HETEROCYCLES, Vol. 103, No. 2, 2021, pp. 902 – 917. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 30th November, 2020, Accepted, 12th January, 2021, Published online, 25th February, 2021
DOI: 10.3987/COM-20-S(K)56

REGIO-COMPLEMENTARY PREPARATION OF 6- AND 7-FLUORO-1,2,3,4-TETRAHYDROQUINOLINES VIA THE CYCLIZATION OF CATECHOLAMINES FOLLOWED BY DEOXYFLUORINATION

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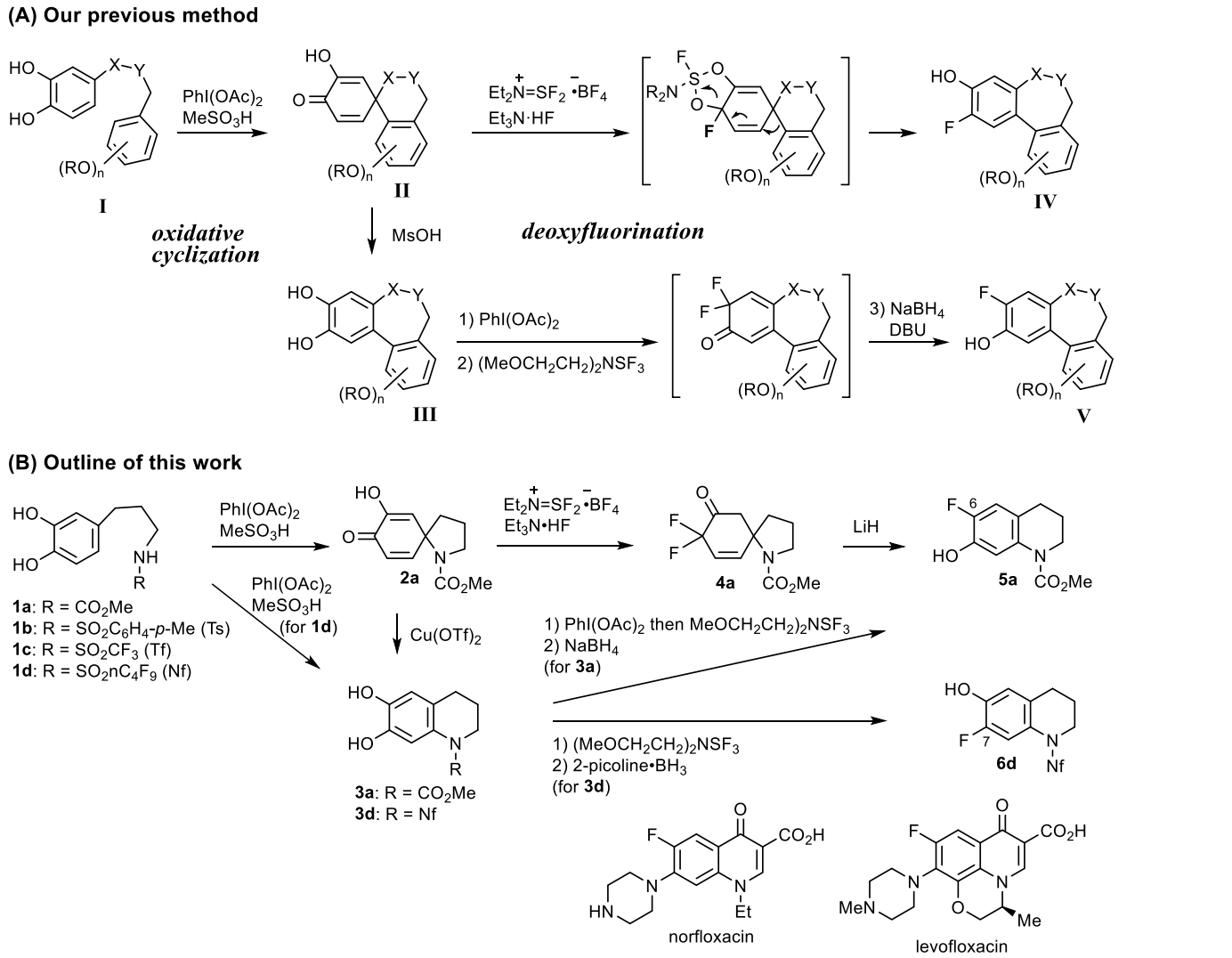
This paper is dedicated with respect to Professor Dr. Yasuyuki Kita on the celebration of his 77th birthday.

Abstract – We herein report a regioselective preparation of 6- and 7-fluoro-1,2,3,4-tetrahydroquinolines by applying the deoxyfluorination strategy, developed by the authors. This method includes the cyclization of catecholamines bearing an *N*-protecting group to form 7-hydroxy-1-azaspiro[4.5]deca-6,9-dien-8-ones and 6,7-dihydroxy-1,2,3,4-tetrahydroquinolines followed by deoxyfluorination, in which the nature of the *N*-protecting group has a significant effect on both the cyclization and the regioselectivity of the deoxyfluorination reaction.

INTRODUCTION

Due to the unique properties of fluorine, including its high electronegativity, very small atomic radius close to that of hydrogen, and its ability to form strong bonds with carbon, the installation of fluorine atoms into bioactive molecules can increase their lipophilicity, bioavailability, and metabolic stability, and so this strategy is frequently used in the discovery of new pharmaceuticals and agrochemicals.[1] Fluorine is also of interest since it frequently used as a biological equivalent (i.e., a bioisostere) of either hydrogen or oxygen in drug discovery research.[2] In addition, radioactive [^{18}F]fluorine is useful for positron emission tomography.[3] Among the wide range of fluorinated pharmaceuticals reported to date,

aromatic moieties bearing fluorine atoms are particularly common. In terms of their preparation, the classical electrophilic aromatic fluorination reaction employed for the synthesis of fluorobenzene units generally produces a mixture of regioisomers. On the other hand, the *ipso*-nucleophilic substitution of pre-functionalized aromatic compounds with fluorine, such as via the Halex (halogen exchange) and Balz–Schiemann reactions, proceeds with an excellent regioselectivity, but requires harsh reaction conditions. Recently, an *ipso*-fluorination method has been devised via arylsulfonium intermediates.[4] Transition-metal-catalyzed carbon–fluorine bond forming reactions of pre-functionalized aromatics have also been developed, where copper, palladium, and silver serve as efficient catalysts,[5] while aromatic C–H fluorination is another rapidly growing protocol.[6] The deoxyfluorination of phenolic hydroxy groups is also intriguing for the regio-controlled fluorination of bioactive aromatic molecules due to the ready availability of different phenolic structures as natural products and synthetic compounds.[7]



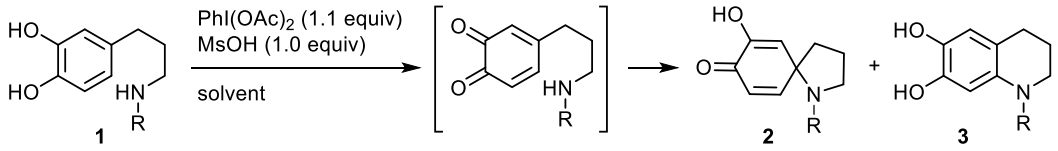
Scheme 1. (A) The regio-complementary deoxyfluorination of bridged biaryls and (B) the outline of this work.

