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A Practical Synthesis of Fibrinogen Receptor Antagonist MK-383. Selective Functionalization of (S)-Tyrosine

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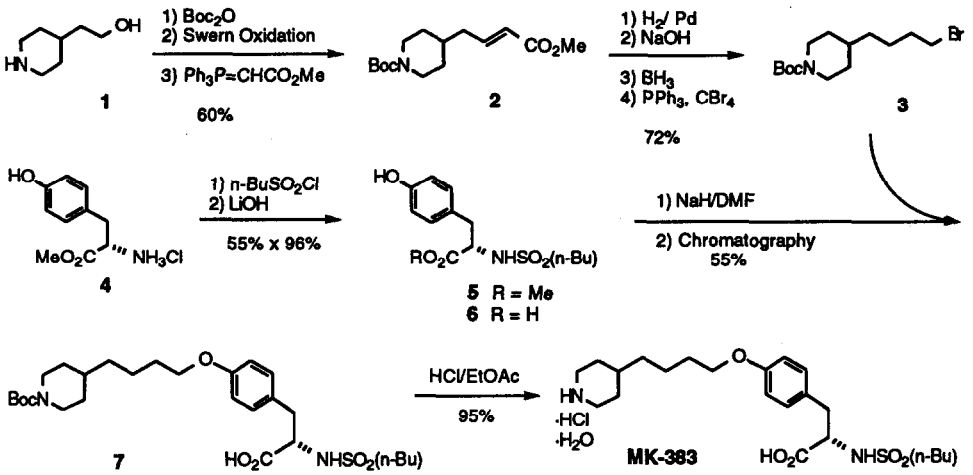
Abstract: A practical 4-step synthesis of fibrinogen receptor antagonist MK-383, N-(*n*-butanesulfonyl)-O-(4-(4-piperidinyl)-butyl)-(S)-tyrosine, is accomplished in 48% overall yield from (S)-tyrosine. Highlights include: (1) the dual use of 4-picoline as a masked form of piperidine, and as a nucleophile precursor for a 3-carbon homologation with 3-bromo-1-chloropropane; (2) the use of trimethylsilyl groups for temporary protection of phenolic and carboxylate oxygens of (S)-tyrosine that enable selective N-sulfonylation to be carried out in high yield; (3) the selective phenolic O-alkylation of the tyrosine derivative in high yield with no racemization using aqueous KOH/DMSO; and (4) the selective hydrogenation of the pyridine ring in the presence of the tyrosine ring using Pd/C in acetic acid.

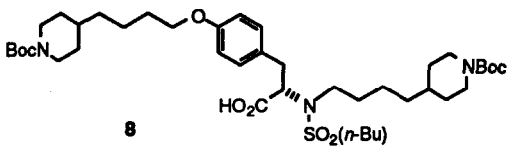
Platelet-mediated thrombus formation is a contributing factor in the many vaso-occlusive disorders, including acute myocardial infarction, reocclusion post angioplasty and transient ischemic attacks, that affect over one million Americans each year. Since the binding of fibrinogen to its platelet receptor GP IIa/IIb is an obligatory component of platelet aggregation, antagonists of this receptor constitute an attractive anti-thrombotic therapy. Thus, extensive efforts have been directed toward the discovery and synthesis of such agents.[1]

MK-383, N-(*n*-butanesulfonyl)-O-(4-(4-piperidinyl)-butyl)-(S)-tyrosine, is a potent, non-peptide fibrinogen receptor antagonist.[1,2] As part of our program on this important clinical candidate, we required an efficient synthesis that is amenable for large-scale preparation. This paper details our efforts in meeting this challenge, in which a highly efficient, chromatography-free 4-step synthesis was developed.

