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Use of Benzofuran for Concomitant Protection of Aldehyde and Phenol Groups in the Preparation of Mycophenolic Acid Analogues

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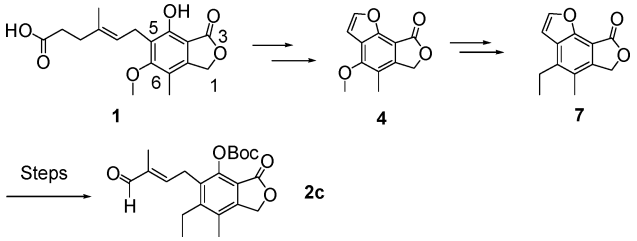

The use of a benzofuran to mask phenol and arylacetaldehyde moieties simultaneously in the synthesis of analogues of mycophenolic acid (MPA) was explored. Benzofuran **4** provided a stable and easily handled intermediate for the preparation of unnatural derivatives at the C-6 position of MPA. Preparation of the highly potent 6-ethyl MPA analogue **2** was accomplished via aldehyde **2c** through this facile route with high-yielding steps and crystalline intermediates.

Introduction

Mycophenolic acid (MPA, compound **1**, Figure 1), produced by *Penicillium brevicompactum* species,[1] has antibiotic,[2] antiviral,[3] and immunosuppressive[4] properties. The morpholinoethyl ester prodrug of MPA, mycophenolate mofetil (MMF, CellCept),[5] is widely used for prevention of kidney allograft rejection. MPA is an inhibitor of inosine monophosphate dehydrogenase (IMPDH),[6] an important enzyme in the *de novo* synthesis of guanine nucleotides. Many analogues of MPA have been prepared, a few of which are more potent in inhibiting IMPDH.[7]

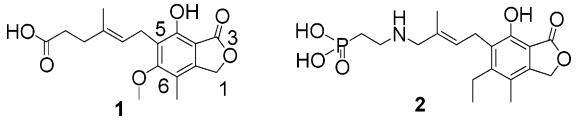

FIGURE 1. Mycophenolic acid (**1**) and target compound **2**.

In particular, replacement of the C-6 methoxy substituent with ethyl or vinyl provides better inhibitors than the parent. As part of a medicinal chemistry program aimed at discovering a phosphonate-containing analogue of MPA that might exhibit prolonged cellular retention, we discovered compound **2**.[8] The attractive general profile of this compound warranted further investigation into a rapid, scalable synthesis making use of minimal protection strategies. A route that would facilitate the exploration of further structural diversity at C-6 was also desirable.

Compound **2** was conveniently prepared from **2a** by global deprotection (Scheme 1). A reductive amination between the commercially available (2-aminoethyl)phosphonic acid diethyl ester **2b** and protected aldehyde **2c** led to preparation of **2a**. Thus, the strategic challenge addressed in this paper relates to the semisynthesis of aldehyde **2c** from MPA.

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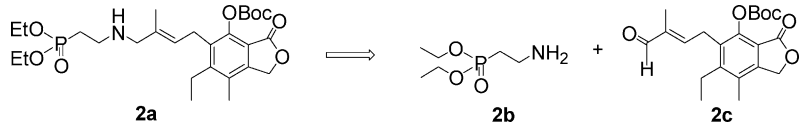
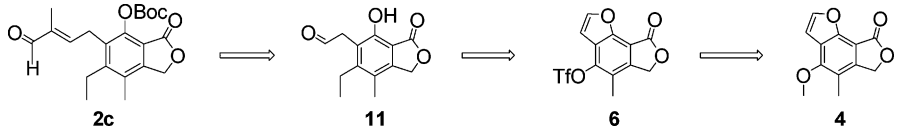
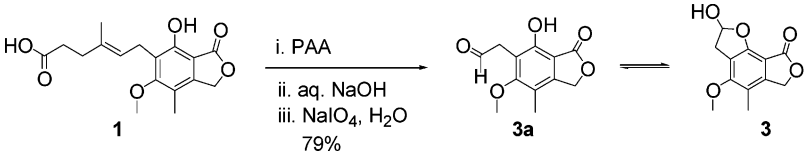
SCHEME 1. Retrosynthetic Analysis for the Preparation of Compound 2a



