ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Communication

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

David Snead, D. Tyler McQuade, Saeed Ahmad, Rudy Krack, Rodger W. Stringham, Justina M. Burns, Irini Abdiaj, Vijayagopal Gopalsamuthiram, Ryan C. Nelson, and B. Frank Gupton

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.0c00083 • Publication Date (Web): 07 Apr 2020

Just Accepted

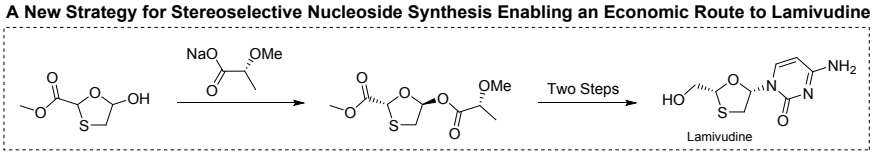
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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

David R. Snead,* D. Tyler McQuade, Saeed Ahmad, Rudy Krack, Rodger W. Stringham, Justina M. Burns, Irini Abdiaj, Vijayagopal Gopalsamuthiram, Ryan C. Nelson, B. Frank Gupton

Supporting Information Placeholder

Table of Contents graphic:



Lamivudine (3TC) is a critical medicine in the fight against HIV. New cost effective routes to the medicine are needed as HIV most heavily impacts countries with low economic purchasing power. This challenging constraint provided a fresh perspective on construction of this subtly complex molecule. A new strategy for stereoselective nucleoside formation was developed with potential to reduce cost of this important drug.

ABSTRACT: An economical synthesis of lamivudine was developed by employing a new method to establish stereochemistry about the heterocyclic oxathiolane ring. Toward this end, an inexpensive and readily accessible lactic acid derivate served the dual purpose of activating the carbohydrate's anomeric center for *N*-glycosylation while transferring stereochemical information to substrate simultaneously. Both enantiomers of the lactic acid derivative are available, and either β-enantiomer in this challenging class of 2′-deoxynucleoside active pharmaceutical ingredient (API) 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 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 due to 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 which lacks an oxygen atom at the C2 position adjacent to the anomeric center. This poses a particular challenge because oxygenated neighboring groups establish absolute stereochemistry

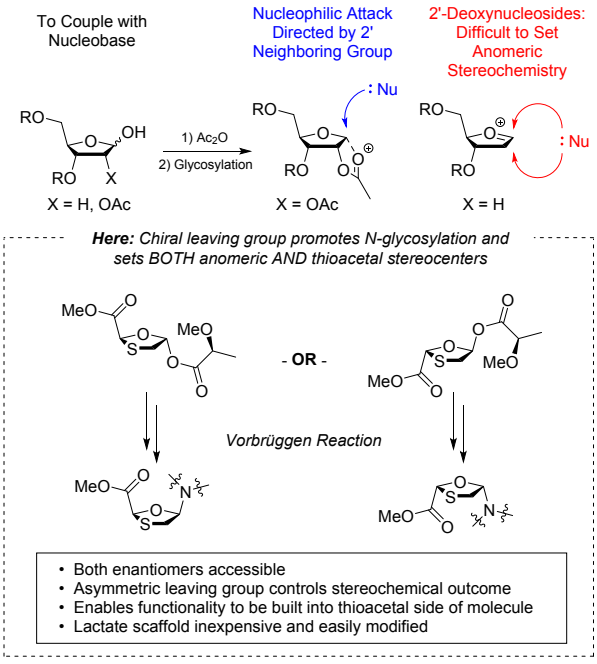


Figure 1. A successful strategy to control stereochemistry of challenging 2′-deoxyoxathiolane nucleosides.

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 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, 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 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]

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 which allowed us to dictate the 2′-deoxynucleoside enantiomer of choice.

