Synthesis of Alkoxycarbonyldifluoromethyl-Substituted Semisquarates and Its Transformations

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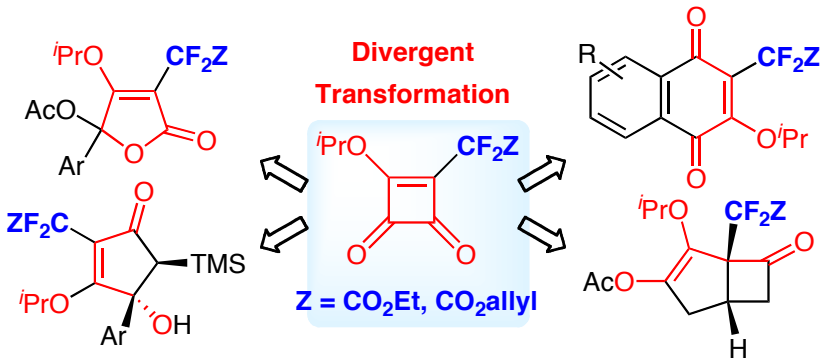

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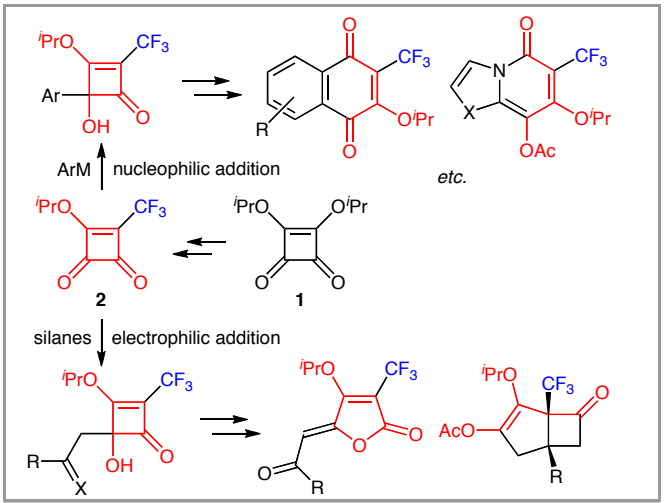
Abstract An EtO_2CCF_2-substituted semisquarate was newly synthesized from diisopropyl squarate by selective 1,2-addition of the Reformatsky reagent derived from $BrCF_2CO_2Et$ followed by rhenium-catalyzed allylic alcohol rearrangement. The compatibility of the highly reactive EtO_2CCF_2 group with ring transformations of the obtained semisquarate was investigated. Various EtO_2CCF_2-substituted, highly functionalized compounds, such as quinones, tetronates, cyclopentenones, and a bicyclo[3.2.0]heptenone, were successfully synthesized by the ring transformations of the EtO_2CCF_2-substituted semisquarate. In addition, an $allylO_2CCF_2$-substituted semisquarate was prepared and converted into the corresponding tetronate. Subsequently, palladium-catalyzed deallylation followed by condensation of the resultant carboxylic acid with several amines under mild conditions afforded the corresponding α,α-difluoroamides in good yields.

Key words squarate, ring expansion, fluorine, quinones, tetronates, cyclopentenones.

Fluorinated compounds often show better biological activities and pharmacokinetic properties compared to the nonfluorinated counterparts.[1] Thus, the introduction of fluorine-containing groups into bioactive molecules has emerged as a powerful strategy in drug discovery.[2] In particular, the trifluoromethyl (CF_3) group is one of the most widely used fluorine-containing groups because it significantly enhances membrane permeability and metabolic stability, leading to the development of an increasing number of trifluoromethylated pharmaceuticals. However, the trifluoromethylated pharmacophore is limited to (hetero)aromatics and alkenes because of the lack of structural variations in traditional CF_3-substituted building blocks (e.g., benzotrifluorides, trifluoroacetates, and trifluoroethanols).[3] In the past decade, various methods have been developed for the direct introduction of a trifluoromethyl group into bioactive molecules.[4]

Previously, we reported a CF_3-substituted semisquarate (CF_3-semisquarate) as a pluripotent building block for the skeletal-divergent synthesis of trifluoromethylated molecules (Scheme 1).[5] CF_3-semisquarate **2** was prepared by 1,2-selective trifluoromethylation of commercially available diisopropyl squarate (**1**) using the Ruppert–Prakash reagent (Me_3SiCF_3), and followed by Re-catalyzed 1,3-rearrangement of the resultant allylic alcohol. Notably, the CF_3-semisquarate could be successfully converted into hitherto inaccessible trifluoromethylated compounds, such as quinones, fused pyridones, tetronates, and bicyclo[3.2.0]heptenones, via nucleophilic or electrophilic derivatization to form a 4-hydroxycyclobutenone intermediate and subsequent ring expansion.

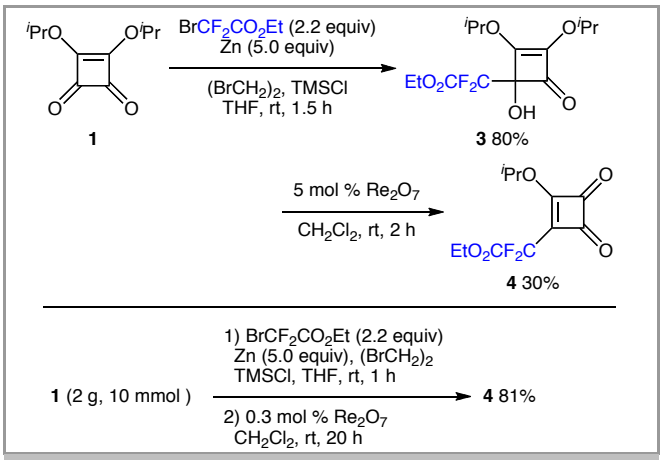


Scheme 1 Short-step synthesis of various trifluoromethylated compounds from CF_3-semisquarate.

To extend our pluripotent building block strategy, we focused on the synthesis of a new semisquarate building block bearing a

alkoxycarbonyldifluoromethyl group (RO_2CCF_2), because alkoxycarbonyldifluoromethyl groups have attracted much attention because of their simple introduction using readily available $BrCF_2CO_2R$[6] and easy conversion into other difluoromethylene-containing groups such as CF_2H,[7] CF_2CH_2OH,[8] and CF_2CONH_2.[9] Nevertheless, the selective transformation of compounds possessing an alkoxycarbonyldifluoromethyl group is a significant challenge in organic synthesis because the high reactivity of this group causes functional group incompatibility. Herein, we present an efficient synthesis of alkoxycarbonyldifluoromethyl-substituted semisquarates (RO_2CCF_2-semisquarates) and their transformation into various difluoromethylene-containing compounds.

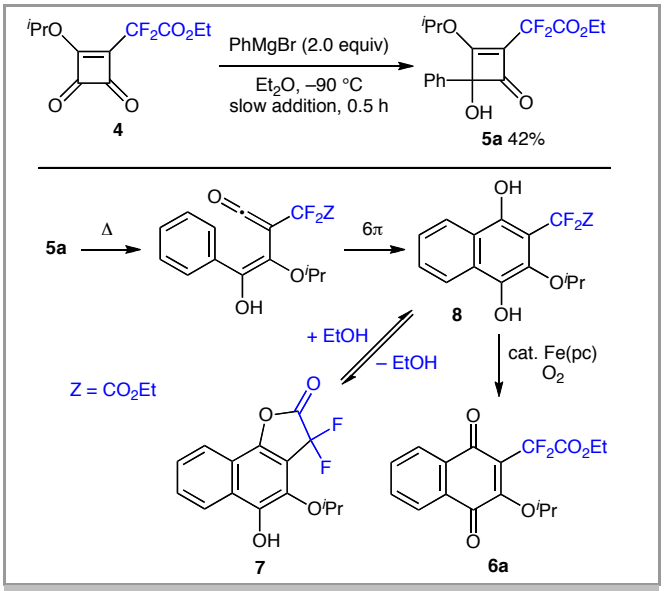
First, we investigated the introduction of an EtO_2CCF_2 group into diisopropyl squarate (**1**) by Reformatsky reaction using commercially available $BrCF_2CO_2Et$ (Scheme 2).[9] According to a previous report,[9a] a THF solution of squarate **1** and $BrCF_2CO_2Et$ (2.2 equiv) was added to a suspension of activated zinc powder (5.0 equiv) in THF at room temperature. After stirring for 1.5 h, the desired 4-hydroxycyclobutenone **3** was obtained in 80% yield. Next, **3** was treated with 5 mol % of Re_2O_7 in CH_2Cl_2 at room temperature for 2 h. ^1H NMR analysis of the crude product revealed the good purity of the expected EtO_2CCF_2-semisquarate **4**; however, isolation by distillation resulted in a moderate yield (30%). Notably, the yield of **4** increased to 81% when the synthesis was carried out on a 10 mmol scale, with a lower Re_2O_7 loading (0.3 mol %), and without purification of intermediate **3**. In this scale-up procedure, the amount of the Lewis-acidic rhenium catalyst could be reduced, suppressing the product decomposition during the distillation.



Scheme 2 Synthesis of EtO_2CCF_2-semisquarate **4**.

Regioselective 1,2-addition of aryl Grignard reagents in the presence the highly reactive EtO_2CCF_2 group is essential for the transformation of the obtained semisquarate. Thus, the reaction of **4** with PhMgBr was carried out by the strictly controlled addition procedure previously optimized for the CF_3-semisquarate (Scheme 3).[5a] PhMgBr (2.0 equiv) was slowly added to a solution of **4** in dry Et_2O using a syringe pump at –90 °C. Although reaction proceeded smoothly, purification by silica gel column chromatography afforded the expected product **5a** along with trace amounts of impurities. A final precipitation from hexane/$CHCl_3$ with sonication at room temperature afforded pure **5a** as a colorless solid in 42% yield.

The regioselectivity can be explained as PhMgBr added to the most reactive ketone carbonyl, which is conjugated to the EtO_2CCF_2 substituent through the double bond.

