JOC The Journal of Organic Chemistry

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Enantioselective Synthesis of *cis*-3-Fluoropiperidin-4-ol, a Building Block for Medicinal Chemistry

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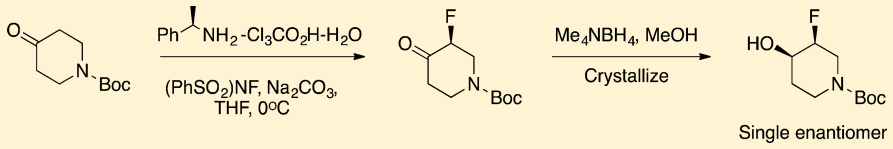
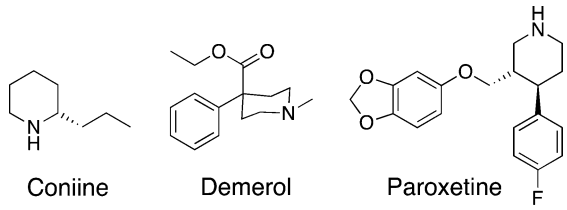
Supporting Information



ABSTRACT: The first enantioselective route to both enantiomers of *cis*-1-Boc-3-fluoropiperidin-4-ol, a highly prized building block for medicinal chemistry, is reported. An enantioselective fluorination is employed, taking advantage of the methodology reported by MacMillan, which uses a modified cinchona alkaloid catalyst. In studying the fluorination reaction, we have shown that the catalyst can be replaced by commercially available primary amines, including α-methylbenzylamine, with similar levels of enantioselectivity. The piperidinols are readily crystallized to obtain enantiopure material.

Piperidines are common heterocycles in medicinal chemistry; the group is found in many pharmaceuticals both naturally occurring and synthetic, from the alkaloid coniine found in poison hemlock, to the opioid pethidine (commonly known as Demerol) and antidepressants such as paroxetine (Chart 1). More recently the introduction of a fluorine atom onto the piperidine ring has been described as an effective method to modulate the pK_a of the piperidine. Indeed it has been reported that an axial fluorine atom on a piperidine ring lowers the pK_a of the nitrogen by one log unit, while an equatorial piperidine can reduce the pK_a by almost two units.[1−3] The unique features of β-fluoroamines have recently been discussed.[4] The introduction of the fluorine atom onto the piperidine ring has also been associated with improvements to pharmacokinetic properties, with reports of improved bioavailability[1,5] and apparent permeability.[6] In all of the syntheses reported to date, including those described in the patent literature, the fluorine atom is installed directly on the piperidine ring through a racemic approach from the silyl enol ether using Selectfluor.[1,2,7] Indeed the only means of obtaining single enantiomers has been through the use of preparative chiral HPLC,[3,7] an undesirable route for large scale manufacture of these building blocks.[8]

Chart 1. Piperidine-Containing Pharmaceuticals



The introduction of a fluoro or trifluoromethyl group into organic molecules is a topic of current investigation in a number of groups.[9−13] The recent results from the MacMillan group[14] in the enantioselective fluorination were particularly striking for the discussion included the piperidinone example, suggesting for the first time that an enantioselective route to a 3-fluoropiperidin-4-ol might be possible.

The MacMillan procedure[14] makes use of the modified cinchona alkaloid, 9-deoxy-9-*epi*-aminohydroquinidine **1**, synthesized using a one-pot Mitsunobu−Staudinger reduction procedure from dihydroquinidine reported by Connon,[15,16] as a catalyst in 20 mol % with *N*-fluorobenzenesulfonimide at −10 °C to obtain (3*R*)-1-Boc-3-fluoropiperidin-4-one **2** from 2 equiv of 1-Boc-piperidin-4-one **3** in 24 h.

We were able to repeat this fluorination procedure, maintaining the temperature between −20 and −10 °C; however, it was not possible to determine the enantiomeric excess (ee) of the ketone **2**; therefore, we reduced the piperidinone to the corresponding *cis*-(3*R*,4*S*)-1-Boc-3-fluoropiperidin-4-ol **4** prior to determination of the ee,[17] which was determined to be 97% ee. As a confirmation, the corresponding tosylate **5** (96% ee) was also synthesized (Scheme 1). Our fluorination reaction, in terms of both yields and ee, is in line with that reported by MacMillan.

In order to obtain the enantiomeric (3*S*,4*R*)-fluoropiperidinol we generated the pseudoenantiomer of catalyst **1** derived from dihydroquinine, 9-deoxy-9-*epi*-aminodihydroquinine **6**. In this instance the (3*S*,4*R*)-1-Boc-3-fluoropiperidin-4-ol **7** and the corresponding tosylate **8** were obtained in 70% ee under similar conditions, significantly lower than that from the quinidine series (Scheme 1).

