Mild Rhodium(III)-Catalyzed Intramolecular Annulation of Benzamides with Allylic Alcohols to Access Azepinone Derivatives

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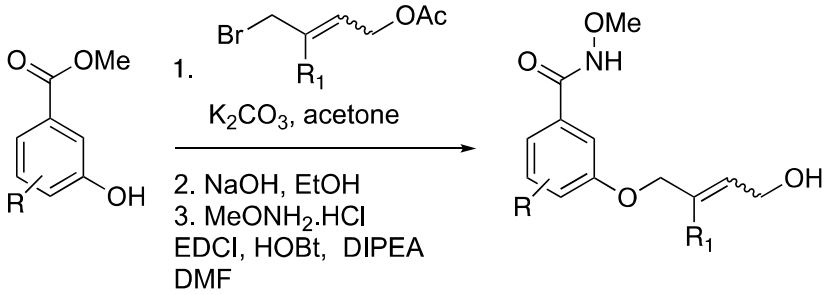
1. GENERAL METHODS

All reactions were carried out under argon with dry solvents unless otherwise noted. Reactions were monitored by thin-layer chromatography on Merck silica gel plates ($60F_{254}$) with a fluorescent indicator. Yields refer to chromatographically or crystalline pure compounds. All commercially available reagents were used without further purification. CH_2Cl_2 and THF were dried by activated alumina. Et_2O extra dry 99.5% was purchased from Sigma-Aldrich. $CHCl_3$ and 1,2-dichloroethane were distilled over $CaCl_2$. Anhydrous toluene, 99.8%, Active dry, was purchased from Alfa-Aesar. All separations were carried out under flash chromatographic conditions on silica gel prepacked column Redi Sep (230-400 mesh) at medium pressure (20psi) by using a CombiFlash. All new compounds gave satisfactory spectroscopic analyses (IR, ^{1}H NMR, ^{13}C NMR, HRMS). NMR spectra were determined on Brucker Avance-300 or on Brucker Avance-500. ^{1}H NMR spectra are reported in parts per million (δ) relative to residual solvent peak. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, sept = septuplet, dd = double-doublet, td = triple-doublet, dt = double-triplet, ddd = double double doublet, m = multiplet), coupling constant in Hz, and integration. ^{13}C NMR spectra were obtained Brucker Avance-300 (75 MHz) spectrometer and are reported in parts per million (δ) relative to the residual solvent peak. HRMS spectra were obtained on an E.S.I. TOF Thermoquest AQA Navigator spectrometer. Infrared (IR) (υ, cm^{-1}) spectra were recorded on a Fourier Perkin-Elmer Spectrum BX FT-IR. Melting points were measured in capillary tubes and are uncorrected.

2. ALLYLIC ALCOHOL SYNTHESIS AND DERIVATIVES



General procedure A

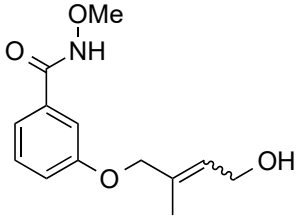
Step 1 : Alkylation. To a solution of phenol (1 equiv.) in acetone (5 mL/mmol) is added the allylic bromide (2 equiv.) then K_2CO_3 (2.2 equiv.) under argon at room temperature. The mixture was stirred at 55°C overnight. Then water was added and the aqueous layer extracted with EtOAc (x3). The combined organic layers were washed with water, brine then dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture purified through silica gel to afford the corresponding ether.

Step 2 : Saponification. To a solution of ester (1 equiv.) in ethanol (5.9 mL/mmol) was added a 3M solution of NaOH (3.5 mL/mmol) at room temperature. The mixture was stirred for 2 h, then HCl (2N) was added at 0°C until pH = 2-3. The aqueous layer was extracted with EtOAc and the solvent was evaporated under vacuum. The crude mixture was used without purification.

Step 3 : Amide coupling. To a solution of carboxylic acid (1 equiv.) in DMF (3 mL/mmol) was added successively, EDCI (1.1 equiv.), HOBT (1.1 equiv.) and the solution was stirred for 30

min. at room temperature. The amine (1.1 equiv.) was added then the mixture stirred for an additional 10 min. *i*Pr_2NEt (2.3 equiv.) was added at 0°C, then the mixture was stirred at overnight at RT. The reaction mixture was poured into water and the aqueous layer extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, then brine. The solvent was removed under vaccum. The crude mixture purified through silica gel to afford the corresponding amide.

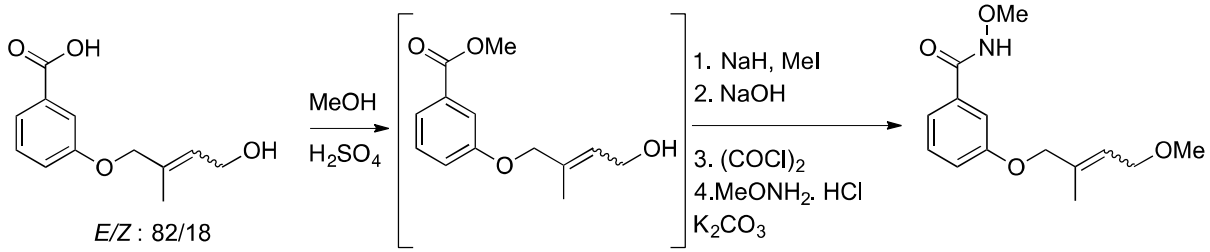
3-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-*N*-methoxybenzamide (6a)



Prepared according to procedure A from methyl 3-hydroxybenzoate (500 mg, 3.29 mmol), 4-bromo-3-methylbut-2-en-1-yl acetate (1.36 g, 6.6 mmol, *Z/E* = 82/18), K_2CO_3 (1.0 g, 7.24 mmol) in acetone (16.4 mL). The crude mixture purified through silica gel (Hept. to Hept./EtOAc 9/1) to afford the corresponding compound as a colorless oil (m = 627 mg, 68%, *E/Z* = 82/18).

The methyl ester (1.05 g, 3.77 mmol) was converted into the acid by treatement with NaOH 3M (13.2 mL) in EtOH (22 mL). The resulting crude carboxylic acid (3.77 mmol) was dissolved in DMF (11.5 mL) and reacted with EDCI (805.1 mg, 4.2 mmol), HOBt (567 mg, 4.2 mmol), $MeONH_2$.HCl (351 mg, 4.2 mmol), and *i*Pr_2NEt (1.53 mL, 8.79 mmol). Purification over silica gel (Hept. to Hept./EtOAc 5/5 to 0/100) afforded the title compound as a colorless oil **(**m = 399 mg, 41% over 2 steps, *E/Z* : 82/18). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): (*E* isomer) 9.25 (brs, 1H), 7.31-7.24 (m, 3H), 7.03 (td, *J* = 6.8, 2.5 Hz, 1H), 5.75 (dt, *J* = 6.7, 1.7 Hz, 1H), 4.42 (s, 2H), 4.22 (d, *J* = 6.7 Hz, 2H), 3.84 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) (*E* isomer) 158.8 (Cq), 133.8 (Cq), 133.0 (Cq), 129.7 (CH), 127.0 (CH), 119.2 (CH), 113.2 (CH), 73.1 (CH_2), 64.4 (CH_3), 58.9 (CH_2), 13.7 (CH_3). IR υ (neat): 3209, 2979-2936, 1735, 1651, 1579, 1235 cm^{-1}. MS (ESI, m/z): 274.10 (100) [M+Na$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{17}NO_4Na^+$: 274.1055. found: 274.1046.

***N*-methoxy-3-((4-methoxy-2-methylbut-2-en-1-yl)oxy)benzamide (6aa)**

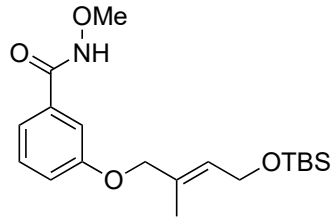


To a solution of acid (487.1 mg, 2.19 mmol) in MeOH (17 mL) was added concentrated H_2SO_4 (cat.). The reaction was stirred at 65°C overnight. The solvent was evaporated and water was added. The aqueous layers were extracted with EtOAc (x3), then the combined organic layers were washed with water, then brine. The solvent was removed under vacuum and the crude ester was used without further purification.

To a solution of alcohol (158.3 mg, 0.67 mmol) in THF (8.7 mL) was added NaH 60% (53.6 mg, 1.34 mmol). The reaction was stirred at RT for 1h then MeI (83 µL, 1.34 mmol). After stirring for 2h, the resulting mixture was quenched with sat. NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (x3). After drying over $MgSO_4$, the solvent was removed in vacuo and the residue was purified by flash chromatography (Hept. to Hept./EtOAc 6/4) to

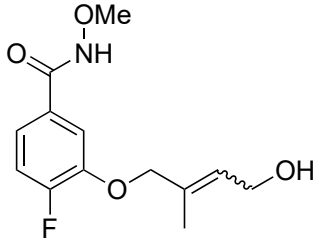
afford the methyl ether as a colorless oil (m = 65.1 mg, 39%) and the acid as colorless oil (39.3 mg, 25%). The ester (65.1 mg, 0.26 mmol) was hydrolyzed by treatment with LiOH (33 mg, 0.78 mmol) in a mixture of MeOH (3.1 mL) and H_2O (0.42 mL) to afford the acid (m = 57.6 mg, 96%).
The combined acids (132.9 mg, 0.563 mmol) were dissolved in DCM (5.6 mL). Then $(COCl)_2$ (0.058 mL, 0.675 mmol) was added dropwise followed by one drop of DMF. The mixture was stirred for 1h at RT, then the volatil were removed under vacuo. The residue was dissolved into EtOAc (3.4 mL) and water (1.5 mL), then $MeONH_2$.HCl (51.7 mg, 0.619 mmol) and K_2CO_3 (186.7 mg, 1.35 mmol) were added. The mixture was stirred at RT overnight. The aqueous layer was separated and extracted once with ethyl acetate. The organic layers were combined, washed with brine, and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The solvent was removed under vacuum and the crude mixture purified through silica gel (Hept. to Hept./EtOAc 5/5) to afford the corresponding amide (m = 121.5 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): (*E/Z* : 80/20) 9.45 (brs, 1H min.), 8.98 (brs, 1H maj.), 7.43-7.22 (m, 3H maj. + 3H min.), 7.05 (m, 1H maj. + 1H min.), 5.73 (m, 1H maj.), 5.67 (m, 1H min.), 4.63 (s, 2H min.), 4.46 (s, 2H maj.), 4.05 (d, *J* = 8.5 Hz, 2H min.), 4.01 (d, *J* = 8.5 Hz, 2H maj.), 3.87 (s, 3H maj. + 3H min.), 3.41 (s, 3H min.), 3.34 (s, 3H maj.), 1.81 (s, 3H min.), 1.75 (s, 3H maj.). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) ((*E/Z* : 80/20) 166.3 (Cq, maj.), 158.8 (Cq, maj.), 158.3 (Cq, min.), 136.5 (Cq, min.), 134.7 (Cq, maj.), 133.1 (Cq, maj.), 132.8 (Cq, min.), 129.9 (CH, min.), 129.7 (CH, maj.), 125.3 (CH, min.), 124.8 (CH, maj.), 119.9 (CH, min.), 119.2 (CH, maj.), 113.2 (CH, maj.), 111.6 (CH, min.), 73.1 (CH_2, maj.), 68.4 (CH_2, maj.), 67.9 (CH_2, min.), 66.5 (CH_2, min.), 64.5 (CH_3, maj.), 64.4 (CH_3, min.), 58.4 (CH_3, min.), 58.1 (CH_3, maj.), 20.9 (CH_3, min.), 14.0 (CH_3, maj.). IR υ (neat): 3202, 2979-2818, 1651, 1581 cm^{-1}. MS (ESI, m/z): 288.1 (100) [M+Na$^+$]. HMRS (ESI, m/z): Calcd for $C_{14}H_{19}NO_4Na^+$: 288.1206. found: 288.1212.

