Supporting Information

Synthesis of Acetal Protected Building Blocks using Flow Chemistry with Flow I.R. Analysis: Preparation of Butane-2,3-Diacetal Tartrates

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General Considerations

Unless specified, reagents were obtained from commercial sources and used without further purification. Solvents were obtained from Fischer Scientific and distilled before use. The petroleum ether used was the 40-60 boiling fraction. THF was dried over calcium hydride and $LiAlH_4$ with triphenylmethane as an indicator and distilled under an atmosphere of dry argon. CH_2Cl_2 and MeCN were dried over calcium hydride and distilled under an atmosphere of dry argon. Quadrapure sulfonic acid resin (QP-SA) and Quadrapure benzylamine resin (QP-BZA) were obtained from Reaxa Ltd and used without further purification

^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX-400 (400 MHz) spectrometer with residual $CHCl_3$ (7.26 ppm) as the internal reference. ^{13}C-NMR spectra were recorded using a Bruker Avance DPX-400 (100 MHz) spectrometer using the central resonance of $CDCl_3$ as the internal reference (77.0 ppm). Additionally, DEPT-135 and COSY experiments were used to assign the signals. Coupling constants are quoted to the nearest 0.1 Hz. Multiplicities are abbreviated as follows: s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, br – broad, dd – doublet of doublets, etc.

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters in parentheses refer to the relative absorbency of the peak: w – weak (< 40% of the most intense peak), m – medium (40-70% of the most intense peak), s – strong (>70% of the most intense peak).

Optical rotations were measured on a Perkin-Elmer Model 343 digital polarimeter at 25 °C using a sodium lamp (589 nm) as the light source over a path length of 10 cm. $[a]_D^{25}$ values are reported in units of 10^{-1} cm^{-1} g^{-1} at concentration (c) in g per 100 ml.

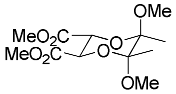
High resolution mass spectrometry was carried out on a Waters Micromass LCT Premier spectrometer using time of flight with positive electrospray ionisation. All measured masses were within +/- 5 ppm of the calculated value.

Elemental analyses within a tolerance of +/- 0.3 ppm of the theoretical values were determined in the microanalytical laboratories at the Departmental of Chemistry, University of Cambridge.

Column chromatography was carried out on a Biotage SP1 Flash Purification System using prepacked SNAP cartridges containing 10 g or 25 g of silica.

All flow chemistry experiments were performed on the Uniqsis FlowSyn with a 100 psi BPR attached to the output of the reactor.

(2*R*,3*R*,5*R*,6*R*)-dimethyl 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate 1[1]



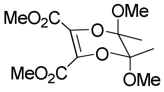
BATCH PROCEDURE

Camphor sulfonic acid (2.3 g, 10 mmol), dimethyl-L-tartrate (17.8 g, 100 mmol), butadione (10.5 mL, 120 mmol) and trimethyl orthoformate (32.5 mL, 300 mmol) were dissolved in MeOH (300 mL) and heated at reflux for 14 h. Sodium bicarbonate (12.2 g) was then added and the resulting suspension stirred for 1 h at room temperature. The slurry was filtered through a sinter and the filtrate evaporated *in vacuo*. The residue was taken up in Et_2O (40 mL), washed with H_2O (2 × 100 mL) and brine (100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield an orange solid. The crude material was purified by recrystallisation from Et_2O to give the title product **1** as a white solid (20.5 g, 70%)

FLOW PROCEDURE

Solutions of dimethyl-L-tartrate (30 g, 170 mmol) and trimethyl orthoformate (55.8 mL, 510 mmol) dissolved in MeOH (30 mL) and butadione (16.7 mL, 190 mmol) and CSA (3.95 g, 17 mmol) dissolved in MeOH (60 mL) were pumped at 0.3 mL/min (0.15 mL/min per pump) into a T-piece and through a 14 mL PTFE coil reactor at 90 °C. The crude solution was passed through a 15 × 150 mm Omnifit® column filled with QP-BZA resin (25 g) and then through a second 15 × 150 mm Omnifit® column containing $PS\text{-}NMe_3IO_4$ **5** (17 g). The output of the reactor was collected until no further product was observed and the solvent removed *in vacuo* to yield the product **1** as a crystalline off-white solid (38 g, 75%). $[\alpha]_D^{25}$ -138.3 (*c* 1.0 in $CHCl_3$); (Found: C, 49.35; H, 6.90. $C_{12}H_{20}O_8$ requires C, 49.31; H, 6.90%); HRMS (+ES): *m/z* Calcd for $C_{12}H_{20}NaO_8$ (MNa^+): 315.1056. Found: 315.1035; υ_{max}/cm^{-1} (neat) 2991w (C-H), 2949w (C-H), 1736s (C=O), 1110s (C-O), 1023s (C-O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 4.53 (2H, s, 2 × C*H*), 3.77 (6H, s, 2 × CO_2CH_3), 3.32 (6H, s, 2 × OCH_3), 1.35 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 168.4 (2 × *C*O), 99.2 (2 × *C*), 68.8 (2 × *C*H), 52.5 (2 × OCH_3), 48.5 (2 × OCH_3), 17.3 (2 × CH_3).

