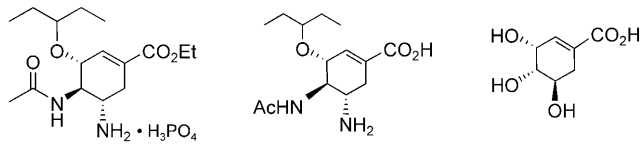
Drug Synthesis

DOI: 10.1002/anie.200901561

Efficient Access to Oseltamivir Phosphate (Tamiflu) via the *O*-Trimesylate of Shikimic Acid Ethyl Ester**

Martin Karpf and René Trussardi**

Oseltamivir phosphate[1] (**1**; Tamiflu), the water-soluble and orally bioavailable prodrug of the corresponding pharmacologically active acid **2** (Scheme 1) was first introduced to the



1 oseltamivir phosphate Tamiflu

2

3 (–)-shikimic acid

Scheme 1. Structures of compounds **1**–**3**.

market in November 1999 by Gilead Sciences and Hoffmann-La Roche for the treatment and prevention of seasonal influenza virus infections, and it was later shown to be active against the currently spreading avian H5N1 influenza strain,[2] as well as the recently emerging H1N1 swine influenza strain. A joint synthetic development effort[3,4] led to the presently used technical synthesis of **1** from shikimic acid (**3**). Thanks to this collaboration with partners worldwide having extensive experience in safely performing azide chemistry on a bulk scale, a yearly production capacity of several hundred metric tons of Tamiflu has been secured; this corresponds to several hundred million doses available in the case of a pandemic.

In response to the increasing threat of a severe influenza pandemic caused by a potentially evolving human variant of the avian H5N1 influenza strain, several groups have published new approaches[5] to **1** from sources other than **3**. Their claims that routes independent of shikimic acid (**3**) are needed are based on unfounded arguments regarding the availability of **3** as a technical starting compound as well as the potential risks of azide chemistry on an industrial scale.[6] Although large quantities of **3** were not available from commercial sources at the outset of this project, also prompting us to create and evaluate shikimic acid independent routes,[7] it became widely available in multi-hundred-ton amounts during the course of our work by extraction of star anis and by a fermentation process using a genetically engineered *E. coli* strain.[8] In a recent independent publication[9] comparing published syntheses of **1** with regard to material efficiency performance and environmental impact factor (*E*-factor), the currently used technical route for the commercial production of **1** rated the most proficient. Herein we describe a new, short, eight-step synthesis of **1** from **3** based on a patent application[10] (priority date: September 19, 2007).

With large amounts of shikimic acid (**3**) on hand and the constructive experience with partners performing azide chemistry on a technical scale, we embarked upon effecting a streamlined transformation of **3** to **1** as depicted in Scheme 2. The synthesis proceeding via the *O*-trimesylate **5** of ethyl shikimate (**4**), which was obtained in high yield from **3** by way of **4**[4] followed by mesylation. Treatment of **5** with sodium azide at room temperature under non-acidic conditions led to the regio- and stereoselective substitution of the allylic *O*-mesylate at position 3 to deliver **6**. Subsequent treatment thereof with triethyl phosphite in toluene at reflux produced the aziridine intermediate **7**, which underwent regio- and stereoselective ring opening at the allylic position with 3-pentanol and Lewis acid catalysis[3] providing crystalline **8** in 45% overall yield from **3** without the need for purification of any intermediates. The configuration of **8** was confirmed by X-ray crystallography (Figure 1).

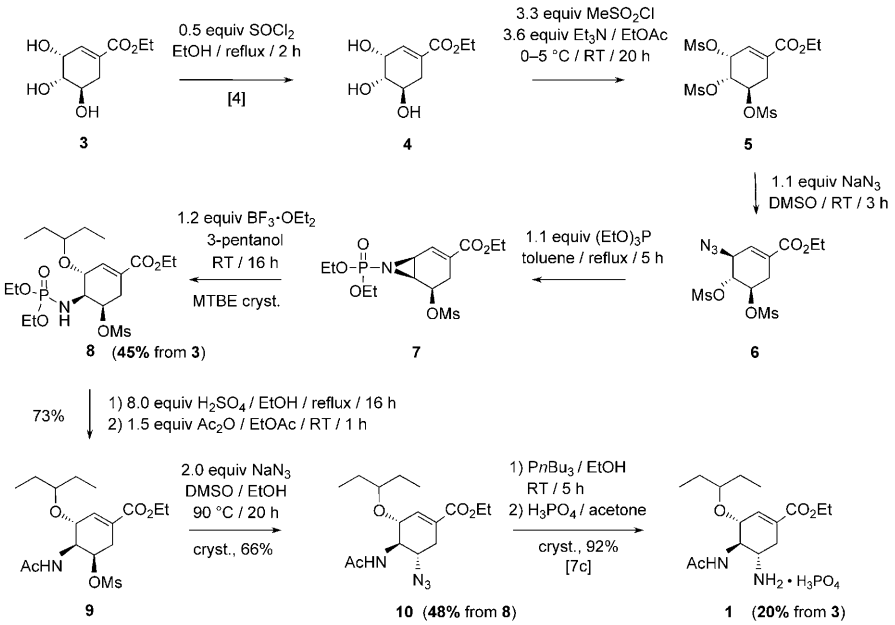
Cleavage of the N–P bond in **8** followed by *N*-acetylation afforded the mesylate **9**, which reacted with sodium azide under neutral conditions to furnish **10**, the last intermediate in the current commercial route of oseltamivir phosphate (**1**).[7c]

