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A CONTINUOUS FLOW SULFURYL CHLORIDE BASED REACTION – SYNTHESIS OF A KEY INTERMEDIATE IN A NEW ROUTE TOWARD EMTRICITABINE AND LAMIVUDINE

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A Continuous Flow Sulfuryl Chloride Based Reaction – Synthesis of a Key Intermediate in a New Route Toward Emtricitabine and Lamivudine

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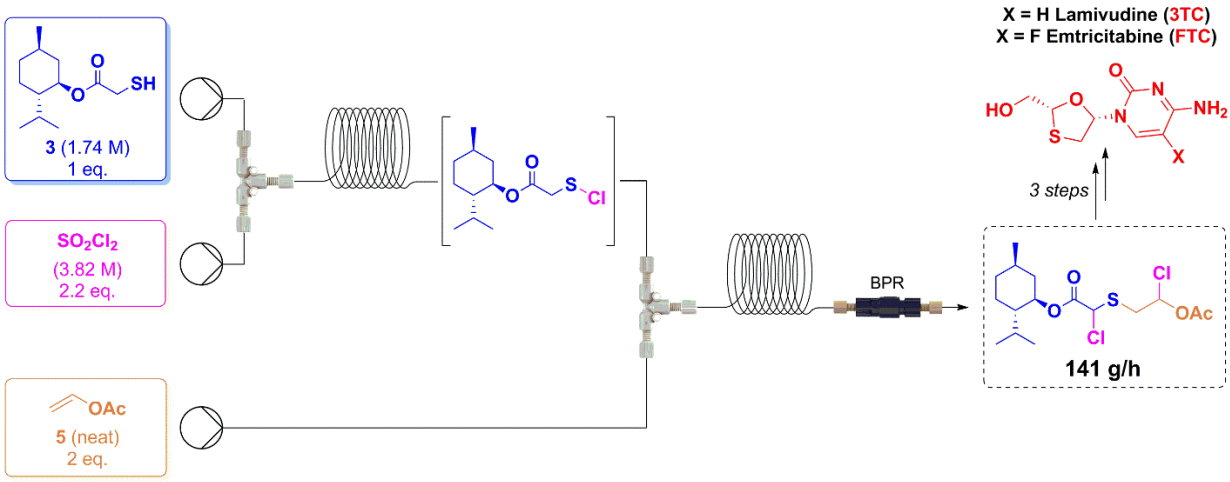


ABSTRACT

We demonstrate a continuous two-step sequence where 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 anti-retroviral 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 141g/h throughput system.

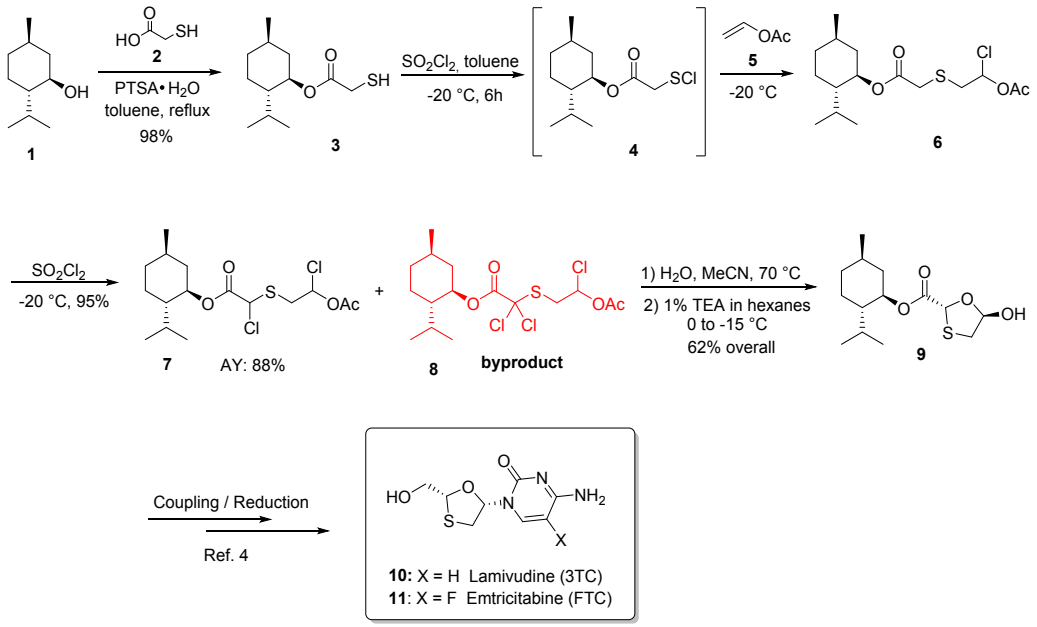
Keywords: Lamivudine, Emtricitabine, API, Flow Chemistry, Continuous Processing, Scale-up

