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A simple one-pot oxidation protocol for the synthesis of dehydrohedione from Hedione

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ABSTRACT

A new method for the oxidation of Hedione **1** to dehydrohedione **2**, a high value intermediate in the flavour and fragrance industry, has developed based upon one pot α-chlorination-elimination sequence which can be readily scaled. The spontaneous elimination of the α-chloro in methanol was unprecedented and has allowed for the oxidation, typically performed in multiple steps/reactions, to be carried out as a one-pot protocol. A continuous flow process for performing the reaction utilising sulfuryl chloride has also demonstrated allowing for steady, safe evolution of SO_2 gas during the reaction.

1. Introduction

The synthetic fragrance ingredient methyldihydrojasmonate (**1**, Trade names, Hedione/Kharismal) is widely used in perfumery being manufactured at a scale of over 1000 tonnes per year [1]. Its unsaturated analogue, dehydrohedione (DHH, **2**), is a highly valuable synthetic target due to its ability to deliver Hedione diastereomeric mixtures through hydrogenation comprising the sort after (1*R*,2*S*)-(+)-*cis* isomer **1a** (Fig. 1) [2–5] the principal constituent responsible for the characteristic odour.

Enhanced *cis* isomer mixtures possess a superior scent profile and hence are worth more than commercial Hedione (90% *trans*). Although a wide variety of synthetic routes towards DHH have been developed [7–13], Hedione is cheap (~$5/kg) and readily available in its predominantly *trans* form (**1c** + **1d**) and so the preferred method of DHH synthesis at scale is through direct oxidation of Hedione [14]. Historically, this has been enacted via a 3 steps sequence involving regioselective formation of ester **3**, followed by bromination with a bromine source (typically Br_2), followed by base induced elimination. However, the stepwise nature of this sequence, the increasing expense of the bromine and the large amounts of waste produced indicated a need for improvement. Following preliminary work conducted by ourselves involving oxidation of **3** *via* an α-bromo intermediate **4** [15], we were interested in developing a more efficient and environmental-friendly method for the oxidation of Hedione based upon an α-chloro intermediate **5** (Scheme 1).

Commonly used α-chlorinating agents for ketones include $CuCl_2$ [16], sulfuryl chloride (SO_2Cl_2) [17], trichloroisocyanuric acid (TCCA, **6**) [18], 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, **7**) [19], *p*-toluenesulfonyl chloride [20], *N*-chlorosuccinimide (NCS, **8**) [21], tetraethylammonium trichloride [22] and elemental chlorine [23] (Fig. 2). From prior work [15], $CuCl_2$ was known to be ineffective for

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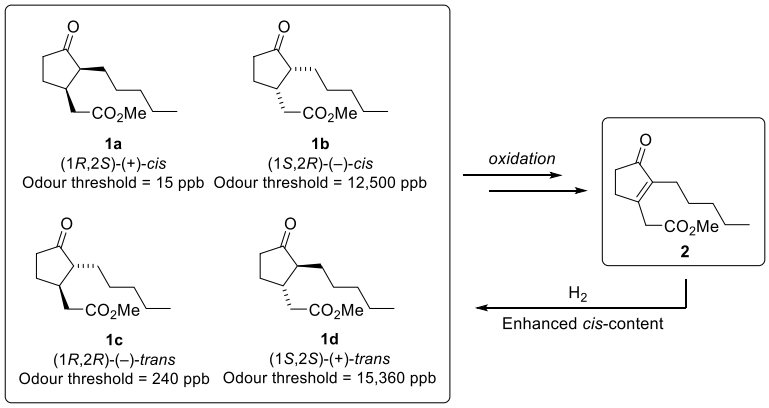
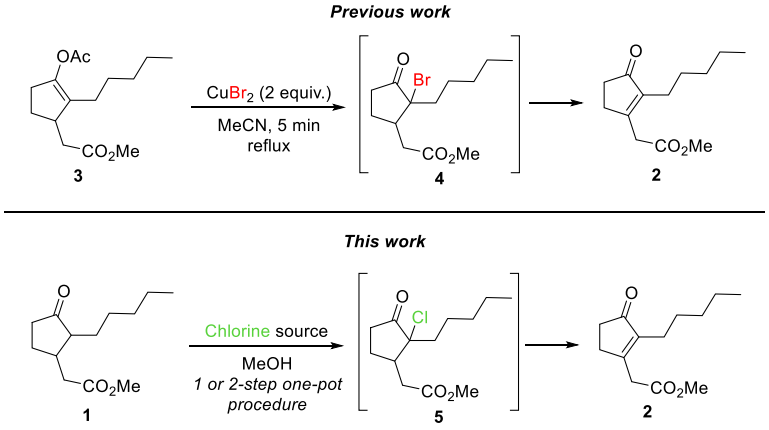


Fig. 1. Methyldihydrojasmonate diastereomer odour thresholds [4,6].



Scheme 1. Our work in the area of DHH synthetic strategies, top previously used copper mediated oxidation route to DHH **2**; bottom, proposed analogous alternative route.

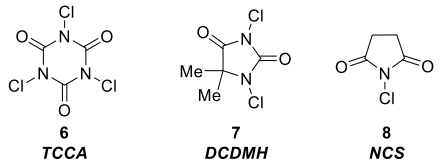


Fig. 2. Structures of TCCA, DCDMH and NCS.

Hedione oxidation. Of the remaining reagents, NCS, Cl_2, and SO_2Cl_2 were previously reported as effective agents for the targeted chlorination, although stoichiometric amounts of amines were required to subsequently induce the HCl elimination to occur [24]. As such SO_2Cl_2, DCDMH, TCCA were selected as potential candidates due to the fact that they are cheap and readily available. We herein report a simple and highly cost effective procedure for the one-pot synthesis of DHH from Hedione using such α-chlorinating methodology.

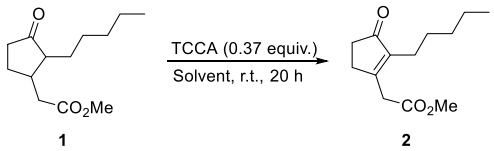
2. Results and discussion

2.1. Implementing a batch process

Upon establishing that TCCA (a cheap industrial disinfectant and bleaching agent used in swimming pools and in the textile industry) was a suitable candidate for the chlorination of Hedione to the desired α-chloro intermediate **5**, initial studies looked to assess the potential for the subsequent elimination. Pleasingly, it was found that the elimination occurred spontaneously when the reaction was conducted in methanol (MeOH) (Table 1). Screening other alcoholic solvents such as EtOH, *i*-PrOH and *t*-BuOH, a reduced rate of elimination to furnish **2** was noticed probably due to the steric hindrance of alkyl group (*Entries 4 – 7*). Employing chlorinated solvents and toluene resulted in only partial chlorination and the subsequent elimination did not occur (*Entries 1 – 3*). Chlorination was not detected in solvents where TCCA is highly soluble, such as acetonitrile (MeCN), ethyl acetate (AcOEt), and acetone (*Entries 8 – 10*). As the addition of liquids can be better controlled than the addition of solid reagents, AcOEt as a co-solvent was still interesting to employ, as it would facilitate the addition of a solution of TCCA. Having gained successful results utilising a mixture 1:1 of AcOEt:MeOH (*Entry 11*), it was speculated whether smaller (stoichiometric) amounts of alcohol could be enough for the reaction to occur (*Entry 12*). Unfortunately, almost no reaction was observed when a 9:1 mixture of AcOEt:MeOH was employed, suggesting the methanol plays a key role in both chlorination and the subsequent elimination steps (*Entry 12*).

Considering the elimination sequence, a mechanistic sequence was postulated (Scheme 2). Our hypothesis comes from experimental observations. It is observed that initially two intermediate stereoisomers of **5** are produced during the chlorination step (TLC shows a major and minor product forming upon addition of TCCA ~9:1 ratio by NMR). However, the minor isomer is observed to

Table 1
Solvent screening for the TCCA oxidation of Hedione.



