The continuous flow synthesis of butane-2,3-diacetal protected building blocks using microreactors†

Catherine F. Carter,[a] Ian R. Baxendale,[a] John B. J. Pavey[b] and Steven V. Ley*[a]

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The continuous flow synthesis of butane-2,3-diacetal protected derivatives has been achieved using commercially available flow chemistry microreactors in concert with solid supported reagents and scavengers to provide in-line purification systems. The BDA protected products are all obtained in superior yield to the corresponding batch processes.

Introduction

The synthesis of complex natural products has reached a high level of sophistication; nevertheless, it is not without its problems, not least of which is the necessary preparation of the required coupling partners and building blocks on scale.[1] More often than not, the scaling process can be frustrated by lack of consistency and consequently this leads to the need for constant route optimisation and redevelopment. In addition, the scale-up procedure involves many repetitive experiments where the knowledge gained is minimal yet the skilled workforce commitment is substantial. This arises due to the multiple problems of down-stream processing and unit work-up operations such as solvent handling and disposal, combined with losses that accrue *via* recrystallisation, chromatography, extractions and aqueous washes. It is our view that many of these labour intensive events are best relegated to a machine assisted synthesis approach whereby skilled operator time is released for improved molecular design and better synthetic planning.[2,3]

In our work we have made extensive use of 1,2-diacetals,[4,5] and in particular butane-2,3-diacetals (BDA), to effect selective vicinal diol and α-hydroxyacid protection,[6–8] diastereoselective and facially selective processes,[9–12] and to prepare a whole variety of chiral building blocks for natural product synthesis programmes (Fig. 1).[13–16] Here, we show how key members of this series can be assembled successfully with high reproducibility using flow chemistry methods and associated continuous processing techniques.

Results

BDA protected tartrates

We have recently reported the synthesis of butane-2,3-diacetal tartrates **1–3** in flow, assisted by the use of an in-line IR flow

[a]*Department of Chemistry, Innovative Technnology Centre, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: svl1000@cam.ac.uk*
[b]*AstraZeneca, Bakewell Road, Loughborough, Leics, LE11 5RH*
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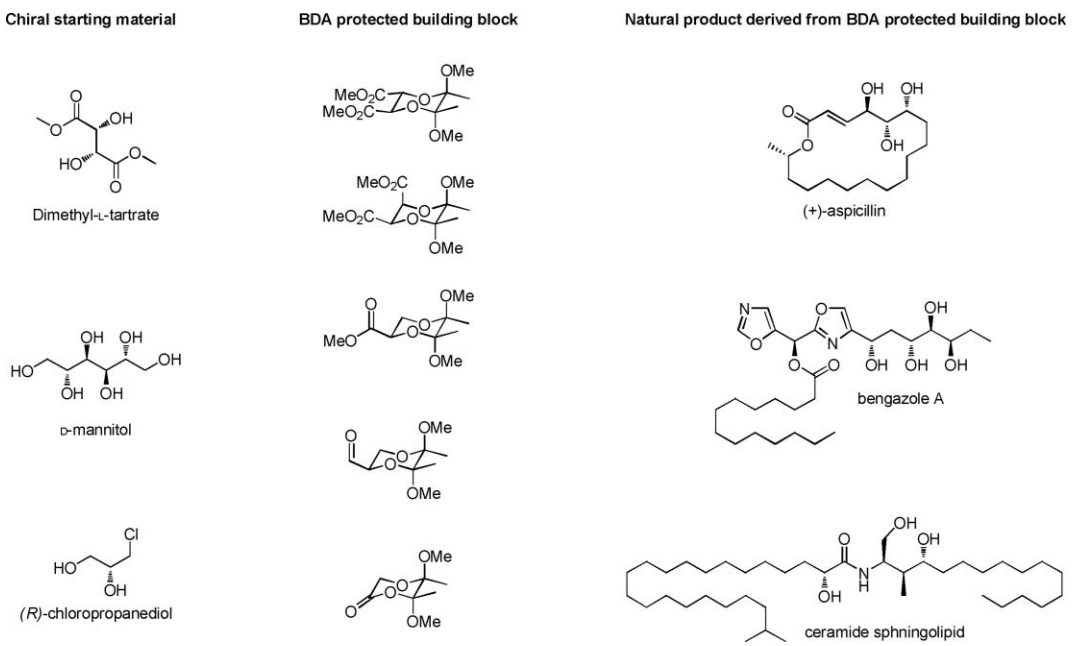
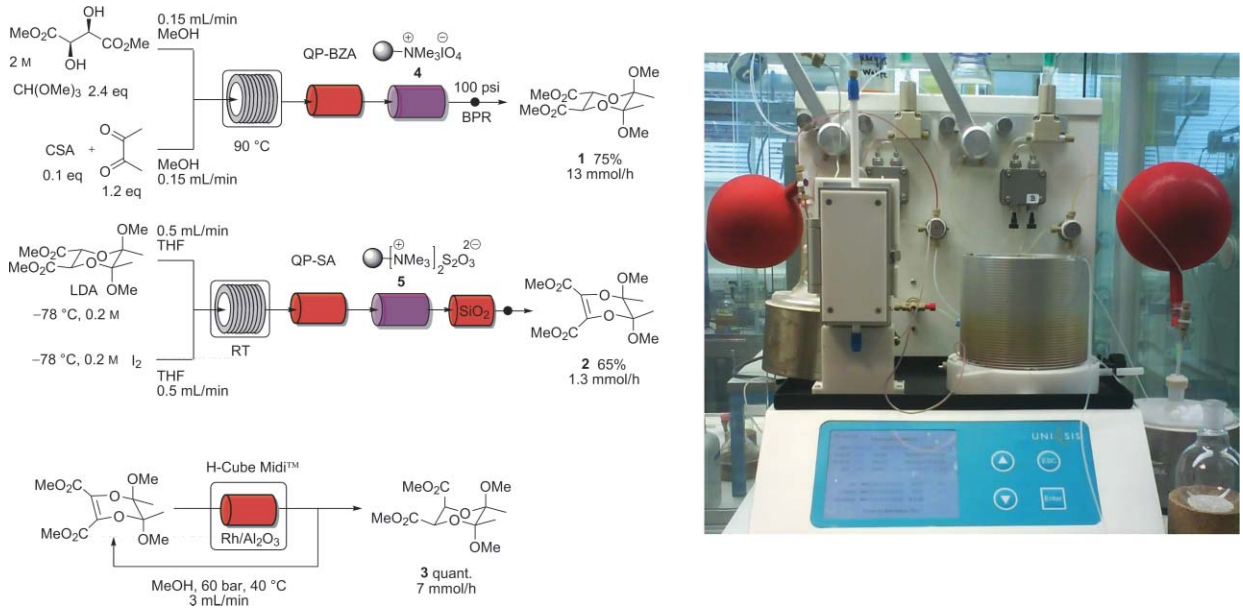