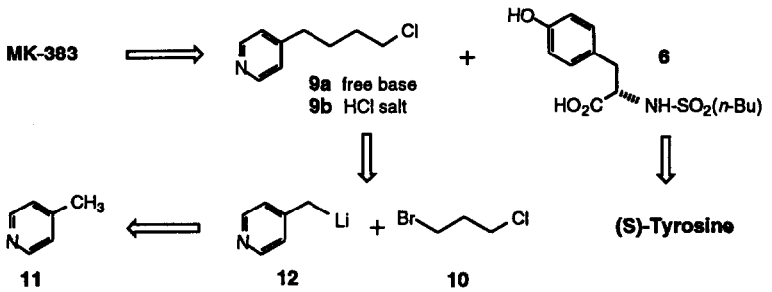
Structurally, MK-383 is a deceptively simple di-functionalized (S)-tyrosine, in which the phenolic oxygen is alkylated with a 4-(4-piperidinyl)butyl moiety and the nitrogen is *n*-butanesulfonylated. The original 11-step synthesis[2] of MK-383 was designed to permit the rapid preparation of many structurally similar compounds (Scheme I). In assessing its viability for scale up, several difficulties became apparent. The preparation of bromide **3** required a lengthy 7-step process, which used expensive reagents, a protecting group and the commercially unavailable starting material, 4-piperidinyl-2-ethanol (**1**). The preparation of N-*n*-BuSO_2-(S)-tyrosine **6** suffered from significant formation of N,O-bis-sulfonylated product in the sulfonylation step and partial racemization in the saponification step. The key phenolic O-alkylation of **6** with **3** used a hazardous NaH/DMF slurry[3] and gave a significant amount of N,O-bis-alkylated byproduct **8** as well as poor conversion. Upon scaling up this reaction, the NaH/DMF mixture formed a thick paste which prevented proper mixing, presumably due to the aggregation of di- and tri-anions. Finally, the production of impurities in many of the steps required purification by chromatography. These problems seriously limited the utility of this approach for large scale preparation.



Scheme I. Original 11-Step Synthesis[2] of MK-383



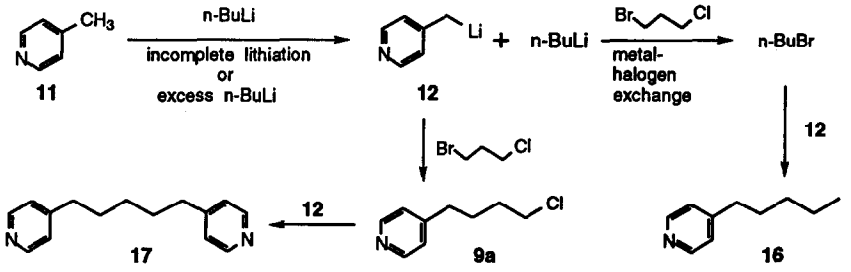
Our retrosynthetic analysis of MK-383 is outlined in Scheme II. Since the preparation of the piperidinylbutyl bromide **3** required seven steps in the original 11-step synthesis, we envisioned that 4-(4-pyridinyl)butyl chloride **9** would be an ideal synthon provided that it could be easily prepared from inexpensive 4-picoline **11** and 1-bromo-3-chloroproane via 4-picolyllithium **12**.[4] Furthermore, the ability of the pyridine group to act as a latent form of piperidine would eliminate the need for a nitrogen protecting group. For the preparation of **6**, we planned to directly sulfonylate (S)-tyrosine itself rather than its ester, so that saponification-induced partial racemization is avoided. The development of a chemoselective phenolic O-alkylation of **6** with **9**, followed by reduction of the pyridine ring would complete the synthesis.



