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Multistep Continuous Flow Synthesis of Stavudine

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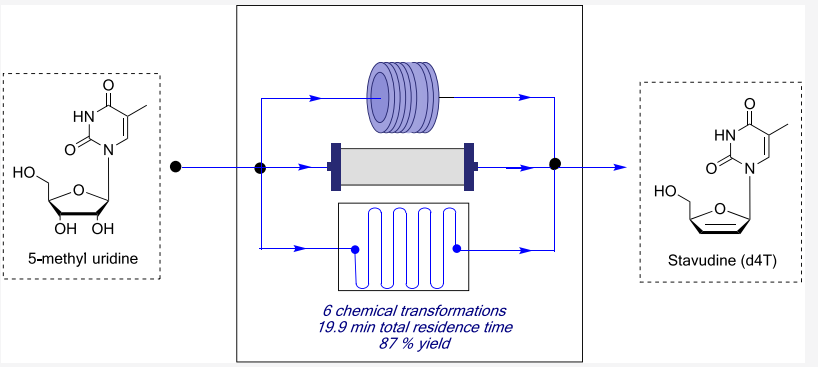

ABSTRACT: Herein, we demonstrate an elegant multistep continuous flow synthesis for stavudine (d4T), a potent nucleoside chemotherapeutic agent for human immunodeficiency virus, acquired immunodeficiency syndrome (AIDS) and AIDS-related conditions. This was accomplished via six chemical transformations in five sequential continuous flow reactors from an affordable starting material, 5-methyluridine. In the first instance, single step continuous flow synthesis was demonstrated with an average of 97% yield, 21.4 g/h throughput per step, and a total of 15.5 min residence time. Finally, multistep continuous flow synthesis of d4T in 87% total yield with a total residence time of 19.9 min and 117 mg/h throughput without intermediate purification was demonstrated.

INTRODUCTION

Stavudine (2′,3′-didehydro-3′-deoxythymidine), also known as d4T (**1**), is a potent nucleoside chemotherapeutic agent for human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS) and AIDS-related conditions (Figure 1).[1,2] It works by being converted to stavudine 5′-triphosphate,

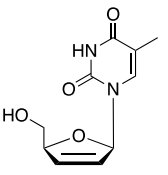

Figure 1. Stavudine (d4T, **1**) structure

which competes with thymidine 5′-triphosphate for incorporation into viral DNA, thus causing DNA chain termination due to the lack of 3′-hydroxyl group.[2] Approved by the US FDA in 1994, this nucleoside reverse transcriptase inhibitor (NRTI) was first marketed by Bristol Myers Squibb under the trade name Zerit.[2,3] Generic stavudine is available from pharmaceutical companies such as Cipla, Genix, and Emcure.[4] Although the World Health Organization (WHO) recommended stavudine's phase out in 2009 due to side effects,[5,6] stavudine-based treatments continue to be used in some developing countries due to its affordability.[7−10] For example, it is still listed as an essential medicine in South Africa.[7]

The synthesis of stavudine (**1**) was first reported by Horwitz et al. in 1964.[11] Early procedures started from an expensive starting material, namely thymidine.[11,12] Alternative procedures have been developed over the years which use a more affordable starting material, 5-methyluridine.[12−17] These procedures are associated with many drawbacks such as long reaction times, formation of side products, formation of byproducts, and tedious purification, among others.[12−16] Most of these drawbacks are inherent to the use of traditional batch technology. Continuous flow synthesis is known to overcome some of the challenges inherent in batch.[18−20] The use of continuous flow technology in the academic and industrial laboratories to synthesize complex compounds and active pharmaceutical ingredients (APIs) has rapidly increased in the past decade.[21−23] This is due to the many advantages of continuous flow

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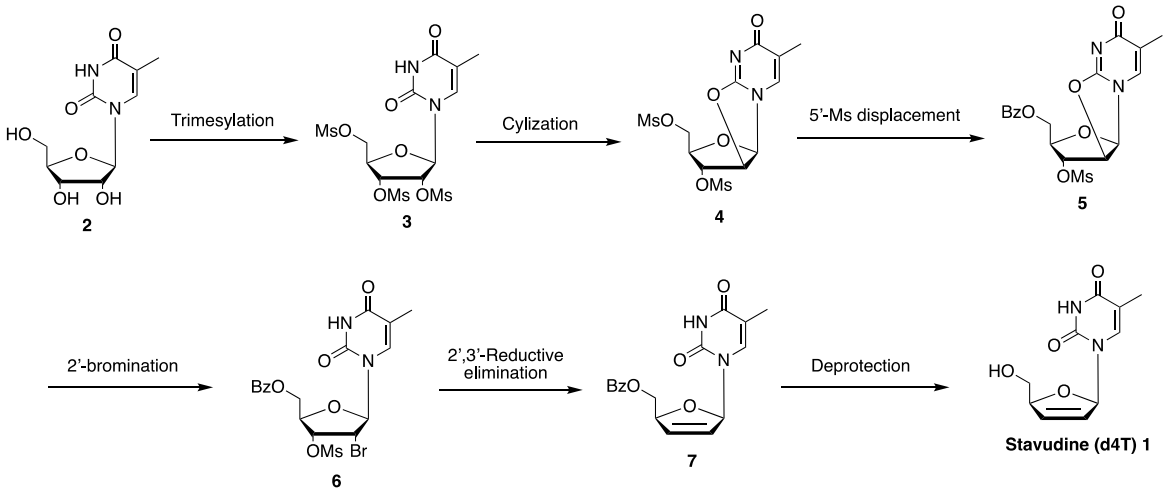

Figure 2. Reaction sequences for stavudine (**1**) synthesis of 5-methyluridine **2**.

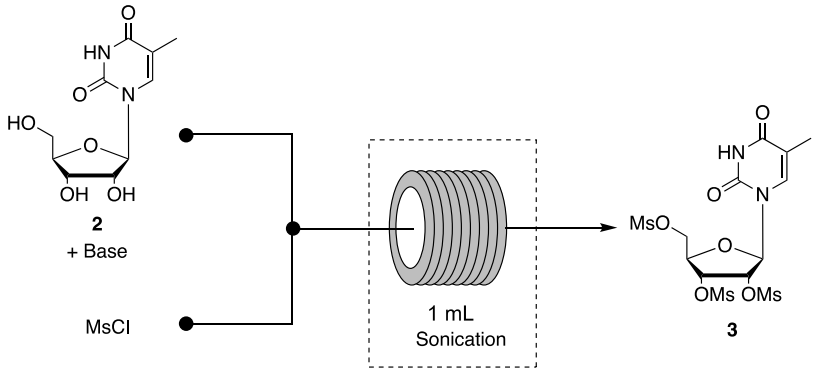

Figure 3. Continuous flow synthesis of trimesylate **3**.

technology over batch technology such as rapid optimization and scale up, improved process safety, and improved product quality and yield.[19,21−23] Furthermore, continuous flow technology allows for telescoping of reactions leading to rapid production and more environmentally benign processes by avoiding intermediate purification and workup. Various integrated multistep continuous flow procedures for APIs synthesis have been reported.[23−31] The current Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) pandemic, also known as COVID-19,[32−35] reminded us of the importance of rapid synthesis of medicines to maintain health and welfare of the society. Continuous flow technology plays an important role in meeting this societal demand. Therefore, we envisage that stavudine (**1**) can be synthesized efficiently and cost-effectively in a continuous flow system to demonstrate rapid multistep continuous flow synthesis in the production of APIs. Leaning on Discordia and Chen et al. approaches,[12,14] we started from a cost-effective and commercially available starting material, namely 5-methyluridine (**2**) (Figure 2).

RESULTS AND DISCUSSION

We began by performing trimesylation of 5-methyluridine (**2**) with MsCl in the presence of a suitable base in a PTFE coil reactor (Figure 3). Mesylation of alcohols is usually accomplished using MsCl in the presence of an amine base, which generates an ammonium chloride precipitate. The precipitate formation presents no challenges in a batch reactor; however on translating this synthesis into a continuous flow process, reactor clogging is bound to be observed, which will lead to pressure buildup, equipment failure, and disruption of the flow process. Nonetheless, a few groups have reported such precipitate-forming reactions in flow albeit with challenges.[36−38] In this reaction, we employed ultrasonication[39−41] to circumvent any issues that would be caused by the formation of the ammonium chloride salt.

