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Total Syntheses and Biological Evaluation of 3-*O*-Methylfunicone and Its Derivatives Prepared by TMPZnCl·LiCl-Mediated Halogenation and Carbonylative Stille Cross-Coupling

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The total syntheses of the natural product 3-*O*-methylfunicone (**1**), a member of the funicone class of compounds, and its derivatives is reported. The key reactions in the construction of the biaryl ketone core are a regioselective TMPZnCl·LiCl halogenation and a carbonylative Stille cross-coupling reaction. In addition, the inhibitory activities of the funicones against Y-family DNA polymerase κ (pol κ) and polymerase η (pol η) were determined. We found that **1** and **12** exhibit inhibitory activity against pol η and **1** also against pol κ.

Introduction

The aim of chemotherapeutic agents such as cisplatin is the induction of apoptosis in tumor cells by impairment of DNA replication.[1] The compounds typically cause DNA lesions, which block not only replication but also transcription processes. DNA lesion repair mechanisms are able to remove these lesions. In particular, translesion DNA synthesis (TLS), which establishes a lesion tolerance mechanism, is a process that promotes the development of chemoresistance.[2] Application of chemotherapeutic agents in combination with specific TLS polymerase inhibitors is consequently a strategy that would reduce the risk of developing resistance and thereby improve the therapeutic efficiency. Thus, selective inhibition of TLS DNA polymerases is a topic of great interest.[3] Specific inhibitory activity against Y-family polymerases, especially against polymerase κ (pol κ), has been reported for the natural product 3-*O*-methylfunicone (**1**, 3-*O*MF).[4] This metabolite of *Penicillium pinophilum* also shows general fungitoxic activity[5] and exhibits antiproliferative effects.[6] Compound **1** is a natural product and a member of the funicone class of compounds (Figure 1), which includes several biologically active natural products like funicone (**2**), which also exhibits fungitoxicity.[7] Other members of the funicone class include rapicone (**3**)[8] and deoxyfunicone.[9] The latter is an inhibitor of the HIV integrase,[10] reduces plant growth,[11] and shows antifungal activities.[12]

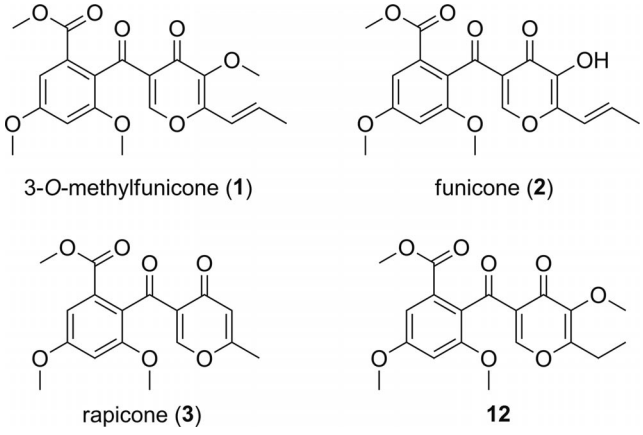

Figure 1. Structures of members of the funicone class of compounds.

Results and Discussion

In a retrosynthetic analysis of the funicone class of compounds, the core skeleton was reduced to an α-resorcylic acid derivative connected to a γ-pyranone ring through a ketone bridge. Such structures are efficiently assembled by carbonylative Stille cross-coupling reactions, as described recently in a publication that appeared in the course of this work.[13] In addition, we envisioned a regioselective functionalization of maltol derivatives to obtain the cross-coupling nucleophile (Scheme 1).

We selected the pyranone ring structure of maltol derivatives as convenient commercially available synthons. Starting from ethylmaltol, the free hydroxy group was readily methylated to introduce the methoxy group at the 3′-position of the pyranone core, affording methylated ethylmaltol

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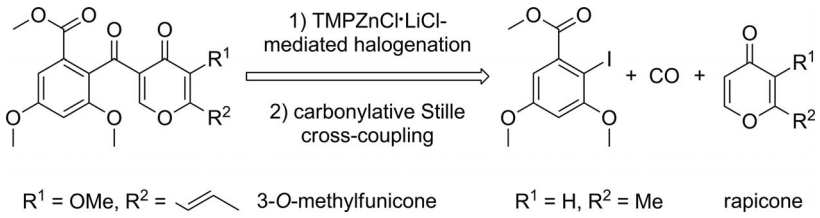
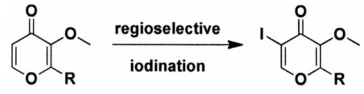


Scheme 1. Retrosynthetic analysis of 3-*O*-methylfunicone and its derivatives.

