Regiocomplementary Synthesis of Fluorinated Bridged Biphenyls

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Abstract: Complementary synthesis of two kinds of fluorinated bridged biphenyls has been developed by the combination of oxidative carbon–carbon bond formation and deoxyfluorination.

Key words: fluorine, deoxyfluorination, biaryls, umpolung, hypervalent iodine

The introduction of fluorine atom(s) to pharmaceuticals or agrochemicals often causes many beneficial effects such as the dramatic improvement of their metabolic stability, biological activity, lipophilicity, and bioavailability compared to the original molecules.[1–3] The substitution of an oxygen functional group with a fluorine atom, which is considered to be a kind of bioisostere, has been widely used in drug discovery processes because the van der Waals radius of fluorine is closer to that of oxygen as is its electronegativity.[2a] While a large number of methodologies for the substitution of aliphatic hydroxyl groups with fluorine atoms have been reported,[4,5] the similar substitution of aromatic hydroxyl groups with fluorine atoms is under development.[6] We recently reported a variety of examples of the novel direct conversion of one of the hydroxy groups of a catechol derivative into fluorine via an *ortho*-quinone generated in situ by oxidation.[7]

A class of compounds possessing a highly oxygenated bridged biphenyl motif, such as metasequirine B,[8] jerusalemine,[9] kreysigine,[10] and NSC 51046[11] (Figure 1), and their derivatives exhibit some important biological activities including an anticancer activity and muscle-relaxant effect. The substitution of one of the oxygen functional groups of these compounds with a fluorine atom may enhance their metabolic stability and lipophilicity and produce novel biological activities, potentially producing new drug candidates.[12] Indeed, some fluorine-containing bridged biphenyls have been synthesized, although only around a dozen such compounds have been already reported.[13–16]

We envisioned that our deoxyfluorination method coupled with oxidative carbon–carbon bond formation would provide the unprecedented regiocomplementary preparation of two types of fluorinated bridged biphenyls **4** and **7**, having various substitution patterns, from the same starting catechol **1** (Scheme 1). This method would feature the use of two specific substrates **2** and **6** for the fluorination.

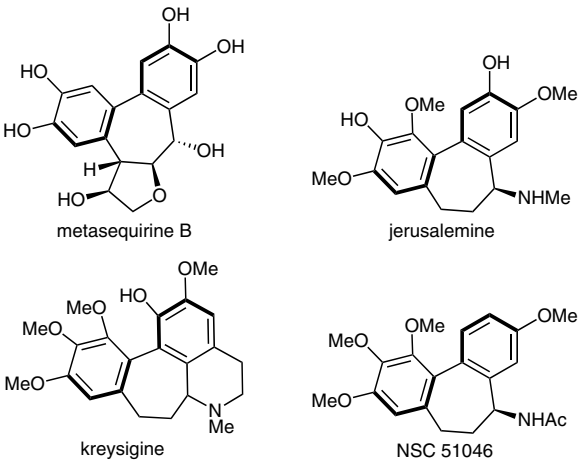

Figure 1 Biologically active bridged biphenyls

Thus, the fluorination of the 3-hydroxyspirodienone **2** would provide a fluorinated intermediate **3**, which led to 2-fluoro bridged biphenyl **4** via the 1,2-migration of the phenyl moiety. On the other hand, the fluorination of *ortho*-quinone **6**, generated in situ by the oxidation of **5**, would selectively proceed at the C3 carbonyl group because the C2 carbonyl group of **6** was stabilized by the phenyl substituent.[17] The substrates **2** and **5** would be available from the same catechol **1** by the oxidative carbon–carbon bond formation and the subsequent dienone–phenol rearrangement,[18] respectively. Our experiments based on this strategy led to the following results.

