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Continuous-Flow Synthesis of (–)-Oseltamivir Phosphate (Tamiflu)

Cloudius R. Sagandira
Paul Watts*

Department of Chemistry, Nelson Mandela University, University Way, Port Elizabeth, 6031, South Africa
Paul.Watts@mandela.ac.za

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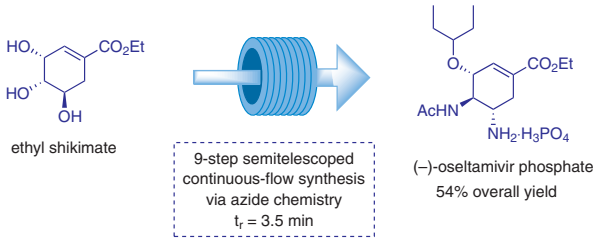

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Abstract Herein the anti-influenza drug (–)-oseltamivir phosphate is prepared in continuous flow from ethyl shikimate with 54% overall yield over nine steps and total residence time of 3.5 min from the individual steps. Although the procedure involved intermediate isolation, the dangerous azide chemistry and intermediates involved were elegantly handled *in situ*. It is the first continuous-flow process for (–)-oseltamivir phosphate involving azide chemistry and (–)-shikimic acid as precursor.

Key words azide chemistry, continuous flow, influenza, (–)-oseltamivir phosphate, total synthesis

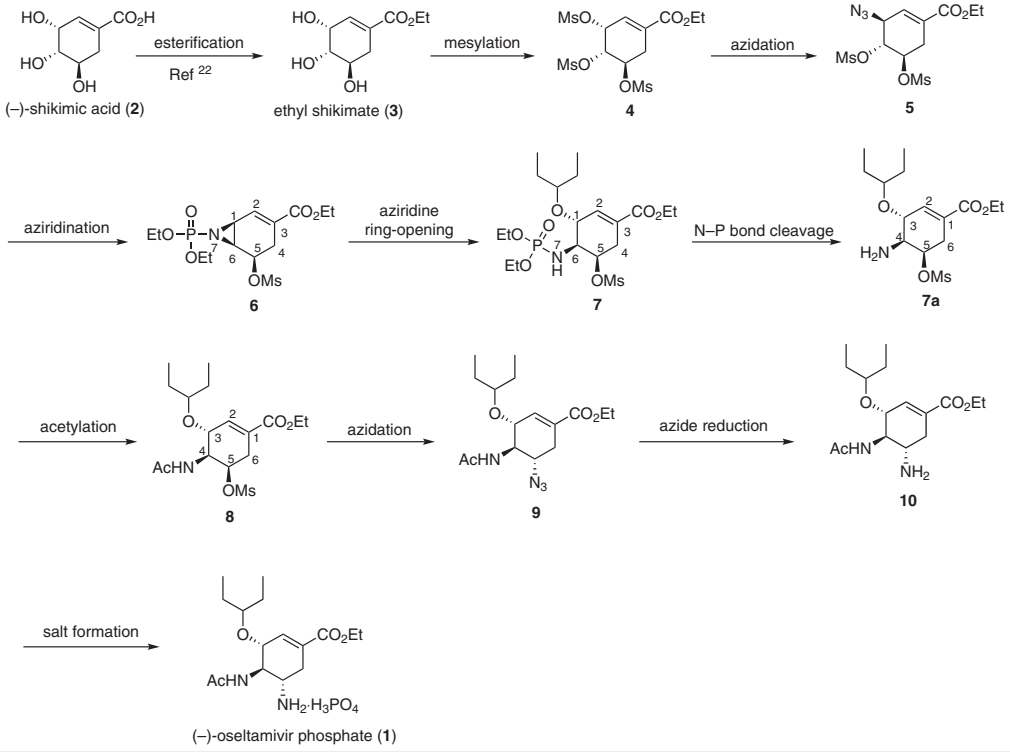
Influenza is a severe viral infection of the respiratory system, which is responsible for a significant morbidity and mortality due to both annual epidemics and predictable pandemics.[1] (–)-Oseltamivir phosphate (Tamiflu) is used for treatment and prophylaxis of influenza.[1–5] According to the World Health Organization (WHO), this drug is one of the most important anti-influenza drugs to guard against a pandemic.[6] This has prompted the research community to focus on the development of new, better, and practical approaches to this drug. In the early years of discovery, (–)-shikimic acid (**2**) was used as starting material and furthermore, the current industrial procedure uses (–)-shikimic acid (**2**). There have been several new approaches to (–)-oseltamivir phosphate (**1**) from sources other than (–)-shikimic acid (**2**) based on arguments regarding the availability of (–)-shikimic acid (**2**) as well-potential risks of azide chemistry on an industrial scale.[1,7–9] The legitimate (–)-shikimic acid (**2**) availability concerns in the early years of the development of this drug have long been solved.[9–11] However, the concerns associated with the use of potentially hazardous azide chemistry are yet to be addressed. There have been enormous efforts in this regard mainly through development of azide-chemistry-free routes. Unfortunately, these alternative azide-free routes are generally inefficient compared to the azide-chemistry approaches. More than 60 synthetic routes have been developed towards Tamiflu to date.[1,7–10] However, most of these synthetic approaches suffer from the use of potentially hazardous azide chemistry, thus raising safety concerns and eventually ruled out for large-scale synthesis in batch systems.[1,2] Therefore, the development of alternative practical and safe processes for (–)-oseltamivir phosphate (**1**) synthesis, which can be adapted at large scale, is imperative.