in an excellent yield of 97% (see Scheme 4). The challenging task in this route was the subsequent regioselective halogenation at the position α to the carbonyl group (Table 1). Various established iodination methods using, for example, NIS, I_2/*m*CPBA, I_2/CAN, or ICl only gave products mono- and diiodinated at the secondary position of the ethyl tail (Table 1, entries 1–4). We therefore switched to a new halogenation method involving the use of TMPZnCl·LiCl recently reported by Knochel and co-workers.[14] Indeed, by using this method we accomplished the desired regioselective mono-iodination at the position α to the carbonyl group. The high regioselectivity can be attributed to the coordination of the hindered zinc amide to the oxygen of the carbonyl group followed by subsequent deprotonation of the α position and zincation. Iodination of the regioselectively formed zinc species afforded the regioselective functionalized compound in 54% yield (Table 1, entry 5, Scheme 4). In addition, in the synthesis of 3-*O*MF by using this new iodination method, we achieved an excellent yield of 99% yield (Table 1, entry 6, Scheme 5).

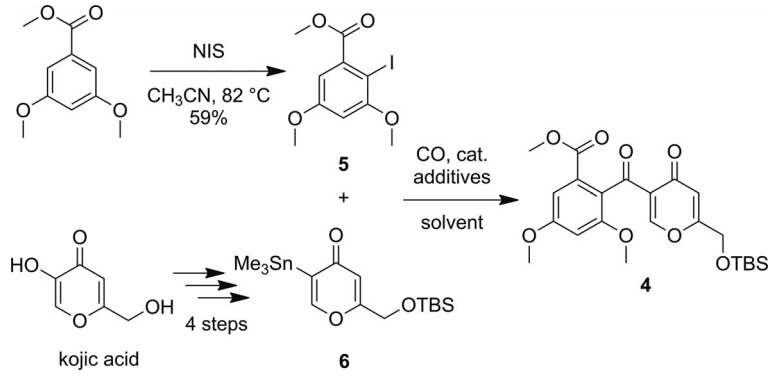
Table 1. Regioselective iodination at the position α to the carbonyl group of maltol derivatives.



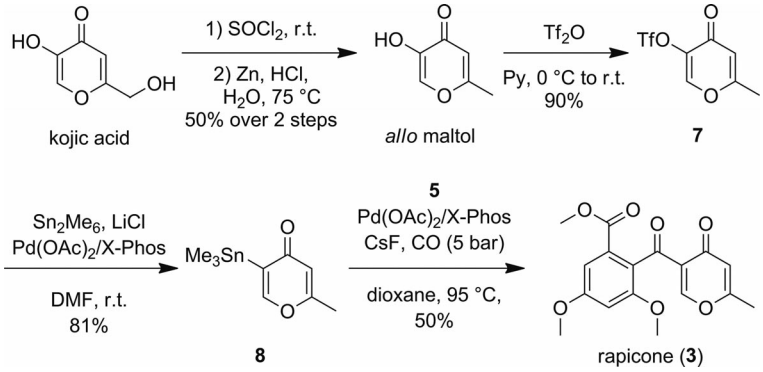
Entry	R	Reagents	Solvent	Yield [%]
1	CH_2CH_3	NIS	MeCN	0
2	CH_2CH_3	I_2/*m*CPBA	DMF	0
3	CH_2CH_3	I_2/CAN	MeCN	0
4	CH_2CH_3	ICl	DCM	0
5	CH_2CH_3	TMPZnCl·LiCl/I_2	THF	54
6	$CHOTBSCH_2CH_3$	TMPZnCl·LiCl/I_2	THF	99

To evaluate the optimal reaction conditions for the carbonylative Stille cross-coupling reaction, first an appropriate test system was established. Due to the high structural analogy of the coupling product **4** to the final targets of the synthesis, iodide **5** as electrophile and stannane **6** as nucleophile were chosen. Iodide **5** was accessed by a regioselective monoiodination of methyl 3,5-dimethoxybenzoate. The second coupling partner stannane **6** was synthesized starting from kojic acid according to a modified protocol of Kamino and Kobayashi (Scheme 2).[15]

With both coupling partners in hand, several carbonylative cross-coupling conditions were screened to identify suitable reaction conditions to couple the sterically hindered aryl halide **5** as electrophile with an electron-deficient heterocycle **6** as nucleophile (Scheme 2).[16] We found the best results involved the use of the $Pd(OAc)_2$/X-Phos catalyst system[17] with CsF as additive in dioxane. The CsF is believed to facilitate the Stille cross-coupling reaction based on the high fluorophilicity of tin.[18] By applying an internal CO pressure of 5 bar at 95 °C, the yield increased to 46% (53% based on recovered starting material) in this test sys-



Scheme 2. Synthesis of the cross-coupling partners **5** and **6** and optimization of the carbonylative Stille cross-coupling conditions.



