

An Ozonolysis–Reduction Sequence for the Synthesis of Pharmaceutical Intermediates in Microstructured Devices

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Abstract:

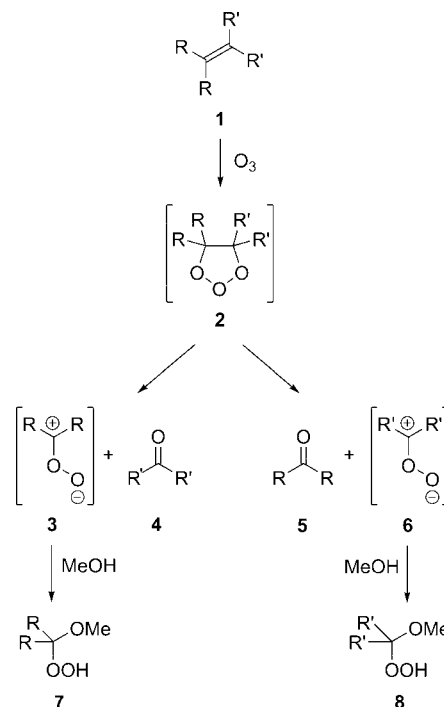
The advantages of microstructured reactors were utilized in a two-step process for the preparation of intermediates of vitamin D analogues, which are known to be important compounds in bone and mineral metabolism. The reaction sequence consisting of an ozonolysis step of a double bond and a subsequent reduction was successfully performed in a microplant. Concerning the feasibility and optimization of the two reaction steps in different microreactors, ozonolysis and reduction have initially been investigated separately. A miniaturized ATR sensor was employed for online monitoring of the ozonolysis step. The overall process was then performed in a continuous manner. The utilization of microstructured devices allows for the realization of a safe and highly controlled multistep process with online analysis via FTIR.

Introduction

Microstructured reactors have recently gained increasing importance as useful devices for chemical reactions on laboratory scale as well as in industrial processes.¹ Improved temperature management, shorter diffusion paths and higher specific interfacial areas increase the mass and heat transfer rates. Furthermore, due to the low hold-up in microdevices the hazard of highly exothermic and explosive reactions is considerably reduced. So far, the benefits of microstructured devices for chemical reactions have been demonstrated in various examples.²

The ozonolysis is considered as a highly exothermic gas/liquid reaction. In the liquid phase ozonides and/or hydroperoxides are generated and in addition explosive mixtures of solvent vapors with oxygen and ozone are present in the gas phase.³ Therefore, microstructured reactors are a particularly suitable tool for processing ozonolysis reactions. However, in spite of its high risk potential the ozonolysis of olefins is

Scheme 1. Reaction mechanism of the ozonolysis of olefins in the presence of methanol



industrially performed as a synthetic step for the production of pharmaceuticals⁴ and fine chemicals. For the latter, typical examples are the formation of glyoxylic acid from maleic acid dimethyl ester and the formation of pelargonic acid and azelaic acid from oleic acid.⁵

Scheme 1 shows the reaction mechanism of the ozonolysis in the presence of methanol, which is generally accepted for

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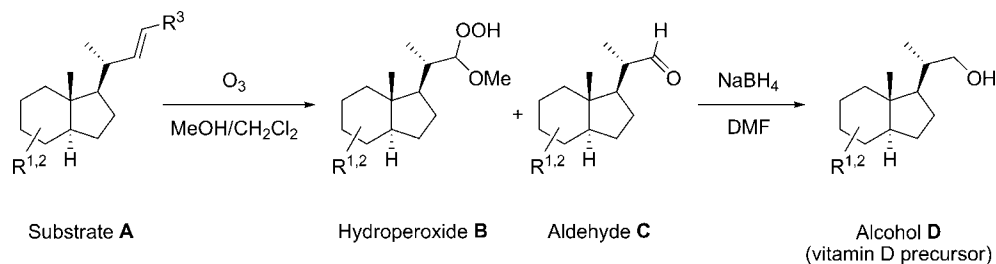
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Scheme 2. Reaction sequence for the preparation of vitamin D analogues in microstructured reactors



olefins.⁶ Primary ozonide **2** is formed by a 1,3-dipolar cycloaddition of ozone to olefin **1**. Due to its instability, the primary ozonide **2** undergoes fast cleavage to the carbonyl compounds **4** and **5**, and zwitterions (carbonyl oxides) **3** and **6**, respectively. In the presence of a protic solvent such as methanol the carbonyl oxide species **3** and **6** react with methanol delivering the methoxyhydroperoxides **7** and **8**, respectively.

The heat of the ozonolysis reaction (in the range of 100 kcal/mol) is due to the formation and cleavage of primary ozonide **2**. The direction of the cleavage is strongly influenced by the nature of substituents. The zwitterion is stabilized by electron-donating substituents, whereas electron-withdrawing substituents are destabilizing.

Recently, we investigated the ozonolysis of acetic acid 1-vinylhexyl ester in a falling film microreactor in order to identify relevant process parameters.⁷ It was found that the ozone absorption rate and the olefin conversion strongly depend on the mass transfer. Within the parameter ranges investigated, temperature and the partial pressure of ozone do not have a considerable impact on the product selectivity. However, increasing olefin concentrations and conversions enhance the formation of byproducts. With this information in hand we turned our attention to an industrially relevant process for the synthesis of intermediates of vitamin D analogues, consisting of ozonolysis and a subsequent reduction step (Scheme 2).

The cleavage of double bonds in vitamin D analogues is typically carried out in a solvent mixture of methanol and dichloromethane with ozone dosing at temperatures below -10 °C, generally at -78 °C. The reduction to the corresponding alcohol is then usually conducted by adding solid sodium borohydride in portions to the reaction mixture.⁸ This procedure affords good yields on laboratory scale. However, the scale up

of this reaction sequence to a continuous process on pilot-plant scale is challenging.

Therefore, we pursued two major goals in our investigation: (1) to develop and optimize a continuous two-step process in microstructured devices, which allows for the preparation of alcohol **D** on kilogram scale without isolation of the major intermediates and (2) to run the ozonolysis at higher temperatures (up to 0 °C).