Given the lower enantioselectivity with **6**, several cinchona alkaloid derivatives were screened to investigate enantioselectivity (Table 1; a more detailed version of this table appears in

Received: June 24, 2013

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Scheme 1. Fluorination of Piperidinone

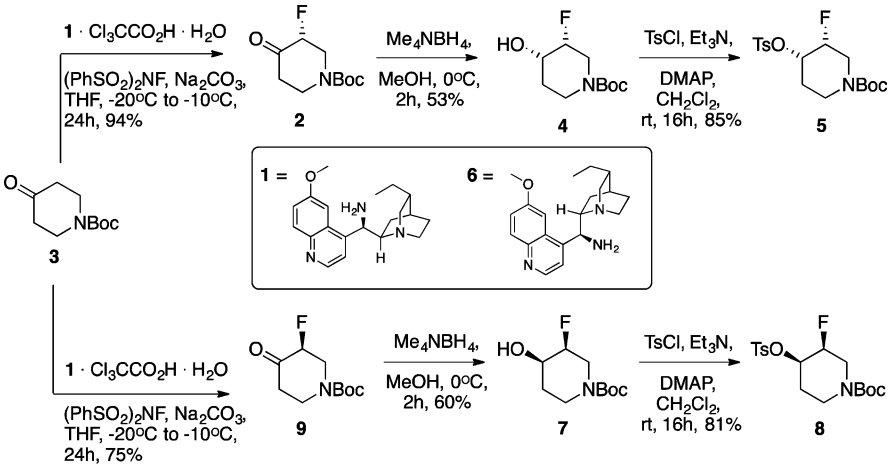
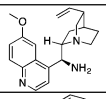
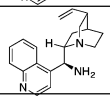
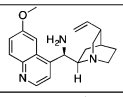
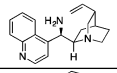


Table 1. Fluorination Using Cinchona Alkaloid-Derived Catalysts

Entry	Catalyst	Yield to **4** / **7** (%)	% ee **4** / **7**	% ee **5** / **8**
1	**6**	**7**, 45	**7**, 70	**8**, 73
2		**7**, 59	**7**, 95	**8**, 94
3		**7**, 59	**7**, 86	**8**, 88
4	**1**	**4**, 50	**4**, 97	**5**, 96
5		**4**, 43	**4**, 87	**5**, 93
6		**4**, 41	**4**, 76	**5**, 77
7		**4**, 3	**4**, 36	nd

the Supporting Information). Although the fluoropiperidinone **2** or **9** was isolated by column chromatography, it was not pure, containing a small quantity of the 3,5-difluoropiperidinone. However, after subsequent reduction of the ketone, high purity *cis*-fluoropiperidinol **4** or **7** was obtained following purification, making the two-step overall yield a more accurate representation of material throughput. Use of tetramethylammonium borohydride as reductant was found to give an improved ratio of the *cis* diastereomer over the *trans* (approximately 4:1), compared with the more commonly used sodium borohydride,[1] which gave diastereomeric ratios of 2:1 to 3:1 in our hands. It was found that the *trans* isomer could be obtained as the major product by using borane as reductant; however, for this study we focused on the *cis* diastereomer.

As can be seen in Table 1, there is a striking difference in ee between the dihydroquinine- and quinine-derived catalysts (entry 1 vs 2), with the catalyst obtained from quinine giving both excellent enantioselectivity and yield. To date we do not have an adequate explanation for this observation; however, it is noted that in synthesizing the catalyst **6**, isolation of the triple HCl salt according to the Connon procedure by crystallization results in a gel-like solid, which while appearing pure by both NMR and HPLC does retain a yellow coloration. This yellow color is not present in any other of the cinchona alkaloid-derived catalysts.[18] In the quinidine-derived series, both catalysts give similar levels of ee (entries 4 and 5). Both the cinchonidine-derived (entry 3) and cinchonine-derived (entry 6) catalyst give lower levels of ee.[19] The 9-aminoquinine catalyst (entry 7) generated by initial inversion of the alcohol through a Mitsunobu-hydrolysis reaction as described by Skarewski[20] resulted in very poor fluorination (5%, for an overall yield to **4** of 3%) and low ee, and it may be the result of the uncatalyzed reaction pathway. It was noted that the amine appears to be much more hindered in this configuration, for more forcing conditions were required to effect the Staudinger reduction of the intermediate azide to the amine. The catalyst has been noted to result in lower conversions in other catalytic systems.[15]