In 2011, our group developed the deoxyfluorination reaction of catechols,[8] which enables the replacement of one of two phenolic hydroxy groups with fluorine, and has been applied in the synthesis of fluorinated allocolchicinols. This method can control the position of fluorine incorporation using either spirodienones **II**, obtained from the oxidative coupling of substituted catechols **I**, and their rearrangement isomers **III**. As reported, the former substrates **II** were converted into monofluorinated derivatives **IV** via regioselective deoxyfluorination of the carbonyl group of **II**, while the latter substrates **III** were transformed to regioisomers **V** through an oxidation-deoxyfluorination-reduction sequence (Scheme 1A).[9] Aimed at the development of a new approach to the 6-fluoroquinoline substructure, which is found in a class of new quinolones such as norfloxacin and levofloxacin, and its 7-fluoro isomer, we herein report the application of our deoxyfluorination method to catecholamines **1**, where the aromatic ring used in our previous method is replaced with a nitrogen substituent, to synthesize 6-fluoro- and 7-fluoro-1,2,3,4-tetrahydroquinolines. The role of the *N*-protecting group in the oxidative coupling and deoxyfluorination reactions is also examined, and the outline of this work is shown in Scheme 1B.

RESULTS AND DISCUSSION

While the oxidative construction of azaspirodienones from 4-(aminoalkyl)phenols and the corresponding phenyl ethers using hypervalent iodine reagents is popular,[10,11] there is only a single report on a similar azaspirodienone formation through the oxidative cyclization of catecholamine derivatives in which $(p\text{-MeOC}_6H_4)_2TeO$ was used as an oxidant.[12] Therefore, we initially studied the oxidative cyclization reaction using **1b** bearing a *p*-toluenesulfonyl (Ts) group on its amino moiety as a test case. The reaction of **1b** with $PhI(OAc)_2$ (1.1 equiv) in 1,2-dimethoxyethane (DME) proceeded within 5 min at 0 °C to give **2b** (38% NMR yield) and **3b** (2% NMR yield) (Table 1, entry 1), while a similar reaction in the presence of methanesulfonic acid (MsOH, 1.0 equiv) resulted in the formation a complex mixture (entry 2). A similar reaction in $CHCl_3$ containing MsOH (1.0 equiv) mainly provided **3b** (52% NMR yield) (entry 3), and the reaction in a 1:2 mixture of DME and $CHCl_3$ gave a significantly improved yield of **2b** (up to 86% NMR yield, entry 4). However, **2b** was found to gradually decompose during the reaction with $PhI(OAc)_2$ and MsOH and also during purification by silica gel column chromatography. This issue was solved through the crystallization of **2b** by the addition of ice-cold Et_2O to the crude product. A similar cyclization in THF at –30 °C was also effective in producing **2b** in 83% yield (entry 5). Similarly, carbamate **2a** (95% yield) was obtained from **1a** (entry 6). On the other hand, perfluoroalkylsulfonyl derivatives **1c** and **1d** exclusively produced **3c** and **3d**, respectively (entries 7 and 8), among which **3d** was obtained quantitatively.

Table 1. Oxidative cyclization of **1**



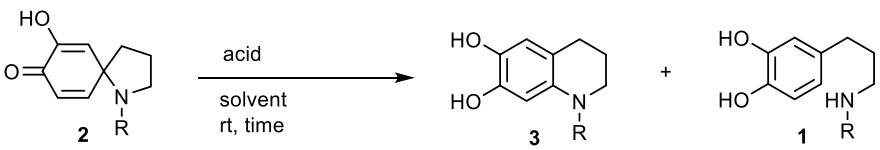
R = CO_2Me (**a**), $SO_2C_6H_4$-*p*-Me (Ts, **b**), SO_2CF_3 (Tf, **c**), $SO_2C_4F_9$ (Nf, **d**)

Entry	**1**[a]	Solvent	Temp (°C)	Time	Yield (%)[b]		
					2	**3**	**1**
1[c]	**1b**	DME	0	5 min	**2b**, 38	**3b**, 2	–
2	**1b**	DME	0	5 min	–	–	–
3	**1b**	$CHCl_3$	0	15 min	–	**3b**, 52	**1b**, 22
4	**1b**	DME/$CHCl_3$ (1:2)	0	15 min	**2b**, 86, 63[d]	**3b**, 8	**1b**, 5
5	**1b**	THF	–30	14 h	**2b**, 83[e]	–	–
6	**1a**	THF	–30	14 h	**2a**, 95[d]	–	–
7	**1c**	DME/$CHCl_3$ (1:2)	0	2 h	**2c**, trace	**3c**, 35[d]	–
8	**1d**	DME/$CHCl_3$ (1:2)	0	15 min	–	**3d**, 98[d]	–

[a] The preparation of **1a**–**1d** is shown in Supporting Information. [b] Yield determined by ^{1}H NMR analysis of a crude product with $Cl_2CHCHCl_2$ as an internal standard unless otherwise noted. [c] Without MsOH. [d] Isolated yield by silica gel column chromatography. [e] Isolated yield by trituration with ice-cold Et_2O.

We then examined the conversion of **2** into **3**, since to the best of our knowledge, no reports exist into the rearrangement of 7-hydroxy-1-azaspiro[4.5]deca-6,9-dien-8-ones besides a single report.[12-14] Initially, **2a** was treated with MsOH (1.0 equiv) in DME at room temperature (rt, 20–25 °C), which mainly resulted in decomposition along with the formation of **1a** (35%) (Table 2, entry 1). Similar reactions using either $FeCl_3$ (1.0 equiv) or $Cu(OTf)_2$ (0.3 equiv) in $CHCl_3$ produced **3a** in 17–26% yields (entries 2 and 3). Solvent screening using $Cu(OTf)_2$ as the catalyst indicated that DME was the optimal solvent for this transformation, giving **3a** in 76% yield (entries 4–7). Under the same conditions, **2b** was converted into **3b** in 83% yield (entry 8).

