Electronic Supplementary Information

**Asymmetric Synthesis of a Tricyclic Benzofuran motif: A Privileged Core Structure in Biologically Active Molecules**

**Henrik Sundén and Roger Olsson**

**General**

Chemicals and solvents were purchased from Sigma-Aldrich. Reactions involving oxygen and/or moisture sensitive reagents were carried out under an atmosphere of nitrogen using anhydrous Toluene. Toluene was distilled from benzophenone/sodium and used freshly distilled. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ on a JEOL JNM-EX 400-spectrometer at 400 and 100 MHz, respectively or $^{13}$C NMR spectra on a 500 Varian Unity Inova-spectrometer at 126 MHz. Chemical shifts are reported in ppm with the solvent residual peak as internal standard (CHCl$_3$ δ 7.26, CDCl$_3$ δ 77.0). The reactions were monitored by thin-layer chromatography (TLC), on silica plated aluminum sheets (Silica gel 60 F254, E. Merck) detecting spots by UV (254 and 365 nm). Flash chromatography was performed on Merck Silica gel 60 (0.040-0.063 mm). Optical rotation was measured on a Perkin Elmer polarimeter 341 LC. Gas chromatography/mass spectrometry analyses were performed on a Varian Saturn 2000 GCMS with a Supelco SLB-5ms fused silica capillary column using helium as carrier gas. Injector temperature 300°C, temperature program: 70 to 330 °C (12 °C/min) with 4 minutes hold time. The MS detector consisted of an ion trap with 70eV ionization. The HRMS-analyses were conducted by SP Sveriges Tekniska Forskningsinstitut Kemi och Materialteknik- Organisk analytisk kemi. Chiral HPLC chromatography analyses were performed on a Varian 9012Q/9050 UV-VIS detector using HPLC-grade solvents; n-hexane and isopropanol.
8: To a stirred solution of cyclohex-2-enone (3 g, 31.2 mmol) in 1:1 THF-H$_2$O (100 mL) was added K$_2$CO$_3$ (5.18 g, 37.5 mmol), I$_2$ (1.18 g, 46.8 mmol) and DMAP (669 mg, 6.24 mmol) successively. The reaction was stirred for 16 h and then diluted with EtOAc (100 mL) and washed with sat. Na$_2$S$_2$O$_3$ (20 mL) and 0.1 M HCl (20 mL), dried over MgSO$_4$, concentrated in vacuo and purified by flash chromatography (pentane:EtOAc, 5:1). α-iodoenone 8 isolated as colorless wet crystals in 82% yield. $^1$H NMR (400 Hz; CDCl$_3$) δ 7.76 (t, $J$ = 4.4 Hz, 1H), 2.65 (d, $J$ = 6.8 Hz, 2H), 2.43 (dd, $J$ = 10.5, 6.0 Hz, 2H), 2.08 (dt, $J$ = 12.6, 6.1 Hz, 2H); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 192.15, 159.43, 103.80, 37.19, 29.87, 22.78; m/z (EI) 222 (M+., 100%), 194 (50), 166 (14).

4-(benzyloxy)phenylboronic acid. 4-Benzylxyphenylbromide (14.0 g, 53.2 mmol) was dissolved in distilled THF (100 mL) in a septa equipped round-bottom flask. The solution was purged with N$_2$ and cooled to -75 °C in a CO$_2$/acetone bath. N-Butyllithium (2.5 M in hexanes, 27 mL) was added slowly while maintaining the temperature below -65 °C. The mixture was stirred for 1 h below -65 °C and then triisopropyl borate (39 mL, 170 mmol) was added while maintaining the temperature at -65 °C. The resulting clear solution was warmed to room temperature and stirred for 16 h. Conc. HCl was added until a pH of 6-7 was reached. The reaction mixture was poured into diethyl ether (200 mL) and the organic layer was washed three times with water, dried over anhydrous MgSO$_4$ and filtered. The solvent was removed and the product was recrystallized from EtOAc/hexanes (1:10). Yield: 82%. $^1$H NMR (400 MHz; CDCl$_3$) δ 8.17 (d, $J$ = 8.4 Hz, 2H), 7.47 (d, $J$ = 7.6 Hz, 2H), 7.41 (t, $J$ = 7.4 Hz, 2H), 7.35 (dd, $J$ = 8.4, 5.8 Hz, 1H), 7.09 (d, $J$ = 8.4 Hz, 2H), 5.16 (s, 2H); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 162.38, 137.51, 136.67, 128.63, 128.07, 127.53, 114.36, 99.77, 69.82.

