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Enantioselective synthesis of BMS-204352 (MaxiPost™) using *N*-fluoroammonium salts of cinchona alkaloids (F–CA–BF_4)

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The enantioselective synthesis of a potent Maxi-K potassium channel opener (BMS-204352) mediated by *N*-fluoroammonium salts of cinchona alkaloids is described. Two synthetic pathways were evaluated. An ee as high as 88% was achieved (>99% after a single recrystallisation).

3-Fluorooxindoles were identified as potent modulators of the large-conductance calcium-activated potassium (Maxi-K) channels and, therefore, are useful in the protection of neuronal cells, especially in the treatment or prevention of ischemic stroke. Among several compounds prepared at Bristol-Myers Squibb laboratories, BMS-204352 (Fig. 1) was found to be a potent opener of Maxi-K channels.[1]

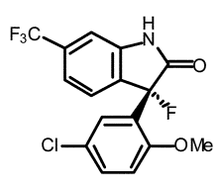
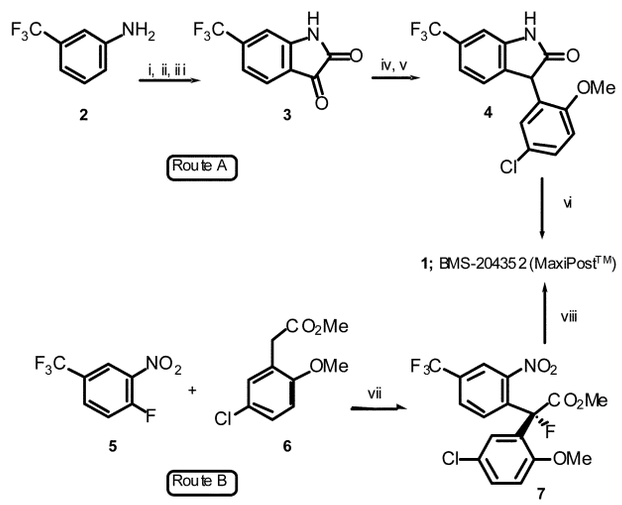


Fig. 1 Structure of (*S*)-(+)-BMS-204352, MaxiPost™, **1**.

The racemic fluorooxindoles were prepared in a straightforward manner. The stereocontrol of the fluorinated carbon center was obtained by asymmetric hydroxylation using the appropriate chiral camphorsulfonyl oxaziridine followed by reaction with diethylaminosulfur trifluoride (DAST).[1c] An alternative method to get enantiomerically pure fluorooxindoles required a separation by preparative chiral HPLC or a resolution of an intermediate through the formation of a pair of diastereomeric salts with (*S*)-(−)-α-methylbenzylamine.[2] We considered that an elegant synthetic route would involve late asymmetric electrophilic fluorination of the prochiral enolate precursor. For this reason we decided to exploit our new family of enantioselective fluorinating agents: the *N*-fluoroammonium salts of cinchona alkaloids.[3] Here, we report a new enantioselective synthesis of BMS-204352 with the aid of these chiral electrophilic fluorinating agents.[4]

Two routes were evaluated as depicted in Scheme 1.† The key step in route A is the enantioselective fluorination of the oxindole **4** whereas in route B the stereogenic fluorinated carbon center is created by enantioselective fluorination at the benzylic position of the acyclic intermediate arising from condensation between **5** and **6**. Route A utilises the reaction of *ortho*-lithiated, protected 3-trifluoromethylaniline with diethyl oxalate, followed by hydrolytic deprotection of the amino moiety and cyclisation to provide the isatin **3**.[5] Isatin **3** was converted to the hydroxy indolone by addition of a Grignard reagent and then dehydroxylated with triethylsilane and trifluoroacetic acid to end up with the key intermediate **4** (Scheme 1).[1c] Next, we submitted compound **4** to enantioselective electrophilic fluorination with various cinchona alkaloid [N–F]$^+$ salts. In route B, ester **6** was deprotonated with a first equivalent of lithium bis-(trimethylsilyl)amide, and reacted in an aromatic nucleophilic substitution with the fluoroaromatic **5**. The resulting product



Scheme 1 Enantioselective synthesis of **1**. *Reagents and conditions*: (i) Boc_2O, 80 °C; (ii) s-BuLi, THF, −78 °C then diethyl oxalate; (iii) 3 M HCl reflux; (iv) NaH, THF then 2-methoxy-5-chlorophenylmagnesium bromide, THF, −20 °C to rt; (v) Et_3SiH, TFA, 110 °C; (vi) F–CA–BF_4, DABCO, THF–CH_3CN–CH_2Cl_2 (1:3:4), −78 °C; (vii) LiHMDS, THF, −10 °C then F–CA–BF_4; (viii) $Na_2S_2O_4$ then HCl.

