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Communication

A Continuous Flow Sulfuryl Chloride-Based Reaction—Synthesis of a Key Intermediate in a New Route toward Emtricitabine and Lamivudine

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ABSTRACT: We demonstrate a continuous two-step sequence in which sulfenyl chloride is formed, trapped by vinyl acetate, and chlorinated further via a Pummerer rearrangement. These reactions produce a key intermediate in our new approach to the oxathiolane core used to prepare the antiretroviral medicines emtricitabine and lamivudine. During batch scale-up to tens of grams, we found that the sequence featured a strong exotherm and evolution of hydrogen chloride and sulfur dioxide. Keeping gaseous byproducts in solution and controlling the temperature led to better outcomes. These reactions are ideal candidates for implementation in a continuous mesoscale system for the sake of superior control. In addition, we found that fast reagent additions at controlled temperatures decreased byproduct formation. Herein we discuss the flow implementation and the final reactor design that led to a system with a 141 g/h throughput.

KEYWORDS: *lamivudine, emtricitabine, API, flow chemistry, continuous processing, scale-up*

INTRODUCTION

Lamivudine (3TC) and emtricitabine (FTC), both nucleoside analogues, are high-dosage/high-demand drugs and manufactured in large volumes (>10^6 kg/yr).[1] In view of the global health applications, the active pharmaceutical ingredient (API) price (~$100/kg) is the major cost contributor toward delivering these medicines to patients. The Medicines for All Institute (M4ALL) seeks to facilitate positive market conditions by creating low-cost API routes to help balance the needs of procurers and producers. M4ALL recently developed a new batch route to the oxathiolane core that serves as a key intermediate for the synthesis of both 3TC and FTC (Scheme 1).

Our route relies on a sulfuryl chloride (SO_2Cl_2)-mediated chlorothiol−ene reaction (Scheme 1). The process begins with a Fischer esterification between L-menthol (**1**) and thioglycolic acid (**2**).[2] The menthyl thioglycolate (**3**) is then treated with SO_2Cl_2 to produce sulfenyl chloride intermediate **4**.[3] The reaction between the thioglycolate **3** and SO_2Cl_2 is exothermic, as is the reaction of **4** with vinyl acetate (**5**). The processing conditions were shown to have a significant influence on the reaction outcome (yield, product distribution, and byproduct formation). In addition to the desired dichloroacetate **7**, the trichloride byproduct **8** is produced in greater amounts when the reaction is not well-controlled (temperature, mixing, and residence time). Cyclization of intermediate **7** was also studied by our group,[2] and the steps following oxathiolane **9** are well-described in the literature.[4] We hypothesized that a continuous approach would enable greater control over the mixing rate and temperature.[5] These features would offer potential adopters an alternative approach to scale up safely with improved selectivity. Herein we present the reaction thermodynamic properties, reactor configurations, and their influence on the yield and selectivity for transforming **3** into **7** (Scheme 1).

RESULTS AND DISCUSSION

Batch Experiments. *Heat Flow Calorimetry.* Reactions between SO_2Cl_2 and thiols are well-known to produce strong exotherms.[6] This is true for our case shown in Scheme 1: when SO_2Cl_2 and **3** are combined, the reaction occurs immediately, and the initially colorless solution becomes yellow with evolution of heat and gas (HCl and SO_2). As shown in our prior publication,[2] the reaction is sensitive to both temperature and pressure control. In scaling our route from milligram to gram scale (batch), the temperature rise was large and fast enough to prompt a safety assessment using heat flow calorimetry. Using a batch-based heat flow calorimeter, we measured the heat released during these transformations (steps 1 and 2; Figure 1).

Batch optimization experiments revealed that 2.2 equiv of SO_2Cl_2 produced the best yields and selectivity. The use of 2 equiv is necessary to support the multiple chlorinations (steps 1 and 2; Figure 1), and we presume that the 10% excess is needed due to reagent decomposition.[2] The heat released during the formation of sulfenyl chloride **4** (step 1) is 242 kJ/mol. The vinyl acetate addition (step 2) is also exothermic, involving both the addition of **4** to **5** and the chlorination at

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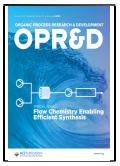

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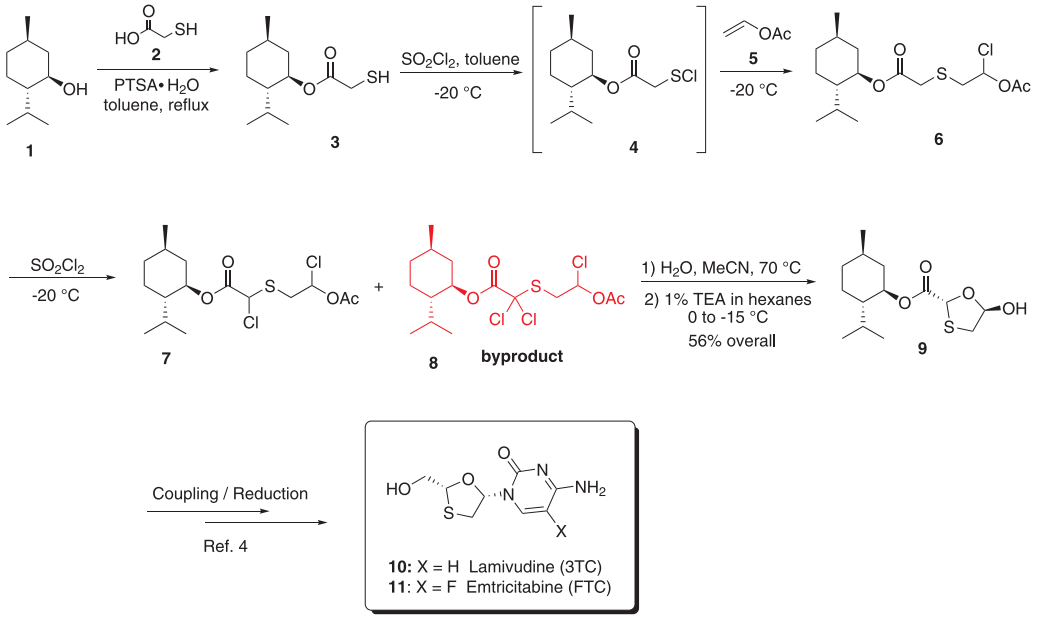
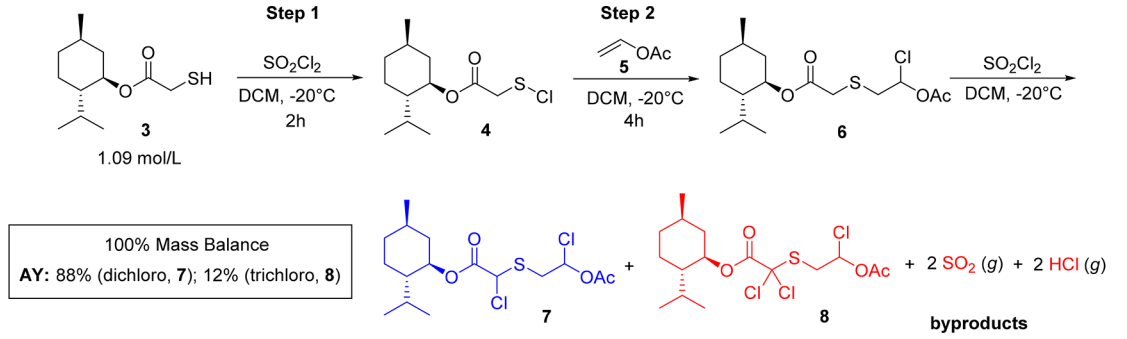
Scheme 1. M4ALL's New Route to Lower-Cost 3TC/FTC Production—Reaction Steps from 3 to 7 are Excellent Candidates for the Presented Continuous Approach





