Organic Process Research & Development

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A One-Pot Diazotation−Fluorodediazoniation Reaction and Fluorine Gas for the Production of Fluoronaphthyridines

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Supporting Information

ABSTRACT: Several synthetic routes to 7-fluoro-2-methoxy-8-methyl-1,5-naphthyridine (**1**) are presented, and their suitability for scale-up is discussed. The way of introducing the fluorine atom is crucial. Early routes start from commercially available fluorinated building blocks or employ F^+ reagents like SelectFluor and delivered up to 70 kg of 7-fluoro-2-methoxy-1,5-naphthyridine (**18**). To prepare for larger scales, the focus turned to the use of HF or elemental fluorine, both one of the cheapest sources of fluorine. The first method, a one-pot diazotation−fluorodediazoniation with 6-methoxy-1,5-naphthyridin-3-amine (**9**) in HF gave the fluorinated naphthyridine **18** in high yield and purity without isolation of the unstable diazonium salt, the latter being a severe drawback of the related Balz−Schiemann protocol. The second method relies on the use of fluorine gas for a surprisingly selective ortho-fluorination of 6-methoxy-1,5-naphthyridin-4-ol (**10**).

INTRODUCTION

More and more methods are emerging for the late-stage introduction of fluorine into advanced intermediates.[1−7] However, once a route has to meet the stringent requirements for scale-up, the range of technologies is still restricted to fluorinations that have proven viable on very large scale, for example for the manufacturing of fluorinated heterocycles as raw materials in the fine chemicals or agrochemical industry. During the route finding and process development for the scale-up of 7-fluoro-1,5-naphthyridines **1** and **18** as intermediates for active pharmaceutical ingredients (API) at Actelion Pharmaceuticals Ltd., different scalable fluorination processes were tested. Amongst these, a diazotation−fluorodediazoniation protocol and an unprecedented selective fluorination with fluorine gas have been most attractive in comparison with other strategies like "buying in" the fluorine via a cheap raw material or using F^+ reagents.[8] In the following, five routes towards **1** are presented with a focus on the different strategies used to introduce the fluorine atom on low-kg to 70 kg-scale. Availability, cost, ease of processing, and the number of chemical steps are finally balanced in order to select the most economical route for scales larger than 100 kg.

The routes 1−5 are summarized in Figure 1. Route 1 uses the F^+ reagent SelectFluor for the fluorination of the enol ether **3**. Route 2 follows the strategy "buying-in F" and starts from readily available dichlorofluoronicotinic acid (**5**). 3-Amino-6-methoxypyridine (**7**) is the common starting material for routes 3, 4, and 5. In route 3, it serves as substrate for the Gould−Jacobs reaction at high temperature for the construction of the 1,5-naphthyridine core that is further elaborated to the 3-aminonaphthyridine **9**. The latter is a common intermediate of routes 3 and 4. Two diazotation−fluorodediazoniation methods then shall deliver the targeted fluorinated product **18**, either using *tert*-butylnitrite/$BF_3{\cdot}OEt_2$ or $NaNO_2$ in HF for the diazotation. The target product **1** is then conceivably produced from **18** following an ortho-lithiation−methylation protocol. The hydroxy-naphthyridine **10** is the common early intermediate of routes 4 and 5, ultimately derived from **7** via another high-temperature reaction, the Conrad−Limpach reaction. All approaches requiring the handling of fluoroacetates[9] were discarded due to their insidious toxicity. Some syntheses could conceivably start from dichlorofluoromethane;[10] however, Freon 21 is banned by the Montreal protocol. Starting from various 3-fluoro-5-amino-6-halopyridines seemed attractive, but their high costs ($2,400−10,000/kg) made them less attractive as raw materials.[11]

The first "fit-for-purpose" route (Route 1, Scheme 1) started from chloronitropyridine **2** that underwent a Stille coupling with tributyl(1-ethoxyvinyl)tin.[12] The fluorine was introduced with SelectFluor and the ensuing α-fluoroketone **4** was condensed with DMF dimethylacetal (DMF−DMA) to get the substrate **12** for the nitro reduction−deoxobromination sequence to bromo-fluoro-naphthyridine **13**. Bromine−lithium exchange with hexyllithium followed by MeI quench gave the targeted fluoronaphthyridine **1**.[13] The benefits of this route are its conciseness and the good yields−the reasons why it served well as "fit-for-purpose" route to deliver the first 10 kg of **1** for the downstream steps towards the API. Still, it suffered from the toxic tin organyls, two cryogenic steps, and the high cost of SelectFluor precluding a further scale-up.[14]

Dichlorofluoronicotinic acid (**5**) is relatively affordable (< $165/kg) and was considered an economically viable fluorinated building block (Scheme 2). Route 2 started with the regioselective dechlorination to **14** under transfer hydrogenation conditions. The carboxyl group was transformed into the amino group via a Curtius reaction with diphenylphosphoryl azide (DPPA) in *tert*-butanol followed by Boc-

Special Issue: Fluorine Chemistry 14

Received: March 24, 2014

   dx.doi.org/10.1021/op500100b | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

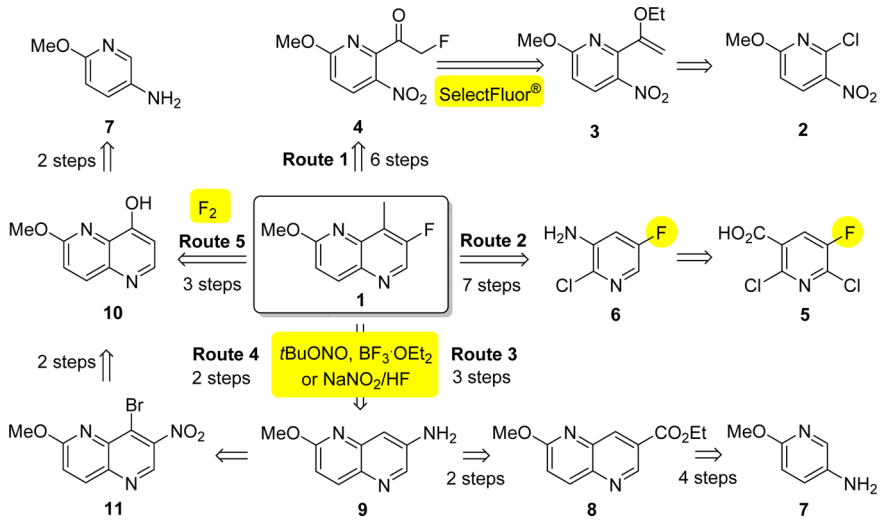
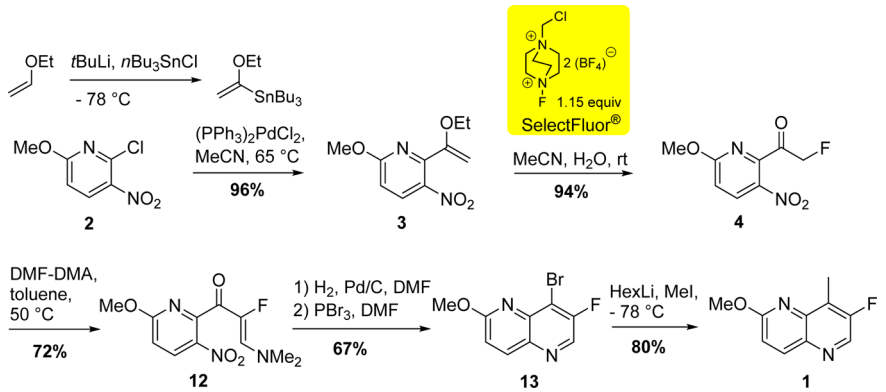
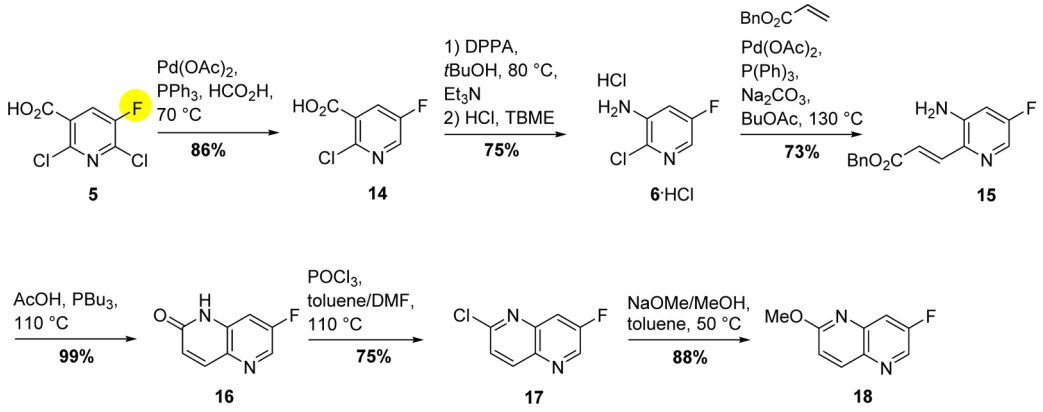