While the intramolecular oxidative carbon–carbon bond formations of phenols and that of their ethers have been intensively investigated,[19] similar reactions of catechols have been limited to a single example which used $FeCl_3$ to produce a bridged biphenyl.[20] According to this procedure, we first treated **1a** [$R^1 = R^2 = R^3 = OMe$, $X = C(CO_2Me)_2$] with $FeCl_3$ (3 equiv) in EtOH–H_2O; however, it gave a complex mixture without including any cyclized products. After extensive experiments using a variety of oxidants, the use of $PhI(OAc)_2$ (1.05 equiv) in the presence of an acid in 1,2-dimethoxyethane (DME) was found to produce **2a** [$R^1 = R^2 = R^3 = OMe$, $X = C(CO_2Me)_2$] (Scheme 2). Methanesulfonic acid (MsOH) proved most efficient that produced **2a** in 95% isolated yield (Table 1, entry 4). Trifluoroacetic acid (TFA) and trifluoromethanesulfonic acid (TfOH) were less effective in producing **2a** in 35% and 58% NMR yields, respectively (Table 1, entries 3 and 5). Without any acid or with AcOH (5 equiv), the reaction gave complex mixtures in-

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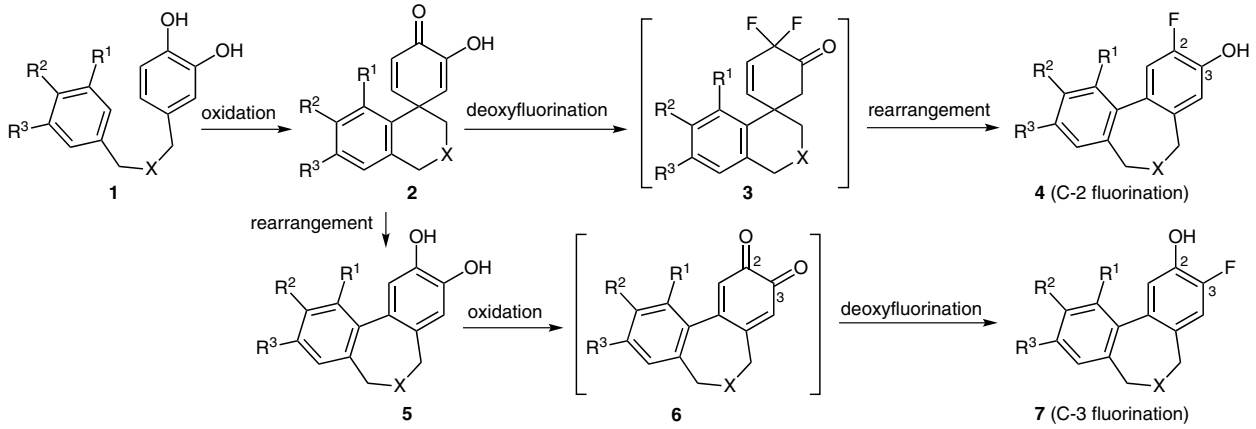
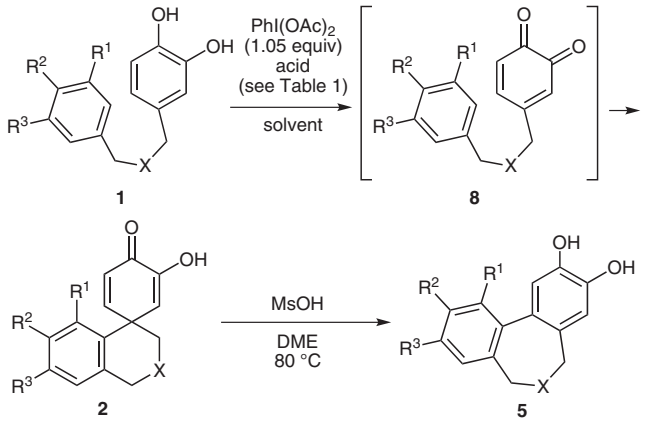


Scheme 1 Outline of the preparation of two types of fluorinated bridged biphenyls **4** and **7**

cluding *ortho*-quinone **8a**, and no cyclization products were obtained (Table 1, entries 1 and 2).



Scheme 2 Oxidative cyclization of catechols **1** to give **2** and **5**

Table 1 Some Typical Results of the Cyclization of **1a** to **2a**[a]

Entry	Solvent	Acid (equiv)	Temp (°C)	Time (h)	Yield of **2a** (%)[b]
1	DME	–	5	48	n.d.[c]
2	DME	AcOH (5)	5	48	n.d.[c]
3	DME	TFA (5)	5	48	35
4	DME	MsOH (1)	5	24	87 (95)[d]
5	DME	TfOH (0.1)	0	1	58
6	THF	MsOH (1)	5	24	85
7	dioxane	MsOH (1)	25	24	71
8	Et_2O	MsOH (1)	5	24	66

[a] Reaction conditions: $PhI(OAc)_2$ (1.05 equiv) was added to a 0.1 M solution of **1** in the presence of an acid, and the reaction mixture was stirred at the given temperature.
[b] Yield was determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard.
[c] Not detected.
[d] Isolated yield.

