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An iron carbonyl approach to the influenza neuraminidase inhibitor oseltamivir†

Karen M. Bromfield,[a] Henrik Gradén,[ab] Daniel P. Hagberg,[a] Thomas Olsson[b] and Nina Kann*[a]

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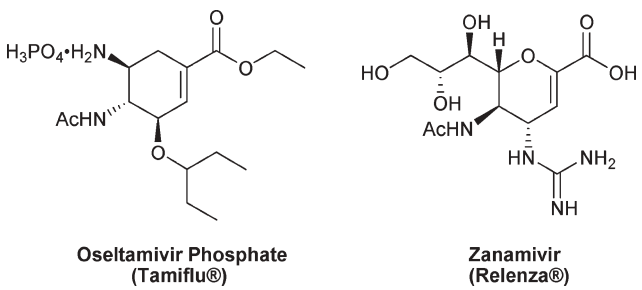
A novel synthetic route towards oseltamivir, an influenza neuraminidase inhibitor, has been achieved employing a cationic iron carbonyl complex, providing an alternate pathway with the potential to access diverse analogues.

Oseltamivir phosphate and zanamivir (marketed as Tamiflu and Relenza, respectively, Fig. 1) are neuraminidase inhibitors used for the treatment and prophylaxis of human influenza A and B.[1] They are also the most promising therapeutics for the treatment of the H5N1 avian flu virus, which currently meets two of the three criteria to be classified as a pandemic.[2] It should also be noted that oseltamivir phosphate is orally active, making it the best choice among currently available anti-influenza drugs, including M2 ion channel blockers which suffer from greater resistance and side effect problems.[1,2] The initial synthesis of oseltamivir phosphate employed (−)-quinic acid as the starting material,[3] with an alternative route starting from (−)-shikimic acid providing kilogram quantities[4] which was later improved for commercial production.[5] Further synthetic investigations have been undertaken,[6] however, the limited availability of the starting material used in the commercial production of oseltamivir phosphate, is an issue that still requires attention if predicted future demands for the drug are to be met.[7]

The need to improve the synthesis of oseltamivir phosphate has recently gained the attention of chemists in academia,[8] resulting in two novel methods for the synthesis of oseltamivir phosphate using alternative starting materials. Shibasaki and co-workers employed a catalytic ring-opening of a *meso*-aziridine as the key step in their asymmetric synthesis.[9] Also, Corey and co-workers prepared oseltamivir phosphate using an asymmetric Diels–Alder reaction as the initial step in an elegant approach, which to date is the shortest pathway to the target compound.[10] In addition, the synthesis of a slightly simplified analogue, starting from L-serine and employing a ring-closing metathesis for construction of the cyclohexene skeleton, was recently described by Cong and Yao.[11] The synthesis of oseltamivir phosphate described herein, based on cationic iron carbonyl chemistry, was developed not only to contribute to the search for novel starting materials and routes, but to provide an alternative with the potential to efficiently access diverse analogues should resistance to oseltamivir become more prevalent.[2,12]



Oseltamivir Phosphate (Tamiflu®) **Zanamivir (Relenza®)**

Fig. 1 Neuraminidase inhibitors.

Cationic iron carbonyl complexes of cyclohexadienes are versatile building blocks due to the fact that a wide range of nucleophiles can react with the cationic functionality, yielding new carbon–carbon or carbon–heteroatom bonds.[13] In addition, the diene moiety liberated after oxidative decomplexation allows for further transformations. As such, there are many examples of the use of cationic iron carbonyls in the total synthesis of natural products.[14] Our application of this chemistry toward the synthesis of oseltamivir, involves an initial nucleophilic attack on the cation, followed by selective epoxidation of one of the double bonds. Subsequent conversion to the corresponding aziridine and then ring opening gives the desired tetra-substituted cyclohexene (Fig. 2). Inherent to this approach, is the possibility to vary the nucleophiles used in the initial reaction with the cation, as well as the nucleophiles applied in the ensuing attack on the aziridine, providing access to a diverse range of oseltamivir analogues.

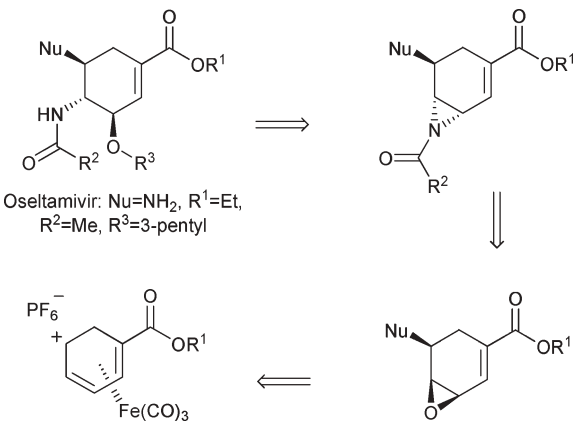


Fig. 2 Retrosynthetic analysis of oseltamivir.

