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The evolution of Tamiflu synthesis, 20 years on: Advent of enabling technologies the last piece of the puzzle?

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ABSTRACT

Influenza is a serious respiratory disease responsible for significant morbidity and mortality due to both annual epidemics and pandemics; its treatment involves the use of neuraminidase inhibitors. (−)-Oseltamivir phosphate (Tamiflu) approved in 1999, is one of the most potent oral anti-influenza neuraminidase inhibitors. Consequently, more than 70 Tamiflu synthetic procedures have been developed to date. Herein, we highlight the evolution of Tamiflu synthesis since its discovery over 20 years ago in the quest for a truly efficient, safe, cost-effective and environmentally benign synthetic procedure. We have selected a few representative routes to give a clear account of the past, present and the future with the advent of enabling technologies.

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Contents

1. Introduction

Tamiflu, also known as oseltamivir phosphate **1** is a potent chemotherapeutic agent for influenza treatment [1–3] Influenza is a severe viral infection of the respiratory system regarded as the most serious respiratory disease, which is responsible for significant morbidity and mortality due to both annual epidemics and predictable pandemics [1–3] More specifically, the avian influenza H5N1 has a mortality rate of about 60% [4] Unfortunately, little has been done to change the influenza infection patterns in past

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decades despite influenza being the most studied viral infection before the arrival of the human immunodeficiency virus (HIV) [5,6] Now in this global society, a highly aggressive strains of the influenza virus such as the H5N1 can mutate to become easily transmitted from human to human and spark another deadly pandemic just as with current Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection (COVID19) pandemic, [7,8] which has brought the world to its knees. The surge in drug-resistant influenza strains resulting from naturally occurring mutations reminds us of the need for continued research to discover more potent neuraminidase inhibitors [9–13] The current anti-influenza drugs are useful templates in the development of new neuraminidase inhibitors through structure-activity relationship studies. As the research towards new and better treatment remains a top priority, it is equally important to improve the availability of the current anti-influenza drugs by developing better synthetic procedures to guard the world against influenza. Drugs such as oseltamivir phosphate (Tamiflu) **1a**, amantadine HCl **1b**, rimantadine HCl **1c**, zanamivir **1d** and peramivir **1e** have been developed for the treatment of influenza over the years [1–3] and more recently, baloxavir marboxil **1f** was developed (Fig. 1) [14] The last four are FDA approved and are currently the recommended influenza drugs by Centres for Disease Control and Prevention (CDC) [15] Of all the drugs, Tamiflu is the most commonly used since its FDA approval in 1999 making its synthesis an important research area (see Fig. 2).

Tamiflu was discovered by Gilead Sciences in 1995, patented in 1996, co-developed with F. Hoffmann-La Roche Ltd and marketed by F. Hoffmann-La Roche and commercially launched in November 1999 [16–21] In the early years of its discovery, (−)-shikimic acid was used as starting material for the synthesis of Tamiflu and furthermore, the current and only industrial synthetic route still uses (−)-shikimic acid. In response to an increasing threat of an influenza pandemic, diverse synthetic approaches have been developed and very insightful reviews of their relative merits have been published [1–3,22–27] However, there were legitimate (−)-shikimic acid availability concerns in the early years of the development of this drug. Shikimic acid, which is a natural product isolated from a plant of Chinese star anise was unavailable in consistent purity and enough quantity, which prompted extensive

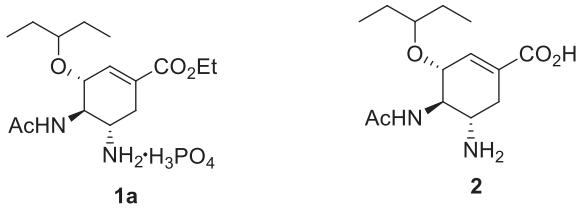


Fig. 2. Structures of oseltamivir carboxylate **2**.

studies into (−)-shikimic acid free synthetic routes in both industry and academia. Fortunately, this has been addressed by the development of more efficient extraction and purification processes or alternatively by fermentation using a genetically engineered *E.coli* bacteria [25,28–30] Furthermore, Yoshida and Ogasawara demonstrated an enantioconvergent synthesis of shikimic acid *via* a palladium mediated elimination reaction [31] Although more studies utilising alternative starting materials are still ongoing, they have not been as efficient as the current shikimic acid based production route. The use of the potentially hazardous azide chemistry for the introduction of amino and acetomido groups to the ring was, and is still, a major concern [1,2,32] Azide chemistry poses many safety concerns because of its hazardous and highly exothermic nature, which become more pronounced at a large scale [2,33–37] As a result, numerous studies towards azide-free synthetic routes were done, which unfortunately have not been as good as the current production route. Herein, this review highlights the evolution towards efficient and safe synthetic routes of Tamiflu since its first approval 20 years ago. Since there has been over 70 published synthetic routes and some review articles, [1–3,22–26] a few selected representative routes will be used to give a clear account of the past, present and the future with the arrival of enabling technologies [38] such as flow chemistry.

2. Discovery and synthesis by Gilead sciences

Oseltamivir carboxylate **2** was the first molecule identified by Gilead scientists for development, but the ethyl ester prodrug

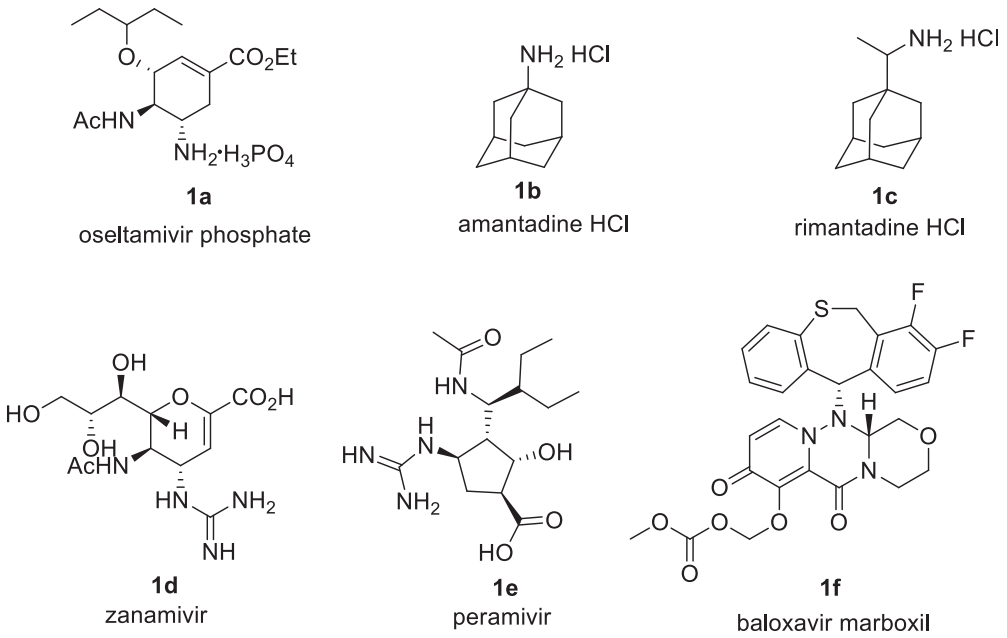


Fig. 1. Commercially available drugs for the treatment of influenza.

oseltamivir phosphate (Tamiflu) **1a** was ultimately chosen as the clinical candidate based on its potent *in vitro* and *in vivo* activities and its good oral bioavailability after extensive diversity-oriented discovery chemistry studies by Kim et al. [16–21].

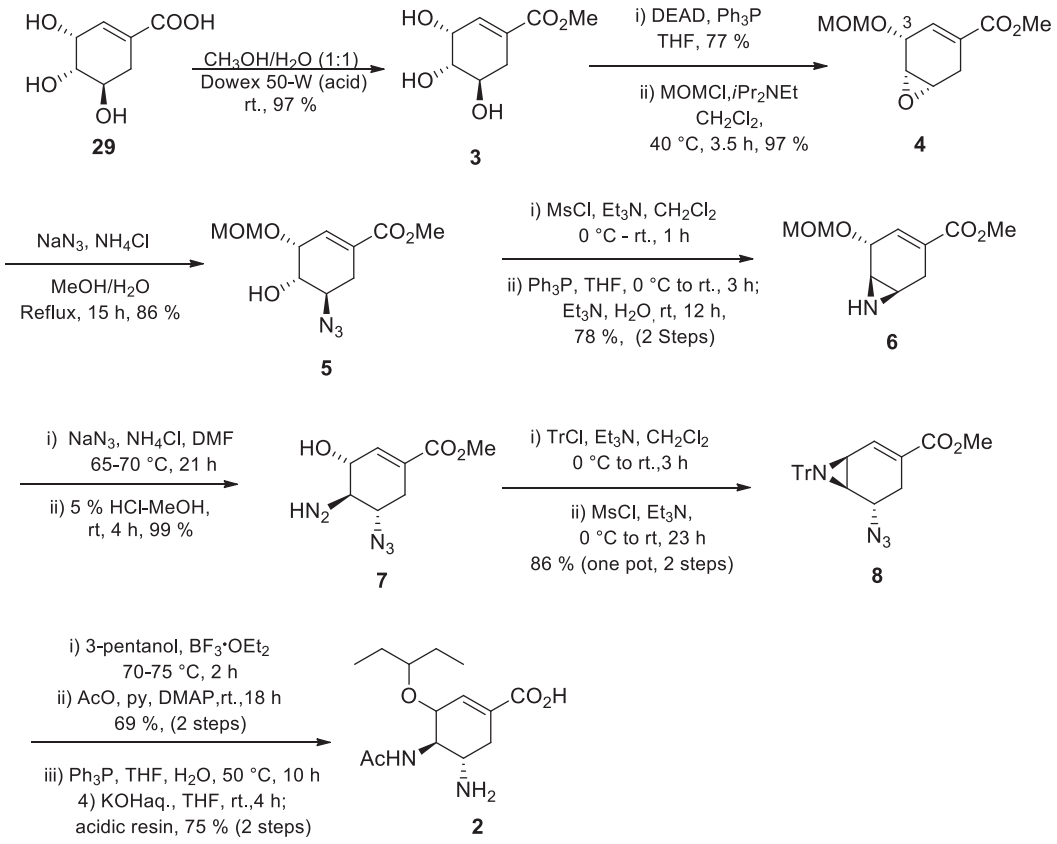
Gilead Sciences researchers first synthesised the oseltamivir carboxylate **2** from a natural product, (−)-shikimic acid **29**, as the starting material (Scheme 1) [20] (−)-Shikimic acid derivative **3** was treated under Mitsunobu conditions resulting in selective activation of the least selectively hindered OH-group at C-5 whilst the C-3 OH is MOM protected, affording epoxide **4** [20] Epoxide **4** was subsequently opened regio-and stereospecifically using azide chemistry, selective azidating the C-5 to afford azido alcohol **5**. Mesylation of **5**, followed by azide reduction afforded aziridine **6**. Once more, azide chemistry was utilised in regioselective aziridine-opening at C-5 followed by MOM group cleavage affording amino alcohol **7** [20] Aziridine **8** was synthesised from **7** by a two-step, one-pot process: (1) protection of the amino functionality with a trityl group, and (2) mesylation of the hydroxyl group. Regio-selective ring-opening of aziridine **8** with 3-pentanol in the presence of Lewis acid catalyst $BF_3{\cdot}OEt_2$ subsequently followed by acetylation of the resulting amine afforded the corresponding amido ether. The azide group on the resulting amido ether was reduced, followed by hydrolysis of the methyl ester under basic conditions affording oseltamivir carboxylate **2** in 15% overall yield over the 14 steps despite using protecting group chemistry [20] The choice of their starting material (−)-shikimic acid was justified; it has the carbocyclic system with chirality which is also present in the target compound **2** or which can be used to handle the introduction of the desired stereochemistry. However, at that time, (−)-shikimic acid availability was one of the major drawbacks since effective extraction and purification methods had not been developed. The use of potentially explosive azide-containing intermediates is another drawback associated with this synthetic route, which restricted the synthesis to milligram scale.

Due to scarcity of (−)-shikimic acid in large quantities at the time, [17,39] Gilead scientists went on to prepare Tamiflu **1a** at multi-gram scale from more available (−)-quinic acid **9** (Scheme 2) [39] The first large scale route by Gilead sciences from (−)-quinic acid consisted of 12 steps and afforded an overall yield of 4.4% [39] Despite the relative low yield, it was successfully implemented in a standard pilot plant producing kilogram quantities of Tamiflu **1a** and the potentially hazardous azide chemistry was safely handled. Furthermore, minimal protecting group manipulations were employed and no chromatography was required for isolation.

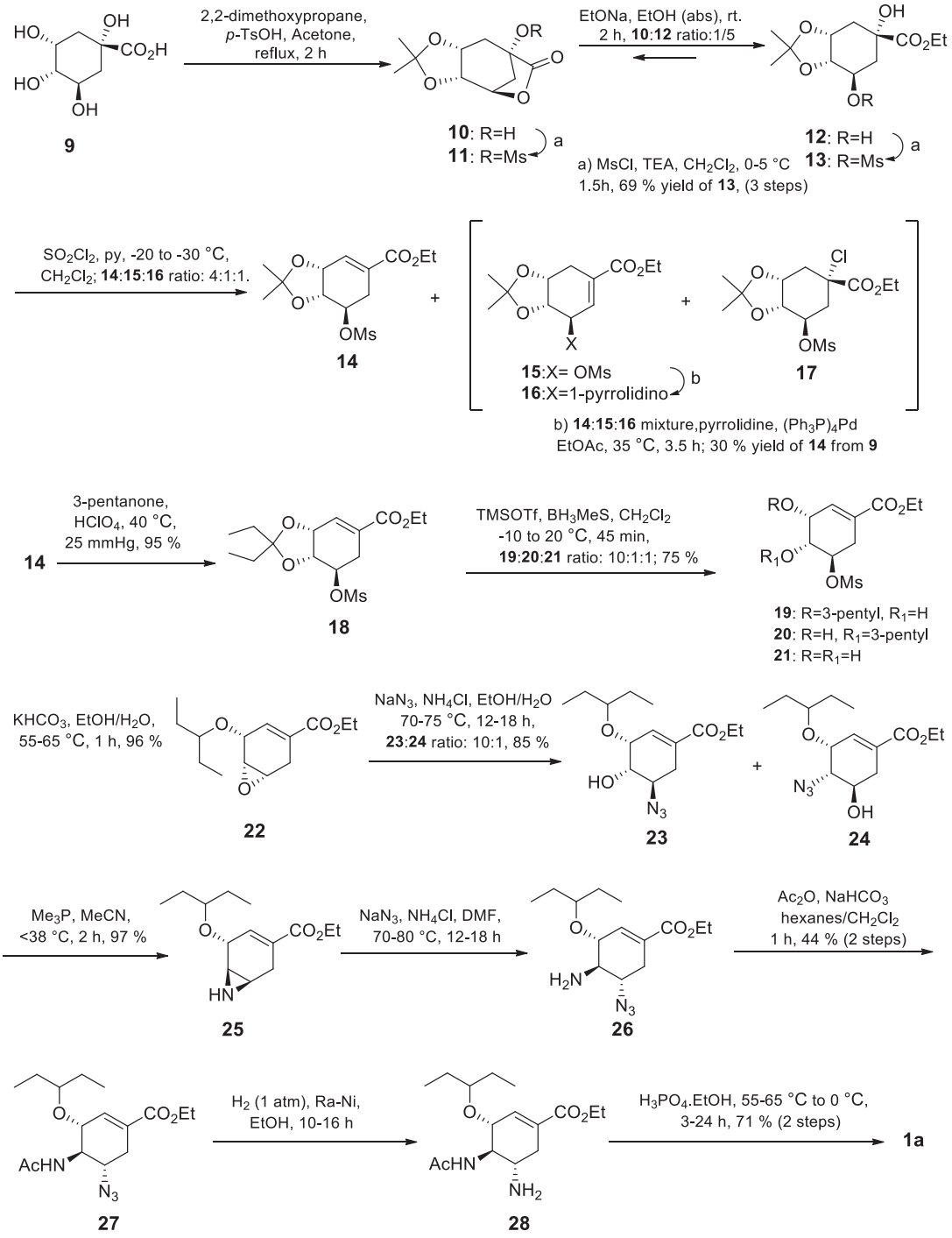
3. Roche industrial approach

There has been extensive research by Gilead Sciences, [16–20,39] Roche [30,40–46] and other numerous scientific laboratories to develop an efficient, safe large-scale route towards Tamiflu since 1995 [1–3,22–26] The efforts led to the 12-steps Roche industrial route starting from (−)-shikimic acid affording an overall yield of ~35% (Scheme 3) [46] after (−)-shikimic acid availability had been improved by the development of more efficient extraction and purification processes or alternatively by fermentation using a genetically engineered *E.coli* bacteria [25,28,29].