The results led us to question if there were alternative commercially available amines that may give similar enantioselectivities in the fluorination reaction that did not require preparation, a practical advantage especially for large scale reactions. Mindful of the original study conducted by the MacMillan group, we chose to focus primarily on benzylic amines. Primary-amine catalysis is a field that is under active study.[21−23] Our own screening paradigm began with investigation of the reaction with the readily available and inexpensive (*R*)-*α*-methylbenzylamine, which has been used to induce chiral selectivity widely,[24] going back to asymmetric Strecker synthesis.[25]

Using this catalyst under the same conditions as those used above, we were able to get catalytic turnover to obtain the fluoropiperidinone **9** in similar yield to that obtained with the dihydroquinine-derived catalyst **6**. Upon reduction to **7** the enantioselectivity was determined to be 64% ee, similar to that obtained with **6**. Conversion to the tosylate **8** confirmed this level of enantioselectivity. Encouraged that we were maintaining catalyst turnover and obtaining appreciable levels of enantioselectivity with the *α*-methylbenzylamine, a collection of commercially available benzylic amines was screened (Table 2).

The results show that enantioselectivities up to 80% ee can be obtained with benzylic amines (entries 12, 14). Increasing the size of the aromatic group in the case of the naphthalenes (entries 11 and 12) and the (*R*)-*α*-methyl-*o*-methoxybenzylamine (entry 13) improves the selectivity. A similar improve-

Table 2. Fluorinations Using Benzylic Amines

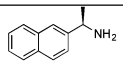
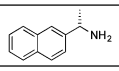
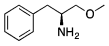
Entry	Catalyst	Yield (%)		% ee	
		9	**7**	**7**	**8**
1	**6**	75	60	70	73
8		72	56	64	61
9		58	45	60	57
10		10	33	31	nd
11		91	53	75	76
12		92	40	80	80
13		91	53	78	78
14		Quant	55	81	81

Table 3. Enantiomeric Fluorination

Entry	Catalyst	Yield (%)		% ee	
		2	**4**	**4**	**5**
4	**1**	94	53	97	96
15		71	49	66	67
16		90	62	74	75
17		81	45	74	80
18		Quant	54	81	81
19		96	62	17	nd
20		Quant	62	51	54
21		38	17	86	nd

ment in enantioselectivity is obtained by the introduction of a methoxy group onto the α-methyl (entry 14), a compound readily available from the reduction of phenylglycine. Furthermore, the results clearly show that the primary amines are superior to secondary amines (entry 8 vs 10). With these catalysts, similar yields are obtained to those for the quinine derivative **6**. Although enantiopure material is not obtained from the reaction, the alcohol **7** can be recrystallized from 70 to >98% ee in a single crystallization from ether−hexane allowing practical access to the enantiopure (3*S*,4*R*)-3-fluoropiperidin-4-ol **7** for the first time. The crystals were suitable for X-ray crystallography (vide infra).

Given the commercial availability of the benzylic amines, access to the enantiomeric series could be readily achieved. As expected, similar levels of enantioselectivity are observed in each case where both enantiomers of the catalyst were used (Table 3). Given the importance of the sterics of the aromatic group in enantioselectivity, it is not surprising that there is a large drop in enantioselectivity when moving from a benzylic amine to the phenethylamine (compare entries 18 and 19). The triphenylethanolamine catalyst (entry 21) shows the highest level of ee of all the commercial catalysts, which is in line with the observation that increasing the steric environment around the amine improves the ee; however, the conversions are low, which may also be a result of the sterically encumbered environment of the catalyst.

Again it was possible to obtain a single enantiomer by crystallization from ether−hexane. X-ray crystallography confirmed both the relative stereochemistry and the absolute configuration (Figure 1). In both of the X-ray structures, the fluorine occupies the axial position, with the vicinal hydroxyl occupying the equatorial position. The solid state structures are in line with previous molecular dynamic and NMR studies[26] on related piperidines as well as a crystal structure of the related 3-fluoro-4,4-diphenylpiperidine,[27] which are thought to be influenced by a charge dipole interaction between the fluorine and the piperidine nitrogen. In these instances, the 4-hydroxyl being equatorial increases the preference for the axial fluorine. However, it should be noted that the solution structure appears

