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MINI REVIEW

Synthetic Approaches to Lamivudine: An Anti-HIV AIDs and Anti-Hepititus B Drug

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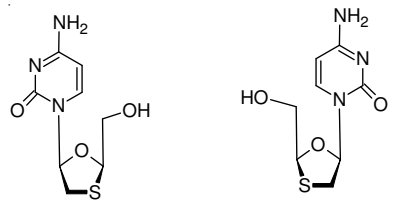
Lamivudine is an extensively used drug in combinational therapies for treatment of AIDS and hepatitis B. Due to the presence of S, O acetal and stereogenic centres, the synthesis of lamivudine in good enantiomeric yield is a challenge for synthetic chemists. The main focus of this review article is to highlight systematically those few synthetic strategies which are reported in literature since its discovery in 1989 to approach this potent synthetic nucleoside analogue.

Key Words: Synthesis, 3TC, (-)-BCH-189, Anti-HIV agent.

INTRODUCTION

Lamivudine (**1**) is one of the synthetic analogues of oxathiolane[1] and is the first approved synthetic nucleoside analogue possessing the unnatural L configuration[2]. It is a potent pyrimidine nucleoside analogue reverse transcriptase inhibitor (nRTI) with activity against human immunodeficiency virus type 1 (HIV-1) and hepatitis B (HBV). IUPAC name of lamivudine is L-2',3'-dideoxy-3'-thiacytidine and it is commonly called as 3TC. In 1989, lamivudine was invented by Belleau *et al.*[3] while their work at McGill University (Montreal, Quebec, Canada) and Nghe Nguyen-Ga at the Montreal-based IAF BioChem International, Inc. Laboratories. The first synthetic report of lamivudine was as (±)-BCH-189 recemic mixture in which 3' carbon of the ribose ring of 2'-deoxycytidine has been replaced by a sulfur atom. This recemic mixture demonstrated the promising anti HIV activity *in vitro* evaluation against HIV[4]. Both enantiomers were active against HIV but only the (-)-BCH-189 (lamivudine) was found non cytotoxic to human cells[5].



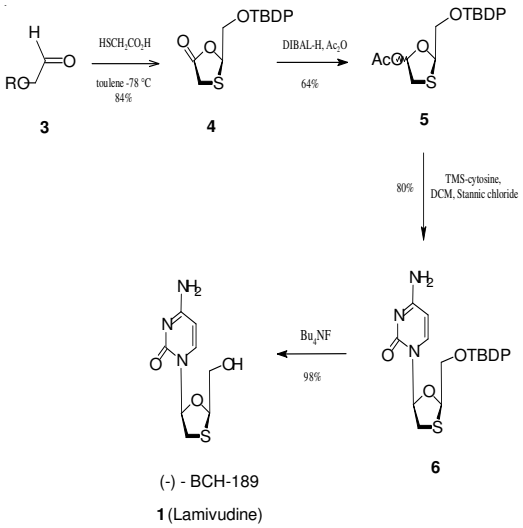
(-) - BCH-189 (+) - BCH-189

1 (Lamivudine) **2**

(**1**): Lamivudine and its positive enantiomer

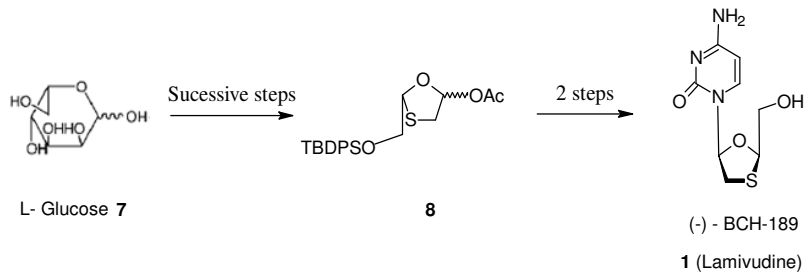
Synthetic approaches to lamivudine: In the coming section we are going to highlight some of the literature reported key synthetic routes to lamivudine systematically.

In 1991, Choi and co-workers[6] report a very effective route for the synthesis of lamivudine (**1**) with 98 % yield. They prepare the anomeric mixture (**4**) from the protected glyco aldehyde (**3**). Then this anomeric mixture (**4**) was treated with sylilated cytosine which results in the formation of the β-cytosine adduct (**6**). The deprotection of (**6**) with tetrabutylammonium finally leads to the synthesis of lamivudine. (**Scheme-I**).