(*E*)-3-((4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)oxy)-*N*-methoxybenzamide (6ab)



To a solution of (E)-3-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-N-methoxybenzamide (154 mg, 0.613 mmol) in dry DMF (5 mL) were added a catalytic amount of DMAP, Et_3N (0.130 mL, 0.919 mmol, 1.5 eq) and TBSCl (101 mg, 0.674 mmol, 1.1 eq). The reaction was stirred at room temperature for 3 hours, then quenched with brine. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, water then dried over $MgSO_4$. Purification over silica gel (Hept. to Hept/EtOAc, 80/20) afforded the title compound as a colorless oil (117 mg, 52% yield, *E/Z* = 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 7.45 – 7.32 (m, 2H), 7.31 – 7.22 (m, 1H), 6.95 (dd, *J* = 2.5, 8.2 Hz, 1H), 5.81 (t, *J* = 6.7 Hz), 4.47 (s, 2H), 4.27 (d, *J* = 4.4 Hz, 2H), 3.87 (s, 3H), 1.79 (s, 3H), 1.00 (s, 9H), 0.26 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 158.5 (Cq), 151.3 (Cq), 134.4 (Cq), 129.1 (CH), 126.6 (Cq), 119.0 (CH), 116.8 (CH), 112.1 (CH), 72.9 (CH_2), 61.0 (CH_3), 59.0 (CH_2), 26.0 (CH_3), 18.9 (Cq), 14.0 (CH_3). -3.7 (CH_3). IR υ (neat): 3158, 1721, 1557, 1225 cm^{-1}. MS (ESI, m/z): 366.5 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{19}H_{34}NO_4Si^+$: 366.2095. found: 366.2090.

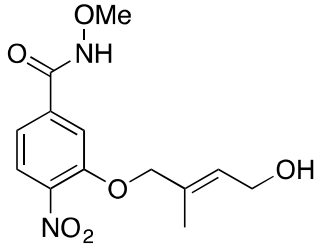
4-fluoro-3-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-*N*-methoxybenzamide (6b)



Prepared according to procedure A from from methyl 4-fluoro-3-hydroxybenzoate (250 mg, 1.47 mmol), 4-bromo-3-methylbut-2-en-1-yl acetate (608.8 mg, 2.94 mmol, *E/Z* = 82/18), K_2CO_3 (446.4 mg, 3.23 mmol) in acetone (7.3 mL). The crude mixture purified through silica gel (Hept. to Hept./EtOAc 8/2) to afford the corresponding compound as a colorless oil (m = 334.2 mg, 77%, *E/Z* = 82/18).

The methyl ester (294.2 mg, 0.993 mmol), was converted into the acid by treatement with NaOH 3M (3.5 mL) in EtOH (5.8 mL). The resulting crude carboxylic acid (0.953 mmol) was dissolved in DMF (2.86 mL) and reacted with EDCI (200.9 mg, 1.05 mmol), HOBt (141.6 mg, 1.05 mmol), $MeONH_2.HCl$ (79.6 mg, 0.953 mmol), and *i*Pr_2NEt (0.38 mL, 2.19 mmol). Purification over silica gel (Hept. to Hept./EtOAc 3/7 to 0/100) afforded the title compound as a white solid **(**m = 133.3 mg, 50% over 2 steps). ^{1}H NMR (300 MHz, MeOD) δ (ppm): (E isomer) 7.50 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.35 (ddd, *J* = 8.4, 4.3, 2.1 Hz, 1H), 7.18 (dd, *J* = 10.9, 8.4 Hz, 1H), 5.77 (m, 1H), 4.83 (s, 3H) 4.56 (s, 2H), 4.17 (d, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, MeOD): (*E* isomer) δ (ppm) 166.8 (Cq), 158.5 (Cq, $J_{C\text{-}F}$ = 250 Hz), 148.5 (Cq, $J_{C\text{-}F}$ = 11 Hz), 134.2 (Cq), 129.7 (Cq), 128.9 (CH), 121.7 (CH, $J_{C\text{-}F}$ = 8 Hz), 117.3 (CH, $J_{C\text{-}F}$ = 20 Hz), 115.8 (CH), 75.5 (CH_2), 64.6 (CH_3), 59.1 (CH_2), 13.9 (CH_3). IR υ (neat): 3246, 2983-2856, 1657, 1509, 1421, 1268 cm^{-1}. MS (ESI, m/z): 270.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{17}O_4F^+$: 270.1142. found: 270.1141. mp = 127-129 °C.

(*E*)-3-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-*N*-methoxy-4-nitrobenzamide (6c)

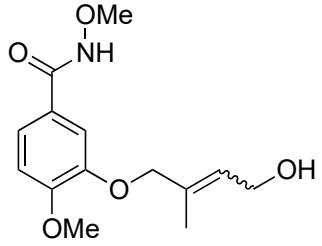


Prepared according to general procedure A from methyl 3-hydroxy-4-nitrobenzoate (300 mg, 1.52 mmol), 4-bromo-3-methylbut-2-en-1-yl acetate (632 mg, 3.04 mmol, *Z/E* = 82/18), K_2CO_3 (462.1 mg, 3.34 mmol) in acetone (7.6 mL). The crude mixture was purified through silica gel (Hept. to Hept./EtOAc 8/2) to afford the corresponding compound as a white pounder (m = 368.4 mg, 75%, *E/Z* = 82/18).

The methyl ester (216.3 mg, 0.67 mmol), was converted into the acid by treatement with NaOH 3M (2.35 mL) in EtOH (3.95 mL). The resulting crude carboxylic acid (0.63 mmol) was dissolved in DMF (1.89 mL) and reacted with EDCI (132.3 mg, 0.69 mmol), HOBt (93.2 mg, 0.69 mmol), $MeONH_2.HCl$ (57.6 mg, 0.69 mmol), and *i*Pr_2NEt (0.25 mL, 1.45 mmol). Purification over silica gel (Hept. to Hept./EtOAc 80/20 to 0/100) afforded the title compound as a slightly yellow solid **(**m = 90.5 mg, 48% over 2 step). ^{1}H NMR (300 MHz, MeOD) δ (ppm): (*E/Z:* 88/12) 7.84 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H min.), 7.61 (d, *J* = 1.7 Hz, 1H maj.), 7.42 (dd, *J* = 8.4, 1.6 Hz, 1H maj.), 5.80 (m, 1H maj.), 5.68 (m, 1H min.), 4.84 (s, 3H maj.), 4.66 (s, 2H maj.), 4.22 (d, *J* = 7.0 Hz, 2H min.), 4.18 (d, *J* = 6.6 Hz, 2H maj.), 3.83 (s, 3H maj.), 1.85 (s, 3H min.), 1.78 (s, 3H maj.). ^{13}C NMR (75 MHz, MeOD): (*E/Z*: 88/12) δ (ppm) 152.8 (Cq maj.), 143.6 (Cq maj.), 138.2 (Cq maj.), 134.1 (Cq maj.), 133.6 (Cq maj.),

130.9 (CH min.), 129.3 (CH maj.), 126.4 (CH maj.), 120.4 (CH min.), 120.3 (CH maj.), 115.2 (CH maj.), 115.1 (CH min.), 75.6 (CH_2 maj.), 69.3 (CH_2 min.), 64.6 (CH_3 maj.), 59.1 (CH_2 maj.), 58.8 (CH_2 min.), 21.2 (CH_3 min.), 13.9 (CH_3 maj.). IR υ (neat): 3212, 2991-2849, 1644, 1514, 1256, 997 cm^{-1} MS (ESI, m/z): 295.1 (55) $[M-H]^-$. HMRS (ESI, m/z): Calcd for $C_{13}H_{15}N_2O_6^-$: 295.0930. found: 295.0928. mp = 104-108 °C.

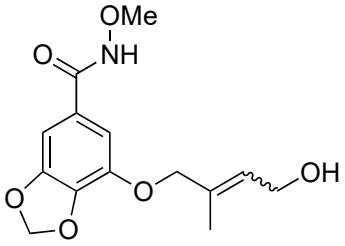
3-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-*N*,4-dimethoxybenzamide (6d)



Prepared according to general procedure A from methyl 3-hydroxy-4-methoxybenzoate (304.5 mg, 1.67 mmol), 4-bromo-3-methylbut-2-en-1-yl acetate (694 mg, 3.34 mmol, *E/Z* = 82/18), K_2CO_3 (507.2 mg, 3.67 mmol) in acetone (8.3 mL). The crude mixture was purified through silica gel (Hept. to Hept./EtOAc 8/2) to afford the corresponding compound as a white solid (m = 382.3 mg, 74%, *E/Z* = 80/20).

The methyl ester (483.8 mg, 1.569 mmol) was converted into the acid by treatement with NaOH 3M (5.5 mL) in EtOH (8.6 mL). The resulting crude carboxylic acid (1.569 mmol) was dissolved in DMF (4.7 mL) and reacted with EDCI (328.8 mg, 1.72 mmol), HOBt (232.4 mg, 1.72 mmol), $MeONH_2.HCl$ (131 mg, 1.569 mmol), and iPr_2NEt (0.63 mL, 3.6 mmol). Purification over silica gel (DCM to DCM/MeOH 95/5) afforded the title compound as a white solid **(**m = 345.5 mg, 52% over 2 steps). ^1H NMR (300 MHz, MeOD) δ (ppm): (*E/Z:* 80/20) 7.40-7.33 (m, 2H, maj.+min.), 7.25 (m, 1H, min.), 7.03-6.92 (m, 1H, maj.+min.), 5.74 (m, 1H, maj.), 5.63 (m, 1H, maj.), 4.62 (s, 2H min.), 4.47 (s, 2H maj.), 4.19 (d, *J* = 7.8 Hz, 2H min.), 4.16 (d, *J* = 7.8 Hz, 2H maj.), 3.88 (s, 3H min.), 3.86 (s, 3H maj.), 3.79 (s, 3H maj.), 3.77 (s, 3H min.), 1.84 (s, 3H min.), 1.76 (s, 3H maj.). ^{13}C NMR (75 MHz, MeOD) δ (ppm) 167.6 (Cq), 154.5 (Cq maj.), 152.5 (Cq min.), 149.5 (Cq maj.), 147.8 (Cq min.), 135.2 () Cq min.), 134.6 (Cq maj.), 130.4 (CH min.), 128.3 (CH maj.), 125.7 (Cq min.), 125.2 (Cq maj.), 122.2 (CH maj.), 120.5 (CH min.), 115.3 (CH min.), 114.0 (CH maj.), 112.5 (CH maj.), 112.1 (CH min.), , 75.3 (CH_2 maj.), 65.9 (CH_2 min.), 64.5 (CH_3 maj.), 64.4 (CH_3 min.), 59.2 (CH_2 maj.), 58.8 (CH_2 min.), 56.6 (CH_3 maj.), 56.5 (CH_3 min.), 21.6 (CH_3 min.), 14.1 (CH_3 maj.). IR υ (neat): 3207, 2936, 1644, 1498, 1266 cm^{-1}. MS (ESI, m/z): 282.1 (100) $[M+H^+]$. HMRS (ESI, m/z): Calcd for $C_{14}H_{20}NO_5$: 282.1341. found: 282.1351. mp = 111-113 °C.

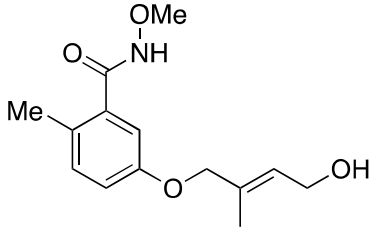
7-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-*N*-methoxybenzo[*d*][1,3]dioxole-5-carboxamide (6e)



Prepared according to general procedure A from methyl 7-hydroxybenzo[*d*][1,3]dioxole-5-carboxylate (263 mg, 1.34 mmol), 4-bromo-3-methylbut-2-en-1-yl acetate (557 mg, 2.86 mmol, *E/Z* = 82/18), K_2CO_3 (407.4 mg, 2.95 mmol) in acetone (6.7 mL). The crude mixture purified through silica gel (Hept. to Hept./EtOAc 8/2) to afford the corresponding compound as a colorless oil (m = 310.7 mg, 72%, *E/Z* = 81/19).