Table 2. Transformation of **2a** and **2b** into **3a**, **b**



R = CO_2Me (**a**), Ts (**b**)

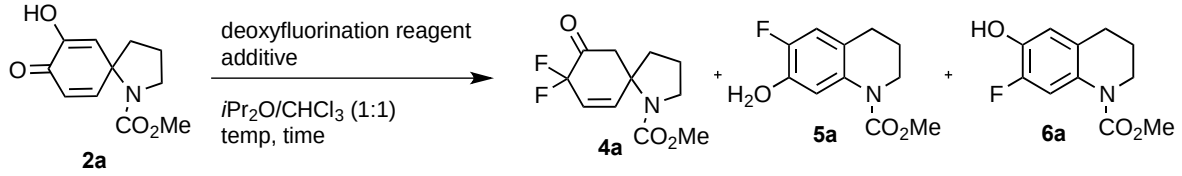
Entry	**2**	Acid (equiv)	Solvent	Time	Yield (%)[a]	
					3	**1**
1	**2a**	MsOH (1.0)	DME	5 min	**3a**, n.d.	**1a**, 35

2	**2a**	$FeCl_3$ (1.0)	$CHCl_3$	24 h	**3a**, 17	**1a**, 21
3	**2a**	$Cu(OTf)_2$ (0.3)	$CHCl_3$	15 min	**3a**, 26	**1a**, 23
4	**2a**	$Cu(OTf)_2$ (0.3)	THF	16 h	**3a**, 47	**1a**, 38
5	**2a**	$Cu(OTf)_2$ (0.3)	MeCN	16 h	**3a**, 27	**1a**, 16
6	**2a**	$Cu(OTf)_2$ (0.3)	DME	16 h	**3a**, 76	**1a**, 24
7	**2a**	$Cu(OTf)_2$ (0.1)	DME	20 h	**3a**, 75, 75[b]	**1a**, 25
8	**2b**	$Cu(OTf)_2$ (0.5)	DME	1 h	**3b**, 83, 83[b]	**1b**, 17

[a] Yield determined by ^{1}H NMR analysis of a crude product with $Cl_2CHCHCl_2$ as an internal standard unless otherwise noted. [b] Isolated yield by silica gel column chromatography.

Subsequently, the deoxyfluorination of **2a** was examined based on our previous study.[9c] Initially, **2a** was treated with Xtal-Fluor E (1 equiv) and Et_3N·HCl (1 equiv) at 50 °C, and the reaction proceeded slowly to produce **4a**[15] (41% NMR yield) along with a very small amount of **5a**[16] (Table 3, entry 1). Increasing the amount of Xtal-Fluor E and Et_3N·HCl up to 4 equiv each was effective in producing **4a** in up to 95% NMR yield (entries 2–4). Then, it was found that the best reaction condition was the use of Xtal-Fluor E (6 equiv) and Et_3N·HCl (6 equiv) at rt, which afforded **4a** in 98% yield (entry 5). DAST and Deoxofluor also produced **4a** in high yields (entries 7 and 8), while Fluolead and Xtal-Fluor M did not (entries 6 and 9). It is noteworthy that 7-fluorotetrahydroquinoline **6a** was not generated in these reactions.

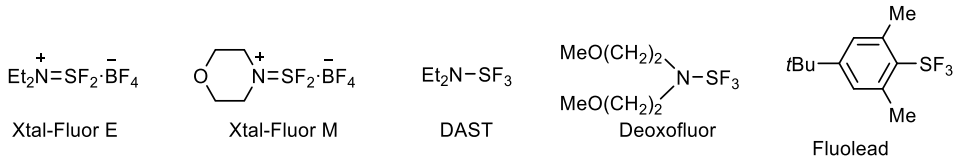
Table 3. Deoxyfluorination of **2a**



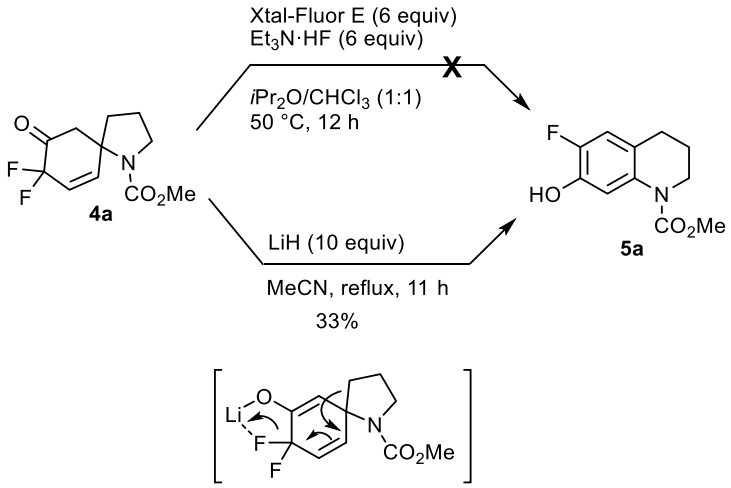
Entry	Deoxyfluorination reagent (equiv)	Additive (equiv)	Temp (°C)	Time (h)	Yield (%)[a]		
					4a	**5a**	**6a**
1[b]	Xtal-Fluor E (1)	Et_3N·HCl (1)	50	23	41	trace	–
2	Xtal-Fluor E (2)	Et_3N·HCl (2)	50	4.5	95	trace	–
3	Xtal-Fluor E (4)	Et_3N·HCl (4)	50	1	95	5	–
4	Xtal-Fluor E (6)	Et_3N·HCl (6)	50	1	77, 71[c]	13, 11[c]	–
5	Xtal-Fluor E (6)	Et_3N·HCl (6)	rt	2	98, 98[c]	trace	–
6	Xtal-Fluor M (3)	Et_3N·HCl (3)	50	3	45	trace	–
7	DAST (3)	–	50	2	89	5	–
8	Deoxofluor (3)	–	50	0.75	86	trace	–

9	Fluolead (3)	HF·pyridine (1)	50	20	14	trace	–

[a] Yield determined by ^{19}F NMR analysis of a crude product with $PhCF_3$ as an internal standard unless otherwise noted. [b] **2a** (58%) was recovered. [c]Isolated yield by silica gel column chromatography.