Figure 1. Synopsis of routes 1−5 to **1** discussed in the text. The source of the fluorine atom is highlighted in yellow.

Scheme 1. Route 1 (Stille) to 1 using F^+ reagent SelectFluor (10-kg scale)



Scheme 2. Route 2 (Heck) from fluorinated pyridine building block 5 (70-kg scale)



deprotection. The chlorofluoropyridine **6**·HCl was coupled with *n*-butyl acrylate in a Heck reaction to **15** that was cyclized to the 1,5-naphthyridinone **16** in HOAc in the presence of tributyl phosphine. The methoxy group was introduced via the chloride **17** by a S_NAr reaction with NaOMe to afford the fluoro-naphthyridine **18** that is the precursor of **1** (Scheme 5 below). This Route 2 proved to be robust and reproducibly delivered 70 kg of **18**, but the cost of goods and the number of steps should be further decreased (see Table 2). In addition, Pd was used in two steps, the phosphine should be avoided, and the Curtius reaction being associated with azides was not preferred for large-scale production.[15]

Diazotation−fluorodediazoniation is a preferred method for the regioselective introduction of fluorine into aromatic rings.[16,17] In the Balz−Schiemann reaction, the diazonium tetrafluoroborates are isolated and thermally decomposed to the fluoroaromatic products either neat or in solution. Two major risks have to be assessed when scaling up diazotation−fluorodediazoniations. First, the thermal instability of the diazonium salt might lead to premature loss of nitrogen

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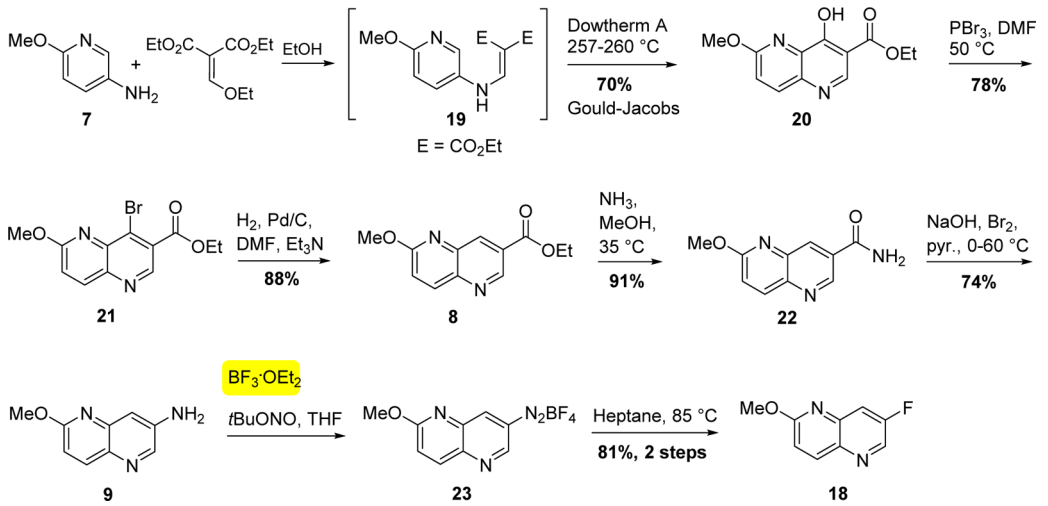
Scheme 3. Route 3 (Gould–Jacobs, Balz–Schiemann) to 18 (100-g scale)



(sudden pressure buildup) so prolonged storage in tanks or transfer through lines is dangerous. In addition, some diazonium salts are friction sensitive and explode after subjection to mechanical stress. Second, the fluorodediazoniation, the release of nitrogen, is performed at elevated temperature and the exothermic reaction, gas evolution, foaming, and accumulation have to be controlled. Three families of NO^+ reagents are mainly used for the production of the diazonium salts: (i) $NaNO_2$,[18,19] nitrosonium tetrafluoroborate ($NOBF_4$),[20] or alkyl nitrites.[21,22]

The required aniline **9** for such an approach was produced as shown in Scheme 3. Gould–Jacobs reaction of the condensation product **19** of the aminopyridine **7** with ethoxymethylene malonate at 280–290 °C in Dowtherm A[23] gave the hydroxy-naphthyridine **20**. Bromination to **21** and hydrogenation delivered the ester **8** that was transformed into the primary amide **22**. The Hofmann rearrangement was run in NaOH and pyridine with bromine and yielded the desired aniline **9** for the Balz–Schiemann reaction. First, the diazonium tetrafluoroborate **23** was prepared with *tert*-butylnitrite and $BF_3{\cdot}OEt_2$ in THF. The diazonium salt was then dosed in portions to heptane at 85 °C to trigger the fluorodediazoniation to **18**. However, the salt **23** decomposed already at rt, as corroborated by a $T_{\text{Left Limit}}$ of 39 °C in the differential scanning calorimetry (DSC, see Figure 2). Stabilizing with heptane was only partially successful, raising the left limit of the exothermic decomposition by 26 to 65 °C, still too low a temperature to allow for handling of **23** on large scale.[24] Running the dediazoniation of **23** at higher temperature in xylenes (70–100 °C) led to 20% of a byproduct (by LC–MS), most probably being derived from a Friedel–Crafts reaction of the diazonium salt with the solvent.[25] Clearly, isolation of the diazonium salt was not acceptable for scale-up. As the fluoronaphthyridine **18** was very pure (99% a/a by LC–MS), we studied this type of transformation further.