Scheme II. Retrosynthetic Analysis

RESULTS AND DISCUSSION

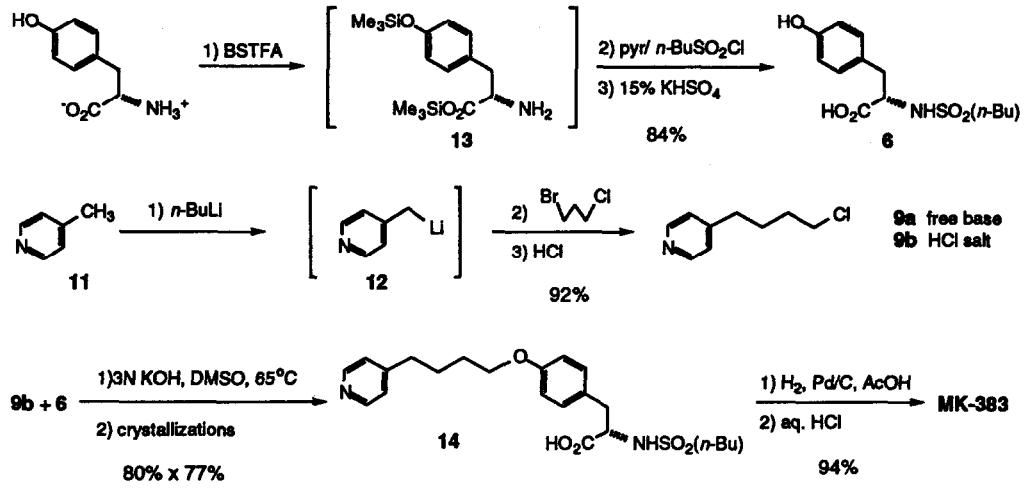
4-(4-Pyridinyl)butyl chloride 9. Although the preparation of **9** was known in the literatures,[5] its synthesis required 3 steps in low overall yield. Typically, the 4-picolyl anion was alkylated with protected 3-halo-propanol, followed by deprotection and conversion of the alcohol to the chloride. We opted for a direct one-step synthesis with 3-bromo-1-chloropropane provided that monoalkylation could be achieved in a highly selective manner.[6] Initial attempts to prepare **9** by lithiation[4] of 4-picoline with *n*-BuLi in THF at -20°C, followed by the addition of 3-bromo-1-chloropropane consistently gave the product contaminated with 4-*n*-pentylpyridine **16** (Scheme III) at ~15% level.[7a] Thus, it appeared that the unreacted *n*-BuLi underwent metal-halogen exchange with 3-bromo-1-chloropropane to give 1-bromobutane which then reacted with 4-picolyllithium to give the impurity.[7b] Another impurity, bis-alkylation product **17**[8] was produced in significant amount when the addition of 3-bromo-1-chloropropane was prolonged during large-scale preparations. To eliminate these two problems, we heated the 4-picoline and *n*-BuLi mixture at 40°C for 2 hours to promote complete lithiation and/or decomposition of excess *n*-BuLi,[9] followed by quenching the anions into a THF solution of 3-bromo-1-chloropropane at -65°C. These modifications provided the desired product **9b** in 92% isolated yield uncontaminated with **16** and **17** after crystallization on a 9 mol scale. 4-Picolyllithium appeared to be stable at temperatures up to 45°C, beyond which significant decomposition took place. Also, during the addition of **12** to 3-bromo-1-chloropropane, the reaction temperature was critically maintained at less then -65°C to avoid the formation of **17**.



Scheme III

N-*n*-Butanesulfonyl-(S)-tyrosine 6. With an efficient synthesis of 4-(4-pyridinyl)butyl chloride hydrochloride **9b** in hand, we next sought an efficient synthesis of N-(*n*-$BuSO_2$)-(S)-tyrosine **6**. A literature survey revealed that the N-arylsulfonylation of tyrosines under Schotten-Baumann conditions usually gave moderate yields of the products in moderate selectivity. However, when we attempted to N-*n*-butanesulfonylate (S)-tyrosine under theses conditions (using aqueous inorganic bases such as NaOH, Na_2CO_3[10] or $NaHCO_3$ with or without an organic co-solvent (THF, *t*-BuOH, DMF)) the reaction gave almost no desired product. The problem was due to rapid hydrolysis of *n*-$BuSO_2Cl$ and bis-sulfonylation. Although sulfonylation of tyrosine methyl ester could be accomplished under nonaqueous conditions such as pyridine/CH_3CN as noted in the original synthesis, but, N,O-bis-sulfonylation was again a significant side reaction.

A solution to these problems was subsequently realized by the use of hydrolytically labile trimethylsilyl groups[11] for the temporary protection of the carboxyl and phenol groups during the introduction of the *n*-butanesulfonyl group. Treatment of a suspension of (S)-tyrosine in CH_3CN at 85°C with bis-trimethylsilyl trifluoroacetamide (BSTFA, 2.1 equiv) for 2 hours resulted in a clear solution (Scheme IV). ^1H NMR studies of this solution revealed that the major product (80-85%) was O,O'-bis-(trimethylsilyl)-(S)-tyrosine **13**,[12] with the remainder being the O,O',N-tris-silylated (S)-tyrosine. This solution was then directly treated with pyridine and *n*-$BuSO_2Cl$, and heated at 70°C for 3 hours. Hydrolytic work up with 15% aqueous $KHSO_4$, followed by crystallization from EtOAc/hexane provided pure **6** in 84% isolated yield. The assay yield of **6** in the reaction crude mixture was 96%, indicating that the tris-silylated (S)-tyrosine was also sulfonylated under the reaction conditions.