Scheme-I: Choi approach to lamivudine

In the same year, Jeong and co-workers[7] reported the synthesis of enantiomerically pure (+)-BCH-189 only from D-mannose but they were not successful in synthesizing (-)-BCH-189 *i.e.*, lamivudine. But a year later in 1992, Jeong[8] along with his co-workers was successful in explaining the enantiomeric synthesis of (-)-BCH-189 (lamivudine) from L-glucose (**7**) and also reported its anti HIV and HBV-hepatitis activity (**Scheme-II**).

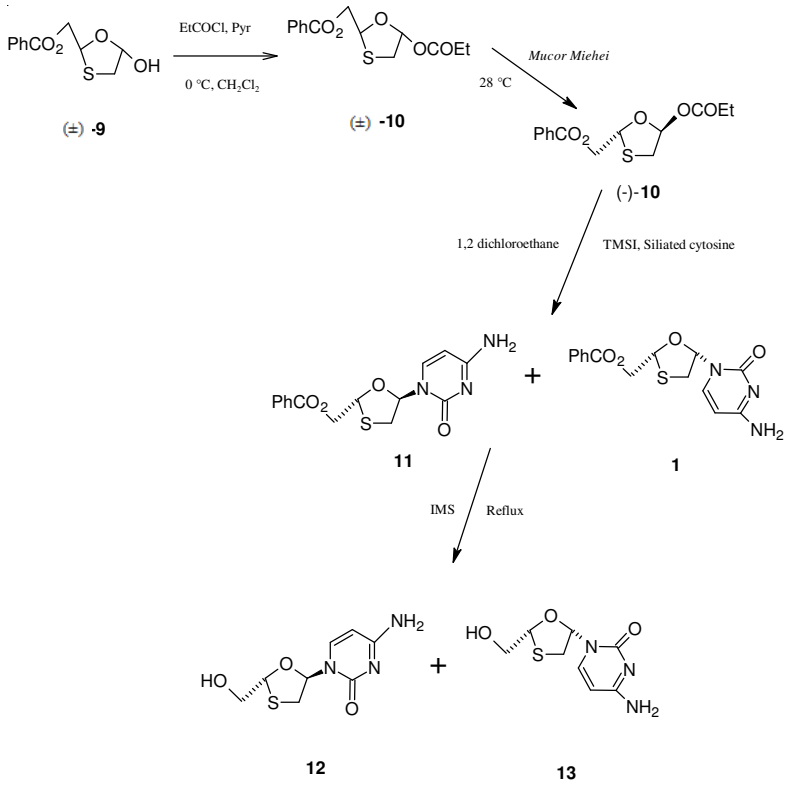


Scheme-II: Jeong's synthesis of lamivudine

Work of Mahmoudian *et al.*[9] was another report of enzymatic production of optically pure lamivudine. Keeping in mind the tremendous importance and need of lamivudine as potent anti HIV agent they have developed a process to produce lamivudine in multikilograms. To obtain lamivudine in optically pure form cytidine deaminase is used to deaminate 2'-deoxy-3'-thiacytidine enantio-selectively.

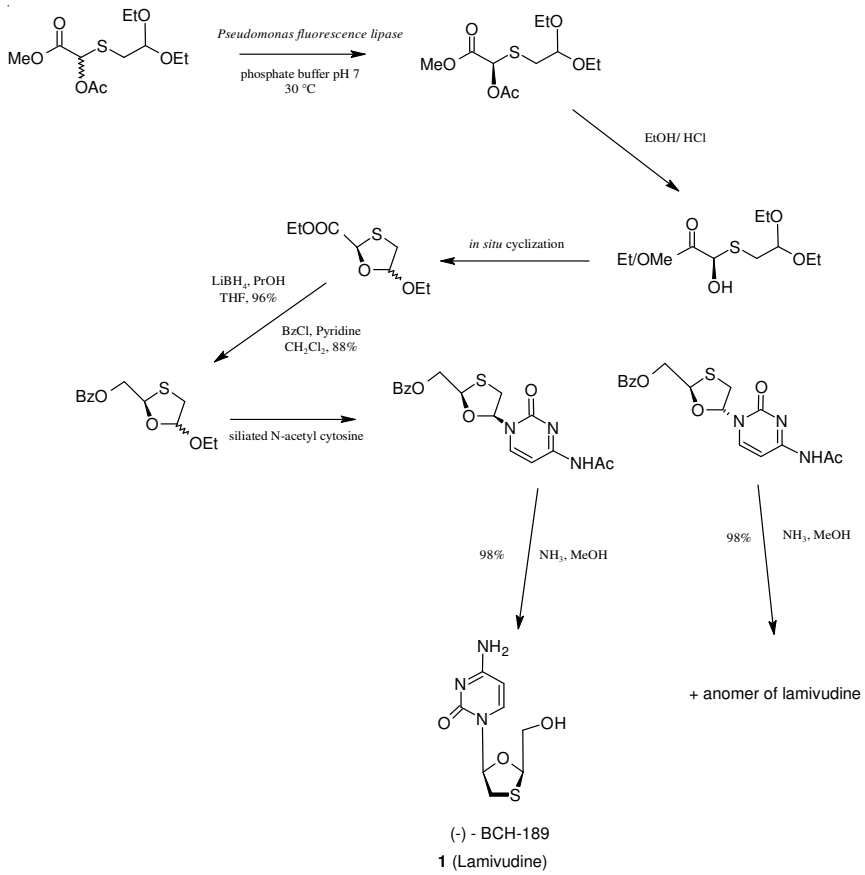
The first diastereoselective synthesis of the lamivudine was described by Jin[10] and co-workers.

