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COMMUNICATION

Modular Continuous Flow Synthesis of Orthogonally Protected 6-Deoxy Glucose Glycals

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Subbarao Yalamanchili [a], Tu-Anh V. Nguyen [a], Nicola L. B. Pohl *[b], and Clay S. Bennett *[a]

An efficient, modular continuous flow process towards accessing two orthogonally protected glycals is described with the development of reaction conditions for several common protecting group additions in flow, including the addition of benzyl, naphthylmethyl and *tert*-butyldimethylsilyl ethers. The process affords the desired target compounds in 57-74% overall yield in just 21-37 minutes of flow time. Furthermore, unlike batch conditions, the flow processes avoided the need for active cooling to prevent unwanted exotherms and required shorter reaction times.

Recently, continuous flow processes have been adapted by many groups in the synthesis of different natural products[1] and active pharmaceutical ingredients (APIs).[2,3] Flow chemistry can provide many benefits,[4–6] including the ability to run continuous processes enabling large scale production[7] of material and increased reaction efficiencies[8] as compared to batch processes. Reactions can be more efficiently heated and cooled and highly reactive intermediates can be made transiently to avoid the safety hazards of larger scale production.

The design of efficient flow reactions requires consideration of several parameters. Although microfluidic systems require careful consideration of parameters to get reproducible temperature transfers and mixing efficiencies,[9] larger tubing-based systems flow systems can be easier to implement. The benefits of microfluidic and larger flow systems have seen applications to chemical glycosylation,[10-15] but almost none of the necessary glycosyl donors and acceptors needed for glycosylation reactions have been produced with the development of continuous flow processes.[16]

Glycals—1,2-unsaturated monosaccharide derivatives—have a wide variety of uses in organic synthesis. From natural product synthesis to the generation of novel structural motifs, glycals are versatile building blocks.7 In carbohydrate chemistry, glycals can be directly used as donors in chemical glycosylation[18] by a variety of different activation conditions.[19-26] Glycals also serve as important intermediates in the construction of glycosyl donors, as they can readily be made into hemiacetals[27,28] or thiogylcosides.[29-33]

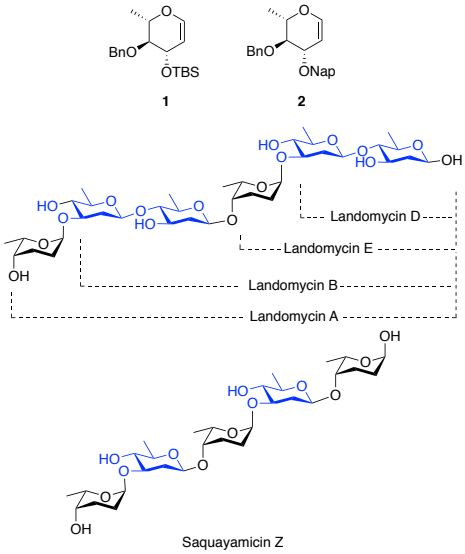

Figure 1. Oligosaccharide portions of angucycline natural products containing 2-6-dideoxy glucose (blue).

A major hurdle in carbohydrate chemistry remains the ability to quickly and efficiently access multiple donor and acceptor building blocks.[34] Our solution to this problem is to take advantage of the faster timescales of continuous flow processes. In continued studies on deoxy-sugar oligosaccharide synthesis, we had need for large quantities of glycal precursors. In an effort to circumvent issues associated with batch synthesis (time consuming reaction sequences, limited scale, potential exotherms, etc.), we chose to examine if these substrates could be

[a] 62 Talbot Ave, Medford, MA, 02145.
[b] 212 S. Hawthorne Dr, Bloomington, IN 47405
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produced in a continuous flow system. As an initial foray into this chemistry, we chose the synthesis of orthogonally protected L-rhamnals **1** and **2**, which serve as precursors for many of the deoxy-sugars found in natural products, such as those in the anthracycline[35] and angucycline[36-38] families of antibiotics (Figure 1).

The synthesis of glycals **1** and **2** commenced with translating a Zemplén deacetylation that we had previously run in batch reaction conditions[28] into a flow process. As is the case with converting manual to automated batch process,[29] the conversion of batch to flow processes is not trivial. Ideally, solvents are found in which all reagents and reactants are soluble and no products or byproducts precipitate during the course of the reaction. We started with 0.4 equivalents (0.24 M in MeOH) of sodium methoxide (Table 1, entry 1). While the desired diol 4 was formed in 76% yield, the reaction did not go to completion. By an increase in the amount of sodium methoxide (NaOMe) to 0.8 equivalents (0.48 M in MeOH), compound **3** was completely consumed and the formation of the desired product **4** was affected in 98% yield (Table 1, entry 2). Importantly, we were able to run the deacetylation on a five gram scale of **3**, at a rate that could produce 35.8 g/h of diol **4**.