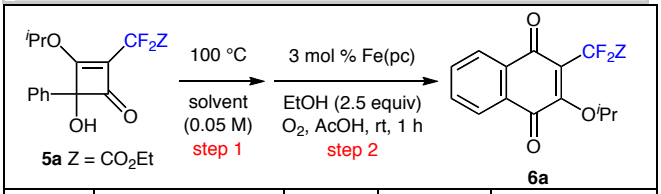


Scheme 3 Preparation of 4-hydroxycyclobutenone **5a** and its thermal ring expansion.

In view of the known anticancer activity of fluorine-containing naphthoquinones,[10] we have previously developed the synthesis of CF_3-substituted quinones by 1,2-selective arylation of the CF_3-semisquarate followed by thermal ring expansion of the resultant 4-aryl-4-hydroxycyclobutenones and Fe-catalyzed aerobic oxidation. In this study, we investigated the synthesis of EtO_2CCF_2-substituted naphthoquinone **6a** and found that the EtO_2CCF_2 substituent is problematic (Scheme 3 and Table 1). 4-Phenyl-4-hydroxycyclobutenone **5a** was heated in toluene at 100 °C for 2 h, and the solution was treated with 3 mol % of Fe(pc) (pc: phthalocyanine) under an oxygen atmosphere at room temperature for 1 h. In the event, the desired quinone **6a** was isolated in a low yield of 30% (Table 1, entry 1). Notably, a side product bearing no ethoxy signal was observed in the ^1H NMR spectrum of the crude products, suggesting the formation of lactone **7**. However, **7** was not isolated probably because of decomposition during silica gel column chromatography. Lactone **7** was produced by intramolecular transesterification of the EtO_2CCF_2 substituent with the phenolic hydroxyl group in hydroquinone intermediate **8** (Scheme 3). In order to suppress the formation of **7**, the aerobic oxidation was carried out in the presence of EtOH. As a result, the desired product **6a** was obtained in an improved yield of 46% (entry 2). When the thermolysis of **5a** was performed at a lower temperature (60 °C), a longer reaction time (24 h) was required (entry 3) to obtain an increased yield of **6a** (54%) along with only traces of **7**. This result suggests that a prolonged heating at 100 °C promoted the formation of **7**. Thus, the heating time was shortened using microwave irradiation. When **5a** was subjected to microwave irradiation in trifluorotoluene at 100 °C, the reaction was complete within 5 min, and **6a** was obtained in 61% yield (entry 4). Moreover, microwave heating under high dilution conditions afforded **6a** in 75% yield (entry 5). Conventional heating in

trifluorotoluene for a longer time of 2 h resulted in a lower yield (entry 6).

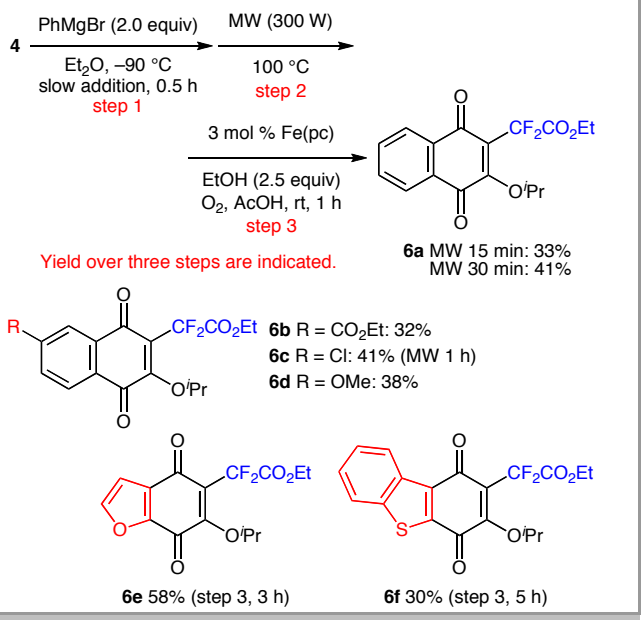
Table 1 Optimization of reaction conditions for the synthesis of quinone **6a**.



Entry	Solvent	MW	Time	Yield, %[a]
1[b]	toluene	No	2 h	30
2	toluene	No	2 h	46
3[c]	toluene	No	24 h	54
4[d]	trifluorotoluene	Yes	5 min	61
5[d,e]	trifluorotoluene	Yes	15 min	75
6	trifluorotoluene	No	2 h	53

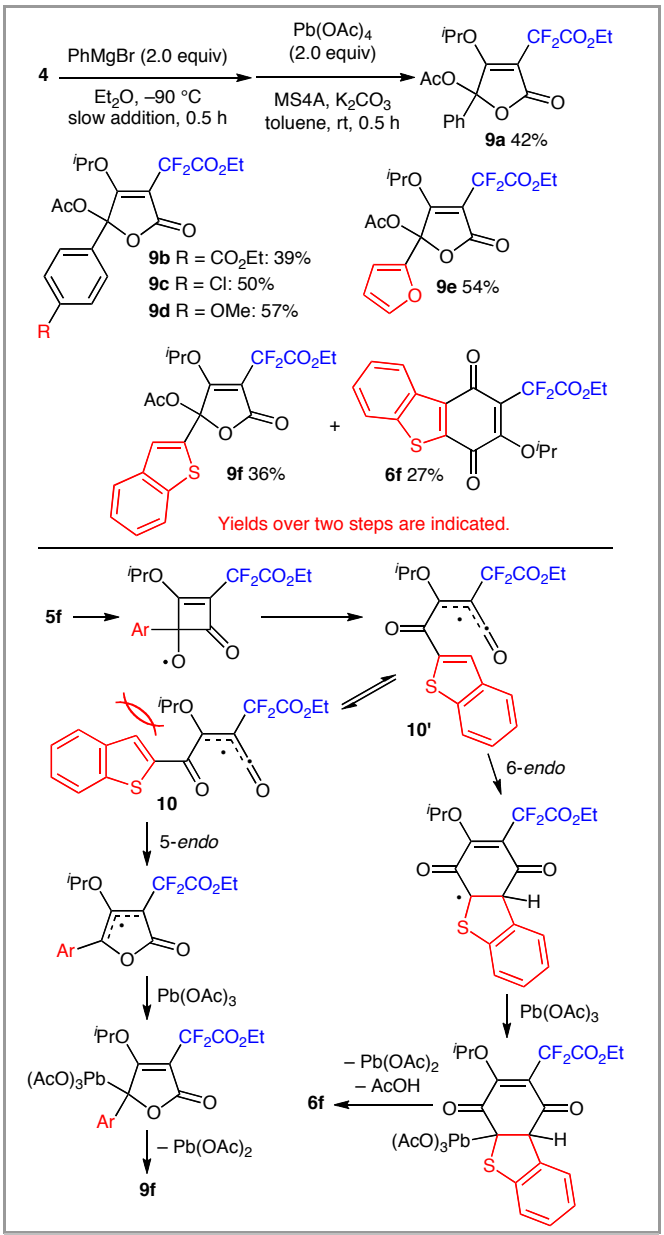
[a] Yields of isolated **6a**. [b] Without EtOH in step 2. [c] 60 °C in step 1. [d] Microwave heating (300 W) in step 1. [e] 0.01 M in step 1.

With the optimized conditions in hand, a telescoping procedure was investigated (Scheme 4). When crude **5a** was directly subjected to thermal ring expansion, subsequent aerobic oxidation afforded **6a** in 33% yield over three steps, and small amounts of unreacted **5a** were detected in the crude product mixture. Notably, prolonging the irradiation time to 30 min, the yield was improved to 41%. The scope of this three-step procedure was explored using different Grignard reagents. Aryl Grignard reagents bearing an ethoxycarbonyl, chloro, or methoxy group were compatible with this process, affording the corresponding quinones **6b–d** in 32–41% yields over three steps. It should be noted that thermal ring expansion of 4-(*p*-chlorophenyl)-4-hydroxycyclobutenone **5c** required a longer reaction time (1 h). Moreover, the use of 2-furyl and benzothiophen-2-yl Grignard reagents resulted in the formation of the corresponding heteroaromatic quinones **6e** and **6f** in 58% and 30% yields, respectively, even though prolonged reaction times (3–5 h) were required for aerobic oxidation.



Scheme 4 Three-step, telescoping synthesis of quinones **6a–f** from **4**.

Next, the oxidative ring expansion of 4-hydroxycyclobutenones **5** was investigated with the expectation that mild radical reaction conditions are compatible with the EtO_2CCF_2 group. (Scheme 5).[11] According to our previous report,[12] crude **5a** was treated with $Pb(OAc)_4$ (2.0 equiv) in toluene in the presence of MS 4A and K_2CO_3. As a result, the desired tetronate **9a** was obtained in 42% yield over two steps from **4**. Other derivatives bearing a substituted phenyl or 2-furyl group at the 5-position (**9b–e**) were also obtained in 39–57% yields. Interestingly, ring expansion of 4-(benzothiophen-2-yl)cyclobutenone **5f** gave the corresponding tetronate **9f** in 36% yield along with quinone **6f** in 27% yield.

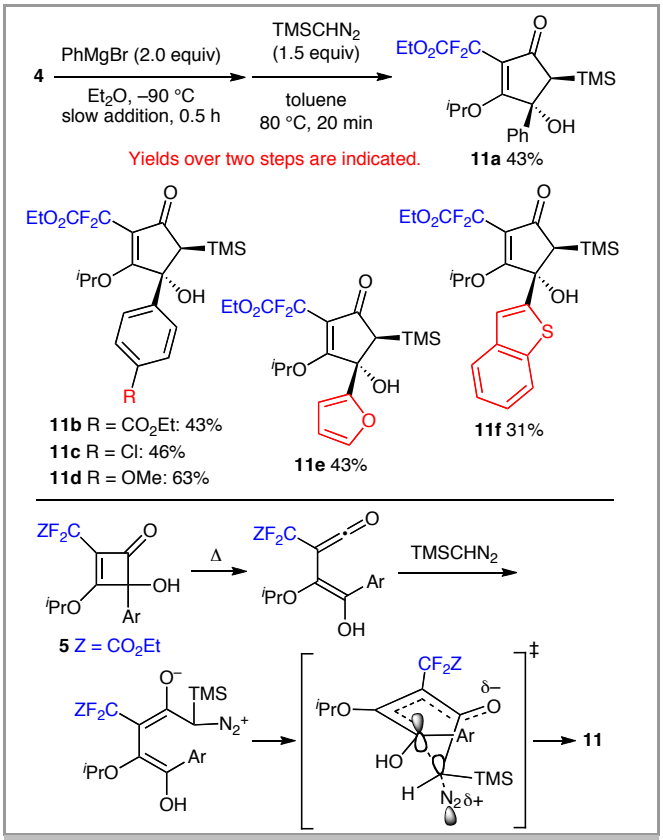


Scheme 5 Two-step, telescoping synthesis of tetronates **9a–f** from **4**.

