

Synthesis of Analogue Structures of the *para*-Quinone Methide Moiety of Kendomycin

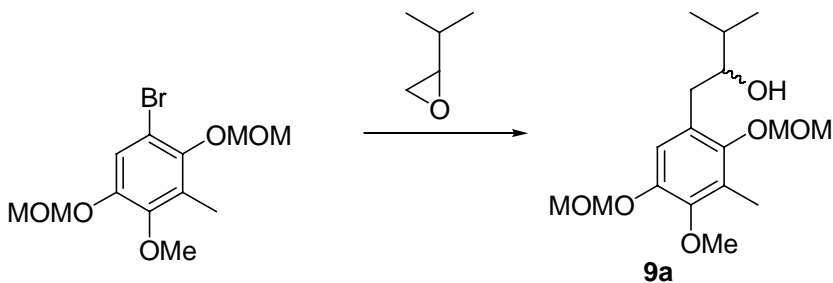
Supporting Information

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General Experimental

All other solvents used HPLC grade. Column chromatography was performed with Merck silica gel (0.04-0.63 μm , 240-400 mesh) under pressure. TLC was carried out with E. Merck silica gel 60-F254 plates. NMR spectra were recorded on either a Bruker Avance DPX 250 MHz or 400 MHz. Unless otherwise stated, all NMR spectra were measured in CDCl_3 solutions and referenced to the residual CHCl_3 signal (^1H , $\delta = 7.27$; ^{13}C , $\delta = 77.0$). All ^1H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; br s = broad signal). Coupling constants J are given in Hz. Mass spectra were measured on a MAT 900 (Finnigan-MAT, San Jose, CA). High-resolution mass spectra (HRMS) were taken with a Finnigan MAT 8230 with a resolution of 10,000 (Finnigan-MAT, San Jose, CA). The EPR experiment was performed at room temperature with a Bruker EMX 10/12 spectrometer operated in the X-band (9-10 GHz). In order to improve the signal-to-noise ratio 20 scans were accumulated in one spectrum.

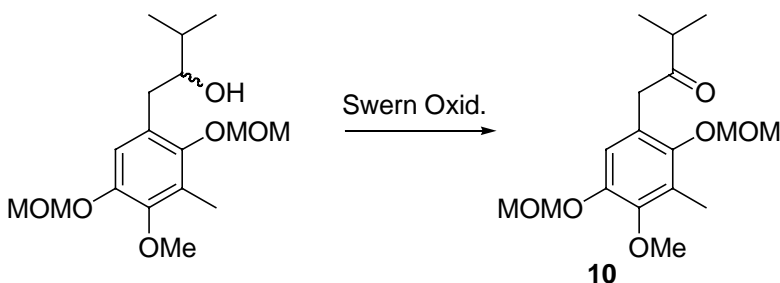
1-(4-Methoxy-2,5-bis-methoxymethoxy-3-methyl-phenyl)-3-methyl-butan-2-ol (**9a**)



The aryl bromide^{2c} (2.00 g, 6.25 mmol) was dissolved in 10 mL of dry THF and Mg (163 mg, 6.25) was suspended in the reaction mixture. Iodine (2 mg) was added and the