A further treatment of **4a** with Xtal-Fluor E (6 equiv) and Et_3N·HCl (6 equiv) at 50 °C for 12 h was then examined, but no reaction took place, and **4a** was completely recovered. Therefore, we investigated the conversion of **4a** into **5a** using either 10-camphorsulfonic acid or a combination of *N*,*O*-bis(trimethylsilyl)acetamide and CsF; however, only trace amounts of **5a** were obtained. In contrast, the use of LiH (10 equiv) in refluxing MeCN afforded **5a** in 33% yield (Scheme 2). Similarly, **5a** was obtained in 11% yield when NaH was employed, but no reaction was observed with CaH_2. These results suggest that coordination of the hard oxygen and fluorine atoms to a hard lithium ion promotes the reaction. In all cases, the formation of **6a** was not observed, thereby indicating that the alkyl group of **4a** preferentially underwent the migration. This tendency coincides with the known dienone-phenol rearrangement of 1-azaspiro[4.5]deca-6,9-dien-8-ones in which carbon generally migrated in preference to nitrogen,[11-14] and this phenomenon is explained by the relative stability of an intermediate carbocation, next to the nitrogen, that is stabilized by the nitrogen's lone pair electrons.[17]

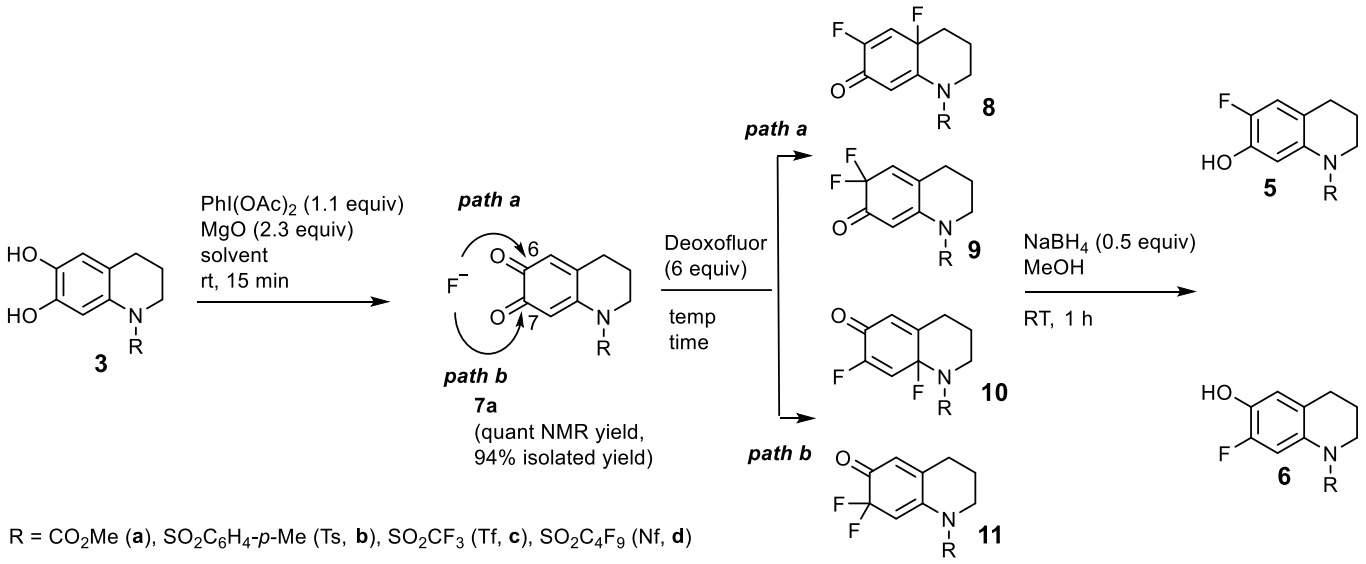


Scheme 2. Some trials to convert **4a** into **5a**

Subsequently, based on our previously reports,[8,9] the deoxyfluorination of catechols **3a–3d** was attempted to obtain either **5** or **6**. Initially, **3a** was oxidized with $PhI(OAc)_2$ (1.1 equiv) in the presence of MgO (2.3 equiv) in $CHCl_3$ at rt. Within 15 min, *ortho*-quinone **7a** was generated quantitatively and was isolated by silica gel chromatography. However, a similar reaction in the absence of MgO resulted in the formation of numerous products, thereby indicating that the addition of MgO was necessary for the effective reaction. Deoxofluor was then added to the crude reaction mixture containing **7a**, and the resulting mixture was stirred at rt. After 7 h, **7a** was no longer detected, and difluorinated intermediates **8a** and **9a**[16] (total 50% NMR yield) were observed by ^1H and ^{19}F NMR analysis of a crude product (Table 4, entry 1). The crude mixture was then treated with $NaBH_4$ in MeOH to give **5a** in 47% overall yield (entry 1). A similar deoxyfluorination reaction of **7a** at 40 °C resulted in the decomposition, while that at 0 °C was very slow. In addition, the yield of **4a** increased to 62% when the oxidation-deoxyfluorination sequence was conducted in a 1:1 mixture of $CHCl_3$ and $PhCF_3$ (entry 2). Under these conditions, the deoxyfluorination took place at the C6-position producing only **5a**, with regioisomer **6a** being undetected. A similar reaction of **3d**, which bears the more strongly electron-withdrawing Nf group, gave **6d** (51% NMR yield) as a major product along with **5d** (26% NMR yield) (entry 3).[16] In this case, the use of 2-picoline•borane (pic•BH_3) in AcOH/EtOH (1:5) instead of $NaBH_4$ in MeOH for reduction of the difluoro intermediates **9d** and **10d** was the key to produce **5d** and **6d** in better yields. We also examined the oxidation and fluorination sequence using Deoxofluor alone, noting that this deoxyfluorinating reagent also serves as an oxidant. Thus, the use of 8 equiv of Deoxofluor in $CHCl_3$/$PhCF_3$ (1:1) at rt successfully converted **3d** into **5d** (38% yield) and **6d** (61% yield) (entry 4), where the yields of these two products were superior to those obtained under the conditions of entry 3. Furthermore, the ratio of **6d** to **5d** was improved by conducting the reaction at temperature between –40 and –20 °C, resulting in a 70% isolated yield of **6d** (entry 5). On the other hand, similar reactions of **3b** and **3c** were not successful to form a mixture of **5b, c** and **6b, c** in poor yields.

Overall, the ratio of **5** to **6** was found to be significantly dependent on the electronic nature of the *N*-protecting group, and either **5** or **6** could be preferentially synthesized simply by selecting a suitable *N*-protecting group of **3**. More specifically, the less electron-withdrawing methoxycarbonyl group exclusively produced **5a**, and the more electron-withdrawing Nf group preferentially gave **6d**.

