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Applications of Flow Chemistry in Drug Development: Highlights of Recent Patent Literature

ABSTRACT: Flow chemistry is playing an increasingly important role in API process development and manufacture in the pharmaceutical and fine chemical industry. The current article reviews routes to approved drugs that employ at least one continuous flow step, disclosed in the patent literature during 2016 and 2017, with a further constraint that the chemistry has not been published in a journal article.

For chemists employed in the pharmaceutical and fine chemical industries, the patent literature is often the primary mode of communicating scientific information, including synthetic routes and crystalline forms of complex molecules of pharmaceutical interest. The current article continues a series of reviews intended to highlight interesting and useful chemistry from recent patents and patent applications that has not been published in journal articles.[1] More specifically, this article reviews routes to approved drugs that employ at least one continuous flow step, disclosed in the patent literature during 2016 and 2017. Since the patent applicants have not disclosed manufacturing routes to these drugs, we do not speculate on whether the flow chemistry routes presented in this review are used for commercial manufacture or if they are intended to be implemented in the future. The seven examples reviewed in this article are shown in Table 1.

Table 1. Flow Chemistry Examples

Patent Application	Drug	Flow Chemistry Benefits
Rempex	vaborbactam	Improved diastereoselectivity, purity, reproducibility, and yield; increased productivity
UCB	brivaracetam	Increased throughput with smaller footprint and reduced waste
SARcode	lifitegrast	Improved yield, purity, and reproducibility of a cryogenic reaction
Asymchem	crizotinib	Improved yield, throughput, and process mass intensity
Alphora	ingenol mebutate	Improved regioselectivity
Aurobindo	valacycloir	Improved purity
Lilly	baricitinib	Improved safety and efficiency

Flow chemistry and continuous processing have been commonplace for decades in the petrochemical and bulk chemical industry, as well as for many unit operations in drug formulation, but only recently has continuous processing technology become a major focus of chemical process development in the pharmaceutical industry. Some of the challenges with implementing flow chemistry are presented on the right side of Table 2 and range from equipment challenges to lack of training and regulatory concerns. With technology advances and a growing cadre of scientists trained in flow chemistry, the benefits of flow chemistry are providing increased momentum for implementing continuous processing in API manufacture.[2]

1. VABORBACTAM

Flow Chemistry Benefits: Improved Diastereoselectivity, Purity, Reproducibility, and Yield; Increased Productivity. Vabomere is a combination product that contains Meropenem, a carbapenem antibacterial drug, and vaborbactam, a cyclic boronic acid β-lactamase inhibitor. The FDA approved Vabomere on Aug 29, 2017, for the treatment of complicated bacterial urinary tract infections.

The Medicinal Chemistry route to vaborbactam comprised six steps with an overall yield of 30% (Scheme 1).[3] The synthesis started with TBS-protected β-hydroxy ester **1**, which was prepared by lipase-catalyzed resolution of the corresponding racemate. Iridium-catalyzed hydroboration with pinacoldiborane afforded boronic ester **2**, which was converted to the pinanediol boronate ester **3**. Matteson homologation of **3**, which inserted a −CHCl group stereoselectively, was carried out at a temperature of −95 to −100 °C to afford an 85/15 mixture of diastereomers. Stereospecific nucleophilic displacement of the chloride with LiHMDS afforded silyl amine **5**, which was coupled with 2-thiopheneacetic acid mediated by EDC/HOBt to furnish **6**. Silyl deprotection with HCl resulted in formation of the cyclic boronate, maintaining the 85/15 diastereomeric ratio. Upgrade to pure vaborbactam was accomplished via crystallization from a two-phase water/EtOAc system.

The Matteson homologation chemistry involves two steps: low temperature formation of a borate complex followed by rearrangement with concomitant stereoselective displacement of one chloride (Scheme 2).[4,5] The rearrangement is often mediated by a Lewis acid, with $ZnCl_2$ as the most common choice. Use of $ZnCl_2$ generally improves diastereoselectivity, hypothesized to occur by chelation in the transition state.[6]

According to a recently published abstract, the Matteson homologration step has been evaluated in continuous flow mode as part of the process development of vaborbactam.[7] The details of the continuous flow process are outlined in a 2016 patent application from Rempex.[8]

The schematic for conducting the Matteson homologation in flow is presented in Scheme 3.[8] In reactor #1, *n*-BuLi in heptane was mixed with THF and cooled to −60 °C. Use of THF as cosolvent was necessary to prevent *n*-BuLi precipitation at low temperature. The outflow of reactor #1 was fed into reactor #2, where dichloromethane was introduced as a 39% solution in THF, resulting in the formation of $LiCHCl_2$. The outflow of reactor 2 was mixed in reactor #3 with an input of

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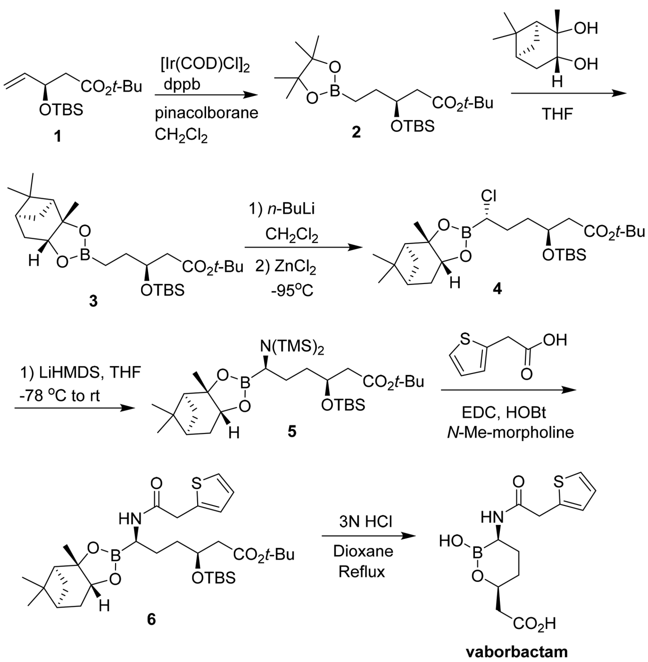
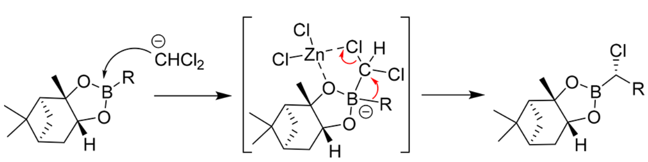
Table 2. Benefits and Challenges for Flow Chemistry/Continuous Processing

