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Construction of Fluorinated Benzoxathiin Skeleton by Successive Perfluorophenylthiolation/Cyclization of Activated α-Methylene Ketones by Perfluorophenyl Diethylaminosulfur Difluoride

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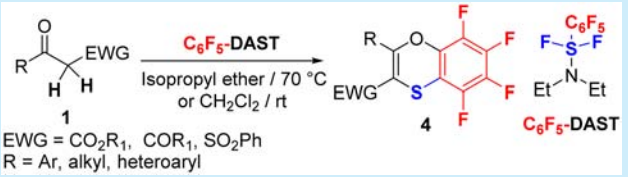
Supporting Information

ABSTRACT: Pharmaceutically attractive fluorinated benzoxathiin (thiaflavan) skeleton **4** was directly constructed by the reaction of activated α-methylene ketones **1** such as β-keto esters, 1,3-diketone, and β-keto sulfones with a perfluorophenyl analogue of diethylaminosulfur trifluoride, C_6F_5-DAST, in high yields via successive perfluorophenylthiolation/cyclization reaction.



Since the seminal work of fluorinated cortisones in the middle of the 20th century and the discovery of potent biological activity of new quinolones in the 1970s, fluorine-containing compounds have gained prominent positions in the drug development of pharmaceuticals and agrochemicals.[1,2] In particular, fluorinated heterocycles[3] are in great demand due to the successful history of heterocycles in the drug market. Thus, novel and efficient synthetic methods to access fluorinated heterocycles have been actively researched worldwide. One of the strategies to prepare fluorinated compounds is to use shelf-stable reagents for fluorination and fluoro-functionalization.[4] These reagents are easy to handle, are commercially available, and have efficient reactivity for organic reactions under conventional conditions, and they are now very popular in both academia and industry. Diethylaminosulfur trifluoride (DAST)[5] is an early, representative example in this field. DAST was developed as an easy to handle alternative to SF_4, and it is used for the direct transformation of the OH group to F. Recently, we discovered an unexpected reaction of DAST toward β-keto esters **1** to provide α-fluoro-α-aminothio-compounds **2** via a sequential electrophilic aminothiolation/fluoro-Pummerer rearrangement reaction.[6a,b] Moreover, the trifluoromethyl (CF_3) analogue of DAST, CF_3-DAST, showed a different type of reaction for the same substrates to provide α-trifluoromethylthiolation products **3** in high yields.[6a,c] Although many papers have been reported concerning the trifluoromethylthiolation reaction including electrophilic and nucleophilic approaches,[7−9] the CF_3-DAST method is rather different from others due to the viewpoint of the reaction mechanism.[7−9] Encouraged by the unique reactivity of DAST-type reagents,[6,10] we were interested in a perfluorophenyl (C_6F_5) analogue of DAST, C_6F_5-DAST, and found that biologically attractive fluorinated thiaflavan, skeleton (benzoxathiin) **4**, was directly constructed by the reaction of α-methylene ketones **1** with C_6F_5-DAST.

Namely, the reaction of activated acyclic α-methylene ketones such as β-keto esters, 1,3-diketone, and β-keto sulfones with C_6F_5-DAST gave tetra-fluorinated benzoxathiin derivatives via the continuous penta-fluorophenylation−cyclization pathway. Since the [1,4]-benzoxathiin/dihydrobenzoxathiin skeleton, also known as thiaflavan (thia-analogue of flavonoid and flavan), is present in a variety of compounds of biological interest,[11] including antihypertensive agents, antioxidants, estrogen receptor modulators, adrenoreceptor antagonists, and artificial sweeteners, fluorinated thiaflavan derivatives[12] should be useful drug candidates in medicinal chemistry research (Figure 1).