The unexpected formation of **6f** can be rationalized according to the oxidative ring expansion mechanism proposed in a previous report (Scheme 5).[11] Single-electron oxidation of 4-hydroxycyclobutenone **5f** induces ring opening to generate delocalized ketenyl radical **10**, which undergoes 5-*endo* ring

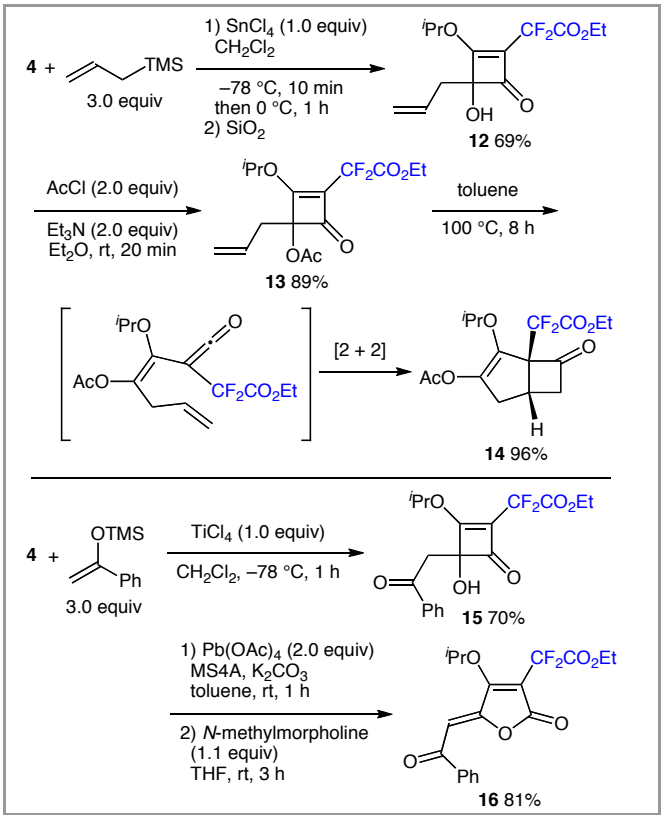
closure involving the ketone carbonyl group to afford the expected tetronate **9f**. At the same time, the steric repulsions between the isopropoxy group and benzothiophen-2-yl substituent leads to an increase in the population of conformer **10'**, which undergoes 6-*endo* ring closure to afford quinone **6f**.

Recently, Hu and co-workers reported the stereoselective transformation of 4-hydroxycyclobutenones into polysubstituted 5-(trimethylsilyl)cyclopentenones by formal [4 + 1] annulation with trimethylsilyldiazomethane (TMSD).[13] Because cyclopentenones are useful building blocks for the synthesis of bioactive molecules,[14] we applied this interesting reaction to the synthesis of EtO_2CCF_2-substituted cyclopentenone derivatives to examine the compatibility of the EtO_2CCF_2 group with thermal addition of TMSD (Scheme 6). According to Hu's report, crude 4-phenyl-4-hydroxycyclobutenone **5a** was treated with TMSD (1.5 equiv) in toluene at 80 °C for 20 min to afford the expected cyclopentenone **11a** in 43% yield over two steps from **4**. Thus, the addition of TMSD preferably occurred at the ketene moiety over the EtO_2CCF_2 group. Similarly, other 4-hydroxycyclobutenones **5b–f** were converted into the corresponding cyclopentenones **11b–f** in 31–63% yields. A good quality single crystal of **11f** suitable for X-ray diffraction analysis was obtained, which allowed unambiguous confirmation of structure (see Supporting Information). The observed relative configurations of **11f** was in good agreement with the mechanism originally proposed by Hu and co-workers.[13]



Scheme 6 Two-step synthesis of cyclopentenones **11a–f** from **4** and plausible mechanism of [4 + 1] annulation.

We previously demonstrated that the CF_3-semisquarate can be efficiently functionalized by electrophilic addition of unsaturated organosilanes.[5b] Thus, the compatibility of the EtO_2CCF_2 group with Lewis acid-promoted Hosomi–Sakurai-type allylation and Mukaiyama-type aldol reaction conditions was investigated (Scheme 7). The reaction of **4** with allytrimethylsilane (3.0 equiv) in the presence of $SnCl_4$ (1.0 equiv) in CH_2Cl_2 at –78 °C to 0 °C smoothly proceeded to afford 4-allyl-4-hydroxycyclobutenone **12** was in 69% yield after desilylation. Subsequent acetylation of **12** afforded **13** in 89% yield. Next, **13** was heated in toluene at 100 °C for 8 h to afford bicyclo[3.2.0]heptenone **14** in 96% yield.[15] The reaction of **4** with trimethyl((1-phenylvinyl)oxy)silane (3.0 equiv) was conducted using $TiCl_4$ (1.0 equiv) in CH_2Cl_2 at –78 °C for 1 h to afford 4-phenacyl-4-hydroxycyclobutenone **15** in 70% yield. Subsequent oxidative ring expansion of **15** using $Pb(OAc)_4$ followed by elimination of acetic acid using *N*-methylmorpholine afforded γ-alkylidenetetoronate **16** in 81% yield.

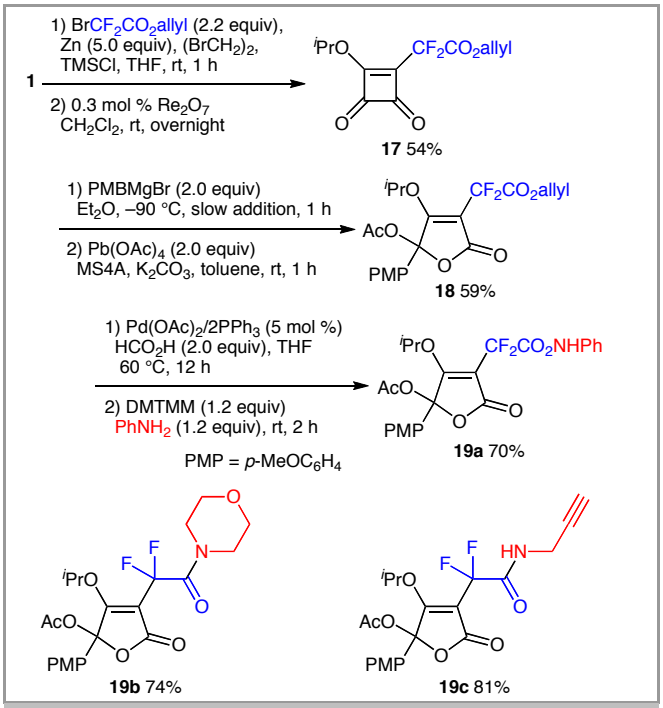


Scheme 7 Synthesis of bicyclo[3.2.0]heptenone **14** and γ-alkylidenetetoronate **16** from **4**.

Finally, we investigated the transformations of the alkoxycarbonyldifluoromethyl group. At the outset, transformation of the EtO_2CCF_2 group to HCF_2 was examined using tetronate **9d** as a model substrate. When **9d** was treated with $NaBH_4$ or $LiCl/H_2O$ following previously reported procedures,[8] no HCF_2-substituted product was detected, and decomposition of the starting material was observed. Unfortunately, the reaction with MeMgBr or NH_3/MeOH was also unsuccessful, and a complex mixture was obtained by hydrolysis with $K_2CO_3/MeOH/H_2O$.[8] Because deallylation proceeds under milder conditions under palladium catalysis, we

turned our attention to allyloxycarbonyldifluoromethyl groups. The required allylO_2CCF_2-semisquarate **17** was successfully synthesized from squarate **1** using $BrCF_2CO_2$allyl in 54% yield over two steps (Scheme 8). Various Tsuji–Trost-type deallylation methods[16] were examined; however, no desired HCF_2-semisquarate was obtained. Thus, we decided to focus on the late-stage decarboxylation of allylO_2CCF_2-tetronate **18**. Tetronate **18** was synthesized in 59% yield over two steps from **17** using the above procedure.

According to Miura's report,[17] **18** was treated with formic acid (2.0 equiv) in the presence of 5 mol % of $Pd(OAc)_2$ and 10 mol % of PPh_3 in THF at 60 °C for 12 h (Scheme 13). However, decarboxylation did not proceeded and the corresponding carboxylic acid was quantitatively obtained as determined by ^{1}H NMR of the crude reaction mixture. Because the carboxylic acid was found to be unstable on silica gel, the crude product was directly used for the subsequent amidation reaction. Using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as the promoter,[18] aniline and morpholine reacted with the carboxylic acid to afford the desired amides **19a** and **19b** in 70% and 74% yields, respectively. Notably, the reaction with propargylamine, which can be used for Huisgen triazole synthesis,[19] afforded **19c** in 81% yield.



Scheme 8 Synthesis of allylO_2CCF_2-semisquarate **17** and tetronate **18** and late-stage transformation of allylO_2CCF_2 group of tetronate **18**.

In conclusion, we have synthesized EtO_2CCF_2-semisquarate in a good yield in two steps from commercially available diisopropyl squarate. Subsequent transformation of the obtained EtO_2CCF_2-semisquarate into a variety of quinones, tetronates, cyclopentenones, and a bicyclo[3.2.0.]heptenone was accomplished by nucleophilic or electrophilic derivatization of the EtO_2CCF_2-semisquarate followed by ring expansion of the resultant 4-hydroxycyclobutenone. In addition, we successfully demonstrated the late-stage transformation of the allylO_2CCF_2 substituent of a tetronate into a R_2NOCCF_2 group under mild conditions.