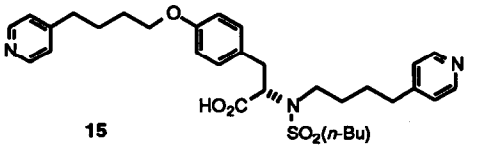


Scheme IV. 4-Step Synthesis of MK-383

Phenolic O-Alkylation. With the efficient synthesis of both **6** and **9b** in hand, we next investigated a practical method to effect the phenolic O-alkylation.[13] Since N-alkylation of the sulfonamide and to less extent the O-alkylation of the carboxylate were serious side reactions in the previous approaches, we sought to block both temporarily by forming the cyclic Cu(II) complex, so that phenolic oxygen was the only site available for reaction. Although the cyclic copper complexes of unprotected amino acids are easily prepared,[14] the existence of cyclic copper complex of nitrogen protected amino acids (such as Boc or Cbz) were less well known. A literature search revealed that Boc or Cbz protected amino acids do not form such cyclic copper complexes, however, the benzenesulfonamides do form a cyclic copper complex at high pH due to their enhanced acidity.[15]

With this encouraging precedent we hoped *n*-butylsulfonamides would form such a complex, and indeed they do. Experimentally, N-*n*-$BuSO_2$-(S)-tyrosine **6** (1 mole) was dissolved in 2 N NaOH (2 mole), then $CuSO_4 \cdot H_2O$ (0.5 mole) was added at 65°C. After stirring for 1 hour, DMSO or MeOH, 2N NaOH (2 mole), chloride **9b** (1 mole) and $(n\text{-}Bu)_4N^+I^-$ (10 mol%) were added and heating continued until starting material was consumed. HPLC analysis of the reaction mixture revealed the bis-alkylated product **15** was present but in only

2-3%. Despite the success with this protocol, the removal of Cu(II) ion to less than 10 ppm proved to be a difficult task. Although most of the Cu(II) could be removed by treatment with EDTA, poly-4-vinylpyridine or Chelex-100™, further removal was not effective nor practical.



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This required carrying out the phenolic O-alkylation of **6** with **9b** without Cu(II). The feasiblity of this reaction was supported by the precedent of Solar and Schumaker[16] who demonstrated selective phenolic O-alkylation of unprotected tyrosine in an aqueous NaOH/DMSO mixture[17] at 80-115°C. However, they did not study the N-sufonylated tyrosine nor determined the optical purity of their tyrosine ether. Thus, treatment of **6** and **9b** in DMSO with 3N KOH and catalytic amount of KI at 80°C indeed proceeded to gave the desired product in good yield. The impurity profile of the reaction was cleaner than with Cu(II); however, the bis-alkylated product **15** was present at about 5%. Nonetheless, this procedure represented a major simplification over the previous methods. Therefore an optimization effort was initiated. The optimal reaction temperature was found to be 65-70°C, which gave no detectable racemization and minimized the formation of **15** while still providing a reasonable rate of reaction. Using this reaction temperature, a solvent effect study was carried out using nine solvents, in which the formation of the product **14** and the bis-alkylated product **15** were monitored over time by HPLC. The three urea-based solvents, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMEU), and tetramethylurea (TMU), as well as methyl sulfoxide (DMSO) gave the best assay yields of **14** (85-96%), whereas dimethyformamide (DMF), acetonitrile and methanol gave the poorest assay yields (20-50%). N,N-dimethylacetamide (DMA) and N-methyl-pyrrolidinone (NMP) gave assay yields of 80-85%. DMPU was found to be the optimal solvent in minimizing the formation of the bis-alkylated product (≤1%). DMSO gave a slightly higher amount of bis-alkylated product (2%); however, due to its low cost and ready accessibility, it was the solvent of choice for large scale preparation. With respect to the base, there was no difference between potassium hydroxide and sodium hydroxide. Pure product **14** was conveniently isolated by adjusting the pH of the reaction mixture to its isoelectric point (pH 4.8), at which point product **14** crystallized. In this manner, an 80% isolated yield of 95 weight % purity material was obtained. This material was further purified to 99.4% purity by recrystallization. The optical purity of **14** was determined to be >99% ee by HPLC analysis on a chiral Ultron ES-OVM column using 10% MeOH/NH_4HCO_2 buffer (pH 4.1).

Hydrogenation Of Pyridine. With **14** in hand, all that was needed to complete the synthesis was to reduce the pyridine ring to piperidine. Initial attempted hydrogenation of **14**, carried out in the presence of 6 N HCl or as its HCl salt using PtO_2/MeOH/40 psi H_2, gave several products, including the desired MK-383, the corresponding methyl ester (10-60%) and the over-hydrogenation (of the phenolic ring) product.[18] After studying various catalysts, supports and solvents, hydrogenation in acetic acid using 10% Pd/C/60°C/40 psi H_2 gave a clean reaction without over-reduction.[19] Subsequent treatment of the hydrogenated product with

concentrated HCl in *i*-propyl acetate gave MK-383 (hydrochloride salt) in 94% overall yield for the two operations with 99.7 weight % chemical purity and 99.9% optical purity.

