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Expedient Synthesis of MLN1251, A CCR5 Antagonist for Treatment of HIV

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Abstract:

An expedient synthesis of MLN1251 has been developed that allows for the production of multikilogram quantities of the target compound. The key transformation is synthesis of a 5-hydroxyindole by a Nenitzescu reaction. The longest linear sequence is five steps with an overall yield of approximately 31%.

Introduction

CCR5 is believed to be involved in the entry of HIV virus into macrophages and T cells.[1] Inhibition of the CCR5 receptor might be protective against HIV infections,[2] and several companies have published research within this area.[3] At the onset of this research, a route for production of several kilograms of MLN1251 (**1**) was requested to be at hand within a few months. Based on the literature it was believed that the shortest route to the target compound would include a Nenitzescu reaction[4] to build up the indole core structure of the molecule. This would be followed by a Mannich reaction and subsequent reaction with a suitable 1,3,4,6,7,8-hexahydro-2*H*-quinolizine salt to form MLN1251. Due to severe constraints in timelines we elected to develop a route suitable for production of the first few kilograms of material followed by more substantial development after this first production.

Results and Discussion

Retrosynthetic Analysis. Our retrosynthetic analysis of MLN1251 indicated a potentially very short route using a Nenitzescu indole formation as a key step, Scheme 1.

Starting from commercially available 2,2,6-trimethyl-1,3-dioxin-4-one and *S*-1-(4-fluorophenyl)ethanol,[5] a β-ketoester could be formed followed by treatment with ammonia to form the corresponding aminocrotonate. This aminocrotonate could be used in a Nenitzescu reaction to form the desired hydroxyl indole with the desired ester already in place. The retrosynthesis indicates a Mannich reaction followed by an alkylation reaction as the two final steps.

Synthesis of Hydroxyindole 6. The reaction between 2,2,6-trimethyl-1,3-dioxin-4-one and an alcohol to form a β-ketoester is well-known and needed minimal research before suitable reaction conditions were achieved. Refluxing a mixture of *S*-1-(4-fluorophenyl)ethanol (**2**) and 2,2,6-trimethyl-1,3-dioxin-4-one (**3**) in toluene gave the desired product **4** after a few hours in quantitative yield after evaporation of the solvent, Scheme 2. Residual toluene and 2,2,6-trimethyl-1,3-dioxin-4-one were observed as minor impurities.

To avoid early introduction of, at that time, the fairly expensive[6] chiral alcohol **2**, we initially investigated this sequence using an ethyl- or methyl-ester. The Nenitzescu reaction in particular gave better yield and purer material compared to those obtained by using the bulkier chiral alcohol. Unfortunately, the saponification of the achiral esters after the Nenitzescu reaction gave large amounts of decarboxylated product. Hence, we performed all the subsequent work with an early introduction of the chiral alcohol.

Formation of the aminocrotonate **5** was done by stirring the ketoester with a solution of ammonia in methanol for 18 h. Some hydrolysis of the benzyl ester was seen during this reaction in methanol, and although slightly less hydrolysis occurred using ethanol as solvent, methanol was chosen because of the availability of a methanolic solution of ammonia at the time of the production run. The crude amino crotonate was isolated in almost quantitative yield with approximately 10% of 1-(4-fluorophenyl)ethanol and 1%

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(5) From chiral reduction of the corresponding ketone, ee > 98%.

(6) Made by chiral reduction of the corresponding ketone in kilogram quantities.