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All air- and moisture sensitive reactions were performed under an argon atmosphere in dried glassware. Microwave irradiation experiments were carried out with a single-mode microwave reactor (CEM Discover LabMate) with open vessels and the temperature was monitored by an on-line IR detector. Analytical thin layer chromatography was performed using 0.25 mm silica gel plate (Merck TLC Silica gel 60 F_{254}). Column chromatography was performed on silica gel (Cica silica gel 60N) with eluents specified below. NMR spectra were recorded on JEOL ESC-400 spectrometer for samples in $CDCl_3$ solutions at 25 °C. ^{1}H NMR chemical shifts are reported in terms of chemical shift (δ, ppm) relative to the singlet at δ 7.26 ppm for chloroform. ^{13}C NMR spectra were fully decoupled and are reported in terms of chemical shift (δ, ppm) relative to the triplet at δ 77.0 ppm for $CDCl_3$. ^{19}F NMR spectra are reported in terms of chemical shift (δ, ppm) relative to the singlet at δ –63.7 ppm for α,α,α-trifluorotoluene as an external standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet. Coupling constants are reported in Hz. Infrared spectra were recorded on JASCO FT/IR-230 specrometer. High resolution mass spectra (HRMS) were obtained on JEOL JMS-T100LP mass spectrometer with ESI or DART-TOF modes. Diisopropyl squarate was synthesized[20] from squaric acid according to the reported procedure. 2-Furyl and 2-benzothienyl Grignard reagents were prepared according to the reported procedure.[21] Allyl 2-bromo-2,2-difluoroacetate was prepared according to the previously reported procedure.[22]

Ethyl 2,2-difluoro-2-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)acetate (3)

A mixture of zinc dust (163.5 mg, 2.5 mmol) and dibromoethane (8 μL) in dry THF (0.25 mL) was heated at 65 °C for 1 min and cooled to room temperature. To this mixture was added TMSCl (10 μL). After stirring for 15 min, a solution of **1** (99.1 mg, 0.5 mmol) and BrF_2CCO_2Et (141.1 μL, 1.1 mmol) in dry THF (3 mL) was added dropwise by cannula. The resultant mixture was stirred for 1.5 h at room temperature and quenched with sat. aq. NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (hexane/AcOEt, 4:1) to afford **3** (126.7 mg, 80% yield) as a colorless solid (mp 42–43 °C).

IR (neat): 3377 (O–H), 1776 (C=O), 1616 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.95 (sept, *J* = 6.4 Hz, 1 H), 4.93 (sept, *J* = 6.4 Hz, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 3.44 (s, 1 H), 1.41 (d, *J* = 6.4 Hz, 6 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.31 (d, *J* = 6.4 Hz, 3 H), 1.29 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.5, 162.5 (t, *J* = 31.5 Hz), 160.4, 135.2, 112.3 (t, *J* = 255.6 Hz), 86.3 (t, *J* = 28.1 Hz), 78.0, 74.4, 63.3, 22.5, 22.4, 22.3, 22.1, 13.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = –115.1.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}F_2O_6$: 323.1306; found: 323.1310.

Ethyl 2,2-difluoro-2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)acetate (4)

To a solution of **3** (58.3 mg, 0.18 mmol) in dry CH_2Cl_2 (2 mL) was added Re_2O_7 (4 mg, 8.3 μmol) at room temperature under an argon atmosphere. The solution was stirred at room temperature for 2 h. The reaction mixture was filtered through a pad of alumina under an argon stream. The filtrate was concentrated in vacuo and the obtained crude product was purified by bulb-to-bulb distillation (bp 110–120 °C/3 hPa) to afford **4** (14.2 mg, 30% yield) as a yellow oil.

IR (neat): 1805 (C=O), 1778 (C=O), 1613 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.51 (sept, *J* = 6.2 Hz, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 1.52 (d, *J* = 6.2 Hz, 6 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 196.0, 193.3, 186.2, 166.0 (t, *J* = 29.6 Hz), 160.8 (t, *J* = 32.5 Hz), 108.3 (t, *J* = 249.3 Hz), 82.6, 64.2, 22.6, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −106.3.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{11}H_{12}F_2O_5$: 263.0731; found: 263.0720.

Ethyl 2,2-difluoro-2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)acetate (4): Telescoping procedure

A mixture of zinc dust (3.27 g, 50 mmol) and dibromoethane (160 μL) in dry THF (5 mL) was heated at 65 °C for 1 min and cooled to room temperature. To this mixture was added TMSCl (200 μL) was added. After stirring for 15 min, a solution of **1** (1.98 g, 10 mmol) and BrF_2CCO_2Et (2.8 mL, 22 mmol) in dry THF (60 mL) was added dropwise by cannula. The mixture was stirred for 1 h at room temperature, and then, insoluble materials were filtered off (celaite, AcOEt). The solvent was removed and the resultant product was extracted with Et_2O (3 × 30 mL) and sat. aq. NH_4Cl (30 mL). The combined organic layer was washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to obtain crude **3**. To a solution of crude **3** in dry CH_2Cl_2 (40 mL) was added Re_2O_7 (14 mg, 29 μmol) at room temperature under an argon atmosphere. The solution was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of alumina under an argon stream (CH_2Cl_2). The filtrate was concentrated in vacuo and the obtained crude product was purified by bulb-to-bulb distillation (bp 110–120 °C/3 hPa) to afford **4** (2.12 g, 81% yield) as a yellow oil.

Ethyl 2,2-difluoro-2-(3-hydroxy-2-isopropoxy-4-oxo-3-phenylcyclobut-1-enyl)acetate (5a)

To a solution of **4** (525.3 mg, 2.0 mmol) in dry Et_2O (20 mL) was added PhMgBr (0.1 M in Et_2O, 40 mL, 1.0 mmol) at −90 °C under an argon atmosphere via syringe pump (40 mL/h). After stirring for 30 min, the reaction was quenched with sat. aq. NH_4Cl (30 mL) at −90 °C. After warming up to room temperature, the reaction mixture was extracted with AcOEt (3 × 30 mL). The combined organic layer was washed with brine (30 mL) and dried over Na_2SO_4. The solvents were evaporated in vacuo, and the obtained crude product was purified by silica gel column chromatography (hexane/$CHCl_3$, 1:3) to afford **5a** including trace impurities. Precipitation from hexane/$CHCl_3$ with sonication at room temperature afforded pure **5a** (288.0 mg, 42% yield) as a colorless solid (mp 74–75 °C).

IR (neat): 3384 (O–H), 1772 (C=O), 1621 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49–7.52 (m, 2 H), 7.36–7.43 (m, 3 H), 4.88 (sept, *J* = 6.0 Hz, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 3.73 (br s, 1 H), 1.43 (d, *J* = 6.0 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.17 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 184.4, 183.4, 162.2 (t, *J* = 32.9 Hz), 135.0, 128.8, 125.4, 116.6 (t, *J* = 29.6 Hz), 106.9 (t, *J* = 247.0 Hz), 93.6, 81.9, 63.7, 22.5, 22.1, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −101.9.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}F_2O_5$: 341.1201; found: 341.1195.

Ethyl 2,2-difluoro-2-(3-isopropoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate (6a)

In a 10 mL shield tube, a solution of **5a** (17.1 mg, 0.05 mmol) in trifluorotoluene (5 mL) was irradiated with a microwave reactor (300W output, 14–16 PSI) at 100 °C for 15 min under an argon atmosphere. After cooling to room temperature, the solution was transferred to 30 mL two-necked round bottom flask washed with trifluorotoluene (1 mL). To this solution was added EtOH (7 μL, 0.125 mmol), Fe(II) phthalocyanine complex (0.8 mg, 1.5 μmol) and AcOH (50 μL). The solution was stirred at room temperature under an oxygen atmosphere for 1 h. The solution was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 8:1) to afford **6a** (12.7 mg, 75% yield) as a yellow oil.

IR (neat): 1780 (C=O), 1683 (C=O), 1658 (C=O), 1600 (C=C), 1579 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.05–8.08 (m, 2 H), 7.72–7.80 (m, 2 H), 5.39 (sept, *J* = 6.0 Hz, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 1.42 (d, *J* = 6.0 Hz, 6 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 182.4, 181.6, 163.1 (t, *J* = 31.5 Hz), 160.0, 134.8, 133.8, 131.3, 131.0, 126.6, 126.5, 124.1 (t, *J* = 21.5 Hz), 111.6 (t, *J* = 251.3 Hz), 79.5, 62.9, 22.8, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −102.7.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}F_2O_5$: 339.1044; found: 339.1050.

Ethyl 2,2-difluoro-2-(3-isopropoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate (6a); Telescoping procedure

To a solution of **4** (52.9 mg, 0.2 mmol) in dry Et_2O (2 mL) was added PhMgBr (0.1 M in Et_2O, 4 mL, 0.4 mmol) at −90 °C under an argon atmosphere via syringe pump (8 mL/h). After stirring for 30 min, the reaction was quenched with sat. aq. NH_4Cl (10 mL) at −90 °C. The reaction mixture was extracted with AcOEt (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4 and the solvent was removed in vacuo. The obtained crude **5a** was transferred to 50 mL round-bottom flask fitted with a reflux condenser and trifluorotoluene (20 mL) was added. The solution was irradiated with a microwave reactor (300W output, ambient pressure) at 100 °C for 30 min under an argon atmosphere. After cooling to room temperature, to the solution was added EtOH (28 μL, 0.5 mmol), Fe(II) phthalocyanine complex (3.4 mg, 1.5 μmol) and AcOH (200 μL). The solution was stirred at room temperature under an oxygen atmosphere for 1 h. The solution was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 10:1) to afford **6a** (28.0 mg, 41% yield) as a yellow oil. Other quinones **6b–f** were synthesized according to this procedure.

Ethyl 7-(2-ethoxy-1,1-difluoro-2-oxoethyl)-6-isopropoxy-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylate (6b)

Yield: 26.4 mg (32%); brown oil.

