Supporting Information

Enantioselective Nozaki-Hiyama-Kishi Allylation-Lactonization for the Syntheses of 3-Substituted Phthalides

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General information:

All reactions were carried out in anhydrous solvents. THF and diethyl ether were distilled from sodium-benzophenone under argon. Toluene, CH$_2$Cl$_2$, and hexane were distilled from CaH$_2$. $^1$H NMR spectra were obtained at 300 or 400 MHz (as indicated), and $^{13}$C NMR spectra were obtained at 75.5 or 100.6 MHz, using a Bruker NMR spectrometer. Chemical shifts ($\delta$) are reported in ppm relative to CDCl$_3$ (7.26 and 77.0 ppm). Mass spectra (EI-MS) and high resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded using a JASCO FT/IR S5 410 spectrometer. All asymmetric reactions were conducted in dry glassware under argon. Enantiomeric excesses were determined using Lab Alliance Series III high performance liquid chromatography (HPLC) with a Chiracel OJ column (Daicel Chemical Industries, LTD). Optical rotations were measured using a JASCO P-1010 Polarimeter at the indicated temperature using a sodium lamp (D line, 589 nm). Flash column chromatography was performed using MN silica gel 60 (70–230 mesh) purchased from Macherey-Nagel.

Synthesis and characterization of ligands
1. (1S,9S)-10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0$_{2,7}$]-undeca-2(7)-3,5-triene (3):

A mixture of compound 1 (6.51 g, 19.97 mmol), compound 2 (3.0 g, 19.97 mmol, ), and ammonium acetate (12.31 g, 159.76 mmol) in glacial acetic acid (20.0 mL) under argon atmosphere was heated at 100–110 °C for 15 h. After cooling to room temperature, the reaction mixture was transferred to a 500-mL conical flask, water (200 mL) was added, and the mixture was basified by sodium hydroxide until it become basic. The aqueous solution was extracted three times with ethyl acetate (3 × 200 mL) and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (10:90) as the mobile phase to obtain compound 3 (3.80 g, 15.18 mmol) as pale yellow solid. Yield: 76%.
[α]20 D –40° (c 1.05, CHCl3), 1H NMR (400 MHz, CDCl3, δ): 8.65 (t, J = 3.5 Hz, 1H), 8.37–8.32 (m, 1H), 8.04 (dd, J = 3.3, 7.7 Hz, 1H), 7.80–7.73 (m, 1H), 7.32 (dd, J = 4.0, 7.7 Hz, 1H), 3.19 (s, 2H), 2.80–2.69 (m, 2H), 2.42–2.30 (m, 1H), 1.42 (s, 3H). 13C NMR (100.6 MHz, CDCl3, δ): 156.8, 156.4, 153.5, 149.1, 142.2, 136.7, 133.7, 123.0, 120.8, 117.8, 46.5, 40.3, 39.5, 36.7, 31.9, 26.0, 21.3. IR (KBr): 3049, 2972, 2923, 1920, 1583, 1577, 1558, 1437, 1432, 1382, 1366, 1245, 1144, 1072, 990, 943, 899, 792, 751, 620, 609, 518 cm⁻¹. LRMS-EI+ (m/z): 251 ([M+H]+, 100), 250 (10) HRMS-TOF-ES+ (m/z): [M+H]+ calcd for C17H19N2, 251.1549, found 251.1549.

2. (1S,8R,9S)-(10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.02,7]-undeca-2(7),3,5-trien-8-yl)-diphenyl-methanol (4)

To a solution of Bipy 3 (0.50 g, 2.00 mol) in dry THF (5 mL) the LDA solution (2 M in hexane, 1.2 mL, 2.3966 mmol) was added at −78 °C and stirred for 2 h to generate a dark blue solution. To this dark blue solution was added a solution of benzophenone (0.36 g, 2.00 mmol) in THF (5 mL) and the temperature was slowly raised to room temperature and stirred for 8 h. The reaction was quenched by adding NH4Cl solution, and extracted with EtOAc. The combined organic phase was dried over anhydrous MgSO4. After concentration to give a residue, the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:9) as the mobile phase, to get product 4 (0.66 g, 1.52 mmol) as off white solid.

