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Enantioselective Fluorination Mediated by *N*-Fluoroammonium Salts of Cinchona Alkaloids: First Enantioselective Synthesis of BMS-204352 (MaxiPost)

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Abstract: We have employed a cinchona alkaloid/Selectfluor-mediated enantioselective fluorination of the oxindole **2** to achieve the first enantioslective synthesis of BMS-204352 (MaxiPost, ***S*-1**), an effective opener of maxi-K channels. Fluorination occurred to produce ***S*-1** with 84% ee using the bis-cinchona alkaloid $(DHQ)_2AQN$. Recrystallization produced enantiomerically pure (>99% ee) product. Quinidine-mediated fluorination of **2** gave the (*R*)-antipode of **1** with 68% ee.

In contrast to nature, which has produced only rare examples of compounds possessing the carbon−fluorine bond, synthetic chemists have produced an enormous inventory of such molecules. Examples of fluorinated compounds include such important classes as chiral liquid crystals and a host of medicinal agents.[1] Development and refinement of several procedures for selective introduction of fluorine have contributed greatly to the rapid increase in the inventory of fluorinated analogues. An important part of these advances was the development of enantioselective fluorination reactions,[2] especially those that proceed by electrophilic mechanisms. Since the initial report over 10 years ago,[3a] these have been studied extensively. These initial efforts revealed several limitations in both the chemical yields and enantioselectivities of the fluorinated products using these first-generation chiral reagents.[3] Recent advances in methodology of electrophilic enantioselective fluorinations by Hintermann and Togni, Cahard et al., Kim and Park, and us have led to significant improvements over the past few years,[4,5] and now enantioselectivities of 90% ee have been reached. Another important contribution to this field is an example of a transition metal complex-mediated nucleophilic enantioselective fluorination reported by Bruns and Haufe.[6] Although the utility of these enantioselective fluorination systems for the synthesis of chiral fluorinated compounds has been demonstrated impressively in several model systems, examples of applications to the synthesis of medically important compounds have been lacking. As part of our ongoing projects related to the design and synthesis of fluorine containing biologically active compounds,[7] we now report the first asymmetric approach to BMS-204352 (***S*-1**) based on our recently described enantioselective fluorination procedure that is mediated by *N*-fluoroammonium salts of cinchona alkaloids.[5]

The novel fluorooxindole ***S*-1**, BMS-204352 (MaxiPost), is being developed by Bristol-Myers Squibb Pharmaceutical Research Institute as a potent, effective opener of maxi-K channels (Figure 1).[8] Worldwide phase III clinical trials of BMS-204352 for treatment of acute ischemic

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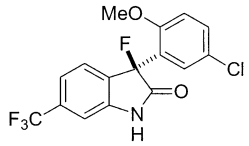
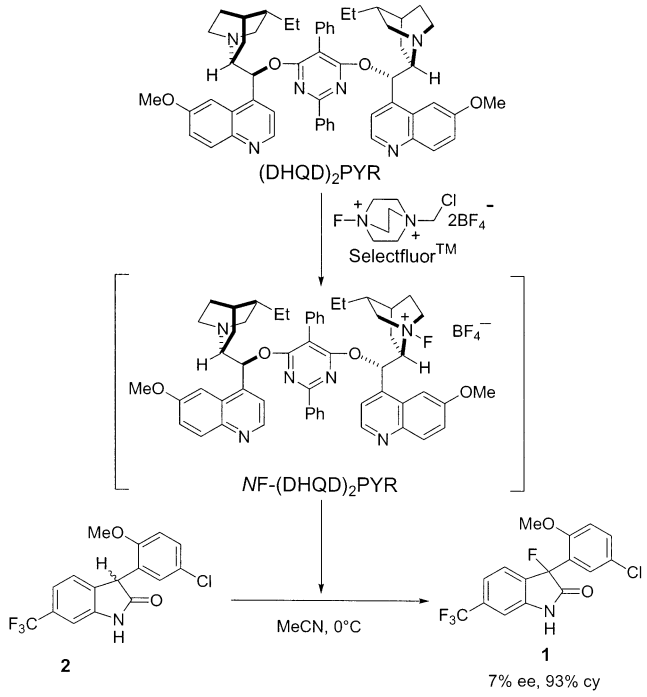


FIGURE 1. BMS-204352 (MaxiPost, ***S*-1**).