As with Gilead Sciences approaches (Schemes 1 and 2), [20,39] the Roche industrial route utilised azide chemistry in structuring the 1,2-diamine moiety in **28** [46] Contrary to the Gilead Sciences' routes, where the pentyloxy group is introduced in the latest stage (Schemes 1 and 2), [20,39] Roche introduced the 3-pentyloxy



Scheme 1. Gilead Sciences' synthetic route of the first candidate **2** for development [20].

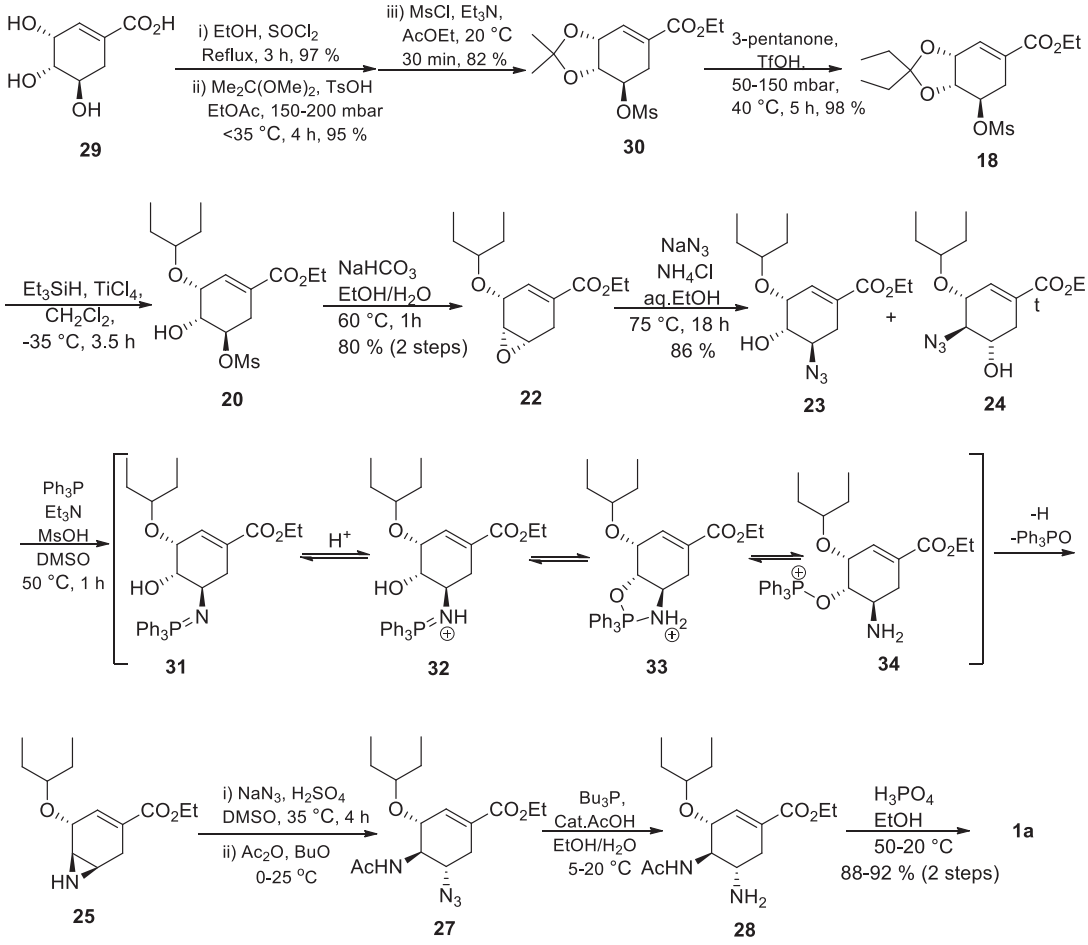


Scheme 2. First large scale synthesis of Tamiflu **1a** by Gilead Sciences [39].

moiety early at C-3 by regio-selective reduction of acetal **18** [46] However as with the Gilead routes (Schemes 1 and 2), the Roche approach has drawbacks that include the challenge to safely handle the thermally unstable azide reagents and intermediates on large scale. Another drawback was associated with the utilisation of shikimic acid which was scarce at that time. These drawbacks prompted the scientific community to extensively develop numerous alternative routes.

4. Alternative synthetic approaches

Although the Roche industrial route is currently supplying the world with enough tonnes of Tamiflu, the route raised three concerns as aforementioned: a) the use of shikimic acid, which had limited availability in the early days of development b) the use of potentially explosive azide chemistry and c) long synthetic route with low overall yield. Consequently, this prompted the



Scheme 3. Roche's industrial synthesis [46].

development of numerous alternative synthetic approaches to address the concerns [1–3,22–26,47] These approaches can generally be categorised into two main classes: shikimic acid-dependent and shikimic acid-independent approaches in which both the azide-dependent and azide-independent approaches can be subclasses. Herein, a few selected and representative alternative synthetic strategies that can potentially be scaled-up after minimal modifications are highlighted in each class.

4.1. Shikimic acid dependent approaches

After (−)-shikimic acid availability improvement with time, researchers embarked on the development of shorter and higher yielding synthetic routes. These routes can be classified into two groups: namely azide chemistry dependent and azide-free routes.

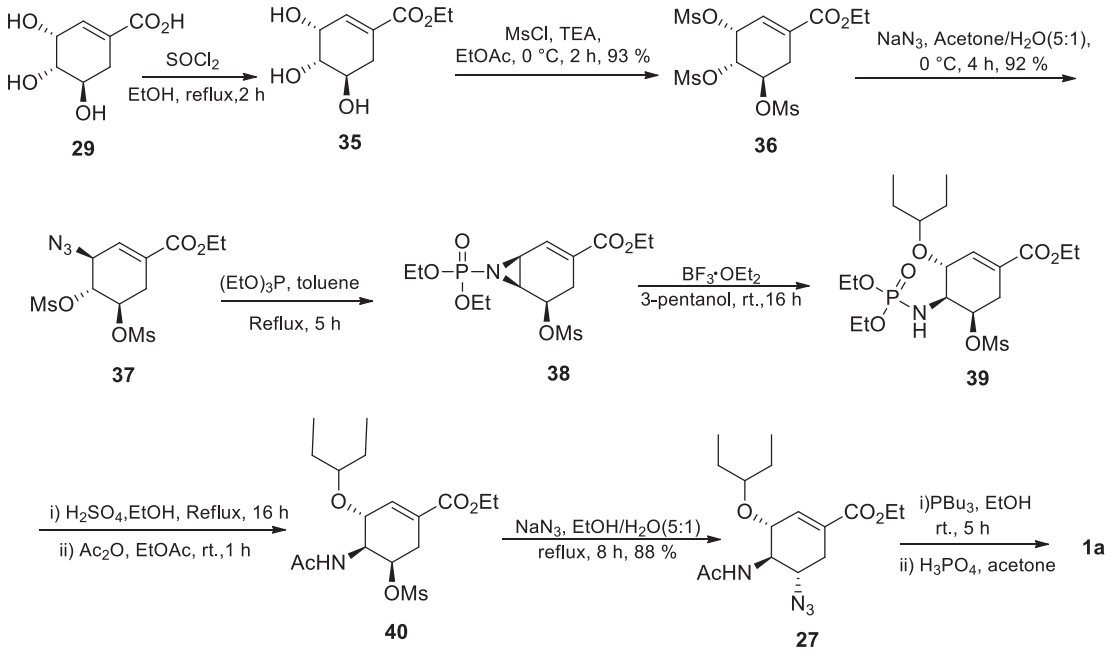
4.1.1. Azide-dependent routes

Azide-dependent routes utilize potentially hazardous azide chemistry to introduce two amino groups on the cyclohexene ring system. In 2009, Karpf and Trussardi at Hoffman-La Roche reported an efficient nine-step synthetic route towards Tamiflu **1a** from (−)-shikimic acid **29** (Scheme 4) [30,44].

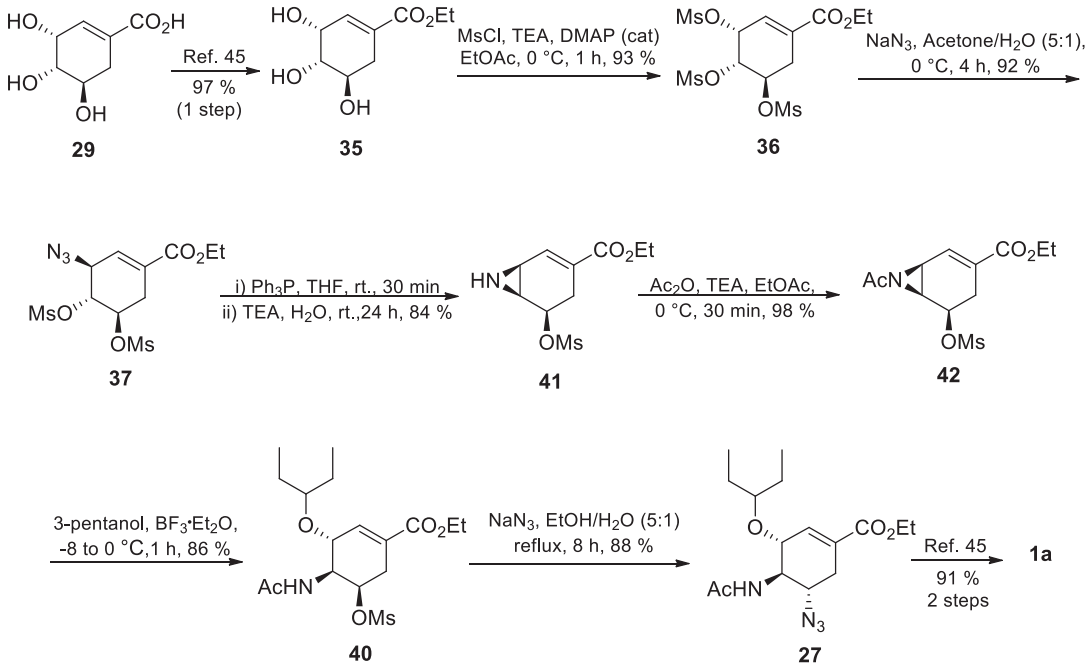
The authors started with (−)-shikimic acid **29** esterification to afford ethyl shikimate **35** according to a reported procedure [46] The synthesis proceeded *via* the *O*-trimesylate **36** followed by regio- and stereoselective nucleophilic substitution of the allylic *O*-mesylate at C-3 by an azide group resulting in azide **37**. In the presence of triethyl phosphite ($P(EtO)_3$) and under reflux, aziridine **38** was formed from the azide **37**. This was followed by regio- and stereoselective aziridine ring opening at the allylic position with 3-pentanol in the presence of a Lewis acid catalyst providing **39**. N—P bond cleavage in **39** followed by *N*-acetylation afforded mesylate **40**, which went on to react with sodium azide to afford **27**. The azide group was reduced to the amine group followed by the addition of phosphoric acid (H_3PO_4) affording the drug Tamiflu **1a**. Protecting group manipulations, chromatographic separations and tedious purifications were not required in this route. It proceeded with an unoptimised overall yield of 20%, utilising cheap and commercially available chemicals [30] Although the route could neither avoid azide chemistry nor improve the overall yield, it presents a potentially scalable, elegant and shorter synthetic route. In addition to Karpf and Trussardi [30] procedure, Trussardi [44] disclosed a similar process in which compound **39** could alternatively be azidated first before acetylation.

In 2013, Kalashnikov et al. [28] reported almost a similar synthetic route to that of Karpf and Trussardi [30] The route afforded an optimised overall yield of 27%. Although this 10-step procedure utilises azide chemistry and is accompanied by lower overall yield, it uses minimum amount of expensive reagents making it attractive.

Utilising the experience accumulated from their first 13 steps approach (44% overall yield) from (−)-shikimic acid, [48] Shi's group developed an optimised 8 steps route (Scheme 5) [49] The route is almost similar to Karpf's approach, [30] but mainly differs



Scheme 4. Eight-step synthesis of Tamiflu by Karpf and Trussardi at Hoffmann-La Roche [30].



Scheme 5. Optimised synthesis of Tamiflu **1a** from shikimic acid **29** by Shi's group [49].

on the Staudinger reaction conditions in the aziridination step. Shi and coworkers [49] uses triphenylphosphine (PPh_3) in the presence of triethyl amine and large excess of water to afford aziridine **41**, whereas Karpf utilises triethyl phosphite under anhydrous conditions to afford aziridine **38** (Schemes 4 and 5) [30,49] The use of triphenyl phosphate involves tedious purification due to the triphenylphosphine oxide by-product. *N*-Acetyl aziridine **42** was formed after a simple acetylation of aziridine **41**. Stereoselective ring opening of *N*-acetyl aziridine **42** was excellently done in the presence of boron trifluoride etherate in 3-pentanol to yield 86% of acetamide **40**. The (*S*)-configuration of C-1 in compound **42** was inverted to the (*R*)-configuration of C-3 in acetamide **44** according to the Walden-type inversion. The allylic C-1 position of compound **42** is more reactive than the C-6 position of compound **42**, thus resulting in a regioselective ring opening reaction. This was followed by a nucleophilic replacement of OMs at C-5 with the N_3 group and it was accomplished by treating acetamide **40** with NaN_3 affording azide **27** in 88% yield, and in the process reversing the (*R*)-configuration of C-5 to the (*S*)-configuration. The azide **27** was finally transformed to Tamiflu **1a** according to reported procedure [46,49].