Yield: 76%. mp: 75–77 °C. [α]20 D –452° (c 1.77, CHCl3). 1H NMR (400 MHz, CDCl3, δ): 9.90 (bs, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.32–8.16 (m, 2H), 7.80–7.74 (m, 1H), 7.56–7.36 (m, 5H), 7.36–7.27 (m, 2H), 7.17–6.96 (m, 5H), 4.48 (s, 1H), 2.75–2.52 (m, 2H), 2.12–2.03 (m, 1H), 1.48 (s, 3H), 0.89 (s, 3H), −0.07–−0.12 (d, J = 10.4 Hz, 1H). 13C NMR (100.6 MHz, CDCl3, δ): 156.8, 155.3, 151.4, 149.3, 146.9, 145.8, 144.3, 137.2, 134.9, 128.3, 128.2, 127.8, 127.2, 127.0, 126.4, 123.6, 120.6, 118.7, 81.9, 47.9, 45.8, 43.0, 41.5, 28.7, 26.3, 21.2. IR (KBr): 3445, 3148, 3054, 2972, 2928, 2862, 1577, 1558, 1462, 1432, 1380, 1284, 1152, 987, 938, 897, 858, 787, 784, 743, 636, 625, 578, 543, 515 cm⁻¹. LRMS-EI+ (m/z): 433 ([M+H]+, 100), 432 (3), 431 (8), 367 (5), 249 (6), 167 (15). HRMS-TOF-ES+ (m/z): [M+H]+ calcd for C30H29N2O, 433.2281, found 433.2281.
3. (1S,8R,9S)-2-(10,10-dimethyl-5-(pyridin-2-yl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7)-3,5-trien-8-yl)-1,3-diphenyl-propan-2-ol (5):

To a solution of Bipy 3 (0.2 g, 0.80 mmol) in dry THF (3 mL) the LDA solution (0.48 mL, 0.95 mmol, 2 M in hexane) was added at -78 °C and stirred for 2 h to generate a dark blue solution. To this dark blue solution was added a solution of 1,3-diphenyl acetone (0.17 mg, 0.7988 mmol) in THF (2 mL) and the temperature was slowly raised to room temperature and stirred for 3 h. The reaction was quenched by adding NH₄Cl solution, and extracted with EtOAc. The combined organic phase was dried over anhydrous MgSO₄. After concentration to give a residue, the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:9) as the mobile phase, to get product 5 (0.27 g, 0.60 mmol) as pale yellow semisolid. Yield: 75%. [α]₂⁰ D –290° (c 1.09, CHCl₃).

¹H NMR (400 MHz, CDCl₃, δ): 8.70‒8.66 (m, 1H), 8.31‒8.20 (m, 2H), 8.18 (d, J = 7.7 Hz, 1H), 7.88‒7.82 (m, 1H), 7.47‒7.34 (m, 3H), 7.35‒7.11 (m, 8H), 3.21 (s, 1H), 2.94‒2.59 (m, 6H), 1.70‒1.37 (m, 4H), 1.29‒1.25 (m, 2H), 0.40 (s, 3H).

¹³C NMR (100.6 MHz, CDCl₃, δ): 158.4, 155.4, 151.9, 149.2, 144.1, 138.2, 130.0, 137.1, 134.6, 131.1, 130.9, 127.7, 126.0, 125.9, 123.5, 120.5, 118.5, 79.1, 47.7, 46.7, 46.3, 42.1, 41.9, 29.9, 26.3, 20.7. IR (KBr): 3280, 2021, 2923, 1555, 1577, 1492, 1432, 1451, 1382, 1372, 1251, 1152, 1166, 1086, 960, 905, 861, 784, 751, 699, 655, 609, 518 cm⁻¹. LRMS-EI⁺ (m/z): 461 ([M+H]⁺, 100), 443 (3), 180 (1). HRMS-TOF-ES⁺ (m/z): [M+H]⁺ calcd For C₃₂H₃₃N₂O, 461.2594, found 461.2596.

4. (1S,8R,9S)-1-(10,10-dimethyl-5-(pyridin-2-yl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7)-3,5-trien-8-yl)-cyclohexan-1-ol (6)
To a solution of Bipy 3 (0.5 g, 2.00 mmol) in dry THF (5 mL) the LDA solution (1.2 mL, 2.40 mmol, 2 M in hexane) was added at −78°C and stirred for 2 h to generate a dark blue solution. To this dark blue solution was added a solution of cyclohexanone (0.20 mg, 1.9972 mmol) in THF (5 mL) and the temperature was slowly raised to room temperature and stirred for 8 h. The reaction was quenched by adding NH₄Cl solution, and extracted with EtOAc. The combined organic phase was dried over anhydrous MgSO₄. After concentration to give a residue, the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:9) as the mobile phase, to get product 6 (0.51 g, 1.46 mmol) as brown oil, Yield: 73%. [α]²⁰ D −322° (c 1.82, CHCl₃).

1H NMR (400 MHz, CDCl₃, δ): 8.65 (d, J = 2.6 Hz, 1H), 8.29–8.11 (m, 2H), 7.90 –7.67 (m, 2H), 7.40 (d, J = 7.7 Hz, 1H), 3.21 (d, J = 15.4 Hz, 1H), 2.80 (dd, J = 5.0, 5.0 Hz, 1H), 2.68–2.60 (m, 1H), 2.47–2.41 (m, 1H), 1.98–1.74 (m, 2H), 1.74–1.50 (m, 4H), 1.50–1.34 (m, 6H), 1.35–1.19 (m, 2H), 1.12 (q, J = 13.0 Hz, 1H), 0.69 (s, 3H).