Other ethereal solvents, such as THF, dioxane, and Et_2O, were also available for producing **2a**, albeit in lower yields (Table 1, entries 6–8). The dienone–phenol rearrangement of **2a** took place to quantitatively give the bridged biphenyl **5a** by the treatment with MsOH (1 equiv) at 80 °C for 24 hours.

We next applied these conditions to various catechols **1b–f** (Table 2). While the yields of the cyclization reaction (**1** → **2**) were dependent on the electron density of the phenyl moiety of the side chain (Table 2, entries 1–4), the Thorpe–Ingold effect[21] was only slightly observed (Table 2, entries 1 and 2 vs. entries 5 and 6). Although the monomethoxy derivative **1c** gave a complex mixture under the standard conditions, the slow addition of a solution of $PhI(OAc)_2$ in DME to a solution of **1c** in DME over 30 minutes followed by the treatment with MsOH (20 equiv) provided **2c** in 43% yield (Table 2, entry 3). The rearrangement reactions of **2b–f** smoothly occurred to give **5b–f** in high yields (Table 2, entries 2–6). A similar cyclization of **1g** directly gave **5g**, and the formation of **2g** was not observed at all (Table 2, entry 7).

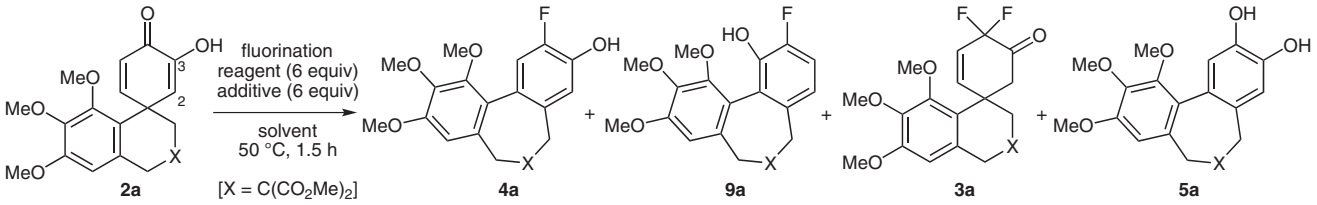
We then turned our attention to the fluorination of spirodienone **2a**. Although α,β-unsaturated carbonyl compounds are known to be poorly reactive substrates for the fluorination,[22] **2a** reacted with Deoxofluor[23] and provided the desired *ortho*-fluorophenol **4a** (40% NMR yield) along with its regioisomer **9a** (19% NMR yield) and a difluoroketone **3a** (14% NMR yield; Table 3, entry 1).[24] The formation of **9a** was unexpected, because **9a** was produced by the migration of the phenyl group onto the more electron-rich C2 position.[25] Compound **3a** was obtained as a major product when DAST[26] was used (Table 3, entry 2). While Xtalfluor-E[27] exclusively caused the dienone–phenol rearrangement of **2a** to give **5a** quantitatively (Table 3, entry 3), the addition of $Et_3N{\cdot}3HF$[27] effectively suppressed the rearrangement and provided **4a** and **9a** in 41% and 14% NMR yields, respectively (Table 3, entry 4). Although a similar reaction was slow in chloroform, the ratio of **4a** to **9a** was higher (Table 3, entry 5). The use of a mixed solvent, *i*-Pr_2O–$CHCl_3$ (1:1), improved the yield of **4a** significantly (63% NMR yield; Table 3, entry 6). The

Table 2 Oxidative Cyclization of Various Catechols **1a–g** to **2a–f** and **5a–g**[a]

Entry	1	R^1	R^2	R^3	X	Isolated yield of **2** (%)	Isolated yield of **5** (%)
1	**1a**	OMe	OMe	OMe	$C(CO_2Me)_2$	**2a** 95	**5a** 99
2	**1b**	H	OMe	OMe	$C(CO_2Me)_2$	**2b** 77	**5b** 96
3	**1c**	H	H	OMe	$C(CO_2Me)_2$	**2c** 43[b]	**5c** 99
4	**1d**	H	$-OCH_2O-$		$C(CO_2Me)_2$	**2d** 64[c]	**5d** 95
5	**1e**	OMe	OMe	OMe	CH_2	**2e** 90	**5e** 88[d]
6	**1f**	H	OMe	OMe	CH_2	**2f** 86	**5f** 86[d]
7	**1g**	OMe	OMe	OMe	NTs	**2g** –	**5g** 58[e]