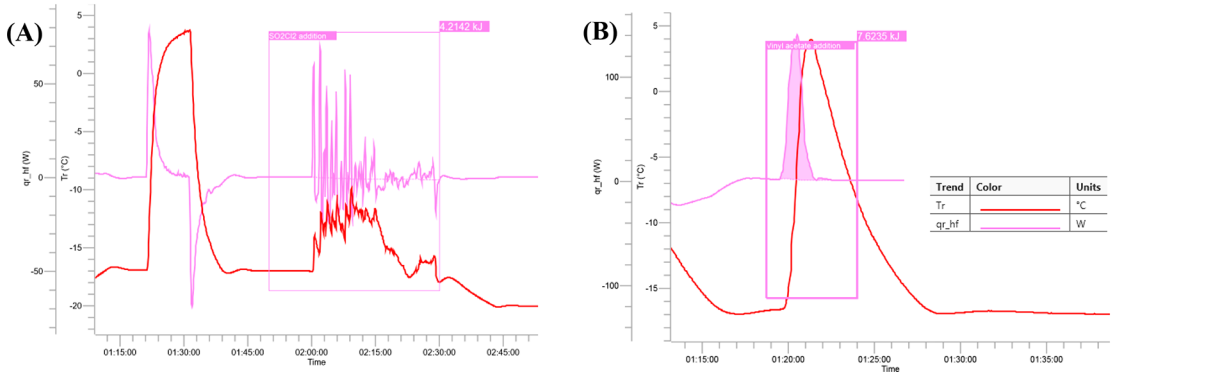


Figure 1. EasyMax HFCal runs (17.4 mmol of **3**). (A) Addition of 38.3 mmol (2.2 equiv) of SO_2Cl_2 over 30 min (step 1): 242 kJ/mol. (B) Addition of 34.8 mmol (2.0 equiv) of vinyl acetate (**5**) over 10 min (step 2): 438 kJ/mol.

the position α to the ester in **6** to yield the desired dichloride **7**. For this sequence of reactions, the generated heat is 438 kJ/mol. We predict that this translates to adiabatic temperature rises of 102−133 °C for step 1 and 138−207 °C for step 2 if the reaction is carried out in toluene. These highly energetic exotherms require either changing the reactor modality, slowing the reagent addition, or using active cooling strategies.[7] We demonstrate below that a continuous approach is a viable strategy to perform this two-step sequence of reactions.

Batch Observations Germane to Creating a Continuous Process. Optimization experiments revealed that step 1 provides **4** in high yields (94−100%) over a wide operating temperature window from −20 to 25 °C. On the other hand, step 2 provides the highest yields and selectivity for **7** when the reaction is carried out at −20 °C. Higher temperatures increase

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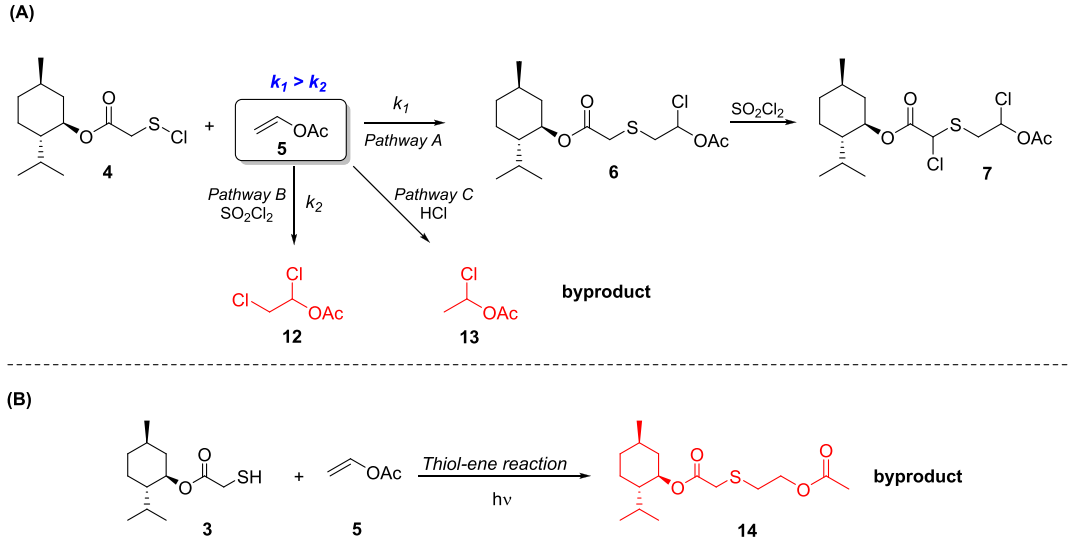
Scheme 2. Possible Pathways Involving Vinyl Acetate (5): (A) Desired Reaction with 4 to Form 6 and Reaction with SO_2Cl_2 Leading to 1,2-Dichloroethyl Acetate (12); (B) Thiol−Ene Reaction (Alkene Hydrothiolation) Leading to Byproduct 14—Radical Click Mechanism Initiated in the Presence of Light



the ratio of trichloro product **8** to dichloro product **7** and reduce the overall yield as a result of material decomposition to a range of unidentified products.