The potential aromatization that threatened early intermediates of this approach was controlled as follows: Elimination leading to aromatization during the formation of the *O*-trimesylate **5** was successfully suppressed by inverse addition, namely by adding the base Et_3N at 0–5 °C to a solution of **4** and mesyl chloride in ethyl acetate. Allylic substitution in **5** without concomitant elimination was possible in our hands only using azide as the nucleophile. All attempts to substitute with another, more basic nitrogen nucleophile (e.g. allylamine, tritylamine) led to aromatization. For the transformation of the β-azido mesylates **6** to the

[*] Dr. M. Karpf, R. Trussardi
F. Hoffmann-La Roche Ltd., Pharmaceuticals Division
Technical Sciences, Synthesis & Process Research
Grenzacherstrasse 124, 4070 Basel (Switzerland)
Fax: (+41) 616-881-670
E-mail: martin.karpf@roche.com
rene.trussardi@roche.com

[**] We thank Patrick Franke for his dedicated and skillful experimental work and Marcel Althaus, Jean-Claude Jordan, and Brigitte Schilter-Horisberger for their analytical work. We are grateful to André Alker for the X-ray crystal structure determination of intermediate **8**, Markus Bürkler for the analysis and interpretation of the ^{1}H NMR spectra, and all the members of the Analytical Services of Hoffmann-La Roche for efficiently and persistently providing spectral and physical data of all compounds described. We gratefully acknowledge Paul Spurr and Ulrich Widmer for carefully reading the manuscript.

Supporting information for this article (including experimental details and spectroscopic data) is available on the WWW under http://dx.doi.org/10.1002/anie.200901561.



Scheme 2. Synthesis of oseltamivir phosphate (**1**) starting from shikimic acid (**3**) via the *O*-trimesylate **5** obtained from ethyl shikimate. MTBE = *tert*-butyl methyl ether, DMSO = dimethylsulfoxide.

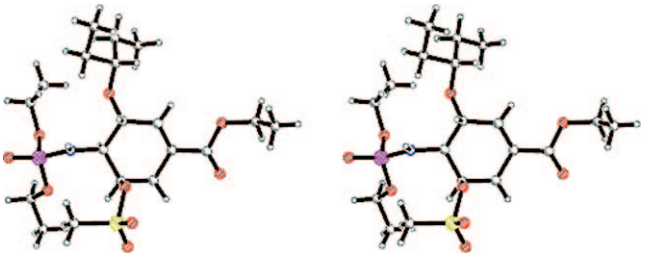
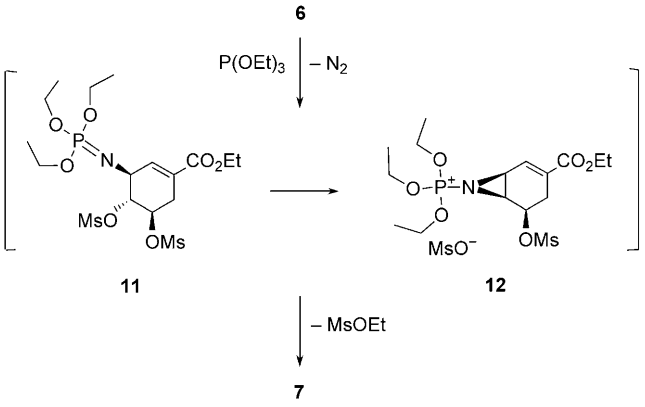


Figure 1. X-ray crystal structure of intermediate **8**.

aziridine **7**, a new protocol[11] had to be established employing triethyl phosphite under water-free conditions[12] since the known direct methods of aziridine formation from β-azido mesylates with triaryl and trialkyl phosphines proceeding via Staudinger iminophosphoranes[3,13] followed by hydrolysis consistently led to decomposition and aromatization. The probable course of the successful reaction with triethyl phosphate under anhydrous conditions is shown in Scheme 3. The detection of ethyl mesylate as a by-product of the conversion of **6** to **7** supports the assumption that this novel direct transformation occurs via the iminophosphite **11** followed by aziridine formation to the nonisolated mesylate **12** and subsequent Arbusov-type cleavage to the phosphoramidite **7**.