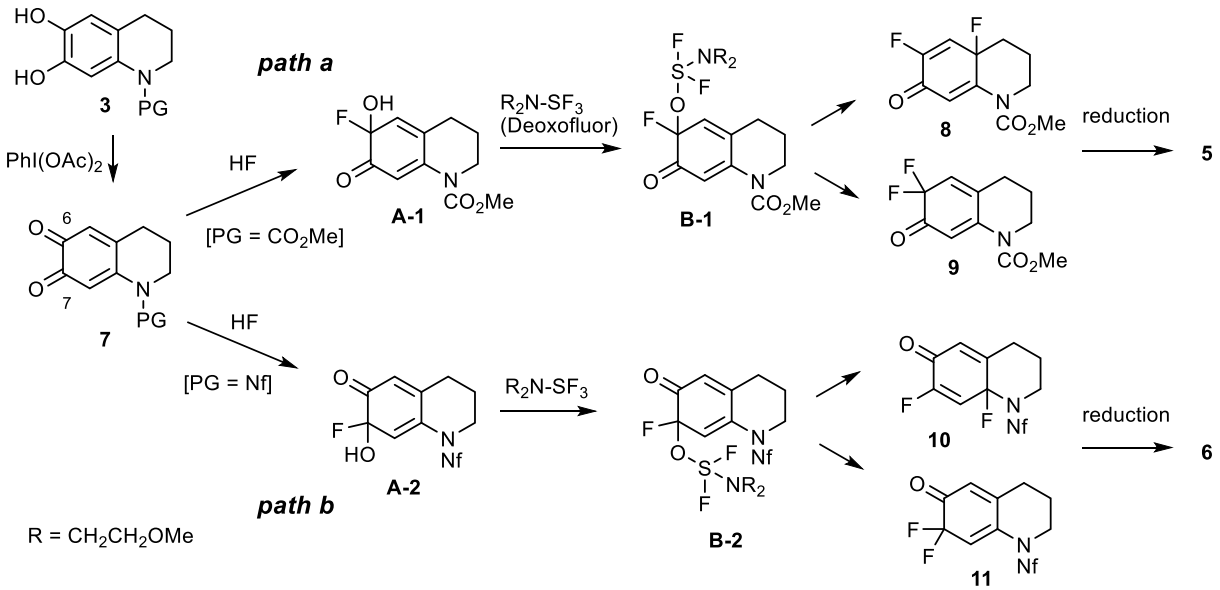
Table 4. Deoxyfluorination of **3**



Entry	**3**	Solvent	Temp, time[a]	Yield (%)		
				8, **9**, **10**, **11**[b]	**5**[c]	**6**[c]
1	**3a**	$CHCl_3$	rt, 7 h	45, 5, --, --	**5a** 47	**6a** ND
2	**3a**	$CHCl_3$/$PhCF_3$ (1:1)	rt, 11 h	66, 17, --, --	**5a** 64, 62[d]	**6a** ND
3[f]	**3d**	$CHCl_3$/$PhCF_3$ (1:1)	rt, 2 h	--, 30, 61, --	**5d** 26	**6d** 51
4[f,g]	**3d**	$CHCl_3$/$PhCF_3$ (1:1)	rt, 1 h	e	**5d** 38, 36[d]	**6d** 62, 61[d]
5[f,g]	**3d**	$CHCl_3$/$PhCF_3$ (1:1)	–40 °C, 1 day then –20 °C, 3 days	e	**5d** 20[d]	**6d** 70[d]

[a] Reaction temperature and time for the deoxyfluorination with Deoxofluor. [b] Yield determined by ^1H NMR (with $Cl_2CHCHCl_2$ as an internal standard) and/or ^{19}F NMR (with $PhCF_3$ as an internal standard) analysis of a crude product unless otherwise noted. [c] ^1H and/or ^{19}F NMR yield based on **3**. ND: not detected. [d] Isolated yield. [e] Not determined. [f] 2-Picoline•borane (pic•BH_3) in AcOH/EtOH (1:5) was used instead of $NaBH_4$ in MeOH. [g] Instead of the use of $PhI(OAc)_2$ and MgO, Deoxofluor (8 equiv) was used for both oxidation and deoxyfluorination steps.

A plausible reaction mechanism for the regiochemistry of deoxyfluorination of **7** is shown in Scheme 3: Initially a trace amount of HF in Deoxofluor reacts with one of the two carbonyl groups of **7** to generate adducts **A-1** and/or **A-2**. Then, they react with Deoxofluor to give the difluorinated intermediates (**8**–**11**) via **B-1** and **B-2**, and finally produce **5** and **6** through reduction of the carbonyl group followed by aromatization. The position of the fluorination of **7** is mainly dependent on the electron density of its two carbonyl groups. In the case of **3a** bearing a less electron-withdrawing methoxycarbonyl group on the nitrogen atom, the C-7 carbonyl group is more electron-rich than the C-6 one due to the electron donation from the nitrogen, resulting in nucleophilic addition of a fluoride ion at the C-6 position (path a) leading to the formation of **A-1** and produce **5**. On the other hand, **3d** bearing a strong electron-withdrawing Nf group on the nitrogen atom favors the formation of **A-2** (path b) and produce **6**.



Scheme 3. A plausible reaction mechanism for the regiochemistry of deoxyfluorination of **7**

In conclusion, we developed a regio-complementary synthesis of 6-fluoro- and 7-fluoro-1,2,3,4-tetrahydroquinolines **5** and **6** from common catecholamines **1** through an oxidative cyclization followed by deoxyfluorination. The selection of an appropriate protecting group for the amino moiety of **1** was critical in determining the outcomes of both reactions. In particular, the electronic nature of the protecting group was found to mainly affect the deoxyfluorination reaction site of 6,7-dihydroxy-1,2,3,4-tetrahydroquinolines **3**: The less electron-withdrawing methoxycarbonyl group exclusively produced 6-fluoro-1,2,3,4-tetrahydroquinoline **5a**, and the more electron-withdrawing Nf group preferentially gave 7-fluoro-1,2,3,4-tetrahydroquinoline **6d**. Further transformation of the obtained products (**5** and **6**) by modification of the remaining hydroxy groups to install other substituents and also functionalization of the tetrahydroquinoline moiety is now under investigation in our laboratory, and the results will be presented in due course.

EXPERIMENTAL

The preparation of **1a**–**1d** is shown in Supporting Information.