13C NMR (100.6 MHz, CDCl₃, δ): 158.0, 155.6, 151.9, 149.1, 143.8, 137.1, 134.5, 123.4, 120.6, 118.5, 75.4, 53.1, 46.5, 42.0, 41.9, 37.2, 35.3, 29.5, 26.0, 21.7, 21.5, 21.1. IR (KBr): 3307, 2928, 2857, 1577, 1555, 1432, 1248, 1218, 1179, 1141, 1091, 1017, 954, 858, 787, 740, 721, 691, 658, 609, 491 cm⁻¹. LRMS-EI⁺ (m/z): 349 ([M+H]⁺, 100), 331 (15), 249 (1), 175 (2).


5. (1S,8R,9S)-2-(10,10-dimethyl-5-(pyridin-2-yl)-6-aza-tricyclo[7.1.1.0²⁷]undeca-2(7)-3,5-trien-8-yl)-propan-2-ol (7)

To a solution of Bipy 3 (0.2 g, 0.80 mmol) in dry THF (3 mL) the LDA solution (0.48 mL, 0.95 mmol, 2 M in hexane) was added at −78 °C and stirred for 2 h to generate a dark blue solution. To this dark blue solution was added a solution of acetone (0.05 mg, 0.80 mmol) in THF (2 mL) and the temperature was slowly raised to room temperature and stirred for 8 h. The reaction was quenched by adding NH₄Cl solution, and extracted with EtOAc. The combined organic phase was dried over anhydrous MgSO₄. After concentration to give a residue, the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:9) as the mobile phase, to get product 7 (0.20 g, 0.65 mmol) as white solid. Yield: 81%. [α]²⁰ D −160° (c 0.19 CHCl₃). 1H NMR (400 MHz, CDCl₃, δ): 8.64 (d, J
= 4.0 Hz, 1H), 8.33–8.11 (m, 2H), 8.00 (s, 1H), 7.75 (dd, J = 7.5, 7.5 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 3.29 (s, 1H), 2.80 (dd, J = 5.5, 5.5 Hz, 1H), 2.61 (dd, J = 5.1, 9.5 Hz, 1H), 2.37 (dd, J = 6.8, 6.8 Hz, 1H), 1.54–1.39 (m, 3H), 1.35 (s, 3H), 1.30–1.17 (m, 2H), 1.12 (s, 3H), 0.71 (s, 3H).

$^{13}$C NMR (100.6 MHz, CDCl$_3$, $\delta$): 158.0, 155.6, 152.1, 149.1, 143.5, 136.9, 134.5, 123.4, 120.5, 118.7, 74.4, 52.8, 46.5, 42.1, 29.5, 27.5, 26.2, 21.0. LRMS-EI$^+$ ($m/z$): 309 ([M+H]$^+$, 100), 291 (13), 249 (3), 148 (1). HRMS-TOF-ES$^+$ ($m/z$): [M+H]$^+$ calcd for C$_{20}$H$_{25}$N$_2$O, 309.1968, found 309.1968.

**Synthesis and characterization of phthalides**

**General procedure for preparation of phthalides.**

Anhydrous THF (1 mL) was added to a mixture of CrCl$_3$ (8.0 mg, 0.05 mmol, 0.1 eq), Mn (82.4 mg, 0.15 mmol, 3.0 eq, 325 mesh), and dried powder 4Å MS (100 mg) under argon, and the mixture was stirred for 1 h at room temperature. After ligand 6 (65.0 mg, 0.15 mmol, 0.3 eq) and anhydrous NEt$_3$ (0.042 mL, 0.30 mmol, 0.6 eq) were added, the suspension was stirred for 1 h at room temperature. Subsequently, allyl bromide (0.064 mL, 0.75 mmol, 1.5 eq) was added. After 1 h at room temperature, aldehyde (0.50 mmol, 1 eq) and Me$_3$SiCl (0.095 mL, 0.75 mmol, 1.5 eq) were added, and the suspension was stirred in ice box at 0 °C for 48 h. Saturated aqueous NaHCO$_3$ was added. Following filtration and evaporation, the aqueous phase was extracted with EtOAc. After the combined organic phases had been evaporated, the residue was dissolved in THF (2 mL). A TBAF solution (1.5 mL, 1.5 mmol, 3 eq, 1M in THF) was added and the mixture was stirred until desilylation was complete (as verified by TLC). Water was added; the solution was extracted using ethyl acetate, and the combined organic phases were dried over MgSO$_4$. Residue was dissolved into THF (2 mL) and p-TsOH (cat.) was added and stirred for 2 h at room temperature. Evaporation of the solvent and flash chromatography (EtOAc/hexane 1:19) gave the products. Enantiomeric excess was determined using high-performance liquid chromatography with a chiral column (Chiralcel OJ column, n-hexane/2-propanol (90/10), flow rate: 1.0 mL/min$^{-1}$).