For a safe scale-up of such deaminofluorinations, continuous flow applications have been developed encompassing the fluorodediazoniation step, however, these methods still require the bulk isolation of dangerous diazonium salts.[26] Methods are known where the labile diazonium salt is not isolated.[27−31] We felt that these fluorodediazoniation reactions are best suited for the scale-up as the diazonium salt **23** posed severe risks of explosion. The following reagents have mostly been used:

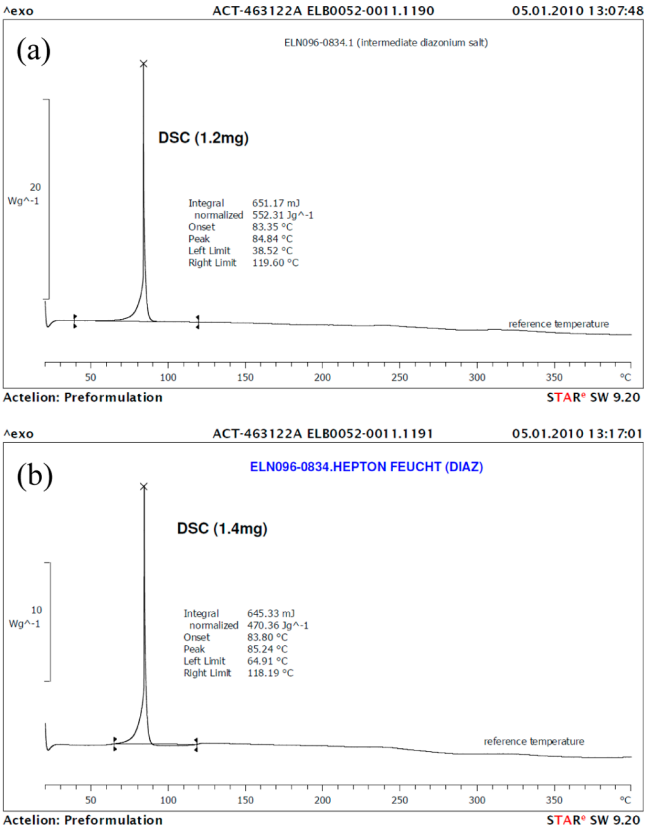


Figure 2. DSC of the diazonium salt **23**. (a) Dry, $T_{\text{Left Limit}}$ = 39 °C (−552 kJ/kg). (b) Heptane-wet, $T_{\text{Left Limit}}$ = 65 °C (−470 kJ/kg).

$NaNO_2$ or $NOBF_4$ in HF or in pyridine/HF solutions (Olah's reagent).

We found that the substrate for the diazotation–fluorodediazoniation **9** can more conveniently be produced from the readily accessible hydroxy-naphthyridine **10**. The latter is derived from 5-amino-2-methoxypyridine (**7**), Meldrum's acid (**24**), and triethyl orthoformate (Scheme 4),[32] or from methyl propiolate.[33] For larger scales, reusing the Dowtherm A for several batches could be an opportunity for savings.

The ortho-nitration of hydroxy-naphthyridine **10** proceeded with high selectivity (Scheme 5). Bromination of hydroxy-nitro-

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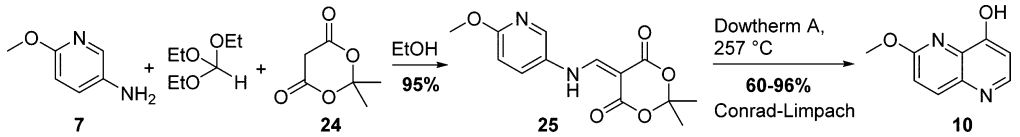
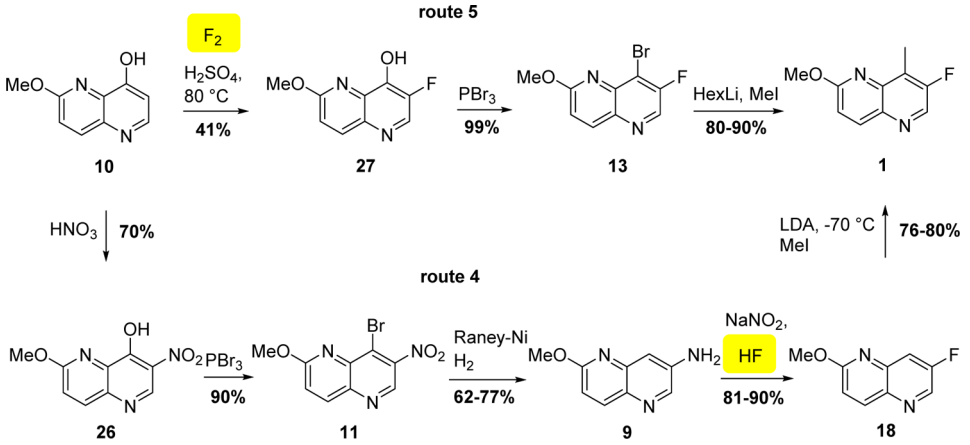
Scheme 4. Conrad–Limpach reaction used for the synthesis of 10



Scheme 5. Route 4 (HF) and Route 5 (F_2) to 1



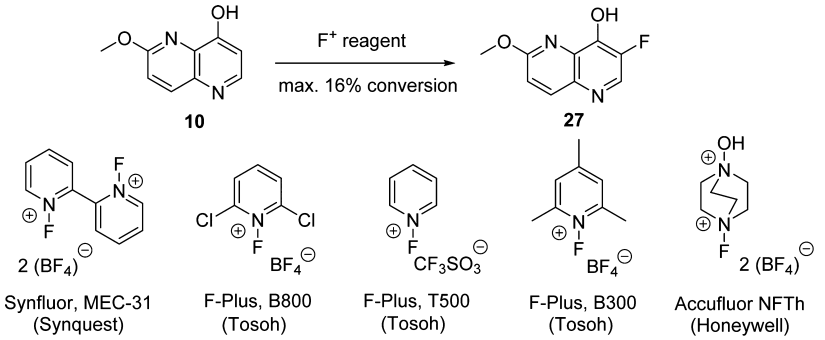


Figure 3. Unsuccessful ortho-fluorinations of **10** with the structures of the used F^+ reagents. Screening parameters: solvent (DMF, MeOH, TFA, AcOH, ACN, water), additive (H_2SO_4), temperature (20 °C, 60 °C).

