Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6927

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COMMUNICATION

An aldol approach to the enantioselective synthesis of (–)-oseltamivir phosphate†

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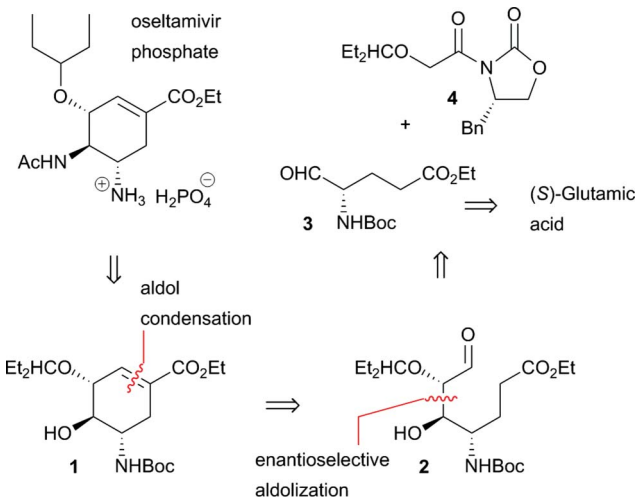
Received 25th July 2011, Accepted 16th August 2011
DOI: 10.1039/c1ob06248d

A formal asymmetric synthesis of the antiviral agent (–)-oseltamivir phosphate is achieved using two aldol reactions as key steps.

The arsenal of antiviral therapeutic agents is relatively modest, as compared to antibacterials, or antifungals.[1] The most recent illustration of this fact has been provided by the actual spread of the avian influenza, where the therapy is practically limited to only two compounds, namely oseltamivir phosphate (Tamiflu™) and zanamivir (Relenza™). The former is much more popular, due to the oral administration, and a high public demand for the compound apparently can not be satisfied by the industrial production, which relies on the impressive semisynthesis from (–)-quinic, or (–)-shikimic acid, developed by Gilead and Roche chemists.[2,3] This stimulated extensive efforts of the synthetic community, with the aim of developing an efficient total synthesis applicable on a large scale.[4] The challenge resulted in quite a number of ingenious synthetic approaches to this small, but densely functionalized molecule, where a range of mechanistically different reactions were used as key steps in syntheses.[5] Interestingly, an approach relaying on the aldol reaction has not been reported so far although, in our opinion, this reaction is well suited for the construction of the array of three contiguous stereocenters in the target structure. We decided to pursue this synthetic possibility.

Compound **1** was recognized as a suitable advanced intermediate: its conversion to oseltamivir has been described earlier, and it contains necessary structural prerequisites for the consecutive application of two aldol transforms, as delineated in Scheme 1. The aldol condensation transform dissects the cyclohexene ring of **1** into ester-aldehyde **2**, in its turn amenable to further retrosynthetic simplification by an enantioselective aldolization transform. While the retrosynthetic cleavage of stereocenters at C-3 and C-4 in **1** relies on the reagent controlled reaction, the absolute configuration of C-5 (the nitrogen-bound carbon atom) is inherited (imported) from the glutamate derived chiral synthon **3**.

The aldol addition was envisaged to proceed *via* a chiral enolate. To this end, 2-(pentan-3-yloxy)acetic acid **5** was prepared by a modification of the literature procedure and subsequently converted into the corresponding Evans oxazolidinone **4** *via* a mixed anhydride method (Scheme 2).



Scheme 1 Retrosynthetic analysis of oseltamivir.

The aldehyde partner for the coupling (**3**) was obtained from the known, (*S*)-glutamic acid derived, Boc-protected monoester **6**,[6] *via* a two step procedure involving its conversion to the corresponding thioester **7**, followed by the ionic hydrogenation.[7] Initial attempts to perform the aldol coupling using the lithium enolate of **4** were unsuccessful, as the aldol product was obtained as a 1 : 1 mixture of diastereoisomers (44% yield). We suspected that the lack of stereoselectivity might be caused by the racemization of configurationally unstable aldehyde **3** in the presence of strongly basic lithium enolate. Attempts to use less basic titanium enolates were unsuccessful, as the corresponding oxazolidinone, oxazolidinethione and thiazolidinethione rapidly decomposed under the enolization conditions.[8] However, the use of a boron enolate proved fruitful:[9] although steric hindrance and lower reactivity of boron enolates (with respect to alkali metal enolates) slowed down the reaction, after 4 h at –20 °C the desired product **8** was obtained as a single isomer. Attempts to cleave the oxazolidinone core in **8** with nucleophiles, such as methoxide, ethoxide or ethanetiolate, led to the oxazolidinone ring opening, or decomposition of starting material. Therefore, **8** was protected as aminal **9**, whose treatment with sodium borohydride in aqueous THF furnished alcohol **10**. Oxidation of **10** with DMP provided the precursor **11** for the aldol condensation. Unfortunately, this

