AtlanChim Pharma

N°4 | Scientific Letter

EDITO

ATLANCHIM PHARMA – Qualité et Réactivité au service de nos clients.

Cette fin d'année 2009 se traduit, pour ATLANCHIM PHARMA, par une démarche d'amélioration par la qualité et par un accroissement de l'équipe scientifique.

En effet, nos premières préoccupations sont de satisfaire nos clients et de pérenniser le devenir de la société. Pour cela, ATLANCHIM PHARMA s'engage à respecter les exigences de la norme ISO 9001 v 2008. Dans ce but, une Responsable Assurance Qualité est arrivée parmi nous depuis plusieurs mois. Nous avons pour objectifs majeurs de développer et fidéliser notre portefeuille clients, de maîtriser nos achats, de maintenir et d'étendre nos compétences, et d'optimiser la planification de nos activités et la gestion de nos ressources.

Par ailleurs, ATLANCHIM PHARMA, après avoir augmenté sa capacité de production de 50% (extension des laboratoires) augmente ses effectifs et va donc recruter et former des Chefs de Projet et assistants. Ces recrutements nous permettront d'être encore plus réactifs vis-à-vis de nos clients et également de mettre à leur disposition notre expertise et notre savoir-faire en synthèse chimique à façon.

Dans cette lettre scientifique, vous trouverez sur le modèle des lettres scientifiques précédentes, le portrait de deux Chefs de Projet en chimie et en biologie ainsi que le portrait de notre Responsable Assurance Qualité,Dr. Isabelle ARNAUD.

Nos équipes d'ATLANCHIM PHARMA se joignent à moi pour vous souhaiter une bonne lecture de notre lettre scientifique.

Ronan LE BOT
Directeur

ATLANCHIM PHARMA – Quality and reactivity for our customers

End of year 2009 means improvement approach through quality and extension of the scientific team for ATLANCHIM PHARMA.

Indeed our customers' satisfaction and the perpetuation of the company's evolution are our priorities. It is with this aim in view that ATLANCHIM PHARMA commits itself to respect ISO 9001 v2008 norm requirements. Thus a Quality Assurance Manager joined us a few months ago. We aim at developing our customer portfolio and our customers' faithfulness, controlling our purchases, maintaining and extending our skills and optimizing our activities' planning and our resources management.

Besides after the laboratory production capacity extension (50% extension) ATLANCHIM PHARMA increases its staff and will recruit Project Managers and technical assistants. This will enable us to be even more reactive towards our customers and put at their disposal our know-how and recognized expertise in custom-made chemical synthesis.

In this scientific letter, you will be up to appreciate the portrait of another chemistry-biology team and also of our Quality Assurance Manager, Isabelle ARNAUD.

ATLANCHIM PHARMA team and I wish you an enjoyable reading of this scientific letter.

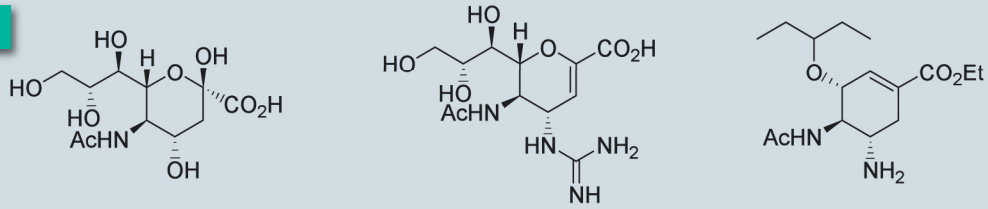
Ronan LE BOT
Director

SOMMAIRE / *SUMMARY*

Recent development in the synthesis of oseltamivir monophosphate (Tamiflu)

Influenza continues to be the most serious respiratory disease in terms of human mortality. In the past few years, the world has witnessed the emergence of two influenza A viruses: the A/H5N1 virus in 2004 and the A/H1N1 in 2009. The ability of these RNA viruses to cause infection in a wide host range (including humans, domestic animals and birds) coupled to their high capacity for genetic variation render them potential pandemic agents. Thus, the A/H1N1 virus, which is a rare recombination of gene segments from swine with avian and human influenza strains, has already spread around the world. Although vaccination is the principal way of attacking influenza and limiting its (possible) disastrous consequences, the high lethality and virulence of the A/H5N1 and A/H1N1 viruses have motivated extensive research into the field of antiviral drugs. To date, two drugs, namely zanamivir **1** and oseltamivir **2** (Scheme 1), have been shown to slow the spread of non-resistant strains of influenza viruses between cells in the body. These drugs, which are structurally related to sialic acid (*N*-acetylneuraminic acid) act as inhibitors of neuraminidase, a glycoprotein of the virus envelope implied in the spreading of new virions in host cells.

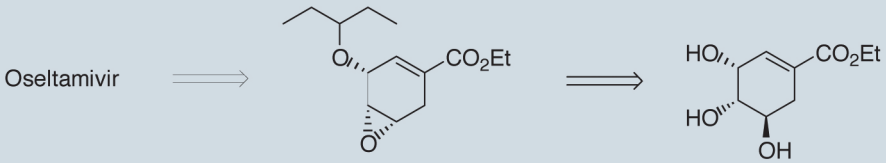
Scheme 1



Sialic acid | Zanamivir **1** (Relenza) | Oseltamivir **2** (**2**.H_3PO_4 = Tamiflu)

Discovered at Gilead Sciences and patented in 1995, the highly water-soluble oseltamivir phosphate salt, currently marketed by F. Hoffmann-La Roche Ltd under the trade name Tamiflu, has been the focus of intense research efforts, which rapidly allowed the finding and development of an industrial process. The reactional sequence features, as key intermediate, epoxide **3**, itself prepared from naturally occurring (-)-shikimic acid (Scheme 2).

Scheme 2



3 | (-)-shikimic acid

The relatively low disponibility, and consequently high cost, of (-)-shikimic acid, which is effectively isolated from Chinese star anise, may constitute the bottleneck of the F. Hoffmann-La Roche Ltd procedure in case of pandemy. Moreover, the reactional sequence is hampered by the use of potentially explosive sodium azide. Although routes to oseltamivir avoiding the use of sodium azide have been explored with success by F. Hoffmann-La Roche scientists, it does not seem that the key modifications have yet been introduced in the industrial process[1]. Next to the shikimic acid route, the last few years have witnessed an impressive growth in research to design other different pathways to oseltamivir. *The purpose of this letter is to provide the reader with a brief overview of these post-shikimic acid syntheses*[2].

Dr. André Guingant
Scientific Director
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[1] Overview of research made at F. Hoffmann-La Roche Ltd: a) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia*, **2004**, *58*, 621-629; b) Abrecht, S.; Cordon-Federspiel, M.; Estermann, H.; Fischer, R.; Karpf, M.; Mair, H-J.; Oberhauser, T.; Rimmler, G.; Trussardi, R.; Zutter, U. *Chimia,* **2007**, *61*, 93-99.

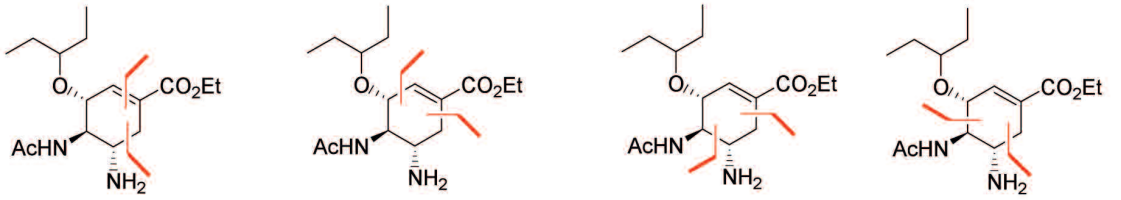
[2] Nevertheless, transformation of (-)-shikimic acid to oseltamivir has continued to attract attention: a) Nie, L-D.; Shi, X-X.; Ko, K, H.; Lu, W-D. *J. Org. Chem.* **2009**, *74*, 3970-3973; b) Nie, L-D.; Shi, X-X. *Tetrahedron: Asymmetry,* **2009**, *20*, 124-129; c) Carr, R.; Ciccone, F.; Gabel, R.; Guinn, M.; Johnston, D.; Mastriona, J.; Vandermeer, T.; Groaning, M. *Green Chem.,* **2008**, *10*, 743-745.

A. Enantioselective syntheses of oseltamivir

I. The Diels-Alder strategy

Four syntheses of oseltamivir featuring a Diels-Alder reaction to fashion the six-membered ring have been reported. These syntheses have in common the fact that the Diels-Alder reaction appears at the very beginning of the reactional sequence. As depicted in Scheme 3, the C-C bonds formed through the cycloaddition process are different, however.

Scheme 3



Hoffmann-La Roche Ltd (2004) | Corey (2006) | Fukuyama (2007) | Shibasaki (2007, 2009)

1. The Hoffmann-La Roche Ltd synthesis (2004)[1,3]

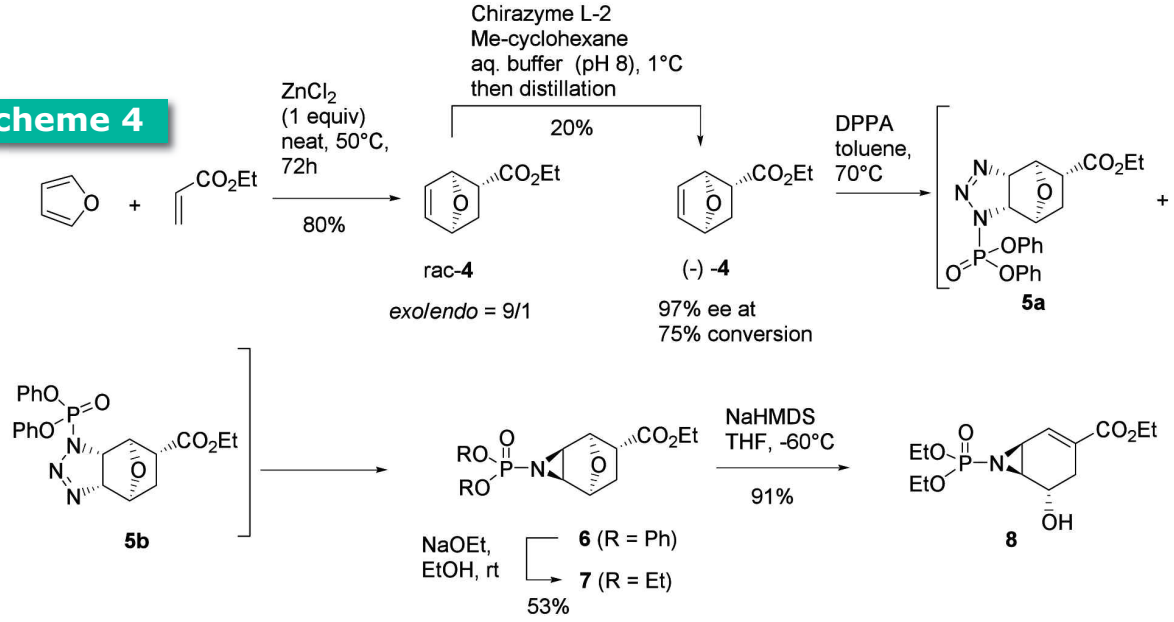
As indicated in Scheme 4, this synthesis commenced with the Lewis-acid-promoted Diels-Alder reaction between furan and ethylacrylate to give racemic **4**. Under the conditions applied, the thermodynamic *exo*-adduct was formed in excess. After considerable efforts, it was found that optical resolution of *rac*-**4** could be achieved via enantioselective ester hydrolysis using Chirazyme L-2 (Lipase B from *Candida Antarctica*). *Endo*-isomers were unaffected under the conditions applied and were subsequently removed by distillation. *Exo*-(-)-**4** was thus isolated in 20% yield and with 97% ee at 75% conversion. The next key step was the [3+2] cycloaddition of (-)-**4** with DPPA. The reaction led to a mixture of *exo*-triazoles **5a** and **5b** (ratio 2/1), which, after thermal N_2 extrusion (→ **6**) and transesterification, afforded *endo*-aziridine **7**. This unexpected (but welcome!) «inversion» was tentatively explained by establishment of an equilibrium leading to the production of small amounts of *endo*-triazoles, which may experience nitrogen extrusion at a much faster rate due to the higher steric strain. Smooth ring opening of **7** under basic conditions gave **8**, which was next transformed to **9** in two steps (mesylation and aziridine opening with 3-pentanol in the presence of BF_3-Et_2O). Unmasking of the amino group of **9** led to **10**, which was next transformed into allylamine **11** via an aziridine intermediate. Acetylation of the primary amine followed by deallylation completed this azide-free synthesis of oseltamivir phosphate.