mixture was heated to reflux for 2 h. The mixture was cooled to room temperature and transferred via cannula to a three necked flask containing CuI (20 mg, 0.1 mmol) which was suspended in 2 mL of dry THF at -50 °C. The temperature was raised to -30 °C and the mixture was stirred at this temperature for 30 min. Afterwards, isobutene oxide (686 mg 8.0 mmol) was added at -60 °C and the temperature was raised to 0 °C over 4 h. The reaction mixture was quenched with NH₄Cl (10 mL) and extracted with diethyl Et₂O (3 x 10 mL). The combined organic phases were washed with H₂O (10 mL), brine (10 mL) dried over MgSO₄ and the solvent was removed by evaporation. The crude material was purified by SiO₂ flash column chromatography using hexane and EtOAc (3:1) to afford **9a**, as a colorless oil (1.74 g, 85 %). δ_{H} (400 MHz; CDCl₃) 6.85 (1 H, s, CH), 5.20 (1 H, d, J = 6 Hz, CHH), 5.17 (1 H, d, J = 6 Hz, CHH), 4.96 (1 H, d, J = 6 Hz, CHH), 4.92 (1 H, d, J = 6 Hz, CHH), 3.81 (3 H, s, CH₃), 3.62 (3 H, s, CH₃), 3.62-3.56 (1 H, m, CHOH), 3.52 (3 H, s, CH₃), 2.75 (1 H, d, J = 3 Hz, CHCHAr), 2.74 (1 H, s, CHHAr), 2.36 (1 H, d, J = 5 Hz, OH), 2.21 (3 H, s, CH₃), 1.80-1.72 (1 H, m, CH(CH₃)), 1.01 (6 H, d, J = 7 Hz, CH₃CH); δ_{C} (100 MHz; CDCl₃) 150.5 (C), 147.8 (C), 147.4 (C), 128.5 (C), 126.1(C), 116.2 (CH), 100.3 (CH₂), 96.0 (CH₂), 60.8 (CH₃), 57.9 (CH₃), 56.6 (CH₃), 35.6 (CH₂), 34.4 (CH), 19.2 (2 x CH₃), 17.8 (CH), 10.8 (CH₃); m/z (EI) 328 (M⁺, 26.3%), 296 (36.5), 266 (29.8), 221 (100.0); (C₁₇H₂₈O₆ requires 328.1886. Found 328.1881).

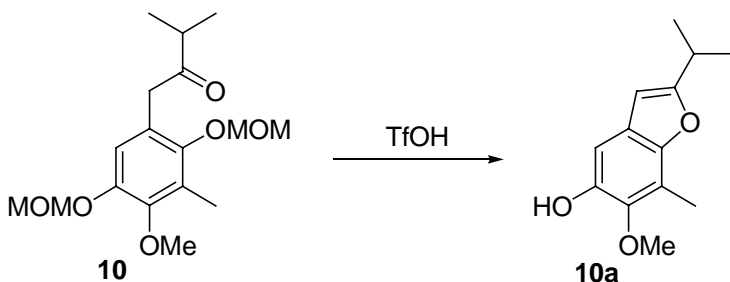
1-(4-Methoxy-2,5-bis-methoxymethoxy-3-methyl-phenyl)-3-methyl-butan-2-one (10**)**



DMSO (1.3 mL, 18.3 mmol) was added dropwise to a solution of oxalyl chloride (0.78 mL, 9.1 mmol) in CH₂Cl₂ (10 mL) at -78 °C. After the reaction mixture was stirred for one hour **9a** (1.50 g, 4.57 mmol) was added slowly and stirring was continued for an additional 10 min. After the dropwise addition of freshly distilled NEt₃ (3.8 mL, 27.5 mmol) a yellow slurry was formed and stirring was continued at -78 °C for 30 min. The reaction mixture was allowed to warm to room temperature (45 min), then hydrolyzed

with H₂O (10 mL) and extracted with diethyl Et₂O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NH₄Cl (5 mL), saturated aqueous NaHCO₃ (5 mL) and brine (5 mL), dried over MgSO₄ and the solvent removed. The crude material was purified by SiO₂ flash column chromatography using hexane and EtOAc (5:1) to afford **10**, as a colorless oil (1.33 g, 89 %). δ_{H} (400 MHz; CDCl₃) 6.77 (1 H, s, CH), 5.17 (2 H, s, CH₂), 4.86 (2 H, s, CH₂), 3.82 (3 H, s, CH₃), 3.77 (2 H, s, CH₂), 3.55 (3 H, s, CH₃), 3.51 (3 H, s, CH₃), 2.73 (1 H, qq, $J = 7$ Hz, and 7 Hz, CH(CH₃), 2.22 (3 H, s, CH₃), 1.13 (6 H, d, $J = 7$ Hz, CH₃CH); δ_{C} (100 MHz; CDCl₃) 212.6 (C), 150.3 (C), 147.3 (C), 147.3 (C), 126.2 (C), 124.0 (C), 116.6 (CH), 100.1 (CH₂), 95.9 (CH₂), 60.8 (CH₃), 57.8 (CH₃), 56.6 (CH₃), 43.1 (CH₂), 40.3 (CH), 18.8 (2 x CH₃), 10.8 (CH₃); m/z (EI) 326 (M⁺, 96.0%), 281 (36.5), 249 (62.9), 211 (41.6); (C₁₇H₂₆O₆ requires 326.1729. Found 326.1737).

