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First Scale-Up Synthesis of WAY-262398, a Novel, Dual-Acting SSRI/5HT1a Antagonist

Antonia Nikitenko,*[,†] Asaf Alimardanov,[†] Jay Afragola,[†] Jean Schmid,[†] Livia Kristofova,[‡] Deborah Evrard,[§] Nicole T. Hatzenbuhler,[§] Vasilios Marathias,[§] Gary Stack,[§] Steve Lenicek,[§] and John Potoski[†]

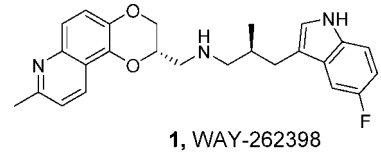
Chemical and Screening Sciences, Wyeth Research, 401 North Middletown Road, Pearl River, New York 10965, U.S.A., Chemical Development, Wyeth Research, 1025 Boulevard Marcel-Laurin, Saint-Laurent, Quebec H4R 1J6, Canada, and Chemical and Screening Sciences and Discovery Neuroscience, Wyeth Research, CN 8000, Princeton, New Jersey 08543, U.S.A.

Abstract:

An alternative synthesis of WAY-262398, 1, a novel, dual-acting SSRI/5-HT$_{1A}$ antagonist, has been developed. The target compound was initially synthesized as a part of diastereomeric mixture which was separated by chiral preparative HPLC. The new route was designed around intermediates suitable for chiral resolution and/or chiral reduction of a suitable intermediate. Both processes had to be employed to achieve the target optical purity.

Introduction

SSRI/5-HT$_{1A}$ antagonists potentially provide a significant improvement over SSRIs in the treatment of depression by addressing a major unmet therapeutic need for a faster-acting antidepressant agent. There has been a substantial amount of work reported by our group,[1,2] as well as by others,[3−5] aimed at creating a single molecular entity that possesses both 5-HT$_{1A}$ antagonism and 5-HT reuptake inhibition. Our recent publication presented the scale-up synthesis of WAY-253752, a potential dual-acting SSRI/5-HT$_{1A}$ antagonist.[6] In preclinical studies, a related analogue **1**, WAY-262398, showed potential as a dual-acting SSRI/5-HT1a antagonist. Herein is described the first scale-up synthesis of **1** (WAY-262398).



1, WAY-262398

Initial Synthesis of 1, WAY-262398

For the initial SAR studies, **1** was synthesized by the general approach utilized for this class of molecules.[2] Reductive amination of aminomethylquinolinodioxane **9** with the racemic aldehyde **8** produced the diastereomeric mixture **10**, from which **1** was isolated using chiral preparative HPLC. The absolute stereochemistry of **1** was assigned on the basis of chiral liquid crystal NMR analysis of its diastereomer.[7] The aldehyde **8** was synthesized in six steps from commercially available 5-fluoroindole **2** (Scheme 1).[1,8]

Amine **9** was synthesized from chiral quinolinodioxane derivative **11** (Scheme 2), which had been used as a common intermediate for several earlier projects,[9−13] by conversion into the azido derivative **12** and subsequent reduction of the azido group.

An alternative route to the intermediate **6** (Scheme 1), from fluoroindole aldehyde, **13**, has been described up to the ester **15** [14,15] and is shown in Scheme 3.

As more material was needed for further investigations, the preparation of multigram quantities of **1** was addressed. Although the SAR synthesis did provide access to milligram quantities of **1**, its large-scale synthesis using either racemic approach to the intermediate **6** would present the major challenge of separating the diastereomeric mixture **10**. It was highly desirable to develop a chiral approach to the "right-hand",

* Author for correspondence. E-mail: nikitea@wyeth.com.
† Chemical and Screening Sciences.
‡ Chemical Development.
§ Chemical and Screening Sciences and Discovery Neuroscience.