2. Corey's synthesis (2006)[4]

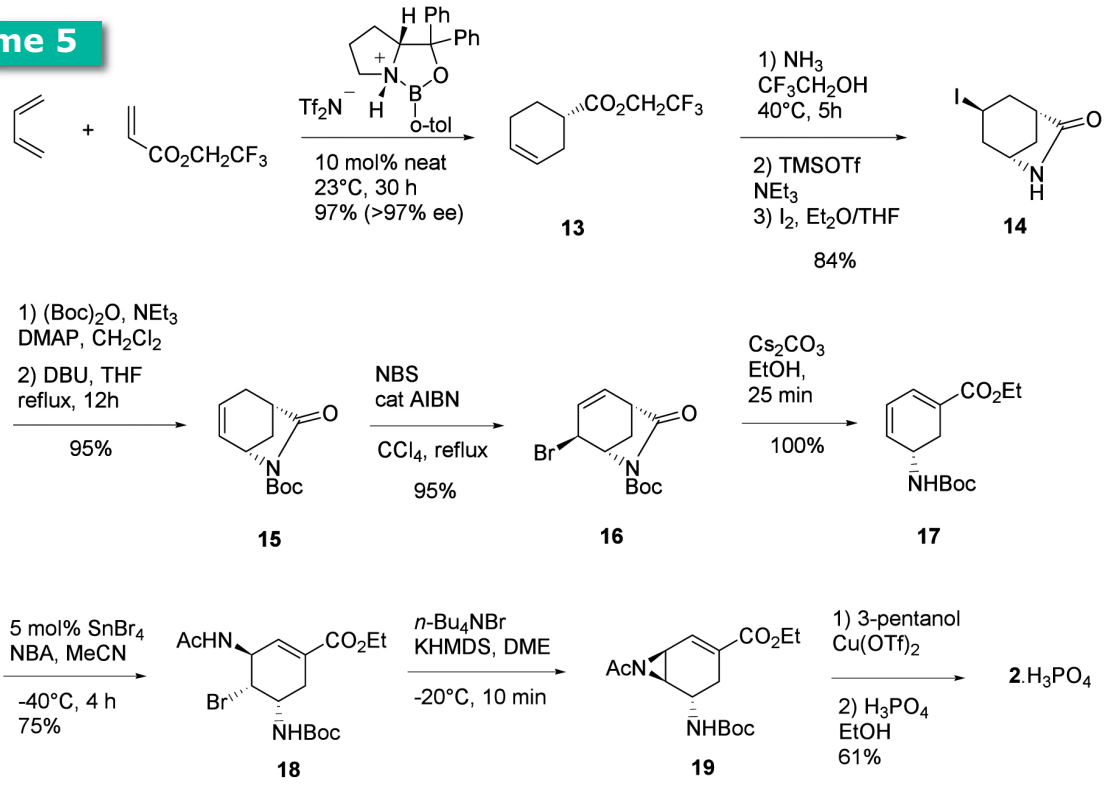
The synthesis (Scheme 5) commenced with a previously reported asymmetric Diels-Alder reaction[5] to give **13**, which was transformed in the bicyclic lactam **14** in two steps (ammonolysis and iodolactonization using the Knapp's protocol[6]). *N*-Boc protection and base-induced dehydroiodination afforded **15**, which was submitted to a regioselective allylic bromination to give **16**. Subsequent treatment of **16** with Cs_2CO_3 in ethanol afforded key diene ester **17**. Treatment of the latter diene with a complex between $SnBr_4$ and *N*-bromoacetamide[7] led to the regio- and stereoselective formation of **18** whose structure was confirmed by X-ray analysis. Cyclization of **18** gave aziridine **19**, which was subsequently transformed (two steps) into oseltamivir phosphate **2** (c.a. 30% global yield).

[3] Abrecht, S.; Karpf, M.; Trussardi, R.; Wirz, B. (F. Hoffmann La Roche AG) EP 112782-A1 (2000)
[4] Yeung, Y-Y.; Hong, S.; Corey, E. J., *J. Am. Chem. Soc.* **2006**, *128*, 6310-6311.
[5] Ryu, D. H; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388-6390.
[6] a) Knapp, S.; Rodrigues, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803-1806; b) Knapp,S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006-4014.
[7] Yeung, Y-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644-9645.

Scheme 4



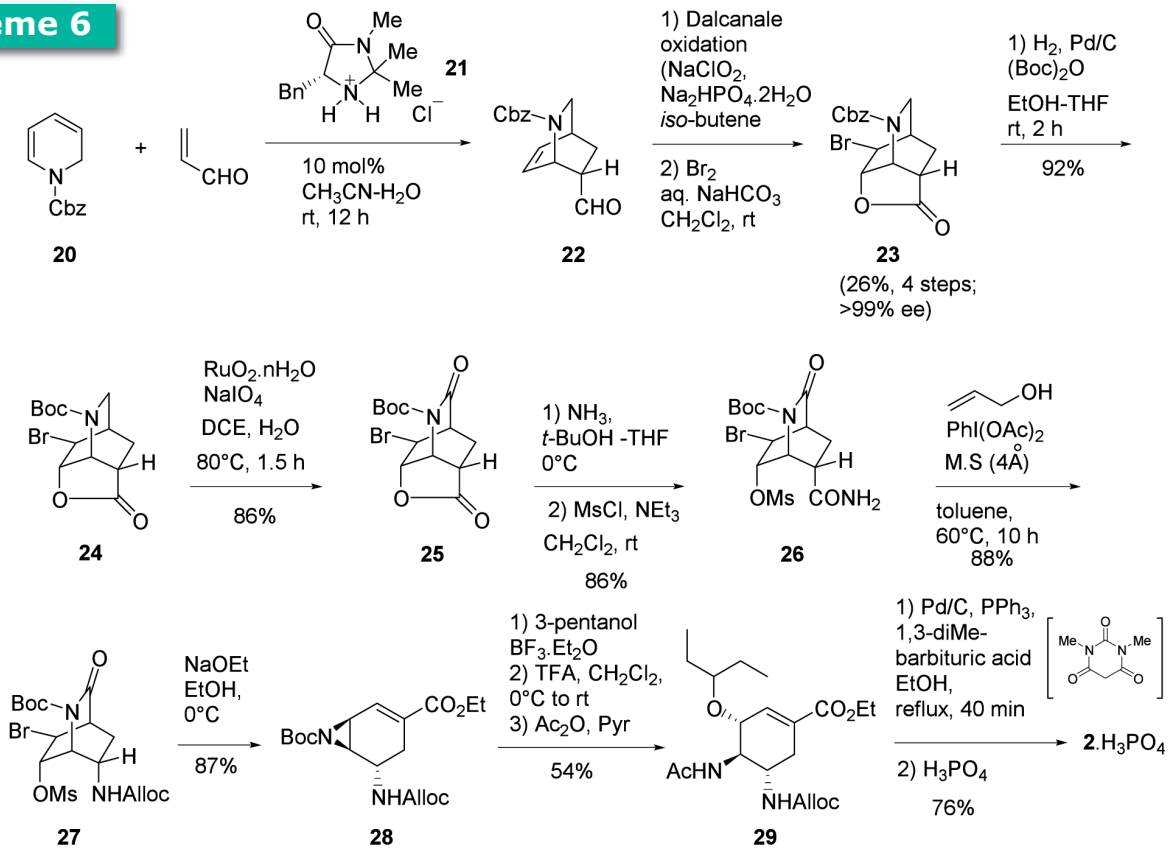
Scheme 5



3. Fukuyama's synthesis (2007)[8,9]

As shown in Scheme 6, the synthesis began with the dihydropyridine **20** (prepared from pyridine[10]) which was engaged in an asymmetric Diels-Alder reaction with acrolein in the presence of the McMillan catalyst[11] **21**. The crude resulting mixture (mainly aldehyde **22**) was transformed to bromo lactone **23** isolated in practically pure form after crystallization (>99% ee). After protecting group exchange (→ **24**) and oxidation (RuO_4), the resulting **25** was submitted to ammonolysis (lactone opening) to give an amide-alcohol, subsequently mesylated to give **26** in good overall yield. At this point, primary amide **26** was subjected to conditions of the Hoffmann rearrangement to give the *N*-Alloc amine **27**. Treatment of the latter with EtONa effected lactame opening, aziridination and dehydrobromation to give compound **28**. Finally, five steps were necessary to transform **28** into oseltamivir phosphate **2** via diprotected amine **29** (5.6% global yield).

Scheme 6

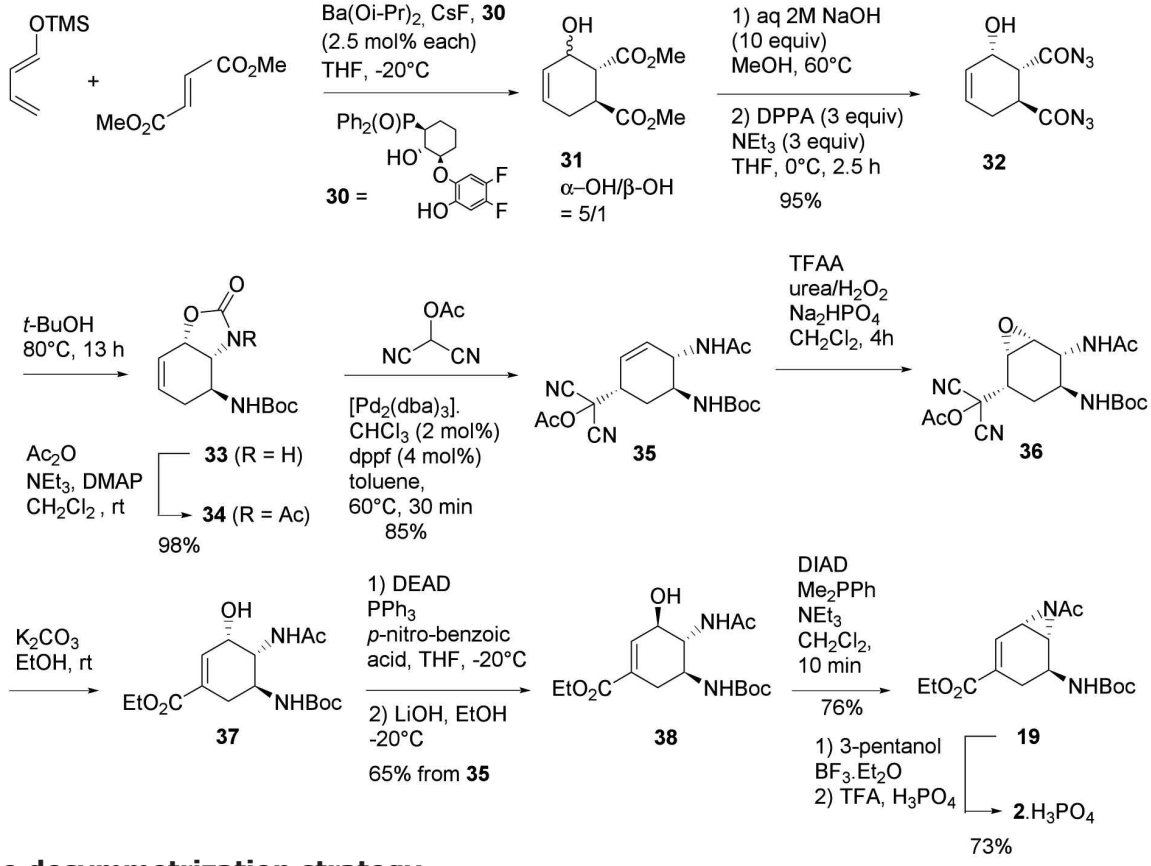


4. Shibasaki's syntheses [12,13]

The Shibasaki group reported two syntheses of oseltamivir phosphate **2** based on a Diels-Alder reaction. The second approach, which distinguishes from the first reported synthesis mainly by recourse to an asymmetric Diels-Alder reaction (instead of chiral HPLC separation of a racemic adduct) and by avoiding the use of sodium cyanide to introduce the ester functionality, will be presented here only. The synthesis started with an asymmetric Diels-Alder reaction between 1-silyloxy-1,3-butadiene and dimethyl fumarate performed in the presence of catalytic amounts of barium diisopropoxide, chiral catalyst **30** and CsF as an additive. The resulting 5/1mixture of adducts **31** was transformed into diacyl azide **32** (95% ee) in two steps (saponification and DPPA treatment). It is to note that the minor and undesired isomer (β-OH) decomposed in the course of this sequence. Subsequent Curtius rearrangement afforded oxazolidinone **33**, which was acetylated to give **34**. Regio- and stereoselective allylic substitution of **34** by treatment with acetoxymalonitrile, as a 1C-acyl anion equivalent, and a palladium source led to **35**. Acetamide-directed epoxidation (CF_3CO_3H) to give **36** followed by basic treatment (ethanolic K_2CO_3) led to unsaturated ester **37**, as the result of acetoxydicyanomethyl group to CO_2Et transformation and subsequent E2 epoxide opening. Transformation of **37** into **2** was best accomplished via aziridine **19** (cf Scheme 5). The latter was formed from **37** by a sequence of two Mitsunobu reactions (alcohol inversion to give **38** and aziridination) and next transformed into **2**.H_3PO_4 in two steps.

