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# Difluorination of Furonaphthoquinones

Jie Li,[†] Yu Xue,[‡] Zhoulong Fan,[§,⊥,∥] Chunyong Ding,*[,§,∥] and Ao Zhang*[,†,§,⊥,∥]

[†]ShanghaiTech University, Shanghai 201210, China

[‡]Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China

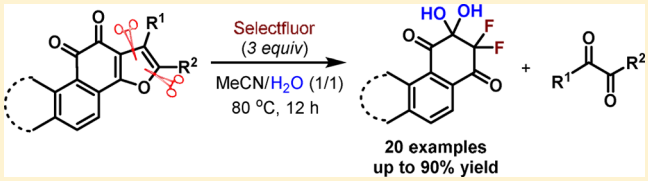
[§]CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

[⊥]State key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

[∥]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

**ABSTRACT:** An unprecedented difluorination reaction was developed based on the furonaphthoquinone skeleton of natural products tanshinones and their analogues. By using Selectfluor as the fluorinating source and $H_2O$ as the hydroxyl source, a wide range of unique polycyclic $\alpha,\alpha$-difluoro $\beta,\beta$-dihydroxyl *para*-quinone products were achieved with yields up to 90%. The mechanistic studies revealed that the reaction might undergo tandem multiple electrophilic and nucleophilic substitutions, as well as cleavages of C−O and C−C bonds. This approach not only provides a new method to synthesis of $\alpha,\alpha$-difluoro ketones, but also affords a series of unique chemotypes for biological activity screening.




## INTRODUCTION

Fluorine-containing compounds play an intrinsic role in the fields of pharmaceuticals, agrochemicals, and materials due to their superior physiochemical and biological properties.[1] Among various fluorinated structural motifs, $\alpha,\alpha$-difluorinated ketone constitutes a valuable subset of bioactive molecules for drug discovery.[2] Indeed, the two fluorine atoms could make the *ortho*-carbonyl form a more stable hydrate or gemdiol with $H_2O$.[3] The formed gemdiol compounds generally have increased aqueous solubility, and some of them also showed good potency against proteolytic enzymes, such as HIV1 protease, and matrix metalloprotease, by mimicking tetrahedral transition state involved in peptide hydrolysis.[4] Accordingly, incorporation of the $\alpha,\alpha$-difluorinated ketone moiety has become a promising strategy for drug design and lead optimization. However, methods for the synthesis of $\alpha,\alpha$-difluorinated ketones are very limited. Current reported approaches include: (a) transition-metal catalyzed $\alpha,\alpha$-difluorocarbonylation,[5] (b) direct electrophilic $\alpha,\alpha$-difluorination,[6] and (c) deoxydifluorination of ketones or aldehydes.[7] Recently, a few new methods for $\alpha,\alpha$-difluorocarbonylation were reported via C−C cleavage of 1,3-dicarbonyl compounds. In 2016, the Pattison group developed a one-pot approach for synthesis of difluoromethyl ketones through cleavage of trifluoroacetyl fragment (Scheme 1a).[8] Very recently, Deng and co-workers described a decarboxylative difluorination reaction of $\beta$-ketoacids (Scheme 1b).[9] Undoubtedly, these methods would spur new interest in the application of $\alpha,\alpha$-difluorocarbonylation products. However, available approaches, especially for the synthesis of cyclic $\alpha,\alpha$-difluorinated ketones, remain largely elusive.

Tanshinones, including tanshinone IIA (**1a**, Tan-IIA), tanshinone I (**2**, Tan-I), and cryptotanshinone (**3**, CPT) (Scheme 1d), represent a large class of tetracyclic furoquinone diterpenoids isolated from traditional Chinese medicinal herb *Salvia miltiorrhiza* Bunge, and have demonstrated various pharmacological activities.[10] However, further clinical development of tanshinones is hampered by its relative low potency and poor drugability.[11] Thus, structural modification of tanshinones, especially on the metabolically unstable furoquinone rings C/D is desired.[12] In our continuing structural modification of natural product tanshinones,[13] we, herein, disclose an unprecedented difluorination reaction of tanshinone analogues for facile construction of polycyclic $\alpha,\alpha$-difluorinated ketones (Scheme 1c).

## RESULTS AND DISCUSSION

Since the *ortho*-quinone moiety was the major issue causing poor aqueous solubility of tanshinones, our initial effort was to convert one of the two carbonyls in **1a** to fluoromethyl moiety, a strategy widely used in the drug discovery.[14] It was found that treating **1a** with the fluorinating agent DAST in 1,4-dioxane at 90 °C afforded two $\alpha,\alpha$-difluorinated ketone products **5** and **6** in 42% and 36% yields, respectively (Scheme 2). The structures of these two regioisomers were discriminated by HRMS, NMR, and X-rays (Figures S2−S3 and Tables S2−S3 in SI). To

