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SYNTHESIS OF γ-DIFLUOROMETHYLATED TETRONATE DERIVATIVES FROM SQUARATES USING DIFLUOROMETHYLPHOSPHONATE

Yoshihiko Yamamoto,* Yuki Ishida, Takashi Kurohara, Masatoshi Shibuya, and Takeshi Yasui

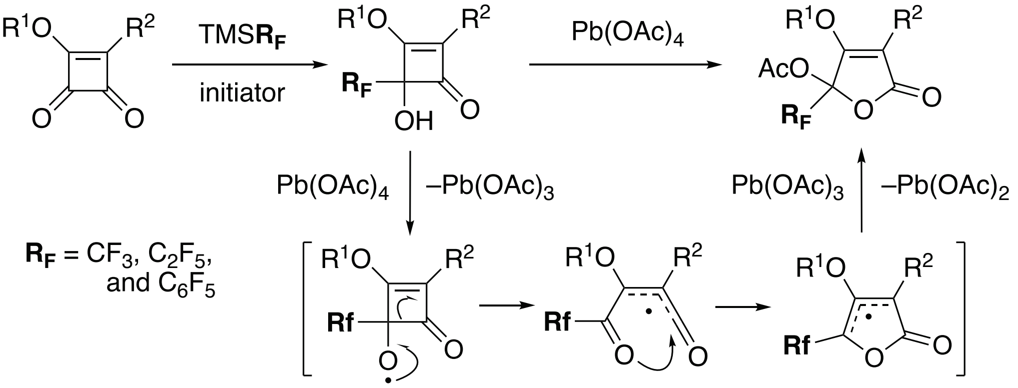
Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan. E-mail: yamamoto-yoshi@ps.nagoya-u.ac.jp

Abstract – A new method for the synthesis of γ-difluoromethylated tetronates was developed using diethyl difluoromethylphosphonate as a difluoromethyl (CF_2H) surrogate. The addition of a lithiated difluoromethylphosphonate to (semi)squarates at –90 °C afforded 4-hydroxycyclobutenones, which were converted into the corresponding tetronates by oxidative ring expansion using $Pb(OAc)_4$. The final dephosphorylation was performed in MeOH using Cs_2CO_3 as the base, affording the desired γ-difluoromethyltetronates.

INTRODUCTION

A trifluoromethyl (CF_3) group can improve the bioactivity of drug molecules by modifying their lipophilicity, receptor interactions, and metabolic stability.[1] Therefore, diverse methods for trifluoromethylation have been extensively developed to date.[2] In contrast, the introduction of a difluoromethyl group (CF_2H) has been less investigated,[3] even though this group is fascinating as a bioisostere of hydroxy and mercapto groups.[4]

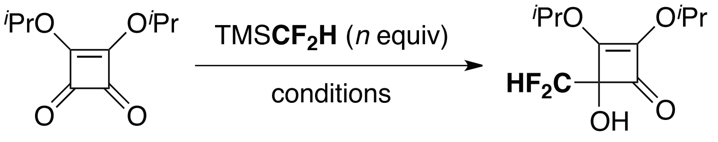
We have reported on the divergent synthesis of organofluorine compounds using semisquarates as the building blocks.[5,6] Although our method allows the introduction of α,α-difluoroacetate substituents to quinones, tetronates, and cyclopentenones, attempts to convert the α,α-difluoroacetate group to a difluoromethyl group resulted in complete failure.[6] Thus, we turned our attention to diethyl difluoromethylphosphonate because its acidic proton can be abstracted by lithium diisopropylamide (LDA) and the anion thus generated efficiently adds to ketones and aldehydes.[7] Moreover, the treatment of the obtained adducts with a base produces difluoromethylated carbinols *via* the C to O phospha-Brook rearrangement.[8] We also previously demonstrated that several perfluorinated groups could be introduced to (semi)squarates by a 1,2-addition using Ruppart–Prakash-type reagents, and the 4-hydroxycyclobutenones obtained undergo oxidative ring expansion to produce tetronate derivatives with the perfluorinated groups (R_F) at the γ-position (Scheme 1).[9,10] Because tetronate is a highly important motif found in diverse bioactive molecules,[11] we investigated an alternative approach to tetronates bearing a CF_2H substituent at the γ position. Herein, we report the results of our study on the synthesis of γ-difluoromethyltetronate derivatives from squarates using diethyl difluoromethylphosphonate as a CF_2H surrogate.



Scheme 1. Previous synthesis of tetronates with perfluorinated groups at the γ-position

RESULTS AND DISCUSSION

At the outset of this study, we investigated the difluoromethylation of diisopropyl squarate (**1**) using $TMSCF_2H$. It had been reported that unlike trifluoromethylation of aldehydes and ketones using $TMSCF_3$, the corresponding difluoromethylation using $TMSCF_2H$ required harsh reaction conditions.[12] Thus, recently developed methods were applied to **1** as shown in Scheme 2. According to a report by Hu and coworkers,[13] **1** and $TMSCF_2H$ (1.5 equiv) were treated with CsF (15 mol%) in DMF for 24 h at room temperature, affording the desired 1,2-adduct **2**, albeit in low yield (conditions a). To improve the yield, an alternative Hu's procedure using $TMSCF_2H$/*t*-BuOK (3 equiv each)[13] was used. The reaction was performed at –78 °C to 0 °C for 1 h, unfortunately resulting in a complex mixture (conditions b). Thus, the same reaction was repeated at –90 °C for 1 h, affording **2** in 19% yield (conditions c). The recently reported method using CsF/18-crown-6 (10 mol%) was also examined;[14] however, the yield of **2** dropped significantly to 7%. Therefore, direct difluoromethylation using $TMSCF_2H$ proved to be infeasible.

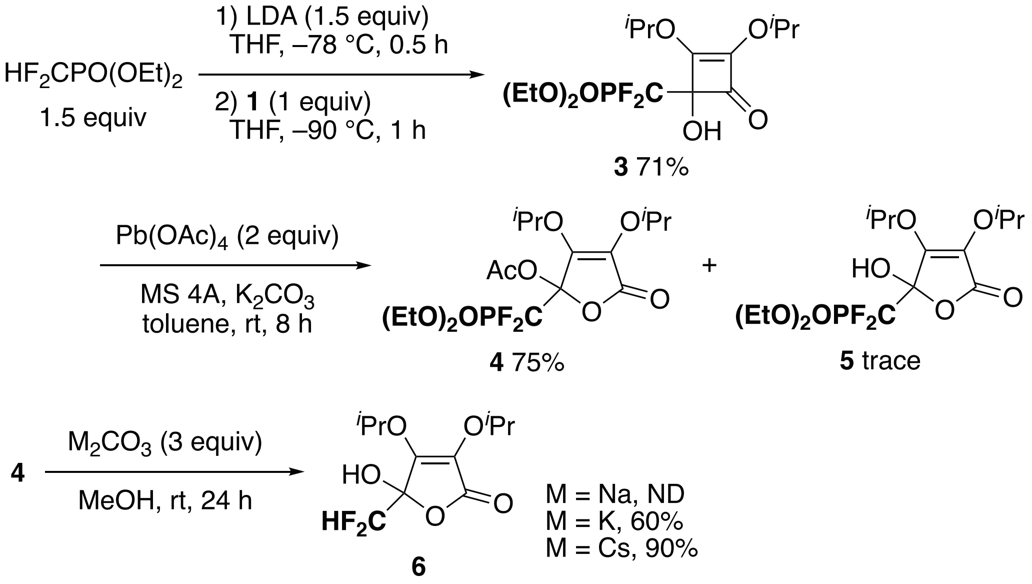


1 **2**

(a) *n* = 1.5, CsF (15 mol%), DMF, rt, 24 h: 29%
(b) *n* = 3.0, ^{t}BuOK (3.0 equiv), THF, –78 °C to 0 °C, 1 h: ND
(c) *n* = 3.0, ^{t}BuOK (3.0 equiv), THF, –90 °C, 1 h: 19%
(d) *n* = 3.0, CsF/18-crown-6 (10 mol%), THF, rt, 15 h: 7%