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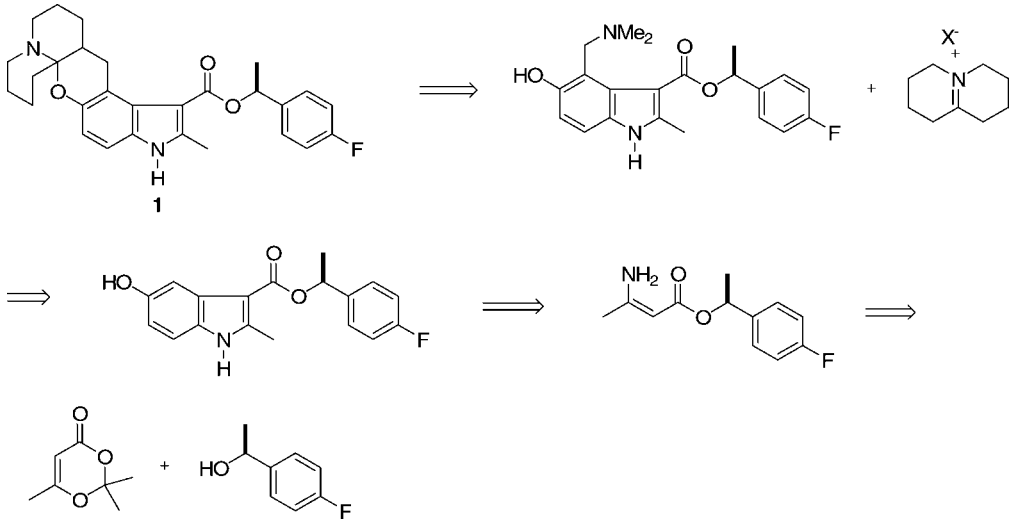
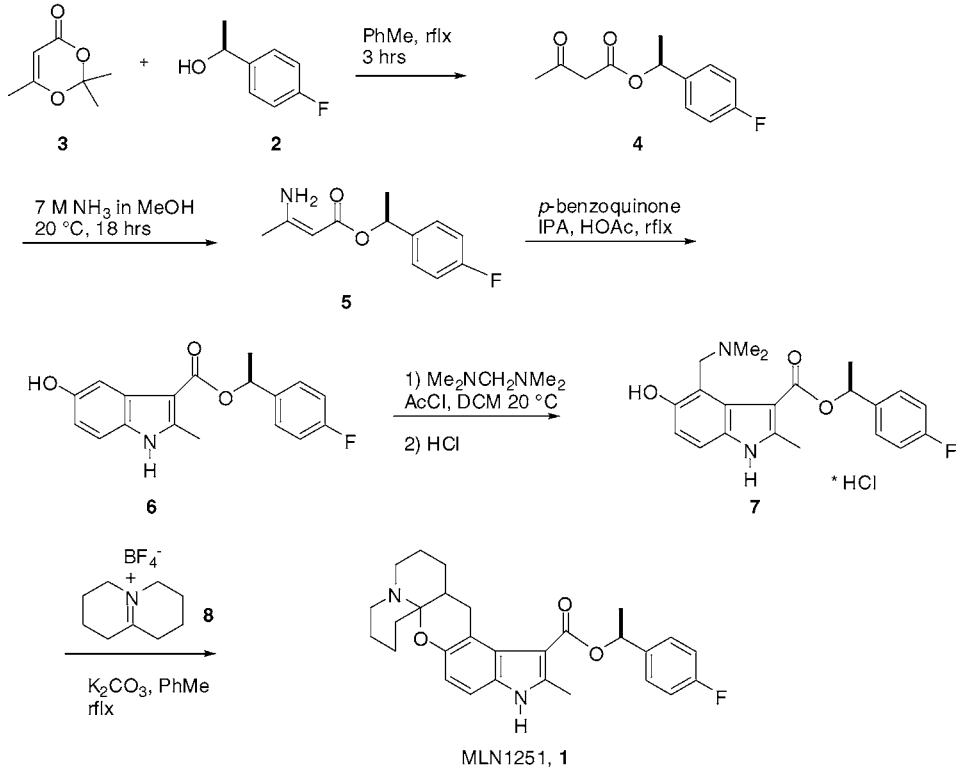
Scheme 1. **Retrosynthetic analysis of MLN1251**



