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Practical enantioselective synthesis of lamivudine (3TC™) via a dynamic kinetic resolution

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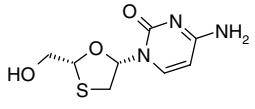
Abstract—A practical enantioselective synthesis of lamivudine **1** is described. A highly effective dynamic kinetic resolution of the 5-hydroxyoxathiolane, followed by chlorination and introduction of cytosine provides an efficient synthesis of lamivudine.

Lamivudine **1** also known as 3TC™ is an anti-HIV agent, which has also been developed for the treatment of hepatitis B.[1]



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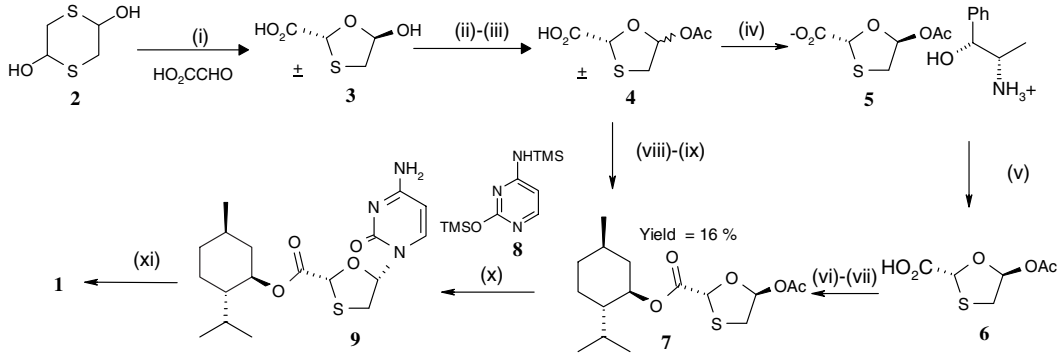
Although there are several different methods reported[2] for the synthesis of **1** as a single enantiomer, we required an efficient route, which was suitable for large-scale synthesis to support the development of this compound.

In the first instance a route was developed, which utilised a Vorbrüggen reaction[3] of the enantiomerically pure 5-acetoxy-oxathiolane **7** with pre-silylated cytosine **8** as the key convergent step as disclosed in Scheme 1. This approach required a significant quantity of trimethylsilyl iodide (TMSI) as the Lewis acid for the Vorbrüggen reaction in order to achieve an acceptable yield of the desired cytodine **9**. Furthermore the approach proved to be rather inefficient as the preparation of



Scheme 1. Reagents and conditions: (i) *t*-BuOMe, reflux, 70%; (ii) Ac_2O, cat $MeSO_3H$; (iii) $NaHCO_3$, *i*-PrOAc, 70%; (iv) norephedrine, *i*-PrOAc, 35%; (v) 5 M HCl; (vi) $(COCl)_2$, DMF; (vii) (−)-menthol, py; 80%; (viii) $(COCl)_2$, DMF, CH_2Cl_2; (ix) (−)-menthol, py, 2,2,4-trimethylpentane, 16%; (x) TMSI, CH_2Cl_2, 60%; (xi) $NaBH_4$, EtOH, 83%.