C_6F_5-DAST was prepared by the reaction of C_6F_5−$SiMe_3$ with DAST in the presence of $^iPr_2NEr$ and used directly for the next reaction without the need to be isolated.[6a] The formation of fluorinated [1,4]-benzoxathiin **4a** was steadily observed by

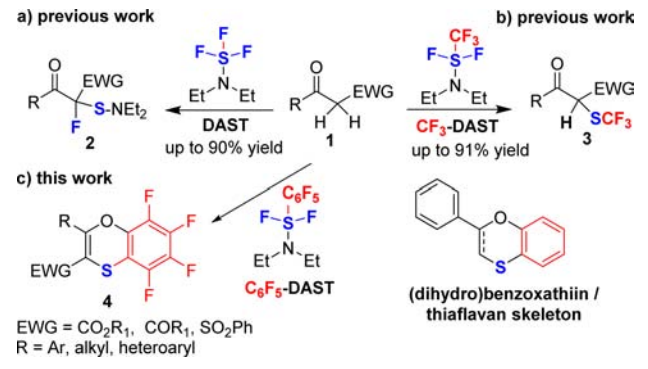


Figure 1. (a) Reaction of **1** with DAST (previous work); (b) reaction of **1** with CF_3-DAST (previous work); (c) reaction of **1** with C_6F_5-DAST (this work).

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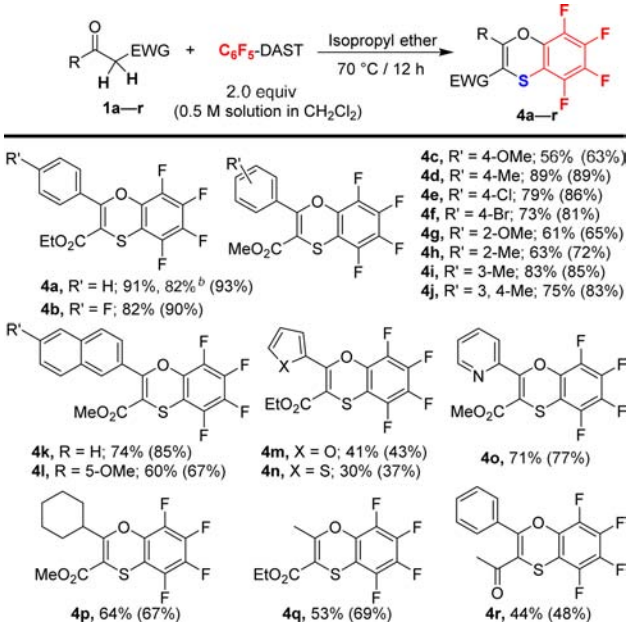
the reaction of **1a** with C_6F_5-DAST, while yields were dependent on the solvent, temperature, and conditions for the preparation of C_6F_5-DAST. After optimizing the reaction conditions (see Table S1 in Supporting Information (SI)), an excellent yield of 93% was obtained by the reaction of **1a** with 2.0 equiv of C_6F_5-DAST (prepared from DAST and C_6F_5–$SiMe_3$ in the presence of 1.2 equiv of $^iPr_2NEt$ in dichloromethane) in isopropyl ether at 70 °C for 12 h.

With the established optimal reaction conditions in hand, we expanded the substrate scope of *β*-keto esters, **1a–q** and 1,3-diketone **1r** (Scheme 1). Independent of the electronic nature

Scheme 1. Reaction of *β*-Keto Esters and 1,3-Diketone[a]



[a]The reaction of **1a–r** (0.2 mmol) with 2.0 equiv of C_6F_5-DAST (0.5 M mixture in CH_2Cl_2) was carried out in isopropyl ether at 70 °C for 12 h. For detailed reaction conditions, see SI. Yields are isolated yields. ^{19}F NMR yields with an internal standard, C_6H_5F, are also shown in parentheses. [b]The reaction was carried out with 1.0 mmol of **1a**.

of the substitution on the benzene ring of **1a–f** (H, F, OMe, Me, Br, Cl) and their different positions **1g–i** (2-OMe, 2-Me, 3-Me), corresponding products **4a–i** were obtained in good to excellent yields. The more electron-rich 3,4-dimethylbenzene substrate **1j** and naphthalene substrates **1k–l** also underwent the same transformations to give corresponding products **4j–l** in good to high yields. Heterocyclic substrates **1m–o** and nonaromatic substrates **1p–q** were suitable substrates for this transition to furnish desired products **4m–q** in good to high yields. It is interesting to note that this strategy was also effective for 1,3-diketone substrate **1r** to provide desired product **4r** in 48% yield. The structure of **4r** was unambiguously confirmed by single crystal X-ray structure analysis (CCDC 1524751, Figure 2).

