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Multistep Continuous Flow Synthesis of Stavudine

Featured Article

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Cite This: [*J. Org. Chem.* 2021, 86, 13934−13942](https://pubs.acs.org/action/showCitFormats?doi=10.1021/acs.joc.1c01013&ref=pdf)



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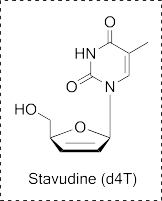
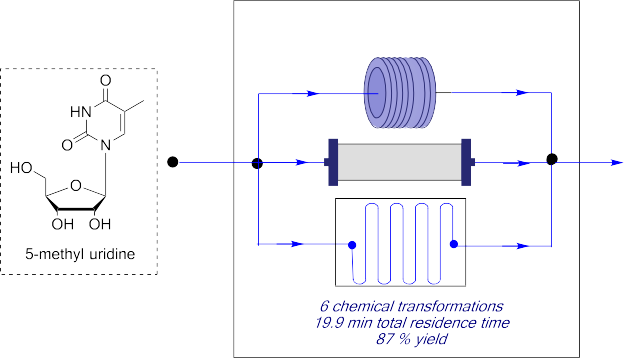
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# INTRODUCTION



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.

Stavudine (2′,3′-didehydro-3′-deoxythymidine), also known as

d4T (1), is a potent nucleoside chemotherapeutic agent for human immunodeﬁciency virus (HIV), acquired immunodeﬁ- ciency syndrome (AIDS) and AIDS-related conditions ([Figure](#_bookmark0) [1](#_bookmark0)).[1](#_bookmark6),[2](#_bookmark6) It works by being converted to stavudine 5′-triphosphate,

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig1&ref=pdf)

Figure 1. Stavudine (d4T, 1) structure

which competes with thymidine 5′-triphosphate for incorpo- ration 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](#_bookmark6),[3](#_bookmark6) 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](#_bookmark6),[6](#_bookmark6) stavudine-based

treatments continue to be used in some developing countries due to its aﬀordability.[7](#_bookmark6)−[10](#_bookmark7) For example, it is still listed as an essential medicine in South Africa.7

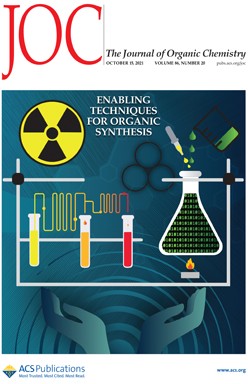
The synthesis of stavudine (1) was ﬁrst reported by Horwitz et al. in 1964.11 Early procedures started from an expensive starting material, namely thymidine.[11](#_bookmark7),[12](#_bookmark7) Alternative procedures have been developed over the years which use a more aﬀordable

starting material, 5-methyluridine.[12](#_bookmark7)−[17](#_bookmark7) 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](#_bookmark7)−[16](#_bookmark7) Most of these draw- backs are inherent to the use of traditional batch technology. Continuous ﬂow synthesis is known to overcome some of the challenges inherent in batch.[18](#_bookmark7)−[20](#_bookmark7) 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](#_bookmark7)−[23](#_bookmark7) This is due to the many advantages of continuous ﬂow



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Received: April 30, 2021

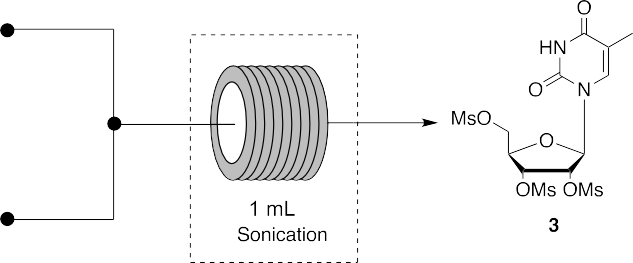
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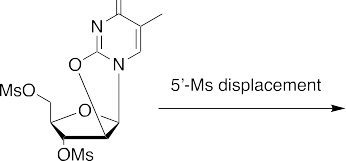
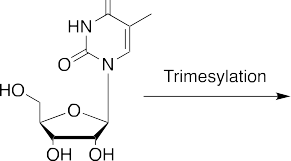
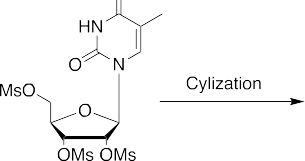
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[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig2&ref=pdf)Figure 2. Reaction sequences for stavudine (1) synthesis of 5-methyluridine 2.



