SYNTHESIS OF $\gamma$-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 $\gamma$-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. Although the efficient introduction of a CF$_3$ group on the $sp^2$ carbons of heterocyclic scaffolds has been extensively investigated, 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). We also accomplished the skeletal divergent synthesis of trifluoromethylated functional molecules using 1 as a novel CF$_3$-containing building block. In this study, $\alpha$-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)$_4$. Since tetronate is a highly important scaffold found in diverse bioactive molecules, we decided to develop an alternative approach to $\gamma$-CF$_3$-substituted tetronates 3, which have a CF$_3$ group on the $sp^3$ carbon (Scheme 2). The synthesis of $\gamma$-CF$_3$-substituted tetronic acid derivatives has been almost neglected and, to the best of our knowledge, only two methods
have been reported previously. However, these methods require multi-step synthetic sequences and/or lack generality. Herein, we report our study on the short-step synthesis of $\gamma$-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 $\gamma$-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$_3$, under modified Mukaiyama conditions. 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$_4$NCl proved to be efficient as initiator in this solvent. However, AcONa was reported to efficiently initiate the trifluoromethylation in the absence of Bu$_4$NCl in the highly polar solvent DMF. 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](image)

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.
To improve the yield of 3b, the reaction of 5b was reinvestigated by adding the inorganic base K$_2$CO$_3$ (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$_2$CO$_3$ are required for the oxidative ring expansion of 5b as the yield of 3b significantly dropped to 17% in the absence of MS 4A.

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$_2$CO$_3$ in MeOH) to afford 8a in 77% yield. Conversely, the acetylation of 8a using acetyl chloride and Et$_3$N produced 3a in 83% yield. Therefore, it was reasoned that 8a was formed via hydrolysis of the acetate moiety.
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$_2$F$_5$ 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$_6$F$_5$ 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 9 outlines the plausible mechanism of oxidative ring expansion of 4-hydroxycyclobutenones 5, 7, and 9. As previously suggested, 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 \(\gamma\)-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.

In conclusion, we successfully developed a new route to \(\gamma\)-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 \(\gamma\)-CF\(_3\)-substituted tetronates were efficiently obtained in approximately 70% yield upon treatment of 4-hydroxycyclobutenones possessing isoproxy 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\(_2\)CO\(_3\) 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\textsubscript{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 (\textsuperscript{1}H/400 MHz, \textsuperscript{13}C/100 MHz, and \textsuperscript{19}F/376MHz) for samples in CDCl\textsubscript{3} solutions at 25 °C. \textsuperscript{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. \textsuperscript{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\textsubscript{3}. \textsuperscript{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.\textsuperscript{2} CF\textsubscript{3}SiMe\textsubscript{3} (Fluorochem), Pb(OAc)\textsubscript{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\textsubscript{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\textsubscript{2}O (3 × 15 mL). The combined organic layer was washed with H\textsubscript{2}O (3 × 20 mL) and brine (20 mL), and dried over MgSO\textsubscript{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;\textsuperscript{3} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{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); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}, 25 °C): δ –76.7.

2,3-Di-tert-butoxy-4-hydroxy-4-(trifluoromethyl)cyclobut-2-enone (5b);\textsuperscript{2} colorless solid; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, 25 °C): δ 1.50 (s, 9 H), 1.55 (s, 9 H), 3.00 (br s, 1 H); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{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): \(\delta\) 3.40 (s, 1 H), 4.03 (s, 3 H), 4.20 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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): \(\delta\) –75.4; IR (neat) 3379 (OH), 1785 (C=O), 1631 (C=C) cm\(^{-1}\); HRMS (DART) \(m/z\) calcd for C\(_{14}\)H\(_{13}\)F\(_3\)O\(_5\)•NH\(_3\) 230.0640, found 230.0644 [M+NH\(_3\)]\(^+\).

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): \(\delta\) 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): \(\delta\) 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): \(\delta\) –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\(_3\)O\(_5\)+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): \(\delta\) 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): \(\delta\) 22.2, 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): \(\delta\) –76.4; IR (neat) 3382 (OH), 1762 (C=O), 1647 (C=C), 1549 (C=C) cm\(^{-1}\); HRMS (DART) \(m/z\) calcd for C\(_{16}\)H\(_{14}\)F\(_3\)O\(_5\)+H 277.0688, found 277.0706 [M+H]\(^+\).