Rick *et al.*[11] also proposed very effective method for the synthesis of lamivudine with good enantiomeric yield of about 70 %. With *Mucor miehei* lipase they have done the enzymatic resolution of oxathiolane propionate (**10**) at 28 °C to obtain enantiomefically-enriched residual substrate (-)-9 which was ultimately converted into lamivudine (**Scheme-III**).



Scheme-III: Lamivudine synthesis *via* enzymatic resolution of oxathiolane propionate

In an effort to develop enantioselective synthesis of lamivudine, Milton and co-workers[12] have done enzymatic resolution of α-acetoxysulfides. This synthetic strategy proceeds through stable hemithioacetal (**15**) which cyclized to form the oxathiolane nucleus (**16**), which was converted into lamivudine in sucessive four steps which are shown in **Scheme-IV**.



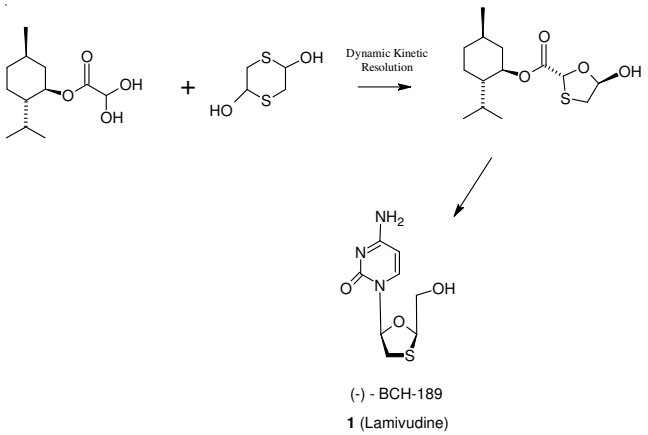
Scheme-IV: Enantioselective synthesis to lamivudine

Stephen and co-workers[13] reported the enantioselective synthesis of lamivudine using a variety of optically active α-acetoxy sulphides and demonstrated that by using proper substituent α-acetoxy sulphides can be utilized to synthesize lamivudine by novel enzymatic hydrolysis.

Via diastereoselective synthesis Noshena and her group[14] fruitfully achieved L-homolamivudine and its fluoro derivative from (R)-glycidol.

Hyung *et al.*[15] developed the enzymatic conversion process to obtain lamivudine *via* enantioselective deamination using thermostable *Bacillus caldolyticus* eaminase. In the same year Li *et al.*[16] also reported a method for synthesis of lamivudine which comprises of acylating 2-hydroxymethyl-5-(cytosine-1-yl)-1,3-oxathiolane with acetic anhydride to obtain lamivudine in successive steps.

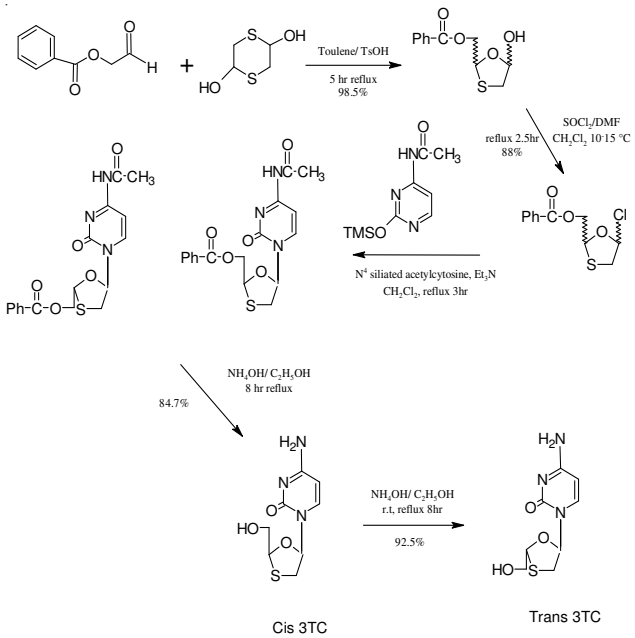
Another very efficient synthetic route for the partial enantioselective synthesis of lamivudine was reported in 2005. In order to obtain the enantiomerically pure compound in large scale Michael and co-workers[17] utilizes highly effective dynamic resolution as key step. Their **Scheme-V** of reaction was.