Fig. 1 Butane-2,3-diacetals in synthesis.



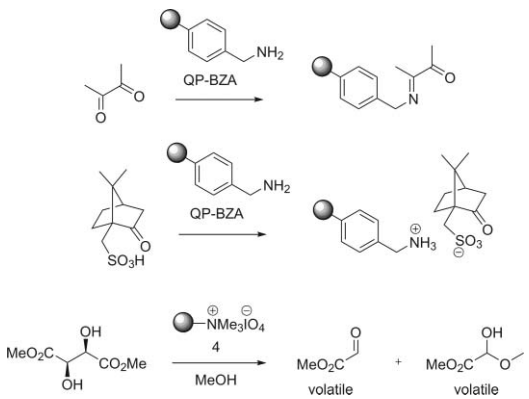
Scheme 1 Flow syntheses of butane-2,3-diacetal tartrates using the Uniqsis FlowSyn.

cell for reaction monitoring.[17] Three tartrate building blocks were successfully synthesised and purified in-line using commercially available flow chemistry equipment, resulting in higher yields than the corresponding batch processes (Scheme 1).

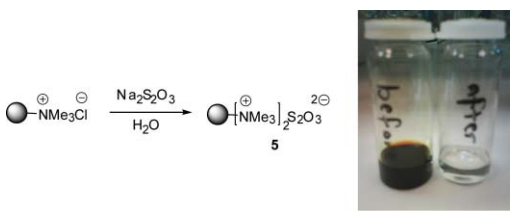
The full details of these syntheses and additional new work is further reported here. All experiments were performed using the Uniqsis FlowSyn platform.[18] For our purposes the system was operated with two HPLC pumps, a 14 mL PTFE reactor coil and OmniFit® columns packed with solid-supported reagents and scavengers (typically 10 × 150 mm columns, see experimental section for full details), with a 100 psi back pressure regulator fitted at the output flow stream.

A particularly successful feature of the BDA tartrate procedures (Scheme 1) was the use of in-line solid-supported reagents[19] to purify the reaction stream. BDA protected tartrate **1** was synthesised on a 38 g scale by passing stock solutions of the reagents in MeOH through a reactor coil held at 90 °C. As previously described, the in-line purification consisted of firstly an OmniFit® column filled with benzylamine resin (QP-BZA) followed by a second column containing periodate resin **4**.[20] As shown in Scheme 2, when the crude reaction mixture enters the first column the excess butanedione becomes immobilised as the imine species and the camphor sulfonic acid (CSA) catalyst is sequestered as an ion pair salt. In order to remove unreacted dimethyl-L-tartrate, the supported periodate performs a rapid glycol cleavage leading to volatile byproducts. On exiting these columns, the reaction stream contains pure product **1**.

For the synthesis of alkene **2**, a polymer-supported reagent was required to remove the residual iodine that was employed in forming the alkene double bond. To facilitate this, thiosulfate resin **5** was freshly prepared according to a procedure reported by Parlow *et al.* (Scheme 3).[21] The image shows the crude reaction mixture from the synthesis of alkene **2** before and after being passed through a column of the resin, visibly demonstrating its effectiveness at removing the iodine from the reaction mixture. The sulfonic acid column attached after the reactor coil (Scheme 1)



Scheme 2 In-line work-up and purification procedure for the synthesis of BDA protected tartrate **1**.



Scheme 3 A resin for scavenging iodine.

