

Multistep Synthesis

International Edition: DOI: 10.1002/anie.201802256
German Edition: DOI: 10.1002/ange.201802256

7-Step Flow Synthesis of the HIV Integrase Inhibitor Dolutegravir

Robert E. Ziegler, Bimbisar K. Desai, Jo-Ann Jee, B. Frank Gupton, Thomas D. Roper,* and Timothy F. Jamison*

Abstract: Dolutegravir (DTG), an important active pharmaceutical ingredient (API) used in combination therapy for the treatment of HIV, has been synthesized in continuous flow. By adapting the reported GlaxoSmithKline process chemistry batch route for Cabotegravir, DTG was produced in 4.5 h in sequential flow operations from commercially available materials. Key features of the synthesis include rapid manufacturing time for pyridone formation, one-step direct amidation of a functionalized pyridone, and telescoping of multiple steps to avoid isolation of intermediates and enable for greater throughput.

HIV is a disease that currently affects around 37 million people.^[1] A number of innovative medicines has made HIV a manageable disease; however, the cost of treatment is still prohibitive for many patients in lower income countries.^[2] As part of the “Medicines for All” initiative funded by the Bill and Melinda Gates Foundation,^[3] our research groups are focused on providing greater access to essential medicines for serious diseases such as HIV, tuberculosis, and malaria. The initiative has led to a number of reported studies.^[4] We became interested in Dolutegravir due to its importance in HIV combination therapy.

Dolutegravir (DTG) **1** (Figure 1) is an HIV integrase inhibitor co-developed by GlaxoSmithKline (GSK) and Shinogi that was approved by the Food and Drug Administration (FDA) in 2013. Integrase inhibitors prevent the HIV virus from inserting into cellular DNA by blocking trans-esterification, a process that is vital for replication and spread of the disease.^[5] Raltegravir **2** and Elvitegravir **3** were the first integrase inhibitors to be approved and used in combination therapy; however, these two drugs require large doses and a pharmacokinetic booster, respectively, and have shown vulnerability to HIV virus mutations.^[6] DTG is an un-

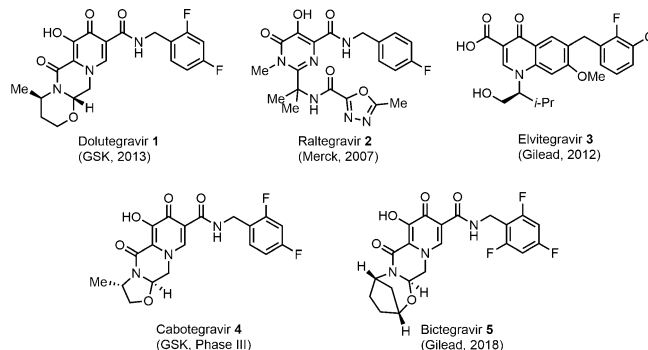


Figure 1. Integrase inhibitors for HIV treatment.

boosted, once daily 50 mg tablet that is recommended as a universal first-line treatment in combination therapy due to its low dosage and limited side effects.^[7] Only minimal resistance has been observed thus far, which has not led to significant spread of HIV virus after mutation.^[6] The high resistance and minimal side effects have led DTG to be placed on the World Health Organization’s List of Essential Medicines.^[8] Recently, the first two drug combination therapy for HIV (Dolutegravir and Rilpivirine) was approved by the FDA.^[9] A number of DTG analogues are currently in clinical trials, including Cabotegravir **4** and Bictegravir **5**; the latter was recently approved by the FDA in a single tablet, three drug regimen (Figure 1).^[10] These analogues differ from Dolutegravir **1** in the oxazine ring size; thus, a synthesis for DTG should also be amenable to **4** or **5** if they emerge as the integrase inhibitor of choice in the future.

GSK and Shinogi disclosed a number of approaches to the synthesis of **1** and its analogues.^[11] Initial medicinal chemistry routes exploited commercially available heterocycles such as nicotinic acid and maltol, and subsequently installed the requisite functionalized N-H pyridone in ten or more steps.^[11b-d] Wang and co-workers from GSK later published a highly efficient, chromatography-free approach to Cabotegravir **4** through rapid formation of the functionalized pyridone core **8** and subsequent cyclization with (*S*)-alaninol **11** to synthesize the 5-membered oxazine ring (Scheme 1).^[11e-f] We wished to optimize and adapt the synthesis to a continuous flow system in order to streamline manufacturing of the API.^[12] Continuous flow reactions benefit from increased mixing due to high surface area to volume ratio and the ability to heat solvents well past their boiling point.^[13] By developing an efficient flow synthesis and telescoping steps to avoid purifications, we felt we could achieve a short, scalable synthesis of DTG **1**.