[8] Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734-5736.
[9] Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron*, **2009**, *65*, 3239
[10] a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321-1323; b) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836-4842.
[11] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
[12] Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M.; *Tetrahedron Lett.* **2007**, *48*, 1403-1406.
[13] Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibazaki, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1070-1076.

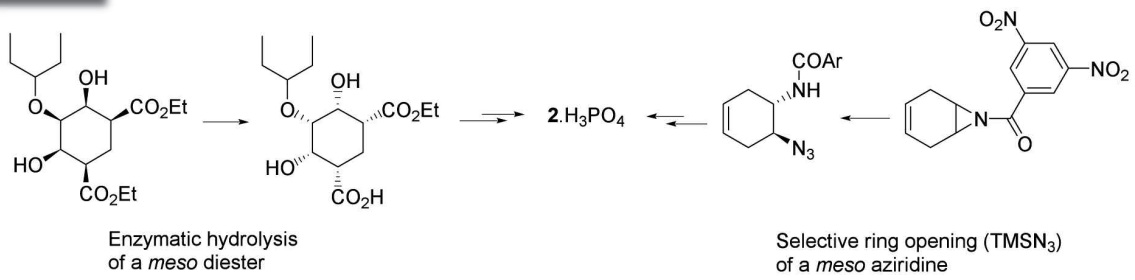
Scheme 7



II. The desymmetrization strategy

Two syntheses of oseltamivir phosphate featuring a desymmetrization reaction have been reported. Enzymatic hydrolysis of a *meso* diester on one hand and a selective opening of a *meso* aziridine on the other one are the key steps of these syntheses.

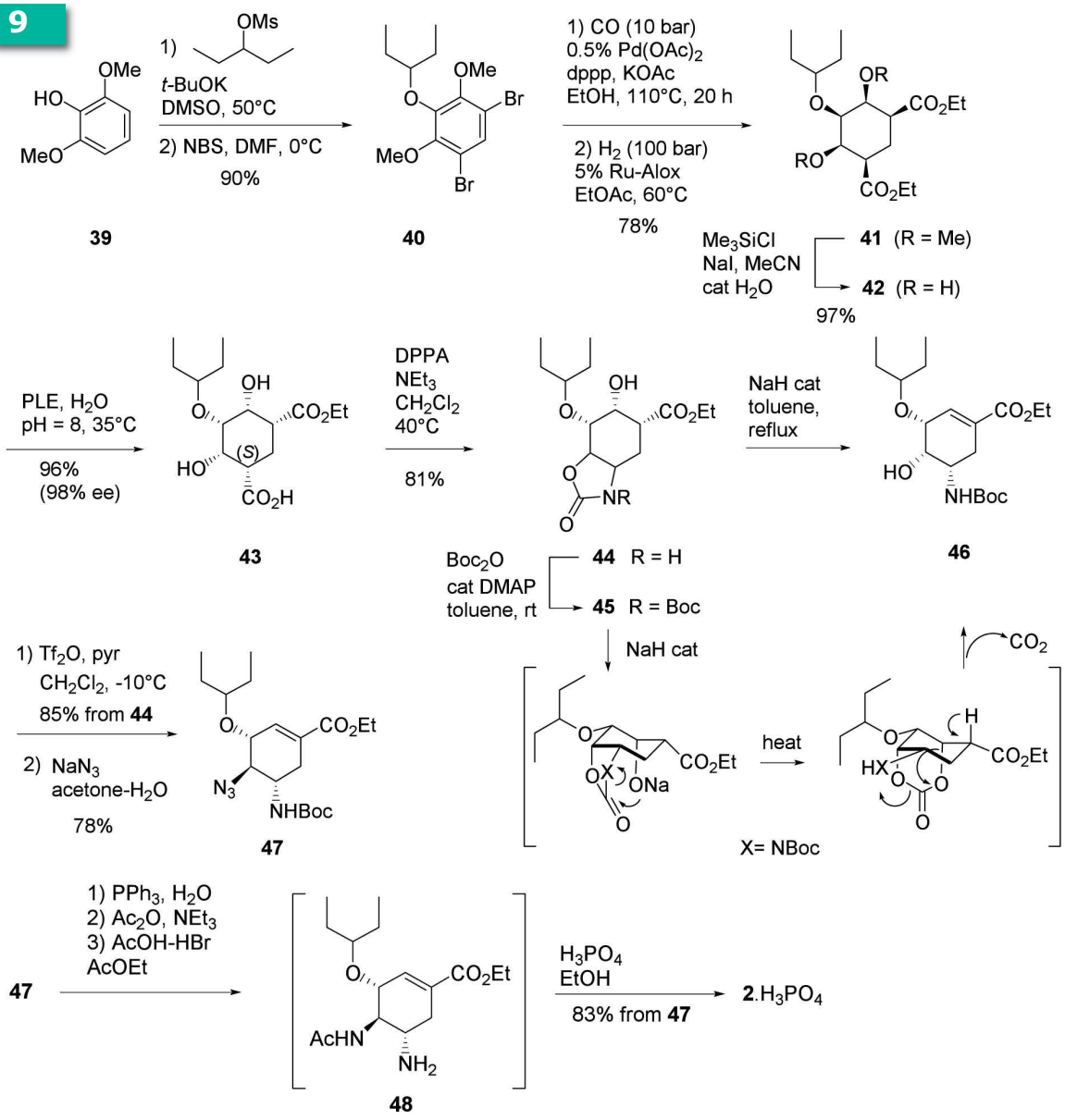
Scheme 8



1. The F. Hoffmann-La Roche Ltd synthesis (2004, 2008)[1, 3]

This synthesis commenced with etherification of the cheap and commercially available 2,6-dimethoxyphenol **39** with 3-pentyl mesylate followed by a bromination step to give **40** (Scheme 9). A succession of reactions featuring ethoxycarbonylation, *cis*-hydrogenation (→ **41**) and OMe deprotection then afforded *meso* diester **42** in good overall yield. At this stage, the key enantioselective hydrolysis of **42** was best effected by PLE to give (*S*)-monoacid **43** with high ee. This desymmetrization step was followed by a Curtius reaction to give a crystalline oxazolidinone **44**, next *N*-protected to give **45**. Treatment of crude **45** with a catalytic amount of NaH in refluxing toluene effected an interesting selective transformation leading to the advanced intermediate **46** following the mechanism shown in Scheme 8. After triflatation of the crude **46**, azide substitution of the resulting crystalline tosylate substrate led to **47** with complete inversion of configuration. Sequential azide reduction, primary amine acetylation and *N*-Boc removal then transformed **47** to the free amine **48**. Finally, salt formation completed the synthesis of oseltamivir phosphate **2**, which was achieved in an overall yield of c.a. 30%.

Scheme 9

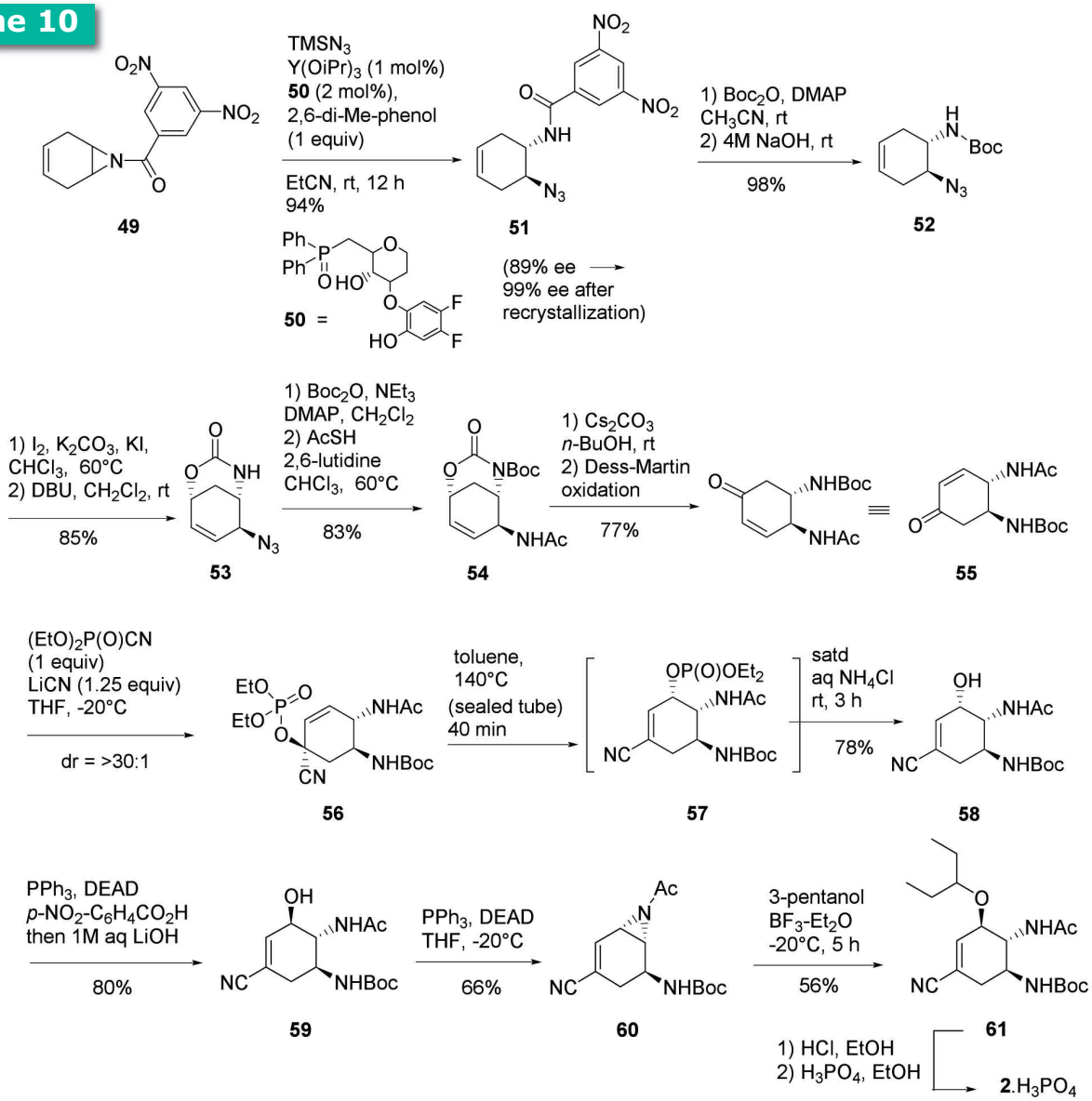


2. Shibasaki's synthesis (2006, 2007)[14,15]

In this approach to **2**, the desymmetrization step took place advantageously at the very beginning of the reactional sequence. Thus, under the selected conditions, *meso* aziridine **49** was enantioselectively opened (conditions shown in Scheme 10) to give azide **51** in excellent yield and ee (transformation performed in up to 30g). After protecting group exchange to give **52**, the latter compound was subjected to iodocyclization and the resulting iodo carbamate was dehydroiodated to provide **53**. *N*-Boc protection and reductive acylation of the azide functionality led to urethane **54**, which was next transformed to enone **55** through urethane opening and alcohol oxidation. At this stage, stereoselective cyanophosphorylation of **55** afforded cyanophosphate **56**, which was submitted to a key allylic rearrangement to give **58** after hydrolysis of the presumed allylic phosphate intermediate **57**. Transformation of **58** into aziridine **59** was next accomplished by recourse to two Mitsunobu reactions (OH inversion and aziridination). Finally, the synthesis of **2** was completed in a few additional steps involving Lewis acid-catalysed aziridine opening by 3-pentanol, ethanolysis of the cyanide function, *N*-Boc deprotection and salt formation.