Benefits	Challenges
Enabling chemistry that is difficult to scale in batch mode such as electrochemistry, microwave heating, and photochemistry	Chemists have been traditionally trained using batch chemistry; most laboratories are set up for conducting experiments in batch mode
Readily accessing extreme conditions, such as high and low temperatures and high pressures	Large capacity, infrastructure, and knowledge-base worldwide that supports batch chemistry, coupled with lack of such for continuous processing
Straightforward scaleup since mixing and heat transfer are maintained as scale is increased	Uncertainty regarding implementing GMP in continuous processing and concern about acceptance of flow chemistry by regulatory authorities
Safer execution of hazardous chemistry since only a small amount of an unstable intermediate is generated at any one time and the high ratio of surface area to volume allows excellent control of exothermic chemistry.	Handling slurries, heterogeneous reactions
Operational advantages: process intensity, smaller equipment footprint, amenable to automated operation and process analytical technology (PAT), which can lower operating costs and improve reproducibility	Coupling flow chemistry with continuous workup and isolation to maximize environmental gains and reduce overall footprint

Scheme 1. Synthetic Route to Vaborbactam



Scheme 2. Reaction Pathway for Matteson Homologation

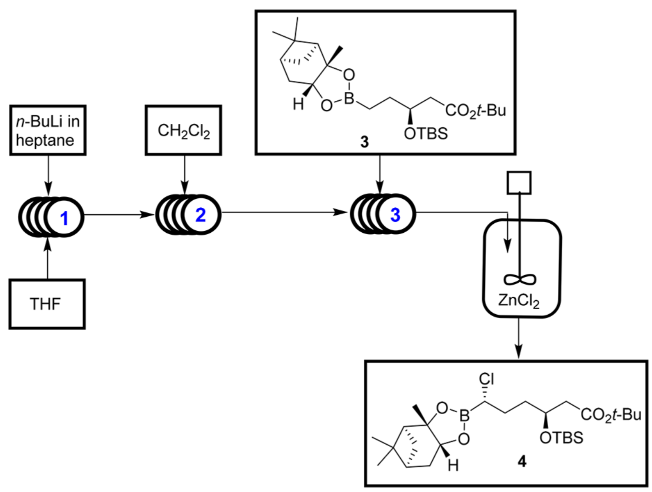


compound **3** as a 29% solution in 1:10 heptane/THF. The output of reactor #3 was then quenched into a 0.7 M $ZnCl_2$ solution in THF at −20 °C. While the $ZnCl_2$ quench could also be carried out in flow, yields were lower and more variable by flow processing than in batch mode.

The isolation was carried out via batch processing. The quench solution was washed with 1 M aqueous HCl followed by bicarbonate and water washes, and then the organic layer was concentrated to an oil and used directly in the next step. Twelve GMP batches were completed in 89% average yield to produce 880 kg of compound **4**.[8]

In addition to substantial productivity gains relative to batch mode, the continuous process also afforded improved diastereoselectivity (95:5 vs 85:15), yield (91% vs 75%), and reproducibility. No rationale was provided for the improved selectivity when the reaction was conducted in flow but may be due to improved mixing and temperature control.

Scheme 3. Schematic of Flow Chemistry for Vaborbactam Matteson Homologation



2. BRIVARACETAM

Flow Chemistry Benefit: Increased Throughput with Smaller Footprint and Reduced Waste. Brivaracetam, marketed under the trade name Briviact, was approved in early 2016 in Europe and the U.S. as adjunct therapy in the treatment of partial-onset seizures in patients with epilepsy.

A route to brivaracetam, described in patent applications from UCB, is presented in Scheme 4.[9] In the first step, valeraldehyde (**7**) was condensed with glyoxylic acid (**8**) catalyzed by morpholine in a two-phase water/heptanes mixture to afford furanone **10** in 96% yield after workup with diisopropyl ether and concentration to a liquid. In step 2, reductive amination with (*S*)-2- aminobutanamide (**11**) was conducted as a three-step one-pot sequence. In the first reaction, an imine was generated from **10** and **11** in 2-PrOH at 5 °C, and then $NaBH_4$ and ammonia were added to reduce the resulting imine, followed by addition of HOAc and warming to 50 °C for 16 h to generate lactam **12**, which was crystallized from 2-PrOAc/heptanes in an overall 88% yield. In the final chemical step, hydrogenation of the double bond using Pd/C afforded a nearly 1:1 mixture of brivaracetam and its diastereomer **13**. The diastereomers were then separated by multicolumn continuous (MCC) chromatography followed by crystallization from 2-PrOAc.