In our preliminary studies, the treatment of 5-methyluridine (**2**) (0.1 M) premixed with TEA (6 equiv) in DMF with MsCl (6 equiv., effectively 2 equiv to OH on 5-methyluridine (**2**) in DCM in a 1 mL PTFE coil reactor under sonication at 0 °C afforded no product in 5 min residence time (Figure 3). Doubling the residence time did not improve the reaction conversion. However, it was noteworthy that by HPLC analysis, **2** was fully consumed to give two products of which none was the desired compound **3**. Since this reaction involves trimesylation of OH groups with different reactivities, we reasoned that the two products were as a result of dimesylation. This was not the case when DMF was used as a solvent for both **2** and MsCl, **2** remained completely unconsumed. This meant that the presence of DMF was detrimental, most likely because of its reactivity with MsCl to form sulfonyl chloride-*N*,*N*-dimethylformamide complexes.[42,43] Due to the poor solubility of **2** in most inert solvents, we used a minimum amount of DMF, just enough to dissolve **2** and DCM as the bulk solvent. Regulating the ratio of DMF to reagents was important. The treatment of **2** (0.1 M) in DMF (32 equiv) premixed with TEA (6 equiv) in DCM with MsCl (6 equiv) in DCM in a 1 mL PTFE coil reactor

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under sonication at 0 °C afforded trimesylate **3** in full conversion in 1 min residence time. We then performed comprehensive investigations to optimize the reaction in continuous flow (Table 1).

Table 1. Continuous Flow Synthesis of Trimesylate 3 Optimization[a]

entry	MsCl (equiv)	base (equiv)	temp (°C)	res time (min)	conv to 3[g] (%)
1	6	6	0	1	100
2	6	6	rt	1	100
3	6	6	rt	0.25	100
4	3	6	rt	0.25	43
5	4.5	6	rt	0.25	100 (97)[h]
6	4.5	4.5	rt	0.25	75
7	4.5	6[b]	rt	0.25	100
8	4.5	6[b,c]	rt	0.25	100
9	4.5	6[d]	rt	0.25	0
10[e]	4.5	6	rt	0.25	100
11[f]	4.5	-	rt	0.25	0

[a]Standard conditions: premix of **2** (0.1 M, 1 equiv) with TEA as base, DMF (5 mL) in DCM, and MsCl in DCM in a coil reactor under sonication. [b]Base is TBA or DIPEA or THA. [c]No sonication of coil reactor. [d]Base is DBU. [e]Chloroform was used in place of DCM. [f]5-Methyluridine **2** (0.1 M, 1 equiv) in pyridine and MsCl in DCM in a coil reactor under sonication. [g]Conversion was determined by the product peak area on HPLC at 254 nm. [h]Number in parentheses is isolated yield.

Following preliminary investigations, the use of MsCl (6 equiv) and TEA (6 equiv) afforded trimesylate **3** in full conversion in 1 min residence time at 0 °C (Table 1, entry 1). Raising the temperature to room temperature gave the same results (Table 1, entries 1 and 2). The use of shorter residence time (0.25 min) still gave trimesylate **3** in full conversion (Table 1, entries 2 and 3). A decrease in MsCl equivalents (3 equiv) resulted in a decrease in conversion to **3** (Table 1, entries 3 and 4). However, the use of MsCl (4.5 equiv) and TEA (4.5 equiv) improved the conversion (75%) (Table 1, entry 6). Best results were found when MsCl (4.5 equiv) and TEA (6 equiv) were used, and mesylate **3** was afforded in full conversion and 97% isolated yield at room temperature (Table 1, entry 5). The use of alternative bases such as tributyl amine, trihexyl amine, and *N,N*-diisopropylethylamine gave comparative results (Table 1, entries 5 and 7). Due to the soluble chloride salts formed by these bases, reactions were performed in the absence of sonication without affecting conversion (Table 1, entries 7 and 8). Although 5-methyluridine (**2**) was completely consumed, no trimesylate **3** was detected when DBU was used (Table 1, entry 9). The same was observed when pyridine was used as both solvent and base (Table 1, entry 11). Chloroform was also found to be an alternative solvent to DCM (Table 1, entries 7 and 10). In summary, although, DMF was important in solubilizing **2**, minimal use was important for the success of the reaction in flow. The optimum conditions were found to be MsCl (4.5 equiv), TEA (6 equiv), room temperature, and 15 s residence time to afford trimesylate **3** in 97% isolated yield using DMF and DCM as solvents with a throughput of 6.4 g/h. Our procedure was more efficient compared to Discordia's[14] 3 h batch procedure in pyridine at room temperature and Chen et al.'s[12,44] 5 h batch procedure in pyridine at 0 °C, which afforded trimesylate **3** in 89% isolated yield. Furthermore, we avoided the use of toxic pyridine.

Moving on to the second reaction, compound **4** was prepared in continuous flow via DBU-initiated intermolecular nucleophilic attack on 2′-carbon (Figure 4 and 5). Trimesylate **3** (1 M, 1 equiv) was treated with DBU (1 equiv) to afford compound **4** and optimized in continuous flow (Figures 4 and 5). The conversion was determined by following the product peak on HPLC at 254 nm.

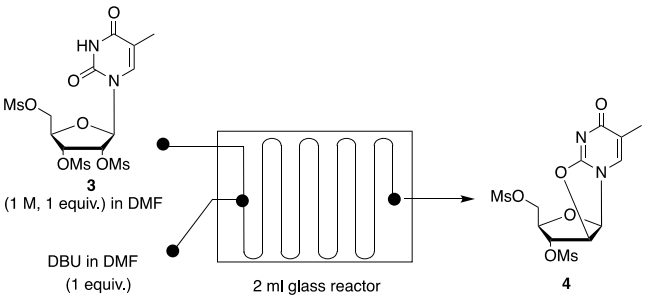

Figure 4. Continuous-flow synthesis of compound **4**.

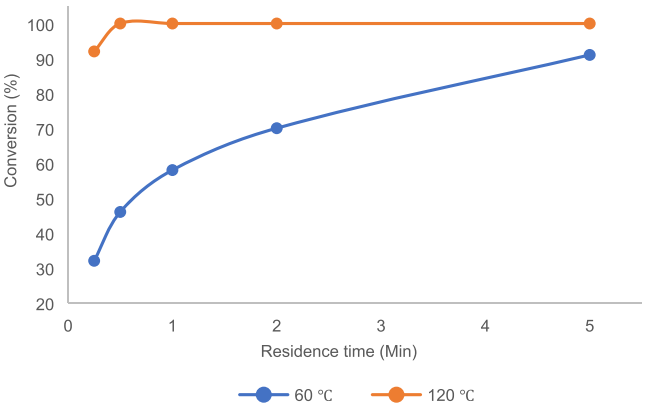

Figure 5. Continuous-flow synthesis of compound **4**.

Using trimesylate **3** (1 M) and DBU (1 equiv), the conversion of mesylate **3** to compound **4** increased with an increase in temperature and residence time (Figure 5). Optimum conditions were found to be 120 °C and 30 s residence time to afford compound **4** in 100% conversion by HPLC and 97% isolated yield. Compound **4** was not detected in the absence of DBU. Furthermore, the use of alternative bases such as TBA, TEA, imidazole, DMAP, and DIPEA gave no product under the optimum conditions. DBU is necessary for N−H deprotonation and initiate intermolecular nucleophilic attack (Figure 6).