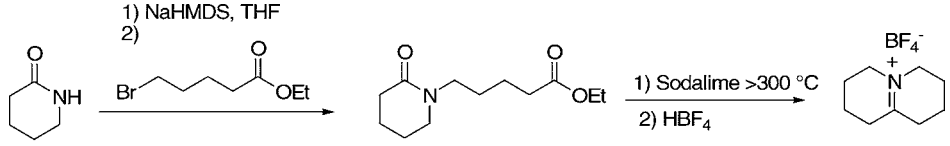
Scheme 2. **Synthesis of MLN1251**



methanol as impurities. The Nenitzescu reaction was optimized extensively. Initially, a large number of solvent systems were investigated using 2 equiv of *p*-benzoquinone (*p*-BQ) with catalytic amounts of HOAc. Solvents with less polarity, such as toluene and acetone, did not perform acceptably, whereas more polar solvents, such as alcohols, $MeNO_2$ or DMF/H_2O, gave the desired product in satisfactory yields. EtOH was chosen as solvent for the following research on the basis of good yields, fast reaction time, and the possibility of performing the subsequent Mannich reaction as a telescoped reaction. We next examined the role of HOAc. An absence of HOAc led to slow reaction rates, whereas a catalytic amount of HOAc led to markedly increased rates. Greater than catalytic amounts of HOAc led to faster reaction rates and decreased amounts of impurities. However, if several equivalents of HOAc were used, an increase in the rate of hydrolysis of the benzyl ester was observed. In our large production run, approximately 1.7 equiv HOAc was used. The reaction was sluggish at room temperature; therefore, reflux was deemed an appropriate reaction temperature. The amount of *p*-BQ could be reduced from 2 equiv to 1.1 or 1.2 equiv without significantly reducing the reaction rate or increasing the impurities. With these improvements the reaction usually completed within 1 h.

We first tried the Mannich reaction as a one-pot reaction following the Nenitzetscu reaction. Three equivalents of Me_2-NH and HCHO were added, in one portion, sequentially, in

Scheme 3. **Formation of the 1,3,4,6,7,8-hexahydro-2*H*-quinolizine (8)**



9 **8**

parallel, or as a premixed solution to the already refluxing reaction mixture from the Nenitescu reaction. Under these conditions, the reaction was completed after several hours. Alternatively, if a premixed solution was added dropwise, the reaction was essentially done after all reagents had been added. Although this was a convenient way to produce Mannich product **7**, the purification of **7** was cumbersome, and the overall yield was low. After flash chromatography only about 40−50% of the desired product was isolated. Despite several attempts to isolate the product by crystallization or salt formation and crystallization, none were successful. Purification of the Nenitzescu reaction product before the Mannich reaction gave good yield of **7**. Based on TLC and HPLC analysis of the reaction mixture, and isolated yields of purified material from the Nenitzescu reaction, it was obvious that using crude material from the Nenitzescu reaction resulted in low yields in the two-step reaction sequence. To allow for a simplified isolation and purification of **7**, we adopted an aqueous workup after the Nenitzescu reaction. In addition, an in situ formation of the Mannich reagent using *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine and AcCl, which allowed the Mannich reaction to be performed at room temperature instead of reflux in IPA as solvent. These improvements apparently reduced several side products and allowed for a convenient isolation of a HCl salt of the Mannich product **7** in approximately 45−50% yield from the aminocrotonate.

Synthesis of 1,3,4,6,7,8-Hexahydro-2*H*-quinolizine 8. Although simple in appearance, quinolizine **8** proved quite a challenge to produce. After pursuing more than a dozen different routes to this molecule we had to resort to a nonscaleable route to avoid delays in preclinical research. The compound was conveniently made in a two-step sequence by alkylation of valerolactam followed by a high-temperature soda lime distillation,[7,8] Scheme 3.

The alkylation was done using NaHMDS in THF, and after aqueous workup the alkylated valerolactam was isolated as an oil in >90% yield with hexamethyldisilazane as a minor impurity. The soda lime distillation was done by adding **9** to solid soda lime followed by heating the vessel using a mantle without stirring. EtOH and water started to distill initially (distillate temperature below 110 °C) followed by the product and water (distillate temperature 110−210 °C). The second fraction was taken up in MTBE, washed with brine, dried, and cooled. Tetrafluoroboric acid was added as a diethyl ether solution to form a precipitate. The salt was collected by filtration, and after drying approximately 200−300 g of **8** was isolated from each soda lime distillation. Due to safety concerns with the high temperature, the batch size was not increased beyond this scale.