A Novel Strategy to Control Oxathiolane Stereochemistry

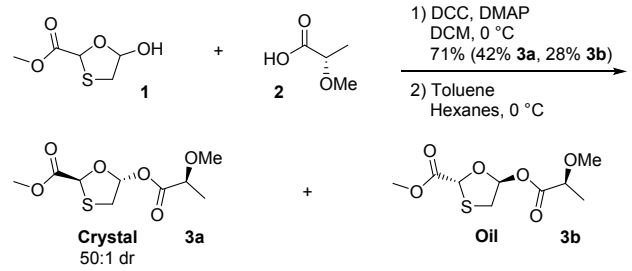
Use of a chiral acid to activate the sugar at the anomeric position was the lynchpin of our strategy (Figure 1). Acylation of sugars is one of the most common means to prepare carbohydrates for coupling with nucleobases,[3b,6] and in this manner, the stereochemistry of the rapidly epimerizing sugar can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

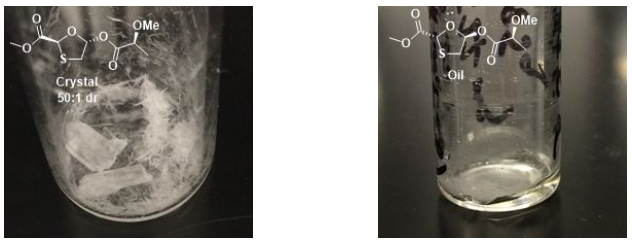
Proof of Concept

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 which is 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 nucleobase, the ester dictates stereochemistry of the incoming nucleophile at the anomeric center via anchimeric effect. In this manner, acylation establishes both 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 proof of concept in hand 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





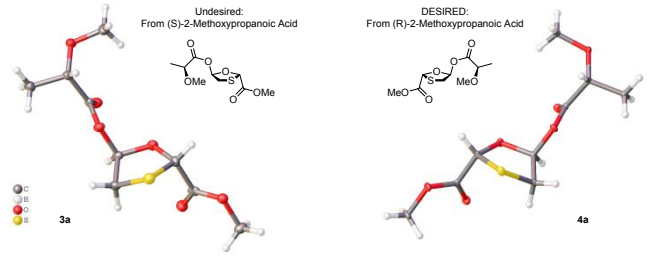


Figure 2. Anomeric acylation controls proximal and remote stereochemistry of oxathiolane ring system. Either enantiomer can be obtained, and nucleating ability of the acyl handle enables isolation in high purity.

was observed in 5:1 ratio using DMAP as a catalyst with a 2:1 preference for the desired 2R,5R isomer, but yield was in the mid-30%. Maximizing stereoselective outcome was an important goal to optimize the overall yield of **4a**.[8] Lower temperature resulted in decreased selectivity as did increasing equivalents of the mixed anhydride. Presumably, lowering temperature decreased the rate of hydroxyoxathiolane epimerization thus leading to the lower selectivity. Despite the reaction proceeding to a single compound, mass balance was low, and ring opening of the hydroxyoxathiolane by base was suspected as a possible route of decomposition. As such, order of addition had the most profound impact on the reaction (entries 8-11). Both yield and selectivity were optimized by first mixing acid halide and carboxylate to preform the anhydride and then slowly adding the mixture to a heated solution of 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 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 API used in 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 others catalysts or enzymes.

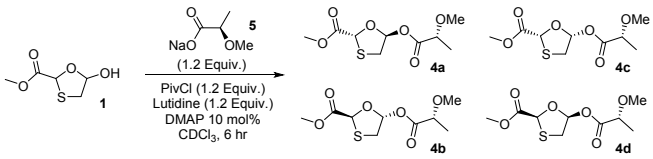


Table 1. Acylation of oxathiolane **1**.

Entry	Temp. (° C)	RSM	Yield 4 (%)	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]	"	95	-	-	-	-
6[d]	"	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]	"	-	80	44	7.0	1.7
10[h]	"	14	74	48	7.2	2.8
11[h,i]	"	-	90	57	7.2	2.6
12[j]	40	-	93	67	3.8	9.5

a) Order of addition: $CDCl_3$ added to sodium lactate under dry air atmosphere followed by oxathiolane, lutidine, PivCl, and then DMAP. b) 0.375 equiv. lutidine. c) No lutidine added. d) No DMAP added. e) No DMAP or lutidine added. f) Order of addition: $CDCl_3$ added to sodium lactate under dry air atmosphere followed by PivCl, lutidine, oxathiolane, and then DMAP. g) Order of addition: $CDCl_3$ added to sodium lactate under dry air atmosphere followed by PivCl, oxathiolane, lutidine, and then DMAP. h) Sodium lactate and PivCl reacted 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 hr period. i) 1.8 equiv. of sodium lactate and PivCl. j) Levamisole hydrochloride (1 mol%) used in place of DMAP. Sodium lactate (1.6 equiv.) and PivCl (1.6 equiv.) 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 hr period.