The methyl ester (262.4 mg, 0.814 mmol), was converted into the acid by treatement with NaOH 3M (2.85 mL) in EtOH (4.8 mL). The resulting crude carboxylic acid (0.807 mmol) was dissolved in DMF (2.42 mL) and reacted with EDCI (170.2 mg, 0.888 mmol), HOBt (120 mg, 0.888 mmol), $MeONH_2.HCl$ (67.4 mg, 0.807 mmol), and *i*Pr_2NEt (0.32 mL, 1.86 mmol). Purification over silica gel (Hept. to Hept./EtOAc 3/7 to 0/100) afforded the title compound as a colorless oil (m = 126.9 mg, 52% over 2 steps**).** ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): (*E*-isomer) 9.78 (brs, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H), 5.99 (s, 2H), 5.74 (m, 1H), 4.50 (s, 2H), 4.20 (d, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) (*E*-isomer) 165.8 (Cq), 148.9 (Cq), 142.2 (Cq), 138.8 (Cq), 133.5 (Cq), 127.6 (CH), 125.8 (Cq), 109.9 (CH), 102.1 (CH_2), 101.5 (CH), 74.6 (CH_2), 64.2 (CH_3), 58.7 (CH_2), 13.7 (CH_3). IR υ (neat): 3212, 2974-2936, 1622, 1486, 1083 cm^{-1}. MS (ESI, m/z): 296.1 (100) [$M+H^+$]. HMRS (ESI, m/z): Calcd for $C_{14}H_{18}O_7^+$: 296.1134. found: 296.1128.

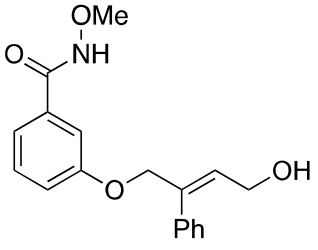
(*E*)-5-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-*N*-methoxy-2-methylbenzamide (6f)



Prepared according to general procedure A from methyl 5-((4-acetoxy-2-methylbut-2-en-1-yl)oxy)-2-methylbenzoate (300 mg, 1.65 mmol), 4-bromo-3-methylbut-2-en-1-yl acetate (683.3 mg, 3.29 mmol, *Z/E* = 82/18), K_2CO_3 (502 mg, 3.63 mmol) in acetone (8.25 mL). The crude mixture purified through silica gel (Hept. to Hept./EtOAc 8/2) to afford the corresponding compound as a white solid (m = 388 mg, 80%, *E/Z* = 82/18).

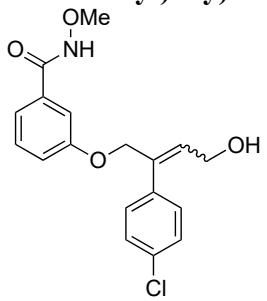
The methyl ester (352.1 mg, 1.20 mmol), was converted into the acid by treatement with NaOH 3M (4.2 mL) in EtOH (7.08 mL). The resulting crude carboxylic acid (1.17 mmol) was dissolved in DMF (3.51 mL) and reacted with EDCI (247.3 mg, 1.29 mmol), HOBt (174.3 mg, 1.29 mmol), $MeONH_2.HCl$ (97.7 mg, 1.17 mmol), and *i*Pr_2NEt (0.47 mL, 2.70 mmol). Purification over silica gel (DCM to DCM/MeOH 95/5) afforded the title compound as a white solid **(**m = 136.3 mg, 48% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): (*E/Z*: 82/18) 8.79 (brs, 1H), 7.14-7.06 (m, 1H maj. + 1H min.), 6.93-6.82 (m, 2H maj. + 2H min.), 5.73 (m, 1H maj.), 5.65 (m, 1H min.), 4.54 (s, 2H min.), 4.39 (s, 2H maj.), 4.21 (d, *J* = 6.9 Hz, 2H maj. + 2H min.), 3.85 (s, 3H maj. + 3H min.), 2.36 (s, 3H min.), 2.34 (s, 3H maj.), 1.81 (s, 3H min.), 1.73 (s, 3H maj.). ^{13}C NMR (75 MHz, $CDCl_3$): (*E/Z*: 82/18) δ (ppm) 167.6 (Cq), 156.2 (Cq), 134.7 (Cq), 133.7 (Cq), 133.2 (Cq), 132.2 (CH min.), 132.0 (CH maj.), 118.0 (CH min.), 117.3 (CH maj.), 113.8 (CH maj.), 113.3 (CH min.), 73.1 (CH_2 maj.), 66.8 (CH_3 min.), 64.4 (CH_3 maj.), 58.7 (CH_2 maj.), 58.2 (CH_2 min.), 21.2 (CH_3 min.), 18.7 (CH_3 min.), 18.5 (CH_3 maj.), 13.8 (CH_3 maj.). IR υ (neat): 3170, 2930, 1647, 1605, 1497, 1228, 1004 cm^{-1}. MS (ESI, m/z): 266.1 (100) [$M+H^+$]. HMRS (ESI, m/z): Calcd for $C_{14}H_{20}NO_4^+$: 266.1392. found: 266.1401. mp = 141-143 °C.

3-((4-hydroxy-2-methylbut-2-en-1-yl)oxy)-*N*,4-dimethoxybenzamide (6g)



Prepared according to general procedure A from methyl 3-hydroxy-4-methoxybenzoate (678.4 mg, 4.46 mmol), (*E*)-4-bromo-3-phenylbut-2-en-1-yl acetate[1] (1.32 g, 4.9 mmol, *E/Z* : 80/20), K_2CO_3 (1.23 g, 8.92 mmol) in acetone (22.3 mL). The crude mixture was purified through silica gel (Hept. to Hept./EtOAc 95/5 to 90/10) to afford the corresponding compound as a a yellow oil (m = 1.07 g, 70%, *E/Z* : 80/20).
The methyl ester (100 mg, 0.293 mmol) was converted into the acid by treatement with NaOH 3M (1.0 mL) in EtOH (1.65 mL). The resulting crude carboxylic acid was dissolved in DMF (2.6 mL) and reacted with HATU (368.8 mg, 0.97 mmol), $MeONH_2.HCl$ (81 mg, 0.97 mmol), and *i*Pr_2NEt (0.35 mL, 2.03 mmol). Purification over silica gel (Hept. to Hept./EtOAc 50/50 to 0/100) afforded the title compound as a colorless oil **(**m = 141.4 mg, 51% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41-7.21 (m, 9H), 6.97 (m, 1H), 6.22 (t, *J* = 7.0 Hz, 1H), 4.98 (s, 2H), 4.46 (d, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.4 (Cq), 139.9 (Cq), 137.3 (Cq), 132.2 (CH), 129.8 (CH), 128.9 (Cq), 128.4 (CH), 127.9 (Cq), 127.7 (CH), 126.3 (CH), 119.9 (CH), 119.7 (CH), 112.7 (CH), 71.8 (CH_2 min.), 65.3 (CH_2 maj.), 64.4 (CH_3 maj.), 59.7 (CH_2 min.), 58.9 (CH_2 maj.). IR υ (neat): 3205, 1652, 1580, 1230 cm^{-1}. MS (ESI, m/z): 296.1 (100) [M-OH^-]. HMRS (ESI, m/z): Calcd for $C_{18}H_{18}NO_3$: 296.1287. found: 296.1296.

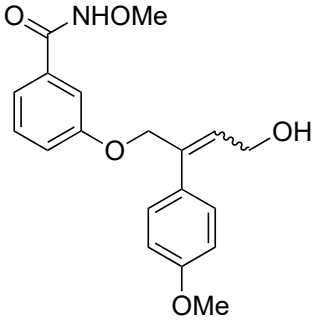
3-((2-(4-chlorophenyl)-4-hydroxybut-2-en-1-yl)oxy)-*N*-methoxybenzamide (6h)



Prepared according to general procedure A from methyl 3-hydroxy-4-methoxybenzoate (129 mg, 0.848 mmol), 4-bromo-3-(4-chlorophenyl)but-2-en-1-yl acetate[1] (257.2 mg, 0.848 mmol, *E/Z* = 82/18), K_2CO_3 (234.4 mg, 1.7 mmol) in acetone (4.2 mL). The crude mixture was purified through silica gel (Hept. to Hept./EtOAc 8/2) to afford the corresponding compound as a white solid (m = 291.7 mg, 92%, *E/Z* = 80/20).
The methyl ester (292 mg, 0.878 mmol) was converted into the acid by treatement with NaOH 3M (7 mL) in EtOH (10 mL). The resulting crude carboxylic acid (0.878 mmol) was dissolved in DMF (6 mL) and reacted with HOBt (148 mg, 0.966 mmol, 1.1 eq), EDCI (148 mg, 0.966 mmol, 1.1 eq), $MeONH_2.HCl$ (80 mg, 0.996 mmol, 1.1 eq), and iPr_2NEt (0.350 mL, 2.02 mmol, 2.3 eq). Purification over silica gel (Hept. to EtOAc) afforded the title compound as a white solid (m = 212 mg, 69% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): (*E/Z*: 7/3) 7.30 – 7.15 (m, 5H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.99 – 6.88 (m, 2H), 6.14 (t, *J* = 6.8 Hz, 1H, major.), 6.03 (t, *J* = 6.8 Hz, 1H, minor.), 4.91 (s, 2H, major.), 4.67 (s, 2H, minor.), 4.4 (d, *J* = 6.9 Hz, 2H, major.), 4.08 (d, *J* = 6.8 Hz, 2H, minor.), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.6 (Cq), 158.3 (Cq), 138.2 (Cq), 137.4 (Cq), 136.3 (Cq), 133.6 (Cq), 132.7 (CH), 132.6 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 128.6 (CH), 128.6 (CH), 128.8 (CH), 127.7 (CH), 120.0 (CH), 119.5 (CH), 119.3 (CH), 113.3 (CH), 112.6 (CH), 71.9 (CH_2), 65.0 (CH_2), 64.5 (CH_3), 59.6 (CH_2), 58.9 (CH_2). IR υ (neat): 3208, 2972, 2935, 2245, 1651, 1580, 1483 cm^{-1}. MS (ESI, m/z): 330.1 (100) [M+OH^-]. HMRS (ESI, m/z): Calcd for $C_{18}H_{17}ClNO_3^+$: 330.0897. found: 330.0909. mp = 119-121 °C.

[1] C. Wang, Z. Li, Y. Ju and S. Koo, *Eur. J. Org. Chem.*, 2012, **2012**, 6976.

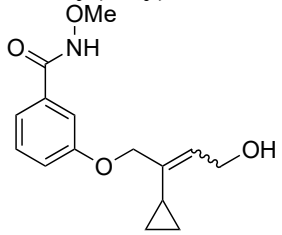
4-(3-(methoxycarbamoyl)phenoxy)-3-(4-methoxyphenyl)but-2-en-1-yl acetate (6i)



Prepared according to general procedure A from methyl 3-hydroxy-4-methoxybenzoate (118 mg, 0.773 mmol), 4-bromo-3-(4-methoxyphenyl)but-2-en-1-yl acetate[1] (231.4 mg, 0.773 mmol, *E/Z* = 82/18), K_2CO_3 (213.6 mg, 1.55 mmol) in acetone (3.9 mL). The crude mixture was purified through silica gel (Hept. to Hept./EtOAc 95/5) to afford the corresponding compound as a white solid (m = 161.6 mg, 46%, *E/Z* = 80/20).

The methyl ester (130 mg, 0.41 mmol) was converted into the acid by treatement with NaOH 3M (3 mL) in EtOH (4 mL). The resulting crude carboxylic acid (0.41 mmol) was dissolved in DMF (5 mL) and reacted with HOBt (70 mg, 0.45 mmol, 1.1 eq), EDCI (70 mg, 0.45 mmol, 1.1 eq), $MeONH_2$.HCl (38 mg, 0.45 mmol, 1.1 eq), and iPr_2NEt (0.160 mL, 0.95 mmol, 2.3 eq). Purification over silica gel (Hept. to EtOAc) afforded the title compound as a white solid (m = 77 mg, 55% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): (*E/Z*: 8/2) 10.03 (brs, 1H major.), 9.77 (1H, minor.), 7.44 – 7.14 (m, 4H), 7.06 – 6.73 (m, 4H), 6.16 (t, *J* = 7.0 Hz, 1H major.), 6.0 (t, *J* = 7.0 Hz, 1H minor.),4.93 (brs, 2H, major.), 4.18 (d, *J* = 6.6 Hz, 2H minor.) 4.69 (brs, 2H, minor.), 4.42 (d, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): (*E/Z*: 8/2) 166.0 (Cq), 159.3 (Cq), 158.4 (Cq), 136.7 (Cq), 132.8 (Cq), 132.2 (Cq), 130.5 (CH major.), 129.8 (CH major.), 129.6 (CH minor.), 128.6 (CH minor.), 127.5 (CH major. + minor.), 120.0 (CH major.), 119.9 (CH major.), 113.8 (CH major. + minor.), 112.6 (CH major.), 72.0 (CH_2 minor.), 65.2 (CH_2 major.), 64.4 (CH_3 major.), 59.8 (CH_2 minor.), 58.9 (CH_2 major.), 55.3 (CH_3 major.). IR υ (neat): 3320, 2937, 2838, 2251, 1659, 1606, 1582, 1512 cm^{-1}. MS (ESI, m/z): 344.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{19}H_{22}NO_5^+$: 344.1492. found: 344.1493. mp = 120-122 °C.