naphthyridine **26** with PBr_3 in DMF to **11** followed by an excessive reduction of both the bromide and the nitro group afforded the naphthyridylamine **9** in good yields. For the ensuing pivotal transformation, two different conditions turned out to yield **18** in high purity and 90% yield.[34] If HF (bp 19.5 °C) was used as a single solvent, the reaction was carried out in an autoclave. The addition of pyridine reduces the vapor pressure of HF, thus allowing to perform the reaction at normal pressure at reduced operation costs.[35] According to the first method, $NaNO_2$ was added to a solution of **9** in HF at −5 °C in a perfluoralkoxyalkane flask. Only traces of fluoro-naphthyridine **18** were detected after warming up to 10 °C within 1 h. The mixture was transferred into a Monel autoclave, and the fluoro-dediazoniation was triggered by heating the mixture at 65 °C for 30 min, recording a pressure of 6.6 bar. HF was removed by distillation, and **18** was obtained with >99% a/a purity after aqueous work-up. The second method differed from the first one by the addition of pyridine and by a different order of addition: in a perfluoralkoxyalkane flask, $NaNO_2$ was added to 30% w/w pyridine/HF at −5 °C, followed by charging of aniline **9** at −40 °C. The mixture was then heated to 60 °C until the gas evolution ceased. After quenching the mixture on ice and neutralization with aqueous ammonia, **18** was obtained in the same yield of 90% and >94% a/a purity. The methyl group was installed onto **18** by ortho-lithiation with lithium diisopropylamide (LDA), followed by methylation with MeI to yield **1** (80% yield). Route 4 was uneventfully demonstrated on pilot plant scale (250–1000 L) by a CRO up to the naphthyridylamine **9**. The diazotation–fluorodediazoniation was demonstrated on 50-g scale, the larger-scale production depending on clinical milestones. It would be a conceivable approach for our intended larger scales.

The rapid access to hydroxy-naphthyridine **10** (Scheme 5) rendered an ortho-fluorination with a F^+ reagent an attractive option. To estimate the reactivity of **10**, this hydroxy-naphthyridine was successfully ortho-iodinated, -brominated, and -chlorinated in HOAc with NIS, NBS, and NCS, respectively. The yields were higher than 81% on 50-g scale. This prompted us to examine the ortho-fluorination with commercially available F^+ reagents (Figure 3). However, under the depicted reaction conditions, the best result was 16% conversion to **27** with Accufluor NFTh in MeOH at 60 °C, the remainder being mostly unreacted starting material.

Elemental fluorine would be the ideal F^+ reagent from a cost perspective, most electrophilic F^+-reagents being produced with F_2. However, fluorine gas suffers from extreme reactivity

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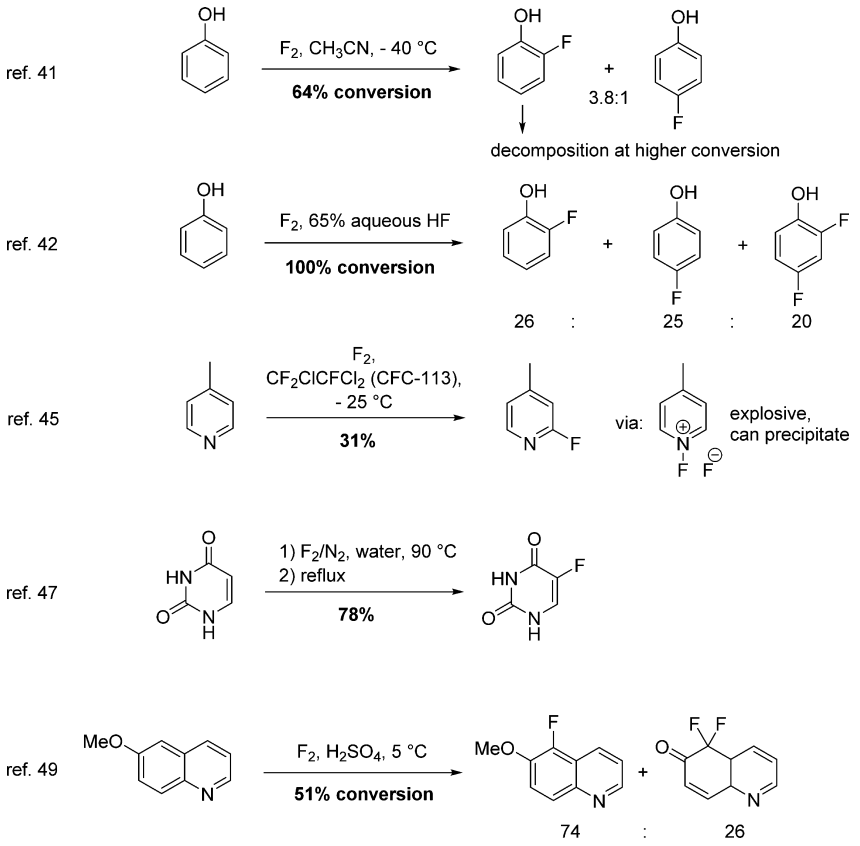
Scheme 6. Published fluorinations with F_2 of related substrates



(nonselectivity), associated with exothermic reactions, oxidations, and polymerization side reactions.[36−40] F_2 was applied for the fluorination of phenols[41−44] and pyridines,[45,46] albeit in moderate yields (Scheme 6). A notable example is 5-fluorouracil that is produced from uracil with fluorine in water.[47,48] High functionalization is typically not tolerated, and moderate yields are prevailing.[8] An example most similar to **10** is 6-methoxyquinoline that has been fluorinated in 5-position in low yield, accompanied by an overfluorinated byproduct.[49] Hence, the chances for a highly regioselective fluorination of **10** were low.

Surprisingly, an excellent selectivity was observed when 10% F_2 in N_2 was bubbled through a solution of **10** in conc. H_2SO_4 (100 vol) at 80 °C for 4 h, the IPC (HPLC) indicating a 89:11 mixture of starting material and product without any byproducts or side products (Table 1, entry 1). Heating to higher temperatures to accelerate the reaction led to significant byproduct formation (entry 2, byproducts were not identified). The use of a sintered glass frit for a better dispersion of F_2 doubled the reaction velocity (entry 3). When the concentration was increased by a factor of 10 to 10 vol, excessive foaming resulted in a slower reaction rate (entry 4). A higher concentration is desirable as it will reduce the amount of base required for the quench. The slower reaction rate could successfully be compensated by the use of a glass frit with double-sized pores (20 instead of 10 μm, entry 5). On 50-g scale, 10% F_2 in N_2 was bubbled into the solution of **10** in conc. H_2SO_4 (10 vol) via a 20-μm frit at 80 °C for 27 h, leading to 93% conversion (no byproduct by HPLC). SiO_2 was added as antifoaming agent and the flow rate was varied between 30 and 60 L/h to control remaining foaming (entry 6).[50] **27** was obtained in a moderate yield of 41% yield after a quench with aqueous ammonia and filtration (nonoptimized work-up).[51] All six alternative solvents tested (entries 7−15) either led to no conversion or to multiple byproducts. HF would be a preferred solvent due to the ease of its removal by distillation. The reaction in HF was carried out in an autoclave and did give the expected product, albeit accompanied by side products (entry 16). Remaining challenges for the scale-up of the ortho-fluorination with elemental fluorine are the high corrosivity of the reaction media, the foaming, and the isolation of the product from conc. H_2SO_4 leading to large volumes during the aqueous work-up.[52]