1. 3-allyl-5,7-dimethoxyisobenzofuran-1(3$H$)-one (8) [I]
Yield: 87%. Off white solid. \([\alpha]_{D}^{25} = -66.3^\circ (c 0.55, CHCl_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\)): 6.43 (s, 1H), 6.41 (s, 1H), 5.81–5.70 (m, 1H), 5.35–5.32 (t, \(J = 11.7\) Hz, 1H), 5.20–5.12 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 2.73–2.67 (m, 1H), 2.60–2.53 (m, 1H). \(^1\)C NMR (100.6 MHz, CDCl\(_3\), \(\delta\)): 168.2, 166.6, 159.6, 154.3, 131.4, 119.4, 107.0, 98.7, 97.8, 55.9, 55.9, 39.7. IR (KBr): 3076, 2923, 2846, 1753, 1610, 1459, 1349, 1333, 1218, 1157, 1100, 1034, 836, 757, 691, 554 cm\(^{-1}\). LRMS-EI\(^+\) (\(m/z\)): 235 ([M+H]\(^+\), 4), 217 (8), 289 (1), 290 (3), 174 (2). HRMS-TOF-ES\(^+\) (\(m/z\)): [M+H]\(^+\) calcd for C\(_{13}\)H\(_{15}\)O\(_4\), 235.0971 found 235.0970. 97 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

2. 3-allyl-5,6-dimethoxyisobenzofuran-1(3\(H\))-one (9) \[^2\]

3. 3-allyl-4,5,6-trimethoxyisobenzofuran-1(3\(H\))-one (10)

Yield: 85%. White solid. \([\alpha]_{D}^{25} = -52.6^\circ (c 0.45, CHCl_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\)): 7.32–7.17 (m, 1H), 6.85 (s, 1H), 5.85–5.70 (m, 1H), 5.40 (dd, \(J = 5.9, 5.9\) Hz, 1H), 5.30–5.05 (m, 2H), 4.01–3.89 (m, 6H), 2.72–2.60 (m, 2H). \(^1\)C NMR (100.6 MHz, CDCl\(_3\), \(\delta\)): 154.7, 150.5, 143.8, 131.4, 119.5, 118.3, 106.2, 103.4, 79.5, 56.3, 56.2, 38.8. IR (KBr): 3076, 2934, 2840, 1753, 1640, 1602, 1286, 1133, 1236, 1059, 984, 916, 812, 768, 732, 658, 551 cm\(^{-1}\). LRMS-EI\(^+\) (\(m/z\)): 235 ([M+H]\(^+\), 9), 230 (2), 228 (3), 226 (4), 191 (6). HRMS-TOF-ES\(^+\) (\(m/z\)): [M+H]\(^+\) calcd for C\(_{13}\)H\(_{15}\)O\(_4\), 235.0971 found 235.0971. 94 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

3. 3-allyl-4,5,6-trimethoxyisobenzofuran-1(3\(H\))-one (10)

Yield: 90%. Pale yellow oil. \([\alpha]_{D}^{25} = -29.9^\circ (c 0.50, CHCl_3)\). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\)): 7.11 (s, 1H), 5.72–5.60 (m, 1H), 5.53–5.48 (m, 1H), 5.10–5.04 (m, 2H), 4.00 (s, 3H), 3.97–3.85 (m, 6H), 3.00–2.91 (m, 1H), 2.58–2.52 (m, 1H); \(^1\)C NMR (100.6 MHz, CDCl\(_3\), \(\delta\)): 170.3, 155.7, 147.5, 146.7, 134.4, 131.5, 121.6, 119.1, 102.5, 79.1, 61.1, 60.7, 56.3, 53.4, 37.1, 29.6. IR (KBr): 2918, 2848, 1766, 1615, 1478, 1420, 1344, 1301, 1250, 1198, 1106, 1033, 968, 921, 845, 761, 661 cm\(^{-1}\). LRMS-EI\(^+\) (\(m/z\)): 265 ([M+H]\(^+\), 18), 253 (8), 253 (5) 149 (2). HRMS-TOF-ES\(^+\) (\(m/z\)):
[M+H]+ calcd for C_{14}H_{16}O_{5}, 265.1077, found 265.1080. 99 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

4. 3-allylisobenzofuran-1(3H)-one (11) \[^3\]