SCHEME 1. Enantioselective Fluorination Mediated by *N*-Fluoroammonium Salts of (DHQD)$_2$PYR



stroke are currently in progress. BMS-204352 (***S*-1**) is a chiral, nonracemic compound, a key structural feature of which is the fluorine atom bonded to the asymmetric quaternary carbon center at C3 in the oxindole ring. Although both enantiomers of **1** are active, the *S* isomer consistently gives a more robust response and has been developed as BMS-204352. The *S*-enantiomer (BMS-204352) was isolated using chiral HPLC resolution of racemic **1**[8b,e] or through the formation and separation of a diastereomeric salts of corresponding ring-opening compound with (*S*)-α-methyl benzylamine.[8c,e] No enantioselective synthesis has been reported to date.

In our previous work,[5b] the best conditions for fluorination of oxindoles [*N*-fluoroammonium salt of (DHQD)$_2$PYR (hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether), *N*F-(DHQD)$_2$PYR, prepared in situ from (DHQD)$_2$PYR and Selectfluor] gave up to 82% ee. We examined the enantioselective fluorination of the parent oxindole **2**, prepared from commercially available 3-aminobenzotrifluoride in five steps,[8b,d] using these conditions. Because of the high acidity of the reactive center, compound **2** was fluorinated very smoothly without any additives or preconversion to the corresponding silyl ether. The result, however, was very disappointing, and the fluorinated compound **1** was obtained with poor enantioselectivity (Scheme 1, run 1 in Table 1), possibly a result of the high reactivity. Fluorination using other previously optimized conditions[5a,b] (*N*F-DHQB prepared in situ from DHQB and Selectfluor, up to 91% ee for indanones, *N*F-DHQDA prepared in situ from DHQDA and Selectfluor, up to 87% ee for acyclic compounds) also gave unacceptable enantioselectivities in the formation of **1** (18% ee, and 32% ee, respectively, Table 1, runs 2 and 3).

TABLE 1. Cinchona Alkaloid/Selectfluor-Mediated Enantioselctive Fluorination of 2[a]

run	alkaloid[b]	yield[c] (%)	ee[d] (%)	*S*/*R*[e]
1	(DHQD)$_2$PYR	93	7	*S*
2	DHQB	94	18	*S*
3	DHQDA	82	32	*R*
4	QD	98	52	*R*
5	QN	91	25	*S*
6	CD	90	13	*S*
7	CN	94	37	*R*
8	DHQMQE	93	24	*S*
9	DHQA	93	16	*S*
10	DHQPE	90	2	*R*
11	DHCB	88	20	*R*
12	DHCDB	97	11	*R*
13	DHQDB	97	38	*R*
14	(DHQD)$_2$AQN	92	3	*R*
15	(DHQ)$_2$PYR	90	14	*R*
16	(DHQD)$_2$PHAL	98	54	*R*
17	(DHQ)$_2$PHAL	89	53	*S*
18	(DHQ)$_2$AQN	89	74	*S*
19[f]	(DHQ)$_2$AQN	89	8	*S*
20[f]	QD	81	18	*R*

[a] All of the fluorinations were performed at 0 °C in MeCN for 1−2 h unless otherwise noted. [b] DHQB = dihydroquinine 4-chlorobenzoate, DHQDA = dihydroquinidine acetate, QD = quinidine, QN = quinine, CD = cinchonidine, CN = cinchonine, DHQMQE = dihydroquinine 4-methyl-2-quinoyl ether, DHQA = dihydroquinine acetate, DHQPE = dihydroquinine 9-phenanthyl ether, DHCB = dihydrocinchonine benzoate, DHCDB = dihydrocinchonidine benzoate, DHQDB = dihydroquinidine benzoate. [c] Isolated yield of **1**. [d] ee values were determined by HPLC analysis using a Chiralcel OD column eluting with 10% 2-propanol in hexane. [e] The absolute configuration of **1** was assigned on the basis of the HPLC analysis according to ref 8e. [f] The fluorination was performed in EtOH.

On the other hand, the simple *N*-fluoroammonium salt of quinidine (*N*F-QD, Table 1, run 4) showed substantially better asymmetric induction, again proceeding in high chemical yield. This suggested that proper choice of alkaloids could be important for optimization of the enantioselective fluorination of **2**. Our next efforts focused on screening reactions at 0 °C in MeCN as a solvent using a variety of cinchona alkaloids (Scheme 1 and Table 1). All reactions were completed within 1−2 h to give **1** in high yields. The results confirm that varying the structure of cinchona alkaloids has a great effect on the ee of the product. Even bis-cinchona alkaloids of similar structures can lead to significantly different effects on enantioselectivity. On the basis of the results shown in Table 1 (runs 4, 16, 17, and 18 in Table 1 and Figure 2), the cinchona alkaloids QD, (DHQD)$_2$PHAL, (DHQ)$_2$PHAL, and (DHQ)$_2$AQN were chosen as candidates for further optimization of conditions to achieve enhanced selectivity. The use of EtOH as a solvent caused a decrease in enantioselectivity (runs 19 and 20).

