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Synthesis of the Orally Active Spiroindoline-Based Growth Hormone Secretagogue, MK-677

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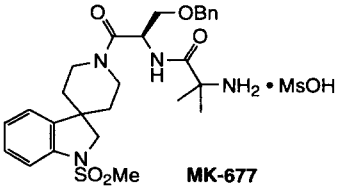
Abstract: The preparation of the Merck Growth Hormone Secretagogue; MK-677 is described. A Fischer indole/reduction based strategy provides the novel spiroindoline nucleus of this potent compound. This optimized sequence necessitates the isolation of only one intermediate **10** and provides MK-677 in 48% overall yield from isonipecotic acid **3**.

INTRODUCTION

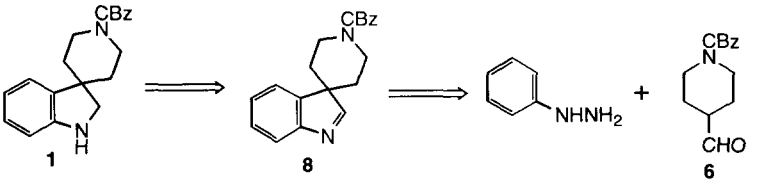
Human Growth Hormone (GH) is in great demand for the treatment of GH deficient children and has potential uses in burn victims, hip fracture cases, and the frail elderly. The relatively high expense and difficulty in preparation of natural GH has stimulated research for peptidomimetic GH secretagogues; small molecules that can induce the endogenous release of GH. An initial breakthrough in this area came with the discovery of L-692,429,[1] which demonstrated GH release after i.v. dosing in humans. More recently, an orally bioavailable drug candidate, MK-677,[2] has been discovered and is currently in Phase II clinical studies. Thus, an efficient process for the preparation of MK-677 was desired.[3]



MK-677

RESULTS AND DISCUSSION

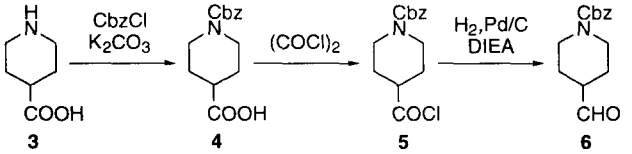
Retrosynthetic analysis of the spiroindoline **1** revealed the Fischer indole type approach below (eq 1), which required the *N*-protected piperidine carboxaldehyde partner **6**.



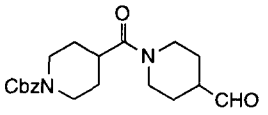
(1)

Aldehyde **6** potentially could be obtained from commercially available isonipecotic acid **3** by *N*-protection, conversion of the acid **4** to the acid chloride **5** and Rosenmund type reduction of **5** to **6** (Scheme 1). The Cbz group was chosen for protection of the piperidine nitrogen because it would be compatible with a variety of acidic Fischer indole reaction conditions.[4] The success of this approach clearly relied on the selective hydrogenolysis of the acid chloride of **5** in the presence of the benzyl carbamate group, and on the stability of the intermediate spiroindolenine **8** towards acid catalyzed rearrangement of the skeleton.[5]

Scheme 1



Classical Rosenmund hydrogenation conditions dictated passage of hydrogen at atmospheric pressure through a mixture of the acid chloride and Pd-$BaSO_4$ in hot toluene.[6] However, conditions more suitable for stirred autoclave implementation were desired for this transformation. Thus, hydrogenation of **5** in toluene with 40 psi H_2 at 10°C in the presence of 10% Pd/C, 1.2 equiv of DIEA, and 0.04 mol% thioanisole[7] gave aldehyde **6** in 97% yield. Rosenmund type reductions have been performed in the presence of hindered bases such as 2,6-lutidine or DIEA as HCl scavengers and mild catalyst deactivators.[8] The Rosenmund reduction was not reproducible with different lots of catalyst; in the absence of added poisons varying degrees of hydrogenolysis of the Cbz group was observed resulting in the production of the dimeric aldehyde-amide by-product **7**.[9,10] Of the poisons investigated to moderate catalyst reactivity, thioanisole gave the most reliable results with less than 1% dimer **7** formation.