Subsequent displacement of 5′-OMs of compound **4** with −OBz was accomplished by the use of an Amberlite IRA 400-

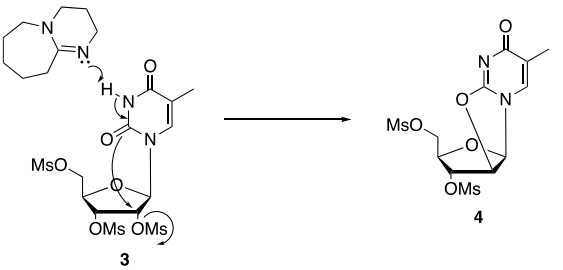

Figure 6. Proposed mechanism for intermolecular nucleophilic attack to afford compound **4**.

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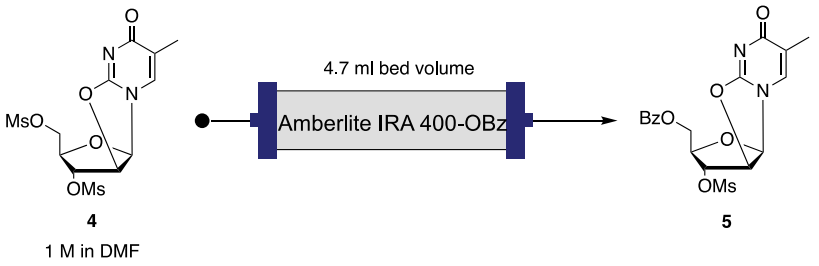

Figure 7. Continuous-flow synthesis of 5′-benzoyl-5-methyluridine (**5**) from compound **4**.

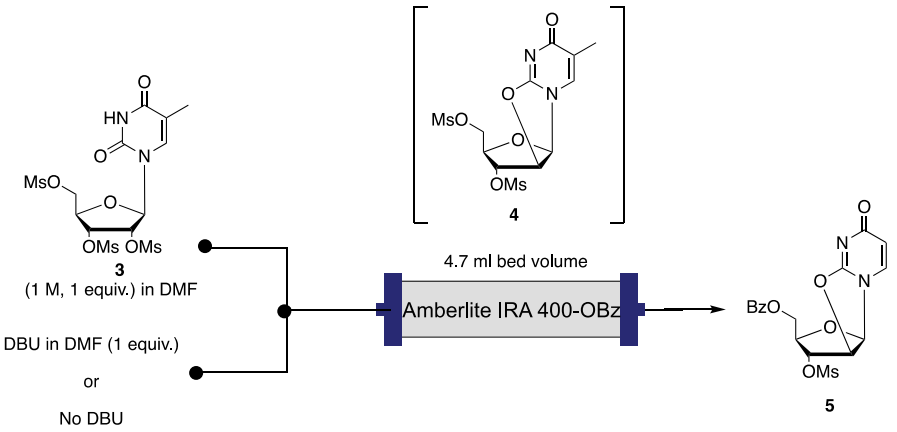

Figure 8. Synthesis of 5′-benzoyl-5-methyluridine (**5**) from trimesylate **3**.

OBz ion-exchange resin packed column (Omnifit EZ column 10 mm/100 mm, 3.6 g of resin = 4.7 mL bed volume, 1.8 mmol g^{-1} exchange capacity) to afford **5** (Figures 7 and 8). Amberlite IRA 400-OBz was prepared by treating Amberlite IRA 400-Cl ion-exchange resin with sodium benzoate.

Pumping compound **4** (1 M) through an Amberlite IRA 400-OBz packed column reactor held at 80 °C for 2 min residence time afforded **5** in 17% conversion (Table 2, entry 1). Increasing

Table 2. Continuous Flow Synthesis of 5′-Benzoyl-5-methyluridine (5) from Compound 4 Optimization[a]

entry	temp (°C)	res time (min)	conv to **5** (%)[b]
1	80	2	17
2	80	5	28
3	100	5	56
4	120	5	92
5	120	8	100

[a]Standard conditions: compound **4** (1 M) in DMF. [b]Conversion determined by the product peak area on HPLC at 254 nm.

the residence time improved the conversion (Table 2, entries 1 and 2). An increase in temperature afforded better conversion to **5** (Table 2, entries 3 and 4). Conditions were found at 120 °C and 8 min residence to afford **5** in 100% conversion.

After successful synthesis of compound **4** and its subsequent conversion to **5**, we attempted **5** synthesis from trimesylate **3** via compound **4** formed *in situ*. Since we observed rapid synthesis of compound **4** (30 s) at 120 °C from trimesylate **3** in the 2 mL glass reactor (Figure 4), we found it reasonable to just use an Amberlite IRA 400-OBz packed column reactor held at 120 °C for this study (Figure 8). Guided by the above studies, we first pumped trimesylate **3** and DBU through an Amberlite IRA 400-OBz packed column reactor held at 120 °C to effect compound **4** synthesis and its subsequent conversion to **5** (Figures 8 and 9). Compound **5** was afforded in 100% conversion cleanly.

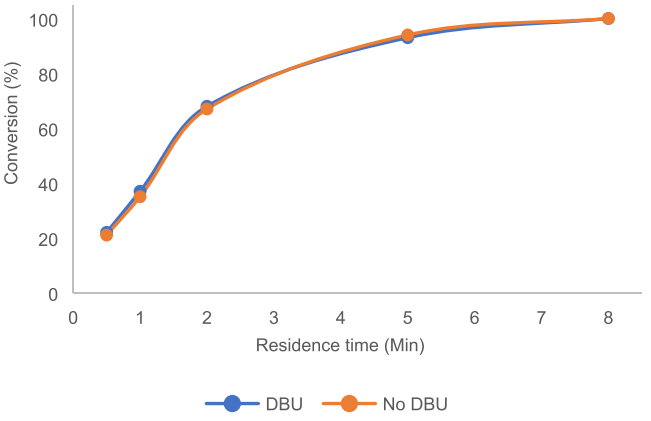

Figure 9. Synthesis of 5′-benzoyl-5-methyluridine (**5**) from trimesylate **3** optimization.

Interestingly, comparable product **5** was observed in the absence of DBU (Figures 8 and 9). This is consistent with some of the batch literature, where excess sodium benzoate was used to make **5** from **3** in the absence of a base.[12,14,44] Generally, the conversion of **3** to **5** improved with an increase in residence time, and optimum conditions were found to be 120 °C and 8 min residence (Figure 9). Compound **5** was afforded in full conversion and 97% isolated yield with throughput of 24.7 g/h. Our procedure is more efficient than the reported literature, which is 1−7.5 h long with ∼90% isolated yield.[12,14,44] At optimum conditions, a fresh Amberlite IRA 400-OBz packed column reactor was used for each run, and used columns were regenerated for reuse. The study was not extended beyond this

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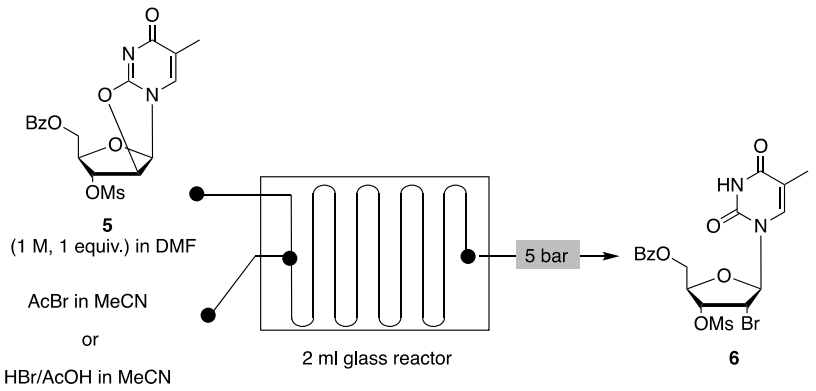

Figure 10. Synthesis of compound **6** from 5′-benzoyl-5-methyluridine (**5**).

to specifically determine the life span of each Amberlite IRA 400-OBz packed column reactor with usage.