Scheme 3. Total synthesis of rapicone (**3**).

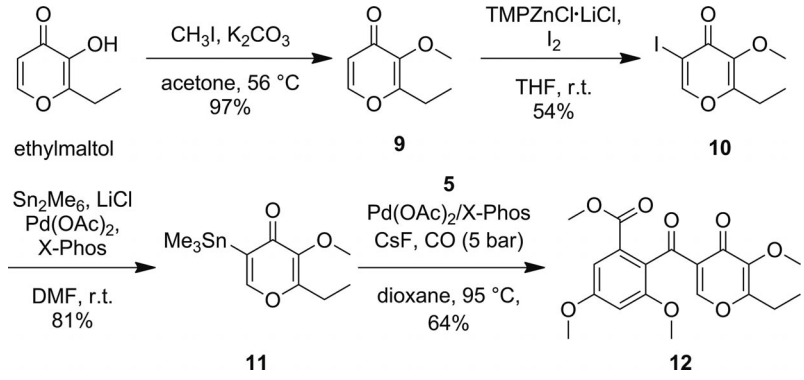
tem and to 67% in the synthesis of 3-*O*MF (**1**; see Scheme 5). Our conditions have to be compared with those reported during the preparation of this manuscript by Manzo and Ciavatta.[13] In contrast to the 35% yield reported by using the known catalyst $[Pd(allyl)Cl]_2$,[15] our catalyst system together with CsF afforded significantly higher yields.

In summary, the TMPZnCl·LiCL-mediated regioselective functionalization of maltol derivatives in combination with the carbonylative Stille cross-coupling reaction has led to a new and concise synthetic route towards funicone derivatives bearing a methoxy group at the 3′-position of the pyranone ring.

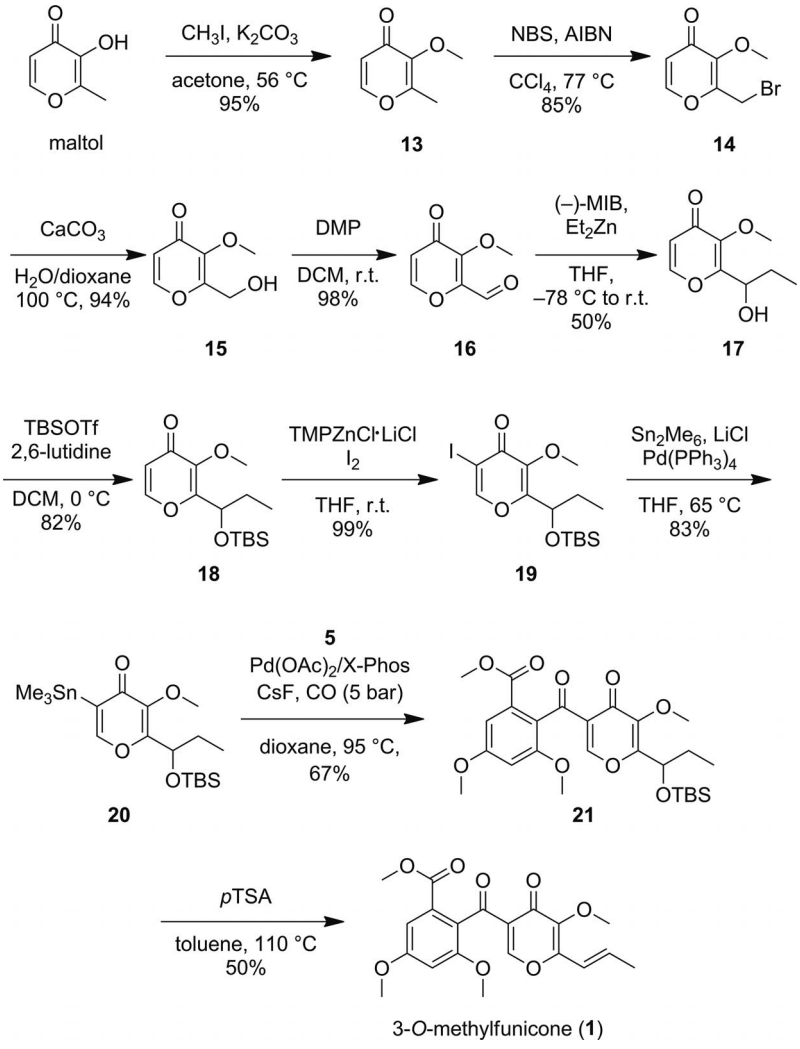
Next, we used the developed conditions for the synthesis of rapicone (**3**) (Scheme 3). Starting from kojic acid, defunctionalization according to the protocol of Ozturk et al.[19] gave rise to allo maltol. To convert this synthon into a tin–organyl, the hydroxy group was triflated to provide **7**. Subsequent direct stannylation with hexamethylditin afforded the cross-coupling partner **8**. The carbonylative Stille cross-coupling reaction with **5** using the $Pd(OAc)_2$/X-Phos system yielded the final product rapicone (**3**) as expected based on the results of the model reaction in 50% yield.