We next examined the reaction of *β*-keto sulfones with C_6F_5-DAST. While the same reaction conditions were not suitable for this transformation of **1s**, desired compound **4s** was obtained in 66% yield after surveying reaction conditions (Table S2, in SI). The optimized conditions were selected: 2.0 equiv of C_6F_5-DAST at rt in CH_2Cl_2 for 12 h. Substrate scope for the transformation of *β*-keto sulfones **1s–w** having substituted phenyl, bulky naphthalenyl, and aliphatic cyclohexyl

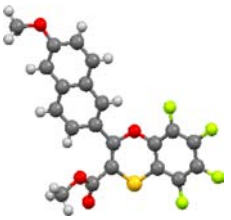
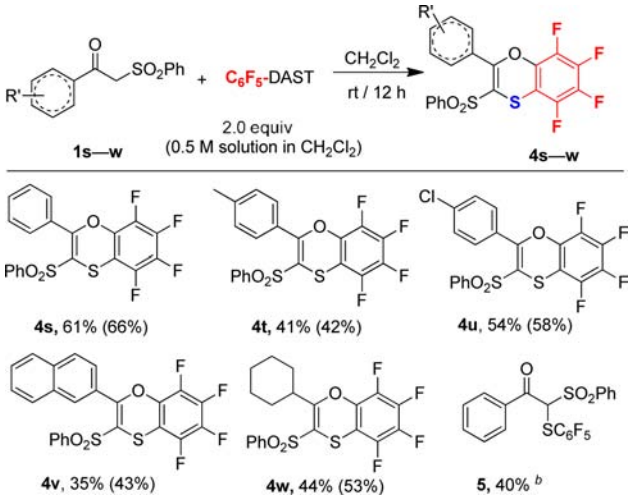


Figure 2. X-ray crystal structure of product **4l** (CCDC 1524751).

groups to corresponding fluorinated benzoxathiins are shown in Scheme 2. Benzoxathiins **4s–w** were obtained in moderate to

Scheme 2. Reaction of *β*-Keto Sulfones[a]

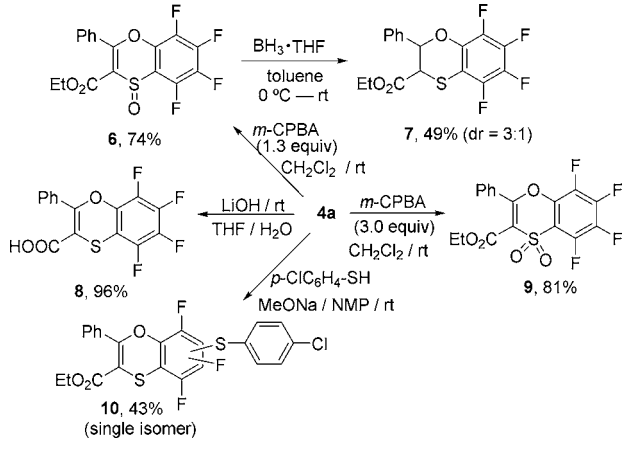


[a]The reaction of **1s–w** with 2.0 equiv of C_6F_5-DAST (0.5 M mixture in CH_2Cl_2) was carried out in dichloromethane at rt for 12 h. For detailed reaction conditions, see SI. Yields are isolated yields. ^{19}F NMR yields with an internal standard, C_6H_5F, are also shown in parentheses. [b]The reaction was carried out in CH_3CN at −20 °C for 4 h.

good yields. It should be noted that when the reaction of **1s** with C_6F_5-DAST was carried out at a low temperature of −20 °C for 4 h, acyclic *α*-perfluorophenylthio-*β*-keto sulfone **5** was obtained in 40% yield. This result suggests that acyclic **5** could be an intermediate for the formation of benzoxathiin **4s**.

To exemplify the synthetic utility of the benzoxathiins **4**, several transformations were attempted as shown in Scheme 3.