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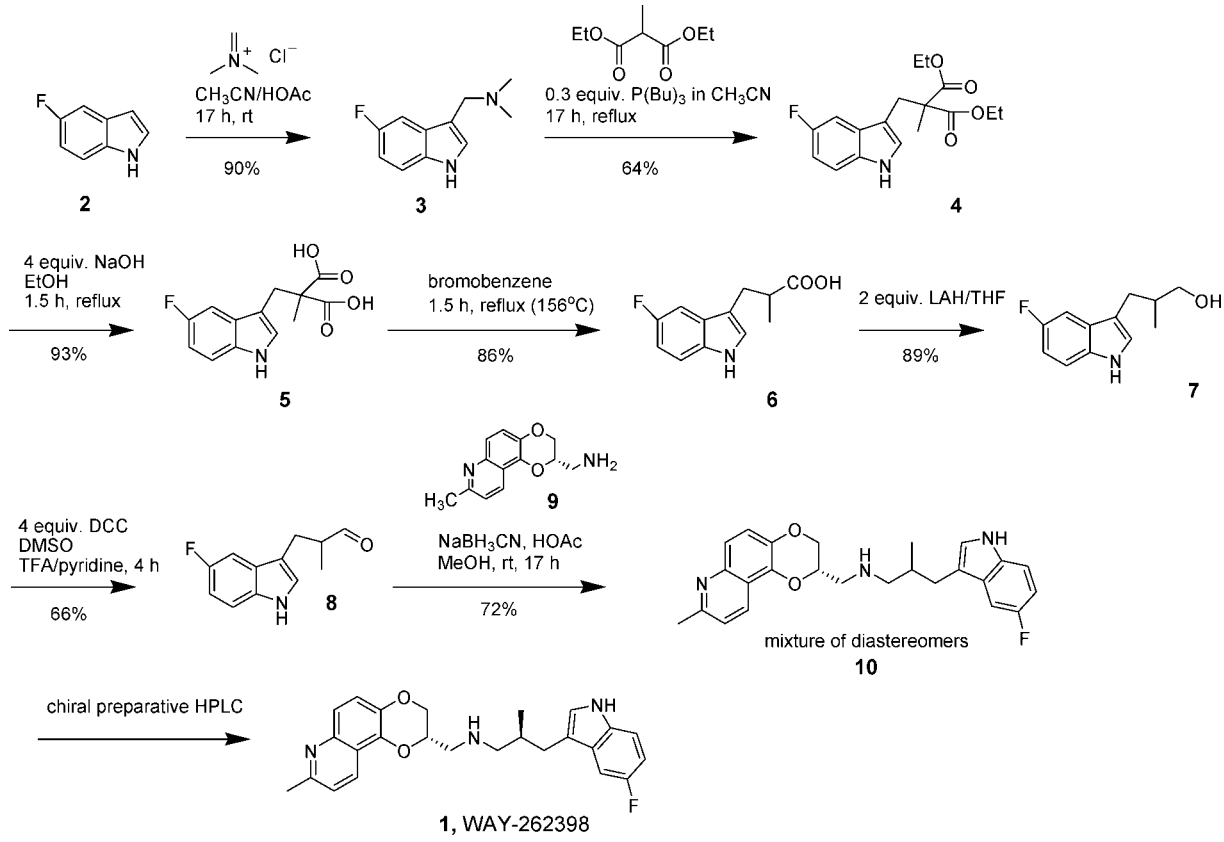
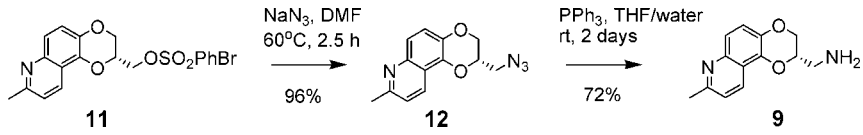
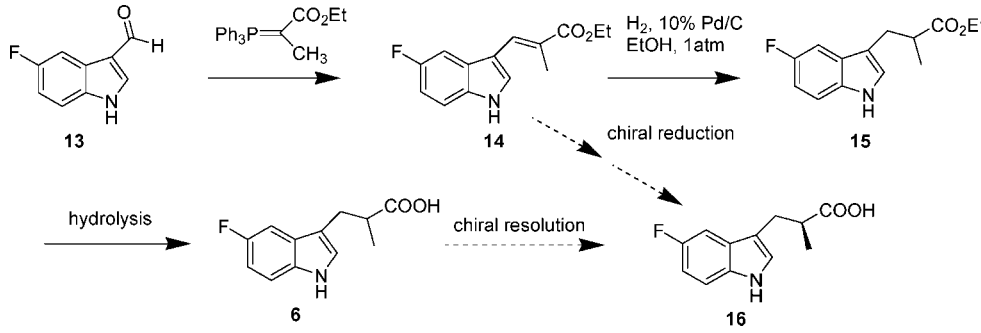
Scheme 1. **Initial synthesis of 1, WAY-262398**



Scheme 2. **Synthesis of compound 9**



Scheme 3. **Alternative synthesis of the key intermediate 6**



fluoroindole, part of the molecule. From this point of view, this alternate approach, shown in Scheme 3, seemed more suitable, as it allowed a possibility for chiral hydrogenation of the double bond in the ester **14**, or resolution of the acid **6** in order to get the key intermediate, chiral acid **16**.

The acid **16** could be converted to the corresponding aldehyde or used directly to provide a wider set of options for making the final connection with quinaldine dioxane brosylate **11**. Thus, the chiral acid **16** could either be converted to the amine **18** through the amide **17**, followed by alkylation with the brosylate **11** (Route A, Scheme 4), or to the penultimate amide **19** *via* an acid derivative and the amine **9**, followed by reduction as the last step (Route B, Scheme 4).