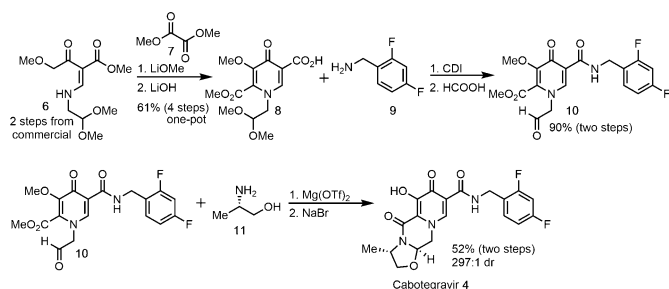
We began our investigation with the condensation reaction of methyl 4-methoxyacetate **12** and dimethylforma-

[*] Dr. R. E. Ziegler, Prof. Dr. T. F. Jamison
Department of Chemistry, Massachusetts Institute of Technology
77 Massachusetts Avenue, Cambridge, MA 02139 (USA)
E-mail: tfj@mit.edu

Dr. B. K. Desai, Dr. J. Jee, Prof. Dr. B. F. Gupton, Prof. Dr. T. D. Roper
Department of Chemical and Life Science Engineering
Virginia Commonwealth University, Biotech 8
737 N. 5th Street, Richmond, VA 23219 (USA)
E-mail: tdroper@vcu.edu

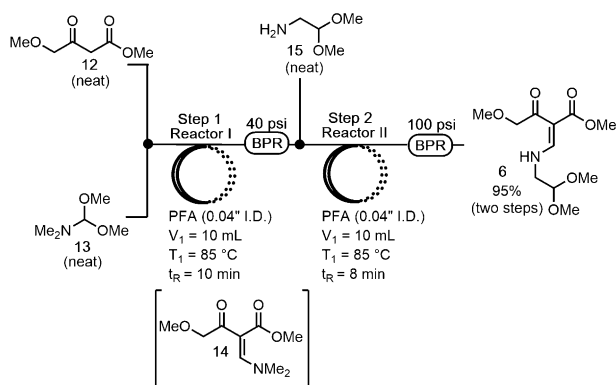
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.201802256>.

© 2018 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.



Scheme 1. GSK process synthesis of Cabotegravir **4**.

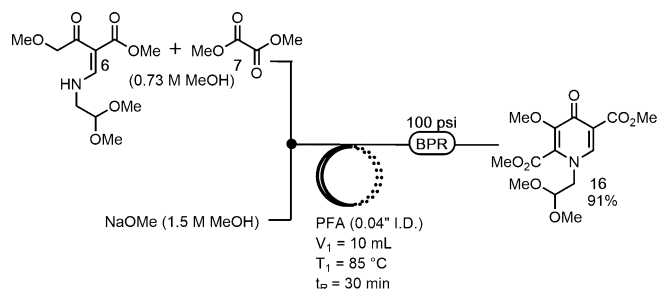
mid dimethylacetal (DMF-DMA) **13**. Our first attempt at the analogous flow reaction proceeded with 60% conversion to **14** when an equimolar ratio of the neat reactants **12** and **13** were streamed through a T-mixer at 30°C with a residence time (t_R) of 10 min. Further optimization led to the discovery that an elevated reaction temperature of 85°C and 1.6 equiv of DMF-DMA **13** resulted in full conversion of **12** to **14** via HPLC with the same 10 min residence time.^[14] With an efficient approach to the dimethyl vinylogous amide **14**, we next sought to telescope Steps 1 and 2 in continuous flow (Scheme 2). This was achieved by connecting Reactor I with



Scheme 2. Telescoped flow synthesis of vinylogous amide **6**. PFA = perfluoroalkoxy, I.D. = inside diameter.

a T-mixer and adding neat aminoacetaldehyde dimethylacetal **15** directly to the output of Reactor I. Due to the high crystallinity of the product **6**, we conducted Step 2 at 85°C to increase solubility and avoid clogging. The optimized telescoped flow process produced **6** in an isolated yield of 95% and a throughput of 43 g h⁻¹.