[a] Reaction conditions: $PhI(OAc)_2$ (1.05 equiv) was added to the 0.1 M solution of **1** in the presence of MsOH (1.0 equiv) and stirred at 0 °C for 24 h.
[b] Slow addition of a solution of $PhI(OAc)_2$ (1.05 equiv) in DME to a solution of **1c** in DME over 30 min followed by the treatment with MsOH (20 equiv) and stirred for 18 h.
[c] MsOH (3.0 equiv) was used.
[d] Overall yield from **1e** or **1f**.
[e] The reaction was conducted at 0.01 M using 50 equiv of MsOH and stirred at 0 °C for 1 h.

Table 3 Optimization of Conditions for the Fluorination of **2a**[a]



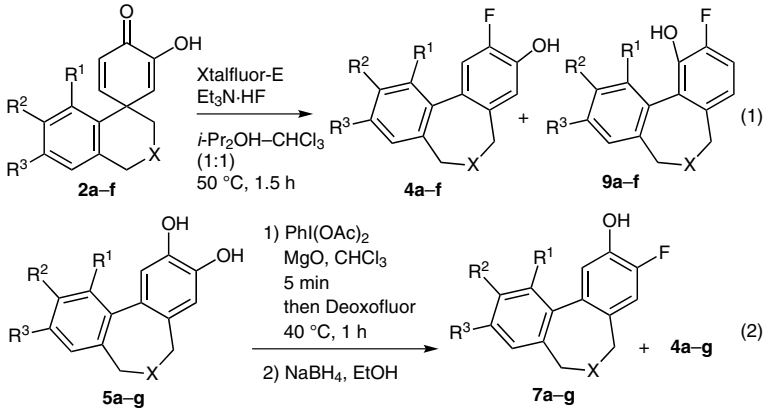
Entry	Fluorination reagent	Additive	Solvent	Yield of **4a** (%)[b]	Yield of **9a** (%)[b]	Yield of **3a** (%)[b]	Yield of **5a** (%)[b]	Yield of **2a** (%)[b]
1	Deoxofluor	–	*i*-Pr_2O	40 (30)[c]	19	14	–	–
2	DAST	–	*i*-Pr_2O	21	15	47	–	–
3	Xtalfluor-E	–	*i*-Pr_2O	–	–	–	99	–
4	Xtalfluor-E	$Et_3N{\cdot}3HF$	*i*-Pr_2O	41	14	–	–	–
5	Xtalfluor-E	$Et_3N{\cdot}3HF$	$CHCl_3$	28	5	–	54	–
6	Xtalfluor-E	$Et_3N{\cdot}3HF$	*i*-Pr_2O–$CHCl_3$ (1:1)	63	16	–	–	–
7	Xtalfluor-E	$Et_3N{\cdot}5HF$	*i*-Pr_2O–$CHCl_3$ (1:1)	–	–	–	–	–
8	Xtalfluor-E	$Et_3N{\cdot}2HF$	*i*-Pr_2O–$CHCl_3$ (1:1)	65	17	–	18	18
9	Xtalfluor-E	$Et_3N{\cdot}HF$	*i*-Pr_2O–$CHCl_3$ (1:1)	79	21	–	–	–
10	Xtalfluor-E	$Et_3N{\cdot}HF$	*i*-Pr_2O–$CHCl_3$ (2:1)	33	10	–	–	–
11	Xtalfluor-E	$Et_3N{\cdot}HF$	*i*-Pr_2O–$CHCl_3$ (1:2)	34	8	–	–	–
12	Xtalfluor-M	$Et_3N{\cdot}3HF$	*i*-Pr_2O	dec.				
13	Fluolead	$Et_3N{\cdot}3HF$	*i*-Pr_2O	dec.				

