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Communication

An Economical Route to Lamivudine Featuring a Novel Strategy for Stereospecific Assembly

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ABSTRACT: An economical synthesis of lamivudine was developed by employing a new method to establish the stereochemistry about the heterocyclic oxathiolane ring. Toward this end, an inexpensive and readily accessible lactic acid derivative served the dual purpose of activating the carbohydrate's anomeric center for N-glycosylation and transferring stereochemical information to the substrate simultaneously. Both enantiomers of the lactic acid derivative are available, and either β-enantiomer in this challenging class of 2′-deoxynucleoside active pharmaceutical ingredients can be formed.

KEYWORDS: *antiviral agents, API, emtricitabine, lamivudine, nucleoside*

INTRODUCTION—THE NEED AND CHALLENGE IN DEVELOPING NEW APPROACHES TOWARD 3TC

Finding a new route to lamivudine (3TC) and emtricitabine (FTC) with less expensive raw materials constitutes an impactful yet difficult goal. These medications are part of the front-line treatment of HIV,[1a] and low-income countries constitute the principal markets. Both drugs rely on the original synthesis developed at GSK.[2] The route's longevity testifies to the excellence of the work—these treatments have been on the market for 25 years. 3TC is produced in large volumes (>1.5 MM kg/yr) as a result of high demand and dosage.[1a] While the price of 3TC drug substance is comparatively low (~$140/kg), a significant sum is still spent annually on these essential medications because of the large volume consumed. Some countries experience rates of HIV infection in excess of 25% of the population, yet these same countries have some of the world's lowest per capita GDPs.[1b−d]

Cost-effective control of the oxathiolane stereochemistry is a primary challenge encountered in attempts to improve the synthetic route. 3TC and FTC contain subtle structural complexity. These nucleoside analogues have a non-natural sense of chirality, and they possess a 2′-deoxy framework, a system that lacks an oxygen atom at C2 adjacent to the anomeric center. This poses a particular challenge because oxygenated neighboring groups establish absolute stereochemistry by directing an incoming nucleophile's orientation (Figure 1).[3] In place of an oxygen directing group, an anchimeric effect is frequently used to guide the relative stereochemistry of N-glycosylation (α/β);[2] however, to achieve an optically pure compound rather than a mixture of enantiomers, one must be able to dictate the configuration of the preceding thioacetal ester. Further complicating matters, the stereochemistry of this ester is often established in the bond-forming sequence that leads to the parent 5-hydroxyoxathiolane ring, yet the stereochemistry of this compound is

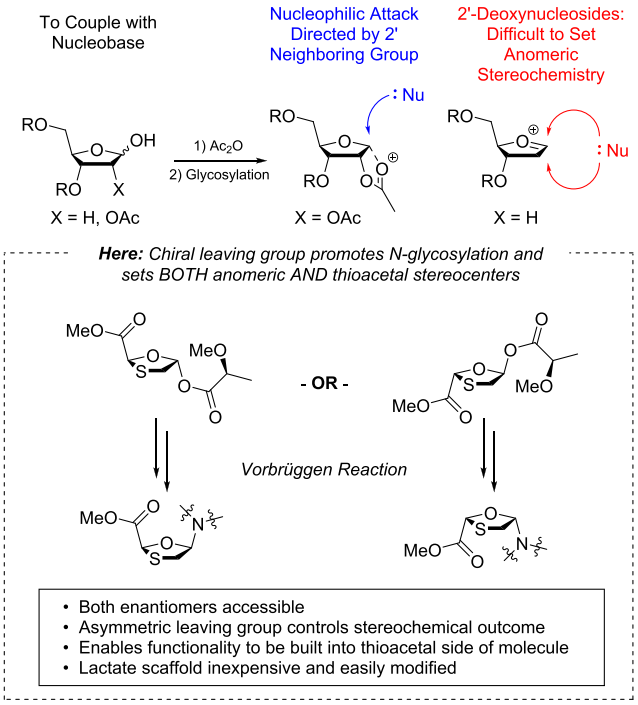

Figure 1. A successful strategy to control the stereochemistry of challenging 2′-deoxyoxathiolane nucleosides.