1 2

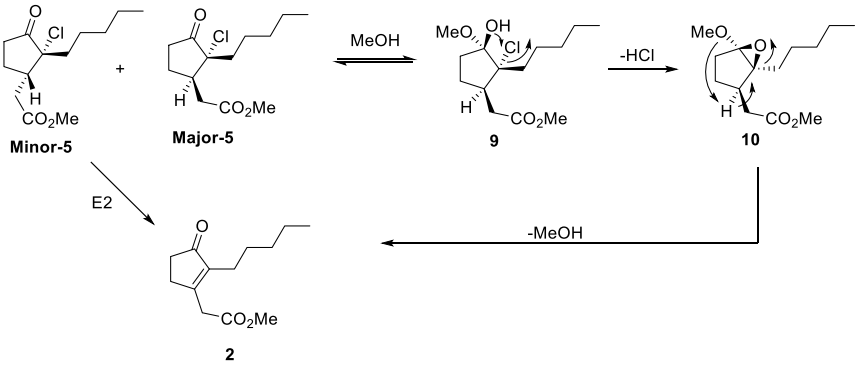
Entry[a]	Solvent	Yield (%)[b]
1	CH2Cl2	0
2	CHCl3	0
3	Toluene	0
4	MeOH	28
5	EtOH	19
6	*i*-PrOH	11
7	*t*-BuOH	traces
8	AcOEt	0
9	Acetone	0
10	MeCN	0
11	MeOH:AcOEt (1:1)	20
12	MeOH:AcOEt (1:9)	3

[a] Reactions conducted on a 5 mmol scale (1 M).
[b] Calculated using 1,3,5-trimethoxybenzene as an internal ^{1}H NMR standard. The reactions 4–6, and 11 all showed full consumption of the Hedione starting material and formation of the mixture of intermediates isomers of **5**.

enhanced by the addition of acid sources, both Brønsted (e.g., AcOH, HCl) and Lewis (e.g., BF_3, $ZnCl_2$, $CeCl_3$), of particular note was that the use of trifluoroethanol or hexafluoroisopropanol lead to rapid formation of the chloro intermediates **5** but interestingly failed to induce any elimination. In overview we took as supporting evidence indicating methanol's key attributes as a protic solvent for the chlorination step and suitably nucleophile (electronics and sterics) to fulfil the elimination stage.

To gain further evidence, we wished to establish the stereoselectivity of the chlorination however despite repeated attempts only one of the two isomers could be successfully isolated. In an attempt to evaluate the process via analogue we determined it interesting to prepare the more stable fluoro intermediates **12** and compare the data by correlation (Scheme 3). Unfortunately, we found no obvious correlations when comparing the two fluoro diasteroisomers to the major chloro isomer **5** previously isolated by chromatography.

Despite being unable to categorically identify the mechanistic process involved we elected to further investigate the potentially valuable reactions optimisation (Table 2). It was shown that gradual addition of the TCCA was preferable to control the exotherm and avoid a runaway reaction especially upon scaling the reaction. The solid was added directly to the reaction in portions (or as a solution in e.g EtOAc) such that the temperature was maintained within the

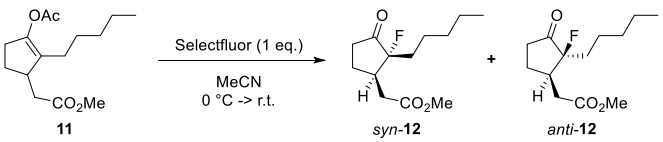


Scheme 2. Proposed mechanism sequence for the elimination to DHH.

diminish over time with the appearance of the desired product **2**. This can also be seen through the use of 2D TLC analysis and NMR time-based monitoring. This transformation is also rendered instantaneous if any form of base is added to the reaction. We therefore speculate this material is the antiperiplanar H–Cl configured species **Minor-5** which can readily undergo E2 elimination to generate compound **2** (Scheme 2). Consequently, we propose the relative configuration of the predominant chloro intermediate as **Major-5** which is more stable due to its inability to undergo an E2 process and has thus been isolated. We rationalise the role of the alcohol solvent and its ability to induce elimination due to the electrophilicity of the carbonyl group, methanol could add into the ketone **Major-5**, forming the hemiketal intermediate **9**. Depending on the relative configuration of the chloro atom and the hydroxyl group, the chlorohydrin **9** could convert into the epoxide **10** *via* intra-molecular S_N2 substitution, eliminating hydrogen chloride. The methanol would finally eliminate through E2 ring opening of the epoxide yielding the target molecule **2**. A similar process to based promoted epoxide isomerisation to form allylic alcohols [25,26].

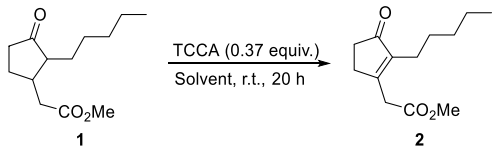
It was also noted that the initial chlorination process was rate quoted range. At higher temperatures (Table 2, entry 1), the reaction occurred immediately upon addition of the TCCA which made controlling the temperature unchallenging. At lower temperatures, however, a long and unpredictable delay was always observed between addition of TCCA and reaction initiation. This suggests that TCCA itself was not reacting directly with the starting material (as an electrophilic chlorinating agent) but that it was instead probably acting as a source of Cl_2 or Cl radicals.

The observed delay was explained by considering the fact that cleavage of an N–Cl bond in TCCA is first required in order to generate a chlorine radical/Cl_2 and initiate the reaction. With radical initiators such as AIBN, this is classically achieved by heating



Scheme 3. Reaction conditions for the synthesis of the fluoro intermediates **12** and performed strategy to establish the HCl elimination step.

Table 2
Chlorine source (reagent) screening for the oxidation of Hedione.



Entry[a]	Conditions	Yield (%)[b]
1	Reflux, TCCA (0.5 equiv.), 20 h	36
2	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), HCl (2 drops), 20 h	48
3	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), HCl (5 drops), 20 h	35
4	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), SiO_2 (0.5 g), 20 h [29]	47
5	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), 20 h	56
6	Thermal initiation → < 30 °C, TCCA (0.33 equiv.), 20 h	51
7	Thermal initiation → < 30 °C, TCCA (0.67 equiv.), 20 h	54*c*

[a] Reactions conducted on a 50 mmol scale (1 M in MeOH), 0.37 equiv. of TCCA equates to 1.1 equiv. of active chlorine content.
[b] Calculated using *n*-undecane as an internal GC standard; [c] Product isolated by SiO_2 column chromatography in 52%.

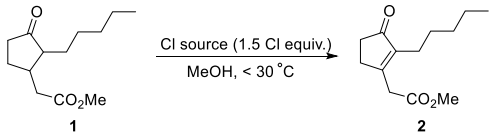
or irradiating with UV–visible light [27]. By heating the reaction therefore, this 'initiation' can be induced and made to occur predictably. The initiation is highly exothermic and leads to a rapid propagation in the presence of additional TCCA. Initiating the reaction in the presence of small amounts of TCCA and then dosing the balance of the TCCA portion wise was therefore the safest and most favourable way to carry out the process (*Entries 2 – 7*). Thermal initiation was found to occur within the temperature range of 45–51 °C and it was also possible to initiate the reaction by irradiation with visible light (also previously demonstrated for the chlorination of chloro(methyl)pyridine with TCCA) [28]. Interestingly, the reaction proceed smoothly and initiate at the same temperature in the presence of an added radical scavenger (Na_2SeO_3). Thus, indicating a Cl_2 mediated reaction. Indeed, a blue litmus paper test showed the rapid indicative red then bleaching effect.

By performing the reaction at reflux, a lower yield was observed (Table 2, entry 1). The reaction was therefore heated briefly in the presence of ~5 mol% of TCCA to induce initiation and then cooled intermittently while the remainder of the TCCA was added. In the presence of catalytic acid, the rate of the reaction was enhanced, however, poorer yields and selectivity was observed (*Entries 2 – 3*). The addition of acidic silica gel did not lead to initiation of the reaction (E*ntry 4*). TCCA stoichiometry could be lowered to 0.33 equivalents without a drastic impact on yield (*Entries 5 – 6*) and using more than 0.5 equivalents resulted in a slightly poorer yield due to over-chlorination (E*ntry 7*).

Using the conditions for TCCA (Table 2, entry 5), other chlorinating agents were also investigated (Table 3). Of these, the best yield was obtained with TCCA, with NCS giving the product in 48% (Table 3, entry 2) and DCDMH resulting in a 35% yield (Table 3, entry 3) as estimated by GC (*n*-undecane internal standard). Based upon the probable Cl_2 involvement Cl_2 gas was generated from TCCA in a separate vessel and bubbled into a solution of Hedione in methanol under a stream of nitrogen, this resulted in a 28% yield of the product (Table 3, entry 4), reinforcing the proposed mechanism. The reduced yield was attributed to loss of Cl_2 through nitrogen purging.