[14] Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am.Chem. Soc.* **2006**, *128*, 6312-6313.
[15] Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259-262.

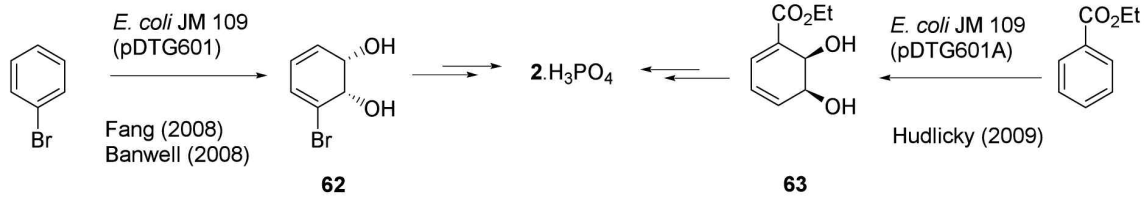
Scheme 10



III. Chemoenzymatic approaches to 2

Three chemoenzymatic syntheses of oseltamivir phosphate have been reported in the recent literature. They exploit the potentialities of enantiomerically pure *cis*-1,2-dihydrodiols **62** and **63**, which can be produced on medium or large scale by microbial oxidation[16]. Compound **62** is also commercially available.

Scheme 11

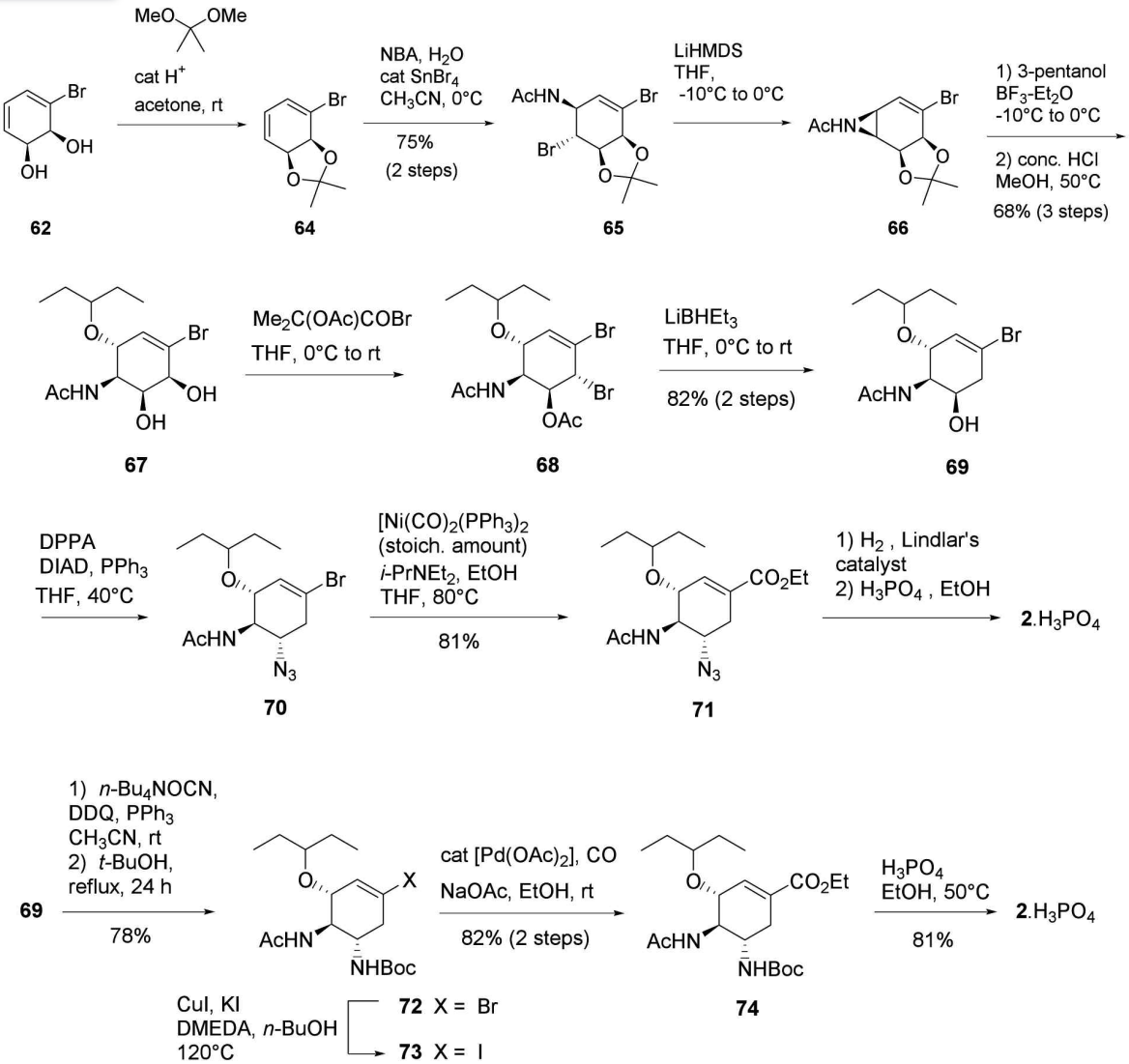


[16] See, inter al. Endoma, M. A.; Bui, V. P.; Hansen, J.; Hudlicky, T. *Org. Process Res. Dev.* **2002**, *6*, 525-532.

1. The Fang synthesis (2008)[17]

As illustrated in Scheme 12, the synthesis commenced with diol protection of **62** (→ **64**) and subsequent regioselective bromoamidation[7] to give the dibromo compound **65** (75%). After aziridination (→ **66**), aziridine opening by 3-pentanol (BF_3-Et_2O) and acetal hydrolysis, the resulting diol **67** was submitted to the action of α-acetoxyisobutyryl bromide[18] to afford the sole cyclohexenyl derivative **68**. Treatment of **68** with super hydride effected both C(sp_3)-Br and OAc reduction to give alcohol **69** next transformed in azido compound **70** under the action of DPPA. Nickel promoted-ethoxycarbonylation of **70** then allowed introduction of the ester functionality to give **71**, which was transformed to **2** by way of conventional reactions. In another approach to **2**, alcohol **69** was transformed to carbamate **72** via an isocycanate intermediate. After conversion of **72** into its more reactive iodide analogue **73**, installation of the diethylester function was achieved by palladium-catalyzed carbonylation to give **74** in good yield. Final transformation of **74** into oseltamivir phosphate **2** was achieved in a one pot operation through the action of H_3PO_4. This alternate transformation of alcohol **69**, which constitutes an azide-free route to **2**, and also avoids the use of stoichiometric amount of a toxic nickel complex, represents a significant improvement over the first studied process.

Scheme 12



[17] Shie, J-J.; Fang, J-M.; Wong, C-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5788-5791.
[18] For a possible mechanism of this reaction, see: Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016-4025.

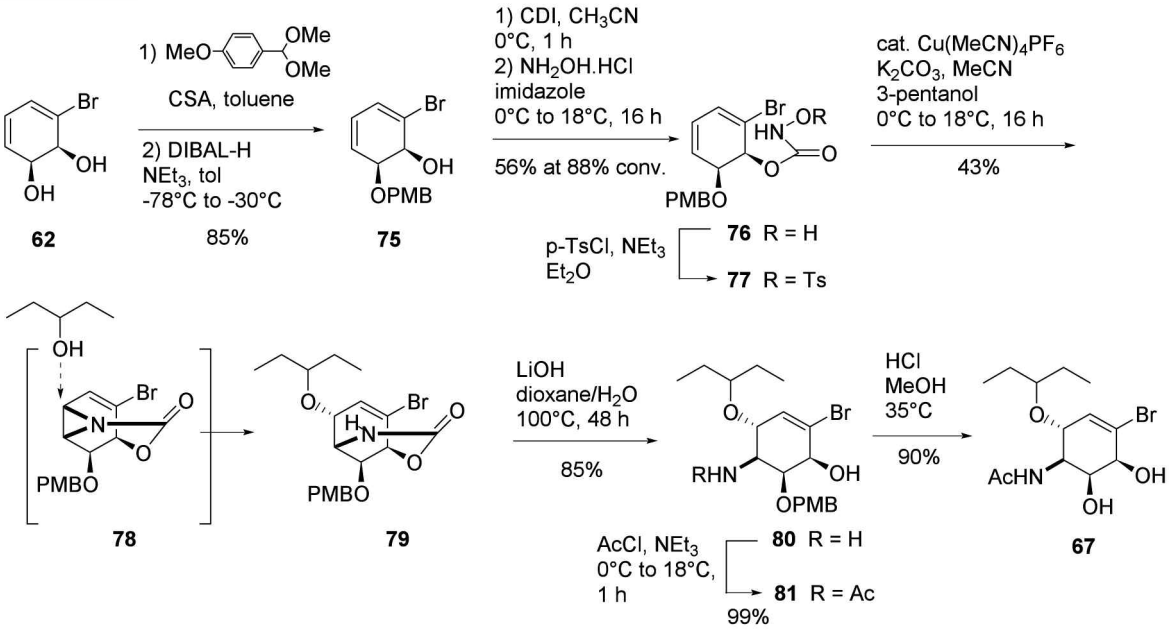
2. The Banwell synthesis (2008)[19]

At the beginning of the synthesis (Scheme 13) the 1,2-diol function of **62** was protected under the form of a PMP acetal, which was next regioselectively opened under reductive conditions to give the PMB-ether **75**, along with its regioisomer as a 6:1 unseparable mixture. Successive treatment of **75** with CDI then hydroxylamine afforded, at 88% conversion, a separable mixture of *N*-hydroxycarbamate **76** (56%) and unreacted PMB-ether (minor isomer in the initial mixture). The crystalline **76** was then tosylated and the resulting **77** subjected to aziridine formation by copper-catalyzed intramolecular nitrene addition[20] to the disubstituted double bond. The highly constrained aziridine **78** was not isolated but immediately intercepted by 3-pentanol to afford carbamate **79**, whose further treatment with aq. lithine led to the amino alcohol **80**. The next two operations, i.e. *N*-acylation (→ **81**) and PMB deprotection (HCl, MeOH), led to the Fang's intermediate **67** (Scheme 12), thus achieving a formal synthesis of oseltamivir phosphate **2**.