In summary, a highly efficient, chromatography-free 4-step synthesis of fibrinogen receptor antagonist MK-383 was developed and demonstrated on kilogram scale in 48% overall yield from (S)-tyrosine. The salient features of the chemistry were: (1) the use of trimethylsilyl groups as temporary protective groups that enable the selective N-sulfonylation of (S)-tyrosine to be carried out in high yield; (2) a masked form of 4-(4-piperidinyl)butyl chloride was conveniently prepared from 4-picolyllithium and 3-bromo-chloropropane; (3) the chemoselective O-coupling of these two components was achieved in good yield and with no racemization using aqueous KOH/DMSO; and finally (4) the selective hydrogenation of pyridine ring to the piperidine was accomplished using Pd/C in HOAc.

EXPERIMENTAL SECTION

General. Melting points were determined on Thomas-Hoover melting point apparatus and were uncorrected. NMR spectra were recorded on a Bruker AM-300 spectrometer (^{1}H NMR at 300 MHz, ^{13}C NMR at 63 MHz). Specific rotations were determined on a Perkin-Elmer 241 polarimeter. Concentrations (c) for specific rotations are reported in units of g/100 mL. Analytical high-performance liquid chromatography (HPLC) was carried out using a Spectra Physics SP-8800 pump, Spectra 100 variable wavelength detector, and the following columns: 4.6 mm x 25 cm Zorbax C-8 (DuPont), 4.6 mm x 25 cm Zorbax Phenyl (DuPont), and 4.6 mm x 25 cm ES-OVM (Ultron). Reactions were carried out under an atmosphere of N_2. As necessary, CH_3CN, THF, 4-picoline, and 3-bromo-1-chloropropane were dried over 3A or 4A molecular sieves. Residual water content was determined by Karl Fisher titration.

N-*n*-Butanesulfonyl-(S)-tyrosine 6. In a 50 L three-necked round bottom flask equipped with a mechanical stirrer, condenser, nitrogen inlet, HCl trap, heating unit and a thermometer probe were charged (S)-tyrosine (1040.0 g, 5.74 mol), CH_3CN (20.8 L), *N,O*-bis-trimethylsilyl-trifluoromethyl-acetamide (3103.0 g, 12.05 mol). The mixture was gently refluxed for 2 h. The resulting clear solution was cooled to 40°C, and pyridine (544.8 g, 6.89 mol) and *n*-$BuSO_2Cl$ (989.0 g, 6.31 mol) were added. The reaction mixture was then aged at 70°C for 3 h and room temperature for 14 h. Most of the solvent was evaporated and the resulting oily residue was treated with 15% $KHSO_4$ (20.8 L) and stirred vigorously for 1 h. The mixture was extracted with *i*-propyl acetate (3 x 6.2 L). The combined organic layers were treated with Ecosorb™ S-402 (3.12 kg) (a mixture of Charcoal and cellulose) and stirred at 22°C for 14 h. Ecosorb™ was removed by filtration and the filter cake was washed with *i*-propyl acetate (4.2 L). The filtrate was evaporated to dryness and the resulting yellow oil was dissolved in hot EtOAc (1.25 L). Hexane (3.74 L) was added slowly to the stirring solution and the resulting slurry was stirred at room temperature overnight. The solid was collected by filtration and the filter cake was washed with EtOAc/Hexane (0.2 L/1.89 L). After drying under vacuum, 1457 g (84%) of **6** was obtained as a white solid: mp 125-126.5°C; $[\alpha]^{25}_D$ = -25.2° (c 0.80, MeOH); ^{1}H NMR (CD_3OD) δ 0.81 (t, J = 7.2 Hz, 3H), 1.24 (m, 2H), 1.45 (m, 2H), 2.61 (t, J = 7.9 Hz, 2H), 2.73 (A of ABX, J_{AB} = 13.8 Hz, J_{AX} = 9.8 Hz, 1H), 3.07 (B of ABX, J_{BA} = 13.8 Hz, J_{BX} = 4.7 Hz, 1H), 4.07 (X of ABX, J_{XA} = 9.8 Hz, J_{XB} = 4.7 Hz, 1H), 6.72 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H); ^{13}C NMR (CD_3OD) δ 13.9, 22.5, 26.5, 39.1,

54.1, 59.5, 116.3, 129.2, 131.6, 157.5, 175.3; MS *m/z* 301 (M^+). Anal. Calcd for $C_{13}H_{19}O_5SN$: C, 51.81; H, 6.35; N, 4.65; S, 10.64. Found: C, 51.73; H, 6.28; N, 4.60; S, 10.82.