Completing an Economical 3TC Synthesis

Attention turned to efficient and economical completion of the synthesis of 3TC 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) 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 (AOPPs) and thus available in large quantities.[10]

Securing supply of methyl glyoxylate was important, as it has been made in bulk quantities but is not currently offered at commercial scale.[11] As a consequence a glyoxylate equivalent is required and found in dimethyl maleate. The oxathiolane core was synthesized in 87% yield by cleaving dimethylmaleate 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 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* 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 product from 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 to the

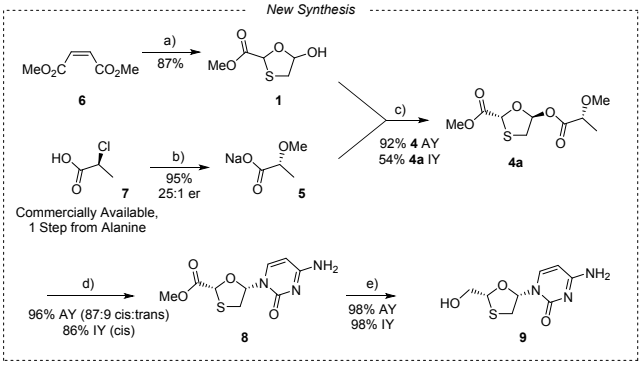


Figure 3. New route to lamivudine. a) O_3, then 1,4-dithiane-2,5-diol. b) NaOMe. c) PivCl and levamisole hydrochloride (1 mol%). d) Br_2 and mesitylene, then cytosine. e) $NaBH_4$.

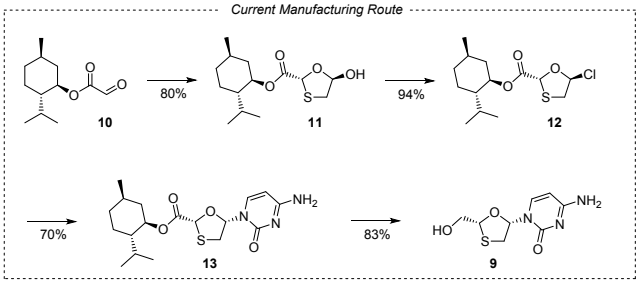


Figure 4. The current manufacturing route developed at GSK.[2]

brominated analogue *in situ*, an active precursor to 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 *trans*-bromo isomer preference.

The desired *cis* isomer of nucleoside **8** was isolated in 86% 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 crystallizing from methanol. X-Ray analysis confirms the stereochemical assignment and the hydrogen bond between substrate and methanol. Interestingly, this process resulted in an insoluble complex with methanol which seems to facilitate purification by forming an intermolecular hydrogen bond network. We expect the chemistry is applicable to FTC as well, and cursory examination showed that fluorocytosine coupled in 70% yield.

3TC synthesis 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 by-products. The product is isolated in 82% purity due to the presence of inorganic salts. Complexing 3TC with either phthalic or oxalic acid can be used to increase 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 cost of goods of $96-112/kg depending on degree of solvent recycle compared to current sales price of ~$140/kg. 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 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 use of menthol in the manufacturing route was identified as a key program goal (Figure 5). Despite its relatively low price (~$15/kg), menthol is still a raw material cost driver that adds significant molecular weight to intermediates which are not incorporated in 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 kg of ester, and thus corresponding to an increase in cost per kg of resultant API. Here, an alternate intermediate can be made with little loss in molecular weight upon reduction, increasing 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 3TC final product.

