Stereoselective synthesis of bicyclic lactones by annelation with functionalised orthoesters.

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Electronic Supporting Information.

Instrumentation and procedures.

Routine nuclear magnetic resonance (NMR) spectra were recorded on a VARIAN GEMINI-300 (^{1}H 300MHz and ^{13}C 75MHz). ^{1}H NMR chemical shifts (δ_H) are reported in ppm downfield from internal tetramethyl silane (TMS). ^{13}C NMR spectra were recorded using $CDCl_3$ as the internal standard. Splitting patterns in ^{1}H spectra are designed as s, singlet; d, doublet; t, triplet; b, broad and m, multiplet.

Low resolution mass spectra (EI) were recorded using VARIAN MATT-44 and FINNIGAN MAT-TSQ 70 spectrometers.

Infra-red spectra (IR) were taken as thin films on a SHIMADZU spectrometer and recorded in cm^{-1}.

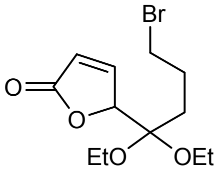
Thin layer chromatography (TLC) was performed on MERCK silica gel 60 F_{254} aluminum-backed plates. The plates were visualised using 254 nm UV light and developed using an alkaline KMnO4 solution (1% $KMnO_4$/ 5% Na_2CO_3). Flash chromatography was performed using Rocc silica gel 60 (40-63 μm) under pressure with the stated solvents.

All solvents were routinely distilled prior to use. Reactions were performed under a dry, inert atmosphere of argon unless stated otherwise.

The following abbreviations are used: rt, room temperature; hr, hour; min, minute; mmol, millimole; mol, mole; mg, milligram; g, gram; mL, milliliter, μL, microliter.

Typical experimental procedures.

Condensation step: Preparation of 7c

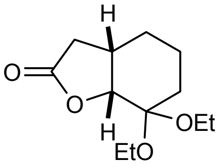


7c

To a suspension of $ZnCl_2$ (116 mg, 0.85 mmol, 0.7 eq.) in CH_2Cl_2 (5 mL) at -78ºC are sequentially added with stirring orthoester **6c** (480 mg, 1.82 mmol, 1.5 eq.) and furan derivative **5a** (0.2 mL, 1.2 mmol, 1 eq.). The mixture is slowly warmed to rt and monitored by TLC. Upon completion, the reaction is quenched by adding 5 mL of a sat. $NaHCO_3$ solution. The aqueous layer is repeatedly extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by rapid flash chromatography (silica, PE/AcOEt 4:1) afforded **7c** (385 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 5.7, 1.8 Hz, 1 H), 6.126 (dd, *J* = 5.7, 2.1 Hz, 1 H), 5.08 (br s, 1 H), 3.61-3.22 (m, 6 H), 1.92-1.66 (m, 4 H), 1.24-1.11 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 154.5, 122.0, 100.8, 84.0, 56.8, 56.7, 33.9, 27.2, 21.1, 15.5, 15.1 ; IR(cm^{-1}): 2975, 2362, 1759, 1732, 1596, 1443, 1375; MS (APCI+ev): *m/z* (%): 262 (100) $[M\text{-}OEt]^{+\cdot}$, 233 (50), 227 (25), 181 (20), 153 (20), 111 (15); HRMS (ES) calcd. for $C_{12}H_{19}O_4NaBr$ (M+Na): 329.0364; found 329.0363.

Cyclisation step: Preparation of 8b



8b

To a solution of **7c** (200 mg, 0.65 mmol, 1 eq.) in benzene (6.5 mL) were sequentially added in one portion TTMSS (0.31 mL, 1.0 mmol, 1.5 eq) and AIBN (16 mg, 0.1 mmol, 0.15 eq.) and the mixture was refluxed for 2 hours. After cooling, removal of the solvent under reduced pressure and flash chromatography of the residue (silica, PE/AcOEt 6:1) afforded **8b** (130 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (d, *J* = 3.9 Hz, 1 H), 3.60-3.45 (m, 4 H), 2.60-5.52 (m, 2 H), 2.34-2.28 (m, 1 H), 1.82-1.40 (m, 6 H), 1.23-1.17 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 98.1, 79.9, 55.5, 55.4, 36.8, 35.0, 28.5, 26.6, 19.2, 15.3, 15.2; IR(cm^{-1}): 2972, 2927, 2854, 1786, 1662; MS (APCI+ev): *m/z* (%): 183 (100) $[M\text{-}OEt]^{+\cdot}$, 169 (25), 155 (35), 137 (15), 123 (15), 109 (20), 95 (30), 81 (12); Elemental analysis calcd. for $C_{12}H_{20}O_4$: C 63,18%; H 8.84%; found C 62,74%; H 8,86%.