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SYNTHESIS OF γ-TRIFLUOROMETHYL TETRONATE DERIVATIVES FROM SQUARATES‡

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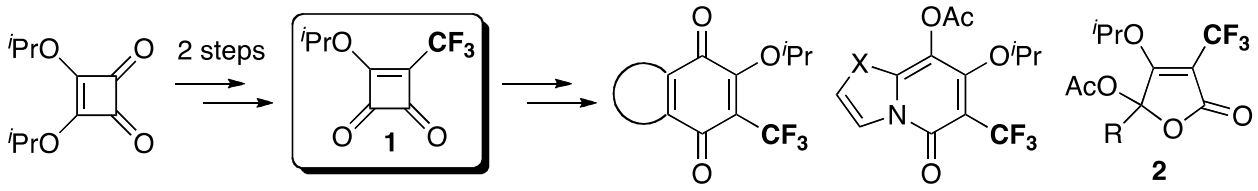
Abstract – Squarates and semisquarates were treated with $TMSCF_3$ in the presence of a catalytic amount of AcONa in DMF at room temperature to afford 4-trifluoromethyl-4-hydroxycyclobutenones. Subsequent oxidative ring expansion of these products was performed using $Pb(OAc)_4$ in the presence of MS 4A in 1,2-dichloroethane at 50 °C to afford γ-trifluoromethyl tetronate derivatives.

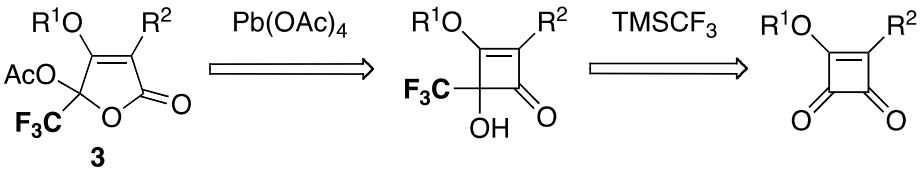
The synthesis of trifluoromethylated heterocyclic compounds has gained increased attention in recent years because of the ability of CF_3 groups to improve the biological activity of the parent heterocyclic compounds by enhancing lipophilicity, interaction with the target receptor, and/or metabolic stability.[1] Although the efficient introduction of a CF_3 group on the sp^2 carbons of heterocyclic scaffolds has been extensively investigated,[2] new strategies that would enable the introduction of a CF_3 group into the sp^3 carbons of heterocyclic frameworks are lacking.

Previously, our group for the first time synthesized CF_3-semisquarate **1** in two steps from commercially available diisopropyl squarate (Scheme 1).[3] We also accomplished the skeletal divergent synthesis of trifluoromethylated functional molecules using **1** as a novel CF_3-containing building block. In this study, α-CF_3-substituted tetronates **2**, which have a CF_3 group on the sp^2 carbon, were efficiently synthesized from **1** in two steps, including addition of aryl Grignard reagents and subsequent oxidation of the resultant 4-hydroxycyclobutenones with $Pb(OAc)_4$.[4] Since tetronate is a highly important scaffold found in diverse bioactive molecules,[5] we decided to develop an alternative approach to γ-CF_3-substituted tetronates **3**, which have a CF_3 group on the sp^3 carbon (Scheme 2). The synthesis of γ-CF_3-substituted tetronic acid derivatives has been almost neglected and, to the best of our knowledge, only two methods

have been reported previously.[6] However, these methods require multi-step synthetic sequences and/or lack generality. Herein, we report our study on the short-step synthesis of γ-CF_3-substituted tetronates from squarates *via* nucleophilic trifluoromethylation and subsequent oxidative ring expansion.

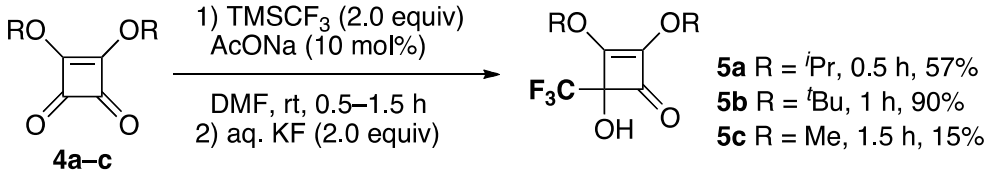


Scheme 1. Skeletal divergent synthesis of trifluoromethylated functional molecules using CF_3-semisquarate **1** as a building block



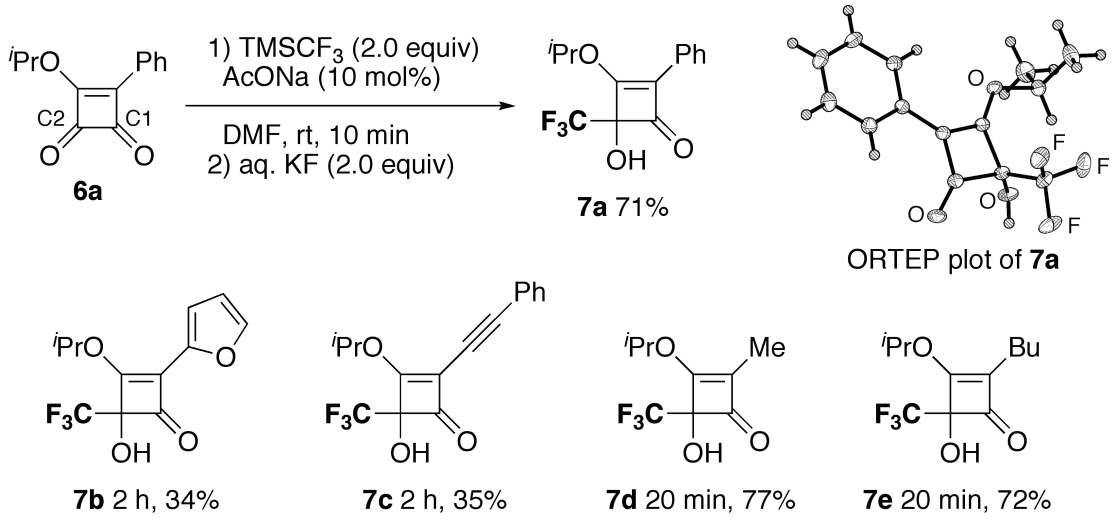
Scheme 2. New method for the synthesis of γ-trifluoromethylated tetronates **3** from squarates

