Supporting Information
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Supporting Material – Synlett.

Synthesis of a Series of Promising Isobenzofuranones for the Treatment of Acute Mucositis caused by Chemo- and Radiotherapy.

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NMR spectra were recorded with a Bruker AV 400 spectrometer in the solvents indicated CDCl$_3$ and DMSO-d$_6$; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hertz. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl$_3$: δC = 77.0 ppm; residual CHCl$_3$ in CDCl$_3$: δH = 7.24 ppm; DMSO-d$_6$: δC = 39.5 ppm; residual DMSO in DMSO-d$_6$: δH = 2.5 ppm). The data are reported as follows: chemical shift, integration, multiplicity (s for singlet, d for doublet, t for triplet and m for multiplet). The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (cosygs and cosydtq); HSQC (invietgssi) optimized for $^1$J(C,H) = 145 Hz; HMBC (inv4gslplrd) for correlations via $^3$J(C,H); HSQC-TOCSY (invietgsm) using an MLEV17 mixing time of 120 ms. Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determination. Unless stated otherwise, all commercially available compounds (Fluka, Lancaster, Aldrich) were used as received. Solvents were purchased from VWR and Fisher. Reactions were carried out in oven-dried glassware under argon atmosphere, unless otherwise noted. Flash chromatography: Merck silica gel 60 (230-400 mesh).
Part I:

**Supporting Scheme 1** - Preparation of (2E,6E)-8-((tert-butyldiphenylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-ol; coupling partner c:

**Supporting Scheme S1** - Preparation of (2E,6E)-8-((tert-butyldiphenylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-ol; coupling partner c.

Reagents and conditions (i) Geranyl acetate, salicylic acid, H$_2$SeO$_3$, tBuOOH, 70% in water, in dichloromethane for 16h at RT, 73%; (ii) TBDPSCl, imidazole, 16 h, RT, 94%; (iii) K$_2$CO$_3$, 4 h, RT, 94%; RT = room temperature, TBDPS = terbutyl-diphenyl-silyl.

**Step (i):** H$_2$SeO$_3$ (0.059 g, 0.459 mmol, 0.03 equiv) and tBuOOH (70% in water, 5.47 mL, 38.2 mmol, 2.5 equiv) were added to a solution of geranyl acetate (3.28 mL, 15.28 mmol, 1 equiv) in CH$_2$Cl$_2$ (30 mL) at room temperature. After 15 minutes, salicylic acid neat (0.211 g, 1.528 mmol, 0.1 equiv) was added to the reaction mixture and stirred overnight. Reaction was monitored by TLC (EtOAc/Heptane: 1/1, Rf= 0.59). After completion, the reaction mixture was concentrated under reduced pressure and extracted in diethyl ether (100 mL). The organic phase was washed successively with 3 M NaOH (3x50 mL), water (3x50 mL) and solution of NaCl sat. (30 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (loaded onto 100 g of silica and eluted with a gradient of heptane/EtOAc starting at 100-0% and going to 0-100%) to afford the desired (2E,6E)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate as a colorless oil (m=1.217 g, colorless oil, 73%).

$^1$H NMR (400 MHz, (CD$_3$)$_2$SO) $\delta$ 5.30 (t, $J = 6.61$ Hz, 2 H), 4.64 (t, $J = 5.62$ Hz, 1 H), 4.52 (d, $J = 7.07$ Hz, 2 H), 3.76 (d, $J = 5.57$ Hz, 2 H), 2.05 - 2.13 (m, 2 H), 2.03 (d, $J = 7.88$ Hz, 2 H), 1.99 (s, 3 H), 1.66 (s, 3 H), 1.54 (s, 3 H). ROESY spectrum was also consistent with structure as: (2E,6E).
1H-NMR Spectrum of compound **12**: \((2E,6E)\)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate.