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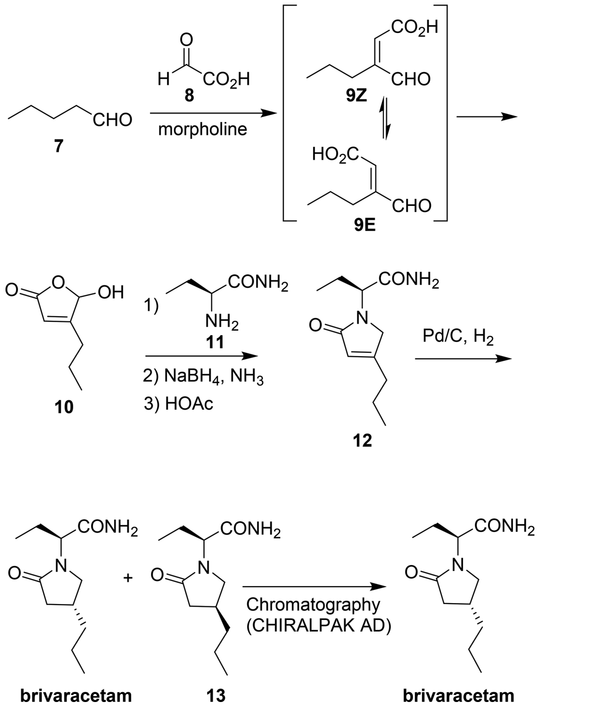
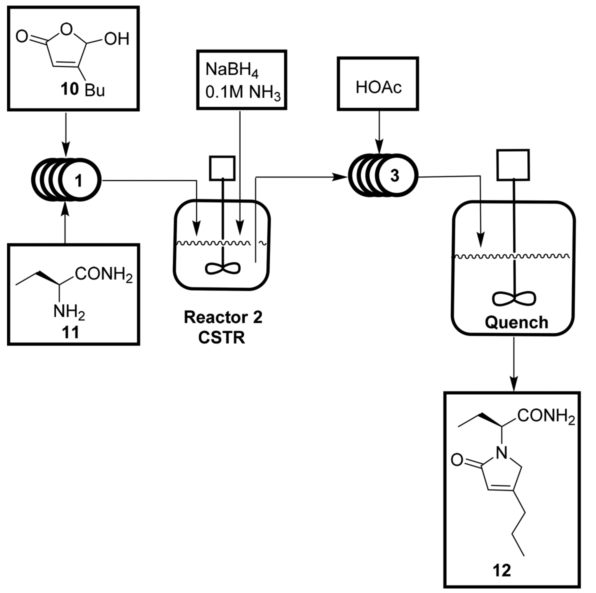
Scheme 4. Route to Brivaracetam



Scheme 5. Continuous Flow Design for Reductive Amination Step of Brivaracetam



In a recent patent application, UCB has reported achieving an 80:20 mixture of diastereomers by conducting the hydrogenation with Pd/C in the presence of citric acid or by use of Pt/C with citric acid or formic acid.[10] UCB has now adapted this route to a process that includes continuous flow processing for each of the three steps combined with batchwise workups.[11a]

For step 1 of the flow process, valeraldehyde (**7**) (1.2 equiv) and glyoxylic acid (**8**) (1.0 equiv) were continuously introduced into a plug flow reactor at 180 °C with a residence time of 5 min. No catalyst nor solvent was used. Batch quench using water, *n*-heptane, and 2-PrOAc was carried out to isolate the crude furanone **10** in 88% yield, which also contained 5–9% of **9E**.

For step 2, (*S*)-2- aminobutanamide (**11**) (1.0 equiv) in EtOH and furanone **10** (1.2 equiv) were introduced in separate streams into plug flow reactor #1 at 40 °C with a residence time of 5 min (Scheme 5). The product from this reactor was fed into a continuous stirred tank reactor (CSTR) in which $NaBH_4$ (0.4 equiv) and ammonia were added continuously, with a residence time of 10 min at 40 °C. The output of this reactor was then fed into a third plug flow reactor along with HOAc (2.55 equiv) with a residence time of 9 min at 105 °C, to afford lactam **12** in 96% yield prior to workup. Purification was carried out via batch processing by extractive workup, with no further details provided.[11a]

The step 3 hydrogenation step incorporated the use of citric acid that afforded improved diastereoselectivity and was carried out in a series of four reactors. Each reactor was set up as a CSTR equipped with a Rushton self-gas-inducing agitator and a filter at the outlet to prevent catalyst transfer. The temperature and catalyst load were adjusted for each reactor. The first reactor was loaded with 10% citric acid and 5% Pd/C in water, warmed to 60 °C, and placed under 20 bar of H_2 pressure. A 20% aqueous solution of **12** along with 10% citric acid was added to reactor #1 in a continuous flow. Steady state in this reactor was reached at 40 min with 50% conversion and an 80/20 ratio of diastereomeric products. This mixture was then fed into reactor #2, also containing catalyst and citric acid under H_2 pressure, at a rate to balance the inflow of starting materials. By the fourth reactor, the typical conversion was 99% with an 80/20 ratio of diastereomers. No details were provided on workup and isolation of the crude product.[11a]

Separation of the 80/20 ratio of diastereomers was carried out on a CHIRALPAK AD stationary phase and a 45/55 mixture of *n*-heptane/EtOH at 25 °C. The purified brivaracetam was recrystallized from 2-PrOAc. Although outside the scope of this review, we note that UCB and Novasep have collaborated to pioneer the use of continuous flow chromatography (simulated moving bed chromatography) for manufacture of Keppra in the 1990s, one of the early examples of the use of continuous processing in API manufacture.[11b]

3. LIFITEGRAST

Flow Benefits: Improved Yield, Purity, and Reproducibility of a Cryogenic Reaction. Lifitegrast (trade name Xiidra) is an ophthalmic solution that was approved in July 2016 in the US for treatment for signs and symptoms of dry eye.

The synthetic route to lifitegrast, described in patents granted to SARcode, involves the preparation of three fragments that are subsequently combined via amide couplings (Scheme 6).[12,13]

The preparation of the central fragment **15** involves a low temperature carboxylation reaction as the final step (Scheme 7). According to a recent patent application from SARcode, this reaction was difficult to scale in batch mode, leading to lower yields and formation of tarry material upon scaleup. Therefore, the SARcode group developed a continuous flow process for the carboxylation reaction, outlined in Scheme 8.[14]

Compound **20** and TMEDA were dissolved in THF and cooled to −78 °C in the first reactor and then introduced into reactor #2 along with 2.5 M *n*-BuLi at −78 °C to generate the anion. The output of this mixture was fed into the third reactor