The 2′-bromination of **5** using either AcBr or HBr was investigated in continuous flow to afford compound **6** (Figures 10 and 11). In our preliminary studies, we observed that

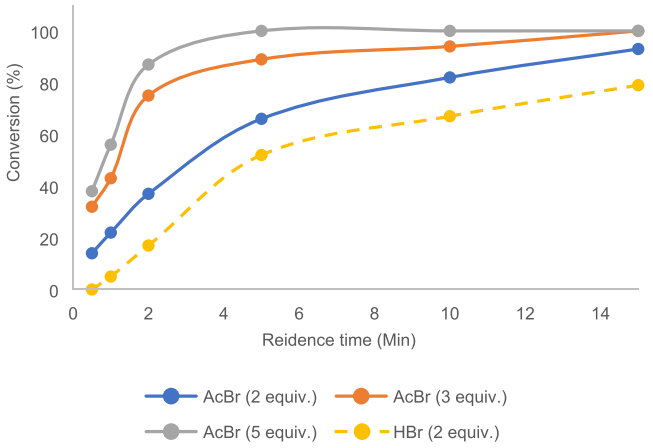

Figure 11. Synthesis of compound **6** optimization.

performing the reaction at 120 °C afforded compound **6** in good conversion. We also observed that an excess of the brominating agent was necessary. Therefore, for reaction optimization, we treated **5** with an excess of either AcBr or HBr at 120 °C to afford **6** (Figures 10 and 11). The conversion of **5** to **6** increased with an increase in AcBr equivalents, and AcBr proved to be a better brominating agent than HBr (Figure 11). The optimum conditions were found to be 120 °C, 5 min residence time using AcBr (5 equiv) to afford **6** cleanly in full conversion and 98% isolated yield with throughput of 5.9 g/h. The use of excess AcBr was consistent with the reported batch literature.[12,44]

We went on to perform 2′,3′-olefination of compound **6** to afford 5′-benzoyl-d4T (**7**) in a heated Zn/Celite packed column reactor (Omnifit EZ column 6.6 mm/100 mm, 1.47 g Celite/Zn mixture = 1.5 mL bed volume) (Figures 12 and 13); a freshly

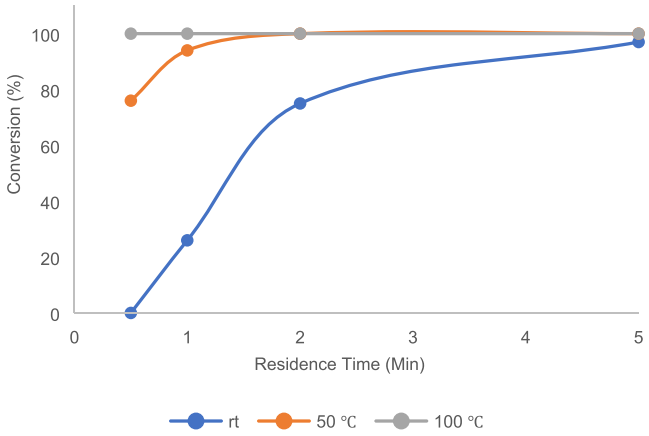

Figure 13. 2′,3′-Olefination of **6** to 5′-benzoyl-d4T (**7**).

packed column was used for each experiment. The reductive elimination of 2′-Br and 3′-OMs of **6** using Zn and acetic acid in continuous flow afforded 5′-benzoyl-d4T **7** cleanly. An increase in temperature improved the reaction (Figure 13). Optimum conditions were found to be 100 °C and 15 s residence time to afford 5′-benzoyl-d4T (**7**) in 100% conversion and 97% isolated yield with throughput of 57.2 g/h. This is quicker than literature procedures, which are ∼3−12 h long and afford **7** in 87−97% isolated yield.[12,14]

The last step involved Bz-deprotection of 5′-benzoyl-d4T (**7**) using NaOMe to afford d4T (**1**) in continuous flow (Figure 14). We optimized the residence time and reaction temperature for Bz-deprotection (Figure 15). An increase in residence time and

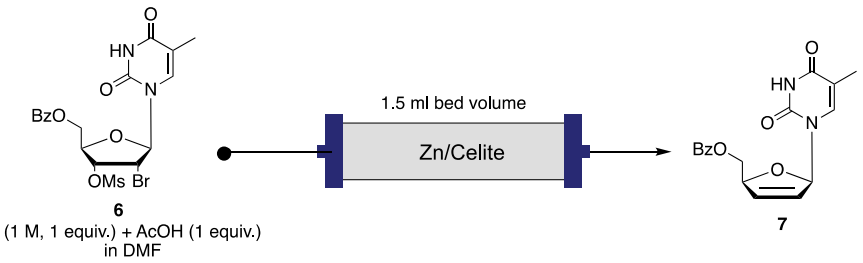

Figure 12. 2′,3′-Olefination of **6** to 5′-benzoyl-d4T (**7**).

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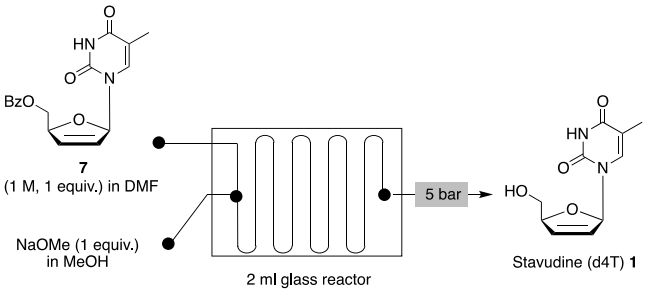

Figure 14. Deprotection of 5′-benzoyl-d4T (**7**) to stavudine (d4T, **1**).

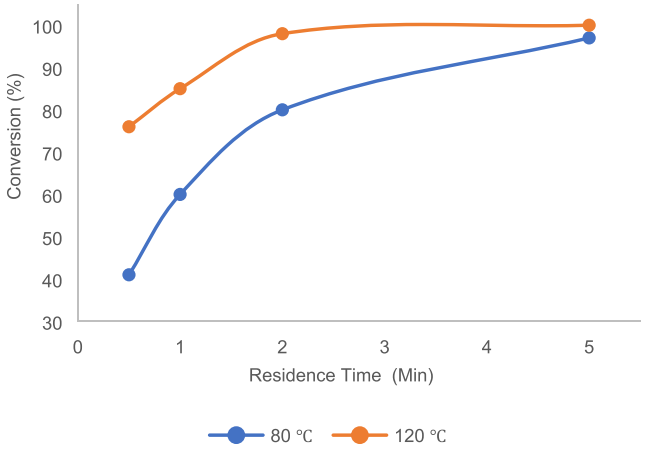

Figure 15. Deprotection of 5′-benzoyl-d4T (**7**) optimization.

temperature improved the reaction (Figure 15). Optimum conditions were found to be 2 min residence time and 120 °C to afford d4T (**1**) in 100% conversion and 94% isolated yield with a throughput of 12.6 g/h. Our procedure is more efficient than the reported literature procedures,[12,14] which are 1.5−3 h long affording **1** in 79% isolated yield.

With the optimum conditions for individual steps determined, and guided by them, we went on to combine them into a multistep continuous process (Figure 16). Flow unit 1 involved trimesylation of **2** with MsCl in the presence TBA in a PTFE coil reactor at room temperature for 0.5 min residence time without sonication. Subsequently, flow unit 2 consisting of a Amberlite IRA 400-OBz packed column reactor (3.6 g of resin, 4.7 bed volume) held at 120 °C for 10 min residence time effected 5′-benzoylation and 2′-cyclization to afford **5** *in situ*. Flow unit 3 involved 2′-bromination of **5** using excess AcBr at 120 °C for 5 min residence time. Excess AcOH was subsequently used to quench the excess AcBr inline as well as effect reductive elimination of 2′-Br and 3′-OMs resulting in 2′,3′-olefin using a Zn/Celite packed column reactor (1.47 g of Zn/Celite mixture, 1.5 mL bed volume) to afford **7** *in situ* at 100 °C and 1.9 min in flow unit 4. Flow unit 5 subsequently effected Bz-deprotection of **7** using NaOMe at 120 °C and 2.5 min residence time and subsequently enters flow unit 6 consisting of a column reactor packed with Dowex 50WX8 H^+ resin (0.82 g of resin = 1 mL bed volume) for workup (neutralization). Compound **1** was afforded in 87% yield from **2** in 19.9 min total residence time with a throughput of 117 mg/h. Although the total residence time of the multistep continuous flow process was slightly longer (19.9 min) than the five single-step processes (15.5 min) because of the rigidness of the multistep flow system, the total overall yield was better (87%). Our procedure demonstrated time economy in the total synthesis of stavudine as described by Hayashi.[45,46] This was due to the avoidance of intermediate purification and isolation in the multistep continuous flow synthesis which usually results in product loss. Overall, multistep synthesis was elegant and less tedious than the single-step procedure.