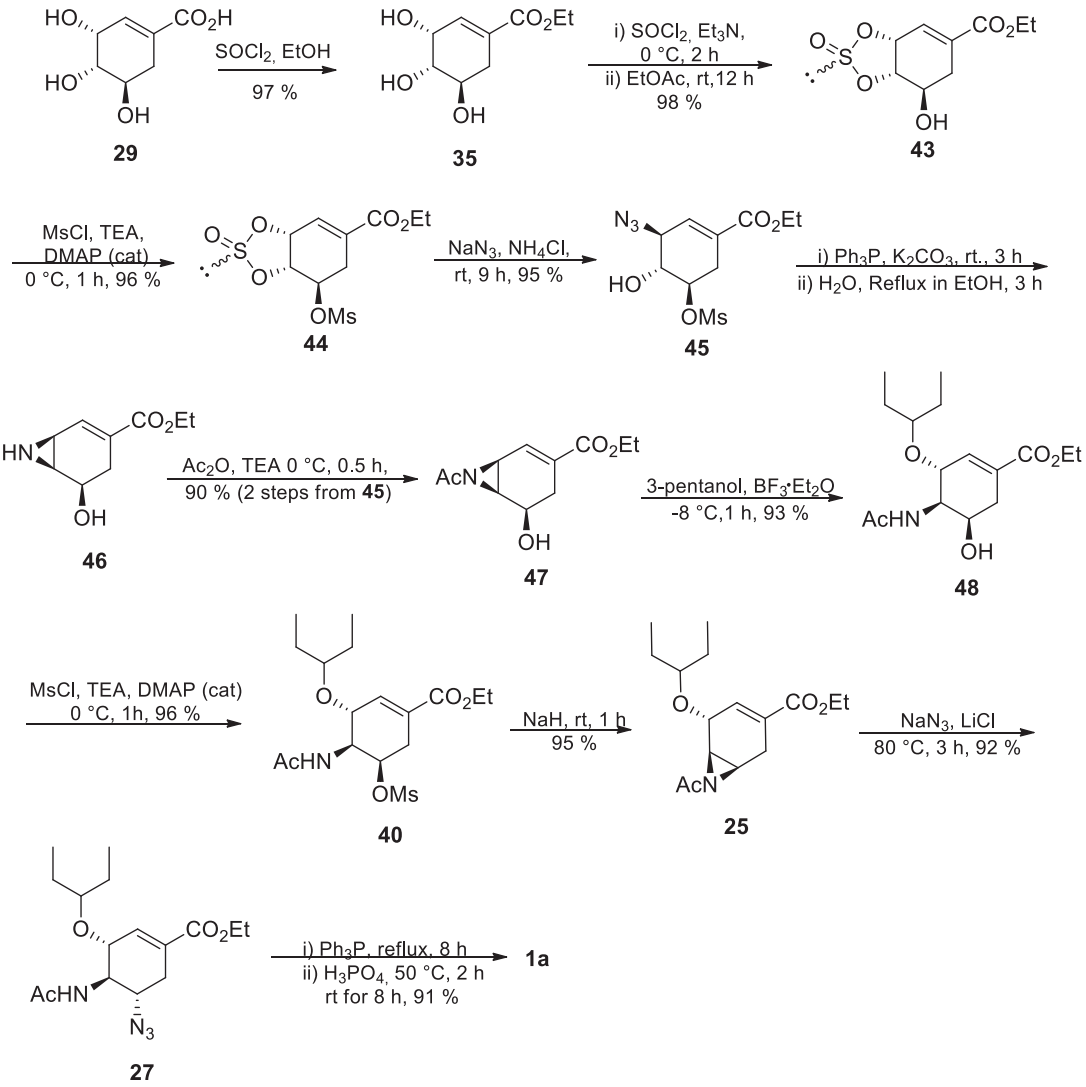
A short and practical approach towards Tamiflu **1a** with an

impressive 47% overall yield was developed by Shi et al. [49] The overall yield improved slightly (35–47%) and the number of transformations were considerably reduced relative to the Roche industrial approach (12 steps to 8 steps) [46,49] This approach represents a model of atom economy since no protecting group manipulations were needed. Unfortunately, the researchers resorted to the potentially hazardous azide chemistry on two occasions after other safer nitrogen-containing nucleophiles such as ammonia, benzylamine and allylamine failed to afford the desired products [49] This drawback is however more than compensated by the elegance, simplicity and efficiency of the approach. This synthetic route is evidently a major player in the goal to develop an efficient scalable process towards oseltamivir phosphate synthesis. However, there is need to find ways of dealing with the potentially hazardous steps involved to guarantee a truly scalable and safe process, which is applicable in industry.

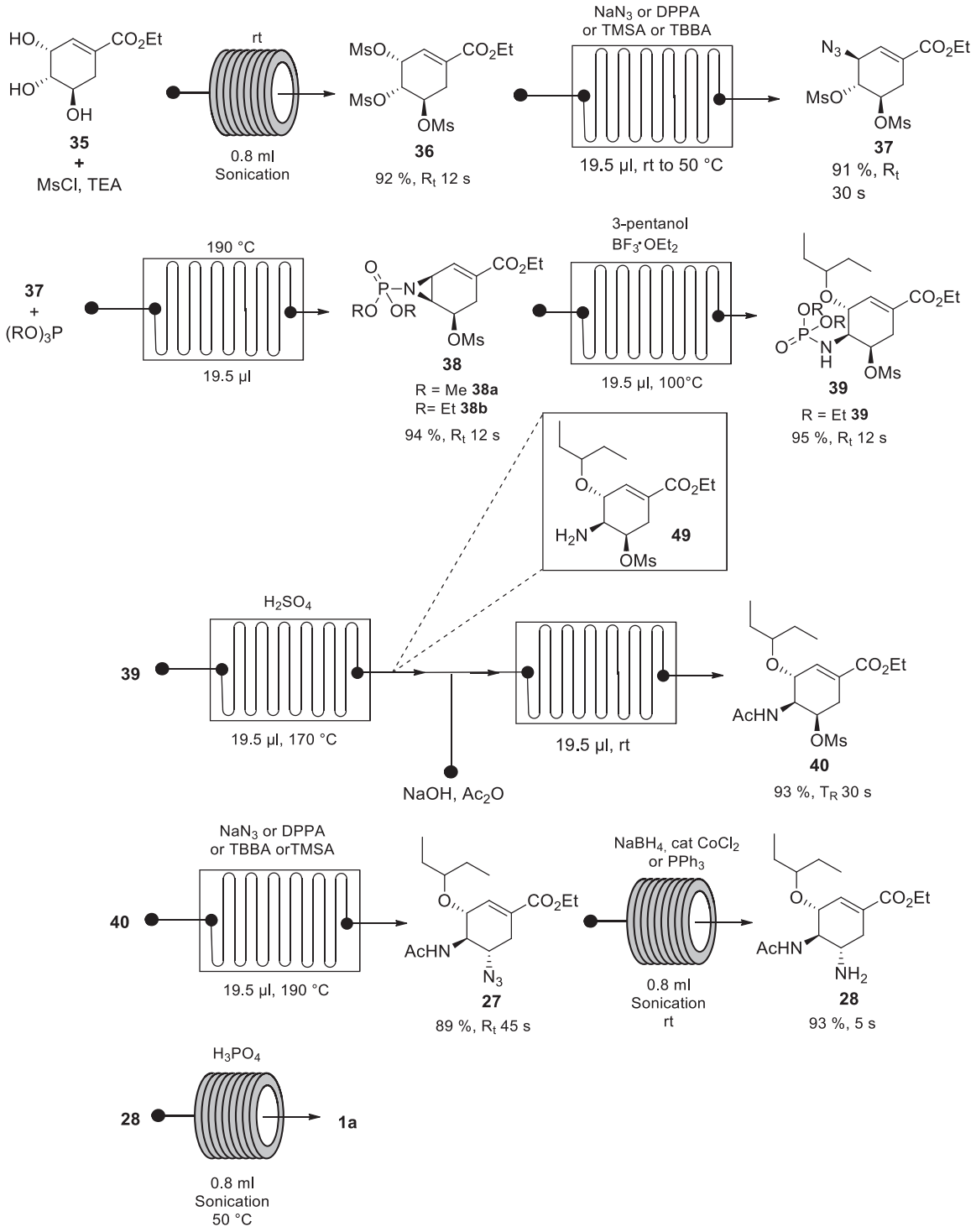
Building on their earlier work in which they synthesised Tamiflu **1a** from shikimic acid *via* cyclic sulfite intermediates, [50] Shi and coworkers reported an improved 11-step route starting from shikimic acid *via* a 3,4-cyclic sulfite intermediate **43** affording Tamiflu in 55% overall yield (Scheme 6), [51] which is significantly better than the industrial route (35% overall yield). All the transformations were clean with each step affording yields greater than 90%, meaning that subsequent steps could be performed without purification of crude products. This approach generally shares some similarities with other shikimic acid dependent routes such as the use of azide chemistry and can be scaled-up easily.

Generally, the shikimic acid-azide chemistry dependent procedures proceeded in good yields. They can potentially be performed at large scale if the azide chemistry safety is guaranteed, as with the current industrial route. This can be achieved by performing holistic process calorimetric studies before scale-up, use of highly skilled personals and working under very strict conditions. This is usually not easy to achieve. However, the use of either enabling technologies such as continuous flow technology that are known to enhance process safety or alternative safe chemistry to introduce the two amino groups on the cyclohexene ring system can be considered.

Most recently, Watts group reported a 8-step total flow synthesis of Tamiflu starting from ethyl shikimate **35** derived from shikimic acid (Scheme 7) [52,53] Taking lessons from the previously reported shikimic acid-based routes, [28,30,48,49,51,54] the authors aimed to ensure azide chemistry safety, processing time reduction and process overall yield improvement by taking advantage of continuous flow chemistry technology. Flow chemistry technology is an enabling technology, which has attracted



Scheme 6. Shi's 11-step Tamiflu **1a** synthetic route via a 3,4-cyclic sulfite intermediate **43** [51].



Scheme 7. Continuous flow synthesis towards Tamiflu **1a** by Sagandira and Watts.

considerable attention in synthetic chemistry and pharmaceutical industry owing its efficiency, easy scale-up, safety and reproducibility; industry is now using the technology up to 2000 tonnes per annum [55–59] This has seen numerous approaches for pharmaceutical drugs being redesigned into continuous flow synthesis [56,58,60–65] The technology allows for *in situ* generation and consumption of dangerous intermediates, preventing their accumulation thus enhancing process safety [55,66–68] Additionally, microreactors can handle exotherms extremely well, due to the inherent high surface area to volume ratio and rapid heat dissipation unlike the conventional batch process [55,69].

The authors started by treating ethyl shikimate **35** with MsCl in the presence of TEA at room temperature under sonication to afford mesyl shikimate **36** (Scheme 7) [53] Subsequent treatment of mesyl shikimate **36** with NaN_3 afforded azide **37**. Other azidating agents such as DPPA, TMSA and TBBA gave comparable results although

they are accompanied by poor atom efficiency [53,68] The treatment of azide **37** with either $(MeO)_3P$ or $(EtO)_3P$ at 190 °C afforded the desired aziridines **38a** and **38b** respectively. Aziridine **38b** ring opening was accomplished in the presence of 3-pentanol and $BF_3 \cdot Et_2O$ at 100 °C to afford 3-pentyl ether **39**. Acetamide **40** was subsequently afforded *via* a tandem of reactions; N–P bond cleavage of 3-pentyl ether **39** using H_2SO_4 at 170 °C forming intermediate **49** *in situ*, subsequently followed by acetylation with Ac_2O at room temperature to afford acetamide **40**. Acetamide **40** was then treated with NaN_3 to afford azide **27** [53,68] Subsequent azide **27** reduction at room temperature under sonication using $NaBH_4$ in the presence of catalytic $CoCl_2$ afforded oseltamivir **28**. In the final step, Tamiflu **1a** was afforded by treating oseltamivir **28** with H_3PO_4 at 50 °C under sonication.

The authors demonstrated an efficient synthetic route for Tamiflu **1a** with 58% overall yield and 3.5 min total residence time starting from ethyl shikimate **35**. This process elegantly handled the hazardous azide chemistry involved in this procedure by taking advantage of flow chemistry technology. The overall yield of the process is literature comparable, however, processing time is significantly shorter than all the reported procedures, which are mostly greater than 30 h [1,2] Without doubt, this presents a safe, efficient and scalable procedure for the synthesis of the drug.

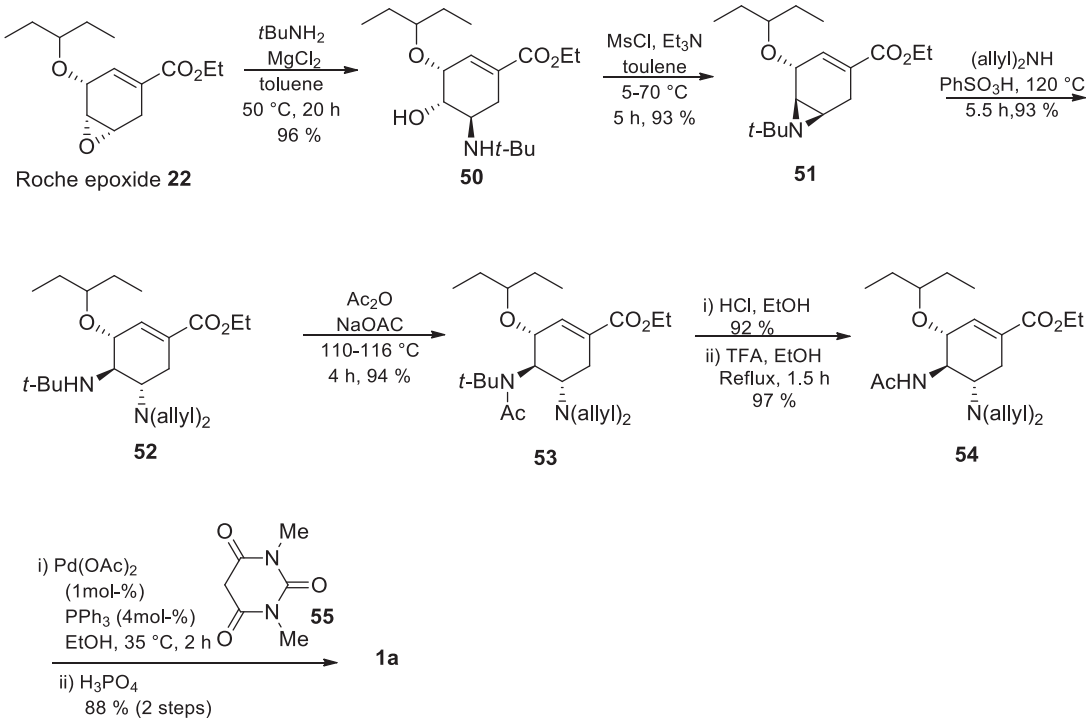
4.1.2. Shikimic acid dependent azide-free routes

Due to azide safety concerns, azide-free routes were developed to introduce the two amino groups on the cyclohexene ring system [39,70,71] The goal was to identify a non-azide nucleophile that is compatible with the rest of the functional groups on the molecule and with the strong tendency of the cyclohexene intermediates towards aromatization. In 2000, Karpf and Trussardi [41] at Roche reported an azide free transformation of Roche epoxide **22** to Tamiflu **1a** in 35% overall yield over 6 steps at a multi-gram scale without the use of chromatography purification. The authors used allyl amine as the nitrogen nucleophile instead of azide chemistry. Hughes and coworkers developed a 9-step azide free route starting from shikimic acid *via* the so called Roche epoxide **22** (Scheme 8) [45] The authors used tBuNH$_2$ as the non-azide nitrogen nucleophile. The epoxide **22** opening was regio-selective and it was treated with tBuNH$_2$-$MgCl_2$ complex affording amino alcohol **50** in 96% yield. The presence of a bulky *tert*-butyl group on the nitrogen atom enabled selective mesylation at the oxygen atom resulting in aziridine **51** formation. Aziridine **51** opening was done using diallylamine in the presence of $PhSO_3H$ and then the secondary amine **52** was acetylated to give **54**. There was only one purification in the sequence between epoxide **22** to Tamiflu **1a** where **54** was purified by precipitation of the corresponding HCl salt. Finally, acidic conditions were used in cleavage of the *N-tert*-butyl group and deallylation through Pd-catalyzed allyl transfer to 1,3-dimethylbarbituric acid, followed by phosphate salt formation to afford Tamiflu **1a**. The overall yield for this azide-free approach was 35–38%, which is comparable to the industrial route [45,46] This approach represented the first example that avoids the utilisation of potentially hazardous azide chemistry, the convectional way of introducing nitrogen functionality on the ring.