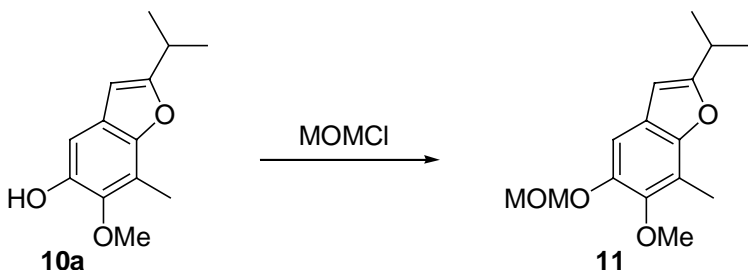
2-Isopropyl-6-methoxy-7-methyl-benzofuran-5-ol (**10a**)



Ketone **10** (1.00 g, 3.10 mmol) was dissolved in a solution of PhMe (200 mL) and EtOH (50 mL) and 3.0 g of MS 4Å were added. The suspension was heated to 80 °C and CF₃CO₃H (92 μ L, 1.24 mmol) was added. After 5 min, the reaction flask was put into an ice bath to cool down to room temperature as quickly as possible. A saturated aq. solution of NaHCO₃ (100 mL) solution was added and the resulting mixture was filtered over a pad of Celite[®] to remove the molecular sieves. The layers were separated and the aq. layer was extracted with Et₂O (3 x 100 mL), dried over MgSO₄, and the solvent removed. The crude material was purified by SiO₂ column chromatography using hexane and EtOAc (8:1) to afford **10a**, as a brown oil (660 mg, 95 %). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3750, 2966, 2934, 2873, 1608, 1463, 1420, 1352, 1318, 1265, 1218, 1189, 1158, 1131, 1111, 1070, 991, 942 and 881; δ_{H} (400 MHz; CDCl₃) 6.91 (1 H, s, CH), 6.23 (1 H, s, CH), 5.65 (1 H, br s, OH), 3.85 (3 H, s, OMe), 3.06 (1 H, qq, $J = 7$ Hz, CH(CH₃)₂), 2.48 (3 H, s, CH₃), 1.35 (6

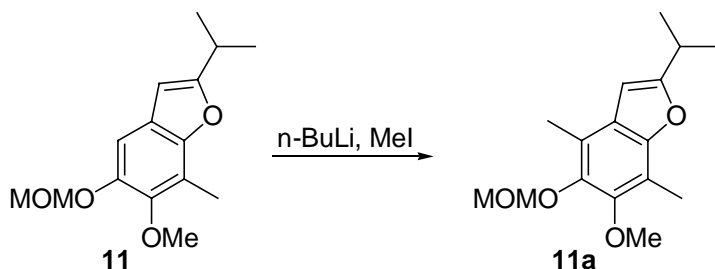
H, d, $J = 7$ Hz, $\text{CH}(\text{CH}_3)_3$); δ_{C} (100 MHz; CDCl_3) 165.2 (C), 147.9 (C), 145.1 (C), 142.5 (C), 124.1 (C), 113.8 (C), 102.1 (CH), 99.7 (CH), 61.3 (CH_3), 28.2 (CH), 20.4 (2 x CH_3), 9.3 (CH_3); m/z (EI) 220 (M^+ , 64.9 %), 205 (100.0); ($\text{C}_{13}\text{H}_{16}\text{O}_3$ requires 220.1099. Found 220.1096).

