, 27.3, 27.1, 26.0, 25.8, 24.5, 21.4, 21.2; mass spec 559 au; IR 1658 cm^{-1}; $[\alpha]_D$ +15.7° (c = 1, MeOH). Anal. Calcd for $C_{33}H_{53}Cl_2N_5O_6$: C, 57.72, H, 7.78; N, 10.20. Found: C, 58.00; H, 7.54; N, 10.16.

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