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fluxional by nature since this hydroxyl group causes rapid epimerization of both stereocenters via ring-opening mechanisms. The current manufacturing route cleverly obtains this compound through a dynamic kinetic resolution that selectively crystallizes the desired compound.[2]

The fact that all but two routes[4] to 3TC/FTC establish the absolute stereochemistry of the oxathiolane core via chemical or enzymatic resolution[5] rather than setting stereocenters in bond-forming steps speaks to the difficulty of the task. In the course of our effort to develop an improved synthesis of 3TC, we discovered a strategy that allowed us to dictate the 2′-deoxynucleoside enantiomer of choice.

A NOVEL STRATEGY TO CONTROL THE OXATHIOLANE STEREOCHEMISTRY

The use of a chiral acid to activate the sugar at the anomeric position was the lynchpin of our strategy (Figure 1). Acylation of sugars is one of the most common means to prepare carbohydrates for coupling with nucleobases,[3b,6] and in this manner, the stereochemistry of the rapidly epimerizing sugar can be established at the same time that the molecule is prepared for glycosylation. We expected that combining the sugar activation and stereoinduction steps of the synthesis could possibly reduce the cost by either cutting a step out of the synthesis, reducing the molecular weights of the intermediates, or using less expensive raw materials.

PROOF OF CONCEPT

Low-molecular-weight lactic acid derivatives were selected for screening, as both enantiomers are accessible via lactic acid or alanine. To test the hypothesis, oxathiolane **1** was acylated with (*S*)-lactic acid derivative **2** (Figure 2). Crystallization from a toluene/hexanes mixture resulted in isolation of a single isomer (50:1 dr), while the minor isomer was rejected and isolated as an oil from the mother liquor. Crystalline material **3a** had the opposite configuration of that required to form 3TC. The outcome was reversed (**4a**), however, by beginning from the enantiomer of **2**. Most critically, the desired stereochemistry of the thioacetal is established. In coupling with the nucleobase, the ester dictates the stereochemistry of the incoming nucleophile at the anomeric center via the anchimeric effect. In this manner, acylation establishes both the proximal and remote stereocenters in a single step, and either enantiomer of the β-2′-deoxynucleoside can easily be made from inexpensive raw materials.

OPTIMIZING THE ACYLATION

With the proof of concept in hand, our attention turned to a more efficient, economical, and selective means of making **4a** (Table 1). It became apparent that both the anomeric and thioacetal stereocenters could be influenced in the course of acylation. Mixed anhydrides from Ishihara esterification conditions presented themselves as viable options.[7] Selectivity for the *trans* product was observed in a 5:1 ratio when 4-(*N*,*N*-dimethylamino)pyridine (DMAP) was used as a catalyst with a 2:1 preference for the desired 2*R*,5*R* isomer, but the yield was in the mid-30% range. Maximizing the stereoselective outcome was an important goal to optimize the overall yield of **4a**.[8] Lower temperature resulted in decreased selectivity, as did increasing the number of equivalents of the mixed anhydride. Presumably, lowering the temperature decreased the rate of hydroxyoxathiolane epimerization, thus leading to the lower