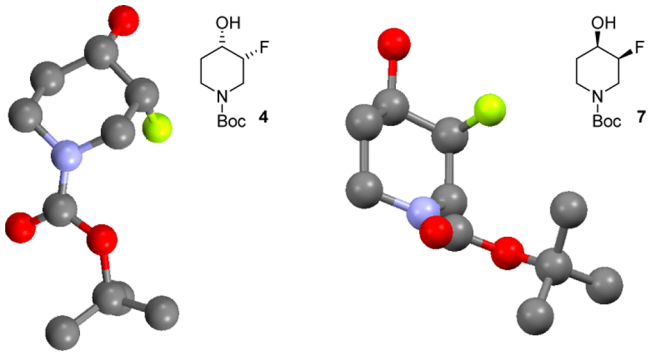
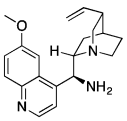


Figure 1. X-ray crystal structures of the fluoropiperidinols.

to be more dynamic as evidenced by the broad proton NMR at room temperature and two resonances in the fluorine NMR; both phenomena are resolved at 50 °C (see Supporting Information), an observation that was previously noted with 3-fluoro-4,4-diphenylpiperidine.[27]

Finally, we chose to investigate the effect of raising the temperature above −10 °C used in the original procedure. Taking both the best catalyst we had identified, the quinine-derived catalyst, and the most readily available, the inexpensive (*R*)-α-methylbenzylamine, under the same conditions at 0 °C and room temperature resulted in fluoropiperidinone **9** formation, which in each instance was reduced to the corresponding piperidinol **7**. The results show that at 0 °C the enantioselectivity is not impacted with either catalyst, while at 20 °C (room temperature) there appears to be a lowering of enantioselectivity with both catalysts (Table 4). The result is more pronounced in the case of α-methylbenzylamine. The results were confirmed by the tosylate **8**. Further, when carrying out the reaction at 0 °C, the amount of catalyst could be reduced from the original 20 to 10% without seeing a drop in either yield or ee with both catalysts investigated. It is interesting to note that using the optimized reaction conditions with Selectfluor as fluorinating agent and acetonitrile as solvent failed to yield any fluorinated product. The increased ease of synthesis provided by a 0 °C reaction temperature and reduced catalyst loading has practical advantages, particularly in larger

Table 4. Effect of Temperature on the Fluorination Reaction

Temp	Catalyst	Yield (%)		% ee	
		9	**7**	**7**	**8**
<-10 °C		96	61	95	94
0 °C		77	56	96	96
0 °C[a]		81	54	95	96
20 °C		76	59	92	92
<-10 °C		72	56	64	61
0 °C		73	42	68	64
0 °C[a]		81	50	69	nd
20 °C		73	41	53	54

[a]Using 10 mol % of catalyst.

scale synthesis. The refinements in the reaction allowed the procedure to be scaled-up to produce 23 g of enantiopure 1-Boc-3*S*-fluoro-4*R*-piperidinol **7** in one batch (see the Experimental Section).

In summary, we have developed the first enantioselective route to either enantiomer of the important medicinal chemistry building block 3-flouropiperidin-4-ol using an enantioselective fluorination of the corresponding piperidinone. Further, during our investigation we have carried out a screen of catalysts and shown that the modified cinchona alkaloid originally reported to catalyze the fluorination reaction may be replaced by a commercially available primary benzylic amine and carried out at 0 °C with 10 mol % catalyst without detriment. The resulting *cis*-alcohols can be crystallized from 65% ee to enantiomerically pure material in two rounds of crystallization (from 70% ee and above, only one crystallization is required). These refinements will make the reaction more amenable to scale-up for this key building-block.

■ EXPERIMENTAL SECTION

All commercial reagents were used without further purification. All solvents were reagent or HPLC grade. Anhydrous tetrahydrofuran and dichloromethane were purchased and used directly. All reactions were carried out under a nitrogen atmosphere in oven-dried glassware. Analytical TLC was performed on silica gel 60 F_{254} plates and visualized by UV if possible and *p*-anisaldehyde or ceric ammonium molybdate staining. Flash chromatography was carried out using an automated system with prepacked silica columns. Yields refer to chromatographically and spectroscpically pure compounds. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a 300 MHz spectrometer at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to residual solvent $CDCl_3$ (^{1}H 7.26 ppm; ^{13}C 77.0 ppm) and unreferenced for ^{19}F. Multiplicities are reported as follows: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. Proton assignments were made based on COSY spectra. High resolution mass spectra were recorded using a time-of-flight mass spectrometer. Chiral analysis was performed using either HPLC or supercritical fluid chromatography (SFC). The methods chosen were based upon ability to obtain baseline separation of the racemic mixtures for the compounds of interest. The mobile phase for the HPLC experiments was an isocratic hexane/alcohol mixture, whereas the SFC mobile phase was an isocratic mixture of CO_2 and alcohol. Stationary phases for both HPLC and SFC were purchased from commercial suppliers; see the Supporting Information for more details.

