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ARTICLE TYPE

Stereospecific Synthetic Approach Towards Tamiflu Using Ramberg-Backlund Reaction from Cysteine Hydrochloride

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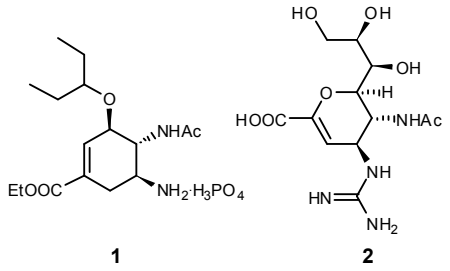
The stereospecific formal synthesis of tamiflu from L-cysteine hydrochloride as the chiral source is described. The notable feature of the present strategy is the Ramberg-Backlund reaction and Sharpless-Reich protocol as the key chemical transformations to access cyclohexene skeleton of tamiflu. Accomplished synthesis is efficient and practical.

Introduction

H5N1 and H1N1 strains of virus cause viral flu and have been shown to contribute to pandemic disease and pose a worldwide threat which has caused deaths of thousands of people till date.[1] These viruses actually cut surface protein of infected host cell and allow their spreading to other cells. Oseltamivir phosphate (**1**, Tamiflu, Ro 64-0796, GS4104) and Zanamivir (**2**, Relenza, GG 167) are currently used as neuraminidase inhibitor drugs.[2]



1 **2**

Figure 1. Structures of neuraminidase inhibitors **1** and **2**.

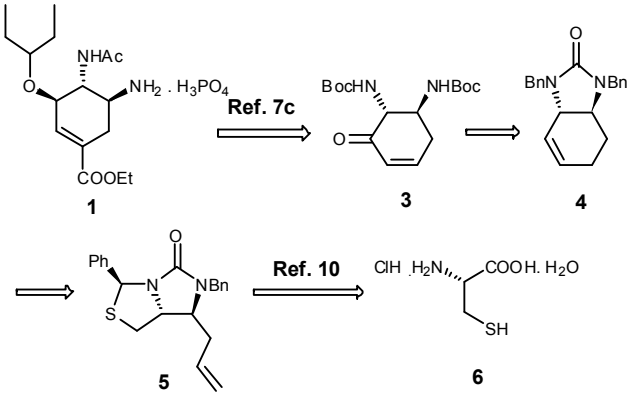
Oseltamivir phosphate is recommended as the best choice due to bioavailability in orally active form (Fig 1).[3, 4] The *anti*-influenza drug **1** was initially discovered by Gilead Sciences[5] and subsequently licensed to Roche for production from (-)-shikimic acid.[6] The demand of tamiflu has inevitably increased due to the threat of avian flu and influenzas. As a consequence there is a huge pressure on the availability of drugs and raw material supply to meet worldwide demand of tamiflu.

Currently manufacturing process for tamiflu uses (-)-shikimic acid as the raw material. The insufficient quantities of (-)-shikimic acid either by extraction from its natural sources, fermentation or chemical synthesis, is a drawback in meeting with the global demands. Thus far the unabated efforts of chemical community have led to many alternative syntheses of tamiflu. This synthetic target appears to be deceptively simple but is synthetically challenging. Some groups have used readily available and inexpensive starting materials and reported the key intermediates for tamiflu.[7] Despite the existence of several methods for tamiflu **1** synthesis, there is still a pressing need to develop synthetic strategy for it, where the use of azide and aziridine intermediate should be avoided to minimize the hazard and complexity associated with the processes.

Synthesis of chiral compounds is a vital task and as a result many chemists have been engaged in the development of asymmetric methodologies. The chiral diamines are major class of ligands which provide enantiopure compounds by asymmetric catalysis. Their preparation is always a challenge and only a few processes have been reported.[8]

However, 1, 2-diamines are not only used as ligands but are also important structural motifs of several bioactive compounds.[9]

