ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

pubs.acs.org/OPRD

Communication

Synthesis of an Oxathiolane Drug Substance Intermediate Guided by Constraint-Driven Innovation

K. Kashinath,[†] David R. Snead,*[,†] Justina M. Burns, Rodger W. Stringham, B. Frank Gupton, and D. Tyler McQuade*

Cite This: *Org. Process Res. Dev.* 2020, 24, 2266–2270

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A new route was developed for construction of the oxathiolane intermediate used in the synthesis of lamivudine (3TC) and emtricitabine (FTC). We developed the presented route by constraining ourselves to low-cost, widely available starting materials—we refer to this as supply-centered synthesis. Sulfenyl chloride chemistry was used to construct the framework for the oxathiolane from acyclic precursors. This bond construction choice enabled the use of chloroacetic acid, vinyl acetate, sodium thiosulfate, and water to produce the oxathiolane.

KEYWORDS: *antiviral, nucleoside, oxathiolane, supply chain, HIV*

Lamivudine (3TC, **1**) and emtricitabine (FTC, **2**) are essential components of widely prescribed multidrug regimens.[1] Both nucleoside analogues are high-dosage/high-demand drugs and manufactured in large volumes (>1000 MT/year). Though the price of 3TC (~$140/kg) is low in comparison with those of other active pharmaceutical ingredients (APIs) of similar structural complexity, procurers (governmental and nongovernmental organizations) spend more than $200MM/year, and the number of patients that receive these life-saving medicines is fixed by procurer budgets. For this reason, decreasing production costs constitutes an impactful yet difficult challenge.

The vast majority of innovation related to 3TC and FTC has focused on improved methods to establish the stereochemistry about the oxathiolane ring[2] and install the cytosine and 5-fluorocytosine nucleobases.[2a,h,k,3] Despite these efforts, the original synthesis developed at GSK by Whitehead and co-workers remains in place today as the manufacturing bond-forming sequence of choice (Figure 1).[2i,k] The GSK approach features a dynamic kinetic resolution (DKR) to afford optically pure hydroxyoxathiolane **4**, a key intermediate in the synthesis. L-Menthol (**6**) controls the stereochemical outcome of the DKR, which is driven to completion via selective crystallization of a single isomer from solution.

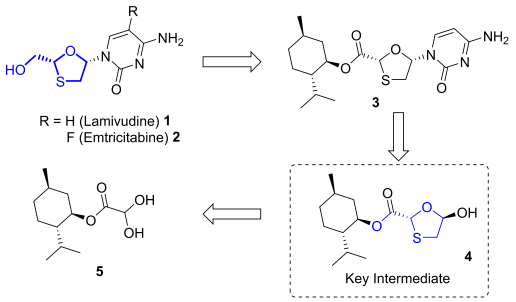


Figure 1. Commercial retrosynthetic route for lamivudine and emtricitabine.

Perhaps a different way to approach the problem would be to work within the current manufacturing route. One such strategy would be to improve the route to oxathiolanes themselves, thus complementing the existing knowledge, supply chain, and regulatory framework. The majority of syntheses make use of condensation of 1,4-dithiane-2,5-diol with L-menthol glyoxylate (**5**), with an exception presented in the stepwise ring closing of a protected hemithioacetal by Rayner and co-workers, also at GSK.[2f] We hypothesized that a new approach that replaced the use of the glyoxylate ester and the dithianediol could accomplish three outcomes: (1) decrease the raw material costs; (2) increase the supply chain security for making 3TC and FTC; and (3) increase the number of producers because an entirely new approach might fit well into the skill set of new market entrants.

Our team at the Medicine for All Institute starts designing new routes from the perspective that APIs can be built from simple, high-volume, low-cost raw materials using modern synthetic methods/knowledge. We call this approach "supply-centered synthesis". To envision new economical routes to oxathiolanes, we developed a subset of building blocks with the right oxidation state, functionality, and carbon count for each fragment of the ring (Figure 2). The viability of each building block was assessed by examining the volume and price of each chemical as found through import/export records of India, a major player in the global manufacture of APIs. Instead of considering the most straightforward retrosynthetic assembly

Special Issue: Flow Chemistry Enabling Efficient Synthesis

Received: March 31, 2020
Published: May 13, 2020

https://dx.doi.org/10.1021/acs.oprd.0c00145
Org. Process Res. Dev. 2020, 24, 2266–2270