Keywords: Practical; Enantioselective; Dynamic kinetic resolution; Lamivudine.
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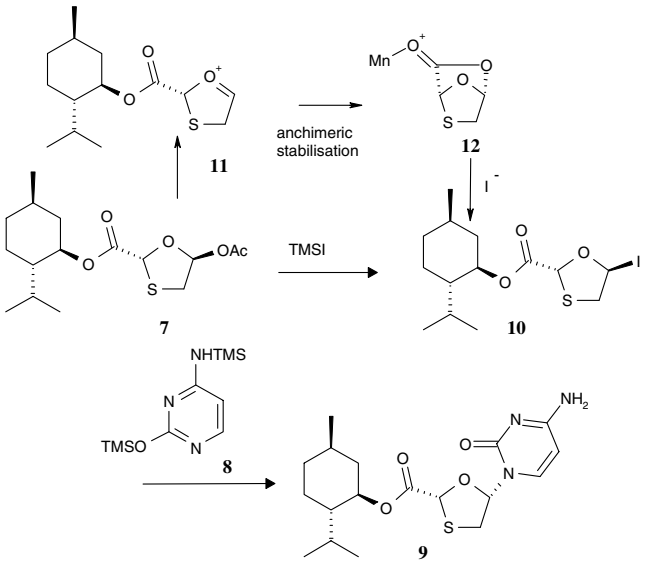
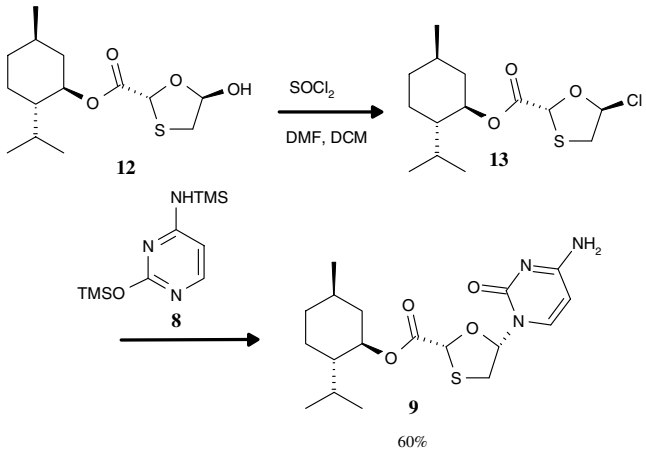


Scheme 2.

the enantiomerically pure crystalline 5-acetoxy-oxathiolane **7** was achieved either by its selective crystallisation in the presence of the other three diastereoisomers, albeit in only 16% yield, or by a classical resolution via the norephedrine salt of acid **5**. Therefore an alternative, more efficient route was sought.

Closer inspection of the reaction mechanism of the Vorbrüggen reaction revealed that when 5-acetoxyoxathiolane **7** was reacted with TMSI 5-α-iodoacetoxyoxathiolane **10** was formed, which reacted with pre-silylated

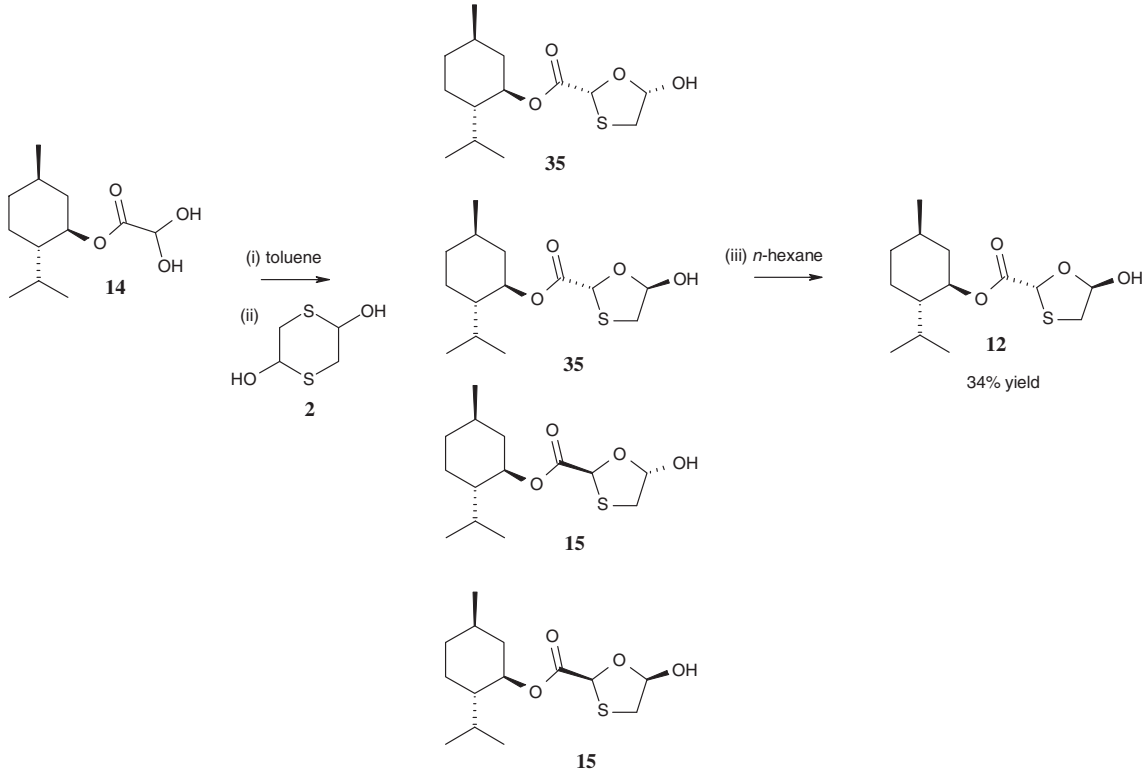


Scheme 3.