The use of sulfuryl chloride (SO_2Cl_2) had to be evaluated separately as MeOH would result in decomposition of the chlorinating agent generating the highly toxic dimethyl sulfate. Addition of methanol was still required in order for the α-chloro intermediate **5** to undergo elimination. The process was therefore carried out in two steps and a solvent screen for the initial chlorination step was

Table 3
Chlorine source (reagent) screening for the oxidation of Hedione.



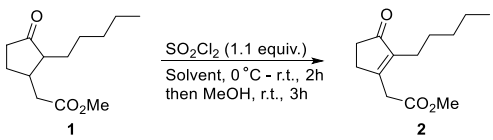
Entry[a]	Reagent	Yield (%)[b]
1	TCCA	56
2	NCS	48
3	DCDMH	35
4	Cl_2 gas	28
5	SO_2Cl_2	79[c]

[a] Reactions conducted on a 50 mmol scale (1 M).
[b] Calculated using *n*-undecane as an internal GC standard.
[c] Conducted as a two-step process, SO_2Cl_2 added in $CHCl_3$ followed by addition of MeOH after 5 h.

conducted (Table 4). The yield was found not to be greatly affected by the solvent used in the first step (*Entries 1 – 3*), however, conducting the reaction under solvent-free conditions led to a lower yield of 58% (*Entry 4*).

Beneficially for the reaction using SO_2Cl_2, 'initiation' was not necessary – the reaction occurred immediately upon mixing with a solution of Hedione both at room temperature and at 0 °C. These

Table 4
Solvent screening for the oxidation of Hedione with SO_2Cl_2.



Entry[a]	Solvent	Yield (%)[b]
1	$CHCl_3$	79
2	EtOAc	74
3	toluene	75
4	neat	58

[a] Reactions conducted on a 5 mmol scale (1 M).
[b] Calculated using 1,3,5-trimethoxybenzene as an external ^{1}H NMR standard.

results point towards a potentially different chlorination mechanism than is in operation with TCCA. It is likely that SO_2Cl_2 reacts directly with the enolised starting material, acting as an electrophilic chlorinating agent.

Gradual addition of SO_2Cl_2 was used to regulate the temperature below 30 °C, however, the reaction was far less exothermic than with TCCA and hence much easier to control. Cooling during SO_2Cl_2 addition was found to be unnecessary and so was not used from this point onwards. The stoichiometry of SO_2Cl_2 was investigated (Table 5) and it was found that the number of equivalents could be reduced to 0.75 equivalents without a significant impact on the yield (*Entries 2 − 3*). The reaction was scaled up to 0.5 then 5 mol at an increased concentration of 2 M. Monitoring the reaction by both GC and ^{1}H NMR revealed that the first step was essentially complete in 2 h (typically no more starting material was identified within 2.25–2.5 h) and the second step (following addition of MeOH) required 3 h to reach completion (Fig. 3). At the larger 5 mol scale (1.1 Kg of **1**), the product was isolated in 85% yield by vacuum distillation (Table 5, e*ntry 5*).

The optimum reagent for chlorination-elimination of Hedione was therefore shown to be SO_2Cl_2 (85% isolated yield *vs* 56% with TCCA). While SO_2Cl_2 has been widely used as an α-chlorinating agent [17,30], its use in a one-pot chlorination-elimination sequence is completely new. In 1957, the use of SO_2Cl_2 for the synthesis of 2-methyl-2-cyclohexenone from 2-methylcyclohexanone was demonstrated [31]. However, this was performed as a discrete 2-step procedure wherein CCl_4 was used as a solvent for the initial chlorination and either collidine or a LiCl/DMF system was used to promote elimination in a completely separate reaction of a fully worked up α-chloro product. Aside from the fact that SO_2Cl_2 gives the best yield of all chlorinating agents tested, its liquid nature (at room temperature) makes the process highly attractive in terms of transposition into a continuous-flow process. Another advantage in this regard is that no precipitates are formed during the reaction with SO_2Cl_2, as is the case with TCCA, NCS and DCDMH. The development of a flow process was therefore subsequently investigated.

2.2. Creating a flow process

Having devised a successful batch procedure for the oxidation of **1**, as a research group interested in applying continuous-flow applications toward flavour & fragrance manufacturing [32], we decided to investigate a flow approach to determine outline criteria suitable for potential industrial applications. Although TCCA had proven in batch to be less viable than SO_2Cl_2 it still offers the highest active chlorine content (45.8 wt% of active chlorine compared to 26.3 wt% respectively) and as such we wished to further explore its use.

The continuous flow oxidation of **1** employing TCCA presented several challenges based upon precipitation of cyanuric acid [33] and the inherently corrosive nature of TCCA solutions. We first needed to modify a set of Vapourtec SF-10 peristaltic pumps to withstand the corrosive nature of the TCCA input solution [34]. We noted that Vapourtec already offered a red pump tube which utilises PEEK seals, however, the plastic construction material of the tubing swells when using polar organic solvents such MeOH, AcOEt or acetone leading to rapid rupture. Consequently, Vapourtec engineers designed a customised 'blue' tube peristaltic unit with PEEK seals to be applied under these reaction conditions.

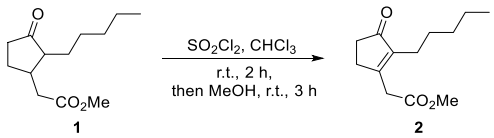
We established a three pumps system where the chlorinating agent was added in two stages simulating the initiation procedure in batch. In the first coil, a certain amount of the TCCA was mixed with the solution of **1** in MeOH and heated to 45 °C to initiate the chlorination. At a second downstream input the remainder of the TCCA was mixed with the reacting biphasic mixture and streamed into two connected 10 mL 1.5 mm FEP coils maintained at room temperature (Scheme 4). The chlorinated mixture was then collected into a flask where the HCl elimination occurred overnight.

Unfortunately, the accumulation of the cyanuric acid led to clogging of the system after ~10 min of runtime. To avoid clogging, the coil reactors were placed in an ultrasonic bath where the water was regulated to maintain a constant specified temperature. Ultrasound-induce mixing has also been employed in prevention of clogging when solids are formed in the reaction mixture, it allows the formation of smaller solids and prevents accumulation [35–40]. We decided to employ two ultrasonic baths and vary the temperature of the final coil, however this did not significantly change the reaction outcomes (Table 6, entries 1–5). The low yields obtained were also attributed to a possible decomposition of the final material **2** occurring under strong acidic conditions. Surprisingly, quenching the reaction with either water or sodium bicarbonate was not successful as we mainly recovered starting material, suggesting **1** was being substantially chlorinated in the collection flask (*Entries 6&7*). Finally, splitting in to two equal additions the equivalents of TCCA allowed for the reaction to occur in the coils, albeit with no real improvement in efficiency (*Entry 7*). Increasing the residence time to 0.8 min did not increase the final yields (*Entry 8*). The best flow conditions (Scheme 5) were run for 30 min to collect 6 g of final material **2** (35% NMR conversion).

The alternative reaction using SO_2Cl_2 is potentially well suited to flow since all materials used are miscible liquids. Another feature of the reaction making flow attractive is the fact that SO_2 gas evolution occurs. In batch, exothermic reactions that involve the generation of gas are prone to rapid gas evolution and overpressures, hence, very careful addition of reagents to such reactions are necessary at scale. Gas generation can be easily managed in flow by pressurising the system with a suitable back pressure regulator (BPR) [41]. The gas can be kept in solution whilst in the flow stream and then ejected from the reaction upon passing the BPR. This allows for steady, constant release of the gas in a manner that carries with it improved safety implications compared to batch.

A semi-continuous system was devised in which the chlorination step was performed in flow and the elimination was performed batch-wise (Scheme 6). Neat Hedione was fed into a 0.27 mL Uniqsis mixing chip along with a solution of SO_2Cl_2 in $CHCl_3$ at a rate such that 1.1 equiv. of SO_2Cl_2 was used with a residence time of either 1 or 2 h within the subsequent reactor(s). The flow system

Table 5
SO_2Cl_2 equivalents screening for the oxidation of Hedione with SO_2Cl_2.