reacted *in situ* with a second equivalent of base and the benzylic anion was fluorinated with a cinchona alkaloid [N–F]$^+$ salt. Reduction of the nitro group in **7** with sodium hydrosulfite and cyclisation in acidic conditions led to the target molecule **1**.[6]

In previous work, we demonstrated that quinine and quinidine-based [N–F]$^+$ agents were superior to the two other cinchona alkaloids: cinchonine and cinchonidine.[3c] For the present study, we also noticed that [QN–F]$^+$ and [QD–F]$^+$ salts induce a higher degree of enantioselection. Moreover, protection of the hydroxy group in the [N–F]$^+$ reagent was crucial to achieve high enantioselectivity. Therefore Table 1 only shows a selection of the best results obtained with the reagents depicted in Fig. 2 The nature of the ester group influences enantioselectivity; the best results have been obtained with F-2NaphtQN-BF_4 (88% ee; Table 1, entry 5). Among commercially available bis-alkaloids which were evaluated in this study, 1,4-bis(9-*O*-dihydroquinyl)phthalazine served to produce F-$(DHQN)_2$PHAL-BF_4 which shows the same high level of enantioselectivity (Table 1, entry 6). Nevertheless, this fluorinating agent was not further considered because of the high cost of the starting bis-alkaloid. Both enantiomers of BMS-204352 are thus attainable, however the (*S*) enantiomer has demonstrated higher biological efficiency.[2] The nature of the base was next examined with DABCO being the most efficient base for high yield and enantioselectivity. A single recrystallisation from dichloromethane–hexane afforded enantiomerically pure crystals of **1**.

Phase-transfer conditions were also examined by means of an achiral fluorinating agent (Selectfluor or *N*-fluorobenzenesulfonimide) in the presence of a chiral phase-transfer catalyst

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Table 1 Enantioselective electrophilic fluorination (route A)

Entry	Chiral $[N–F]^+$ agent	Base	Ee (%)[a]	Yield (%)[a]
1	F-pClBzQN-BF_4	Quinuclidine	66 (*S*)	>98
2	F-pClBzQD-BF_4	Quinuclidine	66 (*R*)	>98
3	F-2NaphtQN-BF_4	Quinuclidine	84 (*S*)	>98
4	F-pClBzQN-BF_4	DABCO	57 (*S*)	>98
5	F-2NaphtQN-BF_4	DABCO	88 (*S*)	>98 (96)
6	F-$(DHQN)_2$PHAL-BF_4	DABCO	88 (*S*)	90
7	F-pClBzQN-BF_4	Cs_2CO_3	84 (*S*)	>98
8	F-2NaphtQN-BF_4	Cs_2CO_3	81 (*S*)	>98

[a] The ee values were determined by HPLC analysis using a Chiralcel OD-H column (hexane–^{i}PrOH) and the absolute configuration was assigned by comparison with literature data.[2] [b] HPLC determined yields based on starting material. In brackets are isolated yields.

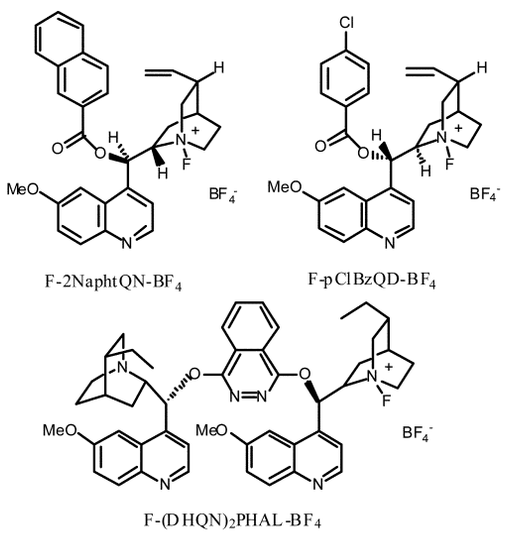

Fig. 2 Selected structures of *N*-fluoroammonium salts of cinchona alkaloids.

derived from cinchona alkaloids (for example *O*(9)-allyl-*N*-9-anthracenylmethylcinchonidinium bromide).[7] Unfortunately, the enantioselection never exceeded 13%, however the conversion into **1** was total.