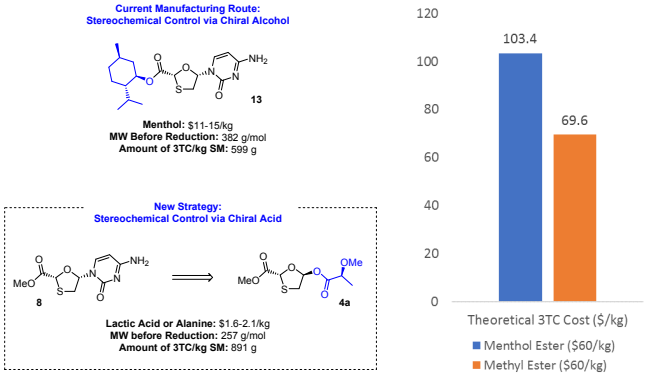


Figure 5. Stereoselective installation of a low molecular weight asymmetric glycosylation unit can decrease raw material costs for 3TC. Theoretical cost of 3TC based on 100% yield in reduction and equivalent price of ester starting materials ($60/kg).

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. 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 4-step longest linear sequence, making use of low cost raw materials. The efficiency created by use of low molecular weight intermediates increases 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 on the ACS Publications website including technoeconomic analysis, xray analysis, and experimentals (PDF).

AUTHOR INFORMATION

Corresponding Author

* David Snead
Medicines for All Institute
737 N 5th St.
Box 980100
Richmond, Virginia 23298
E-mail: drsnead@vcu.edu

ACKNOWLEDGMENT

We thank the Bill and Melinda Gates Foundation for their longstanding support of our research. This work was also partially supported by Structural Biology resources provided by Institutes of Health Shared Instrumentation Grant S10-OD-021756 (MKS) and Virginia General Assembly Higher Education Equipment Trust Fund (HEETF) to VCU. We would like to express gratitude to Trevor Laird and John Dillor for insightful discussions and suggestions.

REFERENCES

1) a) Panos, Z.; Fox, J.; Prabhu, V. "*HIV Market Report*" from Clinton Health Access Initiative, **2019**, *10*. (Accessed Feb. 6, 2020 at: http://clintonhealthaccess.org/wp-content/uploads/2019/12/2019-HIV-Market-Report.pdf) b) World Health Organization, HIV country profiles, https://www.who.int/hiv/data/profiles/en/ (Accessed Apr. 2, 2020). c) World Health Organization, Data on the size of the HIV/AIDS epidemic, https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/data-on-the-size-of-the-hiv-aids-epidemic (Accessed Apr. 2, 2020). d) World Atlas, Countries with the highest Rates of HIV/AIDS, https://www.worldatlas.com/articles/countries-with-the-highest-rates-of-hiv-aids.html (Accessed Apr. 2, 2020).

2) a) Commercial route confirmed through conversation with manufacturers and by analysis of high-volume transaction records of API intermediate moving through market (menthol glyoxylate and menthol ester of hydroxyl or cytosinyl oxathiolane) b) Goodyear, M.D.; Dwyer, P.O.; Hill, M.L.; Whitehead, A.J.; Hornby, R.; Hallet, P. Process for the diastereoselective synthesis of nucleoside analogues, US6051709, **2000**. c) Goodyear, M.D.; Hill, M.L.; West, J.P.; Whitehead, A.J. Practical enantioselective synthesis of

lamivudine (3TC™) via a dynamic kinetic resolution, *Tet. Lett.*, **2005**, *46*, 8535-8538.

3) a) Watanabe, K.A.; Hollenberg, D.H.; Fox, J.J. Nucleosides. 85. On mechanisms of nucleoside synthesis by condensation reactions, *J. Carbohydr. Nucleos. Nucleot.*, **1974**, *1*, 1-37. b) Wilson, L.J.; Hagar, M.W.; El-Kattan, Y.A.; Liotta, D.C. Nitrogen lycosylation reactions involving pyrimidine and purine nucleoside bases with furanoside sugars, *Synthesis*, **1995**, *12*, 1465-1479. c) Mukaiyama, T.; Hirano, N.; Nishida, M.; Uchiro, H. Catalytic stereoselective synthesis of pyrimidine 2-deoxyribonucleosides, *Chem. Lett.*, **1996**, *25*, 99-100. d) McLaughlin, M.; Kong, J.; Belyk, K.M.; Chen, B.; Gibson, A.W.; Keen, S.P.; Lieberman, D.R.; Milczek, E.M.; Moore, J.C.; Murray, D.; Ji Qi, F.-P.; Reamer, R.A.; Song, Z.J.; Tan, L.; Wang, L.; Williams, M.J. Enantioselective synthesis of 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA) via enzymatic desymmetrization, *Org. Lett.*, **2017**, *19*, 926-929.