3-((2-cyclopropyl-4-hydroxybut-2-en-1-yl)oxy)-*N*-methoxybenzamide (6j)

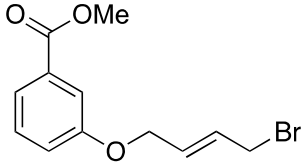


Prepared according to general procedure A from methyl 3-hydroxy-4-methoxybenzoate (301.2 mg, 1.98 mmol), 4-bromo-3-cyclopropylbut-2-en-1-ol[1] (385.1 mg, 1.65 mmol, *E/Z* = 82/18), K_2CO_3 (547.3 mg, 3.96 mmol) in acetone (9.9 mL). The crude mixture was purified through silica gel (Hept. to Hept./EtOAc 9/1) to afford the corresponding compound as a white solid (m = 303 mg, 50%, *E/Z* = 80/20).

The methyl ester (145 mg, 0.476 mmol) was converted into the acid by treatement with NaOH 3M (1.6 mL) in EtOH (2.6 mL). The resulting crude carboxylic acid (0.446 mmol) was dissolved in DMF (1.34 mL) and reacted with HATU (186.3 mg, 0.49 mmol), $MeONH_2$.HCl (40.9 mg, 0.49 mmol), and *i*Pr_2NEt (0.18 mL, 1.02 mmol). Purification over silica gel (Hept. to EtOAc) afforded the title compound as a white solid (m = 95.5 mg, 77% over 2 steps). ^{1}H NMR

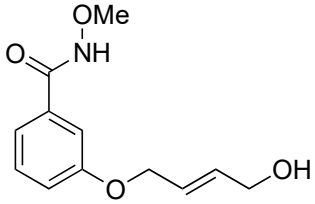
(300 MHz, MeOD) δ (ppm): (*E/Z:* 80/20) 7.43-7.25 (m, 3H, maj.+min.), 7.17-7.07 (m, 1H, maj.+min.), 5.81 (t, *J* = 6.5 Hz, 1H, min.), 5.57 (t, *J* = 6.8 Hz, 1H, maj.), 4.60 (s, 2H maj.), 4.36 (s, 2H min.), 4.34 (d, *J* = 6.9 Hz, 2H min.), 4.19 (d, *J* = 6.9 Hz, 2H maj.), 3.80 (s, 3H maj.+min.), 1.54 (m, 1H maj.+min.), 0.67 (m, 2H maj.+min.), 0.48 (m, 2H maj.+min.). ^{13}C NMR (75 MHz, MeOD) δ (ppm) 160.5 (Cq), 134.5 (Cq maj.), 131.4 (Cq maj.), 131.0 (CH maj.), 128.1 (CH maj.), 120.6 (CH maj.), 120.5 (CH min.), 114.5 (CH maj.), 114.3 (CH min.), 71.3 (CH_2 min.), 67.1 (CH_2 maj.), 64.5 (CH_3 maj.), 59.3 (CH_2 min.), 59.0 (CH_2 maj.), 16.3 (CH maj.), 11.5 (CH min.), 6.21 (CH_2 maj.), 5.45 (CH_2 min.). IR υ (neat): 3212, 3004-2938, 1653, 1581, 1234 cm^{-1}. MS (ESI, m/z): 300.1 (100) [M+Na$^+$]. HMRS (ESI, m/z): Calcd for $C_{15}H_{19}NO_4Na$: 300.1212. found: 300.1225. mp = 109-111 °C. (decomp.)

Methyl (*E*)-3-((4-bromobut-2-en-1-yl)oxy)benzoate (S1)



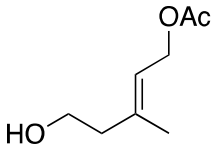
To a solution of phenol (100 mg, 0.657 mmol) in acetone (3.3 mL) is added K_2CO_3 (99.7 mg, 0.722 mmol) then (*E*)-1,4-dibromobut-2-ene (280.2 mg, 1.31 mmol) under argon at room temperature. The mixture was stirred at 25°C overnight. Then water was added and the aqueous layer extracted with EtOAc (x3). The combined organic layers were washed with water, brine then dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture purified through silica gel (Hept. to Hept./EtOAc 95/5 to 90/10) to afford the corresponding ether as a white solid (m = 106.1 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 7.64 (td, *J* = 7.6, 1.5 Hz, 1H), 7.54 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.09 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.15-5.92 (m, 2H), 4.59 (d, *J* = 4.6 Hz, 2H), 3.98 (d, *J* = 7.3 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 166.8 (Cq), 158.3 (Cq), 131.5 (Cq), 129.5 (CH), 129.4 (CH), 122.3 (CH), 120.0 (CH), 114.8 (CH), 67.3 (CH_2), 52.1 (CH_3), 31.4 (CH_2). IR υ (neat): 3066-2835, 1705, 1442 cm^{-1}. MS (ESI, m/z): 285.1 (100) [M+H]$^+$. HMRS (ESI, m/z): Calcd for $C_{12}H_{14}BrO_3^+$: 285.0126. found: 285.0140. mp = 65-67 °C.

(*E*)-3-((4-hydroxybut-2-en-1-yl)oxy)-*N*-methoxybenzamide (6k)



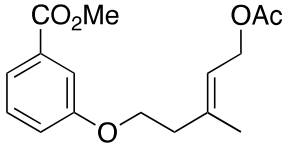
The methyl ester **S1** (106.1 mg, 0.372 mmol) was converted into the acid by treatement with NaOH 3M (1.3 mL) in THF (2.0 mL). The resulting crude carboxylic acid (71.4 mg, 0.343 mmol) was dissolved in DMF (1.0 mL) and reacted with HATU (143.3 mg, 0.377 mmol), $MeONH_2$.HCl (31.5 mg, 0.377 mmol), and *i*Pr_2NEt (0.137 mL, 0.742 mmol). Purification over silica gel (Hept. to EtOAc) afforded the title compound as a colorless oil **(**m = 42.4 mg, 48% over 2 steps). ^{1}H NMR (300 MHz, MeOD) δ (ppm) : 7.40-7.28 (m, 3H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.06-5.85 (m, 2H), 4.59 (d, *J* = 4.5 Hz, 2H), 4.10 (d, *J* = 3.9 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 167.6 (Cq), 160.4 (Cq), 134.3 (CH), 131.0 (CH), 126.6 (CH), 120.5 (CH), 119.8 (CH), 114.5 (CH), 69.3 (CH_2), 64.5 (CH_3), 62.9 (CH_2). IR υ (neat): 3208, 2960-2930, 1734, 1650, 1568 cm^{-1}. MS (ESI, m/z): 238.1 (100) [M+H]. HMRS (ESI, m/z): Calcd for $C_{12}H_{16}NO_4^+$: 238.1079. found: 238.1078.

(E)-5-hydroxy-3-methylpent-2-en-1-yl acetate (S2)



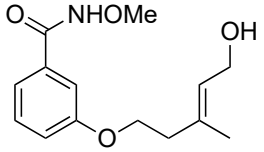
To a solution of (E)-5-((tert-butyldimethylsilyl)oxy)-3-methylpent-2-en-1-ol[2] (310 mg, 1.35 mmol) in DCM (20 mL) were added DMAP (Cat. amount) and Et_3N (0.375 mL, 2.69 mmol). The reaction mixture was cooled with an ice-bath, then Ac_2O (0.150 ml, 1.61 mmol) was added. After stirring 2 hours at this temperature, the reaction mixture was quenched with saturated NH_4Cl and the aqueous layer was extracted with DCM (x3). The combined organic layers were washed with water, brine then dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture was immediately dissolved in THF (10 mL) and TBAF (1M in THF, 1.2 ml) was added dropwise. After stirring at room temperature for 3 hours, brine was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with water, brine then dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture was through silica gel (Hept. to Hept./EtOAc, 60/40) to give the desired product as a colorless oil (m = 142 mg, 67% yield over two steps). Analytical data matched with those reported in the literature.[3]

Methyl (E)-3-((5-acetoxy-3-methylpent-3-en-1-yl)oxy)benzoate (S3)



To a solution of (E)-5-hydroxy-3-methylpent-2-en-1-yl acetate (131 mg, 0.83 mmol) in THF (20 mL), were added methyl 3-hydroxybenzoate (126 mg, 0.83 mmol) and PPh_3 (282 mg, 1.07 mmol). The reaction mixture was cooled with an ice-bath and DEAD (0.168 ml, 1.07 mmol) was added dropwise. The reaction was allowed to reach room temperature and stirred overnight. Brine was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with water, brine then dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture was through silica gel (Hept. to Hept./EtOAc, 70/30) to give the desired product as a colorless oil (m = 185 mg, 59% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.66 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.60- 7.57 (m, 1H), 7.37 (t, *J* = 15.9 Hz, 1H), 7.12 (dd, *J* = 2.6, 8.2 Hz, 1H), 5.5 (dd, *J* = 6.6, 7.5 Hz, 1H), 4.65 (d, *J* = 7.20 Hz, 2H), 4.14 (t, *J* = 6.8 Hz, 2H), 3,95 (s, 3H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.09 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.1 (Cq), 166.9 (Cq), 158.8 (Cq), 138.3 (Cq), 131.4 (Cq), 129.4 (CH), 122.1 (CH), 120.8 (CH), 120.0 (CH), 114.7 (CH), 66.5 (CH_2), 61.2 (CH_2), 52.2 (CH_3), 38.8 (CH_2), 21.0 (CH_3), 16.9 (CH_3). IR υ (neat): 3223, 2943-2916, 1702, 1644, 1595, 1198 cm^{-1}. MS (ESI, m/z): 293.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{16}H_{21}O_5^+$: 293.1384. found: 293.1391.

(*E*)-3-((5-hydroxy-3-methylpent-3-en-1-yl)oxy)-*N*-methoxybenzamide (6l)

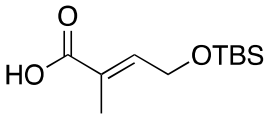


The methyl ester (185 mg, 0.63 mmol) was converted into the acid by treatement with NaOH 3M (3 mL) in EtOH (5 mL). The resulting crude carboxylic acid (0.63 mmol) was dissolved in

[2] Bajpai, R.; Curran, D.; *J. Am. Chem. Soc*, **2011**, *133* (50), 20435 - 20443
[3] Saikia, A. K, *et al*.; *Tetrahedron Letters*, **2013**, *54* (12), 1576 - 1578

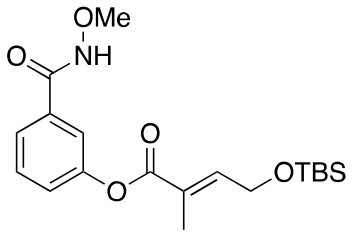
DMF (4 mL) and reacted with HATU (264 mg, 0.69 mmol), $MeONH_2.HCl$ (58 mg, 0.69 mmol), and iPr_2NEt (0.253 mL, 1.46 mmol). Purification over silica gel (Hept. to EtOAc) afforded the title compound as a colorless oil (m = 140 mg, 684% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.27 – 7.18 (m, 3H), 6.96 – 6.92 (m, 1H), 5.41 (dt, *J* = 1.60, 6.9 Hz, 1H), 4.1 (d, *J* = 6.8 Hz, 2H), 3.99 (t, *J* = 6.7 Hz, 2H), 3.78 (s, 3H), 2.39 (t, *J* = 6.8 Hz, 2H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.9 (Cq), 159.0 (Cq), 135.5 (Cq), 133.0 (Cq), 129.7 (CH), 125.8 (CH), 119.3 (CH), 118.9 (CH), 113.0 (CH), 66.6 (CH_2), 64.4 (CH_2), 59.2 (CH_3), 38.7 (CH_2), 16.6 (CH_3). IR υ (neat): 3217, 2981-2946, 1789, 1641, 1559, 1225 cm^{-1}. MS (ESI, m/z): 266.1 (100) [$M+H^+$]. HMRS (ESI, m/z): Calcd for $C_{14}H_{20}NO_4^+$: 266.1387. found: 266.1388.