Results and Discussion

In order to develop and optimize a procedure for the continuous ozonolysis–reduction sequence (Scheme 2) in microreactors, the two steps have initially been investigated separately. We tested different microstructured reactors at varying liquid flow rates, in order to find the most suitable microreactor and the appropriate reaction conditions for quantitative substrate conversion at the highest possible substrate throughput.

For the ozonolysis, five different microstructured devices have been applied. Details on the microreactors are given in the Experimental Section in Table 4. Two microstructured reactors which were especially designed for gas/liquid reactions are the falling film microreactors made by *IMM* (Germany) and *mikroglas chemtech GmbH* (Germany), respectively, which are both working on the basis of the same principle (see Figure 1).

Another microstructured reactor for gas/liquid reactions is the cyclone mixer made by *mikroglas* (Figure 2). Here, gas and liquid are brought into contact in a mixing chamber, where intensive mixing occurs due to the gaseous flow rate.

Moreover, the five- and one-channel mixers (*mikroglas*) which are typical devices for liquid/liquid reactions were tested (Figure 3). Both the mixers possess multilaminar mixing units. The five-channel mixer exhibits five mixing units each leading

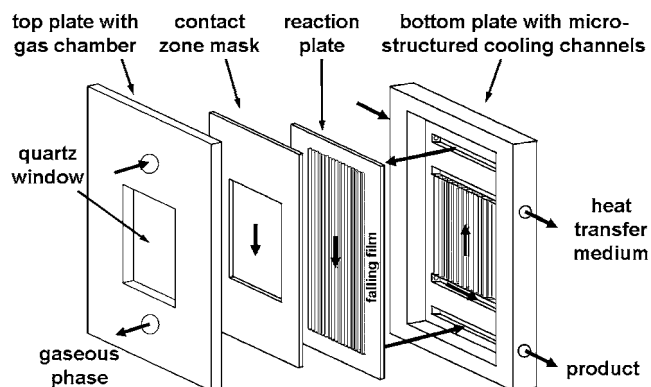


Figure 1. Working principle of the falling film microreactor by *IMM*⁹ (by courtesy of V. Hessel, *IMM*, Germany).

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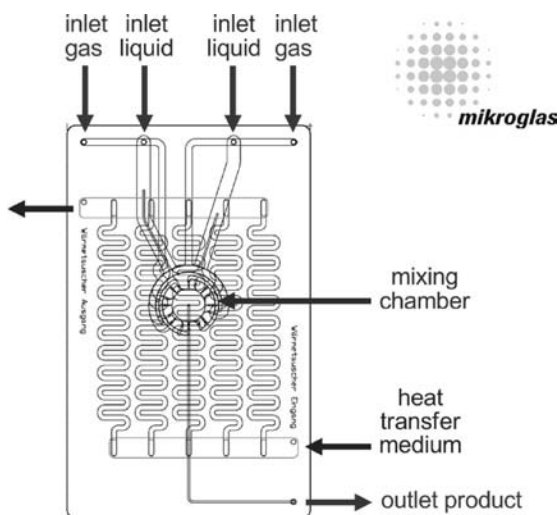


Figure 2. Microstructured gas/liquid contactor which was utilized for the ozonolysis reaction: the cyclone mixer.

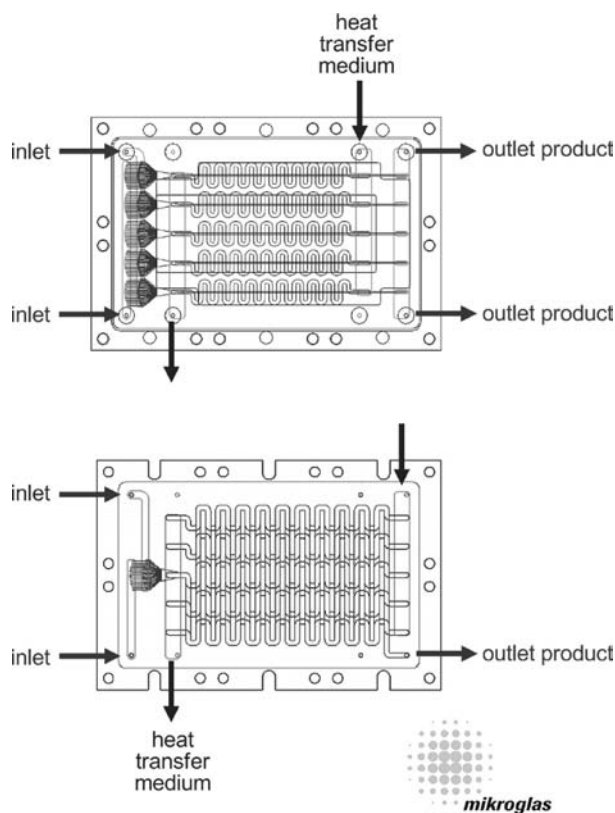


Figure 3. Microstructured reactors which were utilized for the ozonolysis reaction. Top: five-channel mixer. Bottom: one-channel mixer.

into a separate reaction channel ($14 \mu\text{L}$ internal volume each), whereas the mixing unit in the one-channel mixer leads to one reaction channel with an internal volume of $580 \mu\text{L}$ (Figure 3).

The experimental setup for the ozonolysis reaction is shown in Figure 6 (left). With a syringe pump a solution of substrate A in $\text{MeOH}/\text{CH}_2\text{Cl}_2$ was fed to the microreactor, where it was contacted with ozone in an oxygen stream. In case of the falling film microreactors the reaction mixture was pumped out of the reactors with an additional gear pump. The reaction mixtures were then subjected to HPLC analysis.