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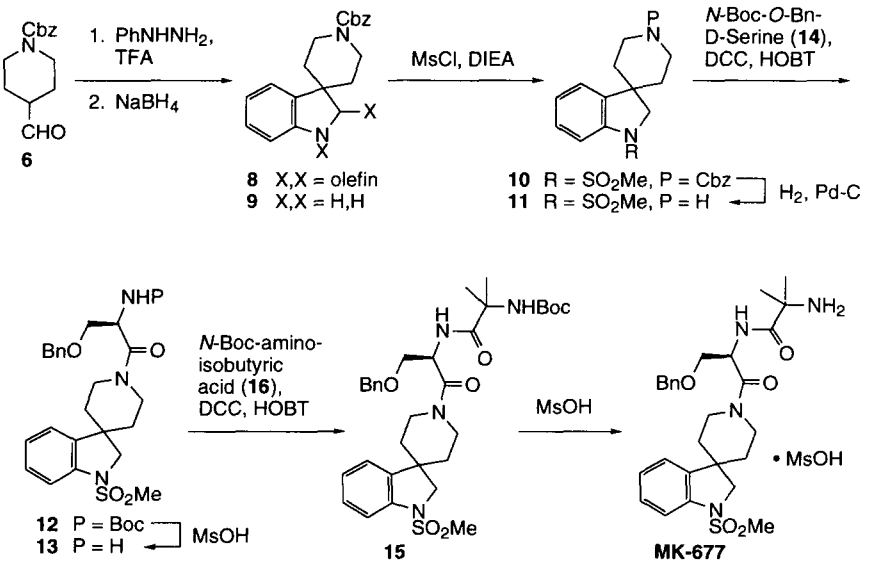
The stage was now set for the Fischer indole reaction (Scheme 2). Aldehyde **6** and phenylhydrazine reacted instantaneously at 20°C in various solvents to give the unstable hydrazone. In the optimized Fischer indole process, *addition of the aldehyde **6** to a mixture of phenylhydrazine and TFA in 98:1 toluene-MeCN (16 h, 35°C)*[11] *followed by the addition of MeOH and $NaBH_4$ at -10°C gave spiroindoline **9** in 93% overall yield.* Classical Fischer indole catalysts such as the aqueous protic acids and Lewis acids gave either complex mixtures or no reaction.[12] Strong Brønsted acids such as HCl, MsOH and CSA in dry CH_2Cl_2 gave varying yields of the desired spiroindolenine **8**. However, treatment of an equimolar mixture of aldehyde **6** and phenylhydrazine with 2.5 equiv of TFA in CH_2Cl_2 at 35°C for 16 h gave a nearly quantitative yield of **8**[13] with no evidence of the Wagner-Meerwein ring expansion product. *In-situ* reduction of **8** could be effected with $NaBH_4$ giving spiroindoline **9**.

Scheme 2



Sulfonamidation of **9** with MsCl and DIEA in THF gave the sulfonamide **10** which after hydrogenolysis with 10% Pd on C in EtOH gave deprotected piperidine **11**[14] in 93% yield. Deprotected spiroindoline **11** was coupled with *N*-Boc-*O*-benzyl-(D)-serine **14**[15] in the presence of DCC and 1-hydroxybenzotriazole (HOBt) in 2:1 isopropyl acetate (IPAC)-water to provide the *N*-Boc-monopeptide **12** with < 0.1% racemization. Treatment with MsOH in EtOH gave **13** in 92% yield from **10**. The second coupling with *N*-Boc-

aminoisobutyric acid **16** was followed by Boc-deprotection to give MK-677 in 82% yield from **10** without isolation of any intermediates. Crystallization of crude MK-677 as the MsOH salt from EtOAc-EtOH gave the pure drug substance in 74% overall yield from **10**.

In summary, an efficient process for the preparation of multikilogram quantities of the Growth Hormone Secretagogue MK-677 from commercially available and economical isonipecotic acid has been developed.

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EXPERIMENTAL SECTION

General

Reagents were used as received unless otherwise stated; 3A molecular sieves were used to dry solvents for anhydrous reactions. Unless otherwise noted, all manipulations were carried out under an inert atmosphere of nitrogen gas. In general, glassware was not specially dried prior to use. Analytical TLC was performed using Merck Kieselgel G60 F_{254} precoated plates (0.25 mm) followed by visualization with UV light (254 nm), staining with iodine vapor or staining with a solution of 14% ammonium molybdate and 0.5% ceric sulfate in 10% aqueous sulfuric acid then heat. Flash column chromatography was performed using silica gel (Merck, 70-230 mesh ASTM). ^1H and ^{13}C NMR chemical shifts are reported in ppm; coupling constants are reported in Hz. ^1H and ^{13}C spectra were recorded on Bruker AM and AMX systems. IR spectra were recorded on a Nicolet Magna-IR 550 spectrophotometer. Mass spectra were acquired on a Finnigan MAT TSQ-700 instrument under direct exposure probe (EI) conditions, and high resolution mass spectra (HRMS) were acquired on a JEOL SX102 instrument (EI). Elemental analyses were obtained from Quantitative Technologies Inc, Whitehouse, NJ.

Isonipecotic acid-*N*-benzyl carbamate (4) Isonipecotic acid **3** (4.02 kg, 31.1 mol) and K_2CO_3 (10.1 kg, 72.9 mol) were dissolved in water (40.2 L) in a 100 L 4 neck flask with mechanical stirring, and the solution was cooled to 10°C. Benzyl chloroformate (6.91 kg, 40.5 mol) was added over 4 h, maintaining the temperature between 9 and 14°C, and the mixture was aged for 58 h at 22°C. The reaction mixture (pH = 9.0) was transferred to a 200 L extractor and washed with EtOAc (3 × 15 L) and toluene (8 L). The aqueous phase was acidified to pH = 1.8 by the cautious addition of 37% aqueous HCl (10 L), and extracted with toluene (3 × 66 L). The toluene extracts were dried with sodium sulfate (2 kg) and filtered through a pad of Solkafloc. Quantitative HPLC analysis indicated the yield of carbamate **4** was 7.89 kg (97%). The filtrates were concentrated at 10 mbar at < 25°C to a volume of 18 L. The product **4** was 99.1 area % pure by HPLC with 0.9 area % benzyl alcohol as the only impurity. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, isocratic elution with 35% MeCN, 65% of 0.1% aqueous H_3PO_4, 1.5 mL/min flow at 25°C with detection at 254 nm, retention times: **4** = 6.9 min, benzyl alcohol = 3.3 min, toluene = 17.3 min. An analytical sample of **4** was prepared by evaporation of the concentrated toluene solution *in vacuo*. Benzyl carbamate **4:** mp = 71-74°C; ^1H NMR (300.1 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.13 (s, 2H), 4.10 (br d, J = 12.2 Hz, 2H), 2.96 (br t, J = 4.0 Hz, 2H), 2.51 (tt, J = 10.8, 4.0 Hz, 1H), 1.93 (br m, 2H), 1.67 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.2, 155.3, 136.6, 128.5, 128.0, 127.9, 67.3, 43.2, 40.6, 27.6; FTIR (thin film) ν_{max} 3100, 2956, 1701, 1436 cm^{-1}; MS (EI) m/z 263 (M^+), 218, 128, 91 (base peak); Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.75; H, 6.59; N, 5.20.