2-Isopropyl-6-methoxy-5-methoxymethoxy-7-methyl-benzofuran (11)



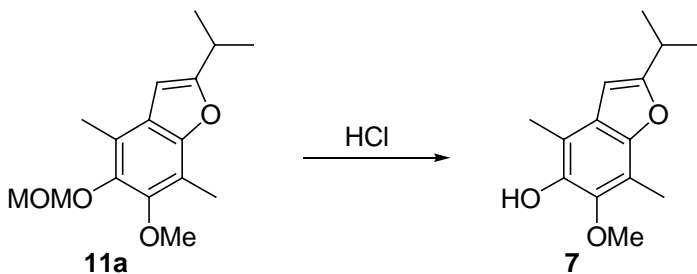
10a (180 mg, 0.82 mmol), was dissolved in dry DMF (2 mL) and NaH (60 % in min. oil suspension, 66 mg, 1.64 mmol) was added at 0 °C and the mixture stirred for 10 min, forming a black suspension. Treatment with MOMCl (0.20 mL, 2.46 mmol) changed the color of the suspension to slightly brown. After 30 min a diethyl Et_2O (3 mL) and H_2O (3 mL) were added. The layers were separated and the organic phase was extracted with diethyl Et_2O (3 x 3 mL) and the combined organic layers were dried over MgSO_4 , filtered and distilled. The crude material was purified by flash column chromatography using hexane and EtOAc (5:1) to afford **11**, as a colorless oil (180 mg, 83%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2966, 2934, 2873, 1608, 1434, 1218, 1190, 1158, 1131, 1111, 1070, 991, 942, 881, 854, 793, 739 and 688; δ_{H} (400 MHz; CDCl_3) 7.09 (1 H, s, CH), 6.25 (1 H, d, $J = 1$ Hz, CH), 5.21 (2 H, s, CH_2), 3.84 (3 H, s, CH_3), 3.54 (3 H, s, CH_3), 3.05 (1 H, qqd, $J = 7$ Hz, 7 Hz and 1 Hz, $\text{CH}(\text{CH}_3)_2$), 2.43 (3 H, s, CH_3), 1.33 (6 H, d, $J = 7$ Hz, $(\text{CH}_3)_2\text{CH}$); δ_{C} (100 MHz; CDCl_3) 165.6 (C), 149.7 (C), 147.3 (C), 146.0 (C), 123.9 (C), 115.6 (C), 105.5 (CH), 100.2 (CH), 96.6 (CH_2), 61.4 (CH_3), 56.5 (CH_3), 28.7 (CH), 21.4 (2 x CH_3), 9.5 (CH_3); m/z (EI) 264 (M^+ , 100%), 219 (60.0); ($\text{C}_{15}\text{H}_{20}\text{O}_4$ requires 264.1362. Found 264.1358).

2-Isopropyl-6-methoxy-5-methoxymethoxy-4,7-dimethyl-benzofuran (11a)