[a]*Organic Chemistry, Department of Chemical and Biological Engineering, Chalmers University of Technology, 41296, Göteborg, Sweden. E-mail: kann@chalmers.se; Fax: 46 31 7723657; Tel: 46 31 7723070*
[b]*Medicinal Chemistry, AstraZeneca R&D Mölndal, 43183, Mölndal, Sweden*

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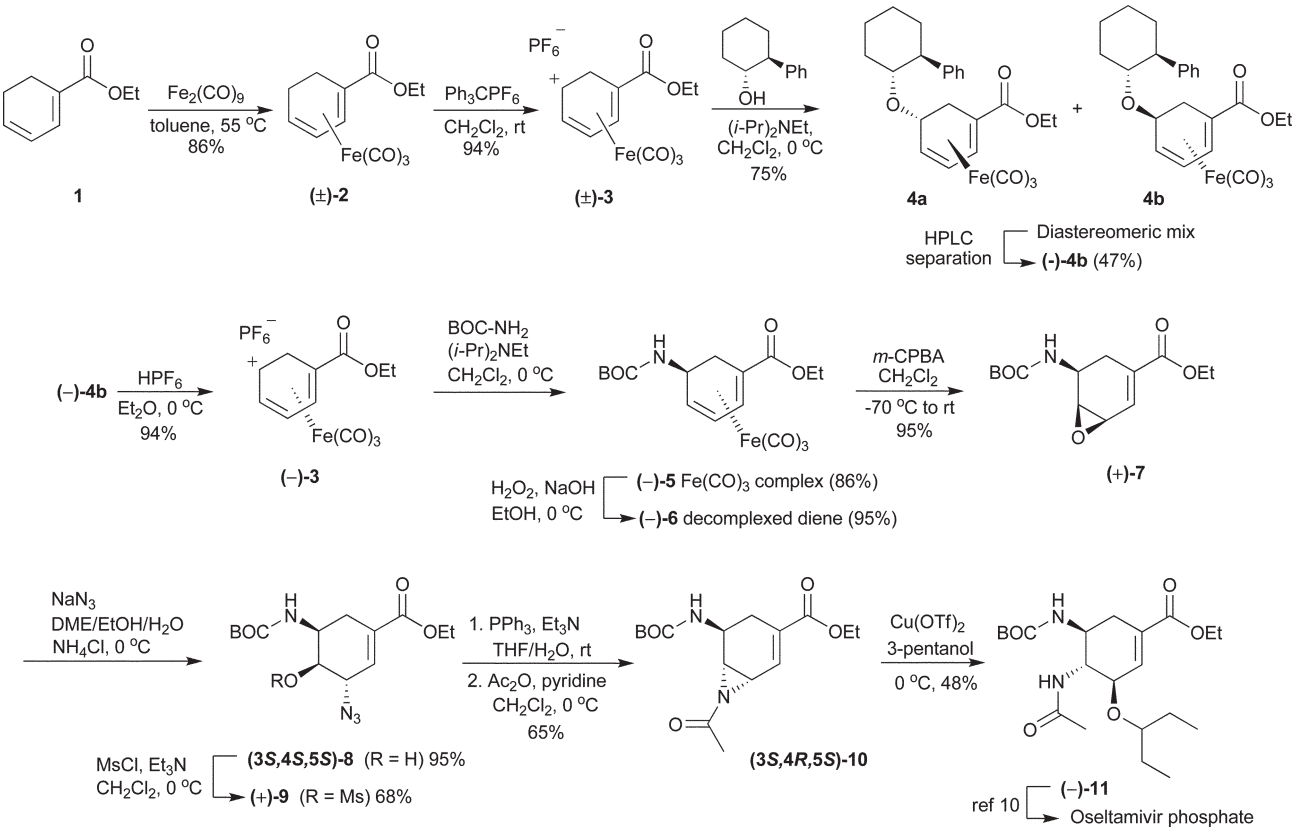

Scheme 1 Synthesis of oseltamivir phosphate from cyclohexadienoic acid ethyl ester (**1**).‡

The synthetic route (Scheme 1) started with the synthesis of the key iron carbonyl cation. This was undertaken following the earlier work by Birch and Williamson on methyl cyclohexadienecarboxylate tricarbonyliron complexes.[15] Cyclohexadienoic acid ethyl ester (**1**) was prepared from acrolein and the phosphonium salt of 4-bromobut-2-enoic acid ethyl ester in a tandem Michael/Wittig reaction using a published procedure.[16] The diene **1** was then heated with diiron nonacarbonyl in toluene at 55 °C overnight, affording iron carbonyl complex **(±)-2** in 86% yield after purification by chromatography. While our initial synthesis continued from this point to the final compound in a racemic fashion, it has previously been shown that the iron carbonyl complex **(±)-2** in the form of the corresponding carboxylic acid can be resolved through formation of a diastereomeric amine salt that can be separated by recrystallisation.[17] Unfortunately, such a method would significantly lengthen the synthetic route and a more efficient pathway was sought. Consequently, **(±)-2** was converted to the corresponding cationic complex **(±)-3** *via* hydride abstraction, with the racemic product **(±)-3** isolated in 94% yield and high purity.