**Step (ii):** Imidazole (0.582 g, 8.55 mmol, 1.5 equiv) followed by TBDPSCl (1.750 mL, 6.84 mmol, 1.2 equiv) were added in one portion to a solution of compound **13** (1.21 g, 5.70 mmol, 1 equiv) in dry THF (20 mL) and stirred overnight at room temperature. After completion, the reaction mixture was quenched with 30 mL of water. The aqueous layer was extracted with dichloromethane (2x 50 mL) and the combined organic extracts were washed successively with water (2x 50 mL), a solution of NaCl sat. (2x 50 mL); dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was then purified by flash chromatography (loaded onto a silica column of 100 g and eluted with a gradient of heptane/EtOAc going from 100-0% to 70-30%; \(R_f\) = 0.70 for a mixture of EtOAc/heptane, 2:8) to provide the expected compound as a colorless oil (2.53 g, 94%). **1H NMR** (400 MHz, (CD₃)₂SO) \(\delta\) ppm 7.58 - 7.65 (m, 4 H), 7.36 - 7.50 (m, 6 H), 5.30 (s, 1 H), 5.41 (s, 1 H), 4.50 (d, \(J = 7.07\) Hz, 2 H), 4.00 - 4.04 (m, 2 H), 2.09 - 2.18 (m, 2 H), 2.01 - 2.08 (m, 2 H), 1.94 (s, 3H), 1.67 (s, 3 H), 1.55 (s, 3 H), 0.99 (s, 9 H). **LC-MS** (Retention time = 1.7 min for a 2 min. run): 451.69 [M + H+]; calcd for \([C_{28}H_{38}O_{3}Si + H+]\).
Step (iii): K₂CO₃ (2.024 g, 14.64 mmol, 3 equiv) was added in one portion to a MeOH (50 mL) solution containing the (2E,6E)-8-((tert-butyldiphenylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl acetate (2.2 g, 4.88 mmol, 1 equiv). The reaction was stirred at room temperature for 4h. The crude mixture was washed with 100 mL of water and extracted with dichloromethane (2x 50 mL). The combined organic phases were washed with saturated solution of NaCl (2x50 mL), dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluted with a gradient going from heptane/EtOAc 100-0% to 50-50%). The clean fractions were combined and volatiles evaporated to afford the coupling partner c, as a colorless oil (1.89 g, 94 %). ¹H NMR (400 MHz, (CD₃)₂SO) δ ppm 7.56 - 7.65 (m, 4 H), 7.39 - 7.50 (m, 6 H), 5.42 (s, 1 H), 5.28 (s, 1 H), 4.03 (s, 2 H), 3.92 (d, J = 6.38 Hz, 2 H), 2.06 - 2.17 (m, 2 H), 1.96 - 2.00 (m, 2 H), 1.59 (s, 3 H), 1.56 (s, 3 H), 0.99 (s, 9 H). LC-MS (Retention time = 7.33 min. for 10min. run): 409.25 [M + H⁺]; calcd for [C₂₆H₃₂O₂Si + H⁺].
1H-NMR Spectrum of: (2E,6E)-8-((tert-butyldiphenylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-ol:

Part II:

**General procedure for the Grignard reaction.**

To a stirring solution of 3M methyl magnesium bromide (1.1 eq.) in dry diethyl ether (2 mL) was added, under argon, cadmium chloride anhydrous (0.55 eq.) in one portion. The reaction mixture was heated under reflux for 1 h, allowed to cool to room temperature and substituted benzofuran-1,3-dione (1 eq.) was added dropwise. The mixture was heated under reflux for an additional 4 h. Upon completion, the reaction was quenched with a 2M solution of HCl (1mL). After addition of diethyl ether (10-20 mL), the organic layer was extract, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel (FC ISCO) eluting with a gradient of 0 to 60 % EtOAc in heptane. The appropriate fractions were pooled and solvent was concentrated under reduced pressure to afford the expected substituted 3-hydroxy-7-methoxy-3,6-dimethylisobenzofuran-1(3H)-one (40-58% yield).
**Compound 1:**

3-Hydroxy-7-methoxy-3,6-dimethyl-5-((3-methylbut-2-en-1-yl)oxy)isobenzofuran-1(3H)-one