To obtain further members of the funicone class for future structure–activity relationship studies, we next synthesized a derivative bearing a methoxy moiety at the 3′-position of the pyranone core. To this end, ethylmaltol was chosen as a convenient synthon. The methylated ethylmaltol **9** was regioselectively iodinated as described above to provide iodide **10** (Scheme 4), which was stannylated with hexamethylditin and the $Pd(OAc)_2$/X-Phos catalyst system in combination with LiCl as additive to afford stannane **11** in good yield. Finally, the coupling of **11** with **5** provided the synthetic funicone derivative **12** in 64% yield (Scheme 4).

We finally applied both developed methods to the synthesis of 3-*O*MF (**1**) (Scheme 5). Starting from maltol, the methoxy group was introduced by methylation with iodomethane to afford **13** in 95% yield. Regioselective monobromination at the allylic position was achieved by using NBS and AIBN to provide bromide **14**. In the next step, bromide **14** was substituted in aqueous dioxane to afford alcohol **15**, which was subsequently oxidized with Dess–Martin periodinane to yield aldehyde **16** in 98% yield. Unfortunately, the intended olefination to introduce the (*E*)-propenyl tail to the pyranone core was not possible using standard olefination methods. We therefore established the *E* double bond by addition of diethylzinc to introduce a hydroxy group followed by elimination. Diethylzinc was added to **16** by using (2*S*)-3-*exo*-morpholinoisoborneol [(–)-MIB] as additive.[20] The secondary alcohol **17** was TBS-protected to give **18**. At this point, the protected pyranone **18** was regioselectively iodinated at the α position with



Scheme 4. Total synthesis of **12**.



Scheme 5. Total synthesis of 3-*O*-methylfunicone (**1**).

TMPZn·LiCl in 99% yield. Subsequent direct stannylation of iodide **19** with Sn_2Me_6, [$Pd(PPh_3)_4$], and LiCl as additive provided stannane **20**. Carbonylative Stille cross-coupling yielded the precursor **21** of 3-*O*MF in 67% yield. Finally, deprotection and dehydration was accomplished in a one-pot reaction with *p*TSA to yield exclusively the *E* isomer of the final target 3-*O*MF (**1**). The analytical data are consistent with those previously reported for the isolated natural product.[4,21]

To determine the inhibitory activity of the synthesized compounds **1**, **3**, and **12**, primer extension assays with the purified TLS polymerases pol η and pol κ were performed.[22] The inhibitor assay is depicted in Figure 2 and is based on an in vitro primer extension reaction performed with one of the two TLS polymerases and a fluorescein-labeled primer (13mer). The primer was hybridized to a template strand (30mer). The primer extension reaction was performed in the presence of different inhibitors at increasing concentrations. The inhibitory activities of the tested compounds were determined by subsequent analysis of the degree of primer elongation by denaturing polyacrylamide gel electrophoresis (PAGE). The data are shown in Figure 3.

Determination of the inhibitory effect of **1** confirmed that the compound indeed inhibits both pol κ and pol η. To achieve full inhibition of the polymerase, a concentration of 5 mM of **1** was necessary. No inhibition of either polymerase was detected at a concentration of 500 μM (Figure 3), which shows that the inhibitor possesses IC_{50} values in the mM range. This result is in sharp contrast to previously reported IC_{50} values of 12.5 and 50.1 μM against pol κ and pol η, respectively.[4] The discrepancy may result from the higher polymerase concentrations used in our primer extension assay. Rapicone (**3**) showed no inhibition of pol η and only weak inhibition of pol κ at a concentration of 5 mM. An inhibitory effect of **12** was determined at a concentration of 1 mM against pol η, but no inhibition against pol κ was observed (see Figure S4 in Supporting Information).