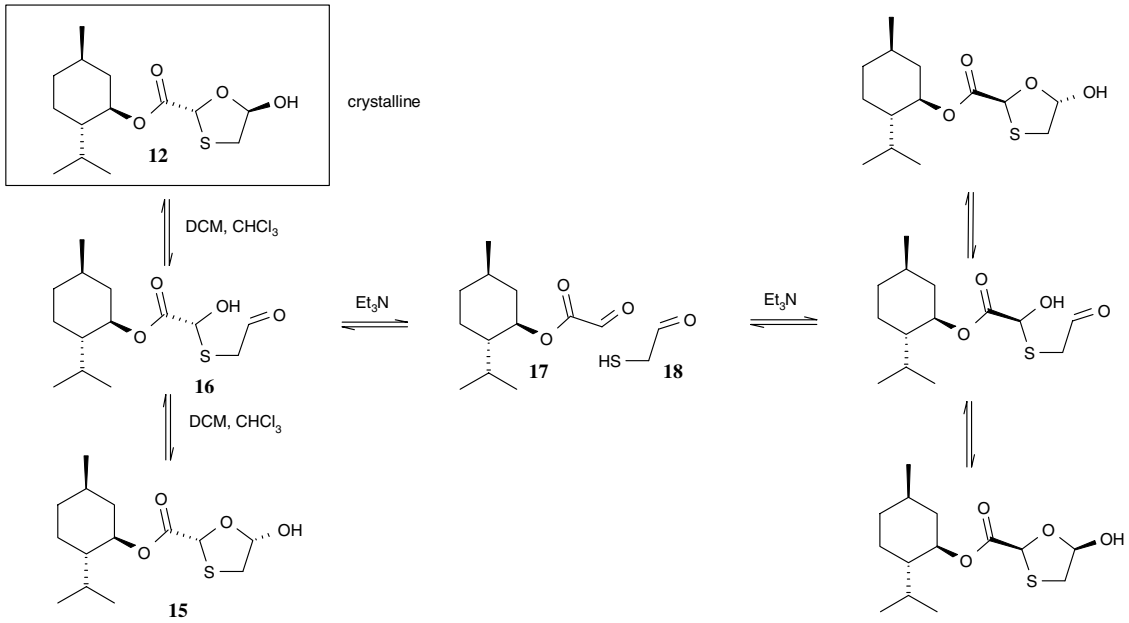
cytosine **8** to give the cytodine **9** as a 10:1 mixture of β and α anomers in 70% yield (Scheme 2).

It is postulated that 5-α-iodooxathiolane **10** is formed stereoselectively by reaction of the oxonium ion **11**, generated by reaction of **7** with TMSI, undergoing stabilisation through anchimeric assistance from the C-2 ester substituent. Iodide then attacks the stabilised oxonium ion **12** to afford the α anomer **10**, which then reacts with pre-silylated cytosine **8** in an S_N2 type nucleophilic substitution reaction to give predominantly the β-cytodine adduct **9** (Scheme 2).[4]

We were interested in examining other leaving groups than iodide in this substitution reaction. Consequently

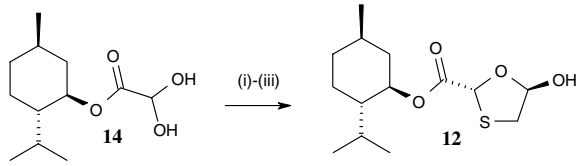


Scheme 4.



Scheme 5.

5-α-chloro-oxathiolane **13** was prepared from 5-hydroxy-oxathiolane **12** on reaction with thionyl chloride and catalytic DMF in dichloromethane. This was also found to react with the pre-silylated cytosine **8** to give **9** in good yield and selectivity (β:α, 10:1) (Scheme 3). The desired β-anomer **9** could then be efficiently isolated by crystallisation on addition of *n*-hexane to the crude reaction mixture.

