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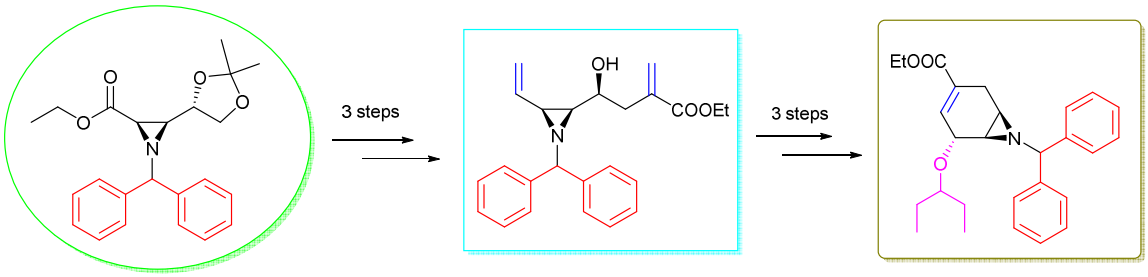

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COMMUNICATION

A concise synthetic approach toward Tamiflu (Oseltamivir phosphate): *Cis*-aziridine as the key synthon and RCM†

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The key synthon *cis*-aziridine has been efficiently utilised for the synthesis of the oseltamivir phosphate, using Wittig olefination, Barbier addition, Mitsunobu reaction and ring closing metathesis (RCM) as key essentials.

The constant and continuous world-wide threat of the seasonal influenza to human and animal health is the cause for concern due to the mortality and mobility of viral strain.[1] Neuraminidase inhibition is necessary for stopping the spreading the viral infection from the infected host cell. These surface glycoproteins cleave the sialic acid complex, which invade the lead of the viron in new cells. The molecules which were investigated for blocking the neuraminidase active site, help the inhibition of the viral infection and avoid the viron aggregation. Two of these molecules such as Zanamivir (Relenza®) and Oseltamivir phosphate (Tamiflu®) are the drugs available in the market for the treatment and prevention of the seasonal influenza caused by mutant viral strains (Fig. 1).

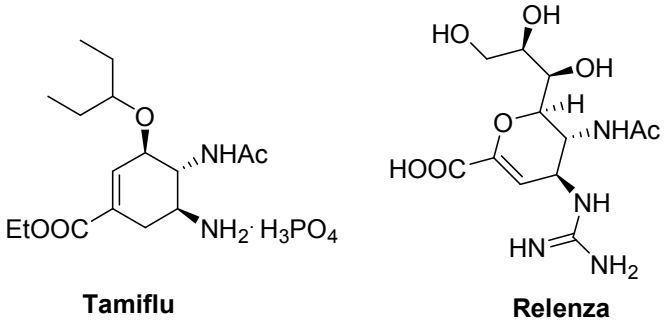


Fig. 1 Neuraminidase inhibitors

The Zanamivir has low bioavailability and is administrated by inhalation which could be problematic in case of patients suffering from the respiratory disease. Whereas the Oseltamivir phosphate (tamiflu) is given in the form of an oral prodrug and it has high bioavailability.

Tamiflu is effective against both H5N1 and H1N1 viral strains but its dose should be administered within 36-48 h after influenza symptoms detection.[2] The first report for tamiflu synthesis by Gilead science[3] and Roche's[4] processes from the (–)-shikimic acid is utilized for industrial scale synthesis of tamiflu.

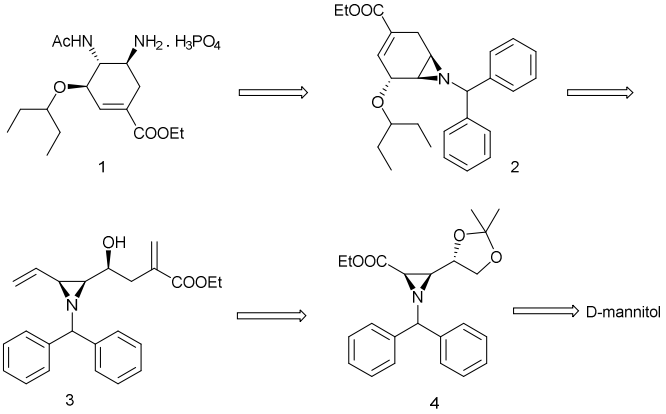
One of the major factors which restrict the large scale production of neuraminidase inhibitor drugs is the shortage of the synthetic precursor (–)-shikimic acid, whose natural source is limited. The 30 kg of dried star anise plant provides 1 kg (–)-shikimic acid through extraction method. Whereas 30% of its total requirement supplied by fermentation process.[5] Recently many synthetic groups focused on the alternative synthetic strategies from the cheap and more readily available starting materials which resulted in the different synthetic routes for the synthesis of the tamiflu.[6]