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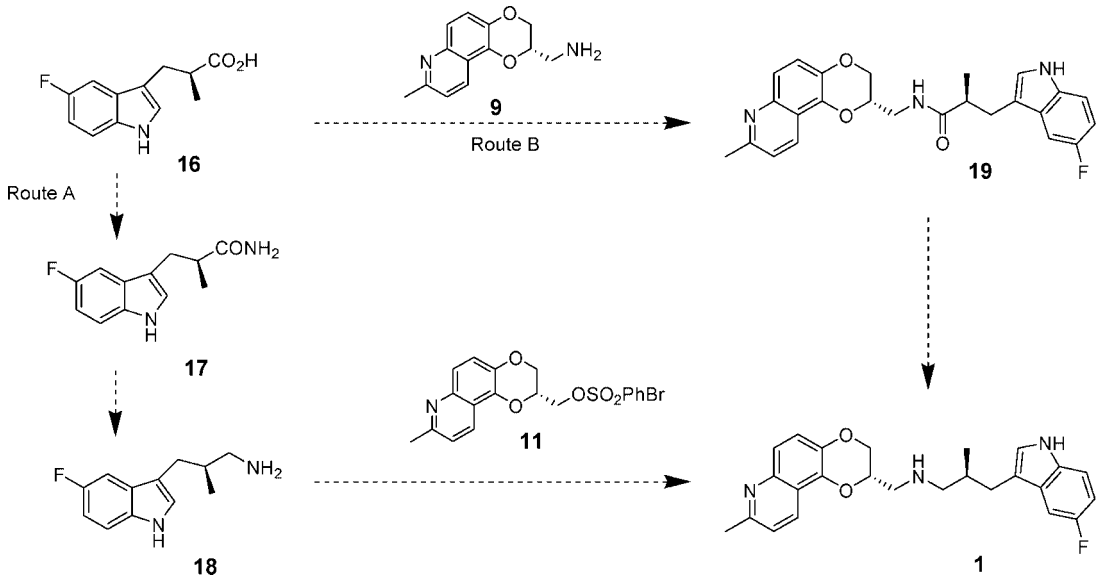
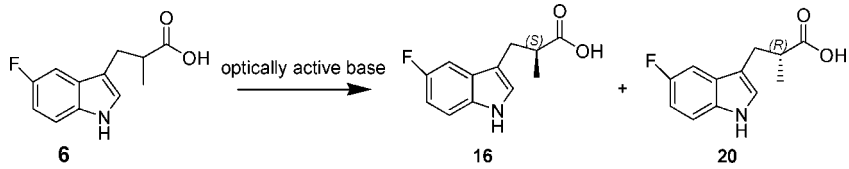
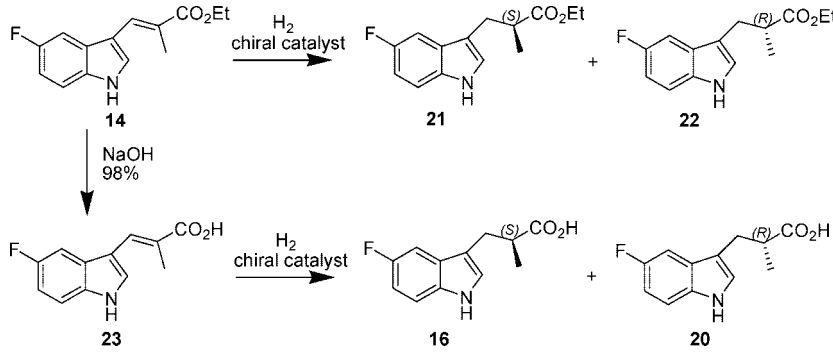
Scheme 4. **Possible approaches to scale-up of 1, WAY-262398**



Scheme 5. **Chiral resolution of the racemic acid 6**



Scheme 6. **Chiral hydrogenation of acrylic ester 14 and acrylic acid 23**



Approaching Optically Active 3-(5-Fluoro-1H-indol-3-yl)-2-methylpropanoic Acid: Chiral Reduction or Chiral Resolution?

The chiral resolution of the racemic acid **6** by crystallization with various chiral bases was evaluated (Scheme 5). The best result was achieved using (−)-norephedrine,[16] affording of 72:28 *S*/*R* ratio of isomers. Further recrystallization of the salt did not significantly improve chiral purity.

In parallel, chiral hydrogenation was addressed by screening a number of chiral catalysts in reduction of the ester **14**, as well as the acid **23** (Scheme 6). Several catalytic systems for the asymmetric hydrogenation of α-methyl-*β*-aryl-acrylic acids, with variable enantiomeric excess values (17−92%), have been reported.[17] Our choice of catalysts for screening was based on two factors: commercial availability, and the lack of potential patent issues. The best catalytic system for the ester **14** was Rh/*R*,*S*-Josiphos,[18] and for the acid **23**, Rh/*R*,*S*-Mandyphos.[19] Other parameters, such as solvents, temperature, and pressure, were screened as well. Early in the course of screening it was observed that the preferred substrate for chiral reduction was the acrylic acid **23** rather than the corresponding ester **14** (the best ratio of **21**:**22** was 77:23, vs the 92:8 ratio of **16**:**20**[21]).