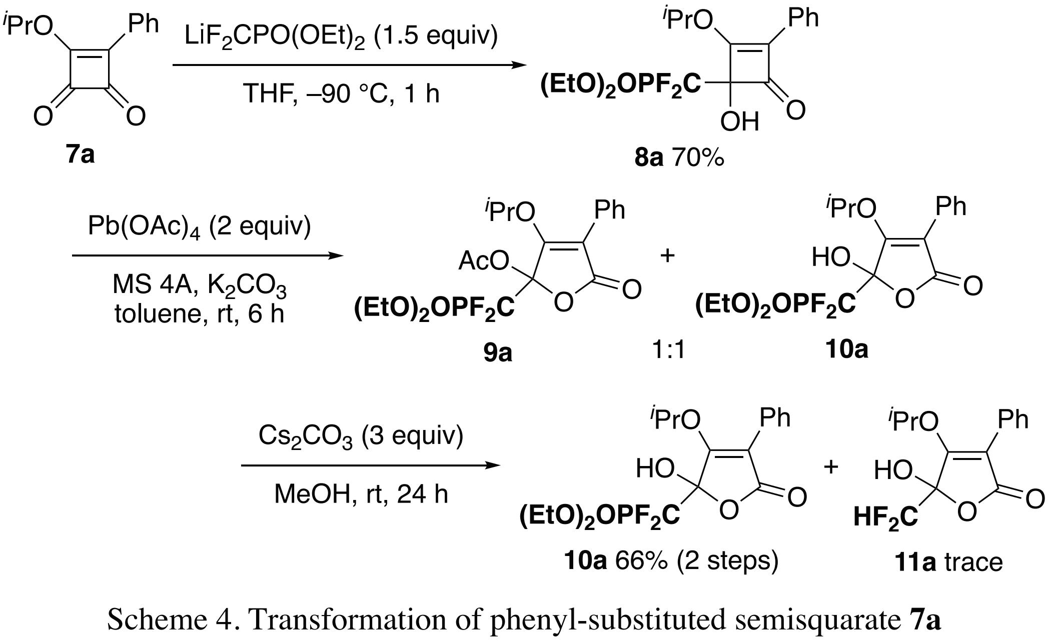
Scheme 2. Direct difluoromethylation of squarate **1** using TMSCF$_2$H

We therefore turned to an alternative method for adding a CF$_2$H group by introducing difluoromethylphosphonate as a CF$_2$H surrogate. Diethyl difluoromethylphosphonate (1.5 equiv) was treated with LDA in THF at –78 °C, and then squarate **1** was added to a solution of the resultant lithiated phosphonate at –90 °C to obtain the desired 1,2-addition product **3** in 71% yield (Scheme 3). It was necessary to carry out the reaction of **1** with the phosphonate anion at –90 °C; the yield of **3** was lower (56%) at –78 °C. The isolated product **3** was treated with Pb(OAc)$_4$ (2 equiv) in the presence of MS 4A and K$_2$CO$_3$ in toluene at ambient temperature for 8 h. The desired tetronate **4** was obtained in 75% yield along with trace amounts of deacetylation byproduct **5**. The promoting effect of MS 4A had been observed in our previous study.[9] The addition of K$_2$CO$_3$ was also required for the efficient conversion of **3**. In the absence of K$_2$CO$_3$, a longer reaction time of 15 h was required, even at 50 °C, and the yield of **4** decreased to 66%. Subsequently, dephosphorylation of **4** with concomitant deacetylation was investigated. First, **4** was treated with NaOMe/MeOH according to the previous report;[7] however, a rather complicated mixture including at least three products with a CF$_2$H group was obtained. Thus, milder reaction conditions were sought. The treatment of **4** with K$_2$CO$_3$ (3 equiv) at 0 °C in MeOH resulted in only deacetylation. However, at ambient temperature dephosphorylation proceeded slowly for 24 h, affording the desired γ-difluoromethyltetronate **6** in 60% yield. When Cs$_2$CO$_3$ was used instead of K$_2$CO$_3$, the reaction mixture became homogeneous and afforded **6** in 90% yield. In contrast, when Na$_2$CO$_3$ was used as a base, only deacetylation occurred, even at room temperature. These results show the importance of the counter-cations of the M$_2$CO$_3$ bases.



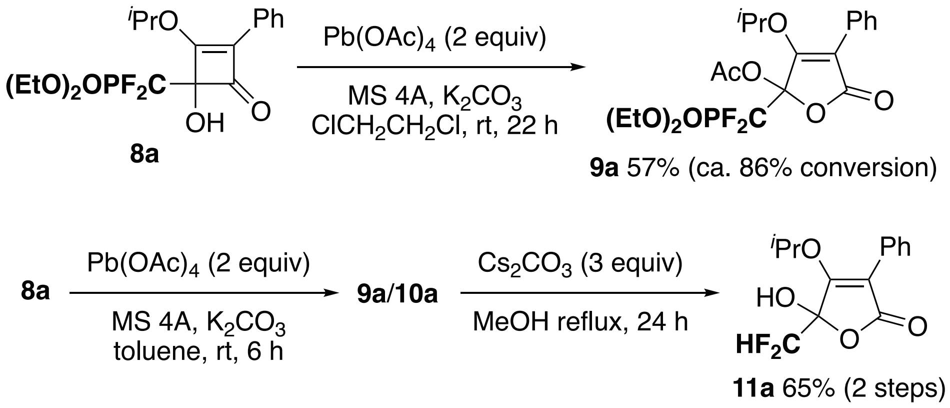
Scheme 3. Synthesis of γ-difluoromethyltetronate **6** from squarate **1**

Next, the transformation of semisquarates into the corresponding γ-difluoromethylated tetronates was investigated. Phenyl-substituted semisquarate **7a** was employed as a representative substrate (Scheme 4). Similar to the transformation of **1**, the addition of the lithiated phosphonate to **7a** was performed in THF at –90 °C for 1 h. As a result, the phosphonate was selectively introduced to the more reactive vinylogous ketone carbonyl to afford 4-hydroxycyclobutenone **8a** in 70% yield. The obtained adduct **8a** was then treated with $Pb(OAc)_4$ under the optimized conditions above. The complete consumption of **8a** within 6 h was confirmed by TLC analysis, but two products were detected.