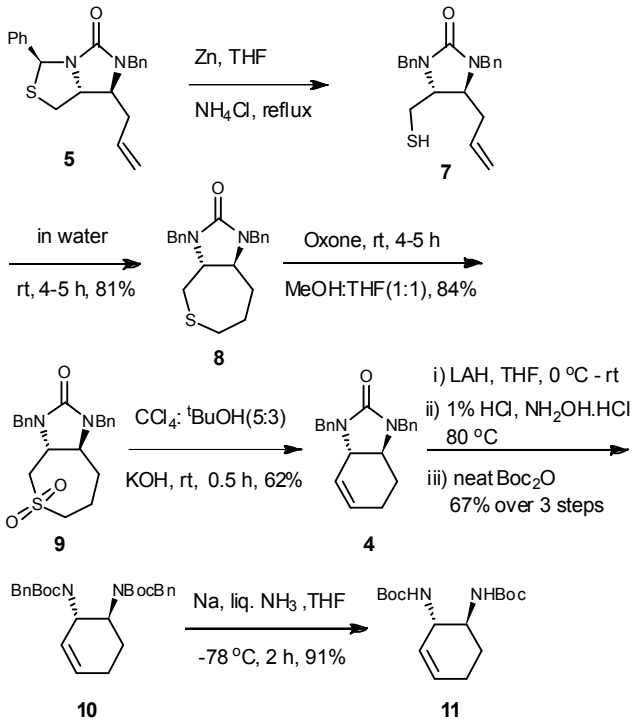
In view of the significance of chiral diamines and our own interest in synthesis of biologically active molecules, it was decided to pursue the synthesis of tamiflu **1**. Recently, we have reported a concise synthesis of tamiflu **1** starting from D-mannitol employing aziridine chemistry.[7y] Earlier we have developed a highly stereospecific protocol for amidoalkylation of imidazothiazolone and efficiently demonstrated its application for the synthesis of (+)-biotin.[10] This protocol potentially and readily provides *trans* diamine by urea hydrolysis. In continuation of our interest in *trans* diamines, we planned to utilize this novel protocol for the synthesis of tamiflu, which also has *trans* diamine motif.



Scheme 1 Retrosynthetic analysis for tamiflu (**1**)

Encouraged by our earlier success of generating protected *tran* sdiamine functionality, it was decided to extend this strategy for construction of *trans* diamine of tamiflu.

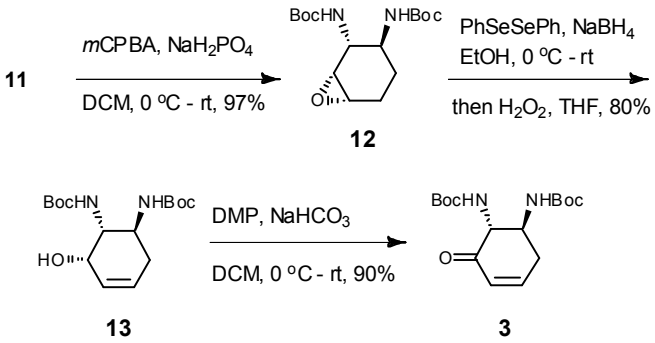
It was surmised that the intermediate **5** can be explored and exploited, for the synthesis of tamiflu **1**. The intermediate **5** can be easily synthesised from L-cysteine hydrochloride, which is commercially readily available in enantiomerically pure form as the renewable resource. We envisioned that the synthesis of enone **3**, which is the known intermediate reported by Shibasaki *et al.*[7c] can be obtained by urea hydrolysis, Birch reduction, epoxidation and regiospecific epoxide ringopening followed by oxidation of cyclohexene compound **4**. The compound **4** can be readily



Scheme 2 Synthesis of intermediate **11**.

derived from intermediate **5** using stereospecific amidoalkylation protocol developed by us, intramolecular thiol olefin cyclisation and Ramberg-Backlund reaction. The intermediate **5** in turn can be readily obtained from L-cysteine hydrochloride salt **6** (Scheme 1).[10]

Actual synthesis began with crude thiol **7** (Scheme 2), which



Scheme 3 Synthesis of Enone **3**

was obtained from **5** by Zn induced C-S bond cleavage. Compound **5** in turn was obtained from abundantly available L-cysteine by the reported procedure by us.[10] The thiol **7** on treatment with DBU underwent intramolecular cyclisation to afford cyclic seven membered sulphide **8** in 54% yield. The yield of sulphide **8** was improved to 81% by simply stirring the thiol **7** in water as a medium without any base.[11] It is pertinent to mention here that to the best of our kmoledge this is first report of formation and utilization of cyclic sulfide in water for synthesis of tamiflu. Having synthesized cyclic sulphide **8**, our next plan was to obtain compound **4**. Accordingly, cyclic sulphide **8** was oxidised by oxone to afford sulfone **9** in 84% yield. Sulfone **9** was subjected for Ramberg-Backlund reaction[12] to furnish the cyclohexene urea **4** in 62% yield.