INTRODUCTION

Lamivudine and Emtricitabine (3TC and FTC, respectively), both nucleosides analogs, are high dosage/high demand drugs and manufactured in large volumes (>10^6 kg/yr).[1] Considering global health applications, the active pharmaceutical ingredient (API) price (~$100/kg) is the major cost contributor towards delivering these medicines to the 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 chloro-thioene 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 a sulfenyl chloride intermediate **4**.[3] The reaction between the thioglycolate **3** and SO_2Cl_2 is exothermic along with the reaction of **4** with vinyl acetate (**5**). The processing conditions were shown to have significant influence over the reaction outcome – yield, product distribution and byproduct formation. In addition to the desired dichloro acetate **7**, trichloride byproduct **8** is produced in greater amounts when the reaction is not well-controlled (temperature, mixing and residence time). Intermediate **7** cyclization 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 mixing rate and temperature.[5] These features would offer potential adopters an alternative approach to safely scale-up with improved selectivity. Herein, we present the reaction

thermodynamic properties, reactor configurations and their influence on yields and selectivity for transforming **3** into **7** (Scheme 1).



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.

RESULTS AND DISCUSSION

BATCH EXPERIMENTS

Heat Flow Calorimetry. Reaction 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, the reaction is sensitive to both temperature and pressure control.[2] 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 (Step 1 and 2, Figure 1).