During reaction optimization, we observed that reactions carried out under autogenous pressure provided better outcomes. Small perturbations to the system headspace such as sampling the reaction by opening the reactor decreased the yield by at least 10%. The reaction produces a number of gaseous byproducts, including HCl and SO_2. We observed that **7** is more stable in acidic solutions, which may indicate that HCl loss in the headspace can affect the yield. It appears that a lower reaction temperature for step 2 increases the reaction tolerance to pressure changes. This is likely due to dissolution of larger amounts of HCl gas in the reaction mixture. The combination of the exotherm and pressure sensitivity suggests that a continuous flow approach might be an ideal modality to run this reaction sequence.

The order of addition was expected to be important. We confirmed this suspicion by evaluating whether the first step could tolerate premixing of **3** and **5**. This is an important consideration for our potential flow system because the holding time of reagent/substrate solutions within reservoirs is an opportunity for unanticipated chemistry. Unfortunately, when **3** and **5** were combined, a thiol−ene reaction took place, forming byproduct **14** (Scheme 2B). After SO_2Cl_2 addition, the overall reaction provided **7** in a lower assay yield (AY) of 57%.[8] Vinyl acetate also reacts with SO_2Cl_2 to form 1,2-dichloroethyl acetate (**12**) (only traces were observed) and with hydrogen chloride to produce 1-chloroethyl acetate (**13**) (Scheme 2A).

The occurrence of different side reactions involving **5** prompted us to consider its rate of addition before designing our continuous reactor arrangement. In particular, we sought to define a set of starting conditions. We elected to run each stage at −20 °C and add the SO_2Cl_2 over 15 min (213 μL/min) on the basis of our earlier observations. Using these standard batch conditions, we varied the addition rate of **5** (2 equiv) (640, 213, and 53 μL/min) and analyzed the outcome by measuring the product distribution of the crude reaction after 4 h from the beginning of addition of **5**. The results are shown in Table 1 and indicate that the addition rate of **5** is related to the selectivity. As the rate of addition decreases, the proportion of byproduct **8** increases; however, since the reaction is temperature sensitive yet also highly exothermic, slow addition is required. As the reaction is progressively scaled, required addition time may escalate to maintain low temperatures. This indicates that precise temperature control is required for step 2.

Table 1. Variation of the Rate of Addition of Vinyl Acetate (5) for a 4.0 g Scale Reaction

				yields (%)			
entry	add. rate of **5** (μL/min)	addition time (min)	ΔT (°C)	**6**	**7**	**8**	mass balance (%)
1	640	5	24	0	88	11	99
2	213	15	13	0	73	26	99
3	53	60	1.5	1	63	36	100

Continuous Flow Experiments. *System Design and Considerations.* The formation of HCl and SO_2 during the reaction sequence limits the use of certain materials for system construction because of the chemical resistance incompatibility, which can generate safety issues. The rapid heat rise observed for both steps suggested the use of better heat conductors such as stainless steel reaction loops. However, this option was discarded because of the poor compatibility of stainless steel with strong acid.[9] Glass systems were also considered, but the possible risk of polymerization/clogging encouraged us to take a different approach. Finally, we selected perfluoroalkoxy (PFA) tubing as the material for our coil reactor because of its high chemical resistance against strong acid and solvent. We also leveraged a variety of pumping options—syringe, peristaltic, and HPLC pumps—to facilitate multiple reactor configurations. We avoided pumping SO_2Cl_2 with piston-based pumps to avoid corrosion. We used spring-type back-pressure regulators (BPRs) to be able to easily clean the solid deposited on the BPR spring after each reaction.

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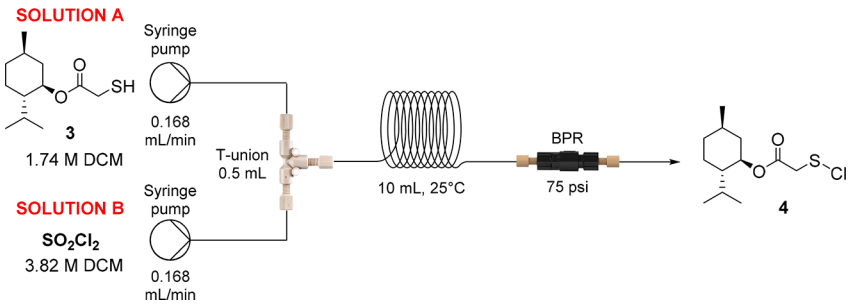

Figure 2. Initial flow setup for the synthesis of sulfenyl chloride **4**.

Reactor Configurations. We began surveying reactor configurations by focusing on step 1, the formation of sulfenyl chloride **4**. Thiol **3** (1.74 mol/L in dichloromethane (DCM); solution A) and SO_2Cl_2 (3.82 mol/L in DCM, 2.2 equiv; solution B) were delivered using syringe pumps at a flow rate of 0.168 mL/min through a T-union (internal volume = 0.5 mL) and then through a 10 mL coil reactor ($^1/_{16}$″ o.d., 0.030″ i.d. PFA tubing) (Figure 2). We initially used $^1/_{16}$″ o.d. tubing for a high surface-to-volume ratio and therefore short diffusion paths (no need for extra mixing elements) and efficient heat transfer (no need for extra cooling). Because of the HCl and SO_2 formation, a BPR (75 psi) was added at the end of the coil reactor to keep the gases dissolved in the reaction mixture and achieve a stable flow rate (Figure 2).

When a total flow rate of 0.336 mL/min was applied at 25 °C, compound **4** was obtained in 92% AY, and no remaining starting material **3** was detected (Table 2, entry 1). When the temperature was lowered to 0 °C, sulfenyl chloride **4** was obtained in 80% AY, and 15% of thiol **3** remained unreacted (Table 2, entry 2). When the residence time was decreased to 15 min at 25 °C, comparable results were obtained (Table 2, entry 3). Although mesitylene was used as the ^{1}H NMR internal standard during the first experiments (Table 2), we decided to replace it with 1,2,3-trichloropropane (see the Supporting Information). This nonstandard trichloride is inert toward SO_2Cl_2, while mesitylene can present reactivity toward ring chlorination.[10] This may be the cause of the variable mass balance observed when the reaction in entry 1 of Table 2 was repeated in triplicate (95 ± 3%).