9: To a Mw-vial containing, iodoenone 8, (167 mg, 0.75 mmol), Na$_2$CO$_3$ (159 mg, 1.5 mmol), Ar-B(OH)$_2$ (342 mg, 1.5 mmol), and Pd/C (40 mg, 5 mol%) was added DME (1.5
mL) and H2O (1.5 mL). The mixture was degassed by alternating vacuum and N2 three times, pre
stirred for 5 min and then subjected to microwave irradiation (80 °C) for 15 min. Without
removing the Mw-cap the reaction mixture was extracted with diethylether (5 x 3ml), the
combined organic phase was dried (Na2SO4), evaporated and purified by flash chromatography
(pentane:EtOAc, 5:1). The title compound 9 was obtained in 168mg, 80% yield as an of white
solid.1H NMR (400 MHz; CDCl3) δ 7.46 – 7.35 (m, J = 7.6, 6.6 Hz, 4H), 7.35 – 7.30 (m, 1H), 7.25
(d, J = 8.7 Hz, 2H), 6.99 (t, J = 4.3 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 5.07 (s, 2H), 2.58 (t, J = 6.9 Hz,
2H), 2.52 (dd, J = 10.4, 6.0 Hz, 2H), 2.10 (p, J = 6.1 Hz, 2H); 13C NMR (101 MHz; CDCl3) δ 198.24,
158.36, 146.96, 139.74, 137.02, 129.76, 129.25, 128.56, 127.92, 127.43, 114.39, 69.98, 39.11,
26.60, 22.96; m/z (EI) 278 (M+, 48%), 187 (9), 91 (100).