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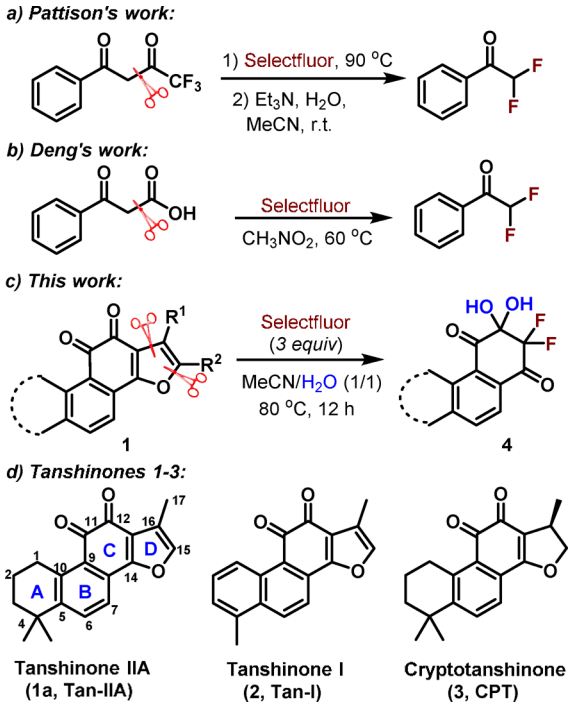
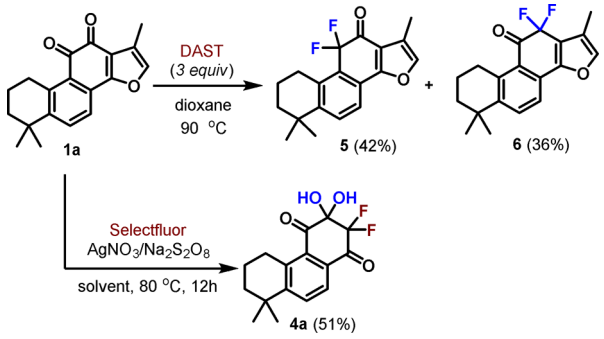
**Scheme 1. Synthesis of α,α-Difluorinated Ketones via C−C Bond Cleavage and Structures of Representative Tanshinones 1−3**




**Scheme 2. Direct Difluorination of 1a**



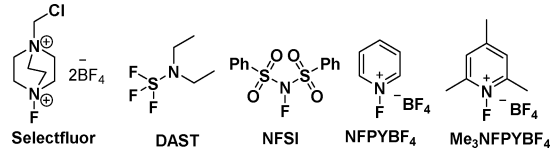

improve the regioselectivity of the two α,α-difluorinated products, other fluorinating agents were explored as alternatives. To our surprise, when the electrophilic fluorinating agent Selectfluor was used, reaction with **1a** in the presence of $AgNO_3/Na_2S_2O_8$ in $CH_3CN/H_2O$ provided an unprecedented tricyclic α,α-difluoro ß,ß-dihydroxyl *para*-quinone product **4a** in 51% yield with the furan portion truncated (Scheme 2). The unique structure of **4a** was determined by HRMS and NMR, and further secured by X-ray crystallography (Figure S1 and Table S1 in SI).

In view of the structural novelty of **4a**, we decided to optimize the reaction condition to improve the yield and to explore the substrate scope and limitation as well. Interestingly, we found that the reaction proceeded even better without $AgNO_3/Na_2S_2O_8$ leading to **4a** in 77% yield (Table 1, entry 2). When other fluorinating agents were used (entries 3−5), such as NFSI, $NFPYBF_4$, and $Me_3NFPYBF_4$, the yields were decreased in varying degrees (33−56%). Different reaction solvents, such as DMF/$H_2O$ and 1,4-dioxane/$H_2O$, were also investigated, and none of them gave better yields (entries 6−7).

**Table 1. Optimization of Reaction Condition**[a]

| entry | [F] source (equiv) | solvent | yield (**4a**, %)[b] |
|---|---|---|---|
| 1[c] | Selectfluor (3.0) | MeCN/$H_2O$ | 51 |
| 2 | Selectfluor (3.0) | MeCN/$H_2O$ | 77 |
| 3 | NFSI (3.0) | MeCN/$H_2O$ | 40 |
| 4 | $NFPYBF_4$ (3.0) | MeCN/$H_2O$ | 56 |
| 5 | $Me_3NFPYBF_4$ (3.0) | MeCN/$H_2O$ | 33 |
| 6 | Selectfluor (3.0) | DMF/$H_2O$ | 56 |
| 7 | Selectfluor (3.0) | dioxane/$H_2O$ | 62 |
| 8[d] | Selectfluor (3.0) | MeCN/$H_2O$ | 67 |
| 9[e] | Selectfluor (3.0) | MeCN/$H_2O$ | 65 |
| 10 | Selectfluor (2.0) | MeCN/$H_2O$ | 52 |
| 11 | Selectfluor (4.0) | MeCN/$H_2O$ | 69 |
| 12[f] | Selectfluor (3.0) | MeCN/$H_2O$ | 42 |

[a]Reaction condition: **1a** (0.1 mmol), [F] source (equiv), solvent (1 mL, v/v = 1/1), 80 °C, 12 h. [b]Isolated yield. [c]In the presence of $AgNO_3$ (0.1 eqiv)/$Na_2S_2O_8$ (0.5 eqiv). [d]At 70 °C. [e]At 90 °C. [f]Reaction time: 6 h.




Decreasing or elevating reaction temperature led to slightly decreased yields (entries 8−9). Using 2.0 equiv of Selectfluor, the yield was decreased to 52%, and 4.0 equiv of Selectfluor also failed to improve the yield (entries 10−11). Shorter reaction time resulted in a dramatically decreased yield (entry 12). Taken together, using 3.0 equiv of Selectfluor in $CH_3CN/H_2O$ at 80 °C was determined to be the optimal reaction condition for this unique difluorination reaction.

With the optimized reaction conditions in hand, we next explored the scope and limitations. First, a series of A-ring substituted tanshinone substrates were investigated (Scheme 3). It was found that **1b**, close analogue of **1a** but bearing an aromatic A-ring also isolated from *Salvia miltiorrhiza*, was tolerant in this reaction to provide the desired product **4b** in 47% yield. Tanshinone analogue **1c** with the A-ring bearing a α,β-unsaturated ketone function afforded the corresponding product **4c** in 88% yield. For the substrate without the A-ring, the reaction still went through and provided product **4d** in 61% yield. In addition, we also investigated the substrates bearing aryloxy substituents on the A-ring. Pentafluorphenyl ester substituent was tolerated well and provided the corresponding product **4e** in 83% yield. Aryl ethers bearing strong electron-withdrawing substituents (e.g., $CF_3$ and $NO_2$) gave the corresponding product **4f** and **4g** in 62% and 60% yields, respectively. In the case of the substrate with a 4-bromophenyloxy substituent, the yield was much lower (**4h**, 30%). In addition, a subseries of tanshinones bearing diverse esteric functions were also tested. Cinnamate substrate was tolerated very well and gave product **4i** in 76% yield. The alkyl acyloxylated derivatives also proceeded well in this reaction and provided dihydroxydifluorination compounds **4j−l** in 53−59% yields. For the aryl acyloxylated derivatives, the yields were slightly higher (63−64% yields for **4m−n**). However, the naphthoate derivative afforded corresponding product **4o** in a lower yield of 47%.