4) a) Jeong, L.S.; Schinazi, R.F.; Beach, W.J.; Kim, H.O.; Nampallia, S.; Shanmuganathan, K.; Alves, A.J.; McMillan, A.; Chu, C.K.; Mathis, R. Asymmetric synthesis and biological evaluation of β-L-(2R,5S)- and α-L-(2R,5R)-1,3-oxathiolane-pyrimidine and -purine nucleosides as potential anti-HIV agents, *J. Med. Chem.*, **1993**, *36*, 181-195. b) Hu, L.; Schaufelberger, F.; Zhang, Y.; Ramström, O. Efficient asymmetric synthesis of lamivudine via enzymatic dynamic kinetic resolution, *Chem. Commun.*, **2013**, *49*, 10376-10378.

5) a) Hoong, L.K.; Strange, L.E.; Liotta, D.C. Enzyme-mediated enantioselective preparation of pure enantiomers of the antiviral agent 2', 3'-dideoxy-5-fluoro-3'-thiacytidine (FTC) and related compounds, *J. Org. Chem.*, **1992**, *57*, 5563-5565. b) Mahmoudian, M.; Baines, B.S.; Drake, C.S.; Hale, R.S.; Jones, P.; Piercey, J.E.; Montgomery, D.S.; Purvis, I.J.; Storer, R.; Dawson, M.J.; Lawrence, G.C. Enzymatic production of optically pure (2′ R-cis)-2′-deoxy-3′-thiacytidine (3TC, Lamivudine): A potent anti-HIV agent, *Enzyme Microb. Technol.*, **1993**, *15*, 749-755. c) Milton, J.; Brand, S.; Jones, M.F.; Rayner, C.M. Enzymatic Resolution of α-acetoxysulfides: A new approach to the synthesis of homochiral S, O-Acetals, *Tet. Asymm.*, **1995**, *6*, 1903-1906. d) Milton, J.; Brand, S.; Jones, M.F.; Rayner, C.M. *Tet. Lett.*, **1995**, *36*, 6961-6964. e) Cousins, R.P.C.; Mahmoudian, M.; Youds, P.M. Enantioselective enzymatic synthesis of the anti-viral agent lamivudine (3TC™), *Tet. Asymm.*, **1995**, *6*, 393-396. f) Jin, H.; Siddiqui, A.; Evans, C.A.; Tse, H.L.A.; Mansour, T.S. Diastereoselective synthesis of the potent antiviral agent (-)-2'-deoxy-3'-thiacytidine and its enantiomer, *J. Org. Chem.*, **1995**, *60*, 2621-2623. g) Li, J.-Z.; Gao, L.-X.; Ding, M.-X. The chemical resolution of racemic cis-2-hydroxymethyl-5-(cytosine-1′-yl)-1,3-oxathiolane (BCH-189)—One direct method to obtain lamivudine as anti-HIV and anti-HBV agent, *Synth. Commun.*, **2002**, *32*, 2355-2359. h) Roy, B.N.; Singh, G.P.; Srivastava, D.; Jadhav, H.S.; Saini, M.B.; Aher, U.P. A Novel Method for Large-Scale Synthesis of Lamivudine through Cocrystal Formation of Racemic Lamivudine with (S)-(−)-1,1′-Bi(2-naphthol) [(S)-(BINOL)], *Org. Process Res. Dev.*, **2009**, *13*, 450-455. i) Reddy, B.P.; Reddy, K.R.; Reddy, R.R.; Reddy, D.M.; Srinivas, A.S. Optical resolution of substituted 1,3-oxathiolane nucleosides, US20110245497, **2011**.

6) a) Knapp, S. Synthesis of complex nucleoside antibiotics, *Chem. Rev.*, **1995**, *95*, 1859-1876. b) Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. Chemical synthesis of heterocyclic− sugar nucleoside analogues, *Chem. Rev.*, **2010**, *110*, 3337-3370.

7) Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. Widely useful DMAP-catalyzed esterification under auxiliary base-and solvent-free conditions, *J. Am. Chem. Soc.*, **2007**, *129*, 14775-14779.

8) See Supporting Information for details regarding optimization of synthesis.