(16) See Table 1, Salt Screening for the Chiral Resolution of Acid **6**, Supporting Information.

(17) Fox, M. E.; Jackson, M.; Lennon, I. C.; Klosin, J.; Abboud, Kh. A. *J. Org. Chem.* **2008**, *73*, 775–784, and references 21−23 therein.

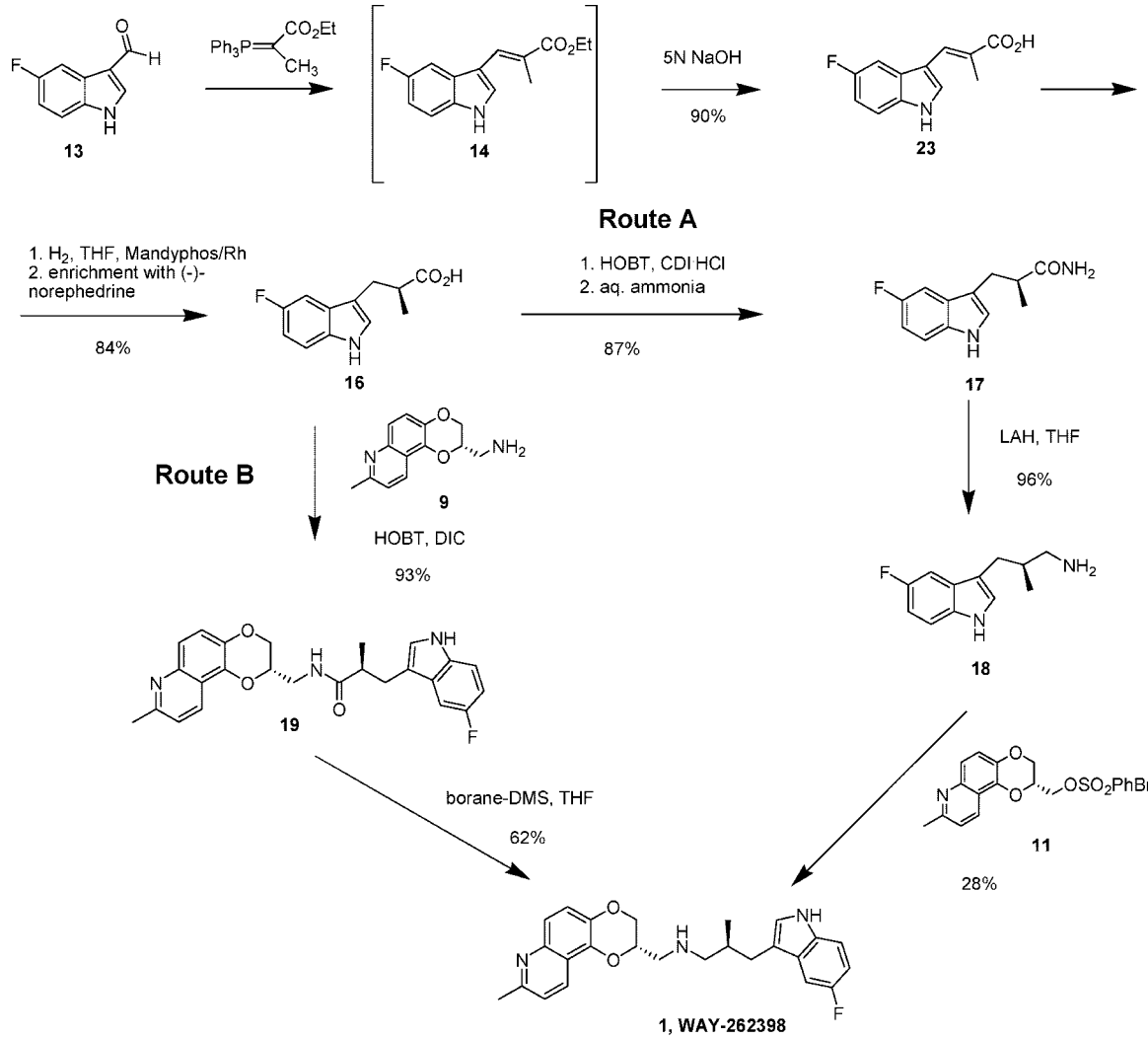
(18) (*R*)-(−)-1-[(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine, Solvias SL-J009.

(19) (α*R*,α*R*)-2,2′-Bis(α-*N*,*N*-dimethylaminophenylmethyl)-(*S*,*S*)-1,1′-bis-[di(3,5-dimethyl-4-methoxyphenyl-phosphino]ferrocene (*R*)-(*S*)-NMe_2-P(3,5-Me-4-MeOPh)$_2$-Mandyphos, Solvias SL-M004. The sense of stereoinduction reported for a similar substrate using the same metal/ligand combination[20] provided further evidence in support of the assigned absolute stereochemistry.

