A general strategy for the diastereoselective synthesis of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans.

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EXPERIMENTAL DATA

LEWIS ACID PROMOTED CYCLISATION

Kinetic Cyclisation Protocol – as illustrated by the synthesis of **12**

A solution of *trans* alcohol (**11**) (96 mg, 0.51 mmol) in DCM (7 mL) was added to a mixture of *p*-methoxybenzaldehyde dimethyl acetal (**10**) (220 μ L, 1.30 mmol) and TMSOTf (110 μ L, 0.60 mmol) in DCM (13 mL) at -40 $^{\circ}$ C. The resulting mixture was stirred for 4 hours at -40 $^{\circ}$ C before being quenched with methanol and then sat. NaHCO_3 solution (15 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with sat. aq. NaHSO_3 solution (5 x 15 mL), to scavenge any anisaldehyde and with brine (3 x 15 mL), dried over MgSO_4 and concentrated. Purification by flash chromatography (ether:petrol:triethylamine 25:75:1), afforded the expected *exo-endo* furofuryl acetal (**12**) (88 mg, 53%).

Thermodynamic Cyclisation procedure as illustrated by the synthesis of **13**

A solution of *trans* alcohol (**11**) (105 mg, 0.60 mmol) in DCM (7 mL) was added to a mixture of *p*-methoxybenzaldehyde dimethyl acetal (**10**) (240 μ L, 1.42 mmol) and TMSOTf (120 μ L, 0.65 mmol) in DCM (13 mL). The resulting mixture was stirred for 16 hours at -40 $^{\circ}$ C then for 3 hours at room temperature before being quenched by methanol, stirred for 3 more hours and then treated with sat. NaHCO_3 solution (15 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with sat. aq. NaHSO_3 solution (5 x 15 mL), to scavenge any anisaldehyde and with brine (3 x 15 mL), dried over MgSO_4 and concentrated. Purification by flash chromatography (ether:petrol:triethylamine 25:75:1) afforded a mixture of *exo:endo* acetals (**13**) in a 2:1 ratio (88 mg, $y=45\%$).

4-exo-Methoxy-6-endo-(4'-methoxyphenyl)-2-endo-phenyl-3,7-dioxabicyclo[3.3.0]octane (**8**) Found C = 73.41%, H = 6.62% C₂₀H₂₂O₄ requires C = 73.6%, H = 6.74%. $\nu_{\max}$ (cm⁻¹) 2880, 1580, 1320, 1065 cm⁻¹; δ_{H} (500 MHz): 7.45-7.39 (m, 4H, Ph), 7.35-7.30 (3H, m, Ph, Ar), 6.93 (2H, d J 9Hz, Ar), 5.27 (d, J = 6.5Hz, 1H, 2-H), 4.86 (1H, d, J = 6.5Hz, 6-H), 4.54 (1H, s, 4-H), 3.82 (3H, s, 4'-OCH₃), 3.64 (1H, d J = 10Hz, 8-H_{endo}), 3.47 (1H, dd J = 10, 6Hz, 8-H_{exo}), 3.17 (1H, m, 1-H), 3.09 (3H, s, 4-OCH₃), 3.05 (1H, m, 5-H). δ_{C} (125 MHz): 159, 138, 131, 128, 126, 127, 127, 114, 105 (C-4), 83 (C-2), 82 (C-6), 69 (C-8), 56 (C-5), 55 (4'-OCH₃), 54 (C-1), 48 (4-OCH₃). m/z (EI): 326 (30% M⁺), 192 (100), 159, 135, 117, 84.

Figure 1: Selected NOESY correlations for **8** (a = *exo*, b = *endo*)