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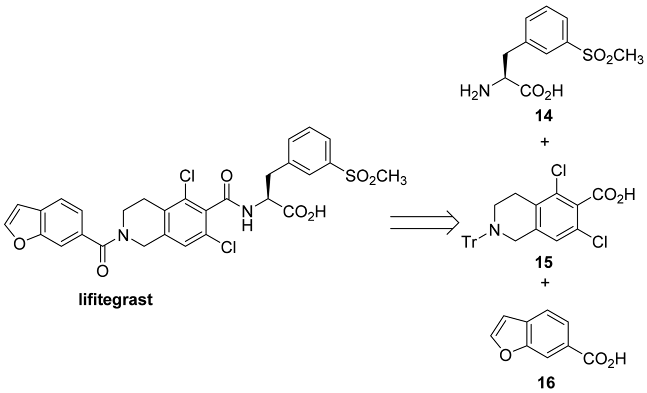
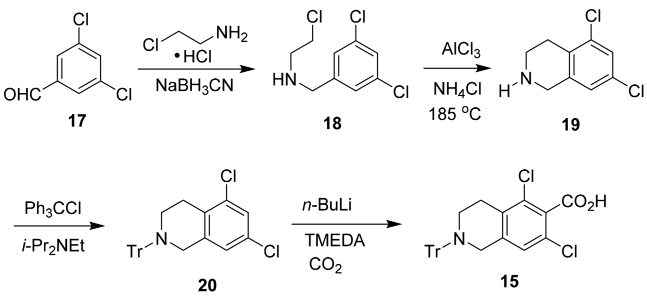
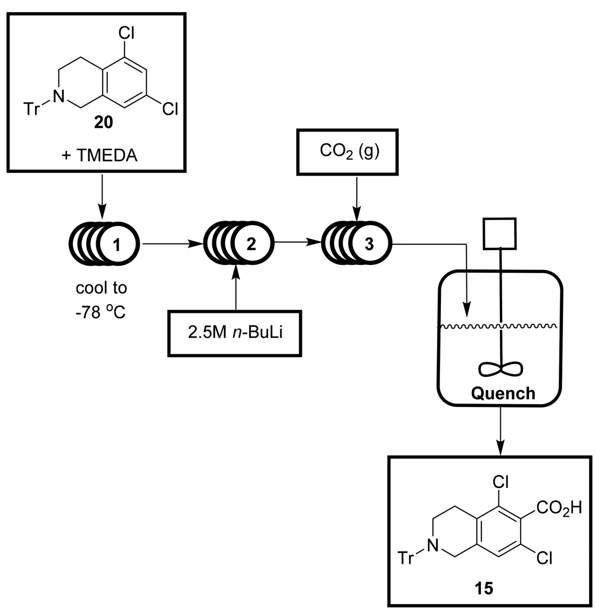
Scheme 6. Retrosynthetic Approach to Lifitegrast



Scheme 7. Synthetic Route to Carboxylic Acid Intermediate 15



Scheme 8. Flow Carboxylation of Intermediate 15



where gaseous CO_2 was introduced to effect the carboxylation of the anion. The outflow was quenched batchwise with 2 N HCl and extracted with EtOAc to afford carboxylic acid **15**.

A few notes of interest from the patent:

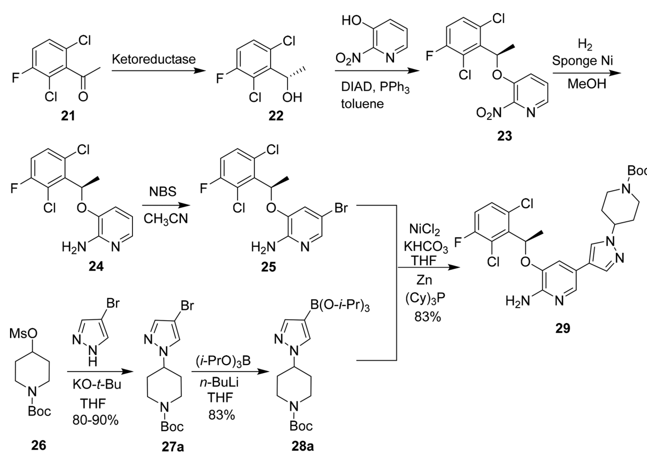
1. *n*-BuLi (1.5 M) had variable lot-to-lot quality that made optimization difficult. The more concentrated 2.5 M BuLi was found to have more consistent quality and was selected for further optimization and scaleup. Residues in the 2.5 M *n*-BuLi required prior filtration to avoid seizing the pumps.
2. Reaction of excess *n*-BuLi with CO_2 resulted in formation of valeric acid, which froze (mp −20 °C) in the lines if the flow rates were too variable.
3. Increasing the concentration of **20** in THF to 10% and lowering the residence time for anion formation to 3.6 min resulted in high conversion at scale.
4. The reaction with CO_2 at −78 °C required a residence time of 1.6 min for complete conversion at scale.
5. Reproducible yields of 88−91% of **15** were achieved in several runs at 4−5 kg scale with consistent product purity of 97−98%. A total of 22 kg of carboxylic acid **15** were prepared.

4. CRIZOTINIB

Flow Benefits: Improved Yield, Throughput, and Process Mass Intensity. Crizotinib (trade name Xalkori) is an ALK inhibitor indicated for the treatment of metastatic nonsmall cell lung cancer whose tumors are ALK-positive. The US approved crizotinib in 2011 followed by Japan and Europe in 2012.

The Pharmacodia Web site provides five graphical summaries of routes to crizotinib or intermediates that have been described in several patents and journal publications.[15] Asymchem recently filed a Chinese patent application for an alternate approach to crizotinib (Scheme 9) that employs flow chemistry for the two-step synthesis of intermediate **28a.**[16]

Scheme 9. Asymchem Route to Crizotinib



The flow chemistry step of the nucleophilic substitution reaction of mesylate **26** with 4-bromopyrazole was described on a 400 g scale. Mesylate **26** was dissolved in 10 volunes of THF containing formic acid (amount not specified). 4-Bromopyrazole and KO-*t*-Bu were dissolved in THF. Both solutions were fed into a coiled tube reactor at 50−60 °C with a residence time of 1−10 min. The outflow of the reactor was quenched batchwise into water, extracted with EtOAc, and concentrated to an oil, providing a yield of 80−90% of **27a** with a crude purity of 93%. This material was used directly in the next step, also conducted in flow.