Scheme 4. Transformation of phenyl-substituted semisquarate **7a**

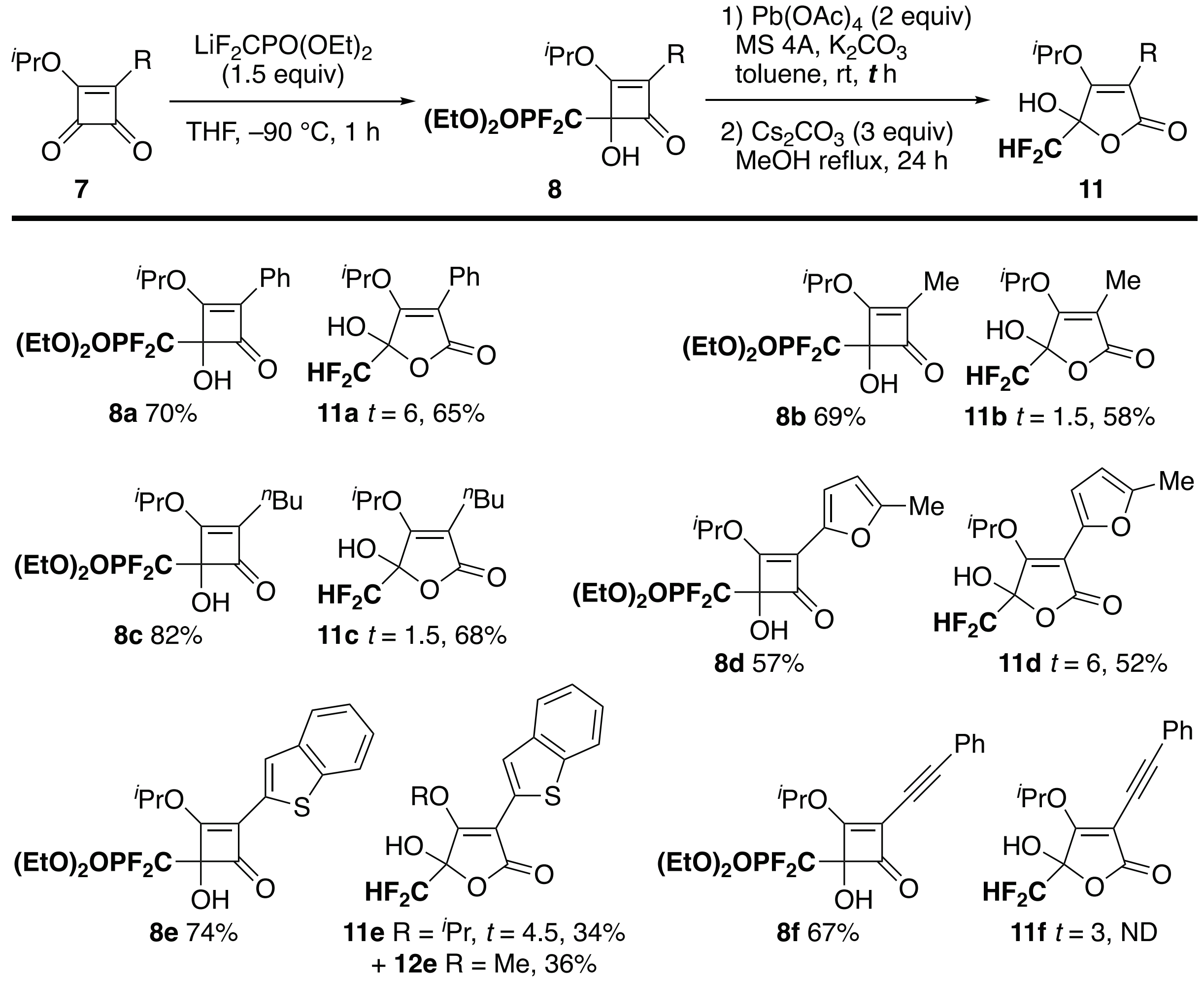
The ^{1}H NMR analysis of the crude material revealed that the expected acetoxylated tetronate **9a** and its deacetylated product **10a** were formed in a 1:1 ratio. Because the subsequent dephosphorylation is accompanied by deacetylation, the obtained mixture was directly treated with Cs_2CO_3 in MeOH at room temperature. Although deacetylation rapidly proceeded under these conditions, very little dephosphorylation was observed after 24 h. The deacetylation product **10a** was therefore isolated in 66% yield over the two steps. The oxidative ring expansion/dephosphorylation process was therefore reoptimized for 4-hydroxycyclobutenone **8a** (Scheme 5). First, 1,2-dichloroethane was examined as the solvent for oxidative ring expansion because it was as effective as toluene in our previous study.[9] However, the oxidative ring expansion of **8a** proved to be sluggish in this solvent and it took 22 h to reach a conversion of ca. 86%. Interestingly, deacetylation was suppressed in this solvent and acetoxylated product **9a** could be isolated in 57% yield. The crude product mixture derived from the oxidative ring expansion of **8a** in toluene was treated with Cs_2CO_3 in MeOH under reflux for 24 h. As a result, dephosphorylation efficiently proceeded to afford the desired γ-difluoromethyltetronate **11a** in 65% yield over the two steps.



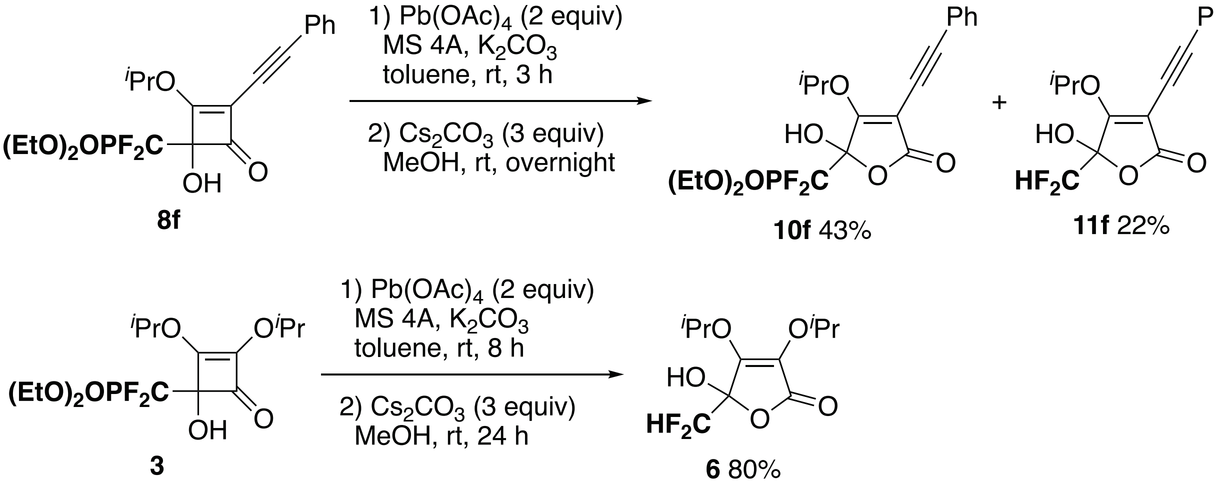
Scheme 5. Synthesis of γ-difluoromethyltetronate **11a** from 4-hydroxycyclobutenone **8a**