Isonipecotic acid chloride-*N*-benzyl carbamate (5) Toluene (10 L) and DMF (5 mL) were added to the solution of benzyl carbamate **4** (7.89 kg, 30.0 mol in toluene) from the preceding step. Oxalyl chloride (3.94 kg, 31.0 mol) was added over a period of 20 min. The reaction mixture was aged for 16 h at 18°C under a slow stream of nitrogen, and the mixture was concentrated at 10 mbar and 20-25°C until 5 L of solvent had been removed. Quantitative HPLC analysis indicated > 98% yield of crude **5**.[16] An analytical sample of **5** was prepared by evaporation of the concentrated toluene solution *in vacuo*. Acid chloride **5:** ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.34 (m, 5H); δ 5.18 (s, 2H); δ 4.17 (m, 2H); δ 2.98 (br t, J = 4.1 Hz, 2H); δ 2.91 (tt, J = 10.8, 3.9 Hz, 1H); δ 2.10 (br m, 2H); δ 1.77 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.7, 155.0, 136.5, 128.6, 128.2, 128.0, 67.4, 52.6, 42.8, 28.2; FTIR (thin film) ν_{max} 2957, 1792, 1701, 1431, 1226 cm^{-1}; MS (EI) m/z 281 (M$^+$), 202, 174, 91 (base peak).

Piperidine-4-carboxaldehyde-1-benzyl carbamate (6) DIEA (1.55 kg, 15.0 mol) and thioanisole (0.56 g) were added to the solution of **5** (3.38 kg, 12.0 mol) in toluene (5.54 kg) from the previous step, and 10% Pd/C catalyst (101 g) was suspended in this mixture. The mixture was immediately placed into a 5 gal autoclave and hydrogenated at 20°C and 40 psi of H_2. After 18 h a second charge of catalyst (101 g) and thioanisole (0.54 g) were added as a slurry in 1375 mL toluene to the autoclave and hydrogenation was continued for a further 4 h. The catalyst and precipitated DIEA•HCl were removed by filtration through Solkafloc, and the filter cake was washed with toluene (10 L). The filtrates were transferred to a 50 L extractor and washed with 1 M aqueous HCl (2 × 7.2 L) and water (2 × 7.2 L). The mixture was concentrated at 10 mbar and 25-30°C until 5 L of residue remained. Quantitative HPLC analysis indicated 94% yield of aldehyde **6** with < 1% of dimer **7**, and < 1% of **3**. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, isocratic elution with 42% MeCN, 58% of 0.1% aqueous H_3PO_4, 1 mL/min flow at 50°C with detection at 220 nm, retention times: **7** = 6.6 min, **6** = 8.1 min. An analytical sample of **6** was prepared by evaporation of the concentrated toluene solution *in vacuo*. Aldehyde **6**: R_f = 0.52 (4/1 diethyl ether/pentane); ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 9.65 (d, J = 0.6 Hz, 1H), 7.34 (m, 5H), 5.12 (s, 2H), 4.04 (br d, J = 13.0 Hz, 2H), 3.01 (ddd, J = 13.3, 10.9, 3.1 Hz, 2H), 2.43 (m, 1H), 1.91 (br m, 2H), 1.57 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.7, 155.1, 136.7, 128.5, 128.0, 127.9, 67.2, 47.8, 43.0, 25.1; FTIR (thin film) ν_{max} 2945, 2857, 1725, 1699, 1430, 1222 cm^{-1}; MS (EI) m/z 247 (M$^+$), 219, 156, 91 (base peak).

Cbz-Spiroindolenine 8 Phenylhydrazine (5.41 g, 0.050 mol) was added via a weighed syringe over 5 min to the Cbz-aldehyde **6** (12.37 g, 0.050 mol) in dichloromethane (500 mL) in a 1 L flask while maintaining the temperature < 3°C under nitrogen.[17] After 10 min at 0-2°C TFA (11.56 mL, 17.10 g, 0.150 mol) was added by syringe maintaining the temperature between 2 and 7°C. The reaction mixture was aged at 35°C for 17 h. The mixture was cooled to 10°C, and a mixture containing 28-30% ammonium hydroxide (60 mL), water (100 mL) and crushed ice (150 g) was added with good stirring. The organic phase was separated and washed with water (2 × 400 mL) then saturated aqueous NaCl (100 mL). The organic phase was dried over magnesium sulfate and filtered through a plug of silica (5 g). The filtrate was evaporated to give 15.84 g (99%) of indolenine **8** as a pale orange oil.[13] HPLC conditions: 25 cm Dupont Zorbax RXC8 25 × 4.6 cm column, gradient elution over 15 min 57/43 → 75/25 MeCN/water, 1.0 mL/min flow at 30°C with detection at 254 nm, retention times: indolenine **8** = 7.5 min. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 15 min 57/43 → 75/25 MeCN/water, 1.0 mL/min flow at 30°C with detection at 254 nm, retention times: indolenine **9** = 8.2 min. Cbz-Spiroindolenine **8**: R_f = 0.18 (ethyl ether); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.4-7.3 (m, 7H), 7.24 (t, J = 7.6 Hz, 1H), 5.19 (s, 2H), 4.06 (br d, J = 14 Hz, 2H), 3.54 (m, 2H), 1.79 (br m, 2H), 1.63 (br d, J = 14 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.6, 155.2, 154.4, 142.5, 136.4, 128.4, 128.2, 128.0, 127.8, 126.2, 122.0, 121.4, 67.2, 55.5, 41.7, 30.4; FTIR (thin film) ν_{max} 2947, 1698, 1432, 1239 cm^{-1}; MS (EI) m/z 320 (M$^+$), 185, 156, 91 (base peak).