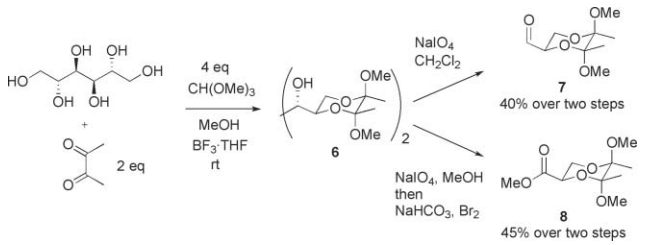
removes diisopropyl amine and the short plug of silica gel effectively traps any inorganic lithium salts.

The corresponding *meso*-BDA-protected derivative **3** was then synthesised as required on a 3 g scale batch using the H-Cube Midi™. The reaction was found to be ineffective in THF so it was not possible to telescope the syntheses of **2** and **3** into a single continuous process without needing a solvent switch. However, recycling a solution of alkene **2** in MeOH through the hydrogenation reactor affords BDA-protected tartrate **3** in quantitative yield, with evaporation of solvent being the only manual operation

required. This represents a considerable advantage over the batch hydrogenation process, which requires 5 days of stirring in a vessel pressurised with 80 bars of hydrogen gas.

BDA-protected glyceraldehyde

Following the preparation of the family of BDA-protected tartrates, we continued to investigate other BDA-protected substrates, namely aldehyde **7** and ester **8**. In batch mode, the synthesis of the BDA-protected mannitol **6** proceeds *via* condensation with butanedione, using trimethyl orthoformate as a dehydrating agent and $BF_3{\cdot}THF$ complex as the activating Lewis acid (Scheme 4).[22–24] Sodium periodate in CH_2Cl_2 is then used to cleave the central diol bond to yield aldehyde **7**. When this transformation is carried out in methanol, the hemiacetal is initially obtained, which is then oxidised *in situ* with bromine to afford the ester derivative **8**.

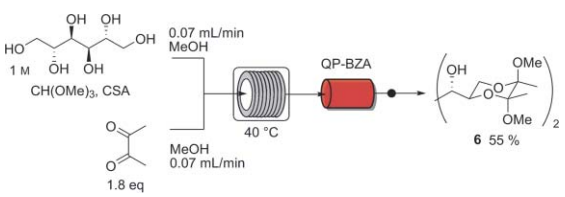


Scheme 4 Batch synthesis of BDA-protected mannitol derivatives.

A significant drawback with this procedure is the purity of the initially formed adduct **6**, since there are seven possible alternatives that could arise from the first step. Consequently, following the glycol cleavage the aldehyde and ester require extensive purification by a non-trivial reduced pressure distillation, resulting in the relatively low yields.

The first challenge in order to achieve a flow synthesis protocol was the insolubility of the D-mannitol itself, since in the batch process it slowly dissolves as the reaction proceeds. Insolubility can be a major issue for flow-based approaches because solid deposits may cause unreliable flow rates and blockages, resulting in overpressure and automatic system shutdown. This problem was solved by premixing D-mannitol with CSA and trimethyl orthoformate. Interestingly, this was the only combination of reagents in which the D-mannitol could be fully dissolved and remain solublised. This observation could be further evidence that the BDA protection mechanism proceeds *via* pre-activation of the diol through an orthoester intermediate, as described in our previous paper.[17]

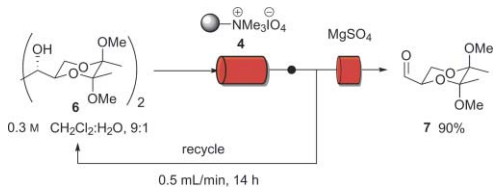
A series of rapid optimisation reactions conducted in flow found that a slight warming of the reaction mixture to 40 °C, and the use of precisely 1.8 eq of butanedione afforded the best yield (55%) of the desired BDA-protected mannitol product **6** (Scheme 5). Although the product still required a simple purification using



Scheme 5 Continuous flow synthesis of BDA protected D-mannitol **6**.

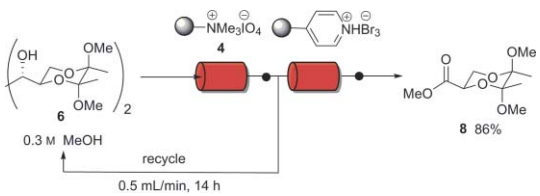
silica gel chromatography we postulated that the use of 1.8 eq of butanedione increases the yield as it reduces the propensity to form tris-protected byproducts.

The next stage of the sequence was to effect the glycol cleavage of the central diol bond. The transformation to the BDA-protected aldehyde **7** was likely to be facile, particularly as $NaIO_4$ supported on silica has previously been used to cleave mannitol protected as the bis-acetonide.[25] The original batch procedure for this transformation involves overnight stirring in CH_2Cl_2 and aqueous $NaHCO_3$, and then stoichiometric addition of $MgSO_4$ and $Na_2S_2O_3$.[24] It was found that the reaction could be performed rapidly, in flow, by recirculating a solution of the bis-protected BDA-protected mannitol **6** through a column packed with periodate resin **4** (Scheme 6). A small amount of water is required for the success of this reaction; therefore, on completion, the solution was finally directed through a drying column of $MgSO_4$. This procedure furnishes the aldehyde **7** in superior yield to the batch process, mainly due to the purity of the starting bis-protected material, providing the aldehyde in high purity and hence avoiding the need for aqueous work-up and reduced pressure distillation.