The scope of the semisquarate substrates was briefly examined as shown in Scheme 6. The reaction of methyl-substituted semisquarate **7b** with the lithiated difluoromethylphosphonate under standard conditions afforded the corresponding 4-hydroxycyclobutenone **8b** in a similar yield to that of phenyl-analog **8a**. The oxidative ring expansion of **8b** was complete within a shorter reaction time than that of **8a**; however, subsequent dephosphorylation afforded γ-difluoromethyltetronate **11b** in a slightly lower yield (58%) than that of **11a**. The yields were improved when *n*-butyl-substituted semisquarate **7c** was used as the starting material: the corresponding 4-hydroxycyclobutenone **8c** and γ-difluoromethyltetronate **11c** were obtained in 82% and 68% yields, respectively. When semisquarate **7d** bearing a labile and electron-rich 5-methylfuran-2-yl group was used, the corresponding 4-hydroxycyclobutenone **8d** and γ-difluoromethyltetronate **11d** were obtained, albeit in modest yields.

Benzothiophene-substituted 4-hydroxycyclobutenone **8e** was obtained in a good yield, however, its oxidative ring expansion/dephosphorylation afforded methoxy-substituted analog **12e** along with the expected γ-difluoromethyltetronate **11e** in 36% and 34% yields, respectively. The reason why this ester exchange occurred only for **11e** is unclear at this time. The addition of the lithiated phosphonate to alkyne-substituted semisquarate **7f** afforded the corresponding 4-hydroxycyclobutenone **8f** in 67% yield. Although the oxidative ring expansion of **8f** proceeded smoothly, the subsequent dephosphorylation led to an intractable product mixture. This failure can be ascribed to the instability of α-alkynyltetronates under the refluxing conditions. In fact, when the dephosphonylation step was conducted at ambient temperature for 20 h, deacetylated product **10f** was obtained as the major product in 43% yield along with γ-difluoromethyltetronate **11f** in 22% yield (Scheme 7).[14] Finally, the telescoped oxidative ring expansion/dephosphonylation was applied to 4-hydroxycyclobutenone **3**, which was derived from diisopropyl squarate (**1**), to directly afford γ-difluoromethyltetronate **6** in an improved 80% yield (Scheme 7) as compared with the initial synthesis (Scheme 3).



Scheme 6. Synthesis of γ-difluoromethylated tetronates **11** from semisquarates **7**



Scheme 7. Oxidative ring expansion/dephosphonylation of **3** and **8f**

CONCLUSION

In conclusion, we have successfully accomplished a short-step synthesis of γ-difluoromethylated tetronates from (semi)squarates using diethyl difluoromethylphosphonate as a difluoromethyl surrogate. The lithiated phosphonate added to (semi)squarates at –90 °C to afford 4-hydroxycyclobutenones, which were subjected to oxidative ring expansion using $Pb(OAc)_4$. The obtained tetronates bearing a difluoromethylphosphonate substituent at the γ-position were treated with Cs_2CO_3 in MeOH to afford the desired γ-difluoromethyltetronates.

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, ^{19}F/376 MHz, and ^{31}P/161 MHz) 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. ^{31}P NMR spectra are reported in terms of chemical shift (δ, ppm) relative to the singlet at δ 0 ppm for 85% H_3PO_4 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 specrometer. High-resolution mass spectra were recorded on JEOL JMS-T100LP mass spectrometer.

Diisopropyl squarate (**1**) and semisquarates **7a**–**c** and **7f** were known compounds and other semisquarates **7d** and **7e** were also prepared according to the reported procedure.[16]

3-Isopropoxy-4-(5-methylfuran-2-yl)cyclobut-3-ene-1,2-dione (7d): yellow solid (mp 103.6–104.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.48 (d, J = 6.8 Hz, 6H), 2.39 (s, 3H), 5.50 (sept, J = 6.8 Hz, 1H), 6.22–6.26 (m, 1H), 7.18 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 14.0, 22.7, 79.7, 110.1, 119.8, 141.2, 159.2, 162.9, 188.0, 188.9, 189.5; IR (neat) 1786 (C=O), 1739 (C=O), 1616 (C=C) cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{12}NaO_4$ 243.0633, found 243.0634.

3-(Benzo[*b*]thiophen-2-yl)-4-isopropoxycyclobut-3-ene-1,2-dione (7e): yellow solid (mp 164.6–166.6 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.57 (d, J = 6.4 Hz, 6H), 5.58 (sept, J = 6.4 Hz, 1H), 7.38–7.45 (m, 2H), 7.85–7.92 (m, 2H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.9, 80.5, 122.5, 125.2, 125.4, 127.0, 127.1, 128.2, 138.9, 142.6, 159.2, 168.5, 190.5, 191.7; IR (neat) 1782 (C=O), 1745 (C=O), 1606 (C=C) cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{12}NaO_3S$ 295.0405, found 295.0416.

Difluoromethylation of Diisopropyl Squarate (1). 4-(Difluoromethyl)-4-hydroxy-2,3-diisopropoxycyclobut-2-enone (2). To a solution of CsF (7 mg, 0.046 mmol) and diisopropyl squarate (**1**, 59.7 mg, 0.30 mmol) in DMF (1.2 mL) was added Me_3SiCF_2H (62 μL, 0.45 mmol) at room temperature under an argon atmosphere. After stirring for 24 h, the reaction was quenched with H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layer was dried over Na_2SO_4. The crude product was purified by silica gel column chromatography (hexane/AcOEt, 10:1–5:1) to afford **2** (22.0 mg, 29% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.28 (d, J = 6.4 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.40 (d, J = 6.4 Hz, 6H), 3.95 (br s, 1H), 4.90 (sept, J = 6.4 Hz, 1H), 4.92 (sept, J = 6.4 Hz, 1H), 5.95 (t, J = 55.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.2, 22.4, 22.5, 22.6, 74.3, 78.2, 85.4 (dd, J = 26.7, 23.8 Hz), 113.2 (dd, J = 246.0, 244.1 Hz), 134.7, 161.4 (d, J = 1.9 Hz), 179.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ −130.5 (dd, J = 300.4, 54.8 Hz), −128.2 (dd, J = 300.4, 54.8 Hz); IR (neat): 3382 (O–H) 1773 (C=O) 1614 (C=C) cm^{-1}; MS (DART) m/z $[M+H]^+$ calcd for $C_{11}H_{17}F_2O_4$ 251.1095, found 251.1104.