IR (neat): 1780 (C=O), 1726 (C=O), 1684 (C=O), 1658 (C=O), 1604 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.70 (d, *J* = 1.0 Hz, 1 H), 8.39 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 5.41 (sept, *J* = 6.0 Hz, 1 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.42 (d, *J* = 6.0 Hz, 6 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 181.6, 181.2, 164.6, 163.0 (t, *J* = 31.5 Hz), 160.0, 136.2, 134.4, 133.5, 131.4, 127.7, 126.9, 124.5 (t, *J* = 21.5 Hz), 111.5 (t, *J* = 252.2 Hz), 79.8, 63.1, 62.0, 22.9, 14.2, 13.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −102.7.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{20}H_{24}F_2NO_7$: 428.1521; found: 428.1520.

Ethyl 2-(7-chloro-3-isopropoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate (6c)

Yield: 30.8 mg (41%); yellow oil.

IR (neat): 1780 (C=O), 1682 (C=O), 1658 (C=O), 1589 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.02 (d, *J* = 2.0 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 7.69 (dd, *J* = 8.0, 2.0 Hz, 1 H), 5.42 (sept, *J* = 6.0 Hz, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 1.41 (d, *J* = 6.0 Hz, 6 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 181.3, 180.6, 163.0 (t, *J* = 31.5 Hz), 160.1, 142.0, 133.9, 132.5, 129.2, 128.3, 126.6, 124.0 (t, *J* = 21.0 Hz), 111.5 (t, *J* = 252.2 Hz), 79.9, 63.1, 22.9, 13.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −102.7.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}ClF_2O_5$: 373.0654; found: 373.0631.

Ethyl 2,2-difluoro-2-(3-isopropoxy-7-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate (6d)

Yield: 28.5 mg (38%); yellow oil.

IR (neat): 1778 (C=O), 1674 (C=O), 1593 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.01 (d, *J* = 8.8 Hz, 1 H), 7.49 (d, *J* = 2.6 Hz, 1 H), 7.19 (dd, *J* = 8.8, 2.6 Hz, 1 H), 5.44 (sept, *J* = 6.0 Hz, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 3.94 (s, 3 H), 1.41 (d, *J* = 6.0 Hz, 6 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 182.4, 180.2, 165.0, 163.2 (t, *J* = 32.0 Hz), 160.5, 133.6, 129.2, 124.5, 123.6 (t, *J* = 21.5 Hz), 120.5, 111.6 (t, *J* = 251.3 Hz), 109.7, 79.5, 62.9, 56.0, 22.9, 13.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −102.6.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}F_2O_6$: 369.1150; found: 369.1142.

Ethyl 2,2-difluoro-2-(6-isopropoxy-4,7-dioxo-4,7-dihydrobenzofuran-5-yl)acetate (6e)

Yield: 37.8 mg (58%); yellow oil.

IR (neat): 1776 (C=O), 1691 (C=O), 1668 (C=O), 1567 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (d, *J* = 1.8 Hz, 1 H), 6.84 (d, *J* = 1.8 Hz, 1 H), 5.38 (sept, *J* = 6.3 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 1.39 (d, *J* = 6.3 Hz, 6 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 179.1, 170.4, 163.0 (t, *J* = 31.5 Hz), 159.2, 149.7, 149.3, 129.0, 111.5 (t, *J* = 251.7 Hz), 122.0 (t, *J* = 21.0 Hz), 108.6, 80.2, 63.0, 22.7, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −102.1.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{15}H_{18}F_2NO_6$: 346.1102; found: 346.1099.

Ethyl 2,2-difluoro-2-(3-isopropoxy-1,4-dioxo-1,4-dihydrodibenzo[*b*,*d*]thiophen-2-yl)acetate (6f)

Yield: 23.8 mg (30%); brown solid; mp 95–100 °C.

IR (neat): 1779 (C=O), 1670 (C=O), 1647 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.68–8.71 (m, 1 H), 7.90–7.94 (m, 1 H), 7.53–7.58 (m, 2 H), 5.36 (sept, *J* = 6.0 Hz, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 1.43 (d, *J* = 6.0 Hz, 6 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 180.2, 177.5, 163.1 (t, *J* = 32.0 Hz), 159.2, 142.82, 142.78, 135.4, 133.5, 128.8, 127.4, 127.2, 123.3 (t, *J* = 21.5 Hz), 122.9, 111.6 (t, *J* = 251.7 Hz), 79.9, 63.0, 22.8, 13.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −102.4.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}F_2O_5S$: 395.0765; found: 395.0749.

Ethyl 2-(5-acetoxy-4-isopropoxy-2-oxo-5-phenyl-2,5-dihydrofuran-3-yl)-2,2-difluoroacetate (9a)

To a solution of **4** (129.5 mg, 0.49 mmol) in dry Et_2O (5 mL) was added PhMgBr (0.1 M in Et_2O, 10 mL, 1.0 mmol) at −90 °C under an argon atmosphere via syringe pump (20 mL/h). After stirring for 1 h, the reaction was quenched with sat. aq. NH_4Cl (20 mL) at −90 °C. The reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to afford crude **5a**. To a suspension of pulverized MS4A (500 mg), $Pb(OAc)_4$ (443.5 mg, 1.0 mmol) and K_2CO_3 (277.0 mg, 2.0 mmol) in toluene (2 mL) was added by cannulation a solution of crude **5a** prepared above in toluene (3 mL). The mixture was stirred for 30 min at room temperature under an argon atmosphere. The reaction was quenched with H_2O (20 mL) and insoluble materials were filtered through a pad of Celite, and the residue was washed with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine (20 mL), and dried over Na_2SO_4. The solvents were evaporated in vacuo, and the crude product was purified by column chromatography (hexane/AcOEt, 6:1) to afford **9a** (82.0 mg, 42 % yield) as a pale yellow solid (mp 45–51 °C). Other tetronates **9b–f** were synthesized according to this procedure.

IR (neat): 1780 (C=O), 1654 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.50–7.53 (m, 2 H), 7.40–7.45 (m, 3 H), 5.03 (sept, *J* = 6.0 Hz, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 2.20 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.9, 167.6, 166.6 (t, *J* = 6.2 Hz), 162.0 (t, *J* = 32.4 Hz), 133.7, 130.2, 128.6, 125.5, 109.9 (t, *J* = 245.5 Hz), 100.7, 95.5 (t, *J* = 29.1 Hz), 81.4 (t, *J* = 5.7 Hz), 63.6, 22.1, 21.8, 21.1, 13.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −95.9.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{19}H_{24}F_2NO_7$: 416.1521; found: 416.1509.

Ethyl 4-(2-acetoxy-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3-isopropoxy-5-oxo-2,5-dihydrofuran-2-yl)benzoate (9b)

Yield: 93.6 mg (42%); yellow oil.

IR (neat): 1783 (C=O), 1721 (C=O), 1657 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.09 (d, *J* = 8.6 Hz, 2 H), 7.59 (d, *J* = 8.6 Hz, 2 H), 5.05 (sept, *J* = 6.0 Hz, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.21 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 1.35 (d, *J* = 6.4 Hz, 3 H), 1.15 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.3, 167.4, 166.4 (t, *J* = 6.2 Hz), 165.6, 161.8 (t, *J* = 32.0 Hz), 138.2, 132.1, 129.7, 125.5, 109.8 (t, *J* = 246.0 Hz), 100.3, 95.6 (t, *J* = 29.6 Hz), 81.8 (t, *J* = 5.7 Hz), 63.6, 61.2, 22.0, 21.7, 21.0, 14.2, 13.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −95.7.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{22}H_{28}F_2NO_9$: 488.1732; found: 488.1732.

Ethyl 2-(5-acetoxy-5-(4-chlorophenyl)-4-isopropoxy-2-oxo-2,5-dihydrofuran-3-yl)-2,2-difluoroacetate (9c)

Yield: 104.4 mg (49%); yellow oil.

IR (neat): 1781 (C=O), 1654 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.46 (d, *J* = 9.2 Hz, 4 H), 7.40 (d, *J* = 9.2 Hz, 2 H), 5.06 (sept, *J* = 6.0 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2 H), 2.19 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.35 (d, *J* = 6.0 Hz, 3 H), 1.19 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.4, 167.5, 166.4 (t, *J* = 6.2 Hz), 161.9 (t, *J* = 32.4 Hz), 136.4, 132.4, 129.0, 128.9, 127.0, 109.8 (t, *J* = 246.0 Hz), 100.2, 95.5 (t, *J* = 29.6 Hz), 81.7 (t, *J* = 6.2 Hz), 63.6, 22.1, 21.9, 21.1, 13.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −95.6.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{19}H_{23}ClF_2NO_7$: 450.1131; found: 450.1139.

Ethyl 2-(5-acetoxy-4-isopropoxy-5-(4-methoxyphenyl)-2-oxo-2,5-dihydrofuran-3-yl)-2,2-difluoroacetate (9d)

Yield: 119.4 mg (57%); yellow oil.

IR (neat): 1779 (C=O), 1655 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.44 (d, *J* = 9.2 Hz, 2 H), 6.93 (d, *J* = 9.2 Hz, 2 H), 5.04 (sept, *J* = 6.0 Hz, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 3.83 (s, 3 H), 2.18 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.0, 167.6, 166.6 (t, *J* = 5.8 Hz), 162.0 (t, *J* = 32.4 Hz), 160.9, 126.9, 125.4, 113.9, 109.9 (t, *J* = 245.6 Hz), 100.6, 95.3 (t, *J* = 29.1 Hz), 81.2 (t, *J* = 5.3 Hz), 63.4, 55.2, 22.0, 21.8, 21.0, 13.6.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −95.9.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{20}H_{26}F_2NO_8$: 446.1627; found: 446.1602.

Ethyl 2-(2-acetoxy-3-isopropoxy-5-oxo-2,5-dihydro-[2,2'-bifuran]-4-yl)-2,2-difluoroacetate (9e)

Yield: 81.1 mg (42%); yellow solid; mp 40–44 °C.