10: A prestirred (10 min, rt) solution of (S)-(−)-2-Methyl-CBS-oxazaborolidine (60mg, 0.22 mmol) and borane dimethyl sulfide complex (BMS) (0.377 mL, 0.75
mmol, 2M solution in toluene) in toluene (3 mL) was placed in an ice bath. The cold reaction
mixture was then added a solution of 9 (200 mg, 0.72 mmol) in toluene (3 mL) via a syringe
pump over 2h. The reaction was continued at 0 °C for an additional 2h before it was quenched
with 2 ml of 1M HCl and diluted with 75 mL diethylether, extracted, washed with water (5mL),
brine (5mL) and dried over MgSO4. The crude product was purified by silica gel chromatography
(pentane:EtOAc, 10:1) to give the allylic alcohol 10 (168 mg, 83% yield and 98% ee) as an of
white solid 1H NMR (400 MHz; CDCl3) δ 7.49 – 7.37 (m, 6H), 7.36 – 7.29 (m, 1H), 6.97 (d, J = 8.6
Hz, 2H), 6.14 – 6.07 (m, 1H), 5.08 (s, 2H), 4.68 (t, J = 3.5 Hz, 1H), 2.35 – 2.09 (m, 2H), 2.03 – 1.93
(m, 1H), 1.91 – 1.57 (m, 4H); 13C NMR (101 MHz; CDCl3) δ 158.00, 138.31, 136.97, 132.87,
128.54, 127.91, 127.43, 127.18, 127.03, 114.82, 69.96, 65.42, 31.51, 25.97, 17.26; m/z (EI) 281
(M+1, 24%), 171 (11), 128 (7), 91 (100); [α]20D =+66.1 (c 1, CHCl3); HPLC: Diacel Chiralpak AD
column (n-hexane: 2-Propanol = 95:5, flow rate 1 ml/min, λ = 254 nm). Retention time (min):
27.9 (minor) and 31.3 (major). The racemic standard was prepared by reducing 9 under Luche
conditions.
12: To a stirred solution of 10 (85 mg, 0.30 mmol), 2-iodophenol (133 mg, 0.61 mmol), and PPh₃ (159 mg, 0.61 mmol) in toluene (15 ml) was added DIAD (122 mg, 0.61 mmol) at 0°C. The solution was allowed to reach room temperature and stirred over night and then diluted with 15 mL toluene and quenched with 4 mL 1 M NaOH. The organic layer was separated and washed with water (5 ml), brine (5 ml) and dried over MgSO₄ and concentrated. The crude product was purified by flash chromatograph (pentane:EtOAc, 20:1) to render the product in 88 mg, 60% yield. ¹H NMR (400 MHz; CDCl₃) δ 7.77 (dd, J = 7.5, 1.5 Hz, 1H), 7.45 – 7.22 (m, 8H), 6.92 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.69 (td, J = 7.4, 1.1 Hz, 1H), 6.28 (dd, J = 5.0, 2.8 Hz, 1H), 5.17 (t, J = 3.0 Hz, 1H), 5.04 (s, 2H), 2.45 – 2.37 (m, 1H), 2.26 – 2.13 (m, 2H), 2.07 – 1.95 (m, 1H), 1.75 – 1.63 (m, 2H); ¹³C NMR (126 MHz; CDCl₃) δ 157.82, 156.63, 139.70, 137.04, 135.07, 134.05, 129.81, 129.23, 128.50, 127.84, 127.40, 127.04, 122.41, 114.60, 113.55, 88.40, 73.24, 69.92, 27.42, 25.89, 17.10; [α]²⁰ᵣ₋₂₆.9 (c 1, CHCl₃); HPLC: Diacel Chiralpak AD column (n-hexane: 2-Propanol = 95:5, flow rate 1 mL/min, λ = 254 nm). Retention time (min): 6.6 (minor) and 7.3 (major).

13: To a vial containing Ag₂CO₃ (56 mg, 0.20 mmol), PPh₃ (5.2 mg, 0.020 mmol) and Pd(OAc)₂ (2.2 mg, 0.010 mmol) was added a solution of aryl ether 12 (33 mg, 0.068 mmol) in toluene (1.5 mL). The mixture was degassed by alternating vacuum and N₂ three times and heated at 80°C in a sealed vial for 16 h at which the completion and selectivity of the reaction was measured by crude-NMR. The reaction was directly purified by silica gel chromatography (pentane:EtOAc, 20:1) to yield the cyclic product as a colorless oil in 95% yield. ¹H NMR (400 MHz; CDCl₃) δ 7.50 – 7.27 (m, 7H), 7.17 (dd, J = 7.6, 1.5 Hz, 1H), 7.00 – 6.93 (m,
3H), 6.91 – 6.82 (m, 2H), 6.02 – 5.93 (m, 1H), 5.72 – 5.64 (m, 1H), 5.06 (s, 2H), 4.73 (t, J = 1.7 Hz, 1H), 2.41 – 2.29 (m, 1H), 2.22 – 2.12 (m, 1H), 2.12 – 2.01 (m, 1H), 1.87 – 1.69 (m, 1H); $^{13}$C NMR (126 MHz; CDCl$_3$) δ 159.94, 157.75, 136.96, 136.69, 134.42, 129.51, 129.38, 128.58, 128.36, 127.97, 127.48, 126.75, 124.67, 120.92, 114.56, 109.95, 89.59, 70.04, 53.87, 18.96; m/z (EI) 354 (M+, 100%), 235 (2), 91 (7); $[\alpha]_{D}^{20} = +60.2$ (c 1, CHCl$_3$).