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\text{Yield: 86\%. Brown oil. [\alpha]^25_D} = -32.6^\circ (c 0.35, \text{CHCl}_3).
\]

\[^1^H\text{NMR (300 MHz, CDCl}_3, \delta): 7.91–7.88 (d, J = 7.7 Hz, 1H), 7.69–7.50 (m, 2H), 7.55–7.45 (d, J = 7.6 Hz, 1H), 5.82–5.68 (m, 1H), 5.55–5.51 (t, J = 12.0 Hz, 1H), 5.21–5.13 (dd, J = 1.3, 8.5 Hz, 2H), 2.80–2.60 (m, 2H).}

\[^1^H\text{NMR (75 MHz, CDCl}_3, \delta): 149.4, 134.1, 131.1, 129.2, 125.8, 122.0, 119.7, 80.4, 38.6. IR (KBr): 3071, 2917, 2851, 1758, 1643, 1591, 1462, 1357, 1308, 1286, 1209, 1070, 979, 921, 740, 696, 603, 573 cm}^{-1}. \text{LRMS-EI}^+ (m/z): 175 ([M+H]^+,1), 174 (4), 169 (10), 168 (40), 157 (70), 14 (50). \text{HRMS-TOF-ES}^+ (m/z): [M+H]^+ calcd for C_{11}H_{11}O_{2}, 175.0760, found 175.0760. 96 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

5. 3-allyl-6-methoxyisobenzofuran-1(3H)-one (12) \[^3\]

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\text{Yield: 90\%. White solid. [\alpha]^25_D} = -38.9^\circ (c 0.65, \text{CHCl}_3).
\]

\[^1^H\text{NMR (300 MHz, CDCl}_3, \delta): 7.80–7.77 (d, J = 8.4 Hz, 1H), 7.04–7.00 (dd, J = 1.7, 2.2 Hz 1H), 6.88–6.87(d, J = 2.9 Hz, 1H), 5.84–5.70 (m, 1H), 5.44–5.40 (t, J = 11.8 Hz, 1H), 5.29–5.13 (m, 2H), 3.89 (s, 3H), 2.77–2.57 (m, 2H).}

\[^1^C\text{NMR (75 MHz, CDCl}_3, \delta): 170.0, 164.6, 152.0, 131.3, 127.2, 119.5, 116.3, 106.1, 79.5, 55.8, 38.7. IR (KBr): 3076, 2923, 2851, 1758, 1604, 1496, 1462, 1349, 1253, 1152, 1102, 1059, 982, 921, 834, 765, 688, 603 cm}^{-1}. \text{LRMS-EI}^+ (m/z): 205 ([M+H]^+ 0.2), 200 (1), 193 (3), 148 (2). \text{HRMS-TOF-ES}^+ (m/z): [M+H]^+ calcd for C_{12}H_{13}O_{3}, 205.0865, found 205.0865. 97 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

6. 7-allyl-[1,3]dioxolo[4,5-f]isobenzofuran-5(7H)-one (13) \[^2\]
Yield: 76%. Colorless oil. \([\alpha]^{25}\text{D} -48.9^\circ\ (c 0.45, \text{CHCl}_3).\) \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\), \(\delta\)): 7.19 (s, 1H), 6.81 (s 1H), 6.11 (s, 2H), 5.78–5.71 (m, 1H), 5.38–5.35 (t, \(J = 12.0\) Hz, 1H), 5.20–5.14 (m, 2H), 2.71–2.56 (m, 2H) \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\), \(\delta\)): 169.8, 153.5, 149.2, 145.9, 131.1, 120.0, 119.7, 104.3, 102.6, 101.7, 79.4, 38.7. IR (KBr): 2923, 1753, 1604, 1500, 1467, 1396, 1341, 1223, 1226, 1097, 1048, 1031, 923, 829, 814, 718,631 cm\(^{-1}\). LRMS-EI\(^+\) (m/z): [M+H]\(^+\) 219 ([M+H]\(^+\) 14), 208 (4), 193 (4), 166 (6). HRMS-TOF-ES\(^+\) (m/z): [M+H]\(^+\) calcd for C\(_{12}\)H\(_{11}\)O\(_4\), 219.0658, found 219.0658. 96 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

7. 3-allyl-6-(dimethylamino)isobenzofuran-1(3H)-one (14) \(^2\)

Yield: 70%. Brown oil. \([\alpha]^{25}\text{D} -48.9^\circ\ (c 0.55, \text{CHCl}_3)\). \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\), \(\delta\)): 7.28 (s 1H), 7.11 (d, \(J = 2.2\) Hz, 1H), 7.01 (dd, \(J = 2.2, 8.4\) Hz, 1H), 5.84–5.72 (m, 1H), 5.43 (t, \(J = 6.1\) Hz, 1H), 5.21–5.12 (m, 2H), 3.02 (s, 6H), 2.72–2.56 (m, 2H), 1.27 (s, 2H). \(^{13}\text{C}\) NMR (100.6 MHz, CDCl\(_3\), \(\delta\)): 171.3, 151.4, 137.0, 131.8, 127.3, 122.2, 119.2, 118.6, 107.0, 80.1, 40.6, 39.1, 29.7. IR (KBr): 3076, 2923, 1758, 1624, 1551, 1437, 1355, 1316, 1278, 1204, 1061, 982, 916, 817, 773, 598, 556 cm\(^{-1}\). LRMS-EI\(^+\) (m/z): 218 ([M+H]\(^+\),52), 180 (4), 174 (5), 158 (4), 152 (2). HRMS-TOF-ES\(^+\) (m/z): [M+H]\(^+\) calcd for C\(_{13}\)H\(_{16}\)NO\(_2\), 218.1182 found 218.1182. 96 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