First the five microstructured reactors were tested at two different O_3/O_2 flow rates. The ozone content in the oxygen stream was set by adjusting the ozone generator power at a given oxygen flow rate. The higher oxygen flow enabled a higher O_3 flow rate. At a given O_3/O_2 flow rate, parameters such as temperature and the initial concentration of the substrate solution were kept constant. The flow rate of the liquid phase was varied solely. Therefore, it has to be stated here that in all microstructured reactors the increasing substrate A flow rate causes a shorter substrate residence time, a lower ozone/substrate ratio, and a higher film thickness of the liquid phase. However, the tested microreactors can be compared directly at the same liquid flow rate and regarding the maximum substrate throughput at complete conversion. Figure 4 summarizes results of the ozonolysis at varying substrate A flow rates in the tested microstructured reactors at constant ozone flow rates of 0.25 mmol/min in 100 mL/min O_2 (left) and 0.37 mmol/min in 200 mL/min O_2 (right).

Figure 4 clearly shows that the order of the three best-performing microstructured reactors remains the same at both O_3/O_2 flow rates. At a given flow rate the five-channel mixer, as a typical liquid/liquid microstructured tool, delivered the highest substrate conversions followed by the falling film microreactor (made by IMM) and the one-channel mixer. Notably, the cyclone mixer delivered better results at a higher gas flow rate. Probably, the mixing in the mixing chamber is more efficient at a higher gas flow rate. Generally, in all the reactors decreasing substrate conversions are obtained with increasing the substrate A flow rate, which could be due to a shorter residence time of the liquid phase, a lower ozone/substrate A ratio, or the flow regime. However, increasing the gas flow rate of $0.25 \text{ mmol/min O}_3$ (in 100 mL/min O_2) to $0.37 \text{ mmol/min O}_3$ (in 200 mL/min O_2) allowed for higher substrate throughputs for all reactors tested, despite the shorter residence times of both the ozone and the substrate A solution. That indicates that the ozonolysis is limited by the substrate/ozone ratio and the mass transfer rather than by the residence time.

In the range of the parameters investigated so far, the maximum substrate A throughput of 0.26 mmol/min delivering complete conversion was achieved in the five-channel mixer at an ozone flow rate of 0.37 mmol/min (200 mL/min O_2 , see Figure 4, right). On the basis of these results, the ozonolysis was then further optimized in the five-channel mixer (Figure 5). We were confident that a higher substrate throughput can be accomplished at higher gas flow rates, which were achieved by adjusting the ozone generator power at an oxygen flow rate of 200 and 400 mL/min , respectively. For comparison the results obtained with an O_2 flow rate of 100 mL/min ($0.25 \text{ mmol/min O}_3$) are also displayed in Figure 5.

First, the ozone content in a constant oxygen stream of 200 mL/min was increased from 0.37 to 0.80 mmol/min . This enabled an enhancement of the substrate throughput with complete conversion from 0.26 to 0.60 mmol/min . Hence, with a sufficient ozone/substrate A ratio of about 1.4 the ozonolysis also proceeds with complete substrate conversion at a shorter residence time of the liquid phase. Further improvement was attained at a higher oxygen flow rate of 400 mL/min ($1.55 \text{ mmol/min O}_3$): a maximum substrate throughput with complete

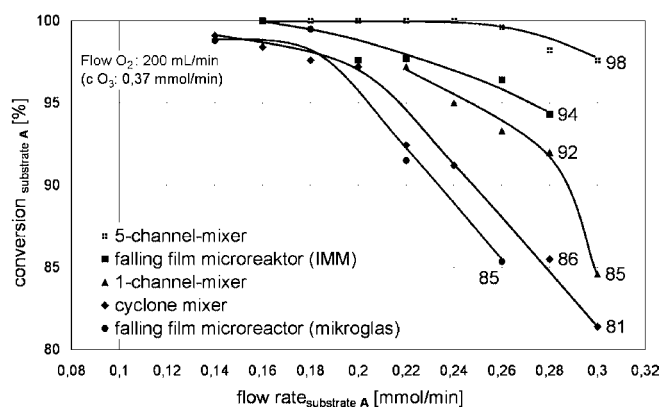
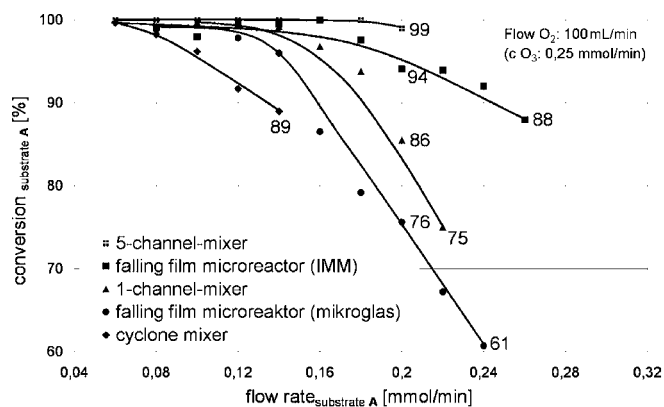


Figure 4. Comparison of performances of microstructured reactors in the ozonolysis reaction: obtained substrate A conversions plotted against the substrate A flow rates at constant O_3/O_2 flow rates. Reaction conditions: $c_{\text{substrate A}} = 0.1$ mmol/mL in MeOH/ $CH_2Cl_2 = 1/4$ at -17 to -10 °C with $c_{O_3} = 0.25$ mmol/min, flow $O_2 = 100$ mL/min (left) and $c_{O_3} = 0.37$ mmol/min, $O_2 = 200$ mL/min (right), respectively.

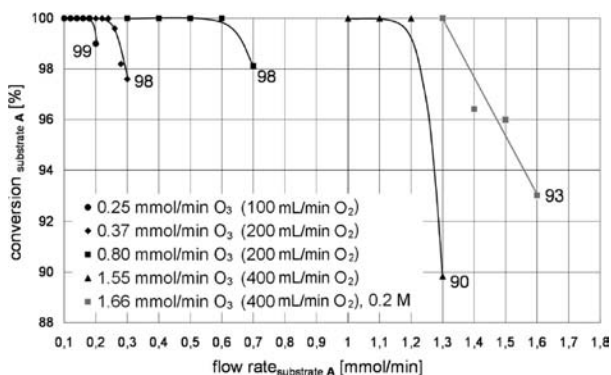


Figure 5. Substrate conversion for the ozonolysis reaction in the five-channel mixer (*mikroglas*) at different ozone flow rates. Reaction conditions: $c_{\text{substrate A}} = 0.1$ mmol/mL (black symbols) and $c_{\text{substrate A}} = 0.2$ mmol/mL (grey symbols), respectively in MeOH/ $CH_2Cl_2 = 1/4$ at -17 to -10 °C.

conversion of 1.2 mmol/min was reached, even though the residence times of both the gaseous and liquid phases were reduced drastically. However, at a higher liquid flow rate the conversion decreased rapidly, probably due to a low ozone/substrate A ratio. Within the parameters investigated, the maximum substrate throughput was further enhanced to 1.3 mmol/min by using a 0.2 M substrate A solution at a comparable gas flow rate (1.66 mmol/min O_3 in 400 mL/min O_2).