Scheme-V

In the same year Sriram *et al.*[18] proposed a method to synthesize series of lamivudine prodrugs and also reported their anti HIV and antitubercular activities of these prodrugs.

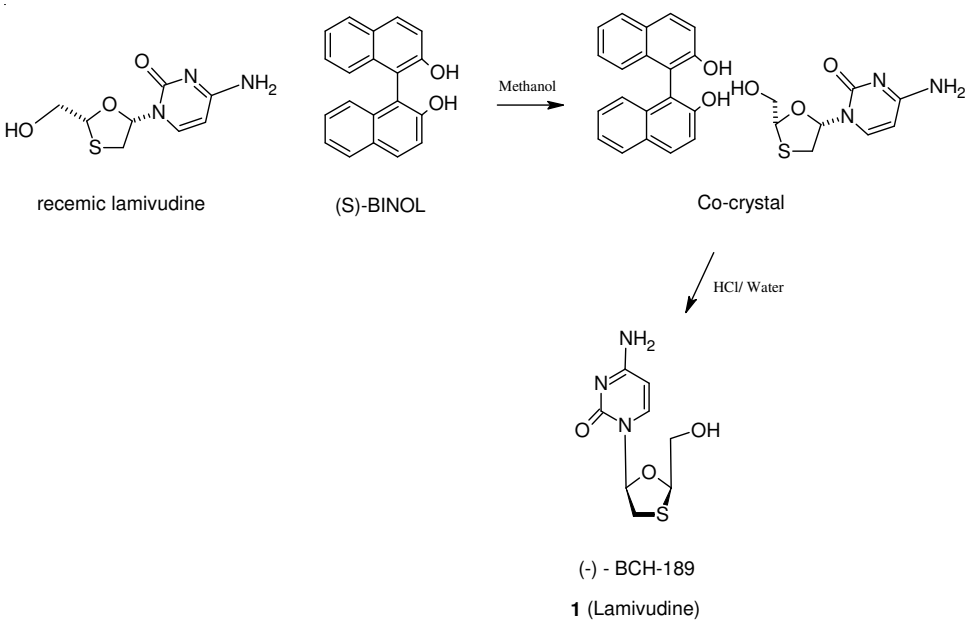
Using very mild conditions Yi and co-workers[19] developed a method to synthesize lamivudine starting from benzoyloxyacetaldehyde and 1,4-dithiane-2,5-diol. They have successfully obtained *cis* isomer of lamivudine in 84.7 % and *trans* isomer in 92.5 %. Successive steps of their reaction to the synthesis of lamivudine are illustrated in **Scheme-VI**.



Scheme-VI: Yi's work to synthesize lamivudine

Krishna *et al.*[20] reported the synthesis of a liver-selective prodrug (3TCSD) of antiviral lamivudine (3TC). They have reported the synthesis of lamivudine-dextran conjugate and also their use of selective delivery of lamivudine to the liver.

More recently (2009) a synthetic route for large scale synthesis of lamivudine *via* cocrystal formation of racemic lamivudine with (S)-(-)-1,1'-Bi(2-naphthol) [(S)-(BINOL)] is reported by Bhairab *et al.*[21] (**Scheme-VII**). The beauty of their reaction is that lamivudine with enantiomeric excess of more than 99.9 % was obtained.



Scheme-VII: Bhairab's work to approach lamivudine

Conclusion

Herein, a brief overview of those few methods which are reported in literature to obtain potent drug lamivudine is presented. It is among those few sulphur containing drugs which are available in market to fight against HIV AIDS. Due to its special stereochemistry only few methods are found in literature for its preparation. Considering this an important drug with convenient dosing and its safety profile for treatment of AIDS a lot of work is still to be done for enantioselective synthesis of lamivudine specially its novel derivatives with enhanced activities.

ACKNOWLEDGEMENTS

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