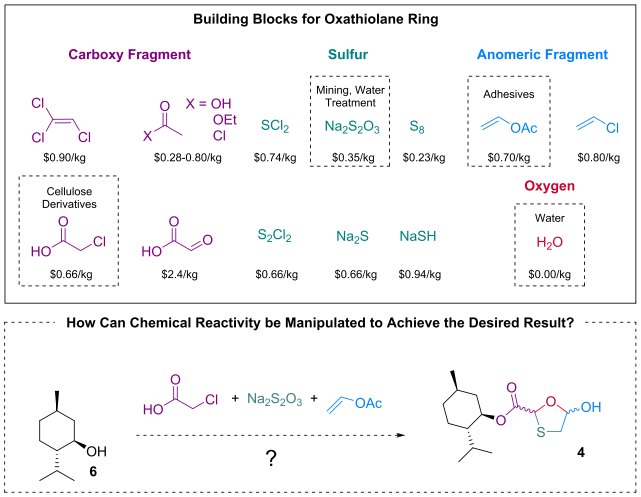


Figure 2. Supply-centered synthesis: molecular construction from commodity chemical materials.

of fragments, we prioritized reagent availability and cost and then sought reactions to render a viable process.

Chloroacetic acid, sodium thiosulfate, and vinyl acetate quickly emerged as lead candidates, presuming that they could be transformed into the oxathiolane core in a modest number of steps. All of these raw materials are fundamental feedstocks for the chemical industry and cost less than $1/kg. Their end uses point toward their high-volume consumption: chloroacetic acid is used to make cellulose derivatives for the food and cosmetics industries, sodium thiosulfate is used in the mining, water treatment, and fertilizer industries; and vinyl acetate is used as the precursor to poly(vinyl acetate), a major adhesive class. Since these are produced in the hundreds of MM kg/year, the supply chain and availability are secure. While starting from low-cost, high-volume raw materials is somewhat obvious, the key to their use is the development of an efficient route. Five bonds must be constructed, three oxidations are needed, and one functional group must be hydrolyzed. Although many routes were considered by our team, we found the route in Figure 3 to be the most promising.

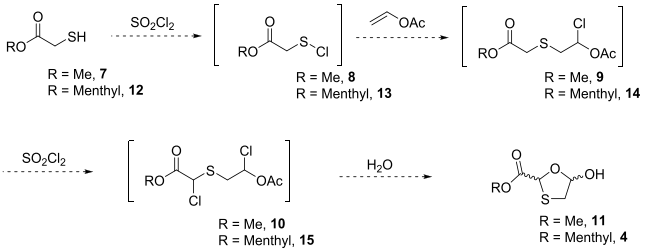
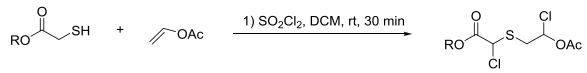


Figure 3. Proposed route to oxathiolane from vinyl acetate and glycolate ester.

The route we envisioned starts with chlorination of thioglycolic acid using the method of Smit (Figure 3).[4] If we wanted to take the process to very high volume starting materials, thioglycolic acid can be accessed from chloroacetic acid and sodium thiosulfate.[5] We imagined that the sulfur−carbon bond could result via regioselective 1,2-insertion of a sulfenyl chloride into the olefin of vinyl acetate to directly couple the two carbon-containing fragments.[6] In this way, the required oxidation state at the anomeric center, a masked aldehyde, could be established. Futhermore, we hypothesized that excess sulfuryl chloride could α-chlorinate the ester, thereby establishing all of the necessary oxidation states.[7] Reaction with water to close the ring would complete the oxathiolane synthesis.

The key transformation was validated by combining methyl thioglycolate (MTG, **7**) and vinyl acetate (VA) (Table 1).