Table 2. Initial Results for the Formation of Sulfenyl Chloride 4 under Continuous Conditions on a 400 mg Scale[a]

entry	total flow rate (mL/min)	reactor vol. (mL)	residence time (min)	T (°C)	AY (%) 3	AY (%) 4	mass balance (%)
1	0.336	10	30	25	0	92	92[b]
2	0.336	10	30	0	15	80	95
3	0.336	5	15	25	12	82	94

[a]The whole volume of reagent solutions injected in the reactor was collected at 25 °C, and then 1 equiv of mesitylene was added relative to starting material **3**. [b]When the crude mixture was diluted with DCM and held at −78 °C during collection, the reaction between the remaining SO_2Cl_2 and mesitylene was suppressed, and product **4** was obtained in 99 ± 1% AY with no mass loss observed (triplicate experiment). The same result was observed when 1,2,3-trichloropropane was used as the ^{1}H NMR internal standard.

We then turned our attention to the addition of vinyl acetate (**5**) (step 2). Sulfenyl chloride **4** is not stable and has to be generated in situ to optimize the second sequence step. The flow setup is essentially made of two combined modules (reactors 1 and 2): the first module produces **4**, and the second combines **4** with **5** to generate **7**. The second module consists of a syringe pump delivering neat **5** to a T-union, where mixing with **4** is commenced. The combined streams were reacted within another PFA coil (reactor 2), and a single BPR (75 psi) was placed after this loop (Figure 3).

Using our initial reactor configuration (Figure 3), we explored different system properties. The residence time in reactor 1 was held constant at 30 min. Lengthening the reactor was necessary to achieve this. The temperature of both modules was kept at 25 °C for all of the experiments shown in Table 3. The first run using this two-module configuration (Figure 3) yielded dichloroacetate **7** in 85% AY and byproduct **8** in 13% AY, with a 98% mass balance (Table 3, entry 1), similar to the results obtained in the batch approach (data not shown). Decreasing step 2 residence from 40 to 20 min produced compound **7** in 92% AY and trichloro **8** in 6% AY (Table 3, entry 2). The highest flow rate, 1.17 mL/min, did not provide a long enough residence time to fully consume monochlorinated intermediate **6** (Table 3, entry 3). Doubling the reactor loop volume from 15 to 30 mL resulted in the highest yield of the desired product **7** (Table 3, entry 4), presumably as a result of improved mixing at higher flow rates. We ran these conditions in triplicate and obtained the same results each time.

Reactor Refinement, Steady-State Evaluation, and Scale-Up. Positive results were obtained using $^1/_{16}$″ o.d. tubing and increasing total flow rate to 1.17 mL/min. However, we wanted to further simplify the setup, assess the steady-state stability, and scale up by increasing the reactor diameter. An early observation indicated that the reactor 1 (step 1) residence time could be drastically reduced. At a residence time of 15 min at 0 °C (step 1), a new unstable intermediate that led to the formation of sulfenyl chloride **4** was detected by ^{1}H NMR spectroscopy (see the Supporting Information). Although this intermediate is not well-described, a few accounts suggest that **15** is formed as a precursor of **4** (Scheme 3).[11,12] We speculated that **15** might form so quickly that we could combine the output from module 1 with the stream of **5** directly without the need for a residence time loop (reactor 1). Our hypothesis is that intermediate **15** would not react directly with **5**, thereby acting as a temporary protecting group against the unwanted thiol−ene reaction to form byproduct **14**.

We tested this hypothesis by building two new reactor configurations. The same reagent concentrations and reaction

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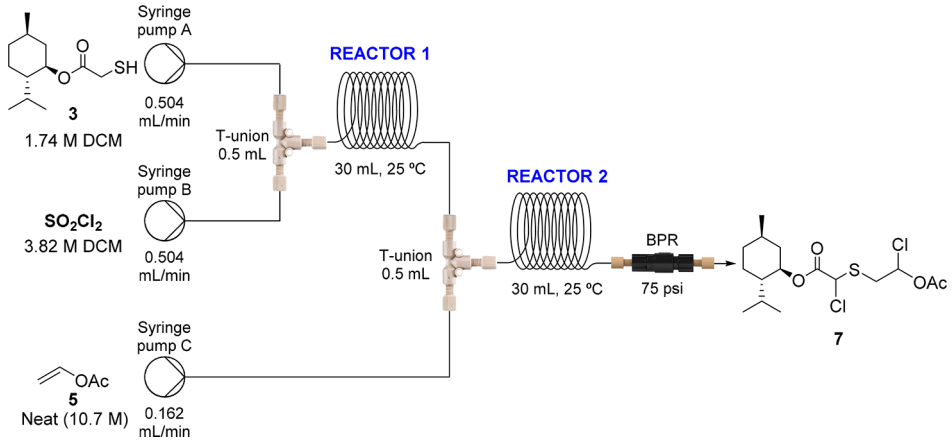


Figure 3. Initial flow setup with two modules. Module 1: production of sulfenyl chloride **4** in reactor 1. Module 2: combination of **4** with **5** in the reactor 2 to produce **7**.

Table 3. Continuous Synthesis of Compound 7 Using the Two-Module Configuration[a,b]

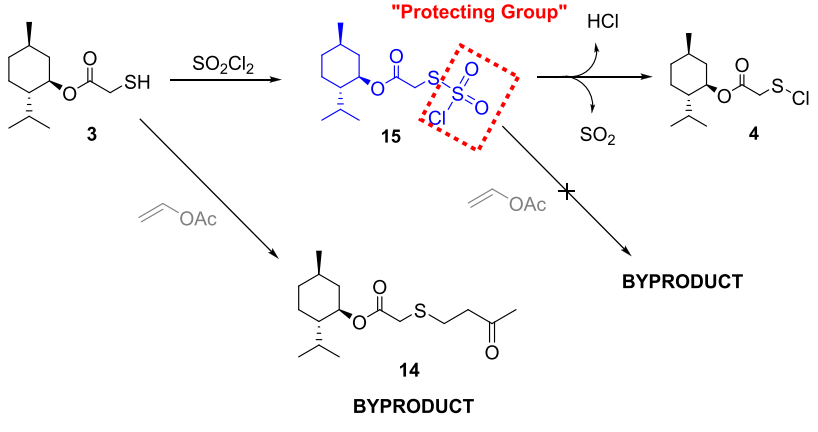
entry	total flow rate (mL/min)	reactor 2 vol. (mL)	residence time (min)	T (°C)	AY (%) 7	AY (%) 8	mass balance (%)
1	0.390	15	40	25	85	13	98
2	0.780	15	20	25	92	8	100
3	1.170	15	13	25	84	3	99[c]
4	1.170	30	26	25	99	1	100