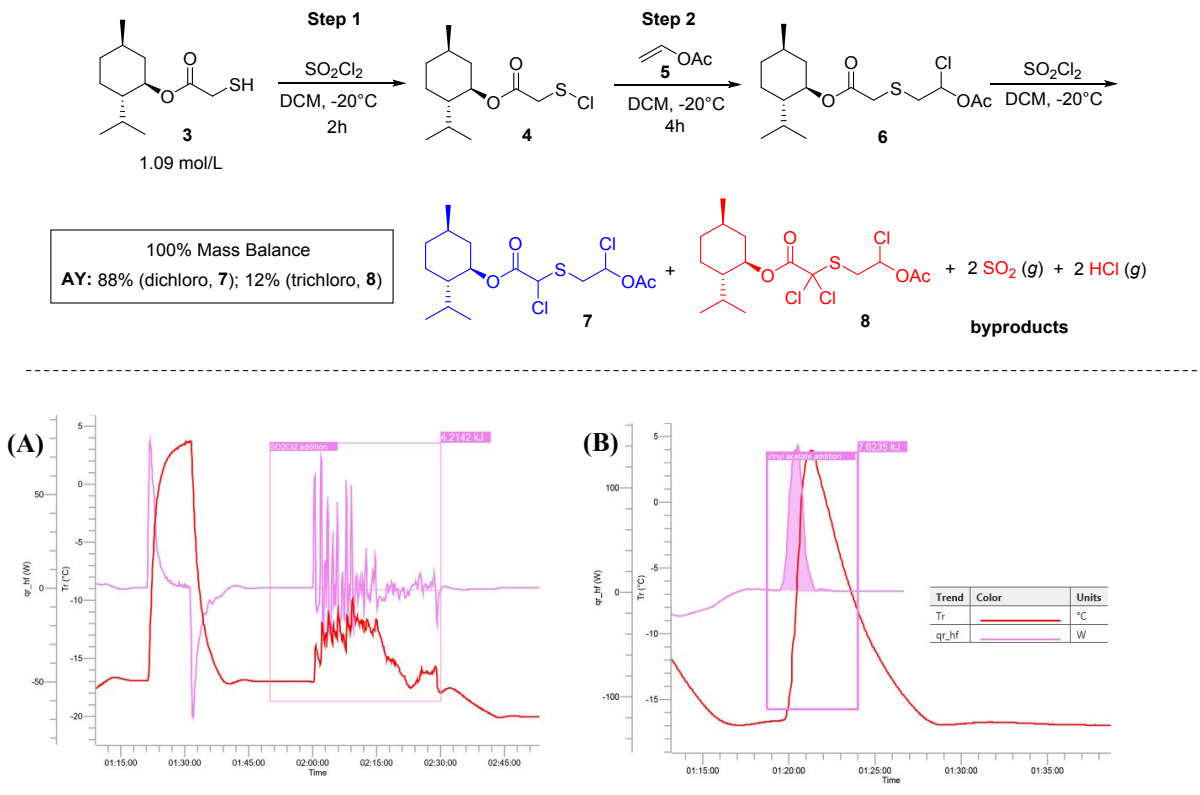


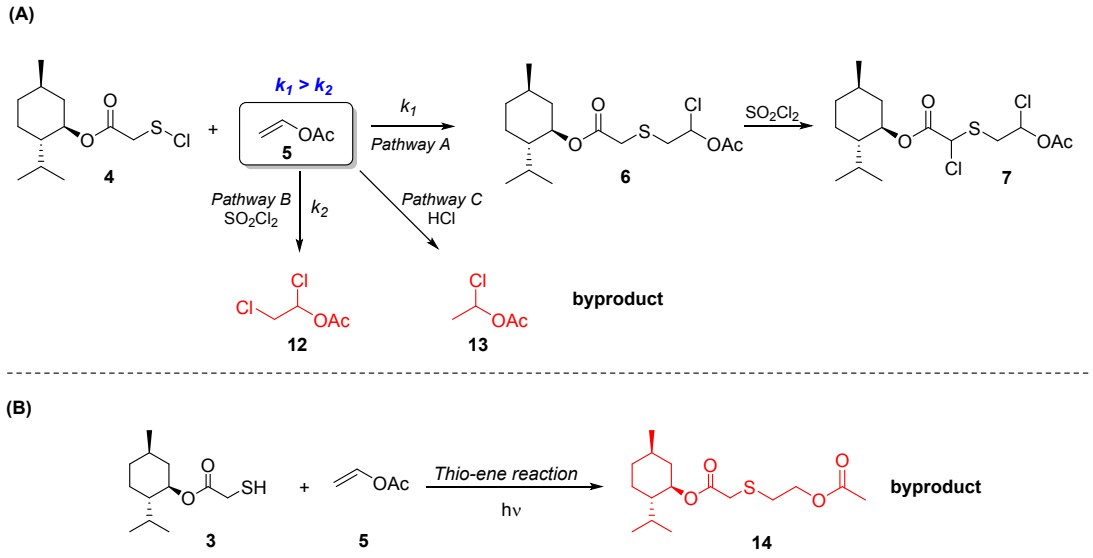
Figure 1. EasyMax HFCal runs (17.4 mmol of **3**). (A) Addition of 38.3 mmol (2.2 equiv.) SO_2Cl_2 over 30 minutes – Step 1: 242 kJ/mol. (B) Addition of 34.8 mmol (2.0 equiv.) vinyl acetate (**5**) over 10 minutes – Step 2: 438 kJ/mol.

Batch optimization experiments revealed that 2.2 equiv. of SO_2Cl_2 produced the best yields and selectivity. Two equivalents are necessary to support the multiple chlorinations (Step 1 and 2, Figure 1) and we presume the 10% excess is due to reagent decomposition.[2] The heat released during the formation of sulfenyl chloride **4** (Step 1) is 242 kJ/mol. The vinyl acetate (**5**) addition (Step 2) is also exothermic involving both the sulfenyl chloride **4** addition to vinyl acetate (**5**) and the chlorination of the alpha position to the ester (**6**) to yield the desired dichloride **7**. For this sequence of reactions, the generated heat is 438 kJ/mol. We predict this translates to an adiabatic temperature rise of 102–133 ^{o}C for Step 1 and 138–207 ^{o}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's addition or 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 **6** in high yields (94–100%) over a wide operating temperature window, −20 ^{o}C to 25 ^{o}C. On the other hand, Step 2 provides the highest yields and selectivity for **7** when the reaction is carried out at −20 ^{o}C. Higher temperatures increase the ratio of trichloro **8** to dichloro **7** products and reduces the overall yield due to 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 yields at least 10%. The reaction produces a number of gaseous byproducts including HCl and SO_2. We observed that **7** is more stable under acidic solutions, which may indicate HCl loss in the headspace can affect the yield. It appears lower reaction temperatures for Step 2 increases reaction tolerance to pressure changes. This is likely due to higher amounts of HCl gas dissolving in the reaction mixture. The combination of exotherm and pressure sensitivity suggest 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 if the first step could tolerate premixing the thiol **3** and vinyl acetate (**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 the thiol **3** and the vinyl acetate (**5**) were combined, a thio-ene reaction took place with byproduct **14** formation (Scheme 2B). After SO_2Cl_2 addition, the overall reaction provided **7** in lower assay yields (AY = 57%).[8] Vinyl acetate (**5**) also reacts with SO_2Cl_2 to form 1,2-dichloroethyl acetate (**12**) (only traces were observed; Scheme 2A) and with hydrogen chloride to produce 1-chloroethyl acetate (**13**).



Scheme 2. Possible pathways involving vinyl acetate (**5**) – (A) Desired reaction with sulfenyl chloride **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 occurrence of different side reactions involving vinyl acetate (**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 minutes (213 µL/min) based on our earlier observations. Using these standard batch conditions, we varied the vinyl acetate (**5**) (2 equiv.) addition rate (640, 213 and 53 µL/min) and analyzed the outcome by measuring product distribution of the crude reaction after 4 h from the beginning of vinyl acetate (**5**) addition. The results are shown in Table 1 and indicate that the addition rate of vinyl acetate (**5**) is inversely proportional 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 the Step 2.