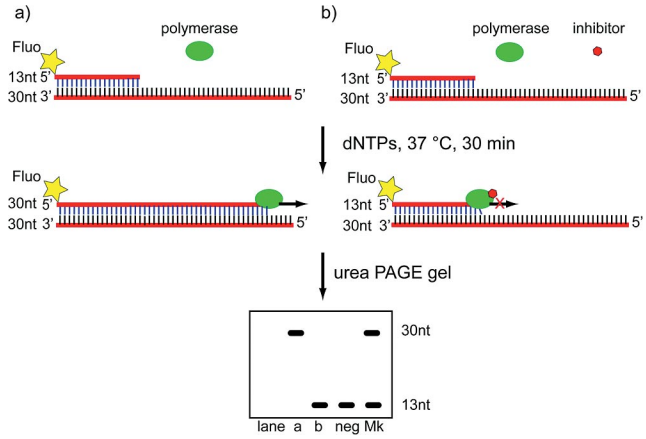


Figure 2. Schematic depiction of the primer extension assay. a) Primer extension reaction of a fluorescein-labeled 13mer primer hybridized to a 30mer template strand by a TLS polymerase. b) Primer extension reaction inhibited by addition of a TLS polymerase inhibitor. The degree of elongation of the fluorescein-labeled primer (13nt) was analyzed by using denaturing PAGE. It shows a new band for the fully elongated primer in lane a and the non-elongated primer in lane b. The lane denoted neg is a negative control without polymerase and lane Mk is a fragment length marker.

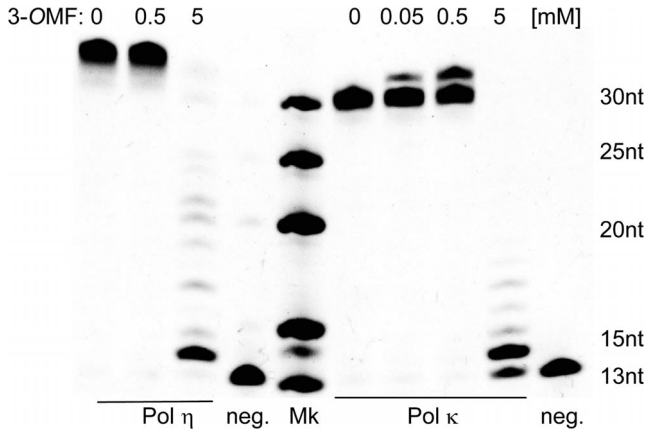


Figure 3. Primer extension assay of inhibitor 3-*O*MF (**1**) denaturing PAGE-urea gel is shown. The 5′-fluorescein-labeled DNA primer was visualized by the gel-imaging system. Extension by pol η (1 μM, lanes 1–3) and pol κ (0.5 μM; lanes 6–9). Concentrations of 3-*O*MF: 0 (positive control, lanes 1 and 6), 0.05 (lane 7), 0.5 (lanes 2 and 8), and 5 mM (lanes 3 and 9). The lanes denoted neg. (lanes 4 and 10) are negative controls without polymerase. Fragment length marker 13–30nt (Mk, lane 5).

Conclusions

A TMPZnCl·LiCl-mediated regioselective iodination of maltol derivatives has been reported. Furthermore, a new catalyst system for carbonylative Stille cross-coupling reactions was identified that has enabled a more efficient synthesis of funicone-related natural products. The protocol allowed the preparation of 3-*O*MF (**1**) and its derivatives **3** and **12**. In addition, the inhibitory activities of **1**, **3**, and **12** against pol κ and pol η were investigated; it was found that compounds **1** and **12** show inhibitory activity against pol η and that **1** is also able to inhibit pol κ, although high concentrations were required. Thus, compounds **1** and **12** are consequently good starting points for further structural optimization with the goal of inhibiting low fidelity polymerases with high efficiency.

Experimental Section

General Methods: All nonaqueous reactions were performed under dry nitrogen or argon in flame- or oven-dried glassware. Commercial reagents from Sigma–Aldrich, ABCR, or Acros were used as received unless otherwise indicated. Nonaqueous reagents were transferred under nitrogen through a syringe or cannula. Solutions were concentrated in vacuo on a Heidolph rotary evaporator. Chromatographic purification of products was performed by using flash column chromatography on Merck Geduran Si 60 (40–63 μM) silica gel (normal phase). TLC was performed on Merck 60 (silica gel F254) plates. The developed chromatogram was visualized by fluorescence quenching. ^{1}H, ^{13}C, ^{19}F, and ^{119}Sn NMR spectra were recorded in deuteriated solvents with Bruker ARX 300, Varian VXR400S, Varian Inova 400, Bruker AMX 600, and JEOL Eclipse 270 spectrometers and calibrated to the residual solvent peak. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ESI and high-resolution ESI mass spectra were obtained with a Thermo Finnigan LTQ FT-ICR mass spectrometer. Acetonitrile for HPLC-ESI-MS analysis was purchased from VWR, HPLC gradient grade. IR measurements were performed with a Perkin–Elmer Spectrum BX FT-IR spectrometer with a diamond-ATR (Attenuated Total Reflection) setup. Melting points were determined with a Büchi melting point B540 instrument.