Typical Procedure for Phosphodifluoromethylation. Synthesis of Diethyl Difluoro(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-enyl)methylphosphonate (3). To a solution of ^{i}Pr$_2$NH (630 μL, 4.5 mmol) in THF (12 mL) was added ^{n}BuLi (2.88 mL, 15 w/w%, 4.5 mmol in hexane) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 20 min and cooled to –78 °C. To this mixture was added diethyl difluoromethylphosphonate (706 μL, 4.5 mmol) and the solution was stirred at –78 °C for 30 min. To the resultant solution was added a solution of diisopropyl squarate (**1**, 594.6 mg, 3.0 mmol) in THF (3 mL) mixture cooled to –90 °C and the solution was stirred at this temperature for 30 min. The reaction was quenched by sat. aq. NH_4Cl (20 mL) at –90 °C and the resultant mixture was extracted with AcOEt (3 × 20 mL). The combined organic layer was washed with brine (10 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, 2:1) to afford **3** (821.2 mg, 71%) as a colorless solid (mp 44.9–45.6 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.28 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.39 (t, *J* = 7.6 Hz, 6H), 1.40 (d, *J* = 6.4 Hz, 6H), 4.24–4.42 (m, 4H), 4.71 (br s, 1H), 4.93 (sept, *J* = 6.4 Hz, 1H), 4.94 (sept, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 16.3 (d, *J* = 5.7 Hz), 22.1, 22.3, 22.5, 22.6, 65.3 (d, *J* = 6.6 Hz), 65.7 (d, *J* = 6.7 Hz), 74.1, 77.7, 86.8–87.4 (m), 116.8 (td, *J* = 267.5, 202.1 Hz), 135.1, 159.6, 177.5 (d, *J* = 5.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –119.7 (dd, *J* = 311.9, 104.2 Hz, 1F), –115.9 (dd, *J* = 311.9, 93.3 Hz, 1F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 6.41 (dd, *J* = 93.3, 104.2 Hz); IR (neat) 3292 (OH), 1778 (C=O), 1633 (C=C), 1388 (P=O) cm^{-1}; HRMS (DART): *m/z* $[M+H]^+$ calcd for $C_{15}H_{26}F_2O_7P$ 387.1384, found 387.1402.

Diethyl Difluoro(1-hydroxy-2-isopropoxy-4-oxo-3-phenylcyclobut-2-enyl)methylphosphonate (8a): colorless solid (mp 133.6–136.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.36 (t, *J* = 7.0 Hz, 3H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.48 (d, *J* = 6.4 Hz, 6H), 4.22–4.45 (m, 4H), 5.16 (sept, *J* = 6.4 Hz, 1H), 5.18 (br s, 1H), 7.27–7.32 (m, 1H), 7.34–7.40 (m, 2H), 7.74–7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): Two sp^2 carbons are obscure because of overlapping. δ 16.2 (d, *J* = 4.8 Hz), 16.3 (d, *J* = 3.8 Hz), 22.5, 23.0, 65.3 (d, *J* = 6.7 Hz), 65.7 (d, *J* = 6.7 Hz), 80.8, 93.5 (dt, *J* = 24.8, 19.5 Hz), 116.9 (td, *J* = 269.8, 204.9 Hz), 127.1, 128.1, 128.4, 173.0, 181.2 (d, *J* = 4.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –118.9 (dd, *J* = 312.1, 104.2 Hz, 1F), –113.0 (dd, *J* = 312.1, 86.7 Hz, 1F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 5.49 (t, *J* = 99.7 Hz); IR (neat) 3390 (OH), 1765 (C=O), 1630 (C=C), 1398 (P=O) cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{23}F_2NaO_6P$ 427.1098, found 427.1092.

Diethyl Difluoro(1-hydroxy-2-isopropoxy-3-methyl-4-oxocyclobut-2-enyl)methylphosphonate (8b): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.40 (t, *J* = 7.0 Hz, 6H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.65 (br s, 1H), 1.80 (s, 3H), 4.24–4.44 (m, 4H), 4.86 (sept, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 7.3, 16.3 (d, *J* = 3.8 Hz), 22.2, 22.5, 65.4 (d, *J* = 6.7 Hz), 65.7 (d, *J* = 6.7 Hz), 77.5, 91.8 (m), 116.5 (td, *J* = 269.6, 203.1 Hz), 126.2, 174.4 (d, *J* = 6.7 Hz), 184.1 (d, *J* = 5.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –119.9 (dd, *J* = 312.1, 104.2 Hz, 1F), –116.1 (dd, *J* = 312.1, 104.2 Hz, 1F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 5.63 (t, *J* = 100.5 Hz); IR (neat) 3265 (OH), 1768 (C=O), 1616 (C=C), 1400 (P=O) cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{21}F_2NaO_6P$ 365.0942, found 365.0957.

Diethyl (3-Butyl-1-hydroxy-2-isopropoxy-4-oxocyclobut-2-enyl)difluoromethylphosphonate (8c): yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.29–1.40 (m, 4H), 1.39 (t, *J* = 6.8 Hz, 6H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.43 (d, *J* = 6.4 Hz, 3H), 1.51–1.60 (m, 2H), 4.24–4.44 (m, 4H), 4.79 (br s, 1H), 4.85 (sept, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ 13.6, 16.2 (d, *J* = 5.8 Hz), 22.1, 22.3, 22.4, 22.6, 29.2, 65.3 (d, *J* = 6.7 Hz), 65.7 (d, *J* = 6.7 Hz), 77.8, 91.8 (m), 116.7 (td, *J* = 268.4, 218.4 Hz), 131.2, 173.9, 183.9 (d, *J* = 5.7 Hz); ^{19}F NMR (376 MHz, CDCl$_3$, 25 °C): δ –120.1 (dd, *J* = 312.1, 104.2 Hz, 1F), –115.4 (dd, *J* = 312.1, 104.2 Hz, 1F); ^{31}P NMR (161 MHz, CDCl$_3$, 25 °C) δ 5.87 (t, *J* = 99.7 Hz); IR (neat) 3267 (OH), 1766 (C=O), 1614 (C=C), 1390 (P=O) cm^{-1}; HRMS (ESI): *m/z* [M+Na]$^+$ calcd for C$_{16}$H$_{27}$F$_2$NaO$_6$P 407.1411, found 407.1413.

Diethyl Difluoro(1-hydroxy-2-isopropoxy-3-(5-methylfuran-2-yl)-4-oxocyclobut-2-enyl)methylphosphonate (8d): yellow solid (mp 118.9–119.8 °C); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ 1.32 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.45 (d, *J* = 6.0 Hz, 3H), 2.26 (s, 3H), 4.17–4.39 (m, 4H), 5.29 (sept, *J* = 6.4 Hz, 1H), 5.30 (br s, 1H), 5.99 (d, *J* = 2.8 Hz, 1H), 6.68 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ 13.4, 16.2 (d, *J* = 4.8 Hz), 22.2, 22.5, 65.3 (d, *J* = 6.7 Hz), 65.7 (d, *J* = 6.7 Hz), 79.9, 92.7 (m), 107.5, 113.1, 116.6 (td, *J* = 268.2, 204.1 Hz), 119.6, 140.1, 152.7, 167.0 (m), 178.7 (d, *J* = 6.6 Hz); ^{19}F NMR (376 MHz, CDCl$_3$, 25 °C): δ –119.0 (dd, *J* = 312.1, 104.2 Hz, 1F), –115.5 (dd, *J* = 312.1, 104.2 Hz, 1F); ^{31}P NMR (161 MHz, CDCl$_3$, 25 °C) δ 5.41 (t, *J* = 99.7 Hz); IR (neat) 3253 (OH), 1768 (C=O), 1653 (C=C), 1392 (P=O) cm^{-1}; HRMS (ESI): *m/z* [M+Na]$^+$ calcd for C$_{17}$H$_{23}$F$_2$NaO$_7$P 431.1047, found 431.1066.