Continuous-flow synthesis has emerged as a useful technique in synthetic chemistry, largely motivated by its numerous advantages relative to batch; these include improved synthetic efficiency, safety, and selectivity.[11–19] The only literature on continuous-flow total synthesis of (–)-oseltamivir phosphate (**1**) is a five-step procedure by Hayashi and Ogasawara,[10] which started from Michael addition and avoided azide chemistry. Although their approach showed ingenuity in synthesizing a compound with three chiral centers through a multistep continuous-flow procedure starting from the Michael reaction in a single passage, the throughput of 58 mg *per* 15 h (total yield of 13%) was insufficient to meet demand.

Herein we report safe and efficient continuous-flow conversion of (–)-shikimic acid (**2**) into (–)-oseltamivir phosphate (**1**) *via* the hazardous azide chemistry. Our flow synthetic route (Scheme 1) was inspired by the batch synthesis by Shi,[9] Kalashnikov *et al.*[20] and Karpf *et al.*[21] It elegantly takes advantage of the chirality present in (–)-shikimic acid (**2**) to introduce the groups at C3, C4, and C5 with the desired stereochemistry.[2]

We started from ethyl shikimate (**3**) already synthesized in flow from shikimic acid (**2**).[22] Trimesylation of ethyl shikimate (**3**) using MsCl in the presence of triethylamine

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 1 Reaction sequence for the synthesis of (–)-oseltamivir phosphate (**1**) from (–)-shikimic acid (**2**)

(TEA) to afford *O*-trimesylate **4** was initially threatened by reactor blockage due to the insoluble byproduct triethylammonium chloride in EtOAc.

Sonication was introduced to resolve this, and *O*-mesylate **4** was rapidly afforded in excellent yield. Sonication was later avoided by using tributylamine (TBA) whose ammonium salt is soluble in EtOAc instead of TEA and optimization was performed (Table 1).

Table 1 Ethyl Shikimate Mesylation Optimization

Entry	Residence time (s)	MsCl (equiv.)[a]	TBA (equiv.)[b]	Temp (°C)	Conv. (%)[c]
1	1	1	2	r.t	54
2	1	1.5	2	r.t	68
3	1	1.5	2	40	69
4	12	1.5	2	r.t	71
5	12	1.5	4	r.t	97 (89)[d]
6	12	1.5	3	r.t	84
7	12	1.5	1	r.t	52

[a] MsCl equiv. per OH on ethyl shikimate (**3**).
[b] TBA equiv. per OH on ethyl shikimate (**3**).
[c] Conversion determined by HPLC.
[d] Number in parentheses corresponds to isolated yield. All reactions were quenched by 1 M HCl.

A slight excess of MsCl (1.5 equiv.) was necessary and conversion improved with increase in the amount of TBA (Table 1, entries 1, 2, and 5). Increase in residence time improved conversion (Table 1, entries 2 and 4) whilst the effect of temperature increase was insignificant (Table 1, entries 2 and 3); 92% isolated yield of *O*-mesylate was afforded at 12 s residence time and room temperature using MsCl (1.5 equiv.) and TBA (4 equiv.). DBU can be used to achieve comparable results.