This study started by revisiting the trifluoromethylation reaction of squarates. We previously performed the nucleophilic trifluoromethylation of diisopropyl and di-*tert*-butyl squarates using the Ruppert-Prakash reagent $TMSCF_3$,[7] under modified Mukaiyama conditions.[3,8] In order to maximize ease of solvent removal in a one-pot process, THF was used as solvent, and a combination of AcONa and Bu_4NCl proved to be efficient as initiator in this solvent. However, AcONa was reported to efficiently initiate the trifluoromethylation in the absence of Bu_4NCl in the highly polar solvent DMF.[8] Owing to the simplicity of the latter protocol, the trifluoromethylation of several squarates **4** was performed in DMF, as shown in Scheme 3. The reactions of isopropyl and *tert*-butyl esters **4a** and **4b** were performed using 2.0 equiv of $TMSCF_3$ in the presence of 10 mol% AcONa in DMF at room temperature. After desilylation with aq. KF, the desired 4-hydroxycyclobutenones **5a** and **5b** were obtained in 57% and 90% yields, respectively. In striking contrast, the reaction of dimethyl squarate **4c** resulted in the formation of **5c** in a lower yield. These results suggest that bulky alkoxy groups are required to achieve efficient trifluoromethylation. This is presumably because undesired Michael addition is suppressed by the bulky alkoxy groups.



Scheme 3. Trifluoromethylation of squarates **4a**–**c**

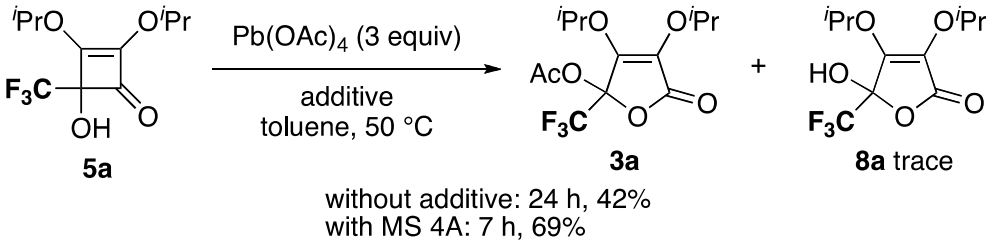
Then, the trifluoromethylation of semisquarate **6a**, possessing a phenyl group at the 4-position, was examined under the same conditions (Scheme 4). It should be noted that semisquarates possess two different carbonyl groups and, hence, the regioselectivity could be controlled by taking advantage of the difference in electrophilicity of these groups. In general, vinylogous ester carbonyl groups are less electrophilic than the others. Therefore, the trifluoromethylation of **6a** was expected to occur at the C2 carbon rather than C1. In accordance with this notion, the reaction of **6a** was complete in a shorter reaction time (10 min), selectively affording **7a** as a single product in 71% yield. The regioselectivity was unambiguously confirmed by single X-ray diffraction analysis (see Supporting Information). Other semisquarates were also subjected to trifluoromethylation under identical conditions. The reactions of substrates **6b** and **6c**, possessing a 2-furyl and phenylethynyl group, respectively, were sluggish, and after 2 h the corresponding products **7b** and **7c** were obtained in much lower yields. On the other hand, alkyl-substituted semisquarates **6d** and **6e** uneventfully underwent trifluoromethylation to afford the corresponding products **7d** and **7e** in 77% and 72% yields, respectively.



Scheme 4. Trifluoromethylation of semisquarates **6a**–**e**

Subsequently, the oxidative ring expansion of 4-hydroxycyclobutenones was investigated using **5a** as representative substrate (Scheme 5). In our previous study, 2-trifluoromethyl-4-hydroxycyclobutenones smoothly underwent oxidative ring expansion upon treatment with 2 equiv of $Pb(OAc)_4$ in toluene at

room temperature for 2 h, affording the expected tetronates in 62–77% yields.[3] In striking contrast, the reaction of **5a** was found to be sluggish even when using 3 equiv of $Pb(OAc)_4$ at 50 °C, resulting only in the partial conversion of **5a** after 24 h. The expected tetronate **3a** was obtained in a moderate 42% yield and trace amounts of the deacetylated side product **8a** were also detected. It was reasoned that the bulky CF_3 group might hamper the access of $Pb(OAc)_4$ to the hydroxyl group, and the strong electron-withdrawing effect of the CF_3 group considerably lessen the nucleophilicity of the hydroxyl group. Since the formation of **8a** was also ascribed to the presence of adventitious water, the reaction was repeated upon addition of MS 4A (100 mg/mL). Surprisingly, **5a** was completely consumed after 7 h, affording **3a** in an improved 69% yield, although trace amounts of **8a** were still detected. Thus, we further examined other molecular sieves at the reaction time of 7 h. As a result, the yield of **3a** decreased to 60% and **8a** was detected in ca. 12% when using MS 3A. The use of MS 5A led to incomplete reaction, affording **3a** in 35% yield along with the recovery of **5a** in 45% yield. In the presence of the optimal MS 4A, solvents other than toluene were used under otherwise same conditions. Trifluorotoluene and 1,2-dichloroethane (DCE) afforded comparable yields of **3a** (76% and 74%, respectively), while the yields decreased to 64% and 16% in the case of THF and acetonitrile, respectively. The reaction was quenched in acetic acid solvent. In the following experiments, DCE was used owing to its easy evaporation.



Scheme 5. Oxidative ring expansion of 4-hydroxycyclobutenone **5a**

The scope of the oxidative ring expansion was examined and the results are summarized in Figure 1. As mentioned above, diisopropyl derivative **5a** was subjected to the optimized conditions to afford **3a** in 69% yield. In contrast, the bulkier *tert*-butyl analog **5b** proved to be an inefficient substrate: the reaction of **5b** was sluggish and **3b** was obtained in a low yield probably due to the decomposition of both **3b** and **5b** under acidic conditions. Conversely, the reaction of less sterically demanding methyl derivative **5c** was complete in the shorter reaction time of 3 h, affording **3c** in 67% yield. The reaction of semisquarate-derived substrates **7a**–**e** also efficiently proceeded under the optimized conditions for 1.5–2 h to produce the corresponding tetronates **3d**–**h** in 67–79% yields. Thus, the oxidative ring expansion well tolerates alkyl, aryl, furyl, and alkynyl substituents.