Scheme 6 Continuous flow synthesis of BDA-protected aldehyde **7**.

The synthesis of the BDA-protected ester **8** proceeded in a similar fashion, with oxidation of the intermediate hemiacetal being carried out in-line with a polymer-supported perbromide resin (Scheme 7).[26]

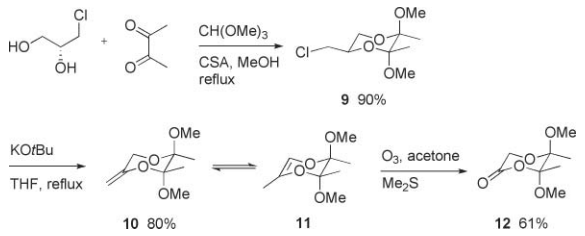


Scheme 7 Continuous flow synthesis of BDA-protected ester **8**.

The simplicity of the above processes makes them more amenable and reproducible in scale up experiments than the corresponding batch protocols.

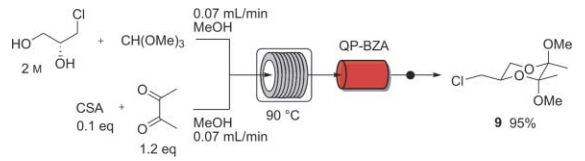
BDA-protected glycolate

The final BDA-protected building block investigated was protected glycolate **12**. In the batch preparation of this compound, the standard BDA protection conditions of refluxing in methanol with CSA, butanedione and trimethyl orthoformate gave **9** in excellent yield (Scheme 8).[27] Elimination of HCl using KO*t*Bu then yields alkene **10**. A problem, however, with this step is that the *exo*-alkene readily isomerises to the more stable *endo*-alkene **11**. Finally, ozonolysis of **10** under reductive work-up conditions furnishes the BDA-protected glycolate **12**.



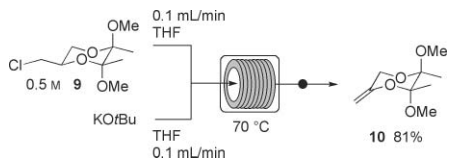
Scheme 8 Batch synthesis of BDA glycolate **12**.

As the batch synthesis of BDA derivative **9** requires similar conditions to the preparation of BDA-protected tartrate **1**, the optimum conditions for the flow synthesis of **1** were first investigated (Scheme 9). The procedure proved highly successful, providing **9** in 95% yield with no temperature-induced racemisation of the starting material and no manual purification required. Additionally, due to the higher conversion achieved, there was no need to remove any unreacted diol.



Scheme 9 Continuous flow synthesis of BDA-protected chloropropanediol **9**.

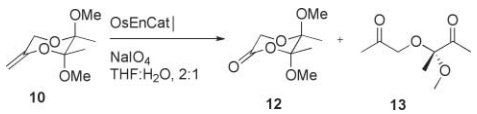
Ideally, for flow applications, a polymer-supported base would have been used to deprotonate **9** and generate the alkene **10**. This then would have allowed facile telescoping of these two steps, giving alkene **10** as a continuous procedure from the starting chloropropanediol. Unfortunately, none of the bases screened achieved this transformation cleanly. The best conditions, therefore, involve the use of a solution of KO*t*Bu in THF, combined at a T-piece with a solution of the BDA-protected chloropropane diol also in THF. The reaction mixture was then passed through a 14 mL reactor coil, maintained at 70 °C with a residence time of 70 min, affording alkene **10** in 81% isolated yield (Scheme 10).



Scheme 10 Flow synthesis of BDA protected alkene **9**.

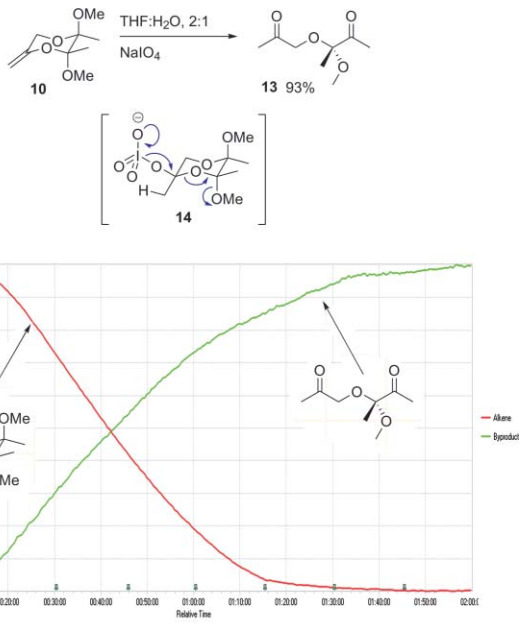
Due to the known problems of isomerisation of the double bond in **10**, it was not possible to add a further column of solid supported acid in-line to scavenge excess KO*t*Bu. Instead, the reaction stream was collected directly into water and extracted in a typical batch manner. However, flow chemistry provides one major advantage for this reaction, which is the precise control over the ratio of products. The reaction was found to be very reproducible, with a ratio of 24 : 1 for *exo* : *endo* alkene observed consistently. In contrast, the batch process is reported to result in ratios varying from 15 : 1 to 5 : 1 in the worst case. This improvement is probably a factor of the precise temperature control in the reactor compared with global temperature measurement recorded in a round-bottomed flask.