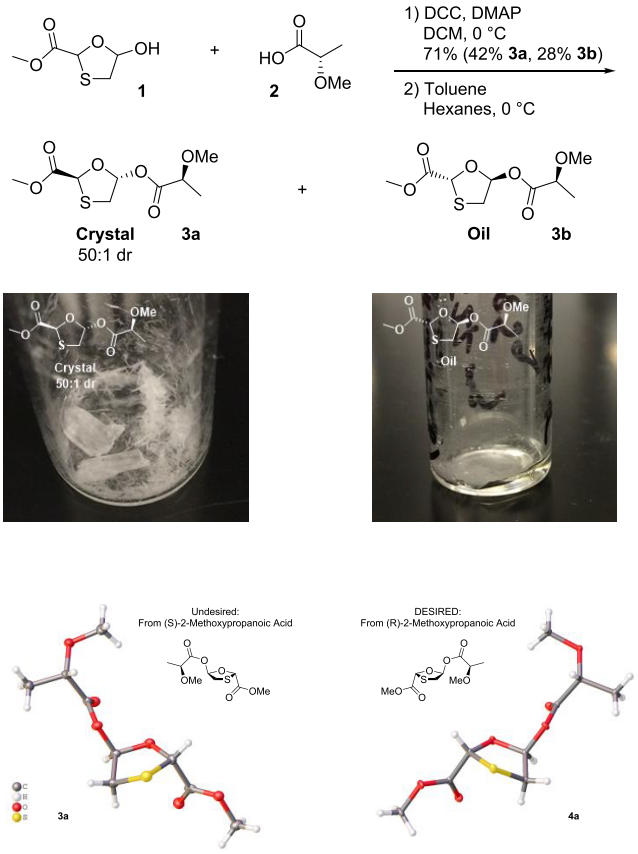

Figure 2. Anomeric acylation controls the proximal and remote stereochemistry of the oxathiolane ring system. Either enantiomer can be obtained, and the nucleating ability of the acyl handle enables isolation in high purity.

selectivity. Although the reaction proceeded to a single compound, the mass balance was low, and ring opening of the hydroxyoxathiolane by base was suspected as a possible route of decomposition. Therefore, the order of addition had the most profound impact on the reaction (entries 8−11). Both the yield and selectivity were optimized by first mixing the acid halide and carboxylate to preform the anhydride and then slowly adding the mixture to a heated solution of the oxathiolane. This mode of addition gives the hydroxyoxathiolane time to epimerize and reform the desired stereoisomer as it is consumed by acylation (entry 11).

Our curiosity was piqued as to whether other catalysts might further improve the reaction outcome. Levamisole has demonstrated success in stereoselective acylation of hemiacetals.[9] Here, levamisole was able to influence the thioacetal stereocenter in addition to the anomeric position and improve overall yield of **4a** to 67% (entry 12). Levamisole is itself an inexpensive active pharmaceutical ingredient (API) used in the treatment of livestock, and at low catalyst loadings its use in a commercial setting is quite feasible. Perhaps even higher selectivities can be reached with other catalysts or enzymes.

COMPLETING AN ECONOMICAL 3TC SYNTHESIS

Our attention next turned to efficient and economical completion of the synthesis of 3TC after having successfully demonstrated the key strategy (Figure 3).[8] A low-cost, stereoselective route to (*R*)-2-methoxypropanoic acid was a primary objective, as natural lactic acid is present with the (2*S*)

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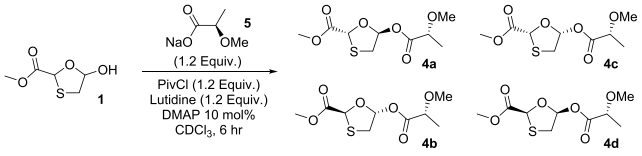
Table 1. Acylation of Oxathiolane 1[a]



entry	T (°C)	RSM	yield of 4 (%)	yield of 4a (%)	*trans*:*cis*	4a:4b (*trans*)
1	−15	11	58	30	5.4	1.6
2	20	–	61	34	5.1	2.0
3	50	–	56	32	5.2	2.1
4[b]	20	–	68	37	5.2	1.9
5[c]	20	95	–	–	–	–
6[d]	20	63	29	12	2.2	1.5
7[e]	70	7	83	18	1.3	0.6
8[f]	20	–	83	46	6.5	1.8
9[g]	20	–	80	44	7.0	1.7
10[h]	20	14	74	48	7.2	2.8
11[h,i]	20	–	90	57	7.2	2.6
12[j]	40	–	93	67	3.8	9.5

[a]Order of addition: $CDCl_3$ was added to sodium lactate under a dry air atmosphere followed by oxathiolane, lutidine, PivCl, and then DMAP. [b]0.375 equiv of lutidine. [c]No lutidine was added. [d]No DMAP was added. [e]No DMAP or lutidine was added. [f]Order of addition: $CDCl_3$ was added to sodium lactate under a dry air atmosphere followed by PivCl, lutidine, oxathiolane, and then DMAP. [g]Order of addition: $CDCl_3$ was added to sodium lactate under a dry air atmosphere followed by PivCl, oxathiolane, lutidine, and then DMAP. [h]Sodium lactate and PivCl were allowed to react for 90 min in $CDCl_3$, at which point lutidine and DMAP were added. The suspension was then slowly added to a solution of oxathiolane in $CDCl_3$ over a 2 h period. [i]1.8 equiv of sodium lactate and PivCl. [j]Levamisole hydrochloride (1 mol %) was used in place of DMAP. Sodium lactate (1.6 equiv) and PivCl (1.6 equiv) were reacted for 90 min in $CDCl_3$, at which point 2-picoline (0.4 equiv) and levamisole were added. The suspension was then slowly added to a solution of oxathiolane in $CDCl_3$ over a 2 h period.