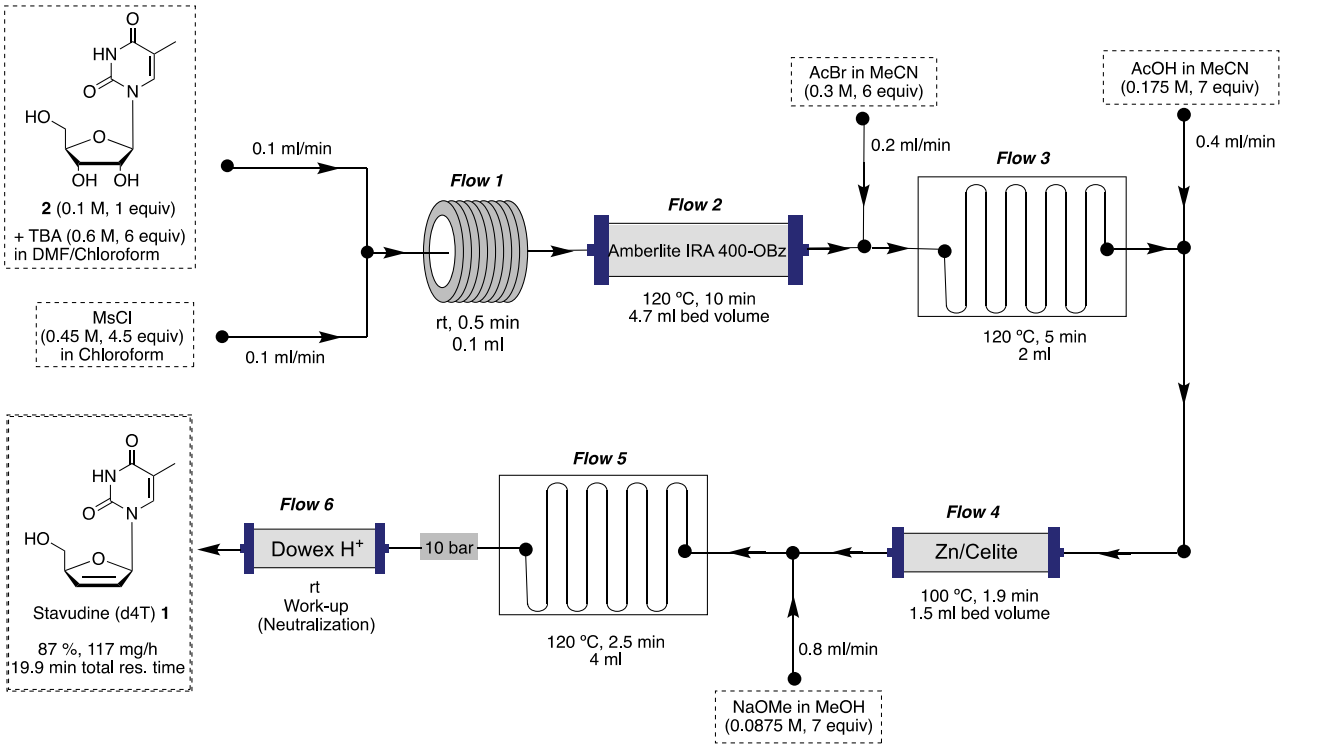

Figure 16. Multistep continuous flow synthesis of stavudine (d4T).

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CONCLUSION

We successfully synthesized stavudine (d4T, **1**) by a continuous flow process accomplishing six chemical transformations over five continuous flow reactors from an affordable starting material (5-methyluridine). Single step continuous flow synthesis was demonstrated with an average of 97% yield, 21.4 g/h throughput per step and a total of 15.5 min residence time over five individual steps. We postulate that the total residence time of the multistep flow system can be reduced in more flexible flow systems where the individual reactor volumes can be altered to match the single step conditions better. Furthermore, we demonstrated an elegant multistep continuous flow synthesis of **1** in 87% total yield with a total residence time of 19.9 min and a 117 mg/h from a 0.1 M starting material without intermediate purification and isolation. The total residence time is better than the reported procedures (13.5−28 h).[12,14] Unlike in the single-step procedure, a slight excess of reagents was necessary in some of the multistep continuous flow steps. However, inline workup procedure could be incorporated in flow to neutralize excess base before carrying further workup processes offline. Continuous flow technology has an important role to play in ensuring rapid and local production of important medicines on demand to maintain the health and welfare of the society.

EXPERIMENTAL PROCEDURES

General Information. Chemicals were supplied by Sigma-Aldrich, Merck and Industrial Analytical and used as received. Anhydrous solvents were sourced from Sigma-Aldrich. Nuclear magnetic resonance (NMR) spectra were recorded at room temperature as solutions in deuterated dimethyl sulfoxide (DMSO-d_6). A Bruker Avance-400 spectrometer (400 MHz) was used to record the spectra, and the chemical shifts are reported in parts per million (ppm) with coupling constants in hertz (Hz). Infrared spectra were recorded from 4000 to 500 cm^{-1} using a Bruker spectrometer, and peaks (υ_{max}) are reported in wavenumbers (cm^{-1}). High-performance liquid chromatography (HPLC) data was obtained using Agilent 1100 with a UV detector. HPLC analysis was performed on ACE Generix 5 C18(2) column (150 mm × 4.6 mm i.d) at ambient temperature using an isocratic system. The mobile phase consisted of 30% water and 70% MeCN. The sample injection volume was 1 μL, eluted at a flow rate of 1 mL/min, and detected at 254 nm with a run time of 6 min.

Procedure 1: Synthesis of 2′,3′,5′-Tris(methanesulfonyl)-5-methyluridine (3).[12,44] 5-Methyluridine (**2**) (0.1 M, 1 equiv) in DMF (32 equiv) premixed with an appropriate amine base in DMF/DCM or DMF/chloroform was treated with MsCl in DCM or chloroform in a 1 mL PTFE coil reactor (0.8 mm i.d.) (Figure S1). The PTFE reactor was sonicated where necessary to prevent reactor clogging. The effects of bases, temperature, solvents, and residence time were investigated for reaction optimization. Reactions were analyzed by HPLC. For spectroscopic characterization, a 10 mL sample was collected under optimum conditions and DCM or chloroform was removed *in vacuo*. The product was precipitated with ice-diluted aqueous NH_4Cl. The solid product was collected by filtration and washed with water and vacuum-dried to afford 2′,3′,5′-tris-(methanesulfonyl)-5-methyluridine (**3**) as an off-white solid (0.24 g, 97% yield, mp 77.3−78.2 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.58 (s, 1H), 5.97 (d, J = 4.5, 1H), 5.68−5.51 (m, 1H), 5.44−5.24 (m, 1H), 4.56−4.43 (m, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 3.26 (s, 3H), 1.80 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 164.2, 150.9, 136.9, 110.5, 88.4, 78.9, 76.7, 74.4, 38.4, 37.3, 12.5. FTIR (cm^{-1}) ν: 3027.3, 2939.6, 1689.0, 1470.1, 1348.6, 1334.7, 1272.2, 1171.5, 1068.8, 967.5, 946.7, 835.7, 583.7, 522.2.