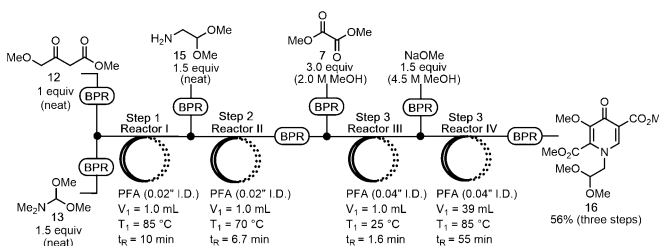
The next step in the reaction sequence was the pyridone **16** formation (Scheme 3). Given the complexity of adapting to continuous flow, we first examined the independent flow process by starting with purified vinylogous amide **6**. The choice of solvent for the reaction proved to be crucial given both **6** and dimethyl oxalate **7** are solids. A solvent screen in batch showed that CH₃CN afforded the highest conversion (93%) to product **16** compared to *N*-methylpyrrolidinone and MeOH (both 85%); however the CH₃CN condition suffered from poor solubility that led to clogging in flow.^[14] In addition, when examining different bases for the deprotonation/cyclization sequence, NaOMe in MeOH had much better sol-



Scheme 3. Pyridone **16** formation in flow.

ubility and conversion to **16** than LiOMe, which was utilized in the GSK synthesis.^[11e,f] These screening results in batch led us to investigate Step 3 in flow using NaOMe as base and MeOH as solvent in order to simplify the system through the use of a single solvent. Following optimization of residence time and temperature,^[14] flow conditions of 85°C and 30 min t_R led to a 91% isolated yield of **16** (Scheme 3).

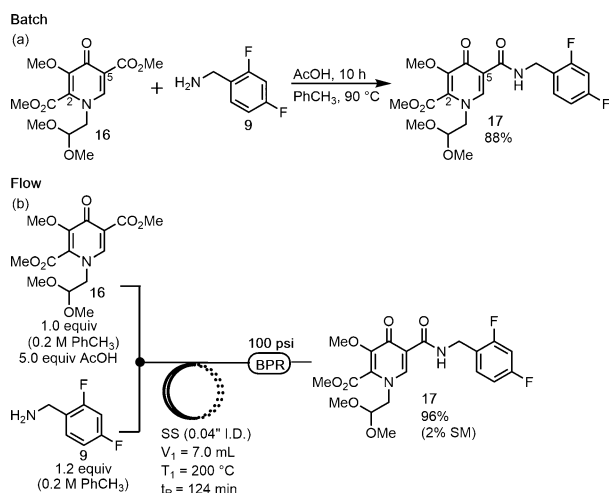
Next, we examined the synthesis of pyridone **16** from **12** in a three-step telescoped process to obviate time consuming purification operations and work towards our goal of a fully continuous synthesis (Scheme 4). After minor modifications



Scheme 4. Three-step telescoped synthesis of pyridone **16**.

to the previously optimized flow conditions from Scheme 2 and Scheme 3, the telescoped synthesis of **16** was achieved. In this setup, several 40 psi back pressure regulators (BPR) were utilized as check valves and Reactor III was used to facilitate premixing of solution **7** with the output from Reactor II prior to the addition of NaOMe. A 55 min residence time in Reactor IV was required for the reaction to reach completion. The three-step telescoped synthesis of pyridone **16** led to a 56% isolated yield in a total residence time of 74 min with a throughput of 3.4 g h⁻¹.

When considering ways to shorten the reported GSK synthesis, the ester saponification to form **8** and subsequent amide coupling stood out as an opportunity. Specifically, in GSK's synthesis of Cabotegravir **4** (Scheme 1),^[11e,f] ester **16** was saponified to the 5-carboxylic acid **8** and then treated with carbonyldiimidazole (CDI) and difluorobenzylamine **9** to form amide product **17**. The process required a filtration and extraction, and took 17 h in total. We were encouraged by a similar direct amidation that was reported in the midst of our own studies.^[15] Application of Kumar and co-workers' AcOH-catalyzed conditions led to high yield and chemoselectivity for amidation at the 5-position, producing amide **17**