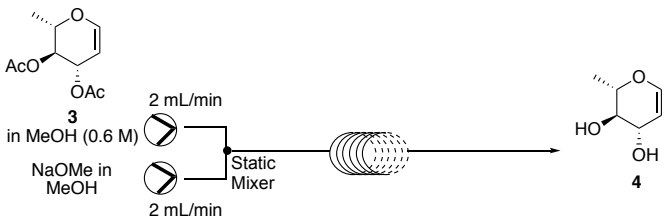


Table 1. Optimization of Zemplén Deacetylation in Flow

Entry	Eq. of NaOMe in MeOH	Flow Rate in Main Reaction Tube (mL/min)	Total T_r (min)	Yield[b] (%)
1[a]	0.4	4	5	76
2[a]	0.8	4	5	98

[a.] Run at Ambient Temperature, [b.] Isolated Weight

With **4** in hand, we next sought to convert the traditional Corey silylation conditions[39] to a flow process by regioselectively protecting the allylic alcohol as a *tert*-butyldimethylsilyl (TBS) ether. Following optimization, we found that using 1.1 equivalents of TBSCl (0.66 M in DMF) and 1.5 equivalents of imidazole (0.89 M in DMF) was sufficient to selectively protect the C3 alcohol over the C4 position in 40 minutes of retention time to afford **5** in 91% yield (Table 2, entry 2). Efforts to reduce the retention time by increasing flow rate resulted in formation of product in 49% yield with recovery of unreacted starting material (Table 2, entry 3). In order to increase the rate of the reaction, we looked into using a different auxiliary base such 4-dimethylaminepyridine (DMAP) which is known to have improved rates of silylation relative to imidazole.[40] Using 1.5 equivalents (0.89 M in DMF) of DMAP, we were able to get complete conversion of diol **4** to corresponding silyl ether **5** in 88% yield in 10 minutes of total retention time (Table 2, entry 5). After increasing the scale of the reaction to 2.97 g of diol **4**, we were able to achieve regioselective protection of the allylic alcohol at a rate of 29.4 g/h. These conditions are an improvement to traditional TBS silylation conditions that typically use a large excess of base to increase the rate of reaction. Interestingly, we also found that the reaction could be run at ambient temperature and it was not necessary to cool the reaction down to 0 ˚C in order to selectively protect the C3 position.

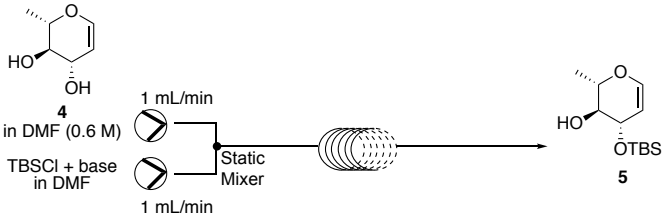


Table 2. Optimization of Regioselective TBS Protection in Flow

Entry	Base	Eq. of Base in DMF	Flow Rate in Main Reaction Tube (mL/min)	Total T_r (min)	Yield[b] (%)
1[a]	Imidazole	1.1	2	40	83
2[a]	Imidazole	1.5	2	40	91
3[a]	Imidazole	1.5	2	10	49
4[a]	4-DMAP	1.1	2	10	64
5[a]	4-DMAP	1.5	2	10	88

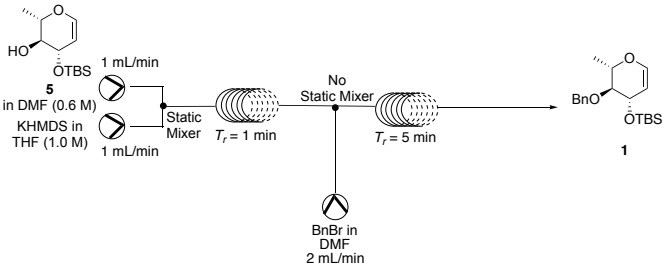
[a.] Run at Ambient Temperature, [b.] Isolated Weight

With the allylic alcohol successfully protected, we next chose to protect the C4 alcohol with an orthogonal protecting group such as an alkyl ether. Recently, the Pohl lab has demonstrated continuous flow benzylation, acetylation, and thioglycoside formation in the synthesis of protected levoglucosan and glucose.[16] While acetylation and thioglycoside formation proceeded smoothly, the use of BaO packed bed reactors had issues with pressure buildup and possibly product absorption to the solid phase that warranted a reenvisioning of this reaction.[41] In our case, only a single hydroxyl group was free for protection, which expanded the choice of solvents and conditions that could be considered for the benzylation reaction.