Synthesis of MLN1251 (1). The final step in the sequence was initially done by forming the free base of **8** using a basic aqueous solution and an organic solvent, followed by evaporation of the organic solvent. The resulting isolated free base of quinolizine **8** was then used in the alkylation step. This procedure required an excess of the quinolizine due to its volatile nature and instability. As we had some problems in producing **8** in large amounts it was necessary to thoroughly study this step to reduce the amount of quinolizine required. Neither changing the solvent for the extraction of the free base of **8** nor the solvent for the reaction improved the yield or decreased the amount of **8** required. Instead, an in situ method of forming the free base and performing the reaction was developed. Using a two-phase system, wherein **7** and **8** were heated with toluene and aqueous $NaHCO_3$ in a 1:1 mix at reflux, allowed us to decrease the amount of quinolizine salt **8** to approximately 1 equiv. After the reaction was complete, usually 2−3 h at reflux, the two layers were separated, and the organic layer was dried and concentrated. The target compound **1** could then be isolated in 70% yield with a HPLC purity of >99% (AN) after crystallization from EtOH and water, Scheme 2.

Conclusions/Summary

An enabling route to MLN1251 has been developed allowing for production of kilogram quantities of the target compound. The key reaction is a Nenitzescu reaction which is used to build up the core indole structure.

Experimental Section

All reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise noted. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise.

Ethyl 5-(2-Oxopiperidin-1-yl)pentanoate (9). In a 20-L jacketed vessel with a large anchor stirrer, δ-valerolactam (991.3 g, 10 mol) in THF (1 L) was added over 15 min to a cooled solution of sodium bis(trimethylsilyl)amide (10 mol) in THF (9 L) under nitrogen, such that the reaction temperature was maintained below 10 °C. A very thick precipitate formed, and the mixture was warmed to 20 °C over 25 min. Ethyl 5-bromovalerate (1.9 kg, 9.1 mol) was added over 10 min, and the mixture was heated to 60 °C over 5 h and then maintained at this temperature for 13 h. After this time the precipitate was finer and free flowing. The reaction was quenched by addition of saturated ammonium chloride solution (5 L) containing concentrated HCl (250 mL). The mixture was allowed to settle, and the layers

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(8) **WARNING:** This reaction is potentially hazardous and should be examined very carefully before using it at any scale.

were separated. The organic layer was washed with 1 M HCl (2.5 L). The aqueous layers were combined and extracted with ethyl acetate (2 × 2.5 L). The organics were combined, washed with brine (2.5L), dried ($MgSO_4$, 655 g), filtered, and concentrated to give 1.925 kg (93%) of **9** as a dark brown oil. ^{1}H NMR was consistent with the structure with hexamethyldisilazane as a minor impurity.

1,3,4,6,7,8-Hexahydro-2*H*-quinolizine Tetrafluoroboric Acid Salt (8). Ethyl 5-(2-oxopiperidin-1-yl)pentanoate (394.0 g, 1.73 mol) and crushed soda lime (524.2 g) were charged to a 2-L, three-necked round-bottomed flask with thermometer, distillation apparatus, and heating mantle. The apparatus was vacuum flushed with nitrogen, and the mixture was heated and distilled to give two fractions. Fraction 1: approx 150 mL, distillate temp below 110 °C (mainly ethanol and water distilled over). Fraction 2: approx 300 mL, distillate temp 110−210 °C (up to 300 °C pot temperature, water and product distilled).