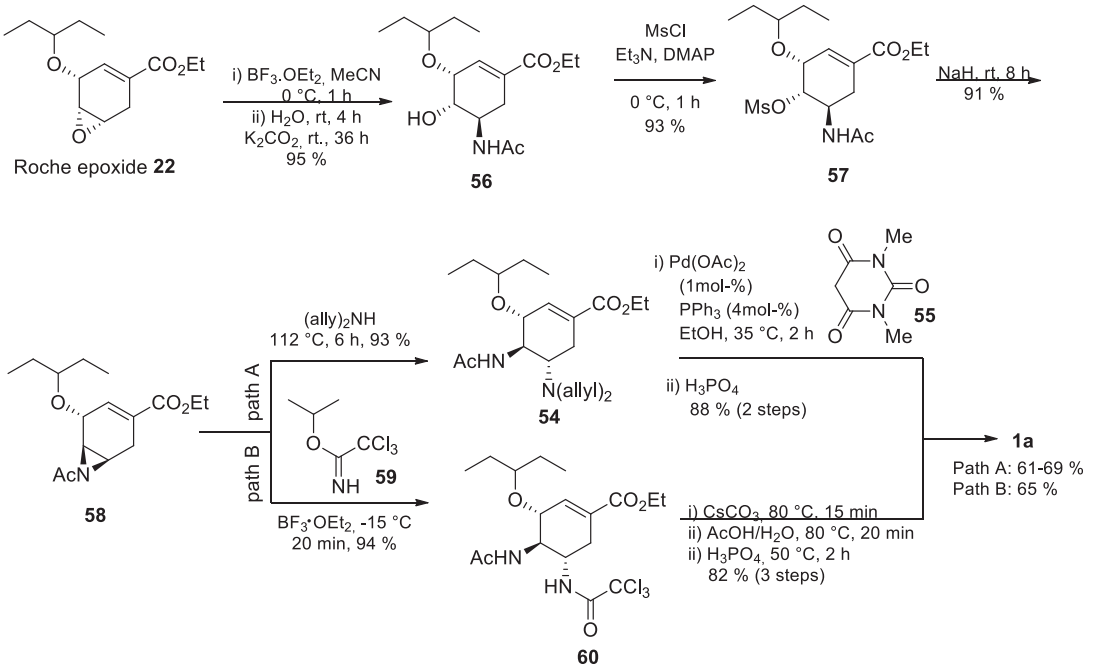
In 2013, Shi and coworkers reported a high yielding novel azide-free asymmetric synthesis of Tamiflu starting from the Roche's epoxide **22** affording Tamiflu **1a** in 61–69% overall yield (Scheme 9) [54] Compared with Roche azide-free syntheses, this route from Roche's epoxide **22** has been shortened from 9 to 6 steps accompanied by a yield increase from 35–38% to 61–69% [45,54] Furthermore, the process is high yielding and shorter compared to the current industrial approach (35%, 12 steps). This presents a truly efficient and safe approach which can potentially be performed at large scale.

4.2. Shikimic acid-independent approaches

The legitimate (−)-shikimic acid availability concerns in the early years of the development of Tamiflu led to the development of



Scheme 8. Hughes and coworkers azide free synthesis of Tamiflu **1a** [45].



Scheme 9. Azide-free asymmetric synthesis of Tamiflu starting from the Roche's epoxide **22** by Shi and coworkers [54].

shikimic acid-free routes. Although the shikimic acid availability improved with time, alternative routes are still being explored to date. Unlike the shikimic acid-dependent approaches which take advantage of the already present chiral cyclohexene backbone to introduce the groups at C3, C4, and C5 with the desired stereochemistry, the shikimic acid independent approaches construct the cyclohexene backbone through various strategies such as Diels-Alder reaction, Horner-Wadsworth-Emmons reaction, aldol condensation, Michael addition, sugars, nitroalkenes by Curtius rearrangement. These approaches display ingenuity in the construction of the cyclohexene ring system, the induction of the three stereogenic centres, the introduction of the two amino groups, the introduction of the 3-pentylether side chain and the regioselective introduction of the 1,2-double bound on the cyclohexene ring of the drug starting from readily available and affordable starting materials.

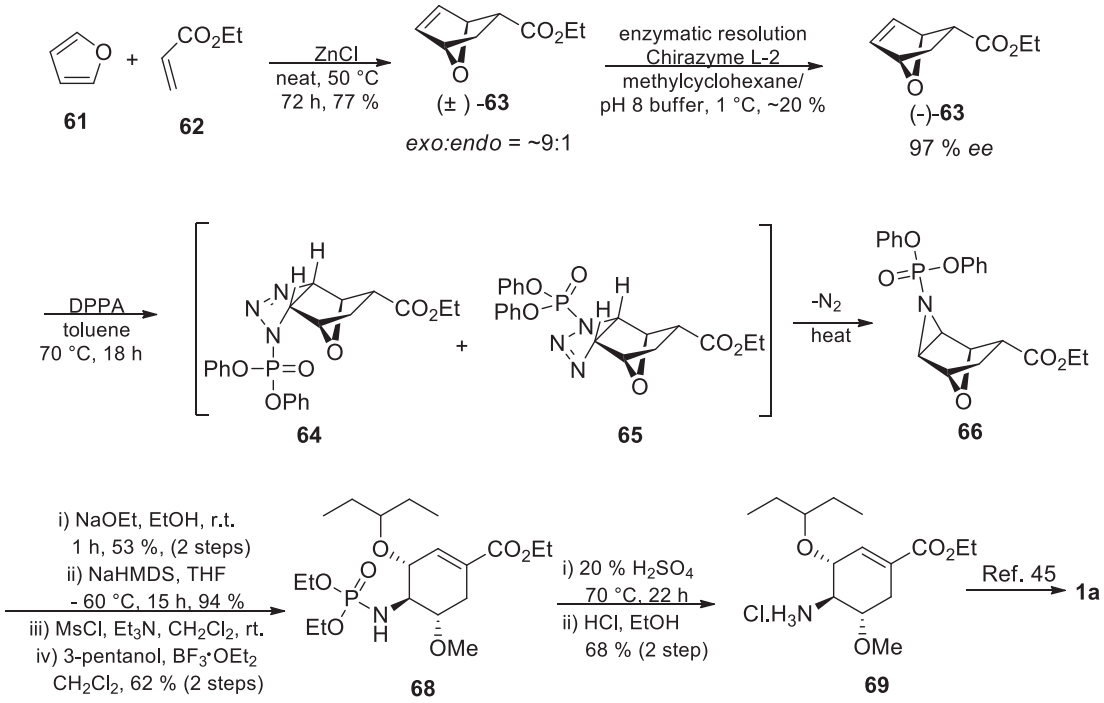
4.2.1. *Tamiflu via Diels-Alder approach*

Approaches in this class utilize the Diels-Alder reaction to construct the cyclohexene ring system of the drug based on the investigations by Brion [72] The chemo-enzymatic enantioconvergent synthesis of Tamiflu **1a** by Roche group used furan **61** and ethyl acrylate **62** as starting materials (Scheme 10) [25] The Diels-Alder reaction and [3 + 2] cycloaddition to afford *endo*-aziridine (−)-**63** were the key steps of this route. The main advantages of this approach are the use of very inexpensive starting materials and reagents, minimal protecting group manipulations, and the fact that resolution of the material was carried out very early in the synthesis, which should considerably increase the throughput. Conversely, the low overall yield of 3.2% and use of azide are detrimental. In 2013, Yamashita et al. [73] reported an enantioconvergent approach to an important Tamiflu **1a** intermediate (ethyl shikimate **29**) *via* Diels-Alder reaction and subsequent lipase-mediated kinetic resolution.

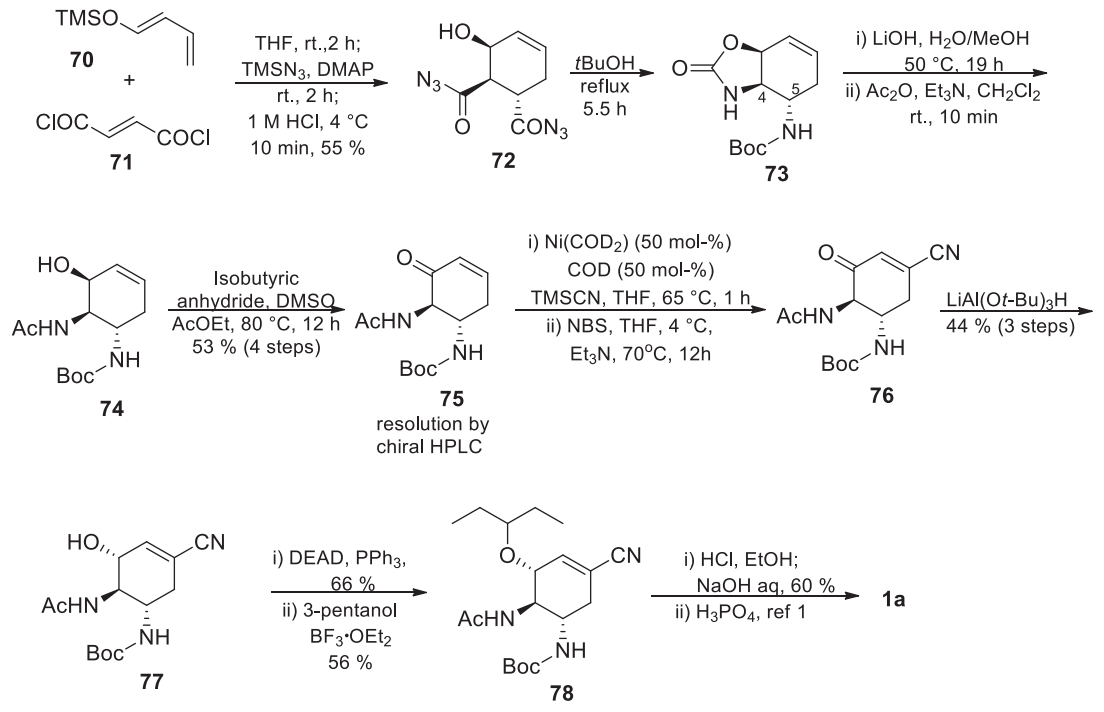
Shibasaki and coworkers [47,74–78] have been very active in Tamiflu synthesis research since their first procedure in 2006 which afforded Tamiflu in 1.4% overall yield over 17 steps [78] This procedure was characterised by extensive protection group chemistry, very low yield as well as the use of azide chemistry [78] In 2007, Shibasaki and coworkers reported a 12-step approach towards Tamiflu **1a** *via* the Diels-Alder reaction and Curtius rearrangement reaction as the key steps [77] In this approach, chirality is introduced with the help of a chiral ligand, and relies on the preparative chiral HPLC to obtain enantiomerically pure material (Scheme 11) [77].

The synthetic route started with a Diels-Alder reaction between diene **70** and dienophile **71**, in the presence of an azidating agent, affording an appropriately functionalised cyclohexene azidated skeleton **72** [77] The Curtius rearrangement of the acyl azide **72** and subsequent intramolecular trapping of the resulting isocyanate by *t*-BuOH gave the unsymmetrically protected 1,2-*trans*-diamine **73** exclusively [77] Selective hydrolysis of cyclic carbamate moiety of **73** with LiOH and subsequent *N*-acetylation afforded derivative **74**, which was then oxidised to enone **75** under modified Moffat conditions with isobutyric anhydride as an activator for DMSO [77] Chiral HPLC was then used to separate the enantiomers at this stage, and enantiomerically pure **75** was obtained. The Michael addition of cyanide was carried out by treating **75** with TMSCN in the presence of $Ni(COD)_2$ and 1,5-cyclooctadiene (COD) affording silyl enol ether followed by α-bromination with NBS and subsequent HBr elimination with trimethylamine resulting in β-cyanoenone **76**. This was then followed by the introduction of the ethoxy carbonyl group at the β-position of the enone and then the introduction of the pentyloxy group. Stereoselective reduction of the ketone **76** with $LiAl(Ot\text{-}Bu)_3H$ afforded **77** in 44% yield in three steps. The aziridine formed under Mitsunobu conditions went through a ring-opening reaction with 3-pentanol affording **78**. In the final stages, ethanolysis of the cyanide and cleavage of the Boc group proceeded in one pot using acidic ethanol. The free amine form of **2** was formed after basification, which was then followed by treatment with H_3PO_4 to give Tamiflu **1a** [77].

This 12 steps route has advantages over the previous routes because it utilises commercially available starting materials and requires minimal protection group manipulations. It however still



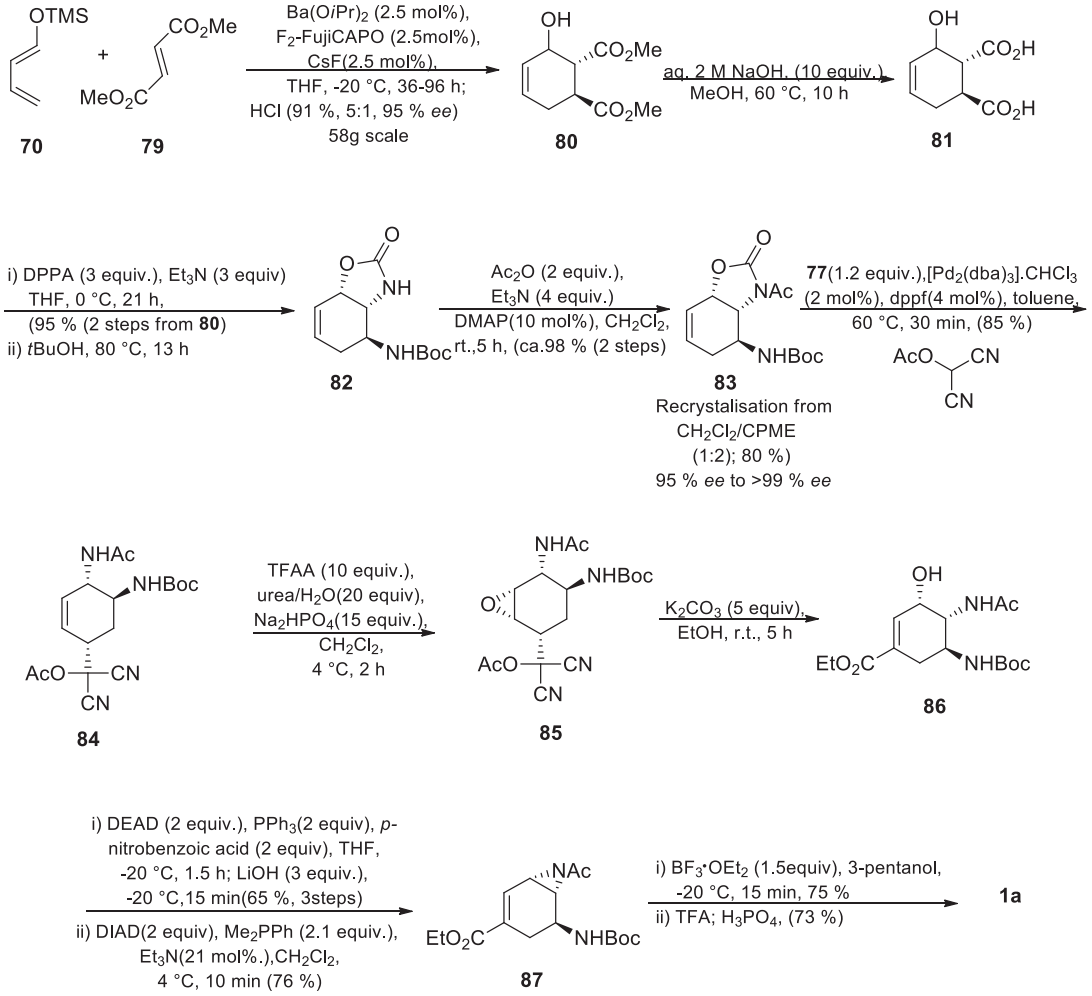
Scheme 10. Diels-Alder approach towards Tamiflu **1a** by Roche group [25].