SCHEME 2. Retrosynthetic Analysis for the Preparation of Aldehyde 2c



SCHEME 3. Oxidative Cleavage of MPA to Aldehyde 3a, which Is in Equilibrium with the Cyclic Hemiacetal 3



The key intermediates envisaged for the synthesis of **2c** are outlined in Scheme 2. We foresaw benzofuran **4** as a precursor of **6**, a flexible intermediate that could be used for preparation of various C-6 analogues. In benzofuran **4**, both the phenol and a side-chain aldehyde (generated by oxidative cleavage of the side chain of MPA) are masked in a highly atom-efficient manner. Furthermore, we expected that benzofuran intermediates would be solids, allowing for crystallization as a convenient method of purification. From prior efforts in the preparation of C-6 analogues, we had noted that the hexasubstituted benzene ring creates a sterically congested environment, and we anticipated that formation of a benzofuran might alleviate the strain and facilitate reactions at this position. Masking the side chain and phenol of MPA as a benzofuran also provides a robust intermediate (**4**) for demethylation, allowing for the use of reagents such as boron tribromide. Such demethylation reactions on MPA or its esters are generally poor yielding, requiring toxic thiols, or lithium iodide in a large volume of collidine[9] at high temperature with mechanical stirring. Therefore, we foresaw broad utility in the use of benzofurans for the preparation of novel MPA analogues.

Results and Discussion

The synthesis of **2c** from MPA requires transformations at C-5 and C-6. We elected to manipulate the side chain at C-5 first for several reasons: (1) the trisubstituted olefin is prone to participate in intramolecular cyclizations with phenols or carboxylates under a variety of electrophilic reaction conditions; (2) we wished to introduce diversity at C-6, and this is inherently more efficiently done at a later stage in the synthesis, and (3) by manipulating the C-5 side chain to mask the C-4 phenol prior to demethylation at C-6, the ensuing problem of phenol chemoselectivity is avoided. While cleavage of this side chain has been reported on protected derivatives of MPA,[10] we chose to oxidize the olefin in the unprotected compound to avoid multiple protection steps.[11] The diol has been generated directly using OsO_4.[12] However, since we were interested in the large scale preparation of aldehyde **2c** and wished to avoid the use of OsO_4, we devised new conditions for the oxidative cleavage of the side chain to aldehyde **3a** using the water soluble peracetic acid (PAA) (Scheme 3). The olefin epoxide is a highly sensitive intermediate that is prone to intramolecular reaction with either the C-4 phenol or the side-chain carboxylic acid if it is not immediately hydrolyzed to the corresponding diol,[13] which is conveniently achieved using aqueous NaOH. Subsequent oxidative cleavage of the diol using sodium periodate resulted in the formation of aldehyde **3a** in a one-pot, three-step sequence. The aqueous conditions also facilitate isolation by simple precipitation. Aldehyde **3a** is in solvent-dependent equilibrium with the hemiacetal **3**. While in $CDCl_3$ a mixture of both isomers is observed, only the hemiacetal **3** is detected in DMSO-d_6. This conversion worked equally well using *m*-CPBA, but the product isolated by precipitation contained some 3-chlorobenzoic acid which was not removed by water washes.

We initially planned on protecting both the phenol and the aldehyde in **3a** since the subsequent reactions involve harsh reaction conditions. Attempts to isolate protected forms of **3a** by acylation or alkylation of the phenol were unsuccessful; mixtures including derivatives of **3** were invariably observed. We decided instead to dehydrate the mixture of **3** and **3a** to the corresponding benzofuran **4** which would provide a stable protecting group for both the aldehyde and the phenol (Scheme 4). Exposure of the mixture to acidic conditions with azeotropic removal of water yielded **4** in quantitative yield. In addition, this compound is crystalline, leading to ease of isolation and purification during scale-up. Demethylation of benzofuran **4** proceeded smoothly and rapidly to provide phenol **5**. The use of boron tribromide for this transformation represents a sub-