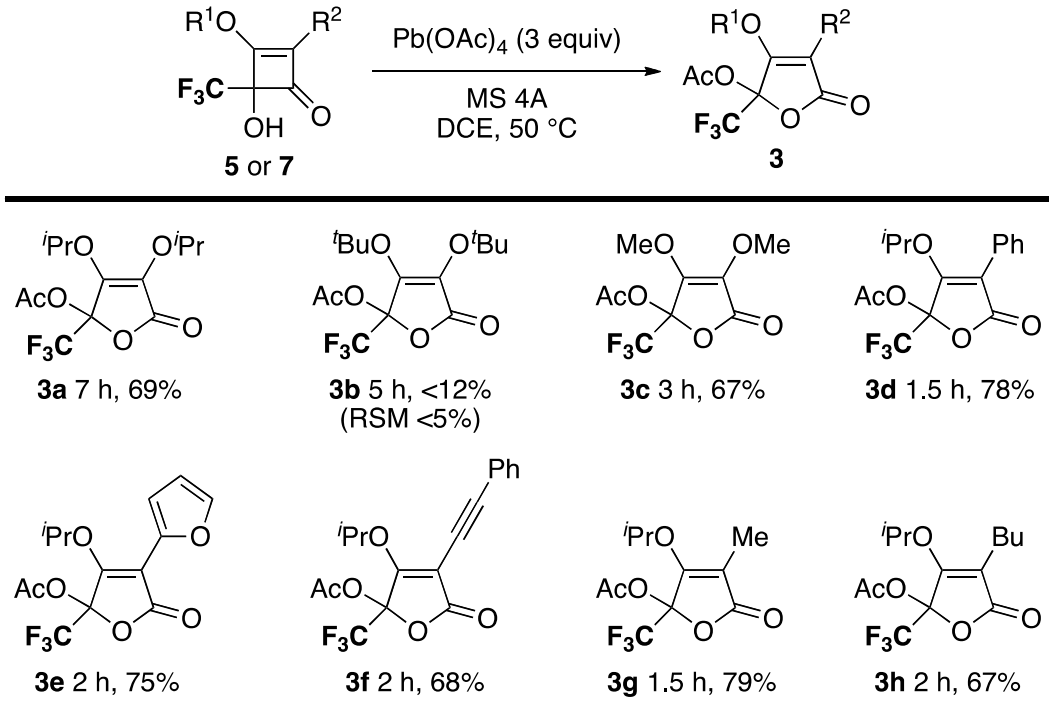
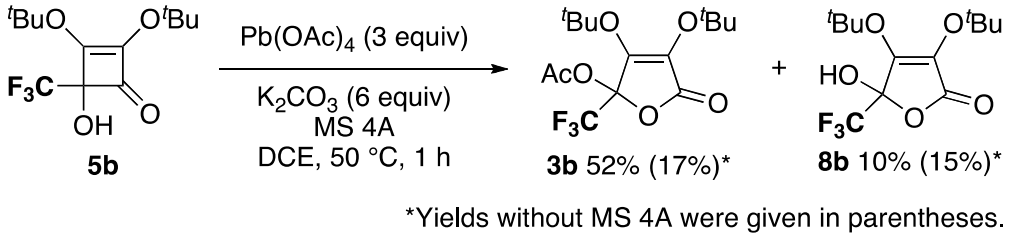


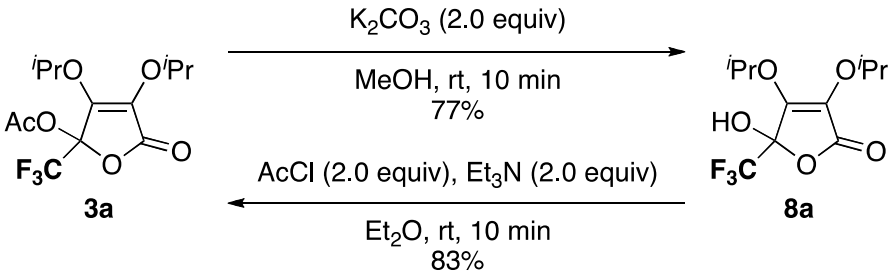
Figure 1. Scope of oxidative ring expansion

To improve the yield of **3b**, the reaction of **5b** was reinvestigated by adding the inorganic base K_2CO_3 (6 equiv) as an acid scavenger under otherwise same conditions (Scheme 6). As a result, **5b** was completely consumed after 1 h and the desired product **3b** was obtained in 52% yield along with the deacetylated side product **8b** (10%). It should be noted that both MS 4A and K_2CO_3 are required for the oxidative ring expansion of **5b** as the yield of **3b** significantly dropped to 17% in the absence of MS 4A.



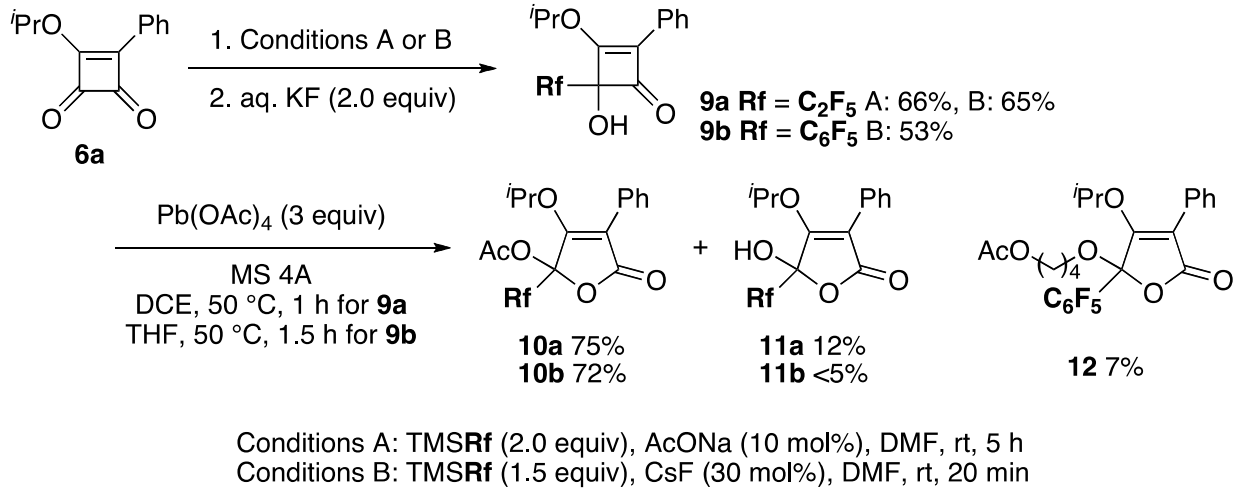
Scheme 6. Oxidative ring expansion of **5b** in the presence of K_2CO_3