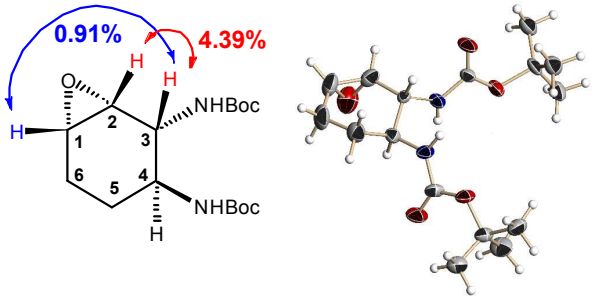


Figure 2: NOSEY and X-ray single crystal analysis of epoxide **12** (ORTEP diagram; ellipsoids are drawn at 30 probability).

With success in synthesis of key intermediate **4**, next task was to access diboc derivative **10** from cyclic urea **4** (Scheme 2). Generally cyclic ureas are quite stable to both acidic as well as basic conditions. This was once again confirmed when numerous efforts to cleave the cyclic urea moiety under basic as well as acidic conditions proved to be futile. So, urea **4** was reduced with LAH to furnish imidazolidine, which without purification was directly subjected to hydrolysis with 1% HCl, to afford corresponding vicinal diamine. The crude diamine was masked as its carbamate derivative by treatment with neat Boc anhydride to afford diboc derivative **10** in 67% yield.[13] Attempts to epoxidize compound **10** unexpectedly met with failure and this was attributed to steric hindrances exerted by benzyl and boc groups. In order to minimise the steric crowding, compound **10** was subjected to debenzylation under Birch reduction conditions at -78 °C in THF, herein the debenzylated compound **11** was obtained in 91% yield.

The compound **11** when subjected to similar epoxidation condition, smoothly furnished epoxide **12** in 97% yield as a single diastereomer (Scheme 3) giving credence to our hypothesis.[14] The relative stereochemistry of epoxide **12** was confirmed by NOE and NOESY studies. A significant NOESY correlation was observed between H3-H2 and H3-H1 confirming *syn* relationship between H3, H2 and H1. The molecular structure of epoxide **12** was further unambiguously confirmed by its single crystal X-ray analysis (Fig. 2).[15]

Final task was to rearrange epoxide **12** to enone **3**. Accordingly, following a well documented protocol by Sharpless[16a] and Reich,[16b] epoxide **12** was converted in one pot to allylic alcohol **13** in 80% yield involving two steps, without isolation of intermediate. Allylic alcohol **13** on DMP oxidation in DCM afforded enone **3** in 90 % yield. ^{1}H NMR and ^{13}C NMR data of intermediate compound **3** was in full agreement with the literature data.[7d] Since the conversion of **3** thus obtained to tamiflu has been accomplished by Shibasaki *et al.*, this constitutes a formal synthesis of **1**.

The compound **11** can also be easily converted to cyclohexene 1,2-diamine ligand, which is used as a ligand in asymmetric catalysis.

Conclusions

In conclusion, the formal synthesis of tamiflu has been achieved from inexpensive and abundant L-cysteine hydrochloride as the natural renewable resource. The notable features of the synthesis involve utilisation of efficient stereospecific amidoalkylation protocol and first report on exploitation of intramolecular thiol-olefin cyclisation in an anti-Markownikoff fashion to form cyclic sulphide, Ramberg-Backlund reaction to access required *trans* diamine and cyclohexene core skeleton of neuraminidase inhibitor drug **1** respectively. We have successfully demonstrated azide and aziridine intermediate-free synthetic route and utilised simple reaction conditions throughout the synthesis. Our novel methodology could be helpful for preparation of 1, 2-diamine functional ligands and other related bioactive compounds. The present work synthesis of key intermediate of tamiflu **1** from commercially available and renewable starting material *viz*. L-cysteine hydrochloride for key intermediate in 15.7% overall yield in 15 steps. The significant features of the current method lie in its simplicity and practicality as compared to the reported method which although is short and efficient, it involves use of azide reagents and azide and aziridine intermediates[7c] which are difficult to handle. Additionally our method involves the use of homochiral cysteine hydrochloride as the starting material and due to highly stereoselective reactions, there is no loss in the chiralit and no additional purification is required to upgrade the enantiopurity as compared to the reported method.[7c]

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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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