Fraction 1 was taken up in TBME (400 mL), shaken, and separated. The organic layer was washed with brine (400 mL), added to Fraction 2, and diluted with additional TBME (400 mL). The solution was washed with brine (400 mL), the aqueous was extracted with TBME (400 mL), and the organic layers were combined, dried ($MgSO_4$, 84 g), and filtered. The solution was cooled while stirring in an ice−water bath, and tetrafluoroboric acid (215 mL of a 54 wt % solution in diethyl ether, 1.56 mol) was added at a rate such that the temperature was maintained below 30 °C. The tetrafluoroborate salt precipitated, was collected by filtration, and dried under vacuum at ambient temperature for 16 h to give 287.35 g, 74%, of **8** as a light-peach solid, which was stored in a freezer. ^{1}H NMR (DMSO-d_6), 300 MHz) δ (ppm): 1.62 (m, 4H), 1.83 (m, 4H), 2.68 (m, 4H), 3.60 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 186.0, 53.2, 31.8, 20.1, 16.3.

1-(4-Fluorophenyl)ethyl 3-Oxobutanoate (4). 2,2,6-Trimethyl-1,3-dioxin-4-one (1.5 kg, 10.6 mol), 1-(4-fluorophenyl)ethanol (*S*-enantiomer 1.345 kg, 9.6 mol), and toluene (8.07 L) were charged to a 20-L jacketed reactor, and heated. Reflux was obtained after 1 h and the mixture stirred at reflux (internal temperature (IT) 96−98 °C) for 3 h. The mixture was cooled to IT 30 °C and concentrated to give 2.284 kg, 106% (uncorrected for purity), of **4** as a dark brown oil. ^{1}H NMR consistent with structure with toluene and 2,2,6-trimethyl-1,3-dioxin-4-one as minor impurities.

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.56 (d, J = 6.6 Hz, 3H), 2.23 (s, 3H), 3.45 (s, 2H), 5.91 (q, J = 6.6 Hz, 1H), 7.00−7.08 (m, 2H), 7.30−7.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 200.3, 166.2, 162.3 (d, $^1J_{CF}$ = 246 Hz), 136.7 (d, $^4J_{CF}$ = 3.3 Hz), 127.9 (d, $^3J_{CF}$ = 8.2 Hz), 115.3 (d, $^2J_{CF}$ = 21.4 Hz), 72.7, 50.1, 29.9, 21.8. MS ES 223.2 [M − H]. R_f 0.5 (1:1 EtOAc/hexanes).

1-(4-Fluorophenyl)ethyl 3-Aminobut-2-enoate (5). 1-(4-Fluorophenyl)ethyl 3-oxobutanoate (3.068 kg, 1.37 mol) in a solution of ammonia in methanol (7 M, 10 L) was stirred at 20 °C in a 20-L jacketed vessel for 18 h. The mixture was concentrated to give 2.971 kg, 97%, of the aminocrotonate as a brown oil. Yield: ^{1}H NMR consistent with structure, with ca. 10% of 1-(4-fluorophenyl)ethanol and 1% of methanol as impurities. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.50 (d, J = 6.6 Hz, 3H), 1.89 (s, 3H), 4.58 (s, 1H), 5.85 (q, J = 6.6 Hz, 1H), 6.97−7.07 (m, 2H), 7.29−7.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.1, 162.0 (d, $^1J_{CF}$ = 245 Hz), 160.8, 139.1 (d, $^4J_{CF}$ = 3.0 Hz), 127.7 (d, $^3J_{CF}$ = 8.0 Hz), 115.4 (d, $^2J_{CF}$ = 21 Hz), 83.4, 69.2, 22.4, 21.9. MS 224.1 ES [M + H]$^+$. R_f 0.5 (1:1 EtOAc/hexanes).