This new eight-step transformation starting from abundant shikimic acid (**3**), which requires only three work-ups and purifications, represents the most direct route so far to Tamiflu (**1**). It requires no protecting group manipulations, chromatographic separations, or tedious purifications, uses cheap chemicals, and proceeds with an overall yield of 20% already at a technically unoptimized stage and thus compares favorably with other published pathways to **1**.[14]



Scheme 3. Proposed mechanism of aziridine formation.

Received: March 22, 2009
Revised: May 19, 2009
Published online: June 29, 2009

Keywords: aziridine formation · oseltamivir phosphate · shikimic acid · Tamiflu

[1] a) C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver, R. C. Stevens, *J. Am. Chem. Soc.* **1997**, *119*, 681–690; b) C. U. Kim, W. Lew, M. A. Williams, H. Wu, L. Zhang, X. Chen, P. A. Escarpe, D. B. Mendel, W. G. Laver, R. C. Stevens, *J. Med. Chem.* **1998**, *41*, 2451–2460.

[2] A. C. Hurt, P. Selleck, N. Komadina, R. Shaw, L. Brown, I. G. Barr, *Antiviral Res.* **2007**, *73*, 228–231.

[3] J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu, L. Zhang, *J. Org. Chem.* **1998**, *63*, 4545–4550.

[4] M. Federspiel, R. Fischer, M. Hennig, H.-J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Göckel, S. Götzö, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Röckel-Stäbler, R. Trussardi, A. G. Zwahlen, *Org. Process Res. Dev.* **1999**, *3*, 266–274.

[5] H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem.* **2009**, *121*, 1330–1333; *Angew. Chem. Int. Ed.* **2009**, *48*, 1304–1307; M. Shibasaki, M. Kanai, *Eur. J. Org. Chem.* **2008**, 1839–1850, and references therein.

[6] V. Farina, J. D. Brown, *Angew. Chem.* **2006**, *118*, 7488–7492; *Angew. Chem. Int. Ed.* **2006**, *45*, 7330–7334.

[7] a) S. Abrecht, P. Harrington, H. Iding, M. Karpf, R. Trussardi, B. Wirz, U. Zutter, *Chimia* **2004**, *58*, 621–629; b) S. Abrecht, M. Cordon Federspiel, H. Estermann, R. Fischer, M. Karpf, H.-J. Mair, T. Oberhauser, G. Rimmler, R. Trussardi, U. Zutter, *Chimia* **2007**, *61*, 93–99, and references therein; c) H. Iding, B. Wirz, P. Spurr, U. Zutter, *J. Org. Chem.* **2008**, *73*, 4895–4902.

[8] S. C. Chandran, J. Yi, K. M. Draths, R. von Daeniken, W. Weber, J. W. Frost, *Biotechnol. Prog.* **2003**, *19*, 808 – 814; D. R. Knop, K. M. Draths, S. C. Chandran, J. L. Barker, R. von Daeniken, W. Weber, J. W. Frost, *J. Am. Chem. Soc.* **2001**, *123*, 10173 – 10182.
[9] J. Andraos, *Org. Process Res. Dev.* **2009**, *13*, 161 – 185.
[10] R. Trussardi (F. Hoffmann-La Roche AG), US 2009/0076296A1 (priority date: September 19, 2007).
[11] The stepwise transformation of β-azido-mesylates into phosphoryl aziridines using strong bases (NaH) for the cyclization step is known: for example, S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge, B. E. Segmuller, *J. Am. Chem. Soc.* **1985**, *107*, 3891 – 3898; Y. Naruta, N. Nagai, K. Maruyama, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1143 – 1148; however, basic conditions are detrimental in our case.
[12] Since the presence of even small amounts of water is deleterious to the aziridine formation step (**6**→**7**) scrupulous drying of **6** by repeated azeotropic removal of traces of water with toluene is mandatory.
[13] A. Breuning, R. Vicik, T. Schirmeister, *Tetrahedron: Asymmetry* **2003**, *14*, 3301 – 3312; Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, *48*, 1353 – 1406, and references therein.
[14] Note added in proof: a related approach to **1** via **5** was recently published: L.-D. Nie, X.-X. Shi, K. H. Ho, W.-D. Lu, *J. Org. Chem.* **2009**, *74*, 3970 – 3973.