8. 3-allyl-5-bromo-6-(dimethylamino)isobenzofuran-1(3H)-one(15)
Yield: 90%. Brown solid. $[^\alpha]_D^{25} = -56.9^\circ$ (c 0.56, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.67 (s, 1H), 7.53 (s, 1H), 5.82–5.70 (m, 1H), 5.42 (t, $J = 5.9$ Hz, 1H), 5.24–5.16 (m, 2H), 2.85–2.84 (m, 6H), 2.74–2.58 (m, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$, $\delta$): 169.7, 153.5, 144.0, 131.0, 127.6, 126.5, 126.4, 119.9, 116.4, 79.4, 44.2, 38.6. IR (KBr): 3082, 2917, 2851, 2780, 1758, 1635, 1610, 1478, 1451, 1396, 1330, 1283, 1256, 1207, 1187, 1157, 1059, 971, 919, 883, 765, 740, 600 cm$^{-1}$. LRMS-EI$^+$ (m/z): 296 ([M+H]$^+$ 100), 294, (7), 284 (2), 281 (3), 271 (7), 258 (9), 240 (8). HRMS-TOF-ES$^+$ (m/z): [M+H]$^+$ calcd for C$_{13}$H$_{15}$BrNO$_2$, 296.0287, found 296.0287. 98 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

9. 3-allyl-4-bromo-6-(methylamino)isobenzofuran-1(3H)-one (16)

Yield: 90%. Yellow oil. $[^\alpha]_D^{25} = -53.7^\circ$ (c 0.48, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.53 (s, 1H), 7.01 (s, 1H), 5.81–5.70 (m, 1H), 5.42–5.38 (m, 1H), 5.22–5.14 (m, 2H), 4.65 (s, 1H), 2.97–2.94 (d, $J = 5.1$ Hz, 3H), 2.69–2.56 (m, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$, $\delta$): 163.0, 146.9, 137.8, 131.2, 126.8, 125.7, 119.6, 116.0, 105.0, 79.4, 38.9, 30.6. IR (KBr): 3395, 2923, 2851, 1753, 1615, 1514, 1456, 1407, 1333, 1270, 119, 1061, 984, 910, 872, 773, 721, 721, 632 cm$^{-1}$. LRMS-EI$^+$ (m/z): 296 ([M+H]$^+$,1), 264 (18), 213 (28), 160 (6). HRMS-TOF-ES$^+$ (m/z): [M+H]$^+$ calcd for C$_{13}$H$_{15}$BrNO$_2$, 296.0287, found 296.0287. 97 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

10. 8-allyl-[1,3]dioxolo[4,5-e]isobenzofuran-6(8H)-one (17)
Yield: 77%. Colorless oil. $[\alpha]^2_{25}D = -43.9^\circ$ (c 0.50, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.08–7.06 (d, $J = 7.9$ Hz 1H), 6.85–6.83 (d, $J = 7.9$ Hz 1H), 6.17 (s, 2H), 5.79–5.69 (m, 1H), 5.48–5.45 (t, $J = 11.6$ Hz, 1H), 5.19–5.13 (m, 2H), 2.74–2.57 (m, 2H) $^{13}$C NMR (100.6 MHz, CDCl$_3$, $\delta$): 167.2, 149.1, 144.8, 142.2, 131.1, 119.7, 114.3, 109.1, 103.3, 80.7, 39.1. IR (KBr): 2923, 2851, 1761, 1640, 1500, 1473, 1323, 1251, 1240, 1207, 1108, 968, 908, 825, 871, 743, 639 cm$^{-1}$. LRMS-EI$^+$ ($m/z$): 219 ([M+H]$^+$, 3), 217 (3), 210 (1), 166 (4). HRMS-TOF-ES$^+$ ($m/z$): [M+H]$^+$ calcd for C$_{12}$H$_{11}$O$_4$, 219.0658, found 219.0656. 98 % ee by HPLC analysis (Chiralcel OJ column, hexane:2-propanol = 9:1, 1.0 mL/min, 254 nm UV detector).