Next, we examined the scope of the C/D ring of tanshinones (Scheme 4). Interestingly, most of these substrates gave the same product **4a**. β-Chloromethyl substituent on the D-ring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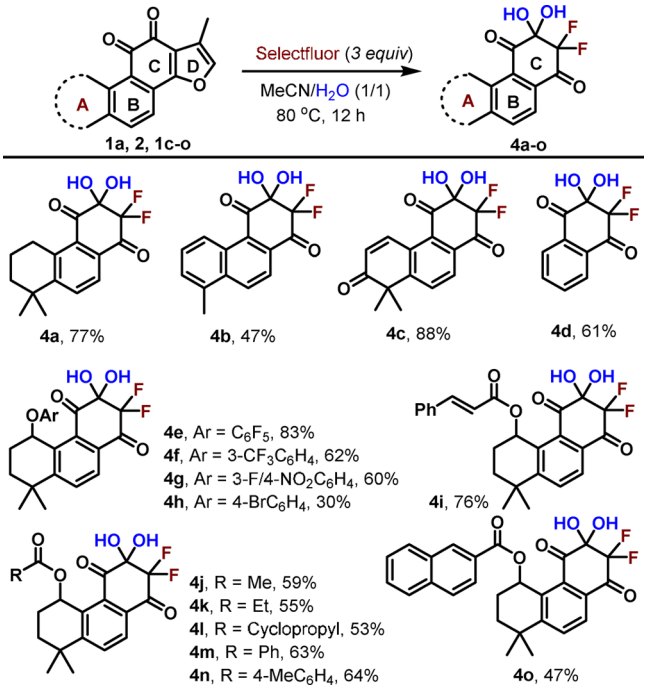
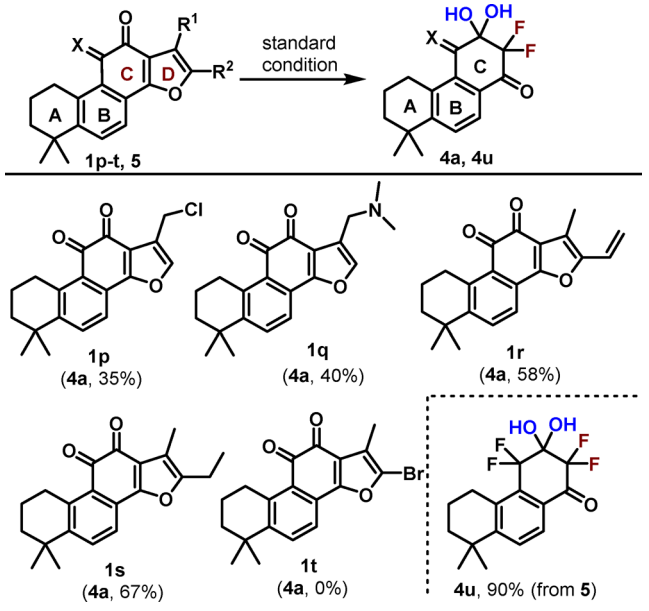
**Scheme 3. Substrate Scope of the A-Ring of Tanshinones**[a]




[a]Reaction condition: **1** or **2** (0.1 mmol), Selectfluor (3 equiv), $MeCN/H_2O$ (1 mL, v/v = 1/1), 80 °C, 12 h. Isolated yields.

**Scheme 4. Substrate Scope of the C/D-Ring Tanshinones**[a]

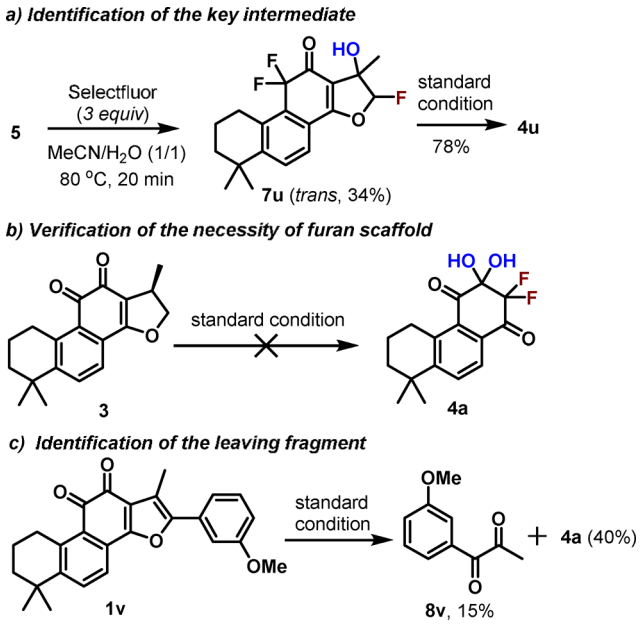



[a]Reaction condition: **1p−t**, **5** (0.1 mmol), Selectfluor (3 equiv), $MeCN/H_2O$ (1 mL, v/v = 1/1), 80 °C, 12 h. Isolated yields.

(**1p**) led to the tricyclic product **4a** in 35% yield. The substrate **1q** with 16-amino substituent afforded **4a** in 40% yield. When the C-2 position of the D-ring was substituted by vinyl or ethyl (**1r−s**), the yields of **4a** were increased to 58−67%. Unfortunately, the substrate **1t** failed to provide product **4a** probably due to electronic effect of the bromo-substituent. Interestingly, the difluorinated substrate **5** also participated in the reaction and the corresponding product **4u** was obtained in 90% yield.