Investigations were then undertaken into the resolution of the racemic cationic iron carbonyl complex, through separation of the diastereomeric pairs formed by the stereospecific nucleophilic addition (*exo* with respect to the coordinated metal) of chiral alcohols.[18] Diastereomers produced by the reaction of **(±)-3** with several available chiral alcohols were evaluated for ease of purification and separability. It was found that (−)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol performed the best, affording the diastereomers **4a,b** in 75% yield. Preparative HPLC allowed separation of the diastereomers, which were subsequently treated with hexafluorophosphoric acid to obtain the enantiopure cationic salts **(+)-3a** and **(−)-3b** in high yield, although only the desired enantiomer is shown in Scheme 1. It should be noted that while the selected chiral reagent is used in excess and is quite expensive, the majority can readily be recovered from both the initial reaction and upon elimination. While assignment of absolute configuration can be suggested at this point, through comparison to literature for the corresponding methyl ester cationic iron carbonyl complexes,[19] it was necessary to advance both enantiomers to an identical known literature compound for confirmation.

Introduction of the BOC–amine was then achieved through a protocol similar to that used by Birch and co-workers in their synthesis of (+)- and (−)-gabaculine.[19] Treatment of each individual enantiomer of **3** with an excess of BOC–NH_2 in CH_2Cl_2 at 0 °C over 20 min gave **(+)-5** and **(−)-5**, respectively. Slow addition of the base, as well as dry and inert conditions, are important to achieve high yields (86%) in this reaction. Decomplexation was also rapid and achieved using hydrogen peroxide in aqueous sodium hydroxide,[20] to afford intermediate **(+)-6** and **(−)-6**, both in a 95% crude yield of sufficient purity for use in further reactions. The slight amount (less than 5% by ^{1}H NMR) of by-product formed was attributed to over-oxidation and elimination to the aromatic ethyl ester which would not interfere with the next few steps and could be removed more easily at a later stage. The optical activity of these crude samples were equal and opposite to each other, although of a higher value to that reported in the literature.[10] This may be explained by a difference in purity between the two syntheses and thus allowed confirmation of the absolute configuration.

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With the appropriate diene **(−)-6** in hand, selective epoxidation of the more electron-rich alkene with *m*-CPBA resulted in the desired *cis*-isomer **(+)-7** (95% crude yield) of sufficient purity to be used directly in the next step. The observed stereoselectivity can be attributed to the directing effect of the carbamate moiety.[21] Reaction of **(+)-7** with sodium azide gave the azido alcohol **8** in 95% crude yield followed by mesylation and purification to afford **(+)-9** in 68% yield. Treatment of **(+)-9** with triphenylphosphine followed by Et_3N, formed the aziridine which was acetylated *in situ* to give **10** with an overall yield of 65% after chromatography.

The final stage of our synthetic design involved opening of the aziridine ring by nucleophilic attack of 3-pentanol in the presence of a Lewis acid. A similar approach has been used in the synthetic routes starting from (−)-quinic and (−)-shikimic acid,[3–6] in some instances to introduce the β-amino functionality and others the alkoxy moiety, as is required for this synthesis. The first attempt utilised $BF_3{\cdot}OEt_2$ as the Lewis acid to facilitate not only aziridine ring opening, but also the β-amino BOC-deprotection, to afford free base oseltamivir in one step. Unfortunately, while some product has been observed, appropriate conditions are yet to be achieved. Alternatively, $Cu(OTf)_2$ has been found to be an efficient catalyst for such ring openings,[10] and was utilised to afford the oseltamivir precursor **(−)-11** in comparable yield and high purity, with analytical data as reported in the literature. It is therefore foreseeable that concomitant removal of the BOC protecting group and precipitation with phosphoric acid would afford oseltamivir phosphate.[10] Thus, this novel route employing iron carbonyl chemistry allows the synthesis of oseltamivir phosphate in a total of 12 steps from cyclohexadienoic acid ethyl ester (**1**).

The highlight of this particular approach to the synthesis of oseltamivir is the potential for greater access to analogues in the future. It is anticipated that all four substituents on the cyclohexene scaffold of oseltamivir can be varied (Fig. 2) *via* (1) employing nucleophiles (Nu) other than BOC–NH_2 for the nucleophilic attack on the iron carbonyl cation; (2) using an activated ester of **3** (*e.g.*, R^1 = *p*-nitrophenyl), which after oxidative decomplexation can be converted to different esters/amides; (3) using alternate alcohols (R^3) or other nucleophiles in the aziridine ring-opening; (4) varying the aziridine acylating reagent (R^2). Studies concerning the versatility of the iron carbonyl chemistry to such a diversity oriented approach have been initiated both employing polymer-bound reagents[16a] and on solid phase,[22] and results from further investigations toward oseltamivir analogues will be reported in due course.

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Notes and references

‡ Compounds **3**, **5** and **6** were individually synthesised as both enantiomers to allow assignment of absolute configuration, however, only the required enantiomer is shown.

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