Shibasaki and co-workers reported different approaches based on asymmetric aziridine opening, Diels-Alder reaction and ring closing metathesis.[7] whereas Corey *et al* reported the synthesis of tamiflu involving a Diels-Alder reaction[8] while Hayashi's report on three "one-pot" operational stratergy for tamiflu synthesis is the highest yielding protocol so far fro the tamiflu.[9] There are also other synthetic routes reported for the tamiflu synthesis which involve L-serine, D-xylose, D-ribose, D-mannitol, L-methionine and D-tartarate chiral starting materials as alternatives to the (-)-shikimic acid.[10] However these synthetic strategies suffer from several limitations, which include the utilization of expensive starting materials, hazardous chemicals, tedious reaction conditions, azide intermediates and low yielding reaction steps. Due to this there is still a need to design and develop new synthetic routes which overcome the drawbacks of the reported strategies. The main task is to substitute the raw material of current manufacturing process. The

increasing demand of the tamiflu on worldwide seasonal pandemics of influenza puts increasing pressure to fulfill this need.

Since its discovery by Gabriel in 1888, aziridines are synthetically attractive intermediates and the building blocks for the synthesis of natural products.[11] They have been extensively explored for the construction of stereogenic centers containing nitrogen compounds. Tamiflu contains ether, *vicinal trans* diamine as three contiguous chiral centers in the cyclohexene structure. Hence, the well-organized and accurate placement of these groups is essential for its synthesis. The aziridine ring can be used to access the *trans* diamine. We herewith report the synthetic approach towards oseltamivir phosphate from the D-mannitol as an inexpensive and abundant chiral starting material involving aziridine as key precursor.

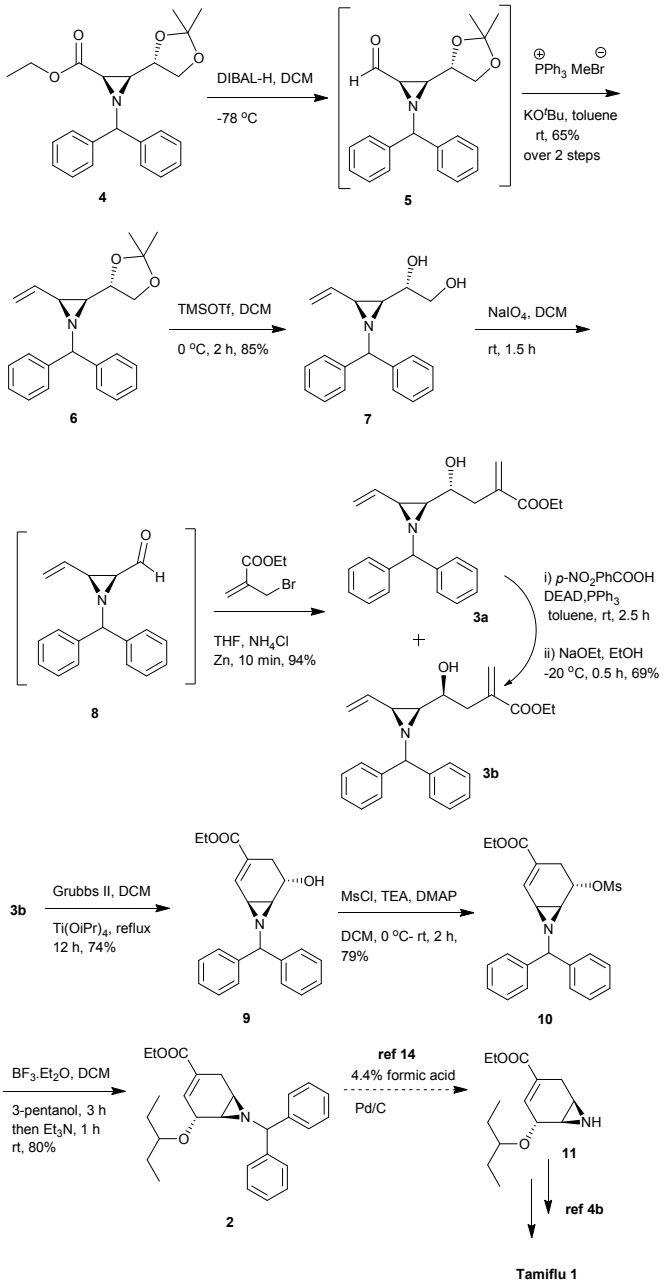
Retrosynthetic analysis is shown in scheme 1. Aziridine **2** was considered a key precursor, which could be obtained by intramolecular RCM of *bis*-olefin **3**. *Bis* olefin **3** in turn could be obtained from the aziridine **4** by consecutive DIBALH reduction, one carbon Wittig olefination, acetonide deprotection, oxidative cleavage of diol and Barbier addition. The aziridine **4** is the key synthon which could be easily prepared from D-mannitol.[12]