Table 1. Variation of the vinyl acetate (**5**) addition rate – 4.0 g scale reaction.

Entry	Add. rate of **5** (µL/min)	Addition time (min)	ΔT (°C)	Monochloro **6** (%)	Dichloro **7** (%)	Trichloro **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

Continuous flow experiments, system design and considerations. Formation of HCl and SO_2 during the reaction sequence limits the use of certain materials for the system construction due to 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 due to its poor compatibility 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 material for our coil reactor due to 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 (BPR) to be able to easily clean the solid deposited on the BPR spring after each reaction.

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 DCM, Solution A) and SO_2Cl_2 (3.82 mol/L in DCM, 2.2 equiv., Solution B) were delivered using syringe pumps at 0.168 mL/min flow rate 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). Due to the HCl and SO_2 formation, a BPR (75 psi) was added at the end of the coil reactor to maintain the gases dissolved into the reaction mixture and achieve a stable flow rate (Figure 2).

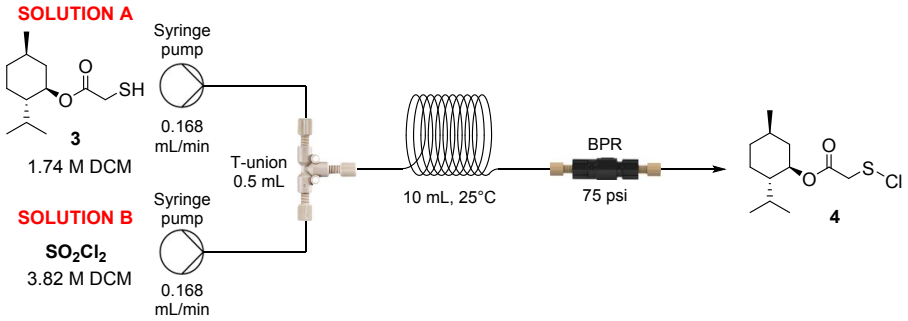


Figure 2. Initial flow setup for sulfenyl chloride **4** synthesis.

When a total flow rate of 0.336 mL/min was applied at 25 °C, compound **4** was obtained in 92% AY and no remaning starting material **3** was detected (Table 2, Entry 1). Lowering the temperature to 0 °C, sulfenyl chloride **4** yield obtained was 80% AY and 15% of thiol **3** remained unreacted (Table 2, Entry 2). By decreasing residence time 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 for 1,2,3-trichloropropane (see Supporting Information). This non-standard trichloride is inert to SO_2Cl_2, while mesitylene can present reactivity toward ring chlorination.[10] This may be the cause of the variable mass balance observed when Entry 1 (Table 2) was repeated in triplicate (95 ± 3 %).

Table 2. Initial results for sulfenyl chloride **4** formation in continuous conditions – 400 mg scale.[a]

Entry	Total flow rate (mL/min)	Reactor vol. (mL)	Residence time (min)	T (°C)	Thiol **3** AY (%)	Compound **4** AY (%)	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 ^{0}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 is suppressed and product **4** is obtained in 99 ± 1% AY and no loss in mass is observed (triplicate experiment) – the same result is observed if 1,2,3-trichloropropane is used as the ^{1}H NMR internal standard.

We turned our attention to the vinyl acetate (**5**) addition (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 vinyl acetate (**5**) to generate **7**. The second module consists of a syringe pump delivering neat vinyl acetate (**5**) to a T-union where mixing of **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).