In order to try and avoid the use of ozone, a new approach was required for the flow synthesis of lactone **12**. Various polymer-supported osmium species have been reported as alternatives to in solution OsO_4 for the dihydroxylation of double bonds.[28] It has also been shown in our laboratories that combining OsEnCat™ (osmium tetroxide encapulsated in a polyurea matrix) with sodium periodate in solution achieves the cleavage of the diol to the corresponding carbonyl group in high yields.[29] Using this procedure, alkene **10** was converted to lactone **12**, although a second byproduct was also observed (1 : 1) which was identified to be the enantioenriched diketone **13** (Scheme 11).



Scheme 11 Formation of byproduct **13**.

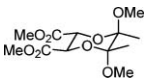
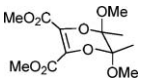
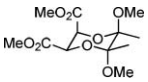
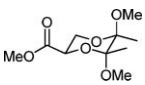
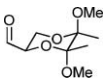
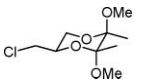
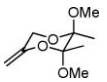
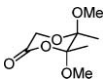
To investigate this side product further, the reaction was followed using a ReactIR 45m with a fibre optic cable and diamond probe to monitor the peak intensity of the alkene C=C and ketone C=O stretches over time.[30] After a series of control experiments, it was determined that the formation of ketone **13** was dependant on the periodate, as none of the byproduct was observed by IR when the alkene was simply stirred in the presence of OsEnCat™. However, when the alkene was stirred together with sodium periodate in THF–H_2O (2 : 1), it decayed linearly into exclusively product **13** over 2 h (Scheme 12). A plausible mechanism for this transformation is shown below, resulting from the formation of periodic acid, which could add to the enol ether to form species **14**, which then eliminates to give the observed product.



Scheme 12 Synthesis of diketone **13** monitored using an FTIR diamond probe.

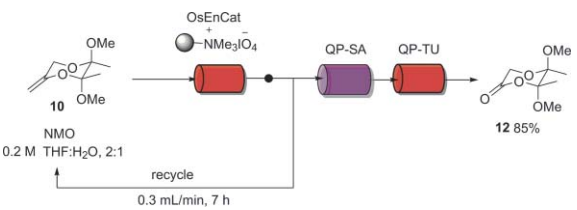
Despite varying the reaction conditions, the formation of this byproduct could not be entirely suppressed and a modified

Table 1 A comparison of the batch and flow syntheses of BDA-protected derivatives

Product	Synthetic method	Yield (%)	Purification technique	Product	Synthetic method	Yield (%)	Purification technique
	Batch	70	Aqueous extraction, recrystallisation		Batch	42[b]	Aqueous extraction, reduced pressure distillation
	Flow	75[a]	In-line		Flow	49[b]	In-line
	Batch	60	Aqueous extraction, recrystallisation		Batch	90	Aqueous extraction
	Flow	65[a]	In-line		Flow	95	In-line
	Batch	100	Filtration, column chromatography		Batch	80	Aqueous extraction
	Flow	100[a]	In-line		Flow	81	Aqueous extraction
	Batch	41[b]	Aqueous extraction, reduced pressure distillation		Batch	61	Recrystallisation
	Flow	47[b]	In-line		Flow	85	In-line

[a] See ref. 17. [b] Yield determined over two steps from D-mannitol.

approach was required. We initially evaluated using a supported periodate resin **4** to exclude the formation of periodic acid in solution. In this experiment, in order to use 5 mol% of OsEnCat™, a stoichiometric amount of *N*-methylmorpholine *N*-oxide (NMO) was added as a reoxidant because the supported periodate was unable to effectively turnover the catalyst. Pleasingly, using this protocol, the BDA-protected alkene was converted in 85% yield to the BDA-protected lactone **12** with none of the undesired byproduct **13** (Scheme 13). In practise, the reaction mixture was recycled though an OmniFit® column containing a mixed bed of OsEnCat™ and the supported periodate resin **4**. When the reaction was judged to have reached completion by LCMS, the flow stream was redirected through two scavenger columns; firstly, a supported acid to remove stoichiometric quantities of *N*-methyl morpholine and then Quadrapure thiourea (QP-TU), a metal scavenging resin, to remove any leached osmium contaminants.



Scheme 13 Continuous flow synthesis of BDA protected lactone **12**.

Conclusions

In conclusion, the syntheses of the family of BDA-protected chiral building blocks have been achieved using flow chemistry in concert with supported reagents and scavengers. As shown in Table 1, the yields are superior to the batch processes and no manual purification is required, with the exception of BDA alkene **10**. In this case, the machine-assisted approach has the added advantage that precise control can be achieved more readily than the manually operated batch method. We believe that these new technologies have real value for the on demand generation of starting materials for natural product synthesis programmes.