To gain more insight on the reaction mechanism, as shown in Scheme 5, we first attempted to capture the key intermediate

**Scheme 5. Preliminary Mechanistic Studies**




of this reaction. We carried out the reaction by using **5** as the substrate and quenched in 20 min. To our delight, an intermediate was successfully isolated in 34% yield and the structure was demonstrated to be **7u** by X-ray crystallography (Figure S4 and Table S4 in SI). Under the standard condition, **7u** could be smoothly converted to **4u** in 78% yield. In the meantime, we found that the furyl ring-saturated substrate **3** failed to give the desired product **4a** under the standard reaction, indicating the unsaturated furan moiety is necessary in the reaction. Finally, we conducted the reaction using **1v** as the substrate, and the leaving fragment **8v** was successfully obtained.

On the basis of the experiments above, a possible mechanism is proposed in Scheme 6. Initially, electrophilic substitution of **1** with $F^+$ generated the intermediate **I**, which then underwent Michael addition to give the stable intermediate **7** (**7u**, $R^1$ = Me, $R^2$ = H). A second electrophilic substitution with $F^+$ occurred at the C-13 position of **7**, followed by intramolecular nucleophilic cyclization to yield intermediate **III** (Path a). Subsequently, hydroxyl anion ($OH^-$) attacked the oxirane ring to generate an unstable ketal **IV**, which was then converted to **V**. Alternatively, as shown in Path b, addition of $H_2O$ to the oxonium ion **II** led to the opening of the furan ring to give **VIII**, which was also transformed to **V**. Subsequent fragmentation of **V** released diketone **8** (**8v**, $R^1$ = Me, $R^2$ = 3-MeO-Ph), leading to fluoroketone **VI**. A third electrophilic substitution with $F^+$ accompanied by ketone-hydration generated the final product **4**.

## CONCLUSION

In conclusion, we have developed an unprecedented difluorination reaction based on the furonaphthoquinone skeleton of natural products tanshinones and its analogues. A wide range of unique polycyclic *α,α*-difluoro *β,β*-dihydroxyl *para*-quinone products were obtained by using Selectfluor as the fluorinating source and $H_2O$ as the hydroxyl source. The mechanistic



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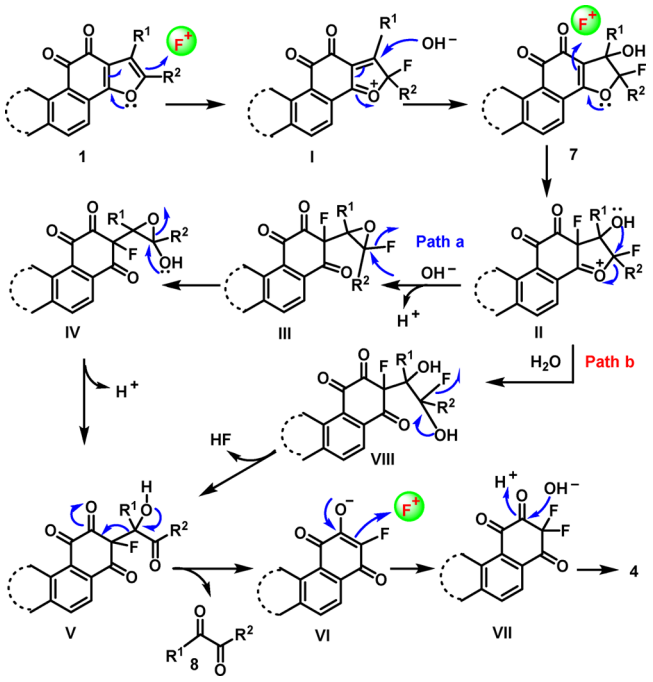
**Scheme 6. Proposed Mechanism**




studies revealed that the reaction might undergo tandem multiple electrophilic and nucleophilic substitutions, as well as cleavages of C−O and C−C bonds. This approach not only provides a new method for the synthesis of *α,α*-difluoro ketones, but also affords a series of unique chemotypes of tricyclic *α,α*-difluoro *β,β*-dihydroxyl *para*-quinones for biological activity screening.

## EXPERIMENTAL SECTION

**General Information.** All reactions were performed in flame-dried sealed tubes. Liquids and solutions were transferred with syringes. All solvents and chemical reagents were obtained from commercial sources and used without further purifications. $^{1}H$ and $^{13}C$ NMR spectra were recorded with tetramethylsilane as an internal reference. Low and high-resolution mass spectra were recorded on EI or ESI mode. Flash column chromatography on silica gel (200−300 mesh). The column output was monitored by TLC on silica gel (100−200 mesh) precoated on glass plates (15 × 50 mm), and spots were visualized by UV light at 254 nM. Starting materials were synthesized according to previous literatures or obtained from commercial sources, such as Strem Chemicals, Adamas-beta, Sigma-Aldrich, J&K, and TCI, which were used without further purification.

**General Procedure for the Synthesis of 4a−o and 4u.** A 10 mL sealed tube was charged with Tan-IIA substrates (0.1 mmol) and Selectfluor (0.3 mmol). MeCN/$H_2O$ (0.5 mL/0.5 mL) was added, and the resulting mixture was stirred at 80 °C for 12 h. After cooling to rt, the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layer was washed with saturated NaCl aqueous solution, dried over $Na_2SO_4$, and concentrated *in vacuo* to give a brown residue. The residue was purified by chromatography on silica gel column to furnish the desired compounds **4a−o** and **4u** as white solids.