In order to gain insight into the formation of **8a**, the deacetylation of **3a** was attempted (Scheme 7). Because of its strong electron-withdrawing effect, we failed to abstract the acetoxy group from **3a** using Lewis acids such as $TiCl_4$ and $SnCl_4$. However, the deacetylation of **3a** occurred under basic conditions (K_2CO_3 in MeOH) to afford **8a** in 77% yield. Conversely, the acetylation of **8a** using acetyl chloride and Et_3N produced **3a** in 83% yield. Therefore, it was reasoned that **8a** was formed *via* hydrolysis of the acetate moiety.



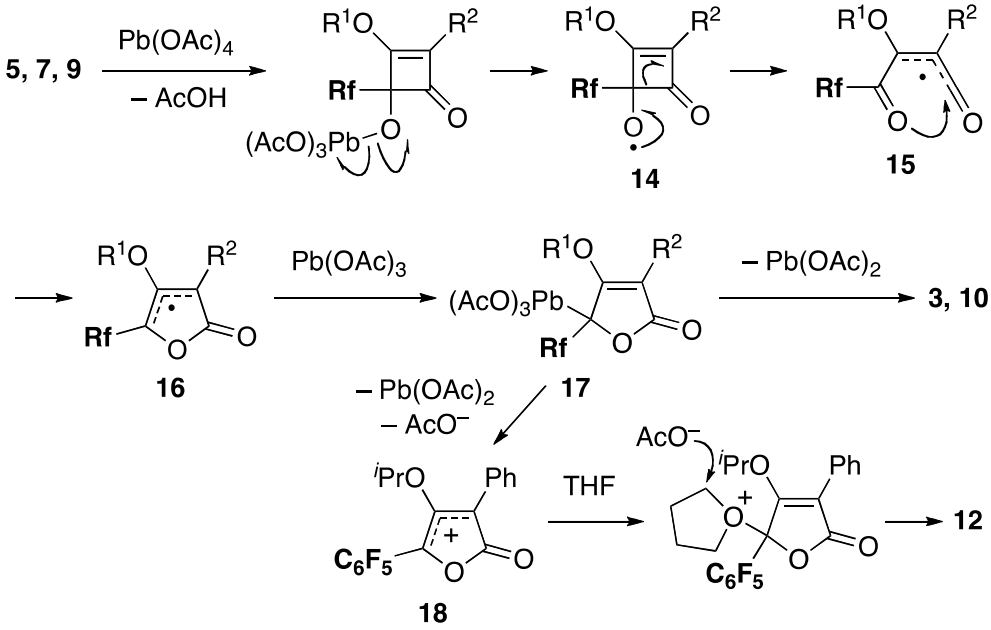
Scheme 7. Interconversion between **3a** and **8a**

Having achieved the short-step synthesis of γ-trifluoromethyltetronates, the extension of this method to higher perfluoroalkyl or perfluoroaryl groups was briefly investigated (Scheme 8). The perfluoroethylation of semisquarate **6a** was conducted using $TMSC_2F_5$ in the same manner with trifluoromethylation. Although longer reaction time of 5 h was required, the desired product **9a** was obtained in moderate 66% yield. The reaction time could be shortened to 20 min without lowering the yield (65%) when the same reaction was performed using CsF (30 mol%) as a promoter. The perfluorophenylation was also conducted using $TMSC_6F_5$ in the presence of 30 mol% CsF in DMF at room temperature for 20 min to afford **9b** in 53% yield. Oxidative ring expansion of **9a** under the standard conditions produced the desired tetronate **10a** and its deacetylated analog **11a** in 75% and 12% yields, respectively. Because **9b** was sparingly soluble in DCE, its oxidative ring expansion was performed in THF for 1.5 h. As a result, the expected **10b** was obtained in 72% yield. The formation of deacetylation byproduct **11b** was effectively suppressed, but instead, small amounts of unexpected product **12**, in which one THF molecule is incorporated after its ring opening, were obtained.



Scheme 8. Synthesis of C_2F_5- and C_6F_5-analogs

Scheme 9 outlines the plausible mechanism of oxidative ring expansion of 4-hydroxycyclobutenones **5**, **7**, and **9**. As previously suggested,[4] one-electron oxidation of 4-hydroxycyclobutenones generate alkoxy radicals **14**, which undergo facile ring opening to generate ketenyl radicals **15**. Subsequent recyclization of **15** produces allylic radicals **16**, which are trapped with $Pb(OAc)_3$ to afford intermediates **17**. Reductive elimination of $Pb(OAc)_2$ predominantly occurs from **17**, affording γ-acetoxytetronates **3** and **10**. However, small amounts of highly delocalized cation **18** is presumably produced from **9b**. Thus, **18** is trapped by solvent THF and then, an acetate anion to ultimately afford **12**.



Scheme 9. Plausible mechanism for oxidative ring expansion

In conclusion, we successfully developed a new route to γ-CF_3-substituted tetronates starting from squarates. The first step of this process, i.e., the nucleophilic trifluoromethylation of squarates, was conducted using $TMSCF_3$ in the presence of AcONa as initiator in DMF at room temperature, affording 4-trifluoromethyl-4-hydroxycyclobutenones in 15–90% yields. The second oxidative ring expansion step proved to be problematic for the obtained 4-trifluoromethyl-4-hydroxycyclobutenones. However, a significant beneficial effect due to the use of MS 4A was found during the optimization process. Thus, various γ-CF_3-substituted tetronates were efficiently obtained in approximately 70% yield upon treatment of 4-hydroxycyclobutenones possessing isopropoxy or methoxy substituents with $Pb(OAc)_4$ in the presence of MS 4A in DCE at 50 °C. On the other hand, a 4-hydroxycyclobutenone possessing *tert*-butoxy substituents underwent oxidative ring expansion in the presence of K_2CO_3 and MS 4A to afford the corresponding tetronate, albeit in a moderate yield. Moreover, perfluoroethyl and perfluorophenyl analogs were also synthesized in similar manners.