[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig3&ref=pdf)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](#_bookmark7),[21](#_bookmark7)−[23](#_bookmark7) 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 APls synthesis have been reported.[23](#_bookmark7)−[31](#_bookmark7) The current Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) pandemic, also known as COVID-19,[32](#_bookmark7)−[35](#_bookmark7) 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](#_bookmark7),[14](#_bookmark7) we started from a cost-eﬀective and commercially available starting

material, namely 5-methyluridine (2) ([Figure 2](#_bookmark1)).

# 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](#_bookmark1)). Mesylation of alcohols is usually accom- plished 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](#_bookmark7)−[38](#_bookmark7) In this

reaction, we employed ultrasonication[39](#_bookmark7)−[41](#_bookmark7) 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](#_bookmark1)). 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*-dimethyl- formamide complexes.[42](#_bookmark7),[43](#_bookmark7) 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

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](#_bookmark2)).

Moving on to the second reaction, compound 4 was prepared in continuous ﬂow via DBU-initiated intermolecular nucleo- philic attack on 2′-carbon ([Figure 4](#_bookmark2) and [5](#_bookmark2)). Trimesylate 3 (1 M,

Table 1. Continuous Flow Synthesis of Trimesylate 3 Optimizationa



MsCl

entry (equiv)

base (equiv)

temp (°C)

res time conv to 3*g*

(min)

(%)

6 0 1 100

|  |  |
| --- | --- |
| 1 | 6 |
| 2 | 6 |
| 3 | 6 |
| 4 | 3 |
| 5 | 4.5 |
| 6 | 4.5 |
| 7 | 4.5 |
| 8 | 4.5 |
| 9 | 4.5 |

6 rt 1 100

6 rt 0.25 100

6 rt 0.25 43

6 rt 0.25 100 (97)*h*

4.5 rt 0.25 75

6*b* rt 0.25 100

6[*b*,*c*](#_bookmark2)rt 0.25 100

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 MsCI (6 equiv) and TEA (6 equiv) aﬀorded trimesylate 3 in full conversion in 1 min residence time at 0 °C ([Table 1](#_bookmark2), entry 1). Raising the temperature to room temperature gave the same results ([Table 1](#_bookmark2), entries 1 and 2). The use of shorter residence time (0.25 min) still gave trimesylate 3 in full conversion ([Table](#_bookmark2) [1](#_bookmark2), entries 2 and 3). A decrease in MsCl equivalents (3 equiv) resulted in a decrease in conversion to 3 ([Table 1](#_bookmark2), entries 3 and 4). However, the use of MsCl (4.5 equiv) and TEA (4.5 equiv) improved the conversion (75%) ([Table 1](#_bookmark2), 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](#_bookmark2), entry 5). The use of alternative bases such as tributyl amine, trihexyl amine, and *N,N*- diisopropylethylamine gave comparative results ([Table 1](#_bookmark2), 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](#_bookmark2), entries 7 and 8). Although 5-methyluridine (2) was completely consumed, no trimesylate 3 was detected when DBU was used ([Table 1](#_bookmark2), entry 9). The same was observed when pyridine was used as both solvent and base ([Table 1](#_bookmark2), entry 11). Chloroform was also found to be an alternative solvent to DCM ([Table 1](#_bookmark2), 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’s14 3 h batch procedure in pyridine at room temperature and Chen et al.’s[12](#_bookmark7),[44](#_bookmark7) 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.

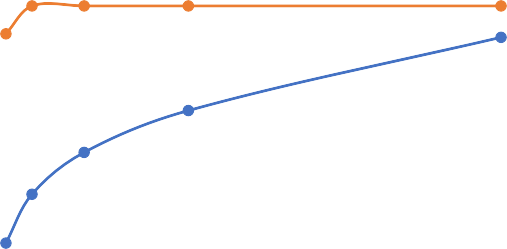


Figure 4. Continuous-ﬂow synthesis of compound 4.

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig5&ref=pdf)



Figure 5. Continuous-ﬂow synthesis of compound 4.