*2,2-Difluoro-3,3-dihydroxy-8,8-dimethyl-2,3,5,6,7,8-hexahydrophenanthrene-1,4-dione* (***4a***). Yield: 77% (24 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.11 (d, $J$ = 8.2 Hz, 1H), 7.87 (d, $J$ = 8.3 Hz, 1H), 4.55 (s, 2H), 3.19 (t, $J$ = 6.3 Hz, 2H), 1.89−1.79 (m, 2H), 1.75−1.67 (m, 2H), 1.35 (s, 6H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 190.0, 183.4 (t, $J$ = 24.6 Hz), 156.3, 142.0, 134.1, 131.9, 129.4, 126.0, 110.6 (t, $J$ = 259.2 Hz), 92.5 (t, $J$ = 24.4 Hz), 37.5, 35.3, 31.7 (2C), 29.6, 18.9; $^{19}F$ NMR (471 MHz, $CDCl_3$) $\delta$ −124.76; HRMS $m/z$ (ESI) calcd for $C_{16}H_{15}F_2O_4$ $(M-H)^-$ 309.0944, found 309.0938.

*2,2-Difluoro-3,3-dihydroxy-8-methyl-2,3-dihydrophenanthrene-1,4-dione* (***4b***). Yield: 47% (14 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.13 (d, $J$ = 8.2 Hz, 1H), 8.53 (d, $J$ = 8.8 Hz, 1H), 8.31 (d, $J$ = 9.0 Hz, 1H), 7.75−7.67 (m, 1H), 7.61 (d, $J$ = 6.7 Hz, 1H), 4.61 (s, 2H), 2.79 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 190.5, 184.0 (t, $J$ = 25.0 Hz), 136.3, 135.5, 133.3, 133.0, 131.0, 130.7, 130.6, 128.9, 125.6, 122.3, 110.8 (t, $J$ = 259.4 Hz), 93.1 (t, $J$ = 24.3 Hz), 19.9; HRMS $m/z$ (ESI) calcd for $C_{15}H_{11}F_2O_4$ $(M+H)^+$ 293.062, found 293.0618.

*2,2-Difluoro-3,3-dihydroxy-8,8-dimethyl-2,3-dihydrophenanthrene-1,4,7(8H)-trione* (***4c***). Yield: 88% (28 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.66 (d, $J$ = 10.4 Hz, 1H), 8.29 (d, $J$ = 8.3 Hz, 1H), 7.90 (d, $J$ = 8.3 Hz, 1H), 6.40 (d, $J$ = 10.5 Hz, 1H), 4.54 (s, 2H), 1.49 (s, 6H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 201.2, 190.6, 156.8, 138.1, 132.8, 132.6, 130.6, 129.4, 128.8, 128.6, 110.5 (t, $J$ = 254.5 Hz), 93.0 (t, $J$ = 21.4 Hz), 48.6, 27.4 (2C); HRMS m/s (ESI) calcd for $C_{16}H_{13}F_2O_5$ $(M+H)^+$ 323.0726, found 323.0725.

*2,2-Difluoro-3,3-dihydroxy-2,3-dihydronaphthalene-1,4-dione* (***4d***). Yield: 61% (14 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.29−8.23 (m, 2H), 7.95−7.89 (m, 2H), 4.33 (s, 2H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 188.9, 183.1 (t, $J$ = 25.4 Hz), 136.1, 135.7, 133.0, 131.4, 128.6, 128.5, 111.1 (t, $J$ = 260.4 Hz), 92.2 (t, $J$ = 24.6 Hz); HRMS $m/z$ (ESI) calcd for $C_{10}H_7F_2O_4$ $(M+H)^+$ 229.0307, found 229.0301.

*2,2-Difluoro-3,3-dihydroxy-8,8-dimethyl-5-(perfluorophenoxy)-2,3,5,6,7,8-hexahydrophenanthrene-1,4-dione* (***4e***). Yield: 83% (41 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.31 (d, $J$ = 8.4 Hz, 1H), 7.99 (d, $J$ = 8.6 Hz, 1H), 6.66 (s, 1H), 4.64 (s, 1H), 4.00 (s, 1H), 2.33−2.09 (m, 3H), 1.66−1.60 (m, 1H), 1.51 (s, 3H), 1.33 (s, 3H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 190.6, 182.8 (t, $J$ = 25.2 Hz), 157.1, 142.3 (m), 140.7 (m), 138.9 (m), 137.9 (m), 137.2 (m), 135.0, 134.8, 132.1, 131.4 (m), 130.6, 129.1, 110.4 (t, $J$ = 255.6 Hz), 110.4, 92.9 (t, $J$ = 23.1 Hz), 73.1, 35.5, 31.4, 31.2, 31.0, 24.6; HRMS $m/z$ (ESI) calcd for $C_{22}H_{14}F_7O_5$ $(M-H)^-$ 491.0735, found 491.0730.

*2,2-Difluoro-3,3-dihydroxy-8,8-dimethyl-5-(3-(trifluoromethyl)-phenoxy)-2,3,5,6,7,8-hexahydrophenanthrene-1,4-dione* (***4f***). Yield: 62% (29 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.29 (d, $J$ = 8.4 Hz, 1H), 7.96 (d, $J$ = 8.4 Hz, 1H), 7.45 (t, $J$ = 7.8 Hz, 1H), 7.29−7.24 (m, 2H), 7.20 (m, 1H), 6.40 (t, $J$ = 3.3 Hz, 1H), 4.63 (s, 1H), 4.07 (s, 1H), 2.19−2.01 (m, 3H), 1.62 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 190.2, 183.0 (t, $J$ = 25.1 Hz), 157.6, 156.7, 136.4, 134.3, 132.4, 131.9 (q, $J$ = 32.8 Hz), 131.0, 130.2, 128.5, 124.0 (q, $J$ = 272.4 Hz), 119.0, 118.0 (q, $J$ = 3.8 Hz), 112.9 (q, $J$ = 3.8 Hz), 110.5 (t, $J$ = 264.6 Hz), 92.9 (t, $J$ = 25.2 Hz), 68.7, 35.4, 31.8, 31.0, 31.0, 22.9; HRMS $m/z$ (ESI) calcd for $C_{23}H_{19}F_5O_5Na$ $(M+Na)^+$ 493.1045, found 493.1052.