Benzofuran **11** (180 mg, 0.68 mmol) was dissolved in dry THF (3 mL) cooled to $-40\text{ }^{\circ}\text{C}$ and *n*-Buli (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added. After one hour at -30 ° the solution was cooled to $-78\text{ }^{\circ}\text{C}$ and methyl iodide (0.43 mL, 68 mmol) was added. The reaction mixture was warmed to $-25\text{ }^{\circ}\text{C}$ over 2 h and finally quenched with saturated aqueous NH_4Cl solution (3 mL). The reaction mixture was extracted with diethyl Et_2O (3 x 3 mL), dried over MgSO_4 , filtered and the solvent was removed. The crude material was purified by flash column chromatography using hexane and EtOAc (7:1) to afford **11a**, as a colorless oil (180 mg, 95%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2964, 2926, 2361, 2344, 1654, 1560, 1458, 1389, 1338, 1160, 1118, 1093, 972, 1160, 1118, 1093, 972, 880, 738 and 610; δ_{H} (400 MHz; CDCl_3) 6.30 (1 H, d, $J = 1\text{ Hz}$, CH), 5.09 (2 H, s, CH_2), 3.82 (3 H, s, CH_3), 3.63 (3 H, s, CH_3), 3.06 (1 H, qqd, $J = 7\text{ Hz}$, 7 Hz and 1 Hz , $\text{CH}(\text{CH}_3)$), 2.41 (3 H, s, CH_3), 2.40 (3 H, s, CH_3), 1.34 (6 H, d, $J = 7\text{ Hz}$, CH_3CH); δ_{C} (100 MHz; CDCl_3) 165.1 (C), 150.0 (C), 148.4 (C), 144.7 (C), 124.5 (C), 120.2, (C), 112.9 (C), 100.0 (CH_2), 99.1 (CH), 61.2 (CH_3), 57.9 (CH_3), 28.7 (CH), 21.5 (2 x CH_3), 13.2 (CH_3), 9.5 (CH_3); m/z (EI) 278 (M^+ , 91.7%), 233 (100.0).

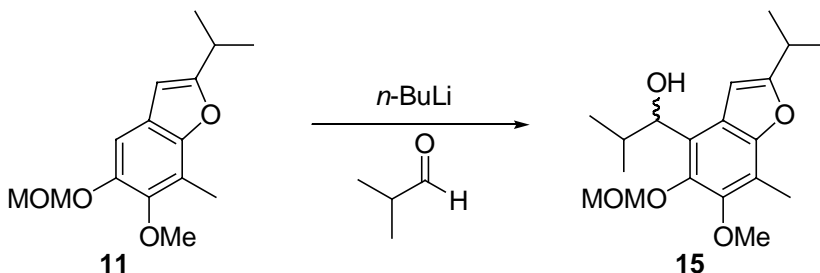
2-Isopropyl-6-methoxy-4,7-dimethyl-benzofuran-5-ol (**7**)



To a solution of **11a** (150 mg, 0.54 mmol) in MeOH (3 mL) was added aqueous HCl (1.0 M, 0.3 mL, 0.3 mmol). The reaction was warmed to 50°C . After 5 h, H_2O (3 mL) was

added and the product was extracted to Et₂O (3 x 5 mL). The organic fractions were combined, washed with brine and dried over MgSO₄. The solvent was removed and the crude material purified by flash column chromatography using hexane and EtOAc (4 : 1) to afford **7** as a light brown oil (123 mg, 96%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3751, 2964, 2926, 1458, 1398, 1289, 1115, 1073, 880, 738 and 610; δ_{H} (400 MHz; CDCl₃) 6.29 (1 H, d, J = 1 Hz, CH), 5.51 (1 H, s, OH), 3.83 (3 H, s, CH₃), 3.05 (1 H, qqd, J = 7 Hz, 7 Hz and 1 Hz, CH(CH₃)), 2.43 (3 H, s, CH₃), 2.35 (3 H, s, CH₃), 1.34 (6 H, d, J = 7 Hz, CH₃CH); δ_{C} (100 MHz; CDCl₃) 165.0 (C), 147.4 (C), 143.0 (C), 142.8 (C), 124.8 (C), 111.6 (C), 111.1 (C), 98.8 (CH), 61.8 (CH₃), 28.7 (CH), 21.4 (2 x CH₃), 12.3 (CH₃), 9.6 (CH₃); m/z (EI) 234 (M^+ , 52.1%), 219 (100.0).

