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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The syntheses of butane-2,3-diacetal protected tartrate derivatives are described using continuous flow processing techniques with in-line purification and I.R. analytical protocols.

The production of starting materials for use in complex synthesis programmes often entails repetitive experiments and routine reaction optimisation, especially when using conventional batch-mode approaches. Furthermore, extensive unit operations are required to deliver pure products when chromatography or other labour intensive methods are used. Additionally, because of the repetitive nature of these experiments, there is little to be gained in terms of acquiring new knowledge. We believe a better approach in these circumstances is to employ more machine assisted synthesis techniques of which flow chemistry and related continuous processing concepts are of particular value.[1,2] A good case in point is the preparation of butane-2,3-diacetal (BDA) protected tartrates since our group[3,4] and others[5] have used these widely as starting materials for the syntheses of various natural products such as muricatetrocin C,[6] 10-hydroxyasimicin,[7] didemniserinolipid B,[8] (+)-aspicillin,[9] antascomicin B,[10] epipyriculol,[11] (+)-nephrosteranic acid[12] and (+)-*O*-methylpiscidic acid dimethylester (Fig. 1).[13]

These embedded diol motifs are introduced *via* the condensation of dimethyl-L-tartrate with butanedione to give an enantiopure BDA building block **1**.[14-16] The particularly useful and spatially differentiated *meso* derivative **3** is also accessed *via* oxidation of **1** to the dehydro species **2**, followed by stereospecific introduction of hydrogen.[17] While in the past we have scaled up these processes by application of the conventional batch methods, these are time consuming and often wasteful of materials, particularly during the necessary recrystallisations to yield high quality products (Scheme 1).

In this new work we describe a method suitable for automation and scale-up using commercially available flow chemistry equipment in combination with packed tubes containing appropriate solid-supported reagents and scavengers. We also report the use of flow I.R. equipment to monitor reaction pathways *in-situ* to provide important mechanistic information concerning the reaction progress in real-time.

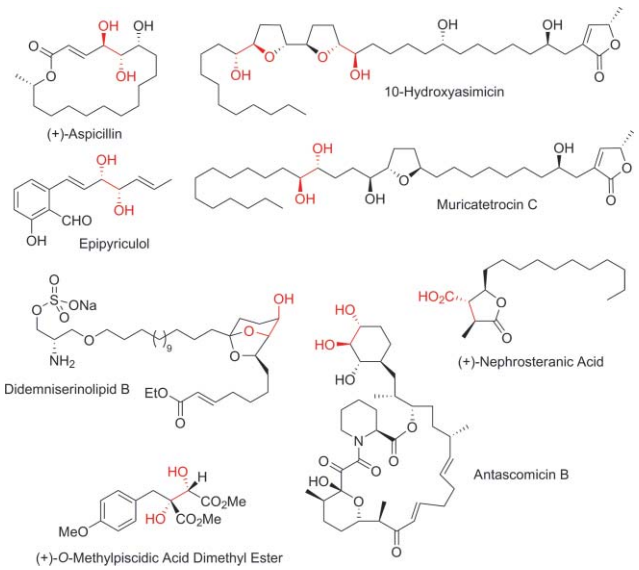
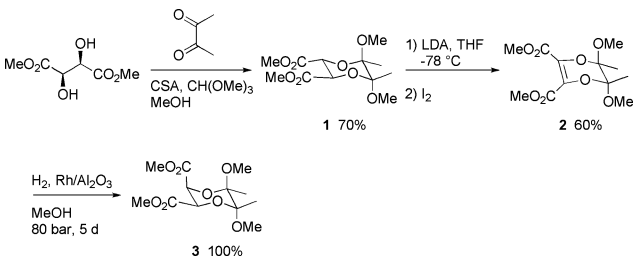


Fig. 1 Natural products derived from BDA protected building blocks.



Scheme 1 Batch synthesis of butane-2,3-diacetal protected tartrate derivatives.

As a platform to carry out the flow synthesis of BDA protected tartrate **1** we selected the Uniqsis FlowSyn system,[18] comprising of two HPLC pumps and fitted with a 14 mL PTFE coil and a column heater suitable for heating Omnifit® columns of 10 × 100 mm dimensions. A back pressure regulator (BPR) at the end of the flow stream allows for the superheating of solvents above their standard boiling point. In the first instance we envisaged solutions of dimethyl-L-tartrate, butanedione and trimethyl orthoformate being pumped through an Omnifit® column packed with Quadrapure sulfonic acid resin (QP-SA), to mimic the use of DL-camphorsulfonic acid (CSA) in the batch synthesis (Scheme 2). This set-up was expected to eliminate the need for a traditional reaction work-up step.