(20) Briner, P. H.; Fyfe, M. C. T.; Madeley, J. P.; Murray, P. J.; Procter, M. J.; Spindler, F. PCT Int. Appl. WO 2006/016178, 2006; *Chem Abstr.* **2006**, *144*, 232918.

(21) See Table 2, Conditions for the Chiral Reduction of Ester **14**, and Table 3, Conditions for the Chiral Reduction of Acid **23**, Supporting Information.

Scheme 7. **Final synthesis of 1, WAY-262398**



Disappointingly, no further improvement of the ee was attained in the course of screening experiments.

Although neither chiral reduction nor chiral resolution afforded acceptable optical purity, a combination of both methods could be utilized in this case. Thus, chiral hydrogenation followed by crystallization in the presence of (−)-norephedrine afforded **16** in 95% ee.[22] This optical purity was deemed sufficient at this point, since crystallization at later stages would further increase the ee to the desirable level (*vide infra*).

Synthesis of WAY-262398: Final Choice of the Route

Two routes (A and B, Scheme 7) were utilized in parallel for converting acid **16** to the target compound **1**, WAY-262398. Following Route A, acid **16** was converted to amine **18** through amide **17**. The subsequent alkylation with brosylate **11** required the use of 1.17 equiv of the amine in order to avoid the formation of dialkylation byproduct. Separation of the target compound from the excess of the amine presented a serious problem, required multiple crystallizations, and resulted in only 28% unoptimized isolated yield of **1**.

Route B required conversion of the brosylate **11** in two steps to the amine **9** (Scheme 2), which was subsequently condensed with the acid **16** to afford the penultimate amide **19**. Several reducing agents were screened for the final reduction. Incomplete conversion was the major problem when LAH and DIBAL were used. Multiple byproducts were also observed with Red-Al, LAH-$AlCl_3$, and borane−dimethylsulfide/boron trifluoride etherate combination. The byproduct presumably formed due to over-reduction, as judged by LC/MS analysis of the reaction mixtures. Gratifyingly, it was found that use of excess BH_3−DMS minimized these problems. Reduction of the amide with borane−dimethylsulfide complex afforded target compound **1** in 62% isolated yield.

Comparing routes A and B in the present form, one can easily see that route B has fewer problems. In principle, it is possible to optimize the problematic last step in the route A to improve the isolation procedure and, consequently, the isolated yield. However, it still has a drawback of using an excess of the optically active acid **16**. Due to the pressing timelines, further optimization of route A was not done. The bulk of the material was processed through route B. Thus, compound **1**, WAY-262398, was synthesized from 5-fluoroindole-2-carboxaldehyde **13** in six steps (including enrichment via crystallization with (−)-norephedrine) with a 41% overall yield (Scheme 7).

(22) For an example of double resolution in a similar class of compounds, see ref 6.

Conclusion

In the initial rapid scale-up, chirality often becomes a major issue and a main factor in choosing the synthetic route. In the Discovery phase of the presented project, chiral preparative HPLC purification of the penultimate diastereomers allowed for the separation, identification, and comparison of the biological activity of two close analogues. However, this method was not feasible for bulk preparation of the target compound. When developing a scalable approach to the selected compound, both chiral reduction and resolution were evaluated. Neither method alone was adequate to achieve the desired outcome. An approach was developed that combined chiral reduction of the acrylic acid **23** with the subsequent chiral enrichment of the resulting chiral acid **16** by its crystallization with an optically active base, (−)-norephedrine, affording the target compound in high optical purity.

Experimental Section

General Methods. NMR spectra of the intermediates were recorded on a Bruker 300 NMR spectrometer. HPLC analysis of the intermediates and reaction monitoring was performed on an Agilent 1100 liquid chromatograph equipped with a Phenomenex Prodigy ODS3 4.6 mm × 50 mm column. Standard method: 90:10 to 10:90 gradient of water/acetonitrile containing 0.02% TFA over 8 min, flow rate 1 mL/min. Chiral HPLC analysis was performed on Agilent 1100 liquid chromatograph equipped with a Whelk O1 RR 4.6 mm × 250 mm column. Mobile phase composition: 60% heptane containing 0.02% TFA, 40% isopropyl alcohol, flow rate 1 mL/min.

(2*E*)-3-(5-Fluoro-1H-indol-3-yl)-2-methylacrylic Acid (23). A suspension of 5-fluoroindole-3-carbaldehyde (**13**, 135.5 g, 0.83 mol) and (carbethoxyethylidene)triphenylphosphorane (Wittig reagent, 465 g of 97% purity, 1.28 mol, 1.5 equiv) in absolute ethanol was stirred at ambient temperature for 3 days. To the reaction were added 5 N NaOH (465 mL) and water (310 mL), and the mixture was heated to reflux for 1.5 h. The reaction mixture was poured onto water (2.9 L), and the triphenylphosphine oxide byproduct was extracted with diethyl ether (2 × 1.25 L). The ethereal layers were back extracted with 1.0 N NaOH (2 × 500 mL), and the combined aqueous layers were extracted with methylene chloride (1 L). The aqueous layer was then treated with 6 N HCl (500 mL). A solid precipitate was formed and isolated by filtration. The solid was washed with water (1 L) and dissolved in ethyl acetate (1.5 L). The organic solution was washed with brine and dried over $MgSO_4$. The solvent was removed, and the solid was dried *in vacuo* to give **23**, 162.0 g (89%). Mp 207−210 °C. MS 218.1 (M − H). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 12.10 (s, 1H), 11.84 (s, 1H), 7.85−7.81 (m, 2H), 7.49−7.42 (m, 2H), 7.03 (dt, 1H J_1 = 9.3 Hz, J_2 = 2.5 Hz), 2.06 (d, 3H, J = 1.0 Hz).