Table 1. Oxidative Coupling of Thioglycolic Acid and Vinyl Acetate



entry	R	order of addition	volumes of solvent	temp. (°C)	yield (%)
1[a,c]	Me	VA last	10×	20	76
2[b,c]	Me	VA last	10×	20	91
3[b,d]	Me	SO_2Cl_2 last	10×	20	90
5[b,e]	Me	MTG last	10×	20	89
6[b,c]	Me	VA last	2×	20	83
7[b,c]	Me	VA last	6×	20	91
8[b,c]	Me	VA last	10×	20	91
9[b,c]	Me	VA last	2×	−20	90
10[b,c]	Me	VA last	6×	−20	97
11[b,c]	Me	VA last	10×	−20	95
12[b,f]	menthyl	VA last	6×	−20	99
13[g]	menthyl	VA last	6×	−20	95

[a]The reaction was run in a 4 mL vial open to the atmosphere. [b]The reaction was run in a sealed NMR tube. [c]VA was added to a mixture of MTG and SO_2Cl_2. [d]SO_2Cl_2 was added to a mixture of MTG and VA. [e]MTG was added to a mixture of VA and SO_2Cl_2. [f]The reaction was run in $CDCl_3$. [g]The reaction was run in toluene.

Optimization increased the yield of dichlorinated intermediate **10** to >95%. The model system was quickly extended to the l-menthyl ester with performance matching that of the methyl ester, and the reaction was conducted in toluene for increased sustainability.

We observed an unanticipated feature of the reaction early on, where reactions run in sealed vessels provided much higher yields than reactions run in open vessels (Table 1, entries 1 and 2). When sealed reaction vessels were opened, gas release was evident. Furthermore, in a pressurized NMR tube, HCl reacted with vinyl acetate to make 1-chloroethyl acetate. The reaction appears to be sensitive to the HCl gas concentration in solution, and we suspect that this is the origin of the pressure dependence.

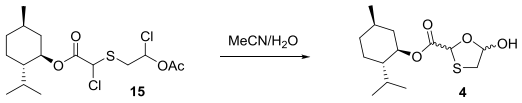
The reaction also showed a strong temperature dependence. Lowering the reaction temperature increased the yield significantly (Table 1, entries 6−8 vs 9−11). A large exotherm was observed both on addition of sulfuryl chloride and addition of vinyl acetate. Presumably cooling helps to mitigate the detrimental effects of the exotherm. Reactions run at room temperature rather than −20 °C contained primarily monochlorinated sulfide **9** as a major impurity, a surprising result of incomplete reaction. One would expect a system to be overly reactive at elevated temperatures. Perhaps the reason for this phenomenon is similar to that of the observed pressure sensitivity. There is a need to maintain headspace control and keep gases in solution; however, gases become less soluble as the temperature increases. Sulfuryl chloride is stated to behave as a source of chlorine gas, a compound that is known to promote α-chlorination.[8] Possibly HCl or Cl_2 is required for

https://dx.doi.org/10.1021/acs.oprd.0c00145
Org. Process Res. Dev. 2020, 24, 2266−2270

the transformation to take place, and a temperature rise might drive these out of the system. This is consistent with the decrease in yield as the reaction concentration increases because tight temperature control is more difficult to maintain.

A proof of concept for the process was completed by demonstrating the viability of ring closing to form the oxathiolane from **15** (Table 2). Combining **15** with water

Table 2. Optimization of Ring Closing in Water



entry	MeCN:H_2O[a]	temp. (°C)	additive	time (h)	yield (%)
1[c]	1.5	65	–	15	42
2[b]	2	55	NaOAc	15	48
3[b,d]	2	55	TEA	22	69
4[b,d]	1	80	1 M TEA in MeCN	2	64
5[b,d]	1	80	1 M $NaHCO_3$	2	68
6[c]	1	60	α-pinene	8	63
7[c]	1	80	α-pinene	3	66
8[c]	1	100	α-pinene	2	69
9[c]	1	90	styrene oxide	2.5	66
10[c]	1	90	2,2-dimethyloxirane	2.5	62

[a]20 vol of acetonitrile. [b]The reaction was run at 100 mg scale. [c]The reaction was run at 1 g scale. [d]The additive was added portionwise.

and acetonitrile provided the desired material in a modest 42% yield, and with optimization the yield was improved to 69%. During optimization, we discovered that the highest yields were obtained when the ring closure was run between pH 3 and pH 4 using base additions to maintain the pH within those constraints. While selective transesterification is necessary to initiate the reaction, an overly reactive system leads to cleavage of the menthyl ester, as observed by the presence of free menthol. Controlling the pH to neutralize the HCl generated in the course of the reaction led to a slight improvement in the yield, but it was important not to reach alkaline pH because base rapidly decomposes the starting material and product.