11. 3-heptyl-4,5,6-trimethoxyisobenzofuran-1(3H)-one (18)

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 7.11 (s, 1H), 5.47–5.42 (dd, $J = 2.8$, 7.9 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 2.20–2.13 (m, 1H), 1.74–1.63 (m, 1H), 1.37–1.22 (m, 1H), 0.91–0.84
(t, J = 7.1 Hz, 3H). IR (KBr): 2927, 2856, 1761, 1479, 1420, 1345, 1253, 1199, 1106, 1036, 967, 848, 765, 725 cm\(^{-1}\). \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\), \(\delta\)): 170.6, 155.5, 147.6, 146.8, 135.4, 121.4, 102.5, 80.2, 61.1, 60.7, 33.4, 31.7, 29.2, 29.0, 24.7, 22.6, 14.0. LRMS-EI\(^+\) (\(m/z\)): [M+H]\(^+\), 323 (100), 225 (25), 180 (30), 148 (12). HRMS-TOF-ES\(^+\) (\(m/z\)): [M+H]\(^+\) calcd for C\(_{18}\)H\(_{26}\)O\(_5\), 323.1780, found 323.1860.


### 12. 3 heptyl-4,5,6-trihydroxyisobenzofuran-1(3\(H\))-one (19)

![Chemical Structure](image)

To a solution of 19 (0.12 g, 0.372 mmol) in CH\(_2\)Cl\(_2\) (2.5 mL) at −30 °C was added BBr\(_3\) (0.37 mL of a 1.0 M solution in CH\(_2\)Cl\(_2\), 0.37 mmol).[4] After 1 h the reaction is warmed to room temperature for 2 h after which it was poured into ice-water and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) twice. The combined organic layers were washed with brine and dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH/CHCl\(_3\)) to afford Cytosporone E in 87% yield (0.090 g, 0.3211 mmol). Lit. [5] 98.4%ee, [\(\alpha\)]\(^{20}\)D \(\approx \) −90.7\(^\circ\) (c 1.00, acetone). [\(\alpha\)]\(^{20}\)D \(\approx \) −87.6\(^\circ\) (c 0.99, acetone). \(^1\)H NMR (400 MHz, DMSO, \(\delta\)): 9.9 (s, 1H), 9.4 (s, 1H), 9.3 (s 1H), 6.68 (s, 1H), 5.40 (dd, J = 2.8, 7.5 Hz, 1H), 2.11 (m, 1H), 1.59 (m, 1H), 1.30–1.16 (m, 10H), 0.84 (t, J = 7.1 Hz, 3H). IR (KBr): 3408, 2924, 2853, 2258, 1739, 1628, 1519, 1494, 1346, 1146, 1075, 1024, 999, 869, 765, 637 cm\(^{-1}\). \(^{13}\)C NMR (100.6 MHz, DMSO, \(\delta\)): 170.8, 147.8, 140.3, 139.9, 129.5, 116.2, 102.0, 79.6, 32.8, 31.6, 29.1, 29.0, 24.6, 22.5, 14.3. LRMS-EI\(^+\) (\(m/z\)): [M-H]\(^+\) 279 (100), 235 (5). HRMS-TOF-ES\(^+\) (\(m/z\)): [M-H]\(^+\) calcd for C\(_{15}\)H\(_{19}\)O\(_5\), 279.1311, found 279.1233

References

$^{1}H$ NMR and $^{13}C$ NMR spectra
Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is (c) The Royal Society of Chemistry 2018

Current Data Parameters

NAME: SVK-3-236 new C4C
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PS: 2 µm C18 16/13
TD: 30 µL
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NS: 9999
DS: 0
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ACQ: 1.0976128 sec
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CHANNEL 1

PF: 10.00 usec
F1: 6.20 dB
SPC: 100.626989 MHz

CHANNEL 2

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F1: -0.40 dB
F1: 18.50 dB
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F2 - Processing parameters

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S20
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CB_   0
FC_   1.00
Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is (c) The Royal Society of Chemistry 2018
HPLC data:
3-allyl-5,7-dimethoxyisobenzofuran-1(3H)-one (8)
HPLC conditions: Chiralse OJ column, n-Hexane/2-Propanol (90/10), 1.0 mL/min, (t_{major} = 30.91 min, area\% = 98.4586), (t_{minor} = 37.13 min, area\% = 1.5414), 254nm UV detector.
3-allyl-5,6-dimethoxyisobenzofuran-1(3H)-one (9)

HPLC conditions: Chiralcel OJ column, *n*-Hexane/2-Propanol (90/10), 1.0 mL/min, ($t_{\text{major}}$ = 20.51 min, area% = 97.0743), ($t_{\text{minor}}$ = 24.78 min, area% = 2.9257), 254nm UV detector.

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100
3-allyl-4,5,6-trimethoxyisobenzofuran-1(3H)-one (10)

HPLC conditions: Chiralcel OJ column, $n$-Hexane/2-Propanol (90/10), 1 mL/min, ($t_{\text{major}}=18.43$ min, area% =99.5680), ($t_{\text{minor}}=21.82$ min, area% =0.4320), 254 nm UV detector.
3-allylisobenzofuran-1(3H)-one (11)

HPLC conditions: Chiralcel OJ column, *n*-Hexane/2-Propanol (90/10), 1.0 mL/min, (*t*<sub>major</sub> = 20.87 min, area% = 98.0672), (*t*<sub>minor</sub> = 24.72 min, area% = 1.9328), 254nm UV detector.