Procedure 2: Synthesis of 5′,3′-bis(methanesulfonyl)-2.2′-anhydro-5-methyluridine (4).[12,14,44] Trimesylate **3** (1 M, 1 equiv) in DMF was treated with DBU (1 equiv) in a Uniqsis 2 mL chip reactor (Figure S2). The effect of temperature and residence time was investigated for reaction optimization. The use of alternative bases was also investigated. Reactions were analyzed by HPLC. For spectroscopic characterization, a 5 mL sample was collected under optimum conditions, and the product was precipitated with ice−water. The solid product was collected by filtration, washed with water, and vacuum-dried to afford 5′,3′-bis(methanesulfonyl)-2.2′-anhydro-5-methyluridine (**4**) as a white solid (0.97 g, 97% yield, mp 237.8−238.3 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (s, 1H), 6.44 (d, J = 5.8, 1H), 5.65 (d, J = 5.7, 1H), 5.49 (s, 1H), 4.75−4.65 (m, 1H), 4.37−4.28 (m, 1H), 4.20−4.08 (m, 1H), 3.44 (s, 3H), 3.15 (s, 3H), 1.81 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 171.7, 159.4, 132.3, 117.7, 90.4, 86.3, 82.3, 81.5, 68.1, 38.1, 37.3, 13.9. FTIR (cm^{-1}) ν: 3101.1, 3011.8, 2998.4, 2936.5, 1674.5, 1624.8, 1572.8, 1561.4, 1354.8, 1172.3, 996.6, 882.5.

Procedure 3: Preparation of Amberlite IRA 400-OBz. Amberlite IRA 400-Cl ion-exchange resin (14−52 mesh) was treated with 20% aqueous sodium benzoate at room temperature and stirred for 6 h. The resultant Amberlite IRA 400-OBz ion-exchange resin (loading = 1.8 $mmolg^{-1}$) was collected by filtration and washed with water followed by methanol and oven-dried at 40 °C. The success was confirmed by FTIR by the presence of Bz-carbonyl group on the resin. The used ion-exchange resin was regenerated by repeating the above process and reused. FTIR (cm^{-1}) ν: 3355.7, 1595.2, 1554.5, 1476.2, 1371.9, 888.7, 827.7, 720.8.

The exchange capacity of the Amberlite IRA 400-OBz resin was determined by treating Amberlite IRA 400-OBz (0.2 g) with sodium chloride (1 M, 30 mL) at room temperature and stirred for 2 h. The resin was subsequently removed by filtration. The amount of sodium benzoate in the filtrate was then titrated with HCl (0.01 M) using methyl orange as indicator. The exchange capacity or loading of the polymer supported nucleophile was determined to be 1.8 mmol g^{-1} of OBz^-.

Procedure 4: Synthesis of 5′-Benzoyl-3′-methanesulfonyl-2.2′-anhydro-5-methyluridine (5) from Compound 4.[12,44] Compound **4** (1 M) in DMF was pumped through a heated Amberlite IRA 400-OBz (prepared in procedure 3) packed column reactor (Omnifit EZ column 10 mm/100 mm, 3.6 g of resin = 4.7 mL bed volume, 1.8 $mmolg^{-1}$ exchange capacity) (Figure S3). The effect of residence time and temperature was investigated for reaction optimization. Reactions were analyzed by HPLC.

Procedure 5: Synthesis of 5′-benzoyl-3′-methanesulfonyl-2.2′-anhydro-5-methyluridine (5) from Trimesylate 3.[12,44] Trimesylate **3** (1 M, 1 equiv) in DMF was pumped through a heated Amberlite IRA 400-OBz (prepared in section 1.4) packed column reactor (Omnifit EZ column 10 mm/100 mm, 3.6 g of resin = 4.7 mL bed volume, 1.8 mmol g^{-1} exchange capacity) held at 120 °C (Figure S4). Reactions were analyzed by HPLC. For spectroscopic characterization, a 5 mL sample was collected under optimum conditions, and the product was precipitated with ice−water. The solid product was collected by filtration, washed with water, and oven-dried at 80 °C to afford 5′-benzoyl-3′-methanesulfonyl-2.2′-anhydro-5-methyluridine (**5**) as a white solid (2.07 g, 98% yield, mp 238−239.7 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98−7.75 (m, 3H), 7.72−7.58 (m, 1H), 7.58−7.41 (m, 2H), 6.47 (d, J = 7.5, 1H), 5.79−5.53 (m, 2H), 4.80 (s, 1H), 4.43−4.11 (m, 2H), 3.46 (s, 3H), 1.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 171.7, 165.6, 159.3, 134.1, 132.4, 129.7, 129.2, 117.8, 90.4, 86.3, 82.4, 81.6, 63.0, 38.0, 13.9. FTIR (cm^{-1}) ν: 3004.7, 2995.8, 2924.3, 1719.9, 1639.7, 1562.4, 1480.2, 1457.6, 1346.6, 1269.0, 1256.3, 1175.4, 1119.7, 1084.9, 1017.1, 978.1, 819.9, 713.4

Procedure 6: Synthesis of 5′-Benzoyl-3′α-methanesulfonyl-2′α-bromothymidine (6).[12,44] Compound **5** (1 M, 1 equiv) in DMF was treated with either AcBr (1 equiv) in MeCN or HBr (33% wt % in AcOH) (1 equiv) in MeCN in a Uniqsis 2 mL chip reactor fitted with a Zaiput 5 bar back pressure regulator (Figure S5). The effect of temperature, residence time and brominating agent concentration was investigated for reaction optimization. Reactions were analyzed by HPLC. For spectroscopic characterization, a 5 mL sample was collected from a reaction in which AcBr was used and quenched with aqueous NaOH. MeCN was removed *in vacuo*, and the product was precipitated with ice−water. The solid product was collected by filtration and washed with water and oven-dried at 50 °C to afford 5′-benzoyl-3′α-

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methanesulfonyl-2′α-bromothymidine (**6**) as an off-white solid (1.22 g, 97% yield, mp 78.2−79.8 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H), 8.05 (d, J = 7.2, 2H), 7.70 (t, J = 7.4, 1H), 7.58−7.51 (m, 3H), 6.16 (d, J = 7.4, 1H), 5.52−5.46 (m, 1H), 5.14−5.08 (m, 1H), 4.69−4.61 (m, 2H), 4.58−4.50 (m, 1H), 3.39 (s, 3H), 1.66 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 165.9, 163.9, 151.0, 135.8, 134.1, 129.9, 129.3, 111.0, 89.1, 80.3, 77.6, 63.3, 47.0, 38.6, 12.4. FTIR (cm^{-1}) ν: 3168.7, 3011.0, 2932.5, 2827.1, 1725.0, 1707.3, 1661.2, 1470.1, 1376.3, 1357.4, 1271.7, 1262.9, 1174.3, 1098.9, 1011.9, 921.3, 854.0, 711.0, 609.9.

Procedure 7: Synthesis of 5′-Benzoyl-2′,3′-didehydro-3′-deoxvthymidine (5′-Benzoyl-d4T, 7).[12,14] Compound **6** (1 M, 1 equiv) premixed with AcOH (1 equiv) in DMF was pumped through a column reactor (Omnifit EZ column 6.6 mm/100 mm, 1.47 g Celite/Zn mixture = 1.5 mL bed volume) packed with a mixture of Celite 545 and activated Zn in a 3:2 mass ratio) (Figure S6). The effect of residence time and temperature was investigated for reaction optimization. Reactions were analyzed by HPLC. For spectroscopic characterization, a 5 mL sample was collected under optimum conditions and the product was precipitated with ice−water. The solid product was collected by filtration and washed with water and oven-dried at 60 °C to afford 5′-benzoyl-d4T) (**7**) as an off-white solid (1.59 g, 97% yield, mp 101.2−102.7 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (s, 1H), 7.99−7.93 (m, 2H), 7.68 (t, J = 7.4, 1H), 7.54 (t, J = 7.7, 2H), 7.13 (s, 1H), 6.86−6.80 (m, 1H), 6.54 (d, J = 5.9, 1H), 6.06 (d, J = 5.8, 1H), 5.12 (s, 1H), 4.63−4.53 (m, 1H), 4.52−4.41 (m, 1H), 1.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 166.0, 164.1, 151.2, 135.8, 134.0, 129.9, 129.4, 127.3, 110.2, 89.7, 84.3, 65.8, 40.0, 12.0.