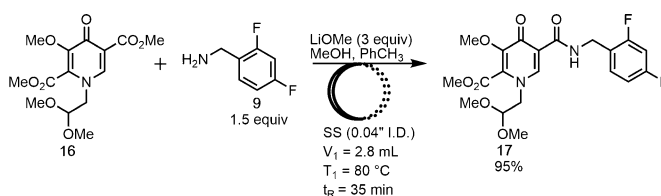
Scheme 5. Direct amidation comparison. SS = stainless steel.

after 10 h (Scheme 5a). We reason that there is both an electronic and steric effect which led to the selectivity. When the corresponding N-H pyridone was reacted under the same conditions, a 2:1 selectivity for 5-amidation over 2-amidation was observed. The only byproducts observed on a gram scale batch reaction of **16** were ring opened starting material **6** and the analogous difluorobenzyl vinylogous amide (< 5% each). An ethyl ester substrate gave comparable yield and AcOH was found to be necessary for practical reaction time.^[16] A brief screen of Brønsted and Lewis acids revealed that the batch reaction could be accelerated compared to the AcOH condition, but with a decrease in isolated yield due to other byproducts and generally poorer solubility.

The next step was to adapt the process to a flow setup. Initially, we examined the reaction at 120 °C with a residence time of 1 h. Gratifyingly, product **17** was obtained with the use of a 100 psi BPR albeit in low conversion of starting material **16**. A systematic evaluation of temperature and residence time led to good conversion at 150 °C with a 1 h residence time and at 180 °C with a 30 min residence time.^[14] We screened other solvents and found that dioxane and CH₃CN were viable, but gave lower conversion than PhCH₃ in the flow setup. DCE led to clogging in the system, and DMF and MeOH failed to produce any desired amide **17** after 1 h. Under the optimal conditions of 200 °C with a residence time of 124 min, we obtained 96% isolated yield of amide **17** (2% recovered **16**) on a 3 mmol scale, which amounted to 3.5 g h⁻¹ (Scheme 5b).

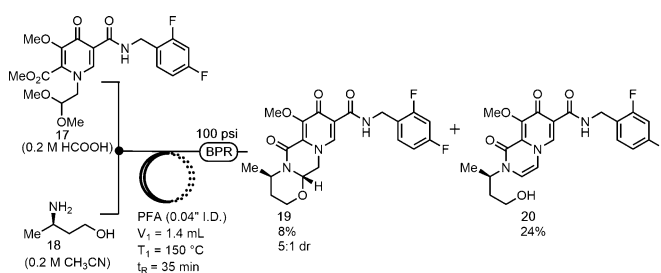
The analogous base-promoted amidation^[17] was also feasible using either LiOMe or NaOMe as base in a MeOH/PhCH₃ mixed solvent system. The optimized flow process led to both shorter residence time and milder temperature compared to the acid-mediated method (Scheme 6). However, attempts to telescope the basic amidation into the subsequent downstream process led to extensive clogging issues.

Next, we examined the acetal deprotection of **17** and cyclization with (*R*)-3-aminobutan-1-ol **18** in flow. Initial attempts were conducted on purified pyridone amide **17** with an acid additive and amino alcohol **18**. Ultimately, we found



Scheme 6. Base-promoted direct amidation in flow.

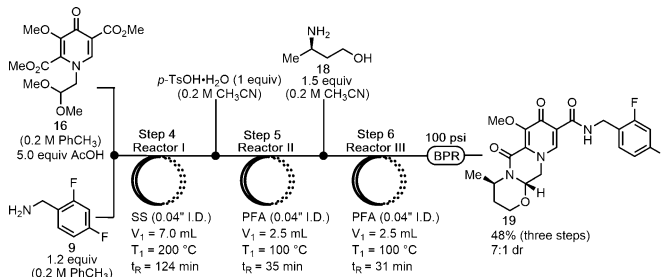
that formic acid was required as a co-solvent to observe any conversion of **17**. Our best result afforded an 8% yield of DTG-OMe **19** as a 5:1 mix of diastereomers favoring the desired product (Scheme 7).^[18] The major byproducts were ring-opened **20**, produced through elimination of the hemi-



Scheme 7. Initial cyclization attempts.

aminal ether functionality, and the deprotected pyridone aldehyde **10**. We reasoned that a two-step flow procedure in which an acid would deprotect acetal **17** in one reactor and then meet amino alcohol **18** in a subsequent reactor may be more fruitful for conversion and milder conditions. Gratifyingly, separating the steps gave full conversion and allowed for stoichiometric amounts of *p*-TsOH-H₂O instead of neat formic acid with no observation of elimination byproduct **20**.