We propose that the reaction proceeds first through hydrolysis of acetate **15** to generate aldehyde **17** (Figure 4). The α-chloride is then hydrolyzed, and the ring closes. This hypothesis is supported by generation of the dimethoxyacetal

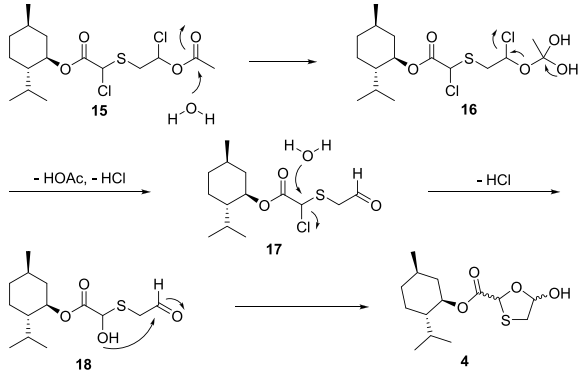


Figure 4. Proposed mechanism for the formation of oxathiolane **4** from **15** commencing with hydrolysis of the acetate.

in 90% yield along with methyl acetate when **15** is exposed to methanolic HCl. The α-chloro functionality is retained. Conversion of **15** slows significantly in the absence of HCl, as the transesterification requires an acid catalyst. Indeed, when the reaction is run in water, a trace aldehyde peak (<5%) is detected by NMR spectroscopy. The α-chlorosulfide can then be functionalized with a variety of oxygenated nucleophiles, including alcohols and carboxylates. Many unsuccessful attempts were made to isolate byproducts and side products, including preparative HPLC and liquid nitrogen trapping of any gaseous compounds. Both NMR and LC traces showed little besides oxathiolane **4**, leading to frustratingly little evidence to aid optimization.

This route depends on access to L-menthyl ester **12**. Fortunately, esterification of thioglycolic acid provided entry to this compound in high yield (98%).[9] Only trace solvent (0.5 vol of toluene) was needed for the sake of temperature control and removal of water to drive the esterification (Figure 5).

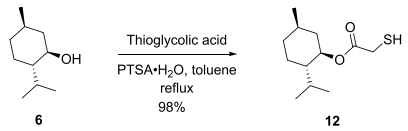


Figure 5. Esterification of L-menthol.

The individual transformations were stitched together to take L-menthol directly to oxathiolane intermediate **4**, needing only a water rinse prior to isolation by crystallization (Figure 6). L-Menthol (10 g) was reacted with thioglycolic acid in 5 vol

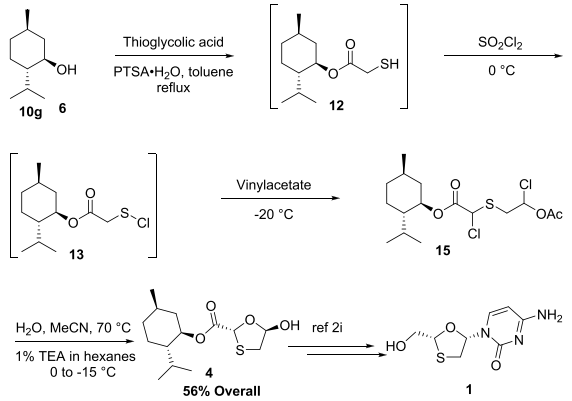


Figure 6. Synthesis of **4** directly from L-menthol.

of toluene. After 2 h, the reaction mixture was cooled to 0 °C, and sulfuryl chloride was added to ester **12** to afford sulfenyl chloride **13**. The reaction mixture was further cooled to −20 °C before the addition of vinyl acetate. Reagents were added over 15 min by syringe pump because of the large exotherms. The reaction mixture was partially quenched with sodium bicarbonate, and the toluene was stripped from the chlorinated residue. Acetonitrile and water were added after chlorinated intermediate **15** was returned to a reaction flask. Heating at 70 °C formed the oxathiolane, which was isolated by extraction with toluene and crystallization with hexanes as the antisolvent in 56% overall yield with >99% purity. Compound **4** was converted to lamivudine with 99% chiral purity by following the known procedure.[2i]

https://dx.doi.org/10.1021/acs.oprd.0c00145
Org. Process Res. Dev. 2020, 24, 2266−2270