General Procedure 1 (GP1). Carbonylative Stille Cross-Coupling Reaction: A dry argon-flushed pressure reactor system (miniclave steel, Büchi) was charged with catalyst, stannane, iodide, and, when indicated, additives. This mixture was dissolved in degassed solvent (5–10 mL). Subsequently the reactor was sealed and flushed twice with CO. The reactor was then heated to the indicated reaction temperature and stirred at an internally defined CO pressure. After the indicated reaction time, the resulting reaction mixture was concentrated and purified by column chromatography on silica gel to afford the cross-coupling product.

Rapicone (3): The carbonylative Stille cross-coupling reaction was carried out according to GP1. Two ground palladium(II) acetate/X-Phos ChemDose® tablets (2 μmol loading per tablet, Pd/P = 1:2), 2-methyl-5-(trimethylstannyl)-4*H*-pyran-4-one (**8**; 49 mg, 0.18 mmol, 1.0 equiv.), methyl 2-iodo-3,5-dimethoxybenzoate (**5**; 103 mg, 0.32 mmol, 1.8 equiv.), and dry caesium fluoride (60 mg, 0.37 mmol, 2.2 equiv.) were dissolved in degassed dioxane (5 mL). The reactor was heated to 95 °C for 72 h with an internal carbon monoxide pressure of 5 bar. The resulting reaction mixture was concentrated and purified by column chromatography on silica gel (*i*Hex/EtOAc = 1:1) to afford rapicone (**3**; 30 mg, 50%) as a colorless solid, m.p. 162–163 °C. R_f (*i*Hex/EtOAc = 1:4) = 0.36. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.50 (s, 1 H), 7.08 (d, J = 2.2 Hz, 1 H), 6.63 (d, J = 2.2 Hz, 1 H), 6.12–6.11 (m, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 2.27 (d, J = 0.7 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 192.0, 175.7, 166.6, 165.2, 161.1, 161.0, 157.5, 130.0, 126.2, 126.1, 117.5, 105.4, 103.2, 56.2, 55.8, 52.5, 19.5 ppm. IR: $\tilde{\nu}$ = 2956 (w), 1713 (m), 1678 (s), 1652 (s), 1602 (s), 1436 (m), 1398 (m), 1320 (s), 1250 (s), 1217 (s), 1140 (s), 1060

(s), 894 (s), 791 (s), 657 (m) cm^{-1}. HRMS (ESI^+): calcd. for $[C_{17}H_{17}O_7]^+$ 333.0969; found 333.0969 $[M + H]^+$.

2-Ethyl-5-iodo-3-methoxy-4*H*-pyran-4-one (10): In a dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum, 2-ethyl-3-methoxy-4*H*-pyran-4-one (**9**; 400 mg, 2.59 mmol, 1.0 equiv.) was dissolved in THF (6 mL) and TMPZnCl·LiCl (2.6 mL, 2.85 mmol, 1.1 equiv.) was added dropwise at room temperature and stirred for 30 min. Iodine (790 mg, 3.11 mmol, 1.2 equiv.) was added to this violet solution and the dark-brown reaction mixture was stirred for 90 min and then concentrated. The resulting residue was purified by column chromatography on silica gel (*i*Hex/EtOAc = 9:1) to afford 2-ethyl-5-iodo-3-methoxy-4*H*-pyran-4-one (**10**; 390 mg, 54%) as a yellow oil. n_d = 1.59. R_f (*i*Hex/EtOAc = 4:1) = 0.28. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 3.87 (s, 3 H), 2.70 (q, J = 7.6 Hz, 2 H), 1.22 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 163.6, 156.2, 141.9, 92.2, 60.5, 21.9, 11.5 ppm. IR: $\tilde{\nu}$ = 2978 (w), 1650 (s), 1561 (m), 1460 (m), 1442 (m), 1320 (m), 1233 (s), 1170 (s), 1133 (s), 1009 (s), 971 (s), 937 (m), 847 (s), 781 (m), 709 (m) cm^{-1}. HRMS (EI^+): calcd. for $[C_8H_9IO_3]^{+\cdot}$ 279.9591; found 279.9591 $[M]^{+\cdot}$.