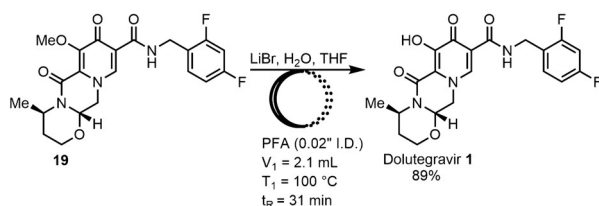
We next sought to telescope the acid-mediated direct amidation into the deprotection/cyclization steps to form a three-step telescoped sequence. Initially, incomplete conversion was observed due to issues with PhCH₃ from Step 4 inhibiting the subsequent steps; however, it was eventually found that more concentrated reaction solutions and longer residence times in Steps 5 and 6 led to full conversion of intermediate amide **17** and aldehyde **10**. The optimized setup proceeded in a total residence time of just over 3 h and a 48% isolated yield of DTG-OMe **19** in 7:1 dr (Scheme 8). The



Scheme 8. Telescoped synthesis of DTG-OMe **19**.

major diastereomer was separated by silica gel chromatography to give analytically pure material.

Finally, we examined the demethylation step in continuous flow as a discrete operation using purified **19**. Following a batch screen of different demethylating reagents, it was found that GSK's published reaction using LiBr gave the best conversion and lowest amount of byproducts.^[11e,f] Reaction temperatures higher than 120 °C led to formation of a similar elimination byproduct to **20**. The batch conditions translated well to flow, with 89% yield of DTG observed at 100 °C with a residence time of 31 min (Scheme 9). The reaction concen-



Scheme 9. Demethylation to form DTG **1**.

tration proved crucial to reproducible, extended running of the continuous flow reactor. DTG **1** was insoluble upon cooling to room temperature, which led to clogging at concentrations higher than 0.5 M THF. Attempts to telescope this final demethylation with the previous three-step sequence in Scheme 8 led to an 8% isolated yield over four steps; however, the same clogging issue meant the system could not be run for more than 10 h at a time.

In conclusion, we have developed a continuous flow synthesis of the HIV integrase inhibitor Dolutegravir **1**. The optimized process described involved seven total steps in three separate flow operations in 24% overall yield (37% overall when Step 3 was run as a separate flow operation).^[19] The key features of the flow route are rapid manufacturing time, direct amidation of ester **16** to reduce the step count, and separation of the acetal deprotection/oxazine formation flow reactors to attain high reactivity and selectivity for tricyclic product DTG-OMe **19**. Importantly, our synthesis should be adaptable to both Cabotegravir **4** and Bictegravir **5** by switching the benzylamine and amino alcohol used in the synthesis. Further studies will focus on the telescoping of all steps to achieve an end-to-end continuous flow synthesis as well as formulation of the final API as its sodium salt and to produce cGMP formulations in an engineered system without the use of silica gel chromatography.

Acknowledgements

We thank the Bill & Melinda Gates Foundation ("Medicines for All" initiative) for funding. We thank Dr. Rachel L. Beingessner and Dr. Justin Lummiss (MIT) as well as Matt Graham, Pooja Panchal, Megan Freeman and Dr. Daniel Cook (VCU) for helpful discussions.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amidation · continuous flow · HIV · multistep synthesis · pyridone

How to cite: *Angew. Chem. Int. Ed.* **2018**, *57*, 7181–7185
Angew. Chem. **2018**, *130*, 7299–7303