3. The Hudlicky synthesis (2009)[21]

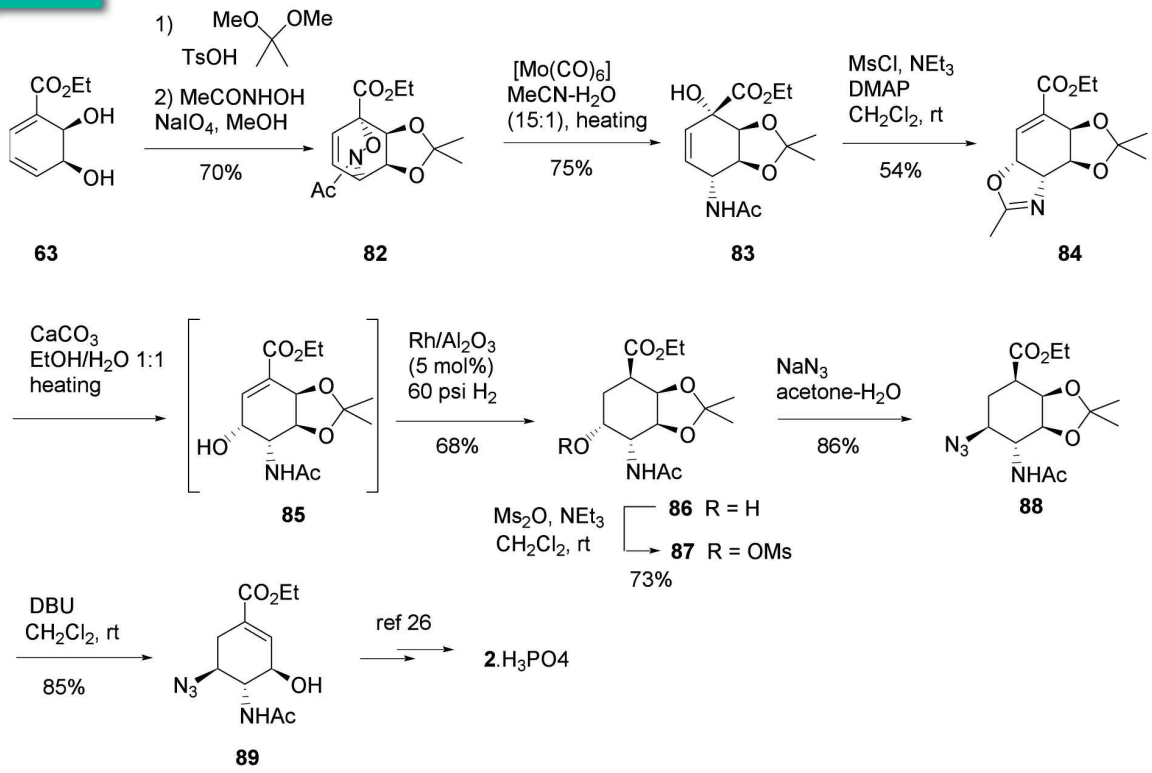
As depicted in Scheme 14, the synthesis began with protection of the diol of **63** as an acetonide followed by an inverse electron-demand Diels-Alder reaction involving an *in situ* prepared acyl nitroso dienophile. Subsequent reduction of the N-O bond of the resulting adduct **82** led to tertiary alcohol **83**, which, under the action of methanesulfonyl chloride, afforded the bicyclic oxazoline **84** through an intramolecular SN2′ displacement of an allylic mesylate intermediate. Opening of the oxazoline ring in basic conditions gave rise to **85**, which, without isolation, was stereoselectively hydrogenated to provide alcohol **86**, next mesylated to give **87**. Displacement of the mesylate of **87** with sodium azide to give **88** and final installation of the double bond through a base-induced β-elimination reaction afforded the Fang's intermediate **89** (vide infra, B.1, Scheme 18 and also reference 26) and completed a formal synthesis of **2**.

Scheme 13



[19] Matveenko, M.; Willis, A. C.; Banwell, M. G. *Tetrahedron Lett.* **2008**, *49*, 7018-7020.
[20] Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587-5591.
[21] Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 4229-4231.

Scheme 14



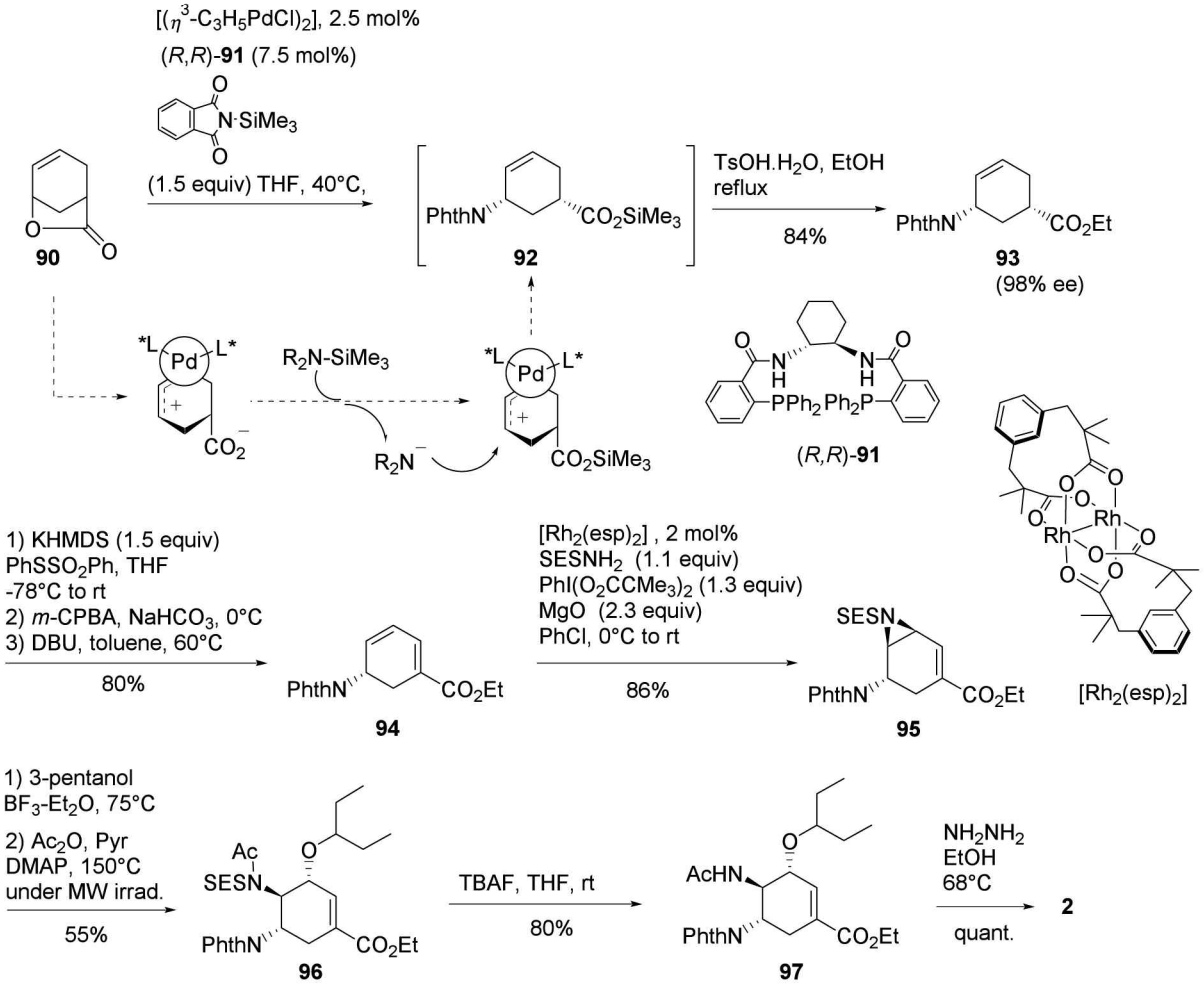
IV. Other enantioselective routes

1. Asymmetric ring opening of a lactone (Trost and Zhang, 2008)[22]

Trost and Zhang reported an original synthesis of oseltamivir featuring the deracemization of a *cis*-bicyclic lactone through the use of a palladium-catalyzed asymmetric allylic alkylation reaction (Scheme 15). Thus, reaction of lactone **90** with *N*-TMS-phtalimide in the presence of $[(\eta^3\text{-}C_3H_5PdCl)_2]$ and chiral ligand **91** afforded amino silylester **92**, which, without isolation, was transformed into the amino ethylester **93** in 84% yield and 98% ee. Three synthetic operations, i.e. sulfenylation, sulfide to sulfoxide oxidation and thermal elimination were next necessary to transform **93** into 1,3-diene **94** (isolated with a small amount of 1,4-diene). At this stage, direct aziridination of **94** proved to be unexpectably difficult, mainly because usual conditions (use of a copper catalyst to generate the nitrene species) were inoperent. After some considerable trials, the authors finally discovered that selective formation of **95** could be effectively accomplished (86%) by recourse to a recently reported bis-rhodium catalyst[23], $[Rh_2(esp)_2]$, in the presence of $PhI(O_2CCMe_3)_2$ and $SESNH_2$ $[Me_3Si\text{-}(CH_2)_2\text{-}SO_2NH_2]$ as the nitrene source. Straightforward transformation of **95** into oseltamivir was next readily accomplished. Thus, opening of **95** with 3-pentanol and subsequent *N*-acylation provided compound **96**, which was now readily bis-deprotected under the sequential action of TBAF (→ **97**) and hydrazine to afford **2**.

[22] Trost, B. M.; Zhang, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 3759-3761.
[23] This catalyst was originally designed to effect C-H insertion reactions a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378-15379 ; b) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562-568.

Scheme 15



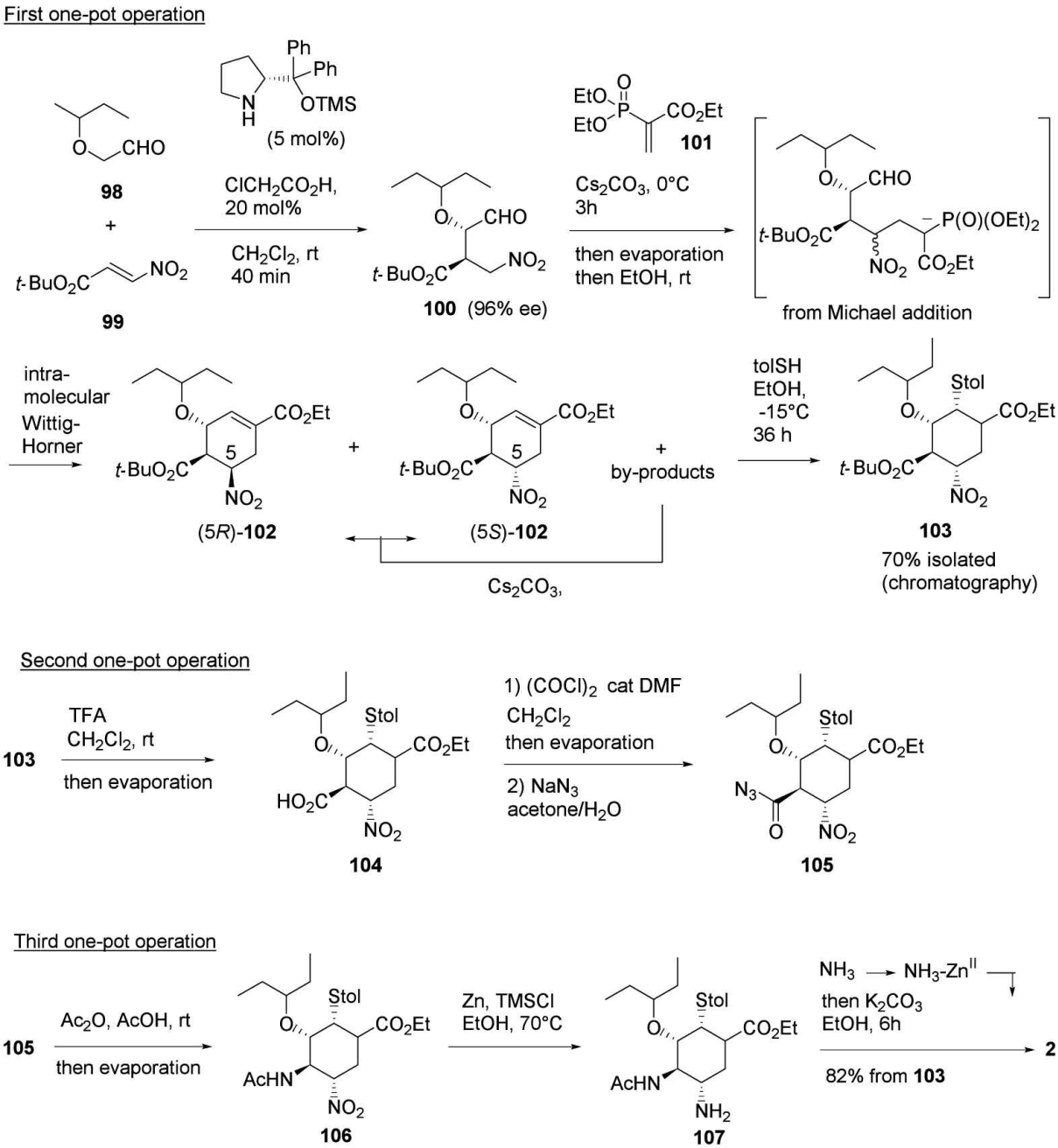
2. The asymmetric Michael strategy (Hayashi et al., 2009)[24]

Hayashi and colleagues reported a synthesis of **2** based on an asymmetric Michael addition of an *in situ* generated chiral enamine onto an unsaturated nitro compounds. The other main characteristics of the synthesis are its achievement in three one-pot operations and the use of domino reactions, in particular for constructing a highly functionalized six-membered ring (Scheme 16). The first set of one-pot reactions commenced with the diphenylprolinol silyl ether-organocatalyzed Michael reaction between aldehyde **98** and nitroethylenic **99** to give nitro aldehyde **100** in excellent ee. The latter, in the presence of the vinylphosphonate **101** and Cs_2CO_3, led to two isomeric cyclohexene derivatives, (5*R*)-**102** and (5*S*)-**102** (ratio 5 : 1), as the result of consecutive Michael and intramolecular Wittig-Horner reactions. In fact, it was demonstrated that compounds **102** were initially formed along with two by-products (a hydroxyphosphonate and the Michael addition product of **102** onto **101**) and that both of these by-products evolved toward compounds **102** under the influence of Cs_2CO_3. Finally, the fact that (5*R*)-**102** was the major and undesired isomer formed could be circumvented by treatment of the mixture of **102** with tolSH, which afforded the sole Michael addition product (5*S*)-**103**. When the above sequence of reactions was effected in a one-pot manner, **103** was isolated in 70% global yield after chromatographic purification.