Entry[a]	SO_2Cl_2 equiv.	Yield (%)[b]
1	0.5	48
2	0.75	72
3	0.9	73
4	1.0	75
5	1.1	77[c] (85)[d]

[a] Reactions conducted on a 50 mmol scale (1 M).
[b] Calculated using n-undecane as an internal GC standard.
[c] Isolated yield - reaction conducted on 0.5 mol scale (2 M) and product isolated by distillation.
[d] Isolated yield - reaction conducted on 5 mol scale (2 M) and product isolated by distillation.

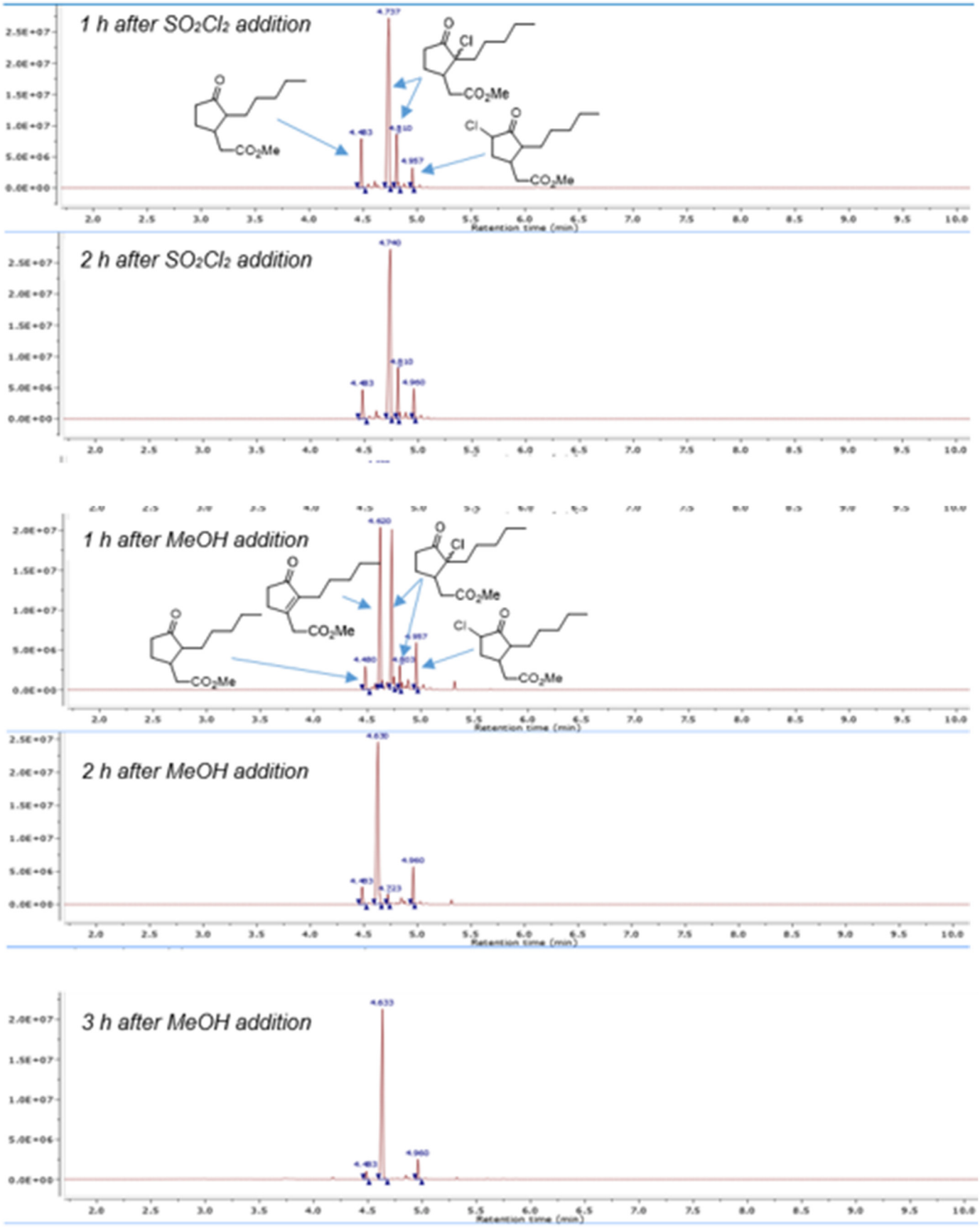
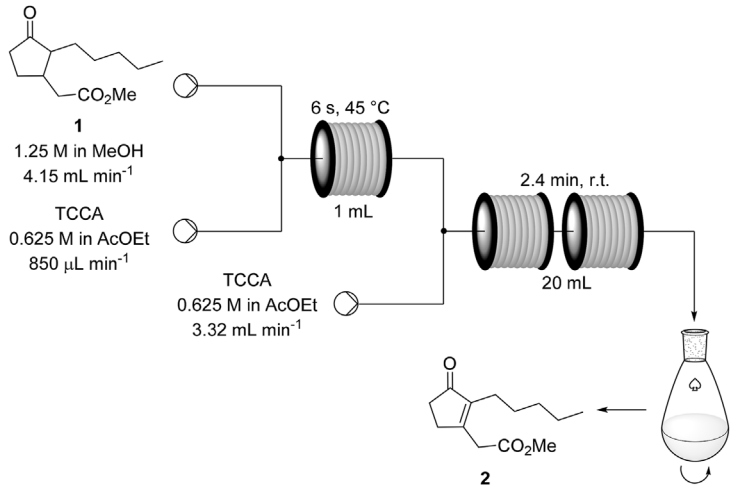


Fig. 3. Monitoring of the reaction by GC-MS.

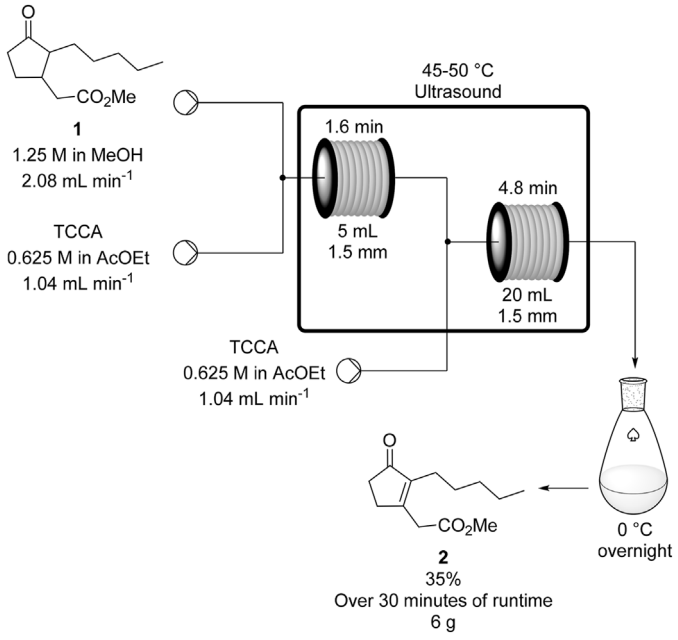


Scheme 4. Setup for the continuous preparation of **2** employing TCCA.

Table 6
Reaction conditions for the optimisation of continuous-flow oxidation of **1** employing TCCA.

Entry[a]	T_1 (°C)	T_2 (°C)	t_1 (min)	%Loading	Yield (%)[b]
1	45–50	45–50	0.8	0.15	36[c]
2	45–50	30–35	0.8	0.15	29[c]
3	45–50	45–50	0.8	0.15	26[c]
4	45–50	45–50	1.6	0.15	35[c]
5[d]	45–50	45–50	1.6	0.15	traces
6[e]	45–50	45–50	1.6	0.15	traces
7	45–50	45–50	1.6	0.25	35
8	45–50	45–50	0.8	0.25	24

[a] Reactions conducted on a 5 mmol scale (1.25 M).
[b] Calculated using 1,2-dimethoxybenzene as an internal ^{1}H NMR standard.
[c] The chlorination only occurs partially in the coil.
[d] Reaction was quenched with water when collected.
[e] Reaction was quenched with a saturated solution of sodium carbonate when collected.



Scheme 5. Optimised reaction conditions for the chlorination of **1** employing TCCA.