The findings are in agreement with our assumption that the ozonolysis of substrate A is a very fast reaction which can be processed even at high substrate flow rates (i.e., short residence times). In addition, it is known from the falling film microreactor that the ozone absorption rate and olefin conversion strongly depend on the mass transfer.⁷ Therefore, the conversion in the ozonolysis reaction should benefit from a high interfacial area between the gaseous and the liquid phase on the one hand and short ways for mass transfer on the other hand. Obviously, these requirements are fulfilled best in the five-channel mixer. Here, two features are conceivable to enhance the mass transfer. First, the small dimensions in the five multilaminar mixing units (see Table 4 in the Experimental Section) and second, the flow regime in the channels. We assume that, under the conditions applied, an annular flow regime is present during the reaction in each of the channels of the five-channel mixer, i.e. a thin

liquid film covers the wall while the gas flows in the middle of the channel. However, to our knowledge this is the first application of a five-channel mixer to a gas/liquid reaction, and in contrast to the falling film microreactor by IMM it is not characterized yet.

Due to the instability of the hydroperoxide species the HPLC results did not allow drawing any conclusions about the product selectivity in the ozonolysis step. However, we recently reported on the *in situ* monitoring of reactions in liquid phase by the utilization of a diamond ATR probe.¹⁰ This method enables semiquantitative FTIR analysis and offers an application for process control. Thus, it was shown during the ozonolysis batch procedure that the formation of the hydroperoxide was accompanied by the simultaneous formation of the aldehyde species. Furthermore, side reactions, such as the overoxidation of the aldehyde to the corresponding acid, occur at longer reaction times.

For a better implementation of the diamond ATR probe into the continuous ozonolysis process in microstructured devices a special micro flow-through cell was developed (*Infrared fiber sensors*). This cell was integrated close to the outlet of the microreactor (see Figure 6).

Typical FTIR-spectra which were obtained during the ozonolysis in the continuous process are depicted in Figure 7. The grey spectrum represents the substrate A solution passed through the microreactor at -8 °C, whereas the black spectrum was obtained when ozone was fed to the substrate solution in the microreactor. The formation of an aldehyde band (1720 cm^{-1}) and a band at 1089 cm^{-1} , which is assigned to a hydroperoxide species, can be observed. Hence, as in the batch procedure¹⁰ hydroperoxide and aldehyde species are formed simultaneously in the continuous ozonolysis step as major products. Overoxidation of the aldehyde to the corresponding acid was not observed.

The calculation of the integral intensities of the characteristic bands in the reaction mixture allows for a semiquantitative analysis. The integral intensities of the aldehyde and the hydroperoxide bands were determined from the difference spectra (see Figure 7). In order to get a better insight, the ozonolysis process was carried out in the two best-performing microstructured reactors, the five-channel mixer

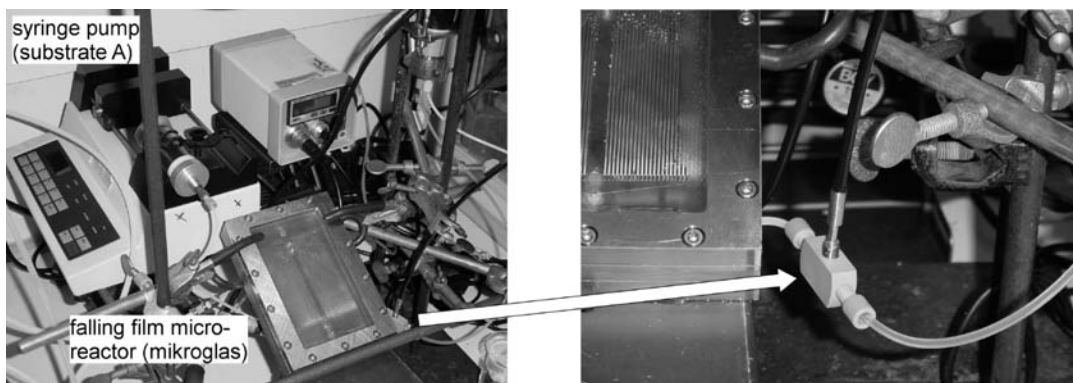


Figure 6. (Left) Experimental setup for the ozonolysis in a microreactor. (Right) Integrated micro flow-through cell (*Infrared fiber sensors*) with diamond ATR probe for online FTIR analysis.

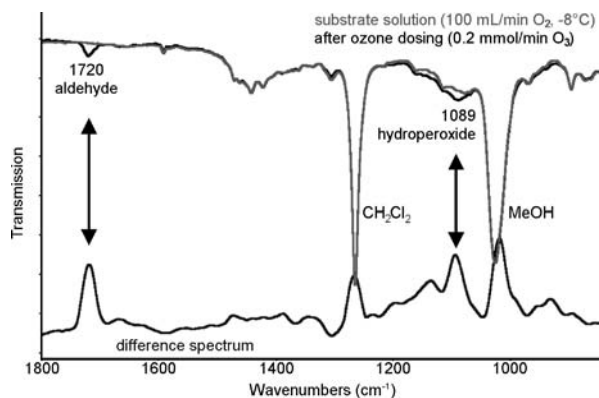


Figure 7. Typical ATR FTIR-spectra of the reaction mixture, measured with the micro flow-through ATR cell (*Infrared fiber sensors*) in the continuous process before (grey) and after (black) dosing of ozone in a microreactor.