[a] Reaction conditions: The fluorination reagent was added to a solution of **2a** and an additive in the given solvent, and the reaction mixture was stirred at 50 °C for 1.5 h.
[b] The yield was determined by ^1H NMR and ^{19}F NMR analysis using 4-fluorotoluene as the internal standard; dec. = decomposed.
[c] Isolated yield in parentheses.

addition of $Et_3N{\cdot}5HF$ completely inhibited the reaction (Table 3, entry 7), and the yield of **4a** increased as the ratio of Et_3N to HF increased (Table 3, entries 7–9). The change in the *i*-Pr_2O–$CHCl_3$ ratio had little effect on improving the yield of **4a** (Table 3, entries 10 and 11). The use of other fluorination reagents, such as Xtalfluor-M[27] and Fluorlead,[28] caused substrate decomposition. As a consequence, the use of Xtalfluor-E and $Et_3N{\cdot}HF$ in *i*-Pr_2O–$CHCl_3$ (1:1; Table 3, entry 9) were the optimal conditions, and **4a** was isolated in 74% yield along with **9a** (18% yield; Table 4, entry 1).[29,30]

We next applied the optimal conditions to the spirodienones **2b**–**f** (equation 1 in Scheme 3, Table 4). The substrates **2b**,**c** provided **4b**,**c** in good yields accompanied by **9b**,**c** (Table 4, entries 2 and 3). Although the reactions of **2d**–**f** with Xtalfluor-E led to complex mixtures, those with Deoxofluor provided **4d**–**f** in 23–52% yields (Table 4, entries 4–6). Compounds **4a**–**f** and **9a**–**f** were easily separated by silica gel column chromatography.

The fluorination of the bridged catechols **5a**–**g** was conducted according to our previous study[7] (equation 2 in Scheme 3). Thus, **5a**–**g** was treated with $PhI(OAc)_2$ (1.05 equiv) in the presence of MgO (2.3 equiv) in $CHCl_3$ at 0 °C for five minutes, and Deoxofluor (6 equiv) was then added. The reaction mixture was stirred at 40 °C for one hour.



for **2**, **4**, **5**, **7**, and **9**:

	R^1	R^2	R^3	X
a	OMe	OMe	OMe	$C(CO_2Me)_2$
b	H	OMe	OMe	$C(CO_2Me)_2$
c	H	H	OMe	$C(CO_2Me)_2$
d	H	-OCH_2O-		$C(CO_2Me)_2$
e	OMe	OMe	OMe	CH_2
f	H	OMe	OMe	CH_2
g	OMe	OMe	OMe	NTs

Scheme 3 Deoxyfluorination of **2** and **5**

Table 4 Isolated Yields of **4** and **9** from **2**[a] and of **7** and **4** from **5**[b]

Entry	Compd **2**	Isolated yield of **4** (%)	Isolated yield of **9** (%)	Entry	Compd **5**	Isolated yield of **7** (%)	Isolated yield of **4** (%)
1	**2a**	**4a** 74	**9a** 18	7	**5a**	**7a** 43	**4a** 23
2	**2b**	**4b** 54	**9b** 28	8	**5b**	**7b** 37[d]	**4b** 18[d]
3	**2c**	**4c** 54	**9c** 32	9	**5c**	**7c** 37	**4c** 17
4[c]	**2d**	**4d** 26	**9d** 15	10	**5d**	**7d** 41	**4d** 25
5[c]	**2e**	**4e** 52	**9e** 4	11	**5e**	**7e** 41	**4e** 25
6[c]	**2f**	**4f** 23	**9f** 7	12	**5f**	**7f** 44	**4f** 32
				13	**5g**	**7g** 62	**4g** 10

[a] Reaction conditions: Xtalfluor-E (6.0 equiv) was added to a solution of **2** and $Et_3N{\cdot}HF$ (6.0 equiv) in *i*-Pr_2O–$CHCl_3$ (1:1, 0.2 M), and the reaction mixture was stirred at 50 °C for 1.5 h.

[b] Reaction conditions: $PhI(OAc)_2$ (1.05 equiv) was added to a solution of **5** in $CHCl_3$ (0.2 M) in the presence of MgO (2.3 equiv), and the reaction mixture was stirred at 0 °C for 5 min. Deoxofluor (6.0 equiv) was added to the solution, and the reaction mixture was stirred at 40 °C for 1 h.