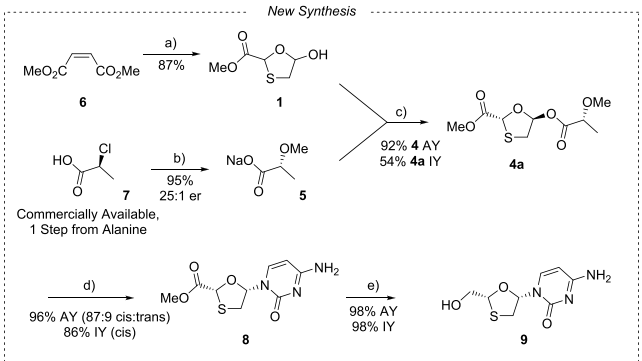


Figure 3. New route to lamivudine. (a) O_3, then 1,4-dithiane-2,5-diol. (b) NaOMe. (c) PivCl and levamisole hydrochloride (1 mol %). (d) Br_2 and mesitylene, then cytosine. (e) $NaBH_4$.

configuration. Fortunately, this was easily accomplished by alkoxylation of (2*S*)-chloropropanoic acid with sodium methoxide. (2*S*)-Chloropropanoic acid is made in one step from alanine (~$2/kg) and is a key material in the synthesis of aryloxyphenoxypropionates and thus is available in large quantities.[10]

Securing a supply of methyl glyoxylate was important, as it has been made in bulk quantities but is not currently offered at

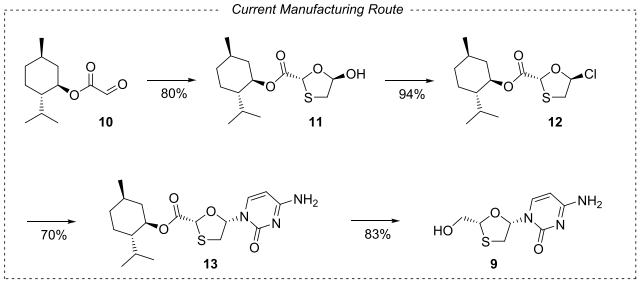


Figure 4. Current manufacturing route developed at GSK.[2]

commercial scale.[11] As a consequence, a glyoxylate equivalent was required and found in dimethyl maleate. The oxathiolane core was synthesized in 87% yield by cleaving dimethyl maleate with ozone[12] and reacting the aldehyde generated in situ with dithianediol. It can be used directly or purified through a brine-based extraction procedure. We expect that the rise of continuous methodologies mitigates the hazard of ozone and presents a feasible means to reach methyl glyoxaldehyde.[13]

With a route to **4a** in hand, confirming the ability of the lactic acid derivative to serve as an acetate mimic in nucleobase coupling was the next critical hypothesis to test. Adjacency of the methyl ester to the oxathiolane ring sets up a selective addition of cytosine to the acylated oxathiolane. Caso's demonstration of in situ generation of HI and silyl iodide from I_2 served as inspiration for development of a cost-effective glycosylation.[14] While this system demonstrated functionality of the lactate and high α:β selectivity, the high cost of iodine ($20/kg) relative to 3TC (~$140/kg) precluded its use. The much less expensive bromine ($2.9/kg) was an effective replacement; however, separation of the product from polymethylhydrosiloxane (PMHS) byproducts remains an unresolved challenge.

Instead, HBr was generated directly from bromine and mesitylene, avoiding complications from siloxanes. The acylated oxathiolane was quantitatively converted in situ to the brominated analogue, an active precursor to the nucleoside, and then upon addition of cytosine the nucleoside was formed in 96% overall yield. Some erosion in the diastereoselectivity is observed during bromination (9:1 *trans*:*cis*), with the anchimeric effect of the methyl ester accounting for the preference for the *trans*-bromo isomer.