EXPERIMENTAL

All air- and moisture-sensitive reactions were performed under an argon (Ar) atmosphere in dried glassware. 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 solvents specified below. Melting points were recorded on SRS OptiMelt MPA100. NMR spectra were recorded on JEOL ESC-400 spectrometer (^{1}H/400 MHz, ^{13}C/100 MHz, and ^{19}F/376MHz) 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; sept, septet; m, multiplet. Coupling constants are reported in Hz. Infrared spectra were recorded on JASCO FT/IR-230 spectrometer. High-resolution mass spectra were recorded on JEOL JMS-T100LP mass spectrometer.

Reagents and Solvents. Squarates and semisquarates were prepared according to reported procedures.[9] CF_3SiMe_3 (Fluorochem), $Pb(OAc)_4$ (TCI) and other reagents and solvents were purchased and used as received.

Typical Procedure for Trifluoromethylation of Squarates and Semisquarates. 4-Hydroxy-2,3-diisopropoxy-4-(trifluoromethyl)cyclobut-2-enone (5a). To a solution of diisopropyl squarate (198.2 mg, 1.0 mmol) and AcONa (8.2 mg, 0.10 mmol) in dry DMF (2 mL) was added $TMSCF_3$ (296 μL, 2.0 mmol) via a syringe under an Ar atmosphere at room temperature and the resultant mixture was stirred for 0.5 h. The reaction was quenched with aq. KF (1.0 M, 2 mL, 2.0 mmol), and was extracted with Et_2O (3 × 15 mL). The combined organic layer was washed with H_2O (3 × 20 mL) and brine (20 mL), and dried over $MgSO_4$. The solvents were evaporated *in vacuo*, and the obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 10:1) to afford **5a** (151.9 mg, 57% yield) as a colorless solid. The following spectral data are in good agreement with those previously reported;[3] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.30 (d, J = 6.4 Hz, 3 H), 1.32 (d, J = 6.4 Hz, 3 H), 1.42 (d, J = 6.4 Hz, 6 H), 3.42 (br s, 1 H), 4.94 (sept, J = 6.4 Hz, 1 H), 4.95 (sept, J = 6.4 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –76.7.

2,3-Di-*tert*-butoxy-4-hydroxy-4-(trifluoromethyl)cyclobut-2-enone (5b):[3] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.50 (s, 9 H), 1.55 (s, 9 H), 3.00 (br s, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –76.9.

4-Hydroxy-2,3-dimethoxy-4-(trifluoromethyl)cyclobut-2-enone (5c): colorless solid (mp 77.4–80.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 3.40 (s, 1 H), 4.03 (s, 3 H), 4.20 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 59.0, 61.1, 85.2 (q, J = 34.0 Hz), 122.7 (q, J = 281.6 Hz), 137.3, 160.4, 176.9; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –75.4; IR (neat) 3379 (OH), 1785 (C=O), 1631 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_7H_7F_3O_4$•NH_4 230.0640, found 230.0644 $[M+NH_4]^+$.

4-Hydroxy-3-isopropoxy-2-phenyl-4-(trifluoromethyl)cyclobut-2-enone (7a): colorless solid (mp 161.7–164.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.51 (d, J = 6.0 Hz, 3 H), 1.55 (d, J = 6.0 Hz, 3 H), 5.15 (sept, J = 6.0 Hz, 1 H), 5.60 (br s, 1 H), 7.30–7.37 (m, 3 H), 7.70–7.73 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.8, 23.1, 81.7, 91.1 (q, J = 33.4 Hz), 122.8 (q, J = 282.2 Hz), 127.2, 127.48, 128.53, 129.0, 129.2, 173.3, 180.8; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –75.3; IR (neat) 3249 (OH), 1751 (C=O), 1629 (C=C), 1598 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{14}H_{13}F_3O_3$•H 287.0895, found 287.0904 $[M+H]^+$.

2-(Furan-2-yl)-4-hydroxy-3-isopropoxy-4-(trifluoromethyl)cyclobut-2-enone (7b): colorless solid (mp 107.8–108.7 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.48 (d, J = 6.4 Hz, 3 H), 1.51 (d, J = 6.4 Hz, 3 H), 3.43 (br s, 1 H), 5.36 (sept, J = 6.4 Hz, 1 H), 6.49 (dd, J = 3.2, 1.6 Hz, 1 H), 6.90 (d, J = 3.2 Hz, 1 H), 7.46 (dd, J = 1.6, 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.3, 22.6, 81.3, 90.6 (q, J = 33.4 Hz), 111.6, 112.5, 120.1, 122.5 (q, J = 282.2 Hz), 141.2, 143.2, 168.1, 178.3; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –76.4; IR (neat) 3382 (OH), 1762 (C=O), 1647 (C=C), 1549 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{12}H_{11}F_3O_4$•H 277.0688, found 277.0706 $[M+H]^+$.

4-Hydroxy-3-isopropoxy-2-(phenylethynyl)-4-(trifluoromethyl)cyclobut-2-enone (7c): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.55 (d, J = 6.4 Hz, 6 H), 5.46 (sept, J = 6.4 Hz, 1 H), 7.38–7.48 (m, 3 H), 7.53–7.57 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.0, 22.2, 74.6, 80.8, 90.1 (q, J = 33.4 Hz), 95.1, 111.8, 121.3, 122.3 (q, J = 282.2 Hz), 128.5, 129.5, 131.8, 176.4, 180.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –76.7; IR (neat) 3366 (OH), 2214 (C≡C), 1769 (C=O), 1615 (C=C), 1592 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{16}H_{13}F_3O_3$•NH_4 328.1161, found 328.1180 $[M+NH_4]^+$.

4-Hydroxy-3-isopropoxy-2-methyl-4-(trifluoromethyl)cyclobut-2-enone (7d): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.45 (d, J = 6.4 Hz, 3 H), 1.46 (d, J = 6.4 Hz, 3 H), 1.79 (s, 3 H), 4.40 (br s, 1 H), 4.88 (sept, J = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 7.0, 22.2, 22.4, 78.7, 89.6 (q, J = 33.1 Hz), 122.7 (q, J = 281.6 Hz), 127.1, 175.9, 184.6; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –76.6; IR (neat) 3345 (OH), 1766 (C=O), 1611 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_9H_{11}F_3O_3$•NH_4 242.1004, found 242.1012 $[M+NH_4]^+$.