[a]The residence time in reactor 1 was held constant at 30 min for all experiments (25 °C). This table presents the parameters only for reactor 2. All of the experiments were run on a 1.0 g scale. [b]1,2,3-Trichloropropane was used as the internal standard for ^{1}H NMR analysis. [c]10% intermediate **6** and 2% sulfenyl chloride **4** were left.

conditions were kept to perform these experiments. The first configuration fed a reactor with a stream containing SO_2Cl_2, a stream containing **5**, and a stream containing **3** into a single four-way union at the same time—this served as a control experiment in which no thiol **3**/SO_2Cl_2 premixing occurred before the addition of **5** (see the Supporting Information). As expected, because of the different rates of the reactions of thiol **3** with SO_2Cl_2 and **5** and the reaction of SO_2Cl_2 with **5**, a complex mixture of products was obtained. For the second reactor configuration, we premixed thiol **3** and SO_2Cl_2 streams using a small loop (1 mL) right after the first T-union and immediately combined the resulting solution with the stream of **5** (see the Supporting Information). For this configuration, syringe pumps A and B operated at 0.504 mL/min and syringe pump C at 0.162 mL/min (1.17 mL/min total flow rate), yielding product **7** in 95% AY and byproduct **8** in 5% AY during a 26 min residence time. This result supports the model presented in Scheme 3 and enabled us to refine our initial reactor setup to decrease the residence time between the two modules.

As we refined the system and moved our efforts toward confirming the steady-state stability and increasing the throughput, we ran the system for longer periods of time. Increasing the reaction scale and the volume of highly corrosive SO_2Cl_2 forced us to change the form of solution delivery from a syringe pump to a peristaltic pump. Since a concentrated solution of SO_2Cl_2 (3.82 mol/L) is pumped through the system, we were unsure how the pulsing of the peristaltic pump would affect the reaction. Therefore, we selected chemically resistant peristaltic pumps from Vapourtec (E-series). Initial testing was challenging because the rubber hose swelled over time when in contact with the SO_2Cl_2 solution. This caused the system performance to decrease or fluctuate over time. To avoid swelling, we replaced the tubing before long reaction runs, and no tubing deformation was observed for the following ~100 h of SO_2Cl_2 pumping. It is worth mentioning that the E-series pumps must be properly calibrated from time to time. For some experiments we

Scheme 3. First-Stage Reaction of 3 with SO_2Cl_2 Working as a Thiol "Protecting Group"



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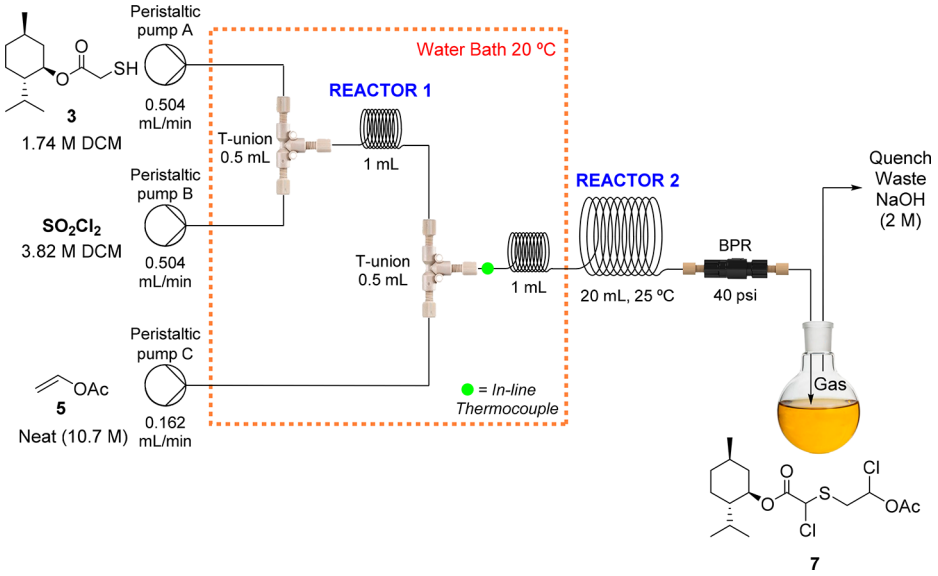

Figure 4. Improved configuration in which the residence time feature for the sulfenyl chloride **4** module is reduced in volume (1 mL). The temperature after T-union 2 is monitored via an in-line thermocouple, and part of the two-module system is cooled via two 1 mL residence time loops submerged in a water bath at 20 °C (highlighted by the red dotted line). The 75 psi BPR was replaced with a 40 psi BPR, and the final product is collected in a holding tank fitted with a base scrubber.