Methanesulfonamide 10 In a 2 L 3 neck flask equipped with a mechanical stirrer, toluene-MeCN (49;1 v/v, 617 mL) was degassed by passing a stream of nitrogen through the solution for 5 min. Phenylhydrazine (23.8 g, 0.22 mol) and TFA (75.3 g, 0.66 mol) were added to the mixture during the degassing. The solution in the flask was heated to 35°C, and a solution of Cbz-aldehyde **6** (49.5 g, 0.20 mol) in degassed 49:1 toluene-MeCN (50 mL) was slowly added to the phenylhydrazine-TFA over 2 h. The mixture was aged at 35°C for 16 h. The mixture was cooled to -10°C, and MeOH (50 mL) was added. A suspension of sodium borohydride (11.3 g, 0.30 mol) in toluene (20 mL) was added in small portions (1 mL) over 30 min taking care that the temperature did not exceed -2°C. The mixture was washed with 6% aq NH_4OH (200 mL). MeCN (20 mL) and MeOH (20

mL) were added to the organic phase, and it was washed with 15% brine (150 mL). Quantitative HPLC analysis indicated the organic phase contained 60.0 g of **9** (93%). An analytical sample of **9** was prepared by evaporation of an aliquot of the IPAC solution and crystallization from IPAC (99.5 HPLC area % purity). HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 15 min 57/43 → 75/25 MeCN/water, 1.0 mL/min flow at 30°C with detection at 254 nm, retention times: Cbz-spiroindoline **9** = 8.2 min. Cbz-Spiroindoline **9**: R_f = 0.33 (ethyl ether); mp = 118-120°C; ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.38 (m, 5H), 7.05 (m, 2H), 6.75 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 5.18 (s, 2H), 4.16 (br m, 2H), 3.77 (br m, H), 3.49 (s, 2H), 3.01 (br t, J = 11.2 Hz, 2H), 1.76 (br m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.4, 150.5, 136.8, 136.1, 128.5, 128.0, 127.9, 122.6, 118.8, 109.8, 67.1, 55.9, 44.4, 41.3, 35.4; FTIR (thin film) ν_{max} 3332, 2859, 1694, 1440 cm^{-1}; MS (EI) m/z 322 (M^+), 143, 130, 91 (base peak); Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.47; H, 6.77; N, 8.65.

The crude solution of Cbz-spiroindoline **9** was concentrated in a 1L 3 neck flask (60-70°C, 150-200 Torr) until 250 g of residue remained. THF (150 mL) and DIEA (29.7 g, 40.1 mL, 0.230 mol) were added, and the resulting homogeneous solution was cooled to 0°C. A solution of MsCl (21.1 g, 0.184 mol) in THF (50 mL) was added dropwise via a 125 mL dropping funnel over 2 h to the reaction mixture maintaining the temperature between 0 and 4°C and the mixture was aged for 2 h at 5-8°C. The HPLC assay yield was 94% from **9**. The mixture was warmed to 50°C and washed with 1M aqueous HCl (200 mL), water (100 mL), 5% aqueous sodium bicarbonate (100 mL), and water (100 mL). The organic phase was transferred to a 1 L 3 neck flask equipped for distillation. The mixture (ca 400 mL) was distilled at atmospheric pressure until 150 mL of distillate had been collected (head temperature: 107°C; pot temperature: 110°C). The distillation was continued with continuous addition of n-propanol at such a rate as to maintain a constant volume (ca 350 mL) in the pot. The distillation was stopped when a total of 525 mL of n-PrOH had been added and a total of 800 mL of distillate had been collected. The temperature of both the head and pot rose from 94°C to 98°C during the solvent switch. The mixture was allowed to cool gradually to 20°C over 3 h and aged for 12 h. The crystalline slurry was filtered and washed with n-PrOH (3 × 100 mL). The product was dried in a vacuum oven at 50°C to furnish 65.5 g (82% from aldehyde **5**) of **6** as a tan solid with 93.5 wt% purity by HPLC. For additional purification, a 40.0 g sample of the n-PrOH crystallized sulfonamide was dissolved in of EtOAc (134 mL) at 60°C to give a brown solution which was treated with Darco G-60 carbon (8.0 g) for 1 h at 60°C. The slurry was filtered through a pad of Solkafloc (4.0 g), and the pad was washed with EtOAc (90 mL) at 60°C. The golden yellow filtrate was distilled at atmospheric pressure in a 500 mL flask (pot temperature 80-85°C) until 100 g (100 mL) of residue remained. This solution was allowed to cool to 35°C over 3 h. Over a 1 h period, cyclohexane (116 mL) was added with good agitation at 35°C. The mixture was cooled to 20°C over 1 h and aged at 20°C for 12 h. The crystalline slurry was filtered and the cake was washed with 2:1 cyclohexane-EtOAc (2 × 77 mL) and cyclohexane (2 × 77 mL). The product was dried in a vacuum oven at 50°C to furnish 34.2 g of **10** as a white crystalline solid (85% recovery from crude **10**, 70% from **4** with > 99.9 wt% purity by HPLC). HPLC conditions: Zorbax RXC8 250 × 4.6 mm column, isocratic elution with 55% MeCN, 45% of 0.1% aqueous H_3PO_4, 1 mL/min flow at 50°C with detection at 220 nm, retention times: phenylhydrazine = 1.6 min, dimer **7** = 4.1 min, aldehyde **6** = 4.7 min, spiroindoline **9** = 5.0 min, toluene = 6.3 min, spiroindolenine **8** = 6.9 min, sulfonamide **10** = 7.8 min, phenylhydrazone = 10.3. Sulfonamide **10**: mp = 126-128°C; ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.37 (m, 5H), 7.24 (m, 2H), 7.09 (m, 2H), 5.17 (s, 2H), 4.23 (br m, 2H), 3.85 (br s, 2H), 2.96 (br m, 1H), 2.91 (s, 3H), 1.78 (br m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.2, 140.9, 138.0, 136.6, 128.9, 128.6, 128.1, 128.0, 123.9, 123.3, 113.3, 67.3, 59.0, 42.9, 41.0, 36.0, 34.5; FTIR (thin film) ν_{max} 2930, 1698, 1348 cm^{-1}; MS (EI) m/z 400 (M^+), 185, 130, 91 (base peak); Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99. Found: C, 62.75; H, 6.02; N, 6.90.