Experimental

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), Quadrapure benzylamine resin (QP-BZA), Quadraupre thiourea (QP-TU) and OsEnCat™ 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). Coupling constants are quoted to the nearest 0.1 Hz. 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. High resolution mass spectrometry was carried out on a Waters Micromass LCT Premier spectrometer using time of flight with positive electrospray ionisation. Elemental analyses were determined in the microanalytical laboratories at the Departmental of Chemistry, University of Cambridge. Column chromatography was carried out using a Biotage SP1 Flash

Purification system with prepacked SNAP cartridges containing 10 g of silica gel.

(2*R*,3*R*,5*R*,6*R*)-dimethyl 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate 1[17]

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^{-1} (0.15 mL min^{-1} per channel) into a T-piece and through a 14 mL CFC 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-NMe_3IO_4 **4** (17 g). The output of the reactor was collected until no further product was eluted and the solvent removed *in vacuo* to yield the product 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%); $\tilde{\nu}_{max}/cm^{-1}$ (neat) 2991w (C–H), 2949w (C–H), 1736s (C=O), 1110s (C–O), 1023s (C–O); ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 4.53$ (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, $CDCl_3$): $\delta_C = 168.4$ (2 × *C*O), 99.2 (2 × *C*), 68.8 (2 × *C*H), 52.5 (2 × O*C*H$_3$), 48.5 (2 × O*C*H$_3$), 17.3 (2 × *C*H$_3$); HRMS (+ES): *m*/*z* Calcd. for $C_{12}H_{20}NaO_8$ (MNa^+): 315.1056. Found: 315.1035.

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

A solution of *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 each pumped at 0.5 mL min^{-1} (combined flow rate of 1.0 mL min^{-1}), 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 QP-SA resin (1 g) and then through a second 10 × 100 mm Omnifit column containing PS-$NMe_3S_2O_3$ **5** (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 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%); $\tilde{\nu}_{max}/cm^{-1}$ (neat) 2960w (C–H), 1733m (C=O), 1648m (C=C), 1133s (C–O), 1090s (C–O); ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 3.76$ (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, $CDCl_3$): $\delta_C = 162.2$ (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$_3$); HRMS (+ES): *m*/*z* Calcd. for $C_{12}H_{18}NaO_8$ (MNa^+): 313.0899. Found: 313.0922.

(2*R*,3*S*,5*R*,6*R*)-dimethyl 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate 3[17]

BDA-protected oxidised tartrate **2** (3.78 g, 13.0 mmol) was dissolved in MeOH (30 mL) and pumped at a flow rate of 3 mL min^{-1} 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* 0.7 in $CHCl_3$); $\tilde{\nu}_{max}/cm^{-1}$ (neat) 2954w (C–H), 1770m (C=O), 1736m (C=O), 1140s (C–O), 1034s (C–O); ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 4.69$ (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, $CDCl_3$): $\delta_C = 169.6$ (*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), HRMS (+ES): *m*/*z* Calcd. for $C_{12}H_{20}NaO_8$ (MNa^+): 315.1056. Found: 315.1074.

Polymer-supported periodate 4[17]

Amberlite IRA 900, chloride form (25 g, 100 mmol, 4 mmol g^{-1} loading) 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 **4** (28 g, 2.0 mmol g^{-1}). (Found: Cl^-, 0.00. PS–NMe_3IO_4 requires Cl^-, 0.00).

Polymer-supported thiosulfate 5[17]

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 **5** (8.3 g, 3.4 mmol g^{-1}). (Found: N, 4.81. PS–$NMe_3S_2O_3$ requires N, 4.76).

(1*S*,2*S*)-1,2-bis((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)ethane-1,2-diol 6[22]

D-mannitol (1 g, 5.5 mmol), CSA (127 mg, 0.6 mmol) and trimethyl orthoformate (2.41 mL, 22 mmol) were dissolved in MeOH (2 mL) and heated to 60 °C for 1 min by microwave irradiation using a Biotage Initiator before being transferred to a 5 mL sample loop. Butanedione (0.92 mL, 10.5 mmol) in MeOH (4 mL) was also loaded into a second 5 mL sample loop. The two solutions were pumped at 0.07 mL min^{-1}, mixed at a T-piece and passed through a 14 mL CFC reactor held at 40 °C. The output was then passed through a 10 × 100 mm Omnifit column filled with QP-BZA resin (2 g). The solvent was evaporated *in vacuo* and the residue purified by column chromatography (SP1, 6 : 4 Pet ether: EtOAc, 25 column volumes on 10 g silica, 15 mL min^{-1}, R_f 0.15) to yield the product **6** as a white foam (1.25 g, 55%). $[\alpha]_D^{25}$ −78.8 (*c* 0.85, $CHCl_3$); $\tilde{\nu}_{max}/cm^{-1}$ (neat) 3482br (OH), 2994w (C–H), 1114s (C–O), 1033s (C–O); ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 4.10$ (2H, ddd, $J = 10.9, 6.2, 3.6$ Hz, 2 × C*H*H), 3.80-3.71 (4H, m), 3.65 (2H, dd, $J = 11.4$, 3.5 Hz, 2 × C*H*H), 3.28 (6H, s, 2 × OCH_3), 3.27 (6H, s, 2 × OCH_3), 2.75 (2H, br, 2 × O*H*), 1.29 (6H, s, 2 × CCH_3),

1.28 (6H, s, 2 × CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 99.3 (2 × *C*), 98.1(2 × *C*), 69.5 (2 × *C*H), 68.5 (2 × *C*H), 60.9 (2 × *C*H_2), 48.1 (2 × O*C*H_3), 48.1 (2 × O*C*H_3), 17.8 (2 × *C*H_3), 17.5 (2 × CH_3); HRMS (+ES): *m*/*z* Calcd. for $C_{18}H_{34}NaO_{10}$ (MNa^+): 433.2050. Found: 433.2030.