Scheme 3. Transformation of 4a



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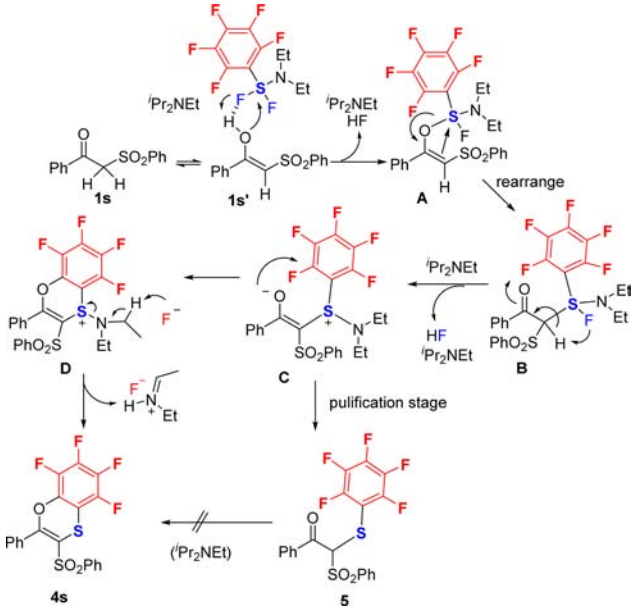
4a was successfully transformed into corresponding fluorinated thiaflavan **7** via its sulfoxide **6** by oxidation (74%) and reduction (49%). **4a** was also tolerated under hydrolysis by LiOH and oxidation by *m*-CPBA to provide acid **8** (96%) and sulfone product **9** (81%). It should be noted that one of the C−F bonds of **4a** was selectively substituted by the nucleophilic substitution reaction with *p*-chlorothiophenol to generate **10** in 43% yield as a single isomer (Scheme 3).

Since the compound **5** was suggested as an intermediate in Scheme 2, we attempted the cyclization of **5** to **4s**. Surprisingly, the acyclic sulfone **5** did not react in the presence or absence of $^{i}Pr_2NEt$ (1.5 equiv) in CH_2Cl_2 at rt, or in isopropyl ether at 70 °C, for 12 h (Scheme S1 in SI). We thus carefully investigated the reaction of **1s** to **4s** using ^{19}F, ^{1}H NMR and mass spectroscopy of the reaction mixture (Scheme S2 in SI), and the postulate reaction mechanism is depicted in Scheme 4 as

Scheme 4. Proposed Reaction Mechanism



exemplified from **1s** to **4s**. Initially, the enol oxygen of **1s′** derived from **1s** attacks the sulfur atom of C_6F_5-DAST to furnish an intermediate **A** by the elimination of HF. The enol **A** is rearranged to **B** via enol-keto tautomerization. The acidic proton in intermediate **B** is released as a HF salt of $^{i}Pr_2NEt$ with the reduction of sulfur(IV) to sulfur(III) to provide acyclic sulfonium salt **C**. A cyclization in **C** should occur via an intramolecular substitution at the fluorine atom by an enol oxygen to furnish sulfonium salt **D** followed by the elimination of *N*-ethylidene ethanamine with the release of HF via the reduction of sulfur(III) to sulfur(II) to provide the final product **4s**. Two equivalents of $^{i}Pr_2NEt$ should be required for trapping of HF in the initial and middle stages of this transformation. This is in good agreement with the use of 2 equiv of C_6F_5-DAST (prepared from DAST and $C_6F_5-SiMe_3$ in the presence of 1.2 equiv of $^{i}Pr_2NEt$) as the best condition. When the reaction was carried out at low temperature, the reaction stopped at the formation of **C** (Scheme S1), which converted to **5** by purification and isolation processes with silica-gel column chromatography (Scheme 2). It should be noted that the intermediate **C** is somewhat stable and it was tolerated under the workup process with water. The structure of **C** is supported by the ^{1}H and ^{19}F NMR and LC mass analysis of the crude reaction mixture. The crude **C** was gradually cyclized to **4s** even in an NMR tube in $CDCl_3$ at rt for 12 h with the formation of byproduct **5** (Figure S1 in SI).

In conclusion, a novel method for the construction of fluorinated benzoxathiin skeleton **4** was disclosed by the reaction of α-methylene-β-keto esters with C_6F_5-DAST in high yields. 1,3-Diketone and β-keto sulfones were also converted to benzoxathiin derivatives by C_6F_5-DAST in moderate to good yields. The benzoxathiin derivative is stable and quite tolerant to a variety of organic reaction conditions including oxidation, reduction, hydrolysis, and nucleophilic substitution providing corresponding compounds in good to high yields. A reaction mechanism was also proposed that involved successive perfluorophenylthiolation/cyclization. The biological activity of a series of benzoxathiins will be investigated soon.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03875.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2013. (b) Ojima, I. *Front Matter: Fluorine in Medicinal Chemistry and Chemical Biology*; John Wiley & Sons, Ltd.: Chichester, UK, 2009.