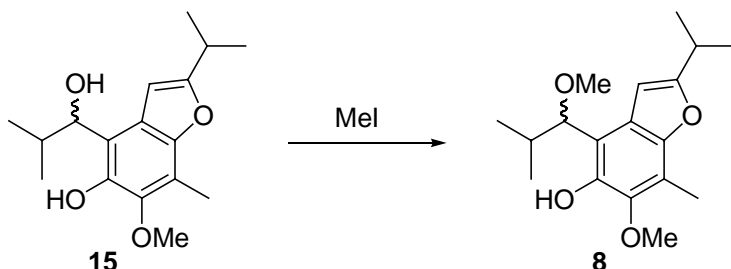
1-(2-Isopropyl-6-methoxy-5-methoxymethoxy-7-methyl-benzofuran-4-yl)-2-methylpropan-1-ol (15**)**



Benzofuran **11** (180 mg, 0.68 mmol) was dissolved in dry THF (3 mL) cooled to $-40\text{ }^{\circ}\text{C}$ and $n\text{-BuLi}$ (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added. After one hour at -30 ° the solution was cooled to $-78\text{ }^{\circ}\text{C}$ and isobutyraldehyde (0.25 mL, 2.7 mmol) was added. The reaction mixture was warmed to $-25\text{ }^{\circ}\text{C}$ over 2 h and finally quenched with saturated aqueous NH₄Cl solution (2 mL). The reaction mixture was extracted with diethyl Et₂O (3 x 5 mL), dried over MgSO₄, filtered and the solvent was removed. The crude material was purified by SiO₂ flash column chromatography using hexane and EtOAc (5:1) to afford **15**, as a colorless oil (205 mg, 90 %). δ_{H} (400 MHz; CDCl₃) 6.51 (1 H, d, J = 1 Hz, CH), 5.12 (2 H, s, CH₂) 4.74 (1 H, dd, J = 9.5 Hz, 5.5 Hz, CHOH), 3.80 (3 H, s, CH₃), 3.59 (3 H, s, CH₃), 3.05 (1 H, qq, J = 7 Hz, 7 Hz and 1 Hz, CH(CH₃)), 2.77 (1 H, d, J = 5.5 Hz, OH), 2.41 (3 H, s, CH₃), 2.35-2.25 (1 H, m, CH), 1.34 (3 H, d, J = 7 Hz, CH₃CH), 1.33 (3 H, d, J = 7 Hz, CH₃CH), 1.18 (3 H, d, J = 7 Hz, CH₃CH), 0.74 (3 H, d, J = 7 Hz, CH₃CH); δ_{C} (100 MHz; CDCl₃) 165.1 (C), 150.6 (C), 147.9 (C), 144.6 (C),

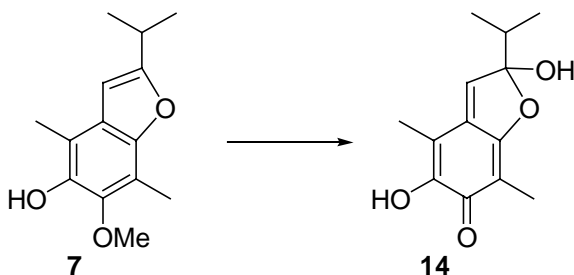
126.2 (C), 122.7 (C), 114.8 (C), 100.5 (CH₂), 100.2 (CH), 76.1 (CH), 61.1 (CH₃), 58.0 (CH₃), 34.6 (CH), 28.6 (CH), 21.4 (2 x CH₃), 20.1 (CH₃), 19.9 (CH₃) 9.5 (CH₃); *m/z* (EI) 336 (M⁺, 44.0%), 293 (26.7), 274 (100), 233 (94.6); (C₁₉H₂₈O₅ requires 336.1937. Found 336.1942).