7-Hydroxy-1-(4-methylbenzenesulfonyl)-1-azaspiro[4.5]deca-6,9-dien-8-one (2b) (Table 1, entry 5)

Under argon atmosphere, $PhI(OAc)_2$ (0.55g, 1.80 mmol) and MsOH (0.11 mL, 1.7 mmol) were added to a solution of **1b** (0.55 g, 1.72 mmol) in dry THF (17 mL) at –30 °C, and the reaction mixture was stirred at the same temperature for 14 h. Saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added, and the reaction mixture was stirred at ambient temperature for additional 15 min. Products were extracted with EtOAc (20 mL x 3), and the combined organic layers were dried over

Na_2SO_4, filtered and concentrated in vacuo. The crude product was triturated with ice-cold Et_2O (10 mL x 3) to provide **2b** (0.45 g, 83% yield). A yellow solid, mp 74–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90–2.03 (m, 2H), 2.03–2.15 (m, 1H), 2.15–2.29 (m, 1H), 2.44 (s, 3H), 3.50–3.59 (m, 1H), 3.73–3.83 (m, 1H), 5.63 (d, *J* = 2.5 Hz, 1H), 6.29 (s, 1H), 6.32 (d, *J* = 10.0 Hz, 1H), 7.03 (dd, *J* = 10.0, 2.5 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CHCl_3$) δ 21.7, 23.6, 40.4, 49.0, 65.1, 117.0, 124.5, 127.9, 129.6, 135.9, 143.7, 145.8, 155.0, 181.3. IR (neat): 3405, 1654 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{16}H_{17}NO_4NaS$ $[M+Na]^+$: 342.0770, found: 342.0769.

Methyl 7-hydroxy-8-oxo-1-azaspiro[4.5]deca-6,9-diene-1-carboxylate (2a) (Table 1, entry 6)

Similarly to the preparation of **2b**, a mixture of **1a** (2.2 g, 9.8 mmol), $PhI(OAc)_2$ (3.4 g, 10.3 mmol) and MsOH (0.66 mL, 10.2 mmol) in THF (40 mL) was stirred at –30 °C for 14 h. The crude mixture was purified by silica gel column chromatography (EtOAc/hexane = 1:1) to provide **2a** (2.1 g, 95% yield). A pale yellow solid, mp 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94–2.32 (m, 4H), 3.54 (br s, 1H), 3.57–3.92 (m, 4H), 6.02 (d, *J* = 2.5 Hz, 1H), 6.22–6.41 (m, 2H), 6.86–6.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 24.0, 39.3, 40.3, 47.6, 48.4, 52.6, 62.5, 63.0, 118.5, 119.4, 124.7, 125.4, 146.1, 146.6, 154.8, 155.2, 181.6 (^{1}H and ^{13}C NMR data were obtained as a mixture of two isomers). IR (neat): 3387, 1654 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{11}H_{14}NO_4$ $[M+H]^+$: 224.0917, found: 224.0920.

1-(Trifluoromethylsulfonyl)-1,2,3,4-tetrahydroquinoline-6,7-diol (3c) (Table 1, entry 7)

Similarly to the preparation of **2b**, a mixture of **1c** (0.100 g, 0.33 mmol), $PhI(OAc)_2$ (0.113 g, 0.35 mmol) and MsOH (0.022 mL, 0.33 mmol) in a mixture of DME (1.0 mL) and $CHCl_3$ (2.0 mL) was stirred at 0 °C for 2 h. A crude product was purified by silica gel column chromatography (EtOAc/hexane=1:2) to provide **3c** (35 mg, 35% yield). A white solid, mp 80–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97–2.13 (m, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 5.18 (br s, 2H), 6.66 (s, 1H), 7.09 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 25.5, 48.0, 111.1, 115.4, 120.0 (q, *J* = 324 Hz), 124.3, 127.7, 141.4, 142.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –78.6 (s, 3F). IR (neat): 3502, 1615 cm^{-1}. HRMS (FAB, NBA): *m/z* calcd for $C_{10}H_{10}NO_4F_3S$ $[M]^+$: 297.0283, found: 297.0286.

1-(Nonafluorobutanesulfonyl)-1,2,3,4-tetrahydroquinoline-6,7-diol (3d) (Table 1, entry 8)

Similarly to the preparation of **2b**, a mixture of **1e** (45 mg, 0.100 mmol), $PhI(OAc)_2$ (34 mg, 0.105 mmol) and MsOH (0.007 mL, 0.10 mmol) in a mixture of DME (0.17 mL) and $CHCl_3$ (0.34 mL) was stirred at 0 °C for 15 min. A crude product was purified by silica gel column chromatography (EtOAc/hexane = 1:3) to provide **3d** (44 mg, 98% yield). A white solid, mp 115–117 °C (decomp). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.97–2.13 (m, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 3.85 (t, *J* = 6.0 Hz, 2H), 5.42 (br s, 2H), 6.65 (s, 1H), 7.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.6, 48.5, 111.0, 115.5, 124.3, 128.1, 141.4, 142.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.9 (br s, 2F), -121.2 (br s, 2F), -112.4 (br s, 2F), -80.6 (br s, 3F). IR (neat) 3105 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{13}H_{10}NO_4F_9S$ $[M+H]^+$: 447.0181, found: 447.0178.

6,7-Dihydroxy-1-methoxycarbonyl-1,2,3,4-tetrahydroquinoline (3a) (Table 2, entry 7)

Under argon atmosphere, a mixture of **2a** (22 mg, 0.10 mmol) and $Cu(OTf)_2$ (3.6 mg, 0.010 mmol) in DME (1.0 mL) was stirred at ambient temperature for 20 h, and aqueous NH_4Cl was added. The product was extracted with EtOAc (5 mL x 3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (AcOH/EtOAc/hexane = 1:50:50) to provide **3a** (16.6 mg, 75% yield). A white solid, mp 166–170 °C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 1.78–1.91 (m, 2H), 2.62 (t, *J* = 6.5 Hz, 2H), 3.60–3.68 (m, 2H), 3.69 (s, 3H), 6.53 (s, 1H), 7.24 (br s, 1H), 7.64 (br s, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 24.3, 27.3, 45.4, 52.8, 112.1, 115.4, 121.8, 131.5, 142.4, 143.4, 155.6. IR (KBr): 3310, 1653 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{11}H_{13}NO_4Na$ $[M+Na]^+$: 246.0737, found: 246.0734.