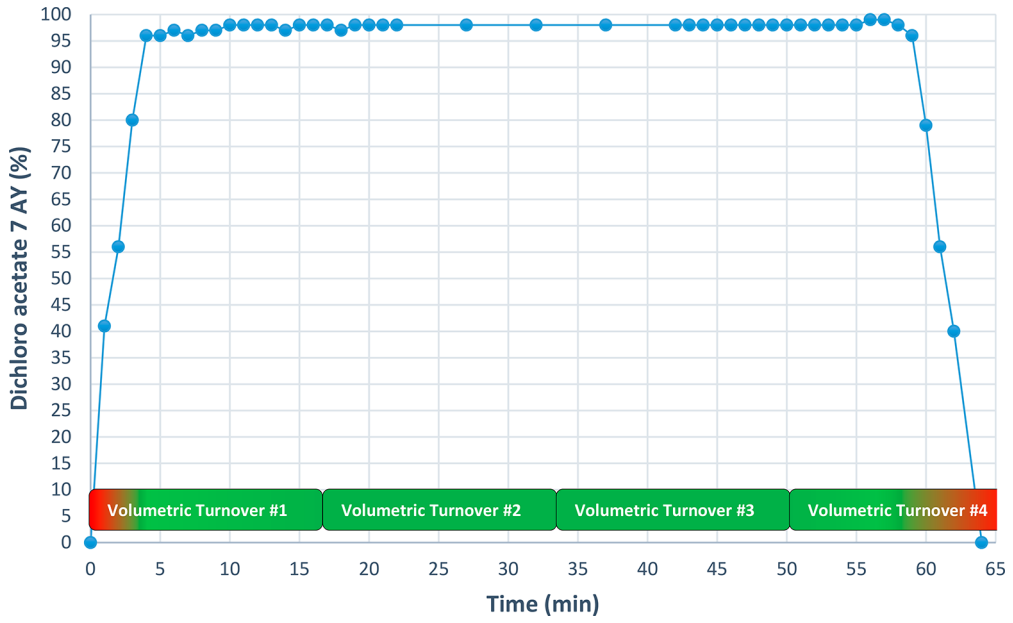

Figure 5. Variation of the assay yield of dichloroacetate **7** over time at a total flow rate of 1.17 mL/min with a residence time of 17 min. In the steady state, the assay yield of product **7** was 98 ± 1% and that of **6** was 0%, as observed by ^{1}H NMR analysis with 1,2,3-trichloropropane as the internal standard. The volumetric turnover was ~20 mL.

observed irregular pumping. Different volumes of the thiol **3** and SO_2Cl_2 solutions were injected into the system even though equal flow rates were applied to the two solutions. This issue can be easily overcome after the calibration.

During these longer runs (reagent solutions with total volume $V_{total} \geq 100$ mL, ca. 5 reactor volumes), a yield decrease was detected. This appeared to be correlated with a temperature increase in T-union 2 (Figure 4, without the second 1 mL loop). In this case, the compound **7** assay yield was about 90%, and 10% trichloroacetate **8** was formed. Temperature control was achieved by submerging both T-unions into a 2 L water bath at 20 °C. A thermocouple was placed in-line immediately after T-union 2 (ca. 20 mm) and a second one inside the water bath. A temperature rise of 2 °C was observed right after T-union 2, which remained constant through the entire experiment. The 1 mL PFA loop positioned after T-union 2 provides a long enough residence time for the reaction mixture to reestablish its original temperature. High yields of compound **7** were recovered (98 ± 2% AY), most likely because of the better temperature control, which limited the rate of byproduct **8** formation. During these long runs, the pressurized system was ca. 2 bar higher than the applied back pressure (5 bar) because of pressure drop across the system at the larger scale. This observation prompted us to lower the system pressure using a 40 psi BPR and work the peristaltic

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pumps closer to their optimum operating pressure as indicated by Vapourtec (3 bar).

A study of the steady-state stability over time was performed (approximately 70 min or 3.5 times the reactor volume) using the flow setup shown in Figure 4. Nearly 50 samples were collected over the total experiment time and analyzed by ^{1}H NMR spectroscopy for assay yield determination. The steady state was reached after 5 min (Figure 5), and the average assay yield of compound **7** was 98 ± 1%. The switch between starting material solutions and solvent caused small variations at the end of the steady state.

During solvent screening, we found that DCM and toluene provide the best yields of compound **7**. Sulfuryl chloride reacts with many solvents, so the range of options is smaller than usual.[13] During batch experiments, DCM provided higher assay yields than toluene (88% vs 78%, respectively). However, no difference was observed under continuous conditions (steady state). Thus, we decided to proceed with toluene on the basis of economic and environmental considerations. Having defined a configuration that functioned at steady state for long runs, we continued to define the best operating conditions for scale-up. Increasing the flow rates of this refined system (Figure 4) from 1.17 to 2.11 mL/min did not alter the yield of **7** but did increase the system productivity (Table 4).

Table 4. Optimization of the Reaction in Toluene and Steady-State Conditions[a,b]

				AY (%)			
entry	solvent	total flow rate (mL/min)	residence time (min)	**6**	**7**	**8**	mass balance (%)
1	toluene	1.17	17	0	96	4	100
2	toluene	1.40	14	0	97	3	100
3	toluene	1.76	11	1	96	3	100
4	toluene	2.11	9	1	97	2	100

[a]All of the samples were collected in vials containing a saturated $NaHCO_3$ aqueous solution to quench the remaining SO_2Cl_2 and the HCl to avoiding over-reaction. [b]1,2,3-Trichloropropane was used as the internal standard for ^{1}H NMR analysis.

We decided to use the middle residence time of 14 min (Table 4, entry 2)—a condition where no unreacted intermediate **6** was observed—to test scaling up the system by doubling the tubing diameter from 0.03″ i.d. ($^1/_{16}$″ o.d.) to 0.06″ i.d. ($^1/_8$″ o.d.).

Using the conditions previously described (Table 4, entry 2), we confirmed that scaling up from $^1/_{16}$″ to $^1/_8$″ o.d. tubing did not impact the product yield or selectivity, and the in-line thermocouple did not register an increase in temperature (Table 5, entry 1). Furthermore, we observed that increasing the flow rate by a factor of 5 enabled a production campaign of ca. 32 g without changing the reaction conditions (Table 5, entry 2). Finally, we increased the run time at the 7 mL/min flow rate and produced around 260 g of dichloroacetate **7**, corresponding to a throughput of 141 g/h (Table 5, entry 3).

CONCLUSION

We recently created a new approach to synthesize the oxathiolane core used in the commercial route to the high-volume antiretroviral medicines lamivudine and emtricitabine. This new route uses SO_2Cl_2 to produce alkyl sulfenyl chloride **4** followed by a chlorothiol−ene reaction to yield **7**. This

Table 5. Scale-Up Experiments under Steady-State Conditions[a,b]

				AY (%)			
entry	scale (g) of **3**	total flow rate (mL/min)	residence time (min)	**6**	**7**	**8**	mass balance (%)
1	8	1.40	14	0	98	2	100
2	20	7.00	14	1	97	2	100
3	158	7.00	14	0	98	2	100

[a]Reaction mixture fractions were collected over 1.5 h every 6 min (all of them in steady state). All of the samples were collected in vials containing a saturated $NaHCO_3$ aqueous solution. [b]1,2,3-Trichloropropane was used as the internal standard for ^{1}H NMR analysis.

intermediate undergoes a cyclization step to produce oxathiolane **9**. This sequence of reactions is sensitive to mixing and produces strong exotherms (Figure 1). We first conducted a number of experiments in batch to determine how to implement these two steps in a continuous flow approach. A two-module setup was developed (Figure 3) in which thiol **3** was first premixed with SO_2Cl_2 (module 1) and the resulting solution was combined with the stream of vinyl acetate (**5**) (module 2). While studying this module, we noticed that intermediate **15** is readily formed when **3** reacts with SO_2Cl_2, thus acting as a thiol protecting group. This avoids the reaction of **3** with **5** to form byproduct **14** (Scheme 3). This enabled a considerable reduction of the residence time in module 1 (Figure 4). While studying the reaction in steady-state runs, we observed that the overall yield of **7** and stability of the system can be improved with better temperature control and heat removal from the mixing zones, where the temperature increase is more evident (T-unions region, highlighted in red in Figure 4). Finally, we designed a stable flow system that can be scaled up and deliver compound **7** in high yields (98 ± 2%). The final run produced around 260 g of **7** with a throughput of 141 g/h. The data suggest that a continuous production strategy is feasible for producing the oxathiolane core precursor **7**.