IR (neat): 1782 (C=O), 1662 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (dd, *J* = 1.6, 1.2 Hz, 1 H), 6.64 (dd, *J* = 3.0, 1.2 Hz, 1 H), 6.44 (dd, *J* = 3.0, 1.6 Hz, 1 H), 5.12 (sept, *J* = 6.0 Hz, 1 H),

4.41 (q, *J* = 7.2 Hz, 2 H), 2.19 (s, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.28 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.0, 167.2, 165.7 (t, *J* = 5.7 Hz), 162.0 (t, *J* = 32.5 Hz), 145.5, 144.2, 110.9, 110.4, 109.8 (t, *J* = 246.0 Hz), 97.0, 96.5 (t, *J* = 29.6 Hz), 81.4 (t, *J* = 4.8 Hz), 63.6, 22.16, 22.13, 21.1, 13.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −96.8.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{17}H_{22}F_2NO_8$: 406.1314; found: 406.1305.

Ethyl 2-(5-acetoxy-5-(benzo[b]thiophen-2-yl)-4-isopropoxy-2-oxo-2,5-dihydrofuran-3-yl)-2,2-difluoroacetate (9f)

Yield: 76.5 mg (36%); orange solid; mp 101–104 °C.

IR (neat): 1781 (C=O), 1657 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78–7.86 (m, 2 H), 7.52 (s, 1 H), 7.38–7.42 (m, 2 H), 5.15 (sept, *J* = 6.0 Hz, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 2.21 (s, 3 H), 1.388 (t, *J* = 7.2 Hz, 3 H), 1.386 (d, *J* = 6.0 Hz, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.7, 167.3, 165.7 (t, *J* = 5.8 Hz), 161.9 (t, *J* = 32.5 Hz), 140.1, 138.4, 136.6, 125.6, 124.8, 124.5, 123.8, 122.3, 109.9 (t, *J* = 246.0 Hz), 99.4, 95.4 (t, *J* = 29.6 Hz), 81.9 (t, *J* = 5.7 Hz), 63.6, 22.2, 22.0, 21.1, 13.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −95.4 (d, *J* = 271.5 Hz), −96.2 (d, *J* = 271.5 Hz).

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{21}H_{24}F_2NO_7S$: 472.1242; found: 472.1216.

Ethyl 2,2-difluoro-2-((3R*,4S*)-3-hydroxy-2-isopropoxy-5-oxo-3-phenyl-4-(trimethylsilyl)cyclopent-1-en-1-yl)acetate (11a)

To a solution of **4** (127.6 mg, 0.49 mmol) in dry Et_2O (5 mL) was added PhMgBr (0.1 M in Et_2O, 10 mL, 1.0 mmol) at −90 °C under an argon atmosphere via syringe pump (20 mL/h). After stirring for 40 min, the reaction was quenched with sat. aq. NH_4Cl (20 mL) at −90 °C. The reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to afford crude **5a**. To a solution of crude **5a** prepared above in dry toluene (6.25 mL) was added $TMSCHN_2$ (1.25 mL, 0.75 mmol). The mixture was stirred for 20 min at 80 °C under an argon atmosphere. The mixture was concentrated in vacuo, and the obtained crude product was purified by column chromatography (hexane/AcOEt, 6:1) to afford **11a** (87.6 mg, 42% yield) as a yellow solid (mp 115–126 °C). Other cyclopentenes **11b–f** were synthesized according to this procedure.

IR (neat): 3422 (O–H), 1778 (C=O), 1672 (C=O), 1618 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.47 (m, 5 H), 5.01 (sept, *J* = 6.0 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 2.62 (s, 1 H), 2.53 (d, *J* = 1.2 Hz, 1 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 1.23 (d, *J* = 6.0 Hz, 3 H), 0.97 (d, *J* = 6.0 Hz, 3 H), −0.23 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.7, 186.0, 163.3 (t, *J* = 32.4 Hz), 140.0, 128.4, 128.2, 126.0, 112.0 (t, *J* = 25.3 Hz), 110.7 (t, *J* = 246.0 Hz), 81.6, 63.0, 57.0, 22.7, 21.6, 13.8, −1.20.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.6 (d, *J* = 277.3 Hz), −102.0 (d, *J* = 277.3 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{21}H_{29}F_2O_5Si$: 427.1752; found: 427.1763.

Ethyl 4-((1R*,5S*)-3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-hydroxy-2-isopropoxy-4-oxo-5-(trimethylsilyl)cyclopent-2-en-1-yl)benzoate (11b)

Yield: 107.2 mg (44%); yellow solid; mp 143–145 °C.

IR (neat): 3431 (O–H), 1778 (C=O), 1719 (C=O), 1692 (C=O), 1622 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07 (d, *J* = 9.2 Hz, 2 H), 7.57 (m, 2 H), 4.98 (sept, *J* = 6.0 Hz, 1 H), 4.398 (q, *J* = 7.6 Hz, 2 H), 4.396 (q, *J* = 7.2 Hz, 2 H), 2.88 (br s, 1 H), 2.56 (s, 1 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 1.39 (t, *J* = 7.6 Hz, 3 H), 1.22 (d, *J* = 6.0 Hz, 3 H), 1.00 (br s, 3 H), −0.22 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.4, 185.5, 166.2, 163.2 (t, *J* = 32.5 Hz), 145.3, 130.2, 129.6, 126.2, 112.2 (t, *J* = 24.8 Hz), 110.6 (t, *J* = 246.0 Hz), 81.5, 77.7, 63.0, 61.2, 56.9, 22.6, 21.7, 14.2, 13.8, −1.16.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.4 (d, *J* = 277.3 Hz), −102.0 (d, *J* = 277.3 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{24}H_{33}F_2O_7Si$: 499.1964; found: 499.1969.

Ethyl 2-((3S*,4R*)-3-(4-chlorophenyl)-3-hydroxy-2-isopropoxy-5-oxo-4-(trimethylsilyl)cyclopent-1-en-1-yl)-2,2-difluoroacetate (11c)

Yield: 103.0 mg (45%); yellow solid; mp 120–126 °C.

IR (neat): 3419 (O–H), 1777 (C=O), 1673 (C=O), 1621 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.43 (m, 4 H), 5.00 (sept, *J* = 6.0 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 2.83 (br s, 1 H), 2.54 (s, 1 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.24 (d, *J* = 6.0 Hz, 3 H), 1.03 (d, *J* = 6.0 Hz, 3 H), −0.20 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.7, 185.6, 163.3 (t, *J* = 32.9 Hz), 138.8, 134.1, 128.5, 127.6, 112.1 (t, *J* = 24.8 Hz), 110.6 (t, *J* = 246.0 Hz), 81.3, 77.7, 63.1, 56.9, 22.6, 21.7, 13.8, −1.16.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.3 (d, *J* = 277.1 Hz), −101.8 (d, *J* = 277.1 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{21}H_{28}ClF_2O_5Si$: 461.1363; found: 461.1365.

Ethyl 2,2-difluoro-2-((3R*,4S*)-3-hydroxy-2-isopropoxy-3-(4-methoxyphenyl)-5-oxo-4-(trimethylsilyl)cyclopent-1-en-1-yl)acetate (11d)

Yield: 140.7 mg (63%); yellow solid; mp 124–125 °C.

IR (neat): 3425 (O–H), 1777 (C=O), 1672 (C=O), 1617 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37 (br d, *J* = 8.0 Hz 2 H), 6.90 (d, *J* = 9.2 Hz, 2 H), 5.03 (sept, *J* = 6.0 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 3.83 (s, 3 H), 2.64 (br s, 1 H), 2.51 (d, *J* = 1.6 Hz, 1 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.24 (d, *J* = 6.0 Hz, 3 H), 0.98 (dd, *J* = 6.0, 1.6 Hz, 3 H), −0.21 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.6, 185.8, 163.3 (t, *J* = 32.4 Hz), 159.4, 132.0, 127.3, 113.6, 111.8 (t, *J* = 24.8 Hz), 110.7 (t, *J* = 246.0 Hz), 81.5, 77.6, 62.9, 56.9, 55.3, 22.7, 21.8, 13.9, −1.12.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.7 (d, *J* = 277.1 Hz), −102.1 (d, *J* = 277.1 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{22}H_{31}F_2O_6Si$: 457.1858; found: 457.1863.

Ethyl 2,2-difluoro-2-((3R*,4S*)-3-(furan-2-yl)-3-hydroxy-2-isopropoxy-5-oxo-4-(trimethylsilyl)cyclopent-1-en-1-yl)acetate (11e)

Yield: 87.2 mg (43%); yellow solid; mp 142–144 °C.

IR (neat): 3392 (O–H), 1772 (C=O), 1669 (C=O), 1620 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39 (dd, *J* = 2.0, 1.2 Hz, 1 H), 6.40–6.43 (m, 2 H), 5.08 (sept, *J* = 6.0 Hz, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 2.84 (s, 1 H), 2.51 (d, *J* = 2.0 Hz, 1 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.24 (d, *J* = 6.0 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H), −0.09 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.1, 183.3, 163.2 (d, *J* = 32.4 Hz), 152.8, 141.4, 111.7 (d, *J* = 24.8 Hz), 111.4, 110.5 (t, *J* = 245.6 Hz), 108.2, 78.9, 77.9, 62.9, 54.9, 22.6, 22.1, 13.8, −1.98.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −98.7 (d, *J* = 277.3 Hz), −99.9 (d, *J* = 277.3 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{19}H_{27}F_2O_6Si$: 417.1545; found: 417.1551.

Ethyl 2-((3R*,4S*)-3-(benzo[b]thiophen-2-yl)-3-hydroxy-2-isopropoxy-5-oxo-4-(trimethylsilyl)cyclopent-1-en-1-yl)-2,2-difluoroacetate (11f)

Yield: 64.0 mg (27%); yellow solid; mp 115–117 °C.

IR (neat): 3413 (O–H), 1776 (C=O), 1674 (C=O), 1619 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (d, *J* = 6.4 Hz, 1 H), 7.72 (dd, *J* = 6.4, 2.0 Hz 1 H), 7.32–7.40 (m, 2 H), 7.20 (s, 1 H), 5.15 (sept, *J* = 6.0 Hz, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 3.16 (br s, 1 H), 2.64 (d, *J* = 1.6 Hz, 1 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.28 (d, *J* = 6.0 Hz, 3 H), 1.14 (d, *J* = 6.0 Hz, 3 H), −0.10 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 199.4 (d, *J* = 1.9 Hz), 184.2, 163.2 (t, *J* = 32.5 Hz), 146.1, 139.4, 139.2, 124.63, 124.57, 123.6, 122.4, 121.2, 111.4 (t, *J* = 25.3 Hz), 110.6 (t, *J* = 246.0 Hz), 81.0, 78.9, 63.1, 56.3, 22.7, 22.1, 13.9, −1.34.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −98.4 (d, *J* = 277.3 Hz), −101.4 (d, *J* = 277.3 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{23}H_{29}F_2O_5SSi$: 483.1473; found: 483.1485.