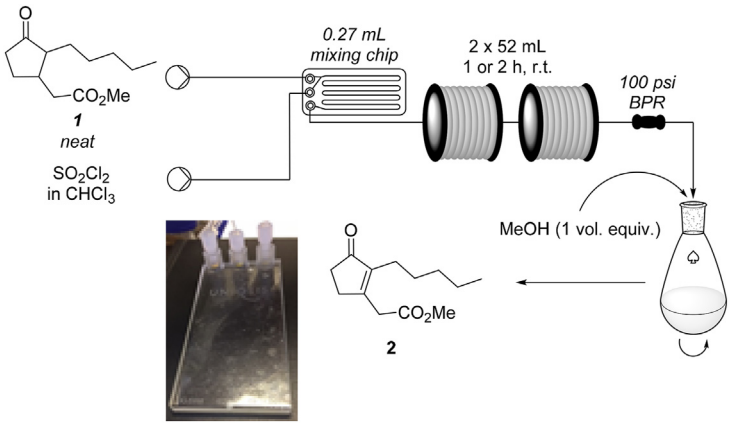
was pressurised using a 100 psi (~6.9 bar) BPR for the chlorination step and the outlet was collected in a collection flask to which a stream of methanol was added (1 vol equiv.). The reaction mixture was left to stir overnight at r.t.

This simple system worked well and gave comparable yields to the batch process (Table 7 & Table 5) under the conditions initially tested (Table 7, *entries 1&2*). Improved heat dissipation/transfer meant that the exotherm was well controlled and the release of SO_2 gas was steady and controlled upon the stream passing the BPR.

Higher concentrations were investigated to explore the productivity of the reaction (throughput at 0.76 M = 12 g h^{-1}). This initially proved detrimental to the yield due to lower selectivity at the higher reaction concentrations (Table 7, entries 3&5). However, it was considered that potential inadequate mixing of the highly concentrated reagents streams could be influencing these results. As such a larger replacement 2 mL Uniqsis mixing chip was substituted into the set-up and the experiments repeated (Table 7, entries 6&7). This gave improved selectivity and resulted in a proportionally higher yield although it still appears that an engineering limitation was reached (Table 7, entry 7) which still showed an improvement but indicated significant levels of by-product formation (over chlorination). As such any future commercial flow unit would need to be designed to enhance mixing for this initial step to maximise productivity. Finally, comparing the equivalent concentration over different residence times (Table 7, entry 1 v's 2 and 3 v's 4) indicates negligible differences again indicating a rapid reaction and highlighting the need for effective mixing.

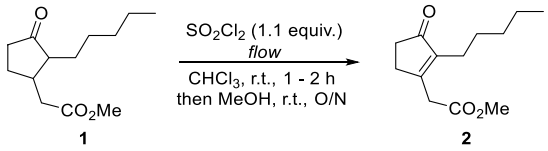
Next, as a demonstration of process consistency, a prolonged 8 h run at 1 M concentration was performed (Table 7, entry 8). To test the steady state operation, four 30 min samples (1, 2.5, 5 and 7.5 h) were taken and treated with MeOH in batch (16 h) before the product was isolated using column chromatography in a consistent 73–75% yield. This indicates a high fidelity for the first chlorination stage of the process under steady state processing conditions.

As a final scoping exercise, we modified the flow system to integrate the downstream MeOH quench step. The reactor (Scheme 6) was thus extended to incorporate a further input stream (MeOH) sited prior to the inline BPR along with an additional 156 mL residence time tubular reactor (3 × 52 mL coils), for the quench before collection. Furthermore, based upon the evidence of increase mixing we retained the 2 mL Uniqsis mixing chip. To enable direct comparison of the reaction we used a Hedione reagent concentration of 1.69 M (Table 7, entry 6). A 3 M stock solution of sulfuryl chloride in



Scheme 6. Flow setup used for the SO_2Cl_2 oxidation of Hedione.

Table 7
Screening for the oxidation of Hedione with SO_2Cl_2 in flow.



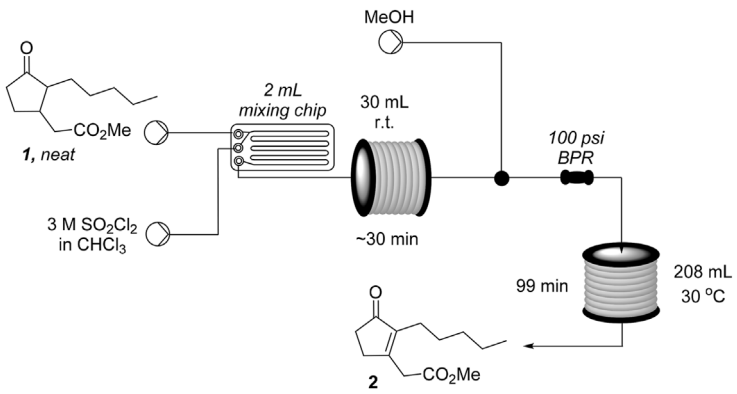
Entry	Hedione conc. (M)	time (h)[a]	Yield (%)[b]
1	0.76	1	76
2	0.76	2	79
3	1.69	1	67
4	1.69	2	66
5	2.45	1	60
6	1.69	1	78[d]
7	2.45	1	71[d]
8	1	1	75[c]

[a] Residence time for first step.
[b] Calculated using *n*-undecane as an internal GC standard.
[c] Isolated yield based upon 30 min of sample collection – product isolated by SiO_2 column chromatography.
[d] 2 mL mixing chip used.

chloroform was pumped at a flow rate of 0.651 mL min^{-1} to combine with the Hedione stream (flow rate 0.402 mL min^{-1}). The streams were mixed in the 2 mL mixer chip and directed into a 52 mL tubular flow coil (residence time 51 min). A T-piece mixer was used to add the MeOH flow stream (flow rate 1.053 mL min^{-1}) giving a residence time of 74 min for the quench step. Direct sampling and GC-MS analysis indicated the reaction had essentially undergone full chlorination but that about 12–15% of this material remained. Consistent with our batch results if this material was left to stand for a further 0.5–1 h complete consumption of this chloro intermediate was observed. As such reconfiguring the reactor to give a 1.5–2 h quench based incubation time would be necessary. To facilitate this the first 52 mL coil was exchanged for a 30 mL coil allowing it to be used to supplement the residence time for the quench step (Scheme 7). We also found a value in maintaining the quench step at ~30 °C [42]. Overall, this enabled us to achieve complete conversion of the chloro intermediate **5** to the desired product **2**, permitting isolation of dehydrohedione **2** in an 80% (38.88 g) yield based upon a 9 h run following distillation. This equates to a nominal throughput of 4.32 g h^{-1} and a STY of 0.077 mol L^{-1} h^{-1} (based upon a 250 mL total volume reactor inclusive of feedlines) for this evaluation system.

3. Conclusion

A new method for the oxidation of Hedione to dehydrohedione has been developed that offers significant advantages upon prior work in terms of cost-effectiveness and potential for transfer to flow. The reaction with chlorinating agents such as TCCA could be conveniently performed in a single step, however, superior yields were obtained using SO_2Cl_2 in a two-step procedure. Flow processes for the two procedures were developed which showed improved characteristics such as exotherm control, solid handling, and gas evolution over the batch procedures. The reaction with SO_2Cl_2 has been deemed feasible for use at industrial scale and is currently being used by IFF Benicarló.



Scheme 7. Final integrated flow setup used for the SO_2Cl_2 oxidation of Hedione.

4. Materials and methods

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Substrates, their precursors and reagents were purchased from either Alfa Aesar, Sigma Aldrich, Fluorochem, TCI or Acros Organics or supplied by IFF and used as received. ^{1}H NMR spectra were recorded on Bruker Avance-400 instrument and are reported relative to residual solvent: $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.50 ppm). ^{13}C NMR spectra were recorded on the same instruments and are reported relative to $CDCl_3$ (δ 77.16 ppm) and DMSO-d_6 (δ 39.52 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ/ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s, br = broad singlet, app. = apparent. Data for ^{13}C NMR are reported in terms of chemical shift (δ_C/ppm). DEPT-135, COSY, HSQC, HMBC, PSYCHE and NOESY experiments were used in structural assignments. IR spectra were obtained using a PerkinElmer Spectrum Two UATR Two FT-IR Spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21–70% of tallest signal) or strong (s, >71% of tallest signal).