(5*R*,6*R*)-dimethyl 5,6-dimethoxy-5,6-dimethyl-5,6-dihydro-1,4-dioxine-2,3-dicarboxylate 2[1]



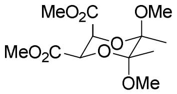
BATCH PROCEDURE

*n*BuLi (1.6 M in hexanes, 5.2 mL) was added dropwise to a stirred solution of diisopropylamine (1.26 mL, 8.91 mmol) in THF (10 mL) at -78 °C under a nitrogen atmosphere. The solution was warmed to 0 °C over 10 min and then re-cooled to -78 °C. A solution of BDA protected tartrate **1** (1.10 g, 3.76 mmol) in THF (10 mL) was added dropwise *via* a cannula over 10 min and the solution stirred for 30 min. A solution of iodine (1.05 g, 4.13 mmol) in THF (10 mL) was then added dropwise *via* a cannula over 10 min and the solution warmed to 0 °C and stirred for a further 30 min. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and the slurry allowed to warm to room temperature. The reaction was diluted with Et_2O (20 mL) and H_2O (5 mL) and the organic phase washed with aqueous sodium thiosulfate (10 mL) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a yellow residue which was purified by column chromatography (SP1, 60: 40 Et_2O: Pet ether, 20 column volumes on 25 g silica, 25 mL/min, R_f 0.3) to yield the desired product **2** as a yellow crystalline solid (0.65 g, 60%).

FLOW PROCEDURE

n-BuLi (1.6 M in hexanes, 1.38 mL, 2.2 mmol) was added dropwise to a stirred solution of diisopropylamine (0.35 mL, 2.5 mmol) in THF (3 mL) at -78 °C. A solution of BDA tartrate **1** (292 mg, 1.0 mmol) in THF (3 mL) was then added dropwise over 10 min. A second solution of iodine (254 mg, 1 mmol) in THF (8 mL) was prepared and also held at -78 C. The two stock solutions were pumped at 1.0 mL/min (0.5 mL/min per pump), mixed in a T-piece and allowed to warm to RT through a 14 mL PTFE coil. The crude solution was passed through a 10 × 100 mm Omnifit® column packed with QPSA resin (1 g) and then through a second 10 × 100 mm Omnifit® column containing PS-$(NMe_3)_2S_2O_3$ **6** (2 g) and a short plug of silica gel (0.5 g). The output of the reactor was collected until no further product was observed by LCMS and the solvent removed *in vacuo* to yield the product as pale yellow needles (188 mg, 65%). $[\alpha]_D^{25}$ -293 (*c* 1.0 in $CHCl_3$); (Found: C, 49.94; H, 6.27. $C_{12}H_{18}O_8$ requires C, 49.65; H, 6.25%); HRMS (+ES): *m/z* Calcd for $C_{12}H_{18}NaO_8$ (MNa^+): 313.0899. Found: 313.0922; υ_{max}/cm^{-1} (neat) 2960w (C-H), 1733m (C=O), 1648m (C=C), 1133s (C-O), 1090s (C-O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 3.76 (6H, s, 2 × CO_2CH_3), 3.31 (6H, s, 2 × OCH_3), 1.49 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 162.2 (2 × *C*O), 130.3 (2 × *C*), 98.2 (2 × *C*H), 51.8 (2 × O*C*H_3), 48.8 (2 × O*C*H_3), 16.1 (2 × *C*H_3).