Scheme 1 Retrosynthetic analysis for Tamiflu **1**

According to retrosynthetic plan, the synthesis began with *cis*-aziridine **4**, which was easily prepared from the D-mannitol and benzhydril amine in good yield using the reported protocol.[12] The aziridine ester **4** was reduced to the corresponding aldehyde **5** using DIBAL-H at -78 ^{o}C (Scheme 2). The resultant aldehyde **5** without purification was directly subjected to one carbon Wittig homologation using KO^{t}Bu in toluene to furnish olefin **6** in 65% yield over two steps. Our next task was to obtain the RCM precursor **3a** from the olefin **6** by appropriate chemical transformation.

Accordingly, acetonide deprotection of olefin **6** was carried out with TMSOTf in DCM to afford diol **7** in 85% yield. Diol **7** was subjected to oxidative cleavage using $NaIO_4$ in DCM to afford aldehyde **8**. The crude aldehyde **8** was directly subjected to the Barbier addition of ethyl 2-(bromomethyl)-acrylate/Zn in THF/aq NH_4Cl to furnish the diastereomeric mixture of **3a:3b** in 3:2 ratio in 94% yield. The diastereomers **3a** and **3b** were separated by careful flash chromatography using pet.ether:ethyl acetate (90:10) as eluent. The undesired stereoisomer **3a** was readily converted to the desired **3b** by Mitsunobu inversion followed by ester hydrolysis with NaOEt/EtOH to afford **3b** in 69% yield. [13]



Scheme 2 Synthesis of Aziridine **2**

The relative stereochemistry of distereomer **3a** and **3b** was confirmed by transforming the compound **3b** to **10** by ring closing metathesis using Grubbs' II generation catalyst in refluxing DCM to furnish cyclohexene aziridine **9**, which on mesylation furnished the corresponding mesylate **10**. The data of mesylate **10** was found to be in good agreement with the documented data for **10** synthesized by different route.[14] From this the stereochemistry of compound **3b** as well as **3a** as assigned. According to our retrosynthetic plan, remaining job was to convert the aziridine **10** to intermediate **2**, which was carried out by the treatment with 3-pentanol in the presence of $BF_3.Et_2O$, which resulted into the regio and stereospecific ring opening of aziridine **10** and *in situ* re-aziridination to afford intermediate **2** in 80% yield (Scheme 2). Since

the conversion of intermediate **2** to aziridine **11** and from aziridine **11** to tamiflu **1** are reported in the literature,[14, 4a,4b] this constitutes for the formal synthesis of tamiflu **1**.

We would like to stress that although synthesis of tamiflu has been earlier reported from D-mannitol,[10d,10e] it required 16 and 18 steps respectively. Our synthesis requires only 13 purification steps. It may be further pointed out that the previous two syntheses in addition to chiral pool strategy employ catalytic asymmetric dihydroxylation to install additional chirality. Our synthesis on the contrary exploits the existing chiral center of mannitol and utilizes it for introducing the desired chirality without resorting any further asymmetric catalysis. In addition to this our synthesis does not generate undesired isomers, as is the case with other two syntheses, except **3a** which in turn can be readily transformed to the desired isomer **3b**. The aziridine intermediate **11** can be readily transformed to tamiflu by azide free route following the procedure described in ref 4a, in 5.5% overall yield which is better than the one reported by Mandai et al.

Conclusions

In conclusion a novel, practical and formal synthesis of the tamiflu has been accomplished starting with inexpensive and abundant chiral material *viz.* D-mannitol in 5.5% overall yields. The key building block *cis*-aziridine is utilised in the synthesis to fix the desired stereocenters of the neuraminidase inhibitor drug oseltamivir phosphate. This notable synthetic attempt involved Wittig olefination and Barbier reaction to access acyclic diene precursor and which was converted to cyclohexene, the core skeleton of tamiflu by ring closing metathesis (RCM). The undesired diastereomer of Barbier reaction was fruitfully converted into desired isomer using Mitsunobu conditions. The synthetic route is concise, involving inexpensive reagents throughout the synthesis and involves high yielding reaction steps.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data and copies of ^{1}H and ^{13}C-NMR spectra for the compounds. See DOI: 10.1039/b000000x/

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