25 mg of compound 1 were obtained as a colorless oil (0.090 mmol, 58% yield). ¹H NMR (400 MHz, (CD₃)₂SO) δ ppm: 1.72 (3H, s), 1.74 (3H, s), 1.77 (3H, s), 2.05 (3H, s), 3.90 (3H, s), 4.68 (2H, m), 5.47 (1H, t, J = 6.78 Hz), 7.02 (1H, s), 7.55 (1H, s, exchange D₂O). ¹³C NMR (100 MHz, CDCl₃): 8.7, 16.3, 25.7, 26.1, 62.1, 65.9, 99.8, 103.9, 109.2, 118.7, 122.0, 138.3, 151.2, 157.0, 163.8, 166.1. LC-MS (Retention time = 1.08 min [M+H]⁺ = 293 amu (>99% by LC-MS, UV). The site of alkylation and the structure of compound 1 was assigned unambiguously. The following ROESY correlations spectroscopy data were observed:

\[
\begin{align*}
A & 1.72 \text{ H11} & 7.02 \text{ H6} \\
B & 7.55 \text{ OH10} & 7.02 \text{ H6}
\end{align*}
\]

**Compound 2:**

(E)-5-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-hydroxy-7-methoxy-3,6-dimethylisobenzofuran-1(3H)-one
Compound 2 was obtained as a colorless oil (24 mg, 0.065 mmol, 41% yield). $^1$H NMR (400 MHz, (CD$_3$)$_2$SO) $\delta$ ppm 1.56 (3H, s), 1.63 (3H, s), 1.71 (3H, s), 1.73 (3H, s), 2.05-2.10 (7H, [4H & 3H], m), 3.90 (3H, s), (2H, d, $J$ = 6.40 Hz), 5.07 (1H, m), 5.45 (1H, t, $J$ = 6.40 Hz), 7.01 (1H, s), 7.56 (1H, s, exchange D$_2$O). $^{13}$C NMR (100 MHz; CDCl$_3$): 8.5, 16.56, 17.5, 25.4, 26.1, 39.3, 61.9, 65.8, 99.7, 100.9, 118.4, 121.8, 123.4, 131.7, 141.8, 151.0, 156.8, 165.9. LC-MS (Retention time = 1.33 min [M+H]$^+$ = 361 (>98 % by LC-MS, UV). The site of alkylation and the structure of compound 2 was assigned unambiguously. The following ROESY correlations spectroscopy data were observed:

$A$ 1.71 H1 7.01 H6  
$B$ 7.56 OH10 7.01 H6

**Compound 3:**

2-hydroxy-5-(((2$E$,$E$)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)- 7-methoxy-3,6-dimethylisobenzofuran-1(3H)-one

**Supporting Scheme S3:** Preparation of 2-hydroxy-5-(((2$E$,$E$)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)- 7-methoxy-3,6-dimethylisobenzofuran-1(3H)-one. Reagents and conditions (i) MeMgBr 3 M in Diethylether, CdCl$_2$, Diethyl ether, 40°C, reflux, 1 h ; 11c, Diethyl ether, 40°C, reflux, 4 h; (ii) 1M solution of TBAF, 4h, RT. RT= room temperature, TBDPS= terbutyl-diphenyl-silyl, TBAF= tetrabutyl-ammonium fluoride.
To a stirring solution of compound 11c (140 mg, 0.228 mmol) in 2 mL tetrahydrofuran, 1M TBAF in THF (0.455 ml, 0.455 mmol) was added at 0ºC. After stirring 4 h. at room temperature, the reaction was completed. The crude mixture was concentrated under reduced pressure and the crude residue was purified by chromatography on silica gel (FC-ISCO eluting with a gradient of 0 to 30% methanol in dichloromethane). The appropriate fractions were recovered and concentrated under reduced pressure to afford the corresponding product 3 (65 mg, 0.171 mmol, 75% yield) as a colorless oil. 