Procedure 8: Synthesis of Stavudine (d4T, 1) from 5′-Benzoyl-d4T (7).[12,14] 5′-Benzoyl-d4T (**7**) (1 M, 1 equiv) in DMF was treated with NaOMe (25 wt % in MeOH) (1 equiv) in MeOH in a Uniqsis 2 mL chip reactor fitted with a Zaiput 5 bar back-pressure regulator (Figure S7). The effects of temperature and residence time were investigated for reaction optimization. Reactions were analyzed by HPLC. For spectroscopic characterization, a 5 mL sample was collected under optimum conditions, and MeOH was removed *in vacuo*. Toluene was added to the product solution in DMF. Both DMF and toluene were distilled off under reduced pressure at 80 °C. The crude solid product was recrystalised in hot acetone. The solid product was collected by filtration and air-dried to afford stavudine (d4T, **1**) as a white solid (0.53 g, 94% yield, mp 159.6−160.2 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 7.65 (s, 1H), 6.82 (s, 1H), 6.50−6.32 (m, 1H), 5.99−5.81 (m, 1H), 5.08 (s, 1H), 4.77 (s, 1H), 3.67−3.51 (m, 2H), 1.73 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 164.4, 151.3, 137.2, 135.4, 126.4, 109.4, 89.3, 87.8, 62.7, 12.6. FTIR (cm^{-1}) ν: 3172.8, 3037.0, 2928.5, 2826.3, 1671.8, 1645.2, 1461.5, 1255.7, 1224.72, 1070.9, 802.7.

Procedure 9: Multistep Synthesis of Stavudine (d4T, 1) from 5-Methyluridine (2). This was performed in six connected flow units (Figure S8). In flow unit 1, compound **2** (0.1 M, 1 equiv) in DMF (32 equiv) premixed TBA (1 equiv) in chloroform was treated with MsCl (1 equiv) in a PTFE coil reactor (0.8 mm i.d.) at room temperature for 0.5 min residence time. The resultant stream through flow unit 2 consisting of a Amberlite IRA 400-OBz (prepared in procedure 3) packed column reactor (Omnifit EZ column 10 mm/100 mm, 3.6 g of resin = 4.7 mL bed volume, 1.8 mmol g^{-1} exchange capacity) held at 120 °C for 10 min residence time. In flow unit 3, the resultant stream was treated with AcBr (0.3 M, 6 equiv) in a 2 mL Uniqsis glass reactor at 120 °C for 5 min residence time. The resultant stream was treated with AcOH (0.175 M, 2 equiv) and passed through a column reactor (Omnifit EZ column 6.6 mm/100 mm, 1.47 g Celite/Zn mixture = 1.5 mL bed volume) packed with a mixture of Celite 545 and activated Zn in a 3:2 mass ratio) held at 100 °C and 1.9 min. In flow unit 5, the resultant stream was treated with NaOMe (25 wt % in MeOH) (0.025 M, 1 equiv) in MeOH using a Uniqsis 2 mL glass reactors held at 120 °C and 2.5 min residence time. The resultant stream subsequently passed through Flow unit 6 workup (neutralization) consisting of a column reactor (Omnifit EZ column 6.6 mm/100 mm, 0.82 g of resin = 1 mL bed volume) packed with Dowex 50WX8 H$^+$ resin. Compound **1** was confirmed with HPLC against an authentic standard. For spectroscopic characterization, a sample was collected for 20 min. Toluene was added to the collected sample and washed with water and followed by brine. The organic phase was then concentrated *in vacuo* and the product was purified using a short silica gel column chromatography (Hexane/AcOEt). The solid product afforded after concentration was recrystallized in hot acetone to afford **1** as a white solid (39 mg, 87% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01013.

FTIR, ^{1}H NMR, and ^{13}C NMR spectra for all compounds and continuous flow system setups (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Sriram, D.; Yogeeswari, P.; Srichakravarthy, N.; Bal, T. R. Synthesis of Stavudine Amino Acid Ester Prodrugs with Broad-Spectrum Chemotherapeutic Properties for the Effective Treatment of HIV/AIDS. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1085−1087.

(2) Mateo, M. G.; Gutierrez, M. D. M.; Vidal, F.; Domingo, P. Stavudine Extended Release (Once-Daily, Bristol-Myers Squibb) for the Treatment of HIV/AIDS. *Expert Opin. Pharmacother.* **2013**, *14*, 1055−1064.

(3) Alapi, E. M.; Fischer, J. Table of selected analogue classes. In *Analogue-Based Drug Discovery*; Sataloff, R. T., Johns, M. M., Kost, K. M., Ed.; Wiley-VCH Verlag, 2006; pp 441−552.

(4) Stavudine Price of 14 Brands/Trade Names/Medindia. https://www.medindia.net/drug-price/stavudine.htm (accessed 2021-03-16).

(5) New WHO guidelines urge phase-out of major HIV drug/Reuters. https://www.reuters.com/article/us-aids-drugs-idUSTRE5AT00K20091130 (accessed 2021-03-16).

(6) WHO Report. *Rapid Advice: Antiretroviral Therapy for HIV Infection in Adults and Adolescents*. https://www.who.int/hiv/pub/arv/advice/en/, 2009 (accessed 2021-05-24).

(7) Department of Health, S.A. *Standard Treatment Guidelines and Essential Medicines List for South Africa 2018*. https://extranet.who.int/ncdccs/Data/ZAF_D1aia_STG%20and%20EML%20PHC%202018.pdf (accessed 2021-05-24).

(8) Brennan, A. T.; Davies, M. A.; Bor, J.; Wandeler, G.; Stinson, K.; Wood, R.; Prozesky, H.; Tanser, F.; Fatti, G.; Boulle, A.; Sikazwe, I.; Wool-Kaloustian, K.; Yuannoutsos, C.; Leroy, V.; De Rekeneire, N.; Fox, M. P. Has the Phasing out of Stavudine in Accordance with