2-Butyl-4-hydroxy-3-isopropoxy-4-(trifluoromethyl)cyclobut-2-enone (7e): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 0.89 (t, J = 7.6 Hz, 3 H), 1.27–1.38 (m, 2 H), 1.43 (d, J = 6.4 Hz, 3 H), 1.45

(d, J = 6.4 Hz, 3 H), 1.49–1.60 (m, 2 H), 2.10–2.23 (m, 2 H), 4.26 (br s, 1 H), 4.86 (sept, J = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 13.5, 22.19, 22.22, 22.3, 22.5, 28.9, 79.0, 89.8 (q, J = 32.7 Hz), 122.8 (q, J = 281.6 Hz), 132.1, 175.9, 184.5; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –76.4; IR (neat) 3347 (OH), 1761 (C=O), 1607 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{12}H_{17}F_3O_3$•H 267.1208, found 267.1213 $[M+H]^+$.

Typical Procedure for Perfluoroethylation and Perfluorophenylation of Semisquarate. 4-Hydroxy-3-isopropoxy-4-(perfluoroethyl)-2-phenylcyclobut-2-enone (9a). In a flask, CsF (25.0 mg, 0.165 mmol) was heated at 200 °C under vacuum for 2 h. To this flask, diisopropyl squarate (108.1 mg, 0.5 mmol) and dry DMF (1 mL) were added. To this solution was added $TMSC_2F_5$ (140 μL, 0.765 mmol) via a syringe under an Ar atmosphere at room temperature and the resultant mixture was stirred for 20 min. The reaction was quenched with aq. KF (1.0 M, 2 mL, 2.0 mmol), and was extracted with Et_2O (3 × 15 mL). The combined organic layer was washed with H_2O (3 × 20 mL) and brine (20 mL), and dried over $MgSO_4$. The solvents were evaporated *in vacuo*, and the obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 10:1) to afford **9a** (108.9 mg, 65% yield) as a colorless solid (mp 139.4–140.2 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.49 (d, J = 6.0 Hz, 3 H), 1.50 (d, J = 6.0 Hz, 3 H), 3.87 (br s, 1 H), 5.07 (sept, J = 6.0 Hz, 1 H), 7.31–7.42 (m, 3 H), 7.71–7.74 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.5, 23.1, 81.7, 92.1 (dd, J = 28.2, 22.4 Hz), 112.4 (ddq, J = 262.2, 255.0, 38.0 Hz), 118.6 (tq, J = 285.7, 35.4 Hz), 127.27, 127.32, 128.5, 129.0, 129.2, 173.9, 180.6; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –122.9 (d, J = 277.5 Hz), –118.5 (d, J = 277.1 Hz), –82.1; IR (neat) 3322 (OH), 1756 (C=O), 1625 (C=C), 1594 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{15}H_{13}F_5O_3$•H 337.0863, found 337.0834 $[M+H]^+$.

4-Hydroxy-3-isopropoxy-4-(perfluorophenyl)-2-phenylcyclobut-2-enone (9b): colorless solid (mp 171.8–174.4 °C); ^{1}H NMR (400 MHz, acetone-d_6, 25 °C): δ 1.49 (d, J = 6.0 Hz, 3 H), 1.58 (d, J = 6.0 Hz, 3 H), 5.10 (sept, J = 6.0 Hz, 1 H), 6.64 (s, 1 H), 7.32 (tt, J = 7.4, 1.5 Hz, 1 H), 7.38–7.43 (m, 2 H), 7.73–7.77 (m, 2 H); ^{13}C NMR (100 MHz, acetone-d_6, 25 °C): δ 22.7, 23.4, 81.2, 91.3, 113.5 (t, J = 13.3 Hz), 124.9, 127.6, 129.1, 129.4, 129.8, 138.8 (dm, J = 248.9 Hz), 141.6 (dm, J = 250.7 Hz), 145.7 (dm, J = 249.4 Hz), 179.1, 183.5; ^{19}F NMR (376 MHz, acetone-d_6, 25 °C): δ –161.6 (t, J = 23.1 Hz), –153.9 (t, J = 23.1 Hz), –140.8 (d, J = 22.9 Hz); IR (neat) 3349 (OH), 1748 (C=O), 1618 (C=C), 1591 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{19}H_{13}F_5O_3$•H 385.0863, found 385.0871 $[M+H]^+$.

Typical Procedure for Oxidative Ring Expansion of 4-Trifluoromethyl-4-hydroxycyclobutenones. 3,4-Diisopropoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3a). A mixture of 4-hydroxycyclobutenone **5a** (107.2 mg, 0.4 mmol), $Pb(OAc)_4$ (554.2 mg, 1.2 mmol), and pulverized MS 4A (400 mg) in dry DCE (4 mL) was stirred under an Ar atmosphere at 50 °C for 7 h. 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 (20 mL). The filtrate 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 obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 10:1) to afford **3a** (89.5 mg, 69% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.28 (d, *J* = 6.4 Hz, 3 H), 1.31 (d, *J* = 6.4 Hz, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.33 (d, *J* = 6.0 Hz, 3 H), 2.17 (s, 3 H), 4.93 (sept, *J* = 6.4 Hz, 1 H), 5.21 (sept, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 20.9, 22.0, 22.2, 22.3, 74.2, 76.0, 94.4 (q, *J* = 35.3 Hz), 119.9 (q, *J* = 284.4 Hz), 122.1, 149.7, 164.3, 166.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –83.4; IR (neat) 1798 (C=O), 1690 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{13}H_{17}F_3O_6$•NH_4 344.1321, found 344.1323 $[M+NH_4]^+$.

3,4-Di-*tert*-butoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3b): colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.50 (s, 18 H), 2.16 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.2, 28.9, 29.4, 84.8, 86.7, 95.2 (q, *J* = 35.0 Hz), 120.1 (q, *J* = 284.5 Hz), 124.1, 150.3, 166.1, 166.5; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –83.0; IR (neat) 1805 (C=O), 1665 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{15}H_{21}F_3O_6$•NH_4 372.1634, found 372.1635 $[M+NH_4]^+$.