Unfortunately, low yields of product were obtained from this arrangement, despite attempted optimisation of flow rates, stoichiometries and temperatures. To investigate this process further

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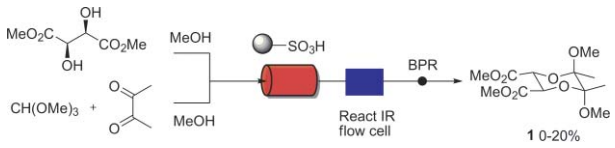


Scheme 2 Attempted flow synthesis of **1** with in-line I.R. monitoring.

we attached a recently devised flow cell containing an FTIR diamond probe[19] to monitor the progress of the reaction in-line (Fig. 2).[20]

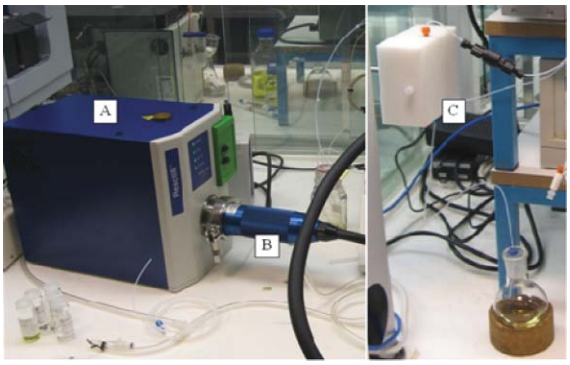


Fig. 2 **A** React IR 45 m. **B** Fibre optic cable. **C** Flow cell.

By obtaining the I.R. reference spectra of the reagents and monitoring the intensity in peak height over time, the consumption of reagents and formation of products can be readily monitored in real-time, along with any unexpected byproducts being generated. As can be seen in Fig. 3, butanedione and trimethyl orthoformate are immediately consumed to form a new intermediate, which was later identified to be the tetramethoxyacetal of butanedione.

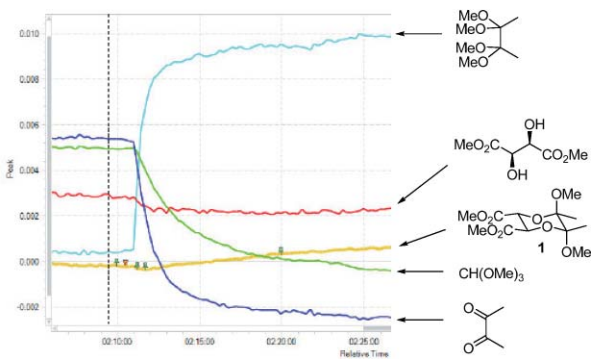
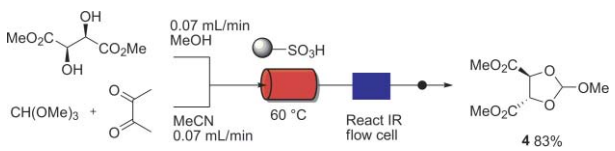


Fig. 3 Relative trends from peak height analysis.

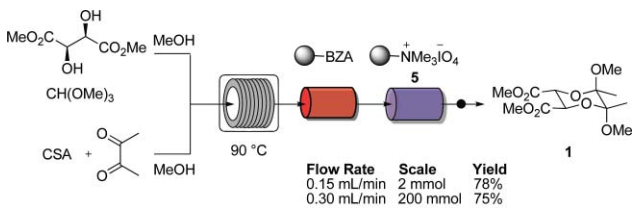
In order to investigate the effect of methanol on this process the reaction was carried out using 1:1 MeOH:MeCN as the solvent system. Surprisingly, the reaction afforded only the orthoester **4** (Scheme 3). This suggests that the role of the trimethyl orthoformate is not to simply act as a dehydrating agent but

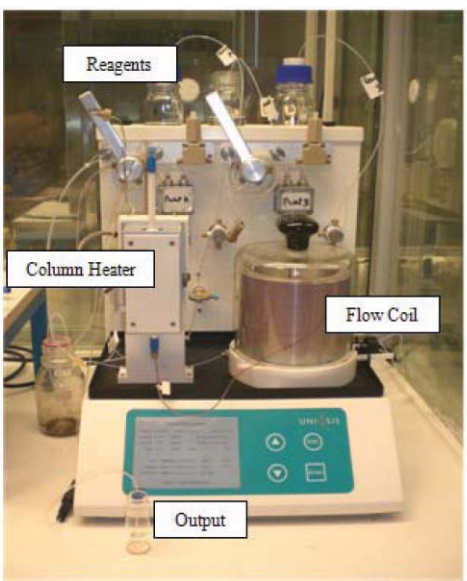


Scheme 3 Production of orthoester **4**.

rather increases the activity of the diol by forming an orthoester *in-situ*. In addition, QP-SA was not a strong enough acid to carry this intermediate through to product **1**. Although we did not generate the desired product, these experiments show the value of being able to monitor a reaction in-line. Despite running similar experiments in batch mode many times, we had not observed these intermediates previously.