Whereas Routes 1 and 2 delivered enough material for preclinical and phase 1 clinical development, Routes 3, 4, and 5 were proposed for larger scales to reduce the cost of goods. A rough cost estimate was performed based on a standard dilution (10 vol), 1 day cycle time for simple reactions (e.g., no work-up required), 2 days cycle time for standard reactions, 3 days cycle time for special reactions (nitration, azide, fluorination), and commercial scale raw material prices with a 1,000 kg API target (Table 2).[53] Route 1 was not considered for this analysis due to the toxicity of tin organyls and high costs of SelectFluor. For reasons of confidentiality, the estimated costs are presented relative to the normalized costs of Route 2. Interestingly, the major cost driver of all routes is the step that introduces the fluorine atom, except for Route 2 where the fluorine source is a purchased raw material. The overall yield is similar for all five routes although the number of steps varies from 5−8. The one-pot diazotation−fluorodediazoniation was calculated for routes 3 and 4. Routes 3 and 4 are roughly 20% and 40% less expensive than Route 2, respectively. As Route 5 (F_2 gas) is not yet deemed fit for pilot-plant scale due to its cumbersome work-up, the costs have not been assessed. Still, the low

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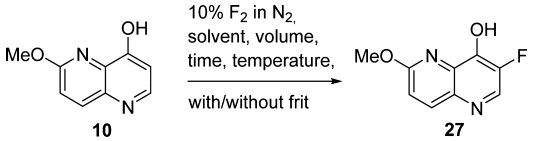
Table 1. Optimization of the ortho-fluorination of 10. 10/27/byproducts denoting the ratio of starting material/desired product/byproducts (HPLC)[a]



entry	solvent	frit pore size (μm)	T (°C)	t (h)	10/27/byproducts
1	conc. H_2SO_4	–	80	4	89/11/0
2	conc. H_2SO_4	–	125	2	40/18/42
3	conc. H_2SO_4	10	80	2	10/90/0
4[b]	conc. H_2SO_4	10	80	10	24/76/0
5[c]	conc. H_2SO_4	20	80	10	0/100/0
6[d]	conc. H_2SO_4	20	80	27	7/93/0
7	conc. H_2SO_4/dioxane	10	80	1	94/0/6
8	HCO_2H	–	20	1.5	44/3/53
9	HCO_2H	–	60	3	20/3/77
10	AcOH	–	20	1	0/0/100
11	$CHCl_3$	–	60	7	93/2/5
12	DMF	–	20	2	45/0/55
13	MeCN	–	0	1	85/0/15
14	MeCN	–	20	2	0/0/100
15	10% aqueous H_2SO_4	–	20	1	43/6/51
16[e]	anhydrous HF	–	60	2	68/24/8

[a]1 g **10**, 100 vol H_2SO_4, 10% F_2 in N_2 at 20 L/h. [b]10 g **10**, 10 vol H_2SO_4, heavy foaming observed. [c]10 g **10**, 10 vol H_2SO_4, 30 L/h, foaming. [d]50 g **10**, 10 vol H_2SO_4, 30–60 L/h, SiO_2 (0.2 wt), foaming. [e]In a Monel autoclave.

number of steps and the 100% selectivity bear a large potential for a significant increase of the yield and further cost reduction.

Table 2. Comparison of the Routes 1–5 to fluoro-naphthyridine 1

route (F-source)	steps	overall yield (%)	major cost drivers	relative costs (%)
No. 1 Stille, (Selectfluor)	6	35	SelectFluor	*a*
No. 2 Heck, (**5**)	8	25	$Pd(OAc)_2$ DPPA azide reaction	100
No. 3 Gould–Jacobs, fluorodediazoniation, (HF)	8	21	amino-pyridine 7 HF reaction	84
No. 4 Conrad–Limpach, fluorodediazoniation, (HF)	7	32	amino-pyridine 7 HF reaction	64
No. 5 ortho-fluorination, (F_2)	5	30[b]	F_2 reaction	n.a.

[a]Not considered due to toxicity of tin organyls and high costs of SelectFluor.[14] [b]Calculated with 41% isolated yield of the fluorination step (>93% purity of the reaction mixture).

CONCLUSION

Several routes to 7-fluoro-2-methoxy-8-methyl-1,5-naphthyridine (**1**) have been developed as kg-amounts of this intermediate were urgently required for the production of an API at Actelion Pharmaceuticals Ltd. The synthetic route design was guided by an efficient introduction of the fluorine atom. The first two routes either used a F^+ reagent (SelectFluor) or started from a commercially available fluorinated building block (**5**) and successfully delivered the fluoronaphthyridines **1** and **18** with high purity for the GMP production. Later introduction of the fluorine was accomplished by the following routes, employing lower-cost fluorination reagents HF or F_2 gas, both being routinely used on large scale by specialists in the fine chemicals industry. The one-pot diazotation–fluorodediazoniation protocol of aniline **9** with $NaNO_2$ in HF or pyridine/HF is an attractive option for scale-up as it afforded **18** in high yield. An additional alternative is offered by the surprisingly selective ortho-fluorination of hydroxy-naphthyridine **10** with F_2 gas, without the ubiquitous tarry byproducts reported for such transformations. A critical parameter was the mass transfer, hence the dispersion of F_2 gas in the mixture, and the work-up. The preferred solvent was conc. H_2SO_4. It might be worthwhile to further investigate other solvents (ideally acidic solvents that can be removed by distillation) with additives (e.g., HBF_4) that will facilitate the work-up of fluorohydroxynaphthyridine **27**.

EXPERIMENTAL SECTION

Caution: strict precautions have to be taken when working with HF and F_2![54–56]

5-(((6-Methoxypyridin-3-yl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (25). A double-jacketed flask was charged with 5-amino-2-methoxypyridine (**7**, 0.5 kg, 1 equiv), 2,2 dimethyl-1,3-dioxane-4,6-dione (0.7 kg, 1.2 equiv), triethyl orthoformate (0.74 L, 1.1 equiv), and EtOH (4 L). The mixture was heated to reflux for 1 h. The dark suspension was cooled to 5 °C, and the mixture was filtered. The product was washed with EtOH (1 L) and dried on a rotary evaporator to obtain **25** as a purple solid. Yield: 1.058 kg (95%). Purity (LC–MS method 1): 100% a/a, t_R = 1.22 min, $[M + 1]^+$ = 279; ^1H NMR (400 MHz, $CDCl_3$): δ 11.20 (d, J = 13.9 Hz, 1H), 8.51 (d, J = 14.2 Hz, 1H), 8.14 (d, J = 2.9 Hz, 1H), 7.54 (dd, J = 8.9, 3.0 Hz, 1H), 6.85 (d, J = 8.9 Hz, 1H), 3.98 (s, 3H), 1.77 (s, 6H).