EXPERIMENTAL SECTION

General Information. All commercially available reagents and solvents were purchased from Sigma-Aldrich, TCI Chemicals, J. T. Baker, or MilliporeSigma and used as received. Thin-layer chromatography (TLC) and column chromatography were performed using silica gel 60 F_{254} plates (0.25 mm) and silica gel (pore size 60 Å, 70−230 mesh, 63−200 μm), respectively, from Sigma-Aldrich. ^{1}H and ^{13}C NMR spectra were acquired using a Bruker 600 MHz spectrometer. Chemical shifts for hydrogens and carbons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift (multiplicity, coupling constant, integration). Multiplicities are denoted as follows: singlet (s), broad singlet (br. s), doublet (d), broad doublet (br. d), triplet (t), quadruplet (q), octet (oct), doublet of doublets (dd), doublet of triplets (dt), doublet of doublets of doublets (ddd), triplet of doublets (td), and multiplet (m). Coupling constants (J) are given in hertz.

NMR data were processed using the ACD Laboratories software, and the names of compounds were generated using the PerkinElmer ChemDraw Ultra v12.0.2 software package. Syringe pumps utilized to perform flow experiments were

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purchased from Chemyx (Fusion 4000 and Fusion 6000). For the scale-up, Vapourtec E-series peristaltic pumps were used. Perfluoroalkoxy tubing ($^1/_{16}$″ o.d., 0.030″ i.d. and $^1/_8$″ o.d., $^1/_{16}$″ i.d.), back-pressure regulators, connections, and fittings were purchased from Swagelok, Cole-Parmer, and IDEX Corporation.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-Mercaptoacetate (3). L-Menthol (**1**) (100.0 g; 0.64 mol) was loaded in a 500 mL round-bottom flask and partially dissolved in toluene (100 mL). Thioglycolic acid (46.0 mL; 61.7 g; 0.67 mol) and PTSA (881.7 mg; 5.12 mmol) were added at 25 °C. The reaction mixture was refluxed (111 °C) for 2.5 h using a Dean−Stark apparatus to remove the water formed during the reaction. The mixture was allowed to reach room temperature, neutralized with NaOH 1 M (100 mL), and extracted with toluene (3 × 100 mL). The organic phases were combined and dried with anhydrous Na_2SO_4, and the solvent was removed in a rotary evaporator. Remaining toluene was removed under reduced pressure using a vacuum pump for 6 h. Compound **3** was obtained as a colorless oil in 96% AY with 95% purity (141.5 g; 0.61 mol) and used in the next step without further purification. *Reagents and solvents:* L-menthol, ≥99%, FCC, FG (Sigma-Aldrich); thioglycolic acid, 98% (Sigma-Aldrich); *p*-toluenesulfonic acid monohydrate, ACS reagent, ≥98.5% (Sigma-Aldrich); toluene, 99.5%, Baker Analyzed ACS reagent (J. T. Baker). ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 4.64 (dt, J_1 = 11.0 Hz, J_2 = 4.4 Hz, 1H), 3.15 (d, J = 8.3 Hz, 2H), 1.91−1.99 (m, 2H), 1.80−1.89 (m, 1H), 1.58−1.66 (m, 2H), 1.38−1.48 (m, 1H), 1.30−1.38 (m, 1H), 0.89−1.05 (m, 2H), 0.76−0.88 (m, 7H), 0.70 (d, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ_C 170.1, 75.3, 46.8, 40.4, 34.0, 31.2, 26.6, 26.0, 23.2, 21.8, 20.6, 16.1.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(Chlorothio)acetate (4): Initial Experiments to Study the Formation of 4 under Continuous Flow Conditions Using Syringe Pumps. Thiol **3** (4.00 g; 17.4 mmol) was loaded in a volumetric flask (10 mL), and DCM was added up to the level of the etched line (solution A). The same was done to prepare a solution of SO_2Cl_2 (3.2 mL; 38.2 mmol; 2.2 equiv) in DCM (solution B). The entire flow system was previously flushed with DCM and pressurized at 75 psi using a BPR. A shut-off valve was placed between the T-union and the reactor coil to maintain the system pressure and to enable switching from solvent to reagent solution and vice versa. Solutions A and B were transferred into 8 mL Harvard syringes with 2 mL of extra tubing to accommodate the 10 mL solutions. Both solutions were pumped with Chemyx syringe pumps at a flow rate of 0.168 mL/min through a 10 mL PFA coil reactor ($^1/_{16}$″ o.d. tubing, Vapourtec). When the two solutions were totally injected, fresh DCM was pumped at 0.336 mL/min (through the shut-off valve) to keep the reaction mixture moving forward at the same flow rate (see Figures S2 and S3). Compound **4** was not isolated. Data for the crude mixture: ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 4.77 (dt, J_1 = 10.8 Hz, J_2 = 4.4 Hz, 1H), 3.88 (s, 2H), 2.00−2.06 (m, 1H), 1.89−1.97 (m, 1H), 1.67−1.73 (m, 2H), 1.34−1.55 (m, 2H), 0.99−1.12 (m, 2H), 0.84−0.94 (m, 7H), 0.77 (d, J = 7.0 Hz, 3H).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-((2-Acetoxy-2-chloroethyl)thio)acetate (6). Intermediate **6** was isolated only for use as a reference to compare with the ^{1}H NMR spectrum of the crude reaction mixture. It was obtained as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 6.48 (dd, J_1 = 8.1 Hz, J_2 = 4.0 Hz, 1H), 4.65−4.74 (m, 1H), 3.26−3.11 (m, 4H), 2.11 (s, 3H), 1.94−2.01 (m, 1H), 1.81−1.89 (m, 1H), 1.62−1.68 (m, 2H), 1.33−1.51 (m, 2H), 0.93−1.07 (m, 2H), 0.79−0.90 (m, 7H), 0.73 and 0.72 (d, J = 2.8 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ_C 169.2, 168.1, 81.8, 75.5 and 75.4, 46.9 and 46.8, 40.6 and 40.5, 39.0 and 38.9, 34.2 and 34.1, 34.0, 31.2, 26.1 and 26.0, 23.2, 21.8, 20.6, 16.1 (duplicate signals are for the mixture of diastereoisomers).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-((2-Acetoxy-2-chloroethyl)thio)-2-chloroacetate (7): Batch Procedure. Thiol **3** (4.00 g; 17.4 mmol) was loaded in a round-bottom flask and dissolved in anhydrous DCM (16 mL). The solution was transferred to an EasyMax reactor under a nitrogen atmosphere. When the system stabilized at −20 °C, SO_2Cl_2 (3.2 mL; 5.16 g; 38.2 mmol) was added at 213 μL/min. The reaction mixture was kept under these conditions for 2 h. Vinyl acetate (3.2 mL; 3.00 g; 34.8 mmol) was added at a rate of 640 μL/min. After 4 h, the reaction was neutralized with a saturated $NaHCO_3$ solution (50 mL) and extracted with DCM (3 × 50 mL). The organic phase was separated and dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Compound **7** was obtained in 88% AY (15.3 mmol; 5.90 g) and the trichloride byproduct **8** in 11% AY (1.91 mmol; 0.80 g). *Reagents and solvents:* sulfuryl chloride, 97% (Sigma-Aldrich); vinyl acetate monomer (stabilized with HQ) (TCI Chemicals); dichloromethane, anhydrous, ≥99.8% stabilized, DriSolv (MilliporeSigma); toluene, anhydrous, ≥99.5%, DriSolv (MilliporeSigma).