2-(Furan-2-yl)-4-hydroxy-3-isopropoxy-4-(trifluoromethyl)cyclobut-2-enone (7c): yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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): \(\delta\) 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): \(\delta\) –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\(_{14}\)F\(_3\)O\(_5\)+H 328.1161, found 328.1180 [M+NH\(_3\)]\(^+\).

4-Hydroxy-3-isopropoxy-2-(phenylethynyl)-4-(trifluoromethyl)cyclobut-2-enone (7d): yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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): \(\delta\) 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): \(\delta\) –76.6; IR (neat) 3345 (OH), 1766 (C=O), 1611 (C=C) cm\(^{-1}\); HRMS (DART) \(m/z\) calcd for C\(_{16}\)H\(_{13}\)F\(_3\)O\(_5\)+H 242.1004, found 242.1012 [M+NH\(_3\)]\(^+\).

2-Butyl-4-hydroxy-3-isopropoxy-4-(trifluoromethyl)cyclobut-2-enone (7e): yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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); 
\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{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; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}, 25 °C): δ –76.4; IR (neat) 
3347 (OH), 1761 (C=O), 1607 (C=C) cm\textsuperscript{-1}; HRMS (DART) m/z calcd for C\textsubscript{12}H\textsubscript{17}F\textsubscript{3}O\textsubscript{3}•H 267.1208, 
found 267.1213 [M+H]+.

**Typical Procedure for Perfluoroethylolation 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\textsubscript{2}F\textsubscript{5} (140 \textmu L, 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\textsubscript{2}O (3 × 
15 mL). The combined organic layer was washed with H\textsubscript{2}O (3 × 20 mL) and brine (20 mL), and dried 
over MgSO\textsubscript{4}. The solvents were evaporated \textit{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): \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{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); \textsuperscript{13}C 
NMR (100 MHz, CDCl\textsubscript{3}, 25 °C): δ 22.5, 23.1, 81.7, 92.1 (dd , J = 28.2, 22.4 Hz), 11 2.4 (ddq, J = 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; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{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\textsuperscript{-1}; 
HRMS (DART) m/z calcd for C\textsubscript{15}H\textsubscript{13}F\textsubscript{5}O\textsubscript{3}•H 337.0863, found 337.0834 [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-hydroxycyclobutene 5a (107.2 mg, 0.4 mmol), Pb(OAc)\textsubscript{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 H₂O (20 mL), and insoluble materials were filtered through a pad of Celite®, and the residue was washed with CH₂Cl₂ (20 mL). The filtrate was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layer was washed with brine (20 mL), and dried over Na₂SO₄. 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: ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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; ¹⁹F NMR (376 MHz, CDCl₃, 25 °C): δ −83.4; IR (neat) 1798 (C=O), 1690 (C=C) cm⁻¹; HRMS (DART) m/z calcd for C₁₃H₁₇F₃O₆•NH₄⁺ 344.1321, found 344.1323 [M+NH₄⁺].

3,4-Di-tert-butoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3b): colorless oil: ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 1.50 (s, 18 H), 2.16 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃, 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; ¹⁹F NMR (376 MHz, CDCl₃, 25 °C): δ −83.0; IR (neat) 1805 (C=O), 1665 (C=C) cm⁻¹; HRMS (DART) m/z calcd for C₁₅H₂₁F₃O₆•NH₄⁺ 372.1634, found 372.1635 [M+NH₄⁺].

3,4-Dimethoxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3c): colorless oil: ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 2.18 (s, 3 H), 3.92 (s, 3 H), 4.17 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃, 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; ¹⁹F NMR (376 MHz, CDCl₃, 25 °C): δ −83.4; IR (neat) 1809 (C=O), 1699 (C=C) cm⁻¹; HRMS (DART) m/z calcd for C₉H₉F₃O₆•NH₄⁺ 288.0696, found 288.0702 [M+NH₄⁺].

3-Isopropoxy-5-oxo-4-phenyl-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3d): colorless solid (mp 65.3–67.7 °C); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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, 166.8, 168.0; ¹⁹F NMR (376 MHz, CDCl₃, 25 °C): δ −82.6; IR (neat) 1794 (C=O), 1670 (C=C) cm⁻¹; HRMS (DART) m/z calcd for C₁₆H₁₅F₃O₅•NH₄⁺ 362.1215, found 362.1233 [M+NH₄⁺].