Low and high resolution mass spectrometry were performed using the indicated techniques. Low resolution gas chromatography mass spectrometry (GC-MS) was performed on a Shimadzu QP2010-Ultra equipped with an Rxi-5Sil MS column (0.15 μm × 10 m x 0.15 mm) in EI mode. Low resolution liquid chromatography mass spectrometry (LC-MS) was performed using a Waters TQD mass spectrometer and an Acquity UPLC BEH C18 1.7 μm column (2.1 mm × 50 mm) in ESI mode. ESI-HRMS was performed using a Waters QtoF Premier mass spectrometer. For accurate mass measurements the deviation from the calculated formula is reported in ppm. Reactions were conducted in flow using Vapourtec SF-10 as peristaltic pumps, along with 0.5–1.5 mm PTFE tubing and Uniqsis glass static mixer reactor block 2 input 0.27 mL. All the connectors tubing were 1/4″ OD. The ultrasonic cleaning bath employed is an Ultrawave U300H.

SiO_2 column chromatography was performed using Sigma Aldrich silica gel (grade 9385, pore size 60A) and standard manual column apparatus. For TLC, Sigma Aldrich glass-backed plates were used and visualisation was performed using UV-irradiation or a $KMnO_4$ stain. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator and hi-vacuum was achieved using an Edwards RV5 pump and Schlenk line. Kugelrohr distillation was performed using a Buchi Glass Oven B-3585 and vacuum distillation was performed using a Buchi V-700 vacuum pump equipped with a V-850 vacuum controller attached to a standard distillation pig setup.

4.1. Batch synthesis of **2** by TCCA oxidation of Hedione

Hedione **1** (11.3 g, 50 mmol) was dissolved in MeOH (40 mL) and trichloroisocyanuric acid (TCCA), (0.58 g, 5 mol%) was added. The mixture was stirred and heated to 50 °C in order to initiate the reaction. After initiation, the reaction was brought back to room temperature and the remainder of the TCCA (5.23 g, 45 mol%) was added over 10 min, keeping the temperature below 30 °C. The reaction was then left to stir at r.t. for 20 h before the resultant suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was purified using SiO_2 column chromatography (8:2, hexane:EtOAc) to give the pure product as a colourless liquid (5.83 g, 52%).

4.2. Batch synthesis of **2** by SO_2Cl_2 oxidation of Hedione

Hedione (113.0 g, 0.50 mol) was dissolved in $CHCl_3$ (110 mL) and sulfuryl chloride (40.4 mL, 1.1 equiv.) was slowly added, keeping the reaction below 30 °C. The reaction was then left to stir at r.t. for 2 h before MeOH (100 mL) was added. The resultant mixture was then stirred for 3 h before solvents were removed under reduced pressure. To the residue, saturated aqueous Na_2CO_3 (200 mL) was added and the mixture was then stirred for 16 h at r.t. before the product was extracted with EtOAc (2 × 200 mL). After concentration of the organic layers *in vacuo* the resultant liquid was purified using vacuum distillation (100–110 °C & 1 mbar) to give the product **2** as a colourless liquid (86.2 g, 77%).

4.3. Flow synthesis of **2** by TCCA oxidation of Hedione

A solution of **1** (1.25 M in MeOH) was pumped employing a Vapourtec SF-10 (blue pump tube) and directed into Y piece where it was mixed with a solution of TCCA (0.625 M in AcOEt) pumped with another Vapourtec SF-10 (blue pump tube with PEEK seal). The mixed solution was streamed through a 1.5 mm FEP coil (5 mL) placed into an ultrasound bath maintained at 45–50 °C. The output stream was then mixed with another pumped solution of TCCA (0.625 M in AcOEt) employing a Y piece and then directed into two connected 1.5 mm FEP coils (2 × 10 mL) and placed in the ultrasound bath. The exit stream was collected into an ice-cooled 250 mL flask (collection time 10 min). After collection, the mixture was allowed to warm at room temperature and left stirring overnight. The white suspension was then filtered off and the mixture concentrated under vacuum. A 30 min sample was collected after waiting the system to reach the steady state (10 min). After concentration of the organic layers *in vacuo* the resultant liquid was purified using SiO_2 column chromatography (8:2, hexane:EtOAc) to give the pure product **2** as a colourless liquid (6.0 g, 35%).

4.4. Flow synthesis of **2** by SO_2Cl_2 oxidation of Hedione

A solution of SO_2Cl_2 (1.45 M in $CHCl_3$) and neat Hedione ($d = 0.998$ g cm^{-3}) were directed into a Uniqsis 2 mL mixing chip at 0.682 mL min^{-1} and 0.201 mL min^{-1} respectively where they were blended. The outlet of the mixing chip was directed into a 52 mL reactor coil at r.t. ($R_t = 1$ h) and collected in a stirred round-bottom flask (collection time 8 h). Four 30 min sample were collected separately for testing (1, 2.5, 5 and 7.5 h) to which MeOH (7 mL) was added and the mixture was stirred at r.t. for 16 h. The solvents were removed *in vacuo* and saturated aqueous Na_2CO_3 (20 mL) was added to the residue, the mixture was then stirred for 20 h at r.t. and the product was extracted with EtOAc (2 × 20 mL). After concentration of the organic layers *in vacuo* the resultant liquid was purified using SiO_2 column chromatography (8:2, hexane:EtOAc) to give the pure product as a colourless liquid (Sample 1 (1 h): 4.46 g, 75%; Sample 2 (2.5 h): 4.40 g, 74%; Sample 3 (5 h): 4.34 g, 73%; Sample 4 (7.5 h): 4.46 g, 75%).

Methyl 2-(3-oxo-2-pentylcyclopentyl)acetate (**1**)*:* ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.65–2.57 (m, 1H), 2.22 (dddd, J = 11.3, 7.1, 5.5, 2.3 Hz, 1H), 2.16–2.04 (m, 1H), 1.78 (dtd, J = 11.3, 5.0, 2.3 Hz, 1H), 1.57–1.42 (m, 3H), 1.39 (dddd, J = 11.0, 9.6, 8.2, 6.5 Hz, 0H), 1.32–1.16 (m, 5H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 219.80, 172.78, 54.35, 51.76, 39.08, 38.22, 37.81, 32.21, 27.97, 27.35, 26.46, 22.60, 14.15. FT-IR ν_{max} 2954 (CH, w), 2929 (CH, w), 2858 (CH, w), 1733 (C═O, s), 1443 (w), 1436 (w), 1253 (w),

1194 (m), 1158 (m), 1125 (m), 1019 (w), 989 (w). GC-MS R_t 4.48 min, *m/z* 226 $[M]^+$; LC-MS (ESI+) Rt = 2.61 min m/z $[M+H]^+$ = 227.5. HR-MS calculated for $C_{13}H_{23}O_3$ 227.1647, found 227.1658 (Δ = 4.8 ppm, 1.1 mDa).

Methyl 2-(3-oxo-2-pentylcyclopent-1-en-1-yl*)acetate* (**2**) [11]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.46 (s, 2H), 2.63 (m, 2H), 2.42 (m, 2H), 2.19 (m, 2H), 1.21–1.44 (m, 6H), 0.88 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 209.2, 169.6, 163.3, 143.3, 52.3, 36.6, 34.3, 31.8, 29.7, 28.0, 23.2, 22.5, 14.0 ppm; FT-IR ν_{max} 1171 (s), 1194 (s), 1435 (m), 1644 (m), 1698 (s), 1738 (s), 2860 (w), 2929 (w), 2954 (w) cm^{-1}; GC-MS R_t 4.70 min, *m/z* 224 $[M]^+$, 193 $[M\text{-}OMe]^+$, 154 $[M - C_5H_{11}]^+$, 151 $[M\text{-}CH_2CO_2Me]^+$. LC-MS (ESI+) Rt = 2.40 min m/z $[M+H]^+$ = 225.5. HR-MS calculated for $C_{13}H_{21}O_3$ 225.1491, found 225.1497 (Δ = 2.7 ppm, 0.6 mDa).

