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Synthetically attractive chiral cyclopentenone building blocks conjugated with tetrahydro- and 2-oxotetrahydrofurans

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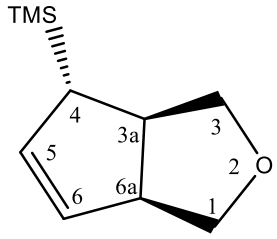
Experimental

Solvents were purified and dried before use according to standard procedures. Reagents were of the best quality commercial grade and used without further purification unless otherwise indicated. All reactions were carried out in oven-dried glassware. TLC was performed using Sorbfil STC-1A 110 μm layer, on silica gel 5–17 precoated foil plates. Column chromatography was conducted using 210–280 mesh silica gel. Optical rotations were measured using the sodium D line (589 nm) on a Perkin–Elmer 241 MC polarimeter at 20 °C. IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer as Nujol mull or as neat thin films on KBr plates. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-300 (300 MHz for ^{1}H and 75.47 MHz for ^{13}C) or BrukerAvance III (500 MHz for ^{1}H and 125.77 MHz for ^{13}C) spectrometers as solutions in $CDCl_3$ (Aldrich; spectra grade). Chemical shifts are reported as δ unit-parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal reference. Mass spectra were recorded on a Shimadzu LCMS QP-2010EV (APCI) spectrometer. Elemental analyses were performed on a Euro EA 3000 CHNS-analyzer.

(3a*S*,6*S*,6a*R*)-6-(trimethylsilyl)-3,3a,6,6a-tetrahydro-1*H*-cyclopenta[c]furan-1-one **5** was obtained according to ref. 14, ***[(1*R*,2*S*,5*S*)-5-(trimethylsilyl)cyclopent-3-ene-1,2-diyl]dimethanol*** **6** was obtained according to ref. 15, the spectral characteristics conform to those given in the references.

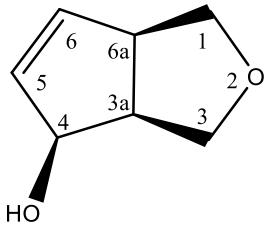


Trimethyl[(3a*R*,4*S*,6a*S*)-3,3a,4,6a-tetrahydro-1*H*-cyclopenta-[c]furan-4-yl]silane **7.** Pyridine (0.12 ml, 1.53 mmol) and MsCl (0.05 ml, 0.61 mmol) were added to a solution of diol **6** (0.1 g, 0.51 mmol) in anhydrous CH_2Cl_2 (10 ml) at 0°C. The mixture was stirred at this temperature for 8 h, and then refluxed for 1 h (TLC monitoring). The mixture was cooled to room temperature, water was added, and the product was extracted with

EtOAc (3×10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on SiO_2 (light petroleum–ethyl acetate, 5 : 1). The product was isolated as transparent viscous oil. R_f (light petroleum–ethyl acetate, 5 : 1) 0.5. The yield 85%.$[\alpha]_D^{20}$: +120.2 (*c* = 0.80, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.66 (dt, 1H, C^5H, *J* 2.13 and *J* 5.5 Hz), 5.43 (dt, 1H, C^6H, *J* 2.14 and *J* 5.5 Hz), 3.93 (t, 1H, C^1H_2, *J* 8.24 Hz), 3.85 (t, 1H, C^1H_2, *J* 8.24 Hz), 3.60 (dd, 1H, C^3H_2, *J* 3.36 Hz and *J* 8.54 Hz), 3.38 (dd, 1H, C^3H_2, *J* 5.80 Hz and *J* 8.54 Hz), 3.35–3.29 (m, 1H, $C^{6a}H$), 2.70 (qd, 1H, $C^{3a}H$, *J* 2.14 Hz and *J* 6.10 Hz), 1.74 (quin, 1H, C^4H, *J* 2.14 Hz), -0.01 (s, 9H, Me_3Si). ^{13}C NMR (125.76 MHz, $CDCl_3$), δ: 132.43, 128.56, 76.91, 73.18, 51.99, 43.69, 41.01, -3.32. IR, ν/cm^{-1}: 2954, 2927, 2848, 1248, 1085, 1063, 1046, 973, 957, 921, 839, 746, 698. Found (%): C, 65.70; H, 9.78. Calc. for $C_{10}H_{18}OSi$ (%): C, 65.93; H, 9.89%.