Methyl 2-(6-Ethyl-5-methoxy-4-oxo-4*H*-pyran-3-ylcarbonyl)-3,5-dimethoxybenzoate (12): The carbonylative Stille cross-coupling reaction was carried out according to GP1. Five ground palladium(II) acetate/X-Phos ChemDose® tablets (2 μmol loading per tablet, Pd/P = 1:2), 2-ethyl-3-methoxy-5-(trimethylstannyl)-4*H*-pyran-4-one (**11**; 122 mg, 0.38 mmol, 1.0 equiv.), methyl 2-iodo-3,5-dimethoxybenzoate (**5**; 223 mg, 0.69 mmol, 1.8 equiv.), and dry caesium fluoride (129 mg, 0.84 mmol, 2.2 equiv.) were dissolved in degassed dioxane (8 mL). The reaction was heated at 95 °C for 120 h with an internal carbon monoxide pressure of 5 bar. The resulting reaction mixture was concentrated and purified by column chromatography on silica gel (*i*Hex/EtOAc = 3:1) to afford methyl 2-(6-ethyl-5-methoxy-4-oxo-4*H*-pyran-3-ylcarbonyl)-3,5-dimethoxybenzoate (**12**; 93 mg, 64%) as a colorless solid, m.p. 148–152 °C. R_f (*i*Hex/EtOAc = 2:1) = 0.16. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 7.08 (d, J = 2.2 Hz, 1 H), 6.64 (d, J = 2.2 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 2.70 (q, J = 7.6 Hz, 2 H), 1.24 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.2, 172.3, 166.7, 162.8, 161.0, 159.8, 157.6, 146.34, 130.0, 126.8, 126.5, 105.4, 103.3, 60.7, 56.3, 55.8, 52.6, 22.0, 11.6 ppm. IR: $\tilde{\nu}$ = 2943 (w), 1719 (m), 1677 (m), 1640 (s), 1601 (s), 1442 (m), 1328 (s), 1249 (s), 1214 (s), 1142 (s), 1080 (s), 1034 (s), 953 (m), 850 (s), 788 (m), 727 (m) cm^{-1}. HRMS (ESI^+): calcd. for $[C_{19}H_{21}O_8]^+$ 377.1231; found 377.1229 $[M + H]^+$.

2-{1-[(*tert*-Butyldimethylsilyl)oxy]propyl}-5-iodo-3-methoxy-4*H*-pyran-4-one (19): In a dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum, 2-{1-[(*tert*-butyldimethylsilyl)oxy]propyl}-3-methoxy-4*H*-pyran-4-one (**18**; 99.0 mg, 0.33 mmol, 1.0 equiv.) was dissolved in THF (5 mL) and TMPZnCl·LiCl (0.44 mL, 0.49 mmol, 1.5 equiv.) was added dropwise at room temperature and stirred for 30 min. Iodine (126 mg, 0.50 mmol, 1.5 equiv.) was added to this solution and the dark-brown reaction mixture was stirred for 90 min and then concentrated. The resulting residue was purified by column chromatography on silica gel (*i*Hex/EtOAc = 3:1) to afford 2-{1-[(*tert*-butyldimethylsilyl)oxy]propyl}-5-iodo-3-methoxy-4*H*-pyran-4-one (**19**; 139 mg, 99%) as a colorless oil. n_D = 1.60. R_f (*i*Hex/EtOAc = 9:1) = 0.60. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 4.92 (dd, J = 7.4, 6.5 Hz, 1 H), 3.92 (s, 3 H), 1.75 (m, 2 H), 0.91 (t, J = 7.4 Hz, 3 H), 0.87 (s, 9 H), 0.09 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.6, 161.0, 156.5, 141.0, 92.1, 68.1, 60.5, 29.0, 25.8, 18.3, 10.1, –4.8, –4.9 ppm. IR: $\tilde{\nu}$ = 3066 (w), 2955 (w), 2929 (w), 2856 (w), 2349 (w), 1828 (w), 1637 (s), 1562 (w), 1463 (w), 1444 (w), 1390 (w), 1344 (w), 1294 (w), 1239 (s), 1201 (w), 1101 (s), 1060 (m), 1004 (w), 970 (w), 939 (w), 898 (m), 849 (w), 835 (s), 800 (w), 776 (s), 722 (w), 673 (w) cm^{-1}. HRMS (ESI^+): calcd. for $[C_{15}H_{26}IO_4Si]^+$ 425.0640; found 425.0644 $[M + H]^+$.