O-Trimesylate **4** in the presence of an appropriate azidating agent undergoes highly regio- and stereoselective nucleophilic substitution of allylic *O*-mesylate at the C-3 position affording azide **5**. NaN_3 (aq) is the commonly used azidating agent, and azide **5a** is a known minor side product (Figure 1).[9,20,21] Comprehensive optimization studies on this reaction have been reported in a preliminary publication.[23]

Mesyl shikimate (**4**) azidation performed at 0 °C and 30 s residence time using NaN_3 (aq) afforded 86% conversion and 100% azide **5** selectivity (Table 2, entry 1). An increase in temperature and residence time improved conversion but promoted side product **5a** formation, thus lowering azide **5** selectivity (Table 2, entries 1–4). Using NaN_3 (aq), the best results were found at 25 °C and 30 s residence time affording azide **5** in 91% isolated yield. Other azidating agents such as Diphenylphosphoryl azide (DPPA), Trimethylsilyl azide (TMSA), and Tetrabutylammonium azide

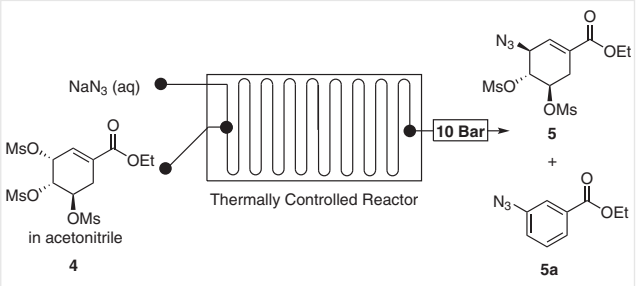


Figure 1 Optimization of *O*-trimesylate **4** azidation in flow

(TBAA) can be used. Azide **5** isolated yield of 78% was achieved using DPPA in acetonitrile at 25 °C and 30 s residence time.

Table 2 Optimization of *O*-Trimesylate **4** Azidation[a]

Entry	Azidating agent	Temp (°C)	Residence time (s)	Conv. (%)[c]	Azide **5** selectivity (%)[d]
1	NaN_3 (aq)	0	30	86	100
2	NaN_3 (aq)	25	30	100	100 (91)
3	NaN_3 (aq)	100	30	100	69
4	NaN_3 (aq)	25	60	100	73
5	DPPA[b]	25	30	93	89 (78)
6	TMSA[b]	25	30	100	90
7	TBAA	25	30	100	66

[a] Standard conditions: *O*-trimesylate **4** (0.1 M, 1 equiv.), azidating agent (1.1 equiv.), acetonitrile as solvent.
[b] TBA (1.1 equiv.), quenched by 1 M HCl.
[c] Conversion determined by HPLC.
[d] Number in parentheses corresponds to isolated yield.

Azide **5** undergoes aziridination when treated with $(EtO)_3P$ (1.1 equiv.) under water-free conditions to afford aziridine **6**. When the reactor was heated at 100 °C and 12 s residence time, only a 7% conversion was obtained (Table 3, entry 1). Temperature and residence time increase improved the results, at 190 °C affording the highest conversion and yield (Table 3, entry 3). The use of $(MeO)_3P$ also produced comparable results.

With the azidation and aziridination reactions separately optimized, multistep synthesis of aziridine **6** from synthetic mesyl shikimate (**4**) *via* azide **5** formation and consumption *in situ* was performed to enhance process safety (Figure 2). Although NaN_3 (aq) was the most efficient azidating agent, more affordable and its use is accompanied by better atom efficiency compared to DPPA; we used DPPA for telescoping because water (NaN_3 (aq)) was detrimental in the succeeding aziridination step. The total residence time for this multistep synthesis was 25 s affording aziridine **6** in 84% yield.

Table 3 Aziridine **6** Formation Optimization[a]

Entry	Residence time (s)	Temp (°C)	Conv. (%)[b]
1	12	100	7
2	12	150	58
3	12	190	100 (94)[c]
4	60	150	92

[a] Standard conditions: azide **5** (0.1 M, 1 equiv.), $(EtO)_3P$ (1.1 equiv.), acetonitrile as solvent.
[b] Conversion determined by HPLC.
[c] Number in parentheses corresponds to isolated yield.