Scheme 11. Shibasaki's group third-generation synthesis of Tamiflu **1a** [77].

employs potentially hazardous azide chemistry as a means to prepare the substrate for a Curtius rearrangement, which would most likely make this approach be ruled out on scale for safety reasons, unless other processing techniques such as flow chemistry are utilised to address these safety concerns [2,79] The resolution of (±)-**75** *via* chiral HPLC was a major contributing factor to the very low overall yield (2.8%). Just as the commercial route, the hazardous azide chemistry is employed, which was unfortunately accompanied by very low yield. To address this low yield drawback, Shibasaki's group later developed a barium-catalyzed asymmetric Diels-Alder route that would increase the throughput (Scheme 12) [47].

The cyclohexene skeleton was synthesised through a Diels-Alder reaction between diene **70** and dienophile **79** affording **80** on a 58g scale [47] This was followed by the hydrolysis of the methyl esters to afford **81**. Azidation of **81** yielded diacyl azide *in*

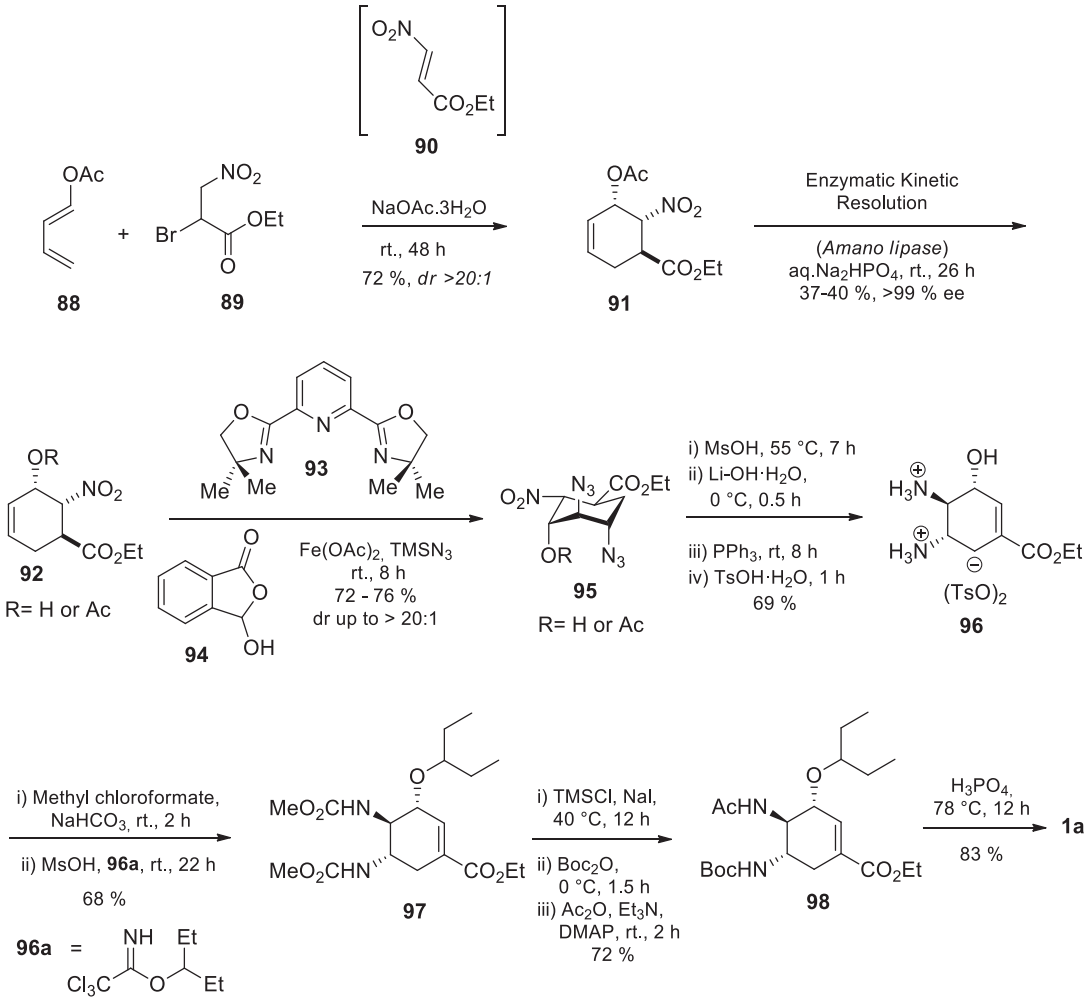


Scheme 12. Catalytic asymmetric Diels-Alder approach towards synthesis of oseltamivir phosphate by Shibasaki group (Fourth generation approach) [47].

situ which was subsequently converted to cyclic carbamate **82** *via* Curtius rearrangement in the presence of anhydrous *t*-BuOH. The carbamate **82** was acetylated to provide enantiomerically pure intermediate **83** was obtained in 80% yield (>99% *ee*) after recrystallization of the crude product from CH_2Cl_2/cyclopentyl methyl ether (1:2). Enantiomerically pure intermediate **83** was subsequently treated with protected hydroxyl malononitrile in the presence of $[Pd_2(dba)_3].CHCl_3$ to generate alkene **84** after regioselective allylic substitution. The alkene **84** was epoxidised with TFAA to exclusively afford epoxide **85**. Alcohol **86** was generated by the conversion of the acetoxydicyanomethyl group to an ethoxycarbonyl group and subsequent E2 epoxide opening with ethanolic K_2CO_3. The stereochemistry of the hydroxyl group on **86** was inverted under Mitsunobu conditions and the second Mitsunobu conditions generated aziridine **87**. The aziridine **87** was treated with 3-pentanol in the presence of $BF_3 \cdot Et_2O$ followed by Boc-protecting group removal and treatment with H_3PO_4 to give Tamiflu **1a** [47].

This approach is unique in its chirality introduction as it is introduced in the first step through asymmetric Diels-Alder reaction. This considerably increased the overall yield (16%) of the approach compared to their previous approach [47,77] The synthetic route is also characterised by low catalytic loading which is advantageous. An interesting way of introducing an ester group on the cyclohexene using malononitrile was unearthed. Although the procedure is low yielding compared to the current industrial, it has the potential to become a scalable process if necessary optimisation and safety measures for dealing with potentially hazardous azides intermediates are developed.

Most recently, Li and coworkers demonstrated enantioselective synthesis of Tamiflu **1a** on a gram scale, in which the key trans-diamino moiety was efficiently installed *via* an iron-catalyzed stereo-selective olefin diazidation (Scheme 13) [80] Based on Danishefsky and coworkers's work, the authors prepared racemic **91** *via* a Diels–Alder reaction of diene **88** with nitroacrylate **90** generated *in situ* from bromo-3-nitropropanoate **89** [80,81] Nitroacrylates decompose under the reaction conditions, therefore efficient cycloaddition was achieved by *in situ* generation of the nitroacrylate **90** from its precursor, bromo-3-nitropropanoate **89**. Subsequent enzymatic kinetic resolution of **91** using Amano Lipase afforded **92** in 44% yield. Due to known safety concerns associated with azide chemistry, a chemical hazard assessment of the olefin diazidation to investigate the feasibility of Tamiflu **1a** production on a larger scale was conducted. To avoid the risk associated with the azidation process, the authors performed an iron-catalyzed olefin diazidation with $TMSN_3$ in the presence of $Fe(OAc)_2$ **93** and benziodoxole **94** to afford diazide **95** in 72% yield. A straightforward hydrolysis-elimination procedure converted **95** to intermediate *trans*, *trans*-diazido alcohol, which was converted to *trans*, *trans*-hydroxyl diaminium tosylates **96** *via* a standard reduction-protonation procedure. Subsequently, **96** acylation afforded a carbamate which underwent selective alkylation to afford **97**. The



Scheme 13. Enantioselective synthesis of Tamiflu **1a** via the iron-catalyzed stereoselective olefin diazidation [80].

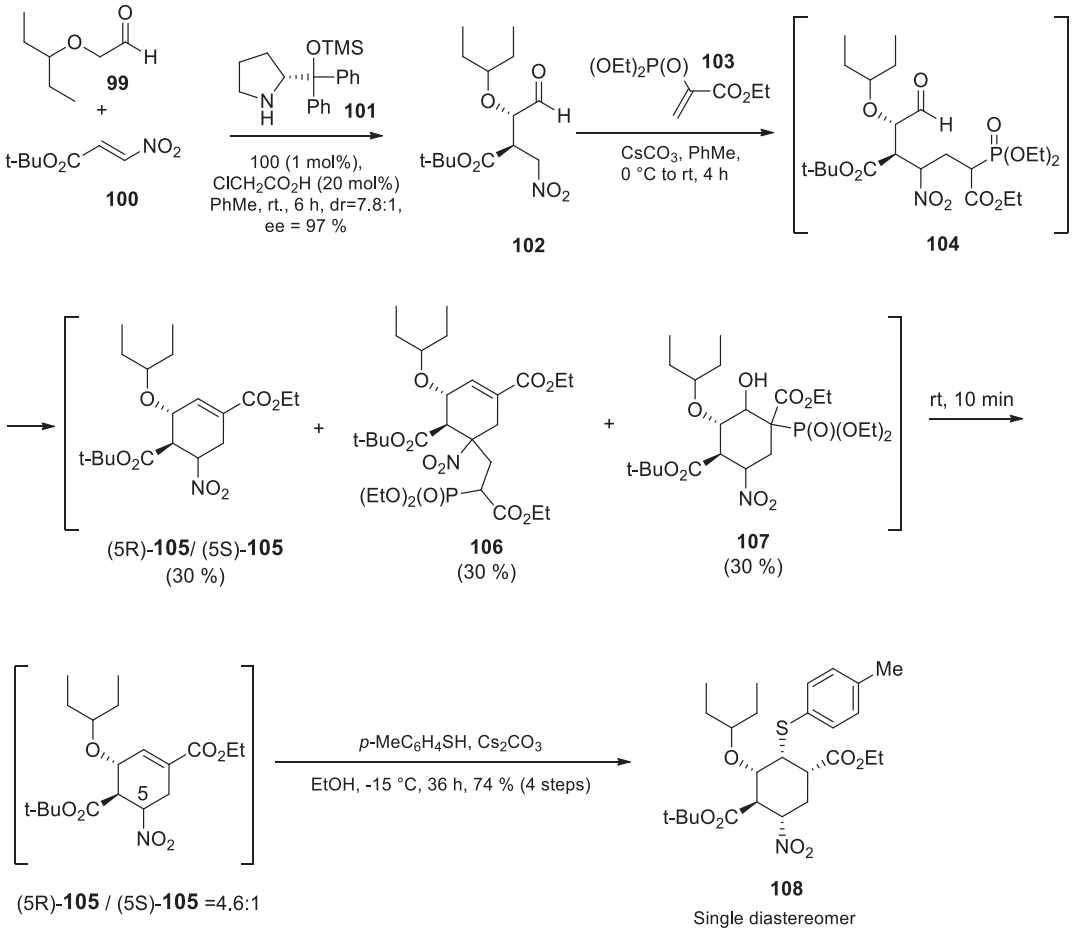
crystalline solid **97** was further converted to **98**, the penultimate synthetic target, *via* a gram-scale procedure that involves TMSCl–NaI-mediated carbamate deprotection and selective *N*-acylation of both Boc and Ac groups. Finally, *N*-Boc deprotection of **98** using H_3PO_4 in hot EtOH afforded Tamiflu **1a**.

Although the authors demonstrated an improved and effective iron-catalyzed procedure for highly functionalised yet electronically deactivated substrates that have been otherwise problematic and an oligomeric iron-azide catalyst was uniquely effective for the stereoselective diazidation, the procedure was accompanied by an unimpressively low overall yield (5%). Although the chemical hazard assessment of olefin diazidation using both differential scanning calorimetry (DSC) and the drop weight test (DWT) demonstrated the feasibility of performing this olefin diazidation reaction for large scale synthesis of Tamiflu **1a**, an excess of $TMSN_3$ (5 equiv.) was necessary for the reactivity and the reaction was only scaled up to 5 g scale.

In 2006, Corey and coworkers demonstrated a 11-steps procedure starting from a Diels- Alder reaction to afford Tamiflu **1a** in 27% yield [82] Building on Corey et al. [82] work, other researchers reported various interesting synthetic routes towards Tamiflu **1a** *via* Corey's intermediate [74,75,83–85] Fukuyama *coworkers* [86,87] have also reported procedures which involved Diels–Alder reaction and avoids azide chemistry in which Tamiflu was synthesised in 22% and 5.6% overall yield respectively. More recently, Fang et al. [88] reported the synthesis of various substituted cyclohexenes which can be useful for building Tamiflu scaffolds starting from a Morita–Baylis–Hillman reaction and goes *via* a Diels– Alder reaction. Savoia and coworkers [89] also reported the synthesis of 1,2-diamine moiety, a valuable building block and precursor for Tamiflu starting from glyoxal through the corresponding 1,2-diimine.

4.2.2. Tamiflu via a Horner-Wadsworth-Emmons (H–W-E) reaction/aldol condensation/Michael addition

Hayashi and coworkers have been immensely involved in oseltamivir research since its discovery. They have published at least five different synthetic routes towards Tamiflu **1a** to date [32,90–94] Some of their most recent and interesting approaches are reviewed herein. The authors designed a highly efficient two 'one-pot' sequences approach towards oseltamivir starting from aldehyde **99** and nitroolefin **100** (Scheme 14)[91] after their initial three 'one-pot' sequences procedure [93] The first 'one-pot' sequence started with the asymmetric addition of aldehyde **99** to nitroolefin **100** in the presence of the catalyst **101** to afford Michael adduct **102** in 7.8:1 diastereomeric ratio (dr) and 97% *ee*. Michael addition of the nitroaldehyde **102** to vinylphosphonate **103** subsequently followed by an intra-molecular H–W-E reaction *via* transient intermediate **104** created the cyclohexene ring. In the presence of Cs_2CO_3 as a base, an equimolecular mixture of (5*R*)-**105**/



Scheme 14. Hayashi's group first 'one-pot' sequence towards oseltamivir **28** [91].

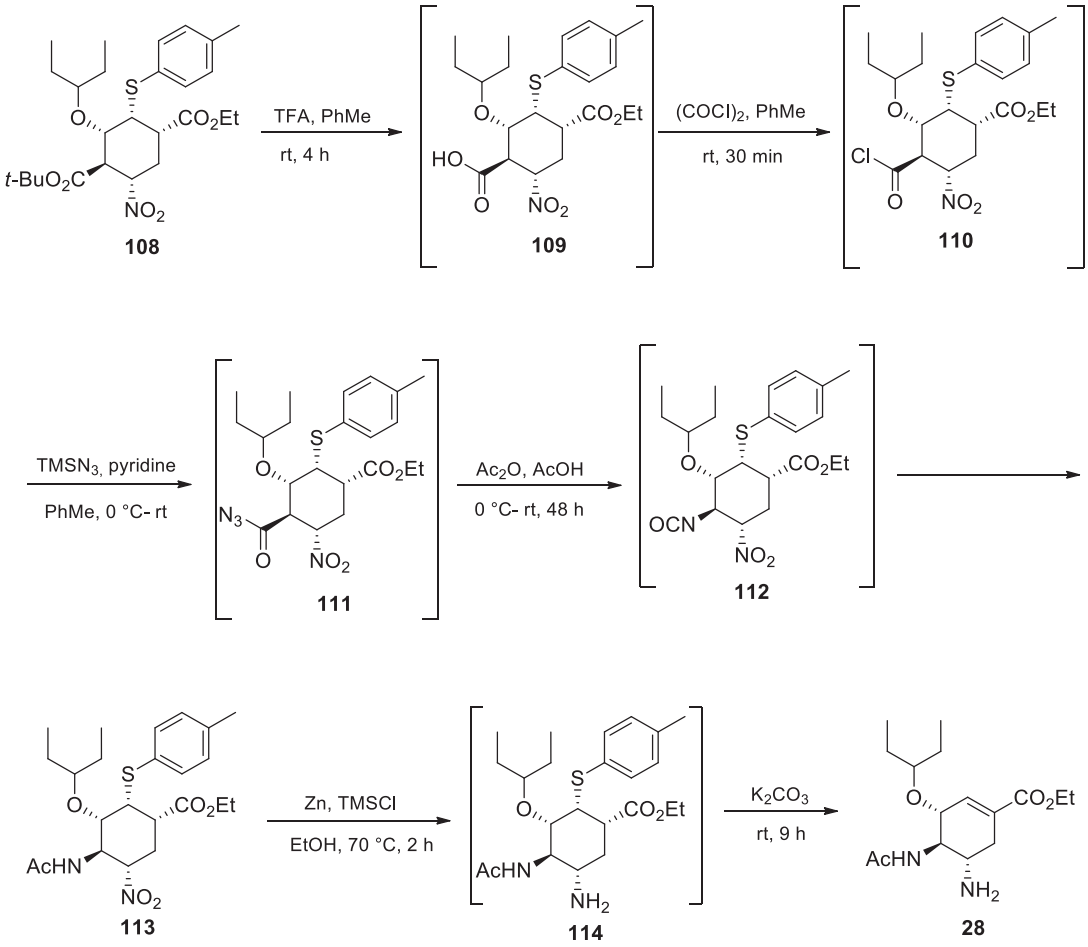
(5*S*)-**105**, **106** and **107** (30% each) was obtained. Treating this mixture with ethanol resulted in a 4.6:1 diastereomeric mixture of (5*R*)-**105** (undesired) and (5*S*)-**105** (desired). The (5*R*)-**105**/(5*S*)-**105** mixture was then treated with 4-methylthiophenol and Cs_2CO_3 in ethanol afforded a Michael-addition product **108** as a single diastereomer in 74% yield [91] This first 'one-pot' sequence product **108** was used as the starting material in the second 'one-pot' sequence (Scheme 15) [91].