1-(4-Methylbenzenesulfonyl)-1,2,3,4-tetrahydroquinoline-6,7-diol (3b) (Table 2, entry 8)

Similarly to the preparation of **3a**, a mixture of **2b** (30 mg, 0.094 mmol) and $Cu(OTf)_2$ (16.3 mg, 0.047 mmol) in DME (0.90 mL) was stirred at ambient temperature for 1 h. The crude product was purified by column chromatography (AcOH/EtOAc/hexane 1:25:75) to provide **3b** (25 mg, 83% yield). A white solid, mp 152–154 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45–1.65 (m, 2H), 2.25 (t, *J* = 7.0 Hz, 2H), 2.38 (s, 3H), 3.73 (t, *J* = 6.0 Hz, 2H), 6.51 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.42 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.7, 25.8, 46.6, 113.0, 114.9, 124.2, 127.3, 129.0, 129.7, 136.4, 141.5, 142.5, 143.8. IR (KBr): 3312 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{16}H_{17}NO_4NaS$ $[M+Na]^+$: 342.0770, found: 342.0769.

Methyl 8,8-difluoro-9-oxo-1-azaspiro[4.5]dec-6-ene-1-carboxylate (4a) (Table 3, entry 5)

Under argon atmosphere, XtalFluor-E (0.25 g, 1.1 mmol) and **2a** (40 mg, 0.180 mmol) were added in this order to a solution of $Et_3N\cdot 3HF$ (0.058 mL, 0.36 mmol) and Et_3N (0.10 mL, 0.72 mmol) in a 1:1 v/v mixture of iPr$_2$O-$CHCl_3$ (total 1.8 mL) at 0 °C, and the mixture was stirred at ambient temperature for 2 h before being quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4 and

concentrated in vacuo. The residue was subjected to ^{19}F NMR analysis with $PhCF_3$ as an internal standard to find the formation of **4a** (98% yield) and **5a** (2% yield) and was purified by column chromatography (EtOAc/hexane = 1:2) to obtain **4a** (43 mg, 98% yield). A pale yellow solid, mp 100–102 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.84–2.06 (m, 4H), 2.68 (dd, *J* = 13.5, 2.5 Hz, 1H×7/10), 2.78 (d, *J* = 13.5 Hz, 1H×3/10), 3.25 (d, *J* = 14.0 Hz, 1H×7/10), 3.33–3.81 (m, 5H+1H×3/10), 5.92–6.03 (m, 1H), 6.11 (d, *J* = 10.0 Hz, 1H×3/10), 6.16 (d, *J* = 10.0 Hz, 1H×7/10). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.8, 38.7, 40.4, 47.0 (d, *J* = 44.5 Hz), 48.0 (d, *J* = 44.5 Hz), 52.1, 52.6, 63.7, 64.7, 107.7 (t, *J* = 241 Hz), 108.1 (t, *J* = 241 Hz), 121.4 (t, *J* = 27.5 Hz), 121.8 (t, *J* = 27.5 Hz), 143.0 (t, *J* = 11.0 Hz), 143.5 (t, *J* = 11.0 Hz), 154.4, 154.7, 193.4 (t, *J* = 25.0 Hz), 193.9 (t, *J* = 25.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.1 (d, *J* = 303 Hz, 1F×7/10), -104.4 (d, *J* = 305 Hz, 1F×3/10), -100.5 (d, *J* = 305 Hz, 1F×3/10), -97.3 (d, *J* = 303 Hz, 1F×7/10) (^1H, ^{13}C, ^{19}F NMR data were obtained as a mixture of two geometric isomers). IR (KBr): 1753, 1699 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{11}H_{13}NO_3F_2Na$ $[M+Na]^+$: 268.0756, found: 268.0758.

6-Fluoro-7-hydroxy-1-methoxycarbonyl-1,2,3,4-tetrahydroquinoline (5a) (Scheme 3)

Into a flame-dried flask, **4a** (25 mg, 0.10 mmol) and LiH (8.0 mg, 1.0 mmol) were added, and the mixture was dried in vacuo at rt for 30 min. Argon was filled, and MeCN (1 mL) was added. The reaction mixture was stirred at reflux for 11 h before being quenched with aqueous NH_4Cl (2 mL). The product was extracted with EtOAc three times, and the combined organic layers were dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (AcOH/EtOAc/hexane = 1:33:66) to provide **5a** (7.5 mg, 33% yield). A white solid, mp 87–92 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.85–1.96 (m, 2H), 2.68 (t, *J* = 6.5 Hz, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 5.13 (d, *J* = 3.5 Hz, 1H), 6.78 (d, *J* = 11.0 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 26.7, 44.9, 53.3, 112.9, 115.1 (d, *J* = 18.0 Hz), 122.3, 134.1, 141.6 (d, *J* = 14.5 Hz), 147.8 (d, *J* = 236 Hz), 155.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ –149.0 (ddd, *J* = 11.0, 7.5, 2.5 Hz, 1F). IR (neat): 3328, 1676 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{11}H_{12}NO_3F$ $[M+H]^+$: 225.0796, found: 225.0795.

1-Methoxycarbonyl-6,7-dioxo-1,2,3,4-tetrahydroquinoline (7a)

Under argon atmosphere, $PhI(OAc)_2$ (152 mg, 0.47 mmol) was added to a mixture of **3a** (100 mg, 0.45 mmol) and MgO (42 mg, 1.03 mmol) in dry $CHCl_3$ (2.3 mL) at ambient temperature. The reaction mixture was stirred for 15 min at ambient temperature and passed through a short pad of silica gel (EtOAc/hexane = 2:1) to provide **7a** (94 mg, 94% yield). A red solid, mp 89–92 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.93–2.03 (m, 2H), 2.62 (td, *J* = 6.5, 1.5 Hz, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 3H), 6.17 (t, *J* = 1.5 Hz, 1H), 6.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 29.2, 46.6, 54.2, 116.8, 125.6,

148.1, 149.6, 154.7, 179.8, 179.9. IR (KBr): 1765, 1679 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{11}H_{11}NO_4Na$ $[M+Na]^+$: 244.0580, found: 244.0579.