Pyrazole **27a** and 1.5 equiv of (i-PrO)$_3$B were dissolved in THF in one vessel and continuously fed to a coiled tube reactor along with *n*-BuLi (2.5 M in heptane) at a temperature of −25 to −35 °C with a residence time of 1−10 min. The outflow was quenched into water, the pH was adjusted to pH 3 to 5 with HCl, and then the product was extracted into EtOAc and

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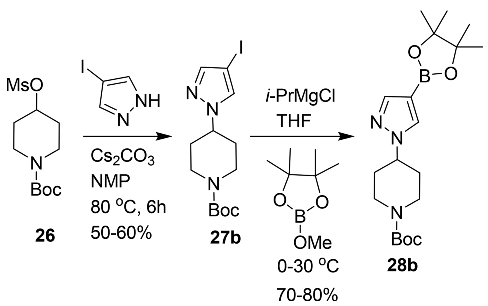
concentrated to afford crude **28a** with 93% purity. Recrystallization from MTBE/EtOAc provides material of 99% purity in 83% yield.

The flow chemistry approach developed by Asymchem improved yield and efficiency relative to the Pfizer route (Scheme 10)[17] and used inexpensive (i-PrO)$_3$B instead of 2-methoxy-4,4,5,5- tetramethyl-1,3,2-dioxaborolane and 4-bromopyrazole instead of 4-iodopyrazole.

Scheme 10. Pfizer Fit-For-Purpose Route to Intermediate 28b



Finally, the Suzuki–Miyaura cross-coupling of **25** and **28a** was carried out with NiCl$_2$/Zn catalysis, replacing the Pd(dppf)$_2$Cl$_2$ used in the Pfizer route,[18] providing Boc-crizotinib **29** in 83% yield after recrystallization from THF/toluene. This step was not conducted under flow conditions.

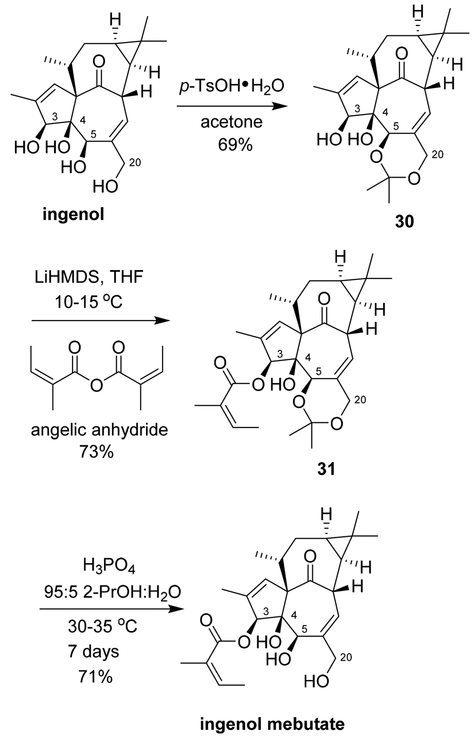
5. INGENOL MEBUTATE

Flow Chemistry Benefit: Improved Regioselectivity. Ingenol mebutate (trade name Picato) is a protein kinase C activator that is approved in the U.S. and Europe for the topical treatment of actinic keratosis, a skin disease associated with sun exposure which potentially can develop into skin cancer. According to the European Public Assessment Report (EPAR), published in 2012, ingenol mebutate is obtained by extraction of the aerial (above ground) portion of the plant *Euphoria peplus* followed by a series of purification steps and a final crystallization.[18] In a paper on the total synthesis of ingenol from the Baran group, the authors note that only 1.1 mg of ingenol mebutate can be isolated per kilogram of plant material. Ingenol itself is available in larger quantities (275 mg per kilogram) from the seeds of the plant *E. lathryis* and, therefore, could serve as a starting material for a less expensive semisynthesis of ingenol mebutate.[19]

Ingenol has four hydroxyl groups that can potentially be acylated (3, 4, 5, and 20). To achieve selective acylation of the desired alcohol at the 3-position, Leo Laboratories developed a process in which the C5- and C20-hydroxyl groups were protected as acetonide **30**, thereby allowing selective acylation of the 3-position to afford ester **31** (Scheme 11).[20] The overall yield for the 3-step sequence was 37%. While this sequence achieved regioselective acylation and a crystalline final product, the overall yield was modest and the final deprotection of **31** had to be carefully controlled (aqueous phosphoric acid in 2-PrOH, 7 day reaction time) to avoid isomerization of the double bond of the side chain to the *E*-form (ingenol tiglate, Figure 1). This impurity arose under stronger acid conditions and required removal by chromatography when present at a level ≥2%.[20]

To avoid the protection/deprotection sequence, a 2017 patent application from Alphora describes use of flow chemistry

Scheme 11. Three-Step Regioselective Acylation of Ingenol



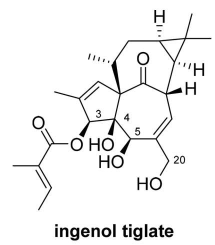


Figure 1. Structure of ingenol tiglate.

to synthesize ingenol mebutate directly from ingenol using no protecting groups.[21] According to the patent application, the batchwise acylation of unprotected ingenol using the best conditions reported by Leo Laboratories[20] (LiHMDS, THF, angelic anhydride, 10–15 °C, 10 min reaction time) resulted in a yield of 11% of the desired C3-acylated product, with the major products resulting from acylation of the C20 primary alcohol and the C3,C20-bis acylated product. Optimization of the chemistry in batch mode provided improved yields to 20–30% of the C3 product but with high variability.