[24] Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 1304-1307.

The second one-pot operation features hydrolysis of the *tert*-butyl ester of **103** to acid **104** and transformation of the latter to acyl azide **105** via an acid chloride derivative. Compound **105** was then, without further purification, engaged in the third one-pot operation. Curtius rearrangement of **105** followed by amide formation was effected in smooth conditions to give **106**. The nitro group of **106** was next reduced (→ **107**) and, after formation of a Zn^{II}-NH_3 complex, addition of K_2CO_3 promoted the retro-Michael reaction of tolSH to give the target **2** in 82% from **103**. On the whole, this synthesis required 9 steps and was achieved in 57% overall yield.

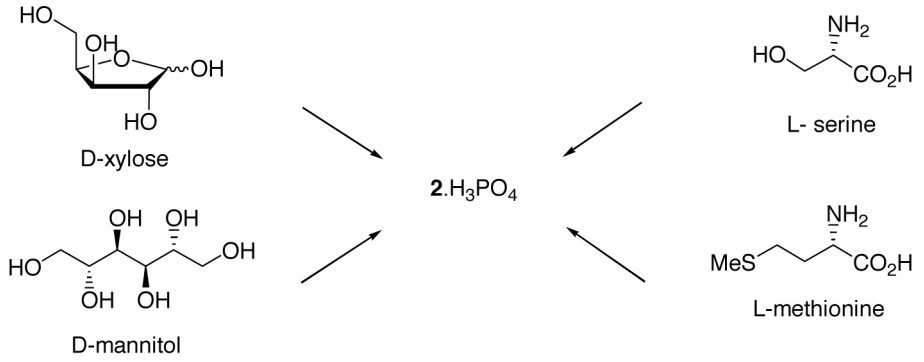
Scheme 16



B. Syntheses of oseltamivir from the chiral pool

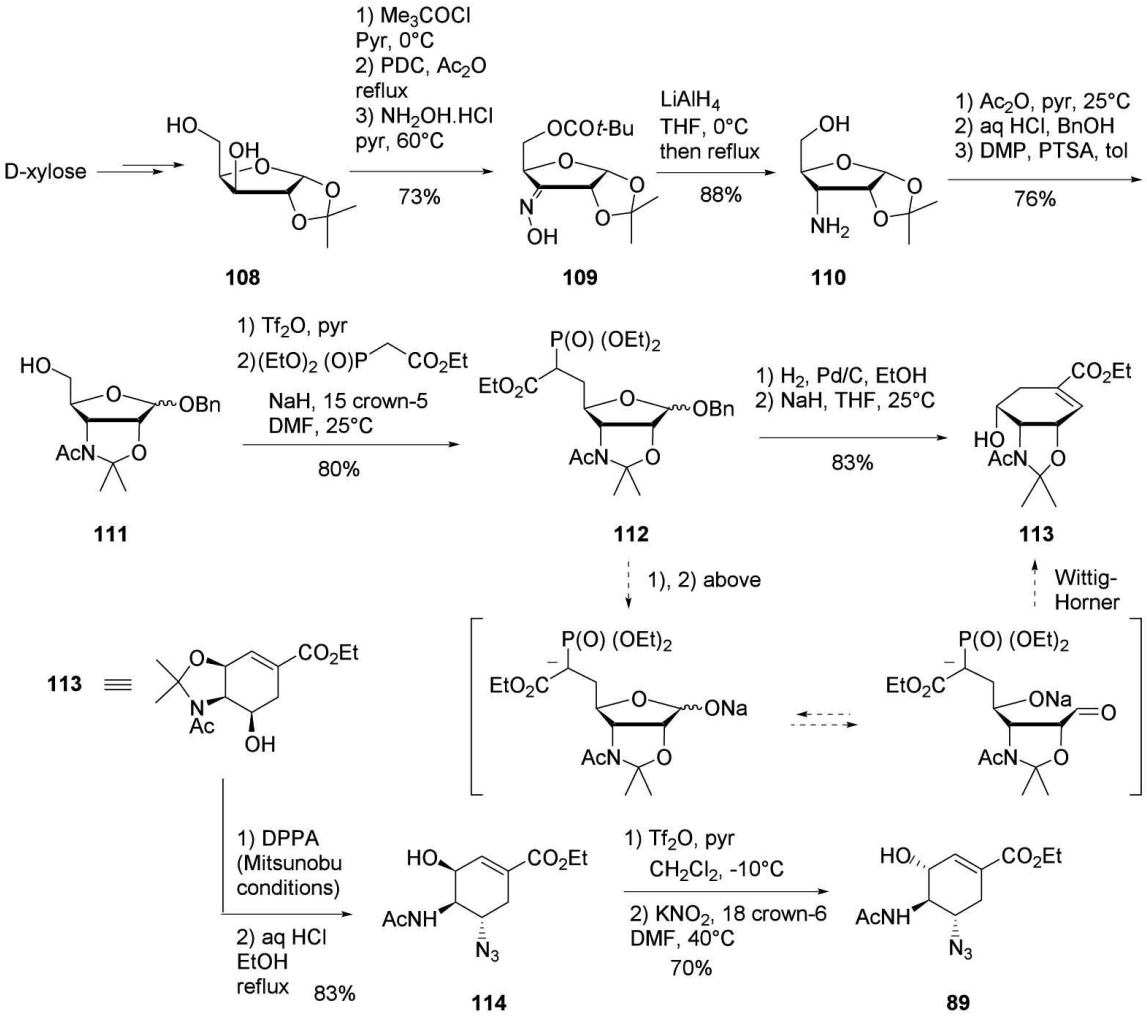
In addition to approaches from shikimic acid, four syntheses of oseltamivir using a chiral precursor derived from nature's chiral pool have been reported[25]. In all of them, the six-membered ring of **2** has to be elaborated from an acyclic precursor and this has been accomplished through the use of Wittig-Horner, aldol condensation and RCM reactions.

Scheme 17



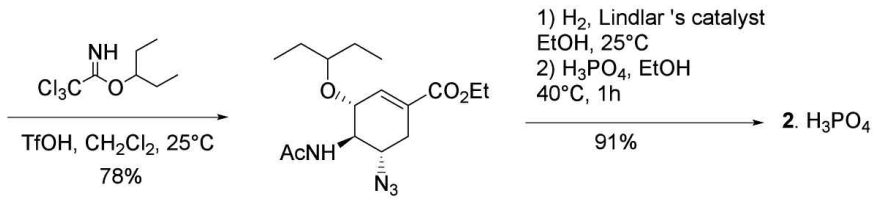
Scheme 18

1. Synthesis from D-xylose (Fang et al. 2007)[26]



[25] A synthesis of **2** starting from (*D*)-glucose has been released on the net : Available from Nature Precedings at <http://hdl.handle.net/10101/npre.2009.3351.1> (2009)

[26] Shie, J-J.; Fang, J-M.; Wang, S-Y.; Tsai, K-C.; Cheng, Y-S, E.; Yang, A-S.; Hsiao, S-C.; Su, C-Y.; Wong, C-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892-11893.



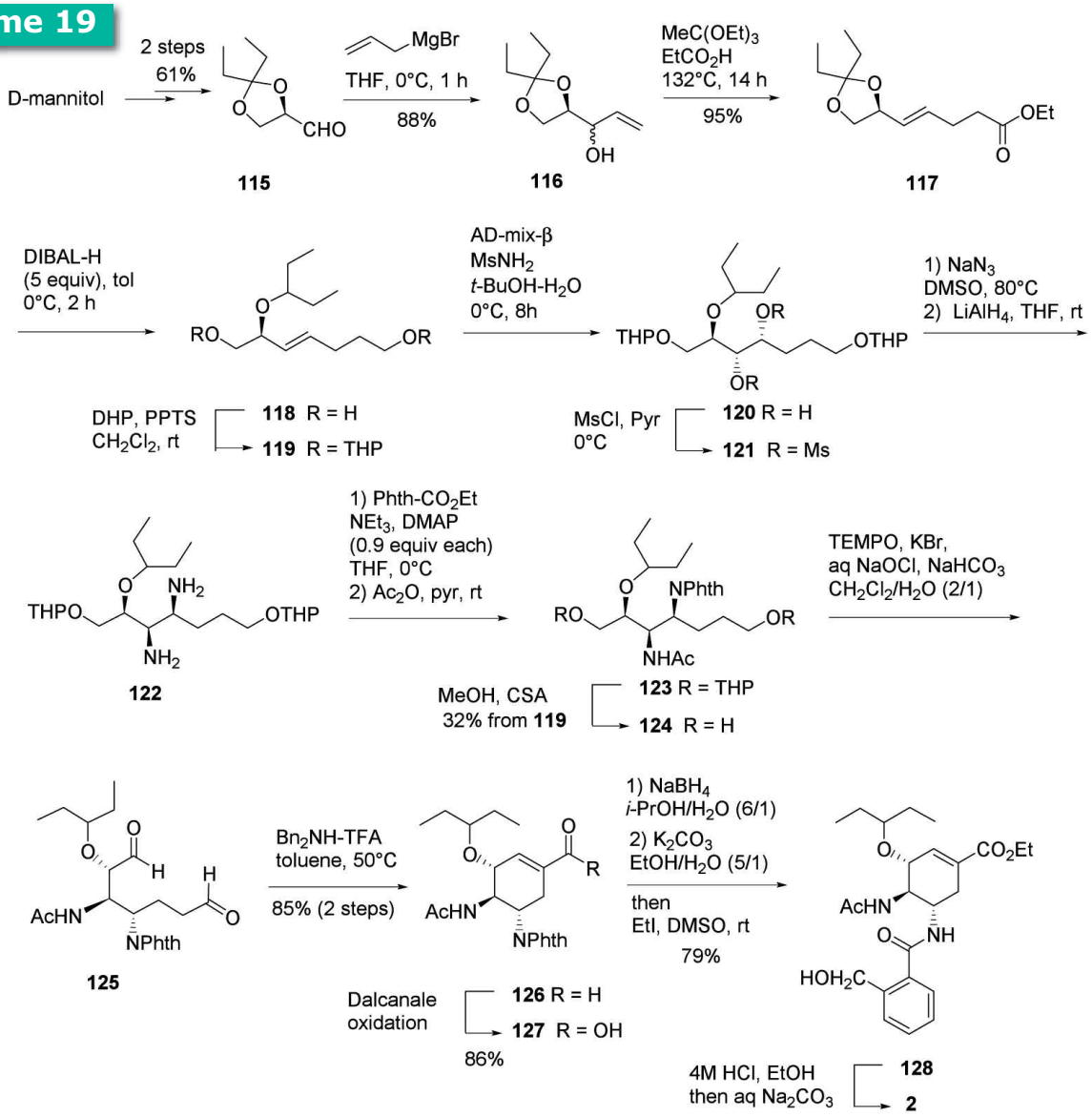
D-xylose monoacetonide **108** (Scheme 18) was first transformed to oxime **109** via a three-step procedure. After reduction of **109** to amino alcohol **110**, amine protection, acetal hydrolysis with concominant benzyle protection at the anomeric center, and amino-(secondary) alcohol protection afforded the primary alcohol **111**. At this stage, the triflate derived from alcohol **111** was submitted to the action of the sodium anion of ethyl diethylphosphonoacetate to afford the key intermediate **112**. After benzyl deprotection, treatment of the resulting alcohol with NaH afforded cyclohexenol **113** through an intramolecular Wittig-Horner reaction. Transformation of **113** into azido-alcohol **114** was next accomplished in two steps, without recourse to the use of sodium azide. Thus, treatment of **113** with DPPA under Mitsunobu conditions (OH → N_3 with inversion of configuration), followed by hydrolysis of oxazoline ring, afforded **114** in good yield. At this stage, and before introducing the pentyloxy group, it was necessary to inverse the configuration of the alcohol of **114**. This was best accomplished in two steps with recourse to the method of Moriarty[27]. The resulting alcohol **89** (cf Scheme 14) was then etherified by reaction with 3-pentyl trichloroacetamidate to give **71** (cf Scheme 12). Finally, reduction of the azide of **71** and salt formation led to **2**.