(2*R*,3*S*,5*R*,6*R*)-dimethyl 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate 3[1]



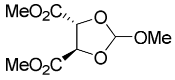
PROCEDURE WITH H-CUBE®

BDA protected oxidised tartrate **2** (290 mg, 1.0 mmol) was dissolved in MeOH (5 mL) and pumped at a flow rate of 1.0 mL/min through a 5% Rh/Al_2O_3 cartridge installed in the H-Cube® flow hydrogenation reactor. The solution was recycled for 4 h at 60 bar of H_2 and 40 °C. After this time the product was pumped out and the reactor was flushed with MeOH (5 mL). Evaporation of the solvent *in vacuo* yielded BDA protected *meso* tartrate **3** as a white solid (292 mg, 100%).

PROCEDURE WITH H-CUBE MIDI™

BDA protected oxidised tartrate **2** (3.78g, 13.0 mmol) was dissolved in MeOH (30 mL) and pumped at a flow rate of 5 mL/min through a 5% Rh/Al_2O_3 cartridge installed in the H-Cube Midi™ flow hydrogenation reactor. The solution was recycled for 2 h at 60 bar of H_2 and 40 °C. After this time the product was pumped out and the reactor was flushed with MeOH (30 mL). Evaporation of the solvent *in vacuo* yielded BDA protected *meso* tartrate **3** as a white solid (3.80 g, 100%). $[\alpha]_D^{25}$ -95.5 (*c* 0.66 in $CHCl_3$); HRMS (+ES): *m/z* Calcd for $C_{12}H_{20}NaO_8$ (MNa^+): 315.1056. Found: 315.1074; υ_{max}/cm^{-1} (neat) 2954w (C-H), 1770m (C=O), 1736m (C=O), 1140s (C-O), 1034s (C-O);. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 4.69 (1H, d, *J* =3.8 Hz, C*H*), 4.50 (1H, d, *J* =3.8 Hz, C*H*), 3.77 (3H, s, CO_2CH_3), 3.75 (3H, s, CO_2CH_3), 3.30 (3H, s, $COCH_3$), 3.21 (3H, s, $COCH_3$), 1.38 (3H, s, CCH_3), 1.33 (3H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 169.6 (*C*O), 168.8 (*C*O), 100.4 (*C*), 99.3 (*C*), 69.1 (*C*H), 66.1 (*C*H), 52.1 (CO_2CH_3), 51.9 (CO_2CH_3), 50.1 ($COCH_3$), 48.4 ($COCH_3$), 17.8 (CCH_3), 17.3 (CCH_3).

(4*R*,5*R*)-dimethyl 2-methoxy-1,3-dioxolane-4,5-dicarboxylate 4



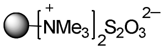
Dimethyl-L-tartrate (178 mg, 1 mmol) and trimethyl orthoformate (0.22 mL, 2 mmol) were dissolved in MeOH (1mL) and butadione (100 µL, 1.2 mmol) was dissolved in MeCN (1 mL). The two solutions were pumped at 0.14 mL/min (0.07 mL/min per pump) over a 10 × 100 mm Omnifit® column containing QP-SA resin (1 g) held at 60 °C. After collection of the output the solvent was removed *in vacuo* to yield orthoester **4** as a yellow oil (202 mg, 83%). $[\alpha]_D^{25}$ -4.2 (*c* 1.0 in $CHCl_3$); HRMS (+ES): *m/z* Calcd for $C_8H_{12}NaO_7$ (MNa^+): 243.0481. Found: 243.0472; υ_{max}/cm^{-1} (neat) 2957w (C-H), 1745s (C=O), 1129s (C-O), 1081s (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H = 5.97 (1H, s,

O_2C*H*O), 5.02 (1H, d, *J* = 4.2 Hz, C*H*), 4.72 (1H, d, *J* = 4.2 Hz, C*H*), 3.81 (3H, s, CO_2C*H_3*), 3.79 (3H, s, CO_2C*H_3*), 3.36 (3H, s, OC*H_3*); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 169.3 (2 × *C*), 117.8 (O_2*C*HO), 76.0 (*C*H), 75.8 (*C*H), 52.9 (CO_2*C*H_3), 52.9 (CO_2*C*H_3), 52.1 (O*C*H_3);

Polymer supported periodate 5[2]