Formation of 9-Deoxy-9-*epi*-aminoquinine 3HCl. A similar procedure is used to that reported in by Connon.[15] To a solution of quinine (40.0 g, 123.5 mmol, 1.0 equiv) and triphenylphosphine (38.8 g, 148.1 mmol, 1.0 equiv) in tetrahydrofuran (400 mL) at 0 °C was added diisopropyl azodicarboxylate (29.9 g, 29.1 mL, 148.1 mmol, 1.2 equiv) dropwise. The reaction was stirred at 0 °C for 10 min, and diphenylphosphoryl azide (40.7 g, 32.0 mL, 148.1 mmol, 1.2 equiv) was added dropwise. The reaction was stirred at room temperature for 4 h and heated to 45 °C for 2 h. Triphenylphosphine (38.8 g, 148.1 mmol, 1.2 equiv) was added, and the reaction was stirred at 45 °C for a further 2 h (Note: some evolution of nitrogen was observed on addition of the triphenylphosphine). Water (40 mL) was added, and the reaction was stirred at room temperature for 16 h. The reaction was concentrated, and the residue was partitioned between CH_2Cl_2 (400 mL) and HCl (2M, 350 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 240 mL) and concentrated to dryness to obtain a yellow solid. The solid was recrystallized from EtOAc−MeOH (1:1, 320 mL) to yield the title compound (44.9 g, 84%) as a pale yellow solid: ^{1}H NMR (DMSO-d_6) δ 9.75 (2H, br s, NH_2), 9.14 (1H, d, J = 5.0 Hz, H-2′ or H-3′), 8.46 (1H, d, J = 5.0 Hz, H-2′ or H-3′), 8.35 (1H, d, J = 9.0 Hz, H-8′), 8.00 (1H, d, J = 2.0 Hz, H-5′), 7.75 (1H, dd, J = 9.0, 2.0 Hz, H-7′), 5.99 (1H, d, J = 10.0 Hz, H-9), 5.86 (1H, ddd, J = 17.0, 10.5, 6.5 Hz, $CH_2{=}C\underline{H}$), 5.27 (1H, d, J = 17.0 Hz, *trans*$C\underline{H}_2{=}CH$), 5.13 (1H, d, J = 10.5 Hz, *cis*$C\underline{H}_2{=}CH$), 4.80 (1H, m, H-8), 4.10 (1H, m, 1 × H-6), 4.06 (3H, s, OCH_3), 3.72 (1H, dd, J = 12.5, 10.5 Hz, 1 × H-2), 3.37 (2H, m, 1 × H-2, 1 × H-6), 2.75 (1H, m, H-3), 1.87 (3H, m, 1 × H-2, H-5), 1.50 (1H, dd, J = 12.5, 9.5 Hz, 1 × H-7), 0.86 (1H, m, 1 × H-7); ^{13}C NMR (DMSO-d_6) δ 160.0, 144.2 (2C), 138.3, 129.2, 126.8, 126.0, 122.1, 117.1, 103.7, 59.1, 57.2, 52.4, 48.3, 42.2, 36.3, 26.0, 23.9 (2C); m/z 324 $[M + H]^+$; HRMS m/z $[M + H]^+$ calcd for $C_{20}H_{26}N_3O^+$ 324.2070, found 324.2072.

Formation of (*R*)-α-Methylbenzylamine Monotrichloroacetic Acid Salt Monohydrate. To a solution of (*R*)-α-methylbenzylamine (0.236 g, 1.95 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) was added trichloroacetic acid (0.334 g, 2.05 mmol, 1.05 equiv) and water (0.035 mL, 1.95 mmol, 1.0 equiv). The solution was used directly in the following reaction.