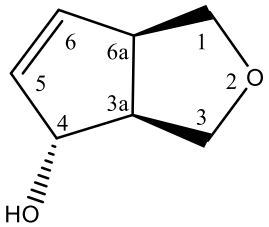
***(3aS,4S,6aR)-3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan-4-ol* 8a and *(3aS,4R,6aR)-3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan-4-ol* 8b.**

General procedure. Solid $NaHCO_3$ (0.7 g, 8.33 mmol) was placed in a round-bottom flask, then water (15 ml) and acetone (20 ml) were added. The resulting mixture was cooled to 0 °C and stirred for 20 min. Oxone (0.7 g, 1.1 mmol) was added in one portion and stirring was continued at 0 °C for 15 min. Then, silane **7** (0.1 g, 0.55 mmol) was added in one portion. Cooling was removed and the reaction mixture was stirred at room temperature for 1 h. TLC monitoring showed that the reaction was complete (light petroleum–ethyl acetate, 1 : 1). The reaction mixture was diluted with water and extracted with EtOAc (3×10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The treatment with 9N H_2SO_4 in THF was carried out without purification due to the instability of product on chromatography column, providing alcohols **8a** and **8b** as a mixture of isomers (*cis* : *trans* = 3 : 2). These isomers were separated by column chromatography on SiO_2 (light petroleum–ethyl acetate, 1 : 1).

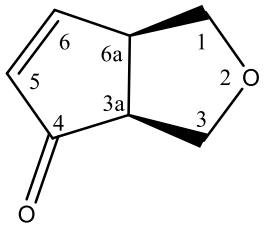


***(3aS,4S,6aR)-3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan-4-ol* 8a.** The yield 42%, transparent viscous oil. R_f (light petroleum–ethyl acetate, 1 : 1) 0.3. $[\alpha]_D^{20}$: +5,5 (*c* = 1.025, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.85 (dd, 1H, C^6H, *J* 1.7 Hz and *J* 5.7 Hz), 5.82 (d, 1H, C^5H, *J* 5.6 Hz), 4.76 (d, 1H, C^4H, *J* 7.8 Hz), 4.33 (d, 1H, C^3H_2, *J* 9.3 Hz), 3.65 (dd, 1H, C^1H_2, *J* 1.8 Hz and *J* 8.8 Hz), 3.53 (t, 1H, C^1H_2, *J* 7.6 Hz), 3.44 (dd, 1H, C^3H_2, *J* 6.3 Hz and *J* 9.3 Hz), 3.28 (td, 1H, $C^{3a}H$, *J* 2.3 Hz and *J* 9.7 Hz), 2.91 (qd, 1H, $C^{6a}H$, *J* 1.4 Hz and *J* 7.8 Hz). ^{13}C NMR (125.76 MHz, $CDCl_3$), δ: 135.52, 134.96, 77.32, 72.25, 68.40, 50.76,

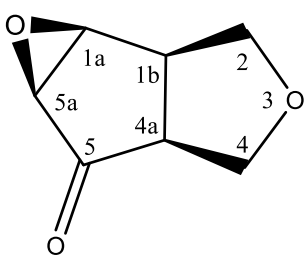
44.86. IR, ν/cm^{-1}: 3395, 2922, 2849, 1733, 1370, 1243, 1194, 1124, 1085, 1060, 1031, 972, 913, 764, 747. Found (%):C, 66.12; H, 7.65. Calc. for $C_7H_{10}O_2$ (%): C, 66.67; H, 7.94%.



***(3aS,4R,6aR)-3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan-4-ol* 8b.** The yield 28%, transparent viscous oil. R_f (light petroleum–ethyl acetate, 1 : 1) 0.2; $[\alpha]_D^{20}$: +4,5 (c = 0.966, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.86 (dd, 1H, C^{6}H, J 1.6 Hz and J 5.7 Hz), 5.83 (dd, 1H, C^{5}H, J 1.8 Hz and J 5.6 Hz), 4.63 (dd, 1H, C^{4}H, J 2.0 Hz and J 3.3 Hz), 3.79 (dd, 1H, C^{3}H$_2$, J 3.2 Hz and J 9.3 Hz), 3.76 (dd, 1H, C^{3}H$_2$, J 7.4 Hz and J 9.3), 3.68 (dd, 1H, C^{1}H$_2$, J 2.0 Hz and J 8.8 Hz), 3.61 (dd, 1H, C^{1}H$_2$, J 6.8 Hz and J 8.8 Hz), 3.52 (tt, 1H, C^{6a}H, J 2.0 Hz and J 7.0 Hz), 2.69 (tdd, 1H, C^{3a}H, J 1.4 Hz, J 3.2 Hz, and J 7.4 Hz). ^{13}C NMR (125.76 MHz, $CDCl_3$), δ: 137.29, 133.75, 84.02, 73.39, 71.45, 52.26, 50.61. IR, ν/cm^{-1}: 3412, 2926, 2854, 1746, 1370, 1359, 1248, 1359, 1248, 1193, 1085, 1060, 1038, 973, 933, 913, 765, 749. Found (%): C, 66.35; H, 7.77. Calc. for $C_7H_{10}O_2$ (%): C, 66.67; H, 7.94%.