We investigated a wide range of conditions to improve the yield of the cyclization from **15** to **4**. The modest yield of the product is accompanied by off-products that appeared as broad signals in the NMR spectrum and were not observed using HPLC or other characterization techniques. We speculate that either **15** decomposes to materials that evaporate readily or oligomerize. Because our attempts at byproduct analysis did not provide actionable insights, we explored the effect of replacing vinyl acetate with ethyl vinyl ether (Figure 7). Ethyl

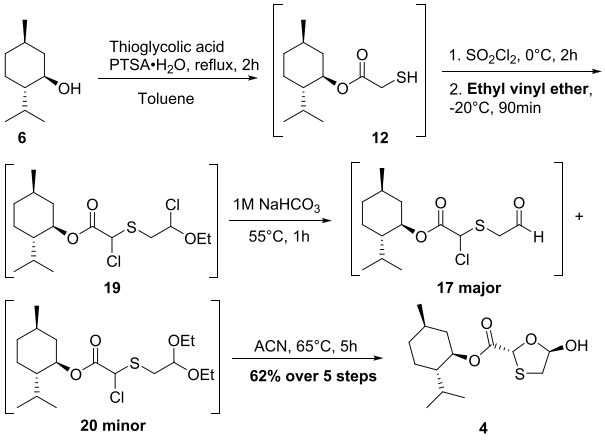


Figure 7. One-pot synthesis of **4** from L-menthol and ethyl vinyl ether.

vinyl ether is widely available via vinylation of ethanol with acetylene and is used in a variety of adhesive applications.[10] The more electron-rich olefin was highly reactive with sulfenyl chloride, and unexpectedly, aldehyde **17** rather than chloroether **19** was obtained upon workup of the addition of sulfenyl chloride to the olefin. Perhaps accelerated C−Cl cleavage is also an effect of the ether's greater electron density. The overall yield increased moderately after cyclization, but more importantly, the solvent quantity required for cyclization was reduced by half compared with the vinyl acetate approach.[11] Alkyl chlorides are quite hydrophobic, and presumably the reduced need for solvent is an effect of cleaving one of the alkyl chlorides.

In this way, the sulfenyl chloride methodology proved to be a versatile platform for entry into oxathiolane chemistry. Relevant thiol esters were made from thioglycolic acid. The resultant thiol was halogenated with sulfuryl chloride, and this sulfenyl chloride was used to construct a sulfur−carbon bond with vinyl acetate and ethers. Presence of excess sulfuryl chloride halogenated the ester at the α-position. This dichlorinated intermediate was cyclized in water to generate the oxathiolane used in the synthesis of 3TC and FTC. By focusing on the chemical industry's supply chain and base reagents, a novel route was tailored to fit the starting materials. Combining a target-oriented retrosynthetic perspective with a supply-centered viewpoint served as a useful constraint to generate creative and novel solutions for longstanding challenges.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00145.

Experimental details and compound characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

David R. Snead − *Medicines for All Institute, Virginia Commonwealth University, Richmond, Virginia 23298, United States;* orcid.org/0000-0003-1239-533X; Email: drsnead@vcu.edu

D. Tyler McQuade − *Medicines for All Institute, Virginia Commonwealth University, Richmond, Virginia 23298, United States;* orcid.org/0000-0002-9243-8813; Email: tmcquade@vcu.edu

Authors

K. Kashinath − *Medicines for All Institute, Virginia Commonwealth University, Richmond, Virginia 23298, United States*

Justina M. Burns − *Medicines for All Institute, Virginia Commonwealth University, Richmond, Virginia 23298, United States*

Rodger W. Stringham − *Medicines for All Institute, Virginia Commonwealth University, Richmond, Virginia 23298, United States*

B. Frank Gupton − *Medicines for All Institute, Virginia Commonwealth University, Richmond, Virginia 23298, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.0c00145

Author Contributions

†K.K. and D.R.S. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Bill and Melinda Gates Foundation for their longstanding support of our research.

■ REFERENCES

(1) Panos, Z.; Fox, J.; Prabhu, V. *HIV Market Report: The State of HIV Treatment, Testing, and Prevention in Low- and Middle-Income Countries*, issue 10. Clinton Health Access Initiative, September 2019. http://clintonhealthaccess.org/wp-content/uploads/2019/12/2019-HIV-Market-Report.pdf (accessed 2020-02-06).