(2*S*)-3-(5-Fluoro-1H-indol-3-yl)-2-methylpropanoic Acid (16). The ligand (Mandyphos SL-M004-1 by Solvias, 1.99 g) and bis(norbornadiene)Rh(I)BF_4 (788 mg) were dissolved in nonaqueous methanol under N_2, and the resulting orange solution was stirred at room temperature for 30 min. The acrylic acid, **23** (41.5 g, 189 mmol), was added, and the solution was hydrogenated at 35−50 psi H_2 for 15 h. The resulting solution of the title compound (84% ee) was concentrated and then dissolved in 350 mL of hot acetonitrile. A solution of (1*R*,2*S*)-(−)-norephedrine (26.5 g, 175 mmol) in 100 mL of acetonitrile was added. The mixture was cooled to 0 °C in an ice bath. The precipitated crystals were filtered, washed with cold acetonitrile, and air-dried to afford 63 g of the title product as norephedrine salt (90% ee). The salt was dissolved in 1.2 L of acetonitrile at reflux and allowed to crystallize overnight at room temperature. The resulting suspension was cooled to 0 °C, filtered, washed with cold acetonitrile, and air dried to give 57.4 g of the norephedrine salt of the target compound, which was taken into a mixture of ethyl acetate (750 mL) and 2 N HCl (250 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford 33.8 g of the title compound **16** (80% yield, 95% ee). Mp 81−83 °C. MS 220.1 (M − H). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 12.03 (s, 1H), 10.92 (s, 1H), 7.32 (dd, 1H, J_1 = 8.9 Hz, J_2 = 4.7 Hz), 7.26 (dd, 1H, J_1 = 10.1 Hz, J_2 = 2.6 Hz), 7.19 (d, 1H, J = 2.4 Hz), 6.90 (dt, 1H, J_1 = 9.5 Hz, J_2 = 2.6 Hz), 2.97 (dd, 1H, J_1 = 13.7 Hz, J_2 = 6.7 Hz), 2.76−2.64 (m, 2H), 1.085 (d, 3H, J = 6.7 Hz).

(*S*)-3-(5-Fluoro-1H-indol-3-yl)-2-methylpropanamide (17). To a solution of (*S*)-3-(5-fluoro-1H-indol-3-yl)-2-methylpropanoic acid, **16** (30 g, 135.6 mmol) and HOBt (22.67 g, containing 11.12 wt % water, 149.17 mmol, 1.1 equiv) in THF (350 mL) was added a suspension of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (31.2 g, 172.7 mmol, 1.2 equiv) in THF (200 mL). The mixture was stirred at room temperature for 18 h (HPLC monitored) and then added to conc. ammonia solution (800 mL) at 7−8 °C. Residual heavy oil was dissolved in 100 mL of conc. ammonia and added to the mixture. The resultant mixture was stirred for 1 h and allowed to warm up to 12 °C. THF was distilled off *in vacuo*. The residual aqueous phase was extracted with MTBE (250 + 100 mL). The combined MTBE solution was washed with 2 N HCl (3 × 150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated to afford 25.83 g of the title product, **17**, as a white solid (87% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.06 (s, 1 H), 7.30−7.19 (m, 2 H), 7.08 (s, 1 H), 6.94 (dt, 1 H, J = 9, 2.5 Hz), 5.25 (br s, 2 H), 3.07 (dd, 1 H, J = 14.5, 8 Hz), 2.82 (dd, 1 H, J = 14.5, 6 Hz), 2.72−2.59 (m, 1 H), 1.26 (d, 3 H, J = 7 Hz).

(*S*)-3-(5-Fluoro-1H-indol-3-yl)-2-methylpropan-1-amine (18). To a solution of (*S*)-3-(5-fluoro-1H-indol-3-yl)-2-methylpropanamide **17** (25.83 g, 117.4 mmol) in THF (130 mL), $LiAlH_4$ (235 mL of 1 M THF solution, 235 mmol, 2 equiv) was added at 10−20 °C. The mixture was heated to 65 °C, stirred for 1 h, and cooled to 5 °C. Saturated Rochelle salt solution (73 mL) was added. The precipitated solids were filtered off and washed with 2 × 100 mL of MTBE. The combined organic fraction was concentrated and chased with THF (100 mL; to remove residual moisture) to afford 23.2 g

of the title product as an off-white solid (96% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.37 (s, 1H), 7.29−7.18 (m, 2H), 7.01 (s, 1H), 6.91 (dt, 1H, J = 9, 2.5 Hz), 2.81−2.68 (m, 2H), 2.61−2.47 (m, 2H), 2.01 (br s, 2H), 1.96−1.80 (m, 1H), 0.95 (d, 3H, J = 7 Hz).