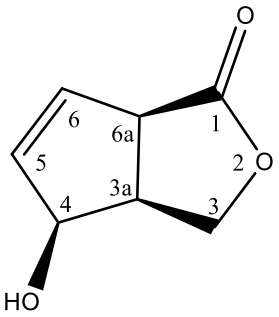


***(3aS,6aR)-1,3,3a,6a-tetrahydro-4H-cyclopenta[c]furan-4-one* 1**. Dess-Martin periodinane (2.7g, 6.35 mmol) was added to a mixture of isomeric alcohols **8a** and **8b** (0.32 g, 2.54 mmol) dissolved in DCM (30 ml) at 0 °C. The reaction mixture was stirred at room temperature for 3 h (TLC monitoring) and treated with $NaHCO_3$ (sat. aq., 5 ml) and $Na_2S_2O_3$ (sat. aq., 5 ml). The resulting mixture was stirred for 1 h and extracted with DCM (3×10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (light petroleum–ethyl acetate, 3 : 1). The product was isolated as transparent viscous oil. R_f (light petroleum–ethyl acetate, 1 : 1) 0.4. The yield 70%. $[\alpha]_D^{20}$: -102.9 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.58 (dd, 1H, C^{6}H, J 2.5 Hz and J 5.5 Hz), 6.20 (d, 1H, C^{5}H, J 5.5 Hz), 4.13 (d, 1H, C^{3}H$_2$, J 9.3 Hz), 3.88 (d, 1H, C^{3}H$_2$, J 9.3 Hz), 3.65 (q, 2H, C^{1}H$_2$, J 8.3 Hz), 3.55 (m, 1H, C^{6a}H), 2.90 (dd, 1H, C^{3a}H, J 6.3 Hz and J 7.5 Hz). ^{13}C NMR (125.76 MHz, $CDCl_3$), δ: 211, 164.91, 135.08, 71.03, 69.63, 49.59, 47.08. IR, ν/cm^{-1}: 2969, 2952, 2930, 2863, 1709, 1587, 1367, 1339, 1237, 1192, 1175, 1085, 1070, 1035, 997, 912, 865, 788, 768, 753. Found (%): C, 67.10; H, 6.40. Calc. for $C_7H_8O_2$ (%): C, 67.74; H, 6.45%.

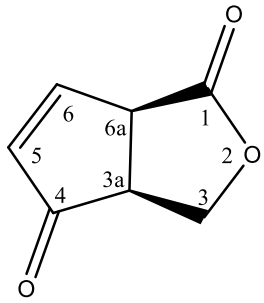


***(1aR,1bR,4aS,5aR)-hexahydro-5H-oxireno[2',3':3,4]-cyclopenta[1,2-c]furan-5-one* 9**. *Tert*-butyl hydroperoxide (70 wt% in water, 0.11 ml, 0.81 mmol) and DBU (0.02 ml, 0.13 mmol) were

added to a solution of lactone **1** (0.1 g, 0.81 mmol) in CH_2Cl_2 (5 ml). After 3 h, the solution was treated with 10% HCl solution (1 ml), then Na_2SO_3 (sat. aq., 1 ml) was added. The resulting mixture was extracted with CH_2Cl_2 (3×10 ml), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (light petroleum–ethyl acetate, 1 : 1). The product was isolated as transparent viscous oil. R_f (light petroleum–ethyl acetate, 1 : 1) 0.5. The yield 63%. $[\alpha]_D^{20}$: -41 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.22 (d, 1H, C^4H_2, *J* 9 Hz), 3.97 (dd, 1H, C^2H_2, *J* 3.0 Hz and *J* 9.8 Hz), 3.8 (s, 1H, $C^{1a}H$), 3.78 (dd, 1H, C^2H_2, *J* 8.6 Hz and *J* 9.6 Hz), 3.63 (dd, 1H, C^4H_2, *J* 6.4 Hz and *J* 9 Hz), 3.48 (d, 1H, $C^{5a}H$, *J* 2.1 Hz), 3.30 (td, 1H, $C^{4a}H$, *J* 3.1 Hz and *J* 7.8 Hz), 2.78 (t, 1H, $C^{1b}H$, *J* 7.2 Hz). ^{13}C NMR (125.76 MHz, $CDCl_3$), δ: 209.67, 71.67, 68.93, 58.96, 56.05, 48.56, 42.83. IR,ν/cm^{-1}: 2956, 2927, 2871, 1745, 1355, 1232, 1212, 1186, 1169, 1083, 1068, 1042, 1010, 965, 911, 838, 805, 767. Found (%): C, 59.91; H, 5.70. Calc. for $C_7H_8O_3$ (%): C, 60.00; H, 5.71%.