To address this, we chose to examine the use of alternative bases in the reaction. Typical Williamson ether conditions include sodium hydride, which is incompatible with flow-based setups due to it being a heterogeneous

solution. However, benzylation has successfully been demonstrated under a variety of homogeneous conditions, such as LiHMDS/BnBr/TBAI[42] or benzyl trichloroacetimidate/TfOH.[43] To this end, we pictured glycal **5** first going through a deprotonation sequence with KHMDS, followed by treatment with BnBr and TBAI to achieve benzylation (Table 3, entry 1). Through optimizations, we found that TBAI was unnecessary in the reaction, perhaps due to the high reaction concentration leading to fast rates of reaction (Table 3, entry 2). Further optimization of the reaction led to finding that 5.0 equivalents of BnBr (1.8 M in DMF) was optimal for benzylation, affording **1** in 86% yield without any observed migration of the silyl ether (Table 3, entry 5). With a total retention time of only 6 minutes, this is a large improvement to traditional batch Williamson ether conditions that we have observed in our previous work where benzylations can take between 3-16 hours.[44–46] Increasing the scale of the reaction to 2.7 grams of **5** enabled production of target glycal **1** at a rate of 31.6 g/h. Importantly, to prevent clogging due to the formation of insoluble salts that was observed through the course of the reaction, we chose to exclude a static mixer at the T-junction between the deprotonated glycal and solution of benzyl bromide. Furthermore, the reaction proceeded smoothly at ambient temperature, thus avoiding a cooling bath for another reaction that is typically run at 0 ˚C.

Table 3. Optimization of Benzylation in Flow



Entry	Additive	Eq. of BnBr in DMF	Flow Rate in Main Reaction Tube (mL/min)	Total T_r (min)	Yield[ba] (%)
1[a]	TBAI	neat	4	6	79
2[a]	none	neat	4	6	81
3[a]	none	1.0	4	6	52
4[a]	none	3.0	4	6	65
5[a]	none	5.0	4	6	86

[a.] Run at Ambient Temperature, [b.] Isolated Weight

We chose to next investigate replacing the silyl ether with a naphthylmethyl (Nap) ether[47] to further illustrate the general applicability of this method. Following similar reaction conditions as Corey,[39] TBS removal proceeded smoothly with 2.0 equivalents of tetra-butylammonium fluoride (TBAF, 1.0 M in THF) to afford **7** in 93% yield in 10 minutes of total retention time (Figure 2). Upon scale up to 1.7 g of **1**, we were able to produce **6** at a rate of 6.4 g/h. Importantly, while typical silyl ether removals are run in THF, we found that it was possible to run this reaction in DMF, which was used for the previous two reactions in this sequence. This use of the same solvent opens up the future possibility of telescoping these reactions into a single step if only a particular product is needed.

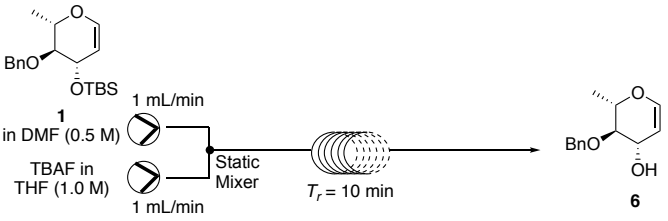


Figure 2. Silyl ether removal using TBAF.

To finish the synthesis of L-olivose glycal **2,** we protected the C3 hydroxyl with naphthylmethyl ether following similar conditions as we did with the benzyl ether alkylation. Gratifyingly, naphthylmethyl ether synthesis proceeded smoothly to afford **2** in 82% yield in 6 minutes of total retention time (Figure 3). Scaling up to 1.1 g of **6** proceeded without incident, allowing for production of **2** at a rate of 14.4 g/h. Similar to the benzylation, we found that this reaction could be run at ambient temperatures and did not require cooling to 0 ˚C.

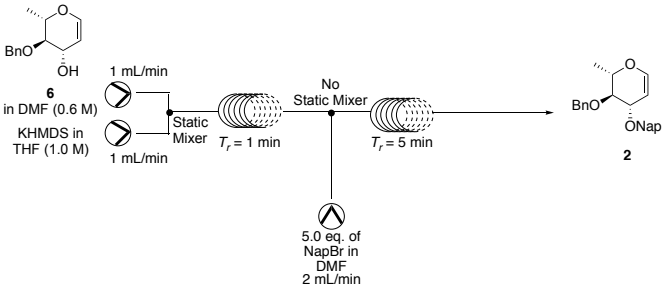


Figure 3. Naphthylmethyl ether installation.