4-exo-Methoxy-6-exo-(4'-methoxyphenyl)-2-endo-phenyl-3,7-dioxabicyclo[3.3.0]octane (**9**) Found C = 73.14%, H = 6.68% C₂₀H₂₂O₄ requires C = 73.6%, H = 6.74%. $\nu_{\max}$ (cm⁻¹) 2880, 1512, 1234, 1205 cm⁻¹; δ_{H} (500 MHz): 7.3-7.2 (m, 7H, Ph, Ar), 6.84 (2H, d J = 9Hz, Ar), 5.31 (1H, d J = 6Hz, 2-H), 5.04 (1H, s, 4-H), 4.51 (1H, s, 6-H), 3.73 (3H, s, 4'-OCH₃), 3.67 (1H, d J = 9Hz, 8-H_{endo}), 3.33 (3H, s, 4-OCH₃), 3.32 (1H, m, 1-H), 3.22 (1H, dd J = 9, 6Hz, 8-H_{exo}), 2.91 (1H, m, 5-H). δ_{C} (125 MHz): 159, 138, 132, 128, 127, 127, 125, 114, 107 (C-4), 85 (C-6), 79 (C-2), 69 (C-8), 60 (C-5), 55.3 (4'-OCH₃), 54.7 (C-1), 49 (4-OCH₃). m/z (EI): 326 (34%, M⁺), 192, 159, 135, 91, 84(100).

Figure 2: Selected NOESY correlations for **9** (a = *exo*, b = *endo*)

4-*exo*-Methoxy-6-*endo*-(4'-methoxyphenyl)-2-*exo*-phenyl-3,7-dioxabicyclo[3.3.0]octane
(12) $\nu_{\max}$ (cm^{-1}) 2955, 2927, 2854 (CH aromatics); δ_{H} (500 MHz): 7.43-7.32 (7 H, m, aromatics); 6.93 (2 H, d, J = 9 Hz, Ar); 4.95 (1 H, d, J = 7.3 Hz, 6-H); 4.90 (1 H, d, J = 5.6 Hz, 2-H); 4.37 (1 H, d, J = 1.8, 4-H); 4.16 (1 H, d, J = 9.2 Hz, 8- H_{endo}); 3.86-3.82 (4 H, m, 4'- OCH_3 and 8- H_{exo}); 3.17-3.08 (5 H, m, 4- OCH_3 , 1-H and 5-H); δ_{C} (500 MHz): 158.9, 142.5, 130.2, 128.5, 127.6, 127.5, 126.4, 113.7 (aromatics); 108.0 (C-4); 88.1 (C-2); 82.0 (C-6); 71.6 (C-8); 56.3 (C-5); 55.4 (4- OCH_3); 55.2 (4'- OCH_3); 52.6 (C-1); m/z (EI)= 326 (8%) (M^+), 192 (100%); m/z (ES)= 348.9 (MNa^+), 674.9 (2MNa^+); HRMS (ES) found (MNa^+) 349.1397 (calc. 349.1416).

Figure 3: Selected NOESY correlations for **12** (a = *exo*, b = *endo*)

4-*exo*-Methoxy-6-*exo*-(4'-methoxyphenyl)-2-*exo*-phenyl-3,7-dioxabicyclo[3.3.0]octane
(13a): $\nu_{\max}$ (cm^{-1}) 2955, 2835 (CH aromatics); δ_{H} (500 MHz): 7.42-7.29 (7 H, m, aromatics); 6.91 (2 H, d, J = 8.5 Hz, Ar); 5.09 (1 H, s, 4-H); 5.07 (1 H, d, J = 6.4 Hz, 2-H); 4.86 (1 H, d, J = 7.5, 6-H); 4.27 (1 H, dd, J = 6.0, 9.0, 8- H_{exo}); 4.05 (1 H, dd, J = 2.6, 9.1 Hz, 8- H_{endo}); 3.81 (3 H, s, 4'- OCH_3); 3.40 (3 H, s, 4- OCH_3); 3.26-3.20 (1 H, m, 1-H); 2.99 (1 H, t, J = 6.0 Hz, 5-H); δ_{C} (125 MHz): 159.3, 142.4, 133.4, 128.56, 127.7, 127.2, 126.5, 114.0 (aromatics); 108.3 (C-4); 88.4 (C-2); 83.2 (C-6); 72.6 (C-8); 61.2 (C-1); 55.3 (4'- OCH_3); 55.2 (4- OCH_3); 53.0 (C-1); m/z (ES)= 348.9 (MNa^+), 674.9 (2MNa^+); HRMS (ES) found (MNa^+) 349.1407 (calc. 349.1416)

Figure 4: Selected NOESY correlations for **13a** (a = *exo*, b = *endo*)