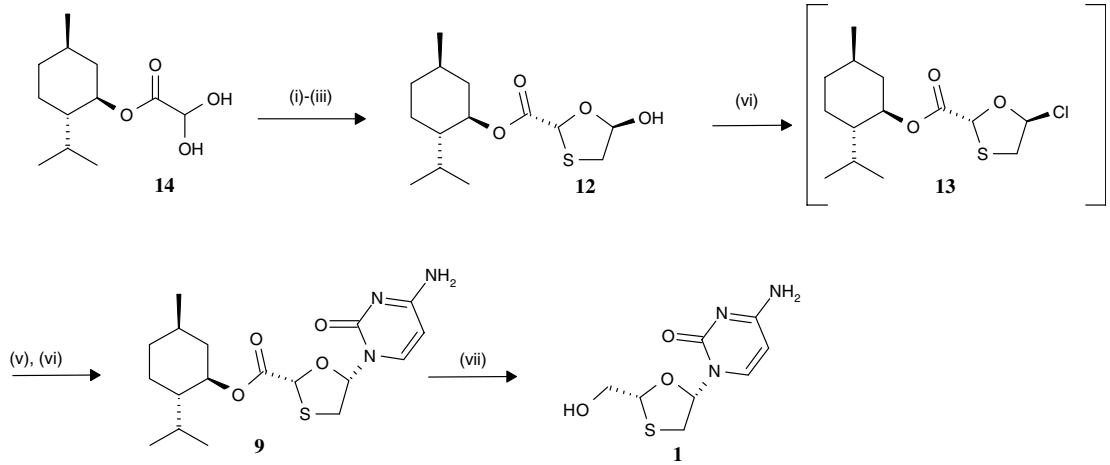


Scheme 6. Reagents and conditions: (i) toluene; (ii) dithiane diol; (iii) *n*-hexane, Et_3N, 80% overall yield.

All that remained now was to identify an improved synthesis of hydroxyoxathiolane **12**. Initially, the 5-hydroxyoxathiolane **12** was prepared by heating a mixture of menthyl glyoxylate hydrate **14**[5] with dithiane diol **2** in toluene. This procedure gave a mixture of four diastereoisomers as a 35:35:15:15 ratio as depicted in Scheme 4.

Crystallisation from *n*-hexane gave the desired diastereoisomer **12** in 34% yield, which corresponds to approximately all of that isomer in solution. To increase the yield of the desired diastereoisomer **12** the interconversion of the other diastereoisomers was investigated.

It was initially found that in certain solvents, for example, dichloromethane or chloroform, rapid equilibration at C-5 occurred giving a mixture of β and α isomers **15** and **12**, but there was no isomerisation at C-2. We



Scheme 7. Reagents and conditions: (i) toluene, reflux; (ii) dithiane diol; (iii) *n*-hexane, Et_3N crystallisation (80% for three stages); (iv) $SOCl_2$, DMF, DCM; (v) **8**, Et_3N, toluene; (vi) Et_3N, water, *n*-hexane (66% for three stages); (vii) $NaBH_4$, EtOH, 83%.

postulated that this equilibration could be further distorted via cleavage of the hemithioacetal **16** to give menthyl glyoxalate **17** and mercaptoacetaldehyde **18**. Coupling together these two equilibria should then provide a method for converting the unwanted diastereoisomers to the desired one, which would be removed from the equilibrium by crystallisation (Scheme 5).

Hence, a reagent capable of effecting the equilibration at C-2, but not detrimental to the crystallisation was needed. It seemed likely that a base would carry out this function. A number of bases were evaluated; pyridine gave only a small amount of interconversion whereas triethylamine caused rapid interconversion. Furthermore it was necessary to add only a catalytic amount of triethylamine to achieve rapid interconversion and crystallisation of **12** in 80% yield as depicted in Scheme 6.

This highly effective crystallisation-induced dynamic kinetic resolution then provided an efficient synthesis of the 5-hydroxy-oxathiolane **12**, which in turn was used to prepare lamivudine **1** in an efficient process (Scheme 7).[6]

In conclusion, an efficient and enantioselective, synthesis of lamivudine has been developed, which utilises a highly effective dynamic kinetic resolution as the key step.

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