(*mikroglas*) and the falling film microreactor (*IMM*). The substrate **A** flow rate and concentration as well as the oxygen flow rate were kept constant. The ozone content in the oxygen stream was varied from 0.02 to 0.24 mmol/min. The results of the online FTIR analysis are shown in Figure 8 (left) and compared to those results obtained from HPLC analysis (Figure 8, middle).

It is clearly seen that aldehyde formation (FTIR analysis) and substrate conversion (HPLC analysis) correlate very well. Both the aldehyde formation and substrate conversion increase with increasing ozone content up to about 0.14 mmol/min. A

further excess of ozone does not increase the aldehyde formation or substrate conversion (see Figure 8, left and middle). Therefore, it can be concluded for the two microstructured reactors tested that an ozone/substrate **A** ratio of about 1.4 is sufficient for complete conversion of substrate **A** under the applied conditions. This is in agreement with our results on the ozonolysis reaction in the five-channel mixer presented in the Figures 4 and 5.

So far, we have shown the successful integration of the micro flow-through cell (*Infrared fiber sensors*) with diamond ATR probe in the continuous ozonolysis process and proved its suitability for the process control *via* online FTIR analysis.

Next, we set out to investigate the reduction step. The main goal was to show the feasibility of the reduction of the ozonolysis reaction mixture in microstructured reactors without isolation of the intermediates. Therefore, the liquid/liquid microstructured reactors made by *mikroglas* (one- and five-channel mixer, see Figure 3) were utilized. The cooled, freshly prepared ozonolysis reaction mixture was fed to the microstructured reactor with a micro annular gear pump. A 3-fold excess of NaBH_4 as a 3.5 M solution in DMF was dosed to the micromixer with a syringe pump. After having passed the micromixer, the reaction mixture was subjected to analysis. Due to overlapping of bands in the ν (C–O) range, which is characteristic for alcohol **D** as well as the hydroperoxide species, differentiation of the substances was not possible by online FTIR analysis. Moreover, DMF causes overlapping IR-bands at 1666,

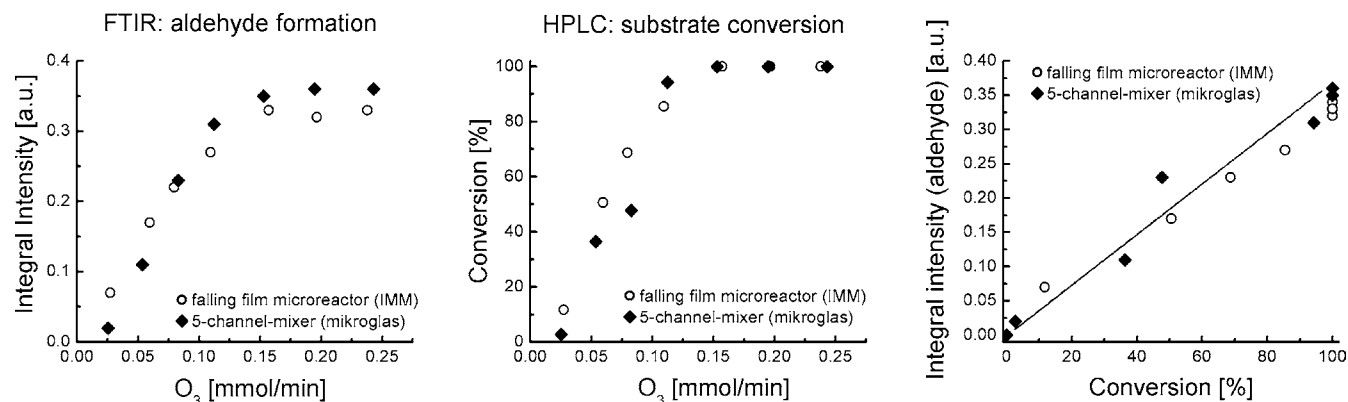


Figure 8. Product formation (left, online FTIR analysis) and substrate conversion (middle, HPLC analysis) in the ozonolysis reaction at different O_3 flow rates in a falling film microreactor (*IMM*) and a five-channel mixer (*mikroglas*). Right: Correlation of integral intensity (FTIR) and conversion (HPLC). Reaction conditions: $\text{flow}_{\text{substrate A}} = 0.1$ mmol/min, $c_{\text{substrate A}} = 0.1$ mmol/mL in $\text{MeOH}/\text{CH}_2\text{Cl}_2 = 1/4$ at -10°C , $\text{flow}_{\text{O}_2} = 100$ mL/min.

Table 1. Obtained conversions of the continuous reduction of the ozonolysis reaction mixture with NaBH₄ in DMF in a five-channel mixer at different substrate flow rates^a

flow (ozonolysis solution) ^b		flow (NaBH ₄) ^c	
[mL/min]	[mmol/min]	[mmol/min]	conv. ^d
0.6	0.06	0.18	quant.
1.0	0.10	0.30	quant.
1.5	0.15	0.45	n. q.

^a Reaction conditions: 3 equiv NaBH₄ in DMF, *c* (NaBH₄) = 3.5 mmol/mL, 10 °C to 15 °C. ^b Freshly prepared from a 0.1 M solution of substrate **A** in the typical ozonolysis procedure with complete conversion. ^c Solution in DMF. ^d Conversion estimated from TLC, quant. = quantitative, n. q. = not quantitative.

Table 2. Obtained conversions of the continuous reduction of the ozonolysis reaction mixture with NaBH₄ in DMF in a five-channel mixer with 5 m residence time module at different substrate flow rates^a

flow (ozonolysis solution) ^b		flow (NaBH ₄) ^c	
[mL/min]	[mmol/min]	[mmol/min]	conv. ^d
1.5	0.15	0.45	quant.
2.0	0.20	0.60	quant.
4.0	0.40	1.20	quant.
6.0	0.60	1.80	quant.

^a Reaction conditions: 3 equiv NaBH₄ in DMF, *c* (NaBH₄) = 3.5 mmol/mL, 10 °C to 15 °C. ^b Freshly prepared from a 0.1 M solution of substrate **A** in the typical ozonolysis procedure with complete conversion. ^c Solution in DMF. ^d Conversion estimated from TLC, quant.=quantitative.