(3aS,4S,6aR)-4-hydroxy-3,3a,4,6a-tetrahydro-1H-cyclopenta-[c]furan-1-one **10**. mCPBA (0.18 g, 1.02 mmol) was added to a solution of lactone **5** (0.1 g, 0.51 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The mixture was stirred at this temperature for 8–10 h, then treated with $Na_2S_2O_3$ (sat. aq., 3 ml), and stirred for 1 h with subsequent treament with $NaHCO_3$ (sat. aq., 5 ml) and strring for 1 h. The resulting mixture was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was treated with 9N H_2SO_4 in THF. The resulting solution was stirred for 30 min, then treated with $NaHCO_3$ (sat. aq., 0.5 ml), drained with $MgSO_4$, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on SiO_2 (light petroleum–ethyl acetate, 1 : 3). The product was isolated as transparent viscous oily liquid. R_f (light petroleum–ethyl acetate, 1 : 3) 0.3. The yield 85%. $[\alpha]_D^{20}$: –162.4 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.91–5.96 (br. s, 2H, CH=CH), 5.02 (d, 1H, C^4H, *J* 7.5 Hz), 4.62 (dd, 1H, C^3H_2, *J* 5.3 Hz and *J* 9.7 Hz), 4.38 (t, 1H, C^3H_2, *J* 9.1 Hz), 3.61 (d, 1H, $C^{6a}H$, *J* 8.5 Hz), 3.29 (qd, 1H, $C^{3a}H$, *J* 5.5 Hz and *J* 8.8 Hz), 3.20–2.33 (br. s, 1H, OH). ^{13}C NMR spectrum was identical to the published one[14]. IR, ν/cm^{-1}: 3423, 2976, 2920, 1759, 1477, 1379, 1186, 1097, 1020, 960. Found (%): C, 59.89; H, 5.60. Calc. for $C_7H_8O_3$ (%): C, 59.99; H, 5.75 %.

***(3aS,6aR)-3a,6a-dihydro-1H-cyclopenta[c]furan-1,4(3H)-dione* 4.** 

To Dess-Martin periodinane (0.77g, 1.81 mmol) was added to a solution of enone **10** (0.1 g, 0.72 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The reaction mixture was stirred at room temperature for 3 h (TLC monitoring) and treated with $NaHCO_3$ (sat. aq., 5 ml) and $Na_2S_2O_3$ (sat. aq., 5 ml). The resulting mixture was stirred for 1 h and extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (light petroleum–ethyl acetate, 5 : 1). The product was isolated as transparent viscous oil. R_f (light petroleum–ethyl acetate, 5 : 1) 0.4. The yield 70%. $[\alpha]_D^{20}$: –317.5 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.77 (dd, 1H, C^6H, *J* 3.3 Hz and *J* 5.5 Hz), 6.28 (dd, 1H, C^5H, *J* 2.2 Hz and *J* 5.5 Hz), 4.57 (t, 1H, C^3H_2, *J* 9.9 Hz), 4.41 (dd, 1H, C^3H_2, *J* 3.3 Hz and *J* 9.8 Hz), 4.0 (ddd, 1H, $C^{6a}H$, *J* 2.2 Hz, *J* 3.1 Hz, and *J* 9.4 Hz), 3.30 (ddd, 1H, $C^{3a}H$, *J* 3.5 Hz, *J* 7.4, and *J* 10.0 Hz). ^{13}C NMR spectrum was identical to the published one[16]. IR, ν/cm^{-1}: 3078, 2980, 1770, 1714, 1585, 1334, 1174, 1029, 1008, 947. Found (%): C, 60.59; H, 4.17. Calc. for $C_7H_6O_3$ (%): C, 60.87; H, 4.35 %.