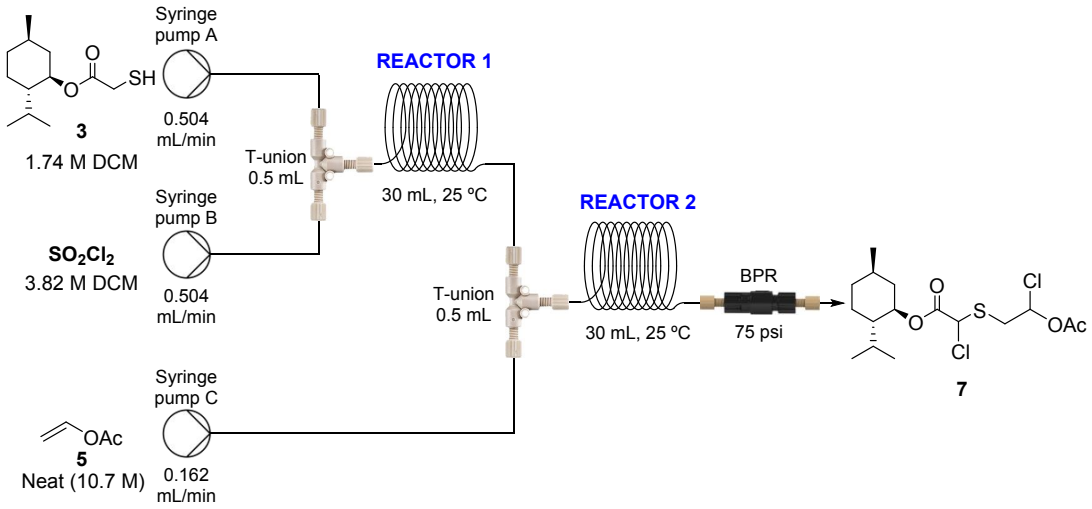


Figure 3. The initial flow setup with two modules - Module 1: Production of the sulfenyl chloride **4** in the Reactor 1; Module 2: Combination of **4** with the vinyl acetate (**5**) stream at the Reactor 2 to produce **7**.

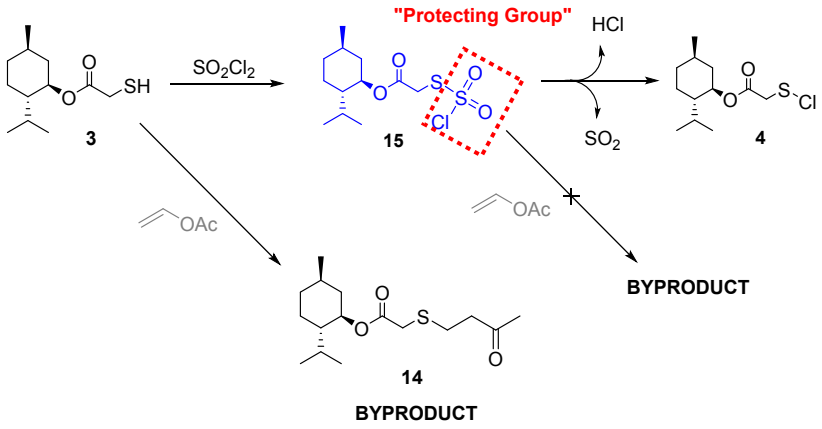
Using our initial reactor configuration (Figure 3), we explored different system properties. The residence time in Reactor 1 was held constant at 30 min. Lengthening the reactor was necessary to achieve this. The temperature of both modules was kept at 25 °C for all experiments shown in Table 3. The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

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)	Dichloro **7** (%)	Trichloro **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] Residence time in the Reactor 1 was held constant at 30 min for all experiments (25 °C). This table presents the parameters only for the Reactor 2. All experiments were ran in a 1.0 g scale.
[b] 1,2,3-trichloropropane was used as the internal standard (^{1}H NMR).
[c] 10% intermediate **6** and 2% sulfenyl chloride **4** left.

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 steady state stability and scale-up by increasing reactor diameter. An early observation indicated that Reactor 1 (Step 1) residence time could be drastically reduced. At residence time of 15 min at 0 °C (Step 1), a new unstable intermediate that leads to the formation of sulfenyl chloride **4** was detected by ^{1}H NMR (see Supporting Information). Although this intermediate is not well-described, a few accounts suggest that **14** is formed as a precursor of the sulfenyl chloride **4** (Scheme 3).[11,12] We speculated that **14** might form so quickly that we could combine the output from module 1 with the vinyl acetate (**5**) stream directly without need for a residence time loop (Reactor 1). Our hypothesis is that intermediate **14** would not react directly with **5**, thereby acting as a temporary protecting group against unwanted thio-ene reaction.



Scheme 3. First stage reaction of **3** with SO_2Cl_2 working as a thiol "protecting group".

We tested this hypothesis by building two new reactor configurations. The same reagent concentrations and reaction conditions were kept to perform these experiments. The first configuration fed a reactor with a SO_2Cl_2, a vinyl acetate (**5**) and a thiol **3** containing stream into a single T-union at the same time – this served as a control experiment where no thiol **3**/SO_2Cl_2 premixing occurred before vinyl acetate (**5**) addition (see Supporting Information). As expected, due to the different rates of the thiol **3** reaction with SO_2Cl_2 and vinyl acetate (**5**) and SO_2Cl_2 reaction with **5**, a complex mixture of products was obtained. For the second reactor configuration, we premixed the thiol **3** and the SO_2Cl_2 using a small loop (1 mL) right after the first T-union and immediately combined the resulting solution with the vinyl acetate (**5**) stream (see 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% during a 26 minutes 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 steady-state stability and increasing 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 syringe to 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. As such we selected chemically resistant peristaltic pumps from Vapourtec (E-series). Initial testing was challenging because the rubber hose swelled overtime when contacting the SO_2Cl_2 solution. This caused the system performance to decrease or fluctuate overtime. To avoid swelling, we replaced the tubing before long reaction runs and no tubing deformation was observed for the following ~100 h of pumping SO_2Cl_2. It is worth mentioning that the E-series pumps must be properly calibrated from time to time. For some experiments we observed