(2) (a) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (d) Huang, Y.-Y.; Yang, X.; Chen, Z.; Verpoort, F.; Shibata, N. *Chem. - Eur. J.* **2015**, *21*, 8664. (e) Champagne, A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. (f) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (g) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (h) Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev.* **2015**, *115*, 871. (i) Kawai, H.; Shibata, N. *Chem. Rec.* **2014**, *14*, 1024. (j) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (k) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (l) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(3) (a) Gakh, A. A; Kirk, K. L. *Fluorinated Heterocycles*; ACS symposium series; American Chemical Society: Washington, DC, 2009. (b) Weaver, G. In *Fluorinated Heterocyclic Compounds, Synthesis,*

DOI: 10.1021/acs.orglett.6b03875
Org. Lett. 2017, 19, 1012−1015

Chemistry and Applications; V. A., Petrov, Ed.; John Wiley & Sons, Ltd.: Hoboken, NJ, 2009. (c) Nenajdenko, V. *Fluorine in Heterocyclic Chemistry, Vols. 1 and 2*; Springer International Publishing: Switzerland, 2014.

(4) (a) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 65. (b) Shibata, N. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 1307. (c) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (d) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469. (e) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227. (f) Ismalaj, E.; Le Bars, D.; Billard, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 4790. (g) Groult, H.; Leroux, F.; Tressaud, A. Modern Synthesis Processes and Reactivity of Fluorinated Compounds, 1st ed., Vol. *3*; Tressaud, A., Editor-in-chief; Elsevier: France, 2017.

(5) (a) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, *1973*, 787. (b) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (c) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.

(6) (a) Saidalimu, I.; Suzuki, S.; Tokunaga, E.; Shibata, N. *Chem. Sci.* **2016**, *7*, 2106. (b) Saidalimu, I.; Guo, M.; Tokunaga, E.; Shibata, N. *Asian J. Org. Chem.* **2016**, *5*, 1208. (c) Saidalimu, I.; Suzuki, S.; Yoshioka, T.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2016**, *18*, 6404.

(7) (a) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (b) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (c) Xu, X. − H.; Shibata, N. *Yuki Gosei Kagaku Kyokaishi* **2013**, *71*, 1195.

(8) Selected examples of the electrophilic approach: (a) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782. (b) Chachignon, H.; Maeno, M.; Kondo, H.; Shibata, N.; Cahard, D. *Org. Lett.* **2016**, *18*, 2467. (d) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316. (e) Alazet, S.; Ismalaj, E.; Glenadel, Q.; Le Bars, D.; Billard, T. *Eur. J. Org. Chem.* **2015**, *2015*, 4607. (f) Xu, C.; Shen, Q. *Org. Lett.* **2014**, *16*, 2046. (g) Yang, T.; Lu, L.; Shen, Q. *Chem. Commun.* **2015**, *51*, 5479. (h) Xu, C.; Shen, Q. *Org. Lett.* **2015**, *17*, 4561. (i) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *J. Org. Chem.* **2008**, *73*, 9362. (j) Alazet, S.; Zimmer, L.; Billard, T. *J. Fluorine Chem.* **2015**, *171*, 78. (k) Alazet, S.; Ollivier, K.; Billard, T. *Beilstein J. Org. Chem.* **2013**, *9*, 2354. (l) Ferry, A.; Billard, T.; Bacqué, E.; Langlois, B. R. *J. Fluorine Chem.* **2012**, *134*, 160. (m) Alazet, S.; Ollivier, K.; Billard, T. *Beilstein J. Org. Chem.* **2013**, *9*, 2354. (n) Milandou, L. J. C. B.; Carreyre, H.; Alazet, S.; Greco, G.; Mingot, A. M.; Loumpangou, N.; Ouamba, J. − M.; Bouazza, F.; Billard, T.; Thibaudeau, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 169. (o) Zhu, D.; Shao, X.; Hong, X.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 15807.