6-Fluoro-7-hydroxy-1-methoxycarbonyl-1,2,3,4-tetrahydroquinoline (5a) (Table 4, entry 2)

Under argon atmosphere, $PhI(OAc)_2$ (46 mg, 0.141 mmol) was added to a mixture of **3a** (30 mg, 0.134 mmol) and MgO (12.5 mg, 0.31 mmol) in a 1:1 v/v mixture $CHCl_3$ and $PhCF_3$ (total 1.4 mL) at ambient temperature, the whole mixture was stirred at ambient temperature for 15 min, and Deoxofluor (0.18 mL, 0.81 mmol) was added. The mixture was stirred at ambient temperature for 11 h and quenched with saturated aqueous $Na_2S_2O_3$ at 0 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was subjected to ^{19}F NMR analysis (with $PhCF_3$ as an internal standard) to find the formation of **8a** (66% yield) and **9a** (17% yield). $NaBH_4$ (2.5 mg, 0.067 mmol) was added to an ice-cold solution of the above-mentioned crude product in MeOH (1.4 mL), and the mixture was stirred at ambient temperature for 1 h before being quenched with 1N HCl. EtOAc was added, the layers were separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (AcOH/EtOAc/hexane = 1:33:66) to provide **5a** (18.8 mg, 62% yield). NMR data for **5a** were in good agreement with those obtained in Scheme 3.

A mixture of **8a** and **9a** was isolated from the crude product, obtained by the aforementioned reaction, by silica gel column chromatography (acetone/hexane = 1:3) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.76–1.90 (m, 8/5H), 1.92–196 (m, 2/5H), 2.17–2.37 (m, 8/5H), 2.51–2.56 (m, 2/5H), 3.39–3.46 (m, 2/5H), 3.67–3.80 (m, 8/5H), 6.09 (tt, *J* = 6.0 Hz, 2.0 Hz, 1/5H), 6.26 (dd, *J* = 13, 7.0 Hz, 4/5H), 6.43 (d, *J* = 8.0 Hz, 4/5H), 6.70 (t, *J* = 2.0 Hz, 1/5H). IR (neat): 1666, 1625 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{11}H_{11}NO_3F_2$ $[M+H]^+$: 243.07015, found: 243.0702.

8a: ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.13– -143.00 (m, 1F), –128.49– -128.43 (m, 1F).

9a: ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.13– -105.08 (m, 2F).

6-Fluoro-7-hydroxy-1-(nonafluorobutanesulfonyl)-1,2,3,4-tetrahydroquinoline (5d) and 7-fluoro-6-hydroxy-1-(nonafluorobutanesulfonyl)-1,2,3,4-tetrahydroquinoline (6d) (Table 4, entry 5)

Under argon atmosphere, Deoxofluor (0.062 mL, 0.36 mmol) was added to a solution of **3d** (20 mg, 0.045 mmol) in a 1:1 v/v mixture of $CHCl_3$ and $PhCF_3$ (total 0.50 mL) at –40 °C. The reaction mixture was stirred at the same temperature for 1 day, then warmed up to –20 °C and stirred for another 3 days before being quenched with saturated aqueous $Na_2S_2O_3$. The layers were separated, and the aqueous layer

was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give a mixture of **9d** and **10d**. The residue was dissolved in a 1:5 v/v mixture of AcOH and EtOH (total 0.60 mL), to which 2-picoline•borane (8.0 mg, 0.13 mmol) was added. The mixture was stirred at ambient temperature for 3 h before being quenched with 1N aqueous solution of HCl. The mixture was stirred at same temperature for 2 h. CH_2Cl_2 was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (AcOH/EtOAc/hexane = 1:25:75) to provide **5d** (4.4 mg, 20% yield) and **6d** (13.8 mg, 70% yield).

5d: A white solid: mp 78–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–2.31 (m, 2H), 2.97–2.53 (m, 2H), 4.04–3.51 (m, 2H), 5.37–4.78 (m, 1H), 6.87 (d, *J* = 11.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 25.6, 48.4, 112.7, 115.7 (d, *J* = 19.0 Hz), 123.6, 131.7, 141.8 (d, *J* = 15.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -142.2 (dd, *J* = 11.0, 8.0 Hz, 1F), -126.1– -125.4 (m, 2F), -121.0 (br s, 2F), -111.54– -111.47 (m, 2F), -80.59– -80.54 (m, 3F). IR (neat): 3497, 1580 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{13}H_9F_{10}NO_3SNa$ $[M+Na]^+$: 472.1487, found: 472.1487.

6d: A white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00–2.18 (m, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 3.87 (t, *J* = 6.0 Hz, 2H), 5.05 (br s, 1H), 6.79 (d, *J* = 9.5 Hz, 1H), 7.38 (d, *J* = 11.5 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 23.4, 25.9, 48.3, 111.4 (d, *J* =18.0 Hz), 117.1, 128.0, 142.0 (d, *J* = 14.5 Hz), 148.8 (d, *J* = 235 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -140.7 (dd, *J* = 11.5, 9.5 Hz, 1F), -125.8 (br t, *J* = 13 Hz, 2F), -121.0 (br s, 2F), -111.54– -111.47 (m, 2F), -80.5 (br t, *J* = 10 Hz, 3F). IR (neat): 3240, 1516 cm^{-1}.

A mixture of **9d** and **10d** was isolated from the crude product (Table 4, entry 3) by silica gel column chromatography (acetone/hexane = 1:3) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85–1.92 (m, 4/3H), 1.96–2.02 (m, 2/3H), 2.55 (br t, *J* = 6.5 Hz, 2/3H), 2.65 (t, *J* = 5.0 Hz, 4/3H), 3.87 (t, *J* = 6.0 Hz, 2/3H), 3.95 (t, *J* = 7.0 Hz, 4/3H), 6.15 (dt, *J* = 6.5, 2.0 Hz, 2/3H), 6.19 (tt, *J* = 6.5, 2.0 Hz, 1/3H), 6.35 (dd, *J* = 10, 5.5 Hz, 2/3H), 6.49 (s, 1/3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -147.84 – -147.26 (m, 2/3F), -125.88– -125.79 (m, 2F), -121.16– -121.12 (m, 2F), -111.43– -111.42 (m, 2F), -108.98– -108.91 (m, 2/3F), -102.58 (d, *J* = 7.0 Hz, 1/3F), -80.61– -80.48 (m, 3F). IR (neat) 1678 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{13}H_8F_{11}NO_3S$ $[M+H]^+$: 468.0122, found: 468.0127.

ACKNOWLEDGEMENTS

This work was financially supported by the JSPS KAKENHI [18HO4411 (Middle Molecular Strategy)] and Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting

Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP20am0101084.

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15. The structure of **4a** was determined by the similarity of its ^{13}C NMR data and those of difluorinated spiro compounds obtained by our previous work (ref. 9c).
16. The structures of **5a**, **5d**, **6d**, **8a**, **9a**, **9d**, and **10d** were determined by NMR data including nuclear Overhauser effect, see: Supporting Information.
17. S. A. Glover, C. A. Rowbottom, A. P. Scott, and J. L. Schoonraad, *Tetrahedron*, 1990, **46**, 7247.