irregular pumping. Different volumes of thiol **3** and SO_2Cl_2 solutions were injected into the system despite equal flow rates being applied to both 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), yield decrease was detected. This appeared to be correlated with a temperature increase in the T-union 2 (Figure 4, without the second 1 mL loop). In this case, compound **7** assay yield was about 90% and 10% trichloro acetate **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 the T-piece 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 enough residence time for the reaction mixture to reestablish its original temperature. The high yields of compound **7** were recovered (98 ± 2% AY) most likely due to the better temperature control, which limited byproduct **8** rate formation. During these long runs, the pressurized system was *ca.* 2 bar higher than the applied back pressure (5 bar) due to pressure drop across the system at larger scale. This observation prompted us to lower system pressure using a 40 psi BPR and work the peristaltic pumps closer to their optimum operation pressure as indicated by Vapourtec (3 bar).

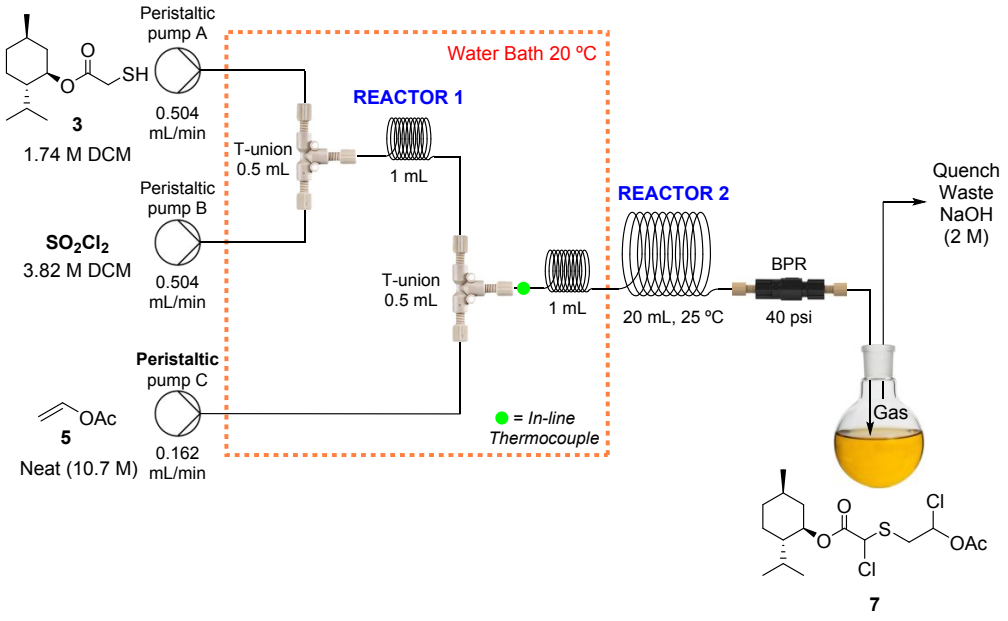


Figure 4. The improved configuration where the residence time feature for the sulfenyl chloride **4** module is reduced in volume (1 mL); the temperature after T-union 2 is monitored via an in-line thermocouple and part of the two-module system is cooled via two units of a 1 mL residence time loop submerged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

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 to assay yield determination. The steady state is reached after 5 minutes and the assay yield average of compound **7** is 98 ± 1%. The switch between starting material solutions and solvent (Figure 5) causes small variations at the end of the steady state.