4-(4-Pyridinyl)butyl Chloride Hydrochloride 9b. A 22 L four-necked round bottom flask equipped with a mechanical stirrer, condenser, addition funnel with side-arm and a thermometer probe was purged with nitrogen overnight. THF (4.1 L) and 4-picoline (838.2 g, 9.0 mol) were added and the solution was cooled to ≤ -70°C. *n*-Butyllithium (7.02 L of 1.41 M) in hexane was added slowly while keeping the internal temperature ≤ -50°C. The addition took about 1 h, giving an orange solution with precipitate. The dry ice bath was removed and the reaction was allowed to warm to room temperature and then heated at 40-45°C for 2 h. THF (4.1 L) was added to dissolve the 4-picolyllithium slurry to give a deep orange solution. The reaction was cooled to 0°C, then added carefully via a polypropylene tube using a pneumatic pump to a -75°C solution of 3-bromo-1-chloropropane (1487.8 g, 9.45 mol) in THF (1.5 L) in a dry 50 L three-necked round bottom flask equipped with a mechanical stirrer, nitrogen inlet/outlet and a thermometer probe, while keeping the internal temperature ≤ -65°C. The reaction was allowed to gradually warm to 0°C overnight and then worked up by adding 9 L water, stirring for 10 min, separating layers and extracting the aqueous layer with *i*-propyl acetate (5 L). The organic layer was concentrated *in vacuo* at 40°C to one-third of the original volume, then *i*-propyl acetate (6 L) was added and again concentrated to one-third of the original volume. (This azeotropic removal of THF and water was critical for the subsequent smooth HCl salt formation. If THF was present, it reacted readily with HCl to give 4-chlorobutanol which increased the solubility of **9b** and lowered the recovery. The presence of water made filtration of the HCl salt very difficult, due to gummy nature of the hydrate.) The batch was cooled to -10°C and then treated with a solution of 9.0 mol of HCl in 3 L *i*-propyl acetate. After stirring for 1 h, the resulting slurry was transferred via a polypropylene tube using pneumatic pump into a nitrogen-filled enclosed coarse filter funnel placed under vacuum. The solid was washed several times with THF (4.5 L total volume) and dried with a stream of nitrogen under reduced pressure to give 1710.4 g (92%) of **9b** as a white solid: mp 119-120.5 °C; ^1H NMR (CD_3OD) δ 1.79-2.00 (m, 4H), 3.01 (t, J = 7.3 Hz, 2H), 3.36 (t, J = 6.1 Hz, 2H), 8.00 (d, J = 6.7 Hz, 2H), 8.75 (d, J = 6.7 Hz, 2H); ^{13}C NMR (CD_3OD) δ 28.1, 33.0, 36.1, 45.3, 128.6, 142.2, 166.1; MS *m/z* 205 (M^+). Anal. Calcd for $C_9H_{13}NCl_2$: C, 52.45; H, 6.36; N, 6.80; Cl, 34.40. Found: C, 52.22; H, 6.40; N, 6.51; Cl, 34.11.

N-(*n*-Butanesulfonyl)-O-(4-(4-pyridinyl)-butyl)-(S)-tyrosine 14. To a 50 L four-necked round bottom flask equipped with a mechanical stirrer, condenser, nitrogen inlet and a thermometer probe were charged N-*n*-butanesulfonyl-(S)-tyrosine **6** (1386.3 g, 4.60 mol), 4-(4-pyridinyl)butyl chloride hydrochloride **9b** (1137.8 g, 5.52 mol) and DMSO (16.56 L). With vigorous stirring, 3 N aq. KOH (5.52 L, 16.56 mol) was added over 15 min. Potassium iodide (7.64 g, 46.0 mmol) was added, and the mixture was heated at 60-65°C for 36 h (or until 95% completion as judged by HPLC analysis). After cooling to room temperature, the mixture was diluted with 0.25 N NaOH (46 L) and extracted once with *t*-butyl methyl ether (23 L). The aqueous layer was treated with Ecosorb S-402 (2.0 kg) and Nuchar SA (150 g) and the resulting mixture (~67 L) was mechanically stirred for 1 h. The mixture was filtered through a coarse-porosity sintered funnel and the filtered cake was washed with 69 L water. The combined filtrate (~136 L) was placed in a 200 L vessel equipped with a pH meter probe and a mechanical stirrer. With vigorous stirring, NaCl (2.5 kg) was added, stirred for 30 min, and then 50% aq. acetic acid (~4 L) was added until pH 4.80, and stirring continued for 2-3 h. The resulting slurry was filtered through a coarse-porosity sintered funnel, and the cake was washed with 23