Integration Result

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3-allyl-6-methoxyisobenzofuran-1(3H)-one (12)

HPLC conditions: Chiralcel OJ column, n-Hexane/2-Propanol (90/10), 1.0 mL/min, ($t_{\text{major}}=17.91$ min, area% =98.6356), ($t_{\text{minor}}=21.45$ min, area% =1.3644), 254 nm UV detector.

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7-allyl-[1,3]dioxolo[4,5-f]isobenzofuran-5(7H)-one (13)

HPLC conditions: Chiralcel OJ column, n-Hexane/2-Propanol (90/10), 1.0 mL/min, ($t_{\text{major}}$ =12.47 min, area% =98.5012), ($t_{\text{minor}}$ =14.79 min, area% =1.4988), 254nm UV detector.
3-allyl-6-(dimethylamino)isobenzofuran-1(3H)-one (14)

HPLC conditions: Chiralcel OJ column, n-Hexane/2-Propanol (90/10), 1.0 mL/min, ($t_{\text{major}} = 18.95$ min, area% = 98.0199), ($t_{\text{minor}} = 22.67$ min, area% = 1.9801), 254nm UV detector.
3-allyl-5-bromo-6-(dimethylamino)isobenzofuran-1(3H)-one(15)

HPLC conditions: Chiralcel OJ column, \textit{n}-Hexane/2-Propanol (90/10), 1.0 mL/min, ($t_{\text{major}} = 12.02$ min, area\% = 98.8410), ($t_{\text{minor}} = 14.17$ min, area\% = 1.1590), 254nm UV detector.
3-allyl-4-bromo-6-(methylamino)isobenzofuran-1(3H)-one (16)

HPLC conditions: Chiralcel OJ column, \( n \)-Hexane/2-Propanol (90/10), 1.0 mL/min, \( t_{\text{major}} = 30.52 \) min, area\% = 98.4807, \( t_{\text{minor}} = 36.65 \) min, area\% = 1.5193, 254nm UV detector.
8-allyl-[1,3]dioxolo[4,5-e]isobenzofuran-6(8H)-one (17)

HPLC conditions: Chiralcel OJ column, n-Hexane/2-Propanol (90/10), 1.0 mL/min, (t\text{major} = 14.03 min, area\% = 99.0390), (t\text{minor} = 16.67 min, area\% = 0.9610), 254nm UV detector.
IR Spectra

1. (1S,9S)-10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^2,7]-undeca-2(7)-3,5-triene (3)

2. (1S,8R,9S)-(10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^2,7]-undeca-2(7),3,5-trien-8-yl)-diphenyl-methanol (4)
3. \((1S,8R,9S)-2-(10,10\text{-dimethyl-5-(pyridin-2-yl)-6-aza-tricyclo}[7.1.1.0^{2,7}]\text{-undeca-2(7)-3,5-trien-8-yl})-1,3\text{-diphenyl-propan-2-ol}(5)\)

![Graph 1](image1)

4. \((1S,8R,9S)-1-(10,10\text{-dimethyl-5-(pyridin-2-yl)-6-aza-tricyclo}[7.1.1.0^{2,7}]\text{-undeca-2(7)-3,5-trien-8-yl})\text{-cyclohexan-1-ol}(6)\)

![Graph 2](image2)
5. (1S,8R,9S)-2-(10,10-dimethyl-5-(pyridin-2-yl)-6-aza-tricyclo[7.1.1.0^2,7]-undeca-2(7)-3,5-trien-8-yl)-propan-2-ol (7)

6. 3-allyl-5,7-dimethoxyisobenzofuran-1(3H)-one (8)
7. 3-allyl-5,6-dimethoxyisobenzofuran-1(3H)-one (9)

8. 3-allyl-4,5,6-trimethoxyisobenzofuran-1(3H)-one (10)
9. 3-allylisobenzofuran-1(3H)-one (11)

10. 3-allyl-6-methoxyisobenzofuran-1(3H)-one (12)
11. 7-allyl-[1,3]dioxolo[4,5-f]isobenzofuran-5(7H)-one (13)

12. 3-allyl-6-(dimethylamino)isobenzofuran-1(3H)-one (14)
13. 3-allyl-5-bromo-6-(dimethylamino)isobenzofuran-1(3H)-one (15)

14. 3-allyl-4-bromo-6-(methylamino)isobenzofuran-1(3H)-one (16)
15. 8-allyl-[1,3]dioxolo[4,5-e]isobenzofuran-6(8H)-one (17)

16. 3-heptyl-4,5,6-trimethoxyisobenzofuran-1(3H)-one (18)
17. 3-heptyl-4,5,6-trihydroxyisobenzofuran-1(3H)-one (19)