Diethyl (3-(Benzo[*b*]thiophen-2-yl)-1-hydroxy-2-isopropoxy-4-oxocyclobut-2-enyl)difluoromethylphosphonate (8e): orange solid (mp 152.0–153.0 °C); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ 1.41 (t, *J* = 7.4 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.51 (d, *J* = 6.0 Hz, 6H), 4.25–4.50 (m, 4H), 5.08 (br s, 1H), 5.21 (sept, *J* = 6.0 Hz, 1H), 7.32–7.38 (m, 2H), 7.70 (s, 1H), 7.77–7.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): One *sp*^{2} carbon is obscure because of overlapping. δ 16.29 (d, *J* = 5.7 Hz), 16.31 (d, *J* = 5.7 Hz), 22.6, 23.1, 65.6 (d, *J* = 7.7 Hz), 66.0 (d, *J* = 6.6 Hz), 81.3 (d, *J* = 3.9 Hz), 93.9 (td, *J* = 19.5, 12.4 Hz), 116.6 (td, *J* = 262.5, 204.1 Hz), 122.1, 124.0, 124.2, 124.6, 125.0, 127.5, 139.2, 139.9, 171.2 (dd, *J* = 7.2, 2.4 Hz), 179.5 (d, *J* = 6.6 Hz); ^{19}F NMR (376 MHz, CDCl$_3$, 25 °C): δ –118.6 (dd, *J* = 312.1, 104.2 Hz, 1F), –113.4 (dd, *J* = 312.1, 104.2 Hz, 1F); ^{31}P NMR (161 MHz, CDCl$_3$, 25 °C) δ 5.23 (t, *J* = 59.3 Hz); IR (neat) 3246 (OH), 1766 (C=O), 1630 (C=C), 1389 (P=O) cm^{-1}; HRMS (ESI): *m/z* [M+Na]$^+$ calcd for C$_{20}$H$_{23}$F$_2$NaO$_6$PS 483.0819, found 483.0815.

Diethyl Difluoro(1-hydroxy-2-isopropoxy-4-oxo-3-(phenylethynyl)cyclobut-2-enyl)methylphosphonate (8f): yellow solid (mp 72.0–74.3 °C); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ 1.28 (t, *J* = 7.0 Hz, 6H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.44 (d, *J* = 6.4 Hz, 3H), 4.14–4.32 (m, 4H), 5.22 (sept, *J* = 6.4 Hz, 1H), 5.81 (br s, 1H), 7.19–7.27 (m, 3H), 7.30–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 15.91 (d, *J* = 4.8 Hz), 15.94 (d, *J* = 5.7 Hz), 21.6, 21.9, 65.1 (d, *J* = 6.7 Hz), 65.4 (d, *J* = 6.6 Hz), 75.2, 79.7, 92.2 (td, *J* = 24.8, 15.2 Hz), 93.8, 110.5, 116.5 (td, *J* = 267.5, 206.0 Hz), 121.4, 128.1, 128.9, 131.3, 177.2, 180.8; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –120.6 (dd, *J* = 312.1, 104.2 Hz, 1F), –116.9 (dd, *J* = 312.1, 104.2 Hz, 1F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 5.28 (t, *J* = 99.8 Hz); IR (neat) 3236 (OH), 1776 (C=O), 1616 (C=C), 1403 (P=O) cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}F_2NaO_6P$ 451.1098, found 451.1116.

Typical Procedure for Oxidative Ring Expansion. Synthesis of 2-((Diethoxyphosphoryl)difluoromethyl)-3,4-diisopropoxy-5-oxo-2,5-dihydrofuran-2-yl Acetate (4). To a suspension of pulverized MS 4A (2 g), K_2CO_3 (1.115 g, 8.1 mmol), and $Pb(OAc)_4$ (1.776 g, 4.0 mmol) in toluene (6 mL) was added a solution of **3** (792.7 mg, 2.1 mmol) in toluene (14 mL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 8 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 AcOEt. The organic layer was separated and the aqueous layer was extracted with AcOEt (3 × 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/Acetone, 5:1) to afford **4** (671.0 mg, 75% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.28–1.04 (m, 18H), 2.16 (s, 3H), 4.25–4.38 (m, 4H), 4.89 (sept, *J* = 6.0 Hz, 1H), 5.20 (sept, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 16.2 (d, *J* = 5.7 Hz), 21.2, 22.29, 22.31, 22.39, 22.41, 65.1 (d, *J* = 6.7 Hz), 65.2 (d, *J* = 6.6 Hz), 74.0, 75.7, 96.3 (td, *J* = 27.2, 14.3 Hz), 112.5 (dt, *J* = 274.8, 206.9 Hz), 122.2, 151.1 (d, *J* = 3.8 Hz), 164.8, 166.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –112.1 (d, *J* = 95.0 Hz, 2F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 3.16 (t, *J* = 95.0 Hz); IR (neat) 1792 (C=O), 1685 (C=C), 1375 (P=O) cm^{-1}; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{17}H_{28}F_2O_9P$ 445.1439, found 445.1413.

2-((Diethoxyphosphoryl)difluoromethyl)-3-isopropoxy-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl Acetate (9a): 1,2-Dichloroethane was used instead of toluene; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.03 (d, *J* = 6.0 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.41 (t, *J* = 7.0 Hz, 3H), 2.21 (s, 3H), 4.24–4.44 (m, 4H), 4.66 (sept, *J* = 6.0 Hz, 1H), 7.35–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 16.2 (d, *J* = 5.8 Hz), 16.3 (d, *J* = 4.7 Hz), 21.2, 21.6, 21.8, 65.3 (d, *J* = 6.7 Hz), 65.4 (d, *J* = 6.7 Hz), 76.1, 97.7 (m), 106.2, 114.8 (td, *J* = 274.1, 207.9 Hz), 128.3, 128.7, 129.1, 130.0, 164.5 (d, *J* = 2.8 Hz), 167.0, 168.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –120.9 (d, *J* = 92.5 Hz, 2F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 2.69 (t, *J* = 95.5 Hz); IR (neat) 1788 (C=O), 1668 (C=C), 1377 (P=O) cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{25}F_2NaO_8P$ 485.1153, found 485.1149.

Typical Procedure for Dephosphorylation. Synthesis of 5-(Difluoromethyl)-5-hydroxy-3,4-diisopropoxyfuran-2(5*H*)-one (6): A solution of **4** (134.5 mg, 0.30 mmol) and Cs_2CO_3 (296 mg, 0.91 mmol) in MeOH (2.4 mL) was stirred at room temperature under an argon atmosphere for 24 h. The reaction was quenched with sat. aq. NH_4Cl (6 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic layer was dried over Na_2SO_4. The solvents were evaporated *in vacuo*, and the crude product was purified by column chromatography (hexane/Acetone, 3:1) to afford **6** (72.1 mg, 90% yield) as a colorless solid (mp 55.3–55.4 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.26 (d, *J* = 6.4 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.37 (d, *J* = 6.4 Hz, 3H), 4.52 (br s, 1H), 4.82–4.91 (m, 1H), 5.17 (sept, *J* = 6.4 Hz, 1H), 5.84 (t, *J* = 54.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.2, 22.26, 22.29, 74.1, 75.7, 95.7 (t, *J* = 25.8 Hz), 111.3 (t, *J* = 249.4 Hz), 120.6, 152.6, 167.5; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –139.3 (dd, *J* = 288.8, 57.5 Hz, 1F), –133.3 (dd, *J* = 288.8, 57.5 Hz, 1F); IR (neat) 3338 (OH), 1763 (C=O), 1678 (C=C) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{11}H_{16}F_2NaO_5$ 289.0864, found 289.0852.