Hayashi's second 'one-pot' sequence towards oseltamivir starts with the treatment of compound **108** (made in the first 'one-pot' sequence) with TFA, thus cleaving the *tert*-butyl ester, to afford carboxylic acid **109** which was subsequently converted to acid chloride **110** *via* oxalyl chloride and catalytic DMF treatment [91] The acid chloride **110** was converted to acyl azide **111** by $TMSN_3$ and pyridine treatment in toluene. Without isolation, the compound underwent a Curtius rearrangement reaction at room temperature to give an isocyanate **112**, which was then trapped with AcOH in the presence of Ac_2O affording acetamide **113**. Zinc powder was used for the nitro group reduction on compound **113** to afford amine **114**. In the presence of K_2CO_3 in EtOH, oseltamivir **28** (free base) was afforded [91].

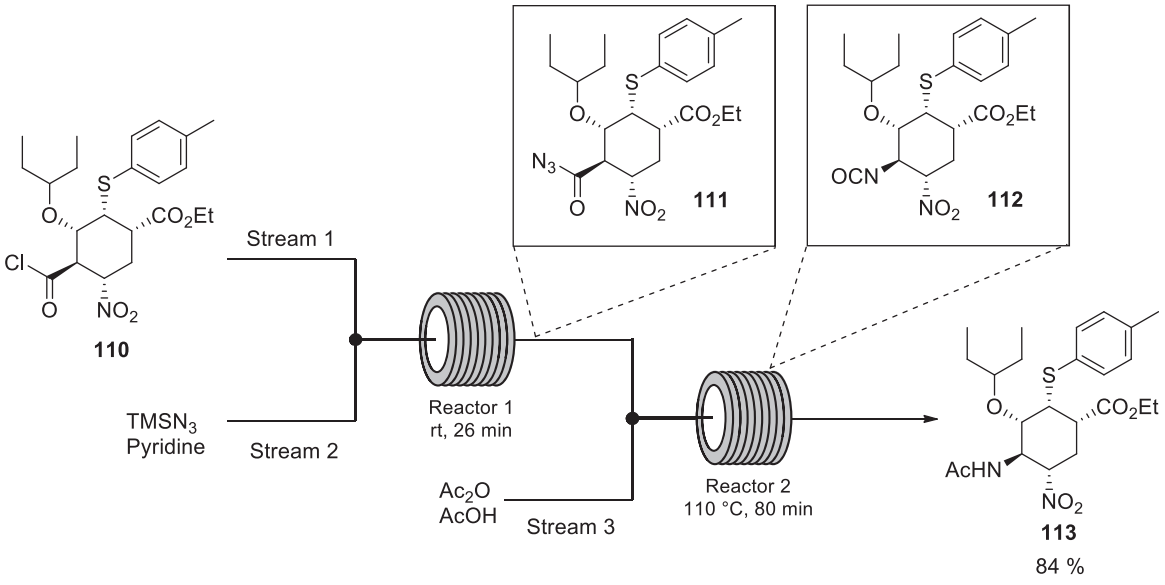
According to Hayashi and coworkers, [91] Tamiflu's synthesis was accomplished by two 'one-pot' reaction sequences, with excellent overall yield (60%) and required only one purification by column chromatography. The approach required five isolations only. Unlike Ma and coworkers, [95] the authors could not avoid the use of the potentially explosive azide chemistry. The azide intermediate was not isolated to address the safety concerns posed by azides. Positively, their approach was characterised by low catalyst loading, no protecting group chemistry and the absence of halogenated solvents [91] Though, this approach is attractive for large scale manufacturing, the safety concerns posed by the use of azide chemistry needs to be addressed especially at large scale where the risk is very high.

To address the aforementioned safety concerns associated with the use of potentially explosive acyl azide **111**, [91] Hayashi and coworkers [32] demonstrated the handling of the Curtius rearrangement reaction of acyl azide **111** to isocyanate **112** by taking advantage of continuous flow technology (Scheme 16). Acyl azide **111** is a potentially explosive compound owing to its nitro and azide moieties [32] As aforementioned, continuous flow technology allows for *in situ* generation and consumption of dangerous intermediates, preventing their accumulation thus enhancing process safety [55,66–68] Additionally, microreactors can handle exotherms extremely well, due to the inherent high surface area to volume ratio and rapid heat dissipation unlike the conventional batch process [55,69] With this in mind, the authors treated acyl chloride **110** with $TMSN_3$ and pyridine in the first reactor at room temperature for 26 min to afford acyl azide **111**. Acyl azide **111** formed *in situ* underwent Curtius rearrangement to isocyanate **112** which is trapped with AcOH in the second reactor at 110 °C for 80 min residence time to afford acetamide **113** in 84% yield and the same yield was obtained at 10 g scale (Scheme 16) [32] The reaction was easily scaled-up in this system using parallel experiments.

Evidently, the authors safely performed the hazardous Curtius rearrangement of azide **111** to isocyanate **112** in continuous flow at



Scheme 15. Hayashi's group second 'one-pot' sequence towards oseltamivir **28** [91].



Scheme 16. Synthesis of acetamide **113** from acyl chloride **110** *via* Curtius rearrangement of acyl azide **111** using a continuous flow system [32].

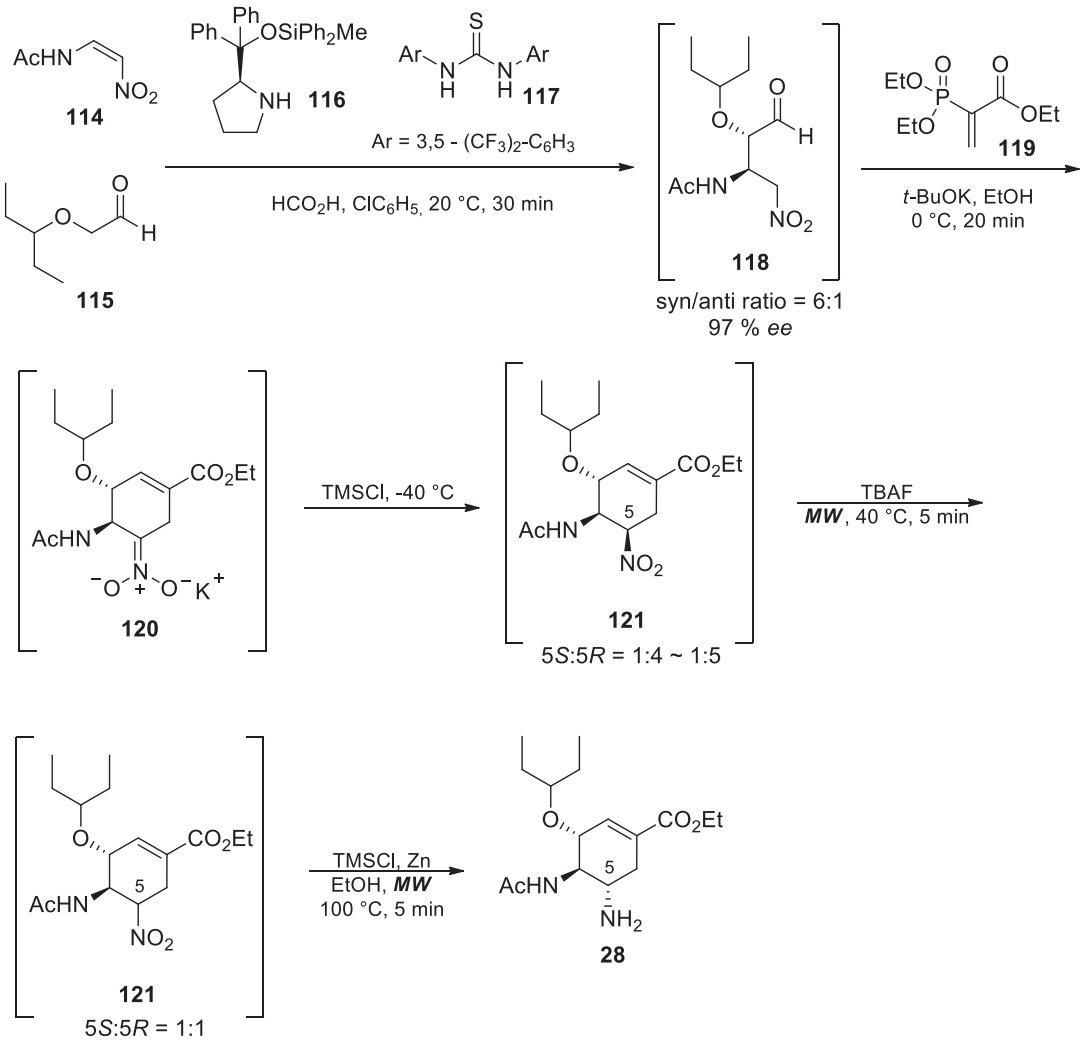
high temperature 110 °C accompanied by significantly shorter reaction time 80 min compared to the batch process (room temperature and 48 h) [32,91] They successfully demonstrated the possibilities of using continuous flow systems as a way of solving the problems associated with handling hazardous intermediates and products in the synthesis of Tamiflu. This technique has the

potential of being utilised for good synthetic approaches towards Tamiflu, which were previously ruled out for large scale synthesis in batch systems on the basis of safety concerns poised by the use of the potentially explosive azide chemistry and other hazardous chemistry. Therefore, problems inherent in scale-up are effectively reduced, making microreactor technology an enabling tool in the synthesis of Tamiflu.

In 2016, Hayashi and Ogasawara published a time economical synthetic approach of (−)-oseltamivir (Scheme 17) [90] This 60 min total synthesis was accomplished in a single vessel over 5 steps.

This 60 min economical total synthesis approach involved an asymmetric Michael addition reaction of nitroalkene **114** and α-alkoxyaldehyde **115** in the presence catalytic amount of diphenylprolinol silyl ether **116**, Schreiner's thiourea **117** and formic acid affording a Michael adduct **118** [90] Diphenylprolinol silyl ether **116** is key for the generation of a reactive intermediate enamine, thiourea **117** activates nitroalkene **114** *via* hydrogen bonding and formic acid suppresses side reactions. Cyclohexene **120** was produced *via domino* Michael addition and H−W-E reactions in the presence of ethyl acrylate derivative **119**, *t*-BuOK, EtOH and Cs_2CO_3 in chlorobenzene. Protonation instantly occurred on the nitronate ion by a reaction with HCl generated *in situ* from trimethylsilyl chloride. In the presence of TMSCl, a mixture of 5(*R*) and 5(*S*) isomers of nitrocyclohexene **121** was obtained. The undesired 5(*R*) isomer was predominantly formed in this reaction [5(*S*)/5(*R*) = 1:4−5]. This was subsequently followed by epimerisation from the 5(*R*) to 5(*S*) isomer in the presence of TBAF and microwave (MW) irradiation to afford a mixture of isomers of 5(*R*) and 5(*S*) of nitrocyclohexene **121** [5*S*/5*R* = 1:1]. Lastly, the nitro group on compound **121** was reduced to an amine using Zn and MW irradiation to afford base free oseltamivir **28** [90].

This efficient 5-step approach was accomplished in just 60 min reaction time with an overall yield of 15% (Scheme 17). Although there are many economies in syntheses such as atom economy, redox economy, and step economy, [90] this synthetic approach serves as a perfect example of time economy as some of the previous syntheses are more than 30 h long [91] The synthetic design also satisfies step economy and pot economy as few steps (5 steps) were used and only one vessel was used throughout. An effective catalyst cocktail was developed for rapid asymmetric Michael addition reaction in excellent yield with excellent diastereo- and enantioselectivities [90] Time economy should also be considered in synthesis along with other efficiency factors in ideal organic synthesis such as greenness, yield and selectivity. The use of hazardous azide chemistry and protection group chemistry was avoided however no information was provided on scale. Without doubt, the approach is a major player in the goal to develop a safe and an efficient scalable process towards oseltamivir **28**.

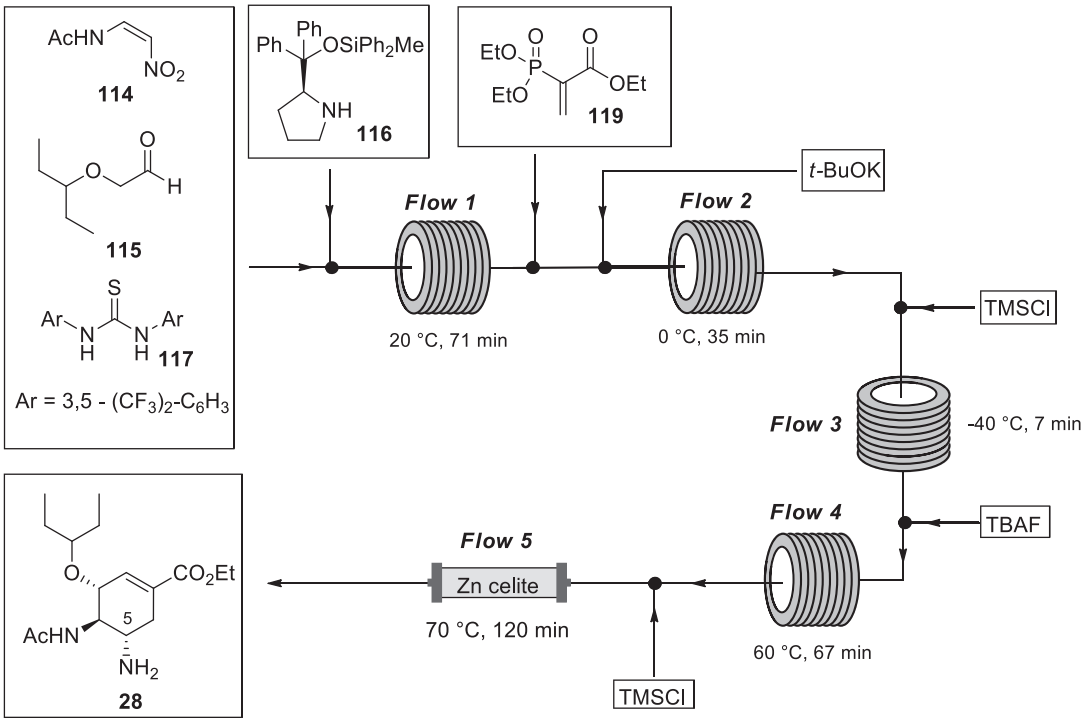


Scheme 17. Hayashi's group 60 min time economical synthesis of (−)-oseltamivir **28** [90].