6-Methoxy-1,5-naphthyridin-4-ol (10). *Caution*: high temperature reaction with release of gas! A 4-L glass flask was equipped with a still head and a large reflux condenser (no water cooling), connected to a Liebig condenser (no water cooling) with a receiving flask. The receiving flask was equipped with a reflux condenser cooled by water. Dowtherm A (1.3 L) was heated to 255 °C under N_2 with an electrical heating mantle. **25** (161 g, 1 equiv) was dissolved in 1,3-dimethyl-imidazolidinone (0.5 L) at 80 °C. The hot solution was added to the boiling Dowtherm A at 255–235 °C over a period of about 35 min. *Caution*: gas release; foaming is controlled by dosage speed. Liquid (acetone) distilled into the receiver. The reaction mixture was cooled to 20 °C. At approximately 140 °C, a precipitation occurred. The suspension was filtered and slurried in EtOH (0.8 L) at 80 °C. The mixture was cooled to 20 °C, filtered, and washed with EtOH (0.15 L). The product was dried on a rotary evaporator at 50 °C at 5 mbar to yield **10** as a brown solid. Yield: 69.6 g (68%). Purity (LC–MS method 1): 99% a/a, t_R = 0.49 min, $[M + 1]^+$ = 177; ^1H NMR (400 MHz, D_6-DMSO): δ 11.78 (m, 1H), 7.97 (m, 2H), 7.17 (d, J = 9.0 Hz, 1H), 6.28 (m, 1H), 3.94 (s, 3H).

6-Methoxy-3-nitro-1,5-naphthyridin-4-ol (26). Hydroxy-naphthyridine **10** (80 g, 1 equiv) was added in portions to fuming HNO_3 (0.5 L) at 10–15 °C within 20 min. The reaction mixture was heated to 67 °C for 4 h. The mixture was cooled to 20 °C and added on ice (2 kg). The yellow

dx.doi.org/10.1021/op500100b | Org. Process Res. Dev. XXXX, XXX, XXX–XXX

suspension was filtered and the product was washed with water (1.5 L). After drying, **26** was obtained as a yellow solid. Yield: 70 g (70%). Purity (LC−MS method 2): 100% a/a, t_R = 0.540 min, $[M + 1]^+$ = 222; ^{1}H NMR (400 MHz, D_6-DMSO) δ 13.00 (m, 1H), 9.15 (s, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 3.99 (s, 3H).

8-Bromo-2-methoxy-7-nitro-1,5-naphthyridine (11). PBr_3 (68 mL, 1.2 equiv) was added to a suspension of hydroxy-nitro-naphthyridine **26** (132.3 g, 1 equiv) in DMF (1.2 L) at 20 °C and within 15 min. The mixture was stirred at 65 °C for 1 h, cooled to 20 °C, poured on ice (0.8 kg), and filtered. The product was slurried in EtOH (0.5 L), filtered and dried on a rotary evaporator at 65 °C, affording **11** as a yellow solid. Yield: 155.8 g (92%). Purity (LC−MS method 2): 100% a/a, t_R = 1.624 min, $[M + 1]^+$ = 283, 285; ^{1}H NMR (400 MHz, D_6-DMSO): δ 9.21 (s, 1H), 8.44 (d, J = 9.1 Hz, 1H), 7.52 (d, J = 9.1 Hz, 1H), 4.13 (s, 3H).

6-Methoxy-1,5-naphthyridin-3-amine (9). Bromo-nitro-naphthyridine **11** (60 g, 1 equiv) and Raney nickel (approximately 20 g) were suspended in MeOH (600 mL) in a 1-L autoclave equipped with gas stirrer and thermometer. The autoclave was inertized before being pressurized with hydrogen (5 bar), and the mixture was stirred for 2 h. Et_3N (59 mL, 2 equiv) and Raney nickel (approximately 10 g) were added after inertization. The mixture was hydrogenated at 50 °C and 10 bar for 3 h. IPC (LC−MS) was indicating full conversion. Activated charcoal (7 g) was added, and the reaction mixture was heated to 60 °C and filtered hot over Celite (70 g). The filter cake was rinsed with MeOH (280 mL) at 20 °C. Water (120 mL) was added to the combined filtrates, the yellow solution was concentrated on a rotary evaporator at 60 °C under reduced pressure to remove solvent (800 mL). The suspension was cooled to 5 °C and filtered. The product was washed with water (50 mL) and dried on a rotary evaporator at 75 °C below 20 mbar to afford **9** as an off-white solid. Yield: 28.4 g (77%). Purity (LC−MS method 2): 100% a/a, t_R = 0.71 min, $[M + 1]^+$ = 176; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.28 (d, J = 2.5 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 5.92 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, D_6-DMSO): δ 162.4 (s), 146.5 (s), 143.8 (s), 140.6 (s), 139.8 (s), 133.5 (s), 111.6 (s), 110.5 (s), 53.6 (s).

7-Fluoro-2-methoxy-1,5-naphthyridine (18). *Balz−Schiemann.* $BF_3{\cdot}OEt_2$ (49 mL, 2.5 equiv) was added dropwise to a suspension of naphthyridylamine **9** (27 g, 1.0 equiv) in THF (200 mL) at −20 °C. *tert*-Butyl nitrite (22.3 mL, 1.1 equiv) was added at −20 °C. The yellow suspension was allowed to warm to 25 °C and stirred at 25 °C for 15 min prior to filtration and washing of the filter cake with heptane (3 × 25 mL). After drying on a rotary evaporator at 20 °C and 5 mbar pressure for a few min, the diazonium salt **23** (41 g) was added to heptane (200 mL) in 10 portions at 85 °C within 30 min. The mixture was stirred at 85 °C for 10 min before it was cooled to 20 °C. EtOAc (250 mL) and water (250 mL) were added. After layer separation, the organic layer was washed with water (200 mL), filtered over Na_2SO_4 (20 g), and concentrated to dryness on a rotary evaporator at 55 °C under reduced pressure to afford **18** as a brown crystalline solid. Yield: 22.3 g (81%). Purity (LC−MS method 2): 98.6% a/a, t_R = 1.302 min, $[M + 1]^+$ = 176; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.86 (d, J = 2.7 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.07 (dd, J = 10.0, 2.4 Hz, 1H), 7.26 (d, J = 9.1 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (100 MHz, D_6-DMSO): δ 163.3 (s), 158.8 (d, J = 258 Hz), 142.5 (d, J = 9 Hz), 140.4 (s), 139.1 (s), 138.9 (d, J = 26 Hz), 118.8 (d, J = 17 Hz), 116.4 (d, J = 3 Hz), 54.3 (s).

One-Pot Diazotation−Fluorodediazoniation; in 30 wt % Pyridine/HF. A 200 mL perfluoralkoxyalkane flask was charged with liquid HF (60 g, 105 equiv) at −40 °C, and pyridine (26.1 g, 11.56 equiv) was added at −50 to −40 °C within 30 min. *Caution*: very exothermic! $NaNO_2$ (2.2 g, 1.1 equiv) was added at −50 to −60 °C within 5 min. The aniline **9** (5 g, 1.0 equiv) was added to the reaction mixture at −50 to −40 °C within 10 min. The yellow solution was warmed to 20 °C within 30 min, and then to 65 °C. *Caution*: an exothermic reaction with gas (N_2) evolution occurred! The mixture was stirred at 60 °C for 2 h until the gas evolution ceased and IPC (TLC) indicated complete conversion. The mixture was cooled to 0 °C and poured onto ice (100 g) and EtOAc (80 mL). Aqueous 25% NH_3 (90 mL) was carefully added (pH 4−5). The aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were washed with water (20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness at 50 °C under reduced pressure, yielding **18** as a yellow crystalline solid. Yield: 4.80 g (90%). Purity (LC−MS method 2): 94.4% a/a.