Consequently it was decided to return to the use of CSA as a heterogeneous acid catalyst (Scheme 4). Optimisation of the process conducted in flow revealed the best conditions for the reaction to be flowing a 2 M stock solution of the reagents into a 14 mL PTFE flow coil held at 90 °C with a residence time of 2 h. This gave the product in 78% yield, which constituted a consistent 8% improvement on the batch process. In order to purify the product in-line a column packed with a benzylamine resin (QP-BZA) was introduced into the flow stream to scavenge out the acid catalyst and also to trap out any unreacted butanedione as the imine species. Subsequently, passing the flow stream over periodate resin **5** removed any unreacted diol. Immobilised reagent **5** was freshly prepared by stirring commercially available quaternary ammonium chloride ion exchange resin (A-900) with sodium periodate in water,[21] and effects a glycol cleavage to yield volatile byproducts. After passing the flow stream through these clean-up columns solvent evaporation is the only manual operation required to yield elementally pure BDA tartrate **1**.



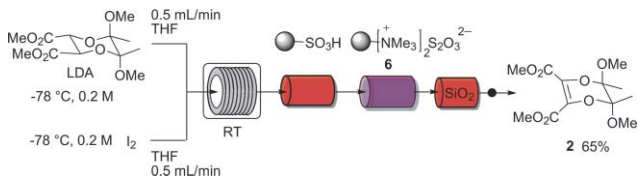


Scheme 4 Continuous flow synthesis of **1** with the Uniqsis FlowSyn.

One of the many advantages of flow chemistry is the ease of scale up, with minimal change to the reaction set-up. To demonstrate this principle the same reaction was carried out on a 200 mmol scale and 40 g of elementally pure product was obtained in just

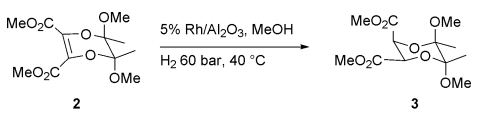
10 h of processing time with no manual purification required. The only change was doubling of the flow rate to 0.30 mL/min to increase the throughput with only a corresponding drop in yield.

With a process for the preparation of the enantiopure BDA tartrate **1** established we turned our attention to the precursor for the *meso* BDA protected tartrate **3**, namely oxidised product **2** (Scheme 5). The optimum conditions for preparing this building block involved mixing equimolar solutions of the *bis*-enolate in THF with iodine in THF, both held at −78 °C, in a T-piece and allowing the reaction to warm to room temperature by passage through a 14 mL PTFE coil. The combined flow rate for this process was 1.0 mL/min, allowing for a high throughput of material. The in-line purification process for the work-up of this reaction involved three stages: firstly, the reaction mixture was passed through a column of sulfonic acid resin (QP-SA) to scavenge the diisopropylamine, then through a column of thiosulfate resin **6**[22] to remove any excess iodine and finally through a short plug of silica gel to trap any inorganic lithium salts. This overall sequence yielded compound **2** in 65% yield, which was an improvement over the batch process since no manual work-up or purification procedures were required.



Scheme 5 Continuous flow synthesis of BDA derivative **2**.

The final step to produce synthetically useful quantities of *meso* tartrate **3** required a flow hydrogenation procedure (Scheme 6). Using the H-Cube® reactor[23] and a Rh/Al_2O_3 cartridge as the catalyst, 1 mmol of oxidised substrate **2** was dissolved in 5 mL methanol and recycled through the machine at 60 bar of H_2 for 4 h to obtain full conversion to spatially desymmetrised BDA protected *meso* tartrate **3** in 100% yield. This represents a vast improvement on the batch procedure which required five days of stirring at 80 bar of H_2 in a pressurised reactor vessel, which carries with it many safety concerns, particularly on a large scale.



Reactor	Scale	Flow rate	Yield
H-Cube®	1 mmol	1 mL/min	100%
H-Cube Midi™	13 mmol	5 mL/min	100%

Scheme 6 Continuous flow synthesis of BDA derivative **3**.

Using the commercially available H-Cube Midi™, a preparative version of the H-Cube®, the reaction was performed on a 13 mmol scale at an increased flow rate of 5 mL/min, giving 3.8 g of pure product in just 2 h with no further purification necessary. As this valuable motif is not commercially available our reproducible route to large amounts of pure material is particularly attractive.

In conclusion, we have reported the syntheses of three BDA protected derivatives for use in total synthesis programmes using continuous flow processing technology, giving higher yields than the corresponding batch processes. All purification steps have been carried out in-line with solid-supported reagents. These new processes allow large amounts of material to be generated in a less labour-intensive fashion. In this work we have also demonstrated the utility of a flow I.R. system in the monitoring of intermediates which we believe will find more general application than using other I.R. probe devices.

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