3,4-Dimethoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3c): colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 2.18 (s, 3 H), 3.92 (s, 3 H), 4.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.0, 60.0, 60.2, 94.0 (q, *J* = 35.9 Hz), 119.7 (q, *J* = 283.8 Hz), 125.4, 150.6, 163.7, 166.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –83.4; IR (neat) 1809 (C=O), 1699 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_9H_9F_3O_6$•NH_4 288.0696, found 288.0702 $[M+NH_4]^+$.

3-Isopropoxy-5-oxo-4-phenyl-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3d): colorless solid (mp 65.3–67.7 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.10 (d, *J* = 6.0 Hz, 3 H), 1.15 (d, *J* = 6.0 Hz, 3 H), 2.22 (s, 3 H), 4.67 (sept, *J* = 6.0 Hz, 1 H), 7.36–7.45 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.0, 21.5, 21.7, 76.4, 96.0 (q, *J* = 35.3 Hz), 106.6, 120.0 (q, *J* = 284.1 Hz), 128.48, 128.54, 129.1, 130.0, 163.1, 166.8, 168.0; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –82.6; IR (neat) 1794 (C=O), 1670 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{16}H_{15}F_3O_5$•NH_4 362.1215, found 362.1233 $[M+NH_4]^+$.

4-(Furan-2-yl)-3-isopropoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3e): pale-yellow solid (mp 46.9–49.2 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.24 (d, *J* = 6.0 Hz, 3 H), 1.33 (d, *J* = 6.0 Hz, 3 H), 2.20 (s, 3 H), 5.18 (sept, *J* = 6.0 Hz, 1 H), 6.52 (dd, *J* = 3.2, 2.0 Hz, 1 H), 6.88 (dd, *J* = 3.2, 0.8 Hz, 1 H), 7.50 (dd, *J* = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 20.9, 22.0, 78.9, 96.1 (q, *J* = 35.3 Hz), 97.9, 111.7, 112.5, 119.9 (q, *J* = 284.8 Hz), 141.9, 143.3, 162.2, 166.2, 166.6; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –82.5; IR (neat) 1794 (C=O), 1676 (C=C) cm^{-1}; HRMS

(DART) *m/z* calcd for $C_{14}H_{13}F_3O_6$•NH_4 352.1008, found 352.1005 $[M+NH_4]^+$.

3-Isopropoxy-5-oxo-4-(phenylethynyl)-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3f): pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.46 (d, *J* = 6.0 Hz, 3 H), 1.49 (d, *J* = 6.0 Hz, 3 H), 2.21 (s, 3 H), 5.65 (sept, *J* = 6.0 Hz, 1 H), 7.32–7.40 (m, 3 H), 7.46–7.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 20.7, 22.1, 78.4, 90.4, 95.9 (q, *J* = 35.6 Hz), 96.6, 119.7 (q, *J* = 284.8 Hz), 121.8, 128.4, 129.2, 131.5, 165.5, 166.5, 167.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –82.7; IR (neat) 2221 (C≡C), 1807 (C=O), 1658 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{18}H_{15}F_3O_5$•NH_4 386.1215, found 386.1199 $[M+NH_4]^+$.

3-Isopropoxy-4-methyl-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3g): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.35 (d, *J* = 6.0 Hz, 3 H), 1.38 (d, *J* = 6.0 Hz, 3 H), 2.01 (s, 3 H), 2.17 (s, 3 H), 4.94 (sept, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 8.9, 21.0, 22.2, 22.4, 75.4, 96.0 (q, *J* = 35.2 Hz), 100.2, 119.9 (q, *J* = 284.1 Hz), 162.5, 166.6, 169.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –83.0; IR (neat) 1796 (C=O), 1679 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{11}H_{13}F_3O_5$•NH_4 300.1059, found 300.1055 $[M+NH_4]^+$.

4-Butyl-3-isopropoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3h): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 0.94 (t, *J* = 7.4 Hz, 3 H), 1.36 (d, *J* = 6.4 Hz, 3 H), 1.37 (d, *J* = 6.4 Hz, 3 H), 1.33–1.43 (m, 2 H), 1.45–1.60 (m, 2 H), 2.16 (s, 3 H), 2.36 (t, *J* = 7.8 Hz, 2 H), 4.84 (sept, *J* = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 13.7, 20.9, 22.0, 22.2, 22.3, 23.5, 31.0, 75.4, 96.0 (q, *J* = 35.0 Hz), 105.4, 120.0 (q, *J* = 284.4 Hz), 161.9, 166.5, 169.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –83.0; IR (neat) 1794 (C=O), 1670 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{14}H_{19}F_3O_5$•NH_4 342.1528, found 342.1517 $[M+NH_4]^+$.

3-Isopropoxy-5-oxo-4-phenyl-2-(perfluoroethyl)-2,5-dihydrofuran-2-yl acetate (10a): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.07 (d, *J* = 6.0 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H), 2.21 (s, 3 H), 4.67 (sept, *J* = 6.0 Hz, 1 H), 7.35–7.45 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 20.9, 21.5, 21.6, 76.6, 96.9 (dd, *J* = 30.5, 26.7 Hz), 106.6, 110.0 (ddq, *J* = 267.8, 262.7, 37.4 Hz), 118.1 (tq, *J* = 286.7, 34.6 Hz), 128.45, 128.54, 129.0, 129.9, 163.3, 166.5, 167.8; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –127.3 (d, *J* = 277.1 Hz), –126.3 (d, *J* = 277.5 Hz), –80.5; IR (neat) 1796 (C=O), 1670 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{17}H_{15}F_5O_5$•NH_4 412.1183, found 412.180 $[M+NH_4]^+$.

5-Hydroaxy-4-isopropoxy-5-(perfluoroethyl)-3-phenylfuran-2(5*H*)-one (11a): colorless solid (mp 143.3–147.7 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.16 (d, *J* = 6.0 Hz, 3 H), 1.17 (d, *J* = 6.0 Hz, 3 H), 4.72 (sept, *J* = 6.0 Hz, 1 H), 5.24 (br s, 1 H), 7.35–7.43 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.7, 76.8, 97.2 (dd, *J* = 29.1, 26.2 Hz), 106.2, 110.8 (ddq, *J* = 266.5, 262.7, 37.3 Hz), 118.3 (tq, *J* = 286.4, 34.7 Hz), 128.1, 128.5, 129.1, 129.9, 165.8, 169.8; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ

–126.6 (d, J = 288.8 Hz), –125.1 (d, J = 277.5 Hz), –80.7; IR (neat) 3227 (OH), 1745 (C=O), 1660 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{15}H_{13}F_5O_4 \bullet NH_4$ 370.1078, found 370.1063 $[M+NH_4]^+$.