Deprotected-spiroindoline 11 A mixture of Cbz-Methanesulfonamide **10** (1.00 kg, 2.50 mol) in EtOH (9 L) at 60-70°C was placed in a 20 L autoclave. A slurry of 10% palladium on charcoal (75 g, 7.5% by weight) in EtOH (750 ml) was added to the autoclave and rinsed in with a further portion of EtOH (250 ml). The mixture was hydrogenated at 65°C with vigorous stirring under 40 psi hydrogen pressure for 3 h. A second portion of 10% palladium on charcoal (75 g) was added, and the batch was hydrogenated for a further 2 h. The mixture was evaporated *in vacuo* with the simultaneous addition of EtOH (18 L) to remove formic acid. Two other runs using 1.00 kg, 7.49 mol **10** each were completed in a similar fashion, and all three batches were combined and filtered at 60-65 °C through a pad of Solkafloc (2.5 kg). The pad was rinsed with a hot (60-65 °C) mixture of concentrated aqueous ammonia (500 ml) in EtOH (25 L). Quantitative HPLC analysis of the combined filtrates indicated a yield of 1.86 kg of **11** (93%). The filtrates were concentrated *in vacuo* to 15 L.

The mixture was evaporated with the simultaneous addition of isopropyl acetate (IPAC, 45 L) maintaining a batch volume of *ca.* 15 L. The mixture was then diluted to *ca.* 33 L with IPAC (20 L), and this solution was used in next step. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 35 min 5/95 → 95/5 MeCN/aqueous solution of 0.05% H_3PO_4 and 0.01% Et_3N, 1.2 mL/min flow at 48°C with detection at 210 nm, retention time: Cbz-methanesulfonamide **10** = 25.2 min, *NH*-methanesulfonamide **11** = 8.5 min. An analytical sample of **11** was prepared by evaporation of an aliquot of the IPAC solution and crystallization from 1:1 (by vol) IPAC-heptane. *NH*-Methanesulfonamide **11**: mp = 102-105°C; ^{1}H NMR (300.1 MHz, CD_3OD) δ 7.34 (d, *J* = 7.7 Hz, 1H), 7.21 (m, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 3.86 (s, 2H), 3.00 (br d, *J* = 6.4 Hz, 3H), 2.71 (dt, *J* = 12.6, 2.7 Hz, 2H), 1.83 (dt, *J* = 12.6, 4.2 Hz, 2H), 1.64 (br d, *J* = 12.4 Hz, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 143.2, 139.9, 129.5, 124.9, 124.5, 114.3, 60.5, 44.2, 43.8, 37.6, 34.5; FTIR (thin film) ν_{max} 2990, 1478, 1345, 1161 cm^{-1}; MS (EI) m/z 266 (M^+), 187 ($M^+ - CH_3SO_2$, base peak), 158, 144, 129; Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.61; H, 6.81; N, 10.52. Found: C, 58.61; H, 6.80; N, 10.43.

