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Pd(II)-Catalyzed Aminofluorination of Alkenes in Total Synthesis 6-(*R*)-Fluoroswainsonine and 5-(*R*)-Fluorofebrifugine

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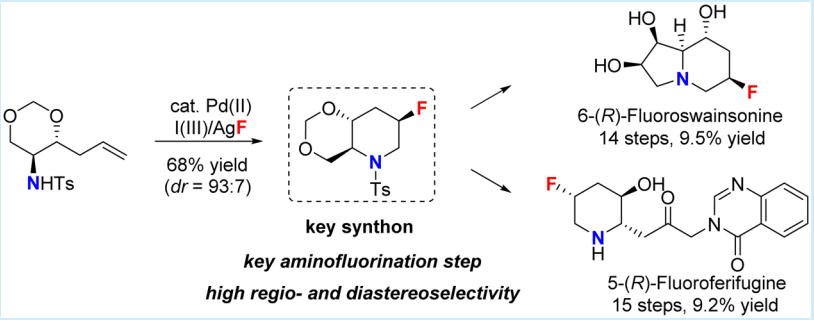
Supporting Information



ABSTRACT: The total syntheses of two fluorinated alkaloids, 6-(*R*)-fluoroswainsonine and 5-(*R*)-fluorofebrifugine, are described. Both encompass (4a*S*,7*R*,8a*R*)-7-fluoro-5-tosylhexahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine as a key synthon which is obtained through a further optimized palladium-catalyzed aminofluorination of alkenes with high diastereoselectivity. 6-(*R*)-Fluoroswainsonine is synthesized from the key synthon in 14 steps, and 5-(*R*)-fluorofebrifugine requires a sequential 15-step transformation.

Introduction of fluorine into organic moleculars could dramatically improve their druggability.[1] For instance, the introduction of fluorine into pipemidic acid could dramatically enhance antibacterial potency, named as norfloxacin.[2] Similar improvement was observed with capecitabine as a drug for breast and colorectal cancers[3] and ezetimibe for coronary heart disease.[4] Furthermore, the hydrolytic stability of 7-F-PGI$_2$ (prostacyclin) at pH 7.4 is prolonged from 10 min to more than one month (Figure 1).[5] Additional effort has been dedicated to the discovery of fluorinated bioactive compounds, some of which have been launched by pharmaceutical companies.

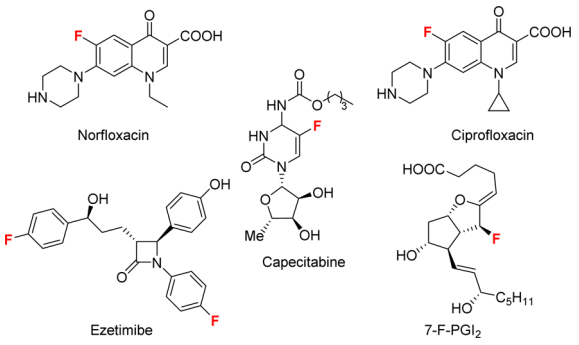


Figure 1. Representative fluorinated drugs.

Swainsonine is an anticancer alkaloid with potential to treat glioma and gastric carcinoma, and it also exhibits potential in its use as an adjuvant for anticancer drugs.[6] Febrifugine, which is a quinazolinone alkaloid first isolated from the Chinese herb *Dichroa febrifuga*, possesses antimalarial properties.[7] Both have attracted much attention in a synthetic sense due to their special bioactivities.[8,9] It is reported that the involvement of a vicinal fluorine atom to an amine could decrease its basicity,[10] resulting in increased biological activity,[11] and lipophilicity.[12] We envisioned the specified introducing fluorine atom into these bioactive compounds, such as at the C5 position of Febrifugine and the C6 position of Swainsonine, might modulate their bioactivities. These two fluorinated natural products have a similar 3-fluorinated piperidine core structure and could be derived from the same synthon. Furthermore, we envisioned that our previously reported intramolecular aminofluorination of alkenes might be a good method to selectively build this synthon (Scheme 1). Herein, we report the total synthesis of fluorinated swainsonine and febrifugine with highly selective aminofluorination as the key reaction.