(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde 7[22]

BDA-protected D-mannitol (350 mg, 1.3 mmol) was dissolved in CH_2Cl_2–H_2O (9 : 1, 4 mL) and recycled through a 10 × 100 mm Omnifit column of PS-periodate **4** (1 g, 2 mmol) at 0.5 mL min^{-1} for 14 h. After this time the flow stream was directed through a 10 × 100 mm Omnifit containing $MgSO_4$ (500 mg) and the solvent removed *in vacuo* to give aldehyde **7** as a colourless liquid (477 mg, 90%). $[\alpha]_D^{25}$ −101.3 (*c* 0.8, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} (neat): 2949w (CH), 1733w (C=O), 1110s (C–O), 1033s (C–O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 9.63 (1H, s, C*H*O), 4.32 (1H, dd, *J* = 10.1, 4.9 Hz, C*H*), 3.73-3.65 (2H, m, CH_2), 3.30 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 1.36 (3H, s, CCH_3), 1.28 (3H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 200.2 (*C*HO), 99.8 (*C*), 98.3 (*C*), 72.4 (*C*H), 58.2 (*C*H_2), 48.4 (O*C*H_3), 48.2 (O*C*H_3), 17.6 (C*C*H_3), 17.5 (C*C*H_3).

(2*R*,5*R*,6*R*)-methyl 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxylate 8[22]

BDA-protected D-mannitol (350 mg, 1.3 mmol) was dissolved in MeOH (4 mL) and recycled through a 10 × 100 mm Omnifit column of PS-periodate **4** (1 g, 2 mmol) at 0.5 mL min^{-1} for 14 h. After all the starting material had been consumed (monitored by TLC, Pet ether: EtOAc (6 : 4), R_f 0.4) the output stream was directed into a column of PS-pyridinium perbromide (1 g, 2.7 mmol) at a flow rate of 0.05 mL min^{-1}. Excess solvent was removed *in vacuo* to yield ester **8** as a colourless oil (489 mg, 86%). (Found: C, 51.53; H, 7.70. $C_{10}H_{18}O_6$ requires C, 51.27; H, 7.75%); $[\alpha]_D^{25}$ −119.6 (*c* 1.22, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} (neat) 2952w (C–H), 1764m (C=O), 1734m (C=O), 1140s (C–O), 1034s (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 4.56 (1H, dd, *J* = 11.2, 3.7 Hz, C*H*), 3.85 (1H, t, *J* = 11.3 Hz, C*H*H), 3.76-3.71 (4H, m, CO_2CH_3, C*H*H), 3.31 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 1.37 (3H, s, CCH_3), 1.29 (3H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 169.2 (*C*O), 99.7 (*C*), 98.0 (*C*), 67.1 (*C*H), 59.9 (*C*H_2), 52.2 (CO_2CH_3), 48.4 (O*C*H_3), 48.1 (O*C*H_3), 17.6 (C*C*H_3), 17.4 (C*C*H_3); HRMS (+ES): *m*/*z* Calcd. for $C_{10}H_{18}NaO_6$ (MNa^+): 257.1001. Found: 257.1007.

(2*R*,3*R*)-5-(chloromethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane 9[27]

(*R*)-Chloropropanediol (2 g, 18 mmol) and CSA (417 mg, 1.8 mmol) were dissolved in MeOH (6 mL). A second solution was prepared containing butanedione (1.93 mL, 22 mmol) and trimethyl orthoformate (4.38 mL, 40 mmol) in MeOH (3 mL). The two solutions were mixed at a T-piece at a flow rate of 0.14 mL min^{-1} (0.07 mL per channel) and directed into a CFC reactor heated at 90 °C. The solution was then passed through a 10 × 100 mm Omnifit column filled with QP-BZA resin (2 g) and the output collected. Evaporation of the solvent *in vacuo* yielded the desired product **9** as a colourless oil (426 mg, 95%). The product was of sufficient purity to be used for further synthesis. A small amount was isolated by column chromatography for analytical purposes (SP1, Pet ether–Et_2O, 25 column volumes on 10 g silica, 15 mL min^{-1}, R_f 0.3). $[\alpha]_D^{25}$ −101.3 (*c* 0.8, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} (neat) 2948w (C–H), 1374, 1114s (C–O), 1035s (C–O), 878m (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 4.08 (1H, ddd, *J* = 11.3, 9.2, 6.2 Hz, C*H*), 3.62-3.58 (2H, m, OCH_2), 3.43 (1H, dd, *J* = 11.3, 6.2 Hz, C*H*HCl), 3.38 (1H, dd, *J* = 11.3, 6.2 Hz, CH*H*Cl), 3.29 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 1.30 (3H, s, CH_3), 1.28 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 99.2 (*C*), 97.9 (*C*), 67.3 (*C*H), 61.3 (*C*H_2Cl), 47.8 (O*C*H_3), 47.7 (O*C*H_3), 17.4 (C*C*H_3), 17.2 (C*C*H_3); HRMS (+ES): *m*/*z* Calcd for $C_9H_{17}ClNaO_4$ (MNa^+): 247.0713. Found: 247.0733.