Ethyl 2-(3-allyl-3-hydroxy-2-isopropoxy-4-oxocyclobut-1-en-1-yl)-2,2-difluoroacetate (12)

To a solution of **4** (78.4 mg, 0.3 mmol) in dry CH_2Cl_2 (2.0 mL) was added $SnCl_4$ (1.0 M in CH_2Cl_2, 300 µL, 0.3 mmol) at −78 °C under an argon atmosphere. After stirring for 10 min, allyltrimethylsilane (142 µL, 0.9 mmol) was added to the reaction mixture. The reaction mixture was further stirred for 10 min at −78 °C and then 1 h at 0 °C. The reaction was quenched with H_2O (10 mL). After warming to room temperature, the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. To the obtained crude product was added silica gel (500 mg) and CH_2Cl_2 (1 mL). The mixture was stirred for 30 min and then concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 4:1) to afford **12** (63.3 mg, 69% yield) as a colorless oil.

IR (neat): 3398 (O–H), 1770 (C=O), 1618 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.78 (ddt, *J* = 17.2, 9.6, 7.6 Hz, 1 H), 5.19–5.24 (m, 2 H), 5.00 (sept, *J* = 6.0 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 2.96 (br s, 1 H), 2.67 (dd, *J* = 14.2, 7.2 Hz, 1 H), 2.61 (dd, *J* = 14.2, 7.6 Hz, 1 H), 1.47 (d, *J* = 6.4 Hz, 6 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 186.6, 184.1, 162.1 (t, *J* = 33.4 Hz), 130.7, 120.1, 113.7 (t, *J* = 29.1 Hz), 106.6 (t, *J* = 247.0 Hz), 91.7, 81.8, 63.6, 37.4, 22.4, 22.2, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −100.3.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{14}H_{19}F_2O_5$: 305.1201; found: 305.1205.

Ethyl 2-(3-acetoxy-3-allyl-2-isopropoxy-4-oxocyclobut-1-en-1-yl)-2,2-difluoroacetate (13)

To a solution of **12** (61.8 mg, 0.2 mmol) in dry Et_2O (2 mL) was added Et_3N (55 µL, 0.4 mmol) and AcCl (28 µL, 0.4 mmol) at room temperature under an argon atmosphere. After stirring for 20 min, the reaction was quenched with H_2O (10 mL), and extracted with AcOEt (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 6:1) to afford **13** (61.6 mg, 89% yield) as a colorless oil.

IR (neat): 1765 (C=O), 1624 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.71 (ddt, *J* = 16.8, 10.4, 6.8 Hz, 1 H), 5.15–5.20 (m, 2 H), 4.99 (sept, *J* = 6.0 Hz, 1 H), 4.39 (q, *J* = 7.0 Hz, 2 H), 2.71 (dd, *J* = 14.0, 6.8 Hz, 1 H), 2.64 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.06 (s, 3 H), 1.45 (dd, *J* = 6.0, 2.4 Hz, 6 H), 1.44 (d, *J* = 6.0 Hz, 3 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 181.3 (t, *J* = 3.8 Hz), 180.4, 169.2, 162.0 (t, *J* = 26.6 Hz), 129.9, 120.1, 113.4 (t, *J* = 28.6 Hz), 106.8 (t, *J* = 247.9 Hz), 93.6, 82.3, 63.7, 36.1, 22.2, 22.1, 20.8, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.5 (d, *J* = 277.2 Hz), −100.5 (d, *J* = 277.2 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}F_2O_6$: 347.1306; found: 347.1287.

Ethyl 2-((1S*,5S*)-3-acetoxy-2-isopropoxy-7-oxobicyclo[3.2.0]hept-2-en-1-yl)-2,2-difluoroacetate (14)

A solution of **13** (52.2 mg, 0.15 mmol) in toluene (2 mL) was heated at 100 °C for 8 h under an argon atmosphere. The solvent was removed in vacuo. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 6:1) to afford **14** (50.3 mg, 96% yield) as a colorless oil.

IR (neat): 1790 (C=O), 1768 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 4.44 (sept, *J* = 6.0 Hz, 1 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 3.44 (dd, *J* = 18.4, 9.2 Hz, 1 H), 3.11 (dd, *J* = 18.4, 5.6 Hz, 1 H), 2.92–3.02 (m, 2 H), 2.47 (d, *J* = 14.4 Hz, 1 H), 2.16 (s, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.21 (d, *J* = 6.0 Hz, 3 H), 1.11 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.4, 168.0, 162.2 (t, *J* = 32.5 Hz), 133.7 (dd, *J* = 6.7, 2.9 Hz), 133.1, 113.2 (dd, *J* = 250.7, 257.4 Hz), 78.2 (dd, *J* = 22.9, 26.7 Hz), 73.1, 63.2, 52.8, 33.2, 24.7 (t, *J* = 3.4 Hz), 22.4, 21.8, 20.6, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −108.1 (d, *J* = 277.5 Hz), −111.1 (d, *J* = 277.5 Hz).

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{16}H_{24}F_2NO_6$: 364.1572; found: 364.1562.

Ethyl 2,2-difluoro-2-(3-hydroxy-2-isopropoxy-4-oxo-3-(2-oxo-2-phenylethyl)cyclobut-1-en-1-yl)acetate (15)

To a solution of **4** (78.5 mg, 0.3 mmol) in dry CH_2Cl_2 (2.0 mL) was added $TiCl_4$ (1.0 M in DCM, 300 µL, 0.3 mmol) at −78 °C under an argon atmosphere. After stirring for 10 min, trimethyl((1-phenylvinyl)oxy)silane (184 µL, 0.9 mmol) was added to this solution. After stirring for 1 h at −78 °C, the reaction was quenched with H_2O (10 mL). After warming to room temperature, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to afford **15** (80.7 mg, 70% yield) as a pale yellow oil.

IR (neat): 3400 (O–H), 1770 (C=O), 1616 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.93–7.95 (m, 2 H), 7.63 (tt, *J* = 7.2, 1.4 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 5.18 (br s, 1 H), 5.03 (sept, *J* = 6.0 Hz, 1 H), 4.42 (dq, *J* = 6.8, 3.2 Hz, 1 H), 4.38 (dq, *J* = 6.8, 3.2 Hz, 1 H), 3.52 (d, *J* = 17.6 Hz, 1 H), 3.47 (d, *J* = 17.2 Hz, 1 H), 1.46 (d, *J* = 6.0 Hz, 3 H), 1.39 (d, *J* = 6.0 Hz, 3 H), 1.37 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.5, 183.8, 182.8, 162.0 (t, *J* = 32.9 Hz), 136.0, 134.2, 128.8, 128.4, 113.7 (t, *J* = 28.1 Hz), 106.7 (t, *J* = 247.9 Hz), 90.4, 82.1, 63.7, 38.9, 22.1, 22.0, 13.8.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.6 (d, *J* = 271.5 Hz), −100.5 (d, *J* = 271.5 Hz).

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{19}H_{21}F_2O_6$: 383.1306; found: 383.1304.

Ethyl (Z)-2,2-difluoro-2-(4-isopropoxy-2-oxo-5-(2-oxo-2-phenylethylidene)-2,5-dihydrofuran-3-yl)acetate (16)

To a suspension of pulverized MS4A (150.6 mg), $Pb(OAc)_4$ (133.4 mg, 0.3 mmol), and K_2CO_3 (82.9 mg, 0.6 mmol) in dry toluene (0.5 mL) was added a solution of **15** (57.6 mg, 0.15 mmol) in dry toluene (1.0 mL) at room temperature under an argon atmosphere. The solution was stirred at room temperature for 1 h. To this solution was added H_2O (10 mL), and insoluble materials were filtered off (Celite, AcOEt). The filtrate was extracted with AcOEt (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvents were removed in vacuo, and the obtained crude product was treated with *N*-methylmorpholine (18 µL, 0.16 mmol) in THF (1.5 mL) at room temperature for 3 h. After concentration in vacuo, the obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 9:1) to afford **16** (46.3 mg, 81%) as a yellow solid (mp 46–47 °C).

IR (neat): 1786 (C=O), 1614 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.92–7.74 (m, 2 H), 7.92–7.74 (m, 2 H), 7.61 (tt, *J* = 7.6, 1.0 Hz, 1 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 6.68 (s, 1 H), 5.21 (sept, *J* = 6.0 Hz, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 1.50 (d, *J* = 6.0 Hz, 6 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.0, 165.8, 164.7 (t, *J* = 6.7 Hz), 161.5 (t, *J* = 32.0 Hz), 150.0, 137.2, 133.7, 128.74, 128.68, 109.6 (t, *J* = 246.0 Hz), 103.3, 98.4 (t, *J* = 30.1 Hz), 81.8 (t, *J* = 6.2 Hz), 63.9, 22.3, 13.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −94.9.

HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}F_2O_6$: 381.1150; found: 381.1145.

Allyl 2,2-difluoro-2-(2-isopropoxy-3,4-dioxocyclobut-1-enyl)acetate (17)

This compound was synthesized using the above described procedure for the synthesis of **4**. Semisquarate **17** (1.47g, 54% yield) was obtained as a yellow oil.

IR (neat): 1805 (C=O), 1778 (C=O), 1616 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.94 (ddt, *J* = 17.2, 10.8, 5.6 Hz, 1 H), 5.51 (sept, *J* = 6.0 Hz, 1 H), 5.42 (ddd, *J* = 16.8, 2.0, 1.6 Hz, 1 H), 5.35 (ddd, *J* = 10.8, 2.4, 0.8 Hz, 1 H), 4.82 (dd, *J* = 5.6, 1.6 Hz, 2 H), 1.51 (d, *J* = 6.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 196.0, 193.2, 186.1, 165.7 (t, *J* = 29.6 Hz), 160.5 (t, *J* = 32.9 Hz), 130.0, 120.5, 108.3 (t, *J* = 249.8 Hz), 82.7, 68.2, 22.6.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −106.2.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{12}H_{16}F_2NO_5$: 292.0997; found: 292.1000.