Formation of 1-Boc-3*S*-fluoropiperidin-4-one 9 Using (*R*)-α-Methylbenzylamine. A similar procedure was used to that reported by MacMillan.[14] To a suspension of freshly ground sodium carbonate (1.55 g, 14.63 mmol, 1.5 equiv) and *N*-fluorobenzenesulfonimide (3.07 g, 9.75 mmol, 1.0 equiv) in tetrahydrofuran (20 mL) at −20 °C was added (*R*)-α-methylbenzylamine trichloroacetic acid salt monohydrate (1.95 mmol, 0.2 equiv) as a solution in tetrahydrofuran (10 mL). The reaction was stirred at −20 °C for 10 min before adding 1-Boc-piperidin-4-one (3.88 g, 19.50 mmol, 2.0 equiv) in three portions. The reaction was stirred between −20 and −10 °C for 24 h, before Et_2O (30 mL) was added. The reaction was filtered through silica to remove insolubles, eluting with Et_2O (200 mL). The filtrate was concentrated under reduced pressure. Column chromatography (20 → 60% EtOAc−hexane) yielded the title compound (1.52 g, 72%) as a white solid: ^{1}H NMR δ 4.87 (1H, ddd, J = 48.0, 9.5, 6.5 Hz, pipH-3), 4.43 (1H, m, 1H of pipH-2, H-6), 4.16 (1H, m, 1H of pipH-2, H-6), 3.23 (2H, m, 2H of pipH-2, H-6), 2.64−2.44 (2H, m, pipH-5), 1.48 (9H, s, $C(CH_3)_3$); ^{19}F NMR δ −197.4.

1-Boc-3*R*-fluoropiperidin-4-one 2. A similar procedure was used to that for **9** using (*S*)-α-methylbenzylamine on a 9.75 mmol scale to yield the title compound (1.50 g, 71%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.87 (1H, ddd, J = 48.0, 9.5, 6.5 Hz, pipH-3), 4.43 (1H, m, 1H of pipH-2, H-6), 4.16 (1H, m, 1H of pipH-2, H-6), 3.23 (2H, m, 2H of pipH-2, H-6), 2.64−2.44 (2H, m, pipH-5), 1.48 (9H, s, $C(CH_3)_3$); ^{19}F NMR δ −197.3.

Formation of 1-Boc-3*S*-fluoro-4*R*-piperidinol 7. To a solution of the piperidinone (1.52 g, 7.00 mmol, 1.0 equiv) in methanol (70 mL) at 0 °C was added tetramethylammonium borohydride (0.75 g, 8.41 mmol, 1.2 equiv) over 20 min. The reaction was stirred at 0 °C for 4 h before NH_4Cl (20 mL) was added, and then mixture was stirred at room temperature for 45 min. The reaction was concentrated to remove methanol and partitioned between EtOAc (100 mL) and NH_4Cl (100 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (silica, 20 → 70% EtOAc−hexane) yielded the title compound (0.86 g, 56%) as a white solid. Chiral HPLC determined the material to be 64% ee: IR (film) 3423 (br), 2973, 2934, 1709, 1687, 1427, 1366, 1246, 1166,

1128, 1089, 999, 870 cm^{-1}; ^1H NMR δ 4.58 (1H, br ddt, J = 48.5, 6.5, 3.5 Hz, pipH-3), 3.95−3.80 (2H, m, 1H of pipH-2, pipH-4), 3.68 (1H, m, 1H of pipH-6), 3.39 (1H, m, 1H of pipH-2), 3.14 (1H, m, 1H of pipH-6), 2.39−2.30 (1H, m, OH), 1.84−1.68 (2H, m, pipH-5), 1.43 (9H, s, $C(CH_3)_3$); ^{13}C NMR δ 154.9, 88.5 (d, J = 178.0 Hz), 80.1, 67.9 (d, J = 18.0 Hz), 44.3 (br), 40.0 (br), 29.3, 28.3; ^{19}F NMR δ −201.8, −202.9; m/z 164 $[M + H - C_4H_8]^+$, 120 $[M + H - CO_2 - C_4H_8]^+$; HRMS m/z $[M + H - C_4H_8 - CO_2]^+$ calcd for $C_5H_{11}FNO^+$ 120.0819, found 120.0820. Recrystallization from 1:1 Et_2O−hexane resulted in white crystals, which were obtained by filtration and dried under a vacuum. The crystals were determined to be >98% ee by chiral HPLC: $[\alpha]_D^{20}$ +16.0 (c 1.40, $CHCl_3$).