[c] The reaction was conducted using Deoxofluor in $CHCl_3$ instead of using Xtalfluor-E/$Et_3N{\cdot}HF$ in *i*-Pr_2O–$CHCl_3$.

[d] Compounds **7b** and **4b** were obtained as a mixture, and their yields were determined by ^1H NMR analysis.

The subsequent reduction of the crude products by $NaBH_4$ (5 equiv) afforded the desired *ortho*-fluorophenols **7a–g** as the major products along with their regioisomers **4a–g** (Table 4, entries 7–13).[30]

In summary, we have developed the complementary synthesis of two kinds of fluorinated bridged biphenyls **4** and **7**.[31] The appropriate use of the 3-hydroxyspirodienones **2** and the biphenyls **5**, as the substrates of the fluorination reaction, both of which were available from the same compounds **1**, was the key for the selective preparation. This is the first example of the concurrent formation of a C–F bond and a new C–C bond by the combination of the deoxyfluorination and the 1,2-phenyl migration (**2** → **4**). Because fluorine is considered to be a bioisostere not only of oxygen, but also of hydrogen,[2] this method allows the synthesis of the core structure of the deoxyfluorinated analogues of multioxygenated bridged biphenyls, such as metasequirine B,[8] jerusalemine,[9] and also of the fluorinated analogues of bridged biphenyls, such as NSC 51046.[11] We are currently investigating the improvement of the regioselectivity of the fluorination reactions, and the application of this methodology to the synthesis of fluorinated analogues of biologically important bridged biphenyls.

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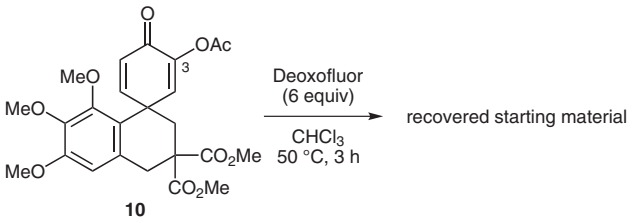
(24) The presence of the 3-hydroxyl moiety of **2a** was found to be essential for the fluorination by the fact that a similar fluorination of the acetyl derivative **10** of **2a** did not proceed at all (Scheme 4).