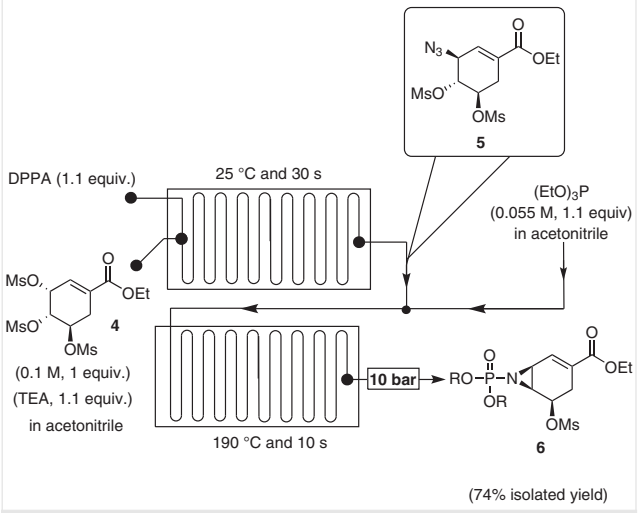


Figure 2 Two-step reaction sequence to aziridine **6**

Pure aziridine **6** (1 equiv.) subsequently undergoes regio- and stereoselective ring opening with 3-pentanol in the presence of $BF_3{\cdot}OEt_2$ (1.5 equiv.) at the allylic position to introduce the N-based substituent on C-4 of the cyclic carbon backbone. High temperatures and longer residence times favored 3-pentyl ether **7** synthesis (Figure 3). Full conversion (95% isolated yield) was achieved at 100 °C and 12 s (Figure 3).

Due to the safety concerns of handling aziridines,[24–27] we further demonstrated *in situ* generation and consumption of aziridine **6** to afford 3-pentyl ether **7** in 87% yield in 20 s residence time (Figure 4).

Acetylation of 3-pentyl ether **7** was achieved *via* a tandem of reactions; N–P bond cleavage of 3-pentyl ether **7** by H_2SO_4 and subsequently treated with Ac_2O to afford acetamide **8** in flow. We began with N–P bond-cleavage optimization first (Table 4). Higher temperatures gave better results, the best being 170 °C and 3 s residence time using H_2SO_4 (5 equiv., Table 4, entry 3). In the two-step process, the reaction was neutralized in-line with NaOH (aq), and the crude was treated with Ac_2O (1.6 equiv.) in acetonitrile at room temperature and 30 s residence time affording acetamide **8** in 93% isolated yield.

Table 4 Optimisation of N–P Bond Cleavage of 3-pentyl ether **7**[a]

Entry	Residence time (s)	Temp (°C)	Conv. (%)[b]
1	3	80	53
2	3	120	71
3	3	170	100

[a] Standard conditions: 3-pentyl ether **7** (0.1 M, 1 equiv.), H_2SO_4 (5 equiv.), (1.1 equiv.), acetonitrile as solvent.
[b] Conversion determined by HPLC.

Acetamide **8** azidation was accomplished using various azidating agents such as NaN_3, DPPA, TMSA, and TBAA to afford azide **9**. NaN_3 (aq, 3 equiv.) at 190 °C and 45 s residence time gave the best yield (89%) as reported in a preliminary publication.[23]