1-(4-Fluorophenyl)ethyl 5-Hydroxy-2-methyl-1*H*-indole-3-carboxylate (6). A 20-L jacketed vessel was charged with 2-propanol (10 L), acetic acid (700 mL), and 1,4-benzoquinone (850 g, 7.87 mol). The mixture was heated, and reflux was obtained after 1 h (IT 85 °C). A solution of 1-(4-fluorophenyl)ethyl 3-aminobut-2-enoate (1.569 g, 7.04 mol) in 2-propanol (3 L) was added over 25 min, and heating was continued. A sample was taken after 30 min and concentrated, and NMR analysis indicated the reaction was complete. After an additional 10 min, the mixture was cooled to 20 °C over 1 h. The mixture was concentrated, taken up in dichloromethane (8 L), and washed with 10% aqueous potassium carbonate (2 × 6 L). The aqueous layers were combined and extracted with dichloromethane (2 L). The organic layers were combined, dried with magnesium sulfate (700 g), filtered, and concentrated to approximately 7.5 L total volume. This solution was used directly in the subsequent Mannich reaction. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.65 (d, J = 6.6 Hz, 3H), 2.65 (s, 3H), 5.67 (br s, 1H), 6.12 (q, J = 6.6 Hz, 1H), 6.75 (dd, J = 8.6, 2.4 Hz, 1H), 6.95−7.02 (m, 2H), 7.11 (d, J = 8.6 Hz, 1H), 7.37−7.43 (m, 2H), 7.61 (d, J = 2.4 Hz, 1H), 8.47 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.8, 161.8 (d, $^1J_{CF}$ = 245 Hz), 151.3, 145.4, 138.0 (d, $^4J_{CF}$ = 3.0 Hz), 129.5, 128.2, 127.5 (d, $^3J_{CF}$ = 8.1 Hz), 115.0 (d, $^2J_{CF}$ = 21.4 Hz), 111.7, 111.3, 105.9, 103.1, 71.0, 22.5, 13.9. MS 314.1 ES [M + H]$^+$. R_f 0.15 (3:7 EtOAc/hexanes). HR-MS [M + H]$^+$ observed = 314.1201, calculated = 314.1192.

1-(4-Fluorophenyl)ethyl 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate Hydrochloride (7). A 20-L jacketed vessel was charged with dichloromethane (7.5 L) and *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine (1.25 L, 9.16 mol) and was cooled to IT 0 °C. Acetyl chloride (625 mL, 8.79 mol) was added over 30 min, causing the internal temperature to rise to 20 °C (jacket reaching −25 °C). After 35 min, potassium carbonate (1.31 kg, 9.48 mol) was added (IT 0 °C), the mixture was stirred for 5 min more, and 1-(4-fluorophenyl)ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (7.32 mol in 7.5 L of dichloromethane, prepared as described in previous paragraph) was added over 10 min causing the IT to rise to 8 °C. The mixture was warmed to 20 °C over 30 min and stirred at this temperature. The reaction was monitored by ^{1}H NMR using concentrated aliquots. After stirring at 20 °C for 100 min, water (5 L) was added and the mixture stirred vigorously for 10 min and allowed to settle. The layers were separated, and the organic phase was washed with an additional portion of water (5 L). The aqueous layers were combined and extracted with dichloromethane (2.5 L). The organic layers were combined, dried with magnesium sulfate (824 g), filtered, and concen-

trated. The residue was taken up in ethanol (4.5 L) and transferred to a 10-L round-bottomed vessel with overhead anchor stirring. A solution of HCl in ethanol was prepared by addition of acetyl chloride (657 mL, 9.24 mol) to ethanol (1.5 L) with cooling. This solution was added over 85 min to the Mannich product, using an ice bath to control the IT < 35 °C. Precipitation was observed before the addition was complete. The mixture was stirred at ambient temperature for 2.5 days. The mixture was then cooled in an ice−water bath for 30 min (IT 6 °C) before dividing into two portions and filtering. The cakes were washed with ice cold ethanol (2×500 mL each) and dried in a vacuum oven at ambient for 23 h to give 1.375 kg, 46% from aminocrotonate **5**, as a light-purple solid. ^{1}H NMR consistent with structure with ethanol in a 1.33:1 ratio. Corrected yield is 1.267 kg, 43%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.60 (d, $J = 6.5$ Hz, 3H), 2.63 (s, 3H), 2.68 (d, $J = 4.8$ Hz, 3H), 2.73 (d, $J = 4.8$ Hz, 3H), 4.73−4.75 (m, 2H), 6.04 (q, $J = 6.5$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 7.16−7.24 (m, 2H), 7.32 (d, $J = 8.7$ Hz, 1H), 7.49−7.56 (m, 2H), 8.63 (br s, 1H), 9.89 (s, 1H), 12.21 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 165.3, 161.5 (d, $^1J_{CF} = 243$ Hz), 152.7, 145.4, 138.3 (d, $^4J_{CF} = 2.7$ Hz), 129.6, 128.3 (d, $^3J_{CF} = 8.2$ Hz), 127.2, 115.1 (d, $^2J_{CF} = 21.3$ Hz), 114.1, 111.6, 106.2, 103.4, 70.8, 52.8, 42.2, 41.8, 22.3, 15.9. MS 371.1 ES $[M + H]^+$. R_f 0.2 (8:2 EtOAc/hexanes 2 wt % NEt_3). HR-MS $[M + H]^+$ observed = 371.1771, calculated = 371.1771.