9) a) Birman, V.B.; Li, X. Benzotetramisole: A remarkably enantioselective acyl transfer catalyst, *Org. Lett.*, **2006**, *8*, 1351-1354. b) Birman, V.B.; Li, X. Homobenzotetramisole: an effective catalyst for kinetic resolution of aryl-cycloalkanols, *Org. Lett.*, **2008**, *10*, 1115-1118. c) Müller, C.E.; Schreiner, P.R. Organocatalytic Enantioselective Acyl Transfer onto Racemic as well as meso Alcohols, Amines, and Thiols, *Angew. Chem., Int. Ed.*, **2011**, *50*, 6012-6042. d) Ortiz, A.; Benkovics, T.; Beutner, G.L.; Shi, Z.; Bultman, M.; Nye, J.; Sfouggatakis, C.; Kronenthal, D.R. Scalable Synthesis of the Potent HIV Inhibitor BMS-986001 by Non-Enzymatic Dynamic Kinetic Asymmetric Transformation (DYKAT), *Angew. Chem., Int. Ed.*, **2015**, *54*, 7185-7188. e) Wang, H.-Y., Blaszcyk, S.A.; Xiao, G.; Tang, W. Chiral reagents in glycosylation and modification of carbohydrates, *Chem. Soc. Rev.*, **2018**, *47*, 681.

10) a) Fleer, M.P.M.; Verkuijl, B.J.V. Optimization of the use of a chiral bio-based building block for the manufacture of DHPPA, a key intermediate for propionate herbicides, *Green Chem.*, **2014**, *16*, 3993-3998. b) Whittingham, W.G. Herbicidal Aryloxyphenoxypropionate Inhibitors of Acetyl-CoA Carboxylase in *Bioactive Carboxylic Compound Classes: Pharmaceuticals and Agrochemicals*; Lamberth, C.; Dinges, J., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinham, Germany, 2016, 325-337.

11) a) Baltes, H.; Leupold, E.I.; Wunder, F. Process for the manufacture of glyoxylic acid esters, US4340748, **1982**. b) Dyroff, D. R.; Chou, Y.; Cova, D.R. Production of high purity alkyl glyoxylate by plural stage distillation, US4502923, **1985**. c) Baba, H.; Miura, S.; Nonoguchi, M.; Saito, N. Method of purifying glyoxylic esters and distillation equipment for purifying glyoxylic esters, US6037489, **1996**. d) Hayashi, T.; Inagaki, T. Catalyst for the preparation of carboxylic esters and method for producing carboxylic esters, US7326806, **2002**.

12) Jung, M.E.; Shishido, K.; Davis, L.H. Simple syntheses of diethyl oxomalonate and alkyl glyoxylates, *J. Org. Chem.*, **1982**, *47*, 891-892.

13) a) Nobis, M.; Roberge, D.M. Mastering ozonolysis: production from laboratory to ton scale in continuous flow, *Chim. Oggi*, **2009**, *29*, 56-58. b) Allian, A.D.; Richter, S.M.; Kallemeyn, J.M.; Robbins, T.A.; Kishore, V. The development of continuous process for alkene ozonolysis based on combined in situ FTIR, calorimetry, and computational chemistry, *Org. Process Res. Dev.*, **2011**, *15*, 91-97. c) Fisher, T.J.; Dussault, P.H. Alkene ozonolysis, *Tet.*, **2017**, *73*, 4233-4258.

14) Caso, M.F.; D'Alonzo, D.; D'Errico, S.; Palumbo, G.; Guaragna, A. Highly Stereoselective Synthesis of Lamivudine (3TC) and Emtricitabine (FTC) by a Novel N-Glycosidation Procedure, *Org. Lett.*, **2015**, *17*, 2626-2629.

15) a) da Silva, C.C.; Coelho, R.R.; Cirqueira, M.L.; de Melo, A.C.C.; Rosa, I.M.L.; Ellena, J.; Martins, F.T. Salts of the anti-HIV drug lamivudine with phthalic and salicylic acids, *CrystEngComm*, **2012**, *14*, 4562-4566. b) Perumalla, S.R.; Sun, C.C. Significant expansion of the solid state landscape of salicylic acid based on charge-assisted hydrogen bonding interactions, *Cryst. Growth Des.*, **2014**, *14*, 3990-3995.