Diethyl Difluoro(2-hydroxy-3,4-diisopropoxy-5-oxo-2,5-dihydrofuran-2-yl)methylphosphonate (5): Deacetylation occurred using K_2CO_3 at 0 °C otherwise under the same conditions to afford **5** in 95% yield; colorless solid (mp 79.2–80.0 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.29 (d, *J* = 6.0 Hz, 6H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.38 (d, *J* = 6.4 Hz, 3H), 1.41 (t, *J* = 7.0 Hz, 6H), 4.28–4.47 (m, 4H), 4.87 (sept, *J* = 6.0 Hz, 1H), 5.20 (sept, *J* = 6.0 Hz, 1H), 6.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 16.1 (d, *J* = 5.7 Hz), 16.2 (d, *J* = 5.7 Hz), 22.26, 22.30, 66.0 (d, *J* = 6.7 Hz), 66.4 (d, *J* = 5.7 Hz), 73.8, 75.4, 96.8 (td, *J* = 27.2, 13.3 Hz), 114.5 (dt, *J* = 274.6, 196.5 Hz), 122.0, 151.3 (d, *J* = 7.6 Hz), 165.5; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –123.3 (d, *J* = 92.5 Hz, 2F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 5.66 (t, *J* = 95.4 Hz); IR (neat) 3176 (OH), 1780 (C=O), 1680 (C=C), 1311 (P=O) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{15}H_{25}F_2NaO_8P$ 425.1153, found 425.1136.

Diethyl Difluoro(2-hydroxy-3-isopropoxy-5-oxo-4-phenyl-2,5-dihydrofuran-2-yl)methylphosphonate (10a): Deacetylation occurred under the typical conditions; colorless solid (mp 108.7–113.0 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.21 (d, *J* = 6.0 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.43 (t, *J* = 7.0 Hz, 6H), 4.32–4.53 (m, 2H), 4.49 (quint, *J* = 7.0 Hz, 2H), 4.88 (sept, *J* = 6.0 Hz, 1H), 6.61 (br s, 1H), 7.34–7.44 (m, 3H), 7.55–7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 16.17 (d, *J* = 6.7 Hz), 16.23 (d, *J* = 5.7 Hz), 22.0, 22.2, 66.0 (d, *J* = 6.6 Hz), 66.7 (d, *J* = 6.6 Hz), 76.4, 98.2 (td, *J* = 27.7, 12.4 Hz), 108.3, 114.7 (td, *J* = 277.7, 196.4 Hz), 128.3, 128.4, 128.8, 129.3, 164.7 (d, *J* = 6.7 Hz), 168.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –123.0 (d, *J* = 104.2 Hz, 2F); ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ 5.55 (t, *J* = 95.4 Hz); IR (neat) 3165 (OH), 1776 (C=O), 1660 (C=C), 1379 (P=O) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{18}H_{23}F_2NaO_7P$ 443.1047, found 443.1069.

Typical Procedure for Sequential Oxidative Ring Expansion/Dephosphonrylation. Synthesis of 5-(Difluoromethyl)-5-hydroxy-4-isopropoxy-3-phenylfuran-2(5*H*)-one (11a): A suspension of pulverized MS 4A (200 mg), K_2CO_3 (110.6. mg, 0.8 mmol), $Pb(OAc)_4$ (179.0 mg, 0.4 mmol), and **8a** (78.2 mg, 0.198 mmol) in toluene (2 mL) was stirred at room temperature under an argon atmosphere for 6 h. The reaction was quenched with H_2O (10 mL) and insoluble materials were filtered through a pad of Celite, and the residue was washed with AcOEt. The organic layer was separated and the aqueous layer was extracted with AcOEt (2 × 25 mL). The combined organic layer was washed with brine (5 mL), and dried over Na_2SO_4. The solvents were evaporated *in vacuo*, and the obtained crude products were used for the subsequent step.

A solution of the crude products and Cs_2CO_3 (197 mg, 0.60 mmol) in MeOH (1.6 mL) was stirred under reflux for 24 h. The reaction was quenched with sat. aq. NH_4Cl (6 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic layer was dried over Na_2SO_4. The solvents were evaporated *in vacuo*, and the crude product was purified by column chromatography (hexane/Acetone, 6:1) to afford **11a** (36.7 mg, 65% yield over two steps) as a colorless solid (mp 119.6–120.3 °C): ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.14 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 4.74 (sept, *J* = 6.4 Hz, 1H), 5.90 (br s, 1H), 5.91 (t, *J* = 54.4 Hz, 1H), 7.34–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 21.8, 21.9, 76.4, 97.8 (t, *J* = 26.3 Hz), 106.1, 111.6 (t, *J* = 249.3 Hz), 128.3, 128.5, 128.7, 129.7, 166.5, 171.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –137.5 (dd, *J* = 288.8, 57.9 Hz, 1F), –133.0 (dd, *J* = 288.8, 57.5 Hz, 1F); IR (neat) 3296 (OH), 1751 (C=O), 1660 (C=C) cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{14}H_{14}F_2NaO_4$ 307.0758, found 307.0783.

5-(Difluoromethyl)-5-hydroxy-4-isopropoxy-3-methylfuran-2(5*H*)-one (11b): colorless solid (mp 94.5–95.2 °C); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.35 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.90 (s, 3H), 4.93 (sept, *J* = 6.0 Hz, 1H), 5.73 (br s, 1H), 5.84 (t, *J* = 54.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 8.4, 22.4, 75.1, 97.6 (t, *J* = 25.3 Hz), 99.3, 111.4 (t, *J* = 248.9 Hz), 165.9, 173.0; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –138.8 (dd, *J* = 288.8, 46.2 Hz, 1F), –133.1 (dd, *J* = 288.8, 57.9 Hz, 1F); IR (neat) 3309 (OH), 1755 (C=O), 1670 (C=C) cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_9H_{12}F_2NaO_4$ 245.0601, found 245.0594.

3-Butyl-5-(difluoromethyl)-5-hydroxy-4-isopropoxyfuran-2(5*H*)-one (11c): colorless solid (mp 65.7–67.0 °C); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.27–1.50 (m, 4H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.38 (d, *J* = 6.0 Hz, 3H), 2.25 (t, *J* = 7.8 Hz, 2H), 4.86 (sept, *J* = 6.0 Hz, 1H), 5.75 (br s, 1H), 5.84 (t, *J* = 54.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 13.6, 22.2, 22.3, 22.4, 22.8, 31.0, 75.2, 97.6 (t, *J* = 26.3 Hz), 105.4, 111.5 (t, *J* = 248.9 Hz), 165.6, 172.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –138.4 (dd, *J* = 288.8, 57.9 Hz, 1F), –135.5 (dd, *J* = 288.8, 57.9 Hz, 1F); IR (neat) 3298 (OH), 1751 (C=O), 1662 (C=C) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{12}H_{18}F_2NaO_4$ 287.1071, found 287.1100.