\[ ^1H \text{NMR} \ (400 \text{ MHz, (CD}_3\text{)}_2\text{SO}) \delta \text{ ppm: } 1.54 \ (3\text{H, s}), \ 1.70 \ (3\text{H, s}), \ 1.74 \ (3\text{H, s}), \ 2.05 \ (3\text{H, s}), \ 2.10-2.25 \ (4\text{H, m}), \ 3.74 \ (2\text{H, d, } J = 5.40 \text{ Hz}), \ 3.90 \ (3\text{H, s}), \ 4.69 \ (1\text{H, t, exchange D}_2\text{O}), \ 4.70 \ (2\text{H, d, } J = 5.20 \text{ Hz}), \ 5.30 \ (1\text{H, t, } J = 6.6\text{Hz}), \ 5.48 \ (1\text{H, t, } J = 6.40 \text{ Hz}), \ 7.02 \ (1\text{H, s}), \ 7.57. \]

\[ ^{13}C \text{NMR} \ (100 \text{ MHz, CDCl}_3): \ 9.1, \ 13.7, \ 16.8, \ 25.2, \ 26.2, \ 38.9, \ 62.1, \ 65.7, \ 68.0, \ 100.1, \ 104.4, \ 109.3, \ 119.4, \ 121.8, \ 124.3, \ 134.7, \ 141.5, \ 151.6, \ 157.1, \ 163.6, \ 166.6. \]

LC-MS (Retention time = 1.04 min [M+H]^+ = 377 (>99% by LC-MS, UV). The site of alkylation and the structure of compound 3 was assigned unambiguously. The following ROESY correlations spectroscopy data were observed:

\[ A \ 1.70 \text{H1} \quad 7.02 \text{H6} \]
\[ B \ 7.57 \text{OH10} \quad 7.02 \text{H6} \]
\[ C \ 4.69 \text{OH25} \quad 3.74 \text{H24} \]
**Compound 4:**
3-hydroxy-5-(((2E,5E)-7-hydroxy-3,7-dimethylocta-2,5-dien-1-yl)oxy)-7-methoxy-3,6-dimethylisobenzofuran-1(3H)-one

**Supporting Scheme S3-** Preparation of 3-hydroxy-5-(((2E,5E)-7-hydroxy-3,7-dimethylocta-2,5-dien-1-yl)oxy)-7-methoxy-3,6-dimethylisobenzofuran-1(3H)-one. Reagents and conditions (i) (PhSe)$_2$, BAIB, KSCN in acetonitrile, 5 mins, RT then 2, acetonitrile, 3 h, RT, 34%; (ii) NaHCO$_3$, NaIO$_4$ in water, dioxane, 16 h, RT, 62%. BAIB = [bis(acetoxy)iodo]benzene.

Compound 4 was obtained as a colorless (18 mg, 0.048 mmol, 62% yield). $^1$H NMR (400 MHz; DMSO-$d_6$): $\delta$ ppm 7.57 (1H, s, exchange D$_2$O), 7.02 (1H, s), 5.59 (1H, d, $J = 14.95$ Hz), 5.50 (2H, m), 4.71 (2H, m), 4.48 (1H, s, exchange D$_2$O), 3.90 (3H, s), 2.72 (2H, d, $J = 6.35$ Hz), 2.05 (3H, s), 1.71 (3H, s), 1.70 (3H, s), 1.61 (6H, 2xCH$_3$, s), $^{13}$C NMR (100 MHz; CDCl$_3$): 166.4, 163.9, 157.7, 151.7, 141.1, 140.0, 124.6, 122.6, 120.4, 109.7, 104.2, 100.6, 71.4, 66.1, 62.5, 42.2, 30.4, 30.0, 26.6, 17.4, 9.3; LC-MS Retention time = 1.03 min [M+H]$^+$ = 377 (>99 % by LC-MS, UV). The site of alkylation and the structure of compound 4 was assigned unambiguously. The following ROESY correlations spectroscopy data were observed:

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<td>A</td>
<td>7.02 H6</td>
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