Optimization of the Synthesis of 7 under Continuous Flow Conditions Using Syringe Pumps. The outcome of the previously described sulfenyl chloride **4** synthesis flow setup was combined with vinyl acetate (**5**) through a T-union. The flow rate of **5** (syringe pump) was adjusted to 2 equiv relative to thiol **3**. After the second T-union, the reaction mixture was pushed through a second PFA coil reactor (15 mL). The entire setup was pressurized at 75 psi using a BPR (see Figures S4 and S5).

Continuous Flow Synthesis of 7 Using Vapourtec Peristaltic Pumps. Thiol **3** (8.00 g; 34.8 mmol) was loaded in a volumetric flask (20 mL), and toluene was added up to the level of the etched line (solution A). The same was done to prepare a solution of SO_2Cl_2 (6.24 mL; 76.4 mmol; 2.2 equiv) in toluene (solution B). Each solution was transferred to a 20 mL vial under a nitrogen atmosphere and then connected to the V-3 peristaltic pumps (Vapourtec E-Series flow system). The whole system was previously flushed with toluene and pressurized to 40 psi using a BPR. A 50 mL Harvard syringe was filled with vinyl acetate **5** (neat) and pumped using a Chemyx syringe pump. The two-step reaction was carried out at 25 °C. The crude mixture was neutralized with a saturated $NaHCO_3$ solution before NMR analysis. The thiol **3** used in these reactions was not purified by chromatographic column with silica gel. The crude starting material was treated only with a basic wash to remove the PTSA. The same result was obtained using purified and nonpurified starting material. However, water traces in thiol **3** can quench part of the SO_2Cl_2. After the basic wash, efficient drying was required to control the addition of the optimized amount of SO_2Cl_2 (see Figure S6). Compound **7** was obtained as a white goop after extraction with a saturated aqueous solution of $NaHCO_3$. The overall assay yield starting from thiol **3** was 98% (0.67 mol; 258.2 g considering 158 g scale-up condition in flow). A crystal of one isomer (**7a**) was obtained (see Figure S8). ^{1}H NMR

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(600 MHz, $CDCl_3$): δ_H 6.56 (dd, J_1 = 8.3 Hz, J_2 = 4.03 Hz, 1H), 4.75 (dt, J_1 = 11.0 Hz, J_2 = 4.4 Hz, 1H), 5.43 (s, 1H), 3.48 (dd, J_1 = 14.7 Hz, J_2 = 8.3 Hz, 1H), 3.37 (dd, J_1 = 14.7 Hz, J_2 = 4.0 Hz, 1H), 2.17 (s, 3H), 2.02−2.07 (m, 1H), 1.87−1.97 (m, 1H), 1.43−1.56 (m, 2H), 1.01−1.12 (m, 2H), 0.92 (dd, J_1 = 14.0 Hz, J_2 = 6.6 Hz, 6H), 0.84−0.94 (m, 1H), 0.77 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ_C 168.1, 165.5, 81.6, 77.6, 61.5, 47.0, 40.3, 37.4, 34.0, 31.4, 26.1, 23.3, 22.0, 20,7, 20.6, 16.1.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-((2-Acetoxy-2-chloroethyl)thio)-2,2-dichloroacetate (8). Intermediate **8** was isolated only for use as a reference to compare with the ^1H NMR spectrum of the crude reaction mixture. It was obtained as a slightly yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ_H 6.65−6.76 (m, 1H), 4.74−4.81 (m, 1H), 3.55−3.68 (m, 2H), 1.89−2.18 (m, 5H), 1.66−1.74 (m, 2H), 1.44−1.58 (m, 2H), 1.02−1.16 (m, 2H), 0.85−0.95 (m, 7H), 0.76 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ_C 167.8, 163.0, 87.3 and 87.2, 80.7 and 80.6, 79.8, 46.8, 40.2, 39.8 and 39.7, 33.8, 31.3, 26.0, 23.1, 21.8, 20.6 and 20.5, 16.0 (duplicate signals are for the mixture of diastereoisomers).

1,2-Dichloroethyl Acetate (12). Compound **12** was obtained from the reaction of vinyl acetate with SO_2Cl_2. It was synthesized for use as a reference to compare with the ^1H NMR spectrum of the crude reaction mixture. ^1H NMR (600 MHz, $CDCl_3$): δ_H 6.45 (dd, J_1 = 7.2 Hz, J_2 = 4.4 Hz, 1H), 3.77−3.85 (m, 2H), 2.13 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00146.

Adiabatic temperature rise calculation, additional figures (system configuration), X-ray structure of **7**, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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