(2) (a) Humber, D. C.; Jones, M. F.; Payne, J. J.; Ramsay, M. V. J.; Zacharie, B.; Jin, H.; Siddiqui, A.; Evans, C. A.; Tse, H. L. A.; Mansour, T. S. Expeditious preparation of (−)-2′-deoxy-3′-thiacytidine (3TC). *Tetrahedron Lett.* **1992**, *33*, 4625−4628. (b) Hoong, L. K.; Strange, L. E.; Liotta, D. C.; Koszalka, G. W.; Burns, C. L.; Schinazi, R. F. 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. (c) Jeong, L. S.; Schinazi, R. F.; Beach, W. J.; Kim, H. O.; Nampalli, S.; Shanmuganathan, K.; Alves, A. J.; McMillan, A.; Chu, C. K.; Mathis, R. Asymmetric synthesis and biological evaluation of β-L-(2*R*,5*S*)- and α-L-(2*R*,5*R*)-1,3-oxathiolane-pyrimidine and -purine nucleosides as potential anti-HIV agents. *J. Med. Chem.* **1993**, *36*, 181−195. (d) 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. (e) 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. *Tetrahedron: Asymmetry* **1995**, *6*, 1903−1906. (f) Milton, J.; Brand, S.; Jones, M. F.; Rayner, C. M. Enantioselective enzymatic synthesis of the anti-viral agent lamivudine (3TC). *Tetrahedron Lett.* **1995**, *36*, 6961−6964. (g) Cousins, R. P. C.; Mahmoudian, M.; Youds, P. M. Enzymic resolution of oxathiolane intermediates - an alternative approach to the anti-viral agent lamivudine (3TC). *Tetrahedron: Asymmetry* **1995**, *6*, 393−396. (h) Jin, H.; Siddiqui, A.; Evans, C. A.; Tse, H. L. A.; Mansour, T. S.; Goodyear, M. D.; Ravenscroft, P.; Beels, C. D. Diastereoselective Synthesis of the Potent Antiviral Agent (−)-2′-Deoxy-3′-thiacytidine and Its Enantiomer. *J. Org. Chem.* **1995**, *60*, 2621−2623. (i) Goodyear, M. D.; Dwyer, P. O.; Hill, M. L.; Whitehead, A. J.; Hornby, R.; Hallet, P. Process for the Diastereoselective Synthesis of Nucleoside Analogues. US 6,051,709, 2000. (j) 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. (k) Goodyear, M. D.; Hill, M. L.; West, J. P.; Whitehead, A. J. Practical enantioselective synthesis of lamivudine (3TC) via a dynamic kinetic resolution. *Tetrahedron Lett.* **2005**, *46*, 8535−8538. (l) 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. (m) Reddy, B. P.; Reddy, K. R.; Reddy, R. R.; Reddy, D. M.; Srinivas, A. S. Optical resolution of substituted 1,3-oxathiolane nucleosides. US 20110245497, 2011. (n) Hu, L.; Schaufelberger, F.; Zhang, Y.; Ramström, O. Efficient asymmetric synthesis of lamivudine via enzymatic dynamic kinetic resolution. *Chem. Commun.* **2013**, *49*, 10376−10378. (o) Chen, Y.; Zhang, X.; Zheng, G.; Gao, S. Preparation of the Enantiomerically Enriched Precursor of Lamivudine (3TC™) via Asymmetric Catalysis Mediated by Klebsiella Oxytoca. *Process Biochem.* **2019**, *81*, 77−84. (p) Zhang, Y.; Sun, Y.; Tang, H.; Zhao, Q.; Ren, W.; Lv, K.; Yang, F.; Wang, F.; Liu, J. One-Pot Enzymatic Synthesis of Enantiopure 1,3-Oxathiolanes Using *Trichosporon laibachii* Lipase and the Kinetic Model. *Org. Process Res. Dev.* **2020**, *24*, 579−587. Snead, D. R.; McQuade, D. T.; Ahmad, S.; Krack, R.; Stringham, R. W.; Burns, J. M.; Abdiaj, I.; Gopalsamuthiram, V.; Nelson, R. C.; Gupton, B. F. An Economical Route to Lamivudine Featuring a Novel Strategy for Stereospecific Assembly. *Org. Process Res. Dev.* **2020**, DOI: 10.1021/acs.oprd.0c00083.