L water. The crude product was dried at 40°C under house vacuum under a positive nitrogen pressure for 20 h to give 1599 g (80%) of beige solid having a purity of 95 wt%.

The solid was further purified to 99.4 wt% purity by the following procedure: To a 50 L RB flask equipped with a thermometer probe and addition funnel were charged the crude **14** (1.50 kg, 3.45 mol) and 0.25 N NaOH (19.33 L, 4.83 mol). After complete dissolution of the solid by gentle heating at 60-70°C for a few minutes, 0.25 N $NaHCO_3$ (4.83 L, 1.21 mol) was added. The solution was cooled to room temperature, and adjusted to pH 7 by slow addition of 1 N HCl (~2.65 L). The pH of the solution was brought down to 5.5 by slow addition of 0.5 N HCl (~5.10 L). Stirring was continued for 1 h, then the slurry was filtered and the cake was washed with water (10 L). The solid was dried under house vacuum with nitrogen sweep to give 1.42 kg of beige solid. The solid was suspended in 10% acetic acid in water (1g/15 mL), and heated with steam to 80°C for 5 min, then allowed to cool slowly to room temperature overnight. After stirring for 18h, the solid was filtered, washed with water (20 L) and partially dried using house vacuum with nitrogen sweep for several hours. This treatment was repeated and the solid was washed with water (20 L), methanol (3 x 4 L) and dried under vacuum at 35°C with a nitrogen sweep for two days. 1.16 kg (77%; 62% overall from **6**) of **14** as an off-white solid was obtained: mp 137-138°C; ^{1}H NMR (CD_3OD) δ 0.86 (t, J = 7.2 Hz, 3H), 1.26 (hex, J = 7.2 Hz, 2H), 1.50 (m, 2H), 1.85 (m, 4H), 2.67 (t, J=7.9 Hz, 2H), 2.75-2.87 (m, 3H, containing B of ABX), 3.14 (A of ABX, J_{AB} = 13.8 Hz, J_{AX} = 4.7 Hz, 1H), 4.00 (t, J = 5.5 Hz, 2H), 4.12 (X of ABX, J_{XA} = 4.7 Hz, J_{XB} = 9.4 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 5.5 Hz, 2H), 8.45 (d, J = 5.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 13.5, 21.5, 25.4, 26.5, 28.6, 35.1, 38.9, 53.0, 57.9, 67.0, 114.3, 125.0, 128.7, 130.8, 145.9, 155.8, 157.7, 175.0; MS(CI) *m/z* 435 (MH^+). Anal. Calcd for $C_{22}H_{30}N_2O_5S$: C, 60.81; H, 6.96; N, 6.45; S, 7.38. Found: C, 60.53; H, 6.88; N, 6.26; S, 7.65.

N-(*n*-Butanesulfonyl)-O-(4-(4-piperidinyl)butyl)-(S)-tyrosine (MK-383 free base). Pyridine **14** (1.051 kg, 2.42 mol) and 10% Pd/C (53 g, 5 wt%) in acetic acid (14 L) were hydrogenated in a 5-gallon stainless steel vessel at 40 psi and 60°C. The reaction was sampled hourly when near completion and terminated as soon as complete consumption of starting material was observed (5.5 h). Longer reaction time led to formation of impurities. The reaction mixture was filtered through a pad of Solka-Flock (820 g, washed with 5 L acetic acid) and washed with acetic acid (14 L). The filtrate was concentrated to a thick oil containing approximately 1 kg acetic acid. Water (15 L) was added to give a concentration of 1g/15 mL 6% acetic acid in water and the resulting slurry was stirred for 18 h at room temperature. The solid was filtered, washed with water (10 L) and dried under vacuum with a nitrogen sweep to give 1.03 kg (97%) of MK-383 free base as a white solid: mp 223-225°C. ^{1}H NMR (CD_3OD) δ 0.88 (t, J = 7.3 Hz, 3H), 1.33 (m, 6H), 1.58 (m, 5H), 1.76 (m, 2H), 1.81 (m, 2H), 2.77 (t, J = 7.5, 2H), 2.80 (m, 1H), 2.88 (m, 2H), 3.03 (B of ABX, J_{BA} = 13.9 Hz, J_{BX} = 4.6 Hz, 1H), 3.30 (m, 2H), 3.90-4.0 (m, 3H), 6.80 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H). Anal. Calcd for $C_{22}H_{36}O_5N_2S$: C, 59.97; H, 8.24; N, 6.36; S, 7.28. Found: C, 59.98; H, 8.40; N, 6.40; S, 7.24.