The desired *cis* isomer of nucleoside **8** was isolated in 86% yield by crystallization from the reaction mixture. The other stereoisomers were rejected, and the product was isolated with >99% optical purity. Residual impurities, including cytosine, were rejected with quantitative product recovery by crystallization from methanol. X-ray analysis confirmed the stereochemical assignment and the hydrogen bond between the substrate and methanol. Interestingly, this process resulted in an insoluble complex with methanol, which seems to facilitate purification by the formation of an intermolecular hydrogen-bonding network. We expect the chemistry to be applicable to FTC as well, and cursory examination showed that fluorocytosine coupled in 70% yield.

The synthesis of 3TC was completed through reduction of the methyl ester. **8** was reduced to 3TC and isolated in 98% yield. Running the reduction at 0 °C rather than with mild heating was important to avoid generation of byproducts. The product was isolated in 82% purity due to the presence of inorganic salts. Complexation of 3TC with either phthalic or

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oxalic acid can be used to increase the purity of final product and facilitate separation from the inorganic materials.[15]

ECONOMIC IMPACT AND CONCLUSIONS

This constitutes a new route to 3TC with high economic potential. Our calculations estimate a cost of goods of $96–112/kg depending on the degree of solvent recycle compared with the sales price of approximately $140/kg based on the current manufacturing route (Figure 4). This investigational route has further cost reduction potential to $73–98/kg depending on the degree of optimization.[8] The synthesis features inexpensive reagents, and all of the steps proceed in high assay yield.

The mass-efficient conversion of methyl ester **8** to 3TC might represent the greatest economic benefit, however. At the outset, eliminating the use of menthol in the manufacturing route was identified as a key program goal (Figure 5). Despite

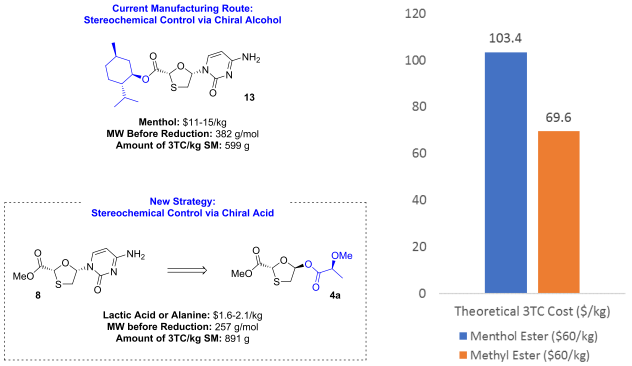

Figure 5. (left) Stereoselective installation of a low-molecular-weight asymmetric glycosylation unit can decrease raw material costs for 3TC. (right) Theoretical cost of 3TC based on 100% yield in reduction and equivalent price of ester starting materials ($60/kg).

its relatively low price (~$15/kg), menthol is still a raw material cost driver that adds significant molecular weight to intermediates that are not incorporated into the final API. This is a problem because reduction of menthyl ester **13** causes a large decrease in molecular weight of the product, necessarily reducing the quantity of alcohol **9** generated per kilogram of ester and thus corresponding to an increase in cost per kilogram of the resultant API. Here, an alternate intermediate can be made with little loss in molecular weight upon reduction, increasing the throughput. If the two penultimate 3TC intermediates were able to be made at the same cost, the methyl ester would result in a 67% lower cost of the 3TC final product.

In summary, a new method to tailor nucleoside stereochemistry was discovered by combining the sugar activation and stereodetermining steps in route to an economical synthesis of 3TC. The use of an asymmetric leaving group for selective acylation governed the absolute stereochemistry of the resultant nucleoside, providing access to either enantiomer. The synthesis was completed in a high-yielding four-step longest linear sequence, making use of low-cost raw materials. The efficiency created by the use of low-molecular-weight intermediates increases the material throughput, setting the stage for reduced costs of goods associated with 3TC. We are hopeful that with further refinement to make this early process development route more suitable for manufacturing scale, the advances described herein will result in lower market prices for this critical HIV treatment.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00083.

Technoeconomic analysis, X-ray analysis, NMR and MS spectra, and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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