(3) (a) Nair, D. S.; Rai, B. P.; Nizar, H.; Meeran, P. N.; Tewari, N. Process and intermediates for the preparation of substituted 1,3-oxathiolanes, especially lamivudine. US 20100311961, 2010. (b) Tewari, N.; Nair, D. S.; Nizar, H.; Meeran, P. N.; Prasad, M. Process for the preparation of substituted 1,3-oxathiolanes. US 20100311970, 2010. (c) Shankar, R.; Vennapureddy, R. R.; Sayyed, A. P.; Ankaraju, M. K.; Madasu, S. B.; Vascuri, J. R.; Meenakshisunderam, S. Process for preparation of *cis*-nucleoside derivative. US 20110282046, 2011. (d) Rama, S.; Gorantla, S. C. S.; Vadali, L. R.; Inupakutika, V. B. K. S.; Dasari, S. R.; Mittapelly, N.; Singh, S. K.; Datta, D. Novel process for the preparation of *cis*-nucleoside derivative. US 20120295930, 2012. (e) Roy, B. N.; Singh, G. P.; Srivastava, D.; Aher, U. P.; Patil, S. U. Stereoselective process for preparation of 1,3-oxathiolane nucleosides. US 20130296562, 2013. (f) 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. (g) Mandala, D.; Watts, P. An Improved Synthesis of Lamivudine and Emtricitabine. *Chemistry Select* **2017**, *2*, 1102−1105. (h) Aher, U. P.; Srivastava, D.; Jadhav, H. S.; Singh, G. P.; B. S., J.; Shenoy, G. G. Large-Scale Stereoselective Synthesis of 1,3-Oxathiolane Nucleoside, Lamivudine, via $ZrCl_4$-Mediated N-Glycosylation. *Org. Process Res. Dev.* **2020**, *24*, 387−397.

(4) Smit, V. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. Episulfonium ions: myth and reality. *Acc. Chem. Res.* **1979**, *12*, 282−288.

(5) (a) Martin, H. M. Manufacture of thio-acids and derivatives. US 2,413,361, 1945. (b) Coons, R. J.; Todaro, C. A. Process for producing α-mercapto-carboxylic acids. US 2,594,030, 1950.

(6) (a) Smit, W. A.; Gromov, A. V.; Yagodkin, E. A. Adducts of ArSCl with vinyl ethers or esters as synthones in geminal alkylation. *Mendeleev Commun.* **2003**, *13*, 21−23. (b) Smit, W. A.; Yagodkin, E. A.; Zatonsky, G. V. Reactions of *p*-toluenesulfenyl chloride with enol acetates. The synthetic potential of the resulting adducts. *Russ. Chem. Bull.* **2005**, *54*, 743−747.

(7) (a) Worley, J. W.; Ratts, J. W.; Cammack, K. L. 2-Dialkylphosphonyl- and 2-Alkylidene-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines. *J. Org. Chem.* **1975**, *40*, 1731−1734. (b) Pommelet, M.-C.; Nyns, C.; Lahousse, F.; Merenyi, R.; Viehe, H. G. A Novel Method of CC-Bond Formation: Thermolytic Elimination of Sulfur and Hydrogen Halides from α-Halosulfides. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 585−586. (c) Griesbaum, K.; Scaria, P. M.; Döhling, T. Halogenated epoxides. Reaction of trans-2,3-dichlorooxirane with dimethyl sulfide. *J. Org. Chem.* **1986**, *51*, 1302−1305.

(8) Lauss, H.-D.; Steffens, W. Sulfur Halides. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2000.

(9) Rozwadowska, M. D.; Sulima, A.; Gzella, A. Synthesis, crystal structure and oxidation of (*R*)-(+)-8,9-dimethoxy-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one. *Tetrahedron: Asymmetry* **2002**, *13*, 2329−2333.

(10) Schröder, G. Poly(vinyl ethers). In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2000.

(11) See the Supporting Information for complete details.

https://dx.doi.org/10.1021/acs.oprd.0c00145
Org. Process Res. Dev. 2020, 24, 2266−2270