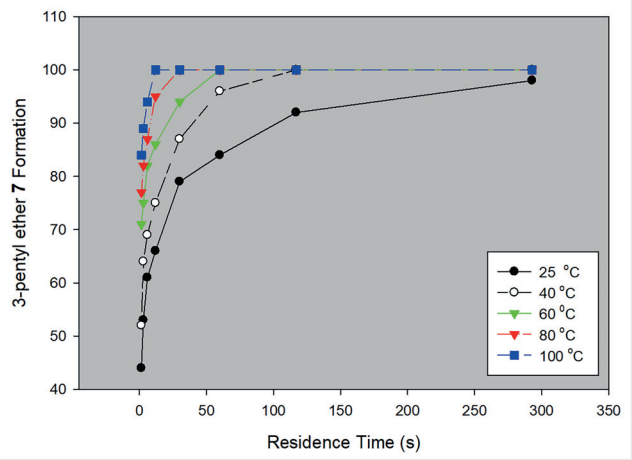


Figure 3 Optimization of 3-pentyl ether **7** synthesis

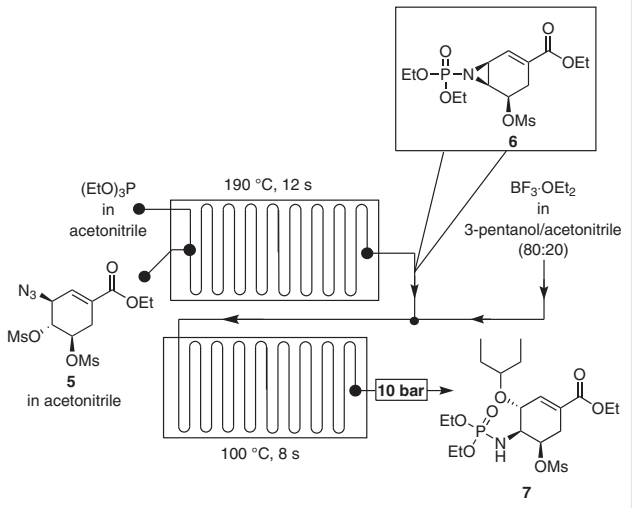


Figure 4 Two-step reaction sequence to 3-pentyl ether **7**

With the pure azide **9** in hand, the last intermediate oseltamivir (**10**) was obtained *via* azide group reduction. Various azide **9** reduction procedures such as P(*n*-Bu)$_3$, Ph_3P, and H_2 in the presence of Pd/C, Lindler catalyst, and Raney-Ni to obtain oseltamivir (**10**) have been reported.[8,20,21] Inspired by the work of Fringuelli *et al.*[28], we employed the $CoCl_2$-catalyzed chemoselective reduction of azide **9** using $NaBH_4$ in water (pH = 8) at ambient temperature to afford a novel procedure towards oseltamivir (**10**). The formation of the black cobalt boride precipitate which threatened our flow procedure was resolved by introduction of sonication to avoid blockages. Azide **9** reduction was performed and optimized at room temperature using $NaBH_4$ (2 equiv.) and $CoCl_2$ (0.1 equiv.) affording 96% conversion (93% yield) at 5 s residence time (Figure 5)

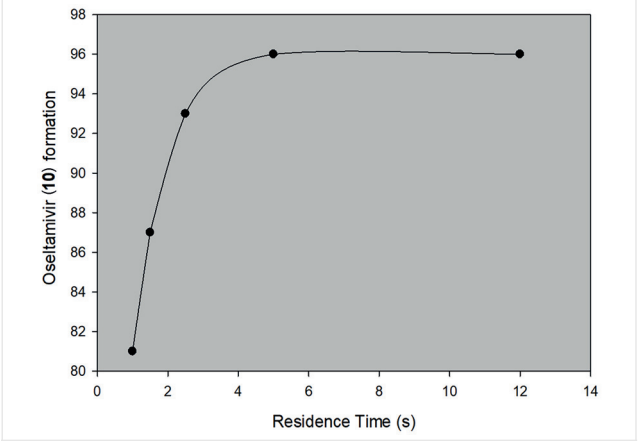


Figure 5 Optimization of oseltamivir (**10**) synthesis

Use of either ethanol or methanol as $NaBH_4$ solvent gave comparable results (see Supporting Information, Table 1). In the final step, oseltamivir (**10**) was treated with H_3PO_4 (1.2 equiv.) to immediately afford (–)-oseltamivir phosphate (**1**) in 97% yield at 50 °C and 60 s residence time.

In summary, we successfully developed an efficient nine-step total synthesis procedure in continuous flow for (–)-oseltamivir phosphate (**1**) in remarkable 3.5 min total residence time, 54% untelescoped and 48% semitelescoped overall yield. This process is significantly shorter and higher-yielding than most of the reported procedures.[1,2] Although our procedure is not multistep like the only reported (–)-oseltamivir phosphate (**1**) continuous-flow process by Hayashi and Ogasawara (310 min residence time and 13 % total yield),[10] we had superior total yield and residence time. To the best our knowledge, this is the first (–)-shikimic acid based synthetic procedure for (–)-oseltamivir phosphate (**1**) which takes advantage of continuous-flow technology to elegantly handle the hazardous azide chemistry. Consequently, we believe that application of flow is the last piece of the puzzle in solving the long-standing azide chemistry concerns in the large-scale synthesis of (–)-oseltamivir

phosphate in industry and academia. The route is scalable and has great potential to become an alternative to the current commercial route due to its operational simplicity, inexpensive reagents, and lack of protecting group chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690878.

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