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig5&ref=pdf)1 equiv) was treated with DBU (1 equiv) to aﬀord compound 4 and optimized in continuous ﬂow ([Figures 4](#_bookmark2) and [5](#_bookmark2)). The conversion was determined by following the product peak on HPLC at 254 nm.

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](#_bookmark2)). 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](#_bookmark2)).

Subsequent displacement of 5′-OMs of compound 4 with

−OBz was accomplished by the use of an Amberlite IRA 400-

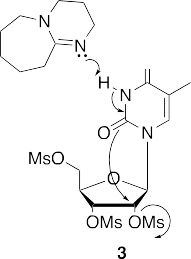


Figure 6. Proposed mechanism for intermolecular nucleophilic attack to aﬀord compound 4.

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

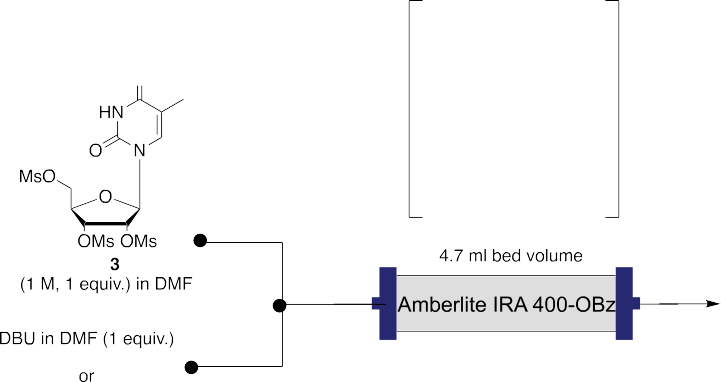
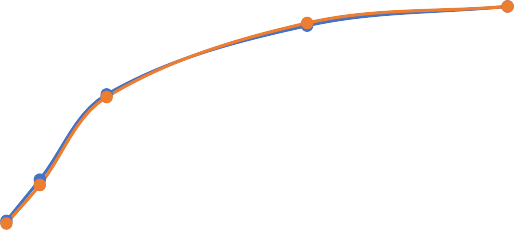


Figure 8. Synthesis of 5′-benzoyl-5-methyluridine (5) from trimesylate 3.

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](#_bookmark3) and [8](#_bookmark3)). Amberlite IRA

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig9&ref=pdf)400-OBz was prepared by treating Amberlite IRA 400-Cl ion- exchange resin with sodium benzoate.

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig9&ref=pdf)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](#_bookmark3), entry 1). Increasing

Table 2. Continuous Flow Synthesis of 5′-Benzoyl-5- methyluridine (5) from Compound 4 Optimizationa

|  |  |  |  |
| --- | --- | --- | --- |
| 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.

4 synthesis and its subsequent conversion to 5 ([Figures 8](#_bookmark3) and [9](#_bookmark3)). Compound 5 was aﬀorded in 100% conversion cleanly.

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig9&ref=pdf)



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

the residence time improved the conversion ([Table 2](#_bookmark3), entries 1 and 2). An increase in temperature aﬀorded better conversion to 5 ([Table 2](#_bookmark3), 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](#_bookmark2)), we found it reasonable to just use an Amberlite IRA 400-OBz packed column reactor held at 120 °C for this study ([Figure 8](#_bookmark3)). 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

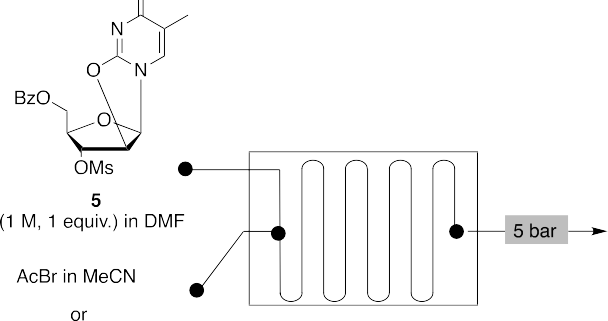
Interestingly, comparable product 5 was observed in the absence of DBU ([Figures 8](#_bookmark3) and [9](#_bookmark3)). This is consistent with some of the batch literature, where excess sodium benzoate was used to make 5 from 3 in the absence of a base.[12](#_bookmark7),[14](#_bookmark7),[44](#_bookmark7) 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](#_bookmark3)). 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](#_bookmark7),[14](#_bookmark7),[44](#_bookmark7) 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