4.5. Synthesis of the chloro intermediate **5**

The chloro intermediates were prepared following the procedure described above. After the TCCA addition, the mixture was partially concentrated under vacuum keeping the water batch at around 20 °C. Celite was added into the mixture to prepare a dry loading. Once the solid was dry, the mixture was purified via column chromatography adopting a deactivated silica gel prepared following literature procedure (Eluent: Hexane:AcOEt 1:99) [43]. The isolated intermediate **5** was rapidly characterised via High Field NMR. Unfortunately, we were unable to fully characterise the material further as it decomposed overnight.

Methyl 2-(2-chloro-3-oxo-2-pentylcyclopentyl)acetate (***5***): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.68 (dd, *J* = 16.1, 4.0 Hz, 1H), 2.63–2.54 (m, 2H), 2.46 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.17–2.07 (m, 2H), 2.04 (ddd, *J* = 14.0, 12.1, 4.0 Hz, 1H), 1.83 (ddd, *J* = 14.0, 12.3, 4.0 Hz, 1H), 1.77–1.66 (m, 1H), 1.40–1.31 (m, 1H), 1.26 (dtdt, *J* = 13.9, 12.0, 6.3, 3.2 Hz, 5H), 1.14–1.03 (m, 1H), 0.84 (dd, *J* = 8.0, 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.53, 172.43, 75.56, 51.92, 41.08, 35.11, 35.04, 34.74, 32.02, 24.76, 22.38, 13.96.

Methyl 2-(4-chloro-3-oxo-2-pentylcyclopentyl)acetate (regioisomer by-product from chlorination see Fig. 3).

R_f (9:1, hexane:EtOAc) 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (d, *J* = 6.7 Hz, 1H), 3.76 (s, 3H), 3.10–3.00 (m, 1H), 2.75 (dd, *J* = 16.3, 4.4 Hz, 1H), 2.57–1.88 (m, 4H), 1.56–1.12 (m, 8H), 0.97–0.79 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 171.8, 74.7, 54.0, 52.0, 38.0, 35.8, 35.5, 34.2, 31.8, 24.6, 22.3, 13.9 ppm; FT-IR ν_{max} 998 (w), 1173 (m), 1284 (m), 1377 (w), 1436 (m), 1739 (s), 1768 (s), 2955 (m); GC-MS R_t 4.96 min, *m/z* 260 $[M]^+$.

4.6. Synthesis of the fluoro intermediate **12**

To an ice-cooled solution of **11** (1.39 g, 5.19 mmol, 1 eq.) in MeCN (50 mL), selectfluor (1.82 g, 5.19 mmol, 1 eq.) was added within 30 min. The solution was then allowed to warm at room temperature. The mixture was partitioned in AcOEt (20 mL) and a 10% aqueous solution of $Na_2S_2O_3$ (20 mL). The organic phase was then washed with water, brine, and concentrated under vacuum. The residue was purified through chromatography (Eluent: Hexane:AcOEt 1:9) to gain *anti*-**12** and *syn*-**12** as white oils.

*methyl 2-(-2-fluoro-3-oxo-2-pentylcyclopentyl)acetate (anti-***12***):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.70–2.31 (m, 4H), 2.28–2.10 (m, 2H), 1.92–1.61 (m, 4H), 1.38–1.10 (m, 6H), 0.93–0.83 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.90 (d, *J* = 16.7 Hz), 172.73, 98.05 (d, *J* = 183.8 Hz), 51.98, 39.52 (d, *J* = 19.3 Hz), 34.80, 32.95 (d, *J* = 7.7 Hz), 32.14, 31.35 (d, *J* = 23.3 Hz), 24.19 (d, *J* = 1.4 Hz), 22.98 (d, *J* = 7.9 Hz), 22.50, 14.04. ^{19}F NMR (376 MHz, CDCl3) δ −168.06 to −168.38 (m). FT-IR ν_{max} 2955 (CH, w), 2931 (CH, w), 2861 (CH, w), 1758 (C=O, s), 1736 (C=O, s), 1464 (w), 1437 (w), 1316 (w), 1273 (w), 1181 (CF, m), 1174 (CF, m), 1000 (w), 943 (w), 890 (w), 812 (w). LC-MS (ESI+) Rt = 2.71 min m/z $[M+H]^+$ = 245.6. HR-MS calculated for $C_{13}H_{22}FO_3$ 245.1553, found 245.1570 (Δ = 6.9 ppm, 1.7 mDa).

*methyl 2-(-2-fluoro-3-oxo-2-pentylcyclopentyl)acetate (syn-***12***):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, *J* = 2.6 Hz, 3H), 2.81–2.58 (m, 2H), 2.47–2.11 (m, 4H), 1.73–1.39 (m, 4H), 1.39–1.16 (m, 5H), 0.97–0.79 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 212.10, 172.12, 99.44 (d, *J* = 193.4 Hz), 52.06, 41.44 (d, *J* = 21.0 Hz), 33.59, 33.22 (d, *J* = 1.6 Hz), 32.21, 29.25 (d, *J* = 24.9 Hz), 22.78 (d, *J* = 8.2 Hz), 22.52, 21.81 (d, *J* = 3.7 Hz), 14.07. FT-IR ν_{max} 2955 (CH, w), 2933 (CH, w), 2873 (CH, w), 1758 (C=O, s), 1735 (C=O, s), 1464 (w), 1437 (w), 1262 (w), 1196 (CF, m), 1164 (CF, m), 1135 (m), 1037 (w), 1000 (w), 947 (w). LC-MS (ESI+) Rt = 2.89 min m/z $[M+H]^+$ = 245. HR-MS calculated for $C_{13}H_{22}FO_3$ 245.1553, found 245.1570 (6.9 ppm, Δ = 1.7 mDa).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: James S. Sharley and Guido Gambacorta reports financial support was provided by International Flavors & Fragrances Inc. Ian R. Baxendale and James S Sharley has patent #US 20170174607 pending to International Flavours & Fragrances Inc. Ian R. Baxendale and James S. Sharley has patent #USP201762479919 issued to International Flavors & Fragrances.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2022.133068.

References

[1] V.T. Politano, E.M. Lewis, A.M. Hoberman, M.S. Christian, R.M. Diener, A.M. Api, Evaluation of the developmental toxicity of methyl dihydrojasmonate (MDJ) in rats, Int. J. Toxicol. 27 (2008) 295–300, https://doi.org/10.1080/10915810802210158.

[2] E. Demole, E. Lederer, D. Mercier, Isolement et détermination de la structure du jasmonate de méthyle, constituant odorant caractéristique de l'essence de jasmin, Helv. Chim. Acta 45 (1962) 675–685, https://doi.org/10.1002/hlca.19620450233.

[3] E. Demole, E. Lederer, D. Mercier, Synthèse du dihydrojasmonate de méthyle (pentyl-2-oxo-3-cyclopentylacétate de méthyle), Helv. Chim. Acta 45 (1962) 685–692, https://doi.org/10.1002/hlca.19620450234.

[4] P. Werkhoff, G. Krammer, S. Brennecke, M. Roloff, H.-J.J. Bertram, Methyl dihydrojasmonate and its stereoisomers: sensory properties and enantioselective analysis, Food Rev. Int. 18 (2002) 103–122, https://doi.org/10.1081/FRI-120014353.

[5] E. Davies, The sweet scent of success, Chem. World-UK (2009) 40–44. https://www.chemistryworld.com/features/the-sweet-scent-of-success/3004856.article.

[6] P. Kraft, J.A. Bajgrowicz, C. Denis, G. Fráter, Odds and trends: recent developments in the chemistry of odorants, Angew. Chem. Int. Ed. 39 (2000) 2980–3010, https://doi.org/10.1002/1521-3773(20000901)39:17<2980::aid-anie2980>3.0.co;2-#.

[7] T. Shono, M. Okawa, I. Nishiguchi, Electroorganic chemistry. XXI. Selective formation of .alpha.-acetoxy ketones and general synthesis of 2,3-disubstituted 2-cyclopentenones through the anodic oxidation of enol acetates, J. Am. Chem. Soc. 97 (1975) 6144–6147, https://doi.org/10.1021/ja00854a030.