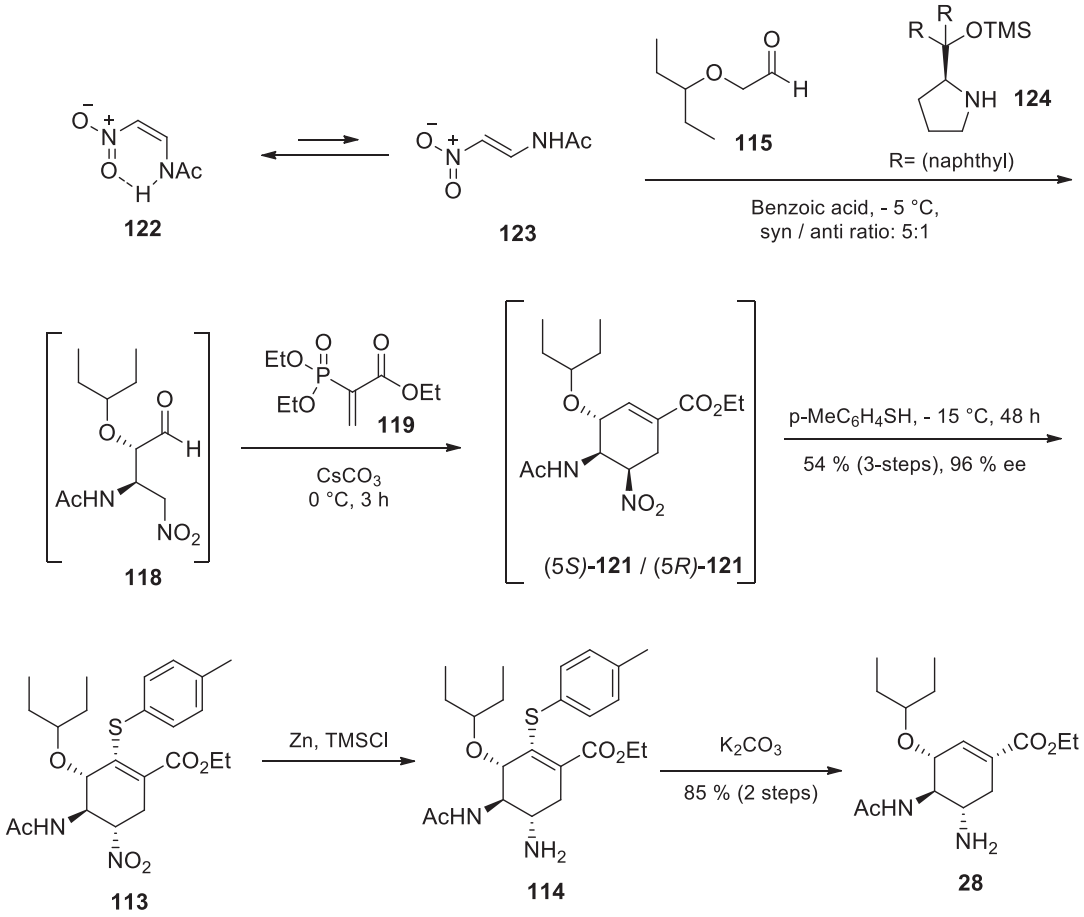
After successful accomplishment of the 60 min synthetic approach towards oseltamivir **28** in batch, Hayashi and Ogasawara [92] subsequently transferred the approach to continuous flow technology (Scheme 18). To successfully transfer the 60 min synthetic approach (Scheme 17) from the batch system to the flow system, the authors had to address the following problems: 1) In a flow system, generally all reagents have to be soluble in the solvent except for polymer-supported reagents, but nitroalkene **114** was barely soluble in the reaction solvent, 2) Zn was employed in the reduction of the nitro group to an amine which is a problematic transformation to conduct in continuous flow systems. The authors first optimised the 60 min approach in the batch system before the successfully development of a continuous-flow synthesis of (−)-oseltamivir summarised (Scheme 18) [92].

The (−)-oseltamivir **28** continuous flow synthesis system consisted of five flow units (Scheme 18) [92] Asymmetric Michael addition reaction was performed in the flow unit 1. A toluene solution of nitroalkene **114**, α-alkoxyaldehyde **115**, theourea derivative **117** and $ClCH_2CO_2H$ was mixed with a toluene solution of catalyst **116** using a Comet-X-01 micro-mixing device at 20 °C (Scheme 19). The resulting mixture reacted in the tube for 71 min affording a Michael adduct **118**. When the reaction was quenched at this stage, the conversion (91%, dr = 10:1, 97 *ee*) was almost the same as in the batch system ((95%, dr = 14:1, 97 *ee*). Domino Michael reaction and intermolecular Horner-Wadsworth-Emmons reactions occurred in the flow unit 2. Phosphoryl acrylate **119** was added into the system at a T-mixer followed by the addition of *t*-BuOK in EtOH at the next mixer (Comet-X-01) resulting in cyclohexene **121** (Scheme 17, 60% yield) at 0 °C after 35 min residence time. When the reaction was quenched, the undesired 5*R*-isomer was found to be predominant (5*S*/5*R* = 1:5). Flow unit 3 was used to protonate the nitronate ion. Potassium nitronate **120** (Scheme 17) was formed at the end of the domino reaction by the addition of TMSCl in EtOH at - 40 °C, which produced HCl *in situ*, with a residence time of 7 min. Epimerisation from 5*R*-isomer to the 5*S* isomer occurred in the flow unit 4 where potassium nitronate **120** was treated with a solution TBAF in EtOH at the Comet-X-01 mixer at 60 °C and residence time of 67 min to afford nitrocyclohexene **121** (5*S*/5*R* = 1:1). Flow unit 5 effected reduction of the nitro group to amine using Zn. Since Zn is a solid, a column reactor was used. The column reactor was packed with Zn (5 g) and Celite (8 g) in the presence of TMSCl in EtOH (0.6 M). This was done at 70 °C and 120 min residence time. Zn activity gradually decreased with time thus it was necessary to replace the column after every 5h. Oseltamivir **28** was isolated using an acid-base extraction and purified by column chromatography to afford (−)-oseltamivir **28** in 13% overall yield which is comparable to the batch approach (15%). Noteworthy, continuous flow synthesis can easily be scaled-up compared to batch making the flow procedure more attractive [57,65,67,79,96–100] The authors easily increased continuous flow productivity by long-time operation or directly scaling-up to a larger scale after optimisation on a small scale. However, batch scale-up is flawed at each stage of the scale-up, modifications made to the reactor vessel result in changes to the surface to volume ratio, process will need process re-optimisation at every stage of scale up due change is mass transfer ratios, which in turn have a profound effect on the thermal and mass-transport properties of the reaction. Evidently, this continuous flow synthesis technology is efficient and convenient. This work unearthed valuable insights towards the goal of developing efficient and safe processes for (−)-oseltamivir **28** continuous flow manufacturing.

Ma and coworkers developed an approach towards oseltamivir *via* organocatalytic Michael addition of an aldehyde to 2-amino-1-nitroethene (Scheme 19) [95] Nitroolefin **122** was prepared by (*Z*)-2-nitroethanamine acetylation due to the intra-molecular hydrogen bonding. Nitroolefin **122** was subsequently subjected to Michael addition with aldehyde **115** in the presence of an organic catalyst **124** and benzoic acid to afford a Michael-addition product **118** in 80% yield and 5:1 *syn*/*anti* ratio. Going forth, Ma et al. utilised Hayashi and coworkers' [90,91] strategy to transform aldehyde **118**



Scheme 18. Continuous-flow synthesis of (−)-oseltamivir **28** by Hayashi and Ogasawara [92].



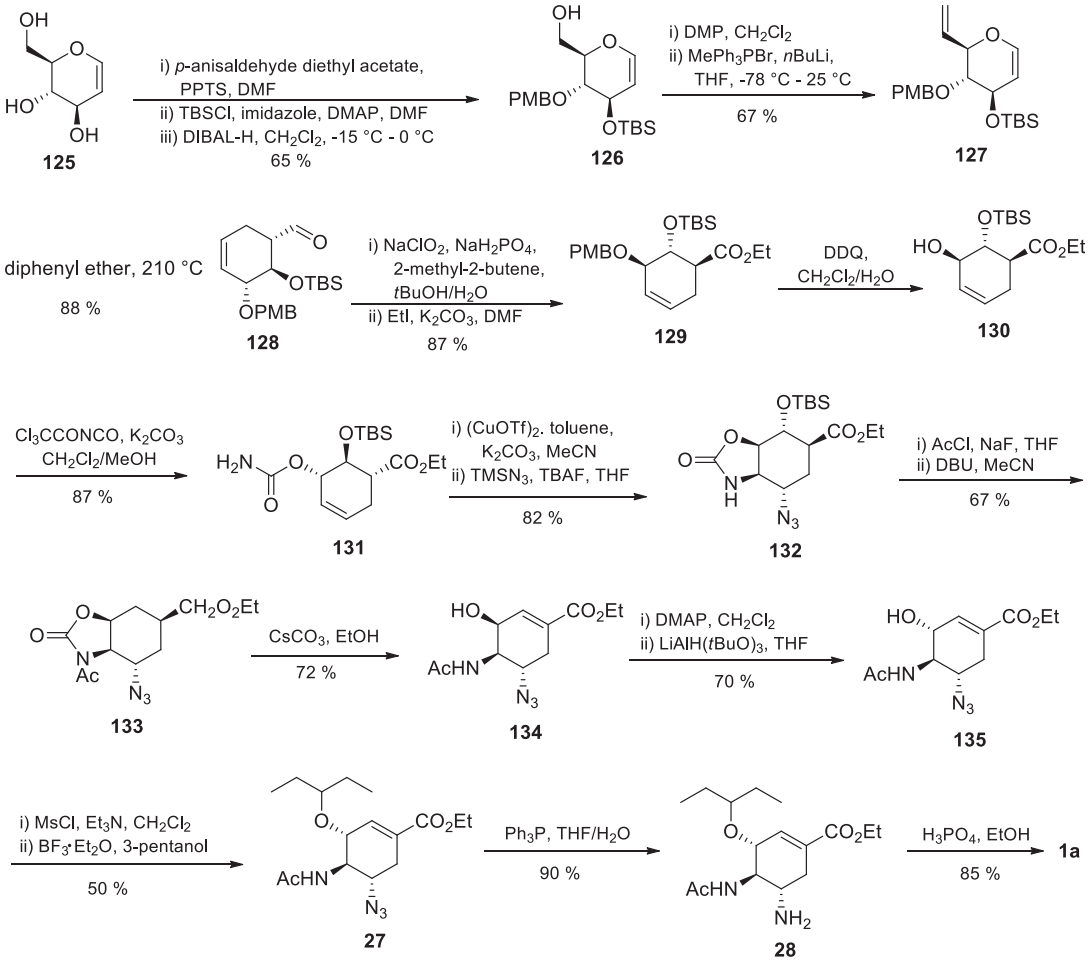
Scheme 19. Ma's group oseltamivir **28** synthesis *via* organocatalytic Michael addition [95].

to (−)-oseltamivir **28**. Aldehyde **118** was treated with vinylphosphonate **119** and Cs_2CO_3 to give cyclohexane **121** as a mixture of epimers at C-5. Cyclohexane **121** was subsequently treated with 4-methylthiophenol affording intermediate **113** [95] The combined yield for the 3 steps was 54% and **113** was obtained in 96% *ee*. Compound **113** nitro reduction was accomplished in the presence of Zn and TMSCl to afford **114**. Elimination of 4-methylthiophenol on compound **114** with K_2CO_3 in MeOH regenerated the double bond to afford oseltamivir **28** in 85% yield. This 5 steps approach had an excellent overall yield of 46% from aldehyde **115** and nitroolefin **122**. Furthermore, procedure required only two intermediate isolation operations which made the approach practically feasible in the preparation of the drug molecule. The authors utilised an asymmetric Michael addition to incorporate amino groups on the carbon skeleton as nitro and acetomido groups, thus avoiding the use of azide chemistry. This route was only carried out at 10 mmol scale and no protection group chemistry was required [95] This route is a potential industrial candidate, however extensive scale up studies, optimisation and safety concerns associated with nitro compounds need to be assessed.

4.2.3. *Tamiflu synthesis from sugars*

Affordable and abundantly available sugars such as D-xylose, [101] D-ribose, [102] D-mannitol, [103] D-glucal, [104] and D-glucose [105] have also been used as starting material for Tamiflu **1a** synthesis [1,2,24,26] However, sugar dependent synthetic procedures are characteristically long (12–22 steps) accompanied with extensive chromatographic purification (9–16 operations) and low yields (2.6–15%). Herein, Liu and coworkers' D-glucal procedure, [104] Wong et al. D-xylose procedure [101] and Kongkathip et al. [105] D-glucose procedure towards Tamiflu **1a** are reviewed in detail.

Just as with Ko et al. D-mannitol procedure, [103] Liu and coworkers [104] explored a Claisen rearrangement strategy in the construction of oseltamivir's cyclohexene backbone from D-glucal **125** and the addition of diamino groups onto the cyclohexene backbone was accomplished *via* tandem intramolecular aziridination and ring opening (Scheme 20) [104] The D-glucal **125** was protected *via* conversion to 4,6-benzylidene acetal with *p*-anisaldehyde diethyl acetal in the presence of catalytic pyridinium *p*-toluene sulphonate (PPTS) and silylation of the 3-hydroxy group as the *tert*-butyldimethylsilyl ether. Subsequent reductive cleavage of an acetal followed by treatment with diisobutylaluminium hydride (DIBAL-H) afforded free alcohol **126** in 65% yield. The primary hydroxyl group of the alcohol was subjected to Desse-Martin periodinane oxidation yielding an aldehyde which underwent Wittig methylenation in the presence of methyltriphenylphosphonium bromide to afford alkene **127** in 67% yield. Claisen rearrangement of alkene **127** in diphenyl ether affording the cyclohexene core was accomplished at 210 °C in a sealed environment forming diastereoselective aldehyde **128** in 88% yield. Aldehyde **128** was subsequently oxidised to an acid using $NaClO_2/NaH_2PO_4$ in the presence of 2-methyl-2-butene followed by esterification with ethyl iodide to afford ester **129** in 87% yield. Selective removal of *p*-methhoxybenzyl (PMB) protecting group was achieved with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford **130** in 92% yield.