N-(*n*-Butanesulfonyl)-O-(4-(4-piperidinyl)butyl)-(S)-tyrosine, Hydrochloride, Monohydrate (MK-383). To a 22 L 3-necked round bottom flask equipped with a mechanical stirrer, nitrogen inlet and an addition funnel was charged MK-383 free base (316.0 g, 0.717 mol) and isopropyl acetate (9.5 L). The mixture was stirred at room temperature (20°C) for 10-15 min, then concentrated hydrochloric acid (120 mL) was added dropwise. The addition took about 40 min and the temperature remained at 19°C

throughout addition. The mixture was then stirred at room temperature (20°C) for a further 5 hours. The product was isolated by filtration under nitrogen. The solid product was washed with isopropyl acetate (2 x 1 L) and dried under vacuum with a nitrogen sweep overnight to afford MK-383 HCl monohydrate (348 g) in 98% yield: mp 131-132°C; $[\alpha]^{25}_D$ = -14.4° (c 0.92, MeOH); ^{1}H NMR (CD_3OD) δ 0.84 (t, J = 7.3 Hz, 3H), 1.23 (hex, J = 7.3 Hz, 2H), 1.30-1.70 (m, 9H), 1.75 (m, 2H), 1.95 (m, 2H), 2.64 (t, J = 7.4, 2H), 2.77 (A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 9.8 Hz, 1H), 2.95 (m, 2H), 3.11 (B of ABX, J_{BA} = 13.9 Hz, J_{BX} = 4.6 Hz, 1H), 3.47 (m, 2H), 3.95 (t, J = 6.2 Hz, 2H), , 4.09 (X of ABX, J_{XA} = 9.8 Hz, J_{XB} = 4.6 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H). ^{13}C NMR (CD_3OD) δ 14.0, 22.5, 24.0, 26.5, 30.0, 30.4, 34.8, 36.8, 39.0, 45.3, 54.1, 59.4, 68.7, 115.5, 130.4, 131.7, 159.6, 175.2. IR (Nujol, cm^{-1}) 3520, 3208, 3166, 2800-2300, 1727, 1610, 1595, 1324, 1256, 1141, 1119, 829. HRMS calcd for $C_{22}H_{37}N_2O_5S$ 441.2423, found 441.2423 ($MH^+ - H_2O - Cl$). Anal. Calcd for $C_{22}H_{36}O_6ClN_2S \cdot HCl \cdot H_2O$: C, 53.37; H, 7.94; N, 5.66; Cl, 7.16; S, 6.48. Found: C, 53.56; H, 8.04; N, 5.62; Cl, 7.36; S, 6.53.

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7. (a) **16**: ^{1}H NMR (CD_3OD, 250 MHz) δ 8.39 (d, J = 6.7 Hz, 2H), 7.28 (d, J = 6.7 Hz, 2H), 2.67 (t, J = 7.0 Hz, 2H), 1.65 (m, 2H), 1.35 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H). MS(EI) *m/z* 149 (M^+). (b) One possibility is that 4-picolyllithium metal-halogen exchanges and then couples with n-BuLi to give **16**; however, this pathway is highly unlikely due to the thermodynamic considerations and the absence of picolyl dimer (from the reaction of 4-picolyllithium with 4-picolyl bromide) in the reaction mixture.
8. **17**: ^{1}H NMR (CD_3OD, 250 MHz) δ 8.39 (d, J = 6.7 Hz, 4H), 7.26 (d, J = 6.7 Hz, 4H), 2.68 (t, J = 7.0 Hz, 4H), 1.70 (quintet, J = 7.0 Hz, 4H), 1.40 (quintet, J = 7.0 Hz, 2H). ^{13}C NMR (CD_3OD, 63 MHz) δ

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