[8] U. Ravid, R. Ikan, New syntheses in dihydrojasmone series, J. Org. Chem. 39

(1974) 2637–2639, https://doi.org/10.1021/jo00931a045.
[9] B. Winter, C. Chapuis, R. Brauchli, J.-Y. de Saint Laumer, Further explorations into the synthesis of dehydro -Hedione, Helv. Chim. Acta 96 (2013) 246–258, https://doi.org/10.1002/hlca.201200440.
[10] C. Chapuis, G.H. Büchi, H. Wüest, Synthesis of cis-Hedione® and Methyl Jasmonate via cascade Baylis-Hillman reaction and Claisen ortho ester rearrangement, Helv. Chim. Acta 88 (2005) 3069–3088, https://doi.org/10.1002/hlca.200590248.
[11] T. Shono, N. Kise, T. Fujimoto, N. Tominaga, H. Morita, Electroorganic chemistry. 140. Electroreductively promoted intra- and intermolecular couplings of ketones with nitriles, J. Org. Chem. 57 (1992) 7175–7187, https://doi.org/10.1021/jo00052a036.
[12] T. Shono, N. Kise, Electroreductive intramolecular coupling of γ- and δ-cyanoketones, Tetrahedron Lett. 31 (1990) 1303–1306, https://doi.org/10.1016/S0040-4039(00)88791-2.
[13] C. Chapuis, C.A. Richard, A one pot synthesis of Dehydrohedione (DHH) from a Hedione® precursor, Helv. Chim. Acta 101 (2018) 1–20, https://doi.org/10.1002/hlca.201800063.
[14] K. Crawford, V. Rautenstrauch, A. Uijttewaal, Process for the Preparation of Alkyl 3-Oxo-2-Pentyl-1-Cyclopenteneacetates, July 1, 2003. US6586620B1.
[15] J.S. Sharley, A.M. Collado Pérez, E.E. Ferri, A.F. Miranda, I.R. Baxendale, α,β-Unsaturated ketones via copper(II) bromide mediated oxidation, Tetrahedron 72 (2016) 2947–2954, https://doi.org/10.1016/j.tet.2016.04.011.
[16] H. Hu, T.J. Harrison, P.D. Wilson, A modular and concise total synthesis of (±)-daurichromenic acid and analogues, J. Org. Chem. 69 (2004) 3782–3786, https://doi.org/10.1021/jo049703f.
[17] V.N. Moussa, Sulfuryl chloride: a versatile alternative to chlorine, Aust. J. Chem. 65 (2012) 95, https://doi.org/10.1071/CH11367.
[18] U. Tilstam, H. Weinmann, Trichloroisocyanuric Acid: a safe and efficient oxidant, Org. Process Res. Dev. 6 (2002) 384–393, https://doi.org/10.1021/op010103h.
[19] Z. Xu, D. Zhang, X. Zou, α-Chlorination of acetophenones using 1,3-dichloro-5,5-dimethylhydantoin, Synth. Commun. 36 (2006) 255–258, https://doi.org/10.1080/00397910500334637.
[20] K.M. Brummond, K.D. Gesenberg, α-Chlorination of ketones using p-toluenesulfonyl chloride, Tetrahedron Lett. 40 (1999) 2231–2234, https://doi.org/10.1016/S0040-4039(99)00213-0.
[21] N. Halland, A. Braunton, S. Bachmann, M. Marigo, K.A. Jørgensen, Direct organocatalytic asymmetric α-chlorination of aldehydes, J. Am. Chem. Soc. 126 (2004) 4790–4791, https://doi.org/10.1021/ja049231m.
[22] T. Schlama, K. Gabriel, V. Gouverneur, C. Mioskowski, Tetraethylammonium Trichloride: a versatile reagent for chlorinations and oxidations, Angew Chem. Int. Ed. Engl. 36 (1997) 2342–2344, https://doi.org/10.1002/anie.199723421.
[23] J.P. Guthrie, J. Cossar, The chlorination of propiophenone; determination of p K a value and of the course of the reaction, Can. J. Chem. 68 (1990) 2060–2069, https://doi.org/10.1139/v90-315.
[24] X. Huang, C. Ou, W. Mao, H. Fang, Preparation of 3-Oxo-2-Pentyl Cyclopentenyl Methyl Acetate, November 12, 2008. CN101302157A.
[25] J. Sicher, Angew Chem. Int. Ed. Engl. 11 (1972) 200–214, https://doi.org/10.1002/anie.197202001.
[26] A. Yasuda, H. Yamamoto, H. Nozaki, Bull. Chem. Soc. Jpn. 52 (1979) 1705–1708, https://doi.org/10.1246/bcsj.52.1705.
[27] J.M.G. Cowie, V. Arrighi, Polymers: Chemistry and Physics of Modern Materials, third ed., CRC Press, Third, 2008.
[28] G. Wen, D. Yawei, Y. Bing, Z. Zeyong, D. Yan, Z. Ning, Preparation Method of 2-Chloro-5-Chloromethylpyridine, CN104086480A, June 20, 2014.
[29] Z. Chen, B. Zhou, H. Cai, W. Zhu, X. Zou, Simple and efficient methods for selective preparation of α-mono or α,α-dichloro ketones and β-ketoesters by using DCDMH, Green Chem. 11 (2009) 275–278, https://doi.org/10.1039/B815169E.
[30] D. Masilamani, M.M. Rogic, Sulfuryl chloride as a reagent for selective chlorination of symmetrical ketones and phenols, J. Org. Chem. 46 (1981) 4486–4489, https://doi.org/10.1021/jo00335a033.
[31] E.W. Warnhoff, D.G. Martin, S.J. William, 2-chloro-2-methylcyclohexanone and 2-methyl-2-cyclohexenone, Org. Synth. 37 (1957) 8, https://doi.org/10.15227/orgsyn.037.0008.
[32] G. Gambacorta, J.S. Sharley, I.R. Baxendale, A comprehensive review of flow chemistry techniques tailored to the flavours and fragrances industries, Beilstein J. Org. Chem. 17 (2021) 1181–1312, https://doi.org/10.3762/bjoc.17.90.
[33] G. Gambacorta, I.R. Baxendale, Continuous-flow Hofmann tearrangement using trichloroisocyanuric acid for the preparation of 2-benzoxazolinone, Org. Process Res. Dev. 26 (2022) 422–430, https://doi.org/10.1021/acs.oprd.1c00440.
[34] SF 10 peristalic pumps from vapourtec. https://www.vapourtec.com/products/sf-10-pump-features/ (Accessed 01/06/2022) for further details.
[35] R.L. Hartman, J.R. Naber, N. Zaborenko, S.L. Buchwald, K.F. Jensen, Overcoming the challenges of solid bridging and constriction during Pd-catalyzed C–N bond formation in microreactors, Org. Process Res. Dev. 14 (2010) 1347–1357, https://doi.org/10.1021/op100154d.
[36] M. Schoenitz, L. Grundemann, W. Augustin, S. Scholl, Fouling in microstructured devices: a review, Chem. Commun. 51 (2015) 8213–8228, https://doi.org/10.1039/c4cc07849g.
[37] K. Wu, S. Kuhn, Strategies for solids handling in microreactors, Chim. Oggi/Chem. Today 32 (2014) 62–66.
[38] Z. Dong, S. Zhao, Y. Zhang, C. Yao, Q. Yuan, G. Chen, Mixing and residence time distribution in ultrasonic microreactors, AIChE J. 63 (2017) 1404–1418, https://doi.org/10.1002/aic.15493.
[39] D. Fernandez Rivas, S. Kuhn, Synergy of microfluidics and ultrasound: process intensification challenges and opportunities, Top. Curr. Chem. 374 (2016) 1–30, https://doi.org/10.1007/s41061-016-0070-y.
[40] Z. Dong, C. Delacour, K.M. Carogher, A.P. Udepurkar, S. Kuhn, Continuous ultrasonic reactors: design, mechanism and application, Materials (Basel) 13 (2020), https://doi.org/10.3390/ma13020344.
[41] C.J. Mallia, I.R. Baxendale, The use of gases in flow synthesis, Org, Process Res. Dev. 20 (2016) 327–360, https://doi.org/10.1021/acs.oprd.5b00222.
[42] This aspect of the work has not been fully evaluated due to time and funding constraints thus it offers potential for further optimisation of the process.
[43] P. Panne, J.M. Fox, Rh-Catalyzed intermolecular reactions of Alkynes with α-Diazoesters that possess β-Hydrogens: ligand-based control over divergent pathways, J. Am. Chem. Soc. 129 (2007) 22–23, https://doi.org/10.1021/ja0660195.