*2,2-Difluoro-5-(3-fluoro-4-nitrophenoxy)-3,3-dihydroxy-8,8-dimethyl-2,3,5,6,7,8-hexahydrophenanthrene-1,4-dione* (***4g***). Yield: 60% (28 mg); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.32 (d, $J$ = 8.4 Hz, 1H), 8.14 (t, $J$ = 9.1 Hz, 1H), 8.00 (d, $J$ = 8.4 Hz, 1H), 6.85 (dq, $J$ = 7.7, 2.5 Hz, 2H), 6.39 (t, $J$ = 3.3 Hz, 1H), 4.53 (s, 1H), 4.26 (s, 1H), 2.13 (m, 3H), 1.67−1.62 (m, 1H), 1.49 (s, 3H), 1.36 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 190.3, 182.9 (t, $J$ = 25.1 Hz), 163.5 (d, $J$ = 10.9 Hz), 157.7 (d, $J$ = 265.8 Hz), 156.7, 135.0, 134.7, 132.7, 130.9 (d, $J$ = 6.7 Hz), 130.7, 129.0, 128.1, 111.5 (d, $J$ = 2.52 Hz), 110.5 (d, $J$ = 258.3 Hz), 104.6 (d, $J$ = 24.2 Hz), 92.8 (t, $J$ = 24.4 Hz), 69.9, 35.4, 31.6, 31.1, 30.9, 23.1; HRMS $m/z$ (ESI) calcd for $C_{22}H_{18}F_3NO_7Na$ $(M+Na)^+$ 488.0928, found 488.0923.

*5-(4-Bromophenoxy)-2,2-difluoro-3,3-dihydroxy-8,8-dimethyl-2,3,5,6,7,8-hexahydrophenanthrene-1,4-dione* (***4h***). Yield: 30% (14 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 8.4 Hz, 1H), 7.94 (d, $J$ = 8.4 Hz, 1H), 7.43 (d, $J$ = 7.9 Hz, 2H), 6.92 (d, $J$ = 8.0 Hz, 2H), 6.31 (s, 1H), 2.20−1.92 (m, 3H), 1.62−1.55 (m, 1H), 1.47 (s, 3H), 1.34 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 190.3, 183.0 (t, $J$ = 25.0 Hz), 156.7, 156.6, 136.6, 134.2, 132.5 (2C), 132.3, 131.2, 128.4, 117.7 (2C), 113.6, 110.6 (dd, $J$ = 264.7, 254.3 Hz), 93.0 (dd, $J$ = 26.2, 22.6 Hz), 68.7, 35.4, 31.9, 31.0 (2C), 22.8; HRMS $m/z$ (ESI) calcd for $C_{22}H_{18}BrF_2O_5$ $(M-H)^-$ 479.0311, found 479.0305.

*7,7-Difluoro-6,6-dihydroxy-1,1-dimethyl-5,8-dioxo-1,2,3,4,5,6,7,8-octahydrophenanthren-4-yl Cinnamate* (***4i***). Yield: 76% (35 mg); $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 8.4 Hz, 1H), 7.93 (d, $J$ = 8.4 Hz, 1H), 7.64 (d, $J$ = 16.0 Hz, 1H), 7.46 (m, 2H), 7.35 (m, 3H), 6.57 (s, 1H), 6.35 (d, $J$ = 16.0 Hz, 1H), 5.24 (s, 1H),



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5.18 (s, 1H), 2.25−2.05 (m, 3H), 1.73−1.64 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 191.2, 183.3 (t, $J$ = 25.5 Hz), 167.2, 157.1, 146.2, 135.0, 134.1, 134.0 (2C), 132.4, 131.5, 130.7 (2C), 128.9, 128.6, 128.3, 117.3, 110.8 (t, $J$ = 259.7 Hz), 93.6 (t, $J$ = 24.3 Hz), 67.3, 35.5, 32.2, 31.5, 31.3, 24.8; HRMS $m/z$ (ESI) calcd for $C_{25}H_{21}F_2O_6$ $(M-H)^-$ 455.1312, found 455.1303.

*7,7-Difluoro-6,6-dihydroxy-1,1-dimethyl-5,8-dioxo-1,2,3,4,5,6,7,8-octahydrophenanthren-4-yl Acetate (**4j**).* Yield: 59% (22 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.19 (d, $J$ = 8.4 Hz, 1H), 7.85 (d, $J$ = 8.2 Hz, 1H), 6.36 (s, 1H), 4.79 (m, 2H), 2.09−1.93 (m, 6H), 1.63−1.51 (m, 1H), 1.40 (s, 3H), 1.25 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 190.9, 171.1, 157.0, 135.1, 134.0, 132.2, 131.6, 128.5, 93.4, 67.1, 35.4, 32.1, 31.5, 31.2, 24.7, 21.2; HRMS $m/z$ (ESI) calcd for $C_{18}H_{17}F_2O_6$ $(M-H)^-$ 367.0999, found 367.0998.

*7,7-Difluoro-6,6-dihydroxy-1,1-dimethyl-5,8-dioxo-1,2,3,4,5,6,7,8-octahydrophenanthren-4-yl Propionate (**4k**).* Yield: 55% (21 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 8.4 Hz, 1H), 7.91 (d, $J$ = 8.4 Hz, 1H), 6.45 (s, 1H), 4.98 (s, 2H), 2.29 (q, $J$ = 7.6 Hz, 2H), 2.20−2.02 (m, 3H), 1.69−1.64 (m, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 1.10 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 191.1, 183.2 (t, $J$ = 25.3 Hz), 174.7, 157.0, 135.0, 134.0, 132.2, 131.5, 128.5, 113.1−108.3 (t, $J$ = 259.6 Hz), 93.4 (t, $J$ = 24.3 Hz), 66.9, 35.4, 32.1, 31.5, 31.3, 27.8, 24.7, 9.1; HRMS $m/z$ (ESI) calcd for $C_{19}H_{19}F_2O_6$ $(M-H)^-$ 381.1155, found 381.1154.