Table 2 shows the results of fluorination at −80 °C using the selected alkaloids. The reaction was conducted in a mixed solvent of MeCN/CH_2Cl_2 (3/4) because the freezing point of MeCN is greater than −80 °C. A lower temperature improved enantioselectivities with all the

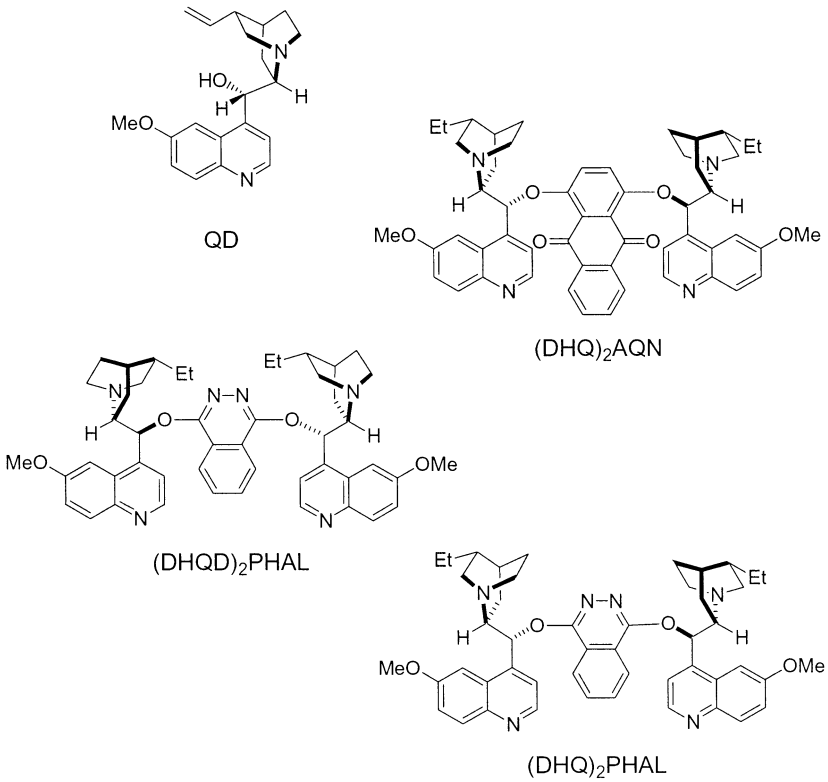


FIGURE 2. Structures of QD, $(DHQ)_2AQN$, $(DHQD)_2PHAL$, and $(DHQ)_2PHAL$.

TABLE 2. Enantioselective Synthesis of BMS-204352 (1)[a]

run	alkaloid	yield[b] (%)	ee[c] (%)	*S*/*R*[d]
1	$(DHQ)_2AQN$	94	84	*S*
2	$(DHQ)_2PHAL$	75	78	*S*
3	$(DHQD)_2PHAL$	93	38	*R*
4	QD	96	68	*R*

[a] All of the fluorinations were performed overnight at −80 °C in $MeCN/CH_2Cl_2$ (3/4). [b] Isolated yield of **1**. [c] ee values were determined by HPLC analysis using a Chiralcel OD column eluting with 10% 2-propanol in hexane. [d] The absolute configuration of **1** was assigned on the basis of the HPLC analysis according to ref 8e.

alkaloids except with $(DHQD)_2PHAL$, in which case a decrease in selectivity was observed.

Using the optimized conditions, BMS-204352 (***S*-1**) was produced in 94% yield with 84% ee. Isolation by simple re-crystallization from CH_2Cl_2/hexane in a usual way gave enantiomerically pure BMS-204352 (>99% ee). The optical purity was determined by HPLC analysis on a Chiralcel OD column and by comparison of the optical rotation with the reported value. Using QD, (*R*)-**1** was obtained with 68% ee, which was improved to 93% ee by re-crystallization.

In conclusion, we have developed the first direct asymmetric synthesis of BMS-204352 using cinchona alkaloid/Selectfluor-mediated enantioselective fluorination. The commercial availability of both Selectfluor and $(DHQ)_2AQN$/QD, as well as an in situ protocol for generation of the chiral *N*-fluoroammomium salts, all contribute to the convenience of this procedure for the preparation of ***S*-1**. We suggest that this strategy using chiral fluoroammonium salts should be readily adapted to the preparation of many other chiral fluorine-containing compounds, where the best cinchona alkaloid for each target compound would be easily found by simple screening of the alkaloids. Included in our ongoing research is the determination of an X-ray crystal structure of *N*F-$(DHQ)_2AQN$. This will be used for clarification of the mechanism of induction of enantioselectivity.