Methyl 2-(6-{1-[(*tert*-Butyldimethylsilyl)oxy]propyl}-5-methoxy-4-oxo-4*H*-pyran-3-ylcarbonyl)-3,5-dimethoxybenzoate (21): The carbonylative Stille cross-coupling was carried out according to GP1. Two ground palladium(II) acetate/X-Phos ChemDose® tablets (2 μmol loading per tablet, Pd/P = 1:2), 2-{1-[(*tert*-butyldimethylsilyl)oxy]propyl}-3-methoxy-5-(trimethylstannyl)-4*H*-pyran-4-one (**20**; 12.0 mg, 0.03 mmol, 1.0 equiv.), methyl 2-iodo-3,5-dimethoxybenzoate (**5**; 13.0 mg, 0.04 mmol, 1.5 equiv.), and dry caesium fluoride (8.00 mg, 0.06 mmol, 2.2 equiv.) were dissolved in degassed dioxane (5 mL). The reactor was heated at 95 °C for 120 h with an internal carbon monoxide pressure of 5 bar. The resulting reaction mixture was concentrated and purified by column chromatography on silica gel (*i*Hex/EtOAc = 5:1) to afford methyl 2-(6-{1-[(*tert*-butyldimethylsilyl)oxy]propyl}-5-methoxy-4-oxo-4*H*-pyran-3-ylcarbonyl)-3,5-dimethoxybenzoate (**21**; 9 mg, 67%) as a colorless resin. R_f (*i*Hex/EtOAc = 2:1) = 0.43. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 7.07 (d, J = 2.3 Hz, 1 H), 6.63 (d, J = 2.2 Hz, 1 H), 4.88 (dd, J = 7.4, 6.4 Hz, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 1.75 (m, 2 H), 0.93 (t, J = 7.5 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.7, 172.4, 166.7, 161.1, 160.1, 159.8, 157.7, 145.6, 130.4, 127.1, 126.0, 105.7, 103.1, 68.2, 60.6, 56.2, 55.8, 52.5, 28.8, 25.9, 18.3, 10.1, –4.8, –4.9 ppm. IR: $\tilde{\nu}$ = 2955 (w), 2918 (w), 2850 (m), 1722 (w), 1681 (m), 1649 (s), 1603 (s), 1580 (w), 1566 (w), 1463 (w), 1443 (w), 1407 (w), 1330 (s), 1294 (w), 1249 (s), 1214 (s), 1144 (s), 1100 (m), 1063 (s), 1012 (m), 972 (w), 953 (m), 896 (m), 855 (w), 836 (s), 804 (w), 777 (s), 729 (w), 680 (w) cm^{-1}. HRMS (ESI^+): calcd. for $[C_{26}H_{37}O_9Si]^+$ 521.2201; found 521.2206 $[M + H]^+$.

3-*O*-Methylfunicone (1): Methyl 2-(6-{1-[(*tert*-butyldimethylsilyl)oxy]propyl}-5-methoxy-4-oxo-4*H*-pyran-3-ylcarbonyl)-3,5-dimethoxybenzoate (**21**; 35.0 mg, 67.0 μmol, 1.0 equiv.) and *p*-toluenesulfonic acid (13 mg, 67.0 μmol, 1.0 equiv.) were dissolved in toluene (4 mL) and heated at reflux for 12 h. Afterwards the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica (*i*Hex/EtOAc = 2:1) to afford 3-*O*-methylfunicone (**1**; 13 mg, 50%) as a colorless solid, m.p. 185–187 °C. R_f (*i*Hex/EtOAc = 1:1) = 0.34. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 7.08 (d, J = 2.2 Hz, 1 H), 6.64 (d, J = 2.3 Hz, 1 H), 6.61 (dq, J = 15.8, 6.7 Hz, 1 H), 6.55 (dq, J = 15.8, 1.5 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 1.97 (dd, J = 6.7, 1.5 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 192.1, 172.7, 166.7, 161.0, 159.3, 157.6, 154.8, 144.4, 135.1, 130.0, 126.6, 126.4, 118.7, 105.5, 103.3, 60.8, 56.3, 55.8, 52.6, 19.2 ppm. IR: $\tilde{\nu}$ = 2920 (m), 2850 (w), 2357 (m), 2339 (w), 1717 (m), 1675 (w), 1635 (m), 1602 (m), 1558 (m), 1456 (m), 1330 (m), 1295 (m), 1247 (m), 1213 (s), 1140 (s), 1062 (s), 953 (m), 857 (m), 788 (m), 668 (m) cm^{-1}. HRMS (ESI^+): calcd. for $[C_{20}H_{21}O_8]^+$ 389.1231; found 389.1233 $[M + H]^+$.

Supporting Information (see footnote on the first page of this article): Synthetic and biochemical experimental details, NMR spectra and primer extension assays for **3** and **12**.

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