- [1] M. Vitoria, A. M. Hill, N. P. Ford, M. Doherty, S. H. Khoo, A. L. Pozniak, *J. Int. AIDS Soc.* **2016**, *19*, 20504–20512.
- [2] A. Gupta, S. Juneja, M. Vitoria, V. Habiyambere, B. D. Nguimfack, M. Doherty, D. Low-Beer, *PLoS One* **2016**, *11*, 1–18.
- [3] Medicines For All website: <https://medicines4all.vcu.edu>.
- [4] For recent publications, see: a) C. E. Ocampo, D. Lee, T. F. Jamison, *Org. Lett.* **2015**, *17*, 820–823; b) A. Sevenich, G.-Q. Liu, A. J. Arduengo 3rd, B. F. Gupton, T. Opatz, *J. Org. Chem.* **2017**, *82*, 1218–1223; c) J. Verghese, C. J. Kong, D. Rivalenti, E. C. Yu, R. Krack, J. Alcazar, J. B. Manley, D. T. McQuade, S. Ahmad, K. Belecki, B. F. Gupton, *Green Chem.* **2017**, *19*, 2986–2991; d) J. Britton, T. F. Jamison, *Angew. Chem. Int. Ed.* **2017**, *56*, 8823–8827; *Angew. Chem.* **2017**, *129*, 8949–8953; e) J. Britton, T. F. Jamison, *Eur. J. Org. Chem.* **2017**, 6566–6574.
- [5] For recent reviews, see: a) M. Su, J. Tan, C.-Y. Lin, *Drug Discovery Today* **2015**, *20*, 1337–1348; b) S.-X. Gu, P. Xue, X.-L. Ju, Y.-Y. Zhu, *Bioorg. Med. Chem.* **2016**, *24*, 5007–5016; c) N. A. Meanwell, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5355–5372; d) M. Psychogiou, G. Poulakou, D. Basoulis, D. Paraskevis, A. Markogiannakis, G. L. Daikos, *Curr. Pharm. Des.* **2017**, *23*, 2552–2567; e) Y. Han, T. Mesplede, M. A. Wainberg, *Expert Opin. Invest. Drugs* **2017**, *26*, 1207–1213.
- [6] M. A. Wainberg, T. Mesplede, *J. Int. AIDS Soc.* **2015**, *18*, 20824–20826.
- [7] P. Cahn, *Curr. Opin. HIV AIDS* **2017**, *12*, 318–323.
- [8] WHO Model List of Essential Medicines. 20th list, March **2017**.
- [9] A. F. Capetti, M. V. Cossu, L. Paladini, G. Rizzardini, *Expert Opin. Pharmacother.* **2018**, *19*, 65–77.
- [10] a) J. Gallant, A. Lazzarin, A. Mills, C. Orkin, D. Podzamczar, P. Tebas, P.-M. Girard, I. Brar, E. S. Daar, D. Wohl, J. Rockstroh, X. Wei, J. Custodio, K. White, H. Martin, A. Cheng, E. Quirk, *Lancet* **2017**, *390*, 2063–2072; b) P. E. Sax, A. Pozniak, M. L. Montes, E. Koenig, E. DeJesus, H.-J. Stellbrink, A. Antinori, K. Workowski, J. Slim, J. Reynes, W. Garner, J. Custodio, K. White, D. SenGupta, A. Cheng, E. Quirk, *Lancet* **2017**, *390*, 2073–2082; c) A. Markham, *Drugs* **2018**, *78*, 601–606.
- [11] For a review, see: a) E. Schreiner, F. Richter, S. Nerdinger, *Top. Heterocycl. Chem.* **2016**, *44*, 187–208; for selected articles, see: b) T. Kawasuji, B. A. Johns, H. Yoshida, T. Taishi, Y. Taoda, H. Murai, R. Kiyama, M. Fuji, T. Yoshinaga, T. Seki, M. Kobayashi, A. Sato, T. Fujiwara, *J. Med. Chem.* **2012**, *55*, 8735–8744; c) T. Kawasuji, B. A. Johns, H. Yoshida, J. G. Weatherhead, T. Akiyama, T. Taishi, Y. Taoda, M. Mikamiyama-Iwata, H. Murai, R. Kiyama, M. Fuji, N. Tanimoto, T. Yoshinaga, T. Seki, M. Kobayashi, A. Sato, E. P. Garvey, T. Fujiwara, *J. Med. Chem.* **2013**, *56*, 1124–1135; d) B. A. Johns, T. Kawasuji, J. G. Weatherhead, T. Taishi, D. P. Temelkoff, H. Yoshida, T. Akiyama, Y. Taoda, H. Murai, R. Kiyama, M. Fuji, N. Tanimoto, J. Jeffrey, S. A. Foster, T. Yoshinaga, T. Seki, M. Kobayashi, A. Sato, M. N. Johnson, E. P. Garvey, T. Fujiwara, *J. Med. Chem.* **2013**, *56*, 5901–5916; e) S. N. Goodman, M. D. Kowalski, D. M. Mans, H. Wang, US 8889877B220141118, **2014**; f) H. Wang, M. D. Kowalski, A. S. Lakdawala, F. G. Vogt, L. Wu, *Org. Lett.* **2015**, *17*, 564–567.