Experimental Section

General Information. Melting points were uncorrected. ^1H NMR spectra were measured as solutions in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal Me_4Si (0.00 ppm) and were recorded on a 270 MHz spectrometer. ^{19}F NMR spectra were measured with $CFCl_3$ as an internal standard and were taken with a 254 MHz spectrometer. Upfield shifts are quoted as negative values. Mass spectra were recorded by electron impact. Column chromatography was performed on silica gel. High-performance liquid chromatography (HPLC) was performed with a UV detector.

Enantioselective Synthesis of (*S*)-1, BMS-204352. A solution of **2** (100 mg, 0.29 mmol) in CH_2Cl_2 (16.7 mL) was added to a stirred solution of *N*F-$(DHQ)_2AQN$ [prepared in situ from $(DHQ)_2AQN$ (376 mg, 0.44 mmol) and Selectfluor (135 mg, 0.38 mmol) in MeCN (12.5 mL) at room temperature for 25 min] at −80 °C under nitrogen atmosphere. After the mixture was stirred overnight, water was added to the reaction mixture and extracted with AcOEt. The organic phase was washed with 3% HCl, saturated $NaHCO_3$, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude product, which was purified by silica gel column chromatography eluting with 20% AcOEt in hexane to give **1** (97.8 mg, 94%) as colorless crystals. The ee was determined to be 84% by HPLC analysis (at a wavelength of 224 nm) using a Chiralcel OD (250 mm, 4.6 mm) eluting with 10% 2-propanol in hexane at a flow rate of 2.0 mL/min. The title compound, BMS-204352 (**1**), was eluted as the first fraction from the column with retention time of about 3.1 min. ^1H NMR ($CDCl_3$, 270 MHz): δ 7.97 (brs, 1H),

7.80 (d, $J = 5.9$ Hz, 1H), 7.16−7.37 (m, 4H), 6.78 (d, $J = 8.4$ Hz, 1H), 3.55 (s, 3H). ^{19}F NMR ($CDCl_3$, 254 MHz): δ −159.7 (s), −63.4 (s). IR (KBr) 3261, 1755, 1708, 1312, 1263, 1129 cm^{-1}. HRMS: calcd for $C_{16}H_{10}{}^{35}ClF_4NO_2$ 359.0336, found 359.0337.

Isolation by simple re-crystallization from CH_2Cl_2/hexane gave enantiomerically pure BMS-204352 with >99% ee. $[\alpha]^{28}_D$: +168 (*c* 0.132, MeOH) [lit.[8c] $[\alpha]^{25}_D$ +156 (*c* 1, MeOH); lit.[8b] $[\alpha]^{25}_D$ +150 (MeOH)]. Mp: 200−203 °C (hexane/CH_2Cl_2) (lit.[8c] mp 203 °C; lit.[8b] mp 198−200 °C).

Enantioselective Synthesis of (*R*)-1, an Antipode of BMS-204352. A solution of **2** (20 mg, 0.059 mmol) in CH_2Cl_2 (2.0 mL) was added to a stirred solution of *N*F-QD [prepared in situ from qunidine (28.5 mg, 0.088 mmol) and Selectfluor (27.0 mg, 0.076 mmol) in MeCN (1.5 mL) at room temperature for 25 min] at −80 °C under nitrogen atmosphere. After the mixture was stirred overnight, water was added and the reaction mixture was extracted with AcOEt. The organic phase was washed with 5% HCl, saturated $NaHCO_3$, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oil that was purified by silica gel column chromatography eluting with 20% AcOEt in hexane to give **1** (20.3 mg, 96%) as a colorless crystals. Spectral data (^{1}H NMR, ^{19}F NMR, and IR) for the compound corresponded to **1** mentioned above. The ee was determined to be 68% by HPLC analysis (at a wavelength of 224 nm) using a Chiralcel OD (250 mm, 4.6 mm) eluting with 10% 2-propanol in hexane at a flow rate of 2.0 mL/min. The title compound, (*R*)-**1** was eluted as the second fraction from the column with retention time of about 4.5 min. Isolation by simple re-crystallization from CH_2Cl_2/hexane in a usual way gave (*R*)-**1** with 93% ee. $[\alpha]^{27}_D$: −145 (*c* 0.505, MeOH) [lit.[8c] $[\alpha]^{25}_D$ −158 (*c* 1, MeOH); lit.[8b] $[\alpha]^{25}_D$ −149 (MeOH)]. Mp: 198−200 °C (hexane/CH_2Cl_2) (lit.[8c] mp 202 °C; lit.[8b] mp 199−201 °C).

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