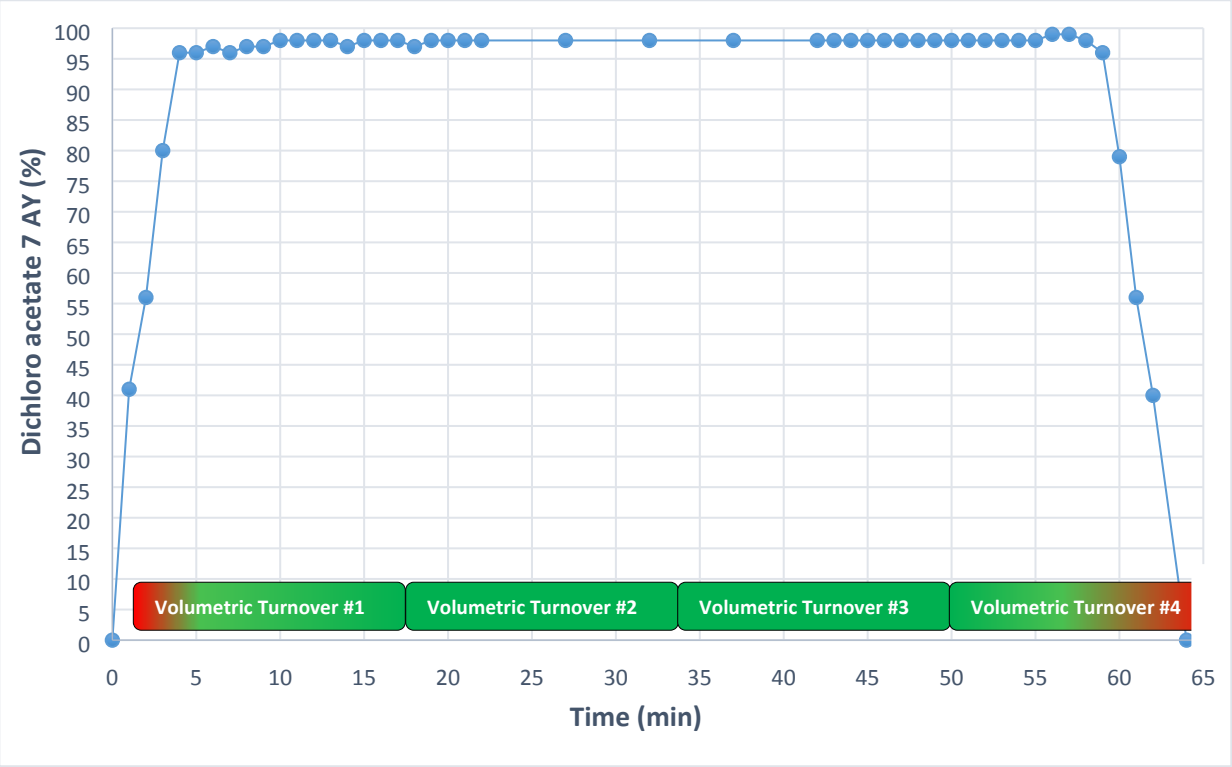


Figure 5. Variation of dichloro acetate **7** yield over time – total flow rate 1.17 mL/min with a 17 minutes residence time – In the steady state product **7** assay yield is 98 ± 1% and **0**% of **6** was observed using ^{1}H-NMR with 1,2,3-trichloropropane as the internal standard. Volumetric turnover ≈ 20 mL.

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% *versus* 78%, respectively). However, no difference was observed under continuous conditions (steady state). Thus, we decided to proceed with toluene for both economic and environmental considerations. Having defined a configuration that functioned at steady state for long runs, we continued defining best operating conditions for scaling-up. Increasing the flow rates of this refined system (Figure 4) from 1.17 up to 2.11 mL/min does not alter the yield of **7**, but does increase the system productivity (Table 4). We decided to use the middle residence time

of 14 minutes (Table 4, Entry 2) – a condition where no unreacted intermediate **6** is observed – to test scaling-up the system by doubling the tubing diameter from 0.03 in I.D. (1/16" O.D.) to 0.06 in I.D. (1/8" O.D.).

Table 4. Optimization of reaction in toluene and steady state conditions.[a, b]

Entry	Solvent	Total flow rate (mL/min)	Residence time (min)	Monochloro **6** (%)	Dichloro **7** (%)	Trichloro **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 samples were collected in vials containing a saturated $NaHCO_3$ aqueous solution to quench the remaining SO_2Cl_2 and the HCl, avoiding over-reactions.
[b] 1,2,3-trichloropropane was used as the internal standard (^{1}H NMR).

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 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 five 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 dichloro acetate **7** corresponding to a throughput of 141 g/h (Table 5, Entry 3).

Table 5. Scale-up experiments in steady state conditions.[a, b]

Entry	Scale (g) Thiol **3**	Total flow rate (mL/min)	Residence time (min)	Monochloro **6** (%)	Dichloro **7** (%)	Trichloro **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 six minutes (all them in steady state). All samples were collected in vials containing a saturated $NaHCO_3$ aqueous solution.
[b] 1,2,3-trichloropropane was used as the internal standard (^{1}H NMR).