1387, and 1098 cm⁻¹ in the reaction mixture. However, the feasibility of the reduction in microstructured reactors can easily be shown by thin layer chromatography (TLC) analysis. First, the one-channel mixer was utilized, but the maximum flow rate of the ozonolysis reaction mixture at complete conversion was 0.6 mL/min which is not sufficient for application on kilogram scale. Therefore, the five-channel mixer was tested in the reduction step. Table 1 summarizes the results.

As already stated, the ozonolysis reaction mixture was freshly prepared from substrate **A** and the flow rates given for the ozonolysis solution (mmol/min, see Table 1) correlate to the initial substrate **A** flow rate assuming complete conversion. This is also true for all following tables. However, quantitative conversion of the intermediates was observed up to a flow rate of 0.1 mmol/min. A 5 m residence time module with an internal volume of 5 mL (*Little Things Factory*) was therefore added to the five-channel mixer for completion of the reduction (Table 2). The results clearly show that this experimental setup allows a complete conversion up to a substrate throughput of at least 0.6 mmol/min.

On the basis of the results of the single steps we started to investigate the overall process. The general flow scheme is presented in Figure 9: ozone and the substrate **A** solution were dosed into the first five-channel mixer (1), where the ozonolysis takes place. The micro flow-through cell (2) for process control *via* online FTIR analysis can be integrated close to the reactor outlet as indicated in Figure 9. The reaction mixture was then passed through a gas separator (3). Here, samples were taken for the offline HPLC analysis of the ozonolysis reaction mixture. For the reduction step with NaBH₄ in DMF the liquid phase was pumped further into the second five-channel mixer (4) and

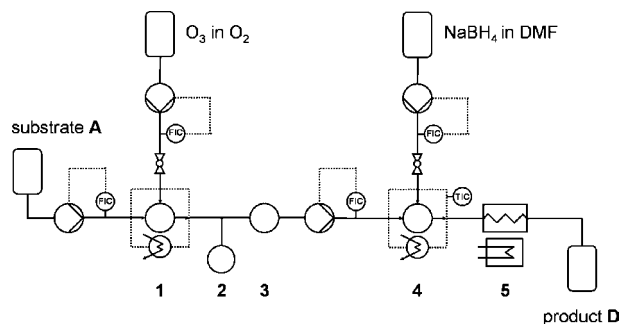


Figure 9. Flow scheme for the overall process: (1) five-channel mixer (ozonolysis), (2) FTIR-online analysis, (3) gas separator, (4) five-channel mixer (reduction), (5) residence time module.

the 5 m residence time module (5), subsequently. Then the reaction mixture was collected and subjected to analysis once again.

Figure 10 shows the experimental setup of the continuous overall process. Most of the experiments presented here were carried out in a multipurpose plant, which was engineered by *mikroglas*. The plant is controlled by Siemens-Simatic software and was designed for three different processes, one of which is the ozonolysis–reduction sequence.

The results of the overall process are summarized in Table 3. The substrate **A** flow rate ranged from 0.1 to 1.2 mmol/min. In the continuous overall process the ozone flow rates for the ozonolysis were adjusted by variation of the ozone generator power at different oxygen flow rates and a 3-fold excess of NaBH₄ compared with substrate **A** was applied for the reduction.

It can generally be stated here, that in the range of the applied parameters conversions >95% were achieved in both steps. With increasing substrate **A** flow rate (0.1 to 0.3 mmol/min), ozone content and oxygen flow rate were initially increased from 0.24 mmol/min O₃ in 100 mL/min to 0.40 mmol/min O₃ in 250 mL/min. The incomplete conversion in the ozonolysis step at 0.3 mmol/min is probably mainly due to the low O₃/substrate **A** ratio. After setting the ozone content to 1.65 mmol/min complete conversion was obtained in the ozonolysis step (compare entries 3.0 mL/min). Then the substrate **A** flow rate was further increased. Utilizing a 0.1 M substrate **A** solution, a substrate throughput of up to 0.6 mmol/min is feasible. Application of a substrate solution with doubled concentration (0.2 M) allows an enhanced substrate throughput of 1.2 mmol/min. In this case the reaction mixture was collected over 5.5 min. After workup and purification of the alcohol **D** by column chromatography 2.9 g (69%) were obtained. Hence, an extrapolated substrate **A** throughput of about 1.22 kg/d (i.e., 0.76 kg/d isolated alcohol **D**) is feasible.

Conclusion

Here, we reported on the development of an industrially important ozonolysis–reduction sequence for the continuous processing in microstructured reactors with an integrated micro flow-through cell for the online process analysis *via* FTIR. The two reaction steps were initially investigated separately utilizing different microstructured reactors. A five-channel mixer (*mikroglas*) performed best in both reactions, which was rather surprising for the ozonolysis as a typical gas/liquid reaction.

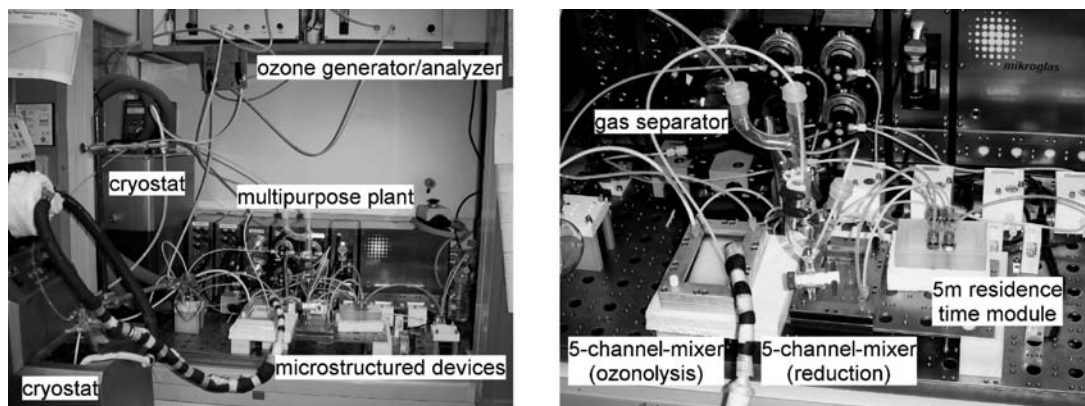


Figure 10. Experimental setup for the ozonolysis–reduction sequence in a multipurpose plant (*mikroglas*). Left: overall view. Right: detailed view of the microstructured devices.