(E)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-enoic acid (S4)



To a solution of 4-hydroxytiglic acid (414 mg, 3.56 mmol) in DCM (20 mL), were added DMAP (cat. amount), Et_3N (1.5 ml, 10.68 mmol) and portionwise TBSCl (1.18 g, 7.83 mmol). The solution was stirred at room temperature for 2 hours, then quenched with saturated $NaHCO_3$. The aqueous layer was extracted with DCM (x3) and the combined organic layers were washed with saturated NH_4Cl, water and brine. Solvent was removed under vacuum and the crude bis-protected product was dissolved in THF (20 mL). The solution was cooled at 0°C with an ice-bath, then AcOH (1 mL) was added. After stirring 2 hours at this temperature, the reaction mixture was quenched with saturated $NaHCO_3$ and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with water, brine then dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture purified through silica gel to afford the corresponding acid as colorless oil (m= 281 mg, 33% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.84 (dt, *J* = 1.6, 5.6 Hz, 1H), 4.29 (dd, *J* = 1.5, 5.6 Hz, 2H), 1.73 (d, *J* = 1.4 Hz, 3H), 0.82 (s, 9H), 0.0 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.6 (Cq), 144.4 (CH), 126.3 (Cq), 60.6 (CH_2), 25.9 (Cq), 18.3 (CH_3), 12.3 (CH_3), -5.2 (CH_3). IR υ (neat): 3200, 1670, 1633 cm^{-1}. MS (ESI, m/z): 231.1 (100) [$M+H^+$]. HMRS (ESI, m/z): Calcd for $C_{11}H_{23}O_3Si^+$: 231.1411. found: 231.1423.

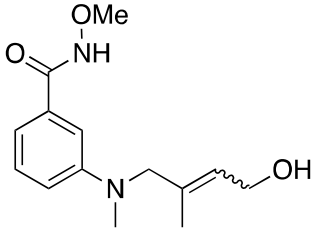
3-(methoxycarbamoyl)phenyl (*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-enoate (6m)



To a solution of (E)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-enoic acid (150 mg, 0.632 mmol) in DMF (5 mL), were added 3-hydroxy-N-methoxybenzamide (140 mg, 0.837 mmol), EDCI·HCl (143 mg, 0.921 mmol) and DMAP (153 mg, 1.25 mmol). The reaction mixture was stirred at room temperature overnight, then quench with brine and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with water, brine then dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture purified through silica gel (Hept. to EtOAc) to afford the corresponding acid as a colorless oil (m= 220 mg, 92% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.26 (brs, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 2.0 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.16 – 7.10 (m, 1H), 6.92 (dt, *J* = 1.6, 5.5 Hz, 1H), 4.32 (dd, *J* = 1.4, 5.5 Hz, 2H), 3.71 (s, 3H), 1.8 (d, *J* = 1.5 Hz, 3H), 0.81 (s, 9H), 0.0 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.1 (Cq), 165.5 (Cq), 151.1 (Cq), 144.6 (CH),

133.4 (Cq), 129.7 (CH), 126.3 (Cq), 125.4 (CH), 124.4 (CH), 120.8 (CH), 64.5 (CH_3), 60.6 (CH_2), 25.9 (Cq), 18.4 (CH_3), 12.8 (CH_3), -5.3 (CH_3). IR υ (neat): IR υ (neat): 3203, 2987-2899 1798, 1563, 1226 cm^{-1}. MS (ESI, m/z): 380.1 (100) [M+H^+]. HMRS (ESI, m/z): Calcd for $C_{19}H_{30}NO_5Si^+$: 380.1888. found: 380.1889.

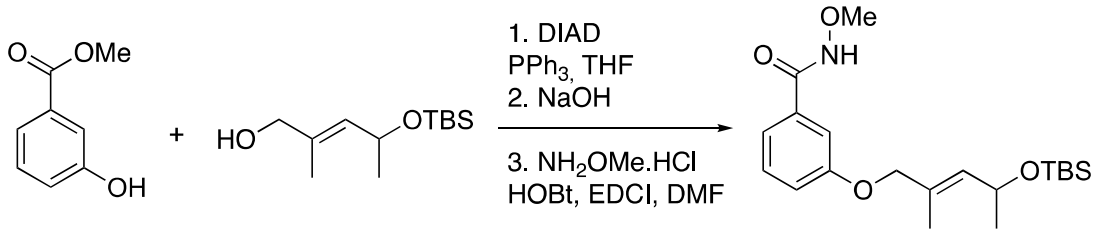
3-((4-hydroxy-2-methylbut-2-en-1-yl)(methyl)amino)-*N*-methoxybenzamide (6n)



Prepared according to procedure A from methyl 3-(methylamino)benzoate (197 mg, 1.19 mmol) and 4-bromo-3-methylbut-2-en-1-yl acetate (296 mg, 1.43 mmol, *Z/E* = 82/18), K_2CO_3 (493 mg, 3.57 mmol) in acetone (7 mL). The crude mixture purified through silica gel (Hept. to Hept./EtOAc 9/1) to afford the corresponding compound as a colorless oil (m = 260 mg, 75%, *E/Z* = 82/18).

The methyl ester (250 mg, 0.86 mmol) was converted into the acid by treatement with NaOH 3M (3 mL) in EtOH (5 mL). The resulting crude carboxylic acid (0.86 mmol) was dissolved in DMF (3 mL) and reacted with HATU (358 mg, 0.94 mmol), $MeONH_2$.HCl (79 mg, 0.94 mmol), and iPr_2NEt (0.340 mL, 1.97 mmol). Purification over silica gel (Hept. to EtOAc) afforded the title compound as a colorless oil (m = 137 mg, 60% over 2 steps, E/Z : 82/18). ^{1}H NMR (300 MHz, MeOD) δ (ppm): (*E*-isomer) 7.23 (t, *J* = 7.9 Hz, 1H), 7.06 (dd, *J* = 1.6, 2.7 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 2.7, 8.4 Hz, 1H), 5.4 (dt, *J* = 1.8, 6.7 Hz, 1H), 4.13 (d, *J* = 6.7 Hz, 1H), 3.88 (brs, 2H), 3.79 (s, 3H), 2.99 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, MeOD) δ (ppm): (*E*-isomer) 167.3 (Cq), 149.7 (Cq), 133.5 (Cq), 132.2 (Cq), 128.8 (CH), 123.6 (CH), 115.1 (CH), 113.9 (CH), 109.9 (CH), 62.8 (CH_2), 58.8 (CH_3), 57.6 (CH_2), 37.1 (CH_3), 12.9 (CH_3). IR υ (neat): 3223, 2978-2927, 1753, 1648, 1432, 1223 cm^{-1}. MS (ESI, m/z): 265.3 (100) [M+H^+]. HMRS (ESI, m/z): Calcd for $C_{14}H_{21}N_2O_3^+$: 265.3325. found: 265.3328.

(E)-3-((4-((tert-butyldimethylsilyl)oxy)-2-methylpent-2-en-1-yl)oxy)-N-methoxybenzamide (S5)

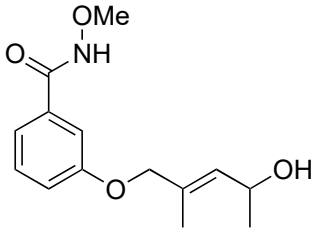


To a solution of methyl 3-hydroxybenzoate (256 mg, 1.86 mmol) in THF (15 mL) were added (*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-2-en-1-ol (428 mg, 1.86 mmol) and triphenylphosphine (585 mg, 2.23 mmol). The reaction mixture was cooled with an ice-bath, then DEAD (0.350 mL, 2.23 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred overnight. Solvent was removed under vacuum and purification over silica gel (Hept. to Hept/EtOAc, 85/15) afforded the title compound as a colorless oil (m = 530 mg mg, 78%).

The methyl ester (554 mg, 1.52 mmol) was converted into the acid by treatement with NaOH 3M (6 mL) in EtOH (8 mL). The resulting crude carboxylic acid (1.52 mmol) was dissolved in DMF (5 mL) and reacted with HOBt (254 mg, 1.66 mmol, 1.1 eq), EDCI (250 mg, 1.66 mmol, 1.1 eq), $MeONH_2$.HCl (138 mg, 1.66 mmol, 1.1 eq), and iPr_2NEt (0.660 mL, 3.49 mmol, 2.3

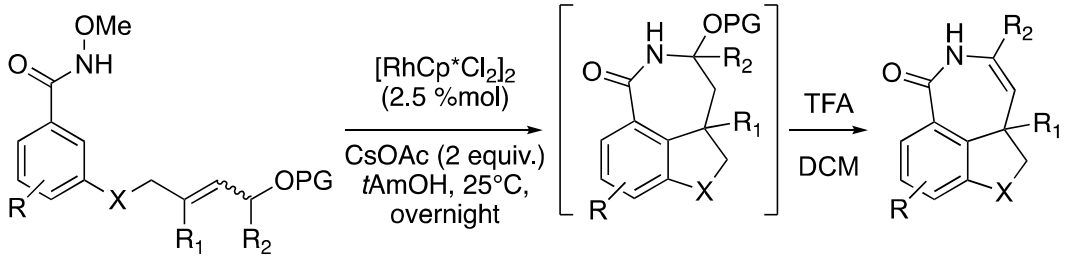
eq). Purification over silica gel (Hept. to EtOAc) afforded the title compound as a colorless oil (m = 260 mg, 45% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.77 (brs, 1H), 7.35 – 7.14 (m, 3H), 7.02 (d, *J* = 7.8 Hz, 1H), 5.54 (d, *J* = 8.2 Hz, 1H), 4.55 (dd, *J* = 6.7, 8.1 Hz, 1H), 4.37 (s, 2H), 3.84 (s, 3H), 1.68 (s, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 3H), -0,02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4 (Cq), 159.0 (Cq), 134.0 (CH), 133.1 (Cq), 129.7 (CH), 128.9 (Cq), 118.9 (CH), 113.6 (CH), 73.5 (CH_2), 65.5 (CH_3), 64.7 (CH), 25.9 (CH_3), 24.4 (CH_3), 18.2 (Cq), 13.9 (CH_3), -4.5 (CH_3), -4.9 (CH_3). IR υ (neat): 3197, 2955, 2925, 2856, 1650, 1582 cm^{-1}. MS (ESI, m/z): 380.6 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{20}H_{34}NO_4Si^+$: 380.2252. found: 380.2255.

(*E*)-3-((4-hydroxy-2-methylpent-2-en-1-yl)oxy)-*N*-methoxybenzamide (6o)



A solution of the corresponding protected alcohol (53.2 mg, 0.151 mmol) in EtOH (4.4 mL) was treated with conc. HCl (0.096 mL) at 0°C. The reaction mixture was allowed to reach room temperature and stirred overnight. After quenching with saturated $NaHCO_3$, solvent was removed under reduced pressure. DCM was added and the organic layer was washed with water, dried over $MgSO_4$ and reduced under vacuum. Purification over silica gel (Hept. to EtOAc) afforded the title compound as a colorless oil (m = 19.8 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.52 (brs, 1H, NH), 7.40 – 7.23 (m, 3H), 7.08 – 7.01. (m, 1H), 5.6 (d, *J* = 8.6 Hz, 1H), 4.65 (qd, *J* = 6.3, 8.6 Hz, 1H), 4.40 (s, 2H), 3.86 (s, 3H), 2.13 (brs, 1H, OH), 1.76 (d, *J* = 1.4 Hz, 3H), 1.27 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.8 (Cq), 132.4 (Cq), 132.1 (Cq), 129.7 (CH), 119.2 (CH), 113.3 (Cq), 73.2 (CH_2), 64.4 (CH), 23.4 (CH_3), 13.9 (CH_3). IR υ (neat): 3206, 2960-2923, 1734, 1650, 1232 cm^{-1}. MS (ESI, m/z): 266.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{14}H_{20}NO_4^+$: 266.1387. Found: 266.1386.

3- Rh(III)-CATALYZED HECK-TYPE REACTION

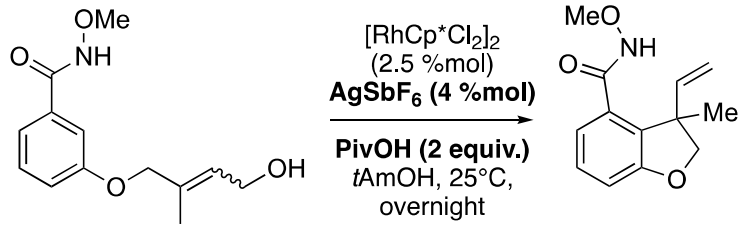


General procedure B

A seal tube was charged with a stirbar, amide (1 equiv.), $[RhCp^*Cl_2]_2$ (0.025 equiv.) and CsOAc (2 equiv.). The tube was purged three times by vacuum and argon, then *t*AmOH (0.2 M) was added. The vial was sealed and stirred at the indicated temperature for the indicated time. The reaction mixture was concentrated in vacuo. The crude residue was used without purification. The cyclic hemiaminal can be isolated by purification over silica gel.