***N*-Boc-*O*-benzyl-(D)-serine (14)** A solution of *N*-Boc-(D)-serine (2.05 g, 10 mmol) in DMF (10 mL) was added to a solution of NaOt-Am (2.203 g, 20 mmol) in DMF (10 mL) at 0°C over 1 h. The resulting white suspension was cooled to -20°C, and BnBr (1.881 g, 11 mmol) was added over 1 h maintaining the temperature < -10°C. The mixture was aged at -10°C for 1 h and diluted with water (40 mL). The mixture was washed with MTBE (20 mL), acidified to pH = 2.0 with 2 M aq HCl (5.5 mL), and extracted with 1:1 MTBE-hexane (2 × 20 mL). The organic phase was washed with water (20 mL) and satd aq NaCl (20 mL), dried over $MgSO_4$, and filtered through a plug of silica (5 g). The filtrate was diluted to 100 mL with 1:1 MTBE-hexane and Et_2NH (0.816 g, 11 mmol) was added. After an 18 h age at 20°C the resulting slurry was filtered and the filter cake was washed with 3:1 hexane-MTBE (30 mL) to give **14** (2.73 g, 74%) as a fluffy white crystalline solid. The product was found to have a purity > 99.5% and > 99.8% ee by HPLC analysis. HPLC conditions: Diacel Crownpak CR(-) 150 × 4.6 mm column, gradient elution over 20 min 10/90 → 12/88 MeOH/pH 1.9 aq $HClO_4$, 1.0 mL/min flow at 25°C with detection at 217 nm, retention times: *N*-Boc-*O*-benzyl-(D)-serine **14**[15] = 10.3 min, *N*-Boc-*O*-benzyl-(L)-serine = 15.7 min.

MK-677 Methanesulfonic acid salt Water (20 L), DCC (1.58 kg, 7.65 mol), HOBt (1.03 kg, 7.62 mol), IPAC (7 L), and finally *N*-Boc-*O*-benzyl-D-serine **14** (2.26 kg, 7.65 mol) were added to the stirred solution of the deprotected spiroindoline **11** (1.86 kg, 6.96) in IPAC (33 L) at 25°C. The mixture was stirred at room temperature under a nitrogen atmosphere for 5 h and filtered rinsing with IPAC (22 L). The lower aqueous layer was separated, and the organic phase was washed with 1M aqueous NaOH (26 L), 0.5M aqueous HCl (2 × 26 L), and saturated aqueous $NaHCO_3$ (26 L). Quantitative HPLC analysis of the organic phase indicated an assay yield of 3.79 kg of **12** (93% from **10**). The organic phase was concentrated *in vacuo* to *ca.* 15 L. The mixture was evaporated with the simultaneous addition of EtOH (50 L) maintaining a batch volume of *ca.* 15 L. This solution of *N*-Boc monopeptide **12** was used in next step. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 35 min 5/95 → 95/5 MeCN/aqueous solution of 0.05% H_3PO_4 and 0.01% Et_3N, 1.2 mL/min flow at 48°C with detection at 210 nm, retention times: *N*-Boc-monopeptide **12** = 26.3 min. Chiral HPLC analysis indicated > 99.8 %ee. HPLC conditions: Chirasphere RXC8 250 × 4.6 mm column, isocratic elution with 74:4:22 hexane-dioxane-iPrOH, 0.9 mL/min flow at 18°C with detection at 234 nm, retention times: **12** = 9.7 min, **12** antipode (L-isomer) = 8.6 min.

Methanesulfonic acid (2.01 kg, 1.36 L, 96.1 mol) was added to the above solution of *N*-Boc-monopeptide **12** (3.79 kg, 6.96 mol) in EtOH (total volume *ca.* 15 L) at 25°C and the mixture was warmed to 35-40°C for 7.5 h. The mixture was cooled to 20°C and water (44 L) was added. The mixture was cooled to *ca.* 5°C for 30 minutes and filtered. The pH was adjusted to pH > 10 with 1M aqueous NaOH (16 L) and 50% aqueous NaOH (1.6 L), and the mixture was extracted with IPAC (38 L). The organic phase was separated (quantitative HPLC analysis indicated it contained 3.06 kg of **13**, 92% overall yield from **10**) and this solution was used for the next step. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 35 min 5/95 → 95/5 MeCN/aqueous solution of 0.05% H_3PO_4 and 0.01% Et_3N, 1.2 mL/min flow at 48°C with detection at 210 nm, retention time: monopeptide amine **13** = 14.8 min.

Water (49 L) was added to the stirred solution of the monopeptide amine **13** (3.06 kg, 6.89 mol) in IPAC (total volume *ca.* 51 L) at room temperature under a nitrogen atmosphere. DCC (1.56 kg, 7.56 mol), HOBt (1.02 kg, 7.55 mol) and finally *N*-Boc-2-aminoisobutyric acid **16** (1.54 kg, 7.58 mol) were added, and the mixture was stirred vigorously at room temperature for 2 h. The mixture was filtered using IPAC (22 L) to

wash the filter cake. The biphasic mixture was separated, and the organic phase was washed sequentially with 1M aqueous NaOH (38 L), 0.5M aqueous HCl (38 L), and saturated aqueous $NaHCO_3$ (38 L). The organic phase was filtered rinsing with IPAC (10 L). Quantitative HPLC assay indicated the combined filtrates contained 4.40 kg of Boc-dipeptide **15** i.e. 93% overall from **10**. The filtrates were concentrated *in vacuo* to *ca.* 15 L. The mixture was evaporated with the simultaneous addition of EtOH (45 L) maintaining a batch volume of *ca.* 15 L. This solution (25 L) containing 4.40 kg of Boc-dipeptide **15** was used for the next step. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 35 min 5/95 → 95/5 MeCN/aqueous solution of 0.05% H_3PO_4 and 0.01% Et_3N, 1.2 mL/min flow at 48°C with detection at 210 nm, retention time: *N*-Boc-dipeptide **15** = 25.6 min. An analytical sample of **15** was prepared by crystallization from EtOH. *N*-Boc-Dipeptide **15**: mp = 110-113°C; FTIR (thin film) ν_{max} 3402, 2932, 1715, 1639, 1457, 1350 cm^{-1}.