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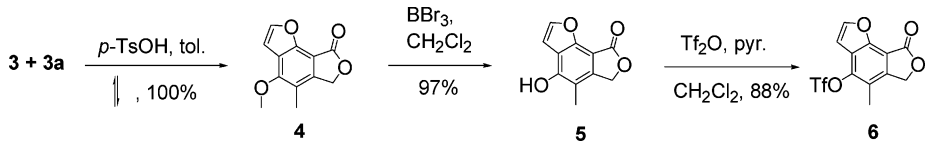
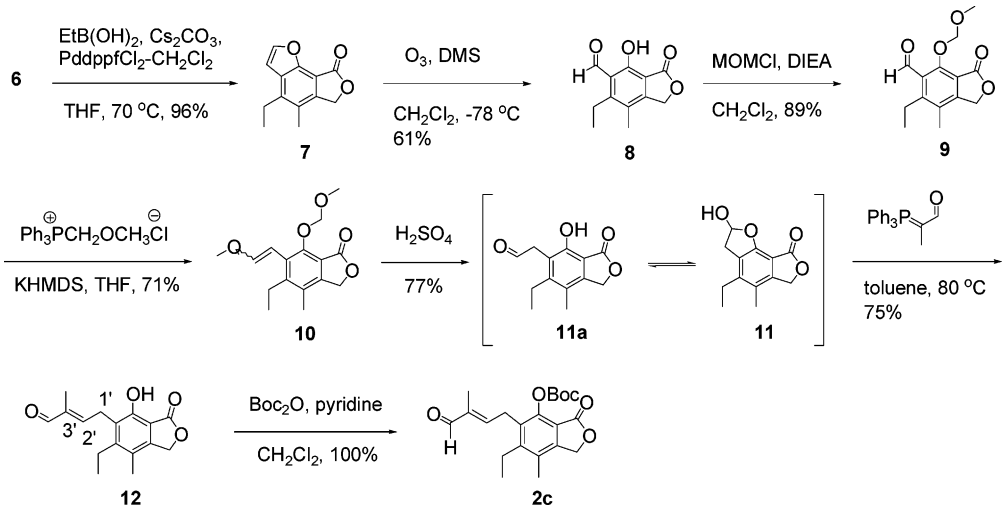
SCHEME 4. Preparation of Key Triflate Intermediate 6



SCHEME 5. Completion of the Synthesis of Aldehyde 2c



stantial improvement on the methods that have been required to demethylate other MPA derivatives.[9]

Converting the phenol **5** to triflate **6** was accomplished using triflic anhydride and pyridine. This intermediate proved very flexible in the synthesis of various analogues of MPA with modifications at C-6, generated by nucleophilic displacement or palladium-mediated coupling reactions. We exemplify its utility in the preparation of the ethyl variant (Scheme 5).

The previous route to the 6-ethyl analogue of MPA exploited the corresponding 6-vinyl intermediate, which was in turn synthesized via a tin-mediated Stille coupling.[7] We chose direct transformation of **6** to the ethyl analogue **7** using Suzuki coupling conditions with ethylboronic acid. The reaction proceeded smoothly to provide **7** in 96% yield. With the desired transformation at C-6 complete, we explored methods for opening of the benzofuran to liberate the C-4 phenol and a functional group at C-5 suitable for elaboration to a variety of side chains. Unexpectedly, benzofuran **7** was resistant to aqueous hydrolysis conditions reported,[14] even under strongly acidic conditions at high temperature. Solvolysis of the benzofuran **7** using 6 N HCl in THF at reflux overnight did not lead to formation of any product as intact starting materials persisted. Mercury-mediated opening of the benzofuran was not attempted as we preferred a scalable route applicable to an industrial setting. Ozonolysis with reductive workup, however, produced aldehyde **8** quickly and cleanly, and so we explored homologation to provide access to the phenacetaldehyde **11a**. We rapidly established that in order for the conventional Wittig reaction using methoxymethyl triphenylphosphonium chloride[15] to proceed, the phenol had to be protected; presumably the unusually acidic phenol ortho to the aldehyde is responsible for the lack of reactivity. This posed a dilemma as to the choice of protecting group. BOC would have been ideal, as it is the moiety present in the ultimate target **2c**. However, its thermal stability was insufficient to survive the conditions necessary for further elaboration of the side chain. We eventually settled on temporary protection with MOM, with concomitant removal during the hydrolysis of the enol ether. Operationally, this was facile: the reaction provided a mixture of *E* and *Z* isomers which were initially separated and characterized individually, but were hydrolyzed together upon scale-up to provide aldehyde **11a** in good yield. As observed for compound **3**, compound **11a** is in solvent-dependent equilibrium with the hemiacetal **11**. Purification was performed using chromatography on a short column, collecting both isomers. No longer in conjugation with the phenol, this aldehyde undergoes the second Wittig reaction smoothly without protection to generate the unsaturated aldehyde **12**. Protection of the phenol in **12** proceeded in quantitative yield to form the desired aldehyde **2c**.