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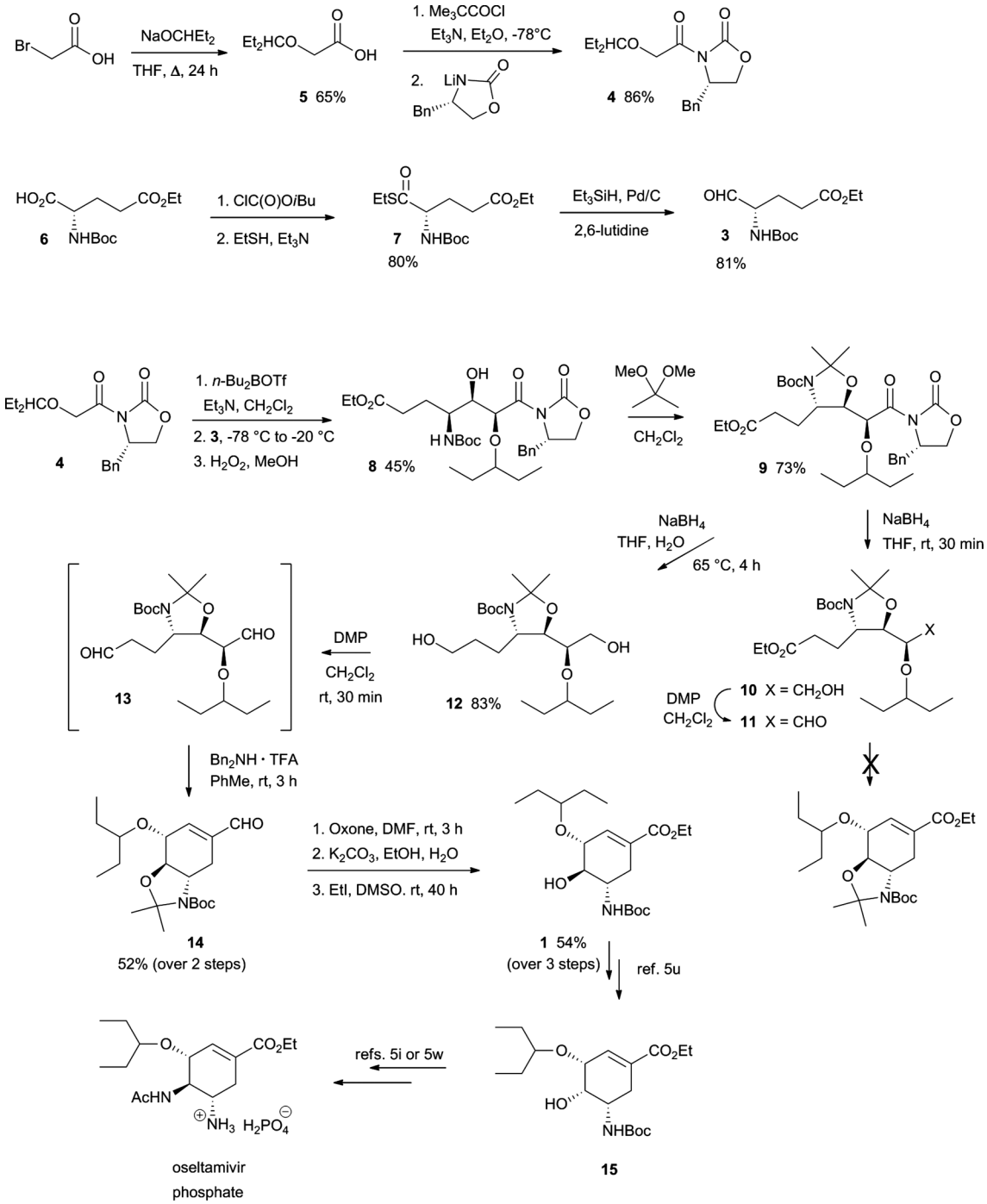
† Electronic supplementary information (ESI) available: Experimental details, spectroscopic data and copies of NMR spectra for new compounds. See DOI: 10.1039/c1ob06248d



Scheme 2 Synthesis of oseltamivir.

transformation was unfeasible, as we isolated only the starting compound **11** under a variety of conditions.

Therefore, we resorted to the dialdehyde cyclization protocol, introduced by Woodward,[10] improved by Corey,[11] and successfully applied by Mandai[5o] in a recent synthesis of oseltamivir. Interestingly, upon exposure to sodium borohydride in aqueous THF, ester-oxazolidinone **9** was slowly reduced to diol **12**. As the reaction required several days at room temperature, it proved more practical to perform it at 65 °C, where it was complete within 4 h. Although examples of sodium borohydride reductions of activated esters are known in the literature, to the best of our knowledge this is the first example of the reduction of an ester not containing alkoxy, amino, or any other activating group in neither α nor β position. Upon exposure to excess DMP, diol **12** was converted into dialdehyde **13**, which was not isolated, but treated with dibenzylamine to cyclize into enal **14** (52% over 2 steps). Treatment of **14** with oxone effected both oxidation[12] of the aldehyde and the deprotection of the cyclic aminal functionality in **14**; subsequent esterification under basic conditions[5o] gave optically pure intermediate **1**. Epimerization of **1**, which was

described earlier on the racemic material,[5u] gave optically pure **15**, thus completing the formal synthesis of oseltamivir.[5i,w]

Conclusions

Formation of all carbon–carbon bonds and stereocenters, in a formal enantioselective synthesis of (−)-oseltamivir phosphate, was achieved using two aldol reactions: three stereocenters in the acyclic intermediate were installed in the reaction of the Evans oxazolidinone derived boron enolate with glutaraldehyde, while the cyclization was achieved *via* enamine catalyzed intramolecular condensation. Research oriented towards the development of an anti-selective aldol reaction, thus obviating the need for the epimerization in the later step of the synthesis (**1**→**15**), is underway in our laboratories.

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