MLN1251 (1). A 10-L round-bottomed flask with anchor stirrer, reflux condenser, and heating mantle was charged with toluene (1 L), saturated aqueous sodium hydrogencarbonate (1 L), 1,3,4,6,7,8-hexahydro-2*H*-quinolizine tetrafluoroboric acid salt (104.8 g, 464 mmol), and 1-(4-fluorophenyl)-ethyl 4-dimethylaminomethyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate hydrochloride (100 g, 442 mmol), and the mixture was heated at reflux for 160 min. The mixture was cooled, and the layers were separated. The organic layer was dried ($MgSO_4$, 60 g), filtered, and concentrated. The residue was taken up in ethanol (300 mL) and heated to 60 °C. Water (100 mL) was added, and the mixture stirred while cooling. When the temperature was 42 °C, 300 mg of seeds were added. The mixture was stirred at ambient temperature for 2.5 days. The resulting precipitated solid was collected by filtration, washed with 4:1 ethanol/water (2×125 mL), and dried in a vacuum oven at 30 °C for 23 h to give 80.0 g, 70% of **1** as an off-white solid. ^{1}H, ^{19}F NMR consistent with structure. Ratio of diastereomers by ^{19}F NMR: 1.02:1.00. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.55 (br s, 1H), 7.45−7.53 (m, 2H), 7.16−7.24 (m, 2H), 7.03−7.07 (m, 1H), 6.59−6.63 (m, 1H), 5.94−6.03 (m, 1H), 3.10−3.32 (m, 2H), 2.86−2.94 (m, 1H), 2.63−2.71 (m, 2H), (2.54, 2.53; s, 3H), 2.35−2.47 (m, 2H), 1.83−1.92 (m, 1H), 1.09−1.76 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 14.7, 19.4, 21.9, 22.2, 24.6, 25.0, 26.8, (30.0, 30.1), 30.5, 36.0, (48.8, 48.9), (70.3, 70.4), (86.4, 86.5), 104.4, (109.9, 109.9), (110.2, 110.3), 112.7, 115.0 (d, $^2J_{CF} = 21.3$ Hz), (125.8, 125.8), (128.0, 128.4; d $^3J_{CF} = 8.2$ Hz), 129.5, (138.2, 138.5; d $^4J_{CF} = 3.0$ Hz), (142.6, 142.7), (147.9, 148.0), (161.4, 161.5; d $^1J_{CF} = 243$ Hz), (164.2, 164.2). MS 463.2 ES $[M + H]^+$. R_f 0.2 (1:1 EtOAc/hexanes). HR-MS $[M + H]^+$ observed = 463.2389, calculated = 463.2397. Anal. Calcd for $C_{28}H_{31}FN_2O_3$: C, 72.70; H, 6.76; N, 6.06. Found: C, 72.94; H, 6.72; N, 6.07.

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Supporting Information Available

Analytical details. This material is available free of charge via the Internet at http://pubs.acs.org.

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