CONCLUSION

We recently created a new approach to synthesize the oxathiolane core used in the commercial route to the high volume anti-retroviral medicines Lamivudine and Emtricitabine. This new route uses SO_2Cl_2 to produce the alkyl sulfenyl chloride **4** followed by a chloro-thioene reaction to yield **7**. This intermediate undergoes a cyclization step to produce the 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), where thiol **3** was first premixed with SO_2Cl_2 (Module 1) and the resulting solution combined with the vinyl acetate (**5**) stream (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 vinyl acetate (**5**) and consequently, byproduct **14** formation (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, 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 141g/h. The data suggests 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 SigmaAldrich, TCI Chemicals, J. T. Baker and MilliporeSigma and used as received. Thin layered chromatography (TLC) and column chromatography were performed using silica gel 60 F254 plates (0.25 mm) and silica gel (pore size 60 Å, 70–230 mesh, 63–200 μm) respectively (from Sigma-Aldrich). Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were acquired using a Bruker-600 MHz spectrometer. Chemical shifts for hydrogens and carbons are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) or referenced to residual solvent. Data are represented as follows: chemical shift (δ), multiplicity singlet (s), broad singlet (br. s), doublet (d), broad doublet (br. d), triplet (t), quadruplet (q), octet (oct), double doublet (dd), double triplet (dt), double double doublet (ddd), triple doublet (td), and multiplet (m), coupling constants in Hertz (Hz) and integration.

NMR data was processed using the ACD Laboratories software, and the names of compounds were generated using the PerkinElmer ChemDraw Ultra v.12.0.2 software package. Syringe pumps utilized to perform flow experiments were purchased from Chemyx (Fusion 4000 and Fusion 6000). For the scale-up, peristaltic pumps from Vapourtec E-series were used. Perfluoroalkoxy (PFA) tubing (1/16 inch O.D.; 0.030

inch I.D. and 1/8 inch O.D.; 1/16 inch I.D.), back-pressure regulators (BPR), connections and fittings were purchased from Swagelok, Cole-Parmer and IDEX Corporation.

(1R,2S,5R)-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 1M (100 mL) and extracted with toluene (3 x 100 mL). The organic phases were combined, dried with anhydrous Na_2SO_4 and the solvent was removed in a rotatory evaporator. Remaining toluene was removed under reduced pressure in a vacuum pump for 6 h. Compound **3** was obtained as a colorless oil in 96% AY and 95% purity (141.5 g; 0.61 mol). Thiol **3** was 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.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-(chlorothio)acetate (4). *Initial experiments to study sulfenyl chloride **4** formation under continuous flow conditions (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 SO_2Cl_2 (3.2 mL; 38.2 mmol; 2.2 equiv.) solution 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 be able to switch 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 0.168 mL/min flow rate each 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 ESI – Fig. S2 and S3). Compound **4** was not isolated. 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).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-((2-acetoxy-2-chloroethyl)thio)acetate (6). Intermediate isolated only to use as a reference to compare with the ^{1}H NMR 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 signal – diastereoisomers mixture).

(1R,2S,5R)-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 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 was kept under these conditions for 2 h. Vinyl acetate (3.2 mL; 3.00 g; 34.8 mmol) was added at 640 µL/min addition rate. After 4 h, the reaction was neutralized with $NaHCO_3$ saturated solution (50 mL) and extracted with DCM (3 x 50 mL). The organic phase was separated, 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 compound 7 synthesis under continuous flow conditions (syringe pumps). The outcome of the previously described sulfenyl chloride **4** synthesis flow setup was combined with vinyl acetate (**5**) through a T-union. Vinyl acetate (**5**) flow rate was adjusted (syringe pump) 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 ESI – Fig. S4 and S5).

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 SO_2Cl_2 (6.24 mL; 76.4 mmol; 2.2 equiv.) solution in toluene (Solution B). Each solution was transferred to a 20 mL vial under nitrogen atmosphere, and then connected to the V-3 peristaltic pumps (E-Series – Vapourtec 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 (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 $NaHCO_3$ saturated 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 not purified starting material. However, water traces in thiol **3** can quench part of SO_2Cl_2. After basic wash, efficient drying is required to control the addition of the optimized amount of SO_2Cl_2 (see ESI – Fig. S6). Compound **7** was obtained as a white goop after extraction with a saturated solution of $NaHCO_3(aq)$. Overall assay yield, starting from thiol **3**, is 98% (0.67

mol; 258.2 g considering 158 g scale-up condition in flow): Crystal (**7a**, see ESI – Fig. S8) ^{1}H NMR (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{^{1}H} 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.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-((2-acetoxy-2-chloroethyl)thio)-2,2-dichloroacetate (8). Intermediate isolated only to use as reference to compare with the ^{1}H NMR of the crude reaction mixture. It was obtained as a slightly yellow oil. ^{1}H 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{^{1}H} 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 signal – diastereoisomers mixture).

1,2-dichloroethyl acetate (12). Obtained from the reaction of vinyl acetate with SO_2Cl_2. It was synthesized to use as a reference to compare with the ^{1}H NMR of the crude reaction mixture. ^{1}H 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 – Adiabatic temperature rise calculation, additional figures (system configuration), X-ray of compound **7** and ^{1}H and ^{13}C NMR spectra.

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