2. Synthesis from D-mannitol (Mandai et al. 2009)[28]

This synthesis (Scheme 19) commenced with the reaction of allylmagnesium bromide onto aldehyde **115** derived from D-mannitol following an already reported procedure[29]. The resulting alcohols **116** (mixture of diastereomers) were submitted to the conditions of the Claisen-Johnson rearrangement to give the γ,δ-unsaturated ester **117** as the only isomer. Treatment of **117** with DIBAL-H in excess effected both ester reduction and regioselective acetal cleavage to give alcohol **118** as the predominent isomer (10:1). After alcohol protection to give THP ether **119**, the latter was *cis*-dihydroxylated under the conditions of the Sharpless reaction to give diol **120**, next bis-mesylated to **121**. Bis-substitution of the mesylates of **121** by sodium azide and hydride reduction of the resulting bis-azide compound afforded diamino derivative **122**. At this stage, treatment of **122** with *N*-ethoxycarbonylphthalimide (0.9 equiv) effected highly regioselective protection of one amino group, leaving the second free for subsequent acetyl protection. The O-THP groups of the resulting bis-protected diamine **123** were then deprotected and the unmasked dialcohol **124** next cleanly oxidized to key dialdehyde **125** using the Anelli-Montanari conditions[30]. Elaboration of the six-membered ring was then accomplished via an intramolecular aldol condensation (enamine intermediate) to give unsaturated aldehyde **126**, further oxidized to the corresponding acid **127** under the conditions of Dalcanale. Sequential reductive opening of the phthalimido group to an amide, esterification of the acid group (to give **128**) and acidic treatment (amide hydrolysis) achieved the synthesis of **2** (18 steps). It should be mentioned that no chromatographic purification was required throughout the all process.

[27] Moriarty, R.M.; Zhuang, H.; Penmasta, R.; Liu, K.; Awasthi, A.K.; Tuladhar, S.M.; Rao, M.S.C.; Singf, V.K. *Tetrahedron Lett.* **1993**, 8029-8032.
[28] Mandai, T.; Oshitari, T. *Synlett*, **2009**, 783-786.
[29] Schmid, C. R.; Bradley, D.A. *Synthesis*, **1992**, 587-589.
[30] Anelli, P-L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559-2562.

Scheme 19



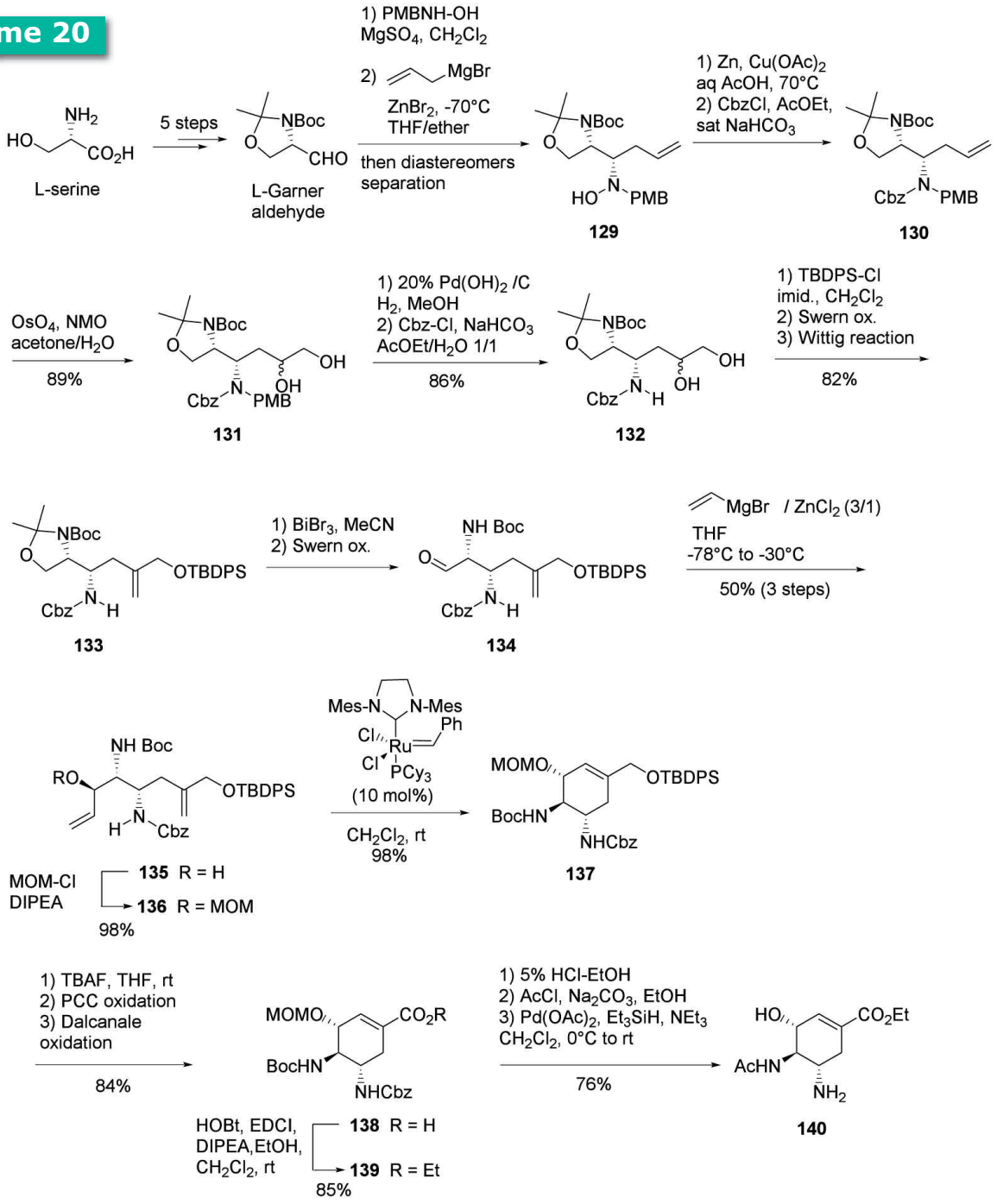
3. Synthesis from L-serine (Cong and Yao, 2006) [31]

The Chinese researchers reported the synthesis of the functionalized cyclohexenol **140**. Although its transformation to **2** was not reported, we have included their work in this review[32].

At the beginning of this synthesis, the L-Garner aldehyde (prepared from L-serine) was transformed to the bis-protected amine **129** following a sequence already reported by the same group[33]. Reduction of the hydroxylamine function of **129** and *N*-Cbz protection of the resulting secondary amine led to diamine **130**. Osmylation of the latter afforded a mixture of diastereomeric diols **131**, which, after a sequence of bis-deprotection and mono-reprotection of the non cyclic amine, afforded the amino diol **132**. After a series of three standard reactions, **132** was then transformed to silyl-protected allylic alcohol **133**, the *N*,*O*-acetal group of which was deprotected to reveal a terminal primary alcohol next oxidized (Swern) to aldehyde **134**. Action of vinylmagnesium bromide on **134** in the presence of a Lewis acid ($ZnCl_2$) led to the major formation of alcohol **135**, which was subsequently protected as a MOM ether (**136**). Elaboration of the six-membered ring occurred at the next step under the action of the 2nd generation Grubbs catalyst to give **137** in almost quantitative yield. **137** was then transformed to acid **138** in a three-step sequence, the latter being subsequently esterified to give ethyl ester **139**. Transformation of **139** into cyclohexenol **140** was achieved after *O*-MOM and *N*-Boc deprotection, *N*-acetylation and $Pd(OAc)_2$-catalyzed *N*-Cbz deprotection.

[31] Cong, X.; Yao, Z-J. *J. Org. Chem.* **2006**, *71*, 5365-5368.
[32] Later on, Shibazaki et al. reported the transformation of (NHBoc)-**140** (i.e. NHBoc instead of NH_2 in **140**) to **2** via an aziridine intermediate (cf ref. 12).
[33] Cong, X.; Liao, Q-J. ; Yao, Z-J. *J. Org. Chem.* **2004**, *69*, 5314-5321.

Scheme 20



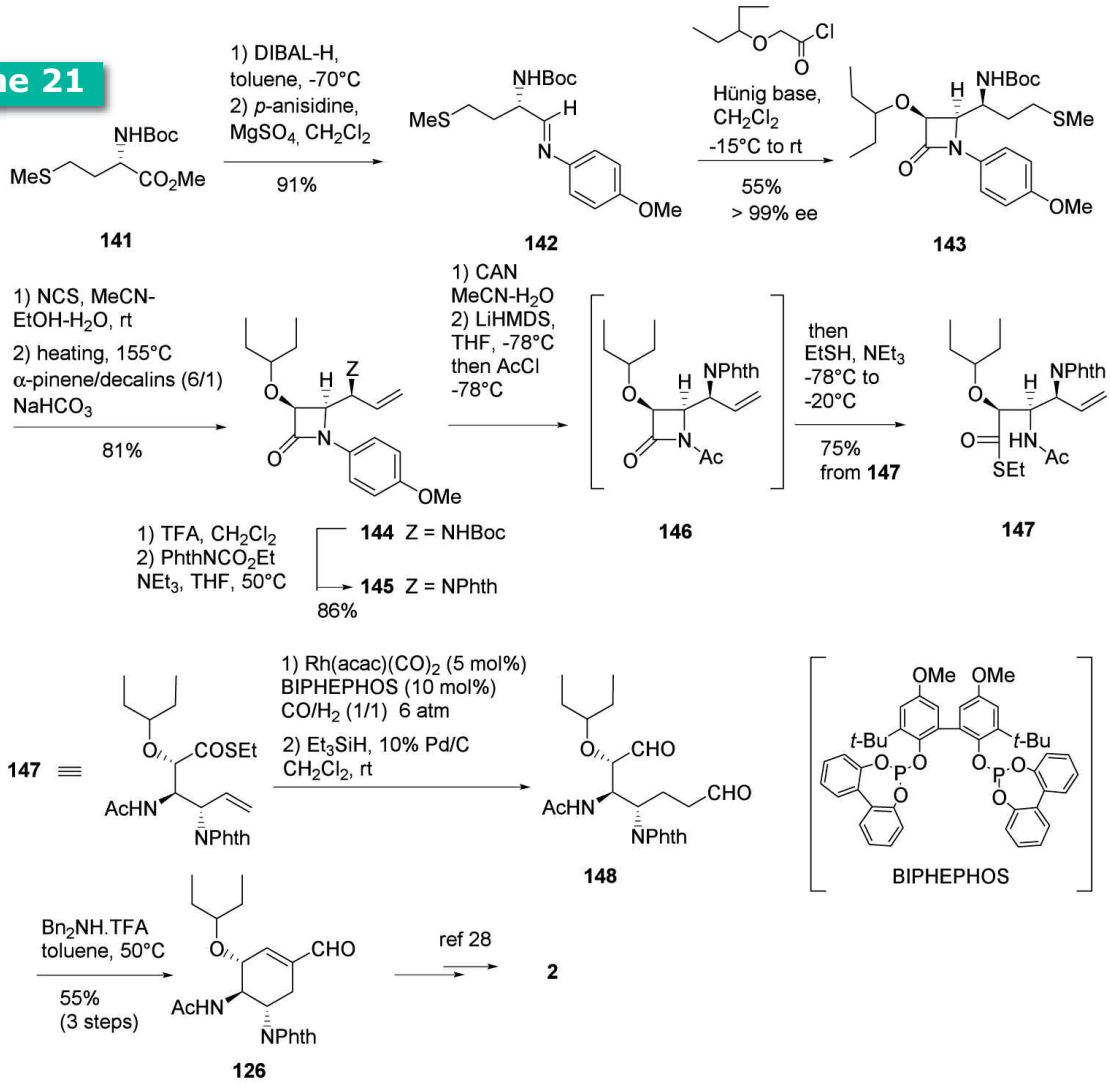
4. Synthesis from L-methionine (Mandai, 2009)[34]