Scheme 4

(25) Only one example has been reported of the migration of a phenyl group onto the more electron-rich carbon, see:Guinaudeau, H.; Elango, V.; Shamma, M.; Fajardo, V. *J. Chem. Soc., Chem. Commun.* **1982**, 1122.
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(29) For detailed discussion on a plausible reaction mechanism for the fluorination of 3-hydroxydienones **2** producing **4**, **9**, and **3**, see Supporting Information.
(30) Similar fluorination reactions using three equivalents of the same fluorination reagents proceeded very slowly and provided the products in lower yields (<30%).
(31) **3,3-Bis(methoxycarbonyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroxy-naphthalene-1-spiro-1′-[3′-hydrooxy-cyclohexa-2′,5′-dien-4′-one] (2a) – Typical Procedure for the Cyclization of 1 to 2**
Under a nitrogen atmosphere, $PhI(OAc)_2$ (78 mg, 0.24 mmol) was added to a solution of **1a** (100 mg, 0.23 mmol) and MsOH (15 μL, 0.23 mmol) in DME (2.3 mL) at 0 °C. The reaction mixture was stirred for 24 h at 5°C before being quenched with a sat. aq $Na_2S_2O_3$ solution and H_2O. EtOAc was added, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The purification of the residue by flash column chromatography (silica gel, hexanes–EtOAc = 2:1) afforded **2a** (95 mg, 95% yield) as a colorless solid; mp 159.0–162.0 °C. IR ($CHCl_3$): 3447, 1734, 1647, 1238 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.36 (1 H, d, *J* = 15.0 Hz), 2.49 (1 H, d, *J* = 15.0 Hz), 3.13 (1 H, d, *J* = 16.5 Hz), 3.37 (1 H, d, *J* = 16.5 Hz), 3.60 (3 H, s), 3.75 (6 H, s), 3.77 (3 H, s), 3.85 (3 H, s), 5.94 (1 H, d, *J* = 3.0 Hz), 6.26 (1 H, s), 6.38 (1 H, d, *J* = 10.0 Hz), 6.51 (1 H, s), 6.89 (1 H, dd, *J* = 3.0, 10.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.0, 40.5, 42.7, 51.6, 52.9, 55.7, 60.5, 61.0, 107.3, 118.8, 122.9, 123.5, 129.0, 140.7, 146.0, 152.7, 153.2, 158.8, 171.1, 171.3, 181.5. HRMS: *m/z* calcd for $C_{22}H_{25}O_9$ $[M + H]^+$: 433.1493; found: 433.1503.
Dimethyl 5,7-Dihydro-9,10-dihydroxy-1,2,3-trimethoxy-6*H*-dibenzo[*a*,*c*]cycloheptene-6,6-dicarboxylate (5a) – Typical Procedure for the Dienone–Phenol Rearrangement of 2 to 5
Under a nitrogen atmosphere, MsOH (15 μL, 0.23 mmol) was added to a solution of **2a** (100 mg, 0.23 mmol) in DME (2.3 mL). The reaction mixture was stirred at 80 °C until **2a** was completely consumed (monitored by TLC analysis). After cooling, the reaction was quenched with H_2O. EtOAc was added, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The purification of the residue by flash column chromatography (silica gel, hexanes–EtOAc = 1:1) afforded **5a** (100 mg, quant.) as a colorless solid; mp 162.5–164.0 °C. IR ($CHCl_3$): 3595, 3554, 1732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.727 (1 H, d, *J* = 14.0 Hz), 2.731 (1 H, d, *J* = 14.0 Hz), 3.09 (1 H, d, *J* = 14.0 Hz), 3.10 (1 H, d, *J* = 14.0 Hz), 3.54 (3 H, s), 3.74 (3 H, s), 3.75 (3 H, s), 3.85 (3 H, s), 3.90 (3 H, s), 5.94 (1 H, br s), 6.21 (1 H, br s), 6.62 (1 H, s), 6.83 (1 H, s), 7.08 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.2, 37.1, 52.8, 52.9, 56.0, 60.8, 61.2, 64.5, 109.5, 116.5, 116.8, 125.7, 128.0, 128.2, 131.6, 141.3, 142.4, 143.0, 150.3, 151.9, 171.2, 171.3. HRMS: *m/z* calcd for $C_{22}H_{24}NaO_9$ $[M + Na]^+$: 455.1313; found: 455.1339.
Typical Procedure for the Fluorination of 2
Under a nitrogen atmosphere, Xtalfluor-E (95 mg, 0.41 mmol) was added to a solution of **2a** (30 mg, 0.069 mmol) and $Et_3N{\cdot}HF$ (0.41 mmol), in situ prepared from $Et_3N{\cdot}3HF$ (22 μL, 0.14 mmol) and Et_3N (38 μL, 0.28 mmol), in *i*-Pr_2O–$CHCl_3$ (1:1, 0.35 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 50 °C before being quenched with ice water. CH_2Cl_2 was added, the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The purification of the residue by flash column chromatography (silica gel, hexanes–EtOAc = 3:1) afforded **4a** (22 mg, 74% yield) and **9a** (6.0 mg, 18% yield).
Dimethyl 10-Fluoro-5,7-dihydro-9-hydroxy-1,2,3-trimethoxy-6*H*-dibenzo[*a*,*c*]cycloheptene-6,6-dicarboxylate (4a)
Colorless solid; mp 146.0–147.0 °C. IR ($CHCl_3$): 3578, 1734, 1254 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.72 (1 H, d, *J* = 14.5 Hz), 2.76 (1 H, d, *J* = 14.5 Hz), 3.13 (2 × 1 H, d, *J* = 14.5 Hz), 3.60 (3 H, s), 3.76 (6 H, s), 3.87 (3 H, s), 3.90 (3 H, s), 5.39 (1 H, br), 6.63 (1 H, s), 6.93 (1 H, d, *J* = 9.0 Hz), 7.26 (1 H, d, *J* = 11.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.2, 37.0, 52.8, 52.9, 56.0, 60.8, 61.1, 64.4, 109.4, 117.1 (d, *J* = 18.0 Hz), 118.3, 124.8, 128.5 (d, *J* = 7.0 Hz), 131.4, 132.3 (d, *J* = 3.5 Hz), 141.6, 142.2 (d, *J* = 14.5 Hz), 150.0 (d, *J* = 238 Hz), 150.6, 152.4, 170.8, 171.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –146.5 (1 F, dd, *J* = 9.0, 11.5 Hz). HRMS: *m/z* calcd for $C_{22}H_{23}FNaO_8$ $[M + Na]^+$: 457.1269; found: 457.1289.
Dimethyl 10-Fluoro-5,7-dihydro-11-hydroxy-1,2,3-trimethoxy-6*H*-dibenzo[*a*,*c*]cycloheptene-6,6-dicarboxylate (9a)
Colorless solid; mp 104.0–109.0 °C. IR ($CHCl_3$): 3327, 1732, 1240 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.71 (1 H, d, *J* = 14.0 Hz), 2.73 (1 H, d, *J* = 14.0 Hz), 3.13 (1 H, d, *J* = 14.0 Hz), 3.20 (1 H, d, *J* = 14.0 Hz), 3.70 (3 H, s), 3.76 (3 H, s), 3.77 (3 H, s), 3.90 (3 H, s), 3.93 (3 H, s), 6.70 (1 H, s), 6.81 (1 H, dd, *J* = 5.0, 8.0 Hz), 6.99 (1 H, s), 7.01 (1 H, d, *J* = 8.0, 10.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.8, 36.9, 52.88, 52.92, 56.1, 61.3, 62.2, 64.2, 110.9, 115.1 (d, *J* = 18.0 Hz), 121.3 (d, *J* = 2.0 Hz), 122.1 (d, *J* = 7.0 Hz), 126.4, 131.9 (d, *J* = 3.5 Hz), 132.4, 141.4, 141.5 (d, *J* = 12.0 Hz), 149.4, 152.9 (d, *J* = 241 Hz), 153.1, 170.6, 170.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –138.9 (1 F, dd, *J* = 5.0, 10.0 Hz). HRMS: *m/z* calcd for $C_{22}H_{23}FNaO_8$ $[M + Na]^+$: 457.1269, found: 457.1271.
Typical Procedure for the Fluorination of 5
Under a nitrogen atmosphere, $PhI(OAc)_2$ (78 mg, 0.24 mmol) was added to a mixture of **5a** (100 mg, 0.23 mmol) and MgO (21 mg, 0.53 mmol) in $CHCl_3$ (1.2 mL) at 0 °C, and the reaction mixture was stirred at the same temperature