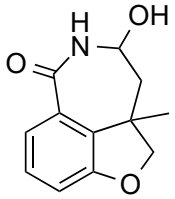
The crude hemiaminal (1 equiv.) was dissolved in CH_2Cl_2 (10 mL/mmol), then TFA (6 equiv.) was added dropwise at 0°C. The reaction was stirred at RT until completion. The solvent was removed under vacuo and the residue purified aluminium oxide to afford the cyclic enamide.

***N*-methoxy-3-methyl-3-vinyl-2,3-dihydrobenzofuran-4-carboxamide (10)**



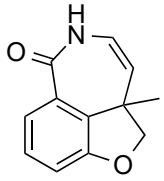
A seal tube was charged with a stirbar, amide (44.2 mg, 0.17 mmol), $[Cp^*RhCl_2]_2$ (2.6 mg, 0.00425 mmol), $AgSbF_6$ (4.3 mg, 0.017 mmol) and PivOH (34.7 mg, 0.34 mmol). The tube was purged three times with argon followed by addition of 1,4-dioxane (0.85 mL). The reaction mixture was stirred at RT overnight. The solvent was then removed under vacuo and the residue purified over silica gel (Hept. to Hept./EtOAc 5/5) to afford the titled compound as a colorless oil (m = 20.4 mg, 51%) and recovered starting material (14.4 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.61 (brs, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.94 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.91 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.12 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 5.11 (d, J = 17.4, 0.9 Hz, 1H), 4.36 (d, *J* = 8.6 Hz, 1H), 4.21 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 160.5 (Cq), 142.2 (Cq), 131.8 (Cq), 130.3 (Cq), 128.9 (CH), 120.3 (CH), 114.6 (CH_2), 112.7 (CH), 64.5 (CH_3), 48.8 (Cq), 23.1 (CH_3). IR υ (neat): 3198, 2968-2815, 1657, 1438 cm^{-1}. MS (ESI, m/z): 234.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{16}NO_3^+$: 234.1130. found: 234.1131.

3-hydroxy-4a-methyl-3,4,4a,5-tetrahydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (11)



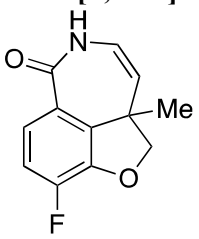
Prepared according to general procedure B from amide (39.4 mg, 0.156 mmol, *E/Z* = 80/20), $[RhCp^*Cl_2]_2$ (2.4 mg, 0.0039 mmol) and CsOAc (60.2 mg, 0.313 mmol) in *t*-AmOH (0.78 mL). The solvent was removed under vacuum and the crude mixture purified through silica gel (Hept. to Hept./EtOAc 5/5) to afford the corresponding compound as a white solid (m = 25.6 mg, 90%, dr = 88/12). ^{1}H NMR (300 MHz, DMSO) δ (ppm): (dr 88/12) 8.34 (d, *J* = 5.7 Hz, 1H min.), 7.88 (d, *J* = 4.1 Hz, 1H maj.), 7.25 (t, *J* = 7.8 Hz, 1H maj.), 7.13 (dd, *J* = 7.6, 1.0 Hz, 1H maj.), 6.95 (dd, *J* = 7.9, 1.0 Hz, 1H maj.), 6.89 (dd, *J* = 7.0, 2.1 Hz, 1H min.), 6.38 (d, *J* = 5.4 Hz, 1H maj.), 5.69 (d, *J* = 4.2 Hz, 1H min.), 4.91-4.81 (m, 1H maj.+ 1H min.), 4.40 (d, *J* = 8.7 Hz, 1H maj.), 4.35 (d, *J* = 8.7 Hz, 1H min.), 4.28 (d, *J* = 8.7 Hz, 1H maj.), 4.35 (d, *J* = 8.7 Hz, 1H min.), 4.18 (d, *J* = 8.7 Hz, 1H maj.), 2.19 (dd, *J* = 13.4, 3.5 Hz, 1H maj.), 2.00 (dd, *J* = 14.0, 10.4 Hz, 1H maj.), 1.22 (s, 3H maj.), other signals of the minor isomer are masked by the major diastereomer. ^{13}C NMR (75 MHz, DMSO) δ (ppm) (dr 88/12) 166.1 (Cq maj.), 158.2 (Cq maj.), 133.1 (Cq maj.), 131.3 (Cq maj.), 128.8 (CH maj.), 127.7 (CH min.), 120.8 (CH min.), 120.3 (CH maj.), 112.0 (CH maj.), 111.6 (CH min.), 85.5 (CH_2 maj.), 85.1 (CH_2 min.), 77.4 (CH maj.), 74.6 (CH min.), 49.1 (CH_2 maj.), 47.4 (CH_2 min.), 42.3 (Cq min.), 41.5 (Cq maj.), 30.1 (CH_3 maj.), 29.0 (CH_3 min.). IR υ (neat): 3171, 2955-2892, 1657, 1628, 1584 cm^{-1}. MS (ESI, m/z): 220.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{14}NO_3^+$: 220.0974. found: 220.0967. mp = 125-129 °C.

4a-methyl-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7a)



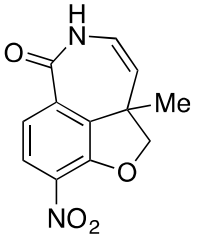
Prepared according to general procedure B from hemiaminal (16.4 mg, 0.0748 mmol), TFA (0.035 mL, 0.448 mmol) in DCM (0.75 mL). The reaction mixture was stirred for 10 min at RT. Purification through Al_2O_3 (Hept. to Hept./EtOAc 5/5) to afford the corresponding compound as a white solid (m = 12.8 mg, 85% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (brs, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 5.97 (dd, *J* = 8.5, 4.9 Hz, 1H), 5.13 (d, *J* = 8.7 Hz, 1H), 4.47 (d, *J* = 8.6 Hz, 1H), 4.39 (d, *J* = 8.6 Hz, 1H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.7 (Cq), 158.1 (Cq), 135.0 (Cq), 128.7 (CH), 123.1 (CH), 122.4 (CH), 118.5 (CH), 113.8 (CH), 83.8 (CH_2), 44.6 (Cq), 25.1 (CH_3). IR υ (neat): 3248, 2972-2878, 1635, 1586 cm^{-1}. MS (ESI, m/z): 202.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{12}H_{12}NO_2^+$: 202.0868. found: 202.0872. mp = 179-181 °C.

7-fluoro-4a-methyl-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7b)



Prepared according to general procedure B from amide (28.9 mg, 0.107 mmol, *E/Z* = 80/20), $[RhCp^*Cl_2]_2$ (1.65 mg, 0.00267 mmol) and CsOAc (41.2 mg, 0.21 mmol) in *t*-AmOH (0.54 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.05 mL, 0.64 mmol) in DCM (0.84 mL). Purification through alumina (Hept. to Hept./EtOAc 5/5) to afford the corresponding compound as a white solid (m = 13.8 mg, 75% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.92 (brs, 1H), 7.56 (dd, *J* = 8.7, 4.3 Hz, 1H), 7.05 (dd, *J* = 10.0, 8.7 Hz, 1H), 5.97 (dd, *J* = 8.7, 5.8 Hz, 1H), 5.12 (d, *J* = 8.7 Hz, 1H), 4.57 (d, *J* = 8.5 Hz, 1H), 4.48 (d, *J* = 8.6 Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.5 (Cq), 151.6 (Cq), 148.2 (Cq), 143.9 (Cq, $J_{C\text{-}F}$ = 10.2 Hz), 138.3 (Cq, $J_{C\text{-}F}$ = 4.8 Hz), 124.1 (CH, $J_{C\text{-}F}$ = 7 Hz), 123.4 (CH), 117.5 (CH), 116.4 (CH, $J_{C\text{-}F}$ = 18 Hz), 85.1 (CH_2), 45.5 (Cq), 25.1 (CH_3). IR υ (neat): 3195, 3057-2881, 1602 cm^{-1}. MS (ESI, m/z): 261.1 (100) [M+CH_3CN+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{14}H_{14}N_2O_2F^+$: 261.1039. found: 261.1050. mp = 156-159 °C.

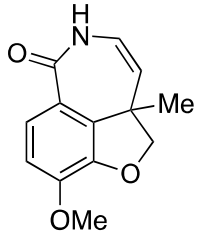
4a-methyl-7-nitro-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7c)



Prepared according to general procedure B from amide (20.6 mg, 0.0695 mmol, *E/Z* = 80/20), $[RhCp^*Cl_2]_2$ (2.00 mg, 0.00323 mmol) and CsOAc (26.7 mg, 0.139 mmol) in *t*-AmOH (0.35 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.032 mL, 0.417 mmol) in DCM (0.56 mL). Purification

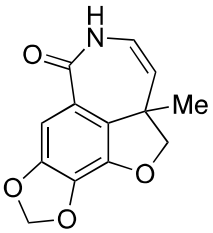
through alumina (DCM/MeOH 95/5) to afford the corresponding compound as a slightly yellow solid (m = 12.3 mg, 72% over 2 steps). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 9.86 (d, *J* = 5.6 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 5.97 (dd, *J* = 8.7, 5.5 Hz, 1H), 5.30 (d, *J* = 8.6 Hz, 1H), 4.81 (d, *J* = 9.1 Hz, 1H), 4.69 (d, *J* = 9.1 Hz, 1H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ (ppm) 164.4 (Cq), 152.9 (Cq), 139.9 (Cq), 133.7 (Cq), 133.1 (Cq), 123.8 (CH), 123.7 (CH), 121.7 (CH), 117.1 (CH), 85.9 (CH_2), 43.5 (Cq), 24.3 (CH_3). IR υ (neat): 3218, 3075-2963, 1644, 1603, 1217 cm^{-1}. MS (ESI, m/z): 247.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{12}H_{11}N_2O_4^+$: 247.0719. found: 247.0721. mp = 226-228 °C (decomp.).

7-methoxy-4a-methyl-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7d)



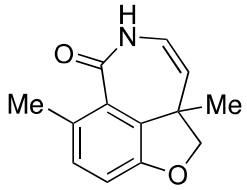
Prepared according to general procedure B from amide (26.8 mg, 0.0953 mmol, *E/Z* = 80/20), [RhCp*Cl$_2$]$_2$ (1.5 mg, 0.00238 mmol) and CsOAc (36.6 mg, 0.19 mmol) in *t*-AmOH (0.48 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.065 mL, 0.57 mmol) in DCM (0.95 mL). Purification through alumina (Hept. to EtOAc) to afford the corresponding compound as a white solid (m = 13 mg, 59%, over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 8.6 Hz, 1H), 7.34 (brs, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 5.93 (dd, *J* = 8.7, 5.8 Hz, 1H), 5.09 (d, *J* = 8.7 Hz, 1H), 4.53 (d, *J* = 8.5 Hz, 1H), 4.42 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 1.43 (s 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.8 (Cq), 148.2 (Cq), 145.5 (Cq), 135.7 (Cq), 124.6 (CH), 123.2 (CH), 120.1 (Cq), 117.6 (CH), 111.8 (CH), 84.3 (CH_2), 56.1 (CH_3), 45.5 (Cq), 25.2 (CH_3). IR υ (neat): 3206, 2959-2924, 1639, 1612, 1287 cm^{-1}. MS (ESI, m/z): 232.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{14}NO_3^+$: 232.0974. found: 232.0984. mp = 60-62 °C.