Conclusion

A facile synthetic route for the preparation of various C-6 analogues of MPA is described. Simultaneous protection of both a phenol and a phenacetaldehyde was achieved through the use of a benzofuran. Demethylation of the 6-MeO substituent via this route using BBr_3 is much more facile than prior methods described on other analogues of MPA. This sequence was developed for ease of scale-up, utility of nontoxic reagents and crystalline intermediates.

Experimental Section

2-Hydroxy-4-methoxy-5-methyl-3,6-dihydro-*2H*-1,7-dioxa-*as*-indacen-8-one (3) and (4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)acetaldehyde (3a). To a solution of mycophenolic acid (60 g, 0.19 mol) in THF (250 mL) was added peracetic acid (78 mL of a 32% solution, 0.37 mmol). The reaction mixture was stirred at rt overnight. To the white slurry was added a solution of aqueous 2 N NaOH (850 mL, 1.65 mol), giving a

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clear yellow solution. The mixture was stirred at rt for another 30 min, when a solution of 1 N aq HCl (1000 mL, 1 mol) was added. The reaction mixture was then cooled to 5 °C, and a solution of sodium periodate (80 g, 0.419 mol) in water (1 L) was added in 200 mL portions over 15 min. The product began precipitating before the addition of the sodium periodate solution was complete. The reaction mixture was stirred for another 0.5 h to allow for complete precipitation. The product was filtered, dried, and lyophilized to afford 36.7 g of **3** (79%) as a white solid: mp 152−154 °C; ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3H), 3.09 (d, J = 16.2 Hz, 1H), 3.56 (dd, J = 6.9 Hz, J = *16*.2 Hz, 1H), 3.94 (s, 3H), 5.22 (s, 2H), 6.17 (m, 1H), 7.62 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.2, 36.2, 59.2, 69.2, 101.6, 103.8, 114.2, 114.4, 147.4, 156.0, 159.8, 168.6; HRMS for $C_{12}H_{13}O_5$ calcd [M + H]$^+$ 237.0763, found 237.0760.

4-Methoxy-5-methyl-6*H*-1,7-dioxa-*as*-indacen-8-one (4). The mixture of **3a** and **3** (52 mg, 0.22 mmol) and *p*-toluenesulfonic acid monohydrate (1 mg) was suspended in 2 mL of toluene. The mixture was heated at 110 °C for 4 h, when the reaction was complete as judged by LCMS analysis. The reaction was allowed to cool to rt and quenched by the addition of water. The product was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexanes) to give 49 mg (100%) of the benzofuran **4** as a white solid. Subsequent batches were purified by recrystallization of the product from hot EtOAc/hexanes: mp 171−172 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 4.23 (s, 3H), 5.28 (s, 2H), 7.06 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 59.9, 69.5, 103.8, 105.1, 115.2, 118.1, 144.7, 145.7, 156.7, 168.8, 169.2; HRMS for $C_{12}H_{11}O_4$ calcd [M + H]$^+$ 219.0657, found 219.0655.