Changes in WHO Guidelines Led to a Decrease in Single-Drug Substitutions in First-Line Antiretroviral Therapy for HIV in Sub-Saharan Africa? *AIDS* **2017**, *31*, 147−157.
(9) Wadley, A. L.; Cherry, C. L.; Price, P.; Kamerman, P. R. HIV Neuropathy Risk Factors and Symptom Characterization in Stavudine-Exposed South Africans. *J. Pain Symptom Manage.* **2011**, *41*, 700−706.
(10) Venter, W. D. F.; Innes, S.; Cotton, M. Low-Dose Stavudine Trials: A Public Health Priority for Developing Countries. *South. Afr. J. HIV Med.* **2012**, *13*, 20−21.
(11) Horwitz, J. P.; Chua, J.; Noel, M. Nucleosides. V. The Monomesylates of l-(2′-Deoxy-β-D-Lyxofuranosyl)Thymine. *J. Org. Chem.* **1964**, *29*, 2076−2078.
(12) Chen, B.-C.; Stark, D. R.; Baker, S. R.; Quinlan, S. L. 5-Methyluridine Process for Large-Scale Preparation of 2′,3′-Didehydro-3′-Deoxythymidine (D4T). EP0653436B1, 1998.
(13) Mansuri, M. M.; Starrett, J. E.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. Preparation of 1-(2,3-Dideoxy-.Beta.-D-Glycero-Pent-2-Enofuranosyl)Thymine (D4T) and 2′,3′-Dideoxyadenosine (DdA): General Methods for the Synthesis of 2′,3′-Olefinic and 2′,3′-Dideoxy Nucleoside Analogs Active against HIV. *J. Org. Chem.* **1989**, *54*, 4780−4785.
(14) Discordia, R. P. SYNTHESIS OF 1′-[^{14}C]-STAVUDINE (D4T). *J. Labelled Compd. Radiopharm.* **1996**, *38*, 613−623.
(15) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. General Syntheses of 2′,3′-Dideoxynucleosides and 2′,3′-Didehydro-2′,3′-Dideoxynucleoside. *J. Org. Chem.* **1989**, *54*, 2217−2225.
(16) Shiragami, H.; Irie, Y.; Shirae, H.; Yokozeki, K.; Yasuda, N. Synthesis of 2′,3′-Dideoxyuridine via Deoxygenation of 2′,3′-O-(Methoxymethylene)Uridine. *J. Org. Chem.* **1988**, *53*, 5170−5173.
(17) Livni, E.; Berker, M.; Hillier, S.; Waller, S. C.; Ogan, M. D.; Discordia, R. P.; Rienhart, J. K.; Rubin, R. H.; Fischman, A. J. Preparation and Pharmacokinetics of ^{11}C labeled stavudine (d4T). *Nucl. Med. Biol.* **2004**, *31*, 613−621.
(18) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J. C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. On-Demand Continuous-Flow Production of Pharmaceuticals in a Compact, Reconfigurable System. *Science* **2016**, *352*, 61−67.
(19) Baumann, M.; Moody, T. S.; Smyth, M.; Wharry, S. A Perspective on Continuous Flow Chemistry in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2020**, *24*, 1802−1813.
(20) Trojanowicz, M. Flow Chemistry in Contemporary Chemical Sciences: A Real Variety of Its Applications. *Molecules* **2020**, *25*, 1434.
(21) Bloemendal, V. R. L. J.; Janssen, M. A. C. H.; Van Hest, J. C. M.; Rutjes, F. P. J. T. Continuous One-Flow Multi-Step Synthesis of Active Pharmaceutical Ingredients. *React. Chem. Eng.* **2020**, *5*, 1186−1197.
(22) Britton, J.; Raston, C. L. Multi-Step Continuous-Flow Synthesis. *Chem. Soc. Rev.* **2017**, *46*, 1250−1271.
(23) Bana, P.; Örkényi, R.; Lövei, K.; Lakó, Á.; Túrós, G. I.; Éles, J.; Faigl, F.; Greiner, I. The Route from Problem to Solution in Multistep Continuous Flow Synthesis of Pharmaceutical Compounds. *Bioorg. Med. Chem.* **2017**, *25*, 6180−6189.
(24) Russell, M. G.; Jamison, T. F. Seven-Step Continuous Flow Synthesis of Linezolid Without Intermediate Purification. *Angew. Chem., Int. Ed.* **2019**, *58*, 7678−7681.
(25) Lin, H.; Dai, C.; Jamison, T. F.; Jensen, K. F. A Rapid Total Synthesis of Ciprofloxacin Hydrochloride in Continuous Flow. *Angew. Chem., Int. Ed.* **2017**, *56*, 8870−8873.
(26) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. The Continuous-Flow Synthesis of Ibuprofen. *Angew. Chem., Int. Ed.* **2009**, *48*, 8547−8550.
(27) Ziegler, R. E.; Desai, B. K.; Jee, J. A.; Gupton, B. F.; Roper, T. D.; Jamison, T. F. 7-Step Flow Synthesis of the HIV Integrase Inhibitor Dolutegravir. *Angew. Chem., Int. Ed.* **2018**, *57*, 7181−7185.
(28) Snead, D. R.; Jamison, T. F. A Three-Minute Synthesis and Purification of Ibuprofen: Pushing the Limits of Continuous-Flow Processing. *Angew. Chem., Int. Ed.* **2015**, *54*, 983−987.
(29) Correia, C. A.; Gilmore, K.; McQuade, D. T.; Seeberger, P. H. A Concise Flow Synthesis of Efavirenz. *Angew. Chem., Int. Ed.* **2015**, *54*, 4945−4948.
(30) Lévesque, F.; Seeberger, P. H. Continuous-Flow Synthesis of the Anti-Malaria Drug Artemisinin. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706−1709.
(31) Ogasawara, S.; Hayashi, Y. Multistep Continuous-Flow Synthesis of (−) -Oseltamivir. *Synthesis* **2016**, *49*, 424−428.
(32) Cai, Y.; Hao, Z.; Gao, Y.; Ping, W.; Wang, Q.; Peng, S.; Zhao, B.; Sun, W.; Zhu, M.; Li, K.; Han, Y.; Kuang, D.; Chu, Q.; Fu, X.; Zhang, N. Coronavirus Disease 2019 in the Perioperative Period of Lung Resection: A Brief Report From a Single Thoracic Surgery Department in Wuhan, People's Republic of China. *J. Thorac. Oncol.* **2020**, *15*, 1065−1072.
(33) Lim, S.; Bae, J. H.; Kwon, H. S.; Nauck, M. A. COVID-19 and Diabetes Mellitus: From Pathophysiology to Clinical Management. *Nat. Rev. Endocrinol.* **2021**, *17*, 11−30.
(34) Sharma, A.; Adhikary, A.; Borah, S. B. Covid-19′s Impact on Supply Chain Decisions: Strategic Insights from NASDAQ 100 Firms Using Twitter Data. *J. Bus. Res.* **2020**, *117*, 443−449.
(35) UNAIDS. *The Impact of the COVID-19 Response on the Supply Chain, Availability and Cost of Generic Antiretroviral Medicines for HIV in Low- and Middle-Income Countries*. https://www.unaids.org/en/resources/documents/2020/covid19-supply-chain-availability-cost-generic-arv (accessed 2021-05-24).
(36) Brasholz, M.; MacDonald, J. M.; Saubern, S.; Ryan, J. H.; Holmes, A. B. A Gram-Scale Batch and Flow Total Synthesis of Perhydrohistrionicotoxin. *Chem. - Eur. J.* **2010**, *16*, 11471−11480.
(37) Mathieu, G.; Patel, H.; Lebel, H. Convenient Continuous Flow Synthesis of N-Methyl Secondary Amines from Alkyl Mesylates and Epoxides. *Org. Process Res. Dev.* **2020**, *24*, 2157−2168.
(38) Sagandira, C. R.; Watts, P. Continuous-Flow Synthesis of (−) -Oseltamivir Phosphate (Tamiflu). *Synlett* **2020**, *31*, 1925−1929.
(39) Wang, H.; Mustaffar, A.; Phan, A. N.; Zivkovic, V.; Reay, D.; Law, R.; Boodhoo, K. A Review of Process Intensification Applied to Solids Handling. *Chem. Eng. Process.* **2017**, *118*, 78−107.
(40) Hartman, R. L.; Naber, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. Overcoming the Challenges of Solid Bridging and Constriction during Pd-Catalyzed C-N Bond Formation in Microreactors. *Org. Process Res. Dev.* **2010**, *14*, 1347−1357.
(41) Dong, Z.; Delacour, C.; McCarogher, K.; Udepurkar, A. P.; Kuhn, S. Continuous Ultrasonic Reactors: Design, Mechanism and Application. *Materials* **2020**, *13*, 344.
(42) Ding, R.; He, Y.; Wang, X.; Xu, J.; Chen, Y.; Feng, M.; Qi, C. Treatment of Alcohols with Tosyl Chloride Does Not Always Lead to the Formation of Tosylates. *Molecules* **2011**, *16*, 5665−5673.
(43) Albright, J. D.; Benz, E.; Lanzilotti, A. E.; Goldman, L. Reactions of Sulphonyl Chloride-NN-Dimethylformamide Complexes. *Chem. Commun.* **1965**, *17*, 413−414.
(44) Chen, B.-C.; Quinlan, S. L. Process for Preparing AZT. US005466787A, 1995.
(45) Hayashi, Y. Time Economy in Total Synthesis. *J. Org. Chem.* **2021**, *86*, 1−23.
(46) Hayashi, Y. Time and Pot Economy in Total Synthesis. *Acc. Chem. Res.* **2021**, *54*, 1385−1398.

https://doi.org/10.1021/acs.joc.1c01013
J. Org. Chem. XXXX, XXX, XXX−XXX