14: To a stirred solution of 13 (99mg, 0.28 mmol) in ethanol (3mL) was added Pd/C (10mg, 10% wt). The reaction vessel was purged by alternating vacuum and H$_2$ three times before it was subjected to an atmosphere of H$_2$. When complete conversion of starting material could be determined (TLC) the reaction was directly purified by silica gel chromatography (pentane:EtOAc, 5:1) to yield the final product as a colorless oil in 49 mg, 67% yield. $^1$H NMR (400 MHz; CDCl$_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 7.19 – 7.11 (m, 1H), 6.90 – 6.83 (m, 3H), 6.78 (d, J = 8.7 Hz, 2H), 4.83 (t, J = 3.6 Hz, 1H), 4.68 (s, 1H), 2.37 – 2.24 (m, 1H), 2.08 – 1.95 (m, 1H), 1.87 – 1.51 (m, 6H); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 158.63, 153.97, 137.98, 136.84, 128.79, 127.95, 123.63, 120.84, 115.05, 110.12, 89.78, 50.95, 33.81, 26.19, 21.44, 19.64; m/z (EI) 266 (M+, 100), 223 (84), 195 (17); $[\alpha]_{D}^{20} = +2.5$ (c 0.4, CHCl$_3$); HRMS (FI-ICR-MS) m/z Calcd for: C$_{18}$H$_{18}$O$_2$ [M+H]$^+$ 267.1379, (found) 267.1385.

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Run File: C:\STAR\SUNDER\MS47001.RUN
Method File: C:\star\sunder\untitled.mth
Sample ID: hs4701_md_95_c

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Operator: Operator Detector Type: 9050
Workstation: Bus Address: 3
Instrument: Sample Rate: 10.00 Hz
Channel: 1 = 254 nm Run Time: 44.907 min

************ Star Chromatography Workstation ************ Version 4.51 ************

Run Mode: Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

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Manual injection

Revision Log:
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Method File: C:\star\clae\untitled.mth
Sample ID: h610D

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**Operator:** Operator  **Detector Type:** 9050
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**Instrument:** 1  **Sample Rate:** 10.06 Hz
**Channel:** 1 = 254 nm  **Run Time:** 37.162 min

**Star Chromatography Workstation Version 4.51**

**Run Mode:** Analysis  **Peak Measurement:** Peak Area
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**Manual injection**
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Method File: C:\star\sundehs49001.mth
Sample ID: hs49001

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**Operator:** Operator  **Detector Type:** 9050
**Workstation:**  **Bus Address:** 3
**Instrument:**  **Sample Rate:** 10.00 Hz
Channel: 1 = 254 am  **Run Time:** 17.102 min

************ Star Chromatography Workstation ************ Version 4.51 **************

**Run Mode:** Analysis - Subtract Blank Baseline
**Peak Measurement:** Peak Area
**Calculation Type:** Percent

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Manual injection

Revision Log:
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**Title**

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Method File: C:\star\sundeg\ms49001.mth
Sample ID: ms49004

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**Operator:** Operator  **Detector Type:** 9050
**Workstation:**  **Bus Address:** 3
**Instrument:** 1  **Sample Rate:** 10.00 Hz
**Channel:** 1 = 254 nm  **Run Time:** 27.360 min

********** Star Chromatography Workstation ****** Version 4.51 **********

**Run Mode:** Analysis - Subtract Blank Baseline

**Peak Measurement:** Peak Area

**Calculation Type:** Percent

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**Multiplier:** 1  **Divisor:** 1

**Baseline Offset:** -21 microAU

**Noise (used):** 129 microAU - monitored before this run

**Manual injection**
Supplementary Material (ESI) for Organic and Biomolecular Chemistry

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Supplementary Material (ESI) for Organic and Biomolecular Chemistry

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Compound 14 was used in a standard $^1$H-$^1$H NOESY NMR experiment (400 MHz; CDCl3). A cross peak representing a nuclear overhauser effect (NOE) of the ether proton (H20) and the aromatic protons (H22 and H23) is clearly detectable. This finding is an excellent indication of the cis-fused conformation.