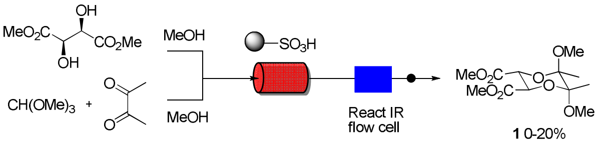
Amberlite IRA 900, chloride form (25 g, 100 mmol) was added to a solution of sodium metaperiodate (20 g, 94 mmol) in H_2O (200 mL). The mixture was agitated at 250 rpm for 18 h using an orbital shaker and then filtered. The resin was then added to a further solution of sodium metaperiodate (20 g, 94 mmol) in H_2O (200 mL) and shaken for a further 24 h. The reaction was filtered and the resin washed with H_2O (600 mL), THF (200 mL) and Et_2O (200 mL) and dried *in vacuo* to yield the desired product **5** (28 g, 2.0 mmol/g). (Found: Cl^-, 0.00. PS-IO_4 requires Cl^-, 0.00)

Polymer supported thiosulfate 6[3]



Amberlyst A900, chloride form (11 g, 46.4 mmol) was added to a solution of sodium thiosulfate (36 g, 230 mmol) in H_2O (200 mL) and the mixture agitated at 250 rpm for 16 h using an orbital shaker. The reaction was filtered, the resin washed with H_2O (100 mL), THF (200 mL) and Et_2O (200 mL) and dried *in vacuo* to give the desired product **6** (8.3 g, 3.4 mmol/g). (Found: N, 4.81. PS-$NMe_3S_2O_3$ requires N, 4.76).

React IR Experiments.



A Mettler Toledo[4] ReactIR 45m equipped with a 1.5m AgX fibre optic cable and a 9.5mm DiComp (Diamond) probe mounted in a custom PTFE flow cell was attached in-line to the flow reactor with standard Omnifit® connectors. Taking background spectra of the reagents using the ReactIR iC IR™ software revealed appropriate areas for monitoring peak intensity (Fig 1).

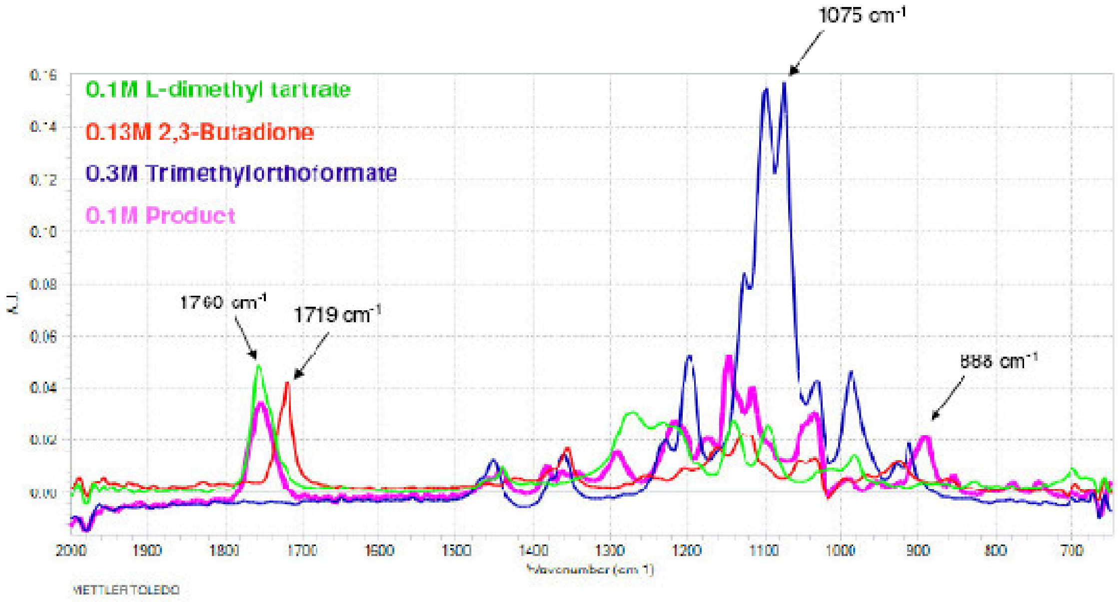


Fig 1. Reference spectra of reagents

As the reaction is flowed through the cell an IR spectrum is collected every 15 seconds. Spectra are displayed in realtime, providing dynamic information when the spectra are overlayed (Fig 2).