Flow conditions afforded improved regioselectivity of the C3 product (Scheme 12).[21] Under optimized conditions, a stream containing ingenol/LiHMDS (0.25 M in 2-MeTHF) was mixed with a stream of angelic anhydride (0.25 M in 2-MeTHF) at 0 °C, followed by a continuous quench with a third stream of 1 M HCl at 25 °C. Regioselectivity for the C3 product of 40% was achieved. Purification by silica gel chromatography afforded the C3 product (95% purity) in 40% isolated yield, 29% recovery of ingenol, 12% yield of C20 monoacylated product, and 10% yield of the C3,C20-bis acylated product. The fractions containing C20 and C3,C20-bis esters were hydrolyzed back to ingenol with LiOH in THF/water.[21]

The 40% yield for acylation at the C3 secondary alcohol is surprising given the likely kinetic preference for the C20

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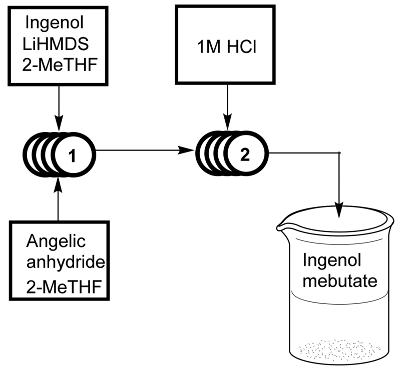
Scheme 12. C3 Acylation of Ingenol Using Flow Chemistry



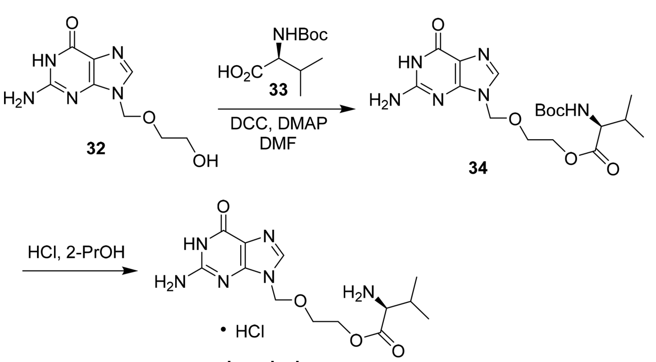
primary alcohol, and it remains unclear why the regioselectivity would be improved under flow conditions relative to batch mode. While the ratio of ingenol to angelic anhydride is not provided in the patent application, from the reported results it appears that angelic anhydride is undercharged relative to ingenol. Under these conditions, where bis-acylation is less likely to occur, the C3 position may represent the thermodynamically most stable product and transesterification from C20 to C3 may be occurring.

The 40% yield, while modest, is comparable to the overall 37% yield for the three-step process using the protection/deprotection (Scheme 11), is operationally simpler in requiring just a single step, and offers the opportunity to recover and recycle starting material and the side products, which can also be hydrolyzed back to ingenol. Although the route requires chromatography for purification, this may not be a significant downside considering the low volume of product and high expense of the ingenol starting material.

6. VALACYCLOVIR

Flow Chemistry Benefit: Improved Purity. Valacyclovir is a generic antiviral drug used for the treatment of the herpes virus. The two-step synthetic route to valacylovir (Scheme 13)

Scheme 13. Two-Step Preparation of Valacyclovir



includes a DCC-mediated amide bond formation of acyclovir (**32**) with Boc-L-valine (**33**) followed by acidic deprotection of the Boc-group. Aurobindo has published a patent application describing flow chemistry for the deprotection step.[22] The batchwise deprotection involved treatment of the penultimate intermediate **34** with aqueous HCl at room temperature for 2 h followed by addition of 2-PrOH to crystallize valacyclovir. However, according to the Aurobindo patent application, the yield was only 30% and the purity of the product was 96.6% with the major impurities of acyclovir (**32**, 2.45%) and guanine (0.24%). By conducting the deprotection in flow, the inventors were able to increase the yield and product purity.

The deprotection was carried out in flow mode as follows: penultimate **34** was prepared as a 10% solution in 1:3 MeOH/CH_2Cl_2 and fed into a reactor at 80 °C simultaneously with 2.5 M HCl in 4:1 water/MeOH. The residence time was not provided. The outflow of the reactor was collected batchwise, forming two layers. The aqueous layer containing product was separated, and then the pH was adjusted to 2.5−2.8 with triethylamine. EtOH was added to crystallize valacyclovir, which was isolated in 65% yield and 99% purity.

7. BARICITINIB

Flow Chemistry Benefits: Safer and More Efficient Oxidation with Oxygen at High Pressure; No Need for Specialized Large Scale Equipment. Baricitinib phosphate (trade name Olumiant) was approved in the EU in Feb 2017 for the treatment of moderate-to-severe rheumatoid arthritis in adult patients.[23]

The Medicinal Chemistry disconnections to baricitinib described in Incyte patents are shown in Figure 2, with the

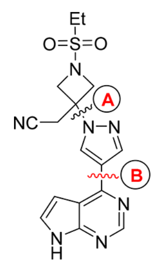


Figure 2. Retrosynthetic disconnections of baricitinib.

lower and central fragments coupled first at point B followed by appending the upper portion via coupling at point A.[24] In a recent patent application from Lilly, coupling at point A is carried out first followed by point B.[25]

Of interest for this article is the use of flow chemistry for a high pressure, oxygen-based oxidation in the Lilly route to azetidine intermediate **40**. The Medicinal Chemistry route to this fragment, Scheme 14, began with epichlorohydrin (**35**) and required protecting group manipulations en route to **40**. The oxidation of alcohol **37** to ketone **38** was accomplished using TEMPO/bleach.[24]

The Lilly approach requires no protecting groups and starts with unprotected azetidin-3-ol (**42**) (Scheme 15).[25] In the first step, **42** was reacted with $EtSO_2Cl$ to generate sulfonamide **43**. Oxidation to the ketone is described both in batch and flow mode. Batch processing using 6% oxygen in nitrogen, a concentration of oxygen that will not support combustion, was carried out at 500 psi with the headspace being refreshed every minute over 17 h. For the reaction in flow, the reactants and reagents were supplied in four feeds: (1) TEMPO in CH_3CN, (2) $NaNO_2$ in water, (3) alcohol **43** in 1:6 $HOAc/CH_3CN$, and (4) 6% O_2 in N_2. The back pressure was set at 500 psi and the residence time was 12 h, resulting in an assay yield of 98%, and an 87% yield after batch workup. The productivity under flow conditions was similar to that in batch, with similar concentrations of starting material and reagents. The advantages of the flow route include (1) no need for a