1-Boc-3*R*-fluoro-4*S*-piperidinol 4. A similar procedure was used to that for **7** using 1-Boc-3*S*-fluoropiperidinone **2** on a 6.91 mmol scale to yield the title compound (0.74 g, 49%) as a white solid. Chiral HPLC determined the material to be 66% ee: IR (film) 3419 (br), 2977, 2934, 1683, 1446, 1426, 1366, 1244, 1167, 1126, 1087, 1001, 871 cm^{-1}; ^1H NMR δ 4.58 (1H, br d, J = 48.0 Hz, pipH-3), 3.96−3.82 (2H, m, 1H of pipH-2, pipH-4), 3.69 (1H, m, 1H of pipH-6), 3.38 (1H, m, 1H of pipH-2), 3.15 (1H, m, 1H of pipH-6), 2.29 (1H, d, J = 6.0 Hz, OH), 1.88−1.66 (2H, m, pipH-5), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR δ 154.9, 88.5 (d, J = 177.0 Hz), 80.1, 67.9 (d, J = 18.0 Hz), 44.6 (br), 40.0 (br), 29.2, 28.3; ^{19}F NMR δ −201.8, −202.9; m/z 164 $[M + H - C_4H_8]^+$, 120 $[M + H - C_4H_8 - CO_2]^+$; HRMS m/z $[M + H - C_4H_8 - CO_2]^+$ calcd for $C_5H_{11}FNO^+$ 120.0819, found 120.0821. Recrystallization from 1:1 Et_2O−hexane (two rounds) resulted in crystals, which were determined to be >98% ee by chiral HPLC: $[\alpha]_D^{20}$ −16.4 (c 1.73, $CHCl_3$).

Formation of *cis*-1-Boc-3*S*-fluoro-4*R*-toluenesulfonylpiperidine 8. To a solution of 1-Boc-3*S*-fluoro-4*R*-piperidinol (0.037 g, 0.169 mmol, 1.0 equiv) and *p*-toluenesulfonyl chloride (0.039 g, 0.203 mmol, 1.2 equiv) in dichloromethane (1.5 mL) was added triethylamine (0.036 mL, 0.253 mmol, 1.5 equiv) and dimethylaminopyridine (0.002 g, 0.017 mmol, 0.1 equiv). The reaction was stirred at room temperature for 14 h before pouring into $NaHCO_3$ (20 mL). The organics were extracted with CH_2Cl_2 (3 × 20 mL), combined, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (20 → 60% EtOAc−hexane) yielded the title compound (0.051 g, 81%) as a white solid. Chiral HPLC determined the material to be 61% ee: IR (film) 2977, 1699, 1423, 1367, 1244, 1191, 1177, 1010, 967, 879, 842, 673 cm^{-1}; ^1H NMR (50 °C) δ 7.80 (2H, d, J = 8.5 Hz, 2H of C_6H_4Me), 7.33 (2H, d, J = 8.0 Hz, 2H of C_6H_4Me), 4.73 (1H, dddd, J = 19.0, 9.0, 4.0, 2.5 Hz, pipH-4), 4.58 (1H, dddd, J = 47.5, 6.0, 3.0, 2.5 Hz, pipH-3), 3.93 (1H, dt, J = 14.5, 6.5 Hz, 1H of pipH-2), 3.76 (1H, m, 1H of pipH-6), 3.34 (1H, ddd, J = 24.0, 14.0, 2.0 Hz, 1H of pipH-2), 3.15 (1H, br dd, J = 10.5, 9.5 Hz, 1H of pipH-6), 2.44 (3H, s, $C_6H_4C\underline{H}_3$), 2.16−2.02 (1H, m, 1H of pipH-5), 1.76−1.69 (1H, m, 1H of pipH-5), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR (50 °C) δ 154.6, 144.9, 134.2, 129.8, 127.7, 118.3, 85.5 (d, J = 187.0 Hz), 80.4, 77.1, 40.1, 28.2, 27.4, 21.5; ^{19}F NMR (50 °C) δ −201.2; m/z 274 $[M + H - C_4H_8 - CO_2]^+$; HRMS m/z $[M + H - C_4H_8 - CO_2]^+$ calcd for $C_{12}H_{17}FNO_3S^+$ 274.0908, found 274.0915. The reaction was carried out on enantiopure piperidinol **7** to obtain the tosylate **8**, which was determined to be >98% ee by chiral HPLC: $[\alpha]_D^{20}$ +11.4 (c 1.03, $CHCl_3$).