(2*S*)-3-(5-Fluoro-1H-indol-3-yl)-2-methylpropyl]{[(2*S*)-8-methyl-2,3-dihydro[1,4]dioxino- [2,3-*f*]quinolin-2-yl]methyl}-amine (1) (Route A). A mixture of (2*R*)-quinaldine dioxane brosylate **11** (43.14 g, 95.87 mmol), (*S*)-3-(5-fluoro-1H-indol-3-yl)-2-methylpropan-1-amine, **18** (23.2 g, 112.62 mmol, 1.17 equiv), 4-dimethylaminopyridine (11.7 g, 95.87 mmol, 1 equiv), and DMSO (300 mL) was stirred at 90 °C for 3 h (HPLC monitored), then cooled to room temperature, and poured into 600 mL of saturated $NaHCO_3$ solution. The resultant mixture was stirred at room temperature for 20 min. The precipitated heavy oil was separated from aqueous suspension by decantation, washed with water (100 mL + 50 mL), and dissolved in 500 mL of EtOAc. The EtOAc solution was washed with $NaHCO_3$ solution (200 mL), dried over Na_2SO_4, and concentrated to afford 26.73 g of heavy oil.

The oil was dissolved in 280 mL of i-PrOH. HCl (70 mL of 2 N solution in Et_2O) was added dropwise (exothermic). The resultant suspension was stirred at room temperature for 1 h. The solids were filtered and washed with i-PrOH (40 mL). The filtered salt was added to a stirred mixture of CH_2Cl_2 (300 mL) and saturated $NaHCO_3$ solution (300 mL). The mixture was stirred at room temperature for 1 h. Phases were separated. Aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic fractions were concentrated to afford 20.76 g of the crude title product as an oil (52% crude yield). The oil was dissolved in acetonitrile (24 mL). The solution was stirred at room temperature for 18 h. The precipitated solid was filtered, washed with acetonitrile to afford 11.3 g of the title product, **1**, as an off-white solid (28% yield).

(2*S*)-2-(Azidomethyl)-8-methyl-2,3-dihydro[1,4]dioxino[2,3-*f*]quinoline (12). A solution of (2*R*)-quinaldine dioxane brosylate (**11**) (90.06 g, 0.2 mol) and sodium azide (52.66 g, 4.0 equiv, 0.81 mol) in DMF (700 mL) was stirred at 60 °C for 2.5 h. The reaction was poured onto ice water (2 L) and allowed to precipitate. The solid was isolated by filtration and dried *in vacuo* overnight at ambient temperature to give the target compound **12**, 49.3 g (96%). Mp 98−100 °C. MS 257.1 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.23 (d, 1H, J = 8.8 Hz), 7.49−7.32 (m, 3H), 4.67−4.59 (m, 1H), 4.44 (dd, 1H, J_1 = 11.5 Hz, J_2 = 2.4 Hz), 4.14 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.9 Hz), 3.78−3.63 (m, 2H), 2.61 (s, 3H).

[(2*S*)- 8-Methyl-2,3-dihydro[1,4]dioxino[2,3-*f*]quinolin-2-yl]methylamine (9). A solution of azide **12** (49.3 g, 0.19 mol) and triphenylphosphine (63.08 g, 1.25 equiv, 0.24 mol) in THF (1 L) and water (10 mL) was stirred at room temperature for 2 days. The reaction was concentrated, acidified, and extracted with diethyl ether (2 × 1 L). The ethereal layer was concentrated and treated with 1 N NaOH (250 mL) for 6 h. This basic solution was acidified with 6 N HCl (50 mL) and extracted with diethyl ether (2 × 1 L) and methylene chloride (1 × 1 L). The organic layers were back extracted with water (250 mL). The combined aqueous layers were basified with 5 N NaOH (75 mL) and extracted with methylene chloride (2 × 1 L). The organic layer was dried over $MgSO_4$ and concentrated to afford 32.0 g of the title compound as oil (72% yield). MS 231.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.31 (d, 1H, J = 8.7 Hz), 7.55 (d, 1H, J = 8.7 Hz), 7.28 (d, 1H, J = 8.7 Hz), 7.24 (d, 1H, J = 8.7 Hz), 4.39 (dd, 1H, J_1 = 11.4 Hz, J_2 = 2.4 Hz), 4.34−4.25 (m, 1H), 4.12 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.2 Hz), 3.18−3.03 (m, 2H), 2.71 (s, 3H).