for 5 min. Deoxofluor (0.25 mL, 1.4 mmol) was added, and the reaction mixture was stirred for 1 h at 40 °C before being quenched with ice water. CH_2Cl_2 was added, the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in EtOH (1.2 mL), and $NaBH_4$ (44 mg, 1.2 mmol) was added to the solution at 0 °C. The reaction mixture was stirred overnight at r.t. before being quenched with 1 M HCl. EtOAc was added, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, hexanes–EtOAc–Et_3N = 33:66:1) afforded **4a** (24 mg, 23% yield) and **7a** (43 mg, 43% yield).

Dimethyl 9-Fluoro-5,7-dihydro-10-hydroxy-1,2,3-trimethoxy-6*H*-dibenzo[*a*,*c*]cycloheptene-6,6-dicarboxylate (7a)

Colorless solid; mp 188.5–189.5 °C. IR ($CHCl_3$): 3580, 1732, 1238 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.68 (1 H, d, *J* = 14.0 Hz), 2.73 (1 H, d, *J* = 14.0 Hz), 3.13 (1 H, d, *J* = 13.0 Hz), 3.15 (1 H, d, *J* = 13.0 Hz), 3.61 (3 H, s), 3.76 (6 H, s), 3.88 (3 H, s), 3.90 (3 H, s), 5.26 (1 H, br), 6.64 (1 H, s), 7.03 (1 H, d, *J* = 11.0 Hz), 7.17 (1 H, d, *J* = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.0, 37.0, 52.8, 52.9, 56.0, 60.9, 61.1, 64.3, 109.4, 116.7 (d, *J* = 18.0 Hz), 119.0, 124.9, 128.3 (d, *J* = 6.0 Hz), 131.3, 132.5 (d, *J* = 3.5 Hz), 141.6, 142.1 (d, *J* = 13.0 Hz), 149.6 (d, *J* = 237 Hz), 150.7, 152.5, 170.9, 171.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –145.4 to –145.2 (1 F, m). HRMS: *m/z* calcd for $C_{22}H_{23}FNaO_8$ $[M + Na]^+$: 457.1269; found: 457.1292.