1-Boc-3*R*-fluoro-4*S*-toluenesulfonylpiperidine 5. A similar procedure was used to that for 1-Boc-3*S*-fluoro-4*R*-toluenesulfonylpiperidine **8** on a 0.169 mmol scale using 1-Boc-3*R*-fluoro-4*S*-piperidinol **4** to yield the title compound (0.050 g, 79%) as a white solid. Chiral HPLC determined the material to be 67% ee: IR (film) 2977, 2934, 1698, 1424, 1366, 1244, 1176, 1010, 967, 879, 842 cm^{-1}; ^1H NMR (50 °C) δ 7.81 (2H, d, J = 8.5 Hz, 2H of C_6H_4Me), 7.34 (2H, d, J = 8.0 Hz, 2H of C_6H_4Me), 4.73 (1H, dddd, J = 20.5, 9.5, 4.0, 2.5 Hz, pipH-4), 4.58 (1H, dddd, J = 47.5, 6.0, 3.5,2.0 Hz, pipH-3), 3.92 (1H, br dt, J = 14.0, 7.0 Hz, 1H of pipH-2), 3.76 (1H, m, 1H of pipH-6), 3.33 (1H, ddd, J = 23.5, 14.0, 2.0 Hz, 1H of pipH-2), 3.15 (1H, br dd, J = 9.5, 8.5 Hz, 1H of pipH-6), 2.45 (3H, s, $C_6H_4C\underline{H}_3$), 2.14−2.02 (1H, m, 1H of pipH-5), 1.77−1.65 (1H, m, 1H of pipH-5), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR (50 °C) δ ; ^{19}F NMR (50 °C) δ −200.9; m/z 274 $[M + H - C_4H_8 - CO_2]^+$; HRMS m/z $[M + H - C_4H_8 - CO_2]^+$ calcd for $C_{12}H_{17}FNO_3S^+$ 274.0908, found 274.0922. The reaction was carried out on enantiopure piperidinol **4** to obtain the tosylate **5**, which was determined to be 97% ee by chiral HPLC: $[\alpha]_D^{20}$ −10.6 (c 1.08, $CHCl_3$);

Scale-up Procedure for the Formation of 9. To a suspension of freshly ground sodium carbonate (59.9 g, 563.3 mmol, 1.5 equiv) and *N*-fluorobenzenesulfonimide (99.5 g, 379.9 mmol, 1.0 equiv) in tetrahydrofuran (800 mL) at 0 °C was added 9-deoxy-9-*epi*-aminoquinine trichloroacetic acid salt monohydrate (44.6 mmol, 0.12 equiv) as a solution in tetrahydrofuran (200 mL). The reaction was stirred at 0 °C for 10 min before 1-Boc-piperidin-4-one (150.0 g, 753.8 mmol, 2.0 equiv) was added in three portions. The reaction was stirred at 0 °C for 24 h, before Et_2O (400 mL) was added. The reaction was filtered through silica to remove insolubles, eluting with Et_2O (500 mL). The filtrate was concentrated under reduced pressure. Column chromatography (silica, 20 → 60% EtOAc−hexane) yielded the title compound (53.8 g, 66%) as a white solid: data agrees with that stated.

Scale-up Procedure for the Formation of 7. To a solution of the 1-Boc-3*S*-fluoropiperidin-4-one (53.8 g, 247.9 mmol, 1.0 equiv) in methanol (1000 mL) at 0 °C was added tetramethylammonium borohydride (22.1 g, 247.9 mmol, 1.0 equiv) over 1.25 h. The reaction was stirred at 0 °C for 3 h before NH_4Cl (300 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction was concentrated to remove methanol and partitioned between EtOAc (500 mL) and NH_4Cl (300 mL). The aqueous phase was extracted with EtOAc (3 × 300 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (silica, 20 → 70% EtOAc−hexane) yielded the title compound (30.6 g, 56%) as a white solid, which was determined to be 96% ee by chiral HPLC. Recrystallization from Et_2O−hexane (1:1, 500 mL) yielded white crystals (23.0 g, 75%) that were isolated by filtration and dried under a vacuum. The crystals were shown to be >97% ee by chiral HPLC: data agrees with that stated.

On purifying the piperidinol, two further compounds were obtained, 1-Boc-3,5-difluoro-4-piperidinol (4.4 g, 8%) and the 1-Boc-3*S*-fluoro-4*S*-piperidinol (5.1 g, 9%).

■ ASSOCIATED CONTENT

Supporting Information

An expanded version of Table 1 is given. NMR spectra of the 9-deoxy-9-*epi*-aminoquinine 3HCl, compounds **4**, **5**, **7**, and **8**, and a comparison of the ^1H and ^{19}F NMR of the 3-fluoropiperidin-4-ol at both room temperature and 50 °C are included. COSY spectra of **4**, **8**, and 9-deoxy-9-*epi*-aminoquinine 3HCl are provided. Detailed chiral chromatography conditions, chromatograms for the racemic mixtures of both **4**/**7** and **5**/**8** are given along with examples of the chromatograms obtained in the reactions and after crystallization. Crystallographic data for compounds **4** and **7** is provided, along with ellipsoid plots and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s):The authors are all employees of Rigel, Inc.

■ ACKNOWLEDGMENTS

We thank Van Ybarra and Duayne Tokushige for high resolution mass spectral determinations. X-ray crystallography was performed by Dr. Peter S. White at the University of North Carolina, Chapel Hill.

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