Methanesulfonic acid (2.02 kg, 1.36 L, 96.1 mol, *ca.* 3 equivs.) was added to the stirred solution of crude Boc-dipeptide **15** (4.40 kg, 6.99 mol) in EtOH (total volume *ca.* 25 L) at 25°C and the mixture was warmed to 35-40°C overnight. The mixture was concentrated *in vacuo* to *ca.* 15 L volume and then diluted with water (44 L). The mixture was cooled to *ca.* 5°C for 30 minutes and filtered using water (10 L) for rinsing. The pH was adjusted to pH > 10 with 1M aqueous NaOH (16L) and 50% aqueous NaOH (2.6 L), and the mixture was extracted with EtOAc (36 L). The organic phase was separated and concentrated *in vacuo* to *ca.*. 20 L. The mixture was evaporated, first with the simultaneous addition of a mixture of EtOAc (35 L) and EtOH (5 L), then with EtOAc (40 L) maintaining a pot volume of *ca.* 20 L. At this point, 19.2 L of the above solution (20.0 L total) was diluted with EtOAc (16 L) and treated with Darco G-60 carbon (900 g) at room temperature overnight. The slurry was filtered through Solkafloc (2.5 kg) using EtOAc (22 L) to wash the filter cake. Quantitative HPLC analysis indicated the combined filtrates contained 3.15 kg of MK-677 free base, 82% overall yield from **10** corrected for the 100 g of MK-677 removed earlier. The filtrates (58 L) were concentrated *in vacuo* to 20-25 L, and diluted to 46.0 L with EtOAc (25 L).

A 45.2 L portion of the above solution of MK-677 free base (3.10 kg, 5.86 mol) in EtOAc was diluted to 62 L with EtOAc and EtOH (6.4 L). The mixture was warmed to 50°C, and a solution of methanesulfonic acid (620 g, 412 ml, 6.45 mol) in EtOAc (11L) was added over *ca.* 5 minutes at 50-54°C. The mixture was seeded with MK-677 MsOH salt (70 g), and the resulting slurry was stirred at 55°C overnight. The slurry was cooled to 15-20°C for 2 h and filtered under a nitrogen atmosphere. The solid product was washed with a mixture of EtOH (2.3 L) in EtOAc (26 L) and dried in a vacuum oven at 35°C for 2 days to provide MK-677 MsOH salt (3.35 kg including seed, 74% overall yield from **10**, 4% correction for samples removed) as anisotropic acicular crystals. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 35 min 5/95 → 95/5 MeCN/aqueous solution of 0.05% H_3PO_4 and 0.01% Et_3N, 1.2 mL/min flow at 48°C with detection at 210 nm, retention time: MK-677 = 13.4 min. Chiral capillary electrophoresis indicated > 99.8 %ee. Capillary electrophoresis conditions: ABI 270 A/HP 3D instrument, 70 cm × 76 μm fused silica capillary, elution with pH 4.2 buffer containing 25% EtOH, 24 mM in NaH_2PO_4, 40 mM in L-tartaric acid, and 30 mM in β-cyclodextrin, 20 kV at 25°C with detection at 200 nm, retention times: MK-677 = 43.9 min, MK-677 antipode (L-isomer) = 45.0 min. MK-677 • MsOH: R_f = 0.64 (90:10:1 $CHCl_3$-MeOH-30% aq NH_4OH); mp = 166-168°C; $[\alpha]^{25}_{365}$ = -15.71 (*c* 2.00, MeOH); ^1H NMR (400.1 MHz, CD_3OD-compound exists as a 1/1 mixture of amide rotamers, 1H represents 1 proton in a single rotamer) δ 7.38-7.21 (m, 12H), 7.24-7.18 (m, 3H), 7.05 (t, *J* = 7.4 Hz, 1H), , 6.99 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 5.16 (m, 2H), 4.58-4.45 (om, 6H), 4.05 (m, 2H), 3.90 (s, 4H), 3.82-3.70 (m, 4H), 3.23 (m 2H), 2.96 (s, 3H), 2.95 (s, 3H), 2.85 (m 2H), 2.68 (s, 6H), 1.95 (m, 1H), 1.87-1.59 (m, 7H), 1.63 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 173.1, 173.0, 170.1, 169.9, 142.6, 142.5, 139.5, 139.3, 139.2, 129.7_4, 129.6_6, 129.6, 129.5, 129.1, 129.0_1, 128.9_7, 124.8, 124.5, 114.4, 114.3, 74.4, 74.2, 70.9, 70.1, 60.2, 60.0, 58.2, 51.5, 50.9, 44.3, 44.0_5, 55.4, 44.1_2, 41.0, 40.7, 39.5, 37.5, 36.8, 34.5, 24.3, 24.2, 24.1, 24.0; FTIR (thin film) ν_{max} 2930, 1636, 1558, 1540, 1458, 1345 cm^{-1}; MS (EI) m/z 528 (M^+), 449, 428, 243, 187, 91, 58 (base peak); HRMS calcd for $C_{27}H_{36}N_4O_5S$: 528.2385 Found: 528.2406; Anal. Calcd for $C_{28}H_{40}N_4O_8S_2$: C, 53.83; H, 6.45; N, 8.97. Found: C, 53.82; H, 6.40; N, 8.89.