2a-methyl-2a,5-dihydro-[1,3]dioxolo[4',5':6,7]benzofuro[4,3-*cd*]azepin-6(2*H*)-one (7e)



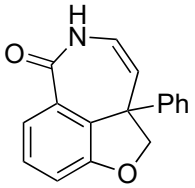
Prepared according to general procedure B from amide (39.7 mg, 0.134 mmol, *E/Z* = 80/20), [RhCp*Cl$_2$]$_2$ (2.07 mg, 0.00335 mmol) and CsOAc (51.6 mg, 0.269 mmol) in *t*-AmOH (0.67 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.091 mL, 0.804 mmol) in DCM (0.91 mL). Purification through alumina (Hept. to EtOAc) to afford the corresponding compound as a white solid (m = 18 mg, 81% over 2 steps). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 9.39 (d, *J* = 5.7 Hz, 1H), 6.87 (s, 1H), 6.07 (d, *J* = 9.7 Hz, 1H), 5.87 (dd, *J* = 8.7, 5.8 Hz, 1H), 5.12 (d, *J* = 8.7 Hz, 1H), 4.56 (d, *J* = 8.7 Hz, 1H), 4.41 (d, *J* = 8.8 Hz, 1H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.1 (Cq), 149.0 (Cq), 139.0 (Cq), 133.0 (Cq), 132.9 (Cq), 123.6 (CH), 121.4 (Cq), 116.1 (CH), 102.2 (CH), 101.5 (CH_2), 85.0 (CH_2), 44.0 (Cq), 24.8 (CH_3). IR υ (neat): 3188, 3047-2900, 1627, 1614, 1432 cm^{-1}. MS (ESI, m/z): 246.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{12}NO_4^+$: 246.0766. found: 246.0768. mp = 195-200 °C.

4a,9-dimethyl-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7f)



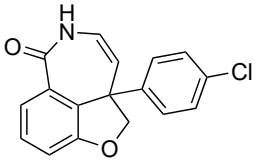
Prepared according to general procedure B from amide (23.9 mg, 0.09 mmol, *E/Z* = 80/20), $[RhCp^*Cl_2]_2$ (1.4 mg, 0.00225 mmol) and CsOAc (34.5 mg, 0.18 mmol) in *t*-AmOH (0.45 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.041 mL, 0.54 mmol) in DCM (0.72 mL). Purification through alumina (Hept. to EtOAc) to afford the corresponding compound as a colorless oil (m = 11.6 mg, 75% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.31 (brs, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 5.91 (dd, *J* = 8.3, 5.0 Hz, 1H), 5.2 (d, *J* = 8.3 Hz, 1H), 4.46 (d, *J* = 8.5 Hz, 1H), 4.41 (d, *J* = 8.5 Hz, 1H), 2.49 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 168.1 (Cq), 155.8 (Cq), 136.0 (Cq), 132.0 (Cq), 131.7 (CH), 126.2 (Cq), 123.2 (CH), 121.9 (CH), 112.1 (CH), 84.6 (CH_2), 44.4 (Cq), 23.9 (CH_3), 20.8 (CH_3). IR υ (neat): 3183, 2926-2894, 1644, 1574 cm^{-1}. MS (ESI, m/z): 216.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{14}NO_2^+$: 216.1025. found: 216.1025.

4a-phenyl-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7g)



Prepared according to general procedure B from amide (52.2 mg, 0.166 mmol, *E/Z* = 80/20), $[RhCp^*Cl_2]_2$ (2.5 mg, 0.0041 mmol) and CsOAc (63.9 mg, 0.333 mmol) in *t*-AmOH (0.83 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.077 mL, 0.99 mmol) in DCM (1.6 mL). Purification through alumina (Hept. to Hept./EtOAc : 5/5) to afford the corresponding compound as a yellow oil (m = 21 mg, 48%, over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 7.7 Hz, 1H), 7.42 (brs, 1H), 7.28 (t, *J* = 8.3 Hz, 1H), 7.20-7.09 (m, 3H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.98 (m, , 2H), 6.01 (dd, *J* = 8.5, 5.5 Hz, 1H), 5.47 (d, *J* = 8.5 Hz, 1H), 4.67 (d, *J* = 8.6 Hz, 1H), 4.63 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.1 (Cq), 158.9 (Cq), 144.4 (Cq), 133.3 (Cq), 129.4 (CH), 129.1 (Cq), 128.6 (CH), 127.1 (CH), 125.7 (CH), 124.3 (CH), 122.7 (CH), 118.9 (CH), 113.9 (CH), 85.9 (CH_2), 52.3 (Cq). IR υ (neat): 3058, 2956-2871, 1726, 1592, 1266 cm^{-1}. MS (ESI, m/z): 264.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{17}H_{14}NO_2^+$: 264.1025. found: 264.1019.

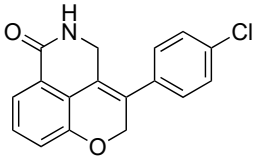
4a-(4-chlorophenyl)-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7ha)



Prepared according to general procedure B from amide (64 mg, 0.184 mmol, *E/Z* = 70/30), $[RhCp^*Cl_2]_2$ (2.8 mg, 0.0046 mmol) and CsOAc (73.0 mg, 0.368 mmol) in *t*-AmOH (0.4 mL). The solvent was removed under vacuum and the crude mixture was treated with TFA (0.035 mL, 0.448 mmol) in DCM (1.2 mL). The reaction mixture was stirred for 3 hours at RT. Purification through Al_2O_3 (DCM to DCM/MeOH 98/2) to afford the corresponding compound

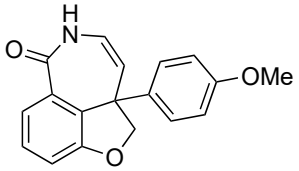
as a colorless oil (m = 19.6 mg, 36%).). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.57 (d, *J* = 7.8 Hz, 1H), 7.54 (brs, 1H, NH), 7.35 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.08 (dd, *J* = 5.6, 8.5 Hz, 1H), 5.5 (d, *J* = 8.5 Hz, 1H), 4.67 (d, *J* = 1.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.0 (Cq), 158.8 (Cq), 142.8 (Cq), 133.0 (Cq), 129.6 (CH), 128.9 (Cq), 128.8 (CH), 127.2 (CH), 124.7 (CH), 122.8 (CH), 118.3 (CH), 114.1 (CH), 85.7 (CH_2), 51.9 (Cq). IR υ (neat): 3213, 3061, 2951, 2886, 1641, 1588, 1489 cm^{-1}. MS (ESI, m/z): 298.0 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{12}H_{13}ClNO_2^+$: 298.0629. found: 298.0626.

3-(4-chlorophenyl)-4,5-dihydropyrano[4,3,2-de]isoquinolin-6(2H)-one (7hb)



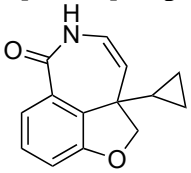
Purification through Al_2O_3 (DCM to DCM/MeOH 98/2) to afford the corresponding compound as a colorless oil (m = 19.6 mg, 37%).). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.98 (brs, 1H, NH), 7.82 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.2 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.56 (q, *J* = 8.6, 21.1 Hz, 2H), 3.66 (dd, *J* = 1.8, 15.9 Hz, 1H), 3.33 (d, *J* = 15.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.1 (Cq), 163.4 (Cq), 159.8 (Cq), 139.8 (Cq), 134.0 (Cq), 131.8 (Cq), 130.5 (CH), 129.5 (CH), 127.3 (CH), 126.7 (Cq), 124.6 (CH), 115.6 (CH), 84.8 (CH_2), 48.6 (Cq), 46.1 (CH_2).IR υ (neat): 3247, 3102, 2882, 1679, 1597, 1492 cm^{-1}. MS (ESI, m/z): 298.0 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{12}H_{13}ClNO_2^+$: 298.0629. found: 298.0627.

4a-(4-methoxyphenyl)-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7i)



Prepared according to general procedure B from amide (45.3 mg, 0.132 mmol, *E/Z* = 80/20), [RhCp*Cl_2]$_2$ (2.0 mg, 0.00329 mmol) and CsOAc (50.6 mg, 0.264 mmol) in *t*-AmOH (0.66 mL). The solvent was removed under vacuum and the crude mixture was treated with TFA (0.035 mL, 0.448 mmol) in DCM (0.8 mL). The reaction mixture was stirred for 3 hours at RT. Purification through Al_2O_3 (DCM to DCM/MeOH 95/5) to afford the corresponding compound as a colorless oil (m = 25.5 mg, 66% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 7.9 Hz, 1H), 7.30 (brs, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.9 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 6.0 (dd, *J* = 5.6, 8.5 Hz, 1H), 5.46 (d, *J* = 8.5 Hz, 1H), 4.62 (d, *J* = 2.1 Hz, 2H), 3.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.2 (Cq), 158.9 (Cq), 158.6 (Cq), 136.5 (Cq), 133.7 (Cq), 129.3 (CH), 129.0 (Cq), 126.9 (CH), 124.2 (CH), 122.7 (CH), 119.1 (Cq), 114.0 (CH), 113.9 (CH), 86.0 (CH_2), 55.3 (CH_3), 51.8 (Cq). IR υ (neat): 3327, 2928, 2845, 1661, 1654, 1593, 1513 cm^{-1}. MS (ESI, m/z): 294.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{18}H_{16}NO_3^+$: 294.1125. found: 294.1132.

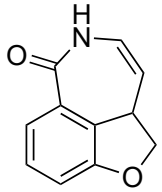
4a-cyclopropyl-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7j)



Prepared according to general procedure B from amide (24.7 mg, 0.089 mmol, *E/Z* = 80/20),

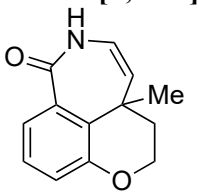
[RhCp*Cl$_2$]$_2$ (1.4 mg, 0.0022 mmol) and CsOAc (34.2 mg, 0.178 mmol) in *t*-AmOH (0.45 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.041 mL, 0.534 mmol) in DCM (0.89 mL). Purification through alumina (DCM to DCM/MeOH : 99/1) to afford the corresponding compound as a colorless oil (m = 15 mg, 74%, over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71 (brs, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 5.99 (dd, *J* = 8.9, 5.8 Hz, 1H), 4.85 (d, *J* = 8.9 Hz, 1H), 4.56 (d, *J* = 8.3 Hz, 1H), 4.29 (d, *J* = 8.4 Hz, 1H), 1.19 (m, 1H), 0.42 (m, 2H), 0.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.8 (Cq), 158.8 (Cq), 132.4 (Cq), 128.9 (CH), 124.1 (CH), 122.5 (CH), 117.2 (Cq), 114.0 (CH), 113.8 (CH), 82.2 (CH_2), 48.8 (Cq), 19.4 (CH), 1.3 (CH_2), 1.04 (CH_2). IR υ (neat): 3234, 3065-2884, 1649, 1591 cm^{-1}. MS (ESI, m/z): 228.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{14}H_{14}NO_2^+$: 228.1025. found: 228.1032.

4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (7k)



Prepared according to general procedure B from amide (32.3 mg, 0.136 mmol, *E/Z* = 80/20), [RhCp*Cl$_2$]$_2$ (2.1 mg, 0.0034 mmol) and CsOAc (52.2 mg, 0.272 mmol) in *t*-AmOH (0.68 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.063 mL, 0.816 mmol) in DCM (1.4 mL). Purification through alumina (Hept. to Hept./EtOAc : 5/5 then EtOAc) to afford the corresponding compound as a white solid (m = 13 mg, 51%, over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.73 (brs, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.0 (ddd, *J* = 8.4, 5.5, 2.8 Hz, 1H), 5.09 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.92 (dd, *J* = 10.1, 8.4 Hz, 1H), 4.54 (tdd, *J* = 10.1, 9.5, 2.6 Hz, 1H), 4.37 (dd, *J* = 9.5, 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 168.0 (Cq), 158.4 (Cq), 130.3 (Cq), 128.8 (CH), 124.6 (CH), 122.0 (CH), 115.1 (CH), 113.4 (CH), 76.8 (CH_2), 39.1 (CH). IR υ (neat): 3230, 3094-2894, 1721, 1670, 1638, 1592 cm^{-1}. MS (ESI, m/z): 188.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{11}H_{10}NO_2^+$: 188.0712. found: 188.0705. mp = 160-164 °C.