Table 3. Obtained conversions of the continuous overall process with two five-channel mixers and a 5-min residence time module at different substrate flow rates^a

flow (substrate A)		flow (O ₃)	flow (O ₂)	ratio	conv. ozonolysis ^c	flow (NaBH ₄) ^d	conv. reduction ^e
[mL/min]	[mmol/min]	[mmol/min]	[mL/min]	(O ₃ /sub. A)	[%]	[mmol/min]	[%]
1.0	0.1	0.24	100	2.4	100	0.3	100
2.0	0.2	0.36	200	1.8	100	0.6	100 ^f
3.0	0.3	0.40	250	1.3	97	0.9	>95
3.0	0.3	1.65	400	5.5	100	0.9	>95
6.0	0.6	1.66	400	2.8	100	1.8	>95
6.0	1.2 ^b	1.62	400	1.4	100	3.6	>95 ^g

^a Reaction conditions: ozonolysis: *c* (substrate A) = 0.1 mmol/mL in MeOH/CH₂Cl₂ = 1/4 at –17 °C to –10 °C; reduction: 3 equiv NaBH₄ in DMF, *c* (NaBH₄) = 3.5 mmol/mL, 10 °C to 15 °C. ^b *c* (substrate A) = 0.2 mmol/mL. ^c Obtained from HPLC. ^d Solution in DMF. ^e Conversion estimated from TLC. ^f Isolated yield of alcohol D: 72%. ^g Isolated yield of alcohol D: 69%.

The acquired reaction conditions of the single steps were successfully transferred to the overall process. Under an optimized set of conditions (ozonolysis: *c*_{substrate A} = 0.2 mmol/mL in MeOH/CH₂Cl₂ = 1/4 with a flow rate of 1.2 mmol/min at –10 to –17 °C; reduction: *c*_{NaBH₄} = 3.5 mmol/mL in DMF with a flow rate of 3.6 mmol/min at 10 to 15 °C) an extrapolated substrate throughput of about 1.22 kg/d (i.e., 0.76 kg/d isolated product) is feasible. Therewith, the processing in microstructured devices allows for the synthesis of the desired product (alcohol D) on a kilogram scale. The application of microstructured devices holds three major advantages over the batch procedure: First, the ozonolysis was carried out at a reaction temperature of –10 to –17 °C. Second, in microstructured reactors the ozone is dosed continuously to the substrate and an ozone excess of about 1.4 equiv is sufficient for complete conversion. Thus, long ozone dosing and probable accumulation of undesired products in a batch is avoided. Third, the desired product was obtained in a two-step procedure without the isolation of any intermediates.

Experimental Section

Analytics. Quantitative analyses of the ozonolysis reaction mixtures for the determination of the substrate A conversion were carried out by HPLC (*Merck Hitachi L-6200 A* with UV Detector *L-4000 A*, $\lambda = 230$ nm) equipped with a Nucleosil 100-5 C18 column (250 mm length; Φ 4 mm; mobile phase: 4 mL/min, gradient, A = water, B = acetonitrile, 90 to 98% B in 10 min then 98% B for 15 min). The concentrations of the ozonolysis products in the reaction mixtures could not be determined by HPLC due to instability of the hydroperoxide

species and overlapping peaks in case of the diastereomeric aldehyde C. Therefore, semiquantitative online FTIR analyses of the ozonolysis reaction mixtures were performed using a micro flow-through cell with an implemented diamond ATR probe (*Infrared fiber sensors*). The mid-infrared ATR spectra were collected by a FTIR-spectrometer *Nicolet Avatar 370* (Thermo Electron). The probe is connected to the spectrometer by permanently aligned mirror optics.¹⁰ Measurements were carried out in the spectral range of 4000 to 650 cm⁻¹ using a 4 cm⁻¹ resolution by accumulating 128 scans.

Materials. Substrate A was synthesized in a well-established procedure from a precursor by SO₂ addition in dichloromethane according to literature.^{8a} The precursor was provided by the Bayer Schering Pharma AG for substance identification and for conversion in the continuous processes. The purity of compound A was determined by TLC and HPLC. The substrate was then consumed in the ozonolysis reaction within two days. Aldehyde C and alcohol D were provided by Bayer Schering Pharma AG for substance identification. Substrate A: HPLC *R*_t = 16.40 and 18.48 min, *R*_f = 0.76 and 0.63 (SiO₂, *n*-heptane/EtOAc = 7:3). Hydroperoxide: IR (characteristic band in the reaction mixture) $1/\lambda = 1089$ cm⁻¹ (w). Aldehyde C: HPLC *R*_t = 4.22 and 5.08 min, *R*_f = 0.51 and 0.44 (SiO₂, *n*-heptane/EtOAc = 7:3), IR (characteristic band in the reaction mixture) $1/\lambda = 1720$ cm⁻¹ (w). Alcohol D: HPLC *R*_t = 3.63 and 4.32 min, *R*_f = 0.21 and 0.16 (SiO₂, *n*-heptane/EtOAc = 7:3).