In HF. A 200 mL perfluoralkoxyalkane flask was charged with liquid HF (60 g, 105 equiv) at −40 °C. The aniline **9** (5 g, 1.0 equiv) was added at −50 to −40 °C within 10 min. The yellow solution was warmed to −5 °C. $NaNO_2$ (2.2 g, 1.1 equiv) was added in portions at −9 to −5 °C within 5 min. *Caution*: exothermic! The reaction mixture was warmed to 10 °C and stirred for 1 h before being cooled to −30 °C and transferred to a Monel stirring autoclave. It was heated to 65 °C within 30 min. During the heating-up a pressure increase to 6.6 bar occurred, indicative of the liberation of N_2. Upon cooling to 0 °C, IPC (TLC) showed complete conversion. HF was evaporated using a water jet pump, and the residue was poured on ice/EtOAc. Aqueous 25% NH_3 (40 mL) was carefully added (pH 8). The aqueous phase was extracted with EtOAc (2 × 20 mL), and the organic phases were washed with water (20 mL). The organic phases were dried over $MgSO_4$ and evaporated to dryness at 50 °C under reduced pressure to yield **18** as a yellow crystalline solid. Yield: 4.84 g (90%). Purity (LC−MS method 2): 99.3% a/a.

Ortho-Fluorination with F_2. 3-Fluoro-6-methoxy-1,5-naphthyridin-4-ol (27). Conc. H_2SO_4 (500 mL) was charged in a 1-L fluorination apparatus. Hydroxy-naphthyridine **10** (50 g, 1 equiv) was added, followed by SiO_2 (10 g). The suspension was magnetically stirred. *Caution*: very exothermic! After 5 min, a clear brown solution was obtained. The solution was heated to 80 °C, and 10% F_2 in N_2 was bubbled through the reaction mixture at 80 °C with a rate of approximately 30 L/h using a Teflon tube with a glass frit (20-μm pore size) at the lowest point of the apparatus (note: the gas flow rate was adjusted to 30−60 L/h throughout the reaction to control foaming). IPC (LC−MS) showed 93% conversion after 27 h. The reaction mixture was slowly added on crushed ice (100 g) at 0−20 °C. *Caution*: very exothermic! This mixture was added dropwise to a precooled (about 5 °C) aqueous 28% NH_3 solution (1.65 L) at 0−20 °C. *Caution*: very exothermic, external cooling with −70 °C. The final pH of the suspension was 7.4. The mixture was stirred at rt for 2 h. The product was filtered and dried at 70 °C in a vacuum oven for 16 h to yield **27** as a grey solid. Yield: 22.5 g (41%). Purity (LC−MS method 3): 94% a/a (**10**: 6% a/a), t_R = 3.2 min, $[M + 1]^+$ = 195; ^{1}H NMR (400 MHz,

dx.doi.org/10.1021/op500100b | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

D_6-DMSO): δ 12.05 (br. s, 1H), 8.39 (br. s, 1H), 8.01 (br. s, 1H), 7.20 (d, J = 9.0 Hz, 1H), 3.97 (s, 3H).

8-Bromo-7-fluoro-2-methoxy-1,5-naphthyridine (13). PBr_3 (0.82 mL, 1.1 equiv) was added to a mixture of fluoro-hydroxy-naphthyridine **27** (1.50 g, 1 equiv) in DMF (10 mL) at 50 °C. The mixture was stirred at 70 °C for 1 h. After cooling to rt, the reaction mixture was diluted with water (500 mL), and 6 N NaOH (1.3 mL) was added. The solid was filtered off and thoroughly washed with water. The resulting solid was taken up in EtOAc, and the solution was filtered through a pad of SiO_2 to afford **13** as a beige solid. Yield: 2.0 g (100%). ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.86 (s, 1H), 8.34 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 9.1 Hz, 1H), 4.08 (m, 3H).

7-Fluoro-2-methoxy-8-methyl-1,5-naphthyridine (1). *From Bromo-fluoro-naphthyridine **13**.* Bromo-fluoro-naphthyridine **13** (50 g, 1 equiv) was dissolved in THF (500 mL) and cooled to −78 °C. To the suspension was added 2.5 M hexyllithium in hexane (83 mL, 1.1 equiv) at −78 to −70 °C. The mixture was stirred at −78 °C for 1 h. To the mixture was added MeI (13.4 mL, 1.1 equiv) at −78 to −70 °C. The mixture was allowed to warm to 20 °C. To the mixture was added water (2 mL) and TBME (250 mL). The mixture was washed with water (2 × 250 mL). The organic layer was dried with $MgSO_4$ and concentrated to dryness to give **1** as yellow solid. The crude product (61.7 g) was purified by chromatography using silica gel (500 g) and, as eluent, a mixture of heptane/EtOAc (15:1 v/v). Yield: 32.3 g (86%). Purity (LC−MS method 2): 99% a/a, t_R = 1.465 min, $[M + 1]^+$ = 193; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.75 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 4.05 (s, 3H), 2.57 (d, J = 2.1 Hz, 3H); ^{13}C NMR (125 MHz, D_6-DMSO): δ 162.4 (s), 157.2 (d, J = 254 Hz), 141.6 (d, J = 7 Hz), 140.7 (s), 138.3 (d, J = 2 Hz), 138.0 (d, J = 27 Hz), 128.0 (d, J = 13 Hz), 115.6 (d, J = 3 Hz), 54.0 (s), 8.8 (d, J = 3 Hz).

*From Fluoro-naphthyridine **18**.* Hexyllithium in hexane (2.5 M, 400 mL, 1.15 equiv) was added to a solution of diisopropylamine (144 mL, 1.15 equiv) in THF (1.4 L) at −26 to −20 °C. The solution was cooled to −75 °C. A solution of fluoro-naphthyridine **18** (158 g, 1 equiv) in THF (500 mL) was added to the LDA solution at −75 to −70 °C. The suspension was stirred at −74 °C for 0.5 h. MeI (68 mL, 1.2 equiv) was added at −74 to −72 °C over a period of 1 h. The mixture was allowed to warm to 20 °C prior addition of water (10 mL) and TBME (530 mL). The mixture was washed with water (2 × 530 mL). The organic layer was concentrated to dryness to give crude **18** as a beige solid. Yield: 182 g (107%). Purity (LC−MS method 2): 100% a/a. Four batches were produced and combined for the following crystallization. Crude **18** (703 g in total) was dissolved in acetonitrile (2 L) at 65 °C, the solution was cooled to rt and stirred at rt for 2 h. The suspension was cooled to 5 °C, stirred at 5 °C for 2 h, and filtered. The cake was washed with cold acetonitrile (0.3 L) and dried at 60 °C under reduced pressure to yield **18** as an off-white solid. Yield: 534 g (76%). Purity (LC−MS method 2): 100% a/a. ^{1}H NMR assay: 98.5% w/w.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Conditions of the LC−MS methods and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.A. and G.S. thank Dr. Martin Kesselgruber for assistance in the cost-of-goods analysis and are grateful to Dr. Thomas Weller for his support. Dr. Cornelia Zumbrunn and Dr. Jean-Philippe Surivet are acknowledged for their first synthesis of **18** via Route 2, and we are indebted to Dr. Reber for help on Route 3.