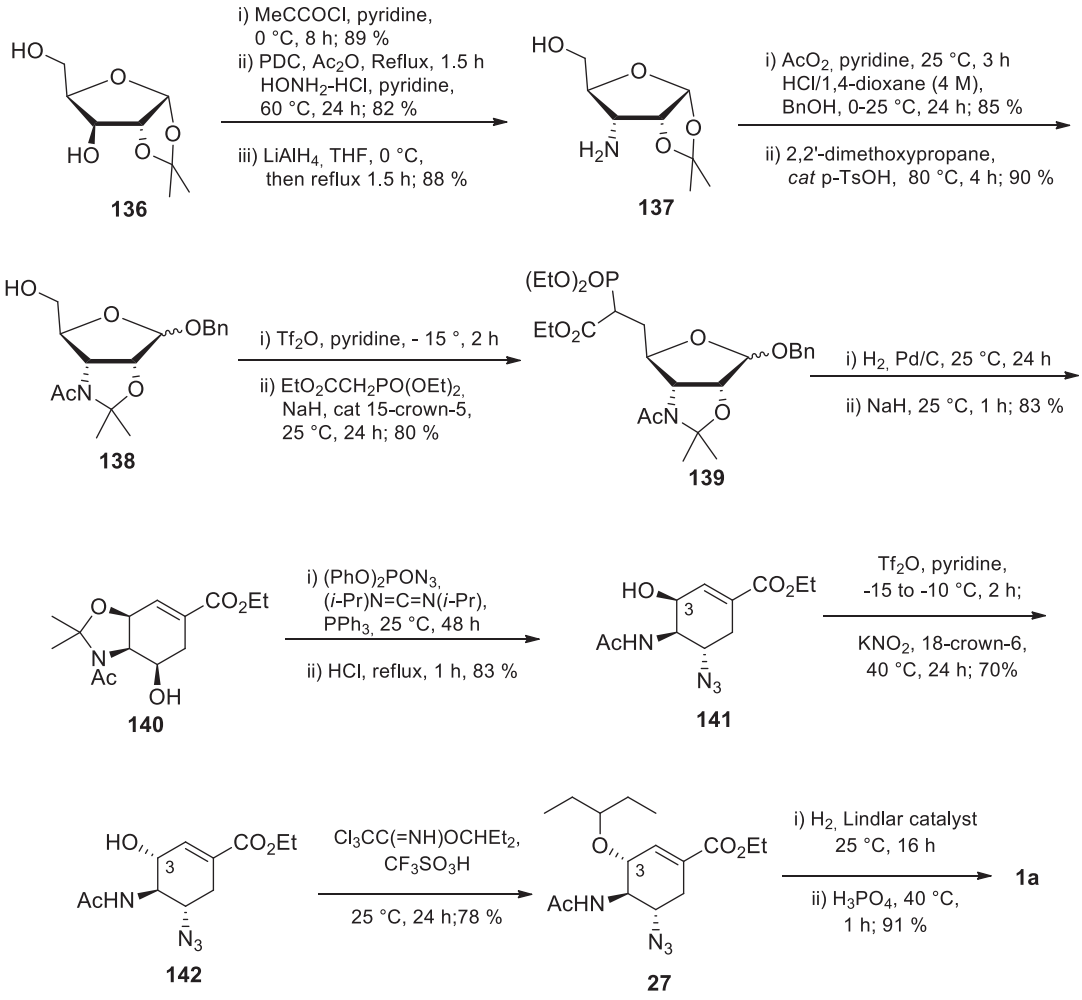


Scheme 20. Tamiflu **1a** synthesis via Claisen rearrangement starting from D-glucal by Liu and coworkers [104].

Treatment of compound **130** with trichloroacetyl isocyanate and potassium carbonate afforded carbamate **131** in 87% yield which was subsequently treated with $Cu(OTf)_2$-toluene and $TMSN_3$. This mechanistic step introduced a nitrogen functionality through stereo and regioselective aziridine opening afforded by $TMSN_3$. Subsequent addition of TBAF in THF in stoichiometry amounts prompted formation of compound **132** in 82% yield**.** To avoid racemisation at C1 and aromatization owing to directly treatment of **132** with DBU, the authors first acetylated **132** with AcCl/NaH then followed by treatment with DBU to afford **133** in 67% yield. Subsequent hydrolysis of **133** with Cs_2CO_3 in ethanol afforded alcohol **134** in 72% yield. Alcohol **134** was oxidised with Dess-Martin periodinane, inverting the configuration at C3 and affording a ketone which was subsequently reduced with LiAlH(t-BuO)$_3$ to afford a 70% yield of stereospecific **135**. Treatment of compound **135** with MsCl/Et_3N led to an aziridine intermediate and aziridine ring opening with 3-pentanol/BF_3Et_2O afforded azide **27** in 50% yield. Azide **27** reduction with Ph_3P in (THF)/H_2O afforded oseltamivir **28** in 90% yield, which upon treatment with H_3PO_4 in EtOH afforded Tamiflu **1a** in 85% yield.

Although Liu et al. D-glucal approach started from an affordable, commercially and abundantly available D-glucal, it involves 22 steps accompanied by 16 tedious intermediate column chromatography purification operations and very low overall yield (2.6%) [104] Furthermore, the synthesis had a mechanistic step which required reaction at high temperature in a sealed tube in addition to protection group chemistry. These limitations make it difficult for the synthesis process to be scaled up to industrial scale.

Wong and coworkers' D-xylose approach is the highest yielding procedure (15% overall yield) [104] in the Tamiflu **1a** 'sugar-depended' synthesis procedure class (Scheme 21) [1,2] The authors started from 1,2-*O*-isopropylidene-α-D-xylofuranose **136**, prepared from D-xylose. The 1,2-*O*-isopropylidene-α-D-xylofuranose **136** was transformed to aminoalcohol **137** sequentially using pivaloyl chloride followed by alcohol oxidation with PDC affording ketone intermediate and reduction of the oxime derived from ketone with $LiAlH_4$. Aminoalcohol **137** amino group was acetylated to afford acetamide which was sequentially treated with benzyl alcohol under acidic conditions to afford ribofuranoside intermediate as a mixture of anomers (α/β) = 7:3) and then with 2,2-dimethoxypropane to afford *N,O*-ketal **138** in the same anomeric ratio. *N,O*-Ketal **138** mixture was converted to triflate and the triflate group was subsequently displaced with triethyl phosphonoacetate to afford phosphoryl ester **139**. Subsequent intramolecular Horner-Wadsworth-Emmons reaction using NaH and catalytic 15-crown-5 afforded cyclohexene **140**. Azide **141** was prepared from cyclohexene **140** *via* a Mitsunobu reaction followed by deprotection of the amino and hydroxy groups using HCl. Subsequent stereo-chemistry inversion of the hydroxy group on Azide **141** using Tf_2O, pyridine and KNO_2 and 18-crown-6 afforded alcohol **142** which was then treated with 3-pentyl trichloroacetimidate to introduce the 3-pentyl ether functionality on azide **27**. Hydrogenation of azide **27** in the presence of Lindlar catalyst followed by the addition of H_3PO_4 afforded Tamiflu **1a** in 15% overall yield over the



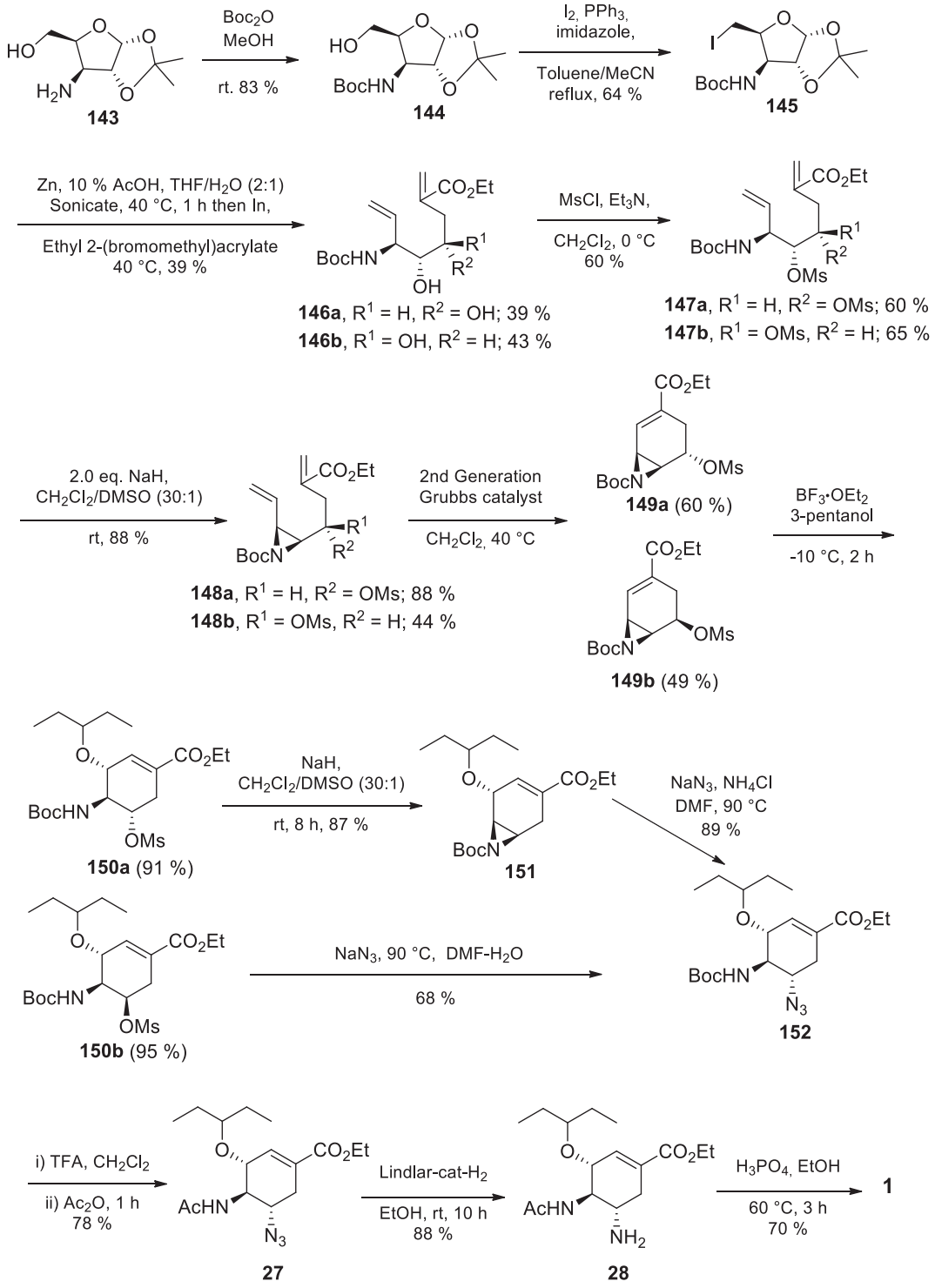
Scheme 21. Wong and coworkers' enantioselective synthesis of Tamiflu **1a** from D-xylose [104].

16 steps. As with all sugar-dependent approaches, this procedure has extensive column chromatographic purification operations. Furthermore, protection group chemistry and hazardous azide chemistry was used.

More recently, Kongkathip et al. demonstrated a 13-step procedure for Tamiflu starting from D-glucose (Scheme 22) [105] The 3-amino-3-deoxy-1,2-*O*-(1-methylethylidene)-α-D-xylofuranose **143** derived from D-glucose, underwent *N*-Boc protection in the presence of Boc_2O to afford alcohol **144** in 83% yield. Subsequent alcohol **144** iodination by I_2 in the presence of PPh_3 and imidazole afforded iodide **145** in 64% yield. Zn-mediated fragmentation of iodide **145** afforded aldehyde intermediate, which subsequently underwent indium-mediated coupling with ethyl 2-(bromomethyl)acrylate to afford corresponding diene **146a** and **146b** in 39% and 43% yield, respectively. Protection of the dihydroxyl group of both **146a** and **146b** was achieved upon treatment with MsCl affording mesylate **147a** and **147b** in 60% and 65% yield, respectively. Subsequent treatment of **147a** and **147b** with NaH afforded aziridine **148a** and **148b** in 88% and 44%, respectively. Heating **148a** and **148b** to 40 °C with the Hoveyda-Grubbs 2nd generation catalyst resulted in ring closing metathesis, afforded cyclohexene aziridine **149a** and **149b** in 60% and 49% yield, respectively. Regio-and stereospecific *N*-Boc aziridine **149a** and **149b** ring opening with 3-pentanol and $BF_3.OEt_2$ afforded compounds **150a** and **150b** in 91% and 95% yield respectively, which can both be transformed to Tamiflu **1a**. Compound **150a** underwent intermolecular S_N2 type when treated with NaH affording *N*-Boc aziridine **151a** (87% yield) and subsequent azidation with NaN_3 afforded azide **152** in 89% yield. Compound **150b** was directly azidated to azide **152** in 68% yield. Treatment of azide **152** with TFA and subsequent acetylation with Ac_2O afforded *N*—Ac azido **27** in 78% yield. *N*—Ac azido **27** reduction with H_2 and Lindlar catalyst afforded oseltamivir **28** in 88% yield. Lastly, oseltamivir **28** was treated with H_2PO_4 to afford Tamiflu **1a** in 70% yield. The key transformations in this approach are the three consecutive organometallic reactions: Zn-mediated fragmentation of **145**, indium-mediated coupling between the aldehyde intermediate and ethyl 2-(bromomethyl)acrylate and the Hoveyda-Grubbs 2nd generation catalyzed ring closing metathesis of **148**. Typical of sugar-dependent approaches, this procedure was characterised with low yield (3.8% over 13 steps) and extensive column chromatographic purification (12 operations). Furthermore, the authors could not avoid azide chemistry and protection group chemistry.

5. Conclusions

As with the current Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection (COVID19) pandemic, a highly aggressive strain of the influenza virus such as the H5N1 can mutate and spark another deadly pandemic. This reminds us of the need for continued research to discover more potent neuraminidase inhibitors. As the research towards new and better treatment remains a top priority, it is equally important to improve the



Scheme 22. Kongkathip et al. D-glucose procedure towards Tamiflu **1a** [105].

availability of the current anti-influenza drugs by developing better synthetic procedures to guard the world against influenza. Though other influenza antiviral drugs such as peramivir, zanamivir and baloxavir marboxil are on the market, Tamiflu remains the most used anti-influenza drug 20 years after its approval. Consequently, Tamiflu synthesis remains an important research area. Although the Roche industrial route is currently supplying the world with enough tonnes of Tamiflu but it remains to be seen if will be suffice in the face of a pandemic, the route raised three concerns; a) the use of shikimic acid, which had limited availability in the early days of development b) the use of potentially explosive azide chemistry and c) long synthetic route with low overall yield. To address these concerns, academic and industrial researchers have made tremendous efforts in the quest for a truly efficient, safe, cost-effective and environmentally benign synthetic procedure resulting in more than 70 synthetic procedures to date since its discovery.

As reflected in this review and complimented by the published reviews, [1–3,22–27,47] both the shikimic acid-free and azide chemistry-free approaches are mostly low yielding compared to their competitors despite their ingenuity in Tamiflu assembling. Having solved the shikimic acid availability concerns over the years by developing more efficient extraction and purification processes or alternatively by fermentation using genetically engineered *E.coli* bacteria, [25,28–30] the use of hazardous azide chemistry needs more attention. The application of continuous flow technology in Tamiflu synthesis proved to be a potential enabling tool for safe handling of the hazardous azide chemistry as well as improving efficiency [32,53,92] Continuous flow synthesis has attracted considerable attention in synthetic chemistry and pharmaceutical industry in the last decade owing to its well-documented advantages, [55–59,65,67,79,96–100] resulting in numerous pharmaceutical drugs approaches being redesigned into continuous flow synthesis [56,58,60–65,106] In this light, we envisage that Tamiflu synthesis can hugely benefit from continuous flow technology application to afford truly efficient synthetic procedures. Furthermore, the promising Tamiflu synthetic approaches which were previously ruled out for large scale synthesis in batch based on either safety concerns or poor efficiency can be reconsidered in flow. We envisage that the incorporation of other enabling technologies such as artificial intelligence, machine learning for “Big data” analysis, can challenge the dogma of the past and come up with a truly efficient, safe, cost-effective and environmentally benign Tamiflu synthetic procedure. With this in mind, we are looking forward to see what the future of Tamiflu synthesis holds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Paul Watts started his career as a lecturer at the University of Hull (UK) in 2002, being promoted to full professor in 2011. At the University of Hull he led the micro reactor and flow technology group. In February 2013, he moved to Nelson Mandela University to hold the distinguished position of 'SARChI Research Chair in Microfluidic Bio/Chemical Processing'. He has published over 120 highly cited papers. He strongly believes that scientists should conduct research that impacts society; the biggest project underway involves the local production of key drugs as the morbidity and mortality from major diseases are much more devastating in Africa than in other regions of the world. The vision is that new technology will be used within South Africa to manufacture generic drugs; this could create jobs and a new manufacturing industry within the country.