4-endo-Methoxy-6-exo-(4'-methoxyphenyl)-2-exo-phenyl-3,7-dioxabicyclo[3.3.0]octane (13b): $\nu_{\max}$ (cm⁻¹) 2955, 2835 (CH aromatics); δ_{H} (500 MHz): 7.38-7.26 (7 H, m, aromatics); 6.89 (2 H, d, J = 8.5 Hz, Ar); 5.44 (1 H, d, J = 4 Hz, 6-H); 5.30 (1 H, d, J = 5.8 Hz, 4-H); 4.90 (1 H, d, J = 7.3, 2-H); 4.06 (1 H, dd, J = 6.7, 8.9 Hz, 8-H_{exo}); 3.95 (1 H, dd, J = 4.3, 8.9 Hz, 8-H_{exo}); 3.80 (3 H, s, 4'-OCH₃); 3.51 (3 H, s, 4-OCH₃); 3.41-3.39 (1 H, m, 5-H); 3.15-3.00 (1 H, m, 1-H); δ_{C} (500 MHz): 158.8, 137.7, 134.4, 129.3, 128.6, 128.0, 127.2, 126.1 (aromatics); 104.7 (C-4); 83.1 (C-2); 79.0 (C-6); 70.2 (C-8); 58.1 (C-5); 55.7 (4-OCH₃); 55.3 (4'-OCH₃); 55.1 (C-1); m/z (ES) = 348.9 (MNa⁺), 674.9 (2MNa⁺); HRMS (ES) found (MNa⁺) 349.1449 (calc. 349.1416).

Figure 5: Selected NOESY correlations for **13b** (a = *exo*, b = *endo*)

Reduction of the Glycosidic Acetal

Method A – Kinetic Control

Triethylsilane (10 eq) was slowly added to a solution of acetal (1 eq), in DCM at -78 °C under argon. BF₃·OEt₂ (1.7 eq) was then added at -78 °C and the colour of the solution turned to dark red. The resulting solution was stirred for 1 min at -78 °C under argon

before being poured into a saturated solution of sodium bicarbonate. The resulting mixture was filtered through a Whatman PTFE filter tube and concentrated. The residue was then purified by flash chromatography (ether:petrol:triethylamine 25:75:1) to afford the desired furofuran.

Method B – Thermodynamic Control

Triethylsilane (10 eq) was slowly added to a solution of acetal (1 eq), in DCM at 0 °C under argon. $\text{BF}_3 \cdot \text{OEt}_2$ (1.7 eq) was then added at 0 °C and the resulting solution was stirred for 1 hour at 0 °C under argon before being poured into a saturated solution of sodium bicarbonate. The resulting mixture was filtered through a Whatman PTFE filter tube and concentrated. The residue was then purified by flash chromatography (ether:petrol:triethylamine 25:75:1) to afford the desired furofuran.

2-exo-Phenyl-6-endo-4'-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane (18)

ν_{max} (cm^{-1}) 2961, 2928, 2872, 1455, 1190; δ_{H} (500 MHz $\text{CDCl}_3 + \text{C}_6\text{D}_6$): 7.32-7.19 (7 H, m, aromatics); 6.83 (2 H, d, $J = 8.7$ Hz, Ar); 4.67 (1 H, d, $J = 5.9$ Hz, 6-H); 4.44 (1 H, d, $J = 6.8$ Hz, 2-H); 4.03 (1 H, d, $J = 9.4$ Hz, 8- H_{endo}); 3.78 (1 H, t, $J = 8.8$ Hz, 4- H_{exo}); 3.64 (1 H, dd, $J = 6.2, 9.4$ Hz, 8- H_{exo}); 3.57 (3 H, s, 4'- OCH_3); 3.38-3.30 (1 H, m, 4- H_{endo}); 3.10-3.03 (2 H, m, 5-H); 2.73-2.68 (1 H, m, 1-H); δ_{C} (125 MHz): 158.6, 141.3, 130.4, 128.6, 127.8, 126.7, 126.0, 113.7 (aromatics); 87.7 (C-6); 82.0 (C-2); 71.1, 69.8 (C-4, C-8); 55.2 (4'- OCH_3); 54.7 (C-1); 50.2 (C-5); m/z (ES^+): 319.1 (MNa^+); 731 (2MNa^+); HRMS (ES) found (MNa^+) 319.1322 (calc. 319.1310).