4-Hydroxy-5-methyl-6*H*-1,7-dioxa-*as*-indacen-8-one (5). Compound **4** (516 mg, 2.37 mmol) was dissolved in 5 mL of anhydrous dichloromethane. Under an argon atmosphere, boron tribromide (1 M in dichloromethane, 3.55 mL, and 3.55 mmol) was added dropwise. After being stirred at rt for 1 h, the reaction was quenched by the addition of methanol (10 mL). The volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexanes) to give 470 mg (97%) of the title compound as an off-white solid: mp 247−249 °C; ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3H), 5.35 (s, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.9, 69.8, 101.1, 105.2, 111.4, 117.7, 145.1, 147.6, 149.5, 154.9, 168.6; HRMS for $C_{11}H_9O_4$ calcd [M + H]$^+$ 205.0501, found 205.0500.

Trifluoromethanesulfonic Acid 5-Methyl-8-oxo-6,8-dihydro-1,7-dioxa-*as*-indacen-4-yl Ester (6). Compound **4** (200 mg, 0.980 mmol) was suspended in 0.98 mL of dichloromethane. To the solution was added pyridine (600 μL, 7.42 mmol) followed by trifluoromethanesulfonic anhydride (248 μL, 1.47 mmol). The reaction mixture was stirred at rt for 1.5 h, when the reaction was complete as judged by LCMS analysis. The reaction was quenched by the addition of water and CH_2Cl_2. The organic layer was washed with aqueous copper(II) sulfate, dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/hexanes) to give 269 mg (88%) of the triflate **6** as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 5.40 (s, 2H), 6.98 (d, J = 2.7 Hz, 1H), 7.83 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz) δ 11.9, 69.6, 104.4, 110.3, 116.4, 120.3, 122.1 (d, J = 225 Hz), 143.5, 145.4, 147.5, 149.4, 167.1; ^{19}F NMR (282.6 MHz, $CDCl_3$) δ −73.7; HRMS for $C_{12}H_8O_6F_3S$ calcd [M + H]$^+$ 336.9994, found 337.0000.

4-Ethyl-5-methyl-6*H*-1,7-dioxa-*as*-indacen-8-one (7). A solution of triflate **6** (266 mg, 0.791 mmol), cesium carbonate (516 mg, 1.58 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (65 mg, 0.079 mmol), and ethylboronic acid (117 mg, 1.58 mmol) in 4 mL of anhydrous THF under argon was heated at 70 °C overnight. The reaction mixture was worked up by removing the THF under reduced pressure and dissolution of the residue in CH_2Cl_2. The organic layer was washed with water, dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/hexanes) to give 164 mg (96%) of the benzofuran **7** as a white solid: mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3H), 2.31 (s, 3H), 2.96 (q, J = 7.5 Hz, 2H), 5.32 (s, 2H), 6.88 (d, J = 1.8 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 14.2, 23.6, 70.0, 105.3, 107.7, 123.2, 128.6, 143.2, 144.6, 145.8, 148.1, 169.1; HRMS for $C_{13}H_{13}O_3$ calcd [M + H]$^+$ 217.0865, found 217.0869.

6-Ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-carbaldehyde (8). A solution of benzofuran **7** (1.2 g, 5.50 mmol) in anhydrous dichloromethane (5 mL) was cooled to −78 °C in a dry ice/acetone bath. O_3 gas was bubbled through the reaction solution for five minutes, turning the solution blue. The ozone generator was turned off and O_2 gas was bubbled through to purge away any remaining O_3 in the reaction flask. The reaction was quenched by addition of dimethyl sulfide (500 μL, 6.81 mmol). The solution was concentrated *in vacuo* and the residue was purified by silica gel chromatography (EtOAc/hexanes) to give 745 mg (61%) of aldehyde **8** as a white solid: mp 169−170 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.5 Hz, 3H), 2.20 (s, 3H), 3.04 (q, J = 7.5 Hz, 2H), 5.19 (s, 2H), 10.35 (s, 1H), 12.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 15.8, 21.1, 68.8, 110.8, 117.9, 121.0, 154.0, 156.0, 160.7, 168.2, 195.5; HRMS for $C_{12}H_{13}O_4$ calcd [M + H]$^+$ 221.0814, found 221.0816.