Conclusions

In summary, we have demonstrated the first modular syntheses of two orthogonally protected glycals of the 2,6-dideoxy glucose L-olivose using only continuous flow processes for each reaction step. Glycal **1** was synthesized in 74% overall yield over three steps with a total retention time of 21 minutes. Similarly, glycal **2** was synthesized in 57% overall yield in 5 steps in 37 minutes of total retention time. These processes are in stark contrast to batch approaches to these molecules, which in our experience can take over 1 week.[44–46] All of the reactions in question are run at ambient temperature and most are in the same solvent (DMF), again in contrast to batch approaches to these molecules. Through increased

reaction concentration, all reactions were able to be run in less than 10 minutes of total retention time. Furthermore, due to the efficient heat transfer enabled by the flow processes, both TBS silyl protection and alkyl ether installations could be run at ambient temperatures rather than 0 ˚C, which is typically required for these transformations in batch. We anticipate that this flow-based approach will accelerate glycal synthesis and also provide an invaluable tool to organic chemists who are looking to adopt these steps in their own synthetic pathways to increase rates of substrate production. Efforts to automate this chemistry and telescope it into a single sequence for the continuous production of protected glycans from commercial materials are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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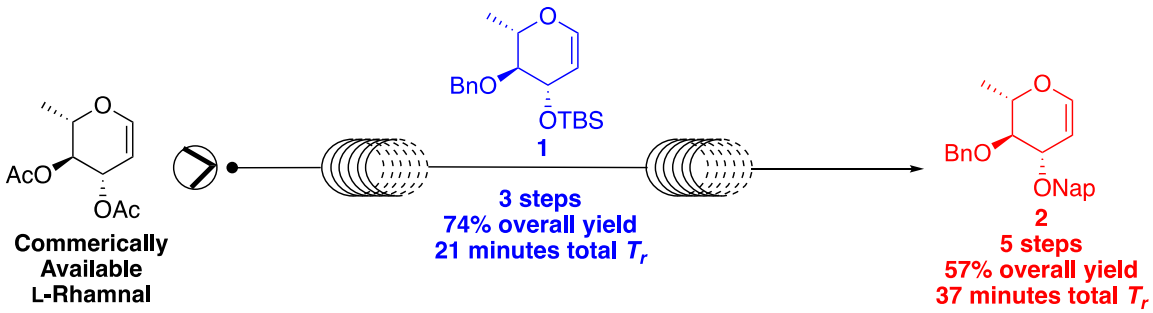
Notes and references