Figure 6: Selected NOESY correlations for **18** (a = exo, b = endo)

2-exo-Phenyl-6-exo-4'-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane (19)

$\nu_{\max}$ (cm^{-1}) 2957, 2929, 2855, 1512, 1247, 1033; δ_{H} (500 MHz): 7.37-7.27 (7 H, m, aromatics); 6.89 (2 H, d, 8.8 Hz, Ar); 4.83 (1 H, d, J = 4.9 Hz, 2-H); 4.77 (1 H, d, J = 4.9 Hz, 6-H); 3.80 (3 H, s, 4'-OCH₃); 4.29-4.24 (2 H, m, 4-H_{endo}, 8-H_{endo}); 3.93-3.89 (2 H, m, 4-H_{exo}, 8-H_{exo}); 3.16-3.07 (2 H, m, 1-H, 5-H); δ_{C} (125 MHz): 159.2, 141.2, 133.0, 128.6, 127.6, 127.4, 125.9, 113.9 (aromatics); 85.9 (C-2); 85.6 (C-6); 71.85, 71.80 (C-4, C-8); 55.3 (4'-OCH₃); 54.4, 54.2 (C-5, C-1); m/z (ES⁺): 319.1 (MNa⁺); 731 (2MNa⁺); HRMS (ES) found (MNa⁺) 319.1306 (calc. 319.1310).

Figure 7: Selected NOESY correlations for **19** (a = *exo*, b = *endo*)

2-endo-Phenyl-6-endo-4'-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane (20)

$\nu_{\max}$ (cm^{-1}) 2958, 2931, 2855, 1513, 1248; δ_{H} (500 MHz): 7.40-7.29 (7 H, m, aromatics); 6.92 (2 H, d, J = 9 Hz, Ar); 4.97 (1 H, d, J = 5.7 Hz, 2-H); 4.93 (1 H, d, J = 5.9 Hz, 6-H); 3.83 (3 H, s, 4'-OCH₃); 3.13 (1 H, dd, J = 2.3, 9.6 Hz, 4-H_{endo}); 3.67 (1 H, dd, J = 2.2, 9.4 Hz, 8-H_{endo}); 3.55 (1 H, dd, J = 7.3, 9.6 Hz, 4-H_{exo}); 3.53 (1 H, dd, J = 7.3, 9.4 Hz, 8-H_{exo}); 3.29-3.08 (2 H, m, 1-H, 5-H); δ_{C} (125 MHz): 138.9, 130.6, 128.6, 128.3, 127.6, 126.3, 113.7 (aromatics); 84.3 (C-2); 84.0 (C-6); 68.85 (C-4); 68.75 (C-8); 55.3 (4'-OCH₃); 49.6 (C-5); 49.5 (C-1); m/z (ES⁺): 319.1 (MNa⁺); 731 (2MNa⁺); HRMS (ES) found (MNa⁺) 319.1317 (calc. 319.1310).

Figure 8: Selected NOESY correlations for **20** (a = *exo*, b = *endo*)

2-endo-Phenyl-6-exo-4'-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane (21)

$\nu_{\max}$ (cm^{-1}) 2957, 2871, 2835, 1513, 1248, 1055; δ_{H} (500 MHz): 7.38-7.29 (7 H, m, aromatics); 6.90 (2 H, d, J = 9 Hz, Ar); 4.93 (1 H, d, J = 5.9 Hz, 2-H); 4.44 (1 H, d, J = 7.25 Hz, 6-H); 4.13 (1 H, d, J = 9.5 Hz, 4- H_{endo}); 3.88-3.80 (2 H, m, 8- H_{exo} , 4- H_{exo}); 3.81 (3 H, s, 4'- OCH_3); 3.42-3.38 (1 H, m, 1-H); 3.26 (1 H, d, J = 9 Hz, 8- H_{endo}); 2.95-2.90 (1 H, m, 5-H); δ_{C} (125 MHz): 158.3, 138.4, 133.1, 128.6, 127.5, 127.1, 125.6, 113.9 (aromatics); 87.5 (C-6); 82.2 (C-2); 70.9 (C-4); 69.7 (C-8); 55.3 (4'- OCH_3); 54.5 (C-5); 50.1 (C-1); m/z (ES^+): 319.1 (MNa^+); 731 (2MNa^+); HRMS (ES) found (MNa^+) 319.1296 (calc. 319.1310).

Figure 9: Selected NOESY correlations for **21** (a = *exo*, b = *endo*)

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