*7,7-Difluoro-6,6-dihydroxy-1,1-dimethyl-5,8-dioxo-1,2,3,4,5,6,7,8-octahydrophenanthren-4-yl Cyclopropanecarboxylate (**4l**).* Yield: 53% (21 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.17 (d, $J$ = 8.4 Hz, 1H), 7.83 (d, $J$ = 8.4 Hz, 1H), 6.41 (s, 1H), 4.84 (s, 1H), 4.81 (s, 1H), 2.14−1.99 (m, 3H), 1.66−1.59 (m, 1H), 1.53 (s, 3H), 1.42 (s, 3H), 1.25 (s, 3H), 0.93−0.86 (m, 2H), 0.83−0.76 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 191.3, 183.2 (t, $J$ = 25.3 Hz), 175.3, 157.0, 134.7, 133.8, 132.8, 131.1, 128.5, 112.9−108.6 (t, $J$ = 254.2 Hz), 93.8−93.3 (t, $J$ = 22.6 Hz), 66.9, 35.4, 32.2, 31.7, 31.3, 24.8, 13.2, 8.9, 8.8; HRMS $m/z$ (ESI) calcd for $C_{20}H_{19}F_2O_6$ $(M-H)^-$ 393.1155, found 393.1147.

*7,7-Difluoro-6,6-dihydroxy-1,1-dimethyl-5,8-dioxo-1,2,3,4,5,6,7,8-octahydrophenanthren-4-yl Benzoate (**4m**).* Yield: 63% (27 mg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 8.4 Hz, 1H), 7.93 (d, $J$ = 8.2 Hz, 3H), 7.55 (t, $J$ = 7.2 Hz, 1H), 7.40 (t, $J$ = 7.5 Hz, 2H), 6.76 (s, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 2.32−2.16 (m, 3H), 1.75 (m, 1H), 1.50 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 191.2, 183.4−182.9 (t, $J$ = 25.3 Hz), 166.6, 157.1, 134.9, 134.0 (2C), 133.4 (2C), 132.6, 131.4, 129.7 (2C), 128.6, 128.5, 93.7−93.2 (t, $J$ = 26.2 Hz), 67.6, 35.5, 32.4, 31.6, 31.4, 24.9; HRMS $m/z$ (ESI) calcd for $C_{23}H_{19}F_2O_6$ $(M-H)^-$ 429.1155, found 429.1174.

*7,7-Difluoro-6,6-dihydroxy-1,1-dimethyl-5,8-dioxo-1,2,3,4,5,6,7,8-octahydrophenanthren-4-yl 4-Methylbenzoate (**4n**).* Yield: 64% (28 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 8.4 Hz, 1H), 7.92 (d, $J$ = 8.4 Hz, 1H), 7.80 (d, $J$ = 8.2 Hz, 2H), 7.18 (d, $J$ = 8.0 Hz, 2H), 6.71 (s, 1H), 5.02 (s, 1H), 4.92 (s, 1H), 2.37 (s, 3H), 2.30−2.13 (m, 3H), 1.73 (m, 1H), 1.50 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 191.3, 183.2 (t, $J$ = 25.4 Hz), 166.8, 157.1, 144.3, 134.9, 133.9 (2C), 132.7, 131.3, 129.8, 129.2, 128.6 (2C), 126.8, 113.0−108.5 (t, $J$ = 254.8 Hz), 93.8−93.3 (t, $J$ = 25.7 Hz), 67.4, 35.5, 32.4, 31.6, 31.4, 24.9, 21.7; HRMS $m/z$ (ESI) calcd for $C_{24}H_{21}F_2O_6$ $(M-H)^-$ 443.1312, found 443.1312.

*7,7-Difluoro-6,6-dihydroxy-1,1-dimethyl-5,8-dioxo-1,2,3,4,5,6,7,8-octahydrophenanthren-4-yl 2-Naphthoate (**4o**).* Yield: 47% (23 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.48 (s, 1H), 8.28 (d, $J$ = 8.3 Hz, 1H), 7.98−7.80 (m, 5H), 7.55 (m, 2H), 6.80 (s, 1H), 4.85 (s, 1H), 4.75 (s, 1H), 2.36−2.17 (m, 3H), 1.83−1.73 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 191.2, 183.2 (t, $J$ = 25.3 Hz), 166.8, 157.2, 135.7, 135.1, 134.1, 132.5, 132.4, 131.5, 131.4, 129.4, 128.7, 128.6, 128.3, 127.8, 126.8, 126.8, 125.1, 112.6−108.9 (t, $J$ = 254.8 Hz), 93.7−93.3 (t, $J$ = 25.5 Hz), 67.9, 35.5, 32.5, 31.6, 31.4, 24.9; HRMS $m/z$ (ESI) calcd for $C_{27}H_{21}F_2O_6$ $(M-H)^-$ 479.1312, found 479.1317.

*2,2,4,4-Tetrafluoro-3,3-dihydroxy-8,8-dimethyl-3,4,5,6,7,8-hexahydrophenanthren-1(2H)-one (**4u**).* Yield: 90% (30 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.97 (d, $J$ = 8.5 Hz, 1H), 7.69 (d, $J$ = 8.3 Hz, 1H), 3.80 (s, 2H), 3.11 (t, $J$ = 5.6 Hz, 2H), 1.90−1.79 (m, 2H), 1.74−1.68 (m, 2H), 1.34 (s, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 182.5 (t, $J$ = 24.2 Hz), 156.5, 138.3, 131.2, 130.2 (t, $J$ = 22.7 Hz), 127.03 (t, $J$ = 6.3 Hz), 125.4, 116.7 (t, $J$ = 253.3 Hz), 109.4 (t, $J$ = 256.7 Hz), 92.2 (t, $J$ = 24.0 Hz), 38.0, 35.5, 31.9 (2C), 27.6 (t, $J$ = 5.4 Hz), 19.1; HRMS $m/z$ (ESI) calcd for $C_{16}H_{15}F_4O_3$ $(M-H)^-$ 331.0963, found 331.0959.