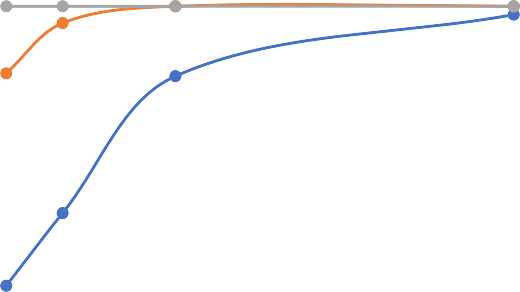
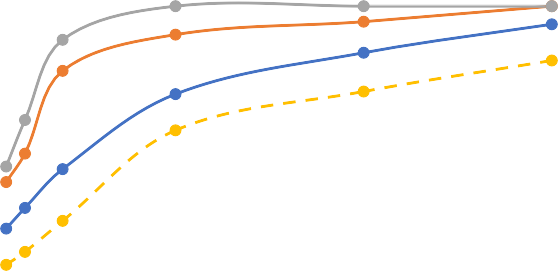
Figure 10. Synthesis of compound 6 from 5′-benzoyl-5-methyluridine (5).



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](#_bookmark4)

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig11&ref=pdf)[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig13&ref=pdf)[10](#_bookmark4) and [11](#_bookmark4)). In our preliminary studies, we observed that



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](#_bookmark4) and [13](#_bookmark4)); a freshly

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig11&ref=pdf) [](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig13&ref=pdf)

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig11&ref=pdf) [](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig11&ref=pdf)



[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig11&ref=pdf)

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](#_bookmark4) and [11](#_bookmark4)). 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](#_bookmark4)). 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](#_bookmark7),[44](#_bookmark7)

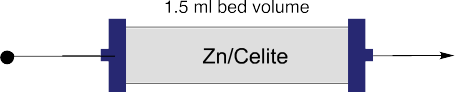
Figure 13. 2′,3′-Oleﬁnation of 6 to 5′-benzoyl-d4T (7).

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](#_bookmark4)). 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%

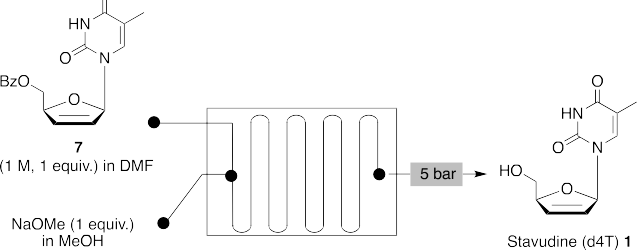
isolated yield.[12](#_bookmark7),[14](#_bookmark7)

The last step involved Bz-deprotection of 5′-benzoyl-d4T (7) using NaOMe to aﬀord d4T (1) in continuous ﬂow ([Figure 14](#_bookmark5)). We optimized the residence time and reaction temperature for Bz-deprotection ([Figure 15](#_bookmark5)). An increase in residence time and

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[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig12&ref=pdf)

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



[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig15&ref=pdf)Figure 14. Deprotection of 5′-benzoyl-d4T (7) to stavudine (d4T, 1).

[](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?fig=fig15&ref=pdf)



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

temperature improved the reaction ([Figure 15](#_bookmark5)). 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](#_bookmark7),[14](#_bookmark7) 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](#_bookmark5)). 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](#_bookmark7),[46](#_bookmark7) 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.