5-(Difluoromethyl)-5-hydroxy-4-isopropoxy-3-(5-methylfuran-2-yl)furan-2(5*H*)-one (11d): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.31 (d, *J* = 6.4 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 2.31 (s, 3H), 5.11 (sept, *J* = 6.4 Hz, 1H), 5.40 (br s, 1H), 5.90 (t, *J* = 54.2 Hz, 1H), 6.04–6.06 (m, 1H), 6.67 (t, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 13.6, 22.28, 22.31, 78.1, 97.8 (t, *J* = 25.3 Hz), 98.3, 107.6, 111.5 (t, *J* = 249.8 Hz), 113.2, 140.4, 153.1, 164.3, 169.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –138.2 (dd, *J* = 288.8, 57.5 Hz, 1F), –132.7 (dd, *J* = 288.8, 57.5 Hz, 1F); IR (neat) 3326 (OH), 1755 (C=O), 1672 (C=C) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{13}H_{14}F_2NaO_5$ 311.0707, found 311.0677.

3-(Benzo[*b*]thiophen-2-yl)-5-(difluoromethyl)-5-hydroxy-4-isopropoxyfuran-2(5*H*)-one (11e): orange solid (mp 148.5–150.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.42 (d, *J* = 6.0 Hz, 3H), 1.47 (d, *J* = 6.0 Hz, 3H), 5.32 (sept, *J* = 6.0 Hz, 1H), 5.96 (t, *J* = 54.8 Hz, 1H), 6.20 (br s, 1H), 7.29–7.35 (m, 2H), 7.69–7.77 (m, 2H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 22.5, 23.2, 78.8, 98.3 (t, *J* = 27.2 Hz), 104.5, 111.8 (t, *J* = 250.8 Hz), 121.9, 123.9, 124.38, 124.43, 124.9, 129.0, 138.8, 139.8, 165.9, 169.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –133.8 (dd, *J* = 288.8, 57.5 Hz, 1F), –132.5 (dd, *J* = 288.8, 57.5 Hz, 1F); IR (neat) 3259 (OH), 1753 (C=O), 1649 (C=C) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{16}H_{14}F_2NaO_4S$ 363.0479, found 363.0470.

3-(Benzo[*b*]thiophen-2-yl)-5-(difluoromethyl)-5-hydroxy-4-methoxyfuran-2(5*H*)-one (12e): orange solid (mp 135.0–135.9 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 4.24 (s, 3H), 5.98 (t, *J* = 54.8 Hz, 1H), 6.08 (br s, 1H), 7.30–7.35 (m, 2H), 7.67–7.77 (m, 2H), 7.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 61.0 (d, *J* = 3.8 Hz), 98.4 (t, *J* = 27.7 Hz), 103.7, 111.7 (t, *J* = 250.3 Hz), 121.9, 124.0, 124.5, 125.0, 125.1, 128.4, 138.9, 139.9, 166.6, 169.0; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ –133.4 (dd, *J* = 288.8, 57.5 Hz, 1F), –130.8 (dd, *J* = 288.8, 57.5 Hz, 1F); IR (neat) 3267 (OH), 1753 (C=O), 1653 (C=C) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{14}H_{10}F_2NaO_4S$ 335.0166, found 335.0180.

Sequential Oxidative Ring Expansion/Dephosphonrylation of 4-Hydroxycyclobutenone 8f: According to the typical procedure, oxidative ring expansion of **8f** (207.2 mg, 0.484 mmol) was carried out for 3 h, and the resultant product mixture was subjected to dephosphonylation at ambient temperature for 20 h. The crude product was purified by column chromatography (hexane/Acetone, 3:1) to afford **11f** (33.0 mg, 22% yield over two steps) as a pale-yellow solid (mp 135.0–140.3 °C) and further elution (hexane/Acetone, 3:1) to afford **10f** (92.5 mg, 43% yield over two steps) as a colorless solid (mp 119.8–121.2 °C).

Diethyl Difluoro(2-hydroxy-3-isopropoxy-5-oxo-4-(phenylethynyl)-2,5-dihydrofuran-2-yl)methylphosphonate (10f): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.41 (t, *J* = 7.0 Hz, 6H), 1.48 (d, *J* = 6.0 Hz, 3H), 1.51 (d, *J* = 6.0 Hz, 3H), 4.29–4.39 (m, 2H), 4.44 (quint, *J* = 7.0 Hz, 2H), 5.63 (sept, *J* = 6.0 Hz, 1H), 6.61 (br s, 1H), 7.30–7.37 (m, 3H), 7.44–7.49 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): One *sp*^{2} carbon is obscure because of overlapping. δ 16.1 (d, *J* = 6.6 Hz), 16.2 (d, *J* = 7.7 Hz), 22.27, 22.33, 66.1 (d, *J* = 6.7 Hz), 66.6 (d, *J* = 6.7 Hz), 77.6, 89.9, 95.7, 98.9 (td, *J* = 27.4, 13.3 Hz), 114.4 (td, *J* = 274.9, 196.4 Hz), 121.9, 128.4, 129.0, 131.5, 166.7, 168.9 (d, *J* = 7.6 Hz); ^{19}F NMR (376 MHz, CDCl$_3$, 25 °C): δ –123.1 (d, *J* = 92.5 Hz, 2F); ^{31}P NMR (161 MHz, CDCl$_3$, 25 °C) δ 5.12 (t, *J* = 91.0 Hz); IR (neat) 3145 (OH), 1786 (C=O), 1647 (C=C), 1396 (P=O) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{20}H_{23}F_2NaO_7P$ 467.1047, found 467.1048.

5-(Difluoromethyl)-5-hydroxy-4-isopropoxy-3-(phenylethynyl)furan-2(5*H*)-one (11f): ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ 1.48 (d, *J* = 6.4 Hz, 3H), 1.50 (d, *J* = 6.4 Hz, 3H), 5.60 (sept, *J* = 6.4 Hz, 1H), 5.90 (t, *J* = 54.2 Hz, 1H), 7.30–7.38 (m, 3H), 7.43–7.47 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): One *sp*^{2} carbon is obscure because of overlapping. δ 22.3, 77.9, 89.2, 95.8, 98.1 (t, *J* = 26.2 Hz), 111.2 (t, *J* = 249.8 Hz), 121.9, 128.4, 129.1, 131.5, 168.7 (d, *J* = 9.5 Hz), 170.0; ^{19}F NMR (376 MHz, CDCl$_3$, 25 °C): δ –137.9 (dd, *J* = 289.1, 46.2 Hz, 1F), –133.1 (dd, *J* = 288.8, 46.2 Hz, 1F); IR (neat) 3298 (OH), 1757 (C=O), 1649 (C=C) cm^{-1}; HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{16}H_{14}F_2NaO_4$ 331.0758, found 331.0763.

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REFERENCES AND NOTES

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