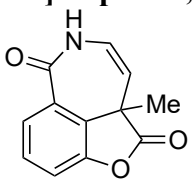
3a-methyl-2,3,3a,6-tetrahydro-7*H*-chromeno[5,4-*cd*]azepin-7-one (7l)



Prepared according to general procedure B from amide (29.5 mg, 0.111 mmol, *E/Z* = 80/20), [RhCp*Cl$_2$]$_2$ (1.7 mg, 0.0028 mmol) and CsOAc (42.6 mg, 0.222 mmol) in *t*-AmOH (0.56 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.051 mL, 0.66 mmol) in DCM (1.1 mL). Purification through alumina (DCM to DCM/MeOH : 99/1) to afford the corresponding compound as a yellow oil (m = 19 mg, 80%, over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (brs, 1H), 7.55 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.04 (dd, *J* = 8.4, 4.6 Hz, 1H), 5.18 (d, *J* = 8.4 Hz, 1H), 4.14 (dd, *J* = 5.6, 4.8 Hz, 2H), 2.16 (m, 1H), 2.04 (m, 1H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.4 (Cq), 152.6 (Cq), 133.1 (Cq), 131.1 (Cq), 127.0 (CH), 124.9 (CH), 124.3 (CH), 123.4 (CH), 121.5 (CH), 62.6 (CH_2), 39.1 (CH_2), 33.5 (Cq), 25.1 (CH_3). IR υ (neat): 3195, 2929, 1635, 1574, 1250 cm^{-1}. MS (ESI,

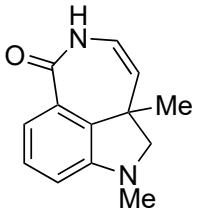
m/z): 216.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{14}NO_2^+$: 216.1025. found: 216.1035.

4a-methyl-2,4a-dihydrobenzofuro[4,3-*cd*]azepine-1,5-dione (7m)



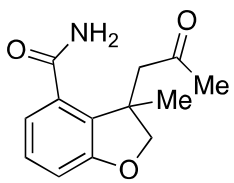
Prepared according to general procedure B from 3-(methoxycarbamoyl)phenyl (*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-enoate (30 mg, 0.079 mmol), [RhCp*Cl$_2$]$_2$ (1.2 mg, 0.002 mmol) and CsOAc (30.4 mg, 0.217 mmol) in *t*-AmOH (0.39 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.036 mL, 0.474 mmol) in DCM (0.79 mL). Purification through alumina (DCM to DCM/MeOH : 99/1) to afford the corresponding compound as a yellow oil (m = 4.1 mg, 25%, over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.48 (brs, 1H), 7.45 (t, *J* = 8.0, Hz, 1H), 7.36 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.09 (dd, *J* = 8.6, 5.8 Hz, 1H), 5.48 (d, *J* = 8.5 Hz, 1H), 1.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 177.6 (Cq), 166.4 (Cq), 150.8 (Cq), 131.8 (Cq), 129.1 (Cq), 127.8 (Cq), 125.5 (CH), 125.2 (CH), 114.8 (CH), 112.9 (CH), 45.9 (Cq), 23.5 (CH_3). IR υ (neat): 3235, 3075-2855, 1814, 1647, 1600 cm^{-1}. MS (ESI, m/z): 216.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{12}H_{10}NO_3^+$: 216.0661. found: 216.0665.

4a,6-dimethyl-2,4a,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-one (7n)



Prepared according to general procedure B from amide (28.7 mg, 0.108 mmol, *E/Z* = 80/20), [RhCp*Cl$_2$]$_2$ (3.3 mg, 0.0054 mmol) and CsOAc (41.7 mg, 0.217 mmol) in *t*-AmOH (0.54 mL). The solvent was removed under vacuum. The crude residue was used without further purification and treated with TFA (0.05 mL, 0.65 mmol) in DCM (1.1 mL). Purification through alumina (Hept. to Hept./EtOAc : 5/5) to afford the corresponding compound as a yellow oil (m = 18.7 mg, 80%, over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.90 (dd, *J* = 8.7, 5.6 Hz, 1H), 5.07 (d, *J* = 8.7 Hz, 1H), 3.44 (d, *J* = 8.5 Hz, 1H), 3.17 (d, *J* = 8.5 Hz, 1H), 2.80 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 168.4 (Cq), 150.6 (Cq), 137.6 (Cq), 128.4 (CH), 120.0 (CH), 119.8 (CH), 111.1 (CH), 69.3 (CH_2), 43.2 (Cq), 35.8 (CH_3), 24.2 (CH_3). IR υ (neat): 3203, 2925-2857, 1726, 1645, 1593 cm^{-1}. MS (ESI, m/z): 215.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{15}N_2O^+$: 215.1184. found: 215.1177.

3-methyl-3-(2-oxopropyl)-2,3-dihydrobenzofuran-4-carboxamide (7ob)

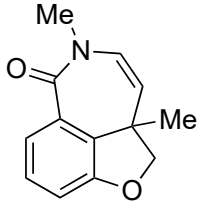


Prepared according to general procedure B from amide (68 mg, 0.256 mmol), [RhCp*Cl$_2$]$_2$ (4 mg, 0.0064mmol) and CsOAc (98.0 mg, 0.512 mmol) in *t*-AmOH (0.6 mL). The solvent was

removed under vacuum and the crude mixture was treated with TFA (0.122 mL, 1.024 mmol) in DCM (3.4 mL). The reaction mixture was stirred for 3 hours at RT. Purification through Al_2O_3 (DCM to DCM/MeOH 98/2) to afford the corresponding compound as a colorless oil (m = 44.8 mg, 61%). Traces of cyclized compound **7oa** were detected in the crude mixture ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.18 (t, *J* = 7.84 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 5.99 (brs, 1H, NH), 5.86 (brs, 1H, NH), 4.57 (d, *J* = 9.1 Hz, 1H), 4.37 (d, *J* = 9.0 Hz, 1H), 3.47 (d, *J* = 17.8 Hz, 1H), 3.03 (d, *J* = 17.7 Hz, 1H), 2.09 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 207.7 (Cq), 170.88 (Cq), 160.58 (Cq), 133.18 (Cq), 132.18 (Cq), 128.6 (CH), 119.2 (CH), 112.7 (CH), 82.7 (CH_2), 50.9 (CH_2), 44.6 (Cq), 30.9 (CH_3), 23.9 (CH_3). IR υ (neat): 3345, 3193, 2694, 2884, 1710, 1658, 1585, 1439 cm^{-1}. MS (ESI, m/z): 234.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{16}NO_3^+$: 234.1125. found: 234.1126.

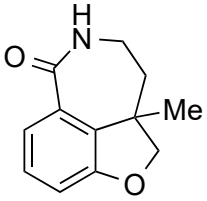
4- FUNCTIONALIZATION

2,4a-dimethyl-4a,5-dihydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (12)



To a solution of amide (23 mg, 0.114 mmol) in THF (1.48 mL) was added NaH (60 %w/w, 9.1 mg, 0.228 mmol) portionwise at 0°C. The solution was stirred at 0°C for 30 min then MeI (14.2 µL, 0.228 mmol) was added. The mixture was stirred 1h at RT then saturated NH_4Cl was added. The aqueous layer was extracted with EtOAc, then the combined organic layers were washed with water and brine. The solvent was removed under vacuum and the crude mixture purified through silica gel (Hept. to Hept./EtOAc 5/5) to afford the methylated amide as a colorless oil (m = 21.4 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 7.89 Hz, 1H), 7.23 (t, *J* = 7.95 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 5.89 (d, *J* = 8.6 Hz, 1H), 5.26 (d, *J* = 8.6 Hz, 1H), 4.48 (d, *J* = 8.7 Hz, 1H), 4.41 (d, *J* = 8.5 Hz, 1H), 3.31 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.4 (Cq), 157.4 (Cq), 136.0 (Cq), 129.3 (CH), 128.8 (Cq), 128.6 (CH), 122.6 (CH), 122.0 (CH), 112.6 (CH), 84.3 (CH_2), 43.5 (Cq), 37.6 (CH_3), 24.4 (CH_3). IR υ (neat): 2962-2887, 1635, 1589, 1355 cm^{-1}. MS (ESI, m/z): 216.1 (100) [M+H$^+$]. HMRS (ESI, m/z): Calcd for $C_{13}H_{14}NO_2^+$: 216.1025. found: 216.1018.

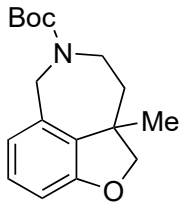
4a-methyl-3,4,4a,5-tetrahydrobenzofuro[4,3-*cd*]azepin-1(2*H*)-one (13)



The enamide (26.7 mg, 0.132 mmol) was dissolved in ethanol (1.3 mL) and 10% Pd/C (5 mg) was added. The suspension was stirred overnight at RT under hydrogen (1 atm). The suspension was filtered through celite and washed with ethanol. The crude mixture purified through silica gel (Hept. to EtOAc) to afford the corresponding compound as a white solid (m = 25.6 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (d, *J* = 7.7 Hz, 1H), 7.26 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.20 (brs, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 4.39 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 8.5 Hz, 1H), 3.49-3.21 (m, 2H), 2.21 (ddd, *J* = 14.1, 12.9, 4.8 Hz, 1H), 1.94 (ddd, *J* = 14.1, 3.2, 2.6 Hz), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.6 (Cq), 158.6 (Cq), 133.1 (Cq), 129.8 (Cq),

129.1 (CH), 121.4 (CH), 112.6 (CH), 86.1 (CH_2), 45.2 (Cq), 42.6 (CH_2), 41.3 (CH_3), 30.8 (CH_3). IR υ (neat): 3262, 2976-2870, 1652, 1583, 1243 cm^{-1}. MS (ESI, m/z): 204.1 (100) [M+H^+]. HMRS (ESI, m/z): Calcd for $C_{12}H_{14}NO_2^+$: 204.1025. found: 204.1021. mp = 147-149 °C.

Tert-butyl 4a-methyl-3,4,4a,5-tetrahydrobenzofuro[4,3-cd]azepine-2(1H)-carboxylate (14)



To a solution of 4a-methyl-3,4,4a,5-tetrahydrobenzofuro[4,3-cd]azepin-1(2H)-one (51 mg, 0.250 mmol) in THF (10 mL) was added $LiAlH_4$ (10 mg, 0.263 mmol). The reaction was refluxed overnight. After cooling with an ice-bath, NaOH (3N, 0.250 mL), then water (0.250 mL) and finally NaOH (3N, 0.750 mL) were added dropwise. The reaction mixture was filtered over a pad of celite and solvent was removed under vacuum. The crude amine was dissolved in DCM (10 mL), then a catalytic amount of DMAP, Et_3N (0.05 mL, 0.378 mmol) and Boc_2O (66 mg, 0.302 mmol) were added. After stirring for 3 hours, the reaction mixture was quenched with saturated NH_4Cl. Purification over alumina (DCM to DCM/MeOH, 98/2) afforded the title compound as a colorless oil (m = 60.3 mg, 83% over two steps). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) (2 rotamers): 7.04 – 6.56 (m, 3H), 5.11 (d, *J* = 15.4 Hz, 1H, minor.) 4.64 (d, *J* = 15.6 Hz, 1H, major.), 4.42 (td, *J* = 3.3, 14.5 Hz, 1H, major.), 4.06 (dd, J = 5.0, 15.2 Hz, 1H, minor.), 4.04 – 3.64 (m, 3H), 2.96 (t, *J* = 13.3 Hz, 1H, minor.), 2.85 (t, *J* = 13.5 Hz, 1H, major.), 1.95 (td, *J* = 12.7, 13.7 Hz, 1H, major.), 1.73 (td, *J* = 11.7, 16.4 Hz, 1H, minor.), 1.46 (s, 9H, minor.), 1.44 (s, 9H, major.), 1.28 (d, *J* = 11.7 Hz, 1H, minor.), 1.19 (d, *J* = 14.5 Hz, 1H, major.), 1.03 (s, 3H, minor.), 1.00 (s, 3H, major.). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) (2 rotamers): 160.4 (Cq), 154.7 (Cq), 138.1 (Cq),137.9 (Cq), 133.1 (Cq), 128.5 (Cq), 128.2 (CH), 120.9 (CH), 119.9 (CH), 109.5 (CH), 109.3 (CH), 84.8 (CH_2), 84.6 (CH_2), 79.1 (Cq), 51.9 (CH_2), 51.4 (CH_2), 46.1 (CH_2), 45.7 (Cq), 38.1 (CH_2), 36.8 (CH_2), 28.3 (CH_3), 28.2 (Cq), 27.6 (CH_3), 23.3 (CH_3), 23.0 (CH_3). IR υ (neat): 2973, 2929, 1762, 1689, 1594, 1450, 1409 cm^{-1} MS (ESI, m/z): 190.1 (100) [M-Boc+H^+]. HMRS (ESI, m/z): Calcd for $C_{12}H_6NO^+$ (M-Boc+H^+): 190.1226. Found: 190.1227.