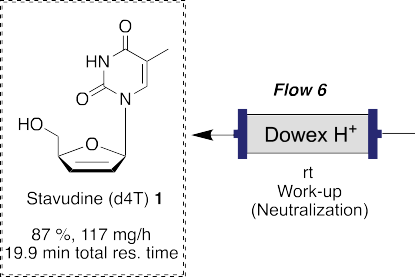
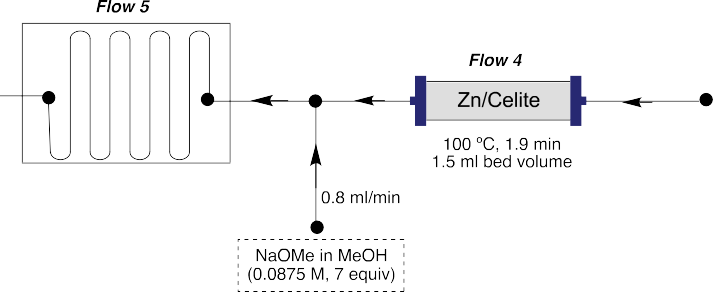
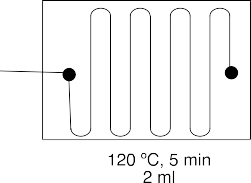
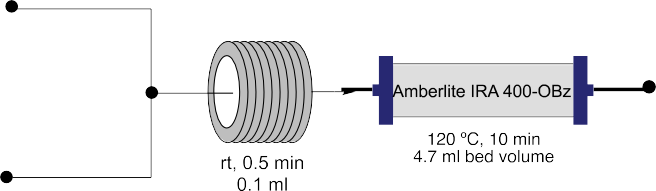


Figure 16. Multistep continuous ﬂow synthesis of stavudine (d4T).

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](#_bookmark7),[14](#_bookmark7) 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

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). 1H 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−

* CONCLUSION

also investigated. Reactions were analyzed by HPLC. For spectroscopic

4.28 (m, 1H), 4.20−4.08 (m, 1H), 3.44 (s, 3H), 3.15 (s, 3H), 1.81 (s,

3H). 13C{1H} 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) *v*: 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) *v*: 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](#_bookmark7),[44](#_bookmark7)

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

4000 to 500 cm−1 using a Bruker spectrometer, and peaks (*υ*

−1

max) are

volume, 1.8 mmolg−1 exchange capacity) ([Figure S3](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). The eﬀect of

residence time and temperature was investigated for reaction

reported in wavenumbers (cm ). High-performance liquid chroma-

tography (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 *μ*L, 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](#_bookmark7),[44](#_bookmark7) 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](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). 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 NH4Cl. 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). 1H 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). 13C{1H} 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) *v*:

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](#_bookmark7),[14](#_bookmark7),[44](#_bookmark7) Trimesylate 3 (1 M, 1 equiv) in DMF was treated with DBU (1 equiv) in a Uniqsis 2 mL chip reactor ([Figure S2](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). The eﬀect of temperature and residence time was investigated for reaction optimization. The use of alternative bases was

optimization. Reactions were analyzed by HPLC.

Procedure 5: Synthesis of 5′-benzoyl-3′-methanesulfonyl- 2.2′-anhydro-5-methyluridine (5) from Trimesylate 3.[12](#_bookmark7),[44](#_bookmark7) 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](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf) [S4](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). Reactions were analyzed by HPLC. For spectroscopic character-

ization, 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). 1H 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). 13C{1H} 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) *v*: 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](#_bookmark7),[44](#_bookmark7) 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](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). 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*-

methanesulfonyl-2′*α*-bromothymidine (6) as an oﬀ-white solid (1.22 g, 97% yield, mp 78.2−79.8 °C). 1H 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).

13C{1H} 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)

*v*: 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](#_bookmark7),[14](#_bookmark7) 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](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). 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). 1H 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). 13C{1H} 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](#_bookmark7),[14](#_bookmark7) 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](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). 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). 1H 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). 13C{1H} 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) *v*: 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](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf)). 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 recrystal- lized in hot acetone to aﬀord 1 as a white solid (39 mg, 87% yield).

# ASSOCIATED CONTENT

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## \*sı Supporting Information

The Supporting Information is available free of charge at [https://pubs.acs.org/doi/10.1021/acs.joc.1c01013](https://pubs.acs.org/doi/10.1021/acs.joc.1c01013?goto=supporting-info).

FTIR, 1H NMR, and 13C NMR spectra for all compounds and continuous ﬂow system setups ([PDF](https://pubs.acs.org/doi/suppl/10.1021/acs.joc.1c01013/suppl_file/jo1c01013_si_001.pdf))

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Notes

The authors declare no competing ﬁnancial interest.

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# ACKNOWLEDGMENTS

We thank the National Research Fund (NRF SARChI Grant) for ﬁnancial support.

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