In 2009, our group developed a Pd-catalyzed intermolecular aminofluorination of alkenes, which provided a variety of fluorinated piperidines.[13] Later, further studies were surveyed to provide other types of fluorinated heterocycles.[14] Based on our previous *endo*-cyclized aminofluorination reaction, we

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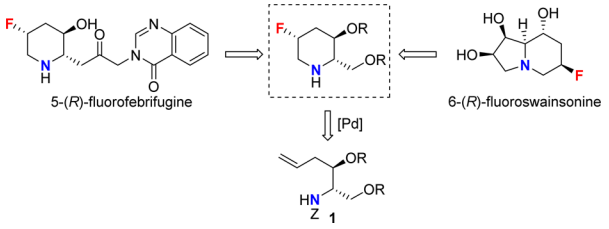
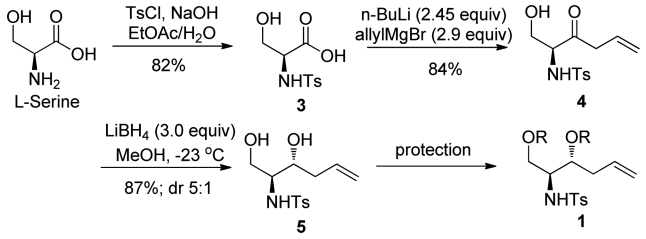
Scheme 1. Retrosynthetic Analysis



speculated that chiral substrates **1a−1d** might be good substrates to test the aminofluorination, which might deliver the expected synthon for the next total synthesis. According to literature procedure, the ketone **4** could be obtained through sequential protection of L-serine with tosyl chloride followed by the allylation reaction in 69% yield over two steps (Scheme 2).[15] The reduction of ketone **4** with $LiBH_4$ afforded the

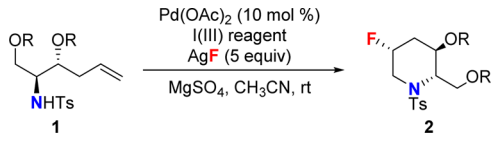
Scheme 2. Preparation of Alkene Substrates 1a−1d



desired diol **5** as a major product in 87% yield with moderate diastereoselectivity (dr 5:1), while another reduction system such as $NaBH_4$ with or without a Lewis acid as activator gave the desired diol **5** in slightly lower yield and poor diastereoselectivity, and the use of L-Selectride changed the diastereoselectivity affording the diastereoisomer of **5** as the major product (dr 1:7). Finally, substrates **1a−1d** were obtained through the corresponding protection processes (see Supporting Information).

These substrates were initially tested with the previously reported aminofluorination reaction conditions in CH_3CN.[13] As shown in Table 1, substrate **1a** gave only trace desired product **2a**, in which the isopropylidene ketal protected 1,2-diol moiety was not compatible with the strong oxidation conditions resulting in the decomposition of substrate (entry 1). Then, when the protection group was changed to a carbonyl group, the reaction of substrate **1b** gave the desired product **2b** in 37% yield, but with moderate diastereoselectivity (*dr* = 77:23, entry 2). For the simple dimethyl-protected **1c**, the reaction also failed to afford the target product (entry 3). When the diol was protected with the most stable acetal group, excitingly, the reaction of **1d** provided product **2d** in 51% yield with good diastereoselectivity (dr = 84:16, entry 4). Further screening of iodine(III) oxidants, such as $PhI(OAc)_2$, $PhI(O_2CCF_3)_2$, and $PhI(O_2CPh)_2$, showed that these oxidants could also deliver product **2d**, but less effectively than $PhI(OPiv)_2$ (entries 5−7). The screening of palladium catalysts indicated that $Pd(OAc)_2$ was the best. Finally, when the solvent was switched from acetonitrile to toluene, both the yield and diastereoselectivity were significantly improved, and the best result was obtained in the case of $PhI(OPiv)_2$ (1.5 equiv) with a diluted solution (0.1 M) to give **2d** in 68% yield with a 93:7 dr ratio (entries 8−9).[16] The reaction could also be carried out on 2 mmol scale without a significant drop in yield and diastereoselectivity (entry 10).