5-Ethyl-7-methoxymethoxy-6-(2-methoxyvinyl)-4-methyl-3*H*-isobenzofuran-1-one (10). (Methoxymethyl)triphenylphosphonium chloride (1.11 g, 3.24 mmol) was placed in a flask in 2 mL of anhydrous THF to form a slurry. Potassium hexamethyldisilazide (0.91 M in THF, 3.60 mL, 3.28 mmol) was added dropwise to the reaction mixture, forming a deep red color. The mixture was stirred for 30 min to ensure complete ylide formation. In a separate flask, protected aldehyde **9** (284 mg, 1.076 mmol) was dissolved in 1.5 mL of THF. The red ylide solution was then added dropwise to the stirred solution of **7,** and the mixture was stirred for another 30 min at rt, when reaction was complete as indicated by LCMS. The solvents were removed under reduced pressure, and the crude material was partitioned between ethyl acetate (60 mL) and water (40 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (1 × 30 mL) and brine (1 × 30 mL), dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/Hexanes) to provide 222 mg (71%) of a mixture of isomers of enol ether **10** as a white solid. The isomers were separated by chromatography and characterized individually. Eluting first was the *E* isomer as the major product (R_f = 0.8 in 1:1 EtOAc/hexanes) followed by the more polar minor product *Z* isomer (R_f = 0.7). ***E* configuration:** mp 87−88 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.8 Hz, 3H), 2.19 (s, 3H), 2.76 (q, J = 7.5 Hz, 2H), 3.54 (s, 3H), 3.73 (s, 3H), 5.14 (s, 2H), 5.26 (s, 2H), 5.68 (d, J = 12.6 Hz, 1H), 6.96 (d, J = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 14.3, 23.8, 56.6, 57.8, 68.4, 96.933, 100.7, 114.3, 124.9, 129.3, 145.3,149.9, 152.0, 153.4, 169.6; HRMS for $C_{16}H_{21}O_5$ calcd [M + H]$^+$ 293.1389, found 293.1389. ***Z* configuration**: mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.5 Hz, 3H), 2.21 (s, 3H), 2.75 (q, J = 7.5 Hz, 2H), 3.59 (s, 3H), 3.65 (s, 3H), 5.15 (s, 2H), 5.30 (s, 2H), 5.313 (d, J = 6.6 Hz, 1H), 6.246 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 14.1, 24.1, 57.6, 59.9, 68.5, 99.8, 100.3, 114.1, 124.8, 128.8, 146.4, 148.1, 150.7, 152.4, 169.5; HRMS for $C_{16}H_{21}O_5$ calcd [M + H]$^+$ 293.1389, found 293.1389.

Carbonic Acid *tert*-Butyl Ester 6-Ethyl-7-methyl-5-(3-methyl-4-oxobut-2-enyl)-3-oxo-1,3-dihydroisobenzofuran-4-yl Ester (2c). Conjugated aldehyde **12** (25 mg, 0.091 mmol) and di-*tert*-butyl dicarbonate (20 mg, 0.091 mmol) were dissolved in 0.91 mL of anhydrous dichloromethane. Pyridine (36 mg, 0.445 mmol) was added to the mixture, and after 30 min of stirring at rt, the reaction was complete as indicated by TLC. The reaction was quenched by adding dichloromethane and 1 N aqueous HCl. The organic layer was washed with 1 N HCl and aqueous copper(II) sulfate, dried

(Na_2SO_4), and concentrated *in vacuo* to give 35 mg (100%) of the title compound **2c** as white solid: mp 143−146 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.5 Hz, 3H), 1.53 (s, 9H), 1.93 (s, 3H), 2.27 (s, 3H), 2.76 (q, J = 7.5 Hz, 2H), 3.78 (d, J = 6.9 Hz, 2H), 5.20 (s, 2H), 6.33 (m, 1H), 9.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 13.8, 14.5, 23.3, 26.5, 27.6, 29.7, 68.7, 84.7, 128.1, 130.3, 139.5, 145.6, 146.1, 149.5, 150.7, 150.9, 168.2, 194.8; HRMS for $C_{21}H_{27}O_7$ calcd $[M + H]^+$ 375.1808, found 375.1810.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all compounds as well as experimental details for noncritical procedures described in this document. This material is available free of charge via the Internet at http://pubs.acs.org.

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