(1) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849–8869.
(2) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chemie Int. Ed.* **2015**, *54*, 6688–6728.
(3) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2–25.
(4) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796–11893.
(5) Yoshida, J.; Kim, H.; Nagaki, A. *ChemSusChem* **2011**, *4*, 331–340.
(6) Lummiss, J. A. M.; Morse, P. D.; Beingessner, R. L.; Jamison, T. F.. *Chem. Rec.* **2017**, *17*, 667–680.
(7) Cole, K. P.; Groh, J. M.; Johnson, M. D.; Burcham, C. L.; Campbell, B. M.; Diseroad, W. D.; Heller, M. R.; Howell, J. R.; Kallman, N. J.; Koenig, T. M.; et al. *Science.* **2017**, *356*, 1144 LP – 1150.
(8) Morse, P. D.; Beingessner, R. L.; Jamison, T. F. *Isr. J. Chem.* **2017**, *57*, 218–227.
(9) Nagy, K. D.; Shen, B.; Jamison, T. F.; Jensen, K. F. *Org. Process Res. Dev.* **2012**, *16*, 976–981.
(10) Ratner, D. M.; Murphy, E. R.; Jhunjhunwala, M.; Snyder, D. A.; Jensen, K. F.; Seeberger, P. H. *Chem. Commun.* **2005**, 578–580.
(11) Sniady, A.; Bedore, M. W.; Jamison, T. F. *Angew. Chemie Int. Ed.* **2011**, *50*, 2155–2158.
(12) Matthies, S.; McQuade, D. T.; Seeberger, P. H. *Org. Lett.* **2015**, *17*, 3670–3673.
(13) Cancogni, D.; Lay, L. *Synlett* **2014**, *25*, 2873–2878.
(14) Xolin, A.; Stévenin, A.; Pucheault, M.; Norsikian, S.; Boyer, F.-D.; Beau, J.-M. *Org. Chem. Front.* **2014**, *1*, 992–1000.
(15) Aronow, J.; Stanetty, C.; Baxendale, I. R.; Mihovilovic, M. D. *Monatshefte für Chemie - Chem. Mon.* **2019**, *150*, 11–19.
(16) Marion, K. C.; Wooke, Z.; Pohl, N. L. B. *Carbohydr. Res.* **2018**, *468*, 23–29.
(17) Kinfe, H. H. *Org. Biomol. Chem.* **2019**, *17*, 4153–4182.
(18) Bennett, C. S.; Galan, M. C. *Chem. Rev.* **2018**, *118*, 7931–7985.
(19) Palo-Nieto, C.; Sau, A.; Galan, M. C. *J. Am. Chem. Soc.* **2017**, *139*, 14041–14044.
(20) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304–4309.
(21) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515–13516.
(22) Gin, D. *J. Carbohydr. Chem.* **2002**, *21*, 645–665.
(23) Di Bussolo, V.; Liu, J.; Huffman Jr., L. G.; Gin, D. Y. *Angew. Chemie* **2000**, *112*, 210–213.
(24) Shi, L.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 6939–6940.
(25) Sau, A.; Williams, R.; Palo-Nieto, C.; Franconetti, A.; Medina, S.; Galan, M. C. *Angew. Chemie* **2017**, *129*, 3694–3698.
(26) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4* (22), 3979–3981.
(27) Chen, G.; Franck, R. W.; Yang, G.; Blumenstein, M. *Can. J. Chem.* **2002**, *80* (8), 894–899.
(28) Yalamanchili, S.; Lloyd, D.; Bennett, C. S. *Org. Lett.* **2019,** *21*, 3674-3677.
(29) Saliba, R. C.; Wooke, Z. J.; Nieves, G. A.; Chu, A.-H. A.; Bennett, C. S.; Pohl, N. L. B. *Org. Lett.* **2018**, *20* (, 800–803.
(30) Ganguly, D.; Tang, H.; Rodriguez, M. J. *Synth. Commun.* **2007**, *37*, 4219–4226.
(31) Noecker, L.; Duarte, F.; Bolton, S. A.; McMahon, W. G.; Diaz, M. T.; Giuliano, R. M. *J. Org. Chem.* **1999**, *64*, 6275–6282.
(32) Yadav, J. S.; Subba Reddy, B. V; Vijaya Bhasker, E.; Raghavendra, S.; Narsaiah, A. V. *Tetrahedron Lett.* **2007**, *48*, 677–680.
(33) Paul, S.; Jayaraman, N. *Carbohydr. Res.* **2004**, *339*, 2197–2204.
(34) Panza, M.; Pistorio, S. G.; Stine, K. J.; Demchenko, A. V.. *Chem. Rev.* **2018**, *118*, 8105–8150.
(35) Xie, T.; Zheng, C.; Chen, K.; He, H.; Gao, S. *Angew. Chemie Int. Ed.* **2020**, *11*, 4360-4364..

(36) Antal, N.; Fiedler, H.-P.; Stackebrandt, E.; Beil, W.; Ströch, K.; Zeeck, A. *J. Antibiot. (Tokyo).* **2005**, *58*, 95–102.
(37) Henkel, T.; Rohr, J.; Beale, J. M.; Schwenen, L. *J. Antibiot. (Tokyo).* **1990**, *43*, 492–503.
(38) Lee, J.; Kang, J.; Lee, S.; Rhee, Y. H. *Angew. Chemie Int. Ed.* **2020**, *59* (6), 2349–2353.
(39) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
(40) Patschinski, P.; Zhang, C.; Zipse, H. *J. Org. Chem.* **2014**, *79*, 8348–8357.
(41) Glöckner, S.; Tran, D. N.; Ingham, R. J.; Fenner, S.; Wilson, Z. E.; Battilocchio, C.; Ley, S. V. *Org. Biomol. Chem.* **2015**, *13*, 207–214.
(42) Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888–12896.
(43) Iversen, T.; Bundle, D. R. *J. Chem. Soc. Chem. Commun.* **1981**, 1240–1241.
(44) Mizia, J. C.; Bennett, C. S. *Org. Lett.* **2019**, *21*, 5922–5927.
(45) Yalamanchili, S.; Miller, W.; Chen, X.; Bennett, C. S. *Org. Lett.* **2019**, *21* (23), 9646–9651.
(46) Lloyd, D.; Bennett, C. S. *Chem. Eur. J.* **2018**, *24*, 7610–7614.
(47) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63* (13), 4172–4173.



The use of continuous flow platform for the rapid and highly efficient construction of differentially protected glycals from commercial sources is described.