Allyl 2-(5-acetoxy-4-isopropoxy-5-(4-methoxyphenyl)-2-oxo-2,5-dihydrofuran-3-yl)-2,2-difluoroacetate (18)

This compound was synthesized using the above described procedure for the synthesis of **9a**. Tetronate **18** (556.8 mg, 63% yield) was obtained as a yellow oil.

IR (neat): 1776 (C=O), 1652 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.44 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.99 (ddt, *J* = 16.8, 10.4, 6.0 Hz, 1 H), 5.41 (ddd, *J* = 16.8, 2.4, 1.6 Hz, 1 H), 5.32 (ddd, *J* = 10.4, 2.4, 0.8 Hz, 1 H), 5.03 (sept, *J* = 6.0 Hz, 1 H), 4.83 (d, *J* = 6.0 Hz, 2 H), 3.83 (s, 3 H), 2.18 (s, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.2, 167.7, 166.9 (t, *J* = 6.2 Hz), 161.9 (t, *J* = 32.9 Hz), 161.0, 130.7, 127.0, 125.6, 119.7, 114.0, 110.0 (t, *J* = 245.6 Hz), 100.8, 95.2 (t, *J* = 29.6 Hz), 81.3, 67.8, 55.4, 22.2, 22.0, 21.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −95.6.

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{21}H_{26}F_2NO_8$: 458.1627; found: 458.1648.

4-(1,1-Difluoro-2-oxo-2-(phenylamino)ethyl)-3-isopropoxy-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl acetate (19a)

In a Schlenk tube, a degassed solution of **18** (44.5 mg, 0.1 mmol) in THF (3 mL) was mixed with $Pd(OAc)_2$ (1.2 mg, 5 μmol), triphenylphosphine (2.7 mg, 10 μmol), and formic acid (7.5 μL, 0.2 mmol). The solution was further degassed at −78 °C and stirred for 12 h at 60 °C under an argon atmosphere. After cooling to room temperature, 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (33.4 mg, 0.12 mmol) and aniline (11 μL, 0.12 mmol) were added to the solution. After stirring for 1 h, the reaction was quenched with H_2O (10 mL), and extracted with AcOEt (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the obtained crude product was purified by silica gel column chromatography (hexane/Acetone, 4:1) to afford **19a** (33.2 mg, 70% yield) as a colorless oil. Amides **19b** and **19c** were also synthesized in the same manner.

IR (neat): 1776 (C=O), 1712 (C=O), 1655 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.61 (dt, *J* = 7.4, 1.2 Hz, 2 H), 7.47 (d, *J* = 9.2 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.18 (tt, *J* = 7.4, 1.2 Hz, 1 H), 6.92–6.93 (d, *J* = 9.2 Hz, 2 H), 5.13 (sept, *J* = 6.4 Hz, 1 H), 3.83 (s, 3 H), 2.19 (s, 3 H), 1.29 (d, *J* = 6.0 Hz, 3 H), 1.20 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.8 (d, *J* = 1.9 Hz), 168.1, 167.4 (dd, *J* = 5.7, 3.8 Hz), 161.0, 160.2 (t, *J* = 30.5 Hz), 136.3, 129.1, 127.0, 125.5, 125.3, 120.5, 114.1, 111.5 (t, *J* = 250.8 Hz), 101.1, 95.4 (t, *J* = 31.0 Hz), 82.0 (t, *J* = 5.7 Hz), 55.3, 22.5, 22.1, 21.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.9 (d, *J* = 265.8 Hz), −101.1 (d, *J* = 265.8 Hz).

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{24}H_{27}F_2N_2O_7$: 493.1786; found: 493.1776.

4-(1,1-Difluoro-2-morpholino-2-oxoethyl)-3-isopropoxy-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl acetate (19b)

Yield: 34.9 mg (74%); colorless oil.

IR (neat): 1776 (C=O), 1685 (C=O), 1639 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.44 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 5.07 (sept, *J* = 6.0 Hz, 1 H), 3.83 (s, 3 H), 3.62–3.87 (m, 8 H), 2.20 (s, 3 H), 1.28 (d, *J* = 6.0 Hz, 3 H), 1.07 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.3, 168.1, 166.0 (dd, *J* = 5.8 Hz), 161.1, 160.5 (t, *J* = 28.1 Hz), 127.0, 125.3, 114.0, 111.7 (t, *J* = 244.1 Hz), 100.3, 96.5 (t, *J* = 29.6 Hz), 81.2 (dd, *J* = 5.7, 3.8 Hz), 66.3, 66.2, 55.3, 46.4 (d, *J* = 4.8 Hz), 43.4, 22.3, 21.9, 21.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −87.5 (d, *J* = 277.3 Hz), −90.7 (d, *J* = 277.3 Hz).

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{22}H_{29}F_2N_2O_8$: 487.1892; found: 487.1909.

4-(1,1-Difluoro-2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-3-isopropoxy-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl acetate (19c)

Yield: 35.4 mg (81%); colorless oil.

IR (neat): 1776 (C=O), 1709 (C=O), 1655 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45 (d, *J* = 8.8 Hz, 2 H), 6.95 (br s, 1 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 5.11 (sept, *J* = 6.0 Hz, 1 H), 4.15 (dd, *J* = 5.2, 2.4 Hz, 2 H), 3.83 (s, 3 H), 2.29 (t, *J* = 2.4 Hz, 1 H), 2.18 (s, 3 H), 1.29 (d, *J* = 6.0 Hz, 3 H), 1.19 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.7, 168.0, 167.0 (t, *J* = 4.8 Hz), 162.2 (t, *J* = 30.5 Hz), 161.0, 127.0, 125.4, 114.0, 111.5 (t, *J* = 249.8 Hz), 100.9, 95.2 (t, *J* = 30.6 Hz), 81.7 (t, *J* = 6.2 Hz), 77.9, 77.5, 55.3, 29.6, 22.4, 22.0, 21.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = −99.8 (d, *J* = 277.3 Hz), −101.6 (d, *J* = 277.3 Hz).

HRMS (DART): *m/z* $[M+NH_4]^+$ calcd for $C_{21}H_{25}F_2N_2O_7$: 455.1630; found: 455.1641.

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Supporting Information

Yes

Primary Data

No

References

(1) (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.

(2) For reviews, see: (a) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(3) (a) Wang, J.; Roselló, M. S.; Aceña, J. L.; Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.

(4) Selected reviews: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214. (b) Egami, H.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 8294. (c) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2014**, *20*, 16830. (d) Charpentier, J.; Frìh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (e) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (f) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev*. **2015**, *115*, 826.

(5) (a) Yamamoto, Y.; Kurohara, T.; Shibuya, M. *Chem. Commun.* **2015**, *51*, 16357. (b) Kurohara, T.; Shibuya, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2017**, *359*, 1413.

(6) For recent reviews, see: (a) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2015**, *21*, 12836. (b) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. *Chem. Eur. J.* **2017**, *23*, 14676.

(7) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560.

(8) Jung, J.; Kim, E.; You, Y.; Cho, E. J. *Adv. Synth. Catal.* **2014**, *356*, 2741.

(9) (a) Reformatsky, S. *Ber. Deutsch. Chem. Ges.* **1887**, *20*, 1210. (b) Lang, R. W.; Schaub, B. *Tetrahedron Lett.* **1988**, *29*, 2943. (c) Witkowski, S.; Rao, Y. K.; Premchandran, R. H.; Halushka, P. V.; Fried, J. *J. Am. Chem. Soc.* **1992**, *114*, 8464.

(10) (a) Benites, J.; Valderrama, J. A.; Bettega, K.; Pedrosa, R. C.; Calderon, P. B.; Verrax, J.; *Eur. J. Med. Chem.* **2010**, *45*, 6052. (b) Xu, K.; Xiao, Z.; Tang, Y. B.; Huang, L.; Chen, C. H.; Ohkoshi, E.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2772. (c) Prachayasittikul, V.; Pingaew, R.; Worachartcheewan, A.; Nantasenamat, C.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul V. *Eur. J. Med. Chem.* **2014**, *84*, 247. (d) Li, J.; Zhang, X.; Xiang, H.; Tong, L.; Feng, F.; Xie, H.; Ding, J.; Yang, C. *J. Org. Chem.* **2017**, *82*, 6795.

(11) Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Am. Chem. Soc.* **1995**, *117*, 9653.

(12) Yamamoto, Y.; Takamizu, Y.; Kurohara, T.; Shibuya, M. *Heterocycles* **2017**, *95*, 525.

(13) Mao, X.; Song, P.; Hao, Y.; Sun, Z.; Hu, X. *Adv. Synth. Catal.* **2016**, *358*, 3719.

(14) Simeonov, S. P.; Nunes, J. P. M.; Guerra, K.; Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2016**, *116*, 5744.

(15) Hu, S. L.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6094.

(16) Tsuji, J. *Tetrahedron* **2015**, *71*, 6330.

(17) Murayama, T.; Yoshida, A.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.* **1994**, *35*, 2271.

(18) Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron*, **1999**, *55*, 13159.

(19) (a) Huisgen, R. *Proc. Chem. Soc.* **1961**, 357. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

(20) Liebeskind, L. S.; Fengil, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.

(21) (a) Jiao, P.; Kawasaki, M.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3333. (b) Rosquete, L. I.; Cabrera-Serra, M. G.; Piñero, J. E.; Martín-Rodríguez, P.; Fernández-Pérez, L.; Luis, J. G.; McNaughton-Smith, G.; Abad-Grillo, T. *Bioorg. Med. Chem.* **2010**, *18*, 4530.

(22) (a) Itoh, T.; Sakabe, K.; Kudo, K.; Ohara, H.; Takagi, Y.; Kihara, H.; Zagatti, P.; Renou, M. *J. Org. Chem.* **1999**, *64*, 252. (b) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, 507, 215.