Table 1. Further Screening of Aminofluorination Reaction Conditions[a]



entry	R, R	I(III) reagent	yield (%)[b] (dr)
1	$C(CH_3)_2$ (**1a**)	$PhI(OPiv)_2$ (2.0 equiv)	trace
2	CO (**1b**)	$PhI(OPiv)_2$ (2.0 equiv)	37 (77:23)
3	CH_3, CH_3 (**1c**)	$PhI(OPiv)_2$ (2.0 equiv)	0
4	CH_2 (**1d**)	$PhI(OPiv)_2$ (2.0 equiv)	51 (84:16)
5	**1d**	$PhI(OAc)_2$ (2.0 equiv)	22 (74:26)
6	**1d**	$PhI(O_2CCF_3)_2$ (2.0 equiv)	17 (79:21)
7	**1d**	$PhI(O_2CPh)_2$ (2.0 equiv)	33 (80:20)
8[c]	**1d**	$PhI(OPiv)_2$ (2.0 equiv)	58 (91:9)
9[c,d]	**1d**	$PhI(OPiv)_2$ (1.5 equiv)	68 (93:7)
10[c,d,e]	**1d**	$PhI(OPiv)_2$ (1.5 equiv)	67 (93:7)

[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), I(III) reagent (2 equiv), AgF (5 equiv), $MgSO_4$ (50 mg) in CH_3CN (0.5 mL) at rt. [b]^{19}F NMR yield with trifluorotoluene as an internal standard; the data in parentheses are the *dr* ratios. [c]Toluene as solvent. [d]Isolated yield. [e]2 mmol scale.

The structure of **2d** was confirmed by X-ray determination, which showed that the fluorine atom is trans to the 3-hydroxyl group (Figure 2).

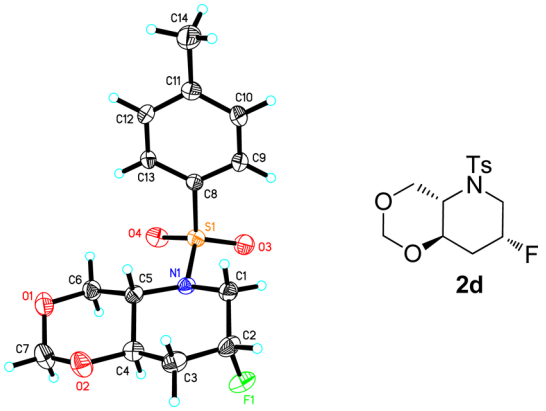


Figure 2. XRD of aminofluorination product **2d**.

With the fluorinated piperidine synthon **2d** in hand, the methylene deprotection of **2d** was carried out to release the diols. We found that compound **2d** was not compatible to the commonly used conditions, such as BCl_3, HCl, $NaI/SiCl_4$, and AcCl/ZnCl. In contrast, treatment of **2d** with PTSA in acetic anhydride at 110 °C, followed by the hydrolysis in ammonia solution, afforded the free diol **6** in 92% yield.[17] Then, the primary alcohol of **6** was selectively protected with a silyl group, followed by the secondary hydroxyl group protection with a benzyl group. Removing the silyl group with TBAF afforded compound **7** in overall 60% yield over three steps (Scheme 3). Next, the primary hydroxyl group was converted to a vinyl group through a subsequent Swern oxidation and Wittig reaction, and compound **8** was obtained in 75% yield. Excitingly, when the tosyl group was removed with sodium in naphthalene, *the carbon−fluorine bond remained intact*. The crude amine was reacted with allyl chloroformate to give the allyl carbamate, which underwent allylic amination under the

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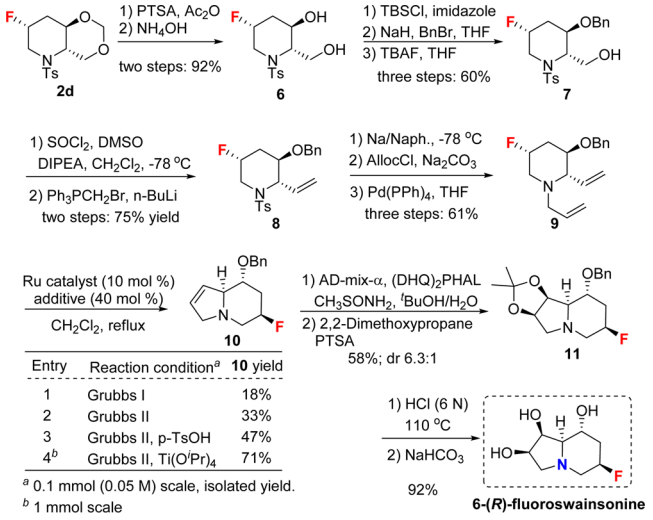
Scheme 3. Synthesis of 6-(*R*)-Fluoroswainsonine