(2*R*,3*R*)-2,3-dimethoxy-2,3-dimethyl-5-methylene-1,4-dioxane 10[27]

A 1 mL PEEK sample loop was loaded with a solution of BDA-protected chloropropanediol **9** (224 mg, 1 mmol) in THF (1 mL) and a second 1 mL loop loaded with a solution of KO*t*Bu (224 mg, 2 mmol) in THF (1 mL). The two solutions were mixed at a T-piece at a combined flow rate of 0.2 mL min^{-1} (0.1 mL min^{-1} per pump) and flowed through a 14 mL CFC reactor heated to 70 °C. The output stream was collected in H_2O (2 mL), diluted with Et_2O (10 mL), separated, and the organic phase dried over sodium sulfate to yield the title compound **10** as a colourless oil (152 mg, 81%). $[\alpha]_D^{25}$ −166.9 (*c* 1.2, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} (neat) 2950w (C–H), 1659m (C=C), 1106s (C–O), 1039s (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (1H, s, C*H*H), 4.27 (1H, d, *J* = 13.1 Hz, OCH*H*), 4.26 (1H, s, C*H*H), 3.97 (1H, d, *J* = 13.3 Hz, OC*H*H), 3.34 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 1.37 (3H, s, CCH_3), 1.30 (3H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6 (*C*CH_2), 101.1 (*C*CH$_3$), 98.1 (*C*CH$_3$), 93.2 (O*C*H_2), 59.728 (C*C*H_2), 48.5 (O*C*H_3), 48.3 (O*C*H_3), 17.6 (C*C*H_3), 17.4 (C*C*H_3).

(5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one 12[27]

BDA-protected alkene **10** (188 mg, 1.0 mmol) and NMO (175 mg, 1.5 mmol) were dissolved in THF–H_2O (2 : 1, 4.5 mL) and recycled through a 10 × 100 mm OmniFit® column packed with a mixed bed of OsEnCat™ (250 mg, 0.05 mmol) and PS-periodate resin **4** (1.5 g, 3 mmol) at 0.3 mL min^{-1} for 7 h at room temperature. After this time the flow stream was directed through a 10 × 150 mm OmniFit® column containing QP-SA (1 g, 3 mmol) and QP-TU (1 g, 3 mmol). Excess solvent was removed *in vacuo* to yield glycolate **12** as a pale yellow oil (146 mg, 85%). $[\alpha]_D^{25}$ −241 (*c* 0.83, $CHCl_3$); $\tilde{\nu}_{max}$/cm^{-1} (neat): 2952w (C–H), 1752m (C=O), 1107s (C–O), 1032s (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 4.31 (1H, d, *J* = 17.6 Hz, C*H*H), 4.15 (1H, d, *J* = 17.6 Hz, CH*H*), 3.44 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 1.50 (3H, s, CCH_3), 1.39 (3H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.5 (*C*O), 105.0 (*C*), 97.8 (*C*), 60.3 (*C*H_2), 50.3 (O*C*H_3), 49.1 (O*C*H_3), 17.8 (C*C*H_3), 16.9 (C*C*H_3); HRMS (+ES): *m*/*z* Calcd. for $C_8H_{14}NaO_5$ (MNa^+): 213.0739. Found: 213.0722.

(*R*)-3-methoxy-3-(2-oxopropoxy)butan-2-one 13

BDA-protected alkene **10** (188 mg, 1.0 mmol) was dissolved in THF–H_2O (2 : 1, 4.5 mL) and sodium periodate (642 mg, 3 mmol) was added. The reaction was stirred at room temperature for 2 h,

monitored with the ReactIR 45 m fiber optic probe. After this time the reaction mixture was filtered, diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. sodium metabisulfite (10 mL). The organic phase was separated and dried over $MgSO_4$ to yield ketone **13** as a yellow oil (162 mg, 93%). $[\alpha]_D^{25}$ –9.5 (*c* 1.4, $CHCl_3$); $\tilde{\nu}_{max}/cm^{-1}$ (neat) 2928m (C–H), 1730s (C=O), 1388w, 1119s (C–O), 1044s (C–O); ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 4.02$ (2H, s, CH_2), 3.27 (3H, s, OCH_3), 2.26 (3H, s, CH_3), 2.21 (3H, s, CH_3), 1.43 (3H, s, CCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 206.0 (CO), 205.6 (CO), 105.0 (C), 68.1 (CH_2), 50.0 (OCH_3), 26.5 (CH_3), 25.9 (CH_3), 19.9 (CCH_3).

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