In an alternative route to **1**, acyclic α-fluoroester **7** was targeted (route B, Scheme 1). Various bases (*t*-BuOM, NaH, LiHMDS and KHMDS) and fluorinating agents (same as in route A) were examined. We demonstrated that LiHMDS is the base of choice for the S_NAr and the fluorination of the ester enolate is best achieved with F-2NaphtQN-BF_4. Nevertheless the best enantiomeric excess recorded did not exceeded 36%. Interestingly, a single recrystallisation of **7** from cyclohexane afforded enantiomerically pure compound (>99% ee). Upon reduction of the nitro group in **7** with sodium hydrosulfite, the anilino-ester spontaneously cyclised to provide enantiomerically pure **1**.

In summary, we have developed an efficient enantioselective synthesis of the potent maxi-K channel opener BMS-204352 with the aid of *N*-fluoroammonium salts of cinchona alkaloids. Among the diverse routes explored, fluorination of the oxindole **4** allowed the efficient synthesis of BMS-204352 in up to 88% ee, and >99% ee after a single recrystallisation.

Notes and references

† *Typical procedure for 3-(5-chloro-2-methoxyphenyl)-3-fluoro-6-trifluoromethyl-1,3-dihydroindol-2-one* **1**. To a solution of 1,4-diazabicyclo[2.2.2]octane (35 mg, 0.31 mmol) in THF (1 mL) was added 3-(5-chloro-2-methoxyphenyl)-6-trifluoromethyl-1,3-dihydroindol-2-one **4** (48 mg, 0.14 mmol) at 20 °C. The mixture was stirred for 30 min, then the temperature was cooled to −78 °C. *N*-Fluoro-2-naphthoylquininium tetrafluoroborate (F-2NaphtQN-BF_4) (99.4 mg, 0.17 mmol) was dissolved in a mixture of 3 mL CH_3CN–4 mL CH_2Cl_2 and added over a period of one hour. The mixture was stirred overnight during which time the temperature rose from −78 to 0 °C and then quenched with 8 mL of water. The aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$) and rotary evaporated. A purification by column chromatography (silica gel, 4% MeOH–CH_2Cl_2) afforded compound **1** in 96% yield. Ee was determined by chiral HPLC (Chiracel OD-H column, 10% 2-propanol–hexane, 1 mL min^{-1}, λ = 254 nm, retention times: (*S*)-**1**: 6.0 min, (*R*)-**1**: 7.8 min). Physical and spectroscopic data are in agreement with ref. 4.

Typical procedure for (5-chloro-2-methoxyphenyl)fluoro(2-nitro-4-trifluoromethylphenyl)acetic acid methyl ester **7**. A solution of lithium bis(trimethylsilyl)amide 1 M in THF (0.88 mL) was added dropwise to a mixture of 1-fluoro-2-nitro-4-trifluoromethylbenzene **5** (0.48 mmol, 100.4 mg) and (5-chloro-2-methoxyphenyl)acetic acid methyl ester **6** (0.4 mmol, 85.8 mg) in THF (10 mL) at −10 °C. The mixture was stirred for 90 min and then cooled to −40 °C for the addition of a solution of F-2NaphtQN-BF_4 (280 mg, 0.48 mmol) in acetonitrile (5 mL). After stirring overnight, during which time the temperature rose to 5 °C, the mixture was quenched with water (15 mL) and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and rotary evaporated. A purification by column chromatography (silica gel, cyclohexane–CH_2Cl_2, 1:1) afforded compound **7** in 88% yield. IR ($CHCl_3$) ν 1766, 1720, 1542, 1326, 1260, 1133, 830, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 3.96 (s, 3H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.20 (m, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.47 (m, 1H), 7.78 (m, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 54.0, 56.7, 95.5 (d, *J* = 193 Hz), 114.1, 122.3 (d, *J* = 3.5 Hz), 122.9 (q, *J* = 272 Hz), 126.5, 126.7, 128.5 (q, *J* = 3.5 Hz), 129.5 (d, *J* = 8 Hz), 131.3 (d, *J* = 4.6 Hz), 132.1, 132.8 (d, *J* = 35 Hz), 135.2 (d, *J* = 23 Hz), 148.9, 156.2 (d, *J* = 3 Hz), 168.3 (d, *J* = 25 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −63.48 (3F), −142.989 (1F); $[\alpha]_D^{20}$ = −8.25 (*c* 0.4, CH_2Cl_2). Ee was determined by chiral HPLC (Chiralpak AS column, 15% 2-propanol–heptane, 0.5 mL min^{-1}, λ = 254 nm, retention times: (*S*)-**7**: 13.3 min, (*R*)-**7**: 15.0 min).

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