**Synthesis of Compounds 5 and 6.** A 10 mL sealed tube was charged with Tan-IIA substrates (0.1 mmol), DAST (0.3 mmol). Dry 1,4-dioxane (2.0 mL) was added, and the resulting mixture was stirred at 90 °C for 12 h. After cooling to room temperature, the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layer was washed with saturated NaCl aqueous solution, dried over $Na_2SO_4$, and concentrated *in vacuo* to give a yellow residue. The residue was purified by chromatography on silica gel column to furnish the desired compounds **5** and **6** as yellow solids.

*10,10-Difluoro-1,6,6-trimethyl-7,8,9,10-tetrahydrophenanthro-[1,2-b]furan-11(6H)-one (**5**).* Yield: 42% (13 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (d, $J$ = 8.1 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.24 (s, 1H), 3.13 (t, $J$ = 5.9 Hz, 2H), 2.19 (s, 3H), 1.84−1.75 (m, 2H), 1.70−1.60 (m, 2H), 1.30 (s, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 189.0 (t, $J$ = 26.3 Hz), 161.4, 149.6, 140.9, 139.1, 130.1, 128.4 (t, $J$ = 22.6 Hz), 121.8 (t, $J$ = 6.3 Hz), 120.0, 119.5, 115.2, 108.8 (t, $J$ = 248.4 Hz), 37.9, 34.4, 31.6 (2C), 26.7 (t, $J$ = 4.6 Hz), 18.7, 8.3; $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ −103.23 (s); HRMS $m/z$ (ESI) calcd for $C_{19}H_{19}F_2O_2$ $(M+H)^+$ 317.1335, found 317.1332.

*11,11-Difluoro-1,6,6-trimethyl-6,8,9,11-tetrahydrophenanthro-[1,2-b]furan-10(7H)-one (**6**).* Yield: 36% (11 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (d, $J$ = 8.1 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.24 (s, 1H), 3.13 (t, $J$ = 5.9 Hz, 2H), 2.19 (s, 3H), 1.84−1.75 (m, 2H), 1.70−1.60 (m, 2H), 1.30 (s, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 188.0 (t, $J$ = 25.5 Hz), 151.8 (t, $J$ = 11.34 Hz), 148.0, 142.7, 140.6, 133.6, 128.0 (t, $J$ = 2.52 Hz), 122.6, 120.2, 118.6, 115.3 (t, $J$ = 27.7 Hz), 107.2 (t, $J$ = 240.8 Hz), 37.5, 34.1, 31.4 (2C), 29.3, 18.7, 7.8; $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ −102.30; HRMS $m/z$ (EI) calcd for $C_{19}H_{18}F_2O_2$ $(M^+)$ 316.1275, found 316.1277.

*2,10,10-Trifluoro-1-hydroxy-1,6,6-trimethyl-1,6,7,8,9,10-hexahydrophenanthro[1,2-b]furan-11(2H)-one (trans-**7u**).* A 10 mL sealed tube was charged with **5** (0.1 mmol) and Selectfluor (0.3 mmol). MeCN/$H_2O$ (0.5 mL/0.5 mL) was added, and the resulting mixture was stirred at 80 °C for 20 min. After cooling to rt, the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layer was washed with saturated NaCl aqueous solution, dried over $Na_2SO_4$, and concentrated *in vacuo* to give a brown residue. The residue was purified by chromatography on silica gel column to furnish the desired compounds **7u** as a white solid in 34% yield (12 mg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.60 (s, 2H), 6.12 (d, $J$ = 60.3 Hz, 1H), 3.13 (t, $J$ = 6.0 Hz, 2H), 2.76 (s, 1H), 1.82 (m, 2H), 1.78 (d, $J$ = 4.5 Hz, 3H), 1.70 (t, $J$ = 5.1 Hz, 2H), 1.33 (s, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 180.9 (t, $J$ = 26.2 Hz), 170.3, 153.7, 139.8, 131.9 (t, $J$ = 22.7 Hz), 130.3, 122.9, 120.0 (t, $J$ = 5.9 Hz), 118.4 (d, $J$ = 245.2 Hz), 112.7, 108.4 (t, $J$ = 248.4 Hz), 80.0 (d, $J$ = 25.1 Hz), 38.1, 35.1, 32.0, 32.0, 27.0 (t, $J$ = 4.5 Hz), 19.4 (d, $J$ = 9.6 Hz), 18.9; $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ −101.43 − −103.19 (m), −130.57 − −130.63 (m), −130.70 − −130.75 (m); HRMS $m/z$ (ESI) calcd for $C_{19}H_{19}F_3O_3$ $(M+H)^+$ 353.1359, found 353.1365.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01064.

Copies of $^1$H and $^{13}$C NMR spectra for all products (PDF)

X-ray crystallographic data for compounds **4a** (CCDC 1544780), **5** (CCDC 1545567), **6** (CCDC 1545568), and **7u** (CCDC 1544777) (CIF)



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## AUTHOR INFORMATION


### Corresponding Authors

*Tel.: +86 (021) 50806035; Fax: +86 (021) 50806035; E-mail: chding@simm.ac.cn

* Tel.: +86 (021) 50806035; Fax: +86 (021) 50806035; E-mail: aozhang@simm.ac.cn

### ORCID

Chunyong Ding: 0000-0003-2379-8740

Ao Zhang: 0000-0001-7205-9202


### Notes

The authors declare no competing financial interest.

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