(9) Selected examples of the nucleophilic approach: (a) Munavalli, S.; Bashir-Hashemi, A.; Rohrbaugh, D. K.; Durst, H. D. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 435. (b) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2003**, *119*, 101. (c) Kong, D.; Jiang, Z.; Xin, S.; Bai, Z.; Yuan, Y.; Weng, Z. *Tetrahedron* **2013**, *69*, 6046. (d) Li, S.-G.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 5898. (e) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1548. (f) Chen, C.; Chu, l.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 12454. (g) Lin, Q.; Chen, L.; Huang, Y.; Rong, M.; Yuan, Y.; Weng, Z. *Org. Biomol. Chem.* **2014**, *12*, 5500. (h) Chen, C.; Xu, X. − H.; Yang, B.; Qing, F.-L. *Org. Lett.* **2014**, *16*, 3372.

(10) Wang, Q.; Tang, X. Y.; Shi, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 10811.

(11) (a) Buzzini, P.; Menichetti, S.; Pagliuca, C.; Branda, E.; Turchetti. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3731. (b) Lodovici, M.; Menichetti, S.; Viglianisi, C.; Caldini, S.; Giuliani, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1957. (c) Salum, L. B.; Polikarpov, I.; Andricopulo, A. D. *J. Mol. Graphics Modell.* **2007**, *26*, 434. (d) Sasaki, T.; Takahashi, T.; Nagase, T.; Mizutani, T.; Ito, S.; Mitobe, Y.; Miyamoto, Y.; Kanesaka, M.; Yoshimoto, R.; Takenaga, N.; Tokita, S.; Sato, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4232. (e) Li, Y.; Doss, G. A.; Li, Y.; Chen, Q.; Tang, W.; Zhang, Z. *Chem. Res. Toxicol.* **2012**, *25*, 2368. (f) Zhuang, S.; Zhang, J.; Zhang, F.; Zhang, Z.; Wen, Y.; Liu, W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7298. (g) Zhang, Z.; Chen, Q.; Li, Y.; Doss, G. A.; Dean, B. J.; Ngui, J. S.; Elipe, M. S.; Kim, S.; Wu, J. Y.; DiNinno, F.; Hammond, M. L.; Stearns, R. A.; Evans, D. C.; Baillie, T. A.; Tang, W. *Chem. Res. Toxicol.* **2005**, *18*, 675. (h) Kim, S.; Wu, J. Y.; Zhang, Z.; Tang, W.; Doss, G. A.; Dean, B. J.; DiNinno, F.; Hammond, M. L. *Org. Lett.* **2005**, *7*, 411. (i) Blizzard, T. A.; Morgan, J. D.; Chan, W.; Birzin, E. T.; Pai, L.-Y.; Hayes, E. C.; DaSilva, C. A.; Mosley, R. T.; Yang, Y. T.; Rohrer, S. P.; DiNinno, F.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5124. (j) Menichetti, S.; Nativi, C.; Sarri, P.; Viglianisi, C. *J. Sulfur Chem.* **2004**, *25*, 317. (k) Kim, S.; Wu, J. Y.; Birzin, E. T.; Frisch, K.; Chan, W.; Pai, L. − Y.; Yang, Y. T.; Mosley, R. T.; Fitzgerald, P. M. D.; Sharma, N.; Dahllund, J.; Thorsell, A. − G.; DiNinno, R.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *J. Med. Chem.* **2004**, *47*, 2171. (l) Bassoli, A.; Drew, M. G. B.; Hattotuwagama, C. K.; Merlini, L.; Morini, G.; Wilden, G. R. H. *Quant. Struct.-Act. Relat.* **2001**, *20*, 3. (m) Bassoli, A.; Merlini, L.; Morini, G.; Vedani, A. *J. Chem. Soc., Perkin Trans. 2* **1998**, *2*, 1449.

(12) For the preparation of related fluorinated compounds, see: (a) Domagala, Z.; Kolinski, R. A.; Wiegat, J. *Roczniki Chemii* **1976**, *50*, 993. (b) Cacioli, P.; Reiss, J. A. *Aust. J. Chem.* **1984**, *37*, 2537. (c) Yu, C.; Hu, G.; Zhang, C.; Wu, R.; Ye, H.; Yang, G.; Shi, X. *J. Fluorine Chem.* **2013**, *153*, 33.

DOI: 10.1021/acs.orglett.6b03875
Org. Lett. 2017, 19, 1012−1015