2-Isopropyl-6-methoxy-4-(1-methoxy-2-methyl-propyl)-7-methyl-benzofuran-5-ol (8)



To a solution of **15** (47 mg, 0.14 mmol) in MeOH (3 mL) was added aqueous HCl (1 N) (0.3 mL, 0.3 mmol). The reaction was warmed to 50°C. After 5 h, H₂O (3 mL) was added and the product was extracted to Et₂O (3 x 5 mL). The organic fractions were combined, washed with brine and dried over MgSO₄. The solvent was removed and the crude material purified by SiO₂ flash column chromatography using hexane and ethyl acetate (4:1) to afford **8** as a colorless oil (33 mg, 77%). $\nu_{\max}/\text{cm}^{-1}$ (film) 2960, 2925, 1603, 1449, 1403, 1356, 1283, 1104, 944, 894, 816, 738 and 610; δ_{H} (400 MHz; CDCl₃) 7.10 (1 H, br s, OH), 6.28 (1 H, s, CH), 4.33 (1 H, d, *J* = 7.5 Hz, CHOMe), 3.85 (3 H, s, CH₃), 3.34 (3 H, s, CH₃), 3.04 (1 H, qq, *J* = 7 Hz and 7 Hz, CH(CH₃)), 2.43 (3 H, s, CH₃), 2.20-2.10 (1 H, m, CH), 1.34 (6 H, d, *J* = 7 Hz, CH₃CH), 1.07 (3 H, d, *J* = 7 Hz, CH₃CH), 0.85 (3 H, d, *J* = 7 Hz, CH₃CH); δ_{C} (100 MHz; CDCl₃) 165.0 (C), 144.8 (C), 143.5 (C), 142.2 (C), 123.2 (C), 114.0 (C), 99.1 (CH), 87.1 (CH), 61.3 (CH₃), 58.0 (CH₃), 34.3 (CH), 28.7 (CH), 21.4 (2 x CH₃), 19.7 (CH₃), 19.2 (CH₃) 9.5 (CH₃); *m/z* (EI) 306 (M⁺, 19.3%), 278, (21.8), 274 (100.0), 263 (63.2), 233 (67.6).

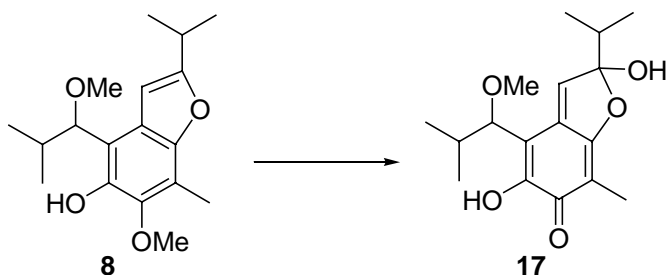
2,5-Dihydroxy-2-isopropyl-4,7-dimethyl-2H-benzofuran-6-one (14)



To a solution of benzofuran **7** (14 mg, 0.06 mmol) in DCM (1 mL) at 0°C was added a 0.2 M solution of boron tribromide and lutidine (1:1) (1.2 mL, 0.24 mmol) in DCM. After stirring for 10 h at 0-4°C, methanol was added and the reaction stirred at room temperature. After 5 h, H₂O (3 mL) and Et₂O (5 mL) were added and the layers separated. The aqueous phase was extracted with Et₂O (3 x 5 mL). The organic fractions were combined, washed with brine and dried over MgSO₄. The solvent was removed to give a crude sample of catechol **18** which was used directly in the next reaction.