Merck TLC aluminium sheets (silica gel 60 F₂₅₄) were utilized for TLC. Ozone was generated from oxygen (*Air Liquide*, 5.5) with the ozone generators *Fischer OZ 500/2* and *Ozonia OZAT CFS-1* (for ozone flow rates >0.46 mmol/min),

Table 4. Characteristic properties of the utilized microstructured reactors

Properties	mikroglas				
	FFMR ^a	FFMR ^a	5-ch.-m. ^b	1-ch.-m. ^b	cyclone mixer
mixing unit:					
numbers of mixing chambers	–	–	5	1	1
type of mixer	falling film	falling film	interdigital	interdigital	chamber
chamber vol. [mL]	–	–	0.004	0.004	0.170 (Ø 10 mm 2.2 mm height)
channel dimensions					
gas: vol. [mL]	–	–			2x0.12
height [mm]	–	–			2x0.5
liquid: vol. [mL]	–	–			2x0.13
height [mm]	–	–			2x0.5
reaction channels:					
number	32	48	5	1	1
length [mm]	66	98			
width [mm]	0.6	0.5			
height [mm]	0.2	0.3	0.25	0.25	
single channel vol. [mL]	0.008	0.015	0.014	0.576	0.023
total channel vol. [mL]	0.25	0.720	0.070	0.576	0.023
gas room vol. [mL]	11.00	45.96	–	–	–
total reactor vol. [mL]	11.25	46.68	0.090	0.580	0.193

^a FFMR = falling film microreactor. ^b ch.-m. = channel-mixer.

respectively. The ozone content in the oxygen stream was analyzed by the ozone analyzer *Fischer Ozotron 23*. All other reagents were used as received from commercial suppliers.

The characteristics of the utilized microstructured reactors are presented in Table 4.

General Reaction Procedures. *Ozonolysis.* Oxygen, dosed by a mass flow controller (*Bronkhorst*) was fed through ozone generator (*Fischer OZ 500/2* or *Ozononia OZAT CFS-1*) and analyzer (*Fisher Ozotron 23*). The ozone content in the oxygen stream was varied by variation of the ozone generator power: 0.02 mmol/min O₃ (at 100 mL/min O₂) to 1.66 mmol/min O₃ (at 400 mL/min O₂). A solution of substrate **A** in MeOH/CH₂Cl₂ (1/4) was dosed into the microstructured reactor with a syringe pump (flow rate range: 0.06–1.60 mmol/min). In the case of the falling film microreactors the reaction mixture was pumped out of the reactor by a gear pump. The ozonolysis reaction was carried out in cocurrent flow of gas and liquid phases. The microstructured reactors were cooled with a cryostat, and ozone was passed into the microreactor. The temperature of the reaction medium measured at the microreactor outlet ranged from –17 to –10 °C. For semiquantitative online FTIR analysis the micro flow-through cell was placed next to the reactor outlet. Two samples each were collected at steady-state conditions at different substrate

flow rates and were subsequently analyzed at room temperature.

Reduction. A cooled, freshly prepared ozonolysis reaction mixture was fed to the microstructured reactor with a micro annular gear pump. The flow rate ranged from 0.6 to 6.0 mL/min (corresponding to a substrate **A** flow rate of 0.06–0.60 mmol/min). The microstructured reactors were cooled with a cryostat. Then a 3-fold excess of NaBH₄ was dosed into the microstructured reactor as a DMF solution ($c_{\text{NaBH}_4} = 3.5$ mmol/mL) with a syringe pump (i.e., flow rate range: 0.18–1.80 mmol/min). The temperature of the reaction medium measured at the microreactor outlet ranged from 10 to 15 °C. Two samples each were collected at steady-state conditions at different substrate flow rates and were subsequently analyzed.

Overall Process: Ozonolysis–Reduction Sequence. Oxygen, dosed by a mass flow controller (*Bronkhorst*) was fed through an ozone generator (*Fischer OZ 500/2* or *Ozononia OZAT CFS-1*) and analyzer (*Fisher Ozotron 23*). The ozone content in the oxygen stream was varied by variation of the ozone generator power: 0.24 mmol/min O₃ (at 100 mL/min O₂) to 1.66 mmol/min O₃ (at 400 mL/min O₂). A solution of substrate **A** in MeOH/CH₂Cl₂ (1/4) was dosed into a five-channel mixer (*mikroglas*) with a syringe pump (flow rate range: 0.1–1.2 mmol/min). The

micromixer was cooled with a cryostat, and ozone was passed into the microreactor in cocurrent flow. The temperature of the reaction medium measured at the microreactor outlet ranged from -17 to -10 °C. The ozonolysis reaction mixture was passed through a gas separator, and the liquid phase was then pumped into the second five-channel mixer (*mikroglas*) for the reduction step. The second micromixer was also cooled with a cryostat. A 3-fold excess of the reducing agent NaBH_4 was dosed into the five-channel mixer (*mikroglas*) as a DMF solution ($c_{\text{NaBH}_4} = 3.5$ mmol/mL) with a syringe pump (i.e., flow rate range: 0.3–3.6 mmol/min). The temperature of the reaction medium measured at the microreactor outlet ranged from 10 to 15 °C. The reaction mixture was then led through a 5 m residence time module (*Little Things Factory*) for completion of the reduction. Two samples each were collected at steady-state conditions at different substrate flow rates and subsequently analyzed.

Workup Procedure for the Isolation of Alcohol D from the Reaction Mixture. For 5.5 min the reaction mixture of the overall process was collected under the optimized set of conditions

(ozonolysis: $c_{\text{substrate A}} = 0.2$ mmol/mL in $\text{MeOH}/\text{CH}_2\text{Cl}_2 = 1/4$ with a flow rate of 1.2 mmol/min and flow rate_{ozone} = 1.62 mmol/min at -10 to -17 °C; reduction: $c_{\text{NaBH}_4} = 3.5$ mmol/mL in DMF with a flow rate of 3.6 mmol/min at 10 to 15 °C). Under ice cooling the mixture was brought to pH 5.5, eluted with 30 mL of water and acidified to pH 5.5 again. The aqueous phase was extracted twice with ethyl acetate. The combined organic phases were then washed with brine, dried over Na_2SO_4 , and purified by column chromatography (gradient elution from petrolether/ethyl acetate 9:1 to 8:2). The alcohol **D** was obtained with an isolated yield of 69% (2.9 g).

Acknowledgment

We thank Manuela Pritzkow for excellent technical assistance. Furthermore, generous financial support from the Bundesministerium für Bildung und Forschung (BMBF, 16SV1963) is gratefully acknowledged.

Received for review March 23, 2009.

OP9000669