3-Isopropoxy-5-oxo-2-(perfluorophenyl)-4-phenyl-2,5-dihydrofuran-2-yl acetate (10b): colorless solid (mp 99.2–101.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.00 (d, J = 6.0 Hz, 3 H), 1.12 (d, J = 6.0 Hz, 3 H), 2.22 (s, 3 H), 4.64 (sept, J = 6.0 Hz, 1 H), 7.38–7.44 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.0, 21.5, 21.7, 76.1, 97.9, 105.0, 109.8 (dt, J = 11.2, 4.4 Hz), 128.4, 128.5, 129.0, 129.8, 138.0 (dm, J = 247.9 Hz), 141.6 (dm, J = 257.5 Hz), 144.8 (dm, J = 253.7 Hz), 166.3, 167.6, 168.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –161.6 (t, J = 23.1 Hz), –152.3 (t, J = 23.1 Hz), –141.4 (d, J = 23.3 Hz); IR (neat) 1789 (C=O), 1670 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{21}H_{15}F_5O_5 \bullet H$ 443.0918, found 443.0901 $[M+H]^+$.

4-(3-Isopropoxy-5-oxo-2-(perfluorophenyl)-4-phenyl-2,5-dihydrofuran-2-yloxy)butyl acetate (12): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.05 (d, J = 6.0 Hz, 3 H), 1.13 (d, J = 6.0 Hz, 3 H), 1.74–1.85 (m, 4 H), 2.06 (s, 3 H), 3.67 (dt, J = 8.8, 6.0 Hz, 1 H), 3.76 (dt, J = 8.8, 6.0 Hz, 1 H), 4.12 (t, J = 6.0 Hz, 2 H), 4.71 (sept, J = 6.0 Hz, 1 H), 7.38–7.45 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 20.9, 21.8, 22.0, 25.3, 25.9, 63.3, 63.9, 75.7, 101.8, 105.6, 111.1 (dt, J = 11.0, 4.3 Hz), 128.5, 128.77, 128.84, 129.8, 138.0 (dm, J = 252.7 Hz), 141.8 (dm, J = 255.5 Hz), 145.5 (dm, J = 253.6 Hz), 166.3, 169.2, 171.1; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –161.9 (t, J = 23.1 Hz), –152.4 (t, J = 23.1 Hz), –138.9 (d, J = 22.9 Hz); IR (neat) 1779 (C=O), 1739 (C=O), 1667 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{25}H_{23}F_5O_6 \bullet H$ 515.1493, found 515.1498 $[M+H]^+$.

Oxidative Ring Expansion of 2,3-Di-*tert*-butoxy-4-hydroxy-4-(trifluoromethyl)cyclobut-2-enone (5b). 3,4-Di-*tert*-butoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3b). A mixture of 4-hydroxycyclobutenone **5b** (118.4 mg, 0.4 mmol), $Pb(OAc)_4$ (665.1 mg, 1.2 mmol), MS 4A (400 mg), and finely pulverized K_2CO_3 (331.7 mg, 2.4 mmol) in dry DCE (4 mL) was stirred under an Ar atmosphere at 50 °C for 1 h. 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 (20 mL). The filtrate 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 obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 100:1~40:1) to afford **3b** (73.8 mg, 52% yield) as a colorless oil. Further elution (hexane/AcOEt 30:1~5:1) afforded **8b** (12.1 mg, 10% yield) as a yellow solid.

3,4-Di-*tert*-butoxy-5-hydroxy-5-(trifluoromethyl)furan-2(5*H*)-one (8b): yellow solid (mp 69.2–70.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.44 (s, 9 H), 1.51 (s, 9 H), 3.98 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 29.0, 29.2, 84.9, 88.0, 94.8 (q, J = 34.7 Hz), 121.0. (q, J = 285.1 Hz), 127.4, 154.4, 167.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –83.2; IR (neat) 3339 (OH), 1777 (C=O),

1663 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{13}H_{19}F_3O_5 \bullet NH_4$ 330.1528, found 330.1534 $[M+NH_4]^+$.

Deacetylation of 3,4-Diisopropoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3a). 5-Hydroxy-3,4-diisopropoxy-5-(trifluoromethyl)furan-2(5*H*)-one (8a). A mixture of butenolide **3a** (65.2 mg, 0.2 mmol) and K_2CO_3 (55.3 mg, 0.4 mmol) in MeOH (2 mL) was stirred under air at room temperature for 10 min. The reaction was quenched with sat. aq. NH_4Cl (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 15 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 obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 4:1) to afford **8a** (43.5 mg, 77% yield) as a colorless solid (mp 79.2–79.9 °C); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.26 (d, *J* = 6.4 Hz, 3 H), 1.28 (d, *J* = 6.4 Hz, 3 H), 1.33 (d, *J* = 6.4 Hz, 3 H), 1.36 (d, *J* = 6.4 Hz, 3 H), 4.84 (sept, *J* = 6.4 Hz, 1 H), 5.19 (sept, *J* = 6.4 Hz, 1 H), 5.27 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.15, 22.20, 22.22, 22.3, 74.3, 76.0, 94.7 (q, *J* = 35.3 Hz), 120.7 (q, *J* = 284.8 Hz), 121.1, 151.8, 166.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –83.4; IR (neat) 3339 (OH), 1769 (C=O), 1676 (C=C) cm^{-1}; HRMS (DART) *m/z* calcd for $C_{11}H_{15}F_3O_5 \bullet NH_4$ 302.1215, found 302.1216 $[M+NH_4]^+$.

Acetylation of 5-Hydroxy-3,4-diisopropoxy-5-(trifluoromethyl)furan-2(5*H*)-one (8a). A mixture of 5-hydroxybutenolide **8a** (56.8 mg, 0.2 mmol), AcCl (28.4 μL, 0.4 mmol), and Et_3N (55.7 μL, 0.4 mmol) in dry Et_2O (2 mL) was stirred under an Ar atmosphere at room temperature for 10 min. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with H_2O (3 × 20 mL), brine (20 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/AcOEt 3:1) to afford **3a** (54.0 mg, 83% yield) as a colorless solid.

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