In addition to their synthesis of oseltamivir from L-serine, Oshitari and Mandai disclosed an azide-free synthesis of **2** starting from L-methionine (Scheme 21). A key intermediate of their synthesis was the β-lactam **143** prepared through the following sequence of reaction. DIBAL-H reduction of the *N*-Boc protected methionine methyl ester **141** gave an aldehyde next transformed to an imine **142** by reaction with para-anisidine. This imine was then reacted with the ketene generated *in situ* through the action of Hünig base on 3-pentyloxyacetyl chloride (obtained in two steps from 3-pentanol) to give, following a [2+2] cycloaddition process, the cis-β-lactam **143** (ee > 99%).

[34] Oshitary, T.; Mandai, T. *Synlett*, **2009**, 787-789.

Transformation of the sulfide substituent of **143** into a sulfoxide via a halosulfonium intermediate, followed by heating to effect desulfinylation, led to β-lactam **144**, in which the acidic sensitive *N*-Boc protecting group was replaced (two steps) by a more robust *N*-Phth group (→ **145**). Oxidative cleavage of the para-methoxyphenyl group of **145** followed by reprotection (acetylation) of the β-lactam nitrogen led to **146**, which, without isolation, was cleaved with an excess of EtSH and triethylamine to give thioester **147**. Regioselective hydroformylation of the double bond of **147** followed by reduction of the thioester group using the Fukuyama's protocol[35] afforded the key dialdehyde **148**, which was transformed to **2** via aldehyde **126** according to a sequence of reactions already reported by the same authors (cf B.2).

Scheme 21



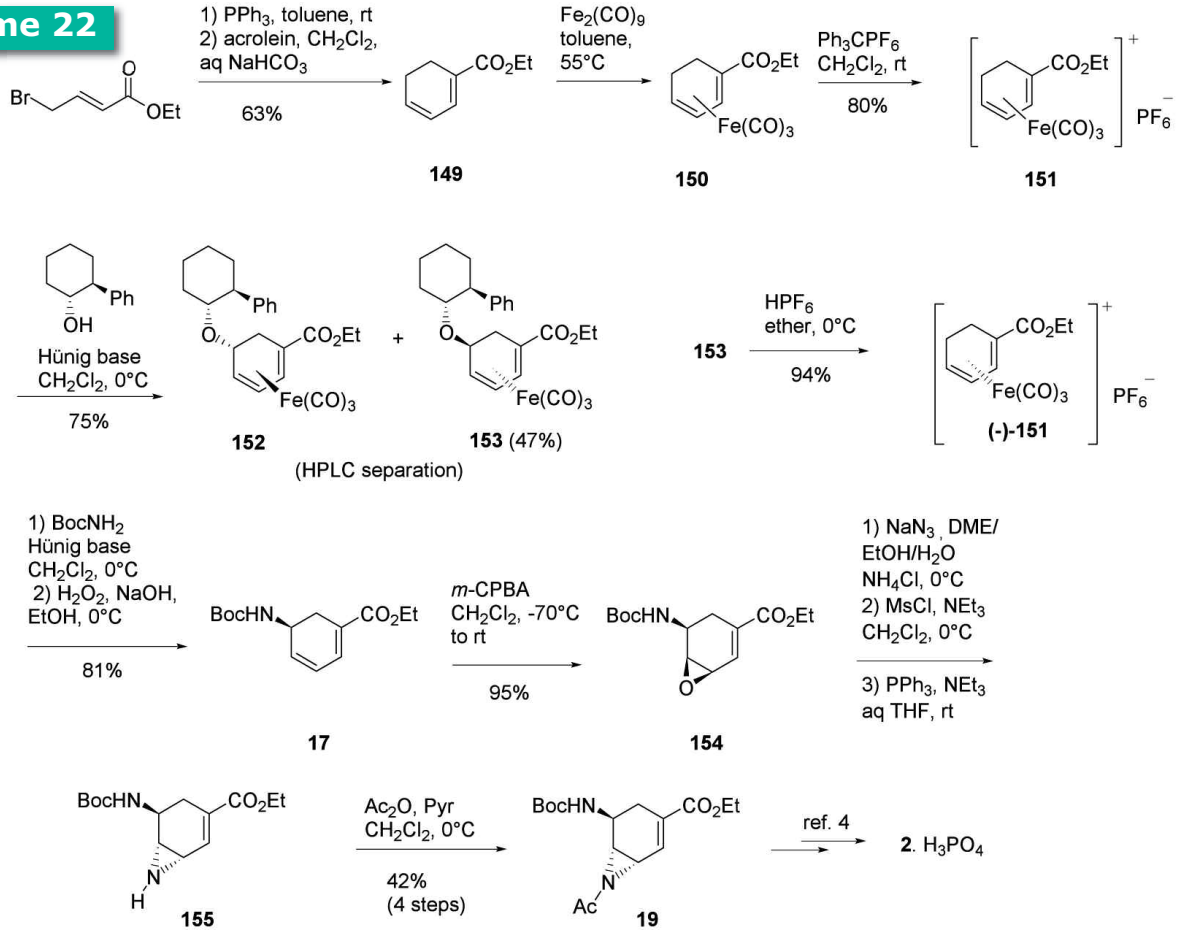
C. Synthesis via a resolution step (Kann, 2007)[36]

A non enantioselective (resolution step) synthesis of oseltamivir has been reported by a Swedish team (Scheme 22). The main feature of their approach is the use of a cationic iron carbonyl complex at two decisive stages of the reactional sequence. The synthesis commenced with formation of complex **150** by exposure of 1,3-cyclohexadienoic ester **149**[37] to diiron nonacarbonyl in hot toluene. After transformation of **150** to a cationic iron carbonyl complex via hydride abstraction (**151**), the latter complex was reacted with chiral (1*R*,2*S*)-2-phenylcyclohexanol to give a pair of diastereomeric complexes that could be separated by preparative HPLC.

[35] Fukuyama, T.; Lin, S-C.; Li, L. *J. Am. Chem. Soc.,* **1990**, *112*, 7050-7051
[36] Bromfield, K. M.; Gradén, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Comm.* **2007**, 3183-3185.
[37] Gradén, H.; Hallberg, J.; Kann, N.; Olsson, T. *J. Comb. Chem.* **2004**, *6*, 783-788.

The desired diastereomer (-)-**153** was then transformed to the previous, but now non racemic, cationic complex (-)-**151**, which was next reacted with the BOC-amine to give stereoselectively amino ester **17** (cf Scheme 5) after a decomplexation step. Epoxidation of **17** took place regio and stereoselectively to give epoxide **154**, which was transformed to aziridine **155** by a sequence of standard reactions. Acetylation of **155** provided **19** whose transformation to **2** had previously been reported (Corey et al.; cf. A.I.2 and ref. 4)

Scheme 22



Conclusion

Even though an industrial procedure is currently available to produce oseltamivir in large quantities, the limited availability of the (-)-shikimic acid, and the fear of an avian H5N1 influenza pandemic, have initiated a large body of research to discover new routes to oseltamivir[38]. From an industrial point of view, it is highly probable that very few of the reported syntheses meet the required criteria for large scale production, in particular if we take into consideration the number of steps, the recourse to nitrogen nucleophiles different from sodium azide, the number of protecting groups, the low costs of goods and the "greenness"[39] of the reactional sequences. However, and beyond these considerations, it should be highlighted that the synthetic chemists involved in the enterprise have identified several and original pathways to oseltamivir and it is expected that other ingenious achievements will be reported in a near future.

Acknowledgment

I would like to thank my colleague Pr. J. LEBRETON for his attentive and critical lecture of the manuscript.

[38] The following review provides a more in-depth and critical treatment of the oseltamivir (and also zanamivir) syntheses than this short scientific letter intended to do: Magano, J. *Chem. Rev.* **2009**, *109*, 4398–4438.
[39] Andraos, J. *Org. Process Res. Dev.* **2009**, *13*, 161-185.

Presentation of a chemistry biology team

Le **Dr. Sylvie ARCHAMBAUD**, Chef de projet chez ATLANCHIM PHARMA depuis 4 ans, est titulaire d'un Doctorat en chimie fine avec une spécialité en synthèse organique. Après avoir réalisé un post-doctorat en Suisse, elle a intégré la société ATLANCHIM PHARMA en novembre 2005. Elle synthétise et optimise des contrats industriels de recherche en synthèse à façon de molécules complexes et est également en charge de la gestion des stocks.

Dr. Sylvie ARCHAMBAUD *has a Doctorate in fine chemistry with a specialization in organic synthesis and is Head of Project at ATLANCHIM PHARMA. She achieved one post-doctoral in Switzerland and then joined the company in November 2005. Dr. Sylvie ARCHAMBAUD is in charge of the synthesis and optimization of industrial contracts of research in custom-chemical synthesis of complex molecules and is also in charge of stocks management.*

Fabien PETIT, Chef de Projet chez ATLANTIC BONE SCREEN depuis janvier 2009, est titulaire d'un Master en biologie moléculaire. Après avoir multiplié les expériences dans les laboratoires publics de recherche et au CNRS, il a suivi une formation de professionalisation aux biotechnologies et a ensuite travaillé pendant un an chez Biomérieux à Lyon. Depuis son intégration dans la société, Fabien PETIT est en charge des études menées *in vitro* pour le compte des clients d'ATLANTIC BONE SCREEN.

Fabien PETIT *is Head of Project at ATLANTIC BONE SCREEN since January 2009 and has a Master's Degree in molecular biology. After several experiences in public laboratories, CNRS, he had a biotechnology professionalizing training and then worked for one year at Biomérieux in Lyon, France. Fabien PETIT is in charge of in vitro studies for the account of ATLANTIC BONE SCREEN's customers.*

Le ***Dr. Isabelle Arnaud*** est Responsable Assurance Qualité chez ATLANCHIM PHARMA depuis septembre 2009. Elle est docteur en Pharmacie et titulaire d'un Doctorat en épidémiologie-thérapeutique et présente un parcours professionnel de plusieurs expériences en secteurs public et privé, dans les domaines du développement clinique et de la Qualité (ISO, BPF, BPC ...). Depuis son intégration, elle est en charge des projets de certification ISO pour les deux sociétés, puis à terme, des projets d'autorisation BPL pour ATLANTIC BONE SCREEN et BPF pour ATLANCHIM PHARMA.

Dr. Isabelle Arnaud *is Quality Assurance Manager at ATLANCHIM PHARMA since September 2009. She is Doctor in Pharmacy and has a Doctorate in epidemiology-therapeutics and presents a career path of several experiences in public and private sectors in the field of clinical development and Quality (ISO, GMP, GCP...). Since her integration, she is in charge of ISO certification projects for both ATLANCHIM PHARMA and ATLANTIC BONE SCREEN companies and then GMP authorization projects for ATLANCHIM PHARMA and GLP authorization projects for ATLANTIC BONE SCREEN.*

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