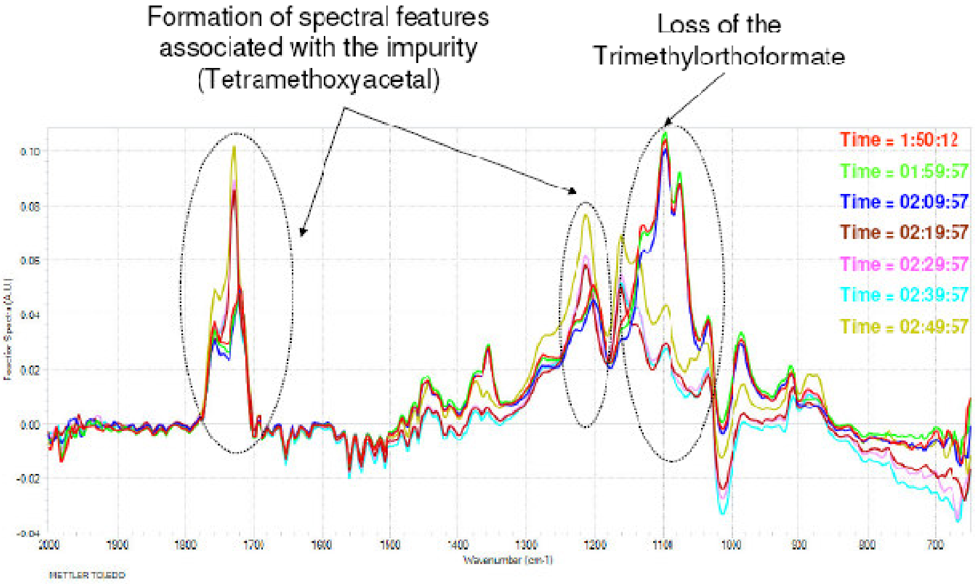


Fig 2. Second derivative spectrum

Integration of selected peaks can provide a second derivative spectrum, showing the reaction profile over time (Fig 3). In our case, information was gained in terms of the starting material, dimethyl-L-tartrate not being consumed under the reaction conditions but rather the butanedione and trimethyl orthoformate reacting to form a new species, as described in the paper.

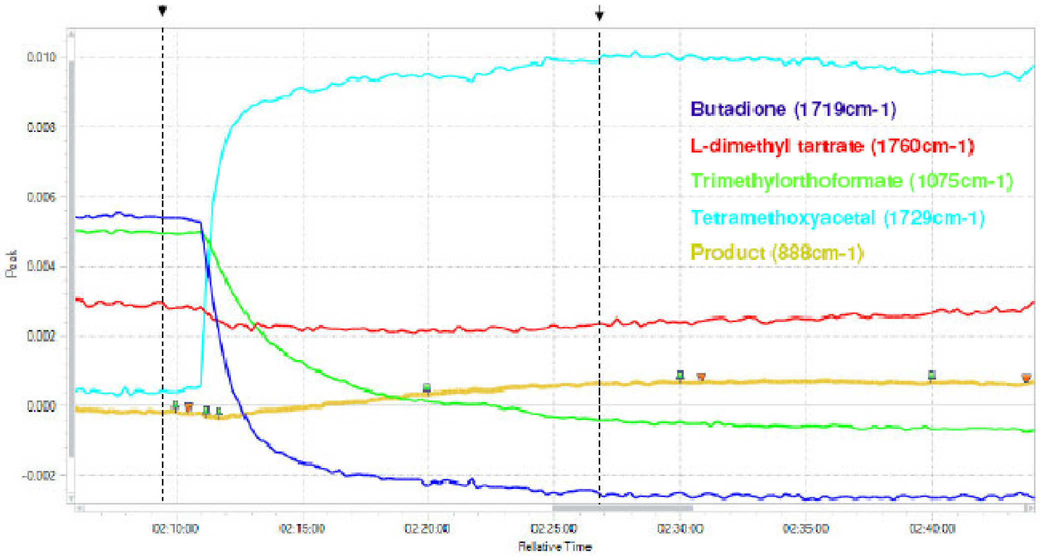


Fig 3 Relative trends from peak height analysis

References

1. D. F. Dixon, A. C. Foster and S. V. Ley, *Can. J. Chem.*, 2001, **79**, 1668-1680.
2. A modified procedure from C. R. Harrison and P. Hodge, *J. Chem. Soc.,Perkin Trans.1*, 1982, 509-511.
3. A modified procedure from J. J. Parlow, B. L. Case and M. S. South, *Tetrahedron*, 1999, **55**, 6785-6796.
4. www.mettlertoledo.com