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); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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; ¹⁹F NMR (376 MHz, CDCl₃, 25 °C): δ −82.5; IR (neat) 1794 (C=O), 1676 (C=C) cm⁻¹; HRMS
(DART) m/z calcd for C_{18}H_{13}F_{3}O_{5}•NH_{4}: 352.1008, found 352.1005 [M+NH_{4}]^+

3-Isoproxy-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): \(\delta\) 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): \(\delta\) 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): \(\delta\) –82.7; IR (neat) 2221 (C=C), 1807 (C=O), 1658 (C=C) cm\(^{-1}\); HRMS (DART) m/z calcd for C\(_{18}\)H\(_{13}\)F\(_3\)O\(_5\)•NH\(_4\): 386.1215, found 386.1199 [M+NH\(_4\)]^+

3-Isoproxy-4-methyl-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3g): colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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): \(\delta\) 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): \(\delta\) –83.0; IR (neat) 1796 (C=O), 1679 (C=C) cm\(^{-1}\); HRMS (DART) m/z calcd for C\(_{18}\)H\(_{13}\)F\(_3\)O\(_5\)•NH\(_4\): 300.1059, found 300.1055 [M+NH\(_4\)]^+

4-Butyl-3-isoproxy-5-oxo-2-(trifluoromethyl)-2,5-dihydrofuran-2-yl acetate (3h): yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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, \(J = 6.0\) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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): \(\delta\) –83.0; IR (neat) 1794 (C=O), 1670 (C=C) cm\(^{-1}\); HRMS (DART) m/z calcd for C\(_{18}\)H\(_{19}\)F\(_3\)O\(_5\)•NH\(_4\): 342.1528, found 342.1517 [M+NH\(_4\)]^+

3-Isoproxy-5-oxo-4-phenyl-2-(perfluoroethyl)-2,5-dihydrofuran-2-yl acetate (10a): colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C): \(\delta\) 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): \(\delta\) 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): \(\delta\) –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\(_{19}\)H\(_{15}\)F\(_5\)O\(_5\)•NH\(_4\): 412.1183, found 412.1800 [M+NH\(_4\)]^+

5-Hydroxy-4-isoproxy-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): \(\delta\) 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): \(\delta\) 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): \(\delta\)
-126.6 (d, \( J = 288.8 \) Hz), -125.1 (d, \( J = 277.5 \) Hz), -80.7; \( ^{13} \)C NMR (100 MHz, CDCl\(_3\), 25 °C): \( \delta \) 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, 131.7; \( ^{19} \)F NMR (376 MHz, CDCl\(_3\), 25 °C): \( \delta \) -158.6 (t, \( J = 23.1 \) Hz), -147.6, -141.4 (d, \( J = 23.7 \) Hz); IR (neat) 1789 (C=O), 1670 (C=C) cm\(^{-1}\); HRMS (DART) \( m/z \) calcd for C\(_{21}\)H\(_{14}\)F\(_{15}\)O\(_{6}\)•H\(_{4}\) 515.1498, found 515.1498 [M+H\(^{+}\)].

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): \( \delta \) 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): \( \delta \) 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): \( \delta \) -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\(_{14}\)F\(_{15}\)O\(_{6}\)•H\(_{4}\) 515.1498, found 515.1498 [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): \( \delta \) 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): \( \delta \) 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, 128.94, 129.3, 130.0 (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): \( \delta \) -161.9 (t, \( J = 23.1 \) Hz), -152.3 (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\(_{15}\)O\(_{6}\)•H\(_{4}\) 515.1498, 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 \textit{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(5H)-one (8b): yellow solid (mp 69.2–70.5 °C); \(^1\)H NMR (400 MHz, CDCl\(_3\), 25 °C): \( \delta \) 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): \( \delta \) 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): \( \delta \) -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$_3$O•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$_2$CO$_3$ (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$_4$Cl (5 mL), and the mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic layer was washed with brine (20 mL), and dried over Na$_2$SO$_4$. 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); $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta$ 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): $\delta$ 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): $\delta$ –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$_3$O•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$_3$N (55.7 µL, 0.4 mmol) in dry Et$_2$O (2 mL) was stirred under an Ar atmosphere at room temperature for 10 min. The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layer was washed with H$_2$O (3 × 20 mL), brine (20 mL), and dried over Na$_2$SO$_4$. 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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**REFERENCES**

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