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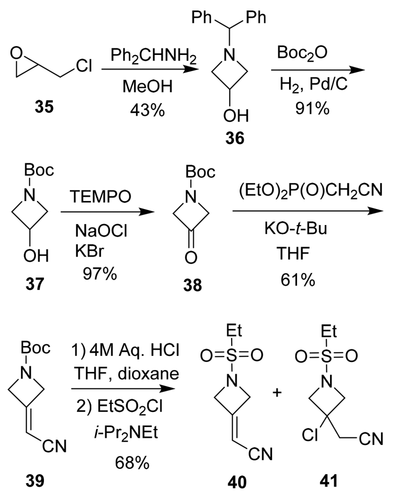
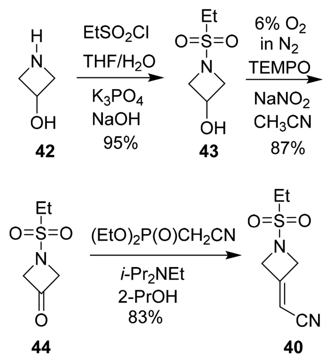
Scheme 14. Medicinal Chemistry Route to Azetidine Fragment 40



Scheme 15. Lilly Route to Azetidine Fragment 40



specialized large scale vessel rated to >500 psi, (2) no need for continuous replacement of oxygen in the head space, and (3) improved safety considering the smaller footprint for the high pressure reaction.

■ SUMMARY

While journal publications on flow chemistry from both academic and industrial scientists have increased enormously over the past two decades, a substantial amount of innovative chemistry from industrial scientists is published only in the patent literature. While patents generally provide few details and minimal perspective, they offer unique insights into chemistry carried out with molecules of pharmaceutical interest not often found in journal publications.

Flow chemistry and continuous processing for API manufacture offer potential advantages relative to batch processing:

- implementation of chemistry not readily amenable to scaleup in batch mode (electrochemistry, photochemistry, microwave heating);
- the opportunity for improved purity and selectivity;
- ready introduction and use of PAT and automation;
- reduced equipment footprint; and
- decreased environmental impact.

Several obstacles that hindered the initial uptake of flow chemistry continue to be addressed through equipment and technological advances, through education and training, and through active and open dialogue with regulatory agencies. In this article we have reviewed seven recent examples where chemistry for API manufacture originally developed for batch processing has been adapted to continuous flow to overcome specific limitations associated with batch processing. These examples offer just a glimpse into the significant effort underway in process chemistry and engineering in the pharmaceutical and fine chemical industries to transition current processes from batch to flow and to design processes for flow processing from the outset of development.

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Notes

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■ ABBREVATIONS

CSTR, continuous stirred tank reactor; DCC, *N,N′*-dicyclohexylcarbodiimide; EPAR, European Public Assessment Report; LiHMDS, Lithium bis(trimethylsilyl)amide; MTBE, Methyl *tert*-butyl ether; PAT, Process Analytical Technology; TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl

■ REFERENCES

(1) Previous article in this series: Hughes, D. L.; Wheeler, P.; Ene, D. *Org. Process Res. Dev.* **2017**, *21*, 1938−1962.

(2) Three special issues of *Org. Process Res. Dev.* have been devoted to flow chemistry (Feb 2016, Nov 2014, and May 2012), speaking to the relevance of flow chemistry in pharmaceutical process chemistry. The 2016 special issue contained 26 articles on flow chemistry. Published reviews and Internet articles regarding flow chemistry: (a) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796−11893. (b) *Sustainable Flow Chemistry, Methods and Applications*, Ed. Vaccaro, L. Wiley-VCH, Weinheim, Germany, 2017. (c) Britton, J.; Raston, C. L. *Chem. Soc. Rev.* **2017**, *46*, 1250−1271. (d) Deadman, B. J. *Flow Chemistry, SSPC Masterclass in Synthetic Organic Chemistry*, Sep 4, 2014. https://s3-eu-west-1.amazonaws.com/pfigshare-u-files/1675768/SSPCMasterclassonFlowChemistry.pdf (accessed Oct 30, 2017). (e) https://syrris.com/applications/flow-chemistry-applications/ (accessed Nov 3, 2017).

(3) Hecker, S. J.; Reddy, K. R.; Totrov, M.; Hirst, G. C.; Lomovskaya, O.; Griffith, D. C.; King, P.; Tsivkovski, R.; Sun, D.; Sabet, M.; Tarazi, Z.; Clifton, M. C.; Atkins, K.; Raymond, A.; Potts, K. T.; Abendroth, J.; Boyer, S. H.; Loutit, J. S.; Morgan, E. E.; Durso, S.; Dudley, M. N. *J. Med. Chem.* **2015**, *58*, 3682−3692.

(4) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077−2078.

(5) http://www-oc.chemie.uni-regensburg.de/OCP/ch/chb/oc5/B_Organometallics.pdf (accessed Nov 15, 2017).

(6) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3711−3713.

(7) Vasiloiu, M.; Stuckler, C.; Steinhofer, S.; Schuster, C.; Boyer, S.; Hecker, S. *Development, Scale up and Manufacturing of Vaborbactam at Patheon Austria: a Case Study for Continuous Processes in Manufacture of APIs*. 17th Austrian Chemistry Days, Salzburg, Austria, Sep 25, 2017. MS-51. Oral Presentation. http://www.chemietage.at/abstracts/MS-51.pdf (accessed Nov 15, 2017).

(8) Felfer, U.; Stueckler, C.; Steinhofer, S.; Pelz, A.; Hanacek, M.; Pabst, T. H.; Winkler, G.; Poechlauer, P.; Ritzen, B.; Goldbach, M.