To a solution of crude catechol **18** in DCM (2 mL) at -78°C was added a solution of dimethyldioxirane (0.09 M in acetone, 0.73 mL, 0.07 mmol). After stirring for 20 min at this temperature, the reagent and solvent were removed by evaporation. The crude product was purified by SiO₂ flash column chromatography using hexane and Et₂O (4:1) to afford *para*-quinone methide **14** as a yellow oil (10 mg, 73%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3356, 2969, 2360, 2343, 1671, 1613, 1584, 1568, 1381, 1329, 1263, 1116, 1091, 926, 891, 788, 737 and 610; δ_{H} (400 MHz; CDCl₃) 7.18 (1 H, br s, OH), 6.63 (1 H, s, CH), 4.09 (1 H, br s, OH), 2.23 (1 H, qq, $J = 7$ Hz and 7 Hz, CH(CH₃)), 2.03 (3 H, s, CH₃), 1.90 (3 H, s, CH₃), 1.07 (3 H, d, $J = 7$ Hz, CH₃CH), 0.99 (3 H, d, $J = 7$ Hz, CH₃CH); δ_{C} (100 MHz; CDCl₃) 182.2 (C), 166.9 (C), 145.9 (C), 135.8 (CH), 133.9 (C), 116.8 (C), 106.3 (C), 104.6 (CH), 35.3 (CH₃), 17.0 (CH₃), 16.4 (CH₃), 10.0 (CH₃), 7.0 (CH₃); m/z (EI) 236 (M^+ , 32.8%), 193 (100.0); (C₁₃H₁₆O₄ requires 236.1049. Found 236.1044).

2,5-Dihydroxy-2-isopropyl-4-(1-methoxy-2-methyl-propyl)-7-methyl-2H-benzofuran-6-one (17**)**



To a solution of benzofuran **8** (9 mg, 0.03 mmol) in DCM (1 mL) at 0°C was added a 0.2 M solution of boron tribromide and lutidine (1:1) (0.60 mL, 0.12 mmol) in DCM. After stirring for 10 h at 0-4°C, methanol was added and the reaction stirred at room temperature. After 5 h, H₂O (3 mL) and Et₂O (5 mL) were added and the layers separated. The aqueous phase was extracted with Et₂O (3 x 5 mL). The organic fractions were combined, washed with brine and dried over MgSO₄. The solvent was removed to give a crude sample of catechol **19** which was used directly in the next reaction.

To a solution of crude catechol **19** in DCM (2 mL) at -78°C was added a solution of dimethyldioxirane (0.9 M in acetone, 0.39 mL, 0.035 mmol). After stirring for 20 min at this temperature, the reagent and solvent were removed by evaporation. The crude product was purified by SiO₂ flash column chromatography using hexane and ethyl acetate (6:1) to afford both diastereoisomers of *para*-quinone methide **17** as a yellow oil (6 mg, 65 %). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3331, 2966, 2926, 1611, 1378, 1332, 1092, 920, 738 and 610; δ_{H} (400 MHz; CDCl₃) 7.46 (1 H, s, OH), 7.06 and 7.05 (1 H, s, CH), 4.20 and 4.18 (1 H, d, $J = 9$ Hz, CHOMe), 3.26 and 3.22 (3 H, s, OMe), 3.00 and 3.97 (1 H, s, OH), 2.26 (1 H, qq, $J = 7$ Hz and 7 Hz, CHCH₃), 2.2.02-2.19 (1 H, m, CHCH₃), 1.94 (3 H, s, CH₃), 1.02 and 1.00 (3 H, d, $J = 7$ Hz, CH₃CH), 0.99 (3 H, d, $J = 7$ Hz, CH₃CH), 0.93 and 0.92 (3 H, d, $J = 7$ Hz, CH₃CH), 0.76 and 0.75 (3 H, d, $J = 7$ Hz, CH₃CH); ¹³C-NMR (CDCl₃, 100 MHz, quaternary carbons missing after 20000 scans): δ_{C} (100 MHz; CDCl₃) 138.9 and 138.8 (CH), 100.2 (C), 83.2 and 83.0 (CH), 57.7 and 57.3 (CH₃), 36.3 (CH), 33.7 and 33.6 (CH), 20.0 and 19.9 (CH₃), 19.2 and 19.1 (CH₃), 18.1 and 18.0 (CH₃), 17.3 and 17.2 (CH₃), 7.99 (CH₃); m/z (EI) 308 (M⁺, 10.3%), 265 (100.0), 205 (55.0); (C₁₇H₂₄O₅ requires 308.1624. Found 308.1617).