- [12] For recent reviews, see: a) L. Malet-Sanz, F. Susanne, *J. Med. Chem.* **2012**, *55*, 4062–4098; b) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194–1219; c) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2–25; d) D. L. Hughes, *Org. Process Res. Dev.* **2018**, *22*, 13–20; for recent examples, see: e) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2013**, *11*, 1822–1839; f) J. Hartwig, S. Ceylan, L. Kupracz, L. Coutable, A. Kirschning, *Angew. Chem. Int. Ed.* **2013**, *52*, 9813–9817; *Angew. Chem.* **2013**, *125*, 9995–9999; g) S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, B. L. Trout, *Angew. Chem. Int. Ed.* **2013**, *52*, 12359–12363; *Angew. Chem.* **2013**, *125*, 12585–12589; h) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329–332; i) A. D. Martin, A. R. Siamaki, K. Belecki, B. F. Gupton, *J. Org. Chem.* **2015**, *80*, 1915–1919; j) C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945–4948; *Angew. Chem.* **2015**, *127*, 5028–5032; k) A. Adamo, R. L. Beingessner, M. Benham, J. Chen, T. F. Jamison, K. F. Jensen, J.-C. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, T. Stelzer, N. Weeranoppanant, S. Y. Wong, P. Zhang, *Science* **2016**, *352*, 61–67; l) J. C. Yang, D. Niu, B. P. Karsten, F. Lima, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 2531–2535; *Angew. Chem.* **2016**, *128*, 2577–2581; m) N. S. Suveges, R. O. M. A. de Souza, B. Gutmann, C. O. Kappe, *Eur. J. Org. Chem.* **2017**, 6511–6517; n) P. Zhang, N. Weeranoppanant, D. A. Thomas, K. Tahara, T. Stelzer, M. G. Russell, M. O'Mahony, A. S. Myerson, H. Lin, L. P. Kelly, K. F. Jensen, T. F. Jamison, C. Dai, Y. Cui, N. Briggs, R. L. Beingessner, A. Adamo, *Chem. Eur. J.* **2018**, *24*, 2776–2784.
- [13] For selected recent reviews on the benefits of continuous flow, see: a) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389; b) S. V. Ley, D. E. Fitzpatrick, R. J. Ingham, R. M. Myers, *Angew. Chem. Int. Ed.* **2015**, *54*, 3449–3464; *Angew. Chem.* **2015**, *127*, 3514–3530; c) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; *Angew. Chem.* **2015**, *127*, 6788–6832; d) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chem. Int. Ed.* **2015**, *54*, 10122–10136; *Angew. Chem.* **2015**, *127*, 10260–10275; e) P. D. Morse, R. L. Beingessner, T. F. Jamison, *Isr. J. Chem.* **2017**, *57*, 218–227; f) J. Britton, C. L. Raston, *Chem. Soc. Rev.* **2017**, *46*, 1250–1271; g) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.
- [14] See the Supporting Information for complete experimental details.
- [15] S. Sankareswaran, M. Mannam, V. Chakka, S. R. Mandapati, P. Kumar, *Org. Process Res. Dev.* **2016**, *20*, 1461–1468.
- [16] Less than 10% conversion was observed when **9** and **16** were refluxed in PhCH₃ overnight.
- [17] For a continuous flow direct amidation mediated by base, see: J. L. Vrijdag, F. Delgado, N. Alonso, W. M. De Borggraeve, N. Perez-Macias, J. Alcazar, *Chem. Commun.* **2014**, *50*, 15094–15097.
- [18] 5:1 is the thermodynamic ratio of diastereomers, see ref. [11f] for calculations and experimental results.
- [19] Note that reference 11f is for the synthesis of Cabotegravir. GSK's Dolutegravir synthesis has been noted in a patent (reference [11e]), but not described in full detail.

Manuscript received: February 20, 2018

Revised manuscript received: March 30, 2018

Version of record online: May 14, 2018