(2*S*)-3-(5-Fluoro-1H-indol-3-yl)-2-methyl-*N*-{[(2*S*)-8-methyl-2,3-dihydro[1,4]dioxino- [2,3-*f*]quinolin-2-yl]methyl}propanamide (19). To a solution of the acid, **16** (28 g, 126.6 mmol), and hydroxybenzotriazole (23.8 g, 176 mmol) in 380 mL of THF cooled to 10−12 °C was added diisopropylcarbodiimide, and the resulting mixture was stirred at room temperature for 15 h. Amine **9** (35 g, 152 mmol) was dissolved in 150 mL of THF and added to the reaction mixture (the temperature increased to 30 °C). The resulting solution was stirred at room temperature and monitored by HPLC, which indicated complete conversion to the target compound in 1 h. The reaction mixture was poured into 1.5 L of water with vigorous stirring. The mixture was stirred for 1 h. The formed precipitate was filtered and washed with water. The wet filtercake was suspended in 400 mL of methanol, stirred for 10 min, filtered, washed with methanol, and dried *in vacuo* at 50 °C to give 51 g of the target compound, **19** (93% yield). MS 434.3 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 10.86 (s, 1H), 8.21 (d, 1H, J = 8.8 Hz), 8.17 (t, 1H, J = 5.8 Hz), 7.42 (d, 1H, J = 9.1 Hz), 7.35−7.28 (m, 3H), 7.25 (dd, 1H, J_1 = 8.9 Hz, J_2 = 4.7 Hz), 7.16 (d, 1H, J = 2.4 Hz), 6.85 (dt, 1H, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 4.32−4.23 (m, 2H), 3.97 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.8 Hz), 3.49−3.37 (m, 2H), 2.93 (dd, 1H, J_1 = 13.0 Hz, J_2 = 6.2 Hz), 2.71−2.61 (m, 2H), 2.60 (s, 3H), 1.04 (d, 3H, J = 6.5 Hz).

(2*S*)-3-(5-Fluoro-1H-indol-3-yl)-2-methylpropyl]{[(2*S*)-8-methyl-2,3-dihydro[1,4]dioxino- [2,3-*f*]quinolin-2-yl]methyl}-amine (1) (Route B). A 2 M solution of borane/dimethylsulfide complex in THF (1180 mL, 2360 mmol) was cooled to 10−15 °C, and the amide **19** (34 g, 78.5 mmol) was added in one portion. The resulting suspension was allowed to warm up to room temperature, at which point the solids dissolved (orange solution). After stirring the reaction mixture at room temperature for 18 h, HPLC analysis indicated 98.4% conversion to the target compound. The reaction was poured into a vigorously stirred mixture of ice, 200 mL of conc. HCl, and 1 L of methanol. The resulting solution was concentrated on a rotovap (bath temperature kept below 45 °C). The residue was partitioned between methylene chloride (1.5 L) and aqueous sodium bicarbonate (1 L). The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to afford 38.7 g of crude product. The crude product was crystallized from acetonitrile (50 mL) to afford 20.5 g of the title compound as off-white crystals (62% yield, 99% ee). Mp 120−122 °C. $[\alpha]_D$ −30.9 (1% solution in methanol, 25 °C). MS 420.2 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 10.87 (s, 1H), 8.27 (d, 1H, J = 8.7 Hz), 7.42 (d, 1H, J = 9.1 Hz), 7.35−7.29 (m, 3H), 7.25 (dd, 1H, J_1 = 10.1 Hz, J_2 = 2.6 Hz), 7.17 (d, 1H, J = 2.2 Hz), 6.88 (dt, 1H, J_1 = 9.3 Hz, J_2 = 2.5 Hz), 4.46 (dd, 1H, J_1 = 11.4 Hz, J_2 = 2.2 Hz), 4.42−4.35 (m, 1H), 4.10

(dd, 1H, $J_1 = 11.4$ Hz, $J_2 = 7.3$ Hz), 2.96−2.75 (m, 3H), 2.60 (s, 3H), 2.60−2.40 (m, 3H), 2.01 (s, 1H), 1.97−1.85 (m, 1H), 0.88 (d, 3H, $J = 6.8$ Hz). ^{13}C NMR (300 MHz, DMSO-d_6, δ): 156.50 (d, $J = 231.3$ Hz), 156.25, 143.16, 137.99, 135.34, 132.76, 128.50, 127.81 (d, $J = 10.2$ Hz), 125.05, 121.21, 120.98, 120.71, 118.08, 113.26 (d, $J = 5.1$ Hz), 112.04 (d, $J = 9.5$ Hz), 108.65 (d, $J = 26.1$ Hz), 102.99 (d, $J = 23.2$ Hz), 73.04, 66.21, 55.68, 49.39, 34.04, 29.71, 24.48, 18.23.

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Supporting Information Available

Conditions screening tables for the chiral reduction of acid **23** and ester **14**, and salt screening tables for the resolution of acid **6**; details for determination of the absolute stereochemistry of the acid **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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