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† This work is dedicated to Professor Samuel J. Danishefsky for over 30 years of excellence in the art of organic synthesis.

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7. Thiophenol gave similar results while other catalyst poisons such as elemental sulfur, thiourea, t-dodecanethiol and quinoline gave less satisfactory results. The addition of thioanisole up to 0.1 mol% did not substantially decrease the rate of hydrogenation of **5** to **6**.

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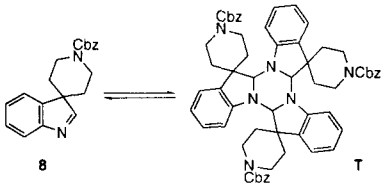
9. Rosenmund reduction of **5** with other solvents such as THF or EtOAc were inferior. The use of 2,6-lutidine led to exothermic formation of a crystalline solid (presumably the *N*-acyl-2,6-lutidinium chloride, ^{1}H NMR) which on hydrogenation gave a complex mixture; quinoline gave similar results. Mixtures of **5** and DIEA in toluene were stable for at least 24 h at 25°C as shown by ^{1}H NMR analysis in d_8-toluene.

10. Varying amounts (1-20%) of dimeric product **7** were formed. Both **6** and **7** are readily oxidized by atmospheric oxygen to the corresponding acids.

11. The Fischer indole reaction is best carried out between 0.1 and 0.25 M concentration in phenylhydrazine and aldehyde. Higher reaction concentrations decreased the yield and purity of **8** and **9**. Other solvents such as $CHCl_3$, PhCl-MeCN, and 1,2-dichlorobenzene-MeCN also gave satisfactory results.

12. Among the acid catalysts examined were: HCl in aq THF or aq MeOH, H_2SO_4 in aq EtOH, TMSCl in toluene, $AlCl_3$ in CH_2Cl_2, $AlBr_3$ in toluene, $MgBr_2$ in toluene or ether, $ZnCl_2$ or $ZnBr_2$ in EtOH, ether, CH_2Cl_2 or toluene, HOAc, CCl_3COOH in CH_2Cl_2, and $MsOH/P_2O_5$.

13. Spiroindolenine **8** was found to be in equilibrium with its cyclic trimer **T**, with monomeric **8** being favored under acidic conditions. (a) Nomura, Y.; Bando, T.; Takeuchi, Y.; Tomoda, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3199-3120, (b) Jackson, A.H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227-2239. Trimer **T** exhibits no symmetry with all aromatic and methine protons of the indoline systems resolved as separate resonances. A HMBC-2D experiment provides proof for the existence of a cyclic system, since all three hexahydro-1,3,5-triazine methines show correlations to two indoline systems (three-bond correlations through nitrogen). Selected data (hexahydrotriazine CH's): ^1H NMR (400.1 MHz, CD_3CN) δ 5.65 (s, 1H), 4.72 (s, 1H), 4.17 (s, 1H); ^{13}C NMR (100.6 MHz, CD_3CN) δ 84.5, 83.2, 85.3.



14. Slow hydrogenation due to insufficient agitation lead to the formation of a byproduct due to partial conversion of Cbz to benzyl which on further hydrogenation gave **11**. HPLC conditions: Dupont Zorbax RXC8 250 × 4.6 mm column, gradient elution over 35 min 5/95 → 95/5 MeCN/aqueous solution of 0.05% H_3PO_4 and 0.01% Et_3N, 1.2 mL/min flow at 48°C with detection at 210 nm, retention time: *N*-Ms-*N'*-benzyl-spiroindoline = 13.4. The formation of the *N*-benzylated byproduct could be readily circumvented by thorough agitation during the hydrogenation. The amine **11** could be crystallized as its free base from EtOAc-MTBE-hexane (82%) or as its HCl salt from MeOH-EtOAc (86%).

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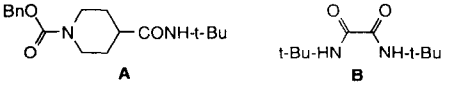
16. A 1.0 mL aliquot of the reaction mixture was quenched with 5.0 mL of tert-butylamine and analyzed after evaporation by HPLC: Dupont Zorbax RXC8 250 × 4.6 mm column, isocratic elution with 42% MeCN, 58% of 0.1% aqueous H_3PO_4, 1 mL/min flow at 50°C with detection at 220 nm. This method shows the quantity of **5** as derivative **A** and quantity $(COCl)_2$ as derivative **B**. Retention times: **4** = 2.1 min, **A** = 11.0 min, toluene = 12.1 min, **B** = 12.7 min.



17. Conversion of **6** to the corresponding phenylhydrazone was monitored by HPLC and TLC. HPLC conditions: Dupont Zorbax RXC8 25 × 4.6 cm column, gradient elution over 15 min 57/43 → 75/25 MeCN/water, 1.0 mL/min flow at 30°C with detection at 254 nm, retention times: phenylhydrazine = 4.5 min, toluene = 7.2 min, phenylhydrazone = 11.4 min. TLC (silica, 4/1 diethyl ether/pentane) aldehyde **6**: R_f = 0.52, phenylhydrazone: R_f = 0.61, phenylhydrazine: R_f = 0.21.

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