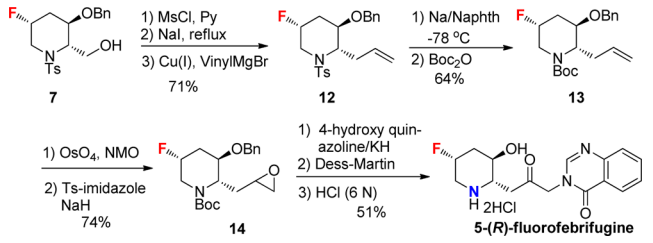
Entry	Reaction condition[a]	10 yield
1	Grubbs I	18%
2	Grubbs II	33%
3	Grubbs II, p-TsOH	47%
4[b]	Grubbs II, Ti(O^{i}Pr)$_4$	71%

[a] 0.1 mmol (0.05 M) scale, isolated yield. [b] 1 mmol scale

catalysis of $Pd(PPh_3)_4$ to give the diene **9** in overall 61% yield over three steps.[18] For the following intramolecular ring-closing metathesis, the Grubbs II catalyst exhibited better reactivity than Grubbs I. Due to the presence of a basic amine, additions of a Lewis acid and Bronsted acid were beneficial to improve the yield. Combination of the Grubbs II catalyst with Ti(O^{i}Pr)$_4$ could afford the indolizidine **10** in 71% yield.[19] Finally, the sequential *cis*-dihydroxylation of **10** using AD-mix-α with methanesulfonamide and protection with acetonide generated compound **11** in 58% yield with a 6.3:1 dr ratio.[20] After column purification, the pure *cis*-**11** was treated by concentrated HCl (6 N) to remove the ketal and benzyl protection groups. Finally, after neutralization with a base, fluorinated swainsonine was obtained in 92% yield. The optical rotation of synthetic 6-(*R*)-fluoroswainsonine ($[\alpha]_D^{20}$ +81.0; *c* 0.21, D_2O) is opposite to (−)-swainsonine ($[\alpha]_D^{25}$ −89.3; *c* 1, H_2O).[21]

Next, we turned to synthesize 5-(*R*)-fluoroferifugine from key synthon **7** (Scheme 4). First, the sequential process was

Scheme 4. Synthesis of 5-(*R*)-Fluorofebrifugine



conducted to convert alchohol to the corresponding iodide, which could couple with vinyl magnesium bromide in the presence of CuI to afford the desired alkene product **12** in overall 71% yield over three steps. Followed by protection group exchange, the related compound **13** was obtained in 64% overall yield. Again, the fluorine atom was tolerant of the reaction conditions. Initially, focus was on the regioselective bromohydroxylation of alkenes, with further nucleophilic attack by quinazolin-4-one. Unfortunately, our efforts with various conditions failed. Alternatively, the sequential expoxidation of alkenes and ring-opening of epoxide by quinazolin-4-one proved to be an efficient approach to introduce a heterocycle. Thus, peperidine **13** was subjected to the Upjohn conditions (OsO_4/NMO) to give the dihydroxylation product, which reacted with Ts-imidazole to give the ring-closure product **14** in 74% yield over two steps. After nucleophilic attack by the quinazolin-4-one anion, the main skeleton of fluorinated febrifugine was obtained. After the final oxidation of the secondary alcohol with Dess-Martin reagent[22] and removal of Boc and benzyl protection groups by HCl, the target fluorinated ferbrifugine was obtained in 51% overall yield over three steps. The optical rotation of 5-(*R*)-fluorofebrifugine ($[\alpha]_D^{20}$ −47.0; *c* 0.18, D_2O) is opposite that of (+)-febrifugine ($[\alpha]_D^{25}$ + 12.8; *c* 0.8, H_2O).[23]

In conclusion, we have reported the first total synthesis of two fluorinated alkaloids, 6-(*R*)-fluoroswainsonine and 5-(*R*)-fluorofebrifugine. Both encompass the (4a*S*,7*R*,8a*R*)-7-fluoro-5-tosylhexahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine as a key synthon, which was obtained through an optimized amino-fluorination of alkenes with high regio- and diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00030.

The detailed experimental procedures, spectral data of new compounds (PDF)

Crystallographic data for **2d** (CIF)

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Notes

The authors declare no competing financial interest.

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