■ REFERENCES

(1) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661−1664.

(2) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795−10798.

(3) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 6821−6824.

(4) Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *135*, 12990−12993.

(5) Liu, W.; Huang, X.; Cheng, M. J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, *337*, 1322−1325.

(6) Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 2470−2473.

(7) Campbell, M. G.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474−480.

(8) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed.; Wiley VCH: Weinheim, Germany, 2013.

(9) Jennings, R. A. U.S. Patent 5,204,478, 1993.

(10) 2-Bromo-3-fluoroquinolines: Ondi, L.; Volle, J.-N.; Schlosser, M. *Tetrahedron* **2005**, *61*, 717−725.

(11) The bromo-fluoronaphthyridine **13** was offered for $44,000−200,000/kg by catalogue companies.

(12) Brown, P.; Dabbs, S. WO/2008/128953, 2008.

(13) This step was not optimized as, originally, **13** was transformed into another intermediate.

(14) Costs for SelectFluor on 100-kg scale: >$1,100/kg.

(15) Later, GSK published a similar route: Voight, E. A.; Yin, H.; Downing, S. V.; Calad, S. A.; Matsuhashi, H.; Giordano, I.; Hennessy, A. J.; Goodman, R. M.; Wood, J. L. *Org. Lett.* **2010**, *12*, 3422−3425.

(16) Langlois, B. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Georg Thieme Verlag: Stuttgart, Germany, 2000; Vol. *E10a*; Chapter 26, pp 686−740.

(17) Osio Barcina, J.; de la Moya Cerero, S. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Georg Thieme Verlag: Stuttgart, Germany, 2000; Vol. *E10b* Part 1; Chapter 1.1.8.5., pp 241−268.

(18) A study of solvents for the fluorodediazoniation: Matsumoto, J.-i.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Heterocycl. Chem.* **1984**, *21*, 673−679.

(19) Dosage of a slurry of a diazonium salt: Hogan, P. J.; Cox, B. G. *Org. Process Res. Dev.* **2009**, *13*, 875−879.

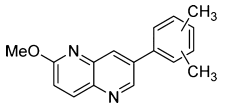
(20) Applied for the synthesis of 4-bromo-3-fluoro-6-methoxy-[1,5] naphthyridine: Miller, W. H.; Rouse, M.; Seefeld, M. A. WO/2006/081181 A2, 2006.

(21) Seminal paper: Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572−1574.

(22) Applied for the synthesis of 3-fluoroquinolines: El-Ahmad Y.; Leconte, J.-P.; Malpart, J.; Mignani, S.; Mutti, S.; Tabart, M. WO/2005/049575 A1, 2005.

(23) Dowtherm A heat transfer fluid is an eutectic mixture of two very stable compounds, biphenyl and diphenyl oxide with a bp of 257 °C.

(24) On a manufacturing scale, a safe processing temperature is considered to be 100 K below the onset temperature of the critical exothermic events.
(25) Byproduct detected when running the decomposition of **23** in xylenes:



(26) Yu, Z.; Lv, Y.; Yu, C. *Org. Process Res. Dev.* **2012**, *16*, 1669−1672.
(27) Boudakian, M. M. U.S. Patent 4,096,196, 1978.
(28) Olah, A. G.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872−3881.
(29) Yoneda, N.; Fukuhara, T. *Tetrahedron* **1996**, *52*, 23−36.
(30) Schurter, R.; Siegrist, U.; Rempfler, H.; Baumeister, P. U.S. Patent 4,831,148A, 1989.
(31) With $NOBF_4$: Milner, D. J. EP0430434, 1991.
(32) Davies, D. T.; Jones, G. E.; Markwell, R. E.; Pearson, N. D. WO/2003/010138 A2, 2006.
(33) Brooks, G.; Davies, D. T.; Jones, G. E.; Markwell, R. E.; Pearson, N. D. WO/2003/87098 A1, 2003.
(34) Abele, S., Schmidt, G. WO/2013/118086 A1, 2013.
(35) Bp of 30% and 40% pyridine in HF: 55 and 90 °C, respectively.
(36) Rock, M. H. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Georg Thieme Verlag: Stuttgart, Germany, 2000; Vol. *E10b* Part 1; Chapters 1.1.2.7. and 1.1.2.8., pp 32−49.
(37) Rozen. S. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Georg Thieme Verlag: Stuttgart, Germany, 2000; Vol. *E10a*; Chapter 2.3.1.4., pp 176−178.
(38) Chambers, R. R.; Skinner, C. J.; Hutchinson, J.; Thomson, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 605−609.
(39) Sandford, G. *J. Fluorine Chem.* **2007**, *128*, 90−104.
(40) A continuous flow process using F_2 gas copes well with these challenges: McPake, C. B.; Sandford, G. *Org. Process Res. Dev.* **2012**, *16*, 844−851.
(41) Misaki, S. *J. Fluorine Chem.* **1981**, *17*, 159−171.
(42) Misaki, S. *J. Fluorine Chem.* **1982**, *21*, 191−199.
(43) Chirakal, R.; Brown, K. L.; Firnau, G.; Garnett, E. S. *J. Fluorine Chem.* **1987**, *37*, 267−278.
(44) Chambers, R. D.; Hutchinson, J.; Sparrowhawk, M. E.; Sandford, G.; Moilliet, J. S.; Thomson, J. *J. Fluorine Chem.* **2000**, *102*, 169−173.
(45) Van der Puy, M. *Tetrahedron Lett.* **1987**, *28*, 255−259.
(46) With F_2/I_2: Chambers, R. D.; Parsons, M.; Sandford, G.; Skinner, C. J.; Atherton, M. J.; Moilliet, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 803−810.
(47) Schuman, P. D.; Tarrant, P.; Warner, D. A.; Westmoreland, G. U.S. Patent 3,954,758, 1971.
(48) Barton, D. H. R.; Hesse, R. H.; Toh, H. T.; Pechet, M. M. *J. Org. Chem.* **1972**, *37*, 329−330.
(49) Chambers, R. D.; Holling, D.; Sandford, G.; Puschmann, H.; Howard, J. A. K. *J. Fluorine Chem.* **2002**, *117*, 99−101.
(50) The glass frit was not stable and had to be replaced every 4 h. A Teflon frit would be required for prolonged reaction.
(51) Abele, S., Meier, H.; Schmidt, G. Steiner, H. WO/2013/16087 A1, 2013.
(52) In *aqueous* HCl, the product **27** was soluble and not stable, leading to partial demethylation.
(53) The software ChemProject was used.
(54) Mietchen, R.; Peters, D.; Rock, M. H. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Georg Thieme Verlag: Stuttgart, Germany, 2000; Vol. *E10a*; Chapter 1.1.4., pp 98−100.
(55) http://web.ornl.gov/sci/physical_sciences_directorate/mst/RSG/pdf/HF_Safety_1.pdf.
(56) Search for fluorine or hydrogen fluoride on: http://gestis-en.itrust.de.