DOI: 10.1021/acs.oprd.7b00363
Org. Process Res. Dev. 2018, 22, 13−20

Apparatus and Continuous Flow Process for Production of Boronic Acid Derivatives. PCT Int. Patent Application WO 2016/100043, Jun 23, 2016.
(9) (a) Differding, E.; Kenda, B.; Lallemand, B.; Matagne, A.; Michel, P.; Pasau, P.; Talaga, P. 2-Oxo-1-pyrrolidine Derivatives, Processes for Preparing Them and Their Uses. U.S. Patent 6,911,461, Jun 28, 2005. (b) Kenda, B.; Pasau, P.; Lallemand, B. 2-Oxo-1-pyrrolidine Derivatives, Processes for Preparing Them and Their Uses. U.S. Patent 8,492,416, Jun 23, 2013.
(10) Defrance, T.; Septavaux, J.; Nuel, D. Process for Preparing Brivaracetam. PCT Int. Patent Application WO 2017/076738A1, May 11, 2017.
(11) (a) Norrant, E.; Nuel, D.; Giordano, L.; LeClaire, J.; Septavaux, J. Continuous Process for Preparing Brivaracetam. PCT Int. Patent Application WO 2017/076737A1, May 11, 2017. (b) Hilbold, N. J.; Rousset, F. *Innovations Pharm. Tech.* **2016**, Issue 48, 44−47. https://www.novasep.com/media/articles-and-publications/85novasep-ipt-continuous-chromatography-in-biopharma.pdf (Accessed Nov 21, **2017**).
(12) The route to lifitegrast is graphically described on the Pharmacodia web site: http://en.pharmacodia.com/web/drug/1_646.html (accessed Nov 10, 2017).
(13) (a) Zeller, J. R.; Venkatraman, S.; Brot, E. C. A.; Iyer, S.; Hall, M. LFA-1 Inhibitor and Methods of Preparation and Polymorph Thereof. U.S. Patent 9,085,553B2, Jul 21, 2015. (b) Burnier, J. Crystalline Pharmaceutical and Methods of Preparation and Use Thereof. U.S. Patent 8,378,105B2, Feb 19, 2013.
(14) Tweedle, S.; Venkatraman, S.; Liu, S.; Zeller, J.; Brot, E.; Hamlin, M.; Newman, M.; McLaws, M.; Rosenberg, J.; Lathbury, D. Continuous Flow Carboxylation Reaction. U.S. Patent Application 2016/0090361A1, Mar 31, 2016. (b) Brot, E.; Hamlin, M.; Lathbury, D.; Liu, S.; Mclaws, M.; Newman, M.; Rosenberg, J.; Tweedle, S.; Venkatraman, S.; Zeller, J. Continuous Flow Carboxylation Reaction. PCT Int. Patent Application AU 2015/320349, Mar 23, 2017. (c) Tweedle, S.; Venkatraman, S.; Zeller, J. Continuous Flow Carboxylation Reaction. U.S. Patent 9,725,413B2, Aug 8, 2017.
(15) The Pharmacodia web page provides graphical summaries of five routes to crizotinib. https://www.pharmacodia.com/web/drug/1_207.html (accessed Nov 13, 2017).
(16) Hong, H.; Gage, J.; Lu, J.; Li, J.; Shen, L. Synthetic Method of Crizotinib Intermediate. Chinese Patent Application CN 105906656, Aug 31, 2016.
(17) de Koning, P. D.; McAndrew, D.; Moore, R.; Moses, I. B.; Boyles, D. C.; Kissick, K.; Stanchina, C. L.; Cuthbertson, T.; Kamatani, A.; Rahman, L.; Rodriguez, R.; Urbina, A.; Sandoval, A.; Rose, P. R. *Org. Process Res. Dev.* **2011**, *15*, 1018−1026.
(18) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002275/WC500135329.pdf (Accessed Nov 13, 2017).
(19) Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878−882 (accessed Nov 13, 2017).10.1126/science.1241606
(20) (a) Högberg, T.; Grue-Sorensen, G.; Liang, X.; Horneman, A. M.; Petersen, A. K. Method of Producing Ingenol-3-angelate. U.S. Patent 9,676,698B2, Jun 13, 2017. (b) Högberg, T.; Grue-Sorensen, G.; Liang, X.; Horneman, A. M.; Petersen, A. K. Method of Producing Ingenol-3-angelate. U.S. Patent 9,416,084B2, Aug 16, 2016. (c) Högberg, T.; Grue-Sorensen, G.; Liang, X.; Horneman, A. M.; Petersen, A. K. Method of Producing Ingenol-3-angelate. U.S. Patent 8,901,356B2, Dec 2, 2014. (d) Liang, X.; Grue-Sørensen, G.; Petersen, A. K.; Högberg, T. *Synlett* **2012**, *23*, 2647−2652. (e) Liang, X.; Hogberg, T.; Grue-Sorensen, G.; Moody, T.; Rowan, A. S. Process for the Preparation of Ingenol-3-angelate. U.S. Patent 9,404,131B2, Aug 2, 2016.
(21) (a) Jordan, R. W.; Dixon, C.; Gorin, B. A Continuous Flow Process for the Preparation of Ingenol-3-mebutate. U.S. Patent Application 2017/0190652A1, Jul 6, 2017. (b) Jordan, R. W.; Dixon, C.; Gorin, B. Continuous Flow Process for the Preparation of Ingenol-3-mebutate. U.S. Patent 9,758,464B2, Sep 12, 2017.
(22) Jain, S.; Ansari, K.; Maddala, S.; Meenakshisunderam, S. Process for the Preparation of Valacyclovir. PCT Int. Patent Application WO 2017/149420, Sep 9, 2017.
(23) https://investor.lilly.com/releasedetail.cfm?ReleaseID=1011661 (accessed Nov 14, 2017).
(24) Rodgers, J. D.; Shepard, S. Azetidine and Cyclobutane Derivatives of JAK Inhibitors. U.S. Patent 8,158,616B2, Apr 17, 2012.
(25) Kobierski, M. E.; Kopach, M. E.; Martinelli, J. R.; Varie, D. L.; Wilson, T. M. Processes and Intermediates for the Prepartion of {1-(Ethylsulfonyl)-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile. PCT Int. Patent Application WO 2016/205487, Jun 16, 2016.

DOI: 10.1021/acs.oprd.7b00363
Org. Process Res. Dev. 2018, 22, 13−20